Safety of Bisphosphonates for Postmenopausal Osteoporosis: An Overview of Systematic Reviews

ABSTRACT

Background Bisphosphonates typically are the first-line therapy for osteoporosis especially postmenopausal osteoporosis, but many reviews exist with conflicting conclusions about the safety of bisphosphonates. We performed an overview of reviews to systematically evaluate the risk of adverse events (AEs) of bisphosphonates used for the treatment of postmenopausal osteoporosis.

Methods We identified systematic reviews with meta-analyses published in English that evaluated the safety of bisphosphonates. Data sources used include the Cochrane library, Pubmed, the Web of Science and hand-searching of reference lists and clinical practice guidelines. The methodological quality of each systematic review was assessed by two reviewers using the assessment of multiple systematic reviews (AMSTAR) tool, and the quality of evidence for key outcomes (all adverse events (all AEs), gastrointestinal events (GI AEs), total cardiovascular events (total CV AEs), atrial fibrillation (AF), serious atrial fibrillation (sAF), stroke, atypical fracture and fracture union) was assessed using the grading of recommendations, assessment, development and evaluation (GRADE) approach.

Results We identified 1,362 potentially relevant citations of which only 16 systematic reviews with meta-analyses met the eligibility criteria. All the included reviews were published between 2009 and 2016, and documented the pooled estimates of effect size [relative risk (RR) or odds ratio (OR)] and their 95% confidence intervals [95% CI] for the incidence of adverse events. The median AMSTAR score was 8 (interquartile range, 7–10). Evidences of the key outcomes were mainly of low or moderate quality.

Conclusions Our overview provides a comprehensive assessment on the safety of bisphosphonates. This overview indicated that bisphosphonates significantly increased the risk of AF, sAF and stroke, but did not significantly increase the risk of atypical fracture or fracture union. It also showed that bisphosphonates could decrease the risk of total adverse CV events, CV death. In despite the vast number of systematic reviews published, high quality research and more complete inclusion criteria are needed.

KEYWORDS bisphosphonates, postmenopausal osteoporosis, safety, overviews of systematic reviews

INTRODUCTION

Osteoporosis is a major public health threat in humans. It affects an enormous number of people, of both sexes and all races, and its prevalence will increase as the population ages. Over 9.9 million Americans have osteoporosis and an additional 43.1 million have low bone density based on data from the National Health and Nutrition Examination Survey III (NHANES III). And fractures are the relevant clinical sequelae of osteoporosis, which will bring a substantial economic burden to society, health care providers, individual patients and their families. Annually, 2 million fractures are attributed to osteoporosis, causing more than 432,000 hospital admissions, almost 2.5 million medical office visits, and about 180,000 nursing home admissions in the USA. Due in part to an aging population, the cost of care is expected to rise to $25.3 billion by 2025. Bisphosphonates agents typically are the first-line therapy for osteoporosis especially postmenopausal osteoporosis, with a vertebral fracture risk reduction of 40–70% and a relative hip fracture risk reduction of 40–50%. However, recent studies have
been reports of several side effects of bisphosphonates, including gastrointestinal adverse event, hypocalcemia, and serious adverse reactions, such as cardiovascular events especially atrial fibrillation.11–13. But there are also evidences which suggest that bisphosphonates may help elderly people reduce cardiovascular incidents by inhibiting atherosclerosis and vascular calcification.14–16. And clinical studies did not find an increased risk of atrial fibrillation in patients taking bisphosphonate therapy.16,17. Consequently, data on the effects of bisphosphonates about the risk of cardiovascular diseases exist with conflicting conclusions. Although an overwhelming volume of knowledge synthesis literature of this theme has been reported, including primarily systematic reviews of randomized controlled trials. Given that existing systematic reviews still have vary in their quality, design and conclusion, and overviews of systematic reviews can provide the best reliable evidence on a subject in one resource18,19; we decided to conduct an overview of systematic reviews to evaluate the risk of adverse events (AEs) with bisphosphonates therapy. It would be finished through summarizing evidence from and assess the quality of published systematic reviews which evaluated the risk of adverse events of bisphosphonates used for the treatment of postmenopausal osteoporosis.

