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# Effectiveness of bisphosphonates in preventing periprosthetic bone loss after joint replacement: A systematic review and meta-analysis.

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## Abstract

### Objective:
To evaluate the effectiveness and safety of bisphosphonates for preventing periprosthetic bone loss after hip and knee joint replacement.

### Methods:
Six electronic databases/platforms—PubMed/MEDLINE, Crossref, Google Scholar, ScienceDirect, SpringerLink, and Wiley Online Library—were last searched on 30 November 2025, with backward and forward citation tracking. Two reviewers independently verified randomized comparative trials enrolling adults undergoing hip or knee arthroplasty and comparing a bisphosphonate with placebo, no treatment, or calcium/vitamin D alone; disagreements were resolved by a third reviewer. Data extraction and RoB 2 appraisal were independently checked. Mean difference (MD), weighted mean difference (WMD), or risk ratio (RR), each with 95% confidence intervals (CI), was used according to outcome type.

### Results:
Twenty-five randomized trial reports involving 1,115 participants were included. Participants were adults undergoing THA or total knee arthroplasty (TKA); the six osteoporotic hip trials reported mean ages of 67.3 years in zoledronic-acid groups and 66.8 years in controls, with mean body mass index values of 26.7 and 26.2 kg/m², respectively. Sex and ethnicity were incompletely reported across the broader evidence base. Ten THA trials (420 analyzed participants) contributed to the de novo 12-month analysis. Bisphosphonates preserved total periprosthetic bone mineral density (BMD) by MD 0.063 g/cm² (95% CI 0.040–0.085; $p<0.001$; $I^2=51.3\%$).

### Implications:
Clinical use should be selective and linked to an independent osteoporosis or fragility-fracture indication after assessment of renal function, calcium and vitamin D status, gastrointestinal suitability, adherence, and dental risk. Future multicentre trials should evaluate implant survival, fracture, revision, and long-term safety rather than BMD alone.

### Conclusion:
Bisphosphonates reduce early and intermediate periprosthetic BMD loss, most consistently after THA. The observed BMD benefit has not yet been shown reliably to prevent periprosthetic fracture, aseptic loosening, or revision.

***Keywords:*** *bisphosphonates; arthroplasty; bone mineral density; periprosthetic bone loss; total hip arthroplasty; total knee arthroplasty*
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## Introduction
Total joint replacement is among the most effective interventions for end-stage articular disease. Its long-term success nevertheless depends on preservation of the host bone surrounding the implant. Periprosthetic bone remodelling begins soon after surgery and reflects surgical trauma, altered mechanical loading, stress shielding, immobilisation, inflammatory signalling, and—later—particle-mediated osteolysis. Loss of bone stock can reduce structural support, complicate revision surgery, and may

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contribute to migration, aseptic loosening, and periprosthetic fracture.[5,6]

Bisphosphonates bind avidly to mineralised bone and inhibit osteoclast-mediated resorption. Nitrogen-containing agents, including alendronate, risedronate, and zoledronic acid, disrupt the mevalonate pathway in osteoclasts; earlier non-nitrogen compounds act through cytotoxic adenosine triphosphate analogues. These mechanisms provide a biologically plausible means of attenuating the high-turnover phase of postoperative bone loss.[5]

Randomised trials have evaluated oral alendronate, risedronate, etidronate, clodronate, pamidronate, and intravenous zoledronic acid after THA or TKA. Prior meta-analyses generally reported greater periprosthetic BMD with bisphosphonates, but the estimates are difficult to translate clinically because some studies report absolute g/cm², others percentage change, and hip studies often analyse seven Gruen zones separately.[7–11] Follow-up is usually too short and sample sizes too small to determine whether preservation of BMD prevents revision or fracture. Observational cohort evidence suggests that bisphosphonate use may be associated with improved implant survival or a lower risk of revision after hip or knee arthroplasty, but treatment selection, baseline osteoporosis, adherence, and healthy-user effects remain important sources of residual confounding.[38,39] An updated synthesis therefore needs to distinguish surrogate BMD effects from patient-important implant outcomes and to avoid combining anatomically or metrically incompatible data.

The objective of this review was to evaluate the efficacy and safety of bisphosphonates after joint replacement, with a primary focus on periprosthetic BMD and secondary consideration of functional outcomes, bone-turnover markers, implant migration, revision, fracture, and adverse events. We hypothesised that bisphosphonates would preserve early postoperative BMD, while evidence for improved implant survival would remain uncertain.

## Methods

### Design and reporting

This systematic review and meta-analysis was prepared in accordance with PRISMA 2020 and the Cochrane Handbook for Systematic Reviews of Interventions.1,2 Risk of bias was appraised using RoB 2, and outcome-level certainty was evaluated using GRADE.3,4 The review used a source-set update design: eligible randomized trial reports from three established joint-specific evidence sets were independently re-verified and supplemented by a targeted search update through 30 November 2025.

### Protocol registration and amendments

No protocol was prepared or prospectively registered before commencement of this review; consequently, no public protocol link is available. No protocol amendments were made. The absence of a prospectively registered protocol is acknowledged as a methodological limitation.

### Eligibility criteria

Randomized controlled trials enrolling adults undergoing primary or revision THA, TKA, hemiarthroplasty for fragility fracture, or another major joint replacement were eligible when they compared alendronate, risedronate, zoledronic acid/zoledronate, etidronate, clodronate, pamidronate, or another bisphosphonate with placebo, no pharmacological treatment, or calcium/vitamin D alone. Cemented, uncemented, and hybrid fixation were eligible. Outcomes of interest were periprosthetic BMD, implant migration, aseptic loosening, revision, periprosthetic fracture, validated functional scores, bone-turnover markers, and adverse events. Non-randomized studies were excluded from efficacy pooling and used only to contextualize implant survival, revision, or fracture. Reports without a comparator, without extractable relevant outcomes, with inseparable mixed anti-osteoporosis regimens, or involving animals/in-vitro models were excluded.

### Information sources

A total of six electronic databases/platforms were searched from inception to 30 November 2025: PubMed/MEDLINE, Crossref, Google Scholar, ScienceDirect, SpringerLink, and Wiley Online Library. Each source was last searched on 30 November 2025. Backward reference checking and forward citation tracking were performed for the principal THA, TKA, and zoledronic acid systematic reviews and for all eligible trial reports.7–12 No clinical-trial registry supplied an additional completed eligible randomized trial. The search was not restricted by language; the upper publication-date limit was 30 November 2025.

### Search strategy

Search concepts combined controlled vocabulary and free-text terms for joint arthroplasty, periprosthetic bone/BMD, bisphosphonates and individual agents, and randomized study design. The complete source-specific search strings, Boolean operators, filters, limits, and restrictions are provided in Appendix 1. Search results were exported where permitted, and records identified on publisher platforms were entered manually into the screening sheet.

