

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

MARCH 31, 2005

VOL. 352 NO. 13

A Randomized Trial of Low-Dose Aspirin in the Primary Prevention of Cardiovascular Disease in Women

Paul M Ridker, M.D., Nancy R. Cook, Sc.D., I-Min Lee, M.B., B.S., David Gordon, M.A.,
J. Michael Gaziano, M.D., JoAnn E. Manson, M.D., Charles H. Hennekens, M.D., and Julie E. Buring, Sc.D.

ABSTRACT

BACKGROUND

Randomized trials have shown that low-dose aspirin decreases the risk of a first myocardial infarction in men, with little effect on the risk of ischemic stroke. There are few similar data in women.

METHODS

We randomly assigned 39,876 initially healthy women 45 years of age or older to receive 100 mg of aspirin on alternate days or placebo and then monitored them for 10 years for a first major cardiovascular event (i.e., nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes).

RESULTS

During follow-up, 477 major cardiovascular events were confirmed in the aspirin group, as compared with 522 in the placebo group, for a nonsignificant reduction in risk with aspirin of 9 percent (relative risk, 0.91; 95 percent confidence interval, 0.80 to 1.03; $P=0.13$). With regard to individual end points, there was a 17 percent reduction in the risk of stroke in the aspirin group, as compared with the placebo group (relative risk, 0.83; 95 percent confidence interval, 0.69 to 0.99; $P=0.04$), owing to a 24 percent reduction in the risk of ischemic stroke (relative risk, 0.76; 95 percent confidence interval, 0.63 to 0.93; $P=0.009$) and a nonsignificant increase in the risk of hemorrhagic stroke (relative risk, 1.24; 95 percent confidence interval, 0.82 to 1.87; $P=0.31$). As compared with placebo, aspirin had no significant effect on the risk of fatal or nonfatal myocardial infarction (relative risk, 1.02; 95 percent confidence interval, 0.84 to 1.25; $P=0.83$) or death from cardiovascular causes (relative risk, 0.95; 95 percent confidence interval, 0.74 to 1.22; $P=0.68$). Gastrointestinal bleeding requiring transfusion was more frequent in the aspirin group than in the placebo group (relative risk, 1.40; 95 percent confidence interval, 1.07 to 1.83; $P=0.02$). Subgroup analyses showed that aspirin significantly reduced the risk of major cardiovascular events, ischemic stroke, and myocardial infarction among women 65 years of age or older.

CONCLUSIONS

In this large, primary-prevention trial among women, aspirin lowered the risk of stroke without affecting the risk of myocardial infarction or death from cardiovascular causes, leading to a nonsignificant finding with respect to the primary end point.

From the Divisions of Preventive Medicine (P.M.R., N.R.C., I-M.L., D.G., J.M.G., J.E.M., J.E.B.), Cardiovascular Medicine (P.M.R., J.M.G.), and Aging (J.M.G., J.E.B.), Department of Medicine, Brigham and Women's Hospital, Harvard Medical School; the Department of Epidemiology, Harvard School of Public Health (P.M.R., N.R.C., I-M.L., J.E.M., J.E.B.); Veterans Affairs Boston Healthcare System (J.M.G.); and the Department of Ambulatory Care and Prevention, Harvard Medical School (J.E.B.) — all in Boston; and the Departments of Medicine and Epidemiology and Public Health, University of Miami School of Medicine, and the Department of Biomedical Science, Center of Excellence, Florida Atlantic University, Miami (C.H.H.). Address reprint requests to Dr. Buring at the Division of Preventive Medicine, Brigham and Women's Hospital, 900 Commonwealth Ave. East, Boston, MA 02215, or at jburing@rics.bwh.harvard.edu.

This article was published at www.nejm.org on March 7, 2005.

N Engl J Med 2005;352:1293-304.
Copyright © 2005 Massachusetts Medical Society.

ALTHOUGH ASPIRIN IS EFFECTIVE IN the treatment of acute myocardial infarction and in the secondary prevention of cardiovascular disease among both men and women,¹ its use in primary prevention remains controversial. To date, five randomized trials involving 55,580 participants have evaluated aspirin in the primary prevention of cardiovascular disease.²⁻⁶ In aggregate, these trials indicate that, as compared with placebo, aspirin therapy was associated with a significant, 32 percent reduction in the risk of myocardial infarction, but the data on the risk of stroke and death from cardiovascular disease remain inconclusive.⁷ Moreover, three of these trials evaluated men exclusively, and fewer than 180 of the 2402 vascular events occurred in women. Thus, at this time, the current recommendations for the use of aspirin in primary prevention in women are based on limited direct data from women.⁸⁻¹⁰

Direct evidence regarding the effects of aspirin in women is necessary because cardiovascular disease is the leading cause of death among both women and men. Direct evidence is also relevant because of the potential for sex-based differences in salicylate metabolism¹¹ and continuing uncertainty regarding the cardiovascular effects of hormone-replacement therapy.¹² Moreover, in addition to a paucity of data on women, the prophylactic use of aspirin in both sexes has prompted concern owing to the potentially increased risk of hemorrhagic stroke.¹³ This issue is particularly complex, since the relative proportion of stroke to myocardial infarction differs between women and men.

We addressed these questions in the Women's Health Study, a large randomized, double-blind, placebo-controlled trial of low-dose aspirin in the primary prevention of cardiovascular disease among 39,876 apparently healthy women followed for a mean of 10 years for the major cardiovascular events of myocardial infarction, stroke, and death from cardiovascular causes.

METHODS

STUDY DESIGN

The Women's Health Study is a two-by-two factorial trial evaluating the balance of risks and benefits of low-dose aspirin (100 mg every other day; Bayer HealthCare) and vitamin E (600 IU every other day; Natural Source Vitamin E Association), in the primary prevention of cardiovascular disease and cancer. The trial was designed to evaluate the lowest dose of aspirin that would have a cardiopro-

TECTIVE effect, while minimizing gastrointestinal side effects through the use of a low dose and alternate-day administration. The design of the study has previously been described in detail.^{14,15} In brief, between September 1992 and May 1995, letters of invitation were mailed to more than 1.7 million female health professionals. A total of 453,787 completed the questionnaires, with 65,169 initially willing and eligible to enroll. Women were eligible if they were 45 years of age or older; had no history of coronary heart disease, cerebrovascular disease, cancer (except nonmelanoma skin cancer), or other major chronic illness; had no history of side effects to any of the study medications; were not taking aspirin or nonsteroidal antiinflammatory medications (NSAIDs) more than once a week (or were willing to forego their use during the trial); were not taking anticoagulants or corticosteroids; and were not taking individual supplements of vitamin A, E, or beta carotene more than once a week. For the purposes of this study, inhibitors of cyclooxygenase, whether selective or nonselective, were considered to be NSAIDs.

