Efficacy of Pharmacological Therapies for the Prevention of Fractures in Postmenopausal Women: A Network Meta-Analysis

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Background: Osteoporosis and osteopenia are associated with increased fracture incidence in postmenopausal women. We aimed to determine the comparative effectiveness of various available pharmacological therapies.

Methods: We searched MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, ISI Web of Science, and Scopus for randomized controlled trials that enrolled postmenopausal women with primary osteoporosis and evaluated the risk of hip, vertebral, or nonvertebral fractures. A network meta-analysis was conducted using the multivariate random effects method.

Results: We included 107 trials (193,987 postmenopausal women; mean age, 66 years; 55% white; median follow-up, 28 months). A significant reduction in hip fractures was observed with romosozumab, alendronate, zoledronate, risedronate, denosumab, estrogen with progesterone, and calcium in combination with vitamin D. A significant reduction in nonvertebral fractures was observed with abaloparatide, romosozumab, denosumab, teriparatide, alendronate, risedronate, zoledronate, lasofoxifene, tibolone, estrogen with progesterone, and vitamin D. A significant reduction in vertebral fractures was observed with abaloparatide, teriparatide, parathyroid hormone 1-84, romosozumab, strontium ranelate, denosumab, zoledronate, risedronate, alendronate, ibandronate, raloxifene, bazedoxifene, lasofoxifene, estrogen with progesterone, tibolone, and calcitonin. Teriparatide, abaloparatide, denosumab, and romosozumab were associated with the highest relative risk reductions, whereas ibandronate and selective estrogen receptor modulators had lower efficacy. The evidence for the treatment of fractures with vitamin D and calcium remains limited despite numerous large trials.

Conclusions: This network meta-analysis provides comparative effective estimates for the various available treatments to reduce the risk of fragility fractures in postmenopausal women. (***J Clin Endocrinol Metab*** **104: 1623–1630, 2019)**

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Abbreviations: PTH, parathyroid hormone; RR, relative risk.

Table 1. Network Meta-Analysis of Hip Fractures

	Abaloparatide	Romosozumab	Calcitonin	Lasofoxifene	Strontium Ranelate	Tibolone	Hormone Therapy	Bazedoxifene
Placebo	0.24 (0.01–4.84)	0.44 (0.24–0.79)[a]	0.48 (0.21–1.10)	0.83 (0.55–1.26)	0.89 (0.67–1.18)	0.69 (0.32–1.51)	0.72 (0.53–0.98)[a]	0.93 (0.37–2.33)
Abaloparatide		1.80 (0.08–38.28)	1.97 (0.09–44.20)	3.44 (0.17–70.76)	3.69 (0.18–74.79)	2.85 (0.13–63.12)	2.98 (0.15–60.61)	3.85 (0.17–88.41)
Romosozumab			1.09 (0.39–3.06)	1.91 (0.92–3.94)	2.04 (1.06–3.96)[a]	1.58 (0.59–4.23)	1.65 (0.84–3.23)	2.14 (0.71–6.38)
Calcitonin				1.75 (0.69–4.45)	1.87 (0.77–4.55)	1.45 (0.46–4.57)	1.51 (0.62–3.71)	1.96 (0.56–6.79)
Lasofoxifene					1.07 (0.65–1.77)	0.83 (0.34–2.01)	0.87 (0.52–1.45)	1.12 (0.41–3.06)
Strontium ranelate						0.77 (0.34–1.78)	0.81 (0.53–1.23)	1.04 (0.40–2.73)
Tibolone							1.04 (0.45–2.43)	1.35 (0.40–4.51)
Hormone therapy								1.29 (0.49–3.40)
Bazedoxifene								
Calcium								
Vitamin D + calcium								
Vitamin D								
Alendronate								
Ibandronate								
Risedronate								
Zoledronate								
Raloxifene								
Denosumab								

(*Continued*)

Osteoporosis is a disorder characterized by low bone mass, microarchitectural changes in bones, and skeletal fragility. These changes result in decreased bone strength and an increased propensity for fractures (1). The prevalence of osteoporosis increases from 4% in women aged 50 to 59 years to 52% in women aged 80 years and older (2). This disease represents a substantial health burden because of the morbidity and mortality associated with vertebral and hip fractures. A study reported that hip fractures and vertebral fractures occurred in 28% and 25%, respectively, of women with osteoporosis (3).

Several effective treatments can result in a decreased fracture risk in postmenopausal women. A previous network meta-analysis commissioned by the Endocrine Society compared these various agents in men and women and in osteoporosis of any cause (4). The results demonstrated that teriparatide may have the highest risk reduction of hip, vertebral, and nonvertebral fractures (ORs: 0.42, 0.30, and 0.50, respectively); however, differences to denosumab and various bisphosphonates were small and not statistically significant. The certainty in the evidence at that time was deemed low to moderate because of the limited head-to-head trials.

