Do meta-analyses of adverse events have adverse effects?

PICOT, Peto and Pitot

Stephen Evans

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Outline

- What is an adverse effect of an AE M-A?
- Where can it go wrong?
- PICOT
- 2 examples
  - with Peto
- Pitot

What is an adverse effect of an AE M-A?

- Getting a wrong or misleading answer
  - Claiming to find an adverse effect wrongly (Type I)
  - Failing to find a real adverse effect (Type II)
- Misleading communication of a correct answer
- Failing to provide the whole picture

Where can it go wrong?

- At all stages of the meta-analysis:
  - Setting the question
  - Design - protocol
  - Execution
  - Analysis
  - Report writing
  - Publication
  - Communication

PICOT

– *Picot stitch in crochet;*

– *Italian grape Nebbiolo in DOCG Barolo wines*

- **P**atient populations - Do they match those treated
- **I**ntervention
- **C**omparison
- **O**utcome
- **T**ime

Example-1

Olanow C, et al. Effect of selegiline on mortality in patients with Parkinson's disease: a meta-analysis. Neurology. 1998;51:825–830.

HR for mortality 1.02 (95% CI 0.44 to 2.37; p = 0.96)
14 deaths

Problem: [**P**]Used young patients & Excluded non-double blind trials: Concluded no increase – wrong?

By far the largest trial was open, used older patients :

HR 1.57 (95% CI 1.07 to 2.30)
76 deaths

Example 2: Nissen

- 42 trials, “randomized comparator group, a similar duration of treatment in all groups, and more than 24 weeks of drug exposure” (and >0 events)
- Compared MIs & CV deaths
  - OR for MI 1.43
  - (95% CI 1.03 to 1.98; P = 0.03)
  - OR for CV death 1.64
  - (0.98 to 2.74; P = 0.06)

