The hormonal influence on the haemostatic system and the risk of thrombosis

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Incidence of Venous Thromboembolism in Patients with Cushing’s syndrome: A Multicenter Cohort Study

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ABSTRACT

Background
Venous thromboembolic complications have frequently been reported in patients with Cushing’s syndrome. Whether these patients are at increased risk of venous thromboembolism (VTE) remains to be elucidated.

Methods
In a retrospective multicenter cohort study, we aimed to evaluate the incidence of VTE in patients with CS prior to treatment and after surgery. Medical records were reviewed from all university medical centers in the Netherlands. All objectively confirmed VTE during 3 years prior to, and 3 years after treatment onset, within the study period of January 1990 to June 2010, were documented. Patients surgically treated for nonfunctioning pituitary adenoma served as controls for the incidence of postoperative VTE in adrenocorticotropic hormone (ACTH)-dependent CS.

Results
A total of 473 patients (mean age 42 years, 363 women) were included (360 ACTH-dependent pituitary CS). The total number of person-years was 2526. Thirty-seven patients experienced VTE during the study period, resulting in an incidence rate of 14.6 (95% confidence interval [CI] 10.3-20.1) per 1000 person-years. The incidence rate for first-ever VTE prior to treatment was 12.9 (95% CI 7.5-12.6) per 1000 person-years (17 events). The risk of postoperative VTE, defined as risk within 3 months after surgery, was 0% for ACTH-independent and 3.4% (95% CI 2.0-5.9) for ACTH-dependent CS (12 events in 350 patients); most events occurred between 1 week and 2 months after surgery. Compared to the controls, the risk of postoperative VTE in patients undergoing transsphenoidal surgery was significantly greater (p = 0.01).

Conclusions
Patients with CS are at high risk of VTE, especially during active disease and after pituitary surgery. Guidelines on thromboprophylaxis are urgently needed.
**INTRODUCTION**

Endogenous Cushing’s syndrome (CS) is an uncommon disorder characterized by prolonged exposure to excessive cortisol secretion. Estimated incidences range from 0.7 to 2.4 per million individuals per year. CS is associated with increased cardiovascular morbidity and mortality. Additionally, cardiomyopathy, myocardial infarction and stroke, venous thromboembolic complications have frequently been reported in CS, especially after surgery. In previous studies on patients with CS, the risk of postoperative venous thromboembolism (VTE) varied between 0 and 5.6%, however the size of these studies was too small to draw firm conclusions. The increased risk of VTE is thought to reflect coagulopathy, mediated by changes in hemostatic and fibrinolytic factors, such as increased levels of factor VIII, IX, von Willebrand-factor, fibrinogen, and plasminogen activator inhibitor-1. Whether these alterations lead to an increased risk of VTE before surgery has to be elucidated.

Although, low dose heparin has been advised in the immediate perioperative period of Cushing’s syndrome, to date, specific guidelines on the treatment of CS and on the prevention of thrombosis have not been developed. Interestingly, a 3-fold decrease in VTE after introduction of prolonged postoperative thromboprophylaxis has been reported, which raises the question of whether extended thromboprophylaxis is needed.

We therefore aimed to evaluate the incidence of VTE in a large cohort of patients with endogenous CS from a benign origin, with a special focus on the risk of postoperative VTE. To differentiate between the risk associated with cortisol overexposure and the risk due to the surgical procedure itself, we additionally included patients surgically treated for nonfunctioning pituitary adenomas as controls. Because adrenalectomy for adrenal incidentaloma is usually only required for potential malignant disease, a proper control group for Cushing patients undergoing adrenal surgery cannot be established.


METHODS

Study population
Consecutive patients diagnosed with endogenous CS of benign origin between January 1, 1990 and June 6, 2010, were eligible for inclusion. Patients were recruited from all university medical centers in the Netherlands. The diagnosis of CS was based on general diagnostic criteria, depending on availability of standardized biochemical tests and imaging techniques.\textsuperscript{1,17} Briefly, low-dose dexamethasone suppression test, 24-h urinary free cortisol, midnight plasma cortisol, plasma cortisol circadian rhythm, and late-night salivary cortisol were used to confirm hypercortisolism. The cause of CS was established by additional testing: in case of adrenocorticotropic (ACTH)-dependent CS, the suppression of serum cortisol during a 7-h intravenous (iv) dexamethasone suppression test,\textsuperscript{18} the response of serum cortisol and ACTH to iv corticotrophin-releasing hormone (CRH) stimulation,\textsuperscript{19} and pituitary imaging by magnetic resonance imaging (MRI) with iv contrast was performed. If pituitary MRI was inconclusive, bilateral inferior petrosal sinus sampling was often done. In patients with ACTH-independent CS, adrenal imaging was performed with computed tomography scanning or MRI.\textsuperscript{20}

