Comparison of 3 and 6 Months of Oral Anticoagulant Therapy After a First Episode of Proximal Deep Vein Thrombosis or Pulmonary Embolism and Comparison of 6 and 12 Weeks of Therapy After Isolated Calf Deep Vein Thrombosis

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Background—The optimal duration of oral anticoagulant therapy after a first episode of venous thromboembolism remains controversial.

Methods and Results—We performed an open-label, randomized trial comparing a short oral anticoagulant course (3 months for proximal deep vein thrombosis [P-DVT] and/or pulmonary embolism [PE]; 6 weeks for isolated calf DVT [C-DVT]) with a long course of therapy (6 months for P-DVT/PE; 12 weeks for C-DVT). The outcome events were recurrences and major, minor, or fatal bleeding complications. A total of 736 patients were enrolled. There were 23 recurrences of venous thromboembolism in the short treatment group (6.4%) and 26 in the long treatment group (7.4%); the 2 treatment regimens had an equivalent effect. For the hemorrhage end point, the difference between the short and the long treatment groups was not significant: 15.5% versus 18.4% for all events (P=0.302), 1.7% versus 2.8% (P=0.291) for major events, and 13.9% versus 15.3% for minor bleeding. Subgroup analysis demonstrated that the rate of recurrence was lower for C-DVT than for P-DVT or PE.

Conclusions—After isolated C-DVT, 6 weeks of oral anticoagulation is sufficient. For P-DVT or PE, we demonstrated an equivalence between 3 and 6 months of anticoagulant therapy. For patients with temporary risk factors who have a low risk of recurrence, 3 months of treatment seems to be sufficient. For patients with idiopathic venous thromboembolism or permanent risk factors who have a high risk of recurrence, other trials are necessary to assess prolonged therapy beyond 6 months. (Circulation. 2001;103:2453-2460.)

Key Words: venous thrombosis | pulmonary embolism | anticoagulants

In the treatment of venous thromboembolism (VTE), heparin therapy and the moment at which to introduce oral anticoagulant therapy in the acute phase are well defined.1–3 The optimal duration of oral anticoagulant therapy after a first episode of VTE remains a matter of debate, and it is essential to balance the desired effect of the anticoagulants in reducing recurrence against the risk of iatrogenic bleeding complications.4,5

The annual cumulative incidence of recurrence ranges from 4% to 17% in prospective studies6–13 and from 4% to 8% in studies published since 1992.6–9 A recent trial14 showed a high recurrence (27%), but all patients included in that trial had idiopathic VTE and one-third of them had hypercoagulable states.

The estimation of the risk of hemorrhage must not be neglected in practice because major bleeding is a rare but severe event.4,15 The annual incidence of major hemorrhagic complications varies from 0.2% to 3% per patient-year.16,17 The incidence of minor hemorrhage is greater (6% to 14%). This bleeding risk is dependent on the duration of treatment, the intensity or variability of anticoagulation, the occurrence of drug interactions, treatment compliance, the patient’s age, and the presence of comorbid illness.15,18,19

A 6-week regimen of oral anticoagulant therapy is currently recommended for isolated calf deep vein thrombosis (C-DVT),20 and a 3- to 6-month treatment is recommended for proximal DVT (P-DVT) or for pulmonary embolism (PE).1–5,7 The existence of risk factors at the initial episode of thrombosis must be considered. Temporary (transient) risk factors include surgery, trauma, plaster for broken leg, puerperium, and immobilization for medical conditions; perma-
ent (continuous) risk factors include obesity, varicosity, heart failure, bedridden status, malignancy, and congenital or acquired thrombophilia. Idiopathic (spontaneous) VTE is defined as VTE that occurs in the absence of triggering risk factors or a family history of thrombosis. A short anticoagulant course is recommended for patients with temporary risk factors, and a long anticoagulant course is recommended for those with permanent risk factors or idiopathic VTE.

