

Zoledronic Acid After Hip Fracture

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Background – Hip Fracture

- A major source of mortality and morbidity in Canada
- In 2005: 28,200 hospitalizations for hip fracture
- 7% died < 30 days of hospital admission
- 1-yr mortality = approx. 25%

Background – Hip Fracture

- Tx of osteoporosis tend to be poorly handled after hip fracture
- In recent Italian study: 22% of post-hip fracture patients received no treatment for osteoporosis on discharge
- Of those receiving treatment: 52% discontinued tx by mean 1.4 years

Background – Zoledronic Acid

- Highly potent bisphosphonate
- Developed for tx of malignant hypercalcemia
- Major advantage: once-YEARLY IV infusion over 15 mins
- IV route lowers risk of erosive esophagitis seen with oral bisphosphonates

Background – Zoledronic Acid

■ Disadvantages:

- 1 dose = CAD\$570
- (vs. risedronate x 12 mos = CAD\$390)
- Requires IV infusion associated cost
- Safety profile not yet well established (e.g., concern over atrial fibrillation)

Background – ZA and A. Fib

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Once-Yearly Zoledronic Acid for Treatment of Postmenopausal Osteoporosis

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for the HORIZON Pivotal Fracture Trial*

Background – ZA and A. fib

- Once-yearly zoledronic acid vs placebo
- N = 7765 postmenopausal women with osteoporosis
- → 70% RRR in vertebral #s and 41% RRR in hip fracture.
- → Serious a. fib (1.3% with ZA vs 0.5% with placebo)

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Zoledronic Acid and Clinical Fractures and Mortality after Hip Fracture

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Participant Selection

INCLUSION CRITERIA

- < 90 days of a hip fracture repair sustained with minimal trauma
- Ambulatory before the fracture
- Unable or unwilling to take an oral bisphosphonate

EXCLUSION CRITERIA

- Previous bisphosphonate intolerance
- Potential pregnancy
- CrCl < 30 mL/min
- Ca^{2+} < 2.0 or > 2.8
- Active cancer
- Bone disease other than osteoporosis
- Life expectancy < 6 mos

Study Design

- RCT
- Randomized to IV zoledronic acid or placebo
- Given < 90 days after hip fracture and every 12 months thereafter
- Vit D deficient patients received a Vit D loading dose 14 days prior to study drug infusion
- Patients were to be followed up to 5 years
- (However, study was prematurely stopped at a median of 1.9 years in lieu of clear efficacy of zoledronic acid)

Study Outcomes

- **Primary:**

- New clinical fracture, excluding facial, digital and pathologic fractures

- **Secondary:**

- Change in bone mineral density
- New vertebral, non-vertebral and hip fractures
- Prespecified safety end points, including death

