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Mhaskar R, Kumar A, Miladinovic B, Djulbegovic B

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[Intervention Review]

Bisphosphonates in multiple myeloma: an updated network meta-analysis

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ABSTRACT

Background

Bisphosphonates are specific inhibitors of osteoclastic activity and are used in the treatment of patients with multiple myeloma (MM). While bisphosphonates are shown to be effective in reducing vertebral fractures and pain, their role in improving overall survival (OS) remains unclear. This is an update of a Cochrane review first published in 2002 and previously updated in 2010 and 2012.

Objectives

To assess the evidence related to benefits and harms associated with use of various types of bisphosphonates (aminobisphosphonates versus non-aminobisphosphonates) in the management of patients with MM. Our primary objective was to determine whether adding bisphosphonates to standard therapy in MM improves OS and progression-free survival (PFS), and decreases skeletal-related morbidity. Our secondary objectives were to determine the effects of bisphosphonates on pain, quality of life, incidence of hypercalcemia, incidence of bisphosphonate-related gastrointestinal toxicities, osteonecrosis of jaw (ONJ) and hypocalcemia.

Search methods

We searched MEDLINE, Embase (September 2011 to July 2017) and the CENTRAL (2017, Issue 7) to identify all randomized controlled trial (RCT) in MM up to July 2017 using a combination of text and MeSH terms.

Selection criteria

Any randomized controlled trial (RCT) comparing bisphosphonates versus placebo/no treatment/bisphosphonates and observational studies or case reports examining bisphosphonate-related ONJ in patients with MM were eligible for inclusion.

Data collection and analysis

Two review authors extracted the data. Data were pooled and reported as hazard ratio (HR) or risk ratio (RR) using a random-effects model. We used meta-regression to explore statistical heterogeneity. Network meta-analysis using Bayesian approach was conducted.

Main results

In this update, we included four new studies (601 participants), resulting in a total of 24 included studies.

Twenty RCTs compared bisphosphonates with either placebo or no treatment and four RCTs involved another bisphosphonate as a comparator. The 24 included RCTs enrolled 7293 participants. Pooled results showed that there was moderate-quality evidence of a

reduction in mortality with on OS from 41% to 31%, but the confidence interval is consistent with a larger reduction and small increase in mortality compared with placebo or no treatment (HR 0.90, 95% CI 0.76 to 1.07; 14 studies; 2706 participants). There was substantial heterogeneity among the included RCTs ($I^2 = 65\%$) for OS. To explain this heterogeneity we performed a meta-regression assessing the relationship between bisphosphonate potency and improvement in OS, which found an OS benefit with zoledronate but limited evidence of an effect on PFS. This provided a further rationale for performing a network meta-analysis of the various types of bisphosphonates that were not compared head-to-head in RCTs. Results from network meta-analysis showed evidence of a benefit for OS with zoledronate compared with etidronate (HR 0.56, 95% CI 0.29 to 0.87) and placebo (HR 0.67, 95% CI 0.46 to 0.91). However, there was no evidence for a difference between zoledronate and other bisphosphonates.

The effect of bisphosphonates on disease progression (PFS) is uncertain. Based on the HR of 0.75 (95% CI 0.57 to 1.00; seven studies; 908 participants), 47% participants would experience disease progression without treatment compared with between 30% and 47% with bisphosphonates (low-quality evidence). There is probably a similar risk of non-vertebral fractures between treatment groups (RR 1.03, 95% CI 0.68 to 1.56; six studies; 1389 participants; moderate-quality evidence). Pooled analysis demonstrated evidence for a difference favoring bisphosphonates compared with placebo or no treatment on prevention of pathological vertebral fractures (RR 0.74, 95% CI 0.62 to 0.89; seven studies; 1116 participants; moderate-quality evidence) and skeletal-related events (SREs) (RR 0.74, 95% CI 0.63 to 0.88; 10 studies; 2141 participants; moderate-quality evidence). The evidence for less pain with bisphosphonates was of very low quality (RR 0.75, 95% CI 0.60 to 0.95; eight studies; 1281 participants).

Bisphosphonates may increase ONJ compared with placebo but the confidence interval is very wide (RR 4.61, 95% CI 0.99 to 21.35; $P = 0.05$; six studies; 1284 participants; low-quality evidence). The results from the network meta-analysis did not show any evidence for a difference in the incidence of ONJ (eight RCTs, 3746 participants) between bisphosphonates. Data from nine observational studies (1400 participants) reported an incidence of 5% to 51% with combination of pamidronate and zoledronate, 3% to 11% with zoledronate alone, and 0% to 18% with pamidronate alone.

The pooled results showed no evidence for a difference in increase in frequency of gastrointestinal symptoms with the use of bisphosphonates compared with placebo or no treatment (RR 1.23, 95% CI 0.95 to 1.59; seven studies; 1829 participants; low-quality evidence). The pooled results showed no evidence for a difference in increase in frequency of hypocalcemia with the use of bisphosphonates compared with placebo or no treatment (RR 2.19, 95% CI 0.49 to 9.74; three studies; 1090 participants; low-quality evidence). The results from network meta-analysis did not show any evidence for differences in the incidence of hypocalcemia, renal dysfunction and gastrointestinal toxicity between the bisphosphonates used.

Authors' conclusions

Use of bisphosphonates in participants with MM reduces pathological vertebral fractures, SREs and pain. Bisphosphonates were associated with an increased risk of developing ONJ. For every 1000 participants treated with bisphosphonates, about one patient will suffer from the ONJ. We found no evidence of superiority of any specific aminobisphosphonate (zoledronate, pamidronate or ibandronate) or non-aminobisphosphonate (etidronate or clodronate) for any outcome. However, zoledronate was found to be better than placebo and first-generation bisphosphonate (etidronate) in pooled direct and indirect analyses for improving OS and other outcomes such as vertebral fractures. Direct head-to-head trials of the second-generation bisphosphonates are needed to settle the issue if zoledronate is truly the most efficacious bisphosphonate currently used in practice.

PLAIN LANGUAGE SUMMARY

Bisphosphonates in multiple myeloma

Review question: What is the effect of bisphosphonates if added to the existing treatments for multiple myeloma?

Background: Multiple myeloma (also known as myeloma or plasma cell myeloma) is a B-cell malignancy or, more precisely, plasma cell neoplasm. This cancer grows inside or outside of bones. The bone damage, or osteolytic lesions, may lead to fractures of the long bones or compression fractures in the spine. The mechanism of bone destruction appears to be related to increased bone resorption by cells called osteoclasts. Bisphosphonates are drugs that can inhibit bone resorption by reducing the number and activity of osteoclasts.

Search date: The evidence is current to July 2017.

Study characteristics: This is an updated review of 24 trials enrolling 7293 participants. Twenty randomized controlled trials compared bisphosphonates with either placebo or no treatment and four randomized controlled trials involved another bisphosphonate as a comparator.

Key results: Use of bisphosphonates in participants with multiple myeloma did not improve overall survival or disease progression-free survival. Use of bisphosphonates in participants with multiple myeloma reduces overall fractures, fractures of the vertebra but not the non-vertebral fractures. Bisphosphonates also alleviates pain without many side effects except a significant increase in reduced blood flow to bones of the jaw resulting in decay of the bone also called osteonecrosis. Overall, for every 1000 participants treated with bisphosphonates, about one patient will suffer from the osteonecrosis of the jaw. Zoledronate was found to be better than etidronate and placebo, but not superior to pamidronate or clodronate for improving overall survival and other outcomes such as fractures in general or

specifically fractures of vertebra. There was no evidence of superiority of any specific aminobisphosphonate (zoledronate, pamidronate or ibandronate) or non-aminobisphosphonate (etidronate or clodronate) for any outcome.

Quality of evidence: The overall quality of evidence ranged from moderate to very low indicating the need for more research on this issue and specifically randomized controlled trials comparing different bisphosphonates directly instead of no treatment or placebo.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Summary of findings (direct comparisons)

Bisphosphonates in multiple myeloma

Patient or population: patients with multiple myeloma

Intervention: bisphosphonates

Control: no treatment/placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Control	Bisphosphonates			
Overall survival##	Medium-risk population#		HR 0.90 (0.76 to 1.07)	2706 (14 studies)	⊕⊕⊕⊖ moderate ^{1,2,3}
	410 per 1000	378 per 1000 (330 to 431)			
Progression-free survival###	Medium-risk population#		HR 0.75 (0.57 to 1.00)	908 (7 studies)	⊕⊕⊕⊖ low ^{1,4,11}
	470 per 1000	379 per 1000 (304 to 470)			
Vertebral fractures	Medium-risk population#		RR 0.74 (0.62 to 0.89)	1116 (7 studies)	⊕⊕⊕⊖ moderate ^{1,5}
	360 per 1000	266 per 1000 (223 to 320)			
Non-vertebral fractures	Medium-risk population#		RR 1.03 (0.68 to 1.56)	1389 (6 studies)	⊕⊕⊕⊖ moderate ^{1,6}
	140 per 1000	144 per 1000 (95 to 218)			
Skeletal-related events	Medium-risk population#		RR 0.74 (0.63 to 0.88)	2141 (10 studies)	⊕⊕⊕⊖ moderate ^{1,7}
	400 per 1000	296 per 1000 (252 to 352)			
Pain	Medium-risk population		RR 0.75 (0.60 to 0.95)	1281 (8 studies)	⊕⊕⊕⊖ very low ^{8,9}

	540 per 1000	410 per 1000 (329 to 508)			
Osteonecrosis of jaw	Medium-risk population#		RR 4.61	1284 (6 studies)	⊕⊕⊕⊕
	NE	0 per 1000 (0 to 2)	(0.99 to 21.35)		low 10,11

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **HR:** Hazard ratio; **NE:** not estimable due to rarity of events in the control arm

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ A total of 20 RCTs were included in the direct meta-analysis. Only 35% (7/20) of trials had adequate allocation concealment. Only 20% (4/20) of trials reported methods of randomization. Similarly, 15% (3/20) of trials reported blinding procedures and personnel who were blinded to the intervention assignment. However, sensitivity analyses based on the methodological quality domains did not change the estimates. Hence, the assessment of studies' limitations may represent the poor quality of reporting rather than true biased estimates.

² Downgraded the quality of evidence for the outcome of overall survival (OS) by one for the observed inconsistency ($I^2 = 65\%$). However we noticed that this heterogeneity in the pooled estimate is driven by studies by Aviles and colleagues (Aviles 2007; Aviles 2013); when we removed these RCTs heterogeneity disappeared.

³ Note that overall mortality data denotes the mortality rates, i.e. the number of events refers to the number of deaths.

⁴ Downgraded the quality of evidence by one level due to the potential for publication bias. The progression-free survival data were extractable from only 35% (7/20) of studies eligible for direct meta-analysis.

⁵ Downgraded the quality of evidence by one level due to the potential for publication bias. Data related to patients with vertebral fractures were extractable from only 35% (7/20) of studies eligible for direct meta-analysis.

⁶ Downgraded the quality of evidence by one level due to the potential for publication bias. Data related to patients with non-vertebral fractures were extractable from only 30% (6/20) of studies eligible for direct meta-analysis.

⁷ Downgraded the quality of evidence by one level due to the potential for publication bias. Skeletal-related events data were extractable from 50% (10/20) of studies.

⁸ Downgraded the quality of evidence by one level due to variation in assessment instruments. There was significant variation in the assessment methods used to measure pain.

⁹ Downgraded the quality of evidence by one level due to variation in assessment of pain based on blinding of the assessors. Only 15% (3/20) of trials reported blinding procedures and personnel who were blinded to the intervention assignment. Moreover, we found that RCTs with double-blinding showed no significant benefit of bisphosphonates over placebo for amelioration of pain, while non-blinded RCTs favored bisphosphonates over placebo for pain relief. We also downgraded the quality of evidence by one level due to imprecision.

¹⁰ Downgraded the quality of evidence by one level due to the potential for publication bias. The Osteonecrosis of jaw data were extractable from 30% (6/20) of studies eligible for direct meta-analysis.

¹¹ Downgraded the quality of evidence by one level due to imprecision. All included RCTs and also the pooled estimate have wide confidence intervals.

The moderate control risk was calculated via GRADEpro software based on average risk in the control arm of the included studies.

We have calculated and presented overall mortality instead of OS. The expected events represent a median timeline of 5 years.

PFS events represent death or progress or relapse. The expected events represent a median timeline of 5 years.

BACKGROUND

Description of the condition

Multiple myeloma (MM) is characterized by neoplastic proliferation of plasma cells, mainly contained within the bone marrow. It is a debilitating malignancy that is a part of a spectrum of diseases ranging from monoclonal gammopathy of unknown significance to plasma cell leukemia (Anderson 2015; Tricot 2000). MM can present outside the bone marrow as a solitary plasmacytoma or extramedullary plasmacytoma. MM is more prevalent after the age of 40 years. A diagnosis of symptomatic myeloma requires the presence of monoclonal protein (M-protein) in serum, urine, or both; bone marrow clonal plasma cells (> 10%) or plasmacytoma; and related organ or tissue impairment (Anderson 2015; Greipp 2005). Ninety-seven per cent of people with MM have M-protein present in serum, urine, or both. A diagnosis of asymptomatic myeloma (also known as smoldering myeloma) requires the presence of M-protein in serum of 30 g/L or more and bone marrow clonal plasma cells of 10%, and no related organ or tissue impairment or symptoms (Anderson 2015). A mnemonic for end-organ damage, which is the hallmark of MM, is CRAB, for hypercalcemia, renal insufficiency, anemia and lytic bone lesions. The most common symptoms of MM are those related to anemia, renal dysfunction, infections and bone lesions. In the majority of patients, slow and steady progressive bone damage (osteolytic lesions) caused by myeloma may lead to fractures of the long bones or compression fractures in the spine. Bone pain is often a symptom of this disease, especially in the form of severe back pain.

Description of the intervention

Bisphosphonates are used in the management of MM as supportive therapy to inhibit progression of osteoclastic activity and affect skeletal-related morbidity and mortality secondary to this process. Several randomized trials (Description of studies) have been conducted investigating the use of bisphosphonates in MM. Etidronate was the first bisphosphonate tested in a clinical setting, but with no apparent benefit (Belch 1991). Pamidronate, a second-generation bisphosphonate, demonstrated a significant clinical effect on the rate of skeletal-related events (SREs) and pain control in a double-blind, placebo-included randomized controlled trial (RCT) (Berenson 1998). This study also suggested a trend toward an increase in survival with pamidronate in a subgroup of participants. Similarly, RCTs comparing zoledronate with no therapy showed a survival benefit with zoledronate (Aviles 2007; Aviles 2013), and more recently an RCT comparing zoledronate with clodronate showed survival benefit with zoledronate as well (Morgan 2010), indicating the need for the updating of previous reviews (Mhaskar 2010; Mhaskar 2012). In another RCT, the proportion of participants who experienced a progression of lytic lesions was smaller in the clodronate-treated group than in the placebo group (Lahtinen 1992). However, no significant effect on survival was seen. In a German open-label study, there was a trend toward reduction in the number of new bone lesions in the clodronate-treated group (Heim 1995). Again, no significant effect on survival was seen. Moreover, our previous systematic reviews published in 2010 and 2012

(Mhaskar 2010; Mhaskar 2012) found that adding bisphosphonates to the treatment of myeloma reduces pathological vertebral fractures and pain but—from the published evidence available then—not mortality.

All bisphosphonates are poorly absorbed after oral administration, but effective plasma levels can be achieved with clodronate. Aminobisphosphonates such as pamidronate have caused gastrointestinal (GI) ulceration when given orally (Lufkin 1994). The other adverse effects associated with the use of bisphosphonates typically consist of renal functional impairment, myalgias and hypocalcemia. Osteonecrosis of the jaw (ONJ) has been described as a serious new complication associated with bisphosphonates (Bagan 2006; Durie 2005; Ruggiero 2004). Bisphosphonate-associated ONJ has been described in various malignancies, including MM, breast cancer and prostate cancer, and can be a debilitating problem associated with significant morbidity.

How the intervention might work

Bisphosphonates are specific inhibitors of osteoclastic activity (Berenson 1998b). In addition, some studies in vitro suggest an additional antitumor effect of bisphosphonates (Aparicio 1998; Shipman 1997). Therefore, there exists a pharmacological rationale for the use of these agents in MM. Bisphosphonates are a heterogeneous group of molecules that resemble pyrophosphates that are used in technical chemistry for calcium binding. The bisphosphonate core structure is formed by two phosphonate groups attached to a single carbon atom (the so called P-C-P structure). In contrast to pyrophosphates, bisphosphonates are stable in biological environments. There are many types of bisphosphonates. Alendronate, risedronate, ibandronate, pamidronate and zoledronate, termed aminobisphosphonates (Figure 1), are bisphosphonates containing nitrogen in one of the side chains. These nitrogen-containing bisphosphonates inhibit the mevalonate pathway (the main target being farnesyl diphosphate synthase). Clodronate, etidronate and tiludronate, termed non-aminobisphosphonates (Figure 1), do not contain nitrogen and are incorporated into hydrolytically stable analogs of adenosine triphosphate. Both events cause impairment of osteoclast cell function and, ultimately, lead to osteoclast apoptosis (Brown 2004). The pathogenesis of osteoclast bone resorption may also be understood to be the result of abnormal cytokine signaling between malignant plasma cells, osteoclasts and osteoblasts. Increased levels of RANK ligand produced by myeloma cells and marrow stromal cells, coupled with suppression of soluble osteoprotegerin, favors osteoclast bone resorption (Cassidy 2006). Other cytokines such as interleukin-6 further support an excess of osteoclast activity (Cassidy 2006). In summary, bisphosphonates are broadly classified into two categories (amino- and non-aminobisphosphonates) based on their chemical structure and molecular mechanism of action. Aminobisphosphonates are considered to be more potent than non-aminobisphosphonates. Based on in vitro data, zoledronate is considered the most potent and etidronate the least potent among bisphosphonates (Drake 2008; Dunford 2001) (Table 1).

Figure 1. Bisphosphonate chemical structures

Why it is important to do this review

This is an update of our previous systematic review addressing the uncertainty regarding the role of bisphosphonates in the management of MM (Mhaskar 2012). While we found no direct effect of bisphosphonates on overall survival (OS) compared with placebo or no treatment, there was statistically significant heterogeneity for the outcome of OS among the included RCTs (Mhaskar 2012). However, since our last review, a new study claiming OS benefit (Aviles 2013) and additional data from a study (Morgan 2010) that was included in our 2012 systematic review have been published. This created the impetus to update our previous review to assess the evidence related to benefits and harms associated with the use of various types of bisphosphonates (aminobisphosphonates versus non-aminobisphosphonates) in the management of patients with MM.

OBJECTIVES

Our primary objective was to determine whether adding bisphosphonates to standard therapy in MM decreases skeletal-related morbidity (pathological fractures) and improves overall survival (OS) and progression-free survival (PFS).

Our secondary objectives were to determine the effects of bisphosphonates on pain, quality of life, incidence of hypercalcemia, incidence of bisphosphonate-related GI toxicities, ONJ and hypocalcemia.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized controlled trials (RCTs) in which interventions consisted of bisphosphonates versus placebo or no treatment or other bisphosphonates in patients with MM.

We excluded studies that used other agents to affect skeletal-related morbidity or mortality (e.g. fluoride), duplicate reports and those studies that reported subgroup analyses from larger RCTs. In the case of duplicate reports, we extracted data from the articles published at later dates. We also excluded studies that included participants with an underlying disease other than MM and studies that reported insufficient data, as well as studies with fewer than 10 participants.

We also included observational studies and case reports regarding bisphosphonate-related osteonecrosis of the jaw (ONJ).

