

Evidence for the cardiovascular effects of osteoporosis treatments in randomized trials of post-menopausal women: A systematic review and Bayesian network meta-analysis

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ABSTRACT

Osteoporosis medications have been reported to have beneficial and harmful cardiovascular effects. Much of this evidence stems from single reports and as such, a comprehensive examination of the evidence is needed. We conducted a network meta-analysis (NMA) of cardiovascular adverse event (CAE) data from randomized trials of osteoporosis medications in postmenopausal women. Trials were identified from recent NMAs of osteoporosis treatment for fracture reduction with an updated literature search (December 2020). Included studies were randomized, included over 100 participants, and reported skeletal primary outcomes. We investigated three-point major adverse cardiovascular events (MACE3), four- (MACE4) and five-point MACE (MACE5), as well as myocardial infarction (MI) and stroke. Data were synthesized in a random-effects network meta-analysis using Bayesian modelling. Probabilistic ranking of treatment safety was performed. Relative to placebo, point estimates for the odds ratios (OR) with 95 % credible intervals (CrI) were also generated. We identified 75 trials (n =

136,940 women), of which 27 (68,699 women, nine arms) reported CAEs. In women randomized to placebo, the overall event rate for the MACE3 outcome was 2.58 % compared with 1.99 % in those randomized to all other active comparators. Probabilistic ranking found abaloparatide, oral bisphosphonates, teriparatide, and menopausal hormone therapy were less likely to have increased risk of CAEs than placebo, while romosozumab ranked more likely to have increased risk of CAEs than placebo for all outcomes. Compared with placebo, abaloparatide (one trial, n = 1642) was associated with a reduced odds for MACE3 (OR = 0.31; 95%CrI: 0.06 to 0.99), MACE4 (0.28; 0.06 to 0.88) and MACE5 (0.25; 0.06 to 0.79). When all PTH analogues were grouped together, magnitude and direction of effects were consistent but no longer statistically significant. We did not find pooled direct and indirect evidence that osteoporosis treatments significantly increased the risk of adverse cardiovascular events relative to placebo.

Keywords: Osteoporosis Post-menopausal women Cardiovascular Meta-analysis

Resumen

Se ha informado que los medicamentos para la osteoporosis tienen efectos cardiovasculares benéficos y dañinos. Gran parte de esta evidencia proviene de informes individuales y, como tal, se necesita un examen exhaustivo de la misma. Se realizó un metanálisis en red (MAR) de los datos de eventos adversos cardiovasculares (EAC) de ensayos aleatorios de medicamentos para la osteoporosis en mujeres posmenopáusicas. Los ensayos se identificaron a partir de MAR más recientes del tratamiento de la osteoporosis para la reducción de fracturas con una búsqueda bibliográfica actualizada (diciembre 2020).

Los estudios incluidos fueron aleatorizados, incluyeron a más de 100 participantes y presentaron resultados primarios esqueléticos. Se investigaron los eventos cardiovasculares adversos mayores de tres puntos (MACE 3), MACE de cuatro (MACE4) y cinco puntos (MACE5), así como el infarto de miocardio (IM) y el accidente cerebrovascular. Los datos se sintetizaron en un metanálisis de red de efectos aleatorios mediante modelos bayesianos. Se realizó una clasificación probabilística de la seguridad del tratamiento. En relación con placebo, también se generaron estimaciones puntuales para los odds ratios (OR) con intervalos creíbles (ICr)

del 95 %. Se identificaron 75 ensayos (n = 136 940 mujeres), de los cuales 27 (68699 mujeres, nueve brazos) informaron EAC. En las mujeres asignadas al azar a placebo, la tasa general de eventos para el resultado MACE 3 fue del 2,58 % en comparación con el 1,99 % en las asignadas al azar a todos los demás comparadores activos. La clasificación probabilística encontró que la abaloparatide, bifosfonatos orales, teriparatida y la terapia hormonal menopáusica tenían menos probabilidades de tener un mayor riesgo de EAC que el placebo, mientras que Romosozumab tenía más probabilidades de tener un mayor riesgo de EAC que el placebo para todos los resultados. En comparación con placebo, la abaloparatida (un ensayo, n = 1642) se asoció con una reducción de las probabilidades de MACE3 (OR = 0.31; 95%CrI: 0.06 a 0.99), MACE4 (0.28; 0.06 a 0.88) y MACE5 (0.25; 0.06 a 0.79). Cuando se agruparon todos los análogos de PTH, la magnitud y la dirección de los efectos fueron consistentes pero ya no estadísticamente significativas. Conclusion: No se encontró evidencia conjunta directa e indirecta de que los tratamientos para la osteoporosis aumentarían significativamente el riesgo de eventos cardiovasculares adversos en relación con placebo.

Palabras Clave: osteoporosis. Mujeres postmenopausicas. Cardiovascular. Metanálisis.



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