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

4 Kristina Isand<sup>1,2,3</sup>; Hiroshi Arima<sup>8</sup>; Jerome Bertherat<sup>16</sup>; Olaf M.  
5 Dekkers<sup>21,22</sup>; Richard A Feelders<sup>9,17</sup>; Maria Fleseriu<sup>6</sup>; Monica R. Gadelha<sup>4</sup>;  
6 Jose Miguel Hinojosa-Amaya<sup>13</sup>; Niki Karavitaki<sup>10, 11,12</sup>; Frederikus A Klok<sup>14</sup>;  
7 Ann McCormack<sup>19</sup>; John Newell-Price<sup>15</sup>; Sue Pavord<sup>20</sup>; Martin Reincke<sup>23</sup>;  
8 Saurabh Sinha<sup>18</sup>; Elena Valassi<sup>7</sup>; John Wass<sup>2</sup>; Alberto M. Pereira<sup>5</sup>

9  
10  
11 <sup>1</sup> University of Tartu, Tartu, Estonia

12 <sup>2</sup>Oxford University Hospitals, Oxford, UK

13 <sup>3</sup>East-Tallinn Central Hospital, Tallinn, Estonia

14 <sup>4</sup>Medical School and Hospital Universitário Clementino Fraga Filho, Universidade Federal do Rio  
15 de Janeiro, Brazil

16 <sup>5</sup>Department of Endocrinology and Metabolism, Amsterdam University Medical Center, Location  
17 University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands

18 <sup>6</sup>Pituitary Center, Departments of Medicine and Neurological Surgery, Oregon Health & Science  
19 University, Portland, OR, USA

20 <sup>7</sup>Endocrinology and Nutrition Department, Germans Trias i Pujol Hospital and Research Institute,  
21 Badalona, Spain; Universitat Internacional de Catalunya (UIC), Barcelona, Spain; Centro de  
22 Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Pituitary Diseases Unit 747

23 <sup>8</sup>Department of Endocrinology and Diabetes, Nagoya University Graduate School of Medicine,  
24 Nagoya, Japan

25 <sup>9</sup>Erasmus Medical Center, Department of Internal Medicine, Division of Endocrinology,  
26 Rotterdam, The Netherlands

27 <sup>10</sup>Department of Metabolism and Systems Science, College of Medicine and Health, University of  
28 Birmingham, Birmingham, UK

29 <sup>11</sup>Centre for Endocrinology, Diabetes and Metabolism, Birmingham Health Partners, Birmingham,  
30 UK

31 <sup>12</sup>Department of Endocrinology, Queen Elizabeth Hospital, University Hospitals Birmingham NHS  
32 Foundation Trust, Birmingham, UK

33 <sup>13</sup> Pituitary Clinic, Endocrinology Division, and Department of Medicine, Hospital Universitario,  
34 Universidad Autónoma de Nuevo León

35 <sup>14</sup> department of Medicine – Thrombosis and Hemostasis, Leiden University Medical Center,  
36 Leiden the Netherlands

37 <sup>15</sup>School of Medicine and Population Health, University of Sheffield, Sheffield, UK

- 1 <sup>16</sup> Department of Endocrinology, National Reference Center for Rare Adrenal Disorders, Hôpital  
2 Cochin, Assistance Publique Hôpitaux de Paris, Université Paris-Cité, Paris, France.  
3 <sup>17</sup> Division of Endocrinology, Diabetes and Metabolism, New York University Langone Medical  
4 Center, New York, NY 10016, United States  
5 <sup>18</sup> Sheffield Teaching Hospitals NHS Foundation Trust | STH · Sheffield Centre for Neurosurgery  
6 <sup>19</sup> St Vincent’s Hospital and Clinical School, University of New South Wales, Australia  
7 <sup>20</sup> Department of Haematology, Oxford University Hospitals NHS FT, UK  
8 <sup>21</sup> Department of Internal Medicine, Division of Endocrinology, Leiden University Medical Center,  
9 Leiden, The Netherlands  
10 <sup>22</sup> Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The  
11 Netherlands  
12 <sup>23</sup> Department of Medicine IV, LMU University Hospital, LMU Munich, Munich, Germany  
13

