European Journal of Endocrinology, 2024, **190**, 75–85
https://doi.org/10.1093/ejendo/lvad176
Advance access publication 26 December 2023
Original Research

High prevalence of venous thrombotic events in Cushing's syndrome: data from ERCUSYN and details in relation to surgery

Kristina Isand,[1,*] Richard Feelders,[2] Thierry Brue,[3] Miklos Toth,[4] Timo Deutschbein,[5] Martin Reincke,[6] Michal Kršek,[7] Alicia Santos,[8,9] Frank Demtröder,[10] Olivier Chabre,[11] Christian J. Strasburger,[12] Anna Aulinas Maso,[8,9] Vallo Volke,[1] Alberto M. Pereira,[13] Rüdiger Lohmann,[14] Ignasi Gich Saladich,[15] Ercusyn Study Group, Susan M. Webb,[8,9] John Wass,[16] and Elena Valassi[9,17]

[1]Institute of Biomedicine and Translational Medicine, University of Tartu, Ülikooli 18, 50090, Tartu, Estonia
[2]Department of Internal Medicine, Section of Endocrinology, ENETS Center of Excellence, Erasmus MC and Erasmus Cancer Institute, 3015 Rotterdam, The Netherlands
[3]Aix Marseille Univ, APHM, INSERM, MMG, Department of Endocrinology Hospital La Conception, MarMaRa Institute, 13305 Marseille, France
[4]Department of Internal Medicine and Oncology, Semmelweis University, 1083 Budapest, Hungary
[5]Division of Endocrinology and Diabetes, Department of Internal Medicine I, University Hospital, University of Würzburg, 97080 Würzburg, Germany
[6]Medizinische Klinik und Poliklinik IV, Campus Innenstadt, Klinikum der Universität München, Ludwig-Maximilians-Universität München, 80336 Munich, Germany
[7]Third Department of Internal Medicine, First Faculty of Medicine, Charles University, General University Hospital, 12808 Prague, Czech Republic
[8]IIB-Sant Pau and Department of Endocrinology, Hospital Sant Pau, Dept Medicine, UAB, and Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBER-ER, Unidad 747), ISCIII, 08025 Barcelona, Spain
[9]Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER, Unidad 747), Barcelona, Spain
[10]Zentrum für Endokrinologie, Diabetologie, Rheumatologie Dr. Demtröder & Kollegen, 44137 Dortmund, Germany
[11]University Grenoble Alpes, UMR 1292 INSERM-CEA-UGA, Endocrinologie CHU Grenoble Alpes, F-38000 Grenoble, France
[12]Clinical Endocrinology, Charite-Universitätsmedizin, Campus Mitte, 10117 Berlin, Germany
[13]Department of Endocrinology & Metabolism, Amsterdam University Medical Center, and University of Amsterdam, 1081 Amsterdam, Netherlands
[14]Health Care Consulting GmbH, Lohmann & Birkner Health Care Consulting GmbH, 13407 Berlin, Germany
[15]Department of Clinical Epidemiology and Public Health, Hospital de la Santa Creu i Sant Pau (IIB Sant Pau), 08025 Barcelona, Spain
[16]Oxford Centre for Diabetes, Endocrinology and Metabolism, Oxford University Hospitals, OX37LE Oxford, United Kingdom
[17]Endocrinology and Nutrition Department, Germans Trias i Pujol Hospital and Research Institute, Badalona 08916, Spain

*Corresponding author: Institute of Biomedicinea nd Translational Medicine, University of Tartu, Ülikooli 18, 50090, Tartu, Estonia. Email: Kristina.iand@gmail.com

Abstract

Objective: The aim of this study was to evaluate the prevalence of venous thromboembolism (VTE) in patients included in the European Registry on Cushing's syndrome (ERCUSYN), compare their clinical characteristics with those who did not develop VTE and identify risk factors for VTE.

Design: A retrospective observational cohort study.

Methods: Data extraction from the registry was taken on February, 7, 2022. At the time there were 2174 patients diagnosed with Cushing's syndrome (CS) and 95 VTEs were reported in the database.

Results: Of 95 VTE events 70 (74%) were in pituitary-dependent CS patients, 12 (12.5%) in adrenal-dependant CS, 10 (10.5%) in ectopic CS, and 3 (3%) in CS due to other causes. Sex, 24-hour urinary free cortisol (UFC) value at diagnosis, as well as the number of operations remained statistically significant predictors of VTE. Of patients who were treated with at least one surgery, 12 (13%) VTE occurred before and 80 (87%) after the surgery. Nearly half of these VTEs occurred within six months since the operation (36; 45%). Over half of the centers that reported VTE did not routinely anticoagulate CS patients. Anticoagulation schemes varied widely.

Conclusion: Patients with CS have an elevated risk of developing VTE for an extended period of time. From ERCUSYN cohort patients have higher risk for VTE if they need multiple surgeries to treat CS, are males and have high UFC values at the diagnosis of CS. Since there is no agreement on thromboprohpylaxis, a protocol for VTE prevention that is widely adopted appears to be necessary for patients with CS.

Keywords: Cushing's syndrome, venous thromboembolism, risk factors, ERCUSYN

Received: August 3, 2023. **Revised:** November 24, 2023. **Editorial Decision:** November 27, 2023. **Accepted:** November 27, 2023
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Significance

This is the largest cohort-based study looking at VTE in Cushing's syndrome (CS), providing data for VTE events and information on anticoagulation protocols for CS patients. We were also able to prove that in most European endocrine centers protocols for thromboprophylaxis are not used on a routine basis and the heterogeneity of prophylaxis is excessively large in various centers.

Introduction

Cushing's syndrome (CS) is a rare disease caused by overt exposure to glucocorticoids.[1] The syndrome can be either exogenous or endogenous. Endogenous CS is a result of a pituitary adenoma (or, more rarely, an extra-pituitary tumour) producing excessive adrenocorticotropic hormone (ACTH) or an adrenocortical tumour secreting excessive cortisol.[1]

Patients with CS have a higher prevalence of several cardiovascular disorders, including arterial hypertension and myocardial infarction.[2] Cardiovascular diseases are the most severe complication and the leading cause of death in patients with Cushing's disease (CD).[3] The UK audit and metanalysis of the literature on CD over 50-years in Stroke-on-Trent by Clayton *et al* concluded that overall mortality in CD is double that of the general population.[4]

Cardiovascular risk is further increased by the comorbidities associated with CS: diabetes mellitus (DM), adiposity, dyslipidaemia, and an impaired coagulation profile.[2,4,5] All this can lead to a metabolic syndrome.[6]

Patients with CS also have an increased risk of developing venous thromboembolic (VTE) complications.[5,7] This is a well-recognized risk first reported more than 50 years ago in various etiologies, including pituitary and adrenal origin.[8–10] It has mainly been reported in the peri-operative period,[5,11,12] but there is increasing evidence that the risk is higher before the diagnosis of CS and several weeks after either medical or surgical treatment of hypercortisolaemia.[13]

The risk of a thrombotic event (TE) in patients with CS has been reported to be up to 10 times higher than that of the general population.[5,14] Stuijver et al. report in their multicentre cohort study including patients with benign CS, an incidence rate of VTE of 14.6%, the risk being higher in pituitary-dependent CS during active disease and after pituitary surgery.[5]

There is no consensus on thromboprophylaxis schedules either before or after surgery and the thromboprophylaxis protocols vary widely.[15,16]

The aim of this article is to identify possible risk factors of VTE by comparing the characteristics of the patients who experienced VTE and those who did not and to look at the strategies adopted to prevent and treat VTE across the centers of the European Registry on CS (ERCUSYN). ERCUSYN is the largest prospective database existing to date for CS patients.[17] It is aimed at gathering data at European Union (EU) level on clinical features, diagnostic procedures, and therapeutic strategies in CS patients. This ultimately should result in earlier recognition of CS and all its comorbidities, and assist clinicians in considering and treating all possible manifestations of the disease, thus improving long-term prognosis.[17]

Subjects and methods

A retrospective observational cohort study across the ERCUSYN database was performed. Data extraction from the registry was taken on February, 7, 2022. Additional data on the VTE details and center's routine thromboprophylaxis protocols were requested for all VTE cases and obtained in 93% of cases.

