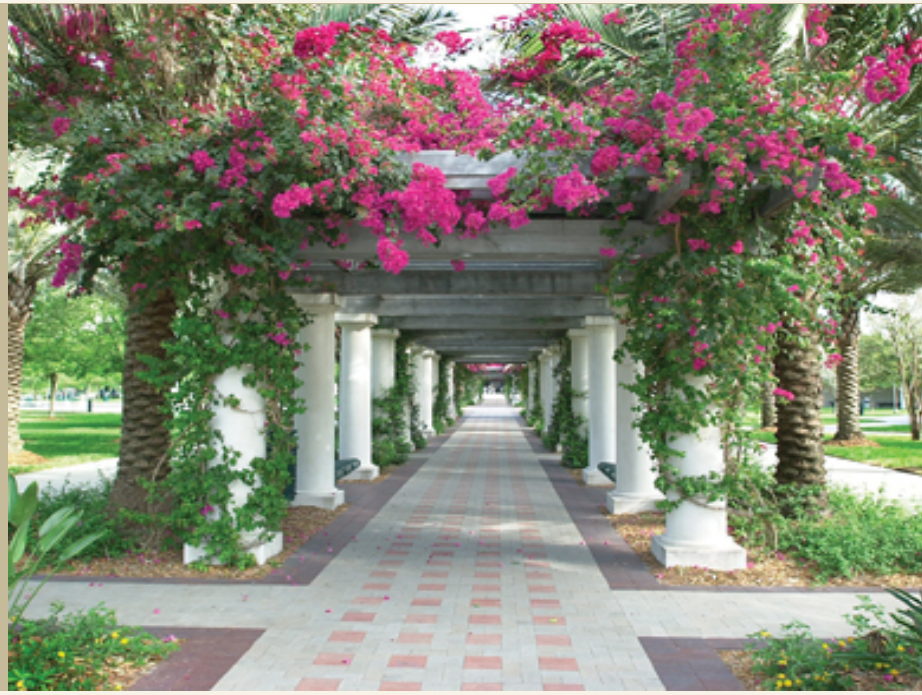
Systematic review and Meta analysis in Healthcare



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UNIVERSITY OF SOUTH FLORIDA

Outline

- Introduction
- Systematic review vs. narrative review
- The rationale for conducting a systematic review
- Steps of a systematic review

Case

A 60 year old woman 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?

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The (conflicting) evidence !

- Randomized controlled trial 1:
  - Bisphosphonates reduce the number of vertebral fractures in patients with multiple myeloma

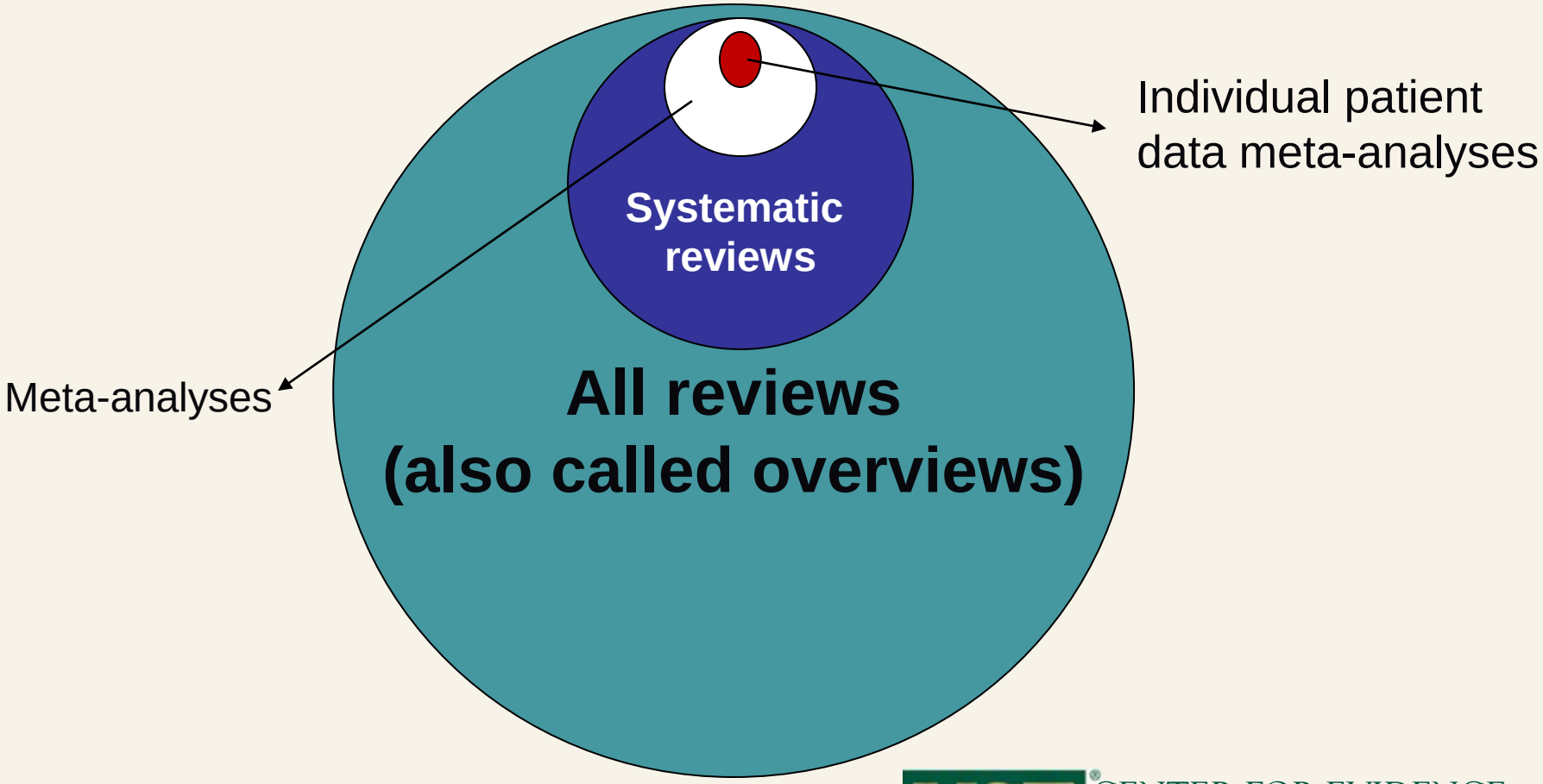
- Randomized controlled trial 2:
  - Bisphosphonates have no effect on vertebral fractures and in fact bisphosphonates can lead to osteonecrosis of jaw (ONJ).

The need for research synthesis

- Health care decision makers need to access research evidence to make informed decisions for both individual patients and populations.

- There are only few important questions in health care which can be informed by consulting the result of **a single** empirical study.

Types of review articles



Are all reviews equal?

- In 1987, researchers examined 50 review articles published in 4 major general medical journals [Annals of Internal Med; Archives of Internal Med; JAMA; New Engl J Med]
- Findings:
  - 80% addressed a focused review question
  - 2% described the method of locating evidence
  - 2% used explicit criteria for selecting studies for inclusion
  - 2% assessed the quality of the primary studies
  - 6% performed a quantitative analysis

Mulrow C. The medical review article: state of the science. Annals Int Med 1987;106:485-88.

Are all reviews equal?

- In 1999, the survey was repeated.
- This time 158 reviews published in 6 major general medical journals [Annals of Internal Med; JAMA; New Engl J Med; BMJ; Am J Med; J of Int Med]
- Findings:
  - 34% addressed a focused review question
  - 28% described the method of locating evidence
  - 14% used explicit criteria for selecting studies for inclusion
  - 9% assessed the quality of the primary studies
  - 21% performed a quantitative analysis

McAlister et al. The medical review article revisited: has the science improved? Annals Int Med 1999;131:947-51

Systematic vs. narrative reviews

Core Feature	Narrative Review	Systematic Review
Study question	Often broad in scope	Often a focused clinical question
Data sources and search strategy	Which databases were searched and search strategy are not typically provided	Comprehensive search of many databases as well as so-called gray literature; explicit search strategy
Selection of articles for study	Not usually specified, potentially biased	Criterion-based selection, uniformly applied
Article review or appraisal	Variable, depending on who is conducting the review	Rigorous critical appraisal, typically using a data extraction form
Study quality	If assessed, may not use formal quality assessment	Some assessment of quality is almost always included as part of the data extraction process
Synthesis	Often a qualitative summary	Quantitative summary (meta-analysis) if the data can be appropriately pooled; qualitative otherwise
Inferences	Sometimes evidence-based	Usually evidence-based

