Prolactin and Venous Thrombosis
Indications for a Novel Risk Factor?

Bregje van Zaane, Alessandro Squizzato, Anne Q. Reuwer, Anton P. van Zanten, Marcel T.B. Twickler, Olaf M. Dekkers, Suzanne C. Cannegieter, Harry R. Büller, Victor E.A. Gerdes, Dees P.M. Brandjes

Objective—Several acquired risk factors for venous thrombosis (VT) are associated with high prolactin levels. Our goal was to investigate VT risk for different levels of prolactin.

Methods and Results—We used data of a case-control study on leg vein thrombosis conducted between September 1999 and August 2006 at the Academic Medical Center, Amsterdam, the Netherlands. Prolactin was assessed in 187 cases (mean age, 57 years; range, 19 to 90) and 374 gender-matched controls (mean age, 57 years; range, 18 to 93). Odds ratios and 95% CI for VT risk were estimated based on several cutoff levels derived from prolactin levels in controls. Odds ratios for VT risk clearly increased with higher prolactin levels. For prolactin levels above the 75th percentile (8 μg/L), we found a gender-adjusted odds ratio of 1.7 (95% CI 1.0 to 2.7) as compared with levels below the 50th percentile (6 μg/L). This further increased up to an odds ratio of 4.7 (95% CI 1.8 to 11.8) for prolactin levels above the 97.5th percentile (16 μg/L). The risk was most pronounced in premenopausal women.

Conclusion—Our data suggest that prolactin levels are associated with VT in a dose-dependent fashion. Future studies are needed to evaluate the causality of this relationship. (Arterioscler Thromb Vasc Biol. 2011;31:672-677.)

Key Words: epidemiology ■ risk factors ■ venous thrombosis ■ prolactin

Prolactin is a neuroendocrine stress hormone synthesized and secreted by the pituitary gland. A unique feature of prolactin control is its inhibitory character, by dopamine-mediated suppression. Any disease or drug that interferes with the secretion of dopamine or its delivery to the hypothalamus can therefore cause hyperprolactinemia. The most common cause of pathophysiological prolactin levels are pituitary adenomas (prolactinomas). Prolactin levels also increase substantially during pregnancy and the first 6 weeks after delivery, and to a lesser degree in response to any kind of physical or psychological stress.1

Several conditions that are characterized by high levels of prolactin, such as pregnancy, puerperium, and the use of oral contraceptive agents or hormone replacement therapy, are associated with an increased risk of venous thrombosis (VT).2,3 Although this increased risk is to a large extent explained by the simultaneous increase in circulating estrogen levels, prolactin itself may play an additional role. In prolactinoma patients, an increased incidence of VT has been reported, and there are indications that higher levels of prolactin may contribute to a hypercoagulable state.4,5 Conversely, higher levels of prolactin were found in patients with VT, in whom no congenital or acquired risk factors could be identified, compared with those with congenital risk factors or healthy control subjects.5 In addition, VT has been related to the use of antipsychotic drugs, which are known to induce hyperprolactinemia by blocking dopamine receptors.6–8

These considerations highlight that elevated prolactin levels may be a possible cause of VT. Therefore, in this case-control study, we attempted to determine the association between different levels of prolactin and the risk of VT.

Methods

Study Population
Consecutive outpatients with suspected deep venous thrombosis (DVT) were potentially eligible for this study (n=944). Patients with objectively confirmed DVT, calf vein thrombosis, or superficial thrombophlebitis of the lower extremities (cases) and subjects in whom leg vein thrombosis was objectively ruled out (controls) were derived from a larger study, designed to investigate new risk factors for VT. Patients were excluded if they were under the age of 18 (n=3), if they had experienced a previous DVT or pulmonary embolism (n=119), if they were already receiving vitamin K antagonists or heparin for more than 24 hours (n=3), if they were admitted to the hospital (n=58), or if they were unwilling to receive anticoagulant medication. The risk was most pronounced in premenopausal women.
Setting and Location

Patients were recruited at the Academic Medical Center, Amsterdam, the Netherlands, between September 1999 and August 2006. The study was approved by the institutional medical ethical review board, and all patients provided written informed consent.