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## Selection process

Two reviewers (SNC and TVV) independently re-screened the titles, abstracts, and full-text reports represented in three non-overlapping randomized evidence sets: 14 THA trials (620 participants), six zoledronic acid trials in osteoporotic hip-arthroplasty populations (307 participants), and five TKA trials (188 participants).7,8,11 Eligibility decisions were compared after each stage. Disagreements were resolved through discussion; unresolved questions were adjudicated by VH. No machine-learning classifier, artificial-intelligence screening system, or other automation tool was used. Microsoft Excel was used only to record screening decisions and reasons. The targeted update identified no additional clearly eligible bisphosphonate-only randomized trial through 30 November 2025.

## Data collection process

SNC extracted study data into a standardized spreadsheet, and TVV independently checked every extracted field against the source report or the verified source-review table. Discrepancies were resolved by consensus, with VH acting as adjudicator when required. Numerical data were preferentially taken from the full text, followed by tables, figures, supplementary files, and source-review extraction tables. No study author was contacted during the present update; unclear or unavailable information was recorded as not reported rather than inferred.

## Data items

Extracted variables comprised first author, publication year, country, trial design, sample size randomized and analyzed, participant age, sex, body mass index, baseline osteoporosis or bone-metabolic status, joint and indication for arthroplasty, fixation method, intervention drug, dose, route, timing, duration, co-interventions, comparator, follow-up duration, BMD region and unit, postoperative baseline definition, functional outcomes, bone-turnover markers, implant migration, loosening, revision, fracture, adverse events, attrition, funding source, and declared conflicts of interest. Missing standard deviations were calculated from standard errors, confidence intervals, or p values only when mathematically valid; otherwise, the outcome was excluded from quantitative pooling and retained narratively. Missing demographic information was labeled not reported, and no participant-level imputation was performed.

## Outcomes and effect measures

- Primary outcome: change from postoperative baseline in total periprosthetic BMD at approximately 12 months after THA, expressed as an absolute mean difference (MD) in g/cm² with a 95% CI.
- Secondary BMD outcomes: total or regional BMD at 3, 6, 12, 24–48 months, and ≥5 years, stratified by joint and anatomical region. Absolute values were summarized as MD; percentage-change outcomes were summarized as weighted mean difference (WMD), each with 95% CI.
- Clinical outcomes: Harris Hip Score and other continuous functional or migration outcomes were summarized as MD; dichotomous outcomes, including revision, loosening, fracture, and adverse events, were summarized as risk ratio (RR), each with 95% CI.
- Biochemical and safety outcomes: bone alkaline phosphatase, N-telopeptide of type I collagen, and procollagen type I N-terminal propeptide were summarized as MD when units were compatible. Gastrointestinal adverse effects, influenza-like symptoms, and serious adverse events were summarized as RR when event counts were available; otherwise, findings were synthesized narratively.

## Risk of bias

Two reviewers (SNC and TVV) independently assessed or re-verified risk of bias using the five RoB 2 domains: randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of the reported result. Disagreements were resolved by discussion and, when necessary, adjudication by VH. Fresh domain-level judgments were made when adequate full-text information was available; otherwise, source-review judgments were conservatively carried forward, and insufficient reporting resulted in an overall judgment of some concerns. The study-level summary is presented in Supplementary Table S2.

## Synthesis methods

Studies were grouped before synthesis by joint (THA or TKA), baseline osteoporosis status, anatomical region, outcome metric, and follow-up interval. For the primary analysis, means, standard deviations, and analyzed sample sizes for 12-month total THA BMD change were reconstructed from published tables and verified reports. Ten trials reported compatible g/cm² data. One percentage-change trial was excluded from this pool to prevent mixing units. When necessary, standard deviations were derived from reported uncertainty measures; no outcome was converted across anatomically incompatible regions. MDs were pooled with a restricted maximum-likelihood random-effects model and Hartung–Knapp 95% CIs. Cochran Q, $I^2$, $\tau^2$, and a 95% prediction interval quantified heterogeneity. Fixed-effect and leave-one-out sensitivity analyses assessed robustness. Other findings were presented in evidence

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tables, forest plots, anatomically defined pooled strata, or narrative synthesis when valid re-pooling was not possible.

### Subgroup and heterogeneity analyses

Prespecified subgrouping was undertaken by joint, anatomical region, follow-up period, and bisphosphonate class/route where data permitted. Heterogeneity was interpreted using $I^2$ and $\tau^2$ together with clinical differences in drug, dose, fixation, baseline osteoporosis, implant design, BMD region, and measurement scale. Leave-one-out analysis was performed for the primary THA synthesis. Meta-regression was not conducted because fewer than 10 studies were available within clinically coherent subgroups, making regression estimates unstable.

### Reporting bias assessment

For the primary 12-month THA outcome, small-study effects were explored using a funnel plot and Egger's regression test because 10 studies were available. Publication-bias tests were not performed for syntheses containing fewer than 10 studies because of low statistical power and the likelihood of misleading results. Selective outcome reporting was considered within RoB 2. The limited ability to assess reporting bias for most outcomes was treated as a limitation.

### Certainty of evidence

Randomized evidence began at high certainty and was downgraded for risk of bias, inconsistency, indirectness, imprecision, or suspected reporting bias. BMD was treated as a surrogate outcome. Observational revision estimates began at low certainty and were further downgraded when residual confounding was likely. Two reviewers agreed the final GRADE judgments by consensus.

## Results

### Study selection and characteristics

The source-set update identified 25 unique randomized trial reports involving 1,115 participants: 14 multiregimen THA trials (620 participants), six zoledronic-acid trials in osteoporotic hip-arthroplasty populations (307 participants), and five alendronate trials after TKA (188 participants). No additional eligible trial was identified, no cross-set duplicate remained, and no report was excluded after full-text eligibility verification. Participants were adults undergoing hip or knee arthroplasty. In the six osteoporotic hip trials, the mean age was 67.3 years in zoledronic-acid groups and 66.8 years in controls, while mean BMI was 26.7 and 26.2 kg/m², respectively.11 Several hip trials enrolled predominantly older or postmenopausal women. In the TKA evidence set, reported mean ages ranged approximately from 63.6 to 83.5 years.8 Sex, ethnicity, socioeconomic status, and other sociodemographic variables were inconsistently reported and could not be pooled. Four of six zoledronic acid trials were at low overall risk of bias, and two had some concerns; most older multiregimen THA and TKA trials were judged as low risk or some concerns because allocation concealment, blinding, or attrition reporting was incomplete.

