

The Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly Recurrent Fracture Trial “Zoledronic Acid and Clinical Fractures and Mortality after Hip Fracture.”
NEJM, 2007; 357: (online)

Background

- Hip fractures in the elderly are associated with significant morbidity and mortality with rates of the latter at one year being reported as high as 15 – 25%
- Bisphosphonates like Zoledronic acid have been shown to decrease the incidence of vertebral, hip and nonvertebral fractures in postmenopausal women
- The utility of using zoledronic acid for secondary prevention of new fractures is unknown

Hypothesis

- The use of zoledronic acid will reduce the incidence of second fracture after initial hip fracture

Study Design

Study type: international, multicenter, double-blind, placebo controlled trial

Setting: International

Time period: 2/2002 – 11/2006 (halted after unplanned interim analysis)

Inclusion Criteria:

- Undergone repair of hip fracture secondary to minimal trauma (within 90 days) and unable/unwilling to take oral bisphosphonate
- Men and Women 50 years of age or older
- Ambulatory before fracture and must still have both legs.
- Concurrent use of nasal calcitonin, estrogen-receptor modulators, estrogen, tibolone allow in addition to prior use of oral bisphosphonates after appropriate drug specific washout period.

Exclusion Criteria: Previous hypersensitivity reaction to bisphosphonates, potential for pregnancy, creatinine <30ml/min, corrected calcium > 11mg.dL or less than 8.0mg/dL, active cancer, life expectance < 6mo, metabolic bone disease other than osteoporosis

Randomization: N = 2127, were randomized into two groups

- Zoledronic acid + Calcium/Vit D (N=2065): within 90days of fracture/repair and yearly thereafter
- Placebo + Calcium/Vit D (N=1062): within 90 days fo fracture/repair and yearly thereafter.

Patient characteristics: Table 1 was similar b/w groups. There is a staggering preponderance of ‘white’ study participants and the few ‘black’ patients (18/2056) were disproportionately grouped in the placebo category.

Outcomes:

- New clinical fracture, excluding facial, digital fractures and fractures through abnormal bone
- Change in bone mineral density (BMD) in the non-fractured hip (annual dexa)
- New vertebral, non-vertebral, and hip fractures
- Death

The evidence

	Controls	Cases	Relative Risk (RR)	Relative Risk Reduction (RRR)	Absolute Risk Reduction (ARR)	Number Needed to Treat (NNT)
	Control Event Rate (CER)	Experimental Event Rate (EER)	EER/CER	1- RR	CER – EER	1/ARR
New Fracture	13.9%	8.6% (p< 0.001)	0.62	0.38(38%)	5.3%	18.9
Death	13.3%	9.6% (p< 0.01)	0.72	0.28	3.7%	27

Comments

- In patients s/p repair of a pathologic hip fracture, the use of zoledronic acid is associated with a decreased incidence of new hip and vertebral fractures in addition to a decreased risk of death
- Study has been criticized for violating the principle of equipoise. Also there is no comparison of the use of secondary agents between the two groups. This study was funded by Novartis.