Types of participants

Participants with the diagnosis of MM as defined by the researchers in each study. We found no uniform criteria for the diagnosis (Alexanian 1994; Anderson 2015) among the studies selected for this systematic review. However, all studies required biopsy-proven myeloma as the diagnostic criterion and bone involvement that met criteria for administration of bisphosphonates according to the studies' investigators.

Types of interventions

- Experimental group: treatment included any bisphosphonate
- Control group: no therapy, placebo or other bisphosphonates

Types of outcome measures

We extracted data on the following outcomes.

Primary outcomes

- Overall survival (OS) (measured as mortality)
- Progression-free survival (PFS)
- Skeletal-related events (SRE): number of participants experiencing pathological fractures (vertebral and non-vertebral), total skeletal-related events (SREs) (as defined by individual authors; these included vertebral fractures, non-vertebral fractures and osteolytic lesions)

Secondary outcomes

- Number of participants with pain relief (as defined by individual authors)
- Incidence of hypercalcemia (defined as ≥ 2.65 mmol/L)
- Adverse events (grade III/IV)
- Quality of life (as defined by individual authors)

Search methods for identification of studies

This is an update of the review published in 2012 (Mhaskar 2012). We searched the electronic databases from September 01 2011 onwards up to 17 July 2017.

Electronic searches

We identified all RCTs in MM in the following databases:

- MEDLINE (2011/09/01 to July 2017) (see Appendix 1);
- Cochrane Central Register of Controlled Trials (CENTRAL) (the Cochrane Library 2017, Issue 7) (see Appendix 2);
- ClinicalTrials.gov (search date: July 2017) (see Appendix 3);
- Embase (2011/09/01 to July 2017) (see Appendix 4).

We also identified observational studies and case reports regarding bisphosphonate-related ONJ in the following database:

- MEDLINE (2011/09/01 to July 2017) (see Appendix 1).

Searching other resources

We searched the American Society of Hematology (date of search 5 February 2016) EudraCT, ISRCTN (date of search 24 May, 2016) and WHO registry (date of search 21 September, 2017).

Contacting authors: Where a study contained unclear information, we contacted the authors to ensure accuracy. This occurred in one instance, but the email listed on the publication was not a valid email address. Hence we were not able to contact the author (Aviles 2013).

Data collection and analysis

Selection of studies

Review authors RM and AK independently scanned the retrieved titles and abstracts of all studies for their eligibility for inclusion in this systematic review. If a decision on inclusion was not made on the basis of the review of the title and abstract, we obtained the full text of the article to assess eligibility. Disagreements in the selection of studies were resolved by consensus (Higgins 2011a). At every stage of searching and screening, the overall numbers of studies identified, excluded and included with reasons, were documented according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Liberati 2009). We used this information to create a flow diagram (Figure 2).

Data extraction and management

For this update two review authors (RM and AK) extracted all data and resolved disagreements by consensus. After the extraction, a third review author (BM) rechecked all data. The outcomes extracted are listed above. Data regarding the methods of trial conduct and design were also extracted. Specifically, we extracted data regarding methods of allocation concealment, method of randomization, adequacy of blinding procedures (who was blinded: participants, investigators, data analysts, etc), description of withdrawals and dropouts, and method of data analysis (intention-to-treat (ITT)/per protocol). To determine whether the analysis was performed according to the ITT principle, data were extracted and matched on the numbers of participants randomized and analyzed. If the numbers of participants randomized and analyzed were the same, we considered the analysis as ITT.

We also extracted details regarding drug, dose, average length of treatment, length of follow-up, number of randomized participants, number of participants excluded from the analysis, OS and PFS, presence of pain, level of calcium and adverse events.

Unfortunately, we were not able to extract all data from all papers (see Table 2;).

Assessment of risk of bias in included studies

Two review authors (RM and AK) independently assessed all eligible studies for their risk of bias (assessment of methodological quality) using methods suggested in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). We used the extracted data to assess the methodological quality (risk of bias and random error) of each trial. The review authors judged each quality domain based on the following three-point scale.

- 'Yes' (low risk of bias: plausible bias unlikely to seriously alter the results if all criteria were met)
- 'No' (high risk of bias: plausible bias that seriously weakens confidence in the results if one or more criteria were not met)
- 'Unclear' (uncertain risk of bias: plausible bias that raises some doubt about the results if one or more criteria were assessed as unclear)

The risk of bias domain included the following: selection bias, performance bias, detection bias and other bias.

The quality items related to risk of random error included details about the power of the study (beta error), predetermination of alpha error and a priori estimation of sample size.

Measures of treatment effect

- For time-to-event outcome: data were summarized as hazard ratio (HR) and 95% confidence intervals (CIs).
- For dichotomous outcome: data were measured as risk ratio (RR) with 95% CIs.
- For continuous outcome: data were summarized as mean difference and standard deviation.

Unit of analysis issues

The unit of analysis was a study from which we extracted the aggregate data as follows: for dichotomous variables, the number of participants in the intervention arm and the number of participants in the control arm. For continuous outcomes, we extracted the mean, standard deviation, and the number of participants in the intervention and control arm. For time-to-event outcomes, we extracted log HR and the standard error of log HR.

Dealing with missing data

We did not conduct analyses for the missing data.

Assessment of heterogeneity

We calculated the χ^2 and I^2 statistics to test for heterogeneity. We assessed the degree of heterogeneity among trials and between subgroups using the I^2 statistic. We used the following guide to interpret the I^2 statistic: $I^2 = 0\%$ to 40% (heterogeneity that might not be important), $I^2 = 30\%$ to 60% (moderate heterogeneity), $I^2 = 50\%$ to 90% (substantial heterogeneity), $I^2 = 75\%$ to 100% (considerable heterogeneity) (Deeks 2011).

Assessment of reporting biases

We investigated the possibility of publication bias using the funnel plot method of Begg and Mazumdar (Begg 1994) and Egger and

colleagues (Egger 2001) as outlined in chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011d).

Data synthesis

Direct comparison of treatment effects (bisphosphonates versus placebo or no treatment)

We summarized dichotomous data using RR and pooled these data using a random-effects model in Review Manager 5.3 (RevMan) (RevMan 5.3). In cases of time-to-event data, for each included RCT, we calculated the observed minus expected events and variance from the reported mortality estimates to calculate HR. In cases where the authors did not report the mortality estimates, we extracted data from papers using methods described by Tierney and colleagues (Tierney 2007). We pooled the time-to-event data using the random-effects model (DerSimonian 1986) in Revman 5.3 (RevMan 5.3) to calculate overall HRs. We also calculated the number of participants who needed to be treated to avoid one adverse outcome and number of participants who were treated to cause an additional harm (Laupacis 1988) to express treatment benefits and harms, respectively, in the context of the estimated absolute risks in the control arms. All data are reported with 95% CIs.

Indirect comparison of treatment effects

For this update, we used the Bayesian method outlined by Lu and colleagues (Lu 2004) to perform the indirect meta-analyses.

We used the Bayesian methods under random-effects multiple treatment comparisons (MTC) for indirect comparisons (Lu 2004; Higgins 1996). The random-effects model assumes homogeneous between-studies variance. We derived posterior estimates for Bayesian methods using Gibbs sampling via Markov chain Monte Carlo simulation in WinBUGS (version 1.4). All means were given a vague prior distribution (normal distribution with mean 0 and sufficiently large variance). We report the HR or RR estimates and credibility intervals based on Bayesian methods (Table 3). In the presence of loops, the consistency of the network was assessed using methods described by Dias and colleagues (Dias 2010). We followed guidelines suggested by Salanti and colleagues (Salanti 2011) for graphical presentations and numerical summaries of the multiple treatment meta-analysis. For each comparison, we also derived ranking probability based on SUCRA (Surface Under the Cumulative Ranking Curve) (Chaimani 2013). A formal assessment of transitivity was not done. The assumption of transitivity was difficult to assess due to the lack of closed loops in the networks for different outcomes. However, since the distribution of treatment effects in direct comparison was in agreement with the results of the network meta-analysis, we had no reason to believe the transitivity principle was violated (Salanti 2014). Additionally, small studies received less weight in our network meta-analysis.

We performed and reported the work according to PRISMA guidelines (Cornell 2015; Liberati 2009). We created a 'Summary of findings' table using the GRADE software for direct comparisons (Balslem 2011; GRADEpro 2008; Guyatt 2011; Guyatt 2011a; Guyatt 2011b; Guyatt 2011c; Guyatt 2011d; Guyatt 2011e) and network meta-analysis (Puhan 2014) separately.

Subgroup analysis and investigation of heterogeneity

Apart from sensitivity analyses, we conducted subgroup analyses based on duration of treatment. We assessed the differences

between the subgroups using the test of heterogeneity between subgroups in RevMan 5.3 (RevMan 5.3). In the presence of relevant heterogeneity, we used meta-regression to estimate the extent to which covariates explain the treatment effects (Thompson 2002). Meta-regression was performed with the Knapp-Hartung modification, which is more sensitive to false-positive rates than the normal approximation estimates (Higgins 2004) using STATA statistical analysis software (STATA V10.1). Meta-regression was performed using only one covariate of bisphosphonate potency and has been reported (not adjusted for any other variables). We used potency as a covariate and expressed the association as a slope of (1-Hazard Ratio) per 1000 unit increase in potency.

Sensitivity analysis

We conducted sensitivity analyses according to methodological quality dimensions to assess the existence of a potential bias in our results (Jüni 2001). In particular, we focused on those dimensions that have been empirically linked to bias and random error on all outcomes.

RESULTS

Description of studies

Results of the search

For this update, we searched the electronic databases from 1 September 2011 onwards until 17 July, 2017. The initial search

identified 994 citations. We excluded 769 studies and reviewed the full text of 15 studies. Our initial search for observational studies reporting osteonecrosis of the jaw (ONJ) identified 39 citations. We excluded 35 citations and included four case reports/case series reporting ONJ (Gabbert 2015; Gander 2014; Watters 2013; Wickham 2013).

Of these, seven studies were found to be ineligible due to following reasons: two were non-randomized studies (Chiang 2013; Teoh 2012), one was a cost-effectiveness study (Delea 2012), three studies addressed the role of denosumab (Henry 2014; Lipton 2012; Vadhan-Raj 2012), and in one study participants in both arms received the same dose of zoledronate with a hypothesis that treatment with thalidomide and zoledronate would prolong the time to progression to MM over alone (Witzig 2013). We identified four publications related to the study by Morgan and colleagues (Morgan 2010), which was included in the previous version. We included additional data from these four publications in this update and we added the citations of these publications under Morgan 2010. In summary, we identified and included three new RCTs (Aviles 2013; Sezer 2010; Zhang 2012) in this review (Figure 2). The study by Zhang and colleagues was published in English and Chinese. We reviewed both publications. However, none of the publications included outcomes that are relevant for our systematic review. One additional study was identified through personal communication with the Cochrane Hematological Malignancies group (Garcia-Sanz 2015) and was not retrieved through the formal search.

Figure 2. Study flowchart

Figure 2. (Continued)

**Final included studies in quantitative meta analysis
N=23**

We also found one ongoing open-label multi-center international RCT comparing zoledronic acid for four years versus stopping treatment with zoledronic acid after two years ([Lund 2014](#)).

Included studies

In this update, we included four new studies ([Aviles 2013](#); [Garcia-Sanz 2015](#); [Sezer 2010](#); [Zhang 2012](#)) that were not part of the previous published version ([Mhaskar 2012](#)), resulting in 20 RCTs comparing bisphosphonates with either placebo or no treatment and four RCTs with a different bisphosphonate as a comparator.

Two trials reported the effects of etidronate compared with placebo or no treatment ([Belch 1991](#); [Daragon 1993](#)); seven trials reported the effects of pamidronate compared with placebo or no treatment ([Attal 2006](#); [Berenson 1998a](#); [Brincker 1998](#); [Kraj 2000](#); [Leng 2002](#); [Musto 2003](#); [Terpos 2000](#)); five trials reported the effects of clodronate compared with placebo or no treatment ([Delmas 1982](#); [Heim 1995](#); [Lahtinen 1992](#); [McCloskey 2001](#); [Zhang 2012](#)) and one trial described the effects of ibandronate compared with placebo ([Menssen 2002](#)). Five trials compared the effects of zoledronate versus no therapy in myeloma ([Aviles 2007](#); [Aviles 2013](#); [Garcia-Sanz 2015](#); [Musto 2008](#); [Sezer 2010](#)).

We also included the following RCTs comparing pamidronate versus ibandronate ([Terpos 2003](#)), zoledronate versus pamidronate ([Morgan 2010](#)), 30 mg of pamidronate versus 90 mg of pamidronate ([Gimsing 2010](#)) and zoledronate versus pamidronate ([Rosen 2003](#)). In this update, we included four additional publications related to the study by Morgan and colleagues ([Morgan 2010](#)).

In total we included 24 RCTs in this systematic review (see details in [Characteristics of included studies](#)).

Excluded studies

The search conducted for our previous review excluded 16 trials (see details in [Characteristics of excluded studies](#)). One trial studied antitumor and bone metabolism effects and reported no outcomes of interest ([Martin 2002](#)). One was a duplicate report ([Kraj 2000a](#)); seven trials were not randomized ([Ali 2001](#); [Barlogie 2008](#); [Bergner 2007](#); [Morris 2001](#); [Spencer 2008](#); [Tassinari 2007](#); [Vogel 2004](#)). One trial with nine enrolled participants was too small to be included ([Kraj 2002](#)). Three studies had used combination therapy ([Caparrotti 2003](#); [Ciepluch 2002](#); [Tosi 2006a](#)). We also excluded two phase II RCTs that tested denosumab ([Fizazi 2009](#); [Vij 2009](#)) and one prognostic study ([Terpos 2010](#)).

For this update, we excluded a further seven studies; two non-randomized studies ([Chiang 2013](#); [Teoh 2012](#)), one cost-effectiveness study ([Delea 2012](#)), three studies addressing the role of denosumab ([Henry 2014](#); [Lipton 2012](#); [Vadhan-Raj 2012](#)), and one study in which patients in both the arms received the same dose of zoledronate with a hypothesis that treatment with thalidomide and zoledronate would prolong the time to progression to MM over zoledronate alone ([Witzig 2013](#)).

In total, in this update we excluded 23 studies (see details in [Characteristics of excluded studies](#)).

Risk of bias in included studies

We have presented the results of the 'Risk of bias' assessment in [Figure 3](#). The study by Sezer and colleagues was published as meeting abstract ([Sezer 2010](#)) and lacked the details needed for us to assess the methodological quality of this study. Hence we have extracted data from www.clinicaltrials.gov related to this study ([Sezer 2010](#)).

Figure 3. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Other bias	Intention to treat Analysis
Attal 2006	+	+	-	-	-	+	-	+
Aviles 2007	-	-	-	-	-	-	-	+
Aviles 2013	+	+	-	-	-	+	+	+
Belch 1991	-	+	+	?	?	-	+	-
Berenson 1998a	+	+	+	+	+	+	-	-
Brincker 1998	-	-	+	?	?	+	+	+
Daragon 1993	-	-	+	-	-	+	-	-
Delmas 1982	-	-	+	?	?	-	-	-
Garcia-Sanz 2015	-	-	-	-	-	+	-	+
Gimsing 2010	+	+	+	+	+	+	+	+
Heim 1995	-	-	-	-	-	+	-	-
Kraj 2000	-	-	-	-	-	-	-	-
Lahtinen 1992	-	-	+	+	+	+	+	+
Leng 2002	-	-	-	-	-	-	-	-
McCloskey 2001	-	+	+	+	+	+	-	-
Menssen 2002	-	-	+	?	?	-	-	+
Morgan 2010	+	+	-	-	-	+	+	+
Musto 2003	+	-	-	-	-	+	-	-
Musto 2008	+	+	-	-	-	+	+	+
Rosen 2003	+	+	-	-	-	+	-	+

Figure 3. (Continued)

Rosen 2003	+	+	-	-	-	+	-	+
Sezer 2010	?	?	-	-	-	+	?	-
Terpos 2000	-	-	-	-	-	-	-	-
Terpos 2003	-	-	-	-	-	-	-	+
Zhang 2012	-	-	-	-	-	-	-	+

Allocation

Twenty-nine per cent (7/24) of trials reported the method of generating the randomization sequence and are deemed as having a low risk of selection bias. Sixteen studies had a high risk of selection bias and one study had an unclear risk of selection bias.

Thirty-seven percent (9/24) of trials had adequate allocation concealment and are deemed as having a low risk of selection bias. Fourteen studies had a high risk of selection bias and one study had an unclear risk of selection bias.

Blinding

Thirty-seven per cent (9/24) of studies were reported as double-blinded and were deemed to have a low risk of performance bias. However, of these nine studies only four reported blinding procedures and details on specific personnel who were blinded to the intervention assignment and therefore to have a low risk of detection bias. Twelve per cent (3/24) of studies were open-label (Aviles 2013; Garcia-Sanz 2015; Morgan 2010).

Incomplete outcome data

Withdrawals and dropouts (attrition bias) were described in 62% (15/24) of trials and deemed to have a low risk of attrition bias. Nine studies were deemed to have a high risk of attrition bias. Sixty-two per cent (15/24) of trials analyzed the data according to the ITT principle and were considered to have a low risk of attrition bias.

Selective reporting

We assessed the included studies for completeness of reporting for both benefits as well as treatment-related harms. All included studies reported the benefits and harms of the interventions in the way specified in the methods section of the trial publications. It is important to note that we did not have access to trial protocols, and hence could not assess the trial publications for selective reporting of outcomes. Overall, the risk of reporting bias was low in the included studies.

Other potential sources of bias

The expected difference in the primary outcomes was prespecified in 37% (9/24) of RCTs. Type I and type II errors were reported in 33% (8/24) of RCTs. A priori sample size calculations were reported in 33% (8/24) of RCTs. (see Figure 3 and Characteristics of included studies for details). We have categorized the elements extracted to calculate the risk of random error (pre-specification of alpha and beta errors and sample size calculation) as "other bias" in the 'risk

of bias' table (Figure 3). The funnel plots for the primary outcome of overall mortality did not suggest publication bias.

Effects of interventions

See: [Summary of findings for the main comparison Summary of findings \(direct comparisons\)](#)

Altogether 24 RCTs enrolled 3680 participants in the bisphosphonates treatment group and 3621 in the control group. The study by Zhang et al did not report data on any of the outcomes of interest for this SR (Zhang 2012). Data on overall survival (OS)/mortality were reported in 67% (16/24) of RCTs, and 37% (9/24) of RCTs reported PFS estimates. Data on vertebral fractures were reported in 353 (8/24) of RCTs, and 29% (7/24) of RCTs reported non-vertebral fracture data. Data on SREs were reported in 58% (14/24) of RCTs. Data on pain amelioration were reported in 37% (9/24) of RCTs. Data on hypercalcemia were reported in 50% (12/24) of RCTs. Data on GI toxicities were reported in 29% (7/24) of RCTs, and data on renal dysfunction were reported in only 12% (3/24) of RCTs. Data on hypocalcemia were reported in 12% (3/24) of RCTs. Calcium data were extractable in the continuous format from only two RCTs. However, effects of bisphosphonates on calcium were reported in the dichotomous (number of participants with hypocalcemia or hypercalcemia) format in most of the studies. Hence, we performed an meta-analysis using the dichotomous data. Data on the quality of life were not reported at all.

