JAMDA 19 (2018) 384–390

JAMDA

journal homepage: www.jamda.com

Review Article

Can Bisphosphonates Prevent Recurrent Fragility Fractures? A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Sang Yoon Lee MD, PhD [a,b], Se Hee Jung MD, PhD [a], Shi-Uk Lee MD, PhD [a,c], Yong-Chan Ha MD, PhD [d], Jae-Young Lim MD, PhD [c,e,*]

[a] Department of Rehabilitation Medicine, Seoul National University Boramae Medical Center, Seoul, Republic of Korea
[b] Seoul National University Institute on Aging, Seoul, Republic of Korea
[c] Department of Rehabilitation Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea
[d] Department of Orthopedic Surgery, Chung-Ang University College of Medicine, Seoul, Republic of Korea
[e] Department of Rehabilitation Medicine, Seoul National University Bundang Hospital, Seongnam-si, Gyeonggi-do, Republic of Korea

Keywords:
Bisphosphonates
osteoporotic fractures
secondary prevention
meta-analysis

A B S T R A C T

Objectives: Although a few trials have explored whether bisphosphonates (BPs) prevented recurrent fragility fractures (FFs), little is known about the secondary preventative effects of BPs. Thus, we performed a meta-analysis to examine the effects of BPs on prevention of subsequent fractures, mortality, and on bone metabolic and functional parameters related to FF. We compared BP and control groups.
Design: A meta-analysis of randomized controlled trials was conducted.
Setting and Participants: Twelve randomized controlled trials that included 5670 participants investigating the effects of BPs following FF were retrieved from PubMed, Embase, and the Cochrane Library.
Measures: We performed a pairwise meta-analysis using fixed- and random-effects models.
Results: BPs exhibited significant secondary preventative effects after FF compared with controls [overall standardized mean difference = 0.766; 95% confidence interval (CI) 0.493–1.038; $P < .001$]. The risks of subsequent fracture (odds ratio = 0.499; 95% CI 0.418–0.596; $P < .001$) and mortality (odds ratio = 0.662; 95% CI 0.511–0.858; $P = .002$) decreased in the BP groups. Bone mineral density, bone turnover marker levels, pain at the fracture site, and health-related quality of life also differed significantly between the groups.
Conclusions/Implications: Our meta-analysis revealed that BPs administered after FF potentially prevented subsequent fractures and reduced mortality. Positive effects in terms of pain, quality of life, and increased bone mineral density and bone metabolism were also verified regardless of the fracture sites and the administration types (oral or intravenous). Therefore, more active BPs use is recommended to prevent recurrent fragility fractures.
Level of Evidence: Level I, meta-analysis.

A fragility fracture (FF) is a fracture that occurs after minimal trauma, such as a fall from a standing height or less, or without any identifiable trauma.[1,2] Typical FFs in patients with osteoporosis include those of the proximal femur (hip), vertebral body (spine), and distal forearm (wrist).[3] As hip and vertebral fractures are associated with particularly high levels of morbidity and mortality,[4] FFs consume extensive healthcare resources associated with high medical costs.[5] Furthermore, an FF per se is an important risk factor for recurrent fracture.[6] One meta-analysis found that patients with a history of fracture were at 1.83–2.03 times increased risk of subsequent fractures.[7] Therefore, it is essential to prevent re-fracture.

Of the several therapeutic options, pharmacotherapy for osteoporosis with bisphosphonates (BPs) is one of the most popular and well-investigated treatments. One large cohort study including 31,069 participants with FFs found that anti-osteoporotic therapy was associated with a 40% decrease in the 3-year risk of subsequent

This research was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HC15C1189).
The authors declare no conflicts of interest.
* Address correspondence to Jae-Young Lim, MD, PhD, Department of Rehabilitation Medicine, Seoul National University Bundang Hospital, 82 Gumi-ro 173 Beon-gil, Bundang-gu, Seongnam-si, Gyeonggi-do 13620, Republic of Korea.
E-mail address: drlim1@snu.ac.kr (J.-Y. Lim).

https://doi.org/10.1016/j.jamda.2018.02.005
1525-8610/

fracture.[8] Interestingly, 1 nationwide study showed that re-fracture risk was associated with BP therapy compliance.[9]

Only a few randomized controlled trials (RCTs) have explored whether BPs prevented recurrent FF, and little is known about the secondary preventative effects. In this meta-analysis, we explored whether BPs (compared with placebos) prevented subsequent fracture and reduced mortality (primary outcomes) and whether they improved metabolic and functional parameters associated with FFs (secondary outcomes). We hypothesized that subjects taking BPs after FFs would fare better.

Methods

Search Methods for Identifying Studies

The meta-analysis was conducted in line with the updated Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) guidelines.[10] PubMed-Medline, Embase, and Cochrane Library searches were performed in September 2017 using the following key terms: (Spinal Fractures OR Vertebral Fracture OR Compression Fracture OR Hip Fractures OR Femoral Neck Fractures OR Femur Intertrochanteric Fracture OR Colles Fracture OR Radius Fracture OR Fragility Fracture OR Osteoporotic Fractures) AND (Bisphosphonates OR Diphosphonates OR Alendronate OR Clodronic Acid OR Etidronic Acid OR Risedronate OR Pamidronate OR Ibandronate OR Zoledronic Acid OR Antiresorptive Agents) AND (Refracture OR Subsequent Fracture OR Second Fracture OR Second Contralateral Fracture OR Recurrent Fracture OR Mortality OR Bone Mineral Density OR Bone Turnover OR Bone Metabolism OR Bone Remodeling OR Bone Regeneration OR Bone Resorption). An overview of the search strategy is presented in Supplementary Appendix A. We included all RCTs comparing BPs and placebos after FFs. We imposed no language restriction.

