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Hopkins study shows low-dose aspirin suppresses clumping of blood platelets in both sexes

Study challenges earlier research claiming little benefit for women

A once-daily pill of low-dose aspirin helps lower the potential for clot-forming blood cells - in both men and women - to stick together in narrow blood vessels, a study from Johns Hopkins shows.

In what is believed to be the first direct comparison of blood cell testing in both sexes of 81 milligrams of acetyl salicylic acid a day, Hopkins researchers found aspirin therapy prevents the clumping together of these clot-forming cells, called platelets. Clots in blood vessels of the heart and brain can cause heart attacks and strokes.

However, while the drug's overall effects on blood cell function were the same for men and women, the investigators found that women's platelets reacted somewhat more strongly to aspirin before the start of therapy, and remained so even after treatment.

The study findings appear in the *Journal of the American Medical Association* online March 21, and challenge the conclusions from several other recent studies, including the federal Women's Health Study, which showed low-dose aspirin had no effect in preventing heart attacks in women, even though it worked in men. Previous results, the researchers say, were not likely caused by the failure of aspirin to prevent platelets from clumping together and forming blood clots in women.

"Women are clearly benefiting from taking aspirin and should continue to take it to improve their cardiovascular health," says study senior investigator Diane Becker, M.P.H., Sc.D., a professor at The Johns Hopkins University School of Medicine and Bloomberg School of Public Health. "Aspirin has been proven by all previous studies to lower the risk of stroke and, as our latest findings show, it also reduces platelet aggregation that can lead to potentially fatal clots in blood vessels."

"Our results show that aspirin does what it is supposed to do in both men and women," says platelet biologist and study co-author Nauder Faraday, M.D., an associate professor at Hopkins. "But women started at a higher baseline level of platelet aggregation and remained slightly higher even after taking aspirin. So, it remains unclear if the residual differences in platelet function impact the drug's overall beneficial effects, and if the doses used in earlier studies were sufficient to decisively prevent heart attacks in women."

"Further research is required to get a definitive answer as to whom aspirin really benefits, under what circumstances it does work and does not work, and just how much is required in different people," he adds.

Results in both men and women showed that aspirin, taken daily for a two-week period, works by inhibiting key biological pathways that lead to platelet clumping.

Using an electrical measure of how well platelets stick together, researchers found that in aspirin-treated men, clumping decreased by 15.1 ohms. The decrease was statistically the same in aspirin-treated women, at 17.3 ohms. In this test, an ohm is the measure of electrical resistance caused by platelets as they impede the flow of electricity in a wire probe inside a test tube filled with blood.

Moreover, platelet aggregation was largely suppressed in at least three other key pathways related to their function when platelets were stimulated with substances that normally trigger clot formation. Each of these tests involved mixing whole blood, or platelet-rich plasma, from aspirin-treated men and women with various concentrations of each of the main chemical compounds involved in the pathways -- collagen, adenosine diphosphate, and epinephrine - to see how platelets responded.

For example, in aspirin-treated men, platelet clumping went down by 14.6 ohms when 1 microgram of collagen per milliliter was added to whole blood, and decreased by 2.4 ohms when exposed to a higher dose of 5 micrograms per milliliter. In treated women, reductions were the same, at 14.9 ohms and 2.42 ohms, respectively.

When 10 micromoles per liter of adenosine diphosphate were added to whole blood, platelet aggregation decreased the same amount, 0.19 ohms in men and 0.21 ohms in women. Addition of 2 micromoles per liter of epinephrine to platelet-rich plasma produced significantly greater reductions in platelet clumping in treated women, a drop of 36.9 percent, while it was less of a reduction for men, at 31.5 percent. Again, the researchers say, these changes would have been zero if aspirin had had no effect.

Further analysis of results highlighted mainly two factors, platelet reactivity levels before therapy starts and gender, as having played a significant role in predicting the effects of aspirin therapy on platelet clumping. Other factors, such as age, race or known risk factors for heart disease, including smoking, obesity and high blood pressure, were not found to be good predictors of aspirin's beneficial effects.

More than 500 men and 700 women participated in the study, called the Genetic Study of Aspirin Responsiveness (GeneSTAR). Conducted solely at Hopkins from June 2004 to November 2005, the study enrolled participants from across the country who ranged in age from 21 to 80; 31 percent were black and the rest were white. None had previous histories of heart problems, such as a heart attack, but all were considered to be at slightly increased risk of heart disease because of a family history. Fifty percent of women participants were postmenopausal.

Blood testing was conducted both before and after treatment. In total, more than 200 different tests of platelet reactivity were performed and analyzed in the study. Because whole blood contains other cells that affect platelet aggregation, testing was repeated using a purified version of test samples made up of strictly platelet-rich plasma.

At the start of the experiment, laboratory tests of blood platelets in women were found four times more likely than in men to aggregate when exposed to arachidonic acid, a clot-inducing chemical in the pathway that is most suppressed by aspirin.

While taking aspirin, participants maintained a strict and consistent dietary and exercise regimen, with no smoking or consumption of foods that by themselves affect platelet activity, such as caffeine, chocolate, wine or grapefruit juice. Physical examinations and pill counts were conducted to ensure that all participants adhered to the study protocol. Because aspirin reaches its maximal effect

in the body at five days, the researchers say a longer study testing period was not required to determine the drug's effects on platelet function.

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Besides Becker and Faraday, other investigators in this research were Jodi Segal, M.D.; Dhananjay Vaidya, M.D., Ph.D.; Lisa Yanek, M.P.H.; J. Enrique Herrera-Galeano, M.S.; Paul Bray, M.D.; Taryn Moy, M.S.; and Lewis Becker, M.D.

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