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Original Article

The Efficacy of Bisphosphonates for Prevention of Osteoporotic Fracture: An Update Meta-analysis

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**Byung-Ho Yoon and Yong-Chan Ha contributed equally to this work and should be considered co-corresponding authors.

Background: The efficacy of bisphosphonates for osteoporotic fracture has been consistently reported in recent randomized controlled trials (RCTs) enrolling hundreds of patients. The objective of this study was to update knowledge on the efficacy of available bisphosphonates in the prevention of vertebral and non-vertebral fractures. **Methods:** An approach "using systematic reviews" on PubMed and Cochrane Library was taken. Twenty-four RCTs investigating the effects of bisphosphonates for the prevention of osteoporotic fracture were included in final analysis. A pairwise meta-analysis was conducted with a random effects model. Subgroup analysis was performed according to the type of bisphosphonate. **Results:** The use of bisphosphonate decrease the risk of overall osteoporotic fracture (odds ratio [OR] 0.62; $P<0.001$), vertebral fracture (OR 0.55; $P<0.001$) and non-vertebral fracture (OR 0.73; $P<0.001$). Subgroup analysis indicated that zoledronic acid showed the lowest risk reduction (OR 0.61; $P<0.001$) for overall osteoporotic fractures but no significance was observed for etidronate (OR 0.34; $P=0.127$). **Conclusions:** This update meta-analysis re-confirmed that bisphosphonate use can effectively reduce the risk of osteoporotic fracture. However, there is a lack of evidence regarding etidronate for the prevention of osteoporotic fracture.

Key Words: Diphosphonates, Fractures bone, Meta-analysis as topic, Osteoporosis

INTRODUCTION

Osteoporotic fracture is recognized as a major social health problem.[1] Patients who sustain osteoporotic fractures have higher rates of morbidity and mortality.[2] Recently, several pharmacologic treatment options including antiresorptive or anabolic agents have been continuously developed.[3,4] However, bisphosphonates such as alendronate, risedronate, ibandronate and zoledronate are still the mainstay of anti-osteoporotic treatment.[5]

The efficacy of bisphosphonate in postmenopausal women has been thoroughly researched and reported in many clinical trials.[6-8] Moreover, a number of meta-analyses of bisphosphonates have been performed, but recently there have been adverse effects related reviews and relatively few reviews on the clinical impact of fracture prevention in the overall population.[9,10] To date, many clinical trials have been undertaken to elucidate the impact of bisphosphonate for osteo-

porotic fracture prevention.

Thus, we conducted an update meta-analysis to evaluate the efficacy of bisphosphonate regarding the prevention of osteoporotic fracture in patients with osteoporosis. The purpose of our update study was to determine the incidence of (1) overall osteoporotic fracture, (2) vertebral/non-vertebral fracture between intervention and placebo group.

METHODS

1. Literature search of previous systemic reviews

This search was conducted according to the updated preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) guidelines (Appendix S1).[11] First, a comprehensive search for systematic reviews or meta-analyses comparing outcomes between bisphosphonate and placebo in patients with osteoporosis on Cochrane Library (Cochrane Database of Systematic Review) was performed on November 13, 2016. The methodological quality of the included systematic reviews was independently assessed by the first two authors using the Assessment of Multiple Systematic Reviews (AMSTAR) tool.[12] Thereafter, we identified relevant randomized controlled trials (RCT) through the examination of reference lists from selected meta-analyses.[13-16]

2. Literature search for update clinical trials

We performed an additional updated searching of primary studies on PubMed-Medline and Cochrane Library search in November 2016 using key terms (bisphosphonate OR osteoporosis OR fracture). An overview of the search strategy and general characteristics about the four included systematic reviews are summarized in Appendix S2. Inclusion criteria were as follows: (1) study was a RCT, (2) patients were above 50 years old, and (3) articles that provided the rate of osteoporotic fracture. The intervention of at least one study group included the following bisphosphonates: alendronate, etidronate, ibandronate, risedronate, clodronate minodronate, pamidronate, tiludronate or zoledronic acid. We restricted our review to English and Korean studies, owing to translation difficulties and lack of resources for review. Basic science articles, comments, and letters were all excluded. When a published, updated study involving the same cohort of patients was identified, only the latest update was included in the analysis.

3. Outcome measure and data extraction

The primary outcome of interest was the rate of osteoporotic fracture including all fractures. Osteoporotic fractures were categorized into vertebral fractures and non-vertebral fractures. Additionally, we performed a subgroup analysis according to the type of bisphosphonate.

For each selected study, the following data were extracted and entered in a spread sheet by the two reviewers: the family name of the first author, the year of publication, enrollment period, study design, number of patients, number of osteoporotic fracture, mean age at the time of intervention, and the duration of follow-up.

4. Quality assessment and publication bias

Two of the authors (BJH, YBH) independently evaluated the quality of all the studies, using the criteria described in the Cochrane Handbook for Systematic Reviews of Interventions. The criteria included the following 7 items: (1) random sequence generation (2) allocation concealment (3) blinding of participants and personnel (4) blinding of outcome data (5) incomplete outcome data addressed (6) selective reporting (7) other biases. We assessed publication bias with Begg's funnel plot and Egger's test.