Numerous randomized trials have been published since. Furthermore, estimates focused on postmenopausal women with primary osteoporosis only are needed to guide decision-making and help patients and clinicians choose among the available therapies. Therefore, to support the Endocrine Society guideline on the management of osteoporosis in postmenopausal women, we conducted this systematic review and network meta-analysis, in which we exclusively studied postmenopausal women with primary osteoporosis or osteopenia randomized to the administration of various drugs for the prevention of fragility fractures. In addition to the interventions studied in the previous network meta-analysis (bisphosphonates, teriparatide, selective estrogen receptor modulators, denosumab, calcium, and vitamin D), we were also interested in the efficacy of other therapies such as hormone therapy, calcitonin, lasofoxifene, strontium ranelate, tibolone, and parathyroid hormone

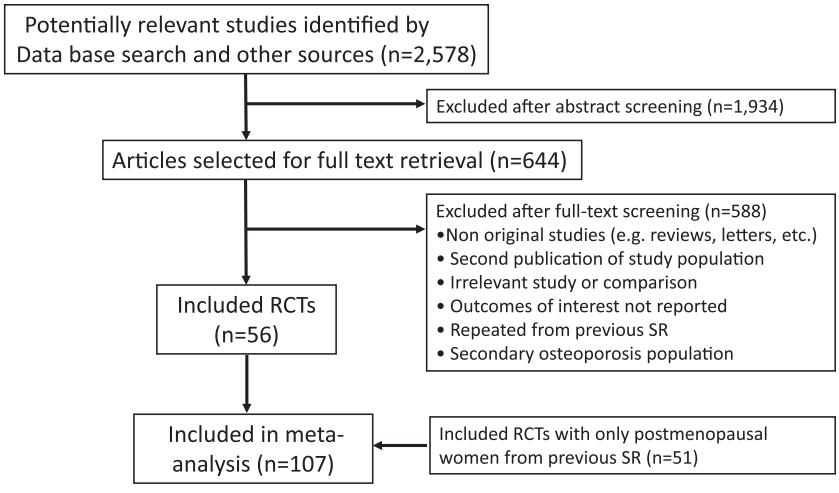

Figure 1. The process of study selection. RCT, randomized clinical trial; SR, systematic review.

Table 1. Network Meta-Analysis of Hip Fractures (Continued)

Calcium	Vitamin D + Calcium	Vitamin D	Alendronate	Ibandronate	Risedronate	Zoledronate	Raloxifene	Denosumab	Teriparatide
1.39 (0.90–2.15)	0.81 (0.71–0.93)[a]	0.69 (0.43–1.09)	0.61 (0.42–0.90)[a]	0.62 (0.29–1.36)	0.73 (0.58–0.92)[a]	0.60 (0.45–0.81)[a]	0.91 (0.71–1.17)	0.56 (0.35–0.90)[a]	0.64 (0.25–1.68)
5.76 (0.28–119.05)	3.35 (0.17–67.30)	2.84 (0.14–58.98)	2.53 (0.12–52.00)	2.58 (0.12–57.08)	3.00 (0.15–60.61)	2.49 (0.12–50.58)	3.78 (0.19–76.39)	2.33 (0.11–48.41)	2.67 (0.12–58.97)
3.20 (1.53–6.68)[a]	1.86 (1.01–3.43)[a]	1.58 (0.74–3.36)	1.40 (0.81–2.45)	1.43 (0.54–3.81)	1.67 (0.88–3.16)	1.38 (0.71–2.69)	2.09 (1.10–3.99)[a]	1.29 (0.61–2.76)	1.48 (0.48–4.56)
2.93 (1.14–7.54)[a]	1.70 (0.73–3.99)	1.45 (0.55–3.77)	1.29 (0.51–3.25)	1.31 (0.42–4.12)	1.53 (0.64–3.65)	1.27 (0.52–3.09)	1.92 (0.80–4.61)	1.19 (0.45–3.10)	1.36 (0.38–4.84)
1.68 (0.92–3.05)	0.98 (0.63–1.51)	0.83 (0.44–1.54)	0.74 (0.42–1.30)	0.75 (0.31–1.81)	0.87 (0.54–1.40)	0.72 (0.43–1.21)	1.10 (0.68–1.78)	0.68 (0.36–1.27)	0.78 (0.27–2.20)
1.56 (0.93–2.62)	0.91 (0.66–1.25)	0.77 (0.45–1.33)	0.69 (0.42–1.11)	0.70 (0.31–1.60)	0.81 (0.56–1.18)	0.68 (0.45–1.02)	1.02 (0.70–1.49)	0.63 (0.37–1.09)	0.72 (0.27–1.96)
2.02 (0.83–4.95)	1.18 (0.53–2.60)	1.00 (0.40–2.48)	0.89 (0.37–2.13)	0.91 (0.30–2.73)	1.05 (0.47–2.38)	0.87 (0.38–2.02)	1.32 (0.58–3.00)	0.82 (0.33–2.04)	0.93 (0.27–3.21)
1.93 (1.14–3.28)[a]	1.12 (0.80–1.58)	0.95 (0.55–1.67)	0.85 (0.52–1.40)	0.87 (0.38–2.00)	1.01 (0.68–1.49)	0.84 (0.54–1.29)	1.27 (0.85–1.89)	0.78 (0.45–1.37)	0.89 (0.33–2.44)
1.50 (0.54–4.13)	0.87 (0.34–2.20)	0.74 (0.26–2.06)	0.66 (0.24–1.78)	0.67 (0.20–2.23)	0.78 (0.30–2.01)	0.65 (0.25–1.70)	0.98 (0.38–2.54)	0.61 (0.22–1.70)	0.69 (0.18–2.60)
	0.58 (0.37–0.91)[a]	0.49 (0.26–0.93)[a]	0.44 (0.25–0.79)[a]	0.45 (0.18–1.09)	0.52 (0.32–0.85)[a]	0.43 (0.25–0.73)[a]	0.66 (0.40–1.08)	0.40 (0.21–0.77)[a]	0.46 (0.16–1.32)
		0.85 (0.52–1.38)	0.76 (0.50–1.14)	0.77 (0.35–1.70)	0.90 (0.68–1.18)	0.74 (0.53–1.03)	1.13 (0.85–1.50)	0.70 (0.43–1.13)	0.80 (0.30–2.09)
			0.89 (0.49–1.63)	0.91 (0.37–2.24)	1.06 (0.63–1.78)	0.88 (0.50–1.52)	1.33 (0.78–2.25)	0.82 (0.42–1.59)	0.94 (0.32–2.71)
				1.02 (0.43–2.43)	1.19 (0.75–1.87)	0.98 (0.60–1.61)	1.49 (0.94–2.35)	0.92 (0.50–1.69)	1.05 (0.38–2.95)
					1.16 (0.52–2.61)	0.96 (0.42–2.21)	1.46 (0.65–3.30)	0.90 (0.37–2.20)	1.03 (0.30–3.53)
						0.83 (0.57–1.21)	1.26 (0.89–1.77)	0.78 (0.46–1.31)	0.89 (0.34–2.33)
							1.52 (1.03–2.24)[a]	0.94 (0.54–1.62)	1.07 (0.40–2.89)
								0.62 (0.36–1.05)	0.71 (0.26–1.89)
									1.14 (0.39–3.31)

