Clinical implications of deficiencies of protein S, protein C or antithrombin

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CHAPTER 6

High long-term absolute risk of recurrent venous thromboembolism in patients with hereditary deficiencies of protein S, protein C or antithrombin

Jan Leendert P. Brouwer, Willem M. Lijfering, Hanneke C. Kluin-Nelemans, Nic J.G.M. Veeger and Jan van der Meer

Summary

Hereditary deficiencies of protein S, protein C and antithrombin are known risk factors for first venous thromboembolism. We assessed the absolute risk of recurrence, and the contribution of concomitant thrombophilic defects in a large cohort of families with these deficiencies. Annual incidence of recurrence was estimated in 130 deficient patients, with separate estimates for those with each of protein S, protein C, and antithrombin deficiency, and in eight non-deficient patients with prior venous thromboembolism. All patients were also tested for factor V Leiden, prothrombin G20210A, high levels of factors VIII, IX and XI, and hyperhomocysteinemia. There were 81 recurrent events among 130 deficient patients. Median follow-up was 4.6 years. Annual incidences (95% confidence interval) of recurrent venous thromboembolism were 8.4% (5.8-11.7) for protein S deficiency, 6.0% (3.9-8.7) for protein C deficiency, 10.0% (6.1-15.4) for antithrombin deficiency, and overall 7.7% (6.1-9.5). Relative risk of recurrence in patients with a spontaneous versus provoked first event was 1.5 (0.95-2.3). Cumulative recurrence rates at 1, 5 and 10 years were 15%, 38% and 53%. Relative risk of recurrence with concomitant defects was 1.4 (0.7-2.6) (1 defect) and 1.4 (0.8-2.7) (≥2 defects). Annual incidence was 1.0% (0.03-5.5) in eight non-deficient patients. Annual incidence of major bleeding in deficient patients on oral anticoagulant treatment was 0.5% (0.2-1.0). We conclude that patients with a hereditary protein S, protein C or antithrombin deficiency appear to have a high absolute risk of recurrence. This risk is increased after a first spontaneous event, and by concomitance of other thrombophilic defects.
**Introduction**

Hereditary deficiencies of protein S, protein C and antithrombin are associated with a high risk of first venous thromboembolism (VTE) (1-3). Whether patients with one of these deficiencies should be treated with anticoagulants for a prolonged time after their first episode of VTE is still a matter of debate (4). This depends on the risk of recurrence, and the risk of major bleeding due to continued anticoagulant treatment. The risk of major bleeding in unselected patients on treatment with vitamin K antagonists (VKA) is estimated to be 2-3% per year (5). Data on this risk in patients with hereditary anticoagulant deficiencies is not available. The risk in unselected patients cannot be extrapolated to deficient patients, considering that hypercoagulability as a result of thrombophilic defects may reduce the risk of bleeding. Two recent prospective studies reported a similar risk of recurrence in patients with first VTE and a thrombophilic defect, compared to patients without a thrombophilic defect (6,7). However, these studies also included patients with factor V Leiden, prothrombin G20210A, high levels of factors VIII, IX and XI, hyperfibrinogenemia, or hyperhomocysteinemia. It is unlikely that the risk of recurrence for all these defects is comparable to the risk of recurrence associated with hereditary deficiencies of anticoagulants, considering the difference in risk of first VTE (8).

We performed a retrospective study in a large cohort of families with hereditary deficiencies of either protein S, protein C or antithrombin to assess the absolute risk of recurrence of VTE and the contribution of concomitant other thrombophilic defects. We also estimated the risk of major bleeding associated with the treatment with VKA.

