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## Comparison of Low-Intensity Warfarin Therapy with Conventional-Intensity Warfarin Therapy for Long-Term Prevention of Recurrent Venous Thromboembolism

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### ABSTRACT

#### BACKGROUND

Warfarin is very effective in preventing recurrent venous thromboembolism but is also associated with a substantial risk of bleeding. After three months of conventional warfarin therapy, a lower dose of anticoagulant medication may result in less bleeding and still prevent recurrent venous thromboembolism.

#### METHODS

We conducted a randomized, double-blind study, in which 738 patients who had completed three or more months of warfarin therapy for unprovoked venous thromboembolism were randomly assigned to continue warfarin therapy with a target international normalized ratio (INR) of 2.0 to 3.0 (conventional intensity) or a target INR of 1.5 to 1.9 (low intensity). Patients were followed for an average of 2.4 years.

#### RESULTS

Of 369 patients assigned to low-intensity therapy, 16 had recurrent venous thromboembolism (1.9 per 100 person-years), as compared with 6 of 369 assigned to conventional-intensity therapy (0.7 per 100 person-years; hazard ratio, 2.8; 95 percent confidence interval, 1.1 to 7.0). A major bleeding episode occurred in nine patients assigned to low-intensity therapy (1.1 events per 100 person-years) and eight patients assigned to conventional-intensity therapy (0.9 event per 100 person-years; hazard ratio, 1.2; 95 percent confidence interval, 0.4 to 3.0). There was no significant difference in the frequency of overall bleeding between the two groups (hazard ratio, 1.3; 95 percent confidence interval, 0.8 to 2.1).

#### CONCLUSIONS

Conventional-intensity warfarin therapy is more effective than low-intensity warfarin therapy for the long-term prevention of recurrent venous thromboembolism. The low-intensity warfarin regimen does not reduce the risk of clinically important bleeding.

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\*The Extended Low-Intensity Anticoagulation for Thrombo-Embolic (ELATE) Investigators are listed in the Appendix.

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UNPROVOKED VENOUS THROMBOEMBOLISM is associated with a higher risk of recurrent thrombosis after the discontinuation of anticoagulant therapy than is thrombosis that is associated with a transient risk factor such as surgery.<sup>1</sup> In an earlier study involving patients who had had an episode of unprovoked venous thrombosis, we found that it is better to continue warfarin therapy for an additional two years than to discontinue treatment after three months.<sup>2</sup> In that study and in another trial of anticoagulant therapy in patients who had had two episodes of venous thrombosis,<sup>3</sup> no patient had recurrent thrombosis while receiving extended warfarin therapy adjusted to achieve an international normalized ratio (INR) of about 2.0 to 3.0. This finding suggests that anticoagulant therapy that achieves an INR of 2.0 may be of greater intensity than is necessary for very effective long-term prevention of recurrent venous thromboembolism. In both earlier studies, the risk of bleeding was a limitation of extended warfarin therapy.<sup>2,3</sup>

Taken together, these findings suggest that extended treatment with anticoagulant therapy at a lower intensity might be similarly effective but associated with a lower risk of bleeding than conventional-intensity treatment. To test this hypothesis, we performed a randomized, double-blind study in patients with unprovoked venous thromboembolism in which we compared warfarin therapy with a target INR of 1.5 to 1.9 (low-intensity therapy) with warfarin therapy with a target INR of 2.0 to 3.0 (conventional-intensity therapy).

## METHODS

### STUDY PATIENTS

Consecutive patients with one or more episodes of unprovoked venous thromboembolism were eligible if they had completed three or more months of oral anticoagulant therapy at the conventional intensity. Unprovoked venous thromboembolism was defined as objectively confirmed, symptomatic, proximal deep venous thrombosis or pulmonary embolism that occurred in the absence of a major risk factor for thrombosis. Such risk factors included fracture or plaster casting of a leg, hospitalization with confinement to bed for three consecutive days, or surgery with general anesthesia lasting longer than 30 minutes, all within three months before thrombosis, and cancer that had been active within the previous two years.

Patients who met these criteria for inclusion were ineligible if they had other indications for warfarin therapy; a contraindication to long-term warfarin therapy, including a high risk of bleeding; antiphospholipid antibodies; an allergy to contrast medium; or a life expectancy of less than two years. Patients with a hypercoagulable state (as determined by genetic or coagulation testing) other than antiphospholipid antibodies were eligible. The study was approved by the institutional review boards of all participating clinical centers.

### RANDOMIZATION AND TREATMENT

After patients provided written informed consent, randomization was performed with stratification according to clinical center and according to whether the patient had completed three to four months or more than four months of initial anticoagulant therapy. A computer algorithm, with a randomly determined block size of two or four within each stratum, generated lists in which patients were assigned to either long-term, low-intensity warfarin therapy (target INR, 1.5 to 1.9) or conventional-intensity warfarin therapy (target INR, 2.0 to 3.0). Allocation lists were sent to an "anticoagulation monitor" at each clinical center who was not involved in the patients' care.

