Effect of Low-Dose Aspirin on Functional Outcome From Cerebral Vascular Events in Women

Pamela M. Rist, ScD; Julie E. Buring, ScD; Carlos S. Kase, MD; Tobias Kurth, MD, ScD

Background and Purpose—Although aspirin is effective in prevention of stroke, fewer studies have examined the impact of aspirin on stroke morbidity.

Methods—The Women’s Health Study is a completed randomized, placebo-controlled trial designed to test the effect of low-dose aspirin and vitamin E in the primary prevention of cardiovascular disease and cancer, which enrolled 39,876 women. We used multinomial logistic regression to evaluate the relationship between randomized aspirin assignment and functional outcomes from stroke. Possible functional outcomes were neither stroke nor transient ischemic attack (TIA), modified Rankin scale (mRS) score 0 to 1, 2 to 3, and 4 to 6.

Results—After a mean of 9.9 years of follow-up, 460 confirmed strokes (366 ischemic, 90 hemorrhagic, and 4 unknown type) and 405 confirmed TIAS occurred. With regard to total and ischemic stroke, women who were randomized to aspirin had a nonsignificant decrease in risk of any outcome compared to women not randomized to aspirin. This decrease in risk only reached statistical significance for those experiencing TIA compared to participants without stroke or TIA (odds ratio=0.77; 95% confidence interval, 0.63–0.94). For hemorrhagic stroke, a nonsignificant increase in the risk of achieving an mRS score 2 to 3 or 4 to 6 compared with no stroke or TIA was observed for the women randomized to aspirin compared to those randomized to placebo.

Conclusions—Results from this large randomized clinical trial provide evidence that 100 mg of aspirin every other day may reduce the risk of ischemic cerebral vascular events but does not have differential effects on functional outcomes from stroke. (Stroke. 2013;44:1-5.)

Key Words: aspirin ■ cerebrovascular disease ■ epidemiology

As the morbidity burden from stroke grows, it has become increasingly important to determine the impact of exposures not only on the risk of stroke but also on stroke morbidity. Finding ways to reduce stroke morbidity is especially critical among women who are at increased risk of worse functional outcomes after stroke compared with men.1 One factor that has been investigated for its ability to reduce the risk of stroke is aspirin. Results from a meta-analysis of primary prevention trials showed that randomized assignment to aspirin resulted in a significantly decreased risk of ischemic stroke among women.2

Although aspirin is effective in the prevention of stroke, fewer studies have examined the impact of aspirin on stroke morbidity. Observational studies among cohorts of stroke patients are inconclusive, with some suggesting a beneficial effect of prestroke aspirin use on functional outcomes after stroke or stroke severity,3,4 whereas other studies showed no benefit.3,5 In a large meta-analysis, randomized assignment to aspirin was associated with nonsignificant increase in the risk of fatal stroke among men and women, which was driven by an increased risk of fatal hemorrhagic stroke.2 A previous analysis in the Women’s Health Study did not observe a significant increase in the risk of fatal stroke events.8 Additionally, those randomized to receive aspirin had a significantly decreased risk of experiencing a transient ischemic attack (TIA).8 Given the decreased risk of TIA observed, it is plausible that aspirin treatment may also reduce the risk of strokes with a mild functional impairment.

Using data from the Women’s Health Study (WHS), we examined the effect of randomized assignment to 100 mg aspirin every other day and functional outcomes after incident cerebral vascular events.

Methods

The WHS was a randomized, placebo-controlled trial designed to test the effect 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 design, methods, and results have been described previously.8-10 In brief, 39,876 US female healthcare professionals aged 45 years or older at study entry without a previous...
history of cardiovascular, cancer or other major illnesses, were randomized to receive aspirin, vitamin E, both active agents, or both placebos according to a 2 by 2 factorial design (see the online-only Data Supplement). Written informed consent was obtained from all trial participants, and the Institutional Review Board of Brigham and Women's Hospital, Boston, MA, approved the trial.