**Patients and methods**

**Patients**

Subjects in the present single center retrospective study were all patients with hereditary deficiencies of either protein S, protein C or antithrombin from a previous large family cohort study (1), who already had experienced a first episode of VTE. In that study, subjects were enrolled between April 1999 and July 2004. Follow-up ended at date of enrolment. Probands were consecutive patients with VTE and with one of these deficiencies. First-degree relatives were identified by pedigree analysis. As the number of antithrombin deficient probands was small, second-degree relatives from a deficient parent were also included. After written informed consent was obtained, detailed information was collected on previous episodes of VTE, exposures to exogenous risk factors, and in women the use of oral contraceptives and their obstetric history. A standardized questionnaire was used (9), and medical records were reviewed. In addition to the index deficiency, all subjects were tested for concomitant thrombophilic defects. These included a second deficiency of either protein S, protein C or antithrombin, factor V Leiden, prothrombin G20210A, elevated plasma levels of...
factors VIII:C, IX:C and XI:C, and hyperhomocysteinemia. A first episode of VTE was initially treated with (low-molecular-weight) heparin, followed by VKA for three to six months. Afterwards, thromboprophylaxis was recommended at exposure to exogenous risk factors, i.e. surgery, immobilization for more than seven days, pregnancy and six weeks after delivery. Oral contraceptives and hormonal replacement therapy were strongly discouraged after VTE had occurred. The study was approved by the institutional review board of our hospital.

Definitions
The first episode of VTE was considered established if proximal deep-vein thrombosis (DVT) was confirmed by compression ultrasound or venography, and pulmonary embolism (PE) by ventilation/perfusion lung scanning, helical computed tomography (CT) scanning or pulmonary angiography, or when the patient had received full dose heparin and a VKA for at least three months without objective testing at a time when these techniques were not available yet. Events were independently adjudicated and were classified with the following criteria: isolated calf-vein thrombosis and superficial phlebitis were not classified as a thrombotic event. Recurrence was considered established if it was demonstrated by objective techniques at another site than the first event, or at the same site if previously repeated tests showed no residual VTE. If recurrence of DVT at the same site was suspected, but objective tests were not conclusive, it was diagnosed when the patient revealed pronounced signs and symptoms of recurrence without preceding postthrombotic syndrome, or when PE was objectively demonstrated. If these criteria were not fulfilled, anticoagulant treatment was omitted. VTE was considered secondary, if it had occurred at or within three months after exposure to one or more exogenous risk factors, including surgery, trauma, immobilization for more than seven days, use of oral contraceptives, hormonal replacement therapy, pregnancy/puerperium, and current malignancy. In the absence of these risk factors, it was classified as spontaneous.

Clinically overt bleedings, which required hospitalization or blood transfusion, were intracranial or retroperitoneal, or if they led directly to death were classified as major (10).

Laboratory studies
Protein S and protein C antigen levels were measured by Enzym Linked Immuno Sorbent Assay (ELISA) (DAKO, Glostrup, Denmark), activity of protein C (Berichrom Protein C, Dade Behring, Liederbach, Germany) and antithrombin (Coatest, Chromogenix, Mölndal, Sweden) by chromogenic substrate assays. Protein S deficiency type I was defined by decreased total protein S levels (<65 IU/dL), and protein S type III deficiency by decreased free protein S levels (< 65 IU/dL) and normal total protein S levels. After we had demonstrated that type III protein S deficiency was not a risk factor for thrombosis, families with this deficiency were excluded from analysis (11). Protein C deficiency type I and type II were defined by decreased levels of either pro-
tein C antigen (< 65 IU/dL) and/or activity (< 65 IU/dL), antithrombin deficiency by decreased levels of antithrombin activity (< 70 IU/dL). Deficiencies were considered inherited if confirmed by measurement of a second sample collected at a three-month interval and demonstrated in at least two family members, while acquired conditions were excluded. Protein S deficiency was considered to be acquired, due to pregnancy or use of oral contraceptives, unless it was established by repeated measurement at least three months after delivery and discontinued use of oral contraceptives, respectively. Factor V Leiden and prothrombin G20210A were demonstrated by polymerase chain reactions (PCR) (12,13). Factors VIII:C, IX:C and XI:C were measured by one-stage clotting assays (Amelung GmbH, Lemgo, Germany) and were considered increased at levels above 150 IU/dL (14). Fasting and post-methionine-loading levels of homocysteine were measured by high performance liquid chromatography (15). Hyperhomocysteinemia was defined as a fasting level above 18.5 μM and/or a post-methionine-loading level above 58.8 μM, as described in the Dutch population (16,17). Because the study was retrospective and laboratory tests were performed at the end of the observation period, clinical outcome was not influenced by the results of these tests.

Blood samples were collected at least three months after VTE had occurred. If patients were on long-term treatment with VKA at time of enrolment, samples were taken after treatment had been interrupted for at least two weeks, meanwhile nadroparin was given subcutaneously.

