ประสิทธิภาพของยากลุ่มบิสฟอสโฟเนตในการป้องกันกระดูกหักจากโรคกระดูกพรุนในหญิงวัยหมดประจำเดือน: การทบทวนวรรณกรรมอย่างเป็นระบบและการวิเคราะห์อภิมาน
Efficacy of Bisphosphonates for Preventing Osteoporotic Fracture in Postmenopausal Women: A Systematic Review and Meta - Analysis

นิพนธ์ต้นฉบับ

Original Article

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บทคัดย่อ

วัตถุประสงค์: เพื่อประมาณประสิทธิภาพของยากลุ่มบิสฟอสโฟเนตในการป้องกันกระดูกหักจากโรคกระดูกพรุนในหญิงวัยหมดประจำเดือนโดยวิธีทบทวนวรรณกรรมอย่างเป็นระบบและการวิเคราะห์อภิมาน **วิธีการศึกษา:** สืบค้นงานวิจัยจากฐานข้อมูลอิเล็กทรอนิกส์ ได้แก่ MEDLINE และ Cochrane Library ตั้งแต่เริ่มมีฐานข้อมูลจนถึงเดือนพฤศจิกายน 2558 โดยคัดเลือกงานวิจัยเชิงทดลองแบบสุ่มที่มีกลุ่มควบคุมที่ศึกษาประสิทธิผลของยากลุ่มบิสฟอสโฟเนต (alendronate, clodronate, etidronate ibandronate, risedronate และ zolendronate) เปรียบเทียบกับการได้รับยาหลอกและ/หรือการให้แคลเซียมร่วมกับวิตามินดี และวัดอุบัติการณ์การเกิดกระดูกหัก **ผลการศึกษา:** จากการสืบค้นพบงานวิจัยที่ผ่านเกณฑ์การคัดเลือก 16 ฉบับ ศึกษาผลของยาเป็นเวลา 1 - 3 ปี การให้ยา alendronate (5 - 10 มก.ต่อวัน) และการให้ยา risedronate (2.5 และ 5 มก.ต่อวัน) ช่วยป้องกันการเกิดกระดูกสันหลังหักได้ร้อยละ 45 (RR = 0.55; 95% CI: 0.46, 0.67) และร้อยละ 38 (RR = 0.62; 95% CI: 0.51, 0.75) ตามลำดับ ส่วนประสิทธิผลในการป้องกันการเกิดกระดูกที่มิใช่กระดูกสันหลังหักพบว่า ยา alendronate, risedronate และ zoledronate (5 มิลลิกรัมต่อปี) ช่วยป้องกันกระดูกหักได้ร้อยละ 15 (RR = 0.85; 95% CI: 0.75, 0.97), ร้อยละ 19 (RR = 0.81; 95% CI: 0.72, 0.90) และร้อยละ 24 (RR = 0.76; 95% CI: 0.66, 0.88) ตามลำดับ ทั้งนี้ยา clodronate, etidronate และ ibandronate ยังมีข้อมูลงานวิจัยที่จำกัด และยังพบว่ายากลุ่มบิสฟอสโฟเนตช่วยป้องกันการเกิดกระดูกหักได้ทั้งบริเวณกระดูกสันหลัง (RR = 0.57; 95% CI: 0.50,0.64) และบริเวณที่มิใช่กระดูกสันหลัง (RR = 0.81 ; 95% CI: 0.76,0.87) ได้อย่างมีนัยสำคัญทางสถิติเมื่อเทียบกับกลุ่มควบคุม **สรุป:** ผลการศึกษาที่ได้เป็นหลักฐานเชิงประจักษ์ที่สนับสนุนประสิทธิผลของยากลุ่มบิสฟอสโฟเนตในการป้องกันการเกิดกระดูกหักจากโรคกระดูกพรุนในหญิงวัยหมดประจำเดือนได้ อย่างไรก็ตาม ยา clodronate, etidronate และ ibandronate ยังมีข้อมูลจากการศึกษาไม่มากพอ จึงควรศึกษาเพิ่มเติมต่อไป

คำสำคัญ: ประสิทธิภาพ, กระดูกหัก, โรคกระดูกพรุน, หญิงวัยหมดประจำเดือน, ยากลุ่มบิสฟอสโฟเนต

