Comparative Effectiveness of Drug Treatments to Prevent Fragility Fractures: A Systematic Review and Network Meta-Analysis

Mohammad Hassan Murad, Matthew T. Drake, Rebecca J. Mullan, Karen F. Mauck, Louise M. Stuart, Melanie A. Lane, Nisrin O. Abu Elnour, Patricia J. Erwin, Ahmad Hazem, Milo A. Puhan, Tianjing Li, and Victor M. Montori

Knowledge and Evaluation Research Unit (M.H.M., R.J.M., L.M.S., M.A.L., N.O.A.E., V.M.M.), Division of Preventive Medicine (M.H.M.), Division of Endocrinology, Diabetes, Metabolism, Nutrition (M.T.D., V.M.M.), Division of General Internal Medicine (K.F.M.), and Mayo Clinic Libraries (P.J.E.), Mayo Clinic, Rochester, Minnesota 55905; Department of Internal Medicine (A.H.), University of North Dakota, Fargo, North Dakota 58102; and Department of Epidemiology (M.A.P., T.L.), Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland 21205

Context: Osteoporosis and osteopenia are associated with increased fracture incidence.

Objective: The aim of this study was to determine the comparative effectiveness of different pharmacological agents in reducing the risk of fragility fractures.

Data Sources: We searched multiple databases through 12/9/2011.

Study Selection: Eligible studies were randomized controlled trials enrolling individuals at risk of developing fragility fractures and evaluating the efficacy of bisphosphonates, teriparatide, selective estrogen receptor modulators, denosumab, or calcium and vitamin D.

Data Extraction: Reviewers working independently and in duplicate determined study eligibility and collected descriptive, methodological quality, and outcome data.

Data Synthesis: This network meta-analysis included 116 trials (139,647 patients; median age, 64 yr; 86% females and 88% Caucasians; median follow-up, 24 months). Trials were at low to moderate risk of bias. Teriparatide had the highest risk reduction of fractures (odds ratios, 0.42, 0.30, and 0.50 for hip, vertebral, and nonvertebral fractures, respectively) and the highest probability of being ranked first for efficacy (probabilities of 42, 49, and 79% for hip, vertebral, and nonvertebral fractures, respectively). However, differences to denosumab, zoledronate, risedronate, ibandronate, and alendronate were not statistically significant. Raloxifene and bazedoxifene were likely less effective, although these data were limited. Calcium and vitamin D were ineffective given separately but reduced the risk of hip fractures if given in combination (odds ratio, 0.81; 95% confidence interval, 0.68–0.96).

Conclusions: Teriparatide, bisphosphonates, and denosumab are most effective in reducing the risk of fragility fractures. Differences in efficacy across drugs are small; therefore, patients and clinicians need to consider their associated harms and costs. **(*J Clin Endocrinol Metab* 97: 1871–1880, 2012)**

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Abbreviations: CI, Confidence interval; OR, odds ratio; SERM, selective estrogen receptor modulator.

Osteoporosis represents a major health burden with about 10 million Americans over the age of 50 having osteoporosis and another 34 million being at risk of developing the disease. An estimated 1.5 million fragility fractures occur every year, costing $20 billion and leading to significant morbidity and mortality (1, 2).

Several effective treatments have been found to reduce the risk of fragility fractures in men and women. Compared with placebo, bisphosphonates, PTH analog (PTH 1-34, teriparatide), denosumab, selective estrogen receptor modulators (SERM), and the combination of calcium and vitamin D have all been shown to reduce fracture risk and are supported by at least moderate quality evidence (3). Despite evidence for individual agents or pharmacological classes, direct head-to-head trials needed for comparative effectiveness research—and sought by decision makers—are scarce. Furthermore, their treatment effect estimates are associated with a small number of events and significant imprecision. Modern statistical techniques, such as network meta-analysis, can analyze simultaneously both direct comparisons of interventions within randomized controlled trials and indirect comparisons across trials based on a common comparator (*e.g.* placebo or some standard treatment) to overcome some of the challenges posed by the paucity of direct evidence (4).

We conducted this systematic review and network meta-analysis to evaluate the comparative effectiveness of the available agents in preventing fragility fractures in men and women.

Materials and Methods

The protocol for this systematic review was established *a priori* and approved by a task force formed by The Endocrine Society.

Eligibility criteria

Trials eligible for inclusion in this review were: 1) randomized controlled trials; 2) trials that enrolled patients with established or at risk for osteoporosis; 3) trials that compared one or more of the interventions of interest to each other or to placebo; and 4) trials that measured the outcomes of interest, *i.e.* fragility fractures (vertebral, hip, and nonvertebral fractures).

