

Aspirin in the Primary Prevention of Myocardial Infarction

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Featured Article: Steering Committee of the Physicians' Health Study Research Group: Belanger C, Buring JE, Cook N, Eberlein K, Goldhaber SZ, Gordon D, et al. Final report on the aspirin component of the ongoing Physicians' Health Study. *N Engl J Med* 1989;321:129–35.⁴

In 1897, Felix Hoffman, a chemist working at Bayer in Elberfeld, Germany, synthesized the first stable form of acetylsalicylic acid. He was motivated, in part, to help his father, who suffered from painful and disabling arthritis. In the 20th century, acetylsalicylic acid, under its trade name, aspirin, became the most widely used drug in the world, but not until 1971 did Sir John Vane elucidate a new and novel mechanism of aspirin to irreversibly inhibit platelet aggregation. In 1982, Vane was awarded the Nobel Prize in physiology or medicine, but the role of aspirin in the prevention of a first myocardial infarction (MI)⁵ was yet to be discovered.

In 1982, the Physicians' Health Study (PHS) was funded by the US NIH as an investigator-initiated research grant. The PHS randomized 22 071 dedicated and conscientious male physicians at low risk of a first cardiovascular disease (CVD) event. On December 18, 1987, the independent Data and Safety Monitoring Board of the PHS unanimously recommended the early termination of the aspirin component, primarily because of the emergence of a statistically extreme ($P < 0.00001$) reduction in risk of a first MI among individuals randomly assigned to aspirin, compared with placebo. In January 1988, the preliminary results were reported (1). In July 1989, the *New England Journal of Medicine* report featured here described the final results, showing that aspirin produced a highly significant 44% reduction in the risk of a first MI.

An important personal motivation for my pursuing the primary prevention of CVD was the fact that my

56-year-old father suffered sudden cardiac death when I was just 17 years of age. I gratefully, gladly, and fully embraced what my mentors from the University of Oxford, Richard Doll and Richard Peto, espoused, that "death is inevitable but premature death is not." Furthermore, the PHS was the first to demonstrate the potential role of inflammatory markers, especially C-reactive protein, as diagnostic tools in the prevention and treatment of CVD (2). In fact, that 1997 report is also a citation classic, having been cited >3000 times since it was published and featured in *Clinical Chemistry* (3). Since the PHS, results for 5 additional large-scale primary prevention trials of aspirin have been published, including 4 studies of low-risk, apparently healthy men and women, as well as their meta-analyses. There is general consensus that aspirin use produces a statistically significant and clinically important reduction in the risk of a first MI. In fact, organizations such as the American College of Cardiology, the American Heart Association, the European Society of Cardiology, the Interamerican Society of Cardiology, and the U.S. Preventive Services Task Force have issued guidelines for aspirin for the primary prevention of a first MI. Nonetheless, as was the case with the PHS, the available data on stroke and CVD death remain inconclusive and statistically nonsignificant (4). The totality of the randomized evidence suggests that there are no differences between men and women in the response to aspirin.

At present, until more compelling evidence becomes available, any decision to prescribe aspirin for primary prevention should be an individual clinical judgment that weighs the absolute benefit in reducing the risk of a first MI against the absolute risk of major bleeding. The necessary compelling evidence may derive from an ongoing large-scale randomized trial of aspirin in the primary prevention of MI, stroke, and CVD death among men and women at moderate to high risk of a first event (5). More importantly, the increasing burden of CVD in developed as well as developing countries underscores the need for the more widespread and appropriate use of therapies of proven benefit in the primary prevention of CVD (6). If the emerging data turn out to be conclusive, then aspirin should be considered routinely for apparently healthy men and women at sufficient risk, as an adjunct, not as an alternative, to therapeutic lifestyle changes. That option would be particularly attractive in developing

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⁴ This article has been cited 980 times since publication.

⁵ Nonstandard abbreviations: MI, myocardial infarction; PHS, Physicians' Health Study; CVS, cardiovascular disease.

countries, because aspirin is extremely inexpensive and is available over the counter.

From bench to bedside, all these endeavors have led us down the trails of research to discoveries that have revealed newer and novel mechanisms of aspirin, as well as important findings from observational epidemiologic studies and randomized trials. Among the newer and novel mechanisms is the enhancement of nitric oxide formation by aspirin. The results of epidemiologic studies and randomized trials indicate definite additive benefits of aspirin and statins. In the context of the totality of the evidence, recent results also suggest the potential of aspirin to prevent and treat migraine, to delay progression of memory loss, and to prevent a variety of cancers, especially colorectal. For all these reasons, aspirin, which was termed the wonder drug of the 20th century, may become the wonder drug of the 21st century.

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