Potential Role of Network Meta-Analysis in Value-Based Insurance Design

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It is estimated that more than 10 million Americans 50 years or older have osteoporosis and more than 43 million have low bone mass.[1] A chronic condition characterized by low bone mass and deterioration of bone microarchitecture, osteoporosis increases patients' risk of bone fracture. Most common fractures include those of the vertebrae, hip, and wrist, and result in substantial morbidity and medical and hospital costs. It is estimated that approximately 2.05 million osteoporosis-related fractures occur annually in the United States, costing about $16.9 billion.[2] Osteoporosis management focuses on reducing fracture risk, and includes lifestyle modification (eg, smoking cessation and alcohol moderation), weight-bearing exercises, and treatment with pharmaceuticals. Various classes of pharmaceuticals are indicated for osteoporosis treatment, among them bisphosphonates (including alendronate, ibandronate, and risedronate), recombinant parathyroid hormone (teriparatide), selective estrogen receptor modulator (raloxifene), and monoclonal antibodies (denosumab). osteoporosis therapies—alendronate, ibandronate, risedronate, raloxifene, teriparatide—are generally available through a health plan's pharmacy benefit.

Historically, drug co-payments and coinsurance have been largely based on drug cost, and did not take treatment benefit into account. However, this paradigm is changing, and a move toward value-based insurance design (V-BID) is gathering momentum.[3-5] Essentially, the aim of V-BID is to improve healthcare and reduce costs by encouraging high-value care—care that offers clinical benefits at a reasonable cost—and discouraging low-value care. First proposed more than a decade ago, various value-based health insurance programs are now established and subject to much discussion and evaluation in the medical literature. V-BID has been applied to many indications, including diabetes, hyperlipidemia, and asthma.[6-9]

In contrast to existing approaches to V-BID in which co-payments are reduced to encourage use of broad categories

ABSTRACT

Objectives

Value-based insurance design (V-BID) has emerged as an approach to improve health outcomes and contain healthcare costs by encouraging use of high-value care. We estimated the impact of a V-BID for osteoporosis treatments using comparative effectiveness evidence and real-world data from a California health insurance plan to estimate the benefits of the design's implementation.

Methods

This study consisted of 4 steps. First, we reviewed randomized clinical trials including osteoporosis treatments—alendronate, ibandronate, risedronate, raloxifene, and teriparatide—reported in a recent Agency for Health Research Quality systematic review. Second, we performed a network meta-analysis to synthesize data from the clinical trials and estimate the comparative effectiveness of included treatments. Third, we implemented a V-BID by removing co-payments for the most effective treatments. Fourth, using a Monte Carlo simulation, we estimated the impact of the V-BID in terms of fracture reduction and cost-savings.

Results

Thirty-two randomized controlled trials were included in the network meta-analysis. We estimated that alendronate, risedronate, and teriparatide have the highest probability of being most effective across each fracture type—vertebral, hip, and nonvertebral/nonhip. After eliminating co-payments, (ie, reducing them to zero), for these treatments, we estimated the health plan would experience a 7% (n = 287) decrease in fractures and an 8% ($6.8 million) decrease in costs.

Conclusions

Our study illustrates the benefits of comparative effectiveness evidence in V-BID development. We show that where clinical trials are lacking, network meta-analysis can provide valuable insights into the potential clinical and economic benefits of V-BID.

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Take-Away Points

In this study, we use network meta-analysis to generate comparative effectiveness evidence and rank osteoporosis treatments in order of efficacy. Using claims data from a large California health plan, we illustrate that where clinical trials are lacking, network meta-analysis can provide valuable insights into the potential clinical and economic benefits of value-based insurance design (V-BID). This study:

- Emphasizes the importance of taking an evidence-based approach to pharmacy benefit design.
- Illustrates the potential value of network meta-analysis in the absence of appropriate clinical trial evidence.
- Provides a framework for using evidence synthesis methods in V-BID.

of high-value care (eg, statins for hypercholesterolemia or hyperglycemic medications for type 2 diabetes mellitus), we sought to use comparative effectiveness evidence to prioritize treatments within a drug class, using drugs that treat osteoporosis as a case study.[7,10] However, as osteoporosis treatments have not been adequately compared against one another in head-to-head studies, we could not rely on clinical trial data to inform our approach, and therefore we used network meta-analysis to synthesize the necessary comparative evidence.

