

# Long-Term Aspirin for Women: What Did the Women's Health Study Really Show?

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The National Heart, Lung and Blood Institute of the National Institutes of Health was the major sponsor of the Women's Health Study,<sup>1</sup> part of which concerned the use of aspirin for the primary prevention of heart disease. The NIH press release of Mar 7, 2005, followed the content of the abstract of the article published in the *New England Journal of Medicine*.<sup>2</sup>

In this trial, the largest and longest one ever done in women, half of 40,000 healthy women aged 45 years or more at the start were assigned to take 100 mg of aspirin every other day, and half to take placebo of like appearance. The average duration of follow-up was 10 years.

It was honestly reported that aspirin did *not* prevent first heart attacks or death from cardiovascular causes. However, neither the press release nor the abstract of the published report mentioned that there was no significant difference in all-cause mortality (relative risk, RR = 0.95, NS), surely the most important endpoint.

Stroke was said to be 17% less frequent with aspirin. First, note that this is a relative number. The absolute reduction, not explicitly stated, was 0.22% for the 10-year period, or about 0.022 % per year, a trivial benefit. Second, note that this was nonfatal stroke only; the incidence of fatal stroke was unchanged. Third, note that the type of stroke meant was actually ischemic stroke (from thrombi or emboli), not hemorrhagic stroke. The 26% reduction of ischemic stroke in women 65 or older was also trivial in absolute terms.

Both the press release and the abstract minimized the side effects of increased incidence of several types of bleeding caused by aspirin. In fact, 2,067 more women on aspirin reported easy bruising; 480 more reported nosebleed (epistaxis); 160 more reported hematuria; 129 more reported peptic ulcer; 159 more reported gastrointestinal bleeding; and of these, 36 required transfusions.

What may be the most serious problem caused by long-term aspirin use, cataracts, was not mentioned at all. In the Australian Blue Mountain study, subjects taking aspirin of unspecified dose for more than 10 years, starting at age 55 or younger, had a RR=2 for cataracts.<sup>3</sup> The United States spent \$3.4 billion for cataract surgery in 1995;<sup>4</sup> the prevalence of cataracts is 17% in persons aged 40 and older.<sup>5</sup> Around 1991, about one-fifth of Americans took aspirin.<sup>6</sup> If all did, the prevalence of cataracts could climb to 30%.

The press release stated: "The bottom line is that many women, especially those 65 and older, may benefit from taking aspirin every other day to prevent stroke." This advice fails to put into perspective the trade-off between risks and benefits: over 10 years possibly 45 nonfatal strokes of unstated severity were prevented in the 20,000 study participants on aspirin, at the cost of hundreds of episodes of nonfatal bleeding, at least 36 of which were severe enough to require transfusion, among other adverse effects.

The aspirin and placebo pills were provided by Bayer HealthCare. Several of the authors of the paper in the *New England Journal of Medicine* cited financial ties with Bayer.

The risks in this study were lower than those in an earlier 3.1-year observational trial that included separate results for women taking daily aspirin of unstated form and dose, in which the RR of mortality was 1.12 (3.8% died vs. 3.4% of those not taking aspirin, unadjusted).<sup>7</sup> One may speculate that the very low dose of aspirin in the Women's Health Study explained the lower risk.

The dose used in the Women's Health Study was much lower than that used in the all-male Physicians Health Study reported in 1989.<sup>8</sup> In that study, 325 mg of "aspirin" every other day was used.

Most reporters were not aware that Bufferin<sup>TM</sup> containing magnesium, a beneficial supplement in its own right,<sup>6</sup> was actually used. After 7 years the result usually making the headlines and the guidelines was a drop in the RR of heart attack to 0.31, seemingly a good result. However, this amounted to an absolute drop of only 0.11% per year, a trivial outcome. Moreover, these were nonfatal heart attacks. Rarely mentioned is that all-cause mortality was unchanged (RR = 0.96, NS). There were also the same sorts of bleeding seen in women, with a RR = 1.32.<sup>6</sup>

A later UK trial of plain aspirin on 5,500 male physicians for 7 years told a different story. The RR of nonfatal heart attack was a less impressive 0.68. The RR of mortality was 1.06, considered a nonsignificant increase.<sup>6,9</sup>

It appears clear that for both men and women the adverse effects of long-term aspirin more than outweigh its small potential benefit for primary prevention of heart disease and stroke. Others agree.<sup>10</sup> On the other hand, in patients who have already had a myocardial infarction, the risk of a second event is high enough to make the use of aspirin worthwhile. (Buffered aspirin is probably better because of the magnesium content.) What is not generally reported in this context is that just 5 weeks of aspirin therapy provides all the benefit.<sup>7</sup>

In conclusion, a critical analysis of the Women's Health Study shows the importance of a careful look at all-cause mortality and the absolute reduction in the risk of the events of interest, compared with the risk of adverse effects of an intervention. This is especially true when an intervention is used in a healthy population for primary prevention.

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