14 Conflict of interest (COI):

- 15 1. Maria Fleseriu has been a PI with research funding to the University from Crinetics and  
16 Sparrow and has received occasional scientific consulting fee from Crinetics, Recordati,  
17 Sparrow, and Xeris  
18 2. Monica Gadelha: MG has received speaker fees from Recordati and attended advisory  
19 boards for Recordati.  
20 3. Martin Reincke has received speaker and consulting fees from Crinetics, Recordati, HRA  
21 Pharma, Damian  
22 4. John Newell-Price has had consultancy fees paid to his University from Crinetics,  
23 Recordati, HRA Pharma, and Diurnal  
24 5. Niki Karavitaki: Speaker for Pfizer, HRA Pharma, Recordati Rare Diseases - Investigator for  
25 HRA Pharma - Scientific Advisory Board for Pfizer, Recordati Rare Diseases  
26 6. Ann McCormack has received speaker and advisory board consulting fees from Recordati,  
27 Novo Nordisk.  
28

29 Abbreviations:

- 30 CS-Cushing’s syndrome  
31 VTE-venous thromboembolism  
32 IPSS- inferial petrosus sinus sampling  
33 MACS-mild autonomous cortisol secretion  
34 ACTH- Adrenocorticotropic hormone  
35 LMWH-low-molecular weight heparin  
36 DOAC- direct oral anticoagulant  
37 CI- Confidence interval  
38 HR-hazard ratio  
39 UFC -24-hour urinary-free cortisol  
40 aPTT-activated partial thromboplastic time  
41 ERCUSYN-European Registry on Cushing’s syndrome  
42 Endo-ERN- European Reference Networks for Rare Endocrine Conditions  
43 SfE- Society for Endocrinology  
44 EuRRECa - European Registries for Rare Endocrine Conditions

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

10

## 11 **ABSTRACT**

### 12 **Objective:**

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

### 16 **Methods:**

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

### 22 **Results:**

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

### 31 **Conclusion:**

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

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

41

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.

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## 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

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

22

### 23 Mechanisms behind the elevated risk for VTE

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

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

4

#### 5 The need for clear guidance for providing thromboprophylaxis

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

19

## 20 **Methods**

21

### 22 ***Participants***

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

## 1 **Consensus formation**

2 The consensus process involved preparing and testing consensus  
3 questions, followed by iterative rounds of feedback and modifications.  
4 A Delphi method, consisting of four rounds, was used to reach a  
5 consensus[1]. Consensus was defined as >75% agreement (Likert scale  
6 4-5). Consensus questions were prepared by three endocrinologists (KI,  
7 JW, AMP), reviewed by the methodologist (OMD), and sent to three  
8 endocrinologists to pilot before being distributed to the panel of  
9 experts. An online platform, Calibrium, was used for voting. The first  
10 round was sent out in March, 2024, and the fourth and final round were  
11 completed July 2024.

12

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

30

1 ***Delphi rounds and organization of the document***

2 Delphi rounds are illustrated in figure 1.

3 The statements are organized into three sections:

4 1) initiation of thromboprophylaxis in patients with CS

5 2) perioperative thromboprophylaxis

6 3) treatment of venous thromboembolism (VTE)

