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Effectiveness of bisphosphonates on bone mineral density in osteopenic postmenopausal women

A systematic review and network meta-analysis of randomized controlled trials

Su-li Dong, MD, Yongqiang Jiao, PhD, Hai-liang Yang, MD*

Abstract

Background: Various bisphosphonate agents have been proven to be effective in preventing bone loss and fracture in osteopenic postmenopausal women. This study was designed to compare the effectiveness of various BPs on preventing the loss of bone mineral density (BMD) for postmenopausal women with osteopenia.

Methods: PubMed, EMBASE, and Cochrane Central Register of Controlled Trials were screened up to identify randomized controlled trails comparing effectiveness of BPs or placebo on the BMD of postmenopausal women with osteopenia. Network meta-analysis and standard pair-wise meta-analyses were performed. The main outcomes include the percentage changes of 6-, 12-, 24-, and 36-month BMD at lumbar, total hip and femoral neck, and frequencies of new fractures and severe adverse events.

Results: Fourteen randomized controlled trials were eligible, involving 11,540 participants. No significant difference was presented among the available interventions for the 6-month BMD at 3 different sites, but the magnitudes of differences among the treatment regimens became gradually increased along with the extending of follow-up periods. Daily aledronate of more than 5 mg provided the maximal percentage increase on BMD of femoral neck and lumbar spine, while zoledronate provided maximal change on BMD of total hip, at different follow-up periods. This network meta-analysis also demonstrated similar frequencies of new clinical fractures and severe adverse events among different interventions.

Conclusions: A ranking spectrum depicting the effectiveness on BMD percentage change following interventions with different bisphosphonate regimens was provided. Generally, regimens with zoledronate and aledronate were found to be the most effective interventions in the 3 sites at different end points.

Abbreviations: ALN = alendronate, BMD = bone mineral density, BP = bisphosphonate, IBA = ibandronate, MD = mean difference, NMA = network meta-analysis, OR = odds ratio, PAM = pamidronate, PLA = placebo, RIS = risedronate, SUCRA = surface under the cumulative ranking curves, ZOL = zoledronate.

Keywords: bisphosphonate, bone mineral density, network meta-analysis, osteopenia, postmenopausal women

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1. Introduction

Osteoporosis is a very common and important cause of fracture in several vital bony sites, such as spine and hip, leading to morbidity and even mortality in postmenopausal women.[1–3] As the elderly population grows, the incidence of osteoporosis related hip fractures would be projected to increase from 1.7 million in 1990 to 6.3 million by 2050, and the risk of sustaining a fracture is estimated to be as high as 40% for a 50-year-old woman in the rest lifespan.[4,5] As shown in the former studies, every decrease of 1 standard deviation in the bone mineral density (BMD) would increase the risk of fracture for 2 to 3 folds, while the women in the lowest BMD quartile are associated with a risk of fracture of 8.5 times higher than those in the highest BMD quartile.[6–8]

Osteopenia is the term used to describe the loss of BMD, which is attributed to demineralization of bone. Although the low BMD status is associated with a decreased fracture risk, comparing to osteoporosis, patients with low bone mass (T-score 1–2.5) are the majority of fragility fractures. It has been reported that more than 50% of the fragility fractures occur in women with low bone mass.[8,9] Moreover, patients with osteopenia will be at risk of developing to osteoporosis when left untreated. The re-fracture

rate of vertebrae is as high as 20% within 1 year following the first arising of fracture, indicating it is crucial for the at-risk women with low BMD to prevent the further bone loss and destruction on microarchitecture of bone trabecula so as to avoid the first occurrence of fracture.[10]

Estrogen replacement is effective on preventing bone mass loss and decreasing the bone turnover for postmenopausal women.[11] However, the estrogen has not been used as the primary anti-resorption agent, as most women administrated with estrogen would not continue for more than 1 year, due to the concern about such side effects such as breast tenderness, headache, fluid retention, and withdrawal bleeding.[12–14] The bisphosphonates (BPs) represent a set of synthetic pyrophosphate analogues, which have a high affinity to the mineralized tissues and subsequently inhibit the osteoclast-mediated bone resorption.[15] Various bisphosphonate (BP) agents, such as pamidronate (PAM), alendronate (ALN), risedronate (RIS), ibandronate (IBA), and zoledronate (ZOL), have been proven to be effective in preventing bone loss and fracture of different bony sites when applied with different regimens, for postmenopausal women.[16–18] However, studies were mainly designed to compare the efficacy of these BPs with the placebo, lacking evidence of direct comparisons among different BPs. Besides, though several indirect treatment comparative studies have compared the efficacy of BPs in the prevention of fractures, they were mainly focused on the postmenopausal women with osteoporosis.

In this network meta-analysis (NMA), we aimed to compare the effectiveness of various regimens of BPs on changing the BMD at lumbar spine, total hip, and femoral neck at several follow-up time-points in postmenopausal women with osteopenia.

2. Materials and methods

2.1. Data sources and searches

This review was conducted according to the guidelines outlined in Preferred Reporting Items for Systematic Reviews and Meta-analysis statement (http://www.prismastatement.org/).[19]

Two individual researchers conducted platform searches on the PubMed, Embase, and Cochrane Central Register of Controlled Trials up to the date of December 2019. Literature retrieving was carried out through a combined searching of subject terms ("MeSH" on PubMed and Cochrane Library and "Emtree" on Embase) and free terms. The keywords used for searching include "bisphosphate," "aledronate," "zoledronate," "ibandronate," "pamidronate," "risedronate," "osteopenia," "postmenopausal women," "bone mineral density," and so on. Additionally, some else reference studies of relative articles and reviews were screened and hand-searched for possible inclusion. The publication language was restricted in English.

2.2. Eligibility criteria

Trials would be eligible for inclusion when meeting the following criteria:

1) all trials had to be randomized, blinded, and controlled to ensure a minimum high quality level;
2) subjects were diagnosed with postmenopausal osteopenia;
3) trials compared interventions of various BPs (i.e., ALN, IBA, RIS, PAM, ZOL, and so on) in different administration regimens with each other or placebo;
4) trials included the primary outcome of percentage changes on the BMD of lumbar spine, total hip, or femoral neck assessed by dual energy X-ray absorptiometry.

Studies would be excluded for the following reasons:

1) subjects were diagnosed to be with postmenopausal osteoporosis;
2) studies used repeated population with each other or studies extended from some other primary trails.

2.3. Study selection

After all duplicates were recognized and merged together, the remained titles and abstracts were independently screened by the former 2 authors. Then, full texts of potentially relevant papers were obtained and assessed by full-text perusing for eligibility. The whole process of selection was strictly followed with the inclusion and exclusion criteria. Discrepancies in study selection between the 2 reviewers were handled by face-to-face discussion or judged by the third senior reviewer.

