

**FAST-TRACK**

# THE LANCET

42 Bedford Square  
London WC1B 3SL  
United Kingdom

Editor: Richard Horton  
Deputy Editor: David Sharp

Tel: +44 (0)171 436 4981  
Fax: +44 (0)171 323 6441  
m.mcmenemy@elsevier.co.uk

Pages 1 of 7

## Urgent facsimile

To: Prof Wayne Taylor

Fax:

00 1 905 ~~577 0017~~

522 7284

From: Marie-Clare McMenemy

Date:

04/06/99

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Dear Professor Taylor,

**Ref: FAST-TRACK paper 99/5388**  
**Subject: Aspirin and carotid endarterectomy**

Please find attached four reports on your paper; three clinicians and one statistician.

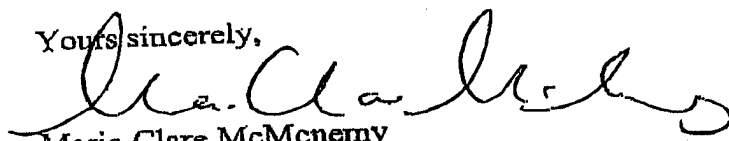
All the reviewers were enthusiastic about your paper, but a few points were raised by them. Please address the points raised, particularly the CONSORT points, and revise your paper accordingly.

Please could you revise your paper by Monday lunchtime and fax and email the revised copy to me, with a covering letter explaining how you have addressed the points. I will try to let you know our final decision on your paper by the end of the day on Monday. Let me know if you can't revise the paper by Monday.

Please acknowledge receipt of this fax.

I look forward to hearing from you.

Yours sincerely,



Marie-Clare McMenemy  
Senior Editor *The Lancet*

**Manuscript number:** 99ART/5388 (Marie-Claire McMeuemy)  
**Authors:** Taylor DW, et al  
**Reviewer number:** 1553

(1)

**Comments for authors:**

This paper reports the results of an important trial conducted to a high standard by a highly reputable group. I have a few relatively minor comments to make, given in the order in which I encountered them in the manuscript, and are not ranked in order of importance:

1. The authors should clarify whether it was the original Rankin scale or the modified Rankin scale (sometimes referred to as the Oxford Handicap scale) which was used to assess disability in patients with stroke. This should be referenced (at least on the website where the protocol is published, but conveniently in the paper if space permits).
2. Whilst the exclusion of 45 people whose endarterectomy was cancelled, was appropriate (and I presume specified in the protocol). The results were given for those patients in the text, but an additional sentence to clarify that the inclusion of the data from these patients in the analysis did not materially alter the conclusions would be helpful.
3. The baseline characteristics of the patients seem to be well balanced, but again it would be helpful if table 1 could include the numbers in each treatment group with a cancelled operation. The table should also include the numbers of patients in each treatment group who had surgery for asymptomatic carotid stenosis.
4. On page 10 there is a short paragraph giving details of compliance. I think this is rather too sketchy, for two main reasons. Firstly, the definition of compliance is not stated clearly and secondly, compliance by allocated treatment is not given. It could reasonably be included in table 4 reporting primary outcome events at 3 months by study treatment group.
5. Table 2 is not particularly informative, since it is not broken down by allocated treatment group. I wonder if it could be omitted.