The ERCUSYN database provides data on the prevalence of VTE, etiology of CS, methods used to treat hypercortisolism, and general characteristics of patients diagnosed with CS. Specific information on VTE management was collected via survey.

At the time of analysis, there were 2174 patients included in the ERCUSYN database. The database was created in 2008, but the centers could include retrospective data from patients diagnosed since January, 1, 2000. Patients registered in the ERCUSYN database came from 57 centers in 26 European countries.

A detailed description of the database layout has been provided previously.[17]

The ERCUSYN study was approved by the ethics committee of the Hospital Sant Pau, Barcelona, Spain, which is the coordinating center of the project. In addition, the local ethics committee approval was obtained for each participating institution and all patients gave their written or verbal informed consent, depending on national legal requirements.

This study has been conducted in accordance with the Declaration of Helsinki.

The extract concentrated only on CS patients with VTE diagnosis. Patients were included when a "follow-up visit" had reported a VTE event. Information concerning sex, age at diagnosis, etiology of CS, body mass index (BMI), hypertension, DM, osteoporosis, smoking, cancer diagnosis, clinical status of CS, CS treatment option (surgical, medical, both), and any cortisol values were analyzed to find any higher risk predictors for VTE. The remission status was based on information included in the "Follow-up visit" section of the database. This section contains several biochemical tests, including morning serum cortisol, 24-h urinary free cortisol, and overnight 1-mg dexamethasone suppression test (DST). Centers are asked to provide information on both the value of hormone measurement and its diagnostic interpretation, that is, "low", "normal", "high", according to whether the value is below, within, or above the normal range of the assay used in each center.

For controls, ERCUSYN patients without VTE diagnosis were used. For all patients, the follow-up time started from the date of diagnosis of CS. For non-VTE patients, the follow-up was until the last follow-up visit and for VTE-patients until the first follow-up visit, where a VTE had been reported.

The next step was reaching out to individual centers that had reported a VTE event. Additional information included the type of VTE (pulmonary embolism (PE), deep venous thrombosis (DVT) or other), number of VTE's per patient, anticoagulation details, and antithrombotic stockings usage. These centers were also asked about their routine practise around anticoagulation in CS patients.

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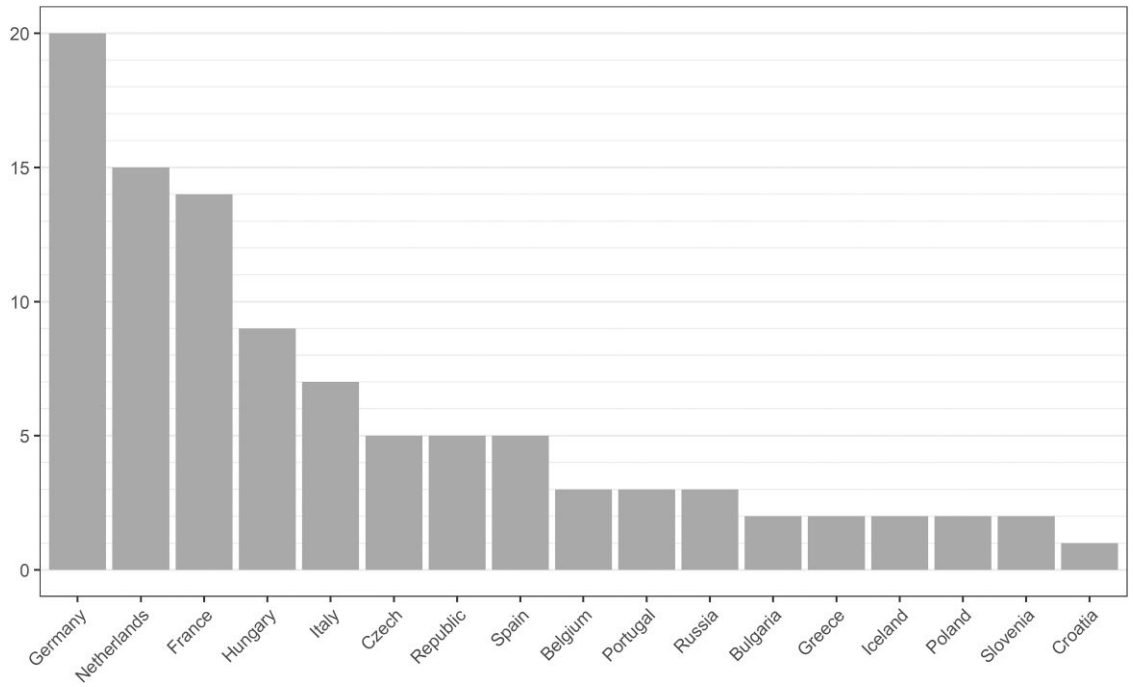

Figure 1. Reported number of VTEs per country.

Statistical analysis

We expressed categorical data as percentages and quantitative data as means and standard deviations (SD) (Gaussian distribution) and as median and interquartile range (q25-q75) (non-Gaussian distribution). We analyzed data distribution using Shapiro-Wilk test. To compare differences in 24 h urine free cortisol levels between different etiologies, Kruskal-Wallis test, and Dunn's test with Bonferroni correction as a posthoc test were used. To compare differences in 24 h urine-free cortisol levels between sexes, Mann-Whitney U-test was used. We used Cox regression to calculate Hazard ratios (HR) with 95% confidence intervals (95% CI) on univariate analysis. For continuous variables, the HR was calculated per unit of measurement. We used Cox proportional-hazards model to analyze the impact of confounding variables on VTE occurrences in multivariate analysis. Time-dependent Cox regression was done to avoid immortal time bias with the second operation time in both univariate and multivariate analysis. We calculated HR with 95% CI for each variable included in multivariate Cox regression analysis. We checked the proportional-hazards assumption using the Schoenfield test as well as using the Log minus log [Ln(-Ln(S))] plot estimation with log-time scale for the categorical variables and quantitative variables binarized from the median.

We obtained Kaplan-Meier survival curve to describe the cumulative incidence of VTE by patient sex.

The level of significance was set at $P < .05$.Statistical analysis was performed using RStudio electronic software, Version 2023.03.0 (Boston, MA, USA)).

Results

VTE events were reported by 28 centers from 16 European countries (Figure 1).

Characteristics of CS patients diagnosed with VTE

There were 95 VTEs among 2174 CS patients (prevalence of 4.4%). VTEs were reported starting from the patients' first entry to the registry until ten years after the first follow-up visit.

The main characteristics of CS patients with and without VTE are summarized in Table 1.

Men had a significantly higher VTE rate compared to women with HR 2.11 (95% CI 1.38–3.22).