At baseline, women completed a questionnaire about lifestyle and demographic characteristics. Follow-up questionnaires asking about study outcomes and other information were sent every 6 months during the first year and annually thereafter. This analysis includes information from randomization to March 31, 2004, the end of the randomized trial. Morbidity and mortality follow-up were 97.2% and 99.4% complete as of the end of the trial, respectively.

Outcome Ascertainment

When a woman reported a newly diagnosed medical condition, including a TIA or stroke, in her yearly questionnaire, her medical record was obtained. An end-points committee of physicians, including a board-certified vascular neurologist blinded to treatment assignment, reviewed the medical record and confirmed the event. A confirmed TIA was defined as a new focal-neurological deficit of sudden or rapid onset that lasted for <24 hours. A confirmed stroke was defined as a new focal-neurological deficit of sudden or rapid onset that persisted for at least 24 hours. In the event of a fatal stroke, autopsy reports, death certificates, medical records, and information obtained from next of kin or other family members were used to find evidence of a cerebrovascular mechanism. Clinical information, computed tomographic scans, and magnetic resonance images were used to distinguish hemorrhagic from ischemic stroke events. Interobserver agreement for stroke subtype classification was excellent.

In the event of a confirmed stroke, medical record information was also used to determine the functional outcome from the stroke according to the 6-point modified Rankin scale (mRS; 0=no symptoms at all, 1=no significant disability, 2=slight disability, 3=mild disability, 4=moderate disability, 5=severe disability, and 6=death). To avoid problems with model convergence attributable to sparse data, we a priori categorized the mRS into 5 levels (0–1, 2–3, and 4–6) similar to previous studies. Possible functional outcomes were no stroke, TIA, and the 3 categories of the mRS. All statistical analyses were performed using SAS 9.1 (Cary, NC). All P values are 2-tailed, and we considered P<0.05 as statistically significant.

Statistical Analysis

We used Cox proportional hazards models to determine the relative risk (RR) of total, ischemic, and hemorrhagic stroke and TIA for those randomized to aspirin compared to those randomized to placebo using an intention-to-treat approach. Our model adjusted for age at randomization and for randomized assignment to vitamin E and beta carotene. Because we considered TIA to be part of our functional outcomes from cerebral vascular events, only the first stroke or TIA was counted in our analysis. This is in contrast to a previous analysis in WHS, which counted first stroke and first TIA separately.

We used multinomial logistic regression to evaluate the relationship between randomized aspirin assignment and functional outcomes from stroke. Multinomial logistic regression is an extension of binary logistic regression that allows the dependent variable to have >2 categories. Each category is then simultaneously compared with the reference category of no stroke or TIA. Unlike ordinal logistic regression, multinomial logistic regression does not assume that the response categories are ordered. We a priori chose multinomial logistic regression because it allows for more flexibility and makes fewer assumptions than ordinal logistic regression. The resulting odds ratios and 95% confidence intervals (CIs) are used as a measure of the RR of each functional outcome among those randomized to aspirin compared to those randomized to placebo. For the analysis testing the effect of randomized assignment to aspirin and functional outcomes from hemorrhagic stroke, TIA was not included as a potential outcome. Our multinomial models adjusted for age at randomization and randomized assignment to vitamin E and beta carotene. In the event that a woman experienced multiple strokes or TIAs, only the first event was included in our analysis. We used an intention-to-treat analysis approach.

In secondary analyses, we examined whether age at randomization (45–54 years of age, 55–64 years of age, ≥65 years of age), smoking status (current, past, or never), body mass index (<25.0, 25.0–29.9, or ≥30.0 kg/m²), postmenopausal status and hormone replacement therapy (premenopausal, uncertain, postmenopausal and current hormone replacement therapy, and postmenopausal and no hormone replacement therapy), history of hypertension (yes/no), history of diabetes mellitus (yes/no), or vigorous physical activity (rarely/never, <1 time/wk, 1–3 times/wk, or ≥4 times/wk) modified the relationship between randomized aspirin assignment and functional outcomes from total stroke by including an interaction between aspirin assignment and each variable in separate models.