Network meta-analysis is a statistical approach to synthesizing comparative effectiveness evidence and is a generalization of meta-analysis, combining head-to-head clinical trial evidence with statistically inferred indirect comparisons across treatments not studied within head-to-head clinical studies.[11,12] The approach requires a connected network of clinical trials. For example, in a data set consisting of pairwise comparisons (eg, A compared with B, and A compared with C), the relative efficacy can be inferred for those comparisons not studied directly (eg, in the previous example, B compared with C through common comparator A). Thus, through a combination of direct and indirect evidence, the network meta-analysis provides the relative efficacy of the whole network. Network meta-analysis has 2 principal roles: first, to strengthen inference of relative effectiveness between a pair of treatments through the combination of direct and indirect evidence; and second, to infer relative efficacies between treatments that have not been evaluated in a head-to-head study. Furthermore, the approach allows estimation of the probability that each included treatment is most effective, an important consideration for V-BID. Network meta-analysis methods are increasingly used and are promoted by health technology assessment agencies including the National Institute for Health and Clinical Excellence (NICE) and the Canadian Agency for Drugs and Technology in Health (CADTH).[13-15]

The objectives of this study were to construct a V-BID for osteoporosis treatments using comparative effectiveness evidence synthesized from a network meta-analysis; and to illustrate the potential of this approach through estimation of the number of avoided osteoporosis-related fractures and of cost savings using a simulation model. These estimates were specific to a large California-based health plan. We considered the osteoporosis treatments alendronate, ibandronate, risedronate, raloxifene, and teriparatide in this research, as these drugs are commonly available through drug formularies. We excluded the intravenously administered osteoporosis treatments denosumab and zoledronic acid, as they are not typically part of a tiered drug formulary and not subject to the same co-payment structure.

METHODS

We used claims obtained from a large California-based private health insurance plan. These data specified the number of patients with an osteoporosis diagnosis, and, for these patients, which one of the included treatments they received. We also used this plan data as the source of drug acquisition cost and patient co-payments.

This study consisted of 4 steps. First, we identified clinical trials of osteoporosis treatments that were included in a 2012 Agency for Healthcare Research and Quality (AHRQ) systematic review. The trials that met our inclusion criteria became part of our study. Second, using these studies, we performed a network meta-analysis to synthesize the baseline fracture risk for vertebral, hip, and nonvertebral/nonhip fracture, and the comparative effectiveness of competing treatments. Third, we simulated a V-BID by adjusting the co-payments of the existing pharmacy benefit in accordance with the synthesized comparative effectiveness data, with co-payments eliminated, ie, reduced to zero, for the most effective treatments. Fourth, we simulated the impact of co-payment adjustment in terms of fracture reduction and cost savings for the health plan. The details of each step follow.

Step 1: Study Identification and Review. We relied on studies reported in the 2012 AHRQ report *Treatment To Prevent Fractures in Men and Women With Low Bone Density or Osteoporosis: Update of a 2007 Report*.[16] Included studies were limited to those that: (i) included adults with low bone density or with osteoporosis; (ii) examined a pharmacological intervention reported within the private

health insurance plan's claims data; (iii) reported vertebral, hip, and/or total fractures; (iv) lasted a minimum of 6 months; and (v) were randomized controlled trials. Eligibility criteria of each of the included studies are listed in the **eAppendix** (available at **www.ajmc.com**). Pairs of reviewers read each article to confirm reported counts for vertebral, hip, nonvertebral, and nonvertebral/nonhip fractures, and in some instances contacted the original authors for clarification.

Step 2: Network Meta-Analysis. Using the extracted data, we performed a Bayesian network meta-analysis to estimate 2 pieces of information—underlying fracture risk, ie, the fracture risk in untreated patients, and comparative effectiveness of the various agents both to the reference treatment (placebo) and to one another.

We conducted the network meta-analysis using a random-effect, binomial logit-linked model implemented in WinBUGS 1.4. We used a binomial distribution because of the binomial nature of fractures, and the logit-link assumes a linearity of effects on the logit scale. We determined to use a random effects model after our inspection of the deviance information criterion showed no significant difference in goodness of fit between fixed and random effects models. The networks of studies for each end point (ie, vertebral fractures, hip fractures, and nonvertebral/nonhip fractures) shared the same structure, with individual studies comparing treatments to placebo, though the individual patient counts varied across the outcome networks. Characteristics of the studies populating these networks are provided in the eAppendix. For each end point, ie, vertebral, hip, and nonvertebral/nonhip fractures, we estimated the underlying fracture risk from the placebo arms of each study. We estimated the comparative effectiveness of the various agents to one another (relative risk and 95% credible interval) indirectly through the reference treatment, ie, placebo. We additionally examined a synthetic end point—total fractures—as this provided a summary efficacy end point with which to rank treatments.

Step 3: Implementation of a Value-Based Insurance Design. In accordance with the results of the network meta-analysis, we modeled the effect of implementing a V-BID by eliminating co-payments for the most effective drugs, ie, alendronate, risedronate and teriparatide. We assumed that co-payment reduction would result in a proportion of patients shifting toward these treatments. How consumers respond to price is typically quantified using the elasticity of demand, which provides an estimate of how utilization of a product is influenced by price. For example, if a product's price decreases 10% and the elasticity of demand is –0.5, then the population will consume 5% more of the product. Based on estimates from the literature, we simulated an elasticity of demand of –0.2 to –0.6 using a uniform distribution.[17] Additionally, as a sensitivity analysis, we estimated the effects of decreasing utilization of the least effective drugs by 50% (range 10%-90%), and increasing utilization of the most effective drugs, accordingly. We used a 50% decrease in utilization of the least effective drugs as we considered it infeasible, in practice, to shift all patients.

