

# The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

NOVEMBER 22, 2012

VOL. 367 NO. 21

## Low-Dose Aspirin for Preventing Recurrent Venous Thromboembolism

Timothy A. Brighton, M.B., B.S., John W. Eikelboom, M.B., B.S., Kristy Mann, M.Biostat., Rebecca Mister, M.Sc., Alexander Gallus, M.B., B.S., Paul Ockelford, M.B., Harry Gibbs, M.B., Wendy Hague, Ph.D., Denis Xavier, M.Sc., Rafael Diaz, M.D., Adrienne Kirby, M.Sc., and John Simes, M.D., for the ASPIRE Investigators\*

### ABSTRACT

#### BACKGROUND

Patients who have had a first episode of unprovoked venous thromboembolism have a high risk of recurrence after anticoagulants are discontinued. Aspirin may be effective in preventing a recurrence of venous thromboembolism.

#### METHODS

We randomly assigned 822 patients who had completed initial anticoagulant therapy after a first episode of unprovoked venous thromboembolism to receive aspirin, at a dose of 100 mg daily, or placebo for up to 4 years. The primary outcome was a recurrence of venous thromboembolism.

#### RESULTS

During a median follow-up period of 37.2 months, venous thromboembolism recurred in 73 of 411 patients assigned to placebo and in 57 of 411 assigned to aspirin (a rate of 6.5% per year vs. 4.8% per year; hazard ratio with aspirin, 0.74; 95% confidence interval [CI], 0.52 to 1.05;  $P=0.09$ ). Aspirin reduced the rate of the two prespecified secondary composite outcomes: the rate of venous thromboembolism, myocardial infarction, stroke, or cardiovascular death was reduced by 34% (a rate of 8.0% per year with placebo vs. 5.2% per year with aspirin; hazard ratio with aspirin, 0.66; 95% CI, 0.48 to 0.92;  $P=0.01$ ), and the rate of venous thromboembolism, myocardial infarction, stroke, major bleeding, or death from any cause was reduced by 33% (hazard ratio, 0.67; 95% CI, 0.49 to 0.91;  $P=0.01$ ). There was no significant between-group difference in the rates of major or clinically relevant nonmajor bleeding episodes (rate of 0.6% per year with placebo vs. 1.1% per year with aspirin,  $P=0.22$ ) or serious adverse events.

#### CONCLUSIONS

In this study, aspirin, as compared with placebo, did not significantly reduce the rate of recurrence of venous thromboembolism but resulted in a significant reduction in the rate of major vascular events, with improved net clinical benefit. These results substantiate earlier evidence of a therapeutic benefit of aspirin when it is given to patients after initial anticoagulant therapy for a first episode of unprovoked venous thromboembolism. (Funded by National Health and Medical Research Council [Australia] and others; Australian New Zealand Clinical Trials Registry number, ACTRN12605000004662.)

From the Department of Haematology, South Eastern Area Laboratory Services (SEALS), Prince of Wales Hospital (T.A.B.), and the National Health and Medical Research Council Clinical Trials Centre, University of Sydney (K.M., R.M., W.H., A.K., J.S.), Sydney, the Department of Haematology, SA Pathology at Flinders Medical Centre, Adelaide, SA (A.G.), and the General Medicine Unit, Alfred Hospital, Melbourne, VIC (H.G.) — all in Australia; the Population Health Research Institute, McMaster University, Hamilton, ON, Canada (J.W.E.); the Thrombosis Unit, Auckland City Hospital, Auckland, New Zealand (P.O.); St. John's Medical College and Research Institute, Bangalore, India (D.X.); and Estudios Clínicos Latinoamérica (ECLA) International, Rosario, Argentina (R.D.). Address reprint requests to Dr. Brighton at [aspire@ctc.usyd.edu.au](mailto:aspire@ctc.usyd.edu.au).

\*The investigators in the Aspirin to Prevent Recurrent Venous Thromboembolism (ASPIRE) trial are listed in the Supplementary Appendix, available at [NEJM.org](http://NEJM.org).

This article was published on November 4, 2012, at [NEJM.org](http://NEJM.org).

*N Engl J Med* 2012;367:1979-87.

DOI: 10.1056/NEJMoa1210384

Copyright © 2012 Massachusetts Medical Society.



**P**ATIENTS WHO HAVE HAD A FIRST EPISODE of unprovoked venous thromboembolism are at high risk for recurrence after anticoagulant therapy is discontinued.<sup>1-4</sup> Long-term treatment with a vitamin K antagonist is very effective in preventing a recurrence of venous thromboembolism while treatment continues<sup>5</sup> but has not been shown to improve survival, is associated with a substantially increased risk of bleeding, and is inconvenient for patients.<sup>6-10</sup> Consequently, many patients who have had a first episode of unprovoked venous thromboembolism discontinue anticoagulant therapy after 3 to 6 months despite recommendations to prolong therapy.<sup>5</sup>

Low-dose aspirin is a simple, inexpensive, and widely available treatment that is effective for the prevention of arterial vascular events and for the primary prevention of venous thromboembolism in high-risk surgical patients.<sup>11-13</sup> Aspirin may also be effective in preventing a recurrence of venous thromboembolism after a first event.<sup>14</sup> The objective of our study was to evaluate the efficacy of low-dose aspirin, as compared with placebo, in preventing a recurrence of venous thromboembolism in patients who had completed initial anticoagulation with warfarin after a first unprovoked episode of venous thromboembolism.

