Risk Factors and Recurrence Rate of Primary Deep Vein Thrombosis of the Upper Extremities

Ida Martinelli, MD, PhD; Tullia Battaglioli, MD; Paolo Bucciarelli, MD; Serena Maria Passamonti, MD; Pier Mannuccio Mannucci, MD

Background—One third of cases of upper-extremity deep vein thrombosis (DVT) are primary, ie, they occur in the absence of central venous catheters or cancer. Risk factors for primary upper-extremity DVT are not well established, and the recurrence rate is unknown.

Methods and Results—We studied 115 primary upper-extremity DVT patients and 797 healthy controls for the presence of thrombophilia due to factor V Leiden, prothrombin G20210A, antithrombin, protein C, protein S deficiency, and hyperhomocysteinemia. Transient risk factors for venous thromboembolism were recorded. Recurrent upper-extremity DVT was evaluated prospectively over a median of 5.1 years of follow-up. The adjusted odds ratio for upper-extremity DVT was 6.2 (95% CI 2.5 to 15.7) for factor V Leiden, 5.0 (95% CI 2.0 to 12.2) for prothrombin G20210A, and 4.9 (95% CI 1.1 to 22.0) for the anticoagulant protein deficiencies. Hyperhomocysteinemia and oral contraceptives were not associated with upper-extremity DVT. However, in women with factor V Leiden or prothrombin G20210A who were taking oral contraceptives, the odds ratio for upper-extremity DVT was increased up to 13.6 (95% CI 2.7 to 67.3). The recurrence rate was 4.4% patient-years in patients with thrombophilia and 1.6% patient-years in those without thrombophilia. The hazard ratio for recurrent upper-extremity DVT in patients with thrombophilia compared with those without was 2.7 (95% CI 0.7 to 9.8).

Conclusions—Inherited thrombophilia is associated with an increased risk of upper-extremity DVT. Oral contraceptives increase the risk only when combined with inherited thrombophilia. The recurrence rate of primary upper-extremity DVT is low but tends to be higher in patients with thrombophilia than in those without. (Circulation. 2004;110:566-570.)

Key Words: thrombosis ■ thrombophilia ■ risk factors

Upper-extremity deep vein thrombosis (DVT) is a rare manifestation of venous thromboembolic disease, accounting for ~4% of all cases. In the past few decades, the clinical importance of upper-extremity DVT has increased because of the wider use of central venous catheters and the development of ultrasonography as a simple and accurate objective diagnostic method. In addition to indwelling catheters, another common risk factor for upper-extremity DVT is cancer. Primary upper-extremity DVT, ie, that which occurs in the absence of the aforementioned risk factors, is recognized in ~30% of cases. Because of the relative rarity of the disease, only studies with small sample sizes are available, and therefore, at variance with lower-extremity DVT, knowledge on risk factors for this thrombotic manifestation is limited. Whether thrombophilia due to deficiencies of the natural anticoagulant proteins antithrombin, protein C, and protein S; gain-of-function mutations in coagulation factor V and the prothrombin gene; or the metabolic abnormality hyperhomocysteinemia is associated with an increased risk of primary upper-extremity DVT remains a matter of debate. In addition, data on oral contraceptives as risk factor for primary upper-extremity DVT are scanty and controversial, whereas their role in lower-limb DVT and cerebral vein thrombosis is well established. Moreover, the rate of recurrence of upper-extremity DVT is unknown. The aim of this case-control study was to investigate the role of potential risk factors and to evaluate the recurrence rate after a period of anticoagulant therapy in a large series of patients with primary upper-extremity DVT.

Methods

Patients

One hundred sixty-seven patients referred between January 1994 and February 2003 to the Thrombosis Center of the Ospedale Maggiore Policlinico of Milan for a thrombophilia screening after a first episode of upper-extremity DVT were considered for the study. Patients were asked to bring to the center the diagnostic documentation of their thrombotic episodes. Eighteen patients were subsequently excluded because thrombosis was related to central venous catheters.
methionine-load increments above fasting levels ex–
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–
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Antiphospholipid antibodies (lupus anticoagulant and

prothrombin gene was performed as described previously.15,16 Func-

tional and/or antigenic assays for antithrombin, protein C, and

DNA analysis for the 1691 guanine-to-adenine substitution in

Information on transient risk factors for thrombosis, such as oral
contraceptive intake and trauma of the upper extremities, was
obtained for both patients and controls. A positive family history of
venous thrombosis was considered when at least 1 first- or second-
degree relative had had objectively documented episodes. Patients
were also interviewed about strenuous muscular efforts with the arms
in the week preceding symptoms of thrombosis. The same informa-
tion was not obtained from controls. Women were considered to be
taking oral contraceptives if they had taken them until 2 weeks or
less before thrombosis for patients or at the time of blood sampling
for controls. No subject had abnormal liver or renal function or overt
in the week preceding symptoms of thrombosis for patients or at the time of blood sampling
for controls. No subject had abnormal liver or renal function or overt