Step 4: Estimation of Fracture Reduction and Cost-Savings. We used a simulation model to estimate the aggregate reduction in fractures and cost savings associated with implementing the V-BID using a 3-year time horizon. The model compares estimated fracture incidence and health plan costs of an existing distribution of osteoporosis treatments among a cohort of patients with an osteoporosis diagnosis covered by a large, private California health plan (n = 13,777) with an alternative distribution of treatments among this same cohort resulting from the V-BID implementation. We relied on the California health insurance plan claims data as the source of baseline drug utilization, annual drug cost, and annual patient drug co-pay, and on Shi et al (2009) for fracture cost (**Table 1**).[18] Using a Monte Carlo simulation approach (Microsoft Excel via Visual Basic), we iterated the model 1000 times, each time using a different set of random values from each input parameter probability function (Table 1 and **Table 2**). Using this method, uncertainties in model inputs are propagated into uncertainties in model outputs, ie, mean estimate and 95% CI.

RESULTS

Thirty-two studies met our inclusion criteria and were included in the network meta-analysis, including 8 randomized, placebo-controlled trials pertaining to alendronate, 4 to ibandronate, 3 to raloxifene, 13 to risedronate, and 4 to teriparatide (details of each study provided in the **eAppendix**, available at **www.ajmc.com**). Results from the network meta-analyses are shown in Table 2. For vertebral, hip, and nonvertebral/nonhip fractures, alendronate, risedronate, and teriparatide were consistently estimated to have the 3 highest probabilities of being the most effective treatment, although rank order varied by end point. Teriparatide and risedronate had the highest probabilities of being the best treatment for vertebral and nonvertebral/nonhip fractures with alendronate ranked third. Alendronate was ranked second to risedronate for hip fracture. To confirm efficacy order and provide an ag-

Table 1. Simulation Model Cost and Drug Utilization Input Parameters[a]

	Source	Estimate	Distribution
Cost			
Vertebral fractures	Shi et al 2009[18]	$14,977	Gamma (1.27, 11,828)
Hip fractures	Shi et al 2009[18]	$26,545	Gamma (1.9, 13,960)
Nonvertebral nonhip fractures	Shi et al 2009[18]	$9183	Gamma (0.8, 11,499)
Elasticity of demand	Goldman et al[17]	0.5	Uniform (0.4, 0.6)
Baseline drug utilization			
Number of patients	CA Health Plan	13,377	
Alendronate	CA Health Plan	44.8%	
Ibandronate	CA Health Plan	19.8%	
Risedronate	CA Health Plan	21.7%	
Raloxifene	CA Health Plan	9.6%	
Teriparatide	CA Health Plan	4.1%	
Annual cost of drugs to plan			
Alendronate	CA Health Plan	$24	
Ibandronate	CA Health Plan	$483	
Risedronate	CA Health Plan	$505	
Raloxifene	CA Health Plan	$634	
Teriparatide	CA Health Plan	$5610	
Annual patient co-pay of drugs			
Alendronate	CA Health Plan	$49	
Ibandronate	CA Health Plan	$166	
Risedronate	CA Health Plan	$179	
Raloxifene	CA Health Plan	$187	
Teriparatide	CA Health Plan	$260	

[a]Relative efficacy of different drugs can be found in Table 2.

gregate efficacy end point, we constructed the synthetic end point of total fractures. Consistent with the other end points, alendronate, risedronate, and teriparatide were estimated to have the highest probability of being the most effective. Across each end point, ibandronate and raloxifene were consistently estimated to have the lowest probability of being most effective. Consistent with these findings, we constructed a V-BID by eliminating co-payments for alendronate, risedronate, and teriparatide, while maintaining the existing co-payment for ibandronate and raloxifene.

We estimated that plan beneficiaries receiving treatments under the current benefit structure would suffer an estimated 3668 total fractures and incur roughly $72.9 million in osteoporosis-related costs, with $67.8 million related to fracture costs (Table 3). Implementing the V-BID resulted in an estimated 3381 total fractures and costs of approximately $66.1 million, with $60.9 million related to fracture costs. Therefore, compared with the status quo, the V-BID was estimated to result in 287 fewer fractures (a 7% reduction) while reducing health plan costs by approximately $6.8 million (an 8% reduction). Percentage reduction in costs was greater than the percentage reduction in fractures as the majority of avoided fractures were of the hip (221, 77% of total fractures), the fracture type associated with the highest average cost ($26,545). Indeed, hip fracture reduction accounted for the majority of cost savings, approximately $6.2 million (approximately 90% of total fracture-related cost saving). Implementing the V-BID reduced co-payment revenue by approximately $113,000 (7%), but this was more than offset by cost savings resulting from reduced hospitalizations of approximately $6.9 million (8%), and reduced drug costs of approximately $63,000 (1%).