Looking at ERCUSYN patients by etiology, the HR for VTE was the highest in ectopic ACTH secretion (HR 4.65 (95% CI 2.04–10.62)), followed by CD (HR 2.09 (95% CI 1.16–3.79) as compared to adrenal source of CS.

Cortisol values (midnight serum cortisol, 24-hour urinary free cortisol (UFC)) were available for 50 (52.6%) patients, of which at the time of the VTE event 23/50 (44.2%) patients had "high" cortisol levels, 24/50 (46.2%) had "normal" cortisol levels and 3/50 (9.6%) patients had "low" cortisol levels.

For the univariate analysis, UFC was included. VTE patients had higher UFC values than CS patients without VTE diagnosis. The HR of VTE for UFC was 1.06 (95% CI (1.02–1.10)). The UFC values were the highest in ectopic ACTH secretion (median 2.59 (1.15–6.07) mmol), followed by CD (median.071 (0.42–1.32) mmol) and adrenal CS (median 0.57 (0.28–1.24) mmol)) (Figure 2). Kruskal-Wallis test revealed statistically significant difference between groups ($P < .01$). In posthoc analysis Dunn's test with Bonferroni correction showed that UFC values between all three pairs of etiologies were statistically significantly different ($P < .01$). When looking at the difference in UFC levels in men and women, men had statistically significantly higher UFC values (median 1.00 (0.51–2.22 mmol) compared to women (median 0.68 (0.37–1.26) mmol) ($P < .01$) (Figure 3).

BMIs were similar in CS patients without VTE. The mean (±SD) BMI was 30.7 (±6.9) kg/m^2 (range 14.8–58.8 kg/m^2). 15/1855 (0.8%) patients were underweight, 434/1855 (23.4%) had a normal BMI, and 1405/1855 (75.8%) patients were either overweight or obese.

In our cohort, the HR of VTE did not differ based on BMI, the presence of DM, or smoking habit. On univariate analysis,

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Table 1. Baseline characteristics and univariate Cox regression of VTE[a] risk factors.

Risk factor	Data available in	All patients[b]	Patients without VTE[b]	Patients with VTE[b]	Hazard ratio (95% confidence interval) for VTE	*P*-value
Total number of patients	2174		2079	95		
Sex	2166					
Female		1707 (78.8)	1645 (79.4)	62 (65.3)	1	
Male		459 (21.2)	426 (20.6)	33 (34.7)	2.11 (1.38–3.22)	<.01
Age at diagnosis (years)	2169	44.9 (±14.3)	44.8 (±14.3)	46.9 (±14.4)	1.01 (0.999–1.03)	.07
24 h urine cortisol (mmol)	1476	0.71 (0.39–1.41)	0.70 (0.39–1.38)	1.07 (0.57–2.12)	1.06 (1.02–1.10)	<.01
Etiology	1869					
Adrenal		470 (25.1)	457 (52.8)	13 (13.7)	1	
Pituitary		1253 (67.0)	1183 (66.7)	70 (73.7)	2.09 (1.16–3.79)	<.05
Ectopic ACTH production		114 (6.1)	104 (5.9)	10 (10.5)	4.65 (2.04–10.62)	<.01
Other		32 (1.7)	30 (1.7)	2 (2.1)	2.26 (0.51–10.03)	.28
BMI[c] (cm/kg^2)	1939	30.7 (±6.9)	30.7 (±6.9)	31.0 (±6.4)	1.01 (0.98–1.04)	.63
Diabetes	1915	666 (34.8)	630 (34.6)	36 (38.3)	1.20 (0.79–1.81)	.40
Hypertension	2170	1492 (68.8)	1420 (68.3)	72 (78.3)	1.71 (1.04–2.80)	<.05
Smoking	1688	558 (33.1)	535 (33.1)	23 (31.9)	0.89 (0.55–1.42)	.62
Number of operations	1589					
One		1337 (84.1)	1274 (84.9)	63 (70.8)	1	
Two or more		252 (15.9)	226 (15.1)	26 (29.2)	2.10 (1.33–3.32)	<.01
Outcome of operation	1237					
In remission		1065 (86.1)	1015 (86.5)	50 (78.1)	1	
Not in remission		172 (13.9)	158 (13.5)	14 (21.9)	1.90 (1.05–3.44)	.03

[a]VTE, venous thromboembolism.
[b]Number (%) of patients for categorical values, mean (±SD) for continuous variables with a Gaussian distribution, median (interquartile range) for continuous variables with a non-Gaussian distribution.
[c]BMI, Body mass index.

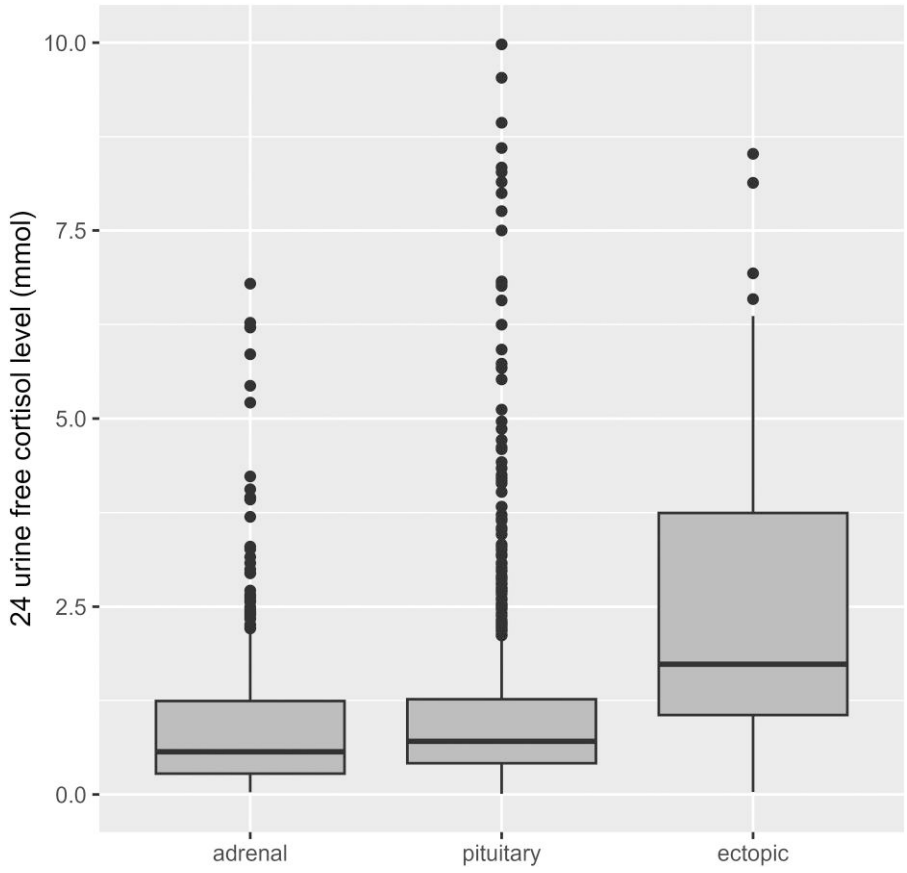

Figure 2. UFC values in different CS etiologies.

the VTE risk was elevated in patients who had been diagnosed with hypertension. HR of VTE was 1.71 (1.04–2.80) if hypertension was diagnosed ($P < .05$).

The VTE group had more surgeries than the non-VTE group. In the VTE group, 89 (93.7%) had had at least one surgery (total number of surgeries per patient ranged from 1 to 5).

