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RESEARCH

Patients with Cushing's syndrome suffer from provoked venous thromboembolism and are anticoagulated in various patterns

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Abstract

Objective: Cushing's syndrome (CS) is associated with an 18-fold greater risk of venous thromboembolism (VTE). We aimed to identify factors which provoke VTE among patients with CS and VTE and to describe the anticoagulant regimen used in these cases.

Methods: In this retrospective observational study, patients included in the European Registry on CS (ERCUSYN) in Krakow center, Poland, were followed for the occurrence of VTE and anticoagulant treatment. We identified factors provoking VTE according to the International Society of Thrombosis and Hemostasis (ISTH), along with factors included in the Padua score and CS-VTE score.

Results: Of the 128 patients followed for a median of 4.3 years, there were nine patients who experienced ten VTE episodes (prevalence of 7.8% and incidence of 13.4 per 1000 patient-years). All VTEs were classified as provoked according to the ISTH guidance, predominantly due to the transient major and minor (50% and 20%, respectively) factors, while they were less commonly due to persistent (30%) factors. In 2/9 patients, we could not identify any risk factor for VTE according to the Padua score, while in 2/6 patients according to the CS-VTE score. Patients were mostly anticoagulated with vitamin K antagonists (4/8 patients), followed by direct oral anticoagulants (3/8) and low-molecular-weight heparin (1/8). The median duration of anticoagulation was 2.75 years and exceeded beyond the primary treatment in 28% of episodes provoked by transient factors.

Conclusion: Further, multicenter studies are required to create a validated thrombotic risk score and guidelines regarding VTE treatment in CS patients.

Keywords: anticoagulants; Cushing's disease; Cushing's syndrome; risk factors for venous thromboembolism; venous thromboembolism

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Introduction

Cushing's syndrome (CS) is a rare disease with an incidence ranging from 0.7 to 2.4 per million people per year (1). In contrast, venous thromboembolism (VTE), which includes pulmonary embolism (PE) and deep-vein thrombosis (DVT), is a common disease (2). A recent meta-analysis of 22 observational studies involving 6537 patients demonstrated that CS is associated with an almost 18-fold greater risk of VTE when compared to the general population with similar demographic characteristics, corresponding to a prevalence of 3.2% (3). The postulated underlying mechanisms for increased risk involve: shortened activated partial thromboplastin time (aPTT), increased activity of factor VIII and von Willebrand factor, hyperactivity of platelets, increased thrombin generation, elevated concentrations of fibrinogen and fibrinolysis inhibitors, and compensatory elevation of endogenous anticoagulants such as protein C and protein S (3, 4, 5, 6). However, no linear relationship with the number of thrombotic episodes or with the level of cortisol was observed (3). The role of hypercortisolemia in triggering thrombotic episodes is still being studied, with a possible inverse correlation between aPTT and urine free cortisol (UFC) (6, 7). In patients with CS, the shortened aPTT probably mainly results from the increased activity of factor VIII and von Willebrand factor, with a possible contribution from many other coagulation factors: II, V, IX, X, XI, and XII (4). On the other hand, a rapid decrease in cortisol levels has also been associated with VTE development (8, 9, 10). This is thought to be due to a rebound inflammatory response after rapid suppression of cortisol (8, 9). Serum cortisol was incorporated into the CS-VTE score to assess the risk of VTE in CS patients (11); however, this score has not yet been validated and requires further development (12).

In addition to hemostatic abnormalities and hypercortisolemia, CS patients can present with a wide spectrum of clinical factors that predispose them to VTE, such as inherited thrombophilia, and acquired conditions such as acute infection or immobilization (9, 11). These factors areŚ included in risk assessment scores such as the Padua score or Caprini score (13, 14). Although the accuracy of the Padua score for CS patients is not known, it was the primary source of some of the factors analyzed when preparing the CS-VTE score (11). Previous surgery is the most analyzed risk factor for VTE in patients with CS. A retrospective analysis of 375 CS patients previously treated surgically, either receiving thromboprophylaxis or not, showed that 62% of VTE episodes occurred within 3 months of surgery (15). The VTE episodes that occurred within 3 months of surgery were categorized as being provoked by a major transient factor. Interestingly, recent evidence shows that VTE often occurs before surgery or is unrelated to surgery (9, 11, 16, 17), with a prevalence of VTEs not being provoked by surgery ranging from 1.5% to 2.9%, as estimated in a meta-analysis by Zaane *et al.* (16), and even higher prevalence in original studies, ranging from 7% (11) to 9% (17). Studies regarding risk factors that predispose to VTE are ongoing (11, 18). Currently, available data were used to prepare the algorithm for the assessment of non-surgery-related thrombotic risk (19). Whether an episode of VTE was provoked by an acquired risk factor has important treatment implications regarding the continuation or discontinuation of anticoagulation after primary treatment (20). To the best of our knowledge, there is no consensus on whether VTE occurring in a CS patient could be defined as VTE provoked by CS as a single factor. Moreover, there is a paucity of data regarding the duration of anticoagulation treatment in CS patients with VTE. We aimed to identify the factors that provoke VTE among CS patients and to describe the anticoagulant regimen used in these cases.

