Antiplatelet prophylaxis

Combination treatment may cause bleeding

EDITOR,—The Antiplatelet Trialists' Collaboration has carried out an important meta-analysis of antiplatelet prophylaxis used to reduce venous thrombosis and pulmonary embolism.¹ The results section of the abstract of the paper states: "Information on adding antiplatelet therapy to heparin was limited but, at least for pulmonary embolism, suggested more protection from the combination than from heparin alone." We suggest that consideration should be given to possible harmful effects of the combination of aspirin and heparin.

The authors found a 62 (SD 33)% reduction in the odds of pulmonary embolism after the combined treatment compared with the same dose of heparin. They also noted a 12 (22)% reduction in the odds of deep vein thrombosis. They do not, however, present any comparisons of total mortality or of complications. We therefore made these comparisons, using data from individual trials given in appendix 1. We found that total mortality was higher with combination treatment than with heparin alone (table). Although this increase was not significant (neither was the reported reduction in pulmonary embolism), it is worrying when considered together with the much higher rate of complications related to bleeding after the combination treatment. In absolute terms the possible benefits of combination treatment could well be overturned by the possible harmful effects. There was a reduction of 0.6 cases of non-fatal pulmonary embolism per 100 patients allocated combination treatment but an increase of 0.9 deaths (all causes) and 4.0 complications related to bleeding per 100.

These results highlight the importance of considering total mortality in any comparison of treatments and emphasise the need for caution in using this combination treatment for thromboprophylaxis. Nevertheless, we do not wish to detract from the importance of the results that were presented and the potential benefits of using aspirin on its own.

VALERIE SEAGROATT
CHRISTOPHER BULSTRODE
DAVID W MURRAY

Unit of Health Care Epidemiology,
University of Oxford,
Oxford OX3 7LF

1 Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy. III. Reduction in venous thrombosis and pulmonary embolism by antiplatelet prophylaxis among surgical and medical patients. *BMJ* 1994; 308:235-46. (22 January.)

The same for men and women?

EDITOR,—The paper by the Antiplatelet Trialists' Collaboration showing the reduction in venous thrombosis and pulmonary embolism with antiplatelet treatment does not give results for men and women separately,¹ although aspirin has been found to be effective as prophylaxis against venous thromboembolism only in men.² Is aspirin now considered to be equally effective in men and women? The collaboration confined its analysis to general and orthopaedic surgery and medical

Outcomes after antiplatelet treatment plus heparin compared with those after same dose of heparin

Outcome	Proportion of patients affected (%)		Odds ratio for antiplatelet treatment plus heparin:heparin*	95% Confidence interval
	Antiplatelet treatment plus heparin	Heparin		
Deep vein thrombosis	41/252 (16.3)	45/249 (18.1)	0.88	0.5 to 1.4
Pulmonary embolism (death)	4 (0)/654 (0.6)	11 (3)/653 (1.7)	0.36	0.1 to 1.2
All deaths	17/654 (2.6)	11/653 (1.7)	1.56	0.7 to 3.6
Major (excluding fatal) bleeding	6/654 (0.9)	1/653 (0.2)	6.04	0.7 to 278
Reoperation, wound haematoma, infection	43/654 (6.6)	17/653 (2.6)	2.68	1.5 to 5.0

*Odds ratio calculated from combined totals.

conditions. What is its view on the use of aspirin in obstetrics, in which thromboembolism remains one of the commonest causes of maternal death?³

Finally, although deaths due to fatal pulmonary embolism fell by 70% in the patients allocated to antiplatelet treatment, total mortality was not significantly reduced. This result is reminiscent of the results of cholesterol lowering trials.⁴

P H WITTMANN
F W WITTMANN

Reigate,
Surrey RH2 7DH

- 1 Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy. III. Reduction in venous thrombosis and pulmonary embolism by antiplatelet prophylaxis among surgical and medical patients. *BMJ* 1994; 308:235-46. (22 January.)
- 2 Harris WH, Salzman EW, Athanasoulis CA, Waltman AC, DeSanctis RW. Aspirin prophylaxis of venous thromboembolism after total hip replacement. *N Engl J Med* 1977;297: 1246-9.
- 3 Confidential enquiries into maternal deaths in the United Kingdom 1985-87. London: HMSO, 1991:37-41.
- 4 Muldoon MF, Manuck SB, Mathews KM. Lowering cholesterol concentrations and mortality: a quantitative view of primary prevention trials. *BMJ* 1990;301:309-14.