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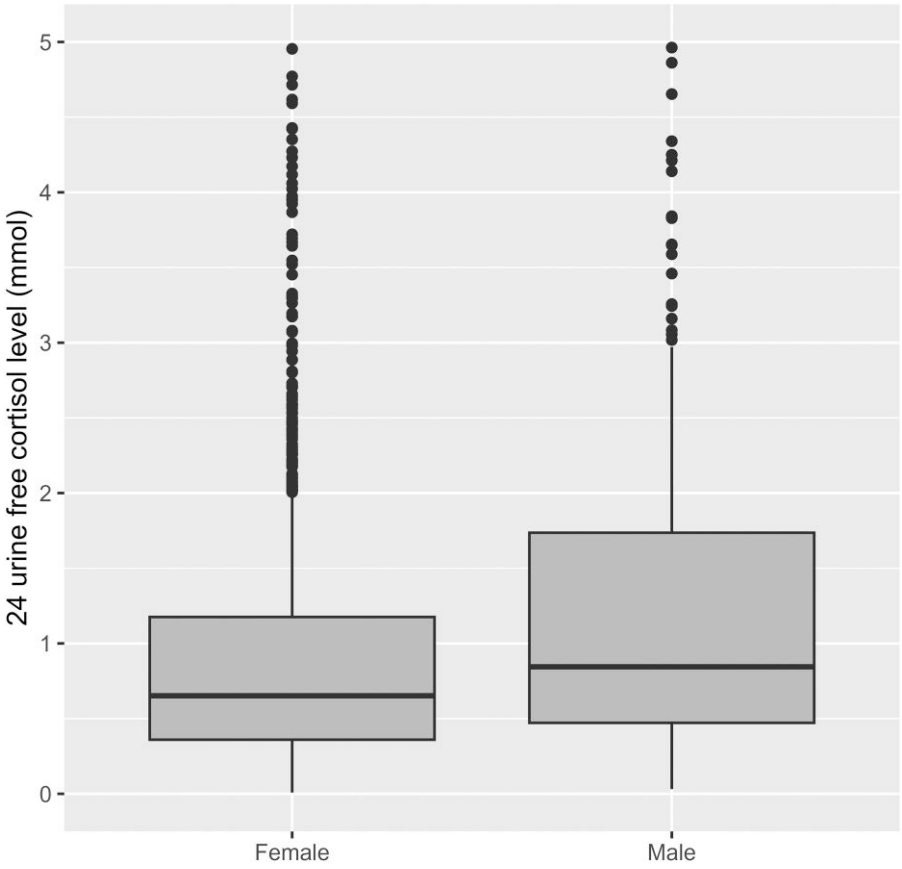

Figure 3. UFC values by sex.

Table 2. Time-dependent Cox multivariate regression analysis of VTE[a] risk factors.

	Hazard rate (95% confidence interval) of VTE[a] on multivariate analysis	*P*-value
Sex		
Female	1	
Male	1.92 (1.17–3.13)	<.01
Age at diagnosis	1.01 (0.99–1.03)	.14
24 h urine free cortisol (mmol)	1.06 (1.01–1.11)	<.05
Etiology		
Adrenal	1	
Pituitary	1.53 (0.77–3.05)	.23
Ectopic ACTH production	2.16 (0.69–6.71)	.18
Hypertension	1.13 (0.64–2.00)	.66
Number of operations		
One	1	
Two or more	1.97 (1.17–3.34)	<.05

[a]VTE, venous thromboembolism.

Sixty-three (70.8%) had one surgery, 26 (29.2%) patients had two or more operations. The HR for VTE was 2.10 (95% CI (1.33–3.32) for patients who had more than one operation on univariate analysis.

Sex, age at diagnosis, UFC value at diagnosis, etiology, hypertension, and the number of operations were included in multivariate Cox regression analysis (Table 2). The second operation was analyzed as a time-dependent variable to avoid immortal time bias. Sex, UFC value at diagnosis, as well as the number of operations, remained independent predictors of VTE.

We also specifically analyzed VTE time in relation to surgery. We were able to look at the surgery date in relation to VTE-positive follow-up visits. From those patients who were treated with at least one surgery, 12 VTEs occurred before and 80 VTEs after surgery. The timing of the VTE's is shown in Figure 4. Fourteen VTE's occurred within 30 days of operation, 18 within 60-days, 24 within 90-days of operation. Of note, nearly half of VTE's occurred in the 6 months' time after operation (36; 45%). Overall VTE timings postsurgery are shown on a Kaplan-Meier curve for men and women (Figure 5).

The mean time from the initial diagnosis of CS to the first VTE was 998.7 days (2.73 years). For adrenal CS it was 881.6 days (2.41 years), for CD 1064.9 days (2.92 years), and ectopic ACTH secretion 549.5 days (1.50 years). Only one patient had VTE diagnosis before the diagnosis of CS.

When it comes to clinical status at the first follow-up visit where VTE was documented, 61/95 (64.2%) were in remission, 27/95 (28.4%) had active hypercortisolism and for 7/95 (7.4%) the status is unknown. The average duration between the first VTE-positive follow-up visit and the next follow-up visit was 3 months.

In the VTE group, there were 7 patients, who were diagnosed with cancer.

Seven patients died during follow-up, 1 patient died 15 days post VTE, 3 died 2 years following VTE diagnosis and three patients died 8, 11, and 13 years after VTE diagnosis. For the cause of death individual centers were contacted to see

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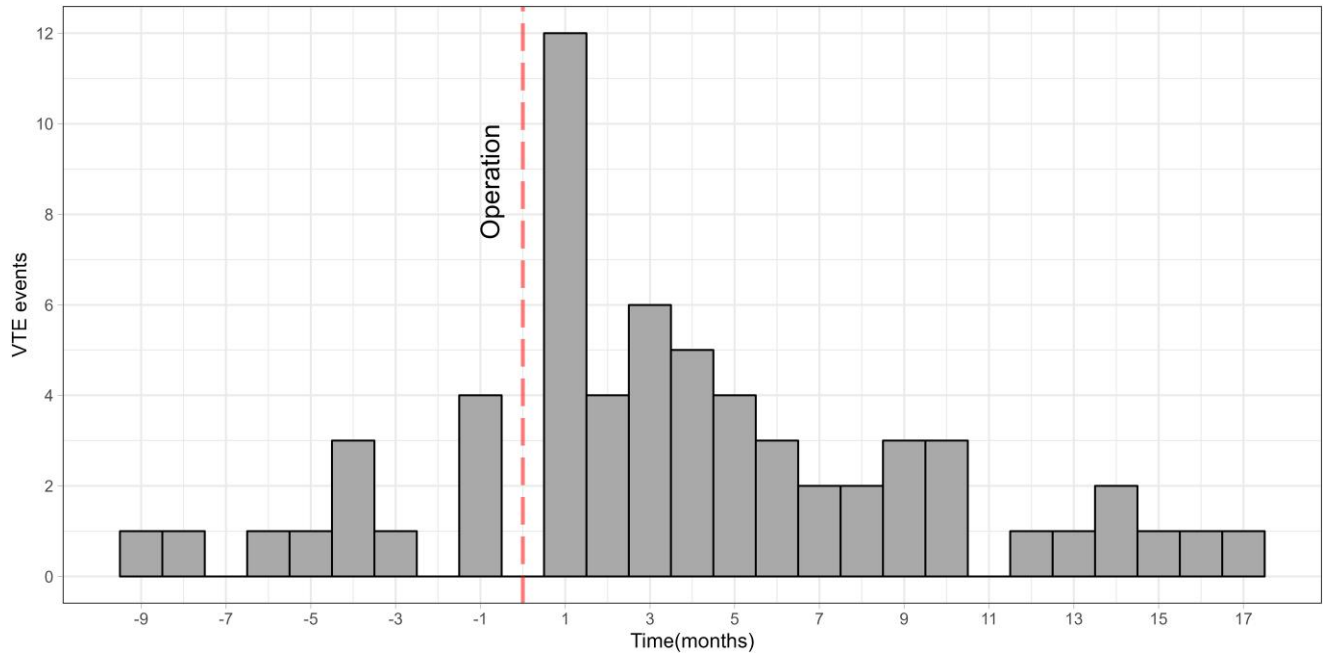
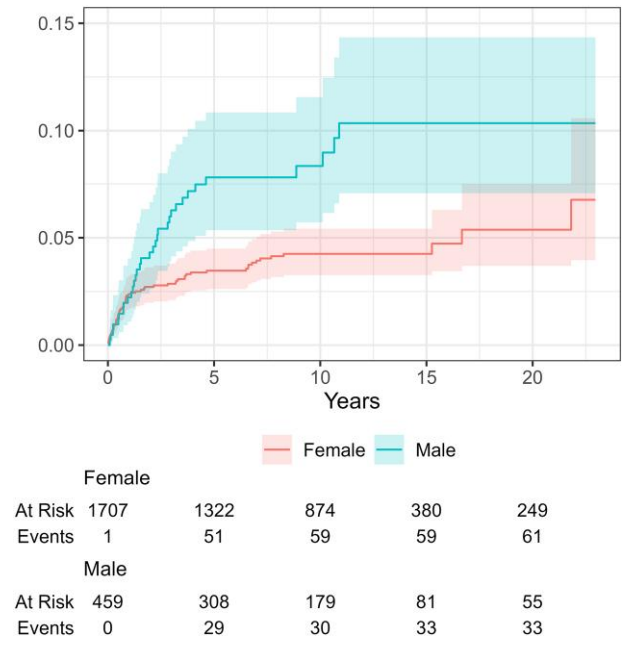


