

## Aspirin for the Primary Prevention of Stroke and Myocardial Infarction: Ineffective or Wrong Dose?

More than 40 million Americans take aspirin for the primary or secondary prevention of myocardial infarction and stroke, including approximately half of all those aged 65 years or more.<sup>1</sup> The daily dose varies from 81 mg (1 baby aspirin) to 325 mg (1 adult aspirin). The efficacy of aspirin for the *secondary* prevention of myocardial infarction and stroke has been validated by multiple randomized clinical trials.<sup>2</sup>

The first randomized clinical trial to establish the efficacy of aspirin for *primary* prevention was the US Physicians Health study published in 1989.<sup>3</sup> More than 22,000 male US physicians were randomized to 325 mg of aspirin every other day versus placebo and followed for 5 years. The incidence of fatal or nonfatal myocardial infarction was 44% lower in those taking aspirin (odds ratio = 0.56; 95% confidence interval, 0.45-0.70;  $P < .0001$ ). The decreased risk of myocardial infarction was present in those aged 50 years or more. There was no significant difference in mortality or stroke incidence.<sup>3</sup>

Multiple organizations and expert panels<sup>4-7</sup> recommend aspirin for the primary prevention of cardiovascular disease, as shown in Table 1. Three of the expert panels recommend a daily dose of 100 mg or less,<sup>4-6</sup> and one panel<sup>7</sup> recommends a daily dose of 75 to 162 mg.

However, the efficacy of aspirin for primary prevention recently has been questioned. Three recent primary prevention trials failed to demonstrate a decrease in either stroke or myocardial infarction.<sup>8-10</sup>

The Japanese Diabetes trial<sup>8</sup> randomized 2359 men and women with type 2 diabetes, aged 30 to 85 years (mean = 65 years), to 81 to 100 mg of aspirin per day versus no aspirin in an open-label trial. There was no significant difference in the incidence of stroke or myocardial infarction at the end of 4.4 years of follow-up.<sup>8</sup>

The Prevention of Progression of Arterial Disease and Diabetes trial<sup>9</sup> randomized 1276 men and women aged 40 years or more (mean = 60 years) with type 1 or 2 diabetes and asymptomatic peripheral artery disease to 100 mg of aspirin per day versus placebo. At the end of 6 to 7 years of follow-up, there was no difference in the incidence of myocardial infarction or stroke.<sup>9</sup>

The most recent trial, Aspirin for Asymptomatic Atherosclerosis,<sup>10</sup> studied 3350 men and women aged 50 to 75 years (mean = 62 years) with asymptomatic peripheral artery disease. They were randomized to receive 100 mg enteric aspirin or placebo and followed for a mean of 8.2 years. There was no significant difference in the incidence of myocardial infarction or stroke.

These 3 negative primary prevention trials have led to questions on the efficacy of aspirin in the primary prevention of myocardial infarction and stroke. The Food and Drug Administration approved aspirin for secondary prevention in 1988, but in 2003 it cited 5 negative primary prevention trials and did not approve the labeling of aspirin for primary prevention.<sup>11</sup> Hiatt<sup>11</sup> concluded that aspirin should be prescribed only in patients with established symptomatic cardiovascular disease for secondary prevention.

The Antithrombotic Trialists Collaboration performed a meta-analysis of 6 aspirin primary prevention trials reported from 1988 to 2005.<sup>12</sup> The analysis did not include the 3 recent primary prevention trials.<sup>8-10</sup> They reported a significant ( $P < .0001$ ) 22% reduction in nonfatal myocardial

**Table 1** Agencies and Organizations Recommending Aspirin for Primary Prevention of Myocardial Infarction and Stroke<sup>a</sup>

| Organization  | Date | Recommended Dosage      |
|---|------|-------------------------|
| American College of Chest Physicians Evidence-Based Practice Guidelines <sup>4</sup>  | 2008 | 75-100 mg/d             |
| ACCF/ACG/AHA 2008 Expert Consensus Document on Reducing the Gastrointestinal Risks of Antiplatelet Therapy and NSAID use <sup>5</sup> | 2008 | "Not more than 81 mg/d" |
| US Preventive Services Task Force Recommendation Statement <sup>6</sup>   | 2009 | "approximately 75 mg/d" |
| American Heart Association <sup>7</sup>   | 2009 | 75-162 mg/d             |

ACCF = American College of Cardiology Foundation; ACG = American College of Gastroenterology; AHA = American Heart Association; NSAID = nonsteroidal anti-inflammatory drug.

<sup>a</sup>Each organization defines the population for whom aspirin for primary prevention is indicated.

