

# A Randomized Trial of Low-Dose Aspirin in the Prevention of Clinical Type 2 Diabetes in Women

ARUNA D. PRADHAN, MD<sup>1,2,3,4</sup>  
NANCY R. COOK, SCD<sup>1,2,3</sup>  
JOANN E. MANSON, MD<sup>3</sup>

PAUL M. RIDKER, MD<sup>1,2,3,5,6</sup>  
JULIE E. BURING, SCD<sup>1,3</sup>

**OBJECTIVE**— Subclinical inflammation is linked with the development of type 2 diabetes, and epidemiologic data suggest that this association may be stronger in women. Although small clinical studies have shown a prominent hypoglycemic effect of short-term high-dose aspirin, no randomized trials have directly evaluated the efficacy of aspirin in diabetes prevention at doses acceptable for use in routine clinical practice. We evaluated whether chronic low-dose aspirin prevents the development of clinical diabetes among initially healthy American women.

**RESEARCH DESIGN AND METHODS**— Subjects were enrolled in the Women's Health Study, a 10-year randomized double-blind, placebo-controlled trial of aspirin and vitamin E for primary prevention of cardiovascular disease and cancer. Between 1992 and 1995, 38,716 women aged  $\geq 45$  years and free of clinical diabetes were randomly assigned to either low-dose aspirin or placebo (median follow-up 10.2 years). Documented clinical type 2 diabetes was prospectively evaluated throughout the trial.

**RESULTS**— Among women randomly assigned to receive aspirin ( $n = 19,326$ ) or placebo ( $n = 19,390$ ), there was no statistically significant difference in the incidence of type 2 diabetes. There were 849 cases of diabetes in the aspirin group and 847 in the placebo group (rate ratio 1.01 [95% CI 0.91–1.11]). Stratification by diabetes risk factors including age, BMI, family history of diabetes, physical activity, A1C, and high-sensitivity C-reactive protein did not support a modulating effect of these variables. Analyses accounting for treatment duration and adherence similarly found no beneficial effects.

**CONCLUSIONS**— These data suggest that long-term low-dose aspirin does not prevent the development of clinical type 2 diabetes in initially healthy women.

*Diabetes Care* 32:3–8, 2009

The ability of salicylates, such as aspirin, to reduce glucose levels was described >125 years ago (1). This effect was largely forgotten until the emergence of recent data linking inflammation with the development of type 2 diabetes. A wealth of experimental and epidemiological evidence now indicates that insulin resistance and type 2 diabetes are, in

part, obesity-linked inflammatory disorders (2), and the presence of subclinical inflammation is now known to be a potent indicator of risk for this disease. This relationship may be of particular importance in the pathogenesis of diabetes in women among whom obesity-triggered inflammation may be heightened compared with that in men (3). These findings

have spurred interest in the use of anti-inflammatory drugs in diabetes prevention and treatment (4). However, data pertaining to this novel approach are sparse with no large-scale randomized studies available to date.

Aspirin is an anti-inflammatory agent with pleiotropic actions, many of which remain poorly understood. The cellular and molecular mechanisms of the hypoglycemic response to aspirin are an area of active investigation but likely involve anti-inflammatory pathways distinct from effects on prostaglandin synthesis (5,6). Several small clinical studies (7–10) have reported that short-term high-dose aspirin (3–10 g/day for 3 days–3 weeks) improves glucose handling and may ameliorate insulin resistance in diabetic patients, albeit with a high rate of side effects. Although data are not available on the hypoglycemic action of low-dose aspirin, several short-term clinical trials demonstrated that aspirin triggers the production of anti-inflammatory mediators (11) and lowers systemic levels of inflammatory biomarkers at doses as low as 30 mg/day (12). Whether chronic low-dose aspirin therapy has favorable clinical effects is unknown.

We assessed whether long-term low-dose aspirin therapy reduces the incidence of clinical type 2 diabetes in the randomized treatment arms of the Women's Health Study (WHS). The WHS tested the efficacy of low-dose aspirin in the primary prevention of cardiovascular disease and cancer over a 10-year period in a large group of initially healthy women. The occurrence of clinical diabetes was ascertained prospectively throughout the trial.

