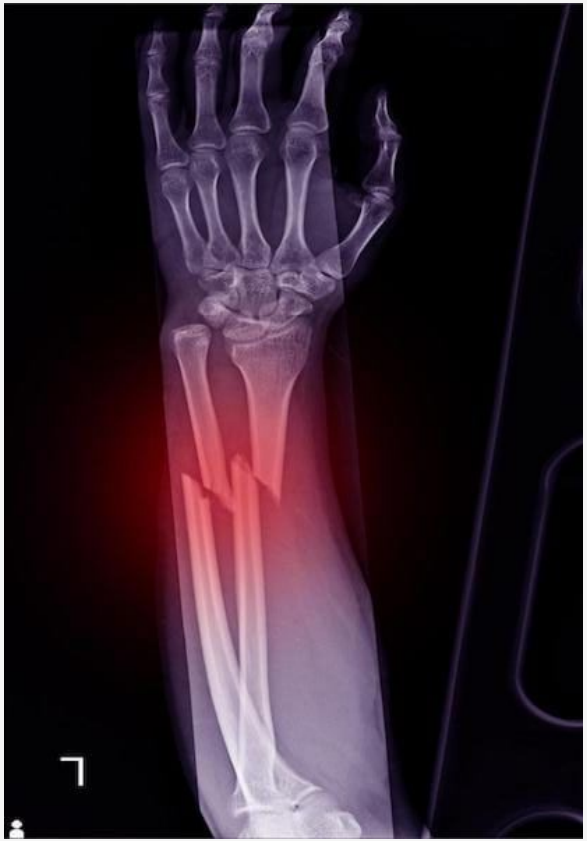


Survival Analysis: Denosumab for Preventing Fractures

Bao Han Ngo

Agenda

01 the experiment

02 modeling survival

03 modeling hazard

04 conclusion

01

the experiment

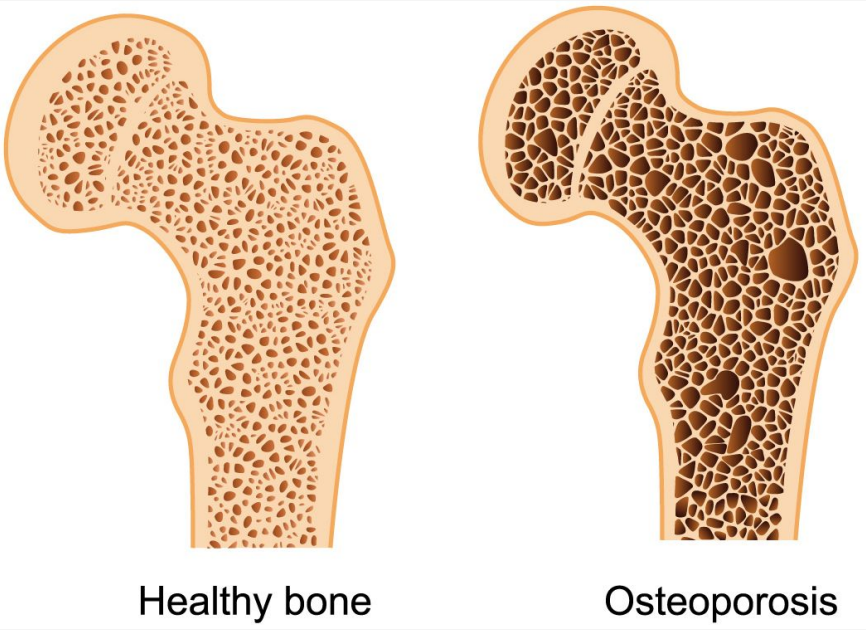
osteoporosis

osteoporosis

a condition in which bones deteriorate, becoming more brittle and prone to fractures

