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

Running title: Di Minno et al.; Mild Antithrombin deficiency and recurrent VTE

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Abstract

Background—Antithrombin (AT) deficiency, defined by AT levels of less than 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 AT levels (70-80%).

Methods and Results—Consecutive patients with a first VTE were stratified according to functional AT 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, males 41.9%) were enrolled. Recurrent VTE occurred in 253 patients (3.53% patients-year). Stratifying for AT levels, VTE recurrence occurred in 19 (5.90% patients-year) <70%AT patients, in 20 (5.35% patients-year) of the 70-80%AT patients and in 214 patients (3.31% patient-year) with >80%AT. After adjusting for major VTE risk factors and for anticoagulation duration, the risk of VTE recurrence was significantly higher in patients with <70%AT (HR: 3.48, 95%CI: 2.16-5.61) and 70-80%AT (HR: 2.40, 95%CI: 1.51-3.80) as compared to >80%AT patients. 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 AT deficiency (70%-80% AT) in patients with unprovoked VTE is associated with a significantly increased risk of recurrence and should be taken into account when deciding the duration of secondary prevention.

Clinical Trial Registration Information—ClinicalTrials.gov; Unique Identifier: NCT01382550.

Key words: antithrombin, thromboembolism, thrombophilia.
Introduction

With an overall incidence of about 1-2/00 individuals/year, venous thromboembolism (VTE) is a severe disorder with potential major complications (death from pulmonary embolism, recurrence, the development of a disabling post-thrombotic syndrome).\textsuperscript{1,2} The interaction among risk factors plays a dominant role in the pathogenesis of VTE.\textsuperscript{3-5} Inherited thrombophilia is a coagulation abnormality that is associated with a tendency toward the development of VTE. Although present in <10\% of VTE patients,\textsuperscript{6} deficiencies of antithrombin (AT), Protein C and Protein S, have been recognized as important thrombophilic conditions,\textsuperscript{7-10} with affected patients showing a high risk of first\textsuperscript{11-14} and of recurrent\textsuperscript{15,16} VTE. The prevalence of AT deficiency is 1 in 600 in the healthy population (blood donors)\textsuperscript{17} and it ranges between 0.5 and 4.9\% in subjects with VTE events.\textsuperscript{18}

Of interest, whereas most of studies available in the literature reported data on patients with an overt AT deficiency (levels ranging from 40\% to 70\%)\textsuperscript{18}, two recent case-control studies\textsuperscript{19,20} recruiting large groups of VTE patients stratified according to AT levels, showed an increased prevalence of a first VTE episode also in patients with “mild” AT deficiency (levels ranging from 70\% to 80\%) as compared to patients with normal AT levels (i.e. >80\%). However, prospective cohort studies evaluating the incidence of VTE recurrence in patients with mild AT deficiency are currently lacking. The aim of this prospective study is therefore to evaluate the risk of symptomatic VTE recurrence in a population of patients stratified according to AT levels.

Methods

Consecutive patients (i.e. in the order of referral to the Hospital) referred by general practitioners (March 1993-March 2003) to the Regional Reference Center for Coagulation Disorders of Federico II University of Naples for the assessment of venous thrombosis risk factors (including
thrombophilia screening), were eligible for this study. Objective diagnosis of VTE was mandatorily based on the results of compression ultrasonography, ventilation/perfusion lung scan, or spiral CT. Patients were excluded if VTE was treated with drugs different from vitamin K antagonists (VKA), if they required indefinite treatment with VKA for a different indication (e.g. prosthetic heart valve, atrial fibrillation); if VTE was secondary to hormonal therapy, pregnancy, puerperium, malignancy, protein C and/or protein S deficiency, or antiphospholipid antibodies; if they had chronic liver disease.

According to standard procedures,21 information about risk factors for venous thrombosis (recent [<3 mo] surgery; trauma/fracture; acute medical disease with bed immobilization > 3 days; leg cast; long distance travel) was collected on admission by a trained staff. Based on established criteria, VTE was adjudicated as “unprovoked” in the absence of any of the abovementioned risk factors and “provoked” in the presence of at least one.

