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## Aspirin for Preventing the Recurrence of Venous Thromboembolism

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### ABSTRACT

#### BACKGROUND

About 20% of patients with unprovoked venous thromboembolism have a recurrence within 2 years after the withdrawal of oral anticoagulant therapy. Extending anticoagulation prevents recurrences but is associated with increased bleeding. The benefit of aspirin for the prevention of recurrent venous thromboembolism is unknown.

#### METHODS

In this multicenter, investigator-initiated, double-blind study, patients with first-ever unprovoked venous thromboembolism who had completed 6 to 18 months of oral anticoagulant treatment were randomly assigned to aspirin, 100 mg daily, or placebo for 2 years, with the option of extending the study treatment. The primary efficacy outcome was recurrence of venous thromboembolism, and major bleeding was the primary safety outcome.

#### RESULTS

Venous thromboembolism recurred in 28 of the 205 patients who received aspirin and in 43 of the 197 patients who received placebo (6.6% vs. 11.2% per year; hazard ratio, 0.58; 95% confidence interval [CI], 0.36 to 0.93) (median study period, 24.6 months). During a median treatment period of 23.9 months, 23 patients taking aspirin and 39 taking placebo had a recurrence (5.9% vs. 11.0% per year; hazard ratio, 0.55; 95% CI, 0.33 to 0.92). One patient in each treatment group had a major bleeding episode. Adverse events were similar in the two groups.

#### CONCLUSIONS

Aspirin reduced the risk of recurrence when given to patients with unprovoked venous thromboembolism who had discontinued anticoagulant treatment, with no apparent increase in the risk of major bleeding. (Funded by the University of Perugia and others; WARFASA ClinicalTrials.gov number, NCT00222677.)

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\*The investigators in the Aspirin for the Prevention of Recurrent Venous Thromboembolism (the Warfarin and Aspirin [WARFASA]) study are listed in the Supplementary Appendix, available at [NEJM.org](http://NEJM.org).

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**T**HE RISK OF RECURRENCE OF VENOUS thromboembolism persists for many years after anticoagulant treatment is withdrawn.<sup>1,2</sup> This risk is particularly high among patients with unprovoked venous thromboembolism,<sup>2</sup> about 20% of whom have a recurrence within 2 years after treatment with vitamin K antagonists has been discontinued.<sup>3-6</sup> Extending treatment with these agents reduces the risk of recurrence but is associated with an increased risk of bleeding, as well as the inconvenience and expense of laboratory monitoring and dose adjustments.<sup>7</sup>

The role of aspirin in the primary prevention of venous thromboembolism has been evaluated in various clinical settings.<sup>8-11</sup> In these studies, aspirin was associated with a risk reduction ranging from 20 to 50%. A potential benefit from antiplatelet therapy in the secondary prevention of venous thromboembolism first became evident with the results of a randomized study involving only 39 patients.<sup>12</sup>

The aim of the Aspirin for the Prevention of Recurrent Venous Thromboembolism (the Warfarin and Aspirin [WARFASA]) study was to assess the clinical benefit of aspirin for the prevention of recurrence after a course of treatment with vitamin K antagonists in patients with unprovoked venous thromboembolism.

## METHODS

### PATIENTS

Patients older than 18 years of age were eligible for the study if they had been treated for 6 to 18 months with vitamin K antagonists (with a target international normalized ratio [INR] of 2.0 to 3.0) for first-ever, objectively confirmed, symptomatic, unprovoked proximal deep-vein thrombosis, pulmonary embolism, or both. Venous thromboembolism was considered to be unprovoked when it occurred in the absence of any known risk factor for this event. The main exclusion criteria can be found in the Supplementary Appendix, available with the full text of this article at [NEJM.org](http://NEJM.org).

### STUDY DESIGN AND INTERVENTION

WARFASA was a multicenter, investigator-initiated, randomized, double-blind clinical trial. Eligible patients were randomly assigned to aspirin,

100 mg once daily, or placebo for 2 years, with the option of extending the study treatment. Randomization occurred within 2 weeks after vitamin K antagonists had been withdrawn.

