Bisphosphonates in multiple myeloma (Review)

Mhaskar R, Redzepovic J, Wheatley K, Clark OAC, Miladinovic B, Glasmacher A, Kumar A, Djulbegovic B

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TABLE OF CONTENTS

[Intervention Review]

Bisphosphonates in multiple myeloma

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ABSTRACT

Background

Bisphosphonates are specific inhibitors of osteoclastic activity and are currently used as supportive therapy for multiple myeloma (MM). However, the exact clinical role of bisphosphonates in MM remains unclear.

Objectives

This update of the first review published in 2002. We have also analyzed observational studies targeting osteonecrosis of jaw (ONJ).

Search strategy

We searched the literature using the methods outlined in the previous review. We also searched observational studies or case reports examining ONJ.

Selection criteria

We selected RCTs with a parallel design related to the use of bisphosphonate in myeloma. We also selected observational studies or case reports examining bisphosphonates related to ONJ.

Data collection and analysis

We have reported pooled data using either hazard ratio or risk ratio and, when appropriate, as absolute risk reduction and the number needed to treat to prevent or to cause a pathological event. We have assessed statistical heterogeneity and reported I^2 statistic.

Main results

This review includes 17 trials with 1520 patients analyzed in bisphosphonates groups, and 1490 analyzed in control groups. In comparison with placebo/no treatment, the pooled analysis demonstrated the *beneficial effect* of bisphosphonates on prevention of pathological vertebral fractures (RR= 0.74 (95% CI: 0.62 to 0.89), P = 0.001), total skeletal related events (SREs) (RR= 0.80 (95% CI: 0.72 to 0.89), P < 0.0001) and on amelioration of pain (RR = 0.75 (95% CI: 0.60 to 0.95), P = 0.01). We found *no significant*

effect of bisphosphonates on overall survival (OS), progression-free survival (PFS), hypercalcemia or on the reduction of non-vertebral fractures. The indirect meta-analyses did not find the superiority of any particular type of bisphosphonate over others. Only two RCTs reported ONJ. The identified observational studies suggested that ONJ may be a common event (range: 0% to 51%).

Authors' conclusions

Adding bisphosphonates to the treatment of MM reduces pathological vertebral fractures, SREs and pain but not mortality. Assuming the baseline risk of 20% to 50% for vertebral fracture without treatment, we estimate that between eight and 20 MM patients should be treated to prevent vertebral fracture(s) in one patient. Assuming the baseline risk of 31% to 76% for pain amelioration without treatment, we estimate that between five to 13 MM patients should be treated to reduce pain in one patient. Also, with the baseline risk of 35% to 86% for SREs without treatment, we estimate that between six and 15 MM patients should be treated to prevent SRE(s) in one patient. No bisphoshphonate appears to be superior to others.

PLAIN LANGUAGE SUMMARY

Bisphosphonates in multiple myeloma

Multiple myeloma (also known as myeloma or plasma cell myeloma) is a B-cell malignancy, or more precisely, plasma cell neoplasm. Multiple myeloma cells migrate to the bone marrow and continuously multiply. Thus, the cancer grows inside or outside of the 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. The review of trials shows that adding bisphosphonates to myeloma treatment reduces fractures of the vertebra (bones in the spine) and bone pain.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Bisphosphonates for prevention of skeletal related events in multiple myeloma

Patient or population: patients with prevention of skeletal related events in multiple myeloma
Settings:
Intervention: Bisphosphonates

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Bisphosphonates				
Overall mortality 2221 patients	**Medium risk population**		**HR 0.93** (0.79 to 1.09)	2221 (11 studies)	⊕⊕◯◯ **low**[1,2,3]	
	530 per 1000	**504 per 1000** (449 to 561)				
Progression free survival 364 Patients	**Medium risk population**		**HR 0.70** (0.41 to 1.19)	364 (4 studies)	⊕◯◯◯ **very low**[1,4]	
	350 per 1000	**260 per 1000** (162 to 401)				
Vertebral fractures 1116 Patients	**Low risk population**[5]		**RR 0.74** (0.62 to 0.89)	1116 (7 studies)	⊕⊕⊕◯ **moderate**[1,6]	
	100 per 1000	**74 per 1000** (62 to 89)				
	Medium risk population[5]					
	350 per 1000	**259 per 1000** (217 to 311)				
	High risk population[5]					

	690 per 1000	**511 per 1000** (428 to 614)			
Non vertebral fractures 1389 patients	**Medium risk population**		**RR 1.03** (0.68 to 1.56)	1389 (6 studies)	⊕⊕⊕◯ **moderate**[1,7]
	140 per 1000	**144 per 1000** (95 to 218)			
Skeletal related events 1497 patients	**Low risk population**[5]		**RR 0.81** (0.72 to 0.92)	1497 (7 studies)	⊕⊕⊕◯ **moderate**[1,8]
	240 per 1000	**194 per 1000** (173 to 221)			
	Medium risk population[5]				
	303 per 1000	**245 per 1000** (218 to 279)			
	High risk population[5]				
	860 per 1000	**697 per 1000** (619 to 791)			
Pain 1281 patients	**Low risk population**[5]		**RR 0.75** (0.6 to 0.95)	1281 (8 studies)	⊕◯◯◯ **very low**[9,10]
	60 per 1000	**45 per 1000** (36 to 57)			
	Medium risk population[5]				
	500 per 1000	**375 per 1000** (300 to 475)			
	High risk population[5]				
	1000 per 1000	**750 per 1000** (600 to 950)			

Hypercalcemia 1934 patients	**Medium risk population**		**RR 0.87** (0.61 to 1.24)	1934 (8 studies)	⊕⊕⊕○ **moderate**[1]
	100 per 1000	**87 per 1000** (61 to 124)			

*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;

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] Only 37% (6/16) of trials had adequate allocation concealment. Only 12% (2/16) of trials reported methods of randomization. Similarly, 12% (2/16) of trials reported blinding procedures and personnel who were ' ' blinded" to the intervention assignment. However sensitivity analyses based on allocation concealment, description of randomization method didn't change the estimates. Hence, the assessment of studies limitations may represent the poor quality of reporting rather than true biased estimates.
[2] I square = 55%. The pooled estimate is driven by studies by Aviles et al and Belch et al; when we removed these RCTs pooled estimates remained the same but heterogeneity disappeared.
[3] The overall mortality data was extractable from 11 out of 16 studies. Also, note that overall mortality data denotes the mortality rates i.e. the number of events refer to the number of deaths.
[4] The progression free survival data could be extracted from only 4 out of 16 studies.
[5] We have denoted only medium risks in controls for statistically non significant outcomes while denoting low, medium and high risks in controls for statistically significant outcomes.
[6] Data related to patients with vertebral fractures were extractable from only 7 out 16 RCTs
[7] Data related to patients with non vertebral fractures were extractable from only 6 out 16 RCTs
[8] Skeletal related events data were extractable from only 7 out 16 RCTs
[9] Only 37% (6/16) of trials had adequate allocation concealment. Only 12% (2/16) of trials reported methods of randomization. Similarly, 12% (2/16) of trials reported blinding procedures and personnel who were ' ' blinded" to the intervention assignment.
[10] There was variation in the pain scales used to measure pain.

BACKGROUND

Description of the condition

Multiple myeloma 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 (MGUS) to plasma cell leukemia (Tricot 2000). Multiple myeloma can present outside the bone marrow as solitary plasmacytoma or extramedullary plasmacytoma. It is most common in people over 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 (ROTI). Ninety-seven per cent of people with multiple myeloma have a presence of M-protein in serum, urine, or both. A diagnosis of asymptomatic myeloma (also known as smouldering myeloma) requires the presence of M-protein in serum of 30 g/L or more, bone marrow clonal plasma cells of 10% or more, or both; and no ROTI or symptoms.The most common symptoms of multiple myeloma 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 a severe back pain.

Description of the intervention

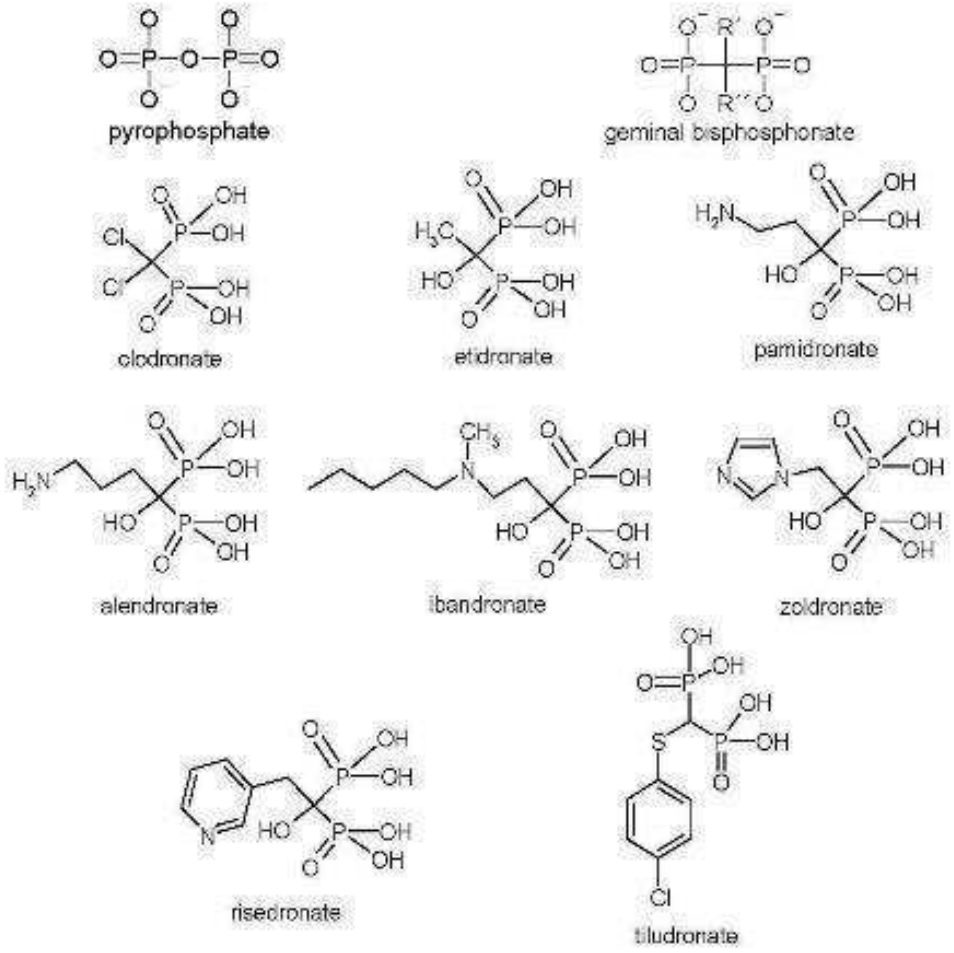
Bisphosphonates are currently used in the management of multiple myeloma as supportive therapy to inhibit progression of osteoclastic activity and affect skeletal-related morbidity and mortality secondary to this process. A number of randomized trials (Description of studies) have been conducted investigating the use of bisphosphonates in multiple myeloma. Etidronate was the first bisphosphonate tested in a clinical arena, but with no apparent benefit (Belch 1991). Pamidronate, a second-generation bisphosphonate, demonstrated a significant clinical effect on the rate of skeletal-related events 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 patients. Similarly the RCT comparing Zolendronate with no therapy showed survival benefit with Zolendronate (Aviles 2007). An oral form of pamidronate, however, appears less beneficial (Brincker 1998). Another oral bisphosphonate, clodronate, was also tested in several randomized trials. In a large Finnish trial, the proportion of patients 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. Our previous systematic review published in 2002 (Djulbegovic 2002) found that adding bisphosphonates to the treatment of myeloma reduces pathological vertebral fractures and pain but - from the published evidence available then - not mortality. In the meantime, additional RCTs have been published raising the question if the estimates about bisphosphonates efficacy made in 2002 are still valid.

All bisphosphonates are poorly absorbed after oral administration, but effective plasma levels can be achieved with clodronate. Aminobisphosphonates like pamidronate have caused gastrointestinal ulceration when given orally (Lufkin 1994). The other adverse effects associated with the use of bisphosphonates typically consist of renal function impairment, myalgias and hypocalcemia. Recently, osteonecrosis of the jaw (ONJ) is described as a serious new complication associated with bisphosphonates (Bagan 2006; Durie 2005; Marx 2003; 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 anti-tumor effect of bisphosphonates (Aparicio 1998; Shipman 1997). Therefore, there exists a pharmacological rationale for the use of these agents in multiple myeloma. Bisphosphonates are a heterogeneous group of molecules that resemble more or less closely 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 multiple types of bisphosphonates. Alendronate, Risedronate, Ibandronate, Pamidronate, Zoledronate, termed as 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, named as non-aminobisphosphonates (Figure 1) do not contain nitrogen and are incorporated into hydrolytically stable analogues 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 signalling 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 (OPG) favors osteoclast bone resorption (Cassidy 2006). Other cytokines such as interleukin-6 further support an excess of osteoclast activity (Cassidy 2006).

Figure 1. Bisphosphonate chemical structures



Why it is important to do this review

There is uncertainty regarding the role of bisphosphonates in management of myeloma. Hence we conducted a systematic review to address the role of bisphosphonates in management of multiple myeloma. In addition, we analyzed data from observational studies and case reports describing bisphosphonates associated with ONJ. Inclusion of observational studies will provide better assessment of risk-benefit of bisphosphonate therapy.

OBJECTIVES

Our primary objective is to determine whether adding bisphosphonates to standard therapy in multiple myeloma decreases skeletal-related morbidity (pathological fractures) and overall survival.

Our secondary objective is to determine the effects of bisphosphonates on pain, progression of disease, quality of life, incidence of hypercalcemia, incidence of bisphosphonates related to gastroin-

testinal toxicities, osteonecrosis of jaw and hypocalcemia.

METHODS

Criteria for considering studies for this review

Types of studies

We have included RCTs with a parallel design in which interventions consist of bisphosphonates against placebo or no treatment or other bisphosphonates in multiple myeloma patients.

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 patients with underlying disease other than multiple myeloma and studies that reported insufficient data, as well as studies with fewer than 10 patients.

Types of participants

Patients with the diagnosis of multiple myeloma as defined by the researchers in each study. No uniform criteria for the diagnosis (Alexanian 1994) were observed 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. For further details see Table 1 'Inclusion criteria'.

Table 1. Inclusion criteria

Study ID	Stage (Durie 1975)	Osteolytic lesion	Creatinine	Calcium	Other criteria
Attal 2006	I-III	Not required	Not specified	Not specified	No cytotoxic chemotherapy prior to entry
Aviles 2007	III	At least one	Not specified	Not specified	No cytotoxic chemotherapy prior to entry
Belch 1991	I-III	Not required	< 3 mg/dl	Normal or elevated	No cytotoxic chemotherapy prior to entry
Berenson 1998	III Only	At least one	< 5mg/dl	Not specified	No bone specific treatment prior to entry
Brincker 1998	II-III	Not specified	< 2.8 mg/dl	Normal or elevated	No cytotoxic chemotherapy prior to entry
Daragon 1993	II-III	Not specified	< 2 mg/dl	Normal or elevated	No cytotoxic chemotherapy prior to entry
Delmas 1992	Not specified	Not specified	< 1.8 mg/dl	Not specified	
Heim 1995	I-III	Not required	< 2.5 mg/dl	Not specified	
Lahtinen 1992	Not Specified	Not required	Any	Normal or elevated	Newly diagnosed and previously untreated patients
Leng 2002	II-III	Not specified	Not specified	Not specified	Verbal rating scale > II
McCloskey 1998	II-III	At least one	Any	Normal or elevated	No cytotoxic chemotherapy prior to entry

Table 1. Inclusion criteria (*Continued*)

Musto 2003	I-II	Any	Not specified	Not specified	No cytotoxic chemotherapy prior to entry
Musto 2008	I (ISS)	Any	< 1.2 mg/dl	< 10 mg/dl	No cytotoxic chemotherapy prior to entry
Menssen 2002	II-III	At least one	<= 3 mg/dl	Normal	No bone specific treatment prior to entry
Terpos 2000	I-III	Not specified	< 5 mg/dl	Not specified	
Terpos 2003	II	At least one	< 4 mg/dl	Not specified	No bone specific treatment within 2 months prior to study entry
Kraj 2000	II-III	Not specified	Unclear	Not specified	

Types of interventions

- Experimental group: treatment included any of the following bisphosphonates: etidronate, clodronate, pamidronate, ibandronate, zoledronate.
- Control group: no therapy, placebo or other bisphosphonates.

For further details see (Table 2) and (Table 3).

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

Study ID	Vertebral fractures	Non-vertebral fractures	Skeletal related events	Pain	Calcium	Creatinine	Mortality (overall)
Belch 1991	No	No	No	No	Yes	No	Yes
Berenson 1998	Yes	Yes	Yes	Yes	Yes	No	Yes
Brincker 1998	No	No	Yes	No	Yes	No	Yes
Delmas 1982	Yes	Yes	No	Yes	No	No	Yes
Daragon 1993	No	No	Yes	Yes	No	Yes	Yes
Heim 1995	No	No	No	Yes	Yes	No	No
Lahtinem 1992	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Table 2. Type and content of reporting in RCTs on bisphosphonates in myeloma (*Continued*)

McCloskey 1998	Yes	Yes	No	Yes	Yes	No	Yes
Terpos 2000	Yes	Yes	No	Yes	Yes	No	Yes
Terpos 2003	No	No	No	No	Yes	No	No
Kraj 2000	Yes	No	No	No	No	No	Yes
Attal 2006	No	No	Yes	No	No	No	Yes
Musto 2003	No	No	Yes	No	No	No	No
Musto 2008	No	No	Yes	No	No	No	No
Aviles 2007	No	No	No	No	No	No	Yes
Menssen 2002	Yes	Yes	Yes	Yes	Yes	No	Yes
Leng 2002	No	No	No	No	No	No	No
EX-TRACTABLE DATA	7/17	6/17	7/17	8/17	9/17	2/17	11/17

Table 3. Type of intervention

Study	Drug	Dose	Interval	Route	Maximum Duration
Attal 2006	pamidronate	90 mg	monthly	i.v.	indefinitely
Aviles 2007	zoledronate	4 mg	monthly	i.v.	indefinitely
Belch 1991	etidronate	5 mg/kg	daily	p.o.	indefinitely
Berenson 1998a	pamidronate	90 mg	monthly	i.v.	24 months
Brincker 1998	pamidronate	300 mg	daily	p.o.	24 months
Delmas 1982	clodronate	1600 mg	daily	p.o.	24 months
Daragon 1993	etidronate	10 mg/kd	daily	p.o.	4 months
Menssen 2002	ibandronate	2 mg	monthly	i.v.	24 months
Heim 1995	clodronate	1600 mg	daily	p.o.	12 months

Table 3. Type of intervention (*Continued*)

Lahtinen 1992	clodronate	2400 mg	daily	p.o.	24 months
Leng 2002	Pamidronate	90 mg	daily	i.v.	indefinitely
McCloskey 2001	clodronate	1600 mg	daily	p.o.	indefinitely or progression
Musto 2003	pamidronate	60 mg	monthly	i.v.	12 months or progression
Musto 2008	zoledronate	4 mg	monthly	i.v.	12 months
Terpos 2000	pamidronate	90 mg	monthly	i.v.	14 months
Terpos 2003	Pamidronate Ibandronate	90 mg 4 mg	monthly monthly	i.v. i.v.	4 months 4 months
Kraj 2000	pamidronate	60 mg	monthly	i.v.	indefinitely

ISS = International staging system

Types of outcome measures

We sought to extract data on the following outcomes:
Overall survival (measured as mortality) and progression free survival.
Skeletal events - number of patients experiencing pathological fractures (vertebral and non-vertebral), total skeletal related events (as defined by individual authors; these included vertebral fractures, non-vertebral fractures, osteolytic lesions etc.)
Number of participants with disease progression, time to progression, presence of pain (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

Electronic searches

This is an update of the first review published in 2002 (Djulbegovic 2002). We have searched the electronic databases from 12/31/2000 onwards till 02/01/2009.
We first sought to identify all RCTs in multiple myeloma in following databases:
MEDLINE (see Appendix 1);
The Cochrane Library (see Appendix 2);
Clinicaltrials.gov (see Appendix 3);
EMBASE (see Appendix 4);
LILACS (see Appendix 5).
We also sought to identify the observational studies and case reports regarding bisphosphonates related ONJ in following databases:
MEDLINE (see Appendix 1)

Searching other resources

We scanned all relevant references in each article. We used additional strategy to contact pharmaceutical companies manufacturing bisphosphonates and researchers in the field. We also handsearched abstracts from the meetings of the American Society of Hematology (ASH), the American Society for Clinical Oncology (ASCO), and the European Haematology Association (EHA) from 2000 to 2008.
We undertook extensive contact with researchers all around the world, including the US, Europe, Japan, Korea, Greece, Saudi Arabia and Brazil. We also contacted the authors of selected papers, and repeated MEDLINE searches at regular intervals.

