Treatment and secondary prevention of stroke (multiple letters)

Dr James Overell, MBChB MRCP
Research Fellow in Cerebrovascular Disease

UNIVERSITY
of
GLASGOW

Dr Richard Horton
The Lancet
42 Bedford Square
London WC1B 3SL
UK

1 November 1999

Sir,

Re: Treatment and secondary prevention of stroke: evidence, costs and effects on individuals and populations

In their recent review [1], Graeme Hankey and Charles Warlow acknowledge that the relative risk reduction (RRR) afforded by aspirin in vascular event prevention after cerebral ischaemia (13%) [2] is less than that calculated from meta-analysis of all studies in high risk patients (including those with previous MI, angina or peripheral vascular disease) [3]. Therefore, they use 13% as the RRR in subsequent calculations. The RRR used for clopidogrel, however, is derived from patients in all high risk groups, chiefly those included in the CAPRIE trial [4]. While CAPRIE was designed and powered to detect a combined event outcome measure in the entire trial cohort, the heterogeneous treatment effects demonstrated in different subgroups should not be ignored. While we acknowledge the difficulties with subgroup analysis, if results for the stroke / TIA subgroup were used in their analysis, the confidence interval for the RRR would cross zero. A high (166) but statistically significant number needed to treat (NNT) then loses its significance.

Acute Stroke Unit & Cerebrovascular Clinic
UNIVERSITY DEPARTMENT OF MEDICINE & THERAPEUTICS
Gardiner Institute, Western Infirmary, Glasgow G11 6NT
Telephone: **+44 141 211 6395/2176** ***Fax:*** **+44 141 211 6396** ***E-Mail:*** **j.overell@clinmed.gla.ac.uk**

Cost effectiveness data are needed on the comparison of new treatments (aspirin/dipyridamole (combination) or clopidogrel therapy) to the cheap and proven standard, aspirin, rather than to placebo. Even using the 'overall cohort' NNT value derived from the CAPRIE trial, the cost of stroke (estimates of which have varied wildly) would need to be extremely high to justify clopidogrel as first line therapy. The CAPRIE population had a low event rate, and the argument that certain subgroups at high risk may have a lower NNT, thus making such a strategy more (cost) effective, may be valid. However, without the benefit of further evidence on the efficacy of clopidogrel in such a group, it remains conjecture.

Combination therapy has been compared to aspirin in 4 published trials in the cerebrovascular population. From a meta-analysis of these data, the combined NNT (over 2 years) to prevent one stroke is 41. Using a low cost of stroke (£8,500) and standard UK drug costs (aspirin treatment for a year= £0.73, dipyridamole 200mg MR for a year= £119), the net cost for the health gain from a stroke prevented is only £1,175. Using the upper limit of the confidence interval for NNT derived from this meta-analysis (130), net cost is £22,400, considerably less than some treatments currently purchased. Moreover, many estimations (including those quoted [1]) of the cost of stroke are considerably higher than £8,500, thus lowering the calculated net cost.

In patients intolerant of aspirin, data on the comparison of clopidogrel to placebo are required, but are not (and never will be) available. The paper rightly makes this comparison using indirect methods. Cost effectiveness of clopidogrel can be argued in the aspirin intolerant subgroup [5] when such approaches are used.

Such arguments mitigate against guidelines that recommend restricting combination treatment to patients with recurrent events on aspirin [6]. Current evidence indicates that combination therapy is both effective and cost effective as first line therapy for secondary prevention in stroke patients.
(486 words)

Yours sincerely,

James R Overell[a]

Christopher J Weir[a]

Andrew Walker[b]

Kennedy R Lees[a]

a: Acute Stroke Unit, University Department of Medicine and Therapeutics, Western Infirmary, Glasgow, G11 6NT

b: Greater Glasgow Health Board, Dalian House, 350 St Vincent Street, Glasgow, G3 8YU

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