For each patient, antithrombin (AT) activity was measured using the Berichrom ATIII kit (Behringwerke, Marburg, Germany). According to manufacturer recommendations, normal AT concentrations are 80-120%. AT activity assessment was performed after at least 3 months from the thrombotic event, while patients were under VKA. The results of these tests were confirmed on a second sample collected 3 months later. Only patients with consistent findings in AT activity were included in the analysis. As the risk of VTE is mainly documented in patients with AT levels <70%,7 we stratified our study population based on AT levels as follows: <70%: overt AT deficiency; 70-80%: mild AT deficiency; >80%: normal AT levels. Protein C, Protein S, antiphospholipid antibodies, homocysteine, factor V Leiden and prothrombin 20210A polymorphisms were determined as previously described.22-24 All study patients were treated with an initial course of weight-adjusted low molecular weight heparin (LMWH) and with VKA.
(INR 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 enrolment 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 was a non-compressible 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 non-compressible venous segment or a substantial increase (4 millimeters or more) 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 computed tomography 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 computed tomography 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, intraocular, retroperitoneal, intraarticular, pericardial, or intramuscular [leading to a compartment syndrome]), or was associated with a decrease in the hemoglobin level of at least 2.0 g/dL or required a transfusion of 2 or more units of whole blood or red cells. Minor bleeding included all cases of bleeding not classified as major. The study was approved by the local Ethics Committee and was carried out according to the declaration of Helsinki and reported according
to the STROBE guidelines for observational studies. All patients provided written informed consent.

**Statistical analysis**

To determine the sample size, we assumed a 15:1 ratio between >80%AT and 70-80%AT patients and, according to a previous study, a 4-year median recurrence-free survival time on the control group. To detect an hazard ratio (HR) greater than 1.5 for VTE recurrence when comparing the two groups, at least 42 70-80%AT and 630 >80%AT patients were needed to obtain a power=80% and a α error <5%.

Statistical analysis was performed with the SPSS 16 system (SPSS Inc., Chicago, IL, USA). Continuous data were expressed as means±Standard deviation (SD); categorical variables were expressed as percentage. The T-test and the ANOVA analysis with the Bonferroni post-hoc test were performed to compare continuous variables; the χ^2 test or the Fisher’s exact test were used to compare categorical data. 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 hazard ratio (HR) with the corresponding 95% confidence interval (CI). In the model, recurrent VTE was the dependent variable; gender, age, age at first event, AT levels, family history of VTE, factor V Leiden mutation, prothrombin 20210A polymorphism, venous stasis, recent surgery, immunological diseases, and the 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 the enrolment until the last clinical visit update. All results are expressed as 2-tailed values, 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 one 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 (7,160.1 patient-years). Of them, 704 (85.5%) had DVT; 30 (3.65%) PE, 89 (10.85%) DVT+PE at enrolment; in 321 (39%) VTE was unprovoked. AT 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 (29.6%) patients and was more common in those with <70% and in those with 70-80 %AT (Table 1).

As shown in table 1, after the first VTE event, 301 (36.6%) patients received an indefinite VKA treatment, the remaining patients were treated with a definite duration (from 3 to 12 months) regimen.

Incidence of Recurrent VTE

During follow-up, recurrent VTE occurred in 253 patients (3.53% 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 angio-CT scan in 22 cases), 28 by angio-CT scan (followed by ultrasound in 23 cases), 1 by abdominal ultrasound followed by angio-CT scan, 1 by MRI 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% patient-year vs 1.26% patient-year, HR: 5.16, 95%CI: 3.57-7.47, p<0.001).
Stratifying for AT levels, VTE recurrence occurred in 19 (5.90% patient-year) <70%AT patients, in 20 (5.35% patient-year) of the 70-80%AT patients and in 214 patients (3.31% patient-year) with >80%AT.

In a multivariate analysis, after adjusting for major VTE risk factors and for VKA treatment duration, the risk of recurrence was significantly higher in patients with <70 %AT (HR: 3.48, 95%CI: 2.16-5.61) and 70-80%AT (HR: 2.40, 95%CI: 1.51-3.80) as compared to >80%AT patients. 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 AT levels were associated with an increasing risk of VTE recurrence (OR: 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 <70%AT [6.98% patients-year], in 16 [8.36% patients-year] with 70-80%AT and in 67 [2.83% patients-year] with >80%AT. This difference in the annual risk of recurrence among groups after adjusting for all other major clinical and demographic characteristics was statistically significant (HR: 5.93, 95%CI: 3.38-10.39 between <70%AT and >80%AT and HR: 3.90, 95%CI: 2.25-6.77, between 70-80%AT and >80%AT).