<p>| Table 1. Baseline Characteristics of Participants by Randomized Treatment Assignment (n=39,876) |</p>
<table>
<thead>
<tr>
<th>Characteristics</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, y</td>
<td>54.6±7.0</td>
<td>54.6±7.0</td>
</tr>
<tr>
<td>45–54 y (%)</td>
<td>60.2</td>
<td>60.2</td>
<td>60.2</td>
</tr>
<tr>
<td>55–64 y (%)</td>
<td>29.5</td>
<td>29.5</td>
<td>29.5</td>
</tr>
<tr>
<td>≥65 y (%)</td>
<td>10.3</td>
<td>10.3</td>
<td>10.3</td>
</tr>
<tr>
<td>Smoking status (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>13.0</td>
<td>13.3</td>
<td>13.1</td>
</tr>
<tr>
<td>Past or never</td>
<td>87.0</td>
<td>86.7</td>
<td>86.9</td>
</tr>
<tr>
<td>Body mass index*</td>
<td>Mean±SD, y</td>
<td>26.1±5.1</td>
<td>26.0±5.0</td>
</tr>
<tr>
<td>&lt;25.0 (%)</td>
<td>50.8</td>
<td>50.8</td>
<td>50.8</td>
</tr>
<tr>
<td>25.0–29.9 (%)</td>
<td>30.9</td>
<td>31.0</td>
<td>30.9</td>
</tr>
<tr>
<td>≥30.0 (%)</td>
<td>18.3</td>
<td>18.2</td>
<td>18.2</td>
</tr>
<tr>
<td>Menopausal status and use of HRT (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premenopausal</td>
<td>27.5</td>
<td>27.6</td>
<td>27.6</td>
</tr>
<tr>
<td>Uncertain</td>
<td>17.7</td>
<td>18.2</td>
<td>18.0</td>
</tr>
<tr>
<td>Postmenopausal and current HRT</td>
<td>30.4</td>
<td>29.7</td>
<td>30.0</td>
</tr>
<tr>
<td>Postmenopausal and no HRT</td>
<td>24.4</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>No</td>
<td>74.0</td>
<td>74.3</td>
<td>74.1</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>Yes</td>
<td>2.7</td>
<td>2.5</td>
</tr>
<tr>
<td>No</td>
<td>97.3</td>
<td>97.5</td>
<td>97.4</td>
</tr>
<tr>
<td>Physical activity at baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rarely/never</td>
<td>38.4</td>
<td>38.3</td>
<td>38.3</td>
</tr>
<tr>
<td>&lt;1 wk</td>
<td>19.5</td>
<td>20.2</td>
<td>19.9</td>
</tr>
<tr>
<td>1–3 times/wk</td>
<td>31.3</td>
<td>31.0</td>
<td>31.1</td>
</tr>
<tr>
<td>≥4 times/wk</td>
<td>10.7</td>
<td>10.5</td>
<td>10.6</td>
</tr>
</tbody>
</table>

HRT indicates hormone replacement therapy.

*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, diastolic blood pressure of at least 90 mm Hg, or self-reported physician-diagnosed hypertension.
**Results**

The baseline characteristics of the aspirin and placebo groups were similar (Table 1). After a mean of 9.9 years of follow-up, 460 confirmed strokes (366 ischemic, 90 hemorrhagic, and 4 unknown type) and 405 confirmed TIA s occurred. Those randomly assigned to 100 mg of aspirin every other day had lower risk of TIA (RR=0.77; 95% CI, 0.63–0.94) and a tendency toward a lower risk of total stroke (RR=0.86; 95% CI, 0.72–1.04), which was driven by a significant decrease in the risk of ischemic stroke (RR=0.80; 95% CI, 0.65–0.98) but not in the risk of hemorrhagic stroke (RR=1.30; 95% CI, 0.86–1.97).

