Six Months vs Extended Oral Anticoagulation After a First Episode of Pulmonary Embolism
The PADIS-PE Randomized Clinical Trial

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IMPORTANCE The optimal duration of anticoagulation after a first episode of unprovoked pulmonary embolism is uncertain.

OBJECTIVES To determine the benefits and harms of an additional 18-month treatment with warfarin vs placebo, after an initial 6-month nonrandomized treatment period on a vitamin K antagonist.

DESIGN, SETTING, AND PARTICIPANTS Randomized, double-blind trial (treatment period, 18 months; median follow-up, 24 months); 371 adult patients who had experienced a first episode of symptomatic unprovoked pulmonary embolism (ie, with no major risk factor for thrombosis) and had been treated initially for 6 uninterrupted months with a vitamin K antagonist were randomized and followed up between July 2007 and September 2014 in 14 French centers.

INTERVENTIONS Warfarin or placebo for 18 months.

MAIN OUTCOMES AND MEASURES The primary outcome was the composite of recurrent venous thromboembolism or major bleeding at 18 months after randomization. Secondary outcomes were the composite at 42 months (treatment period plus 24-month follow-up), as well as each component of the composite, and death unrelated to pulmonary embolism or major bleeding, at 18 and 42 months.

RESULTS After randomization, 4 patients were lost to follow-up, all after month 18, and 1 withdrew due to an adverse event. During the 18-month treatment period, the primary outcome occurred in 6 of 184 patients (3.3%) in the warfarin group and in 25 of 187 (13.5%) in the placebo group (hazard ratio [HR], 0.22; 95% CI, 0.09-0.55; P = .001). Recurrent venous thromboembolism occurred in 3 patients in the warfarin group and 25 patients in the placebo group (HR, 0.15; 95% CI, 0.05-0.43); major bleeding occurred in 4 patients in the warfarin group and in 1 patient in the placebo group (HR, 3.96; 95% CI, 0.44 to 35.89). During the 42-month entire study period (including the study treatment and follow-up periods), the composite outcome occurred in 33 patients (20.8%) in the warfarin group and in 42 (24.0%) in the placebo group (HR, 0.75; 95% CI, 0.47-1.18). Rates of recurrent venous thromboembolism, major bleeding, and unrelated death did not differ between groups.

CONCLUSIONS AND RELEVANCE Among patients with a first episode of unprovoked pulmonary embolism who received 6 months of anticoagulant treatment, an additional 18 months of treatment with warfarin reduced the composite outcome of recurrent venous thrombosis and major bleeding compared with placebo. However, benefit was not maintained after discontinuation of anticoagulation therapy.

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Group Information: Members of the Prolongation d’un traitement par Antivitamine K pendant Dix-huit mois vs placebo au décours d’un premier épisode d’embolie pulmonaire Idiopathique traité Six mois (PADIS-PE) Study Group are listed at the end of this article.

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When anticoagulant therapy is stopped after 3 to 6 months of treatment, patients with a first episode of unprovoked venous thromboembolism have a much higher risk of recurrence than those with venous thromboembolism provoked by a transient risk factor (eg, surgery).\(^1\)\(^-\)\(^6\) In this high-risk population, extending anticoagulation beyond 3 to 6 months is associated with a reduction in the risk of recurrence as long as treatment is continued.\(^4\)\(^-\)\(^7\) However, whether this benefit is maintained thereafter remains uncertain because most previous studies did not include follow-up of patients after discontinuation of treatment.\(^2\)\(^,\)\(^3\)\(^,\)\(^7\)\(^-\)\(^13\)

Among studies assessing extended duration of anticoagulation for secondary prophylaxis after unprovoked venous thromboembolism, only one specifically enrolled patients with a first unprovoked pulmonary embolism.\(^9\) Because the case-fatality rate of recurrent venous thromboembolism is approximately 4-fold higher after pulmonary embolism than after proximal deep-vein thrombosis,\(^14\)\(^,\)\(^15\) the benefit-risk ratio of extended anticoagulation is likely to differ between these 2 types of events, and thus should be evaluated separately.

