Annals of Internal Medicine | Review

Systematic Review: Comparative Effectiveness of Treatments to Prevent Fractures in Men and Women with Low Bone Density or Osteoporosis

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Background: Although several agents are available to treat osteoporosis, the relative efficacy and toxicity of these agents when used to prevent fractures has not been well described.

Purpose: To compare the benefits in fracture reduction and the harms from adverse events of various therapies for osteoporosis.

Data Sources: MEDLINE (1966 to November 2007) and other selected databases were searched for English-language studies.

Study Selection: For the efficacy analysis, investigators selected studies that reported the rate of or risk for fractures. For the adverse event analysis, they selected studies that reported the relationship between an agent and cardiovascular, thromboembolic, or upper gastrointestinal events; malignant conditions; and osteonecrosis.

Data Extraction: Using a standardized protocol, investigators abstracted data on fractures and adverse events, agents and comparators, study design, and variables of methodological quality.

Data Synthesis: Good evidence suggests that alendronate, etidronate, ibandronate, risedronate, zoledronic acid, estrogen, parathyroid hormone (1-34), and raloxifene prevent vertebral fractures more than placebo; the evidence for calcitonin was fair. Good evidence suggests that alendronate, risedronate, and estrogen prevent hip fractures more than placebo; the evidence for zoledronic acid was fair. The effects of vitamin D varied with dose, analogue, and study population for both vertebral and hip fractures. Raloxifene, estrogen, and estrogen–progestin increased the risk for thromboembolic events, and etidronate increased the risk for esophageal ulcerations and gastrointestinal perforations, ulcerations, and bleeding.

Limitation: Few studies have directly compared different agents or classes of agents used to treat osteoporosis.

Conclusion: Although good evidence suggests that many agents are effective in preventing osteoporotic fractures, the data are insufficient to determine the relative efficacy or safety of these agents.

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Osteoporosis is a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture (1). Approximately 44 million people in the United States are affected by osteoporosis and low bone mass (2). The clinical complications include fractures, disability, and chronic pain. About 54% of women age 50 years or older will have an osteoporotic fracture during their lifetime (3). Furthermore, approximately 4% of patients older than 50 years of age who have a hip fracture die while in the hospital and 24% die within 1 year after the hip fracture (4).

The economic burden of osteoporosis is large and growing. Most estimates are based on the cost of fracture alone: A 1995 estimate of costs incurred by osteoporotic fractures in the United States was $13.8 billion (5). A 2003 review estimated the total costs in the United States at $17 billion (6). Although the bulk of these costs were incurred by retired individuals older than age 65 years, direct costs and work loss are significant among employed postmenopausal women (7). The increasing prevalence and cost of osteoporosis have heightened interest in the efficacy and safety of the many agents available to treat the loss of bone mineral associated with osteoporosis.

This systematic review, developed under the Agency for Healthcare Research and Quality (AHRQ) Effective Health Care Program, describes the benefits in fracture reduction and the harms from adverse events among and within the various classes of pharmacotherapies for osteoporosis. The agents evaluated were bisphosphonates (alendronate, etidronate, ibandronate, pamidronate, risedronate, and zoledronic acid), calcitonin, estrogen, teriparatide, selective estrogen receptor modulators (raloxifene and tamoxifen), testosterone, and vitamins (vitamin D) and minerals (calcium).

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Context

Sorting through the proven benefits and harms of the agents available for treating osteoporosis is difficult.

Contribution

This systematic review of 76 randomized trials and 24 meta-analyses found good evidence that multiple agents, including alendronate, zoledronic acid, and estrogen, prevented vertebral and hip fractures more than placebo. Harms included increased risk for thromboembolic events with raloxifene, estrogen, and estrogen–progestin and increased gastrointestinal symptoms with bisphosphonates. No large trials directly compared 2 or more agents and established superiority of any agent.

Implication

Available data insufficiently characterize the benefits and harms of various therapies for osteoporosis relative to one another.

—The Editors

METHODS

We followed a standardized protocol for the review. The full technical report (8) provides detailed methods, evidence tables, and risk estimates for individual studies. The full report also enumerates studies included in the meta-analyses described in this review.

Data Sources and Study Selection

We searched MEDLINE (1966 to December 2006), the *ACP Journal Club* database, the Cochrane Central Register of Controlled Trials (no date limits), the Cochrane Database of Systematic Reviews (no date limits), and the Web sites of the National Institute for Health and Clinical Excellence (no date limits) and Health Technology Assessment Programme (January 1998 to December 2006) for materials pertaining to the specified agents, limiting our searches to English-language publications and human studies. We first identified systematic reviews and meta-analyses of trials that reported pooled estimates of the effect of the agents on fracture risk. When such reviews were identified for specific agents, we truncated our searches for randomized trials to include only those published after the last search date used in the review or meta-analysis. We manually searched reference lists of all review articles obtained for any reports of original research not already identified, and we reviewed U.S. Food and Drug Administration (FDA) medical and statistical reviews, scientific information packets from pharmaceutical companies, and additional studies recommended by our technical expert panel and by stakeholders during a public review period. To supplement the information in systematic reviews on estrogen, we reviewed the Women's Health Initiative and Heart and Estrogen/progestin Replacement Study trials, as suggested by our technical expert panel. Finally, we conducted an additional search for large observational studies that reported any of the following adverse events: 1) cardiovascular events (myocardial infarction and stroke); 2) thromboembolic events (pulmonary embolism and venous thromboembolic events); 3) malignant conditions (breast cancer, colon cancer, lung cancer, and osteosarcoma); 4) upper gastrointestinal events (perforations, ulcers, bleeding, and esophageal ulcerations); and 5) osteonecrosis. The search was updated for this paper, but not for the full report, by searching MEDLINE (1 January 2007 to 10 November 2007) for large clinical trials that reported fracture outcomes for the specified agents.

For information on efficacy, we selected meta-analyses that reported pooled risk estimates for fracture and randomized trials that compared any of the agents with placebo or with each other and reported fracture outcomes. For information on harms, we selected systematic reviews, randomized trials, and large case–control or cohort studies with more than 1000 participants. We also reviewed cases of osteonecrosis at AHRQ's request.

Data Extraction and Study Quality

Two physicians independently abstracted data about study populations, interventions, follow-up, and outcome ascertainment by using a structured form. For each group in a randomized trial, a statistician extracted the sample size and number of persons who reported fractures. Two reviewers, under the supervision of the statistician, independently abstracted information about adverse events. Disagreements were resolved by the statistician or the principal investigator. Adverse events were recorded onto a spreadsheet that identified numbers of participants in each trial group and the description of the adverse event as listed in the original article. Each event was counted as if it represented a unique individual. Because an individual may have experienced more than 1 event within a category of adverse events (for example, both stroke and myocardial infarction), this assumption may have overestimated the number of people who had an adverse event in that category. If a trial report mentioned a particular type of adverse event but did not report data on it, we did not include the trial in that particular event's analysis. In other words, we did not assume an occurrence of zero events unless it was specifically reported as such. By taking this approach, we may have overestimated the number of patients for whom a particular adverse event was observed. We used predefined criteria to assess the quality of systematic reviews and randomized trials, based on internal and external validity assessment detailed in the QUOROM (Quality of Reporting of Meta-Analyses) statement (9), and items related to randomization, blinding, and accounting for withdrawals and dropouts (10, 11). Each element is detailed in appendices to the full report (8). For this review, we characterized the overall strength of evidence for estimating fracture risk as good, fair, or weak on the basis of the characteristics previously described, as well as the number

of studies, total number of participants across studies, whether fractures were a primary outcome, reproducibility of results across studies, and precision of the CIs surrounding the point estimates. Evidence was classified as good if the total sample size was greater than 1000, the results across all studies were consistent, and the studies were of high methodological quality. Evidence was classified as fair if results were inconsistent across the studies. The evidence was classified as weak if no studies assessed fracture as a primary outcome, the total sample size across studies was less than 500, and the CIs around the point estimates were wide and crossed null.

Data Synthesis and Statistical Analysis

Comparisons of interest were single agent versus placebo and single agent versus another agent for agents within the same class and across classes. We also compared estrogen–progestin versus placebo or single drugs. Studies that included either calcium or vitamin D in all study groups were classified as comparisons between the other agents in each group; for example, alendronate plus calcium versus risedronate plus calcium would be classified as alendronate versus risedronate.

In this review, we summarize data on vertebral, nonvertebral, and hip fractures; data on total, wrist, and humerus fractures are included in the full report (8). The number of people with at least 1 fracture was our primary outcome of interest. Because fractures rarely occurred and zero events were often observed in at least 1 treatment group, we calculated odds ratios (ORs) by using the Peto method (12). Trials with zero events in both groups have an undefined OR. Because fractures are rare events, the OR approximates the relative risk (RR) for fracture. We combined data from multiple study groups in an individual study to calculate a single OR for comparisons of interest. In these instances, the same outcome had been reported for each group, and the individuals in each group were unique. For example, to develop an OR for the risk for vertebral fractures regardless of dose, we combined the participants in the various dose groups and compared them with those in the placebo group. We conducted the meta-analysis by using StatXact PROCs (Cytel, Cambridge, Massachusetts) for SAS software (SAS Institute, Cary, North Carolina).

Recognizing that characteristics of the study population may affect risk for fracture, we defined risk groups to categorize the study populations included in each meta-analysis and randomized, controlled trial on the basis of the risk factors that could be abstracted from these studies (**Table 1**). Based primarily on bone mineral density (13), the expected lifetime risk for fracture in the high-, intermediate-, and low-risk groups would be approximately 33%, 21%, and less than 10% to 21%, respectively. The 10-year risks would range from at least 3% at age 50 years to 10% at age 70 years, at least 1% at age 50 years to 4% at age 70 years, and less than 1% at age 50 years to approximately 2% at age 70 years for the high-, intermediate-, and low-risk groups, respectively.