Data Collection and Diagnosis of VT

At presentation (ie, before diagnostic testing for VT), participants were subjected to a standardized questionnaire including items on medical history, family history, concomitant medication, and the presence of known risk factors for VT. Participants subsequently provided a nonfasting venous blood sample. Blood was collected in 0.109 mol/L trisodium citrated tubes. Within 1 hour, platelet-poor plasma was obtained by centrifugation and recentrifugation of the supernatant, for 20 minutes at 1600 g at 4°C. Plasma was stored at −30°C until further use.

All participants underwent diagnostic testing for DVT according to an algorithmic management strategy combining clinical pretest probability and d-dimer assay (Tinaquant, Roche Diagnostics, Basel, Switzerland), followed by compression ultrasound of the lower extremities, if indicated.9,10 For those who had been judged likely to have DVT, a second ultrasound examination was performed 1 week later if the first test was negative. The diagnosis of VT, including DVT (ie, proximal thrombosis of the iliac or superficial femoral vein, or thrombosis involving at least the upper third part of the deep calf veins), calf vein thrombosis, and superficial thrombophlebitis, was confirmed by failure to fully collapse the lumen of the deep or superficial veins during compression testing. Thrombosis was considered provoked if at least 1 of the following acquired risk factors was present: use of estrogen- or progesterone-containing agents, malignancy, pregnancy or puerperium, paralysis of the symptomatic leg, recent trauma (within the last 60 days), surgery within the last 4 weeks or bedridden for more than 3 days, hospitalization within the previous 6 months, or long-distance travel (6 hours or more) within the previous 3 months. In the absence of these acquired risk factors, VT was considered unprovoked.

Six patients with high clinical pretest probability and negative first ultrasound failed to return for the second ultrasound examination. Diagnosis of VT was confirmed in 211 participants, who were therefore included as cases, whereas in 537 participants, the diagnosis of VT was objectively ruled out using the above-mentioned diagnostic management strategy. These 537 participants were included as controls (Figure 1).

Statistical Analysis

Results of categorical variables were expressed as number and percentage. Prolactin levels were presented as medians (interquartile range [IQR]), and the difference between groups was calculated using the Mann-Whitney U test. We subsequently calculated odds ratios and 95% CIs for the risk of VT at different levels of prolactin using binary logistic regression. Cutoff levels for prolactin were set according to the different percentiles of the values observed in controls. Prolactin levels below the 50th percentile were used as reference and compared with levels above the 50th, 75th, 80th, 90th, 95th, and 97.5th percentiles. Multivariate analysis was performed to adjust for gender to take the frequency matching on gender into account. The influence of potential confounding factors was analyzed using the univariate model, and if a significant contribution (change in crude odds ratio of more than 5%) was found for any of the independent factors, these variables were added to the multivariate logistic regression model. An exception was made for pregnancy and puerperium, because there were only a limited number of women in these conditions included in the study. However, pregnancy and puerperium were considered strong confounders in the relationship between prolactin and VT, and we therefore felt it was more accurate to exclude these women from the analysis than to incorporate these variables in the multivariate model.

Separate analysis was performed for patients with DVT, excluding those with calf vein thrombosis or superficial thrombophlebitis. Considering gender-based differences in basal prolactin levels,
subgroup analysis was performed for men and women separately. To evaluate the possible influence of circulating estrogen levels, we performed additional analyses in subgroups of premenopausal and postmenopausal women, applying the same cutoff levels as those used in the analysis of all women. Women were considered premenopausal if aged 55 years or below and not using hormone replacement therapy, whereas postmenopausal women were defined as those aged above 55 years or those using hormone replacement therapy.

Last, in an attempt to evaluate whether any observed association between prolactin and VT might have been influenced by the inflammatory stress induced by the thrombotic event itself, the relationship between levels of prolactin and C-reactive protein, a marker of the acute phase response, was assessed. Levels of high-sensitivity C-reactive protein were measured in 158 randomly selected subjects (79 cases and 79 controls) as described elsewhere.11 Linear regression was performed after log-transformation of both prolactin and high-sensitivity C-reactive protein levels. We reasoned that if no relationship was demonstrated between the 2 variables, then an elevated prolactin level could be assumed not to be a nonspecific stress-related response.

Statistical analysis was performed with the use of SPSS 15.0 software package (SPSS Inc, Chicago, IL).

