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Original Article

Comparison of the Clinical Efficacy of Anabolic Agents and Bisphosphonates in the Patients With Osteoporotic Vertebral Fracture: Systematic Review and Meta-analysis of Randomized Controlled Trials

Corresponding Author
Jongtae Kim
https://orcid.org/0000-0002-4906-0560

Department of Neurosurgery, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 56 Dongsu-ro, Bupyeong-gu, Incheon 21431, Korea
Email: kjtns@catholic.ac.kr

Co-corresponding Author
Sung Uk Kuh
https://orcid.org/0000-0003-2566-3209

Department of Neurosurgery, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea
Email: kuhsu@yuhs.ac

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Ikchan Jeon[1,*], Sung Bae Park[2,*], Bong Ju Moon[3], Miyoung Choi[4], Sung Uk Kuh[5,†], Jongtae Kim[6]

[1]Department of Neurosurgery, Yeungnam University Hospital, Yeungnam University College of Medicine, Daegu, Korea
[2]Department of Neurosurgery, Seoul Metropolitan Government-Seoul National University Boramae Medical Center, Seoul National University College of Medicine, Seoul, Korea
[3]Department of Neurosurgery, Spine and Spinal Cord Institute, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea
[4]Clinical Evidence Research, Division of Health Technology Assessment Research, National Evidence-Based Healthcare Collaborating Agency, Seoul, Korea
[5]Department of Neurosurgery, Spine and Spinal Cord Institute, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea
[6]Department of Neurosurgery, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Incheon, Korea

Objective: We investigated the clinical efficacy of anabolic agents compared with bisphosphonates (BPs) for the incidence of new osteoporotic vertebral fracture (OVF) and fracture healing of OVF in the patients with OVF via meta-analyses of randomized controlled trials (RCTs).
Methods: Electronic databases, including PubMed, Embase, and Cochrane Library were searched for published RCTs till December 2022. The RCTs that recruited participants with osteoporosis at high-/very high-risk of fracture (a history of osteoporotic vertebral or hip fracture) or fresh OVF were included in this study. We assessed the risk of bias on every included RCTs, estimated relative risk (RR) for the incidence of new OVF and fracture healing of OVF, and overall certainty of evidence. Meta-analyses were performed by Cochrane review manager (RevMan) ver. 5.3. Cochrane risk of bias 2.0 and GRADEpro/GDT were applied for evaluating methodological quality and overall certainty of evidence, respectively.
Results: Five hundred eighteen studies were screened, and finally 6 eligible RCTs were included in the analysis. In the patients with prevalent OVF, anabolic agents significantly reduced the incidence of new OVF (teriparatide and romosozumab vs. alendronate and risedronate [RR, 0.57; 95% confidence interval, 0.45–0.71; $p < 0.00001$; high-certainty of evidence]; teriparatide vs. risedronate [RR, 0.50; 95% confidence interval, 0.37–0.68; $p < 0.0001$; high-certainty of evidence]). However, there was no evidence of teriparatide compared to alendronate in fracture healing of OVF (RR, 1.23; 95% confidence interval, 0.95–1.60; $p = 0.12$; low-certainty of evidence).
Conclusion: In the patients with prevalent OVF, anabolic agents showed a significant superiority for preventing new OVF than BPs, with no significant evidence for promoting fracture healing of OVF. However, considering small number of RCTs in this study, additional studies with large-scale data are required to obtain more robust evidences.

Keywords: Teriparatide, Romosozumab, Bisphosphonate, Osteoporosis, Vertebral fracture, Meta-analysis

*Ikchan Jeon and Sung Bae Park contributed equally to this study as co-first authors.

†Current affiliation: Department of Neurosurgery, Spine and Spinal Cord Institute, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea

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INTRODUCTION

Osteoporotic vertebral fracture (OVF) is among the most common fragile fractures, affecting 30% to 50% of individuals over the age of 50.[1] The presence of at least one OVF substantially increases the risk of future OVFs, more than quadrupling it within a two-year period.[2-5] Repeated vertebral fractures and severe vertebral collapse associated with osteoporosis can lead to spinal deformity. In addition to causing chronic pain, severe spinal deformity impairs gastrointestinal and respiratory functions, resulting in reduced daily activities and a lower quality of life.[6-9] Furthermore, when bone union at the fracture site is delayed, pseudarthrosis can occur, accompanied by persistent pain. Neurological issues such as delayed myelopathy, if they result from delayed union, may necessitate surgery in some cases.[10-13] Therefore, it is crucial to treat patients with OVF early to minimize vertebral collapse, facilitate early bone union, and prevent pseudoarthrosis, as well as to reduce the incidence of new OVFs.

For patients at a higher risk of subsequent fractures with continuous significant bone loss, current evidence and recent guidelines increasingly support the use of anabolic agents promoting bone formation as the first-line treatment.[14-16] Anabolic agents rapidly reduce the risk of fractures, especially in the first year following a fracture, and significantly enhance clinical outcomes. The primary anabolic agents widely used in recent times are teriparatide and romosozumab. Teriparatide is effective in decreasing the incidence of new OVFs in postmenopausal women with severe osteoporosis, which can be achieved by preferentially promoting the differentiation of preosteoblasts into osteoblasts, stimulating existing osteoblasts to form new bone, and decreasing osteoblast apoptosis.[17,18] In previous clinical trials, romosozumab exhibited a rapid and significant decrease in the incidence of new OVFs, along with an increase in bone mineral density (BMD) compared with the control group.[19,20] Romosozumab, as an antisclerostin monoclonal antibody, has a dual effect of enhancing bone formation and inhibiting its resorption by blocking the sclerostin pathways.[21] Sclerostin, a molecule derived from osteocytes and encoded by the SOST gene, has been discovered to regulate bone turnover by inhibiting osteoblastogenesis and bone formation. It does so by blocking the Wnt signaling pathways, which play a crucial role in bone formation and morphogenesis.[22-24]

