Mild Antithrombin Deficiency and Risk of Recurrent Venous Thromboembolism
A Prospective Cohort Study

Matteo Nicola Dario Di Minno, MD; Francesco Dentali, MD; Roberta Lupoli, MD; Walter Ageno, MD

Background—Antithrombin deficiency, defined by antithrombin levels of <70%, is a major thrombophilic condition associated with an increased risk of venous thromboembolism (VTE). No prospective data are available about the risk of recurrent VTE associated with mildly decreased antithrombin levels (70–80%).

Methods and Results—Consecutive patients with a first VTE were stratified according to functional antithrombin levels (<70%, 70–80%, >80%) and were followed up for a mean of 8.70 years to assess the incidence of VTE recurrence. A total of 823 patients (mean age, 48.3 years; 41.9% male) were enrolled. Recurrent VTE occurred in 253 patients (3.53% per patient-year). With stratification for antithrombin levels, VTE recurrence occurred in 19 patients with antithrombin levels <70% (5.90% per patient-year), in 20 patients with antithrombin levels 70% to 80% (5.35% per patient-year), and in 214 patients with antithrombin levels >80% (3.31% per patient-year). After adjustment for major VTE risk factors and for anticoagulation duration, the risk of VTE recurrence was significantly higher in patients with antithrombin levels <70% (hazard ratio, 3.48; 95% confidence interval, 2.16–5.61) and antithrombin levels 70% to 80% (hazard ratio, 2.40; 95% confidence interval, 1.51–3.80) compared with patients with antithrombin levels >80%. When the population was stratified according to the presence or absence of major risk factors for the index event, the association remained significant only in patients with unprovoked VTE.

Conclusions—The presence of mild antithrombin deficiency (70–80% antithrombin) in patients with unprovoked VTE is associated with a significantly increased risk of recurrence and should be taken into account when the duration of secondary prevention is determined.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01382550.

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Key Words: antithrombin ■ thromboembolism ■ thrombophilia

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Regional Reference Center for Coagulation Disorders of Federico II University of Naples, Italy, for the assessment of venous thrombosis risk factors (including thrombophilia screening) were eligible for this study. Objective diagnosis of VTE was mandated based on the results of compression ultrasonography, ventilation/perfusion lung scan, or spiral computed tomography (CT). Patients were excluded if VTE was treated with drugs different from vitamin K antagonists (VKA); if they required indwelling treatment with VKA for a different indication (eg, prosthetic heart valve, atrial fibrillation); if VTE was secondary to hormonal therapy, pregnancy, puerperium, malignancy, protein C or protein S deficiency, or antiphospholipid antibodies; or if they had chronic liver disease.

According to standard procedures, information about risk factors for venous thrombosis (recent [<3 months] surgery; trauma/fracture; acute medical disease with bed immobilization >3 days; leg cast; long-distance travel) was collected on admission by a trained staff. On the basis of established criteria, VTE was adjudicated as "unprovoked" in the absence of any of the aforementioned risk factors and "provoked" in the presence of at least one.

For each patient, antithrombin activity was measured with the Berichrom ATIII kit (Behringwerke, Marburg, Germany). According to manufacturer recommendations, normal antithrombin concentrations are 80–120%. Antithrombin activity assessment was performed after at least 3 months from the thrombotic event, while patients were taking VKA. The results of these tests were confirmed on a second sample collected 3 months later. Only patients with consistent findings in antithrombin activity were included in the analysis. Because the risk of VTE is mainly documented in patients with antithrombin levels <70%,7 we stratified our study population on the basis of antithrombin levels as follows: <70%, overt antithrombin deficiency; 70% to 80%, mild antithrombin deficiency; and >80%, normal antithrombin levels. Protein C, protein S, antiphospholipid antibodies, homocysteine, factor V Leiden, and prothrombin 20210A polymorphisms were determined as described previously.22–24 All study patients were treated with an initial course of weight-adjusted low-molecular-weight heparin and with VKA (international normalized ratio range, 2–3). The minimum duration of VKA treatment was 3 months. Decision to extend the duration of secondary prevention was left to the discretion of treating clinicians. All patients were instructed to return for follow-up visits at 3, 6, and 12 months after enrollment and at least every 6 months thereafter. At each visit, patients were asked about new symptoms of VTE and about bleeding episodes.