5. Statistical analysis

For each study, we calculated the odds ratio (OR) with a 95% confidence interval (CI) by using crude 2×2 tables, whenever possible, from the comparative studies.[17] The Mantel–Haenszel method was used to calculate the OR due to zero values in any cell count in a table.[18] Heterogeneity between comparable studies was tested with the chi-square and Higgins I^2 test. *P*-value of less than 0.1 or an I^2 value higher than 50% meant significant heterogeneity and a random-effects model should be applied. There was significant heterogeneity between the included studies ($P=0.001$). Thus, we reported the data from a randomized-effect. All analyses were performed using STATA version 14.0 software (Stata Corporation, College Station, TX, USA).

This study was exempted from institutional review board review since it did not involve any human subjects.

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RESULTS

1. Description of selected trials

A primary search of databases yielded 2,755 records and a total of 24 studies were included in the final systematic review. From the initial searches, studies selected for final inclusion or exclusion are displayed in the flowchart (Fig. 1). Twenty-four randomized placebo controlled trials investigating the effects of alendronate (6 studies), risedronate (5 studies), etidronate (4 studies), zoledronic acid (4 studies), clodronate (2 studies), ibandronate (1 study), minodronate (1 study), and pamidronate (1 study) were identified with a systematic literature search.[6-8,19-39] The characteristics of studies included are summarized in Table 1. A final total of 39,197 patients were included in our meta-analysis: 21,335 patients in the bisphosphonate group and 17,862 patients in the placebo group.

2. The overall rate of osteoporotic fracture

The overall rate of osteoporotic fracture was 7.7% (3,036/39,197): 5.9% (1,268/21,355) in the bisphosphonate group and 9.9% (1,768/17,862) in the placebo group. The overall rate of vertebral fracture was 5.9% (446/7,585) in the bisphosphonate group and 10.3% (741/7,190) in the placebo group. The overall rate of non-vertebral fracture was 6.0% (822/13,750) in the bisphosphonate group and 9.6% (1,027/10,672) in the placebo group.

3. Efficacy of bisphosphonate for osteoporotic fracture risk reduction

In the random effects model for all studies, the use of bisphosphonate was associated with a decreased risk of osteoporotic fracture (OR 0.62; 95% CI 0.54 to 0.71 $P<0.001$). In vertebral fracture, the use of bisphosphonate was associated with a decreased risk of osteoporotic fracture (OR 0.55; 95% CI 0.44 to 0.69 $P<0.001$) and non- vertebral fracture (OR 0.73; 95% CI 0.67 to 0.81 $P<0.001$) (Fig. 2). In the subgroup analysis, zoledronic acid showed the lowest OR with significance for overall osteoporotic fractures (Table 2).

4. Quality assessment and publication bias

In terms of the methodological quality, subjects were randomized by established allocation sequence, and investigators and research assistants were all blind to allocation. However, it is unclear whether the included trials met all the quality assessment criteria (Fig. 3). The Begg's funnel plot was symmetrical, and *P*-value for bias was 0.192 in the Egger's test for the included trials (Fig. 4).

DISCUSSION

One potential approach to enhance the management of osteoporosis is drug treatment that decreases osteoclastic activity.[40] Bisphosphonates are widely used as first-line drug therapy for preventing osteoporotic fracture and their

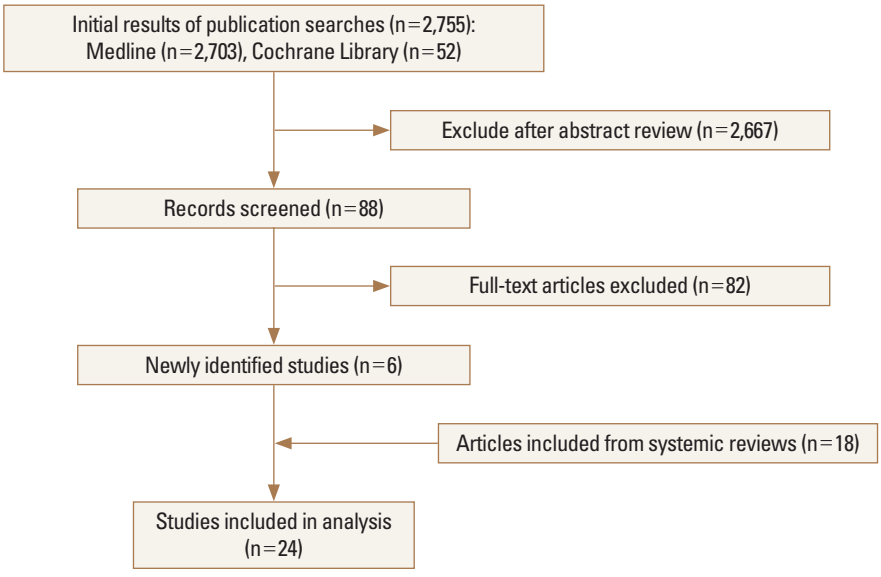

Fig. 1. Flow diagram detailing the selection process of relevant clinical studies.