We simulated a scenario in which 50% (range 10% to 90%) of individuals using the least effective treatments were shifted to the most effective treatments. In this scenario, the number of total fractures was reduced by 8.5% (range 1.8% to 15.5%; corresponding to a 10% and 90% shift, respectively) and total costs for the plan were reduced by 9.0% (range 1.9% to 16.0%).

Table 2. Relative Treatment Effect Estimated From Network Meta-Analysis

	Hip Fractures		Vertebral Fractures		Nonvertebral/Nonhip Fractures		All/Any Fractures	
	Median RR [95% Credible Interval]	% Best[a]	Median RR [95% Credible Interval]	% Best[a]	Median RR [95% Credible Interval]	% Best[a]	Median RR [95% Credible Interval]	% Best[a]
Alendronate vs		25.17%		6.42%		1.91%		2.37%
placebo	0.541 [0.114~1.814]		0.551 [0.352~0.8378]		0.879 [0.528~1.257]		0.662 [0.421~0.911]	
ibandronate	0.375 [0.042~4.019]		0.879 [0.515~1.698]		0.794 [0.385~1.457]		0.9 [0.514~1.599]	
risedronate	1.178 [0.211~5.795]		1.067 [0.645~1.81]		1.659 [0.969~2.987]		1.46 [0.918~2.255]	
raloxifene	0.623 [0.069~5.352]		0.834 [0.452~1.457]		0.894 [0.489~1.449]		0.762 [0.402~1.216]	
teriparatide	0.733 [0.064~10.6]		1.641 [0.731~3.743]		1.361 [0.718~2.334]		1.496 [0.798~2.456]	
Ibandronate vs		5.73%		2.71%		0.061%		1.32%
placebo	1.456 [0.173~6.472]		0.629 [0.385~0.875]		1.106 [0.657~1.813]		0.738 [0.451~1.043]	
risedronate	3.154 [0.341~20.28]		1.214 [0.711~1.887]		2.093 [1.171~4.237]		1.621 [0.986~2.584]	
raloxifene	1.638 [0.125~17.99]		0.952 [0.481~1.542]		1.126 [0.6188~2.059]		0.848 [0.736~1.390]	
teriparatide	1.945 [0.119~34.37]		1.865 [0.794~4.014]		1.716 [0.894~3.308]		1.666 [0.864~2.795]	
Risedronate vs		36.11%		6.78%		76.21%		43.45%
placebo	0.457 [0.161~1.046]		0.516 [0.379~0.671]		0.525 [0.334~0.742]		0.451 [0.331~0.575]	
raloxifene	0.5266 [0.082~3.758]		0.782 [0.456~1.220]		0.537 [0.305~0.837]		0.521 [0.303~0.789]	
teriparatide	0.6241 [0.072~7.784]		1.537 [0.725~3.241]		0.818 [0.442~1.376]		1.023 [0.601~1.59]	
Raloxifene vs		8.46%		0.097%		0.029%		0.011%
placebo	0.8787 [0.1349~3.967]		0.661 [0.449~1.006]		0.983 [0.696~1.338]		0.873 [0.935~1.305]	
teriparatide	1.196 [0.0873~20.17]		1.963 [0.923~4.546]		1.528 [0.91~2.566]		1.975 [1.131~3.507]	
Teriparatide vs		24.44%		83.11%		20.96%		52.76%
placebo	0.732 [0.064~4.655]		0.336 [0.164~0.658]		0.6425 [0.421~0.955]		0.442 [0.234~0.668]	

Baseline Risk of Vertebral Fracture: 0.0997 [0.03644-0.2455]; RR = relative risk compared with placebo. Median reported RR from 100,000 iterations of network meta-analysis. 95% credible interval of these 100,000 iterations reported.
[a]Proportion of iterations in which treatment is estimated to be best among all alternatives.

DISCUSSION

Osteoporosis is a burdensome disease that will become increasingly prevalent as the population ages.[2] Alongside lifestyle changes, pharmaceuticals are an integral part of disease management. This study builds on a growing body of literature showing how V-BID can lead to improved drug adherence, health outcomes, and cost savings.[6,19,20] We took a novel approach to constructing a V-BID formulary and estimating potential health benefits and cost savings using real-world data from a major California-based private health plan. Our approach incorporated available randomized clinical trial evidence reported in an AHRQ systematic review, and used established statistical approaches to develop a V-BID. We estimated that alendronate, risedronate, and teriparatide were the most