MATERIALS AND METHODS

Data sources and systematic search

A comprehensive literature search of systematic reviews with meta-analyses of randomized controlled trials (RCT) evaluating the safety of bisphosphonates that reported any adverse events as outcomes was performed in the Cochrane library, Pubmed and the Web of Science databases. The original search was conducted on November 19, 2016 and updated on March 5, 2017. Our main search terms consisted of the terms osteoporosis, bisphosphonates, alendronate, ibandronate, etidronate, risedronate and zoledronic acid, adverse effect, safety, adverse events, all AEs, gastrointestinal events (GI AEs), total cardiovascular events (CV AEs), atrial fibrillation (AF), serious atrial fibrillation (sAF), stroke, atypical fracture, fracture union, review, systematic reviews, meta-analyses, in addition to the MeSH term ‘osteoporosis, adverse effect’. And references lists of the appraised systematic reviews or meta-analyses and relevant national clinical guidelines were checked to identify additional relevant reviews.

Study selection

The systematic review, which would be included in this overview, had to meet the following criteria: (1) Be a systematic review with meta-analysis of RCT, which evaluated the risk of any adverse events of bisphosphonates; (2) include patients with postmenopausal osteoporosis; (3) have evaluated bisphosphonate (alendronate, ibandronate, etidronate, zoledronic acid or risedronate) as a single agent or in combination regimens, in comparison with other drugs or placebo; (4) be published in English. Articles were excluded if they were reviews without a clear search strategy, systematic reviews only investigating effectiveness, systematic reviews including patients with secondary osteoporosis, systematic reviews without data on any adverse events or RCTs, observation studies, abstracts, letters, or meeting proceedings.

Two independent reviewers (Lu and Chen) independently screened the titles and abstracts of citations to identify potentially relevant studies. According to the inclusion and exclusion criteria full-text of citations that were potentially relevant were further reviewed. Any disagreements were resolved by consensus or by a third reviewer (Zhong) through discussion.

Data extraction

Two independent reviewers (Lu and Chen) extracted the following information from the eligible systematic reviews by using a standardized form in Microsoft Excel: author, year of publication, number of included RCTs, intervention, comparators, target population, age, sample size, follow-up duration, outcome of any adverse events and methods of analysis used. Discrepancies were resolved by discussion.

Quality assessment

The methodological quality of each systematic review was assessed by using the assessment of multiple systematic reviews (AMSTAR) too20,21. The tool consists of 11 questions that each needs reviewers to answer: ’yes’ (clearly done), ‘can’t answer’ (unclear if completed), ‘no’ (clearly not done) or ‘not applicable’. We calculated a summary score for each of included systematic reviews by awarding each ‘yes’ with one point. An AMSTAR score of 0–4 is considered as low quality, 5–8 as moderate quality, and 9–11 as high quality.22–24. In addition, the quality of evidence for key outcomes (all AEs, GI AEs, total CV AEs, AF, sAF, stroke, atypical fracture and fracture union) was assessed using the grading of recommendations, assessment, development and evaluation (GRADE) approach.25. There were four levels of evidence (high, moderate, low, or very low) for assessing the quality of evidence.

Data analysis

A descriptive analysis was conducted on the included studies. Whereby the characteristics and the methodological quality of the systematic reviews were descriptively summarized using standardized forms. The pooled estimates of effect size (RR or OR) and their 95% confidence intervals [95% CI] were plotted for all outcomes of interest.
RESULTS

Search results

The initial literature search identified a total of 1362 potentially relevant citations which were eligible for inclusion in this overview. After removing duplicates, 646 studies were excluded. By reviewing titles and abstracts, 684 reviews were eliminated. Only 12 articles met the eligibility criteria by screening full-text. In addition, 4 records were identified by checking the references of the included studies. Finally, 16 reviews were included in our overview.