Results of direct comparison of treatment effects (bisphosphonates versus placebo or no treatment)

Efficacy of bisphosphonates (benefits)

(see also: [Summary of findings for the main comparison](#))

1) Effect on overall survival (OS)

Data were extractable from 14 RCTs. These studies enrolled 2706 participants. The pooled results showed no evidence for a difference in improvement of OS with the use of bisphosphonates compared with placebo or no treatment. The pooled hazard ratio (HR) for the outcome of OS was 0.90 (95% confidence interval (CI) 0.76 to 1.07; $P = 0.24$) (Analysis 1.1). There was substantial heterogeneity among included trials ($I^2 = 65\%$; $P = 0.0004$) (see 'Assessment of bias: sensitivity analysis' section below for explanation of heterogeneity). The overall quality of evidence for OS was moderate (Summary of findings for the main comparison).

2) Effect on progression-free survival (PFS)

Data were extractable from seven RCTs. These studies enrolled 908 participants. Use of bisphosphonates showed no evidence for a difference in improvement in PFS compared with placebo or no treatment. The pooled HR for PFS was 0.75 (95% CI 0.57 to 1.00; $P = 0.05$) (Analysis 1.2). There was no heterogeneity among trials reporting PFS estimates ($I^2 = 41\%$; $P = 0.12$). The overall quality of evidence for PFS was low (Summary of findings for the main comparison).

3) Effect on the number of participants with vertebral fractures

Data were extractable from seven RCTs. These studies enrolled 1116 participants. The pooled results showed evidence for a difference in improvement in reducing vertebral fractures with use of bisphosphonates compared with placebo or no treatment. The pooled RR for the outcome of vertebral fractures was 0.74 (95% CI 0.62 to 0.89; $P = 0.001$) (Analysis 1.3). There was no heterogeneity among included RCTs ($I^2 = 7\%$; $P = 0.38$). The overall quality of evidence for vertebral fractures was moderate (Summary of findings for the main comparison).

4) Effect on the number of participants with non-vertebral fractures

Data were extractable from six RCTs. These studies enrolled 1389 participants. The pooled results showed no evidence for a difference in reducing non-vertebral fractures with use of bisphosphonates compared with placebo or no treatment. The pooled RR for the outcome of vertebral fractures was 1.03 (95% CI 0.68 to 1.56; $P = 0.90$) (Analysis 1.4). We noted moderate heterogeneity among the included trials ($I^2 = 54\%$; $P = 0.07$). The overall quality of evidence for non-vertebral fractures was moderate (Summary of findings for the main comparison).

5) Effect on the total skeletal-related events (SREs)

Data were extractable from 10 RCTs. These studies enrolled 2141 participants. The pooled results showed evidence for a difference in reducing SREs with use of bisphosphonates compared with placebo or no treatment. The pooled RR for the outcome of SREs was 0.74 (95% CI 0.63 to 0.88; $P = 0.0005$) (Analysis 1.5). We noted moderate heterogeneity among included RCTs ($I^2 = 48\%$; $P = 0.04$). The overall quality of evidence for SREs was moderate (Summary of findings for the main comparison).

6) Effect on pain

Data were extractable from eight RCTs. These studies enrolled 1281 participants. The pooled results showed evidence for a difference in amelioration of pain with use of bisphosphonates compared with placebo or no treatment. The pooled RR for the outcome of pain was 0.75 (95% CI 0.60 to 0.95; $P = 0.01$) (Analysis 1.6). There was substantial heterogeneity among included RCTs ($I^2 = 63\%$; $P = 0.008$) (see 'Assessment of bias: sensitivity analysis' section below for explanation of heterogeneity). The overall quality of evidence for pain was very low (Summary of findings for the main comparison).

7) Effect on the incidence of hypercalcemia (≥ 2.65 mmol/L)

Data were extractable from 10 RCTs. These studies enrolled 2174 participants. The pooled results showed no evidence for a difference in reducing hypercalcemia with use of bisphosphonates compared with placebo or no treatment. The pooled RR for the outcome of hypercalcemia was 0.78 (95% CI 0.56 to 1.09; $P = 0.14$)

(Analysis 1.7). There was no heterogeneity among included RCTs ($I^2 = 21\%$; $P = 0.25$).

Treatment-related harms

The bisphosphonate-related harms that were extractable among eligible studies were gastrointestinal (GI) symptoms, hypocalcemia, renal dysfunction and ONJ. No bisphosphonate-related mortality was reported in any of the studies eligible for the analysis.

1) Osteonecrosis of the jaw (ONJ)

Data were extractable from six RCTs. These studies enrolled 1284 participants. The pooled results showed evidence for a difference in frequency of ONJ with use of bisphosphonates compared with placebo or no treatment. The pooled RR for the outcome of ONJ was 4.61 (95% CI 0.99 to 21.35; $P = 0.05$) (Analysis 2.1). There was no statistically significant heterogeneity among included RCTs ($I^2 = 0\%$; $P = 0.95$). The overall quality of evidence for ONJ was low (Summary of findings for the main comparison).

Two RCTs with bisphosphonate as the comparator also reported estimates of ONJ. In the RCT by Morgan et al (Morgan 2010), zoledronate was associated with higher rates of ONJ (35/983 (4%)) than was clodronate (3/979 (< 1%)). In the RCT by Gimsing et al, ONJ was reported in 2 of 252 participants receiving 30 mg of pamidronate compared with 8 of 250 participants receiving 90 mg of pamidronate (Gimsing 2010). Even though only 5 RCTs reported ONJ, a growing number of ONJ case reports and observational studies evaluating ONJ have been published in recent years (Table 4; Table 5; Table 6). We analyzed 9 observational trials that evaluated 1400 participants regarding ONJ. The highest frequencies of ONJ were seen in studies that used a combination of pamidronate and zoledronate (range 5% to 51%). Zoledronate was associated with ONJ in 3% to 11% of cases. Pamidronate related frequencies of ONJ ranged from 0% to 18%. Overall, for every 1,000 participants treated with bisphosphonates, about one patient will suffer from the ONJ.

2) Gastrointestinal symptoms

Data were extractable from seven RCTs. These studies enrolled 1829 participants. The pooled results showed no evidence for a difference in frequency of GI symptoms with use of bisphosphonates compared with placebo or no treatment. The pooled RR for the outcome of GI symptoms was 1.23 (95% CI 0.95 to 1.59; $P = 0.12$) (Analysis 2.2). There was no significant statistical heterogeneity among included RCTs ($I^2 = 0\%$; $P = 0.95$).

One RCT with bisphosphonate as the comparator also reported estimates of GI symptoms (Morgan 2010). In the RCT by Morgan and colleagues, 24 of 981 participants enrolled in the zoledronate arm had GI symptoms, and 30 of 979 participants receiving clodronate had GI symptoms (Morgan 2010).

The most common adverse events with oral bisphosphonates are upper GI toxicities, such as gastritis (Van Holten-Verzantvoort 1993) and diarrhea (Atula 2003). The intravenous infusions can be associated with injection site reaction and acute systematic inflammatory reactions (Tanvetyanon 2006). Different authors have used various methods to assess GI symptoms. Our first choice was to use the overall number of participants with GI symptoms.

When this number was not available, we used the most common symptoms; in the majority of cases, it was abdominal pain. However, in some studies, nausea or vomiting was a more prevalent symptom. For our analysis, we pooled all GI symptoms together.

3) Hypocalcemia

Data were extractable from three RCTs. These studies enrolled 1090 participants. The pooled results showed no evidence for a difference in frequency of hypocalcemia with use of bisphosphonates compared with placebo or no treatment. The pooled RR for the outcome of hypocalcemia was 2.19 (95% CI 0.49 to 9.74; $P = 0.30$) (Analysis 2.3). There was no statistically significant heterogeneity among included RCTs ($I^2 = 0\%$; $P = 0.88$).

One RCT with bisphosphonate as the comparator also reported estimates of hypocalcemia (Terpos 2003). In the RCT by Terpos and colleagues, none of the 23 participants enrolled in the pamidronate arm had hypocalcemia, while two of 19 participants receiving ibandronate did (Terpos 2003). All bisphosphonates can cause hypocalcemia, regardless of the method of administration, although this only occurs infrequently as a clinically symptomatic problem. Effects of bisphosphonates on calcium were reported in the dichotomous (number of participants with hypocalcemia) rather than in the continuous format in most of the studies, leading to loss of available information.

4) Renal dysfunction

Data were extractable from two RCTs (Daragon 1993; Lahtinen 1992) in the form of serum creatinine estimates. These studies enrolled 414 participants. The pooled results showed no evidence for a difference in the frequency of elevated serum creatinine with the use of bisphosphonates compared with placebo or no treatment. The pooled mean difference for the outcome of renal dysfunction was -0.36 (95% CI -9.75 to 9.03 ; $P = 0.94$) (Analysis 2.4). There was no significant statistical heterogeneity among included RCTs ($I^2 = 18\%$; $P = 0.27$).

One RCT (Garcia-Sanz 2015), reported estimates of renal dysfunction where two of 51 participants enrolled in the zoledronate arm and two of 49 participants in the control arm reported renal dysfunction. One RCT with bisphosphonate as the comparator also reported estimates of renal failure (Morgan 2010); 57 of 983 participants enrolled in the zoledronate arm had renal failure, while 60 of 979 participants receiving clodronate had renal failure (Morgan 2010).

Renal dysfunction is a particularly problematic adverse event that can also occur after infusion of intravenous bisphosphonates. The US Food and Drug Administration reported that 72 participants had renal failure following zoledronate therapy (Chang 2003). As a result, the product labels for pamidronate and zoledronate were amended to include additional nephrotoxicity warnings. However, the true incidence of this adverse event remains unknown.

Quality of life: None of the included studies reported quality of life.

Assessment of bias: sensitivity analysis

Sensitivity analyses were performed to assess the robustness of our findings and explore possible reasons for heterogeneity.

Sensitivity analysis according to methodological quality of reporting

All trials were evaluated according to methodological quality dimensions to assess the existence of potential inaccuracies in our results (Jüni 2001). In particular, we focused on dimensions that have been empirically linked to bias and random error. We preformed sensitivity analyses according to adequacy of allocation concealment (Schulz 1995), blinding, ITT analysis, description of withdrawals and dropouts, and pre specification of type I and II errors for all outcomes (see Characteristics of included studies). The results did not change for any outcome except in case of pain. We found that RCTs with double-blinding showed no significant benefit of bisphosphonates over placebo for amelioration of pain (RR 0.83, 95% CI 0.69 to 1.00), while non-blinded RCTs favored bisphosphonates over placebo for pain relief (RR 0.28, 95% CI 0.12 to 0.67; test of interaction: $P = 0.005$). Similarly, RCTs with ITT analysis showed no significant benefit of bisphosphonates over placebo for amelioration of pain (RR 0.93, 95% CI 0.75 to 1.14), while RCTs with per protocol analysis favored bisphosphonates over placebo for pain relief (RR 0.54, 95% CI 0.33 to 0.89) (test of interaction: $P = 0.04$).

Examples based on the outcome of vertebral fractures and corresponding figures are provided to give a visual impression of results of the sensitivity analyses (Data and analyses). Only two out of seven studies that reported the rate of vertebral fractures had adequate allocation concealment but sensitivity analysis performed according to this criterion indicated no change in the results. Three of seven trials reporting vertebral fractures were performed according to ITT analysis, and these trials showed a smaller treatment effect, which may be due to the exclusion of the largest trial from the analysis (Berenson 1998a). Five of seven studies reporting vertebral fractures were double-blind, but the results were unchanged in this subgroup analysis. Only one of seven studies reporting vertebral fractures described the randomization method, but the results were also unchanged in this subgroup analysis. Furthermore, only two of seven studies reporting vertebral fractures clearly noted the withdrawals and dropouts, but the results remained unchanged in this subgroup analysis. Only Lahtinen 1992 prespecified the type I and II errors out of seven studies reporting vertebral fractures, but the results were unchanged in this subgroup analysis.

Sensitivity analysis according to bisphosphonate potency

The potential cause of heterogeneity was explored by meta-regression. We investigated whether potency of bisphosphonates contributed to the decrease in mortality according to bisphosphonate potency as a covariate (on the log scale) (Figure 4). The Knapp-Hartung meta-regression showed that HR decreases by 7% per 1000 unit increase in bisphosphonate potency (HR 0.94, 95% CI 0.90 to 0.98) given on the log scale. The bisphosphonate potency explained 91.34% of between-study variance (the between-study variance dropped from 0.035 to 0.009). Meta-regression results indicated that the beneficial effect of bisphosphonates on survival in participants with MM may be a function of drug potency, with zoledronate being the most potent bisphosphonate (Figure 4).

Figure 4. Bisphosphonate potency metaregression for overall survival. HR: Hazard ratio.

We also conducted meta-regression for PFS. However, meta-regression results indicated that the effect of a bisphosphonate on restricting disease progression in participants with MM did not differ by bisphosphonate potency (HR 0.94, 95%CI 0.77 to 1.14).

Sensitivity analysis according to treatment duration

We conducted additional sensitivity analyses based on duration of treatment (indefinite versus 0 to 24 months). The results were unchanged for all outcomes except for non-vertebral fractures. The only RCT ([McCloskey 2001](#)) with an indefinite duration of treatment with clodronate showed a statistically significant benefit in favor of clodronate (RR 0.53, 95% CI 0.29 to 0.97), while four RCTs with 0 to 24 months of treatment duration showed no benefit for reduction of non-vertebral fractures (RR 1.25, 95% CI 0.94 to 1.66) (test of interaction: $P = 0.01$).

Sensitivity analysis according to route of administration for gastrointestinal toxicity outcome

We conducted additional sensitivity analyses based on route of administration (oral versus intravenous) for GI toxicity outcome

([Analysis 3.8](#)). The results were unchanged for this outcome (test of interaction: $P = 0.97$).

Results of network meta-analysis of treatment effects

Indirect comparisons or network meta-analysis was conducted for all the outcomes. Data for only the key outcomes are shown here.

Efficacy of bisphosphonates (benefits)

1) Effect on overall survival (OS)

Overall survival/mortality data were available from 16 RCTs involving 5260 participants. A total of 21 indirect comparisons were possible ([Figure 5](#)). The network meta-analysis by MTC method (16 RCTs, 5260 participants) showed the superiority of zoledronate over placebo (HR 0.67, 95% CI 0.46 to 0.91) and etidronate (HR 0.56, 95% CI 0.29 to 0.87) ([Table 3](#)). The results of the MTC method are in agreement with the direct comparison of zoledronate versus placebo in two RCTs ([Aviles 2007](#); [Aviles 2013](#)).

Figure 5. Randomized controlled trial (RCT) network for overall survival (OS), progression free survival (PFS) and skeletal related events (SREs).

2) Effect on progression-free survival (PFS)

Data on PFS were available from nine RCTs involving 3472 participants. A total of 10 indirect comparisons were possible (Figure 5). The network meta-analysis by MTC method (Nine RCTs, 3472 participants) did not show the superiority of any particular bisphosphonate regimen over others (Table 3). MTC analysis did not show a benefit with zoledronate over clodronate (nine RCTs, 3472 participants; HR 1.10, 95% CI 0.46 to 1.95) (Table 3).

3) Effect on the number of participants with vertebral fractures

Data on participants with vertebral fractures were available from eight RCTs involving 3076 participants. A total of six indirect comparisons were possible (Figure 5). The head-to-head (direct) comparison of zoledronate with clodronate in the RCT Morgan 2010 showed a statistically significant benefit with zoledronate over clodronate (one RCT, 1960 participants; RR 0.62, 95% CI 0.44 to 0.87). The MTC method did not show a benefit with zoledronate over clodronate (eight RCTs, 3076 participants; HR 0.59, 95% CI 0.22 to 1.17) (Table 3). The results of MTC analysis showed that zoledronate was superior (eight RCTs, 3076 participants; RR 0.42, 95% CI 0.12 to 0.94) to placebo (Table 3). For all other comparisons the network meta-analysis by MTC method (eight

RCTs, 3076 participants) did not show the superiority of any particular bisphosphonate regimen over others (Table 3).

4) Effect on the total skeletal-related events

Data on participants with SREs were available from 13 RCTs involving 5727 participants. A total of 21 indirect comparisons were possible (Figure 5). Indirect comparison by MTC showed the superiority of zoledronate over placebo (RR 0.57, 95% CI 0.37 to 0.76), zoledronate over ibandronate (RR 0.56, 95% CI 0.26 to 0.98) and pamidronate 90 mg over placebo (RR 0.71, 95% CI 0.49 to 0.96). For all other comparisons the network meta-analysis by MTC method (13 RCTs, 5727 participants) did not show the superiority of any particular bisphosphonate regimen over others (Table 3).

5) Effect on pain

Data on the effect of bisphosphonates on pain control were available from eight RCTs involving 1281 participants. A total of six indirect comparisons were possible. The network meta-analysis by MTC method (eight RCTs, 1281 participants) did not show superiority of any particular bisphosphonate regimen over others (Table 3). MTC analysis did not show a benefit with clodronate over

ibandronate (eight RCTs, 1281 participants; RR 4.13, 95% CI 0.57 to 16.99) (Table 3).

6) Effect on hypercalcemia

Data on the effect of bisphosphonates on hypercalcemia were available from 11 RCTs involving 4146 participants. Indirect comparisons by the MTC method (11 RCTs, 4146 participants) did not show superiority of any particular bisphosphonate regimen over others (Table 3).

Treatment-related harms

We also conducted network meta-analysis by the MTC method for the outcomes of hypocalcemia, renal dysfunction, GI toxicity and ONJ. Results of network meta-analysis by the MTC method were consistent with the results from direct comparisons. Network meta-analysis by the MTC method did not show any differences in the incidence of hypocalcemia, renal dysfunction, and GI toxicity among the bisphosphonates used.

Effect on osteonecrosis of the jaw (ONJ)

Data on the effect of bisphosphonates on ONJ were available from eight RCTs involving 3746 participants. Indirect comparisons by the MTC method show an increased risk of ONJ with zoledronate over clodronate (RR 0.13, 95% CI 0.02 to 0.44). For all other comparisons

network meta-analysis by the MTC method did not show any differences in the incidence of ONJ (Table 3).

Since our network has only one triangle loop, its consistency was assessed using a simple method described by Bucher and colleagues (Bucher 1997). The estimates of consistency indicate that the network was consistent for OS (95% CI -0.86 to 0.07) and PFS (95% CI -0.38 to 0.33). We also ranked each treatment according to the probability that it is best for the outcomes of OS, PFS, SREs, hypercalcemia, GI toxicity and ONJ (Figure 6). We also calculated the surface under the cumulative ranking (SUCRA) line for each treatment, which is equal to 1 when the treatment is certain to be the best and 0 when it is certain to be the worst (Figure 6). As both rankogram SUCRA show, zoledronate consistently ranked as the best treatment, followed by pamidronate and clodronate. Since the choice of prior for between-studies variance can lead to drastic variation in results (Lambert 2005), especially in a small number of studies, we had already performed an extensive sensitivity analysis in our previous systematic reviews (Mhaskar 2010; Mhaskar 2012), in which we assessed a total of five priors (gamma, uniform, Pareto, logistic and half-normal) based on their application in the literature (Scurrah 2000; Thompson 1997). Gamma and logistic priors exhibited poor convergence. Generally, as the number of studies decreased, the selection of prior dominated the estimates. We noted that the credibility intervals became wider for the less informative priors.

Figure 6. A: Ranking probabilities of competing bisphosphonates. The size of each bar corresponds to the probability of each treatment to be at a specific rank. OS: Overall survival; PFS: Progression-free survival; SRE: Skeletal-related events; Osteonecrosis; GI: Gastrointestinal toxicity; Hyper: Hypercalcemia. B: Surface under the cumulative ranking curve (SUCRA) plots for each treatment. The outcomes are listed on the horizontal axis. SUCRA for each outcome are on the vertical axis.