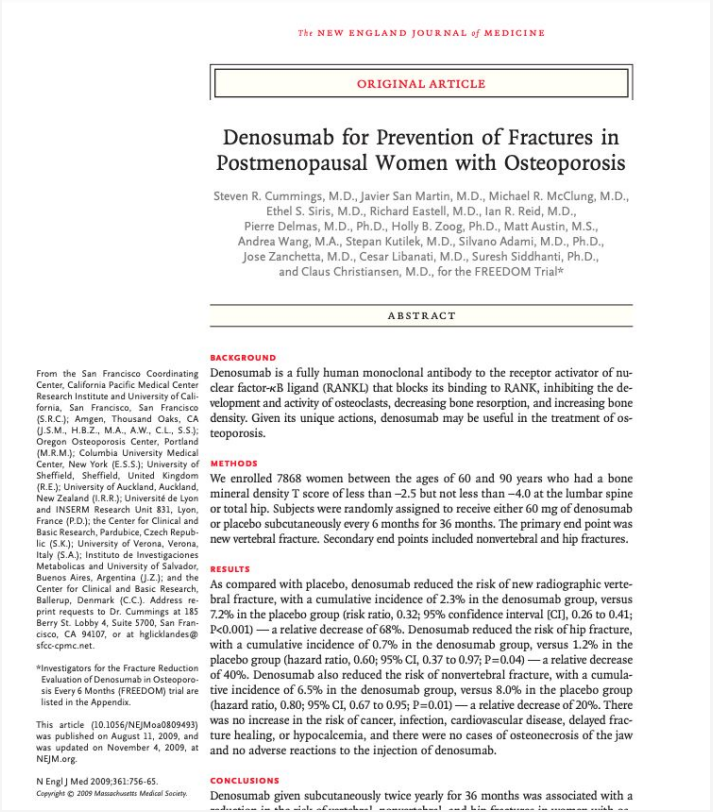
denosumab

prevents the resorption of bone by osteoclasts without inhibiting osteoclast formation



the experiment

- 7808 post-menopausal women
- 60mg injections every 6 months for up to 36 months
- placebo or denosumab
- measured time to first non-vertebral fracture



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Denosumab for Prevention of Fractures in Postmenopausal Women with Osteoporosis

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*Investigators for the Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) trial are listed in the Appendix.

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N Engl J Med 2009;361:756-65.

ABSTRACT

BACKGROUND

Denosumab is a fully human monoclonal antibody to the receptor activator of nuclear factor-κB ligand (RANKL) that blocks its binding to RANK, inhibiting the development and activity of osteoclasts, decreasing bone resorption, and increasing bone density. Given its unique actions, denosumab may be useful in the treatment of osteoporosis.

METHODS

We enrolled 7868 women between the ages of 60 and 90 years who had a bone mineral density T score of less than −2.5 but not less than −4.0 at the lumbar spine or total hip. Subjects were randomly assigned to receive either 60 mg of denosumab or placebo subcutaneously every 6 months for 36 months. The primary end point was new vertebral fracture. Secondary end points included nonvertebral and hip fractures.

RESULTS

As compared with placebo, denosumab reduced the risk of new radiographic vertebral fracture, with a cumulative incidence of 2.3% in the denosumab group, versus 7.2% in the placebo group (risk ratio, 0.32; 95% confidence interval [CI], 0.26 to 0.41; P<0.001) — a relative decrease of 68%. Denosumab reduced the risk of hip fracture, with a cumulative incidence of 0.7% in the denosumab group, versus 1.2% in the placebo group (hazard ratio, 0.60; 95% CI, 0.37 to 0.97; P=0.04) — a relative decrease of 40%. Denosumab also reduced the risk of nonvertebral fracture, with a cumulative incidence of 6.5% in the denosumab group, versus 8.0% in the placebo group (hazard ratio, 0.80; 95% CI, 0.67 to 0.95; P=0.01) — a relative decrease of 20%. There was no increase in the risk of cancer, infection, cardiovascular disease, delayed fracture healing, or hypocalcemia, and there were no cases of osteonecrosis of the jaw and no adverse reactions to the injection of denosumab.

