Risk of Recurrent Venous Thromboembolism in Patients With Common Thrombophilia

A Systematic Review

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The 2 most common genetic polymorphisms that predispose to a first episode of venous thromboembolism (VTE) are factor V Leiden (FVL) and prothrombin G20210A. However, the effect of these polymorphisms on the risk of recurrent VTE is unclear.

We performed a meta-analysis to obtain best estimates of the relative risk of recurrent VTE associated with these genetic polymorphisms. Electronic and manual searches were used to identify cohort studies of patients with a first episode of VTE that reported the incidence of objectively confirmed recurrence following discontinuation of anticoagulation among those with or without heterozygous FVL or prothrombin G20210A polymorphism. Thirteen reports fulfilled our criteria for inclusion. Pooled results from 10 studies involving 3104 patients with first-ever VTE revealed that FVL was present in 21.4% of patients (95% confidence interval [CI], 20%-23%) and associated with an increased odds of recurrent VTE of 1.41 (95% CI, 1.14-1.75; \( P = .08 \) for heterogeneity). Pooled results from 9 studies involving 2903 patients with first-ever VTE revealed that prothrombin G20210A was present in 9.7% of patients (95% CI, 9%-11%) and associated with an increased odds of recurrent VTE of 1.72 (95% CI, 1.27-2.31; \( P = .19 \)). The estimated population-attributable risk of recurrence for FVL was 9.0% (95% CI, 4.5%-13.2%) and for prothrombin G20210A was 6.7% (95% CI, 3.4%-9.9%). Heterozygous FVL and prothrombin G20210A are each associated with a significantly increased risk of recurrent VTE after a first event, but the magnitude of the increase in risk is modest and by itself is unlikely to merit extended-duration anticoagulation.

These data call into question the cost-effectiveness of routine testing for these common inherited thrombophilic polymorphisms among patients with a first episode of VTE.

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term warfarin treatment while those at lower risk of recurrence or increased risk of bleeding can stop warfarin therapy.

Patients can be stratified according to their risk of recurrent VTE by considering the setting in which the initial event occurred. Those in whom VTE is provoked by a self-limited risk factor (eg, hospitalization or surgery) have a 1% to 4% incidence each year of recurrence when warfarin treatment is discontinued and are therefore unlikely to benefit from long-term warfarin therapy. In contrast, patients with unprovoked VTE have a 5% to 10% or higher annual incidence of recurrent venous thromboembolism. The 2004 American College of Chest Physicians Guidelines suggest that these patients should be considered for indefinite warfarin therapy. However, even in this group, most patients do not experience recurrent VTE and would therefore be taking warfarin unnecessarily. This suggests that better approaches to risk stratification are required.

Attention has recently focused on the possible role of inherited thrombophilia to predict the risk of recurrent thrombosis. In the general white population, the 2 most common inherited thrombophilic disorders are factor V Leiden (FVL) (prevalence, 2%-7%) and prothrombin G20210A (prevalence, 2%-3%). Factor V Leiden increases the risk of a first episode of VTE by 3- to 7-fold, whereas prothrombin G20210A increases the risk by 2- to 3-fold. In white patients with a history of VTE, the prevalence of FVL is reported to be about 20%, and that of prothrombin G20210A about 7%. Yet it is unclear whether these polymorphisms also increase the risk of recurrent VTE, with conflicting reports published in the medical literature.

Obtaining reliable estimates of the risk of recurrent VTE associated with heterozygosity for FVL or prothrombin G20210A is important for clinicians and patients because (1) at least 1 of these thrombophilic disorders affect approximately one quarter of unselected patients with VTE; (2) genetic testing is readily available and is increasingly being requested by patients; (3) some experts already recommend extended (>6 months) or indefinite anticoagulation in affected patients after a first VTE; and (4) testing for FVL or prothrombin G20210A potentially has important social, medicolegal, and economic implications.

The aim of this meta-analysis was to obtain the most reliable estimates of the prevalence of heterozygous carriage of FVL or prothrombin G20210A among patients with first-ever VTE, and risk of recurrent VTE conferred by heterozygous carriage of FVL or prothrombin G20210A compared with noncarriers.

**STUDY IDENTIFICATION**

We searched the literature from January 1, 1993, to June 30, 2005, using the MEDLINE database to identify studies that examined the association between FVL or prothrombin G20210A and recurrent VTE using the following terms: pulmonary embolism, venous thrombosis, deep vein thrombosis, venous thromboembolism, recurrence, recurrent, factor V Leiden, activated protein C resistance, prothrombin G20210A, and prothrombin gene mutation. The search strategy had no language restrictions.