Eligible women were enrolled in a three-month run-in period of placebo administration to identify a group likely to be compliant with long-term treatment. A total of 39,876 women were willing, eligible, and compliant during the run-in period and underwent randomization: 19,934 were assigned to receive aspirin and 19,942 to receive placebo. Written informed consent was obtained from all participants. The trial was approved by the institutional review board of Brigham and Women's Hospital, Boston, and was monitored by an external data and safety monitoring board.

Every 12 months, the women were sent a year's supply of monthly calendar packs containing active agents or placebo as well as questionnaires on compliance, side effects, the occurrence of relevant clinical end points, and risk factors. Study medications and end-point ascertainment were continued in a blinded fashion through the scheduled end of the trial (March 31, 2004). Follow-up and validation of reported end points were completed in February 2005. Rates of follow-up with respect to morbidity and mortality were 97.2 percent complete and 99.4 percent complete, respectively.

All the women were followed for myocardial infarction, stroke, or death from cardiovascular causes. Medical records were obtained for all women in whom a cardiovascular end point was reported to occur and were reviewed in a blinded fashion by an end-points committee of physicians. Myocardial

infarction was confirmed if symptoms met World Health Organization criteria and if the event was associated with abnormal levels of cardiac enzymes or diagnostic electrocardiograms. A confirmed stroke was defined as a new neurologic deficit of sudden onset that persisted for at least 24 hours. Clinical information, computed tomographic scans, and magnetic resonance images were used to distinguish hemorrhagic from ischemic events.¹⁶ Death was confirmed to be from cardiovascular causes on the basis of an examination of autopsy reports, death certificates, medical records, and information obtained from the next of kin or other family members. The use of coronary revascularization (bypass surgery or percutaneous coronary angioplasty) was confirmed by a review of the medical records. A confirmed transient ischemic attack was defined as a neurologic deficit of sudden onset that lasted for less than 24 hours. Death from any cause was confirmed by the end-points committee or on the basis of a death certificate. Only confirmed end points were included in this analysis. For women with a reported myocardial infarction, the most common diagnoses among those in whom the diagnosis was not confirmed were stable or unstable angina or chest pain without evidence of infarction. For women with a reported stroke, the most common alternative diagnosis was transient cerebral ischemia.

STATISTICAL ANALYSIS

All primary analyses were performed on an intention-to-treat basis. The primary end point was a combination of major cardiovascular events, including nonfatal myocardial infarction, nonfatal stroke, and death from cardiovascular causes, and the trial was initially designed to have a statistical power of 86 percent to detect a 25 percent reduction in this end point. Secondary end points included the individual end points of fatal or nonfatal myocardial infarction, fatal or nonfatal stroke, ischemic stroke, hemorrhagic stroke, and death from cardiovascular causes. Additional analyses included the incidence of death from any cause, transient ischemic attack, and the need for coronary revascularization. If more than one end point occurred in a given woman, only the first event within each category was counted; for the primary combined end point, the first event in each woman was counted.

Cox proportional-hazards models were used to calculate relative risks and 95 percent confidence intervals for the comparison of event rates in the aspirin and placebo groups after adjustment for age

and other randomized treatment assignments (vitamin E and beta carotene, which was a component of the trial for a median of 2.1 years¹⁷). Prespecified subgroup analyses were performed according to the presence or absence of major cardiovascular risk factors. Modification of the effect of aspirin by the risk factors was assessed with the use of interaction terms between subgroup indicators and aspirin assignment, with tests for trend performed when subgroup categories were ordinal. To examine effects among women who were compliant, we performed a sensitivity analysis in which follow-up data were censored at the time a woman reported having taken less than two thirds of the study medication during the previous year. In additional analyses, data were censored on women if and when they started taking NSAIDs more than three times a month.

RESULTS

PRIMARY ANALYSES

As shown in Table 1, the aspirin and placebo groups were similar with respect to baseline characteristics. The average duration of follow-up from randomization to the end of the trial was 10.1 years (range, 8.2 to 10.9). At the completion of the trial, 999 women had had a first major cardiovascular event (Table 2), for an absolute event rate of 253 per 100,000 person-years. Of these women, 477 were in the aspirin group and 522 were in the placebo group, indicating that there was a nonsignificant reduction in risk of 9 percent (relative risk, 0.91; 95 percent confidence interval, 0.80 to 1.03; $P=0.13$).

Regarding individual end points, women in the aspirin group had a 17 percent reduction in the risk of stroke (relative risk, 0.83; 95 percent confidence interval, 0.69 to 0.99; $P=0.04$), as compared with women in the placebo group; a 24 percent reduction in the risk of ischemic stroke (relative risk, 0.76; 95 percent confidence interval, 0.63 to 0.93; $P=0.009$); and a nonsignificant increase in the risk of hemorrhagic stroke (relative risk, 1.24; 95 percent confidence interval, 0.82 to 1.87; $P=0.31$) (Table 2). There was no significant difference between the groups in the risk of fatal stroke (relative risk in the aspirin group, 1.04; 95 percent confidence interval, 0.58 to 1.86; $P=0.90$), but the aspirin group had a decreased risk of nonfatal strokes (relative risk, 0.81; 95 percent confidence interval, 0.67 to 0.97; $P=0.02$), as compared with the placebo group.

There was no evidence that, as compared with

Table 1. Baseline Characteristics of the Women.