### OUTCOME MEASURES

All suspected study outcome events were assessed by a central, independent adjudication committee whose members were unaware of the group assignments and who reviewed the imaging results. The primary efficacy outcome was symptomatic, objectively confirmed recurrence of venous thromboembolism, defined as the composite of deep-vein thrombosis or nonfatal or fatal pulmonary embolism.<sup>13,14</sup> (Criteria for the diagnosis of recurrence are provided in the Supplementary Appendix.) Pulmonary embolism was considered to be the cause of death if it was confirmed on autopsy or if death was preceded by a diagnosis of either pulmonary embolism (objectively confirmed on computed tomography or lung scanning) or deep-vein thrombosis (objectively confirmed on compression ultrasonography) and whenever the cause could not be attributed to an alternative diagnosis.<sup>15</sup> Deaths were classified as being due to pulmonary embolism, bleeding, or other causes. Secondary efficacy outcomes included nonfatal myocardial infarction, unstable angina, stroke, transient ischemic attack, acute ischemia of the lower limbs, and death from any cause.

The principal safety outcome was major bleeding. An overt bleeding event was defined as major if it was fatal, occurred in a critical location (intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial, or intramuscular [leading to a compartment syndrome]), or was associated with a decrease in the hemoglobin level of at least 2.0 g per deciliter or required a transfusion of 2 or more units of whole blood or red cells. Clinically relevant, nonmajor bleeding, defined as any overt bleeding that required a medical intervention and did not meet any of the criteria for major bleeding, was a secondary safety outcome.

### SURVEILLANCE AND FOLLOW-UP

Patients were reexamined every 3 months during the first year after randomization and every 6 months thereafter. Patients were instructed to report to the study center immediately if they had symptoms suggestive of recurrent venous throm-

boembolism or bleeding complications. In cases of suspected recurrence, objective testing was required.

#### STUDY OVERSIGHT

The study was designed by the members of the steering committee. Data were collected, maintained, and analyzed by the Clinical Research Unit of the University of Perugia, Italy. The protocol and amendments were approved by the institutional review board or ethics committee at each study center. During the course of the study, two substantial protocol amendments were made and submitted to the ethics committees in May 2009 and December 2009. The first of these amendments reflected the change to an event-driven design, and the second reflected the change of the primary study end point to venous thromboembolism only. These changes were made so that the study design would be consistent with that of contemporary trials of extended treatment for venous thromboembolism (i.e., the EINSTEIN-Extension study [ClinicalTrials.gov number, NCT00439725] and the RE-SONATE study [NCT00558259]). The study was performed in accordance with the protocol and with the provisions of the Declaration of Helsinki and local regulations. (The protocol and statistical analysis plan are available at NEJM.org.) Written informed consent was obtained from all patients before randomization.

The steering committee had final responsibility for verification and analyses of the data. The writing committee wrote the manuscript and vouches for the accuracy and completeness of the reported data. All authors contributed to the interpretation of the results, approved the final version of the manuscript, and made the decision to submit the manuscript for publication. The study was supported by a grant-in-aid from Bayer HealthCare. Aspirin and placebo tablets were supplied by Bayer HealthCare. Bayer played no role in the design of the study, in data collection or analysis, or in manuscript preparation.

#### STATISTICAL ANALYSIS

Assuming a 40% relative risk reduction with aspirin,<sup>8-11</sup> a total of 70 events would provide a power of 80% to show the superiority of aspirin over placebo at a two-sided alpha level of 0.05. With an expected event rate of 8.0% per year in

the placebo group, we calculated that we would need to enroll 400 patients (200 in each study group) to observe the expected number of events.