The interventions of interest were: bisphosphonates (alendronate, risedronate, zoledronate, and ibandronate), PTH 1-34 (teriparatide), SERM such as raloxifene or bazedoxifene, denosumab, and calcium and vitamin D. The task force decided to not include calcitonin because its fracture-preventing effect is generally considered to be very weak (5) and supported by low-quality evidence (3, 6), and because it is not commonly used for modern long-term preventive therapy (7, 8). Pamidronate, etidronate, strontium and lasofoxifene were also not included in this review because they are not approved by the Food and Drug Administration for the treatment of osteoporosis, the main focus of the accompanying guidelines (9).

Literature search

An expert reference librarian and study authors with expertise in conducting systematic reviews developed the search strategy. An exploratory literature search identified recent and well-conducted systematic reviews about this topic. Avenell *et al.* (10) pooled data from trials that evaluated the effect of vitamin D and calcium on fractures and was used as an index publication to identify these trials. MacLean *et al.* (3) also compared bisphosphonates, SERM, and PTH 1-34. We updated the literature search by MacLean *et al.* through March 2010 because their search was done in November 2007. Subsequently, we updated the literature search through December 9, 2012. We also conducted additional searches using the names of individual drugs as textwords. We searched MEDLINE and EMBASE through the Ovid interface; we also searched Cochrane Central Register of Controlled Trials (CENTRAL), ISI Web of Science, and Scopus. Our search was not limited by sex of study participants included or language of the publication. In MEDLINE and EMBASE, we used the controlled hierarchical vocabularies (MeSH and EMTREE) with the explode function to maximize sensitivity (osteoporosis, osteopenia, fractures, bone, bone density conservation agents, and drug categories). We employed the Cochrane validated search filter for identifying randomized controlled trials in both MEDLINE and EMBASE. We adapted the MEDLINE search strategy and searched EMBASE and CENTRAL using a combination of textwords and subject headings. We searched ISI Web of Science and Scopus using only textwords. We excluded recent trials without fracture data (11–13) and trials in which the drugs of interest were given to treat bone metastases (14–16). The latter group of studies was not within the scope of this review because enrolled patients did not necessarily have low bone mineral density and the outcomes were pathological rather than fragility fractures. We also excluded a recent trial in which the majority of patients received bisphosphonate therapy for an average of 3 yr before the beginning of the trial (17). The detailed search strategy is available in the Supplemental Data.

Study selection

Pairs of reviewers independently evaluated eligibility of candidate titles and abstracts. When at least one reviewer determined an article was potentially eligible, the full text version was retrieved and pairs of reviewers assessed its eligibility. We used standardized and piloted electronic forms using an online reference management system (Distiller SR, Ottawa, Canada).

Data extraction and quality assessment

Pairs of reviewers extracted data in duplicate, with disagreements resolved by discussion and consensus. Study selection and data extraction (focusing on judgment of quality indicators) had adequate chance-adjusted interreviewer agreement above 0.80. We evaluated the quality of trials using elements from the Cochrane risk of bias tool (18) focusing on allocation concealment, blinding (patients, investigators, data collectors, and outcome assessors), outcome assessment, loss to follow-up (attrition), and the extent of prognostic balance of study arms at the start of the study. The quality of evidence was judged using the GRADE framework (Grading of Recommendations, Assessment, Development, and Evaluation) (19).

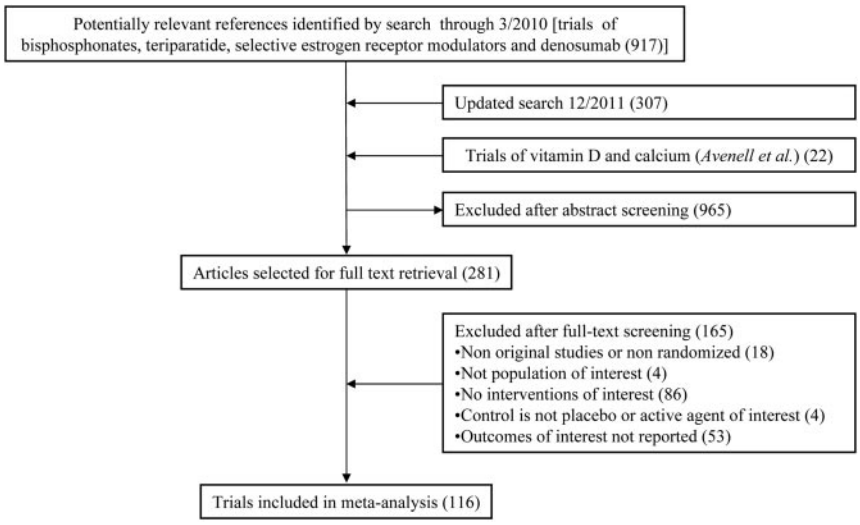

FIG. 1. Study selection process.

