Objective: To determine efficacy of non-bisphosphonate drugs for preventing osteoporotic vertebral fracture in postmenopausal women by systematic review and meta-analysis. Methods: Published reports were searched through the electronic databases including MEDLINE and the Cochrane Library (CENTRAL) from inception to November 2015. Randomized controlled trial (RCT) studies on efficacy of non-bisphosphonate drugs including denosumab, raloxifene, strontium ranelate, teriparatide and tibolone compared with placebo and/or calcium plus vitamin D with the outcome of incidence of vertebral fracture were selected. Results of pooled efficacy from meta-analysis were presented as risk ratio (RR) with 95% confidence interval (CI). Results: The search identified 12 articles consistent with inclusion criteria. The studies compared effects of non-bisphosphonates with placebo for 1 - 3 years. It was found that denosumab, strontium ranelate and teriparatide significantly prevented vertebral fracture with RR = 0.33 (95% CI: 0.26 - 0.41), 0.60 (95% CI: 0.53 - 0.69) and 0.26 (95% CI: 0.14 - 0.49) respectively. Conclusion: Non-bisphosphonate drugs including denosumab, strontium ranelate and teriparatide were efficacious in preventing osteoporotic vertebral fracture in post-menopausal women. However, evidences indicating efficacy of raloxifene and tibolone were limited; the use of these drugs should be cautious. Further studies are needed. Keywords: bone fracture, postmenopausal women, osteoporosis, non-bisphosphonate, systematic review, meta-analysis
This study employed a systematic literature review and meta-analysis approach. Only randomized controlled trials (RCTs) examining efficacy of denosumab, raloxifene, strontium ranelate, teriparatide and tibolone were included in this analysis. These RCTs needed to compare a given non-bisphosphonate either with placebo and/or calcium plus vitamin D in postmenopausal women with osteoporosis.

**Methods**

This study employed a systematic literature review and meta-analysis approach. Only randomized controlled trials (RCTs) examining efficacy of denosumab, raloxifene, strontium ranelate, teriparatide and tibolone were included in this analysis. These RCTs needed to compare a given non-bisphosphonate either with placebo and/or calcium plus vitamin D in postmenopausal women with osteoporosis.

**Database and data searching**

Studies were searched from electronic databases such as MEDLINE and the Cochrane Library from inception up to November 2015 with Medical Subject Heading (MeSH) and keywords of “Osteoporosis” [MeSH], “Osteoporosis, Postmenopausal” [MeSH], “Fractures, Bone” [MeSH], “Denosumab”, “Raloxifene”, “Strontium ranelate”, “Teriparatide”, and “Tibolone,” with conjunction operators of “and” and “or.” Additional RCT studies cited in systematic review papers and clinical research papers were also further searched.

**Selection of RCT studies**

Two investigators (SS, WA) independently selected RCT studies based on inclusion criteria. If any disagreement or discrepancy, opinion from the third investigator (WB) was obtained. To be eligible, the study needed to be an RCT examining efficacy of denosumab, raloxifene, strontium ranelate, teriparatide or tibolone compared with placebo and/or calcium plus vitamin D in postmenopausal women with osteoporosis. Outcomes of the study needed to be incidence of vertebral fractures. The study had to be published in English language. Studies about cost-effectiveness or with information inadequate for meta-analysis were excluded.

**Data extraction and RCT study quality evaluation**

Selected RCT studies were independently evaluated for quality by two investigators (SS, WA). In case of discrepancy if any, the third investigator (WB) was asked for final judgement. Quality evaluation on the RCT studies was guided by Maastricht-Amsterdam scale. The scale has a high internal validity in evaluating trial bias in 11 aspects including (1) adequate randomization, (2) concealed treatment allocation, (3) comparable baseline characteristics, (4) interventions blinded to patients, (5) interventions blinded to care providers, (6) interventions blinded to outcome assessors, (7) co-interventions avoided or similar, (8) compliance acceptable in all groups, (9) drop-out rate described and acceptable, (10) similar time of outcome assessment in all groups, and (11) intention-to-treat analysis included. The answer of each of these 11 aspects of bias is in yes-no and unsure format where 1 point is awarded for no
risk of bias. An RCT with a total score of 6 points or higher was considered a high quality trial; while those with scores lower than 6 points are low quality ones and have a high risk of bias. For data extraction on individual selected RCTs, authors, year of publication, study setting, interventions, study duration, and age and number of participants.