**Statistical analysis**

Probands and deficient relatives were pooled to estimate the absolute risk of a first recurrence for each of the three deficiencies separately and overall. Annual recurrence rates were calculated by dividing the number of relatives with a second episode of VTE by the total number of observation years. Observation time was defined as the period from the end of treatment with VKA for the first episode of VTE until the onset of the second episode or the end of follow-up. To assess the effects of concomitant other thrombophilic defects on the risk of recurrence, patients were categorized as to the number of concomitant defects. Accurate estimates for separate combinations could not be performed, because numbers in subgroups were too small. Relative risks and 95% confidence intervals (CI) were used to compare absolute risks. Recurrence-free survival was estimated by the Kaplan-Meier method.

Continuous variables were expressed as median values and ranges and categorical data as counts and percentages. Differences between groups were evaluated by the Student t-test or Mann-Whitney U-test, depending on the normality of data for continuous data and by Fisher exact test for categorical data. A two-tailed P-value of less than 0.05 indicated statistical significance. All analyses were performed using SAS® for Windows TM version 9.1 (Cary, NC, USA).
Results

Ninety-one probands with deficiencies of either protein S (n=39), protein C (n=40) or antithrombin (n=12) were identified (Figure 1). Of their 725 relatives, 528 were alive and aged 15 years or older. Consent was not obtained from 41 relatives (7.8%). Seven probands (5 protein S deficient and 2 protein C deficient) and their relatives (15 and 4, respectively) were excluded because inheritance of the index deficiency was not established by testing relatives. Of the remaining 468 relatives (224 deficient, 244 non-deficient), 374 had a history of VTE (141 deficient, 233 non-deficient) and were not eligible for the present study. Another 40 patients (13 probands, 24 deficient relatives, and 3 non-deficient relatives) were excluded because they were on treatment with VKA, while this treatment could not be interrupted. All these patients were on long-term treatment since their first venous thromboembolic event. In two patients a previous ischemic stroke had occurred, three patients had had a mesenteric vein or cerebral sinus thrombosis, whereas 35 patients were on long-term treatment, as decided by the treating physician, although not strictly indicated. None of these patients had recurrent VTE. Only 11 of 244 non-deficient relatives had a first episode of VTE. Their first thromboembolic event was provoked by major trauma or surgery (n=7), pregnancy (n=2), or oral contraceptive use (n=1), and was idiopathic in only one patient. Three

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**Figure 1.** Recruitment of three family cohorts with hereditary deficiencies of either protein S, protein C or antithrombin.
non-deficient patients had no follow-up, as they were on long-term oral anticoagulant treatment. Of the remaining 138 subjects, 130 were deficient for either protein S (n=53), protein C (n=52) or antithrombin (n=25), and eight were non-deficient. The number of non-deficient patients with a first episode of VTE was too small to enable a proper comparison with deficient patients.

Characteristics of probands and deficient relatives are summarized in Table 1. Relative risk of recurrent VTE in probands compared to relatives was 1.3 (95% CI, 0.8-2.0). Because no statistical differences were found, both groups were pooled. Median ages at onset of the first thrombotic event and recurrence were 29 years and 37 years, respectively. DVT was the most frequently recorded event; 69% of first events and 84% of recurrences. Of first events, 39% were classified spontaneous, compared to 64% of recurrences. Most recurrences (74%) occurred at another site than the first event. Median follow-up after the end of anticoagulant treatment was 4.6 years. Concomitant thrombophilic defects were observed in 72% of all patients. These defects exceeded the prevalences as reported in the normal population excepted for increased factor IX levels (i.e., factor V Leiden, 5%; prothrombin G20210A, 3%; increased levels of factors VIII, IX and XI, each 10%; and hyperhomocysteinemia, 10%) (18).