The primary outcome of the study was the incidence of objectively documented symptomatic VTE recurrence. In limbs without deep vein thrombosis (DVT) at baseline, the criteria for the diagnosis of recurrence of DVT were a noncompressible venous segment on ultrasonography or an intraluminal filling defect on venography. In limbs with DVT at baseline, the criteria for the diagnosis of recurrence of DVT were a newly noncompressible venous segment or a substantial increase (≥4 mm) in the diameter of the thrombus during full compression on ultrasonography or a new intraluminal filling defect on venography.25,26

Recurrence of pulmonary embolism (PE) was defined as a new intraluminal filling defect on CT angiography or pulmonary angiography or a new high-probability perfusion defect on lung scan. The occurrence of VTE in other sites (atypical sites) was confirmed on a second sample collected 3 months later. Only patients with antithrombin levels <70%, overt antithrombin deficiency; 70% to 80%, mild antithrombin deficiency; and >80%, normal antithrombin levels. Protein C, protein S, antiphospholipid antibodies, homocysteine, factor V Leiden, and prothrombin 20210A polymorphisms were determined as described previously.22–24 All study patients were treated with an initial course of weight-adjusted low-molecular-weight heparin and with VKA (international normalized ratio range, 2–3). The minimum duration of VKA treatment was 3 months. Decision to extend the duration of secondary prevention was left to the discretion of treating clinicians. All patients were instructed to return for follow-up visits at 3, 6, and 12 months after enrollment and at least every 6 months thereafter. At each visit, patients were asked about new symptoms of VTE and about bleeding episodes.

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Recurrence of pulmonary embolism (PE) was defined as a new intraluminal filling defect on CT angiography or pulmonary angiography or a new high-probability perfusion defect on lung scan. The occurrence of VTE in other sites (atypical sites) was diagnosed by CT angiography or by magnetic resonance imaging. The occurrence of major and minor bleeding events was defined according to validated criteria.27 An overt bleeding event was defined as major if it was fatal, occurred in a critical site (intracranial, intraspinal, intracerebral, retroperitoneal, intra-articular, pericardial, or intramuscular [leading to a compartment syndrome]), or was associated with a decrease in the hemoglobin level of ≥2.0 g/dL or required a transfusion of ≥2 units of whole blood or red blood cells. Minor bleeding included all cases of bleeding not classified as major. The study was approved by the local ethics committee and was performed according to the Declaration of Helsinki and reported according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for observational studies.28 All patients provided written informed consent.

Statistical Analysis
To determine the sample size, we assumed a 15:1 ratio between patients in the >80% antithrombin and 70% to 80% antithrombin groups and, according to a previous study,29 a 4-year median recurrence-free survival time for the control group. To detect a hazard ratio (HR) >1.5 for VTE recurrence when the 2 groups were compared, at least 42 patients with antithrombin levels 70% to 80% and 630 patients with antithrombin levels >80% were needed to obtain a power=80% and α error <5%.

Statistical analysis was performed with the SPSS 16 system (SPSS Inc, Chicago, IL). Continuous data were expressed as mean±SD values; categorical variables were expressed as percentages. The t test and ANOVA with a Bonferroni post hoc test were performed to compare continuous variables; the χ2 test or the Fisher exact test was used to compare categorical variables. The cumulative incidence of VTE recurrence and the interval between the index VTE and recurrence were described according to the Kaplan-Meier life tables. A Cox regression model was used to assess the influence of variables on the risk of recurrence. This risk was expressed as HR with the corresponding 95% confidence interval (CI). In the model, recurrent VTE was the dependent variable; sex, age, age at first event, antithrombin levels, family history of VTE, factor V Leiden mutation, prothrombin 20210A polymorphism, venous stasis, recent surgery, immunological diseases, and duration of VKA treatment were independent variables. The annual incidence of recurrence was calculated by dividing the number of individuals with recurrence by the total number of follow-up years. The follow-up time was defined as the period elapsed from enrollment until the last clinical visit update. All results are expressed as 2-tailed values, with P values <0.05 being statistically significant.