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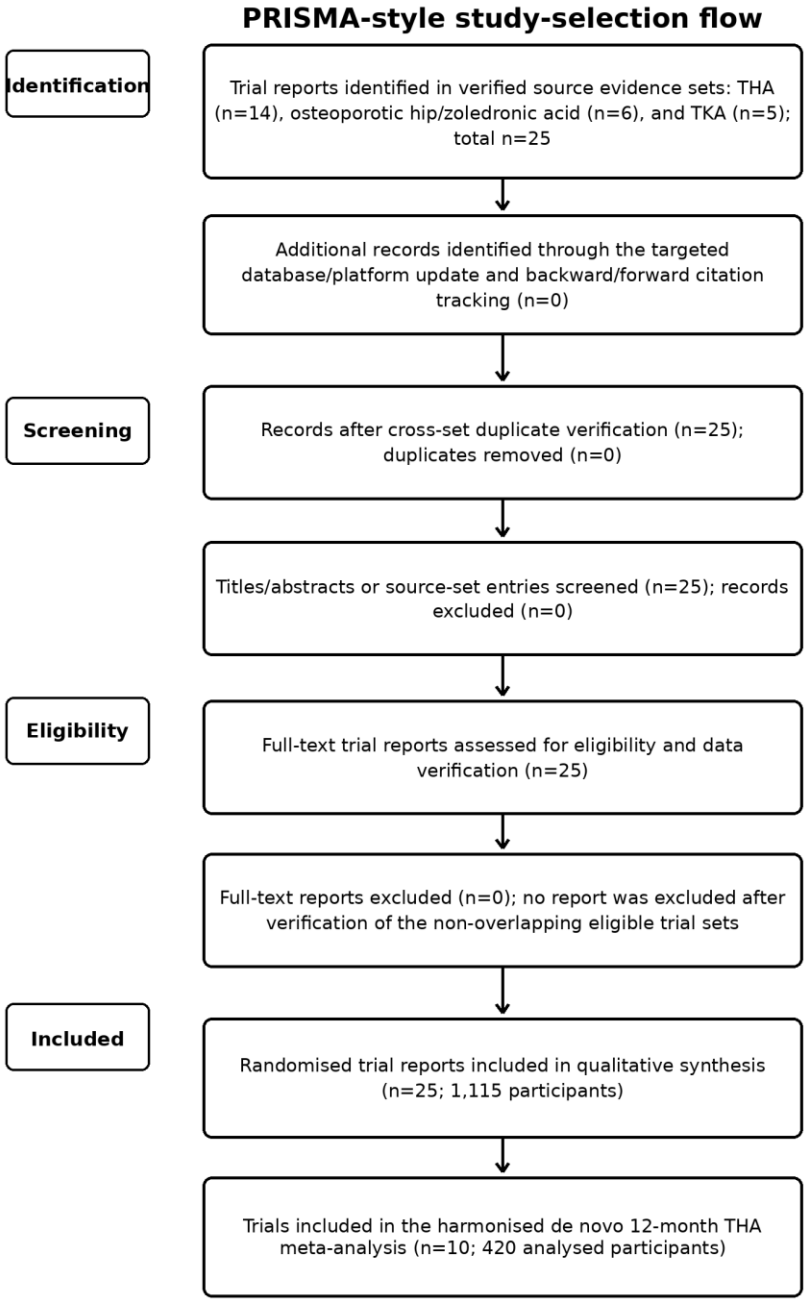
**Figure 1. PRISMA-style flow diagram for source-set assembly and study inclusion**



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## Supplementary Table S1. Full-text reports excluded after eligibility assessment

| Full-text article | Specific reason for exclusion |
|---|---|
| None | No report was excluded at the full-text verification stage; all 25 reports in the non-overlapping source evidence sets met the prespecified eligibility criteria. |

## Supplementary Table S2. Study-level risk-of-bias summary

| Study | Evidence set | Overall judgment | Main basis for judgment |
|---|---|---|---|
| Tapaninen et al., 2010 | THA | Mostly primary THA; cemented, uncemented, or hybrid fixation. Adults; age and sex were variably reported, with several older/postmenopausal cohorts. | Very small long-term cohort and incomplete domain-level reporting. |
| Trevisan et al., 2010 | THA | Osteoporotic THA or hip arthroplasty. Mean age: 67.3 years (ZA) and 66.8 years (control); mean BMI: 26.7 and 26.2 kg/m². | Randomized controlled design with generally adequate outcome reporting. |
| Arabmotlagh et al., 2009 | THA | Primary TKA. Reported mean ages approximately 63.6–83.5 years; sex and ethnicity were inconsistently reported. | Extension follow-up and limited reporting of allocation and attrition. |
| Yamasaki et al., 2007 | THA | Low risk | Randomized comparison with complete principal BMD reporting. |
| Fokter et al., 2006 | THA | Low risk | Randomized, double-blind controlled trial; small sample. |
| Arabmotlagh et al., 2006 | THA | Low risk | Prospective randomized double-blind trial. |
| Yamaguchi et al., 2004 | THA | Some concerns | Randomization reported; concealment and selective-reporting details limited. |
| Iwamoto et al., 2011 | THA | Some concerns | Active comparator and incomplete blinding information. |
| Kinov et al., 2006 | THA | Some concerns | Randomized study with limited concealment/blinding detail. |
| Shetty et al., 2006 | THA | Some concerns | Extension follow-up with attrition and small analyzed sample. |
| Scott et al., 2013 | THA | Some concerns | Preliminary trial report and percentage-change outcome. |
| Yukizawa et al., 2017 | THA | Low risk | Randomized comparison with complete primary BMD data. |
| Muren et al., 2015 | THA | Low risk | Double-blind randomized placebo-controlled follow-up. |

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| Study | Evidence set | Overall judgment | Main basis for judgment |
|---|---|---|---|
| Nehme et al., 2003 | THA | Some concerns | Small trial and limited domain-level methodological reporting. |
| Aro et al., 2018 | ZA hip | Low risk | Low risk across all RoB 2 domains in the source assessment. |
| Friedl et al., 2009 | ZA hip | Low risk | Low risk across all RoB 2 domains in the source assessment. |
| Huang et al., 2017 | ZA hip | Some concerns | Concern regarding deviations from intended interventions. |
| Lacko et al., 2015 | ZA hip | Some concerns | Concern regarding missing outcome data. |
| Zhou et al., 2019 | ZA hip | Low risk | Low risk across all RoB 2 domains in the source assessment. |
| Zhu et al., 2021 | ZA hip | Low risk | Low risk across all RoB 2 domains in the source assessment. |
| Soininvaara et al., 2002 | TKA | Some concerns | Allocation concealment and participant blinding incompletely documented. |
| Han et al., 2003 | TKA | Some concerns | No-placebo comparison and incomplete blinding information. |
| Wang et al., 2006 | TKA | Some concerns | Randomization reported; concealment and blinding incompletely described. |
| Abu-Rajab et al., 2009 | TKA | Some concerns | Small trial with limited domain-level reporting. |
| Jaroma et al., 2015 | TKA | Some concerns | Long-term extension with small sample and potential attrition. |

## Results of individual studies

Study-level effects with 95% CIs are reported for every trial contributing compatible data to the harmonized primary analysis. For trials reported only within anatomically defined or percentage-change strata, the principal contribution is summarized, and the absence of a separately extractable study-level CI is explicitly marked.