Bisphosphonates (BPs), as antiresorptive agents that work by inhibiting osteoclast-mediated bone resorption, continue to be widely considered and used as one of the treatment options for patients with osteoporosis.[25,26] Nevertheless, recent head-to-head trials comparing BPs with anabolic agents have shown the superiority of anabolic agents in reducing the risk of fractures.[20,27] New guidelines now recommend initial treatment with anabolic agents for patients at imminent or very high-risk of fractures.[14-16,28] Some relevant meta-analyses have demonstrated the effectiveness of anabolic agents in reducing new OVFs compared to BPs in postmenopausal osteoporosis patients.[29-32] However, unfortunately, there is significant heterogeneity in the participants and outcomes among the included studies in meta-analyses, and other randomized controlled trials (RCTs) on this subject have been published without providing conclusive results. There is still a lack of relevant and comprehensive meta-analyses with RCTs comparing the clinical efficacy between anabolic agents and BPs for reducing of the incidence of new OVFs in the patients with OVF, commonly referred to as subsequent OVFs. Furthermore, the previous comparative studies of clinical efficacy between the 2 drugs for the fracture healing of fresh OVF shows heterogenous and unclear conclusions. We think that the reliable recommendations in clinical fields related with the use of anabolic agents and BPs in the patients with OVF are required via scientific verification process.

In this study, we conducted a systematic review and meta-analysis of RCTs to determine whether anabolic agents are superior to BPs for preventing of new OVFs and promoting fracture healing of OVF in the patients with OVF.

MATERIALS AND METHODS

1. Protocol

This meta-analysis was conducted in accordance with the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions and was reported following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[33]

2. Search Strategy

Three researchers conducted a systematic search of major electronic databases (PubMed, Embase, and the Cochrane Library) using a carefully designed search strategy for relevant studies published in English up to December 2022. We aimed to gather RCTs that compared the effects of anabolic agents and BPs on the incidence of new OVFs or fracture healing of OVF in patients with osteoporosis at high-risk or very high-risk of fracture. We established the search terms included keywords found in the titles, abstracts, or MeSH (medical subject headings) terms in each database's search engine (Supplementary

Material). Additionally, we reviewed the reference lists of other relevant reviews and studies for potentially pertinent articles. Titles and abstracts of retrieved studies were screened to exclude clearly irrelevant ones, and then the full texts of the remaining articles were thoroughly assessed to determine their eligibility. These screening processes were carried out independently by 3 authors (SBP, BJM, and IJ), and the references were managed using Endnote X20 (Clarivate Analytics, Philadelphia, PA, USA).

3. Selection Criteria

Only published RCTs meeting the following criteria were included: (1) Population: participants with high-risk or very high-risk fracture osteoporosis; (2) intervention: administration with teriparatide or romosozumab; (3) comparison: administration with BPs; and (4) ≥1 of the following outcomes: incidence of new OVF or fracture healing of OVF. The 2020 American Association of Clinical Endocrinology (AACE) guidelines[15] define osteoporosis at high-risk fracture as those meeting any of the following criteria: having a BMD T-score of ≤ -2.5 in the lumbar spine, femoral neck, total proximal femur, or 1/3 radius; having experienced a low-trauma spine or hip fracture (regardless of BMD); having a BMD T-score -1.0 to -2.5 and suffering a fragility fracture of the proximal humerus, pelvis, or distal forearm; or having a BMD T-score -1.0 to -2.5 with a high FRAX (or trabecular bone score-adjusted FRAX when available) fracture probability based on country-specific thresholds. Additionally, individuals who have recently experienced a fracture (e.g., within the past 12 months), sustained a fracture while on approved osteoporosis therapy, incurred fractures due to medications causing skeletal harm, encountered multiple fractures, have a very low BMD T-score (e.g., ≤ -3.0), are at high risk for falls or have a history of injurious falls, or exhibit a very high fracture probability per FRAX (e.g., > 30% major osteoporotic fracture, > 4.5% hip) are categorized as osteoporosis at very high-risk fracture.

However, studies that recruited patients with traumatic vertebral fracture, secondary osteoporosis, or did not report results in dichotomous data (i.e., patient-years, etc.), were excluded. *Post hoc* analyzed RCTs were also included, with taking care of duplicated data input. Disagreements between reviewers were resolved by discussion or, if unresolved, by consultation with consultation with librarians and a statistic expert.

4. Data Extraction

The basic characteristics of each study were independently extracted by 3 authors using a structured table that included information on study design, the number of participants, interventions, comparisons, and outcomes. The primary outcomes assessed in this study were the development of new OVFs and fracture healing of OVF. The validity of extracted data was reviewed by the other authors.

5. Risk of Bias Assessment of Studies

In this study, 3 authors independently evaluated the methodological quality of the RCTs using the Cochrane risk of bias 2 tool.[34] The tool assessed the risk of bias as high, low, or unclear across several criteria; including random sequence generation, allocation concealment, blinding of participants and personnel to the study protocol, blinding of outcome assessment, incomplete outcome data, selective reporting, and other potential sources of bias. Disagreements were addressed by consensus with the involvement of a third review author. RCTs that were found to have a high risk of bias in more than one key domain were categorized as high risk, while RCTs with a low risk of bias in all key domains were considered low risk. RCTs that did not fit either of these categories were categorized as having an unclear risk of bias. Assessment of publication bias was attempted through the use of funnel plots.

6. Data Synthesis

The relative risk (RR) and its corresponding 95% confidence intervals (CIs) were employed to assess the impact of interventions for RCTs, with p-values less than 0.05 considered statistically significant. Data analysis was conducted using RevMan 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) to estimate a pooled effect through a fixed-effect model. Heterogeneity among the studies was assessed using the I^2 statistics, where an I^2 value greater than 50% indicated significant heterogeneity.[35] In cases of high heterogeneity that remained unexplained, sensitivity analysis was planned, taking into account factors such as subjects, interventions, or outcomes. However, sensitivity analysis was skipped in low heterogeneity with I^2 value significantly lesser than 50%.

