Meta-Analysis (or Overview)

Clinical Scenario

- Mrs BW 64 y.o.
- Hysterectomy
- Dx of osteoporosis (Spinal BMD < 2SD below normal)
- ? aminobisphosphonate (etidronate, alendronate)
- Pt concern: cost

Osteoporosis

- Affects 30-40% of postmenopausal women
- 1.5M fractures annually
- Vertebral fractures most common
- Nonvertebral fractures (esp. hip) major causes of morbidity, mortality, cost
- Risk of hip fracture (50yo white woman): 1/6
- Risk of wrist fracture (50yo white woman): 1/6

Postmenopausal osteoporosis

- Imbalance of bone formation and resorption
- Progressive decline in bone mass, + risk of fracture
- Aminobisphosphonates: potent, specific inhibitor of osteoclast-mediated bone resorption
- Eg: etidronate, alendronate

Alendronate

- + Bone mineral density
  - —But is new bone weaker?
- Mineralization unaffected at therapeutic does
  - —But is there a clinical effect?
- - Vertebral fracture incidence
  - —But most morbidity from hip, wrist
- Does it reduce nonvertebral fractures?

Meta-Analysis is

- A formal method for research synthesis
- A quantitative and potentially more objective alternative to the expert review paper.

Aspirin and MI

- How strong is the effect of aspirin in reducing post-MI mortality?
- Answer: about 10% reduction
- How do we know?
- Many studies “inconclusive”

Finding small effects

Small effects can be important

A 10% reduction is hard to find
(reducing 20% mortality to 18%)

—Without a long, huge (thus expensive) study

How large a study?

Need to have 95% CI narrower than roughly 0.20 ± 0.02

This gives 50-50 chance of detection

Thus, need se(difference) < 0.01

SE(difference of two proportions) =

$$\sqrt{0.8 \times 0.2 \times \left[\frac{1}{n} + \frac{1}{n}\right]}$$

Setting this equal to 0.01 and solving for n we have n 800 in each group

Combine evidence from many studies

- Assess whether there really is any effect
- Estimate the size of the effect

Reasons for doing meta-analysis

- Increase power by increasing sample size (pooling)
- Resolve conflicting reports (consensus)
- Improve estimates of effect size
- Answer new questions

Meta-analysis

- Combines features of multicenter trials and retrospective studies
- Multicenter trials similarities—we are combining studies with
  - Common questions
  - Similar study designs
  - Simultaneous controls within each study unit
- Similarities to retrospective studies
  - Investigators choose which studies to include and exclude
  - Susceptible to selection biases
  - Susceptible to ascertainment biases (Are "negative" studies as likely to be published?)

Alendronate meta-analysis

- Karpf, et al, JAMA (April 9, 1997)
- Five studies
  - RCT
  - Placebo controlled
  - ≥2 yr duration

Meta-analysis Issues

- Were criteria for including and excluding studies clearly defined in advance?
- Were criteria for evaluating the results from studies clearly defined in advance?
- Does the overview use patient-level data?
- How objective was the review?
- Does the overview assess heterogeneity?

How objective was the review?

- Review by more than one reader
- Procedures for resolving disagreements between readers
- Blinded review
- Use of prepared data-extraction forms

Does the overview assess heterogeneity?

- Variation in the validity of the studies being used?
- Homogeneity of the studies regarding study design?
- Homogeneity of the studies with respect to the size of measured effects?
- Possible factors accounting for heterogeneity?

Reader's Guide: All articles

- Are the results valid?
- What were the results?
- Will the results help me in caring for my patients?

Are the results valid?

- Did the review address a focused clinical question?
- Were the criteria used to select articles for inclusion appropriate?
- Secondary guides
  - Is it unlikely that important, relevant studies were missed?
  - Was the validity of the included studies appraised?
  - Were assessments of studies reproducible?
  - Were the results similar from study to study?

What are the results?

- What are the overall results of the review?
- How precise were the results?

Table 3.—Nonvertebral Fracture Rates by Study and Overall

Type of Study	Treatment Group	No.	Cases	Patient-Years at Risk	Rate (per 100 Patient-Years)	Relative Risk Alendronate/ Placebo (95% CI)*
Phase 2b[13]	Placebo	31	3	49.4	6.07	. . .
	Alendronate	93	8	160.9	4.97	0.83 (0.22-3.11)
Primary phase 3[14]						
United States	Placebo	192	21	486.1	4.32	. . .
	Alendronate	286	28	720.1	3.89	0.91 (0.51-1.60)
Multinational	Placebo	205	17	528.9	3.21	. . .
	Alendronate	311	17	804.9	2.11	0.66 (0.34-1.29)
Calcitonin comparison study[15]	Placebo	71	3	128.4	2.34	. . .
	Alendronate	140	2	256.2	0.78	0.34 (0.06-2.02)
Elderly/low-dose study[16]	Placebo	91	16	154.2	10.38	. . .
	Alendronate	182	18	298.2	6.04	0.57 (0.29-1.12)
Combined	Placebo	590	60	1347.0	4.45	. . .
	Alendronate	1012	73	2240.3	3.26	0.71 (0.50-0.99)

*Combined relative risk is based on the Cox proportional hazards model with treatment as a model effect and protocol as a stratification factor, and does not represent an average of the relative risks in the individual studies. Risk reduction (%) = 100 × (1 − relative risk). CI indicates confidence interval.