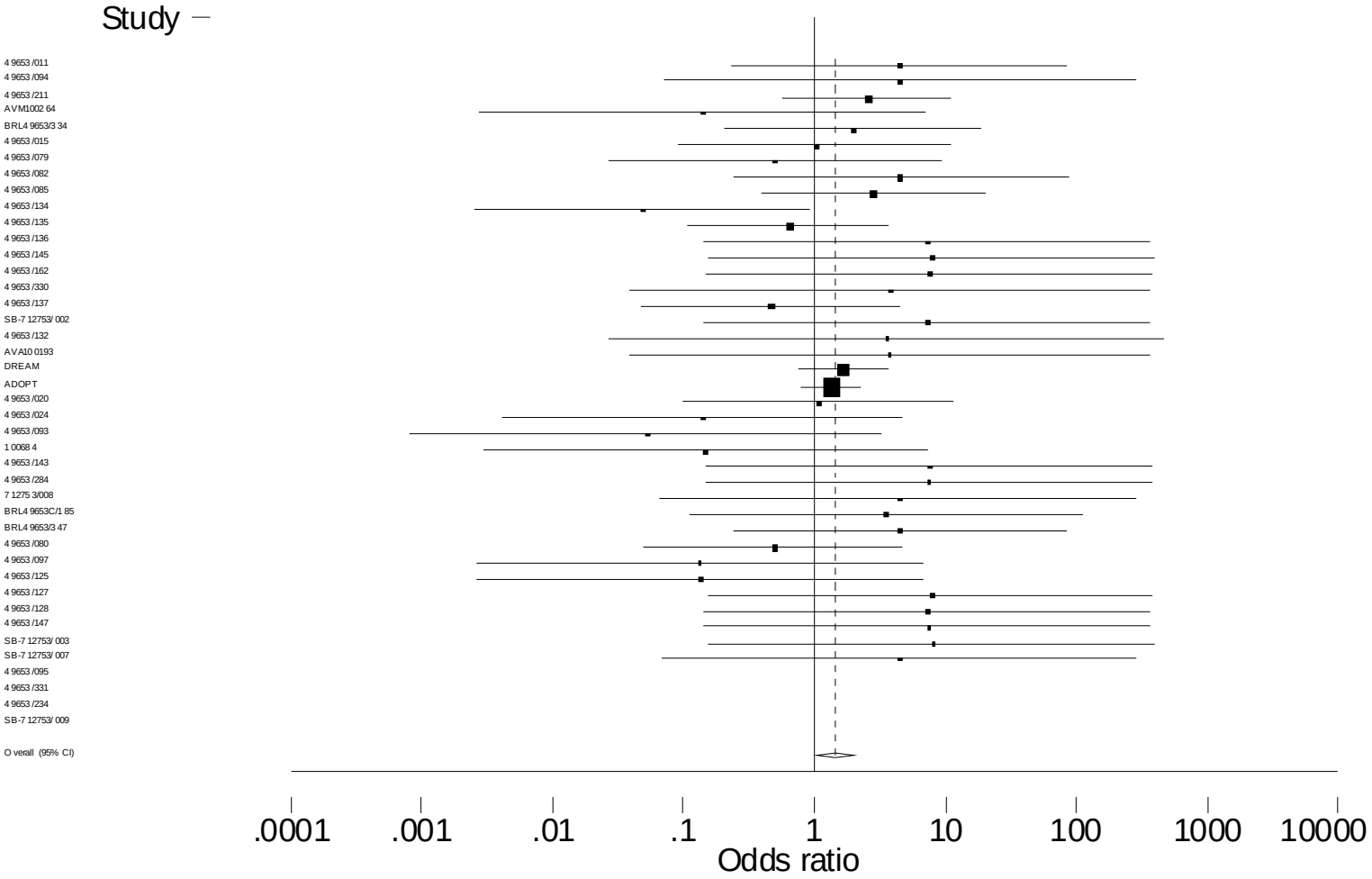
Some Comments on Nissen M-A

- Not clear why MI chosen & CV death
- ?All CV events & all cause mortality? [**O**]
- Pooled comparison groups (ADOPT)
- Statistical method used is Peto
  - Fixed effects, good for rare events, see
  - Bradburn et al. Much ado about nothing: a comparison of the performance of meta-analytical methods with rare events. Stat Med 2007;26:53-77
  - but slightly biased with unequal randomisation

