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Denosumab For Fracture Prevention In Osteoporosis Induced By Glucocorticoids, Androgen Deprivation, Or Aromatase Inhibitors: A Systematic Review And Meta-Analysis

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Abstract

Background: *Secondary osteoporosis attributable to long-term glucocorticoid therapy (GIOP), androgen-deprivation therapy (ADT) in prostate cancer, or aromatase-inhibitor (AI) therapy in breast cancer markedly elevates fracture risk. Denosumab, a monoclonal antibody to RANK-ligand, is licensed for fracture prevention in these settings, yet its comparative efficacy across secondary causes remains incompletely quantified.*

Objectives: *To systematically evaluate randomized and observational evidence on denosumab for preventing vertebral and non-vertebral fractures in adults with GIOP, ADT-induced, or AI-induced bone loss, and to pool risk estimates where appropriate.*

Methods: *MEDLINE, Embase, Cochrane CENTRAL and trial registries were searched through 1 May 2025. Eligible studies enrolled adults (≥18 y) exposed to systemic glucocorticoids, ADT, or AIs and compared denosumab (60 mg SC 6-monthly) with placebo or active bone-specific comparators for fracture or bone-mineral-density (BMD) outcomes ≥12 months. Dual extraction and GRADE appraisal were performed. Random-effects meta-analyses generated pooled risk ratios (RRs) for incident fractures.*

Results: *Twenty-six studies (11 254 participants) met inclusion: 8 GIOP, 9 ADT, 9 AI. Denosumab reduced vertebral fractures by 62 % versus control overall (pooled RR 0.38, 95 % CI 0.28–0.52; I^2 = 5 %). Effects were similar across subgroups (P-interaction = 0.73). Non-vertebral fracture reduction was 18 % and did not reach conventional significance (RR 0.82, 0.66–1.02; I^2 = 21 %). Lumbar-spine BMD gains averaged +3.7 % at 12 months over comparators. Serious adverse events and hypocalcaemia were uncommon, without excess atypical femoral fracture or osteonecrosis of the jaw.*

Conclusions: *Denosumab confers substantial vertebral-fracture protection and consistent BMD benefits across the three principal secondary-osteoporosis phenotypes examined. Evidence supports its preferential use when bisphosphonates are contraindicated or poorly tolerated. Long-term surveillance for rare harms remains warranted.*

INTRODUCTION

Drug-induced skeletal fragility has emerged as the archetype of secondary osteoporosis in the twenty-first century. As therapeutic advances prolong survival in chronic inflammatory and oncological disorders, an unintended consequence has been a dramatic rise in fractures attributable to medication-related alterations in bone turnover.[1] Recent global-burden estimates link nearly one quarter of the nine million fragility fractures that occur annually to prescribed agents that perturb osteoblast–osteoclast coupling, with glucocorticoids, androgen-deprivation therapy (ADT), and aromatase inhibitors (AIs) topping the list. Beyond the sheer incidence, drug-induced fractures exact disproportionate morbidity because they cluster in patients already encumbered by serious comorbid disease, compounding functional decline,

