

An Update on Aspirin in the Primary Prevention of Cardiovascular Disease

Rachel S. Eidelman, MD; Patricia R. Hebert, PhD; Steven M. Weisman, PhD; Charles H. Hennekens, MD, DrPH

Background: In 1988, the aspirin component of the Physicians' Health Study, a randomized, double-blind, placebo-controlled trial of 22071 apparently healthy men was terminated early, due principally to a statistically extreme ($P < .00001$) 44% reduction in the risk of a first myocardial infarction (MI). The Cardio-Renal Drugs Advisory Committee recommended that the US Food and Drug Administration approve professional labeling of aspirin to prevent first MI. The agency did not act on this recommendation because the only other trial, the British Doctors' Trial of 5139 men, showed no significant benefits. Since that time, 3 additional randomized trials (which included men and women) of aspirin in the primary prevention of MI have been published.

Methods: A computerized search of the English literature from 1988 to the present revealed 5 published trials: the Physicians' Health Study (22071 participants), the British Doctors' Trial (5139), the Thrombosis Prevention Trial (5085), the Hypertension Optimal Treatment

Study (18790), and the Primary Prevention Project (4495).

Results: Among the 55 580 randomized participants (11 466 women), aspirin was associated with a statistically significant 32% reduction in the risk of a first MI and a significant 15% reduction in the risk of all important vascular events, but had no significant effects on non-fatal stroke or vascular death.

Conclusions: The current totality of evidence provides strong support for the initial finding from the Physicians' Health Study that aspirin reduces the risk of a first MI. For apparently healthy individuals whose 10-year risk of a first coronary event is 10% or greater, according to the US Preventive Services Task Force and the American Heart Association, the benefits of long-term aspirin therapy are likely to outweigh any risks.

Arch Intern Med. 2003;163:2006-2010

THE FIRST reported trial of aspirin in the primary prevention of cardiovascular disease (CVD) was the Physicians' Health Study (PHS).¹ This double-blind, placebo-controlled, 2 × 2 factorial design study randomized 22071 apparently healthy male physicians aged between 40 and 84 years to 325 mg of aspirin (supplied as Bufferin by Bristol-Myers Squibb) with placebo on alternate days; 50 mg of beta carotene (supplied as Lurotin by BASF Corp) with its placebo on alternate days; both active agents; or both placebos. The trial was terminated early, after 5 years of treatment and follow-up, based on the unanimous recommendation of the independent Data and Safety Monitoring Board. This recommendation was due principally to the emergence of a statistically extreme ($P < .00001$) 44% reduction in the risk of a first myocardial infarction (MI) among aspirin users.² The British Doc-

tors' Trial³ randomized 5139 apparently healthy male physicians aged between 50 and 78 years to 500 mg of aspirin daily (regular, soluble, or effervescent, supplied by the Aspirin Foundation) or to open control for 6 years. There was no significant benefit on the risk of a first MI, but this trial had less than 50% power to detect even a 44% or greater reduction. An overview of these 2 trials⁴ demonstrated a statistically extreme ($P < .00002$) 33% reduction in the risk of a first MI due to aspirin use. At that time, the Cardio-Renal Drugs Advisory Committee to the US Food and Drug Administration voted to approve professional labeling of aspirin to reduce the risk of a first MI. The agency did not accept that recommendation, largely because the only 2 reported trials were interpreted to show divergent results.⁵ Ten years later, in 1998, 2 additional trials of primary prevention were published, namely, the Thrombosis Prevention Trial⁶ and the Hypertension Optimal Treat-

Author affiliations are listed at the end of this article.

Table 1. Features of the 5 Randomized Trials of Aspirin in the Primary Prevention of Cardiovascular Disease

Features	Physicians' Health Study (1988)	British Doctors' Trial (1988)	Thrombosis Prevention Trial (1998)	Hypertension Optimal Treatment Study (1998)	Primary Prevention Project (2001)
Subjects randomized, No.	22 071	5139	5085	18 790	4495
Follow-up, y	5 (mean)	6 (mean)	≥5	4 (mean)	3.6 (mean)
Patient population	Apparently healthy male physicians	Apparently healthy male physicians	Men at high risk for cardiovascular disease	Men and women with hypertension and diastolic blood pressure from 100 to 115 mm Hg	Men and women with ≥1 major cardiovascular risk factor
Age range, y	40-84	50-78	45-69	50-80	50-80+
Female sex, %	0	0	0	47	57.7
Aspirin dosage	325 mg every other day	500 mg/d	75 mg/d (controlled release)	75 mg/d	100 mg/d