Table 1. Characteristics of included individual studies

References	Treatment duration	Intervention	Outcome	Intervention/Placebo	
				Patients enrolled	No. of osteoporotic fracture
Storm et al. 1990 [38]	3 years	Etidronate 400 mg	VF	100/100	6/54
Reid et al. 1994 [37]	2 years	Pamidronate (150 mg/day)	VF	26/22	7/10
Liberman et al. 1995 [28]	2 years	Alendronate 5, 10, 20 mg	VF	526/355	17/22
Black et al. 1996 [19]	2 years	Alendronate 5, 10 mg	VF	975/967	78/145
Clemmesen et al. 1997 [23]	2 years	Risedronate 2.5 mg	VF	62/31	28/20
Herd et al. 1997 [26]	2 years	Etidronate	VF	75/77	0/0
Meunier et al. 1997 [33]	2 years	Etidronate	VF & NVF	VF 27/27 NVF 27/27	VF 1/0 NVF 2/3
Pouilles et al. 1997 [35]	2 years	Etidronate	VF & NVF	VF 54/55 NVF 54/55	VF 0/0 NVF 3/6
Cummings et al. 1998 [24]	2 years	Alendronate 5, 10 mg	VF	2,048/2,053	43/78
Hosking et al. 1998 [27]	2 years	Alendronate	VF & NVF	498/468	22/14
Harris et al. 1999 [25]	3 years	Risedronate 2.5, 5 mg	VF & NVF	VF 696/678 NVF 812/812	VF 61/93 NVF 33/33
Orwoll et al. 2000 [34]	2 years	Alendronate 10 mg	VF	146/95	1/7
Reginster et al. 2000 [36]	2 years	Risedronate 2.5, 5 mg	VF & NVF	VF 344/346 NVF 406/406	VF 53/89 NVF 36/51
McClung et al. 2001 [32]	2 years	Risedronate 2.5, 5 mg	NVF	6,197/3,134	137/95
McCloskey et al. 2004 [31]	3 years	Clodronate 800 mg	VF	260/270	33/63
Chesnut et al. 2004 [22]	3 years	Ibandronate 2.5 mg	VF	787/760	37/73
McCloskey et al. 2007 [39]	3 years	Clodronate 800 mg	NVF	2,779/2,785	264/337
Lyles et al. 2007 [29]	2 years	Zoledronic acid 5 mg	VF & NVF	1,065/1,062	92/139
Boonen et al. 2009 [20]	2 years	Risedronate 35 mg	VF	191/93	59/28
Matsumoto et al. 2009 [30]	2 years	Minodronate 1 mg	VF	246/219	4/17
Boonen et al. 2012 [21]	2 years	Zoledronic acid 5 mg	VF	553/574	9/28
Chao et al. 2013 [7]	2 years	Zoledronic acid 5 mg	VF & NVF	327/333	21/35
Bai et al. 2013 [8]	2 years	Zoledronic acid 5 mg	NVF	242/241	19/32
van de Glind et al. 2016 [6]	2 years	Alendronate	VF & NVF	1,841/1,817	215/296

VF, vertebral fracture; NVF, non-vertebral fracture.

Table 2. The efficacy of bisphosphonate for prevention of osteoporotic fracture by subgroup analysis

Type of bisphosphonate	No. of trials	Odds ratio	*P*-value
Alendronate	6	0.64 (0.48-0.84)	0.002
Risedronate	5	0.74 (0.63-0.85)	<0.001
Etidronate	4	0.34 (0.08-1.36)	0.127
Zoledronic acid	4	0.61 (0.49-0.76)	<0.001
Clodronate	2	0.69 (0.49-0.98)	0.035

efficacy is well-established. The objective of the current study was to synthesize updated evidence of bisphosphonates in the prevention of vertebral and non-vertebral fractures among patients with osteoporosis. A previous meta-analysis which included 8 RCTs reported that the use of bisphosphonates may result in anti-fracture and bone mineral density-increasing effects in postmenopausal women.[41]

Our update review included quality-proven 24 RCTs and the observed OR was 0.62 for total osteoporotic fracture and 0.55 for vertebral fracture. The effect of bisphosphonates on anti-fracture was similar to that obtained in a previous meta-analysis reporting beneficial effects of bisphosphonates in postmenopausal women. Relative risk reduction in vertebral fractures ranged from 0.55 to 0.61.[13-16] However, etidronate use did not show significant risk reduction for non-vertebral fractures.[14] This finding was similarly observed in our analysis from four RCTs (Table 2).