Data synthesis and summary
For a given drug namely denosumab, raloxifene, strontium ranelate and teriparatide, there needed to be at least two RCTs for meta-analysis. In the analysis, pooled result of the risk ratio of incidence of vertebral fractures was estimated. The overall effects were presented as risk ratio (RR) with 95% confidence interval (95% CI) in the form of Forest’s plot. Heterogeneity among RCTs was tested based on the work of Higgins and colleagues including Q statistics with a significance level ($\alpha$) of 0.10 and percentage of inconsistency index ($I^2$). In pooled result analysis, $I^2$ of $< 25\%$ indicated no heterogeneity and fixed effect model was chosen; while $I^2$ of $> 25\%$ indicated significant heterogeneity and random effect model was chosen. Analysis was performed using Review Manager® (Revman version 5.3.5). We included 11 RCTs, both high and low quality studies, in this analysis.

Results

From a total of 902 articles, after duplicate papers were excluded, 12 articles of 12 studies met the inclusion criteria (Figure 1). Most studies had high quality (11 of 12 articles) with a score of 6 points or higher; while only one was with low quality. Most studies were on denosumab (4 studies), followed by raloxifene (3 studies), strontium ranelate (2 studies), teriparatide (2 studies) and tibolone (1 study).

There were 12 studies examining efficacy of non-bisphosphonate drugs in preventing vertebral fractures. However, since only one study of tibolone was found, there was no need to perform meta-analysis on the drug. As a consequence, 11 studies were included in meta-analysis.

Of all 11 RCT studies included for meta-analysis, they were published in 1998 to 2014. Participants were postmenopausal women with osteoporosis aged 45 to 95 years old with and without bone fracture. Most studies were placebo controlled 91.67 (11 studies) while 1 study (8.33%) was active controlled with calcium plus vitamin D. Most studies were conducted in North America, followed by Latin America, Europe and Asia, respectively, and had study durations of 1 to 3 years (Table 1).

The outcomes in these studies were incidences of bone fractures including vertebral fractures, non-vertebral fractures, hip fractures, and wrist fractures. Five non-bisphosphonate drugs were found in these 11 studies including denosumab, raloxifene, strontium ranelate, teriparatide and tibolone. Of these 12 studies examining vertebral fracture prevention, the majority tested the efficacy of denosumab (4 studies), raloxifene (3 studies), strontium ranelate (2 studies), teriparatide (2 studies), and tibolone (1 study). Efficacy of non-bisphosphonates in preventing non-vertebral fractures was found in a small number of studies. Specifically, only one study reported hip fracture prevention. Wrist fracture prevention was tested with raloxifene and teriparatide, each with one study.

