

EDITORIALS



The Puzzle of Aspirin and Sex

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Recently, in New York, the geneticist Luigi Luca Cavalli-Sforza began a brilliant seminar with this introduction: “To understand the present, you have to understand history, and to understand biology, you have to understand evolution, because evolution is the history of biology.” Although Cavalli-Sforza’s life of exploration along the branches of the human genetic tree has led him to conclude that there is no genetic basis for race,¹ there is most obviously a genetic basis for sex. So powerful is *la différence* that sexual differentiation probably emerged with the appearance of eukaryotes at least 2 billion years ago, Y emerged from X perhaps 300 million years ago,² and evolution has maintained the duet assiduously ever since. The biologic speculations to explain this success are many, varied, and wonderful. The biologic differences between women and men are equally so, but in this issue of the *Journal*, Ridker and colleagues³ describe a difference between the sexes in the cardiovascular response to aspirin that is at once a puzzle and a coda to the recent crescendo of demands that clinical research must always be organized to account for the biologic differences between women and men.

To an approximation, this study, the Women’s Health Study, is to women what the earlier Physicians’ Health Study, also by the varying group of prolific investigators centered at the Harvard School of Public Health,⁴ was to men. What they find now in women is the inverse of what they found then in men, and that is the puzzle. The Physicians’ Health Study showed that aspirin significantly reduced the risk of myocardial infarction: the reduction was 44 percent in men 50 years of age or older who did not have clinical evidence of coronary disease. There was no significant effect on the risk of stroke and no effect on mortality from cardiovascular causes. The current Women’s Health Study shows, at least in women 65 years of age or older who do not have a

history of cardiovascular disease, that aspirin has no significant effect either on the risk of myocardial infarction or on the risk of death from cardiovascular causes but that it is associated with a 24 percent reduction in the risk of ischemic stroke and a 17 percent reduction in the risk of stroke overall. Furthermore, the authors strengthen their observations with a meta-analysis comprising an additional 55,580 subjects. The findings in men and women are opposite. How can this be?

Aspirin, or acetylsalicylic acid, was synthesized in the mid-19th century as a product of European chemistry and was perhaps designed to be a less irritating version of salicylic acid.⁵ The well-known mechanism of aspirin as a permanent inactivator of both forms of cyclooxygenase, the first enzyme in the biosynthetic pathway of prostanoids, is the basis of its prevention of thrombotic vascular events⁶ and the chemoprevention of cancer. The optimal dose, that which prevents atherothrombosis and minimizes hemorrhage, is unknown; doses as low as 30 mg per day may be effective, and lower doses have not been systematically studied.⁶ Although there are no reports suggesting that the molecular pharmacology of aspirin differs between the sexes, the pharmacodynamics do differ: concentrations of salicylate are higher in women than in men after identical doses of aspirin, and platelets from women and men who have ingested aspirin show different responses when tested *in vitro*.⁷ Aspirin has been shown to be effective in both sexes in many secondary-prevention trials. However, Patrono and colleagues,⁶ in analyzing this field, have shown that absolute atherothrombotic benefit from aspirin is related to the cardiovascular risk in the population studied, and so a comparison of the control cohorts of the Physicians’ Health Study and the Women’s Health Study is relevant.

Table 1 lists some features of the two studies.

The most striking, of course, is the absolute separation of the sexes. Equally salient is the temporal separation, with a span of more than two decades encompassing not only both studies, but also the watershed of our understanding of vascular disease. We cannot know how secular trends during this period contributed to the changed sociobiology of atherosclerosis, but mortality from cardiovascular causes showed an upward trend among women and a downward trend among men.⁸ Time alone makes the studies not directly comparable. What is quite clear, however, is the difference in the risk of myocardial infarction between the two placebo cohorts: the risk was 97.3 per 100,000 person-years in the current Women's Health Study and 439.7 per 100,000 person-years in the Physicians' Health Study. The Women's Health Study enrolled a healthy and health-conscious group of women, 84.5 percent of whom had a 10-year Framingham risk score of less than 5 percent.³ Conversely, and as the authors point out, the relative risk of stroke is much higher in women than it is in men. Thus, on the basis of Patrono and colleagues' conditional-probability analysis,⁶ we might understand why the two studies yielded opposite results for myocardial infarction and stroke. But such conjecture would belie the likely biologic basis of these very different results.