The efficacy of bisphosphonates varied between the included studies. A previous network meta-analysis demonstrated that zoledronic acid was most effective for reducing vertebral fractures.[41] Our study also noted the lowest

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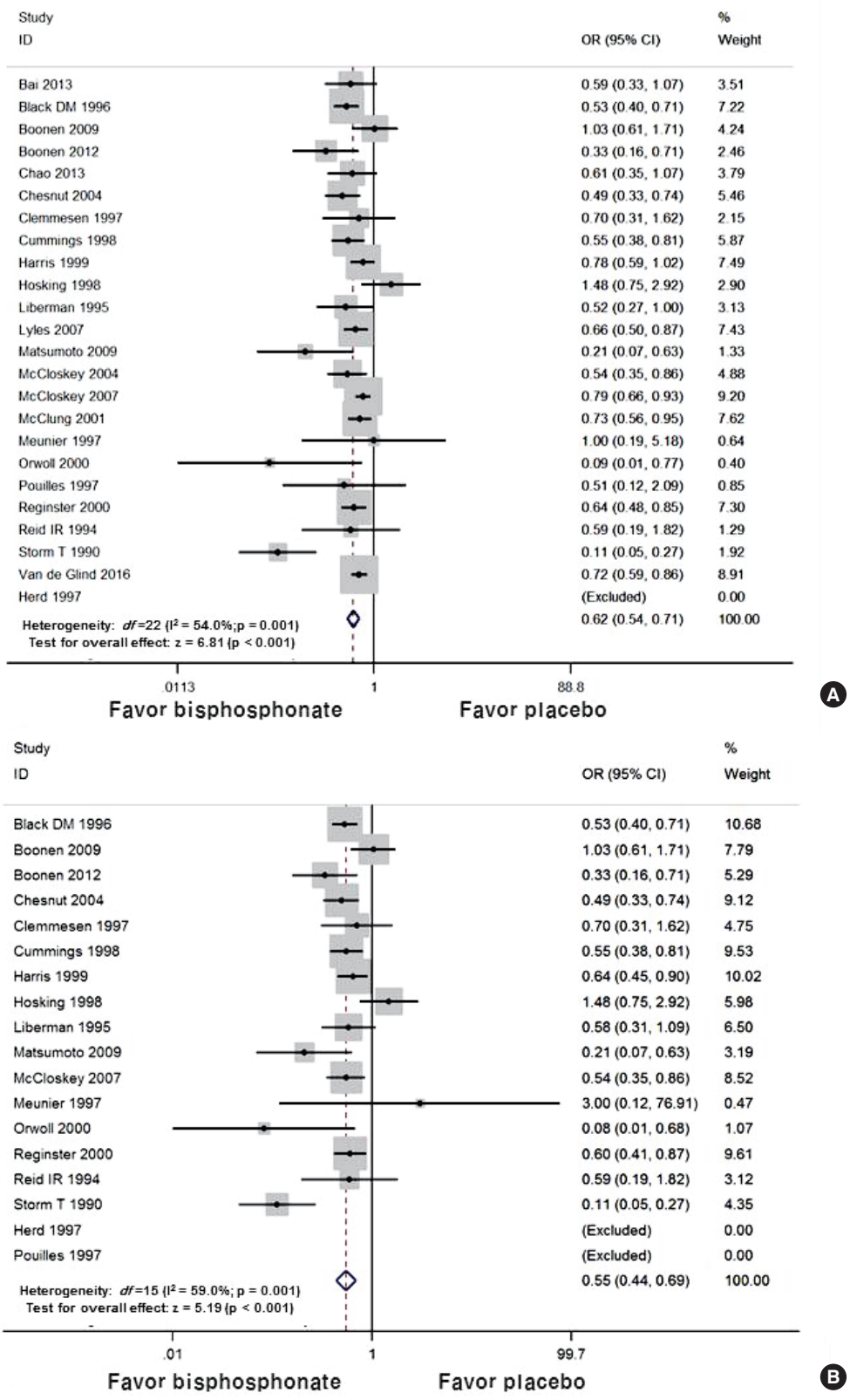

Fig. 2. (A) The forest plot of overall osteoporotic fracture reductions relative to placebo by bisphosphonate treatment. The forest plot of odds ratio for (B) vertebral fracture.
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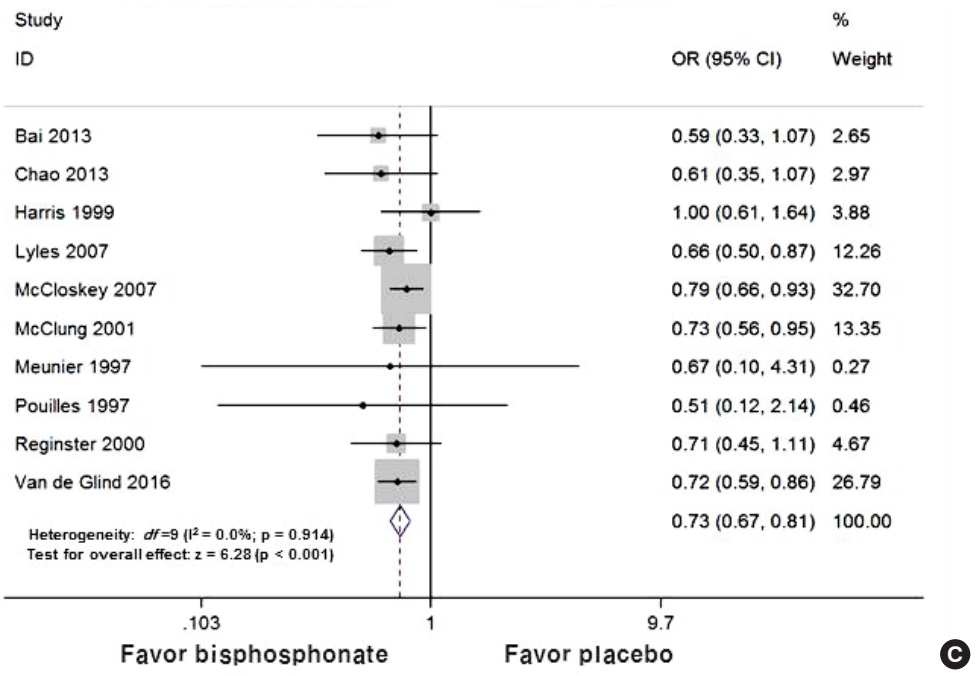

