

3-1-2017

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Recommended Citation

Nayak, Smita and Greenspan, Susan L, "Osteoporosis Treatment Efficacy for Men: A Systematic Review and Meta-Analysis." (2017). *Articles, Abstracts, and Reports*. 1582.

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Published in final edited form as:

J Am Geriatr Soc. 2017 March ; 65(3): 490–495. doi:10.1111/jgs.14668.

Osteoporosis Treatment Efficacy for Men: A Systematic Review and Meta-Analysis

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Abstract

BACKGROUND/OBJECTIVES—Osteoporosis affects approximately 2 million men in the U.S., however, few osteoporosis clinical studies include men. The objective of this study was to evaluate the evidence for efficacy of treatment options to reduce osteoporotic fracture risk for men.

DESIGN—Systematic review and meta-analysis.

DATA SOURCES—PubMed, Embase, and Cochrane Library databases.

STUDY SELECTION—Randomized clinical trials that evaluated the efficacy of a treatment for osteoporosis or low bone mineral density for adult male participants and reported fracture outcomes.

DATA EXTRACTION—Information extracted included participant sociodemographic characteristics; number of male participants; treatment/intervention(s) and comparator evaluated; study duration; and fracture outcome(s). Risk of bias of individual studies was assessed using measures recommended by the Cochrane Collaboration.

RESULTS—Twenty-four articles reporting results for 22 different studies (including 4868 male participants) met strict inclusion criteria. Fixed-effects meta-analyses using the Mantel-Haenszel method demonstrated significantly reduced risk of vertebral fractures with alendronate (RR 0.328, 95% CI 0.155–0.692) and risedronate (RR 0.428, 95% CI 0.245–0.746), but not with calcitonin (RR 0.272, 95% CI 0.046–1.608) or denosumab (RR 0.256, 95% CI 0.029–2.238). For bisphosphonates as a treatment category, meta-analyses demonstrated significantly reduced risk of vertebral fractures (RR 0.368, 95% CI 0.252–0.537) and nonvertebral fractures (RR 0.604, 95% CI 0.404–0.904). The meta-analysis finding that bisphosphonates significantly reduce nonvertebral fracture risk was not robust to sensitivity analysis.

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Conflict of Interest Statement: Dr. Greenspan is on the scientific advisory board for Merck & Co. Dr. Nayak has no conflicts of interest.

Author Contributions: Study concept and design: SN and SG. Acquisition, analysis, or interpretation of data: SN and SG. Data interpretation: SN and SG. Drafting manuscript: SN. Critical revision of the manuscript for important intellectual content: SN and SG. Approving final version of manuscript: SN and SG.

CONCLUSION—Bisphosphonates reduce the risk of vertebral and possibly nonvertebral fractures for men with osteoporosis. Further studies are needed to evaluate the efficacy of bisphosphonates for reducing nonvertebral fracture risk and the efficacy of non-bisphosphonates for reducing vertebral and nonvertebral fracture risk for men with osteoporosis.

Keywords

osteoporosis; fractures; systematic review; meta-analysis

INTRODUCTION

Osteoporosis affects 2 million men in the United States,¹ and approximately 1 in 5 white men will sustain an osteoporotic fracture in his lifetime.² Men are estimated to incur 29% of all osteoporotic fractures and account for 25% of total osteoporosis-related costs.³ Furthermore, men have higher mortality rates after hip fracture than women, with nearly 1 in 3 men over the age of 65 years who incur a hip fracture dying within the following year.⁴ The morbidity, mortality, and costs secondary to osteoporotic fractures in the U.S. are considerable and likely to increase in upcoming years with the aging of the population.^{2–9}

Despite the prevalence of osteoporosis among older men and potential severity of its health consequences, osteoporosis in men is significantly understudied compared with women; most osteoporosis clinical studies to date have not included male participants.¹⁰ FDA-approved osteoporosis treatment options for men include alendronate, risedronate, zoledronic acid, teriparatide, and denosumab, and osteoporosis treatment for men is recommended by several organizations.^{11,12} We performed a systematic review and meta-analysis of the evidence for fracture risk reduction for different osteoporosis treatment options for men.