After enrollment, all subsequent measurements of the INR were forwarded only to the center-specific anticoagulation monitor. For patients assigned to conventional-intensity therapy, this monitor relayed the true INR results to the clinical center. For those assigned to low-intensity therapy, the anticoagulation monitor converted the INR result to a higher value with the use of a predefined table, and the converted INR value was relayed to research personnel at each clinical center, who then provided instructions about warfarin doses to the patients. This procedure allowed patients to receive warfarin therapy adjusted to achieve an INR of 1.5 to 1.9 or an INR of 2.0 to 3.0 while maintaining the double-blind design of the study (with the patients and the personnel at the clinical centers remaining unaware of the treatment-group assignment). The frequency of INR monitoring was left to the discretion of the clinical center. There was no predefined maximal duration of participation.

### FOLLOW-UP AND OUTCOME MEASURES

Patients were assessed every six months and were told to report to the center immediately if symptoms developed that were suggestive of venous throm-

boembolism or if they had bleeding. Suspected recurrent venous thromboembolism was evaluated by means of objective diagnostic testing, as described previously.<sup>2</sup> No surveillance was performed to detect asymptomatic venous thromboembolism. Bleeding was defined as major if it was clinically overt and associated with a decrease in the hemoglobin level of at least 2.0 g per deciliter or a need for transfusion of two or more units of red cells or if it involved a critical site (e.g., retroperitoneal or intracranial bleeding). All suspected outcome events and all deaths were classified by a central adjudication committee whose members were unaware of the treatment-group assignments.

#### LABORATORY ASSAYS

Assays for factor V Leiden<sup>4</sup> and the G20210A mutation in the prothrombin gene<sup>5</sup> were performed in a central laboratory by technologists who were unaware of the patient's treatment-group assignment and clinical course. The results of laboratory testing were not made available to the clinical centers or to the central adjudication committee during the study.

#### STATISTICAL ANALYSIS

The trial was designed to establish whether low-intensity warfarin therapy would cause less bleeding than conventional-intensity warfarin therapy and would be similarly effective at preventing recurrent thrombosis. We expected a rate of major bleeding episodes of 3.0 per 100 patient-years among patients assigned to conventional-intensity therapy,<sup>2,3</sup> a rate of 1.0 per 100 patient-years among those assigned to low-intensity therapy,<sup>6</sup> an average of 2.5 years of follow-up per patient, and loss to follow-up representing no more than 5 percent of the total number of patient-years. Given these assumptions, 357 patients were needed in each group for the study to be able to detect a reduction in the incidence of major bleeding with a power of 90 percent, with a 5 percent chance of an incorrect conclusion that low-intensity therapy caused less bleeding.

Kaplan–Meier methods were used to analyze each type of outcome event (major bleeding episode, recurrent thromboembolism, death, and any bleeding episode) according to treatment group.<sup>7</sup> Hazard ratios associated with low-intensity therapy as compared with conventional-intensity therapy (with 95 percent confidence intervals) and log-rank tests were used to compare the treatment groups. A Cox proportional-hazards model and likelihood-ratio tests

were used to assess the influence of prespecified base-line clinical and laboratory variables on the relation between treatment-group assignment and outcome and to determine whether there was any evidence of interactions between treatment and covariates.<sup>8</sup> All reported P values are two-sided.

## RESULTS

#### STUDY PATIENTS

Patients were recruited at 16 clinical centers from December 1, 1998, through May 30, 2001, and follow-up was stopped on June 30, 2002, as originally planned. A total of 1455 patients met the criteria for inclusion, and 366 of these patients met one or more criteria for exclusion. The four most common reasons for exclusion were another indication for warfarin (in 101 patients), a life expectancy of less than two years (in 98 patients), a contraindication to long-term warfarin therapy (in 45 patients), and positive antiphospholipid-antibody status (in 31 patients). Of the 1089 eligible patients, 738 (68 percent) provided written informed consent and were randomly assigned to continue receiving conventional-intensity warfarin therapy (369 patients) or to begin receiving low-intensity warfarin therapy (369 patients) (Table 1).