Courtesy: Dr. Djulbegovic

Research synthesis: systematic review and meta analysis

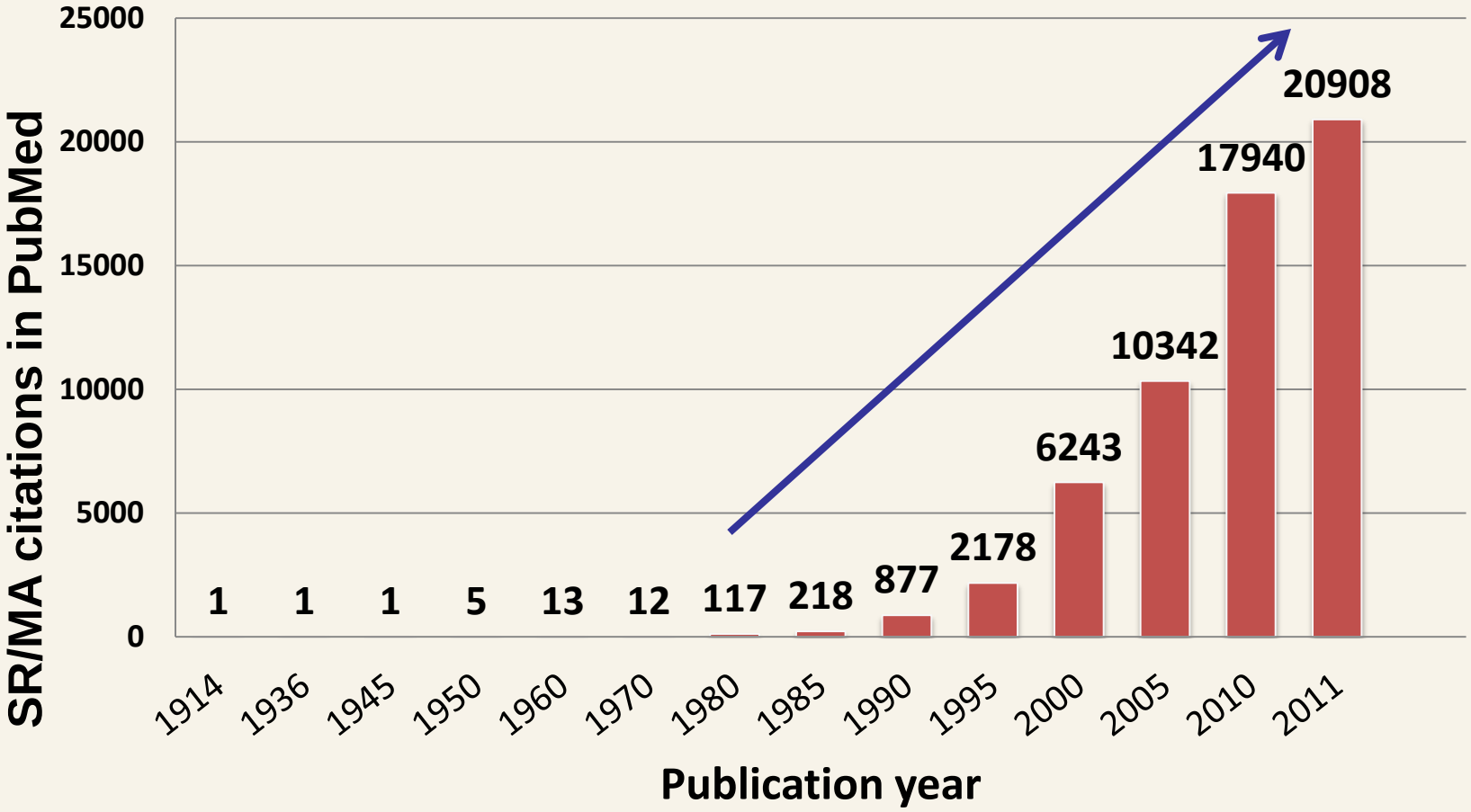
- Systematic Review (SR)
  - "The application of strategies that limit bias in the **assembly**, **critical appraisal**, and **synthesis** of **all** relevant studies on a specific topic. Meta-analysis may be, but is not necessary, used as part of this process.“

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

Courtesy: Dr. Djulbegovic

Last JM. Dictionary of Epidemiology, 2001

The rise of SR/MA



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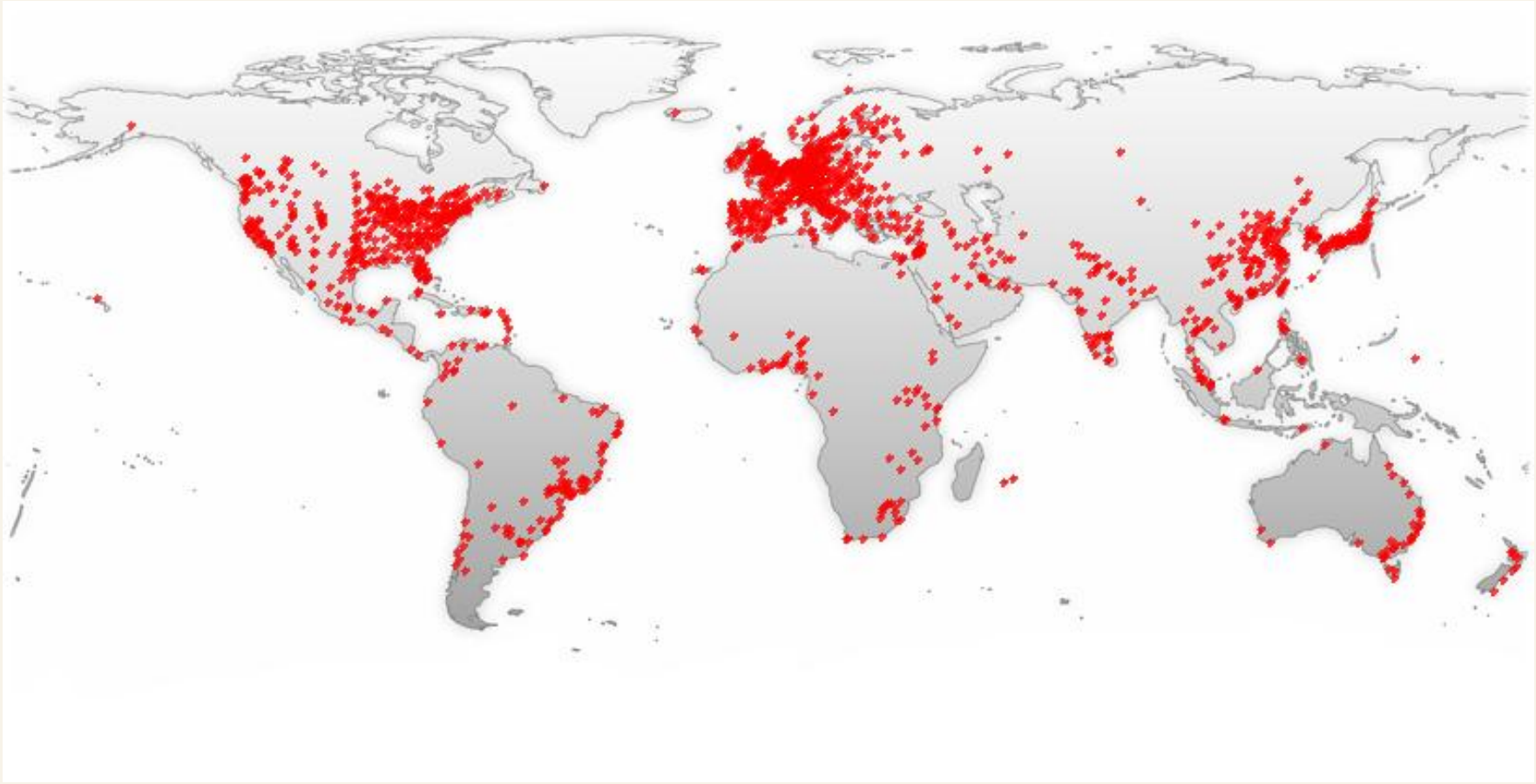
SR/MA publications in 2012: World



Ethical and (regulatory) obligations

- Clinical trials should be preceded by a systematic review and should be reported with a discussion of assessing the trial's results in the context what is already known
  - Ethical requirement for updating systematic reviews

JAMA 1998;280:280-282;Lancet 2001:358:1648

- Mandating search or conduct of SR before a new clinical trial is done
  - Required in UK, Denmark, Holland
  - Peer-reviewed high impact journals require discussion of current findings in the context of a SR. (Lancet, JAMA etc.)

Chalmers I. Clin Trials 2005;2:229-31;
Young C, Horton R. Lancet 2005;366:107-8

Courtesy: Dr. Djulbegovic

Case studies: rationale for SR/MA

Case Study 1: “Egg on their faces: the story of human albumin solution”*

- Human albumin solution, a blood product, has been used in the treatment of blood loss and burns since the attack on Pearl Harbour over half a century ago.
- In 1996, the global albumin market was worth $ 1.5 billon

- <u>But is human albumin administration beneficial?</u>

*1. Roberts I, et al. Egg on their faces. The story of human albumin solution. Eval Health Prof. 2002;25(1):130-8.
2. Cochrane Injuries Group Albumin Reviewers. Human albumin administration in critically ill patients: systematic review of randomised controlled trials. BMJ 1998;317:235-40.

Courtesy: Dr. Pai

“Egg on their faces: the story of human albumin solution”

- SR of RCTs comparing albumin with crystalloid was conducted by the Cochrane Injuries Group.
- 30 RCTs including 1,419 randomised patients identified.

- Meta-analysis showed that the risk of death among those treated with albumin was higher than in the comparison groups.
- The pooled risk ratio was 1.68 (95% CI 1.26, 2.23)

Roberts I, et al. Egg on their faces. The story of human albumin solution. Eval Health Prof. 2002;25(1):130-8.