2.4. Data extraction and quality assessment

Two review authors pair independently extracted data including:

(1) characteristics of studies: title, author, publication year, country, allocation concealment, blind method, randomization, and follow-up;
(2) participants' characteristics: age, randomized sample size, period after menopause, and subjects dropped;
(3) therapeutic modality: treatment drug, dosage, frequency, route of administration, and basic medicine;
(4) primary outcomes: percentage change on the BMD of lumbar spine, total hip, and femoral neck at 6, 12, 24, and 36 months (sample sizes, mean value, and standard difference);
(5) second outcomes: participants suffered from newly diagnosed clinical fractures at any site and participants presented to be with any severe adverse events.

We also contacted the first or corresponding authors of the included trials to obtain some missing information as possible.

Two reviewers assessed the risk of bias of the included studies independently using the Cochrane risk of bias tool, which contains 7 domains including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias (funding and baseline imbalance).[20] The judgment for each domain was a low risk of bias (sufficient information to describe the right methods), a high risk of bias (sufficient information to describe the wrong methods), or an unclear risk of bias (insufficient information to describe the methods).

2.5. Methods of NMA

Network plots were firstly generated using 'network' suite of commands for Stata version 14.0 (StataCorp LLC, College Station, Texas), to illustrate which interventions were directly compared in the primary randomized controlled trials.[21] Bayesian NMA was conducted for each of the percentage change on BMD of lumbar spine, total hip, and femoral neck at 6, 12, 24, and 36 months, and for all recorded severe adverse events and fractures during the whole follow-up period, using WinBUGS

1.4.3 software (MRC Biostatistics Unit, Cambridge, UK). A random-effect model was used to compare treatments using Markov chain Monte Carlo methods with Gibbs sampling from 40,000 iterations obtained after a 10,000 burn-in phase. For the BMD from the 3 locations, treatment effects are presented as the mean difference (MD) of the percentage change from baseline BMD level. While for serious adverse events and fracture outcomes, treatment effects are presented as odds ratio (OR) relative to another drug or placebo, with a OR less than 1 reflecting a reduced risk of adverse event and fracture relative to the comparative treatment. A classic half integer continuity correction was used so that studies with no events would still be included for analyses.[22] Following NMA, interventions were ranked according to their estimated effect sizes to display which treatment ranked highest, second highest, and so on, using the surface under the cumulative ranking curves (SUCRA).[23] Additionally, radar map was generated to display the SUCRA values of the interventions for each outcome.

Standard pair-wise meta-analysis was also performed for all direct head-to-head comparisons, using random-effect model for considering of the anticipated variety in study populations. Both of the pooled effect estimates in NMA and pairwise meta-analysis were presented as the estimated summary effects (MD or OR) combining with the 95% credibility intervals as well as the 95% prediction intervals. The consistency between results of NMA and pairwise meta-analyses was compared on both of the significance and tendency for each comparison. Between-study variance parameter (tau square, τ^2) was used for assessing the magnitude of the global heterogeneity for each NMA. Inconsistency is estimated as the difference between direct and indirect comparisons for a randomly chosen contrast within each closed loop, with the method of DerSimonian-Laird estimator under the random-effects model.[24]

Novel presentational approaches were used to display results of NMA, including the forest plots and estimated effects both for NMA and pairwise meta-analysis, SUCRA value for each intervention and the between-study heterogeneity, as described by Tan et al[25] R 3.5.3 software (R Core Team, Vienna, Austria) was used to invoke the program of WinBUGS for NMA and generate the summary forest plot matrices.

We also generated comparison-adjusted funnel plot to assess the presence of small-sample effect for each NMA using Stata software.[26] Statistical significance was defined as a two-sided *P*-value of less than .05.

2.6. Ethics and dissemination

Ethical approval was not essential as all included data were obtained from published articles.

2.7. Patient and public involvement

This meta-analysis was performed by previously published data, thus no patient and public content was included in this study.

3. Results

3.1. Studies included

The flowchart of study retrieval and selection is shown in Figure 1. The initial retrieval on the electronic platforms yielded a total of 2764 records, and addition 4 records were identified through manual searching. Then, following excluding the 837 duplicates, the remained 1931 titles/abstracts were screened for possible eligibility. We excluded 1649 titles/abstracts that did not accord with the inclusive criteria, remaining 282 potentially related records for full-text assessing. Finally, a total of 14 trails[27–40] were included for qualitative and quantitative syntheses, while the rest 268 articles were excluded with various reasons.

Table 1 displays the characteristics of the included randomized controlled trials. In these studies, a number of 11,540 subjects were initially randomized, and 1047 of them dropped at the final follow-up. The mean ages of the patients in the treatment arms were ranged from 51.2 to 72.0 years old. Five types of BPs were applied in these trails with different administration regimens (dosage, frequency, and administration route), making a total of 17 different interventions comparing with the placebo group. All available interventions are presented in Table 2. Most of the trials (11/14, 87.6%) involved with basic daily intake of calcium with or without supplement of vitamin D. The follow-up periods of the studies were ranged from 2 to 4 years, including 8, 5, and 1 studies followed for 2, 3, and 4 years, respectively.

Summaries of the risk of bias and the risk of bias graph for each study are presented in Figure 2. The included studies were generally of low risk of bias on the items of Cochrane Collaboration tool, except for allocation concealment,[29,34–36] selective reporting,[36] and other bias[35] in several studies which present high risk of bias.

3.2. NMA for percentage changes on BMD

Figure 3A–L represents the network plots for percentage changes on BMD of femoral neck, total hip, and lumbar spine, at the time-points of 6, 12, 24, and 36 months. Summary of the numbers of studies, patients, and interventions involved in the network of each outcome variable is available in Supplementary Table S1, http://links.lww.com/MD/G325. The summary forest plot matrices are presented in Supplementary Fig. S1A–L, http://links.lww.com/MD/G324, corresponding to the networks shown in Fig. 3A–L. These matrices are consisted of the forest plots (below the diagonals) as well as the estimated effect sizes (above the diagonals) for pairwise meta-analyses and NMA, the SUCRA curves (along the diagonals ordered by SUCRA values), and the between-study variance (τ^2). We listed the ranking spectrum of the interventions for each observed outcome in Figure 4, and the SUCRA values are plotted in radar maps in Figure 5A–L.