METHODS

Data sources and search strategies

We developed broad literature search strategies for PubMed, Embase, and Cochrane Library databases to locate randomized clinical trials reporting on the efficacy of osteoporosis treatment options. We performed initial literature searches on 8/15/14 for Embase; 8/28/14 for PubMed; and 11/28/14 for the Cochrane Library. The PubMed search was updated on 3/18/16. The database search strategies are available upon request. We identified additional studies by reviewing the reference lists of topical review papers and studies meeting our inclusion criteria as well as studies identified by experts.

Study selection

We applied inclusion and exclusion criteria to literature identified with the search strategies to select studies of interest. We included studies that evaluated the efficacy of a treatment for adults with osteoporosis or low bone mineral density (BMD); were randomized clinical trials; reported separate data for male participants or had male participants only; and reported fracture outcomes, with provision of either numbers or percentages of men in each study group who sustained incident fractures. We included studies published in any

language, and had no restrictions on study participant comorbidities. We excluded studies in which not all participants were identified as having osteoporosis or low BMD (T-score ≤ -1). We evaluated studies for inclusion in two stages – we first reviewed titles and abstracts, followed by full-text review of studies that were identified as potentially relevant after title/abstract review.

Data extraction

Information extracted from eligible studies included study participant sociodemographic characteristics; number of male participants; study location; treatment/intervention(s) evaluated; comparator for evaluated treatment/intervention; duration of study/follow-up period for fracture outcomes; fracture outcome(s) evaluated; and results reported for fracture outcomes in intervention and comparator groups. For fracture outcomes, we extracted data on numbers of participants in the intervention and comparator groups who sustained incident fractures.

Data analysis

We qualitatively described included study characteristics and study quality. For study quality assessment, we used measures recommended by the Cochrane Collaboration for assessing risk of bias for individual studies, including criteria to evaluate risk of selection bias, performance bias, detection bias, attrition bias, and reporting bias.¹³ We also performed fixed-effects meta-analyses using the Mantel-Haenszel method¹⁴ to calculate summary relative risk of fracture estimates for each individual treatment option for which there were at least two studies with similar comparators and fracture outcomes assessed; and for bisphosphonates when considered as a treatment category. Between-study heterogeneity in each performed meta-analysis was assessed with I^2 values. For studies that reported fracture outcomes for multiple follow-up time periods, we used the fracture outcomes reported for the longest follow-up time period when performing meta-analyses. For meta-analyses that included 3 or more studies, we also performed influence (sensitivity) analysis in which we excluded individual studies one at a time to assess whether meta-analysis findings were robust to exclusion of individual studies. We used Stata version 11.0 (StataCorp, College Station, TX) to perform these analyses.

RESULTS

Literature search and study selection

The literature searches identified a total of 6475 records (citations) for review; 2673 of these records were excluded because they were duplicates (same citation found in different databases), leaving 3802 unique records for review. Twenty-four of these records reporting results for 22 different studies met inclusion criteria.^{15–38} Figure 1 shows a flow diagram of the literature search and study selection.

Study characteristics

Supplementary Table S1 shows included study characteristics. Included studies were published between 1998 and 2013, number of male study participants ranged from 23 to 1199, and study duration ranged from 1 to 3 years. Approximately half of the included

studies evaluated the efficacy of bisphosphonate medications, with more studies assessing alendronate or zoledronic acid than other bisphosphonates. Most included studies compared a treatment option to placebo and/or calcium and vitamin D only; very few had active comparators. A majority of studies included only men with primary osteoporosis and/or hypogonadal osteoporosis, and did not include men with other causes of secondary osteoporosis. Many of the included studies had largely white study participant populations. Commonly assessed osteoporosis fracture outcomes included all vertebral fractures (morphometric – detected by x-rays, including asymptomatic as well as symptomatic vertebral fractures); clinical vertebral fractures (meaning symptomatic vertebral fractures only); nonvertebral fractures; and clinical fractures (clinically symptomatic fractures at any site). Vertebral fractures were the most commonly assessed fracture outcomes, followed by nonvertebral fractures and clinical fractures.

