

INPLASY

INPLASY202660034

doi: 10.37766/inplasy2026.6.0034

Received: 6 June 2026

Published: 6 June 2026

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Comparative Efficacy and Safety of Anti-Osteoporosis Drugs with Calcium and Vitamin D3 Supplementation for Prevention of Subsequent Fragility Fractures After First Hip Fracture Surgery in the Elderly: A Systematic Review and Bayesian Network Meta-Analysis with Sex-Stratified Analysis

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ADMINISTRATIVE INFORMATION

Support - None. Institutional support only.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202660034

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 6 June 2026 and was last updated on 6 June 2026.

INTRODUCTION

Review question / Objective In elderly patients (≥ 50 years) who have undergone surgery for a first osteoporotic hip fracture and are receiving calcium ($\geq 1,000$ mg/d) plus vitamin D3 (≥ 800 IU/d) supplementation, what is the comparative efficacy and safety of bisphosphonates, denosumab, teriparatide, and romosozumab for the prevention of subsequent fragility fractures, and does the relative efficacy differ between males and females?

Rationale Despite major international guidelines (ACP, NOGG, Chinese 2023) uniformly recommending anti-osteoporosis pharmacotherapy after hip fracture, recommendations diverge on optimal drug selection. The ACP grades male-specific recommendations as "conditional, low-certainty" while female recommendations are "strong, high-certainty." No existing network meta-analysis has: (1) required standardized calcium/vitamin D3 baseline in all arms, (2) pre-specified sex-stratified

analysis, or (3) focused exclusively on post-hip-fracture surgical patients. This NMA directly addresses these guideline evidence gaps.

Condition being studied Subsequent fragility fracture (including contralateral hip fracture) following surgical treatment of a first osteoporotic hip fracture in adults aged ≥ 50 years, in the context of anti-osteoporosis pharmacotherapy on a calcium and vitamin D3 supplementation background.

METHODS

Participant or population Adults aged ≥ 50 years who have undergone surgical treatment (internal fixation or arthroplasty) for a first, low-energy, osteoporotic hip fracture (femoral neck, intertrochanteric, or subtrochanteric). Both sexes included.

Exclusion: high-energy trauma fractures, pathological fractures due to malignancy, bone disorders other than osteoporosis (e.g., Paget disease, osteogenesis imperfecta).

Intervention Any anti-osteoporosis drug from four pre-defined classes — bisphosphonates (alendronate, risedronate, zoledronic acid, ibandronate, oral or intravenous), denosumab (60 mg subcutaneously every 6 months), teriparatide (20 µg/day subcutaneously), or romosozumab (210 mg subcutaneously monthly) — administered in combination with documented calcium ($\geq 1,000$ mg/day) and vitamin D3 (≥ 800 IU/day) supplementation.

Comparator (1) Calcium ($\geq 1,000$ mg/day) plus vitamin D3 (≥ 800 IU/day) supplementation alone (placebo-controlled trials), serving as the reference node in the network; or (2) another eligible anti-osteoporosis drug from the intervention list administered on the same calcium–vitamin D3 background (head-to-head comparisons). Studies with no calcium/vitamin D3 in the comparator arm are excluded.

Study designs to be included Randomized controlled trials (RCTs) and comparative observational studies (prospective or retrospective cohort studies; nested case-control studies within defined cohorts). Minimum follow-up: 12 months. Minimum sample size: $N \geq 50$ per arm. Excluded: single-arm studies, case series, cross-sectional studies, case reports, ecological studies, systematic reviews/meta-analyses (reference lists screened for primary studies).

Eligibility criteria Inclusion:

- Adults aged ≥ 50 years with first low-energy osteoporotic hip fracture (femoral neck, intertrochanteric, subtrochanteric), surgically treated
- Any anti-osteoporosis drug (bisphosphonates, denosumab, teriparatide, romosozumab) combined with calcium $\geq 1,000$ mg/d and vitamin D3 ≥ 800 IU/d as intervention
- Comparator: calcium/vitamin D3 alone or another eligible drug on the same background
- Outcomes: any subsequent fragility fracture (primary); contralateral hip fracture, all-cause mortality, vertebral fracture, medication adherence, serious adverse events (secondary)
- Study design: RCT or comparative observational study, follow-up ≥ 12 months, $N \geq 50$ per arm
- Languages: English or Chinese

Exclusion:

- High-energy trauma fractures; pathological fractures due to malignancy; bone disorders other than osteoporosis
- No calcium/vitamin D3 in comparator arm or dose not specified

- Non-comparative study designs (case series, case reports, cross-sectional, ecological)
- Systematic reviews/meta-analyses (reference lists screened).

Information sources Electronic databases: PubMed (MEDLINE), EMBASE (Ovid), Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science Core Collection, CNKI (中国知网), Wanfang Data (万方数据), VIP (维普)

Trial registries: ClinicalTrials.gov, WHO International Clinical Trials Registry Platform (ICTRP)

Grey literature: Conference proceedings from ASBMR, ECTS, IOF-WCO-ESCEO (2020–2026)

Other: Reference lists of included studies and relevant systematic reviews; contact with corresponding authors for unpublished data.