## RESEARCH DESIGN AND METHODS

The WHS was a  $2 \times 2$  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  $\alpha$ -tocopherol every other day; Natural Source Vitamin E Association) in the primary prevention of cardiovascular disease and cancer (13–15). The dose of 100 mg every other day was chosen to be the lowest dose that

From the <sup>1</sup>Center for Cardiovascular Disease Prevention, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts; the <sup>2</sup>Donald W. Reynolds Center for Cardiovascular Research, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts; the <sup>3</sup>Division of Preventive Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts; the <sup>4</sup>Division of Cardiology, VA Boston Medical Center, Boston, Massachusetts; the <sup>5</sup>Leducq Center for Molecular and Genetic Epidemiology of Cardiovascular Disorders, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts; and the <sup>6</sup>Division of Cardiovascular Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts.

Corresponding author: Aruna D. Pradhan, apradhan@partners.org.

Received 1 July 2008 and accepted 18 September 2008.

Published ahead of print at <http://care.diabetesjournals.org> on 3 October 2008. DOI: 10.2337/dc08-1206.

Clinical trial reg. no. NCT00000479, clinicaltrials.gov.

© 2009 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. See <http://creativecommons.org/licenses/by-nc-nd/3.0/> for details.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

would have a cardioprotective effect while minimizing gastrointestinal side effects. Although not a prespecified primary end point of the WHS, clinical diabetes was a key outcome of interest and prospectively ascertained throughout the duration of the trial.

Written informed consent was obtained from all women. The study was approved by the institutional review board of the Brigham and Women's Hospital and monitored by an external data and safety monitoring board.

### Setting and participants

Details of the study design have previously been described (13,16). Women were eligible if they were at least 45 years of age without a previous history of cancer (except nonmelanoma skin cancer), cardiovascular disease, or other major chronic illness; had no history of adverse effects from aspirin; were not taking aspirin or nonsteroidal anti-inflammatory drugs (or were willing to forgo their use during the trial); and were not taking anticoagulants or individual supplements of vitamin A, E, or  $\beta$ -carotene more than once a week. A total of 39,876 women were willing, eligible, and compliant during a 3-month placebo run-in period and underwent random assignment: 19,934 were assigned to receive aspirin and 19,942 to receive placebo. In the present analyses, we excluded women with reported physician-diagnosed diabetes at baseline ( $n = 1,160$ ), leaving a total of 38,716 women free of clinical diabetes at entry into the trial; 19,326 were assigned to receive aspirin and 19,390 to receive placebo. Additional details including a Consolidated Standards of Reporting Trials (CONSORT) flow diagram are provided in supplemental data and supplemental Fig. 1 (available in an online appendix at <http://dx.doi.org/10.2337/dc08-1206>).

### Randomization and interventions

With use of a computer-generated table of random numbers, treatment assignments were made within seven age-groups (45–49, 50–54, 55–59, 60–64, 65–69, 70–74, and  $\geq 75$  years) using block sizes of 16. Random assignment took place from 30 April 1993 through 24 January 1996. Each year, women received calendar packs that contained amber capsules (vitamin E or placebo) and white pills (aspirin or placebo) on alternate days. Every 6 months for the first year and annually thereafter, they also received follow-up

questionnaires inquiring about compliance with pill-taking, potential adverse effects, occurrence of end points, and risk factors. Study medications were continued in blinded fashion through the scheduled end of the trial (31 March 2004).

### Compliance

On the basis of self-reported adherence, compliance, defined as taking at least two-thirds of their aspirin or matching placebo tablets, was 76.1% at 5 years and 67.0% at 10 years. Averaged throughout the trial, compliance was slightly higher in the placebo (73.7%) group than in the active (72.5%) group ( $P = 0.004$ ). Non-trial use of aspirin or aspirin-containing products on  $\geq 4$  days/month ("drop-ins") was 11.6% at 5 years and 19.2% at 10 years. Averaged throughout the trial, it was somewhat higher in the placebo (13.0%) group than in the active (12.7%) group ( $P = 0.10$ ).

### Outcomes and follow-up

Details regarding the ascertainment of incident diabetes in the WHS have been reported previously (17). Information on newly diagnosed diabetes was collected on every follow-up questionnaire from baseline through the end of the trial. All participants were asked annually "In the past year, were you newly diagnosed with diabetes mellitus?" Subjects also provided the month and year of diagnosis. Confirmation of diabetes was conducted in a blinded fashion using American Diabetes Association diagnostic criteria (18). Self-reported cases were investigated by either telephone interview conducted by a physician or a previously validated self-administered supplemental questionnaire that inquired about symptoms, diagnostic testing, and use of diabetes medications (19). The response rate was high with  $>90\%$  of women who reported incident diabetes responding to either the telephone interview or supplemental questionnaire. On the basis of responses to the supplemental questionnaire, 77.2% of those with confirmed cases reported use of antidiabetic agents. Only women with confirmed cases were analyzed in this report. Because the vast majority of diabetes diagnosed at age  $\leq 45$  years is of the type 2 variant, incident diabetes in the WHS is considered to be type 2 diabetes.