We therefore conducted a multicenter, randomized, double-blind, parallel-group trial involving patients with a first episode of unprovoked pulmonary embolism who received an initial 6-month course of anticoagulant therapy. Our objectives were to assess the benefits and harms of an additional 18 months of treatment with warfarin vs placebo among patients who had completed a nonrandomized 6 months of treatment with a vitamin K antagonist. We also studied outcomes for 24 months after discontinuation of study treatments.

Methods

Ethical Review and Study Organization

The Prolonged Anticoagulation During Eighteen Months vs Placebo After Initial Six-month Treatment for a First Episode of Idiopathic Pulmonary Embolism (PADIS-PE) study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki, Good Clinical Practice, and relevant French regulations regarding ethics and data protection. The protocol and amendments were approved by a central independent ethics committee and written informed consent was obtained from all patients before randomization (see the Study Protocol in Supplement 1).

The study was supervised by an academic steering committee. An independent data and safety monitoring committee periodically reviewed study outcomes (recurrence, bleeding, and death). Its role was to recommend study discontinuation to the steering committee if it believed that patient safety was compromised.

Participants

Consecutive patients aged 18 years or older who experienced a first episode of symptomatic unprovoked pulmonary embolism and had been treated initially for 6 uninterrupted months (5.5-7 months) with a vitamin K antagonist (target international normalized ratio [INR], 2.0-3.0; mean percentage of time spent within the therapeutic range: 69.1% allocated to warfarin and 67.8% to placebo) were potentially eligible. Unprovoked pulmonary embolism was defined as objectively confirmed symptomatic pulmonary embolism occurring in the absence of any major reversible risk factor for venous thromboembolism within 3 months before diagnosis, including surgery with locoregional or general anesthesia lasting more than 30 minutes, trauma with or without plaster cast of the lower limbs, and bed rest for more than 72 hours and in the absence of active cancer or cancer resolved within the 2 years prior to diagnosis.\(^2\)\(^-\)\(^7\) Objective tests confirming the index pulmonary embolism were ventilation-perfusion lung scanning and spiral computerized tomography angiography.

The main exclusion criteria were previously confirmed pulmonary embolism or proximal deep-vein thrombosis, recurrent venous thromboembolism, or bleeding during the initial 6-month anticoagulation, known major thrombophilia, indication for vitamin K antagonist therapy for reasons other than venous thromboembolism, increased bleeding risk, platelet count below 100 × 10\(^9\)/µL, major surgery planned within 18 months from randomization, and life expectancy less than 18 months (for the full list, see the “Inclusion criteria” and “Exclusion criteria” of the Study Protocol in Supplements 1 and 2).

All participants were ambulatory patients who had been enrolled at 1 of 14 French hospitals from July 13, 2007, to March 15, 2012. The last visit was September 30, 2014.

Randomization, Masking, and Interventions

Patients were randomized to receive either warfarin (target INR, 2.0-3.0) or placebo (target sham INR, 2.0-3.0) for 18 months using a central computerized Internet-based system. Using a computer algorithm, an independent statistician (ClinInfo SA) generated the assignment list in randomly permuted blocks of 4 or 6, with stratification by center. Before the first patient was enrolled, this list was forwarded to a central anticoagulation clinic not involved in patient care.

Patients were provided with consecutively numbered supplies of the study drug containing either warfarin tablets of 2 mg and 5 mg or identical-looking placebo (packaged at the sponsor’s central pharmacy). At day 0 (date of randomization), all patients underwent laboratory testing (including D-dimer measurement), leg ultrasound examination, ventilation-perfusion lung scanning, and echocardiography. Screening for thrombophilia was performed at the time of statistical analysis from centralized frozen blood samples taken at day 0.

