Mixed treatment comparison analysis of 7 treatments for acute myocardial infarction

Deborah Caldwell[1]

Tony Ades[1]

Julian Higgins[2]

[1] MRC Health Services Research Collaboration, Department of Social Medicine, Bristol, UK

[2] MRC Biostatistics Unit, Institute of Public Health, University of Cambridge, UK

MRC Medical Research Council

HSRC Health Services Research Collaboration

Outline of presentation

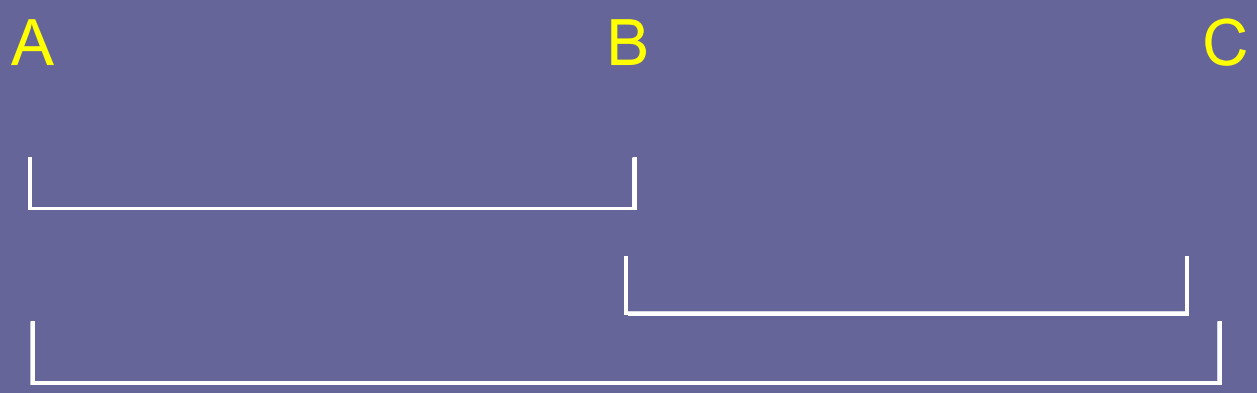
- Background: multiple treatment options.
- Mixed (multiple) treatment comparisons (MTC).
- Worked example: thrombolysis for acute myocardial infarction (AMI)
- Potential concerns regarding use of MTC.

Background

- For any given condition there is often an array of possible interventions/ treatments.
- Treatment recommendations & decisions should be evidence based.
- Principle sources are systematic reviews of randomised controlled trials.
- Systematic reviews focus on pairwise, direct comparisons of treatments.

~~Indirect~~ comparisons

- In absence of trials comparing treatments A versus B, an *indirect* estimate of odds ratio d_{AB} is obtained from RCTs comparing A vs C and B vs C:



$$d_{AB} = d_{AC} - d_{BC}$$

“Early thrombolysis for AMI”*

RCTs	SK	t-PA	At-PA	Sk+tPA	r-PA	TNK
8	✓	✓				
1	✓		✓	✓		
1	✓			✓		
1	✓				✓	
2			✓		✓	
1			✓			✓

Streptokinase (SK), Tissue-plasminogen activator (t-PA), Accelerated tissue-plasminogen activator (At-PA), Tenecteplase (TNK), Reteplase (r-PA)

*(Boland et al 2003)

Thrombolysis conclusions

- "streptokinase is as effective as non-accelerated alteplase… tenecteplase is as effective as accelerated alteplase… reteplase is at least as effective as streptokinase."

- "…(is) streptokinase as effective as, or inferior to accelerated alteplase… (is) reteplase is as effective as accelerated alteplase or not"

- "two further questions on indirect comparisons arise, whether tenecteplase is superior to streptokinase or not and whether reteplase is as effective as tenecteplase or not."