Subjects and methods

Patients

In this retrospective observational study, we included consecutive adult patients diagnosed with CS in the Department of Endocrinology at the University Hospital in Krakow from January 2002 to February 2023. These patients were included in the European Registry on Cushing's syndrome (ERCUSYN). Diagnosis of CS was based on elevated 24-h urinary UFC, elevated midnight cortisol levels, and cortisol concentrations greater than 1.8 µg/dL following a 1 mg dexamethasone suppression test (12, 21). Cushing's disease (CD) was diagnosed by the presence of a pituitary adenoma, increased adrenocorticotropic hormone (ACTH) with at least a 40% increase in corticotropin-releasing hormone stimulation test and/or positive central-to-peripheral gradient on inferior petrosal sinus sampling. Adrenal Cushing's syndrome (ACS) was diagnosed in the presence of suppressed ACTH levels and imaging which confirmed the presence of an adrenal mass. Adrenocortical cancer (ACC) was diagnosed based on histopathological findings. Ectopic ACTH syndrome (EAS) was diagnosed based on elevated ACTH levels, lack of ACTH response in the corticotropin-releasing hormone stimulation test, and/or gradient-negative inferior petrosal sinus sampling (suggestive of a nonpituitary ACTH origin of production). Remission of CS was defined as a requirement for hydrocortisone supplementation or either of the following: normalization of 24-h urinary UFC or cortisol level in the plasma or saliva, or in the case of surgically-induced remission, cortisol concentrations less than 1.8 µg/dL after a 1 mg dexamethasone suppression test, measured approximately 4–6 weeks following surgery. This study was performed in line with the principles of the Declaration of Helsinki. This study was approved by the Jagiellonian University Bioethics Committee

(no. 1072.6120.58.2020) and the Committee for the Ethics of Scientific Research at the Jagiellonian University Medical College (no. 118.6120.49.2023). All patients provided written informed consent.

Study design

We collected data on the signs and symptoms of CS, laboratory test results, comorbidities, and medication upon admission to the Department of Endocrinology (baseline). The follow-up started at the presentation to the Department of Endocrinology and continued until the last visit to the Department (November 2023). The primary endpoint was VTE. The diagnosis of lower or upper limb DVT required a positive finding on color duplex sonography. The diagnosis of PE was based on the presence of typical symptoms and positive results on high-resolution spiral computed tomography or ventilation-perfusion lung scintigraphy. The length of follow-up was censored at the time of VTE or death. When VTE occurred before the initiation of follow-up, we arbitrarily defined the duration of follow-up as 1 day. We followed patients for recurrent VTE, the duration of anticoagulation, and possible modification of administered anticoagulant. Available medical documentation was analyzed regarding the risk factors for VTE according to the International Society of Thrombosis and Hemostasis (ISTH) guidance (20) as it would present on the day of the VTE episode. Here, the risk factors are divided into three groups: transient major, transient minor, and persistent, based on the risk of VTE recurrence and increase in the risk of having a first-time VTE (for the detailed definitions, see the description in Table 1). The presence of at least one risk factor from any of the groups categorizes the VTE as provoked, while the absence of risk factors categorizes it as an unprovoked VTE episode. We also screened patients who suffered from VTE for the presence of risk factors included in the Padua score. Since this score has been validated for hospitalized patients (13), we scored our patients upon admission to the Department of Endocrinology. The Padua score includes 11 risk factors that are assigned 1–3 points, with a maximum cumulative score of 20 if all of these factors are present and a cumulative score of 4 indicating increased VTE risk. Since the Padua score is not targeted at patients with CS, we also screened patients for risk factors included in the CS-VTE score. The CS-VTE score includes six risk factors that are assigned 1–2 points, with a maximum cumulative score of 8 and a cumulative score of 3 points indicating increased VTE risk. The list of risk factors included in the ISTH guidance, Padua score, and CS-VTE score are provided in Tables 1 and 2 along with the results of our analysis. We screened the medical history for the results of the activated partial thrombin time (upper limit of normal, 26 s). If aPTT was performed during anticoagulant treatment due to previous VTE, the international normalized ratio (INR) was also verified. Out of multiple aPTT results, we chose the first available result or the one which was the

Table 1 The factors predisposing to venous thromboembolism (VTE) according to the International Society of Thrombosis and Hemostasis guidance, in patients with Cushing's syndrome complicated with VTE. A risk factor is considered 'major' if it has been shown to be associated with: (i) half the risk of recurrent VTE after stopping anticoagulant therapy (compared with if there was no transient risk factor), when the risk factor occurred up to 3 months before the VTE; or (ii) a greater than 10-fold increase in the risk of having a first VTE. A risk factor is considered 'minor' if it has been shown to be associated with: (i) half the risk of recurrent VTE after stopping anticoagulant therapy (compared with if there was no transient risk factor), when the risk factor occurred up to 2 months before the VTE; or (ii) a 3 to 10-fold increase in the risk of having a first VTE. VTE provoked by a persistent factor includes active cancer or on-going non-malignant conditions associated with at least a 2-fold risk of recurrent VTE after stopping anticoagulant therapy (example: inflammatory bowel disease) (18).

Factor	**All VTE episodes** (*n* = 10)
Transient major (any of the following during the 3 months before diagnosis of VTE)	5 (56)
Surgery with general anesthesia for > 30 min up to 3 months prior to VTE	3 (30)
Confined to bed in hospital (only 'bathroom privileges') for at least 3 days with an acute illness	1 (10)
Cesarean section up to 3 months prior to VTE	1 (10)
Transient minor (any of the following during the 2 months before diagnosis of VTE)	2 (20)
Surgery with general anesthesia for less than 30 min	0 (0)
Admission to the hospital for less than 3 days with an acute illness	0 (0)
Estrogen therapy	1 (10)
Pregnancy or puerperium	0 (0)
Confined to bed out of the hospital for at least 3 days with an acute illness	1 (10)
Leg injury associated with reduced mobility for at least 3 days	0 (0)
Persistent	
Active cancer	1 (10)
Autoimmune disease	2 (20)

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Table 2 The risk factors for venous thromboembolism (VTE) according to the Padua prediction score (PPS) and CS-VTE score in patients with Cushing's syndrome (CS) complicated with VTE.