-2-

6. Table 3 I think would be more informative if percentages for each of the totals for each of the bleeding complications could be given. The text states that there were no significant differences between the groups, but the result of a statistical test for significance should really be stated somewhere in the table. A simple chi-squared test for trend over the four doses or other appropriate statistical test result could reasonably be included as a foot note to the table. It would not make the table unduly complicated to also include in the table (as a foot note) an estimate of relative risk and the 95% confidence interval for the difference between high and low dose: 'for total haemorrhagic stroke', 'total wound haematoma' and 'total gastric or intestinal complaints'. In this respect it is of some interest that for total haemorrhagic stroke the odds ratio comparing low dose with high dose is 0.6 (95% confidence interval is 0.3-1.3) with an absolute risk difference of 5 per 1000. I accept that the differences are non significant, but I think it is helpful for readers to see the imprecision of the estimate of relative treatment difference and the potential size of the absolute risk difference. Given the wording of the final paragraph of the discussion, (pointing out the harm from the higher dose) I suppose the foot note should also include the number needed to harm with a higher dose.
7. Table 4. My comments are similar to table 3. In particular, the discussion explains that the benefit of low dose aspirin is a reduction in mild stroke and non fatal MI, but does not give any estimates of relative or absolute treatment effect or their precision. I calculate the reduction in the odds of mild stroke to be 40% (95% confidence interval is 5%-62%) corresponding to an absolute risk difference of 14 per 1000. I think this sort of information could again usefully be included in a foot note.
8. Table 5 is, by and large satisfactory, but again 95% confidence intervals for the estimate of relative risk would give a clearer idea of how imprecise these estimates are.
9. Finally, Ian Chalmers and others have suggested that the discussion section of reports of randomised trials should include a presentation of the results of the trial in the context of all the available randomised evidence; preferably in the form of a systematic review. In the case of this trial, this would be relatively straight forward since the trials directly comparing one aspirin dose with another are very few in number. This would require simply the addition of one extra figure (which could perhaps occupy the space that might otherwise have been occupied by table 2) to show the present trial data, comparing 300mgs with 1600mgs separately and combined with the data from the UK-TIA aspirin study which compared 300 with 1300mgs. Similarly the comparison of 80mgs versus 300mgs could be included with the data from the Dutch-TIA trial comparing 30mgs with 300mgs daily. I realise that the schedule duration of treatment for these different trials is of course different but the primary outcome measure (stroke MI vascular death) is the same.

2

**Review for the Lancet: Paper 995388:**  
**Subject: Aspirin and carotid endarterectomy**

**Comments for Editors:**

The question being addressed by the investigators in conducting this trial is an important one: there is currently no evidence upon which to base decisions concerning post-endarterectomy therapy in terms of aspirin usage. Given the number of carotid endarterectomies performed worldwide and the ease of adjustment of the dose of what is one of the world's cheapest medicines, this information will be widely generalisable. The investigators are among the most experienced clinical trialists in the area and this is supported by the quality of trial conduct and reporting. Apart from the very minor issues to which I have drawn attention in comments to the authors, I believe the article should be accepted in its current format.

**Comments for Authors:**

The authors have successfully completed a trial to determine as to whether differing aspirin doses will influence surgical risk in terms of vascular outcomes, peri and post-carotid endarterectomy. The trial is very well conducted and reported. The results are certainly somewhat surprising based on the observational information produced from the NASCET trial. This point is commented upon by the authors. Because of the less expected nature of the outcomes, the efficacy analysis provides additional support for its validity. The importance of the results lie in its generalisability to centres worldwide undertaking this procedure. By administering the appropriate dose of aspirin peri-operative vascular events may be reduced. There are some minor points which the authors may wish to address:

1. In the background section of the abstract (second sentence) it is inferred that ASA is known to reduce peri-operative surgical risk. This is not true since there have been no randomised controlled trials of aspirin versus placebo to address this specific question. The authors may really mean that aspirin is known to reduce the risk of stroke and death after initial TIA or minor stroke, as stated at the top of page 2.
2. Telephone follow-up was used in 95 patients at 30 days and 165 patients at 3 months. Since the Rankin score obtained by telephone has been validated previously, it would be nice to mention and reference this.
3. On page 32 between references 14 and 15 appears the "floating reference" of Harrison M.J.G., et al Lancet 1971. The reference should be numbered appropriately or excluded from the reference list.

# FAST TRACK

## THE LANCET MANUSCRIPT REVIEW

Manuscript number: 99ART/5388 (Marie-Claire McMenemy)

Authors: Taylor DW, Barnett H, Haynes B, et al

Reviewer number: 923

Please give a frank account of the strengths and weaknesses of the article.