Study Selection Criteria

The identified records were saved to EndNote software (X7.2; Thomson Reuters). Two independent reviewers (SYL, JYL) first screened all titles and abstracts to identify relevant investigations. Inclusion criteria were (1) articles reporting an RCT that (2) described the effects of BPs after FFs. All types of BPs (alendronate, clodronate, etidronate, risedronate, pamidronate, ibandronate, and zoledronate) were included. All controls received placebos. Concomitant therapies (such as calcium carbonate or vitamin D) were permitted if both the BP and control groups received the therapies. Reviews, basic science articles, comments, letters, and protocols were excluded. When updates of earlier studies were identified, we used only the latest updates.

Outcome Measures and Data Extraction

The primary outcomes of interest were subsequent fracture and mortality after FFs. All new fractures were diagnosed clinically and radiographically. The secondary outcomes were (1) bone mineral density (BMD) measured by dual energy X-ray absorptiometry at and around the fracture site; (2) the levels of bone turnover markers (serum levels of ionized calcium, parathyroid hormone, and N-telopeptide); (3) pain at the fracture site measured using a visual analog or a numerical rating scale; and (4) health-related quality of life. We performed subgroup analyses based on types of BP (oral vs intravenous) and fracture sites (hip vs spine vs wrist). For every eligible study, the following data were extracted and entered into a spreadsheet by the 2 reviewers (SYL, JYL): first author's family name, year of publication, number of patients, mean age at the time of FF, enrolment time, BP type used, treatment duration, follow-up duration, and outcomes.

Quality Assessment and Publication Bias

Two authors (SYL, JYL) independently evaluated study quality using the criteria of the Cochrane Handbook for Systematic Reviews of Interventions.[11] These included (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome data; (5) any incomplete outcome data addressed; (6) selective reporting; and (7) other bias. We assessed publication bias using the Begg funnel plot[12] and the Egger test.[13]

Statistical Analysis

Effect sizes were computed as odds ratios (ORs) for primary outcomes (subsequent fracture and mortality) and standardized mean differences (SMDs)[14] for secondary outcomes (the magnitude of the pretest–posttest difference for each outcome). To derive overall Hedges g-pooled effect sizes, ORs were converted to SMDs. Pooled SMDs were computed separately for the control and treatment groups of each study. Heterogeneity among comparable studies was explored using the χ^2 and I^2 tests. Values of $P > .1$ and $I^2 < 50\%$ were considered statistically significant. As significant heterogeneity was evident among the selected studies ($P < .001$ and $I^2 = 87.5\%$), we used a random-effects model to quantify the pooled effect size of the included studies. BMD ($P < .001$ and $I^2 = 83.4\%$) and bone turnover marker levels ($P = .024$ and $I^2 = 80.3\%$) were also analyzed using a random-effects model. However, we employed a fixed-effects model to analyze the effects on subsequent fracture ($P = .337$ and $I^2 = 11.3\%$), mortality ($P = .252$ and $I^2 = 23.7\%$), pain at the fracture site ($P = .570$ and $I^2 = 0.0\%$), and health-related quality of life ($P = 1.000$ and $I^2 = 0.0\%$). In addition, we performed subgroup analyses by the type of BP (oral and intravenous) and fracture site (hip, wrist, and spine). The Q-test for heterogeneity was used when performing subgroup analyses.[15] All analyses were conducted with the aid of Comprehensive Meta-Analysis software (v 3.3; Biostat, Englewood, NJ). The study did not require institutional review board approval because we did not personally enroll any human participants.

Results

Description of Included Studies

The primary database search yielded 360 records. After duplicates were removed, the titles and abstracts of 149 articles were initially screened, and 24 selected for full-text review. The full texts were read, and 12 met all quality-assessment inclusion criteria.[16–27] The studies selected for final inclusion (or exclusion) are shown in Figure 1, and the characteristics of the included studies are summarized in Table 1. In terms of quantitative analysis, these 12 RCTs (published from 1996 to 2016) fulfilled our inclusion criteria. The studies identified for meta-analysis included 5670 participants. Study sample sizes varied from 32 to 2127 (16–1065 cases and 16–1062 controls). The selected studies included 2857 patients prescribed BPs and 2813 given placebos. Follow-up duration ranged from 1 month to 3 years.

Results after Analysis

BPs significantly prevented secondary FFs [overall Hedges g-pooled SMD = 0.766; 95% confidence interval (CI) 0.493–1.038; $P < .001$] (Figure 2). The risks of subsequent fracture (OR = 0.499; 95% CI 0.418–0.596; $P < .001$) and mortality (OR = .662; 95% CI 0.511–0.858; $P = .002$) after FF were reduced in the BP group. In terms of secondary outcomes, BMD (pooled SMD = 0.809; 95% CI 0.261–1.357; $P = .004$), bone turnover marker levels (pooled SMD = 1.805; 95% CI 0.844–2.766; $P < .001$), pain at the fracture site (pooled SMD = 0.629; 95% CI 0.210–1.048; $P = .004$), and health-

