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Comparison of denosumab vs. bisphosphonates in osteoporosis patients: A meta-analysis of randomized controlled trials

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Background: Among the currently available osteoporosis therapeutics, bisphosphonates and denosumab are widely used. However, it remains uncertain which therapy is more effective.
Objective: To determine whether the use of denosumab increases bone mineral density (BMD) and reduces the risk of fractures more than bisphosphonates in patients with low BMD or osteoporosis.
Data Sources: We searched PubMed, Embase and the Cochrane Library through Nov 2018.
Study Selection: Head-to-head randomized controlled trials comparing denosumab versus bisphosphonates among adult patients with low BMD or osteoporosis.
Data Extraction and Synthesis: Random-effects models were used. We identified 10 eligible trials including 5361 participants. Denosumab increased BMD more than bisphosphonate at 12 months, with a mean difference of 1.42% (95% CI 0.95-1.89%, p<0.001) at lumbar spine, 1.11% (95% CI 0.91-1.30%; p<0.001) at total hip, and 1.00% (95% CI 0.78-1.22%, p<0.001) at femoral neck. At 24 months, the increase difference was 1.74% (95% CI 1.05-2.43%, p<0.001) at lumbar spine, 1.22% (95% CI 0.66-1.77%, p<0.001) at total hip, and 1.19% (95% CI 0.65-1.72%, p<0.001) at femoral neck. There was no difference in fracture endpoint at 12 months, but denosumab had a lower osteoporotic fracture incidence than alendronate at 24 months (RR 0.51, 95% CI 0.27-0.97).

Conclusions: Denosumab improved BMD significantly more than bisphosphonates at the lumbar spine, total hip and femoral neck at 12 and 24 months. There was only one study demonstrating greater osteoporotic fracture reduction using denosumab. Future longitudinal studies with longer follow-up and large sample size are needed to confirm the efficacy difference.

This is a meta-analysis of 10 head-to-head trials comparing of the efficacy of denosumab versus bisphosphonates in patients with low bone mineral density or osteoporosis. .

INTRODUCTION

Osteoporosis is a chronic, progressive skeletal condition characterized by decreased bone mass and microarchitectural deterioration, leading to increased risk of fracture[1]. It is estimated that more than 9.9 million Americans have osteoporosis and an additional 43.1 million have low bone mineral density (BMD) [2]. The annual direct costs of osteoporosis are estimated to reach $25.3 billion by 2025[3].

Among the currently available osteoporosis therapeutics, bisphosphonates and denosumab are the most widely used[1,4]. Bisphosphonates are the most prescribed anti-resorptive agents, which selectively adhere to and remain within bone. When internalized from the bone surface, bisphosphonates inactivate or promote apoptosis of osteoclasts[5]. On the other hand, denosumab is a fully human monoclonal IgG2 antibody that binds to the receptor activator of nuclear factor-κB ligand (RANKL) with high specificity and affinity. Denosumab impairs the development, activation, and survival of osteoclasts, thus inhibiting bone resorption[6]. Due to their different mechanisms of action, bisphosphonates typically provide persistent antiresorptive effect after discontinuation, while the effect of denosumab on bone turnover are quickly reversible with discontinuation, leading to a transient rebound phenomenon[7]. Previous phase III clinical trials found both drugs increased BMD and reduced the risk of fracture compared to placebo[8–12]. However, the relative efficacy of bisphosphonates or denosumab remain uncertain [13,14].

Five meta-analyses have compared denosumab and bisphosphonates in osteoporosis [13–17] and while current evidence suggests denosumab might increase BMD and reduce fracture risk more than bisphosphonates, these results are not conclusive. Two of these studies adopted a network meta-analysis design and reported the indirect treatment comparison of denosumab and bisphosphonates[14,16]. The other three meta-analyses included only head-to-head trials[13,15,17] and gave results of direct comparisons. However, several key issues remain unresolved. First, results from indirect comparison and direct comparison are inconsistent[16,17], which deserves further clarification. Second, the efficacy comparison of BMD increase and fracture risk reduction were not well reported at 24 months. Third, current direct comparison meta-analyses did not include all key studies and requires an update[15,17]. Since 2014, five more pivotal head-to-head trials have been published. We performed a direct comparison of denosumab and bisphosphonate efficacy, incorporating these recent studies.

This meta-analysis of head-to-head randomized control trials (RCTs) aims to determine whether denosumab is more effective than bisphosphonates in increasing bone mass and reducing fracture risk in patients with low bone mineral density or osteoporosis.

MATERIALS AND METHODS

The current meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[18,19]. This study did not require ethical approval as there was no human or animal experiment.

Study inclusion and exclusion criteria

Studies included in this meta-analysis were required to meet the following inclusion criteria: (1) study design: RCT with a duration of at least 12 months; (2) study subjects: adult patients diagnosed with osteoporosis (T-score at or below −2.5) or low bone mineral density (T-score between −1.0 and −2.5) receiving the study intervention[1]; (3) study intervention: denosumab 60 mg subcutaneously every 6 months for at least 12 months (intervention group), or bisphosphonate treatment (comparator group), including alendronate (35 or 70 mg once weekly), ibandronate (150 mg once monthly), risedronate (150 mg once monthly) or zoledronic acid (5 mg infusion once yearly); and (4) the outcome measurement included the mean percentage change in BMD measured by dual-energy X-ray absorptiometry (DXA) of lumbar spine, total hip or femoral neck. Trials were excluded if (1) the study population included cancer patients or glucocorticoid-induced osteoporosis patients; (2) the same RCT was re-analyzed (i.e. we only included the most complete data of each trial once); (3) subjects were not randomly allocated to treatments; and (4) studies published as abstracts, reviews articles, editorials and letters.

Information sources and search strategy

We systematically searched PubMed, Embase and the Cochrane Library from Jan 1, 1980 until November 8, 2018 with no language restrictions. Additionally, relevant studies were obtained by searching references of articles identified in the initial searches, relevant meta-analyses and systematic reviews. The literature search was performed independently by two authors (HL, BJ). Search strategies were developed using text words as well as medical subject headings (MeSH) associated with terms relevant to “osteoporosis”, “denosumab”, “bisphosphonate” together with “randomized controlled trial”. The full search strategies used in PubMed, Embase and Cochrane Library are provided here.[20]

Study selection

Our search records were imported into ENDNOTE X8 reference management software (Clarivate Analytics, Philadelphia, PA), and two authors (HL, BJ) independently reviewed the titles and abstracts of the literature searches. Trials that did not meet the eligibility criteria were excluded. After excluding the duplicated and irrelevant articles, the full text of the remaining studies was reviewed to ascertain whether they should be included by the eligibility criteria. After completion, both authors met and reviewed their selections for agreement. Any disagreements were resolved by discussion or by seeking an independent third author (CX).

