

## Original Article

# A meta-analysis of the antitumor effect and safety of bisphosphonates in the treatment of multiple myeloma

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**Abstract:** Background: The objective of this meta-analysis was to determine the effectiveness and safety of bisphosphonates (BPs) for patients with multiple myeloma (MM). Methods: The study included patients with MM, who were randomly allocated to receive either BPs or control. PubMed/Medline, Embase, the Cochrane Database of Systematic Reviews (CDSR), and the Cochrane Central Register of Controlled Trials were searched up to January 2014, and only published trials were included in the analysis. There was no language restriction. The results were analyzed using RevMan 5.2 software, which was provided by Cochrane Collaboration. Results: Six randomized controlled trials (RCTs) covering 1951 patients with MM were included in the analysis. The clodronate subgroup showed superior progression-free survival compared to the other groups. The pooled hazard ratio (HR) was 0.57 [95% confidence interval (CI) 0.33-0.99,  $P = 0.04$ ]. Regarding overall survival (OS), only zoledronic acid showed a clear advantage (HR = 0.51, 95% CI 0.33-0.77,  $P = 0.002$ ). All BPs were effective at reducing skeletal-related events (SREs). The pooled risk ratios for the outcome of SREs were 0.72 (95% CI: 0.62-0.84,  $P < 0.0001$ ) for the clodronate subgroup, 0.66 (95% CI: 0.48-0.91,  $P = 0.007$ ) for the pamidronate subgroup, and 0.65 (95% CI: 0.46-0.91,  $P = 0.01$ ) for the zoledronic acid subgroup. Several adverse events (AEs) were mentioned in the included RCTs; however, the pooled results showed no statistically significant differences between the BP groups and the control. Conclusions: The present meta-analysis demonstrated that zoledronic acid may improve the OS of patients with MM. All BPs markedly decreased SREs and were tolerated well.

**Keywords:** Multiple myeloma, bisphosphonates, clodronate, pamidronate, zoledronic acid, meta-analysis

## Introduction

MM is a relatively common hematological malignancy characterized by a proliferative disorder of plasma cells in the bone marrow, and it currently has no known cure [1]. Current treatments of patients with MM include stem cell transplantation, combination chemotherapy, and the use of novel agents such as thalidomide, lenalidomide, and bortezomib. Bisphosphonates (BPs) have shown significant results in terms of reduction of skeletal-related events (SREs) in patients with MM and are widely incorporated into treatment strategies. BPs has been shown to have direct or indirect antitumor effects in some malignancies such as breast cancer, prostate cancer, lung cancer, and bladder cancer [2-5]. Several clinical trials have shown that the use of BPs can confer a survival advantage in patients with MM [6, 7].

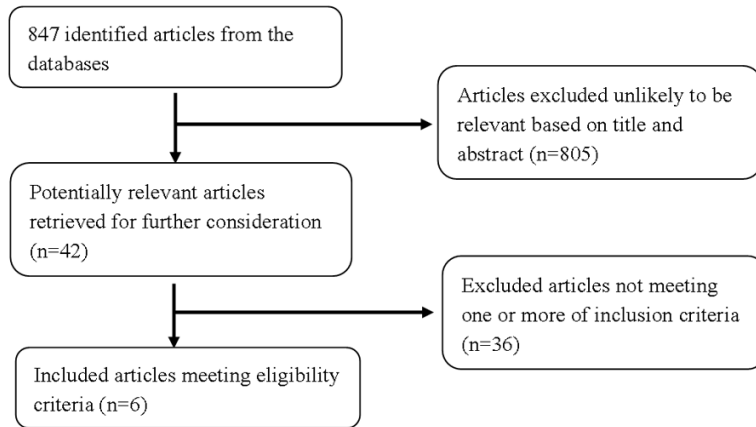
Patients with MM treated with BPs as an adjuvant to chemotherapy showed improved survival compared to controls treated with chemotherapy alone. Therefore, the antitumor activity of BPs has attracted increasing attention. Here, we performed a meta-analysis of randomized controlled trials (RCTs) to assess the antitumor effects and safety of BPs in the treatment of MM.

## Methods

### Retrieval strategy

An electronic search of PubMed/Medline, Embase, the Cochrane Database of Systematic Reviews, and the Cochrane Central Register of Controlled Trials was performed up to January 2014 using the medical subject headings "myeloma", "bisphosphonates", "clodronate",

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**Figure 1.** The selection procedure of included studies.

“pamidronate” and “zoledronic acid”. Only published trials were included. The reference lists of all selected studies were reviewed for further identification of potentially relevant articles. The initial search retrieved 847 citations. Eventually 6 RCTs enrolling 1951 patients fulfilled the inclusion criteria. In each patient, we identified SREs, including radiation to the bone, pathological or osteoporotic fractures, spinal cord compression, and surgery to the bone [8].