7. Assessment of Certainty of Evidence

In assessing the overall certainty of evidence, we utilized the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework, and we employed the GRADEpro/GDT (Guideline Development Tool) software, which is accessible at https://gradepro.org/. GRADE represents a widely accepted and transparent framework for summarizing evidence and offers a systematic approach for formulating clinical practice recommendations.[36,37] It takes into account various

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factors such as study design, risk of bias, inconsistency, indirectness, imprecision, and other relevant considerations. The final determination of the overall certainty of evidence according to GRADE falls into one of 4 categories: very low, where the true effect is likely markedly different from the estimated effect; low, where the true effect may be markedly different from the estimated effect; moderate, where the true effect is likely close to the estimated effect; and high, where the true effect closely aligns with the estimated effect. To address imprecision, we calculated the Optimal Information Size (OIS), the minimum sample size required in a single and adequately powered study to evaluate the effects of intervention in the general population, using a Sample Size Calculator, available at https://www.stat.ubc.ca/~rollin/stats/ssize/n2.html.

RESULTS

1. Search Selection and Characteristics

The PRISMA flow diagram (Fig. 1) illustrates the selection and exclusion process of the studies. Initially, a total of 518 studies were screened (204 from PubMed, 224 from Embase, and 90 from Cochrane Library). Subsequently, 259 of these studies underwent a full-text assessment. Following a thorough examination of the full texts, 6 RCTs involving 3,642 and 3,655 patients with osteoporosis at high-risk fracture treated with anabolic agents and BPs, respectively, were ultimately included in this meta-analysis. Among the included RCTs, 4 of them compared the effects of anabolic agents (3 of teriparatide and 1 of romosozumab) with BPs (2 of alendronate and 2 of risedronate) in terms of the incidence of new OVFs.[18,38-40] The other 2 RCTs compared the effects on fracture healing in OVF between teriparatide and alendronate.[41,42] The detailed characteristics of these 6 RCTs are summarized in Table 1.

2. Risk of Bias Assessment

Fig. 2 provides a summary of the details regarding the risk of bias. In total, 3 RCTs were categorized as having a low risk of bias, while 2 RCTs were deemed to have a high risk of bias. All RCTs exhibited adequate random sequence generation, managed incomplete outcome data, and avoided selective reporting. However, there was uncertainty in 3 RCTs regarding appropriate allocation concealment, one RCT in blinding of outcome assessment, and one RCT in other bias, respectively. Blinding of participants and personnel assessments showed high-risk in 2 RCTs and unclear in one RCT. We assessed publication bias using funnel plots in each analysis (Figs. 3–5). Although sufficient analyses could not be performed due to small number of RCTs included in this study, there was no suspicious evident for pub-

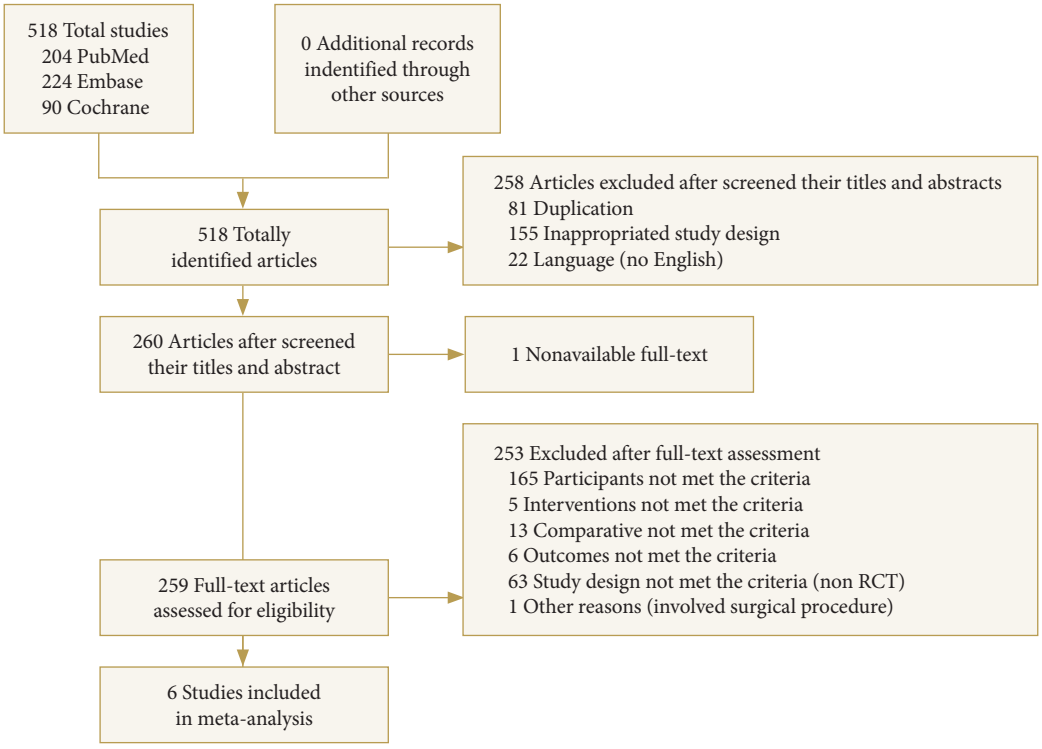

Fig. 1. The flow diagram of study selection.