Abstract

Objective: To estimate the efficacy of bisphosphonates in preventing osteoporotic fractures in postmenopausal women systematic review and meta- analysis. **Methods:** Published reports were searched through electronic database including MEDLINE and the Cochrane Library from inception to November 2015. We selected randomized controlled trials (RCTs) examining efficacy of bisphosphonates compared with placebo and/or calcium plus vitamin D with outcomes of incidence of bone fracture. **Results:** Sixteen RCTs with duration of 1 – 3 years met the eligibility criteria. Meta-analysis showed that alendronate (5 - 10 mg/day) and risedronate (2.5 and 5 mg/day) could prevent vertebral fracture by 45% (RR = 0.55; 95% CI: 0.46, 0.67) and 38% (RR = 0.62; 95% CI: 0.51, 0.75), respectively. Alendronate, risedronate and zoledronate (5 mg/day) could prevent non-vertebral fractures by 15% (RR = 85; 95% CI: 0.75, 0.97), 19% (RR = 0.81; 95% CI: 0.72, 0.90) and 24% (RR = 0.76; 95% CI: 0.66, 0.88), respectively.There were a limited number of studies on clodronate, etidronate and ibandronate. All bisphosphonates combined could significantly prevent vertebral fracture (RR = 0.57; 95% CI: 0.50, 0.64) and non-vertebral fracture (RR = 0.81; 95% CI: 0.76, 0.87). **Conclusion:** Bisphosphonates were efficacious in preventing bone fractures in postmenopausal women with osteoporosis. However, studies on clodronate, etidronate and ibandronate were limited, thus further studies should be conducted.

Keywords: efficacy, fracture, osteoporosis, postmenopausal, bisphosphonate

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Introduction

Osteoporosis is an abnormality of which bone mineral density is decreased leading to a decrease in bone strength and finally an increase in risk of bone fracture especially vertebra, hip and wrist.[1] World Health Organization estimated that there were 75 patients with osteoporosis in Europe, North America and Asia combined. Of all osteoporosis patients

worldwide, 9 million of them would progress to bone fractures annually.[2] Bone fractures associated with osteoporosis is a cause of disability and high healthcare expenditure. In the US, the expense for osteoporosis treatment is as high as 18 billion dollars annually.[3] Osteoporosis related bone fractures also impair quality of life and increase a risk of mortality in the elderly.[4] Postmenopausal women have a higher risk of osteoporosis than other age groups with age-adjusted risk of 289 per 100,000 women and 114 per 100,000 men.[5]

The treatment for osteoporosis is targeting at reducing the risk of various bone fractures. There have been several medications for preventing bone fractures. Bisphosphonates are first-line therapy for postmenopausal women with osteoporosis recommended by the clinical practice guideline of the Royal College of Orthopaedic Surgeons of Thailand and Thai Osteoporosis Foundation.[5-7] Bisphosphonates have bone-mineral balance effect, cellular effect, and inhibition of aggregation, hydroxyapatite breakdown and bone resorption. These effects lead to an increase in bone mineral density.[8]

There have been randomized controlled trial (RCT) studies on efficacy of bisphosphonate drugs with various results. Few meta-analysis studies have been conducted but probably with some shortcomings such as diverse populations, outcomes, and comparator interventions.[9,10] However, there has been a relative lack of meta-analysis studies with conclusive results of bisphosphonate drugs for preventing bone fractures in postmenopausal women with osteoporosis.

In this present study, we aimed to examine the efficacy of bisphosphonate drugs in preventing bone fractures both vertebral and non-vertebral in postmenopausal women with osteoporosis by means of systematic review and meta-analysis. The findings could be useful for selecting the optimal drug treatment in postmenopausal women with osteoporosis.

Methods

In this systematic literature review and meta-analysis study, we selected randomized controlled trials (RCTs) to examine efficacy of bisphosphonate drugs including alendronate, clodronate, etidronate ibandronate, risedronate and zolendronate in preventing bone fractures both vertebral and non-vertebral. Comparators could be placebo and/or calcium plus vitamin D as an active control. Patients were limited to postmenopausal women with osteoporosis.