### Methods

The Durée Optimale du Traitement AntiVitamines K (DOTAVK) study was a open-label, randomized, controlled trial in parallel groups that compared different durations of anticoagulation in patients with a first episode of VTE. It was approved by the Lyons local ethics committee.

### Eligibility

Inclusion criteria were age >18 years, written informed consent, and symptomatic C-DVT (thrombus below popliteal vein), P-DVT, or PE that was confirmed by positive Doppler ultrasonography or venography (venography was indispensable if the upper extremity thrombus was not clearly seen by ultrasound methods). The diagnosis of PE was based on clinical, biological, ECG, or radiological criteria, and confirmation by perfusion-ventilation lung scanning was requested. Pulmonary angiography was required if the lung scan showed a low probability of PE or an absence of DVT on duplex scan or venography. More recently, thoracic helical computed tomography was used to diagnosis PE.

Exclusion criteria were pregnancy, breast feeding, previous VTE, vena cava filter implantation, surgical thrombectomy, free-floating thrombus in the inferior vena cava lumen, DVT or PE whose diagnosis did not fulfill the criteria described above, evolutive cancer or malignant hematological disease, known biological thrombophilia, severe PE (defined by an amputation of >50% of vascularization), PE treated by thrombolysis (considered a marker of severe PE), myocardopathy or other diseases justifying prolonged anticoagulation therapy, and liver insufficiency.

### Randomization and Study Treatment

Patients were sequentially randomized at the end of the heparin therapy using a centralized, computer-generated allocation schedule in blocks of 4; the schedule was stratified for C-DVT or P-DVT/PE.

Day 1 of the protocol was the first day when oral anticoagulants were used alone. All patients received fluindione, a vitamin K antagonist with a long half-life that is usually started in the first 5 days after beginning heparin therapy. During the acute phase of VTE, physicians were free to use either intravenous or subcutaneous unfractionated heparin or 1 or 2 daily injections of low-molecular-weight heparin. The recommended duration of heparin therapy was at least 5 days and until an anticoagulation value within the international normalized ratio (INR) target range had been achieved.

### TABLE 1. Patient Characteristics at Enrollment According to the Treatment Group

<table>
<thead>
<tr>
<th></th>
<th>Short TG (n=375)</th>
<th>Long TG (n=361)</th>
<th>Total (n=736)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>54.2±1</td>
<td>58.9±0.9</td>
<td>58.5±0.9</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>47.6</td>
<td>47.0</td>
<td>47.3</td>
</tr>
<tr>
<td>C-DVT, %</td>
<td>34.9</td>
<td>33.5</td>
<td>34.2</td>
</tr>
<tr>
<td>With PE</td>
<td>6.9</td>
<td>8.0</td>
<td>7.0</td>
</tr>
<tr>
<td>P-DVT, %</td>
<td>60.3</td>
<td>62.3</td>
<td>61.3</td>
</tr>
<tr>
<td>With PE</td>
<td>19.2</td>
<td>17.5</td>
<td>18.0</td>
</tr>
<tr>
<td>PE, * , %</td>
<td>30.9</td>
<td>29.6</td>
<td>30.0</td>
</tr>
<tr>
<td>Without DVT</td>
<td>4.8</td>
<td>4.2</td>
<td>4.5</td>
</tr>
<tr>
<td>Temporary risk factors, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least one</td>
<td>52.2</td>
<td>52.0</td>
<td>52.1</td>
</tr>
<tr>
<td>Surgery</td>
<td>12.5</td>
<td>11.9</td>
<td>12.2</td>
</tr>
<tr>
<td>Immobilization</td>
<td>16.6</td>
<td>14.7</td>
<td>15.7</td>
</tr>
<tr>
<td>Trauma, plaster for broken leg</td>
<td>15.5</td>
<td>15.6</td>
<td>15.6</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>13.6</td>
<td>15.0</td>
<td>14.3</td>
</tr>
<tr>
<td>Other (travel, infection, etc.)</td>
<td>9.2</td>
<td>8.8</td>
<td>9.0</td>
</tr>
<tr>
<td>Permanent risk factors, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least one</td>
<td>53.8</td>
<td>56.4</td>
<td>55.0</td>
</tr>
<tr>
<td>Venous insufficiency</td>
<td>28.3</td>
<td>32.6</td>
<td>30.4</td>
</tr>
<tr>
<td>Obesity†</td>
<td>31</td>
<td>33.1</td>
<td>32.0</td>
</tr>
<tr>
<td>Myocardial disease</td>
<td>4.1</td>
<td>6.0</td>
<td>5.0</td>
</tr>
<tr>
<td>Other (hemiplegia, etc.)</td>
<td>5.4</td>
<td>4.5</td>
<td>5.0</td>
</tr>
<tr>
<td>Idiopathic VTE, %</td>
<td>44.0</td>
<td>45.3</td>
<td>44.6</td>
</tr>
</tbody>
</table>