The primary efficacy analysis, which considered all outcome events occurring from randomization to the end of the study, was performed according to a modified intention-to-treat principle, with all patients who received at least one dose of the assigned study drug after randomization included in the analysis. An “on-treatment” efficacy analysis was also performed, in which recurrences were included if they took place during the treatment period or within 2 days after its withdrawal. Event rates are reported as proportions of patients per year. Hazard ratios, confidence intervals, and P values were calculated with the use of Cox proportional-hazards models and SPSS statistical software, version 11.0, with treatment as the only covariate.

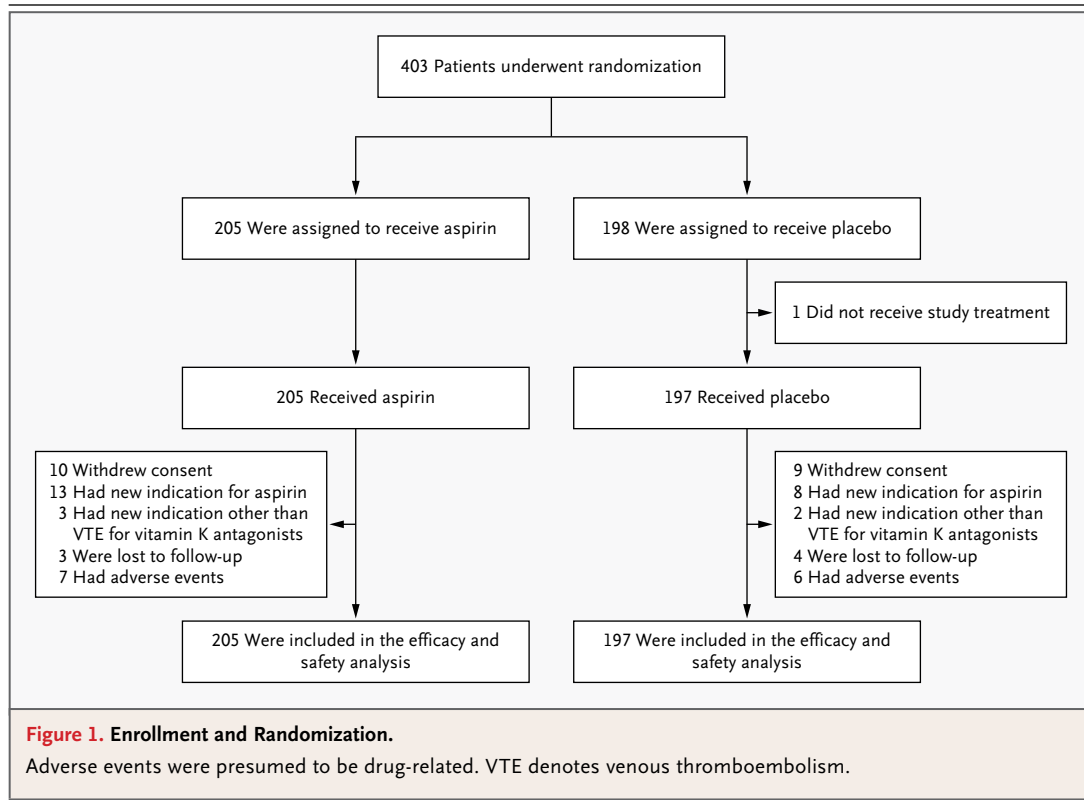
A Cox proportional-hazards model analysis was also performed with adjustment for age, sex, type of index event (pulmonary embolism or deep-vein thrombosis), and duration of anticoagulant treatment before randomization (6 months or >6 months).

The safety analysis included all patients who received at least one dose of the study drug. Bleeding events were included in the analyses if they occurred during the period of administration of the study drug or within 2 days after its discontinuation.