After written informed consent had been obtained, all INRs and changes in vitamin K antagonist dose recorded during the initial 6 months of therapy (before randomization) were collected from local laboratories and sent to the anticoagulation clinic, which established individual patient profiles. The aim was to build plausible predefined scenarios for each patient to allow subsequent management of sham INR for those assigned to receive placebo. Study INRs were determined at each patient’s usual local laboratory and were sent directly to the anticoagulation clinic. Patients and investigators remained unaware of the local results to maintain double-blind conditions. For patients assigned to receive
Duration of Oral Anticoagulation After PE

Sample Size and Statistical Methods

The trial was designed to establish superiority of warfarin over placebo in preventing the composite primary outcome while patients were receiving the 18-month study treatment. Based on previous studies,

Outcome Measures

The primary outcome was the composite of symptomatic recurrent venous thromboembolism (including objectively confirmed nonfatal symptomatic pulmonary embolism or proximal deep-vein thrombosis or fatal venous thromboembolism) and nonfatal or fatal major bleeding up to 18 months. This composite outcome and its components were also assessed during the entire study period (ie, up to 42 months). Other secondary outcomes were death unrelated to pulmonary embolism or major bleeding during the 18-month treatment period and 42-month study period. Secondary outcomes were specified in the statistical analysis plan (see the Outcomes sections in Supplements 2 and 3) after the protocol was finalized but before the database was locked and any data were analyzed. The choice of the composite outcome to evaluate the net clinical benefit of warfarin was based on the results of studies showing that case-fatality rates of recurrent venous thromboembolism and major bleeding were similar.

Symptomatic recurrent deep-vein thrombosis or pulmonary embolism was diagnosed if clinical suspicion was objectively confirmed by ultrasonography, ventilation-perfusion lung scanning, spiral computerized tomographic angiography, pulmonary angiography, or autopsy, in the event of a sudden death for which no other cause could be identified. Bleeding was considered major if it was fatal, involved a critical organ, or was overt and associated with a decrease in hemoglobin level of 2 g/dL or more, or required transfusion of at least 2 units of packed red cells (Supplements 1, 2, and 3). All outcomes were adjudicated blindly by an independent central critical events committee. The committee had full access to any relevant medical reports and images from objective tests to adjudicate suspected events notified by investigators or detected during routine site monitoring. All images from ventilation-perfusion lung scanning, spiral computerized tomographic angiography, and ultrasonography were reviewed centrally by independent dedicated panels.

Results

Of the 374 enrolled patients, 3 withdrew consent and vetoed inclusion of their data in the analysis, leaving 184 patients randomized to warfarin and 187 to placebo (371 in total). Of these, 363 (97.8%) attended the 18-month visit; 283 (76.3%), the 42-month visit. Four patients (1.1%) who ended participation were lost to follow-up after month 18 (Figure 1 and eTable 1 in Supplement). Median follow-up was 23.4 months (interquartile range [IQR], 21.5-23.9) after the treatment period, and 41.0 months (IQR, 39.0-41.5) overall. Baseline characteristics were

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well balanced between the 2 groups, except that more women were assigned to warfarin than were men (Table 1).

**Treatment and INR Evaluation**

Median study treatment duration was 17.5 months in the warfarin group and 17.4 months in the placebo group. Double-blind treatment was permanently discontinued for 38 warfarin-treated patients (none presented recurrent venous thromboembolism, 3 had major bleeding, and 35 discontinued for other reasons) and for 49 placebo-treated patients who discontinued treatment (22 manifested confirmed recurrent venous thromboembolism, none experienced major bleeding, 1 withdrew consent, and 26 discontinued for other reasons). Of the 35 warfarin-treated patients who discontinued for reasons other than major bleeding, 13 continued to receive anticoagulant therapy; of
the 26 placebo-treated patients who discontinued for other reasons, 14 started anticoagulant therapy. In the warfarin group, the INR was within the therapeutic range (2.0-3.0) for 69.8% of the time; 18% of the time, below; and 11.9% of the time, above this range; corresponding figures for sham INR in the placebo group were 75.1% of the time between 2.0 and 3.0; 12.6%, below 2.0; and 12.3%, above 3.0 (eTable 2 in Supplement 2). The mean interval between INR measurements was 19.6 days for the warfarin-treated patients and 23.5 days for the placebo-treated patients.