**Values are mean±SE or percentage of patients. TG indicates treatment group.**

*All episodes of PE were symptomatic.
†Obesity was defined as a body mass index >27 kg/m² for men and >26 kg/m² for women.

### TABLE 2. Patient Characteristics at Enrollment by Initial Site of Thrombosis and Treatment Group

<table>
<thead>
<tr>
<th></th>
<th>C-DVT</th>
<th>P-DVT or PE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;60 years</td>
<td>38.5</td>
<td>27.0</td>
</tr>
<tr>
<td>Family history of DVT/PE</td>
<td>19.2</td>
<td>25.8</td>
</tr>
<tr>
<td>Venous insufficiency</td>
<td>29.8</td>
<td>24.7</td>
</tr>
<tr>
<td>Oral contraceptive use</td>
<td>17.3</td>
<td>24.7</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>22.1</td>
<td>18.0</td>
</tr>
<tr>
<td>Obesity</td>
<td>35.6</td>
<td>29.2</td>
</tr>
<tr>
<td>Hypertension</td>
<td>19.2</td>
<td>12.4</td>
</tr>
<tr>
<td>Dislipidemia</td>
<td>15.5</td>
<td>10.1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>7.7</td>
<td>3.4</td>
</tr>
<tr>
<td>Surgery</td>
<td>10.6</td>
<td>15.7</td>
</tr>
<tr>
<td>Trauma or plaster</td>
<td>27.9</td>
<td>28.1</td>
</tr>
<tr>
<td>Temporary risk factor(s)</td>
<td>68.3</td>
<td>69.7</td>
</tr>
<tr>
<td>Permanent risk factor(s)</td>
<td>56.7</td>
<td>43.8</td>
</tr>
<tr>
<td>Idiopathic thrombosis</td>
<td>27.9</td>
<td>31.5</td>
</tr>
<tr>
<td>Received thrombolytic therapy</td>
<td>0</td>
<td>1.1</td>
</tr>
</tbody>
</table>

**Values are percentages. UFH indicates unfractionated heparin; LMWH, low-molecular-weight heparin.**

*Effective heparin therapy was defined as a therapeutic anti-Xa activity or activated cephaline time 24 hours after the start of heparin therapy.
For P-DVT, thrombolytic therapy could be given initially if indicated; for patients with DVT, graduated compression stockings were systematically recommended.

Oral anticoagulation was targeted to an INR of 2.0 to 3.0. INR determinations were repeated daily during the initiation of oral anticoagulants. When the dose of fluindione had been adjusted and heparin stopped, the recommended frequency of testing was 3 times weekly for the first week, twice weekly for the next 2 weeks, once weekly for the next 3 weeks, and subsequently every 2 weeks. The INR value had to be measured quickly if a bleeding complication occurred.

Follow-Up
A 15-month follow-up was requested to obtain a mean follow-up of 12 months for all patients after withdrawal of anticoagulants. Follow-up visits were scheduled at 1.5, 3, 6, and 15 months after randomization; during visits, the patients were asked about new symptoms of VTE and possible hemorrhage.

End Points
Recurrent VTE and hemorrhage (major, minor, or fatal) were the end points. An independent central adjudication committee blindly reviewed and validated each end point.