## METHODS

### STUDY DESIGN

The Aspirin to Prevent Recurrent Venous Thromboembolism (ASPIRE) study was a double-blind, randomized, placebo-controlled study of the use of low-dose aspirin in patients who had had a first-ever unprovoked venous thromboembolism and who had completed initial anticoagulation therapy. We randomly assigned patients who had completed anticoagulation therapy to aspirin, at a dose of 100 mg daily, or placebo; randomization was performed through a central Web-based randomization system, with stratification according to center and duration of initial oral anticoagulation therapy ( $\leq 26$  weeks or  $> 26$  weeks). Enteric-coated aspirin, in 100-mg tablets, and matching placebo were provided without charge by Bayer HealthCare Pharmaceuticals; the company played no other role in the study and was not involved in the collection or analysis of the data or in the preparation of the manuscript. Patients were asked to take one tablet daily for a minimum of 2 years. The

maximum duration of treatment was subsequently capped at 4 years.

### PATIENTS

Male and female patients were eligible for inclusion if they were at least 18 years of age and had had a first unprovoked episode of objectively diagnosed symptomatic deep-vein thrombosis involving the popliteal vein or more proximal leg veins or an acute pulmonary embolism. Venous thromboembolism was considered to be unprovoked if it occurred in the absence of the following transient risk factors during the preceding 2 months: confinement to bed for more than 1 week, major surgery, trauma requiring a cast, pregnancy or the puerperium, and the use of the oral contraceptive pill or hormone-replacement therapy. All patients were required to have completed initial anticoagulation therapy with heparin followed by warfarin (or an effective alternative anticoagulant). The duration of the initial anticoagulation therapy had to be between 6 weeks and 24 months; however, it was recommended that a target international normalized ratio of 2 to 3 be maintained with warfarin therapy for 6 to 12 months.

Patients were not eligible for inclusion if the first unprovoked episode of venous thromboembolism had occurred more than 2 years before enrollment; if they had an indication or contraindication for the use of aspirin, other antiplatelet therapy, or a nonsteroidal antiinflammatory drug; if they had an indication for continuing oral anticoagulation therapy; or if they had other medical problems that would interfere with participation in the trial or limit life expectancy. A detailed description of the eligibility criteria is provided in the study protocol, available with the full text of this article at NEJM.org.

### FOLLOW-UP

Patients attended follow-up visits at 1 month and 6 months after randomization and every 6 months thereafter and were contacted by telephone or e-mail at the 3-month mark between visits. All patients who were enrolled after a first episode of unprovoked deep-vein thrombosis underwent venous ultrasound examination within 1 month after randomization to determine whether there was residual thrombus, in order to distinguish between residual thrombosis and a recurrence of thrombosis in subsequent assessments. Patients were instructed to report to their study center immedi-

ately if symptoms suggestive of a recurrence of venous thromboembolism, bleeding, adverse effects of a study drug, or other clinically significant changes developed. Information for each patient was included up to 4 years after enrollment or up to the scheduled final visit, whichever came first. The final visit was scheduled for each site during the first quarter of 2012, after the decision was made to close the trial.

#### OUTCOME MEASURES

The primary outcome of the study was a recurrence of venous thromboembolism, defined as a composite of symptomatic, objectively confirmed deep-vein thrombosis, nonfatal pulmonary embolism, or fatal pulmonary embolism. Prespecified secondary outcomes were major vascular events (a composite of venous thromboembolism, myocardial infarction, stroke, or cardiovascular death) and a measure of the net clinical benefit (a reduction in the rate of the composite of venous thromboembolism, myocardial infarction, stroke, major bleeding, or death from any cause). The risks of arterial thrombosis and cardiovascular death are increased in patients with unprovoked venous thromboembolism<sup>15,16</sup>; these events were included as secondary outcomes because they are clinically important and are likely to be influenced by aspirin therapy. The diagnosis of a recurrence of venous thromboembolism required the presence of new symptoms and objective evidence on appropriate imaging of new thrombosis that was not identified on previous imaging (as detailed in the study protocol). Pulmonary embolism was considered to be the cause of death if it was confirmed at autopsy or if death was preceded by a recurrence of symptomatic deep-vein thrombosis or pulmonary embolism and the cause of death could not be attributed to an alternative diagnosis. All episodes of venous thromboembolism, myocardial infarction, and stroke and the causes of death were adjudicated by an independent outcome assessment committee whose members were unaware of the group assignments.

The primary safety outcome was bleeding, either major or clinically relevant nonmajor bleeding. Major bleeding was defined as overt bleeding that was associated with a decrease in hemoglobin of at least 2 g per deciliter or that necessitated transfusion of 2 or more units of blood, involved a critical site (e.g., retroperitoneal or intracranial bleeding), was disabling, required sur-

gical intervention, or contributed to death. Bleeding episodes that did not meet the definition of major bleeding were considered to be clinically relevant only if they led to discontinuation of the study drug for more than 14 days.

With plans developed a priori to subsequently pool the results of the ASPIRE trial and the Warfarin and Aspirin (WARFASA) trial,<sup>14</sup> the protocols of the two trials were prospectively harmonized to ensure that the randomized treatments were identical and that eligibility criteria and outcome definitions were similar.