Data collection and analysis

Data extraction and management

Two review authors extracted all data, and resolved disagreements by consensus. After the extraction, a third review author re-checked all data. The outcomes extracted are listed above. We also extracted data regarding methods of trial conduct and design, specifically data regarding methods of allocation concealment, method of randomization, adequacy of blinding procedures (who was blinded), description of withdrawals and drop-outs and method of data analysis (intention to treat (ITT)/per protocol). To determine if the analysis was performed according to the ITT principle, we extracted and matched data on the numbers of patients randomized and analyzed. If the number of patients randomized and analyzed were the same, we considered the analysis ITT. We used these data as criteria for the quality assessment (risk for bias) of each trial. We considered randomization adequately concealed if a central randomization was employed; envelopes were opaque, sealed, and sequentially numbered; or a code provided by a pharmacy or a company was described in a given study. Other quality items included details about power of study (beta-error) and predetermined alpha error.

We extracted details of drug, dose, average length of treatment, length of follow up, number of randomized patients, number of patients excluded from the analysis, overall survival and progression-free survival, presence of pain, level of calcium and adverse events. Unfortunately, we were not able to extract all data from all papers (see Table 2, Table 4 and Table 5). Therefore, the final analysis focused only on those outcomes that were reported in more than two trials.

Table 4. Type and content of reporting in RCTs on bisphosphonates in myeloma

Study ID	Adverse events (Gastrointestinal symptoms)	Adverse events (Hypocalemia)	PFS
Belch 1991	No	No	No
Berenson 1998	Yes	Yes	No
Brincker 1998	Yes	No	No
Delmas 1982	No	No	No
Daragon 1993	Yes	No	No
Heim 1995	No	No	Yes
Lahtinen 1992	Yes	No	No
McCloskey 1998	Yes	Yes	No
Terpos 2000	Yes	No	No
Terpos 2003	No	Yes	No
Kraj 2000	No	No	No
Attal 2006	No	No	No
Musto 2003	No	No	Yes
Musto 2008	No	No	Yes
Aviles 2007	No	No	Yes
Menssen 2002	No	No	No

Table 4. Type and content of reporting in RCTs on bisphosphonates in myeloma (*Continued*)

Leng 2002	No	No	No
Extractable data	6/17	3/17	4/17
PFS - Progression free survival (as defined by individual authors)			

Table 5. Data extraction

Outcome	Study	Data extraction method
OS	Delmas, 1982	Data obtained from publication
OS	Lahtinen, 1992	Data obtained from publication
OS	McCloskey, 2001	Data obtained from authors
OS	Belch, 1991	Data obtained from authors
OS	Daragon, 1993	Tierney method used
OS	Menssen, 2002	Data obtained from authors
OS	Brincker, 1998	Tierney method used
OS	Kraj, 2000	Data obtained from publication
OS	Terpos, 2000	Data obtained from authors
OS	Berenson, 1998	Data obtained from publication
OS	Aviles, 2007	Data obtained from publication
PFS	Heim, 1995	Data obtained from publication
PFS	Musto, 2003	Data obtained from publication
PFS	Aviles, 2007	Data obtained from publication
PFS	Musto, 2008	Data obtained from publication
Vertebral fractures	Delmas, 1982	Data obtained from publication
Vertebral fractures	Lahtinen, 1992	Data obtained from publication
Vertebral fractures	McCloskey, 2001	Data obtained from publication

Table 5. Data extraction (*Continued*)

Vertebral fractures	Berenson, 1998	Data obtained from publication
Vertebral fractures	Kraj, 2000	Data obtained from publication
Vertebral fractures	Terpos, 2000	Data obtained from authors
Vertebral fractures	Menssen, 2002	Data obtained from publication
Non vertebral fractures	Delmas, 1982	Data obtained from publication
Non vertebral fractures	Lahtinen, 1992	Data obtained from publication
Non vertebral fractures	McCloskey, 2001	Data obtained from authors
Non vertebral fractures	Berenson, 1998	Data obtained from publication
Non vertebral fractures	Terpos, 2000	Data obtained from authors
Non vertebral fractures	Menssen, 2002	Data obtained from publication
SREs	Daragon, 1993	Data obtained from publication
SREs	Lahtinen, 1992	Data obtained from publication
SREs	Attal, 2006	Data obtained from publication
SREs	Berenson, 1998	Data obtained from publication
SREs	Musto, 2003	Data obtained from publication
SREs	Musto, 2008	Data obtained from publication
SREs	Menssen, 2002	Data obtained from publication
Hypercalcemia	Belch, 1991	Data obtained from publication
Hypercalcemia	Heim, 1995	Data obtained from publication
Hypercalcemia	Lahtinen, 1992	Data obtained from publication
Hypercalcemia	McCloskey, 2001	Data obtained from authors
Hypercalcemia	Berenson, 1998	Data obtained from publication
Hypercalcemia	Brincker, 1998	Data obtained from publication

Table 5. Data extraction (*Continued*)

Hypercalcemia	Terpos, 2000	Data obtained from authors
Hypercalcemia	Terpos, 2003	Data obtained from publication
Hypercalcemia	Menssen, 2002	Data obtained from authors
Pain	Daragon, 1993	Data obtained from publication
Pain	Delmas, 1982	Data obtained from publication
Pain	Lahtinen, 1992	Data obtained from publication
Pain	McCloskey, 2001	Data obtained from publication
Pain	Heim, 1995	Data obtained from publication
Pain	Berenson, 1998	Data obtained from publication
Pain	Terpos, 2000	Data obtained from publication
Pain	Menssen, 2002	Data obtained from publication

Data synthesis

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

We summarized dichotomous data using risk ratio (RR) based on Mentel-Haenszel (MH) estimates and pooled using a random-effects model in Review Manager 5 (RevMan 5) (RevMan 2008). In cases of time-to-event data, for each included RCT, we calculated the observed minus expected events (O minus E) and variance from the reported mortality estimates. In cases where the authors didn't report the mortality estimates (Belch 1991; Brincker 1998; Daragon 1993), we have extracted the data from the papers using methods described by Tierney et al (Tierney 2007). We pooled the time-to-event data under the random-effects model in RevMan 5 and reported hazard ratios (HR). We also used the number of patients that needed to be treated to avoid one adverse outcome such as stroke etc. (NNT) and number of patients that are treated to inflict an additional harm (NNH) (Laupacis 1988) statistics to express treatment benefits and harms, respectively, in the context of the estimated absolute risks in the control arms. We have reported all data with 95% confidence intervals (CI). We have calculated the Chi^2 and I^2 statistics to test for heterogeneity. We considered significant heterogeneity to exist if $I^2 > 50\%$.

Indirect comparison of treatment effects

For each included RCT, for the purpose of analysis, we calculated the logarithm of the hazard ratio (HR) or RR, as applicable, and its standard error (SE) and used each in indirect comparisons (Bucher 1997; Glenny 2005). These comparisons included both the direct within-trial comparisons between two treatment strategies and the indirect comparisons constructed from trials that have one treatment in common (see Figure 2, Figure 3 and Figure 4).

Figure 2. Vertebral Fractures Direct and Indirect Comparisons.P= pamidronate, C= clodronate, I=Ibandronate ..... =direct comparisons ---------- = indirect comparisons

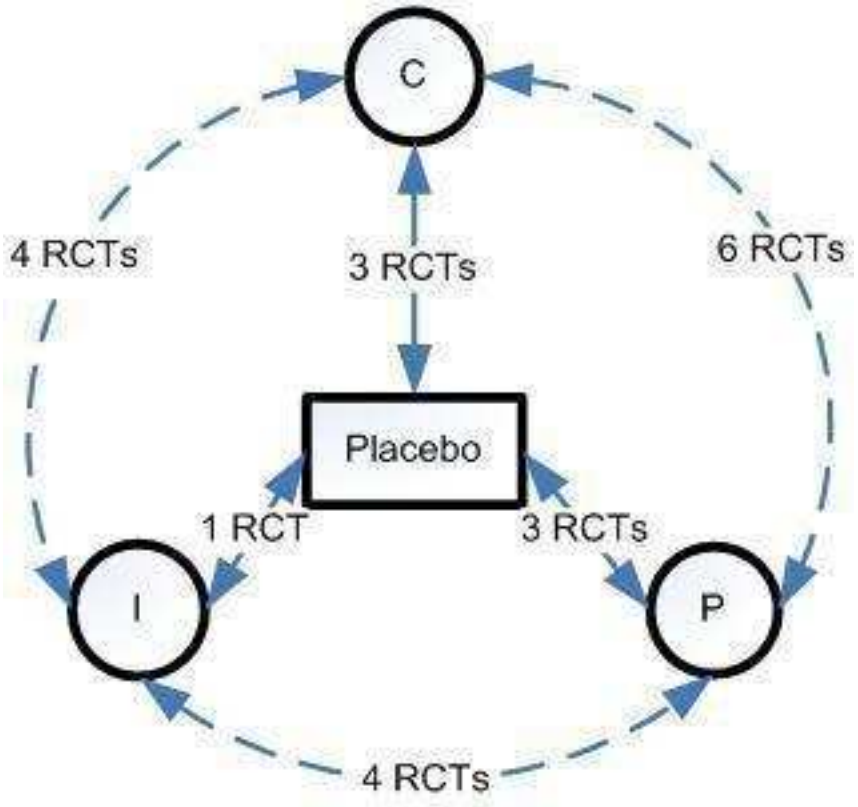


Figure 3. Total skeletal related events Direct and Indirect Comparisons.E= etidronate, I=Ibandronate, C= clodronate, Z= zoledronate,P= pamidronate, ····· =*directcomparisons* **---------- = indirect comparisons**

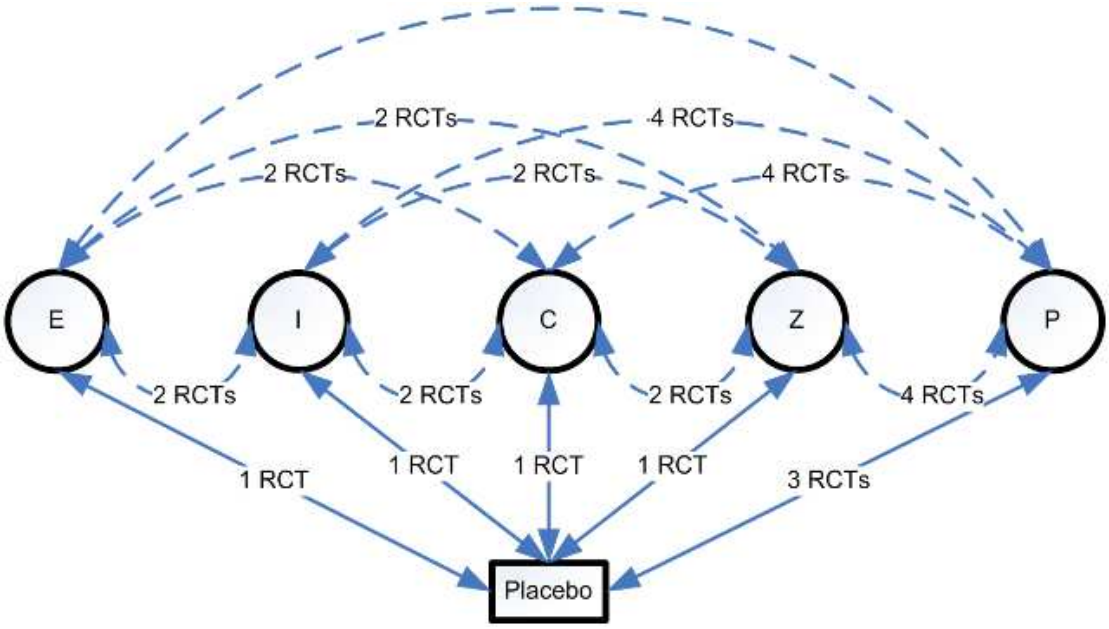
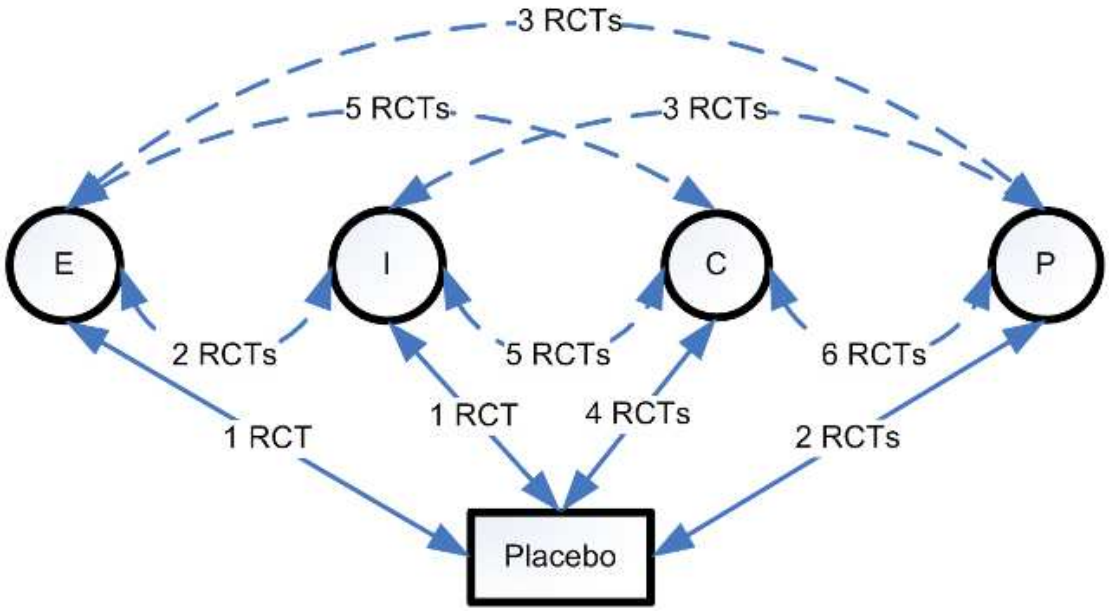


Figure 4. Pain Direct and Indirect Comparisons.E= etidronate, I=Ibandronate, C= clodronate, P= pamidronate, ····· =*directcomparisons* **---------- = indirect comparisons**



When more than one RCT was available for comparison (e.g. clodronate versus placebo), we first calculated the pooled estimates using standard meta-analytic techniques for that comparison (Egger M 2001). Using similar meta-analytic techniques, we obtained a pooled estimate from RCTs that compared other interventions (e.g. pamidronate versus placebo). Since both comparisons use placebo as control, the summary estimates obtained from respective meta-analysis (clodronate versus placebo and pamidronate versus placebo) can be used to provide estimates of the HR or RR for the indirect comparison of clodronate versus pamidronate. We performed the adjusted indirect comparisons using the method described by Bucher (Bucher 1997),Glenny (Glenny 2005) and Caldwell et al (Caldwell 2005) to calculate HR.

According to this method, an unbiased indirect comparison of interventions clodronate versus pamidronate can be obtained by adjusting the results of their direct comparisons with a common intervention of placebo. If we assume that CL_{MA} is the estimate of direct comparison between intervention clodronate versus placebo, and PD_{MA} is the direct comparison of intervention pamidronate versus placebo, then the estimate of the adjusted indirect comparison of intervention clodronate versus pamidronate ($AD_{ad\_indirect}$) (such as log HR or log RR etc.) is estimated by $AD_{ad\_indirect} = CL_{MA} - PD_{MA}$. Since the estimates are obtained from different studies, the results are statistically independent and variance can be obtained by $Var(\log(AD_{ad\_indirect}) = Var(\log(CL_{MA}) + Var(\log(PD_{MA})$ (Bucher 1997; Caldwell 2005; Glenny 2005).

We also calculated an adjusted indirect comparison at conventional difference of $P < 0.05$ levels using the random-effects model (Bucher 1997; Caldwell 2005; Glenny 2005).

We pooled time-to-event data and reported as HR, while we expressed dichotomous data as RR, using a 95% confidence interval (CI), under a random-effects model (DerSimonian 1986). We performed formal statistical tests for heterogeneity using the Chi^2 test (DerSimonian 1986) and I^2(Higgins 2003) models. We performed the indirect comparisons using STATA software (STATA V10.1).

We also used the Bayesian methods under both fixed-effect and random-effects models for indirect comparisons (Lu 2004; Higgins 1996). The fixed-effect model assumes no variance between studies, while 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/ RR estimates and credibility intervals based on Bayesian methods alongside the results of Caldwell, Bucher and Glenny et al methods described above (Table 6).

Table 6. Indirect comparison characteristics

Outcome	Comparison	Number of RCTs	Total number of patients enrolled	Bucher Method HR / RR (95%CI)	Bayesian Method FEM RR (95% CI)	Bayesian Method REM RR (95% CI), sigma~Unif(0,2)	Bayesian Method REM RR (95% CI), sigma~Unif(0,1)	Bayesian Method REM RR (95% CI), sigma~Unif(0,0.5)
Vertebral fractures	I vs C	4 (1 I vs PL + 3 C vs PL)	631	1.49 (0.82,2.70)	2.11 (0.87, 4.39)	3.47 (0.32, 12.72)	2.51 (0.52, 8.02)	2.24 (0.71, 5.54)
Vertebral fractures	P vs C	6 (3 P vs PL + 3 C vs PL)	918	0.99 (0.57,1.71)	0.94 (0.49, 1.65)	1.12 (0.18, 3.34)	1.03 (0.29, 2.58)	0.98 (0.39, 2.00)
Vertebral fractures	P vs I	4 (3 P vs PL + 1 I vs PL)	683	0.66 (0.32,1.39)	0.51 (0.19, 1.07)	0.72 (0.05, 2.52)	0.58 (0.11, 1.75)	0.53 (0.16, 1.32)
Total SREs	E vs C	2 (1 E vs PL + 1 C vs PL)	282	0.96 (0.50,1.86)	2.56 (0.64, 7.12)	7.33 (0.17, 24.39)	3.26 (0.35, 12.67)	2.72 (0.50, 8.59)
Total SREs	P vs C	4 (3 P vs PL + 1 C vs PL)	1058	1.02 (0.79,1.30)	2.48 (1.08, 5.03)	4.77 (0.27, 14.04)	2.78 (0.55, 8.14)	2.56 (0.82, 6.17)
Total SREs	I vs C	2 (1 I vs PL + 1 C vs PL)	402	1.37 (1.09,1.85)	4.15 (1.52. 9.57)	11.38 (0.31, 40.25)	5.31 (0.73, 19.64)	4.44 (1.15, 12.45)

Table 6. Indirect comparison characteristics (*Continued*)

Total SREs	Z vs C	2 (1 Z vs PL + 1 C vs PL)	367	0.92 (0.55,1.52)	2.29 (0.76, 5.52)	8.91 (0.17, 23.01)	2.94 (0.37, 11.48)	2.47 (0.59, 6.97)
Total SREs	P vs E	4 (3 P vs PL + 1 E vs PL)	932	1.05 (0.54,2.05)	1.23 (0.39, 2.98)	1.95 (0.12, 7.48)	1.39 (0.23, 4.63)	1.28 (0.33, 3.51)
Total SREs	I vs E	2 (1 I vs PL + 1 E vs PL)	276	1.42 (0.71,2.82)	2.06 (0.57, 5.39)	6.46 (0.15, 20.5)	2.62 (0.30, 10.01)	2.23 (0.47, 6.73)
Total SREs	Z vs E	2 (1 E vs PL + 1 Z vs PL)	241	0.95 (0.43,2.12)	1.16 (0.3, 3.16)	3.52 (0.08, 12.7)	1.5 (0.16, 5.91)	1.24 (0.24, 3.8)
Total SREs	I vs P	4 (1 I vs PL + 3 P vs PL)	1052	1.34 (0.97,1.85)	1.71 (0.86, 3.12)	3.18 (0.26, 12.75)	2.1 (0.49, 6.54)	1.83 (0.66, 4.11)
Total SREs	Z vs P	4 (1 Z vs PL + 3 P vs PL)	1017	0.90 (0.54, 1.51)	0.96 (0.42, 1.9)	1.97 (0.13, 7.47)	1.17 (0.25, 3.78)	1.02 (0.35, 2.44)
Total SREs	Z vs I	2 (1 I vs PL + 1 Z vs PL)	361	0.67 (0.39, 1.16)	0.61 (0.23, 1.32)	1.93 (0.05, 6.26)	0.77 (0.10, 2.76)	0.65 (0.17, 1.76)
Pain	E vs C	5 (1 E vs PL + 4 C vs PL)	644	1.13 (0.42, 3.04)	1.16 (0.30, 3.01)	8.4 (0.09, 45.63)	2.15 (0.22, 9.56)	1.42 (0.27, 4.46)
Pain	I vs C	5 (1 I vs PL + 4 C vs PL)	764	1.93 (1.09,3.44)	2.22 (0.95, 4.45)	14.45 (0.21, 83.63)	4.13 (0.57, 16.99)	2.70 (0.83, 7.13)
Pain	P vs C	6 (2 P vs PL + 4 C vs PL)	1005	1.65 (0.93, 2.93)	1.29 (0.68, 2.23)	2.83 (0.08, 14.84)	1.76 (0.57, 16.99)	1.46 (0.53, 3.38)
Pain	I vs E	2 (1 I vs PL + 1 E vs PL)	276	1.71 (0.75,3.95)	2.6 (0.59, 7.77)	19.66 (0.05, 87.15)	4.07 (0.23, 19.62)	2.89 (0.45, 9.85)
Pain	P vs E	3 (2 P vs PL + 1 E vs PL)	517	1.46 (0.63,3.35)	1.52 (0.39, 4.18)	3.21 (0.02, 17.58)	1.75 (0.11, 7.64)	1.57 (0.27, 5.13)
Pain	P vs I	3 (2 P vs PL + 1 I vs PL)	637	0.85 (0.69,1.05)	0.65 (0.27, 1.32)	1.64 (0.01, 8.06)	0.75 (0.06, 3.00)	0.67 (0.17, 1.76)

OS = Overall survival,PFS= Progression free survival, SREs= skeletal related events, GI= Gastro intestinal
E= Etidronate, C= Clodronate, P = Pamidronate, I = Ibandronate, Z= Zolendronate, PL = Placebo
HR= Hazard ratio, RR= Risk Ratio, 95%CI= 95% confidence interval
FEM= Fixed effects model, REM= Random effects model

We have performed and reported the work according to PRISMA guidelines (Liberati 2009).

