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Delphi Panel consensus on recommendations for thromboprophylaxis of venous thromboembolism in endogenous Cushing's syndrome: a Position Statement

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Conflict of interest (COI):

1. Maria Fleseriu has been a PI with research funding to the University from Crinetics and Sparrow and has received occasional scientific consulting fee from Crinetics, Recordati, Sparrow, and Xeris
2. Monica Gadelha: MG has received speaker fees from Recordati and attended advisory boards for Recordati.
3. Martin Reincke has received speaker and consulting fees from Crinetics, Recordati, HRA Pharma, Damian
4. John Newell-Price has had consultancy fees paid to his University from Crinetics, Recordati, HRA Pharma, and Diurnal
5. Niki Karavitaki: Speaker for Pfzer, HRA Pharma, Recordati Rare Diseases - Investigator for HRA Pharma - Scientific Advisory Board for Pfizer, Recordati Rare Diseases
6. Ann McCormack has received speaker and advisory board consulting fees from Recordati, Novo Nordisk.

Abbreviations:

CS-Cushing's syndrome
VTE-venous thromboembolism
IPSS- inferial petrosus sinus sampling
MACS-mild autonomous cortisol secretion
ACTH- Adrenocorticotropic hormone
LMWH-low-molecular weight heparin
DOAC- direct oral anticoagulant
CI- Confidence interval
HR-hazard ratio
UFC -24-hour urinary-free cortisol
aPTT-activated partial thromboplastic time
ERCUSYN-European Registry on Cushing's syndrome
Endo-ERN- European Reference Networks for Rare Endocrine Conditions
SfE- Society for Endocrinology
EuRRECa - European Registries for Rare Endocrine Conditions

CD-Cushing's Disease
vWF-von Willebrand factor
PE- pulmonary embolism
DVT- deep venous thrombosis
GCS- graduated compression stockings
BMI-Body mass index
ULN-upper limit of normal
TSA-transsphenoidal adenectomy
NICE- The National Institute for Health and Care Excellence

ABSTRACT

Objective:

To establish recommendations for thromboprophylaxis in patients with endogenous Cushing's syndrome (CS), addressing the elevated risk of venous thromboembolism (VTE) associated with hypercortisolism.

Methods:

A Delphi method was used, consisting of four rounds of voting and subsequent discussions. The panel included 18 international experts from 11 countries and 4 continents.
Consensus was defined as ≥75% agreement among participants. Recommendations were structured into the following categories: thromboprophylaxis, perioperative management, and VTE treatment.

Results:

Consensus was reached on several critical areas, resulting in 14 recommendations. Key recommendations include: thromboprophylaxis should be considered at time of CS diagnosis and continued for three months after biochemical remission, provided there are no obvious contraindications. The standard weight-based prophylactic dose of low molecular weight heparin is the preferred agent for thromboprophylaxis in patients with CS. Additionally, perioperatively and around inferior petrosal sinus sampling, thromboprophylaxis should be reconsidered if not already initiated at diagnosis. For VTE treatment, extended thromboprophylaxis is advised continuing for three months after Cushing is resolved.

Conclusion:

These Delphi consensus-based recommendations aim to standardise care practices and enhance patient outcomes in CS by providing guidance on thromboprophylaxis, including its initiation and continuation across various disease states, as well as the preferred agents to use. The panel also highlighted key areas for further research, particularly regarding the use of direct oral anticoagulants in CS and the management of mild CS and mild autonomous cortisol secretion. Additionally, the optimal duration of anticoagulant prophylaxis following curative treatment remains uncertain.

Key words: Cushing's syndrome, thromboprophylaxis, venous thromboembolism, perioperative, remission, low molecular weight heparin, pituitary, adrenal, ACTH, cortisol, position statement

Significance:

This document represents the first position statement on thromboprophylaxis for patients with endogenous Cushing's syndrome (CS). Prior to this, there has been a significant gap in guidance, leading to considerable heterogeneity in clinical practice. This statement provides recommendations on the initiation of thromboprophylaxis at the time of CS diagnosis, during the perioperative period, and in case of diagnosis of venous thromboembolism (VTE). Implementing these guidelines is expected to reduce the incidence of VTE in this high-risk population. The position statement will be updated every 3-5 years dependent on new evidence as it emerges.

Background

CS definition

Endogenous Cushing's syndrome (CS) is an endocrine condition characterised by prolonged exposure to elevated levels of cortisol, leading to significant morbidity and mortality[1].
Cushing disease is the underlying cause in approximately 60% to 70% of patients, corticotropin-independent adrenal production of cortisol is the underlying cause in approximately 20% to 30% of patients, and ectopic paraneoplastic neuroendocrine tumours that secrete corticotropin account for 6% to 10% of patients [2].

