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


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.
ALTHOUGH ASPIRIN IS EFFECTIVE IN the treatment of acute myocardial infarction and in the secondary prevention of cardiovascular disease among both men and women, 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. 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. 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.

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 metabolism and continuing uncertainty regarding the cardiovascular effects of hormone-replacement therapy. 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. 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 cardioprotective 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. 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 as-
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 in-
formation, computed tomographic scans, and mag-
netic resonance images were used to distinguish
hemorrhagic from ischemic events.\textsuperscript{16} Death was
confirmed to be from cardiovascular causes on the
basis of an examination of autopsy reports, death
certificates, medical records, and information ob-
tained from the next of kin or other family mem-
bers. The use of coronary revascularization (bypass
surgery or percutaneous coronary angioplasty) was
confirmed by a review of the medical records. A con-
firmed transient ischemic attack was defined as a
neurologic deficit of sudden onset that lasted for
less than 24 hours. Death from any cause was con-
firmed 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 di-
agnoses among those in whom the diagnosis was
not confirmed were stable or unstable angina or
chest pain without evidence of infarction. For wom-
en with a reported stroke, the most common alter-
native diagnosis was transient cerebral ischemia.

**STATISTICAL ANALYSIS**

All primary analyses were performed on an inten-
tion-to-treat basis. The primary end point was a
combination of major cardiovascular events, in-
cluding 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 reduc-
tion in this end point. Secondary end points in-
ed the individual end points of fatal or nonfatal myo-
cardial infarction, fatal or nonfatal stroke, ischemic
stroke, hemorrhagic stroke, and death from cardio-
vascular causes. Additional analyses included the
incidence of death from any cause, transient isch-
emic attack, and the need for coronary revascular-
ization. If more than one end point occurred in a
given woman, only the first event within each cate-
gory 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 as-
pirin and placebo groups after adjustment for age
and other randomized treatment assignments (vi-
tamin E and beta carotene, which was a component
of the trial for a median of 2.1 years\textsuperscript{17}). 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 in-
teraction terms between subgroup indicators and
aspirin assignment, with tests for trend performed
when subgroup categories were ordinal. To exam-
ine effects among women who were compliant,
we performed a sensitivity analysis in which fol-
low-up data were censored at the time a woman re-
ported having taken less than two thirds of the
study medication during the previous year. In addi-
tional 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 characteris-
tics. The average duration of follow-up from ran-
donization 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 hem-
orrhagic stroke (relative risk, 1.24; 95 percent con-
figure 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
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

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**Table 1. Baseline Characteristics of the Women.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Aspirin (N=19,934)</th>
<th>Placebo (N=19,942)</th>
<th>Total (N=39,876)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Mean ±SD (yr)</td>
<td>54.6±7.0</td>
<td>54.6±7.0</td>
</tr>
<tr>
<td></td>
<td>45–54 yr (%)</td>
<td>60.2</td>
<td>60.2</td>
</tr>
<tr>
<td></td>
<td>55–64 yr (%)</td>
<td>29.5</td>
<td>29.5</td>
</tr>
<tr>
<td></td>
<td>≥65 yr (%)</td>
<td>10.3</td>
<td>10.3</td>
</tr>
<tr>
<td>Smoking status (%)</td>
<td>Current</td>
<td>13.0</td>
<td>13.3</td>
</tr>
<tr>
<td></td>
<td>Past or never</td>
<td>87.0</td>
<td>86.7</td>
</tr>
<tr>
<td>Body-mass index*</td>
<td>Mean ±SD</td>
<td>26.1±5.1</td>
<td>26.0±5.0</td>
</tr>
<tr>
<td></td>
<td>&lt;25.0 (%)</td>
<td>50.8</td>
<td>50.8</td>
</tr>
<tr>
<td></td>
<td>25.0 to 29.9 (%)</td>
<td>30.9</td>
<td>31.0</td>
</tr>
<tr>
<td></td>
<td>≥30.0 (%)</td>
<td>18.3</td>
<td>18.2</td>
</tr>
<tr>
<td>Menopausal status and use of HRT(%)†</td>
<td>Prenopausal</td>
<td>27.5</td>
<td>27.6</td>
</tr>
<tr>
<td></td>
<td>Uncertain</td>
<td>17.7</td>
<td>18.2</td>
</tr>
<tr>
<td></td>
<td>Postmenopausal and current HRT</td>
<td>30.4</td>
<td>29.7</td>
</tr>
<tr>
<td></td>
<td>Postmenopausal and no HRT</td>
<td>24.4</td>
<td>24.4</td>
</tr>
<tr>
<td>Hypertension (%)‡</td>
<td>Yes</td>
<td>26.0</td>
<td>25.7</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>74.0</td>
<td>74.3</td>
</tr>
<tr>
<td>Blood pressure (%)</td>
<td>&lt;120/&lt;75 mm Hg</td>
<td>32.2</td>
<td>32.9</td>
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<td></td>
<td>120–129/75–84 mm Hg</td>
<td>32.2</td>
<td>31.8</td>
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<tr>
<td></td>
<td>130–139/85–89 mm Hg</td>
<td>19.5</td>
<td>19.3</td>
</tr>
<tr>
<td></td>
<td>≥140/≥90 mm Hg</td>
<td>16.1</td>
<td>15.9</td>
</tr>
</tbody>
</table>