Database and data searching

Two databases namely Pubmed and the Cochrane Library were searched for relevant records from inception up to November 2015. We used the Medical Subject Headings (MeSH) of "Osteoporosis," " Osteoporosis, Postmenopausal," "Fractures, Bone," and "Diphosphonates" and key words of alendronate, clodronate, etidronate, ibandronate, risedronate and zolendronate with conjunction operators of “and” and “or.” We also searched for additional RCT studies cited in systematic review papers and clinical research papers.

Selection and quality evaluation of RCT studies

Records of studies were independently searched by two investigators (WA, SS) based on inclusion and exclusion criteria. If any disagreement, a third opinion from the third investigator (WB) was obtained to form the conclusion. To meet with the inclusion criteria, studies had to be RCT randomized controlled trial (RCT) examining efficacy of bisphosphonate drugs including alendronate, clodronate, etidronate, ibandronate, risedronate and zolendronate. The comparators could be placebo and/or calcium plus vitamin D as an active control. The studies had to have outcomes of bone fracture, either vertebral and/or non-vertebral. The studies had to be in English language. Cost-effectiveness studies and those unavailable for full data access were excluded.

The selected articles of studies were examined for quality using the Maastricht-Amsterdam scale.[11] The use of the scale helped assure the internal validity of our study. The scale measures bias in 11 aspects as follows: (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. For each statement, 1 point is awarded for “yes” and 0 for “no” or “unsure.” A given article with a score of 6 points or higher was considered a high quality study; while one with a score of lower than 6 points a low quality study. Studies with low quality had a higher risk of bias. However, both high and low quality studies were included in meta-analysis. Two investigators performed study quality evaluation independently and the third

investigator was asked for opinion if any disagreement between the first two investigators.

Data extraction

Data from individual selected RCTs were extracted as follows: interventions, authors, year of publication, study duration, age and number of participants, study setting, interventions, and quality of study.

Data synthesis and summary

In this meta-analysis, for given indications namely (1) prevention of vertebral fractures and (2) prevention of non-vertebral fractures, at least two studies for each bisphosphonate were required to determine pooled efficacy of the drug. Meta-analysis of all bisphosphonate drugs combined for each of the two indications was also performed.

Once summarized, pooled results of the risk ratio (RR) of incidence of the fractures were estimated with 95% confidence interval (95% CI) in the form of Forest's plot. Based on the effect size estimate of Hedges & Olkin, test of heterogeneity (or differences between studies) was used to select method of pooling. If significant heterogeneity was not found among studies, fixed effects model was used for pooling the outcomes; if found, a random effect model was used. The test of heterogeneity among RCTs was based on Q statistics[12] with a significance level (α) of 0.10 and percentage of inconsistency index (I^2). In pooling the outcomes, if I^2 was 25, no heterogeneity was found and fixed effect model was chosen. If I^2 was > 25%, significant heterogeneity was indicated and random effect model was chosen.[12] Analysis was performed using Review Manager® (Revman version 5.3.5).

Results

A total of 2,250 records of studies on bisphosphonates were found. Once duplicate studies were excluded and inclusion and exclusion criteria were applied, a total of 16 articles of 16 studies were retained with the most studies of risedronate (6 studies), followed by alendronate (4 studies), etidronate and zolendronate (2 studies each), and clodronate and ibandronate (1 study each) (Figure 1).

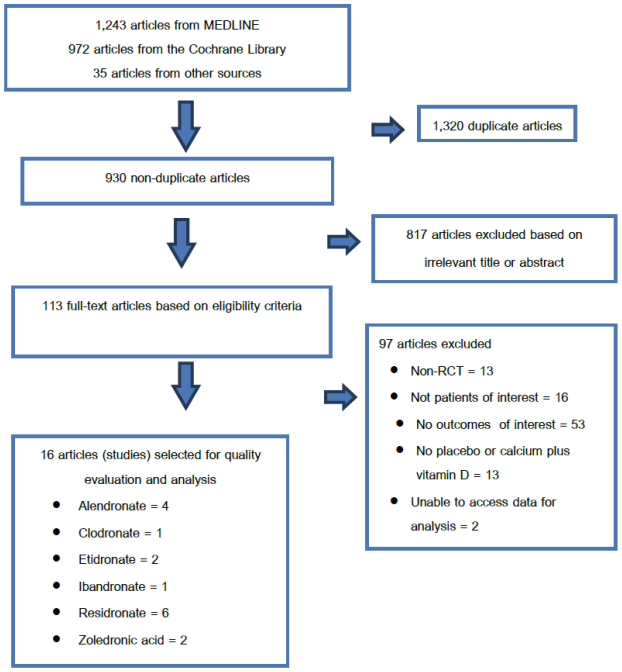

Figure 1 Flow diagram of literature search and study selection.