Glucose screening rates were assessed during follow-up. When asked about screening for diabetes on the 9-year questionnaire, 71.8 and 68.2% of nondiabetic women reported having a fasting glucose

test performed within the preceding 5 and 3 years, respectively. Screening rates were equivalent between the two treatment arms: 68.3 versus 68.1% in the preceding 3 years in the aspirin and placebo groups, respectively ( $P = 0.78$ ). These values are similar to contemporaneous diabetes screening rates; among patients in a U.S. managed care population, the occurrence of any glucose testing (random or fasting) over a 3-year period was 71.5% for women  $\geq 45$  years (20).

### Statistical analysis

All primary analyses were performed on an intention-to-treat basis. We used Cox proportional hazards models to estimate the rate ratio (RR) and 95% CIs, comparing 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 years) (21). The proportionality assumption of constant hazards over time was tested using an interaction term of aspirin with the logarithm of time. The divergence of diabetes incidence over time between groups was estimated using Kaplan-Meier survival curves and the log-rank test was computed to compare curves.

Exploratory subgroup analyses were conducted to examine the effect of aspirin according to the baseline presence of major risk factors for type 2 diabetes including age-group, BMI group, family history of diabetes in a first-degree relative, physical activity, menopausal status, and hormone therapy. Categories are specified in Table 1. Among women providing baseline blood specimens ( $n = 27,167$ ), subgroup analyses were performed after stratification by levels of total cholesterol, LDL cholesterol, HDL cholesterol, the total cholesterol-to-HDL cholesterol ratio, non-HDL cholesterol, A1C, and high-sensitivity C-reactive protein (hsCRP).

To estimate the effect of treatment duration, we fit two separate proportional hazards models to the experience of the first 5 years and after 5 years of follow-up. To assess the impact of potentially undiagnosed diabetes at baseline, we conducted sensitivity analyses in which women with diabetes diagnosed during the first 2 and 5 years of follow-up were excluded. To examine the effect of actual as opposed to assigned aspirin use, we performed additional analyses in which subjects were censored if and when they stopped tak-

Table 1—Baseline characteristics of the study population

	Aspirin	Placebo
Total population		
<i>n</i>	19,326	19,390
Age category (%)		
45–54 years	60.6	60.6
55–64 years	29.2	29.2
≥65 years	10.2	10.1
BMI category (%)		
<25.0 kg/m <sup>2</sup>	51.8	51.8
25.0–29.9 kg/m <sup>2</sup>	30.8	31.0
≥30.0 kg/m <sup>2</sup>	17.4	17.2
Ethnicity (%)		
White not of Hispanic origin	95.1	95.0
African American	2.3	2.1
Hispanic	1.0	1.1
American Indian or Alaskan Native	0.3	0.2
Asian or Pacific Islander	1.3	1.5
Unknown (none of the above)	0.2	0.2
Family history of diabetes (%)*	24.6	25.1
Current smoker (%)	12.9	13.4
Exercise ≥ once weekly (%)†	42.4	41.8
Alcohol consumption ≥ once weekly (%)	42.4	42.5
History of hypertension (%)	24.9	24.7
History of hyperlipidemia (%)	29.5	28.5
Postmenopausal (%)	54.6	53.9
Baseline use of hormone therapy (%)	41.6	40.9
Available baseline blood specimen		
<i>n</i>	13,595	13,572
Total cholesterol (mmol/l)	5.41 (4.76–6.10)	5.38 (4.76–6.08)
LDL cholesterol (mmol/l)	3.15 (2.60–3.74)	3.13 (2.60–3.72)
HDL cholesterol (mmol/l)	1.35 (1.13–1.62)	1.35 (1.12–1.61)
Total cholesterol-to-HDL cholesterol ratio	4.0 (3.2–4.9)	3.9 (3.2–4.9)
Non-HDL cholesterol (mmol/l)	3.99 (3.33–4.72)	3.98 (3.34–4.68)
A1C (%)	5.0 (4.8–5.2)	5.0 (4.8–5.2)
hsCRP (mg/l)	2.0 (0.8–4.2)	2.0 (0.8–4.3)

Data are % or median (interquartile range). \*Family history of diabetes in a first-degree relative (mother, father, sister, or brother). †Physical activity defined by number of episodes of vigorous physical activity per week.

ing at least two-thirds of their study pills. To assess the effect of nontrial aspirin use, we also performed analyses in which censoring occurred when women either stopped taking at least two-thirds of their study pills or reported outside use of aspirin or aspirin-containing products for ≥4 days/month.