Clinical Outcomes During the Treatment Period
During the 18-month treatment period, the primary outcome occurred in 6 of 184 patients (3.3%) in the warfarin group (2.3 events per 100 person-years) and in 25 of 187 patients (13.5%) in the placebo group (10.6 events per 100 person-years), resulting in a relative risk reduction of 78% in favor of warfarin (hazard ratio [HR], 0.22; 95% CI, 0.09-0.55; P = .001) (Table 2). In the warfarin group, 3 patients (1.7%) had symptomatic recurrent venous thromboembolism (1.1 events per 100 person-years); all events were unprovoked and manifested after

Table 1. Baseline Characteristics of Study Participantsa

<table>
<thead>
<tr>
<th></th>
<th>Warfarin (n = 184)</th>
<th>Placebo (n = 187)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, mean (SD), y</strong></td>
<td>58.7 (17.9)</td>
<td>57.3 (17.4)</td>
</tr>
<tr>
<td>&gt;65 y, No. (%)</td>
<td>74 (40.2)</td>
<td>70 (37.4)</td>
</tr>
<tr>
<td><strong>Women, No. (%)</strong></td>
<td>106 (57.6)</td>
<td>84 (44.9)</td>
</tr>
<tr>
<td><strong>Body mass index, mean (SD)</strong></td>
<td>27.8 (5.9)</td>
<td>27.1 (5.1)</td>
</tr>
<tr>
<td>≥30, No. (%)</td>
<td>53 (28.8)</td>
<td>39 (20.9)</td>
</tr>
<tr>
<td><strong>Creatinine clearance category, mL/min, No. (%)b</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>≥30–&lt;50</td>
<td>16 (8.9)</td>
<td>7 (3.9)</td>
</tr>
<tr>
<td>≥50</td>
<td>164 (91.1)</td>
<td>173 (96.1)</td>
</tr>
<tr>
<td><strong>Medical conditions, No. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous cancerc</td>
<td>8 (4.3)</td>
<td>6 (3.2)</td>
</tr>
<tr>
<td>Previous distal deep-vein thrombosis or superficial-vein thrombosis</td>
<td>17 (9.2)</td>
<td>14 (7.5)</td>
</tr>
<tr>
<td>Chronic heart failure</td>
<td>4 (2.2)</td>
<td>9 (4.8)</td>
</tr>
<tr>
<td>Chronic respiratory failure</td>
<td>40 (21.7)</td>
<td>35 (18.7)</td>
</tr>
<tr>
<td><strong>Method used to diagnose the incident pulmonary embolism, No. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-probability ventilation/perfusion lung scanning</td>
<td>47 (25.5)</td>
<td>39 (20.9)</td>
</tr>
<tr>
<td>Spiral computed tomography angiography</td>
<td>137 (74.5)</td>
<td>148 (79.1)</td>
</tr>
<tr>
<td>** Associated proximal deep-vein thrombosis at diagnosis, No. (%)**</td>
<td>56 (31.1)</td>
<td>56 (31.6)</td>
</tr>
<tr>
<td><strong>Characteristics of pulmonary embolism at inclusion</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Residual perfusion defect ≥10% on lung scan, No. (%)</td>
<td>68 (37.6)</td>
<td>56 (30.8)</td>
</tr>
<tr>
<td>Residual deep-vein thrombosis, No. (%)</td>
<td>25 (13.7)</td>
<td>36 (19.7)</td>
</tr>
<tr>
<td>Systolic pulmonary arterial pressure, mean (SD), mm Hg</td>
<td>30.6 (8.2)</td>
<td>29.9 (8.2)</td>
</tr>
<tr>
<td>D-dimer level, mean (SD), ng/mLc</td>
<td>382.3 (555.9)</td>
<td>322 (336.4)</td>
</tr>
<tr>
<td><strong>Thrombophilia, No. (%)d</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor</td>
<td>46 (26.0)</td>
<td>35 (20.1)</td>
</tr>
<tr>
<td>Major</td>
<td>6 (3.4)</td>
<td>8 (4.6)</td>
</tr>
<tr>
<td><strong>Treatment of pulmonary embolism prior to randomization</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin, No. (%)</td>
<td>135 (73.4)</td>
<td>115 (61.5)</td>
</tr>
<tr>
<td>Fluindione, No. (%)</td>
<td>49 (26.6)</td>
<td>74 (39.6)</td>
</tr>
<tr>
<td>Acecoumarol, No. (%)</td>
<td>2 (1.1)</td>
<td>4 (2.1)</td>
</tr>
<tr>
<td>Duration of initial anticoagulation, mean (SD), mo</td>
<td>6.3 (0.5)</td>
<td>6.4 (0.5)</td>
</tr>
<tr>
<td>Percentage of time in therapeutic INR range, mean (SD)</td>
<td>69.1 (23.3)</td>
<td>67.8 (22.7)</td>
</tr>
<tr>
<td><strong>Use of compression stockings, No. (%)</strong></td>
<td>113 (61.7)</td>
<td>120 (64.2)</td>
</tr>
<tr>
<td><strong>Main concomitant treatments, No. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiplatelet agent</td>
<td>16 (8.7)</td>
<td>11 (5.9)</td>
</tr>
<tr>
<td>Statins</td>
<td>35 (19.0)</td>
<td>34 (18.2)</td>
</tr>
<tr>
<td><strong>ACCP bleeding risk at inclusion, No. (%)e</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (no risk factor)</td>
<td>39 (22.5)</td>
<td>45 (26.2)</td>
</tr>
<tr>
<td>Moderate (1 risk factor)</td>
<td>55 (31.8)</td>
<td>57 (33.1)</td>
</tr>
<tr>
<td>High (≥2 risk factor)</td>
<td>79 (45.7)</td>
<td>70 (40.7)</td>
</tr>
</tbody>
</table>