#### TREATMENT AND INR EVALUATIONS

The mean duration of follow-up was 2.4 years in both groups; the mean period during which patients received double-blind treatment was 2.1 years in the low-intensity–therapy group and 2.2 years in the conventional-intensity–therapy group. Double-blind treatment was permanently discontinued in 84 patients assigned to low-intensity therapy (because of bleeding in 6, another contraindication to anticoagulant therapy in 4, confirmed venous thromboembolism in 10, another indication for conventional-intensity anticoagulant therapy in 14, the preference of the patient in 29, and other reasons in 21) and in 58 patients assigned to conventional-intensity therapy (because of bleeding in 7, confirmed venous thromboembolism in 2, another indication for conventional-intensity anticoagulant therapy in 5, the preference of the patient in 21, and other reasons in 23). Of the 74 patients in the low-intensity–therapy group who discontinued double-blind treatment for reasons other than recurrent venous thromboembolism, 2 continued to receive warfarin therapy with a target INR of 1.5 to 2.0, 21 continued to receive warfarin therapy with a target INR of 2.0

**Table 1. Base-Line Characteristics of the Patients.**

| Characteristic   | Low-Intensity-<br>Therapy Group<br>(N=369) | Conventional-Intensity-<br>Therapy Group<br>(N=369) | All Patients<br>(N=738) |
|--|--|---|-------------------------|
| Age  |  |   |                         |
| Mean $\pm$ SD — yr   | 57 $\pm$ 16                                | 57 $\pm$ 16   | 57 $\pm$ 16             |
| $\geq$ 65 Yr — no. (%)   | 133 (36)                                   | 127 (34)  | 260 (35)                |
| Female sex — no. (%)   | 157 (43)                                   | 175 (47)  | 332 (45)                |
| Previous episodes of venous thromboembolism  |  |   |                         |
| >1 episode — no. (%)   | 261 (71)                                   | 248 (67)  | 509 (69)                |
| Mean no.   | 2.0  | 1.9   | 2.0                     |
| Duration of warfarin therapy (INR, 2.0–3.0) before enrollment  |  |   |                         |
| 3–4 Mo — no. (%) <sup>*</sup>  | 146 (40)                                   | 143 (39)  | 289 (39)                |
| No. of mo  |  |   |                         |
| All participants   | 12.0                                       | 12.5  | 12.2                    |
| Patients with 3–4 mo of therapy  | 3.2  | 3.2   | 3.2                     |
| Patients with >4 mo of therapy   | 17.7                                       | 18.4  | 18.1                    |
| Most recent type of venous thromboembolism — no. (%)   |  |   |                         |
| Deep venous thrombosis only  | 252 (68)                                   | 227 (62)  | 479 (65)                |
| Pulmonary embolism   | 117 (32)                                   | 142 (38)  | 259 (35)                |
| Risk factors for bleeding — no. (%) <sup>†</sup>   |  |   |                         |
| 0  | 194 (53)                                   | 205 (56)  | 399 (54)                |
| 1  | 133 (36)                                   | 122 (33)  | 255 (35)                |
| $\geq$ 2   | 42 (11)                                    | 42 (11)   | 84 (11)                 |
| Abnormal results on compression ultrasonography of proximal deep veins at enrollment — no./total no. (%) | 139/293 (47)                               | 138/292 (47)  | 277/585 (47)            |
| Factor V Leiden — no./total no. (%) <sup>‡</sup>   | 91/328 (28)                                | 80/318 (25)   | 171/646 (26)            |
| Prothrombin-gene mutation — no./total no. (%) <sup>§</sup>   | 32/327 (10)                                | 28/317 (9)  | 60/644 (9)              |

\* INR denotes international normalized ratio.

<sup>†</sup> Risk factors for bleeding at enrollment included an age of 65 years or more, previous stroke, previous peptic ulcer disease, previous gastrointestinal bleeding, renal impairment, anemia, thrombocytopenia, liver disease, diabetes mellitus, and the use of antiplatelet therapy.

<sup>‡</sup> Seven patients in the low-intensity-therapy group and three patients in the conventional-intensity-therapy group were homozygous for factor V Leiden.

<sup>§</sup> Two patients in the conventional-intensity-therapy group were homozygous for the prothrombin-gene mutation.

to 3.0, and 2 began therapy with low-molecular-weight heparin. Of the 57 patients in the conventional-intensity-therapy group who discontinued the double-blind treatment for reasons other than recurrent venous thromboembolism, 9 continued to receive warfarin therapy with a target INR of 2.0 to 3.0, 1 continued to receive warfarin therapy with a target INR of 1.8 to 2.5, and 2 began therapy with low-molecular-weight heparin. Only one patient was lost to follow-up.