## *Inclusion criteria*

The following inclusion criteria were used for the selection of each study: 1) prospective phase 3 RCT study on MM patients; 2) intervention: treatment with bisphosphonates including clodronate, pamidronate or zoledronic acid; 3) control: no treatment or placebo; 4) sufficient information in the literature to calculate hazard ratios (HRs) for progression free survival (PFS) and overall survival (OS) and risk ratios (RRs) for SREs; 5) information on adverse events (AEs) of drugs should be provided; 6) studies published before January 2014 and written in English; 7) full text of the study should be available.

## *Exclusion criteria*

Studies that met the following criteria were excluded: 1) retrospective studies or non-RCTs; 2) studies that did not focus on the treatment of MM; 3) Repeated reports (if centers published duplicate trials with an increased number of patients or follow-up time period, we included the most complete report in the meta-

analysis); 4) letters, meeting records, reviews or abstracts.

## *Data extraction and critical appraisal*

All the titles and abstracts of the retrieved literature were reviewed by two investigators (W.X.X. and Y.X.J.) independently, and the studies to be included were then identified. Discrepancies between the two reviewers were resolved through discussion and consensus. The authors, publication years, country of investigators, sample size, treatment regimens, follow-up periods, curative effects, and AEs of each trial were extracted. The quality of the trials was evaluated using Jaded quality scores [9], including methods for randomization, allocation concealment, blinding, and loss to follow-up. Disease progression was reported by investigators according to the criteria of the European Group for Blood and Marrow Transplantation (EBMT) [10]. We assessed the grades of AEs using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 3.0. Data extraction was performed by the two investigators (W.X.X. and Y.X.J.) independently.

## *Statistical analysis*

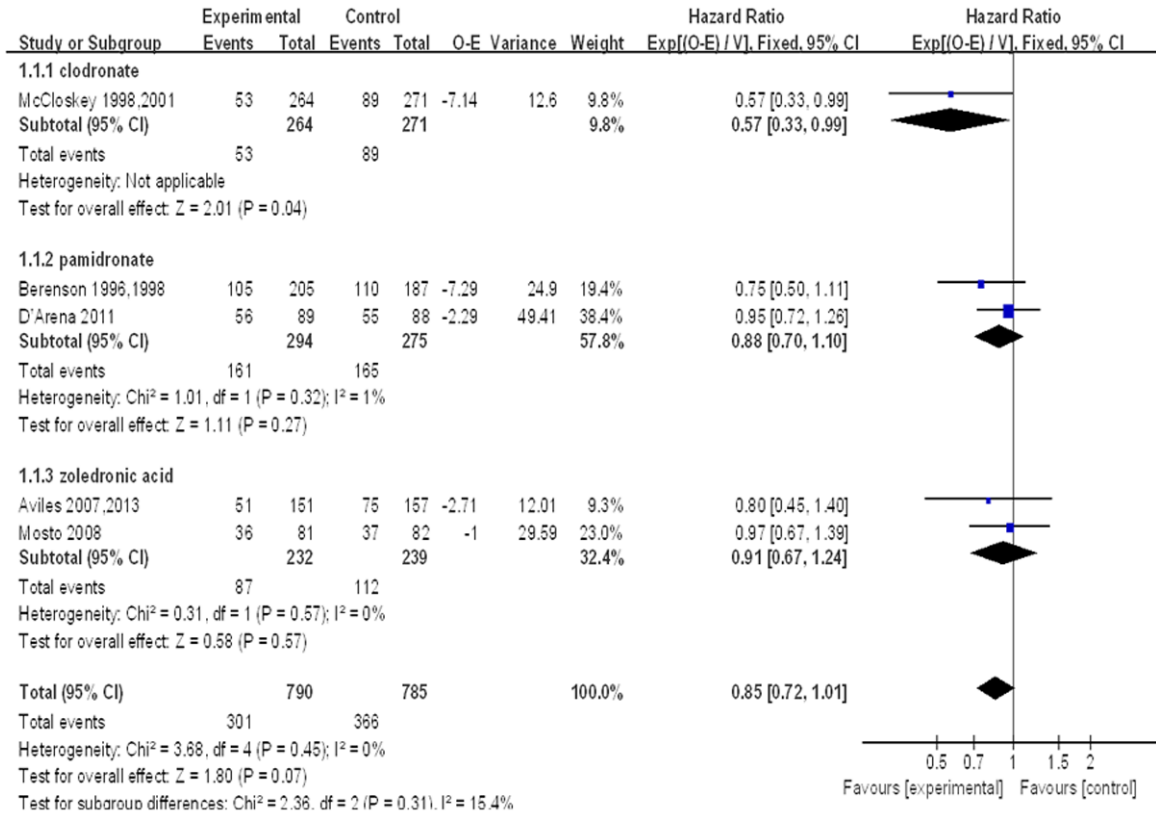
All meta-analyses were completed using REVMAN version 5.2. Dichotomous data were expressed as RRs using a 95% confidence interval (CI). Time-to-event data were pooled and reported as HRs. Forest plots of HRs were completed using the Exp [(O-E/V)] method. Events and total number of participants in the BP and control arms were also entered. The specific HR and 95% CI could be directly used if available in the literature. If not, Engauge Digitizer V4.1 was used to estimate the survival rates at any point on the survival curves. Then, the variance and O-E were calculated by using the method described by Tierney [11]. Between-study and between-subgroup heterogeneity were assessed using the Cochrane  $c^2$ -test and its extent was quantified with the  $I^2$ -statistic. A  $P$ -value  $< 0.05$  was defined as statistically significant for all outcomes.