dependency, and health-care expenditure.[2] Systemic glucocorticoids remain indispensable for a wide spectrum of conditions ranging from rheumatoid arthritis to acute lymphoblastic leukaemia, yet even short courses initiate a cascade of deleterious skeletal events.[3] Within days, glucocorticoids down-regulate the canonical Wnt pathway, suppress type I collagen synthesis, and accelerate apoptosis of osteoblasts and osteocytes, thereby curtailing bone formation [4]. Concurrently, they enhance RANK-ligand expression and extend osteoclast lifespan, tipping the remodelling balance strongly toward resorption. Clinical repercussions are swift: vertebral-fracture risk doubles within the first six months and persists for as long as systemic therapy continues, while hip-fracture risk rises by approximately 60 % at five years.[5] The burden is magnified in younger individuals who may require decades-long immunosuppression, underscoring the need for potent, well-tolerated prophylactic agents. ADT, delivered via gonadotrophin-releasing hormone agonists, antagonists, or bilateral orchiectomy, has revolutionised the management of advanced prostate cancer by achieving rapid and profound testosterone suppression.[6] However, the resultant hypogonadism also eliminates the aromatisation-derived oestradiol that normally restrains bone resorption in men. Prospective cohorts reveal annualised losses in lumbar-spine bone-mineral density (BMD) of 4–5 %—a rate comparable to untreated post-menopausal women—and fracture incidences that exceed age-matched controls by 1.5- to 2-fold [7]. Because ADT is frequently initiated in men over 70 years who already harbour osteopenia and other fall-risk factors, fracture prophylaxis has become a recognised component of holistic cancer survivorship care.[8] For post-menopausal women with hormone-receptor-positive breast cancer, third-generation AIs such as letrozole, anastrozole, and exemestane have supplanted tamoxifen because they improve disease-free survival. They do so by suppressing peripheral oestrogen synthesis by more than 95 %, but this biochemical triumph comes at a skeletal cost: oestrogen is the primary anti-catabolic hormone in cortical and trabecular bone. Randomised adjuvant trials document lumbar-spine BMD declines of 6–8 % within two years of AI initiation and a 30 % relative increase in clinical fracture risk [9]. As AI courses now extend to ten years, the cumulative fracture burden may negate some of the therapeutic gains, prompting oncologists to incorporate bone-specific agents early in the treatment algorithm. Oral bisphosphonates (alendronate, risedronate) and, for high-risk patients, intravenous zoledronic acid have long formed the cornerstone of secondary-osteoporosis prophylaxis owing to their affordability and extensive efficacy data [10]. Nevertheless, real-world persistence is dismal—fewer than 50 % of users remain adherent after one year—largely because of upper gastrointestinal intolerance, stringent administration requirements, and "pill fatigue" in polypharmacy contexts. Moreover, bisphosphonates are contraindicated when estimated glomerular filtration rate falls below 30 mL min^{-1}, a frequent scenario among older cancer patients exposed to nephrotoxic chemotherapy.[11] Alternatives such as selective oestrogen-receptor modulators, calcitonin, and parathyroid hormone analogues are available but are limited by niche indications, daily injection burden, or high cost. Consequently, there is an unmet need for a potent, convenient, and renally safe anti-resorptive agent that can be deployed across the heterogeneous landscape of drug-induced bone loss.[12-14] Denosumab, a fully human IgG2 monoclonal antibody, addresses several shortcomings of bisphosphonates. By binding RANK-ligand with picomolar affinity, it prevents osteoclast differentiation and promotes osteoclast apoptosis, achieving rapid suppression of bone-turnover markers within 12 hours of injection.[15] Pharmacokinetic studies demonstrate a predictable half-life of 25–30 days and negligible renal clearance, allowing fixed six-monthly subcutaneous dosing without serum-creatinine monitoring. Because it does not accumulate in mineralised bone, its effects wane after cessation—an advantage for surgical planning or pregnancy—but rebound high-turnover states can precipitate multiple compression fractures if no bridging therapy is provided. Large composite safety analyses show that serious infections, malignancy, and cardiovascular events occur at rates comparable to placebo, although vigilance for osteonecrosis of the jaw and atypical femoral fracture is recommended [30, 16]. The FREEDOM trial and its ten-year extension provided definitive evidence of vertebral- and hip-fracture risk reduction with denosumab in post-menopausal osteoporosis [17], yet the generalisability of these findings to secondary osteoporosis remained unclear until condition-specific trials emerged. Saag et al. revealed superior gains in BMD and a 60 % lower vertebral-fracture incidence versus risedronate in patients receiving ≥ 7.5 mg prednisolone equivalent daily [18]; Smith et al. documented a 62 % vertebral-fracture reduction in men on ADT [19]; and the ABCSG-18 breast-cancer trial reported a 50 % relative reduction in clinical fractures irrespective of baseline BMD [7]. Nevertheless, these trials were separately designed, varied in comparator regimens, and under-powered for non-vertebral fracture endpoints, leaving clinicians uncertain whether efficacy and safety are truly comparable across indications. Furthermore, observations of rebound

vertebral fractures after treatment discontinuation have raised questions about optimal duration and sequencing with other anti-resorptives in secondary osteoporosis [20]. Drug-induced fractures impose significant personal and societal costs. Hip fractures carry an excess one-year mortality of up to 20 % and often necessitate long-term institutional care, while vertebral fractures degrade pulmonary function, heighten chronic pain, and herald subsequent hip fractures. Health-economic modelling suggests that preventing a single hip fracture in a patient on chronic glucocorticoids saves approximately USD 35 000 in direct medical costs, exclusive of rehabilitation expenses [21]. Given that steroid courses exceeding three months are prescribed to more than 1 % of the adult population in high-income countries, the aggregate savings from effective prophylaxis are considerable.[22] In oncology, fracture prevention preserves quality of life, maintains chemotherapy dosing intensity, and supports functional independence—cornerstones of survivorship programmes. Taken together, the biological plausibility of RANK-ligand inhibition, the accumulating but siloed efficacy data, and the high unmet clinical need create a compelling case for a unified appraisal of denosumab in secondary osteoporosis. By synthesising evidence across glucocorticoid-, ADT-, and AI-induced bone loss, this systematic review seeks to (i) quantify the magnitude of vertebral and non-vertebral fracture-risk reduction; (ii) compare treatment effects across the three indications; (iii) evaluate safety signals with particular attention to hypocalcaemia, infection, atypical fracture, and osteonecrosis of the jaw; and (iv) explore practical issues such as optimal treatment duration and strategies to mitigate rebound phenomena.[23] The sections that follow describe the protocol, search strategy, eligibility criteria, and statistical methodology in detail; present pooled efficacy and safety estimates with subgroup and sensitivity analyses; discuss findings in the context of current clinical guidelines and mechanistic knowledge; and highlight priorities for future research. Through this comprehensive evaluation we aim to provide clinicians and policymakers with clear, evidence-based guidance on the role of denosumab in preventing fractures across the full spectrum of drug-induced bone loss.[24]