Elevated risk for VTE in patients with CS

Patients with CS have a higher risk of thromboembolic events due to the hypercoagulable state induced by excessive cortisol levels [3]. Several studies have assessed this increased risk based on epidemiological data. A Dutch nationwide cohort study reported an overall incidence of VTE in patients with CS of 14.6 (95% CI 10.3-20.1) per 1000 person-years (vs 1-2 in the general population). Within this cohort the incidence rate for VTE prior to treatment was 14.1 (95% CI 8.5–22.0) per 1000 person-years. The risk of postoperative VTE, defined as risk within 3 months

after surgery, in this study was 3.4% (95% CI 2.0 –5.9) for ACTH dependent CS [4].
Babic et al reported in their retrospective analysis the risk for VTE being 2.6% after adrenalectomy for CS[5]. A population-based cohort study including the entire population of Denmark (1980 to 2010) demonstrated a hazard ratio (HR) of 2.6 (95%CI 1.5– 4.7) for patients with CS to be diagnosed with VTE compared to the general population. Intriguingly, the increased risk was already present three years before the diagnosis of CS. The risk for VTE was markedly increased during the year after diagnosis (HR 20.6, 95% CI 7.8 –53.9), suggesting an additional risk from surgery [6]. A Swedish Nationwide study also reported an elevated risk for VTE compared to the general population [7]. During the three years before diagnosis, standardised incidence ratio (SIR) for deep vein thrombosis (DVT) was 13.8 (CI 3.8 to 35.3), which increased from diagnosis to 1 year after remission to 18.3 (CI 7.9 to 36.0), and remained increased during long-term remission (4.9 (CI 2.6 to 8.4) [7]. A meta-analysis of available cohort studies confirmed that patients with CS have a markedly increased risk of VTE, with an odds ratio of 17.8 thirty days after surgery compared to the general population [8].
In a recent systematic review the pooled postoperative VTE incidence in patients after transsphenoidal surgery for CD was 2%[9].

Mechanisms behind the elevated risk for VTE

Mechanisms that are involved in the thromboembolic complications of hypercortisolism include endothelial dysfunction, hypercoagulability, and stasis (Virchow's triad)[10]. The hypercoagulable state in CS (reflected by a decreased activated partial thromboplastic time (aPTT) in some patients) with heightened VTE risk is attributable to various factors including increased levels of coagulation factors, such as von Willebrand factor and Factor VIII, and impaired fibrinolytic activity[11] [12]. A hypercoagulable phenotype seems to persist even after surgical remission, further stressing the necessity for vigilant

thromboprophylaxis [13]. Remarkably, most studies do not demonstrate a relation between severity of hypercortisolism, according to UFC values, and risk on VTE[8].

The need for clear guidance for providing thromboprophylaxis

Although the increased risk of VTE in patients with CS is clear, translating these data into clinical practice guidelines remains challenging [13][14]. Several surveys have been conducted to assess thromboprophylaxis practices for patients with CS. A 2013 survey by the Pituitary Society revealed that the use of thromboprophylaxis was neither routine nor standardised[15]. Even a decade later, recent surveys from the Society for Endocrinology (SfE), European Registry on Cushing's syndrome (ERCUSYN), and the European Reference Network on Rare Endocrine Conditions (Endo-ERN) report similar findings, highlighting significant heterogeneity in thromboprophylaxis protocols[16], [17], [18]. The recommendations in this position statement aim to standardise care practices and improve patient outcomes by mitigating the risk of VTE in patients with CS.

Methods

Participants

The experts were identified by their recognised clinical and research activity for the care of patients with CS, aiming to create a global panel involved in the diagnosis and treatment of patients with CS. The experts were from the following countries: the Netherlands, the United Kingdom, the USA, Australia, Japan, Brazil, Mexico, Spain, France, Germany, and Estonia. The panel consisted of 14 endocrinologists, 1 haematologist, 1 vascular medicine specialist, 1 methodologist-endocrinologist, and 1 neurosurgeon. Ethical approval was deemed unnecessary as there was no involvement of individual patient data. The research complied with the Declaration of Helsinki.

Consensus formation

The consensus process involved preparing and testing consensus questions, followed by iterative rounds of feedback and modifications. A Delphi method, consisting of four rounds, was used to reach a consensus[1]. Consensus was defined as >75% agreement (Likert scale 4-5). Consensus questions were prepared by three endocrinologists (KI, JW, AMP), reviewed by the methodologist (OMD), and sent to three endocrinologists to pilot before being distributed to the panel of experts. An online platform, Calibrum, was used for voting. The first round was sent out in March, 2024, and the fourth and final round were completed July 2024.