Fig. 2. (*Continued*) (C) non-vertebral fracture. OR, odds ratio; CI, confidence interval.

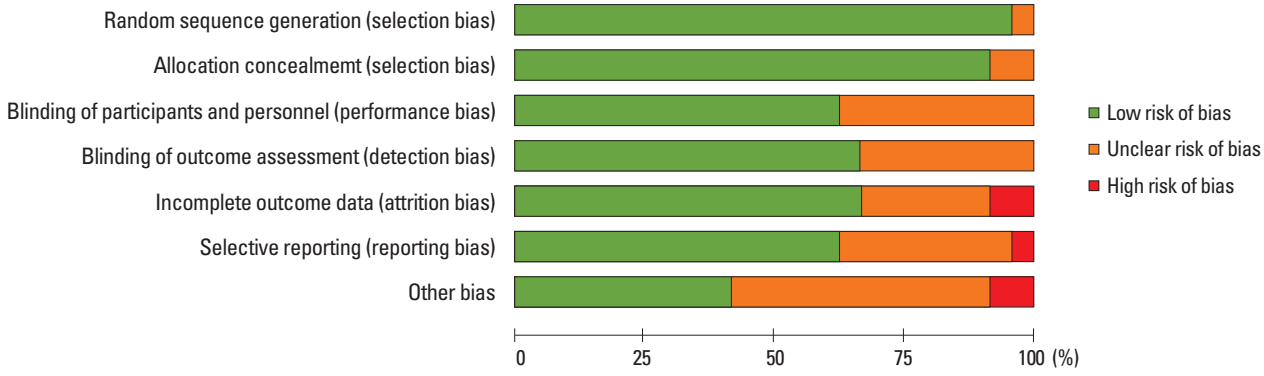

Fig. 3. The funnel plot shows publication bias for osteoporotic fracture related to the use of bisphosphonate. There was symmetry, suggesting that there was no significant publication bias in the twenty-four studies.

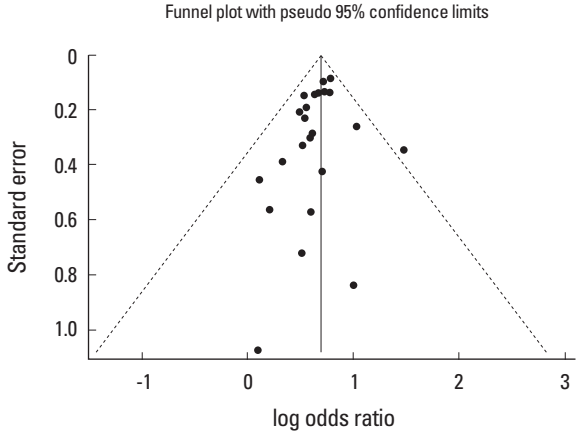

Fig. 4. The summary of bias risk of randomized controlled trials.

OR in zoledronic acid. Improved compliance and poor gastrointestinal absorption of oral bisphosphonates are suggested as a possible explanation. Although there is a difference of efficacy between different types of bisphosphonate, the efficacy of bisphosphonate was predominantly dependent on the compliance to bisphosphonate.[42]

This study has some limitations. First, the current analysis did not involve evidence on quality of life or survival. Secondly, the potential adverse effects of bisphosphonates were not evaluated in this study. Third, hip fractures which are significantly associated with morbidity and mortality were not analyzed separately.

In conclusion, this update meta-analysis re-confirmed

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the efficacy of bisphosphonate in patients with osteoporosis. In terms of their anti-osteoporotic fracture efficacy, bisphosphonates except etidronate still demonstrate its effectiveness.

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Appendix 1. The updated checklist consists of 17-items intended to facilitate the preparation and reporting of a robust protocol for the meta-analysis and systematic review

Section and topic	Item no.	Checklist item	Page no.
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	1
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Not applicable
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	1
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	Not applicable
Support:			
Sources	5a	Indicate sources of financial or other support for the review	7
Sponsor	5b	Provide name for the review funder and/or sponsor	7
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	7
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	2
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	2
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	2
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	2
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	2
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	2
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	2
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	2
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	2
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	2
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	3
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	3
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2 , Kendall's τ)	3-6
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	3-6
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Not applicable
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Fig. 3
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	2-3

Appendix 2. The search strategy that details the selection process of relevant clinical studies