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**Table 1.** Basic characteristics and the quality of the included trials of trials included in the present study

Author year	country	No.	Regimes	Follow-up (month)	Randomization	Blind	Allocation concealment	Withdrawal and dropout	Jadad Score
Aviles 2007, 2013	Mexico	308	E: Zol24 cyc* C: no treatment	69.8	Well reported	No	Well reported	Well reported	4
Musto 2008	Italy	163	E: Zol12 cyc* C: no treatment	64.7	Well reported	No	Unclear	Well reported	3
D'Arena 2011	Italy	177	E: PAM12 cyc* C: no treatment	60	Well reported	No	Unclear	Well reported	3
Berenson 1996, 1998	America, Canada, Austr-alia, New Zealand	392	E: PAM21 cyc* C: placebo	29	Well reported	Without details	Without details	Well reported	5
McCloskey 1998, 2001	UK	535	E: clodronate24 cyc* C: placebo	93	Well reported	Well reported	Well reported	Well reported	6
Lahtinen 1992	Europe	376	E: clodronate24 cyc* C: placebo	24	Without details	Without details	Unclear	Well reported	3

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**Figure 2.** Meta-analysis of PFS with BPs vs. control in MM patients.

### Results

#### Description of trials

A comprehensive literature search was performed. The initial search yielded 847 citations, of which six RCTs [12-20] enrolling 1951 patients fulfilled the inclusion criteria. The selection procedure is summarized in **Figure 1**. All the RCTs were reported as full publications. Two RCTs tested clodronate-based regimens, two tested pamidronate-based regimens, and the remaining two RCTs tested zoledronic acid-based regimens. Three subgroups were generated for the analysis according to the different types of bisphosphonates used as follows: a clodronate subgroup, a pamidronate subgroup, and a zoledronic acid subgroup. The characteristics and quality of the included trials are described in **Table 1**.

#### Progression free survival

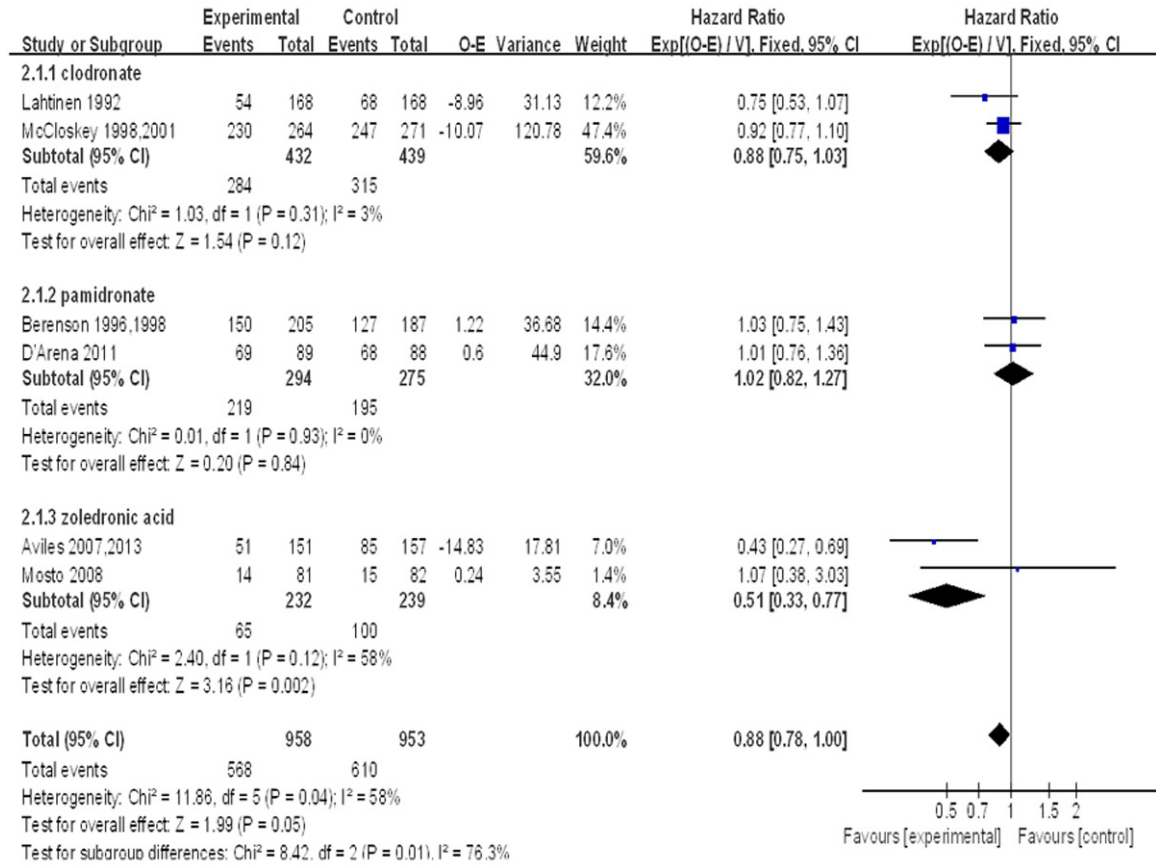
Data for PFS were available from five trials, including 1575 patients who were recruited to