The mean INR was 1.8 among patients assigned to low-intensity therapy and 2.4 among those assigned to conventional-intensity therapy. When linear interpolation was used to estimate the INR between measurements, the low-intensity-therapy group had an INR of 1.5 to 1.9 during 63 percent of

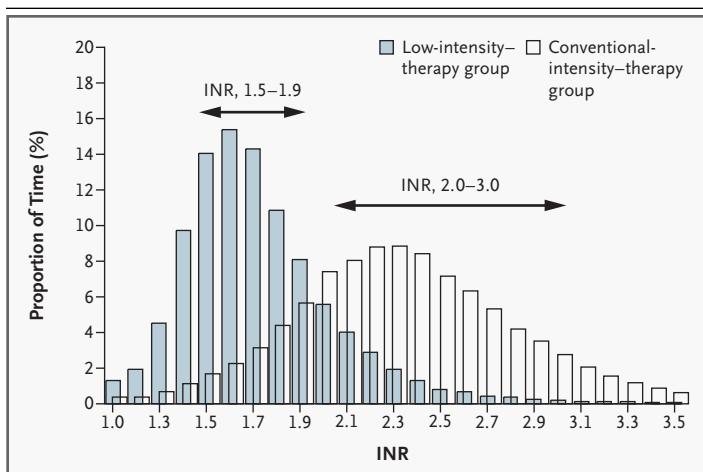
the period when they were receiving double-blind treatment, below this range during 18 percent of this period, and above this range during 19 percent of this period (Fig. 1). The conventional-intensity-therapy group had an INR of 2.0 to 3.0 during 69 percent of the period when they were receiving double-blind treatment, below this range during 20 percent of this period, and above this range during 11 percent of this period (Fig. 1). The average interval between INR measurements was 24 days in the low-intensity-therapy group and 26 days in the conventional-intensity-therapy group. In order to avoid revealing the treatment-group assignment, the INR measurements obtained at the time of suspected recurrent venous thromboembolism or bleeding were not recorded; when possible, these

results were obtained retrospectively for confirmed events after the study was completed.

**BLEEDING COMPLICATIONS**

There were 9 major bleeding episodes among the 369 patients assigned to low-intensity therapy (1.1 per 100 person-years) and 8 major bleeding episodes among the 369 patients assigned to conventional-intensity therapy (0.9 per 100 person-years; hazard ratio, 1.2; 95 percent confidence interval, 0.4 to 3.0) (Table 2). When both major and minor bleeding episodes were included, bleeding occurred in 39 patients assigned to low-intensity therapy (4.9 per 100 person-years) and 31 patients assigned to conventional-intensity therapy (3.7 per 100 person-years; hazard ratio, 1.3; 95 percent confidence interval, 0.8 to 2.1).

INR values were obtained when bleeding was diagnosed in seven of the nine patients in the low-intensity-therapy group who had a major bleeding episode (INR, 1.7, 1.7, 2.9, 4.9, 5.3, 7.2, and 11.3). None of these episodes were fatal or intracranial; five were treated with blood transfusion; and five resulted in admission to the hospital. The INR values at the time bleeding was diagnosed in the eight patients in the conventional-intensity-therapy group who had a major bleeding episode were 1.9, 2.7, 2.9, 2.9, 3.1, 3.7, 3.8, and 7.7. None of these episodes were fatal or intracranial; two were subdural hematomas caused by falls (one of which was surgically evacuated); one was a spinal hematoma; four were treated with transfusion; and seven resulted in admission to the hospital. There was no evidence



**Figure 1.** Proportions of Time during Which the International Normalized Ratio (INR) Values Were at Various Levels in the Two Treatment Groups.

of an interaction between base-line variables and the hazard of bleeding with low-intensity therapy as compared with conventional-intensity therapy (Table 3).

There was a higher rate of major bleeding episodes among patients 65 years of age or older than among those younger than 65 years (hazard ratio, 2.6 [95 percent confidence interval, 1.0 to 6.9]), and the rate increased with the number of predefined risk factors for bleeding that were present at enrollment (risk factors included an age of 65 years or more, previous stroke, previous peptic ulcer disease, previous gastrointestinal bleeding, renal im-

**Table 2.** Main Outcomes According to Treatment Group.\*

| Outcome                             | Low-Intensity-<br>Therapy Group<br>(N=369) |                      | Conventional-Intensity-<br>Therapy Group<br>(N=369) |                      | Hazard Ratio<br>(95% CI) | Difference<br>between Rates<br>(95% CI) | P<br>Value |
|-------------------------------------|--|----------------------|---|----------------------|--------------------------|---|------------|
|                                     | No. of<br>Events                           | No./100<br>Person-Yr | No. of<br>Events                                    | No./100<br>Person-Yr |                          |   |            |
| Major bleeding episode              | 9  | 1.1                  | 8   | 0.9                  | 1.2 (0.4 to 3.0)         | 0.1 (-0.8 to 1.1)                       | 0.76       |
| Any bleeding episode                | 39   | 4.9                  | 31  | 3.7                  | 1.3 (0.8 to 2.1)         | 1.2 (-0.8 to 3.2)                       | 0.26       |
| Recurrent venous<br>thromboembolism | 16   | 1.9                  | 6   | 0.7                  | 2.8 (1.1 to 7.0)         | 1.2 (0.2 to 2.7)                        | 0.03       |
| Death                               | 16   | 1.9                  | 8   | 0.9                  | 2.1 (0.9 to 4.8)         | 1.0 (-0.2 to 2.1)                       | 0.09       |

\* Because of rounding, the figures given for the differences between rates may not match the differences calculated from the rates given for each group. CI denotes confidence interval.