Statistical analysis

Direct head-to-head comparisons were conducted using a random effects model to estimate pooled odds ratios (OR) and 95% confidence intervals (CI) incorporating within- and between-study heterogeneity (20). We assessed publication bias by examining funnel plots symmetry and by conducting Egger's regression test (21). Heterogeneity was assessed using the I^2 statistic (22), which represents the proportion of heterogeneity that is not due to chance (but rather due to real differences across studies' populations and interventions). I^2 values over 50% indicate substantial heterogeneity. Direct comparisons were performed using the Comprehensive Meta-analysis version 2 software package (Biostat Inc., Englewood, NJ).

To incorporate indirect comparisons, we conducted random-effects network meta-analyses using Markov chain Monte Carlo methods in WinBUGS 1.4.3 (MRC Biostatistics Unit, Cambridge, UK) following methods described by Lu and Ades (23). We modeled the comparative effectiveness of any two treatments as a function of each treatment relative to the reference treatment (*i.e.* placebo in this study). This approach assumes "consistency" of treatment effects across all included trials—that is, the direct and indirect estimates of effect for each pair-wise comparison do not disagree beyond chance. We evaluated inconsistency by comparing the estimates from the direct comparisons and those from the indirect comparisons for the magnitude and direction of the point estimates and the extent of overlap of CI. We estimated the posterior distribution of all parameters using noninformative (*i.e.* vague, flat) priors to limit inference to data derived from the trials at hand (*i.e.* we made no assumptions about the efficacy of these drugs from data external to the 116 trials included in this systematic review). We updated three Markov chain Monte Carlo chains with 60,000 simulated draws after a burn in of 30,000 iterations using the same seed number (seed = 1000) for all chains. We reported the pair-wise OR and 95% credible interval and adjusted for multiple arm trials.

We estimated the probability that each drug was the most efficacious regimen by calculating the OR for each drug compared with an arbitrary common comparison drug (which was placebo in most cases due to the minimal number of head-to-head trials), and counting the proportion of iterations of the Markov chain in which each drug had the largest OR in reducing fracture risk.

Results

The process of selecting the trials is described in Fig. 1. A total of 116 studies provided data for meta-analysis. These studies included 139,647 patients with a median age of 64 yr; 86% were females and 88% Caucasians. The median length of follow-up was 24 months. The description of the included trials is in Supplemental Table 1. The quality indicators of these studies are described in Supplemental Table 2.

Meta-analysis

The available direct comparisons (*i.e.* two interventions are being compared against each other in a randomized controlled trial setting) are graphically depicted in network graphs in Supplemental Figs. 1–3, including the number of trials, participants, and events (fractures). The estimates obtained from direct comparisons are presented as OR and 95% CI and summarized in Supplemental Tables 3–5. There was no significant association between the duration of the intervention and the effect size (log OR) for all the included agents (P value for the slope of feasible meta-regression analyses >0.05). Vitamin and calcium given separately did not reduce the risk of any fracture.

Hip fractures

Network meta-analysis combining direct and indirect estimates demonstrates that teriparatide had the highest probability (42%) of being ranked as most effective and had the highest reduction in the risk of hip fracture (OR, 0.42). Results are summarized in Table 1. Compared with placebo, there was significant reduction in the risk of hip fracture with alendronate, zoledronate, risedronate, denosumab, and the combination of calcium and vitamin D. Results are summarized in Fig. 2.

Vertebral fractures

Network meta-analysis combining direct and indirect estimates demonstrates that teriparatide had the highest probability (49%) of being ranked as most effective and had the highest reduction in the risk of vertebral fracture (OR, 0.30). Results are summarized in Table 2. Compared with placebo, there was significant reduction in the risk of vertebral fractures with teriparatide, denosumab, alendronate, zoledronate, ibandronate, risedronate, and raloxifene. Results are summarized in Fig. 2.

TABLE 1. Pair-wise OR (95% Bayesian credible interval) of the outcome of hip fracture (combining direct and indirect estimates)