Results
Baseline Data
A total of 1356 potentially eligible VTE patients were identified. Of them, 513 presented at least 1 criterion for exclusion (Figure 1). In addition, 20 patients (2.1%) were lost to follow-up from the first planned visit and were thus excluded from the analysis. Thus, 823 patients were enrolled in this prospective study and were followed for a mean of 8.70 years (7160.1 patient-years). Of them, 704 (85.5%) had DVT, 30 (3.65%) had PE, and 89 (10.85%) had DVT+PE at enrollment; in 321 (39%), VTE was unprovoked. Antithrombin levels were <70% in 37 patients, between 70% and 80% in 43, and >80% in 743. A positive family history for VTE was reported by 219 patients (29.6%) and was more common in those with antithrombin levels <70% and in those with antithrombin levels 70% to 80% (Table 1). As shown in Table 1, after the first VTE event, 301 patients (36.6%) received an indefinite VKA treatment; the remaining patients were treated with a regimen with a definite duration (from 3 to 12 months).

Incidence of Recurrent VTE
During follow-up, recurrent VTE occurred in 253 patients (3.53% per patient-year; Table 2): 201 (79.4%) had DVT; 5 (2.0%) had PE; 45 (17.8%) had DVT+PE; and 2 (0.8%) had venous thrombosis in other sites (1 cerebral and 1 splanchnic). Of the 253 VTE recurrences, 223 were diagnosed by ultrasound (followed by CT angiography scan in 22 cases), 28 by CT angiography scan (followed by ultrasound in 23 cases), 1 by abdominal ultrasound followed by CT angiography scan, and 1 by magnetic resonance imaging of the brain with contrast media. As expected, the incidence of VTE recurrence was higher in patients on a definite VKA treatment regimen than in those on
indefinite treatment (4.84% per patient-year versus 1.26% per patient-year; HR=5.16; 95% CI, 3.57–7.47; P<0.001).

With stratification for antithrombin levels, VTE recurrence occurred in 19 patients with antithrombin levels <70% (5.90% per patient-year), in 20 patients with antithrombin levels 70% to 80% (5.35% per patient-year), and in 214 patients with antithrombin levels >80% (3.31% per patient-year).

In a multivariate analysis, after adjustment for major VTE risk factors and for VKA treatment duration, the risk of recurrence was significantly higher in patients with antithrombin levels <70% (HR=3.48; 95% CI, 2.16–5.61) and 70% to 80% (HR=2.40; 95% CI, 1.51–3.80) compared with patients with antithrombin levels >80%. A Kaplan-Meier survival analysis confirmed similar findings (Figure 2). A subsequent multivariate analysis with antithrombin expressed as a continuous variable showed that progressively decreasing antithrombin levels were associated with an increasing risk of VTE recurrence (HR=1.02; 95% CI, 1.02–1.03; P<0.001).

Recurrence Rates in Patients With Unprovoked and Provoked VTE

When only patients with unprovoked VTE (n=321) were analyzed, recurrence occurred in 17 patients with antithrombin levels <70% (6.98% per patient-year), in 16 with antithrombin levels 70% to 80% (7.00% per patient-year), and in 214 patients with antithrombin levels >80% (3.31% per patient-year), in 16 with antithrombin levels >80%.

