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RESEARCH

Venous thromboembolism in Cushing syndrome: results from an EuRRECa and Endo-ERN survey

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Abstract

Background: Patients with Cushing syndrome (CS) are at increased risk of venous thromboembolism (VTE).

Objective: The aim was to evaluate the current management of new cases of CS with a focus on VTE and thromboprophylaxis.

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Design and methods: A survey was conducted within those that report in the electronic reporting tool (e-REC) of the European Registries for Rare Endocrine Conditions (EuRRECa) and the involved main thematic groups (MTG's) of the European Reference Networks for Rare Endocrine Disorders (Endo-ERN) on new patients with CS from January 2021 to July 2022.

Results: Of 222 patients (mean age 44 years, 165 females), 141 patients had Cushing disease (64%), 69 adrenal CS (31%), and 12 patients with ectopic CS (5.4%). The mean follow-up period post-CS diagnosis was 15 months (range 3–30). Cortisol-lowering medications were initiated in 38% of patients. One hundred fifty-four patients (69%) received thromboprophylaxis (including patients on chronic anticoagulant treatment), of which low-molecular-weight heparins were used in 96% of cases. VTE was reported in six patients (2.7%), of which one was fatal: two long before CS diagnosis, two between diagnosis and surgery, and two postoperatively. Three patients were using thromboprophylaxis at time of the VTE diagnosis. The incidence rate of VTE in patients after Cushing syndrome diagnosis in our study cohort was 14.6 (95% CI 5.5; 38.6) per 1000 person-years.

Conclusion: Thirty percent of patients with CS did not receive preoperative thromboprophylaxis during their active disease stage, and half of the VTE cases even occurred during this stage despite thromboprophylaxis. Prospective trials to establish the optimal thromboprophylaxis strategy in CS patients are highly needed.

Significance statement

The incidence rate of venous thromboembolism in our study cohort was 14.6 (95% CI 5.5; 38.6) per 1000 person-years. Notably, this survey showed that there is great heterogeneity regarding time of initiation and duration of thromboprophylaxis in expert centers throughout Europe.

Keywords: endogenous hypercortisolism; Cushing disease; Cushing syndrome; thromboprophylaxis; venous thromboembolism

Introduction

Endogenous hypercortisolism (Cushing syndrome, CS) is a rare disorder with an estimated incidence of 0.2–5.0 cases per million inhabitants per year in various populations, whereas its prevalence is close to 39–79 cases per million (1, 2). The majority of cases are adrenocorticotropic hormone (ACTH) dependent, of which a pituitary corticotrope adenoma (Cushing disease, CD) is the most prevalent cause, whereas ACTH-secreting non-pituitary tumors (ectopic ACTH and corticotropin-releasing hormone syndrome secretion) are responsible for about 5–10% of cases. ACTH-independent cases of CS (adrenal adenomas or uni- or bilateral adrenal hyperplasia) account for the remaining 20% of cases (1, 3).

It is well-known that endogenous hypercortisolism is associated with increased morbidity and mortality (4, 5, 6). This increased risk is mainly driven by cardiovascular events, including venous thromboembolic events (VTEs) such as pulmonary embolism (PE) and deep vein thrombosis (DVT). It has been demonstrated that the primary risk factors associated with VTE include older age (>69 years), reduced mobility, acute severe infections, previous cardiovascular events, higher midnight plasma cortisol levels, and shorter activated partial thromboplastin time (7). Additionally, a recent analysis of the ERCUSYN database found a higher prevalence of VTE among male patients, patients with a history of multiple surgeries, and those with high urinary cortisol levels (8). Several studies have observed an increased risk of VTE in patients with endogenous hypercortisolism even long after successful treatment. A study showed that the VTE incidence is almost seven times higher in the years before diagnosing endogenous hypercortisolism and almost 17 times higher in the first year after diagnosis; this incidence remains increased in the initial months following successful treatment (9). This results in an increased incidence rate of 14.6 per 1000 person-years for VTE in patients with endogenous hypercortisolism compared to the general population (10). The cortisol-induced hypercoagulability is thought to be partially caused by activation of the coagulation cascade with an increase in, e.g. von Willebrand factor, fibrinogen, and factor VIII concentrations (11, 12), impaired fibrinolysis (4) and endothelial dysfunction (13). Changes in pro- and anticoagulant factors may persist after successful surgery or medical therapy for at least several months (14, 15).