The comparison in this table is column heading compared with row heading. All numbers in parentheses represent 95% CIs.

[a]Statistically significant.

(PTH 1-84), as well as newer agents such as abaloparatide and romosozumab.

Methods

Supplemental material to this manuscript is publicly shared in an online repository (5). This systematic review followed an *a priori* protocol developed by the methodologists and members of the task force of the Endocrine Society, and is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement (6).

Eligibility criteria

Studies were eligible for this review if they met the following criteria: they (i) were randomized controlled trials; (ii) enrolled postmenopausal women with primary osteoporosis or osteopenia at risk for developing fragility fractures; (iii) compared one or more of the interventions of interest to each other or to placebo; and (iv) reported the outcomes of interest (vertebral, hip, and nonvertebral fragility fractures) as a primary or secondary outcome or as an adverse event.

The interventions of interest included the various bisphosphonates, teriparatide, selective estrogen receptor modulators, denosumab, abaloparatide, romosozumab, estrogen with or without progesterone, calcitonin, lasofoxifene, strontium ranelate, tibolone, PTH 1-84, calcium, or vitamin D. The treatment had to be given for a minimum of 3 months to be eligible for inclusion.

When calcium and/or vitamin D were given to both arms of a trial, their effect was considered neutralized and equal in both arms, allowing the arm that received calcium and/or vitamin D plus placebo to be considered placebo.

Literature search

An experienced librarian updated the literature search that was used in the previous systematic review through 7 July 2017 (4), added the new agents to be studied in this network meta-analysis, and restricted the inclusion criteria to postmenopausal women. The searched databases included MEDLINE through the Ovid interface, EMBASE, Cochrane Central Register of Controlled Trials, ISI Web of Science, and Scopus. The search was not restricted by the language of the publication or the country of origin of the study. The detailed search strategy is available in an online repository (5).

Study selection

Two reviewers independently evaluated eligibility based on the titles and abstracts of the studies. If at least one reviewer determined that an article was potentially eligible, the full text version was retrieved, and pairs of reviewers assessed its eligibility. Conflicts between the two reviewers were resolved through discussion and consensus.

Data extraction and risk of bias assessment

Pairs of reviewers independently extracted data, with disagreements resolved by discussion and consensus. We used a