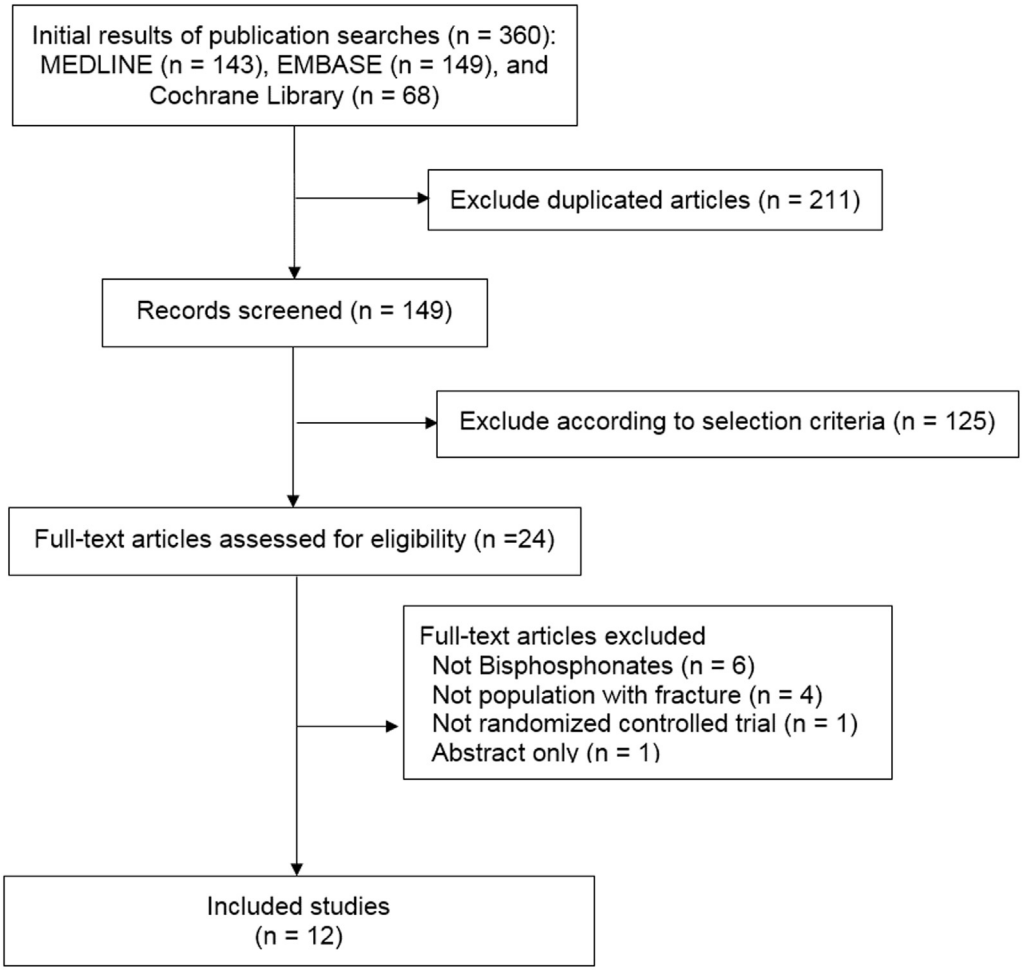

Fig. 1. A preferred reporting items for systematic review and meta-analysis flow diagram detailing the selection of clinical studies.

related quality of life (pooled SMD = 0.804; 95% CI 0.278–1.330; $P = .003$) also exhibited significant between-group differences (Figure 3). Both oral and intravenous BPs prevented re-fracture after FF (pooled SMD = 0.889; 95% CI 0.523–1.255; $P < .001$ and pooled SMD = 0.422; 95% CI 0.036–0.808; $P = .032$, respectively); no among-subgroup difference was apparent ($Q = 1.258$ and $P = .262$). BPs effectively reduced hip (pooled SMD = 0.851; 95% CI 0.385–1.317; $P < .001$), wrist (pooled SMD = 1.085; 95% CI 0.558–1.612; $P < .001$),

Table 1
Characteristics of Included Individual Studies

Study	Study Period	Region	Type of Bisphosphonate, Route	Joint	Participant Sex	Participant Age Range or Mean ± SE (y)	Administration Duration	Follow-Up Period	No. of Participants		Outcomes
									Intervention	Control	
Black 1996	-	USA	Alendronate, oral	Spine	F	55–81	36 mo	36 mo	1022	1005	New vertebral fractures
Adolphson 2000	-	Sweden	Clodronate, oral	Wrist	F	50–76	2 mo	12 mo	16	16	BMD
Clement 2000	-	Netherlands	Alendronate, oral	Wrist	F	66.0 ± 7.4	12 mo	12 mo	18	19	BMD of both forearms
Qiu 2004	1995-1999	China	Alendronate, oral	Hip	M, F	65.8 ± 7.7	12 mo	12 mo	39	38	BMD
Sato 2004	2001-2002	Japan	Etidronate, oral	Hip	F	70–79	1 mo	3 mo	40	40	Bone turnover markers
Armingeat 2006	-	France	Pamidronate, IV	Spine	M, F	75.2 ± 4.5	1 mo	1 mo	16	16	Standing pain
Altintaş 2007	2004	Turkey	Risedronate, oral	Hip	F	75.0	3 mo	3 mo	26	20	N-telopeptide
Lyles 2007	-	International	Zoledronate, IV	Hip	M, F	74.4 ± 9.5	23 mo*	23 mo*	1065	1062	Refracture, mortality, BMD
Cecilla 2009	2004-2005	Spain	Alendronate, oral	Hip	M, F	60–97	12 mo	12 mo	125	114	BMD, bone turnover markers
Beaupre 2011	-	USA	Alendronate or risedronate, oral	Hip	M, F	>75 56%	36 mo	36 mo	101	108	Refracture, mortality
Hagino 2013		Japan	Minodronate, oral	Spine	F	55–80	24 mo	24 mo	359	345	Refracture, bone turnover marker
Li 2016	2011	China	Zoledronate, IV	Hip	M, F	75.0 ± 4.8	12 mo	12 mo	30	30	Pain