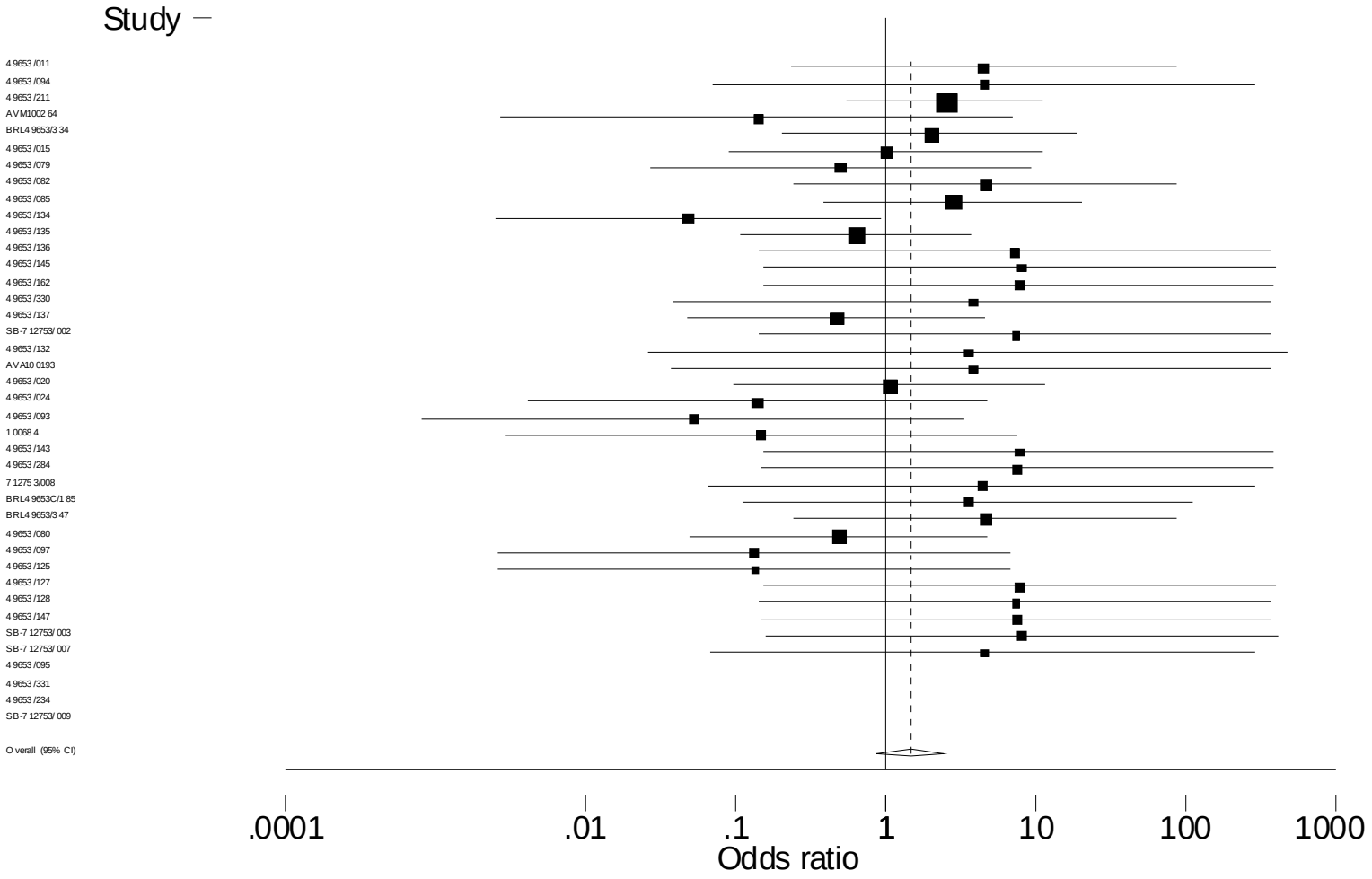
Nissen M-A

- No forest plots? No protocol? [**Design,Ex**]
- No discussion of absolute event rates
- Highest risk when RSG+insulin v insulin
  - OR 2.78 (0.58–13.3)
  - RSG contraindicated with insulin in EU
  - if these excluded all “significance” disappears
- **Peto** type methods gives a significant result for MI, others do not
- 2 large trials have 42 RSG MI & 14 RSG deaths from CVD
- Small trials have 44 RSG MI, 25 RSG deaths from CVD
  - 21 trials with 1v 0 events for MI