**Table 3. Rates and Hazard Ratios for Major Bleeding in Subgroups.\***

| Characteristic                                 | Low-Intensity–Therapy Group (N=369) |                   | Conventional-Intensity–Therapy Group (N=369) |                   | Hazard Ratio (95% CI) | P Value for Interaction† |
|--|-------------------------------------|-------------------|--|-------------------|-----------------------|--------------------------|
|  | No. of Events                       | No./100 Person-Yr | No. of Events                                | No./100 Person-Yr |                       |                          |
| Age  |                                     |                   |  |                   |                       |                          |
| <65 Yr   | 3                                   | 0.5               | 4  | 0.7               | 0.8 (0.2–3.5)         | 0.46                     |
| ≥65 Yr   | 6                                   | 2.0               | 4  | 1.3               | 1.7 (0.5–6.0)         |                          |
| Duration of warfarin therapy before enrollment |                                     |                   |  |                   |                       |                          |
| 3–4 Mo   | 3                                   | 1.0               | 5  | 1.6               | 0.6 (0.1–2.5)         | 0.22                     |
| >4 Mo  | 6                                   | 1.1               | 3  | 0.5               | 2.1 (0.5–8.3)         |                          |
| No. of previous episodes of thromboembolism    |                                     |                   |  |                   |                       |                          |
| 1  | 3                                   | 1.1               | 1  | 0.4               | 3.2 (0.3–30.7)        | 0.31                     |
| >1   | 6                                   | 1.0               | 7  | 1.2               | 0.9 (0.3–2.6)         |                          |
| No. of risk factors for bleeding‡              |                                     |                   |  |                   |                       |                          |
| 0  | 1                                   | 0.2               | 2  | 0.4               | 0.5 (0.0–5.9)         | 0.66                     |
| 1  | 6                                   | 2.0               | 5  | 1.8               | 1.2 (0.4–4.0)         |                          |
| ≥2   | 2                                   | 2.3               | 1  | 1.0               | 2.2 (0.2–23.8)        |                          |
| Factor V Leiden or prothrombin-gene mutation§  |                                     |                   |  |                   |                       |                          |
| None   | 4                                   | 0.8               | 3  | 0.6               | 1.4 (0.3–6.2)         | 0.33                     |
| Single mutation¶                               | 2                                   | 0.9               | 2  | 0.9               | 1.0 (0.1–6.8)         |                          |
| Double mutation¶                               | 0                                   | 0                 | 1  | 4.2               | —                     |                          |

\* CI denotes confidence interval.

† The null hypothesis is that the influence of the treatment group does not differ among subgroups.

‡ Risk factors for bleeding included an age of 65 years or more, previous stroke, previous peptic ulcer disease, previous gastrointestinal bleeding, renal impairment, anemia, thrombocytopenia, liver disease, diabetes mellitus, and the use of antiplatelet therapy.

§ A total of 94 subjects, of whom 5 had major episodes of bleeding, did not have factor V Leiden or prothrombin-gene mutation assays.

¶ Double mutations included homozygosity for factor V Leiden (in 7 patients in the low-intensity–therapy group and 3 in the conventional-intensity–therapy group), homozygosity for the prothrombin-gene mutation (in 2 patients in the conventional-intensity–therapy group), and heterozygosity for both factor V Leiden and the prothrombin-gene mutation (in 11 patients in the low-intensity–therapy group and 6 in the conventional-intensity–therapy group).

pairment, anemia, thrombocytopenia, liver disease, diabetes, and use of antiplatelet therapy; hazard ratio associated with each additional risk factor, 1.7 [95 percent confidence interval, 1.1 to 2.6]). The frequency of major bleeding did not differ significantly between patients who had been receiving warfarin therapy for more than four months at the time of enrollment and those who had been receiving warfarin therapy for three to four months ( $P=0.37$ ).

#### RECURRENT VENOUS THROMBOEMBOLISM

In the low-intensity–therapy group, there were 16 episodes of recurrent venous thromboembolism (1 fatal event strongly suspected to have been a pulmonary embolism although diagnostic testing was not performed, 2 nonfatal pulmonary embolisms, and 13 cases of deep venous thrombosis; 1.9 events

per 100 person-years); in the conventional-intensity–therapy group, there were 6 episodes (2 events categorized as fatal pulmonary embolisms [1 of them a sudden death and 1 a possible embolism, although myocardial infarction was suspected] and 4 cases of deep venous thrombosis; 0.7 event per 100 person-years; hazard ratio, 2.8; 95 percent confidence interval, 1.1 to 7.0) (Table 2). The cumulative probability of recurrent venous thromboembolism in each treatment group is shown in Figure 2; the difference between the two groups was statistically significant ( $P=0.03$ ).