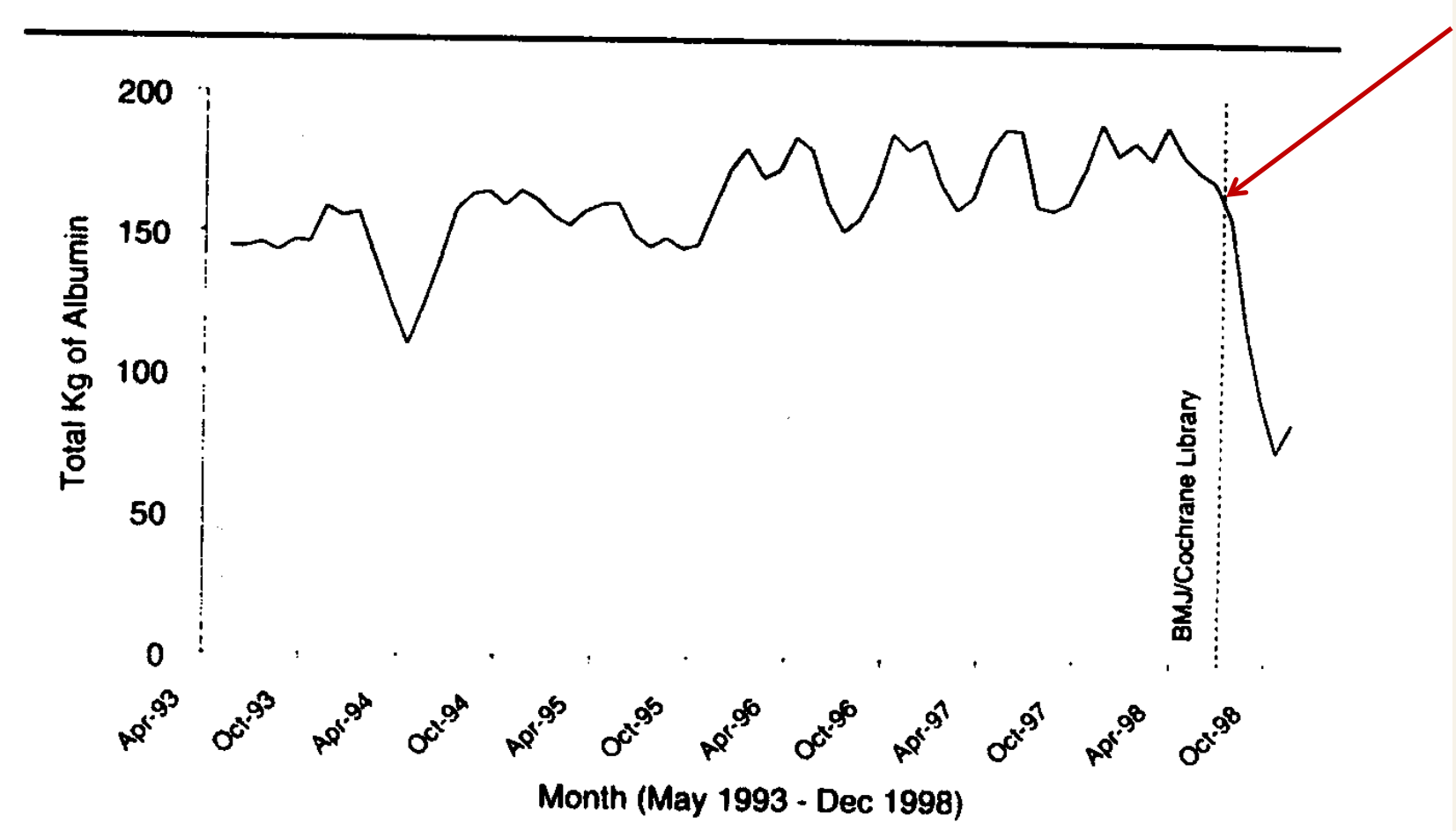
“Egg on their faces: the story of human albumin solution”

- The results were widely reported in the media and stimulated an immediate response from the regulatory agencies, the industry and the medical profession.
- The industry launched a “Albumin Support Programme” to resuscitate the ailing $ 1.5 billion global albumin market.

  The objective was to disseminate evidence supporting albumin:
  - the preparation of literature reviews supporting the use of albumin to be sent to leading regulatory authorities
  - preparation and dissemination of a Cochrane critique dossier
  - the establishment of a medical advisory panel to write articles supporting the use of albumin.
- The industry set aside $2.2 million for the program.

Roberts I, et al. Egg on their faces. The story of human albumin solution. Eval Health Prof. 2002;25(1):130-8.

“Egg on their faces: the story of human albumin solution”



Roberts I, et al. Egg on their faces. The story of human albumin solution. Eval Health Prof. 2002;25(1):130-8.

Case study 2: “Is passive smoking harmful?”

- A topic of great debate and controversy for many years
- First few epidemiologic studies were published in **1918**
- Vigorously attacked by the tobacco industry
  - Too small an association
  - Potential bias
  - Potential confounding
  - Lack of biological proof
- Evidence accumulated over the **next 2 decades**
- It was not until about 15 years ago when several official bodies/agencies concluded that passive smoking is a cause of lung cancer
  - *The tobacco industry continues to dispute this claim!!*

Hackshaw AK et al. BMJ 1997;315:980-88.
Hackshaw AK. Stat Meth Med Res 1998;7:119-136.

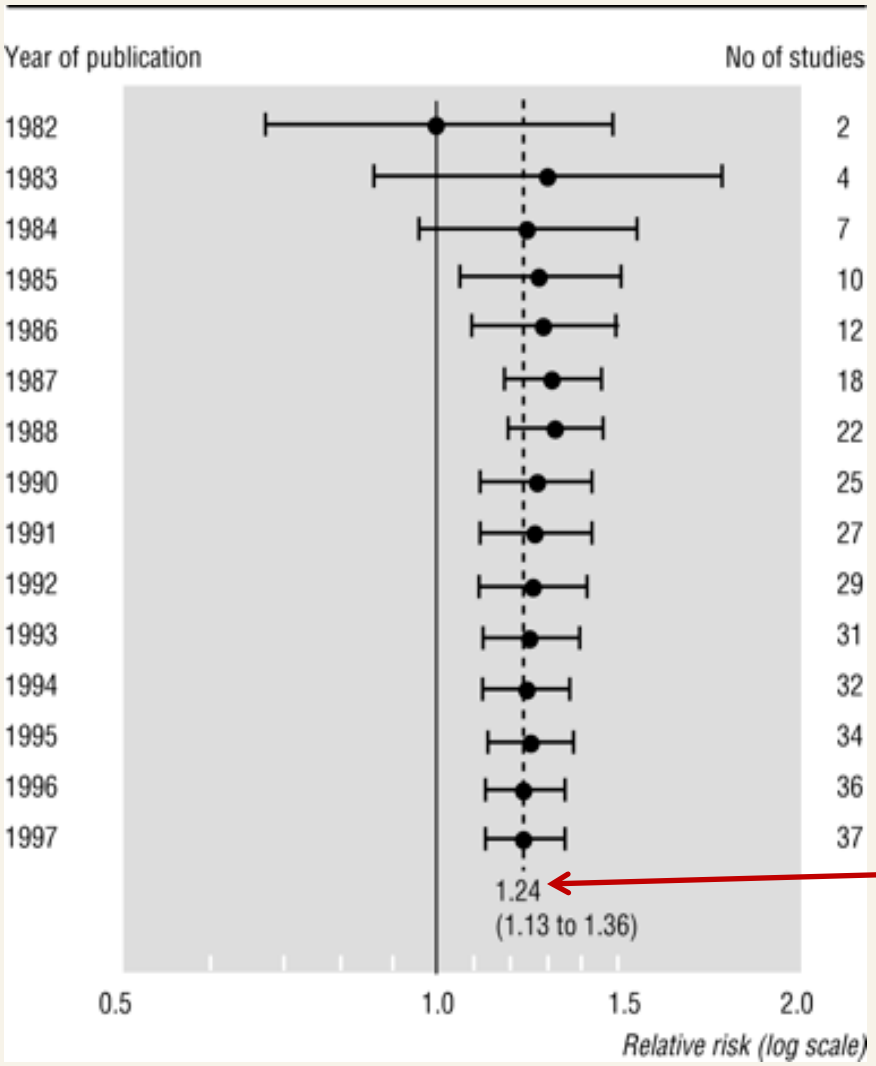
 Courtesy: Dr. Pai

“Is passive smoking harmful?”

- Hackshaw et al. conducted a SR in 1997:
  - They identified 37 published studies that reported risk of lung cancer among lifelong non-smoking women according to the husband’s smoking status
  - Their meta-analysis revealed that the overall risk of lung cancer among lifelong non-smoking women was 1.24 times higher when their husbands smoked, as compared to those women whose husbands did not smoke.

Hackshaw AK et al. BMJ 1997;315:980-88.
Hackshaw AK. Stat Meth Med Res 1998;7:119-136.

“Is passive smoking harmful?”



Yes it is !

Hackshaw AK et al. BMJ 1997;315:980-88.
Hackshaw AK. Stat Meth Med Res 1998;7:119-136.