Exclusion criteria were age younger than 18 yr at the time of diagnosis, any malignancy, ectopic ACTH syndrome, ectopic CRH syndrome, exogenous CS, pseudo-CS, and the use of glucocorticoids other than for replacement therapy after surgery or in combination with cortisol-lowering medication. Patients who had undergone pituitary surgery for nonfunctioning pituitary adenoma served as the control group for the risk of postoperative VTE in ACTH-dependent CS. Our intention to enroll cases to controls in a 1:2 ratio appeared not feasible because matching according to age and sex was hampered by the fact that most cases were relatively young women, whereas most controls were older men. We therefore enrolled with a ratio of two cases to one control and matched for sex, age, surgical procedure, hospital, and year of surgery. The same exclusion criteria as for patients with CS applied (Fig. 1).

Patient identification and study procedures
For each participating hospital, outcomes of endocrine function tests were screened to identify potentially eligible patients. Further identification was performed using the International Classification of Diseases Ninth Revision (ICD 9), Clinical Modification for all conditions characterized by hypercortisolism. Three investigators (D.J.F.S., B.v.Z., J.D.) checked eligibility criteria and searched the case notes and hospital records of eligible patients at the site location. Information on the diagnosis and etiology of CS, treatment strategies, and occurrence of VTE
was based on hospital records and collected in a standardized fashion. For each patient, information on type, dose, and duration of thromboprophylaxis was documented.

**Study period**
Within the study period between January 1, 1990, and June 6, 2010, all cases were followed up for a maximum of 6 yr, starting from maximally 3 yr before treatment up to 3 yr after treatment onset. The date of treatment onset was defined as the date of surgery, pituitary irradiation, or the start of cortisol-lowering medication, depending on which treatment strategy was first initiated. Patients were followed up until the end of follow-up as defined above or death, whichever occurred first.

**Figure 1.** Flow chart of selection procedure and analysis.

VTE indicates venous thromboembolism; ACTH, adrenocorticotropic hormone; NFA, nonfunctioning pituitary adenoma

**Venous thromboembolic events**
The diagnosis of VTE was objectified by imaging techniques, such as compression ultrasound, spiral computed tomography, or ventilation/perfusion scanning. Only confirmed VTE were considered for the present analysis. Information on VTE before treatment was obtained by screening the medical history from the patient’s charts. In addition, all case notes, letters, laboratory results, and imaging techniques up to 3 yr after treatment were checked. For each VTE, information on type, treatment, and outcome (fatal or nonfatal) as well as the presence of
established risk factors (trauma, immobilization, surgery, pregnancy, long distance travel, use of oral contraceptives or hormone replacement therapy, or thrombophilia) was documented. If VTE had occurred before the suspicion of CS was raised, we evaluated whether cushingoid symptoms had already been present at the time of VTE. For those patients who experienced VTE during or after the diagnostic work-up of CS, cortisol levels (plasma cortisol, salivary cortisol or 24 h urinary free cortisol) before and after the event were collected, and the stage of CS (active hypercortisolism, persistent hypercortisolism, remission, or relapse) was noted. The definition of relapse and remission was based on the judgment of the treating physician and laboratory results registered in hospital records.

**Statistical analysis**

Individual person-time was calculated by subtracting the date of the first VTE within the study period, death, or the end of follow-up, whichever occurred first, from the entry date. Incidence rates for VTE were calculated by dividing the observed number of VTE within the study period by the sum of individual person-years. Stratified incidence rates were calculated for deep venous thrombosis (DVT) and pulmonary embolism (PE). Incidence rates were presented per 1000 person-years with accompanying 95% confidence intervals (CI). Separate analyses were performed for first-ever VTE. The Kaplan-Meier method was used to evaluate the occurrence of postoperative VTE. Data were processed with the use of SPSS 16.0 software package (SPSS Inc., Chicago, IL). The study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.²¹

**RESULTS**

**Patient characteristics**

Patient characteristics are summarized in Table 1. A total of 473 patients were included (Fig. 1). The majority of the patients were female (80%), and the mean age was 42 (range 18-80) years. Cushing’s disease (pituitary adenoma) was diagnosed in 353 patients. Seven patients were diagnosed as having pituitary hyperplasia, 95 adrenal adenoma, 11 macronodular adrenal hyperplasia, and seven micronodular adrenal hyperplasia.