In the meta-analysis, 11 studies with incidence of vertebral fractures were included. Non-bisphosphonate drugs included for meta-analysis were denosumab (4 studies), raloxifene (3 studies), strontium ranelate (2 studies) and teriparatide (2 studies). There was no need to perform meta-analysis on tibolone since only one study with incidence of vertebral fractures was found.
Table 1  Characteristics of selected RCT studies.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Study</th>
<th>Year of publication</th>
<th>Study setting</th>
<th>Study populations</th>
<th>Tested Intervention</th>
<th>Study duration</th>
<th>Study quality*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denosumab</td>
<td>1. McClung 2006 24</td>
<td>2006 America</td>
<td>Denosumab 60 mg q 6 mo.</td>
<td>12 mo. High</td>
<td></td>
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<td></td>
<td>2. Bone 2009 25</td>
<td>2008 America, Canada</td>
<td>Denosumab 60 mg sc q 6 mo.</td>
<td>24 mo. High</td>
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<td></td>
<td>3. Cummings 2009</td>
<td>2009 Europe, Latin America, North America, Australia, New Zealand</td>
<td>Denosumab 60 mg sc q 6 mo.</td>
<td>36 mo. High</td>
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<tr>
<td></td>
<td>4. Nakamura 2014: DIRECT trial 26</td>
<td>2014 Japan</td>
<td>Denosumab 60 mg sc q 6 mo.</td>
<td>24 mo. Low</td>
<td></td>
<td></td>
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<tr>
<td>Raloxifene</td>
<td>5. Lutfi 1998 14</td>
<td>1998 America</td>
<td>Raloxifene 60 mg/d, 120 mg/d</td>
<td>12 mo. High</td>
<td></td>
<td></td>
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<td></td>
<td>6. Ettinger 1999: MORE Trial 20</td>
<td>1999 N/A</td>
<td>Raloxifene 60 mg/d, 120 mg/d</td>
<td>36 mo. High</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7. Mori 2003 27</td>
<td>2008 Japan</td>
<td>Raloxifene 60 mg/d, 120 mg/d</td>
<td>52 wk. High</td>
<td></td>
<td></td>
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<tr>
<td>Strontium ranelate</td>
<td>8. Meunier 2004: SOTI trial 24</td>
<td>2004 Europe, Australia</td>
<td>Strontium ranelate 2 g/d</td>
<td>36 mo. High</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>9. Reginster 2005: TROPOS trial 21</td>
<td>2005 Europe, Australia</td>
<td>Strontium ranelate 2 g/d</td>
<td>36 mo. High</td>
<td></td>
<td></td>
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<tr>
<td>Teriparatide</td>
<td>10. Neer 2001: Fracture Prevention Trial (FPT) 22</td>
<td>2001 N/A</td>
<td>Teriparatide 20 µg sc OD, 40 µg sc OD</td>
<td>24 mo. High</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Tibolone</td>
<td>12. Cummings 2008: LIFT study 23</td>
<td>2008 N/A</td>
<td>Tibolone 12.5 mg/d</td>
<td>34 mo. High</td>
<td></td>
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</table>

* Study quality based on Maastricht-Amsterdam scale (high quality: ≥ 6 points; low quality: < 6 points).

**Effects of non-bisphosphonate drugs in preventing vertebral fractures**

**Denosumab**

In 4 studies of denosumab19,24-26, the dose was 60 mg sc every 6 months for 1 to 3 years. With a total of 9,026 patients, denosumab 60 mg sc every 6 months offered a significant 67% protection of vertebral fracture compared with placebo (RR = 0.33; 95%CI: 0.26 - 0.41). Among these 4 studies, no heterogeneity was found ($I^2 = 2%$, $P$-value = 0.38) (Figure 2).

**Raloxifene**

In 3 studies of raloxifene16,20,27, the dose was 60 to 120 mg/day for 1 to 3 years. With a total of 7,241 patients, raloxifene 60 - 120 mg/day resulted in a 24% protection of vertebral fracture compared with controls with no statistical significance (RR = 0.76; 95%CI: 0.41 - 1.40). This could be in part due to a significant heterogeneity among studies ($I^2 = 78\%$, $P$-value = 0.01) (Figure 3).

**Strontium ranelate**

In 2 studies of strontium ranelate21,28, the dose was 2 g/day for 3 years. With a total of 5,082 patients, strontium ranelate 2 g/day offered a significant 40% protection of vertebral fracture compared with controls (RR = 0.60; 95%CI: 0.53 - 0.69). Between the 2 studies, no heterogeneity was found ($I^2 = 0\%$, $P$-value = 0.85) (Figure 4).

**Teriparatide**

In 2 studies of teriparatide22,29, the dose was v for 2 years. With a total of 1,888 patients, teriparatide 20 – 40 µg/day and 56.5 µg/week resulted in a significant 74% protection of vertebral fracture compared with controls (RR = 0.26; 95%CI: 0.14 - 0.49). Between the 2 studies, a moderate heterogeneity was found ($I^2 = 53\%$, $P$-value = 0.14) (Figure 5).

**Tibolone**

The was only one study on tibolone with a dose of 1.25 mg/day for 2 years and 10 months.23 With a total of 4,506 patients, tibolone 1.25 mg/day offered a significant 44% protection of vertebral fracture compared with controls (RR = 0.56; 95%CI: 0.42 - 0.74).
Discussions and Conclusion

In this meta-analysis, more RCTs studies were included compared with previous meta-analysis studies. As a result, our present study was supposedly to offer a more robust finding of efficacy of non-bisphosphonate drug for preventing vertebral fractures in postmenopausal women. Findings from our study were consistent with the previous ones.