The first round comprised multiple-choice questions, while the subsequent rounds involved statements where panellists could select their responses on a 5-point Likert scale (1-Strongly Disagree, 2-Disagree, 3-Neutral, 4-Agree, 5-Strongly Agree). For the fourth round, the scale was modified by removing the "Neutral" option to get a clearer view of the panellists' opinions. After the 1st and 3rd Delphi rounds, there was a virtual meeting with the panel of experts; after the 2nd round, there was a hybrid (in-person and virtual) discussion; and after the last round, no discussion was held as only two statements were left, and there was a strong agreement regarding these two statements. When a statement was agreed upon by 75% of the experts or more, consensus was considered reached, and the statement was removed from further rounds. When consensus was not reached after two rounds or the panel decided to leave it out from further discussion, it was removed from the consensus. Participants were encouraged to comment on each statement to facilitate further dialogue. After each round, the statements were analysed and modified by KI, JW, AMP.

Delphi rounds and organization of the document

Delphi rounds are illustrated in figure 1.

The statements are organized into three sections:

1) initiation of thromboprophylaxis in patients with CS

2) perioperative thromboprophylaxis

3) treatment of venous thromboembolism (VTE)

In addition, for perioperative thromboprophylaxis and thromboprophylaxis related to Inferior Petrosal Sinus Sampling (IPSS), practical *"How to"* examples are provided to guide clinicians. It is crucial to consider each patient's individual health factors and circumstances when applying these recommendations in clinical practice. The main recommendations are summarised in Table 1 and Figure 2.

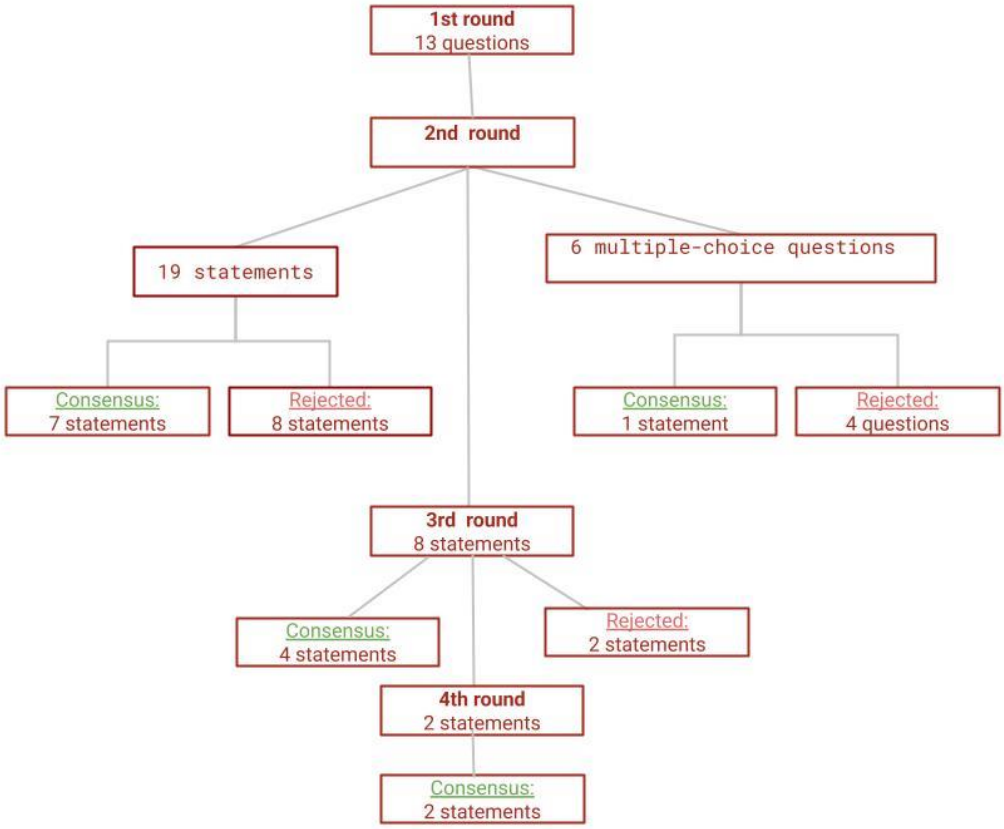

Figure 1: Delphi flowchart

In the first round, there were 13 questions, including multiple-choice and yes/no questions. All 18 panellists voted in the first round. In the second round, there were 19 statements and 6 multiple-choice questions. Eight statements reached consensus (>75%) in the second round. In the second round, 17/18 panellists voted. In the third round, there were eight statements, and four statements reached consensus. Seventeen out of eighteen panellists voted in the third round. The fourth round consisted of two statements, both of which reached consensus. Sixteen out of eighteen experts participated in the fourth round.