Authors' reply

EDITOR,—As is discussed explicitly in our paper, although the overall reduction in deaths observed when antiplatelet treatment was used in general and orthopaedic surgery was not significant, the reduction ascribed to pulmonary embolism or haemorrhage was substantial and highly significant and not associated with any significant difference in deaths from other causes. As most of the trials assessed the thromboprophylactic efficacy of antiplatelet treatment in the absence of subcutaneous heparin, however, information on adding antiplatelet treatment to heparin is severely limited (as was made clear in the abstract and elsewhere in the paper).

The available data do not allow reliable direct assessment of the benefits and safety of such combination treatment. For this reason the paper concluded by endorsing the need for much larger trials that would be able to do this. One such trial—the pulmonary embolism prevention trial, supported by the British Heart Foundation—is in progress. We hope that, through the collaboration of orthopaedic surgeons in Britain and elsewhere, this important question will soon be answered reliably for orthopaedic patients. Similar studies in other high risk groups would also be worthwhile.

RORY COLLINS
COLIN BAIGENT
RICHARD PETO
BARBARA FARRELL

Clinical Trial Service Unit,
Radcliffe Infirmary,
Oxford OX2 6HE

Consider the protective effect of blood loss from the gut

EDITOR,—A potentially important effect of aspirin not directly addressed by "the aspirin papers"¹ is loss of iron from occult gastrointestinal bleeding. The decreased incidence of acute myocardial infarction in people taking aspirin regularly may partly result from a protective effect of decreased iron stores.^{2,4} Cumulative gastrointestinal blood loss from repeated doses of aspirin can exceed typical menstrual blood losses.^{3,5} Trivial, clinically invisible blood losses from the stomach can have large, non-trivial effects on stored iron concentrations if they are repeated regularly for months or years.

The finding of increasing protection against myocardial infarction with increased duration of use¹ is consistent with a protective effect of iron loss induced by aspirin. For subjects with substantial amounts of stored iron several years of "menstruating" from the stomach may be needed to exhaust all body iron stores. A typical 50 year old man may have a stored iron burden of 1000 mg. With loss of 3 ml of blood with each daily dose of aspirin, he would take nearly two years to achieve complete iron depletion (1 ml of blood contains approximately 0.5 mg iron).

Even with the highest tolerated doses, regular use of aspirin is not the most effective method of depleting iron stores. This may explain some of the observed variation in protection. The protocols were not designed to decrease stored iron. Minimal protective effects in some trials may have been the result of limited effectiveness of the aspirin regimens in depleting stored iron.

The Antiplatelet Trialists' Collaboration assumes that the immediate antiplatelet effect of aspirin is the only protective mechanism. This assumption imposes narrow limits on interpretation of the data and may jeopardise future investigation on the mechanisms of protection by aspirin. As an initial approach, ferritin should be measured in any frozen serum samples from subjects in the studies cited. Serum ferritin concentrations before and after prolonged regular use of aspirin would allow an estimate of the impact on body iron stores under the trial protocols. Such measurements may confirm an association between decreased stored iron concentrations and a lower incidence of myocardial infarction. Establishing iron loss as a mechanism is important because iron stores can be safely depleted by more effective methods—for example, regular phlebotomy—without adversely affecting platelet function and increasing the risk of serious haemorrhage.

J L SULLIVAN

VAMC (113),
109 Bee Street,
Charleston, SC 29401-5799,
USA