IV, intravenous.
*Median value of follow-up period

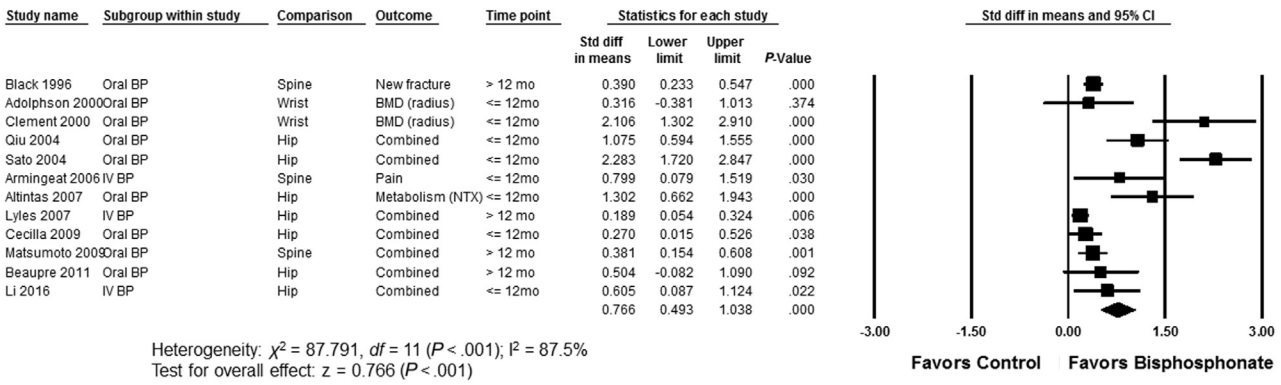

Fig. 2. Forest plot of the overall effect of bisphosphonates in terms of secondary preventative effects after fragility fractures as determined using a random-effects model. Effect sizes are indicated as Hedges g-standardized mean differences with 95% CIs.

and spine (pooled SMD = 0.400; 95% CI 0.273–0.527; $P < .001$) re-fractures; subgroup analysis revealed no difference among the fracture sites ($Q = 1.762$ and $P = .414$) (Figure 4).

Quality Assessment and Publication Bias

In terms of methodological quality, all participants were randomized appropriately, and all investigators and research assistants were blinded to the allocations. However, it is unclear whether the included trials met all quality-assessment criteria (Supplementary Appendix B). A significant publication bias was evident; the Begg funnel plot was asymmetric (Supplementary Appendix C), and the *P* value for bias was .003 (Egger test; all 12 trials). After trimming by imputing missing studies, adding these studies to the analysis, and recomputing the effect size (the trim-and-fill method of Duval and Tweedie),[28] the overall Hedges g-pooled SMD decreased from 0.766 to 0.311. However, the adjusted effect size remained statistically significant (95% CI 0.020–0.601).

Discussion

BPs prevented subsequent fractures of the hip, spine, and wrist, reduced mortality, relieved pain, improved the quality of life, and increased BMD and bone metabolism. Such valuable effects were associated with the use of both oral and intravenous BPs. To the best of our knowledge, this is the first meta-analysis to show that BPs prevent recurrent FF.

Several meta-analyses have suggested that BPs effectively reduce the risk of osteoporotic fracture.[29–31] Therefore, BPs are widely prescribed as first-line drugs in this context. However, the ability of BPs to prevent subsequent fracture has been little studied; no high-quality meta-analysis has appeared. One meta-analysis found that BPs prevented subsequent hip fractures and reduced mortality among elderly patients with such fractures.[32] However, only 4 articles were examined, and bone metabolism and functional outcomes were not considered.

Several reports have compared oral and intravenous forms of BPs. Vis et al[33] suggested that BMD changes in the vertebral spine and total hip were comparable in groups given intravenous pamidronate and oral alendronate for 1 year. One multicenter RCT also found that the efficacy (assessed by BMD change and the levels of bone turnover markers) and safety of intravenous alendronate were similar to those of oral alendronate.[34] However, 1 prospective study including approximately 600 postmenopausal Germans found that intravenous zoledronate afforded a greater and more rapid reduction in N-telopeptide level than did oral alendronate.[35] We found no difference between the preventative effects of oral and intravenous BPs, although oral BPs exhibited higher effect sizes (pooled SMDs = 0.889 and 0.422, respectively). Only 3 papers on intravenous BPs[21,23,27] were included in our review. Also, the study by Lyles et al[23] (which included the largest number of participants) exhibited a relatively small effect size, perhaps reducing the overall effect size. As the primary outcomes of that study were more terminal (subsequent fracture or mortality), the effect size would be smaller than those for changes in BMD or the levels of bone turnover markers. Therefore, it is impossible to directly compare the effects of oral and intravenous BPs on prevention of re-fracture using only the data evaluated in this meta-analysis.

BPs exhibited preventative effects on FF at all 3 sites; no intergroup difference was apparent. However, a recent network meta-analysis reported that zoledronate reduced spine fracture (relative risk 0.30, 95% CI 0.23–0.37) to a greater extent than hip joint fracture (relative risk 0.58, 95% CI 0.41–0.82).[36] The cited study explored primary fracture prevention, thus it is, difficult to compare the data with BP-mediated secondary fracture prevention after FF. In addition, the work of Black et al[16] (which included the largest number of participants) used only confirmed subsequent fracture as the outcome variable; this might have contributed to the lower overall effect size for the spine. Furthermore, the higher effect sizes of studies on the wrist joint[17,18] were associated with bias; only 2 studies with large effect sizes but small samples (n = 32 and 37) were selected. Therefore, the re-fracture preventative effect of BPs for different joints must be compared in further well-designed trials.

The use of BPs during the acute phase after fracture has long been controversial. One animal (rabbit) study suggested that zoledronates did not prevent bone healing and probably inhibited trabecular bone remodeling after fibular osteotomy.[37] Several case studies also reported that BPs given after fracture might delay union of the fractured sites.[38–40] However, 1 meta-analysis of 10 RCTs with 2888 patients concluded that patients treated with BPs exhibited no significant difference in radiologic fracture healing time compared with control patients (mean difference 0.47, 95 % CI −2.75 to 3.69).[41] In addition, BMD increased by 0.79% to 2.8% and N-telopeptide of type I collagen decreased by 48.6% to 49.7% in BP group for 12 months,[41] which were similar to our current meta-analysis.

In this study, there was a definite benefit of bone metabolism by BPs use (effect size 1.805, 95% CI 0.844–2.766) although only 2 studies[20,22] were included in this outcome variable. Altintas et al[22] showed that the mean urine N-telopeptide level decreased by 49.7% at the end of 3 months of treatment with risedronate while it increased by 5.8% in the control group. In the study by Sato et al,[20] there were also positive results in serum ionized calcium, parathyroid hormone, and urinary deoxypyridinoline4321. With the increase of BMD, these positive effects of the bone metabolism may be a key role to decrease the subsequent fracture rate by BPs use.