3

### COMMENTS FOR AUTHORS:

#### Major comments

- The *research question* is important. Indeed reduction of complications during and immediately after carotid endarterectomy is a major concern; there are few trials, if any, about the efficacy of aspirin in that situation, let alone about optimal dosage of this drug.
  1. From a purely empirical point of view the authors might well have chosen to include a placebo group. Instead they have relied on the collective evidence that aspirin prevents ischaemic events in a variety of arterial diseases, and have gone on to address the question of optimal dose. This is a reasonable approach, but it should be made explicit in the Introduction.
  2. Ironically, the Background section of the Abstract implies that acetylsalicylic acid is known to reduce postoperative risk; no doubt the authors actually wish to refer to the totality of the evidence, not to this specific indication.
- The *originality* of the study is considerable. No other study has addressed this question prospectively.
- The *methods* of the study are impeccable: randomisation, conduct, follow up and analysis meet the highest standards for clinical trials.
- The *presentation* of the study results can be improved in some respects:
  3. The Methods section is unclear about the dosage regimen. First of all, the four dosage groups are not explicitly mentioned; the reader would be totally lost without having read the Abstract first. The content and order of the five consecutive tablets is difficult to reconstruct even with this knowledge. The 81 mg group must have received the active dose once and placebo (P) four times; for the 325 mg group this may have been 81-81-81-81-P, for the 650 mg group 325-1<sup>a</sup>-P-325-P, and for the 1300 mg group 325-325-325-325-P. This should be clarified.
  4. If the Rankin scale (page 7) is relevant for this report, it should be referenced (was a modified version used?), and the number of steps on the scale should be mentioned. Yet I cannot find severity of stroke mentioned in the analysis.
  5. The choice of a two-day 'wash out period for pre-trial medication' in the efficacy analysis (page 8) should be explained, with reference to the pharmacology of platelet inhibition by aspirin.
  6. Table 2 (non-end point complications) is perhaps not necessary, and certainly too detailed.



7. The four percentages at the bottom of page 12 constitute the essence of the study, but unfortunately these are somewhat confusing. First, most readers will be more familiar with relative risks expressed as a fraction (as is done in Table 5) than with those calculated as percentages increase. Also it is awkward that these percentages do not readily correspond with the (rounded) percentages of events in Table 5 (though they can be computed from the absolute event rates). Second, it can be inferred only from the preceding sentences that percentage 1 and 3 refer to events at 30 days, and percentages 2 and 4 to those at 3 months.
8. When was heparin (page 10) given in 97% of patients, and when was it reversed in 44? May this have interfered with the effects of aspirin?
- The *Interpretation* of the results is commendable in that the authors destroy their own a priori hypothesis and use it as an example to point out the dangers of drawing conclusions from observational studies. Yet the Discussion is not quite logical where it refers to aspirin dosage in general.
9. The aim of the study was the optimal dosage of aspirin after carotid endarterectomy; it is therefore surprising that the discussion starts off with the question of aspirin dosage in the long term prevention of stroke.
10. It is not unreasonable to extend the Discussion to the implications for aspirin dosage for secondary prevention of stroke in the long term, but in doing that the authors should refer at least - if not exclusively - to analyses of *all previous studies* (including recent ones such as the ESPS-2 trial), for *aspirin alone*, and for *stroke prevention alone* (for example: J Neurol Neurosurg Psychiatry 1996;60:197-9 and 1999;66:255).

#### Minor comments

- *Style*: a few linguistic quibbles (irresistible for a non-anglophone):
  11. 'Compared to' is almost always used where 'compared with' would have been appropriate (here the expression is not a poetical resemblance, such as in 'I compare thee to a summer's day'); sometimes it is used instead of 'than'.
  12. On pages 7 and 8 the word 'using' appears in a passive sentence, where the 'user' is not the subject (cf. "Birds were observed using 10x40 binoculars"); this word might be changed to 'by using', or simply in 'with'.

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My specific comments are of a relatively minor nature:

1. I note with concern the lack of the CONSORT diagram. This would be so useful to have and its absence now produces difficulties in clearly establishing just what went on in the trial design and conduct.
2. The manuscript would also benefit from a clear diagram of the randomisation strategy and the how the drug was administered. The current part of the Methods Section describing "dosing" is not at all clear and deserves some careful attention. A good diagram would solve these problems and make everything clearer; from the Methods section it is virtually impossible to know what the doses delivered were.
3. It is also quite unclear what the compliance really was and the section which discusses this issue should examine the impact of potential differences in "self-report" between the four study groups. The compliance in the four groups in the study should be reported.
4. In table 5, it is essential that the authors calculate 95% confidence intervals and include them in the table.
5. The rationale decision at the beginning of the study, based on the information cited by the authors in this text, appears to have been to conduct the study without a placebo group. I think that there will be many clinicians who read this and forget that there is no placebo control group here. I think that this aspect of the study design deserves attention of two forms:
  - (a) the authors should discuss in a little more detail the impact of not having a placebo control group; and
  - (b) this article should be published with a Commentary which should focus on the results and other aspects of the significance of the study and also discuss issues surrounding the lack of a placebo control group, particularly where it may have led to a potential inappropriate estimation of the risks and benefits of different doses of aspirin.