**Funding:** None.

**Conflict of Interest:** None.

**Authorship:** Dr. Dalen is the sole author of this manuscript and had full access to the data.

**Table 2** Aspirin Primary Prevention Trials

| Study, Year   | ASA Dosage  | Stroke <sup>a</sup><br>ASA/Control, <i>P</i> | MI <sup>a</sup><br>ASA/Control, <i>P</i> |
|---|-------------|--|--|
| British Doctors, 1988 <sup>13</sup>   | 500 mg/d    | 48.4/41.2 <sup>b</sup> NS                    | 89.8/92.9 <sup>b</sup> NS                |
| US Physicians Health Study, 1989 <sup>3</sup>                                 | 325 qod     | 119/98 NS                                    | 139/239 <.00001                          |
| Thrombosis Prevention Trial, 1998 <sup>14</sup>                               | 75 mg/d     | 47/48 NS                                     | 154/190 .04                              |
| Hypertension Optimal Treatment Trial, 1998 <sup>15</sup>                      | 75 mg/d     | 146/148 NS                                   | 157/184 NS                               |
| Primary Prevention Project, 2001 <sup>16</sup>                                | 100 mg/d    | 16/24 NS                                     | 19/28 NS                                 |
| Women's Health Study 2005 <sup>17</sup>                                       | 100 mg qod  | 221/266 0.04                                 | 198/193 NS                               |
| Japanese Diabetes Trial 2008 <sup>8</sup>                                     | 81-100 mg/d | 28/32 NS                                     | 12/14 NS                                 |
| POPADAD Trial 2009 <sup>9</sup>   | 100 mg/d    | 37/50 NS                                     | 90/82 NS                                 |
| Aspirin for Asymptomatic Atherosclerosis Trial 2009 Trial, 2009 <sup>10</sup> | 100 mg/d    | 44/50 NS                                     | 90/86 NS                                 |

ASA = acetylsalicylic acid; MI = myocardial infarction; NS = not significant; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; qod = 4 times per day.

<sup>a</sup>Fatal + nonfatal.

<sup>b</sup>Per 10,000 person-years.

infarction in those taking aspirin. There was no significant reduction in stroke. The incidence of major bleeding was 0.1% per year in the aspirin group and 0.07% per year in the control group ( $P = .0001$ ). They concluded, "In primary prevention without previous disease, aspirin is of uncertain net value as the reduction in occlusive events needs to be weighed against any increase in major bleeds."<sup>12</sup>

There have been 9 randomized clinical trials of aspirin for primary prevention, as shown in Table 2.<sup>3,8-10,13-17</sup> Each of the 7 trials reported since 1998 chose an aspirin dosage of 100 mg per day or less.<sup>8-10,14-17</sup> One of these 7 trials reported a reduction in stroke with a  $P$  value of .04;<sup>17</sup> the other 6 trials found no significant decrease in strokes. One of the 7 trials found that 100 mg or less of aspirin per day significantly ( $P = .04$ ) decreased the incidence of myocardial infarction,<sup>14</sup> and the other 6 trials found no significant decrease in myocardial infarction.

It is difficult to ignore the results of 7 consecutive randomized clinical trials. There are 2 possible conclusions. One conclusion is that the recommendations of aspirin for primary prevention by the organizations shown in Table 1 are incorrect because aspirin is ineffective. Millions of people throughout the world are taking aspirin for primary prevention. Should they be told to discontinue aspirin?

The other conclusion is that the recommended dose<sup>4-7</sup> is insufficient; 7 clinical trials have documented that doses of 100 mg or less are ineffective. The US Physicians Health study reported a 44% reduction in myocardial infarction in physicians taking 325 mg every other day (162 mg/d).<sup>3</sup> One might reasonably conclude that the recommended dosage should be increased to 162 mg per day. I will continue to recommend 162 mg per day to my patients.<sup>2</sup>

James E. Dalen, MD, MPH  
University of Arizona  
Tucson

## References

- Soni A. Aspirin use among the Adult U.S. noninstitutionalized population, with and without indicators of heart disease, 2005. Agency for Healthcare Research and Quality. July, 2007.
- Dalen JE. Aspirin to prevent heart attack and stroke: what's the right dose? *Am J Med.* 2006;119:198-202.
- Steering Committee of the Physicians' Health Study Research Group. Final report of the aspirin component of the ongoing physicians' health study. *N Engl J Med.* 1989;321:129-135.
- Becker RC, Meade TW, Berger PB, et al. The primary and secondary prevention of coronary artery disease. *Chest.* 2008;133:776S-814S.
- ACCF/ACG/AHA 2008 Expert Consensus Document on Reducing the Gastrointestinal Risks of Antiplatelet Therapy and NSAID Use. *J Am Coll Cardiol.* 2008;52:1502-1517.
- US Preventive Services Task Force. Aspirin for the prevention of cardiovascular disease: U.S. preventive services task force recommendation statement. *Ann Intern Med.* 2009;150:396-404.
- American Heart Association. Available at: <http://www.americanheart.org/presenter.jhtml?identifier=4704>. Accessed October 28, 2009.
- Ogawa H, Nakayama M, Morimoto T, et al. Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes. *JAMA.* 2008;300:2134-2141.
- Belch J, MacCuish A, Campbell I, et al. The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. *BMJ.* 2008;337:a1840.
- Fowkes G. Aspirin for asymptomatic atherosclerosis trial. Presented at European Society of Cardiology 2009 Congress, August 30, 2009, Barcelona, Spain.
- Hiatt WR. Aspirin for prevention of cardiovascular events. *BMJ.* 2008;337:a1806.
- Antithrombotic Trialists (ATT) Collaboration. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet.* 2009;373:1849-1860.
- Peto R, Gray R, Collins R, et al. Randomised trial of prophylactic daily aspirin in British male doctors. *Lancet.* 1988;296:313-316.
- 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 ischemic heart disease in men at increased risk. *Lancet.* 1998;351:233-241.
- Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the hypertension optimal treatment (HOT) randomised trial. *Lancet.* 1998;351:1755-1762.
- 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.
- Ridker PM, Cook NR, Min Lee I, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. *N Engl J Med.* 2005;353:1293-1304.