Online Advanced Methods for Cost-Effectiveness Analysis

Presentation 3: Population decision models: effectiveness evidence
3.8: Network meta-analysis: its role and examples

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Objectives

- Detailed example:
  - The difference between direct and indirect treatment evidence
  - Combining direct and indirect evidence in a network
  - Benefits of the NMA approach for decision making

The role of network meta-analysis

Simultaneous comparison of multiple treatments: combining direct and indirect evidence

Deborah M Caldwell, A E Ades, J P T Higgins

How can policy makers decide which of five treatments is the best? Standard meta-analysis provides little help but evidence based decisions are possible

Several possible treatments are often available to treat patients with the same condition. Decisions about optimal care, and the clinical practice guidelines that inform these decisions, rely on evidence based evaluation of the different treatment options.[1 2] Systematic reviews and meta-analyses of randomised controlled trials are the main sources of evidence. However, most systematic reviews focus on pair-wise, direct comparisons of treatments (often with the comparator being a placebo or control group), which can make it difficult to determine the best treatment. In the absence of a collection of large, high quality, randomised trials comparing all eligible treatments (which is invariably the situation), we have to rely on indirect comparisons of multiple treatments. For example, an indirect estimate of the benefit of A over B can be obtained by comparing trials of A *v* C with trials of B *v* C,[3–5] even though indirect comparisons produce relatively imprecise estimates.[6] We describe comparisons of three or more treatments, based on pair-wise or multi-arm comparative studies, as a multiple treatment comparison evidence structure.

Angioplasty balloon device used to unblock and widen arteries

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BMJ 2005;331:897–900

The need to combine direct and indirect evidence

Example: Thrombolysis for MI – problems with pairwise

- 7 (k) different treatments, 21 [k.(k-1)/2] possible pairwise comparisons (aka contrasts)
- Evidence on 10 direct pairwise comparisons
- Outcome: 35 day mortality

No of trials	Streptokinase	Alteplase-	Acclerated alteplase	Streptokinase +alteplase	Reteplase	Tenecteplase	PCTA
Boland et al[15]:							
8	P	P					
1	P		P	P			
1	P			P			
1	P				P		
2			P		P		
1			P			P	
Keeley et al[16]:							
8	P						P
3		P					P
11			P				P

PCTA = primary percutaneous transluminal coronary angioplasty.