For the analyses of adverse events, we compared agent versus placebo and agent versus agent for agents within the same class and across classes. We compiled a list of all unique adverse events that were reported in any study, and a physician grouped them into clinically sensible categories and subcategories. For groups of events that occurred in 3 or more trials, we estimated the pooled OR and its associated 95% CI. Because many events were rare, we used exact conditional inference to perform the pooling rather than applying the usual asymptotic methods that assume normality.

Role of the Funding Source

Although AHRQ formulated the initial study questions, it did not participate in the literature search, determination of study eligibility criteria, data analysis, or interpretation. Staff from AHRQ reviewed and provided comments on the report from which this paper is derived.

RESULTS

We identified 2641 titles through various sources (**Figure 1**). After reviewing available titles and abstracts, we ordered 1835 articles and could not obtain 10 articles.

Table 1. **Risk Groups for Likelihood of Fracture***

High risk†
1) Transplant population
2) Study entry criteria require T-score ≤−2.5
3) Study entry criteria require ≥1 fracture
4) ≥50% population has ≥1 fracture at baseline
5) Clinically significant neuromuscular impairment

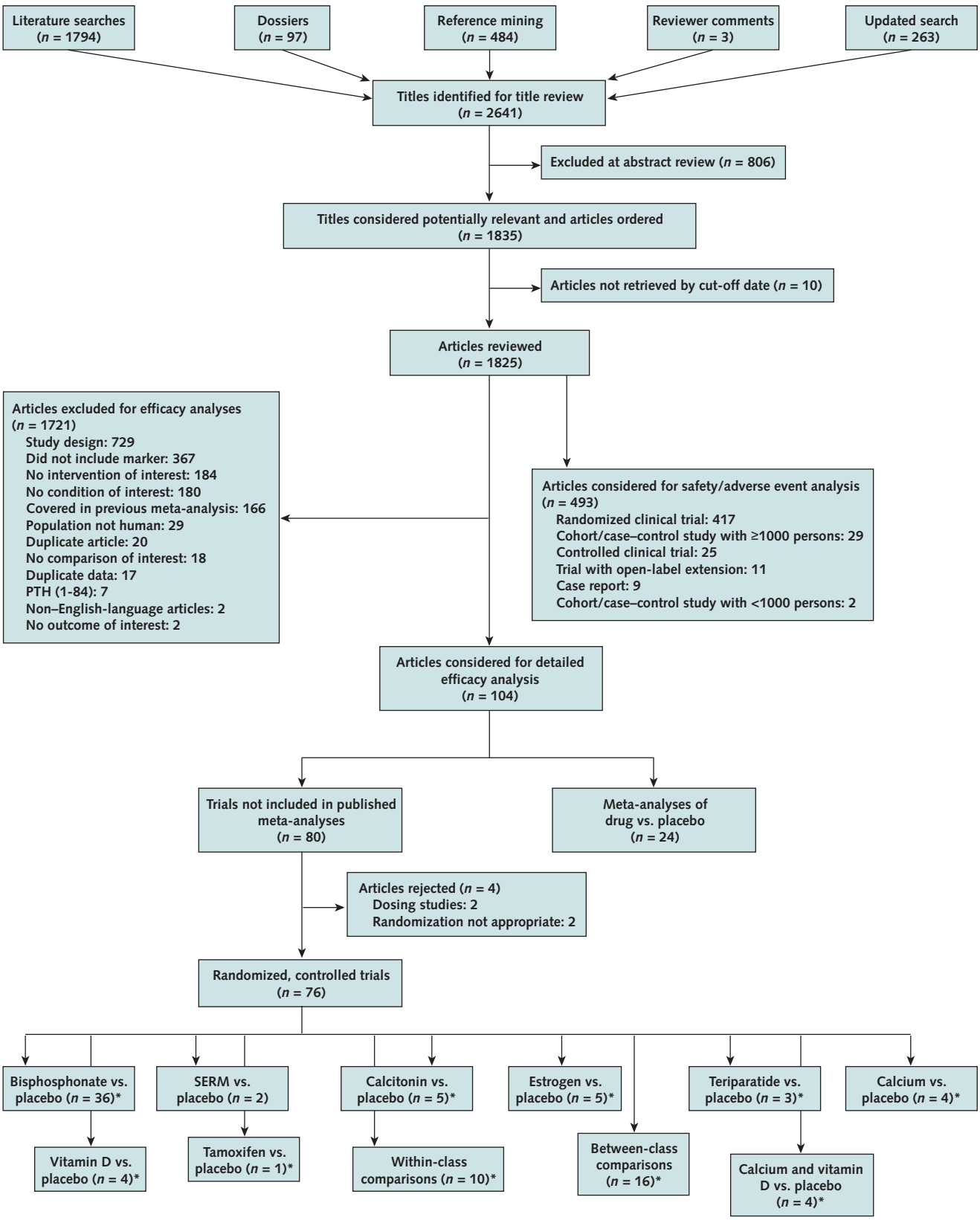
Intermediate risk‡
1) Study entry criteria require T-score ≤−1.5
2) 10%–49.99% of population has ≥1 fracture at baseline
3) Study population has chronic disease that is commonly treated with glucocorticoids
4) In the absence of data on BMD or fractures, mean age of population ≥62 years

Low risk§
1) Study entry criteria require T-score ≤0.0
2) <10% of population has BMD of 8 g/cm^2 at baseline
3) <10% of population has ≥1 fracture at baseline
4) In the absence of data on BMD or fracture, mean age of population <62 years

Unknown risk
BMD, fracture history, and age not reported as entry criteria or in baseline characteristics of population

* The expected lifetime risk for fracture was based primarily on BMD (13). BMD = bone mineral density.
† The expected lifetime risk for fracture for the high-risk group would be approximately 33%, and the 10-year risk would range from at least 3% at age 50 years to 10% at age 70 years.
‡ The expected lifetime risk for fracture for the intermediate-risk group would be approximately 21%, and the 10-year risk would range from at least 1% at age 50 years to 4% at age 70 years.
§ The expected lifetime risk for fracture for the low-risk group would range from <10% to approximately 21%, and the 10-year risk would range from <1% at age 50 years to approximately 2% at age 70 years.

Figure 1. **Study flow diagram.**



PTH = parathyroid hormone; SERM = selective estrogen receptor modulator. *Articles are not mutually exclusive.

Of the 1825 articles screened, we excluded 1721 from efficacy analyses for reasons detailed in **Figure 1**. Because comprehensive systematic reviews had recently been conducted for alendronate, risedronate, etidronate, raloxifene, calcitonin, parathyroid hormone (PTH), and estrogen, we did not reanalyze 166 articles on trials of these drugs. We included 76 randomized, controlled trials, 4 of which were identified in the updated search, and 24 meta-analyses in the efficacy analyses. Our analyses of adverse events included 493 articles, representing 417 randomized trials, 25 other controlled clinical trials, 11 open-label trials, 31 large observational studies, and 9 articles reporting cases of osteonecrosis among bisphosphonate users.

Comparative Benefits in Fracture Reduction

Drug versus Placebo Comparisons

For 9 of the 14 agents (alendronate, etidronate, risedronate, calcitonin, estrogen, PTH, raloxifene, calcium, and vitamin D), we identified 24 meta-analyses (14–38) and 35 additional randomized trials that were published after the meta-analyses (39–73) and described the effect of the agent compared with placebo on fracture incidence. For 4 of the 5 agents for which we did not identify meta-analyses (ibandronate, pamidronate, zoledronic acid, and tamoxifen), we identified 14 randomized trials (74–87) that described the effect on the risk for fracture compared with that of placebo. We found no studies that reported fracture rates for testosterone. For calcium plus vitamin D—the only agent combination evaluated for this report—we identified 3 randomized trials that evaluated the risk for fracture compared with that of placebo (39, 88, 89).

Table 2 summarizes the key findings from all studies. **Figures 2** to **4** display the risk for vertebral, nonvertebral, and hip fracture of the agents compared with placebo for high-risk populations for studies that provided information on risk groups. **Appendix Figures 1** to **3** (available at www.annals.org) display the risk for vertebral, nonvertebral, and hip fracture of the agents compared with placebo for populations not described as high risk in those studies. Data include pooled risk estimates from published meta-analyses, where available. The full report provides (8) complete details, including the calculated point estimates and CIs for all comparisons.

We found good evidence from more than 1 randomized trial or meta-analysis that alendronate, etidronate, ibandronate, risedronate, calcitonin, PTH (1-34), and raloxifene, compared with placebo, prevent vertebral fractures. Good evidence from multiple trials and meta-analyses also indicate that both alendronate and risedronate, compared with placebo, prevent nonvertebral and hip fractures. Two large randomized trials showed that zoledronic acid prevents vertebral and nonvertebral fractures in high-risk populations (85, 87). The risk for hip fracture was reduced in both trials, although the reduction was statistically significant in only 1 trial (85). A smaller trial was not powered to detect a fracture risk reduction with zoledronic acid (84). Although 1 large randomized trial detailed in a systematic review showed that PTH (1-34) prevents nonvertebral fractures (90), 2 smaller trials did not (69, 91).