7

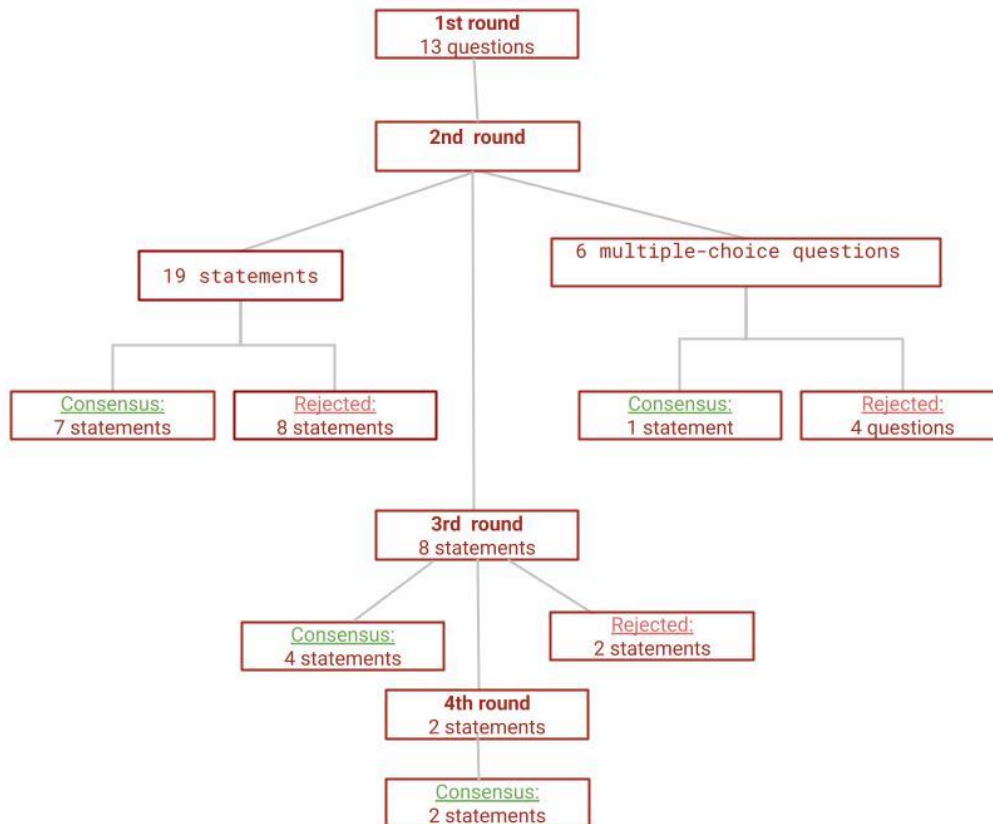
8 In addition, for perioperative thromboprophylaxis and  
9 thromboprophylaxis related to Inferior Petrosal Sinus Sampling (IPSS),

10 practical “How to” examples are provided to guide clinicians. It is crucial

11 to consider each patient’s individual health factors and circumstances

12 when applying these recommendations in clinical practice. The main

13 recommendations are summarised in Table 1 and Figure 2.



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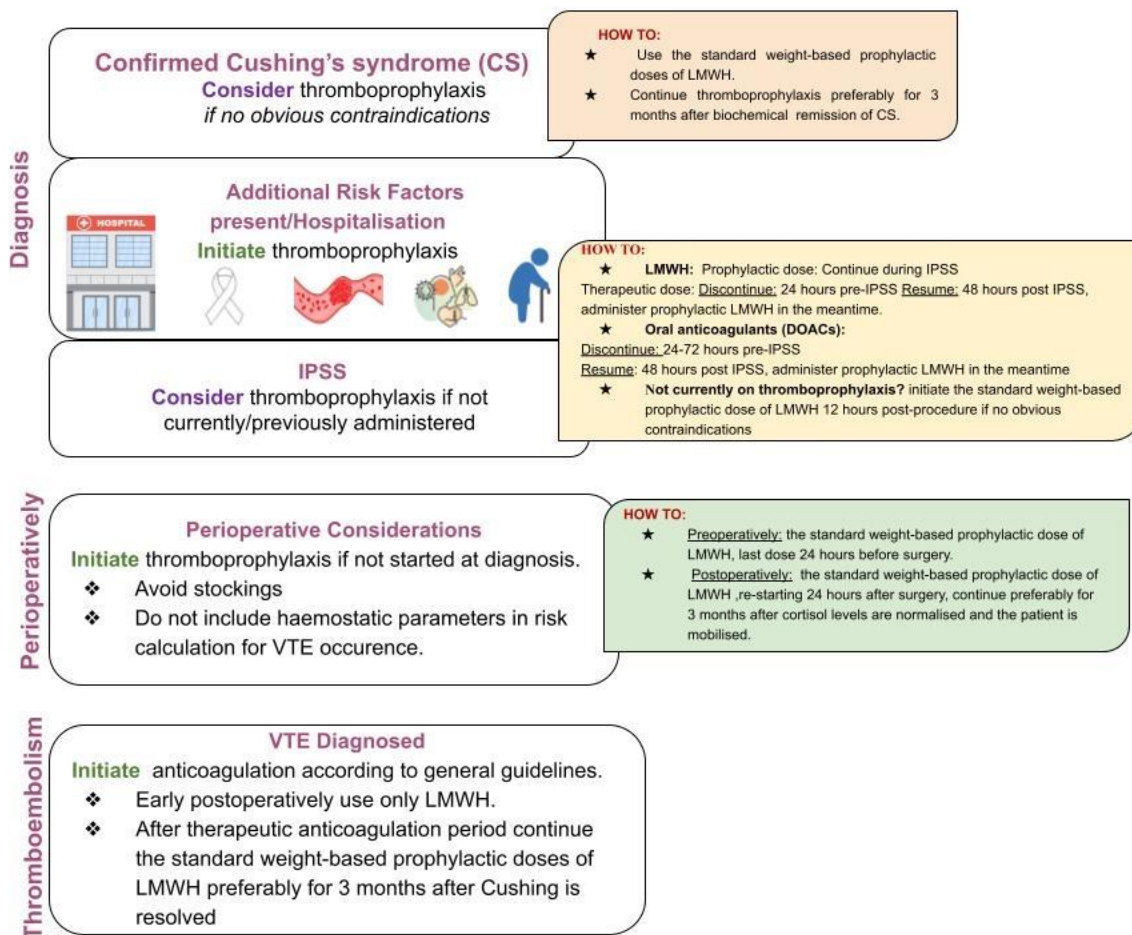
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## Figure 1: Delphi flowchart