#### STUDY OVERSIGHT

The study protocol was written by members of the executive committee of the trial (see the Supplementary Appendix, available at NEJM.org) and was approved by the University of Sydney human research ethics committee, as well as by the ethics committees at each participating site. Written informed consent was obtained from all patients before they underwent randomization. Clinical data were collected from electronic case-report forms with the use of an InForm clinical trial database (Oracle). The National Health and Medical Research Council (NHMRC) Clinical Trials Centre was responsible for the collection, maintenance, integrity, and confidentiality of all data. The executive committee was responsible for all aspects of the conduct of the study. An independent safety and data monitoring committee reviewed the progress of all aspects of the study, including data on safety, and met annually. All primary and secondary events were adjudicated by an independent event adjudication committee whose members were unaware of the group assignments. The final analysis plan and adjudication of all primary and secondary events were completed before unblinding of results according to group assignments. The analysis was performed at the NHMRC Clinical Trials Centre. The first draft of the manuscript was written by the first two authors and the last author, and all the authors contributed to the final manuscript and attest to the accuracy of the data and to the fidelity of the study to the protocol. No one who is not an author contributed to the manuscript.

#### STATISTICAL ANALYSIS

The ASPIRE study was originally designed to recruit 3000 patients, which would have given the study 90% power to detect a relative-risk reduc-

tion of 30% in the incidence of venous thromboembolism with aspirin as compared with placebo, assuming an event rate of 7% per year in the placebo group, at a two-sided alpha level of 0.05. The study commenced in 2003, but because of slow recruitment, the target sample size was reduced in 2005 to 1500 patients with an expected duration of follow-up of 4 years, and plans were made (with interim trial results concealed) to combine the final results with those of the WARFASA trial<sup>14</sup> in a prospectively planned meta-analysis (Australian New Zealand Clinical Trials Registry number, ACTRN12611000684921). The ASPIRE study with the reduced sample size, when combined with the WARFASA study, had 80% power to detect a 30% reduction in the primary outcome of recurrence of venous thromboembolism (and the ASPIRE study alone had 80% power to detect a 32% reduction in the secondary outcome of all major vascular events). Recruitment closed in August 2011 because of declining recruitment rates and limited resources, with an additional 12 months of follow-up planned for the last patient enrolled. The study follow-up was subsequently closed on March 31, 2012, after publication of the results of the WARFASA study, since it was believed that continuation of the trial would provide limited additional information if patients decided to switch to open-label aspirin on the basis of the results of the WARFASA trial.

In the primary analysis, we compared the two study groups with respect to the first occurrence of symptomatic and objectively confirmed deep-vein thrombosis, nonfatal pulmonary embolism, or fatal pulmonary embolism using an intention-to-treat approach and including events up to the final scheduled visit or up to a maximum of 4 years from the time of randomization. Data from patients who withdrew consent or who were lost to follow-up were censored at the time of the last follow-up assessment. All patients who stopped using the study drug continued to be followed and were included in the intention-to-treat analysis. Survival curves were estimated with the use of the Kaplan–Meier procedure and were compared with the use of log-rank tests.

In the primary analysis, treatment effects (with their 95% confidence intervals) were estimated by means of Cox regression analysis unadjusted for patient risk factors. In a similar analysis, we evaluated the effect of aspirin on prespecified secondary outcomes of major vascular events (a composite of venous thromboembolism, myocar-

dial infarction, stroke, or cardiovascular death) and net clinical benefit (reduction in the rate of the composite of venous thromboembolism, myocardial infarction, stroke, major bleeding, or all-cause death). Additional adjusted analyses of primary and secondary outcomes incorporated adjustment for prespecified characteristics (age, sex, smoking history, body-mass index [BMI], type of first unprovoked event, and duration of initial anticoagulation therapy). Interactions in Cox models were used to assess differences in the effect of aspirin across prespecified subgroups defined according to age, sex, duration of initial anticoagulation therapy, BMI, and type of first unprovoked event. In a time-to-event analysis that included only data from patients while they were receiving the study drug, data were censored at the time of the first discontinuation of the study drug for 90 or more days without recommencement and excluded outcome events that occurred after discontinuation. In addition, we estimated the efficacy of aspirin in a fully adherent group by adjusting the treatment effect in the intention-to-treat analysis for the nonadherence rates averaged over the study period; the nonadherence rates were defined as the proportion of patients assigned to aspirin who discontinued it and the proportion of patients assigned to placebo who initiated antiplatelet or anticoagulation treatment.<sup>17</sup> We combined the results from the ASPIRE and WARFASA studies by performing a meta-analysis of the log hazard ratios for the treatment effect on vascular events from each study weighted by their inverse variances.<sup>18</sup> All analyses were performed with the use of SAS software, version 9.3 (SAS Institute).