We conducted sensitivity analyses according to several 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 on all outcomes. Additionally

we conducted subgroup analyses based on stage of disease. We will assess the differences between the subgroups using the test of heterogeneity between subgroups in RevMan.

RESULTS

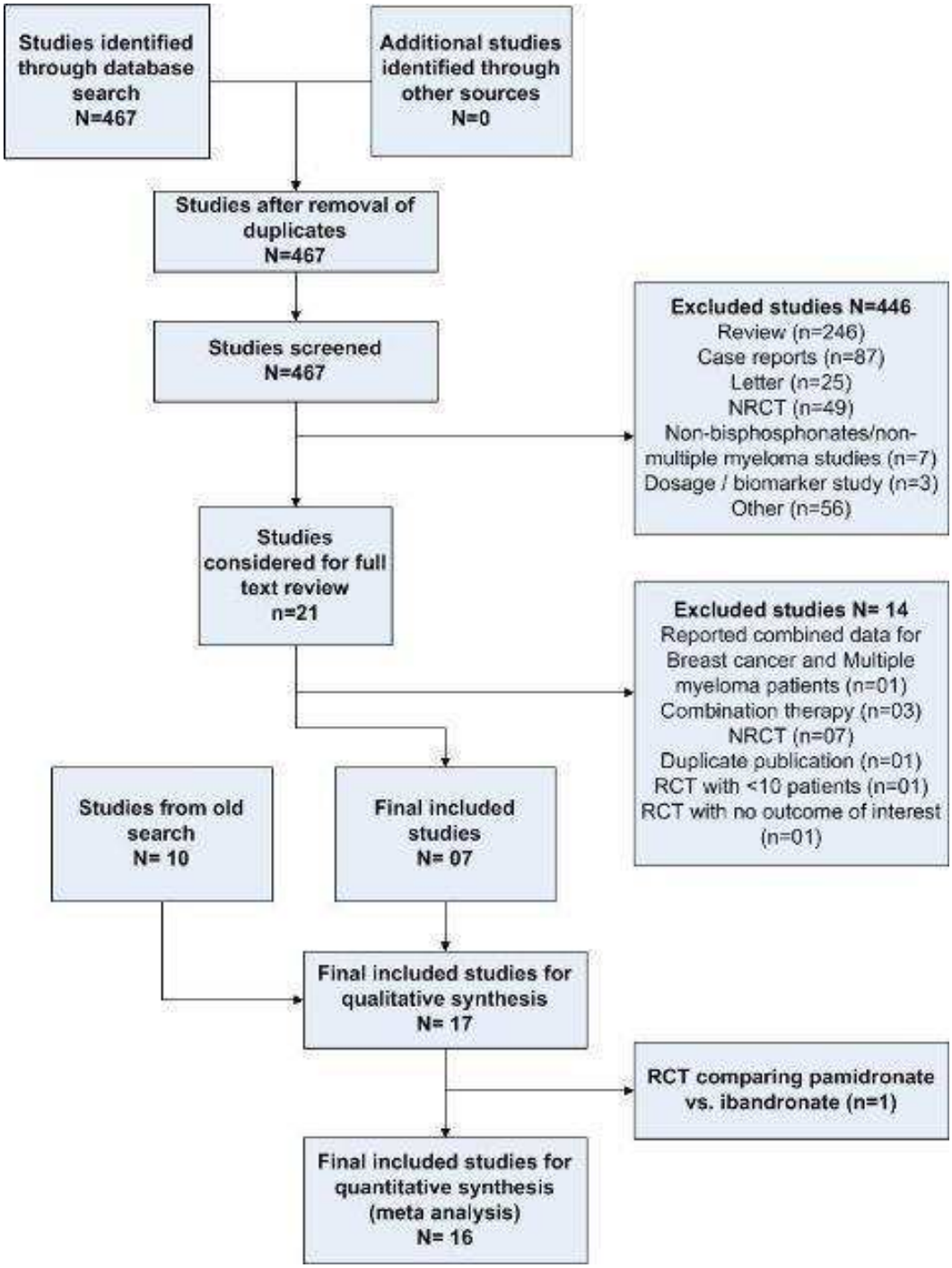
Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

For this update, we searched the electronic databases from 12/31/2000 onwards. Our updated search of electronic databases identified 467 papers that compared various treatment interventions in multiple myeloma. We didn't identify any studies through other search methods. Thirty-nine of these trials were related to the use of bisphosphonates in myeloma and weselected these for full text appraisal. From 21 selected trials, we excluded 14 based on our selection criteria and included seven for analysis. Thus, in addition to the 10 old studies, we included seven new studies, bringing the included total to 17 (see Figure 5 for details). However, we were not able to extract data from Terpos 2003.

Figure 5. Flow chart



Included studies

We have included 17 RCTs (10 old studies and seven new studies). Two trials reported effects of etidronate (Belch 1991; Daragon 1993); seven trials reported effects of pamidronate (Attal 2006; Berenson 1998; Brincker 1998; Kraj 2000; Leng 2002; Musto 2003; Terpos 2000;); four trials reported effects of clodronate (Delmas 1982; Heim 1995; Lahtinen 1992; McCloskey 2001) and one trial described effects of ibandronate (Menssen 2002).Two trials compared effects of zoledronate versus no therapy in myeloma (Aviles 2007; Musto 2008) and one trial compared effects of pamidronate versus ibandronate in myeloma (Terpos 2003).

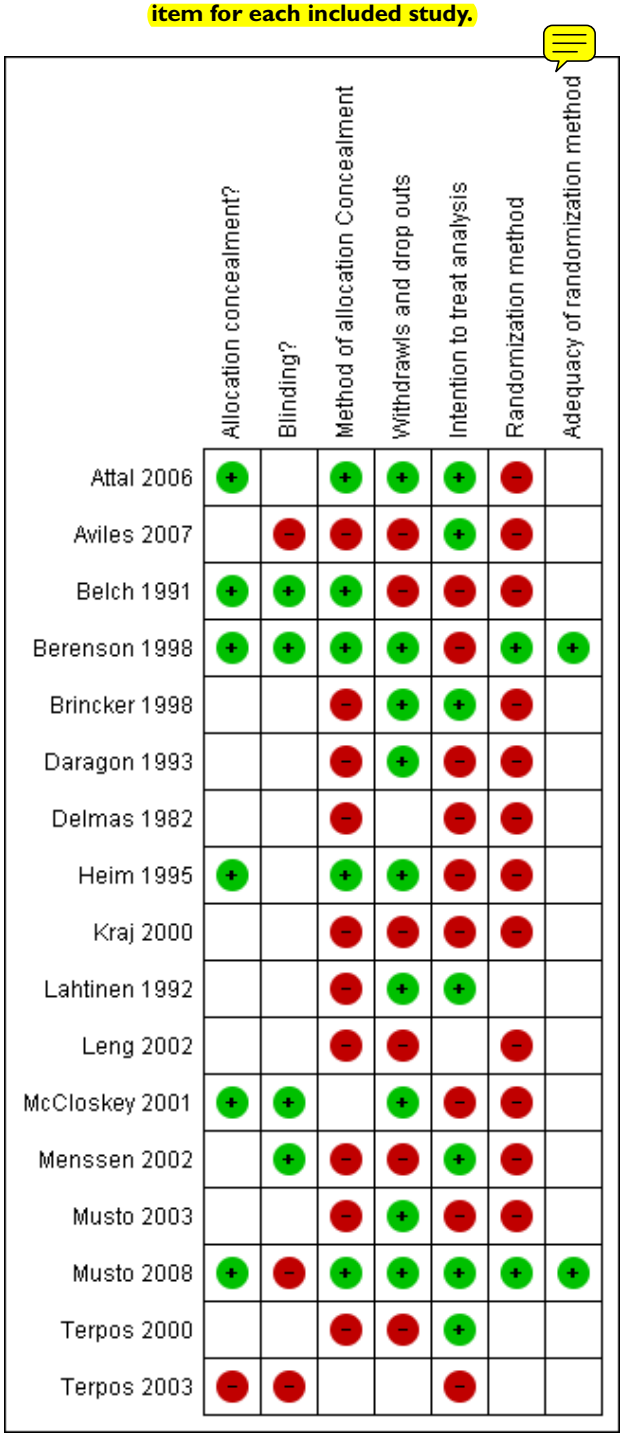
Excluded studies

One trial studied the anti-tumor and bone metabolism effects and reported no outcomes of interest (Martin 2002). One was a duplicate report (Kraj 2000b); seven trials were not randomized (Ali 2001; Bergner 2007; Barlogie 2008; Morris 2001; Spencer 2008; Tassinari 2007; Vogel 2004). One trial with nine enrolled patients was too small to be included (Kraj 2002). One study reported combined data for breast cancer and myeloma patients; thus, the data of interest, for myeloma patients alone, was not extractable (Rosen 2004). Three studies had used combination therapy (Caparrotti 2003; Ciepluch 2002; Tosi 2006a) with a total of 14 excluded trials.

Risk of bias in included studies

Thirty-five percent (6/17) of trials had adequate allocation concealment. Only 12% (2/17) of trials had reported methods of randomization. Similarly, 12% (2/17) of trials had reported blinding procedures and personnel who were "blinded" to the intervention assignment. However, 47% (8/17) of studies were reported as "double blinded". Withdrawals and drop outs were described in 53% (9/17) of trials. Forty-one percent (7/17) of trials analyzed the data according to the ITT principle (see Figure 6 and Characteristics of included studies for details).

Figure 6. **Methodological quality summary: review authors' judgements about each methodological quality item for each included study.**



Effect of random error in included studies

Only 24% (4/17) of trials reported type I and type II error (see Table 7 and Characteristics of included studies for details).

Table 7. Effect of random error

Study	Alpha error pre specified	Beta error pre specified
Attal 2006	No	No
Aviles 2007	No	No
Belch 1991	Yes	Yes
Berenson 1998a	No	No
Brincker 1998	Yes	Yes
Delmas 1982	No	No
Daragon 1993	No	No
Menssen 2002	No	No
Heim 1995	No	No
Lahtinen 1992	Yes	Yes
Leng 2002	No	No
McCloskey 2001	No	No
Musto 2003	No	No
Musto 2008	Yes	Yes
Terpos 2000	No	No
Terpos 2003	No	No
Kraj 2000	No	No
Total reporting	4/17	4/17

Effects of interventions

See: **Summary of findings for the main comparison** Summary of findings (benefits); **Summary of findings 2** Summary of findings (harms)

There were 1520 patients in the bisphosphonates treatment group

and 1490 in the control group from the 17 studies which we selected for analysis. Data on the quality of life were not reported at all. Data on bone density were extractable from one study only and, thus, we were unable to perform a meta-analysis of these data. It was not possible to extract data on toxicity other than GI symptoms and hypocalcemia (such as anemia and renal toxicity). Effects of bisphosphonates on calcium were reported in the dichotomous (number of patients with hypocalcaemia/hypercalcaemia) format in most of the studies. Calcium data were extractable in the continuous format from only two RCTs and hence we could not perform a meta-analysis of this data.

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

Efficacy of bisphosphonates (benefits)

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

1) Effect on overall mortality

We extracted data from 11 studies. These studies included 2221 patients. There were 566 deaths among 1125 patients treated with bisphosphonates versus 580 deaths in 1096 controls resulting in HR of 0.96 (95% CI: 0.80, 1.14) P = 0.64 (Analysis 1.1). There was significant statistical heterogeneity among these trials. (I^2 = 59%; P = 0.007) The heterogeneity was attributed to one RCT (Aviles 2007) with unrealistic treatment effects ("an outlier effect") and to another RCT by Belch 1991. These results indicate that there is no evidence of a beneficial effect of bisphosphonates on mortality in patients with myeloma.

2) Effect on progression-free survival (PFS)

We extracted data from only four studies. Fifty-seven out of 181 patients in the bisphosphonates group progressed while 70 out of 183 patients enrolled in the control group showed evidence of disease progression (HR= 0.70 (95% CI: 0.41 to 1.19), P = 0.18) (Analysis 1.2). There was no heterogeneity among trials reporting disease progression estimates (I^2= 35%; P = 0.20). These results indicate no beneficial effect of bisphosphonates in improving PFS in patients with myeloma.

3) Effect on the number of patients with vertebral fractures

The total number of reported patients with pathological vertebral fractures in the sample of seven eligible studies with 1116 patients available for the analysis, amounted to 141patients with fracture out of 575 patients in the bisphosphonates group versus 188 patients with fracture out of 541 controls, corresponding to RR with bisphosphonates of 0.74 (95% CI: 0.62 to 0.89), P = 0.001 (Analysis 1.3). There was no heterogeneity among the trials (I^2 = 7%; P = 0.38). These results indicate a beneficial effect of bisphosphonates on reduction of vertebral fractures in patients with myeloma.

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

The total number of reported patients with pathological non-vertebral fractures in the sample of six studies with 1389 patients amounted to 102 patients with fracture out of 708 patients in the bisphosphonates group versus 93 patients with fracture out of 681 controls, corresponding to RR of 1.03 (95% CI: 0.68 to 1.56), P = 0.90 (Analysis 1.4). Some heterogeneity among the trials was noted (I^2 = 54%; P = 0.07). No beneficial effect of bisphosphonates on the prevention of pathological non-vertebral fractures was observed.

5) Effect on the total skeletal related events

Total skeletal related events data was extractable from seven studies.There were 277 total skeletal related events in 761 patients in the bisphosphonates group and 327 total skeletal related events in 736 patients enrolled in the control group corresponding to RR of 0.80 (95% CI: 0.72 to 0.89), P < 0.0001 (Analysis 1.5). There was no heterogeneity among the trials (I^2 = 2%; P = 0.41). Thus bisphosphonates have a statistically significant beneficial effect on the prevention of total skeletal related events.

6) Effect on the incidence of hypercalcemia (=> 2.65 mmol/L)

In eight studies, 80 cases of hypercalcemia out of 932 patients in the bisphosphonates group and 106 cases out of 1002 patients in the control group were reported, corresponding to RR of 0.79 (95% CI: 0.56 to 1.11), P = 0.17 (Analysis 1.6). There was no heterogeneity among the trials. (I^2 = 24%; P = 0.24). These results indicate that there is no evidence of a beneficial effect of bisphosphonates on the incidence of hypercalcemia in patients with myeloma. Also, none of the patients receiving either pamidronate (n = 23) or ibandronate (n = 21) in the RCT by Terpos et al (Terpos 2003) suffered from hypercalcemia.

7) Effect on pain

Data on pain reduction were not reported in continuous format but we were able to extract dichotomous data from eight trials according to the author's definitions about presence or absence of pain. Effect on pain was not uniformly described (Table 8). McCloskey 2001 reported the effect on back pain only, while other studies reported the effect on "pain" without specifying the site of pain. Lahtinen 1992 also reported on pain according to its severity. We extracted data on the number of patients with pain on bisphosphonates versus control, except in the study by McCloskey et al., where the effect on pain was referred to patients without "marked improvement in back pain". Also we could not

combine data from the study by Leng et al as they reported pain estimates as continuous data (Leng 2002). The data were extracted from the latest follow up reported. From eight eligible studies with a total of 1281 patients, there were 276 patients who reported pain in 657 patients treated with bisphosphonates, versus 318 in 624 of controls, corresponding to RR of 0.75 (95% CI: 0.60 to 0.95), P = 0.01 (Analysis 1.7). There was statistically significant heterogeneity among these trials (I^2 = 63%; P = 0.008). Although there was a beneficial effect of bisphosphonates on the number of myeloma patients reporting bone pain, these data must be treated with caution because of the lack of uniformity in data reporting (Table 8) and the presence of statistically significant heterogeneity.

Table 8. Methods used to report pain

Study ID	Method
Delmas, 1982	Pain index at 12 months
Lahtinem, 1992	Pain index at 12 months
Daragon , 1993	Analgesic use at 4 months
Heim, 1995	Analgesic use OR presence of pain at 9 months
Berenson, 1998	Bone pain reported by authors at 29 months
McClosky, 1998	Severe pain at 24 months
Menssen, 2004	Opiate usage
Terpos, 2000	Opiate usage
Leng, 2002	Visual analog scale

Treatment related harms (see also: Summary of findings 2)
The identified RCTs almost only reported gastro-intestinal (GI) toxic effects and incidence of hypocalcemia. Evidence regarding other bisphosphonate-related adverse events could only be found in either descriptive studies such as case reports or in observational studies without a control group.
One criterion for high-quality reporting is that the data should be reported in a form that allows it 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 patients or multiple events occurring in a single patient.
The only common treatment-related harms that were extractable among eligible studies were GI symptoms and hypocalcaemia. No bisphosphonate-related mortality was reported in any of the studies eligible for the analysis.

1) Gastro intestinal symptoms

The most common adverse events with oral bisphosphonates are upper GI toxicities, such as gastritis (Van Holten-Verzantvoort 1993) and diarrhoea (Atula 2003). The intra venous (IV) infusions can be associated with injection site reaction and acute systematic inflammatory reactions (Tanvetyanon 2006).
Different authors have used various methods to assess GI symp-

toms. Our first choice was to use the overall number of patients with GI symptoms. When this number was not available, we used the most common symptoms; in the majority of the 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. In six eligible studies,1689 patients were analyzed. There was no significant statistical heterogeneity among these trials (I^2 = 0%; P = 0.90). Overall, bisphosphonates were associated with a non-significant increase in frequency of GI symptoms. In the bisphosphonates group, 110 of 853 patients developed GI symptoms versus 86 of 836 patients in the control group (RR=1.23 (95% CI: 0.95 to 1.60), P = 0.11) (Analysis 2.1).