DISCUSSION

Summary of main results

Key benefits with use of bisphosphonates:

The potential beneficial effect of bisphosphonates on survival is the most intriguing question, as anti-tumor effects against myeloma cells were seen both in vitro (Aparicio 1998; Shipman 1997) and in vivo (Dhodapkar 1998). The direct comparisons in this meta-analysis demonstrate no evidence for a difference related to survival with bisphosphonate compared to placebo. However, evidence for a difference in overall survival (OS) with bisphosphonates compared with placebo/other bisphosphonate was seen in three RCTs (Aviles 2007; Aviles 2013; Morgan 2010). The two studies by Aviles and colleagues comparing zoledronate with placebo showed evidence for a difference with zoledronate in improving OS compared with placebo (Aviles 2007; Aviles 2013). The study by Morgan and colleagues showed a clinically significant anti-MM effect of zoledronic acid compared with clodronate on OS (Morgan 2010). However, the results from our network meta-analysis of 15 randomized controlled trials (RCTs) and 4866 participants showed no evidence for a difference with zoledronate over any other amino-bisphosphonates or clodronate for OS. Similarly, direct comparisons and network meta-analysis did not show superiority of any specific bisphosphonate over placebo or no treatment and other bisphosphonates in improving progression-free survival (PFS).

The results of this meta-analysis show a reduction in total skeletal-related events (SREs) and vertebral fractures, a significant advantage for the participants treated with bisphosphonates. Our results show evidence for a difference with bisphosphonates compared with placebo for the prevention of pathological fractures, most likely due to the effect on preventing pathological vertebral collapses. Interestingly, there was no evidence for a difference with bisphosphonates compared with placebo on reduction of non-vertebral fractures. Bisphosphonates inhibit osteoclastic bone resorption and thereby increase the degree of bone mineralization. Animal models focusing on trabecular bones have also shown that the mechanical properties of the bone (torsion stiffness and elasticity) are improved with the use of bisphosphonates. A comparative study of trabecular and cortical bones in beagle dogs demonstrated that the effect of pamidronate to improve torsion stiffness and elasticity is restricted to trabecular bones, whereas no change was seen in cortical bones (Acito 1994). Similar observations have been made in postmenopausal women treated with pamidronate (Fromm 1991). These studies support our findings that the vertebral fractures are clearly reduced and there was no significant effect on non-vertebral fractures. However, it must be taken into consideration that several studies did not report these events in sufficient detail.

Key harms with use of bisphosphonates:

There was evidence for a difference with bisphosphonates related to increased risk for osteonecrosis of the jaw (ONJ) in participants using bisphosphonates compared with placebo or no treatment, which was not seen in the previous meta-analysis (Mhaskar 2012). RCTs showed that, on average, for every 1000 participants treated with bisphosphonates, about one patient will suffer from the ONJ. Only eight RCTs reported ONJ, and the network meta-analysis showed that no specific bisphosphonate was associated with an increased incidence of ONJ compared with other bisphosphonates.

However, this in part could be a reflection of rare events and thus RCTs with more power are needed for more precise estimates. We also identified 61 observational studies (including case reports) reporting 676 cases of ONJ. The observational studies estimated ONJ to be 0% to 51%, which is in a stark contrast with the estimates obtained from RCTs. The reason for this discrepancy is probably due to the combined effect of inherent limitations associated with observational studies and different eligibility criteria in RCTs versus non-RCTs. No other significant adverse effects associated with the administration of bisphosphonates were identified in the included RCTs.

Overall completeness and applicability of evidence

Physicians' choices regarding type of bisphosphonates for the management of people with multiple myeloma should ideally be based on evidence from comparative trials. There are only four head-to-head comparative studies of bisphosphonates (Gimsing 2010; Morgan 2010; Rosen 2003; Terpos 2003). Unfortunately, the data from Rosen 2003 were not extractable for participants with MM for outcomes other than SREs, and Terpos and colleagues (Terpos 2003) report data addressing only two outcomes (hypercalcemia and hypocalcemia) of interest for this systematic review. Terpos 2003 concluded that a monthly dose of 90 mg of pamidronate is more effective than 4 mg of ibandronate in reducing osteoclast activity, bone resorption and possibly tumour burden in MM. The RCT by Morgan and colleagues compared the effects of zoledronate versus clodronate in participants with MM. The results of this head-to-head comparison showed that treatment with zoledronate was associated with a significant reduction in the proportion of participants with SREs (27% versus 35% with clodronate) and vertebral fractures (5% versus 9% with clodronate), and slightly increased median PFS by two months. But most remarkably, the median OS was significantly improved by 5.5 months with zoledronate compared with clodronate (Morgan 2010; Rajkumar 2010). Our meta-regression analysis showed a significant trend ($P = 0.007$) based on the bisphosphonate potency (7% reduction in mortality for each 1000 unit increase in bisphosphonate potency), with zoledronate being the most potent bisphosphonate (Figure 4). This would imply that zoledronate indeed is the most effective bisphosphonate. However, no such effect was seen in a meta-regression for PFS raising the issue of the mechanism of improving survival, if PFS is not affected, it does not appear to be plausible to improve OS. In addition, our network meta-analyses of 15 RCTs and 5160 participants indicated that zoledronate was not superior to any other bisphosphonate for any outcomes except etidronate. Nevertheless, we should note that in the context of MTC uncertainty analysis, zoledronate ranked as the best treatment, followed by clodronate and pamidronate. However, we noted no difference when pamidronate was compared with clodronate or zoledronate for all outcomes. These findings underscore the need for comparative evaluation of the newer potent amino-bisphosphonates, especially zoledronate versus pamidronate, in an RCT to enable appropriate healthcare decision making. Also, future studies should investigate bisphosphonate treatments as a palliative treatment by measuring its influence on quality-of-life outcomes.

Quality of the evidence

We assessed the potential risk of bias of the included trials according to the previously described quality domains; these are represented in Figure 3. The majority of included trials suffered

from a high risk of selection bias. The majority of the included studies reported analyses according to the principle of intention to-treat (ITT). The majority of included trials had a high risk of performance and detection bias. Twelve per cent (3/24) of studies were open-label (Aviles 2013; Garcia-Sanz 2015; Morgan 2010).

Overall, the quality of evidence according to the GRADE criteria was moderate to low. The study by Zhang and colleagues was published in both English and Mandarin language. We have reviewed and have included both of these publications in this systematic review (Zhang 2012). Nonetheless, we noticed that the publication in the Mandarin language referred to this study as a randomized study but the English language publication does not explicitly mention any details regarding randomization. However, it is important to note that, this study did not report any of the outcomes of interest for this systematic review. We also noticed a discrepancy between the www.clinicaltrials.gov record and the publication of the study by Aviles and colleagues (Aviles 2013). Specifically, on the www.clinicaltrials.gov this study has been labeled as an observational case-control type of study and the publication refers to this study as a randomized control trial.

One criterion for high-quality reporting is that the data should be reported in a form that allow them to be extracted and used in a quantitative research synthesis (i.e. meta-analysis). In most of the studies included in this systematic review, treatment-related morbidities were not reported as events per patient and thus could not be used in the meta-analysis. That is, treatment-related morbidities were reported using statements that did not allow us to

distinguish between specific adverse events occurring in multiple participants or multiple events occurring in a single patient.

Potential biases in the review process

We did not find any methodological issues in the preparation of the review that could put it at risk for bias. We identified one ongoing study comparing zoledronic acid with no treatment. No findings were available as the trial is still recruiting participants (Lund 2014). Sezer 2010 was published as a meeting abstract only. We were able to obtain some data form www.clinicaltrials.gov record for this study. Nonetheless, for reasons unknown to us, this study was not published as a full manuscript, and hence we were not able to access the complete data and findings from this study. Indeed, we were not able to extract data on all outcomes from all the studies (Table 2). Furthermore, one RCT (Garcia-Sanz 2015) did not come up in the formal search and was identified by the Cochrane Hematological Malignancies Group which, we suspect, was due to inadequate cataloguing. The funnel plot for assessment of publication bias showed asymmetry only for the outcome of pain, indicating the possibility of outcome reporting bias or publication bias (Figure 7). However, the findings are also consistent with heterogeneity in interventions or the tendency for the smaller studies to show larger treatment effects (Sterne 2001). Similarly, the observed between-trial heterogeneity makes interpretation of funnel plots difficult and increases the false-positive rate of the tests. Given the comprehensiveness of our search efforts and the fact that most of the trials testing bisphosphonates were small and underpowered, the small-study effect is the most likely explanation for the asymmetry seen in the funnel plots (Sterne 2001).

Figure 7. Funnel plot of comparison: 1 Bisphosphonates vs. control (efficacy), outcome: 1.6 Pain.

Agreements and disagreements with other studies or reviews

A Cochrane systematic review examined relief of pain secondary to bone metastases by using bisphosphonates in 30 identified RCTs (Wong 2002). The review concluded that the evidence is insufficient to recommend bisphosphonates for immediate pain-relief effect. This finding contradicts our results, as well as those of earlier reviews examining the role of bisphosphonates in myeloma patients (Mhaskar 2010; Mhaskar 2012), indicating a likely beneficial effect of bisphosphonates on pain reduction. The discrepancy between the results of our systematic review and the systematic review by Wong and colleagues lies in the decision about which studies should be included and methods of pain reporting as extensively discussed in our previous reviews (Mhaskar 2010; Mhaskar 2012). Although there was a beneficial effect of bisphosphonates on the number of patients with myeloma reporting bone pain in this review, these data must be treated with caution because of the lack of uniformity in data reporting and the presence of statistically significant heterogeneity. The variation in the methods of reporting pain and the quality of included RCTs contributed to the statistically significant heterogeneity observed in pain estimates.

AUTHORS' CONCLUSIONS

Implications for practice

Adding bisphosphonates to the treatment of multiple myeloma (MM) reduces vertebral fractures and probably pain. We found no evidence for a difference for overall survival (OS) and progression-free survival (PFS) with bisphosphonates compared with placebo. The benefits of bisphosphonates should be considered, keeping in mind the risk of developing osteonecrosis of the jaw (ONJ). Zoledronate appears to be superior to etidronate (non-aminobisphosphonate) and placebo for the outcome of OS. However, whether zoledronate is superior to pamidronate and other aminobisphosphonates remains to be determined.

Implications for research

Our findings underscore the urgent need for a randomized controlled trial (RCT) with a head-to-head comparison of zoledronate and pamidronate for their efficacy and safety in patients with MM. In addition, future studies should investigate bisphosphonate treatments as a palliative treatment by measuring its influence on quality-of-life outcomes. There is also a need for studies addressing cost-effectiveness and adverse events, especially ONJ, of bisphosphonate therapy.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Attal 2006

Methods	<p>Study design: Parallel, not double-blind</p> <p>Study length: not reported</p> <p>Study conducted during: not reported (study started in 1999)</p>
Participants	<p>Bisphosphonates: enrolled 196, analyzed 196. Bisphosphonates + thalidomide: enrolled 201, analyzed 201. Placebo: enrolled 200, analyzed 200.</p> <p>Sex (M/F):</p> <p>Bisphosphonates: 109/87 Bisphosphonates + thalidomide: 112/89 Placebo: 110/90</p> <p>Age: mean(SD):</p> <p>Bisphosphonates: 59 (8) Bisphosphonates + thalidomide: 58 (8) Placebo: 59 (8)</p> <p>Inclusion criteria:</p> <p>Stage (Durie 2005): I-III</p> <p>Osteolytic lesion: NR</p> <p>Creatinine: NS</p> <p>Calcium: NS</p> <p>Other criteria: No cytotoxic chemotherapy prior to entry</p>
Interventions	<p>Pamidronate: 90 mg IV, every 4 weeks; Indefinitely.</p> <p>Pamidronate and thalidomide: 400 mg orally, dose reduction to a minimum dose of 50 mg was allowed for treatment-related toxicity.</p>
Outcomes	Total skeletal-related events; total mortality; response rates; ONJ.
Notes	<p>SRE: bone lesion requiring a specific therapy (chemotherapy, irradiation or surgery).</p> <p>Funding: Supported by a major grant from the Programme Hospitalier de Recherche Clinique and by the Swiss Group for Clinical Cancer Research (SAKK).</p> <p>COI statement included: The authors declare no competing financial interests.</p>

Attal 2006 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Methods used for generation of sequence of randomization are not described.
Allocation concealment (selection bias)	Low risk	Methods of allocation concealment are adequately described.
Blinding (performance bias and detection bias) All outcomes	High risk	Study does not involve any blinding.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Study does not involve any blinding.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Study does not involve any blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts are adequately described.
Other bias	High risk	Alpha and beta errors are not prespecified.
Intention to treat Analysis	Low risk	Benefits data are analyzed according to ITT principle.

Aviles 2007

Methods	<p>Study design: Parallel, not double-blind; not placebo-controlled study</p> <p>Study length: not reported</p> <p>Study conducted during: Mar 1999 - Dec 2001</p>
Participants	<p>Bisphosphonates: enrolled 46, analyzed 46. Control: enrolled 48, analyzed 48.</p> <p>Sex (M/F):</p> <p>Bisphosphonates: 26/20 Control: 23/25</p> <p>Mean age (range):</p> <p>Bisphosphonates: 67.3 (43-75) Control: 65.4 (39-75)</p> <p>Inclusion criteria:</p> <p>Stage (Durie 2005): III</p> <p>Osteolytic lesion: At least one</p> <p>Creatinine: NS</p>

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Aviles 2007 (Continued)

	Calcium: NS
	Other criteria: No cytotoxic chemotherapy prior to entry
Interventions	Zoledronate: 4 mg IV, every 4 weeks; indefinitely. Control: no zoledronate.
Outcomes	Total mortality; PFS.
Notes	SRE: appearance of a new lytic lesion (excluding skull), after patient began zoledronate or progression of previous bone lesion according to criteria of Union Internationale Centre le Cancer. Funding: Not reported. COI statement included: Not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Methods used for generation of sequence of randomization are not described.
Allocation concealment (selection bias)	High risk	Methods used for concealment of allocation are not described.
Blinding (performance bias and detection bias) All outcomes	High risk	Study does not involve any blinding.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Study does not involve any blinding.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Study does not involve any blinding.
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropouts are not described.
Other bias	High risk	Alpha and beta errors are not prespecified.
Intention to treat Analysis	Low risk	Benefits data are analyzed according to ITT principle.

Aviles 2013

Methods	Study design: Parallel, open-label; not placebo-controlled study Study length: not reported Study conducted during: Jun 2002 – Dec 2007
Participants	Bisphosphonates: enrolled 151, analyzed 151. Control: No zoledronate: enrolled 157, analyzed 157.

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Aviles 2013 (Continued)

Sex (M/F):

Bisphosphonates: 71/80

Control: 85/72

Mean age (range):

Bisphosphonates: 56.4 (29-65)

Control: 57.8 (33-65)

Inclusion criteria:

Stage (Durie 2005): IIB- IIIB

Osteolytic lesion: NS

Creatinine: creatinine clearance > 30 mL/min

Calcium: NS

Other criteria: Adult patients at least 18 years but less than 65 years of age with untreated symptomatic multiple myeloma and measurable paraprotein in serum and urine, Eastern Cooperative Oncology Group performance status 0–2, and adequate renal (no end-stage renal failure and creatinine clearance > 30 mL/min), hematologic (platelet count > 50×10⁹/L, neutrophil count > 0.75×10⁹/L), and liver function were eligible

Interventions	<p>Zoledronate: IV; 4 mg (or dose-adjusted based on creatinine clearance) once every 28 days for 24 months.</p> <p>Control: no zoledronate.</p>
Outcomes	SRE; overall survival *\$; progression free survival *\$;
Notes	<p>PFS is defined as time from the start of high-dose induction therapy (or time from the start of next treatment) to time of progression, relapse, or death.</p> <p>The primary endpoints were PFS and OS at 10 years, and the secondary endpoints included overall response, rates of complete response and very good partial response, and safety.</p> <p>Funding: This study was supported entirely with resources from the Mexican Institute of Social Security. Financial support for medical editorial assistance was provided by Novartis Pharmaceuticals Corporation, but the study was not sponsored by Novartis or by any other pharmaceutical company. ProEd Communications, Inc., provided medical editorial assistance with this manuscript.</p> <p>COI statement included: Aside from support from Novartis Pharmaceuticals Corporation for medical editorial assistance, all authors declare that they have no financial conflicts of interest.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Methods used for generation of sequence of randomization are described.
Allocation concealment (selection bias)	Low risk	Methods of allocation concealment are adequately described.
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label study

Aviles 2013 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts are described.
Other bias	Low risk	Alpha and beta errors are prespecified.
Intention to treat Analysis	Low risk	Benefits data are analyzed according to ITT principle.

Belch 1991

Methods	<p>Study design: Parallel, double-blind; placebo-controlled study</p> <p>Study length: not reported</p> <p>Study conducted during: Nov 1983 – Feb 1987 (enrollment in the high dose arm was stopped in Jun 1984)</p>
Participants	<p>Bisphosphonates: enrolled 98, analyzed 92. Control: enrolled 78, analyzed 74.</p> <p>Sex (M/F):</p> <p>Bisphosphonates: 60/32 Control: 44/30</p> <p>Mean age (SD/range): not reported</p> <p>Inclusion criteria:</p> <p>Stage (Durie 2005): I-III</p> <p>Osteolytic lesion: NR</p> <p>Creatinine: < 3 mg/dL</p> <p>Calcium: Normal or elevated</p> <p>Other criteria: No cytotoxic chemotherapy prior to entry</p>
Interventions	<p>Etidronate: capsules (20 mg/kg for 28 days every other 28 days: but this arm was discontinued); enrollment took place for: 5 mg/kg until death or discontinuation.</p> <p>Placebo: identical appearance.</p>
Outcomes	<p>Vertebral index; total mortality*; pain; calcium.***</p>
Notes	<p>SRE: bone progression (appearances of new lesions or worsening of existing ones)\$; mortality* (from the date of randomization); calcium reported as a dichotomous variable.</p>

Belch 1991 (Continued)

Funding: Supported by Norwich Eaton Pharmaceuticals Inc. and The National Cancer Institute of Canada.

COI statement included: not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Methods used for generation of sequence of randomization are not described.
Allocation concealment (selection bias)	Low risk	Methods of allocation concealment are adequately described.
Blinding (performance bias and detection bias) All outcomes	Low risk	Study is double-blinded.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study is double-blinded but who was blinded is not mentioned.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study is double-blinded but who was blinded is not mentioned.
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropouts are not described.
Other bias	Low risk	Alpha and beta errors are prespecified.
Intention to treat Analysis	High risk	Benefits data are not analyzed according to ITT principle.

Berenson 1998a

Methods	<p>Study design: Parallel, double-blind; placebo-controlled study</p> <p>Study length: not reported</p> <p>Study conducted during: Aug 1990 – Jun 1993</p>
Participants	<p>Bisphosphonates: enrolled 205, analyzed 198. Placebo: enrolled 187, analyzed 179.</p> <p>Sex (M/F):</p> <p>Bisphosphonates: 108/88 Control: 109/72</p> <p>Mean age (SD):</p> <p>Bisphosphonates: 64 (10) Control: 63 (10)</p> <p>Inclusion criteria:</p>

Berenson 1998a (Continued)

Stage (Durie 2005): III only

Osteolytic lesion: at least one

Creatinine: < 5 mg/dL

Calcium: NS

Other criteria: No bone specific treatment prior to entry

Interventions	Pamidronate: 90 mg in 500 mL of 5% dextrose in water, every 4 weeks for 24 months. Control: identical placebo in 5% dextrose.
Outcomes	SRE (total); vertebral fractures; non-vertebral fractures; total mortality (#); calcium***; pain; adverse events.
Notes	SRE: pathologic fracture or radiation treatment/surgery on bone or spinal cord compression. Pain control assessment: Bone pain reported by authors at 29 months. Funding: Supported by a grant from the Pharmaceuticals Division, Ciba-Geigy Corporation, Summit, N.J. COI statement included: not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Methods used for generation of sequence of randomization are adequately described.
Allocation concealment (selection bias)	Low risk	Methods of allocation concealment are adequately described.
Blinding (performance bias and detection bias) All outcomes	Low risk	Study is double-blinded.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Methods for blinding of participants and personnel are adequately described.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Methods for blinding of participants and personnel are adequately described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts are adequately described.
Other bias	High risk	Alpha and beta errors are not prespecified.
Intention to treat Analysis	High risk	Benefits data are not analyzed according to ITT principle.