Table 2. Network Meta-Analysis of Nonvertebral Fractures

	Abaloparatide	Romosozumab	PTH 1-84	Calcium	Vitamin D	Lasofoxifene	Calcitonin	Hormone Therapy	Tibolone
Placebo	0.51 (0.29–0.87)[a]	0.67 (0.53–0.86)[a]	0.98 (0.71–1.35)	0.77 (0.56–1.05)	0.44 (0.23–0.85)[a]	0.84 (0.72–0.99)[a]	0.84 (0.68–1.05)	0.78 (0.68–0.89)[a]	0.73 (0.58–0.94)[a]
Abaloparatide		1.33 (0.73–2.40)	1.93 (1.03–3.63)[a]	1.52 (0.81–2.84)	0.88 (0.38–2.04)	1.67 (0.95–2.93)	1.67 (0.93–2.99)	1.54 (0.88–2.68)	1.45 (0.80–2.63)
Romosozumab			1.46 (0.97–2.19)	1.14 (0.77–1.71)	0.66 (0.33–1.32)	1.26 (0.94–1.68)	1.26 (0.90–1.75)	1.16 (0.88–1.53)	1.10 (0.78–1.55)
PTH 1-84				0.79 (0.50–1.24)	0.45 (0.22–0.94)[a]	0.86 (0.60–1.24)	0.86 (0.58–1.28)	0.80 (0.56–1.13)	0.75 (0.50–1.13)
Calcium					0.58 (0.28–1.19)	1.10 (0.77–1.57)	1.10 (0.75–1.62)	1.01 (0.72–1.43)	0.96 (0.64–1.43)
Vitamin D						1.90 (0.97–3.72)	1.91 (0.96–3.78)	1.76 (0.91–3.39)	1.66 (0.83–3.32)
Lasofoxifene							1.00 (0.76–1.32)	0.92 (0.74–1.14)	0.87 (0.65–1.17)
Calcitonin								0.92 (0.71–1.20)	0.87 (0.63–1.21)
Hormone therapy									0.95 (0.71–1.25)
Tibolone									
Bazedoxifene									
Vitamin D + calcium									
Strontium ranelate									
Alendronate									
Ibandronate									
Risedronate									
Zoledronate									
Raloxifene									
Denosumab									

(*Continued*)

standardized and piloted form to extract data using an online reference management system (Distiller SR, Ottawa, Canada). We extracted the following variables: baseline characteristics, patient demographics, type of interventions, and outcome data. The outcome data extracted corresponded to the number of patients with the outcome of fracture, unless only the number of fractures (not patients) was reported instead. If the fracture outcome was reported as a clinical fracture and if the fracture was assessed by radiography, the radiographic fracture was extracted. Some studies reported fractures by location without the "nonvertebral" label; in these cases, all the fractures, including hip and/or pelvis fractures, were considered nonvertebral. For studies reporting hip and pelvis fractures separately, only the hip fracture outcome was analyzed as hip fracture.

The risk of bias in the trials was evaluated using the Cochrane risk of bias tool (7), which includes allocation concealment, blinding (patients, caregivers, investigators, data collectors, and outcome assessors), outcome assessment, loss to follow-up (attrition), and the extent of imbalance of the study arms at the beginning of the trial. A loss to follow-up >10% qualified the study as having a high risk of attrition bias. We applied the Grading of Recommendations, Assessment, Development, and Evaluation (8) framework for rating the certainty in the estimates of the direct and network analyses (9, 10). Certainty was rated down because of methodological limitations of the trial, imprecision, inconsistency, indirectness, and reporting bias. The confidence in the estimates was rated as high, moderate, low, or very low.

Statistical analysis

Direct (head-to-head) comparisons were conducted using the random effects model as described by DerSimonian and Laird to estimate pooled relative risks (RRs) and 95% CIs. The random effects model was chosen because of anticipated heterogeneity between studies. Heterogeneity was assessed using the I^2 statistic, for which a value >50% suggests substantial heterogeneity. We conducted a multivariate random effects network meta-analysis to combine the direct and indirect comparisons of agents using a frequentist consistency model (11, 12). We did not present ranking probabilities because such probabilities do not provide a meaningful evaluation of the magnitude of difference (9, 10). Potential evidence of inconsistency between the direct and network analyses was evaluated using the node-splitting method by comparing the direct and indirect estimates and conducting z tests (with P = 0.05 considered statistically significant and suggestive of inconsistency). Sensitivity analyses for the effects of zoledronate and calcitonin based on dosage and administration route were conducted. We evaluated potential publication bias using Egger's regression test and the visual inspection of funnel plots. All statistical analyses were performed using STATA, version 15 (StatCorp LP, College Station, TX).

Results

Included studies

The study selection process is described in detail in Fig. 1. We included 107 trials in this systematic review. A total of 193,987 postmenopausal women were included, with a mean age of 66.2 years. The majority (55.1%) of participants were white. The trials lasted for a median of 27.7 months (range, 3 to 120 months).

The available direct (head-to-head) comparisons are depicted in the appendix for vertebral, nonvertebral,

Table 2. Network Meta-Analysis of Nonvertebral Fractures (Continued)