Figure 4. VTE event time in relation to surgery.



Female					
At Risk	1707	1322	874	380	249
Events	1	51	59	59	61
Male					
At Risk	459	308	179	81	55
Events	0	29	30	33	33

Figure 5. A Kaplan-Meier curve showing the cumulative incidence of VTE after the operation.

whether any of these events had a relation to the VTE. One patient died of a fatal PE, and an autopsy confirmed DVT for the second patient. Three patients died of tumor progression, one died of cardiac failure and for one patient the reason for death was not documented.

Additional information concerning VTEs requested from individual centers

Details on VTEs were available for 84/95 (88.4%) patients.

Altogether there were 105 VTE's. One VTE was diagnosed in 69/84 (82.1%) patients, 2 VTE's in 9/84 (10.7%), and 3 VTE's in 6/84 (7.1%). DVT was diagnosed in 50/105 (47.6%) cases, PE in 29/105 (27.6%) cases, other VTE's in 21/105 (20%) cases, and PE/DVT with VTE in uncommon locations or together were diagnosed in 5/105 (4.8%) cases.

At the time of the VTE, 30.4% were anticoagulated and 69.6% were not anticoagulated. Most commonly, low-molecular-weight heparin (LMWH) was used (68%), other medications used were vitamin-K antagonist (VKA) (24%) and Xa-inhibitor 8%. Following the VTE 93.4% were anticoagulated, and the agent used varied widely: 41% received VKA, 34.6% LMWH, 21.8% Xa inhibitor, and 2.6% aspirin. Compression stockings were used in 50.9% of the VTE cases and they were always used together with medical thromboprophylaxis. The duration of anticoagulation varied from 2 weeks to lifelong. In 13.7% of cases, the duration was three months, in 24.1% the duration was 6 months, in 3.2% 12 months and 40% thromboprophylaxis was continued lifelong. In 19% of the cases the duration was variable suggesting that there was no clear guidance on the duration of thromboprophylaxis given or the patient was lost to follow-up.

Centers routine thromboprophylaxis schemes

VTEs were reported by 28 centers of which 26 returned the survey. The results are summarized in Table 3.

Looking at the center's routine thromboprophylaxis protocols, less than half (12/26, 46.2%) anticoagulated on a routine basis. Of the centers that did anticoagulate 1/12 anticoagulated only pituitary CS, 3/12 both pituitary and ectopic sources of CS, and 8/12 anticoagulated all CS patients, regardless of the etiology.

Anticoagulation schemes varied as far as initiation, duration of thromboprophylaxis, and agent used. Looking at the schemes 29.1% anticoagulated perioperatively, 25% after confirmation of the diagnosis of CS, and 45.9% only in particular situations: high-risk patients, depending on comorbidities, only cancer patients, following VTE or if medical therapy for hypercortisolism was started. The duration of routine thromboprophylaxis reported by 17 centers also varied

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Table 3. Thromboprophylaxis protocols in ERCUSYN centers with VTE-positive cases.

	Number of patients (percentage)
Routine anticoagulation (Total = 26)	
YES	12 (46.2%)
NO	14 (53.8%)
Centers that provide thromboprophylaxis (Total = 12)	
Etiology	
Pituitary source	1 (8.3%)
Pituitary + ectopic	3 (25%)
All	8 (66.7%)
Timing of the thromboprophylaxis (Total = 12)	
Perioperatively	4 (29.1%)
After confirmation of hypercortisolaemia	3 (25%)
Particular situations[a]	9 (49.5%)
Duration (Reported by 17 centers)	
Short-term (up to 3 months)	7 (41.2%)
Long-term (over 3 months)	4 (23.5%)
Individual	6 (35.3%)
Agent used (Total = 12)	
LMWH	9 (75%)
VKA	2 (16.7%)
Xa-inhibitor	1 (8.3%)

[a]Particular situations: high-risk patients, depending on comorbidities, only cancer patients, following VTE, once medical therapy for hypercortisolism started.

widely: 7/17 anticoagulated short-term (until 3 months), 4/17 long-term (more than three months) and in 6/17 (35.3%) the duration was decided individually for each patient.

In 9/12 of the centers LMWH was used, and less frequently VKA and Xa inhibitors were used.

Discussion

The evaluation and risk stratification for VTEs of patients with CS is key to preventing events, and balancing the risk-benefit of anticoagulation in this population.[18]

Across the ERCUSYN cohort, the prevalence of VTE was 4.4%. This is comparable, albeit a bit lower to previously published data. For example, Stuijver et al. showed in a multicentre cohort study that the incidence rate for VTE'sin CS patients was 14.6 per 1000 person-years (37 VTE's per 473 patients (7.8%)) and Suarez et al. demonstrated in a single-center retrospective study 29 VTE's in 208 CS patients (13.9%).[5,7] At the same time van Zaane presented in a systematic review a preoperative VTE risk varying between 1.9 and 2.5% and postoperative between 0 and 56% for CS patients.[14] Of note, despite the prevalence of VTE, fatality was relatively uncommon, although potentially fatal PE's were observed in 27.6% of the cases.