Example: Thrombolysis for MI – problems with pairwise

35 day mortality, OR and 95% CI

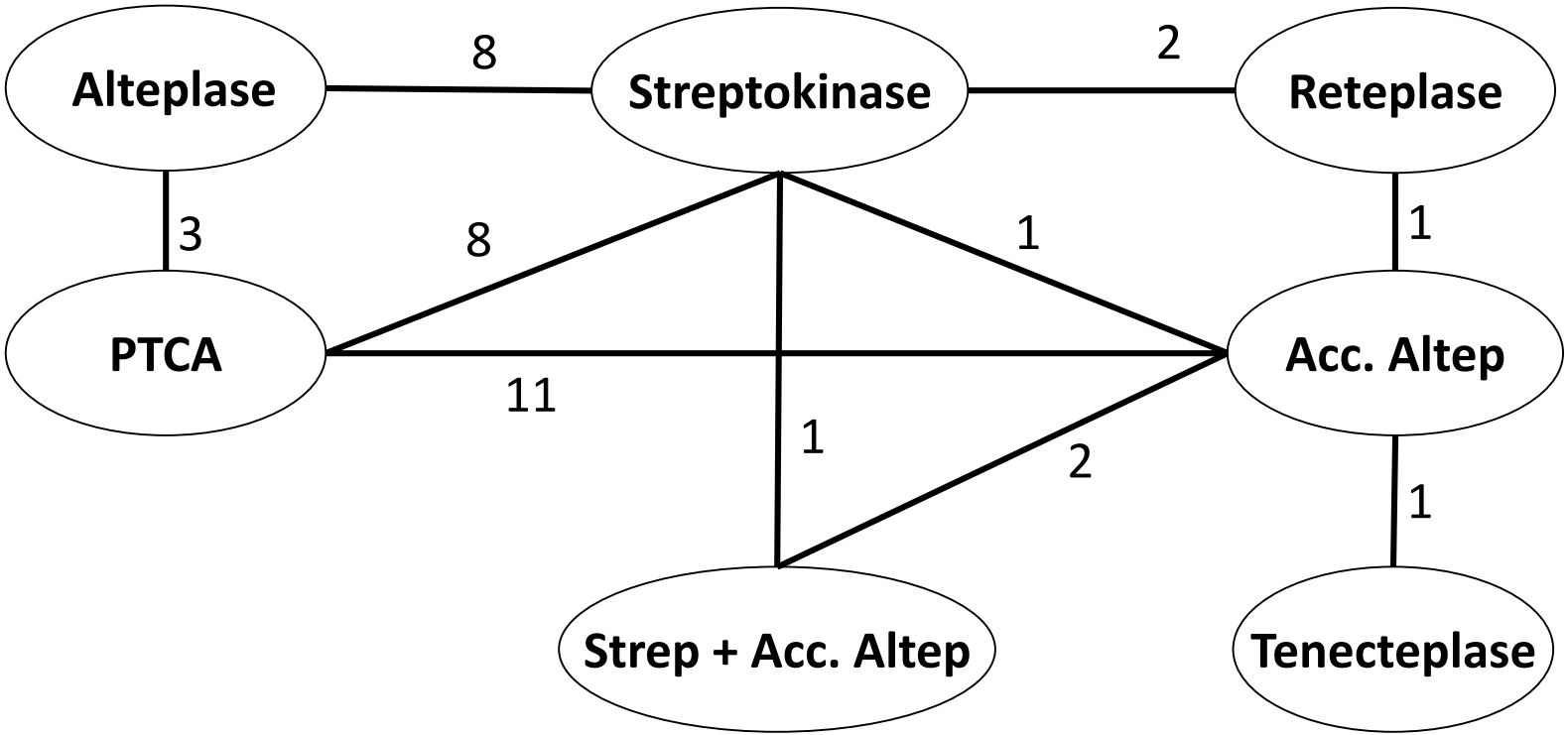
Treatment comparison	Direct comparisons
Streptokinase *v*:	
Alteplase	1.00 (0.94 to 1.06)
Accelerated alteplase	0.86 (0.78 to 0.94)
Streptokinase+alteplase	0.96 (0.87 to 1.05)
Reteplase	0.95 (0.79 to 1.12)
Tenecteplase	
PCTA	0.52 (0.36 to 0.73)
Alteplase *v*:	
Accelerated alteplase	
Streptokinase+alteplase	
Reteplase	
Tenecteplase	
PCTA	0.63 (0.25 to 1.29)

Treatment comparison	Direct comparisons
Accelerated alteplase *v*:	
Streptokinase+alteplase	1.12 (1.00 to 1.25)
Reteplase	1.02 (0.90 to 1.16)
Tenecteplase	1.01 (0.88 to 1.14)
PCTA	0.81 (0.64 to 1.02)
Streptokinase+alteplase *v*:	
Reteplase	
Tenecteplase	
PCTA	
Reteplase *v*:	
Tenecteplase	
PCTA	
Tenecteplase *v* PCTA	