The distribution of TIA and scores on the mRS for total, ischemic, and hemorrhagic stroke can be seen in Figures 1 through 3. The effect between randomized assignment to aspirin and functional outcomes from total, ischemic, and hemorrhagic stroke are shown in Table 2. With regard to total and ischemic stroke, women who were randomized to aspirin had a significantly lower risk of TIA compared to participants without any stroke or TIA (odds ratio=0.77; 95% CI, 0.63–0.94) and a tendency towards lower risk of other outcomes compared to women not randomized to aspirin, but this reduction in risk did not reach statistical significance. With regard to hemorrhagic stroke, a nonsignificant increase in the risk of experiencing mRS 2 to 3 or mRS 4 to 6 compared to no stroke was observed for the women randomized to aspirin compared with those randomized to placebo.

Secondary analyses showed no evidence of effect modification by age at randomization, body mass index, postmenopausal status and hormone replacement therapy status, history of hypertension, history of diabetes mellitus, or vigorous physical activity ($P>0.14$). We did observe evidence of effect modification by smoking status ($P=0.03$). Among never or past smokers, there was a significant decrease in the risk of TIA or mild functional outcomes from stroke for those randomized to aspirin compared to those randomized to placebo (odds ratio=0.71; 95% CI, 0.58–0.89 for TIA and odds ratio=0.67; 95% CI, 0.48–0.93 for mRS 0–1). Among current smokers, however, we did not observe a beneficial effect of aspirin use on the risk of functional outcomes from cerebral vascular events (Table 3).

**Discussion**

Results from this large randomized clinical trial provide evidence that 100 mg of aspirin every other day prevent first TIA and stroke, particularly ischemic stroke. However, our results do not show differential effects of aspirin on functional outcome from stroke. We observed interaction with smoking status, showing that the beneficial effect of aspirin on ischemic cerebral vascular events is not apparent for current smokers for any functional outcome.

Two other primary prevention trials of the effect of aspirin on incident stroke have enrolled women besides the WHS. One trial did not present information on stroke severity. In the other trial, 3 of the 16 stroke events were considered disabling in the group randomized to aspirin, whereas in the placebo group, 4 of the 24 stroke cases were considered disabling.

![Figure 1. Distribution of transient ischemic attack (TIA) and scores on the modified Rankin scale (mRS) for total stroke (n=39876).](image1)

![Figure 2. Distribution of transient ischemic attack (TIA) and scores on the modified Rankin scale (mRS) for ischemic stroke (n=39782).](image2)
Other studies on the impact of aspirin on stroke severity have been observational and only enrolled stroke patients. One study using data from the Trial of Org 10172 in Acute Stroke Treatment (TOAST) assessed aspirin use in the 7 days before stroke and found lower mean National Institutes of Health Stroke Scale scores and Supplemental Motor Examination scores within 24 hours of stroke onset among aspirin users compared with nonusers.4 Another study also found lower median National Institutes of Health Stroke Scale scores at admission and greater odds of a good outcome according to the mRS (mRS=0 or 1) among those taking antiplatelet agents (including aspirin) compared with those not taking antiplatelet agents.3 In contrast, another study using data from the International Stroke Trial found no benefit of aspirin use in the 3 days before stroke on stroke severity as measured by the Oxford Community Stroke Project stroke syndrome, baseline-predicted poor outcome, and observed poor outcome. However, this study did not have information on previous vascular events, including a history of previous stroke.7 A small study among those with first ischemic stroke in the territory of the middle cerebral artery found that low-dose aspirin use was not associated with decreased stroke severity, as assessed by the Mathew scale, or better stroke outcome, as assessed by the Barthel Index, and mortality 21 days after the stroke event.5 Another larger study enrolling stroke patients found no difference in stroke severity as measured by impairment of activities of daily living within 24 hours of admission between those in whom aspirin treatment of any dose had been initiated because of previous ischemic heart disease, peripheral vascular disease, or migraine and who took aspirin regularly for at least 1 month before their stroke compared to those who did not meet these criteria. A nonsignificant reduction in stroke mortality was observed among aspirin users.6

Unlike the previous observational studies, the present study enrolled a cohort of apparently healthy individuals and randomized them to receive aspirin or placebo. This allowed us to assess the impact of randomized assignment to aspirin on the risk of experiencing a TIA or a mild, moderate, or severe stroke outcome compared to not experiencing any cerebral vascular event.

