Increased risk of venous thrombosis in persons with clinically diagnosed superficial vein thrombosis: results from the MEGA study

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Running title: Superficial vein thrombosis and venous thrombosis risk
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ABSTRACT

Superficial vein thrombosis (SVT) is regarded a self-limiting disorder, although recent studies showed that ultrasonographically diagnosed SVT is a precursor for venous thrombosis. We aimed to determine whether the same holds true for clinically diagnosed SVT, and to what extent it is associated with thrombophilia in a population-based case-control study (MEGA). We found that a history of clinical SVT was associated with a 6.3-fold (95%CI 5.0-8.0) increased risk of deep-vein thrombosis and a 3.9-fold (95%CI 3.0-5.1) increased risk of pulmonary embolism. Blood group non-O and factor V Leiden showed a small increase in SVT risk in controls, with odds ratios of 1.3 (95%CI 0.9-2.0) and 1.5 (95%CI 0.7-3.3), respectively. In conclusion, clinically diagnosed SVT was a risk factor for venous thrombosis. Given that thrombophilia was only weakly associated with SVT, it is likely that other factors (varicosis, obesity, stasis) also play a role in its etiology.
INTRODUCTION

Superficial vein thrombosis (SVT) is a controversial disease entity.¹ Previously called thrombophlebitis, the name suggests that both thrombosis and inflammation play a role in the disease mechanism. Recent studies provide evidence that SVT should be seen as a form of venous thrombosis (VT), together with pulmonary embolism and deep-vein thrombosis.¹⁶ A recent clinical trial (CALISTO) showed a symptomatic VT rate of 1.5% within 77 days after SVT diagnosis in placebo users.² This VT rate was probably positively influenced by the definition of SVT that CALISTO investigators used.

Although most physicians learn that SVT is identifiable by a red, painful, palpable cord in the course of a superficial vein,¹⁷ in CALISTO SVT was only regarded as definitely diagnosed when in addition to these clinical signs an ultrasonography of the superficial vein showed a clot of at least 5 centimeters long. Current literature agrees that such SVTs should be regarded as “real” SVT,²⁸ but this does not follow clinical practice, nor does it imply that there is no clot present in less definite presentations. It is therefore uncertain whether patients with clinically diagnosed, but not necessarily ultrasonographically confirmed SVT are at risk of VT and whether this risk can be explained by underlying thrombogenic causes.

For these reasons we set out to determine whether a history of clinically diagnosed SVT is associated with an increased risk of subsequent VT in a large population-based case-control study (MEGA study). We also analyzed whether common thrombophilic genetic risk factors for VT increase SVT risk, as well as whether the presence of such thrombophilia could explain the link between the two conditions.
STUDY DESIGN

The MEGA study is a population-based case-control study that has been described in detail elsewhere. Approval for this study was obtained from the Medical Ethics Committee of the Leiden University Medical Center, and all participants provided written informed consent according to the Helsinki Declaration. Participants were aged 18 to 70 years. 4956 consecutive patients with deep-vein thrombosis or pulmonary embolism were enrolled, together with 6297 age- and sex-matched controls. A questionnaire was filled in to assess VT risk factors; one of the topics was the presence of SVT at any time before VT event onset or enrollment. In addition, participants provided a blood or buccal swab sample for DNA. Common genetic risk factors were assessed, i.e., the factor V Leiden mutation, prothrombin G20210A and ABO-bloodgroup. These were determined by polymerase chain reactions using the TaqMan assay. Technicians were blinded to whether the samples came from patients or controls. For the present analysis, questionnaire data on SVT were available from 4290 patients and 5754 controls. No acquired risk factors for SVT (like varicosis or cancer) were analyzed to avoid temporality issues, i.e., the questionnaire did not provide data on the time relation between these acquired risk factors in relation to date of SVT and enrollment in the study. Besides, previous studies have already shown that acquired risk factors such as varicosis, malignancy, and obesity are associated with SVT.

Odds ratios (ORs) with 95% confidence intervals (CIs) for the risk of SVT on VT were calculated by using logistic regression models. ORs for genetic risk factors were calculated for SVT as a binary outcome. This was done in the case group and in the control group separately. As the relation between SVT and VT could be explained by the
presence of thrombophilia, we adjusted the association between SVT and VT for factor V Leiden, prothrombin G20210A and ABO-bloodgroup. All analyses were adjusted for age and sex to take the matching into account.
RESULTS AND DISCUSSION

Our study included 2887 patients with deep-vein thrombosis only, 447 patients with pulmonary embolism only and 1622 with both deep-vein thrombosis and pulmonary embolism. Median age (interquartile range) was 50 years (39-59) for patients and 48 years (37-57) for controls. SVT prevalence was 10% (N=414) in patients and 2% (N=110) in controls (Table 1). Participants with prior SVT were 6 times more likely to have a deep-vein thrombosis (OR 6.3; 95% CI 5.0-8.0) than controls, and 4 times more likely to have a pulmonary embolism (OR 3.9; 95% CI 3.0-5.1) than controls. Genetic risk factors for SVT are shown in Table 2. In both patients and controls, blood group non-O had a 1.3-fold increased risk for SVT with blood group O as a reference group. For patients with factor V Leiden, this OR was 2.0 (95% CI 1.6-2.6), whereas for controls the OR was 1.5 (95% CI 0.7-3.3). Prothrombin G20210A was associated with a 1.3-fold (95% CI 0.9-2.0) increased risk of SVT in patients, and 0.9-fold (95% CI 0.2-3.7) in controls. Subsequently, we adjusted the association between SVT and DVT for factor V Leiden, prothrombin G20210A and ABO-blood group. This attenuated the effect estimates slightly, indicating that a small part of the association could be explained by these prothrombotic mutations.