## RESULTS

### PATIENTS

From May 2003 through August 2011, a total of 822 patients underwent randomization at 56 sites in five countries (Fig. S1 in the Supplementary Appendix). Twelve patients (6 in the placebo group and 6 in the aspirin group) who were enrolled after a diagnosis of first unprovoked proximal deep-vein thrombosis and who were included in the analysis were subsequently found to be ineligible after a review of the records: 8 (4 in each group) were found not to have had proximal deep-vein thrombosis, 2 (1 in each group) had a provoked venous thromboembolism, 1 in the placebo group had an indication for long-term anticoagu-

lation, and 1 in the aspirin group had had a prior unprovoked venous thromboembolism. The baseline characteristics of the patients did not differ significantly between the two groups (Table 1). A total of 447 patients enrolled in the ASPIRE study (54%) were men, the median age was 54 years, 36% had a BMI (the weight in kilograms divided by the square of the height in meters) of 30 or higher, 15% reported that a first-degree relative had had a venous thromboembolism, 5% had a prior provoked venous thromboembolism, and 2% had active cancer (with non-melanoma skin cancer not included) at the time of randomization. The index event was proximal deep-vein thrombosis alone in 57% of the patients, pulmonary embolism alone in 28%, and co-occurring deep-vein thrombosis and pulmonary embolism in 14%. A total of 73% of the patients had received anticoagulation therapy for at least 6 months before randomization. The median time between the cessation of anticoagulation therapy and random assignment in the ASPIRE study was 7 days in both groups. The median duration of follow-up was 37.2 months.

**RECURRENT VENOUS THROMBOEMBOLISM**

During the follow-up period, the primary outcome of recurrent venous thromboembolism occurred in 73 of 411 patients (18%) assigned to placebo and 57 of 411 (14%) assigned to aspirin (a rate of 6.5% per year vs. 4.8% per year; hazard ratio with aspirin, 0.74; 95% confidence interval [CI], 0.52 to 1.05; P=0.09) (Fig. 1A and Table 2). After adjustment for baseline characteristics, the hazard ratio was 0.72 (95% CI, 0.51 to 1.01; P=0.06) (Fig. S2 in the Supplementary Appendix). There were 132 episodes of nonfatal venous thromboembolism and 2 cases of fatal venous thromboembolism in 130 patients. One fatal pulmonary embolism occurred in each group. In 103 of the 134 cases (77%), the recurrent venous thromboembolism event was unprovoked. Most of the recurrent deep-vein thrombosis events without a concurrent pulmonary embolism occurred in patients who had been enrolled with a diagnosis of first unprovoked deep-vein thrombosis alone (70%, 57 of 82 events). Similarly, 73% of the recurrent pulmonary embolism events (35 of 48 events) — with or without concurrent deep-vein thrombosis — occurred in patients who were enrolled with a diagnosis of unprovoked pulmonary embolism (with or without deep-vein thrombosis). In 100 patients (58 in the placebo group and 42 in the aspirin group), venous

**Table 1. Baseline Characteristics of the Patients.\***

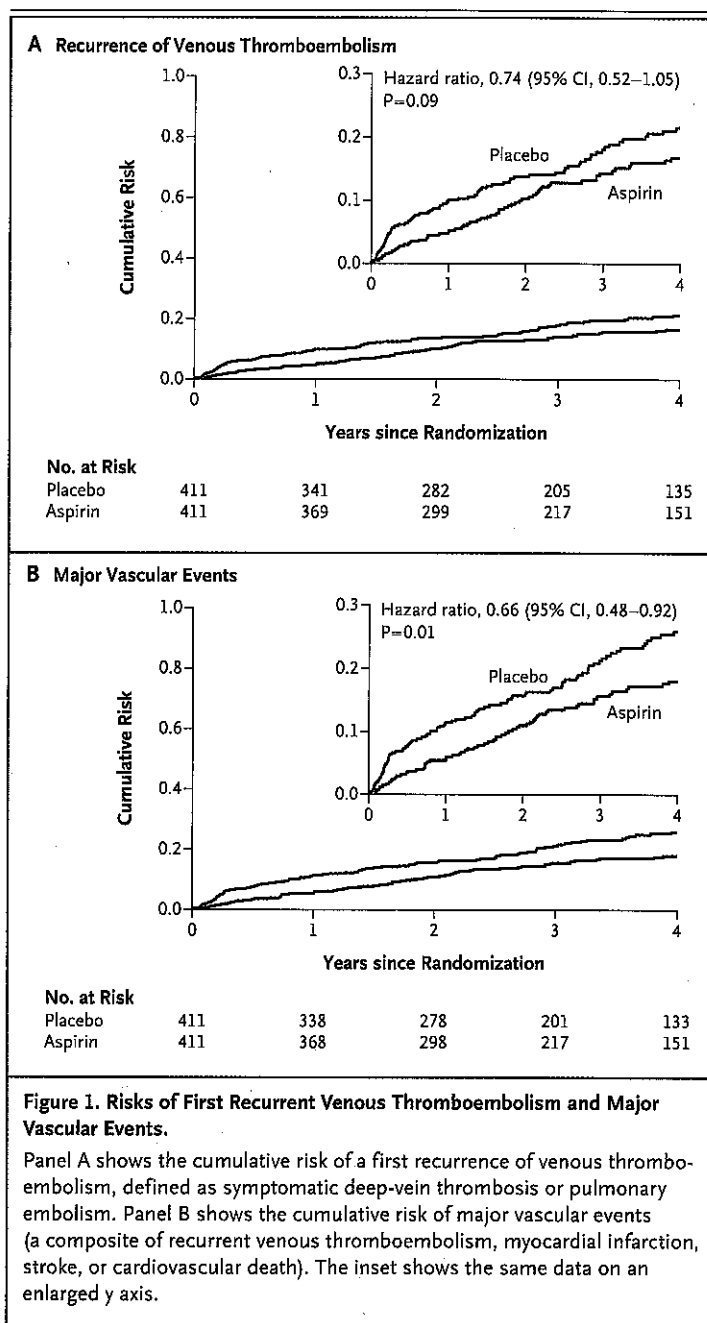
| Characteristic                                                             | Placebo (N=411) | Aspirin (N=411) |
|----------------------------------------------------------------------------|-----------------|-----------------|
| Age — yr                                                                   | 54±15.8         | 55±16.0         |
| Male sex — no. (%)                                                         | 221 (54)        | 226 (55)        |
| Body-mass index — no. (%)†                                                 |                 |                 |
| <30                                                                        | 271 (66)        | 249 (61)        |
| ≥30                                                                        | 140 (34)        | 160 (39)        |
| Index event — no. (%)                                                      |                 |                 |
| Proximal deep-vein thrombosis only                                         | 232 (56)        | 236 (57)        |
| Pulmonary embolism only                                                    | 119 (29)        | 112 (27)        |
| Both deep-vein thrombosis and pulmonary embolism                           | 56 (14)         | 59 (14)         |
| Duration of anticoagulation before randomization — no. (%)                 |                 |                 |
| <3 mo                                                                      | 4 (1)           | 5 (1)           |
| 3 to <6 mo                                                                 | 100 (24)        | 115 (28)        |
| 6 to <12 mo                                                                | 266 (65)        | 258 (63)        |
| ≥12 mo                                                                     | 41 (10)         | 33 (8)          |
| Time from completion of anticoagulation therapy to randomization — no. (%) |                 |                 |
| ≤1 day                                                                     | 150 (36)        | 151 (37)        |
| >1 to 7 days                                                               | 71 (17)         | 71 (17)         |
| >7 to 30 days                                                              | 102 (25)        | 86 (21)         |
| >30 days                                                                   | 88 (21)         | 103 (25)        |
| Immediate anticoagulation therapy — no. (%)                                |                 |                 |
| Low-molecular-weight heparin                                               | 360 (88)        | 351 (85)        |
| Unfractionated heparin                                                     | 26 (6)          | 26 (6)          |
| Other‡                                                                     | 25 (6)          | 34 (8)          |
| Subsequent anticoagulation therapy — no. (%)                               |                 |                 |
| Low-molecular-weight heparin                                               | 4 (1)           | 5 (1)           |
| Warfarin                                                                   | 341 (83)        | 343 (83)        |
| Other‡                                                                     | 66 (16)         | 63 (15)         |