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Table 1. (Continued.)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Aspirin (N=19,934)</th>
<th>Placebo (N=19,942)</th>
<th>Total (N=39,876)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperlipidemia (%)§</td>
<td>29.9</td>
<td>29.1</td>
<td>29.5</td>
</tr>
<tr>
<td>Yes</td>
<td>70.1</td>
<td>70.9</td>
<td>70.5</td>
</tr>
<tr>
<td>No</td>
<td>2.7</td>
<td>2.5</td>
<td>2.6</td>
</tr>
<tr>
<td>No. of risk factors (%)§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>41.8</td>
<td>42.4</td>
<td>42.1</td>
</tr>
<tr>
<td>1</td>
<td>34.1</td>
<td>34.1</td>
<td>34.1</td>
</tr>
<tr>
<td>2</td>
<td>18.0</td>
<td>17.2</td>
<td>17.6</td>
</tr>
<tr>
<td>≥3</td>
<td>6.2</td>
<td>6.3</td>
<td>6.2</td>
</tr>
</tbody>
</table>

* 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 Cardiovacular End Points.

<table>
<thead>
<tr>
<th>End Point</th>
<th>Aspirin (N=19,934)</th>
<th>Placebo (N=19,942)</th>
<th>Relative Risk (95% CI)*</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of events</td>
<td>477</td>
<td>522</td>
<td>0.91 (0.80–1.03)</td>
<td>0.13</td>
</tr>
<tr>
<td>Major cardiovascular event†</td>
<td>221</td>
<td>226</td>
<td>0.83 (0.69–0.99)</td>
<td>0.04</td>
</tr>
<tr>
<td>Stroke</td>
<td>170</td>
<td>221</td>
<td>0.76 (0.63–0.93)</td>
<td>0.009</td>
</tr>
<tr>
<td>Ischemic</td>
<td>51</td>
<td>41</td>
<td>1.24 (0.82–1.87)</td>
<td>0.31</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>23</td>
<td>22</td>
<td>1.04 (0.58–1.86)</td>
<td>0.90</td>
</tr>
<tr>
<td>Fatal</td>
<td>198</td>
<td>244</td>
<td>0.81 (0.67–0.97)</td>
<td>0.02</td>
</tr>
<tr>
<td>Nonfatal</td>
<td>198</td>
<td>193</td>
<td>1.02 (0.84–1.25)</td>
<td>0.83</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>14</td>
<td>12</td>
<td>1.16 (0.54–2.51)</td>
<td>0.70</td>
</tr>
<tr>
<td>Fatal</td>
<td>184</td>
<td>181</td>
<td>1.01 (0.83–1.24)</td>
<td>0.90</td>
</tr>
<tr>
<td>Nonfatal</td>
<td>120</td>
<td>126</td>
<td>0.95 (0.74–1.22)</td>
<td>0.68</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>186</td>
<td>238</td>
<td>0.78 (0.64–0.94)</td>
<td>0.01</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>389</td>
<td>374</td>
<td>1.04 (0.90–1.20)</td>
<td>0.61</td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>609</td>
<td>642</td>
<td>0.95 (0.85–1.06)</td>
<td>0.32</td>
</tr>
</tbody>
</table>

* CI denotes confidence interval.
† 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 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 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. 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.