ment (HOT) study.⁷ The Thrombosis Prevention Trial randomized in a 2 × 2 factorial design 5085 men aged between 45 and 69 years who were at high risk for CVD to 75 mg/d of controlled-release aspirin (supplied by Bayer); a 4.1 mg/d mean dose of warfarin; both active agents; or placebo for more than 5 years. This trial demonstrated a significant 32% reduction in the risk of a first nonfatal MI among aspirin users.⁶ In the HOT trial, 18 790 participants (9907 men and 8883 women) aged between 50 and 80 years who had diastolic blood pressure measurements between 100 and 115 mm Hg were randomized in a 2 × 2 factorial design to 75 mg/d of aspirin (supplied by Bamycor and Astra); 5 mg/d of felodipine with variable escalating doses; both active agents; or placebo for 4 years. This trial demonstrated a significant 36% decrease in the risk of a first MI as well as a significant 15% reduction in the risk of any important vascular event among aspirin users.⁷

METHODS

OBJECTIVE

From 1988 to 1998 we conducted a computerized search of the English literature and identified 4 published randomized trials of aspirin in the primary prevention of CVD. In our previous meta-analysis of these trials, aspirin therapy significantly reduced the risk of a first MI by 32% and the risk of any important vascular event (nonfatal MI, nonfatal stroke, or vascular death) by 13%.⁸ From 1998 to the present, a subsequent review of the English literature revealed 1 additional primary prevention trial of aspirin as well as new guidelines on the use of aspirin in the primary prevention of CVD.

The fifth and most recently published trial of aspirin in the primary prevention of MI is the Primary Prevention Project.⁹ In this trial, 4495 apparently healthy men (1912) and women (2583) aged from 50 to more than 80 years who had 1 or more major risk factors for CVD were randomized in a 2 × 2 factorial design to take 100 mg/d of enteric-coated aspirin (supplied by Bayer AG); 300 mg/d of vitamin E; both active agents; or open control. The trial was terminated early principally because of a significant 23% reduction in the risk of all cardiovascular events and of a 44% reduction in the risk of cardiovascular death among aspirin users, in the context of the beneficial effects of aspirin in the previously reported indi-

vidual trials and their meta-analysis. There was also a possible but nonsignificant 31% reduction in the risk of MI and a 33% reduction in the risk of stroke.

Recently, the US Preventive Services Task Force¹⁰ and the American Heart Association¹¹ issued new guidelines for aspirin in the primary prevention of MI in apparently healthy men and women. In this article, we update our meta-analysis and address the recently reported guidelines.

DATA SOURCES AND STUDY SELECTION

To perform the meta-analysis, we used the published data from the PHS,² the British Doctors' Trial,³ the Thrombosis Prevention Trial,⁶ the HOT study⁷ and the Primary Prevention Project⁹ (Table 1). The outcomes examined were the same as those used for the meta-analysis of secondary prevention,¹² namely, a combined end point of any important vascular event (nonfatal MI, nonfatal stroke, or vascular death), and each of these individual components separately.

The criteria for inclusion of trials were as follows: (1) aspirin alone was used for the primary prevention of CVD, as opposed to combined interventions; (2) comparisons of outcomes were made between aspirin groups and either placebo or open control groups; and (3) data were available on MI, stroke, and vascular deaths.

DATA EXTRACTION

We performed stratified analyses by trial to avoid direct comparisons between individuals within trials. We calculated the difference between the observed (*O*) and the expected (*E*) number of events, and its variance, from standard 2 × 2 tables of outcome by treatment. Difference and variance (*V*) were then summed over trials to give the grand total for *O* - *E* events and its *V*. We then based significance tests on comparisons of *z* scores, with $z = (O - E) / \sqrt{V}$, assuming the standard normal distribution and *P* denoting the 2-sided significance level. The typical odds ratio for these trials was calculated by the 1-step method from $b = (O - E) / \sqrt{V}$, either as $\exp(b)$ or, for rare events, as $(2 + b) / (2 - b)$. For odds ratios between 0.5 and 2, these 2 methods gave almost identical answers.¹²

The British Doctors' Trial³ used a 2:1 randomization ratio, so we multiplied the control group in this trial by 2 when calculating "adjusted" control totals. When comparing the percentages affected in the treatment and in the adjusted control groups, we calculated the standard error of the difference (*D*) between these percentages as D/z .¹²

Table 2. Nonfatal Myocardial Infarction (MI) and Nonfatal Stroke in the 5 Randomized Trials of Aspirin in the Primary Prevention of Cardiovascular Disease