Given the lack of evidence from clinical trials, there is a large practice variation regarding thromboprophylaxis management and perioperative medical treatment in

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patients with endogenous hypercortisolism, even among reference centers that have obtained specific national and international accreditation for the diagnosis and treatment of CS (16). To further map local practice patterns and associated VTE complications in CS, we performed a study across the European Reference Network on Rare Endocrine Conditions (Endo-ERN) expert centers using the European Registries for Rare Endocrine Conditions (EuRRECa), and the contributors to the relevant main thematic groups (MTGs), i.e. Adrenal (one) and Pituitary (six) of the Endo-ERN.

Methods

The main objective of this study was to collect epidemiological and routine clinical data on new CS cases reported on the EuRRECa electronic reporting tool (e-REC) and Endo-ERN with a focus on VTE and thromboprophylaxis.

EuRRECa was constructed to support the needs of Endo-ERN, maximizing the opportunity for all patients, healthcare professionals, and researchers to participate and use high-quality, patient-centered registries for these rare conditions. The two platforms of the EuRRECa project encompass the Core registry, which collects a common dataset and clinician- and patient-reported outcomes, and an electronic surveillance system, the e-Reporting on Rare Endocrine Conditions (e-REC) program (17).

e-REC is a program that monthly captures the number of new cases of rare endocrine conditions seen at the participating centers.

e-REC is used for continuous monitoring of the expert centers of ERNs (Endo-ERN, ERN BOND), for mapping expert centers not only within European Union, for understanding the occurrence of the rare endocrine and bone conditions, and for conducting secondary surveys.

Because e-REC only provides a number of cases with a specific diagnosis without any personal data, there is no informed consent needed. e-REC is open to Endo-ERN and other centers involved in the care of patients with rare endocrine conditions.

Secondary survey

Secondary surveys (https://eurreb.eu/registries/e-rec/secondary-survey/) on e-REC-reported cases allow for the collection of well-defined routine clinical data for quality assurance and for understanding the clinical presentation of the reported condition. No personally identifiable data, such as date of birth, date of surgery, date of VTE, or exact laboratory tests, were collected.

First, the e-REC team sorted e-REC IDs of patients with endogenous hypercortisolism (ORPHA443287, ORPHA1501, ORPHA99408, ORPHA96253) reported between January 2021 and July 2022. Then the centers were provided with the list of IDs and queried to revisit these cases and to add clinical data to the online questionnaire. The survey questionnaire utilized Webropol survey, a secure online tool endorsed and supported by NHS Greater Glasgow & Clyde and NHS Scotland. The use of e-REC and secondary surveys was approved by the institutional board of the Leiden University Medical Center, and participating centers were advised to seek local approval if needed.

In addition, healthcare providers (not reporting in e-REC) of the relevant main thematic groups ('Adrenal' and 'Pituitary') of Endo-ERN were queried regarding any of their reported new encounters with a confirmed diagnosis of CS from January 2021 to July 2022. Patients with suspected but not confirmed CS were excluded (according to the current guideline) (18).

VTE in CS survey

The survey was open for entry from October 2022 to June 2023. Follow-up started on the date of initial CS diagnosis (within the period of interest – January 2021 till July 2022) and ended when an endpoint of interest occurred (VTE, bleeding, death) or on the date of filling in the questionnaire, whichever came first.