Of the 16 episodes of recurrent thromboembolism in patients in the low-intensity–therapy group, 5 occurred after warfarin therapy was discontinued (in 1 case because of bleeding) and 11 occurred during warfarin therapy; at the time when the recur-

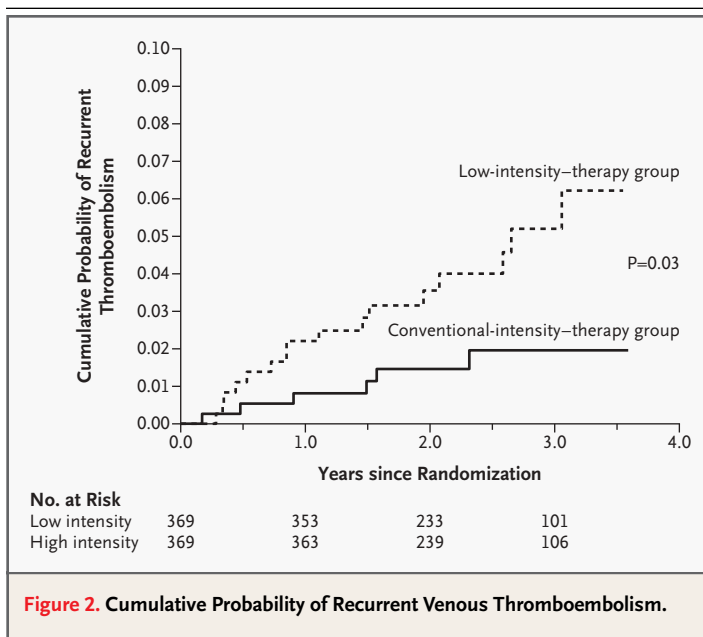
rence was diagnosed, the INR in these patients was 1.4, 1.5, 1.5, 1.8, 1.8, 1.9, 2.1, 2.1, and 3.1 (the INR was not available for two of the patients). Of the six episodes of recurrent venous thromboembolism in patients in the conventional-intensity-therapy group, three occurred after warfarin therapy had been discontinued (in one case because of bleeding), and three occurred during warfarin therapy; at the time when the recurrence was diagnosed, the INR was 1.7 in one patient, 1.9 in another patient, and not available in the third patient.

The rate of recurrent venous thromboembolism during double-blind warfarin therapy was 1.4 events per 100 person-years in the low-intensity-therapy group and 0.4 event per 100 person-years in the conventional-intensity-therapy group (hazard ratio, 3.8; 95 percent confidence interval, 1.1 to 13.6). A history of more than one episode of venous thromboembolism was the only base-line variable that may have interacted with the treatment effect ( $P=0.05$ ) but, since such an interaction was unexpected, it could have occurred by chance (Table 4).

Among all patients, the rate of recurrent venous thromboembolism was higher among those who were enrolled three to four months after their most recent thrombosis than among those who had been treated for longer than four months at the time of enrollment (hazard ratio, 3.1; 95 percent confidence interval, 1.3 to 7.3) and increased with the number of risk factors for bleeding that were present at enrollment ( $P=0.03$ ) (Table 4). Rates of recurrent venous thromboembolism did not differ according to whether patients had presented with deep venous thrombosis or pulmonary embolism ( $P=0.51$ ), whether they had more than one previous episode of venous thrombosis ( $P=0.94$ ), whether they had abnormal results on compression ultrasonography at enrollment ( $P=0.82$ ), or whether they had factor V Leiden or the G20210A mutation of the prothrombin gene ( $P=0.21$ ) (Table 4).

**DEATHS**

There were 16 deaths in the low-intensity-therapy group and 8 deaths in the conventional-intensity-therapy group (hazard ratio, 2.1 [95 percent confidence interval, 0.9 to 4.8]) (Table 2). Causes of death in the low-intensity-therapy group were pulmonary embolism in one patient, cancer in seven patients, and other causes in eight patients; causes of death in the conventional-intensity-therapy group were pulmonary embolism in two patients, cancer in one patient, and other causes in five patients.



**Figure 2. Cumulative Probability of Recurrent Venous Thromboembolism.**

**DISCUSSION**

The results of this study show that conventional-intensity warfarin therapy is more effective than low-intensity warfarin therapy at preventing recurrent thrombosis in patients who have had unprovoked venous thromboembolism, reducing their risk by about two thirds. The low-intensity regimen did not reduce the frequency of bleeding, which was low with treatment of either intensity. These findings were consistent among various subgroups.