Table 1. General characteristics of the included studies

Study	Journal	Participants	Sample size and medication		Medication period	Age (yr)		Follow-up	Outcomes
			Anabolic agent	BP		Anabolic agent	BP		
Kendler et al.[18] (2018)	*Lancet*	Postmenopausal women >45 years with BMD T-score ≤1.5 and either ≥2 moderate or a severe vertebral fracture	N=680, teriparatide (20 μg, daily SC)	N=680, risedronate (35 mg, weekly PO)	24 Months	72.6±8.8	71.6±8.6	24 Months	New OVF (morphometric fracture-radiograph)
Hadji et al.[38] (2012)	*Osteoporosis International*	Postmenopausal women ≥45 years with BMD T-score ≤-2.0 and ≥1 moderate vertebral fracture	N=360, teriparatide (20 μg, daily SC)	N=350, risedronate (35 mg, weekly PO)	18 Months	70.5±8.8	71.6±8.1	18 Months	New OVF (morphometric fracture-radiograph)
Geusens et al.[39] (2022)	*Bone*	Postmenopausal women with BMD T-score ≤-2.5 and either ≥1 moderate or severe vertebral fracture, or BMD T-score of ≤-2.0 and either ≥2 moderate or a severe vertebral fracture	N=2,046, romosozumab (210 mg, monthly SC)	N=2,047, alendronate (70 mg, weekly PO)	12 Months	74.4±7.5	74.2±7.5	12 Months	New OVF (morphometric fracture-radiograph)
Hagino et al.[40] (2021)	*Osteoporosis International*	Postmenopausal women ≥75 years with osteoporosis at high fracture risk (BMD T-score <-3.3 and either ≥2 vertebral fractures, a grade 3 vertebral fracture, or hip fracture)	N=489, teriparatide (56.6 μg, weekly SC)	N=496, alendronate (5 mg daily PO, 35 mg weekly PO, or 900 μg every 4 weeks IV)	72 Weeks	81.4±4.5	81.5±4.7	72 Weeks	New OVF (morphometric fracture-radiograph)
Shigenobu et al.[41] (2019)	*Bone Reports*	Patients (43; 5 men and 38 women) with fresh osteoporotic vertebral compression fracture	N=19, teriparatide (56.6 μg, weekly SC)	N=24, alendronate (35 mg weekly PO, risedronate 17.5 mg weekly PO, or 75 mg monthly PO)	12 Weeks	80.2	75.6	12 Weeks	Fracture healing of OVF (CT scan)
Ikeda et al.[42] (2020)	*Journal of Bone and Mineral Metabolism*	Women with fresh osteoporotic vertebral fractures	N=48, teriparatide (56.6 μg, weekly SC)	N=48, alendronate (35 mg, weekly PO)	12 Weeks	78.9	80.3	12 Weeks	Fracture healing of OVF (radiograph)

BP, bisphosphonate; BMD, bone mineral density; SC, subcutaneous; PO, per os (oral); OVF, osteoporotic vertebral fracture; IV, intravenous; CT, computed tomography.

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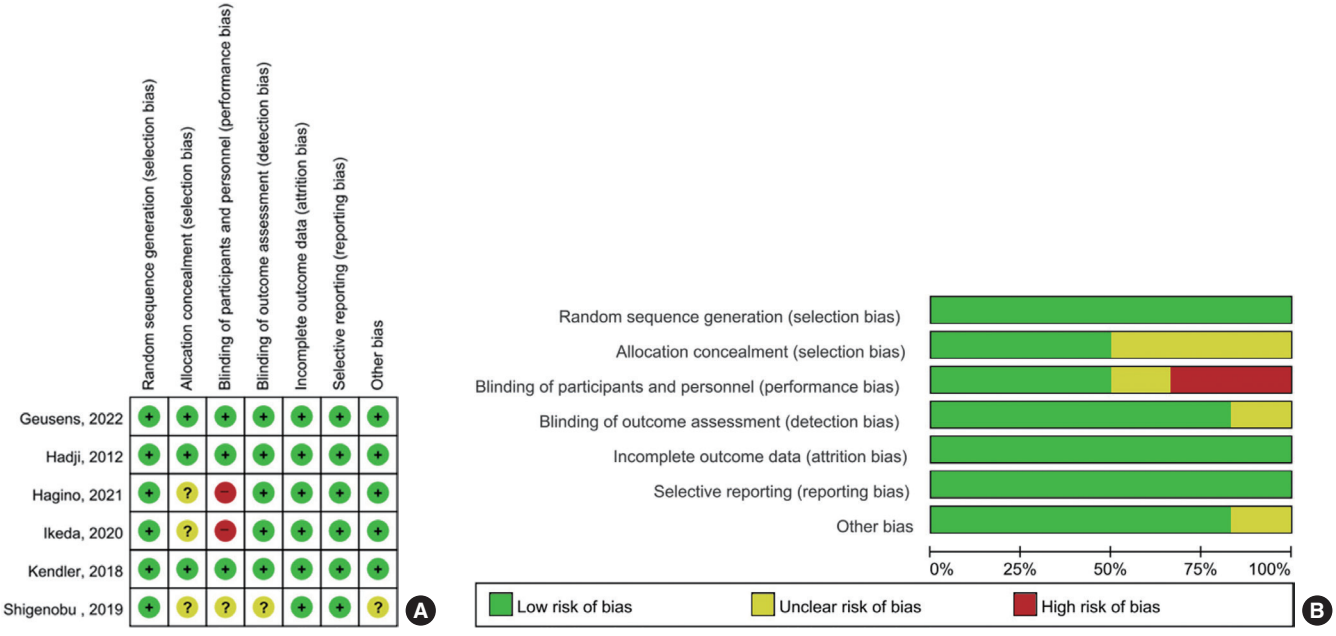

Fig. 2. Risk of bias summary (A) and graph (B).

