

Effect of Low-Dose Aspirin on the Occurrence of Venous Thromboembolism

A Randomized Trial

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Background: Short-term aspirin therapy can lower the risk for venous thromboembolism (VTE) in high-risk patients, but whether the long-term use of low-dose aspirin reduces risk in healthy adults is uncertain.

Objective: To test the efficacy of long-term aspirin therapy for preventing VTE.

Design: Secondary analysis of a 10-year randomized, double-blind, placebo-controlled trial.

Setting: U.S. female health care professionals in the Women's Health Study.

Participants: 39 876 initially healthy women age 45 years or older (26 779 gave blood samples that were evaluated for factor V Leiden, G20210A prothrombin, and MTHFR 677C>T polymorphisms).

Measurements: Documented VTE (deep venous thrombosis or pulmonary embolism) and unprovoked VTE (no recent surgery, trauma, or cancer diagnosis) were prospectively evaluated, secondary end points.

Intervention: Aspirin, 100 mg, or placebo on alternate days.

Results: Venous thromboembolism occurred in 482 women during follow-up, an incidence higher than that of myocardial infarction and nearly equal to that of stroke. The incidence of VTE (per 1000 person-years) was 1.18 among women randomly assigned to active aspirin, compared with 1.25 among women randomly assigned to placebo (relative hazard, 0.95 [95% CI, 0.79 to 1.13]; rate difference, -0.06 [CI, -0.28 to 0.16]). For unprovoked VTE, the relative hazard was 0.90 (CI, 0.70 to 1.16) and the rate difference was -0.06 (CI, -0.21 to 0.10). Relative hazards associated with aspirin use in higher-risk subgroups were 0.83 (CI, 0.50 to 1.39) among women with either factor V Leiden or the prothrombin mutation and 1.36 (CI, 0.77 to 2.41) among those with a history of VTE.

Limitation: Venous thromboembolism was a secondary end point in the Women's Health Study.

Conclusion: These data suggest that long-term, low-dose aspirin treatment has little effect on the prevention of VTE in initially healthy women.

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Clinically significant venous thromboembolism (VTE) is an age-related condition that affects 1 to 2 of every 1000 adults per year (1–3). Surgery, trauma, immobilization, and cancer frequently trigger VTE, but between one third and one half of all first VTE events occur without these triggers (3–6).

Short-term aspirin therapy has some efficacy in preventing VTE in certain high-risk patients. A meta-analysis of 62 randomized trials in orthopedic surgical, general surgical, and high-risk medical patients found that a few weeks of antiplatelet therapy (usually with aspirin) reduced the risk for pulmonary embolism by about 67% and the risk for deep venous thrombosis by about 40% (7). Subsequently, the randomized Pulmonary Embolism Prevention trial (8) found a statistically significant 34% reduction overall in risk for VTE associated with short-term aspirin therapy in patients with hip fracture or elective arthroplasty. An updated meta-analysis, focused on patients at high risk for occlusive vascular events, found a statistically significant 25% reduction in the odds of pulmonary embolism associated with antiplatelet therapy (9). However, recent randomized trials indicate that therapy with low-molecular-weight heparin may be more effective than aspirin, and such treatments are preferred in current treatment guidelines (10, 11).

The relevance of these findings for individuals not in

high-risk settings is unclear. An effective treatment to lower risk for VTE with an acceptable risk–benefit ratio would be particularly valuable for individuals with permanent risk factors, such as prothrombotic mutations or a personal or family history of VTE. Limited evidence from observational studies on the relationship of aspirin with occurrence of VTE in usual-risk patients is equivocal, with reports both of substantially reduced risk (12) and no association (4). Because aspirin users differ in complex ways from nonusers, randomized aspirin assignment may yield the best evidence for aspirin's effect on reducing the risk for VTE.

The Women's Health Study tested whether low-dose aspirin for 10 years decreased the risk for cardiovascular

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Context

The effect of aspirin on venous thromboembolism (VTE) in healthy adults is uncertain.

Contribution

In a secondary analysis of the Women’s Health Study, the authors measured VTE rates in 39 876 health professionals randomly assigned to low-dose aspirin or placebo for 10 years. Aspirin did not affect overall VTE rates or those in women with increased rates because of inherited thrombophilia.

Caution

The 95% CIs for VTE rates in inherited thrombophilia were wide.

Implication

Aspirin is ineffective prophylaxis for VTE in women with few or no risk factors.

—The Editors

disease or cancer in a large group of initially healthy women. The occurrence of VTE was a prospectively evaluated, secondary end point of the trial.