\* Plus–minus values are means ±SD. None of these baseline characteristics differed significantly between the two groups.

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

‡ Other anticoagulant therapy included other vitamin K antagonists, direct thrombin inhibitors, and factor Xa inhibitors.

thromboembolism recurred for the first time while they were receiving the study drug or within 7 days after discontinuation of the study drug, whereas in 30 patients recurrences happened after discontinuation of the study drug. The analysis of data from patients while they were receiving the study drug showed a significant benefit with as-



pirin (event rate of 7.6% per year with placebo vs. 4.8% per year with aspirin; hazard ratio, 0.65; 95% CI, 0.44 to 0.96; P=0.03). The risk of a recurrence of venous thromboembolism was higher during the first year of follow-up (10.6% with placebo and 4.9% with aspirin) than in subsequent years (Fig. 1A). The treatment effects were similar within prespecified subgroups (Fig. S3 in the Supplementary Appendix).

**SECONDARY OUTCOMES AND BLEEDING EVENTS**

The secondary outcome of major vascular events (a composite of venous thromboembolism, myocardial infarction, stroke, or cardiovascular death) occurred in 88 patients assigned to placebo and 62 assigned to aspirin (a rate of 8.0% per year vs. 5.2% per year; hazard ratio with aspirin, 0.66; 95% CI, 0.48 to 0.92; P=0.01) (Fig. 1B). Clinically relevant bleeding occurred in 8 patients assigned to placebo (6 of whom had an episode of major bleeding) and 14 assigned to aspirin (8 of whom had an episode of major bleeding). In 2 patients, both in the placebo group, the major bleeding was fatal. The rates of all bleeding episodes did not differ significantly between the study groups. The analysis of net clinical benefit, defined as a reduction in the rate of the composite of venous thromboembolism, myocardial infarction, stroke, major bleeding, or death from any cause, showed that aspirin was associated with a reduction of 33% in that composite outcome, with an event rate of 9.0% per year in the placebo group as compared with 6.0% per year in the aspirin group (hazard ratio with aspirin, 0.67; 95% CI, 0.49 to 0.91; P=0.01).

**ADVERSE EVENTS AND DISCONTINUATION OF STUDY DRUG**

Adverse events leading to hospitalization occurred in 117 patients (28%) assigned to placebo and in 102 patients (25%) assigned to aspirin (Table S1 in the Supplementary Appendix). During the follow-up period, 132 patients assigned to placebo and 117 patients assigned to aspirin discontinued the study drug (a rate of 15.1% per year vs. 11.9% per year; hazard ratio with aspirin, 0.79; 95% CI, 0.62 to 1.01; P=0.06) (data not shown). More patients in the placebo group than in the aspirin group (32 vs. 21) discontinued the study drug because of an indication for thromboprophylaxis, whereas more patients in the aspirin group than in the placebo group (14 vs. 2) discontinued the study drug owing to gastrointestinal adverse effects or bleeding (Table S2 in the Supplementary Appendix). The median length of time that patients received a study drug was 27.2 months, and the median total follow-up time was 37.2 months. A total of 68 patients assigned to placebo and 54 assigned to aspirin initiated open-label antiplatelet therapy or anticoagulation therapy before a defined vascular event occurred. The times to permanent discontinuation of the study drug and commence-