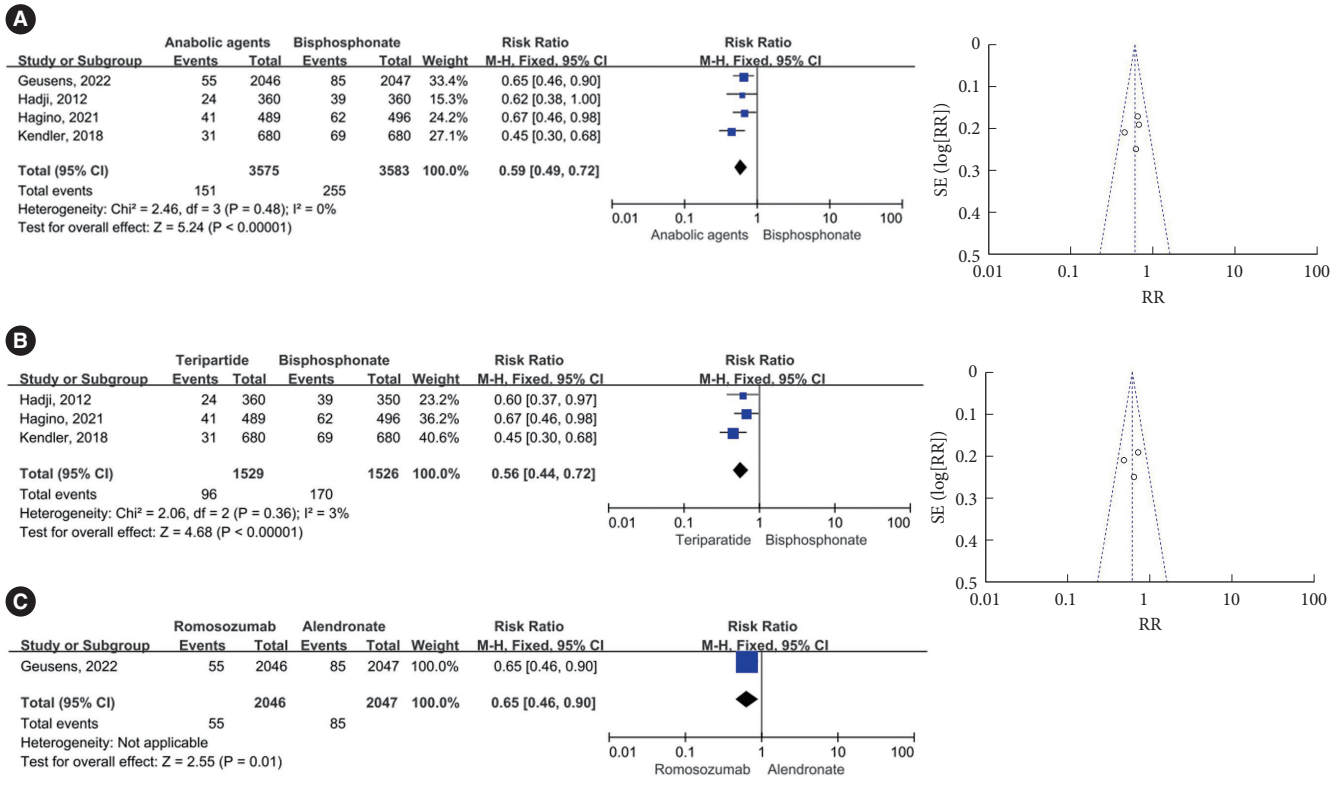

Fig. 3. Forest and funnel plots for comparing anabolic agents versus bisphosphonates of the incidence of new osteoporotic vertebral fracture in the patients with osteoporotic vertebral and hip fracture. (A) Anabolic agents versus bisphosphonates. (B) Teriparatide versus bisphosphonates. (C) Romosozumab versus alendronate. M-H, Mantel-Haenszel; CI, confidence interval; df, degrees of freedom.

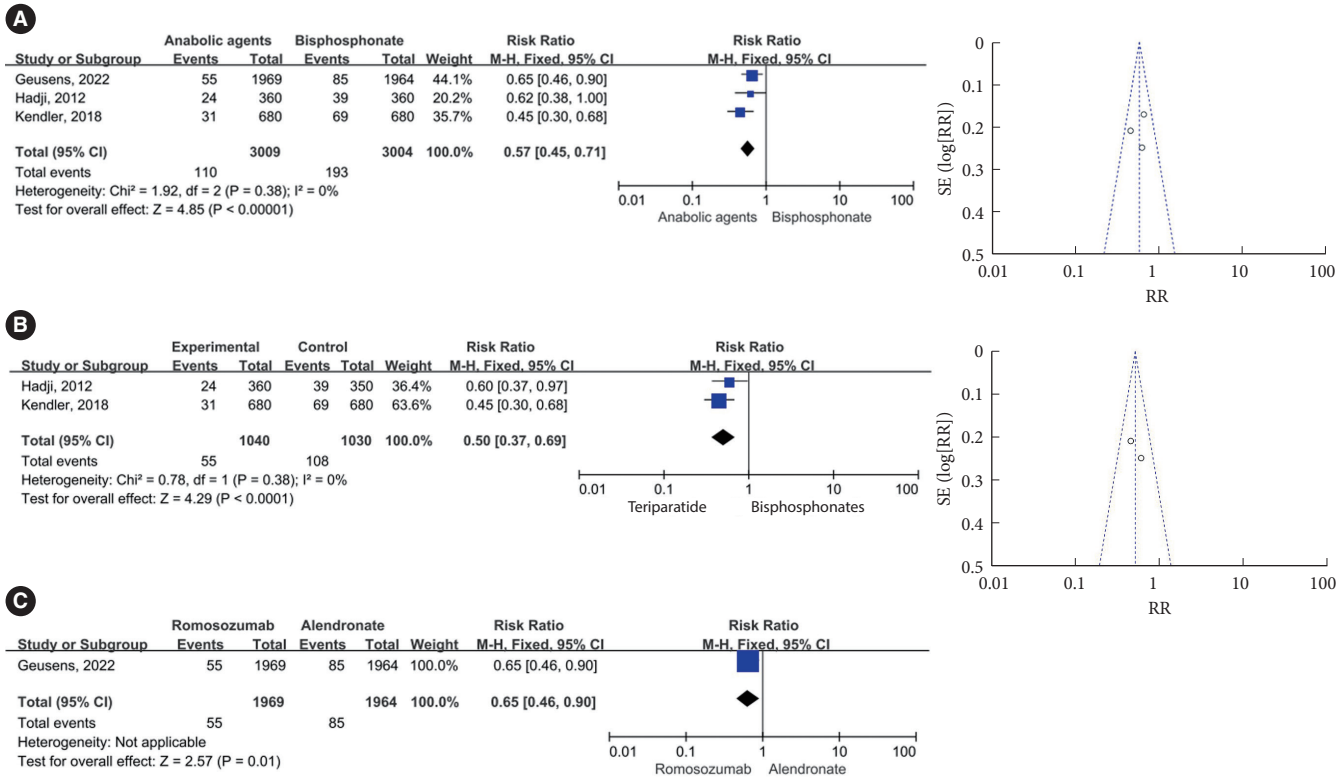

Fig. 4. Forest and funnel plots for comparing anabolic agents versus bisphosphonates of the incidence of new osteoporotic vertebral fracture in the patients with osteoporotic vertebral fracture. (A) Anabolic agents versus bisphosphonates. (B) Teriparatide versus bisphosphonates. (C) Romosozumab versus alendronate. M-H, Mantel-Haenszel; CI, confidence interval; df, degrees of freedom.

