The Risk of Recurrent Venous Thromboembolism in Heterozygous Carriers of Factor V Leiden and a First Spontaneous Venous Thromboembolism

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Background: Factor V (FV) Leiden is a risk factor for venous thrombosis (VT). Data on its influence on the risk of recurrent venous thromboembolism (VTE) are controversial owing to different study designs and patient cohorts.

Methods: We reevaluated the risk of recurrence among heterozygous carriers and noncarriers of FV Leiden with a first spontaneous proximal VT of the leg and/or pulmonary embolism. Patients with secondary VTE, homozygous FV Leiden, natural inhibitor deficiencies, lupus anticoagulant, cancer, or long-term anticoagulation were excluded. The study end point was objectively documented, symptomatic, recurrent VTE.

Results: After discontinuation of oral anticoagulant therapy for a first VTE, we prospectively observed 287 patients, 83 (29%) of whom were heterozygous for FV Leiden. Recurrent VTE was seen in 17 (20%) of 83 patients with and 44 (21.6%) of 204 without FV Leiden. The probability of recurrence among heterozygotes was 12% (95% confidence interval [CI], 8%-16%), 27% (95% CI, 21%-33%), and 27% (95% CI, 21%-33%) after 2, 4, and 6 years, respectively, and was not higher than that among patients without the mutation (16%, 23%, and 34%, respectively). The relative risk of recurrence in heterozygotes was 0.9 (95% CI, 0.5-1.6; \( P = .60 \)) after adjustment for confounding variables. The risk of recurrence among patients with and without FV Leiden was not different when sex distribution or duration of anticoagulation therapy was taken into account.

Conclusions: The risk of recurrence is similar among carriers and noncarriers of FV Leiden. Heterozygous patients should receive secondary thromboprophylaxis for a similar length of time as patients without FV Leiden.

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The G1691A mutation in the factor V (FV) gene (FV Leiden) is currently the most frequent genetic cause of thrombophilia. Factor V Leiden is common among whites, with a prevalence of up to 15% in healthy individuals and 17% to 56% (depending on patient selection) in thrombosis cohorts. In contrast to less common thrombotic risk factors, such as deficiency in antithrombin, protein C, or protein S, the high prevalence of FV Leiden facilitated evaluation of its thrombotic potency in large controlled trials. In several studies, FV Leiden has been established as an important risk factor for a first venous thrombosis (VT) with a 7-fold increased risk in heterozygotes and an approximately 80-fold increased risk in homozygotes.

However, the importance of FV Leiden as a risk factor for a subsequent VT has become a matter of debate. An increased risk of recurrent venous thromboembolism (VTE) in carriers of the 1691A allele was found in 2 prospective studies, with odds ratios of 4.17 and 2.48. Recently, a reevaluation of the Italian cohort9 again showed an association between FV Leiden and the risk of recurrence. In contrast, in a retrospective analysis,10 no association was found between FV Leiden and a higher risk of recurrence. In 1997, a prospective study demonstrated that the recurrence rate after discontinuation of secondary thromboprophylaxis was not higher in carriers of FV Leiden than in patients without the mutation.11 These findings were confirmed by 4 large clinical trials.12-15

Since recommendations for the duration of secondary thromboprophylaxis strongly depend on the rate of recurrence, one must consider explanations for these conflicting results. The most likely reasons are differences in patient cohorts and study design. In some studies, the number of patients might have been too small to provide consistent results.17,13 The follow-up of patients was retrospective in
3 studies,\textsuperscript{10,14,15} and 1 study\textsuperscript{7} was restricted to men only. Results are based on homozygous and heterozygous carriers of FV Leiden. In all studies, the determination of FV Leiden was performed—at least in a subset of patients—in retrospect. Several studies included patients with secondary\textsuperscript{10,12,14,15} or recurrent\textsuperscript{10,11,13} thrombosis or patients with arm or calf VT.\textsuperscript{7,10-12,15} Nonobjective diagnostic procedures were allowed for the diagnosis of VT at presentation or at recurrence.\textsuperscript{8,9,14} The duration of oral anticoagulation and follow-up times varied widely.

The primary aim of the present analysis was to assess the association of FV Leiden with the risk of recurrent VTE in a well-defined cohort of patients with thrombosis (ie, in heterozygous carriers and noncarriers of the mutation with a first spontaneous episode of a VT of the proximal leg and/or pulmonary embolism). Another objective of the present analysis was to evaluate the influence of various patient and study characteristics on the risk of recurrence in patients with and without FV Leiden.