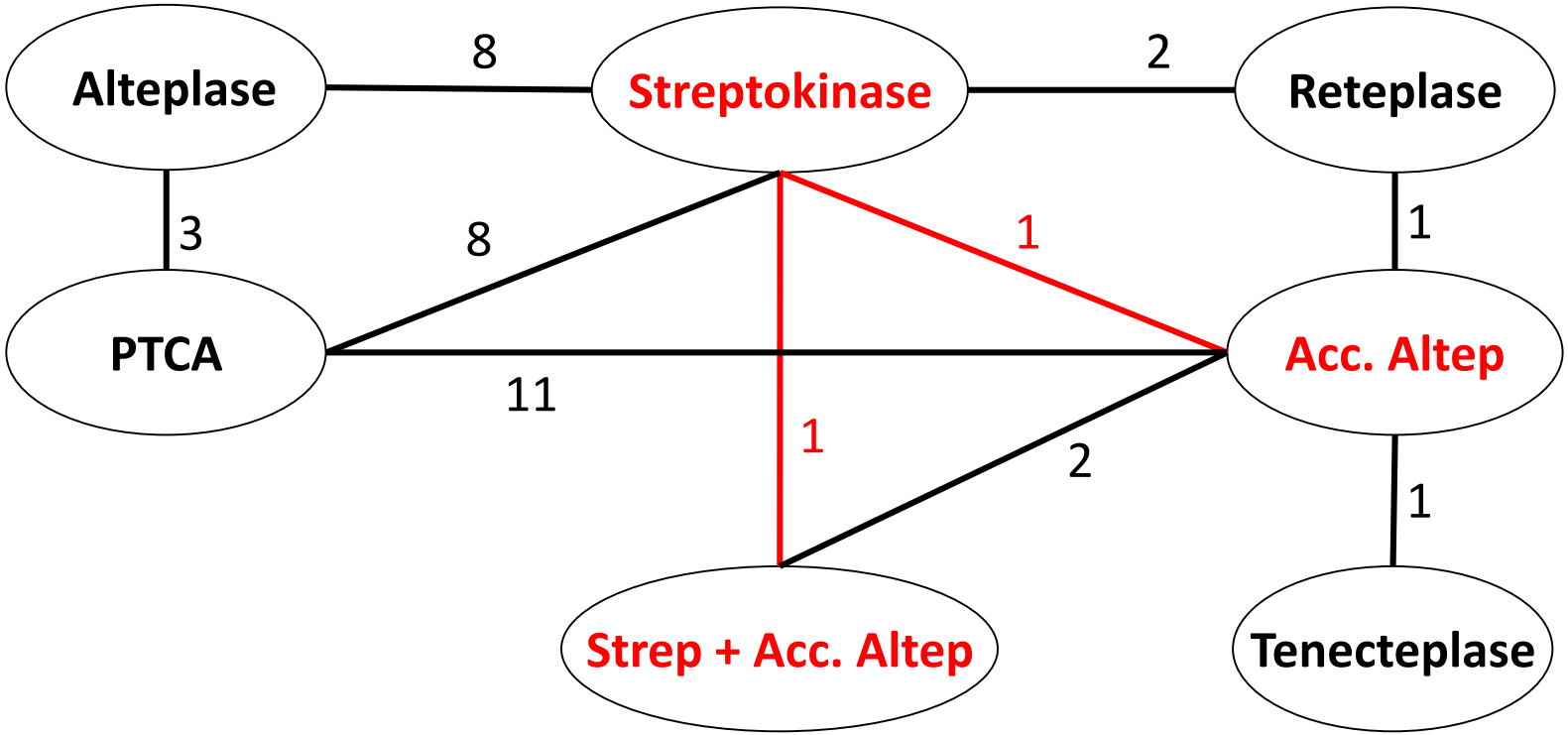
Thrombolysis for MI – interpretation example results?

- “Definitive conclusions on efficacy are that streptokinase is as effective as accelerated alteplase, that tenecteplase is as effective as accelerated alteplase, and that reteplase is at least as effective as streptokinase.”
  - Difficult to draw a conclusion about which treatment is ‘best’
  - Only represents subset of relevant alternatives
- Require simultaneous comparison of all relevant options to establish the most effective (and cost-effective)

Example: Thrombolysis for MI – Network of evidence



Example: Indirect comparisons (IC)