Good evidence suggests that estrogen by itself is associated with a reduced incidence of vertebral (28, 92), nonvertebral (93), and hip fractures compared with placebo (92). Among 3 meta-analyses that assessed the effect of estrogen on the risk for vertebral fracture in postmenopausal women, the pooled sample size in 1 meta-analysis was too small to detect even large differences in fracture risk among groups (22). Of the remaining 2 meta-analyses, the one with the largest pooled sample size ($n = 6723$) showed that estrogen reduced fracture risk more than placebo (RR, 0.45 [95% CI, 0.45 to 0.98]) (28), and the other (29) demonstrated a reduction in risk that was not statistically significant (RR, 0.68 [CI, 0.41 to 1.07]).

A published meta-analysis (24) and several large randomized trials (39, 72, 73, 94) showed no statistically significant difference between calcium alone and placebo in preventing vertebral, nonvertebral, and hip fractures in postmenopausal women. The risk for vertebral fracture for calcium versus placebo among all participants ranged from 0.70 (CI, 0.42 to 1.14) in a trial with 1471 participants (73) to 2.77 (CI, 0.39 to 19.65) in a trial with 2643 participants (39). The magnitude of risk reduction for nonvertebral and hip fractures was similar. In 1 trial that performed a preplanned, per-protocol analysis of the effect of adherence, the risk for vertebral fractures for calcium versus placebo was lower among the 830 participants (56.8%) who consumed 80% of their study tablets than among the participants who did not, with the risk reduction reaching statistical significance for nonvertebral fracture (RR, 0.63 [CI, 0.41 to 0.96]) (72).

The risks for vertebral, nonvertebral, and hip fractures were not significantly reduced by standard vitamin D (vitamin D_2, vitamin D_3, or 25-hydroxyvitamin D) versus placebo in 4 meta-analyses (pooled RR range, 0.33 [CI, 0.01 to 8.05] to 1.13 [CI. 0.05 to 2.55]) (22, 25, 26, 33). Likewise, risk for vertebral fracture (RR, 1.17 [CI, 0.71 to 1.95]) or hip fracture (RR, 1.14 [CI, 0.75 to 1.75]) was not significantly reduced for vitamin D_3 (800 IU/d) versus placebo in 1 large trial performed after the 4 meta-analyses (39). In contrast to these findings, a fifth meta-analysis reported a significantly reduced pooled risk for nonvertebral fractures (RR, 0.77 [CI, 0.68 to 0.87]) and hip fractures (RR, 0.74 [CI, 0.61 to 0.88]) for vitamin D_2 or D_3 (700 to 800 IU/d) compared with placebo. For vitamin D analogues (1,25-hydroxyvitamin D and 1-hydroxyvitamin D), the risk for vertebral fracture was significantly reduced compared with placebo (pooled RR range, 0.52 [CI, 0.41 to 0.67] to 0.64 [CI, 0.44 to 0.92]) in 3 meta-analyses (25, 33, 36). For nonvertebral and hip fractures, the pooled risk for vitamin D analogues compared with placebo ranged from 0.16 (CI, 0.04 to 0.69) to 0.87 (CI, 0.29 to 2.59), with vitamin D analogues showing significant decreases in risk in 4 of 7 reported comparisons.

Table 2. **Effect of Agents on Fracture Risk Reduction Compared with Placebo, by Agent***

Agent	Vertebral Fracture			Nonvertebral Fracture		
	Risk	Meta-analyses/RCTs (Total Participants), *n/n (n)*†	Strength of Evidence	Risk	Meta-analyses/RCTs (Total Participants), *n/n (n)*†	Strength of Evidence
Bisphosphonates						
Alendronate	Reduced	3/3 (11 834)	Good	Reduced	5/1 (8630)	Good
Etidronate	Reduced	2/5 (1555)	Good	No change	2/1 (895)	Fair
Ibandronate	Reduced	0/3 (4919)	Good	No change	0/1 (2929)	Good
Pamidronate	No change	0/6 (327)	Weak	No change	0/2 (109)	Weak
Risidronate	Reduced	3/4 (3785)	Good	Reduced	3/4 (14 147)	Good
Zoledronic acid	Reduced	0/2 (7382)	Good	Reduced	0/2 (7627)	Good
Calcitonin	Reduced	3/5 (2127)	Fair	No change	2/0 (1744)	Good
Estrogen	Reduced	3/5 (34 423)	Good	Reduced	3/1 (8793)	Good
PTH (1-34)	Reduced	1/2 (1972)‡	Good	Reduced	1/2 (2464)‡	Fair
Selective estrogen receptor modulators						
Raloxifene	Reduced	3/2 (18 232)	Good	No change	1/0 (6828)‡	Good
Tamoxifen	No change	0/1 (13 135)	Good	NA	0/0	NA
Testosterone	NA	0/0	NA	NA	0/0	NA
Vitamins and minerals						
Calcium	No change	1/4 (5751)	Good	No change	1/1 (1679)	Good
Vitamin D	Reduced/no change§	5/2 (8505)	Good	Reduced/no change§	6/0 (9820)	Good

* NA = not applicable; PTH = parathyroid hormone; RCT = randomized, controlled trial.
† The RCTs were published after or were not included in the meta-analyses. Total participants were estimated by summing the number of participants in RCTs that were not included in meta-analyses with that from the largest meta-analysis. Exact numbers of participants in each meta-analysis and RCT can be viewed in the full report (8).
‡ Meta-analysis included 1 study for this comparison.
§ Effect varies by preparation and dose; see text.

Within- and Between-Class Comparisons

We identified 9 randomized trials that compared different bisphosphonates (42, 95–102) and 1 randomized trial that compared different selective estrogen receptor modulators (103). Sixteen randomized trials included head-to-head comparisons of agents from different classes (39–41, 49–51, 68, 100, 101, 104–110). Most were designed to compare changes in intermediate outcomes, such as bone mineral density and changes in markers of bone turnover, but were too small and too short to detect clinically important differences in fracture incidence between groups. We identified only 2 head-to-head trials designed to compare fracture outcomes. One found no difference between risedronate and etidronate for the prevention of vertebral fractures (RR, 0.66 [CI, 0.32 to 1.36]) (95). The other, which compared raloxifene and alendronate (108), did not recruit enough participants to test differences in fracture outcomes. This study found no difference in the incidence of hip, wrist, or total vertebral fractures, but it was not powered to do so. However, a significant difference in moderate-to-severe vertebral fractures (3 of 713 alendronate recipients with fractures, 0 of 699 raloxifene recipients with fractures; $P = 0.04$) was found in a prespecified analysis.

Thus, the head-to-head studies had 3 key findings: 1) within the bisphosphonate class, superiority for prevention of fractures has not been shown for any agent; 2) superiority for the prevention of vertebral fractures has not been demonstrated for bisphosphonates compared with calcitonin, calcium, or raloxifene; and 3) on the basis of 6 inadequately powered randomized trials, fracture prevention did not differ between bisphosphonates and estrogen.

Effects in Different Risk Groups

Of the 24 meta-analyses that we reviewed, 6 evaluated the effect of therapy for groups at varying risk for fracture (14, 16, 18, 22, 26, 38). The criteria used to define risk groups in these studies overlapped but were not identical. In addition, because the risk groups were not always identical to those that we defined for this report, we used expert judgment to match each with one of our risk groups.

Low-Risk Populations

Four meta-analyses (14, 16, 22, 38) included a group categorized as low risk according to our criteria, which corresponds approximately to a 10-year risk for fracture of up to 2% and a lifetime risk of up to 21%. Summary estimates from 2 of these analyses suggested possible reductions in the risk for vertebral fracture (RR, 0.45 [CI, 0.06 to 3.15]) and nonvertebral fracture (RR, 0.79 [CI, 0.28 to 2.24]) with alendronate versus placebo (14) and a decrease in the risk for vertebral fracture with etidronate (RR, 0.61 [CI, 0.29 to 1.26]) versus placebo (16), but the width of the 95% CIs suggests that these agents may in fact have had no effect on or increased the risk for fracture.

For estrogen compared with placebo, 1 meta-analysis reported insignificant results with very wide confidence