forest plot MI



MI - Small trials only



Weights for **A**DOPT, **D**REAM, **O**thers **in M-A**

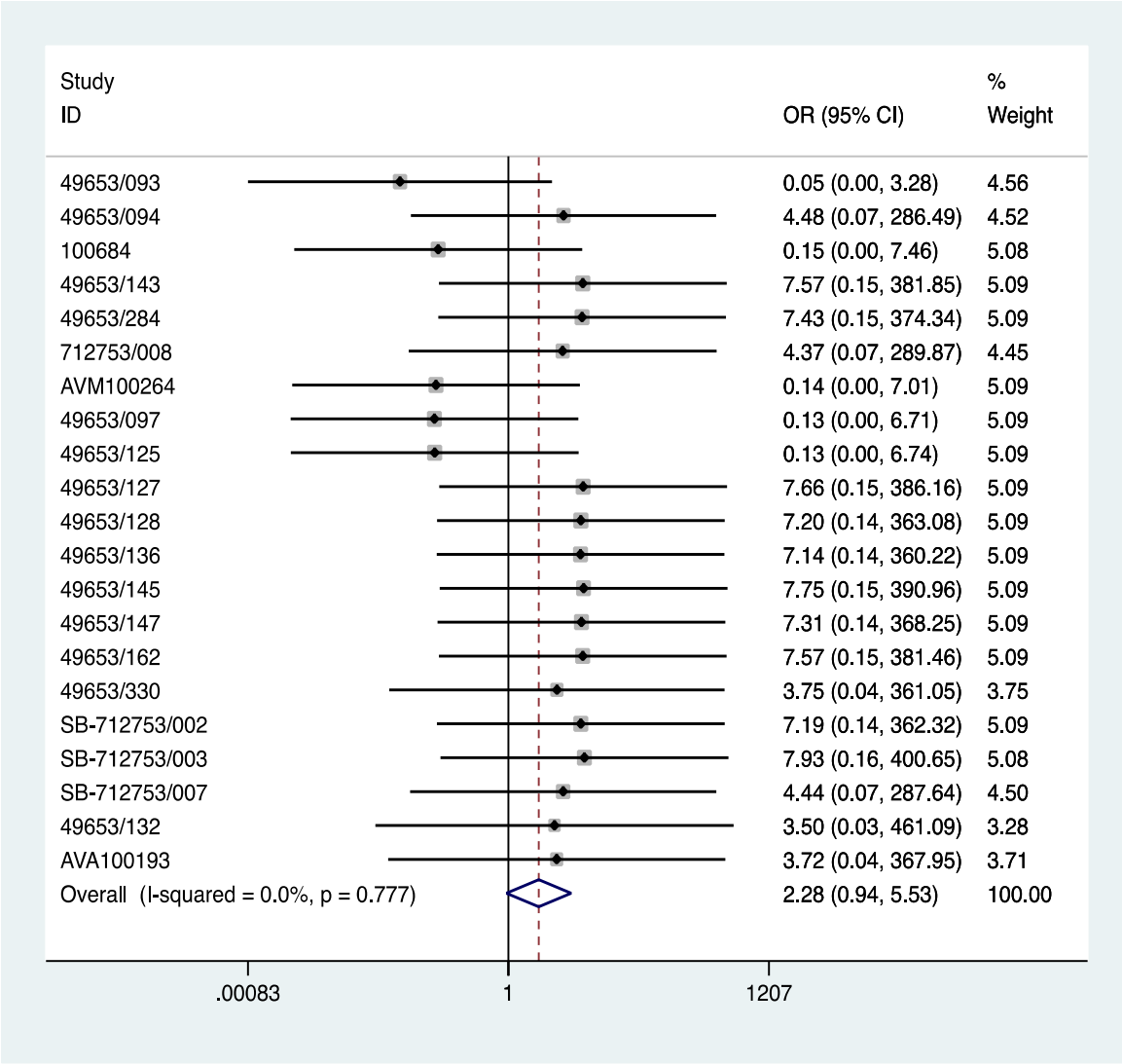
Odds Ratios MI

- (Peto) A 41 D 17 O 42
- (RE) A 41 D 14 O 45

Risk Differences MI

- (M-H) A 15 D 21 O 64
- (RE) A 4 D 20 O 76

MIs in trials with only 1 event



Comments

- Reliability of data from many small trials with zero or 1 event per arm is dependent on very good reporting
- *If M-A result very sensitive to the method used- be careful, even with Peto method- weights for many small trials can be equivalent to large trial*
- No benefit on MI for RSG, & possible harm, absolute rate uncertain (Singh JAMA Sept 2007)
- Need to see how hazard changes over time [**T**]
  - M-A for all surgery would show hazard of operations
- No benefit or harm on all-cause deaths

Pitot

- Pitot- 18th century French engineer.
- A pitot tube measures fluid flow – notably airspeed in aircraft.
- Can be used for “hot air”
- Media publicity around “scare” meta-analyses is often **“hot air”**