Were all relevant treatments included?*

- Primary percutaneous transluminal coronary angioplasty (PTCA).
- Keeley et al (2003) meta-analysis of PTCA vs thrombolysis (22 RCTs)
  - PTCA is better than thrombolysis (OR 0.70 [0.58 – 0.85])
  - But surely the relevant comparison is the 'best' thrombolytic NOT the 'average' one?

* Caldwell, Ades & Higgins. "Simultaneous comparison of multiple treatments: combining direct and indirect evidence" ***BMJ*** 2005;331:897-900

Mixed treatments comparison:
Evidence structure

	SK	t-PA	At-PA	Sk+tPA	r-PA	TNK	PTCA
Boland							
8	✓	✓					
1	✓		✓	✓			
1	✓			✓			
1	✓				✓		
2			✓		✓		
1			✓			✓	
Keeley							
8	✓						✓
3		✓					✓
11			✓				✓

What is needed?

1. A single statistical analysis combining all available evidence for the 21 possible pairwise comparisons, between 7 treatments.
2. An assessment of which of these treatments is most likely to be best.

Method

1. Using classical or Bayesian statistical methods.
2. Simulation based technique - Bayesian Markov chain Monte Carlo method (Higgins & Whitehead, 1996)
   - See website for WinBUGS programmes **(http://www.hsrc.ac.uk/)**

Results: Pairwise odds ratios

(upper triangle – direct comparisons)

	SK	t-PA	Acc t-PA	SK + t-PA	r-PA	TNK	PCTA
SK	**	1.00	0.86	0.96	0.95		0.52
t-PA		**					0.63
Acc t-PA			**	1.12	1.02	1.01	0.81
SK + t-PA				**			
r-PA					**		
TNK						**	
PCTA							**

Results: pairwise odds ratios

(upper triangle – direct comparisons, lower triangle – MTC)

	SK	t-PA	Acc t-PA	SK + t-PA	r-PA	TNK	PCTA
SK	**	1.00	0.86	0.96	0.95		0.52
t-PA	0.99	**					0.63
Acc t-PA	0.86	0.86	**	1.12	1.02	1.01	0.81
SK + t-PA	0.96	0.96	1.12	**			
r-PA	0.90	0.90	1.05	0.94	**		
TNK	0.86	0.86	1.01	0.90	0.96	**	
PCTA	0.63	0.64	0.74	0.66	0.71	0.74	**

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Results: SK vs t-PA

	SK	t-PA	Acc t-PA	SK + t-PA	r-PA	TNK	PCTA
SK	**	1.00					0.52
t-PA	0.99	**					0.63
			**	1.12	1.02	1.01	0.81
SK + t-PA	0.96	0.96	1.12	**			
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TNK	0.86	0.86	1.01	0.90	0.96	**	
PCTA	0.63	0.64	0.74	0.66	0.71	0.74	**

CI: (*0.94– 1.06*)

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Keeley et al conclusion

PTCA is better than thrombolysis
(OR 0.70 [0.58 – 0.85])

Keeley et al (2003)

Results: Acc t-PA vs PTCA

	SK	t-PA	Acc t-PA	SK + t-PA	r-PA	TNK	PTCA
SK	**	1.00	0.86	0.96	0.95		0.52
t-PA	0.99	**					0.63
Acc t-PA	0.86	0.86	**	1.12	1.02	1.01	0.81
SK + t-PA	0.96	0.96	1.12	**			
r-PA	0.90	0.90	1.05	0.94	**		
TNK	0.86	0.86	1.01	0.90	0.96	**	
PTCA	0.63	0.64	0.74	0.66	0.71	0.74	**

CI: *(0.64 – 1.02)*

CI: *(0.61 – 0.89)*

Results: SK vs TNK

	SK	t-PA	Acc t-PA	SK + t-PA	r-PA	TNK	PTCA
SK	**	1.00	0.86	0.96	0.95		0.52
t-PA	0.99	**					
Acc t-PA	0.86	0.86	**	1.12	1.02	1.01	0.81
SK + t-PA	0.96	0.96	1.12	**			
r-PA	0.90	0.90	1.05	0.94	**		
TNK	0.86	0.86	1.01	0.90	0.96	**	
CI: (*0.74 – 1.00*)			0.74	0.66	0.71	0.74	**