Annual incidences of first recurrence were 8.4% (95% CI, 5.8-11.7) in protein S-deficient patients, 6.0% (95% CI, 3.9-8.7) in protein C-deficient patients, 10.0% (95% CI, 6.1-15.4) in antithrombin-deficient patients, and overall 7.7% (95% CI, 6.1-9.5) (Table 2). Of eight non-deficient patients, one had recurrent VTE; annual incidence 1.0% (95% CI, 0.03-5.5). Annual incidence of first recurrence in patients with a spontaneous first event was 9.7% (6.8-13.4) and 6.6% (95% CI, 4.8-8.8) in patients with a secondary first

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**Table 1. Characteristics of 130 probands and relatives with hereditary deficiencies of either protein S, protein C or antithrombin and a history of venous thromboembolism**

<table>
<thead>
<tr>
<th></th>
<th>Probands (n=71)</th>
<th>Relatives (n=59)</th>
<th>P</th>
<th>All (n=130)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>46 (65)</td>
<td>34 (58)</td>
<td>0.47</td>
<td>80 (62)</td>
</tr>
<tr>
<td>Age at inclusion, y</td>
<td>47 (21-77)</td>
<td>52 (23-89)</td>
<td>0.07</td>
<td>49 (21-89)</td>
</tr>
<tr>
<td>First thrombotic event</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at onset, y</td>
<td>27 (1-68)</td>
<td>31 (15-64)</td>
<td>0.18</td>
<td>29 (1-68)</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>47 (66)</td>
<td>43 (73)</td>
<td>0.45</td>
<td>60 (69)</td>
</tr>
<tr>
<td>Spontaneous</td>
<td>25 (35)</td>
<td>26 (44)</td>
<td>0.37</td>
<td>51 (39)</td>
</tr>
<tr>
<td>First recurrence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at onset, y</td>
<td>46 (65)</td>
<td>35 (42)</td>
<td>0.59</td>
<td>81 (62)</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>36 (18-70)</td>
<td>39 (16-75)</td>
<td>0.40</td>
<td>37 (16-75)</td>
</tr>
<tr>
<td>Spontaneous</td>
<td>37 (80)</td>
<td>31 (89)</td>
<td>0.38</td>
<td>68 (84)</td>
</tr>
<tr>
<td>Concomitant thrombophilic defects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factor V Leiden</td>
<td>14 (20)</td>
<td>11 (19)</td>
<td>1.00</td>
<td>25 (19)</td>
</tr>
<tr>
<td>Prothrombin G20210A</td>
<td>5 (13)</td>
<td>6 (18)</td>
<td>0.54</td>
<td>11 (15)</td>
</tr>
<tr>
<td>FVIII:C &gt;150 IU/dL</td>
<td>34 (51)</td>
<td>32 (62)</td>
<td>0.73</td>
<td>66 (54)</td>
</tr>
<tr>
<td>FIX:C &gt;150 IU/dL</td>
<td>5 (8)</td>
<td>5 (9)</td>
<td>0.55</td>
<td>10 (8)</td>
</tr>
<tr>
<td>FXI:C &gt;150 IU/dL</td>
<td>13 (20)</td>
<td>7 (13)</td>
<td>0.34</td>
<td>20 (15)</td>
</tr>
<tr>
<td>Hyperhomocysteinemia</td>
<td>13 (20)</td>
<td>11 (21)</td>
<td>1.00</td>
<td>24 (20)</td>
</tr>
</tbody>
</table>

Categorical data presented as number (%), continuous variables as median (range)
Men tended to be at higher risk of recurrence than women (relative risk 1.4; 95% CI, 0.9-2.2). Median age at onset of first VTE in men was 36 years (range, 15-68), and in women 26 years (range, 15-67) \((P<0.001)\). Median recurrence free survival was five years in men compared to 12 years in women (Figure 2). Lifetime risk of recurrence in men and women was approximately 85%.

The risk of recurrence was not significantly increased by concomitance of other thrombophilic defects (Table 4). Annual incidences were 6.0% (95% CI, 3.3-9.8) in deficient patients without concomitant defects, 8.0% (95% CI, 5.4-11.5) in the presence of one concomitant defect and 8.3% (95% CI, 5.6-11.8) in the presence of two or more concomitant defects. Cumulative recurrence rates at 1, 5 and 10 years follow-up were 14%, 32% and 50%, respectively, in patients without concomitant thrombophilic defects \textit{versus} 14%, 40% and 54%, respectively, in patients with one or more concomitant defects.