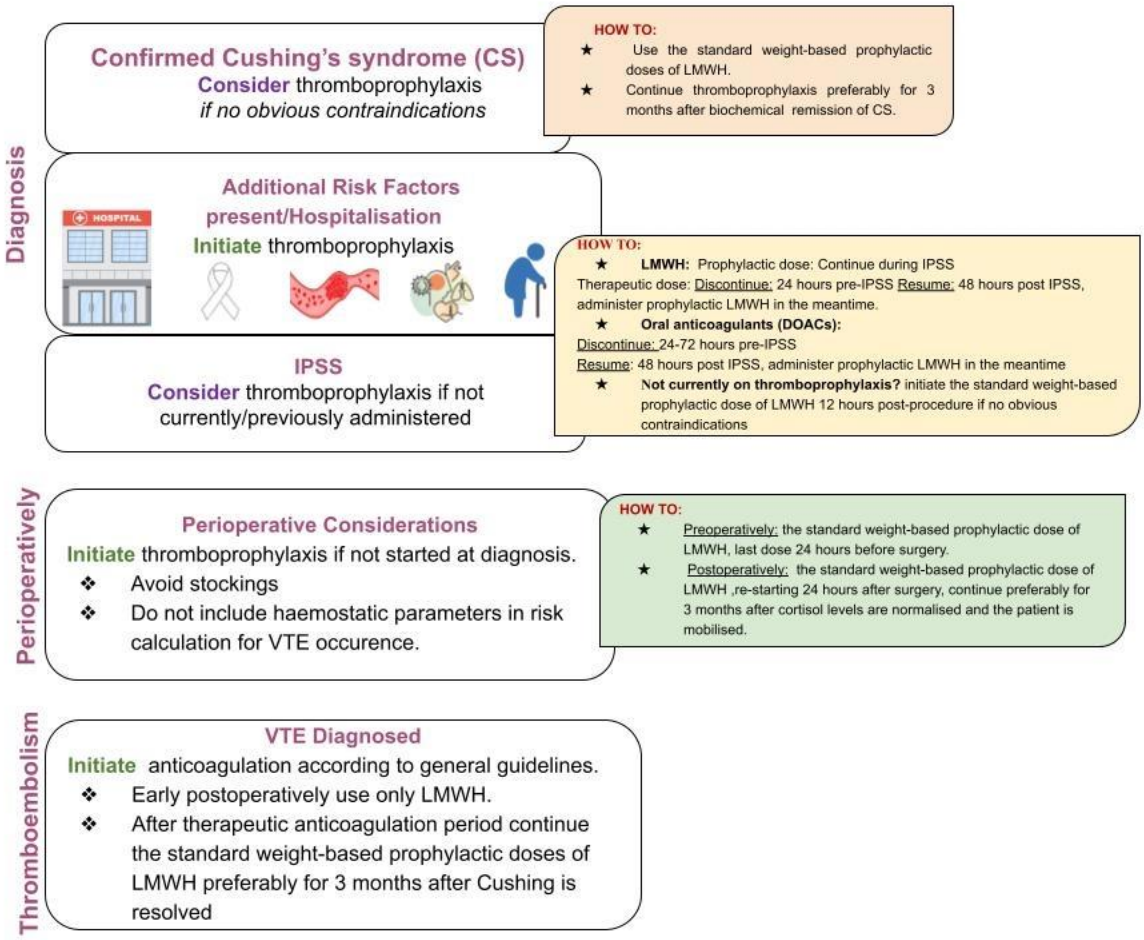

Figure 2: Pocket guide for main summaries

Results

Initiation of thromboprophylaxis for patients with CS

Statement 1

Thromboprophylaxis should be considered for any patient with CS, regardless of the aetiology, in the absence of obvious contraindications.

Comment:

Patients with CS have hypercoagulability, which is associated with an increased risk for VTE.

This statement does not suggest that all patients will inevitably require thromboprophylaxis, but in clinical practice, most patients with CS do unless contraindications are present. The evidence to demonstrate an increased risk for VTE is covered in the background. This recommendation applies to all aetiologies of CS, including pituitary, adrenal, and ectopic ACTH sources[8], [16], [19].

Statement 2

Thromboprophylaxis should start at the time when a definitive CS is diagnosed in the absence of obvious contraindications.

Comment:

If one decides to initiate thromboprophylaxis, it should start at time of definitive CS diagnosis. If a definitive underlying diagnosis is not yet available but the hypercortisolaemia is severe, VTE prophylaxis should however not be delayed[20]. Severe Cushing's syndrome is frequently, but not exclusively, accompanied by random serum cortisol higher than 40 µg/dL (1100 nmol/L), elevation of 24-h urinary free cortisol (UFC) above four- or fivefold the upper limit of normal (ULN) and/or severe hypokalemia (below 3 mmol/L)[20]. Thromboprophylaxis must be carefully considered in patients with severe thrombocytopenia, active bleeding or at high risk of major bleeding, advanced liver disease, heparin-induced thrombocytopenia, or renal failure. Each contraindication requires an individualized assessment to balance the risk of thrombosis and bleeding[21].

Statement 3

Prophylactic anticoagulation in patients with CS should be continued preferably for three months after achieving biochemical remission in the absence of obvious contraindications.