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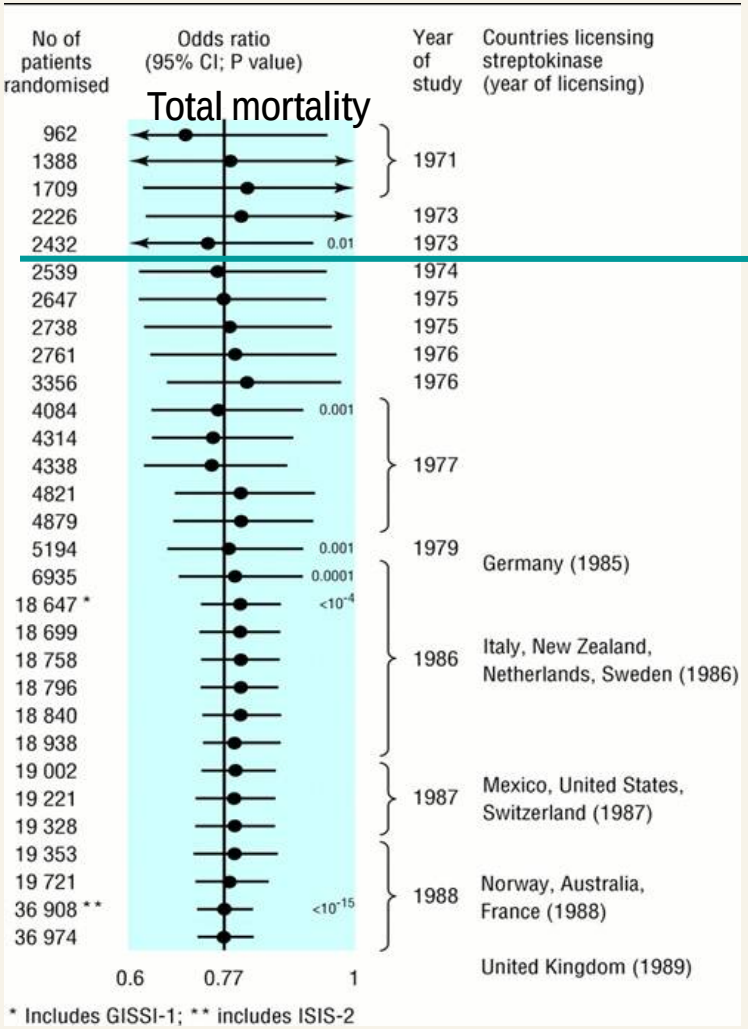
Case study 3:Streptokinase in acute myocardial infarction



Licensing would have been possible in 1973

More than 17,000 patients were treated in placebo arms from 1974 to 1988.

Streptokinase reduced mortality by 20%.

Avoidable deaths approx. 1000 patients

Egger M, BMJ 1997; 15:1371
Lau et al., NEJM 1992; 327: 248

Courtesy of Dr. Djulbegovic

Steps of SR/MA

Steps of a systematic review

Research protocol

- Formulating a research question
- Search of relevant literature
- Data extraction and quality appraisal
- Synthesis (+ / - meta analysis)
- Interpretation

Protocol

Cochrane Library

- Type of SR: Intervention / diagnostic etc.
- Title
- Authors
- Background
- Objectives (research question in PICO format)
- Methods
- Criteria for considering studies for this review
  - Types of studies
  - Types of participants
  - Types of interventions
  - Types of outcome measures
- Search methods for identification of studies
- Data collection and analysis
  - Data extraction and assessment of methodological quality
- Data synthesis (meta analysis)
  - Sensitivity analysis
- Contributions of authors
- Declarations of interest

Research question

- **P**atients: patients diagnosed with multiple myeloma
- **I**ntervention: bisphsophonates
- **C**ontrol: placebo / no treatment / other bisphosphonates
- **O**utcomes: vertebral and non vertebral fractures

Search for the evidence !

Literature search

Talk to the Librarian (John). He is a very helpful guy ☺

- Electronic databases: Medline, Cochrane library, Embase, Lilacs etc.
- Meeting abstracts: ASH, ASCO etc.
- Web: WWW.clinicaltrials.gov

(((“MultipleMyeloma”[Mesh]OR“Plasmacytoma”[Mesh]ORmultiplemyelomaOR plasmacytomaOR plasmacytom*ORmyelom*)

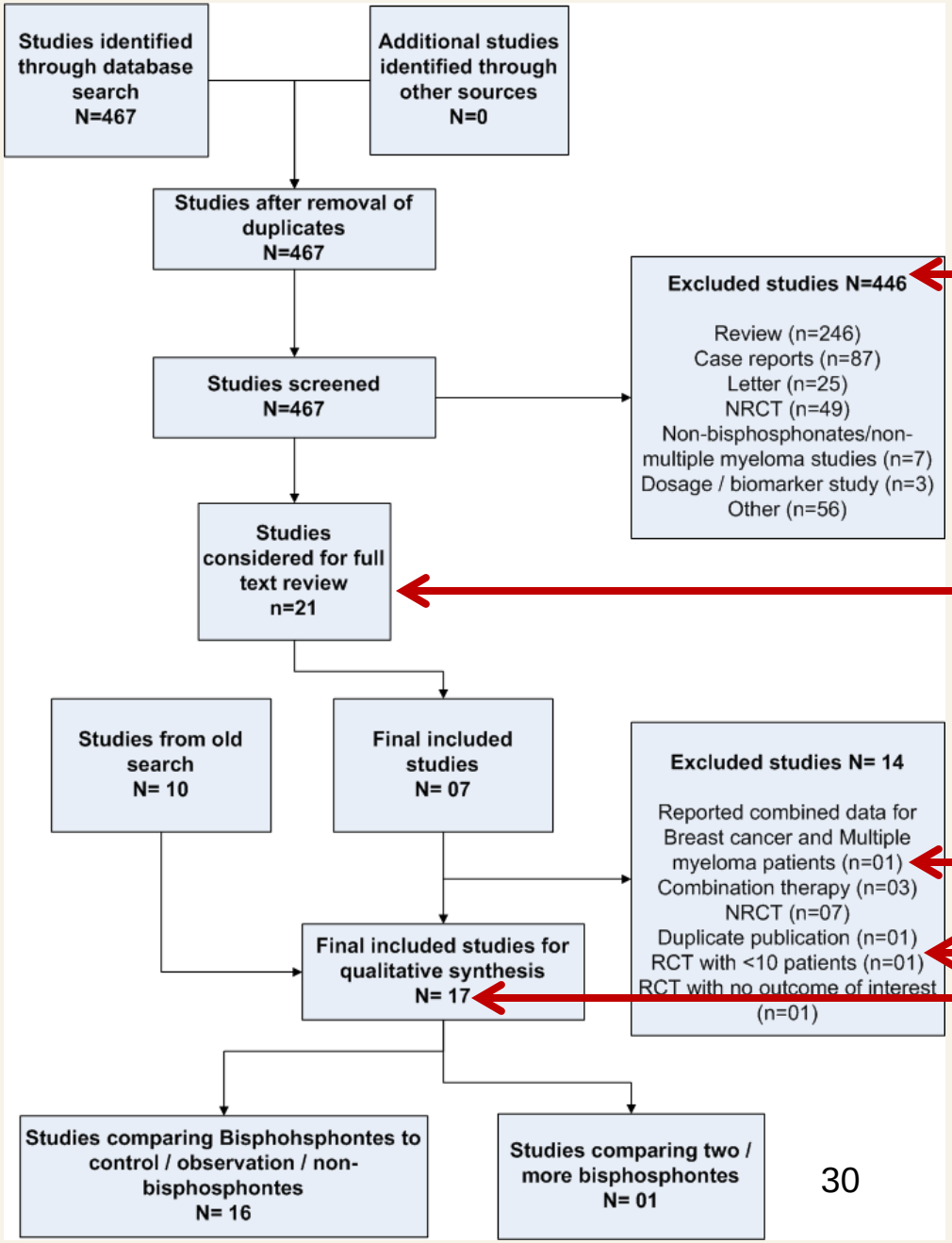
AND(bisphosphonatesOR pamidronate OR zoledronateOR etidronateOR ibandronate OR clodronateOR “Clodronic Acid”[Mesh]

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])

Inclusion and exclusion criteria

- Included studies: RCTs in which interventions consist of bisphosphonates against placebo or no treatment or other bisphosphonates in multiple myeloma patients.

- Excluded studies: Duplicate reports, sub group analysis and studies with fewer than 10 patients.


Studies identified through database search N=467
Additional studies identified through other sources N=0
Studies after removal of duplicates N=467
Studies screened N=467
Excluded studies N=446
Review (n=246)
Case reports (n=87)
Letter (n=25)
NRCT (n=49)
Non-bisphosphonates/non-multiple myeloma studies (n=7)
Dosage / biomarker study (n=3)
Other (n=56)
Studies considered for full text review n=21
Studies from old search N= 10
Final included studies N= 07
Excluded studies N= 14
Reported combined data for Breast cancer and Multiple myeloma patients (n=01)
Combination therapy (n=03)
NRCT (n=07)
Duplicate publication (n=01)
RCT with <10 patients (n=01)
RCT with no outcome of interest (n=01)
Final included studies for qualitative synthesis N= 17
Studies comparing Bisphohsphontes to control / observation / non-bisphosphontes N= 16
Studies comparing two / more bisphosphontes N= 01

Data extraction

- Define the outcomes *a priori*:
  - 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)
- Two review authors will extract all data, and resolve disagreements by consensus.
- After the extraction, a third review author will re-check all data.