Of all the 16 studies selected, the largest study had 7,765 patients and the smallest had 54 patients. Majority of the studies were from Europe (10 of 16 studies), followed by America (5 studies), and others. In these studies, dosage regimens and duration of treatment were different. All 16 students had high quality based on Maastricht-Amsterdam scale (score of 6 points or higher)[11] (Table 1).

Efficacy of bisphosphonates in reducing the risk of vertebral fractures compared with controls

Meta-analysis indicated that alendronate 5 – 10 mg/day and risedronate 2.5 and 5 mg/day could significantly reduce the risk of vertebral fractures by 45% (RR = 0.55; 95% CI: 0.46, 0.67) and 38% (RR = 0.62; 95% CI: 0.51, 0.75), respectively (Figures 2 and 3). In the study of Liberman[13], alendronate 5 - 10 mg/day in postmenopausal women with osteoporosis regardless of history of bone fractures could significantly reduce the risk of vertebral fractures in those with previous bone fracture by 48% (RR = 0.52; 95% CI: 0.28, 0.97) but not in those with no bone fracture history (RR = 1.90; 95% CI: 0.51, 7.00). In addition, since alendronate 20 mg/day caused significant adverse effects, the study was terminated prior to completion. For zolendronate, the dose of 5 mg per year could reduce the risk of vertebral fracture compared with controls but with no statistical significance (RR 0.48; 95%CI: 0.14, 1.64) (Figure 4).

For the pooled efficacy of all bisphosphonates, these drugs could significantly reduce the risk of vertebral fractures in postmenopausal women with osteoporosis by 43% compared with controls (RR = 0.57; 95%CI: 0.55, 0.64) (Figure 5).

Table 1 Characteristics of selected studies (16 studies, 30,123 patients).

Drug	Authors	Year of publication	Interventions‡	Duration (yr)	Patients		Study setting	Study quality*
					Age (yr)	Number (test / control)		
Alandronate	Liberman UA[13]	1995	T: 5, 10, 20 mg/d C: placebo + calcium	3	45 - 80	881 (526/355)	Europe, Australia, America	high
	Black DM[14]	1996	T: 5, 10 mg/d C: placebo + calcium + vitamin D	2	55 – 81	2027 (1022/1005)	America	high
	Bone HG[15]	1997	T: 2.5, 5 mg/d C: placebo + calcium	2	60 – 85	359 (268/91)	Europe	high
	Cumming SR[16]	1998	T: 5, 10 mg/d C: placebo + calcium + vitamin D	4	45 - 80	4432 (2214/2218)	Europe	high
Clodronate	McCloskey E[17]	2004	T: 800 mg/d C: placebo + calcium	3	< 70	593 (292/301)	Europe	high
Etidronate	Watt NB[18]	1990	T: 400 mg/d C: placebo + calcium	2	> 75	423 (212/211)	America	high
	Meunier PJ[19]	1997	T: 400 mg/round C: placebo + calcium	1	45 - 57	54 (21/16)	Europe	high
Ibandronate	Chesnut CH[20]	2004	T: 2.5 mg/d C: placebo + calcium + vitamin D	3	55 – 80	2946 (1964/982)	Europe	high
Risedronate	Harris ST[21]	1999	T: 2.5, 5 mg/d C: placebo + calcium + vitamin D	3	< 85	2458 (1638/820)	America	high
	Fogelman I[22]	2000	T: 2.5, 5 mg/d C: placebo + calcium	2	> 80	543 (363/180)	Europe	high
	Reginster J.-Y.[23]	2000	T: 2.5, 5 mg/d C: placebo + calcium + vitamin D	3	> 85	1226 (815/411)	Europe, Australia	high
	McClung MR[24]	2001	T: 2.5, 5 mg/d C: placebo + calcium + vitamin D	3	70 - 79	5445 (3624/1821)	Europe, Australia, America	high
	Sorensen OH[25]	2003	T: 5 mg/d C: placebo + calcium + vitamin D	5	< 85	265 (135/130)	Europeย, Australia	high
	Hooper MJ[26]	2005	T: 2.5, 5 mg/d C: placebo + calcium	3	42 – 63	383 (257/126)	Australia	high
Zoledronate	Black DM[27]	2007	T: 5 mg/yr C: placebo + calcium + vitamin D	3	65 - 89	7765 (3876/3889)	America	high
	Hwang JS[28]	2011	T: 5 mg/yr C: placebo + calcium + vitamin D	2	64 - 88	323 (163/160)	Taiwan, Hong Kong	high