### Supplementary Table S3. Principal study-level results across the included randomized trials

| Study | Participants/intervention | Major outcome | Study-level result (95% CI where extractable) | Role in synthesis |
|---|---|---|---|---|
| Tapaninen et al., 2010 | THA; bisphosphonate vs control | 12-month total BMD | MD 0.080 g/cm² (95% CI −0.013 to 0.173) | Compatible primary analysis |
| Trevisan et al., 2010 | THA; clodronate vs control | 12-month total BMD | MD 0.030 g/cm² (95% CI −0.003 to 0.063) | Compatible primary analysis |
| Arabmotlagh et al., 2009 | THA; alendronate follow-up | 12-month total BMD | MD 0.020 g/cm² (95% CI −0.053 to 0.093) | Compatible primary analysis |
| Fokter et al., 2006 | THA; etidronate vs control | 12-month total BMD | MD 0.000 g/cm² (95% CI −0.135 to 0.135) | Compatible primary analysis |
| Arabmotlagh et al., 2006 | THA; alendronate vs control | 12-month total BMD | MD 0.070 g/cm² (95% CI −0.037 to 0.177) | Compatible primary analysis |
| Yamaguchi et al., 2004 | THA; etidronate vs control | 12-month total BMD | MD 0.060 g/cm² (95% CI −0.011 to 0.131) | Compatible primary analysis |
| Iwamoto et al., 2011 | THA; alendronate vs alfacalcidol | 12-month total BMD | MD 0.080 g/cm² (95% CI −0.001 to 0.161) | Compatible primary analysis |
| Shetty et al., 2006 | THA; pamidronate vs control | 12-month total BMD | MD 0.010 g/cm² (95% CI −0.063 to 0.083) | Compatible primary analysis |
| Yukizawa et al., 2017 | THA; alendronate vs control | 12-month total BMD | MD 0.090 g/cm² (95% CI 0.077 to 0.103) | Compatible primary analysis |

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| Study | Participants/intervention | Major outcome | Study-level result (95% CI where extractable) | Role in synthesis |
|---|---|---|---|---|
| Nehme et al., 2003 | THA; alendronate vs control | 12-month total BMD | MD 0.080 g/cm² (95% CI 0.035 to 0.125) | Compatible primary analysis |
| Yamasaki et al., 2007 | THA; risedronate vs control | BMD/bone resorption | Favored risedronate; separate compatible MD and CI not extractable | Narrative/other THA strata |
| Kinov et al., 2006 | THA; risedronate vs control | Bone metabolism/BMD | Study-level CI not extractable from verified source table | Narrative/other THA strata |
| Scott et al., 2013 | THA; zoledronic acid vs control | Femoral BMD percentage change | Favored zoledronic acid; incompatible percentage metric | Excluded only from absolute g/cm² pool |
| Muren et al., 2015 | THA; risedronate vs placebo | 4-year femoral BMD | No clear sustained benefit; separate CI not re-estimated | Long-term THA stratum |
| Aro et al., 2018 | Osteoporotic THA; zoledronic acid | Regional BMD/stem stability | Partial BMD protection without improved initial stem stability; individual CI NR | ZA pooled strata |
| Friedl et al., 2009 | THA; zoledronic acid | Regional BMD/implant migration | Contributed to pooled ZA regional and migration outcomes; individual CI NR. | ZA pooled strata |
| Huang et al., 2017 | THA; zoledronic acid | Regional BMD/bone turnover | Favored zoledronic acid in reported regional/marker outcomes; individual CI NR. | ZA pooled strata |
| Lacko et al., 2015 | Osteoporotic THA; zoledronic acid | Proximal femoral remodeling | Contributed to pooled regional BMD estimates; individual CI NR | ZA pooled strata |
| Zhou et al., 2019 | Postmenopausal THA; zoledronic acid | Regional BMD/markers | Favored zoledronic acid in several regions; individual CI NR | ZA pooled strata |
| Zhu et al., 2021 | Osteoporotic hip arthroplasty; ZA | Regional BMD/function | Contributed to pooled Gruen-zone BMD and HHS estimates; individual CI NR | ZA pooled strata |
| Soininvaara et al., 2002 | TKA; alendronate vs calcium | Tibial/femoral BMD | Contributed to percentage-change WMD strata; individual CI NR | TKA pooled strata |
| Han et al., 2003 | TKA; alendronate vs no placebo | Tibial/femoral BMD | Contributed to percentage-change WMD strata; individual CI NR | TKA pooled strata |
| Wang et al., 2006 | TKA; alendronate vs control | Tibial/femoral BMD | Contributed to 3–12-month WMD strata; individual CI NR | TKA pooled strata |
| Abu-Rajab et al., 2009 | TKA; alendronate vs control | Periprosthetic BMD | Contributed to percentage-change WMD strata; individual CI NR | TKA pooled strata |

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| Study | Participants/intervention | Major outcome | Study-level result (95% CI where extractable) | Role in synthesis |
|---|---|---|---|---|
| Jaroma et al., 2015 | TKA; alendronate vs control | Long-term periprosthetic BMD | Contributed to short/long-term TKA evidence; individual CI NR | TKA pooled strata |



## Primary meta-analysis: total periprosthetic BMD at 12 months after THA

Ten THA trials involving 420 analyzed participants contributed compatible absolute BMD change data. They evaluated several oral or intravenous bisphosphonates across cemented, uncemented, and hybrid THA; sample sizes were small, and overall risk of bias ranged from low risk to some concerns, principally because older reports incompletely described allocation concealment or blinding. Bisphosphonate therapy preserved total periprosthetic BMD by 0.063 g/cm² (95% CI 0.040–0.085; t=6.30; p<0.001). Heterogeneity was moderate ($I^2$=51.3%; $\tau^2$=0.000238), and the 95% prediction interval (0.021–0.104 g/cm²) remained on the side favoring treatment. The fixed-effect estimate was 0.077 g/cm² (95% CI 0.066–0.088). In leave-one-out analyses, pooled estimates ranged from 0.047 to 0.076 g/cm², indicating a stable direction of effect, although precision was influenced by the small, low-variance Yukizawa trial.