Although we did not have information on prestroke disability, the women had to be free of many major diseases to be enrolled in the study and, therefore, are likely to be able-bodied at baseline. Additionally, the mRS accounts for prestroke disability.13 Although there are limitations to using the mRS,18,19 it has strong test-retest reliability, interrater reliability, and validity18 and is widely accepted for use in clinical trials.20,21 Because a previous meta-analysis did not show a

### Table 2. Effect of Low-Dose Aspirin on Functional Outcomes After Stroke and Stroke Subtypes (n=39876)

<table>
<thead>
<tr>
<th></th>
<th>No TIA or Stroke</th>
<th>TIA</th>
<th>mRS 0–1</th>
<th>mRS 2–3</th>
<th>mRS 4–6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n %</td>
<td>n %</td>
<td>OR* (95% CI)</td>
<td>OR* (95% CI)</td>
<td>OR* (95% CI)</td>
</tr>
<tr>
<td>Total stroke</td>
<td>(n = 405)</td>
<td>(n = 185)</td>
<td>(n = 158)</td>
<td>(n = 117)</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>19468 49.9</td>
<td>228 56.3</td>
<td>105 56.8</td>
<td>81 51.3</td>
<td>60 51.3</td>
</tr>
<tr>
<td>Aspirin</td>
<td>19543 50.1</td>
<td>177 43.7</td>
<td>80 43.2</td>
<td>77 48.7</td>
<td>57 48.7</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>(n = 405)</td>
<td>(n = 166)</td>
<td>(n = 141)</td>
<td>(n = 59)</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>19468 49.9</td>
<td>228 56.3</td>
<td>93 56.0</td>
<td>74 52.5</td>
<td>36 61.0</td>
</tr>
<tr>
<td>Aspirin</td>
<td>19543 50.1</td>
<td>177 43.7</td>
<td>73 44.0</td>
<td>67 47.5</td>
<td>23 39.0</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>(n = 17)</td>
<td>(n = 16)</td>
<td>(n = 16)</td>
<td>(n = 57)</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>19468 49.9</td>
<td>NA NA NA</td>
<td>10 58.8</td>
<td>6 37.5</td>
<td>23 40.4</td>
</tr>
<tr>
<td>Aspirin</td>
<td>19543 50.1</td>
<td>NA NA NA</td>
<td>7 41.2</td>
<td>10 62.5</td>
<td>34 59.7</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; mRS, modified Rankin scale; NA, not applicable; OR, odds ratio; and TIA, transient ischemic attack.

*Adjusted for age and randomized assignment to beta carotene and vitamin E.
beneficial effect of aspirin on the risk of stroke among men, our results may not be generalizable to men. Additionally, although the women were randomized to receive aspirin or placebo, they may not have complied with their randomized treatment assignment. A sensitivity analysis only including women who reported taking two thirds of their pills found similar results as our primary analysis (results not shown).

In conclusion, whereas randomized assignment to 100 mg of aspirin every other day may reduce the risk of ischemic cerebral vascular events, especially TIA, we did not observe differential effects on functional outcomes from stroke. This underscores the importance of using primary prevention methods, for example, aspirin or blood-pressure-lowering treatment to reduce stroke incidence and its associated morbidity.

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Supplemental Material
1.7 million women invited to participate

453787 completed baseline questionnaire

65169 entered run-in phase

25293 excluded after run-in (noncompliance, unwillingness or ineligibility)

39876 randomized

19934 assigned to receive aspirin

Status on March 31, 2044
19147 Alive
699 Dead
118 Unknown vital status

19942 assigned to receive placebo

Status on March 31, 2044
19133 Alive
693 Dead
116 Unknown vital status

Figure 1. Enrollment and randomization scheme for the Women’s Health Study.