**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 myocar-
Cardiovascular 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. 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, the Hypertension Optimal Treatment (HOT) study, and the Primary Prevention Project (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, the British Doctors’ Trial, the Thrombosis Prevention Trial, the HOT study, and the Primary Prevention Project 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 (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, and the Primary Prevention Project (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).

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

<table>
<thead>
<tr>
<th>Group</th>
<th>Total No.</th>
<th>Major CV Event</th>
<th>Stroke</th>
<th>Ischemic Stroke</th>
<th>Myocardial Infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Asp Pla RR (95% CI)</td>
<td>Asp Pla RR (95% CI)</td>
<td>Asp Pla RR (95% CI)</td>
<td>Asp Pla RR (95% CI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>n.</td>
<td>n.</td>
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</tr>
<tr>
<td>Age</td>
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<tr>
<td>45–54 yr</td>
<td>24,025</td>
<td>163 161 1.01 (0.81–1.26)</td>
<td>77 90 0.85 (0.63–1.16)</td>
<td>57 71 0.80 (0.57–1.14)</td>
<td>69 56 1.23 (0.87–1.75)</td>
</tr>
<tr>
<td>55–64 yr</td>
<td>11,754</td>
<td>183 186 0.98 (0.80–1.20)</td>
<td>76 90 0.84 (0.62–1.14)</td>
<td>60 75 0.80 (0.57–1.12)</td>
<td>88 75 1.17 (0.86–1.59)</td>
</tr>
<tr>
<td>≥65 yr</td>
<td>4,097</td>
<td>131 175 0.74 (0.59–0.92)</td>
<td>68 86 0.78 (0.57–1.08)</td>
<td>53 75 0.70 (0.49–1.00)</td>
<td>41 62 0.66 (0.44–0.97)</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Current</td>
<td>5,235</td>
<td>157 127 1.30 (1.03–1.64)</td>
<td>63 58 1.14 (0.80–1.63)</td>
<td>50 46 1.14 (0.76–1.70)</td>
<td>76 53 1.50 (1.06–2.13)</td>
</tr>
<tr>
<td>Past or never</td>
<td>34,605</td>
<td>319 392 0.80 (0.69–0.93)</td>
<td>157 207 0.75 (0.61–0.92)</td>
<td>119 174 0.67 (0.53–0.85)</td>
<td>122 139 0.87 (0.68–1.10)</td>
</tr>
<tr>
<td>Body-mass index†</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>&lt;25.0</td>
<td>19,849</td>
<td>184 223 0.82 (0.68–1.00)</td>
<td>95 126 0.75 (0.58–0.98)</td>
<td>67 97 0.69 (0.50–0.94)</td>
<td>67 73 0.92 (0.66–1.28)</td>
</tr>
<tr>
<td>25.0 to 29.9</td>
<td>12,081</td>
<td>158 175 0.89 (0.72–1.11)</td>
<td>70 84 0.83 (0.60–1.13)</td>
<td>57 72 0.78 (0.55–1.11)</td>
<td>76 68 1.11 (0.80–1.54)</td>
</tr>
<tr>
<td>≥30.0</td>
<td>7,126</td>
<td>116 111 1.05 (0.81–1.36)</td>
<td>50 53 0.96 (0.65–1.41)</td>
<td>41 49 0.85 (0.56–1.29)</td>
<td>45 46 0.98 (0.65–1.47)</td>
</tr>
<tr>
<td>Menopause and HRT</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Premenopausal</td>
<td>10,973</td>
<td>55 63 0.88 (0.61–1.26)</td>
<td>30 31 0.97 (0.59–1.60)</td>
<td>23 23 1.01 (0.56–1.79)</td>
<td>18 26 0.69 (0.38–1.26)</td>
</tr>
<tr>
<td>Uncertain</td>
<td>7,149</td>
<td>67 75 0.91 (0.66–1.27)</td>
<td>24 43 0.57 (0.35–0.94)</td>
<td>16 35 0.47 (0.26–0.85)</td>
<td>38 26 1.49 (0.91–2.46)</td>
</tr>
<tr>
<td>Postmenopausal, current HRT</td>
<td>11,948</td>
<td>150 149 0.98 (0.78–1.23)</td>
<td>79 78 0.98 (0.72–1.34)</td>
<td>60 65 0.9 (0.63–1.27)</td>
<td>58 51 1.12 (0.77–1.63)</td>
</tr>
<tr>
<td>Postmenopausal, no HRT</td>
<td>9,704</td>
<td>201 234 0.86 (0.71–1.03)</td>
<td>86 113 0.76 (0.57–1.00)</td>
<td>69 97 0.71 (0.52–0.96)</td>
<td>81 90 0.9 (0.67–1.21)</td>
</tr>
<tr>
<td>Hypertension‡</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>10,317</td>
<td>235 270 0.84 (0.71–1.00)</td>
<td>109 138 0.76 (0.59–0.98)</td>
<td>91 120 0.73 (0.56–0.96)</td>
<td>98 101 0.95 (0.72–1.25)</td>
</tr>
<tr>
<td>No</td>
<td>29,550</td>
<td>241 252 0.96 (0.81–1.15)</td>
<td>111 128 0.88 (0.68–1.13)</td>
<td>78 101 0.78 (0.58–1.05)</td>
<td>100 92 1.10 (0.83–1.46)</td>
</tr>
<tr>
<td>Blood pressure</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>&lt;120/ &lt;75 mm Hg</td>
<td>12,799</td>
<td>72 70 1.04 (0.75–1.45)</td>
<td>40 43 0.94 (0.61–1.45)</td>
<td>27 35 0.78 (0.47–1.29)</td>
<td>24 19 1.28 (0.70–2.34)</td>
</tr>
<tr>
<td>120–129/75–84 mm Hg</td>
<td>12,581</td>
<td>107 113 0.94 (0.72–1.22)</td>
<td>51 57 0.89 (0.61–1.30)</td>
<td>37 45 0.82 (0.53–1.26)</td>
<td>43 42 1.02 (0.66–1.56)</td>
</tr>
<tr>
<td>130–139/85–89 mm Hg</td>
<td>7,642</td>
<td>131 138 0.94 (0.74–1.20)</td>
<td>47 62 0.75 (0.51–1.09)</td>
<td>36 48 0.74 (0.48–1.15)</td>
<td>66 59 1.11 (0.78–1.58)</td>
</tr>
<tr>
<td>≥140/ ≥90 mm Hg</td>
<td>6,295</td>
<td>158 190 0.81 (0.65–1.00)</td>
<td>76 101 0.73 (0.54–0.98)</td>
<td>65 90 0.7 (0.51–0.96)</td>
<td>64 68 0.92 (0.66–1.30)</td>
</tr>
</tbody>
</table>
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.
The new england journal of medicine