our studies [12-19]. **Figure 2** shows the meta-analysis of PFS data between BP and control groups. A significant PFS advantage was found for the clodronate subgroup compared to the control group (HR = 0.57, 95% CI 0.33-0.99; P = 0.04), but not in the other subgroups. The corresponding HRs were 0.88 (95% CI 0.7-1.10, P = 0.27) and 0.91 (95% CI 0.67-1.24, P = 0.57) for the comparisons of the pamidronate subgroup or zoledronic acid subgroup with the control group, respectively. There was no obvious statistical heterogeneity in the trials.

#### Overall survival

OS was reported in all the included studies. As shown in **Figure 3**, no clear OS advantage was observed in the clodronate subgroup or pamidronate subgroup. The pooled HR for OS were 0.88 (95% CI 0.75-1.03, P = 0.12) and 1.02 (95% CI: 0.82-1.27, P = 0.84), respectively. However, zoledronic acid therapy was associated with a clinically and statistically significant 49% improvement in OS when compared with the control (HR, 0.51, 95% CI 0.33-0.77, P =

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**Figure 3.** Meta-analysis of OS with BPs vs. control in MM patients.

0.002). Heterogeneity was observed among subgroups (P = 0.01, I<sup>2</sup> = 76.3%).

### Skeletal-related events

The pooled results showed statistically significant reductions in SREs with use of BPs compared with placebo or no treatment. The pooled RR for the outcomes of SREs were 0.72 (95% CI: 0.62-0.84, P < 0.0001), 0.66 (95% CI: 0.48-0.91, P = 0.007), 0.65 (95% CI: 0.46-0.91, P = 0.01) for clodronate, pamidronate and zoledronic acid subgroup, respectively. There was no heterogeneity among the three subgroups (I<sup>2</sup> = 0%, P = 0.77) (**Figure 4**).