Characteristics of systematic review

The chief characteristics of the 16 systematic reviews with meta-analyses of RCTs included are presented in Table 1. All the included reviews were published between 2009 and 2016, most of which were published after 2012. About 8 of the included reviews consisted of only RCTs, and 8 of the included reviews consisted of only observational studies, 7 other reviews including RCTs and observational studies. Majority of the reviews investigated alendronate (either as a single agent or in combination regimens). But ibandronate and zoledronic acid were also investigated in some reviews. There were multifarious comparators used in the reviews, such as: other anti-osteoporosis drug, parathyroid hormone, non-bisphosphonate care, and/or placebo. All the 23 reviews evaluated one or more adverse effects of bisphosphonates: 3 for total adverse reaction; 3 for gastrointestinal effect which mainly analyzed the incidence of total GI AEs, nausea and esophagitis; 9 for CV AEs containing the incidence and mortality of total CV AEs and AF; 2 for ONJ; 3 for cancer; 3 for atypical fracture and 2 for healing time of fracture. The vast majority of the included reviews had reported the total sample size. However, it should be noted that most of the included reviews did not report the incidence of adverse events or the number of adverse reactions occurred in detail. Only reviews related to CV AEs (9 reviews) reported the explicit incidence of AEs and SAEs. But all of the included reviews documented the pooled estimates of effect size [relative risk (RR) or odds ratio (OR)] and their 95% confidence intervals [95% CI] for the incidence of adverse events (Table 1).

![Flow diagram of literature screening](image-url)
Methodological quality of included reviews

All of the systematic reviews included received an AMSTAR score >6 (high or moderate quality). The median AMSTAR score was 8 (interquartile range, 7–10), with a minimum and maximum AMSTAR score of 6 and 10 respectively. About 9 (56%) received an AMSTAR score >8 (high quality) and 5 (31%) systematic reviews received an AMSTAR score 10. As a whole, the outcomes from included studies were reliable. Detail in every item was shown in Table 2.

ALL AEs

Among the 16 quantitative systematic reviews, there were 3 pooled estimates reported for all AEs, and 5 for discontinued treatment as AEs. Alendronate therapy was more likely to increase all AEs when versus other anti-osteoporosis drug or placebo (evidence of very low to moderate quality). Bisphosphonates treatment slightly increased discontinued treatment as AEs when versus placebo (evidence of low quality). Serrano et al. found that subgroup analyses yielded inconsistent results on discontinued treatment as AEs for alendronate and zoledronate (evidence of low or moderate quality). In addition, Tadrous et al. reported the opposite result that bisphosphonates therapy could decrease the adverse of discontinued treatment as AEs when versus placebo (evidence of low quality). Lee and Song showed ibandronate increased risk of discontinued treatment as AEs when versus alendronate (moderate quality evidence) (Table 3).
Gastrointestinal events

There were 3 pooled estimates reported for GI AEs and 2 reported for discontinued treatment as GI AEs. Lee and Song found that ibandronate increased risk of GI AEs when versus alendronate (moderate quality evidence) and Tadrous et al. reported that alendronate could decrease the adverse of GI AEs when versus zole-
dronate (evidence of low quality). But when compared with placebo alendronate increased risk of GI AEs (low quality evidence) and discontinued treatment as GI AEs (low quality evidence) (Table 3).

CV events

Total adverse CV events was significantly lower in all meta-analyses that assessed bisphosphonates compared with placebo or other anti-osteoporosis drug (evidence of moderate or low quality). Bisphosphonates obviously decreased the risk of CV death in all reviews compared with placebo or other anti-osteoporosis drug (evidence of moderate or low quality). But Kim et al. showed that bisphosphonates therapy in comparison with placebo presented conflicting result (low quality evidence). Moreover, bisphosphonates when compared with placebo or other anti-osteoporosis drug distinctly increased the risk of AF (from low to high quality evidence), sAF (from low to high quality evidence) and the risk of stroke (from low to high quality evidence) (Table 3).