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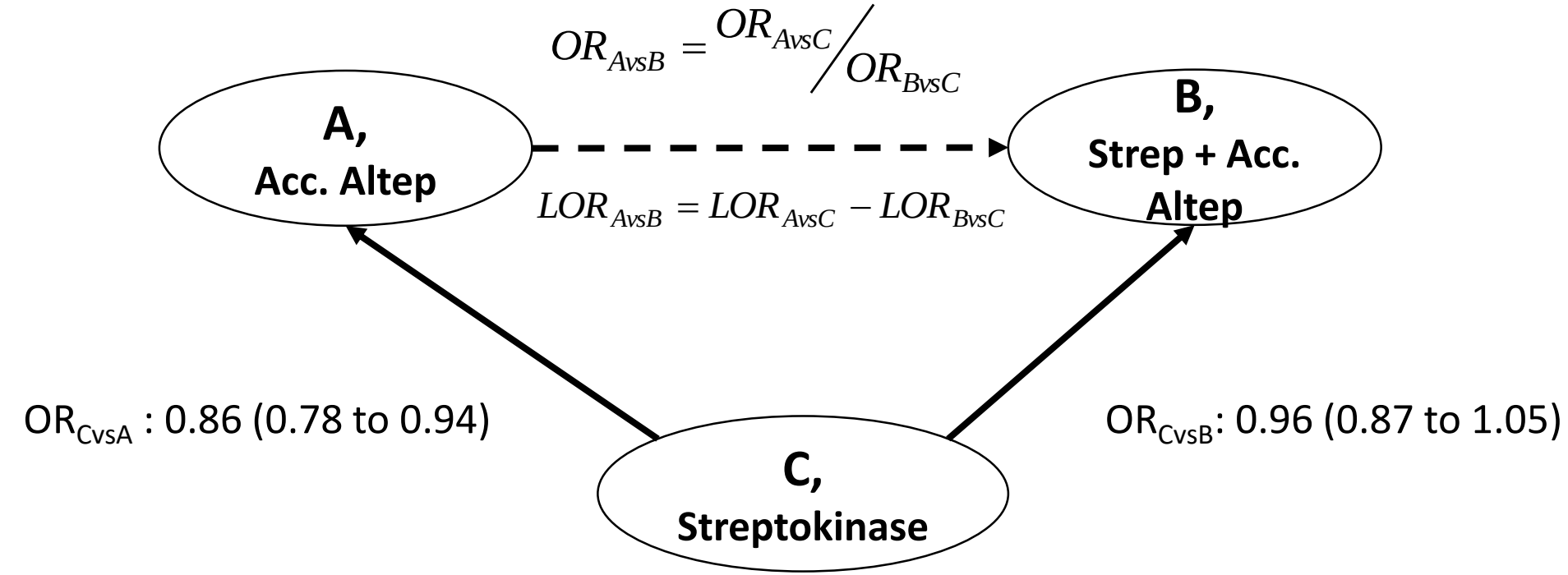
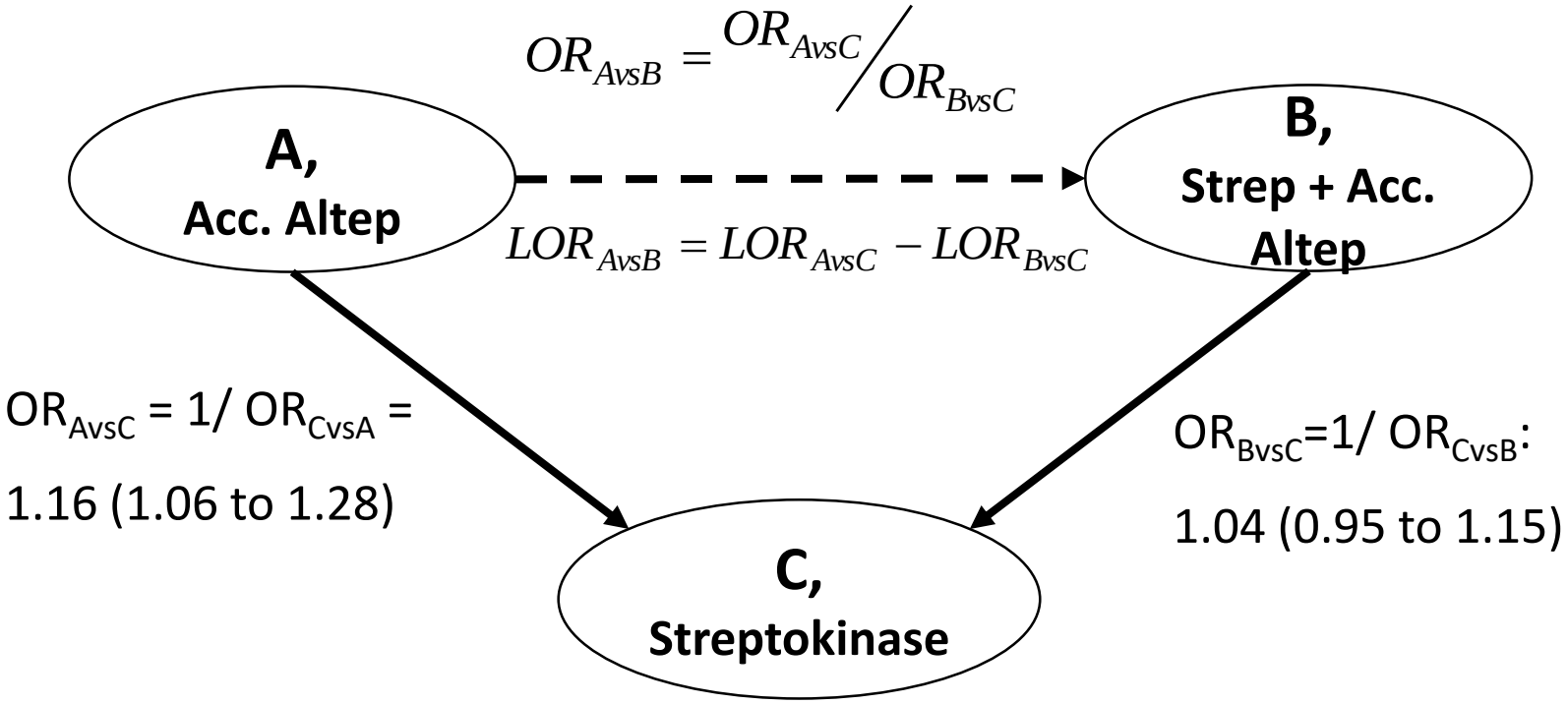