2) Hypocalcemia

All bisphosphonates can cause hypocalcemia, regardless of the method of administration, although this is a clinically symptomatic problem only infrequently. Effects of bisphosphonates on calcium were reported in the dichotomous (number of patients with hypocalcemia) rather than in the continuous format in most of the studies, leading to loss of available information. We were able to extract data on hypocalcemia estimates from only three studies. A total of five out of 462 patients in the bisphosphonates group suffered from hypocalcemia, while two out of 451 patients in the control group reported hypocalcemia (RR= 2.19 (95% CI: 0.49 to 9.74), P = 0.30) (Analysis 2.2). There was no statistically significant heterogeneity among these trials (I^2 = 0%; P = 0.88). Also, none of the 23 patients receiving pamidronate and only two patients out of 21 receiving ibandronate in the RCT by Terpos et al (Terpos 2003) suffered from hypocalcemia.

3) Osteonecrosis of jaw (ONJ)

Typical symptoms for ONJ are pain, soft-tissue swelling and infection, loose teeth and exposed bone. Only two RCTs reported ONJ (Attal 2006; Musto 2008). In the multicenter RCT comparing zoledronic acid versus observation in asymptomatic patients, two out of 81 patients receiving zoledronic acid developed ONJ while none had similar complaints in the observation group (Musto 2008). In fact this RCT was prematurely stopped after the first case of ONJ was reported in patient receiving zoledronate. In a RCT by Attal et al (Attal 2006), one patient out of 196 in the pamidronate arm versus none out of 200 in the no therapy arm suffered from ONJ. Even though only two RCTs reported ONJ, a growing number of ONJ case reports and observational studies evaluating ONJ have been published in recent years (Table 9; Table 10; Table 11). However, we were not able to identify an analytical study addressing ONJ i.e. with a control group (cohort or case-control). We analyzed seven observational trials that evaluated 1068 patients regarding ONJ. The highest frequencies of ONJ were seen in studies which used a combination of pamidronate and zoledronate (range: 5% to 51%). Zolendronate was associated with ONJ in 3% to 11% cases exposed to this drug. Pamidronate-related frequencies of ONJ ranged from 0% to 18%.

Table 9. 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	NR	NR	17.65%
		Zoledronate	34	2			5.88%
		Pamidronate+zc	33	17			51.51%
Calvo-Villas 2006	NC	Zoledronate	64	7	NR	NC	7%(10,9%)
Corso 2007	Retrospective study	Pamidronate	20	0	NC	23 months	0%
		Zoledronate	37	5	NC	28 months	11.9%
		Pamidronate+zc	42	2	NC	47 months	4.55%

Table 9. Included ONJ studies (*Continued*)

Dimopoulos 2006		Pamidronate	93	7	NR	39 months ONJ patients (11-76) vs 28 (4.5-123) months without ONJ	7.5%
		Zoledronate	33	1			3%
		Pamidronate+zc	66	6			9.1%
		Ibandronate	1	0			0%
		Iban-dronate+zoledrc	4	1			25%
		Clo-dronate+zoledrc	1	0			0%
		Alen-dronate+zoledrc	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+zc	30	7		43.5 months (24-59)	23.3%
Tosi 2006	Retrospective study	Zoledronate	225	6	NR	10 months (4-35)	2.7%
Zervas 2006	Retro-spective 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+zc	85	21			24.71%

NR: Not reported; NC: Not Clear

Table 10. Excluded ONJ studies

Study ID	Reason for exclusion
Bujanda 2007	No multiple myeloma patients with ONJ
Hoff 2006	Not extractable data for MM patients (abstract)

Table 10. Excluded ONJ studies (*Continued*)

Kut 2004	ASH 2004 (abstract No- 4933): Approximately 600 MM patients. The reported frequency: 7 patients. Exclusion due to imprecise reporting (e.g. approximately 600 MM patients)

Table 11. ONJ case reports: data stratified by bisphosphonate type

Study	Total number of patients	Clodronate	Pamidronate	Zoledronate	Pamidronate /zoledronate	IV (not specified)	Others
Abu-Id 2006	73*				68		
Agrillo 2006	30*					30	
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		2				
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)
Estilo 2004	13*					13	
Ficarra 2005	2			1	1		
Gibbs 2005	8*		1	7			

Table 11. ONJ case reports: data stratified by bisphosphonate type (*Continued*)

Hansen 2006	5			1	4		
Hay 2006	2			2			
Herbozo 2007	1			1			
Kademani 2006	1			1			
Katz 2005	2			1	1		
Khamaisi 2006	6		6				
Kumar 2007	2		2				
Lenz 2005	1			1			
Lugassy 2004	3		1		2		
Magopoulos 2007	33		6	19	7		1(P,I,Z)
Marunick 2005	2		1	1			
Marx 2005	119*		32	48	36		3(A)
Mavrokokki 2007	114*	2	20	43	13		30(A), 2(R), 2(A/R), 1(P/A), 1(P/I)
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		

Table 11. ONJ case reports: data stratified by bisphosphonate type (*Continued*)

Pozzi 2007	35		3	14	18		
Purcell 2005	3		2	1			
Ruggiero 2004	28		14	4	10		
Pastor-Zuazaga 2006	1				1		
Phal 2007	3			1	1		1(P/C)
Polizzotto 2006	1		1				
Salesi 2006	2			2			
Senel 2007	1	1					
Sitters 2005	1			1			
Treister 2006	1		1				
Vannucchi 2005	1			1			
Walter 2007	9		1	1	7		
Wutzl 2006	12		2	8	2		
Yeo 2005	2		2				
Zarychanski 2006	10		10				
Total	632	4	147	193	198	43	42
MM extractable patients	295	2	95	102	81	13	9
Patients (number,%) not stratified by illness	337 (53,32%)	2 (50%)	52 (35,37%)	91 (41,15%)	117 (59,09%)	30 (69,77%)	33 (78,57%)

* Data on multiple myeloma patients not extractable, A:Alendronate, C: Clodronate, I: Ibandronate, P: Pamidronate, Z: Zoledronate, MM:multiple myeloma

4) Renal dysfunction

We were able to extract data regarding renal function (serum creatinine) from only two RCTs. (Daragon 1993; Lahtinen 1992) Thus, we have not performed meta-analyses of these data. Renal dysfunction is a particularly problematic adverse event that can also occur after infusion of IV bisphosphonates. The US Food and Drug Administration (FDA) reported that 72 patients suffered 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.

Assessment of bias: sensitivity analysis

We observed statistically significant heterogeneity only for the outcomes of OS and pain. We conducted sensitivity analysis to identify the reason for the heterogeneity among the RCTs for the outcome of OS and pain. The OS estimates for Aviles 2007 and Belch 1991 were considered outliers, because the result was outside the range of the pooled estimates. Removing these outlier from the pooled analysis resulted in the disappearance of a statistically significant heterogeneity (I^2 = 37%, P = 0.13). The pooled HR for OS after the removal of outliers was 0.96 (95% CI; 0.84 to 1.11). We couldn't identify the factors contributing to this "unrealistic treatment effect" from the data in the publications. Also, the RCT by Belch et al tested effects of etidronate which is now considered an ineffective bisphosphonate. The variation in the pain reporting methods contributed to the statistically significant heterogeneity observed in pain estimates. Moreover, we found that RCTs with "double blinding" showed no significant benefit of bisphosphonates over placebo for amelioration of pain (RR m0.83; 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 "intention-to-treat" 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). We also found that the beneficial effect of bisphosphonates on pain reduction was greater in patients who were asymptomatic at the start of treatment (RR 0.28; 95% CI 0.12 to 0.67) compared to symptomatic patients (RR 0.83; 95% CI: 0.69 to 1.00) (test of interaction: P = 0.005).

We also evaluated all trials according to several quality dimensions to assess the existence of a potential bias and/or imprecision in our results (Jüni 2001). In particular, we focused on those dimensions that have been empirically linked to bias. We performed sensitivity analyses according to adequacy of allocation concealment (Schulz 1995), blinding of treatment allocation, ITT analysis, description of withdrawals and drop outs and pre-specification of type I and II error for all outcomes (see Characteristics of included studies). The results did not change for any outcome except in case of pain as noted above.

To give a visual impression on results of the sensitivity analysis, figures created for the outcome 'vertebral fractures' are included (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 have been performed according to ITT analysis and these trials have shown a smaller treatment effect, which may be due to the exclusion of the largest trial from the analysis (Berenson 1998). Five out of seven studies reporting vertebral fractures were double-blind but the results were unchanged in this subgroup analysis. Only one out of seven studies reporting vertebral fractures described the randomization method but the results were also unchanged in this subgroup analysis. Furthermore, only two out of seven studies reporting vertebral fractures clearly noted the withdrawals and drop outs, but the results remained unchanged in this subgroup analysis. Only Lahtinen 1992 prespecified the type I and II error out of seven studies reporting vertebral fractures, but the results were unchanged in this subgroup analysis.

We also conducted additional sensitivity analyses based on RCTs that enrolled asymptomatic patients (Musto 2003; Musto 2008), and Salmon Durrie stage 1 (Durie 1975; Durie 2003) myeloma patients (Attal 2006; Belch 1991; Heim 1995; Terpos 2000) versus RCTs that enrolled stage II and stage III myeloma patients for all outcomes (Aviles 2007; Berenson 1998; Brincker 1998; Daragon 1993; Delmas 1982; Kraj 2000; Lahtinen 1992; Leng 2002; McCloskey 2001; Menssen 2002; Terpos 2003).The results did not change for any of the outcomes except in case of pain as noted above. However, it is important to note that current National Comprehensive Cancer Network guidelines advise not to treat asymptomatic patients unless they progress to stage II or higher (NCCN).

Similarly, we conducted sensitivity analyses based on duration of treatment (indefinite versus 0 to 24 months). The results were unchanged for all outcomes except non-vertebral fractures. The only RCT (McCloskey 2001) with 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).

We were not able to extract data on all outcomes from all the studies (Table 2 and Table 4). We investigated the possibility of publication bias using the funnel plot method of Begg and Mazumdar (Begg 1994) and Egger et al (Egger M 2001). This method has its limitations, but nonetheless is widely used to assess publication bias. The funnel plot showed asymmetry only for the outcome of pain, indicating the possibility of outcome reporting bias or other type of publication bias. However, the findings are also consistent with heterogeneity in interventions or 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 of the asymmetry seen in the funnel plots (Sterne 2001).

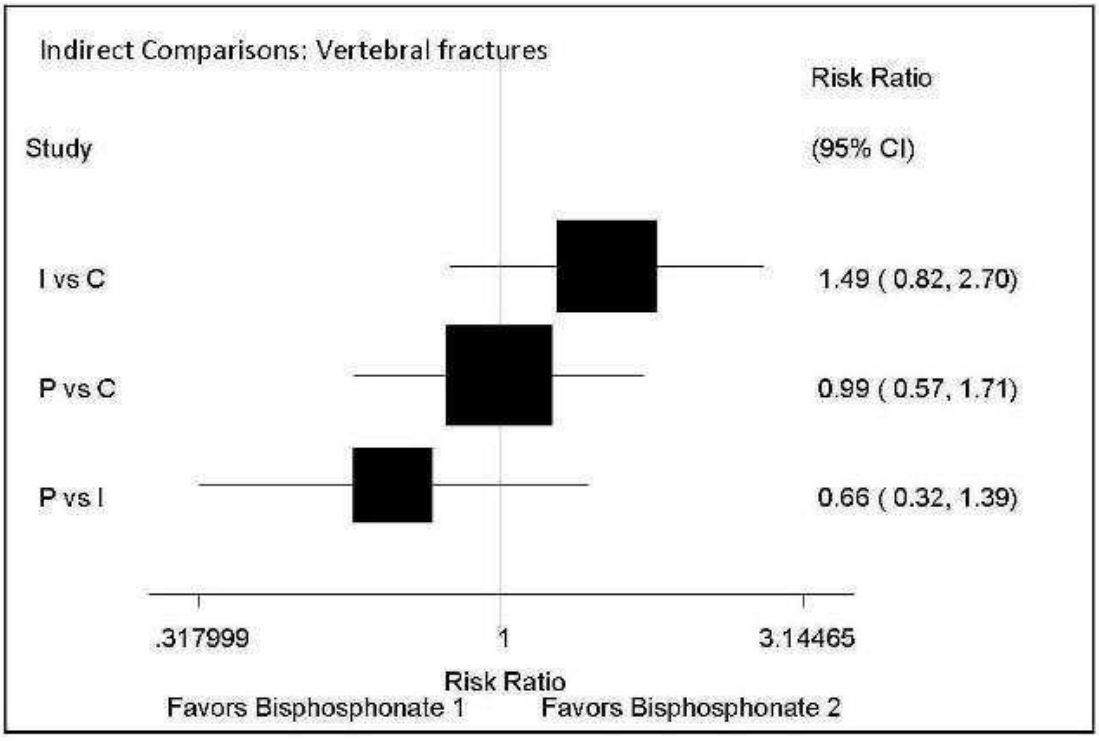
Results of indirect comparison of treatment effects

Bisphoshphonates were found to be superior to placebo/no treatment for the outcomes of vertebral fractures, skeletal related events and pain. Hence, we conducted indirect comparisons to determine whether one bisphosphonate is superior to others for these outcomes.

1) Effect on the number of patients with vertebral fractures

Data on patients with vertebral fractures were available from seven RCTs involving 1116 patients. A total of three indirect comparisons were possible (Table 6, Figure 2). Results of indirect comparisons were consistent with the results from direct comparisons. The indirect comparisons did not find the superiority of any particular bisphosphonate regimen over others (Figure 7).

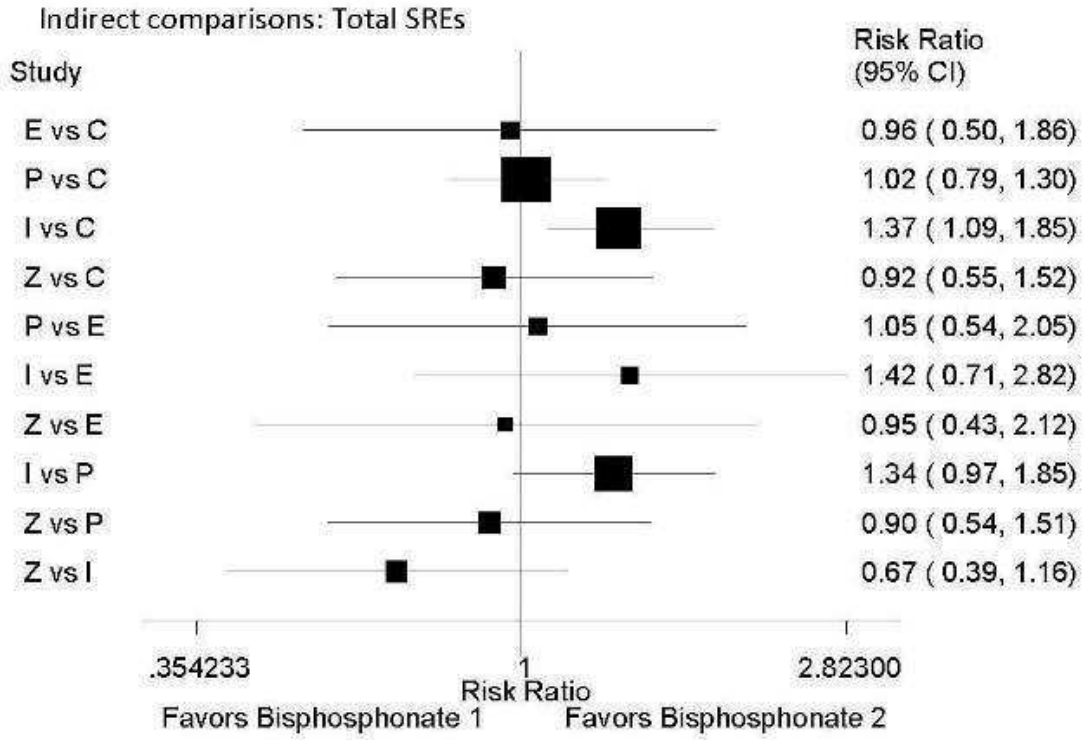
Figure 7. Vertebral Fractures Indirect Comparisons. C = Clodronate, P = Pamidronate, I = Ibandronate, 95% CI= 95% Confidence Interval



2) Effect on the total skeletal related events

Data on patients with skeletal related events were available from seven RCTs involving 1492 patients. A total of 10 indirect comparisons were possible (Table 6, Figure 3). Results of indirect comparisons were consistent with the results from direct comparisons. However, clodronate was found to be superior to ibandronate (Figure 8). A total of 402 patients were enrolled in two RCTs involved in indirect comparison of ibandronate versus clodronate with a resulting RR of 1.37 (95% CI 1.09 to 1.85, P = 0.04) (Figure 5).

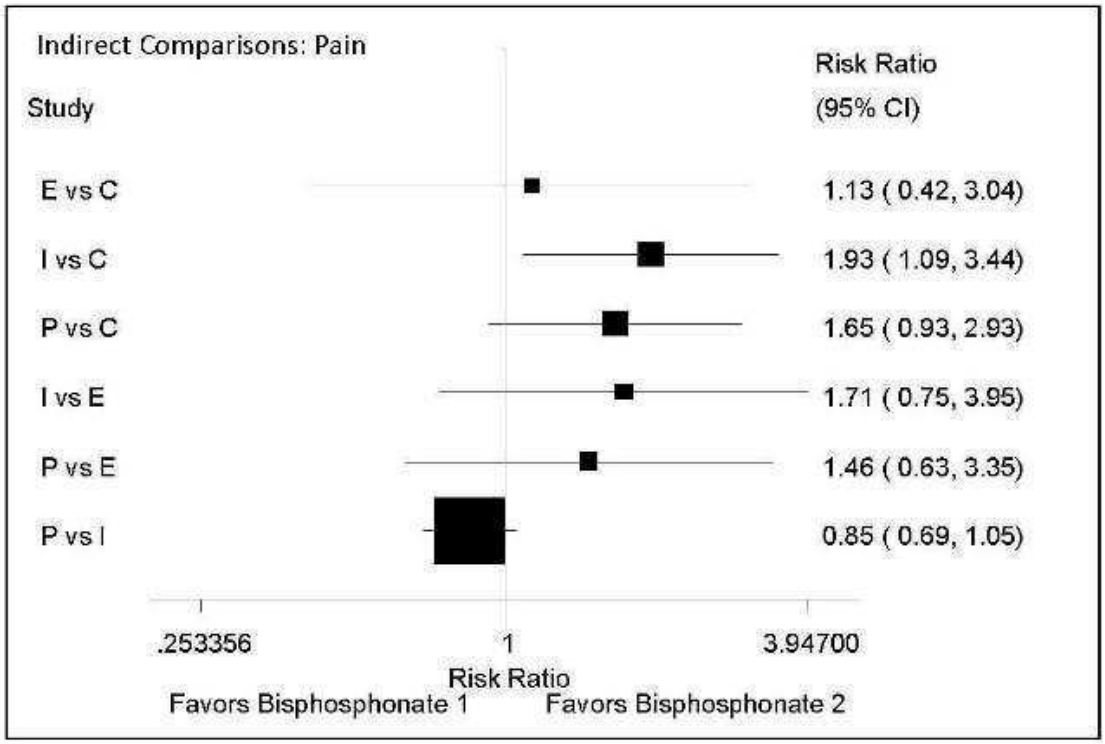
Figure 8. Total skeletal related events Indirect Comparisons. E = Etidronate, C = Clodronate, P = Pamidronate, I = Ibandronate, Z = Zoledronate; 95% CI= 95% Confidence Interval



3) Effect on pain

Data on effect of bisphosphonates on pain control were available from eight RCTs involving 1281 patients. A total of six indirect comparisons were possible (Table 6, Figure 4). Results of indirect comparisons were consistent with the results from direct comparisons. However, clodronate was found to be superior to ibandronate (Figure 9).There were a total of 764 patients enrolled in five RCTs involved in indirect comparison of ibandronate versus clodronate with a resulting RR of 1.93 (95% CI 1.09 to 3.44; P = 0.02) (Figure 9).