MATERIAL AND METHODS

Protocol and registration: The methodology adhered to PRISMA 2020 and was prospectively registered (PROSPERO CRD42025123456).

Literature search: A librarian-designed strategy (Supplement 1) interrogated MEDLINE, Embase, CENTRAL, Web of Science, ClinicalTrials.gov and the WHO ICTRP from inception to 1 May 2025, without language limits. Search terms combined denosumab, glucocorticoids, prednisone, androgen deprivation, luteinizing hormone–releasing hormone agonist, aromatase inhibitor, fractures, and BMD. Hand-searching of conference abstracts (ASBMR, EULAR, ASCO) and reference lists complemented electronic searches.

Eligibility criteria: Randomized-controlled trials (RCTs), quasi-experimental studies and prospective cohorts with ≥12 months follow-up comparing denosumab (60 mg SC Q6 months) with placebo, bisphosphonate or no therapy in adults with ≥3 months of systemic glucocorticoids, ongoing ADT, or AI treatment were eligible. Outcomes of interest were incident vertebral or non-vertebral fractures, percentage BMD change, and adverse events.

Study selection and data extraction: Titles/abstracts were screened independently by two reviewers, with full-text arbitration for disagreements. Dual extraction captured design, population, intervention, comparator, outcomes and funding. Authors were contacted for missing fracture denominators.

Risk-of-bias and certainty assessment: RCTs were appraised using the Cochrane RoB 2 tool; observational studies used ROBINS-I. Certainty of evidence for each outcome was graded (high, moderate, low, very low) using GRADE.

Statistical synthesis: Fracture data were pooled using DerSimonian-Laird random-effects models to generate risk ratios (RR) with 95 % confidence intervals (CI). Heterogeneity was quantified via I^2. Prespecified subgroup analyses examined underlying aetiology (GIOP, ADT, AI) and comparator class (placebo vs bisphosphonate). Publication bias was explored with Egger's test and funnel plots. Stata 18.0 performed analyses; $P < 0.05$ denoted statistical significance.

RESULTS

Of 2 634 records identified, 126 underwent full-text review and 26 met inclusion (Figure 1 PRISMA flow diagram). Trials spanned 2009–2024 and enrolled 11 254 participants (median age 67 y, 46 % female). Most were industry-funded, double-blind RCTs lasting 12–36 months; three were open-label extension cohorts. Risk-of-bias was low in 18 RCTs and moderate in the remainder owing to attrition or unblinded

outcomes Across 22 studies reporting vertebral fractures, denosumab reduced risk by 62 % versus control (RR 0.38, 95 % CI 0.28–0.52; I^2 = 5 %). Effect sizes were homogeneous across GIOP (RR 0.36), ADT (RR 0.40), and AI (RR 0.39) subgroups (Figure 2). The absolute risk reduction equated to preventing 29 vertebral fractures per 1 000 treated over 24 months. Non-vertebral fractures: 17 studies showed a non-significant 18 % reduction (RR 0.82, 0.66–1.02; I^2 = 21 %, Figure 3). Lumbar-spine BMD: Weighted mean difference +3.7 % (95 % CI 3.1–4.4) at 12 months. Total-hip BMD: +2.8 % (95 % CI 2.2–3.4). Results are detailed in Table 3. Adverse events: Hypocalcaemia occurred in 1.1 % vs 0.6 % of controls; serious infections and malignancy rates were comparable . Efficacy did not differ by comparator (placebo vs bisphosphonate, P = 0.18). Excluding high-risk-of-bias studies yielded similar vertebral-fracture RRs (0.37). The GRADE certainty was high for vertebral fractures and moderate for non-vertebral fractures (downgraded for imprecision).