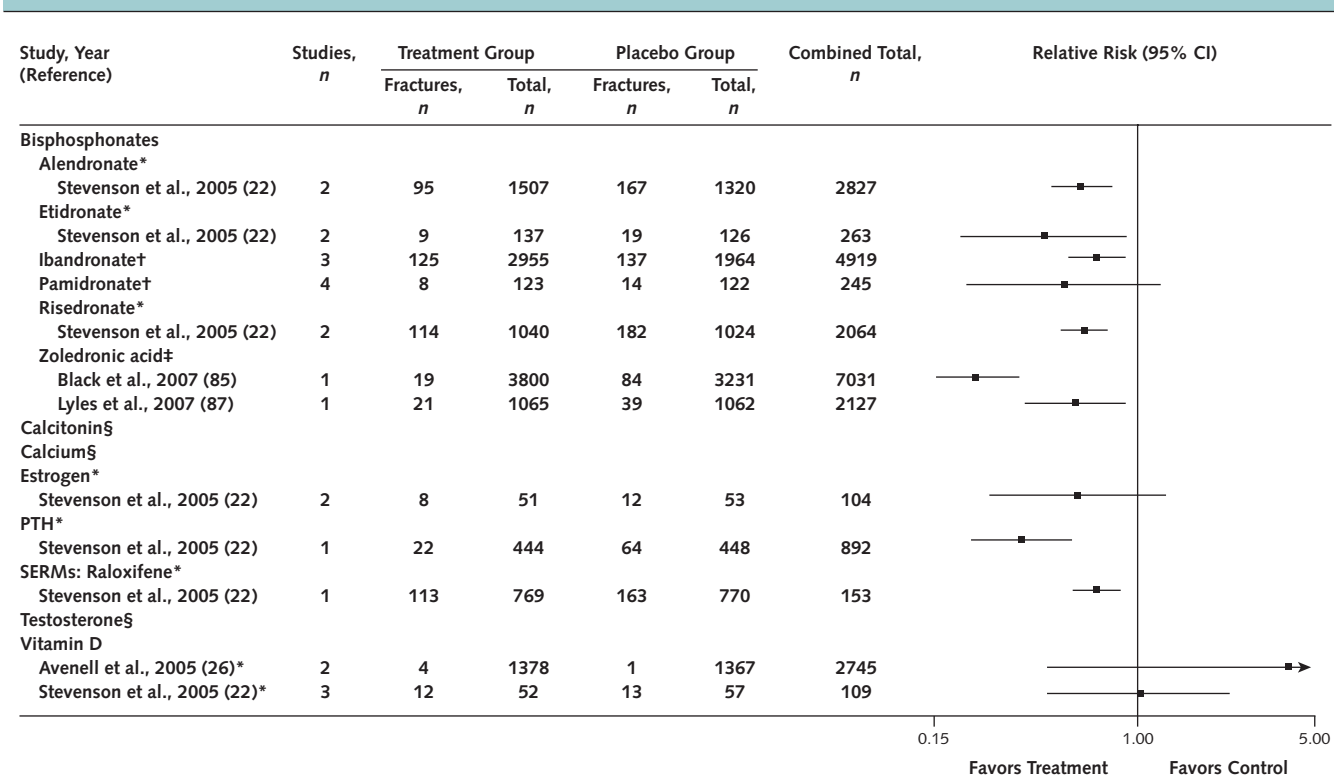
Table 2—Continued

Hip Fracture		
Risk	**Meta-analyses/RCTs (Total Participants), *n/n (n)*†**	**Strength of Evidence**
Reduced	5/1 (12 068)	Good
No change	3/1 (662)	Fair
NA	0/0	NA
No change	0/1 (59)	Weak
Reduced	2/3 (8957)	Good
Reduced	0/2 (7234)	Fair
NA	0/0	NA
Reduced	1/1 (31 528)	Good
No change	1/0 (NR)‡	Weak
No change	1/0 (6828)‡	Good
No change	0/1 (13 135)	Good
NA	0/0	NA
No change	0/3 (5597)	Good
Reduced/no change§	2/2 (21 391)	Good

bounds for vertebral fracture risk (RR, 2.05 [CI, 0.71 to 5.97]) (22). This study and another meta-analysis suggested that estrogen reduced nonvertebral fractures more than placebo (RR, 0.86 [CI, 0.72 to 1.02] vs. 0.67 [CI, 0.46 to 0.98]) (22, 38). The first meta-analysis also found that the selective estrogen receptor modulator raloxifene reduced the risk for vertebral fractures more than placebo (RR, 0.53 [CI, 0.35 to 0.79]) and that vitamin D possibly reduced vertebral fractures more than placebo (RR, 0.86 [CI, 0.72 to 1.02]) (22). The Women's Health Initiative found a nonsignificant difference in hip fracture risk (hazard ratio, 0.17 [CI, 0.02 to 1.43]) among women at relatively low risk (based on age) who were taking estrogen (66, 92). When women were assigned a composite risk score and were stratified by those scores, women in the lowest risk group had a reduction in total fracture risk (hazard ratio, 0.82 [nominal CI, 0.66 to 1.02]) (66).

Two randomized trials in low-risk groups, 1 on the use of calcitonin and 1 on the use of selective estrogen receptor modulators, were completed after publication of the 2 meta-analyses just described. In the first trial, none of 49 calcitonin recipients had fractures at 24 months, compared with 2 of 52 placebo recipients (63). In the second trial, 19 747 postmenopausal women with increased risk for breast cancer (but not selected for fracture risk) were assigned to receive raloxifene or tamoxifen. After 60 months, the proportion of fractures was similar for the 2 groups (104 of 9726 raloxifene recipients with fractures and 96 of

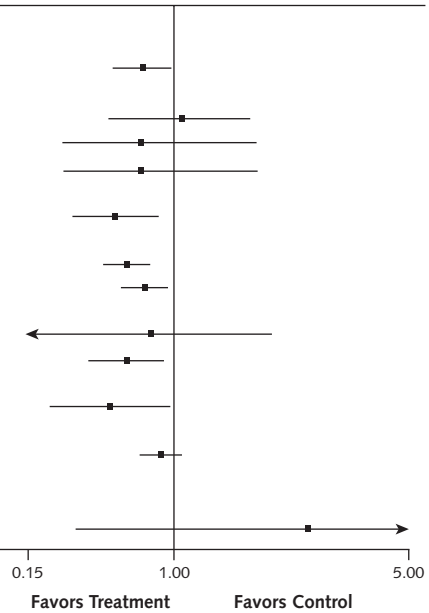
Figure 2. **Risk for vertebral fractures relative to placebo for participants who are at high risk for fracture, by agent.**



PTH = parathyroid hormone; SERM = selective estrogen receptor modulator. *Pooled risk estimate from cited meta-analysis or systematic review. †Pooled risk estimate calculated by authors; restricted to studies with >12 months of follow-up. ‡Risk estimate calculated from cited individual studies. §Insufficient data to calculate risk.

Figure 3. **Risk for nonvertebral fractures relative to placebo for participants who are at high risk for fracture, by agent.**

Study, Year (Reference)	Studies, *n*	Treatment Group		Placebo Group		Combined Total, *n*
		Fractures, *n*	Total, *n*	Fractures, *n*	Total, *n*	
Bisphosphonates						
Alendronate*						
Stevenson et al., 2005 (22)	2	167	1619	186	1402	3021
Etidronate*						
Stevenson et al., 2005 (22)	4	29	205	28	205	410
Ibandronate†	1	176	1954	89	975	2929
Pamidronate†	2	4	50	7	59	109
Risedronate*						
Stevenson et al., 2005 (22)	2	69	1218	103	1221	2439
Zoledronic acid‡						
Black et al., 2007 (85)	1	292	3650	388	3626	7276
Lyles et al., 2007 (87)	1	79	1065	107	1062	2127
Estrogen*						
Stevenson et al., 2005 (22)	2	2	43	3	43	86
Torgerson and Bell-Syer, 2001 (38)	8	NR	NR	NR	NR	NR
PTH*						
Stevenson et al., 2005 (22)	1	34	541	53	544	1085
SERMs: Raloxifene*						
Stevenson et al., 2005 (22)	1	437	4536	240	2292	6828
Testosterone§						
Vitamin D*						
Stevenson et al., 2005 (22)	1	5	101	12	112	213



NR = not reported; PTH = parathyroid hormone; SERM = selective estrogen receptor modulator. *Pooled risk estimate from cited meta-analysis or systematic review. †Pooled risk estimate calculated by authors; restricted to studies with >12 months of follow-up. ‡Risk estimate calculated from cited individual studies. §Insufficient data to calculate risk.

9745 tamoxifen recipients with fractures; RR, 1.09 [CI, 0.82 to 1.44]) (103).

Specific Patient Populations

Men. Few studies assessed the effect of agents to reduce fracture risk among men. Among 9 studies that included men (39, 50, 59–62, 64, 70, 111), 2 demonstrated a reduction in fracture risk: 1 for hip fractures with risedronate (RR, 0.25 [CI, 0.08 to 0.78]) (60) and 1 for vertebral fractures with calcitonin (RR, 0.09 [CI, 0.01 to 0.96]) (64). An additional study found a reduced risk for total fractures (RR, 0.16 [CI, 0.04 to 0.65]) and a possible reduced risk for vertebral fractures (OR, 0.44 [CI, 0.18 to 1.09]) with teriparatide (70). Among the remaining studies, only 1 had a sufficient sample size to assess even a large effect of agents on fracture (39). In the study, which included 672 men and 3809 women, calcium did not decrease the risk for fractures compared with placebo (331 [12.6%] of 2617 vs. 367 [13.7%] of 2675 participants with fractures; hazard ratio, 0.94 [CI, 0.81 to 1.09]). Subgroup analyses found no difference in risk between men and women (hazard ratio, 1.04 [CI, 0.57 to 1.90]).

Patients at Increased Risk for Falls. We found 7 studies that involved patients at increased risk for falling. These included patients with stroke and hemiplegia (55, 60, 112), Alzheimer disease (54), a recent hip fracture (47, 87), or Parkinson disease (46). A reduced risk for vertebral fractures was reported for zoledronic acid compared with placebo among participants who had undergone repair of a hip fracture (hazard ratio, 0.54 [CI, 0.32 to 0.92]) (87). The risk for nonvertebral fractures was also reduced for zoledronic acid versus placebo in this study population (hazard ratio, 0.73 [CI, 0.55 to 0.98]) (87). Nonvertebral fractures were reduced for risedronate compared with placebo among persons with Alzheimer disease (RR, 0.29 [CI, 0.15 to 0.57]) (54). Risk for an additional hip fracture among patients with a recent hip fracture was reduced, although not significantly, for zoledronic acid versus placebo in 1 study (hazard ratio, 0.70 [CI, 0.41 to 1.19]) (87). In another study, no fractures were detected for patients treated with either etidronate or placebo (47). Compared with placebo, risedronate reduced hip fractures in patients with Alzheimer disease (RR, 0.29 [CI, 0.13 to 0.66]) (54) and in patients with stroke and hemiparesis (RR, 0.22 [CI, 0.05 to 0.88] and 0.25 [CI, 0.08 to 0.78]) (55, 60). Compared with placebo, alendronate reduced hip fractures in patients with Parkinson disease (RR, 0.30 [CI, 0.12 to 0.78]) (46), as did vitamin D in patients with stroke and hemiparesis (RR, 0.12 [CI, 0.02 to 0.90]).