CONCLUSIONS

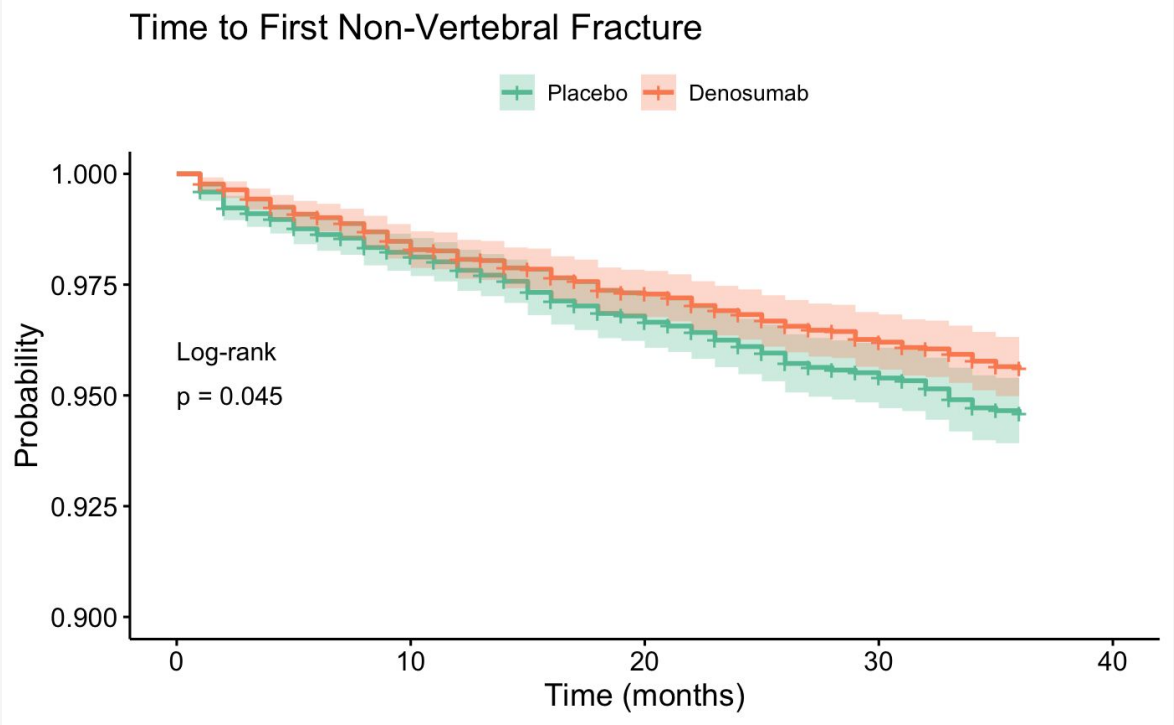
Denosumab given subcutaneously twice yearly for 36 months was associated with a

02

modeling survival

probability that it takes longer than x months until first fracture

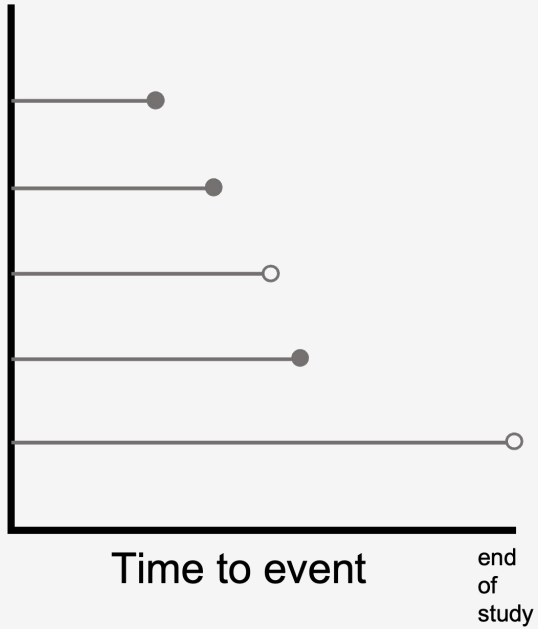
Kaplan-Meier Curves



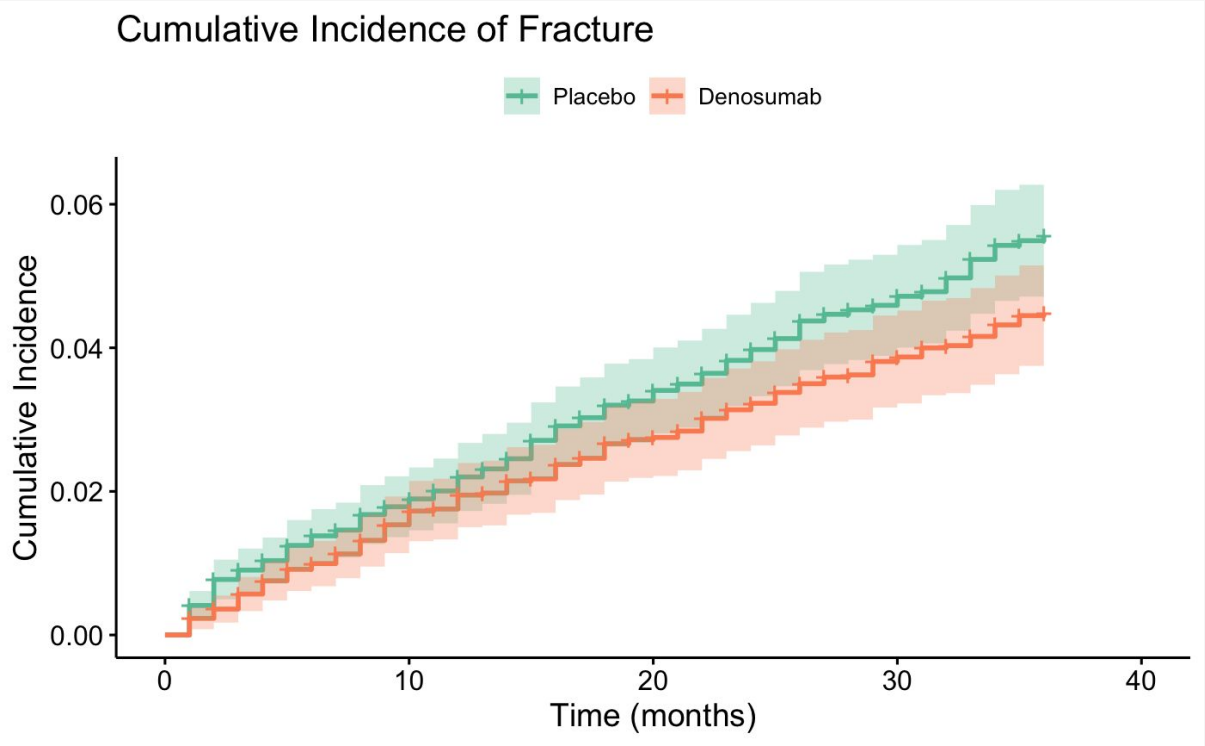
- Kaplan-Meier curves are non-parametric
- 95% CI
- log-rank test to show significance between 2 curves
- assumes random censoring