From the ERCUSYN cohort, we demonstrate that male-gender, number of operations, and UFC values at diagnosis elevate the this for VTE. Males diagnosed with VTE have higher UFC values than women. Giraldi et al. also demonstrate that although CD is more commonly diagnosed in females, males are diagnosed at a younger age, and have higher UFC and ACTH levels. Also, symptoms of hypercortisolaemia are more severe.[19] When looking and people without hypercortisolaemia, the pattern is similar. Yoshikawa et al demonstrate that from COMMAND VTE registry females have more frequently VTEs, but males are younger, more often had prior VTE, and had fewer risk factors for VTE[20]

In the ERCUSYN cohort, we demonstrate that the HR for VTE is 2.18 (95 CI 1.38–3.45) when a reoperation is performed. To our knowledge, this is the first study emphasizing that if reoperating is needed, the risk for VTE rises and therefore thromboprophylaxis needs to be provided perioperatively. Not less importantly, the need for repeat surgery also reflects a recurrent or refractory disease. Active disease per se should be an indication for thromboprophylaxis and the surgical procedure further adds-on the already increased risk.

From our cohort, it is seen that the risk for VTE is the highest 3–6 months postoperation. Increased risk for VTE remains higher for 10 months postsurgery, declining after that to the VTE basal rate.

The high risk for VTE in the postoperative period is related to the surgery itself but also to an acute drop in cortisol levels that occurs in the postoperative period. This could induce a rebound pro-inflammatory response. Similarly, a more aggressive decrease in patients undergoing bilateral adrenalectomy may be associated with higher and prolonged risk of postoperative VTE.[21] We looked VTE's at any timepoint during CS lifespan, but a retrospective multicenter study by Stuijver et al. studied the postoperative risk of VTE, defined as risk within 3 months after surgery and it was 0% for ACTH-independent and 3.4% for ACTH dependent CS.

We were able to demonstrate that hypertension is associated with higher VTE incidence on univariate analysis but when included in multivariate Cox regression analysis, hypertension was not a significant predictor of VTE. This association has been studied in previous studies for non-CS patients and in most of these studies it has not been proved that hypertension would be an independent risk factor.[22,23] In contrast, when hypertension was looked at a risk factor for VTE after orthopedic surgery, Huang et al. demonstrated in a meta-analysis that hypertension may provoke DVT after orthopedic surgeries.[24]

Interestingly, we could not demonstrate that being overweight or obese was an additional risk factor, as patients with and without a diagnosis of VTE had similar BMI distributions. In both groups, more than 3 quarters of patients were either overweight or obese.

It is clear that ectopic CS has a higher prevalence of VTE,[23] and our study also confirmed it. As ectopic CS is considered a malignancy itself, the risk for VTE is significantly higher.

Slightly less than half of the patients had high cortisol levels at the time of VTE (44.2%), 46.2% had "normal" cortisol levels and only 9.6% had "low". Although these data were only available for half of the patients, it suggests that the extent of hypercortisolaemia may have a role in the incidence of VTE. Nevertheless, more than half of the venous thrombotic events occurred when the cortisol levels were either normal or low. It is in line with previously published data and a meta-analysis by Wagner et al.[13,25] When we were looking at UFC at the time of the diagnosis of CS, CS patients diagnosed with VTE had higher values of UFC when presenting for the first time compared to CS patients without VTE diagnosis.

From our cohort, the VTE's occurred until 10 years after the diagnosis of CS. In contrast to hypercortisolaemia, there are several risk factors that further elevate the risk and are at least partly responsible for those VTEs that occurr long after treating hypercholesterolemia itself. For example, Wagner et al. suggest older age (over 70 years), diagnosis of malignancy,

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and acute infection.[13] These factors are VTE risk factors per se and there is a possibility that these VTE events occurring long after treating hypercortisolaemia are not connected to the pervious CS diagnosis. Suarez et al. in their Single-Centre retrospective study also had 13.51% thrombotic events occurring more than 3 years postsurgery.[7] Both of these studies tried to look at risk factors such as age, sex, smoking, DM and found no statistically significant correlation. Wagner et al also looked at hypertension and estrogen/testosterone usage and found no higher risk for VTEs.

There is a considerable debate on how CS patients should be anticoagulated as there are no uniformly used thromboprophylaxis protocols available. The most recent consensus statement by the Pituitary Society also stresses the fact that there is no standard practice for preoperative or postoperative thromboprophylaxis. The consensus statement recommends anticoagulation of patients at risk for VTE, ie, with a history of embolism and abnormal coagulation testing, severe preoperative hypercortisolism, the current use of estrogen or oral contraceptives, poor mobility, extended hospital stay, high postoperative cortisol levels or cortisol over-replacement in patients with adrenal insufficiency.[26] In this ERCUSYN VTE cohort males, presenting with high UFC values and/or needing multiple surgeries were at higher risk for VTE and are worth being considered for more intensive anticoagulation protocols. In addition to our findings, the risk factors highlighted by the consensus statement should be taken into account.

When considering anticoagulant therapy, it is also crucial to evaluate the risk of bleeding. In a meta-analysis of thromboprophylaxis in neurosurgery for brain tumors, the risk was slightly elevated but for minor hemorrhages.[25,27] In the Endo-ERN group Van Haalen et al. suggest that the bleeding tendency in CS may be only theoretical, as no increased bleeding complications were found in patients with CS undergoing laparoscopic adrenalectomy.[28] Nevertheless, the risk for potential bleeding complications must be carefully balanced for each patient when initiating anticoagulation.

When patients were diagnosed with VTE less than half were anticoagulated. It may be due to the fact that clinicians do not rely on clear guidelines. As these VTEs occurred at any timepoint, it is understandable that the patients were not anticoagulated, because CS per se is not an indicator of the need for lifelong thromboprophylaxis but is crucial during a certain period. Following the VTE event thromboprophylaxis schemes varied widely as far as duration and agent used.

We mapped the thromboprophylaxis protocols that were used by ERCUSYN centers that reported VTE events. Similar mapping has been carried out recently across reference centers of the European Reference Network on rare endocrine conditions (Endo-ERN) and across the Society for Endocrinology as an audit.[15,16]

We had a very good response rate to our survey (25/28; 93%), this is the best response rate compared to two other similar surveys. The Society for Endocrinology recent audit had a response rate of 39% and the Endo-ERN primary survey was completed by 78% and the secondary survey by 62%.[15,16] Of note, we only surveyed ERCUSYN centers where a VTE had been diagnosed on a CS patient.

Across Endo-ERN, routine thromboprophylaxis is performed in 74% of centers, followed by the Society for Endocrinology centers (48%), and across ERCUSYN 46% of the centers provide routine thromboprophylaxis. These data together demonstrate the varying standards of care for these patients in the different participating centers at present, and would appear to justify a prospective study to obtain more evidence as to the best management. There is significant room for improvement across Europe. The timing of anticoagulation and duration were extremely variable in all these3 studies showing that there are no uniformly available guidelines on anticoagulation that could orientate physicians. It is crucial that a new consensus statement would provide a clear protocol for thromboprophylaxis. Looking at the agents used for thromboprophylaxis, LMWH is the most commonly used. This finding is controversial and should be reviewed critically as both American Society of Haematology and NICE (National Institute for Health and Care Excellence) latest guidelines on VTE treatment and thromboprophylaxis recommend to use of DOAC (direct oral anticoagulants) as a first choice.[29,30] Using DOAC rather than LMWH as a thromboprophylactic agent is more convenient for the patient and has a good cost-effective. Mechanical thromboprophylaxis (stockings) was routinely described in 36% of Endo-ERN centers and in 26% of Society for Endocrinology centers. Following VTE, 50.9% ERCUSYN centers prescribed compression stockings.[15,16]

A guideline may establish the optimal timing to outweigh the risk of bleeding and benefits of thromboprophylaxis.