Brincker 1998

Methods	<p>Study design: Parallel, double-blind; placebo-controlled study</p> <p>Study length: not reported</p> <p>Study conducted during: Sept 1990 – Jul 1995</p>
Participants	<p>Bisphosphonates: enrolled 152, analyzed 152. Placebo: enrolled 148, analyzed 148.</p> <p>Sex (M/F):</p> <p>Bisphosphonates: 83/69 Control: 109/72</p> <p>Mean age (SD):</p> <p>Bisphosphonates: 69 (NR) Control: 69 (NR)</p> <p>Inclusion criteria:</p> <p>Stage (Durie 2005): II-III</p> <p>Osteolytic lesion: NS</p> <p>Creatinine: < 2.8 mg/dL</p> <p>Calcium: Normal or elevated</p> <p>Other criteria: No cytotoxic chemotherapy prior to entry</p>
Interventions	<p>Pamidronate: 75 mg capsules orally bid (total 300mg /day); for at least 2 years. Control: identical placebo.</p>
Outcomes	<p>Total mortality*§; SRE; pain; calcium(&); adverse events</p>
Notes	<p>SRE: bone fracture other than vertebral or surgery or increase in number of osteolytic lesions + vertebral collapse. Pain reported as the number of events, not as the number of patients experiencing pain.</p> <p>Funding: not reported.</p> <p>COI statement included: not reported.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Methods used for generation of sequence of randomization are not described.
Allocation concealment (selection bias)	High risk	Methods used for concealment of allocation are not described.
Blinding (performance bias and detection bias)	Low risk	Study is double-blinded.

Brincker 1998 (Continued)

All outcomes

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study is double-blinded but who was blinded is not mentioned.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study is double-blinded but who was blinded is not mentioned.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts are adequately described.
Other bias	Low risk	Alpha and beta errors are prespecified.
Intention to treat Analysis	Low risk	Benefits data are analyzed according to ITT principle.

Daragon 1993

Methods	Study design: Parallel, double-blind; placebo-controlled study Study length: not reported Study conducted during: Jan 1985 – Jun 1990
Participants	Bisphosphonates: enrolled 49, analyzed 39. Placebo: enrolled 45, analyzed 39. Sex (M/F): Bisphosphonates: 22/27 Control: 22/23 Mean age (SD): Bisphosphonates: 65.6 (9.8) Control: 66.9 (9) Inclusion criteria: Stage (Durie 2005): II-III Osteolytic lesion: NS Creatinine: < 2.8 mg/dL Calcium: Normal or elevated Other criteria: No cytotoxic chemotherapy prior to entry
Interventions	Etidronate: 10 mg/kg orally daily with lunch; for 4 months. Control: identical placebo.
Outcomes	Total mortality *\$;SRE (total); total fractures; vertebral fractures; non-vertebral fractures; vertebral index;

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Daragon 1993 (Continued)

total mortality;
pain;
calcium;
adverse events.

Notes

SRE: new extraspinal osteolytic bone lesions or fractures or vertebral index; total mortality: total number of deaths reported in the text.

Pain recorded as the number of patients taking class 2 and 3 narcoanalgesics at four months.

Funding: Supported in part by Nativelle, Issy-les-Moulineaux, France and by INSERM ; etudes biochimiques et therapeutiques du myeloma multiple, by association pour la recherche contre le cancer and by Ligue nationale de lutte contre le cancer.

COI statement included: not reported.

Pain control assessment: Analgesic use at 4 months.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Methods used for generation of sequence of randomization are not described.
Allocation concealment (selection bias)	High risk	Methods used for concealment of allocation are not described.
Blinding (performance bias and detection bias) All outcomes	Low risk	Study is double-blinded.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Study is double-blinded but who was blinded is not mentioned.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Study is double-blinded but who was blinded is not mentioned.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts are adequately described.
Other bias	High risk	Alpha and beta errors are not prespecified.
Intention to treat Analysis	High risk	Benefits data are not analyzed according to ITT principle.

Delmas 1982

Methods

Study design: Parallel, double-blind; placebo-controlled study

Study length: not reported

Study conducted during: not reported

Participants

Bisphosphonates: enrolled 7, analyzed 7.

Placebo: enrolled 6, analyzed 6.

Delmas 1982 (Continued)

Sex (M/F): not reported

Mean age (SD): Not reported

Inclusion criteria:

Stage (Durie 2005): NS

Osteolytic lesion: NS

Creatinine: < 1.8 mg/dL

Calcium: Normal or elevated

Other criteria: none

Interventions	Clodronate: 1600 mg/day orally; for 24 months. Control: identical placebo.
Outcomes	SRE; total fractures; vertebral fracture; non-vertebral fractures; total mortality; pain; calcium; adverse events.
Notes	SRE: new osteolytic lesions or fractures or vertebral index (\$); vertebral fractures for control group not reported; total mortality reported for clodronate group only; adverse events stated only (data could not be extracted). Pain control assessment: Pain index at 12 months. Funding: Clodronate: Dichloromethylene diphosphonate (Cl ₂ MDP) was provided by Procter and Gamble Inc, USA. COI statement included: not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Methods used for generation of sequence of randomization are not described.
Allocation concealment (selection bias)	High risk	Methods used for concealment of allocation are not described.
Blinding (performance bias and detection bias) All outcomes	Low risk	Study is double-blinded.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study is double-blinded but who was blinded is not mentioned.
Blinding of outcome assessment (detection bias)	Unclear risk	Study is double-blinded but who was blinded is not mentioned.

Delmas 1982 (Continued)

All outcomes

Incomplete outcome data (attrition bias) All outcomes	High risk	Dropouts are not described.
Other bias	High risk	Alpha and beta errors are not prespecified.
Intention to treat Analysis	High risk	Benefits data are not analyzed according to ITT principle.

Garcia-Sanz 2015

Methods	Study design: Parallel, open-label; not blinded, not placebo-controlled phase IV study Study length: not reported Study conducted during: Jun 2010 – Jul 2012
Participants	Bisphosphonates: enrolled 51, analyzed 51. The original plan was to enroll 96 patients per-group. After enrollment of 75 patients an interim analysis was performed which suggested a beneficial effect with zoledronate. No treatment: 49 enrolled, analyzed 49. Sex (M/F): Bisphosphonates: 30/21 Control: 23/26 Mean age (range): 68 (40 – 87) Inclusion criteria: Stage (Durie 2005): Asymptomatic patients; stage not specified Osteolytic lesion: NS Creatinine: NS Calcium: NS Other criteria: Confirmed biochemical relapse of MM after an initial response, without symptoms derived from the disease
Interventions	Zoledronic acid: 4 mg in a 15-minute intravenous infusion every 4 weeks, for a total of 12 doses, plus standard supportive care. No treatment: supportive care only.
Outcomes	Time to new treatment, overall survival, response rate, time to clinical symptoms, skeletal-related events, time to a skeletal-related event, hypercalcemia, osteonecrosis of jaw and renal dysfunction.
Notes	SRE: bone fracture (vertebral and non-vertebral), requirement for bone radiotherapy, requirement for bone surgery, or hypercalcemia. Funding: supported by an unrestricted grant from Novartis Farmaceutica S.A., Barcelona, Spain and sponsored by GEM/PETHEMA. Part of the work was also supported by grants PS09/01450 and PI12/02311 from the Spanish “Instituto de Salud Carlos III (ISCIII)” and Fondo Europeo de Desarrollo Regional (FEDER), the Spanish Ministry of Economy and Competitiveness and the European Regional Development Fund (ERDF) “Una manera de hacer Europa” (Innocampus; CEI-2010-1-0010), the

Garcia-Sanz 2015 (Continued)

grant RD12/0036/0069 from “Red Temática de Investigación Cooperativa en Cáncer (RTICC), and grant GCB-120981SAN from the “Asociación Española Contra el Cáncer (AECC)”.

COI statement included: not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Methods used for generation of sequence of randomization are not described.
Allocation concealment (selection bias)	High risk	Methods used for concealment of allocation are not described.
Blinding (performance bias and detection bias) All outcomes	High risk	Study does not involve any blinding.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Study does not involve any blinding.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Study does not involve any blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The process for early stoppage is clearly described
Other bias	High risk	It is unclear if the interim analysis was pre-planned or post-hoc
Intention to treat Analysis	Low risk	Benefits data on accrued patients are analyzed according to ITT principle.

Gimsing 2010

Methods	<p>Study design: Parallel, double-blind, comparing 30 mg versus 90 mg pamidronate</p> <p>Study length: median follow-up: 3.4 years (range: 1.1 – 5.7)</p> <p>Study conducted during: Jan 2001 – Aug 2005</p>
Participants	<p>Pamidronate 30 mg: enrolled 252, analyzed 198. Pamidronate 90 mg: enrolled 252, analyzed 179.</p> <p>No treatment: 49 enrolled, analyzed 49.</p> <p>Sex (M/F):</p> <p>Pamidronate 90 mg: 149/101 Pamidronate 30 mg: 155/97</p> <p>Mean age (range): not reported</p> <p>Inclusion criteria:</p> <p>Stage (Durie 2005): I-III</p>

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Gimsing 2010 (Continued)

	<p>Osteolytic lesion: NS</p> <p>Creatinine: < 400 µmol/L</p> <p>Calcium: NS</p> <p>Other criteria: No prior treatment with bisphosphonates</p>
Interventions	<p>Pamidronate: 90 mg in 500 mL of 5% dextrose in water, every 4 weeks for at least 36 months.</p> <p>Control: 30 mg in 500 mL of 5% dextrose in water, every 4 weeks for at least 36 months.</p>
Outcomes	<p>SRE (total);</p> <p>vertebral fractures; non-vertebral fractures;</p> <p>total mortality (#);</p> <p>calcium***;</p> <p>pain;</p> <p>adverse events.</p>
Notes	<p>SRE: pathologic fracture or radiation treatment/surgery on bone or spinal cord compression.</p> <p>Funding: Nordic Cancer Union and Novartis Healthcare.</p> <p>COI statement included: "PG has received grant support from Janssen-Cilag, a speaker's bureau from Celgene, and fee as chairman of the data monitoring committee for BioInvent. AW has received grant support from Janssen-Cilag, fees for consultancy from Janssen-Cilag and Pharmion, and payment for advisory board participation from Novartis. HH-H has received speakers fees. The Nordic Myeloma Study Group has received grant support from Janssen-Cilag, Celgene, Amgen, and Nordpharma. All other authors declared no conflicts of interest."</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Methods used for generation of sequence of randomization are adequately described.
Allocation concealment (selection bias)	Low risk	Methods of allocation concealment are adequately described.
Blinding (performance bias and detection bias) All outcomes	Low risk	Study is double-blind.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Methods for blinding of participants and personnel are adequately described.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Methods for blinding of participants and personnel are adequately described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts are adequately described.
Other bias	Low risk	Alpha and beta errors are prespecified.
Intention to treat Analysis	Low risk	Benefits data are analyzed according to ITT principle.

Heim 1995

Methods	<p>Study design: Parallel, placebo-controlled study</p> <p>Study length: not reported</p> <p>Study conducted during: not reported (stay started in 1989)</p>
Participants	<p>Total: 170; 13 withdrawn after treatment. premature termination in additional 75. Bisphosphonates: analyzed: 39. Placebo: analyzed: 32.</p> <p>Sex (M/F): not available for the entire study cohort</p> <p>Mean age (range): not reported</p> <p>Inclusion criteria:</p> <p>Stage (Durie 2005): I-III</p> <p>Osteolytic lesion: NR</p> <p>Creatinine: < 2.5 mg/dL</p> <p>Calcium: NS</p> <p>Other criteria: none</p>
Interventions	<p>Clodronate: 1600 mg/day orally; for 12 months. Control: no treatment.</p>
Outcomes	<p>SRE; pain; total fractures; calcium; adverse events.</p>
Notes	<p>SRE: bone progression (\$); effect on pain characterized as the number of patients without pain or no need for therapy.</p> <p>Pain control assessment: Analgesic use OR presence of pain at 9 months.</p> <p>Funding: not reported.</p> <p>COI statement included: not reported.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Methods used for generation of sequence of randomization are not described.
Allocation concealment (selection bias)	High risk	Methods used for concealment of allocation are not described.
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding methods are not described.

Heim 1995 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Who was blinded is not described.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Who was blinded is not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts are adequately described.
Other bias	High risk	Alpha and beta errors are not prespecified.
Intention to treat Analysis	High risk	Benefits data are not analyzed according to ITT principle.

Kraj 2000

Methods	Study design: Parallel, not double-blind, placebo-controlled study Study length: not reported Study conducted during: not reported (study started in 1989)
Participants	Bisphosphonates: analyzed 23; Placebo: analyzed 23. Sex (M/F): Bisphosphonates: 10/13 Control: 16/7 Mean age (SD): Bisphosphonates: 60 (10) Control: 66 (9) Inclusion criteria: Stage (Durie 2005): II-III Osteolytic lesion: NS Creatinine: unclear Calcium: NS Other criteria: none
Interventions	Pamidronate 60 mg IV, every 4 weeks; indefinitely. control: no treatment.
Outcomes	Total mortality, vertebral fractures.
Notes	Funding: not reported COI statement included: not reported

Kraj 2000 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Methods used for generation of sequence of randomization are not described.
Allocation concealment (selection bias)	High risk	Methods used for concealment of allocation are not described.
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding methods are not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Who was blinded is not described.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Who was blinded is not described.
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropouts are not described.
Other bias	High risk	Alpha and beta errors are not prespecified.
Intention to treat Analysis	High risk	Benefits data are not analyzed according to ITT principle.

Lahtinen 1992

Methods	Study design: Parallel, double-blind; placebo-controlled study Study length: not reported Study conducted during: 1986 and 1989
Participants	Bisphosphonates (clodronate): enrolled 168, analyzed 168. Placebo: enrolled 168, analyzed 168. Sex (M/F): Bisphosphonates (clodronate): 84/84 Placebo: 82/86 Age: mean(SD): Bisphosphonates: Not reported Placebo: Not reported Inclusion criteria: Stage (Durie 2005): NR Osteolytic lesion: NR Creatinine: NS

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Lahtinen 1992 (Continued)

Calcium: NS

Other criteria: No prior use of bisphosphonates and capacity to tolerate systemic chemotherapy

Interventions	Clodronate 2400 mg capsules orally daily. Identical placebo. Duration 24 months.
Outcomes	SRE (total); total mortality; vertebral fractures; non-vertebral fractures; calcium**
Notes	Total mortality reported as a total number of deaths. Pain control assessment: Pain index at 12 months. Funding: Supported by Huhtamaki Oy, Leiras, Turku and the Finnish Cancer Foundation. COI statement included: NR.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Methods used for generation of sequence of randomization are not described.
Allocation concealment (selection bias)	High risk	Methods used for concealment of allocation are not described.
Blinding (performance bias and detection bias) All outcomes	Low risk	Study is double-blind.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Methods for blinding of participants and personnel are adequately described.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Methods for blinding of participants and personnel are adequately described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts are adequately described.
Other bias	Low risk	Alpha and beta errors are prespecified.
Intention to treat Analysis	Low risk	Benefits data are analyzed according to ITT principle.

Leng 2002

Methods	Study design: Parallel, not double-blind; placebo-controlled study Study length: NR Study conducted during: NR
Participants	Bisphosphonates (pamidronate): enrolled 16, analyzed 16. Placebo: enrolled 18, analyzed 18.

Leng 2002 (Continued)

Sex (M/F):

Bisphosphonates: NR

Placebo: NR

Age: mean(SD):

Bisphosphonates: NR

Placebo: NR

Inclusion criteria:

Stage (Durie 2005): II-II

Osteolytic lesion: NS

Creatinine: NS

Calcium: NS

Other criteria: Verbal rating scale > II

Interventions	Pamidronate 90 mg daily IV. Identical placebo. Duration indefinite.
Outcomes	Pain (continuous data).
Notes	Pain control assessment: Visual analogue scale. Funding: NR. COI statement included: NR.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Methods used for generation of sequence of randomization are not described.
Allocation concealment (selection bias)	High risk	Methods used for concealment of allocation are not described.
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding methods are not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Who was blinded is not described.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Who was blinded is not described.
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropouts are not described.

Leng 2002 (Continued)

Other bias	High risk	Alpha and beta errors are not prespecified.
Intention to treat Analysis	High risk	Benefits data are not analyzed according to ITT principle.

McCloskey 2001

Methods	Study design: Parallel, double-blind; placebo-controlled study Study length: NR Study conducted during: 1986 to 1992
Participants	Bisphosphonates: enrolled/analyzed 264. Placebo: enrolled/analyzed 272. Sex (M/F): Bisphosphonates: 1.33 ratio Placebo: 1.43 ratio Age: Median (Inter-quartile range) Bisphosphonates: 62 (55-67) Placebo: 63 (57-68) Inclusion criteria: Stage (Durie 2005): II-II Osteolytic lesion: at least one Creatinine: any Calcium: normal or elevated Other criteria: No cytotoxic chemotherapy prior to entry
Interventions	Clodronate 1600 mg orally daily. Identical placebo. Duration indefinite or progression.
Outcomes	Total mortality*; SRE; total fractures; vertebral fractures; non-vertebral fracture; pain; calcium.***
Notes	SRE: event-free survival (pathological fractures or hypercalcemia), calculated from survival curves; outcome on calcium also reported as a dichotomous variable on the number of patients with hypercalcemia; pain calculated as the number of patients with maximal pain over 24 months. Pain control assessment: Severe pain at 24 months. Funding: Drug provided by Leiras Oy, Finland and MRC grant. COI statement included: NR.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Methods used for generation of sequence of randomization are not described.

McCloskey 2001 (Continued)

Allocation concealment (selection bias)	Low risk	Methods of allocation concealment are adequately described.
Blinding (performance bias and detection bias) All outcomes	Low risk	Study is double-blind.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Methods for blinding of participants and personnel are adequately described.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Methods for blinding of participants and personnel are adequately described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts are adequately described.
Other bias	High risk	Alpha and beta errors are not prespecified.
Intention to treat Analysis	High risk	Benefits data are not analyzed according to ITT principle.

Menssen 2002

Methods	Study design: Parallel, double-blind; placebo-controlled study Study length: NR Study conducted during: 1994 to 1996
Participants	Bisphosphonates: enrolled 107, analyzed 99. Placebo: enrolled 107, analyzed 99. Sex (M/F): Bisphosphonates: 53/46 Placebo: 51/48 Age: Mean (SD) Bisphosphonates: 62.9 (NR) Placebo: 63.4 (NR) Inclusion criteria: Stage (Durie 2005): II-II Osteolytic lesion: at least one Creatinine: ≤ 3 mg/dL Calcium: normal Other criteria: No bone specific treatment prior to entry
Interventions	Ibandronate 2 mg IV every month. Identical placebo, duration 24 months.