Data collection process

The available information and outcomes of all the eligible studies were independently extracted by two researchers (HL, BJ). The retained data included study characteristics, participant characteristics, type of intervention (type, dose, duration). If data was presented in figures, the GetData software was used to extract data from the figures (http://getdata-graph-digitizer.com/index.php). Mean and SD/standard error/confidence interval (CI) of percentage changes of BMD were extracted for calculation. Disagreements were resolved through discussion.

Outcomes

The primary outcomes were the mean percentage change in BMD (%) at lumbar spine, total hip and femoral neck at 12 months. The secondary outcomes were: (1) mean percentage change in BMD (%) at lumbar spine, total hip and femoral neck at 24 months; (2) overall incidence of vertebral fractures and overall incidence of non-vertebral fractures at 12 and 24 months; (2) total adverse events, severe adverse events and selected adverse events of interest (severe infection, malignancy, death, adverse events leading to withdrawal, gastrointestinal disorders and eczema) at 12 months.

Subgroup and sensitivity analyses

Both a priori specified and exploratory subgroup analyses were performed to examine potential sources of heterogeneity and explore the reasons of inconsistent results between indirect and direct meta-analysis. First, a priori specified subgroup analysis was performed by grouping studies into those including alendronate vs. those including any other bisphosphonates. Second, exploratory subgroup analysis was performed by grouping studies into those including patients who previously received bisphosphonate therapy vs. those including patients who did not receive bisphosphonate therapy. And third, we exploratorily assessed the route of bisphosphonate administration (oral vs. intravenous). Two additional sensitivity analyses for the primary outcomes were performed to examine the heterogeneity (1) by omitting 2 small sample size trials from the overall analysis and (2) by omitting 5 trials in osteopenic populations.

Risk of bias assessment

Two authors (HL, BJ) independently assessed the risk of bias using the Cochrane risk-of-bias tool[21]. This tool assessed bias across the following seven domains: (1) random-sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessment; (5) incomplete outcome data; (6) selective reporting; and (7) other bias. Each domain was determined as 'low risk', 'unclear risk' or 'high risk'. For the first four domains, if the trial clearly reported adequate methods, it was regarded as a low risk of bias. However, if the trial did not clearly report the methods, it was regarded as an unclear risk of bias; if the trial inadequately reported methods, it was regarded as a high risk of bias. For incomplete outcome data, we considered ≥20% loss to follow-up to represent a high risk of bias. For the selective reporting, we assessed it by comparing each publication with its corresponding published protocol, when available. For other sources of bias, we considered major imbalances in key baseline characteristics to represent a high risk of bias. Any disagreements were resolved through discussion, adjudicated by another reviewer (CX) if necessary.

Statistical analysis

We used random effects model to calculate pooled estimates, as heterogeneity was anticipated[22]. For continuous variables (percentage changes in BMD), weighted mean difference and 95% CIs were calculated. For dichotomous variables (fracture and adverse events), risk ratio (RR) and 95% CIs were calculated. To assess the heterogeneity of the results from individual studies, Cochran's Q statistic, the I^2 statistic (I^2 >50% was regarded as substantial heterogeneity) and P values (P <0.10 was considered as substantial heterogeneity) were used[23]. The preplanned subgroup and sensitivity analyses were performed to examine the sources of heterogeneity. Publication bias was assessed visually with a funnel plot and Egger's weighted regression statistic with a P value <0.05 indicating significant publication bias. The meta-analysis was analyzed using the statistical environment R-3.4.3 (https://cran.r-project.org) with the "meta" and "metafor" packages[24]. All the tests were two-tailed and a P value of <0.05 was deemed statistically significant.

RESULTS

Search results

A total of 523 articles were obtained through electronic and manual searches. After 55 duplicates were removed, the titles and abstracts of 468 records were reviewed. Of the 468 records reviewed, 433 records were excluded for not meeting the inclusion criteria, and thus the remaining 35 articles were retrieved for further assessment. Twenty-five trials were excluded for not being head-to-head trials or follow-up reports of same trial. Ten trials[9,25–31] fulfilled criteria and were included in the meta-analysis (Figure 1).

Characteristics of included trials

The main characteristics of the included trials were summarized in Table 1. These trials were published from 2006 to 2018 and involved a total of 5361 patients, with the sample size ranging from 64 to 1189. Mean age ranged from 63 to 78 and 99.0% were females. One thousand five hundred and thirty-three patients (28.6%; 3 studies) had no prior osteoporosis treatment, 714 patients (13.3%; 1 study) had previous fractures, 2914 patients (54.3%, 5 studies) received bisphosphonate treatment before the study and 200 patients (3.7%, 1 study) received teriparatide before the study. The bisphosphonates included alendronate, ibandronate, risedronate and zoledronic acid. The doses of bisphosphonates were equivalent to alendronate 70 mg once weekly for oral bisphosphonate and 5 mg infusion once yearly zoledronic acid for intravenous bisphosphonate, except one study which used 35 mg once weekly alendronate (9.4%, 242 of 2562) [28], the study duration was 12 months for 8 trials and 24 months for 2 trial. Six of the ten studies compared the efficacy of denosumab and alendronate, 2 studies zoledronic acid, and 1 study ibandronate and risedronate. All studies reported concomitant administration of daily oral calcium and vitamin D supplements.

Risk of bias assessment

Risk of bias was assessed with the Cochrane risk-of-bias tool[32]. Two trials did not clearly report the random sequence generation[29,31]. Three trials [28–30]did not clearly report the allocation concealment. Five trials used an open-label design[27,29,30,33,34]. Blinding of outcome assessment was inadequately reported in only 3 trials[27,30,33]. There was a low risk of attrition bias, reporting bias, and other biases in all trials except for one that had a high risk of selective reporting[30]. Two studies had a relatively small sample size (64 and 94) [9,30].