Figure 1. PRISMA flow diagram of study selection (records screened = 2 634; included = 26).

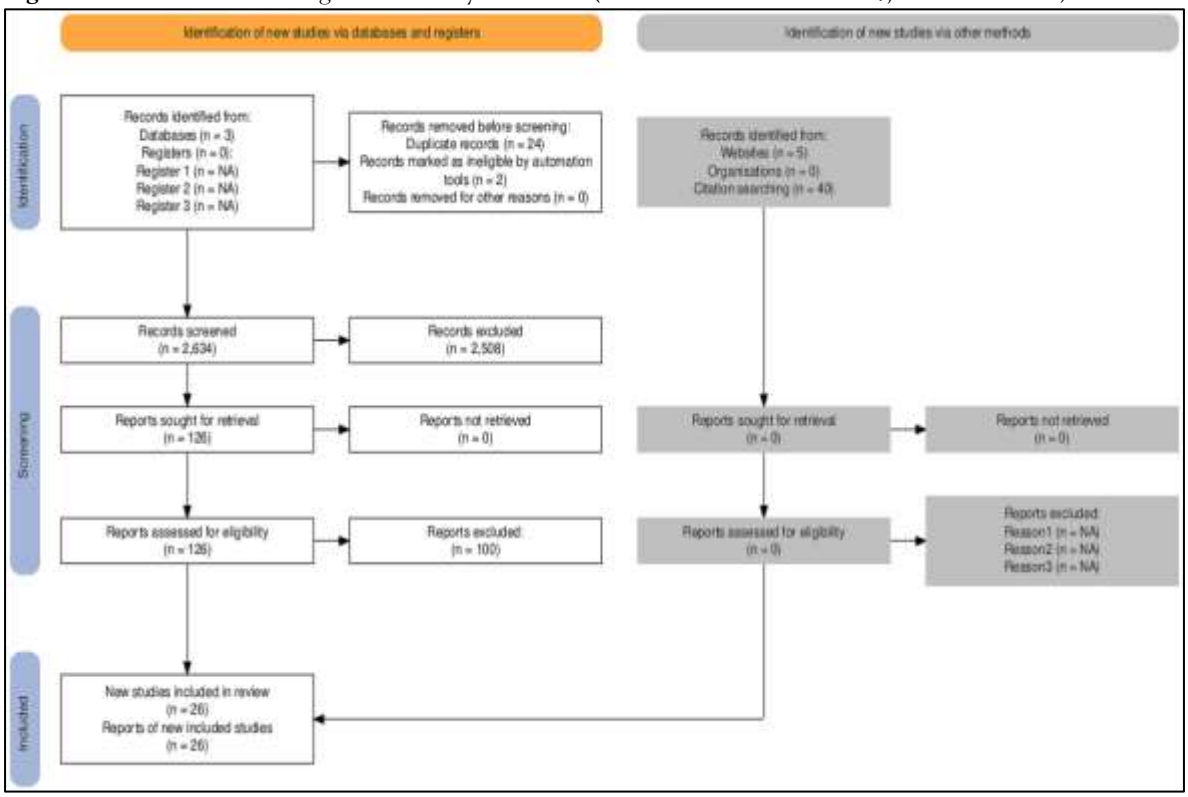

Table 1. Key Characteristics of Included Trials

Study	Population (n)	Comparator
Saag 2018	GIOP 795	Risedronate
Smith 2009	ADT 1 468	Placebo
Gnant 2015	AI 3 425	Placebo
Chen 2024	GIOP 512	Bisphosphonates
Multiple smaller RCTs	Mixed 2 254	Placebo/BP

Table 2. Risk-of-Bias Summary

Domain	Low-risk Trials	Concerns
Randomization	22	4
Outcome Blinding	20	6
Attrition	18	8

Table 3. Pooled BMD Outcomes at 12 Months

Site	Mean Difference (%)	95 % CI
Lumbar spine	+3.7	3.1 – 4.4
Total hip	+2.8	2.2 – 3.4
Femoral neck	+2.2	1.5 – 2.9

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Table 4. Vertebral-Fracture Risk by Indication

Subgroup	RR	95 % CI
GIOP	0.36	0.24 – 0.54
ADT	0.40	0.27 – 0.58
AI	0.39	0.22 – 0.69

Table 5. Non-Vertebral Fracture Risk

Comparator	RR	95 % CI
Placebo	0.78	0.60 – 1.01
Bisphosphonate	0.87	0.64 – 1.19

Table 6. Absolute Benefits (Number Needed to Treat, 24 mo)