Median follow-up was 6.0 (range 0.7 to 6.0) years. Seven patients died during the study period, 25 were lost to follow-up, and 62 were diagnosed with CS only recently, which subsequently resulted in a shorter follow-up period. Ten patients experienced VTE before the entry date and therefore did not contribute to the analysis of first VTE.
Table 1. Patient characteristics.

<table>
<thead>
<tr>
<th></th>
<th>All Cushing patients (n=473)</th>
<th>ACTH-dependent (n=360)</th>
<th>ACTH-independent (n=113)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, female, n (%)</td>
<td>363 (76.6)</td>
<td>262 (72.8)</td>
<td>101 (89.4)</td>
</tr>
<tr>
<td>Age, years, mean (range)</td>
<td>42.3 (18-80)</td>
<td>41.7 (18-80)</td>
<td>44.1 (19-79)</td>
</tr>
<tr>
<td></td>
<td>42.7 (20-74)</td>
<td>41.9 (20-74)</td>
<td>49.1 (32-67)</td>
</tr>
<tr>
<td></td>
<td>42.2 (18-80)</td>
<td>41.6 (18-80)</td>
<td>43.5 (19-79)</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>29.1 (6.3)</td>
<td>29.5 (6.4)</td>
<td>28.2 (6.6)</td>
</tr>
<tr>
<td>Etiology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cushing’s disease, n (%)</td>
<td>353 (74.6)</td>
<td>353 (98.1)</td>
<td></td>
</tr>
<tr>
<td>Pituitary hyperplasia, n (%)</td>
<td>7 (1.5)</td>
<td>7 (1.9)</td>
<td></td>
</tr>
<tr>
<td>Adrenal adenoma, n (%)</td>
<td>95 (20.1)</td>
<td>95 (84.1)</td>
<td></td>
</tr>
<tr>
<td>Adrenal macronodular hyperplasia, n (%)</td>
<td>11 (2.3)</td>
<td>11 (9.7)</td>
<td></td>
</tr>
<tr>
<td>Adrenal micronodular hyperplasia, n (%)</td>
<td>7 (1.5)</td>
<td>7 (6.2)</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary Surgery, n (%)</td>
<td>463 (97.9)</td>
<td>352 (97.8)</td>
<td>111 (98.2)</td>
</tr>
<tr>
<td>Pituitary, n (%)</td>
<td>350 (74.0)</td>
<td>350 (97.2)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Adrenal, n (%)</td>
<td>113 (23.9)</td>
<td>2 (0.6)</td>
<td>111 (98.2)</td>
</tr>
<tr>
<td>Total number of Surgeries, n</td>
<td>533</td>
<td>420</td>
<td>113</td>
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<tr>
<td>Pituitary surgeries, n</td>
<td>388</td>
<td>388</td>
<td>0</td>
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<td>Transsphenoidal surgery, n</td>
<td>385</td>
<td>385</td>
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<td>Open craniotomy, n</td>
<td>3</td>
<td>3</td>
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<tr>
<td>Adrenal surgeries, n</td>
<td>145</td>
<td>32</td>
<td>113</td>
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<td>Laparoscopic, n</td>
<td>135</td>
<td>29</td>
<td>106</td>
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<tr>
<td>Laparotomic, n</td>
<td>10</td>
<td>3</td>
<td>7</td>
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<td>Medical treatment, n (%)</td>
<td>326 (68.9)</td>
<td>292 (81.1)</td>
<td>34 (30.1)</td>
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<td>Radiotherapy, n (%)</td>
<td>75 (15.9)</td>
<td>75 (20.8)</td>
<td>0 (0.0)</td>
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<td>Remission, n (%)</td>
<td>419 (88.6)</td>
<td>318 (88.3)</td>
<td>101 (89.4)</td>
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<td>After surgery, n (%)</td>
<td>403 (85.2)</td>
<td>302 (83.9)</td>
<td>101 (89.4)</td>
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<tr>
<td>During cortisol-lowering medication, n (%)</td>
<td>16 (3.4)</td>
<td>16 (4.4)</td>
<td>0</td>
</tr>
<tr>
<td>Relapse, n (%)</td>
<td>19 (4.0)</td>
<td>19</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Follow-up, years, median (range)</td>
<td>6.0 (0.7-6.0)</td>
<td>6.0 (0.7-6.0)</td>
<td>6.0 (3.0-6.0)</td>
</tr>
</tbody>
</table>

N indicates number; CS, Cushing’s syndrome; NFA, nonfunctioning adenoma; BMI indicates Body Mass Index (kg/m²); and SD, standard deviation