Menssen 2002 (Continued)

Duration: 12 to 24 months.

Outcomes	SRE (total)/year; mortality;* vertebral fractures (!); non-vertebral fractures (!); hypercalcemia (!); pain (!).
Notes	SRE: pathological fractures or vertebral fractures, hypercalcemia, severe bone pain, and bone radiotherapy or surgery. Pain control assessment: Opiate usage. Funding: Roche Diagnostics GmbH, Mannheim, Germany. COI statement included: NR.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Methods used for generation of sequence of randomization are not described.
Allocation concealment (selection bias)	High risk	Methods used for concealment of allocation are not described.
Blinding (performance bias and detection bias) All outcomes	Low risk	Study is double-blinded.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study is double-blinded but who was blinded is not mentioned.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study is double-blinded but who was blinded is not mentioned.
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropouts are not described.
Other bias	High risk	Alpha and beta errors are not prespecified.
Intention to treat Analysis	Low risk	Benefits data are analyzed according to ITT principle.

Morgan 2010

Methods	Study design: Parallel, open-label; comparing zoledronate versus clodronate Study length: NR Study conducted during: 1994 to 1996
Participants	Zoledronate: analyzed 981.

Morgan 2010 (Continued)

Clodronate: analyzed 979

Sex (M/F):

Bisphosphonates: 53/46

Placebo: 51/48

Age: Mean (SD)

Bisphosphonates: NR

Placebo: NR

Inclusion criteria:

Stage (Durie 2005): I-III (International Staging System)

Osteolytic lesion: NS

Creatinine: <5.65 mg/dL

Calcium: NS

Other criteria: No previous or concurrent active malignancies, No acute renal failure (serum creatinine > 500 µmol/L and unresponsive to 72 hours of rehydration)

Interventions	Zoledronate 4 mg IV every 3-4 weeks. Clodronate 1600 mg orally daily. Duration: until progression.
Outcomes	Mortality; SREs; complete response; vertebral fractures, other fractures; hypercalcemia; renal failure; very good partial response; treatment-related toxicities.
Notes	<p>SRE: vertebral fractures, other fractures, spinal cord compression, need for radiation or surgery to bone lesions, and new osteolytic bone lesions were recorded until disease progression. Complete response: negative immunofixation (100% M-protein reduction) very good partial response: at least 90% M-protein reduction with positive immunofixation.</p> <p>Funding: UK MRC, unrestricted educational grants from Novartis, Schering Health Care, Chugai, Pharmion, Celgene, and Ortho Biotech for trial coordination and the laboratory studies. Financial support for medical editorial assistance was provided by Novartis Pharmaceuticals.</p> <p>COI statement included: "F.E. Davies has honoraria from Speakers Bureau of Celgene and is a consultant/advisory board member of Celgene and Novartis. G. Cook is a consultant/advisory board member of and has honoraria from Speakers Bureau of Celgene. R.G. Owen has honoraria from Speakers Bureau of Celgene and Ortho Biotech, United Kingdom. G.H. Jackson has honoraria from Speakers Bureau of Celgene and is a consultant/advisory board member of Celgene and J&J. No potential conflicts of interest were disclosed by the other authors."</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Methods used for generation of sequence of randomization are adequately described.
Allocation concealment (selection bias)	Low risk	Methods of allocation concealment are adequately described.
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label study.

Morgan 2010 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Who was blinded is not described.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Who was blinded is not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts are adequately described.
Other bias	Low risk	Alpha and beta errors are prespecified.
Intention to treat Analysis	Low risk	Benefits data are analyzed according to ITT principle.

Musto 2003

Methods	Study design: Parallel, not double-blind; not placebo-controlled Study length: NR Study conducted during: 1996 to 2001
Participants	Bisphosphonates: analyzed 45. Control: analyzed 45. Sex (M/F): Bisphosphonates: 26/19 Control: 24/21 Age: Median (range) Bisphosphonates: 67 (47-79) Placebo: 68 (45-80) Inclusion criteria: Stage (Durie 2005): I-II Osteolytic lesion: Any Creatinine: NS Calcium: NS Other criteria: No cytotoxic chemotherapy prior to entry
Interventions	Pamidronate 60 mg IV, every month. Control: NS. Duration: 1 year or until progression.
Outcomes	Total skeletal-related events; PFS, adverse events.
Notes	SRE: single/multiple osteolytic lesions, pathological fractures and/or hypercalcemia. Funding: NR

Musto 2003 (Continued)

COI statement included: No.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Methods used for generation of sequence of randomization are described.
Allocation concealment (selection bias)	High risk	Methods used for concealment of allocation are not described.
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding methods are not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Who was blinded is not described.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Who was blinded is not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts are adequately described.
Other bias	High risk	Alpha and beta errors are not prespecified.
Intention to treat Analysis	High risk	Benefits data are not analyzed according to ITT principle.

Musto 2008

Methods	Study design: Parallel, not double-blind; not placebo-controlled Study length: NR Study conducted during: 1996 to 2001
Participants	Bisphosphonates: enrolled 81, analyzed 81. Control: enrolled 82, analyzed 82. Sex (M/F): Bisphosphonates: 43/38 Control: 47/35 Age: Median (range) Bisphosphonates: 66 (41-82) Control: 67 (42-84) Inclusion criteria: Stage (Durie 2005): I Osteolytic lesion: Any

Musto 2008 (Continued)

Creatinine: < 1.2 mg/dL

Calcium: < 10 mg/dL

Other criteria: No cytotoxic chemotherapy prior to entry

Interventions	Zoledronate 4 mg IV, every month. Control: observation. Duration: 1 year or until progression.
Outcomes	SRE (total); PFS; ONJ.
Notes	SRE: single/multiple osteolytic lesions, pathological fractures and/or hypercalcemia. The trial was prematurely stopped due to ONJ case in patient receiving zoledronate. Funding: NR. COI statement included: No.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Methods used for generation of sequence of randomization are described.
Allocation concealment (selection bias)	Low risk	Methods used for concealment of allocation are described.
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding methods are not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Who was blinded is not described.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Who was blinded is not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts are adequately described.
Other bias	Low risk	Alpha and beta errors are prespecified.
Intention to treat Analysis	Low risk	Benefits data are analyzed according to ITT principle.

Rosen 2003

Methods Study design: Parallel, double-blinded; double dummy; stratified; not placebo-controlled

Study length: 25 months

Rosen 2003 (Continued)

Study conducted during: 1998 to 2000

Participants	<p>Zoledronate: enrolled 564, analyzed 561 Pamidronate: enrolled 558, analyzed 555</p> <p>Sex (M/F):</p> <p>Zoledronate: NR Pamidronate: NR</p> <p>Age: Mean (SD)</p> <p>Zoledronate: 58 (NR) Pamidronate: 57 (NR)</p> <p>Inclusion criteria:</p> <p>Stage (Durie 2005): III</p> <p>Osteolytic lesion: at least one</p> <p>Creatinine: ≤ 3 mg/dL</p> <p>Calcium: ≤ 12 mg/dL</p> <p>Other criteria: Serum bilirubin ≤ 2.5 mg/dL. No prior treatment with bisphosphonates within 12 months of the screening visit</p>
Interventions	<p>Zoledronate 4 mg IV, every 4 weeks. Pamidronate 90 mg IV, every 4 weeks. Duration: 24 months.</p>
Outcomes	SREs
Notes	<p>SREs were defined as pathologic fracture, spinal cord compression, radiation therapy to bone, and surgery to bone. Data for MM and breast carcinoma patients were reported in combined manner for all outcomes except SREs.</p> <p>Funding: Novartis Pharmaceuticals Corporation.</p> <p>COI statement included: "Dr. Seaman, Dr. Chen, and Dr. Reitsma are employed by Novartis Pharmaceuticals and may own stock in the company; Dr. Coleman has received honoraria from Novartis; and Dr. Hussein has received a research grant from Novartis."</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Methods used for generation of sequence of randomization are described.
Allocation concealment (selection bias)	Low risk	Methods used for concealment of allocation are described.
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding methods are not described.
Blinding of participants and personnel (performance bias)	High risk	Who was blinded is not described.

Rosen 2003 (Continued)

All outcomes

Blinding of outcome assessment (detection bias) All outcomes	High risk	Who was blinded is not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts are adequately described.
Other bias	High risk	Alpha and beta errors are not prespecified.
Intention to treat Analysis	Low risk	Benefits data are analyzed according to ITT principle.

Sezer 2010

Methods	Study design: Parallel; open-label; placebo-controlled Study length: 48 months Study conducted during: 2000 to 2008
Participants	Bisphosphonates: enrolled 72; analyzed 71. Control: enrolled 71; analyzed 69. Sex (M/F): Zoledronate: 30/42 Control: 40/31 Age: Mean (SD) Zoledronate: 58.8 (12.02) Control: 62.1 (10.79) Inclusion criteria: Stage (Durie 2005): Asymptomatic patients stage I Osteolytic lesion: at least one Creatinine: NS Calcium: NS Other criteria: Patients with evidence of paraprotein in the serum or urine and bone marrow infiltration with plasma cells which represent more than 10% of the nucleated cells.
Interventions	Zoledronate 4 mg IV (or dose-adjusted based on creatinine clearance) monthly. Control: observation. Duration: until progression or 48 months whichever comes first.
Outcomes	Days of PFS; SREs (defined as: pathologic fracture, initiation of radiotherapy or surgery on bone, spinal cord compression or hypercalcemia); adverse events.
Notes	PFS was defined as time from date of randomization to death from any cause or one of the following events: <ul style="list-style-type: none"> • progression to stage II or III per Salmon & Durie classification;

Sezer 2010 (Continued)

- skeletal-related events (pathologic fracture, initiation of radiotherapy or surgery on bone, spinal cord compression or hypercalcemia);
- unequivocal progression of osteolytic lesions (at least a 20% increase in the largest diameter of one existing osteolytic lesion which is measured in at least one dimension as 20 mm with conventional techniques), determined radiologically.

The trial was stopped early due to slow recruitment.

Funding: Novartis Pharmaceuticals Corporation.

COI statement included: No.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Methods used for generation of sequence of randomization are not described.
Allocation concealment (selection bias)	Unclear risk	Methods used for concealment of allocation are not described.
Blinding (performance bias and detection bias) All outcomes	High risk	Study is not blinded
Blinding of participants and personnel (performance bias) All outcomes	High risk	Who was blinded is not described.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Who was blinded is not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts are described.
Other bias	Unclear risk	Alpha and beta errors are not prespecified. However, a total sample size of 220 patients was specified.
Intention to treat Analysis	High risk	Benefits data are not analyzed according to ITT principle.

Terpos 2000

Methods	Study design: Parallel; not double-blind; not placebo-controlled Study length: NR Study conducted during: NR
Participants	Bisphosphonates: enrolled/analyzed 32. Control: enrolled/analyzed 30. Sex (M/F): Pamidronate: 18/14

Terpos 2000 (Continued)

Control: 14/16

Age: Median (range)

Pamidronate: 68 (55-78)

Control: 66 (46-78)

Inclusion criteria:

Stage (Durie 2005): Stage I-III

Osteolytic lesion: NS

Creatinine: <5 mg/dL

Calcium: NS

Other criteria: No prior treatment with any kind of bisphosphonate within 3 months before enrollment or calcitonine or mithramycin within 2 weeks before enrollment , or treatment with corticosteroids for any reason except part of the patient's chemotherapeutic regimen.

Interventions	Pamidronate: 90 mg IV monthly. Control: observation. Duration: 14 months
Outcomes	Total mortality;* total fractures; vertebral fractures; non-vertebral fracture; pain; hypercalcemia; abdominal pain.
Notes	Data provided by the authors of the article. Pain control assessment: Opiate usage Funding: NR COI statement included: No.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Methods used for generation of sequence of randomization are not described.
Allocation concealment (selection bias)	High risk	Methods used for concealment of allocation are not described.
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding methods are not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Who was blinded is not described.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Who was blinded is not described.

Terpos 2000 (Continued)

Incomplete outcome data (attrition bias) All outcomes	High risk	Dropouts are not described.
Other bias	High risk	Alpha and beta errors are not prespecified.
Intention to treat Analysis	High risk	Benefits data are not analyzed according to ITT principle.

Terpos 2003

Methods	Study design: Parallel; Not double-blind; not placebo-controlled Study length: NR Study conducted during: 1999 to 2001	
Participants	Pamidronate: enrolled 23, analyzed 23. Ibandronate: enrolled 21, analyzed 20. Sex (M/F): Pamidronate: 12/11 Ibandronate: 12/9 Age: Median (range) Pamidronate: 66 (55-78) Ibandronate: 65.5 (60-77) Inclusion criteria: Stage (Durie 2005): Stage II-III Osteolytic lesion: at least one Creatinine: >4 mg/dL Calcium: NS Other criteria: No prior treatment with any kind of bisphosphonate within 3 months before enrollment or calcitonine or mithramycin within 2 weeks before enrollment , or treatment with corticosteroids for any reason except part of the patient's chemotherapeutic regimen.	
Interventions	Pamidronate: 90 mg IV monthly. Ibandronate: 4 mg IV monthly. Duration: 4 months.	
Outcomes	Hypocalcemia, hypercalcemia.****	
Notes	Funding: NR. COI statement included: No.	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Methods used for generation of sequence of randomization are not described.

Terpos 2003 (Continued)

Allocation concealment (selection bias)	High risk	Methods used for concealment of allocation are not described.
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding methods are not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Who was blinded is not described.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Who was blinded is not described.
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropouts are not described.
Other bias	High risk	Alpha and beta errors are not prespecified.
Intention to treat Analysis	Low risk	Benefits data are analyzed according to ITT principle.

Zhang 2012

Methods	Study design: Parallel; not double-blind; not placebo-controlled Study length: NR Study conducted during: 2004 to 2009
Participants	Bisphosphonates: enrolled/analyzed 33. Control: enrolled/analyzed 20. Sex (M/F): Clodronate: 23/10 Control: 13/7 Age: Mean (SD) Clodronate: 59.9 (8.1) Control: 58.5 (8.2) Inclusion criteria: Stage (Durie 2005): Stage II-III Osteolytic lesion: NS Creatinine: NS Calcium: NS Other criteria: NS
Interventions	Clodronate: During the intermittent period of chemotherapy, clodronate injection 300 mg (Bonefos®, Bayer Schering Pharma, Leverkusen, Germany) was administered for 5 days in 250 mL glucose injection

Zhang 2012 (Continued)

through slow intravenous drip; after that, Bonefos® capsules were administered orally at 1600 mg every day in the morning.
Control: chemotherapy.
Duration: NS.

Outcomes	Bone metabolic markers
Notes	Other notes: This study did not report any outcome of interest for this systematic review. Funding: NR. COI statement included: No.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Methods used for generation of sequence of randomization are not described.
Allocation concealment (selection bias)	High risk	Methods used for concealment of allocation are not described.
Blinding (performance bias and detection bias) All outcomes	High risk	Study is not blinded
Blinding of participants and personnel (performance bias) All outcomes	High risk	Who was blinded is not described.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Who was blinded is not described.
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropouts are not described.
Other bias	High risk	Alpha and beta errors are not prespecified.
Intention to treat Analysis	Low risk	Benefits data are analyzed according to ITT principle.

COI: conflict of interest; **ITT:** intention-to-treat; **IV:** intravenous; **MM:** multiple myeloma; **ONJ:** osteonecrosis of the jaw; **OS:** overall survival; **PFS:** progression-free survival; **SD:** standard deviation; **SRE:** skeletal-related events.

* mortality data obtained from authors; *\$ mortality data derived using the Tierney method

total number of deaths reported in Berenson 1996

\$ defined by reviewers

**hypercalcemia defined as > 2.65 mmol/L

&hypercalcemia defined as > 2.75 mmol/L

***hypercalcemia defined as > 3.00 mmol/L

**** hypercalcemia defined as presence of symptoms or serum calcium concentration, corrected for the serum albumin concentration, of at least 12.0 mg/dL or 3.0 mmol/L

! Data obtained from (author Fontana et al) and data from previous publication (abstract) were used

The most common adverse effect that was reported was related to gastrointestinal symptoms (abdominal pain, diarrhea, pancreatitis). The number of patients with highest number of gastrointestinal symptoms was recorded and combined in the final analysis (since often

it was not clear whether the same patients had one or more gastrointestinal symptoms). Effects on other organs (blood, kidney, liver, etc) were sporadically reported, and therefore not systematically extracted. However, the narrative summary was presented in the review.

Effect on pain was non uniformly described. Data were extractable from 8 trials. (Study by Brincker et al reported data as the number of pain episodes instead of the number of patients with pain. Paper by Belch et al did not report data in an extractable form.) Study by McCloskey et al reported effect on back pain only, while other studies reported effect on 'pain' without specifying site of pain. The study by Lahtinen et al also reported pain according to its severity. However, we extracted data on the number of patients with pain on bisphosphonates vs. placebo, except in the study by McCloskey et al, where the effect on pain refers to patients without 'marked improvement in back pain'.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ali 2001	Nonrandomized study
Barlogie 2008	Nonrandomized study
Bergner 2007	Nonrandomized study
Caparrotti 2003	Nonrandomized and a combination therapy
Chiang 2013	Observational phase IV study
Ciepluch 2002	Nonrandomized and a combination therapy
Delea 2012	Cost-effectiveness study
Fizazi 2009	Phase II denosumab randomized controlled trial
Henry 2014	Denosumab randomized controlled trial
Kraj 2000a	Duplicate publication
Kraj 2002	Enrolled only 9 patients. Only one pathological fracture was reported among 6 patients enrolled in zoledronate arm and one pathological fracture among 3 patients enrolled in pamidronate arm.
Lipton 2012	Study addressing data from denosumab randomized controlled trials
Martin 2002	No data of interest
Morris 2001	Nonrandomized and a combination therapy
Spencer 2008	Nonrandomized and a combination therapy
Tassinari 2007	Observational study
Teoh 2012	Nonrandomized study
Terpos 2010	Prognostic study
Tosi 2006a	Combination therapy
Vadhan-Raj 2012	Denosumab randomized controlled trial
Vij 2009	Phase II denosumab randomized controlled trial
Vogel 2004	Nonrandomized study

Study	Reason for exclusion
Witzig 2013	Patients in both the study arms received the same dose of zoledronate

Characteristics of ongoing studies *[ordered by study ID]*

Lund 2014

Trial name or title	Prolonged protection from bone disease in multiple myeloma (Magnolia)
Methods	An open-label phase 3 multicenter international randomised trial
Participants	<p>Inclusion Criteria:</p> <ul style="list-style-type: none"> • Symptomatic multiple myeloma regardless of bone disease status • Signed Informed Consent • Age ≥ 18 years • Remaining life expectancy ≥ 2 years • Any concurrently anti-myeloma treatment are allowed <p>Exclusion Criteria:</p> <ul style="list-style-type: none"> • Previous treatment with bisphosphonate within the last 6 months • Severely reduced renal function (creatinine clearance < 30 mL/min despite fluid replacement) • Known concurrent malignancy, excluding skin cancer • Known hypersensitivity to zoledronic acid • Pregnant or lactating women • Women of childbearing potential or men engaging in sexual activity with a woman of childbearing potential who refuse to use contraception
Interventions	<p>Active Comparator: zoledronic acid (treatment with zoledronic acid for 4 years)</p> <p>Placebo Comparator: no treatment (treatment with zoledronic acid withheld after two years)</p>
Outcomes	<p>Primary Outcome Measures:</p> <ul style="list-style-type: none"> • Time to first skeletal-related event after randomizations at year two [Time Frame: From year two to year four] [Designated as safety issue: Yes] After two years of zoledronic acid treatment patients will be randomized to A continue treatment B stop treatment. <p>Secondary Outcome Measures:</p> <ul style="list-style-type: none"> • Value of serum bone marker ratio (bone resorption/bone formation markers) as predictor of skeletal-related events analyzed by time-dependent multiparameter Cox regression analysis. [Time Frame: 4 years] [Designated as safety issue: No]. Development in bone markers prior to progression in osteolytic lesions will be investigated.
Starting date	January 2015
Contact information	<p>Name: Thomas Lund, MD Ph.D.</p> <p>Phone: +45 21450256; Email: thomas.lund1@rsyd.dk</p>
Notes	