Example: Indirect Comparison (IC)



Uncertainty in Indirect Comparisons - *Bucher et al.*

- Variance of the indirect comparison:

$$Var\left(OR_{AvsB}\right) = Var\left(OR_{AvsC}\right) + Var\left(OR_{BvsC}\right)$$

- Standard Error (SE) on the Log scale:

$$SE\left(\ln OR_{AvsB}\right) = \sqrt{SE\left(\ln OR_{AvsC}\right)^2 + SE\left(\ln OR_{BvsC}\right)^2}$$

- Mean and 95% Confidence interval for the OR:

$$mean = \exp\left(\ln OR_{AvsB}\right)$$

$$95\%CI = \exp(\ln OR_{AvsB} \pm 1.96 \times SE(\ln OR_{AvsB}))$$

Source: Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. *Journal of Clinical Epidemiology* 1997; 50(6): 683-691

Example: calculations for an Indirect Comparison

1) Calculate mean difference in log OR

$$\ln\left(OR_{AB}\right) = \ln\left(OR_{AC}\right) - \ln\left(OR_{BC}\right)$$

$$0.11 = 0.15 - 0.04$$

2) Calculate standard errors for mean difference in log OR

$$SE\left(\ln OR_{AB}\right) = \sqrt{SE\left(\ln OR_{AC}\right)^2 + SE\left(\ln OR_{BC}\right)^2}$$

