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EDITORIAL OFFICES

TELEPHONE 617/734-9800

1-800/445-8080

FAX 617/739-9864

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April 30, 1999

Wayne D. Taylor, M.A.
Department of Clinical Epidemiology and Biostatistics
McMaster University
1200 Main Street West
L8N 3Z5 Hamilton Ontario
CANADA

Dear Mr. Taylor:

I am sorry to say that the *Journal* will not be able to use your manuscript, "A Randomized Trial of Low and High Dose Aspirin for Patients Undergoing Carotid Endarterectomy." This decision was based not only on the enclosed comments, but also on the editors' evaluation of the merits of your manuscript compared with those of the many others we receive. In the case of your manuscript, we thought it would be more suitable for publication in a specialty journal.

Thanks very much for the opportunity of reviewing this manuscript.

Sincerely yours,

Gregory D. Curfman, M.D.
Deputy Editor

GDC/drg
Enclosures



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SUGGESTION FOR TRANSMITTAL TO AUTHORS

99-0632B

Please do NOT comment here whether or not the manuscript should be accepted.

Methods

1. The investigators acknowledge the problem of complete exclusion of antiplatelet medications from study patients. Substratification of an "efficacy" group helps compensate for the confounding factors mentioned on the top of page 8. Since this subset addresses the study question with least ambiguity, would the authors consider eliminating the remainder of the study patients?

2. Once excluded from the outset, compliance with the study drug protocol was assessed by pill count and self-report, with average compliance as judged by these means of 87 percent for the full study period. Since many medications other than aspirin have antiplatelet effects, how was the prohibition of such medications mentioned on page 5 confirmed?

3. Following the hypothesis at the bottom of page 2, the rationale for aspirin is based on prevention of thrombotic morbidity without incurring hemorrhagic complications. Thrombotic endpoints should thus be examined, as described on page 6. The firmest of these endpoints are ipsilateral transient ischemic attack, ipsilateral thrombotic stroke, contralateral thrombotic stroke, myocardial infarction and peripheral arterial occlusive events. One could argue that death from such events relates more to their severity but should not be treated as a separate endpoint. Accordingly, A) Did the authors consider including TIA (Table 2) as an endpoint rather than a non-endpoint complication? B) Did the authors separate hemorrhagic stroke (Table 3) from the total (thrombotic?) stroke tally (Table 4)? C) Did the authors evaluate ipsilateral thrombotic stroke alone, without the somewhat confounding additive of death (Table 5)? D) What were the diagnostic criteria used to define myocardial infarction?

Results

1. The non-endpoint complications detailed in Table 2 are slightly confusing with respect to use of mild, moderate and severe categories. "Severe complications resulted in death or permanent disability, assessed at hospital discharge." Three severe hematomas occurred, though it is difficult to believe that a hematoma would be a cause of death or permanent disability. A category labeled "trauma" is also listed but not well-defined. Can the authors clarify?

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2. Reporting of stroke type and laterality on Tables 4 and 5 might be reconsidered in light of suggestions in paragraph 3 above.

3. Table 5 includes death with each outcome category. Eleven of the 57 deaths were from "other cause", evidently unrelated to any vascular thrombotic event. Since the relevance of these deaths to the study hypothesis is not clear, would the authors provide more detail or consider excluding these 11 deaths from the analysis?

Discussion

1. The authors point out that the observed benefit of low dose aspirin relative to high dose aspirin appeared to be due to a reduction in mild strokes and nonfatal myocardial infarction, with no difference observed in disabling strokes or deaths. Would this evidence of a relatively subtle impact on mild-moderate events support inclusion of TIA as an endpoint as suggested above?

2. The fundamental differences between therapy of arteries with native atherosclerosis and those recently treated by carotid endarterectomy cannot be over-emphasized, as discussed on the top of page 16. The preliminary discussion on pages 14-15 is therefore useful only as a backdrop to this surgical series. Further discussion of studies of surgery with placebo or without aspirin would be of interest. Perhaps such an inquiry would offer an alternative explanation for the variance of this study's findings with those of previous studies, otherwise attributed solely to "some unknown patient selection mechanism" (page 16 line 12 - 14).

Appendix

1. Page 24 line 12 should read "Calligaro".