* Study quality based on Maastricht-Amsterdam scale: high quality (□ 6 of 11 poins), low quality (< 6 of 11 points).

‡ T = test drug; C = control.

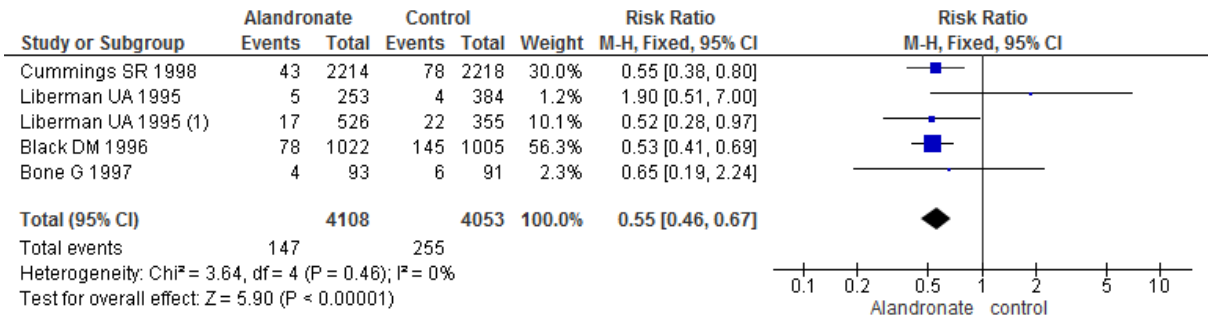

Figure 2 Efficacy of alendronate in reducing the risk of vertebral fracture compared with controls.

Note: Liberman UA = primary prevention of vertebral fractures; Liberman UA(1) = secondary prevention of vertebral fractures.

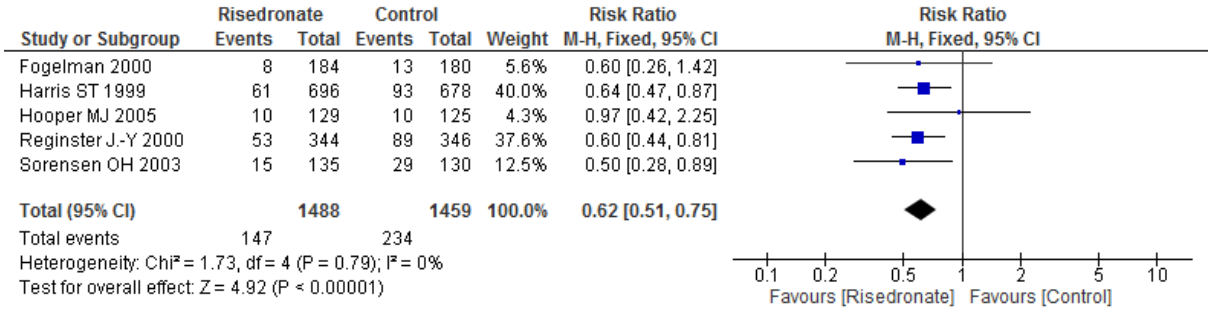

Figure 3 Efficacy of risedronate in reducing the risk of vertebral fracture compared with controls.