Table 3. Results of Simulation Model

	Elasticity of Demand				Shift 10%	Shift 50%	Shift 90%
	Status Quo	VBID	Difference (95% CI)	% Diff	% Diff	% Diff	% Diff
Clinical events							
All clinical events	3668	3381	–287 (–311 to –263)	7.0%	1.8%	8.5%	15.5%
New vertebral fractures	857	838	–19 (–20 to –17)	2.2%	0.5%	2.6%	4.8%
New hip fractures	1563	1342	–221 (–198 to –245)	11.7%	3.0%	14.8%	25.8%
New nonvertebral nonhip fractures	1249	1202	–47 (–51 to –43)	3.8%	1.0%	4.6%	9.1%
Fracture cost							
All clinical events	$67,786,187	$60,922,544	–$6,863,642 (–$7,668,619 to –$6,058,666)	8.4%	2.1%	10.2%	18.1%
New vertebral fractures	$13,470,148	$13,184,785	–$285,363 (–324,219 to –246,507)	2.2%	0.5%	2.6%	4.8%
New hip fractures	$43,519,585	$37,324,929	–$6,194,655 (–$6,997,112 to –$5,392,198)	11.7%	3.0%	14.8%	25.8%
New nonvertebral nonhip fractures	$10,796,454	$10,412,830	–$383,624 (–$434,193 to –$333,054)	3.8%	1.0%	4.6%	9.1%
Revenue and other costs							
Cost of drug to health plan	$6,748,342	$6,685,728	–$62,614 (–$63,711 to –$61,518)	0.9%	0.2%	1.2%	2.1%
Co-payment revenue	$1,637,965	$1,524,886	–$113,079 (–$115,059 to –$111,098)	6.9%	1.7%	8.6%	15.5%
Total cost	$72,896,564	$66,083,387	–$6,813,178 (–$7,618,078 to –$6,008,278)	7.5%	1.9%	9.0%	16.0%
Total cost per person	$5449	$4940	–$509 (–$569 to –$449)	9.3%	2.2%	10.8%	19.9%

efficacious treatments, with ibandronate and raloxifene performing unfavorably across the considered end points. These findings are consistent with other network meta-analyses evaluating these treatments.[21,22] We estimated that implementation of the V-BID would avoid 287 fractures (7%), including 19 vertebral fractures, 221 hip fractures, and 47 nonvertebral nonhip fractures, and would result in $6.8 million (8%) in cost savings for 1 California-based health plan. However, as our approach is associated with inherent uncertainties, and assumptions regarding adherence and therapeutic substitution, study results should be considered illustrative. Nevertheless, our findings support a burgeoning body of literature showing that V-BIDs can lead to both clinical and economic benefits.

Limitations. One limitation of our study is that it does not account for drug adherence, an important aspect of care for which V-BIDs have been shown to have a positive impact.[6,19,20] Another limitation is that we based our V-BID solely on efficacy data, which is only 1 input into prescribing decisions, and did not account for other factors that play a role, including side effect profile and drug interactions. Patient and physician preferences also likely play a role. For example, unlike the other considered orally administered treatments, teriparatide is administered via subcutaneous injection, which may affect patient treatment preference.[23] In addition, the FDA-approved labels for teriparatide and raloxifene include a black box warning for potential increase in the incidence of osteosarcoma, and increased risk of venous thromboembolism and death from stroke, respectively, which may also affect patient and physician choice.[1,23] Further, we did not consider whether physicians account for treatment cost in prescribing decisions; evidence as to whether physicians account for the cost of technology, or patients' ability to pay, in prescribing decisions is conflicting.[24-26] These limitations may have affected estimated health gain and cost savings.

Moreover, network meta-analyses do not possess the validity of head-to-head clinical trials and it is important to recognize the approach's limitations. By extrapolating the

available data, network meta-analysis makes indirect comparisons between treatments not subject to head-to head clinical trials. As is the case for traditional meta-analysis, because randomization only holds within and not across the clinical trials included in a network meta-analysis, there is a risk of consistency violations, ie, that patients included in different comparisons are dissimilar. Therefore, a firm conclusion can be best drawn when a network meta-analysis is restricted to well-conducted, adequately powered randomized trials including similar patient populations.

These caveats notwithstanding, evidence suggests that results from well-conducted network meta-analyses are typically consistent with those from head-to-head randomized clinical trials.[27] Further, while adequately powered prospective randomized clinical trials comparing all competing treatments provide the most robust information, they are infeasible in practice. Network meta-analysis approaches likely will become increasingly recognized and accepted as the source of this evidence, since they allow decision makers to immediately compare treatments as new evidence and treatments are produced.

We did not include osteoporosis treatments administered in an outpatient setting (eg, denosumab and zoledronic acid), because they are typically not part of the pharmacy benefit. While including outpatient drugs in the analysis would more comprehensively account for osteoporosis therapeutic options, the study would need to be redesigned and expanded beyond the scope of a pharmacy benefit.

Osteoporosis was particularly amenable to this study as fracture occurrence is the predominant cause of disease-related morbidity and costs. Minimizing fractures leads to unambiguous health benefits for patients, and the avoidance of costly hospitalizations for the health plan. While this approach could be in theory extended to other indications, complex chronic diseases with multiple health states would require a more elaborate disease model and simulation approach.