Bazedoxifene	Vitamin D + Calcium	Strontium Ranelate	Alendronate	Ibandronate	Risedronate	Zoledronate	Raloxifene	Denosumab	Teriparatide
0.90 (0.72–1.11)	0.93 (0.85–1.01)	0.90 (0.78–1.04)	0.84 (0.74–0.94)[a]	1.06 (0.83–1.36)	0.78 (0.68–0.89)[a]	0.79 (0.67–0.94)[a]	0.94 (0.85–1.05)	0.80 (0.67–0.96)[a]	0.62 (0.47–0.80)[a]
1.77 (0.99–3.17)	1.83 (1.06–3.16)[a]	1.78 (1.02–3.11)[a]	1.65 (0.95–2.87)	2.10 (1.16–3.80)[a]	1.54 (0.89–2.68)	1.57 (0.89–2.76)	1.86 (1.08–3.23)[a]	1.59 (0.90–2.81)	1.22 (0.70–2.11)
1.34 (0.96–1.85)	1.38 (1.07–1.78)[a]	1.34 (1.01–1.78)[a]	1.25 (0.98–1.59)	1.59 (1.13–2.23)[a]	1.16 (0.88–1.53)	1.18 (0.88–1.59)	1.41 (1.08–1.83)[a]	1.20 (0.89–1.62)	0.92 (0.64–1.31)
0.92 (0.62–1.36)	0.95 (0.68–1.32)	0.92 (0.65–1.31)	0.86 (0.61–1.21)	1.09 (0.73–1.63)	0.80 (0.56–1.13)	0.81 (0.56–1.17)	0.96 (0.69–1.36)	0.82 (0.57–1.19)	0.63 (0.42–0.95)[a]
1.17 (0.80–1.72)	1.21 (0.87–1.67)	1.18 (0.83–1.66)	1.09 (0.78–1.53)	1.39 (0.93–2.07)	1.02 (0.72–1.44)	1.03 (0.72–1.48)	1.23 (0.88–1.72)	1.05 (0.73–1.51)	0.80 (0.53–1.21)
2.03 (1.02–4.02)[a]	2.09 (1.09–4.03)[a]	2.04 (1.05–3.96)[a]	1.89 (0.98–3.65)	2.40 (1.20–4.81)[a]	1.76 (0.91–3.42)	1.79 (0.92–3.51)	2.13 (1.10–4.11)[a]	1.82 (0.93–3.57)	1.39 (0.69–2.80)
1.06 (0.81–1.39)	1.10 (0.91–1.32)	1.07 (0.86–1.32)	0.99 (0.81–1.21)	1.26 (0.94–1.69)	0.92 (0.75–1.14)	0.94 (0.75–1.19)	1.12 (0.92–1.36)	0.95 (0.75–1.21)	0.73 (0.54–0.99)[a]
1.06 (0.78–1.45)	1.10 (0.87–1.39)	1.07 (0.82–1.39)	0.99 (0.77–1.27)	1.26 (0.91–1.75)	0.92 (0.71–1.20)	0.94 (0.71–1.24)	1.12 (0.87–1.43)	0.95 (0.72–1.27)	0.73 (0.52–1.03)
1.15 (0.89–1.49)	1.19 (1.01–1.40)[a]	1.16 (0.95–1.41)	1.07 (0.90–1.29)	1.37 (1.03–1.81)[a]	1.00 (0.83–1.21)	1.02 (0.82–1.27)	1.21 (1.02–1.44)[a]	1.03 (0.83–1.30)	0.79 (0.59–1.06)
1.22 (0.88–1.69)	1.26 (0.97–1.63)	1.23 (0.93–1.62)	1.14 (0.87–1.49)	1.45 (1.03–2.04)[a]	1.06 (0.80–1.40)	1.08 (0.80–1.45)	1.28 (0.98–1.67)	1.09 (0.81–1.48)	0.84 (0.59–1.20)
	1.03 (0.82–1.30)	1.01 (0.78–1.30)	0.93 (0.73–1.19)	1.19 (0.86–1.64)	0.87 (0.67–1.12)	0.89 (0.67–1.16)	1.05 (0.84–1.31)	0.90 (0.68–1.19)	0.69 (0.49–0.96)[a]
		0.97 (0.83–1.15)	0.90 (0.79–1.04)	1.15 (0.89–1.49)	0.84 (0.73–0.98)[a]	0.86 (0.71–1.04)	1.02 (0.89–1.16)	0.87 (0.71–1.06)	0.67 (0.51–0.87)[a]
			0.93 (0.77–1.11)	1.18 (0.89–1.56)	0.86 (0.71–1.05)	0.88 (0.71–1.09)	1.05 (0.88–1.25)	0.89 (0.71–1.12)	0.68 (0.51–0.92)[a]
				1.27 (0.98–1.66)	0.93 (0.78–1.11)	0.95 (0.77–1.17)	1.13 (0.97–1.31)	0.96 (0.78–1.19)	0.74 (0.56–0.97)[a]
					0.73 (0.56–0.97)[a]	0.75 (0.55–1.00)	0.89 (0.68–1.16)	0.76 (0.56–1.02)	0.58 (0.41–0.83)[a]
						1.02 (0.81–1.27)	1.21 (1.02–1.43)[a]	1.03 (0.83–1.29)	0.79 (0.60–1.04)
							1.19 (0.97–1.45)	1.01 (0.80–1.29)	0.78 (0.57–1.06)
								0.85 (0.69–1.05)	0.65 (0.49–0.86)[a]
									0.77 (0.56–1.05)

The comparison in this table is column heading compared with row heading. All numbers in parentheses represent 95% CIs.

[a]Statistically significant.

and hip fractures (5). The size of the nodes (circles) in these figures is proportional to the number of patients, and the thickness of the lines reflects the number of randomized controlled trials. Most of the available data were derived from comparisons with placebo. Alendronate and hormone therapy were the most commonly tested agents, followed by vitamin D and calcium. The risk of bias was high in most of the trials examining calcitonin, calcium, and vitamin D, as well as in some older bisphosphonate trials. The characteristics and risk of bias in the included trials are summarized in an online repository (5).