All analyses were performed with SAS (version 9.1; SAS Institute, Cary, NC). A two-sided significance level of 0.05 was used.

**RESULTS**— The aspirin and placebo groups were similar with respect to baseline characteristics (Table 1). Among women providing blood specimens, there were also no significant differences in lipid levels, A1C, or hsCRP. The median duration of follow-up was 10.2 years

(mean 9.8 years). At completion of the trial, 1,696 cases of confirmed incident clinical type 2 diabetes had occurred. There were 849 cases in the aspirin group and 847 cases in the placebo group, with no significant risk reduction (RR for aspirin versus placebo 1.01 [95% CI 0.91–1.11]).

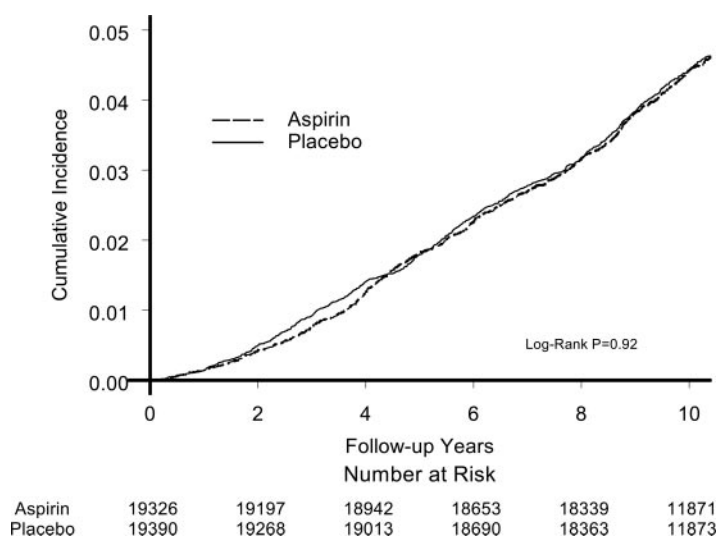
The cumulative incidence curves according to treatment assignment were similar throughout follow-up (Fig. 1) (log-rank  $P = 0.92$ ). A test of the proportionality hazards assumption showed no deviation from proportionality ( $P = 0.27$ ). In separate analyses that considered newly diagnosed diabetes in the first 5 years of follow-up versus thereafter, aspirin therapy was associated with an RR of 0.99 (95% CI 0.86–1.15) during the first 5 years and 1.01 (0.90–1.15) after 5

years. We found no difference when patients with potentially undiagnosed diabetes documented during the first 2 or 5 years of follow-up were excluded. In these analyses the RRs were 0.99 (0.89–1.09) and 1.01 (0.90–1.15), respectively.

There was no evidence that any diabetes risk factors considered modified the effect of aspirin on diabetes incidence (Table 2) ( $P_{\text{interaction}} \geq 0.2$  for clinical risk factors). Although we did find statistically significant risk reductions among women who had total cholesterol levels >6.21 mmol/l (RR 0.77 [95% CI 0.61–0.97],  $P = 0.028$ ) and LDL cholesterol >4.13 mmol/l (0.76 [0.58–1.00],  $P = 0.049$ ), with borderline nonsignificant findings for women with total cholesterol-to-HDL cholesterol ratio ≥6.0 (0.81 [0.66–1.00],  $P = 0.053$ ), these findings must be interpreted with caution given both the lack of a consistent risk increase across biomarker categories and the large number of subgroups examined. There was no statistically significant interaction for any of the biomarkers assessed ( $P_{\text{interaction}} = 0.39$  for total cholesterol, 0.26 for LDL cholesterol, 0.13 for the total cholesterol-to-HDL cholesterol ratio, and ≥0.2 for all others).

