Treatment effect heterogeneity in comparative effectiveness of teriparatide vs bisphosphonates: a multi-database cohort study

Alexandros Rekkas[1], Annika M. Jödicke[2], David van Klaveren[1], Daniel Prieto-Alhambra[1,2], Peter R. Rijnbeek[1]
[1]Erasmus University Medical Center, Rotterdam, The Netherlands, [2]University of Oxford, Oxford, UK

Background

- Osteoporosis is a common condition characterized by decreased bone density and associated with increased risk for fragility fractures, which affects almost 30% of women aged ≥ 50 years
- Oral bisphosphonates (BP) are first line treatments for postmenopausal patients with increased fracture risk in clinical guidelines (#AACE/ACE 2020) as for their favorable cost-effectiveness and safety profile. Teriparatide, a parathyroid hormone analogue administered as a daily injection, was approved by the FDA in 2002 as the first anabolic agent for treatment of severe postmenopausal osteoporosis
- A recent meta-analysis by Diez-Perez and colleagues assessed the effect of teriparatide on hip fracture, indicating a significant 80% risk reduction compared to placebo and a non-significant 46% risk reduction when compared to active controls
- With teriparatide-containing biosimilars being launched in recent years, treatment costs dropped significantly. Subsequently, the discussion of cost-effectiveness in patients with less severe forms of osteoporosis is restarting
- **We aimed to evaluate treatment effect heterogeneity of teriparatide to bisphosphonates using a risk-based approach which evaluates treatment effects within strata of predicted hip fracture**

Methods

Databases

- IBM MarketScan® Medicare Supplemental Database (MDCR),
- Optum® De-Identified Clinformatics Data Mart Database – Date of Death (Optum-DOD)
- Optum® de-identified Electronic Health Record Dataset (Optum-EHR)

Cohorts

- *Treatment cohort*: Patients aged >50, registered for 1+ year, initiating treatment with teriparatide
- *Comparator cohort*: Patients aged >50, registered for 1+ year, initiating treatment with teriparatide
- *Outcome cohorts*: Patients with
  - A hip fracture
  - A major osteoporotic fracture (hip, vertebral or wrist/forearm/proximal humerus fracture)
  - A vertebral fracture

Analysis

- Use large scale propensity scores for 1:4 matching to minimise confounding by indication
- Develop and validated models for the prediction of hip fracture risk in all databases
- Conduct overall and risk-quartile stratified analyses
- Use a total of 129 negative controls to calibrate for residual confounding
- Use Cox regression to estimate calibrated hazard ratios (HR) and Kaplan-Meier estimate differences on day 730 to estimate absolute effects

Results

Overall HRs for hip fracture were 0.94 [0.76-1.18], 0.80 [0.65-0.99] and 0.92 [0.71-1.21] in MDCR, Optum-DOD and Optum-HER respectively. The meta-analytic HR for hip fracture across the 3 databases was 0.88 [0.77-1.00]; I2=0%. (Figure 1).

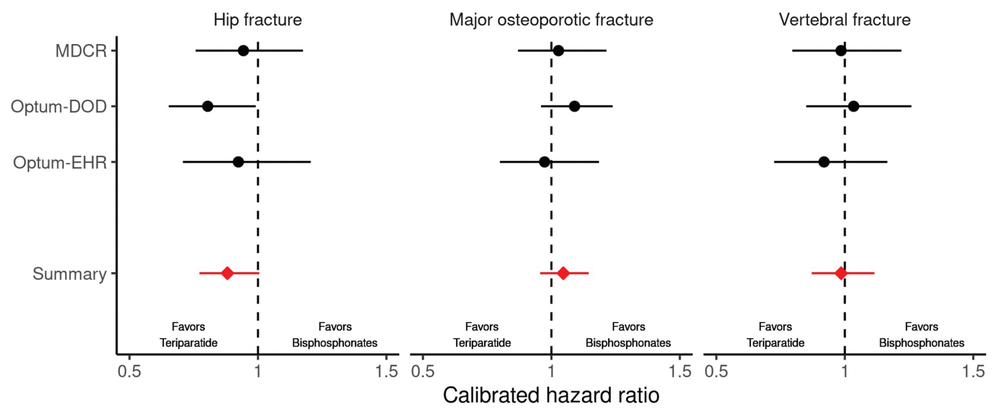

***Figure 1**: Random effects meta-analysis of calibrated hazard ratios for the 3 outcomes of interest across the 3 considered databases using a set of 129 negative controls. Values below 1 favor teriparatide, while values above 1 favor bisphosphonates.*

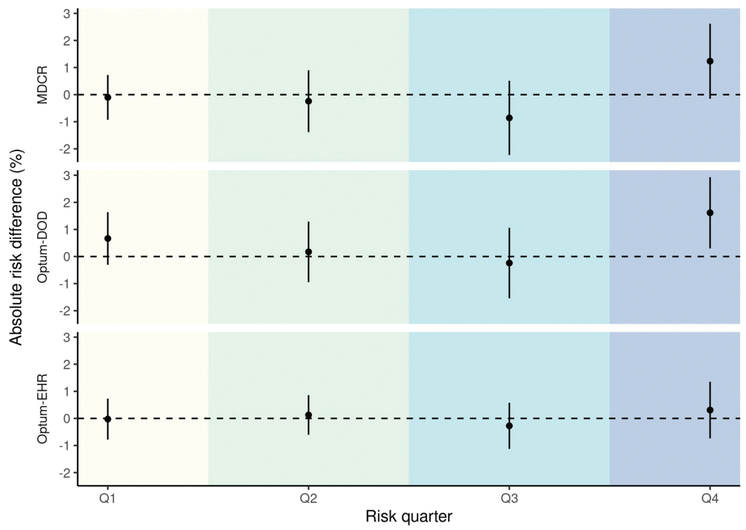

***Figure 2**: Absolute risk differences within quarters of predicted hip fracture risk across the 3 considered databases.*

We found evidence of residual confounding in quartiles 1-3 of predicted risk, but no identifiable imbalances in the top quartile of risk in all 3 databases. HRs for hip fracture in the top risk quarter were 0.83 [0.64-1.08] in MDCR, 0.74 [0.57-0.95] in Optum-DOD and 0.84 [0.62-1.14] in Optum-EHR (meta-analytic HR 0.80 [0.69-0.93]). In the highest risk quarter the 2-year absolute reduction of hip fracture risk with teriparatide was 1.23% [-0.15% to 2.62%] in MDCR, 1.61% [0.30% to 2.93%] in Optum-DOD, and 0.31% [-0.74% to 1.35%] in Optum-EHR (Figure 2).

Conclusions

Our findings are in line with previous trials and suggest a 12% relative risk reduction of hip fracture with teriparatide compared to bisphosphonates. A slightly stronger effect was seen amongst highest risk patients with relative risk reduction of 20% in favor of teriparatide. This translated to absolute risk reductions ranging from 0.3% to 1.6% with teriparatide treatment.

Contact: a.rekkas@erasmusmc.nl