Abbreviation: INR, international normalized ratio.
Conversion factors: to convert D-dimer from μg/mL to nmol/L, multiply by 5.476.

a Denominators may be lower than 184 and 187 due to missing data for some variables. Baseline characteristics of the 2 groups were compared using the t test for quantitative variables and Fisher exact test for qualitative variables. Except for female sex (P = .02), none of the resulting P values was <.05.
b Creatinine clearance was estimated by the Cockcroft-Gault method.
c Cancer resolved more than 2 years before patient inclusion.
d D-dimer level was measured before randomization while patients were receiving vitamin K antagonist therapy.
e Screening for thrombophilia was performed at the time of statistical analysis from centralized frozen blood samples taken at day 0. Thrombophilia was defined as minor if patients had either heterozygous factor V Leiden or heterozygous G20210A prothrombin gene variant or elevated factor VIII (90th percentile). Thrombophilia was defined as major if patients had either antithrombin deficiency or anticardiolipin antibodies (99th percentile) or homozygous factor V Leiden or combined thrombophilia.
f The American College of Chest Physicians (ACCP) score was calculated at the time of the statistical analysis, using baseline patient characteristics. Definitions and references are provided on page 27 in Supplement 3.
warfarin discontinuation. In the placebo group, 25 patients (13.5%) had symptomatic recurrence (10.6 events per 100 person-years); 23 events (92%) were unprovoked and 1 occurred after placebo discontinuation. Major bleeding occurred in 4 patients in the warfarin group (1 epistaxis; 1 retroperitoneal; and 1 upper gastrointestinal bleed associated with hemoglobin decrease, transfusion, or both, all 3 of which occurred during the treatment period; and 1 intraocular bleed 1 month after warfarin discontinuation) and in 1 in the placebo group; none of these events was fatal (Table 2).