Figure 9. Pain Indirect Comparisons. E = Etidronate, C = Clodronate, P = Pamidronate, I = Ibandronate, 95% CI= 95% Confidence Interval



We also used Bayesian methods for indirect comparisons. The results of the Bucher and Bayesian methods differ mostly based on the choice of the priors used in Bayesian analysis. Since the choice of prior for in-between studies variance can lead to drastic variation in results (Lambert 2005), especially in a small number of studies, we performed an extensive sensitivity analysis. We assessed a total of five priors (gamma, uniform, Pareto, logistic, and half-normal) based on their application in 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 (as illustrated in Table 6).

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Bisphosphonates for prevention of skeletal related events in multiple myeloma						
Patient or population: patients with prevention of skeletal related events in multiple myeloma **Intervention:** Bisphosphonates						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Placebo / No treatment	**Bisphosphonates**				
Gastro intestinal toxicity 1689 patients	**Medium risk population**		RR 1.23 (0.95 to 1.6)	6 RCTs (1689 patients)	++00 low	Limitations in design: serious [1] Serious imprecision [2]
	10%	23 more per 1000 (from 5 fewer to 60 more)				
	Number of observed gastro intestinal toxicities : 86/836 (10.3%)	Number of observed gastro intestinal toxicities: 110/853 (12.9%)				
Hypocalcemia 913 patients	**Medium risk population**		RR 2.19 (0.49 to 9.74)	3 RCTs (913 patients)	+000 very low	Limitations in design: serious [1] Very serious imprecision [3] Reporting bias [4]
	9%	107 more per 1000 (from 46 fewer to 787 more)				
	Number of patients with hypocalcemia :2/451 (0.4%)	Number of patients with hypocalcemia :5/462 (1.1%)				

Osteonecrosis of jaw (follow-up 3-60 months; clinically)	ONJ incidence range: 0%-51%	7 Observational studies	+OOO very low	reporting bias reduced effect for RR >> 1 or RR <<1[5] dose response gradient[6]

*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).

[1] Only 35% (6/17) of trials had adequate allocation concealment. Only 12% (2/17) of trials reported methods of randomization. Similarly, 12% (2/17) of trials reported blinding procedures and personnel who were ' ' blinded" to the intervention assignment. However sensitivity analyses based on allocation concealment, description of randomization method didn't change the estimates. Hence, the assessment of studies' limitations may represent the poor quality of reporting rather than true biased estimates.

[2] The pooled estimate has a wide confidence interval.

[3] All the RCTs have estimates with wide confidence intervals.

[4] Data related to patients with hypocalcemia was extractable from only 3 out 17 RCTs

[5] ONJ was observed in case control, case series and prospective observational studies and RCTs. A very few studies included consecutive prospective cohort with clear diagnostic criteria and "blind" assessment of radiological findings. Therefore, while ONJ is considered as a real AE the exact incidence / risk is difficult to assess at this point of time.

[6] While some studies indicate dose response, it could be that ONJ is related to the type of bisphosphonate. So far no ONJ is observed in the studies of clodronate.

CI: Confidence interval; RR: Risk Ratio; ONJ:Osteonecrosis of jaw

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.

DISCUSSION

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). However, the current meta-analysis, as well as all identified clinical trials except one study (Aviles 2007), demonstrates that there is no survival advantage associated with bisphosphonates therapy. Similarly, bisphosphonates were not superior to placebo/no treatment in improving progression-free survival. Nonetheless, data on the use of bisphosphonates in breast cancer revealed controversial results. In one study (Diel 1998), bisphosphonates protected against skeletal and visceral metastasis, while in another study it was associated with an inferior survival of breast cancer and increased non-skeletal metastasis (Saarto 2001). Similar data exist in mouse myeloma models treated with ibandronate (Cruz 2001).

The current meta-analysis points towards reduction in total skeletal-related events and vertebral fractures, a significant advantage for the patients treated with bisphosphonates. Our results show a beneficial effect of bisphosphonates for the prevention of pathological fractures, most likely due to the effect on preventing pathological vertebral collapses. In absolute terms, assuming the baseline risk of 20% to 50% for vertebral fracture without treatment, we estimate that between eight to 20 MM patients should be treated to prevent vertebral fracture(s) in one patient. Similarly, with the baseline risk of 35% to 86% for total skeletal-related events without treatment, we estimate that between six to 15 MM patients should be treated to prevent SRE(s) in one patient.

Interestingly, there was no beneficial effect of bisphosphonates 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 post-menopausal women treated with pamidronate (Fromm 1991). Our findings that the vertebral fractures are clearly reduced and there were no significant effect on non-vertebral fractures are supported by these studies. However, it must be taken into consideration that several studies did not report these events in sufficient detail.

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 effect. This finding is in contradiction with the present review, as well as with the last review examining the role of bisphosphonates in myeloma patients (Djulbegovic 2002), indicating a likely beneficial effect of bisphosphonates on pain reduction. The discrepancy between the results of these Cochrane reviews lies in the decision about which studies should be included. The present review and the review by Djulbegovic et al (Djulbegovic 2002) included 17 and 10 studies respectively; all of these studies measured pain reduction in different ways. In contrast, the Wong and Wiffen study included only studies that reported the proportion of patients with pain relief within 12 weeks of bisphosphonate treatment. Using this inclusion criterion, only one trial of multiple myeloma was identified (Berenson 1998b). A question whether it is appropriate to draw conclusions about pain relief without testing bisphosphonates against an appropriate palliative opiate treatment should however considered a legitimate question. Our review concludes that bisphosphonates are beneficial for pain control based on RCTs using placebo but not other palliative therapies.

There were no significant adverse effects associated with the administration of bisphosphonates identified in the included RCTs. In fact, only two RCTs reported osteonecrosis of jaw (ONJ). We also identified seven observational trials evaluating 1068 patients for ONJ. These studies indicated that ONJ may be a common event (range: 0% to 51%). ONJ is the only clinically relevant effect we observed which may relate to bisphosphonate potency. In 2003, two years after Zometa (zoledronic acid) received US and European authorization, case reports on ONJ appeared in the publication. In the most current review the highest ONJ frequencies were reported for the most potent bisphosphonate (zoledronate) and its combinations. However, since ONJ was only sporadically reported in RCTs, the results from observational studies may be an overestimate due to their non-controlled design. Data regarding other bisphosphonates-related harms reported via observational studies were not investigated, as this would go beyond the scope of this review. However, a general requirement for higher examination standards for other relevant treatment-related harms should be considered legitimate.

We also carried out indirect comparisons of various bisphosphonates used in the treatment of multiple myeloma. Results of indirect comparisons were consistent with the results from direct comparisons. In most indirect comparisons, we did not find the superiority of any particular bisphosphonate regimen over others. Clodronate was found superior to ibandronate for control of bone pain and reducing total skeletal related events. However, a large placebo controlled clodronate trial (McCloskey 2001) might be influencing these comparisons. Physicians' choices regarding which bisphosphonates to apply should ideally be based on evidence from comparative trials. There are only two head-to-head bisphosphonates comparative studies (Rosen 2004; Terpos 2003). Unfortunately the data from Rosen 2004 were not extractable for MM patients and Terpos 2003 reports data addressing only two outcomes (hypercalcemia and hypocalcemia) of interest for this review. Rosen 2004 noted that zoledronic acid reduced the overall proportion of patients with a skeletal related event and reduced

the skeletal morbidity rates similar to pamidronate. 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.

Comparative evaluation of bisphosphonates should be urgently carried out in the future to enable appropriate health care decision-making. Also, future studies should investigate bisphosphonate treatments as a palliative treatment by measuring its influence on QOL outcomes.

AUTHORS' CONCLUSIONS

Implications for practice

Adding bisphosphonates to the treatment of multiple myeloma reduces vertebral fractures and probably pain. The current evidence shows that no bisphosphonate is superior to any other.

Implications for research

There is immediate need to conduct head-to-head comparisons of bisphosphonates via large RCTs. In addition, future studies should investigate bisphosphonate treatments as a palliative treatment by measuring its influence on QOL outcomes.There is also a need for studies addressing cost effectiveness and adverse events of bisphosphonates therapy.

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Zervas K, Verrou E, Teleioudis Z, Vahtsevanos K, Banti A, Mihou D, et al.Incidence, risk factors and management of osteonecrosis of the jaw in patients with multiple myeloma: a single-centre experience in 303 patients. *British Journal of Haematology* 2006; **134**(6):620–3.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Attal 2006

Methods	Not double-blind; placebo-controlled; ITT: yes.
Participants	Bisphos: enrolled 196, analyzed 196. Bisphos. + thalidomide: enrolled 201, analyzed 201. Placebo: enrolled 200, analyzed 200.
Interventions	Pamidronate 90 mg IV, every 4 weeks; control 1: pamidronate and thalidomide, po. a minimum dose reduction of 50 mg for treatment related toxicity.
Outcomes	Total skeletal-related events; total mortality; response rates; ONJ.
Notes	SRE: bone lesion requiring a specific therapy (chemotherapy, irradiation or surgery).

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	
Method of allocation Concealment?	Yes	
Withdrawls and drop outs?	Yes	
Intention to treat analysis?	Yes	
Randomization method?	No	

Aviles 2007

Methods	Not double blind; not placebo-controlled; ITT: yes.
Participants	Bisphosphonates: enrolled 46 analyzed 46. Control: enrolled 48 analyzed 48.
Interventions	Zolendronate 4 mg IV, every 4 weeks.
Outcomes	Total mortality; progression free survival.
Notes	SRE: appearance of a new lytic lesion (excluding skull), after patient began zolendronate or progression of previous bone lesion according to criteria of Union International Centre Cancer.

Aviles 2007 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Blinding? All outcomes	No	
Method of allocation Concealment?	No	
Withdrawls and drop outs?	No	
Intention to treat analysis?	Yes	
Randomization method?	No	

Belch 1991

Methods	Double-blind; placebo-controlled; ITT: no.
Participants	Bisphos: enrolled 98, analyzed 92. Placebo: enrolled 78, analyzed 74.
Interventions	Etidronate capsules (20 mg/kg x 28 days), (then 5 mg/kg) until death or discontinuation. Placebo: identical appearance.
Outcomes	Vertebral index; total mortality*;pain; calcium.***
Notes	SRE = bone-progression (appearances of new lesions or worsening of existing ones)$; mortality* (from the date of randomization); calcium reported as a dichotomous variable.

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	
Blinding? All outcomes	Yes	
Method of allocation Concealment?	Yes	
Withdrawls and drop outs?	No	
Intention to treat analysis?	No	

Belch 1991 (*Continued*)

Randomization method?	No	

Berenson 1998

Methods	Double-blind; placebo-controlled; ITT: no.
Participants	Bisphos: enrolled 205, analyzed 198. Placebo: enrolled 187, analyzed 179.
Interventions	Pamidronate 90 mg in 500ml of 5% dextrose in water, every 4 weeks for 21 months; 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.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	
Blinding? All outcomes	Yes	
Method of allocation Concealment?	Yes	
Withdrawls and drop outs?	Yes	
Intention to treat analysis?	No	
Randomization method?	Yes	
Adequacy of randomization method?	Yes	

Brincker 1998

Methods	Double-blind; placebo-controlled; ITT: yes.

Brincker 1998 (*Continued*)

Participants	Total enrolled: 304. Bisphos. enrolled 152,analyzed 152. Placebo: enrolled 148, analyzed 148.
Interventions	Pamidronate 75 mg capsules po bid; identical placebo; duration at least 2 years.
Outcomes	Total mortality*$; SRE; pain; calcium(&); adverse events.
Notes	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.

Risk of bias

Item	Authors' judgement	Description
Method of allocation Concealment?	No	
Withdrawls and drop outs?	Yes	
Intention to treat analysis?	Yes	
Randomization method?	No	

Daragon 1993

Methods	Double-blind; placebo-controlled; ITT: no.
Participants	Bisphos: enrolled: 49, analyzed: 39. Placebo: enrolled: 45, analyzed: 39.
Interventions	Etidronate 10 mg/kg po qd; identical placebo; duration 4 months.
Outcomes	Total mortality *$;SRE (total); total fractures; vertebral fractures; non-vertebral fractures; vertebral index; total mortality; pain;

Daragon 1993 (*Continued*)

	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 narco-analgesics.

Risk of bias

Item	Authors' judgement	Description
Method of allocation Concealment?	No	
Withdrawls and drop outs?	Yes	
Intention to treat analysis?	No	
Randomization method?	No	

Delmas 1982

Methods	Double-blind; placebo-controlled; ITT: no.
Participants	Bisphos: enrolled 7, analyzed 7. Placebo: enrolled 6, analyzed 6.
Interventions	Clodronate 1600 mg/d po; identical placebo; duration 18 months.
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).

Risk of bias

Item	Authors' judgement	Description

Delmas 1982 (*Continued*)

Method of allocation Concealment?	No	
Intention to treat analysis?	No	
Randomization method?	No	

Heim 1995

Methods	Not double-blind; placebo-controlled; ITT: no.
Participants	Total: 170; 13 withdrawn after treatment. premature termination in add. 75. Bisphos: analyzed: 39. Placebo: analyzed: 32.
Interventions	Clodronate 1600 mg/d po.; control: no treatment; duration 12 months.
Outcomes	SRE; pain; total fractures; calcium; adverse events.
Notes	SRE: bone progression ($); effect on pain characterized as the number of patients without pain or no need for therapy.

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	
Method of allocation Concealment?	Yes	
Withdrawls and drop outs?	Yes	
Intention to treat analysis?	No	
Randomization method?	No	

Kraj 2000

Methods	Not double-blind; placebo-controlled; ITT: no.
Participants	Bisphos: analyzed: 23; Placebo: analyzed: 23.

Kraj 2000 (*Continued*)

Interventions	Pamidronate 60 mg IV, every 4 weeks; control: no treatment.
Outcomes	Total mortality, vertebral fractures.
Notes	

Risk of bias

Item	Authors' judgement	Description
Method of allocation Concealment?	No	
Withdrawls and drop outs?	No	
Intention to treat analysis?	No	
Randomization method?	No	

Lahtinen 1992

Methods	Double-blind; placebo-controlled; ITT: yes.
Participants	Bisphos: enrolled 168, analyzed 168. Placebo: enrolled 168, analyzed 168.
Interventions	Clodronate 400 mg capsules po tid; 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.

Risk of bias

Item	Authors' judgement	Description
Method of allocation Concealment?	No	
Withdrawls and drop outs?	Yes	
Intention to treat analysis?	Yes	

Leng 2002

Methods	Not double-blind, not placebo-controlled; ITT: unclear.
Participants	Bisphos: analyzed 16. Placebo: analyzed 18.
Interventions	Pamidronate 90 mg IV OD; duration 2 days; identical placebo; duration 2 days.
Outcomes	Pain (continuous data).
Notes	

Risk of bias

Item	Authors' judgement	Description
Method of allocation Concealment?	No	
Withdrawls and drop outs?	No	
Randomization method?	No	

McCloskey 2001

Methods	Double-blind; placebo-controlled; ITT: no
Participants	Bisphos: enrolled/analyzed 264. Placebo: enrolled/-analyzed 272.
Interventions	Clodronate 400 mg capsules po qid; identical placebo; duration 24 months.
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.

Risk of bias

McCloskey 2001 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Yes	
Blinding? All outcomes	Yes	
Withdrawls and drop outs?	Yes	
Intention to treat analysis?	No	
Randomization method?	No	

Menssen 2002

Methods	Double-blind; placebo-controlled; ITT: yes.
Participants	Bisphos: enrolled 107, analyzed 99. Placebo: enrolled: 107, analyzed: 99.
Interventions	Ibandronate 2 mg iv every month; identical placebo, duration 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.

Risk of bias

Item	Authors' judgement	Description
Blinding? All outcomes	Yes	
Method of allocation Concealment?	No	
Withdrawls and drop outs?	No	
Intention to treat analysis?	Yes	

Randomization method?	No	

Musto 2003

Methods	Not double blind; not placebo-controlled; ITT: no.
Participants	Bisphos: enrolled 45/analyzed: 40. Control: enrolled 45/analyzed: 41.
Interventions	Zolendronate 4 mg IV, every 4 weeks, duration 12 months.
Outcomes	Total skeletal related events; PFS; time to progression.
Notes	SRE: single/multiple osteolytic lesions, pathological fractures and/or hypercalcemia.

Risk of bias

Item	**Authors' judgement**	**Description**
Method of allocation Concealment?	No	
Withdrawls and drop outs?	Yes	
Intention to treat analysis?	No	
Randomization method?	No	

Musto 2008

Methods	Not double blind; not placebo-controlled; ITT: yes.
Participants	Bisphosphonates: enrolled:81, analyzed: 81. Control: enrolled:82, analyzed: 82.
Interventions	Zolendronate 4 mg IV, every 4 weeks; duration 12 months.
Outcomes	SRE (total); PFS; time to progression; ONJ.
Notes	SRE: single/multiple osteolytic lesions, pathological fractures and/or hypercalcemia. The trial was prematurely stopped due to ONJ case in patient receiving zolendronate.

Risk of bias

Item	**Authors' judgement**	**Description**

Musto 2008 (*Continued*)

Allocation concealment?	Yes	
Blinding? All outcomes	No	
Method of allocation Concealment?	Yes	
Withdrawls and drop outs?	Yes	
Intention to treat analysis?	Yes	
Randomization method?	Yes	
Adequacy of randomization method?	Yes	

Terpos 2000

Methods	Not double blind; not placebo-controlled; ITT: yes.
Participants	Bisphos: enrolled/analyzed: 32. Control: enrolled/analyzed: 30.
Interventions	Pamidronate 90 mg IV, every 4 weeks; duration 14 months.
Outcomes	Total mortality;* total fractures; vertebral fractures; non-vertebral fracture; pain; hypercalcemia; abdominal pain.
Notes	Data extracted by the authors of the article.