Study Flow Diagram

2127 underwent randomization

1065 assigned to
zoledronic acid group

1062 assigned to
placebo group

770 (73%)
completed
follow-up

295 did not
complete
follow-up

746 (70%)
completed
follow-up

316 did not
complete
follow-up

102 died

193 discontinued

- 120 withdrew
- 35 were lost to f/u
- 38 others

142 died

174 discontinued

- 109 withdrew
- 28 were lost to f/u
- 37 others

Table 1. Baseline Characteristics of the Patients.*

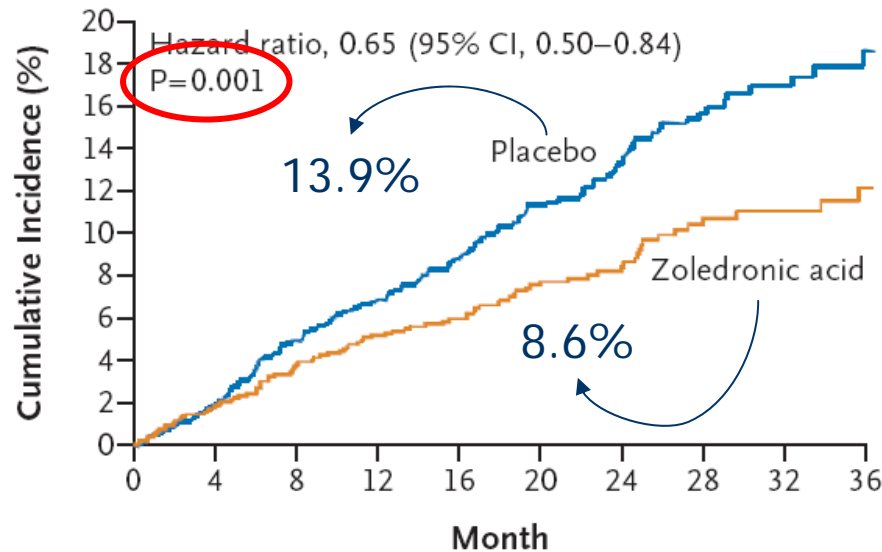
Variable	Placebo (N=1062)	Zoledronic Acid (N=1065)	P Value†‡
Race or ethnic group — no. (%)‡			0.67
White	965 (90.9)	973 (91.4)	
Hispanic	70 (6.6)	70 (6.6)	
Black	12 (1.1)	6 (0.6)	
Other	15 (1.4)	16 (1.5)	
Sex — no. (%)			0.52
Female	802 (75.5)	817 (76.7)	
Male	260 (24.5)	248 (23.3)	
Age			
Mean — yr	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

Table 1. Baseline Characteristics of the Patients.*

Variable	Placebo (N= 1062)	Zoledronic Acid (N= 1065)	P Value†
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

Primary Outcome: New Clinical Fracture

A Any Clinical Fracture



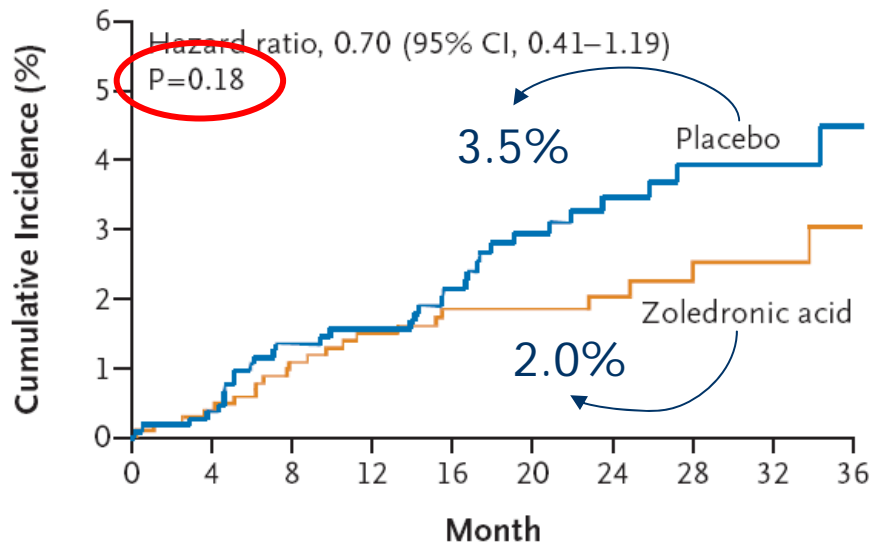
No. at Risk

Zoledronic acid	1065	1013	950	895	762	628	473	316	212	129
Placebo	1062	1010	947	884	742	611	443	305	190	119