Primary analysis: mean percentage change in BMD at lumbar spine, total hip and femoral neck at 12 months

The primary analysis involved ten trials with a total of 5254 patients. Compared to bisphosphonates, the incremental 12-month increase in BMD with denosumab was greater by 1.42% (95% CI 0.95%-1.89%, p<0.001) at lumbar spine, 1.11% (95% CI 0.91%-1.30%; p<0.001) at total hip, and 1.00% (95% CI 0.78%-1.22%, p<0.0001) at femoral neck (Figure 2). Cumulative meta-analysis[35] showed that more BMD improvement with denosumab became evident in 2010, when 1769 patients had been randomized. At the end of 2010, the mean difference in BMD improvement was 1.05% (95% CI 0.66%-1.44%) at lumbar spine, 0.92% (95% CI 0.70%-1.15%) at total hip and 0.68% (95% CI 0.34%-1.01%) at femoral neck. Subsequent trials brought the number of patients to 5254, resulting in a slightly higher point estimate at the above 3 sites.

Sensitivity analyses

After removing five studies in osteopenic population, the mean BMD increase difference was 1.47% (95%CI, 0.97% to 1.96%) at lumbar spine, 1.04% (95%CI, 0.85% to 1.12%) at total hip and 0.97% (95%CI, 0.73% to 1.15%) at femoral neck. After removing the two small trials[9,30], the mean difference increased from 1.42% (95% CI 0.95%-1.89%, p<0.001) to 1.62% (95%CI, 1.14% to 2.09%) at lumbar spine[36]. In addition, mean difference at total hip and femoral neck also increased. After excluding one study including 5% men[28], results were consistent with the primary analysis.

Subgroup analysis

Subgroup analyses were performed based on the specific bisphosphonate and pretreatment status. The results showed that denosumab improved BMD more than each of the three oral bisphosphonates (alendronate, ibandronate and risedronate) at lumbar spine, total hip and femoral neck. However, compared to zoledronic acid, denosumab only showed significant superiority in total hip and femoral neck BMD improvement[37].

Subgroup analysis stratified by prior treatment status: (previously treated with bisphosphonate or not). In patients who did not previously receive bisphosphonate treatment, denosumab increases lumbar spine BMD more than bisphosphonates (mean difference, 0.83%; 95% CI 0.27% to 1.39%; p<0.001). In patients who received previous bisphosphonate treatment, denosumab still resulted in greater lumbar spine BMD improvement than bisphosphonates (mean difference, 1.75%; 95% CI, 1.28% to 2.23%; p<0.001). There was a significant interaction between the subgroups of different bisphosphonate pretreatment status in lumbar spine BMD improvement (previously treated with bisphosphonates 1.75% vs. previously not treated 0.83%, p for interaction=0.014). Similar results were found at total hip (previously bisphosphonates treated 1.22% vs. previously not treated 0.93%, p for interaction=0.089) and femoral neck (previously bisphosphonates treated 1.20% vs. previously not treated 0.83%, p for interaction=0.069), but subgroup difference was not significant (Figure 3).

Another subgroup analyses were performed based on alendronate or non-alendronate bisphosphonates. The BMD increase difference was 1.91% (95% CI 1.36%-2.47%, p<0.001) at lumbar spine for alendronate trials and 1.11% (95% CI 0.63%-1.58%, p<0.001) for non-alendronate bisphosphonate at 12 months, p-value for subgroup difference was 0.031. Similar results could also be seen at two other areas, total hip (subgroup difference p=0.004) and femoral neck (subgroup difference p=0.040)[38].

Subgroup analyses indicated that heterogeneity can be assumed due to two small sample studies (Q=5.37, p=0.021) and the difference in the population characteristics, such as different types of bisphosphonate and pretreatment status.

Secondary outcomes

Two trials (795 patients) reported changes in BMD at 24 months. The pooled results showed at 24 months, BMD increase difference between denosumab and bisphosphonate was 1.74% at spine, 1.22% at total hip, and 1.19% at femoral neck, which was slightly higher than the 12 month BMD increase difference (Figure 4).

Five trials[25,26,29,31,34] (3540 patients) reported fracture data at 12 months and one trial[28] (714 patients) reported fracture data at 24 months. Due to the sparse report of vertebral fractures and non-vertebral fractures, we reported the pooled fracture endpoints, the incidence of any fractures and osteoporotic fractures. Denosumab therapy did not demonstrate significant difference in reducing the risk of any type of fracture (RR 1.32, 95% CI 0.93-1.87) nor osteoporotic fracture (RR 0.92, 95% CI 0.39-2.15) at 12 months (Figure 5). Denosumab therapy showed no significant difference in reducing the risk of any type of fracture (RR 0.81, 95%CI 0.47 to 1.41) at 24 month. However, regarding osteoporotic fracture, denosumab showed better performance than alendronate with RR 0.51 (95%CI 0.27 to 0.97) (Figure 5).

Six trials[25–27,29,31,33] with 4242 patients reported adverse events and severe adverse events at 12 months. Denosumab therapy did not demonstrate a higher adverse events risk (RR 0.99, 95% CI 0.95-1.03) nor severe adverse events risk (RR 1.02, 95% CI 0.79-1.31) than bisphosphonates therapy (Figure 6). Risk of selected adverse events of interest, including severe infection (RR 1.05, 95% CI 0.61-1.80), malignancy (RR 0.99, 95% CI 0.66-1.50), death (RR 0.66, 95% CI 0.16-2.63), adverse events leading to withdrawal (RR 0.62, 95% CI 0.38-1.03), gastrointestinal disorders (RR 0.99, 95% CI 0.75-1.31) and eczema (RR 2.01, 95% CI 0.63-6.42) were also similar for denosumab and bisphosphonates[39].

Publication bias

The publication bias of the primary outcomes was assessed using visual examination of funnel plots [40] and Egger's weighted regression statistic (p=0.671, p=0.863 and p=0.514 for three primary outcomes respectively, mean difference of BMD change at lumbar spine, total

hip and femoral neck) indicated no significant publication bias. Trim-and-Fill results suggested only zero to three missing studies were needed to achieve a symmetrical funnel plot.

DISCUSSION

Main findings

This meta-analysis of head-to-head trials gave evidence of direct comparison between denosumab and bisphosphonates. Our study provides moderately strong evidence[41] that denosumab is more effective in increasing BMD at lumbar spine, total hip and femoral neck than bisphosphonates at 12 and 24 months. However, fracture risk reductions were similar at 12 months. Only one study reported denosumab to have lower osteoporotic fracture incidence than alendronate at 24 months. Safety profiles between denosumab and bisphosphonates were similar.