Methodological quality assessment

- Risk of bias
- Random error

Which clinical studies are (less) biased?

1. All studies published in BMJ, Lancet, JAMA or NEJM
2. All publicly funded studies
3. All studies with more than 100 patients
4. All registered studies
5. Don’t know

Was it a fair race? Critical appraisal

Fair start?

Generation of sequence

Allocation concealment

Pre-specification of alpha and beta error

Few drop outs?

Description of drop-outs

ITT analysis

Fair finish?

ITT analysis

Outcome reporting bias?

Methodological quality of the included studies

Quality assessment tool for RCTs

- 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

Newcastle Ottawa scale for observational studies

The Good The Bad The Ugly (studies)

- We need to include ALL the studies that fulfill the *a priori* set inclusion criteria. Then:
- Conduct a critical appraisal of ALL the included studies.
- <u>We do not pick and choose..</u>

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Data extraction contd.

Method of generation of randomization sequence is considered to be:

- Adequate: if computer generation or table of random number was used;
- Unclear: not reported, or,
- Inadequate: e.g., quasi-randomized.

Allocation Concealment is considered to be:

- Adequate: if central randomization, sealed envelopes, or a code provided by a pharmacy or a company was described in the study;
- Unclear: not reported, or
- Inadequate: e.g., open table of random numbers.

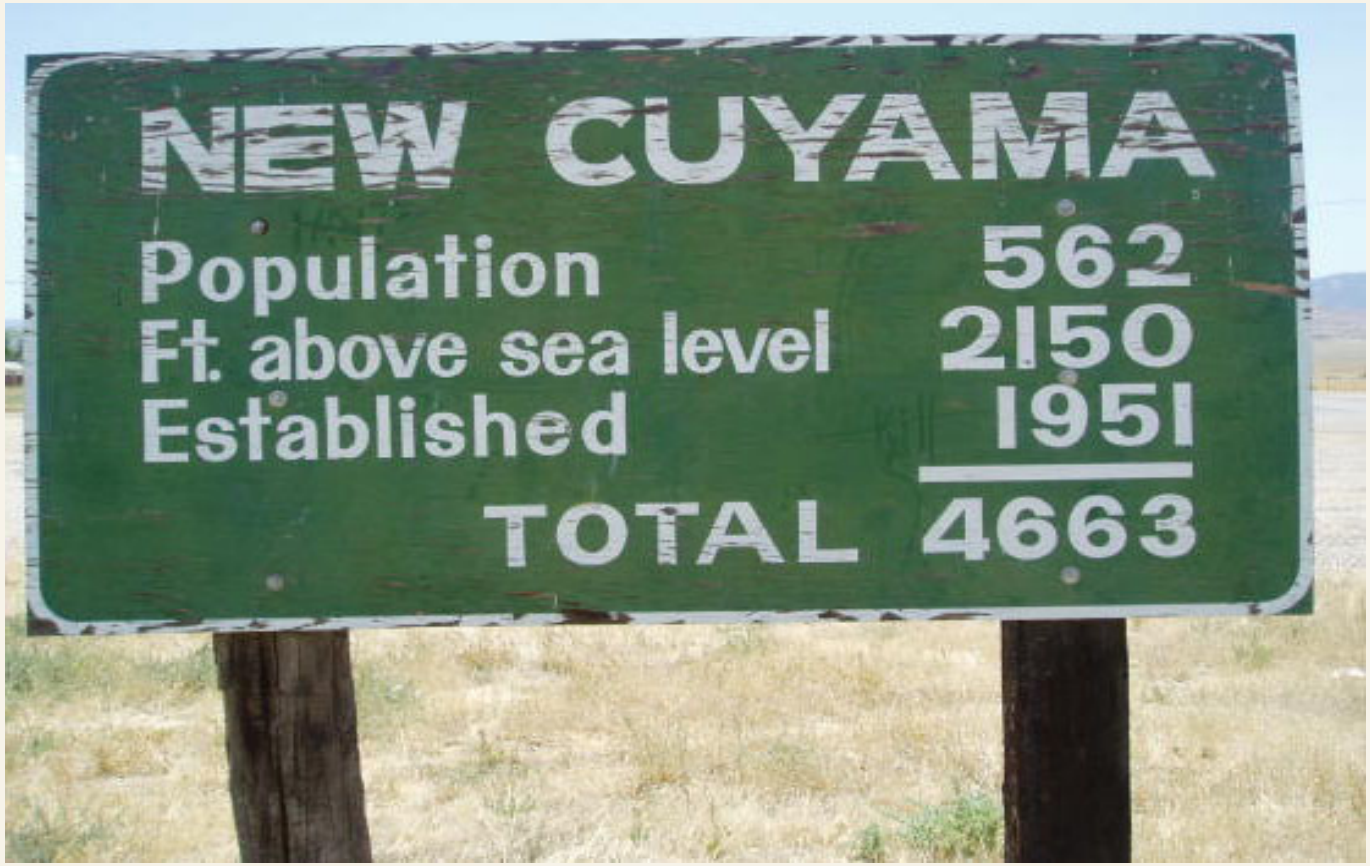
Methodological quality appraisal

	Attal 2006	Aviles 2007	Belch 1991	Berenson 1998	Brincker 1998	Daragon 1993	Delmas 1982	Heim 1995	Kraj 2000	Lahtinen 1992	Leng 2002	McCloskey 2001	Menssen 2002	Musto 2003	Musto 2008	Terpos 2000	Terpos 2003
Allocation concealment?	+		+	+				+				+			+		−
Blinding?		−	+	+								+	+		−		−
Method of allocation Concealment	+	−	+	+	−	−	−	+	−	−	−		−	−	+	−	
Withdrawls and drop outs	+	−	−	+	+	+		+	−	+	−	+	−	+	+	−	
Intention to treat analysis	+	+	−	−	+	−	−	−	−	+		−	+	−	+	+	−
Randomization method	−	−	−	+	−	−	−	−	−		−	−	−	−	+		
Adequacy of randomization method				+											+		