Clinical Outcomes After the Treatment Period
During follow-up after study treatment discontinuation, the composite outcome occurred in 27 warfarin-treated patients (17.7%; 10.0 events per 100 person-years) and in 17 placebo-treated patients (10.3%; 5.7 events per 100 person-years) (Table 2). In the warfarin group, symptomatic recurrent venous thromboembolism occurred in 25 patients (9.3 events per 100 person-years), all in the absence of anticoagulation; 17 events (68.0%) were unprovoked, and 4 were fatal. In the placebo group, symptomatic recurrence occurred in 14 patients (4.7 events per 100 person-years, all in the absence of anticoagulation; 10 events (71.4%) were unprovoked, and none were fatal. Major bleeding occurred in 2 patients in the warfarin group (1 nonfatal event while taking warfarin, and 1 fatal event after discontinuation of warfarin), and in 4 in the placebo group (all nonfatal; 2 while patients were receiving warfarin for recurrence).

Clinical Outcomes During the Entire Study Period
Overall, the composite outcome occurred in 33 patients (20.8%) treated with warfarin (6.7 events per 100 person-years) and in 42 patients (24.0%) treated with placebo (8.9 events per 100 person-years), resulting in a nonsignificant difference (HR, 0.75; 95% CI, 0.47-1.18) (Table 2, Figure 2). Figure 3 shows the time course of recurrent venous thromboembolism and major bleeding.
ing. Sites of major bleeding and causes of death are presented in eTables 3 and 4 in Supplement 2. Results of pre-specified subgroup analyses on the composite outcome during the treatment and entire study periods were consistent with the overall treatment effect (eFigures 1A and 1B in Supplement 2).

**Discussion**

In this multicenter, randomized, double-blind study comparing an additional 18 months of anticoagulation with placebo for patients who had experienced a first episode of unprovoked pulmonary embolism and had received anticoagulant treatment for 6 months, we found a hazard ratio of 0.22 for the risk of the composite of recurrent venous thromboembolism and major bleeding in favor of additional therapy during 18 months. This result was driven by a reduction in the risk of recurrent venous thromboembolism, the risk of bleeding increasing to a minimal extent. However, this benefit of anticoagulation was lost after anticoagulation was discontinued.

Consistently with previous studies evaluating substantially prolonged anticoagulation for secondary prophylaxis after a first episode of unprovoked venous thromboembolism, we observed a high absolute rate of recurrent venous thromboembolism in the placebo group during the 18-month treatment period, with a hazard ratio of 0.15 for risk of such events with warfarin. As previously described, the risk of recurrence in the placebo group was greatest during the first 6 months after discontinuing anticoagulation and then increased linearly by 4% to 5% per year, whereas the risk of major bleeding during treatment with warfarin was low, increasing linearly by less than 2% per year. During the median 24-month posttreatment follow-up, the rate of recurrent venous thromboembolism in the warfarin group was about twice that in the placebo group and was close to that observed with placebo during the 18-month study treatment period. As in other contemporary randomized trials comparing vitamin K antagonists with other anticoagulant therapies, we observed a low risk of major bleeding, although in current practice this risk is likely to be higher. Because the risk of major bleeding during the study was low and similar in both groups, the benefit of extended anticoagulation on the composite outcome was lost at study end.

Previous studies have reported that when patients experience a recurrent episode of venous thromboembolism, it...
usually takes the same form as in their first event.7-9,14-15 We also observed this phenomenon in our study. Regardless of whether patients had been treated for 6 or 24 months, about 80% of recurrences comprised another episode of symptomatic pulmonary embolism, of which 8% (4 of 52 episodes) were fatal. Moreover, the vast majority of recurrences were unprovoked in both study groups (>80%), as in other studies.7-9 Thus, extending the length of secondary anticoagulation to 18 months did not modify the clinical presentation of recurrent venous thromboembolism. Most recurrences were unpreventable and represented the most severe form of venous thromboembolism.