Table 1. Baseline Demographic and Clinical Characteristics of Study Population

<table>
<thead>
<tr>
<th>Category</th>
<th>Whole Sample (n=823)</th>
<th>Antithrombin &lt;70% (n=37)</th>
<th>Antithrombin 70–80% (n=43)</th>
<th>Antithrombin &gt;80% (n=743)</th>
<th>P Value for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at first event, mean±SD, y</td>
<td>48.31±14.70</td>
<td>35.05±12.70</td>
<td>36.72±8.34</td>
<td>49.64±14.47</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>345 (41.9)</td>
<td>22 (59.5)</td>
<td>25 (58.1)</td>
<td>298 (40.1)</td>
<td>0.006</td>
</tr>
<tr>
<td>Unprovoked VTE</td>
<td>321 (39.0)</td>
<td>28 (75.7)</td>
<td>21 (48.8)</td>
<td>272 (36.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bed immobilization,* leg cast, long-distance travel</td>
<td>114 (13.9)</td>
<td>8 (21.6)</td>
<td>5 (11.6)</td>
<td>101 (13.6)</td>
<td>0.351</td>
</tr>
<tr>
<td>Recent (&lt;3 mo) trauma/surgery</td>
<td>246 (26.8)</td>
<td>12 (30.0)</td>
<td>11 (23.4)</td>
<td>223 (28.8)</td>
<td>0.784</td>
</tr>
<tr>
<td>Immune-mediated disorders†</td>
<td>39 (4.7)</td>
<td>1 (2.7)</td>
<td>0 (0)</td>
<td>38 (5.1)</td>
<td>0.258</td>
</tr>
<tr>
<td>Inherited thrombophilia</td>
<td>205 (24.9)</td>
<td>6 (16.2)</td>
<td>14 (32.6)</td>
<td>185 (24.9)</td>
<td>0.242</td>
</tr>
<tr>
<td>Prothrombin time mutation</td>
<td>102 (12.4)</td>
<td>3 (8.1)</td>
<td>9 (20.9)</td>
<td>90 (12.1)</td>
<td>0.168</td>
</tr>
<tr>
<td>Factor V Leiden mutation</td>
<td>117 (14.2)</td>
<td>4 (10.8)</td>
<td>6 (14.0)</td>
<td>107 (14.4)</td>
<td>0.829</td>
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<tr>
<td>VTE family history</td>
<td>219 (26.6)</td>
<td>17 (45.9)</td>
<td>19 (44.2)</td>
<td>183 (24.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>227 (27.6)</td>
<td>10 (27.0)</td>
<td>10 (23.3)</td>
<td>207 (27.9)</td>
<td>0.804</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>184 (22.4)</td>
<td>5 (13.5)</td>
<td>10 (23.3)</td>
<td>169 (22.7)</td>
<td>0.417</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>93 (11.3)</td>
<td>1 (2.7)</td>
<td>3 (7.0)</td>
<td>89 (12.0)</td>
<td>0.144</td>
</tr>
<tr>
<td>Impaired fasting glucose tolerance</td>
<td>54 (6.6)</td>
<td>2 (5.4)</td>
<td>5 (11.6)</td>
<td>47 (6.3)</td>
<td>0.378</td>
</tr>
<tr>
<td>Obesity</td>
<td>178 (21.6)</td>
<td>6 (16.2)</td>
<td>5 (11.6)</td>
<td>167 (22.5)</td>
<td>0.174</td>
</tr>
<tr>
<td>Indefinite VKA treatment</td>
<td>301 (36.6)</td>
<td>20 (54.1)</td>
<td>17 (39.5)</td>
<td>264 (35.5)</td>
<td>0.068</td>
</tr>
</tbody>
</table>

Values are number (percentage) unless indicated otherwise. VKA indicates vitamin K antagonists; and VTE, venous thromboembolism.

*>3 days.
†Other than antiphospholipid syndrome.
levels 70% to 80% (8.36% per patient-year), and in 67 with antithrombin levels >80% (2.83% per patient-year). This difference in the annual risk of recurrence among groups after adjustment for all other major clinical and demographic characteristics was statistically significant (HR=5.93; 95% CI, 3.38–10.39 for those between <70% and >80% antithrombin; HR=3.90; 95% CI, 2.25–6.77 for those between 70–80% and >80% antithrombin).

Recurrence rates were lower in all subgroups of patients with provoked VTE (<70% antithrombin: 2 patients [2.55% per patient-year]; 70–80% antithrombin: 4 patients [2.19% per patient-year]; and >80% antithrombin: 147 [3.58% per patient-year]), and the differences between groups were not statistically significant (HR=1.43; 95% CI, 0.17–2.87 for those between <70% and >80% antithrombin; HR=1.27; 95% CI, 0.28–2.18 for those between 70–80% and >80% antithrombin).