According to the PPS, *n* (%)	**No. of patients positive for each factor** (from the total of *n* = 9)	**Number of points for the factor in the score**	**Total number of points***
Active cancer	1 (11)	3	3
Previous VTE	5 (56)	3	15
Reduced mobility	3 (33)	3	9
Already known thrombophilic condition	0 (0)	3	0
Recent (≤ 1 month) trauma or surgery	0 (0)	2	0
Elderly age (≥ 70 years)	0 (0)	1	0
Heart and/or respiratory failure	3 (33)	1	3
Acute myocardial infarction or ischemic stroke	0 (0)	1	0
Acute infection and/or rheumatological disorder	3 (33)	1	3
Obesity (BMI ≥ 30 kg/m^2)	5 (56)	1	5
Ongoing hormonal treatment	0 (0)	1	0
According to the CS-VTE score, *n* (%)	**No. of patients positive for each factor** (from the total of *n* = 6)**	**Number of points for the factor in the score**	**Total number of points**
Age ≥ 69 years	0	2	0
Acute severe infection	2 (33)	1	2
Reduced mobility	3 (50)	2	6
Midnight plasma cortisol > 3.15 ULN	1 (17)	1	1
Shortened aPTT	3 (50)	1	3
Previous cardiovascular event	1 (17)	1	1

*total number of points = no. of patients positive for each factor × number of points for the factor in the score; **the result of activated partial thromboplastin time (aPTT) was available for six patients. The lower limit of normal for aPTT was 26 s.
BMI, body-mass index; ULN, upper limit of normal.

nearest prior to the current VTE episode. For patients having an aPTT result, we calculated VTE risk using the CS-VTE score upon admission to the Department of Endocrinology (11). According to the original study, a point for hypercortisolemia in the CS-VTE score was given when midnight plasma cortisol exceeded 3.15 times the upper limit of normal (11). The predisposing factors according to the ISTH guidance, Padua score, and CS-VTE score were independently identified and then agreed upon by two independent reviewers (A B-W and MM). Continuous variables are presented as median (minimum-maximum), while categorical variables are presented as number (percentage). Due to the low number of incidents, no comparative analysis was performed.

Results

In total, 128 patients, including 101 females (79%), of whom 59% had CD, 28% ACS, and 13% EAS, were followed for a median of 4.3 years (5 days to 21.8 years). The total number of patient-years was 745. Among them, nine patients experienced VTE. Since there was one recurrent DVT, the total number of VTE episodes was ten (3 PE, 4 DVT, 3 combined PE and DVT), which corresponded with a prevalence of 7.8% and an incidence of 13.4 per 1000 patient-years. Patients who experienced VTE had a median follow-up time of 5 years (21 days to 11 years). Half of the VTE episodes (*n* = 5, 50%) occurred prior to the endocrinological work-up (2 PE, 1 VTE, and 2 combined DVT+PE), with a median time of 1 year between the VTE episode and CS diagnosis (1 month to 9 years). Four out of five of these patients (80%) were treated with anticoagulants at the time of presentation, while one patient had anticoagulation discontinued prior to the endocrinological workup. The median time from CS diagnosis to the VTE episode (four first VTE, one recurrence) was 5 months (21 days to 2 years). Throughout the follow-up period, there were two deaths (out of nine patients, 22%) – one was PE-related while the other was due to ACC.

Clinical presentation of patients with CS and VTE

In our study group, mostly females (*n* = 7, 78%) experienced VTE. The median age at presentation was 52.5 (35–65) years. All patients were overweight or obese with a median body mass index of 31.8 (25.7–53.4) kg/m^2. The etiology of CS was predominently pituitary (*n* = 5), followed by ACS (*n* = 3), including one

ACC. There was one patient with EAS in the course of a bronchopulmonary neuroendocrine tumor stage G1, which was diagnosed postmortem. The majority of patients (five out of nine) achieved surgical remission (Table 3). The median time between the first presentation of signs or symptoms to the time of CS diagnosis was 1 (0.08–9) year. The median post-dexamethasone cortisol concentration was 20.2 (6.5–130.3) µg/dL, with a median ACTH concentration of 92 (63–557) pg/mL in ACTH-dependent CS, and 4.0 (3.9–4.6) pg/mL in ACTH-independent CS. Patients presented with many signs and symptoms (Table 3), with VTE being the reason for referral to the endocrinologist in three out of nine cases (33%).

Table 3 Characteristics of the patients with Cushing's syndrome (CS) and venous thromboembolism. A steroidogenesis inhibitor was used to prepare for surgery in three out of nine patients, but remission was achieved with surgery, with no need for the continuation of medical therapy. In two patients, a steroidogenesis inhibitor had to be used also after surgery to achieve remission. One patient started medical therapy due to severe ectopic adrenocorticotropic hormone (ACTH) syndrome and experienced fatal PE.