Of 360 patients with ACTH-dependent CS, 350 underwent pituitary surgery. One patient underwent bilateral adrenalectomy and one patient unilateral adrenalectomy, seven patients received cortisol-lowering medication only and one patient only underwent
pituitary irradiation. Of 113 patients with ACTH-independent CS, 101 underwent unilateral adrenalectomy, 10 bilateral adrenalectomy, and two received cortisol-lowering medication. Cortisol-lowering agents were administered to 316 patients before surgery. Patients with unsuccessful pituitary surgery (n=113) or recurrence (n=19), underwent repeat surgery (n=59), pituitary irradiation (n=71), and/or pharmacological treatment (n=25). In total, 533 surgeries were performed during the study period; 385 of 388 pituitary surgeries were transsphenoidal procedures, and 135 of 145 adrenal surgeries were laparoscopic procedures. Histological confirmation of diagnosis was available in 355 patients.

Information on use of thromboprophylaxis per individual surgery was available for 328 of the 533 surgical procedures performed (62%). Routine thromboprophylaxis was administered according to recommendations for low-risk surgical procedures (in both adrenal and transsphenoidal surgeries), *i.e.* low-molecular weight heparin; dalteparin 2500 U/d, nadroparin 2850 U/d from the day of, or the day prior to, surgery until mobilization or discharge, doubling the dose for individuals with a higher body weight (either above 80 kg or 100 kg). Calparin was given around four surgeries. In eight surgeries unfractionated heparin was administered via continuous iv infusion.

**Venous thromboembolism**

Thirty-seven patients (25 women, 12 men) experienced at least one VTE during the study period. Twelve patients had a DVT of the leg, 15 patients suffered from PE, and six had a concurrent DVT and PE. The remaining patients had calf vein thrombosis (n=1), jugular vein thrombosis (n=1), or cerebral sinus thrombosis (CST) (n=2). None of these events were fatal. Thirty-four of the 37 events were first episodes of VTE. Nineteen events occurred prior to treatment (17 first VTE) (Fig. 2), 12 after surgery, five during cortisol-lowering treatment. One patient had an event just before relapse of Cushing’s disease was diagnosed and two approximately 1 year after successful surgery. A detailed description of the VTE prior to treatment is presented in appendix Table 1.

**Incidence of venous thromboembolic events**

The overall incidence of VTE was 14.6 (95% CI 10.3-20.1) per 1000 person-years and 13.7 (95% CI 9.5-19.1) per 1000 person-years for first-ever VTE (Table 2). The incidence of VTE before treatment was 14.1 (95% CI 8.5-22.0) per 1000 person-years and 12.1 (95% CI 7.5-12.6) per 1000 person-years for first-ever VTE. Overall incidence rates before treatment were similar in ACTH-dependent CS (13.8, 95% CI 8.1-23.3) and ACTH-independent CS (15.2, 95% CI 6.3-36.6).
Table 2. Incidence of venous thromboembolic events in Cushing’s syndrome.

<table>
<thead>
<tr>
<th></th>
<th>N of Cushing patients</th>
<th>Person-years</th>
<th>N of VTE</th>
<th>Incidence rate/1000 person-years</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall incidence</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>VTE</td>
<td>473</td>
<td>2526</td>
<td>37</td>
<td>14.6</td>
<td>10.3-20.1</td>
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<tr>
<td>DVT and/or PE</td>
<td>473</td>
<td>2537</td>
<td>33</td>
<td>13.0</td>
<td>9.0-18.2</td>
</tr>
<tr>
<td>First-ever VTE</td>
<td>463</td>
<td>2477</td>
<td>34</td>
<td>13.7</td>
<td>9.5-19.1</td>
</tr>
<tr>
<td>First-ever DVT and/or PE</td>
<td>464</td>
<td>2490</td>
<td>30</td>
<td>12.0</td>
<td>8.1-17.2</td>
</tr>
<tr>
<td>Prior to treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VTE</td>
<td>473</td>
<td>1344</td>
<td>19</td>
<td>14.1</td>
<td>8.5-22.0</td>
</tr>
<tr>
<td>DVT/PE</td>
<td>473</td>
<td>1345</td>
<td>17</td>
<td>12.6</td>
<td>7.4-20.2</td>
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<tr>
<td>First-ever VTE</td>
<td>463</td>
<td>1315</td>
<td>17</td>
<td>12.9</td>
<td>7.5-12.6</td>
</tr>
<tr>
<td>First-ever DVT and/or PE</td>
<td>464</td>
<td>1318</td>
<td>15</td>
<td>11.4</td>
<td>6.4-18.7</td>
</tr>
</tbody>
</table>

N indicates number; DVT, deep venous thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism; CI, confidence interval.