Patients with Renal Insufficiency. We identified 1 trial on the efficacy of alendronate for fracture prevention in patients with renal insufficiency compared with those with-

out renal insufficiency. In a retrospective analysis of the Fracture Intervention Trial (113), treatment with alendronate reduced the risk for clinical fractures to a similar degree in patients with and without reduced renal function (RR, 0.78 [CI, 0.51 to 1.21] vs. 0.80 [CI, 0.70 to 0.93]; P for interaction = 0.89). Treatment with alendronate reduced the risk for spine fractures to a similar degree in patients with and without reduced renal function (RR, 0.72 [CI, 0.31 to 1.70] vs. 0.50 [CI, 0.32 to 0.76]; P for interaction = 0.44).

Patients with Long-Term Glucocorticoid Use. We identified 1 systematic review (114) and 6 randomized trials published after it (50, 52, 109, 115–117) that evaluated the effect of bisphosphonates on fracture incidence among patients treated with glucocorticoids. The systematic review identified 9 trials (118–126) published before 1999 that reported fracture data. Of the 6 included trials (118–123) that compared fracture risk between treatment and placebo groups, 3 showed possible rate reductions in vertebral fracture with treatment (118, 120, 121) and 1 demonstrated a decrease of approximately 10% in vertebral fractures among patients treated with risedronate versus a control group (121).

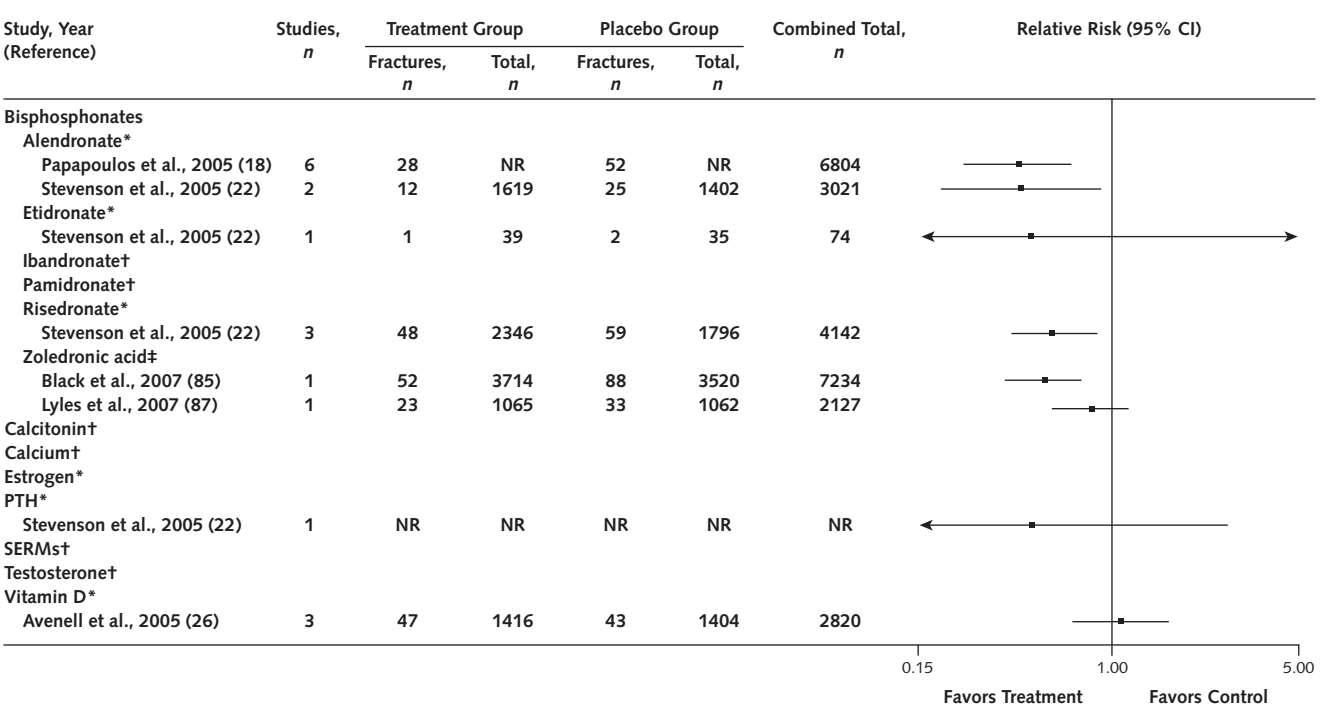
Among the 6 randomized trials published after the systematic review, 3 found that bisphosphonates reduced fracture rate more than placebo (115–117). One trial of risedronate demonstrated a statistically significant reduction in the absolute risk and RR for incident radiographic vertebral fractures (11% and 70%, respectively) after 1 year (117). The study included data from a trial (121) that was included in the systematic review described in the previous paragraph. Another randomized, controlled trial (116) demonstrated a significant reduction in the risk for incident radiographic vertebral fractures for alendronate compared with placebo (0.7% vs. 6.8%; $P < 0.05$). The third trial found a significant (70%) reduction in the incidence of vertebral fractures for risedronate compared with placebo (115). The remaining 3 trials reported no significant difference in fracture risk between etidronate (50, 52) or calcium (50) and placebo, between calcium and etidronate (50), and between calcium and pamidronate (109).

A meta-analysis (17) that pooled the results of 4 trials to assess the effect of calcitonin compared with placebo in preventing and treating glucocorticoid-induced osteoporosis found no significant effect for vertebral fractures (256 patients; OR, 0.71 [CI, 0.26 to 1.89]) or nonvertebral fractures (208 patients; OR, 0.52 [CI, 0.14 to 1.96]).

Short- and Long-Term Harms (Adverse Effects) of Agents

We assessed adverse events by the system affected. Key findings are summarized in the **Appendix Table** (available at www.annals.org).

Figure 4. **Risk for hip fractures relative to placebo for participants who are at high risk for fracture, by agent.**



NR = not reported; PTH = parathyroid hormone; SERM = selective estrogen receptor modulator. *Pooled risk estimate from cited meta-analysis or systematic review. †Insufficient data to calculate risk. ‡Risk estimate calculated from cited individual studies.

Cardiovascular

Across many randomized trials, we found no clinically important differences in the rates of serious cardiac events when calcium, vitamin D, calcitonin, or PTH was compared with placebo. One placebo-controlled trial reported an increased risk for serious atrial fibrillation with zoledronic acid versus placebo (1.3% vs. 0.5% [93 of 3876 vs. 144 of 3889 participants with atrial fibrillation]; $P < 0.001$) (85). However, another large trial did not (1.1% vs. 1.3%; $P = 0.84$) (87). Another placebo-controlled trial suggested a possible increased risk for atrial fibrillation with alendronate (absolute risk, 128 of 3236 vs. 102 of 3223 participants with atrial fibrillation; OR, 1.26 [CI, 0.96 to 1.66]) (127).

The pooled odds of a cerebrovascular accident from 3 randomized trials was increased with estrogen compared with placebo (absolute risk, 185 of 6546 vs. 144 of 7226 participants with cerebrovascular accident; OR, 1.34 [CI, 1.07 to 1.68]) (92, 128, 129). Participants treated with combined estrogen–progestin in 2 studies had higher pooled odds of reported stroke than did participants who received placebo (OR, 1.28 [CI, 1.05 to 1.57]) (67, 130).

We pooled the findings of 2 studies on the risk for selective estrogen receptor modulators for pulmonary embolism. Compared with placebo, raloxifene increased the risk for pulmonary embolism (absolute risk, 24 of 5153 vs. 2 of 2600 participants with pulmonary embolism; OR, 6.26 [CI, 1.55 to 54.80]) (131, 132).

Pooled findings from 7 studies showed that raloxifene increased the risk for thromboembolic events (absolute risk, 167 of 6878 vs. 41 of 3667 participants with thromboembolic events; OR, 2.08 [CI, 1.47 to 3.02]) (131, 133–138) and mild cardiac events (including chest pain, palpitations, tachycardia, and vasodilatation) (6 trials pooled) (absolute risk, 86 of 1658 vs. 39 of 1028 participants with mild cardiac events; OR, 1.53 [CI, 1.01 to 2.35]) (135, 136, 138–141). Pooled findings from 4 studies showed an increased risk for thromboembolic events for estrogen compared with placebo (absolute risk, 105 of 6639 vs. 79 of 7139 participants with thromboembolic events; OR, 1.36 [CI, 1.01 to 1.86]) (40, 92, 128, 129). Similar results were obtained when the findings from 3 trials of estrogen–progestin were pooled (OR, 2.27 [CI, 1.72 to 3.02]) (66, 130, 142).

Gastrointestinal

Trials of all bisphosphonates, except zoledronic acid, reported esophageal ulcerations; however, only 1 trial found a significantly higher risk with etidronate than with placebo (absolute risk, 128 of 3236 vs. 102 of 3223 participants with esophageal ulcerations; OR, 1.33 [CI, 1.05 to 1.68]) (143). Perforations, ulcerations, or bleeding episodes were reported in trials of all bisphosphonates, except zoledronic acid. A pooled analysis of 3 trials found that etidronate users were at increased risk compared with a placebo group (absolute risk, 123 of 8066 vs. 186 of 16 083 participants with perforations, ulcerations, or bleeding episodes; OR, 1.32 [CI, 1.04 to 1.67]) (47, 143, 144), and a pooled analysis of 2 trials found that daily oral ibandronate recipients were at lower risk than placebo recipients (absolute risk, 12 of 2445 vs. 17 of 1137 participants with perforations, ulcerations, or bleeding episodes; OR, 0.33 [CI, 0.14 to 0.74]). Pooled analyses found no significant effects for other bisphosphonates (75, 145).