Risk of bias

Item	**Authors' judgement**	**Description**
Method of allocation Concealment?	No	
Withdrawls and drop outs?	No	
Intention to treat analysis?	Yes	

Terpos 2003

Methods	Not double blind, not placebo-controlled; ITT: no.
Participants	Pamidronate: enrolled 23/analyzed: 23. Ibandronate enrolled 21/analyzed: 20.
Interventions	Pamidronate 90 mg IV, every 4 weeks, duration 4 months. Ibandronate 4 mg IV, every 4 weeks, duration 4 months.
Outcomes	Hypocalcemia, hypercalcemia.****
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	No	
Blinding? All outcomes	No	
Intention to treat analysis?	No	

ITT= intention to treat
IV=intravenous
ONJ=osteonecrosis of jaw
po= oral (by mouth) qd=everyday
SRE = skeletal related events
tid= three times daily
* mortality data obtained from authors; *$ mortality data is 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 a serum calcium concentration, corrected for the serum albumin concentration, of at least 12.0 mg dL)1 or 3.0 mmol L^{-1}
!-Data obtained from (author Fontana et al) and data from previous publication (abstract) is used
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The most common adverse effect that was reported was related to gastro-intenstinal symptoms (abdominal pain, diarrhea, pancreatitis). The number of patients with highest number of GI symptoms was recorded and combined in the final analysis (since often it was not clear if the same patients had 1 or more GI 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]*

Ali 2001	Non-randomized study
Barlogie 2008	Non-randomized study
Bergner 2007	Non-randomized study
Caparrotti 2003	Non-randomized and a combination therapy
Ciepluch 2002	Non-randomized and a combination therapy
Kraj 2000b	Duplicate publication (Kraj 2000)
Kraj 2002	Enrolled only 9 patients. There was only one pathological fracture reported among 6 patients enrolled in zolendronate arm and one pathological fracture among 3 patients enrolled in Pamidronate arm.
Martin 2002	No data of interest
Morris 2001	Non-randomized and a combination therapy

(*Continued*)

Rosen 2004	Data not extractable for multiple myeloma patients
Spencer 2008	Non-randomized and a combination therapy
Tassinari 2007	An observational study
Tosi 2006a	A combination therapy
Vogel 2004	Non-randomized study

DATA AND ANALYSES

Comparison 1. Bisphosphonates vs. control (efficacy)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	11		Hazard Ratio (Random, 95% CI)	0.96 [0.80, 1.14]
1.1 Etidronate	2		Hazard Ratio (Random, 95% CI)	1.24 [0.86, 1.80]
1.2 Clodronate	3		Hazard Ratio (Random, 95% CI)	0.93 [0.66, 1.29]
1.3 Pamidronate	4		Hazard Ratio (Random, 95% CI)	0.78 [0.58, 1.05]
1.4 Ibandronate	1		Hazard Ratio (Random, 95% CI)	1.07 [0.69, 1.64]
1.5 Zolendronate	1		Hazard Ratio (Random, 95% CI)	0.42 [0.22, 0.81]
2 Progression free survival	4		Hazard Ratio (Random, 95% CI)	0.70 [0.41, 1.19]
2.1 Clodronate	1		Hazard Ratio (Random, 95% CI)	0.63 [0.17, 2.34]
2.2 Pamidronate	1		Hazard Ratio (Random, 95% CI)	0.92 [0.39, 2.17]
2.3 Zolendronate	2		Hazard Ratio (Random, 95% CI)	0.61 [0.21, 1.77]
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	7	1497	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.72, 0.89]
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	854	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.64, 0.94]
5.4 Ibandronate	1	198	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.80, 1.35]
5.5 Zoledronate	1	163	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.43, 1.13]
6 Incidence of hypercalcemia	8	1934	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.56, 1.11]
6.1 Etidronate	1	166	Risk Ratio (M-H, Random, 95% CI)	1.32 [0.73, 2.38]
6.2 Clodronate	3	831	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.45, 1.31]
6.3 Pamidronate	3	739	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.31, 1.33]
6.4 Ibandronate	1	198	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.27, 1.42]
7 Pain	8	1281	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.60, 0.95]
7.1 Etidronate	1	78	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.26, 1.32]
7.2 Clodronate	4	566	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.29, 0.91]
7.3 Pamidronate	2	439	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.72, 1.01]
7.4 Ibandronate	1	198	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.86, 1.17]
8 Time to progression			Other data	No numeric data
8.1 Pamidronate			Other data	No numeric data
8.2 Zolendronate			Other data	No numeric data

Comparison 2. Bisphosphonates vs. control (adverse effects)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Gastrointestinal toxicity (grade III/IV)	6	1689	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.95, 1.60]
1.1 Etidronate	1	78	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 7.94]
1.2 Clodronate	2	872	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.82, 1.72]
1.3 Pamidronate	3	739	Risk Ratio (M-H, Random, 95% CI)	1.30 [0.90, 1.88]
2 Hypocalcaemia	2	913	Risk Ratio (M-H, Random, 95% CI)	2.19 [0.49, 9.74]
2.1 Clodronate	1	536	Risk Ratio (M-H, Random, 95% CI)	2.06 [0.38, 11.16]
2.2 Pamidronate	1	377	Risk Ratio (M-H, Random, 95% CI)	2.71 [0.11, 66.19]

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 Adeqaute 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]
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 drop outs well described	3	797	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.55, 0.82]
5.2 Withdrawals and drop outs 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 Clodronate dose (vertebral fractures)	3	433	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.56, 0.89]
8.1 Clodronate 1600 mg/d	2	230	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.51, 0.92]
8.2 Clodronate 2400 mg/d	1	203	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.51, 1.08]
9 In vitro anti-resorptive potency (incidence of hypercalcemia)	8	2046	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.53, 1.16]
9.1 Relative potency = 1 (etidronate)	1	166	Risk Ratio (M-H, Random, 95% CI)	1.32 [0.73, 2.38]
9.2 Relative potency = 10 (clodronate)	3	943	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.30, 1.91]
9.3 Relative potency = 100 (pamidronate)	3	739	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.31, 1.33]
9.4 Relative potency = 10,000 (ibandronate)	1	198	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.27, 1.42]

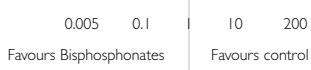
Analysis 1.1. Comparison 1 Bisphosphonates vs. control (efficacy), Outcome 1 Mortality.

Review: Bisphosphonates in multiple myeloma

Comparison: 1 Bisphosphonates vs. control (efficacy)

Outcome: 1 Mortality

Study or subgroup	log [Hazard Ratio] (SE)	Hazard Ratio IV,Random,95% CI	Weight	Hazard Ratio IV,Random,95% CI
1 Etidronate				
Belch 1991	0.46078431 (0.19802951)		11.1 %	1.59 [1.08, 2.34]
Daragon 1993	0.07099303 (0.0344094)		22.9 %	1.07 [1.00, 1.15]
Subtotal (95% CI)			**34.0 %**	**1.24 [0.86, 1.80]**
Heterogeneity: Tau² = 0.06; Chi² = 3.76, df = 1 (P = 0.05); I² =73%				
Test for overall effect: Z = 1.15 (P = 0.25)				
2 Clodronate				
Delmas 1982	1.288 (0.89442719)		1.0 %	3.63 [0.63, 20.93]
Lahtinen 1992	-0.28721312 (0.18107149)		12.2 %	0.75 [0.53, 1.07]
McCloskey 2001	-0.01561644 (0.0955637)		18.7 %	0.98 [0.82, 1.19]
Subtotal (95% CI)			**31.9 %**	**0.93 [0.66, 1.29]**
Heterogeneity: Tau² = 0.04; Chi² = 4.06, df = 2 (P = 0.13); I² =51%				
Test for overall effect: Z = 0.45 (P = 0.65)				



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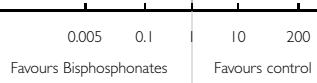
Study or subgroup	log [Hazard Ratio] (SE)	Hazard Ratio IV,Random,95% CI	Weight	Hazard Ratio IV,Random,95% CI
3 Pamidronate				
Berenson 1998	-0.29 (0.16666667)		13.1 %	0.75 [0.54, 1.04]
Brincker 1998	-0.10714286 (0.94491118)		0.9 %	0.90 [0.14, 5.73]
Kraj 2000	0.1168 (0.4)		4.2 %	1.12 [0.51, 2.46]
Terpos 2000	-2.08 (1.41421356)		0.4 %	0.12 [0.01, 2.00]
Subtotal (95% CI)			**18.7 %**	**0.78 [0.58, 1.05]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 2.60, df = 3 (P = 0.46); I^2 =0.0%				
Test for overall effect: Z = 1.64 (P = 0.10)				
4 Ibandronate				
Menssen 2002	0.06341463 (0.22086305)		9.8 %	1.07 [0.69, 1.64]
Subtotal (95% CI)			**9.8 %**	**1.07 [0.69, 1.64]**
Heterogeneity: not applicable				
Test for overall effect: Z = 0.29 (P = 0.77)				
5 Zolendronate				
Aviles 2007	-0.85888889 (0.33333333)		5.6 %	0.42 [0.22, 0.81]
Subtotal (95% CI)			**5.6 %**	**0.42 [0.22, 0.81]**
Heterogeneity: not applicable				
Test for overall effect: Z = 2.58 (P = 0.010)				
Total (95% CI)			**100.0 %**	**0.96 [0.80, 1.14]**
Heterogeneity: Tau^2 = 0.03; Chi^2 = 24.39, df = 10 (P = 0.01); I^2 =59%				
Test for overall effect: Z = 0.47 (P = 0.64)				

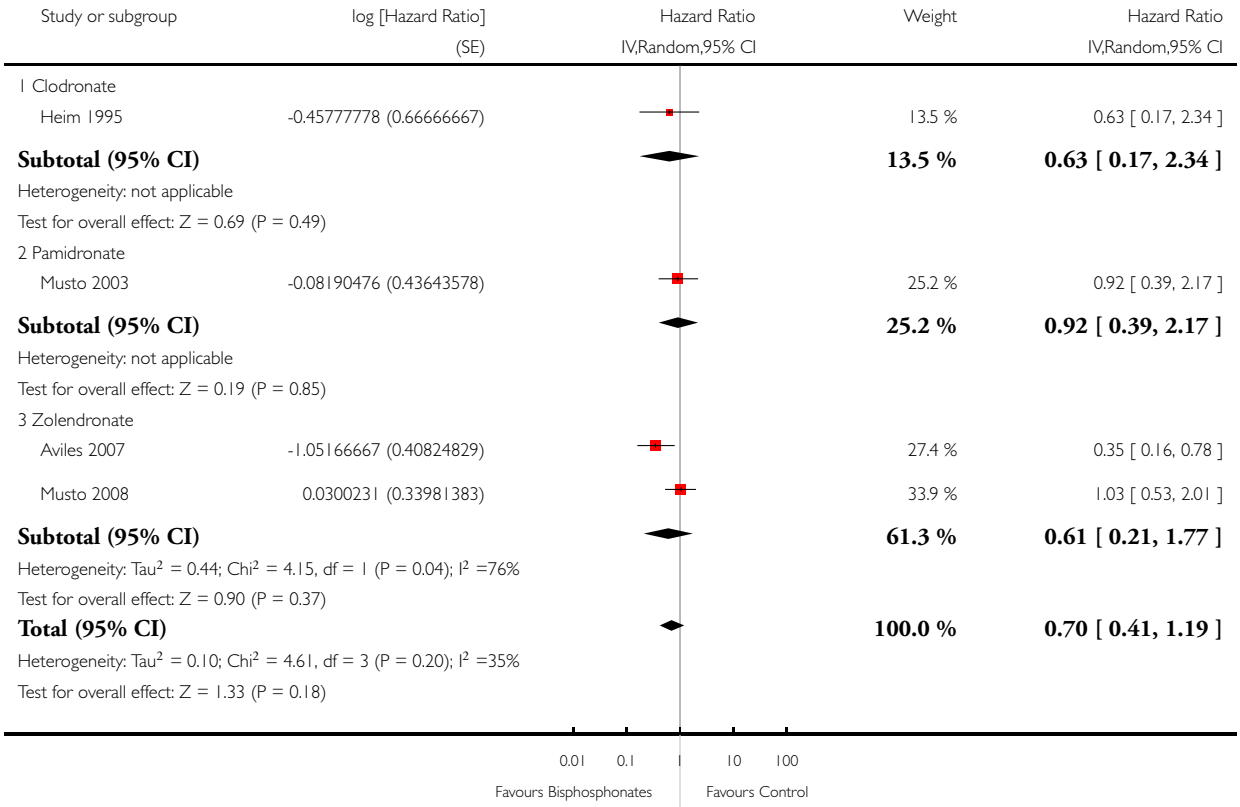


Analysis 1.2. Comparison 1 Bisphosphonates vs. control (efficacy), Outcome 2 Progression free survival.

Review: Bisphosphonates in multiple myeloma

Comparison: 1 Bisphosphonates vs. control (efficacy)

Outcome: 2 Progression free survival

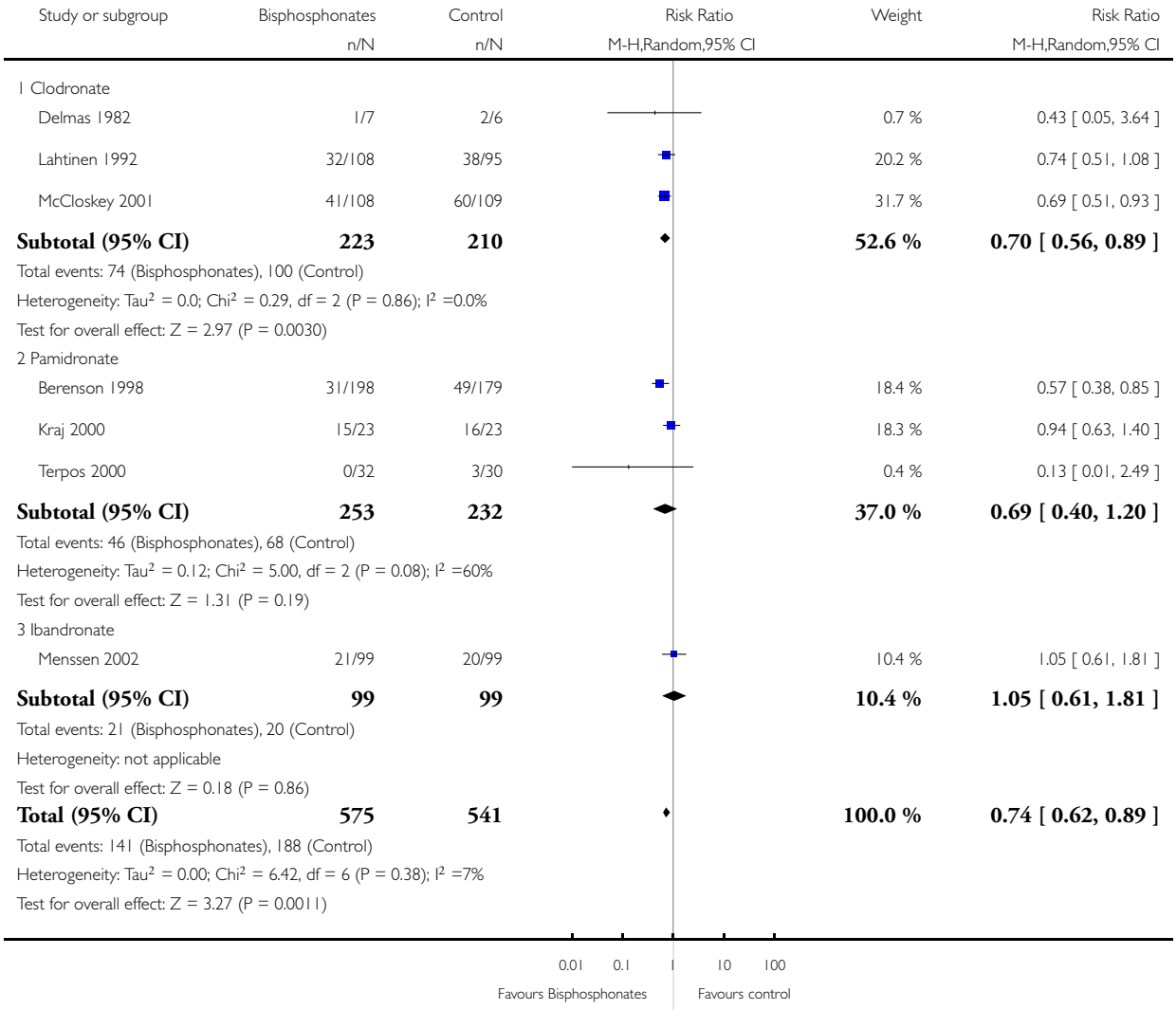


Analysis 1.3. Comparison 1 Bisphosphonates vs. control (efficacy), Outcome 3 Vertebral fractures.

Review: Bisphosphonates in multiple myeloma

Comparison: 1 Bisphosphonates vs. control (efficacy)

Outcome: 3 Vertebral fractures

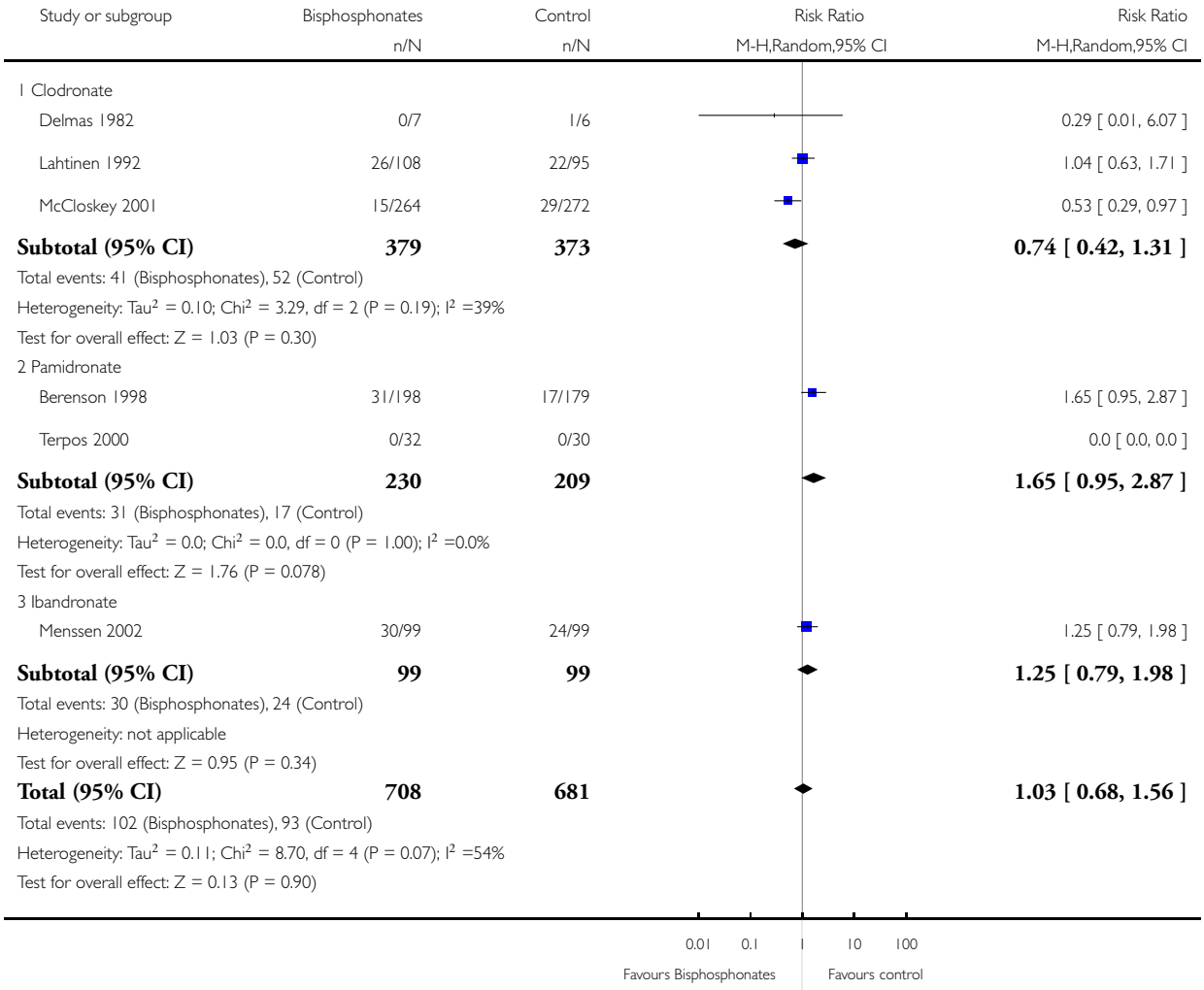


Analysis 1.4. Comparison 1 Bisphosphonates vs. control (efficacy), Outcome 4 Non-vertebral fractures.

