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REVIEW

Effectiveness of anti-osteoporotic drugs to prevent secondary fragility fractures: systematic review and meta-analysis

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Abstract Patients with osteoporotic fractures have an increased risk for secondary fractures. However, a rigorous study that assesses the effectiveness of individual osteoporotic drugs in preventing subsequent fractures is lacking. The purpose of this review was to analyze the effectiveness of anti-osteoporotic drugs in preventing secondary fractures. We searched for randomized controlled trials that showed the incidence of secondary fractures while using anti-osteoporotic drugs (bisphosphonates, selective estrogen receptor modulators, parathyroid hormone (PTH), or calcitonin) in MEDLINE, Embase.com, and Cochrane Central Register databases. We estimated risk ratios (RR) and numbers needed to treat (NNT) to prevent secondary fractures. Twenty-six studies met our eligibility criteria. There was a significant reduction in RR (0.38–0.77) after the use of anti-osteoporotic drugs for secondary vertebral fractures. Bisphosphonates and PTH significantly reduced the risk of a secondary non-vertebral fracture (RR 0.59 and 0.64). PTH needed the fewest number of patients to be treated to prevent a secondary vertebral fracture (NNT: 56). Our study demonstrated the effectiveness of anti-osteoporotic agents included in our systematic review in preventing secondary vertebral fractures. Bisphosphonates and PTH were most effective in preventing non-vertebral fractures. We suggest that clinicians should prescribe these drugs to prevent secondary vertebral/non-vertebral fractures.

Keywords Bisphosphonates · Drug therapy · Fragility fracture · Osteoporosis · Parathyroid hormone · Secondary fractures · Selective estrogen receptor modulators

Ten million people in the USA and 27.6 million in Europe are estimated to have osteoporosis [1, 2]. In osteoporosis, bone resorption exceeds bone formation. This imbalance in skeletal turnover results in a disruption of osseous microarchitecture and an increased risk of fracture [3]. Fragility fractures caused by osteoporosis mainly consist of vertebral fractures, proximal femoral fractures, and distal radial fractures. Thirty to 50% of American women with osteoporosis are affected by these fractures [4, 5]. People who have had an osteoporotic fracture are at a higher risk for secondary osteoporotic fractures [6–8]. Prior osteoporotic fractures of the spine, hip, or wrist double the risk of secondary fractures in postmenopousal women [8]. With a total annual cost estimated at 17 billion US dollars, these secondary fractures present a substantial economic burden [9].

Anti-osteoporotic therapies effectively increase bone mineral density and decrease the risk of future osteoporotic fractures [10]. Anti-osteoporotic drugs prescribed in the USA include bisphosphonates, selective estrogen receptor modulators (SERMs), calcitonin, parathyroid hormone (PTH) (including PTH-related protein), and monoclonal antibodies against the receptor activator of nuclear factor κB ligand (RANKL).

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Bisphosphonates are the most commonly prescribed anti-osteoporotic drugs that prevent bone resorption [11], reducing the risk for primary fragility fractures by as much as 70% [12–14]. SERMs, RANKL, and PTH were effective in preventing primary osteoporotic fractures, with the relative risks (RR) of primary vertebral fractures being 0.63, 0.32, and 0.33, respectively [15–17]. Additionally, treatment with bisphosphonates is cost-effective to prevent osteoporotic fractures in elderly patients [18].

The American Association of Clinical Endocrinologists/American College of Endocrinology Medical Guidelines recommend using teriparatide, denosumab, zoledronic acid, alendronate, or risedronate for patients with prior fragility fractures or high fracture risks. However, treatment rates following an osteoporotic fracture are low (19%) despite the proven effectiveness of anti-osteoporotic agents [19]. Earlier studies that demonstrated the anti-osteoporotic effect of drugs had limited sample size and focused on single fracture type and/or a specific anti-osteoporotic treatment regimen [8, 20–23]. These limitations inhibited the applicability of these results across different fracture types and varied anti-osteoporotic treatment regimens. There are also no comprehensive reviews that present the effectiveness of the existing anti-osteoporotic drugs in use for patients with osteoporotic fractures. The purpose of this systematic review is to demonstrate the effectiveness of each anti-osteoporotic drug in preventing secondary fractures, and determine which one is the most effective for patients with osteoporotic fractures. The outcomes of this meta-analysis can be used to guide clinicians to better understand which types of drugs are most useful for preventing subsequent fractures.