## RESULTS

#### PATIENTS AND STUDY TREATMENT

From May 2004 through August 2010, a total of 403 patients were randomly assigned to a study group; 205 patients received aspirin, 197 received placebo, and 1 patient, who was assigned to the placebo group, did not receive the study drug (Fig. 1). The median period during which the patients participated in the study was 24.8 months in the aspirin group and 24.2 months in the placebo group. The study drug was discontinued prematurely in 16 patients given aspirin and in 15 patients given placebo (Fig. 1). Since the end of the study was event-driven, the duration of treatment was shorter than the intended 2 years for 10 patients in the aspirin group (4.9%) and for 11 patients in the placebo group (5.6%); the treatment period was extended beyond 2 years in 58



patients and 55 patients in the two groups, respectively. The median duration of the study treatment was 24.0 months for the aspirin group and 23.5 months for the placebo group. Three patients in the aspirin group (1.4%) and 4 patients in the placebo group (2.0%) were lost to follow-up. There were no significant between-group differences in baseline characteristics of the patients (Table 1).

#### RECURRENT VENOUS THROMBOEMBOLISM

A recurrence of venous thromboembolism occurred in 71 patients (8.6% patients per year). Recurrent venous thromboembolism was due to deep-vein thrombosis in 44 patients (ipsilateral in 51% of cases) and to pulmonary embolism in 27 patients (fatal in 2 patients). In 77% of cases, recurrence took place in the absence of any known risk factor for venous thromboembolism. A recurrence in the form of pulmonary embolism was more common among the patients who entered the study because of prior pulmonary embolism than among those who entered because of deep-vein thrombosis (12.7% vs. 3.2%; hazard ratio, 5.52; 95% confidence interval [CI], 2.29 to 13.30;  $P < 0.001$ ).

The primary prespecified outcome, recurrence of venous thromboembolism, occurred in 28 of the 205 patients who received aspirin, as compared with 43 of the 197 patients who received placebo (6.6% vs. 11.2% per year; hazard ratio, 0.58; 95% CI, 0.36 to 0.93;  $P = 0.02$ ) (Fig. 2A).

While taking the study drug, 23 patients in the aspirin group had a recurrence, as compared with 39 patients in the placebo group (5.9% vs. 11.0% per year; hazard ratio, 0.55; 95% CI, 0.33 to 0.92;  $P = 0.02$ ) (Fig. 2B). Exploratory, post hoc subgroup analyses revealed that 11 of 83 patients in the aspirin group who entered the study because of pulmonary embolism had a recurrent event, as compared with 16 of 67 patients in the placebo group (6.7% vs. 13.5% per year; hazard ratio, 0.38; 95% CI, 0.17 to 0.88;  $P = 0.02$ ). Among the patients who entered the study because of deep-vein thrombosis, 17 of 122 in the aspirin group and 27 of 130 in the placebo group had a recurrent event (6.5% and 10.2% per year, respectively; hazard ratio, 0.65; 95% CI, 0.65 to 1.20;  $P = 0.17$ ).

An analysis adjusted for age, sex, index event (pulmonary embolism or deep-vein thrombosis), and duration of initial anticoagulant treatment

confirmed that aspirin treatment reduced the risk of recurrence (adjusted hazard ratio, 0.53; 95% CI, 0.32 to 0.85;  $P=0.009$ ) (Fig. 2C). Independent risk factors for recurrent venous thromboembolism included an age of more than 65 years (hazard ratio, 2.26; 95% CI, 1.16 to 4.41;  $P=0.02$ ) and male sex (hazard ratio, 2.02; 95% CI, 1.16 to 3.49;  $P=0.01$ ). No association was found between recurrent venous thromboembolism and prior anticoagulant therapy lasting for 6 months, as compared with a more extended duration (hazard ratio, 1.21; 95% CI, 0.73 to 1.99;  $P=0.46$ ), or between recurrence and pulmonary embolism as the index event (hazard ratio, 1.31; 95% CI, 0.79 to 2.15;  $P=0.29$ ).

#### HEMORRHAGIC COMPLICATIONS

There were two episodes of nonfatal major bleeding: one due to gastric ulcer in a patient in the placebo group and one due to bowel angiodysplasia in a patient in the aspirin group. Clinically relevant, nonmajor bleeding occurred in three patients who were randomly assigned to aspirin (gingival bleeding in one patient and cutaneous hematomas in two patients) and in three patients who were randomly assigned to placebo (musculoskeletal bleeding after trauma in two and hemorrhagic gastritis in one).