Review: Bisphosphonates in multiple myeloma

Comparison: 1 Bisphosphonates vs. control (efficacy)

Outcome: 4 Non-vertebral fractures

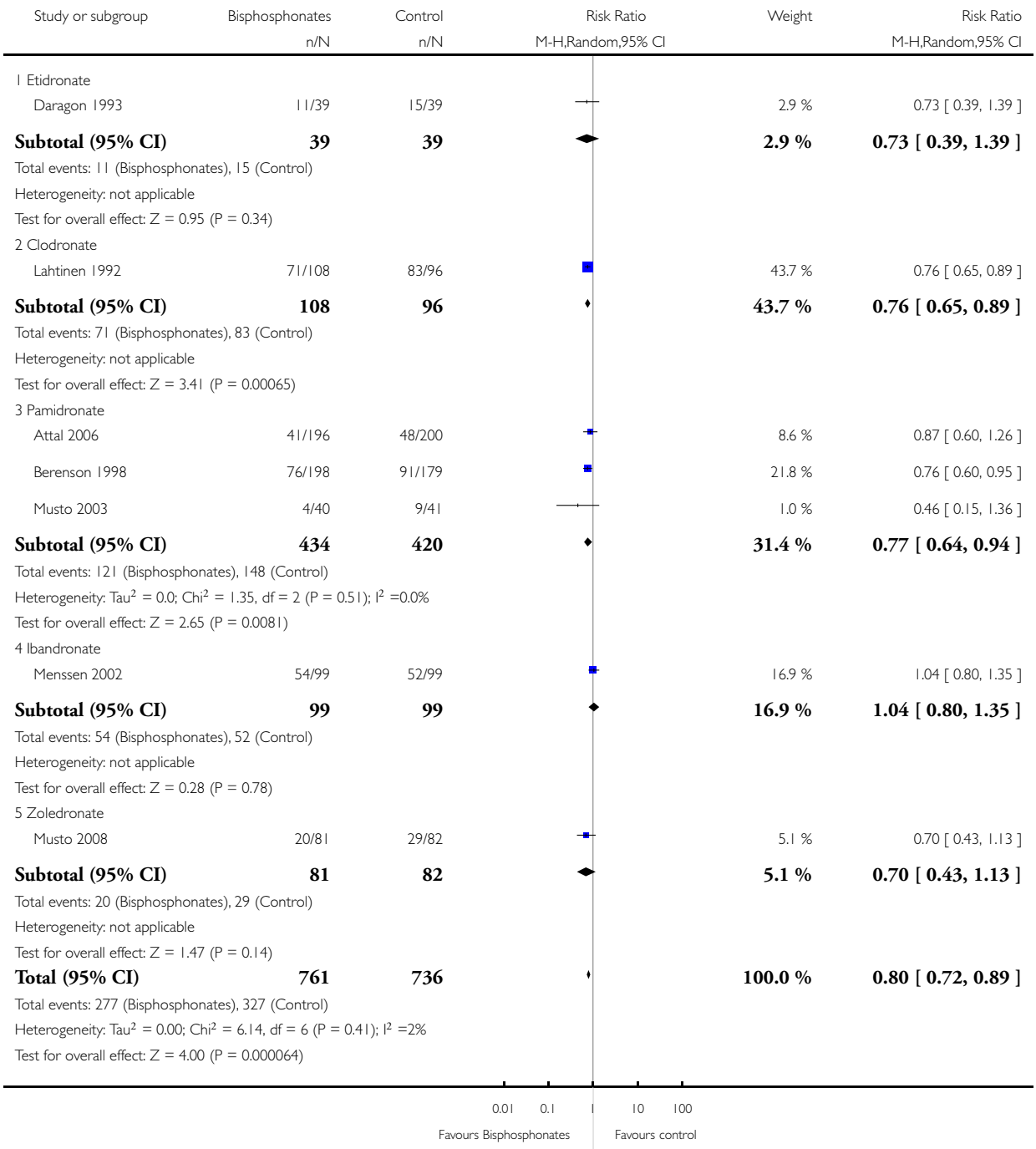


Analysis 1.5. Comparison 1 Bisphosphonates vs. control (efficacy), Outcome 5 Total skeletal related events.

Review: Bisphosphonates in multiple myeloma

Comparison: 1 Bisphosphonates vs. control (efficacy)

Outcome: 5 Total skeletal related events

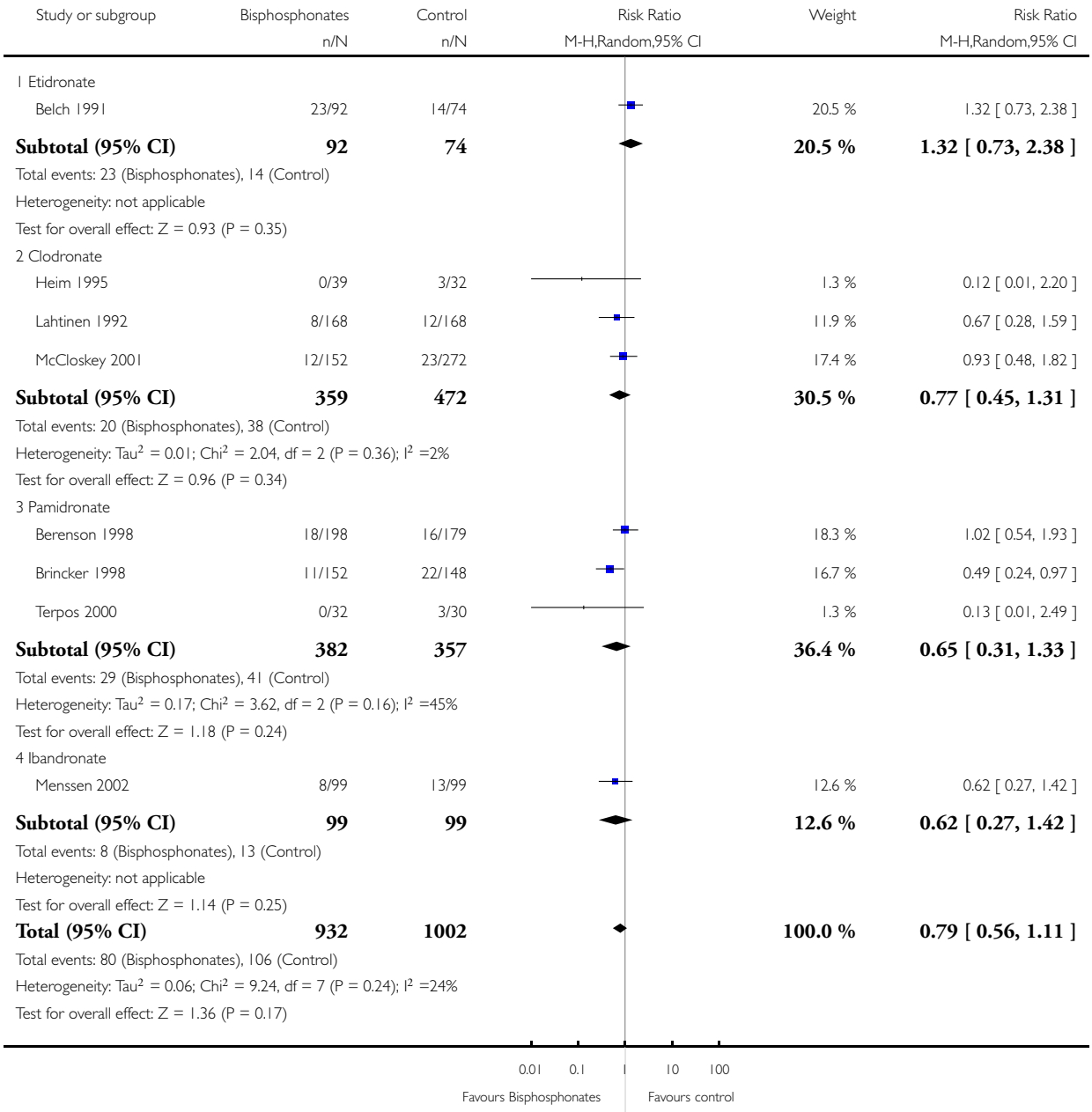


Analysis 1.6. Comparison 1 Bisphosphonates vs. control (efficacy), Outcome 6 Incidence of hypercalcemia.

Review: Bisphosphonates in multiple myeloma

Comparison: 1 Bisphosphonates vs. control (efficacy)

Outcome: 6 Incidence of hypercalcemia



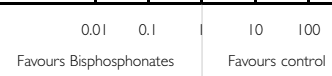
Analysis 1.7. Comparison 1 Bisphosphonates vs. control (efficacy), Outcome 7 Pain.

Review: Bisphosphonates in multiple myeloma

Comparison: 1 Bisphosphonates vs. control (efficacy)

Outcome: 7 Pain

Study or subgroup	Bisphosphonates n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Etidronate					
Daragon 1993	7/39	12/39		6.1 %	0.58 [0.26, 1.32]
Subtotal (95% CI)	**39**	**39**		**6.1 %**	**0.58 [0.26, 1.32]**
Total events: 7 (Bisphosphonates), 12 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.29 (P = 0.20)					
2 Clodronate					
Delmas 1982	1/7	3/3		2.2 %	0.21 [0.05, 0.95]
Heim 1995	5/39	14/32		5.2 %	0.29 [0.12, 0.73]
Lahtinen 1992	53/114	56/100		21.8 %	0.83 [0.64, 1.08]
McCloskey 2001	14/129	28/142		9.9 %	0.55 [0.30, 1.00]
Subtotal (95% CI)	**289**	**277**		**39.0 %**	**0.51 [0.29, 0.91]**
Total events: 73 (Bisphosphonates), 101 (Control)					
Heterogeneity: Tau^2 = 0.20; Chi^2 = 8.63, df = 3 (P = 0.03); I^2 =65%					
Test for overall effect: Z = 2.30 (P = 0.022)					
3 Pamidronate					
Berenson 1998	120/198	127/179		27.3 %	0.85 [0.74, 0.99]
Terpos 2000	0/32	2/30		0.6 %	0.19 [0.01, 3.76]
Subtotal (95% CI)	**230**	**209**		**27.9 %**	**0.85 [0.72, 1.01]**
Total events: 120 (Bisphosphonates), 129 (Control)					
Heterogeneity: Tau^2 = 0.00; Chi^2 = 1.00, df = 1 (P = 0.32); I^2 =0%					
Test for overall effect: Z = 1.86 (P = 0.063)					
4 Ibandronate					
Menssen 2002	76/99	76/99		27.0 %	1.00 [0.86, 1.17]
Subtotal (95% CI)	**99**	**99**		**27.0 %**	**1.00 [0.86, 1.17]**
Total events: 76 (Bisphosphonates), 76 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P = 1.0)					
Total (95% CI)	**657**	**624**		**100.0 %**	**0.75 [0.60, 0.95]**



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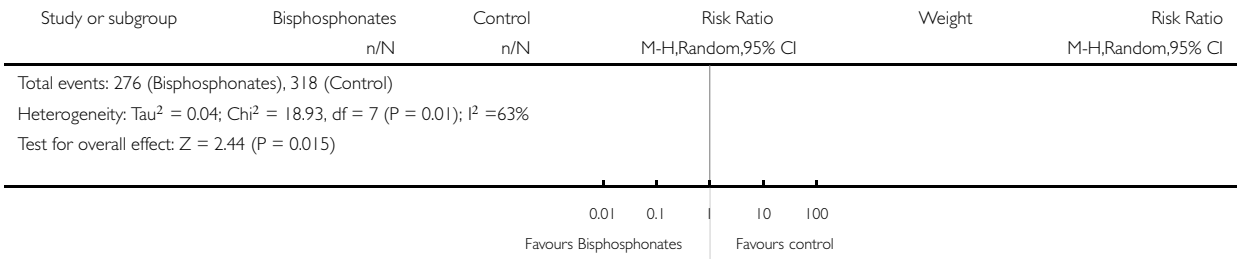


Analysis 1.8. Comparison 1 Bisphosphonates vs. control (efficacy), Outcome 8 Time to progression.

Time to progression

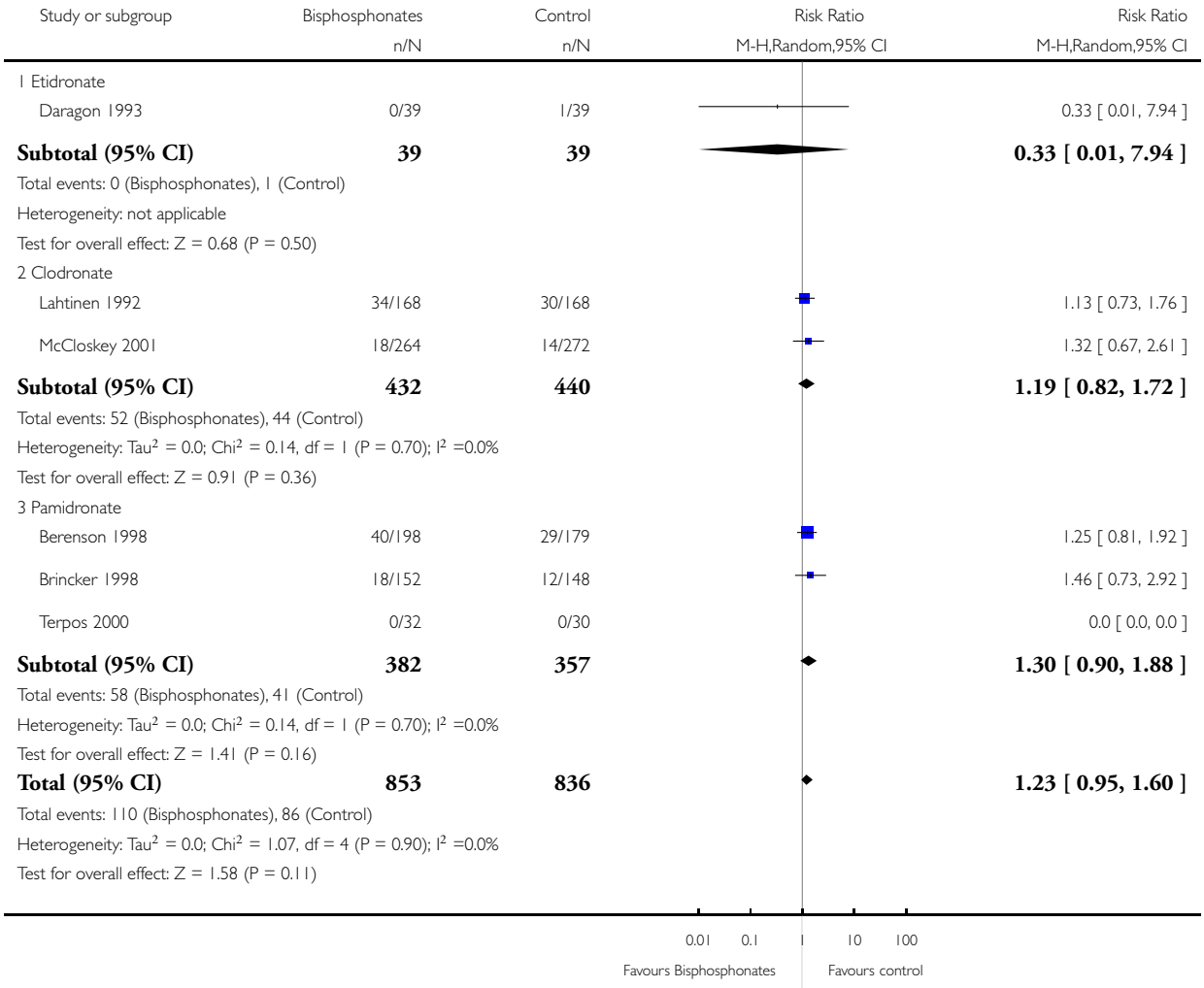
Pamidronate					
Brincker 1998	15	152	14	148	0.3349
Musto 2003	16	40	17.4	41	0.05
Zolendronate					
Musto 2008	67	81	59	82	0.8312

Analysis 2.1. Comparison 2 Bisphosphonates vs. control (adverse effects), Outcome 1 Gastrointestinal toxicity (grade III/IV).

Review: Bisphosphonates in multiple myeloma

Comparison: 2 Bisphosphonates vs. control (adverse effects)

Outcome: 1 Gastrointestinal toxicity (grade III/IV)

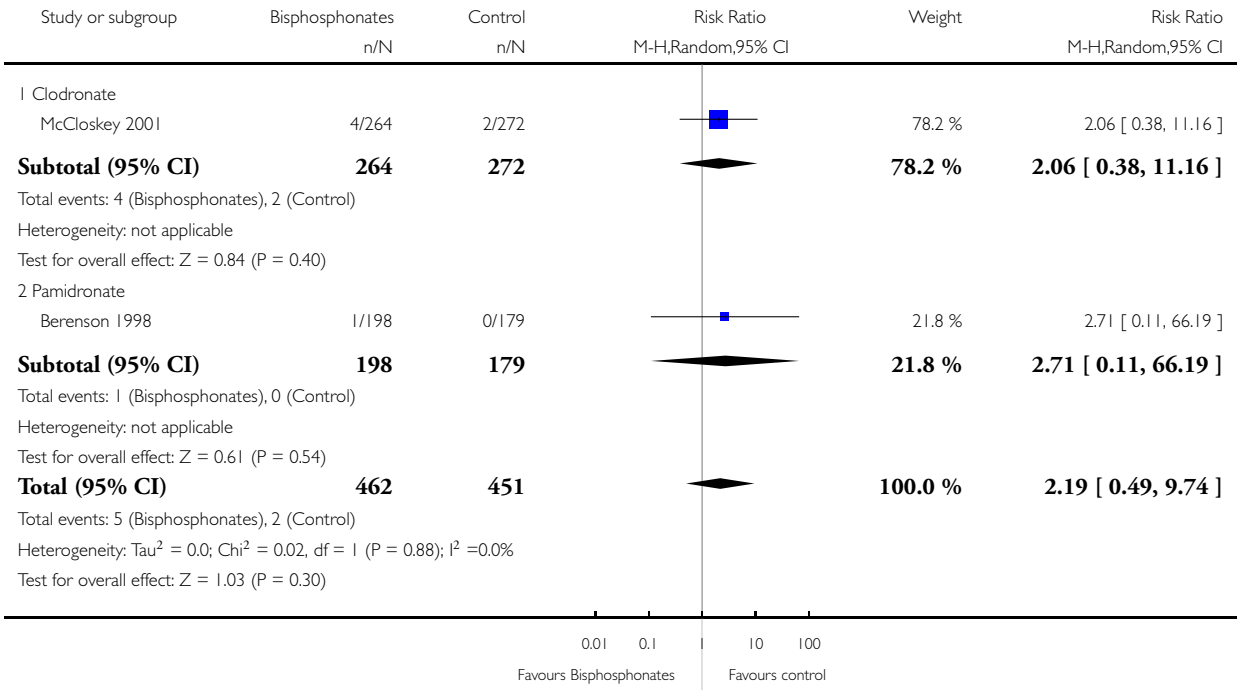


Analysis 2.2. Comparison 2 Bisphosphonates vs. control (adverse effects), Outcome 2 Hypocalcaemia.

Review: Bisphosphonates in multiple myeloma

Comparison: 2 Bisphosphonates vs. control (adverse effects)

Outcome: 2 Hypocalcaemia



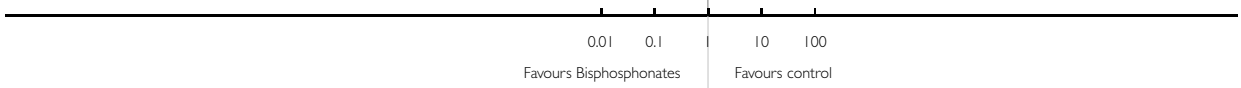
Analysis 3.1. Comparison 3 Sensitivity analyses (assessment of bias: analysed outcome in brackets), Outcome 1 Allocation concealment (vertebral fractures).

Review: Bisphosphonates in multiple myeloma

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

Outcome: 1 Allocation concealment (vertebral fractures)

Study or subgroup	Bisphosphonate n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Adeqaute concealment of allocation					
Berenson 1998	31/198	49/179		18.4 %	0.57 [0.38, 0.85]
McCloskey 2001	41/108	60/109		31.7 %	0.69 [0.51, 0.93]
Subtotal (95% CI)	**306**	**288**		**50.0 %**	**0.65 [0.51, 0.82]**
Total events: 72 (Bisphosphonate), 109 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.56, df = 1 (P = 0.45); I^2 =0.0%					
Test for overall effect: Z = 3.60 (P = 0.00031)					
2 Inadequate concealment of allocation					
Delmas 1982	1/7	2/6		0.7 %	0.43 [0.05, 3.64]
Kraj 2000	15/23	16/23		18.3 %	0.94 [0.63, 1.40]
Lahtinen 1992	32/108	38/95		20.2 %	0.74 [0.51, 1.08]
Menssen 2002	21/99	20/99		10.4 %	1.05 [0.61, 1.81]
Terpos 2000	0/32	3/30		0.4 %	0.13 [0.01, 2.49]
Subtotal (95% CI)	**269**	**253**		**50.0 %**	**0.85 [0.67, 1.09]**
Total events: 69 (Bisphosphonate), 79 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 3.32, df = 4 (P = 0.51); I^2 =0.0%					
Test for overall effect: Z = 1.30 (P = 0.19)					
Total (95% CI)	**575**	**541**		**100.0 %**	**0.74 [0.62, 0.89]**
Total events: 141 (Bisphosphonate), 188 (Control)					
Heterogeneity: Tau^2 = 0.00; Chi^2 = 6.42, df = 6 (P = 0.38); I^2 =7%					
Test for overall effect: Z = 3.27 (P = 0.0011)					



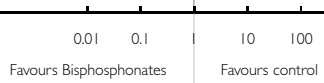
Analysis 3.2. Comparison 3 Sensitivity analyses (assessment of bias: analysed outcome in brackets), Outcome 2 Blinding (vertebral fractures).