Comment:

It is reasonable that during hypercortisolaemia patients need to be offered thromboprophylaxis, but the appropriate duration of thromboprophylaxis for patients with CS remains uncertain and is therefore a highly important area of research in the near future. The literature varies on the duration of thromboprophylaxis post-biochemical remission. Most authors point out the importance of continuing thromboprophylaxis after achieving biochemical remission, either with a surgical approach or medically [22]. The panel discussed the recommended duration of thromboprophylaxis, which ranged from 1 to 12 months following cure. The majority supported an extended thromboprophylaxis period of 3 months after achieving eucortisolaemia. This recommendation will be updated as new evidence becomes available and the Position Statement is revised.

Looking at the time when VTEs happen, Suarez et al. demonstrated that 40.5% of these occur within the first 60 days after surgery.[23]. In line, data from the ERCUSYN database indicate that the risk is the highest for six months post-surgery [16]. Dekkers et al have shown that the risk for VTE is specifically elevated during three months after surgery [6]. When patients are started on medical therapy, cortisol normalisation is not directly accompanied by complete correction of the hypercoagulable state, which involves both increased production of procoagulant factors and impaired fibrinolysis, suggesting the need for prolonged thromboprophylaxis[24]. A low-grade pro-inflammatory state during the glucocorticoid withdrawal phase can last even for at least one year, also potentially elevating the risk for VTE [25].

Statement 4

Patients with CS who are biochemically controlled on medical therapy and do not have additional risk factors may not require thromboprophylaxis.

Comment:

Patients without additional risk factors (e.g. obesity, immobility, a history of VTE, other cardiovascular risk factors) and well-controlled on medical therapy would be good candidates for stopping thromboprophylaxis[8].

Of note, if patients are treated with mitotane, it is important to notice that mitotane can alter haemostasis, affect liver function and metabolism of coagulation factors, potentially increasing bleeding risk. Therefore, the use of mitotane in combination with LMWH may lead to increased risk of bleeding complications. Managing patients who require both mitotane and anticoagulation therapy necessitates careful monitoring of bleeding risk, renal function, and potential changes in platelet counts . In some cases, dose adjustments for LMWH might be needed.

Statement 5

Hospitalised patients with active CS should receive thromboprophylaxis in the absence of obvious contraindications.

Comments:

Thromboprophylaxis should be initiated in all patients with CS on admission regardless the reason for hospitalisation, and regardless of the biochemical severity of hypercortisolism, in the absence of clear contraindications[12], [22]. Immobilisation, whether due to severe illness, postoperative recovery, or reduced physical activity, exacerbates the risk of VTE in patients with CS [8]. Early mobilisation should be encouraged in parallel with thromboprophylaxis initiation [26].

Statement 6:

Patients with CS should receive thromboprophylaxis when they have at least one of the following risk factors.

Note: This list is not exhaustive, and clinicians may consider additional risks.

Incident Risk Factors
Active malignancy or cancer treatment
Dehydration
Sedentary lifestyle
Smoking
Use of oral oestrogen replacement therapy/oestrogen-containing contraceptive therapy
Pregnancy or less than six weeks postpartum

Prevalent (Chronic/Persistent) Risk Factors
Age over 60 years
Known thrombophilia (inherited or acquired)
Obesity (BMI > 30 kg/m^2)
One or more significant medical comorbidities (e.g., heart disease, endocrine metabolic disorders, pulmonary disorders, acute infectious diseases, inflammatory conditions)
Personal history or first-degree relative with a history of VTE varicose veins with phlebitis

Comments:

Incident risk factors are generally temporary or arise due to a particular event or condition, and they increase the immediate risk of VTE. In contrast, prevalent (chronic/persistent) risk factors which are ongoing or

long-term and are associated with a sustained increased risk of developing VTE over time.

If any of these risks are present, thromboprophylaxis should not be delayed, but the distinction helps to decide if thromboprophylaxis is needed during high-risk periods (incident factors) or managing long-term risks (prevalent factors) [27][28].

Of note, prophylactic anticoagulation throughout pregnancy is generally recommended due to the high thrombotic risk associated with CS, irrespective of cortisol levels.

Statement 7

For patients with CS who have not received thromboprophylaxis in the disease course, it should be reconsidered at the time of inferior petrosal sinus sampling (IPSS).

Comments:

IPSS is an invasive procedure that carries certain risks, including brainstem injury, neurologic complications, and VTE [29][30][31][32]. If a patient with CS was not given thromboprophylaxis, it should be started around the time of IPSS and continued following the procedure to reduce the risk of delayed thromboembolic events.

How to:

- **For patients receiving prophylactic dosed LMWH**: continue during IPSS.
- **For patients receiving therapeutically dosed LMWH:**

Discontinue: 24 hours pre-IPSS

Resume: 48 hours post IPSS, administer prophylactic LMWH in the meantime.