We manually searched reference lists of journal articles to locate additional studies. We assessed the relevance of studies by using a hierarchical approach based on title, abstract, and the full manuscript.

**STUDY SELECTION**

Two reviewers independently selected studies for inclusion. To be included, studies had to meet the following criteria: (1) cohort design, in which clinical outcomes in carriers of FVL and prothrombin G20210A were compared with outcomes in noncarriers; (2) include patients with a first episode of VTE, including DVT of the lower limbs and/or PE; (3) the index event had to be treated with effective anticoagulation (eg, unfractionated heparin or low-molecular-weight heparin followed by warfarin therapy) for at least 3 months; (4) the duration of follow-up had to be at least 6 months after discontinuation of anticoagulation; and (5) index and recurrent thrombotic events had to be objectively confirmed.

Studies were excluded if (1) the duration of anticoagulation was not certain; (2) the report concerned family studies, pediatric or obstetric patients, or venous thrombosis in unusual sites only (eg, mesenteric, renal, upper limbs, or cerebral sinuses); and (3) the case involved duplicate reports, in which case only the report containing the most complete data was included.

**STUDY QUALITY**

Study quality was assessed according to the following criteria: (1) design (prospective cohort studies were considered higher quality than retrospective cohort studies); (2) patients (inclusion cohort studies were considered higher quality than noninception cohorts); and (3) follow-up (studies with at least 90% complete follow-up were considered higher quality than studies in which follow-up was less than 90% complete).

**DATA EXTRACTION**

Two reviewers independently extracted the following data: (1) study characteristics (year, design, study center); (2) patients (number, eligibility); (3) index event (DVT or PE); (4) treatment duration; (5) duration of follow-up; and (6) study quality.

We excluded, where relevant data were available, those patients whose index (first) VTE occurred in the setting of cancer because this is an independent predictor of recurrence that can potentially modify the nature of the association between FVL or prothrombin G20210A and recurrent VTE. We contacted authors of potentially suitable studies for missing data.

**STATISTICAL ANALYSIS**

We pooled results from the individual studies using Review Manager (RevMan), version 4.2 for Windows (The Cochrane Collaboration 2002, Oxford, England). We calculated odds ratios (ORs) and 95% confidence intervals (CIs) using a fixed-effects model (Mantel-Haenszel method) and compared these findings with results obtained using a random effects model (DerSimonian and Laird method). We assessed heterogeneity among studies using the Cochran Q and the I² statistic. P < .10 was considered to denote statistically significant heterogeneity, and where I² was greater than 50%...
Sensitivity analyses

We performed sensitivity analyses by examining the results separately in prospective and retrospective studies, by year of study commencement (studies commenced before and after the median year of commencement of all the studies), enrollment of patients with PE at initial presentation, the inclusion of patients with the antiphospholipid syndrome, and by number of years of follow-up.

Publication Bias

We explored the potential for publication bias using funnel plots of effect size vs standard error.

Results

Study Selection

The process of study selection is presented in Figure 1. Our search yielded 241 reports (235 Medline results and 6 found by manual search), of which 213 were excluded on the basis of title/abstract. Of the remaining 28 articles, 15 were excluded for the following reasons: (1) not a cohort study; (2) included patients with recurrent VTE, and data for those with a first event could not be separately obtained; (3) duration of anticoagulation was unknown, and additional information could not be obtained from the author; (4) 1 or more updated reports were available; and (5) the report was a substudy or letter/commentary where the main study results were reported elsewhere.

Study Quality

Four of the studies on the association between FVL and risk of VTE recurrence were prospective inception cohorts with at least 90% complete follow-up and were therefore considered of high quality.

Similarly, 4 studies on prothrombin G20210A carriage were considered of high quality.

Factor V Leiden

Ten studies examining the association between FVL and risk of recurrent VTE fulfilled our inclusion criteria (Table 1). The 4 high-quality studies yielded conflicting results concerning the risk conferred by carriage of this polymorphism. The estimates of risk were between 0.9 to 2.4; in 3 studies, this did not achieve statistical significance, while in the fourth there was a statistically significant increase in odds of recurrence compared with noncarriers of FVL (OR, 2.4; 95% CI, 1.4-4.1).

The 10 studies included a total of 3104 patients with first-ever VTE, 663 (21.4%; 95% CI, 19.9%-22.9%) of whom were heterozygous carriers of FVL. The duration of follow-up ranged from 1.6 to 8.3 years. Among those with recurrent VTE during follow-up, the prevalence of FVL was 28.4%, whereas the polymorphism was present in 19.9% of those with no recurrent events.