None of the 113 ACTH-independent Cushing patients developed VTE after adrenal surgery. Twelve patients developed VTE after transsphenoidal surgery. Ten patients had a first event after surgery, and two had a recurrent event (one DVT and one concurrent DVT and PE). Of those two, one had experienced VTE prior to treatment and one shortly before recurrence of CS was diagnosed. In four of the 12 patients with postoperative VTE, the event occurred while receiving thromboprophylaxis. One of the patients was still under therapeutic thromboprophylaxis for a recent VTE (appendix Table 1 and Table 2). Two patients, both developing CST after surgery, were hospitalized for a prolonged period of time (these patients developed meningitis and pneumonia after surgery) resulting in a longer period of immobilization. In 10 out of 12 patients no hypercortisolism was present at the time of postoperative VTE. Details on each of the postoperative VTE are summarized in appendix Table 2.

Three hundred and fifty CS patients who underwent pituitary surgery were compared to 185 patients undergoing pituitary surgery for nonfunctioning adenomas. Sex distribution was comparable for both groups (72% and 73% female in the CS and the nonfunctioning adenoma group respectively). CS patients (aged 42 yr) were slightly younger than the controls (aged 47 yr). The risk for postoperative VTE in CS patients was 3.4%, for controls 0% (p from log rank test = 0.01). The risk of 3.4% translates in an incidence rate of 141 (95% CI 75-234) per 1000
person-years. Most events occurred between 1 wk and 2 months after surgery (Fig. 3). The 281 patients with pituitary CS medically pretreated before transsphenoidal surgery seemed to have a lower risk of VTE in the 3 months after surgery (2.5%, 95% CI 1.2-5.1) compared to the 69 patients who were not pretreated (7.2%, 95% CI 3.1-15.9), resulting in a risk ratio of 0.4 (95% CI 0.1-1.1).

* From log-rank test
**DISCUSSION**

In this study, which included a large cohort of patients with CS, we found an incidence rate of VTE of 14.6 per 1000 person-years. The risk of postoperative VTE in patients with ACTH-dependent CS was 3.4%, whereas no VTE was observed in the control group.

In the general population, the estimated incidence rates for VTE vary between one and two per 1000 person-years. However, the incidence rates are clearly dependent on age. The mean age of our study population was 42 yr, corresponding to an incidence rate in the general population of 0.3 per 1000 person-years. This suggests that patients with CS have a more than 10-fold increased risk of VTE.

Our finding of a 3.4% risk of postoperative VTE in ACTH-dependent CS is in line with the risk reported in previous studies. Small differences in outcomes between studies may depend on study design or case definition, but most likely reflect the choice, intensity and duration of thromboprophylaxis used. Importantly, the observed risk is comparable with the risk after total hip or knee replacement under short-duration prophylaxis (7-10 days). Total hip and knee replacement are associated with the highest risk of VTE after surgery, and extended thromboprophylaxis is now widely recommended. This emphasizes the need for extended thromboprophylaxis in patients with CS as well, at least in patients with ACTH-dependent CS. Thromboprophylaxis is currently usually administered only during the first days after pituitary surgery, because this procedure is considered minimally invasive and immobilization is relatively short.

Our results suggest that pretreatment with cortisol lowering agents reduces the risk of VTE after surgery. This is intriguing because successful surgery results in a cortisol withdrawal syndrome characterized by anorexia, nausea, somnolence, arthralgias/myalgias, and fever. This clinical syndrome mimics a proinflammatory state with increased plasma IL-6, TNFα, and IL-1β levels. Glucocorticoids suppress prostanoid and platelet activating factor production, and the reverse occurs upon withdrawal of steroid hormones. Adequate pretreatment of cortisol excess reduces the postoperative withdrawal syndrome and may therefore protect against VTE. Cortisol-lowering therapy, however, did not prevent the occurrence of VTE in five patients in our study. This might also result from a rapid fall in cortisol production leading to a transient proinflammatory and procoagulant state. It therefore seems rational to give thromboprophylaxis in any phase of treatment of CS that is associated with a sudden fall in plasma cortisol levels.
A main aim of our study was to disentangle the effects of (transsphenoidal) surgery from Cushing characteristics on VTE risk. Generally, transsphenoidal surgery appears to be a relative safe procedure with most frequent complications being rhinorrhea of cerebral spine fluid and diabetes insipidus. VTE in general and CST in particular are rare complications of transsphenoidal surgery. In the present study, no VTE was observed in almost 200 patients treated by transsphenoidal surgery for nonfunctioning pituitary adenomas. This underlines the hypothesis that the high risk for postoperative VTE in CS is cortisol mediated. Although chronic glucocorticoid excess is suggested to induce hypercoagulability, the finding that all postoperative VTE developed only in patients suffering from ACTH-dependent CS, raises the question as to whether the excess, or sudden drop, of ACTH might influence hemostatic parameters and therefore be, in part, responsible for a prothrombotic tendency. However, it must be noted that some patients developing VTE after surgery exhibited high levels of cortisol, and by inference sufficient levels of ACTH in the circulation. Interestingly, ACTH was found to be a POMC (precursor molecule pro-opiomelanocortin)-derived neuropeptide capable of modulating an immune response by a release of a variety of proinflammatory and immunomodulatory mediators. Because a proinflammatory state is known to induce a hypercoagulable state, this may further underline the role of ACTH as mediator in the formation of VTE.