Treatment	Placebo	Teriparatide[a]	Denosumab[a]	Raloxifene[b]	Zoledronate[a]	Risedronate[b]
Placebo						
Teriparatide[a]	0.42 (0.10; 1.82)					
Denosumab[a]	0.50 (0.27; 0.86)	1.17 (0.24; 5.54)				
Raloxifene[b]	0.87 (0.63; 1.22)	2.05 (0.47; 9.47)	1.76 (0.95; 3.41)			
Zoledronate[a]	0.50 (0.34; 0.73)	1.18 (0.26; 5.30)	1.02 (0.54; 1.93)	0.57 (0.35; 0.93)		
Risedronate[b]	0.48 (0.31; 0.66)	1.12 (0.25; 4.98)	0.96 (0.50; 1.78)	0.55 (0.31; 0.84)	0.96 (0.56; 1.49)	
Ibandronate[a]	0.49 (0.21; 1.20)	1.11 (0.22; 6.42)	0.98 (0.36; 2.79)	0.55 (0.23; 1.42)	0.97 (0.39; 2.55)	1.02 (0.43; 2.66)
Alendronate[b]	0.45 (0.27; 0.68)	1.02 (0.24; 4.82)	0.90 (0.45; 1.78)	0.51 (0.29; 0.87)	0.90 (0.51; 1.51)	0.93 (0.54; 1.62)
Vitamin D[c]	1.13 (0.94; 1.34)	2.67 (0.63; 11.97)	2.28 (1.28; 4.16)	1.30 (0.89; 1.86)	2.26 (1.50; 3.42)	2.35 (1.63; 3.76)
Vitamin D + calcium[c]	0.81 (0.68; 0.96)	1.92 (0.45; 8.42)	1.64 (0.97; 2.87)	0.94 (0.66; 1.31)	1.63 (1.16; 2.30)	1.69 (1.27; 2.54)
Calcium[c]	1.14 (0.82; 1.59)	2.69 (0.63; 12.23)	2.33 (1.25; 4.40)	1.31 (0.83; 2.06)	2.29 (1.44; 3.66)	2.39 (1.56; 4.04)

OR <1 favors the treatment in the *row*, OR >1 favors the treatment in the *column*. *P*, Probability being ranked as first, second, and third most effective. Total number of trials = 40. Total number of participants = 139,647. Total number of hip fractures = 2,567.

[a] With vitamin D and calcium.

[b] With or without vitamin D and calcium.

[c] With or without placebo.

Nonvertebral fractures

Network meta-analysis combining direct and indirect estimates demonstrates that teriparatide had the highest probability (79%) of being ranked as most effective and had the highest reduction in the risk of nonvertebral fracture (OR, 0.50). Results are summarized in Table 3. Compared with placebo, there was significant reduction in the risk of nonvertebral fractures with teriparatide, denosumab, alendronate, zoledronate and risedronate. Results are summarized in Fig. 2.

Subgroup analyses

The majority of data were derived from postmenopausal women, and therefore, the conclusions regarding the relative efficacy on the outcomes of fragility fractures most directly apply to these patients. Quantitative analysis for other subgroups was not feasible due to sparse data.

Trials that exclusively enrolled men were only powered to demonstrate improvement in the surrogate outcomes of bone density and turnover markers and only compared these agents to placebo [risedronate (24–27), alendronate (28, 29), ibandronate (30), teriparatide (31), and denosumab (32)]. Only a few trials were able to demonstrate a significant reduction in fracture risk [reduction in vertebral fracture risk by alendronate (29), risedronate (25), and denosumab (32); reduction in vertebral and nonvertebral fracture risk by risedronate (26); and reduction in hip fracture risk by risedronate (27)].

Several trials enrolled patients on glucocorticoid therapy and demonstrated the efficacy of alendronate (33–37) and risedronate (38–41) on bone density and the incidence of vertebral fractures and raloxifene on bone density (42). Head-to-head trials in this setting demonstrated efficacy of zoledronic acid (43) compared with risedronate and teriparatide compared with alendronate (44).

Quality of the evidence

The quality of the included trials was moderate, with 54% of the trials reporting adequate allocation concealment and 73% reporting blinding patients and caregivers. Outcome assessment was done by medical record review in most trials and appeared adequate. The source of funding included for-profit sources in the majority of the trials. The median loss to follow-up was 10%. Overall, the trials appear to be at low to moderate risk of bias. The quality indicators are in described in Supplemental Table 2.

However, severe imprecision due to the small number of head-to-head comparisons (*i.e.* comparison of two active interventions) undermines the strength of inference associated with network meta-analyses. Heterogeneity was minimal in most analyses ($I^2 < 50\%$). There were no significant discrepancies (inconsistency) between direct and indirect estimates, and the two methods had overlapping CI for all interventions [examples: using calcium and vitamin D as a comparator, hip fracture reduction by alendronate is 0.63 (0.41 to 0.97) *vs.* 0.36 (0.12 to 0.88) and by risedronate is 0.52 (0.23 to 1.19) *vs.* 0.17 (0.04; 0.56)].

We did not find evidence of publication bias (Egger's regression test >0.05 for all comparisons), although the number of studies included in each comparison was very small, thereby making the available methods for evaluating publication bias unreliable (45).