Our findings are consistent with those of the recently published Prevention of Recurrent Venous Thromboembolism (PREVENT) study, a placebo-controlled trial that evaluated warfarin therapy with a target INR of 1.5 to 2.0 for extended treatment of patients who had had unprovoked venous thromboembolism.<sup>9</sup> Among patients assigned to low-intensity warfarin therapy in the PREVENT study, the rate of major bleeding was 0.9 per 100 person-years, and the rate of recurrent venous thromboembolism was 2.6 per 100 person-years — rates that are similar to those in our low-intensity-therapy group (1.1 and 1.9 events per 100 person-years, respectively). Collectively, the results of our study and the three other trials that have evaluated extended treatment of patients who have had unprovoked venous thromboembolism<sup>2,3,9</sup> suggest that low-intensity anticoagulant therapy reduces the risk of

**Table 4. Rates and Hazard Ratios for Recurrent Venous Thromboembolism in Subgroups.**

| Characteristic                                   | Low-Intensity–Therapy Group (N=369) |                   | Conventional-Intensity–Therapy Group (N=369) |                   | Hazard Ratio (95% CI)* | P Value for Interaction† |
|--|-------------------------------------|-------------------|--|-------------------|------------------------|--------------------------|
|  | No. of Events                       | No./100 Person-Yr | No. of Events                                | No./100 Person-Yr |                        |                          |
| Age  |                                     |                   |  |                   |                        | 0.97                     |
| <65 Yr   | 8                                   | 1.5               | 3  | 0.5               | 2.7 (0.7–10.3)         |                          |
| ≥65 Yr   | 8                                   | 2.6               | 3  | 1.0               | 2.7 (0.7–10.0)         |                          |
| Duration of warfarin therapy before enrollment   |                                     |                   |  |                   |                        | 0.84                     |
| 3–4 Mo   | 10                                  | 3.2               | 4  | 1.3               | 2.5 (0.8–8.0)          |                          |
| >4 Mo  | 6                                   | 1.1               | 2  | 0.4               | 3.1 (0.6–15.3)         |                          |
| No. of previous episodes of thromboembolism      |                                     |                   |  |                   |                        | 0.05                     |
| 1  | 3                                   | 1.1               | 4  | 1.5               | 0.8 (0.2–3.5)          |                          |
| >1   | 13                                  | 2.2               | 2  | 0.3               | 6.7 (1.5–29.5)         |                          |
| Most recent type of venous thromboembolism       |                                     |                   |  |                   |                        | 0.48                     |
| Deep venous thrombosis only                      | 9                                   | 1.5               | 4  | 0.7               | 2.1 (0.7–6.9)          |                          |
| Pulmonary embolism                               | 7                                   | 2.6               | 2  | 0.6               | 4.3 (0.9–20.5)         |                          |
| No. of risk factors for bleeding‡                |                                     |                   |  |                   |                        | 0.66                     |
| 0  | 5                                   | 1.1               | 3  | 0.6               | 1.7 (0.4–7.3)          |                          |
| 1  | 6                                   | 2.0               | 2  | 0.7               | 2.9 (0.6–14.2)         |                          |
| ≥2   | 5                                   | 5.6               | 1  | 1.0               | 5.5 (0.6–47.5)         |                          |
| Results on venous ultrasonography at enrollment§ |                                     |                   |  |                   |                        | 0.20                     |
| Normal   | 6                                   | 2.4               | 4  | 1.1               | 1.5 (0.4–5.4)          |                          |
| Abnormal   | 7                                   | 0.9               | 1  | 0.3               | 7.6 (0.9–61.0)         |                          |
| Factor V Leiden or prothrombin-gene mutation¶    |                                     |                   |  |                   |                        | 0.63                     |
| None   | 12                                  | 2.4               | 4  | 0.8               | 3.1 (1.0–9.6)          |                          |
| Single mutation                                  | 2                                   | 0.9               | 2  | 0.9               | 1.0 (0.1–7.0)          |                          |
| Double mutation                                  | 0                                   | 0                 | 0  | 0                 | —                      |                          |

\* CI denotes confidence interval.

† The null hypothesis is that the influence of the treatment group does not differ among subgroups.

‡ Risk factors for bleeding included an age of 65 years or more, previous stroke, previous peptic ulcer disease, previous gastrointestinal bleeding, renal impairment, anemia, thrombocytopenia, liver disease, diabetes mellitus, and the use of antiplatelet therapy.

§ A total of 153 patients, of whom 4 had recurrent venous thromboembolism, did not undergo venous ultrasonography at enrollment.