#### SECONDARY OUTCOME EVENTS

Death occurred in six patients in the aspirin group (1.4% per year) and in five patients in the placebo group (1.3% per year) (Table 2). Sudden death occurred in two patients (one in each group), and both deaths were adjudicated as being the result of pulmonary embolism. In addition, four patients died from cancer and five from other causes. Arterial events occurred in eight patients in the aspirin group and in five patients in the placebo group (1.9% and 1.3% per year, respectively) (Table 2).

#### ADDITIONAL OBSERVATIONS

Five patients had an adverse event that was considered to be due to the study treatment and led to discontinuation of the drug. These events were gastric pain in three patients (one in the aspirin group and two in the placebo group), a cutaneous reaction in one aspirin-treated patient, and renal failure in another aspirin-treated patient.

An indication for antiplatelet therapy other than an acute arterial event occurred in five pa-

**Table 1. Demographic and Clinical Characteristics of the Patients, According to Study Group.\***

Characteristic	Aspirin (N=205)	Placebo (N=197)
Age — yr	61.9±15.3	62.1±15.1
Male sex — no. (%)	135 (65.8)	122 (61.9)
Body-mass index†	27.1±4.0	27.5±3.8
White race — no. (%)‡	203 (99.0)	195 (98.9)
Index event — no. (%)		
Deep-vein thrombosis	122 (59.5)	130 (65.9)
Pulmonary embolism	83 (40.5)	67 (34.1)
Duration of VKA treatment before randomization — no. (%)		
6 mo	76 (37.1)	62 (31.5)
12 mo	111 (54.1)	112 (56.8)
18 mo	18 (8.8)	23 (11.7)

\* Plus-minus values are means ±SD. VKA denotes vitamin K antagonist.

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

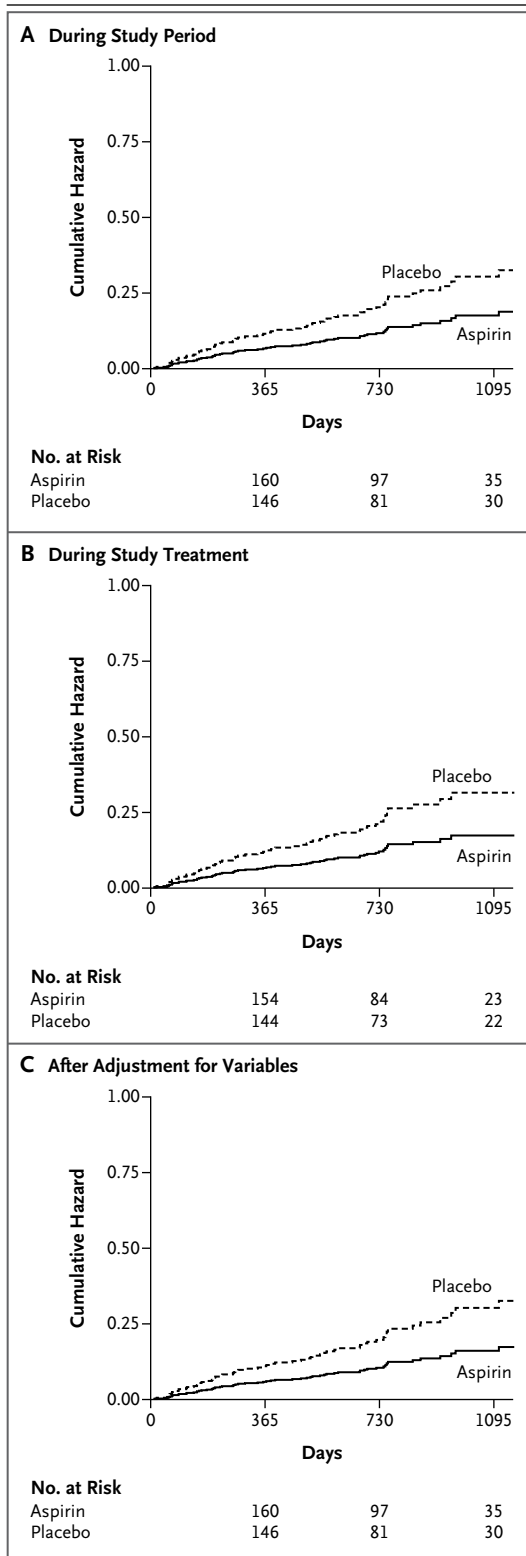
‡ Race was self-reported.