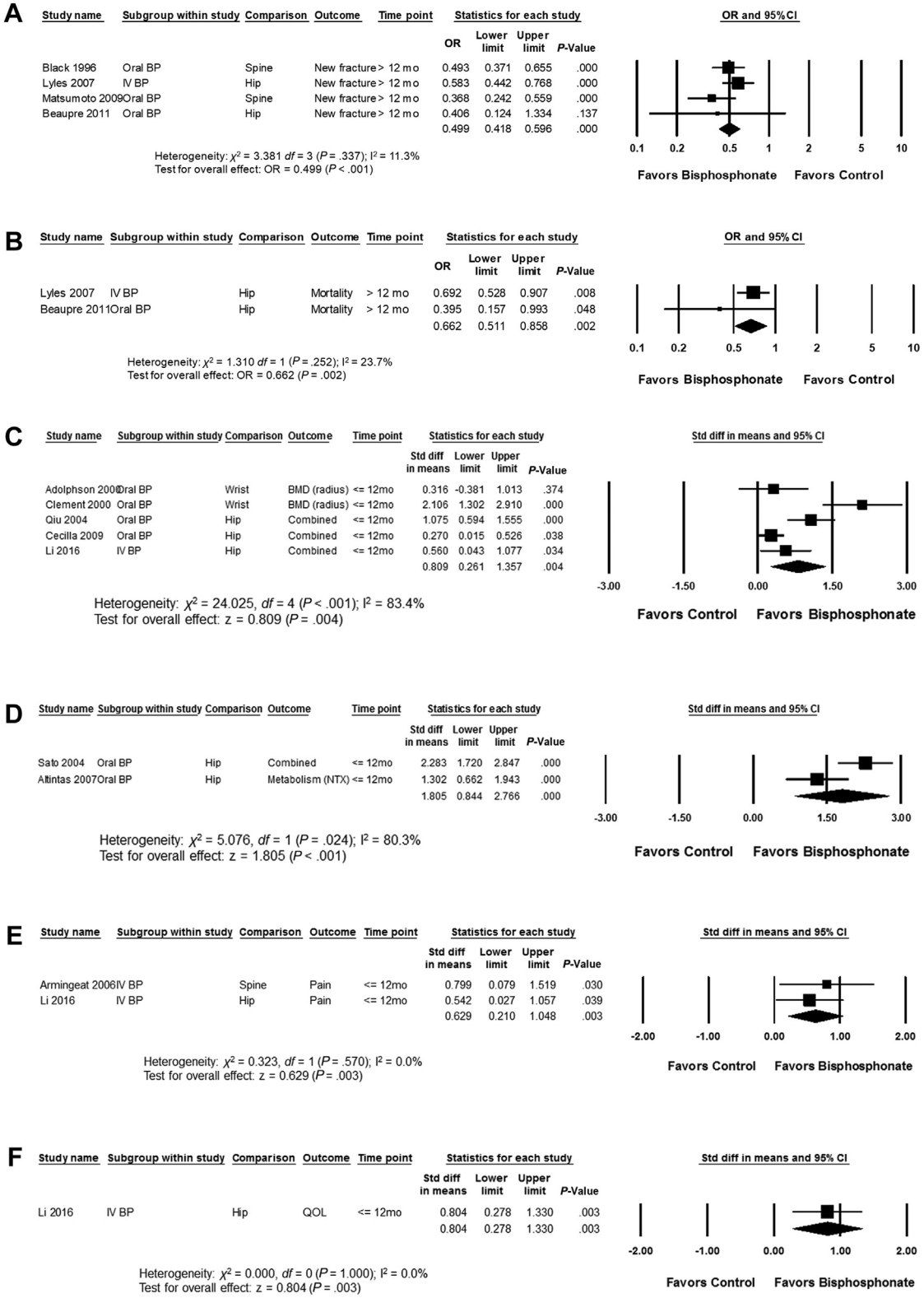

Fig. 3. Forest plots of the trial-level characteristics of bisphosphonates (outcome variables): (A) subsequent fracture, (B) mortality, (C) bone mineral density, (D) bone turnover markers, (E) pain at the fracture site, and (F) health-related quality of life.

This study has certain limitations. First, we included only a small number of reports. Only a few studies evaluated specific BPs and specific fracture sites. To overcome this limitation, we included various types of BPs, several outcomes of fracture, and 3 major fracture sites. However, this increased the heterogeneity of the analysis. Differences in follow-up periods, the duration of BP use after FF, and the outcomes measured are also limitations of our review. Second, we considered the various effect sizes of several outcome variables of