Queries

I. Systemic review searching

1. Patients: Osteoporosis (T-score ≤ -2.5)
2. Intervention: Bisphosphonates (Alendronate, Ibandronate, Risedronate, Zoledronate, Etidronate, Clodronate, Minodronate, Pamidronate, Tiludronate) treatment
3. Comparator: Non-treatment
4. Outcomes: The incidence of osteoporotic fracture
5. Study design : Review or meta-analysis

Cochrane Library (November 20, 2016) - Filters: Cochrane Reviews all

	Queries	Search
#1	Osteoporosis	497
#2	Bisphosphonate	64
#3	Fracture	769
#4	Search (#1 AND #2 AND #3)	44

After primary review, a total of 4 meta-analyses were included

	References	No. of included patients	No. of included studies	AMSTAR
1	Zhou (2016)	16,542	36 RCTs	Yes: 7 No: 4
2	Wells (2008)	12,068	11 RCTs	Yes: 7 No: 4
3	Wells (2008)	14,049	7 RCTs	Yes: 7 No: 4
4	Wells (2008)	1,248	11 RCTs	Yes: 7 No: 4

https://doi.org/10.11005/jbm.2017.24.1.37

II. Update searching of randomized controlled trials

1. Patients: Osteoporosis (T-score ≤ -2.5)
2. Intervention: Bisphosphonates (Alendronate, Ibandronate, Risedronate, Zoledronate, Etidronate, Clodronate, Minodronate, Pamidronate, Tiludronate) treatment
3. Comparator: Non-treatment
4. Outcomes: The incidence of osteoporotic fracture
5. Study design: Randomized controlled trial

PubMed (November 20, 2016)

	Queries	Search
#1	"alendronate"[tw]	4,623
#2	alendronate[MeSH]	3,222
#3	"Aminohydroxybutane Bisphosphonate"[tw] OR "Bisphosphonate, Aminohydroxybutane"[tw] OR "4-Amino-1-Hydroxybutylidene 1,1-Biphosphonate"[tw] OR "4 Amino 1 Hydroxybutylidene 1,1 biphosphonate"[tw] OR "Alendronate Sodium"[tw] OR "Sodium, Alendronate"[tw] OR "Alendronate Monosodium Salt, Trihydrate"[tw] OR "Fosamax"[tw] OR "MK-217"[tw] OR "MK 217"[tw] OR "MK217"[tw]	323
#4	search (#1 OR #2 OR #3)	4,642
#5	risedronate[MeSH]	1,070
#6	"risedronate"[tw]	1,739
#7	"Sodium, Risedronate"[tw] OR "2-(3-pyridinyl)-1-hydroxyethylidene-bisphosphonate"[tw] OR "1-Hydroxy-2-(3-pyridyl)ethylidene diphosphonate"[tw] OR "2-(3-pyridinyl)-1-hydroxyethylidenebisphosphonate"[tw] OR "Risedronic Acid, Monosodium Salt"[tw] OR "Risedronate"[tw] OR "Bisphosphate Risedronate Sodium"[tw] OR "Risedronate Sodium, Bisphosphate"[tw] OR "Sodium, Bisphosphate Risedronate"[tw] OR "Risedronic Acid"[tw] OR "Acid, Risedronic"[tw] OR "Actonel"[tw] OR "Atelvia"[tw]	1,762
#8	search (#5 OR #6 OR #7)	1,762
#9	ibandronate[MeSH]	-
#10	"ibandronate"[tw]	902
#11	"Bondronat"[tw] OR "Bonviva"[tw] OR "ibandronic acid, sodium salt, monohydrate"[tw] OR "RPR 102289A"[tw] OR "RPR-102289A"[tw] OR "Boniva"[tw] OR "BM 21.0955"[tw] OR "BM-21.0955"[tw] OR "BM-210955"[tw] OR "BM 210955"[tw] OR "ibandronate"[tw] OR "(1-hydroxy-3-(methylpentylamino)propylidene)bisphosphonate"[tw] OR "1-hydroxy-3-(methylpentylamino) propylidenebisphosphonate"[tw]	919
#12	search (#9 OR #10 OR #11)	919
#13	"zoledronic acid"[tw]	3,739
#14	zoledronic acid[MeSH]	81
#15	"2-(imidazol-1-yl)-1-hydroxyethylidene-1,1-bisphosphonic acid"[tw] OR "zoledronate"[tw] OR "Zometa"[tw] OR "Novartis brand of zoledronic acid"[tw] OR "CGP 42446A"[tw] OR "CGP-42446"[tw] OR "CGP-42'446"[tw] OR "CGP 42'446"[tw]	1,038
#16	search (#13 OR #14 OR #15)	4,131
#17	"clodronate"[tw]	1,695
#18	clodronate[MeSH]	1,505
#19	"Acid, Clodronic"[tw] OR "Dichloromethane Diphosphonate"[tw] OR "Diphosphonate, Dichloromethane"[tw] OR "Dichloromethylenebisphosphonate"[tw] OR "Dichloromethanediphosphonic Acid"[tw] OR "Acid, Dichloromethanediphosphonic"[tw] OR "Dichloromethylene Biphosphonate"[tw] OR "Biphosphonate, Dichloromethylene"[tw] OR "Dichloromethylene Diphosphonate"[tw] OR "Diphosphonate, Dichloromethylene"[tw] OR "Cl2MDP"[tw] OR "Dichloromethanediphosphonate"[tw] OR "Clodronate"[tw] OR "Clodronate Disodium"[tw] OR "Disodium, Clodronate"[tw] OR "Clodronate Sodium"[tw] OR "Sodium, Clodronate"[tw] OR "Bonefos"[tw] OR "pentoxifylline-tocopherol-clodronate combination"[tw] OR "Pentoclo"[tw]	2,057
#20	search (#17 OR #18 OR #19)	2,393
#21	"etidronate"[tw]	1,231
#22	etidronate[MeSH]	2,723