We categorized such conditions as acid reflux, esophageal irritation, nausea, vomiting, and heartburn as mild upper gastrointestinal events. Pooled analyses of 18 trials of etidronate versus placebo showed that etidronate increased the risk for these events (absolute risk, 880 of 8842 vs. 1248 of 16 814 participants with mild upper gastrointestinal events; OR, 1.33 [CI, 1.21 to 1.46]) (48–52, 118, 119, 125, 126, 143, 146–153). Pooled analyses of 7 trials also showed an increased risk for these events with pamidronate (absolute risk, 125 of 340 vs. 44 of 253 participants with mild upper gastrointestinal events; OR, 3.14 [CI, 1.93 to 5.21]) (79, 81, 154–158). Pooled analyses found no difference between alendronate, ibandronate, risedronate, or zoledronic acid and placebo. However, pooled analysis of 3 head-to-head trials showed that alendronate users had a higher risk for mild upper gastrointestinal events than did etidronate users (absolute risk, 18 of 132 vs. 3 of 105 participants with mild upper gastrointestinal events; OR, 5.89 [CI, 1.61 to 32.7]). Similarly, in 4 head-to-head trials, alendronate recipients had a greater risk for mild upper gastrointestinal events than did calcitonin recipients (absolute risk, 56 of 413 vs. 13 of 288 participants with mild upper gastrointestinal events; OR, 3.42 [CI, 1.79 to 7.00]) or estrogen recipients (absolute risk, 78 of 255 vs. 68 of 306 participants with mild upper gastrointestinal events; OR, 1.57 [CI, 1.00 to 2.46]).

Cancer

Pooled analysis of the results of 5 trials that assessed the risk for breast cancer among women taking estrogen compared with placebo found a lower risk for breast cancer among estrogen users (absolute risk, 238 of 12 124 vs. 312 of 12 742 participants with breast cancer; OR, 0.79 [CI, 0.66 to 0.93]) (92, 128, 129, 159, 160). Conversely, in pooled analysis of 3 studies, women who used estrogen–progestin compared with placebo had an increased risk for breast cancer (absolute risk, 202 of 9922 vs. 152 of 9524 participants with breast cancer; OR, 1.28 [CI, 1.03 to 1.60]) (67, 130, 154). One study showed that women who used estrogen–progestin compared with placebo had a lower risk for colon cancer (absolute risk, 45 of 8506 vs. 67 of 8102 participants with colon cancer; OR, 0.64 [CI, 0.43 to 0.95]) (92). Risk for osteosarcoma was reported in 1 study, a head-to-head trial of raloxifene versus tamoxifen; differences between the groups were not significant (103).

Osteonecrosis

We found several published cases of osteonecrosis of the jaw in patients with cancer who were taking large doses of bisphosphonates intravenously. Cases involved pamidronate, zoledronic acid, and alendronate. Incidence rates and probability of this adverse event could not be calculated (see the Discussion section).

Discussion

This report summarizes the meta-analyses and subsequent randomized trials that have evaluated the effect of various agents on the risk for osteoporotic fractures. These analyses support a role for many of these agents in reducing the risk for fracture compared with placebo. We did not identify any studies that demonstrated superiority of 1 agent over another in preventing fractures. However, no trial with head-to-head comparisons of 2 or more agents enrolled sufficient sample sizes to detect even large differences in risk.

Consistent with FDA requirements to demonstrate reduced fracture risk to obtain approval of an agent for osteoporosis treatment, many trials were powered to detect a difference in fracture risk among postmenopausal osteoporotic women. These studies provide good evidence that the bisphosphonates alendronate, etidronate, ibandronate, and risedronate, as well as the hormones calcitonin and teriparatide and the selective estrogen receptor modulator raloxifene, prevent vertebral, nonvertebral, or hip fractures in this high-risk group. Each of these agents, with the exception of etidronate, has been approved by the FDA for osteoporosis treatment. Also, consistent with FDA requirements to obtain approval for the *prevention* of osteoporosis—that is, demonstration of an improvement in bone mineral density, but not necessarily fracture risk reduction, in a population that has not yet shown evidence of osteoporosis—few studies assessed fracture as a primary outcome among these lower-risk individuals. A meta-analysis reported that raloxifene (30) reduces the risk for vertebral fractures in low-risk populations, and 1 trial demonstrated that ibandronate reduces the risk for any fracture in this group (74). These 2 agents have been approved by the FDA for osteoporosis prevention.

Estrogen is also approved by the FDA for preventing osteoporotic fractures in postmenopausal women. However, the evidence on fracture risk reduction for estrogen is more complex than that for bisphosphonates. The evidence suggests that estrogen reduces the risk for vertebral and hip fracture; however, the effect of estrogen on nonvertebral fracture risk is less clear. Among the 3 meta-analyses that assessed the effect of estrogen on the risk for vertebral fracture in postmenopausal women, only 1 showed an effect that achieved statistical significance (22, 26, 29). Likewise, the Women's Health Initiative showed that estrogen significantly reduced the risk for hip fracture (67), and a meta-analysis that included data from the Women's Health Initiative showed a reduction in risk for hip fracture that was nonsignificant (22). Among the 3 meta-analyses that evaluated the risk for nonvertebral fractures, all reported that estrogen reduced risk, but the significance of the results was lower for the 2 meta-analyses with smaller sample sizes ($n = 7316$ and 5383) (22, 29). The analysis with the largest sample size ($n = 8774$) was the only one that showed a significant effect of estrogen (38).

Neither tamoxifen nor testosterone is approved by the FDA for the treatment or prevention of osteoporosis. Consistent with this fact, we did not identify any evidence that these agents reduce the risk for fractures. One large trial provides evidence that tamoxifen is not associated with fracture risk reduction (86). We did not identify any studies that assessed the effect of testosterone on fracture.

Zoledronic acid is approved by the FDA for the treatment, but not the prevention, of osteoporosis. On the basis of 2 large trials that evaluated the effect of zoledronic acid compared with placebo among postmenopausal women at high risk for fracture, the evidence for a reduced risk for vertebral and nonvertebral fractures is good and that for hip fractures is fair (85, 87).

The evidence for fracture risk reduction is less clear for calcium and vitamin D. For calcium, several large, high-quality trials could not demonstrate a reduction in fractures among postmenopausal women (39, 72, 73). However, many studies have demonstrated that adherence to calcium treatment is low (39, 72, 73, 88, 89), and a prespecified analysis in 1 randomized trial demonstrated a reduction in fracture risk among participants who adhered to calcium supplementation (72).

Across a large body of literature, the effects of vitamin D varied depending on analogue, dose, and fracture type. Among many meta-analyses, some reported a reduced risk for standard vitamin D compared with placebo (25, 27, 33, 36) and some did not (22, 25, 26). The studies included in the meta-analyses contained some overlap, although each included some unique studies. The findings regarding fracture risk were not related to the size of the pooled sample in the meta-analyses. Notably, 1 meta-analysis reported a reduction in fracture risk for standard vitamin D (D_2 and D_3) for doses of 700 to 800 IU/d (27). However, in a large, high-quality trial published after these meta-analyses, 800 IU of vitamin D_3 did not reduce fracture risk compared with placebo among ambulatory patients age 70 years or older with a history of fracture (39). In another trial published after these meta-analyses, 1000 IU of vitamin D reduced hip fracture risk for postmenopausal women with hemiplegia due to stroke (54). For vitamin D analogues (1,25-hydroxyvitamin D and 1-hydroxyvitamin D) compared with placebo, the risk for vertebral fracture was significantly reduced in 3 meta-analyses (25, 33, 36). For nonvertebral and hip fractures, the evidence was mixed. Together, these data do not prove a universal reduction of fracture risk with vitamin D. However, they do suggest that vitamin D analogues reduce the

risk for vertebral fractures and that, in high enough doses, standard vitamin D may prevent fractures in some high-risk populations. The fact that fracture risk reduction was observed among postmenopausal women with hemiplegia suggests that vitamin D might prevent fractures by reducing falls. Indeed, vitamin D–treated patients in the study had a 59% reduction in falls compared with the placebo group, consistent with the vitamin D–associated reduction in falls reported in other studies (161).

Although evidence suggests that many agents reviewed in our report reduce the risk for fracture among postmenopausal women with a high risk for fracture—that is, women with T-scores less than −2.5 SD or a previous osteoporotic fracture—data on other patient populations are limited. More research is needed to determine whether and which osteoporosis agents reduce fracture risk among transplant recipients. Among lower-risk populations, data are limited on whether osteoporosis agents reduce the risk for fracture among women with osteopenia and among men. Coupled with good evidence that all osteoporosis agents are associated with adverse effects ranging from mild to serious, further research is needed to determine whether the benefits of treatment in these lower-risk populations outweigh the risks. Demonstration of fracture risk reduction could lead to broader use of these agents in these populations and reduced fracture rates; the opposite could lead to discontinuation of these agents in these populations, with a concomitant reduction in associated adverse events and unnecessary health care spending. A practical challenge in determining whether osteoporosis agents reduce the risk for fracture in lower-risk populations is that large sample sizes will be required. Given that the time to develop fractures is longer in lower-risk populations, trials designed to assess fracture risk would require larger sample sizes and longer follow-up than those of typical osteoporosis trials.