In Supplementary Fig. S1A–L, http://links.lww.com/MD/G324, significant comparisons in NMA were enclosed by red boxes. Generally, at 6 months after treatment, no significant difference in NMA was found for the percentage changes of BMD on the 3 different sites according to available evidences. At 12 months, ZOL-5/10 mg, ALN-5/10/20 mg, and RIS-5 mg significantly increased the BMD of femoral neck comparing to ALN-1 mg, PAM-150/300 mg and placebo (PLA), and ALN-10/20 mg and RIS-5 mg provided significantly higher femoral neck BMD than RIS-2.5 mg did. However, no statistical significance was shown among ALN-5/10/20 mg, ZOL-5/10 mg and RIS-5 mg, and among ALN-1 mg, PAM-150/300 mg and PLA. At the site of total hip, ZOL-1/2.5/5/10 mg, ALN-2.5/5/10 mg, IBA-20 mg, and RIS-5 mg were associated with higher 12-month BMD than IBA-10/5 mg and PLA, and ZOL-2.5/5/10 mg also provided increased BMD than ALN-2.5/5 mg, IBA-20 mg and RIS-5 mg. At the lumbar spine, ALN-2.5/5/10/20 mg, ZOL-1/2.5/5/10 mg, RIS-5 mg, and IBA-20 mg provided significantly higher BMD than PLA,

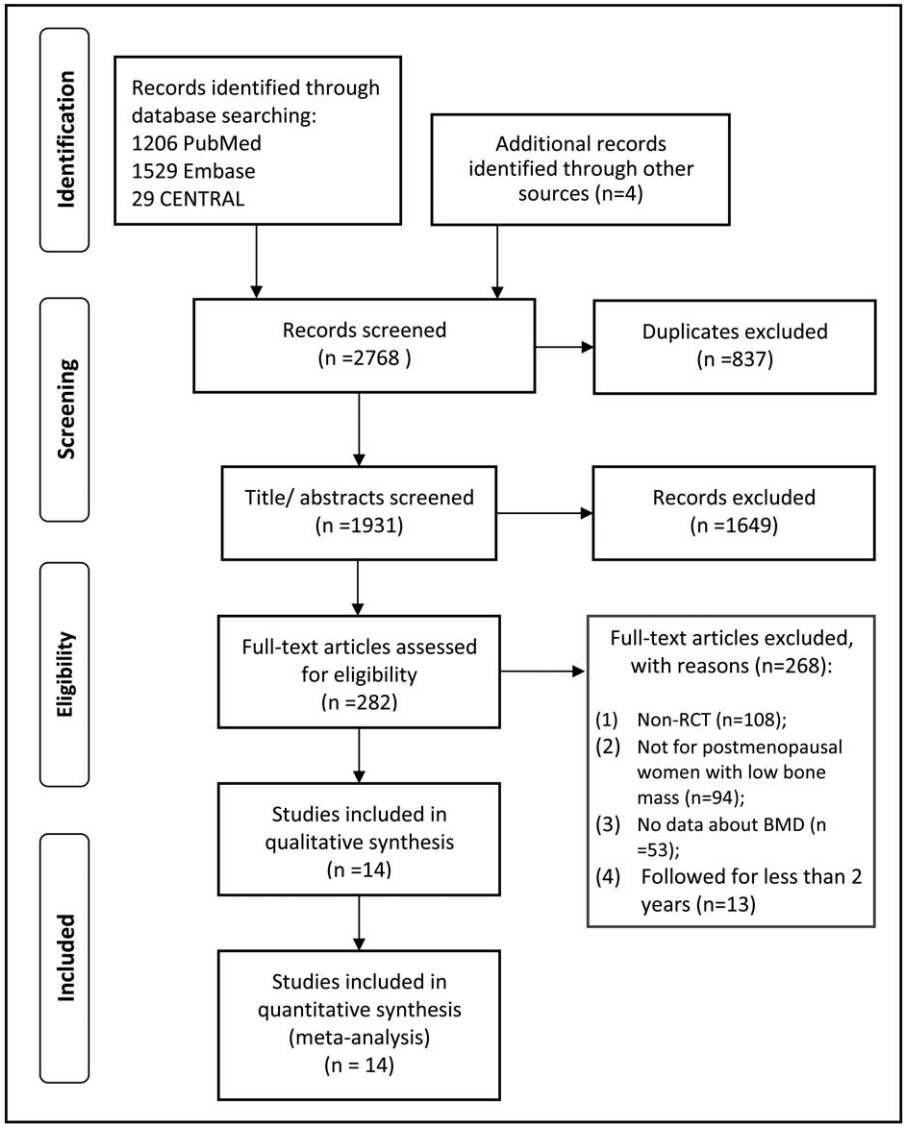

Figure 1. PRISMA flowchart of study searching and selecting. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analysis.

and ALN-2.5/5/10/20 mg, ZOL-1/2.5/5/10 mg, and RIS-5 mg provided higher BMD than IBA-5/10 mg and PAM-150/300 mg. Moreover, ZOL-2.5/5 mg and ALN-5/10/20 mg also showed increased BMD than IBA-20 mg and ALN-1 mg. Concerning the femoral neck BMD at 24 months, the groups of ALN-5/10/20, ZOL-5/10 mg, and RIS-2.5/5 mg were higher than PLA group, and groups of ALN-5/10/20, ZOL-5/10 mg and RIS-5 mg were higher than PAM-150/300 mg groups. Additionally, ALN-20 mg provided higher BMD than ALN-1/5 mg and RIS-2.5 mg, too. The 24-month BMD of total hip was shown to be significantly increased for ZOL-1/2.5/5/10 mg, ALN-2.5/5/10 mg, IBA-20/10 mg, RIS-5 mg comparing to that of PLA. IBA-5/10 mg was associated with lower BMD than IBA-20 mg, ALN-5/10 mg, and ZOL-2.5/5/10 mg. ZOL-1 mg provided lower BMD than ZOL-2.5/5/10 mg. At lumbar spine site, all interventions provided higher 24-month BMD than PLA except for PAM-150/300 mg, which provided lower BMD comparing to other interventions apart from IBA-5 mg. ALN-5/10/20 mg and ZOL-2.5/5/10 mg provided higher BMD than ALN-1/2.5 mg, IBA-5/10/20 mg, and RIS-5 mg. ALN-20 mg was the most effective intervention which provided significantly higher BMD than any other intervention.

Similar tendencies of the rankings of interventions were presented at different follow-up time-points, for the 3 anatomic sites respectively. As for the percentage change on femoral neck BMD, ALN-20 mg and ALN-10 mg were most effective, followed by ZOL-10 mg/ALN-5 mg/ZOL-5 mg/RIS-5 mg, RIS-2.5 mg, ALN-1 mg, PAM-300 mg, PAM-150 mg, and PLA. Regarding to the total hip, however, interventions with ZOL-1/2.5/5/10 mg provided the highest percentage change on BMD, followed by ALN-5/10 mg, IBA-20 mg, RIS-5 mg, ALN-2.5 mg, IBA-10/5 mg, and PLA. At lumbar site, ALN-20/10 mg, followed by ZOL-1/2.5/5/10 mg, ALN-2.5/5 mg, RIS-5 mg, IBA-20 mg, RIS-2.5 mg, ALN-1 mg, IBA-10/5 mg, PAM-300/150 mg, and PLA. Obvious dose–response relationships were shown for all the BPs in the ranking plot (see Fig. 4) and radar plot (see Fig. 5). What's more,

Table 1

Characteristics of the included trails.