What are some of the biologic cardiovascular differences between women and men? Whereas slightly more women than men die annually of cardiovascular disease, the age-adjusted incidence of coronary heart disease among white men is about three times that among white women (12.5 vs. 4.0 per 1000 person-years), and among black men it is about twice that among black women (10.6 vs. 5.1 per 1000 person-years).⁸ Vascular anatomy is also different: women have smaller coronary arteries, and quite remarkably, when a man receives a woman's heart through cardiac transplantation, the smaller female arteries grow larger in the male recipient, independently of body-surface area.⁹ Similarly, carotid anatomy and the distribution of atherosclerotic plaque are different,¹⁰ and histopathologically, plaque has been described as "younger" in women than in men. Vascular reactivity and electrical repolarization of the heart (and its response to drugs) are different, and stress cardiomyopathy is nine times as frequent among women as it is among men.¹¹ Some, but probably not all, of these differences are related to the hormonal milieu. Recently, atheroprotection was linked directly to estrogen,¹² with the observa-

Table 1. Comparison of Selected Features of the Aspirin Components of the Women's Health Study and the Physicians' Health Study.

Variable	Women's Health Study	Physicians' Health Study
Sex of participants	Female	Male
Study period	1993–2004	1982–1988*
No. of participants	39,876	22,071
Age of participants (yr)		
Mean	54.6	53.2
Range	45–89	40–84
Alternate-day dose of aspirin (mg)	100	325
Follow-up (yr)		
Mean	10.1	5.0
Range	8.2–10.9	3.8–6.4*
Rate of myocardial infarction in the placebo group (no./100,000 person-yr)	97.3	439.7
Rate of stroke in the placebo group (no./100,000 person-yr)	134.3	179.4

* Randomization began in August 1981 for 124 participants in the pilot study.

tion that estrogen up-regulates prostacyclin production by receptor-mediated activation of cyclooxygenase-2 — an observation that may be relevant to the Women's Health Study–Physicians' Health Study conundrum. The cardiovascular systems of women and men are not the same, differing expression of disease follows, and the disquieting results of the current study should not be a complete surprise.

The investigators of the Physicians' Health Study⁴ and the Women's Health Study³ have produced two landmark studies on the use of aspirin in asymptomatic persons, the results of which segregate according to sex. On the basis of the Women's Health Study,³ for now it would appear reasonable to avoid prescribing "low-dose" aspirin, defined as a daily dose of 75 to 100 mg or so, as a preventative measure for coronary disease in women under the age of 65 years unless the global risk score is very high. But what about the prevention of stroke? Ridker and colleagues conclude, correctly, that the decision to prescribe aspirin for the primary prevention of stroke and other vascular events should be left to the patient and her physician, invoking an ancient truth. Hippocrates, dean of medicine on the island of Cos some 2400 years ago, popularized white-willow salicin, the precursor of aspirin, and wrote in the first of the Aphorisms, "Life is short, the art long, opportunity fleeting,

experiment treacherous, judgment difficult.” Life is longer now, but the art is longer still. The aspirin saga needs additional chapters, and clinical research, as the current authors and so many other authorities have concluded, needs always to account for the evolutionary biology of sex.

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Warfarin, Aspirin, and Intracranial Vascular Disease

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The Warfarin–Aspirin Symptomatic Intracranial Disease (WASID) Trial, funded by the National Institute of Neurological Disorders and Stroke and reported by Chimowitz et al.¹ in this issue of the *Journal*, was a careful comparison of these two therapies in patients with cerebrovascular events attributed to intracranial atherosclerosis. The WASID Trial, in concert with other, smaller studies,^{2,3} clearly shows that symptomatic intracranial atherosclerotic stenosis is a marker of extremely aggressive vascular disease. Ischemic stroke, brain hemorrhage, or death from vascular causes other than stroke occurred within two years in approximately 22 percent of the patients, whether they were treated with high-dose aspirin (1300 mg per day) or warfarin. In addition, the probability of ischemic stroke at two years did not differ between the two treatment groups: it was 0.20 among patients treated with aspirin and 0.17 among those treated with warfarin. Stroke in patients with intracranial atherosclerosis can occur by multiple mechanisms. In the WASID Trial, 73 percent of the recurrent cerebrovascular events occurred in the territory of the index vessel, defined as one having at least 50 percent stenosis.

Stroke in this population probably also occurred because of hypertensive vascular disease and the risk of embolism from the aortic, cardiac, and cerebrovascular sources associated with systemic atherosclerosis.

The outcome data from WASID clarify some but not all the relevant issues. The use of a nonstandard, large dose of aspirin and the absence of evidence tying the dose of aspirin to a benefit in stroke prevention make it difficult to choose an antiplatelet regimen and a dose in clinical practice. The occurrence of more deaths due to cancer, congestive heart failure, diabetes, and even cardiac causes in the warfarin-treated group than in the aspirin-treated group stands out as incongruous with the results of previous warfarin studies involving tens of thousands of patients with vascular disease.⁴ The lenient classification of bleeding disorders as major hemorrhage, some of which do not carry the same level of disability as stroke, also contributed to a higher rate of “major hemorrhage” among warfarin-treated patients than in previous studies. Given that there was no significant difference in the primary end point between the two treatment groups, the study was appropriately stopped be-