METHODS

Study Design

The Women’s Health Study was a randomized, double-blind, placebo-controlled, 2 × 2 factorial trial that evaluated the balance of risks and benefits of low-dose aspirin (100 mg every other day; Bayer HealthCare, Leverkusen, Germany) and vitamin E (600 IU of α-tocopherol every other day; Natural Source Vitamin E Association, Washington, DC) in the primary prevention of cardiovascular disease and cancer (13–15). Participants were also randomly assigned to β-carotene or placebo, but this component was terminated early in January 1996 after a median treatment duration of 2.1 years (16). The dose and frequency of aspirin administration were chosen with the goal of achieving a cardioprotective effect while minimizing gastrointestinal side effects. The institutional review board of Brigham and Women’s Hospital, Boston, Massachusetts, approved the trial, and an external data and safety monitoring board monitored the trial. All participants gave written informed consent.

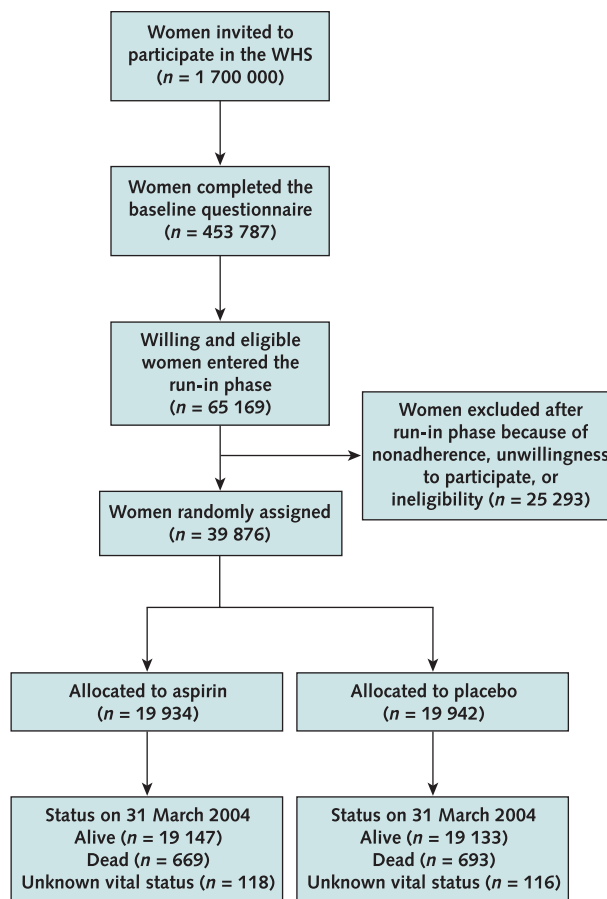
Figure 1 shows a CONSORT (Consolidated Standards of Reporting Trials) diagram for the trial conducted by mail in female health care professionals. Eligibility criteria included age 45 years or older; no history of coronary heart disease, cerebrovascular disease, cancer (except non-melanoma skin cancer), and other major chronic diseases (including dementia, chronic kidney or liver disease, gout, or gastrointestinal bleeding); and no use of aspirin or non-steroidal anti-inflammatory drugs more than once a week

or willingness to forgo use. Before randomization, women were asked whether they ever had deep venous thrombosis or pulmonary embolism, but investigators did not exclude those with a positive history. However, investigators excluded women who currently used anticoagulants.

Willing and eligible women received placebo aspirin and placebo vitamin E during a 3-month run-in phase to identify a group that was likely to adhere to long-term treatment. During the run-in phase, all participants were asked to provide a venous blood sample and were mailed blood collection kits, but return of a sample was not required for randomization and was independent of treatment assignment. A total of 39 876 women were willing, eligible, and adherent during the run-in phase, and investigators randomly assigned the women in blocks of 16 within 5-year age strata to aspirin (19 934 to active aspirin and 19 942 to placebo) and to vitamin E.

Investigators extracted DNA from whole blood samples that 26 779 (67%) of the randomly assigned participants had returned. Women who gave blood samples were less likely to be black and to be cigarette smokers than women who did not. Investigators performed genotyping

Figure 1. Study flow diagram.



WHS = Women’s Health Study.

for factor V Leiden, the G20210A prothrombin mutation, and the MTHFR 677C>T polymorphism by using multiplex polymerase chain reaction and linear immobilized probe array assays (Roche Molecular Systems, Alameda, California), as described previously (17, 18). Linear array processing was facilitated with the AutoRELI-Mark II (DynaL Biotech, Bromborough, United Kingdom). To confirm genotype assignment, 2 independent observers scored the array assays, resolving discordant results (<1% of all scoring) by a joint reading and repeating genotyping when necessary.

Treatment and Follow-up

Each year, women received an annual supply of calendar packs that contained active agents or placebo. Every 6 months for the first year and annually thereafter, they also received follow-up questionnaires about adherence to taking pills, potential adverse effects, occurrence of end points, and risk factors. Treatment and follow-up remained blinded until the scheduled end of the trial (31 March 2004). At the end of blinded treatment, mortality status was known for 99.4% of participants and 97.2% of surviving participants returned questionnaires reporting morbidity.