- **For patients on oral anticoagulants (DOACs):**

Discontinue: 24-72 hours pre-IPSS

Resume: 48 hours post IPSS, administer prophylactic LMWH in the meantime

- **For patients not currently on thromboprophylaxis:** If there are no contraindications, initiate the standard weight-based prophylactic dose of LMWH 12 hours post-procedure.

Statement 8

Low molecular weight heparin (LMWH) in the standard weight-based prophylactic doses should be used for thromboprophylaxis in patients with CS.

Comments:

Local physicians should use the standard weight-based prophylactic doses of LMWH as recommended for their countries.

There was a discussion in the panel regarding the use of direct oral anticoagulants (DOACs) as an alternative to LMWH for thromboprophylaxis in patients with CS. The use of DOACs in patients with CS is off-label. At present there are no data to support the safety of DOACs in CS patients indicating a critical area for further studies. One potential concern with DOACs is the higher reported bleeding risk compared to LMWH[33].

Data from routine thromboprophylaxis schemes across centres who provide care for patients with CS, shows that LMWH is considered the first choice[16][18][17].

Statement 9

Antiembolic stockings are not recommended for thromboprophylaxis in patients with CS.

Comments:

The use of graduated compression stockings (GCS) for preventing VTE is a debated topic. Earlier literature suggested that GCS were valuable tools for VTE prevention, but recent findings do not confirm a benefit and rather highlight complications. . The American Society of Haematology guidelines recommend mechanical prophylaxis for hospitalized patients who have contraindications to pharmacological prophylaxis due to bleeding risk[34]. However, in the context of hospital-associated thrombosis, the literature has not demonstrated that GCS reduce the risk of death due to pulmonary embolism (PE). A recently updated systematic review showed no additional benefit for GCS in preventing VTE and VTE-related mortality. Additionally, GCS pose risks of skin complications, which is relevant for patients with friable skin as in CS and they represent an economic and environmental burden [35]. Pneumatic compression devices may be warranted in the post-operative setting according to risk assessment.

Perioperative thromboprophylaxis

Statement 10

If thromboprophylaxis was not initiated at the diagnosis of CS, perioperative thromboprophylaxis should be reconsidered in any patient with CS, in the absence of obvious contraindications.

Comments:

Perioperative thrombosis risk in CS is the most studied timeframe and it is one of the highest risk periods for VTE development. The results from the European Registries on Rare Endocrine Conditions (EuRRECa) and from Endo-ERN survey demonstrate the incidence rate of VTE in patients with CS who were receiving thromboprophylaxis was 10.2 (95% CI 2.6; 40.5) vs 25.6 (95% CI 6.5; 100.7) per 1000 person years without thromboprophylaxis[36]. Van Zaane et al. reported in a systematic review that the postoperative VTE risk increases from 0% to 5.6%, , with one outlier study, where the risk was considerably higher (20%). Importantly, it must be recognized that the observed risk only applied for in-hospital complications (mean length of stay, 5.5 d), whereas symptomatic VTE more commonly present after discharge. A cohort study by Manetti showed an improvement of coagulation parameters after successful surgery, but the normalisation may take up to one year [13], [39].

In the ERCUSYN cohort, the hazard ratio (HR) for VTE is 2.18 (95% CI 1.38-3.45) when a reoperation is performed[16].

How to:

- **Preoperatively:** Administer the standard weight-based prophylactic dose of LMWH. The last dose should be given 24 hours before surgery.

- **Postoperatively:** Administer the standard weight-based prophylactic dose of LMWH, starting 24 hours after surgery. Continue for 3 months after cortisol levels are normalised* and the patient is mobilised.

* Low postoperative serum levels of cortisol, using a cut-off of <5 µg/dl (<138 nmol/l) or <2 µg/dl (<50 nmol/l) post-TSA; long-term hypocortisolaemia with glucocorticoid replacement at physiological levels; medically treated patients with normal UFC values [14]).

Statement 11

For optimal perioperative thromboprophylaxis management, LMWH is the preferred treatment option.

Comments:

LMWH has a short half-life, is practical, and is considered the safest agent to use. It has a lower bleeding risk compared to direct oral anticoagulants (DOACs)[39].We recommend to use the standard weight-based prophylactic doses of LMWH as recommended in local countries. For comparison with other diseases, for example, the 2021 American Society of Haematology guidelines on the management of VTE in patients with cancer also recommend LMWH vs other medical options [40].

Statement 12

Postoperative laboratory testing should not include haemostatic parameters to guide clinical decision making.

Comments:

Cushing's syndrome (CS) is characterised by haemostatic abnormalities, resulting in a hypercoagulable state and an increased risk of VTE. Patients with CS have elevated levels of factor VIII, von Willebrand factor (vWF), fibrinogen, and plasminogen activator inhibitor-1 (PAI-1) [13][12][38]. Kastelan et al. reported that factors II, V, IX, XI, XII, protein C, protein S, and C1-inhibitor are elevated, but there is also compensatory increased fibrinolytic activity[41].