CONCLUSIONS

Our approach illustrates the potential of using existing systematic review evidence and established evidence synthesis techniques for V-BID. It is a novel evidence-based approach that relies on comparative effectiveness evidence, and allows all available clinical trial evidence to be accounted for. While pharmacy benefit design should be informed by well-structured randomized controlled trials when available, we show that applying properly done network meta-analysis can provide insights where trials alone are lacking, and a realistic means of simulating the clinical and economic benefits of V-BID.

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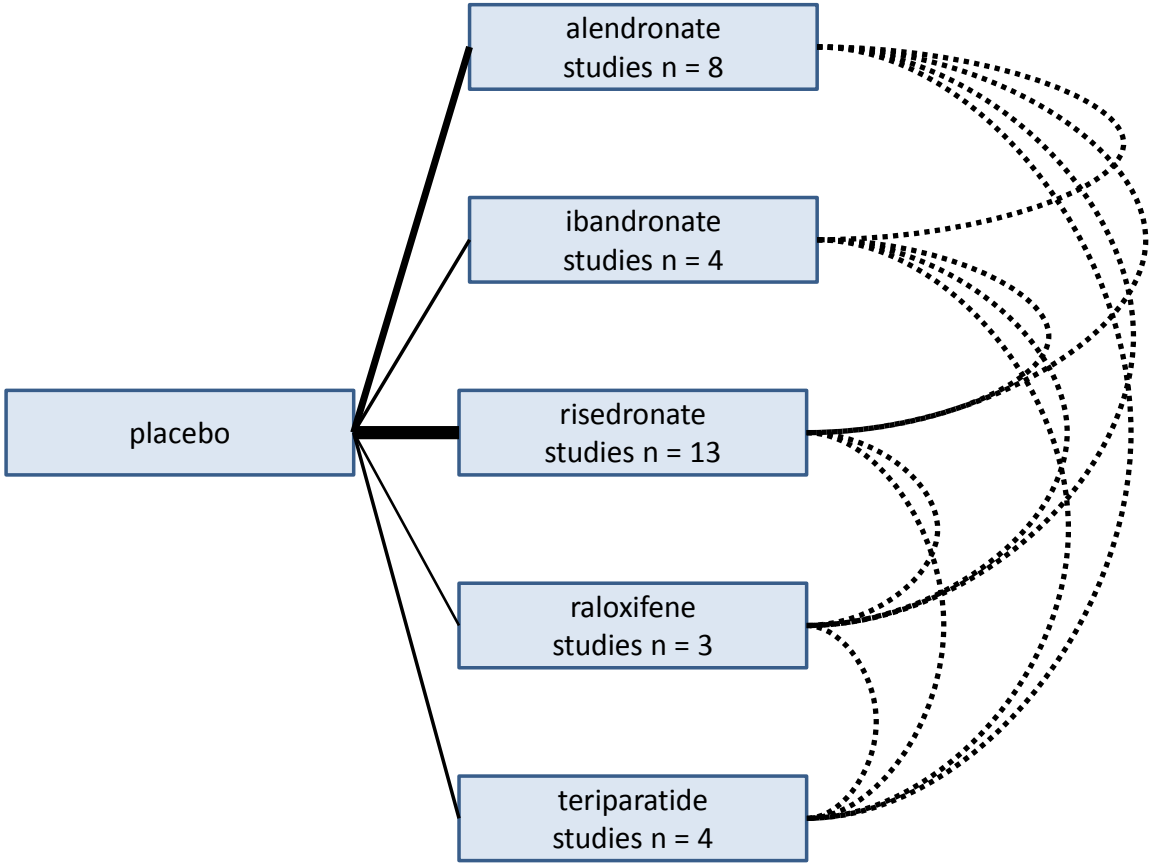
Figure 1: Network of placebo controlled trials used in mixed treatment meta-analyses; trials powered to detect a change in fractures.



*Note: Solid lines denote direct comparison observed in trials, with line boldness indicating the number of included studies. Dashed lines denote indirect comparisons obtained through the network meta-analysis.

Agency for Healthcare Research & Quality (AHRQ) systematic review Study Eligibility Criteria (as reported in *Treatment To Prevent Fractures in Men and Women With Low Bone Density or Osteoporosis: Update of a 2007 Report*)

Populations: Studies were limited to those recruiting adults over 18 (not children); healthy adults, those with low bone density, or those with osteoporosis (but not those with Paget's disease, cancer, or any other disease of bone metabolism); those using drugs indicated for the treatment of osteoporosis (but not if the drugs were being used to treat cancer); adults who had low bone density or were at high risk of developing low bone density as a result of chronic use of glucocorticoids (GC) or a condition associated with the chronic use of glucocorticoids (such as asthma, organ transplant, rheumatoid arthritis); adults who had low bone density or were at high risk of developing low bone density as a result of having a condition associated with low bone density (e.g., rheumatoid arthritis, cystic fibrosis, Parkinson's disease).