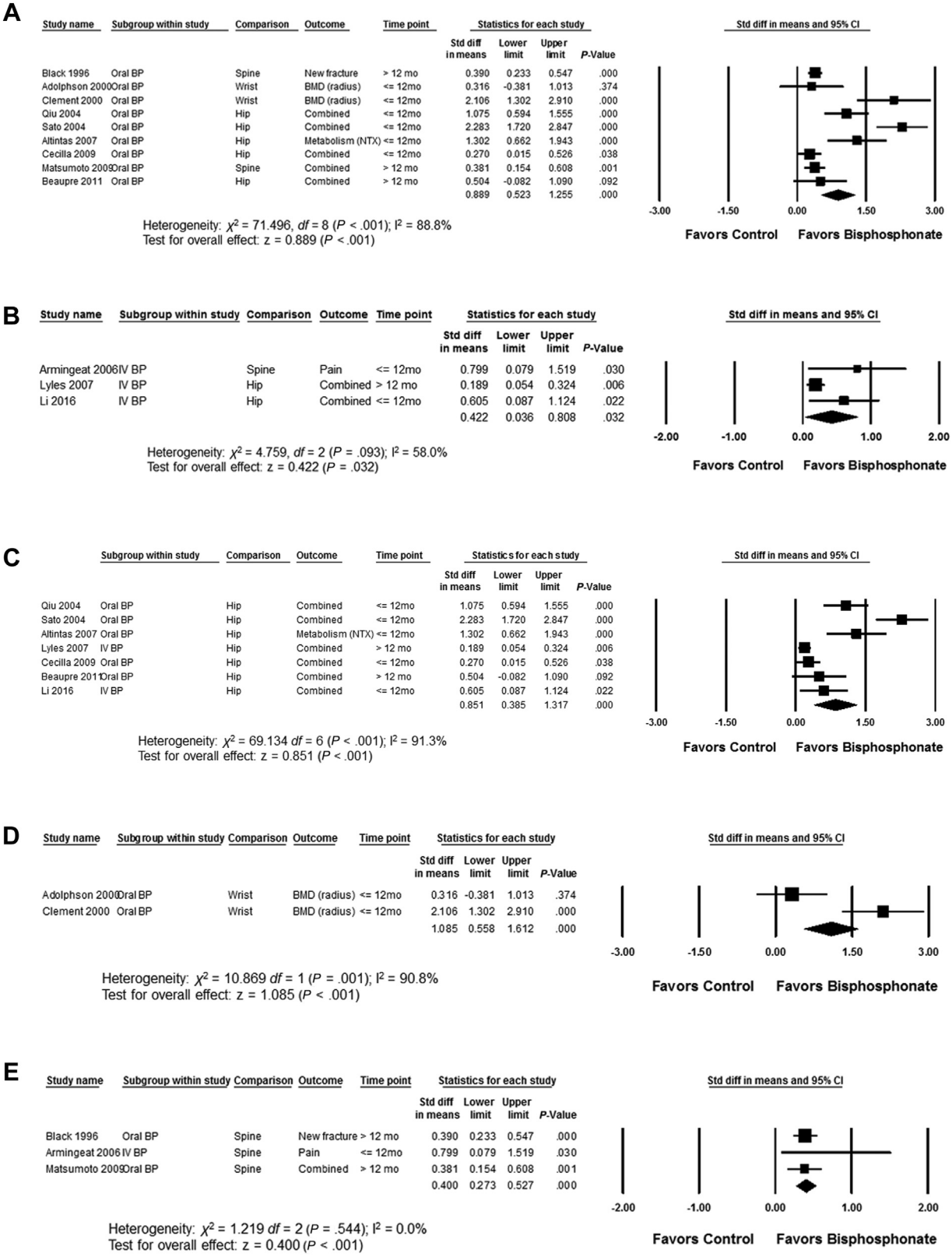

Fig. 4. Forest plots of the subgroup analysis: (A) oral bisphosphonates, (B) intravenous bisphosphonates, (C) hip joint, (D) wrist joint, and (E) spine.

individual studies as pooled effect sizes; these are of limited clinical utility and should be interpreted with caution. As the significance of each outcome variable differs, the absence of weighting is another limitation of this study. Third, we could not investigate the long-term adverse events of BPs use such as atypical femoral fractures and osteonecrosis[42] owing to lack of data from the 12 eligible studies. It is

because these long-term risks of BPs occur when the medication is used for more than 5 years,[43] whereas it was administrated for less than 3 years in the included studies. Because these adverse events of BPs are actually causing to drop the BPs use and hesitate to use them for many physicians despite of several clinical benefits, further studies are needed to compare the advantages and disadvantages of BPs. Finally, a clear publication bias was evident. There was no unpublished report (such as a dissertation) among the final 12 papers, and all but one were written in English.[19] In the studies by Clement et al[18] and Sato et al,[20] the effect sizes were too large; these studies contained only data on BMD[18] or bone turnover markers,[20] which were not the final primary outcomes (ie, not subsequent fracture and mortality). Thus, the relatively strong effect sizes may reflect publication bias. However, after adjustment using the trim-and-fill method of Duval and Tweedie, the effect size, though reduced, remained meaningful (overall pooled SMD 0.766; 95% CI 0.493–1.038, to SMD 0.311; 95% CI 0.020-0.601).

Conclusions/Relevance

The evidence summarized in this review suggests that bisphosphonates prescribed after FF potentially prevent subsequent fractures and reduce mortality. Positive effects on pain and quality of life, as well as an increased BMD and enhanced bone metabolism, were also verified. These positive effects of the drug were significant, regardless of the fracture sites and the administration types (oral or intravenous). Therefore, more active BPs use is recommended to prevent recurrent fragility fracture.

Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jamda.2018.02.005.