Characteristic	*n* (%)
Type of treatment	
TSS + steroidogenesis inhibitor*	4 (44)
TSS + UA	1 (11)
UA	1 (11)
UA + steroidogenesis inhibitor**	2 (22)
Steroidogenesis inhibitor alone	1 (11)
Signs or symptoms	
Easy bruising	6 (67)
Peripheral oedema	5 (56)
Proximal myopathy	5 (67)
Fatigue	5 (56)
Dorsocervical fat pad	4 (44)
Facial plethora	4 (44)
Obesity/weight gain	3 (33)
Striae	3 (33)
Facial fullness	3 (33)
Hirsutism or female bolding	3 (33)
Back pain	2 (22)
Thin skin	1 (11)
Decreased concentration	1 (11)
Overlapping conditions	
Hypertension	9 (100)
Type 2 diabetes	4 (44)
Hypokalemia	3 (33)
Incidental adrenal mass	2 (22)
Vertebral osteoporosis	2 (22)
Unusual infections	1 (11)

*ketoconazole or metyrapone, or osilodrostat or etomidate; **denotes ketoconazole, or metyrapone, or mitotane (in the case of adrenal carcinoma).
TSS, transsphenoidal surgery; UA, unilateral adrenalectomy.

Risk factors for VTE

We identified the provoking risk factors for VTE in all ten VTE cases, which were predominantly transient (*n* = 7, 70%), including five major (50%) and two minor (20%, Table 1). The remaining three VTE episodes (30%) were provoked by persistent risk factors (active disseminated cancer in a patient with ACC and systemic lupus erythematosus in a patient who suffered from two subsequent VTEs). The latter patient suffered from two VTE episodes, with the second VTE occurring while on a subtherapeutic dose of warfarin (INR 1.66).

In two out of nine patients (22%) who suffered from VTE, we could not identify any risk factors for VTE according to the Padua score (*n* = 2, 22%). Still, the majority of patients had a high risk for VTE at presentation, having a Padua score of ≥4 points (*n* = 6, 67%, Tables 1 and 2). The median Padua score was 4 (0–11); however, previous VTE contributed to this result in 55% (*n* = 5) of patients. The results of inherited and acquired thrombophilia screening were available for three (33%) patients (negative), while one patient was negative for antiphospholipid syndrome (investigated due to the coexisting systemic lupus erythematosus).

The results of aPTT were available for six patients, including four post-VTE results. In three post-VTE patients, aPTT was checked when INR was under the reference range (three cases). One post-VTE patient no longer received anticoagulation. The median aPTT was decreased (24.2 s, minimum 21.2 to 27.6 s) and shortened in three (50%) patients (two prior to VTE and one post-VTE). Similarly, as for the Padua score, we could not identify any risk factors for VTE according to the CS-VTE score in two out of six patients (33%). The median CS-VTE score was 2 (0–5), while CS-VTE indicated a high thrombotic risk (≥3 points) in half of the patients (Table 2).

The most common pattern of VTE occurrence was during active hypercortisolemia (*n* = 8, 80%). In one patient, VTE manifested within 1 month following transsphenoidal surgery, and in another patient while on metyrapone-induced remission. At the time of VTE, the patient with medically-induced remission was receiving low-molecular-weight heparin (LMWH) for thrombosis prophylaxis, while the post-surgical patient with biochemical remission was not receiving LMWH.

Anticoagulant treatment in relation to risk factors and type of anticoagulant

The median anticoagulation time was 2.75 years, with a range of 2 months to 9 years. The patient who started to receive anticoagulation 2 months prior to the end of the study (in September 2023) had the shortest duration of anticoagulation (2 months). Among the five remaining patients treated for VTE provoked by a

transient factor, two patients were successfully treated for CS and discontinued anticoagulation after 3–6 months. The patient who had VTE 9 years prior to the diagnosis of CS received acenocoumarol for 1 year. In the other two patients (one in remission of CS, one with recurrent CS; Fig. 1), anticoagulation was continued for 5–9 years. In one of these patients, the decision to discontinue anticoagulation was based on the normalization of the D-dimer level, while in the other patient, this decision was made after an angiologist's consultation. Despite receiving LMWH (40 mg once daily) for thromboprophylaxis, the EAS patient who had VTE provoked by transient factors developed a fatal PE. In the patients with persistent risk factors for VTE, anticoagulation was maintained during the entire follow-up period (4.4–5 years).

Half of the patients (four out of eight, 50%) were treated with vitamin K antagonists (two with warfarin, two with acenocoumarol). Due to major bleeding (subcutaneous hematoma with a decrease in hemoglobin concentration to 6.1 g/dL), the treatment was modified in one patient to apixaban with no further bleeding complications. Additionally, another patient had their anticoagulant switched to rivaroxaban after an angiologist's consultation. The remaining three patients were treated with only direct oral anticoagulants (rivaroxaban once daily in two patients and dabigatran in a reduced dose in one patient). In one patient, VTE was treated with LMWH.

Discussion

To the best of our knowledge, our study is one of the first to investigate risk factors for VTE among patients with CS and VTE. We concluded that applying the ISTH guidance allowed us to identify risk factors for VTE in all patients. However, this list was originally used to retrospectively determine whether the VTE episode was provoked or unprovoked, with an aim to establish the optimal duration of secondary prevention of recurrent VTE. Using the list of factors derived from the Padua score was less effective since it was originally intended for hospitalized patients, while in our cohort, not all VTE events occurred during hospitalization. Some factors which were identified as predisposing for VTE by the ISTH guidance were not identified as thrombotic risk factors in the Padua score. This could be due to the elapsed time between the risk factor and the occurrence of VTE (i.e. recent surgery). According to the ISTH guidance, the surgery would have had to occur within the past 3 months to be classified as a major risk factor for VTE, while in the Padua score, the surgery