Interventions: Studies were included if they examined pharmacological interventions for prevention or treatment of osteoporosis approved (or expected to be soon approved for use in the United States) or if they assessed the effects of calcium, vitamin D, or physical activity.

Comparators: Studies included for assessing effectiveness were those that compared the effects of the intervention in question to that of placebo or another potency or dosing schedule for the same agent or another agent in the same or another class.

Outcomes: For effectiveness analysis, only studies that assessed vertebral, hip, and/or total fractures (and did not state that they were not powered to detect a change in risk for fracture) were included. Studies that reported fracture as an adverse event were excluded from effectiveness analysis because the way that adverse events are typically ascertained does not ensure systematic identification of these events across or even within study

*Non-vertebral fractures calculated as the sum of hip and non-vertebral, non-hip, with greatest number of patients reported.
**Total fractures calculated as the sum of vertebral and non-vertebral fractures, with greatest number of patients reported.
‡: Original study reports an ambiguous non-vertebral outcome, because of the potential for this endpoint to include hip fractures, the values were not included within analyses.

groups; however, fractures reported as adverse events for example atypical (low-stress subtrochanteric or femur) fractures, were included in the adverse event analysis.

Duration: Studies that had a minimum follow-up time of 6 months were included. Design: Only RCTs and published systematic reviews of RCTs that met inclusion criteria were included in the assessment of effectiveness; however, for the assessment of effects in subgroups for which no RCTs were available, for the assessment of the effect of adherence on effectiveness, and for the assessment of particular serious adverse events, large (more than 1,000 participants) observational studies and systematic reviews were included.

*Non-vertebral fractures calculated as the sum of hip and non-vertebral, non-hip, with greatest number of patients reported.
**Total fractures calculated as the sum of vertebral and non-vertebral fractures, with greatest number of patients reported.
‡: Original study reports an ambiguous non-vertebral outcome, because of the potential for this endpoint to include hip fractures, the values were not included within analyses.

Characteristics of Studies Included in Network Meta-Analyses

Reference	Comparison	Study duration (months)	Vertebral fractures		Hip fractures		Non-vertebral Non-hip fractures		Non-vertebral fractures*		Total fractures**	
			Active n/N	Placebo n/N	Active n/N	Placebo n/N	Active n/N	Placebo n/N	Active n/N	Placebo n/N	Active n/N	Placebo n/N
Alendronate vs. placebo												
Cummings et al., 1998	Alendronate (5 mg/d×2yr, 10 mg/d×1yr) vs. placebo	48	43/2057	78/2077	19/2214	24/2218	242/2214	270/2218	261/2214	294/2218	304/2214	372/2218
Quandt et al., 2005	Alendronate (5 mg/d×2yr, 10 mg/d×2.5yr) vs. placebo	54	12/1878	29/1859	N/A		N/A		N/A		12/1878	29/1859
Sato et al., 2006	Alendronate (5 mg/d) vs. placebo	48	N/A		4/131	14/129	N/A		4/131	14/129	4/131	14/129
Zein et al., 2005	Alendronate (10 mg/d) vs. placebo	12	1/14	0/13	N/A		0/14	1/13	0/14	1/13	1/14	1/13
Ringe et al., 2007	Alendronate (10 mg/d) vs. placebo	24	4/30	5/30	N/A		N/A‡		6/30	4/30	10/30	9/30
McClung et al., 2006	Alendronate (10 mg/d) vs. placebo	12	1/46	1/46	N/A		N/A		N/A		1/46	1/46
Papaioannou et al., 2008	Alendronate (10 mg/d) vs. placebo	12	0/23	2/24	N/A		N/A		N/A		0/23	2/24
de Nijs et al., 2006	Alendronate (10 mg/d) vs. placebo	18	N/A		N/A		2/99	3/101	2/99	3/101	2/99	3/101
Ibandronate vs. placebo												
Chesnut et al., 2004	Ibandronate (2.5 mg/d) vs. placebo	36	37/977	73/975	6/977	4/975	68/977	61/975	74/977	65/975	111/977	138/975
Grotz et al., 2001	Ibandronate (1 and 2 mg, intermittent) vs. placebo	12	1/40	1/40	N/A		N/A		N/A		1/40	1/40
Recker et al., 2004	Ibandronate (1 and 0.5 mg, intermittent) vs. placebo	36	80/961	95/949	N/A		N/A		N/A		80/961	95/949
Fahrleitner-Pammer et al., 2009	Ibandronate (2 mg, intermittent) vs. placebo	12	2/17	10/18	N/A		N/A		N/A		2/17	10/18

*Non-vertebral fractures calculated as the sum of hip and non-vertebral, non-hip, with greatest number of patients reported.
**Total fractures calculated as the sum of vertebral and non-vertebral fractures, with greatest number of patients reported.
‡: Original study reports an ambiguous non-vertebral outcome, because of the potential for this endpoint to include hip fractures, the values were not included within analyses.