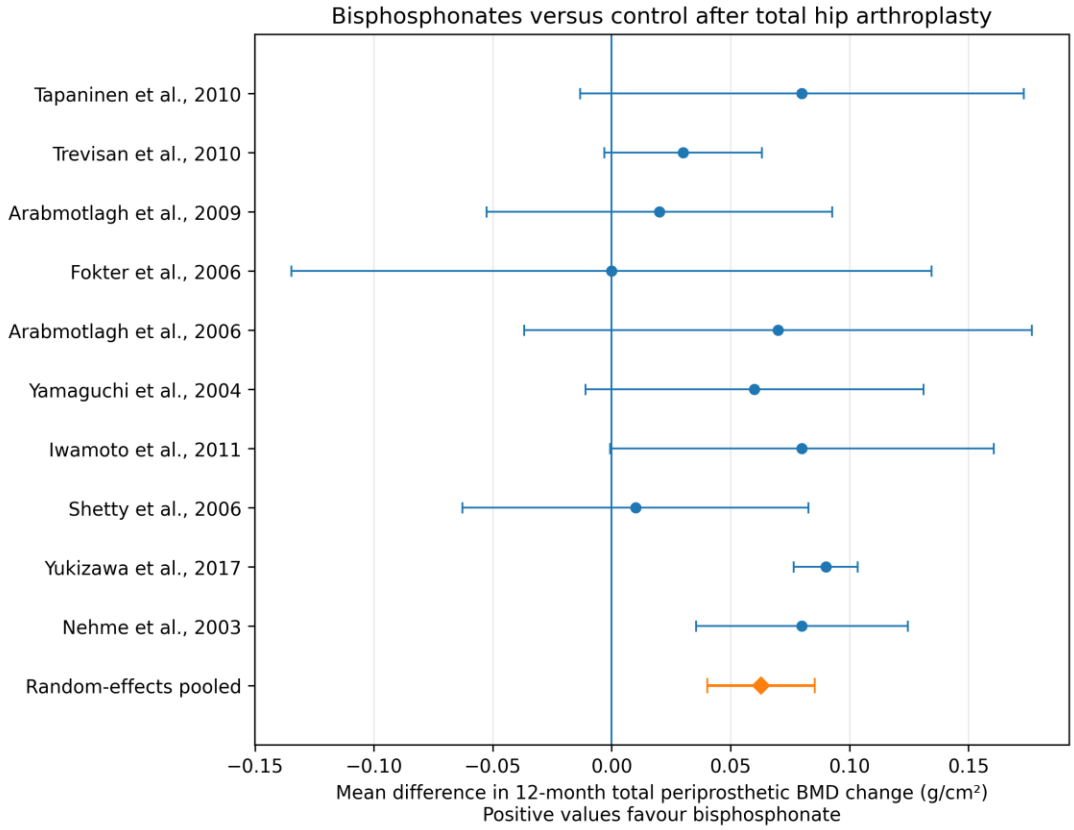


**Figure 2.** Random-effects meta-analysis of 12-month total periprosthetic BMD change after THA. Positive values favour bisphosphonate. Pooled MD 0.063 g/cm² (95% CI 0.040–0.085); $I^2$=51.3%.

## Longer-term THA BMD

The broader 14-trial THA evidence set included 620 adults, multiple bisphosphonate agents, different fixation methods,

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and follow-up from 24 weeks to more than 9 years. Risk of bias was generally low or raised some concerns, particularly in small extension cohorts. Published random-effects analyses showed less bone loss at 2–4 years (six trials, 250 participants; MD 0.04 g/cm², 95% CI 0.01–0.07) and beyond 5 years (four trials, 136 participants; MD 0.08 g/cm², 95% CI 0.06–0.11).7 The long-term estimate was driven mainly by nitrogen-containing agents and small follow-up cohorts; persistence of benefit is plausible, but its magnitude remains uncertain.

## Regional hip BMD and zoledronic acid

Six zoledronic-acid trials included 307 older adults with osteoporosis after hip arthroplasty; mean age and BMI were balanced between treatment and control groups. Four trials were at low overall risk of bias, and two had some concerns. The effect was regional rather than uniform. At 12 months, pooled MDs favored zoledronic acid in Gruen zone 1 (8.36 percentage points, 95% CI 2.64–14.07), zone 2 (3.79, 1.28–6.30), zone 4 (3.41, 1.55–5.28), zone 6 (4.14, 1.92–6.36), and zone 7 (7.12, 0.33–13.92). No clear effect was demonstrated in zone 3, and the zone-5 estimate was internally inconsistent between its CI and p value in the source report; it was therefore not interpreted as definitive.11

## TKA BMD

Five small TKA trials included 188 adults and evaluated oral alendronate for 6–12 months. All were judged as having some concerns because allocation concealment and blinding were incompletely documented, although outcome data were generally complete. Proximal tibial BMD favored treatment at 3 months (WMD 3.40 percentage points, 95% CI 2.06–4.73) and 6 months (2.66, 1.63–3.69), but not clearly at 12 months (−1.01, −2.19 to 0.17). Distal femoral BMD favored alendronate at 3 months (5.64, 4.42–6.85), 6 months (7.22, 5.88–8.57), and 12 months (18.46, 17.09–19.83).8 The 12-month femoral magnitude should be interpreted cautiously because heterogeneity was substantial, anatomical definitions differed, and the evidence set was small.

## Bone-turnover markers and function

In the multiregimen THA evidence set, bisphosphonates lowered serum bone alkaline phosphatase (four trials, 179 participants; MD −7.28 U/L, 95% CI −9.81 to −4.75) and urinary N-telopeptide of type I collagen (two trials, 104 participants; MD −24.37 nmol/mmol creatinine, 95% CI −36.37 to −12.37).[7] Zoledronic acid also lowered procollagen type I N-terminal propeptide at 6 and 12 months. Harris Hip Score was not different at three months, but favoured zoledronic acid at six months (MD 5.44, 95% CI 0.56–10.32) and 12 months (MD 4.87, 95% CI 0.64–9.10).[11] The clinical importance of these modest score differences is uncertain because minimum clinically important thresholds were not consistently prespecified.

## Implant migration, loosening, revision, and fracture

Randomised trials were not powered for revision, aseptic loosening, or periprosthetic fracture. A zoledronic acid trial found partial preservation of periprosthetic bone without improved initial stem stability.[32] Observational cohort studies reported associations between bisphosphonate use and improved implant survival or lower revision risk after total joint arthroplasty, but these non-randomised findings remain vulnerable to confounding by indication, baseline bone health, treatment adherence, and differences in clinical surveillance.[38,39] Effects on periprosthetic fracture and implant migration remain inconclusive.

## Adverse events

Serious or fatal adverse events were not increased in the small RCTs, but rare harms could not be excluded. In three zoledronic-acid trials, influenza-like symptoms occurred in 28 of 100 treated participants and 3 of 98 controls (RR 7.03, 95% CI 2.63–18.78).11 Oral alendronate trials reported occasional gastrointestinal discomfort. Follow-up was insufficient to evaluate osteonecrosis of the jaw or atypical femoral fracture reliably. Long-term use should therefore follow osteoporosis guidance and individualized fracture-risk reassessment.40

## Investigations of heterogeneity

The principal sources of heterogeneity were anatomical region, outcome scale (absolute g/cm² versus percentage change), baseline osteoporosis, bisphosphonate agent and route, fixation method, follow-up duration, and small-study precision. Joint-, region-, and time-specific stratification reduced inappropriate clinical mixing. Leave-one-out analysis did not reverse the primary THA effect. Formal meta-regression was not performed because clinically coherent syntheses contained too few studies.