On the basis of self-reported adherence from follow-up questionnaires, 76% of women reported taking at least two thirds of their aspirin or matching placebo tablets at 5 years. At the 10-year follow-up, 67% of women reported this level of adherence to aspirin therapy. At 5 and 10 years, 20% and 30% of participants, respectively, reported taking none of their aspirin or matching placebo tablets. Throughout the trial, an average of 73% of women reported taking at least two thirds of their aspirin or matching placebo tablets. Adherence to active aspirin treatment versus placebo was slightly but statistically significantly lower in the active treatment group, with proportions averaging about 1% lower from 24 months onward. Use of nontrial aspirin for 4 or more days per month averaged 12% during follow-up and did not statistically significantly differ between women in the active aspirin group and those in the placebo group.

End Point Definition

On each follow-up questionnaire, women were asked about the new occurrence of deep venous thrombosis and pulmonary embolism. Investigators asked women who reported events, or next of kin of decedents, for permission to obtain medical records. An end points committee of physicians reviewed records in a blinded fashion. Diagnosis of deep venous thrombosis was confirmed by a positive venous ultrasonogram or venography report, whereas diagnosis of pulmonary embolism was considered confirmed by a positive angiogram or computed tomography scan of the chest or a ventilation–perfusion scan with 2 or more mismatched defects. Deaths due to pulmonary embolism were confirmed when autopsy reports, symptoms, circumstances of death, and medical history were consistent with this

Table 1. Baseline Characteristics*

Characteristic	Aspirin Group (n = 19 934), %	Placebo Group (n = 19 942), %
Age		
45–54 y	60.2	60.2
55–64 y	29.5	29.5
≥65 y	10.3	10.3
Race		
White	94.8	94.8
Black	2.4	2.2
Hispanic	1.0	1.1
Asian or Pacific Islander	1.3	1.5
Other or unknown	0.4	0.4
BMI†		
<25.0 kg/m ²	50.8	50.8
25.0–29.9 kg/m ²	30.9	31.0
≥30 kg/m ²	18.3	18.2
Menopause status and HT use‡		
Premenopausal	27.5	27.6
Uncertain	17.7	18.2
Postmenopausal and current HT	30.4	29.7
Postmenopausal and no HT	24.4	24.4
Current cigarette smoking	13.0	13.3
Diabetes	2.7	2.5
Hypertension	26.0	25.7
Hyperlipidemia	29.9	29.1
History of VTE at baseline	3.0	2.7
Available blood sample	67.1	67.2
Factor V Leiden§	5.2	5.1
Prothrombin mutation§	2.7	2.7
TT homozygotes for MTHFR 677C>T§	10.9	10.9

* BMI = body mass index; HT = hormone therapy; VTE = venous thromboembolism.

† 820 women had missing data.

‡ 108 women had missing data. “Uncertain” menopause status includes perimenopausal women who were unsure of their status and those <60 years of age with a hysterectomy and ≥1 intact ovary.

§ 13 097 women did not provide blood samples.

diagnosis. We included only the events confirmed by the end points committee. Ninety-three percent of women (or their next of kin) who reported VTE after randomization gave us permission to obtain medical records. We confirmed 71% of reported events.

We defined unprovoked deep venous thrombosis or pulmonary embolism as occurring in the absence of a known malignant condition (diagnosed either before or up to 3 months after the VTE) or trauma or surgery within 3 months before the VTE. Provoked VTE included events that occurred in patients with cancer or during or shortly after trauma or surgery.

The trial also assessed possible adverse effects of the aspirin therapy. Hemorrhagic stroke was a component of the trial’s primary end point. Annual questionnaires asked women about the occurrence of gastrointestinal bleeding, peptic ulcer, hematuria, easy bruising, and epistaxis. We confirmed reports of gastrointestinal bleeding and peptic ulcer with follow-up questionnaires.

Statistical Analysis

The main analyses of the secondary end point of VTE included all randomly assigned women classified by their

Table 2. Incidence and Relative Rates of Venous Thromboembolism and Side Effects*