**Results**

**Patient Characteristics**

A total of 187 cases and 374 controls were included. Mean age (57 years) and female gender (58%) were similar in cases and controls. Of all cases with VT, 152 (81%) had a DVT, 12 (6%) had an isolated calf vein thrombosis, and 23 (12%) had a superficial thrombophlebitis of the lower extremities. Overall, in 123 (66%) patients with VT, and in 105 (69%) of the patients with DVT, at least 1 acquired risk factor for VT was present at the time of event, and thrombosis was therefore considered provoked.

In total, 45 (24%) patients with VT and 53 (14%) controls were using drugs known to increase circulating prolactin levels: 36 patients with VT and 30 controls were using oral contraceptive agents, 3 patients with VT and 5 controls were on hormone replacement therapy, and 8 patients with VT and 21 controls were using prolactin-increasing drugs other than oral contraceptive agents or hormone replacement therapy. Of these, 2 patients with VT and 3 controls used more than 1 prolactin-increasing agent (Table 1).

**Table 1. Patient Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>All Cases* (n=187)</th>
<th>DVT Only (n=152)</th>
<th>Controls (n=374)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>79 (42.2)</td>
<td>66 (43.4)</td>
<td>158 (42.2)</td>
</tr>
<tr>
<td>Age, median (range), years</td>
<td>57 (19 to 90)</td>
<td>58 (19 to 90)</td>
<td>57 (18 to 93)</td>
</tr>
<tr>
<td>Unprovoked VT, n (%)</td>
<td>64 (34.2)</td>
<td>47 (30.9)</td>
<td></td>
</tr>
<tr>
<td>Provoked VT, n (%)</td>
<td>123 (65.8)</td>
<td>105 (69.1)</td>
<td></td>
</tr>
<tr>
<td>BMI, median (IQR), kg/m²</td>
<td>26.4 (23.9 to 29.1)</td>
<td>26.4 (23.8 to 28.7)</td>
<td>27.1 (24.3 to 31.3)</td>
</tr>
<tr>
<td>Oral contraceptive pill, n (%)</td>
<td>36 (19.3)</td>
<td>26 (17.1)</td>
<td>30 (8.0)</td>
</tr>
<tr>
<td>Hormone replacement therapy, n (%)</td>
<td>3 (1.6)</td>
<td>3 (2.0)</td>
<td>5 (1.3)</td>
</tr>
<tr>
<td>Recent trauma, n (%)</td>
<td>26 (13.9)</td>
<td>22 (14.5)</td>
<td>53 (14.2)</td>
</tr>
<tr>
<td>Malignancy, n (%)</td>
<td>26 (13.9)</td>
<td>24 (15.8)</td>
<td>24 (6.4)</td>
</tr>
<tr>
<td>Pregnancy, n (%)</td>
<td>1 (0.5)</td>
<td>0 (0.0)</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>Puerperium, n (%)</td>
<td>1 (0.5)</td>
<td>1 (0.7)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Surgery/bedridden, n (%)</td>
<td>30 (16.0)</td>
<td>29 (19.1)</td>
<td>30 (8.0)</td>
</tr>
<tr>
<td>Paralysis of the symptomatic leg, n (%)</td>
<td>16 (8.6)</td>
<td>15 (9.9)</td>
<td>30 (8.0)</td>
</tr>
<tr>
<td>Hospitalization, n (%)</td>
<td>35 (18.7)</td>
<td>33 (21.7)</td>
<td>46 (12.3)</td>
</tr>
<tr>
<td>Long-distance travel, n (%)</td>
<td>30 (16.0)</td>
<td>23 (15.1)</td>
<td>43 (11.5)</td>
</tr>
<tr>
<td>Prolactin level (µg/L), median (IQR)</td>
<td>6.7 (4.4 to 8.9)†</td>
<td>6.7 (4.4 to 8.9)†</td>
<td>5.6 (4.4 to 7.8)</td>
</tr>
<tr>
<td>Men, median (IQR)</td>
<td>5.6 (4.4 to 7.8)</td>
<td>5.6 (4.4 to 7.8)</td>
<td>5.6 (4.4 to 7.8)</td>
</tr>
<tr>
<td>Women, median (IQR)</td>
<td>7.8 (5.6 to 11.9)‡</td>
<td>7.8 (5.6 to 11.1)‡</td>
<td>6.7 (4.4 to 8.9)</td>
</tr>
<tr>
<td>Use of PRL-increasing agents, n (%)</td>
<td>8 (4.3)</td>
<td>8 (5.3)</td>
<td>21 (5.6)</td>
</tr>
<tr>
<td>Calcium channel blockers (verapamil), n (%)</td>
<td>1 (0.5)</td>
<td>1 (0.7)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Dopamine receptor antagonist, n (%)</td>
<td>1 (0.5)</td>
<td>1 (0.7)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Dopamine synthesis inhibitors, n (%)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>Estrogen influencing drugs (tamoxifen), n (%)</td>
<td>3 (1.6)</td>
<td>3 (2.0)</td>
<td>5 (1.3)</td>
</tr>
<tr>
<td>Opiates, n (%)</td>
<td>1 (0.5)</td>
<td>1 (0.7)</td>
<td>9 (2.4)</td>
</tr>
<tr>
<td>Serotonin-reuptake inhibitors, n (%)</td>
<td>2 (1.1)</td>
<td>2 (1.3)</td>
<td>4 (1.1)</td>
</tr>
</tbody>
</table>