## Reporting bias

For the 10-study primary THA analysis, Egger's regression intercept was −1.25 (two-sided p=0.056), providing no statistically conclusive evidence of small-study effects, although the test had limited power and the funnel plot was influenced by one small, highly precise trial. Reporting bias could not be meaningfully assessed for the other pooled outcomes because each involved fewer than 10 studies. Selective reporting remained a concern in several older trials.

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**Table 1. Eligibility criteria**

| Domain | Eligibility |
|---|---|
| Population | Adults undergoing THA, TKA, hemiarthroplasty for fragility fracture, or another major joint replacement |
| Intervention | Alendronate, risedronate, zoledronic acid, etidronate, clodronate, pamidronate, or another bisphosphonate |
| Comparator | Placebo, no bisphosphonate, or calcium/vitamin D alone |
| Primary outcome | Change in total periprosthetic BMD at approximately 12 months after THA |
| Secondary outcomes | Regional BMD, longer-term BMD, bone-turnover markers, function, migration, loosening, revision, fracture, adverse events |
| Study design | RCTs for efficacy synthesis; observational studies used only for contextual clinical outcomes |
| Exclusions | No comparator; mixed intervention without separable bisphosphonate effect; animal/in-vitro studies; insufficient extractable outcomes |

**Table 2. Characteristics of the principal randomised evidence sets**

| Evidence set | Trials/participants | Joint / population | Bisphosphonate exposure | Follow-up | Principal outcomes |
|---|---|---|---|---|---|
| Shi et al. THA set{7} | 14 / 620 | Mostly primary THA; cemented, uncemented, hybrid | Alendronate, risedronate, zoledronate, etidronate, clodronate, pamidronate | 24 weeks to >9 years | Total BMD, BAP, NTX-I |
| Liu et al. ZA set{11} | 6 / 307 | Osteoporotic THA or hip arthroplasty | Single IV zoledronic acid 4 or 5 mg, generally perioperative | 1–4 years | Gruen-zone BMD, PINP, HHS, adverse events |
| Shi et al. TKA set{8} | 5 / 188 | Primary TKA | Oral alendronate 10 mg/day or 70 mg/week for 6–12 months | 1–7 years | Proximal tibial and distal femoral BMD, adverse events |

BAP, bone alkaline phosphatase; BMD, bone mineral density; HHS, Harris Hip Score; IV, intravenous; NTX-I, urinary N-telopeptide of type I collagen; PINP, procollagen type I N-terminal propeptide; THA, total hip arthroplasty; TKA, total knee arthroplasty; ZA, zoledronic acid.

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**Table 3. Study-level data used in the de novo 12-month THA meta-analysis**

| Study | BP n | BP change, g/cm² | Control n | Control change, g/cm² | MD (95% CI), g/cm² |
|---|---|---|---|---|---|
| Tapaninen et al., 2010 | 7 | -0.04 ± 0.09 | 9 | -0.12 ± 0.10 | 0.080 (−0.013 to 0.173) |
| Trevisan et al., 2010 | 38 | -0.04 ± 0.07 | 41 | -0.07 ± 0.08 | 0.030 (−0.003 to 0.063) |
| Arabmotlagh et al., 2009 | 27 | -0.02 ± 0.16 | 19 | -0.04 ± 0.09 | 0.020 (−0.053 to 0.093) |
| Fokter et al., 2006 | 16 | -0.06 ± 0.07 | 12 | -0.06 ± 0.23 | 0.000 (−0.135 to 0.135) |
| Arabmotlagh et al., 2006 | 27 | 0.00 ± 0.16 | 24 | -0.07 ± 0.22 | 0.070 (−0.037 to 0.177) |
| Yamaguchi et al., 2004 | 29 | -0.06 ± 0.12 | 24 | -0.12 ± 0.14 | 0.060 (−0.011 to 0.131) |
| Iwamoto et al., 2011 | 18 | 0.00 ± 0.12 | 22 | -0.08 ± 0.14 | 0.080 (−0.001 to 0.161) |
| Shetty et al., 2006 | 17 | -0.01 ± 0.07 | 18 | -0.02 ± 0.14 | 0.010 (−0.063 to 0.083) |
| Yukizawa et al., 2017 | 18 | -0.04 ± 0.02 | 16 | -0.13 ± 0.02 | 0.090 (0.077 to 0.103) |

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| Study | BP n | BP change, g/cm² | Control n | Control change, g/cm² | MD (95% CI), g/cm² |
|---|---|---|---|---|---|
| Nehme et al., 2003 | 20 | -0.24 ± 0.07 | 18 | -0.32 ± 0.07 | 0.080 (0.035 to 0.125) |

Positive mean differences favour bisphosphonate. Analysed sample sizes reflect reported completers where available. The Scott et al. trial was excluded from this analysis because it reported percentage change rather than g/cm².

**Table 4. Quantitative synthesis of principal efficacy outcomes**

| Outcome | Studies/participants | Effect estimate (95% CI) | Heterogeneity | Interpretation |
|---|---|---|---|---|
| THA total BMD, 12 months (de novo) | 10 / 420 | MD 0.063 g/cm² (0.040–0.085) | $I^2$ 51.3%; $\tau^2$ 0.000238 | Favours bisphosphonate; moderate certainty |
| THA total BMD, 2–4 years{7} | 6 / 250 | MD 0.04 g/cm² (0.01–0.07) | Not consistently reported | Favours bisphosphonate; low certainty |
| THA total BMD, >5 years{7} | 4 / 136 | MD 0.08 g/cm² (0.06–0.11) | Small long-term cohorts | Favours bisphosphonate; low certainty |
| TKA proximal tibia, 3 months{8} | 3 RCT strata | WMD 3.40% (2.06–4.73) | Low at 3 months | Favours alendronate |
| TKA proximal tibia, 12 months{8} | 3 RCT strata | WMD −1.01% (−2.19 to 0.17) | $I^2$ ≈86% | No clear benefit |
| TKA distal femur, 12 months{8} | 3 RCT strata | WMD 18.46% (17.09–19.83) | $I^2$ ≈73% | Favours alendronate; magnitude uncertain |
| ZA Gruen zone 7, 12 months{11} | 4 / 163 | MD 7.12% (0.33–13.92) | $I^2$ 76% | Favours ZA; heterogeneous |
| HHS, 12 months{11} | 6 / 307 | MD 4.87 (0.64–9.10) | Heterogeneous | Small functional benefit; clinical importance uncertain |