Characteristic	Aspirin (N=19,934)	Placebo (N=19,942)	Total (N=39,876)
Age			
Mean \pm SD (yr)	54.6 \pm 7.0	54.6 \pm 7.0	54.6 \pm 7.0
45–54 yr (%)	60.2	60.2	60.2
55–64 yr (%)	29.5	29.5	29.5
\geq 65 yr (%)	10.3	10.3	10.3
Smoking status (%)			
Current	13.0	13.3	13.1
Past or never	87.0	86.7	86.9
Body-mass index*			
Mean \pm SD	26.1 \pm 5.1	26.0 \pm 5.0	26.0 \pm 5.1
<25.0 (%)	50.8	50.8	50.8
25.0 to 29.9 (%)	30.9	31.0	30.9
\geq 30.0 (%)	18.3	18.2	18.2
Menopausal status and use of HRT(%)[†]			
Premenopausal	27.5	27.6	27.6
Uncertain	17.7	18.2	18.0
Postmenopausal and current HRT	30.4	29.7	30.0
Postmenopausal and no HRT	24.4	24.4	24.4
Hypertension (%)[‡]			
Yes	26.0	25.7	25.9
No	74.0	74.3	74.1
Blood pressure (%)			
<120/<75 mm Hg	32.2	32.9	32.6
120–129/75–84 mm Hg	32.2	31.8	32.0
130–139/85–89 mm Hg	19.5	19.3	19.4
\geq 140/ \geq 90 mm Hg	16.1	15.9	16.0

placebo, aspirin reduced the overall risk of myocardial infarction (relative risk, 1.02; 95 percent confidence interval, 0.84 to 1.25; $P=0.83$), fatal myocardial infarction (relative risk, 1.16; 95 percent confidence interval, 0.54 to 2.51; $P=0.70$), nonfatal myocardial infarction (relative risk, 1.01; 95 percent confidence interval, 0.83 to 1.24; $P=0.90$), or death from cardiovascular causes (relative risk, 0.95; 95 percent confidence interval, 0.74 to 1.22; $P=0.68$). However, aspirin therapy was associated with a 22 percent reduction in the risk of transient ischemic attack (relative risk, 0.78; 95 percent confidence interval, 0.64 to 0.94; $P=0.01$), with no significant effects on the risk of coronary revascularization (relative risk, 1.04; 95 percent confidence interval, 0.90 to 1.20; $P=0.61$) or death from any cause (relative risk, 0.95; 95 percent confidence interval, 0.85 to 1.06; $P=0.32$).

Figures 1 and 2 present the cumulative incidence rates of major cardiovascular events, stroke,

myocardial infarction, ischemic stroke, and hemorrhagic stroke according to the year of follow-up. Because it has been suggested that the ability of aspirin to inhibit platelet function diminishes over time,¹⁸ we also evaluated incidence rates according to the length of follow-up. A beneficial effect of aspirin on stroke was observed early in the trial and persisted throughout the trial, with no apparent benefit of aspirin on myocardial infarction at any point during follow-up.

Neither treatment with vitamin E nor treatment with beta carotene significantly modified the effect of aspirin on the primary or secondary end points.

SUBGROUP ANALYSES

There was no evidence that any of the cardiovascular risk factors considered, except smoking status and age, modified the effect of aspirin on the primary end point of major cardiovascular events (Table 3). We observed a greater benefit of aspirin

Table 1. (Continued.)

Characteristic	Aspirin (N=19,934)	Placebo (N=19,942)	Total (N=39,876)
Hyperlipidemia (%)§			
Yes	29.9	29.1	29.5
No	70.1	70.9	70.5
Diabetes (%)			
Yes	2.7	2.5	2.6
No	97.3	97.5	97.4
Parental history of myocardial infarction before 60 yr of age (%)			
Yes	13.0	12.9	12.9
No	87.0	87.1	87.1
10-yr risk of coronary heart disease (%)¶			
<5.0%	84.4	84.6	84.5
5.0 to 9.9%	11.8	11.3	11.5
≥10.0%	3.9	4.1	4.0
No. of risk factors (%)			
0	41.8	42.4	42.1
1	34.1	34.1	34.1
2	18.0	17.2	17.6
≥3	6.2	6.3	6.2

* The body-mass index is the weight in kilograms divided by the square of the height in meters.

† HRT denotes hormone-replacement therapy.

‡ Hypertension was defined as a systolic blood pressure of at least 140 mm Hg, a diastolic blood pressure of at least 90 mm Hg, or self-reported physician-diagnosed hypertension.

§ Hyperlipidemia was defined as a total cholesterol level of at least 240 mg per deciliter (6.2 mmol per liter) or self-reported physician-diagnosed high cholesterol levels.

¶ This variable was calculated with the Framingham risk score for those with blood specimens.

|| Risk factors were smoking, hypertension, hyperlipidemia, diabetes, and obesity.

Table 2. Incidence and Relative Risk of Confirmed Cardiovascular End Points.

End Point	Aspirin (N=19,934)	Placebo (N=19,942)	Relative Risk (95% CI)*	P Value
	<i>no. of events</i>			
Major cardiovascular event†	477	522	0.91 (0.80–1.03)	0.13
Stroke	221	266	0.83 (0.69–0.99)	0.04
Ischemic	170	221	0.76 (0.63–0.93)	0.009
Hemorrhagic	51	41	1.24 (0.82–1.87)	0.31
Fatal	23	22	1.04 (0.58–1.86)	0.90
Nonfatal	198	244	0.81 (0.67–0.97)	0.02
Myocardial infarction	198	193	1.02 (0.84–1.25)	0.83
Fatal	14	12	1.16 (0.54–2.51)	0.70
Nonfatal	184	181	1.01 (0.83–1.24)	0.90
Death from cardiovascular causes	120	126	0.95 (0.74–1.22)	0.68
Transient ischemic attack	186	238	0.78 (0.64–0.94)	0.01
Coronary revascularization	389	374	1.04 (0.90–1.20)	0.61
Death from any cause	609	642	0.95 (0.85–1.06)	0.32

* CI denotes confidence interval.

† A major cardiovascular event was defined as a nonfatal myocardial infarction, a nonfatal stroke, or death from cardiovascular causes.

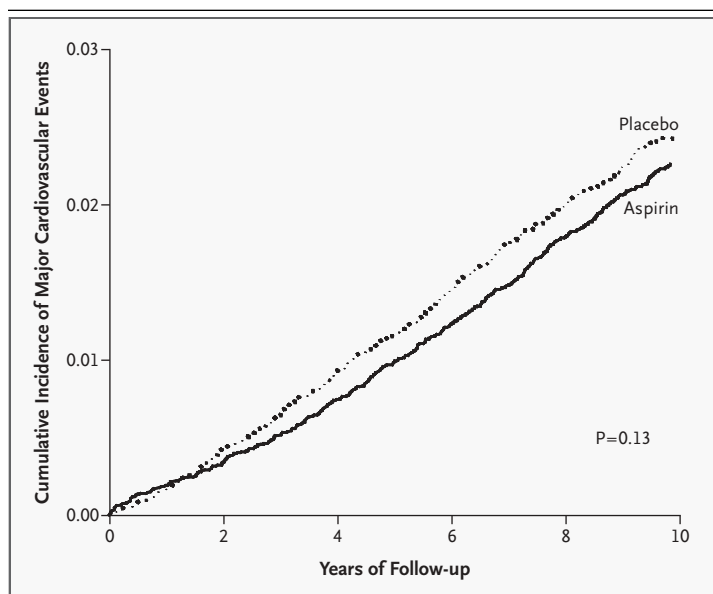


Figure 1. Cumulative Incidence Rates of the Primary End Point of Major Cardiovascular Events.