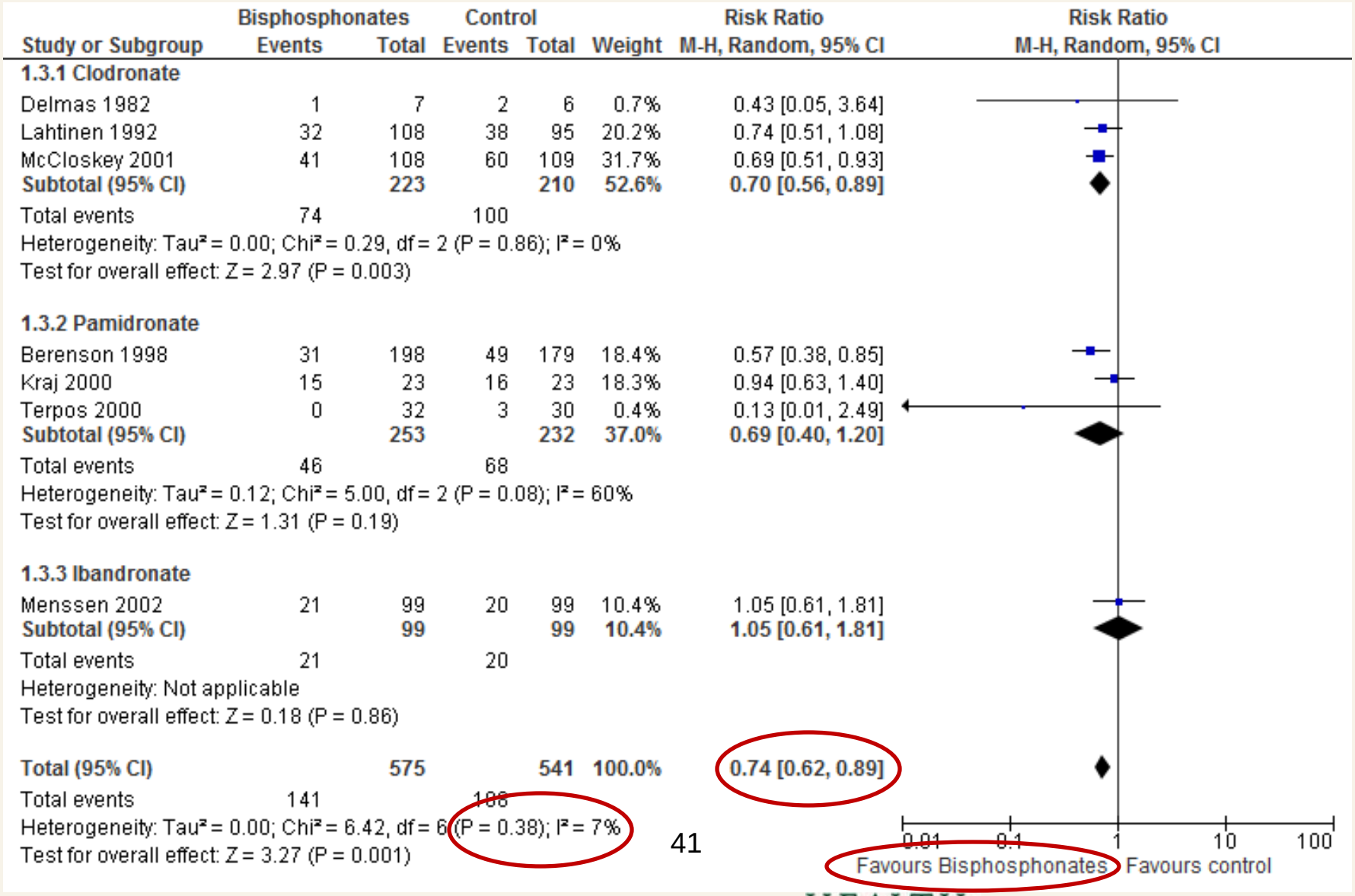
Quantitative data synthesis

Study_id	Inn_Rx	Std_Rx	Event Inn	Noevent Inn	Enrolled Inn	Event Std	Noevent Std	Enrolled Std	LnRiskRatio	SeLnRR
Delmas_1982	Clodronate	Placebo	1	6	7	2	4	6	-0.84729792	1.091089
Lahtinen_1992	Clodronate	Placebo	32	76	108	38	57	95	-0.30010464	0.1943713
McCloskey_2001	Clodronate	Placebo	41	67	108	60	49	109	-0.37155583	0.1504106
Menssen_ 2002	Ibandronate	Placebo	21	78	99	20	79	99	0.04879016	0.2782392
Kraj_2000	Pamidronate	No_RX	15	8	23	16	7	23	-0.06453852	0.2054511
Terpos_2000	Pamidronate	No_RX	0	32	32	3	27	30	-2.00843076	1.491024
Berenson_1998	Pamidronate	Placebo	31	167	198	49	130	179	-0.55871436	0.2050101

Meta analysis is not simple addition !



Meta analysis



Study or Subgroup	Bisphosphonates Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 Clodronate						
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]
Subtotal (95% CI)		**223**		**210**	**52.6%**	**0.70 [0.56, 0.89]**
Total events	74		100			
Heterogeneity: Tau² = 0.00; Chi² = 0.29, df = 2 (P = 0.86); I² = 0%						
Test for overall effect: Z = 2.97 (P = 0.003)						
1.3.2 Pamidronate						
Berenson 1998	31	198	49	179	18.4%	0.57 [0.38, 0.85]
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)		**253**		**232**	**37.0%**	**0.69 [0.40, 1.20]**
Total events	46		68			
Heterogeneity: Tau² = 0.12; Chi² = 5.00, df = 2 (P = 0.08); I² = 60%						
Test for overall effect: Z = 1.31 (P = 0.19)						
1.3.3 Ibandronate						
Menssen 2002	21	99	20	99	10.4%	1.05 [0.61, 1.81]
Subtotal (95% CI)		**99**		**99**	**10.4%**	**1.05 [0.61, 1.81]**
Total events	21		20			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.18 (P = 0.86)						
Total (95% CI)		**575**		**541**	**100.0%**	**0.74 [0.62, 0.89]**
Total events	141		186			
Heterogeneity: Tau² = 0.00; Chi² = 6.42, df = 6 (P = 0.38); I² = 7%						
Test for overall effect: Z = 3.27 (P = 0.001)						

Key statistical principles of meta-analysis: two stage process

Remeber: the unit of analysis of a systematic review is an individiual study.

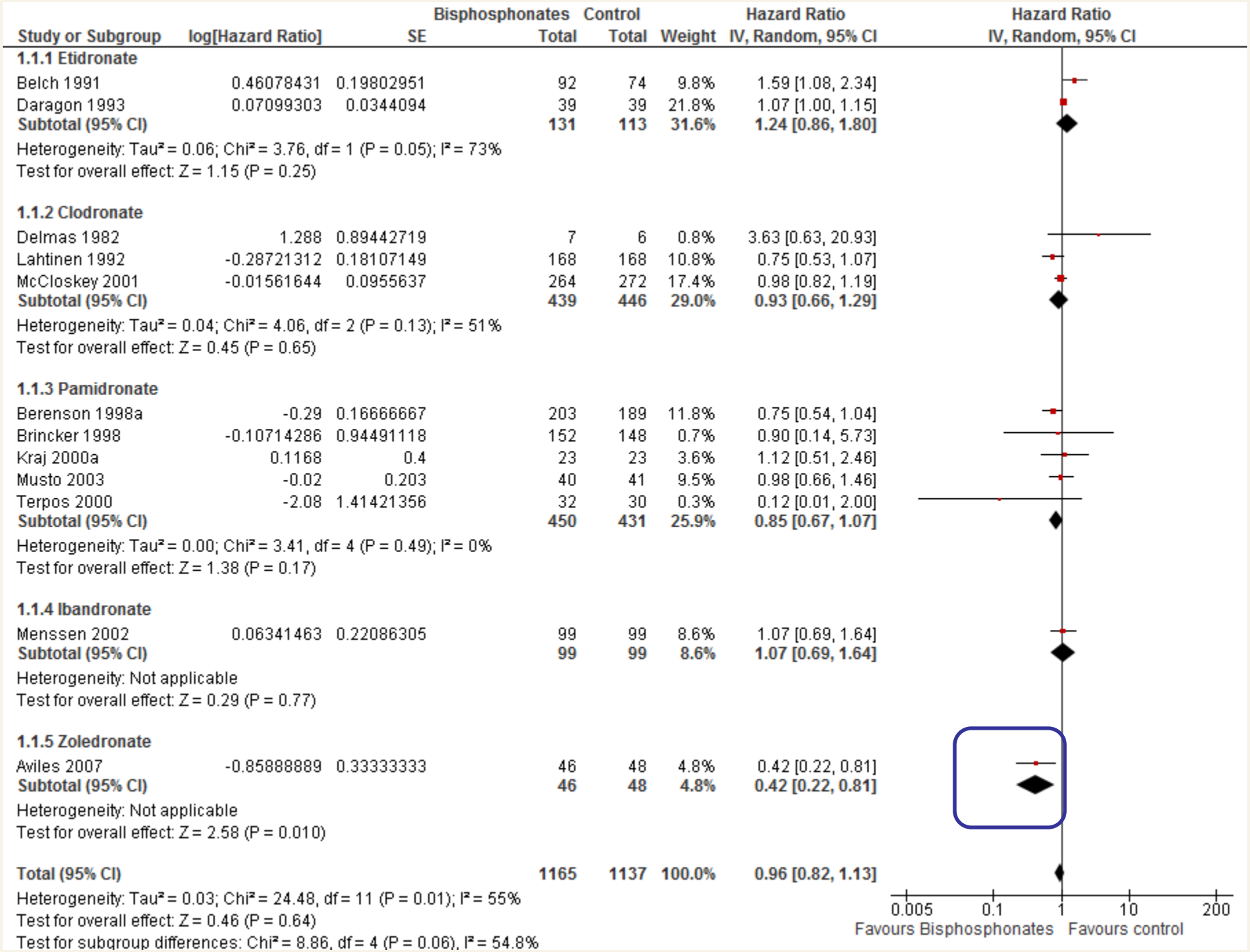
- Patients in one trial are not directly compared with those in another trial
- Each trial is analysed separately
- Summary statistics are calculated for each trial
- These summary statistics are added together in the meta-analysis

Courtesy: Dr. Djulbegovic

Rationale for meta analysis is clinical not statistical

- Similar interventions for similar conditions will produce the similar effects (i.e. in the same direction) in different clinical trials
- While the effect size may not be the same, it will rarely be in the opposite directions
- However, since these are similar studies…there is potential for variation among efficacy estimates. (heterogeneity)
- If there is clinical or statistically significant heterogeneity a meta-analysis may not be valid