Laboratory Tests
DNA analysis for the 1691 guanine-to-adenine substitution in
cogulation factor V gene (factor V Leiden) and for the 20210

Antiphospholipid antibodies (lupus anticoagulant and

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Patient Follow-Up
To minimize selection bias, we chose to limit the follow-up analysis
only to patients who had the first primary upper-extremity DVT after

January 1991, a time when our Thrombosis Center became fully
active and started to assist a similar yearly number of patients. The
median time elapsed from the first primary upper-extremity DVT to
the visit was 6 months (range 1 month to 5 years). For patients who
received oral anticoagulant therapy, the follow-up started after its
discontinuation, whereas for those who did not receive this therapy,
it started after the event. Patients who were still taking oral
anticoagulant therapy at the end of the study were not included in the
analysis. The end of follow-up was July 1, 2003, or the date of the
recurrent upper-extremity DVT. Patients underwent duplex color
ultrasonography when first referred to the Thrombosis Center and, if
thrombosis was still present, after 6 months and then annually.
Subclavian, axillary, and brachial veins were investigated as de-
scribed previously.2,10 Recanalization was judged complete if a
previously abnormal venous segment was normally compressible or for
the subclavian vein, which is not easily compressible in the
subclavicular fossa, if a normal flow pattern (compared with the
contralateral vein) was recorded. In case of symptoms suggestive of
recurrence of upper-extremity DVT, patients were instructed to
return to the Thrombosis Center for objective examination. Recur-
rent upper-extremity DVT was diagnosed if a previously compress-
ible venous segment could no longer be compressed or if, in the
presence of symptoms of recurrence, a previously nonocclusive
thrombus had changed into an occlusive one at ultrasound
examination.

Statistical Analysis
Continuous variables are presented as median and range. The age
difference between patients and controls was calculated by the
Mann-Whitney U test. ORs and 95% CIs were used as a measure of
the association between primary upper-extremity DVT and various
types of thrombophilia. An unconditional logistic regression analysis
was used to adjust ORs for possible confounders, such as age
(continuous variable), gender, and the presence of other causes of
thrombophilia (categorical variables). Interaction between inherited
thrombophilia and oral contraceptive intake or hyperhomocysteinemia
and between oral contraceptive intake and hyperhomocysteinemia
was evaluated by stratification of patients and controls into 4
groups, according to the presence or absence of the specific risk
factors and using the group without specific risk factors as the
reference. The incidence of recurrent upper-extremity DVT was

calculated by dividing the number of events by the sum of patient-
years of observation. To estimate the cumulative probability of
recurrent upper-extremity DVT in patients with and without throm-
bophilia, a survival analysis was performed by the Kaplan-Meier
method and with a Cox proportional hazards model, which allows
adjustment for confounding variables, such as age at first event,
gender, length of follow-up, and presence or absence of recanaliza-
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Results
Risk Factors
The main characteristics of the study population and the
prevalence of thrombophilia are shown in Table 1. The
median age at first visit to the Thrombosis Center was 35
years (range 14 to 61 years) in patients and 44 years (range 12
to 73 years) in controls (P<0.001). Heterozygosity for factor
V Leiden and prothrombin G20210A increased the risk for
upper-extremity DVT by factors of 6 and 5, respectively. No
homozygous carrier of either mutation was found in patients
or controls. The presence of antithrombin, protein C, or
protein S deficiency (considered together) was associated
with an ~5-fold increase in the risk of the disease, whereas
no association was found for hyperhomocysteinemia (Table
1). Because homocysteine plasma levels may be influenced by gender and age, we performed separate analyses for men and women and for 2 age categories (below and above the median age of the study population [43 years]), without finding a significant association (data not shown). The OR for thrombophilia and hyperhomocysteinemia did not change after the exclusion of the 26 patients who were part of our previous study. In terms of transient risk factors, strenuous muscular efforts with the arms were recorded in one fourth of patients and the use of oral contraceptives in one third. Efforts were sports related in 15 patients (8 weightlifting, 3 rowing, 2 tennis, and 2 volley) and related to unusual strenuous exercise in another 14 (7 lifting heavy weights, 4 prolonged above-shoulders extension, 3 repeated abduction). The overall prevalence of thrombophilia was similar in patients who did or did not undergo strenuous muscular efforts, being 31% and 33%, respectively. The prevalence of oral contraceptive users was similar in patients and controls (34% and 30%, respectively), with no association between this transient risk factor and upper-extremity DVT (Table 1). Such risk factors as surgery, pregnancy or puerperium, and prolonged immobilization, frequently found in patients with lower-extremity DVT, were never recorded in our patients.