Major bleeding was observed in eight of 167 deficient patients while they were treated with VKA at median follow-up of 6.2 years (range, 0.6-34); annual incidence was 0.5% (95% CI, 0.2-1.0).

\begin{table}
\centering
\begin{tabular}{|l|c|c|c|c|}
\hline
 & Protein S deficiency (n=53) & Protein C deficiency (n=52) & Antithrombin deficiency (n=25) & All deficiencies (n=130) \\
\hline
All & & & & \\
First recurrence & 34 & 27 & 20 & 81 \\
Observation period, y & 406 & 451 & 200 & 1057 \\
Annual incidence, % per year (95% CI) & 8.4 (5.8-11.7) & 6.0 (3.9-8.7) & 10.0 (6.1-15.5) & 7.7 (6.1-9.5) \\
\hline
Women & & & & \\
First recurrence & 18 & 15 & 14 & 47 \\
Observation period, y & 232 & 310 & 160 & 702 \\
Annual incidence, % per year (95% CI) & 7.8 (4.6-12.3) & 4.8 (2.7-8.0) & 8.8 (4.8-14.7) & 6.7 (4.9-8.9) \\
\hline
Men & & & & \\
First recurrence & 16 & 12 & 6 & 34 \\
Observation period, y & 175 & 142 & 40 & 357 \\
Annual incidence, % per year (95% CI) & 9.2 (5.2-14.9) & 8.5 (4.4-14.8) & 14.9 (5.5-32.5) & 9.5 (6.6-13.3) \\
Relative risk* & 1.2 (0.6-2.3) & 1.7 (0.8-3.7) & 1.7 (0.7-4.5) & 1.4 (0.9-2.2) \\
\hline
Cumulative recurrence rates (%) & & & & \\
1-year & 16 & 10 & 24 & 15 \\
2-year & 27 & 16 & 36 & 24 \\
3-year & 35 & 20 & 49 & 37 \\
4-year & 42 & 29 & 49 & 38 \\
5-year & 44 & 37 & 49 & 42 \\
10-year & 60 & 39 & 59 & 53 \\
15-year & 77 & 59 & 77 & 68 \\
\hline
\end{tabular}
\caption{Risk of recurrent venous thromboembolism in patients with hereditary deficiency of either protein S, protein C or antithrombin}
\end{table}
Discussion
In this study, the annual incidence of first recurrence of VTE was 7.8%, with a median follow-up of 4.6 years, while cumulative recurrence rates were 42% at 5 years and 53% at 10 years follow-up. In a study obtained in the general population, the annual risk of recurrence was 3%, with a median follow-up of 7.4 years in patients with DVT and 6.1 years in patients with PE, and cumulative recurrence rates of VTE amounted to 22% at five years and 30% at 10 years (19). Hence, our patients were at high risk of recurrence. This risk was highest in deficient patients with a spontaneous first event. They had an annual recurrence risk of almost 10%, which was 1.5 times higher compared to patients with a secondary first event ($P=0.08$). The risk of recurrence in our study was higher than in two previous studies, which reported annual incidences of 4.8% and 2.7%, respectively (20, 21). This incongruity may be due to differences in methodology between the studies. We applied strict criteria for deficiencies and excluded familial protein S deficiency type III from analysis because it was not identified as a risk factor for thrombosis (11). Moreover, we enrolled 92% of relatives, hereby avoiding selection bias.

Aggregation of other thrombophilic defects in the here presented families does support the assumed multicausal pathogenesis of VTE (18). It increased the risk of recurrence 1.4-fold, compared to patients without concomitant thrombophilic defects.

Men had a 1.4-fold higher risk of recurrent VTE compared to women. This seems in agreement with a previous meta-analysis that showed a 1.6-fold higher risk of recurrence in men (22). However, lifetime risk in men and women was comparable. Possibly, follow-up was too short (maximum 8 years) in studies that suggested an increased risk of recurrence in men compared to women (7, 23). In our study, median recurrence free survival was 12 years in women and five years in men.

The duration of anticoagulant treatment after a first episode of VTE not only depends on the risk of recurrence, but also on the risk of haemorrhagic complications due to treatment. The risk of major bleeding in our study (0.5% per year in patients on