ATYPICAL FRACTURE AND FRACTURE UNION

There was only one systematic review reported the adverse of atypical fracture and bisphosphonates showed a significant increase when comparison with placebo.
Table 3: GRADE evidence profile for bisphosphonates versus comparison.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Authors (year)</th>
<th>Comparisons</th>
<th>Patients (RCT)n</th>
<th>Study event rates, n/N (%)</th>
<th>Pooled effect [95% IC] (P-value)</th>
<th>Heterogeneity I²</th>
<th>Overall Quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>All AEs</td>
<td>Lee and Song (2011)</td>
<td>IBN vs. ALN</td>
<td>5562 (8)</td>
<td>2804/2758 (99.3%)</td>
<td>RR0.99 [0.91–1.07] (0.78)</td>
<td>64.2%</td>
<td>Low&lt;sup&gt;h&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Lin et al. (2012)</td>
<td>ALN vs. OAO</td>
<td>1938 (4)</td>
<td>792/974 (81%)</td>
<td>RR0.91 [0.72–1.15] (0.45)</td>
<td>0%</td>
<td>Moderate&lt;sup&gt;h&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Zhou et al. (2016)</td>
<td>ALN vs. PLB</td>
<td>15192 (9)</td>
<td>7721/7471 (103.4%)</td>
<td>RR1.01 [0.97–1.06] (NA)</td>
<td>NA</td>
<td>Very low&lt;sup&gt;e,f,h&lt;/sup&gt;</td>
</tr>
<tr>
<td>Discontinued treatment</td>
<td>Cranney et al. (2012)</td>
<td>ALN vs. PLB</td>
<td>12855 (9)</td>
<td>7294/5561 (72.3%)</td>
<td>RR1.15 [0.93–1.42] (NA)</td>
<td>NA</td>
<td>Low&lt;sup&gt;h&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Lee and Song (2011)</td>
<td>IBN vs. ALN</td>
<td>5562 (8)</td>
<td>2804/2758 (99.3%)</td>
<td>RR1.05 [0.78–1.38] (0.77)</td>
<td>0%</td>
<td>Moderate&lt;sup&gt;h&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Serrano et al. (2013)</td>
<td>ALN vs. PLB</td>
<td>11422 (14)</td>
<td>418/6517 (6.7%)</td>
<td>RR0.97 [0.85–1.10] (0.61)</td>
<td>0%</td>
<td>Low&lt;sup&gt;e,f&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Zhou et al. (2016)</td>
<td>ZOL vs. PLB</td>
<td>9825 (2)</td>
<td>101/4916 (2.05%)</td>
<td>RR1.15 [0.86–1.52] (0.35)</td>
<td>0%</td>
<td>Moderate&lt;sup&gt;h&lt;/sup&gt;</td>
</tr>
<tr>
<td>GI AEs</td>
<td>Tadrous et al. (2014)</td>
<td>BPs vs. PLB</td>
<td>24-6197 (40)</td>
<td>24-6197/24-6197 (99.9%)</td>
<td>OR0.97 [0.79–1.17] (NA)</td>
<td>NA</td>
<td>Low&lt;sup&gt;e,f,h&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Zhou et al. (2016)</td>
<td>ALN vs. PLB</td>
<td>15192 (9)</td>
<td>7721/7471 (103.4%)</td>
<td>RR1.04 [0.91–1.19] (NA)</td>
<td>NA</td>
<td>Low&lt;sup&gt;h&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Lee and Song (2011)</td>
<td>IBN vs. ALN</td>
<td>5562 (8)</td>
<td>2804/2758 (99.3%)</td>
<td>RR1.06 [0.94–1.20] (0.36)</td>
<td>0%</td>
<td>Moderate&lt;sup&gt;h&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Tadrous et al. (2014)</td>
<td>ALN vs. ZOL</td>
<td>24-6197 (40)</td>
<td>24-6197/24-6197 (99.9%)</td>
<td>OR0.62 [0.39–0.99] (NA)</td>
<td>NA</td>
<td>Low&lt;sup&gt;e,f&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Zhou et al. (2016)</td>
<td>ALN vs. PLB</td>
<td>15192 (9)</td>
<td>7721/7471 (103.4%)</td>
<td>RR1.02 [0.99–1.06] (NA)</td>
<td>NA</td>
<td>Low&lt;sup&gt;e,h&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Zhou et al. (2016)</td>
<td>ALN vs. PLB</td>
<td>15192 (9)</td>
<td>7721/7471 (103.4%)</td>
<td>RR1.23 [0.97–1.56] (NA)</td>
<td>NA</td>
<td>Low&lt;sup&gt;e,h&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Cranney et al. (2012)</td>
<td>ALN vs. PLB</td>
<td>12855 (9)</td>
<td>7294/5561 (72.3%)</td>
<td>RR1.03 [0.81–1.30] (0.83)</td>
<td>NA</td>
<td>Low&lt;sup&gt;h&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
Table 3  GRADE evidence profile for bisphosphonates versus comparison. (Continued)