End Point	Aspirin Group (n = 19 934)		Placebo Group (n = 19 942)		Rate Difference per 1000 Person-Years (95% CI)	Hazard Ratio (95% CI)†
	Events, n	Events per 1000 Person-Years	Events, n	Events per 1000 Person-Years		
VTE						
All cases of VTE	235	1.18	247	1.25	−0.06 (−0.28 to 0.16)	0.95 (0.79 to 1.13)
Unprovoked VTE‡	115	0.58	126	0.64	−0.06 (−0.21 to 0.10)	0.90 (0.70 to 1.16)
Provoked VTE‡	115	0.58	120	0.61	−0.03 (−0.18 to 0.13)	0.95 (0.74 to 1.23)
Pulmonary embolism§	86	0.43	90	0.45	−0.02 (−0.15 to 0.11)	0.95 (0.71 to 1.28)
DVT only§	149	0.75	157	0.79	−0.04 (−0.21 to 0.13)	0.94 (0.75 to 1.18)
VTE, first 5 years	98	0.99	104	1.05	−0.06 (−0.34 to 0.22)	0.94 (0.71 to 1.23)
VTE, after 5 years	137	1.38	143	1.44	−0.06 (−0.39 to 0.27)	0.95 (0.75 to 1.20)
Side effects						
Hemorrhagic stroke	51	0.26	41	0.21	0.05 (−0.04 to 0.14)	1.24 (0.82 to 1.87)
Gastrointestinal bleeding						
Any	910	4.68	751	3.84	0.83 (0.42 to 1.24)	1.22 (1.10 to 1.34)
Requiring transfusion	127	0.64	91	0.46	0.18 (0.04 to 0.33)	1.40 (1.07 to 1.83)
Peptic ulcer	542	2.76	413	2.10	0.66 (0.35 to 0.97)	1.32 (1.16 to 1.50)
Hematuria	3039	16.65	2878	15.68	0.97 (0.14 to 1.79)	1.06 (1.01 to 1.12)
Easy bruising	10 560	83.6	8494	58.1	25.5 (23.5 to 27.5)	1.40 (1.37 to 1.45)
Epistaxis	3801	21.60	3321	18.51	3.09 (2.16 to 4.02)	1.16 (1.11 to 1.22)

* DVT = deep venous thrombosis; VTE = venous thromboembolism.

† Hazard ratios were based on a proportional hazards model, controlling for age and other randomized treatments and stratified by baseline history of VTE. Tests of the null hypothesis that the hazard ratio was 1.0 had a *P* value >0.20 for each end point.

‡ 6 women with confirmed VTE (5 in the aspirin group and 1 in the placebo group) had insufficient information to determine whether the event was provoked.

§ 76 women (38 in each treatment group) had confirmed pulmonary embolism and DVT diagnosed within 3 days of each other, and they are counted as having only pulmonary embolism.

randomized treatment assignment according to the intention-to-treat principle. The main end point was the first confirmed VTE after randomization, including both women with and without previous VTE reported at baseline. We did not count a second event after randomization, although we did count women who had both pulmonary embolism and deep venous thrombosis within 3 days at the time of their index event toward each of these separate outcomes. Secondary end points included unprovoked VTE, pulmonary embolism (with or without concurrent deep venous thrombosis), and deep venous thrombosis without concurrent pulmonary embolism.

Subgroup analyses focused on the effects of aspirin among women at high baseline risk for VTE who might especially benefit from an effective preventive therapy. These included women with factor V Leiden or the prothrombin mutation and TT homozygotes for the MTHFR 677C>T polymorphism (19). In a post hoc analysis, we considered the effect of aspirin in a combined group of women at highest observed risk for VTE, namely those with a history of VTE at baseline or either the factor V Leiden or prothrombin mutation.

We used the Kaplan–Meier method to estimate the cumulative incidence of VTE by treatment group, as well as the cumulative incidence of secondary end points and within subgroups. We used the log-rank test to compare the incidence by treatment assignment. We estimated the relative hazard of VTE by treatment and associated 95% CIs by using proportional hazards models that controlled

for age and other randomized treatments and stratified by reported VTE at baseline.

In subgroup analyses, women with missing data on a variable used to define that subgroup were excluded. We tested for heterogeneity across categories of subgroups by adding interaction terms between treatment and the risk factor to proportional hazards models, and we performed tests for trend when subgroup categories were ordinal. As a sensitivity analysis to consider the effect of adherence to aspirin therapy, we fitted additional proportional hazards models with follow-up time censored when a woman reported taking less than two thirds of her aspirin (or matching placebo) tablets during the preceding year. We tested the validity of the proportional hazards assumption with regard to the effects of aspirin by including an interaction term between the treatment effect and the log of follow-up time centered at the average log follow-up (20). In addition, we fitted separate proportional hazards models to the experience of the first 5 years of follow-up and that after 5 years to estimate the effects of treatment in early and later follow-up. We performed all statistical analyses by using SAS software, version 9 (SAS Institute, Cary, North Carolina).

Role of the Funding Sources

The Women’s Health Study was primarily funded by investigator-initiated grants from the National Institutes of Health. Bayer HealthCare and Natural Source Vitamin E Association provided pills but did not influence study de-

sign, conduct, analysis, or decisions about manuscript submission.