Hemorrhage was defined as major when it required hospitalization, transfusion, or treatment with blood products or vitamin K; when intracranial, intraocular, intraarticular, or retroperitoneal; and/or when the hemoglobin level fell by ≥20 g/L. It was defined as minor in all other cases. Recurrent thromboembolic events were objectively verified by the same methods as inclusion criteria. Recurrent DVT was defined as a thrombus in the other leg, another deep vein of the same leg, or in the same venous system with a proximal extension at least 5 cm above the original thrombus.

Statistical Analysis
The incidence of recurrent VTE (equivalence outcome) and of bleeding (difference outcome) was assessed by (1) univariate analysis that compared the long treatment regimen (6 months for P-DVT/PE; 12 weeks for isolated C-DVT) with the short regimen (3 months for P-DVT/PE; 6 weeks for C-DVT); (2) a predefined stratification analysis comparing patients with isolated C-DVT and those with P-DVT/PE; and (3) a predefined subgroup analysis with variables such as effective oral anticoagulation, management of heparin treatment before randomization, and risk factors at inclusion.

A χ² test or Fisher’s exact test was performed for dichotomous variables, and a Wilcoxon’s rank-sum test or t test was used for ordinal or quantitative variables. Analyses were performed using SAS software version 6.12 on a computer.

On the basis of published data, we assumed in 1992 a 10% per-year incidence of recurrence with an equivalence interval of 4.5% and an incidence of bleeding (major and minor) of 5% at 6 weeks, 10% at 12 weeks, and 17.5% at 24 weeks. Given these assumptions, at least 1500 patients needed to be included to demonstrate an equivalence for the recurrence end point, and 1800 patients were needed to show a difference for the hemorrhage end point (both with a 2-tailed test, an α risk of 0.05, and a β risk of 0.2). However, the study was interrupted after the enrollment of 736 patients over 5 years because the Steering Committee and the Independent Supervisory Committee, unaware of the results, decided that the slow recruitment rate was not compatible with its continuation.

### TABLE 3. Different Events and End Points After Follow-Up According to the Length of Oral Anticoagulant Therapy

<table>
<thead>
<tr>
<th></th>
<th>Short Treatment, n (%) (n = 375)</th>
<th>Long Treatment, n (%) (n = 361)</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lost to follow-up*</td>
<td>14 (3.7)</td>
<td>8 (2.2)</td>
<td></td>
</tr>
<tr>
<td>Recurrence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intention-to-treat analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with events</td>
<td>23 (6.4)</td>
<td>26 (7.4)</td>
<td>0.87 (0.50, 1.49)</td>
</tr>
<tr>
<td>DVT†</td>
<td>20 (5.5)</td>
<td>17 (4.8)</td>
<td>1.15 (0.61, 2.16)</td>
</tr>
<tr>
<td>And/or PE†</td>
<td>6 (1.7)</td>
<td>7 (2.0)</td>
<td>0.84 (0.28, 2.47)</td>
</tr>
<tr>
<td>VTE during treatment</td>
<td>2 (0.6)</td>
<td>7 (2.0)</td>
<td>0.28 (0.06, 1.34)</td>
</tr>
<tr>
<td>Per protocol analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with events</td>
<td>23 (7.1)</td>
<td>23 (7.6)</td>
<td>0.94 (0.54, 1.63)</td>
</tr>
<tr>
<td>DVT†</td>
<td>20 (6.2)</td>
<td>15 (5.0)</td>
<td>1.25 (0.65, 2.39)</td>
</tr>
<tr>
<td>And/or PE†</td>
<td>6 (1.9)</td>
<td>6 (2.0)</td>
<td>0.94 (0.31, 2.87)</td>
</tr>
<tr>
<td>VTE during treatment</td>
<td>2 (0.6)</td>
<td>6 (2.0)</td>
<td>0.31 (0.06, 1.53)</td>
</tr>
<tr>
<td>Hemorrhage‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>56 (15.5)</td>
<td>65 (18.4)</td>
<td>0.84 (0.61, 1.17)§</td>
</tr>
<tr>
<td>Major</td>
<td>6 (1.7)</td>
<td>10 (2.8)</td>
<td>0.59 (0.22, 1.60)</td>
</tr>
<tr>
<td>Minor</td>
<td>50 (13.9)</td>
<td>54 (15.3)</td>
<td>0.91 (0.63, 1.29)</td>
</tr>
<tr>
<td>Fatal</td>
<td>0</td>
<td>1 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>11 (3.1)</td>
<td>13 (3.7)</td>
<td>0.83 (0.38, 1.82)</td>
</tr>
<tr>
<td>Cancer</td>
<td>11 (3.1)</td>
<td>14 (4.0)</td>
<td>0.77 (0.35, 1.67)</td>
</tr>
</tbody>
</table>