Only one included study, a study by Boonen et al. evaluating zoledronic acid therapy, reported having sufficient statistical power for fracture outcomes for men, for the outcome of morphometric vertebral fractures.³⁶ Only 4 studies reported relative risk, odds ratio, or hazard ratio of fracture for men in the intervention groups compared to the comparator groups;^{17,18,29,30,35,36} of these, 3 studies evaluating alendronate, risedronate, and zoledronic acid reported a statistically significant reduction in risk of fracture for men receiving the evaluated intervention/treatment compared to the comparator; all for the outcome of vertebral fractures,^{18,29,30,36} and only one study evaluating risedronate for the outcome of nonvertebral fractures.³⁰ Only two included studies performed head-to-head comparisons of drugs that are FDA-approved for men – one study that compared teriparatide to alendronate,³³ and another study that compared zoledronic acid to alendronate;³⁸ neither of these studies reported relative risk for fracture outcomes. A majority of studies reported pharmaceutical company funding.^{15,16,19,21–25,27,28,31,33–36,38}

Study quality and potential sources of bias

Supplementary Table S2 shows findings of our assessment of included study quality using criteria recommended by the Cochrane Collaboration for assessing risk of bias for individual studies. In general, studies did not sufficiently describe their methods of random sequence generation, allocation concealment, and whether all pre-specified outcomes in the study protocol were reported on in the pre-specified way to permit judgment of “low risk” or “high risk” of bias for these domains. Thus, most studies were assessed as “unclear risk” of bias for the categories of selection bias and reporting bias. A majority of studies reported blinding of fracture outcome assessment, and thus were assessed as low risk for detection bias. Studies were mixed with respect to domains of reporting of blinding of participants and personnel, as well as incomplete outcome data, which fall within categories of performance bias and attrition bias, respectively. No included study was assessed as low risk of bias for all evaluated domains, and thus no study received a summary assessment of low risk of bias. A slight majority of studies received a summary assessment of high risk of bias (due to at least one bias domain being assessed as high risk of bias), with the remainder of the studies receiving a summary assessment of unclear risk of bias.

Meta-analyses

Sufficiently similar studies were available for separate meta-analyses for the outcome of vertebral fractures for alendronate, calcitonin, denosumab, and risedronate; for the outcome of nonvertebral fractures for alendronate; and for the outcome of clinical fractures with zoledronic acid. When considering bisphosphonates as a treatment category, sufficiently similar studies were available for outcomes of vertebral fractures, clinical vertebral fractures, nonvertebral fractures, and clinical fractures. Meta-analysis results are shown in Table 1. Forest plots for the meta-analyses are shown in Supplementary Figures S1–S10.

For individual treatment options, the meta-analyses findings demonstrated significantly reduced risk of vertebral fractures with alendronate (RR 0.328, 95% CI 0.155–0.692) and risedronate (RR 0.428, 95% CI 0.245–0.746), but not with calcitonin (RR 0.272, 95% CI 0.046–1.608) or denosumab (RR 0.256, 95% CI 0.029–2.238). The meta-analyses findings for individual treatment options did not demonstrate significantly reduced risk of nonvertebral fractures with alendronate (RR 0.751, 95% CI 0.352–1.602) or clinical fractures with zoledronic acid (RR 0.742, 95% CI 0.436–1.263). When considering bisphosphonates as a treatment category, meta-analyses findings demonstrated significantly reduced risk of vertebral fractures (RR 0.368, 95% CI 0.252–0.537) and nonvertebral fractures (RR 0.604, 95% CI 0.404–0.904), but not clinical vertebral fractures (RR 0.398, 95% CI 0.105–1.506) or clinical fractures (RR 0.791, 95% CI 0.500–1.253). Between-study heterogeneity in each performed meta-analysis was low as demonstrated by low I^2 values.

The meta-analysis finding that bisphosphonates significantly reduce risk of vertebral fractures was robust to influence analysis, with summary estimates of relative risk of vertebral fractures with bisphosphonate therapy ranging from 0.353–0.391 with removal of individual studies, and the lower limit of the 95% CI ranging from 0.215–0.265 and the upper limit of the 95% CI ranging from 0.518–0.594 with removal of individual studies. However, the finding that bisphosphonates significantly reduce risk of nonvertebral fractures was sensitive to removal of the study by Ringe et al. in 2009 that evaluated risedronate therapy for men³⁰ – when this study was removed from the analysis, the summary estimate for relative risk of nonvertebral fractures with bisphosphonate therapy was 0.715, with a 95% CI of 0.382–1.337. The meta-analysis findings of nonsignificant reduction in the relative risk of clinical vertebral fractures or clinical fractures with bisphosphonates were robust to influence analysis, with results remaining nonsignificant with removal of any individual study in either analysis.