Trial	Aspirin			Control		
	Nonfatal MI, No.	Nonfatal Stroke, No.	Subjects Randomized, No.	Nonfatal MI, No.	Nonfatal Stroke, No.	Subjects Randomized, No.
PHS	129	110	11 037	213	92	11 034
BDT	80	61	3429*	41	27	1710*
TPT	94	33	2545	137	42	2540
HOT†
PPP	15	15	2226	22	18	2269
Total	318	219	19 237	413	179	17 553
Statistical analysis						
Relative risk	0.68	1.06				
95% Confidence interval	0.59-0.79	0.87-1.29				

Abbreviations: BDT, British Doctors' Trial; HOT, Hypertension Optimal Treatment study; PHS, Physicians' Health Study; PPP, Primary Prevention Project; TPT, Thrombosis Prevention Trial.

*A 2:1 randomization of aspirin to control was used.

†Data not available.

Table 3. Ischemic vs Hemorrhagic Stroke (Fatal and Nonfatal) in the 5 Randomized Trials of Aspirin in the Primary Prevention of Cardiovascular Disease

Trial	Aspirin			Control		
	Ischemic Stroke, No.	Hemorrhagic Stroke, No.	Subjects Randomized, No.	Ischemic Stroke, No.	Hemorrhagic Stroke, No.	Subjects Randomized, No.
PHS	91	23	11 037	82	12	11 034
BDT	21	13	3429*	7	6	1710*
TPT	21	12	2545	33	6	2540
HOT†
PPP	14	2	2226	21	3	2269
Total	147	50	19 237	141	27	17 553
Statistical analysis						
Relative risk	0.97	1.56				
95% Confidence interval	0.77-1.22	0.99-2.46				

Abbreviations: BDT, British Doctors' Trial; HOT, Hypertension Optimal Treatment study; PHS, Physicians' Health Study; PPP, Primary Prevention Project; TPT, Thrombosis Prevention Trial.

*A 2:1 randomization of aspirin to control was used.

†Data not available.

RESULTS

A total of 2402 CVD end points occurred among 55 580 randomized participants (11 466 women). There was no significant evidence of heterogeneity among the trials. **Table 2** shows the number of participants who experienced nonfatal MI and nonfatal stroke. For nonfatal MI, there was a statistically significant risk reduction of 32% associated with aspirin therapy (relative risk [RR], 0.68; 95% confidence interval [CI], 0.59-0.79). For nonfatal stroke, there was no significant effect but the CIs included the plausible decrease seen in the trials of secondary prevention,¹² as well as a small-to-moderate increase (RR, 1.06; 95% CI, 0.87-1.29).

With respect to stroke subtypes, **Table 3** shows a small, nonsignificant 3% reduction in ischemic stroke, but the CIs were wide (RR, 0.97; 95% CI, 0.77-1.22). For hemorrhagic stroke, although based on small numbers of events, there was a 56% increase, which was of borderline statistical significance (RR, 1.56; 95% CI, 0.99-2.46).

Table 4 shows that the proportion of participants who experienced any important vascular event (combined end point of vascular death, nonfatal MI, or nonfatal stroke) was generally lower in the aspirin groups. In the meta-analysis, there was a statistically significant 15% reduction in the risk of any important vascular event associated with aspirin therapy (RR, 0.85; 95% CI, 0.79-0.93). For vascular deaths, there was no significant reduction in risk although the CIs were wide and included the plausible decrease seen in the trials of secondary prevention,¹² as well as a small increase (RR, 0.98; 95% CI, 0.85-1.12).

COMMENT

The current totality of evidence provides strong support for the initial findings from the PHS^{1,2} that aspirin significantly reduces the risk of a first MI in apparently healthy individuals. This meta-analysis indicates that aspirin significantly reduces the risk of a first MI by 32%

Table 4. Any Important Vascular Event and Vascular Death in the 5 Randomized Trials of Aspirin in the Primary Prevention of Cardiovascular Disease

Trial	Aspirin			Control		
	Any Important Vascular Event, No.	Vascular Death, No.	Subjects, No.	Any Important Vascular Event, No.	Vascular Death, No.	Subjects, No.
PHS	307	81	11 037	370	83	11 034
BDT	289	148	3429	147	79	1710
TPT	228	101	2545	260	81	2540
HOT	315	133	9399	368	140	9391
PPP	47	17	2226	71	31	2269
Total	1186	480	28 636	1216	414	26 944
Statistical analysis						
Relative risk	0.85	0.98				
95% Confidence interval	0.79-0.93	0.85-1.12				

Abbreviations: BDT, British Doctors' Trial; HOT, Hypertension Optimal Treatment study; PHS, Physicians' Health Study; PPP, Primary Prevention Project; TPT, Thrombosis Prevention Trial.

and any important vascular event by 15%, but there are still insufficient numbers of strokes or vascular deaths to yield conclusive results. The magnitude of reduction in risk of a first MI is similar to that published in the secondary prevention trials¹²; nonetheless, since the absolute risks are much lower in primary than in secondary prevention, the absolute benefits are similarly lower.