A survey was designed consisting of questions on the occurrence of VTE, and if so, additional questions assessed risk factors of VTE, treatment regimens, and VTE complications. Questions included data about relevant co-morbidities and the different items of the Cushing severity index (CSI) – a validated score for reliable clinometric evaluation of severity in endogenous hypercortisolism (19) using eight different parameters (fat distribution, skin lesions, muscle weakness, mood disorders, hypertension, diabetes mellitus, hypokalemia, and sex-related disturbances), each one graded from 0 to 2 with a maximum score of 16. These components enabled the calculation of the CSI score of all subjects. For the full questionnaire, see Annex 1 (see section on supplementary materials given at the end of this article).

Statistical analyses

Continuous data are presented as mean ± S.D. (range) and were compared using ANOVA. All the other values, if not normally distributed, are expressed as median with interquartile range (IQR) and compared using ANCOVA. Statistical analysis was performed using SPSS version 25.0.

The individual person-time was calculated based on the dates of reporting in e-Rec and filling in the survey and on the date of VTE. Incidence rates for VTE were calculated by dividing the observed number of VTE cases within the study period by the sum of individual person-years and were presented with accompanying

95% CI. Any VTE occurring before diagnosis was ignored in the estimation of the incidence rate.

Results

Patient characteristics

The survey was completed by 35 clinicians in 20 centers from six countries (Fig. 1). Within the 18-month study period, a total of 222 new patients were reported with endogenous hypercortisolism. The mean follow-up period was 15 ± 8 months (range 3–30). The total number of person-years was 274. Table 1 shows the clinical and demographic characteristics of patients with CS.

One hundred forty-one patients had Cushing's disease (64%), 69 had ACTH-independent CS (31%), and 12 patients had ectopic CS (5.4%). One hundred sixty-five (74%) were female with a mean age of 44 ± 16 years (range 3–80). Ninety-one patients (41%) were overweight (BMI 25–30 kg/m^2), and 76 (34%) were obese (BMI ≥ 30 kg/m^2). A previous VTE (not related to CS based on the clinical judgment of the reporters, information on the time of occurrence was unavailable) was reported in 11 (4.9%) patients, and other cardiovascular events (e.g. myocardial infarction, myocarditis, cerebrovascular disease, and stroke) in 11 patients (4.9%). Most patients underwent surgery (n = 204, 92%), pituitary (n = 130, 64%), adrenal surgery (n = 68, 33%), and other surgery (n = 6, 3%); 47 (23%) of them had repeated surgery.

The mean number of comorbidities was 2 ± 1.5 (range 0–10). In 36 (16.2%) patients, no relevant comorbidities were reported, and 25 had more than 4 (11%). Mean CSI was 5.6 ± 2.9 (0–13), patients with CD had higher scores compared to patients with adrenal CS 5.8 ± 2.9 vs 4.8 ± 2.7 (MD 1.0; 95% CI 0.2; 1.8). Patients with ectopic CS had the highest scores (8.5 ± 2.9), with a mean difference of 3.7 (95% CI 2.0; 5.4) compared to adrenal CS, and a mean difference of 2.7 (95% CI 1.0; 4.4) when compared to CD.