DISCUSSION

Relatively few randomized clinical trials have been performed to date to assess efficacy of osteoporosis treatment options for reducing fracture risk for men. Our meta-analysis findings for individual treatment options demonstrated that alendronate and risedronate significantly reduce risk of vertebral fracture for men; however, our meta-analyses for individual treatment options did not demonstrate evidence of statistically significant reduction in vertebral fracture risk for men with calcitonin or denosumab, nonvertebral fracture risk for men with alendronate, or clinical fracture risk for men with zoledronic acid. Our meta-analyses findings for bisphosphonates when considered as a treatment category

demonstrated significantly reduced risk of vertebral fractures and nonvertebral fractures, but not clinical vertebral fractures or clinical fractures. Our results for significant reduction in the relative risk of nonvertebral fractures with bisphosphonate therapy were sensitive to the removal of the study by Ringe et al. in 2009 that demonstrated significantly reduced risk of nonvertebral fracture for men with risedronate therapy.³⁰ There were insufficient data to perform meta-analyses for the efficacy of calcitriol, monoflourophosphate, parathyroid hormone, strontium ranealate, or teriparatide for reducing fracture risk for men.

Our meta-analyses were limited by the number of similar studies assessing each medication, with only 2 studies included in each separate meta-analysis of individual medications that we performed, and 3–6 studies included in each separate meta-analysis we performed for different fracture outcomes when evaluating bisphosphonates as a treatment category. Additionally, many of the included studies in our meta-analyses had small sample sizes. Furthermore, although one included study demonstrated significant reduction in morphometric vertebral fracture risk with zoledronic acid treatment,³⁶ there were not two studies similar enough to perform a meta-analysis for the efficacy of zoledronic acid treatment on fracture outcomes for men. Moreover, our systematic review and meta-analysis findings are limited by the caveat that all studies included in our systematic review and meta-analysis were assessed as having unclear or high risk of bias. However, despite these limitations our findings suggest that in the absence of additional evidence bisphosphonates should preferentially be used as first-line osteoporosis treatment for men given evidence for their efficacy in reducing vertebral fracture risk, and possibly nonvertebral fracture risk as well. Our findings for the evidence of bisphosphonate efficacy to reduce fracture risk for men apply to individuals who have osteoporosis or low BMD by DXA criteria, or who have had a prior osteoporotic fracture, as the studies included in this systematic review and meta-analysis included participants who met these criteria. Further studies are needed to evaluate the efficacy of osteoporosis treatment for men with risk factors for fracture who are not known to have osteoporosis or low BMD by DXA criteria or prior osteoporotic fracture.

Our study highlights the need for additional high-quality, sufficiently powered for fracture outcomes randomized clinical studies of osteoporosis treatment efficacy for men, particularly for nonvertebral fracture outcomes, and for non-bisphosphonate treatment options such as denosumab or teriparatide. Our findings also highlight the lack of active comparator randomized clinical trials of osteoporosis treatment for men; additional studies of osteoporosis treatment for men with active comparators would help clarify the relative efficacy of different treatment options for reducing fracture risk. Additionally, our findings reveal the need for greater diversity of participants in clinical trials of osteoporosis treatment for men; most included studies in our systematic review had largely white study participant populations. Finally, no study included in our systematic review had a duration greater than 3 years, and thus the efficacy of longer osteoporosis treatment durations to reduce fracture risk for men is unknown – additional studies with longer durations would be helpful to evaluate the impact of osteoporosis treatment for longer durations than 3 years on fracture risk for men, similar to longer duration osteoporosis treatment studies that have demonstrated fracture risk reduction benefit for women.³⁹

Our study has several notable strengths. Our study is the most comprehensive systematic review and meta-analysis of randomized clinical trials of osteoporosis treatment efficacy for reducing fracture risk for men to date. A prior systematic review and meta-analysis on the topic of osteoporosis treatment efficacy for men by Schwarz et al. published in 2011 included only five studies that reported fracture outcomes, and concluded that the evidence for osteoporosis treatment for men to reduce fracture risk was inconclusive.⁴⁰ Our systematic review and meta-analysis, which included 22 randomized clinical studies of osteoporosis treatment for men that reported fracture outcomes, finds evidence for the efficacy of bisphosphonate medications for reducing risk of vertebral fractures and possibly nonvertebral fractures for men. Another strength of our study was the assessment of risk of bias of individual randomized clinical trials included in our systematic review using criteria recommended by the Cochrane Collaboration.