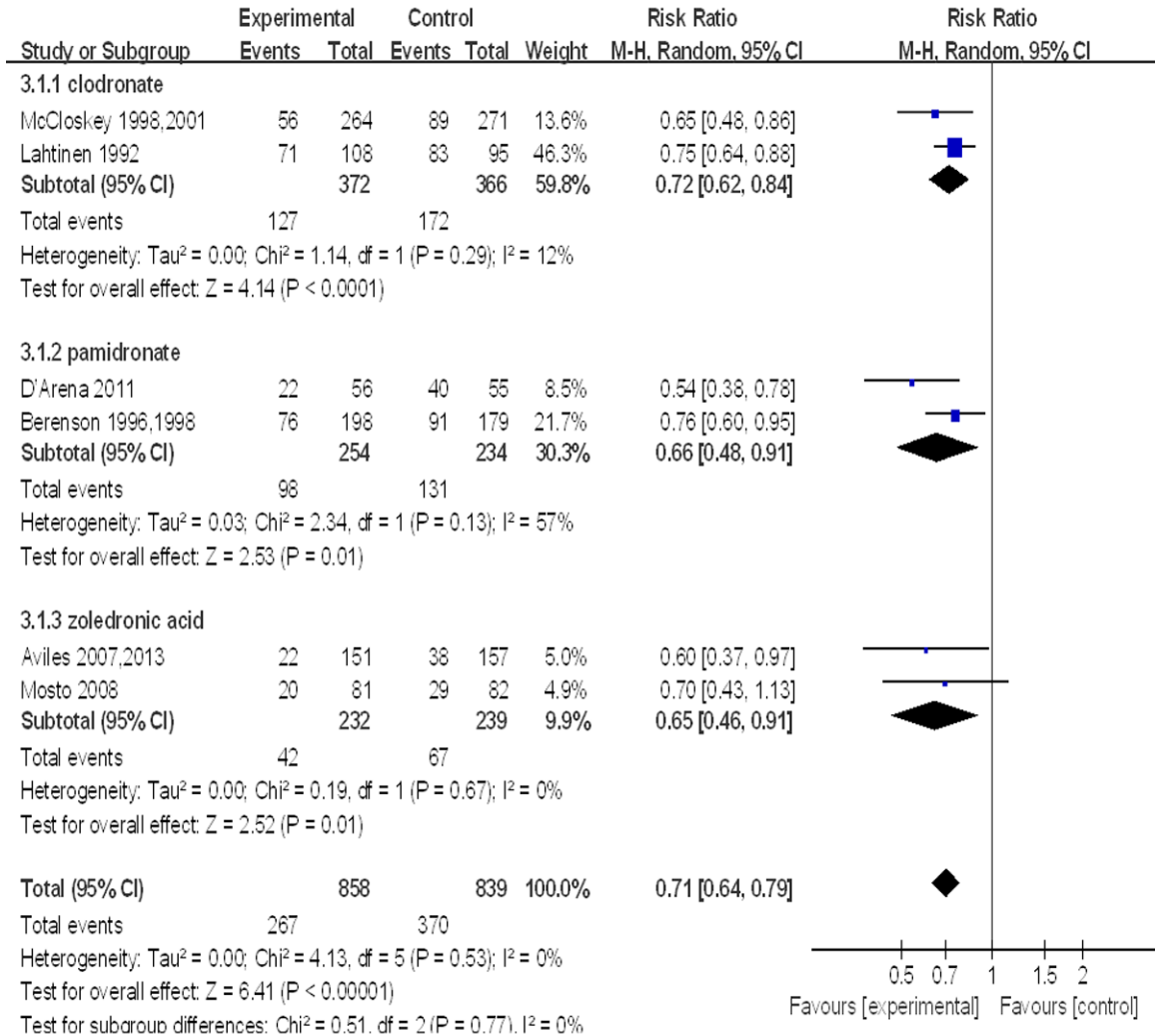
### AEs

Several studies included in this meta-analysis provided data on AEs. Important AEs were extracted among the eligible studies, such as gastrointestinal (GI) events, renal dysfunction, and osteonecrosis of the jaw.

*GI events:* data were extractable from four RCTs [11-13, 16-20]. These studies enrolled 1571 patients. The most common GI associated AEs included nausea, diarrhea, constipation, and vomiting. Different authors used various methods to assess GI symptoms. Our first choice was to use the overall number of patients with GI symptoms. When this number was not available, we pooled all GI symptoms together. The pooled results showed no statistically significant increase in the frequency of GI symptoms associated with the use of BPs compared with the control group. The pooled RR was 0.95 (95% CI: 0.83-1.10, P = 0.5). No statistically significant heterogeneity among the included RCTs was observed (I<sup>2</sup> = 0%; P = 0.52) (**Figure 5**).

*Renal dysfunction:* data were extractable from three RCTs [14, 15, 20]. These studies enrolled 520 patients. Overall, BP therapy had no effect on the risk of renal dysfunction as compared with the control. The pooled RR for was 0.95 (95% CI: 0.8-1.12, P = 0.52). There was no sta-

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**Figure 4.** Meta-analysis of SREs with BPs vs. control in MM patients.

tistical heterogeneity among included RCTs (I<sup>2</sup> = 0%; P = 0.73) (**Figure 6**).

**Osteonecrosis of the jaw (ONJ):** in the present study, of the six RCTs, only one RCT [14] mentioned that ONJ was reported in 2 of 81 patients receiving zoledronic acid treatment compared with 0 of 80 patients with no treatment. The pooled RR for the outcome was 5.06 (95% CI: 0.25-103.81, P = 0.29) (**Figure 7**).