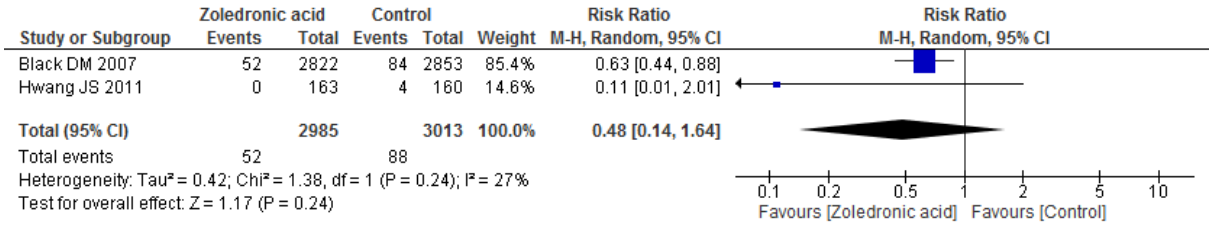

Figure 4 Efficacy of zoledronate in reducing the risk of vertebral fracture compared with controls.

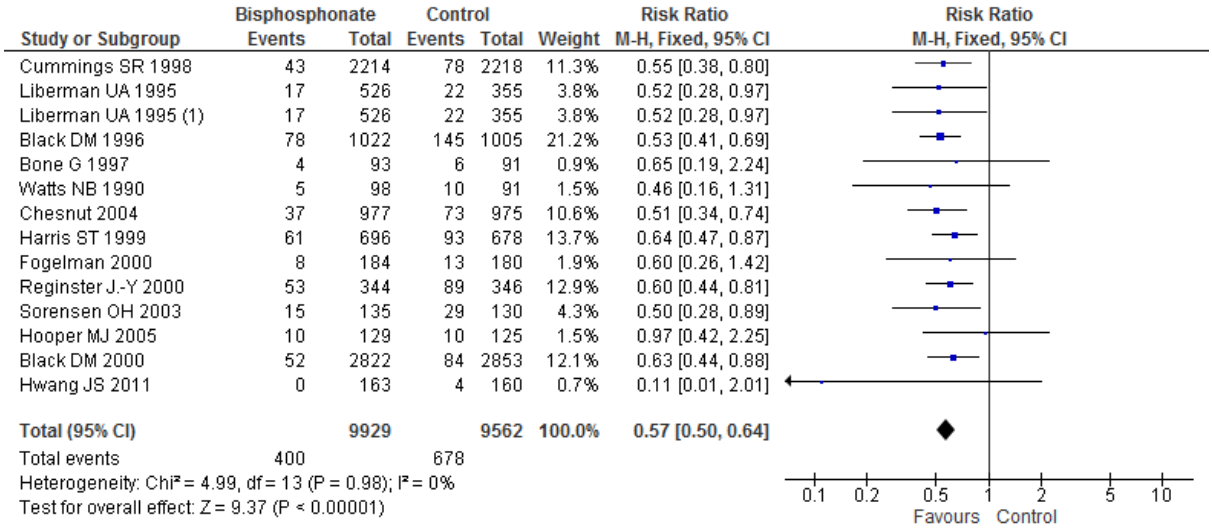

Figure 5 Efficacy of bisphosphonates in reducing the risk of vertebral fracture compared with controls.

Efficacy of bisphosphonates in reducing the risk of non-vertebral fractures compared with controls

Meta-analysis suggested that alendronate 5 – 10 mg/day, risedronate 2.5 and 5 mg/day and zoledronate 5 mg/year could significantly reduce the risk of non-vertebral fractures by 15% (RR = 85; 95% CI: 0.75, 0.97) and 19% (RR = 0.81; 95%CI: 0.72, 0.90), and 24% (RR = 0.76; 95%CI: 0.66, 0.88), respectively (Figures 6 - 8).

For the pooled efficacy of all bisphosphonates, these drugs could significantly reduce the risk of non-vertebral fractures in postmenopausal women with osteoporosis by 19% compared with controls (RR = 0.81; 95% CI: 0.76, 0.87) (Figure 9).