Overall, the strength of inference (quality of evidence) seems to be moderate to high, supporting the efficacy of bisphosphonate, denosumab, and teriparatide for reducing fractures compared with placebo (these drugs had con-

TABLE 1. Continued

Ibandronate[a]	Alendronate[b]	Vitamin D[c]	Calcium[c]	*P* (best)	*P* (2nd best)	*P* (3rd best)
				0.00	0.00	0.00
				0.42	0.11	0.06
				0.13	0.17	0.16
				0.00	0.00	0.00
				0.05	0.13	0.20
				0.06	0.18	0.25
				0.21	0.18	0.11
0.92 (0.34; 2.32)				0.14	0.24	0.22
2.32 (0.92; 5.54)	2.54 (1.63; 4.16)			0.00	0.00	0.00
1.69 (0.69; 3.84)	1.82 (1.24; 2.90)	0.72 (0.57; 0.91)		0.00	0.00	0.00
2.36 (0.92; 5.87)	2.56 (1.57; 4.34)	1.01 (0.72; 1.44)	1.40 (1.03; 1.95)	0.00	0.00	0.00

sistent and fairly large effect, minimal heterogeneity, and a sufficient number of trials). The evidence supporting the efficacy of SERM such as raloxifene or bazedoxifene is of low quality mainly due to imprecision [*i.e.* small number of trials and events (fractures)]. Evidence supporting comparative effectiveness across these therapeutic classes is low [due to imprecision and minimal direct evidence (head-to-head comparisons)], and the ranking probabilities generated in the network meta-analysis are clearly associated with significant uncertainty.

Discussion

We conducted a network meta-analysis of several pharmacological agents available for the prevention of fragility fractures. We found moderate- to high-quality evidence to

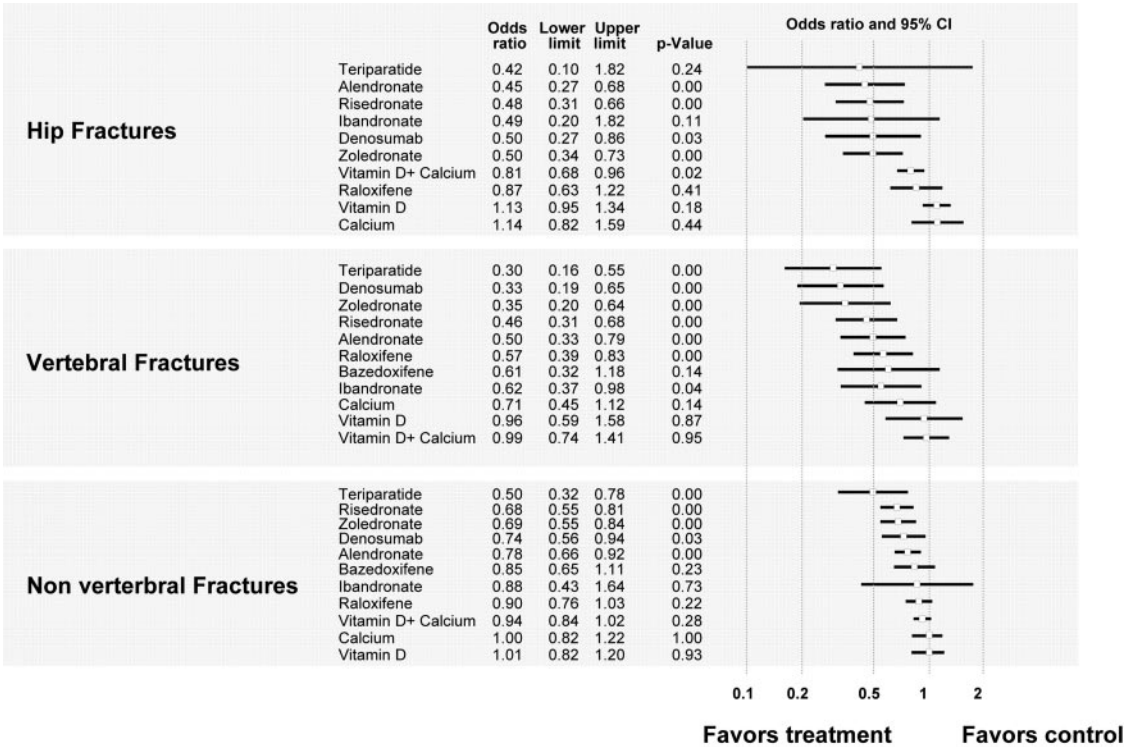

FIG. 2. Agents for the prevention of fragility fractures compared against placebo (combined direct and indirect estimates).