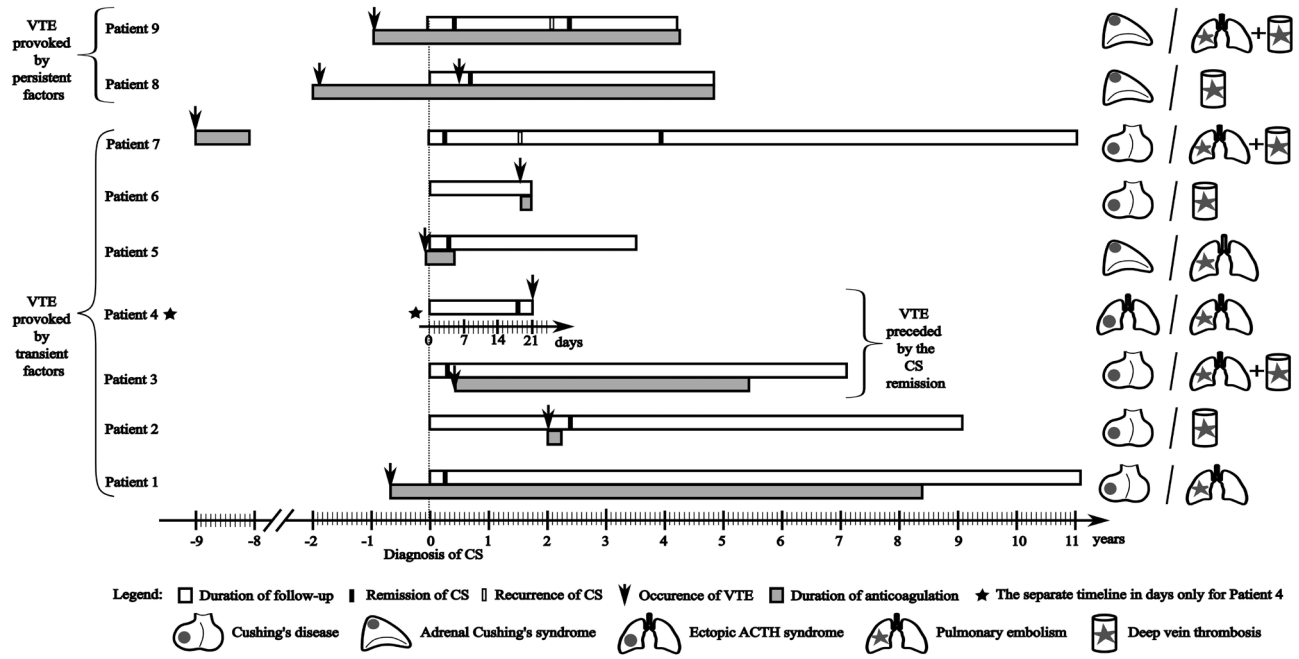

Figure 1

Graphical representation of the occurrence of VTE (in black arrows) in relation to the diagnosis of Cushing's syndrome (CS, left border of the white blocks), the duration of the follow-up (white blocks), the remission and recurrence of CS (thick black vertical line and white inside, respectively), and the duration of anticoagulant treatment (gray blocks). The etiology of CS (Cushing's disease, adrenal CS, ectopic ACTH (adrenocorticotropic hormone) syndrome) and type of VTE (pulmonary embolism, deep vein thrombosis) are presented on the right side of the figure. Anticoagulation was continued beyond the primary treatment not only in the VTE episodes provoked by persistent factors such as cancer and autoimmune disease (upper part of the figure) but also in some of the VTE episodes provoked by transient factors (patient nos 1 and 3). Following an unsuccessful transsphenoidal surgery, patient no. 6 is currently on pharmacological treatment.

must have occurred within the past month to increase the thrombotic risk.

The available literature mainly focuses on establishing the most effective regimen of postoperative thromboprophylaxis in patients with CS (15, 22). These regimens were not applicable in our cohort, since most of the VTEs were not related to surgery but to other factors. Previous publications from our group have described these factors, which include puerperium (23), combined oral contraceptives (24), and acute infection with immobilization (10). Other factors involve autoimmune disease and active cancer. Our data are in contradiction to previous studies which reported no identifiable factor for VTE in 15–52.9% of CS patients complicated with VTE (9, 11). These discrepancies may result from the differences in the considered number of factors which provoke VTE. For example, Zilio *et al.* did not collect data regarding pregnancy or puerperium (11), while one of our patients had VTE provoked by this factor (23). A study by Stuijver *et al.* (9) did not consider active cancer and autoimmune disease as predisposing factors for VTE, while we recorded three out of ten VTE events involving these persistent factors. Kontroumpi *et al.* identified multiple risk factors for VTE in patients with VTE unrelated to surgery (17), while Isand *et al.* demonstrated that hypertension, but not obesity, increased the risk of VTE among CS patients (18). However, most of the latter factors were associated with only a slightly increased VTE risk (25) and would not be categorized as causative for VTE according to the ISTH guidance, with the exception of acute infection with immobilization (20).

In some patients who suffered from VTE, we could not identify any risk factor for VTE included in the Padua score or CS-VTE score. Although previous studies presented the percentage of patients who were positive for the selected single risk included in the Padua score (9, 11, 17, 26), none of them demonstrated the final scoring result. In our cohort of CS patients, high thrombotic risk as assessed via the Padua score was mainly driven by previous VTE. This created a biased VTE risk evaluation. In as many as five patients, VTE preceded the first signs and symptoms of CS. The aPTT value, which was required to calculate the CS-VTE, was only valid with subtherapeutic INR. Since there are no guidelines recommending the measurement of aPTT routinely in CS patients, the retrospective assessment of CS-VTE was not possible in all patients with VTE (11). Notably, we found that only one patient with VTE was given points for increased serum cortisol at midnight, using the cut-off of 3.15 times the upper limit of normal, as described in the original study (11). Even so, these patients had VTE, possibly due to the coexistence of other predisposing factors for VTE, while one fatal PE occurred during metyrapone-induced hypocortisolemia. The role of surgically- or pharmacologically-induced hypocortisolemia in generating the VTE risk remains unclear.