Reduction of uncertainty in MTC: equivalent sample size (per trial arm)

	SK	t-PA	Acc t-PA	SK + t-PA	r-PA	TNK	PTCA
SK	**	34300	14261	14855	4231		1192
t-PA	34277	**					232
Acc t-PA	18021	12243	**	10941	8255	8803	2971
SK + t-PA	15172	10649	12087	**			
r-PA	9158	7236	11877	6804	**		
TNK	5722	4944	8925	5012	5015	**	
PTCA	3947	3654	4438	3529	3407	3096	**

Equivalent sample size (per treatment arm) of a new study required achieve the same reduction in uncertainty as the MTC analysis.

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Increase in precision equivalent to 1467 per arm

Equivalent sample size (per treatment arm) of a new study required achieve the same reduction in uncertainty as the MTC analysis.

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TNK	5722	4944	8925	5012	5015	**	
PTCA	3947	3654	4438	3529	3407	3096	**

Increase in precision equivalent to 5722 per arm

Equivalent sample size (per treatment arm) of a new study required achieve the same reduction in uncertainty as the MTC analysis.

Probability each treatment is best

	35 day Mortality %	Probability best
SK	6.7	0
t-PA	6.7	0
Acc t-PA	5.8	0
SK + t-PA	6.5	0
r-PA	6.1	0
TNK	5.8	0.004
PTCA	4.4	0.995

Potential concerns about MTC

Indirect comparisons produce relatively imprecise estimates of treatment effect.

They are not randomised comparisons

Suffer the biases of observational studies

Direct and indirect evidence should be considered separately.

Direct evidence should take precedence.

Potential concerns about MTC

Combining all direct and indirect evidence improves precision.

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Combining all direct and indirect evidence improves precision.

MTC based solely on relative treatment effects.

Weighted averages of unbiased RCT estimates

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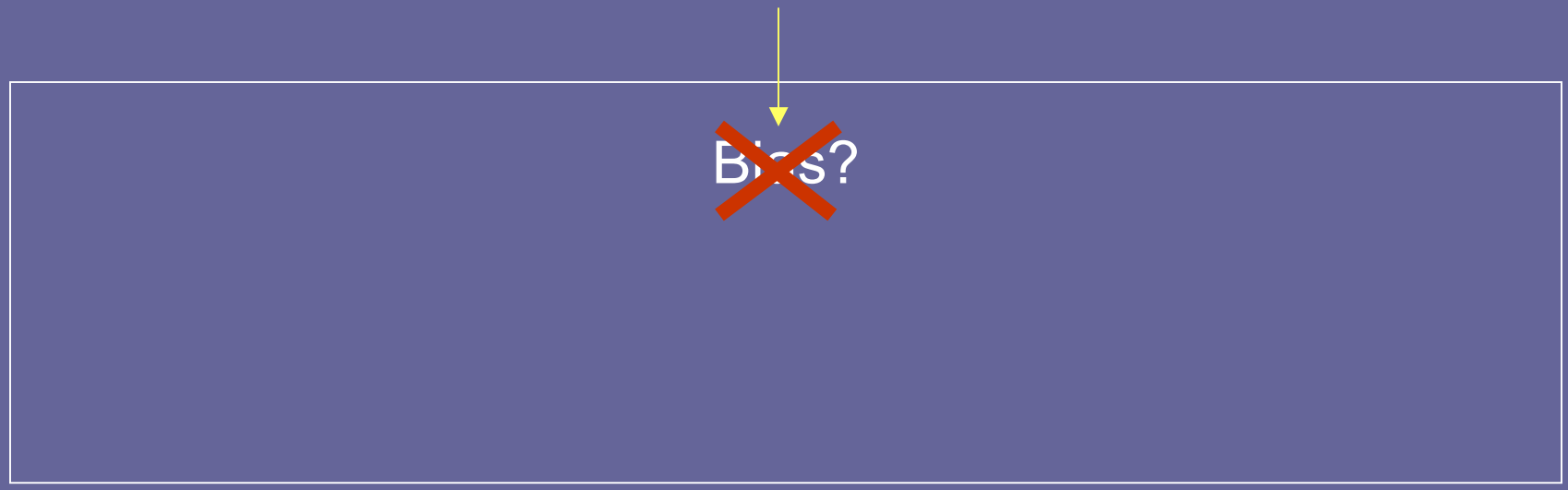