Values for treatment groups are n (%). Percents are calculated from the number of assessed patients, with those lost to follow-up and those with missing data excluded.

*P = 0.2 between the 2 treatment groups.
†Recurrence occurring after the withdrawal of anticoagulants.
‡Intention-to-treat analysis.
§P = 0.3.
For the hemorrhage end point, statistical analysis was performed on an intention-to-treat basis, and for the recurrence end point, it was performed on an intention-to-treat basis and a per-protocol basis.

Results
Between September 1993 and June 1998 (follow-up was completed in September 1999), 736 patients were randomized.

The baseline characteristics in the 2 treatment groups were similar (Tables 1 and 2). The inclusion criteria were not respected for 4 patients. Four other patients were not randomized according to the correct level of their DVT. A total of 82 patients received oral anticoagulation for shorter or longer periods than scheduled for the following reasons: major or fatal hemorrhage (n=5), death (n=3), surgery (n=8), cancer or biological thrombophilia discovered during follow-up (n=34), recent atrial fibrillation (n=4), error or voluntary decision of the patients or the practitioners (n=27), and recurrence during treatment (n=1). There were 20 withdrawals (4 in the short and 16 in the long treatment group) and 62 prolongations of anticoagulant therapy (30 in the short and 32 in the long treatment group). These patients, in addition to those wrongly included (n=90), were not considered in the per-protocol analysis.

The results are shown in Table 3. A total of 24 patients died (3.4%), and 22 dropped out (3%). Cancer was discovered in 25 patients (3.6%).

For recurrent VTE, we observed equivalence between the 2 treatment groups in both the intention-to-treat and per-protocol analyses (risk difference was, respectively, −1.0% and −0.5% in favor of the short duration; 95% CI, respectively, was −4.7 to 2.7 and −4.6 to 3.6). None of the recurrent thromboembolic events were fatal. Among the 49 recurrent events, 9 occurred in patients during treatment; these included bilateral DVT (n=1), ipsilateral DVT (n=3), contralateral DVT (n=1), and isolated PE (n=4). Cancer also occurred in 4 of these patients. The remaining 40 thromboembolic events occurred after the withdrawal of anticoagulants and were distributed between PE (n=13; 3 isolated PE, 6 with ipsilateral DVT, and 4 with contralateral DVT) and isolated DVT (n=27; 16 ipsilateral, 8 contralateral, and 3 bilateral). The cumulative incidence of recurrent thromboembolism for each assigned treatment group is shown in Figure 1.

Figure 1. Cumulative incidence of recurrent thromboembolism in all treatment groups. Numbers after names of treatment groups indicate duration of randomized treatment (weeks).

Figure 2. Cumulative incidence of hemorrhage in all treatment groups. The majority of minor bleeding was recorded during the follow-up visits, which explains the stepwise increase in the incidence of events at these different dates (1.5, 3, and 6 months). Numbers after names of treatment groups indicate duration of randomized treatment (weeks).
Regarding bleeding complications, there was no significant difference between the 2 treatment groups (Table 3). The one fatal hemorrhage was a massive hematemesis that occurred in a 64-year-old man who was not receiving excessive anticoagulation (INR 5 2.3). The major hemorrhages (n = 16) were gastrointestinal (n = 5), muscular or subcutaneous hematoma (n = 5), hematuria (n = 3), hemoptysis (n = 1), epistaxis (n = 1), and intracranial hematoma (n = 1). Nine of these patients were excessively anticoagulated (6 with INR >4.0; 3 with INR between 3.0 and 4.0). The cumulative incidence of bleeding is shown in Figure 2.