We believe our findings are likely to be valid because (1) we used a double-blind, randomized design in a carefully predefined and characterized population; (2) we achieved complete enrollment of the planned sample size with minimal losses to follow-up; (3) there was close adherence to the study protocol during the treatment period and subsequent follow-up; (4) all patients were followed up for a very long period after anticoagulant therapy was discontinued; and (5) all outcomes were reviewed and validated blindly by an independent centralized adjudication committee.

Our study has the following limitations. First, the primary outcome included 2 different outcome measures that may not be clinically equivalent, although each has a high and similar case-fatality rate.14,16 Second, the study required 7 years for completion, probably reflecting its design and patient reluctance to participate in a 42-month follow-up. Third, the characteristics of patients who declined to participate were unavailable. Fourth, we did not use D-dimer levels to guide therapy, but this strategy was not recommended when we designed the study and is still considered investigational.29,30

Fifth, we evaluated warfarin but did not include newer oral anticoagulants or aspirin. New anticoagulants seem to be as effective as warfarin with a lower bleeding risk for the treatment of venous thromboembolism26-28,31 and with an attractive option for prolonged secondary prophylaxis.11-23,24 Aspirin for 2 to 4 years following vitamin K antagonist therapy reduced the risk of recurrence by about 30% compared with placebo,21,22 Although this 30% risk reduction may be viewed as small compared with the 80% to 90% usually reported with anticoagulation,27 and it is uncertain whether our results apply to newer anticoagulants, both aspirin and new anticoagulants may represent valuable alternatives to vitamin K antagonists or no treatment. Our results suggest that patients such as those who participated in our study require long-term secondary prophylaxis measures. Whether these should include systematic treatment with vitamin K antagonists, new anticoagulants or aspirin, or be tailored according to patient risk factors (including elevated D-dimer levels) needs further investigation.

Conclusions

Among patients with a first episode of unprovoked pulmonary embolism who received 6 months of anticoagulant treatment, an additional 18 months of treatment with warfarin reduced the composite outcome of recurrent venous thrombosis and major bleeding compared with placebo. However, benefit was not maintained after discontinuation of anticoagulation therapy.
from Bayer; fees for board memberships from Bayer, Bristol-Myers Squibb/Pfizer; and Daichi Sankyo. Dr Mottier reports having received research grants from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb/Pfizer, Daichi Sankyo, and Sanofi; and fees for the development of educational presentations from Bayer and Bristol-Myers Squibb/Pfizer. Dr Jego reports having received personal fees or nonfinancial support from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb/Pfizer, Daichi Sankyo, and Sanofi; and fees for the development of educational presentations from Bayer and Bristol-Myers Squibb/Pfizer. Dr Lorrilon reports having received personal fees from Astra Zeneca and Bayer and nonfinancial support from Pfizer, Novartis, Leo Pharma, Roche, and Actelion. Dr Girard reports having received personal fees and nonfinancial support from Bayer and Leo Pharma. Dr Laporte reports having received personal fees from Bayer-Health Care, Bristol-Myers Squibb, and Boehringer Ingelheim. Dr Laporte reports having received research grant support from Bayer and Sanofi and fees for board memberships or consultancy from Bayer, Boehringer Ingelheim, Leo Pharma, and Sanofi. Dr Leroyer reports having received research grant support from Pfizer and fees for board memberships or symposia from Bayer and Astra Zeneca; and travel support from Bayer, Daichi Sankyo, Leo Pharma, Internune, and Actelion. Dr Meyer reports having received research grant support from Bayer, Boehringer Ingelheim, Leo Pharma, and Sanofi; having served as an uncompensated board member and a consultant for Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb, Leo Pharma, and Pfizer; and receiving travel support from Bayer, Boehringer Ingelheim, Daichi Sankyo, Leo Pharma, and Sanofi. No other conflicts of interest relevant to this article were reported.

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REFERENCES