Materials and methods

Literature search and criteria

We performed a systematic search of the available literature in Ovid MEDLINE, Ovid MEDLINE In-Process & Other Non-Indexed Citations, Embase.com, and Cochrane Central Register of Controlled Trials (Fig. 1) according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines (PRISMA) [24]. We searched publications containing variations of the following key words and phrases: osteoporotic fracture including wrist, proximal humerus, hip, or spine fracture, and osteoporosis. We also searched for anti-osteoporotic agents including bisphosphonates, calcitonin, SERMs, PTH, and denosumab. These terms were expanded to

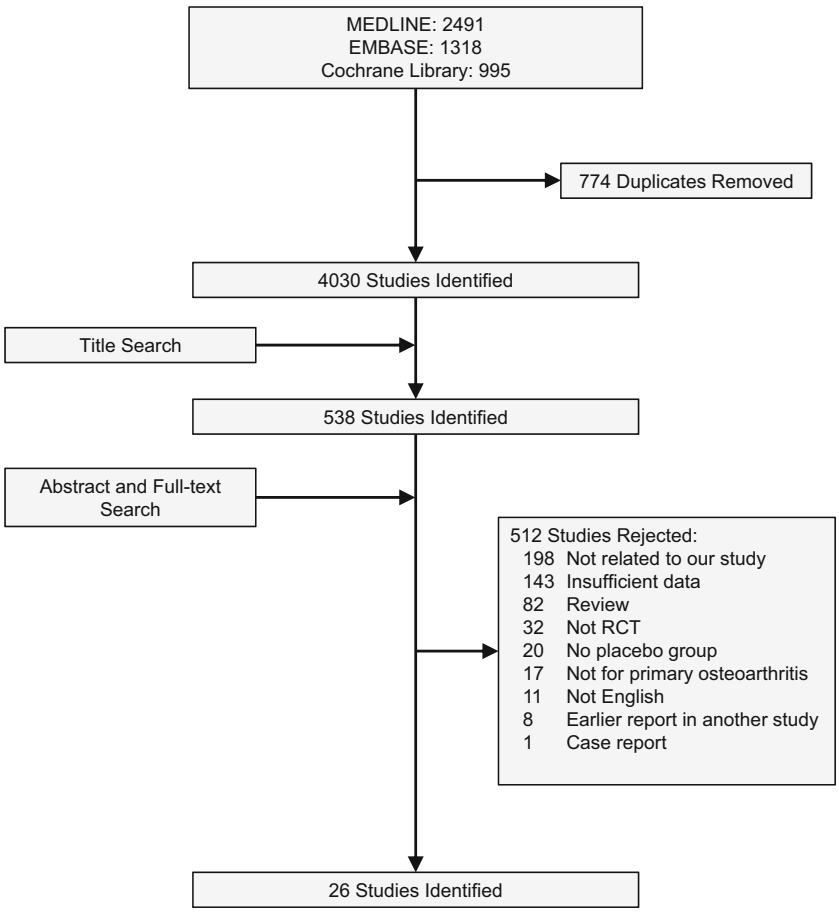

Fig. 1 Flow diagram of database search

Table 1 Predetermined inclusion and exclusion criteria for eligible studies

Inclusion criteria
Randomized controlled trial
English paper
Primary data
Studies that have a placebo group
Studies that included patients who had primary osteoporosis
Studies that showed a secondary fracture rate
Exclusion criteria
Review
Case report
Animal study
Studies of patients who had cancer, osteoporosis, or Paget disease
Studies of patients who had congenital bone diseases

include matching Medical Subject Headings in the MEDLINE and Cochrane database and EMTREE subject headings in Embase.com. Animal studies and select publication types were excluded as part the searches (e.g., case reports and editorials), as were citations with cancer terminology in the titles. The detailed search algorithm is listed in the Appendices 1, 2, and 3. After eliminating duplicates, two reviewers (TS and JS) independently screened the articles in a stepwise fashion (title, abstract, and full text review) according to study eligibility criteria (Table 1).

Data extraction

Data fields extracted include the study population, interventions (drugs), follow-up time, and number of the patients who had vertebral, non-vertebral, hip, and wrist fractures using a structured abstract form. We also gathered information on four study characteristics: "double blind," "intention to treat," "allocation concealment," and "loss to follow-up," to evaluate each randomized controlled trial (RCT). These characteristics impact the quality of a study and measure the effect of treatment. In a double-blind study, neither the investigators nor subjects know which of the groups being studied is the control group and which is the test group. The intention-to-treat principle requires that all participants who are given a randomized treatment assignment are included in the analysis, regardless of the number of participants who withdraw, are non-compliant, or deviate from the treatment plan after randomization. If the articles contained the terms "intention to treat" or "double blind," we considered them to follow the respective protocols.

For allocation concealment, we referred to the Cochrane Handbook for Systematic Reviews of Interventions [25]. If the central randomization office was not in the same location as the patient recruitment centers, if drug containers were sequentially numbered and of identical appearance, or if sequentially numbered, opaque, sealed envelopes were used for allocation after the participants' information was written on the envelopes, we considered the study to follow the protocol for allocation concealment. We considered the number of patients who could not be assessed at the final follow-up as "lost to follow-up." If there were any discrepancies in the data, a third reviewer verified the data and resolved the discrepancy.

The sample population consisted of patients with prior osteoporotic fractures at the baseline measurement. We calculated the incidence of secondary fractures within this population, for participants in both treatment and placebo groups. When a study presented both the number of the participants who had clinical vertebral fractures and those who had radiographic vertebral fractures, we used the number of participants with radiographic fractures. If we could not calculate the number of participants who suffered secondary fractures, we excluded the study from our analysis citing insufficient data.