Study ID	Country	Basic treatment	Treatment	Dosage	Frequency	Route of administration	Patients randomized	Patients dropped	Mean age (yrs)	Period after menopause	Follow-up
Black, 1996[27]	USA	Calcium 500 mg + V_D 250 IU	ALN	5 + 10 mg	Daily	PO	1022	41	70.7 ± 5.6	>2 yrs	3 yrs
			PLA	–	–	–	1005	40	71.0 ± 5.6		
Cummings, 1998[28]	USA	Calcium 500 mg + V_D 250 IU	ALN	5 + 10 mg	Daily	PO	2214	157	67.6 ± 6.2	≥2 yrs	4 yrs
			PLA	–	–	–	2218	141	67.7 ± 6.1		
Fogelman, 2000 [29]	UK	Calcium 1000 mg	RIS	5 mg	Daily	PO	179	37	65.0 ± 6.7	≥1 yr	2 yrs
			RIS	2.5 mg	Daily	PO	184	111	65.0 ± 8.1		
			PLA	–	–	–	180	40	64.0 ± 6.7		
Grey, 2010[30]	New Zealand	None	ZOL	5 mg	At baseline	IV	25	1	62.0 ± 8.0	>5 yrs	3 yrs
			PLA	–	–	–	25	0	65.0 ± 8.0		
Grey, 2014[31]	New Zealand	None	ZOL	1 mg	At baseline	IV	45	5	64.0 ± 8.0	>5 yrs	2 yrs
			ZOL	2.5 mg	At baseline	IV	45	6	66.0 ± 9.0		
			ZOL	5 mg	At baseline	IV	45	3	66.0 ± 8.0		
			PLA	–	–	–	45	6	65.0 ± 9.0		
McClung, 2009[32]	USA	Calcium 500–1200 mg + V_D 400–800 IU	ZOL	5 mg	Yearly	IV	198	17	59.9 ± 7.6	11.5 ± 9.4 yrs	2 yrs
			ZOL	5 mg	At baseline	IV	181	27	59.6 ± 8.0	11.5 ± 10.1 yrs	
			PLA	–	–	–	202	14	60.5 ± 8.0	11.4 ± 9.5 yrs	
Valimaik, 2007[33]	Finland	Calcium 1000 mg + V_D 400 IU	RIS	5 mg	Daily	PO	114	19	66.1 ± 6.8	17.7 ± 7.2 yrs	2 yrs
			PLA	–	–	–	57	14	65.4 ± 6.8	19.5 ± 9.1 yrs	
Greenspan, 2003[34]	USA	Calcium ≥ 1000 mg + V_D 400–800 IU	Estrogen	0.625 mg	Daily	PO	93	9	71.0 ± 5.0	NA	3 yrs
			ALN	10 mg	Daily	PO	93	8	71.0 ± 4.0		
			ALN + estrogen	0.625/10 mg	Daily	PO	94	9	72.0 ± 6.0		
			PLA	–	–	–	93	10	72.0 ± 5.0		
Tankó, 2003[35]	Denmark	Calcium 500 mg	IBA	5 mg	Weekly	PO	155	14 in total	54.9 ± 3.7	1–10 yrs	2 yrs
			IBA	10 mg	Weekly	PO	153		55.6 ± 3.6		
			IBA	20 mg	Weekly	PO	158		55.0 ± 4.0		
			PLA	–	–	–	156		56.0 ± 3.9		
Lees, 1996[36]	UK	None	PAM	300 mg	Daily-4 wk/4 mo	PO	38	4	58.1 ± 3.1	1–15 yrs	2 yrs
			PAM	150 mg	Daily-4 wk/2 mo	PO	41	8	57.5 ± 3.9		
			PLA	–	Daily-4 wk/2 mo	PO	42	6	57.4 ± 3.3		
McClung, 1998[37]	USA	Calcium 1000 mg	ALN	1 mg	Daily	PO	92	4	51.7 ± 0.4	6–36 mo	3 yrs
			ALN	5 mg	Daily	PO	88	4	52.0 ± 0.3		
			ALN	10 mg	Daily	PO	88	4	52.1 ± 0.3		
			ALN	20 mg	Daily-2 yrs/3 yrs	PO	89	11	52.1 ± 0.4		
			PLA	–	–	–	90	8	51.3 ± 0.4		
Hooper, 2005[38]	Australia	Calcium 1000 mg	RIS	5 mg	Daily	PO	129	26	52.5 ± 3.1	43.4 ± 57.5 mo	2 yrs
			RIS	2.5 mg	Daily	PO	128	27	53.0 ± 3.2	48.8 ± 64.9 mo	
			PLA	–	–	–	126	32	52.6 ± 3.3	46.6 ± 68.8 mo	
Mortensen, 1998[39]	Denmark	3 strata: calcium < 400/400–650/ 650–1500 mg	RIS	5 mg	Daily	PO	37	17	52.1 ± 3.9	3.0 ± 2.0 yrs	3 yrs
			RIS	5 mg	Daily-2 wk/1 mo	PO	38	12	51.3 ± 3.4	2.0 ± 2.0 yrs	
			PLA	–	–	–	36	14	51.2 ± 4.2	3.0 ± 1.0 yrs	
Hosking, 1998[40]	UK	Calcium < 500 mg	ALN	5 mg	Daily	PO	498	53	54.0 ± 4.0	6.0 ± 6.0 yrs	2 yrs
			ALN	2.5 mg	Daily	PO	499	47	53.0 ± 4.0	6.0 ± 5.0 yrs	
			PLA	–	–	–	502	41	53.0 ± 4.0	6.0 ± 5.0 yrs	

ALN = alendronate, IBA = ibandronate, IV = intravenous, PAM = pamidronate, PLA = placebo, PO = per ora, RIS = risedronate, V_D = vitamin D, ZOL = zoledronate.

the magnitude of differences (MD) among the interventions was gradually amplified, along with the follow-up time extending.

3.3. NMA for new clinical fractures and severe adverse events

Figure 3M–N represents the network plots for all recorded new fractures and severe adverse events, and the corresponding summary forest plot matrices are presented in Supplementary Fig. S1M and N, http://links.lww.com/MD/G324. We listed the ranking spectrum of the interventions in Figure 4, and the SUCRA values are plotted in radar maps in Figure 5M and N. There were 12 studies (10,403 patients), involving 10 different interventions, included in the NMA for new clinical fractures, showing none significant difference among the interventions. Similarly, no any statistical significance was found for severe adverse events among the 10 interventions, based on evidences from 7 trails (8227 patients).

3.4. Inconsistency assumption and small-sample effect test

Closed loops were available in all of the networks apart from that of percentage change on 36-month total hip BMD. Supplementary Fig. S2, http://links.lww.com/MD/G323 shows the inconsistency between direct and indirect comparisons in each triangular loop, and significant inconsistencies are presented in triangular loops of ALN-5 mg/ALN-1 mg/PLA (inconsistency factor, that is, IF = 4.35, 95% credibility interval 1.17–7.54, $P = .007$) and ALN-10 mg/ALN-5 mg/PLA (IF = 3.52, 95% credibility interval 0.67–6.37, $P = .015$), in the network of 36-month percentage change of femoral neck BMD.

