ประสิทธิภาพของยากลุ่มที่มิใช่บิสฟอสโฟเนตในการป้องกันกระดูกสันหลังหักจากโรคกระดูกพรุนในหญิงวัยหมดประจำเดือน: การทบทวนวรรณกรรมอย่างเป็นระบบและวิเคราะห์อภิมาน

Efficacy of Non-Bisphosphonates for Prevention of Osteoporotic Vertebral Fracture in Postmenopausal Women: A Systematic Review and Meta-Analysis

นิพนธ์ต้นฉบับ | **Original Article**

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บทคัดย่อ

วัตถุประสงค์: เพื่อประมาณประสิทธิภาพของยากลุ่มที่มิใช่บิสฟอสโฟเนต ในการป้องกันกระดูกสันหลังหักจากโรคกระดูกพรุนในหญิงวัยหมดประจำเดือนโดยการทบทวนวรรณกรรมอย่างเป็นระบบและวิเคราะห์อภิมาน **วิธีการศึกษา:** สืบค้นงานวิจัยจากฐานข้อมูลอิเล็กทรอนิกส์ ได้แก่ MEDLINE และ Cochrane Library ตั้งแต่เริ่มมีฐานข้อมูล จนถึงเดือนพฤศจิกายน 2558 คัดเลือกงานวิจัยเชิงทดลองแบบสุ่มที่มีกลุ่มควบคุมที่เปรียบเทียบประสิทธิผลของยากลุ่มที่มิใช่บิสฟอสโฟเนต ได้แก่ denosumab, raloxifene, strontium ranelate, teriparatide และ tibolone กับการให้ยาหลอกหรือ/และแคลเซียมร่วมกับวิตามินดี โดยวัดผลลัพธ์เป็นอุบัติการณ์การหักของกระดูกสันหลัง วิเคราะห์อภิมานประสิทธิผลของยาโดยแสดงด้วยค่าอัตราเสี่ยงสัมพัทธ์ (risk ratio) และช่วงความเชื่อมั่น 95% (95% CI) **ผลการศึกษา:** จากการสืบค้นพบงานวิจัยที่ผ่านการคัดเลือกตามเกณฑ์ที่กำหนดไว้ 12 เรื่อง งานวิจัยศึกษาเปรียบเทียบกับผลของยากลุ่มที่มิใช่บิสฟอสโฟเนตกับการให้ยาหลอก มีระยะเวลาการศึกษาอยู่ในช่วง 1 ปี ถึง 3 ปี ผลการวิเคราะห์อภิมานพบว่าการให้ยา denosumab, strontium ranelate และ teriparatide สามารถป้องกันการเกิดกระดูกสันหลังหักได้มากกว่ากลุ่มควบคุมอย่างมีนัยสำคัญทางสถิติ ด้วยค่า RR = 0.33 (95% CI: 0.26 - 0.41), 0.60 (95%CI: 0.53-0.69) และ 0.26 (95%CI: 0.14-0.49) ตามลำดับ ผลของการให้ยา raloxifene ในการป้องกันการเกิดกระดูกสันหลังหักนั้นไม่แตกต่างจากกลุ่มควบคุม (RR = 0.76; 95% CI: 0.41 - 1.40) ส่วนยา tibolone มีเพียง 1 การศึกษาจึงวิเคราะห์อภิมานไม่ได้ **สรุป:** ยาในกลุ่มที่มิใช่บิสฟอสโฟเนต ได้แก่ denosumab, strontium ranelate และ teriparatide มีประสิทธิภาพในการป้องกันกระดูกสันหลังหักจากโรคกระดูกพรุนในหญิงวัยหมดประจำเดือน อย่างไรก็ตาม หลักฐานเชิงประจักษ์ของยา raloxifene และ tibolone ยังมีจำกัด ดังนั้นการนำข้อมูลของยาสองตัวนี้ไปใช้ในการรักษาผู้ป่วยหญิงวัยหมดประจำเดือนที่เป็นโรคกระดูกพรุนจึงควรระมัดระวังและควรศึกษาเพิ่ม

คำสำคัญ: กระดูกหัก, หญิงวัยหมดประจำเดือน, โรคกระดูกพรุน, ยากลุ่มที่มิใช่บิสฟอสโฟเนต, การทบทวนวรรณกรรม, การวิเคราะห์อภิมาน

