Critical appraisal of a systematic review

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Outline

- Basics of systematic reviews
- Critical appraisal
- Hands on critical appraisal

Research synthesis: systematic reviews and meta analysis

- Systematic Review
  - "The application of strategies that limit bias in the **assembly**, **critical appraisal**, and **synthesis** of **all** relevant studies on a specific topic. Meta-analysis may be, but is not necessary, used as part of this process.“

- Meta-Analysis
  - " The statistical synthesis of the data from separate but similar, i.e. comparable studies, leading to a quantitative summary of the pooled results."

Courtesy of Dr. Djulbegovic

Last JM. Dictionary of Epidemiology, 2001

Critical appraisal of systematic reviews

- Not all systematic reviews are alike.
- Need for critical appraisal of systematic reviews.

- Numerous tools are developed for critical appraisal of the systematic reviews.
  - A measurement tool for the 'assessment of multiple systematic reviews' (AMSTAR)
  - Critical appraisal tool developed by Oxford center for evidence based medicine

Case

A 60 year old man with multiple myeloma is referred to a cancer center for the management of his bone disease.
The attending physician wants to decide whether the patient should be treated with bisphosphonates?

Does bisphosphonates help in reducing fractures in patients with multiple myeloma?

You found a systematic review !

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

Bisphosphonates in multiple myeloma. Cochrane Database of Systematic Reviews 2010,

Issue 3. Art. No.: CD003188. DOI: 10.1002/14651858.CD003188.pub2.

Basics

Did the review address a clearly focused issue?

- **PICOTS clear?**

Did the authors look for the appropriate sort of papers?

- Matching the study design to the research question

Objectives

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-

METHODS

than 10 patients.

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

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

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

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).

- Did the authors select the right sort of studies for the review?

- The right studies would:
  - address the review's question
  - have an adequate study design

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.

Do you think the important, relevant studies were included?

Look for:

- which bibliographic databases were used
- personal contact with experts
- search for unpublished as well as published studies
- search for non-English language studies

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 5. Lilacs search strategy

((mieloma OR myeloma) AND random$))

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.

- **Did the review's authors do enough to assess the quality of the included studies?**

- Did they use:
  - description of randomization?
  - a rating scale?

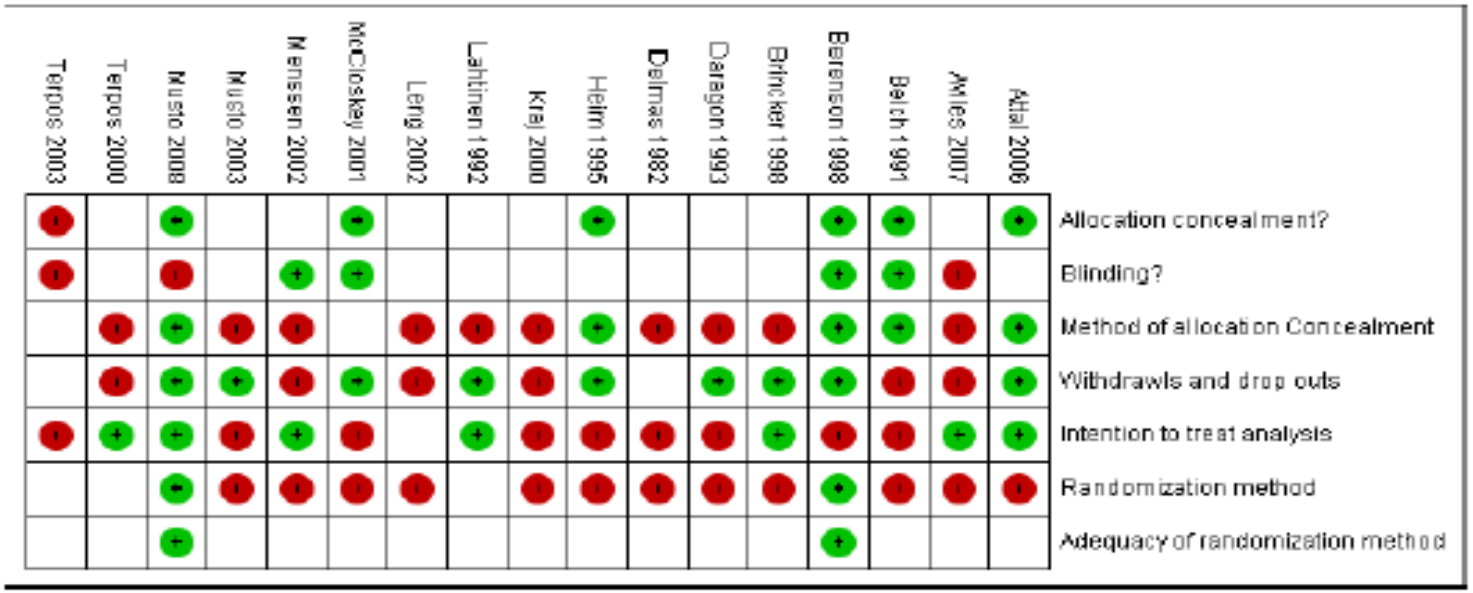
Methodological quality of the included studies

- Assessment of risk of bias
  - Generation of randomization sequence
  - Allocation concealment
  - Description of withdrawals and drop-outs
  - Intention to treat analysis
  - Blinding methods and who were blinded
- Assessment of risk of random error
  - Pre-specification of alpha and beta error
  - *A priori* calculation of sample size

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.