Main outcome(s) Primary outcome: Incidence of any subsequent fragility fracture (hip, vertebral, wrist, humerus, or other non-vertebral fracture) during follow-up, expressed as odds ratio (OR) or hazard ratio (HR) with 95% credible interval (CrI).

Key secondary outcome: Incidence of radiographically confirmed contralateral hip fracture — analyzed in the subset of studies reporting this outcome separately.

Additional secondary outcomes: all-cause mortality, vertebral fracture incidence, medication adherence (proportion of days covered $\geq 80\%$ at 12 months), serious adverse events (osteonecrosis of the jaw, atypical femoral fracture, severe hypocalcemia, rebound vertebral fractures after denosumab discontinuation), and change in bone mineral density at lumbar spine, total hip, and femoral neck at 12 and 24 months.

Quality assessment / Risk of bias analysis RCTs: Cochrane Risk of Bias 2.0 (RoB 2.0) — five domains: randomization process, deviations from intended interventions, missing outcome data, measurement of outcome, selection of reported result.

Observational studies: Newcastle-Ottawa Scale (NOS) — three domains: selection, comparability, outcome/exposure. NOS ≥ 7 considered high quality.

Overall evidence certainty: GRADE (Grading of Recommendations, Assessment, Development and Evaluation) adapted for network meta-analysis — five domains: risk of bias, inconsistency, indirectness, imprecision, publication bias. Evidence rated as high, moderate, low, or very low. Credibility of sex-subgroup effects: ICEMAN tool (Instrument for Credibility of Effect Modification Analyses) — five criteria: a priori design, interaction p-value, replication across studies, biological plausibility, consistency across related outcomes.

Two reviewers independently assess; disagreements resolved by consensus with third-reviewer arbitration.

Strategy of data synthesis Pairwise meta-analysis: Random-effects model (DerSimonian-Laird) when $I^2 > 50\%$; fixed-effects model when $I^2 \leq 50\%$. Odds ratios or hazard ratios with 95% confidence intervals for dichotomous and time-to-event outcomes.

Network meta-analysis: Bayesian hierarchical random-effects model using BUGSnet and gemtc packages in R (≥ 4.3). Non-informative priors for treatment effects; vague prior for between-study standard deviation τ (uniform 0–5). Markov Chain Monte Carlo simulation: 3 chains, 100,000 burn-in iterations, 100,000 posterior samples, thinning = 10. Convergence assessed by Gelman-Rubin diagnostic ($\hat{R} < 1.05$) and visual inspection of trace and density plots.

Treatment rankings expressed as surface under the cumulative ranking curve (SUCRA, 0–100%). League table presenting all pairwise comparisons as posterior median OR/HR with 95% credible intervals.

Network inconsistency: Global — design-by-treatment interaction model. Local — node-splitting method for each closed loop.

Subgroup analyses: Sex (male vs female, separate NMAs with ICEMAN credibility assessment), age (<75 vs ≥ 75 years), drug class (antiresorptive vs anabolic), geographic region (Asia vs Europe vs North America), study design (RCT vs observational), follow-up duration (3 months post-surgery).

Sensitivity analyses: Exclusion of high risk-of-bias studies (RoB 2.0 "high" or NOS < 7), small studies (<100 per arm), pre-2000 publications; alternative prior distributions; leave-one-out analysis.

Publication bias: Comparison-adjusted funnel plot; Egger's test (≥ 10 studies per comparison).

Subgroup analysis 1. Sex (male vs female): Separate network meta-analysis for each sex. Credibility of sex-subgroup effects assessed using the ICEMAN tool across five criteria (a priori design, interaction p-value, replication across studies, biological plausibility, consistency across related outcomes).

2. Age: <75 years vs ≥ 75 years (meta-regression with mean study age as continuous covariate).

3. Drug class: Antiresorptive agents (bisphosphonates, denosumab) vs anabolic agents (teriparatide, romosozumab) — node grouping analysis.

4. Geographic region: Asia vs Europe vs North America (meta-regression). 5. Study design: RCTs

only vs observational studies only (separate NMAs).

6. Follow-up duration: 3 months), where reported.

8. Sensitivity analysis separating oral vs intravenous bisphosphonates.

Sensitivity analysis 1. Excluding studies with high risk of bias (RoB 2.0 "high" or NOS < 7)

2. Excluding studies with sample size <100 per arm

3. Excluding studies published before 2000 (older diagnostic and treatment standards)

4. Excluding studies without contralateral hip fracture as a separately reported outcome (for the key secondary endpoint analysis)

5. Alternative prior distributions for between-study heterogeneity τ (half-normal, uniform 0–2)

6. Leave-one-out analysis: iteratively removing each study to assess influence on network estimates

7. Separating oral and intravenous bisphosphonates as distinct nodes (drug-class vs individual-agent network)

8. Excluding industry-funded studies.

Language restriction English and Chinese. No other language restrictions applied at the search stage.

Country(ies) involved China.

Keywords hip fracture; osteoporosis; bisphosphonates; denosumab; teriparatide; romosozumab; calcium; vitamin D; secondary prevention; network meta-analysis; elderly; sex differences; fragility fracture; contralateral.

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