Abstract

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 Cochran 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% confident 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. Raloxifene was not better than placebo in preventing vertebral fracture (RR =0.76; 95% CI: 0.41 - 1.40). Since only one RCT of tibolone, its pooled result could not be estimated. **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

Editorial note

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Introduction

Post- menopausal women are at a high risk of osteoporosis. As a result of a decrease in estrogen hormone, the loss of bone mineral density is accelerated. The prevalence of osteoporosis has been 7% to 35% and increasing with age.[1] In osteoporosis, the bone health is detrimental both bone mineral density and the bone one quality. Though symptomatic in early stages, but if left untreated, bone fractures at different body parts could be

common. A vertebral fracture could put a huge burden on the patients, family member and caregivers. A low level of daily living and quality of life for all parties is inevitable. Complications such as pressure ulcer and infections are common and could lead to death.[2] Since the treatment is relatively costly and almost life-long[3], measures to prevent bone fractures are paramount for osteoporosis.

Pharmacological treatment has been an effective modality for osteoroposis.[4,5] According the clinical practice guideline of the Royal College of Orthopaedic Surgeons of Thailand and Thai Osteoporosis Foundation, bisphosphonates are considered the first-line drug for postmenopausal women with osteoporosis.[6] However, bisphosphonates are associated with certain adverse effects on gastrointestinal tract and some serious adverse effects such as atypical femoral fractures and osteonecrosis of the jaw. As a result, there are limitations to use bisphosphonates in certain groups of patients with a long-term use. These adverse effects could lead not only to complications and discomforts, but also patient's non-compliance.[5,7-9] To avoid these adverse events and consequences, non-bisphosphonates such as denosumab, raloxifene, strontium ranelate, teriparatide and tibolone could reasonable alternative to bisphosphonates.

At present, studies have shown that efficacy of non-bisphosphonates are inconclusive or contradicting.[10-13] In addition, meta-analysis of randomized controlled trials (RCTs) to summarize efficacy of non-bisphosphonates has been limited.[14,15] Therefore, there was a need to conduct a meta-analysis of RCTs of non-bisphosphonates to determine their efficacy for osteoporosis in postmenopausal women. The finding could be a useful evidence for selecting non-bisphosphonates suitable for specific patients. This study aimed to determine efficacy of non-bisphosphonates including denosumab, raloxifene, strontium ranelate, teriparatide and tibolone in preventing osteoporosis in postmenopausal women.

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", "Reloxifene", "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 lacebo 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.[16] 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 (α) 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.[17] 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

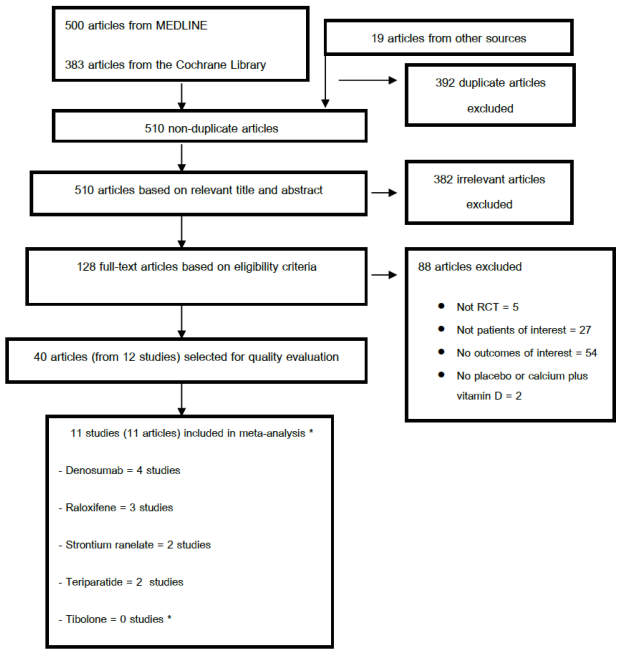

Figure 1 Flow diagram of literature search and study selection. * Only one study on tibolone, therefore there was no need to perform meta-analysis on the drug.