**METHODS**

**PATIENT POPULATION**

All patients enrolled in the ongoing Austrian Study on Recurrent Venous Thromboembolism (AUREC) between July 1992 and July 1999 were eligible. The AUREC is a prospective observational study with 4 participating centers specialized in the diagnosis and treatment of VTE. Patients were included in the present analysis if they had an objectively confirmed first episode of proximal VT of the leg and/or pulmonary embolism. Patients were excluded if the VTE was secondary to trauma, surgery, or pregnancy, if they were homozygous for the 1691A allele, if they had a natural inhibitor deficiency, the lupus anticoagulant, or cancer, or if they needed long-term antithrombotic therapy for reasons other than VTE. The present study was approved by the Ethics Committee of the University of Vienna, and patients had to provide informed consent prior to inclusion.

**DIAGNOSIS OF VTE**

The diagnosis of VT was based on a positive finding on venography or color duplex sonography. To be considered positive, the venograms had to meet at least 1 of the following direct or indirect criteria: an abrupt discontinuation of the contrast-filled vessel at a constant level of the vein; and the absence of filling in the entire deep vein system (without a compression), with or without venous flow through collateral veins. With color duplex sonography, at least 1 of the following criteria for VT had to be met: visualization of an intraluminal thrombus in a deep vein and incomplete compressibility or absence of compressibility.

The diagnosis of pulmonary embolism was established either by a high-probability ventilation-perfusion lung scan (according to the criteria of the Prospective Investigation of Pulmonary Embolism Diagnosis\textsuperscript{16}) or by spiral computed tomography revealing one or several low-attenuation areas that partly or completely filled the lumen of an opacified vessel. Patients with VT and pulmonary embolism were classified as pulmonary embolism.

**STUDY END POINTS**

The end points of the study were recurrent symptomatic VT confirmed by venography or color duplex sonography in cases of proximal VT of the contralateral leg and/or recurrent symptomatic pulmonary embolism confirmed by ventilation-perfusion scanning of the lungs and/or spiral computed tomography according to the aforementioned criteria. In patients undergoing venography, VT was considered to have recurred if the patient had a thrombus in the leg other than affected by the previous thromboembolic event; a thrombus in another deep vein in the same leg as the previous event; or a thrombus in the same venous system as the previous event with proximal extension of the thrombus (if the upper limit of the original thrombus had been visible) or with a constant filling defect surrounded by contrast medium (if the original thrombus had not been visible).

**LABORATORY ANALYSIS**

Venous blood was collected after overnight fasting into 1:10 volume of 0.11M trisodium citrate and centrifuged for 20 minutes at 2000g. The plasma was stored at −80°C. For measurement of homocysteine, venous blood was immediately centrifuged at 1600g for 20 minutes at 4°C. The plasma was snap frozen and stored at −80°C. Genomic DNA was isolated from leukocytes by standard methods.

Screening for FV Leiden and for factor II (FII) G20210A was carried out as previously described.\textsuperscript{17,18} Determination of antithrombin, protein C, protein S, total homocysteine, and factor VIII was performed as previously reported.\textsuperscript{19} The presence of a lupus anticoagulant was established based on the criteria of the Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibody of the Scientific and Standardisation Committee of the International Society of Thrombosis and Haemostasis.\textsuperscript{20} The technicians were unaware of the patient characteristics at all times.

**STATISTICAL ANALYSIS**

Times to recurrence (uncensored observations) or follow-up times in patients without recurrence (censored observations) were analyzed using survival time methods.\textsuperscript{21} The probability of recurrence was estimated according to the Kaplan-Meier method.\textsuperscript{22} To test for homogeneity between strata, we applied the log-rank and the generalized Wilcoxon test. The data were adjusted for age, sex, FII G20210A, hyperhomocysteinemia (dichotomized at the 95th percentile of normal), high factor VIII level (dichotomized at a plasma level of 234 IU/dL), and duration of oral anticoagulation therapy. Categorical data were checked for homogeneity using contingency table analyses ($\chi^2$ test). Simple descriptive statistics were computed to provide a clear presentation of the data. For numerical operations, version 8.2 of the SAS software package (SAS Institute Inc, Cary, NC) was used.

Of the 287 study patients, 83 (29%) were heterozygous carriers of FV Leiden. The demographic features of the patients are summarized in the Table. The 2 patient groups did not significantly differ with regard to age, sex, duration of anticoagulation therapy, the presence of FII G20210A, hyperhomocysteinemia, high factor VIII level, or observation time.