Because compliance diminished over time, sensitivity analyses were performed that censored noncompliant women at the time they stopped taking at least two-thirds of their study pills during the preceding year. In this analysis, there was also no significant benefit of aspirin (RR 1.02 [95% CI 0.91–1.15]). When women were censored at the time they either stopped taking at least two-thirds of their study pills or started outside aspirin or aspirin-containing medications on ≥4 days/month, findings were similarly nonsignificant. In addition, there was no evidence of effect modification by other randomized treatments. With regard to safety, as expected, there were slightly higher rates of clinically significant bleeding episodes and other side effects in the aspirin arm compared with placebo: 4.5 vs. 3.7% (RR 1.22,  $P < 0.001$ ) for any bleeding event, 0.6 vs. 0.4% (RR 1.37,  $P = 0.03$ ) for transfusion-requiring bleeding, 2.7 vs. 2.1% (RR 1.30,  $P < 0.001$ ) for peptic ulcer, 15.2 vs. 14.4% (RR 1.06,  $P = 0.02$ ) for hematuria, and 19.0 vs. 16.5% (RR 1.17,  $P < 0.001$ ) for epistaxis.

**CONCLUSIONS**— In this large-scale, long-term trial of initially healthy women, there was no association of 100



**Figure 1**— Cumulative incidence of type 2 diabetes in the aspirin and placebo groups.

mg aspirin on alternate days with the overall incidence of clinical type 2 diabetes. Treatment duration,  $\leq 5$  years or  $> 5$  years, did not have an impact on our results, and the treatment effect did not vary significantly across subgroups of women at high risk for diabetes due to the presence of clinical risk factors, dyslipidemia, elevated A1C, or hsCRP. There was no difference when women with early cases, presumably undiagnosed at baseline, were excluded or in analyses accounting for adherence to randomized assignment. Aspirin therapy was associated with a higher incidence of clinically important bleeding events.

The increasing incidence of diabetes, high treatment costs, and disproportionate impact on cardiovascular disease in women highlight the need to identify prevention strategies applicable on a broad population basis. Preventive measures with potential dual effects on cardiovascular and diabetes risk reduction are particularly appealing because “cardiometabolic” risk factors often coincide in the same individual. The main findings of the Women’s Health Study were published previously and demonstrated that long-term treatment with low-dose aspirin, although resulting in no significant benefit or harm on the end point of any first major cardiovascular event, did significantly reduce the risk of stroke overall (RR 0.83 [95% CI 0.69–0.99]) and myocardial infarction among women aged  $> 65$  years (0.66 [0.44–0.97]) (13). The current analysis addresses the important question of whether low-dose aspirin has added benefits for diabetes prevention in this large population of otherwise healthy

women. This report provides the only randomized data available in this regard.

One of the least appreciated pharmacological actions of aspirin is its ability to lower glucose levels. Attempts to delineate this effect have been made in several small clinical studies. Among both nondiabetic and diabetic patients, short-term high-dose aspirin (3–10 g/day for up to 3 weeks) is consistently associated with higher basal and stimulated insulin concentrations and reduced glucose excursion during glucose tolerance testing (8–10,22). However, whether aspirin has a net beneficial contribution to glucose homeostasis has been controversial, with several studies suggesting that any favorable hypoglycemic action is offset by deterioration in insulin sensitivity (23,24). Higher doses of aspirin given over a longer period were more recently found to have broad therapeutic benefits in a detailed study of nine patients with overt type 2 diabetes (10). At the end of 2 weeks, aspirin at a dose of 7 g/day lowered fasting glucose ( $\sim 25\%$ ) and C-reactive protein ( $\sim 15\%$ ) while improving glucose tolerance ( $\sim 20\%$ ), reducing basal hepatic glucose production (20%), and increasing insulin-stimulated peripheral glucose uptake (20%). Importantly, however, the high dose of aspirin used in all of these studies is known to cause serious side effects.

The current analysis directly evaluated whether a low dose of aspirin acceptable for long-term use in routine clinical practice is effective in reducing clinical type 2 diabetes. Although we found no evidence to support this approach, there are three main possibilities that could ac-

count for our null results. First, the dose of aspirin used in this study may be insufficient to impart a clinical benefit. As noted, prior studies evaluating the glucose metabolic effects of aspirin have used far higher doses. Data pertaining to potential hypoglycemic actions of low-dose aspirin have not been available. However, short-term treatment with doses as low as 30–81 mg/day have been shown to improve several systemic inflammatory parameters, including lowering soluble CD40 ligand and promoting counter-regulatory anti-inflammatory mediators such as 15-epi-lipoxin  $A_4$  (11,12). Despite these latter findings, our data demonstrate that chronic treatment with 100 mg aspirin on alternate days does not prevent clinical diabetes. However, intermediate doses as high as 1.3 g/day have been used in long-term clinical trials of cardiovascular disease prevention, and these settings may offer additional opportunities to evaluate this issue if diabetes incidence was also ascertained.

