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Treatment-Related Changes in Total Hip Bone Mineral Density and Fracture Risk Reduction for Drugs With Different Mechanisms of Action: The FNIH-ASBMR-SABRE Project

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Introduction: To date, trials of new anti-osteoporosis therapies have used fractures as primary endpoints. In the FNIH-ASBMR-SABRE project, we posited that the treatment-related change in total hip BMD (THBMD) could be used as a surrogate endpoint for fractures in future clinical trials of new osteoporosis therapies. To demonstrate this, we compiled a large dataset of individual patient data (IPD) from randomized trials and showed a strong association between the change in THBMD at 24 months and reduction in fracture risk. To further explore the use of THBMD as a surrogate endpoint, here we examine whether the association is robust across drugs with different mechanisms of action. **Methods:** We used IDP (n>120,000 participants) from 22 randomized, placebo-controlled, double-blind trials of osteoporosis medications (17 anti-resorptive, 3 PTH analogs, 1 odanacatib, and 1 romosozumab). We calculated the treatment-related difference (active-placebo) in mean % change in THBMD at 12, 18, and 24 months for each trial. We determined the treatment-related fracture risk reductions for the entire follow-up period, using logistic regression for radiologic vertebral fractures and Cox regression for all clinical fractures (a combination of non-vertebral and clinical vertebral fractures). We used meta-regression to estimate the study-level association (r^2) between treatment-related differences in THBMD changes and fracture risk reduction, including only the 17 trials of anti-resorptive drugs and then using the entire set of 22 trials. Since there were only 3 trials of anabolic drugs, we did not perform separate analyses for the anabolic trials. **Results:** The r^2 values were similar between all trials and antiresorptive trials only for both

fracture outcomes at all time points. Specifically, for vertebral fractures, the r^2 was 0.59 vs 0.70 at 12 mo, 0.69 vs 0.74 at 18 mo, and 0.73 vs 0.78 at 24 mo for all trials vs anti-resorptive trials only. For all clinical fractures, the r^2 was 0.46 vs 0.51 at 12 mo, 0.64 vs 0.60 at 18 mo, and 0.71 vs 0.65 at 24 mo for all trials vs anti-resorptive trials only. **Conclusion:** These results demonstrate that the associations between treatment-related changes in THBMD and fracture risk reductions are robust across anti-osteoporosis therapies with varying mechanisms of action. We conclude that the treatment-related difference in THBMD change would predict fracture reduction equally well for drugs with different mechanisms of action.

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