Data synthesis and statistical analysis

We calculated a pooled RR of secondary fractures for each drug. We also calculated the number needed to treat (NNT) to prevent a secondary fracture for the drugs that showed a significant reduction in absolute risk reduction (ARR). The NNT was calculated by combining an assumed control risk (ACR) with the pooled RR reductions. All participants in this review had one or more primary fractures and were at high risk for a secondary fracture. Therefore, we used ACRs from pooled estimates from the alendronate treatment trials that enrolled women with low bone mineral density (BMD) for 2 years, referring to the paper that demonstrated a NNT to prevent

Table 2 Study characteristics by fracture type

	Secondary vertebral fractures	Secondary non-vertebral fractures	Secondary fragility fractures
Primary vertebral fractures	23	8	0
Primary non-vertebral (hip) fractures	1	1	1
Primary fragility fracture	0	0	1

Non-vertebral fractures: non-vertebral fractures consist of low-trauma non-vertebral fractures including hip fracture, wrist fracture, proximal humerus fracture, and pelvis fracture. Fragility fractures: fragility fractures consist of vertebral fractures or low-trauma non-vertebral fractures. However, each incidence of vertebral and non-vertebral fractures was not shown

Table 3 Study characteristics by medication

Medication	No. of studies	Double blinding	Intention to treat	Allocation concealment	Loss to follow-up
Bisphosphonate	19	12	12	5	4 trials <10%, 6 trials <20%, 6 trials <30%, 3 trials >30%
Etidronate	7	2	2	0	1 trial <10%, 3 trials <20%, 2 trials <30%, 1 trial >30%
Alendronate	4	3	4	2	2 trials <10%, 1 trial <20%, 1 trial <30%
Risedronate	5	4	4	2	1 trial <20%, 2 trials <30%, 2 trials >30%
Pamidronate	2	2	1	0	1 trial <10%, 1 trial <20%,
Zoledronic acid	1	1	1	1	1 trial <30%
SERMs	3	3	2	0	2 trials <30%, 1 trial >30%
PTH	3	3	1	2	1 trial <10%, 1 trial <20%, 1 trial >30%
Calcitonin	1	1	1	1	1 trial >30%
Denosumab	1	1	0	1	1 trial <10%

SERMs selective estrogen receptor modulators, *PTH* parathyroid hormone

primary fragility fractures (ACR 2.88% in vertebral fractures and 8.65% in non-vertebral fractures) [10]. Ninety-five percent confidence intervals (CIs) for secondary vertebral and non-vertebral fractures were calculated for the pooled results. We compared the effect of each individual drug versus a placebo. If both the treatment and placebo groups were taking calcium and vitamin D, then, their use was disregarded. Patients in various dose groups were combined and compared with those in the placebo group to calculate the RR for fractures. We conducted the meta-analysis using R (www.r-project.org).

Results

Study retrieval and characteristics

A total of 4804 studies were identified through the initial search of the MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials databases. Among these, 774 articles were duplicates. Twenty-six articles matched our inclusion and exclusion criteria after further review. A flow diagram of our database search is shown in Fig. 1.

Twenty-four of the selected papers included only postmenopausal women as participants [8, 12, 15, 20–23, 26–42], and only two papers comprised men [43, 44]. The mean age was 70 years, and the percentage of females in the combined population of this study was 99.6%. The mean follow-up period was 3 years.

Most studies analyzed both primary and secondary vertebral fractures (Table 2) [12, 15, 20–22, 26–42, 44]. Eight studies assessed the incidence of both secondary vertebral and non-vertebral fractures. Only two studies presented non-vertebral fractures (hip fractures) as the primary fracture [8, 43]. One of these two studies demonstrated the incidence of both secondary vertebral and non-vertebral fractures [8]. One study reported fragility fractures, which included vertebral and non-vertebral fractures, as both the primary and secondary

Table 4 Magnitude of effect for preventing secondary vertebral fractures in each drug

Medication	No. of studies	No. of participants	Risk ratio (95% CI)
Bisphosphonate	15	6841	0.53 (0.47, 0.59)
Etidronate	7	985	0.51 (0.36, 0.71)
Alendronate	3	3132	0.55 (0.46, 0.64)
Risedronate	3	2585	0.61 (0.59, 0.62)
Pamidronate	2	139	0.44 (0.24, 0.78)
SERMs	4	7350	0.61 (0.57, 0.65)
PTH	3	2016	0.38 (0.26, 0.54)
Calcitonin	1	1255	0.77 (0.60, 0.99)

CI confidence interval, *SERMs* selective estrogen receptor modulators, *PTH* parathyroid hormone

Table 5 Magnitude of effect for preventing secondary non-vertebral fractures in each drug

Medication	No. of studies	No. of participants	Risk ratio (95% CI)
Bisphosphonate	6	4295	0.59 (0.49, 0.73)
Etidronate	3	474	0.86 (0.51, 1.43)
Alendronate	1	2027	0.52 (0.34, 0.78)
Risedronate	1	1703	0.45 (0.26, 0.79)
Pamidronate	1	91	0.33 (0.04, 3.02)
SERMs	1	614	0.71 (0.47, 1.08)
PTH	1	1326	0.64 (0.45, 0.90)

CI confidence interval, *SERMs* selective estrogen receptor modulators, *PTH* parathyroid hormone

fractures [23]. However, the number of vertebral versus non-vertebral fractures was not reported.