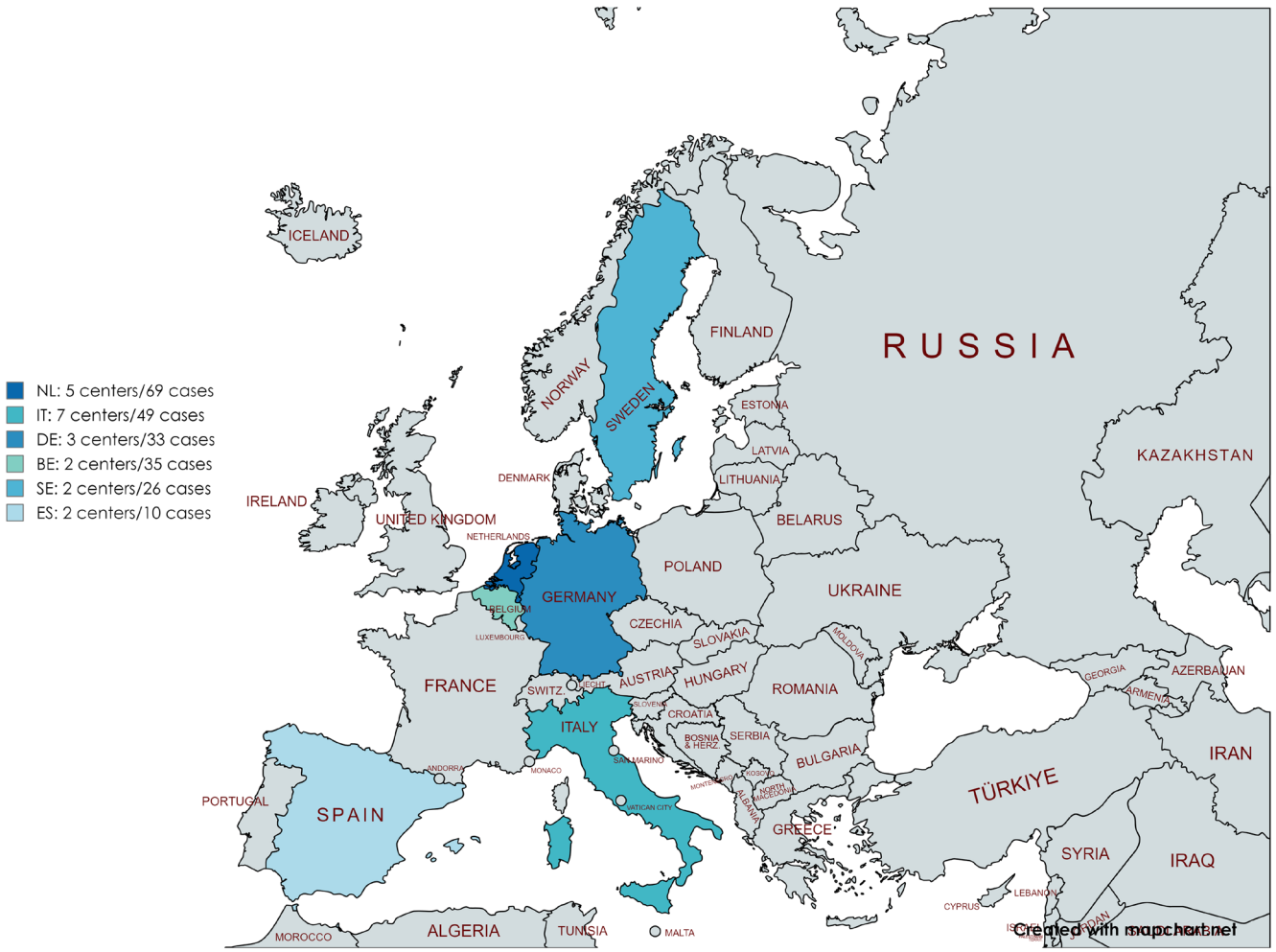

Figure 1

Overview of countries responding to the survey.

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Table 1 Clinical and demographic characteristics of patients with Cushing syndrome of different origin.