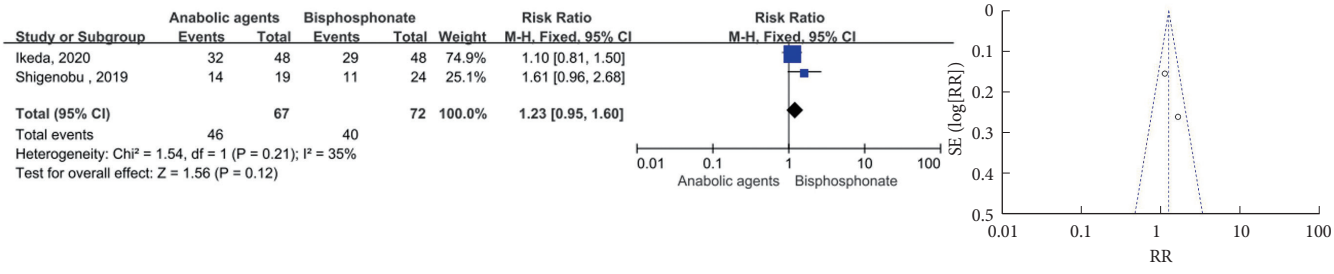

Fig. 5. Forest and funnel plots for comparing anabolic agents versus bisphosphonates of the fracture healing of osteoporotic vertebral fracture. M-H, Mantel-Haenszel; CI, confidence interval; df, degrees of freedom.

lication bias considering narrowly located on the top of the plot with symmetric distribution on both side of graph.

3. Efficacy Outcomes

1) Incidence of new OVF

The incidence of new OVF data in the patients with prevalent osteoporotic vertebral or hip fracture was taken from 4 RCTs with including 3,575 and 3,583 patients in anabolic agents (3 teriparatide and 1 romosozumab) and BPs (2 alendronate and 2 risedronate), respectively. There was a significant decrease in the incidence of new OVF (RR, 0.59; 95% CI, 0.49–0.72; $p < 0.00001$; $I^2 = 0\%$) (Fig. 3A). The analysis with only teriparatide among the anabolic agents was performed with 3 RCTs including 1,529 of teriparatide and 1,526 patients in teriparatide and BPs (1 alendronate and 2 risedronate), respectively. Teriparatide also showed significant decrease in the incidence of new OVF compared to BPs (RR, 0.56; 95% CI, 0.44–0.72; $p < 0.00001$; $I^2 = 3\%$) (Fig. 3B). In the analysis with only romosozumab by one RCT including 2,046 of romosozumab and 2,047 of alendronate, there was a significant decrease in the incidence of new

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Table 2. Summary of findings in new osteoporotic vertebral fracture and fracture healing

Outcomes	Comparison (composition of RCTs)	Incidence of events/sample size		OR (95% CI)/heterogeneity	Certainty of evidence	Importance
		Anabolic agents	Bisphosphonates			
Incidence of new OVF	Osteoporosis with prevalent osteoporotic vertebral or hip fracture					
	Anabolic agents vs. bisphosphonates (3 teriparatide+1 romosozumab vs. 2 alendronate+2 risedronate)	151/3,575	255/3,583	RR = 0.59 (95% CI, 0.49–0.72), p < 0.00001/I^2 = 0%	High	Important
	Teriparatide vs. bisphosphonates (3 teriparatide vs. 1 alendronate+ 2 risedronate)	96/1,529	170/1,526	RR = 0.56 (95% CI, 0.44–0.72), p < 0.00001/I^2 = 3%	High	Important
	Romosozumab vs. bisphosphonate (1 romosozumab vs. 1 alendronate)	55/2,046	85/2,047	RR = 0.65 (95% CI, 0.46–0.90), p = 0.01/NA	NA	Important
	Osteoporosis with prevalent osteoporotic vertebral fracture					
	Anabolic agents vs. bisphosphonates (2 teriparatide+1 romosozumab vs. 1 alendronate+2 risedronate)	110/3,009	193/3,004	RR = 0.57 (95% CI, 0.45–0.71), p < 0.00001/I^2 = 0%	High	Important
	Teriparatide vs. bisphosphonates (2 teriparatide vs. 2 risedronate)	55/1,040	108/1,030	RR = 0.50 (95% CI, 0.37–0.68), p < 0.0001/I^2 = 0%	High	Important
	Romosozumab vs. bisphosphonate (1 romosozumab vs. 1 alendronate)	55/1,969	85/1,964	RR = 0.65 (95% CI, 0.46–0.90), p = 0.01/NA	NA	Important
Fracture healing	Teriparatide vs. bisphosphonates (2 teriparatide vs. 2 alendronates)	46/67	40/72	RR = 1.23 (95% CI, 0.95–1.60), p = 0.12/I^2 = 35%	Low	Important

RCT, randomized controlled trial; OR, odds ratio; CI, confidence interval; OVF, osteoporotic vertebral fracture; RR, relative risk.

OVF compared to alendronate (RR, 0.65; 95% CI, 0.46–0.90; p = 0.01) (Fig. 3C).

The incidence of new OVF data in the patients with only prevalent OVF was taken from 3 RCTs with including 3,009 and 3,004 patients in anabolic agents (2 teriparatide and 1 romosozumab) and BPs (1 alendronate and 2 risedronate), respectively. One RCT that could not measure the incidence of new OVF according to prevalent OVF was excluded, and the selected data with prevalent OVF from the remaining RCTs were used to evaluate the incidence of new OVF according to the presence of prevalent OVF. There was a significant decrease in the incidence of new OVF (RR, 0.57; 95% CI, 0.45–0.71; p < 0.00001; I^2 = 0%) (Fig. 4A). The analysis with only teriparatide among the anabolic agents was performed with 2 RCTs including 1,040 of teriparatide and 1,030 patients in teriparatide and BPs (2 risedronate), respectively. Teriparatide also showed significant decrease in the incidence of new OVF compared to BPs (RR, 0.50; 95% CI, 0.37–0.68; p < 0.0001; I^2 = 0%) (Fig. 4B). In the analysis with only romosozumab by 1 RCT including 1,969 of romosozumab and 1,964 of alendronate, there was a significant decrease in the incidence of new OVF compared to alendronate (RR, 0.65; 95% CI, 0.46–0.90; p = 0.01) (Fig. 4C).

The detailed data of the incidence of new OVF are summarized in Table 2.