<table>
<thead>
<tr>
<th>Total adverse CV events</th>
<th>Study (Year)</th>
<th>Comparator</th>
<th>N</th>
<th>N</th>
<th>RR/OR</th>
<th>95% CI</th>
<th>p-Value</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death</td>
<td>Kim et al. (2015)</td>
<td>BPs vs. PLB</td>
<td>9386 (14)</td>
<td>378/5822 (6.5%)</td>
<td>221/3564 (6.2%)</td>
<td>OR0.98 [0.84–1.14] (NA)</td>
<td>0.0%</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Kranenburg et al. (2016)</td>
<td>BPs vs. control</td>
<td>16888 (12)</td>
<td>939/9577 (9.8%)</td>
<td>630/7311 (8.6%)</td>
<td>RR0.95 [0.87–1.05] (NA)</td>
<td>NA</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Kim et al. (2015)</td>
<td>BPs vs. PLB</td>
<td>25211 (9)</td>
<td>227/15152 (1.5%)</td>
<td>191/10059 (1.9%)</td>
<td>RR1.08 [0.92–1.36] (NA)</td>
<td>0.0%</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Loke et al. (2009)</td>
<td>BPs vs. PLB</td>
<td>19893 (3)</td>
<td>155/9936 (1.6%)</td>
<td>181/9957 (1.82%)</td>
<td>OR0.86 [0.66–1.13] (0.28)</td>
<td>31%</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Sharma et al. (2013)</td>
<td>BPs vs. OAO</td>
<td>26159 (6)</td>
<td>293/15571 (1.88%)</td>
<td>212/10588 (2.00%)</td>
<td>OR0.92 [0.68–1.26] (0.58)</td>
<td>33%</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Kranenburg et al. (2016)</td>
<td>BPs vs. control</td>
<td>10165 (5)</td>
<td>78/5143 (1.52%)</td>
<td>87/5022 (1.73%)</td>
<td>RR0.88 [0.62–1.23] (NA)</td>
<td>NA</td>
<td>Low</td>
</tr>
<tr>
<td>AF</td>
<td>Barrett-Connor et al. (2012)</td>
<td>ALN vs. PLB</td>
<td>17291 (17)</td>
<td>112/9518 (1.18%)</td>
<td>89/7773 (1.14%)</td>
<td>RR1.16 [0.87–1.55] (0.33)</td>
<td>NA</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Kim et al. (2015)</td>
<td>BPs vs. PLB</td>
<td>51212 (41)</td>
<td>440/31460 (1.4%)</td>
<td>296/1975(1.5%)</td>
<td>OR1.08 [0.92–1.25] (NA)</td>
<td>0.0%</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Loke et al. (2009)</td>
<td>BPs vs. PLB</td>
<td>26352 (4)</td>
<td>276/13172 (2.10%)</td>
<td>243/13180 (1.84%)</td>
<td>OR1.14 [0.96–1.36] (0.15)</td>
<td>0.0%</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Sharma et al. (2014)</td>
<td>BPs vs. control</td>
<td>135347 (9)</td>
<td>3236/64974 (4.98%)</td>
<td>3650/70373 (5.19%)</td>
<td>RR1.28 [1.18–1.38] (NA)</td>
<td>37%</td>
<td>High</td>
</tr>
<tr>
<td>SAF</td>
<td>Mak et al. (2009)</td>
<td>BPs vs. PLB</td>
<td>16284 (4)</td>
<td>204/8152 (2.50%)</td>
<td>171/8132 (2.10%)</td>
<td>OR1.18 [0.84–1.66] (0.54)</td>
<td>0.0%</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Barrett-Connor et al. (2012)</td>
<td>ALN vs. PLB</td>
<td>17291 (6)</td>
<td>55/9518 (0.57%)</td>
<td>41/7773 (0.53%)</td>
<td>RR1.25 [0.82–1.93] (0.33)</td>
<td>NA</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Bhuriya et al. (2010)</td>
<td>BPs vs. PLB</td>
<td>26342 (4)</td>
<td>13162</td>
<td>13180</td>
<td>RR1.53 [1.17–2.00] (0)</td>
<td>53%</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Kim et al. (2015)</td>
<td>BPs vs. PLB</td>
<td>51212 (41)</td>