In conclusion, our findings support the use of bisphosphonates to reduce vertebral and possibly nonvertebral fracture risk for men with osteoporosis. Further studies are needed to evaluate the efficacy of bisphosphonates for reducing nonvertebral fracture risk for men, and to evaluate the efficacy of non-bisphosphonate treatment options such as denosumab or teriparatide to reduce vertebral and nonvertebral fracture risk for men.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding Sources: Dr. Nayak was supported by grant R01AR060809 from the National Institute of Arthritis and Musculoskeletal and Skin Diseases and a Swedish Foundation Philanthropy at Work award; Dr. Greenspan was supported by NIH grant P30AG024827 from the National Institute on Aging.

Dr. Greenspan is on the scientific advisory board for Merck & Co.

Sponsor's Role: The sponsors had no role in the design, methods, data collection, analysis, or preparation of the paper.

Additional Contributions: The authors thank Eric S. Orwoll, MD and Arthur C. Santora II, MD, PhD, for providing requested data.

Appendix

Conflict of Interest Checklist:

Elements of Financial/Personal Conflicts	SN		SLG	
	Yes	No	Yes	No
Employment or Affiliation		X		X
Grants/Funds		X		X
Honoraria		X		X

Elements of Financial/Personal Conflicts	SN		SLG	
	Yes	No	Yes	No
Speaker Forum		X		X
Consultant		X		X
Stocks		X		X
Royalties		X		X
Expert Testimony		X		X
Board Member		X	X	
Patents		X		X
Personal Relationship		X		X

For “yes”, provide a brief explanation: Dr. Greenspan is on the scientific advisory board for Merck & Co.

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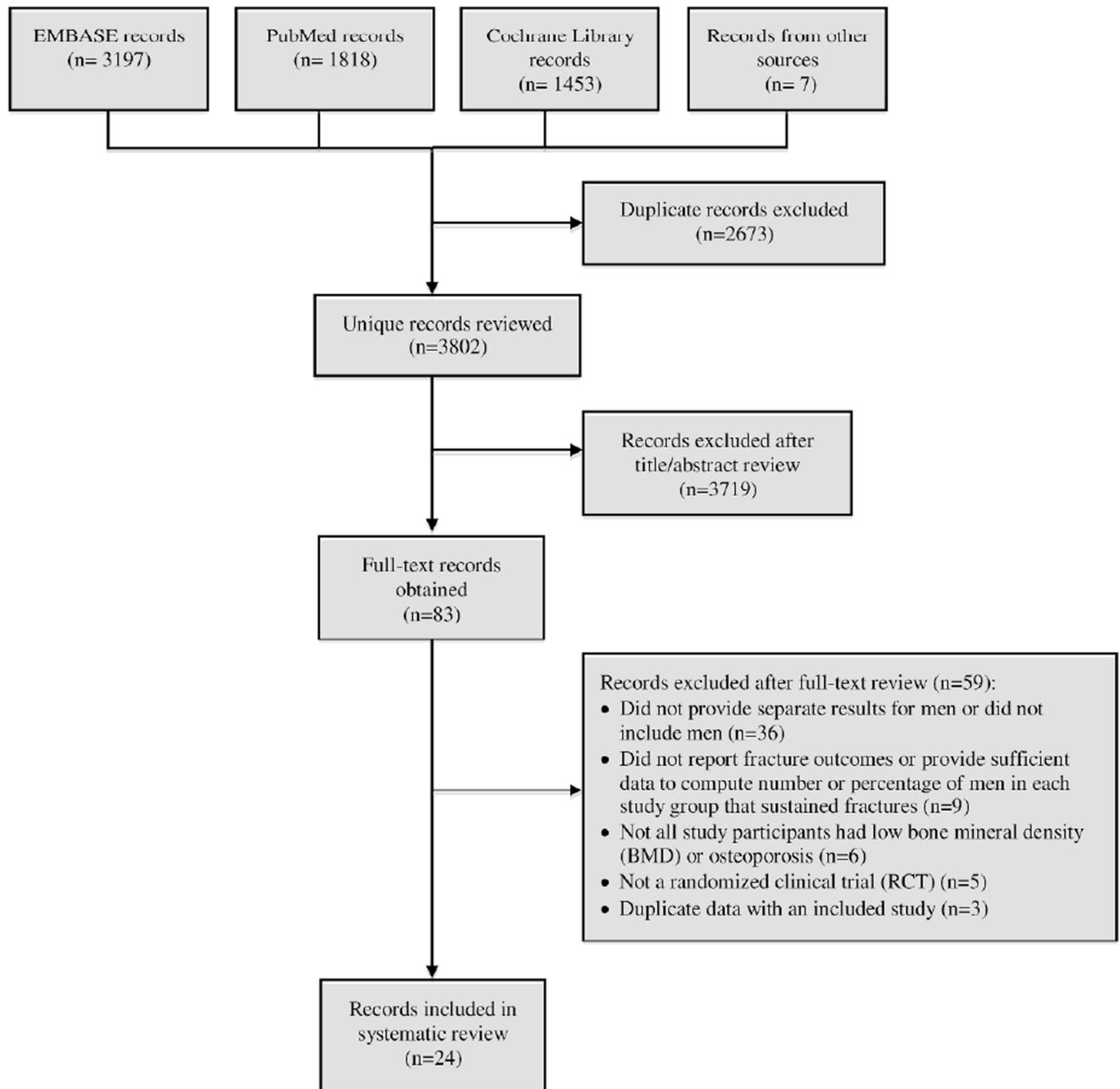