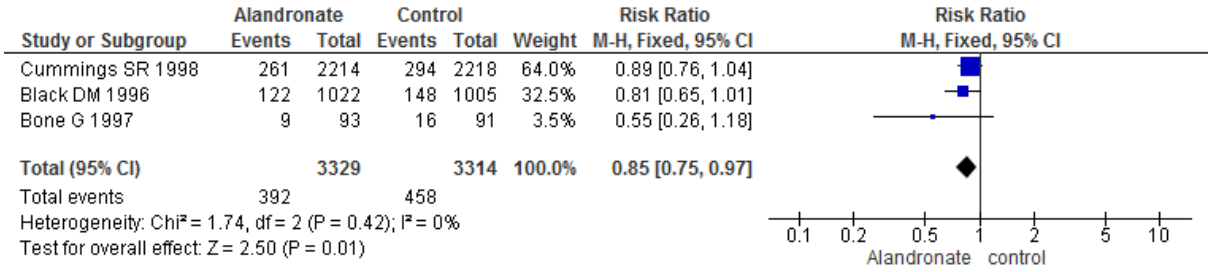

Figure 6 Efficacy of alendronate in reducing the risk of non-vertebral fracture compared with controls.

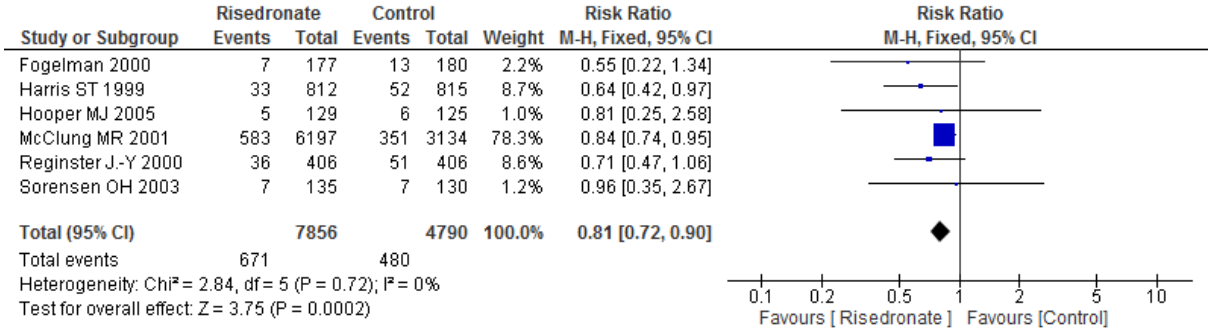

Figure 7 Efficacy of risedronate in reducing the risk of non-vertebral fracture compared with controls.

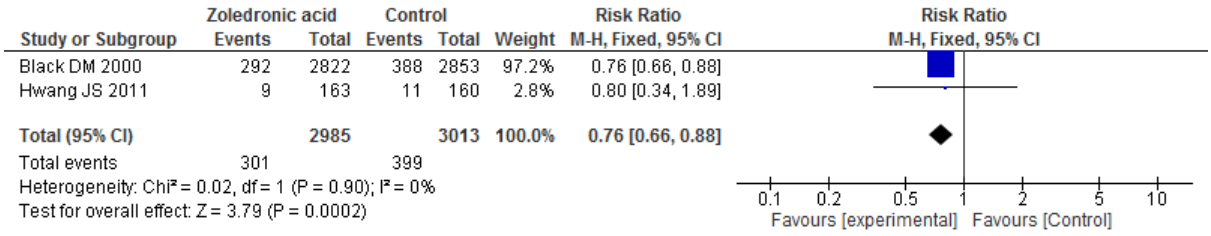

Figure 8 Efficacy of zoledronate in reducing the risk of non-vertebral fracture compared with controls.