Using a fixed-effects model, the OR of recurrence conferred by heterozygous carriage of FVL after a first VTE was 1.41 (95% CI, 1.14-1.75) (Figure 2). Although there was significant statistical heterogeneity (P = .08, F = 41.4%), the random-effects model yielded a similar estimate of increased risk (OR, 1.53; 95% CI, 1.13-2.06).

Statistical heterogeneity was no longer evident when the study by Simioni et al was removed from the analysis (OR, 1.30; 95% CI, 1.03-1.63; P = .37 for heterogeneity; I² = 8.2%). This study was conducted in Padua, Italy, and involved patients with DVT who were referred to a specialist thrombosis center (Table 1). Patients with PE were not eligible for inclusion in this study. Two other studies had similar exclusion criteria but, unlike the study by Simioni et al, were not a major source of heterogeneity. The age of study participants, proportion of men, and prevalence of FVL in the study by Simioni et al were similar to many of the other studies included in our meta-analysis. We were unable to further explore referral bias or differential use of cointerventions as potential sources of heterogeneity because this information was not provided.

Sensitivity analyses demonstrated similar odds of VTE recurrence when studies were analyzed according to their design (prospective vs retrospective), follow-up duration, whether patients with PE or antiphospholipid antibody syndrome were included, and whether
Table 1. Studies Examining FVL Carriage and Risk of Recurrent VTE*

<table>
<thead>
<tr>
<th>Source, Study Location</th>
<th>Design, Years of Study</th>
<th>Eligibility</th>
<th>Exclusion Criteria†</th>
<th>Index Event</th>
<th>Treatment Duration, mo</th>
<th>Follow-up Duration, y</th>
<th>FVL Carriers‡</th>
<th>Non-FVL Carriers§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Christiansen et al,20</td>
<td>Prospective, 1988-1992</td>
<td>Consecutive patients referred for management of OA</td>
<td>Age &gt;70 y</td>
<td>DVT</td>
<td>3-3</td>
<td>7.3</td>
<td>20/92</td>
<td>70/382</td>
</tr>
<tr>
<td>Marcucci et al,21</td>
<td>Retrospective, 1999-2001</td>
<td>Consecutive patients referred to specialist center</td>
<td>APS, history of arterial thromboembolism, deficiencies of NA, and cases of cerebral, mesenteric, portal, and retinal venous thrombosis</td>
<td>DVT and/or PE</td>
<td>3-12</td>
<td>2.8</td>
<td>26/113</td>
<td>49/269</td>
</tr>
<tr>
<td>Schattner et al,27</td>
<td>Retrospective, 1987-1992</td>
<td>Consecutive hospitalized patients aged ≤50 y</td>
<td>APS/SLE, major organ dysfunction and deficiencies of NA</td>
<td>DVT</td>
<td>3-6</td>
<td>7.9</td>
<td>3/8</td>
<td>6/15</td>
</tr>
<tr>
<td>Rehovot, Israel</td>
<td>Prospective, 1982-1983</td>
<td>Male physicians aged 40-84 y enrolled in PHS</td>
<td>Post Surgical status, VTE</td>
<td>DVT and/or PE</td>
<td>3 (mean)</td>
<td>5.7</td>
<td>4/14</td>
<td>7/63</td>
</tr>
<tr>
<td>Lindmark et al,33</td>
<td>Prospective, 1994-1998</td>
<td>Consecutive patients referred to specialist centers</td>
<td>Myeloproliferative disorders, autoimmune disorders (including APS), requirement of long-term (&gt;6 mo) OA, deficiencies of NA, carriage of prothrombin G20210A in isolation or in association with other thrombophilic traits, and FVL homozygosity</td>
<td>DVT</td>
<td>3-6</td>
<td>6</td>
<td>34/112</td>
<td>86/283</td>
</tr>
<tr>
<td>De Stefano et al,34</td>
<td>Retrospective, 1994-1998</td>
<td>Consecutive patients referred to specialist center</td>
<td>APS, requirement of long-term OA, deficiencies of NA, and FVL/G20210A compound heterozygosity</td>
<td>DVT</td>
<td>3-6</td>
<td>8.3</td>
<td>18/38</td>
<td>37/186</td>
</tr>
<tr>
<td>Padua, Italy</td>
<td>Prospective, 1986-1994</td>
<td>Consecutive patients referred to specialist center</td>
<td>APS, requirement of long-term OA, deficiencies of NA, and FVL/G20210A compound heterozygosity</td>
<td>DVT</td>
<td>3-6</td>
<td>8.3</td>
<td>18/38</td>
<td>37/186</td>
</tr>
<tr>
<td>Simioni et al,35</td>
<td>Prospective, 1992-1999</td>
<td>Consecutive patients aged ≥18 y referred to specialist centers and enrolled in AUREC observational study</td>
<td>Prosthetic Valvular Endocarditis, Postsurgical status, or periarticular status, APS, requirement of long-term OA, deficiencies of NA, and FVL homozygosity</td>
<td>Prosthetic DVT and/or PE</td>
<td>10 (mean)</td>
<td>3.0</td>
<td>17/83</td>
<td>44/204</td>
</tr>
<tr>
<td>Eichinger et al,36</td>
<td>Retrospective, 1997-2002</td>
<td>Consecutive patients referred for management of OA</td>
<td>APS, requirement of long-term OA, and FVL homozygosity</td>
<td>DVT and/or PE</td>
<td>6</td>
<td>2</td>
<td>9/77</td>
<td>30/359</td>
</tr>
<tr>
<td>Baglin et al,37</td>
<td>Retrospective, 1995-2002</td>
<td>Consecutive patients referred for management of OA</td>
<td>APS</td>
<td>DVT and/or PE</td>
<td>≥3</td>
<td>1.6</td>
<td>13/73</td>
<td>38/500</td>
</tr>
<tr>
<td>Palareti et al,38</td>
<td>Retrospective, 1997-2002</td>
<td>Consecutive patients referred for management of OA</td>
<td>APS</td>
<td>DVT and/or PE</td>
<td>≥3</td>
<td>1.6</td>
<td>13/73</td>
<td>38/500</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>152/863</td>
<td>383/2441</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: APS, antiphospholipid antibody syndrome; AUREC, Austrian Study of Recurrent Venous Thromboembolism; DURAC, Duration of Anticoagulation; DVT, deep venous thrombosis; FVL, factor V Leiden; NA, natural anticoagulants (protein C, protein S, and antithrombin); OA, oral anticoagulation; PHS, Physicians’ Health Study; SLE, systemic lupus erythematosus; VTE, venous thromboembolism.