(*Continued to the next page*)

(Continued) **PubMed (November 20, 2016)**

	Queries	Search
#23	"Hydroxyethylidene Diphosphonic Acid"[tw] OR "Diphosphonic Acid, Hydroxyethylidene"[tw] OR "(1-hydroxyethylene)diphosphonic acid"[tw] OR "Didronel"[tw] OR "Xidifon"[tw] OR "Xydiphone"[tw] OR "Xidiphon"[tw] OR "Etidronate Disodium"[tw] OR "Phosphonic acid, (1-hydroxyethylidene)bis-, disodium salt"[tw] OR "Disodium Etidronate"[tw] OR "Etidronate, Disodium"[tw] OR "Disodium 1-Hydroxyethylene Diphosphonate"[tw] OR "1-Hydroxyethylene Diphosphonate, Disodium"[tw] OR "Diphosphonate, Disodium 1-Hydroxyethylene"[tw] OR "Disodium 1 Hydroxyethylene Diphosphonate"[tw] OR "HEDSPA"[tw] OR "Sodium Etidronate"[tw] OR "Etidronate, Sodium"[tw] OR "Etidronate, Tetrapotassium Salt"[tw] OR "Salt Etidronate, Tetrapotassium"[tw] OR "Tetrapotassium Salt Etidronate"[tw] OR "(1-hydroxyethylene)diphosphonic acid, Tetrapotassium Salt"[tw] OR "Dicalcium Etidronate"[tw] OR "Etidronate, Dicalcium"[tw] OR "Dicalcium EHDP"[tw] OR "EHDP, Dicalcium"[tw] OR "Etdronate"[tw] OR "1-Hydroxyethane-1,1-Diphosphonate"[tw] OR "1 Hydroxyethane 1,1 Diphosphonate"[tw] OR "1-Hydroxyethylidene-1,1-Bisphosphonate"[tw] OR "1 Hydroxyethylidene 1,1 Bisphosphonate"[tw] OR "Hydroxyethanediphosphonate"[tw] OR "Ethanehydroxydiphosphonate"[tw] OR "Ethanehydroxyphosphate"[tw] OR "HEDP"[tw] OR "1,1-hydroxyethylenediphosphonate"[tw] OR "1,1 hydroxyethylenediphosphonate "[tw] OR "EHDP"[tw]	1,074
#24	search (#21 OR #22 OR #23)	3,403
#25	"minodronate"[tw]	66
#26	"YM529"[tw] OR "ONO-5920"[tw] OR "YM-529"[tw] OR "Phosphonic acid, (1-hydroxy-2-imidazo(1,2-a)pyridin-3-ylethylidene)bis"[tw] OR "YH 529"[tw] OR "YH529"[tw] OR "YH-529"[tw] OR "(1-hydroxy-2-(imidazo(1,2-a)-pyridin-3-yl)ethylidene)bisphosphonic acid monohydrate"[tw] OR "[tw] OR "minodronate"[tw] OR "minodronic acid hydrate"[tw] OR "1-hydroxy-2-(imidazo(1,2-a)pyridin-3-yl) ethane-1,1-bisphosphonic acid monohydrate"[tw]	0
#27	minodronate[MeSH]	0
#28	search (#25 OR #26 OR #27)	66
#29	"pamidronate"[tw]	2,861
#30	pamidronate[MeSH]	0
#31	"(3-amino-1-hydroxypropylidene)-1,1-bisphosphonate"[tw] OR "1-hydroxy-3-aminopropane-1,1-diphosphonic acid"[tw] OR "APD"[tw] OR "AHPrBP"[tw] OR "aminohydroxypropylidene diphosphonate"[tw] OR "aminopropanehydroxydiphosphonate" [tw] OR "amidronate"[tw] OR "(3-amino-1-hydroxypropylidene)-1,1-biphosphonate"[tw] OR "amino-1-hydroxypropane-1,1-diphosphonate"[tw] OR "pamidronate monosodium"[tw] OR "pamidronate disodium"[tw] OR "Aredia"[tw] OR "Novartis brand of pamidronate disodium salt"[tw] OR "pamidronate calcium"[tw]	4,508
#32	search (#29 OR #30 OR #31)	6,965
#33	"tiludronate"[tw]	133
#34	tiludronate[MeSH]	0
#35	"(4-chlorophenyl)thiomethylene bisphosphonic acid"[tw] OR "Cl2SMBP"[tw] OR "tiludronate"[tw] OR "(chloro-4-phenyl)thiomethylene biphosphonate"[tw] OR "(chloro-4-phenyl)thiomethylene bisphosphonate"[tw] OR "tiludronate disodium"[tw] OR "Skelid"[tw]	137
#36	search (#33 OR #34 OR #35)	137
#37	osteoporosis[tw]	7,1974
#38	"osteoporosis"[MeSH]	49,047
#39	"Osteoporoses"[tw] OR "Osteoporosis, Post-Traumatic"[tw] OR "Osteoporosis, Post Traumatic"[tw] OR "Post-Traumatic Osteoporoses"[tw] OR "Post-Traumatic Osteoporosis"[tw] OR "Osteoporosis, Senile"[tw] OR "Osteoporoses, Senile"[tw] OR "Senile Osteoporoses"[tw] OR "Senile Osteoporosis"[tw] OR "Osteoporosis, Involutional"[tw] OR "Osteoporosis, Age-Related"[tw] OR "Osteoporosis, Age Related"[tw] OR "Bone Loss, Age-Related"[tw] OR "Age-Related Bone Loss"[tw] OR "Age-Related Bone Losses"[tw] OR "Bone Loss, Age Related"[tw] OR "Bone Losses, Age-Related"[tw] OR "Age-Related Osteoporosis"[tw] OR "Age Related Osteoporosis"[tw] OR "Age-Related Osteoporoses"[tw] OR "Osteoporoses, Age-Related"[tw]	1,220
#40	search (#37 OR #38 OR #39)	72,232
#41	"fracture"[tw]	166,072
#42	fracture[MeSH]	160,391
#43	"Broken Bones"[tw] OR "Bone, Broken"[tw] OR "Bones, Broken"[tw] OR "Broken Bone"[tw] OR "Bone Fractures"[tw] OR "Bone Fracture"[tw] OR "Fracture, Bone"[tw]	63,905
#44	search (#41 OR #42 OR #43)	228,415
#45	search (#4 OR #8 OR #12 OR #16 OR #20 OR #24 OR #28 OR #32 OR #36)	12,670
#46	search (#40 AND #44 AND #45)	2,703
#47	Search Filters: Clinical Trial; Full-text; Publication dates From 2014/01/01 to 2016/11/20; English, Korean;	36