Clinical meaning

The association between anti-resorptive agents related BMD increase and fracture risk reduction is very important for osteoporosis treatment initiation and monitoring. In our study, the difference in the 12-month BMD increase between denosumab and bisphosphonate was 1.42% at spine, 1.11% at total hip and 1.00% at femoral neck. Although these numbers appear small, such differences would translate into clinically important fracture differences if observed in large enough populations. BMD change, especially hip BMD change, is the most important surrogate for evaluation of therapeutic response[42]. According to a recent meta-analysis using individual patient data from 21 randomized, placebo-controlled osteoporosis trials of > 83,395 subjects showed changes in total hip and femoral neck BMD over two years explained 60%-65% of the treatment-related reduction in fracture risk[42]. More specifically, for patients who received anti-resorptive agents, treatment-related 6% increase of lumbar spine BMD at 1 year was associated with 39% reduction in nonvertebral fracture risk, and 3% increase of hip BMD was associated with 46% reduction in nonvertebral fracture risk[43]. In our study, denosumab and bisphosphonate had different BMD increase profiles. A difference of 1.42% at the lumbar spine may not be associated with clinically significant reduction in fracture risk. However, a difference of 1.11% at total hip BMD and an difference of 1.00% at femoral neck would be expected to yield 15%-21% fracture risk reduction difference at 12 months, and larger number are expected for longer treatment duration (24 months or more).

Comparison with previous studies

Previous indirect comparison, or network meta-analysis by Mandema et al showed that denosumab resulted in greater BMD improvement in lumbar spine and total hip from 12 months to 36 months when compared to alendronate and zoledronic acid[16]. The point estimates of spine BMD improvement difference for denosumab was only 0.4% greater than zoledronic acid, 0.8% greater than alendronate at 12 months. Recent head-to-head meta-analysis by Wu et al reported a pooled estimate of BMD improvement difference 1.55% at lumbar spine, 1.05% at total hip and 1.06% at femoral neck[17]. In our study, we included three more studies and excluded two studies from the same trial, the point estimates of the BMD improvement difference were similar to Wu's study, 1.31% at lumbar spine, 1.11% at total hip and 1.01% at femoral neck. But the inconsistent results between indirect and direct meta-analysis deserve a further clarification. Here we propose a possible explanation from the aspect of denosumab and bisphosphonates mechanisms.

Denosumab increase BMD progressively as long as the treatment is continued[44]. On the other hand, bisphosphonates have persistent but not progressive antiresorptive effect; bisphosphonates increase BMD over the first few years but then plateaus[35]. When

comparing the effect of denosumab and bisphosphonates, prior treatment with bisphosphonates will attenuate the efficacy of subsequent bisphosphonates. This phenomenon may potentially inflate the efficacy difference between denosumab and bisphosphonates as noted in our exploratory subgroup analysis performed by grouping patients with and without prior bisphosphonate therapy. In our current meta-analysis, the point estimates of BMD improvement difference in treatment naïve patients was 0.83% at spine, 0.93% at total hip and 0.83% at femoral neck, which may reflect the true efficacy difference.

In previously bisphosphonate-treated patients, the difference was 1.75% at spine, 1.22% at total hip and 1.20% at femoral neck. The larger efficacy difference in the latter subgroup may help us make clinical decisions regarding the sequential use of osteoporosis medication. In clinical practice, the most commonly used anti-osteoporosis medication are bisphosphonates. When the first bisphosphonate is ineffective (e.g., due to unsatisfactory response or fractures), a different medication should be considered. Results of this study suggest that in patients treated with a prior bisphosphonate switching to denosumab would result in greater increase of BMD than to another bisphosphonate.

Current evidence on the difference in fracture risk reduction between denosumab and bisphosphonates is still limited. A previous network meta-analysis[14] reported that denosumab was more effective than bisphosphonates in preventing new vertebral fractures (RR 0.62; 95%CI 0.44 to 0.87), but not in preventing non-vertebral fracture, hip fracture or wrist fracture. Only one trial reported that denosumab was more effective in preventing osteoporotic fractures than alendronate at 24 months (RR 0.51, 95%CI 0.27 to 0.97)[28]. A recent observational data analysis showed denosumab was associated with a 23% lower risk of vertebral fracture than alendronate (HR 0.77, 95%CI 0.57 to 1.03)[45]. There was only one study demonstrating greater osteoporotic fracture reduction using denosumab. However, future longitudinal studies with longer follow-up and large sample size are needed to confirm the efficacy difference.

Safety profile did not show significant difference between denosumab and bisphosphonates at 12 months. Denosumab does not demonstrate a higher adverse AEs or SAEs than bisphosphonates.

Strengths and limitations

Although several meta-analyses on this topic were published previously, our study has several distinct strengths. First, we incorporated BMD and fracture data at 24 months, and demonstrated better performance using denosumab in reducing osteoporotic fracture at 24 months. Previous published meta-analysis either missed key studies (the study with fracture as endpoint for 2 years and recently published trials) or only focused on 12-month data. Second, all prior meta-analyses overlooked important profiles of the study population, and important subgroup analysis were not performed[15–17], especially prior bisphosphonate treatment status. Our study demonstrated the efficacy difference between denosumab and bisphosphonates in prior bisphosphonate treated patients relative to treatment naïve patients. This result suggested that if the prior use of bisphosphonate was ineffective, switching to denosumab would improve BMD more than switching to another bisphosphonate. However, several limitations should also be noted: (1) There were some methodological limitations in some of the included trials, such as the inadequate concealment of treatment allocation. (2) The quality of evidence for reduced incidence of fracture was only moderate, and only one study reported fracture endpoints at 24 months. (3) There was significant heterogeneity in some outcomes due to the various types of bisphosphonates and patient characteristics. Given these limitations, results of this meta-analysis should be interpreted cautiously.

Implications for future studies

Several knowledge gaps remain regarding the comparative effectiveness of denosumab and bisphosphonates. First, evidence on long-term BMD benefit of denosumab compared to bisphosphonates was very limited. Second, only one study reported the efficacy difference on fracture endpoint between denosumab and bisphosphonates at 2 years; more studies are needed to clarify the fracture risk reduction benefit of denosumab compared to bisphosphonate. Third, whether there would be a response difference to treatment with denosumab between patients previously treated with bisphosphonates and treatment naïve patients also remains unclear. Future studies are needed to fill the above knowledge gaps.