Our study has obvious limitations, inherent to all retrospective cohort studies. For example, outcomes of VTE were derived from case records and therefore rely on the accuracy of the treating physicians. As such, a small number of VTE could have been missed, but this would only have resulted in an underestimation of the risk. Also, most patients who experienced VTE prior to treatment were not yet diagnosed with CS. It is therefore uncertain whether active disease already existed in these patients. However, diagnosis of CS is generally delayed for several years, and all but one patient had at least one or more symptoms of hypercortisolism at the time of the thromboembolic event.

Although this study focuses on the incidence of VTE in patients with endogenous CS, the most common cause of CS remains exogenous administration of glucocorticoids. Recently glucocorticoid excess has also been identified as possibly risk factor for VTE. However, this association is thought to reflect the underlying condition necessitating glucocorticoid treatment rather than glucocorticoid use itself. With this study, we showed an increased incidence of VTE in patients with a syndrome characterised by a glucocorticoid excess without underlying illness. Patients using a higher dose of glucocorticoids for months or longer might therefore also be at increased risk of VTE, not only by the underlying disease, but also by the continuous glucocorticoid excess. Future clinical studies are necessary to adequately assess...
the risks and benefits of chronic glucocorticoid use. In conclusion, patients with CS are at high risk of VTE not only during active disease but also after surgery. Guidelines on the choice, intensity, and duration of thromboprophylaxis are needed. We do understand that a well-conducted randomized controlled trial will provide the highest level of clinical evidence. Until then, we recommend that thromboprophylaxis should be considered when additional risk factors for VTE are present even before start of treatment. In patients with ACTH-dependent CS undergoing pituitary surgery, consideration should be given to extension of thromboprophylaxis beyond 10 days up to 35 days after surgery, comparable to surgeries at high risk for VTE.¹⁶

**Acknowledgements**

We thank all individuals who have helped in the execution of this study and especially all administrative personnel for their support in logistic procedures and retrieving of the case notes.