Table 2

Abbreviations as well as the corresponding description of the interventions.

No.	Abbreviations	BP	Dosage	Frequency	Route
1	ZOL-1 mg	Zoledronic acid	1 mg	At baseline	IV
2	ZOL-2.5 mg	Zoledronic acid	2.5 mg	At baseline	IV
3	ZOL-5 mg	Zoledronic acid	5 mg	At baseline	IV
4	ZOL-10 mg	Zoledronic acid	5 mg	Yearly (for 2 yrs)	IV
5	ALN-1 mg	Alendronate acid	1 mg	Daily	PO
6	ALN-2.5 mg	Alendronate acid	2.5 mg	Daily	PO
7	ALN-5 mg	Alendronate Acid	5 mg	Daily	PO
8	ALN-5 + 10 mg	Alendronate acid	5/10 mg	Daily (5 mg for the first 2 yrs and 10 mg thereafter)	PO
9	ALN-10 mg	Alendronate acid	10 mg	Daily	PO
10	ALN-20 mg	Alendronate acid	20/0 mg	Daily (20 mg for the first 2 yrs and PLA thereafter)	PO
11	IBA-5 mg	Ibandronate acid	5 mg	Weekly	PO
12	IBA-10 mg	Ibandronate acid	10 mg	Weekly	PO
13	IBA-20 mg	Ibandronate acid	20 mg	Weekly	PO
14	RIS-2.5 mg	Risedronate acid	2.5 mg	Daily	PO
15	RIS-5 mg	Risedronate acid	5 mg	Daily	PO
16	PAM-150 mg	Pamidronate acid	150/0 mg	Daily (150 mg for 4 wk and PLA thereafter in every 2 mo)	PO
17	PAM-300 mg	Pamidronate acid	300/0 mg	Daily (300 mg for 4 wk and PLA thereafter in every 4 mo)	PO
18	PLA	None, placebo	–	–	–

ALN = alendronate; BP = bisphosphonate, IBA = ibandronate, IV = intravenous, PAM = pamidronate, PO = per ora, PLA = placebo, RIS = risedronate, ZOL = zoledronate.

Figure 6 represents the comparison-adjusted funnel plots for each primary and secondary outcomes. In general, a subjective symmetry was found in these funnel plots, indicating there is no obvious small-sample effect to increase the risk of publication bias.

4. Discussion

The main finding of this study is that daily ALN of more than 5 mg provided the maximal percentage increase on BMD of femoral neck and lumbar spine, while ZOL provided maximal

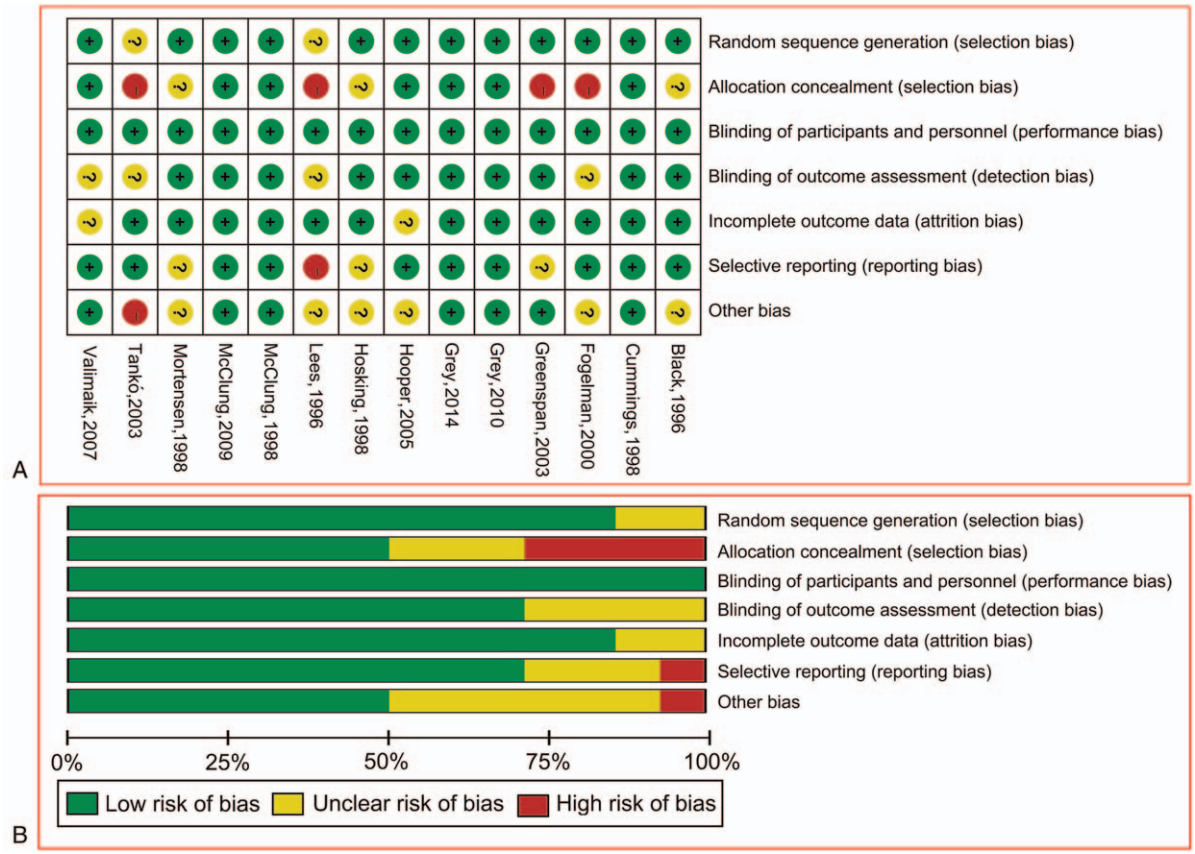

Figure 2. The risk of bias summary (A) and risk of bias graph (B). The percentages of "high risk of bias" (shown as red light with a "−"), "low risk of bias" (shown as green light with a "+") and "unclear risk of bias" (shown as yellow light with a "?") for each item are presented in a bar diagram.