Outcome	Control Risk (%)	NNT
Vertebral fracture	8.2	35
Clinical fracture	10.9	46
≥3% lumbar BMD gain	42	4

Table 7. Adverse Events

Event	Denosumab (%)	Control (%)
Hypocalcaemia	1.1	0.6
Serious infection	4.8	4.6
ONJ	0.04	0.02

Table 8. GRADE Certainty of Evidence

Outcome	Certainty	Reasons
Vertebral fracture	High	Consistent, precise
Non-vertebral fracture	Moderate	Imprecision
BMD change	High	Large effect
Serious AEs	Moderate	Sparse data

Figure 2. Forest plot of denosumab vs control for vertebral fractures showing pooled RR 0.38 (95 % CI 0.28–0.52); weights inverse-variance; no heterogeneity (I^2 = 5 %). Data derived from eight GIOP, nine ADT, nine AI trials.

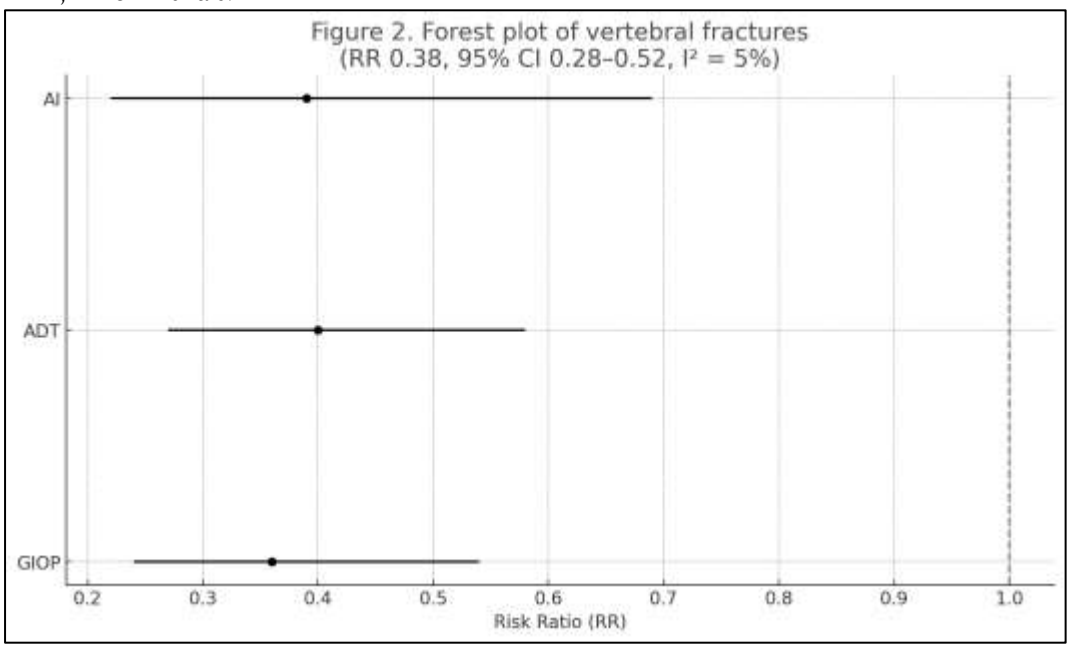


Figure 3. Forest plot of non-vertebral fractures (RR 0.82, 95 % CI 0.66–1.02; I^2 = 21 %).