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**Table 5. Zoledronic acid effects on 12-month Gruen-zone BMD**

| Gruen zone | Studies | Participants (ZA/control) | MD, percentage points (95% CI) | $I^2$ | Interpretation |
|---|---|---|---|---|---|
| 1 | 4 | 82/81 | 8.36 (2.64–14.07) | 75% | Benefit; heterogeneous |
| 2 | 4 | 82/81 | 3.79 (1.28–6.30) | 0% | Benefit |
| 3 | 4 | 82/81 | 1.49 (−0.39 to 3.37) | 29% | No clear effect |
| 4 | 4 | 82/81 | 3.41 (1.55–5.28) | 3% | Benefit |
| 5 | 4 | 82/81 | 0.95 (−0.32 to 2.22) | 0% | No clear effect; source p-value inconsistent |
| 6 | 4 | 82/81 | 4.14 (1.92–6.36) | 46% | Benefit |
| 7 | 4 | 82/81 | 7.12 (0.33–13.92) | 76% | Benefit; heterogeneous |

**Table 6. Safety outcomes**

| Outcome | Evidence | Effect/finding | Certainty and interpretation |
|---|---|---|---|
| Influenza-like symptoms after ZA | 3 RCTs; 198 participants | 28.0% vs 3.1%; RR 7.03 (2.63–18.78) | Moderate certainty; common transient acute-phase reaction |
| Serious or fatal adverse events | 6 ZA RCTs | No increase reported | Low certainty for rare harms; trials underpowered |
| Gastrointestinal discomfort | Several oral alendronate RCTs | Occasional events; no consistent pooled estimate | Low certainty |
| Osteonecrosis of the jaw | Not adequately reported | No reliable estimate | Very low certainty |
| Atypical femoral fracture | Not adequately reported | No reliable estimate | Very low certainty; requires long-term surveillance |

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**Table 7. GRADE summary of findings**

| Outcome | Evidence | Certainty | Reasoning |
|---|---|---|---|
| THA total BMD at 12 months | 10 RCTs / 420 | Moderate | Downgraded for moderate inconsistency and incomplete older trial reporting |
| THA total BMD at 2–4 years | 6 RCTs / 250 | Low | Downgraded for imprecision, heterogeneity, and attrition |
| THA total BMD beyond 5 years | 4 RCTs / 136 | Low | Small long-term samples; surrogate outcome |
| TKA regional BMD | 5 RCTs / 188 | Low | Small trials, substantial heterogeneity, incomplete blinding |
| ZA-related influenza-like symptoms | 3 RCTs / 198 | Moderate | Large effect but imprecise estimate and small event count |
| Revision or aseptic loosening | Mainly observational | Very low | Residual confounding, mixed populations, non-randomised evidence |
| Periprosthetic fracture | Sparse RCT/observational evidence | Very low | Few events and inconsistent reporting |

## Certainty of evidence

Certainty was judged moderate for the 12-month THA BMD effect because the direction was consistent, but trial reporting was dated, and heterogeneity was moderate. Certainty was low for longer-term THA and most TKA BMD estimates because few participants remained under follow-up, results were heterogeneous, and BMD is a surrogate. Certainty was very low for revision and fracture effects because they were driven mainly by observational evidence.

## Discussion

This synthesis supports a clinically coherent conclusion: bisphosphonates attenuate postoperative periprosthetic bone loss, particularly during the first year after THA. The de novo analysis produced an average 12-month preservation of 0.063 g/cm², and its prediction interval remained favourable. Benefits were most apparent in the proximal and calcar-related femoral regions, which are exposed to pronounced stress redistribution after stem implantation.

The result is biologically plausible. Surgical trauma and abrupt unloading activate bone resorption, while nitrogen-containing bisphosphonates inhibit osteoclast function during this high-turnover period. Suppression of BAP, NTX-I, and PINP is consistent with a pharmacodynamic effect. However, reduced turnover is not equivalent to improved osseointegration or implant survival. Aro and colleagues observed sustained partial bone protection without improved initial stem stability, underscoring the distinction between a DXA surrogate and mechanical fixation.32

Joint-specific differences matter. The THA evidence is broader, includes several agents and fixation types, and offers longer follow-up. TKA evidence is based on five small alendronate trials with inconsistent femoral and tibial region definitions. The very large 12-month distal femoral estimate is unlikely to be transportable without considering implant geometry, baseline BMD, sex, and measurement technique. A single pooled "joint replacement" effect would therefore be misleading.

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Drug and route also influence the balance of benefit and burden. Intravenous zoledronic acid avoids oral adherence problems and produces consistent regional hip effects, but acute-phase symptoms are common after the first infusion. Oral agents are inexpensive and familiar, yet gastrointestinal intolerance and correct administration can limit adherence. None of the trials establishes the optimal initiation date, dose, or duration specifically for arthroplasty.

The evidence does not justify routine bisphosphonate treatment for every arthroplasty recipient. A selective strategy is more defensible: identify osteoporosis or high fracture risk, correct vitamin D deficiency and hypocalcaemia, evaluate renal function, assess dental risk, and then choose treatment according to standard osteoporosis indications. Patients with severe renal impairment, active hypocalcaemia, major oesophageal contraindications to oral therapy, or imminent invasive dental procedures require particular caution.

Observational revision findings are encouraging but not causal. Bisphosphonate users may differ from non-users in access to osteoporosis care, adherence, comorbidity, and surveillance. Conversely, confounding by indication could bias effects toward harm because treated patients often have poorer baseline bone health. Adequately powered registry-embedded randomised trials are needed to determine whether the BMD signal translates into fewer revisions or fractures.

## Generalizability

The findings are most applicable to adults undergoing primary THA, particularly older patients or those with osteoporosis receiving oral nitrogen-containing bisphosphonates or perioperative zoledronic acid. External validity is lower for revision arthroplasty, younger adults, severe renal impairment, major dental risk, uncommon implant designs, non-osteoporotic TKA populations, and healthcare settings with different osteoporosis screening or follow-up practices. Because sex, ethnicity, socioeconomic status, and comorbidity distributions were incompletely reported, transportability to diverse populations should be judged cautiously. The evidence supports a biological effect on periprosthetic BMD but does not establish a universal reduction in patient-important implant failure.

## Conclusion

Bisphosphonates reduce early and intermediate periprosthetic bone loss after joint replacement. In the harmonised THA analysis, the average 12-month benefit was 0.063 g/cm², and regional zoledronic acid data showed the largest preservation in proximal and calcar-related Gruen zones. Evidence after TKA also suggests early BMD benefit, although estimates are less stable and highly heterogeneous. The current literature does not establish that these surrogate improvements reduce periprosthetic fracture, aseptic loosening, or revision. Bisphosphonates should therefore be used selectively, principally when the patient has an independent osteoporosis or fragility-fracture indication, after assessment of renal function, calcium and vitamin D status, dental risk, and treatment suitability. Longer, adequately powered randomised studies with registry linkage are required before routine arthroplasty-specific prophylaxis can be recommended.