For both end points, a stratification analysis (Table 4) was performed for patients with isolated C-DVT and with P-DVT or PE (risk difference was, respectively, −1.4% and −0.6% in favor of the short duration; 95% CI was, respectively, −6.1 to 3.2 and −5.3 to 4.2). Overall, the recurrence rate was clearly lower for patients with C-DVT (2.6%) than it was for those with P-DVT or PE (8.4%).

A subgroup analysis revealed equivalence for the recurrence end point and no significant difference for the hemorrhage end point in each subgroup (Table 5). Patients with permanent risk factors, idiopathic VTE, or cancer had a significantly higher risk of recurrence. Those with temporary risk factors had a lower risk of recurrence. The quality of initial heparin therapy did not influence rates of recurrence or bleeding complications. To assess the efficacy of oral anticoagulant therapy, we determined the median INR in patients for whom several INR values were available (77% of patients; n = 564). The therapy was said to be effective when the median INR was ≥2.0 (n = 541) and ineffective when the median INR was <2.0 (n = 23). Treatment efficacy did not influence the incidence of the 2 end points. The quality of

### Table 4. Stratum Analysis of End Points After Follow-Up According to the Site of Thrombosis and the Length of Therapy

<table>
<thead>
<tr>
<th></th>
<th>Short Treatment, n (%)</th>
<th>Long Treatment, n (%)</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>C-DVT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Recurrence</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intention-to-treat analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with events</td>
<td>2 (2.0)</td>
<td>3 (3.4)</td>
<td>0.58 (0.10, 3.36)</td>
</tr>
<tr>
<td>DVT*</td>
<td>2 (2.0)</td>
<td>2 (2.3)</td>
<td>0.86 (0.12, 6.00)</td>
</tr>
<tr>
<td>Or PE*</td>
<td>0</td>
<td>1 (1.1)</td>
<td></td>
</tr>
<tr>
<td>Per-protocol analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with events</td>
<td>2 (2.0)</td>
<td>2 (2.6)</td>
<td>0.86 (0.12, 5.94)</td>
</tr>
<tr>
<td><strong>Hemorrhage</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>13 (12.8)</td>
<td>19 (21.6)</td>
<td>0.59 (0.31, 1.26)†</td>
</tr>
<tr>
<td>Major</td>
<td>1 (1.0)</td>
<td>3 (3.4)</td>
<td>0.29 (0.03, 2.72)</td>
</tr>
<tr>
<td>Minor</td>
<td>12 (11.8)</td>
<td>16 (18.2)</td>
<td>0.65 (0.32, 1.29)</td>
</tr>
<tr>
<td>Fatal</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>P-DVT and/or PE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Recurrence</strong></td>
<td></td>
<td></td>
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<tr>
<td>Intention-to-treat analysis</td>
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</tr>
<tr>
<td>Patients with events</td>
<td>21 (8.1)</td>
<td>23 (8.7)</td>
<td>0.93 (0.53, 1.65)</td>
</tr>
<tr>
<td>DVT*</td>
<td>18 (7.0)</td>
<td>15 (5.7)</td>
<td>1.23 (0.63, 2.38)</td>
</tr>
<tr>
<td>And/or PE*</td>
<td>6 (2.3)</td>
<td>6 (2.3)</td>
<td>1.02 (0.33, 3.13)</td>
</tr>
<tr>
<td>VTE during treatment</td>
<td>2 (0.8)</td>
<td>6 (2.3)</td>
<td>0.34 (0.07, 1.67)</td>
</tr>
<tr>
<td>Per-protocol analysis</td>
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<td></td>
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<tr>
<td>Patients with events</td>
<td>21 (9.0)</td>
<td>21 (9.3)</td>
<td>0.97 (0.54, 1.72)</td>
</tr>
<tr>
<td>DVT*</td>
<td>18 (7.7)</td>
<td>14 (6.2)</td>
<td>1.24 (0.63, 2.44)</td>
</tr>
<tr>
<td>And/or PE*</td>
<td>6 (2.6)</td>
<td>6 (2.7)</td>
<td>0.97 (0.32, 2.95)</td>
</tr>
<tr>
<td>VTE during treatment</td>
<td>2 (0.9)</td>
<td>5 (2.2)</td>
<td>0.39 (0.08, 1.97)</td>
</tr>
<tr>
<td><strong>Hemorrhage</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>43 (16.6)</td>
<td>46 (17.4)</td>
<td>0.96 (0.66, 1.40)‡</td>
</tr>
<tr>
<td>Major</td>
<td>5 (1.9)</td>
<td>7 (2.6)</td>
<td>0.73 (0.24, 2.27)</td>
</tr>
<tr>
<td>Minor</td>
<td>38 (14.7)</td>
<td>38 (14.3)</td>
<td>1.02 (0.68, 1.55)</td>
</tr>
<tr>
<td>Fatal</td>
<td>0</td>
<td>1 (0.4)</td>
<td></td>
</tr>
</tbody>
</table>