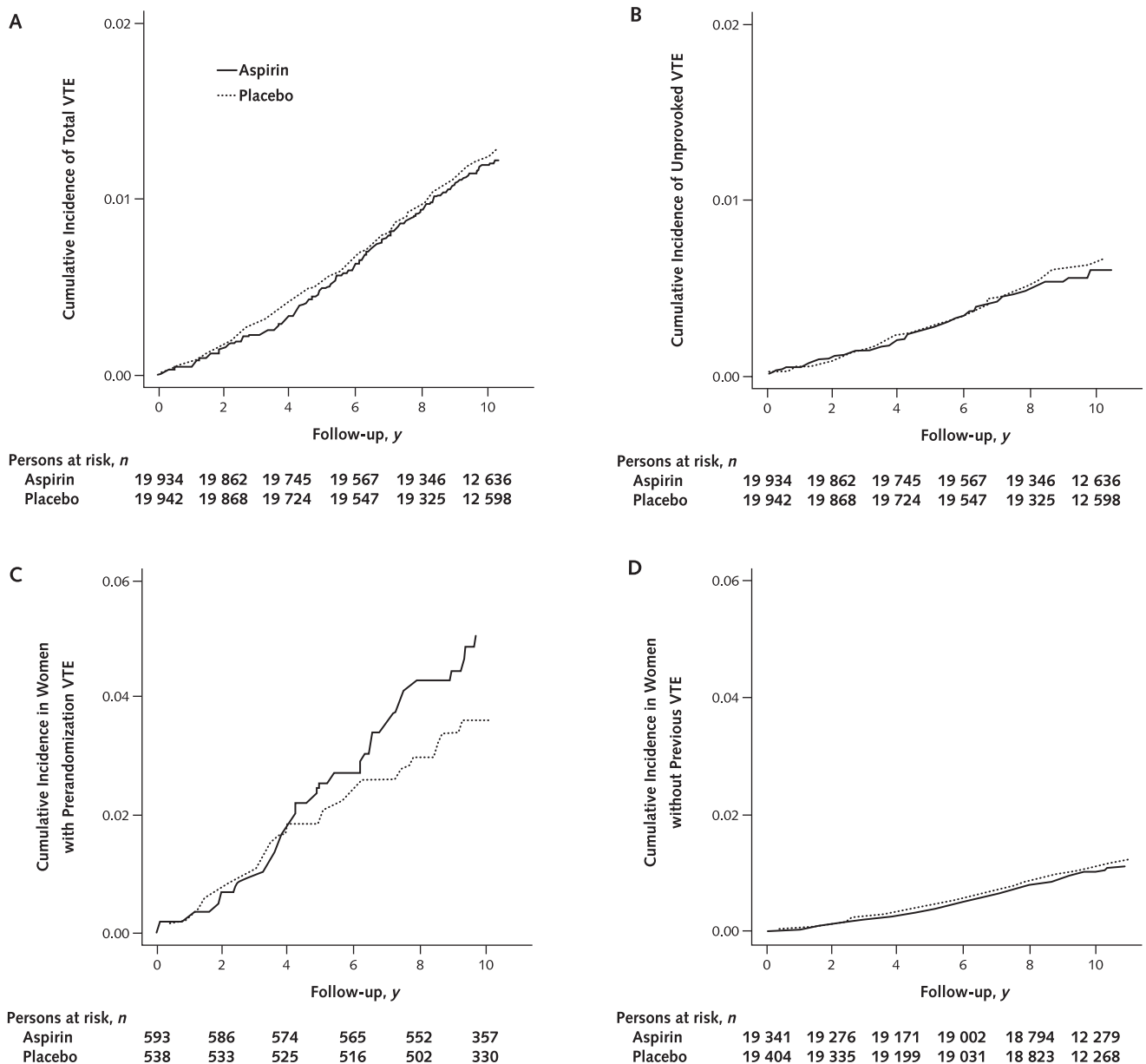
RESULTS

Incidence of VTE

At randomization, women assigned to active aspirin treatment had similar distributions of demographic, clinical, and genetic factors compared with women in the placebo group (Table 1). During a median follow-up of 10.2 years (interquartile range, 9.7 to 10.6 years), 482 women

had a confirmed VTE, for an incidence rate of 1.2 events per 1000 person-years (Table 2). Half of the women with confirmed VTE ($n = 241$) had an unprovoked event. Among confirmed cases, 76 had both pulmonary embolism and deep venous thrombosis, 100 had pulmonary embolism alone, and 306 had deep venous thrombosis alone. The incidence of VTE was similar to that of stroke (487 women had a first stroke) and was greater than that of myocardial infarction (391 women had a first myocardial infarction) during the treatment period (13).

Figure 2. Cumulative incidence of venous thromboembolism (VTE) in the aspirin and placebo groups.



A. Incidence of total VTE ($P = 0.58$, log-rank test). B. Incidence of unprovoked VTE ($P = 0.48$, log-rank test). C. Incidence of VTE in women with a history of VTE at baseline ($P = 0.33$, log-rank test). D. Incidence of VTE in women without a history of VTE at baseline ($P = 0.32$, log-rank test).