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.[18] 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.[19-23] Wrist fracture prevention was tested with raloxifene[20], strontium ranelate[21] and teriparatide[22], 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 denosunab (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.

Drug	Study	Year of publication	Study setting	Study populations		Tested intervention	Study duration	Study quality*
				Age (yr)	Number (test / control)			
Denosumab								
	1. McClung 2006 [24]	2006	America	≥ 80	47 / 46	Denosumab 60 mg q 6 mo.	12 mo.	High
	2. Bone 2008 [25]	2008	America, Canada	Average: 59	166 / 166	Denosumab 60 mg sc q 6 mo.	24 mo.	High
	3. Cummings 2009 (FREEDOM trial) [19]	2009	Europe, Latin America, North America, Australia, Australia, New Zealand	60 – 90	3,906 / 3,902	Denosumab 60 mg sc q 6 mo.	36 mo.	High
	4. Nakamura 2014: DIRECT trial[26]	2014	Japan	≥ 50	500 / 511	Denosumab 60 mg sc q 6mo.	24 mo.	Low
Raloxifene								
	5. Lufkin 1998[18]	1998	America	45 - 75	48,47 / 48	Raloxifene 60 mg/d, 120 mg/d	12 mo.	High
	6. Ettinger 1999: MORE Trial[20]	1999	N/A	Average: 65	5,129 / 2,576	Raloxifene 60 mg/d, 120 mg/d	36 mo.	High
	7. Morii 2003 [27]	2008	Japan	≥ 80	92,92 / 95	Raloxifene 60 mg/d, 120 mg/d	52 wk.	High
Strontium ranelate								
	8. Meunier 2004: SOTI trial[28]	2004	Europe, Australia	≥ 50	828 / 821	Strontium ranelate 2 g/d	36 mo.	High
	9. Reginster 2005: TROPOS trial[21]	2005	Europe, Australia	70 – 74	2,554 / 2,537	Strontium ranelate 2 g/d	36 mo.	High
Teriparatide								
	10. Neer 2001: Fracture Prevention Trial (FPT)[22]	2001	N/A	Average: 69	541,552 / 544	Teriparatide 20 µg sc OD, 40 µg sc OD.	24 mo.	High
	11. Nakamura 2012-b: TOWER trial [29]	2012	Japan	65 – 95	290 / 288	Teriparatide sc 56.5 µg/wk.	72 wk.	High
Tibolone								
	12. Cummings 2008: LIFT study[23]	2008	N/A	60 - 85	2,267 / 2,267	Tibolone 12.5 mg/d	34 mo.	High

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

Effects of non-bisphosphonate drugs in preventing vertebral factures

Denosumab

In 4 studies of denosumab[19,24-26], 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 raloxifene[18,20,27], 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 ranelate[21,28], 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 teriparatide[22,29], 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 dpose 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).

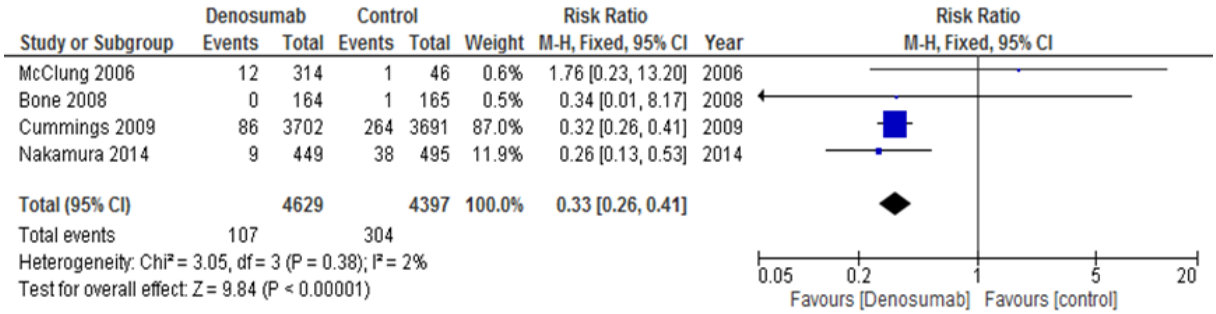

Figure 2 Efficacy of denosumab in reducing the risk of vertebral fracture compared with controls.