Review: Bisphosphonates in multiple myeloma

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

Outcome: 2 Blinding (vertebral fractures)

Study or subgroup	Bisphosphonate n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Double blind					
Berenson 1998	31/198	49/179		18.4 %	0.57 [0.38, 0.85]
Delmas 1982	1/7	2/6		0.7 %	0.43 [0.05, 3.64]
Lahtinen 1992	32/108	38/95		20.2 %	0.74 [0.51, 1.08]
McCloskey 2001	41/108	60/109		31.7 %	0.69 [0.51, 0.93]
Menssen 2002	21/99	20/99		10.4 %	1.05 [0.61, 1.81]
Subtotal (95% CI)	**520**	**488**		**81.3 %**	**0.71 [0.58, 0.85]**
Total events: 126 (Bisphosphonate), 169 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 3.38$, df = 4 (P = 0.50); $I^2 = 0.0\%$					
Test for overall effect: Z = 3.63 (P = 0.00029)					
2 Not blinded					
Kraj 2000	15/23	16/23		18.3 %	0.94 [0.63, 1.40]
Terpos 2000	0/32	3/30		0.4 %	0.13 [0.01, 2.49]
Subtotal (95% CI)	**55**	**53**		**18.7 %**	**0.55 [0.08, 3.72]**
Total events: 15 (Bisphosphonate), 19 (Control)					
Heterogeneity: $Tau^2 = 1.26$; $Chi^2 = 2.11$, df = 1 (P = 0.15); $I^2 = 53\%$					
Test for overall effect: Z = 0.61 (P = 0.54)					
Total (95% CI)	**575**	**541**		**100.0 %**	**0.74 [0.62, 0.89]**
Total events: 141 (Bisphosphonate), 188 (Control)					
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 6.42$, df = 6 (P = 0.38); $I^2 = 7\%$					
Test for overall effect: Z = 3.27 (P = 0.0011)					



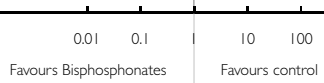
Analysis 3.3. Comparison 3 Sensitivity analyses (assessment of bias: analysed outcome in brackets), Outcome 3 Randomization method (vertebral fractures).

Review: Bisphosphonates in multiple myeloma

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

Outcome: 3 Randomization method (vertebral fractures)

Study or subgroup	Bisphosphonate n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Randomization method is described					
Berenson 1998	31/198	49/179		18.4 %	0.57 [0.38, 0.85]
Subtotal (95% CI)	**198**	**179**		**18.4 %**	**0.57 [0.38, 0.85]**
Total events: 31 (Bisphosphonate), 49 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.73 (P = 0.0064)					
2 Randomization method is NOT described					
Delmas 1982	1/7	2/6		0.7 %	0.43 [0.05, 3.64]
Kraj 2000	15/23	16/23		18.3 %	0.94 [0.63, 1.40]
Lahtinen 1992	32/108	38/95		20.2 %	0.74 [0.51, 1.08]
McCloskey 2001	41/108	60/109		31.7 %	0.69 [0.51, 0.93]
Menssen 2002	21/99	20/99		10.4 %	1.05 [0.61, 1.81]
Terpos 2000	0/32	3/30		0.4 %	0.13 [0.01, 2.49]
Subtotal (95% CI)	**377**	**362**		**81.6 %**	**0.78 [0.65, 0.94]**
Total events: 110 (Bisphosphonate), 139 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 4.42, df = 5 (P = 0.49); I^2 =0.0%					
Test for overall effect: Z = 2.58 (P = 0.0099)					
Total (95% CI)	**575**	**541**		**100.0 %**	**0.74 [0.62, 0.89]**
Total events: 141 (Bisphosphonate), 188 (Control)					
Heterogeneity: Tau^2 = 0.00; Chi^2 = 6.42, df = 6 (P = 0.38); I^2 =7%					
Test for overall effect: Z = 3.27 (P = 0.0011)					



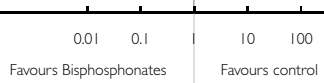
Analysis 3.4. Comparison 3 Sensitivity analyses (assessment of bias: analysed outcome in brackets), Outcome 4 Type of data analysis (vertebral fractures).

Review: Bisphosphonates in multiple myeloma

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

Outcome: 4 Type of data analysis (vertebral fractures)

Study or subgroup	Bisphosphonate n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Intention to treat analysis					
Lahtinen 1992	32/108	38/95		20.2 %	0.74 [0.51, 1.08]
Menssen 2002	21/99	20/99		10.4 %	1.05 [0.61, 1.81]
Terpos 2000	0/32	3/30		0.4 %	0.13 [0.01, 2.49]
Subtotal (95% CI)	**239**	**224**		**31.0 %**	**0.82 [0.55, 1.22]**
Total events: 53 (Bisphosphonate), 61 (Control)					
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 2.54$, df = 2 (P = 0.28); $I^2 = 21\%$					
Test for overall effect: Z = 0.98 (P = 0.33)					
2 Per protocol analysis					
Berenson 1998	31/198	49/179		18.4 %	0.57 [0.38, 0.85]
Delmas 1982	1/7	2/6		0.7 %	0.43 [0.05, 3.64]
Kraj 2000	15/23	16/23		18.3 %	0.94 [0.63, 1.40]
McCloskey 2001	41/108	60/109		31.7 %	0.69 [0.51, 0.93]
Subtotal (95% CI)	**336**	**317**		**69.0 %**	**0.71 [0.56, 0.89]**
Total events: 88 (Bisphosphonate), 127 (Control)					
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 3.49$, df = 3 (P = 0.32); $I^2 = 14\%$					
Test for overall effect: Z = 2.94 (P = 0.0032)					
Total (95% CI)	**575**	**541**		**100.0 %**	**0.74 [0.62, 0.89]**
Total events: 141 (Bisphosphonate), 188 (Control)					
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 6.42$, df = 6 (P = 0.38); $I^2 = 7\%$					
Test for overall effect: Z = 3.27 (P = 0.0011)					



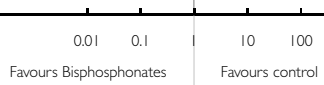
Analysis 3.5. Comparison 3 Sensitivity analyses (assessment of bias: analysed outcome in brackets), Outcome 5 Description of withdrawals and drop outs (vertebral fractures).

Review: Bisphosphonates in multiple myeloma

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

Outcome: 5 Description of withdrawals and drop outs (vertebral fractures)

Study or subgroup	Bisphosphonate n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Withdrawals and drop outs well described					
Berenson 1998	31/198	49/179		18.4 %	0.57 [0.38, 0.85]
Lahtinen 1992	32/108	38/95		20.2 %	0.74 [0.51, 1.08]
McCloskey 2001	41/108	60/109		31.7 %	0.69 [0.51, 0.93]
Subtotal (95% CI)	**414**	**383**		**70.2 %**	**0.67 [0.55, 0.82]**
Total events: 104 (Bisphosphonate), 147 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.91$, df = 2 (P = 0.63); $I^2 = 0.0\%$					
Test for overall effect: Z = 3.87 (P = 0.00011)					
2 Withdrawals and drop outs NOT described					
Delmas 1982	1/7	2/6		0.7 %	0.43 [0.05, 3.64]
Kraj 2000	15/23	16/23		18.3 %	0.94 [0.63, 1.40]
Menssen 2002	21/99	20/99		10.4 %	1.05 [0.61, 1.81]
Terpos 2000	0/32	3/30		0.4 %	0.13 [0.01, 2.49]
Subtotal (95% CI)	**161**	**158**		**29.8 %**	**0.94 [0.68, 1.29]**
Total events: 37 (Bisphosphonate), 41 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.45$, df = 3 (P = 0.48); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.41 (P = 0.68)					
Total (95% CI)	**575**	**541**		**100.0 %**	**0.74 [0.62, 0.89]**
Total events: 141 (Bisphosphonate), 188 (Control)					
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 6.42$, df = 6 (P = 0.38); $I^2 = 7\%$					
Test for overall effect: Z = 3.27 (P = 0.0011)					



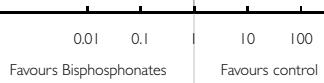
Analysis 3.6. Comparison 3 Sensitivity analyses (assessment of bias: analysed outcome in brackets), Outcome 6 Alpha error (vertebral fractures).

Review: Bisphosphonates in multiple myeloma

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

Outcome: 6 Alpha error (vertebral fractures)

Study or subgroup	Bisphosphonate n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Alpha error pre-specified					
Lahtinen 1992	32/108	38/95		20.2 %	0.74 [0.51, 1.08]
Subtotal (95% CI)	**108**	**95**		**20.2 %**	**0.74 [0.51, 1.08]**
Total events: 32 (Bisphosphonate), 38 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.54 (P = 0.12)					
2 Alpha error NOT pre-specified					
Berenson 1998	31/198	49/179		18.4 %	0.57 [0.38, 0.85]
Delmas 1982	1/7	2/6		0.7 %	0.43 [0.05, 3.64]
Kraj 2000	15/23	16/23		18.3 %	0.94 [0.63, 1.40]
McCloskey 2001	41/108	60/109		31.7 %	0.69 [0.51, 0.93]
Menssen 2002	21/99	20/99		10.4 %	1.05 [0.61, 1.81]
Terpos 2000	0/32	3/30		0.4 %	0.13 [0.01, 2.49]
Subtotal (95% CI)	**467**	**446**		**79.8 %**	**0.74 [0.59, 0.94]**
Total events: 109 (Bisphosphonate), 150 (Control)					
Heterogeneity: Tau^2 = 0.02; Chi^2 = 6.47, df = 5 (P = 0.26); I^2 =23%					
Test for overall effect: Z = 2.43 (P = 0.015)					
Total (95% CI)	**575**	**541**		**100.0 %**	**0.74 [0.62, 0.89]**
Total events: 141 (Bisphosphonate), 188 (Control)					
Heterogeneity: Tau^2 = 0.00; Chi^2 = 6.42, df = 6 (P = 0.38); I^2 =7%					
Test for overall effect: Z = 3.27 (P = 0.0011)					



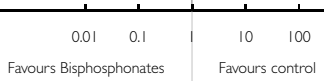
Analysis 3.7. Comparison 3 Sensitivity analyses (assessment of bias: analysed outcome in brackets), Outcome 7 Beta error (vertebral fractures).

Review: Bisphosphonates in multiple myeloma

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

Outcome: 7 Beta error (vertebral fractures)

Study or subgroup	Bisphosphonate n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Beta error pre-specified					
Lahtinen 1992	32/108	38/95		20.2 %	0.74 [0.51, 1.08]
Subtotal (95% CI)	**108**	**95**		**20.2 %**	**0.74 [0.51, 1.08]**
Total events: 32 (Bisphosphonate), 38 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.54 (P = 0.12)					
2 Beta error NOT pre-specified					
Berenson 1998	31/198	49/179		18.4 %	0.57 [0.38, 0.85]
Delmas 1982	1/7	2/6		0.7 %	0.43 [0.05, 3.64]
Kraj 2000	15/23	16/23		18.3 %	0.94 [0.63, 1.40]
McCloskey 2001	41/108	60/109		31.7 %	0.69 [0.51, 0.93]
Menssen 2002	21/99	20/99		10.4 %	1.05 [0.61, 1.81]
Terpos 2000	0/32	3/30		0.4 %	0.13 [0.01, 2.49]
Subtotal (95% CI)	**467**	**446**		**79.8 %**	**0.74 [0.59, 0.94]**
Total events: 109 (Bisphosphonate), 150 (Control)					
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 6.47$, df = 5 (P = 0.26); $I^2 = 23\%$					
Test for overall effect: Z = 2.43 (P = 0.015)					
Total (95% CI)	**575**	**541**		**100.0 %**	**0.74 [0.62, 0.89]**
Total events: 141 (Bisphosphonate), 188 (Control)					
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 6.42$, df = 6 (P = 0.38); $I^2 = 7\%$					
Test for overall effect: Z = 3.27 (P = 0.0011)					



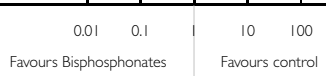
Analysis 3.8. Comparison 3 Sensitivity analyses (assessment of bias: analysed outcome in brackets), Outcome 8 Clodronate dose (vertebral fractures).

Review: Bisphosphonates in multiple myeloma

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

Outcome: 8 Clodronate dose (vertebral fractures)

Study or subgroup	Bisphosphonate n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Clodronate 1600 mg/d					
Delmas 1982	1/7	2/6		1.2 %	0.43 [0.05, 3.64]
McCloskey 2001	41/108	60/109		61.8 %	0.69 [0.51, 0.93]
Subtotal (95% CI)	**115**	**115**		**63.0 %**	**0.68 [0.51, 0.92]**
Total events: 42 (Bisphosphonate), 62 (Control)					
Heterogeneity: Tau² = 0.0; Chi² = 0.19, df = 1 (P = 0.67); I² =0.0%					
Test for overall effect: Z = 2.55 (P = 0.011)					
2 Clodronate 2400 mg/d					
Lahtinen 1992	32/108	38/95		37.0 %	0.74 [0.51, 1.08]
Subtotal (95% CI)	**108**	**95**		**37.0 %**	**0.74 [0.51, 1.08]**
Total events: 32 (Bisphosphonate), 38 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.54 (P = 0.12)					
Total (95% CI)	**223**	**210**		**100.0 %**	**0.70 [0.56, 0.89]**
Total events: 74 (Bisphosphonate), 100 (Control)					
Heterogeneity: Tau² = 0.0; Chi² = 0.29, df = 2 (P = 0.86); I² =0.0%					
Test for overall effect: Z = 2.97 (P = 0.0030)					

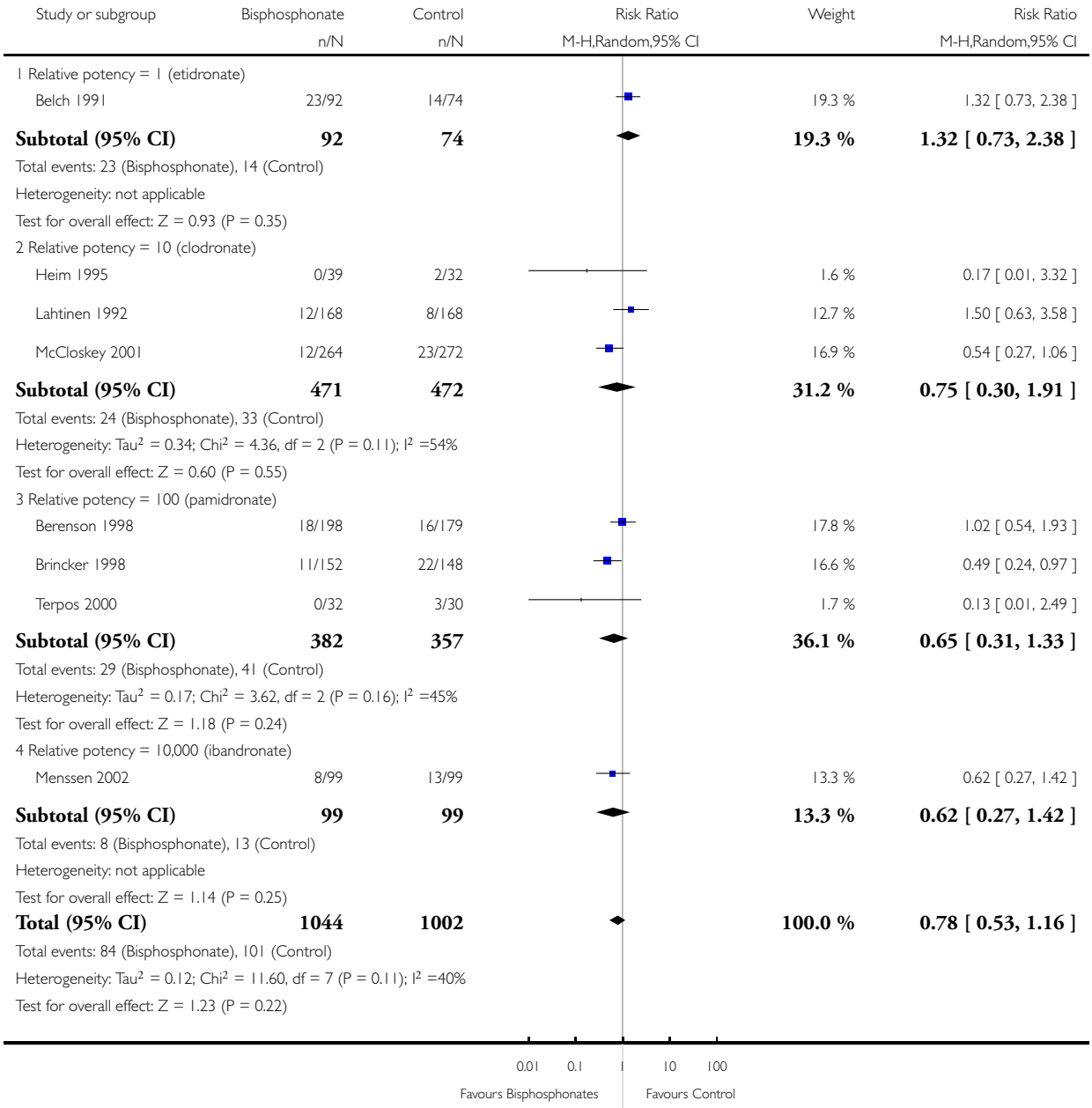


Analysis 3.9. Comparison 3 Sensitivity analyses (assessment of bias: analysed outcome in brackets), Outcome 9 In vitro anti-resorptive potency (incidence of hypercalcemia).

Review: Bisphosphonates in multiple myeloma

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

Outcome: 9 In vitro anti-resorptive potency (incidence of hypercalcemia)



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 ((“2000/12/31”[EDat] : “3000”[EDat]) AND (Humans[Mesh]))
Limts:Publication Date from 2000/12/31
(((((((“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 2000/12/31, Humans
2) Search strategy aimed at identifying observational studies and ONJ case reports.
(“Multiple Myeloma”[Mesh] AND (“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 (“Osteonecrosis ”[Mesh] OR “Jaw Diseases”[Mesh])
Limits: Publication Date from 2003/01/01 to 2007/10 /31, Humans

Appendix 2. Cochrane Library search strategy

“bisphosphonates and myeloma”

Appendix 3. www. clinicaltrials.gov search strategy

“bisphosphonates and multiple myeloma”

Appendix 4. Embase search strategy

(bone neoplasms/ OR bone neoplasm/ OR multiple myeloma/ OR neoplasm metastasis/ OR neoplasms/) AND (alendronate/ OR clodronate/ OR etidronate/ OR risedronate/ OR ibandronate/ OR pamidronate/ OR tiludronate/ OR zoledronate/ OR diphosphonates.mp.) OR (bisphosphonate$ adj (agent$ OR derivative$)).mp.tw.) AND (random.tw. OR clinical trial.mp. OR exp health care quality)

Appendix 5. Lilacs search strategy

((mieloma OR myeloma) AND random$))

WHAT'S NEW

Last assessed as up-to-date: 31 December 2008.

21 December 2009	New citation required and conclusions have changed	Substantive update
21 December 2009	New search has been performed	Substantive update

HISTORY

Protocol first published: Issue 2, 2001

Review first published: Issue 4, 2001

CONTRIBUTIONS OF AUTHORS

RM wrote the initial and final drafts and participated in all phases of the project. BD oversaw and coordinated the group activity, maintained contact with The Cochrane Collaboration, provided vital content and methodological inputs and edited the review. KW provided statistical expertise. RM and JR handsearched and extracted data. RM and JR contacted manufacturers and researchers around the world regarding unpublished data. Methodological problems were discussed by BD, RM and KW. JR provided expertise on basic science aspects of bisphosphonates and osteonecrosis of the jaw. AK reviewed and re-checked all data. BM conducted the indirect comparisons using Bayesian methods. All co-authors interpreted data, provided constructive critiques and agreed on the final version of the paper.

DECLARATIONS OF INTEREST

Dr. Djulbegovic has received the "Incentive reward for Cochrane reviews" for this update which was used to support RM and JR who performed the bulk of work.

SOURCES OF SUPPORT

Internal sources

- The University of South Florida, USA.
- Dpt. of Internal Medicine I, Univ. of Bonn, Germany.

External sources

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

INDEX TERMS

Medical Subject Headings (MeSH)

Antineoplastic Agents [*therapeutic use]; Bone Diseases [*drug therapy; mortality]; Diphosphonates [*therapeutic use]; Fractures, Bone [prevention & control]; Multiple Myeloma [complications; *drug therapy; mortality]; Randomized Controlled Trials as Topic

MeSH check words

Humans