For hemorrhagic stroke, overviews of secondary and primary prevention trials suggest an increased risk of about 1 to 2 per 1000 patients. These comparisons reinforce the observation that in primary and secondary prevention trials, serious adverse effects, principally hemorrhagic stroke, tend to be about the same.

Of the 5 primary prevention trials of aspirin completed to date, HOT⁷ randomized 8883 women and the Primary Prevention Project⁹ 2583, for a total of 11 466. In HOT, subgroup analyses were presented for women and there was a possible but nonsignificant 19% reduction in risk of a first MI.¹³ In the Primary Prevention Project, the authors reported that the magnitude of benefit in women and men equaled the overall 31% reduction in risk of a first MI. Thus, the overall point estimate of the reduction in risk of a first MI for women who use aspirin therapy is about 22%, but the numbers of strokes and vascular deaths remain insufficient for analysis. In this regard, if a daily dose of 50 mg has clinical relevance, the ongoing Women's Health Study¹⁴ should provide important relevant information on the effect of aspirin on stroke and its subtypes, as well as vascular death. In the meta-analysis of secondary prevention trials, daily doses of 75 mg to more than 1500 mg demonstrated a significant 25% ($\pm 3\%$ SE) reduction in important vascular events. In the meta-analysis of the 3 secondary prevention trials of less than 75 mg of aspirin daily, the corresponding estimate was 13% ($\pm 8\%$ SE).¹²

Despite conclusive data from the trials of secondary prevention and professional labeling by the Food and Drug Administration, there is underutilization and mismeasurement with aspirin.¹⁵ As regards underutilization, in a recent survey, fewer than 50% of eligible patients in secondary prevention were prescribed aspirin. With respect to mismeasurement, 21% of the patients prescribed aspirin were actually taking acetaminophen (11%) or nonsteroi-

dal anti-inflammatory drugs (10%). The absolute benefit of aspirin is greater to the individual patient in secondary prevention and greater to the health of the general public in primary prevention. Thus, the more widespread and appropriate use of aspirin would prevent more than 25 000 premature CVD events per year in secondary prevention but more than 150 000 in primary prevention.¹⁶

With respect to aspirin in the primary prevention of CVD, considerations for use include the 10-year risk of the individual, the side effects of the long-term administration of aspirin, and the clear reduction in risk of a first MI. The US Preventive Services Task Force¹⁰ and the American Heart Association recommend aspirin for men and women whose 10-year risk of a first coronary event is 10% or greater.¹¹ These recommendations are virtually identical to the results of a previous meta-analysis of risks.¹⁷ This 10-year risk of 10% or greater is also the level at which the recently published National Cholesterol Education Program guidelines recommend initiation of statin treatment for apparently healthy individuals with low-density lipoprotein cholesterol levels higher than 130 mg/dL (3.36 mmol/L).^{18,19} Furthermore, the different mechanisms of action of aspirin (primarily on thrombosis) and statins (primarily on atherosclerosis) suggested that their benefits were additive,²⁰ and recent data have demonstrated this to be the case.²¹ An unanswered question, however, is the identification of the particular risk factors for the subgroups of apparently healthy men and women who are at such increased risk of a first MI that the benefits of aspirin clearly outweigh the risks.

Accepted for publication November 15, 2002.

From the Division of Cardiovascular Research, Mount Sinai Medical Center—Miami Heart Institute, Miami Beach, Fla (Drs Eidelman and Hennekens); Department of Internal Medicine (Cardiology), Yale University School of Medicine, New Haven, Conn (Dr Hebert); Innovative Science Solutions, Morristown, NJ (Dr Weisman); and Departments of Medicine & Epidemiology and Public Health, University of Miami School of Medicine, Miami, Fla (Dr Hennekens). Dr Eidelman receives grants from Bayer and Pfizer. Dr Hennekens receives grants from Bayer and serves as consultant to Astra-Zeneca, Bayer,

Bristol-Myers Squibb, Chattem, DelacoGlaxo-SmithKline, McNeil, Novartis, Pfizer, and Reliant. Dr Weisman serves as a consultant to Bayer, GlaxoSmithKline, Pharmacia, and Boehringer-Ingelheim.