While there is consensus that understanding these profiles may play a role in future management, there is currently no evidence that knowledge of haemostatic parameters influences clinical decisions.

VTE treatment

There was agreement that VTE in patients with CS should generally be treated according to institutional, national, or international thrombosis

guidelines (e.g. NICE guidelines on venous thromboembolic diseases: diagnosis, management, and thrombophilia testing [42]).

Statement 13

If VTE is diagnosed, patients with CS should receive a therapeutic dose of anticoagulation for three to six months and then a prophylactic dose preferably for three months after Cushing's is resolved.

Comments:

This approach will mitigate the high risk of recurrent thrombotic events associated with ongoing hypercortisolism provided there are no obvious contraindications for thromboprophylaxis [8], [19], [22]. The justification for extending the thromboprophylaxis has been provided above.

Statement 14

LMWH is the preferred initial therapy for VTE treatment in patients with CS if the VTE is diagnosed in the early postoperative period (within 6 weeks postoperatively).

Comments:

The rationale for this statement is the potential need for re-operation. After the acute period, a therapeutic dose of LMWH or direct oral anticoagulants (DOACs) could be used to treat VTE[40].

Considerations and contraindications to LMWH use in patients with CS

When selecting an agent for thromboprophylaxis, it is important to note that exact dosages and dose adjustments for obesity and renal impairment are not standardised and may vary between regions and countries. Also, different types of LMWH are preferred in the different European countries. We recommend using locally approved prophylactic doses, adjusted as necessary for obesity or renal insufficiency. This decision should be made by the endocrinologist or hematologist responsible for thromboprophylaxis in the specific country.

When implementing thromboprophylaxis, it is crucial to also assess the risk of bleeding. Factors that increase bleeding risk include active bleeding, acquired bleeding disorders (e.g., liver failure), concurrent use of other anticoagulants, acute stroke, thrombocytopenia (platelet count $<75 \times 10^9$/L), uncontrolled hypertension (blood pressure >200 mmHg systolic or >120 mmHg diastolic), untreated inherited bleeding disorders (e.g., hemophilia or von Willebrand disease), and recent or planned surgical procedures. Patients with a history of allergic reactions to LMWH or those currently experiencing such reactions should be offered an alternative form or preparation of thromboprophylaxis. The advice should be sought form a hematologist ideally [28][46]

Statements with less than 75% agreement (Likert scale 4-5).

Statements with less than 75% agreement are provided in Table 2.

No	Statement	Agreement	Consensus conceived
	Initiation of thromboprophylaxis for CS patients		
1	Thromboprophylaxis should be considered for any patient with CS, regardless of the aetiology, in the absence of obvious contraindications.	82.4%	Round 2
2	Thromboprophylaxis should start at the time when a definitive CS is diagnosed in the absence of obvious contraindications.	76.4%	Round 2
3	Prophylactic anticoagulation in patients with CS should be continued preferably for three months after achieving biochemical	82.4%	Round 2

	remission in the absence of obvious contraindications.		
4	Patients with CS who are biochemically controlled on medical therapy and do not have additional risk factors may not require thromboprophylaxis	82.4%	Round 2
5	Hospitalised patients with active CS should receive thromboprophylaxis in the absence of obvious contraindications.	93.8%	Round 2
6	Patients with CS should receive thromboprophylaxis when they have at least one of the following risk factors*. *Table 3	83.3%	Round 3
7	For patients with CS who have not received thromboprophylaxis in the disease course, it should be reconsidered at the time of inferior petrosal sinus sampling (IPSS).	88%	Round 4
8	Low molecular weight heparin (LMWH) in standard prophylactic doses (or higher doses in obese patients) should be used for thromboprophylaxis in patients with CS.	83.3%	Round 3
9	Antiembolic stockings are not recommended for thromboprophylaxis in patients with CS.	87%	Round 4
	Perioperative thromboprophylaxis		

10	If thromboprophylaxis was not initiated at the diagnosis of CS, perioperative thromboprophylaxis should be reconsidered in any patient with CS, in the absence of obvious contraindications.	94.1%	Round 2
11	For optimal perioperative thromboprophylaxis management, LMWH is the preferred treatment option.	100%	Round 2
12	Postoperative laboratory testing should not include haemostatic parameters to guide clinical decision making.	76.5%	Round 2
	VTE Treatment		
13	If VTE is diagnosed, patients with CS should receive a therapeutic dose of anticoagulation for three to six months and then a prophylactic dose preferably for three months after Cushing's is resolved.	75%	Round 3
14	LMWH is the preferred initial therapy for VTE treatment in patients with CS if the VTE is diagnosed in the early postoperative period (within 6 weeks postoperatively).	78.4%	Round 3

Table 1: Proportion of panellists indicating some or complete agreement (Ratings 4 and 5 on a Likert-type scale) with topics