*All cases of cancer are excluded. †Features in italics were excluded at data extraction. ‡Data reported as number of patients with VTE recurrence/number of patients with a first VTE.

studies were commenced prior to or after the median year of commencement of all the studies (Table 2). A funnel plot of effect size vs standard error was broadly symmetrical (Figure 3), which is consistent with the conclusion that there was no major publication bias. Among patients with a first VTE, the estimated attributable risk of recurrence conferred by heterozygous carriage of FVL was 9.0% (95% CI, 4.5%-13.2%).

**PROTHROMBIN G20210A**

Nine studies examining the association between prothrombin G20210A and risk of recurrent VTE fulfilled our inclusion criteria (Table 3). Of the 4 high-quality studies, only 1 found a statistically significant increase in risk of recurrence associated with heterozygous carriage of the G20210A polymorphism (OR, 2.4; 95% CI, 1.3-4.7).

The 9 studies included a total of 2903 patients with first-ever VTE, 283 (9.7%; 95% CI, 8.7%-10.9%) of whom were carriers of the G20210A polymorphism. The follow-up duration ranged from 1.7 to 8.3 years. Prothrombin G20210A was pres-
ent in 15.8% of those with recurrent VTE and in 8.6% of those with no recurrences.

The OR of recurrence after a first VTE conferred by heterozygous carriage of prothrombin G20210A was 1.72 (95% CI, 1.27-2.31) under the fixed-effects model, with no statistically significant heterogeneity (P = .19; I² = 28.2%) (Figure 4). The random effects model yielded a similar estimate (OR, 1.81; 95% CI, 1.32-2.49). The funnel plot of effect size vs standard error was broadly symmetrical (Figure 5), suggesting no marked publication bias.

Sensitivity analyses demonstrated similar odds of VTE recurrence when studies were analyzed according to their design (prospective vs retrospective), follow-up duration, whether patients with PE or antiphospholipid antibody syndrome were included, and whether studies were commenced prior to or after the median year of commencement of all the studies (Table 2). The estimated attributable risk of recurrence conferred by prothrombin G20210A was 6.7% (95% CI, 3.4%-9.9%) in this pooled cohort.