Values for treatment are n (%). Short treatment lasted 6 weeks for C-DVT and 3 months for P-DVT/PE; long treatment lasted 12 weeks for C-DVT and 6 months for P-DVT/PE.

*Recurrence occurring after the withdrawal of anticoagulants.

† P = 0.1; ‡ P = 0.8.
long-term anticoagulation was similar in the 2 treatment groups.

Discussion
The DOTAVK study is the first controlled trial in which patients with P-DVT and/or PE were randomly assigned to 3 or 6 months of secondary prophylaxis and in which P-DVT and C-DVT were separately assessed. We found equivalence between the 2 treatment regimens (long and short) for the recurrence outcome and no significant increase in bleeding complications in the long regimen, including patients with permanent risk factors or idiopathic VTE. There was a much lower incidence of recurrent events in patients with isolated C-DVT. For patients with P-DVT/PE, our study demonstrates equivalence between 3 and 6 months of treatment.

Validation of either DVT or PE at diagnosis and during follow-up was not always assessed by objective procedures.10,13 Three methodologically stronger studies were subsequently published; they concluded that the duration of oral anticoagulant therapy should be at least 3 months and probably 6 months.7–9 The British Thoracic Society trial8 has been criticized because objective confirmation of the initial diagnosis and of recurrences was not always obtained. The soundest trial, the DURation of AntiCoagulation (DURAC) trial,7 found a significant reduction in the risk of recurrent VTE when the duration of oral anticoagulant therapy was extended from 6 weeks to 6 months.

The Long Anticoagulation after First episode of Idiopathic Thrombosis (LAFIT) trial14 demonstrated that patients with a first episode of idiopathic VTE should be treated for longer than 3 months, and the recently reported Warfarin Optimal Duration Italian Trial (WODIT)22 suggested that anticoagulation should be prolonged for >1 year.

In conclusion, our study shows equivalence between the 2 treatment regimens for recurrence (ie, 6 or 12 weeks for isolated C-DVT and 3 or 6 months for P-DVT and/or PE), without a significant increase in bleeding complications. A meta-analysis of all the available evidence summarized