Our results show that a history of clinically diagnosed SVT is a risk factor for future VT, wherein the risk for deep-vein thrombosis was 6-fold increased compared to persons without SVT, and 4-fold increased for pulmonary embolism. These results are in line with recent studies that regard SVT diagnosed by ultrasonography as a precursor of VT. Furthermore, we found that clinically diagnosed SVT was weakly associated with thrombophilia, something that has been hypothesized, but has never been studied.
before in an unselected population. As far as we know, three studies have been performed that assessed the same genetic risk factors for SVT.\textsuperscript{10,13,14} The first, a case-control study, found an OR for SVT of 6.1 (95% CI 2.6-14.2) for factor V Leiden carriers vs non-carriers.\textsuperscript{13} The second study, a case series, found a factor V Leiden prevalence of 22%.\textsuperscript{14} Both studies suggest that SVT is a thrombotic disease like DVT, as factor V Leiden prevalences in DVT are very similar to those found for SVT.\textsuperscript{12} However, both studies only considered ultrasonographically confirmed SVT, and the patients had been referred to specialized clinics for thrombophilia testing. Therefore selection must have contributed to the high prevalence of thrombophilia in these studies. The third study resembled our study the most, in that they included SVTs that were not necessarily ultrasonographically confirmed, and compared these with healthy donors.\textsuperscript{10} Here factor V Leiden increased the risk of SVT 2.1 fold (95% CI 0.8-5.3) compared with non-carriers. At any rate, the thrombotic component of SVT is probably much smaller compared to DVT, as the effect of the prothrombotic mutations is clearly less pronounced.

Our study has some methodological issues that warrant a comment. First, SVT has been collected as self-reported data in a questionnaire, so no objective verification of diagnoses was possible. However, this fits with our aim to study the role of common clinical practice in the diagnosis of SVT.\textsuperscript{6,12} It is possible that symptoms of another condition may have erroneously been reported as SVT, which would have led to misclassification of the exposure. Such misclassification would most likely have occurred in cases and controls to the same extent, and the relative risk we found would then be an underestimation of the true effect. Second, we had no data on the time duration between SVT and the subsequent VT event in our study so we could not calculate specific risk
estimates for different time frames. In line with the previous comment, we presented the results unadjusted for possible acquired confounders, because it was unknown whether these possible confounders came before or after SVT in time. Adjusting for confounders in an unknown time relation could introduce rather than remove bias. Therefore, our data continue to erode the notion that SVT is a separate and benign form of VT. We recommend clinicians to include a patient’s history of clinically diagnosed SVT in their risk stratification analysis.

In summary, clinically diagnosed SVT was associated with a 4- to 6-fold increased risk of pulmonary embolism and deep-vein thrombosis, respectively. That genetic VT risk factors were only weakly associated with SVT suggests that other components (inflammation, obesity, stasis) also play a role in causing SVT.
Authorship Contributions

F.R.R.: MEGA study concept and design, revision of the manuscript.

S.C.C.: Revision of the manuscript.

W.M.L.: Design of the analyses, revision of the manuscript.

K.v.L.: Drafting of the manuscript and statistical analyses.

Disclosure of Conflicts of Interest

The authors declare no competing financial interests.

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Role of the Sponsor

The funding organisations are public institutions and had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.
References


Table 1. Superficial vein thrombosis as a risk factor for various types of venous thrombosis

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>Controls, n (%)</th>
<th>Adjusted odds ratio (95% CI)*</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Overall</td>
<td>DVT only</td>
</tr>
<tr>
<td>No SVT</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>SVT</td>
<td>3876 (90)</td>
<td>2211 (89)</td>
</tr>
<tr>
<td>adjusted for</td>
<td>414 (10)</td>
<td>265 (11)</td>
</tr>
<tr>
<td>FVL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>adjusted for</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FVL, FII, ABO</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* adjusted for age and sex

Table 2. Genetic risk factors for SVT (thrombophlebitis) in patients and controls in the MEGA study.

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Thrombophlebitis</td>
<td>Thrombophlebitis</td>
</tr>
<tr>
<td></td>
<td>Yes (n)</td>
<td>No (n)</td>
</tr>
<tr>
<td>Blood group O</td>
<td>96</td>
<td>1034</td>
</tr>
<tr>
<td>Blood group non-O</td>
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<td>2509</td>
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<tr>
<td>No factor V Leiden</td>
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<td>3020</td>
</tr>
<tr>
<td>Factor V Leiden</td>
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<tr>
<td>No prothrombin G20210A</td>
<td>361</td>
<td>3373</td>
</tr>
<tr>
<td>Prothrombin G20210A</td>
<td>26</td>
<td>182</td>
</tr>
</tbody>
</table>

* adjusted for age and sex
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