TABLE 2. Pair-wise OR (95% Bayesian credible interval) of the outcome of vertebral fracture (combining direct and indirect estimates)

Treatment	Placebo	Teriparatide[a]	Denosumab[a]	Raloxifene[b]	Zoledronate[a]	Risedronate[b]
Placebo						
Teriparatide[a]	0.30 (0.16; 0.55)					
Denosumab[a]	0.33 (0.19; 0.65)	1.12 (0.54; 2.46)				
Raloxifene[b]	0.57 (0.39; 0.83)	1.91 (0.99; 3.55)	1.71 (0.87; 3.01)			
Zoledronate[a]	0.35 (0.20; 0.64)	1.16 (0.58; 2.48)	1.03 (0.52; 2.08)	0.61 (0.35; 1.14)		
Risedronate[b]	0.46 (0.31; 0.68)	1.54 (0.82; 2.83)	1.39 (0.73; 2.38)	0.81 (0.54; 1.22)	1.33 (0.75; 2.23)	
Ibandronate[a]	0.62 (0.37; 0.98)	2.07 (1.02; 3.92)	1.86 (0.90; 3.32)	1.09 (0.65; 1.75)	1.78 (0.90; 3.16)	1.34 (0.83; 2.10)
Alendronate[b]	0.50 (0.33; 0.79)	1.67 (0.91; 3.16)	1.49 (0.80; 2.71)	0.88 (0.58; 1.39)	1.45 (0.80; 2.51)	1.09 (0.73; 1.66)
Vitamin D[c]	0.96 (0.59; 1.58)	3.19 (1.49; 6.97)	2.85 (1.30; 5.90)	1.68 (0.93; 3.10)	2.76 (1.31; 5.54)	2.08 (1.15; 3.78)
Vitamin D + calcium[c]	0.99 (0.74; 1.41)	3.32 (1.94; 5.85)	2.97 (1.74; 4.89)	1.74 (1.29; 2.52)	2.88 (1.76; 4.53)	2.15 (1.66; 2.93)
Calcium[c]	0.71 (0.45; 1.12)	2.36 (1.19; 4.56)	2.12 (1.05; 3.95)	1.24 (0.76; 2.02)	2.04 (1.05; 3.67)	1.53 (1.02; 2.28)
Bazedoxifene[a]	0.61 (0.32; 1.18)	2.04 (0.88; 4.64)	1.82 (0.78; 4.00)	1.07 (0.56; 2.06)	1.77 (0.77; 3.73)	1.33 (0.68; 2.62)

OR <1 favors the treatment in the row; OR >1 favors the treatment in the column. *P*, Probability being ranked as first, second, and third most effective. Total number of trials = 67. Total number of participants = 126,423. Total number of vertebral fractures = 2,929.

[a] With vitamin D and calcium.

[b] With or without vitamin D and calcium.

[c] With or without placebo.

support the efficacy of teriparatide, denosumab, and bisphosphonates compared with placebo, vitamin D, and calcium; and very low-quality evidence to support the comparisons among these three classes of drugs. The evidence supporting the efficacy of SERM such as raloxifene or bazedoxifene on fractures remains imprecise due to the small number of events. The combination of vitamin D and calcium appears to be the least effective, and either intervention is not effective given alone. Bayesian analyses ranked the efficacy of drugs producing the "probability of being ranked first," which demonstrated that teriparatide had the highest probability of being most effective. This ranking procedure has several limitations, the most important of which is that the ranking does not convey a sense of the treatment effect in absolute terms. In other words, the ranking has limited value when patients and clinicians are trying to consider the trade-offs of drugs and balance the benefits and harms.

A key aspect to consider is the known phenomenon of overestimation of treatment effect sizes with the first few trials of a novel agent, the *Proteus* phenomenon (46), which may be influencing the relative rankings presented

TABLE 3. Pair-wise OR (95% Bayesian credible interval) of the outcome of nonvertebral fracture (combining direct and indirect estimates)