Demographic/clinical variable	Cushing disease	Adrenal Cushing syndrome	Ectopic Cushing syndrome	Total
Number of patients: *n* (%)	141 (63.5%)	69 (31.1%)	12 (5.4%)	222 (100%)
Age (years): median (IQR) (range)	43 (22.5) (7–79)	46 (25.5) (3–80)	48 (37) (22–77)	43 (25) (3–80)
Female: *n* (%)	105 (74.4%)	54 (78.2%)	6 (50%)	165 (74.3%)
CSI: mean ± S.D.	5.77 ± 2.88	4.81 ± 2.72	8.5 ± 2.87	5.6 ± 2.9
Number of comorbidities: mean ± S.D.	1.9 ± 1.58	1.97 ± 1.39	2.17 ± 1.7	1.93 ± 1.53
Obesity: *n* (%)	49 (34.8%)	23 (33.3%)	4 (33.3%)	76 (34.2%)
Hypertension: *n* (%)	90 (63.8%)	49 (71%)	9 (75%)	148 (66.7%)
Diabetes: *n* (%)	30 (21.3%)	17 (24.6%)	5 (41.7%)	52 (23.4%)
Previous VTE: *n* (%)	9 (6.4%)	2 (2.9%)	0	11 (4.9%)
VTE: *n* (%)	4 (2.8%)	1 (1.4%)	1 (8.3%)	6 (2.7%)
Cortisol-lowering treatment: *n* (%)	60 (42.6%)	14 (20.2%)	10 (83.3%)	84 (37.8%)
Thromboprophylaxis: *n* (%)	103 (73%)	41 (59.4%)	10 (83.3%)	154 (69.3%)
Surgery: *n* (%)	133 (94.3%)	64 (92.8%)	7 (58.3%)	204 (91.9%)

CSI, Cushing severity index; VTE, venous thromboembolism.

Cortisol-lowering medical treatment

Eighty-four patients (38%) received pre-surgical cortisol-lowering medical treatment, the majority receiving metyrapone (68%) or ketoconazole (30%). Other used agents were osilodrostat (8%), mitotane (1%), and levoketoconazole (1%). Of the pre-treated patients, 60 had CD (43% of the total CD group), 14 had adrenal CS (20% of the total adrenal CS group), and 10 had ectopic CS (83% of the total ectopic CS group). Patients with CD and ectopic CS were treated more often in comparison with patients with adrenal CS, with OR 2.9 (1.5; 5.7), $P = 0.0019$ and OR 19.6 (3.9; 100), $P = 0.0003$, respectively.

There were no major differences in patient characteristics between pre-treated and non-pre-treated patients in terms of age (44 ± 17 vs 43 ± 15 years; MD 1.0; 95% CI −3.4; 5.4), sex distribution (65/83 vs 101/138, OR 1.3; 95% CI 0.7; 2.5), number of comorbidities (1.8 ± 1.2 vs 2.0 ± 1.8; MD 0.2; 95% CI −0.2; 0.6), and CSI (6.2 ± 3.0 vs 5.4 ± 2.8; MD 0.8; 95% CI 0.01; 1.6).

Medical cortisol-lowering treatment was initiated at the time of diagnosis in 59 cases (70%) and usually discontinued 1 day before or after surgery (91%). Hypercortisolism was completely controlled in 43 patients (21%) and partially controlled in 40 (20%) before surgery, irrespective of disease origin (based on the cortisol levels).

VTE prophylaxis

Protocolled and unprotocolled initiation of thromboprophylaxis

A thromboprophylaxis protocol specific for patients with CS was present in 6 out of 20 centers (30%), while three centers (15%) had no thromboprophylaxis protocol, and 11 out of 20 (55%) had a protocol not specific for CS. Thromboprophylaxis was given to 154 out of 222 patients (69%); in 15 cases (9.7%), this was a therapeutic treatment due to a previous event/condition. Thromboprophylaxis was initiated from CS diagnosis onward in 43 cases (28%): thirty-one patients (31/43, 72%) were from centers ($n = 3$) with specific thromboprophylaxis protocols for patients with CS, and consequently, the treatment was initiated at the time of diagnosis. The remaining 12 patients (28%) started thromboprophylaxis due to the presence of risk factors such as severe CS, older age, limited mobility, active malignancy, or additional cardiovascular comorbidities. Thromboprophylaxis was initiated 2–6 weeks before surgery – in nine cases (5.8%), 1 week before surgery – in eight cases (5.2%), the day before/of surgery in 50 cases (33%), and after surgery – in 26 cases (19%). The remaining 30% of patients did not receive any thromboprophylaxis. In three cases (1.9%), data about the initiation of thromboprophylaxis were missing. In patients with CD, therapy was started more often on the day before/of surgery (40%) compared to adrenal CS patients (20%), OR 2.7 (95% CI 1.1; 6.5). At the same time, thromboprophylaxis was more often prescribed after surgery in patients with adrenal CS (12/41 vs 13/103; OR 2.86 (95% CI 1.1; 7.0)). The use of elastic compressive stockings was reported in 83 (37%) of patients.