Corresponding author and reprints: Charles H. Hennekens, MD, DrPH, 2800 S Ocean Blvd, PH-A, Boca Raton, FL 33432 (e-mail: PROFCHHMD@prodigy.net).

REFERENCES

1. The Steering Committee of the Physicians' Health Study Research Group. Findings from the aspirin component of the ongoing Physicians' Health Study. *N Engl J Med.* 1988;318:262-264.
2. The Steering Committee of the Physicians' Health Study Research Group. Final report on the aspirin component of the ongoing Physicians' Health Study. *N Engl J Med.* 1989;321:129-135.
3. Peto R, Gray R, Collins R, et al. Randomized trial of prophylactic daily aspirin in British male doctors. *BMJ.* 1988;296:313-316.
4. Hennekens CH, Peto R, Hutchison GB, Doll R. An overview of the British and American aspirin studies [letter]. *N Engl J Med.* 1988;318:923-924.
5. Internal analgesic, antipyretic, and antirheumatic drug products for over-the-counter human use: final rule for professional labeling of aspirin, buffered aspirin, and aspirin in combination with antacid drug products. 63 *Federal Register* 56802-56817 (1998).
6. The Medical Research Council's General Practice Research Framework. Thrombosis Prevention Trial: randomized trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk. *Lancet.* 1998;351:233-241.
7. Hannson L, Zanchetti A, Carruthers SG, et al, for the HOT Study Group. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomized trial. *Lancet.* 1998;351:1755-1762.
8. Hebert PR, Hennekens CH. An overview of the 4 randomized trials of aspirin therapy in the primary prevention of vascular disease. *Arch Intern Med.* 2000;160:3123-3127.
9. Collaborative Group of the Primary Prevention Project. Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomized trial in general practice. *Lancet.* 2001;357:89-95.
10. US Preventive Services Task Force. Aspirin for the primary prevention of cardiovascular events: recommendation and rationale. *Ann Intern Med.* 2002;136:157-160.
11. Pearson TA, Blair SN, Daniels SR, et al. AHA guidelines for primary prevention of cardiovascular disease and stroke: 2002 update: consensus panel guide to comprehensive risk reduction for adult patients without coronary or other atherosclerotic vascular diseases. *Circulation.* 2002;106:388-391.
12. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomized trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ.* 2002;324:71-86.
13. Kjeldsen SE, Kolloch RE, Leonette G, et al, for the HOT Study Group. Influence of gender and age on preventing cardiovascular disease by antihypertensive treatment and acetylsalicylic acid: the Hypertension Optimal Treatment (HOT) study. *J Hypertens.* 2000;18:629-642.
14. Buring JE, Hennekens CH, for the Women's Health Study Research Group. The Women's Health Study: summary of the study design. *J Myocardial Ischemia.* 1992;4:27-29.
15. Cook NR, Chae CU, Mueller FB, Landis S, Saks AM, Hennekens CH. Mis-medication and under-utilization of aspirin in the prevention and treatment of cardiovascular disease. *MedGenMed* [serial online] 1999;1. Available at: <http://www.medscape.com/viewarticle/408025>. Accessed December 20, 2002.
16. Hennekens CH, Buring JE. *Epidemiology in Medicine*. Boston, Mass: Little Brown & Co; 1987.
17. Sanmuganathan PS, Ghahramani P, Jackson PR, Wallis EJ, Ramsay LE. Aspirin for primary prevention of coronary heart disease: safety and absolute benefit related to coronary risk derived from meta-analysis of randomized trials. *Heart.* 2001;85:265-271.
18. Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA.* 2001;285:2486-2497.
19. Eidelman RS, Lamas GL, Hennekens CH. The new National Cholesterol Education Program guidelines: clinical challenges for more widespread therapy of lipids to treat and prevent coronary heart disease. *Arch Intern Med.* 2002;162:2033-2038.
20. Hebert PR, Pfeffer MA, Hennekens CH. Additive effects of aspirin and statins. *J Cardiovasc Pharmacol Ther.* 2002;7:77.
21. Hennekens CH, Sacks F, Tomkin A, et al. Additive benefits of pravastatin and aspirin to reduce risks of cardiovascular disease. *Arch Intern Med.* In press.