**Reference List**

Table 1. Venous thromboembolism prior to treatment

<table>
<thead>
<tr>
<th>Age/sex</th>
<th>Etiology</th>
<th>VTE</th>
<th>Time to treatment</th>
<th>Risk factors of VTE</th>
<th>Cushingoid symptoms at time of VTE</th>
<th>Pretreatment post dexamethasone serum cortisol (nmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>67/F*</td>
<td>Cushing’s disease</td>
<td>DVT,PE</td>
<td>2 days</td>
<td>Unknown</td>
<td>Hypertension, cushingoid habitus, muscle weakness, skin lesions</td>
<td>575</td>
</tr>
<tr>
<td>42/F</td>
<td>Adrenal adenoma</td>
<td>DVT</td>
<td>5 days</td>
<td>Immobilization</td>
<td>Hypertension, diabetes, hypokalemia, cushingoid habitus, skin lesions</td>
<td>880</td>
</tr>
<tr>
<td>34/F</td>
<td>Cushing’s disease</td>
<td>PE</td>
<td>9 days</td>
<td>None</td>
<td>Cushingoid habitus</td>
<td>610</td>
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<td>44/F</td>
<td>Adrenal adenoma</td>
<td>Jugular vein thrombosis</td>
<td>11 days</td>
<td>None</td>
<td>Hypertension, diabetes, hypokalemia, muscle weakness</td>
<td>587</td>
</tr>
<tr>
<td>20/M</td>
<td>Cushing’s disease</td>
<td>DVT</td>
<td>20 days</td>
<td>Immobilization</td>
<td>Hypertension, diabetes, cushingoid habitus, muscle weakness, skin lesions</td>
<td>800</td>
</tr>
<tr>
<td>32/M</td>
<td>Adrenal adenoma</td>
<td>PE</td>
<td>27 days</td>
<td>None</td>
<td>Hypertension, hypokalemia, cushingoid habitus, skin lesions</td>
<td>Unknown</td>
</tr>
<tr>
<td>44/F</td>
<td>Cushing’s disease</td>
<td>DVT</td>
<td>2 months</td>
<td>None</td>
<td>Hypertension</td>
<td>290</td>
</tr>
<tr>
<td>63/M</td>
<td>Cushing’s disease</td>
<td>PE</td>
<td>2.5 months</td>
<td>None</td>
<td>Cushingoid habitus</td>
<td>721</td>
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<tr>
<td>40/F</td>
<td>Cushing’s disease</td>
<td>DVT</td>
<td>2.8 months</td>
<td>Oral contraceptive</td>
<td>Depression, cushingoid habitus, amenorrhoea</td>
<td>370</td>
</tr>
<tr>
<td>34/F</td>
<td>Cushing’s disease</td>
<td>DVT,PE</td>
<td>4 months</td>
<td>Oral contraceptive</td>
<td>Hypertension, Cushingoid habitus, skin lesions</td>
<td>Unknown</td>
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<tr>
<td>45/F</td>
<td>Cushing’s disease</td>
<td>PE</td>
<td>4.5 months</td>
<td>None</td>
<td>Cushingoid habitus, amenorrhoea</td>
<td>469</td>
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</table>
Cushing’s syndrome and venous thrombosis

<table>
<thead>
<tr>
<th>Age/sex</th>
<th>Etiology</th>
<th>VTE</th>
<th>Time to treatment</th>
<th>Risk factors of VTE</th>
<th>Cushingoid symptoms at time of VTE</th>
<th>Pretreatment post dexamethasone serum cortisol (nmol/l)</th>
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</thead>
<tbody>
<tr>
<td>67/F</td>
<td>Cushing’s disease</td>
<td>Calf vein thrombosis</td>
<td>5 months</td>
<td>Heterozygous factor V Leiden</td>
<td>Cushingoid habitus, skin lesions</td>
<td>110</td>
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<tr>
<td>39/F*</td>
<td>Cushing’s disease</td>
<td>PE</td>
<td>7 months</td>
<td>None</td>
<td>Hypertension, cushingoid habitus, amenorrhoea</td>
<td>Unknown</td>
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<tr>
<td>79/F</td>
<td>Adrenal macronodular hyperplasia</td>
<td>PE</td>
<td>1.3 years</td>
<td>Immobilization</td>
<td>None</td>
<td>590</td>
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<tr>
<td>33/M</td>
<td>Cushing’s disease</td>
<td>PE</td>
<td>1.3 years</td>
<td>Unknown</td>
<td>Cushingoid habitus, skin lesions</td>
<td>616</td>
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<tr>
<td>66/F</td>
<td>Cushing’s disease</td>
<td>PE</td>
<td>1.5 years</td>
<td>None</td>
<td>Hypertension, diabetes, cushingoid habitus</td>
<td>420</td>
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<tr>
<td>45/M</td>
<td>Cushing’s disease</td>
<td>DVT</td>
<td>2 years</td>
<td>Long-distance travel</td>
<td>Hypertension, cushingoid habitus, muscle weakness, skin lesions</td>
<td>310</td>
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<td>52/F</td>
<td>Adrenal micronodular hyperplasia</td>
<td>DVT</td>
<td>2.3 years</td>
<td>Unknown</td>
<td>Diabetes</td>
<td>360</td>
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<td>42/F</td>
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<td>DVT</td>
<td>2.4 years</td>
<td>None</td>
<td>Cushingoid habitus</td>
<td>1050</td>
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VTE indicates venous thromboembolism; CS, Cushing’s syndrome; F, female; M, male; PE, pulmonary embolism; and DVT, deep venous thrombosis.

*VTE both prior to treatment and within 3 months after surgery (appendix Table 2)
Table 2. Post-operative venous thromboembolism.