Table 2 shows that when women were stratified according to the presence of the most common causes of thrombophilia, ie, factor V Leiden or prothrombin G20210A, and the use of oral contraceptives, the OR for upper-extremity DVT increased nearly 14-fold in the group sharing both the genetic and transient risk factors compared with the group with neither risk factor. This figure was similar for the interaction of the separate mutations and oral contraceptive use (not shown). The OR (adjusted for age and gender) for the combination of factor V Leiden or prothrombin G20210A and hyperhomocysteinemia (1.7 [95% CI 0.2 to 14.5]) and the OR (adjusted for age and the presence of factor V Leiden or prothrombin G20210A) for the combination of hyperhomocysteinemia and oral contraceptives (1.8 [95% CI 0.3 to 9.7]) were not statistically significant.

**Recurrence Rate**

The incidence of recurrent symptomatic upper-extremity DVT was calculated for 98 patients who had the first event

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**TABLE 1. General Characteristics, Type of Thrombophilia, and Transient Risk Factors for Upper-Extremity DVT in the Study Population**

<table>
<thead>
<tr>
<th></th>
<th>Patients (n=115)</th>
<th>Controls (n=797)</th>
<th>OR (95% CI)</th>
<th>OR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female, n</td>
<td>41/74</td>
<td>363/434</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive family history of venous thrombosis, n (%)</td>
<td>18 (16)</td>
<td>141 (18)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median age at thrombosis, y (range)</td>
<td>32 (14–61)</td>
<td>...</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With thrombophilia, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factor V Leiden</td>
<td>10 (9)</td>
<td>22 (3)</td>
<td>3.4 (1.5–7.3)</td>
<td>6.2 (2.5–15.7)</td>
</tr>
<tr>
<td>Prothrombin G20210A</td>
<td>11 (10)</td>
<td>25 (3)</td>
<td>3.3 (1.6–7.0)</td>
<td>5.0 (2.0–12.2)</td>
</tr>
<tr>
<td>Antithrombin, protein C, or protein S deficiency</td>
<td>3 (3)†</td>
<td>8 (0.8)‡</td>
<td>3.2 (0.8–12.3)</td>
<td>4.9 (1.1–22.0)</td>
</tr>
<tr>
<td>Antiphospholipid antibodies</td>
<td>8 (7)</td>
<td>Not investigated</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Hyperhomocysteinemia</td>
<td>8 (7)</td>
<td>72 (9)</td>
<td>0.7 (0.3–1.6)</td>
<td>0.8 (0.3–1.9)</td>
</tr>
<tr>
<td>With transient risk factors, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strenuous muscular effort</td>
<td>29 (25)</td>
<td>Not investigated</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Trauma of upper limb</td>
<td>5 (4)</td>
<td>0</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Oral contraceptive use§</td>
<td>23 (34)</td>
<td>85 (30)</td>
<td>1.2 (0.7–2.2)</td>
<td>...</td>
</tr>
</tbody>
</table>

*Each variable adjusted for the others, age, and gender.
†One antithrombin deficiency, 1 protein C deficiency, and 1 protein S deficiency.
‡Seven with antithrombin deficiency and 1 with protein S deficiency.
§Percentage calculated based on the number of women of reproductive age (65 patients and 288 controls).

**TABLE 2. Interaction Between Factor V Leiden or Prothrombin G20210A and Use of Oral Contraceptives in Determining Risk of Upper-Extremity DVT in 65 Patients and 288 Controls of Reproductive Age**

<table>
<thead>
<tr>
<th>Factor V Leiden or Prothrombin G20210A</th>
<th>Oral Contraceptive Use*</th>
<th>Patients</th>
<th>Controls</th>
<th>OR (95% CI)</th>
<th>OR † (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>No</td>
<td>35</td>
<td>191</td>
<td>1 (Reference)</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>18</td>
<td>82</td>
<td>1.2 (0.6–2.2)</td>
<td>1.0 (0.5–2.0)</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
<td>7</td>
<td>10</td>
<td>3.8 (1.4–10.7)</td>
<td>4.2 (1.4–12.6)</td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>5</td>
<td>3</td>
<td>9.1 (2.1–39.8)</td>
<td>13.6 (2.7–67.3)</td>
</tr>
</tbody>
</table>

*Information on oral contraceptive use was missing for 2 controls.
†Adjusted for age.
These results did not change substantially if thrombophilia was also not statistically significant (0.8 [95% CI 0.2 to 3.3]).