Thromboprophylactic agents and duration of treatment

Low-molecular-weight heparins (LMWHs) were prescribed in the vast majority of cases, with $n = 147$ (96%). Nadroparine was used in 57 patients (39%), with a dose ranging from 2850 to 5700 IU per day depending on BMI. Enoxaparin, ranging from 4000 to 6000 IU per day, was prescribed in 52 patients (35%), while dalteparin, ranging from 2500 to 5000 IU per day, was used in 32 patients (22%). Other drugs included tinzaparin and fondaparinux. Direct oral anticoagulants (DOACs) were used in only six patients (3.9%) (with dosages ranging from 10 to 20 mg/day for rivaroxaban and 2.5–10 mg/day for apixaban), and warfarin was prescribed in one patient (0.6%).

Thromboprophylaxis was discontinued during the first week after surgery in 55 patients (36%), during 2–4 weeks in 28 patients (18%), 6–12 weeks in 26 patients (17%), and was continued longer in 17 patients (11%). The median pre- and postoperative duration of thromboprophylaxis was 14 days (IQR = Q3–Q1 = 28–7 = 21).

Differences between patients that received and those that did not receive thromboprophylaxis

The 68 patients not receiving any thromboprophylaxis had lower CSI scores 4.3 ± 2.5 vs 6.2 ± 2.9 (MD 1.9; 95% CI 1.1; 2.8), and more often did not undergo surgery, 12/68 vs 6/154 (OR 5.3 (95% CI 1.9; 14.8)). Within the cohort of patients with CD, thromboprophylaxis was prescribed more often to older patients (45 ± 15 vs 37 ± 15 years) and to patients with higher CSI (6.1 ± 2.8 vs 4.7 ± 2.7, MD 1.4, 95% CI 0.4; 2.4). Among the patients with adrenal CS, thromboprophylaxis was initiated more often with higher CSI (5.8 ± 2.9 vs 3.6 ± 1.9, MD 2.2, 95% CI 0.9; 3.5), but no differences were observed in age and number of comorbidities (MD 4.6, 95% CI (−4.0; 13.2) and MD 0.1 (−0.5; 0.8), respectively).

Bleeding complications

No major bleeding was reported; two patients reported epistaxis, not related to pituitary surgery.

Venous thromboembolic event

Six cases of VTE were reported (2.7%, 95% CI 1; 6), (Table 2): four patients with CD, one patient with adrenal CS, and one patient with ectopic CS. At the time of VTE, 5 out of 6 had uncontrolled hypercortisolemia.

Three patients (3/6) had a previous VTE, and most of them had several additional risk factors for thrombosis. There were three cases of PE (one combined with DVT), one case of central retinal vein thrombosis, and one case of thrombophlebitis with thrombus of the vena cephalica. The patient with ectopic CS died because of thrombosis of the vena cava inferior despite cortisol-lowering treatment with four different agents and thromboprophylaxis with LWMH treatment. VTE episodes were registered during a very wide time frame: from 2 years before the diagnosis of CS to 6 weeks after surgery. One VTE episode was reported in the group of patients with elastic stockings usage (1/83), three in group without stockings (3/121), and two in the group with unknown status (OR 0.7 (95% CI 0.1; 8.1)).

The incidence rate of VTE after CS diagnosis in this survey was 14.6 (95% CI 5.5; 38.6) per 1000 person-years (four events for 274 person-years).