Figure 1.
Flow diagram of literature search and study selection

Table 1

Meta-Analysis Results

Treatment	Included studies	Summary estimates of fracture relative risk (RR) from meta-analysis ^a (95% CI; I ² value ^b)
Alendronate	Orwoll 2000 ¹⁶ , ^c & Ringe 2004 ¹⁸	Vertebral fractures: 0.328 (0.155–0.692; I ² =29.4%); Nonvertebral fractures: 0.751 (0.352–1.602); I ² =0.0%
Calcitonin	Toth 2005 ²⁰ & Trovas 2002 ²¹	Vertebral fractures: 0.272 (0.046–1.608; I ² =0.0%)
Denosumab	Nakamura 2013 ²³ & Orwoll 2012 ²⁴	Vertebral fractures: 0.256 (0.029–2.238; I ² =0.0%)
Risedronate	Boonen 2009 ²⁸ & Ringe 2009 ³⁰	Vertebral fractures: 0.428 (0.245–0.746; I ² =27.4%)
Zoledronic acid	Boonen 2011 ³⁵ & Boonen 2012 ³⁶	Clinical fractures: 0.742 (0.436–1.263; I ² =0.0%)
Any bisphosphonate (alendronate, ibandronate, risedronate, or zoledronic acid)	Boonen 2009 ²⁸ , Boonen 2012 ³⁶ , Orwoll 2000 ¹⁶ , Orwoll 2010 ²⁵ , Ringe 2004 ¹⁸ , Ringe 2009 ³⁰ (vertebral fractures meta-analysis); Boonen 2012 ³⁶ , Orwoll 2000 ¹⁶ , Orwoll 2010 ²⁵ (clinical vertebral fractures meta-analysis) ^d ; Boonen 2012 ³⁶ , Orwoll 2000 ¹⁶ , Ringe 2004 ¹⁸ , Ringe 2009 ³⁰ (nonvertebral fractures meta-analysis); Boonen 2009 ²⁸ , Boonen 2011 ³⁵ , Boonen 2012 ³⁶ , Orwoll 2010 ²⁵ (clinical fractures meta-analysis)	Vertebral fractures: 0.368 (0.252–0.537; I ² =0.0%); Vertebral fractures (clinical only): 0.398 (0.105–1.506; I ² =0.0%); Nonvertebral fractures: 0.604 (0.404–0.904; I ² =0.0%); Clinical fractures: 0.791 (0.500–1.253; I ² =0.0%)

^aFixed-effects meta-analysis using Mantel-Haenszel method

^bPercentage of variation across studies attributable to heterogeneity

^cFor Orwoll 2000 study, vertebral fracture results reported when using quantitative assessment method were used for meta-analysis

^dShimon 2005 study excluded from analysis due to no fracture events in intervention or comparator groups