Study characteristics by medication are listed in Table 3. Bisphosphonates were most commonly evaluated for their effectiveness in preventing secondary fractures. One study evaluated the effects of zoledronic acid, calcitonin, and denosumab [23, 34]. Owing to the small number of papers in each category, we could not conduct meta-analyses for

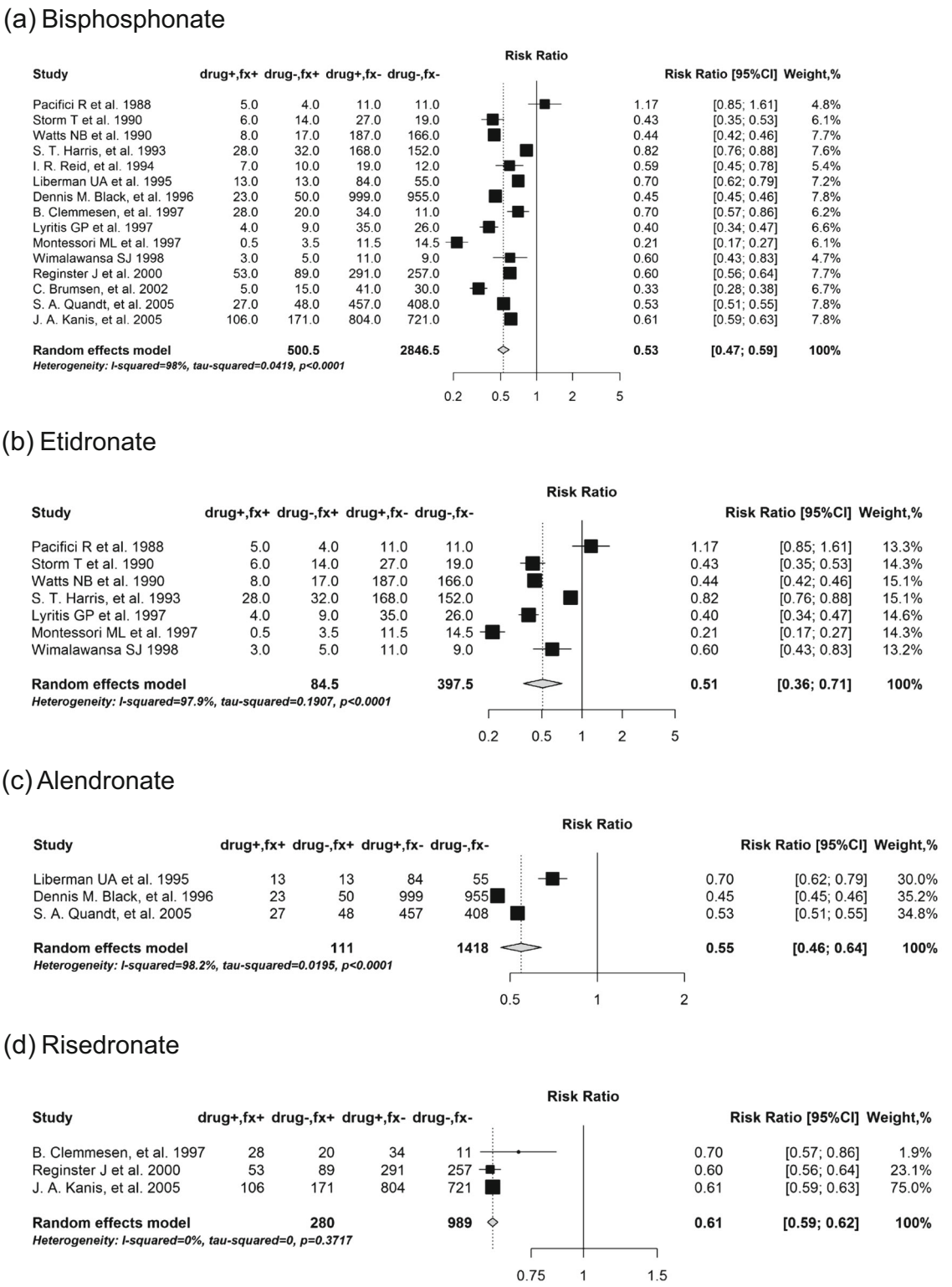

Fig. 2 Effectiveness for preventing secondary fractures (primary fracture: *vertebral* fracture)