References

1. Brown JP, Josse RG. Scientific Advisory Council of the Osteoporosis Society of Canada; 2002 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada. CMAJ 2002;167:S1–S34.
2. Vanasse A, Dagenais P, Niyonsenga T, et al. Bone mineral density measurement and osteoporosis treatment after a fragility fracture in older adults: Regional variation and determinants of use in Quebec. BMC Musculoskeletal Disorders 2005;6:33.
3. Rose SH, Melton LJ III, Morrey BF, et al. Epidemiologic features of humeral fractures. Clin Orthop Relat Res 1982;168:24–30.
4. Cauley JA, Thompson DE, Ensrud KC, et al. Risk of mortality following clinical fractures. Osteoporos Int 2000;11:556–561.
5. Simonelli C, Chen YT, Morancey J, et al. Evaluation and management of osteoporosis following hospitalization for low-impact fracture. J Gen Intern Med 2003;18:17–22.
6. Center JR, Bliuc D, Nguyen TV, Eisman JA. Risk of subsequent fracture after low-trauma fracture in men and women. JAMA 2007;297:387–394.
7. Kanis JA, Johnell O, De Laet C, et al. A meta-analysis of previous fracture and subsequent fracture risk. Bone 2004;35:375–382.
8. Bawa HS, Weick J, Dirschl DR. Anti-osteoporotic therapy after fragility fracture lowers rate of subsequent fracture: Analysis of a large population sample. J Bone Joint Surg Am 2015;97:1555–1562.
9. Soong YK, Tsai KS, Huang HY, et al. Risk of refracture associated with compliance and persistence with bisphosphonate therapy in Taiwan. Osteoporos Int 2013;24:511–521.
10. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: Elaboration and explanation. BMJ 2016;354:i4086.
11. Higgins J, Green S. Cochrane handbook for systematic reviews of interventions. (Version 5.1.0.) 2011.
12. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:1088–1101.
13. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–634.
14. Becker BJ. Synthesizing standardized mean-change measures. Br J Math Stat Psychol 1988;41:257–278.
15. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–560.
16. Black DM, Cummings SR, Karpf DB, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. Lancet 1996;348:1535–1541.
17. Adolphson P, Abbaszadegan H, Boden H, et al. Clodronate increases mineralization of callus after Colles' fracture: A randomized, double-blind, placebo-controlled, prospective trial in 32 patients. Acta Orthop Scand 2000;71:195–200.
18. van der Poest Clement E, Patka P, Vandormael K, et al. The effect of alendronate on bone mass after distal forearm fracture. J Bone Miner Res 2000;15:586–593.
19. Qiu GX, Wu ZH, Shen JX, et al. [Clinic effect of alendronate sodium treatment in osteoporosis patients with hip fracture]. Zhonghua Wai Ke Za Zhi 2004;42:347–350.
20. Sato Y, Kanoko T, Yasuda H, et al. Beneficial effect of etidronate therapy in immobilized hip fracture patients. Am J Phys Med Rehabil 2004;83:298–303.
21. Armingeat T, Brondino R, Pham T, et al. Intravenous pamidronate for pain relief in recent osteoporotic vertebral compression fracture: A randomized double-blind controlled study. Osteoporos Int 2006;17:1659–1665.
22. Altintas F, Ozkut AT, Beyzadeoglu T, et al. The effect of risedronate treatment on bone turnover markers in patients with hip fracture. Acta Orthop Traumatol Turc 2007;41:132–135.
23. Lyles KW, Colon-Emeric CS, Magaziner JS, et al. Zoledronic acid and clinical fractures and mortality after hip fracture. N Engl J Med 2007;357:1799–1809.
24. Cecilia D, Jodar E, Fernandez C, et al. Effect of alendronate in elderly patients after low trauma hip fracture repair. Osteoporos Int 2009;20:903–910.
25. Matsumoto T, Hagino H, Shiraki M, et al. Effect of daily oral minodronate on vertebral fractures in Japanese postmenopausal women with established osteoporosis: A randomized placebo-controlled double-blind study. Osteoporos Int 2009;20:1429–1437.
26. Beaupre LA, Morrish DW, Hanley DA, et al. Oral bisphosphonates are associated with reduced mortality after hip fracture. Osteoporos Int 2011;22:983–991.
27. Li Y, Zhao WB, Wang DL, et al. Treatment of osteoporotic intertrochanteric fractures by zoledronic acid injection combined with proximal femoral nail anti-rotation. Chin J Traumatol 2016;19:259–263.
28. Rostas I, Poto L, Matrai P, et al. In middle-aged and old obese patients, training intervention reduces leptin level: A meta-analysis. PloS One 2017;12:e0182801.
29. Byun JH, Jang S, Lee S, et al. The efficacy of bisphosphonates for prevention of osteoporotic fracture: An update meta-analysis Bone Metab 2017;24:37–49.
30. Zhou J, Ma X, Wang T, Zhai S. Comparative efficacy of bisphosphonates in short-term fracture prevention for primary osteoporosis: A systematic review with network meta-analyses. Osteoporos Int 2016;27:3289–3300.
31. Nayak S, Greenspan SL. Osteoporosis treatment efficacy for men: A systematic review and meta-analysis. J Am Geriatr Soc 2017;65:490–495.
32. Peng J, Liu Y, Chen L, et al. Bisphosphonates can prevent recurrent hip fracture and reduce the mortality in osteoporotic patient with hip fracture: A meta-analysis. Pak J Med Sci 2016;32:499–504.
33. Vis M, Bultink IE, Dijkmans BA, Lems WF. The effect of intravenous pamidronate versus oral alendronate on bone mineral density in patients with osteoporosis. Osteoporos Int 2005;16:1432–1435.
34. Shiraki M, Nakamura T, Fukunaga M, et al. A multicenter randomized double-masked comparative study of different preparations of alendronate in osteoporosis—monthly (four weeks) intravenous versus once weekly oral administrations. Curr Med Res Opin 2012;28:1357–1367.
35. Hadji P, Gamerdinger D, Spieler W, et al. Rapid Onset and Sustained Efficacy (ROSE) study: Results of a randomised, multicentre trial comparing the effect of zoledronic acid or alendronate on bone metabolism in postmenopausal women with low bone mass. Osteoporos Int 2012;23:625–633.
36. Jansen JP, Bergman GJ, Huels J, Olson M. The efficacy of bisphosphonates in the prevention of vertebral, hip, and nonvertebral-nonhip fractures in osteoporosis: A network meta-analysis. Semin Arthritis Rheum 2011;40:275–284.
37. Matos MA, Tannuri U, Guarniero R. The effect of zoledronate during bone healing. J Orthop Traumatol 2010;11:7–12.
38. Grady MK, Watson JT, Cannada LK. Treatment of femoral fracture nonunion after long-term bisphosphonate use. Orthopedics 2012;35:e991–e995.
39. Sheibani-Rad S. Femoral fractures following long-term bisphosphonate use. Orthopedics 2016;39:e1036–e1040.
40. Egol KA, Park JH, Rosenberg ZS, et al. Healing delayed but generally reliable after bisphosphonate-associated complete femur fractures treated with IM nails. Clin Orthop Relat Res 2014;472:2728–2734.
41. Li YT, Cai HF, Zhang ZL. Timing of the initiation of bisphosphonates after surgery for fracture healing: A systematic review and meta-analysis of randomized controlled trials. Osteoporos Int 2015;26:431–441.
42. Diab DL, Watts NB. Bisphosphonate drug holiday: Who, when and how long. Ther Adv Musculoskelet Dis 2013;5:107–111.
43. Watts NB. Long-term risks of bisphosphonate therapy. Arq Bras Endocrinol Metabol 2014;58:523–529.