2) Fracture healing of OVF

The fracture healing of OVF data was taken from 2 RCTs with including 67 and 72 patients in teriparatide and alendronate of groups with osteoporosis at very high fracture risk, respectively. There was no statistically significant difference in the fracture healing of OVF between teriparatide and alendronate (RR, 1.23; 95% CI, 0.95–1.60; p = 0.12; I^2 = 35%) (Fig. 5). The detailed data of fracture healing of OVF are summarized in Table 2.

4. Assessment of Certainty of Evidence - GRADE

The GRADEpro/GDT analyses regarding the overall quality of evidence were conducted in the incidence of new OVF and fracture healing of OVF. In the incidence of new OVF, the GRADEpro/GDT analyses were applied depending on the type of prevalent osteoporotic fracture and use of medication, respectively. There were high-quality of evidences between anabolic agents (teriparatide and romosozumab) to BPs regardless of the type of prevalent osteoporotic fracture. The OISs in each analysis are approximately 1,004 and 978, respectively. Similarly, the quality of evidences between teriparatide and BPs were also showed high-quality of evidences regardless of the type of prevalent osteoporotic fracture, with an OISs of about 525 and 421 in each analysis. However, when evaluating the quality of evi-

dence for the fracture healing of OVF between teriparatide and alendronate, the assessment resulted in a low-quality of evidence. This was primarily due to the limited number of participants (214 of OIS) and the heterogeneity of the CIs between the included RCTs. However, the assessment of certainty of evidence using GRADE was not conducted for subgroup analyses that included only one RCT. The detailed data are summarized in Table 2.

DISCUSSION

BPs, which were first introduced in the 1990s, have long been the cornerstone of osteoporosis treatment. In the United States, there are 4 available BPs (alendronate, ibandronate, risedronate, and zoledronate), and among these, 3 (alendronate, risedronate, and zoledronate) are supported by robust evidence for their broad-spectrum effectiveness in preventing fractures and are considered as first-line treatment options.[43-51] They are effective in reducing the risk of vertebral, nonvertebral, and hip fractures. However, ibandronate has shown effectiveness primarily in preventing vertebral fractures.[43] A recent network meta-analysis revealed that BPs can reduce the risk of vertebral, nonvertebral, and hip fractures by percentages ranging from 33% to 62%, 16% to 21%, and 27% to 40% (excluding ibandronate in nonvertebral and hip fractures), respectively.[51,52] Consequently, the AACE guideline still recommends the use of alendronate and ibandronate for individuals with osteoporosis at high-risk fracture, while zoledronate is recommended specifically for those with osteoporosis at very high-risk fracture.[15] Nevertheless, data from the Danish national health registry indicate that 14.6% of patients continue to be identified as remaining at high-risk fracture despite being compliant with BP treatment.[53] Although BPs are still considered effective for reducing the risk of osteoporotic fractures in osteoporosis at high-risk fracture based on the available evidence, it may be worth considering the potential benefits of anabolic agents over BPs, especially for patients who have already experienced prevalent osteoporotic fractures. This consideration can be supported by the superior efficacy of anabolic agents compared with BPs (especially teriparatide in the patients with prevalent OVF) for reducing the incidence of new OVF in this meta-analysis of RCTs.

Several previous meta-analyses have directly compared the effects of teriparatide and BPs in reducing the incidence of subsequent vertebral fracture. In a meta-analysis comparing teriparatide to alendronate, there was no significant difference in the occurrence of subsequent vertebral fractures.[30] While other meta-analyses have reported the superiority of teriparatide over BPs in reducing the incidence of subsequent vertebral fractures,[27,32] however, these findings come with certain limitations including relatively higher heterogeneity and participant duplication across the included studies. In this study, we reviewed the effect of anabolic agents including teriparatide and romosozumab as well as teriparatide over BPs depending on the kinds of prevalent osteoporotic fractures in the participants. We tried to identify the real effect of the medications for the reducing the incidence of new OVF in the patients with prevalent OVF (subsequent OVF). Notably, the included vast majority of postmenopausal women with osteoporosis at high-risk or very high-risk fracture had prevalent vertebral fractures, and there was only a small portion of participants in a single RCT who have prevalent hip fracture with no vertebral fracture.[40] The results showed statistically significant superiorities of anabolic agents and teriparatide over BPs with high-quality evidence regardless of the prevalent osteoporotic fractures. However, among them, teriparatide showed most powerful efficacy over risedronate for reducing subsequent OVF with 0.5 of RR and high-quality evidence in the patients with prevalent OVF. Consequently, among anabolic agents, teriparatide showed the superiority over BPs for reducing new OVF after osteoporotic fractures, and it has been found to be more effective for preventing subsequent OVF in patients with prevalent OVF. Unfortunately, it is important to note that assessing the effect of romosozumab with meta-analysis was impossible due to the lack of head-to-head RCTs. In the literature, there is still a limited number of meta-analyses comparing the efficacy of romosozumab, and it is difficult to estimate the exact effect of romosozumab on BPs due to the combination of BP and placebo as the control group.[29,54] Nevertheless, in this study, we guess a similar effect in reducing the incidence of new OVF between teriparatide and romosozumab based on the given low heterogeneity with $I^2 = 0\%$ observed between the included 4 RCTs.

We were very surprised that there were very limited number of RCTs comparing anabolic agents and BPs in the prevention of new OVF and fracture healing of OVF in this study. Therefore, we should be more careful to interpret results and obtain the scientific evidence in the meta-analysis using a small number of RCTs. The certainty of evidence was evaluated using the GRADE framework, and meaningful results were obtained for each element, such as study design, risk of bias, inconsistency, indirectness, and imprecision. All RCTs included in this study involved patients with osteoporosis at high-risk or very-high risk fracture. Higher baseline fracture risk is indeed a significant

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contributor to overall fracture risk. However, all RCTs have consistently indicated that the reduction in the incidence of new OVF with anabolic agents is significantly independent. This is supported by the presence of statistically significant RRs with low heterogeneity ($I^2 = 0\%–3\%$) across the included RCTs in all analyses related with new OVF. Heterogeneity is a crucial consideration, especially in small sized meta-analyses. When the results of existing studies of a treatment are homogeneous or nearly homogeneous, there is a reasonable expectation that the treatment will have a similar effect when applied to new subjects. Conversely, when the results are highly heterogeneous, predicting the effect of the treatment on new subjects becomes challenging unless the reasons for the heterogeneity are well-understood.[49] Typically, in meta-analyses comparing studies, definitive conclusions about heterogeneity are often difficult to reach. However, the strengths of our study lie in the very low heterogeneity observed and the sufficient sample sizes included in each analysis for the incidence of new OVFs with head-to-head RCTs. This reduced the potential for type 1 error and addressed the limitation of a small number of RCTs.