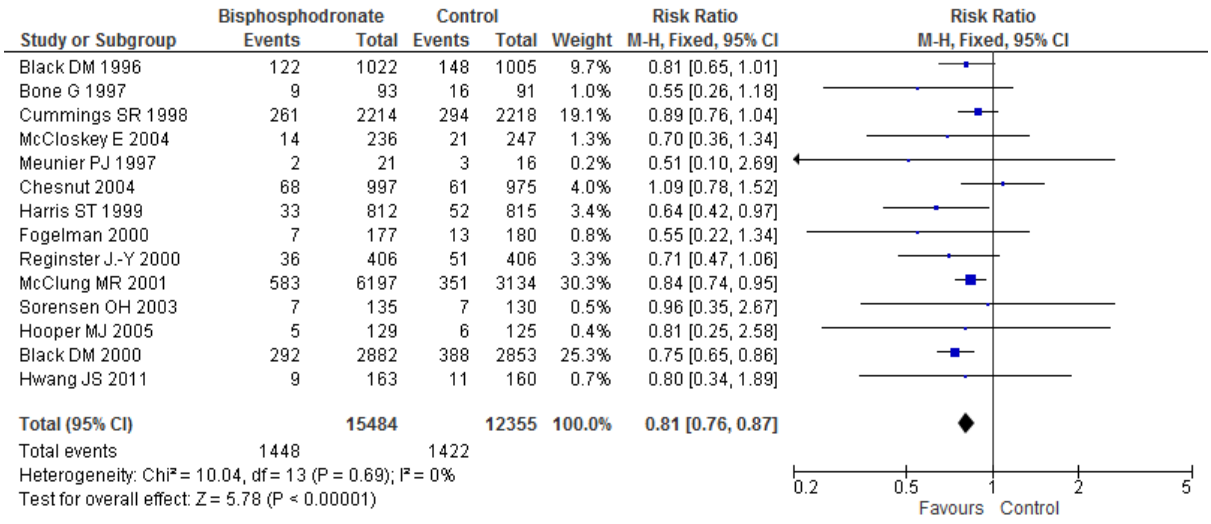

Figure 9 Efficacy of bisphosphonates in reducing the risk of non-vertebral fracture compared with controls.

Discussions and Conclusion

In our systematic review and meta-analysis, individual bisphosphonates had different benefits in preventing bone fractures in postmenopausal women with osteoporosis. These could be in part due to differences in dosage regimen, drug administration, and duration of study among these studies.

The efficacy of alendronate in preventing bone fractures was consistent with the study of Wells and colleagues[29] and Serrano and co-workers.[30] For risedronate 2.5 and 5 mg/day, its efficacy in preventing bone fractures, both vertebral and non-vertebral, found in this study was consistent with the study of Cranney et al where the doses of 2.5 and 5 mg/day were efficacious in reducing risk of vertebral and non-vertebral fractures, respectively.[31]

The meta-analysis indicated that intravenous zoledronate 5 mg per year could significantly reduce the risk of vertebral fractures but not non-vertebral ones. Previous meta-analysis of Zhang and colleagues zoledronate found that intravenous zoledronate 5 mg per year for 1 to 6 years from 9 studies was significantly efficacious in reducing the risk of bone fractures (OR = 0.81; 95% CI = 0.76, 0.87); however, benefits specific to vertebral or non-vertebral fractures were not separately determined.[32] It was noteworthy that in the work of Zhang et al, a high level of heterogeneity among RCTs was found (I^2 = 94%, *P*-value < 0.0001). On the other hand, a low level of heterogeneity was found in our study despite outcomes of only two studies were pooled (I^2 = 27%, *P*-value = 0.24). In addition, while men and women were included in the study of Zhang et al; only women were included in our study. This could contribute to a low heterogeneity in our study despite only two RCTs included in our study.

Our meta-analysis study has some advantages. Since the analyses were on individual drugs in bisphosphonate group and the group as a whole, our study provided a more diverse and up-to-date results than previous studies. In addition, our study included RCTs with high quality, therefore the pooled efficacy results of our meta-analysis were more reliable and applicable in the practice of optimal drug selection.

Certain limitations were found in our study. Even though large databases were used in our study, studies from other sources such as other established databases, local research reports submitted to the granters and proceedings from academic conferences could be missed. As a result, certain bisphosphonates were represented by very few number of studies. The addition of studies found solely in other databases such as Scopus, CINAHL and EMBASE should be strived in the future. Sensitivity analysis and publication bias based on Egger's test should be added in the future studies.

In our systematic review on efficacy of bisphosphonates in preventing bone fractures from osteoporosis in postmenopausal women, the 16 studies included were different regarding studied drugs, groups of investigators, year of publication, interventions, duration of study, study population (age and number) and study setting; especially the doses of these bisphosphonates which ranged from 5 to 800 mg. This analysis was however based on high quality RCT studies as evaluated by Maastricht-Amsterdam scale.[11]

In conclusion, three bisphosphonates namely alendronate, risedronate and zolendronate were confirmed for their efficacy in preventing bone fractures from osteoporosis in postmenopausal women. Other bisphosphonates including clodronate, etidronate and ibandronate were inconclusive with limited RCT studies. Certain bisphosphonates were efficacious in preventing bone fractures both vertebral and non-vertebral ones.

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