$$0.065 = \sqrt{0.05^2 + 0.05^2}$$

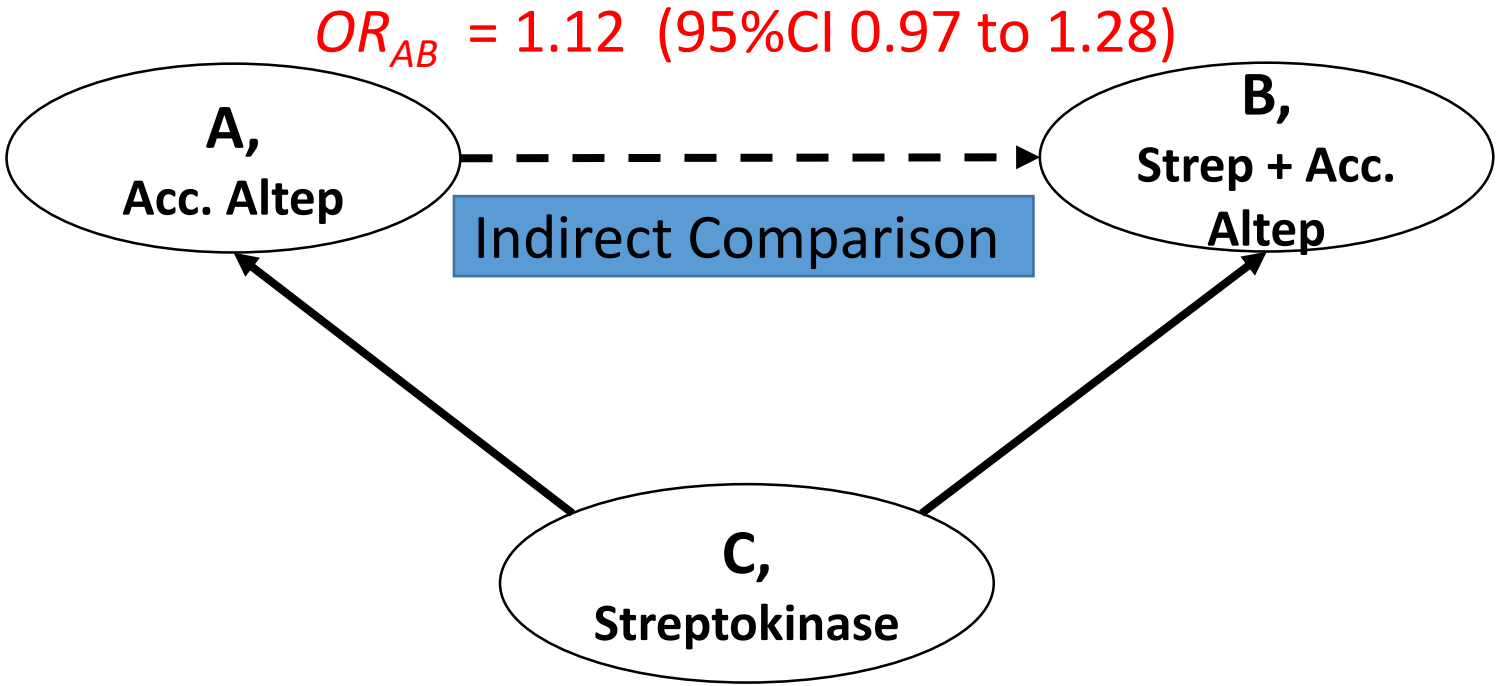
Note: for AvsC
ln(1.06)=0.06
ln(1.28)=0.25
CI width on ln scale=
0.25-0.06=0.19
Ln(SE(OR_{AC}))=
0.19/(2*1.96)=0.05