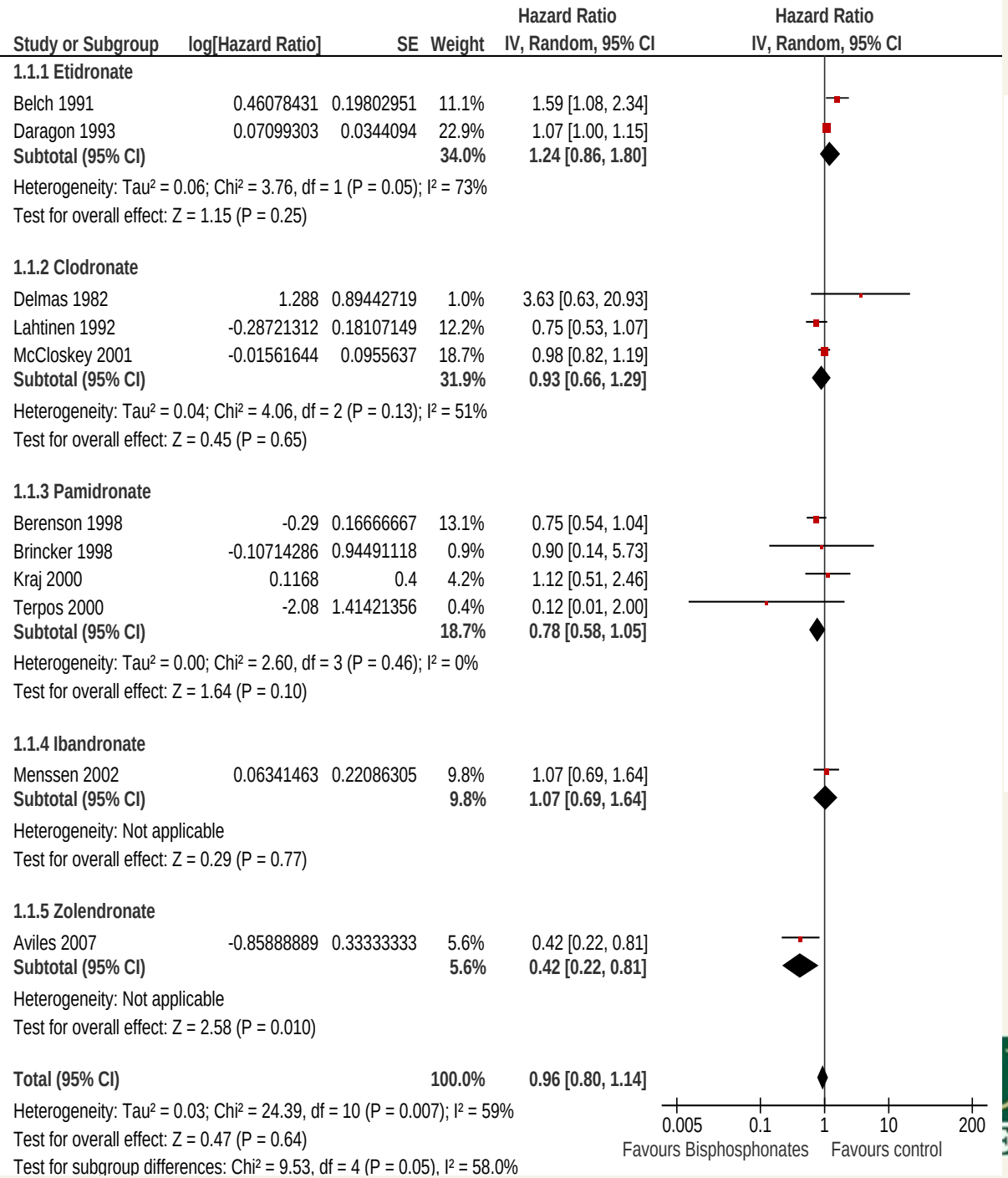


EVIDENCE BASED MEDICINE

USF HEALTH

What are the results?

- Were the results similar from study to study?
- Are the results of all the included studies clearly displayed?
- Are the results from different studies similar?
- If not, are the reasons for variations between studies discussed?



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.