tients in the aspirin group and in three patients in the placebo group, and an indication for anticoagulant therapy other than recurrent venous thromboembolism occurred in three patients and in two patients in the two groups, respectively.

#### DISCUSSION

The WARFASA study shows that in patients with unprovoked venous thromboembolism, aspirin therapy, begun after 6 to 18 months of oral anticoagulant treatment, reduces the rate of recurrence by about 40%, as compared with placebo. This benefit is achieved with no apparent increase in the risk of major bleeding.

Patients with unprovoked venous thromboembolism are at high risk for recurrence after oral anticoagulant treatment is withdrawn.<sup>3-6</sup> Extending anticoagulant therapy reduces the risk of recurrence but only as long as the treatment is continued.<sup>3,5,16</sup> In clinical practice, anticoagulant therapy is generally discontinued when the perceived risk of bleeding or the inconvenience of continuing anticoagulant treatment outweighs the risk of recurrence. Our study shows that aspirin therapy is a potential alternative to extended oral anticoagulant treatment for the long-term secondary prevention of venous thromboembolism.



**Figure 2. Risk of Recurrence of Venous Thromboembolism in Patients Randomly Assigned to Aspirin or Placebo.**

Panel A shows the cumulative risk of recurrent venous thromboembolism during the entire study period, and Panel B shows the risk during treatment. Panel C shows the results of an analysis of risk during the study period after adjustment for age, sex, index event (pulmonary embolism or deep-vein thrombosis), and duration of anticoagulant therapy.

The reduction in the risk of recurrence of venous thromboembolism that was observed with aspirin treatment in our study is consistent with the reduction shown in previous studies evaluating aspirin for the primary prevention of venous thromboembolism.<sup>8-11</sup> In the meta-analysis performed by the Antiplatelet Trialists' Collaboration, aspirin reduced the incidence of deep-vein thrombosis by 20% and that of pulmonary embolism by 69% in patients at high risk for thromboembolic events.<sup>8</sup> However, more recent data showed no effect of aspirin in the prevention of venous thromboembolism among healthy women.<sup>17</sup> The efficacy of antiplatelet therapy in the secondary prevention of venous thromboembolism was suggested in a small study that compared aspirin plus dipyridamole with placebo.<sup>12</sup>

The efficacy of aspirin for primary or secondary prevention of venous thromboembolism is biologically plausible because of the involvement of platelets in the formation of venous thrombi<sup>18-20</sup> and the increased levels of markers of platelet<sup>21,22</sup> and endothelial<sup>23</sup> activation in patients with venous thromboembolism.

As compared with placebo, aspirin was not associated with an increase in the rate of major bleeding, which was about 0.3% per patient-year in both study groups. We used the dose of aspirin recommended for the secondary prevention of cardiovascular or cerebrovascular events. In randomized trials of low-dose aspirin in various clinical settings, the incidence of major intracranial or extracranial bleeding was lower than 1% per year.<sup>24</sup> The rate of major bleeding with warfarin for the long-term treatment of venous thromboembolism is estimated to be about 2%<sup>25</sup> with the conventional regimen (INR, 2.0 to 3.0). In two studies of a low-intensity warfarin regi-