A major cardiovascular event was defined as a nonfatal myocardial infarction, a nonfatal stroke, or death from cardiovascular causes.

on the risk of major cardiovascular events among former smokers and those who had never smoked, with an apparent increased risk among current smokers (P for interaction <0.001), although it is important to interpret this information in the context of multiple comparisons. In addition, age significantly modified the effect of aspirin on the risk of both major cardiovascular events and myocardial infarction (P for interaction = 0.05 and 0.03, respectively). The most consistent benefit of aspirin was observed among the subgroup of women 65 years of age or older at study entry; in this subgroup, the risk of major cardiovascular events was reduced by 26 percent among those who took aspirin as compared with those who took placebo (relative risk, 0.74; 95 percent confidence interval, 0.59 to 0.92; $P=0.008$), and the risk of ischemic stroke was reduced by 30 percent (relative risk, 0.70; 95 percent confidence interval, 0.49 to 1.00; $P=0.05$). This was also the only subgroup in which aspirin, as compared with placebo, significantly reduced the risk of myocardial infarction (relative risk, 0.66; 95 percent confidence interval, 0.44 to 0.97; $P=0.04$).

To address whether compliance may have affected our results, we performed a sensitivity analy-

sis in which follow-up data were censored at the time a woman reported having taken less than two thirds of the study medication during the preceding year. In this analysis, aspirin, as compared with placebo, reduced the risk of major cardiovascular events by 13 percent, reduced the risk of stroke by 26 percent, reduced the risk of ischemic stroke by 33 percent, and had no significant effect on the risk of myocardial infarction (relative risk, 1.03; 95 percent confidence interval, 0.81 to 1.32; $P=0.79$).

Some women started taking NSAIDs during the trial—a potentially important issue with respect to the risk of thrombotic events, since certain NSAIDs can compete with aspirin for receptors on platelets.¹⁹ According to our data, however, the lack of an effect of aspirin therapy on the risk of myocardial infarction was not explained by concomitant use of NSAIDs.²⁰

SIDE EFFECTS

Reports of gastrointestinal bleeding and peptic ulcer were confirmed by means of follow-up questionnaires. These side effects were significantly more common among women in the aspirin group than among women in the placebo group (Table 4). There were 127 episodes of gastrointestinal bleeding requiring transfusion in the aspirin group, as compared with 91 in the placebo group (relative risk, 1.40; 95 percent confidence interval, 1.07 to 1.83; $P=0.02$). Self-reported hematuria, easy bruising, and epistaxis were frequent among women in both groups, with small but significant excesses among those in the aspirin group. The percentage of women reporting any symptoms suggestive of gastric upset was virtually identical in the two groups. There were five fatal gastrointestinal hemorrhages, two in the aspirin group and three in the placebo group.

DISCUSSION

In this large, placebo-controlled, primary-prevention trial involving 39,876 initially healthy women, prophylactic aspirin at a dose of 100 mg every other day was associated with a nonsignificant reduction in the risk of major cardiovascular events, a reduced risk of total stroke and of ischemic stroke, a nonsignificant increase in the risk of hemorrhagic stroke, and no significant effect on the risk of myocardial infarction or death from cardiovascular causes. With respect to the primary end point of major cardiovascular events as well as the individual end points of fatal or nonfatal stroke and my-

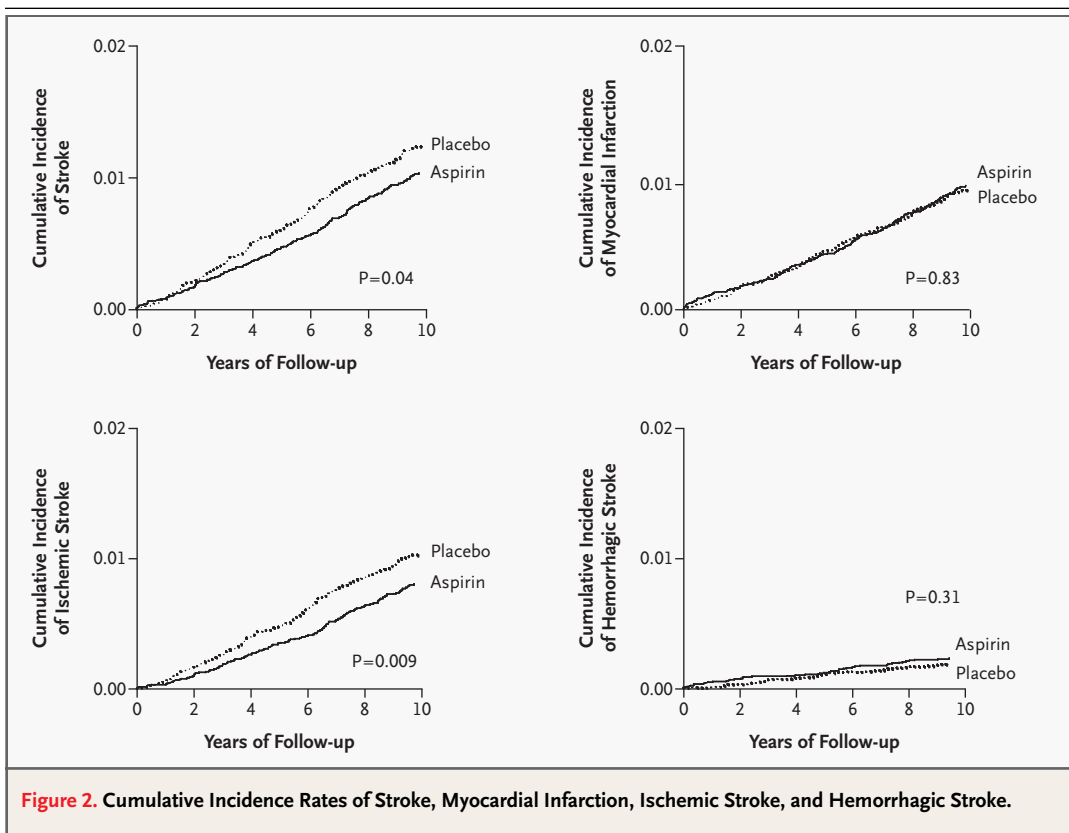


Figure 2. Cumulative Incidence Rates of Stroke, Myocardial Infarction, Ischemic Stroke, and Hemorrhagic Stroke.

ocardial infarction, consistent benefits of aspirin were observed among the subgroup of women who were 65 years of age or older. We found no evidence that menopausal status, the use or nonuse of hormone-replacement therapy after menopause, or global cardiovascular-risk status modified the effect of aspirin. As expected, the frequency of side effects related to bleeding and ulcers was increased among women who received aspirin.