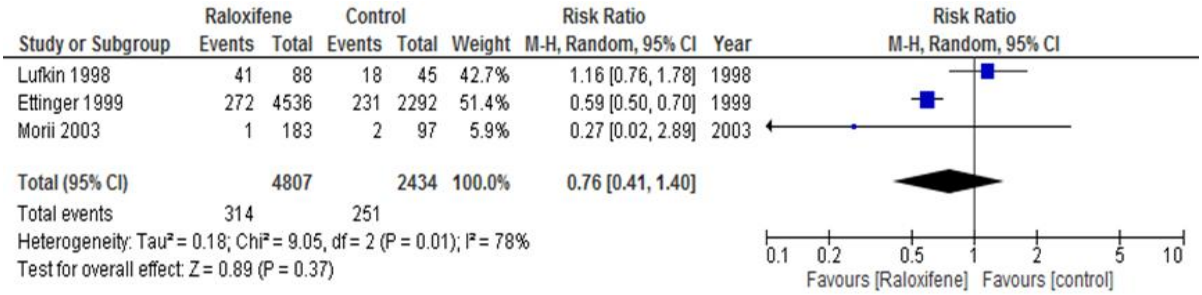

Figure 3 Efficacy of raloxifene in reducing the risk of vertebral fracture compared with controls.

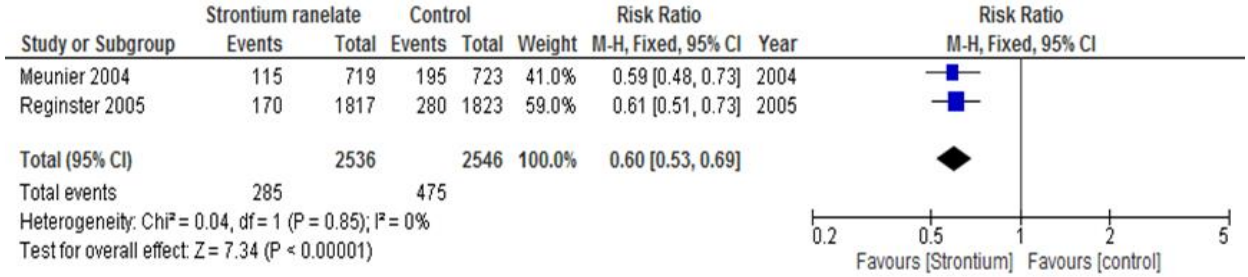

Figure 4 Efficacy of strontium ranelate in reducing the risk of vertebral fracture compared with controls.

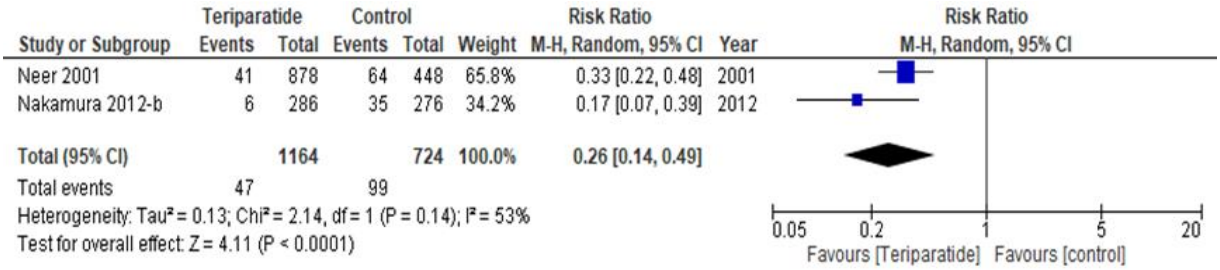

Figure 5 Efficacy of teriparatide in reducing the risk of vertebral fracture compared with controls.

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[10] and Silva-Fernandez and co-workers[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.[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[13], two RCTs of Ettinger et al[20] and Lufkin et al[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[27], yet raloxifene was found not different from control. We found that study of Mori and colleagues[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[31] and meta-analysis of Kanis et al.[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.[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 µg/day and 56.5 µg/week).

For tibolone, there was only one study in postmenopausal women with osteoporosis. This one study was also terminated before completion.[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.

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