Conclusions

Denosumab significantly improved the BMD at lumbar spine, total hip and femoral neck more than bisphosphonates at 12 and 24 months. There was only one study demonstrating greater osteoporotic fracture reduction using denosumab at 24 months. The better performance of denosumab over bisphosphonates in increasing BMD were found in both treatment-naïve patients and previously bisphosphonate treated patients.

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DISCLOSURE SUMMARY

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Disclosure

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Figure 1 Flow diagram shows the process of literature selection.

Figure 2 Forest plot for the mean difference of BMD changes (%) at lumbar spine, total hip and femoral neck at 12 months.

Figure 3 Forest plot of the BMD changes at three sites at 12 months (subgroup analysis stratified by previous treatment status) at lumbar spine (a), total hip (b) and femoral neck (c).

Figure 4 Forest plot for the mean difference of BMD changes (%) at lumbar spine, total hip and femoral neck at 24 months.

Figure 5 Forest plot of any fracture and osteoporotic fractures at 12 and 24 months. Denosumab therapy did not demonstrate significant difference in reducing the risk of any type of fracture (a), osteoporotic fracture (b) at 12 months nor the risk of any type of fracture at 24 months (c), but denosumab had lower osteoporotic fracture than bisphosphonate (d).

Figure 6 Forest plot of adverse events at 12 months. Risk ratio of any adverse events (a) and severe adverse events (b).

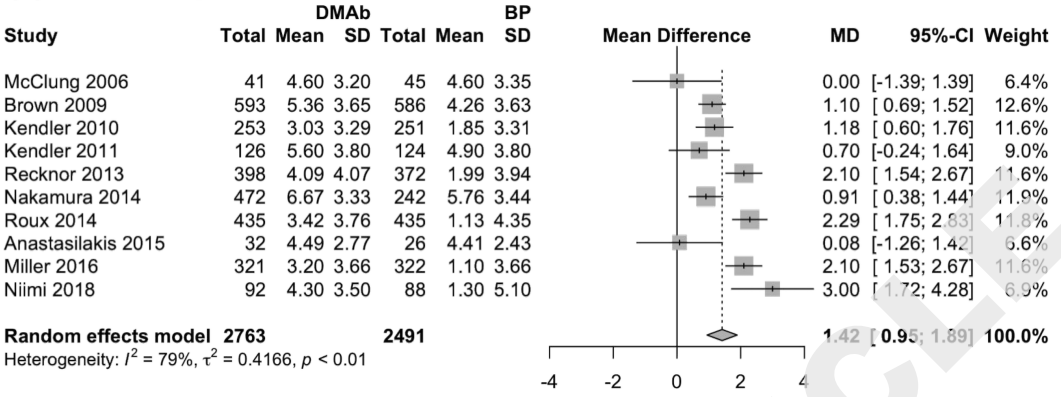
Table 1. Characteristics randomized controlled trials among osteoporosis patients comparing denosumab to bisphosphonates

Included Trials	Treatment status	Basic therapy*	Bisphosphonate type	Denosumab group (60 mg/6 mo)				Bisphosphonate group					Duration (mo)
				N	Age (SD)	BMD TH (SD)#	BMD LS (SD) #	N	Age (SD)	BMD TH (SD) #	BMD LS (SD) #	Dose	
McClung et al, 2006 (United States)	Untreated	1000 mg Ca, 400 IU Vit D	Alendronate	47	63.1 (8.1)	-1.4 (0.8)	-2.2 (0.7)	47	62.8 (8.2)	-2.0 (0.9)	-2.0 (0.9)	70 mg once weekly for 12 mo	12
Kendler et al, 2010 (International)	Bisphosphonate treated	1000 mg Ca, 400 IU Vit D	Alendronate	253	66.9 (7.8)	-1.8 (0.82)	-2.6 (0.75)	251	68.2 (7.7)	-1.8 (0.7)	-2.6 (0.8)	70 mg once weekly for 12 mo	12
Brown et al, 2009 (International)	Untreated	500 mg Ca, 400 or 800 IU Vit D	Alendronate	594	64.1 (8.6)	-1.8 (0.8)	-2.6 (0.8)	595	64.6 (8.3)	−1.7 (0.8)	−2.6 (0.8)	70 mg once weekly for 12 mo	12
Recknor et al, 2013 (International)	Bisphosphonate treated	At least 500 mg Ca, 800 IU Vit D	Ibandronate	417	67.2 (8.1)	-1.8 (0.7)	-2.5 (0.9)	416	66.2 (7.8)	-1.8 (0.7)	-2.5 (0.8)	150 mg once monthly for 12 mo	12
Nakamura et al, 2014 (Japan)[$]	Previous fractures	600 mg or more Ca, 400 IU Vit D	Alendronate	472	69.9 (7.4)	-2.0 (0.8)	-2.8 (0.9)	242	70.2 (7.3)	-2.0 (0.8)	-2.7 (0.9)	35 mg once weekly for 24 mo	24
Roux et al, 2014 (International)	Bisphosphonate treated	At least 1000 mg Ca, 800 IU	Risedronate	435	67.8 (7.0)	−1.6 (0.9)	−2.2 (1.2)	435	67.7 (6.8)	−1.9 (0.7)	−2.3 (1.1)	150 mg once monthly for	12