Reference	Comparison	Study duration (months)	Vertebral fractures		Hip fractures		Non-vertebral Non-hip fractures		Non-vertebral fractures		Total fractures	
			Active n/N	Placebo n/N	Active n/N	Placebo n/N	Active n/N	Placebo n/N	Active n/N	Placebo n/N	Active n/N	Placebo n/N
Risedronate vs. placebo												
Reginster et al., 2000	Risedronate (2.5 or 5 mg/d) vs. placebo	36	53/344	89/346	9/408	11/408	27/408	40/408	36/408	51/408	89/408	140/408
Harris et al., 1999	Risedronate (2.5 or 5 mg/d) vs. placebo	36	61/696	93/678	12/821	15/820	21/821	37/820	33/821	52/820	94/821	145/820
Hooper et al., 2005	Risedronate (5 mg/d) vs. placebo	24	10/129	10/125	N/A		N/A‡		5/129	6/129	15/129	10/125
Sorensen et al., 2003	Risedronate (5 mg/d) vs. placebo	24	15/109	29/103	N/A		7/135	11/129	7/135	11/129	22/135	40/129
Kanaji et al., 2006	Risedronate (2.5 mg/d) vs. placebo	12	0/12	0/11	N/A		N/A		N/A		0/12	0/11
Sato et al., 2005	Risedronate (2.5 mg/d) vs. placebo	18	N/A		5/231	19/230	3/231	8/230	8/231	27/230	8/231	27/230
Sato et al., 2005	Risedronate (2.5 mg/d) vs. placebo	18	N/A		2/134	10/133	N/A		2/134	10/133	2/134	10/133
Palomba et al., 2005	Risedronate (5 mg/d) vs. placebo	12	5/40	14/41	N/A		0/40	4/41	0/40	4/41	5/40	18/41
Sato et al., 2007	Risedronate (2.5 mg/d) vs. placebo	24	N/A		3/121	9/121	N/A		3/121	9/121	3/121	9/121
Ringe et al., 2009	Risedronate (5 mg/d) vs. placebo	24	14/152	35/148	N/A		N/A‡		18/152	33/148	32/152	68/148
Ringe et al., 2006	Risedronate (5 mg/d) vs. placebo	12	8/158	20/158	N/A		N/A‡		10/158	17/158	18/158	37/158
Boonen et al., 2009	Risedronate (5 mg/d) vs. placebo	24	2/191	0/93	N/A		N/A		N/A		2/191	0/93
Palomba et al., 2008	Risedronate (5 mg/d) vs. placebo	36	7/40	16/41	N/A		2/40	11/41	2/40	11/41	9/40	27/41

*Non-vertebral fractures calculated as the sum of hip and non-vertebral, non-hip, with greatest number of patients reported.
**Total fractures calculated as the sum of vertebral and non-vertebral fractures, with greatest number of patients reported.
‡: Original study reports an ambiguous non-vertebral outcome, because of the potential for this endpoint to include hip fractures, the values were not included within analyses.

Reference	Comparison	Study duration (months)	Vertebral fractures		Hip fractures		Non-vertebral Non-hip fractures		Nonvertebral fractures*		Total fractures**	
			Active n/N	Placebo n/N	Active n/N	Placebo n/N	Active n/N	Placebo n/N	Active n/N	Placebo n/N	Active n/N	Placebo n/N
Raloxifene vs. placebo												
Reid et al., 2004	Raloxifene (60 mg/d or 150 mg/d) vs. placebo	36	4/193	1/90	N/A		N/A		N/A		4/193	1/90
Ensrud et al., 2008	Raloxifene (60 mg/d) vs. placebo	67.2	64/5044	97/5057	89/5044	103/5057	339/5044	335/5057	428/5044	438/5057	492/5044	535/5057
Silverman et al., 2008	Raloxifene (60 mg/d) vs. placebo	36	43/1849	77/1885	N/A		89/1849	99/1885	89/1849	99/1885	132/1849	176/1885
Teriparatide vs. placebo												
Gallagher et al., 2005	Teriparatide (20 µg/d) vs. placebo	21	22/403	62/398	1/467	3/464	29/467	43/464	30/467	46/464	52/467	108/464
Kaufman et al., 2005	Teriparatide (20 or 40 µg/d) vs. placebo	30	10/176	12/103	N/A		N/A		N/A		10/176	12/103
Orwoll et al., 2003	Teriparatide (20 or 40 µg/d) vs. placebo	11	N/A		N/A		3/290	3/147	3/290	3/147	3/290	3/147
Neer et al., 2001	Teriparatide (40 µg/d) vs. placebo	24	19/434	64/448	3/552	4/544	34/552	53/544	37/552	57/554	56/552	121/554

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