**Table 2. Outcome Events According to Study Group.\***

Event	Aspirin (N=205) <i>number of events</i>	Placebo (N=197) <i>number of events</i>	Hazard Ratio (95% CI)	P Value
Recurrent VTE				
Total episodes	28	43	0.58 (0.36–0.93)	0.02
Pulmonary embolism	11	14	0.70 (0.32–1.54)	0.37
Fatal pulmonary embolism	1	1		
Deep-vein thrombosis	16	28	0.51 (0.27–0.94)	0.03
Episodes during treatment	23	39	0.55 (0.33–0.92)	0.02
Bleeding				
Major bleeding or clinically relevant nonmajor bleeding	4	4	0.98 (0.24–3.96)	0.97
Major bleeding	1	1		
Clinically relevant nonmajor bleeding	3	3		
Death	6	5	1.04 (0.32–3.42)	0.95
Recurrent VTE or death	33	47	0.62 (0.40–0.97)	0.04
Arterial event	8†	5‡	1.43 (0.47–4.37)	0.53
Recurrent VTE or arterial event	36	48	0.67 (0.43–1.03)	0.06

\* CI denotes confidence interval, and VTE venous thromboembolism.

† These events included two acute myocardial infarctions (after discontinuation of the study drug), two episodes of unstable angina, two ischemic strokes, one transient ischemic attack, and one episode of acute lower-limb ischemia.

‡ These events included two acute myocardial infarctions (after discontinuation of the study drug), one ischemic stroke, and two episodes of acute lower-limb ischemia.

men for extended treatment of venous thromboembolism, the rates of major bleeding were 0.9% per patient-year<sup>26</sup> and 1.1% per patient-year.<sup>27</sup> It should be noted that the risk of major bleeding with aspirin therapy may be greater in real-world populations.

Since patients were excluded from our study if they had cancer, clinically significant thrombophilia, or a bleeding event during the period of anticoagulant treatment, the results are not applicable to these groups. However, we estimate that a substantial proportion (probably the majority) of patients with an initial episode of venous thromboembolism would be eligible for aspirin therapy as secondary prevention.

The oral thrombin inhibitor dabigatran<sup>28,29</sup> and the oral factor Xa inhibitor rivaroxaban<sup>30</sup> were recently evaluated for the extended treatment of venous thromboembolism. As compared with placebo, these agents reduced the risk of recurrent venous thromboembolism by more than 80%. An advantage of these agents over vitamin K

antagonists is that they do not require laboratory monitoring and dose adjustments. As expected, the reduction in the risk of recurrence is lower with aspirin than with these new oral agents. All the available antithrombotic strategies for extended treatment of venous thromboembolism have been compared with placebo. The place of aspirin among these strategies remains to be defined in future studies. However, aspirin is low in cost and its side effects are well known, since its safety has been assessed over the years in millions of patients.<sup>24</sup>

Low-intensity warfarin was evaluated for the extended treatment of venous thromboembolism and was found to be associated with a 64% reduction in risk, as compared with placebo.<sup>26</sup> However, this warfarin regimen still requires laboratory monitoring and dose adjustments.

Our study has several limitations. As in the majority of investigator-initiated studies, the recruitment of patients was slower than planned. Indeed, this study took about 6 years to be com-

pleted. Furthermore, it was underpowered for showing an effect of aspirin on the incidence of ischemic heart disease or cerebrovascular disease, both of which are reported to be common among patients with unprovoked venous thromboembolism.<sup>31,32</sup> In addition, patients with symptomatic atherosclerosis were not included in our study. Thus, our results may not apply to patients who require aspirin for the prevention of arterial events.<sup>33</sup>

Our study also has several strengths. It was a randomized, placebo-controlled, double-blind study, with independent adjudication of outcomes. The study treatment lasted for about 2 years — significantly longer than that in recent studies of extended treatment for venous thromboembolism.<sup>28-30</sup> All patients who received at least one dose of the study drug after randomization were included in the primary efficacy analysis. The results of the on-treatment analysis were consistent with those of the primary study analysis.

We conclude that aspirin, when given after anticoagulant treatment in patients with unprovoked venous thromboembolism, is effective in preventing recurrence, with no apparent increase in the risk of major bleeding.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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