Limitations and strengths of this study

Limitations

In this study we were able to analyze VTEs reported at follow-up visits, therefore, these are not exact VTE dates but refer to a short time period during which the VTE occurred.

Although at each follow-up visits, there is a question on whether any VTE event occurred since the previous follow-up and a thorough data quality control was carried out, we cannot exclude the possibility that some of the VTEs were not reported and therefore missed, especially in countries where fewer VTEs were reported. However, when planning this VTE analysis, a specific mail was sent to all participants who were asked to complete an additional file with the VTE details.

To study thromboprophylaxis protocols, a questionnaire was only sent to those centers where a VTE had been reported. Therefore it only gives information about some centers and does not mirror the thromboprophylaxis schemes for all ERCUSYN centers.

Strengths

This is the largest cohort-based study looking at VTE's in CS patients, where we were able to look at 95 VTE cases in detail and had a large control-group from patients included in the ERCUSYN but not diagnosed with VTE. We were able to show new factors elevating the risk for VTE.

Conclusion

We report a high VTE rate in CS patients within ERCUSYN. The prevalence of VTE in patients with CS is comparable to previous studies performed on smaller cohorts.

From the ERCUSYN cohort, patients have a greater risk for VTE if they are male, need multiple surgeries, and/or have high UFC at the time of diagnosis of CS.

Most patients were not anticoagulated at the time of the event but were put on anticoagulation following VTE.

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There are no uniformly used thromboprophylaxis protocols in centers that reported VTEs. Thus, there is an urgent need to develop clear guidelines for patients, since only then can physicians provide high-quality treatment options for their patients and minimize the risk for VTE.

To our knowledge, this is the largest registry-based study to date looking at VTE in CS patients.

Acknowledgments

We are truly grateful to the ERCUSYN Study Group: C Amaral, Centro Hospitalar do Porto-Hospital Santo António; A Ambrogio, Istituto Auxologico Italiano IRCCS, University of Milan, Italy; G Aranda, Department of Endocrinology, Hospital Clinic Barcelona, IDIBAPS, UB, Barcelona, Spain; M Arosio, Unit of Endocrine Diseases & Diabetology, Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy; M Balomenaki, Evangelismos Hospital, Athens, Greece; P Beck-Peccoz, Endocrinology and Diabetology Unit, Fondazione IRCCS Ca" Granda—Ospedale Maggiore Policlinico, University of Milan, Milan, Italy; C Berr-Kirmair, Medizinische Klinik und Poliklinik IV, Campus Innestadt, Klinikum der Universität München, München, Germany; J Bertherat, Hôpital Cochin; M. Bolanowski, Wroclaw Medical University, Wroclaw, Poland; J Bollerslev, Section of Specialized Endocrinology, Oslo University Hospital, and Faculty of Medicine, University in Oslo, Oslo, Norway; Brue Thierry, Association pour le Devéloppement des Recherches Biologiques et Médicales; H Cardoso, Centro Hospitalar do Porto-Hospital Santo António; D Carvalho, Hospital de San Joao, Porto, Portugal; F Cavagnini, Istituto Auxologico Italiano IRCCS, Milan, Italy; P Ceccato, Endocrinology Unit, University-Hospital of Padova; O Chabre, Hospitalier Universitaire, Grenoble, France; P Chanson, Univ Paris-Sud, Université Paris-Saclay UMR-S1185, Le Kremlin Bicêtre, Paris, France, Assistance Publique-Hôpitaux de Paris, Hôpital de Bicêtre, Service de Endocrinologie et des Maladies de la Reproduction, Le Kremlin Bicêtre, Paris, France; E Christ, University Hospital of Bern, Inelspital, Division of Endocrinology, Diabetology and Clinical Nutrition, Bern, Switzerland; F Demtröder Zentrum fur Endokrinologie, Diabetologie, Rheumatologie Dr Demtröder & Kollegen im MVZ Dr. Eberhard & Partner und Klinikum Dortmund, Germany; J Denes, Division of Endocrinology, 2nd Department of Medicine, State Health Center, Budapest, Hungary; T Deutschbein, Medicover Oldenburg MVZ; C Dimopoulou, Max-Planck-Gessellschaft zur Forderung der Wissenschaften e.V., Munich, Germany; A Dreval, Moscow Regional Research Clinical Institute n.a. Vladimirsky, Moscow, Russia; M Droste, Praxis für Endokrinologie Droste, Oldenburg, Germany; JS Duarte, Serviço Endocrinologia CHLO, Hospital Egas Moniz; T Dusek, Department of Endocrinology, University Hospital Zagreb, School of Medicine University of Zagreb, Kispaticeva 12, 10000 Zagreb, Croatia; E Ertürk, Uludag University School of Medicine, Bursa, Turkey; J A Evang, Section of Specialized Endocrinology, Oslo University Hospital, and Faculty of Medicine, Oslo University in Oslo, Oslo, Norway; C Fajardo, Hospital Universitario de la Ribera, Alzira, Spain; J Fazel, Medizinische Klinik und Poliklinik IV, Campus Innestadt, Klinikum der Universität München, München, Germany; RA Feelders, Erasmus University Medical Centre, Rotterdam, The Netherlands; S Fica, Elias Hospital, Bucharest, Romania; R García-Centeno, Hospital General Universitario Gregorio Marañon; E Ghigo, Molinette Hospital, Department of Internal Medicine, Turin, Italy; M Goth, Division of Endocrinology, 2nd Department of Medicine, State Health Center, Budapest, Hungary; Y Greenman, Institute of Endocrinology, Metabolism and hypertension, Tel Aviv, Israel; I Halperin, Department of Endocrinology, Hospital Clinic Barcelona, IDIBAPS, UB, Barcelona, Spain; FA Hanzu, Department of Endocrinology, Hospital Clinic Barcelona, IDIBAPS, UB, Barcelona, Spain; A Hermus, Radboud University Medical Center, Nijmegen The Netherlands; G Johannsson, Goteborg University, Goteborg, Sweden; E Hubina, Division of Endocrinology, 2nd Department of Medicine, State Health Center, Budapest, Hungary; P Kamenicky, Univ Paris-Sud, Université Paris-Saclay UMR-S1185, Le Kremlin Bicêtre, Paris F-94276, France, Assistance Publique-Hôpitaux de Paris, Hôpital de Bicêtre, Service de Endocrinologie et des Maladies de la Reproduction, Le Kremlin Bicêtre, Paris, F-94275, Institut National de la Santé et de la Recherche Médicale U1185, Le Kremlin Bicêtre, Paris F-94276, France; A Kasperlik-Zaluska, Centre for Postgraduate Medical Education, Warsaw, Poland; J Kirchner, Division of Clinical Endocrinology, Department of Medicine CCM, Charité-Universitätsmedizin, Berlin, Germany; D Kastelan, Department of Endocrinology, University Hospital Zagreb, Kispaticeva 12, 10000 Zagreb, Croatia; I Komerdus, Moscow Regional Research Clinical Institute n.a. Vladimirsky, Moscow, Russia; I Kraljevic, Department of Endocrinology, University Hospital Zagreb, Kispaticeva 12, 10000 Zagreb, Croatia; M Krsek, 2nd Department of Medicine3rd Faculty of Medicine, Charles University and University Hospital Kralovske Vinohrady, Prague, Czech Republic; A Kruszynska, Centre for Postgraduate Medical Education, Warsaw, Poland; C Lamas, Endocrinology and Nutrition Department, Complejo Hospitalario Universitario de Albacete, Albacete, Spain; I Lambrescu, Elias Hospital, Bucharest, Romania; S Lang, Max-Planck-Gessellschaft zur Forderung der Wissenschaften e.V., Munich, Germany; A Luger, Medizinische Universitat Wien, Wien, Austria; D Maiter, UCL Cliniques Universitaires St Luc, Brussels, Belgium; N Marpole, Christie Hospital, NHS Trust, Manchester, UK; S Martin, Elias Hospital, Bucharest, Romania; M Martinie, Service d'Endocrinologie-Diabétologie-Nutrition, Grenoble Cedex, France; MJ Martins Oliveira, Centro Hospitalar Vila Nova Gaia/Espinho; O Moros, Zentrum fur Endokrinologie, Diabetologie, Rheumatologie Dr Demtröder & Kollegen im MVZ Dr. Eberhard & Partner und Klinikum Dortmund; R Netea-Maier, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands; J Newell-Price, The University of Sheffield, Sheffield, UK; M Orbetzova, Clinic of Endocrinology and Metabolic Diseases, "Sv.Georgy" University Hospital, Medical University, Plovdiv, Bulgaria; I Paiva, Hospitais da Universidade de Coimbra; F Pecori Giraldi, Istituto Auxologico Italiano IRCCS, University of Milan, Italy; JC Percovich, Hospital General Universitario Gregorio Marañon; AM Pereira, Leiden University Medical Center, Leiden, The Netherlands; M Pfeiffer, Klinicni Center, Ljubljana, Slovenia; J Pickel, Max-Planck-Gessellschaft zur Forderung der Wissenschaften e.V., Munich, Germany; V Pirags, Pauls Stradiņš Clinical University Hospital, University of Latvia, Riga, Latvia; O Ragnarsson, Goteborg University, Goteborg, Sweden; AD Reghina, Elias Hospital, Bucharest, Romania; M Reincke, Medizinische Klinik und Poliklinik IV, Campus Innestadt, Klinikum der Universität München, Ludwig-Maximilians-Universität München, Munich, Germany; P Riesgo, Neurosurgery Department, Hospital Universitario de la Ribera, Alzira, Spain; M Roberts, Christie Hospital, NHS