Our findings must be interpreted in the context of those of other completed, randomized trials of aspirin in the primary and secondary prevention of cardiovascular disease. In secondary prevention, the Antithrombotic Trialists' Collaboration showed that aspirin clearly reduced the risk of cardiovascular events, myocardial infarction, and ischemic stroke in both men and women.¹ To address the effects of aspirin in primary prevention, we performed a random-effects meta-analysis that included current data from the Women's Health Study, as well as data from five prior trials involving 55,580 participants with no history of heart disease.^{2-6,21} Overall, as compared with placebo, aspirin therapy significantly reduced the risk of myocardial infarction

(relative risk, 0.76; 95 percent confidence interval, 0.62 to 0.95; $P=0.01$) but had no significant effect on the risk of stroke (relative risk, 0.97; 95 percent confidence interval, 0.83 to 1.13; $P=0.69$). In analyses stratified according to sex (Fig. 3), combined data on women from the Women's Health Study, the Hypertension Optimal Treatment (HOT) study,^{5,21} and the Primary Prevention Project⁶ (and Roncaglioni MC: personal communication) indicate that aspirin therapy was associated with a significant, 19 percent reduction in the risk of stroke (relative risk, 0.81; 95 percent confidence interval, 0.69 to 0.96; $P=0.01$), with no reduction in the risk of myocardial infarction (relative risk, 0.99; 95 percent confidence interval, 0.83 to 1.19; $P=0.95$). By contrast, the aggregate data on men from the Physicians' Health Study,² the British Doctors' Trial,³ the Thrombosis Prevention Trial,⁴ the HOT study,^{5,21} and the Primary Prevention Project⁶ indicate that aspirin therapy was associated with a significant, 32 percent reduction in the risk of myocardial infarction (relative risk, 0.68; 95 percent confidence interval, 0.54 to 0.86; $P=0.001$) and a nonsignificant increase in the risk of stroke (rela-

Table 3. Incidence and Relative Risk of Cardiovascular Events, According to Baseline Characteristics.*

Group	Major CV Event				Stroke				Ischemic Stroke				Myocardial Infarction			
	Asp	Pla	RR (95% CI)	P Value	Asp	Pla	RR (95% CI)	P Value	Asp	Pla	RR (95% CI)	P Value	Asp	Pla	RR (95% CI)	P Value
Age	no.															
45-54 yr	24,025	163	1.01 (0.81-1.26)	0.92	77	90	0.85 (0.63-1.16)	0.31	57	71	0.80 (0.57-1.14)	0.21	69	56	1.23 (0.87-1.75)	0.25
55-64 yr	11,754	183	0.98 (0.80-1.20)	0.84	76	90	0.84 (0.62-1.14)	0.26	60	75	0.80 (0.57-1.12)	0.19	88	75	1.17 (0.86-1.59)	0.32
≥65 yr	4,097	131	0.74 (0.59-0.92)	0.008	68	86	0.78 (0.57-1.08)	0.13	53	75	0.70 (0.49-1.00)	0.05	41	62	0.66 (0.44-0.97)	0.04
Smoking status	no.															
Current	5,235	157	1.30 (1.03-1.64)	0.03	63	58	1.14 (0.80-1.63)	0.48	50	46	1.14 (0.76-1.70)	0.52	76	53	1.50 (1.06-2.13)	0.02
Past or never	34,605	319	0.80 (0.69-0.93)	0.003	157	207	0.75 (0.61-0.92)	0.006	119	174	0.67 (0.53-0.85)	0.001	122	139	0.87 (0.68-1.10)	0.25
Body-mass index†	no.															
<25.0	19,849	184	0.82 (0.68-1.00)	0.05	95	126	0.75 (0.58-0.98)	0.04	67	97	0.69 (0.50-0.94)	0.02	67	73	0.92 (0.66-1.28)	0.63
25.0 to 29.9	12,081	158	0.89 (0.72-1.11)	0.31	70	84	0.83 (0.60-1.13)	0.24	57	72	0.78 (0.55-1.11)	0.16	76	68	1.11 (0.80-1.54)	0.52
≥30.0	7,126	116	1.05 (0.81-1.36)	0.72	50	53	0.96 (0.65-1.41)	0.81	41	49	0.85 (0.56-1.29)	0.44	45	46	0.98 (0.65-1.47)	0.91
Menopause and HRT	no.															
Premenopausal	10,973	55	0.88 (0.61-1.26)	0.47	30	31	0.97 (0.59-1.60)	0.91	23	23	1.01 (0.56-1.79)	0.98	18	26	0.69 (0.38-1.26)	0.23
Uncertain	7,149	67	0.91 (0.66-1.27)	0.59	24	43	0.57 (0.35-0.94)	0.03	16	35	0.47 (0.26-0.85)	0.01	38	26	1.49 (0.91-2.46)	0.11
Postmenopausal, current HRT	11,948	150	0.98 (0.78-1.23)	0.85	79	78	0.98 (0.72-1.34)	0.92	60	65	0.9 (0.63-1.27)	0.54	58	51	1.12 (0.77-1.63)	0.57
Postmenopausal, no HRT	9,704	201	0.86 (0.71-1.03)	0.11	86	113	0.76 (0.57-1.00)	0.05	69	97	0.71 (0.52-0.96)	0.03	81	90	0.9 (0.67-1.21)	0.49
Hypertension‡	no.															
Yes	10,317	235	0.84 (0.71-1.00)	0.05	109	138	0.76 (0.59-0.98)	0.04	91	120	0.73 (0.56-0.96)	0.02	98	101	0.95 (0.72-1.25)	0.69
No	29,550	241	0.96 (0.81-1.15)	0.69	111	128	0.88 (0.68-1.13)	0.31	78	101	0.78 (0.58-1.05)	0.10	100	92	1.10 (0.83-1.46)	0.52
Blood pressure	no.															
<120/<75 mm Hg	12,799	72	1.04 (0.75-1.45)	0.81	40	43	0.94 (0.61-1.45)	0.79	27	35	0.78 (0.47-1.29)	0.34	24	19	1.28 (0.70-2.34)	0.42
120-129/75-84 mm Hg	12,581	107	0.94 (0.72-1.22)	0.63	51	57	0.89 (0.61-1.30)	0.54	37	45	0.82 (0.53-1.26)	0.36	43	42	1.02 (0.66-1.56)	0.94
130-139/85-89 mm Hg	7,642	131	0.94 (0.74-1.20)	0.62	47	62	0.75 (0.51-1.09)	0.13	36	48	0.74 (0.48-1.15)	0.18	66	59	1.11 (0.78-1.58)	0.55
≥140/≥90 mm Hg	6,295	158	0.81 (0.65-1.00)	0.05	76	101	0.73 (0.54-0.98)	0.04	65	90	0.7 (0.51-0.96)	0.03	64	68	0.92 (0.66-1.30)	0.65