Although malignancy leads to a significant increase in VTE risk independently of cortisol secretion, we included a patient with ACC in our cohort, just as we included patients with autoimmune disease and other predisposing factors. It should be noted that the CS-VTE score was developed for CS of a non-malignant origin. Unlike malignancy or autoimmune disease, the nature of CS as a VTE-provoking factor is not well established. Moreover, based on our data, it is difficult to extrapolate the risk ratio related to CS as a provoking factor for VTE, as it coexisted with other risk factors. If CS preceded VTE, it is unclear whether this episode would be defined as provoked. The magnitude of increase in VTE risk in CS (> 10-fold increased odds ratio of having a first VTE, for details, see the description in Table 1) (3, 16) would suggest the categorization of the VTE as being provoked by a major transient factor. Although some studies show that hypercoagulability observed in CS patients is self-limiting and reversed following CS remission (27), other studies demonstrate that Cushing's disease often relapses (28) and is complicated by prolonged hypercoagulability (8, 29). The latter evidence would suggest that CS can be categorized as a persistent factor for VTE. Another fact which may support the correct categorization of CS as either a transient or persistent factor provoking VTE is the risk of recurrence after cessation of anticoagulant treatment. The VTE provoked by transient factors has the lowest risk of recurrence, in opposition to the VTE provoked by persistent factors (20). There is a paucity of data regarding the risk of recurrent VTE in CS patients who discontinued anticoagulant treatment. Three out of the 37 episodes of VTE in a study by Stuijver *et al.* were not first-time episodes of VTE; however, no further details were given (9). The majority of CS patients predisposed to VTE by transient risk factors were treated with anticoagulants for 3–12 months, in contrast to almost one-third of such patients who were receiving anticoagulation for several years. This implies the need for guidelines that would specify the duration of prevention of recurrent VTE in patients with CS and whether to include active hypercortisolemia in the decision-making process of continuing anticoagulation after completion of primary treatment. Based on the very limited experience of our center, we can only hypothesize that vitamin K antagonists are not the most desired mode of anticoagulation in patients with CS. During periods outside the therapeutic INR range, patients experienced either recurrent VTE or bleeding episodes. However, these drugs are still used in selected clinical situations (25, 30).

Our study had several limitations, mostly inherent to the retrospective nature of our study. Since there are no recommendations to routinely assess aPTT in patients with CS, it was possible to determine the CS-VTE score only in selected patients. We strongly believe that aPTT should be routinely assessed in all CS patients, along with cortisol levels. We regret that only some of the patients had undergone thrombophilia screening; however,

current guidelines recommend this only in selected cases (31, 32). Although the demographic characteristics and prevalence of VTE were similar to larger studies (9, 33), the small sample size is an important limitation of ourby analysis. Since the time to CS diagnosis is delayed (34), we categorized VTE which occurred prior to the initiation of endocrinological work-up as VTE during active hypercortisolemia. Since VTE has a multifactorial and long-lasting background, the unequivocal decision on whether the complication is CS-related or not might be challenging or impossible. Another limitation that should be addressed is the lack of comparative analyses between the VTE group and the non-VTE group. Finally, we did not actively investigate for VTE in every patient with CS. Only patients who presented with clinical signs and symptoms were tested for VTE, which could result in an underestimation of occult VTE episodes.

In summary, our data confirm the multifactorial etiology of VTE in patients with CS. We also described in detail the variable approach and durability of anticoagulation treatment in patients with CS and VTE. We identified the benefits and limitations of different thrombotic risk assessment scores in everyday clinical practice and the discrepancies between them. We believe that further, multicenter research is needed to elucidate the risk and provoking factors of VTE in CS and also to develop a dedicated risk score tool. Anticoagulation treatment in CS patients complicated by VTE is challenging. The optimal duration of anticoagulation should be discussed with an interdisciplinary team, taking into account both hormonal and vascular assessments.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the study reported. Alicja Hubalewska-Dydejczyk is a Senior Editor of *Endocrine Connections*. Alicja Hubalewska-Dydejczyk was not involved in the review or editorial process for this paper, on which she is listed as an author.

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References

1 Newell-Price J, Bertagna X, Grossman AB & Nieman LK. Cushing's syndrome. *Lancet* 2006 **367** 1605–1617. (https://doi.org/10.1016/S0140-6736(06)68699-6)

2 Heit JA. Epidemiology of venous thromboembolism. *Nature Reviews Cardiology* 2015 **12** 464–474. (https://doi.org/10.1038/nrcardio.2015.83)

3 Wagner J, Langlois F, Ting Lim DST, McCartney S & Fleseriu M. Hypercoagulability and risk of venous thromboembolic events in endogenous Cushing's syndrome: a systematic meta-analysis. *Frontiers in Endocrinology* 2018 **9** 805. (https://doi.org/10.3389/fendo.2018.00805)

4 Isidori AM, Minnetti M, Sbardella E, Graziadio C & Grossman AB. MECHANISMS IN ENDOCRINOLOGY: The spectrum of haemostatic abnormalities in glucocorticoid excess and defect. *European Journal of Endocrinology* 2015 **173** R101–R113. (https://doi.org/10.1530/EJE-15-0308)