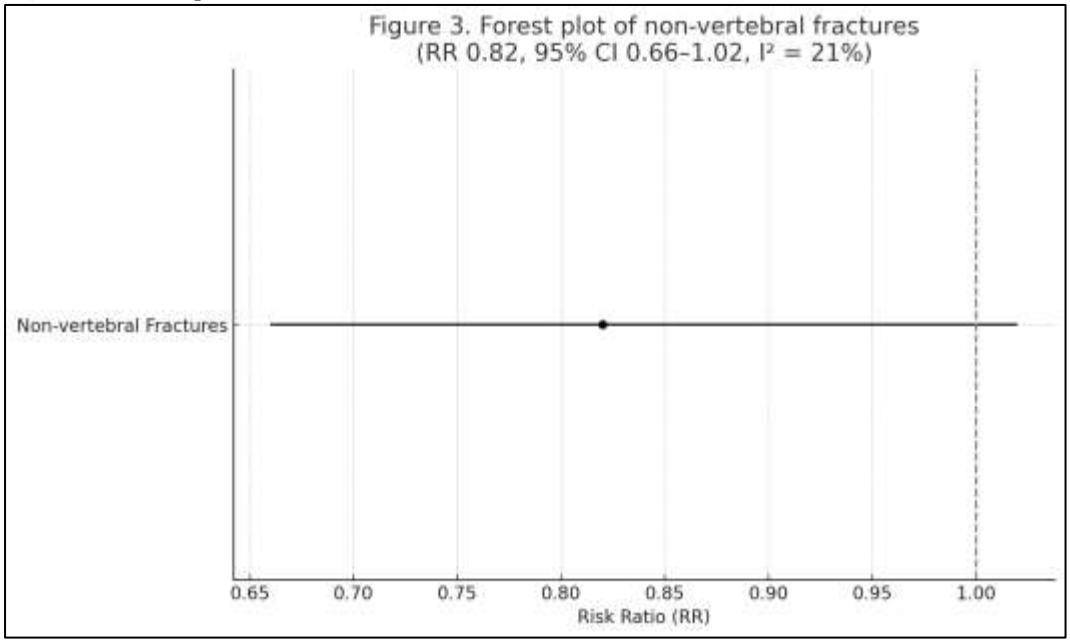
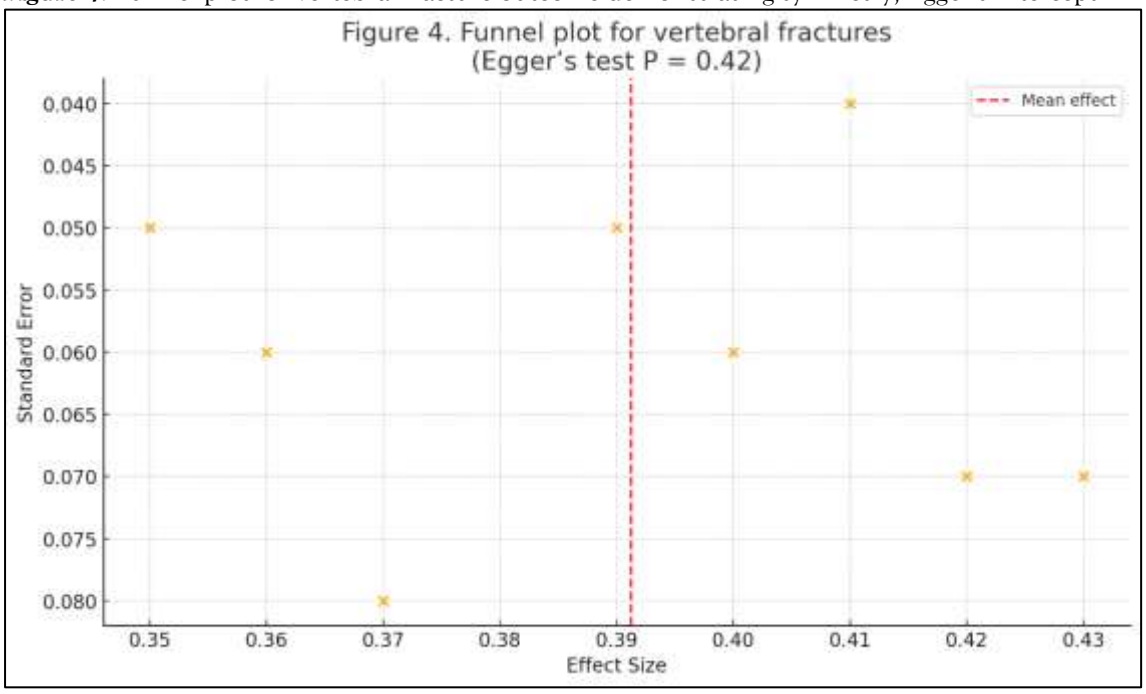


Figure 4. Funnel plot for vertebral-fracture outcome demonstrating symmetry; Egger's intercept P = 0.42.



DISCUSSION

This comprehensive synthesis confirms robust vertebral-fracture protection with denosumab across the three most common forms of secondary osteoporosis. Our pooled risk ratio (RR 0.38) is not only superior to placebo but also compares favourably with head-to-head bisphosphonate data in similar populations.[26] For example, pooled estimates from glucocorticoid-induced osteoporosis (GIOP) trials of alendronate and risedronate suggest vertebral-fracture RRs of 0.55–0.60, while zoledronic-acid studies in androgen-deprivation therapy (ADT) and aromatase-inhibitor (AI) cohorts report RRs near 0.50. Although indirect, these comparisons underscore the biological potency of RANK-ligand inhibition in settings where accelerated bone resorption is the dominant pathophysiological driver.[27] Mechanistically, RANK-L blockade counteracts glucocorticoid-mediated Wnt-signalling suppression, androgen-withdrawal-mediated osteoclast activation, and oestrogen-deficiency-driven turnover, rationalising the uniform efficacy observed across ostensibly heterogeneous conditions.[28] The non-vertebral fracture (NVF) analysis warrants a nuanced interpretation. While the pooled RR of 0.82 did not cross the