Treatment	Placebo	Teriparatide[a]	Denosumab[a]	Raloxifene[b]	Zoledronate[a]	Risedronate[b]
Placebo						
Teriparatide[a]	0.50 (0.32; 0.78)					
Denosumab[a]	0.74 (0.56; 0.94)	1.46 (0.89; 2.38)				
Raloxifene[b]	0.90 (0.76; 1.03)	1.78 (1.12; 2.82)	1.21 (0.93; 1.61)			
Zoledronate[a]	0.69 (0.55; 0.84)	1.37 (0.84; 2.16)	0.93 (0.70; 1.27)	0.77 (0.61; 0.98)		
Risedronate[b]	0.68 (0.55; 0.81)	1.35 (0.85; 2.12)	0.92 (0.69; 1.21)	0.76 (0.60; 0.93)	0.99 (0.75; 1.25)	
Ibandronate[a]	0.88 (0.43; 1.64)	1.78 (0.78; 3.64)	1.20 (0.57; 2.33)	0.99 (0.48; 1.87)	1.29 (0.63; 2.46)	1.29 (0.63; 2.46)
Alendronate[b]	0.78 (0.66; 0.92)	1.56 (1.01; 2.44)	1.07 (0.81; 1.41)	0.88 (0.72; 1.08)	1.14 (0.90; 1.45)	1.15 (0.94; 1.45)
Vitamin D[c]	1.01 (0.85; 1.20)	2.01 (1.26; 3.24)	1.37 (1.03; 1.89)	1.13 (0.91; 1.43)	1.47 (1.14; 1.92)	1.48 (1.18; 1.94)
Vitamin D + calcium[c]	0.94 (0.84; 1.02)	1.86 (1.20; 2.91)	1.27 (1.01; 1.62)	1.05 (0.91; 1.22)	1.37 (1.13; 1.65)	1.37 (1.18; 1.65)
Calcium[c]	1.00 (0.83; 1.22)	1.99 (1.26; 3.20)	1.35 (1.02; 1.88)	1.12 (0.90; 1.43)	1.46 (1.13; 1.93)	1.47 (1.18; 1.93)
Bazedoxifene[a]	0.85 (0.65; 1.10)	1.69 (1.02; 2.76)	1.15 (0.82; 1.64)	0.95 (0.73; 1.23)	1.24 (0.90; 1.70)	1.24 (0.93; 1.71)

OR <1 favors the treatment in the *row*; OR >1 favors the treatment in the *column*. *P*, Probability being ranked as first, second, and third most effective. Total number of trials = 66. Total number of participants = 136,557. Total number of nonvertebral fractures = 12,041.

[a] With vitamin D and calcium.

[b] With or without vitamin D and calcium.

[c] With or without placebo.

TABLE 2. Continued

Ibandronate[a]	Alendronate[b]	Vitamin D	Vitamin D + calcium	Calcium	*P* (best)	*P* (2nd best)	*P* (3rd best)
					0.00	0.00	0.00
					0.49	0.27	0.15
					0.27	0.32	0.24
					0.00	0.01	0.02
					0.21	0.31	0.29
					0.01	0.04	0.14
					0.00	0.01	0.02
0.81 (0.52; 1.38)					0.00	0.02	0.07
1.55 (0.81; 3.11)	1.91 (1.01; 3.53)				0.00	0.00	0.00
1.60 (1.14; 2.50)	1.99 (1.44; 2.74)	1.04 (0.60; 1.83)			0.00	0.00	0.00
1.14 (0.67; 2.01)	1.41 (0.89; 2.17)	0.74 (0.40; 1.34)	0.71 (0.46; 1.05)		0.00	0.00	0.00
0.99 (0.49; 2.11)	1.22 (0.59; 2.42)	0.64 (0.28; 1.41)	0.62 (0.32; 1.13)	0.87 (0.41; 1.81)	0.01	0.03	0.05

here and favoring denosumab and teriparatide. The relative efficacy of these agents would be best appraised when more practical trials accrue, enrolling typical patients and measuring fracture outcomes.

The current study has several limitations. Inference is clearly limited by the imprecise estimates caused by the small number of events (fractures). Confidence in the conclusions of analyses that include indirect comparisons should be lower than that of direct, head-to-head comparisons. Inconsistency evaluation was limited by several comparisons in which either direct comparison was not feasible (no head-to-head trials available) or indirect comparison was not feasible (the drug was not connected in a loop in the evidence network).

In addition, this analysis focused on randomized trials to limit the impact of bias that threatens internal validity of the results. However, randomized trials may have lower external validity (applicability) compared with large observational studies that may represent a real-world setting and provide important contributions to comparative effectiveness research. Cadarette *et al.* (5) studied elderly enrollees in two statewide pharmaceutical benefit pro-

TABLE 3. Continued

Ibandronate[a]	Alendronate[b]	Vitamin D	Vitamin D + calcium	Calcium	*P* (best)	*P* (2nd best)	*P* (3rd best)
					0.00	0.00	0.00
					0.79	0.11	0.04
					0.02	0.13	0.19
					0.00	0.00	0.00
					0.04	0.30	0.28
					0.05	0.31	0.34
					0.09	0.12	0.05
0.89 (0.48; 1.78)					0.00	0.01	0.06
1.14 (0.60; 2.36)	1.29 (1.03; 1.62)				0.00	0.00	0.00
1.06 (0.57; 2.15)	1.19 (1.03; 1.38)	0.93 (0.77; 1.11)			0.00	0.00	0.00
1.13 (0.60; 2.37)	1.28 (1.04; 1.59)	0.99 (0.80; 1.24)	1.07 (0.89; 1.30)		0.00	0.00	0.00
0.96 (0.50; 1.98)	1.08 (0.80; 1.45)	0.84 (0.61; 1.14)	0.91 (0.70; 1.17)	0.85 (0.61; 1.16)	0.00	0.02	0.04

grams and concluded that differences in fracture risk between risedronate or raloxifene and alendronate were small, whereas nasal calcitonin recipients had a higher nonvertebral fracture risk.