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. 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. 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, 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.

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.

Table 4. Incidence and Relative Risk of Side Effects.

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Aspirin (N=19,934)</th>
<th>Placebo (N=19,942)</th>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>910 (4.6)</td>
<td>751 (3.8)</td>
<td>1.22 (1.10–1.34)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Requiring transfusion</td>
<td>127 (0.6)</td>
<td>91 (0.5)</td>
<td>1.40 (1.07–1.83)</td>
<td>0.02</td>
</tr>
<tr>
<td>Peptic ulcer</td>
<td>542 (2.7)</td>
<td>413 (2.1)</td>
<td>1.32 (1.16–1.50)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hematuria</td>
<td>3,039 (15.2)</td>
<td>2,879 (14.4)</td>
<td>1.06 (1.01–1.12)</td>
<td>0.02</td>
</tr>
<tr>
<td>Easy bruising</td>
<td>10,561 (53.0)</td>
<td>8,494 (42.6)</td>
<td>1.40 (1.37–1.45)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>3,801 (19.1)</td>
<td>3,321 (16.7)</td>
<td>1.16 (1.11–1.22)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any report of gastric upset</td>
<td>11,856 (59.5)</td>
<td>11,915 (59.7)</td>
<td>0.99 (0.97–1.02)</td>
<td>0.59</td>
</tr>
</tbody>
</table>

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

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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 Force and the American Heart Association 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, Genevra McNair, Laura Pestana, David Potter, Philomena...
LOW-DOSE ASPIRIN AND CARDIOVASCULAR DISEASE IN WOMEN

Quinn, Claire Ridge, Fred Scherwin, and Harriet Samuelson; to Christine Albert, Michelle Albert, Gavin Blake, Claudia Chaz, 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. Gotch, F. Ferris, L. Friedman, P. Greenwald, N. Kurinij, M. Perloff, E. Schron, and A. Zonderman (ex officio members).

REFERENCES


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