Our report also presents the evidence for selected short- and long-term harms (adverse effects) of the various agents. Among cardiac events, an increased risk for serious atrial fibrillation was found in 1 placebo-controlled trial of zoledronic acid (85). However, this finding was contradicted by the findings of another large trial that was published in the same year (87). Another placebo-controlled trial suggested a possible increased risk for atrial fibrillation with alendronate (127). The increased risk for cerebrovascular events reported for estrogen users was also borne out in 3 separate trials (92, 128, 129).

Among oral bisphosphonate users, the risk for gastrointestinal adverse events has been a concern. The pooled analyses showed a slight increase in esophageal ulcers, as well as mild gastrointestinal events, such as acid reflux. Whereas a pooled analysis of 3 trials also showed a slightly increased risk for more serious adverse events, such as perforations, ulcerations, and bleeding, with etidronate, another pooled analysis showed a decreased risk with daily oral ibandronate. One possible reason for the discrepancy between the apparent risks observed in smaller studies and those of the larger clinical trials is that the larger trials may have enrolled patients who are more likely to adhere to instructions for taking these agents. Alternatively, given the widespread concerns about gastrointestinal side effects, patients enrolled in the large clinical trials may have been given more explicit dosing instructions.

Finally, although we found multiple published cases of osteonecrosis of the jaw in patients with cancer who receive large doses of bisphosphonates intravenously, we could not calculate the risk for this event. A 2006 systematic review (162) identified before preparation of our report analyzed the risk for osteonecrosis of the jaw with bisphosphonate therapy. The researchers found that 94% of published cases were among patients being treated intravenously for cancer. They concluded that although the risk for osteonecrosis of the jaw among patients taking oral bisphosphonates is uncertain, the possible link warrants further investigation (162). Concerned about the apparently mounting evidence that bisphosphonates increase the risk for osteonecrosis of the jaw, the American Society for Bone and Mineral Research appointed a multidisciplinary task force to address the proposed link. After developing a case definition and reviewing all pertinent literature, the task force concluded in their 2007 report (163) that even though the risk for osteonecrosis of the jaw in patients taking oral bisphosphonates for osteoporosis seemed to be low (in contrast to patients taking the agents intravenously for cancer), the incidence might be higher than that suggested by the literature to date. It outlined an agenda for further research in the area (163).

The findings reported here should be viewed in the context of the limitations of this study and the research in the field. Although our literature search procedures were extensive and included canvassing experts from academia and industry for studies, other trials may have appeared in non–English-language publications or may have not been published. Publication bias may occur, resulting in an overestimation of the efficacy of these treatments. As for the research itself, many studies of agents to treat osteoporosis measure only changes in bone mineral density and not fracture risk. Most trials that measured fracture risk were inadequately powered to detect even large differences. Most were heterogeneous with respect to study design (criteria for participation, dosing, duration of administration, length of follow-up, or control group), and few considered adherence to the medication regimens. With regard to the assessment of adverse events, the counts of adverse events were limited to those that were explicitly reported in the reviewed studies. Consequently, if many studies failed to report a particular adverse event (because it did not occur in those studies), our analysis would have no way to capture this "nonoccurrence," which could result in our overestimating the risk for that adverse event.

As for our selection of a method to estimate risk differences, both for fracture risk and for the adverse event

risk, we chose to use the Peto OR because it has been shown to be the least biased method for estimating rates of rare events, especially compared with the DerSimonian and Laird OR and risk difference methods (164). The Peto method can be limited if the sample size between the 2 treatment groups is largely imbalanced. As is the case when any OR or risk ratio estimate is being calculated, studies with zero events in the denominator group cannot be calculated by using the Peto OR (12).

In summary, although good evidence indicates that many agents are effective in preventing osteoporotic fractures, data are insufficient to determine the relative efficacy or safety of these agents. Such studies are unlikely to be performed unless they are required as part of the approval process for these agents.

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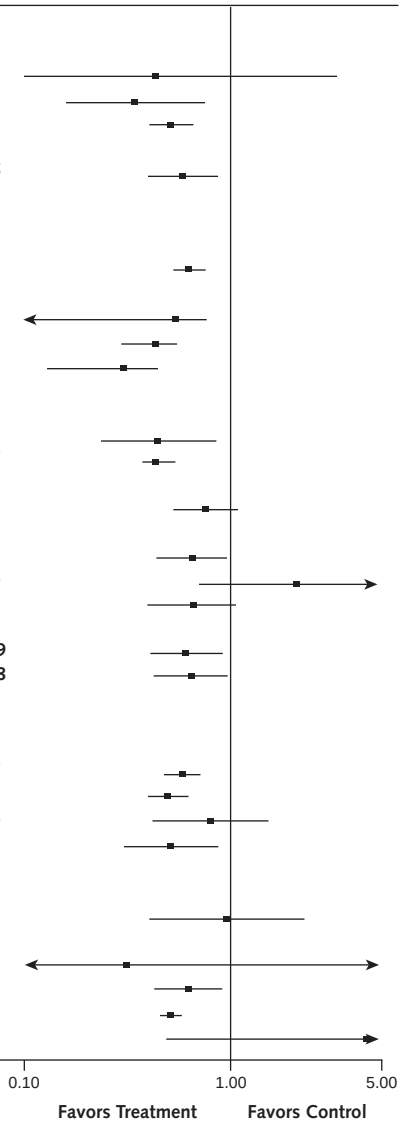
Appendix Figure 1. **Risk for vertebral fracture relative to placebo for participants who are not at high risk for fracture, by agent.**

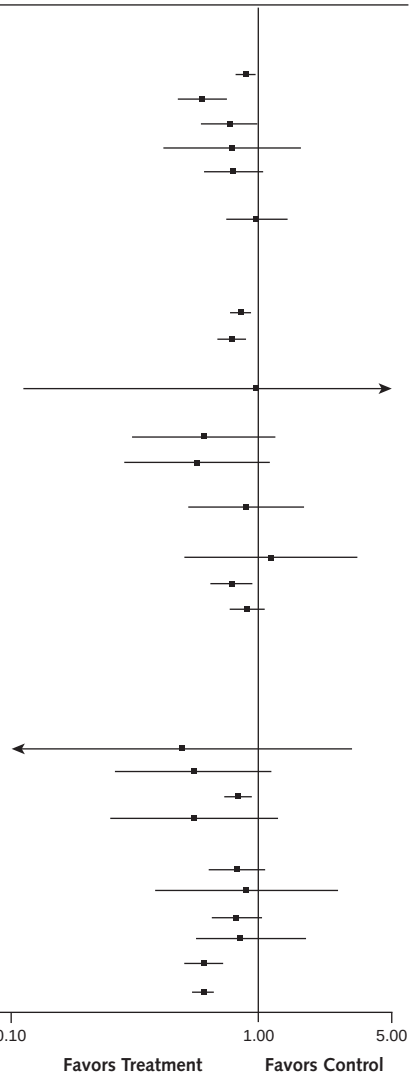
Study, Year (Reference)	Studies, *n*	Treatment Group		Placebo Group		Combined Total, *n*
		Fractures, *n*	Total, *n*	Fractures, *n*	Total, *n*	
Bisphosphonates						
Alendronate*						
Cranney et al., 2002 (14)	2	NR	NR	NR	NR	1355
Sawka et al., 2005 (32)	2	11	214	23	161	375
Stevenson et al., 2005 (22)	3	72	2621	114	2472	5093
Etidronate*						
Cranney et al., 2001 (16)	10	32	538	54	538	1076
Ibandronate†						
Pamidronate†						
Risedronate*						
Cranney et al., 2002 (19)	5	NR	NR	NR	NR	2604
Miller et al., 2005 (35)						
Severe renal impairment	9	NR	301	NR	271	572
Moderate renal impairment	9	NR	2034	NR	2037	4071
Mild renal impairment	9	NR	2161	NR	2192	4353
Zoledronic acid						
Calcitonin*						
Cranney et al., 2002 (20)	4	NR	NR	NR	NR	1404
Kanis and McCloskey, 1999 (21)	10	237	1309	271	678	1987
Calcium*						
Shea et al., 2002 (24)	5	NR	NR	NR	NR	576
Estrogen						
Torgerson and Bell-Syer, 2001 (28)*	13	NR	NR	NR	NR	6723
Stevenson et al., 2005 (22)*	2	10	602	5	616	1218
Wells et al., 2002 (29)*	5	NR	NR	NR	NR	3385
WHI‡						
Estrogen only (92)	1	39	5310	64	5429	10739
Estrogen–progestin (67)	1	41	8506	60	8102	16608
PTH†						
SERMs: Raloxifene*						
Seeman et al., 2006 (30)						
60 mg	4	172	2583	255	2624	5207
120/150 mg	5	147	2682	257	2739	5421
Schachter et al., 2005 (23)	2	NR	NR	NR	NR	7848
Stevenson et al., 2005 (22)	1	35	1490	68	1522	3012
Testosterone†						
Vitamin D*						
Avenell et al., 2005 (26)	2	37	1477	41	1476	2953
Papadimitropoulos et al., 2002 (25)						
Standard	1	NR	NR	NR	NR	160
Calcitrol	7	NR	NR	NR	NR	970
Richy et al., 2004 (36)	9	NR	NR	NR	NR	1665
Stevenson et al., 2005 (22)	1	8	18	9	22	40



NR = not reported; PTH = parathyroid hormone; SERM = selective estrogen receptor modulator; WHI = Women's Health Initiative. *Pooled risk estimate from cited meta-analysis or systematic review. †Insufficient data to calculate risk. ‡Risk estimate calculated from cited individual studies.