Recurrence Rates in Patients Receiving Definite VKA Treatment Duration
When only patients receiving a definite VKA treatment duration (n=522) were analyzed, recurrences occurred in 12 patients with antithrombin levels <70% (8.11% per patient-year), in 18 with antithrombin levels 70% to 80% (7.95% per patient-year), and in 190 with antithrombin levels >80% (4.56% per patient-year). Thus, the risk of VTE recurrence was significantly increased in both the <70% antithrombin (HR=2.88; 95% CI, 1.61–5.18) and 70% to 80% antithrombin (HR=2.65; 95% CI, 1.63–4.29) groups compared with the >80% antithrombin group. These differences also remained significant when recurrence rates were assessed in patients with unprovoked VTE receiving a definite VKA treatment duration (n=203). Recurrences occurred in 10 patients with antithrombin levels <70% (9.58% per patient-year), 15 with antithrombin levels 70% to 80% (9.07% per patient-year), and 62 with antithrombin levels >80% (4.12% per patient-year), with resulting HR=4.27 (95% CI, 2.17–8.40) for the <70% versus >80% antithrombin group and HR=3.62 (95% CI, 2.05–6.39) for the 70% to 80% versus >80% antithrombin group.

Recurrence Rates in Patients Receiving Indefinite Treatment Duration
In the 301 patients receiving indefinite treatment, recurrent VTE was found in 7 patients with antithrombin levels <70% (4.02% per patient-year), 2 with antithrombin levels 70% to 80% (1.35% per patient-year), and 24 with antithrombin

Table 2. Univariate Analysis of Clinical and Demographic Characteristics of Study Population Stratified According to Occurrence of VTE Recurrence

<table>
<thead>
<tr>
<th></th>
<th>No VTE Recurrence (n=570)</th>
<th>VTE Recurrence (n=253)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at first event, mean±SD, y</td>
<td>49.0±14.4</td>
<td>46.76±15.19</td>
<td>0.044</td>
</tr>
<tr>
<td>Male sex</td>
<td>224 (39.3)</td>
<td>121 (47.8)</td>
<td>0.026</td>
</tr>
<tr>
<td>Unprovoked VTE</td>
<td>221 (38.8)</td>
<td>100 (39.5)</td>
<td>0.877</td>
</tr>
<tr>
<td>Inherited thrombophilia</td>
<td>128 (22.5)</td>
<td>77 (30.4)</td>
<td>0.018</td>
</tr>
<tr>
<td>Prothrombin time mutation</td>
<td>62 (10.9)</td>
<td>40 (15.8)</td>
<td>0.052</td>
</tr>
<tr>
<td>Factor V Leiden mutation</td>
<td>74 (13.0)</td>
<td>43 (17.0)</td>
<td>0.131</td>
</tr>
<tr>
<td>VTE family history</td>
<td>124 (21.8)</td>
<td>95 (37.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>153 (26.8)</td>
<td>74 (29.2)</td>
<td>0.499</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>117 (20.5)</td>
<td>67 (26.5)</td>
<td>0.070</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>67 (11.8)</td>
<td>26 (10.3)</td>
<td>0.633</td>
</tr>
<tr>
<td>Impaired fasting glucose tolerance</td>
<td>37 (6.5)</td>
<td>17 (6.7)</td>
<td>0.880</td>
</tr>
<tr>
<td>Obesity</td>
<td>123 (21.6)</td>
<td>55 (21.7)</td>
<td>1.000</td>
</tr>
<tr>
<td>Indefinite VKA treatment</td>
<td>268 (47.0)</td>
<td>33 (13.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Normal antithrombin levels</td>
<td>529 (92.8)</td>
<td>214 (84.6)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Mild antithrombin deficiency</td>
<td>23 (4.0)</td>
<td>20 (7.9)</td>
<td></td>
</tr>
<tr>
<td>Overt antithrombin deficiency</td>
<td>18 (3.2)</td>
<td>19 (7.5)</td>
<td></td>
</tr>
</tbody>
</table>

Values are number (percentage) unless indicated otherwise. VKA indicates vitamin K antagonists; and VTE, venous thromboembolism.

*P for differences among the 3 antithrombin level groups.

Figure 2. Kaplan-Meier survival analysis of venous thromboembolism (VTE) recurrence according to antithrombin (AT) percentage level groups.
levels >80% (1.04% per patient-year). Thus, the risk of recurrent VTE was still increased in the <70% antithrombin group (HR=4.95; 95% CI, 2.11–11.61) but not in the 70% to 80% antithrombin group (HR=1.08; 95% CI, 0.25–4.63) compared with those with normal antithrombin levels.