Hyperlipidemia [‡]																	
Yes	11,745	183	227	0.80 (0.66–0.97)	0.02	75	119	0.62 (0.47–0.83)	0.001	67	98	0.68 (0.50–0.93)	0.01	92	88	1.03 (0.77–1.39)	0.82
No	28,115	294	295	0.98 (0.84–1.16)	0.84	146	147	0.99 (0.78–1.24)	0.9	103	123	0.83 (0.64–1.08)	0.16	106	105	1.00 (0.77–1.31)	0.99
Diabetes																	
Yes	1,027	58	62	0.9 (0.63–1.29)	0.57	15	31	0.46 (0.25–0.85)	0.01	13	29	0.42 (0.22–0.82)	0.01	36	24	1.48 (0.88–2.49)	0.14
No	38,825	418	460	0.9 (0.79–1.03)	0.13	206	235	0.87 (0.72–1.05)	0.15	157	192	0.81 (0.66–1.00)	0.05	162	169	0.96 (0.77–1.18)	0.68
Parental history of myocardial infarction before 60 yr of age																	
Yes	4,633	61	74	0.86 (0.61–1.21)	0.39	23	32	0.74 (0.43–1.26)	0.27	19	27	0.73 (0.41–1.31)	0.29	31	37	0.89 (0.55–1.43)	0.62
No	31,210	355	388	0.90 (0.78–1.04)	0.16	170	206	0.82 (0.67–1.00)	0.05	130	170	0.75 (0.60–0.95)	0.02	141	136	1.03 (0.81–1.30)	0.82
10-yr risk of CHD [¶]																	
<5.0%	23,331	152	175	0.86 (0.69–1.07)	0.17	78	97	0.80 (0.59–1.07)	0.13	54	76	0.70 (0.50–1.00)	0.05	59	59	0.99 (0.69–1.42)	0.94
5.0 to 9.9%	3,186	96	97	0.96 (0.72–1.27)	0.76	48	42	1.11 (0.74–1.68)	0.61	35	37	0.92 (0.58–1.46)	0.72	36	45	0.78 (0.50–1.20)	0.26
≥10.0%	1,100	61	60	1.06 (0.74–1.52)	0.74	17	32	0.54 (0.30–0.98)	0.04	16	29	0.57 (0.31–1.04)	0.07	32	23	1.48 (0.86–2.53)	0.15
No. of risk factors																	
0	16,399	81	95	0.86 (0.64–1.15)	0.31	45	53	0.86 (0.58–1.28)	0.46	31	41	0.76 (0.48–1.22)	0.26	26	29	0.90 (0.53–1.53)	0.70
1	13,291	151	162	0.92 (0.73–1.14)	0.44	75	84	0.88 (0.64–1.20)	0.42	50	70	0.70 (0.49–1.01)	0.06	58	61	0.94 (0.65–1.34)	0.73
2	6,860	128	156	0.80 (0.63–1.01)	0.06	57	79	0.70 (0.50–0.98)	0.04	49	65	0.73 (0.50–1.06)	0.10	54	56	0.94 (0.64–1.36)	0.73
≥3	2,428	96	93	1.07 (0.80–1.42)	0.66	37	46	0.83 (0.54–1.28)	0.40	34	41	0.86 (0.54–1.35)	0.51	50	40	1.30 (0.86–1.98)	0.21

* A major cardiovascular (CV) event was defined as a nonfatal myocardial infarction, a nonfatal stroke, or death from cardiovascular causes. The total number of cardiovascular events may not sum to 39,876 owing to missing data for some variables. Asp denotes aspirin, Pla placebo, no. number of women, RR relative risk, CI confidence interval, HRT hormone-replacement therapy, and CHD coronary heart disease.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ Hypertension was defined as a systolic blood pressure of at least 140 mm Hg, a diastolic blood pressure of at least 90 mm Hg, or as self-reported physician-diagnosed hypertension.

§ Hyperlipidemia was defined as a total cholesterol level of at least 240 mg per deciliter or as self-reported physician-diagnosed high cholesterol levels.

¶ This variable was calculated with the Framingham risk score for those with blood specimens (28,345 women).

|| Risk factors were smoking, hypertension, hyperlipidemia, diabetes, and obesity.

Table 4. Incidence and Relative Risk of Side Effects.*

Side Effect	Aspirin (N=19,934)	Placebo (N=19,942)	Relative Risk (95% CI)	P Value
	<i>no. of events (%)</i>			
Gastrointestinal bleeding				
Any	910 (4.6)	751 (3.8)	1.22 (1.10–1.34)	<0.001
Requiring transfusion	127 (0.6)	91 (0.5)	1.40 (1.07–1.83)	0.02
Peptic ulcer	542 (2.7)	413 (2.1)	1.32 (1.16–1.50)	<0.001
Hematuria	3,039 (15.2)	2,879 (14.4)	1.06 (1.01–1.12)	0.02
Easy bruising	10,561 (53.0)	8,494 (42.6)	1.40 (1.37–1.45)	<0.001
Epistaxis	3,801 (19.1)	3,321 (16.7)	1.16 (1.11–1.22)	<0.001
Any report of gastric upset	11,856 (59.5)	11,915 (59.7)	0.99 (0.97–1.02)	0.59

* The presence of gastrointestinal bleeding or peptic ulcer was confirmed by a specific follow-up questionnaire. CI denotes confidence interval.

risk, 1.13; 95 percent confidence interval, 0.96 to 1.33; $P=0.15$). The differences between men and women were significant at the $P=0.01$ level for myocardial infarction and at the $P=0.005$ level for stroke.