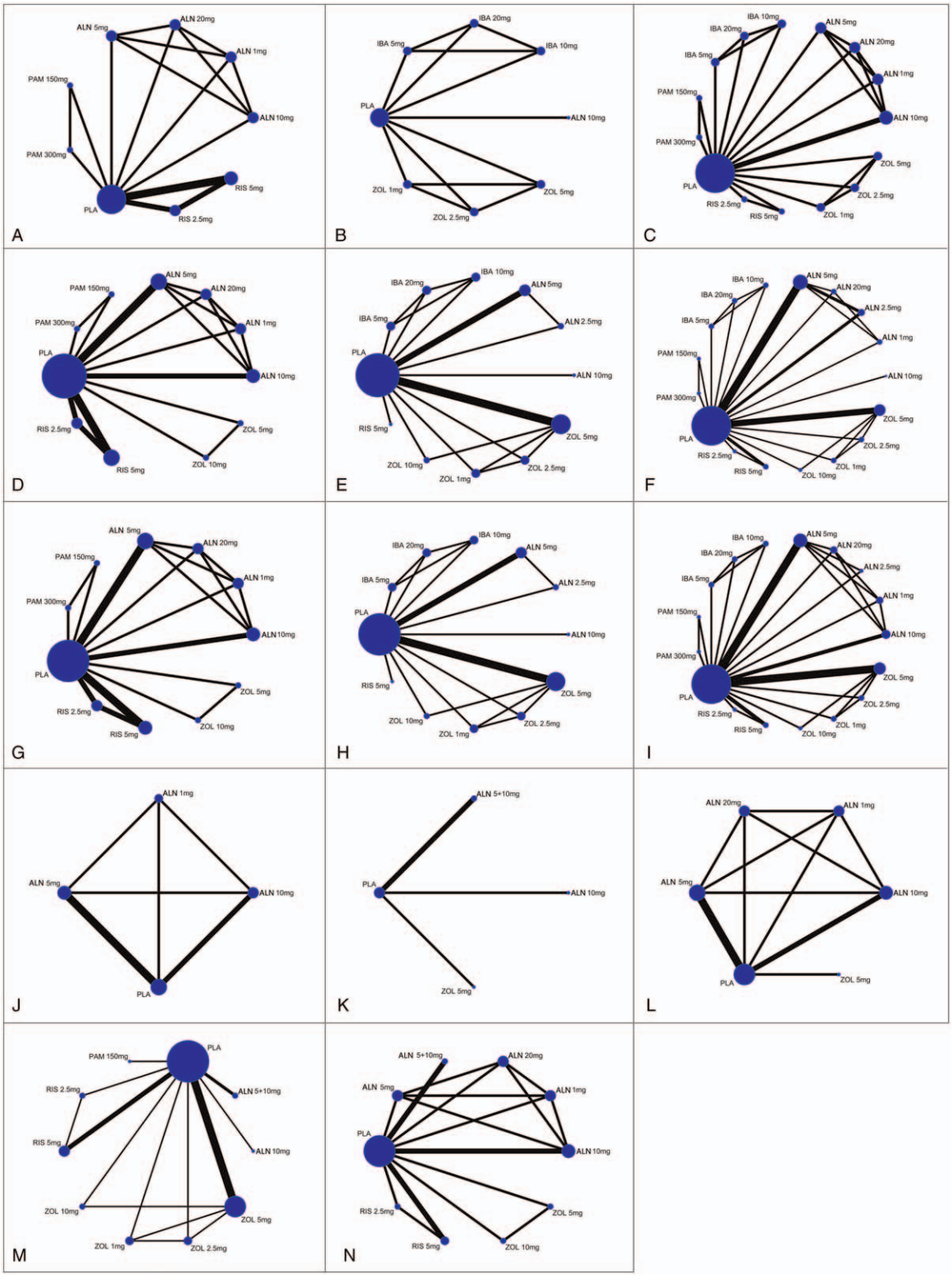

Figure 3. Network plots for all of the primary and secondary outcomes, including the 6-month bone mass density (BMD) percentage changes at femoral neck (A), total hip (B) and lumbar spine (C), 12-month BMD percentage changes at femoral neck (D), total hip (E) and lumbar spine (F), 24-month BMD percentage changes at femoral neck (G), total hip (H) and lumbar spine (I), 36-month BMD percentage changes at femoral neck (J), total hip (K) and lumbar spine (L), all recorded new fractures (M) and severe adverse events (N). Each node represents an individual treatment regimen, and each line represents a direct comparison between 2 treatments. The nodes and lines are weighted by the numbers of related patients and studies. Abbreviations as well as the corresponding description of the interventions are listed in Table 2.

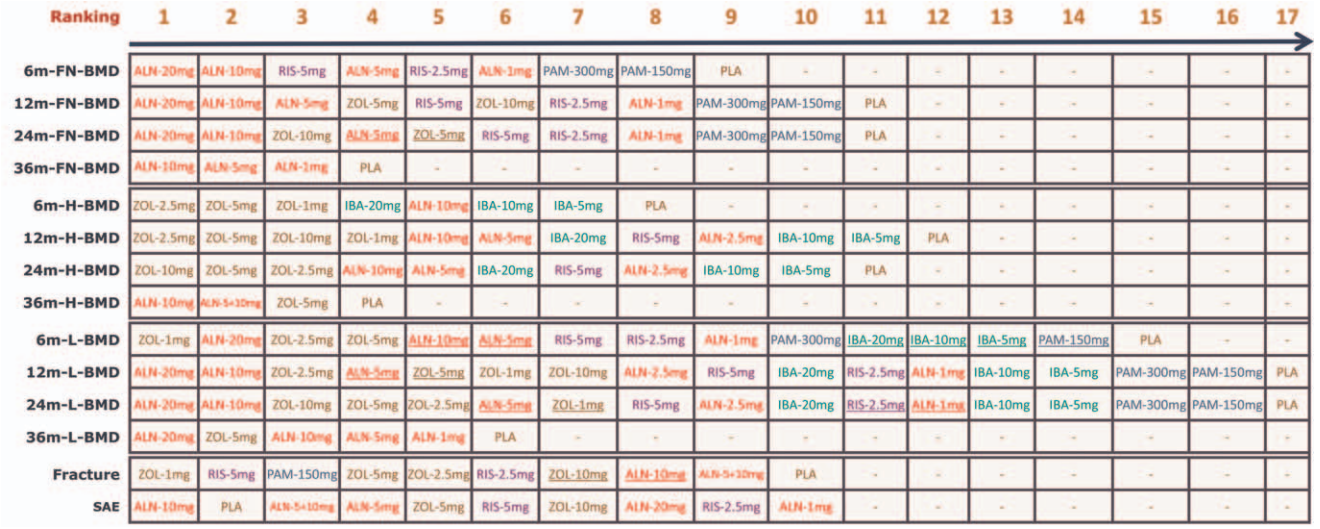

Figure 4. Ranking spectrum depicting the order of treatment efficacy of the interventions on the bone mass density (BMD) percentage change at different bony sites and different follow-up points, as well as the order of anti-fracture efficacy and frequency of severe adverse events, according to the surface under the cumulative ranking curves (SUCRA). Each type of BP drug is marked with an individual color, and interventions with the same SUCRA ranking are underlined. BP = bisphosphonate, FN = femoral neck, H = total hip, L = lumbar spine, SAE = severe adverse events; abbreviations as well as the corresponding description of the interventions are available in Table 2.

change on BMD of total hip, at different follow-up periods. No significant difference was presented among the available interventions for the 6-month BMD at 3 different sites, but the magnitudes of differences among the treatment regimens became gradually increased along with the extending of follow-up periods. This NMA also demonstrated similar frequencies of new clinical fractures and severe adverse events among different interventions.