The results of this network meta-analysis are consistent with those of other evidence synthesis reports. Hopkins *et al.* (47) concluded that teriparatide, zoledronic acid, and denosumab have the highest probabilities of being most efficacious for nonvertebral and vertebral fractures. MacLean *et al.* (3) concluded that bisphosphonates and PTH were effective in reducing the risk of fractures compared with placebo but could not provide inference regarding the relative efficacy of the different agents due to the small number of head-to-head trials and of events in these trials. Study-level meta-analysis (10) and individual patient data pooled analysis (48) demonstrated that vitamin D, only if given with calcium, reduces hip fractures and total fractures, and probably vertebral fractures, irrespective of age, sex, or history of previous fractures. Avenell *et al.* (10) demonstrated in their meta-analysis that vitamin D combined with calcium led to a similar reduction in the risk of hip fracture compared with that demonstrated in our meta-analysis (relative risk, 0.84; 95% CI, 0.73–0.96; *vs.* OR, 0.81; 95% CI, 0.68–0.96). Consistent with our results, they also demonstrated that vitamin D on its own does not reduce the risk of hip, vertebral, or nonvertebral fractures.

The present network meta-analysis brings the evidence base to the present date and allows the evaluation of all the available interventions including denosumab and SERM. The potential relative superiority of teriparatide found in this meta-analysis is consistent with a recent randomized trial that demonstrated lower incidence of new vertebral fractures compared with risedronate in postmenopausal women after 18 months of therapy (4.4 *vs.* 9.4%; $P = 0.01$) (17).

Clinical implications

Treatment options to care for people at increased fracture risk have substantially expanded since the widespread introduction of oral bisphosphonate therapy in the mid-1990s, before which there were comparatively few effective options for treating this condition. At present, there are multiple medication choices across multiple drug classes with varying mechanisms of action, modes of administration, and levels of efficacy related to fracture outcomes. Given the limited comparative effectiveness studies currently available, it remains difficult for clinicians to make informed decisions about which medication or class of medications is most effective for preventing fragility fractures in susceptible individuals.

Herein, we have synthesized and summarized the available evidence to help inform clinical decision making. We found moderate-quality evidence to support the efficacy of teriparatide, denosumab, alendronate, risedronate, zoledronate, and ibandronate compared with placebo or vitamin D and calcium. The evidence supporting the efficacy of raloxifene or bazedoxifene on fractures remains imprecise due to the small number of fracture events. Vitamin D and calcium appear to be least effective. However, due both to the limited number of direct head-to-head trials and the small number of fracture outcomes in trials available for analysis, these data are insufficient to determine the comparative efficacy of each of the available osteoporosis therapies with respect to fracture outcomes. Although it would be easy to call for more comparative effectiveness research, the reality is that the large sample sizes required to generate sufficient fracture outcomes necessary to demonstrate a significant difference in fracture risk reduction between two similarly efficacious treatments would likely prove cost prohibitive and not attractive to sponsors, particularly the pharmaceutical industry.

Importantly, efficacy in fracture reduction is but one of many considerations when choosing a medication to treat osteoporosis. Additional considerations include patient comorbidities, potential side-effect profiles, relative medication costs, mode of administration, and both patient tolerance and likelihood of medication adherence. For example, patients with significant gastroesophageal reflux symptoms should avoid oral bisphosphonates, those with renal impairment should avoid iv bisphosphonates, and those who worry the most about unknown side effects of new agents may not opt for denosumab until long-term safety data are available (8).

Both patients and physicians must consider all of these factors in any informed decision as to which medication is best for a particular patient. Given the evidence state, it seems difficult to justify prescription for particularly expensive, burdensome, or less safe medicines. If this were not to be the case, the cost of conducting comparative effectiveness research with large sample sizes and number of events may become justified by the potential cost savings in providing higher quality information to decision makers (policymakers, formulary designers, clinicians, and patients). The accompanying guideline from The Endocrine Society (9) will provide the practical and clinical implications of our findings in men.

Conclusions

Teriparatide, bisphosphonates, and denosumab are most effective in reducing the risk of fragility fractures. Differences in efficacy across drugs are small; therefore, treatment decisions should also be based on the associated harms and costs.

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Address all correspondence and requests for reprints to: M. Hassan Murad, M.D., M.P.H., Mayo Clinic, The Knowledge and Encounter Research Unit, 200 First Street SW, Rochester, Minnesota 55905. E-mail: Murad.mohammad@mayo.edu.

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