Courtesy: Dr. Djulbegovic

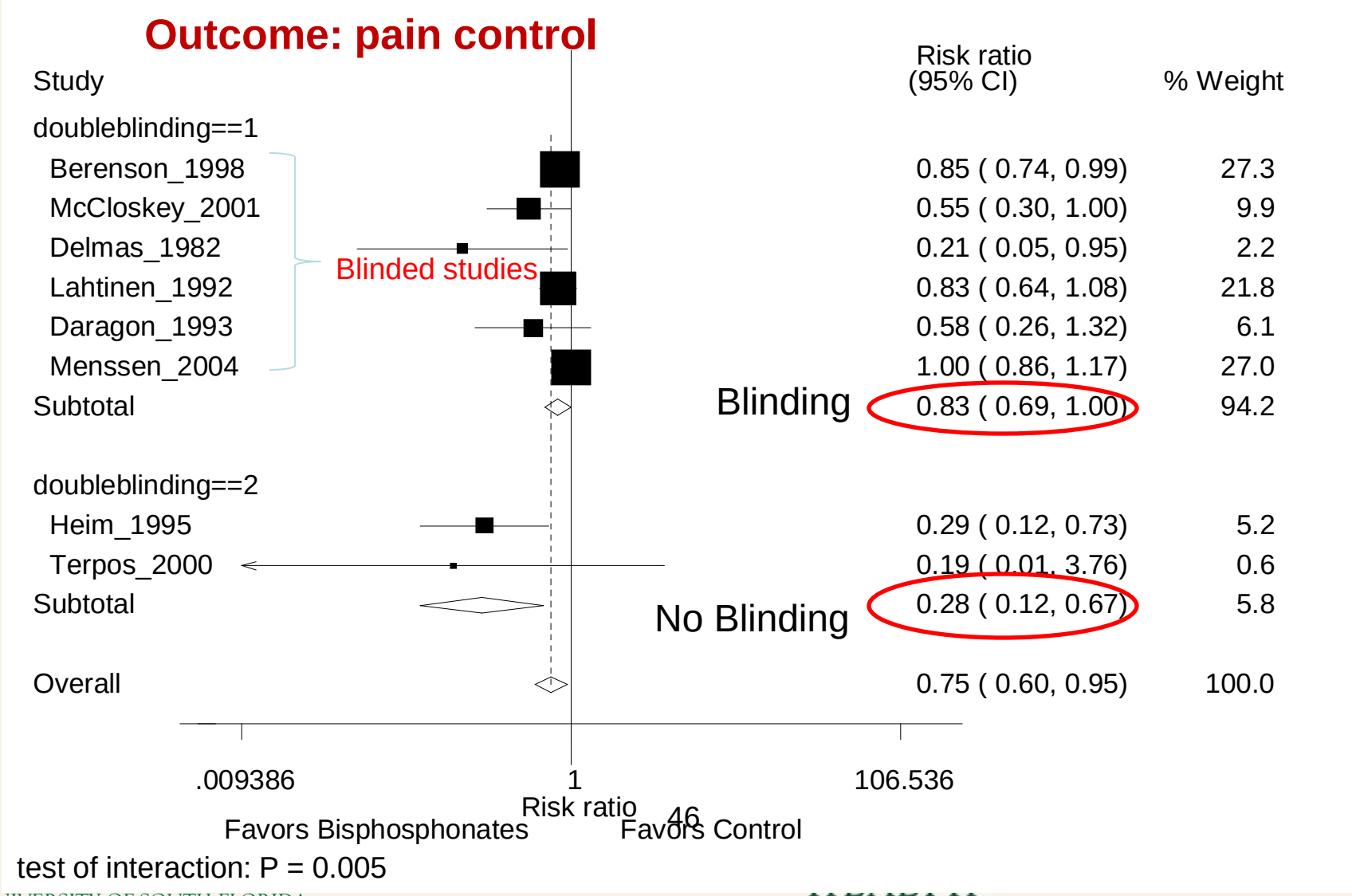

Bisphosphonates
Control
Hazard Ratio
Hazard Ratio
Study or Subgroup
log[Hazard Ratio]
SE
Total
Total
Weight
IV, Random, 95% CI
IV, Random, 95% CI
1.1.1 Etidronate
Belch 1991 0.46078431 0.19802951 92 74 9.8% 1.59 [1.08, 2.34]
Daragon 1993 0.07099303 0.0344094 39 39 21.8% 1.07 [1.00, 1.15]
Subtotal (95% CI) 131 113 31.6% 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)
1.1.2 Clodronate
Delmas 1982 1.288 0.89442719 7 6 0.8% 3.63 [0.63, 20.93]
Lahtinen 1992 -0.28721312 0.18107149 168 168 10.8% 0.75 [0.53, 1.07]
McCloskey 2001 -0.01561644 0.0955637 264 272 17.4% 0.98 [0.82, 1.19]
Subtotal (95% CI) 439 446 29.0% 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)
1.1.3 Pamidronate
Berenson 1998a -0.29 0.16666667 203 189 11.8% 0.75 [0.54, 1.04]
Brincker 1998 -0.10714286 0.94491118 152 148 0.7% 0.90 [0.14, 5.73]
Kraj 2000a 0.1168 0.4 23 23 3.6% 1.12 [0.51, 2.46]
Musto 2003 -0.02 0.203 40 41 9.5% 0.98 [0.66, 1.46]
Terpos 2000 -2.08 1.41421356 32 30 0.3% 0.12 [0.01, 2.00]
Subtotal (95% CI) 450 431 25.9% 0.85 [0.67, 1.07]
Heterogeneity: Tau² = 0.00; Chi² = 3.41, df = 4 (P = 0.49); I² = 0%
Test for overall effect: Z = 1.38 (P = 0.17)
1.1.4 Ibandronate
Menssen 2002 0.06341463 0.22086305 99 99 8.6% 1.07 [0.69, 1.64]
Subtotal (95% CI) 99 99 8.6% 1.07 [0.69, 1.64]
Heterogeneity: Not applicable
Test for overall effect: Z = 0.29 (P = 0.77)
1.1.5 Zoledronate
Aviles 2007 -0.85888889 0.33333333 46 48 4.8% 0.42 [0.22, 0.81]
Subtotal (95% CI) 46 48 4.8% 0.42 [0.22, 0.81]
Heterogeneity: Not applicable
Test for overall effect: Z = 2.58 (P = 0.010)
Total (95% CI) 1165 1137 100.0% 0.96 [0.82, 1.13]
Heterogeneity: Tau² = 0.03; Chi² = 24.48, df = 11 (P = 0.01); I² = 55%
Test for overall effect: Z = 0.46 (P = 0.64)
Test for subgroup differences: Chi² = 8.86, df = 4 (P = 0.06), I² = 54.8%
0.005
0.1
1
10
200
Favours Bisphosphonates
Favours control

Heterogeneity

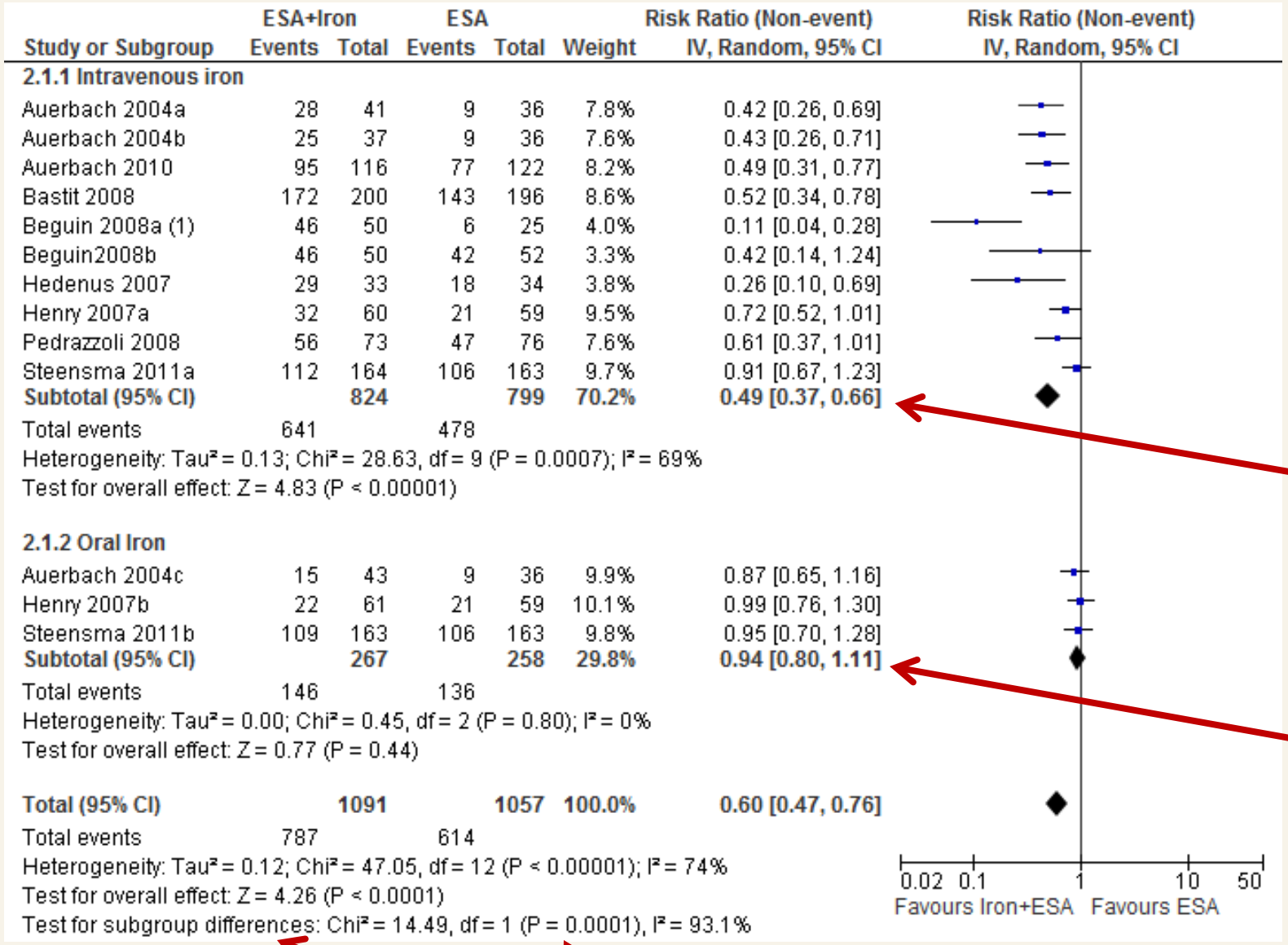
- Heterogeneity = The variability among studies in a systematic review
- May reflect clinical or methodological diversity or both
- How to identify heterogeneity:
  - Graphical: Do the 95%CI overlap poorly?
  - Quantification of inconsistency:
    - I^2 (percentage of variability in effect estimates due to heterogeneity/inconsitency rather than to chance)
      - Values > 50% may be considered to indicate substantial heterogeneity