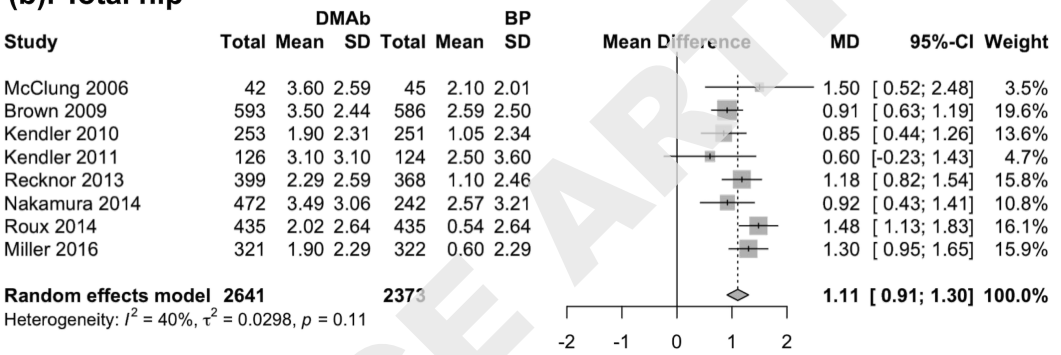
		Vit D										12 mo	
Anastasilakis et al, 2015 (Greece)	Bisphosphonate treated	1000 mg Ca, 800 IU Vit D	Zoledronic acid	34	63.2 (9.6)	-	-1.9 (1.3)	30	63.3 (10.1)	-	-2.18 (0.9)	5 mg infusion once yearly for 12 mo	12
Miller et al, 2016 (International)	Bisphosphonate treated	At least 1000 mg Ca, At least 800 IU Vit D	Zoledronic acid	321	68.5 (7.1)	-1.9 (0.7)	-2.7 (0.8)	322	69.5 (7.7)	-1.9 (0.8)	-2.6 (0.9)	5 mg infusion once yearly for 12 mo	12
Kendler et al, 2011(International)	Untreated	1000 mg Ca, at least 400 IU Vit D	Alendronate	126	65.1 (7.6)	-1.60 (0.74)	-2.04 (1.16)	124	65.3 (7.7)	-1.60 (0.76)	-1.89 (1.13)	70 mg once weekly for 12 mo	12
Niimi et al, 2018 (Japan)$	Teriparatide treated	Active or native Vit D in DMAb arm	Alendronate	100	78.0 (8.0)	-	-1.7 (1.6)	100	78.0 (9.0)	-	-1.7 (1.2)	35 mg once weekly for 12 mo	12

* The doses in basic therapy were given daily, Ca, calcium; Vit D, vitamin D; IU, international unit.
# BMD, Bone mineral density, T-Score were used. TH, total hip; LS, lumbar spine. Mo: months.
$ Nakamura et al's study included both 95% women and 5% men, and Niimi et al's study included 90% women and 10% men, we used the data of the whole population.

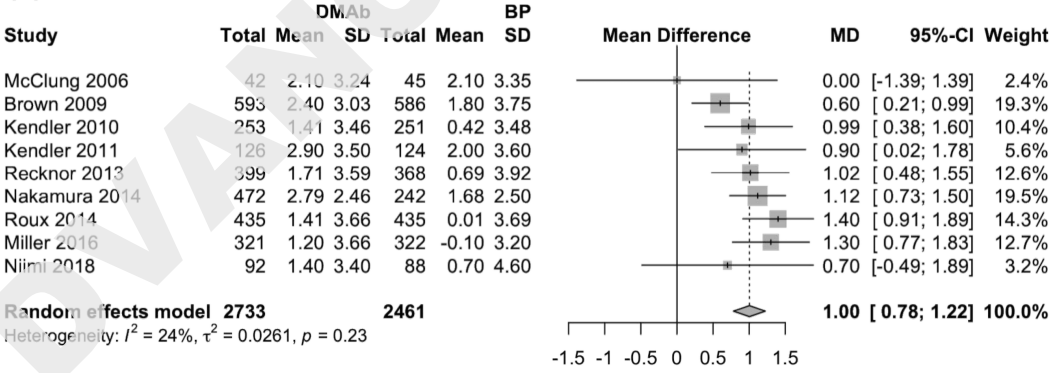
(a). Lumbar spine



(b). Total hip

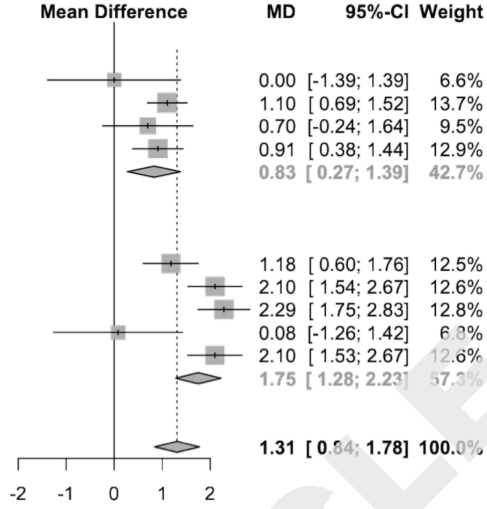


(c). Femoral neck



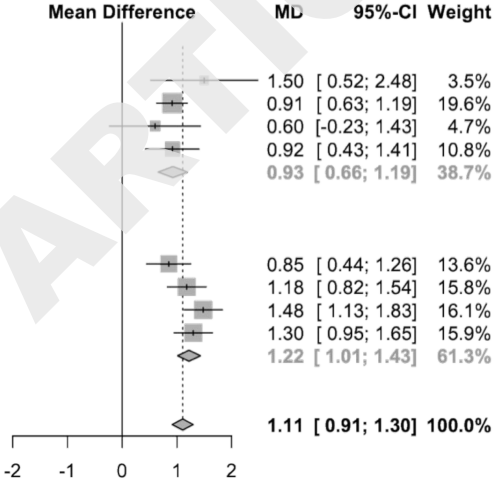
(a). Lumbar spine

Study	DMAb Total	DMAb Mean	DMAb SD	BP Total	BP Mean	BP SD	MD	95%-CI	Weight
Prior BP therapy = No									
McClung 2006	41	4.60	3.20	45	4.60	3.35	0.00	[-1.39; 1.39]	6.6%
Brown 2009	593	5.36	3.65	586	4.26	3.63	1.10	[0.69; 1.52]	13.7%
Kendler 2011	126	5.60	3.80	124	4.90	3.80	0.70	[-0.24; 1.64]	9.5%
Nakamura 2014	472	6.67	3.33	242	5.76	3.44	0.91	[0.38; 1.44]	12.9%
Random effects model	1232			997			0.83	[0.27; 1.39]	42.7%
Heterogeneity: I^2 = 0%, τ^2 = 0.1781, p = 0.45									
Prior BP therapy = Yes									
Kendler 2010	253	3.03	3.29	251	1.85	3.31	1.18	[0.60; 1.76]	12.5%
Recknor 2013	398	4.09	4.07	372	1.99	3.94	2.10	[1.54; 2.67]	12.6%
Roux 2014	435	3.42	3.76	435	1.13	4.35	2.29	[1.75; 2.83]	12.8%
Anastasilakis 2015	32	4.49	2.77	26	4.41	2.43	0.08	[-1.26; 1.42]	6.8%
Miller 2016	321	3.20	3.66	322	1.10	3.66	2.10	[1.53; 2.67]	12.6%
Random effects model	1439			1406			1.75	[1.28; 2.23]	57.3%
Heterogeneity: I^2 = 75%, τ^2 = 0.1781, p < 0.01									
Random effects model	**2671**			**2403**			**1.31**	**[0.84; 1.78]**	**100.0%**
Heterogeneity: I^2 = 79%, τ^2 = 0.3733, p < 0.01									