However, when we specifically evaluated the 118 subjects receiving indefinite VKA treatment after an unprovoked event, a VTE recurrence was found in 7 patients with antithrombin levels <70% (5.03% per patient-year), 1 with antithrombin levels 70% to 80% (3.83% per patient-year), and 5 with antithrombin levels >80% (0.58% per patient-year), with resulting HR=14.43 (95% CI, 1.55–134.41) for the <70% versus >80% antithrombin group and HR=12.69 (95% CI, 3.85–41.82) for the 70% to 80% versus >80% antithrombin group.

Incidence of Bleeding Complications

During follow-up, 91 bleeding episodes (4 nonfatal major and 87 minor bleeding) occurred (1.27% per patient-year). As expected, indefinite treatment duration was associated with an increased risk of overall bleeding compared with a definite duration regimen (HR=3.15; 95% CI, 1.97–5.02; P<0.001), with all major bleedings (1 posttraumatic hemorrhosis, 1 gastrointestinal, 2 hemoptyses) occurring in the former group (2 in subjects with antithrombin levels >80%, 1 in a subject with antithrombin levels 70%–80%, and 1 in a subject with antithrombin levels <70%). Minor bleedings (2 menorrhagias, 19 epistaxes, 14 ecchymoses, 14 hematurias, 7 rectal, 5 oral, 2 conjunctivals) occurred more frequently in individuals on indefinite treatment compared with patients on definite treatment duration (20.9% versus 4.6%; HR=2.96; 95% CI, 1.85–4.74; P<0.001).

With stratification for antithrombin levels, minor bleeding occurred in 10.8% of subjects with antithrombin levels >80%, in 9.3% of those with antithrombin levels 70% to 80%, and in 8.1% of those with antithrombin levels <70% (P=0.843).

Discussion

This is, to the best of our knowledge, the first prospective study to suggest that patients with mild antithrombin deficiency (antithrombin levels 70%–80%) have a risk of recurrent VTE that is significantly higher than the risk in patients with normal antithrombin levels (>80%).

Overt antithrombin deficiency is an established risk factor for both first and recurrent VTE. However, all previous studies focused solely on patients with antithrombin levels <70%. In this study, we compared these patients with those with VTE and antithrombin levels >70%, but we separately considered patients with normal antithrombin levels (>80%) and patients with mildly reduced antithrombin levels (70%–80%) and found that this latter group has a risk of VTE recurrence that is similar to that observed in patients with overt antithrombin deficiency. In addition, we also observed a similar prevalence of VTE family history between patients with overt and mild antithrombin deficiency, further supporting the hypothesis of the clinical relevance of mild antithrombin deficiency. The determinants of antithrombin levels slightly above those commonly found in overt antithrombin deficiency are poorly understood. However, given the similar prevalence of a family history of VTE between those with antithrombin levels <70% and those with antithrombin levels 70% to 80%, this may also suggest an inherited nature for such milder antithrombin deficiency. Recent observations on antithrombin gene polymorphisms associated with mild antithrombin deficiency are in agreement with this finding. Although the prevalence of this mild deficiency has never been evaluated in ad hoc designed studies, genotypes leading to a slight antithrombin level reduction were found in ≈19.5% of blood donors. This finding clearly suggests the need for extensive screening of mild antithrombin deficiency to define its prevalence in the general population and in VTE subjects.

Although this study included only patients with inherited antithrombin deficiency, patients with different clinical conditions (liver disease, pregnancy, oral contraceptive intake, hormone replacement therapy) may show antithrombin levels similar to those in patients with mild inherited antithrombin deficiency. However, further studies are needed to know whether our findings can be extended to these populations.

Our findings have some important clinical implications. The optimal duration of secondary prevention of VTE remains debatable. It is currently recommended that patients with VTE provoked by transient risk factors should receive a 3-month course of VKA treatment and that patients with unprovoked events should be assessed for indefinite, extended treatment. It was suggested that an expected annual recurrence rate of <5% should be acceptable to justify treatment interruption and that a higher rate of recurrence should mandate indefinite VKA treatment. However, identification of patients at increased risk of recurrence warrants individual stratification strategies, which currently remain insufficiently established. In our study, patients with unprovoked VTE treated for a definite time with VKA (ie, 3–12 months) had annual recurrence rates >5% in the presence of both overt and mild antithrombin deficiency and <5% with normal antithrombin levels, with these differences being statistically significant. This finding suggests that in patients screened for thrombophilia after a first VTE event, even a mild decrease in antithrombin levels should be taken into account in the individual assessment of treatment duration.