<td>440/31460 (1.4%)</td>
<td>296/1975(1.5%)</td>
<td>OR1.08 [0.92–1.25] (NA)</td>
<td>0.0%</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Loke et al. (2009)</td>
<td>BPs vs. PLB</td>
<td>26352 (4)</td>
<td>139/13172 (1.06%)</td>
<td>91/13180 (0.69%)</td>
<td>OR1.47 [1.01–2.14] (0.04)</td>
<td>46%</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Sharma et al. (2013)</td>
<td>BPs vs. control</td>
<td>41375 (6)</td>
<td>202/25640 (0.79%)</td>
<td>104/15735 (0.66%)</td>
<td>RR1.40 [1.02–1.93] (0.04)</td>
<td>40%</td>
<td>High</td>
</tr>
<tr>
<td>Table 3</td>
<td>GRADE evidence profile for bisphosphonates versus comparison. (Continued)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------</td>
<td>--------------------------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td>Mak et al. (2009)\textsuperscript{38} BPs vs. PLB 16284 (4) 109/8152 (1.34%) 65/8132 (0.80%) OR1.59 [0.61–3.75] (0.59) 62% Low\textsuperscript{h}</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kim et al. (2015)\textsuperscript{34} BPs vs. PLB 25211 (5) 242/15152 (1.6%) 191/10059 (1.9%) OR1.41 [1.10–1.81] (NA) 5.8% High</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Loke et al. (2009)\textsuperscript{35} BPs vs. PLB 19893 (3) 203/9936 (2.04%) 203/9957 (2.03%) OR1.00 [0.82–1.22] (0.99) 0.0% Moderate\textsuperscript{h}</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sharma et al. (2013)\textsuperscript{37} BPs vs. control 26162 (6) 246/15574 (1.58%) 184/10588 (1.74%) RR1.07 [0.85–1.34] (0.62) 46% Low\textsuperscript{h}</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Atypical fracture</strong></td>
<td>Lee et al. (2015)\textsuperscript{40} BPs vs. PLB NA (1) NA NA OR1.34 [0.37–4.82] (NA) 0.0% Very low\textsuperscript{a,h}</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fracture union</strong></td>
<td>Molvik and Khan (2015)\textsuperscript{41} BPs vs. PLB NA (3) NA NA NA NA NA Very low\textsuperscript{a,e,i}</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GRADE, grading of recommendations assessment, development, and evaluation; OR, odds ratio; RR, relative risk.
\textsuperscript{a}Most trials with unclear random sequence generation and/or allocation concealment.
\textsuperscript{b}High heterogeneity in direct meta-analysis.
\textsuperscript{c}High heterogeneity, but might be explained by subgroup/sensitivity analyses.
\textsuperscript{d}High unexplained heterogeneity.
\textsuperscript{e}Heterogeneity was not measured in direct meta-analysis.
\textsuperscript{f}There is a difference in direction of effect.
\textsuperscript{g}Indirectness of evidence.
\textsuperscript{h}Imprecision, 95% CI includes both benefit and harm.
\textsuperscript{i}Impossible to calculate the optimal information size and the 95% CI overlapped the threshold for appreciable benefit (25% or more).
\textsuperscript{j}Imprecision, did not meet optimal information size.
\textsuperscript{k}Publication bias detected by statistical test.
included 13 observational studies. But a net included 14 observational. As the. Moreover, bis.