The incidence rate of VTE in CS of different origins in patients receiving thromboprophylaxis was 10.2 (95% CI 2.6; 40.5) vs 25.6 (95% CI 6.5; 100.7) cases per 1000 person-years without thromboprophylaxis (two events for 196 person-years vs two events for 78 person-years), which was an incidence rate ratio between the two groups of 2.5 (95% CI 0.18; 34.7), $P > 0.05$.

Discussion

The results of this study, which represent real-world clinical data of patients treated for CS in European reference centers, are consistent with previous cohort studies and demonstrate similar rates. In the presence of heterogeneous policies on thromboprophylaxis in expert centers throughout Europe, our study also provides better insight into the various policies on pre-surgery cortisol-lowering treatment. We found that the incidence rate of VTE in patients with CS was 14.6 (95% CI 5.5; 38.6) per 1000 person-years, and VTE occurred even in patients on cortisol-lowering medication and anticoagulants.

A specific thromboprophylaxis protocol for patients with CS was not available in the vast majority of centers, despite the fact that retrospective cohort studies have shown a decrease in VTE-associated mortality and morbidity in patients with endogenous hypercortisolism on anticoagulant treatment (20, 21). Thromboprophylaxis in CS patients has been reported to be associated with low bleeding rates (22, 23), which is confirmed in the present study.

The optimal timing for initiation of thromboprophylaxis probably depends on the risk profile of individual patients (especially patient's mobility) and remains unclear, which is reflected by the diverse start dates in our study: 28% of patients started at the time of CS diagnosis, 33% the day before/of surgery, and 19% directly after surgery. The duration of thromboprophylaxis is also unclear and differed greatly among the study population. At present, different studies have confirmed that the risk of VTE remains increased at least until 3 months after successful surgery and may normalize after 6 months (9, 24). Prolonging thromboprophylaxis with LMWH until 30 days after surgery appears to reduce the VTE incidence in patients with CD without any significant side effects (9, 14, 20). Of note, in our study, half of the VTE events (n = 3) occurred despite active thromboprophylaxis, highlighting the fact that thromboprophylaxis (or dosages which were used) may be insufficient in the highest risk categories, such as previous VTE and ectopic CS. Unfortunately, the design of the secondary survey does not allow us to answer the question of whether the doses were adapted accordingly to glomerular filtration rate and weight. Nowadays, it is generally accepted that hypercortisolism *per se* is an important risk factor for VTE, although a relation between the severity of hypercortisolism and changes in coagulation factors has not been demonstrated (11). Consequently, it seems beneficial to start cortisol-lowering treatment in patients with CS while awaiting curative surgery regardless of thromboprophylaxis, to decrease the risk of postoperative withdrawal

Table 2 Clinical and demographic characteristics of patients with Cushing syndrome of different origin and VTE.

Demographic/clinical variable	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Type of CS	CD	CD	CD	CD	Benign adrenal CS	Ectopic CS
Sex	F	F	F	M	M	F
Age	48	55	33	54	35	39
Risk factors	Overweight Hypertension Osteoporosis with fractures	Obesity Hypertension Previous VTE	Obesity Hypertension Repeated pituitary surgery	Obesity Hypertension Previous VTE Diabetes	Overweight Hypertension Osteoporosis with fractures Previous VTE	Hypertension
CSI	7	5	7	5	1	11
Medical treatment	No	No	Yes (controlled CS)	No	No	Yes (uncontrolled CS)
TPX start	1 week pre-op	The day of surgery	1 week pre-op	Before Dz of CS	Before Dz of CS	From diagnosis
TPX stop	2 weeks post-op	1 week post-op	6 weeks post-op	Ongoing DOAC	Ongoing LMWH	Ongoing LMWH
TPX type	Nadroparine	Nadroparine	Nadroparine	Rivaroxaban	Fondaparinux	Tinzaparin
VTE type	Central retinal vein occlusion	PE	Thrombophlebitis with thrombus v. cephalica	PE + DVT	PE	Inferior vena cava thrombosis resulting to death
VTE timing	12 weeks pre-op	6 weeks post-op	9 days post-op	24 months before diagnosis	4 weeks before diagnosis	Was not operated