3) Exponentiate to get OR

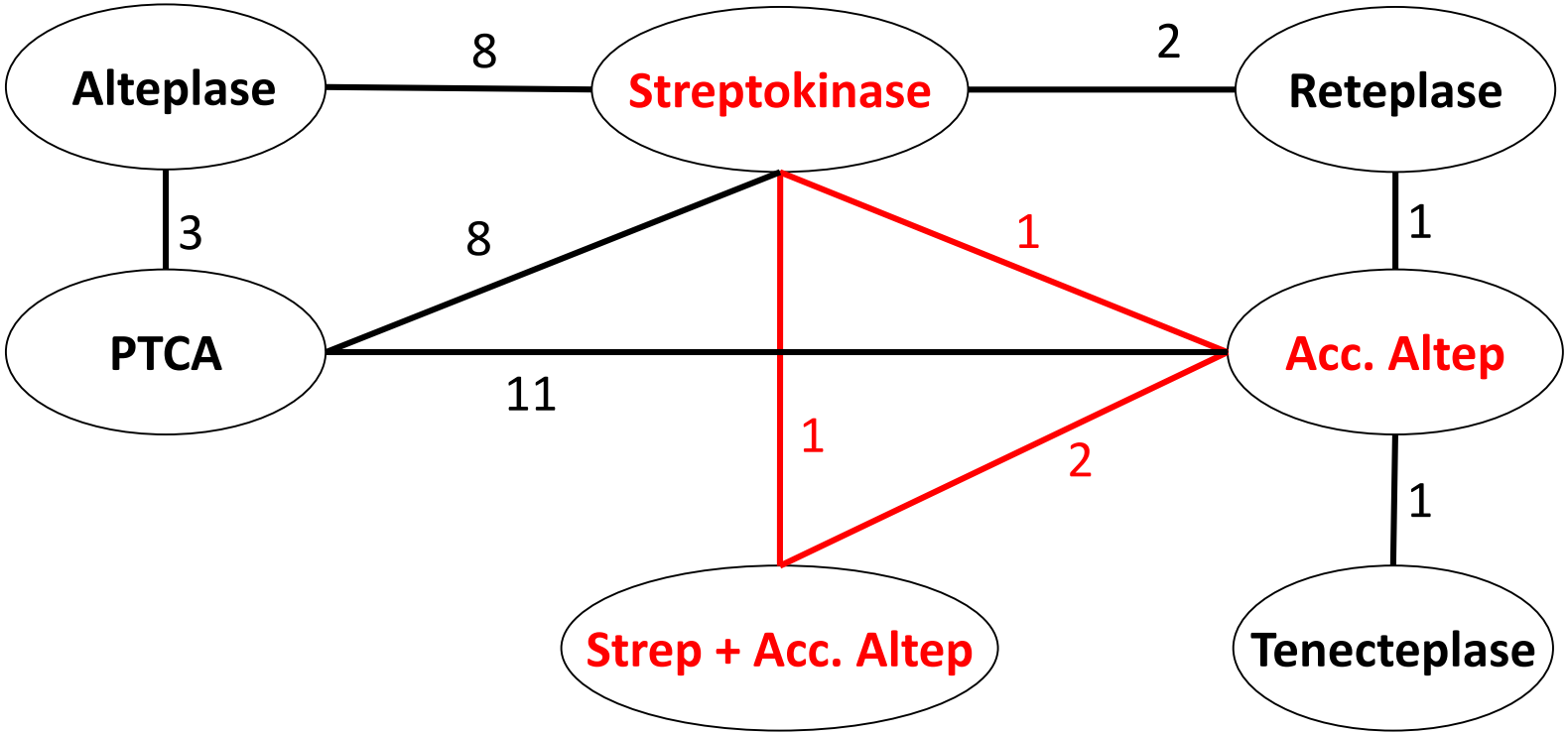
ln(OR_{AB}) = 0.11 (SE=0.065)

OR_{AB} = 1.12 (95%CI 0.97 to 1.28)

Example: Indirect Comparison



Example: Network meta-analysis



Example: Direct *vs* Indirect evidence and mixed estimates

Analysis	**OR** **Mean (95% CI)**	**LOR** **Mean (SE)**
Indirect *via* Streptokinase	1.11(0.97 to 1.28)	0.110 (0.064)
Direct (2 Trials)	1.12 (1.00 to 1.25)	0.113 (0.058)
Combined estimate	**1.12 (1.01 to 1.24)**	**0.112 (0.043)**