¶ A total of 94 subjects, of whom 2 had recurrent venous thromboembolism, did not undergo assays for factor V Leiden and the prothrombin-gene mutation.

|| Double mutations included homozygosity for factor V Leiden (in 7 patients in the low-intensity–therapy group and 3 in the conventional-intensity–therapy group), homozygosity for the prothrombin-gene mutation (in 2 patients in the conventional-intensity–therapy group), and heterozygosity for both factor V Leiden and the prothrombin-gene mutation (in 11 patients in the low-intensity–therapy group and 6 in the conventional-intensity–therapy group).

recurrent thrombosis by about 75 percent, whereas conventional-intensity therapy reduces this risk by over 90 percent.

Our results are likely to be valid, because the random assignment to treatment groups, the use of a double-blind design, the objective diagnosis of recurrent venous thromboembolism, and the central adjudication of study outcomes all minimized the potential for bias. Furthermore, the method of concealment of the treatment (i.e., the double blinding) resulted in a clear separation of true INR values be-

tween the two treatment groups. Therefore, similar rates of bleeding cannot be attributed to failure to achieve different intensities of anticoagulant therapy in the two treatment groups. It could be argued that in a nontrial setting, a higher proportion of INR results might fall outside of the target INR range and that this might result in a higher relative frequency of bleeding with conventional-intensity anticoagulant therapy as compared with low-intensity therapy. We cannot rule out this possibility; however, poorer control of the intensity of anticoagulant

therapy would also be expected to result in a higher relative frequency of recurrent thrombosis with low-intensity therapy.

As in other studies,<sup>2,10</sup> factor V Leiden and prothrombin-gene mutations were not associated with a higher risk of recurrent thromboembolism, although all patients in our study were treated with anticoagulant therapy. Patients who had been treated for three to four months before enrollment had a higher rate of recurrent thrombosis than those who had been treated for a longer period, suggesting that recurrences in patients receiving anticoagulant therapy tend to occur relatively early in the course of therapy. Risk factors for bleeding were also found to be risk factors for recurrent thrombosis, which probably reflects an association with co-existing conditions that is common to these outcomes. There were higher rates of bleeding among

patients who were older and had other previously described risk factors for bleeding.<sup>11</sup>

We conclude that the intensity of anticoagulant therapy for patients who have had unprovoked venous thromboembolism should not be reduced after the first three months of treatment, since such a reduction increases the risk of recurrent thrombosis and there is no evidence that it reduces the risk of bleeding. Long-term conventional-intensity warfarin therapy is very effective at preventing recurrent thrombosis and is associated with a low frequency of bleeding.

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#### APPENDIX

The following institutions, nurses, and anticoagulation monitors participated in the ELATE study (numbers in parentheses are the numbers of patients who underwent randomization). *Canada:* London Health Sciences Centre, London, Ont. — B. Morrow, J. Kovacs, M. Moore (172); Ottawa Hospitals — Civic Campus, Ottawa, Ont. — G. Lewis, M. Colley (104); Hamilton Health Sciences—Henderson Hospital, Hamilton, Ont. — L. Biagioni, C. Burnett (96); Hamilton Health Sciences—McMaster Medical Centre, Hamilton, Ont. — P. Stevens (72); Queen Elizabeth II Health Sciences Centre, Halifax, N.S. — D. MacLeod, S. Pleasance (54); St. Joseph's Hospital, Hamilton, Ont. — T. Schnurr (52); St. John Regional Hospital, St. John, N.B. — C. Mayes, D. Strong (32); Hamilton Health Sciences—Hamilton General Hospital, Hamilton, Ont. — M. Zondag (28); Sunnybrook and Women's College Health Science Centre, Toronto — K. Code, W. Bartle (26); Montreal General Hospital, Montreal — B. St. Jacques, H. Schmaltz (26); Pavillon du Saint-Sacrement, Quebec, Que. — J. Poulin, L. Vu (22); Jewish General Hospital, Montreal — C. Strulowitch, M. Elizov (19); Centre Hospitalier de l'Université de Montréal, Hôtel-Dieu de Montréal, Montreal — B. Lecours, G. Cayer (17); Ottawa Hospitals—General Campus, Ottawa, Ont. — L. Radey (8); Hôpital Maisonneuve-Rosemont, Montreal — F. Beausoleil, L. Busque (7). *United States:* University of California, San Francisco — J. Tatsuno-Roth (3). *Coordinating and Methods Center:* Henderson Research Centre — T. Lychak, L. Goeree, B. MacKinnon, J. Julian, M. Gent; *Central Adjudication Committee:* J. Weitz, M. Levine, J. Hirsh, J. Douketis, J. Ginsberg; *Central Laboratory:* Hemostasis Reference Laboratory, Henderson Research Centre, Hamilton, Ont. — M. Johnston, J. McGrath.

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