Statement	Consensus (Likert scale 4-5)	Delphi round
Preoperative laboratory testing should not include haemostatic parameters.	61.9%	Round 2
IF DOAC's are available in a specific country, this is the preferred agent for thromboprophylaxis for CS patients.	41%	Round 3
For mild* CS patients thromboprophylaxis may not be considered	58%	Round 2
MACS patients may not receive thromboprophylaxis.	58.9%	Round 2
Patients with mild CS patients may not receive thromboprophylaxis around the time of IPSS.	52.8%	Round 2
Thromboprophylaxis should be considered for MACS patients perioperatively.	41.1%	Round 2

Table 2:Statements without >75% agreement

Incident Risk Factors
Active malignancy or cancer treatment
Dehydration
Sedentary lifestyle
Smoking
Use of oral oestrogen replacement therapy/oestrogen-containing contraceptive therapy
Pregnancy or less than six weeks postpartum

Prevalent (Chronic/Persistent) Risk Factors

Age over 60 years
Known thrombophilia (inherited or acquired)
Obesity (BMI > 30 kg/m²)
One or more significant medical comorbidities (e.g., heart disease, endocrine metabolic disorders, pulmonary disorders, acute infectious diseases, inflammatory conditions)
Personal history or first-degree relative with a history of VTE varicose veins with phlebitis

Table 3: Risks for VTE

Mild CS and MACS

While the panel initially attempted to include opinions for patients with mild CS and/or mild autonomous cortisol secretion (MACS), we could not find sufficient evidence to provide recommendations. Also, there is no clear definition for mild CS. The 2021 CS guideline update suggests using late-night salivary cortisol (LNSC) levels just above the upper limit of normal (ULN)[43]. There is a growing interest in comorbidities for patients with MACS, but recent publications specifically addressing the VTE risk in these populations are not available[44][45].

Preoperative laboratory testing for haemostatic parameters

There is not enough evidence to support testing for postoperative haemostatic parameters and for preoperative testing these parameters also did not result in agreement over 75%, mainly due to neutral voting (Likert scale 3). This highlights the need for further research in this area.

Using DOACs as thromboprophylaxis

The consensus panelists generally agree that thromboprophylaxis with DOACs could be an alternative strategy for patients with CS. DOACs offer the advantage of oral administration, which could enhance patient compliance and convenience compared to injectable LMWH.

Despite this, there is a significant gap in the literature, as no studies have specifically addressed the efficacy and safety of DOACs for thromboprophylaxis in patients with CS, therefore this practice would be off-label.

The global availability of DOACs is variable, primarily influenced by economic factors and variable access to healthcare resources. In many regions, including parts of Asia, Latin America, and Africa, the use of DOACs is limited due to higher costs and accessibility. However, the recent introduction of generic formulations could potentially increase their usage.

Further studies are essential to substantiate the safety and efficacy of DOACs in this specific patient population.

Next steps and areas of research

This position statement has been established to provide specific guidelines for offering thromboprophylaxis to patients with Cushing's syndrome, and to increase the general awareness for the increased risk of VTE in patients with Cushing's syndrome. The current recommendations do not address the possibility of using DOACs. Neither do they clarify how long thromboprophylaxis should be continued after remission of hypercortisolism (normalisation of 24-hour urinary free cortisol levels, and the suppression of cortisol secretion during a low-dose dexamethasone suppression test, patients with low postoperative serum levels of cortisol; long-term hypocortisolaemia with glucocorticoid replacement[27]).

Another topic of research should focus on coagulation profile normalisation time.

With widespread implementation of the recommendations of this position statement, an audit should be conducted in 3 to 5 years to assess adherence to this position statement, and consequently, whether the incidence of venous thromboembolisms has decreased. For this purpose, structured documentation of the incidence of VTE in

(inter)national registries is highly recommended. The plan is to recalibrate the statements and provide updated recommendations in light of new knowledge after 3 to 5 years.
There is a need to investigate the coagulation profile in both mild CS patients and MACS patients. These new findings would help determine whether coagulation is also disrupted in these patient groups. Additionally, there is an urgent need to compare different thromboprophylactic treatment regimens for patients with CS.

Conclusion

In conclusion, the consensus statements developed through a Delphi method highlight the critical need for tailored thromboprophylaxis strategies in patients with CS. The consensus underscores the importance of initiating thromboprophylaxis at the time of diagnosis and continuing it at least until biochemical remission has been obtained. Additionally, LMWH is recommended due to its safety and efficacy profile.
The expert panel also identified key areas for future research, including the need for studies on the use of DOACs in patients with CS and for how long thromboprophylaxis should be continued after remission of hypercortisolism. Further research is also needed to refine the criteria for thromboprophylaxis in patients with mild CS and MACS, ensuring that the benefits outweigh the risks.
Overall, these consensus statements aim to standardise care practices and improve patient outcomes by providing clear guidelines for the management of thromboprophylaxis in patients with CS.

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