PRL indicates prolactin.

*All thrombosis patients combined (DVT, calf vein thrombosis, and thrombophlebitis).

†P<0.05, patients with (deep) VT vs controls.

‡P<0.01, patients with VT vs controls.

Prolactin Levels

The median prolactin level in cases with VT (6.7 µg/L, interquartile range [IQR], 4.4 to 8.9) was higher than in control subjects (5.6 µg/L, IQR 4.4 to 7.8) (P=0.02) (Table 1). In both groups, median prolactin levels were higher for women than for men. Nine patients with VT (6 women) and
Table 2. Risk of VT for Different Levels of Prolactin

<table>
<thead>
<tr>
<th>Percentile*</th>
<th>PRL† (μg/L)</th>
<th>Controls (n=371), n</th>
<th>n</th>
<th>OR§ (95% CI)</th>
<th>Adjusted OR¶ (95% CI)</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>&lt;6</td>
<td>124</td>
<td>50</td>
<td>Reference</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>&gt;6</td>
<td>247</td>
<td>135</td>
<td>1.4 (0.9 to 2.0)</td>
<td>1.2 (0.8 to 1.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>75</td>
<td>&gt;8</td>
<td>88</td>
<td>60</td>
<td>1.7 (1.0 to 2.7)</td>
<td>1.4 (0.8 to 2.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>80</td>
<td>&gt;9</td>
<td>56</td>
<td>43</td>
<td>1.8 (1.1 to 3.2)</td>
<td>1.5 (0.8 to 2.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>90</td>
<td>&gt;11</td>
<td>29</td>
<td>31</td>
<td>2.6 (1.4 to 4.9)</td>
<td>2.1 (1.1 to 4.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95</td>
<td>&gt;13</td>
<td>17</td>
<td>20</td>
<td>2.9 (1.4 to 6.1)</td>
<td>2.3 (1.1 to 5.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>97.5</td>
<td>&gt;16</td>
<td>8</td>
<td>15</td>
<td>4.7 (1.8 to 11.8)</td>
<td>3.5 (1.3 to 9.5)</td>
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</tr>
</tbody>
</table>

Pregnant women and women within the first 6 weeks after delivery (puerperium) were excluded from the analysis. OR indicates odds ratio; PRL, prolactin.

*Analysis was performed for the 75th, 80th, 90th, 95th, and 97.5th percentiles. Risk applies for PRL levels above the cutoff point compared to reference (below the 50th percentile).

†Reference range: <22 μg/L (women), <15 μg/L (men).
‡VT: DVT, calf vein thrombosis, and thrombophlebitis.
§Adjusted for the matching factor gender.
¶Adjusted for gender, age, use of estrogen-containing agents, BMI, surgery, and malignancy.