The reasons for any sex-based differences in the efficacy of aspirin for primary prevention are unclear and require further exploration. Although the observed reductions in the risk of stroke could be due to chance, the reduced risk of transient ischemic attack associated with aspirin therapy adds support to the possibility of a causal interpretation. We cannot rule out the possibility that our null finding for the risk of myocardial infarction in women was due to an insufficient dose of aspirin or to the alternate-day regimen. However, we believe these explanations to be unlikely for three reasons.

First, we have previously shown that the dose of 100 mg every other day used in the Women's Health Study reduces thromboxane levels by 93 percent and prostacyclin levels by 85 percent and that these effects are similar in men and women.²² Second, in the HOT study, a 75-mg daily dose of aspirin significantly lowered the risk of myocardial infarction overall, with a 42 percent reduction in the risk among men but a far smaller and nonsignificant reduction among women.²¹ Third, since the dose and alternate-day regimen of aspirin used in our study were adequate to lower the risk of stroke, it is unlikely that any hypothesized sex-based differences in the resistance to aspirin were at play overall. However, resistance to aspirin may be more prevalent among smokers,²³ and this resistance may have played some role in the increased risk with aspirin observed among current smokers. We

also believe it unlikely that a reduction in the efficacy of aspirin over time is a viable explanation, since the cumulative incidence data presented in Figures 1 and 2 offer no support for this hypothesis. Furthermore, suboptimal compliance is an unlikely explanation, since aspirin did not decrease the risk of myocardial infarction among women with high rates of compliance — an observation again in contrast to data on stroke among the same women.

With regard to daily clinical practice, our data demonstrate that aspirin therapy was associated with a net reduction in the risk of stroke among women, with a reduction in the risk of the far more common ischemic stroke and an increase in the risk of hemorrhagic stroke. This observation is particularly relevant, since as compared with men, women have a relatively greater proportion of strokes than of myocardial infarctions. Among women in the placebo group, there were more strokes than myocardial infarctions (266 vs. 193), and thus, the ratio of incident strokes to incident myocardial infarctions was 1.4:1, as compared with the ratio of 0.4:1 among men in the Physicians' Health Study.² From a policy perspective, our findings clearly demonstrate the importance of studying women as well as men in major cardiovascular clinical trials.

An interesting finding in our subgroup analyses was that the most consistent benefit of aspirin was observed among women 65 years of age or older. This group of 4097 women composed 10 percent of the study population yet had almost one third of the cardiovascular events. In this group, aspirin use, as compared with placebo use, led to 44 fewer myocardial infarctions, strokes, or deaths from cardiovascular causes ($P=0.008$) but to 16 more

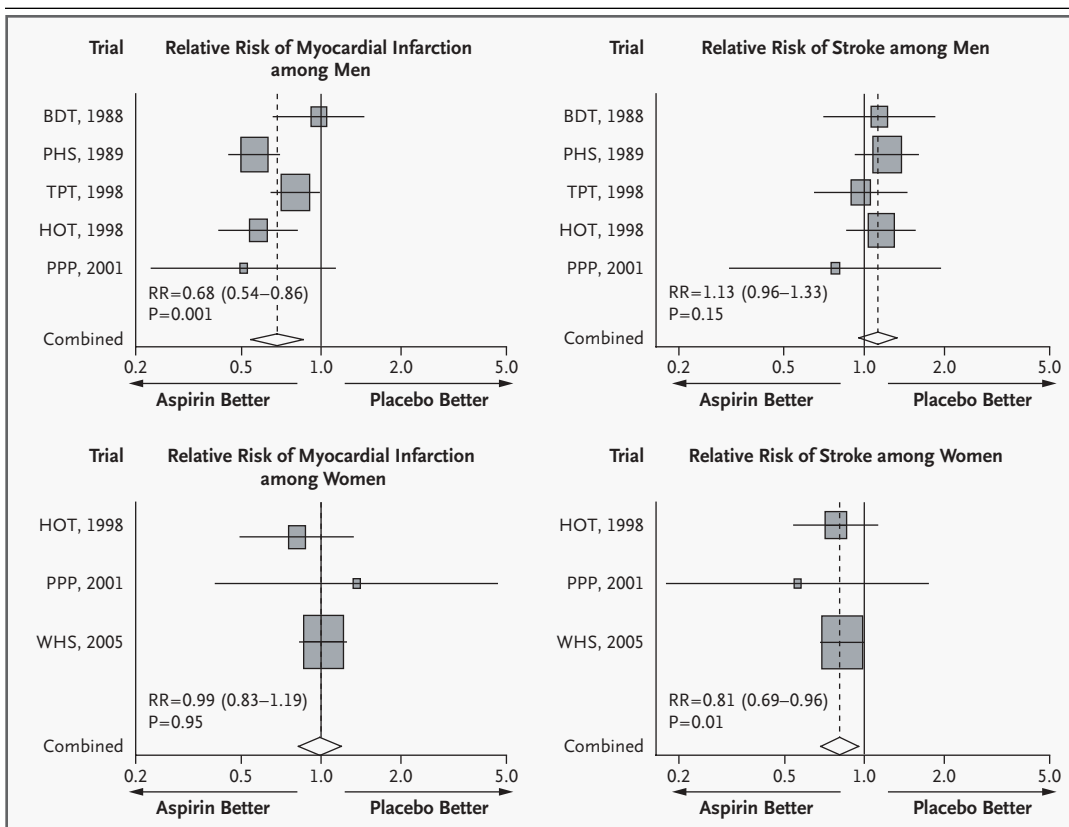


Figure 3. Aspirin in the Primary Prevention of Myocardial Infarction and Stroke among Men and Women.

The results of a sex-specific random-effects meta-analysis of data from six trials are shown: the British Doctors' Trial (BDT), the Physicians' Health Study (PHS), the Thrombosis Prevention Trial (TPT), the Hypertension Optimal Treatment (HOT) study, the Primary Prevention Project (PPP), and the current Women's Health Study (WHS). The relative risk (RR) and 95 percent confidence interval (in parentheses) are shown for each trial (indicated by the box and horizontal line through each box, respectively), and the relative risk is shown for the combined results (indicated by the diamond and the dashed line in each graph). For the relative risk of myocardial infarction among women, the dashed line is coincident with the solid line at 1.00. The size of the box is proportional to the amount of information in the corresponding trial.

gastrointestinal hemorrhages requiring transfusion ($P=0.05$), emphasizing, as with any agent, the importance of balancing benefits and risks. This age-based difference deserves further investigation.