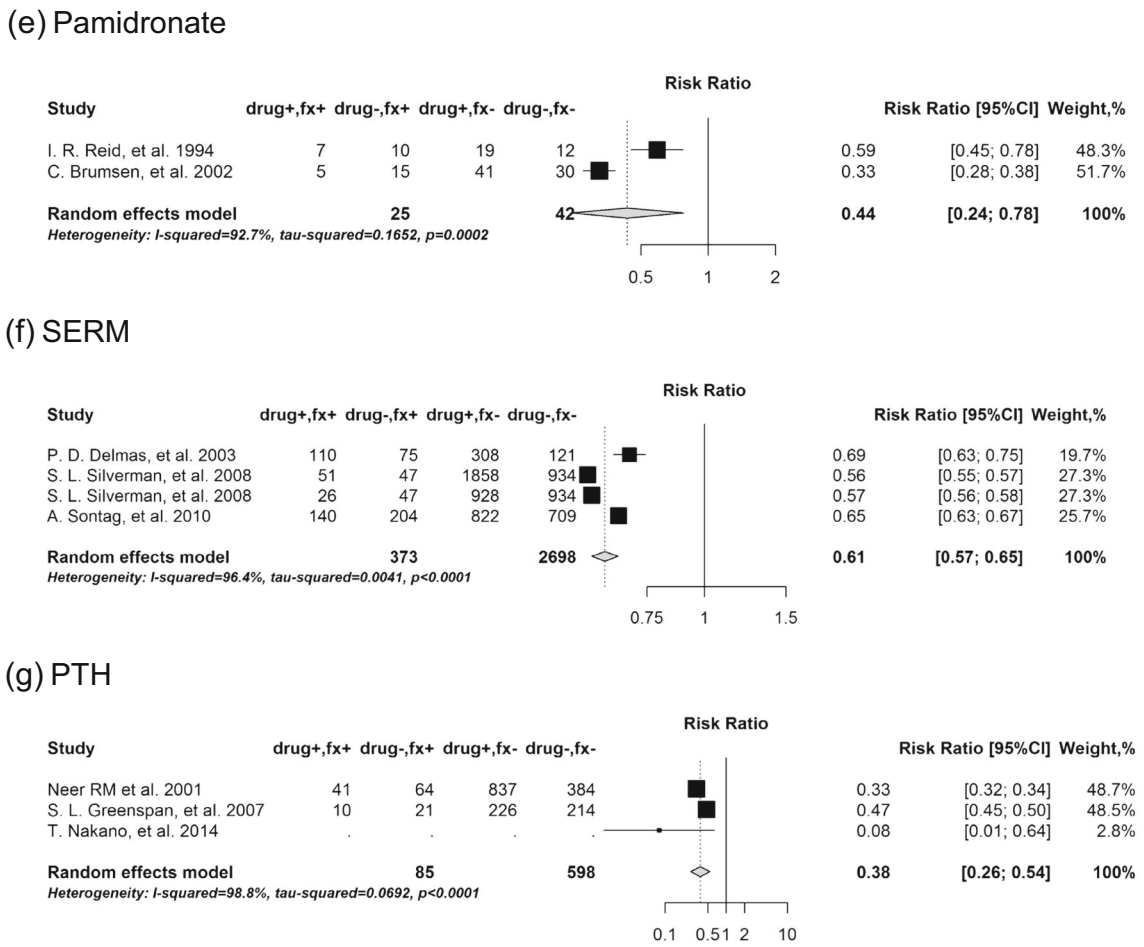

Fig. 2 (continued)

pamidronate, zoledronic acid, calcitonin, and denosumab. Though most studies were double-blind and performed intention-to-treat analyses, there were only three involving etidronate (one double blinded with intention to treat, one only double blinded, and one not double blinded with intention to treat) [22, 29]. One third (9/26) of the studies mentioned allocation concealment [8, 20, 21, 23, 34, 36, 40, 41, 44]. Overall, the studies on all of the drugs, except for etidronate, had strength of validity in relation to double blinding, intention to treat, and allocation concealment. About 60% of the trials (16/26) had less than 30% of their participants lost to follow-up.

Effects of anti-osteoporotic drugs on secondary fracture rates

We summarized the treatment effect of each drug on secondary vertebral and non-vertebral fractures after primary vertebral fractures in Tables 4 and 5, respectively. Forest plots for each drug are shown in Figs. 2 and 3.

There was a significant reduction in the pooled RR for secondary vertebral fractures for all of the drugs except calcitonin (Table 4 and Fig. 2). Calcitonin was reported in only one study [34]; therefore, we could not get the pooled RR. However, statistical inference revealed that all of the drugs