The relationship between BMD and fracture reduction is not completely linear, as multiple factors may contribute to the risk of vertebral and non-vertebral fractures, such as prevalent fractures, patient-reported poor health status, advanced age, smoking and lack of exercise, which have been used to establish clinical algorithms for predicting risk of fracture.[41–43] But even so, BMD is still an important indication for treatment efficacy of BPs, as many studies have revealed well correlation between the increase of BMD and reduction of vertebral and non-vertebral fractures.[44,45] Generally, the process of bone loss is particularly striking within the first few years following the onset of menopausal.[46] When left untreated, women with osteopenia would progress to osteoporosis with the continuous decrease on BMD. Hence, it is crucial to preserve the bone mass and prevent the microarchitecture from destroying in the period of rapid bone mass loss in these women with osteopenia.

Dosing convenience is a key consideration when using BPs for preventing bone loss. Less frequent dosing is usually expected to enhance patient compliance, and therefore maximize the efficacy of the treatment and minimize the related economic costs. Thus, plenty of studies have been devoted to search for a more convenient dosing regimen, which provides similar or even increased effectiveness comparing to that provided by the daily dosing. It has been widely accepted that short- to medium-term compliance of oral BPs therapy is relatively poor, making adverse impact on the effectiveness of anti-fracture.[47,48]

In the current study, 5 different second- or third-generation BPs are available for comparison with each other or placebo. Among the 3 second-generation drugs, RIS and ALN were administrated orally once a day during the follow-up period, while oral PAM was delivered daily for the first 4 weeks in every 2 or 4 months. ZOL and IBA, as the third-generation BP drugs, were delivered less frequently, with regimens of intravenous administration yearly or at baseline and oral administration weekly, respectively. Regarding to the treatment efficacy, ZOL provided optimal percentage change of BMD for total hip site, and suboptimal BMD change for femoral neck and lumbar spine sites. Although oral ALN of more than 10 mg per day was related to the maximal percentage change on BMD of femoral neck and lumbar spine, the intravenous ZOL is provided less frequently and expected to be more compliant. The IBA, as one of the third-generation BPs; however, is shown to be with inferior effectiveness compared to ALN and ZOL. Moreover, similar percentage change of BMD was presented for IBA-5/10 mg at total hip and lumbar spine sites at 12 months, as well as IBA-5 mg at total hip at 24 months, comparing to that of PLA. PAM is identified to be the least effective BP drug among the available interventions, which was always associated with statistically similar result as that of PLA group. Accumulative researches have recorded that despite baseline calcium supplementation, the postmenopausal women with osteopenia also lose the bone mass significantly from the baseline level, at all measured sites.[38,49] Thus, to ensure effectively preserving or even improving the BMD level, thereby preventing women with osteopenia from destructing of trabecular architecture and progressing to osteoporosis, some potent administration regimens should be selected according to our ranking spectrum in Figure 4.

For the new-recorded clinical fractures, no any difference was found among the available regimens, which is not correlated with the results of the BMD change. It could be speculated that the multiple prognostic factors related with risk of clinical fracture had confused the anti-fracture effect of BPs, leading to the unequal relationship with BMD change.[41–43] In addition, it may be not powered to detect the small difference of frequency of new

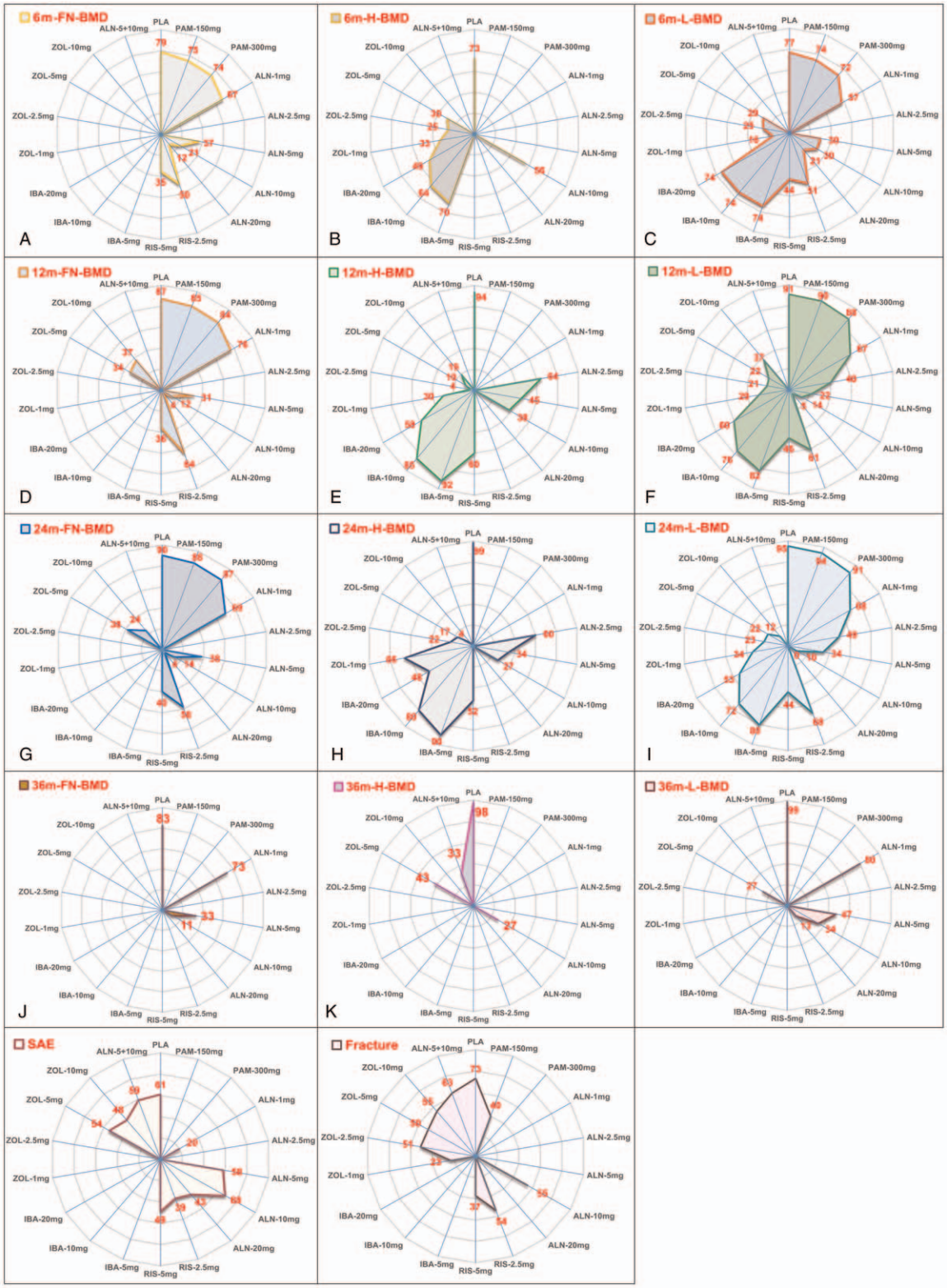

Figure 5. Radar map presenting the surface under the cumulative ranking curves (SUCRA) of the available treatment regimens for each outcome. FN = femoral neck, H = total hip, L = lumbar spine, SAE = severe adverse events; abbreviations as well as the corresponding description of the interventions are available in Table 2.