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

| Outcome                                                              | Placebo (N=411) |            | Aspirin (N=411) |            | Hazard Ratio with Aspirin (95% CI) | P Value |
|----------------------------------------------------------------------|-----------------|------------|-----------------|------------|------------------------------------|---------|
|                                                                      | no. of events   | % per year | no. of events   | % per year |                                    |         |
| Recurrent venous thromboembolism†                                    | 73              | 6.5        | 57              | 4.8        | 0.74 (0.52–1.05)                   | 0.09    |
| Deep-vein thrombosis only                                            | 43              | 3.8        | 39              | 3.3        | 0.86 (0.56–1.33)                   | 0.50    |
| Distal                                                               | 14              |            | 11              |            |                                    |         |
| Proximal                                                             | 38              |            | 30              |            |                                    |         |
| Other site                                                           | 2               |            | 3               |            |                                    |         |
| Pulmonary embolism with or without deep-vein thrombosis              | 30              | 2.7        | 18              | 1.5        | 0.57 (0.32–1.02)                   | 0.06    |
| Major vascular event‡                                                | 88              | 8.0        | 62              | 5.2        | 0.66 (0.48–0.92)                   | 0.01    |
| Myocardial infarction                                                | 6               |            | 2               |            |                                    |         |
| Stroke                                                               | 5               |            | 4               |            |                                    |         |
| Cardiovascular death                                                 | 8               |            | 4               |            |                                    |         |
| Bleeding                                                             | 8               | 0.6        | 14              | 1.1        | 1.73 (0.72–4.11)                   | 0.22    |
| Major                                                                | 6               |            | 8               |            |                                    |         |
| Clinically relevant nonmajor                                         | 2               |            | 6               |            |                                    |         |
| Major vascular event, major bleeding, or death from any cause        | 99              | 9.0        | 71              | 6.0        | 0.67 (0.49–0.91)                   | 0.01    |
| Death from any cause                                                 | 18              |            | 16              |            |                                    |         |
| Pulmonary embolism                                                   | 1               |            | 1               |            |                                    |         |
| Myocardial infarction                                                | 2               |            | 2               |            |                                    |         |
| Other cardiovascular cause including sudden death of uncertain cause | 5               |            | 1               |            |                                    |         |
| Cancer                                                               | 4               |            | 6               |            |                                    |         |
| Bleeding                                                             | 2               |            | 0               |            |                                    |         |
| Other noncardiovascular cause                                        | 4               |            | 6               |            |                                    |         |

\* Only the first event for each patient is counted in each row; the event rate was averaged over the study period (median, 37.2 months).

† The event rate for venous thromboembolism in the first year was 10.6% with placebo, as compared with 4.9% with aspirin.

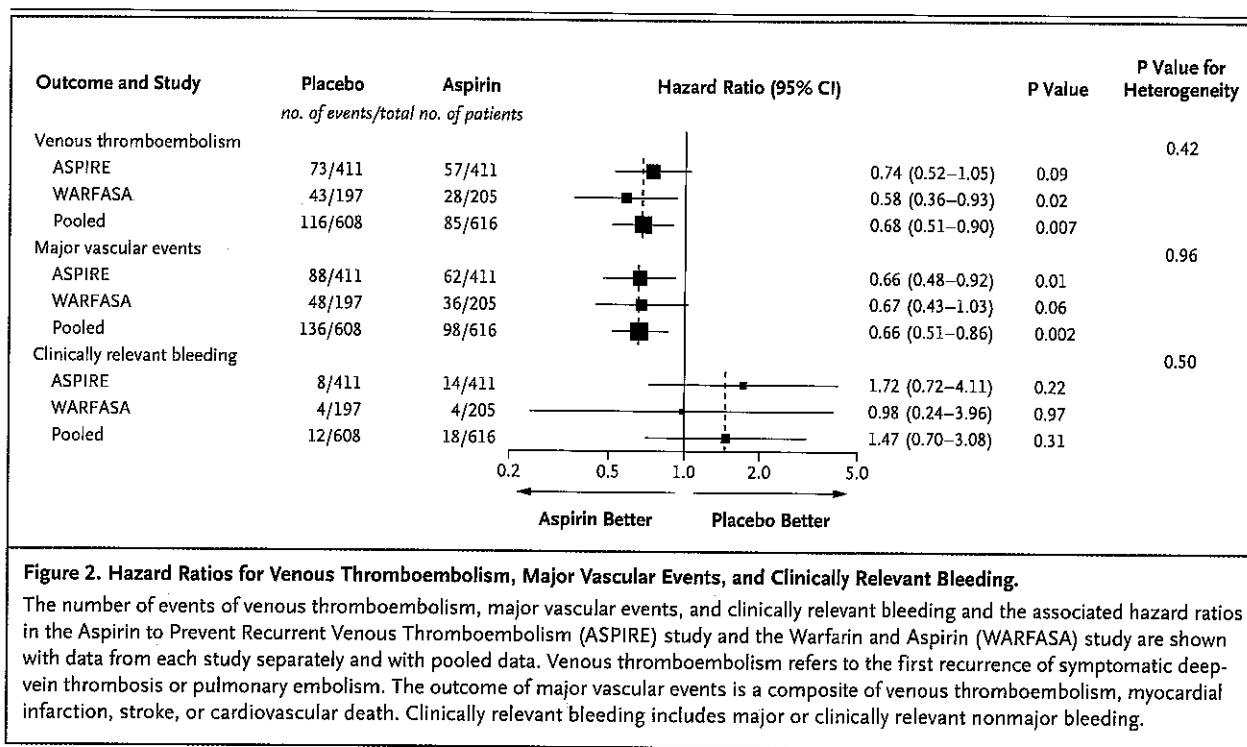
‡ The outcome of major vascular events was a composite of recurrent venous thromboembolism, myocardial infarction, stroke, or cardiovascular death.