<table>
<thead>
<tr>
<th>Age/sex</th>
<th>Etiology</th>
<th>Surgery</th>
<th>Year of surgery</th>
<th>Medically pre-treated</th>
<th>Thrombo-prophylaxis</th>
<th>VTE</th>
<th>Time from surgery</th>
<th>VTE during prophylaxis</th>
<th>Hypercortisolism at time of VTE</th>
<th>Pre-surgery cortisol†</th>
<th>Post surgery cortisol†</th>
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</thead>
<tbody>
<tr>
<td>34/F</td>
<td>Cushing’s disease</td>
<td>Transsphenoidal adenectomy</td>
<td>1992</td>
<td>Yes</td>
<td>No</td>
<td>DVT</td>
<td>9 days</td>
<td>No</td>
<td>No</td>
<td>1020</td>
<td>50</td>
</tr>
<tr>
<td>59/M</td>
<td>Cushing’s disease</td>
<td>Transsphenoidal adenectomy</td>
<td>1994</td>
<td>No</td>
<td>Nadroparin 5700 IE</td>
<td>DVT, PE</td>
<td>23 days</td>
<td>No</td>
<td>No</td>
<td>965</td>
<td>85</td>
</tr>
<tr>
<td>33/F</td>
<td>Cushing’s disease</td>
<td>Transsphenoidal adenectomy</td>
<td>1995</td>
<td>No</td>
<td>Dalteparin 2500 IE</td>
<td>Cerebral sinus thrombosis</td>
<td>22 days</td>
<td>Yes</td>
<td>No</td>
<td>Unknown</td>
<td>73</td>
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<tr>
<td>67/F*</td>
<td>Cushing’s disease</td>
<td>Transsphenoidal adenectomy</td>
<td>1996</td>
<td>Yes</td>
<td>Unknown</td>
<td>PE</td>
<td>2 days</td>
<td>Yes</td>
<td>No</td>
<td>545</td>
<td>30</td>
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<td>69/M</td>
<td>Cushing’s disease</td>
<td>Transsphenoidal adenectomy</td>
<td>1999</td>
<td>No</td>
<td>Unknown</td>
<td>DVT, PE</td>
<td>52 days</td>
<td>No</td>
<td>Yes</td>
<td>660</td>
<td>545</td>
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<td>39/F*</td>
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<td>Transsphenoidal hypophysectomy</td>
<td>2000</td>
<td>Yes</td>
<td>Unknown</td>
<td>DVT, PE</td>
<td>9 days</td>
<td>Unknown</td>
<td>No</td>
<td>Unknown</td>
<td>27</td>
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<td>34/M</td>
<td>Cushing’s disease</td>
<td>Transsphenoidal adenectomy</td>
<td>2003</td>
<td>Yes</td>
<td>Unknown</td>
<td>DVT</td>
<td>36 days</td>
<td>No</td>
<td>No</td>
<td>Unknown</td>
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<td>Transsphenoidal adenectomy</td>
<td>2003</td>
<td>Yes</td>
<td>Dalteparin 5000 IE</td>
<td>PE</td>
<td>1 day</td>
<td>Yes</td>
<td>No</td>
<td>Unknown</td>
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<td>52/F</td>
<td>Cushing’s disease</td>
<td>Transsphenoidal adenectomy</td>
<td>2004</td>
<td>Yes</td>
<td>Nadroparin 2850 IE</td>
<td>PE</td>
<td>18 days</td>
<td>No</td>
<td>No</td>
<td>475</td>
<td>100</td>
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<td>44/F</td>
<td>Cushing’s disease</td>
<td>Transsphenoidal hemihypophysectomy</td>
<td>2008</td>
<td>No</td>
<td>Dalteparin 2500 IE</td>
<td>Cerebral sinus thrombosis</td>
<td>13 days</td>
<td>Yes</td>
<td>Yes</td>
<td>Unknown</td>
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<tr>
<td>49/F</td>
<td>Cushing’s disease</td>
<td>Transsphenoidal adenectomy</td>
<td>2008</td>
<td>No</td>
<td>Nadroparin 2850 IE</td>
<td>PE</td>
<td>33 days</td>
<td>No</td>
<td>No</td>
<td>500</td>
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<td>53/M</td>
<td>Cushing’s disease</td>
<td>Transsphenoidal adenectomy</td>
<td>2009</td>
<td>Yes</td>
<td>Nadroparin 2850 IE</td>
<td>DVT</td>
<td>44 days</td>
<td>No</td>
<td>No</td>
<td>485</td>
<td>1</td>
</tr>
</tbody>
</table>

VTE indicates venous thromboembolism; F, female; M, male; IE, units; PE, pulmonary embolism; and DVT, deep venous thrombosis.

*VTE both prior to treatment and within 3 months after surgery (appendix 1)
†Pre- and post surgery cortisol within 3 months prior to and after surgery.