Davis S, Martyn-St James M, Sanderson J, et al. A systematic review and economic evaluation of bisphosphonates for the prevention of fragility fractures. Health Technol Assess. 2016 Oct;20(78):1-406. (Review) PMID: 27801641

BACKGROUND: Fragility fractures are fractures that result from mechanical forces that would not ordinarily result in fracture.

OBJECTIVES: To evaluate the clinical effectiveness and safety of bisphosphonates [alendronic acid (Fosamax(®) and Fosamax(®) Once Weekly, Merck Sharp & Dohme Ltd), risedronic acid (Actonel(®) and Actonel Once a Week(®), Warner Chilcott UK Ltd), ibandronic acid (Bonviva(®), Roche Products Ltd) and zoledronic acid (Aclasta(®), Novartis Pharmaceuticals UK Ltd)] for the prevention of fragility fracture and to assess their cost-effectiveness at varying levels of fracture risk.

DATA SOURCES: For the clinical effectiveness review, six electronic databases and two trial registries were searched: MEDLINE, EMBASE, The Cochrane Library, Cumulative Index to Nursing and Allied Health Literature, Web of Science and BIOSIS Previews, Clinicaltrials.gov and World Health Organization International Clinical Trials Registry Platform. Searches were limited by date from 2008 until September 2014.

REVIEW METHODS: A systematic review and network meta-analysis (NMA) of effectiveness studies were conducted. A review of published economic analyses was undertaken and a de novo health economic model was constructed. Discrete event simulation was used to estimate lifetime costs and quality-adjusted life-years (QALYs) for each bisphosphonate treatment strategy and a strategy of no treatment for a simulated cohort of patients with heterogeneous characteristics. The model was populated with effectiveness evidence from the systematic review and NMA. All other parameters were estimated from published sources. A NHS and Personal Social Services perspective was taken, and costs and benefits were discounted at 3.5% per annum. Fracture risk was estimated from patient characteristics using the QFracture(®) (QFracture-2012 open source revision 38, Clinrisk Ltd, Leeds, UK) and FRAX(®) (web version 3.9, University of Sheffield, Sheffield, UK) tools. The relationship between fracture risk and incremental net benefit (INB) was estimated using non-parametric regression. Probabilistic sensitivity analysis (PSA) and scenario analyses were used to assess uncertainty.

RESULTS: Forty-six randomised controlled trials (RCTs) were included in the clinical effectiveness systematic review, with 27 RCTs providing data for the fracture NMA and 35 RCTs providing data for the femoral neck bone mineral density (BMD) NMA. All treatments had beneficial effects on fractures versus placebo, with hazard ratios varying from 0.41 to 0.92 depending on treatment and fracture type. The effects on vertebral fractures and percentage change in BMD were statistically significant for all treatments. There was no evidence of a difference in effect on fractures between bisphosphonates. A statistically significant difference in the incidence of influenza-like symptoms was identified from the RCTs for zoledronic acid compared with placebo. Reviews of observational studies suggest that upper gastrointestinal symptoms are frequently reported in the first month of oral bisphosphonate treatment, but pooled analyses of placebo-controlled trials found no statistically significant difference. A strategy of no treatment was estimated to have the maximum INB for patients with a 10-year QFracture risk under 1.5%, whereas oral bisphosphonates provided maximum INB at higher levels of risk. However, the PSA suggested that there is considerable uncertainty regarding whether or not no treatment is the optimal strategy until the QFracture score is around 5.5%. In the model using FRAX, the mean INBs were positive for all oral bisphosphonate treatments across all risk categories. Intravenous bisphosphonates were estimated to have lower INBs than oral bisphosphonates across all levels of fracture risk when estimated using either QFracture or FRAX.

LIMITATIONS: We assumed that all treatment strategies are viable alternatives across the whole population.

CONCLUSIONS: Bisphosphonates are effective in preventing fragility fractures. However, the benefit-to-risk ratio in the lowest-risk patients may be debatable given the low absolute QALY gains and the potential for adverse events. We plan to extend the analysis to include non-bisphosphonate therapies.