Table 3. Incidence and Relative Rates of Venous Thromboembolism in Clinically Important Subgroups*

Characteristic	Sample Size, <i>n</i>	Aspirin Group		Placebo Group		Rate Difference per 1000 Person-Years (95% CI)	Hazard Ratio (95% CI)†
		Events, <i>n</i>	Events per 1000 Person-Years	Events, <i>n</i>	Events per 1000 Person-Years		
Age							
45–54 y	24 025	109	0.91	109	0.91	0.00 (–0.24 to 0.24)	0.99 (0.76 to 1.29)
55–64 y	11 754	86	1.47	79	1.35	0.12 (–0.31 to 0.55)	1.08 (0.79 to 1.46)
≥65 y	4097	40	2.01	59	2.99	–0.97 (–1.96 to 0.01)	0.67 (0.45 to 1.01)
BMI‡							
<25.0 kg/m ²	19 849	90	0.91	85	0.86	0.05 (–0.21 to 0.31)	1.06 (0.79 to 1.43)
25.0–29.9 kg/m ²	12 081	78	1.30	92	1.53	–0.23 (–0.66 to 0.19)	0.84 (0.62 to 1.14)
≥30 kg/m ²	7126	63	1.78	62	1.76	0.02 (–0.60 to 0.64)	1.01 (0.71 to 1.43)
Menopause status and HT use§							
Premenopausal	10 973	48	0.88	52	0.95	–0.07 (–0.43 to 0.29)	0.92 (0.62 to 1.36)
Uncertain	7149	28	0.79	43	1.18	–0.39 (–0.85 to 0.07)	0.67 (0.41 to 1.07)
Postmenopausal and current HT	11 948	90	1.50	80	1.36	0.14 (–0.29 to 0.57)	1.09 (0.81 to 1.47)
Postmenopausal and no HT	9704	66	1.38	70	1.47	–0.09 (–0.56 to 0.39)	0.94 (0.67 to 1.32)
Reported VTE at baseline							
No	38 745	206	1.07	227	1.18	–0.11 (–0.31 to 0.10)	0.91 (0.75 to 1.09)
Yes	1131	29	5.03	20	3.80	1.23 (–1.25 to 3.70)	1.36 (0.77 to 2.41)

* BMI = body mass index; HT = hormone therapy; VTE = venous thromboembolism.

† Hazard ratios were based on a proportional hazards model, controlling for age and other randomized treatments and stratified by baseline history of VTE.

‡ 820 women with missing data on BMI at baseline were excluded.

§ 102 women with missing data on menopause status or HT use were excluded. “Uncertain” menopause status includes perimenopausal women who were unsure of their status and those <60 years of age with a hysterectomy and ≥1 intact ovary.

Aspirin and VTE

The incidence of VTE (per 1000 person-years) was 1.18 among women randomly assigned to active aspirin, compared with 1.25 among women randomly assigned to placebo (relative hazard, 0.95 [95% CI, 0.79 to 1.13]; $P = 0.54$). In analyses restricted to unprovoked events, women in the aspirin group had a relative hazard of 0.90 (CI, 0.70 to 1.16; $P = 0.44$). Analyses restricted to only provoked events, pulmonary embolism, or deep venous thrombosis also found modest, statistically nonsignificant reductions in hazard associated with assignment to active aspirin. Aspirin did not interact significantly with other randomized treatments (with vitamin E, $P = 0.59$; with β -carotene, $P = 0.66$). Analyses that censored participants when they took fewer than two thirds of their tablets found a 0.93 (CI, 0.74 to 1.16) relative hazard of VTE in the aspirin versus placebo groups. The cumulative incidences of both total VTE and unprovoked VTE were similar in those receiving aspirin and those receiving placebo throughout follow-up (Figure 2, A and B). In separate analyses that considered newly diagnosed VTE in the first 5 years of follow-up and thereafter, assignment to active aspirin was associated with a relative hazard of 0.94 during the first 5 years and a relative hazard of 0.95 after 5 years (Table 2).

Subgroup Analyses

No VTE risk factor modified the relationship of aspirin with the overall hazard of VTE ($P > 0.15$ for interaction) (Tables 3 and 4). Women age 65 years or older had a relative hazard of 0.67 (CI, 0.45 to 1.01; $P = 0.055$)

associated with aspirin treatment. In women with a history of VTE at baseline (Figure 2, C), aspirin treatment was associated with a relative hazard of 1.36 (CI, 0.77 to 2.41; $P = 0.29$). A test of the null hypothesis that the proportional hazards assumption held in this subgroup was not significant ($P = 0.67$). No statistically significant benefit or harm associated with aspirin treatment occurred in any subgroup.

Among the 26 779 participants with genetic information (Table 4), those with either factor V Leiden or the prothrombin mutation in the placebo group had an incidence of VTE (3.2 events per 1000 person-years) that was 2.7 times that of women in the placebo group without either risk factor. Among the 2050 women with either factor V Leiden or the prothrombin mutation, the relative hazard associated with aspirin assignment was 0.83 (CI, 0.50 to 1.39).