During follow-up, 74 patients were excluded because they required antithrombotic therapy (1) for reasons other than VTE (37 patients), (2) because they were given a diagnosis of cancer (7 patients), or (3) because they became pregnant (10 patients). Twenty-nine patients were lost to follow-up, and 2 patients died (heart
failure and chronic lung disease, respectively). These patients were censored at the time of exclusion or death.

**RISK OF RECURRENT VTE**

Seventeen (20%) of the 83 patients with FV Leiden and 44 (21.6%) of the 204 patients without the mutation developed recurrent symptomatic VTE (11 and 29 VT, 6 and 15 pulmonary embolism, respectively). At 2, 4, and 6 years, the cumulative probability of recurrence was 12% (95% confidence interval [CI], 8%-16%), 27% (95% CI, 21%-33%), and 27% (95% CI, 21%-33%), respectively, among heterozygous carriers of FV Leiden and was thus not higher than that in patients without the mutation (16% [95% CI, 13%-19%], 23% [95% CI, 19%-26%], and 34% [95% CI, 29%-39%], respectively; P = .60). Compared with patients without FV Leiden, the relative risk (RR) of recurrence was 0.9 (95% CI, 0.5-1.5; P = .60) among carriers of the mutation and remained unchanged after adjustment for age, sex, the presence of FII G20210A, high factor VIII levels, and duration of anticoagulation therapy (RR, 0.9 [95% CI, 0.5-1.6]; P = .60).

We next assessed the risk of recurrence in 143 (49.8%) male study patients and did not find a higher RR (1.0; 95% CI, 0.5-1.9; P = .90) in male heterozygous carriers of FV Leiden than in men with wild-type FV. Adjustment for age, the presence of FII G20210A, hyperhomocysteinemia, high factor VIII levels, and duration of anticoagulation therapy did not affect the RR in heterozygous men (1.0; 95% CI, 0.5-1.9; P = .90).

With regard to differences in secondary thromboprophylaxis, we divided carriers and noncarriers of FV Leiden into 2 groups according to the duration of oral anticoagulant therapy (longer than 6 months vs 6 months or less). In both groups, heterozygous carriers of FV Leiden did not have a higher risk of recurrence than patients with wild-type FV (RR, 0.7 for anticoagulant therapy longer than 6 months [95% CI, 0.3-1.4]; P = .3); and RR, 1.2 for anticoagulant therapy duration of 6 months or less [95% CI, 0.5-2.9; P = .80]) after adjustment for age, sex, the presence of FII G20210A, hyperhomocysteinemia, and high factor VIII levels.

In 1997, a prospective study found that carriers of FV Leiden did not have an increased risk of recurrent VTE. This study, however, had limitations. Patients with recurrent VTE or homozygous carriers of FV Leiden who might have had an increased risk of recurrence were included. Patients with a lower risk of recurrence, such as patients with distal leg or arm VTs or those with VTE secondary to trauma or surgery, were also included. In addition, the relatively short observation time might have skewed the results. To better define the effect of FV Leiden on the risk of recurrence, in the present analysis we included only patients with a first spontaneous proximal VT of the leg with or without pulmonary embolism and excluded homozygous carriers of FV Leiden. The follow-up was extended to 3 years on average (compared with 20 months on average in the 1997 study), and in a large proportion of patients (72%) the determination of FV Leiden was performed at study entry and not during follow-up. In accordance with the earlier results, the present analysis clearly shows that heterozygous carriers of FV Leiden do not have a higher risk of recurrence after a first spontaneous VTE than patients without the mutation (cumulative probability, 12% and 16%, respectively, for patients with and without FV Leiden at 2 years). It is also noteworthy that the risk of recurrence in patients with and without FV Leiden was not different when sex distribution and duration of anticoagulation therapy were taken into account.

Since 1992, several other thrombotic risk factors have been identified. Hyperhomocysteinemia or high factor VIII levels have been shown to be important independent risk factors for recurrent VTE. In contrast, heterozygous carriers of the FII 20210A allele did not have a higher risk of recurrence than patients without the mutation. A confounding effect of the presence of one or more of these risk factors on the risk of recurrence among the patients with FV Leiden is most unlikely be-