<table>
<thead>
<tr>
<th>Variable</th>
<th>Secondary first event</th>
<th>Spontaneous first event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>79</td>
<td>51</td>
</tr>
<tr>
<td>Patients with recurrence, n</td>
<td>45</td>
<td>36</td>
</tr>
<tr>
<td>Observation period, y</td>
<td>686</td>
<td>371</td>
</tr>
<tr>
<td>Annual incidence, % per year (95% CI)</td>
<td>6.6 (4.8-8.9)</td>
<td>9.7 (6.8-13.4)</td>
</tr>
<tr>
<td>Relative risk (95% CI)</td>
<td>1.0</td>
<td>1.5 (0.95-2.3)</td>
</tr>
<tr>
<td>$P$</td>
<td>na</td>
<td>0.08</td>
</tr>
</tbody>
</table>

na denotes not applicable
VKA) was lower than previously reported in unselected patients with VTE, while they were treated with VKA (2-3% per year) (5,27). Recently, we reported on this risk in all patients who received VKA for treatment of VTE in our region. It amounted to 2.8% per year (24). Maybe, thrombophilic defects protect against major bleeding during anticoagulant treatment. However, the lower risk may also be due to the younger age of thrombophilic patients at time of their first thrombotic event. Nevertheless, the low risk of major bleeding will diminish the reluctance to extend anticoagulant treatment, considering the high risk of recurrent VTE after stopping treatment and the low risk of bleeding during treatment. A possible implication of our findings may be longterm anticoagulant treatment after a first episode of VTE.

Some aspects of our retrospective study need comment. First, it is often difficult to establish recurrence of VTE at the same site as the first event, even with objective techniques. Furthermore, patients with clinical suspicion of VTE and who were treated with heparin and VKA for more than three months at a time when there was no objective testing yet, might have overestimated our recurrence rates of thrombosis. However, most recurrences were demonstrated at another site than the first event. Second, the number of non-deficient relatives who had experienced a first episode of VTE was too small to be used as a proper reference group. Therefore, we compared our recurrence rates with population studies that classified recurrent VTE in the same way as we did (19-21). Still, our results should be handled with caution, because of the lack of a proper control group. Third, as death causes were not investigated in detail, an excess of fatal PE in relatives with a deficiency might have underestimated the risk of recurrence. However, these deficiencies were not associated with a reduced life expectancy in previous studies (25,26). Finally, although our study comprised a relatively small number, it has the longest follow-up period and is the largest till date on recurrent VTE in patients with hereditary anticoagulant deficiencies. Of two studies that suggested that thrombophilic defects did not influence the risk of recurrence, one study had a limited follow-up period of two years (6), while the other study contained

### Table 4. Risk for recurrent venous thromboembolism in patients with hereditary protein S, protein C, or antithrombin deficiency

<table>
<thead>
<tr>
<th>Variable</th>
<th>No concomitant defects</th>
<th>1 Concomitant defect</th>
<th>≥2 Concomitant defects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>29</td>
<td>51</td>
<td>42</td>
</tr>
<tr>
<td>Patients with recurrence, n</td>
<td>15</td>
<td>30</td>
<td>31</td>
</tr>
<tr>
<td>Observation period, y</td>
<td>252</td>
<td>373</td>
<td>374</td>
</tr>
<tr>
<td>Annual incidence, %/y (95% CI)</td>
<td>6.0 (3.3-9.8)</td>
<td>8.0 (5.4-11.5)</td>
<td>8.3 (5.6-11.8)</td>
</tr>
<tr>
<td>Relative risk (95% CI)</td>
<td>1</td>
<td>1.4 (0.7-2.6)</td>
<td>1.4 (0.8-2.7)</td>
</tr>
<tr>
<td>na</td>
<td>0.35</td>
<td>0.30</td>
<td></td>
</tr>
</tbody>
</table>

Concomitant defects contained factor V Leiden, prothrombin G20210A, high levels of FVIII:C and FXI:C, and hyperhomocysteinemia; na denotes not applicable
a small number of patients with deficiencies of antithrombin, protein C or protein S (overall number 25, including patients on VKA at time of blood collection, in whom classification of protein C and protein S might consequently be inaccurate) (7).

Strong points of our study are that probands were identified by testing consecutive patients with first VTE; secondly, the study cohort contained 92% of living relatives aged 15 years and older; thirdly, all patients were tested for currently known thrombophilic defects; and finally, its design as a family cohort study enabled us to estimate absolute risks.

In conclusion, patients with hereditary deficiencies of protein S, protein C or antithrombin appear to have a high absolute risk of recurrence. This risk is increased after a first spontaneous event, and by concomitance of other thrombophilic defects.

Figure 2. Recurrence free survival in men and women after a first episode of venous thromboembolism and with a deficiency of either protein S, protein C or antithrombin.
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