ment of antiplatelet or anticoagulant medications are shown in Figure S4 in the Supplementary Appendix. The combined rate of nonadherence to the study drug in the placebo and aspirin groups, averaged over the study period, was 22%: 15% in the aspirin group discontinued the study drug and 7% in the placebo group initiated antiplatelet or anticoagulation treatment (data not shown). The risk reduction with aspirin after adjustment of the intention-to-treat estimate for this nonadherence rate was 33%, as compared with the unadjusted intention-to-treat estimate of risk reduction of 26%.

## DISCUSSION

Although the results of the ASPIRE trial did not show a significant reduction in the primary outcome of recurrent venous thromboembolism with aspirin as compared with placebo in patients who had had a first unprovoked venous thromboembolism, it did show that aspirin reduced the secondary composite outcome of major vascular events by 34% without increasing bleeding and resulted in a significant net clinical benefit. Furthermore, the estimated reduction of 26% (95% CI, -5 to 48) in the rate of recurrence of venous





**Figure 2. Hazard Ratios for Venous Thromboembolism, Major Vascular Events, and Clinically Relevant Bleeding.**

The number of events of venous thromboembolism, major vascular events, and clinically relevant bleeding and the associated hazard ratios in the Aspirin to Prevent Recurrent Venous Thromboembolism (ASPIRE) study and the Warfarin and Aspirin (WARFASA) study are shown with data from each study separately and with pooled data. Venous thromboembolism refers to the first recurrence of symptomatic deep-vein thrombosis or pulmonary embolism. The outcome of major vascular events is a composite of venous thromboembolism, myocardial infarction, stroke, or cardiovascular death. Clinically relevant bleeding includes major or clinically relevant nonmajor bleeding.

thromboembolism with aspirin is consistent with results from the recently reported WARFASA study,<sup>14</sup> which showed a reduction of 42% (95% CI, 7 to 64) in the rate of recurrence of venous thromboembolism.

With fewer patients recruited than originally planned, the ASPIRE trial by itself was not powered to show a significant reduction in the primary outcome, but when combined, as prospectively planned, with the WARFASA study (in which the patients had baseline characteristics that were similar to those of the ASPIRE patients),<sup>14</sup> a clear effect is evident. The combined results of the WARFASA and ASPIRE trials show a highly significant reduction of 32% in the rate of recurrence of venous thromboembolism ( $P=0.007$ ) and a reduction of 34% in the rate of major vascular events ( $P=0.002$ ), with no excess of bleeding (Fig. 2).

Owing to the relatively high rate of discontinuation of the study drug in the ASPIRE study, the estimated treatment effect is likely to have underestimated the potential benefit of aspirin therapy. The estimated effect in the ASPIRE study was 35% for patients while they were receiving aspirin, an estimate that is consistent with the intention-to-treat estimate in the ASPIRE study after adjustment for nonadherence and is also

consistent with the intention-to-treat estimate from the WARFASA trial.

For patients who discontinue anticoagulation, the risk of a late recurrence of venous thromboembolism after a first unprovoked event remains high: approximately 10% in the first year and 30% after 10 years.<sup>1-4</sup> Recurrent venous thromboembolism is associated with a case fatality rate of 5 to 10%<sup>4,19,20</sup> and a risk of post-thrombotic syndrome that is increased by a factor of 6.<sup>4,21,22</sup> Treatment with vitamin K antagonists prevents the recurrence of venous thromboembolism, but many patients are unwilling to accept extended therapy because of the risk of bleeding and the inconvenience.

In this context, aspirin, although substantially less effective than warfarin,<sup>5</sup> provides an attractive alternative because it is simple and inexpensive and its safety profile is well documented. Patients who have had a first unprovoked event of venous thromboembolism appear to be at greater risk for arterial thrombosis and cardiovascular death,<sup>15,16</sup> and an added appeal of aspirin is that it has been associated with an overall reduction in the risk of major thrombotic events (arterial and venous) and cardiovascular death. The ASPIRE study suggests that for every 1000 patients treated for 1 year, aspirin can be ex-

pected to be associated with 17 fewer episodes of recurrent venous thromboembolism and 28 fewer major thrombotic events, at the cost of 5 nonfatal bleeding episodes.

In conclusion, the findings of the ASPIRE study, especially when considered together with data from the WARFASA study, provide consistent evidence that low-dose aspirin is beneficial in preventing recurrent venous thromboembolism and major vascular events in patients who have had a first episode of unprovoked venous thromboembolism. Thus, aspirin is an attractive option for such patients once they have completed an initial course of anticoagulation therapy.

Supported by National Health and Medical Research Council (Australia), Health Research Council (New Zealand), Austral-

asian Society of Thrombosis and Hemostasis, National Heart Foundation of Australia, and Bayer HealthCare.