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

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 <70%AT [8.11% patients-year], in 18 [7.95% patients-year] with 70-80%AT, and in 190 [4.56% patients-year] with >80%AT. Thus, the risk of VTE recurrence resulted significantly increased in both <70%AT (HR: 2.88, 95%CI: 1.61-5.18) and 70-80%AT (HR: 2.65, 95%CI: 1.63-4.29) groups, when compared to >80%AT. These differences remain significant also when recurrence rates were assessed in patients with unprovoked VTE receiving a definite VKA treatment duration (n = 203). Recurrences occurred in 10 patients with <70%AT [9.58% patients-year], 15 [9.07% patients-year] with 70-80%AT and 62 [4.12% patients-year] with >80%AT, with resulting HR 4.27, 95%CI: 2.17-8.40 <70%AT vs >80%AT and HR 3.62, 95%CI: 2.05-6.39 70-80%AT vs >80%AT.

Recurrence rates in patients receiving indefinite treatment duration

In the 301 patients receiving indefinite treatment, recurrent VTE was found in 7 patients with <70%AT [4.02% patients-year], 2 [1.35% patients-year] with 70-80%AT and 24 [1.04% patients-year] with >80%AT. Thus, the risk of recurrent VTE was still increased in <70%AT (HR: 4.95, 95%CI: 2.11-11.61), but not in those with 70-80%AT patients (HR: 1.08, 95%CI: 0.25-4.63) as compared with those with normal AT levels.

However, when specifically evaluating the 118 subjects receiving indefinite VKA treatment after an unprovoked event, a VTE recurrence was found in 7 patients with <70%AT [5.03% patients-year], 1 [3.83% patients-year] with 70-80%AT and 5 [0.58% patients-year] with >80%AT with resulting HR 14.43, 95%CI: 1.55-134.41 <70%AT vs >80%AT and HR 12.69, 95%CI: 3.85-41.82 70-80%AT vs >80%AT.

Incidence of bleeding complications

During follow-up, 91 bleeding episodes (4 non-fatal major and 87 minor bleeding) occurred
(1.27% patients-year). As expected, indefinite treatment duration was associated with an increased risk of overall bleeding as compared with a definite duration regimen (HR: 3.15, 1.97-5.02, p<0.001), with all major bleedings (1 post-traumatic hemarthrosis, 1 gastrointestinal; 2 hemoptyses) occurring in the former group (2 in subjects with >80%AT; 1 in one with 70-80%AT and 1 in one with <70%AT). Minor bleedings (26 menorrhagias; 19 epistaxes; 14 ecchymoses; 14 haematurias; 7 rectal; 5 oral; 2 conjunctival) occurred more frequently in individuals on indefinite treatment as compared with patients on definite treatment duration (20.9% vs 4.6%, HR: 2.96, 1.85-4.74, p<0.001). Stratifying for AT levels, minor bleeding occurred in 10.8% of subjects with >80%AT; in 9.3% of those with 70-80%AT and in 8.1% of those with <70%AT (p = 0.843).

Discussion

This is, to the best of our knowledge, the first prospective study to suggest that patients with mild AT deficiency (70-80% AT) have a risk of recurrent VTE that is significantly higher than the risk in patients with normal AT levels (> 80%). Overt AT deficiency is an established risk factor for both first and recurrent VTE.15,16 However, all previous studies solely focused on patients with AT levels < 70%. In this study, we compared these patients with those with VTE and AT levels equal to or higher than 70%, but we separately considered patients with normal AT levels (>80%) and patients with mildly reduced AT 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 AT deficiency. In addition, we also observed a similar prevalence of VTE family history between overt and mild AT deficient patients, further supporting the hypothesis of the clinical relevance of mild AT deficiency. The determinants of
AT levels slightly above those commonly found in overt AT deficiency are poorly understood. However, given the similar prevalence of a family history of VTE similar between <70%AT and 70-80%AT, this might suggest an inherited nature also for such milder AT deficiency. Recent observations on AT gene polymorphisms associated with mild AT deficiency are in keeping with this finding. Although the prevalence of this mild deficiency has never been evaluated in ad hoc designed studies, genotypes leading to a slight AT levels reduction were found in about 19.5% of blood donors. This finding clearly suggests the need of an extensive screening of mild AT deficiency in order to define its prevalence in general population and in VTE subjects.

Although this study only included patients with inherited AT deficiency, it is relevant to note that patients with different clinical conditions (liver disease, pregnancy, oral contraceptive intake, hormone replacement therapy) may show AT levels similar to patients with mild inherited AT deficiency. However, further studies are needed to know if our findings can be extended also to these populations.

Our finding has some important clinical implications. The optimal duration of secondary prevention of VTE remains debated. 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 less than 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 (i.e. between 3 and 12 months) had annual recurrence rates higher than 5% in the presence of both overt and mild
antithrombin deficiency and lower than 5% with normal AT 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 AT 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 to provide definite indications about the optimal VKA treatment duration in patients with overt and/or mild AT deficiency. However, all differences showed a high statistical significance and are unlikely to be due to chance. In addition, all 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 to have minimized any effect due to chance.

