Aspirin for Preventing Venous Thromboembolism

TO THE EDITOR: In their report on the Aspirin to Prevent Recurrent Venous Thromboembolism (ASPIRE) trial, Brighton et al. (Nov. 22 issue) describe a nonsignificant decrease in the rate of recurrent venous thromboembolism and a significant reduction in the rate of major vascular events in patients receiving low-dose aspirin, as compared with those receiving placebo. These findings are similar to those of Becattini et al. (May 24 issue) in their report on the Aspirin for the Prevention of Recurrent Venous Thromboembolism (the Warfarin and Aspirin [WARFASA]) study. However, the biologic effects of aspirin could in part be sex-dependent. Women seem to have a higher baseline level of platelet reactivity than men, but the effect of low-dose aspirin on arachidonic acid–induced aggregation is greater in women. In addition, women have been found to have higher circulating levels of acetylsalicylic acid, because of its slower clearance. Possible sex differences were further suggested by a meta-analysis showing that the use of aspirin was associated with a reduced rate of myocardial infarction with no effect on stroke among men and a reduced rate of stroke with no effect on myocardial infarction among women. Data from the ASPIRE and WARFASA trials, and particularly pooled data with hazard ratios, regarding the effect of aspirin on venous and arterial cardiovascular events according to sex would be useful clinical information.

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with rosvastatin was associated with a reduction of 43% in the risk of venous thromboembolism, as compared with placebo (hazard ratio for rosvastatin, 0.57; \( P = 0.007 \)). The efficacy of statins in preventing venous thromboembolism has been supported in some studies but not in others.³

A recent study verified that statin use was associated with a reduced risk of venous thromboembolism (hazard ratio, 0.29; \( P < 0.001 \)).⁴ This study also showed that dual antiplatelet therapy with aspirin and clopidogrel decreased the occurrence of venous thromboembolism (hazard ratio, 0.19; \( P < 0.001 \)). The combined use of statins and antiplatelet therapy further reduced the occurrence of venous thromboembolism (hazard ratio, 0.16; \( P < 0.001 \)).⁴ It would be interesting to know whether Brighton et al. recorded statin use in their population and whether their results would be affected after adjustment for statin use.

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THE AUTHORS REPLY: Ćulić highlights potential differences between men and women with respect to the platelet inhibitory effects and clinical efficacy of aspirin. Our results indicated that the 447 men in our study, as compared with the 375 women, were almost twice as likely to have recurrent venous thromboembolism (8.6% vs. 4.5%). However, the use of aspirin was associated with a similar reduction in relative risk in men and women (\( P = 0.58 \) for interaction) (see Fig. 3 in the Supplementary Appendix, available with the full text of our article at NEJM.org). Consequent-ly, larger absolute treatment benefits may be expected in men. The reason for higher recurrence rates in men than in women is uncertain. Our planned prospective meta-analysis of the results with respect to individual patients in the ASPIRE and WARFASA trials may provide further insights into the influence of sex on recurrence risk.

Paraskevas questions whether statin use may have affected the results of our study. On the basis of many randomized trials, statins clearly reduce the rate of arterial events, but their effects on venous thrombotic events are less certain.¹ In our study, 61 patients recorded statin use at enrollment, including 34 of 411 patients (8.3%) who were assigned to receive placebo and 27 of 411 patients (6.6%) who were assigned to receive low-dose aspirin. An analysis of the effect of aspirin on venous thromboembolism after adjustment for initial statin use showed results similar to those in the intention-to-treat analysis (hazard ratio, 0.74; 95% confidence interval, 0.53 to 1.05).

Finally, in response to the statement by Paraskevas that our study “showed that aspirin did not reduce the rate of venous thromboembolism”: we reiterate that our study was not powered to show an effect on this outcome. However, when our results are considered in combination with the findings of the WARFASA trial, they are consistent with a reduction of about one third in the rate of recurrent venous thromboembolism after a first episode of venous thromboembolism.

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Since publication of their article, the authors report no further potential conflict of interest.

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