Second, women enrolled in the WHS were generally at low risk for diabetes as evidenced by the low prevalence of obesity, predominantly non-Hispanic white ethnicity, and lower rates of clinical diabetes compared with similarly aged women in the overall U.S. population (25). It is possible that the use of aspirin in a higher risk group may have led to detection of a beneficial effect. However, in subgroup analyses of women with high-risk features we did not find strong support for differential effects. Furthermore, there was no benefit among women having evidence of inflammation as reflected by elevated hsCRP.

Third, underdiagnosis of diabetes may have influenced our results. Women did not undergo systematic screening for diabetes or glucose intolerance as a part of the study; thus, we detected clinical diabetes as ascertained during routine clinical practice rather than all women with biochemical evidence of disease. However, any misclassification due to unrecognized diabetes would be nondifferential between treatment arms and unlikely to lead to important alterations in the estimation of relative effects. In addition, we are reassured that reported diabetes screening rates among participants in our study were similar to contemporaneous screening rates in the general population and equivalent in the two treatment groups.

Major strengths of this analysis include the randomized setting, large study

Table 2—Incidence rates and rate ratio of type 2 diabetes in clinically important subgroups

Characteristic	Sample size (n)	Aspirin group		Placebo group		RR (95% CI)*	P <sub>interaction</sub>
		No. events	Events per 1,000 patient-years	No. events	Events per 1,000 patient-years		
Age							0.29
45–54 years	23,473	485	4.2	463	4.0	1.05 (0.93–1.20)	
55–64 years	11,317	283	5.1	311	5.6	0.91 (0.77–1.07)	
≥65 years	3,926	81	4.3	73	3.9	1.12 (0.81–1.53)	
BMI							0.73
<25.0 kg/m <sup>2</sup>	19,655	116	1.2	106	1.1	1.10 (0.85–1.43)	
25–29.9 kg/m <sup>2</sup>	11,713	262	4.6	258	4.5	1.02 (0.86–1.21)	
≥30 kg/m <sup>2</sup>	6,563	447	14.5	457	14.9	0.98 (0.86–1.11)	
Family history of diabetes†							0.68
No	29,095	462	3.2	463	3.2	0.99 (0.87–1.13)	
Yes	9,621	387	8.5	384	8.2	1.04 (0.90–1.19)	
Exercise ≥ once weekly‡							0.35
No	22,414	606	5.6	624	5.7	0.98 (0.88–1.10)	
Yes	16,282	243	3.0	222	2.8	1.09 (0.91–1.30)	
Hypertension							0.52
No	29,117	409	2.9	398	2.8	1.03 (0.90–1.19)	
Yes	9,590	439	9.6	449	9.9	0.97 (0.85–1.11)	
Hyperlipidemia							0.75
No	27,492	481	3.6	485	3.6	1.01 (0.89–1.14)	
Yes	11,208	366	6.6	362	6.8	0.98 (0.84–1.13)	
Menopause and HT							0.63
Premenopausal	10,757	188	3.6	167	3.1	1.14 (0.92–1.40)	
Uncertain	6,926	179	5.3	192	5.5	0.96 (0.78–1.18)	
Postmenopausal, HT	11,686	210	3.6	214	3.8	0.96 (0.80–1.16)	
Postmenopausal, no HT	9,248	268	6.0	271	6.1	0.99 (0.83–1.17)	
Total cholesterol							0.38
<5.18 mmol/l	11,067	204	3.8	201	3.7	1.03 (0.85–1.25)	
5.18–6.20 mmol/l	10,170	242	4.9	231	4.6	1.06 (0.88–1.27)	
≥6.21 mmol/l	5,929	130	4.4	162	5.6	0.77 (0.61–0.97)	
LDL cholesterol							0.26
<2.59 mmol/l	6,652	130	4.0	127	3.9	1.04 (0.81–1.32)	
2.59–3.35 mmol/l	9,806	202	4.3	194	4.0	1.06 (0.87–1.29)	
3.36–4.12 mmol/l	6,978	153	4.4	155	4.6	0.97 (0.78–1.21)	
≥4.13 mmol/l	3,731	91	4.9	118	6.5	0.76 (0.58–1.00)	
HDL cholesterol							0.86
<1.30 mmol/l	11,891	454	8.0	467	8.1	0.98 (0.86–1.12)	
≥1.30 mmol/l	15,275	122	1.6	127	1.7	0.96 (0.75–1.22)	
Total cholesterol-to-HDL cholesterol ratio							0.13
<4.0	14,027	102	1.5	108	1.5	0.95 (0.73–1.25)	
4.0–5.9	10,625	314	6.1	295	5.7	1.07 (0.91–1.25)	
≥6.0	2,513	160	13.5	191	16.6	0.81 (0.66–1.00)	
Non-HDL cholesterol							0.29
<3.36 mmol/l	7,045	90	2.6	74	2.6	1.20 (0.88–1.63)	
3.36–4.12 mmol/l	8,185	141	3.6	155	3.8	0.95 (0.76–1.19)	
≥4.13 mmol/l	11,935	345	5.9	365	6.4	0.92 (0.80–1.07)	
A1C							0.16
≤5.0%	13,797	83	1.2	71	1.0	1.19 (0.86–1.63)	
>5.0%	13,306	493	7.7	521	8.2	0.93 (0.83–1.06)	
hsCRP							0.53
<1.0 mg/l	8,250	44	1.1	36	0.9	1.23 (0.79–1.91)	
1.0–2.9 mg/l	9,076	130	2.9	140	3.1	0.94 (0.74–1.20)	
>3.0 mg/l	9,841	402	8.5	418	8.9	0.95 (0.83–1.09)	