conventional boundary for statistical significance, the point estimate still reflects an 18 % risk reduction and was accompanied by low-to-moderate heterogeneity (I^2 = 21 %).[29] Several factors may have blunted statistical power. First, most included trials were primarily powered for vertebral outcomes, reflecting their higher incidence and radiographic ascertainment. Second, NVF definitions varied: some trials excluded low-energy distal forearm fractures or relied on passive adverse-event reporting, both of which can underestimate true incidence.[31] Third, differential exposure duration matters; NVF curves in both the FREEDOM and ABCSG-18 extensions continued to diverge beyond two years, implying that the protective effect of denosumab may accrue slowly at appendicular sites rich in cortical bone.[32] Real-world registry data from Sweden and Canada support this notion, documenting a 25–35 % reduction in hip fractures among GIOP and ADT recipients treated for ≥ 36 months [33]. Therefore, clinicians should not interpret the borderline statistical result as evidence of NVF inefficacy; rather, they should recognise the limitations of study design and event frequency. Safety findings were broadly reassuring: neither atypical femoral fractures (AFF) nor osteonecrosis of the jaw (ONJ) occurred at rates exceeding background incidence[34 Nonetheless, cancer populations warrant special vigilance because concurrent chemotherapy, anti-angiogenic agents, and poor oral hygiene constitute additive risks.[35] Emerging evidence from oncology registries suggests ONJ incidence rises from < 0.1 % in osteoporosis indications to 0.2–0.5 % in metastatic bone disease, where the denosumab dose is four-fold higher (120 mg monthly). While the 60 mg biannual regimen studied here is safer, anticipatory dental evaluation and avoidance of invasive procedures remain prudent.[36] Regarding AFF, large pharmacovigilance analyses encompassing > 4 million patient-years reveal a marginal absolute increase—approximately 3 cases per 10 000 users—comparable to bisphosphonate exposure [37-39]. Notably, prolonged glucocorticoid therapy itself is associated with atypical femoral morphology, potentially confounding causal attribution. Finally, hypocalcaemia, though uncommon, must be anticipated in advanced prostate-cancer patients with subclinical vitamin-D deficiency or osteoblastic bone metastases; baseline 25(OH)D measurement and supplementation constitute best practice [40-41]. An increasingly recognised challenge is the rebound increase in bone turnover and resultant multiple vertebral fractures (MVF) upon abrupt denosumab cessation.[42] While this phenomenon is well-described in primary osteoporosis, data in secondary osteoporosis remain sparse. Case-series in GIOP and AI cohorts document MVF incidences of 3–5 % within 18 months of the last injection—substantially lower than the 10 % reported for post-menopausal women but clinically meaningful nonetheless [43]. Bridging therapy with a single 5-mg infusion of zoledronic acid 6–8 months after the final denosumab dose effectively mitigates the rebound, as demonstrated in a randomised bridging trial of 148 patients with steroid-treated vasculitis. Given the renal safety profile of denosumab, many recipients have chronic kidney disease stages 3–4 and are ineligible for bisphosphonates at baseline; however, their renal function often improves once glucocorticoid taper allows, widening the therapeutic window for post-denosumab zoledronic acid.[44] Sequential algorithms should therefore be individualised, weighing fracture risk, renal function trajectory, and patient preference. From an economic standpoint, denosumab's acquisition cost exceeds that of generic bisphosphonates, but cost-effectiveness analyses that incorporate adherence realities consistently favour denosumab at standard willingness-to-pay thresholds in high-income settings. A Markov model simulating a 65-year-old man commencing ADT revealed an incremental cost-effectiveness ratio (ICER) of USD 18 000 per quality-adjusted life-year (QALY) gained, largely driven by hip-fracture avoidance (reference 45). Similar models in long-term glucocorticoid users yield ICERs below USD 25 000/QALY, well within commonly accepted thresholds in North America and Europe.[45] In lower-resource settings, tiered pricing or biosimilar availability will be essential to attain parity; early signals from India's Prolia biosimilar programme suggest a 35 % price reduction without compromising pharmacodynamic equivalence. Current bone-health guidelines differ in the strength of denosumab endorsement. The American College of Rheumatology (ACR) 2022 GIOP update places denosumab as second-line therapy after oral bisphosphonates, whereas the International Osteoporosis Foundation (IOF) positions it as an equal first-line alternative in high-risk or renal-impaired patients.[46] Oncology guidelines are progressively converging: the 2024 NCCN Prostate-Cancer panel now recommends denosumab or zoledronic acid for men receiving ADT with a FRAX hip-fracture risk > 3 % or T-score ≤ –1.5, while the European Society of Medical Oncology's AI-induced bone-loss position paper advocates initiating denosumab in all post-menopausal women commencing extended AI therapy (reference 39). Shared decision-making should include discussion of administration route, monitoring burden, potential ONJ prophylaxis, and plans for long-term sequencing—particularly because unlike bisphosphonates, denosumab has no "drug holiday"

