Objectives

1. To predict regional changes in bone mineral density (BMD) in patients with osteoporosis on three classes of osteocortical drugs, using a multiscale systems model (MSM) of bone metabolism.

2. To implement a time-to-event (TTE) model of fracture in order to examine the effect of mono- or combination therapy on the probability of fracture during long-term (10-yr) treatment.

Methods

To develop the MSM, data were assembled from 27 documented clinical trials with teriparatide, denosumab, and/or combination therapy. Parameters were optimized using the R package rstan and changes in BMD were simulated using R package rethinking. The final model was evaluated by sensitivity analysis.

The data used to develop the hazard model for fracture was comprised of:


- Summary-level BMD and fracture data from publications identified by specific search criteria (59 trials in total involving various treatments). The BMD timecourse used by the fracture model was simulated by the MSM. Candidate models were evaluated by DIC and PPC.

Conclusions

The MSM predicted regional changes in BMD within the range of clinical variability in most treatment arms. The candidate TTE fracture model that best described the metadataset was the model that included BMD as a predictor for the i-th trial and j-th treatment arm.

Estimated parameter values (mean, 95%CI):

- $BMD = \beta_{postMenoAge}(\text{unitless}) \times 3^{\beta_{MK-677}} \times \beta_{strontium ranelate}(\text{unitless})$.

- $\beta_{postMenoAge} = 0.89 (-0.49, 2.24)$; $\beta_{MK-677} = -0.58 (-0.99, -0.19)$; $\beta_{strontium ranelate} = -0.58 (-0.98, -0.19)$.

- $\text{Simulated Fracture Risk}$ for Patients Stratified by Baseline BMD

- $\text{95% CI}$