The hazard ratio for recurrent upper-extremity DVT, which investigated the prevalence of underlying risk factors and the rate of recurrent events, shows that inherited thrombophilia is associated with an increased risk of primary upper-extremity DVT. A 5- to 6-fold increased risk was found in carriers of thrombophilia due to deficiencies of the naturally occurring anticoagulant proteins antithrombin, protein C, or protein S and to the gain-of-function factor V Leiden or prothrombin mutations. In contrast, the metabolic abnormality hyperhomocysteinemia and the use of oral contraceptives, known to be associated with an increased risk of DVT of the lower extremities and of cerebral vein thrombosis,18 were not associated with primary upper-limb DVT. However, a multiplicative interaction between the use of oral contraceptives and the most common inherited thrombophilic abnormalities, factor V Leiden or prothrombin mutation, was observed, with an increased risk for the disease up to 14-fold. Patients with thrombophilia were more likely to have symptomatic recurrence than those without, for an incidence of 4.4% and 1.6% per year, respectively.

Strenuous muscular effort with the arms was a common predisposing condition, present in one fourth of the patients. This is in agreement with what was reported in the largest series to date of 51 patients with primary upper-extremity DVT.7 We could not calculate the risk associated with strenuous muscular effort in the present study because the corresponding information was not included among those the data we routinely collect in individuals who make up our control population. However, at variance with the study by Héron et al,7 thrombophilia was equally distributed among patients with and without a history of strenuous muscular effort. Data on thrombophilia in the literature are conflicting, perhaps because of different selection criteria for patients and the limited sample size of most studies.2,5-11 In a previous study of only 36 patients with primary upper-extremity DVT,5 we reported a statistically nonsignificant trend toward an association between the disease and all the inherited thrombophilic abnormalities taken together (factor V Leiden and antithrombin, protein C, and protein S deficiency). To date, the role of hyperhomocysteinemia has been investigated only in that study,5 and the role of the prothrombin mutation has only been investigated in 2 additional case-control studies, which showed an association with primary upper-extremity DVT in 48 patients11 and with primary or secondary upper-extremity DVT in 55 patients.19 The prevalence of antiphospholipid antibodies in patients with upper-limb DVT varies from 3.7% to 26.8%.2,7,9,11 Although we could not calculate the risk associated with this acquired thrombophilic condition because it was not investigated in control subjects, we found a prevalence similar to that reported in patients with upper-limb11 or lower-limb20,21 DVT. Recently, an OR of =6 in favor of an association between oral contraceptive intake and primary upper-extremity DVT has been reported.11 The data from the present study failed to confirm such an
association and are in agreement with the low prevalence of oral contraceptive use reported by others.2,8 However, a synergistic effect was found between oral contraceptive intake and thrombophilia in increasing the risk of upper-extremity DVT. A similar interaction is already well established for patients with lower-extremity DVT, although in these patients, oral contraceptives alone are associated with an increased risk. Compared with DVT of the lower extremities, upper-extremity DVT recurs less frequently. A study of patients with a first, idiopathic episode of lower-extremity DVT estimated a 5.0% annual incidence of recurrence after discontinuation of anticoagulant therapy,22 whereas in the present study, it was 2.4%.

One of the limitations of the present study is that patients referred for thrombophilia screening to a specialized center are selected. We believe we minimized such bias by excluding from the follow-up analysis patients who had the first event before the Thrombosis Center had become a national referral for thrombosis patients. The average yearly number of patients referred to the center after 1991 was similar, and there is no reason to think that patients with a higher probability to have thrombophilia were preferentially referred to us. In addition, a positive family history for venous thrombosis was not a selection bias, because this was similar among patients and controls. Diagnostic bias should have been limited by review of the diagnostic documentation of thrombotic episodes and the adoption of strict criteria for diagnosis of recurrent upper-extremity DVT. In particular, a recurrent event at the same venous segment only partially obstructed by thrombus occurred in 2 patients only.

In conclusion, the present study provides evidence that the risk of first primary upper-extremity DVT is higher in individuals with inherited thrombophilia than in those without. The risk of recurrent events appears to be higher in such individuals, but not so high as to suggest the extension of anticoagulant treatment, which in the present series had a mean duration of 6 months. The metabolic abnormality hyperhomocysteinemia and the use of oral contraceptives per se are not associated with an increased risk for this site of thrombosis, which strengthens the concept that risk factors may play a different role in determining venous thrombosis in different sites.23 However, women with inherited thrombophilia have a much greater risk of upper-extremity DVT if they also use oral contraceptives. Therefore, discontinuation of oral contraceptives after a first episode of upper-extremity DVT should be recommended in women with inherited thrombophilia.

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