**DISCUSSION**

Overviews of systematic reviews are through summarizing evidence from published systematic reviews on a common topic and applied to guide researchers and clinicians finding high quality evidence they want. To our knowledge, this is the first study to systematically summarize and assess the quality of systematic reviews with meta-analyses of RCTs evaluating the safety of bisphosphonates (mainly including alendronate, zoledronate and ibandronate) used in the treatment of postmenopausal osteoporosis. Although the methodological quality of all the 16 included systematic reviews received an AMSTAR score $\geq 6$ (high or moderate quality), there was a significant variation in the quality of evidence for safety outcomes, by using the GRADE tool, with the majority of reviews judged as moderate or low quality. Thus, it requires further research to improve confidence in the estimate of effect.

This overview showed that there is no significant difference between bisphosphonates and control group in terms of all AEs or gastrointestinal adverse effects, even though the most common adverse effects reported with bisphosphonates affect the upper GI system. But a network meta-analysis of the included reviews showed that placebo (0.55, 95% CI [0.35–0.84]) had lower odds of causing any GI adverse event compared to zoledronic acid. And we found that zoledronic acid had the highest probability (91%) of causing the greatest number of any GI adverse events followed by etidronate (8%), and alendronate (1%)\(^{10}\).

Bisphosphonates significantly decreased the risk of total adverse CV events, CV death, but there was also opposite result in the included reviews\(^{33}\). Moreover, bisphosphonates distinctly increased the risk of AF, SAF and stroke. Some potential factors can explain the inconsistencies in the evidence. For example, there may have been some potential imbalances between the intervention and control arms about risk factors for CV events like anemia. And we do not know if some CV Events like the stroke in the trials was incident stroke events or whether it was the result of severe exacerbations in participants with existing CV Events. There are still massive uncertainties about the CV events of the evidence. Nevertheless, the risk of CV events of bisphosphonates used for the treatment of postmenopausal osteoporosis deserves further discussion.

In this overview, bisphosphonates did not significantly increase the risk of atypical fracture or fracture union. But we found a few systematic reviews with meta-analysis of observational studies which reported that bisphosphonates significantly increased the incidence of atypical fracture and prolonged union time of limb fracture especially for long-term users. Lee et al.\(^{40}\) made two subgroup analyses for the outcome of subtrochanteric and diaphyseal fractures using only observational studies found that bisphosphonate therapy was associated with a statistically significant risk of developing subtrochanteric fractures (AOR = 2.71, 95% CI: 1.86–3.95) and diaphyseal fractures (AOR = 2.06, 95% CI: 1.70–2.50). Gedminas et al.\(^{42}\) included 11 observational studies in his meta-analysis reported that bisphosphonate exposure was associated with an increased risk of subtrochanteric, femoral shaft, and AFF with adjusted RR of 1.70 (95% CI 1.22–2.37). Subgroup analysis of studies examining at least 5 years of bisphosphonate use showed adjusted RR of 1.62 (95% CI 1.29–2.04).

Molvik and Khan\(^{41}\) included 13 observational studies and a comprehensive comparative analysis found that patients with distal radius fractures on bisphosphonates had a significantly longer union time compared with controls. Yue et al.\(^{43}\) included 14 observational studies and the result suggested that bisphosphonate prolonged the healing time of osteoporotic elderly patients with fracture in the lower limbs (average 8.5 months). Osteoporotic elderly patients with more than 3-years bisphosphonate treatment had a higher incidence of delayed union than ones with less than 3-years treatment.

Since 2003, osteonecrosis of the jaws (ONJ) has been associated with the use of intravenous zoledronic acid, the most potent bisphosphonate (BP)\(^{44}\). As the eligibility criteria of this overview just included systematic review with meta-analysis of RCT, none of any systematic review was included. But there were systematic reviews with meta-analysis of observational studies. Lee et al.\(^{45}\) reported that use of BPs were associated with higher risk on ONJ (OR 2.57; 95% CI 1.37–4.84) than ON of other sites (OR 1.79; 95% CI 0.71–4.47).

Even though our study used the standard rigorous methods for selecting systematic reviews such as a comprehensive search strategy, only including systematic review with meta-analysis of RCT and screening and quality assessment by two independent reviewers, it has several limitations. First, we restricted our data extraction to the level of the systematic review, which kept us from meta-analyzing individual study results. As there may be some latest and multicenter random controlled trials that did not include in any systematic review recently published, which may lead to inaccuracy of part of outcomes. Second, in theory, the best evidence for health care decisions comes from RCTs. Nevertheless, observational studies may also provide important additional information or higher-quality evidence in some cases, such as mortality and some rare adverse events. Lastly, we only included systematic reviews with meta-analysis may have excluded important reviews on this theme, because some systematic reviews without a meta-analysis were not appropriate to pool statistically. All of the above may bring in publication bias for our overview.
Our overview of systematic reviews with meta-analyses of RCTs provides a comprehensive assessment on the safety of bisphosphonates. This overview indicated that bisphosphonates significantly increased the risk of AF, sAF and stroke, but did not significantly increase the risk of atypical fracture or fracture union. It also showed that bisphosphonates could decrease the risk of total adverse CV events, CV death. As the majority of reviews are of poor quality, the relationship between bisphosphonates and some serious adverse events like atypical fracture was often not certain. In despite the vast number of systematic reviews published, high quality research and more complete inclusion criteria are needed.

REFERENCES