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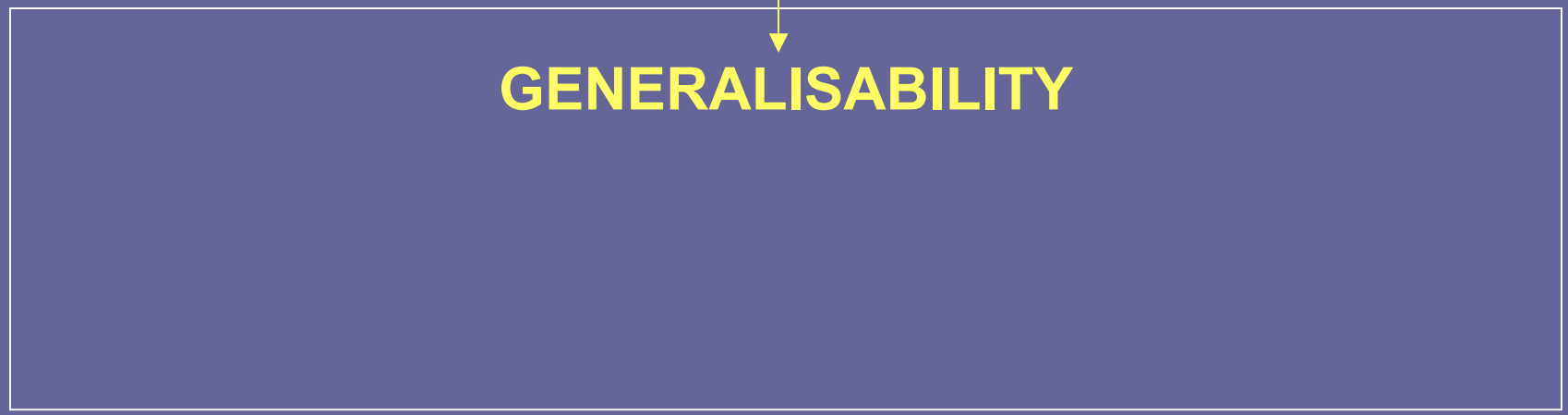

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GENERALISABILITY

- Who is it a valid estimate for?
- Do patient groups & protocols generalise to current target population of interest?

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Contradictory? Indirect used when direct is unavailable but not allowed when direct is available?

Impossible to keep direct & indirect separate.

Summary

- Some form of combined analysis is inevitable
  - No real alternative in multi-treatment decision making.
  - A unified, coherent analysis of multiple treatments can only be achieved by including the entire evidence structure of relevant RCTs.
- Need methodology to be transparent
  - No need to lump treatments
  - No ‘under the table’, informal indirect comparisons
- MTC same assumptions and problems as pairwise meta-analysis

Generalisability

- Key assumption in MTC is that relative treatment effect of one treatment vs another is same across entire set of trials.
  - True odds ratio of A vs B trials is exactly the same as the A vs B odds ratio in the A vs C, B vs C trials.
- Helpful to consider which target population we are making treatment recommendation for.
  - The type of patients in the previous A vs B trials?
  - The kind of patients in ALL the MTC trials?