With respect to guidelines in primary prevention, in 2002, the Preventive Services Task Force²⁴ and the American Heart Association⁹ recommended aspirin for adults whose 10-year risks of a first coronary-heart-disease event were at least 6 percent and 10 percent, respectively. However, this may be complex for women, since in our study overall, aspirin lowered the risk of stroke without affecting the risk of myocardial infarction or death from cardiovascular causes. Thus, as with men, any decision about the use of aspirin in primary prevention among women must ultimately be made after a

woman consults her physician or health care provider, so that the net absolute benefits and risks for the individual patient can be ascertained.

Supported by grants (HL-43851 and CA-47988) from the National Heart, Lung, and Blood Institute and the National Cancer Institute, Bethesda, Md. Aspirin and aspirin placebo were provided by Bayer HealthCare. Vitamin E and vitamin E placebo were provided by the Natural Source Vitamin E Association.

Dr. Ridker reports having received grant support from Bayer. Dr. Cook reports having served as a consultant to Bayer. Dr. Gaziano reports having served as a consultant to, and receiving grant support from, Bayer and McNeil. Dr. Hennekens reports having served as a consultant to Bayer and McNeil and receiving grant support from Bayer.

We are indebted to the 39,876 participants in the Women's Health Study for their dedicated and conscientious collaboration; to the entire staff of the Women's Health Study, under the leadership of David Gordon, Maria Andrade, Susan Burt, Mary Breen, Marilyn Chown, Lisa Fields-Johnson, Georgina Friedenberg, Inge Judge, Jean MacFadyen, Geneva McNair, Laura Pestana, David Potter, Philomena

Quinn, Claire Ridge, Fred Schwerin, and Harriet Samuelson; to Christine Albert, Michelle Albert, Gavin Blake, Claudia Chae, Wendy Chen, Richard Doll, Carlos Kase, Tobias Kurth, Richard Peto, Aruna Pradhan, Kathryn Rexrode, Bernard Rosner, and H. Jacqueline Suk for their assistance in the design and conduct of the trial; and especially to James Taylor for chairing the end-points committee.

APPENDIX

Members of the data and safety monitoring board included L. Cohen, R. Collins, T. Colton, D. DeMets, I.C. Henderson, A. La Croix, R. Prentice, and N. Wenger (chair) and M.F. Cotch, F. Ferris, L. Friedman, P. Greenwald, N. Kurinij, M. Perloff, E. Schron, and A. Zonderman (ex officio members).

REFERENCES

1. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;324:71-86. [Erratum, *BMJ* 2002;324:141.]
2. 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;321:129-35.
3. Peto R, Gray R, Collins R, et al. Randomised trial of prophylactic daily aspirin in British male doctors. *Br Med J (Clin Res Ed)* 1988;296:313-6.
4. The Medical Research Council's General Practice Research Framework. Thrombosis prevention trial: randomised 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;351:233-41.
5. 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;351:1755-62.
6. Collaborative Group of the Primary Prevention Project. Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomised trial in general practice. *Lancet* 2001;357:89-95. [Erratum, *Lancet* 2001;357:1134.]
7. Eidelman RS, Hebert PR, Weisman SE, Hennekens CH. An update on aspirin in the primary prevention of cardiovascular disease. *Arch Intern Med* 2003;163:2006-10.
8. Hayden M, Pignone M, Phillips C, Mulrow C. Aspirin for the primary prevention of cardiovascular events: a summary of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med* 2002;136:161-72.
9. 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;106:388-91.
10. Mosca L, Appel LJ, Benjamin EJ, et al. Evidence-based guidelines for cardiovascular disease prevention in women. *Circulation* 2004;109:672-93.
11. Montgomery PR, Berger LG, Mitenko PA, Sitar DS. Salicylate metabolism: effects of age and sex in adults. *Clin Pharmacol Ther* 1986;39:571-6.
12. Manson JE, Hsia J, Johnson KC, et al. Estrogen plus progestin and the risk of coronary heart disease. *N Engl J Med* 2003;349:523-34.
13. Rodondi N, Bauer DC. Assessing the risk/benefit profile before recommending aspirin for the primary prevention of cardiovascular events. *Am J Med* 2004;117:528-30.
14. Buring JE, Hennekens CH. The Women's Health Study: summary of the study design. *J Myocardial Ischemia* 1992;4:27-9.
15. Rexrode KM, Lee IM, Cook NR, Hennekens CH, Buring JE. Baseline characteristics of participants in the Women's Health Study. *J Womens Health Gend Based Med* 2000;9:19-27.
16. Atiya M, Kurth T, Berger K, Buring JE, Kase CS. Interobserver agreement in the classification of stroke in the Women's Health Study. *Stroke* 2003;34:565-7.
17. Lee I-M, Cook NR, Manson JE, Buring JE, Hennekens CH. β -Carotene supplementation and incidence of cancer and cardiovascular disease: the Women's Health Study. *J Natl Cancer Inst* 1999;91:2102-6.
18. Pulcinelli FM, Pignatelli P, Celestini A, Riondino S, Gazzaniga PP, Violi F. Inhibition of platelet aggregation by aspirin progressively decreases in long-term treated patients. *J Am Coll Cardiol* 2004;43:979-84.
19. Catella-Lawson F, Reilly MP, Kapoor SC, et al. Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. *N Engl J Med* 2001;345:1809-17.
20. Kurth T, Glynn RJ, Walker AM, et al. Inhibition of clinical benefits of aspirin on first myocardial infarction by nonsteroidal antiinflammatory drugs. *Circulation* 2003;108:1191-5.
21. Kjeldsen SE, Kolloch RE, Leonetti G, et al. Influence of gender and age on preventing cardiovascular disease by antihypertensive treatment and acetylsalicylic acid: the HOT study. *J Hypertens* 2000;18:629-42.
22. Ridker PM, Hennekens CH, Tofler GH, Lipinska I, Buring JE. Anti-platelet effects of 100 mg alternate day oral aspirin: a randomized, double-blind, placebo-controlled trial of regular and enteric coated formulations in men and women. *J Cardiovasc Risk* 1996;3:209-12.
23. Sanderson S, Emery J, Baglin T, Kinmonth A-L. Narrative review: aspirin resistance and its clinical implications. *Ann Intern Med* 2005;142:370-80.
24. Preventive Services Task Force. Aspirin for the primary prevention of cardiovascular events: recommendation and rationale. *Ann Intern Med* 2002;136:157-60.

Copyright © 2005 Massachusetts Medical Society.

CLINICAL PROBLEM-SOLVING SERIES

The *Journal* welcomes submissions of manuscripts for the Clinical Problem-Solving series. This regular feature considers the step-by-step process of clinical decision making. For more information, please see <http://authors.nejm.org>.