In this present study, denosumab was found to be significantly efficacious in preventing vertebral fractures in postmenopausal women with osteoporosis. This finding was consistent with previous studies of Keyserlingk and
colleagues\textsuperscript{15} and Silva-Fernandez and co-workers\textsuperscript{30} where similar sample size and osteoporotic postmenopausal women were found. However, our finding was different from that of Anastasilakis et al where a smaller sample size of mixed pre- and post-menopausal women with osteoporosis were recruited in the study.\textsuperscript{11}

For raloxifene, a slight protection on vertebral fracture was found with no statistical significance. As we had learned from the work of Cranney and colleagues\textsuperscript{13}, two RCTs of Ettinger et al\textsuperscript{22} and Luftkin et al\textsuperscript{18} with dramatically different sample sizes were tried for pooling (6,828 and 133 patients, respectively), but not successful. Therefore, in our study, we included another study by Mori and colleagues\textsuperscript{27}, yet raloxifene was found not different from control. We found that study of Mori and colleagues\textsuperscript{27} had a small sample size and the outcomes of fracture also included decrease in bone length. However, the heterogeneity among these studies caused the insignificant finding in our analysis.

We also found that strontium ranelate was significantly protective of vertebral fractures. This finding was consistent with systematic review of O’Donnell and colleagues\textsuperscript{31} and meta-analysis of Kanis et al.\textsuperscript{32} For teriparatide, it was significantly efficacious in preventing vertebral fractures. The finding was consistent with Han and co-workers probably in part due to similar sample size and characteristics.\textsuperscript{33} However, we found that heterogeneity between the two studies included in our analysis was in moderate level probably because of differences in dosage frequencies namely once a day and once a week, as well as the given doses (\(20 – 40\ \mu g/day\) and \(56.5\ \mu g/week\)).

For tibolone, there was only one study in postmenopausal women with osteoporosis. This one study was also terminated before completion.\textsuperscript{23} There has been no study on tibolone since 2008. All studies on tibolone has been small and had no outcomes of incidence of bone fractures.

Our study found that RCT studies on raloxifene and teriparatide had significant heterogeneity probably in part due to differences in sample size, outcomes, and dosage regimens. Our study also faced certain limitations since publication bias and sensitivity were not tested.

There were certain advantages in our study. First, systematic searching of studies was conducted. Second, a wide range of non-bisphosphonates was studied. Third, the outcome of bone fracture especially vertebral ones was a highly objective outcome which is also the major target of the fracture prophylaxis treatment in women with osteoporosis. Fourth, we included mostly high quality RCT studies in our analysis which could offer a robust and practical result.

However, certain limitations were presented in our study. It was possible that some articles might be missed since databases available for us were relatively slightly limited and only studies with English language were included. It was recommended that future research with an access to a wider range of databases should be conducted to get a more precise and reliable effect estimation. Moreover, with a relatively small number of RCT studies, publication bias and sensitivity analysis were not performed in our study. Hence, the robust conclusion could not be drawn with full confidence. In addition, with diverse mechanisms of action of these non-bisphosphonates and their dosage regimens, a comprehensive single estimate on efficacy of these non-bisphosphonates could not be made. The interpretation and practical use of our findings could thus be limited. Another limitation was that non-bisphosphonates are not the first-line drugs for osteoporosis, hence the use was conditional. Some RCT studies included patients with osteopenia but subgroup analysis was not provided. This shortcoming could cause heterogeneity among RCT studies and estimates of efficacy from these studies could be inconclusive.

In conclusion, non-bisphosphonate drugs including denosumab, strontium ranelate and teriparatide were efficacious in preventing vertebral fractures in postmenopausal women with osteoporosis. However, efficacy of raloxifene and tibolone was found inconclusive with limited evidence. The use of raloxifene and tibolone in preventing vertebral fractures in postmenopausal women with osteoporosis should be cautioned and more studies are needed.

\section*{References}


