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Treatment-Related Changes In Total Hip Bone Mineral Density And Fracture Risk Reduction For Trials With Active Control And Sequential Therapy: The Fnih-Asbmr-Sabre Project

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Objectives In the SABRE Study, we showed that treatment-related differences in 24-month total hip bone mineral density (THBMD) changes are strongly associated with reduced fracture risk in placebo-controlled trials. We also determined the surrogate threshold effect (STE): the minimum THBMD change in a trial that would predict a significant reduction in fracture risk in trials. However, the availability of osteoporosis therapies limits use of

placebo-controlled trials, and the need to sustain bone mineral density gains after anabolic therapies leads to the use of sequential therapy. This analysis aimed to determine if these associations and STEs apply to trials using active control or sequential therapies.Material and methods We used individual patient data from 19 trials: 16 randomized, placebo-controlled trials (14 anti-resorptive, 1 teriparatide, 1 odanacatib), and 3 trials with active control or sequential therapy (1 abaloparatide/alendronate and 2 romosozumab/alendronate or denosumab).For each trial, we calculated the treatment-related difference in mean percentage change in THBMD at 24 months and the risk reductions for the entire follow-up period. We used logistic regression for radiologic vertebral fractures and Cox regression for all clinical fractures (combination of non-vertebral and clinical vertebral fractures). We performed linear meta-regression to estimate the study-level association (r^2 and 95% CI) between treatment-related differences in THBMD changes and fracture risk reduction, including the 16 placebo-controlled trials only and all the trials including 3 active control/sequential therapy trials and verified if the change in THBMD observed in the trials with active control or sequential therapy was greater than the STE calculated from placebo-controlled trials.Results We found consistent associations between treatment-related THBMD changes and fracture risk reduction for placebo-controlled trials only and all trials for vertebral fractures [r^2 (CI)= 0.73 (0.33, 0.84) vs. 0.71 (0.36, 0.82)] and for all clinical fractures [0.71 (0.32, 0.83) vs.0.72 (0.39, 0.83)] respectively. In trials with active control or sequential therapy, the increase in THBMD was greater than STE and associated with a significant decrease in fracture risk: the increase in THBMD was 4.57%; 3.69% and 3.12% respectively for romosozumab/denosumab, romosozumab/alendronate and abaloparatide/alendronate trials, and the STE was 1.43% for vertebral and 2.04% for all clinical fractures. Conclusion Our findings show that treatment-related changes in THBMD predict anti-fracture efficacy equally well, regardless of the trial design.

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