A forest plot shows that 95% CIs for the estimated effects within subgroups broadly overlapped. All contained the overall estimated relative hazard of 0.95 (Figure 3).

The highest rates of VTE occurred in women with a history of VTE at baseline, factor V Leiden, or the prothrombin mutation. In the 3097 women with any of these characteristics, the relative hazard of VTE associated with aspirin treatment was 1.06 (CI, 0.71 to 1.59).

Adverse Effects of Treatment

The frequency of potential adverse effects related to bleeding and ulcers was elevated among women who re-

ceived active aspirin, with relative hazards ranging from 1.06 to 1.40 (Table 2).

DISCUSSION

In this large-scale, long-term trial of initially healthy women, 100 mg of aspirin on alternate days had little association with the overall rate of VTE and the rate of unprovoked VTE. The association of low-dose aspirin with the hazard of VTE was uniform during treatment and did not vary substantially across subgroups. No clear benefit of aspirin was observed among subgroups at particularly high risk for VTE who might benefit most from preventive therapies, although 95% CIs in some subgroups were wide.

The frequency of VTE, its common sequelae of venous insufficiency and chronic thromboembolic pulmonary hypertension, and high treatment costs highlight the need for strategies to prevent its occurrence. Previous population-based studies found the incidence of VTE to be similar to that of stroke in Rochester County, Minnesota (2), and of myocardial infarction in the Brest district of France (21). With the observed rate of VTE, and with more than 395 000 person-years of aspirin therapy or placebo, the 95% CI for the observed effect of aspirin excluded a 25% reduction in the rate of VTE associated with aspirin. Thus, a substantial reduction in risk for VTE associated with long-term use of low-dose aspirin applicable across a broad population is unlikely.

The lack of clear benefit of aspirin therapy in the trial is unlikely to be because of incomplete inhibition of platelets with a 100-mg dose on alternate days. Previous studies

indicate that this dose and frequency inhibit platelet function to the same degree as that achieved by larger, daily doses of aspirin (22). Bleeding risks associated with aspirin are dose related. An increased dose or daily administration of aspirin would be expected to further increase the risk for gastrointestinal bleeding, peptic ulcer, epistaxis, hematuria, and easy bruising beyond that observed in the Women's Health Study.

Results of previous studies have suggested that short-term aspirin treatment may be valuable for preventing VTE in some high-risk patients (23). Although our trial yielded fairly wide 95% CIs for estimated aspirin effects in subgroups at elevated risk, a large benefit of aspirin treatment in these women is unlikely. Two ongoing randomized, placebo-controlled trials are evaluating the effects of 100 mg of aspirin daily in patients who have completed a standard course of anticoagulant therapy after an idiopathic VTE (24, 25). Such patients have high recurrence rates, and extended low- or full-intensity warfarin therapy is effective in preventing recurrences (26, 27). However, if low-dose aspirin treatment also reduces the risk for recurrence with a lower rate of bleeding problems than warfarin, aspirin will be a valuable alternative to warfarin. Alternative secondary prevention strategies based on updated risk assessment through D-dimer testing may also be effective (28, 29).

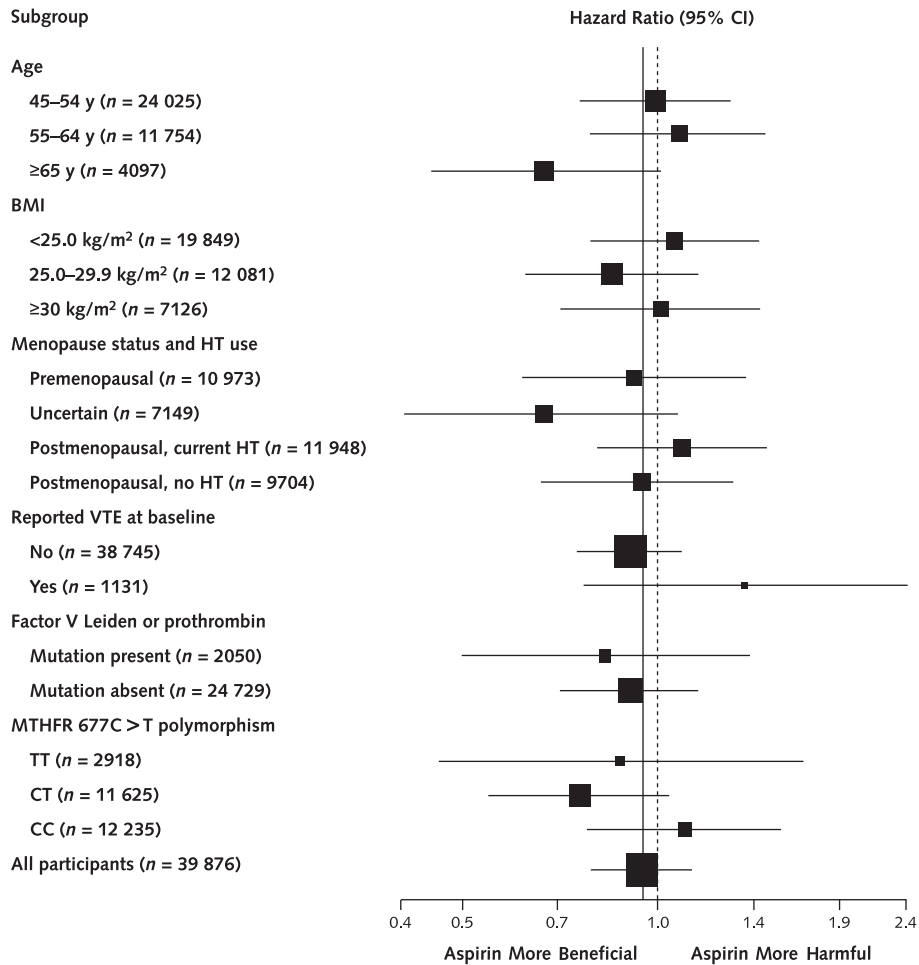
Limitations of our study include its selected population and the potential dilution of the aspirin effect by non-adherence. However, the incidence of VTE generally agreed with estimates from population-based studies. Adherence usually declines in clinical trials over time, and