5 Kastelan D, Dusek T, Kraljevic I, Polasek O, Giljevic Z, Solak M, Salek SZ, Jelcic J, Aganovic I & Korsic M. Hypercoagulability in Cushing's syndrome: the role of specific haemostatic and fibrinolytic markers. *Endocrine* 2009 **36** 70–74. (https://doi.org/10.1007/s12020-009-9186-y)

6 Koutroumpi S, Spiezia L, Albiger N, Barbot M, Bon M, Maggiolo S, Gavasso S, Simioni P, Frigo A, Mantero F, *et al.* Thrombin generation in Cushing's syndrome: do the conventional clotting indices tell the whole truth? *Pituitary* 2014 **17** 68–75. (https://doi.org/10.1007/s11102-013-0467-3)

7 Tirosh A, Lodish M, Lyssikatos C, Belyavskaya E, Feelders RA & Stratakis CA. Coagulation profile in patients with different etiologies for Cushing syndrome: a prospective observational study. *Hormone and Metabolic Research* 2017 **49** 365–371. (https://doi.org/10.1055/s-0043-100113)

8 van der Pas R, de Bruin C, Leebeek FW, de Maat MP, Rijken DC, Pereira AM, Romijn JA, Netea-Maier RT, Hermus AR, Zelissen PM, *et al.* The hypercoagulable state in Cushing's disease is associated with increased levels of procoagulant factors and impaired fibrinolysis, but is not reversible after short-term biochemical remission induced by medical therapy. *Journal of Clinical Endocrinology and Metabolism* 2012 **97** 1303–1310. (https://doi.org/10.1210/jc.2011-2753)

9 Stuijver DJF, van Zaane B, Feelders RA, Debeij J, Cannegieter SC, Hermus AR, van den Berg G, Pereira AM, de Herder WW, Wagenmakers MAEM, *et al.* Incidence of venous thromboembolism in patients with Cushing's syndrome: a multicenter cohort study. *Journal of Clinical Endocrinology and Metabolism* 2011 **96** 3525–3532. (https://doi.org/10.1210/jc.2011-1661)

10 Minasyan M, Bryk-Wiązania AH, Rzepka E, Sowa-Staszczak A, Hubalewska-Dydejczyk A & Gilis-Januszewska A. Saddle pulmonary embolism as a fatal complication of the Cushing syndrome: a call for standardized anticoagulation regimen in hypercortisolism. *Polish Archives of Internal Medicine* 2023 **133** 16382. (https://doi.org/10.20452/pamw.16382)

11 Zilio M, Mazzai L, Sartori MT, Barbot M, Ceccato F, Daidone V, Casonato A, Saggiorato G, Noventa F, Trementino L, *et al.* A venous thromboembolism risk assessment model for patients with Cushing's syndrome. *Endocrine* 2016 **52** 322–332. (https://doi.org/10.1007/s12020-015-0665-z)

12 Fleseriu M, Auchus R, Bancos I, Ben-Shlomo A, Bertherat J, Biermasz NR, Boguszewski CL, Bronstein MD, Buchfelder M, Carmichael JD, *et al.* Consensus on diagnosis and management of Cushing's disease: a guideline update. *Lancet. Diabetes and Endocrinology* 2021 **9** 847–875. (https://doi.org/10.1016/S2213-8587(21)00235-7)

13 Barbar S, Noventa F, Rossetto V, Ferrari A, Brandolin B, Perlati M, de Bon E, Tormene D, Pagnan A & Prandoni P. A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: the Padua prediction score. *Journal of Thrombosis and Haemostasis* 2010 **8** 2450–2457. (https://doi.org/10.1111/j.1538-7836.2010.04044.x)

14 Caprini JA, Arcelus JI, Hasty JH, Tamhane AC & Fabrega F. Clinical assessment of venous thromboembolic risk in surgical patients. *Seminars in Thrombosis and Hemostasis* 1991 **17** (Supplement 3) 304–312.

15 Boscaro M, Sonino N, Scarda A, Barzon L, Fallo F, Sartori MT, Patrassi GM & Girolami A. Anticoagulant prophylaxis markedly reduces thromboembolic complications in Cushing's syndrome. *Journal of Clinical Endocrinology and Metabolism* 2002 **87** 3662–3666. (https://doi.org/10.1210/jcem.87.8.8703)

16 van Zaane B, Nur E, Squizzato A, Dekkers OM, Twickler MTB, Fliers E, Gerdes VEA, Büller HR & Brandjes DPM. Hypercoagulable state in Cushing's syndrome: a systematic review. *Journal of Clinical Endocrinology and Metabolism* 2009 **94** 2743–2750. (https://doi.org/10.1210/jc.2009-0290)

17 Koutroumpi S, Daidone V, Sartori MT, Cattini MG, Albiger NM, Occhi G, Ferasin S, Frigo A, Mantero F, Casonato A, *et al.* Venous thromboembolism in patients with Cushing's syndrome: need of a careful investigation of the prothrombotic risk profile. *Pituitary* 2013 **16** 175–181. (https://doi.org/10.1007/s11102-012-0398-4)

18 Isand K, Feelders R, Brue T, Toth M, Deutschbein T, Reincke M, Kršek M, Santos A, Demtröder F, Chabre O, *et al.* High prevalence of venous thrombotic events in Cushing's syndrome: data from ERCUSYN and details in relation to surgery. *European Journal of Endocrinology* 2024 **190** 75–85. (https://doi.org/10.1093/ejendo/lvad176)

19 Bryk-Wiązania AH, Minasyan M, Świątkowska-Stodulska R, Undas A, Hubalewska-Dydejczyk A, Webb SM, Valassi E & Gilis-Januszewska A. The thrombotic risk in Cushing's syndrome—questions, answers, and the algorithm to consider in its assessment: part I—thrombotic risk not related to surgery. *Frontiers in Endocrinology* 2024 **15** 1350010. (https://doi.org/10.3389/fendo.2024.1350010)