| TABLE 5. Incidence of Outcomes in Different Subgroups According to the Treatment Group |
|-----------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Temporary risk factor                  | Short TG, %     | Long TG, %      | RR (95% CI)     | Short TG, %     | Long TG, %      | RR (95% CI)     |
| Yes (n=375)                            | 5.9             | 4.4             | 1.33 (0.55, 3.23)| 16.1            | 20.0            | 0.81 (0.52, 1.25)|
| No (n=345)                             | 6.9             | 10.8            | 0.64 (0.32, 1.29)| 15.0            | 17.4            | 0.87 (0.53, 1.41)|
| P                                      | 0.06            |                 |                 | 0.5             |                 |                 |
| Permanent risk factor(s)               |                 |                 |                 |                 |
| Yes (n=397)                            | 7.2             | 10.2            | 0.71 (0.37, 1.37)| 18.6            | 20.8            | 0.89 (0.60, 1.33)|
| No (n=324)                             | 5.4             | 4.0             | 1.37 (0.50, 3.77)| 12.1            | 15.9            | 0.76 (0.44, 1.32)|
| P                                      | 0.04            |                 |                 | 0.04            |                 |                 |
| Idiopathic VTE                         |                 |                 |                 |                 |
| Yes (n=322)                            | 8.9             | 9.5             | 0.93 (0.47, 1.87)| 12.7            | 16.5            | 0.77 (0.45, 1.32)|
| No (n=414)                             | 4.5             | 5.8             | 0.77 (0.33, 1.83)| 17.9            | 20.5            | 0.87 (0.58, 1.31)|
| P                                      | 0.03            |                 |                 | 0.1             |                 |                 |
| Cancer during follow-up                |                 |                 |                 |                 |
| Yes (n=25)                             | 18.2            | 35.7            | 0.51 (0.12, 2.14)| 27.3            | 28.6            | 0.96 (0.27, 3.41)|
| No (n=680)                             | 6.1             | 5.7             | 1.07 (0.59, 1.95)| 15.4            | 17.7            | 0.87 (0.62, 1.22)|
| P                                      | 0.001           |                 |                 | 0.1             |                 |                 |
| Heparin therapy effective              |                 |                 |                 |                 |
| Yes (n=646)                            | 6.5             | 7.4             | 0.89 (0.50, 1.57)| 16.2            | 18.3            | 0.89 (0.63, 1.25)|
| No (n=73)                              | 5.4             | 8.6             | 0.63 (0.11, 3.55)| 10.8            | 22.9            | 0.47 (0.16, 1.43)|
| P                                      | 0.99            |                 |                 | 0.9             |                 |                 |
| Effective oral anticoagulant therapy*  |                 |                 |                 |                 |
| Yes (n=541)                            | 7.8             | 8.3             | 0.94 (0.53, 1.66)| 17.0            | 22.2            | 0.77 (0.54, 1.08)|
| No (n=23)                              | 0.0             | 0.0             | 30.0            | 0.0             |                 |                 |
| P                                      | 0.4             |                 |                 | 0.8             |                 |                 |

Values are percentages for treatment. TG indicates treatment group; RR, relative risk. P values were obtained using the χ² test with a comparison of “yes” and “no” subgroups; all treatment regimens were combined. *Defined as a median INR ≥2.0.
above suggests that longer therapy could be beneficial, with an acceptable risk of bleeding. In addition, because the number of risk factors and initial conditions influence the risk of recurrence, a tailored duration might be the proper way to manage each case. To design the appropriate tools, new clinical trials are needed that are specifically designed for patients at a high risk of recurrence who could benefit from a long course of treatment (idiopathic VTE and biological thrombophilia), with assessment of a lower level of prolonged anticoagulation. In addition, a meta-analysis on individual data, regrouping the available data from the controlled trials, is also needed. We propose to perform this meta-analysis in an international collaborative project.

Appendix

DOTAVK Study Group

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Participating Centers


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References


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Comparison of 3 and 6 Months of Oral Anticoagulant Therapy After a First Episode of Proximal Deep Vein Thrombosis or Pulmonary Embolism and Comparison of 6 and 12 Weeks of Therapy After Isolated Calf Deep Vein Thrombosis

Laurent Pinede, Jacques Ninet, Pierre Duhaut, Sylvie Chabaud, Sylvie Demolombe-Rague, Isabelle Durieu, Patrice Nony, Christian Sanson and Jean-Pierre Boissel

for the Investigators of the Durée Optimale du Traitement AntiVitamines K (DOTAVK) Study

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