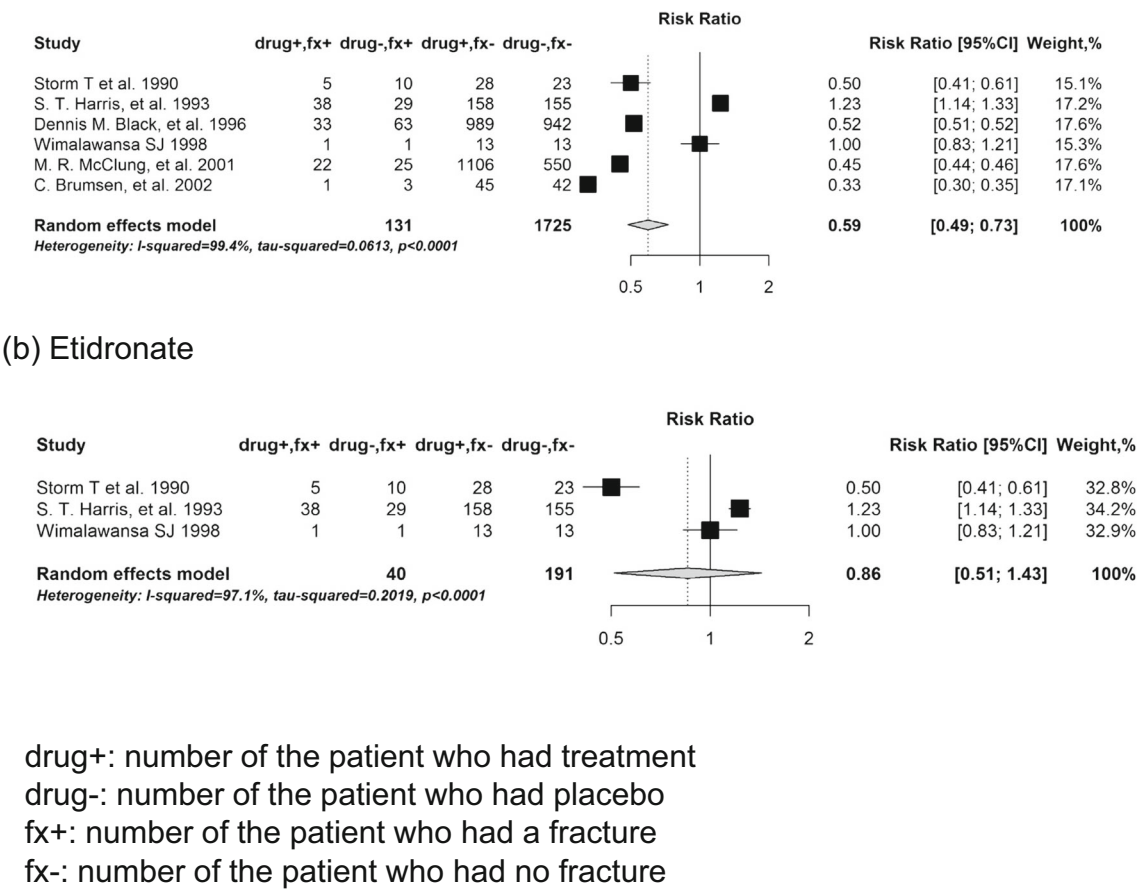

Fig. 3 Effectiveness for preventing secondary fractures (primary fracture: *non-vertebral* fracture)

were effective in preventing secondary vertebral fractures. PTH had the strongest impact on the incidence of secondary vertebral fractures.

Regarding secondary non-vertebral fractures, bisphosphonates showed a significant reduction in the pooled RR (Table 5 and Fig. 3). However, there was only one study that assessed the incidence of secondary non-vertebral fractures for each drug except for etidronate [21] [36–39]. Therefore, we could not determine the pooled RR for these drugs. Etidronate, pamidronate, and SERMS showed trends toward a reduction of secondary non-vertebral fractures, though each CI included 1.0. All other drugs significantly decreased the RR.

Three studies investigated non-vertebral fractures as a primary fracture [8, 23, 43] (Table 6). Lyles et al. reported the incidence of both secondary, vertebral fractures and non-vertebral fractures with zoledronic acid. Palacios et al. revealed the incidence of fragility fractures after primary fragility fractures with denosumab. [23] Denosumab significantly reduced the incidence of secondary fragility fractures (RR

Table 6 Magnitude of effect for preventing secondary fragility fractures on patients with primary non-vertebral fractures

Medication	Authors	No. of participants	Primary fracture	Secondary fracture	Risk ratio (95% CI)
Alendronate or risedronate	Beaupre LA et al.	209	Hip	Fragility fracture	0.96 (0.48, 2.27)
Zoledronic acid	Lyles KW et al.	2111	Hip	Vertebral fracture	0.53 (0.32, 0.91)
Zoledronic acid	Lyles KW et al.	2111	Hip	Non-vertebral fracture	0.74 (0.56, 0.98)
Denosumab	Palacios S et al.	3484	Fragility fracture	Fragility fracture	0.61 (0.51, 0.72)

CI confidence interval. Non-vertebral fractures: non-vertebral fractures consist of low-trauma non-vertebral fractures including hip fracture, wrist fracture, proximal humerus fracture, and pelvis fracture, Fragility fractures: fragility fractures consist of vertebral fractures or low-trauma non-vertebral fractures. However, each incidence of vertebral and non-vertebral fractures were not shown

Table 7 NNT to prevent a secondary vertebral and non-vertebral fracture

Medication	Secondary vertebral fracture (ACR = 2.88%) NNT (95% CI)	Secondary non-vertebral fracture (ACR = 8.65%) NNT (95% CI)
Bisphosphonate	74 (66, 85)	28 (23, 43)
Etidronate	71 (54, 119)	Effectiveness not established
Alendronate	77 (64, 96)	24 (18, 53)
Risedronate	89 (85, 92)	21 (16, 55)
Pamidronate	62 (46, 159)	Effectiveness not established
SERMs	89 (81, 99)	Effectiveness not established
PTH	56 (47, 76)	32 (21, 116)
Calcitonin	152 (87, 3333)	N/A

NNT number needed to treat, *ACR* assumed control risk, *CI* confidence interval, *SERMs* selective estrogen receptor modulators, *PTH* parathyroid hormone, *N/A* not available

0.61, 95% CI 0.52–0.72). The treatment by alendronate or risedronate also reduced the incidence of secondary fractures, but the reduction was not significant (95% CI 0.48–2.27).