Supplementary Appendix A

Queries

1. Population
   Spinal Fractures OR vertebral fracture OR Compression Fracture OR Hip fractures OR Femoral Neck Fractures OR Femur Intertrochanteric Fracture OR Colles' Fracture OR radius fracture OR fragility fracture OR Osteoporotic Fractures
2. Intervention
   Bisphosphonates OR Diphosphonates OR Alendronate OR Clodronic Acid OR Etidronic Acid OR Risedronate OR pamidronate OR Ibandronate OR Zoledronic Acid OR Antiresorptive agents
3. Outcomes
   Refracture OR subsequent fracture OR second fracture OR second contralateral fracture OR recurrent fracture OR mortality OR bone mineral density OR bone turnover OR bone metabolism OR Bone Remodeling OR Bone Regeneration OR Bone Resorption
4. Study Design
   RCT

PubMed 20170906 - 180 articles

("Diphosphonates"[MeSH] OR "Diphosphonates"[All Fields] OR "Bisphosphonates"[All Fields] OR "Diphosphonates"[MeSH] OR "Alendronate"[All Fields] OR "Clodronic Acid"[All Fields] OR "Etidronic Acid"[All Fields] OR "Risedronate"[All Fields] OR "pamidronate"[All Fields] OR "Ibandronate"[All Fields] OR "Zoledronic Acid"[All Fields] OR "Antiresorptive agents""[All Fields]) AND ("Spinal Fractures"[MeSH] OR "Spinal Fractures"[All Fields] OR "vertebral fracture"[All Fields] OR "Compression Fracture"[All Fields] OR "Hip Fractures"[MeSH] OR "Hip fractures"[All Fields] OR "Femoral Neck Fractures"[All Fields] OR "Femur Intertrochanteric Fracture"[All Fields] OR "Colles' Fracture"[MeSH] OR "Colles' Fracture"[All Fields] OR "radius fracture"[All Fields] OR "fragility fracture"[All Fields] OR "Osteoporotic Fractures"[All Fields]) AND ("refracture"[All Fields] OR "subsequent fracture"[All Fields] OR "second fracture"[All Fields] OR "second contralateral fracture"[All Fields] OR "recurrent fracture"[All Fields] OR "mortality"[All Fields] OR "bone mineral density"[All Fields] OR "bone turnover"[All Fields] OR "bone metabolism"[All Fields] OR "Bone Remodeling"[All Fields] OR "Bone Regeneration"[All Fields] OR "Bone Resorption") AND "Randomized Controlled Trial"[ptyp]

EMbase 20170906 – 153 articles

('Bisphosphonates'/exp OR 'Bisphosphonates':ab,ti OR 'Diphosphonates'/exp OR 'Diphosphonates':ab,ti OR 'Alendronate'/exp OR 'Alendronate':ab,ti OR 'Clodronic Acid'/exp OR 'Clodronic Acid':ab,ti OR 'Etidronic Acid'/exp OR 'Etidronic Acid':ab,ti OR 'Bisphosphonates'/exp OR 'Bisphosphonates':ab,ti OR 'Risedronate'/exp OR 'Risedronate':ab,ti OR 'Ibandronate'/exp OR 'Ibandronate':ab,ti OR 'Zoledronic Acid'/exp OR 'Zoledronic Acid':ab,ti OR 'Antiresorptive agents'/exp OR 'Antiresorptive agents':ab,ti) AND ('Spinal Fractures'/exp OR 'Spinal Fractures':ab,ti OR 'vertebral fracture'/exp OR 'vertebral fracture':ab,ti OR 'Compression Fracture'/exp OR 'Compression Fracture':ab,ti OR 'Hip fractures'/exp OR 'Hip fractures':ab,ti OR 'Femoral Neck Fractures'/exp OR 'Femoral Neck Fractures':ab,ti OR 'Femur Intertrochanteric Fracture'/exp OR 'Femur Intertrochanteric Fracture':ab,ti OR 'Colles Fracture'/exp OR 'Colles' Fracture':ab,ti OR 'radius fracture'/exp OR 'radius fracture':ab,ti OR 'fragility fracture'/exp OR 'fragility fracture':ab,ti OR 'Osteoporotic Fractures'/exp OR 'Osteoporotic Fractures':ab,ti) AND ('refracture'/exp OR 'refracture':ab,ti OR 'subsequent fracture'/exp OR 'subsequent fracture':ab,ti OR 'second fracture'/exp OR 'second fracture':ab,ti OR 'second contralateral fracture'/exp OR 'second contralateral fracture':ab,ti OR 'recurrent fracture'/exp OR 'recurrent fracture':ab,ti)

Cochrane Library 20170906 – 118 articles

(Bisphosphonates OR Diphosphonates OR Alendronate OR Clodronic Acid OR Etidronic Acid OR Risedronate OR pamidronate OR Ibandronate OR Zoledronic Acid OR Antiresorptive agents) AND (Spinal Fractures OR vertebral fracture OR Compression Fracture OR Hip fractures OR Femoral Neck Fractures OR Femur Intertrochanteric Fracture OR Colles' Fracture OR radius fracture OR fragility fracture OR Osteoporotic Fractures) AND (refracture OR subsequent fracture OR second fracture OR second contralateral fracture OR recurrent fracture OR mortality OR "bone mineral density" OR "bone turnover" OR "bone metabolism" OR "Bone Remodeling" OR "Bone Regeneration" OR "Bone Resorption") AND Randomized Controlled Trial