Courtesy: Dr. Djulbegovic

Sensitivity analysis



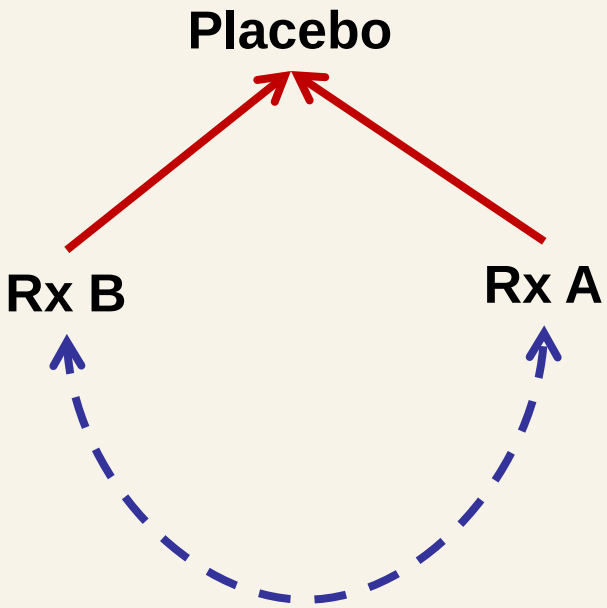
test of interaction: P = 0.005

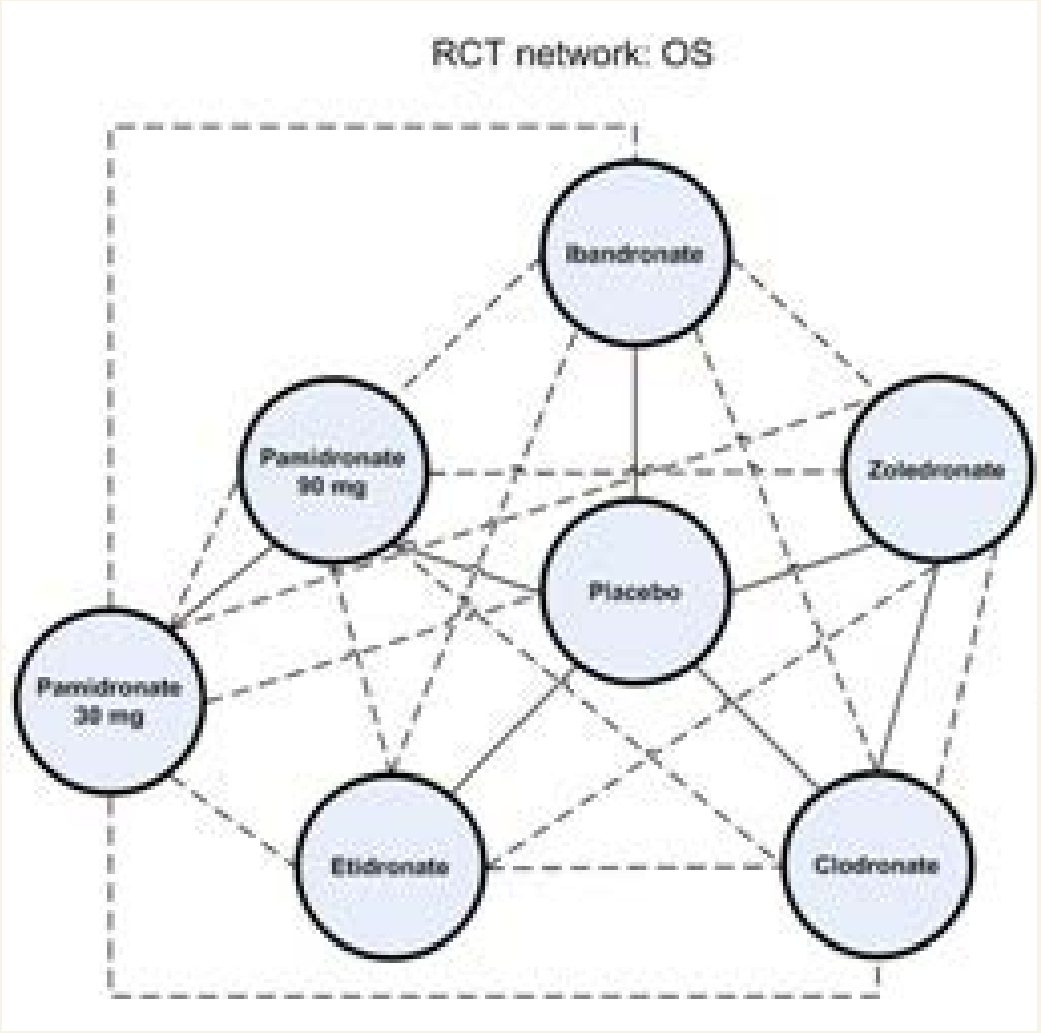


IV Iron

Oral Iron

Network meta analysis





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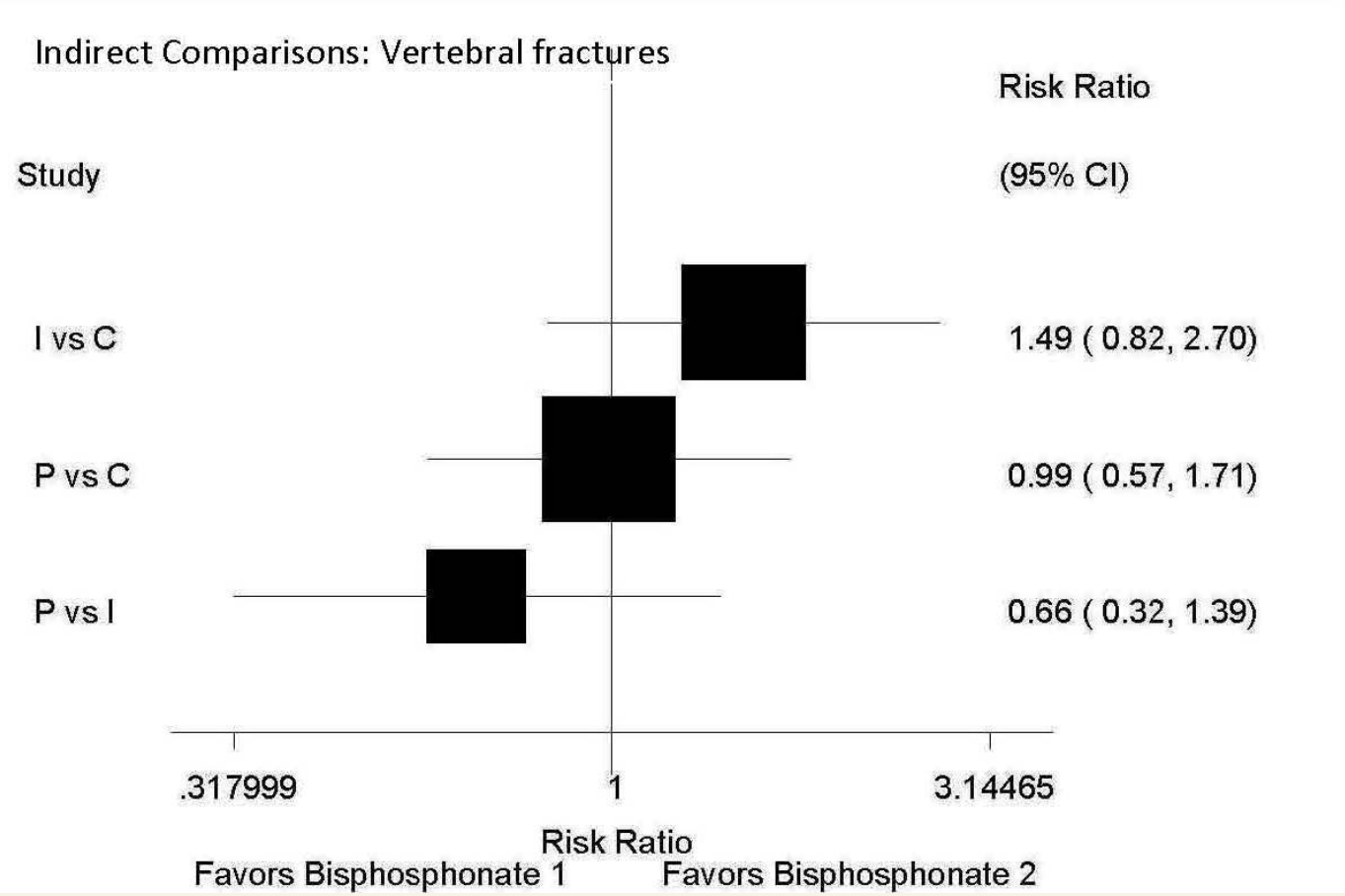
Indirect comparisons



C = Clodronate
P = Pamidronate
I = Ibandronate

Where to look for SR/MA?

- PubMed
- Clinical queries

http://www.ncbi.nlm.nih.gov/pubmed/clinical

- Cochrane Collaboration

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Questions


The latest research shows that we should do something with all this research !

Thank you.

For additional questions:
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