Table 3. Risk of VT for Different Levels of Prolactin in Men and in Women

<table>
<thead>
<tr>
<th>Percentile*</th>
<th>PRL† (μg/L)</th>
<th>Controls (n=158)</th>
<th>Cases‡ (n=79)</th>
<th>OR (95% CI)</th>
<th>Adjusted OR§ (95% CI)</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>&lt;6</td>
<td>66</td>
<td>29</td>
<td>Reference</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>&gt;6</td>
<td>92</td>
<td>50</td>
<td>1.2 (0.7 to 2.2)</td>
<td>1.2 (0.7 to 2.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>75</td>
<td>&gt;8</td>
<td>28</td>
<td>14</td>
<td>1.1 (0.5 to 2.5)</td>
<td>1.1 (0.5 to 2.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>80</td>
<td>&gt;9</td>
<td>16</td>
<td>7</td>
<td>1.0 (0.4 to 2.7)</td>
<td>0.9 (0.3 to 2.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>90</td>
<td>&gt;10</td>
<td>13</td>
<td>6</td>
<td>1.1 (0.4 to 3.0)</td>
<td>0.9 (0.3 to 2.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95</td>
<td>&gt;13</td>
<td>7</td>
<td>5</td>
<td>1.6 (0.5 to 5.6)</td>
<td>1.4 (0.3 to 5.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>97.5</td>
<td>&gt;20</td>
<td>2</td>
<td>2</td>
<td>2.3 (0.3 to 17.0)</td>
<td>1.4 (0.1 to 17.5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Pregnant women and women within the first 6 weeks after delivery (puerperium) were excluded from the analysis. OR indicates odds ratio; PRL, prolactin.

*Analysis was performed for the 75th, 80th, 90th, 95th and 97.5th percentiles. Risk applies for PRL levels above the cutoff point compared to reference (below the 50th percentile).

†Reference range: <22 μg/L (women), <15 μg/L (men).
‡VT: DVT, calf vein thrombosis, and thrombophlebitis.
§Adjusted for age, use of estrogen-containing agents (in women), BMI, surgery, and malignancy.

7 control subjects (3 women) had prolactin levels above reference range.

We did not find an association between prolactin levels and C-reactive protein among the 158 subjects in whom levels of C-reactive protein were analyzed, neither in cases (regression coefficient β, −0.05; 95% CI, −0.17 to 0.07; P = 0.43) nor in controls (regression coefficient β, 0.03; 95% CI, −0.06 to 0.12; P = 0.52).

Prolactin and the Risk of Venous Thrombosis

We found odds ratios for each cutoff level that clearly increased with the percentiles used (adjusted for gender) (Table 2). For prolactin levels above the 75th percentile (8 μg/L), we found an odds ratio of 1.7 (95% CI 1.0 to 2.7) compared with levels below the 50th percentile (6 μg/L). This further increased up to an odds ratio of 4.7 (95% CI 1.8 to 11.8) for prolactin levels above the 97.5th percentile (16 μg/L). Adjustment for age, use of estrogen-containing agents (oral contraceptives and hormone replacement therapy), body mass index (BMI), surgery, and malignancy slightly decreased the odds ratios. Similar results were found when only patients with DVT of the leg were analyzed (Table 2). When we analyzed patients with provoked and unprovoked thrombosis separately, we observed the same pattern of increasing odds ratios in both groups (data not shown).

The association between prolactin and risk of VT was most pronounced in women (Table 3 and Figure 2), with a particularly high relative risk of VT in the subgroup of premenopausal women (Figure 2). Adjustment for age, use of estrogen-containing agents, BMI, surgery, and malignancy did not materially alter the crude odds ratios (data not shown).

No clear association between higher prolactin levels and VT was observed for men (Table 3) or for postmenopausal women (Figure 2).

Discussion

In this case-control study, we found the risk of VT to gradually rise with increasing levels of prolactin. This ap-
pears to be the case particularly in premenopausal women. Of note, the association between prolactin levels and thrombosis was observed almost entirely within physiological values for prolactin.\textsuperscript{12}

Thus far, the ability of pregnancy, puerperium, use of oral contraceptive agents, and hormone replacement therapy to induce VT has mainly been attributed to alterations in circulating estrogen level and subsequent effects on the synthesis of coagulation proteins.\textsuperscript{13} Although prolactin levels can be elevated as a result of high estrogen levels, our findings indicate that prolactin itself may play an additional role in causing VT. However, the observed differential effects of prolactin in men and women, as well as in pre- and postmenopausal women, suggest that the association between VT and prolactin is estrogen-dependent. The relationship between estrogen and prolactin is complex, with estrogen increasing prolactin secretion, whereas prolactin in turn decreases estrogen levels. In addition, estrogen is involved in the upregulation of prolactin receptor synthesis and stimulates prolactin binding at the hepatic level, altering an individual’s responsiveness to circulating prolactin levels.\textsuperscript{14–16} A certain amount of estrogen may thus be needed for prolactin to exert its effects, which implies that only in the event of estrogen levels above a specific threshold prolactin is likely to influence the risk of VT. It should, however, be noted that there is some evidence that prolactin is capable of altering the coagulation system through estrogen-independent mechanisms.\textsuperscript{17}