CSI, Cushing severity index; CS, Cushing syndrome; CD, Cushing disease; DVT, deep vein thrombosis; DOAC, direct oral anticoagulants; LMWH, low-molecular-weight heparin; PE, pulmonary embolism; TPX, thromboprophylaxis; VTE, venous thromboembolism.

syndrome. This might be beneficial for the postoperative VTE risk as the corticosteroid withdrawal syndrome is a pro-inflammatory, and thus a pro-thrombotic, state in itself, thereby theoretically reducing the risk of VTE (11). Unfortunately, no clinical guidance exists on this topic, which is reflected by the real-world outcome data of this study. Initiation of cortisol-lowering medication varies from center to center and between countries and also depends on the origin of the underlying disease. As observed in this study, only 20% of patients with adrenal CS were treated with cortisol-lowering medication vs 83% of patients with ectopic CS and 43% of patients with Cushing's disease. It is plausible to assume that this reflects both differences in disease severity and differences in the pre- and peri-operative management of adrenal and neurosurgical surgeries and the availability or lack of surgical procedures. In agreement with this, it has been suggested that in patients pretreated with cortisol-lowering medication before surgery, VTE risk was lower than patients not receiving cortisol-lowering medication before surgery (10). However, a recent larger study of the European Registry on Cushing syndrome (ERCUSYN) did not observe differences in post-surgical morbidities including thromboembolism within 180 days of surgery (6), although the proportion of patients receiving thromboprophylaxis in their study was lower, which may have influenced the results. Similar data were published in a more recent analysis of the ERCUSYN database (8). However, it has been reported that patients with higher cortisol levels (blood samples measured at midnight and free cortisol measured in urine) also had a higher VTE risk (7, 8, 25). The present study did not detect a difference in VTE risk between the different types of endogenous hypercortisolism, as in other studies, probably due to the small number of events. Also, other preventive measures, such as early mobilization after surgery and the use of elastic compressive stocking until mobilization, may have a role in the management of thromboprophylaxis, but we have not found difference within the groups in our survey (20).

Our study has some limitations as it was a retrospective survey, which may have introduced selection and detection bias. The secondary survey design limits the access to exact data (as precise date of VTE, surgery, details on previous VTE, adjustment of LMWH dosage for weight and others), so the dataset is rather different from a single-center chart review. Even with the use of e-REC, we cannot be sure that all new cases of CS have been included in the registry and in the survey. Also, several centers have reported less than five cases. Additionally, the date of e-REC registration is probably not the exact date of diagnosis, since there could be referral delay before patients are seen in a tertiary center. This might affect the VTE incidence rate.

Moreover, the total number of patients and events related to VTE is comparatively smaller than in previous studies. This limited dataset poses challenges in drawing robust conclusions regarding predisposing factors, subgroupings, optimal dosages, and clinical strategies for preventing VTEs. All these factors should be taken into account when designing a prospective observational study on the incidence of VTEs in patients with Cushing syndrome. However, we do feel that considering the similarities of our data with previously reported studies, the findings of the survey are consistent with current daily clinical practice throughout different expert centers in Europe. Additionally, the unique setup of this real-world multiple tertiary expert center collaborative study can be a starting point for the prospective registry on the EuRRECa platform aimed at improving best practice.

Conclusion

The incidence rate of VTE in patients after CS diagnosis in our study cohort was 14.6 (95% CI 5.5; 38.6) per 1000 person-years.

Of patients with CS, 30% did not receive preoperative thromboprophylaxis, and at the same time, half of the VTE cases occurred despite active thromboprophylaxis. Prospective clinical trials are needed to develop evidence-based guidelines on thromboprophylaxis and harmonized local protocols throughout the Endo-ERN.

Supplementary materials

This is linked to the online version of the paper at https://doi.org/10.1530/EC-24-0046.

Declaration of interest

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