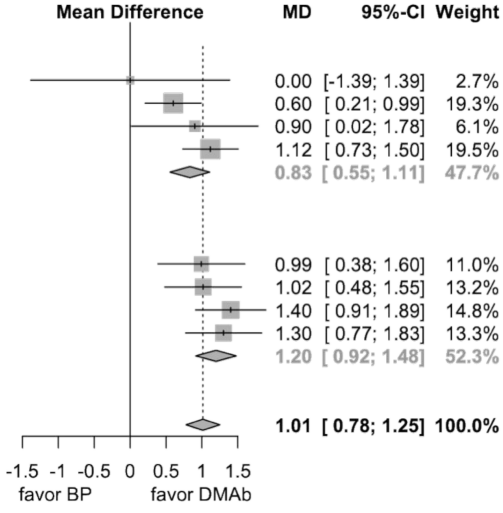
(b). Total hip

Study	DMAb Total	DMAb Mean	DMAb SD	BP Total	BP Mean	BP SD	MD	95%-CI	Weight
Prior BP therapy = No									
McClung 2006	42	3.60	2.59	45	2.10	2.01	1.50	[0.52; 2.48]	3.5%
Brown 2009	593	3.50	2.44	586	2.59	2.50	0.91	[0.63; 1.19]	19.6%
Kendler 2011	126	3.10	3.10	124	2.50	3.60	0.60	[-0.23; 1.43]	4.7%
Nakamura 2014	472	3.49	3.06	242	2.57	3.21	0.92	[0.43; 1.41]	10.8%
Random effects model	1233			997			0.93	[0.66; 1.19]	38.7%
Heterogeneity: I^2 = 0%, τ^2 = 0.0119, p = 0.59									
Prior BP therapy = Yes									
Kendler 2010	253	1.90	2.31	251	1.05	2.34	0.85	[0.44; 1.26]	13.6%
Recknor 2013	399	2.29	2.59	368	1.10	2.46	1.18	[0.82; 1.54]	15.8%
Roux 2014	435	2.02	2.64	435	0.54	2.64	1.48	[1.13; 1.83]	16.1%
Miller 2016	321	1.90	2.29	322	0.60	2.29	1.30	[0.95; 1.65]	15.9%
Random effects model	1408			1376			1.22	[1.01; 1.43]	61.3%
Heterogeneity: I^2 = 46%, τ^2 = 0.0119, p = 0.13									
Random effects model	**2641**			**2373**			**1.11**	**[0.91; 1.30]**	**100.0%**
Heterogeneity: I^2 = 40%, τ^2 = 0.0298, p = 0.11									

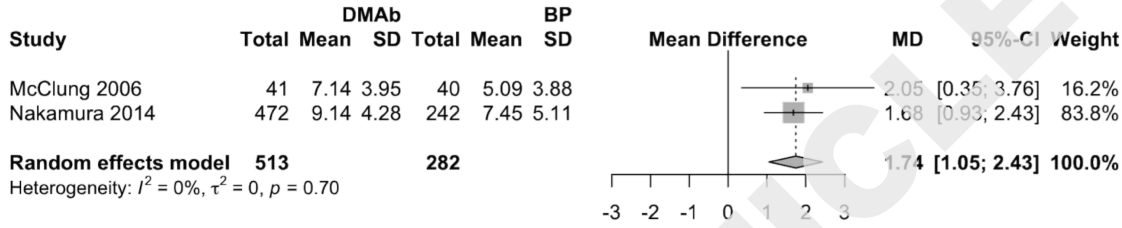


(c). Femoral neck

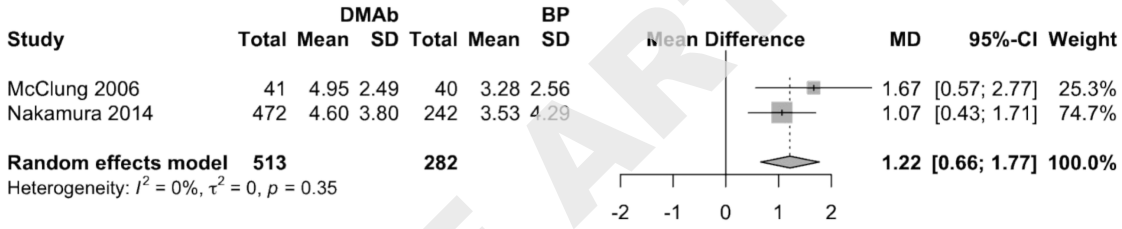
Study	DMAb Total	DMAb Mean	DMAb SD	BP Total	BP Mean	BP SD	MD	95%-CI	Weight
Prior BP therapy = No									
McClung 2006	42	2.10	3.24	45	2.10	3.35	0.00	[-1.39; 1.39]	2.7%
Brown 2009	593	2.40	3.03	586	1.80	3.75	0.60	[0.21; 0.99]	19.3%
Kendler 2011	126	2.90	3.50	124	2.00	3.60	0.90	[0.02; 1.78]	6.1%
Nakamura 2014	472	2.79	2.46	242	1.68	2.50	1.12	[0.73; 1.50]	19.5%
Random effects model	1233			997			0.83	[0.55; 1.11]	47.7%
Heterogeneity: I^2 = 39%, τ^2 = 0.0076, p = 0.18									
Prior BP therapy = Yes									
Kendler 2010	253	1.41	3.46	251	0.42	3.48	0.99	[0.38; 1.60]	11.0%
Recknor 2013	399	1.71	3.59	368	0.69	3.92	1.02	[0.48; 1.55]	13.2%
Roux 2014	435	1.41	3.66	435	0.01	3.69	1.40	[0.91; 1.89]	14.8%
Miller 2016	321	1.20	3.66	322	-0.10	3.20	1.30	[0.77; 1.83]	13.3%
Random effects model	1408			1376			1.20	[0.92; 1.48]	52.3%
Heterogeneity: I^2 = 0%, τ^2 = 0.0076, p = 0.64									
Random effects model	**2641**			**2373**			**1.01**	**[0.78; 1.25]**	**100.0%**
Heterogeneity: I^2 = 32%, τ^2 = 0.0350, p = 0.17									



