Centre for Reviews and Dissemination

Using the adjusted indirect comparison in a health technology assessment:

Clopidogrel versus modified-release dipyridamole in combination with aspirin

Lisa Jones, Caroline Main, and Rob Riemsma. Centre for Reviews and Dissemination, The University of York, UK

Introduction

Competing interventions have not always been compared in randomised trials. In such cases an indirect comparison may be carried out. Undertaking simple indirect comparisons means that the power of randomisation is lost and data is subject to the biases associated with observational studies.[1]

Bucher and colleagues have proposed an adjusted method for indirect comparisons that aims to overcome these potential problems (see Box). However, the method is only valid when the magnitude of the treatment effect is consistent between the different studies being compared.

Methods and objectives

- We conducted a health technology assessment (HTA) of two competing antiplatelet agents for the UK's National Institute for Clinical Excellence.[2]
- Clopidogrel and modified-release dipyridamole alone and in combination with aspirin are licensed for the secondary prevention of occlusive vascular events in patients who have had a stroke.
- Two RCTs (the CAPRIE trial and ESPS-2) were identified for each drug versus aspirin, respectively, but no RCTs compared these drugs directly.
- In terms of preventing secondary events, both clopidogrel and modified-release dipyridamole in combination with aspirin were marginally more effective than aspirin.
- Using the methods proposed by Bucher and colleagues (see box), and outcomes reported in the Antithrombotic Trialists' meta-analysis,[3] we undertook an indirect comparison.

Results of the indirect comparison

Details of the two trials are shown in Table 1. There were obvious differences identified between the two trials:

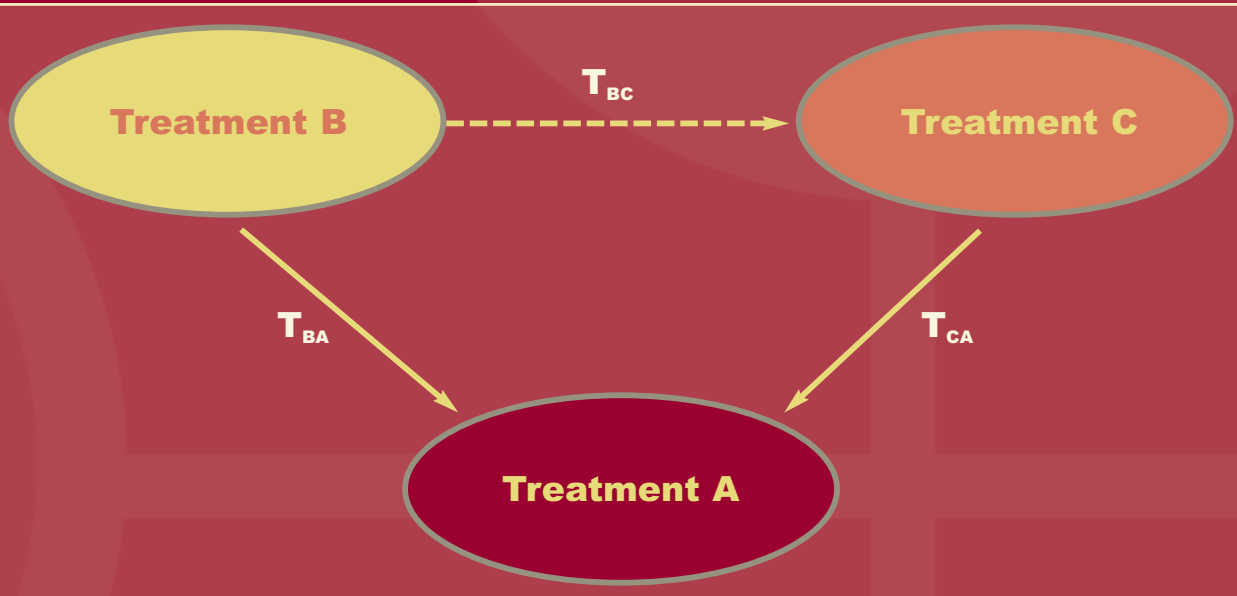
1. *The doses of the comparator, aspirin, differed between the two trials.*

   There remains uncertainty about the effectiveness of doses of aspirin below 75 mg.[3] In particular, experts disagree about the optimal aspirin dose in preventing stroke.[4]

Table 1 Details of the two trials

Trial	Participants	Interventions
Second European Stroke Prevention Study (ESPS-2)	6,602 patients with completed ischaemic stroke or transient ischaemic attack (TIA)	• Aspirin (50 mg/day) • Modified-release dipyridamole (400 mg/day) • Aspirin (50 mg/day) + modified-release dipyridamole (400 mg/day) • Placebo
Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE)	19,185 patients with ischaemic stroke, myocardial infarction (MI) or atherosclerotic peripheral arterial disease	• Clopidogrel (75 mg/day) • Aspirin (325 mg/day)

Summary of adjusted indirect comparison[1]



Using the adjusted method, the treatment effect for T_{BC} is given by: $T_{BC} = T_{BA} - T_{CA}$

Where T represents the treatment effect (e.g. log relative risk) between the two interventions.

The standard error is calculated as follows: $SE(T_{BC}) = \sqrt{(SE(T_{BA})^2 + SE(T_{CA})^2)}$

2. *A broader group of patients were included in the CAPRIE trial than ESPS-2*

   The CAPRIE trial included patients with atherosclerotic disease manifested as ischaemic stroke, MI and peripheral arterial disease. ESPS-2 included patients with TIA and completed ischaemic stroke only.

Because of these differences, it is doubtful that the magnitude of the treatment effect was consistent between the two studies. A number of assumptions would have to be made about the similarities of the patients in the CAPRIE trial and ESPS-2 with regards to the dose of the comparator and the population under study.

Conclusions

- In the context of HTA there is a need for evidence about the relative effectiveness of competing interventions and the adjusted indirect comparison may provide useful information, which is otherwise lacking.
- In our experience, careful assessment of the two trials revealed differences that were likely to limit the interpretation of the findings of the method.
- The internal validity and similarity of the trials being compared should be thoroughly examined and the findings interpreted cautiously.

References

1. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. *J Clin Epidemiol* 1997;50:683-91.
2. Jones L, Griffin S, Palmer S, Main C, Orton V, et al. Clinical effectiveness and cost-effectiveness of clopidogrel and modified-release dipyridamole in the secondary prevention of occlusive vascular events: a systematic review and economic evaluation. *Health Technol Assess* (in press)
3. Baigent C, Sudlow C, Collins R, Peto R, Antithrombotic Trialists Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;324:71-86.
4. Johnson E, Lanes S, Wentworth C. A metaregression analysis of the dose-response effect of aspirin on stroke. *Arch Intern Med* 1999;159:1248-1253.