Furthermore, in order to only evaluate VTE events secondary to an inherited AT deficiency, we excluded from the analysis all patients with deficiencies of other natural anticoagulant (Prot C and Prot S) or with conditions known to be associated with AT deficiency. This choice was aimed at reducing as much as possible the impact of other thrombophilic conditions, and to better estimate the role of AT 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.

A further relevant aspect is that the mean age of the study population was younger than the usual mean age of patients with VTE, such a difference being likely due 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. Yet, 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 INR 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 INR control have been usually assessed every 7-10 days in order to identify the cause of INR 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 on VKA treatment was widely in accordance with literature data (≈ 1% patient-year),\textsuperscript{33} we are confident that the compliance to VKA treatment is far from being a source of bias in the present study.

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

**Conflict of Interest Disclosures:** Matteo Nicola Dario Di Minno, Francesco Dentali and Walter Ageno served on advisory boards and received honoraria and grants for research unrelated to this study. Roberta Lupoli has nothing to declare.

**References:**


Table 1. Baseline demographic and clinical characteristics of the study population.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Whole sample</th>
<th>AT &lt;70%</th>
<th>AT 70-80%</th>
<th>AT &gt;80%</th>
<th>p for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at first event (mean+SD)</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 gender</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 months) trauma/surgery</td>
<td>246 (26.8)</td>
<td>12 (30.0)</td>
<td>11 (23.4)</td>
<td>223 (26.8)</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></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FV Leiden</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<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>

*(> 3 days); # other than antiphospholipid syndrome
PTM: Prothrombin time mutation; FV Leiden: Factor V Leiden mutation; VTE: venous thromboembolism; AT: antithrombin; VKA: Vitamin K antagonists
**Table 2.** Univariate analysis of clinical and demographic characteristics of study population stratified according to the occurrence of venous thromboembolism (VTE) recurrence

<table>
<thead>
<tr>
<th></th>
<th>No VTE recurrence (n = 570)</th>
<th>VTE recurrence (n = 253)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at first event (mean+SD)</td>
<td>49.0±14.4</td>
<td>46.76±15.19</td>
<td>0.044</td>
</tr>
<tr>
<td>Male gender</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>PTM</td>
<td>62(10.9)</td>
<td>40(15.8)</td>
<td>0.052</td>
</tr>
<tr>
<td>FV Leiden</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 AT levels</td>
<td>529(92.8%)</td>
<td>214(84.6)</td>
<td></td>
</tr>
<tr>
<td>Mild AT deficiency</td>
<td>23(4.0%)</td>
<td>20(7.9)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Overt AT deficiency</td>
<td>18(3.2%)</td>
<td>19(7.5%)</td>
<td></td>
</tr>
</tbody>
</table>

*p for trend

PTM: Prothrombin time mutation; FV Leiden: Factor V Leiden mutation; VTE: venous thromboembolism; AT: antithrombin, VKA: Vitamin K antagonists

**Figure Legends:**

**Figure 1.** Study flow-chart. VTE: venous thromboembolism. AT: antithrombin. VKA: Vitamin K antagonists. APA: anti-phospholipid antibody

**Figure 2.** Kaplan-Meier survival analysis of VTE recurrence according to AT% levels groups.

VTE: venous thromboembolism. AT levels: antithrombin levels (%)
SCREENING
1356 patients with a first VTE episode

EXCLUSION
Pre-existing conditions with indication to indefinite VKA treatment:
- Prosthetic heart valve (n = 8)
- Atrial fibrillation (n = 41)
- APA syndrome (n = 109)

EXCLUSION
Natural anticoagulants deficiency or conditions impacting on AT levels:
- Prot C/Prot S deficiency (n = 48)
- Liver disease (n = 78)
- Pregnancy/puerperium (n = 97)
- Oral contraceptive (n = 108)
- Hormone replacement (n = 24)

INCLUSION
843 patients included in the follow-up

EXCLUSION
Patients with missing follow-up visits and outcome data (n = 20)

ANALYSIS
823 patients with complete follow-up data

Figure 1
Figure 2

Incidence of recurrent VTE vs. Follow-up (years) with different AT levels: <70%, 70-80%, 80-130%.

Log-Rank: 20.33, p < 0.001
Mild Antithrombin Deficiency and the Risk of Recurrent Venous Thromboembolism: A Prospective Cohort Study
Matteo Nicola Dario Di Minno, Francesco Dentali, Roberta Lupoli and Walter Ageno