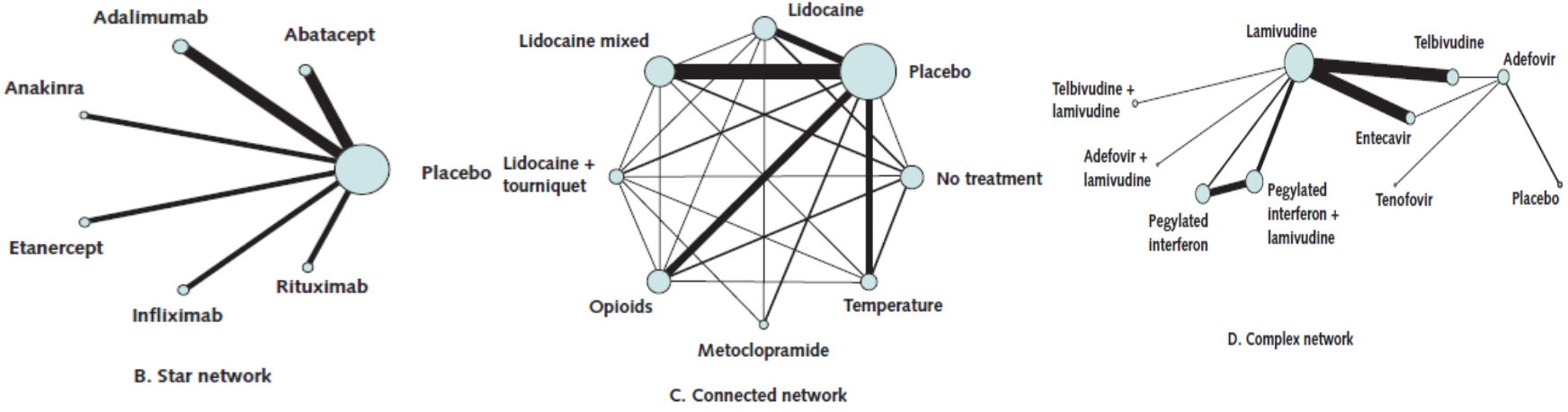
- Combined estimate should reflects both direct and indirect evidence, with relative weight dependent on the variance components

Example: Thrombolysis for MI – NMA results

- NMA 'fills in the blanks', i.e. estimates a relative treatment effect between all treatments of interest, simultaneously using all available evidence

	Fixed effect	
Treatment comparison	Direct comparisons	Multiple comparison
Streptokinase *v*:		
Alteplase	1.00 (0.94 to 1.06)	0.99 (0.94 to 1.06)
Accelerated alteplase	0.86 (0.78 to 0.94)	0.86 (0.78 to 0.93)
Streptokinase+alteplase	0.96 (0.87 to 1.05)	0.96 (0.87 to1.05)
Reteplase	0.95 (0.79 to 1.12)	0.90 (0.80 to 1.01)
Tenecteplase		0.86 (0.74 to 1.00)
PCTA	0.52 (0.36 to 0.73)	0.63 (0.52 to 0.77)
Alteplase *v*:		
Accelerated alteplase		0.86 (0.77 to 0.95)
Streptokinase+alteplase		0.96 (0.86 to 1.07)
Reteplase		0.90 (0.79 to 1.02)
Tenecteplase		0.86 (0.73 to 1.01)
PCTA	0.63 (0.25 to 1.29)	0.64 (0.51 to 0.77)
Accelerated alteplase *v*:		
Streptokinase+alteplase	1.12 (1.00 to 1.25)	1.12 (1.01 to 1.24)
Reteplase	1.02 (0.90 to 1.16)	1.05 (0.94 to 1.17)
Tenecteplase	1.01 (0.88 to 1.14)	1.01 (0.89 to 1.14)
PCTA	0.81 (0.64 to 1.02)	0.74 (0.61 to 0.89)
Streptokinase+alteplase *v*:		
Reteplase		0.94 (0.82 to 1.07)
Tenecteplase		0.90 (0.76 to 1.05)
PCTA		0.66 (0.53 to 0.81)
Reteplase *v*:		
Tenecteplase		0.96 (0.82 to 1.13)
PCTA		0.71 (0.57 to 0.87)
Tenecteplase *v* PCTA		0.74 (0.58 to 0.92)

Evidence networks can become very complicated



Source: Cipriani, Higgins, Geddes and Salanti. Conceptual and technical challenges in network meta-analysis. *Annals Int Med* 2013 Jul 16; 159(2): 130-7

Summary points

- NMA uses all relevant evidence simultaneously in a single model
- NMA provides effect estimates for all comparisons of interest
- NMA provides all relevant information for decision making