- 38% RRR
- 5% ARR
- NNT 20

Secondary Outcome: Recurrent Hip Fracture

D Hip Fracture

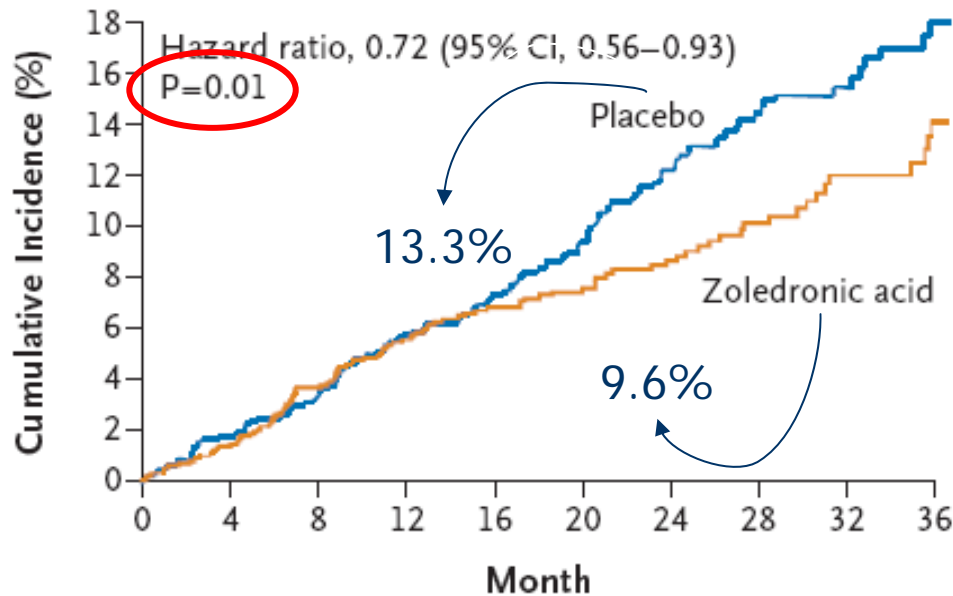


No. at Risk

Zoledronic acid	1065	1027	978	931	794	664	499	344	233	139
Placebo	1062	1025	981	927	787	664	492	347	223	139

- 1.5% ARR
- Not statistically significant

Secondary Outcome: Death



- 28% RRR
- 3.7% ARR
- NNT 27

No. at Risk

Zoledronic acid	1054	1029	987	943	806	674	507	348	237	144
Placebo	1057	1028	993	945	804	681	511	364	236	149

Adverse Events

- Adverse events more common in treatment group than placebo group:
 - Myalgias around infusion time (3.1 vs 0.9%)
 - Pyrexia around infusion time (6.9 vs 0.9%)
- No difference in a. fib.
- No reported cases of osteonecrosis of the jaw

Some EBM Questions To Pose About Study Validity

- Was assignment of patients to treatments randomized?
 - Yes
- Was follow-up complete?
 - About 30% of patients randomized did not complete study.
 - 3% were lost to follow up
 - ~11% of patients withdrew from the study

Are The Results Of The Study Valid?

- **Were patients analyzed in the groups to which they were randomized?**
 - Intent-to-treat analysis was performed with no crossover between groups
- **Were the groups similar at the start of the trial?**
 - Patients were similar except for concomitant osteoporosis therapy

Are The Results Of The Study Valid?

- Were patients, health workers, and study personnel “blind” to treatment assignment?
 - Yes, but the study drug causes an influenza like syndrome (pts pre-treated with tylenol)
- Aside from the experimental intervention, were the groups treated equally?
 - Other osteoporosis treatments were allowed, but physicians were blinded to study groups
 - Rates of concomitant osteoporosis treatments *during* study period were not reported

What Were The Results?

- **How large was the treatment effect?**
 - RRR of any clinical fracture: 38%
 - RRR in mortality: 28%
- **How precise was the estimate of the treatment effect?**
 - Confidence intervals were significant for both of the above

Will The Results Help Me In Caring For My Patients?

- **Were all clinically important outcomes considered?**
 - Most relevant clinical outcome was recurrent fracture
 - Mortality benefit was unexpected and difficult to explain
 - Major concerning adverse events were considered and reported (AF, osteonecrosis)

Will The Results Help Me In Caring For My Patients?

- Can the results be applied to my patient care?
 - Hip fractures are extremely common
 - Osteoporosis risk reduction is often not addressed in this population
 - Long-term bisphosphonate compliance is also a major concern
 - This may be a useful alternative to other forms of secondary fracture risk reduction

Summary

- Hip fractures are a major cause of morbidity and mortality in Canada
- Secondary prevention of osteoporosis is inconsistent in these patients and adherence is challenging

Summary

- Zoledronic acid provides advantages in its ease of administration
- The HORIZON study shows that it may offer a mortality benefit post hip fracture
- Use of zoledronic acid in osteoporosis prevention and treatment in other populations needs investigation

Discussion