20 Kearon C, Ageno W, Cannegieter SC, Cosmi B, Geersing GJ, Kyrle PA & Subcommittees on Control of Anticoagulation, and Predictive and Diagnostic Variables in Thrombotic Disease. Categorization of patients as having provoked or unprovoked venous thromboembolism: guidance from the SSC of ISTH. *Journal of Thrombosis and Haemostasis* 2016 **14** 1480–1483. (https://doi.org/10.1111/jth.13336)

21 Nieman LK, Biller BMK, Findling JW, Newell-Price J, Savage MO, Stewart PM, Montori VM & Edwards H. The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. *Journal of Clinical Endocrinology and Metabolism* 2008 **93** 1526–1540. (https://doi.org/10.1210/jc.2008-0125)

22 Barbot M, Daidone V, Zilio M, Albiger N, Mazzai L, Sartori MT, Frigo AC, Scanarini M, Denaro L, Boscaro M, *et al.* Perioperative thromboprophylaxis in Cushing's disease: what we did and what we are doing? *Pituitary* 2015 **18** 487–493. (https://doi.org/10.1007/s11102-014-0600-y)

23 Minasyan M, Gamrat A, Bryk-Wiązania AH, Hubalewska-Dydejczyk A & Gilis-Januszewska A. Pulmonary embolism after delivery as the first manifestation of Cushing disease in pregnancy. *Polish Archives of Internal Medicine* 2023 **133** 16528. (https://doi.org/10.20452/pamw.16528)

24 Minasyan M, Bryk-Wiązania A, Hubalewska-Dydejczyk A & Gilis-Januszewska A. Pulmonary embolism as the first manifestation of Cushing syndrome in a young woman. *Endokrynologia Polska* 2022 **73** 990–991. (https://doi.org/10.5603/EP.a2022.0083)

25 Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing GJ, Harjola VP, Huisman MV, Humbert M, Jennings CS, Jimenez D, *et al.* 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). *European Heart Journal* 2020 **41** 543–603. (https://doi.org/10.1093/eurheartj/ehz405)

26 Haalen FM van, Kaya M, Pelsma ICM, Dekkers OM, Biermasz NR, Cannegieter SC, Huisman MV, Vlijmen BJM van, Feelders RA, Klok FA, *et al.* Current clinical practice for thromboprophylaxis management in patients with Cushing's syndrome across reference centers of the European Reference Network on Rare Endocrine Conditions (Endo-ERN). *Orphanet Journal of Rare Diseases* 2022 **17** 178. (https://doi.org/10.1186/s13023-022-02320-x)

27 Kastelan D, Dusek T, Kraljevic I & Aganovic I. Hypercoagulable state in Cushing's syndrome is reversible following remission. *Clinical Endocrinology* 2013 **78** 102–106. (https://doi.org/10.1111/j.1365-2265.2012.04479.x)

28 Hinojosa-Amaya JM, Varlamov EV, McCartney S & Fleseriu M. Hypercortisolemia recurrence in Cushing's disease; a diagnostic challenge. *Frontiers in Endocrinology* 2019 **10** 740. (https://doi.org/10.3389/fendo.2019.00740)

29 Witek P, Zieliński G, Szamotulska K, Witek J & Kamiński G. Cushing's disease: fibrinogen and D-dimer levels fail to normalise despite early postoperative remission - A prospective, controlled study. *Endokrynologia Polska* 2016 **67** 283–291. (https://doi.org/10.5603/EP.a2016.0034)

30 Ortel TL, Neumann I, Ageno W, Beyth R, Clark NP, Cuker A, Hutten BA, Jaff MR, Manja V, Schulman S, *et al.* 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. *Blood Advances* 2020 **4** 4693–4738. (https://doi.org/10.1182/bloodadvances.2020001830)

31 Arachchillage DJ, Mackillop L, Chandratheva A, Motawani J, MacCallum P & Laffan M. Thrombophilia testing: a British Society for Haematology guideline. *British Journal of Haematology* 2022 **198** 443–458. (https://doi.org/10.1111/bjh.18239)

32 Kakkos SK, Gohel M, Baekgaard N, Bauersachs R, Bellmunt-Montoya S, Black SA, ten Cate-Hoek AJ, Elalamy I, Enzmann FK, Geroulakos G, *et al.* Editor's Choice – European Society for Vascular Surgery (ESVS) 2021 Clinical practice guidelines on the management of venous thrombosis. *European Journal of Vascular and Endovascular Surgery* 2021 **61** 9–82. (https://doi.org/10.1016/j.ejvs.2020.09.023)

33 Suarez MG, Stack M, Hinojosa-Amaya JM, Mitchell MD, Varlamov EV, Yedinak CG, Cetas JS, Sheppard B & Fleseriu M. Hypercoagulability in Cushing syndrome, prevalence of thrombotic events: a large, single-center, retrospective study. *Journal of the Endocrine Society* 2020 **4** bvz033. (https://doi.org/10.1210/jendso/bvz033)

34 Rubinstein G, Osswald A, Hoster E, Losa M, Elenkova A, Zacharieva S, Machado MC, Hanzu FA, Zopp S, Ritzel K, *et al.* Time to diagnosis in Cushing's syndrome: a meta-analysis based on 5367 patients. *Journal of Clinical Endocrinology and Metabolism* 2020 **105** dgz136. (https://doi.org/10.1210/clinem/dgz136)