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Trust, Manchester, UK; S Roerink, Radboud University Medical Center, Nijmegen The Netherlands; C Rowan, Christie Hospital, NHS Trust, Manchester, UK; P Rudenko, Estonian Endocrine Society, Tallinn, Estonia; MA Sahnoun, Aix-Marseille Université, CNRS, CRN2M UMR 7286, 13344 cedex 15, Marseille, and APHM, Hôpital Conception, Marseille, France; J Salvador, University of Navarra, Pamplona, Spain; A Santos, IIB-Sant Pau, Department of Endocrinology/Medicine, Hospital Sant Pau, UAB, Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBER-ER, Unidad 747), ISCIII, Barcelona, Spain; C Scaroni, Endocrinology Unit, University-Hospital of Padova; HA Sigurjonsdottir, Landspitali University Hospital, Reykjavik, Iceland and Faculty of Medicine, University of Iceland, Reykjavik, Iceland; T Skoric Polovina, Department of Endocrinology, University Hospital Zagreb, Kispaticeva 12, 10000 Zagreb, Croatia; R Smith, Oxford Radcliffe Hospitals NHS Trust, Oxford, UK; B Stachowska, Department of Endocrinology, Diabetology and Isotope Therapy Wroclaw Medical University, Wroclaw, Poland; G Stalla, Max-Planck-Gessellschaft zur Forderung der Wissenschaften e.V., Munich, Germany; C Strasburger, Division of Clinical Endocrinology, Department of Medicine CCM, Charité-Universitätsmedizin, Berlin, Germany; A Tabarin, Department of Endocrinology, Diabetes and Nutrition, University of Bordeaux, Bordeaux, France; M Terzolo, Internal Medicine—Endocrinology, San Luigi Hospital; J Tőke, 2nd Departement of Medicine, Semmelweis University, Budapest, Hungary; M Tóth, 2nd Department of Medicine, Semmelweis University, Budapest, Hungary; P Touraine, GH Pitie Salpetriere—Dep. of endocrinology and repr. med.; PJ Trainer, Department of Endocrinology, Christie Hospital, Manchester, UK; S Tsagarakis, Athens Polyclinic General Hospital & Evangelismos Hospital, Athens, Greece; E Valassi, Department of Endocrinology, Hospital Germans Trias i Pujol, Badalona, Spain, CIBERER Unit 747, ISCIII, Madrid, Spain; G Vila, Medizinische Universitat Wien, Wien, Austria; S Vinay, Christie Hospital, NHS Trust, Manchester, UK; M Wagenmakers, Radboud University Medical Center, Nijmegen The Netherlands; SWebb, IIB-Sant Pau, Department of Endocrinology/Medicine, Hospital Sant Pau, UAB, Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBER-ER, Unidad 747), ISCIII, Barcelona, Spain; S Werner, Praxis für Endokrinologie Droste, Oldenburg, Germany; J Young, Univ Paris-Sud, Université Paris-Saclay UMR-S1185, Le Kremlin Bicêtre, Paris F-94276, France, Assistance Publique-Hôpitaux de Paris, Hôpital de Bicêtre, Service de Endocrinologie et des Maladies de la Reproduction, Le Kremlin Bicêtre, Paris, F-94275, Institut National de la Santé et de la Recherche Médicale U1185, Le Kremlin Bicêtre, Paris F-94276, France; P Zdunowski, Centre for Postgraduate Medical Education, Warsaw, Poland; S Zacharieva, Medical University of Sofia, Sofia, Bulgary; K Zopf, Division of Clinical Endocrinology, Department of Medicine CCM, Charité- Universitätsmedizin, Berlin, Germany; S Zopp, Medizinische Klinik und Poliklinik IV, Campus Innestadt, Klinikum der Universität München, München, Germany; I Zosin, Romanian Society for Endocrinology, Timisoara, Romania.

Funding

ERCUSYN was set up with funding from the EU (PHP 800200) and has been supported by unrestricted grants from Novartis, Ipsen, HRA, and the European Society of Endocrinology. For the VTE-data extraction the funding came from the University of Tartu (Ülikooli 18, Tartu, Estonia).

Conflict of interest: None declared.

Authors' contributions

Kristina Isand (Formal analysis-Equal, Writing—original draft-Lead), Richard Feelders (Data curation-Equal), Thierry Brue (Data curation-Equal), Miklos Toth (Data curation-Equal), Timo Deutschbein (Data curation-Equal), Martin Reincke (Data curation-Equal), Michal Kršek (Data curation-Equal), Alicia Santos (Data curation-Equal, Project administration-Equal), Frank Demtröder (Data curation-Equal), Olivier Chabre (Data curation-Equal), Christian Strasburger (Data curation-Equal), Anna Aulinas (Formal analysis-Equal, Methodology-Equal, Writing—review & editing-Equal), Vallo Volke (Supervision-Equal), Alberto Pereira Arias (Supervision-Equal, Writing—review & editing-Equal), Ruediger Lohmann (Data curation-Equal), IGNASI GICH SALADICH (Methodology-Equal), Susan Webb (Project administration-Equal, Supervision-Equal, Writing—review & editing-Equal), John Wass (Project administration-Equal, Supervision-Equal, Writing—review & editing-Equal), and Elena Valassi (Data curation-Equal, Formal analysis-Equal, Methodology-Equal, Project administration-Equal, Supervision-Equal, Writing—review & editing-Equal)

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