### Discussion

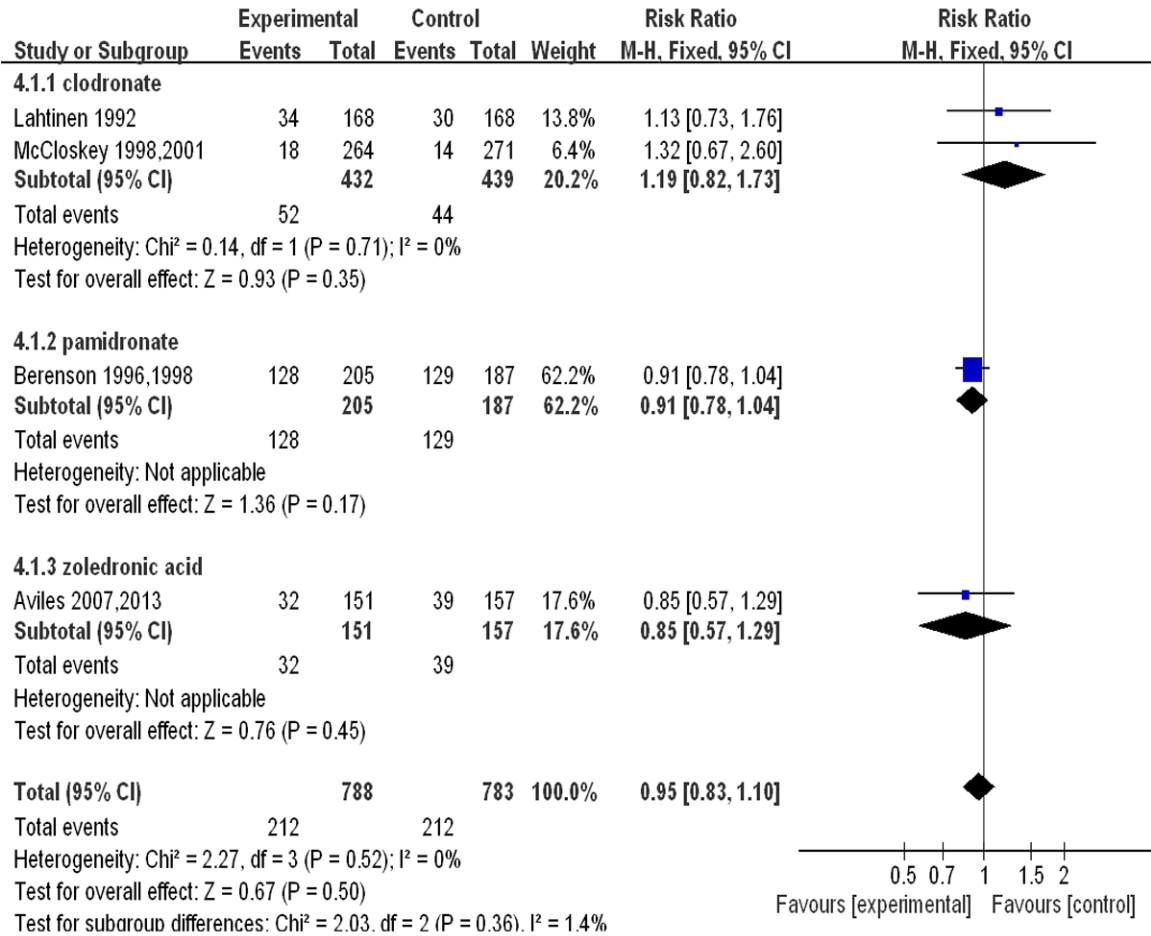
BPs is approved for the treatment of malignant bone disease in advanced cancers. BPs has also been shown to be effective for the prevention of SREs and secondary complications in patients with MM. It is becoming increasingly

evident that BPs may have additional antitumor effects [21]. Therefore, this type of drug could be well integrated into the initial treatment.

Several recent studies showed evidence of the antitumor activity of BPs, as demonstrated by increased PFS or OS in advanced cancers. Two trials suggested that 2 years of oral clodronate (1600 mg daily) can delay bone metastasis and increase disease-free survival (DFS) and OS in women with breast cancer [22, 23]. Similar results were reported by Dearnaley et al., who showed that clodronate improves OS in men with metastatic prostate cancer who are starting hormone therapy (HR 0.77, 95% CI 0.60-0.98; P = 0.032) [24]. In the ABCSG-12 trial, adding zoledronic acid to adjuvant therapy substantially prolonged DFS and recurrence-free



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**Figure 5.** Comparison of BPs vs. control (AEs) - Gastrointestinal events (GI events).

survival, and significantly improved OS compared with the hormonal therapy alone group [25, 26]. The anticancer effects of zoledronic acid were also reported by the Zometa-Femara Adjuvant Synergy Trials (Z-FAST, ZO-FAST, and E-ZO-FAST). The analysis showed that upfront zoledronic acid treatment significantly improved DFS and reduced disease recurrence compared with delayed zoledronic acid treatment [27, 28]. In the AZURE trial, zoledronic acid significantly improved DFS among patients who were postmenopausal for > 5 years before study entry [29]. In a study conducted by Zaghoul et al., zoledronic acid therapy decreased the incidence of SREs and improved the 1-year survival rate of patients with bone metastases from bladder cancer [5]. In a study by Zarogoulidis that included 144 patients, the addition of zoledronic acid increased overall survival in lung cancer patients with bone metastases [30].

The present study focused on the antitumor effects and safety of BPs in the treatment of MM. Our pooled data suggested that the use of BPs can benefit patients with MM, as determined by a lower rate of SREs, and longer PFS and OS. Clodronate was superior regarding PFS (HR = 0.57, 95% CI 0.33-0.99; P = 0.04), whereas zoledronic acid was superior in the control of OS (HR, 0.51, 95% CI 0.33-0.77, P = 0.002). Our results suggested that the use of BPs in patients with MM can reduce the frequency of SREs. The pooled RRs for the outcome of SREs were 0.72 (95% CI: 0.62-0.84, P < 0.0001), 0.66 (95% CI: 0.48-0.91, P = 0.007) and 0.65 (95% CI: 0.46-0.91, P = 0.01) for each subgroup. In our analysis, AEs were also compared between arms. Only with the tolerable toxicity of BPs would the benefits be meaningful. We collected data on three common AEs from the included studies. On the basis of the analysis of