The methodology to define vertebral fractures varies between and within meta-analyses. Vertebral fractures are one of the most common skeletal fractures, and two-thirds to three-quarters of vertebral fractures are not recognized at the time of their clinical occurrence and require spinal imaging to be detected.[55,56] Epidemiologic studies of vertebral fractures have focused primarily on radiographic vertebral fractures, and delineating the prevalence and incidence between clinical and radiological vertebral fractures is complicated (in this meta-analysis, they are named clinical and morphometric fractures, respectively). Additionally, it may be further worse as the lack of consensus as to exactly what changes within a vertebra on spine imaging warrant a diagnosis of vertebral fracture, such that some aspects of the epidemiology of vertebral fractures may depend somewhat on the chosen definition of vertebral fracture.[57-59] Clinical fractures are confirmed on the imaging studies with the occurrence of related symptoms such as back pain. Usually, the incidence of clinical fractures is lower compared to radiological fractures due to the variety of subjective symptoms. Among the included RCTs in this study, 1 RCT presented the overall annual incidences of clinical and radiological fractures with 17.34% and 2.17%, respectively. There was no statistically significant difference in the incidence of new OVF defined as clinical fracture between teriparatide and alendronate due to the extremely low incidence of clinical fracture. The methodological variety is the important point should be carefully considered to conduct meta-analysis and interpret the results of it. In this study, we attempted to objectively measure the incidence of new OVF based on morphometric fracture through serial radiographs with excluding the data of clinical fracture. Nevertheless, the definition of new OVF according to the degree and shape of the fracture is unclear between the RCTs and its effect on the analyses may not be completely excluded.

Currently, there are no approved drug treatments specifically designed to promote fracture healing, despite the availability of several drugs for preventing osteoporotic fractures. Teriparatide or parathyroid hormone (PTH) analogue increases bone mass and reduces bone loss, thereby promoting bone formation.[60-62] While animal studies have provided support for this hypothesis, the evidence regarding its application in humans is less conclusive. Some studies suggest that the administration of PTH analogues has a beneficial impact on fracture healing, whereas others report no discernible effect on fracture healing rates.[62-70] In the prior meta-analyses, the evidence supporting the idea that teriparatide enhances fracture healing was not significant, primarily due to RCTs characterized by high heterogeneity, low-quality evidence, and the inclusion of various types of fractures.[71,72] Notably, subgroup analysis comparing teriparatide to BPs in 2 RCTs showed no significant superiority.[72] Additionally, there is no standardized method for confirming fracture healing, and approaches vary between individual studies. In 2 RCTs included this study, they applied different methods, computed tomography and radiograph, to determine fracture healing. Furthermore, researches focusing on vertebral fracture healing through RCTs has been extremely limited, and, to date, no meaningful meta-analysis on this subject exists. The 2 RCTs included in this meta-analysis aimed to assess the efficacy of fracture healing at 12 weeks after newly developed OVF between teriparatide and alendronate. However, considering the variation in standards used by physicians to make decisions about fracture healing, limited number of participants, and the overall low-quality of evidence, our finding are inconclusive and suggest the need for further researches.

Numerous prospective observational studies have consistently shown that prevalent OVFs are associated with subsequent OVFs, prevalent radiographic vertebral fracture is associated with a 4-fold increase in subsequent radiographic vertebral fractures.[54-58] In a view point of clinical significance for reducing subsequent OVFs, it is important to evaluate the clinical efficacy of anabolic agents compared to BP at high-risk fracture with prevalent OVFs. This meta-analysis has strengths, as it features RCTs characterized by a preplanned parallel comparison between anabolic

agents and BPs for the incidence of new OVF and the fracture healing of OVF as primary outcomes in the homogeneous group of patients with osteoporosis at high-risk or very high-risk fracture. Additionally, we conducted subgroup analyses based on the presence of prevalent OVFs and specific types of anabolic agents and BPs, with long-term follow-ups lasting at least 12 months and ensuring the avoidance of duplication by excluding studies that involved similar participants from the same research subject. However, it is important to acknowledge several limitations in this study. First, despite the subgroup analyses depending on the type of anabolic agents and prevalent osteoporotic fractures, some subgroup analyses were based on the inclusion of only 1 or 2 RCTs, which has limited ability to ascertain their real significance and reliability. Second, variations in the duration of follow-up and different administration routes/dosage of drugs among the included RCTs may have influenced the final outcomes. Third, the cost-effectiveness of anabolic agents compared with BPs should be confirmed to suggest the use of anabolic agents in the patients with osteoporosis at high-risk fracture. Fourth, as previously mentioned, the lack of well-defined criteria and method to confirm the efficacy of anabolic agents in the analysis of new OVF and fracture healing. Considering these limitations, our results may require cautious and conservative interpretation in real clinical field. Additional studies with large-scale data are required to obtain more robust evidences.

CONCLUSION

Anabolic agents demonstrated a significant advantage in preventing new OVF compared to BPs with high-quality evidence in patients with osteoporosis at high-/very high-risk of fractures. Particularly, there was notable significant efficacy of anabolic agents compared to BPs for the prevention of subsequent OVFs. However, considering small number of RCTs in this study, our results may require cautious and conservative interpretation and additional studies with large-scale data are mandatory to obtain more robust evidences.

NOTES

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ORCID

Ikchan Jeon: 0000-0002-1293-2724
Sung Bae Park: 0000-0002-4652-3056
Bong Ju Moon: 0000-0003-1681-9734
Miyoung Choi: 0000-0002-2424-9965
Sung Uk Kuh: 0000-0003-2566-3209
Jongtae Kim: 0000-0002-4906-0560

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