Table 4. Efficacy of Treatment Assignment, by Genetic Risk Factors

Characteristic	Sample Size, n	Aspirin Group		Placebo Group		Rate Difference per 1000 Person-Years (95% CI)	Hazard Ratio (95% CI)*
		Events, n	Events per 1000 Person-Years	Events, n	Events per 1000 Person-Years		
Factor V Leiden or prothrombin mutation							
Present	2050	27	2.67	32	3.16	-0.49 (-1.98 to 1.00)	0.83 (0.50 to 1.39)
Absent	24 729	129	1.05	142	1.15	-0.10 (-0.36 to 0.16)	0.91 (0.71 to 1.15)
Factor V Leiden							
Present	1370	17	2.48	20	2.98	-0.50 (-2.26 to 1.26)	0.81 (0.42 to 1.54)
Absent	25 409	139	1.10	154	1.22	-0.11 (-0.38 to 0.15)	0.90 (0.72 to 1.13)
G20210A prothrombin mutation							
Present	720	11	3.12	14	3.93	-0.81 (-3.58 to 1.96)	0.81 (0.37 to 1.79)
Absent	26 059	145	1.12	160	1.23	-0.11 (-0.38 to 0.15)	0.90 (0.72 to 1.13)
MTHFR 677C>T polymorphism							
TT	2918	17	1.17	20	1.38	-0.21 (-1.03 to 0.61)	0.85 (0.45 to 1.62)
CT	11 625	68	1.17	89	1.55	-0.38 (-0.80 to 0.05)	0.76 (0.55 to 1.04)
CC	12 235	71	1.18	65	1.06	0.12 (-0.26 to 0.49)	1.10 (0.78 to 1.54)
Provided blood sample							
Yes	26 779	156	1.17	174	1.31	-0.13 (-0.40 to 0.14)	0.89 (0.72 to 1.11)
No	13 097	79	1.21	73	1.12	0.08 (-0.29 to 0.45)	1.06 (0.77 to 1.46)

* Hazard ratios were based on a proportional hazards model, controlling for age and other randomized treatments and stratified by baseline history of venous thromboembolism.

Figure 3. Forest plot showing aspirin effects in subgroups.



BMI = body mass index; HT = hormone therapy; VTE = venous thromboembolism.

persistence with preventive therapies of proven efficacy in actual clinical practice also typically lessens with time. Our trial identified only symptomatic VTE, but asymptomatic VTE may also be clinically relevant (30). Because we considered risk factors evaluated before randomization only, we might have misclassified participants whose risk stratifications changed during follow-up. Finally, VTE was a secondary end point of the Women’s Health Study. However, we prospectively established it as an end point and required the same process of confirmation as the primary study end points.

Aspirin treatment has proven efficacy for the secondary prevention of cardiovascular disease in almost all adults and for primary prevention in some high-risk populations. Thus, current guidelines recommend aspirin therapy for many adults, depending on their cardiovascular risk (31, 32). Our results suggest that aspirin therapy may not have broad applicability for the primary prevention of VTE. Trials of aspirin for secondary prevention of VTE in high-risk populations are ongoing.

The current trial shows that aspirin is not effective for primary prevention of VTE in women at low to moderate risk. This finding is important for 2 reasons. First, even low-dose aspirin causes clinically important bleeding episodes in some women. Second, use of low-dose aspirin without knowing the results of the current trial might provide a false sense of security that aspirin was preventing VTE. Our findings indicate the need to continue research for safe and effective antithrombotics and other pharmacologic strategies that do not require dose adjustment on the basis of laboratory coagulation measurements.

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