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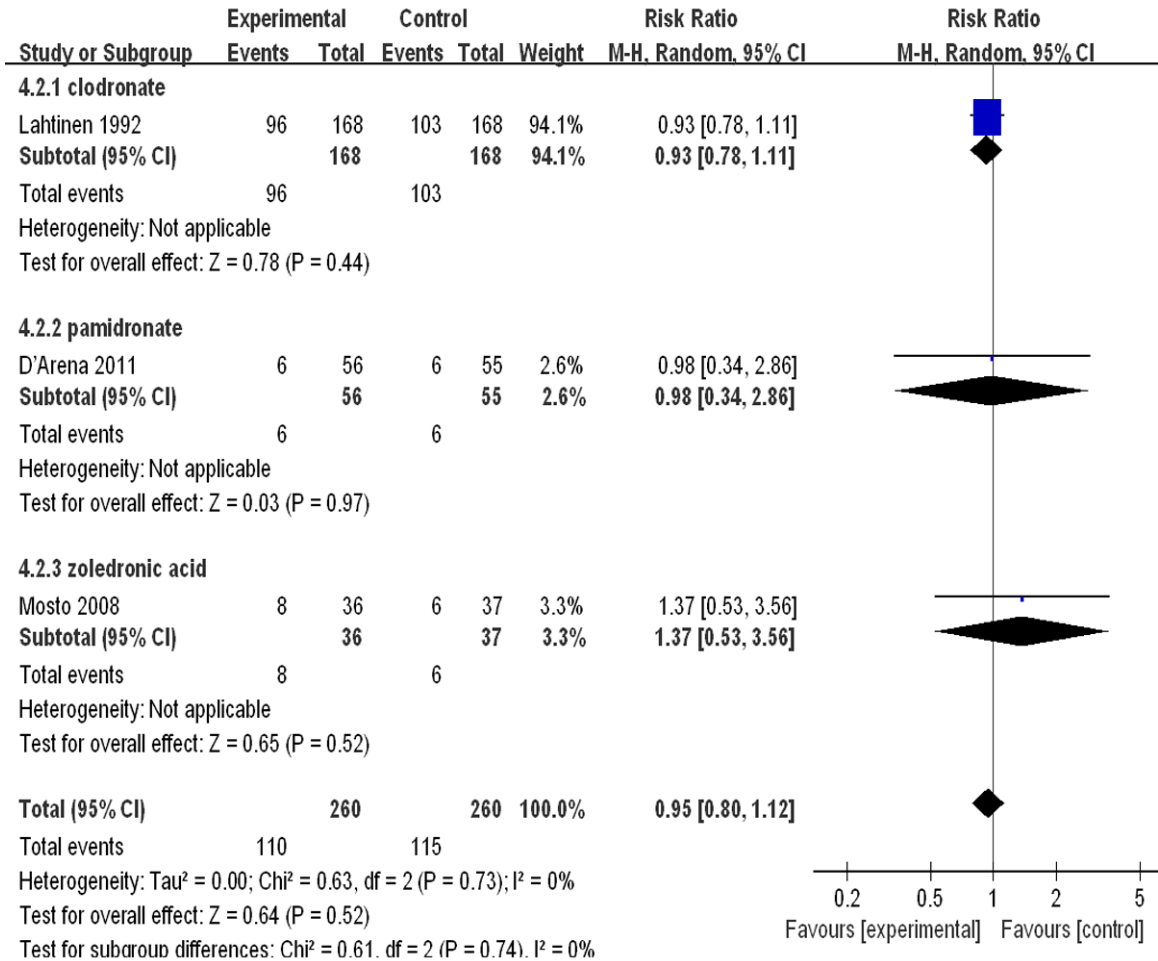


Figure 6. Comparison of BPs vs. control (AEs) - renal dysfunction.