Appendix Figure 2. **Risk for nonvertebral fracture relative to placebo for participants who are not at high risk for fracture, by agent.**

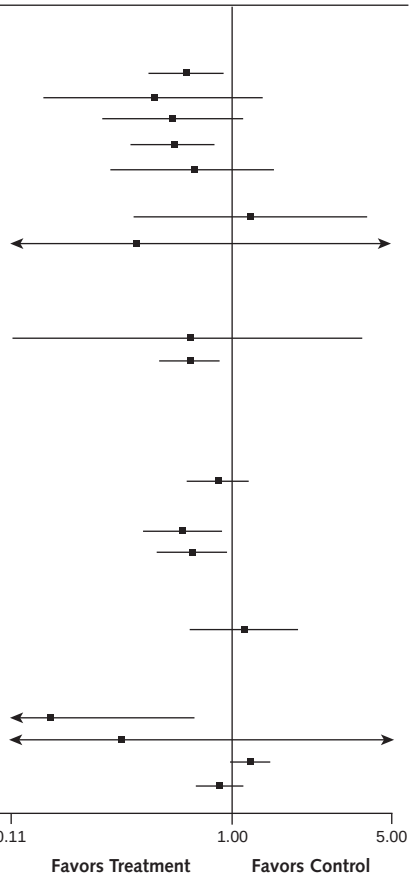
Study, Year (Reference)	Studies, *n*	Treatment Group		Placebo Group		Combined Total, *n*
		Fractures, *n*	Total, *n*	Fractures, *n*	Total, *n*	
Bisphosphonates						
Alendronate*						
Boonen et al., 2005 (37)	3	NR	3833	NR	3620	7453
Cranney et al., 2002 (14)	6	NR	NR	NR	NR	3723
Karpf et al., 1997 (15)	5	73	1012	60	590	1602
Sawka et al., 2005 (32)	2	12	214	13	161	375
Stevenson et al., 2005 (22)	3	287	3258	352	3368	6626
Etidronate*						
Cranney et al., 2001 (16)	8	48	433	49	434	867
Ibandronate†						
Pamidronate†						
Risedronate†						
Boonen et al., 2005 (37)	3	NR	7416	NR	4355	11771
Cranney et al., 2002 (19)	7	NR	NR	NR	NR	12958
Zoledronic acid§						
Reid et al., 2002 (84)	1	1	60	1	59	119
Calcitonin*						
Cranney et al., 2002 (20)	3	NR	NR	NR	NR	1482
Kanis and McCloskey, 1999 (21)	10	NR	NR	NR	NR	1744
Calcium*						
Shea et al., 2002 (24)	2	NR	NR	NR	NR	222
Estrogen*						
Stevenson et al., 2005 (20)	13	229	4112	261	3204	7316
Torgenson and Bell-Syer, 2001 (28)	6	NR	NR	NR	NR	5383
Wells et al., 2002 (29)	22	NR	NR	NR	NR	8774
PTH†						
SERMs: Raloxifene‡						
Testosterone‡						
Vitamin D*						
Avenell et al., 2005 (26)						
Alpha-calcidol	2	5	236	12	230	466
Calcitrol	1	6	123	13	123	246
Bischoff-Ferrari et al., 2005 (27)	7	613	5046	655	4774	9820
Stevenson et al., 2005 (22)	1	NR	18	NR	22	40
Papadimitropoulos et al., 2002 (25)						
Standard vitamin D	3	NR	NR	NR	NR	5399
Calcitriol	3	NR	NR	NR	NR	788
Either	6	NR	NR	NR	NR	6187
Richy et al., 2004 (36)						
Calcitriol	5	NR	NR	NR	NR	381
Alphacalcidol	6	NR	NR	NR	NR	929



NR = not reported; PTH = parathyroid hormone; SERM = selective estrogen receptor modulator. *Pooled risk estimate from cited meta-analysis or systematic review. †Insufficient data to calculate risk. ‡Risk estimate calculated from cited individual studies.

Appendix Figure 3. **Risk for hip fracture relative to placebo for participants who are not at high risk for fracture, by agent.**

Study, Year (Reference)	Studies, *n*	Treatment Group		Placebo Group		Combined Total, *n*
		Fractures, *n*	Total, *n*	Fractures, *n*	Total, *n*	
Bisphosphonates						
Alendronate*						
Cranney et al., 2002 (14)	8	NR	NR	NR	NR	8603
Karpf et al., 1997 (15)	5	6	1012	7	590	1602
Nguyen et al., 2006 (31)	6	40	5511	59	4878	10389
Papapoulos et al., 2005 (18)	6	37	NR	57	NR	6804
Stevenson et al., 2005 (22)	2	20	2811	27	2615	5426
Etidronate*						
Cranney et al., 2001 (16)	4	5	295	4	294	589
Nguyen et al., 2006 (31)	2	2	245	4	244	489
Ibandronate†						
Pamidronate†						
Risedronate*						
Nguyen et al., 2006 (31)	3	76	4519	75	2677	7196
Stevenson et al., 2005 (22)	3	81	4842	80	3042	7884
Zoledronic acid†						
Calcitonin†						
Calcium†						
Estrogen						
Stevenson et al., 2005 (22)*	5	59	10588	78	10210	20798
WHI‡						
Estrogen only (92)	1	38	5310	64	5429	10739
Estrogen–progestin (67)	1	52	8506	73	8102	16608
PTH†						
SERMs: Raloxifine*						
Stevenson et al., 2005 (22)	1	40	4536	18	2292	6828
Testosterone†						
Vitamin D*						
Avenell et al., 2005 (26)						
Alpha-calciferol	3	1	122	11	117	239
Calcitriol	1	0	123	1	123	246
Standard vitamin D	4	195	7932	163	7916	15848
Bischoff-Ferrari et al., 2005 (27)	5	293	4774	318	4520	9294



NR = not reported; PTH = parathyroid hormone; SERM = selective estrogen receptor modulator; WHI = Women's Health Initiative. *Pooled risk estimate from cited meta-analysis or systematic review. †Insufficient data to calculate risk. ‡Risk estimate calculated from cited individual studies.

Appendix Table. **Pooled Risk for Adverse Events for Bisphosphonates Compared with Placebo, by Agent***

Event Group	Alendronate		Etidronate		Ibandronate		Pamidronate		Risedronate		Zoledronic Acid	
	Trials, *n*	OR (95% CI)	Trials, *n*	OR (95% CI)	Trials, *n*	OR (95% CI)	Trials, *n*	OR (95% CI)	Trials, *n*	OR (95% CI)	Trials, *n*	OR (95% CI)
Cardiovascular												
Acute coronary syndrome	4	3.59 (0.35–180)	2	∞ (0.21–∞)	1	∞ (0.01–∞)	1	0 (0–37.7)	2	0.38 (0.01–7.62)	2	0.85 (0.66–1.09)
Cardiac death	2	∞ (0.13–∞)	1	∞ (0.03–∞)	0	NR	1	0 (0–37.7)	1	∞ (0.02–∞)	2	0.88 (0.63–1.22)
Atrial fibrillation	1	1.26 (0.96–1.66)	0	NR	0	NR	0	NR	1	∞ (0.02–∞)	2	1.13 (0.95–1.34)
Cerebrovascular events (serious)	0	NR	0	NR	2	0.32 (0–27.3)	1	∞ (0.09–∞)	0	NR	2	1.06 (0.82–1.36)
Pulmonary embolism	0	NR	0	NR	0	NR	0	NR	1	∞ (0.01–∞)	0	NR
Thromboembolic events	2	∞ (0.03–∞)	0	NR	0	NR	0	NR	0	NR	0	NR
Cancer												
All	2	∞ (0.03–∞)	3	3.12 (0.25–165)	3	∞ (0.12–∞)	2	∞ (0.4–∞)	1	0 (0–34.5)	0	NR
Breast cancer	0	NR	1	∞ (0.03–∞)	1	∞ (0.01–∞)	0	NR	0	NR	0	NR
Colon cancer	0	NR	0	NR	0	NR	1	∞ (0.03–∞)	0	NR	0	NR
Lung cancer	0	NR	1	0 (0–41)	0	NR	1	∞ (0.01–∞)	0	NR	0	NR
Osteosarcoma	0	NR	0	NR	0	NR	0	NR	0	NR	0	NR
Gastrointestinal												
Mild	54	1.05 (0.99–1.13)	18	1.33 (1.21–1.46)	10	1.02 (0.92–1.13)	7	3.14 (1.93–5.21)	22	1.03 (0.95–1.13)	3	1.34 (0.6–3.21)
Upper gastrointestinal (excluding esophagus)	46	1.04 (0.97–1.11)	15	1.53 (1.25–1.88)	5	1.04 (0.89–1.22)	4	4.73 (2.53–9.35)	20	1.07 (0.96–1.19)	2	1.82 (0.53–9.73)
Reflux and esophageal	27	1.11 (0.99–1.23)	0	NR	2	1.35 (0.68–2.88)	3	1.49 (0.33–9.24)	13	0.90 (0.69–1.19)	0	NR
Serious	20	1.01 (0.83–1.24)	7	1.32 (1.12–1.55)	3	0.77 (0.55–1.08)	4	2.7 (0.66–15.9)	12	0.93 (0.72–1.19)	0	NR
Esophageal	8	1.42 (0.89–2.29)	1	1.33 (1.05–1.68)	1	1.25 (0.2–13.1)	1	∞ (0.46–∞)	6	0.69 (0.37–1.32)	0	NR
Upper gastrointestinal perforations, ulcers, or bleeding (not esophageal)	12	0.88 (0.66–1.18)	3	1.32 (1.04–1.67)	2	0.33 (0.14–0.74)	3	1.67 (0.31–11.2)	7	0.64 (0.27–1.53)	0	NR

* NR = not reported; OR = odds ratio.