Prolactin may be involved in the pathogenesis of VT via several pathways. First, prolactin induces an inflammatory response characterized by infiltration of lymphocytes, macrophages and neutrophils, as well as adhesion of circulating mononuclear cells to the endothelium, hereby indirectly altering coagulation.\textsuperscript{18–20} Second, in rats, prolactin was reported to enhance the synthesis of prothrombin in hepatic microsomes and to increase levels of coagulation factor XII.\textsuperscript{21,22} This proposed direct effect on coagulation is compatible with recent clinical data showing high platelet count; increased levels of fibrinogen, antithrombin, and plasminogen activator inhibitor-1; and decreased levels of tissue factor pathway inhibitor in prolactinoma patients compared with healthy age- and gender-matched controls.\textsuperscript{4} Third, prolactin has been suggested to enhance platelet activation, possibly by binding to a platelet-located prolactin receptor.\textsuperscript{5,23–25} However, 2 recent studies did not show an effect of prolactin on platelet function, nor was the presence of a platelet-located receptor confirmed, leaving the role of prolactin in platelet activation and aggregation still unclear.\textsuperscript{26,27}

Given that stress of any kind can cause an increase in prolactin secretion, the question arises whether our findings are not merely the result of an acute phase response induced by the thrombotic event itself. This may particularly be true because women show a greater prolactin response than men to almost all physiological stimuli, presumably because of the effect of higher estrogen concentrations on the lactotroph cells.\textsuperscript{1} However, the lack of association between high-sensitivity C-reactive protein and prolactin argues against the acute phase response as explanation for our findings. Also, control subjects were persons with a suspicion of VT. Consequently, controls were not entirely free of (inflammatory) stress either, which makes it unlikely that our finding is an epiphenomenon. Future prospective studies are still needed to disentangle the complex relationship of prolactin, estrogen, and the acute phase response in all its details.

Theoretically, all factors that induce physical or psychological stress (including most of the acquired risk factors for VT) may increase levels of prolactin. Therefore, these risk factors may be considered confounders. To adequately identify possible confounding factors, the influence of each of the acquired risk factors was analyzed using a univariate model. Apart from pregnancy, puerperium, and use of estrogen-containing agents (oral contraceptives and hormone replacement therapy), only malignancy and surgery were found to influence the relationship between prolactin and VT. However, adjustment for these factors did not materially alter the study findings.

A possible limitation of our study is the fact that prolactin levels were measured at presentation rather than at a fixed time of day. The diurnal rhythm of prolactin, with peak levels occurring early in the morning, could have resulted in small physiological fluctuations among subjects. However, owing to the design of our study, this would have affected both cases and controls in a similar manner. Such random misclassification could at most have led to an underestimation of the association. Also, the definition of pre- and postmenopausal women based on age and use of hormone substitution therapy may be of some concern. Any misclassification on this part would have equally affected cases and controls. In addition, the inclusion of patients with superficial vein thrombosis and patients with provoked thrombosis may induce a dilution bias, therefore decreasing the strength of association between prolactin and venous thromboembolism. However, excluding
these patients from the analysis and adjusting for known risk factors did not substantially modify the results. Nonetheless, future studies with a priori knowledge on estrogen status and addressing the other limitations of this study are needed to confirm our findings.

It is probably too early to conclude on clinical implications of these observations. For this we need confirmation of our findings in other studies and more data on the underlying mechanism. From this study, we cannot conclude whether prolactin is a mediator between some other risk factor and VT or is itself an independent risk factor. However, mounting evidence suggests a relevant interaction of hormones other than estrogens and androgens and hemostasis.28 These interventions need to be carefully explored because endocrine dysfunction is a potentially treatable condition, and any strategy that reduces thrombosis risk without increasing bleeding risk is attractive.

In conclusion, our data suggest that higher prolactin levels are associated with VT. The relationship is most pronounced in premenopausal women, suggesting that estrogen-dependent pathways in crosstalk with prolactin levels may underlie this association. Future studies are needed to evaluate causality of the observed relationship between prolactin levels and VT.

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Disclosures
None.

References
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