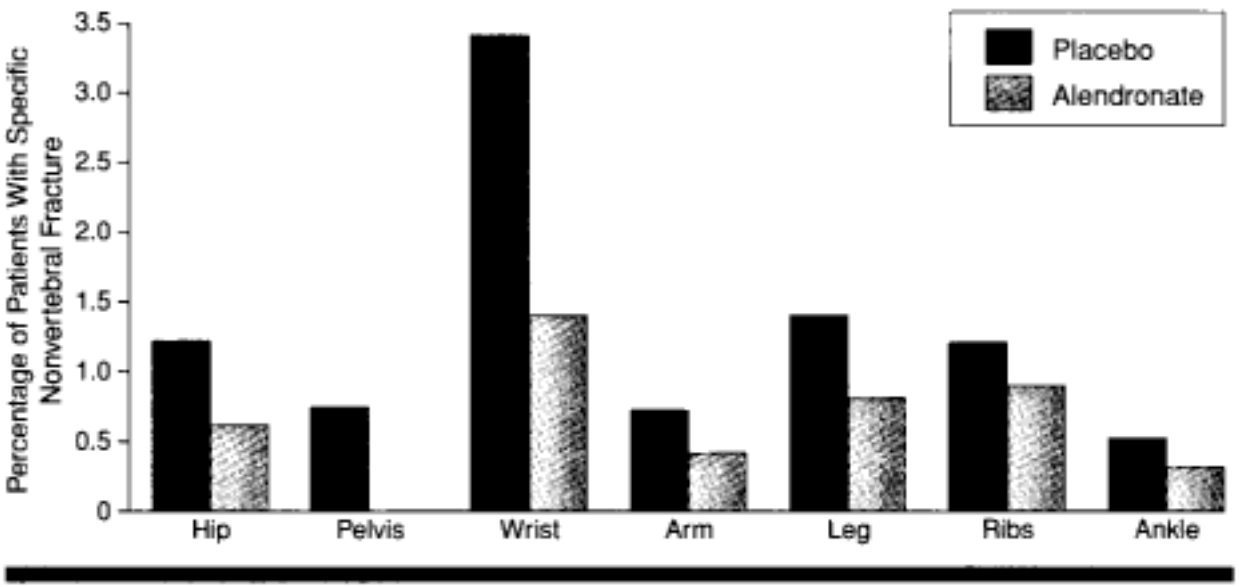

Figure 2.—Percentage of women with specific nonvertebral osteoporotic fractures. "Wrist" includes wrist and proximal forearm; "arm" includes humerus and elbow; and "leg" includes tibia, fibula, and patella.

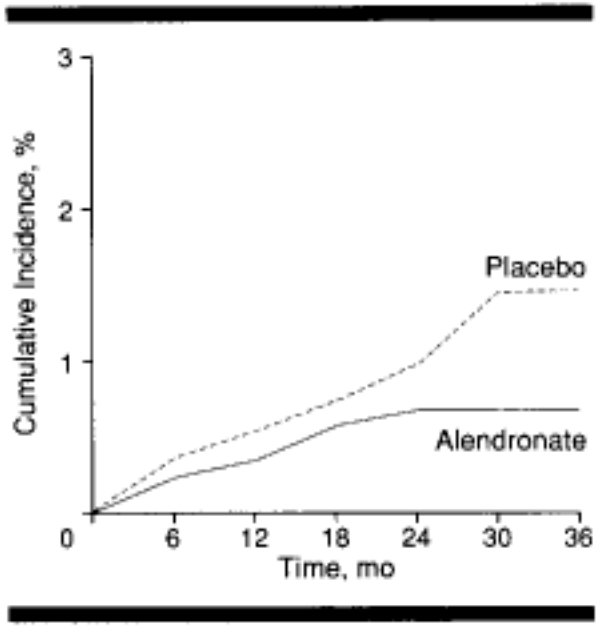

Figure 3.—Cumulative proportion of women with hip fractures. The data were calculated by the life-table method. The data for women on all doses of alendronate higher than 1 mg/d have been pooled.

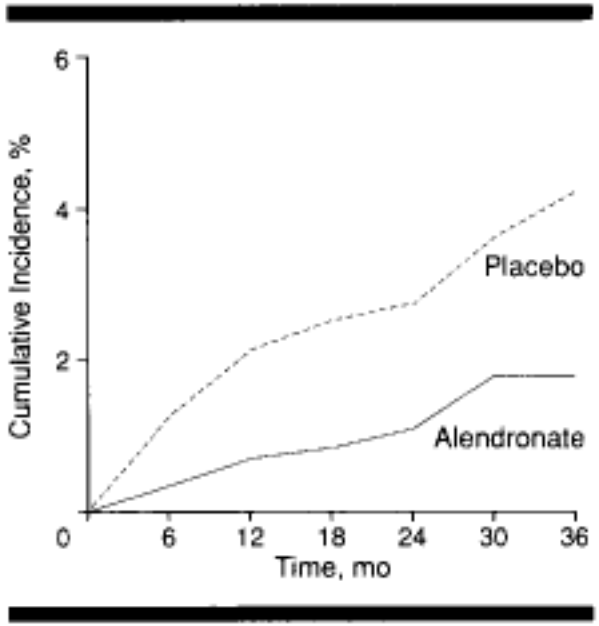

Figure 4.—Cumulative proportion of women with wrist/forearm fractures. The data were calculated by the life-table method. The data for women on all doses of alendronate higher than 1 mg/d have been pooled.

Will the results help me in caring for my patients?

- Can the results be applied in my patient care?
- Were all clinically important outcomes considered?
- Are the benefits worth the harms and costs?