Online Advanced Methods for Cost-Effectiveness Analysis

Presentation 3: Populating decision models: effectiveness evidence
3.5: Meta-analysis: Exploring between-study heterogeneity

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Objectives

- Using subgroup analysis and meta-regression to investigate heterogeneity
- Problems with exploring heterogeneity

Subgroup analysis

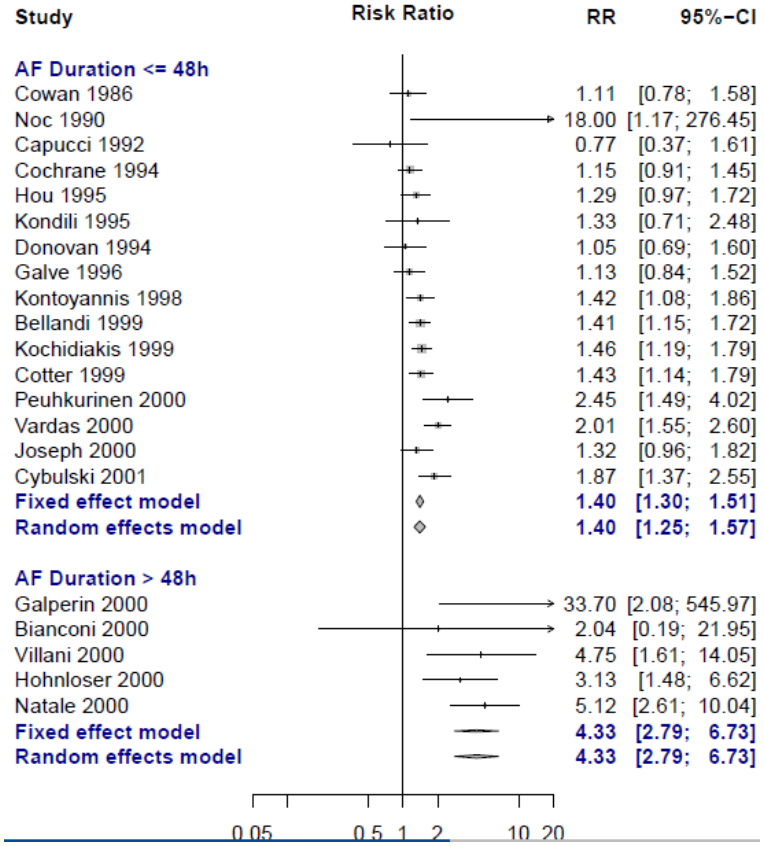
- Split evidence base into subgroups, according to some relevant factor (binary, categorical or continuous), e.g. high risk *vs* low risk (patient-level), high quality *vs* low quality studies (study-level)
- Perform a meta-analysis within each subgroup – a subgroup analysis
- Assess evidence within and across subgroups, comparing meta-analysis subgroup results

Example: Amiodarone for Conversion of Atrial Fibrillation (AF)

- 21 randomised or quasi-randomised controlled trials with AF patients
- Amiodarone compared with placebo, digoxin, CCB, or no treatment
- Primary outcome: conversion to sinus rhythm within 4 weeks (binary outcome)
- A priori specified subgroup analysis: mean duration of the current AF episode (<=48 vs > 48 hours)

Source: Letelier *et al*. (2003), *Arch Intern Med*; 163: 777-85

Example: Amiodarone for Conversion of AF – forest plot with subgroups



Source: Letelier *et al*. (2003), *Arch Intern Med*; 163: 777-85

Meta-regression model

$$Y_i = \theta_i + \beta x_i + e_i \qquad \theta_i \sim N(\theta, \tau^2),$$

- Study level covariates may be included in meta-analysis models to explore and adjust for systematic differences between studies
- β is the regression coefficient for the covariate included, x_i is the value of the covariate for the *i*th study
- This is a random effects model with a study level covariate added
- Similar in principle to standard linear regression, but regression is weighted to take into account the different sizes of studies
- Extends naturally to multiple covariates

Example: Primary angioplasty for AMI

- Previous meta-analyses that compare thrombolysis and primary angioplasty (PCI) following acute MI have shown significant clinical benefits from angioplasty in terms of reducing major adverse clinical events
- Thrombolytic treatment remains the default treatment option in many countries (including the UK).
- Possible reasons include additional delay in initiating reperfusion treatment through angioplasty
- Meta-regression to evaluate the relationship between treatment effect and the time delay involving initiation of angioplasty

Source: Asseburg *et al. Heart* 2007; 93: 1244-1254

Example: Meta-Regression Results

	Alternative time delays		
	30 minutes	**60 minutes**	**90 minutes**
Endpoint	***Odds ratio***	***Odds ratio***	***Odds ratio***
Death	**0.54 (0.29, 0.92)**	**0.77 (0.44, 1.29)**	**1.15 (0.49, 2.36)**
Non-fatal re-infarction	**0.30 (0.14, 0.59)**	**0.39 (0.21, 0.72)**	**0.55 (0.2,9 1.27)**
Non-fatal stroke	**0.47 (0.05, 0.69)**	**0.56 (0.09, 0.75)**	**0.79 (0.08, 1.43)**

Example: Cost-effectiveness results (ICERs)

Base case: 'AVERAGE' DELAY

Time delay	Treatment	Mean costs	Mean QALYs	ICER
Average trials (54.3 minutes)	Primary PCI	£12,760	7.12	£9,241
	Thrombolytics	£10,080	6.83	NA

Scenario analysis: ALTERNATIVE DELAYS

Time delay	Treatment	Mean costs	Mean QALYs	ICER
30 minutes	Primary PCI	£12,820	7.23	£6,850
	Thrombolytics	£10,080	6.83	NA
60 minutes	Primary PCI	£12,750	7.09	£10,269
	Thrombolytics	£10,080	6.83	NA
90 minutes	Primary PCI	£12,670	6.87	£64,750
	Thrombolytics	£10,080	6.83	NA

Problems with subgroup-analysis / meta-regression

- Often too few studies: insufficient data to detect relationships
- *Post hoc* conclusions, inflation of type I error, low power and spurious findings
- Statistically non-significant relationships should not be equated to absence of true relationships.
- Observational relationships – aggregation or ecological bias
- Only subset of trials may have covariate information – potentially biasing results.

Summary points

- Subgroup analysis and meta-regression may be used to investigate heterogeneity
- Applying these approaches may present several problems and results should be interpreted with caution