Hip fractures

Compared with placebo, romosozumab (RR: 0.44), alendronate (RR: 0.61), zoledronate (RR: 0.60), risedronate (RR: 0.73), denosumab (RR: 0.56), estrogen with progesterone (RR: 0.72), and calcium combined with vitamin D (RR: 0.81) showed a significant reduction in fractures. The CIs for the RR estimates greatly overlapped across these effective interventions. The detailed network meta-analysis results are shown in Table 1.

Nonvertebral fractures

Compared with placebo, abaloparatide (RR: 0.51), romosozumab (RR: 0.67), denosumab (RR: 0.80), teriparatide (RR: 0.62), alendronate (RR: 0.84), risedronate (RR: 0.78), zoledronate (RR: 0.79), lasofoxifene (RR: 0.84), tibolone (RR: 0.73), estrogen with progesterone (RR: 0.78), and vitamin D (RR: 0.44) showed a significant reduction in fractures.

Abaloparatide and romosozumab were more effective than vitamin D with calcium, strontium ranelate, ibandronate, and raloxifene. Teriparatide was more effective than PTH 1-84, lasofoxifene, bazedoxifene, strontium ranelate, alendronate, ibandronate, and raloxifene. Risedronate, estrogen with progesterone, and tibolone were more effective than ibandronate. The detailed network meta-analysis results are shown in Table 2.

Vertebral fractures

Compared with placebo, abaloparatide (RR: 0.14), teriparatide (RR: 0.27), PTH 1-84 (RR: 0.41), romosozumab (RR: 0.33), strontium ranelate (RR: 0.60),

Table 3. Network Meta-Analysis of Vertebral Fractures

	Abaloparatide	Romosozumab	Vitamin D	PTH 1-84	Strontium Ranelate	Tibolone	Calcitonin	Hormone Therapy	Lasofoxifene
Placebo	0.14 (0.05–0.42)[a]	0.33 (0.22–0.49)[a]	0.85 (0.46–1.59)	0.41 (0.22–0.77)[a]	0.60 (0.46–0.78)[a]	0.56 (0.36–0.87)[a]	0.65 (0.50–0.85)[a]	0.65 (0.46–0.92)[a]	0.67 (0.46–0.98)[a]
Abaloparatide		2.35 (0.74–7.40)	6.04 (1.74–20.95)[a]	2.89 (0.83–10.10)	4.23 (1.39–12.86)[a]	3.93 (1.22–12.62)[a]	4.62 (1.52–14.03)[a]	4.57 (1.47–14.20)[a]	4.75 (1.52–14.87)[a]
Romosozumab			2.57 (1.23–5.36)[a]	1.23 (0.58–2.60)	1.80 (1.12–2.90)[a]	1.67 (0.92–3.03)	1.97 (1.24–3.12)[a]	1.95 (1.15–3.29)[a]	2.02 (1.17–3.49)[a]
Vitamin D				0.48 (0.20–1.16)	0.70 (0.36–1.38)	0.65 (0.30–1.40)	0.77 (0.40–1.48)	0.76 (0.39–1.47)	0.79 (0.38–1.62)
PTH 1-84					1.46 (0.74–2.91)	1.36 (0.63–2.94)	1.60 (0.81–3.16)	1.58 (0.77–3.25)	1.64 (0.79–3.42)
Strontium ranelate						0.93 (0.55–1.56)	1.09 (0.76–1.58)	1.08 (0.70–1.67)	1.12 (0.71–1.78)
Tibolone							1.18 (0.70–1.97)	1.16 (0.66–2.05)	1.21 (0.68–2.16)
Calcitonin								0.99 (0.64–1.52)	1.03 (0.65–1.63)
Hormone therapy									1.04 (0.62–1.73)
Lasofoxifene									
Bazedoxifene									
Calcium									
Vitamin D + calcium									
Alendronate									
Ibandronate									
Risedronate									
Zoledronate									
Raloxifene									
Denosumab									

(*Continued*)

denosumab (RR: 0.32), zoledronate (RR: 0.38), risedronate (RR: 0.61), alendronate (RR: 0.57), ibandronate (RR: 0.67), raloxifene (RR: 0.59), bazedoxifene (RR: 0.61), lasofoxifene (RR: 0.67), estrogen with progesterone (RR: 0.65), tibolone (RR: 0.56), and calcitonin (RR: 0.65) showed a significant reduction in fractures.

Abaloparatide, teriparatide, denosumab, and romosozumab were more effective than vitamin D, calcium, vitamin D with calcium, strontium ranelate, tibolone, calcitonin, estrogen with progesterone, raloxifene, bazedoxifene, lasofoxifene, risedronate, alendronate, and ibandronate. Zoledronate was more effective than ibandronate. The detailed network meta-analysis results are shown in Table 3.

Sensitivity analyses based on the route of administration

There was no statistically significant difference between 5 mg zoledronate and other doses of zoledronate in effect on nonvertebral fractures. A sensitivity analysis of a single dose of 5 mg zoledronate showed a statistically significant reduction in vertebral fractures. A sensitivity analysis of intranasal calcitonin showed a significant reduction in vertebral fractures (whereas the effects of injectable or oral calcitonin were not statistically significant). The results are presented in an online repository (*5*).