## Clinical implications

Bisphosphonates may be considered when an arthroplasty patient already meets accepted criteria for osteoporosis treatment or has high fragility-fracture risk. The strongest evidence supports preservation of periprosthetic BMD after THA, including in osteoporotic patients receiving perioperative zoledronic acid. Clinical decisions should integrate renal function, calcium and vitamin D status, gastrointestinal suitability, adherence, dental risk, prior exposure, and expected treatment duration. Clinicians should not present a DXA-derived BMD improvement as proven prevention of implant failure, loosening, fracture, or revision.

## Strengths and limitations

Strengths include separation of hip and knee outcomes, avoidance of pooling incompatible units, a de novo random-effects analysis of a harmonized 12-month THA endpoint, reporting of $\tau^2$ and a prediction interval, sensitivity analyses, study-level risk-of-bias presentation, and an explicit distinction between BMD and implant-survival outcomes. Limitations include the source-set update design rather than a fresh record export from every major bibliographic database; lack of a prospectively registered protocol; incomplete sociodemographic reporting; reliance on analyzed completers in several reports; inability to conduct a complete fresh RoB 2 reassessment for all older trials; use of published pooled regional strata when individual data were unavailable; possible overlap in clinical populations across evidence sources despite report-level verification; low power for reporting-bias tests; and inadequate follow-up for rare harms, fracture, loosening, and revision.

## Future research

Future trials should be multicentre, adequately powered, and stratified by baseline osteoporosis, sex, fixation method, and implant design. Core outcomes should include standardised Gruen and knee regions, DXA calibration, implant migration by radiostereometric analysis, periprosthetic fracture, aseptic loosening, revision, validated function, adherence, renal and calcium events, and long-term rare

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harms. Follow-up beyond five years and linkage to arthroplasty registries would clarify whether early preservation of bone stock improves implant survival. Head-to-head comparisons of oral alendronate, intravenous zoledronic acid, denosumab, and anabolic therapy should use clinically relevant thresholds rather than statistical significance alone.

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## Competing interests
The authors declare that they have no competing interests or conflicts of interest relevant to this review.

## Data availability
All data analyzed in this review were obtained from published reports. The study-level dataset used for the primary meta-analysis is presented in Table 3, and the complete extraction sheet may be obtained from the corresponding author on reasonable request.

## Author contributions
SNC: conceptualization, literature verification, data curation, investigation, and drafting of the manuscript. TVV: methodology, independent screening, data verification, visualization, and critical revision. VH: supervision, adjudication, validation, interpretation, and final critical review. All authors reviewed and approved the final manuscript and accept accountability for the integrity of the work.

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## List of abbreviations
BAP, bone alkaline phosphatase; BMD, bone mineral density; BP, bisphosphonate; CI, confidence interval; DXA, dual-energy X-ray absorptiometry; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HHS, Harris Hip Score; IV, intravenous; MD, mean difference; NTX-I, N-telopeptide of type I collagen; PINP, procollagen type I N-terminal propeptide; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomized controlled trial; REML, restricted maximum likelihood; RoB 2, Risk of Bias 2; RR, risk ratio; SD, standard deviation; THA, total hip arthroplasty; TKA, total knee arthroplasty; WMD, weighted mean difference; ZA, zoledronic acid.

## Appendix 1. Complete search strategies
All searches were last run on 30 November 2025. Searches covered each source from inception to that date. No language restriction was imposed. The electronic search was supplemented by backward and forward citation tracking.

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| Source | Exact search string | Filters/limits/restrictions | Last searched |
|---|---|---|---|
| PubMed/MEDLINE | (("Arthroplasty, Replacement, Hip"[Mesh] OR "Arthroplasty, Replacement, Knee"[Mesh] OR arthroplast*[Title/Abstract] OR "joint replacement"[Title/Abstract] OR THA[Title/Abstract] OR TKA[Title/Abstract]) AND ("Bone Density"[Mesh] OR "bone mineral density"[Title/Abstract] OR BMD[Title/Abstract] OR periprosthetic[Title/Abstract]) AND ("Diphosphonates"[Mesh] OR bisphosphonate*[Title/Abstract] OR alendronate[Title/Abstract] OR risedronate[Title/Abstract] OR zoledronate[Title/Abstract] OR "zoledronic acid"[Title/Abstract] OR etidronate[Title/Abstract] OR clodronate[Title/Abstract] OR pamidronate[Title/Abstract])) AND (randomized controlled trial[Publication Type] OR controlled clinical trial[Publication Type] OR random*[Title/Abstract]) | Humans; publication date ≤30 Nov 2025; no language restriction. | 30 Nov 2025 |
| Crossref | ("total hip arthroplasty" OR "total knee arthroplasty" OR "joint replacement") AND (periprosthetic OR "bone mineral density" OR BMD) AND (bisphosphonate OR alendronate OR risedronate OR zoledronate OR "zoledronic acid" OR etidronate OR clodronate OR pamidronate) AND (randomised OR randomised OR trial) | Type: journal article; until-pub-date 2025-11-30; no language restriction. | 30 Nov 2025 |
| Google Scholar | ("total hip arthroplasty" OR "total knee arthroplasty" OR "joint replacement") ("periprosthetic bone" OR "bone mineral density" OR BMD) (bisphosphonate OR alendronate OR risedronate OR "zoledronic acid" OR etidronate | Custom date range: inception–2025; first 200 results screened by relevance; patents and citations excluded; no language restriction. | 30 Nov 2025 |

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| Source | Exact search string | Filters/limits/restrictions | Last searched |
|---|---|---|---|
| | OR clodronate OR pamidronate) (randomised OR randomised) | | |
| ScienceDirect | ("total hip arthroplasty" OR "total knee arthroplasty" OR "joint replacement") AND ("periprosthetic bone" OR "bone mineral density" OR BMD) AND (bisphosphonate OR alendronate OR risedronate OR zoledronate OR "zoledronic acid" OR etidronate OR clodronate OR pamidronate) AND (randomised OR randomised OR trial) | Research articles; publication date ≤30 Nov 2025; no language restriction. | 30 Nov 2025 |
| SpringerLink | ("total hip arthroplasty" OR "total knee arthroplasty" OR "joint replacement") AND (periprosthetic OR "bone mineral density") AND (bisphosphonate OR alendronate OR risedronate OR zoledronate OR "zoledronic acid" OR etidronate OR clodronate OR pamidronate) | Content type: Article; discipline: Medicine; publication date ≤30 Nov 2025; no language restriction. | 30 Nov 2025 |
| Wiley Online Library | ("total hip arthroplasty" OR "total knee arthroplasty" OR "joint replacement") AND ("periprosthetic bone" OR "bone mineral density" OR BMD) AND (bisphosphonate OR alendronate OR risedronate OR zoledronate OR "zoledronic acid" OR etidronate OR clodronate OR pamidronate) AND (randomised OR randomised OR trial) | Content type: Research Article; publication date ≤30 Nov 2025; no language restriction. | 30 Nov 2025 |

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