Censoring

- do not know the exact survival time
  - study ends before subject experiences the event
  - subject withdraws/stops attending follow-ups
- random censoring - failure rate is the same between censored and uncensored
- can use the censored data in survival analysis



Cumulative Fracture Incidence



- Based on Kaplan-Meier estimates of survival probabilities

03

modeling hazard

risk of fracture between the placebo and treatment groups

Cox Proportional Hazards (PH) Model

- semi-parametric model
- assumes hazards are proportional overtime
- HR: 0.807, 95% CI 0.654 - 0.996
- 19.3% reduced chance for fracture on denosumab

	exp(coef)	exp(-coef)	lower .95	upper .95
arm	0.8069	1.239	0.6538	0.9958

##	chisq	df	p
## arm	0.000695	1	0.98
## GLOBAL	0.000695	1	0.98

null hypothesis: hazards are proportional
P = 0.98, fail to reject null

Cox PH and Parametric Models

Model	HR	95% CI
Cox PH	0.807	0.654 - 0.996
Exponential	0.806	0.653 - 0.995
Weibull	0.807	0.654 - 0.996

Semi-parametric model calculates similar HR as parametric models

04

conclusions

denosumab significantly reduces the risk of non-vertebral fracture in post-menopausal women

Considerations in Survival Analysis

parametric or not?

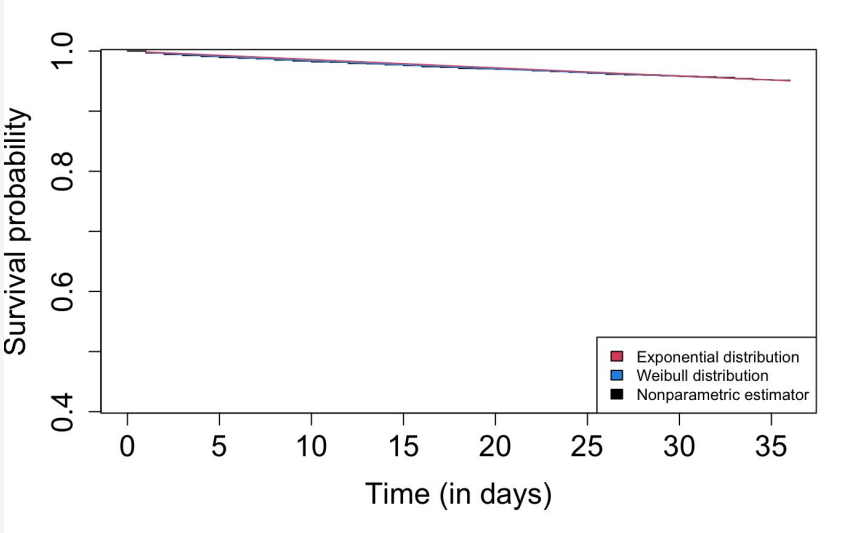
- parametric models require knowing the parameters → estimated parameters
- smoother, more theoretical curve

censoring

- random and independent censoring to prevent bias

log-rank or Cox PH?

- p-value
- hazard ratio



Takeaways

health data is messy

- censoring can occur in many forms

it’s not always death/negative

- ex. time until subject is cancer-free