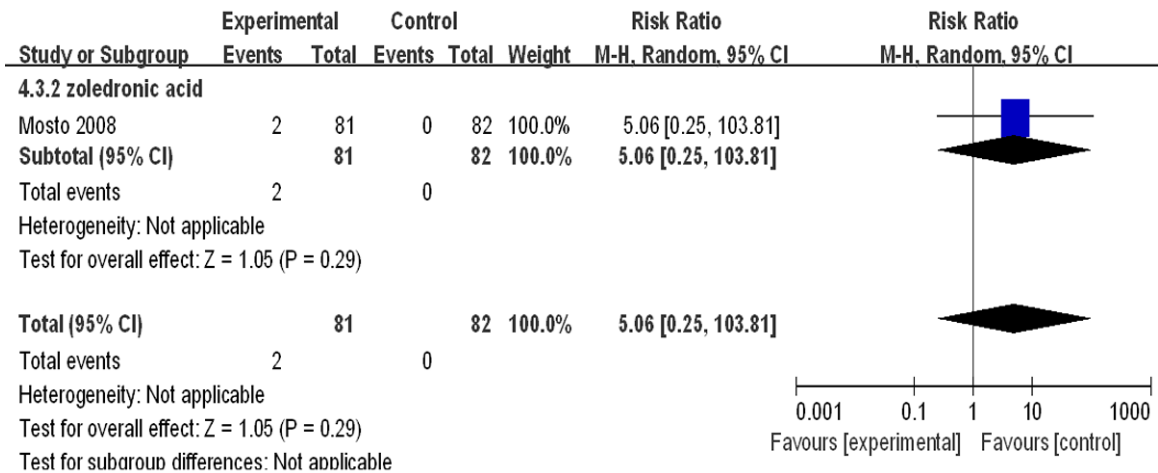


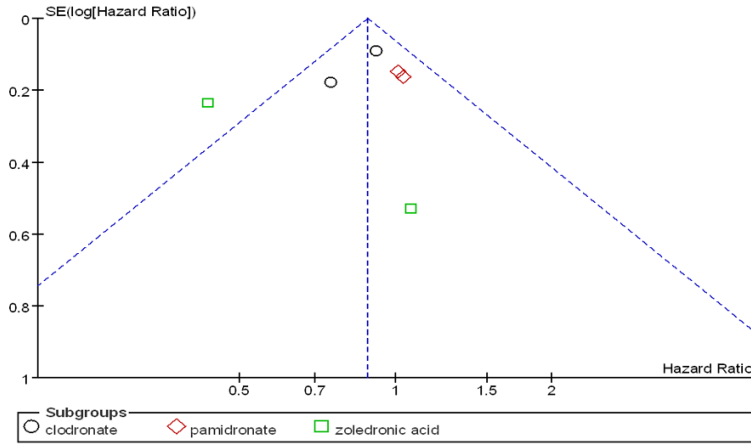
Figure 7. Comparison of BPs vs. control (AEs) - Osteonecrosis of the jaw (ONJ).

pooled data from both arms, no differences in the incidence of gastrointestinal events, renal

dysfunction or osteonecrosis of the jaw were observed between the BP and control groups.



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**Figure 8.** Funnel plot analysis of potential publication bias.

These results are not in accordance with those of previous studies. A recent retrospective analysis that included 94 patients with Durie-Salmon stage 3A/B MM showed that the addition of zoledronic acid was associated with a statistically nonsignificant benefit in the 1-year PFS rate in both the first- and second-line setting. A similar benefit was observed on the 2-year SRE rate. Three cases of osteonecrosis of the jaw were reported; there were no reports of acute renal failure [31]. In a small study conducted by Martin et al. [32], 12 patients with smoldering or indolent multiple myeloma received 12 courses of intravenous pamidronate as a single agent to evaluate both the antitumor and bone metabolism effects. The results suggested that pamidronate treatment reduces bone turnover in smoldering or indolent MM, but has no significant antitumor effect.

Funnel plot analysis of potential publication bias (**Figure 8**) was performed to confirm the reliability of our research results. Publication bias is a problem that is frequently associated with meta-analyses; however, no such bias was detected in our study.

The present meta-analysis had several limitations. The first and major problem was differences in the disease stage of patients, which could have caused the heterogeneity in OS in the zoledronic acid subgroup ( $P = 0.12$ ,  $I^2 = 58\%$ ). Zoledronic acid may show a greater advantage in patients with symptomatic MM than in those with asymptomatic MM. Secondly,

the sample size of included trials was too small for a funnel plot to detect publication bias. Thirdly, in the test for subgroup differences among the three BPs, significant differences in OS were detected ( $P = 0.01$ ), indicating that zoledronic acid may be superior to the other two BPs. However, this analysis lacks a direct head-to-head comparison among clodronate, pamidronate and zoledronic acid; therefore, it is difficult to confirm the superiority of one agent over another. Additional

clinical trials are needed to confirm these results. Recently, the randomized, controlled Medical Research Council Myeloma IX study [33] demonstrated that in newly diagnosed patients with MM, combining conventional therapy with zoledronic acid significantly prolonged both PFS and OS compared to clodronate. Berenson et al. [34], suggested that zoledronic acid may improve survival compared to pamidronate in patients with MM and high BALP levels, but data on this study was not found in our search

Further, many studies have shown a reduction in SREs and improvement of survival in MM patients treated with BPs. Nevertheless, based on the fact that BPs can increase the risk of osteonecrosis of the jaw and other adverse effects, the use of BPs needs to be critically evaluated in the context of the clinical situation of each individual patient [35].

### Conclusion

In conclusion, the findings of the present study indicated that BPs play an important role in the treatment of MM associated bone disease. In addition to the established benefit regarding skeletal health, evidence supports a potential antimyeloma effect of BPs. Zoledronic acid was shown to have a beneficial effect on OS. Despite the AEs of BPs reported in previous analyses, there is evidence of the benefits and safety of BPs including clodronate, pamidronate and zoledronic acid in the treatment of patients with MM [36]. Future studies should assess the antitumor potential of BPs.

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## Disclosure of conflict of interest

None.

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