Data are % unless otherwise indicated. Analyses involving biomarkers are restricted to women providing baseline blood specimens (n = 27,167). \*RR of clinical diabetes in the aspirin versus placebo group adjusted for age and randomized treatment assignment to vitamin E and β-carotene. †Family history of diabetes in a first-degree relative (mother, father, sister, or brother). ‡Physical activity defined by number of episodes of vigorous physical activity per week. HT, hormone therapy.

population, long treatment duration, large number of events, and ability to examine several large high-risk subgroups of women. In addition, baseline blood specimens were provided by roughly 70% of women in whom hsCRP and A1C levels were available. Importantly, systematic data were also collected on the occurrence of significant bleeding events. Limitations of this study have been alluded to previously. An important limitation is the lack of systematic screening for more sensitive measures of glucose intolerance and insulin resistance during follow-up. While the costs associated with such diagnostic testing are prohibitive in this large-scale setting, we cannot with the current data determine the potential impact of low-dose aspirin on these subclinical markers of incipient disease.

In summary, aspirin at a dose of 100 mg on alternate days is not effective for the prevention of clinical type 2 diabetes among otherwise healthy women at generally low risk for this disease. Our data do not pertain to other salicylate agents currently being evaluated for diabetes treatment or to intermediate or high doses of long-term aspirin in primary prevention. However, even at the low dose evaluated in this trial, the use of aspirin was associated with a significant increase in clinically important bleeding events and any potential benefit at higher doses, if found, must take into account this potential for excess risk.

**Acknowledgments**—This work was 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.

No other potential conflicts of interest relevant to this article were reported.