Number of patients needed to treat in event rates

We calculated the NNT to prevent a secondary fragility fracture for a period of 2 years based on the ACRs (Table 7). Treatment with PTH needed the fewest number of patients to prevent a secondary vertebral fracture, whereas the treatment with calcitonin needed the greatest number of patients. For preventing non-vertebral fractures, the treatment with risedronate needed the fewest number of patients. For etidronate, pamidronate, and SERMs, for secondary non-vertebral fractures, there was no significant reduction in the ARRs of these drugs. Therefore, we did not calculate their NNTs.

Discussion

In this meta-analysis, patients treated with anti-osteoporotic agents after primary osteoporotic fractures were significantly less likely to have secondary osteoporotic fractures. In particular, secondary vertebral fractures were significantly prevented by all of the anti-osteoporotic drugs included in our review. This study also showed that PTH needed the fewest number of patients to treat to prevent secondary vertebral fractures, and that the bisphosphonates needed the fewest numbers to treat to prevent secondary non-vertebral fractures.

Treatment rates for patients who have osteoporosis have decreased between 2001 and 2009, and the rates of evaluation and treatment for osteoporosis following fragility fractures are still low [19, 45]. The treatment rates were highest following vertebral fractures and lowest following DRFs (32.3 and 11.0%, respectively) [19]. Preventing subsequent fractures can decrease the demand for healthcare services [46]. The RRs for death following vertebral or hip fractures are sixfold to ninefold greater in postmenopausal women with low bone mineral density [5]. Harvey et al. demonstrated that the first step to prevent all osteoporotic fractures is secondary fracture prevention, and that up to half of patients with hip fractures can be treated to prevent secondary fracture [47]. They also insisted that public awareness of osteoporosis must be emphasized. Additionally, the patients with hip fracture became a considerable portion of the social cost burden for treatment of osteoporotic fractures [48]. Therefore, individuals with fragility fractures, especially hip fractures, need to be identified by the health system and treated according to guidelines that can provide the best practice [50].

The effectiveness of bisphosphonates in preventing initial fragility fractures is known [16, 17, 49]. A systematic review reported a RR of initial vertebral fractures in bisphosphonates ranging from 0.52 to 0.64, and the NNT to prevent initial vertebral fractures with bisphosphonate was 90 for a high-risk population [49]. Cochrane reviews showed relative risk reduction (RRR) and ARR for secondary fracture prevention in alendronate, etidronate, and risedronate, and that these drugs can prevent secondary fractures significantly (RRR for vertebral fracture prevention 0.45 in alendronate, 0.47 in etidronate, 0.39 in risedronate) [50–52]. In our review, the RR of secondary fractures with bisphosphonates is 0.59 and the NNT for preventing secondary fractures with bisphosphonates is 74. These results demonstrate that bisphosphonates are effective for reducing the risk of secondary osteoporotic fractures in addition to primary fractures. Additionally, the NNTs of this review can be used to help form a strategy for preventing secondary osteoporotic fractures.

PTH is also effective at reducing the risk of primary fragility fractures [17, 37, 41, 44]. Neer et al. reported that the use of PTH reduced the incidence of new vertebral fractures (RR 0.35) and the incidence of new non-vertebral fractures (RR 0.54) [37]. Our review revealed that treatment with PTH reduced the risk of secondary vertebral and non-vertebral fractures (RR 0.38 and 0.64). Additionally, PTH has an anabolic

effect on bones, which influences processes associated with bone formation to a greater extent than bone reabsorption. This effect leads to a shorter healing time after fractures [53]. Other RCTs showed that patients treated with PTH had significantly less pain after the fracture than those in the control group [54]. Malouf-Sierra et al. reported that treatment with teriparatide increased BMD and improved pain faster than treatment with risedronate in patients after surgery for pertrochanteric hip fractures [55]. PTH is therefore a rational treatment for patients with primary fractures because it enhances primary fracture healing and prevents secondary fractures.

A recent retrospective study demonstrated the effectiveness of anti-osteoporotic drugs on preventing secondary fragility fractures after a primary fracture (40% risk reduction) across multiple fracture sites in a large population [56]. This finding agrees with the results of our study. However, there are some limitations to this study as well. First, this study was an observational retrospective study without the use of propensity score matching. Thus, there is a possibility of selection bias. Second, the effectiveness of individual drug was not shown [57]. The current review is the first to reveal the effectiveness of anti-osteoporotic treatment after a primary fracture in preventing subsequent fragility fractures across multiple anti-osteoporotic drugs using meta-analysis.