**COMMENT**

Our results indicate that the prevalence of heterozygous carriage of FVL and prothrombin G20210A was more common among patients with recurrent VTE (28.4% and 15.8%, respectively) than among those who had no recurrences (19.9% and 8.6%, respectively). Each polymorphism conferred a significant increase in odds of recurrent VTE: for heterozygous FVL by about 40% (14%-75%) and for heterozygous prothrombin G20210A by about 70% (27%-131%). However, the magnitude of these increases in risk of recurrence are much lower than the risk for first-ever VTE (3- to 7-fold for FVL and 2- to 3-fold for prothrombin G20210A). Consequently, the combined population attributable risk of recurrent VTE associated with FVL and prothrombin G20210A is modest (ie, at most, only up to 1 in 6 recurrent VTEs may be attributable to these mutations).

The strengths of our study are that we carefully searched the literature to identify all studies that explored the association of FVL and prothrombin G20210A with recurrent VTE (as defined by 3- to 28% for prothrombin G20210A). Consequently, the combined population attributable risk of recurrent VTE associated with FVL and prothrombin G20210A is modest (ie, at most, only up to 1 in 6 recurrent VTEs may be attributable to these mutations).
Advocated the risk of recurrent VTE conferred by heterozygous carriage of FVL or prothrombin G20210A compared with noncarriage, thereby ensuring that our analyses provide the most reliable estimates to date of this risk. We restricted inclusion to cohort studies that included patients with a first objectively confirmed VTE because patients with multiple prior events may have a different natural history and may be more likely to be selected for inclusion in studies and investigated for recurrent VTE. Furthermore, those with multiple previous events are candidates for long-term preventive strategies regardless of their thrombophilia status. We also excluded cases of VTE known to be associated with active cancer. Because of the potential for underreporting of negative studies, we examined publication bias by means of funnel plots, and there does not appear to be any.

The potential weaknesses of our study are several. First, although we established predefined criteria for study selection, the quality of meta-analysis remains dependent on the quality of the included studies. Four of the 13 reports included in our meta-analysis were retrospective, and all studies were subject to selection or referral bias because patients with unprovoked VTE, a large thrombotic burden, or significant comorbidities are more likely to be referred to specialist centers, included in studies, and described in the literature. Second, the included studies were conducted over different time periods (1980s to 2002), and it is unclear how changing clinical practices and the introduction and uptake of new diagnostic and therapeutic approaches might have...
influenced referral and treatment patterns. However, sensitivity analyses demonstrated broadly similar odds of VTE recurrence in the cases with FVL and prothrombin G20210A regardless of whether the study was started before or after the median year of commencement of all studies. Third, we could not obtain missing data from all of the studies despite contacting the authors. Finally, VTE is a multifactorial disorder, caused in part by gene-gene and gene-environment interactions, many of which are still poorly defined and understood. Most of the studies included in our meta-analysis were undertaken in European centers, and it is unknown if our findings can be extrapolated to other communities with potentially different genetic and environmental risk factors for VTE.

**FACTOR V LEIDEN**

Our findings for the association between FVL and odds of recurrent VTE are consistent with those of 2 earlier meta-analyses. Marchetti et al reported an odds of recurrence of 1.36 (95% CI, 1.05-1.78) among patients with heterozygous FVL, based on the results of 6 studies involving 1721 patients, while Vink et al reported an odds of recurrence of 1.3 (95% CI, 1.01-1.7) based on 7 studies involving 1984 patients. Our analyses for FVL are based on an additional 1120 patients and, unlike earlier reports, we did not include patients with recurrent VTE or studies in which a minimum duration of anticoagulant therapy could not be established.

**PROTHROMBIN G20210A**

To our knowledge, the only previous meta-analysis examining the association between prothrombin G20210A and risk of recurrent VTE did not demonstrate a significant association (OR, 1.4; 95% CI, 0.9-2.0). This report included 5 studies and about 1922 patients and may have been underpowered to establish a significant association. Our study included an additional 981 patients and provides the most reliable evidence to date that prothrombin G20210A is a predictor of recurrent VTE.

The clinical implications of our study are that while patients with recurrent VTE are more likely to have heterozygous FVL or prothrombin G20210A than those without recurrence, the magnitude of increased risk is modest. Therefore, in the absence of other risk factors, the presence of either FVL or prothrombin G20210A alone is unlikely to merit extended-duration anticoagulation. This calls into question the cost-effectiveness of routine testing for these common inherited thrombophilic disorders in patients with a first episode of VTE. Decisions concerning the optimal duration of anticoagulation in an individual are likely to remain dependent primarily on assessment of the balance between the clinical determinants of recurrence, risk of major bleeding, and patient preferences.

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