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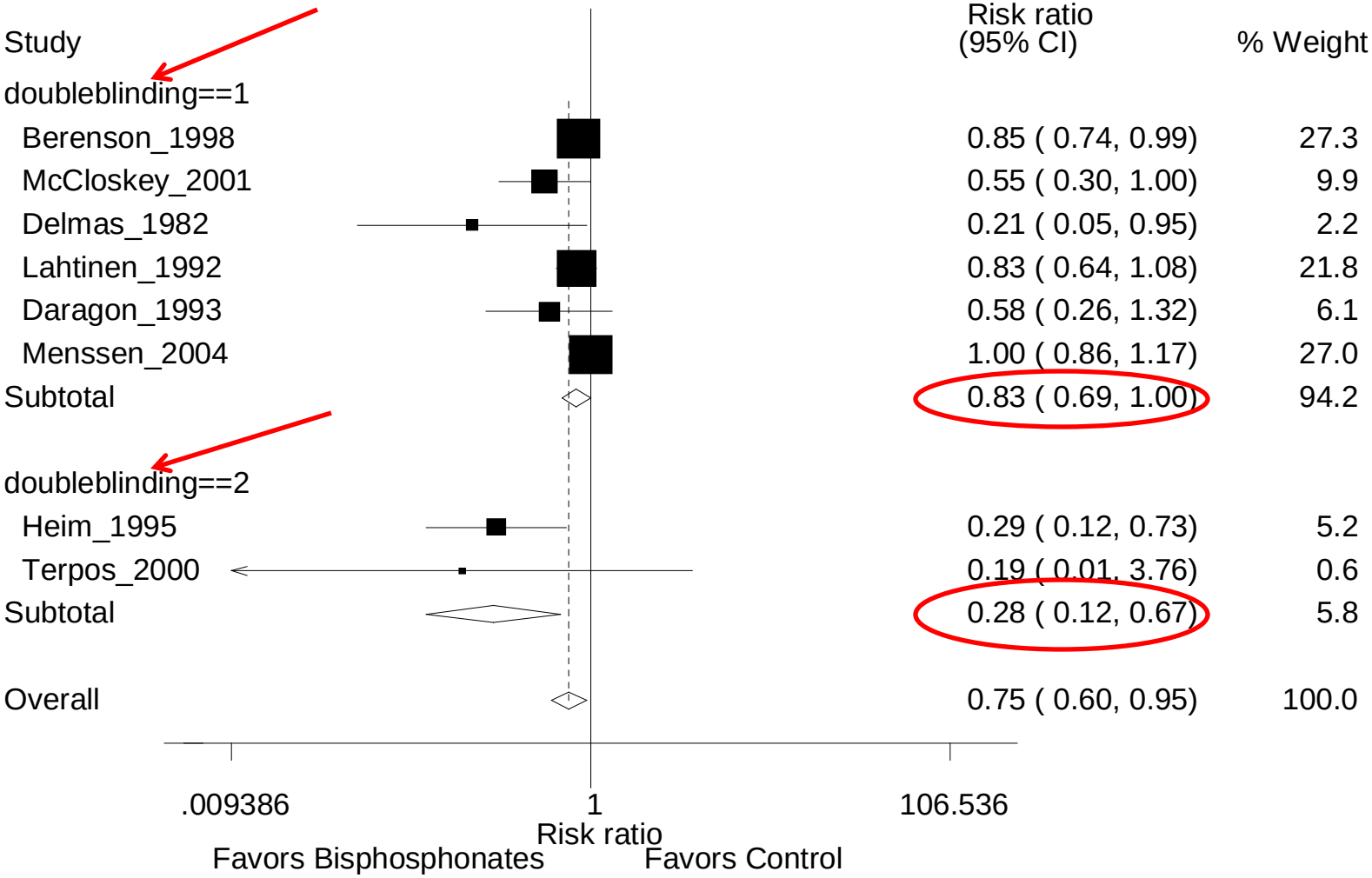
Blinding and pain assesment



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-

What is the overall result of the review?

- Is there a clinical bottom-line?
- What is it?
- What is the numerical result?

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.

- Authors conclusions in the abstract !
- Also look for the summary of finding table in the review text.

How precise are the results?

- Is there a confidence interval?

Look at:

- the forest plots and
- the results section for confidence intervals and
- other details such as test of heterogeneity and
- test of interaction for sub-group analysis.

Can I use the results to help my patient?

- Is this patient so different from those in the trial that the results don't apply?

Look at the characteristics of included studies and the inclusion criteria tables for details regarding patients in the RCTs that were included in the systematic review.

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

Should I apply the results to my patient?

- How great would the benefit of therapy be for this particular patient?
- Is the intervention consistent with my patient's values and preferences?
- Were all the clinically important outcomes considered?
- Are the benefits worth the harms and costs?

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Questions?

Hands on critical appraisal of a systematic review.

Case

- A 49 years old male patient suffering from multiple myeloma (MM) visits your clinic. He is being treated for MM and is an ideal candidate for receiving Autologous Hematopoietic Cell Transplantation (AHCT).
- You want to know whether single versus tandem AHCT is the right choice of treatment for this patient.
- You search the literature and found a systematic review !

Thank you.