## References

1. Ebstein W: Zur therapie des diabetes mellitus, insbesondere über die anwendung der salicylauren natron bei demselben. *Berlin Klin Wochenschr* 13:337–340, 1876
2. Shoelson SE, Lee J, Goldfine AB: Inflammation and insulin resistance. *J Clin Invest* 116:1793–1801, 2006
3. Thorand B, Baumert J, Kolb H, Meisinger C, Chambless L, Koenig W, Herder C: Sex differences in the prediction of type 2 diabetes by inflammatory markers: results from the MONICA/KORA Augsburg case-cohort study, 1984–2002. *Diabetes Care* 30:854–860, 2007
4. Fleischman A, Shoelson SE, Bernier R, Goldfine AB: Salsalate improves glycemia and inflammatory parameters in obese young adults. *Diabetes Care* 31:289–294, 2008
5. Yuan M, Konstantopoulos N, Lee J, Hansen L, Li ZW, Karin M, Shoelson SE: Reversal of obesity- and diet-induced insulin resistance with salicylates or targeted disruption of I $\kappa$ k $\beta$ . *Science* 293:1673–1677, 2001
6. Gao Z, Zuberi A, Quon MJ, Dong Z, Ye J: Aspirin inhibits serine phosphorylation of insulin receptor substrate 1 in tumor necrosis factor-treated cells through targeting multiple serine kinases. *J Biol Chem* 278:24944–24950, 2003
7. Reid J, Lightbody TD: The insulin equivalence of salicylate. *Br Med J* 1:897–900, 1959
8. Micossi P, Pontiroli AE, Baron SH, Tamayo RC, Lengel F, Bevilacqua M, Raggi U, Norbiato G, Foa PP: Aspirin stimulates insulin and glucagon secretion and increases glucose tolerance in normal and diabetic subjects. *Diabetes* 27:1196–1204, 1978
9. Prince RL, Larkins RG, Alford FP: The effect of acetylsalicylic acid on plasma glucose and the response of glucose regulatory hormones to intravenous glucose and arginine in insulin treated diabetics and normal subjects. *Metabolism* 30:293–298, 1981
10. Hundal RS, Petersen KF, Mayerson AB, Randhawa PS, Inzucchi S, Shoelson SE, Shulman GI: Mechanism by which high-dose aspirin improves glucose metabolism in type 2 diabetes. *J Clin Invest* 109:1321–1326, 2002
11. Chiang N, Bermudez EA, Ridker PM, Hurwitz S, Serhan CN: Aspirin triggers antiinflammatory 15-epi-lipoxin A4 and inhibits thromboxane in a randomized human trial. *Proc Natl Acad Sci U S A* 101:15178–15183, 2004
12. Santilli F, Davi G, Consoli A, Cipollone F, Mezzetti A, Falco A, Taraborelli T, Devanagelio E, Ciabattini G, Basili S, Patrono C: Thromboxane-dependent CD40 ligand release in type 2 diabetes mellitus. *J Am Coll Cardiol* 47:391–397, 2006
13. Ridker PM, Cook NR, Lee IM, Gordon D, Gaziano JM, Manson JE, Hennekens CH, Buring JE: A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. *N Engl J Med* 352:1293–1304, 2005
14. Cook NR, Lee IM, Gaziano JM, Gordon D, Ridker PM, Manson JE, Hennekens CH, Buring JE: Low-dose aspirin in the primary prevention of cancer: the Women's Health Study: a randomized controlled trial. *JAMA* 294:47–55, 2005
15. Lee IM, Cook NR, Gaziano JM, Gordon D, Ridker PM, Manson JE, Hennekens CH, Buring JE: Vitamin E in the primary prevention of cardiovascular disease and cancer: the Women's Health Study: a randomized controlled trial. *JAMA* 294:56–65, 2005
16. 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* 9:19–27, 2000
17. Liu S, Lee IM, Song Y, Van Denburgh M, Cook NR, Manson JE, Buring JE: Vitamin E and risk of type 2 diabetes in the Women's Health Study randomized controlled trial. *Diabetes* 55:2856–2862, 2006
18. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 20:1183–1197, 1997
19. Ding EL, Song Y, Manson JE, Pradhan AD, Buring JE, Liu S: Accuracy of administrative coding for type 2 diabetes in children, adolescents, and young adults. *Diabetes Care* 30:e98, 2007; author reply e99
20. Ealovega MW, Tabaei BP, Brandle M, Burke R, Herman WH: Opportunistic screening for diabetes in routine clinical practice. *Diabetes Care* 27:9–12, 2004
21. Lee IM, Cook NR, Manson JE, Buring JE, Hennekens CH:  $\beta$ -Carotene supplementation and incidence of cancer and cardiovascular disease: the Women's Health Study. *J Natl Cancer Inst* 91:2102–2106, 1999
22. Giugliano D, Torella R, Siniscalchi N, Improta L, D'Onofrio F: The effect of acetylsalicylic acid on insulin response to glucose and arginine in normal man. *Diabetologia* 14:359–362, 1978
23. Newman WP, Brodows RG: Aspirin causes tissue insensitivity to insulin in normal man. *J Clin Endocrinol Metab* 57:1102–1106, 1983
24. Bratusch-Marrain PR, Vierhapper H, Komjati M, Waldhausl WK: Acetylsalicylic acid impairs insulin-mediated glucose utilization and reduces insulin clearance in healthy and non-insulin-dependent diabetic man. *Diabetologia* 28:671–676, 1985
25. Centers for Disease Control and Prevention: National Diabetes Surveillance System: incidence of diabetes [article online], 2007. Available from <http://www.cdc.gov/diabetes/statistics/incidence/table5.htm>. Accessed 21 May 2008