Dr. Brighton reports receiving consulting fees from Bayer HealthCare, Boehringer Ingelheim, Daiichi-Sankyo, Pfizer, Amgen Australia, and GlaxoSmithKline; Dr. Eikelboom, receiving consulting and lecture fees from Bayer, Boehringer Ingelheim, and Bristol-Myers Squibb and consulting fees from Corgenix, Daiichi-Sankyo, Eisai, Eli Lilly, McNeil, GlaxoSmithKline, Sanofi-Aventis, and Haemoscope; Dr. Gallus, serving on an advisory board for Bristol-Myers Squibb, Pfizer, Boehringer Ingelheim, and Bayer and receiving consulting fees from Bristol-Myers Squibb, Pfizer, Daiichi-Sankyo, and CSL Australia; Dr. Gibbs, receiving consulting and lecture fees from Boehringer Ingelheim and Bayer HealthCare and lecture fees from Covidien; and Dr. Xavier, receiving grant support from AstraZeneca, Boehringer Ingelheim, Cadila Pharmaceuticals, GlaxoSmithKline, Sanofi-Aventis, Pfizer, and Bristol-Myers Squibb. No other potential conflict of interest relevant to this article was reported.

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

We thank the staff and the patients at many hospitals for their trust and enthusiastic support of the ASPIRE study.

#### REFERENCES

- Prandoni P, Lensing AWA, Cogo A, et al. The long term clinical course of acute deep venous thrombosis. *Ann Intern Med* 1996;125:1-7.
- Heit JA, Mohr DN, Silverstein MD, et al. Predictors of recurrence after deep vein thrombosis and pulmonary embolism. *Arch Intern Med* 2000;160:761-8.
- Couturaud F, Kearon C. Long-term treatment for venous thromboembolism. *Curr Opin Hematol* 2000;7:302-8.
- Rodger M, Carrier M, Gandara E, Le Gal G. Unprovoked venous thromboembolism: short term or indefinite anticoagulation? Balancing long-term risk and benefit. *Blood Rev* 2010;24:171-8.
- Kearon C, Akl E, Comerota AJ, et al. Antithrombotic therapy for VTE: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed.: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141:Suppl:e419S-e494S.
- Schulman S, Granqvist S, Holmstrom M, et al. The duration of oral anticoagulant therapy after a second episode of venous thromboembolism. *N Engl J Med* 1997;336:393-8.
- Kearon C, Gent M, Hirsh J, et al. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. *N Engl J Med* 1999;340:901-7. [Erratum, *N Engl J Med* 1999;341:298.]
- Agnelli G, Prandoni P, Santamaria MG, et al. Three months versus one year of oral anticoagulant therapy for idiopathic deep vein thrombosis. *N Engl J Med* 2001;345:165-9.
- Agnelli G, Prandoni P, Becattini C, et al. Extended oral anticoagulant therapy after a first episode of pulmonary embolism. *Ann Intern Med* 2003;139:19-25.
- Linkins L-A, Choi PT, Douketis JD. Clinical impact of bleeding in patients taking oral anticoagulant therapy for venous thromboembolism: a meta-analysis. *Ann Intern Med* 2003;139:893-900.
- Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy — III: reduction in venous thrombosis and pulmonary embolism by antiplatelet prophylaxis among surgical and medical patients. *BMJ* 1994;308:235-46.
- Pulmonary Embolism Prevention (PEP) Trial Collaborative Group. Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) trial. *Lancet* 2000;355:1295-302.
- Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high-risk patients. *BMJ* 2002;324:71-86. [Erratum, *BMJ* 2002;324:141.]
- Becattini C, Agnelli GA, Schenone A, et al. Aspirin for preventing the recurrence of venous thromboembolism. *N Engl J Med* 2012;366:1959-67.
- Prandoni P, Belora F, Marchiori A, et al. An association between atherosclerosis and venous thrombosis. *N Engl J Med* 2003;348:1435-41.
- Becattini C, Vedovati CM, Ageno W, Dentali F, Agnelli G. Incidence of arterial cardiovascular events after venous thromboembolism: a systematic review and a meta-analysis. *J Thromb Haemost* 2010;8:891-7.
- Simes J, Voysey M, O'Connell R, et al. A novel method to adjust efficacy estimates for uptake of other active treatments in long-term clinical trials. *PLoS One* 2010;5(1):e8580.
- Egger M, Smith GD, Altman DG. Systematic reviews in health care: meta-analysis in context. 2nd ed. London: BMJ Publishing Group, 2001.
- Douketis JD, Kearon C, Bates S, Duku EK, Ginsberg JS. Risk of fatal pulmonary embolism in patients with treated venous thromboembolism. *JAMA* 1998;279:458-62.
- Carrier M, Le Gal G, Wells PS, Rodger MA. Systematic review: case-fatality rates of recurrent venous thromboembolism and major bleeding events among patients treated for venous thromboembolism. *Ann Intern Med* 2010;152:578-89.
- Mohr DN, Silverstein MD, Heit JA, Petterson TM, O'Fallon WM, Melton LJ. The venous stasis syndrome after deep vein thrombosis or pulmonary embolism: a population-based study. *Mayo Clin Proc* 2000;75:1249-56.
- Kahn SR, Schrier I, Julian JA. Determinants and time course of the post-thrombotic syndrome after acute deep venous thrombosis. *Ann Intern Med* 2008;149:698-707.

Copyright © 2012 Massachusetts Medical Society.