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**Characteristics of 287 Patients With and Without Heterozygous Factor V (FV) Leiden and a First Spontaneous VT**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Wild-Type FV (n = 204)</th>
<th>FV Leiden (n = 83)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>52 ± 17</td>
<td>48 ± 18</td>
<td>.10</td>
</tr>
<tr>
<td>Men</td>
<td>101 (49)</td>
<td>42 (51)</td>
<td>.50</td>
</tr>
<tr>
<td>Site of first VTE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>100 (49)</td>
<td>46 (55)</td>
<td>.20</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>104 (51)</td>
<td>37 (45)</td>
<td>.20</td>
</tr>
<tr>
<td>Factor II G20210A</td>
<td>20 (10)</td>
<td>6 (7)</td>
<td>.30</td>
</tr>
<tr>
<td>Homocysteinemia</td>
<td>48 (25)</td>
<td>15 (19)</td>
<td>.20</td>
</tr>
<tr>
<td>Factor VIII</td>
<td>24 (12)</td>
<td>10 (12)</td>
<td>.60</td>
</tr>
<tr>
<td>Oral anticoagulant use, mo</td>
<td>10 ± 6</td>
<td>10 ± 4</td>
<td>.06</td>
</tr>
<tr>
<td>Observation time, mo</td>
<td>35 ± 27</td>
<td>38 ± 25</td>
<td>.30</td>
</tr>
</tbody>
</table>

*Unless otherwise indicated, data are mean ± SD or number (percentage). VTE indicates venous thromboembolism.*

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**Cumulative probability of recurrent venous thromboembolism in 287 patients with heterozygous factor V (FV) Leiden or wild-type FV and a first spontaneous venous thromboembolism.**

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**COMMENT**

In 1997, a prospective study found that carriers of FV Leiden did not have an increased risk of recurrent VTE.

This study, however, had limitations. Patients with recurrent VTE or homozygous carriers of FV Leiden who might have had an increased risk of recurrence were included. Patients with a lower risk of recurrence, such as patients with distal leg or arm VTs or those with VTE secondary to trauma or surgery, were also included. In addition, the relatively short observation time might have skewed the results. To better define the effect of FV Leiden on the risk of recurrence, in the present analysis we included only patients with a first spontaneous proximal VT of the leg with or without pulmonary embolism and excluded homozygous carriers of FV Leiden. The follow-up was extended to 3 years on average (compared with 20 months on average in the 1997 study), and in a large proportion of patients (72%) the determination of FV Leiden was performed at study entry and not during follow-up. In accordance with the earlier results, the present analysis clearly shows that heterozygous carriers of FV Leiden do not have a higher risk of recurrence after a first spontaneous VTE than patients without the mutation (cumulative probability, 12% and 16%, respectively, for patients with and without FV Leiden at 2 years). It is also noteworthy that the risk of recurrence in patients with and without FV Leiden was not different when sex distribution and duration of anticoagulation therapy were taken into account.

Since 1992, several other thrombotic risk factors have been identified. Hyperhomocysteinemia or high factor VIII levels have been shown to be important independent risk factors for recurrent VTE. In contrast, heterozygous carriers of the FII 20210A allele did not have a higher risk of recurrence than patients without the mutation. A confounding effect of the presence of one or more of these risk factors on the risk of recurrence among the patients with FV Leiden is most unlikely be-
cause the distribution of hyperhomocysteinemia, high factor VIII levels, and/or the presence of FII G20210A was well balanced between patients with and without FV Leiden. Adjustment for these thrombotic risk factors did not affect the risk of recurrence among heterozygous carriers of FV Leiden.

Our analysis was restricted to heterozygous carriers of FV Leiden. Among homozygous carriers of the mutation, the risk of recurrence still remains unknown. In a Swedish study of a small number of patients, the risk of recurrence was 4-fold higher among homozygous FV Leiden patients than among heterozygotes or noncarriers of the mutation.12

The finding that a risk factor for a first thrombosis does not also emerge as an independent risk factor for a subsequent event is puzzling and does not easily fit into the pathophysiologic concept of venous thrombotic disease. The fact that patients with FV Leiden are not at a greater risk of recurrence than patients with wild-type FV does not entirely exclude that FV Leiden might contribute—to a small extent—to the risk of recurrence. However, the effect of FV Leiden on the risk of recurrence is most probably outweighed by the presence of other potent risk factors.

The optimal duration of secondary thromboprophylaxis in patients with VTE is a matter of debate. Currently, 3 to 6 months of oral anticoagulant therapy seems to be sufficient in patients with a first spontaneous VT who do not have a major thrombotic risk factor such as a natural inhibitor deficiency, cancer, or the lupus anticoagulant.13,26-28 With regard to patients with FV Leiden and a history of VTE, interventional studies are lacking. The present study performed in a well-defined cohort of patients with thrombosis clearly shows that the risk of recurrence is comparable between carriers and noncarriers of FV Leiden. Therefore, heterozygous FV Leiden patients should receive secondary thromboprophylaxis for a similar length of time as patients without FV Leiden.

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