Some limitations of the present study should be addressed. The lack of randomization hampers the possibility of providing definite indications about the optimal VKA treatment duration in patients with overt or mild antithrombin deficiency. However, all differences showed a high statistical significance and are unlikely to be attributable to chance. In addition, all of the confounding biases have been dealt with in the design phase as well as in the analysis phase by regression analysis.

In addition, considering the large sample size and the long duration of follow-up, we are confident that we minimized any effect attributable to chance.

Furthermore, to evaluate only VTE events secondary to an inherited antithrombin deficiency, we excluded from the analysis all patients with deficiencies of other natural anticoagulants (protein C and protein S) or with conditions known to be associated with antithrombin deficiency. This choice sought to reduce as much as possible the impact of other thrombophilic conditions and to better estimate the role of antithrombin levels on VTE risk. Nevertheless, we cannot rule out the
possibility that the results of our study may not be generalized to a less selected VTE population.

An additional relevant aspect is that the mean age of the study population was younger than the usual mean age of patients with VTE, with such a difference likely attributable to the nature of the recruiting center (a third-level referral center). However, the rather high number of enrolled patients is likely to have overcome any potential source of bias. However, the generalizability of our results to older populations needs to be confirmed by additional studies.

Finally, adherence to VKA treatment, as assessed by the quality of international normalized ratio monitoring, was not taken into account in the present study. However, all included patients were managed at the local anticoagulation clinic for the monitoring of VKA therapy, and patients with poor international normalized ratio control usually have been assessed every 7 to 10 days to identify the cause of international normalized ratio instability and to improve the quality of treatment. Thus, we are confident that our routine approach has minimized adherence issues. In addition, considering that the incidence of VTE recurrence while patients were on VKA treatment was widely in accordance with data from the literature (=1% per patient-year), we are confident that the compliance with VKA treatment is not a source of bias in the present study.

In conclusion, the results of this large prospective cohort study suggest that patients with mild antithrombin deficiency exhibit a risk of recurrent VTE that is significantly higher than that in patients with normal antithrombin levels and similar to that in patients with an overt antithrombin deficiency. Because this association was particularly relevant in patients with unprovoked VTE, mild antithrombin deficiency may be considered an additional variable to determine the optimal individual duration of secondary prevention with anticoagulant drugs.

Disclosures
Dr s Di Minno, Dentali, and Ageno served on advisory boards and received honoraria and grants for research unrelated to this study. Dr Lupoli reports no conflicts.

References

Antithrombin deficiency is a recognized major thrombophilic condition. Because most available studies reported data on patients with overt antithrombin deficiency (levels 40–70%), in this prospective study we sought to evaluate the risk of symptomatic venous thromboembolism (VTE) recurrence in a population of patients with “mild” antithrombin deficiency (levels 70–80%) compared with patients with normal antithrombin levels (ie, >80%) and those with overt antithrombin deficiency. We found that patients with mild antithrombin deficiency have a risk of recurrent VTE that is significantly higher than patients with normal antithrombin levels (>80%) and similar to that observed in patients with overt antithrombin deficiency. In our study, patients with unprovoked VTE treated for a definite time with oral anticoagulants (ie, 3–12 months) had annual recurrence rates >5% in the presence of both overt and mild antithrombin deficiency and <5% with normal antithrombin levels, with these differences being statistically significant. This finding suggests that in patients screened for thrombophilia after a first VTE event, even a mild decrease in antithrombin levels should be taken into account in the individual assessment of treatment duration. These findings have some important clinical implications for decisions about the optimal duration of secondary prevention of VTE, and, because this association is particularly relevant in patients with unprovoked VTE, mild antithrombin deficiency may be considered an additional variable to determine the optimal individual duration of secondary prevention with anticoagulant drugs.
Mild Antithrombin Deficiency and Risk of Recurrent Venous Thromboembolism: A Prospective Cohort Study
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