Quality of the evidence domains

Heterogeneity was not substantial in all analyses, with $I^2 < 50\%$ for most comparisons. We did not find any indication of publication bias (Egger's test > 0.05 for all direct comparisons). The direct and indirect estimates were very consistent (*P* values for the differences between direct and indirect estimates were >0.05 for all comparisons and all three outcomes). The direct estimates were very similar to the network estimates (*i.e.*, combined direct and indirect). This finding suggests that this network analysis is consistent or coherent. Forest plots of all direct estimates are presented in an online repository (*5*). Network transitivity (similarity in the distribution of effect modifiers) was judged to be adequate, although trials examining hormone replacement therapy tended to enroll younger women, and trials examining denosumab, romosozumab, teriparatide, and abaloparatide tended to enroll women who were more likely to have prevalent fractures or an increased risk for fracture. The assessment of the quality of evidence is summarized in an online repository (*5*).

Discussion

Main findings

We conducted a systematic review and network meta-analysis to synthesize the comparative effectiveness evidence for drugs used to prevent fragility fractures in

Table 3. Network Meta-Analysis of Vertebral Fractures (Continued)

Bazedoxifene	Calcium	Vitamin D + Calcium	Alendronate	Ibandronate	Risedronate	Zoledronate	Raloxifene	Denosumab	Teriparatide
0.61 (0.41–0.90)[a]	0.70 (0.48–1.04)	0.88 (0.61–1.27)	0.57 (0.45–0.71)[a]	0.67 (0.48–0.93)[a]	0.61 (0.48–0.78)[a]	0.38 (0.25–0.58)[a]	0.59 (0.46–0.76)[a]	0.32 (0.22–0.45)[a]	0.27 (0.19–0.38)[a]
4.30 (1.37–13.54)[a]	4.97 (1.58–15.67)[a]	6.20 (1.99–19.38)[a]	4.01 (1.33–12.08)[a]	4.73 (1.53–14.59)[a]	4.32 (1.44–12.99)[a]	2.70 (0.85–8.55)	4.16 (1.37–12.61)[a]	2.23 (0.72–6.93)	1.92 (0.63–5.83)
1.83 (1.05–3.19)[a]	2.12 (1.22–3.69)[a]	2.64 (1.55–4.52)[a]	1.71 (1.18–2.48)[a]	2.01 (1.22–3.33)[a]	1.84 (1.16–2.92)[a]	1.15 (0.65–2.05)	1.77 (1.12–2.81)[a]	0.95 (0.56–1.61)	0.82 (0.49–1.37)
0.71 (0.34–1.48)	0.82 (0.40–1.72)	1.03 (0.50–2.11)	0.66 (0.34–1.29)	0.78 (0.39–1.58)	0.72 (0.37–1.39)	0.45 (0.21–0.94)[a]	0.69 (0.35–1.35)	0.37 (0.18–0.75)[a]	0.32 (0.16–0.65)[a]
1.49 (0.71–3.13)	1.72 (0.82–3.62)	2.15 (1.03–4.45)[a]	1.39 (0.71–2.72)	1.64 (0.80–3.33)	1.49 (0.76–2.94)	0.93 (0.44–1.99)	1.44 (0.73–2.85)	0.77 (0.37–1.59)	0.66 (0.32–1.36)
1.02 (0.63–1.63)	1.17 (0.73–1.89)	1.47 (0.93–2.30)	0.95 (0.67–1.35)	1.12 (0.74–1.70)	1.02 (0.71–1.46)	0.64 (0.39–1.05)	0.98 (0.68–1.42)	0.53 (0.34–0.82)[a]	0.45 (0.29–0.70)[a]
1.09 (0.61–1.98)	1.27 (0.70–2.29)	1.58 (0.89–2.81)	1.02 (0.62–1.69)	1.20 (0.69–2.09)	1.10 (0.66–1.82)	0.69 (0.38–1.26)	1.06 (0.63–1.77)	0.57 (0.32–1.00)	0.49 (0.28–0.86)[a]
0.93 (0.58–1.48)	1.08 (0.68–1.71)	1.34 (0.87–2.08)	0.87 (0.61–1.23)	1.02 (0.69–1.51)	0.93 (0.66–1.33)	0.58 (0.34–1.00)	0.90 (0.63–1.28)	0.48 (0.31–0.74)[a]	0.42 (0.28–0.62)[a]
0.94 (0.56–1.59)	1.09 (0.64–1.84)	1.36 (0.82–2.25)	0.88 (0.58–1.33)	1.03 (0.64–1.67)	0.94 (0.62–1.44)	0.59 (0.35–1.01)	0.91 (0.59–1.40)	0.49 (0.30–0.80)[a]	0.42 (0.26–0.68)[a]
0.91 (0.53–1.55)	1.05 (0.61–1.80)	1.31 (0.77–2.21)	0.84 (0.55–1.31)	1.00 (0.60–1.64)	0.91 (0.58–1.42)	0.57 (0.33–0.98)[a]	0.88 (0.56–1.38)	0.47 (0.28–0.78)[a]	0.40 (0.24–0.67)[a]
	1.16 (0.67–2.01)	1.44 (0.85–2.46)	0.93 (0.59–1.47)	1.10 (0.66–1.83)	1.00 (0.64–1.59)	0.63 (0.36–1.11)	0.97 (0.61–1.54)	0.52 (0.31–0.88)[a]	0.45 (0.27–0.75)[a]
		1.25 (0.73–2.13)	0.81 (0.51–1.27)	0.95 (0.57–1.58)	0.87 (0.55–1.37)	0.54 (0.31–0.97)[a]	0.84 (0.52–1.33)	0.45 (0.26–0.76)[a]	0.39 (0.23–0.65)[a]
			0.65 (0.42–1.00)	0.76 (0.47–1.24)	0.70 (0.45–1.08)	0.44 (0.25–0.77)[a]	0.67 (0.43–1.05)	0.36 (0.22–0.60)[a]	0.31 (0.19–0.51)[a]
				1.18 (0.79–1.75)	1.08 (0.77–1.50)	0.67 (0.43–1.06)	1.04 (0.75–1.44)	0.56 (0.37–0.84)[a]	0.48 (0.32–0.72)[a]
					0.91 (0.61–1.37)	0.57 (0.33–0.99)[a]	0.88 (0.58–1.32)	0.47 (0.29–0.75)[a]	0.41 (0.26–0.64)[a]
						0.63 (0.39–1.01)	0.96 (0.68–1.37)	0.52 (0.34–0.79)[a]	0.44 (0.31–0.65)[a]
							1.54 (0.94–2.52)	0.82 (0.48–1.42)	0.71 (0.41–1.24)
								0.54 (0.35–0.83)[a]	0.46 (0.30–0.70)[a]
									0.86 (0.53–1.40)