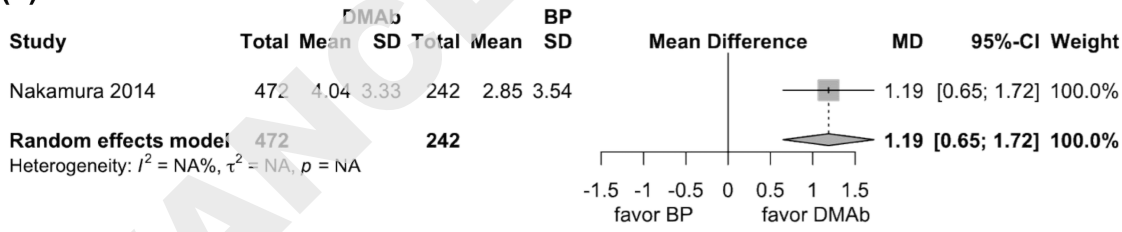
(a). Lumbar spine



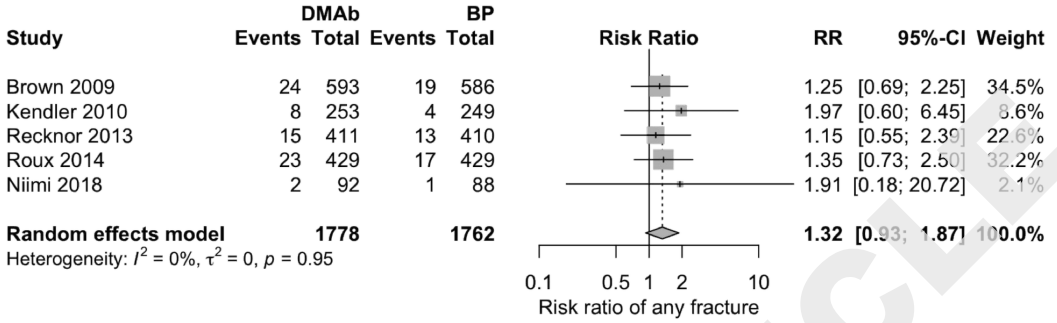
(b). Total hip



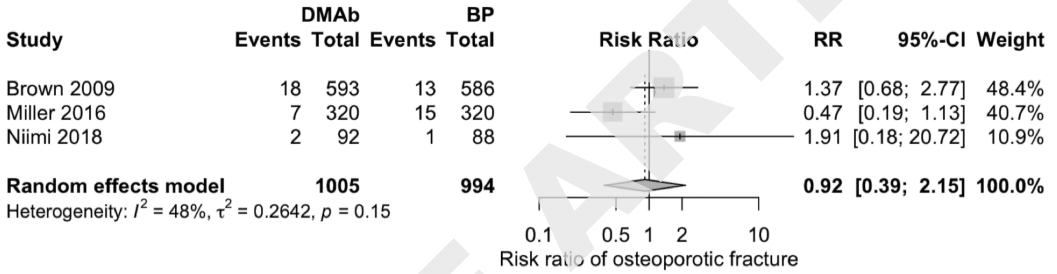
(c). Femoral neck



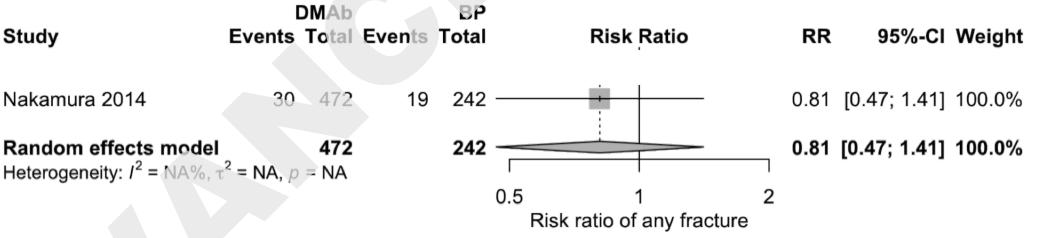
(a). Risk ratio difference of any fracture at 12 months



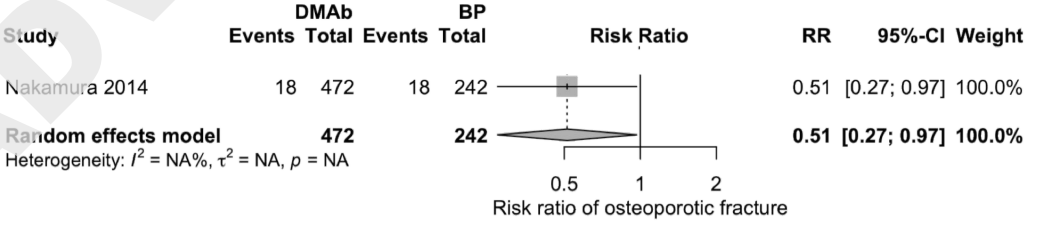
(b). Risk ratio difference of osteoporotic fracture at 12 months



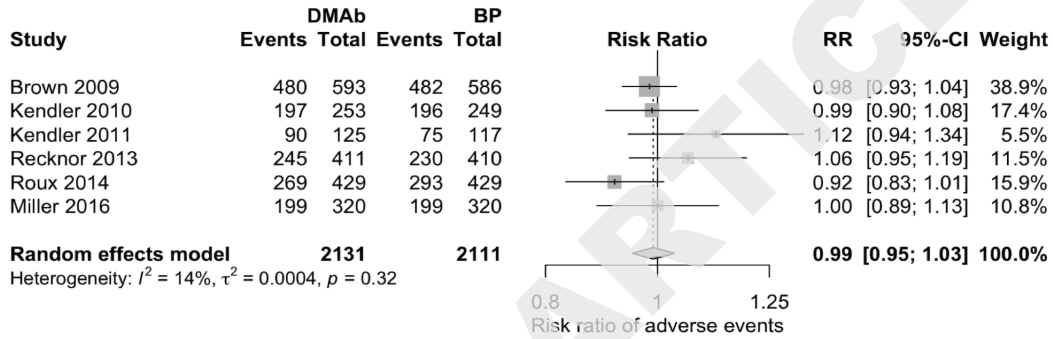
(c). Risk ratio difference of any fracture at 24 months



(d). Risk ratio difference of osteoporotic fracture at 24 months



(a). Risk ratio difference of adverse events



(b). Risk ratio difference of severe adverse events