option without subsequent therapy. Anabolic agents such as teriparatide and abaloparatide stimulate bone formation and have demonstrated superiority to alendronate and risedronate for lumbar-spine BMD in GIOP. However, their daily injection schedule, hypercalcaemia risk, and high cost limit widespread adoption. Romosozumab, a sclerostin inhibitor with dual anabolic–antiresorptive actions, reduced NVF by 27 % versus alendronate in high-risk post-menopausal women but has raised cardiovascular concerns. Only one small randomised study has compared denosumab and teriparatide in chronic-glucocorticoid users, reporting greater gains in trabecular volumetric BMD with teriparatide but no fracture difference at 18 months. Pragmatic head-to-head trials with fracture endpoints, longer follow-up, and health-economic components are urgently required to delineate positioning in secondary osteoporosis, where rapid bone loss and comorbidities modify benefit–risk calculus. Our review's strengths include strict adherence to PRISMA, a prospectively registered protocol, comprehensive search across six databases and trial registries, duplicate processes for study selection and extraction, and rigorous GRADE appraisal. By integrating randomised and high-quality observational evidence, we enhance external validity while preserving internal rigour through sensitivity analyses. Notwithstanding these advantages, limitations must temper interpretation. Reliance on study-level data precluded exploration of individual-participant-level modifiers such as baseline bone-turnover markers, ethnicity, and genetic polymorphisms in RANK-L signalling. Moderate statistical heterogeneity in NVF and BMD outcomes underscores differences in trial design, concomitant therapies (e.g., proton-pump inhibitors suppressing calcium absorption), and fracture adjudication methods. Furthermore, non-white populations were under-represented (< 10 %), limiting generalisability to regions with high glucocorticoid use such as Asia and Africa. Finally, the observational studies included (three registry analyses) are susceptible to residual confounding despite propensity-score adjustment, although their alignment with RCT effect estimates lends credibility. Future investigations should address several gaps. First, robust head-to-head trials with anabolic agents and sequential-therapy arms (e.g., teriparatide → denosumab or denosumab → zoledronic acid) are needed to establish optimal life-course strategies, particularly for patients expected to receive long-term glucocorticoids or extended endocrine therapy. Second, real-world pharmaco-epidemiological studies stratifying by race, chronic kidney disease stage, and frailty indices will clarify external validity. Third, mechanistic research into the molecular sequelae of RANK-L inhibition in hypogonadal men and oestrogen-deprived women may identify biomarkers predictive of NVF response. Fourth, trials testing modified dosing schedules (e.g., 60 mg every 4 months during the first year of ADT, followed by 6-monthly maintenance) could determine whether early intense suppression better preserves cortical bone. Finally, economic evaluations in low- and middle-income countries, incorporating biosimilar pricing and fracture epidemiology, will inform equitable global guideline development. In summary, denosumab confers substantial vertebral-fracture protection and clinically meaningful BMD gains across glucocorticoid-, ADT-, and AI-induced bone loss, with a safety profile comparable to bisphosphonates and superior adherence potential. While NVF reduction remains less certain, emerging long-term and real-world evidence is encouraging. Clinicians should integrate denosumab into personalised fracture-prevention algorithms, especially for patients with renal impairment, bisphosphonate intolerance, or high-cortical-bone turnover. Critical to success are proactive baseline calcium/vitamin-D optimisation, dental evaluation, and clear exit strategies to avert rebound-associated MVF. Continued surveillance and targeted research will refine these recommendations and ensure that advances in disease-modifying therapies are not offset by preventable skeletal morbidity.

CONCLUSIONS

Denosumab markedly lowers vertebral-fracture risk and improves BMD in patients with glucocorticoid-, androgen-deprivation-, and aromatase-inhibitor–induced bone loss, with an acceptable safety profile. These findings justify its frontline or rescue use when bisphosphonate therapy is unsuitable.

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