The comparison in this table is column heading compared with row heading. All numbers in parentheses represent 95% CIs.

[a]Statistically significant.

postmenopausal women with primary osteoporosis or osteopenia. We demonstrated that several effective agents are available, including romosozumab, alendronate, zoledronate, risedronate, denosumab, estrogen with progesterone, and calcium combined with vitamin D, for preventing hip fractures. The effective agents found for nonvertebral fractures were abaloparatide, romosozumab, denosumab, teriparatide, alendronate, risedronate, zoledronate, lasofoxifene, tibolone, estrogen with progesterone, and vitamin D. The effective agents found for vertebral fractures were abaloparatide, teriparatide, PTH 1-84, romosozumab, strontium ranelate, denosumab, zoledronate, risedronate, alendronate, ibandronate, raloxifene, bazedoxifene, lasofoxifene, estrogen with progesterone, tibolone, and calcitonin.

The RR reductions for vertebral fractures were clearly larger than those for hip and nonvertebral fractures. The head-to-head comparisons were limited by wide CIs, although one can conclude increased efficacy with agents such as teriparatide, abaloparatide, denosumab, and romosozumab compared with other agents. Ibandronate had lower efficacy than other bisphosphonates. Selective estrogen receptor modulators also had lower efficacy than other agents. The evidence for the treatment of fractures with vitamin D and calcium is limited despite numerous randomized trials. Several other systematic reviews, including a patient-level pooled analysis (13), have concluded similar findings to this current analysis, suggesting fracture reduction benefit using a combination of vitamin D and calcium, possibly using calcium alone, but not using vitamin D alone (13–15). A recent study using Mendelian randomization suggests no association between vitamin D and fractures (16).

Strengths and limitations

The strengths of this analysis include the comprehensive literature search of multiple databases in multiple languages and the rigorous review process undertaken by independent reviewers. The analysis did not reveal important heterogeneity or inconsistency. We also benefitted from the content knowledge of the expert panel from the Endocrine Society.

There are several limitations related to the inferences provided in this review. The two main limitations relate

to the increased risk of bias in the body of evidence and the small number of head-to-head trials.

Clinical implications

The superiority of a certain drug in relative terms does not necessarily mean that the absolute difference from another drug is substantial. In addition, this analysis focused on fracture prevention; however, decision-making also incorporates other concepts such as the cost of a drug, convenience of administration, related side effects, and tolerability. In addition to pharmacologic therapy, other measures to improve bone health are important, including the adequate intake of calcium and vitamin D, weight-bearing exercise, smoking cessation, and reducing the intake of alcohol and other drugs associated with bone loss (*e.g.*, corticosteroids). Comorbidities such as gastroesophageal reflux disease and breast cancer can also influence the choice of therapy. The expert panel from the Endocrine Society will provide practical advice to integrate the evidence provided here with patients' values and preferences as well as clinical context. Future research is needed to determine the length of treatment required for the various agents.

Conclusions

This network meta-analysis provides comparative effective estimates for the various available treatments to reduce the risk of fragility fractures in postmenopausal women. Teriparatide, abaloparatide, denosumab, romosozumab, and most bisphosphonates appear to have the highest efficacy. The evidence for vitamin D and calcium remains limited.

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