DATA AND ANALYSES

Comparison 1. Bisphosphonates vs. control (efficacy)

Outcome or sub-group title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	14	2706	Hazard Ratio (Random, 95% CI)	0.90 [0.76, 1.07]
1.1 Etidronate	2	244	Hazard Ratio (Random, 95% CI)	1.24 [0.86, 1.80]
1.2 Clodronate	3	885	Hazard Ratio (Random, 95% CI)	0.93 [0.66, 1.29]
1.3 Pamidronate	5	977	Hazard Ratio (Random, 95% CI)	0.85 [0.67, 1.07]
1.4 Ibandronate	1	198	Hazard Ratio (Random, 95% CI)	1.07 [0.69, 1.64]
1.5 Zoledronate	3	402	Hazard Ratio (Random, 95% CI)	0.57 [0.43, 0.75]
2 Progression-free survival	7	908	Hazard Ratio (Random, 95% CI)	0.75 [0.57, 1.00]
2.1 Clodronate	1	26	Hazard Ratio (Random, 95% CI)	0.63 [0.17, 2.34]
2.2 Pamidronate	1	177	Hazard Ratio (Random, 95% CI)	1.24 [0.66, 2.33]
2.3 Zoledronate	5	705	Hazard Ratio (Random, 95% CI)	0.70 [0.52, 0.95]
3 Vertebral fractures	7	1116	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.62, 0.89]
3.1 Clodronate	3	433	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.56, 0.89]
3.2 Pamidronate	3	485	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.40, 1.20]
3.3 Ibandronate	1	198	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.61, 1.81]
4 Non-vertebral fractures	6	1389	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.68, 1.56]
4.1 Clodronate	3	752	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.42, 1.31]
4.2 Pamidronate	2	439	Risk Ratio (M-H, Random, 95% CI)	1.65 [0.95, 2.87]
4.3 Ibandronate	1	198	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.79, 1.98]
5 Total skeletal-related events	10	2141	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.63, 0.88]
5.1 Etidronate	1	78	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.39, 1.39]
5.2 Clodronate	1	204	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.65, 0.89]
5.3 Pamidronate	3	950	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.59, 0.91]
5.4 Ibandronate	1	198	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.80, 1.35]

Outcome or sub-group title	No. of studies	No. of participants	Statistical method	Effect size
5.5 Zoledronate	4	711	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.28, 0.89]
6 Pain	8	1281	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.60, 0.95]
6.1 Etidronate	1	78	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.26, 1.32]
6.2 Clodronate	4	566	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.29, 0.91]
6.3 Pamidronate	2	439	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.72, 1.01]
6.4 Ibandronate	1	198	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.86, 1.17]
7 Incidence of hypercalcemia	10	2174	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.56, 1.09]
7.1 Etidronate	1	166	Risk Ratio (M-H, Random, 95% CI)	1.32 [0.73, 2.38]
7.2 Clodronate	3	831	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.45, 1.31]
7.3 Pamidronate	3	739	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.31, 1.33]
7.4 Ibandronate	1	198	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.27, 1.42]
7.5 Zoledronate	2	240	Risk Ratio (M-H, Random, 95% CI)	0.19 [0.01, 3.91]

Analysis 1.1. Comparison 1 Bisphosphonates vs. control (efficacy), Outcome 1 Mortality.

Analysis 1.2. Comparison 1 Bisphosphonates vs. control (efficacy), Outcome 2 Progression-free survival.

Analysis 1.3. Comparison 1 Bisphosphonates vs. control (efficacy), Outcome 3 Vertebral fractures.

Analysis 1.4. Comparison 1 Bisphosphonates vs. control (efficacy), Outcome 4 Non-vertebral fractures.

Analysis 1.5. Comparison 1 Bisphosphonates vs. control (efficacy), Outcome 5 Total skeletal-related events.

Analysis 1.6. Comparison 1 Bisphosphonates vs. control (efficacy), Outcome 6 Pain.

Analysis 1.7. Comparison 1 Bisphosphonates vs. control (efficacy), Outcome 7 Incidence of hypercalcemia.

Comparison 2. Bisphosphonates vs. control (adverse effects)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Osteonecrosis of jaw	6	1284	Risk Ratio (M-H, Random, 95% CI)	4.61 [0.99, 21.35]
1.1 Pamidronate	2	573	Risk Ratio (M-H, Random, 95% CI)	3.06 [0.13, 74.69]
1.2 Zoledronate	4	711	Risk Ratio (M-H, Random, 95% CI)	5.21 [0.91, 29.90]
2 Gastrointestinal toxicity (grade III/IV)	7	1829	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.95, 1.59]
2.1 Etidronate	1	78	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 7.94]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2 Clodronate	2	872	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.82, 1.72]
2.3 Pamidronate	3	739	Risk Ratio (M-H, Random, 95% CI)	1.30 [0.90, 1.88]
2.4 Zoledronate	1	140	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.06, 15.23]
3 Hypocalcaemia	3	1090	Risk Ratio (M-H, Random, 95% CI)	2.19 [0.49, 9.74]
3.1 Clodronate	1	536	Risk Ratio (M-H, Random, 95% CI)	2.06 [0.38, 11.16]
3.2 Pamidronate	2	554	Risk Ratio (M-H, Random, 95% CI)	2.71 [0.11, 66.19]
4 Renal dysfunction	2	414	Mean Difference (IV, Random, 95% CI)	-0.36 [-9.75, 9.03]

Analysis 2.1. Comparison 2 Bisphosphonates vs. control (adverse effects), Outcome 1 Osteonecrosis of jaw.

Analysis 2.2. Comparison 2 Bisphosphonates vs. control (adverse effects), Outcome 2 Gastrointestinal toxicity (grade III/IV).

Analysis 2.3. Comparison 2 Bisphosphonates vs. control (adverse effects), Outcome 3 Hypocalcaemia.

Analysis 2.4. Comparison 2 Bisphosphonates vs. control (adverse effects), Outcome 4 Renal dysfunction.

Comparison 3. Sensitivity analyses (assessment of bias: analysed outcome in brackets)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Allocation concealment (vertebral fractures)	7	1116	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.62, 0.89]
1.1 Adequate concealment of allocation	2	594	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.51, 0.82]
1.2 Inadequate concealment of allocation	5	522	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.67, 1.09]
2 Blinding (vertebral fractures)	7	1116	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.62, 0.89]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Double-blind	5	1008	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.58, 0.85]
2.2 Not blinded	2	108	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.08, 3.72]
3 Randomization method (vertebral fractures)	7	1116	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.62, 0.89]
3.1 Randomization method is described	1	377	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.38, 0.85]
3.2 Randomization method is NOT described	6	739	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.65, 0.94]
4 Type of data analysis (vertebral fractures)	7	1116	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.62, 0.89]
4.1 Intention-to-treat analysis	3	463	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.55, 1.22]
4.2 Per protocol analysis	4	653	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.56, 0.89]
5 Description of withdrawals and drop outs (vertebral fractures)	7	1116	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.62, 0.89]
5.1 Withdrawals and dropouts well described	3	797	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.55, 0.82]
5.2 Withdrawals and dropouts NOT described	4	319	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.68, 1.29]
6 Alpha error (vertebral fractures)	7	1116	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.62, 0.89]
6.1 Alpha error pre-specified	1	203	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.51, 1.08]
6.2 Alpha error NOT pre-specified	6	913	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.59, 0.94]
7 Beta error (vertebral fractures)	7	1116	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.62, 0.89]
7.1 Beta error pre-specified	1	203	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.51, 1.08]
7.2 Beta error NOT pre-specified	6	913	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.59, 0.94]
8 Gastrointestinal toxicity (grade III/IV: oral vs IV bisphosphonates)	7	1829	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.95, 1.59]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Oral route	4	1250	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.89, 1.70]
8.2 Intravenous route	3	579	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.81, 1.90]

Analysis 3.1. Comparison 3 Sensitivity analyses (assessment of bias: analysed outcome in brackets), Outcome 1 Allocation concealment (vertebral fractures).

Analysis 3.2. Comparison 3 Sensitivity analyses (assessment of bias: analysed outcome in brackets), Outcome 2 Blinding (vertebral fractures).

Analysis 3.3. Comparison 3 Sensitivity analyses (assessment of bias: analysed outcome in brackets), Outcome 3 Randomization method (vertebral fractures).

Analysis 3.4. Comparison 3 Sensitivity analyses (assessment of bias: analysed outcome in brackets), Outcome 4 Type of data analysis (vertebral fractures).

Analysis 3.5. Comparison 3 Sensitivity analyses (assessment of bias: analysed outcome in brackets), Outcome 5 Description of withdrawals and drop outs (vertebral fractures).

Analysis 3.6. Comparison 3 Sensitivity analyses (assessment of bias: analysed outcome in brackets), Outcome 6 Alpha error (vertebral fractures).

Analysis 3.7. Comparison 3 Sensitivity analyses (assessment of bias: analysed outcome in brackets), Outcome 7 Beta error (vertebral fractures).

Analysis 3.8. Comparison 3 Sensitivity analyses (assessment of bias: analysed outcome in brackets), Outcome 8 Gastrointestinal toxicity (grade III/IV: oral vs IV bisphosphonates)).

ADDITIONAL TABLES

Table 1. Bisphosphonate potency

Type of bisphosphonates	Bisphosphonates	Relative potency
Nonaminobisphosphonates	Etidronate	1
	Clodronate	10
	Tiludronate	10
Aminobisphosphonates	Pamidronate	100
	Alendronate	500
	Ibandronate	1,000
	Risendronate	2,000
	Zoledronate	10,000

Based on information from (Drake 2008; Dunford 2001).

Table 2. Type and content of reporting in RCTs on bisphosphonates in myeloma

Study ID	Adverse events (gastrointestinal symptoms)	Adverse events (hypocalcemia)	Adverse events (serum creati- nine)	Adverse events (osteonecrosis of the jaw)
Belch 1991	No	No	No	No
Berenson 1998a	Yes	Yes	No	No
Brincker 1998	Yes	No	No	No
Delmas 1982	No	No	No	No
Daragon 1993	Yes	No	Yes	No
Heim 1995	No	No	No	No
Lahtinen 1992	Yes	No	Yes	No
McCloskey 2001	Yes	Yes	No	No
Terpos 2000	Yes	No	No	No
Terpos 2003	No	Yes	No	No
Kraj 2000	No	No	No	No
Attal 2006	No	No	No	Yes
Musto 2003	No	No	No	Yes
Musto 2008	No	No	No	Yes
Aviles 2007	No	No	No	No
Menssen 2002	No	No	No	No
Leng 2002	No	No	No	No
Morgan 2010	Yes	No	No	Yes
Rosen 2003	No	No	No	No
Gimsing 2010	No	No	No	Yes
Aviles 2013	No	No	No	Yes
Sezer 2010	Yes	No	No	Yes
Zhang 2012	No	No	No	No
Garcia-Sanz 2015	No	No	No	Yes

Table 3. Indirect comparisons

MTC method (REM)								
Outcome	Treatment1	Treatment2	NRCTs	Patients	HR/RR	95% LCRL	95% UCRL	Quality of the evidence (GRADE)
OS	PL	CLO	16	5260	1.19	0.88	1.63	⊕⊕⊕⊖ moderate
OS	ETI	CLO	16	5260	1.48	0.96	2.51	⊕⊕⊕⊖ moderate
OS	IBAN	CLO	16	5260	1.34	0.60	2.62	⊕⊕⊕⊖ moderate
OS	PAM 90 mg	CLO	16	5260	1.04	0.64	1.64	⊕⊕⊕⊖ moderate
OS	ZOL	CLO	16	5260	0.78	0.52	1.14	⊕⊕⊕⊖ moderate
OS	PAM 30 mg	CLO	16	5260	1.04	0.48	2.09	⊕⊕⊖⊖ low*
OS	ETI	PL	16	5260	1.25	0.88	1.95	⊕⊕⊖⊖ low*
OS	IBAN	PL	16	5260	1.13	0.54	2.06	⊕⊕⊖⊖ low*
OS	PAM 90 mg	PL	16	5260	0.87	0.60	1.23	⊕⊕⊕⊖ moderate
OS	ZOL	PL	16	5260	0.67	0.46	0.91	⊕⊕⊕⊖ moderate
OS	PAM 30 mg	PL	16	5260	0.87	0.44	1.64	⊕⊕⊖⊖

Table 3. Indirect comparisons *(Continued)*

								low*
OS	IBAN	ETI	16	5260	0.94	0.37	1.80	⊕⊕⊕⊕ low*
OS	PAM 90 mg	ETI	16	5260	0.73	0.38	1.14	⊕⊕⊕⊕ low*
OS	ZOL	ETI	16	5260	0.56	0.29	0.87	⊕⊕⊕⊕ moderate
OS	PAM 30 mg	ETI	16	5260	0.72	0.30	1.40	⊕⊕⊕⊕ low*
OS	PAM 90 mg	IBAN	16	5260	0.87	0.39	1.74	⊕⊕⊕⊕ low*
OS	ZOL	IBAN	16	5260	0.67	0.29	1.31	⊕⊕⊕⊕ low*
OS	PAM 30 mg	IBAN	16	5260	0.87	0.32	2.06	⊕⊕⊕⊕ low*
OS	ZOL	PAM 90 mg	16	5260	0.79	0.46	1.26	⊕⊕⊕⊕ low*
OS	PAM 30 mg	PAM 90 mg	16	5260	1.00	0.57	1.74	⊕⊕⊕⊕ low*
OS	PAM 30 mg	ZOL	16	5260	1.35	0.62	2.76	⊕⊕⊕⊕ low*
PFS	PL	PAM 90 mg	9	3472	0.84	0.30	1.88	⊕⊕⊕⊕ very low**^

Table 3. Indirect comparisons *(Continued)*

PFS	ZOL	PAM 90 mg	9	3472	0.59	0.20	1.39	⊕○○○ very low ^{*,^}
PFS	CLO	PAM 90 mg	9	3472	0.66	0.16	1.71	⊕○○○ very low ^{*,^}
PFS	PAM 30 mg	PAM 90 mg	9	3472	1.04	0.38	2.16	⊕○○○ very low ^{*,^}
PFS	ZOL	PL	9	3472	0.70	0.46	1.03	⊕○○○ very low ^{*,^}
PFS	CLO	PL	9	3472	0.77	0.30	1.47	⊕○○○ very low ^{*,^}
PFS	PAM 30 mg	PL	9	3472	1.55	0.34	4.29	⊕○○○ very low ^{*,^}
PFS	CLO	ZOL	9	3472	1.10	0.45	1.95	⊕○○○ very low ^{*,^}
PFS	PAM 30 mg	ZOL	9	3472	2.30	0.45	6.78	⊕○○○ very low ^{*,^}
PFS	PAM 30 mg	CLO	9	3472	2.38	0.43	8.15	⊕○○○ very low ^{*,^}
SREs	PL	CLO	13	5727	1.27	0.81	1.84	⊕⊕○○ low [*]
SREs	ETI	CLO	13	5727	1.01	0.37	2.20	⊕⊕○○ low [*]
SREs	PAM 90 mg	CLO	13	5727	0.90	0.51	1.38	⊕⊕○○

Table 3. Indirect comparisons (Continued)

								low*
SREs	IBAN	CLO	13	5727	1.37	0.68	2.55	⊕⊕⊕⊕ low*
SREs	ZOL	CLO	13	5727	0.72	0.41	1.02	⊕⊕⊕⊕ low*
SREs	PAM 30 mg	CLO	13	5727	0.89	0.44	1.62	⊕⊕⊕⊕ low*
SREs	ETI	PL	13	5727	0.79	0.33	1.61	⊕⊕⊕⊕ low*
SREs	PAM 90 mg	PL	13	5727	0.71	0.49	0.96	⊕⊕⊕⊕ moderate
SREs	IBAN	PL	13	5727	1.08	0.60	1.86	⊕⊕⊕⊕ low*
SREs	ZOL	PL	13	5727	0.57	0.37	0.76	⊕⊕⊕⊕ moderate
SREs	PAM 30 mg	PL	13	5727	0.71	0.38	1.23	⊕⊕⊕⊕ low*
SREs	PAM 90 mg	ETI	13	5727	1.06	0.40	2.25	⊕⊕⊕⊕ low*
SREs	IBAN	ETI	13	5727	1.61	0.55	3.79	⊕⊕⊕⊕ low*
SREs	ZOL	ETI	13	5727	0.84	0.31	1.76	⊕⊕⊕⊕ low*

Table 3. Indirect comparisons *(Continued)*

SREs	PAM30mg	ETI	13	5727	1.06	0.35	2.57	⊕⊕⊕⊕ low*
SREs	IBAN	PAM 90 mg	13	5727	1.56	0.80	2.90	⊕⊕⊕⊕ low*
SREs	ZOL	PAM 90 mg	13	5727	0.81	0.52	1.14	⊕⊕⊕⊕ low*
SREs	PAM 30 mg	PAM 90 mg	13	5727	1.00	0.60	1.70	⊕⊕⊕⊕ low*
SREs	ZOL	IBAN	13	5727	0.56	0.26	0.98	⊕⊕⊕⊕ moderate
SREs	PAM 90 mg	IBAN	13	5727	0.70	0.29	1.44	⊕⊕⊕⊕ low*
SREs	PAM 30 mg	ZOL	13	5727	1.28	0.68	2.51	⊕⊕⊕⊕ low*
Pain	ETI	CLO	8	1281	2.15	0.22	9.56	⊕⊕⊕⊕ very low**^
Pain	IBAN	CLO	8	1281	4.13	0.57	16.99	⊕⊕⊕⊕ very low**^
Pain	PAM 90 mg	CLO	8	1281	1.76	0.57	16.99	⊕⊕⊕⊕ very low**^
Pain	IBAN	ETI	8	1281	4.07	0.23	19.62	⊕⊕⊕⊕ very low**^
Pain	PAM 90 mg	ETI	8	1281	1.75	0.11	7.64	⊕⊕⊕⊕

Table 3. Indirect comparisons (Continued)

								very low ^{^^}
Pain	PAM 90 mg	IBAN	8	1281	0.75	0.06	3	⊕⊕⊕⊕
								very low ^{^^}
Vertebral fractures	PL	CLO	8	3076	1.50	0.87	2.62	⊕⊕⊕⊕
								low [*]
Vertebral fractures	IBAN	CLO	8	3076	1.76	0.56	4.45	⊕⊕⊕⊕
								low [*]
Vertebral fractures	PAM 90 mg	CLO	8	3076	1.07	0.45	2.07	⊕⊕⊕⊕
								low [*]
Vertebral fractures	ZOL	CLO	8	3076	0.59	0.22	1.17	⊕⊕⊕⊕
								low [*]
Vertebral fractures	IBAN	PL	8	3076	1.16	0.41	2.56	⊕⊕⊕⊕
								low [*]
Vertebral fractures	PAM90mg	PL	8	3076	0.72	0.35	1.18	⊕⊕⊕⊕
								low [*]
Vertebral fractures	ZOL	PL	8	3076	0.42	0.12	0.94	⊕⊕⊕⊕
								moderate
Vertebral fractures	PAM90mg	IBAN	8	3076	0.76	0.21	1.91	⊕⊕⊕⊕
								low [*]
Vertebral fractures	ZOL	IBAN	8	3076	0.45	0.08	1.29	⊕⊕⊕⊕
								low [*]
Vertebral fractures	ZOL	PAM 90 mg	8	3076	0.64	0.17	1.68	⊕⊕⊕⊕
								low [*]