https://doi.org/10.11005/jbm.2017.24.1.37

Cochrane Library (November 20, 2016) – 56 articles

	Queries	Search
#1	alendronate	1,097
#2	"Aminohydroxybutane Bisphosphonate" OR "Bisphosphonate, Aminohydroxybutane" OR "4-Amino-1-Hydroxybutylidene 1,1-Biphosphonate" OR "4 Amino 1 Hydroxybutylidene 1,1 biphosphonate" OR "Alendronate Sodium" OR "Sodium, Alendronate" OR "Alendronate Monosodium Salt, Trihydrate" OR "Fosamax" OR "MK-217" OR "MK 217" OR "MK217"	101
#3	search (#1 OR #2)	1,098
#4	risedronate	481
#5	"Sodium, Risedronate" OR "2-(3-pyridinyl)-1-hydroxyethylidene-bisphosphonate" OR "1-Hydroxy-2-(3-pyridyl)ethylidene diphosphonate" OR "2-(3-pyridinyl)-1-hydroxyethylidenebisphosphonate" OR "Risedronic Acid, Monosodium Salt" OR "Risedronate" OR "Bisphosphate Risedronate Sodium" OR "Risedronate Sodium, Bisphosphate" OR "Sodium, Bisphosphate Risedronate" OR "Risedronic Acid" OR "Acid, Risedronic" OR "Actonel" OR "Atelvia"	526
#6	search (#4 OR #5)	526
#7	ibandronate	312
#8	"Bondronat" OR "Bonviva" OR "ibandronic acid, sodium salt, monohydrate" OR "RPR 102289A" OR "RPR-102289A" OR "Boniva" OR "BM 21.0955" OR "BM-21.0955" OR "BM-210955" OR "BM 210955" OR "ibandronate" OR "(1-hydroxy-3-(methylpentylamino)propylidene)bisphosphonate" OR "1-hydroxy-3-(methylpentylamino)propylidenebisphosphonate"	314
#9	search (#7 OR #8)	314
#10	search (#3 OR #6 OR #9)	1678
#11	MeSH descriptor: [Osteoporosis] explode all trees	3,468
#12	MeSH descriptor: [Bone disease, Metabolic] this term only (SINGLE MESH TERM)	312
#13	MeSH descriptor: [Bone density, Metabolic] this term only	0(BONE DENISTY, 4306)
#14	search (#11 OR #12 OR #13)	5,793
#15	MeSH descriptor: [Colles' Fractures] this term only	86
#16	MeSH descriptor: [Hip Fractures] explode all trees	1,269
#17	MeSH descriptor: [spinal Fractures] this term only	717
#18	MeSH descriptor: [Fractures, Bone] this term only	1,329
#19	MeSH descriptor: [Lumbar Vertebrae] this term only	2,469
#20	search (#15 OR #16 OR #17 OR #18 OR #19)	5,466
#21	search (#10 AND #14 AND #20) Publication year from 2014 to 2016, in Trials	56