Health economics are integral to decision-making to accomplish the maximum healthcare benefits possible. Treatment with bisphosphonates, especially risedronate, is most cost-effective for women aged 75 years with a prior fracture [58]. Pfister et al. reported that treatment with bisphosphonates was more cost-effective than treatment with PTH [59]. However, PTH has a strong impact on preventing secondary fractures. If the impact continues for a long time, PTH may show improved cost-effectiveness. Therefore, longer estimates of cost-effectiveness are needed for an adequate evaluation.

There was only one paper that showed the effectiveness of denosumab on preventing secondary osteoporotic fractures. Thus, we could not calculate pooled RR by meta-analysis and therefore were unable to suggest the use of denosumab from our outcomes. However, Palacious et al. reported that denosumab reduced the risk of a secondary fracture for both women with vertebral fractures (RR 35%) and those with non-vertebral fractures (RR 34%) [23]. It was also demonstrated that denosumab is cost-effective compared with oral bisphosphonates in patients over 75 years of age, because patients with denosumab have a lower fracture risk and a lower risk of dropping out due to the injection twice a year instead of daily oral medication [60]. Considering this, treatment with denosumab may be recommended.

Recently, some studies revealed that fracture liaison services (FLS) are an effective way to prevent a secondary fracture [61–63]. The International Osteoporosis Foundation and the American Society for Bone and Mineral Research also recommended the creation and use of FLS [64–66]. In these services, patients 50 years and over with a history of fragile fracture are identified, evaluated for their bone status, and given osteoporosis treatment according to national guidelines to prevent a subsequent fracture. FLS has been instituted in some countries that include Australia, Ireland, the Netherlands, Spain, Sweden, Switzerland, the UK, Canada, and the USA [66]. Nakayama et al. reported that patients with FLS care could have up to 30% reduction in secondary fractures compared with patients with non-FLS care [63]. In addition, the FLS system was demonstrated to reduce mortality, and is also cost-effective.

Our study has some limitations. First, many RCTs evaluating anti-osteoporotic agents included calcium and vitamin D in both the treatment and control groups. These supplements may influence the effectiveness of anti-osteoporotic drugs. However, the influence may not be strong because we excluded studies with calcium or vitamin D use in one group. Second, the definition of non-vertebral fractures was not standardized across the studies. Some researchers considered only fractures of the wrist, hip, and pelvis as osteoporotic non-vertebral fractures. Others included fractures of the humerus, as well as rib. Third, there was a lack of clarity in the allocation concealment and a large number of withdrawals in some studies. Eight trials lost over 30% of their participants, and two thirds of the trials (17/26) did not report allocation concealment. The follow-up time was also a limitation because the inclusive studies presented different RRs for different follow-up times. For example, the RR of etidronate for preventing secondary fractures is 0.44 in a study with a 2-year follow up [28] and 0.40 in a study with a 4-year follow up [32]. When we combined these RRs to estimate a pooled RR by meta-analysis, we found that they were not statistically different. These limitations may be sources of heterogeneity related to the incidences of the secondary osteoporotic fractures. Therefore, we performed additional subgroup analyses using studies matched on more restricted inclusion criteria such as gender, same follow-up period (3 years), double-blinding, concealed allocation, and intention-to-treat analysis. We calculated RRs categorized by primary fracture types. Five studies were matched based on the above criteria [8, 20, 21, 36, 40]. We calculated RRs categorized by primary fracture types (Appendix 4). These data demonstrated that alendronate, risedronate, and zoledronic acid were effective in preventing secondary fracture for the patients with vertebral fractures or non-vertebral fractures. However, the power to detect statistical heterogeneity was limited because of the low number of fractures in each subgroup.

We could not calculate the pooled RRs of preventing secondary fractures for some drugs. This was because there was only one study that we could use to calculate the RR for preventing secondary fractures for calcitonin, SERMs, or

PTH, especially for preventing a non-vertebral fracture. For these drugs, we presented the individual RR's of preventing secondary fracture calculated from each study. Thus, the RRs of these drugs are not robust. Regarding the studies that assessed secondary fractures after non-vertebral fractures, there were RCTs that reported the effectiveness of drugs in preventing secondary fractures after hip fractures but none that demonstrated the effectiveness after other non-vertebral fractures, such as distal radius (DRF) and proximal humeral fractures. Focused attention to osteoporosis can reduce the risk of recurrent fractures and the associated impact on quality of life and longevity [67, 68]. Therefore, further education of osteoporosis treatment and studies are needed to reveal the effectiveness of anti-osteoporotic drugs on preventing secondary fractures after fragility fractures.

This meta-analysis demonstrated that secondary vertebral fractures were prevented by all of the anti-osteoporotic drugs included in our review. Bisphosphonate and PTH had demonstrated effectiveness in decreasing non-vertebral fracture risk. Clinicians who treat osteoporotic fractures should prescribe these drugs to prevent secondary vertebral or non-vertebral fractures.

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Compliance with ethical standards

Conflict of interest None.

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