Table 3. Indirect comparisons (Continued)

Nonvertebral fractures	PL	CLO	7	3349	1.47	0.65	3.10	⊕⊕○○ low*
Nonvertebral fractures	IBAN	CLO	7	3349	2.13	0.44	7.20	⊕⊕○○ low*
Nonvertebral fractures	PAM 90 mg	CLO	7	3349	3.17	0.52	10.88	⊕⊕○○ low*
Nonvertebral fractures	ZOL	CLO	7	3349	0.82	0.24	2.32	⊕⊕○○ low*
Nonvertebral fractures	IBAN	PL	7	3349	1.46	0.40	3.98	⊕⊕○○ low*
Non vertebral fractures	PAM 90 mg	PL	7	3349	2.01	0.46	6.32	⊕⊕○○ low*
Non vertebral fractures	ZOL	PL	7	3349	0.66	0.13	2.30	⊕⊕○○ low*
Non-vertebral fractures	PAM 90 mg	IBAN	7	3349	1.98	0.25	7.66	⊕⊕○○ low*
Non-vertebral fractures	ZOL	IBAN	7	3349	0.64	0.07	2.82	⊕⊕○○ low*
Non-vertebral fractures	ZOL	PAM 90 mg	7	3349	0.49	0.04	2.14	⊕⊕○○ low*
Hypercalcemia	PL	CLO	11	4146	1.64	0.71	3.58	⊕○○○ very low*\$
Hypercalcemia	ETI	CLO	11	4146	2.59	0.51	8.80	⊕○○○

Table 3. Indirect comparisons (Continued)

								very low *\$
Hypercalcemia	IBAN	CLO	11	4146	1.27	0.20	4.53	⊕○○○ very low *\$
Hypercalcemia	PAM90mg	CLO	11	4146	1.14	0.32	3.05	⊕○○○ very low *\$
Hypercalcemia	ZOL	CLO	11	4146	1.04	0.32	2.47	⊕○○○ very low *\$
Hypercalcemia	ETI	PL	11	4146	1.55	0.40	4.27	⊕○○○ very low *\$
Hypercalcemia	IBAN	PL	11	4146	0.76	0.16	2.27	⊕○○○ very low *\$
Hypercalcemia	PAM 90 mg	PL	11	4146	0.70	0.26	1.40	⊕○○○ very low *\$
Hypercalcemia	ZOL	PL	11	4146	0.73	0.16	1.92	⊕○○○ very low *\$
Hypercalcemia	IBAN	ETI	11	4146	0.68	0.08	2.53	⊕○○○ very low *\$
Hypercalcemia	PAM 90 mg	ETI	11	4146	0.62	0.11	1.92	⊕○○○ very low *\$
Hypercalcemia	ZOL	ETI	11	4146	0.65	0.08	2.28	⊕○○○ very low *\$
Hypercalcemia	PAM 90 mg	IBAN	11	4146	1.42	0.22	4.79	⊕○○○ very low *\$

Table 3. Indirect comparisons (Continued)

Hypercalcemia	ZOL	IBAN	11	4146	1.50	0.15	5.74	⊕⊕⊕⊕ very low *\$
Hypercalcemia	ZOL	PAM 90 mg	11	4146	1.23	0.21	4.05	⊕⊕⊕⊕ very low *\$
GIToxicity	PL	CLO	8	3789	0.87	0.45	1.49	⊕⊕⊕⊕ low* \$\$
GIToxicity	ETI	CLO	8	3789	1.14	0.01	7.59	⊕⊕⊕⊕ low* \$\$
GIToxicity	PAM 90 mg	CLO	8	3789	1.18	0.45	2.49	⊕⊕⊕⊕ low* \$\$
GIToxicity	ZOL	CLO	8	3789	0.86	0.35	1.74	⊕⊕⊕⊕ low* \$\$
GIToxicity	ETI	PL	8	3789	1.32	0.01	8.73	⊕⊕⊕⊕ low* \$\$
GIToxicity	PAM 90 mg	PL	8	3789	1.36	0.69	2.39	⊕⊕⊕⊕ low* \$\$
GIToxicity	ZOL	PL	8	3789	1.07	0.38	2.39	⊕⊕⊕⊕ low* \$\$
GIToxicity	PAM 90 mg	ETI	8	3789	15.96	0.14	102.19	⊕⊕⊕⊕ low* \$\$
GIToxicity	ZOL	ETI	8	3789	12.63	0.10	81.10	⊕⊕⊕⊕ low* \$\$
GIToxicity	ZOL	PAM 90 mg	8	3789	0.86	0.24	2.27	⊕⊕⊕⊕

Table 3. Indirect comparisons (Continued)

								low* \$\$
ONJ	PL	PAM 90 mg	8	3746	1.10	0.04	5.99	⊕⊕⊕⊕ very low ^{*,^}
ONJ	ZOL	PAM 90 mg	8	3746	6.19	0.09	38.16	⊕⊕⊕⊕ very low ^{*,^}
ONJ	CLO	PAM 90 mg	8	3746	0.77	0.01	4.94	⊕⊕⊕⊕ very low ^{*,^}
ONJ	PAM 30 mg	PAM 90 mg	8	3746	0.44	0.05	1.83	⊕⊕⊕⊕ very low ^{*,^}
ONJ	ZOL	PL	8	3746	5.70	0.72	21.26	⊕⊕⊕⊕ very low ^{*,^}
ONJ	CLO	PL	8	3746	0.71	0.04	3.43	⊕⊕⊕⊕ very low ^{*,^}
ONJ	PAM 30 mg	PL	8	3746	2.19	0.03	13.55	⊕⊕⊕⊕ very low ^{*,^}
ONJ	CLO	ZOL	8	3746	0.13	0.02	0.44	⊕⊕⊕⊕ very low ^{**,^}
ONJ	PAM 30 mg	ZOL	8	3746	0.77	0.00	5.09	⊕⊕⊕⊕ very low ^{*,^}
ONJ	PAM 30 mg	CLO	8	3746	11.14	0.04	76.15	⊕⊕⊕⊕ very low ^{*,^}

REM: Random effects model, for multiple treatment comparison method: $\sigma^2 \sim \text{Unif}(0,1)$; **ONJ:** osteonecrosis of the jaw; **PL:** Placebo; **#RCTS:** Number of randomized controlled trials; **LCRL:** Lower credibility limit; **UCRL:** Upper credibility limit; **OS:** Overall survival; **PFS:** Progression-free survival; **SRES:** Skeletal-related events; **HR:** Hazard ratio; **RR:** Risk ratio; **ETI:** Etidronate; **CLO:** Clodronate; **PAM 90 mg:** Pamidronate 90 mg; **PAM 30 mg:** Pamidronate 30 mg; **IBAN:** Ibandronate; **ZOL:** Zoledronate; ^{*}Randomized controlled trial

with direct (head-to-head) comparison of zoledronate versus clodronate (Morgan 2010).* Imprecision; ^ Contributing direct evidence of low quality;\$ For the contributing direct evidence, the pooled estimate along with individual studies have wide confidence intervals. Therefore, we downgraded the quality of evidence by two levels resulting in low quality evidence. \$\$ For the contributing direct evidence, individual studies have wide confidence intervals. Therefore, we downgraded the quality of evidence by one level resulting in moderate quality evidence.**The results from head to head RCT comparing zoledronate with clodronate showed no difference in risk of ONJ (Morgan 2010). However, the results from network meta-analysis showed an increased risk of ONJ with zoledronate over clodronate which is indicative of incoherence.

Table 4. Included ONJ studies

Study	Study design	Type of bisphosphonate	Total number of patients	Number of patients with ONJ	Route, dose, frequency	Treatment duration	ONJ frequency
Badros 2006	Retrospective study	Pamidronate	17	3	Not reported	Not reported	17.65%
		Zoledronate	34	2			5.88%
		Pamidronate + zoledronate	33	17			51.51%
Berenson 2011	Retrospective study	Zoledronate	300	14	Not clear	Median: 18 months Range: 1-121 months	5%
Calvo-Villas 2006	Not clear	Zoledronate	64	7	Not reported	Not clear	9%
Cetiner 2009	Prospective study	Zoledronate	32	5	15 minute infusion of 4 mg IV zoledronate once a month	Mean duration: 26.5 months, SD 18.7 months	15%
Corso 2007	Retrospective study	Pamidronate	20	0	Not clear	23 months	0%
		Zoledronate	37	5	Not clear	28 months	11.9%
		Pamidronate + zoledronate	42	2	Not clear	47 months	4.55%
Dimopoulos 2006		Pamidronate	93	7	Not reported	39 months ONJ patients (11-76) vs 28 (4.5-123) months without ONJ	7.5%
		Zoledronate	33	1			3%
		Pamidronate + zoledronate	66	6			9.1%
		Ibandronate	1	0			0%
		Ibandronate + zoledronate	4	1			25%

Table 4. Included ONJ studies *(Continued)*

		Clodronate + zoledronate	1	0			0%
		Alendronate + zoledronate	1	0			0%
Garcia-Garay 2006	Retrospective study	Pamidronate	49	1	90 mg monthly	28 months	2%
		Zoledronate	64	6	4 mg monthly	12 months (7-28)	9.3%
		Pamidronate + zoledronate	30	7		43.5 months (24-59)	23.3%
Tosi 2006b	Retrospective study	Zoledronate	225	6	Not reported	10 months (4-35)	2.7%
Zervas 2006	Retrospective study from 1991, prospective from 2001-2006	Pamidronate	78	1	90 mg	24 months (4-120)	1.28%
		Pamidronate	91	6	4 mg 4-6 weeks		6.59%
		Pamidronate + zoledronate	85	21			24.71%

ONJ: Osteonecrosis of the jaw; **SD:** standard deviation; **IV:** intravenous.

Table 5. Excluded ONJ studies

Study_ID	Reason for exclusion
Bujanda 2007	No multiple myeloma patients with ONJ
Hoff 2006	No extractable data for multiple myeloma patients (abstract)
Kut 2004	American Society of Hematology 2004 (abstract no 4933): Approximately 600 multiple myeloma patients. Reported frequency: 7 patients. Excluded due to imprecise reporting (e.g. approximately 600 multiple myeloma patients)

ONJ: Osteonecrosis of the jaw.

Table 6. ONJ case reports/case series: data stratified by bisphosphonate type

Study	Total number of patients	Clodronate	Pamidronate	Zoledronate	Pamidronate /zoledronate	Not specified	Others
Bagan 2006	9		2	7			
Battley 2006	1			1			
Braun 2006	1			1			
Broglia 2006	1				1		
Capalbo 2006	9		2	4	3		
Carneiro 2006	1			1			
Carter 2005	1		1				
Clarke 2007	21		12	1	8		
Curi 2007	1			1			
Dannemann 2007	7			2	5		
Diego 2007	3			3			
Dimitrakopoulos 2006	5			2	3		
Elad 2006	22			17	4		1(A)
Ficarra 2005	2			1	1		
Fortuna 2012	13			13			
Gabbert 2015	101		18	78			5
Gander 2014	1			1			
Hansen 2006	5			1	4		
Hay 2006	2			2			

Table 6. ONJ case reports/case series: data stratified by bisphosphonate type (Continued)

Herbozo 2007	1		1		
Junquera 2009	21	1	19		1(A)
Kademani 2006	1		1		
Kamoh 2012	1			1	
Katz 2005	2		1	1	
Khamaisi 2006	6	6			
Kumar 2007	2	2			
Lazarovici 2009	101	30	31	23	17(16:A,1:U)
Lenz 2005	1		1		
Lugassy 2004	3	1		2	
Magopoulos 2007	33	6	19	7	1(P,I,Z)
Marunick 2005	2	1	1		
Melo 2005	7	4	2	1	
Merigo 2006	1		1		
Migliorati 2005	3	1		2	
Montazeri 2007	1	1			
Mortensen 2007	4	2	2		
Murad 2007	2		2		
Pires 2005	4			4	
Pozzi 2007	35	3	14	18	
Purcell 2005	3	2	1		

Table 6. ONJ case reports/case series: data stratified by bisphosphonate type *(Continued)*

Ruggiero 2004	28	14	4	10	
Pastor-Zuazaga 2006	1			1	
Phal 2007	3		1	1	1(P/C)
Polizzotto 2006	1	1			
Saad 2012	6				6
Salesi 2006	2		2		
Saussez 2009	34	3	20	5	6 (:l/Z,3:A,1:U)
Senel 2007	1	1			
Sitters 2005	1		1		
Tennis 2012	11				11
Then 2012	23				23
Thumbigere-Math 2012	6				6
Treister 2006	1	1			
Vannucchi 2005	1		1		
Vescovi 2012	56				56
Walter 2007	9	1	1	7	
Watters 2013	27				27
Wickham 2013	1	1			
Wutzl 2006	12	2	8	2	
Yeo 2005	2	2			
Zarychanski 2006	10	10

Table 6. ONJ case reports/case series: data stratified by bisphosphonate type *(Continued)*

Total	676	3	128	270	113	130	32
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A: Alendronate; **C:** Clodronate; **I:** Ibandronate; **P:** Pamidronate; **R:** Risedronate; **Z:** Zoledronate; **MM:** multiple myeloma; **U:** Unknown.

APPENDICES

Appendix 1. MEDLINE search strategy

((("Multiple Myeloma"[MeSH] OR "Plasmacytoma"[MeSH] OR multiple myeloma OR plasmacytoma OR plasmacytom* OR myelom*) AND (bisphosphonates OR pamidronate OR zoledronate OR etidronate OR ibandronate OR clodronate OR "Clodronic Acid"[MeSH] OR "pamidronate "[Substance Name] OR "Etidronic Acid"[MeSH] OR "zoledronic acid "[Substance Name] OR "ibandronic acid "[Substance Name])) AND ((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials[MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading]) AND (("2011/09/01"[EDat] : "3000"[EDat]) AND (Humans[MeSH]))

Limits:Publication Date from 2011/09/01

(((((("pamidronate "[Substance Name] OR "Etidronic Acid"[MeSH] OR "ibandronic acid "[Substance Name] OR "Clodronic Acid"[MeSH] OR "zoledronic acid "[Substance Name]) OR "Alendronate"[MeSH] OR "risedronic acid "[Substance Name] OR "tiludronic acid "[Substance Name]) AND "Multiple Myeloma"[MeSH]

Limits:Publication Date from 2011/09/01, Humans

2) Search strategy aimed at identifying observational studies and ONJ case reports.

("MultipleMyeloma"[MeSH]AND("pamidronate "[SubstanceName]OR"EtidronicAcid"[MeSH]OR"ibandronic acid "[Substance Name]) OR "Clodronic Acid"[MeSH] OR "zoledronic acid "[Substance Name])) OR "Alendronate"[MeSH] OR "risedronic acid "[Substance Name] OR "tiludronic acid "[Substance Name]) AND ("Osteonecrosis "[MeSH] OR "Jaw Diseases"[MeSH])

Limits: Publication Date from 2011/09/01, Humans

Appendix 2. Cochrane Library search strategy

"bisphosphonate and myeloma"

Appendix 3. www.clinicaltrials.gov search strategy

"bisphosphonates and multiple myeloma"

Appendix 4. Embase search strategy

'bone'/exp OR bone AND ('neoplasms'/exp OR neoplasms) OR 'bone'/exp OR bone AND ('neoplasm'/exp OR neoplasm) OR multiple AND ('myeloma'/exp OR myeloma) OR 'neoplasm'/exp OR neoplasm AND ('metastasis'/exp OR metastasis) OR 'neoplasms'/exp OR neoplasms AND ('alendronate'/exp OR alendronate) OR 'clodronate'/exp OR clodronate OR 'etidronate'/exp OR etidronate OR 'risedronate'/exp OR risedronate OR 'ibandronate'/exp OR ibandronate OR 'pamidronate'/exp OR pamidronate OR 'tiludronate'/exp OR tiludronate OR 'zoledronate'/exp OR zoledronate OR diphosphonates. AND mp OR 'bisphosphonate'/exp OR bisphosphonate AND adj AND agent OR derivative.mp.tw. AND random.tw. OR clinical AND trial.mp. OR exp AND ('health'/exp OR health) AND care AND quality Date limits used: 09012011 onwards (till 07132017)

WHAT'S NEW

Date	Event	Description
31 July 2017	New citation required but conclusions have not changed	Update of previous version. Four new studies added. Conclusions remain unchanged.
31 July 2017	New search has been performed	Update of previous systematic review published in 2012

HISTORY

Protocol first published: Issue 2, 2001

Review first published: Issue 4, 2001

Date	Event	Description
19 June 2012	Amended	Affiliation JR corrected
6 February 2012	New citation required and conclusions have changed	Revised conclusions
20 October 2011	Feedback has been incorporated	Amendments done
15 October 2011	New search has been performed	New search

CONTRIBUTIONS OF AUTHORS

For this update:

RM handsearched journals and references, extracted and analyzed data, wrote the initial and final drafts and participated in all phases of the project.

BD oversaw and co-ordinated the group activity, maintained contact with Cochrane, provided vital content and methodological inputs, and edited the review.

AK extracted data, contacted a researcher regarding unpublished data, and maintained contact with Cochrane.

BM conducted the indirect comparisons using Bayesian methods.

BD, RM and AK discussed methodological problems.

All co-authors interpreted data, provided constructive critiques and agreed on the final version of the paper.

DECLARATIONS OF INTEREST

RM: None known.

AK: None known.

BM: None known.

BD: None known.

SOURCES OF SUPPORT

Internal sources

- Center for Evidence-based Medicine, The University of South Florida, USA.
- Department of Internal Medicine, University of Bonn, Germany.

External sources

- Leukämie-Initiative Bonn e.v., Germany.
- Cochrane Haematological Malignancies Group (CHMG), Germany.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Compared with the last version of this systematic review, we employed only the Bayesian method for the network meta-analysis. That is, we have not used the frequentist method for performing adjusted indirect comparisons as described by Bucher, Glenny and Caldwell and colleagues. According to the revised guidelines for network meta analysis; we used the Bayesian methods under random-effects multiple treatment comparisons (MTC) for indirect comparisons/network meta analysis ([Higgins 1996](#); [Lu 2004](#)). Also, as per the peer reviewer's suggestions; we conducted additional sensitivity analyses based on the route of administration (oral versus intravenous) for gastrointestinal toxicity outcome ([Analysis 3.8](#)), which was not part of the protocol.

We also identified observational studies and case reports regarding bisphosphonate-related ONJ in the MEDLINE database

INDEX TERMS

Medical Subject Headings (MeSH)

Antineoplastic Agents [*therapeutic use]; Bone Density Conservation Agents [*therapeutic use]; Bone Diseases [*drug therapy] [mortality]; Clodronic Acid [therapeutic use]; Diphosphonates [*therapeutic use]; Disease-Free Survival; Etidronic Acid [therapeutic use]; Fractures, Bone [epidemiology] [prevention & control]; Imidazoles [therapeutic use]; Multiple Myeloma [complications] [*drug therapy] [mortality]; Pamidronate; Randomized Controlled Trials as Topic; Spinal Fractures [epidemiology] [prevention & control]; Zoledronic Acid

MeSH check words

Humans