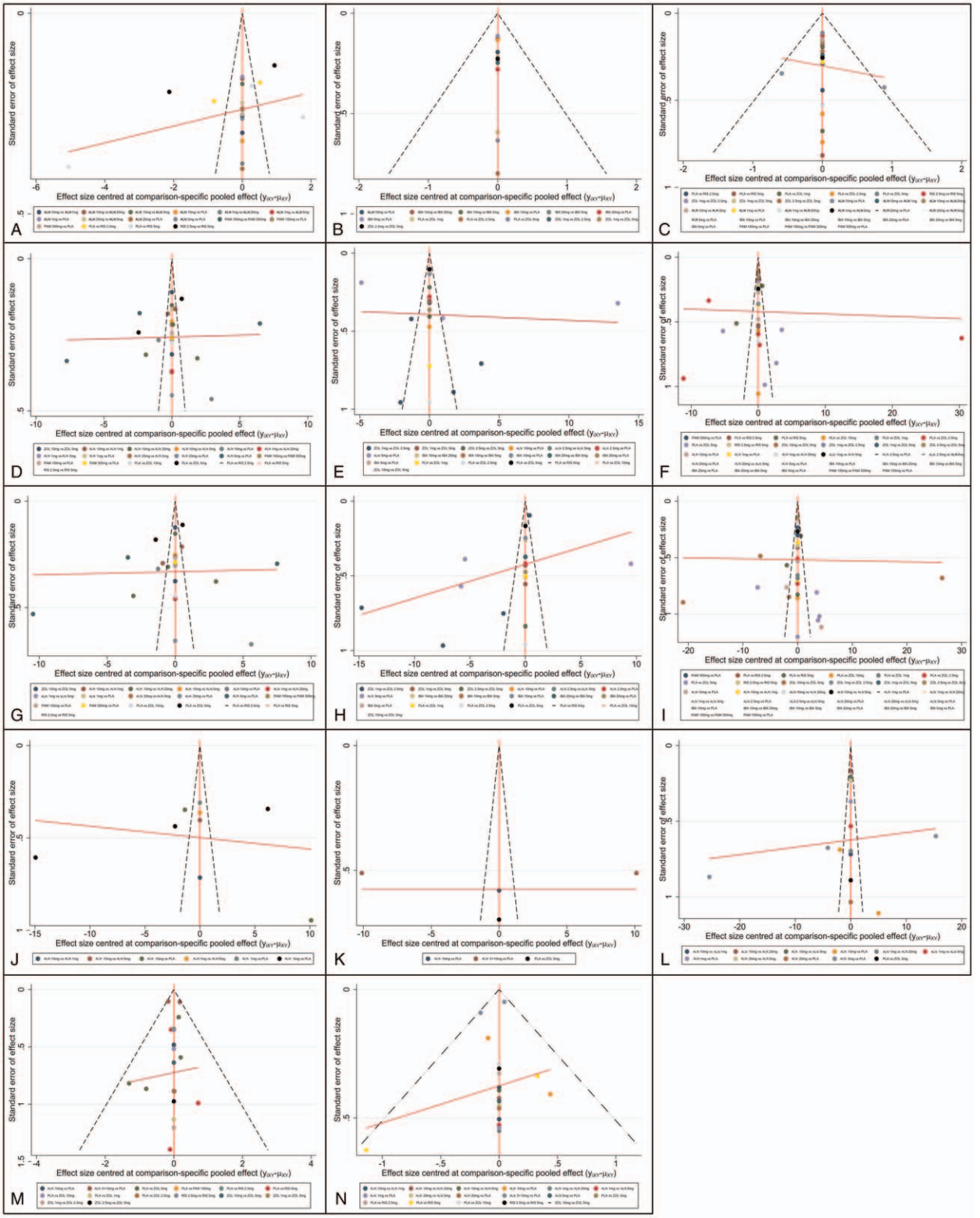

Figure 6. Comparison-adjusted funnel plots for all of the primary and secondary outcomes, including the 6-month bone mass density (BMD) percentage changes at femoral neck (A), total hip (B) and lumbar spine (C), 12-month BMD percentage changes at femoral neck (D), total hip (E) and lumbar spine (F), 24-month BMD percentage changes at femoral neck (G), total hip (H) and lumbar spine (I), 36-month BMD percentage changes at femoral neck (J), total hip (K) and lumbar spine (L), all recorded new fractures (M) and severe adverse events (N). No subjective asymmetry in these funnel plots is presented, indicating there is no obvious small-sample effect to increase the risk of publication bias. Abbreviations as well as the corresponding description of the interventions are available in Table 2.

fracture, due to the inherent low incidence of fracture events among postmenopausal women with ostopenia, which may even be further decreased following treatment with BP drugs. When compared with PLA, all available regimens were demonstrated to be well tolerated in terms of incidence of severe adverse events in our results, which is in accordance with many former studies.[33,38,40] This is a crucial factor to ensure the patients to experience positive treatment effect, as the tolerability to the regimens is an important factor to affect the patients' compliance especially for those osteopenia women in need of long-term intervention.[50]

The current study has some limitations. The BMD change on several bony sites was the primary outcome as the surrogate for fracture risk, but it only partly explains the treatment effect on reduction of the fracture risk. Thus, future studies should provide a more thorough ranking spectrum for fracture data at different end points and sites. Different doses of baseline calcium and vitamin D supplementary were applied in the primary trails, and the periods after menopause were quite inconsistent, which therefore may confound the treatment outcome of each regimens. Finally, osteopenic postmenopausal women were recruited in the eligible trails exclusively, so the results could only be generalizable to the population groups with osteopenia.

5. Conclusions

A ranking spectrum was provided to describe the effectiveness on BMD percentage change continuously at femoral neck, total hip, and lumbar spine, following intervention with different BP regimens. Generally, regimens with ZOL and ALN were demonstrated to be the most effective interventions in the 3 sites at different end points. To select an optimal intervention program for a osteopenic postmenopausal women, clinicians should consider both treatment efficacy and dose frequency, to gain long-term adherence and the maximal treatment effect, as well as the least economic consumption. The regimens of ZOL, with a combination of effectiveness on increasing BMD, convenience of infrequent dosing, and favorable tolerance, were likely to be the optimal selections for the treatment of osteopenia in the postmenopausal women.

Author contributions

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Writing – review & editing: Su-li Dong.

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