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.



14  
15 Figure 2: Pocket guide for main summaries

1 **Results**

2 **Initiation of thromboprophylaxis for patients with CS**

3 **Statement 1**

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

6 *Comment:*

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

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

15

16 **Statement 2**

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

19 *Comment:*

20 If one decides to initiate thromboprophylaxis, it should start at time of  
21 definitive CS diagnosis. If a definitive underlying diagnosis is not yet  
22 available but the hypercortisolaemia is severe, VTE prophylaxis should  
23 however not be delayed[20]. Severe Cushing's syndrome is frequently,  
24 but not exclusively, accompanied by random serum cortisol higher than  
25 40 µg/dL (1100 nmol/L), elevation of 24-h urinary free cortisol (UFC)  
26 above four- or fivefold the upper limit of normal (ULN) and/or severe  
27 hypokalemia (below 3 mmol/L)[20]. Thromboprophylaxis must be  
28 carefully considered in patients with severe thrombocytopenia, active  
29 bleeding or at high risk of major bleeding, advanced liver disease,  
30 heparin-induced thrombocytopenia, or renal failure. Each  
31 contraindication requires an individualized assessment to balance the  
32 risk of thrombosis and bleeding[21].

33

1 **Statement 3**

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

5 *Comment:*

6 It is reasonable that during hypercortisolaemia patients need to be  
7 offered thromboprophylaxis, but the appropriate duration of  
8 thromboprophylaxis for patients with CS remains uncertain and is  
9 therefore a highly important area of research in the near future. The  
10 literature varies on the duration of thromboprophylaxis post-  
11 biochemical remission. Most authors point out the importance of  
12 continuing thromboprophylaxis after achieving biochemical remission,  
13 either with a surgical approach or medically [22]. The panel discussed  
14 the recommended duration of thromboprophylaxis, which ranged from  
15 1 to 12 months following cure. The majority supported an extended  
16 thromboprophylaxis period of 3 months after achieving eucortisolaemia.  
17 This recommendation will be updated as new evidence becomes  
18 available and the Position Statement is revised.

19 Looking at the time when VTEs happen, Suarez et al. demonstrated that  
20 40.5% of these occur within the first 60 days after surgery.[23]. In line,  
21 data from the ERCUSYN database indicate that the risk is the highest for  
22 six months post-surgery [16]. Dekkers et al have shown that the risk for  
23 VTE is specifically elevated during three months after surgery [6]. When  
24 patients are started on medical therapy, cortisol normalisation is not  
25 directly accompanied by complete correction of the hypercoagulable  
26 state, which involves both increased production of procoagulant factors  
27 and impaired fibrinolysis, suggesting the need for prolonged  
28 thromboprophylaxis[24]. A low-grade pro-inflammatory state during the  
29 glucocorticoid withdrawal phase can last even for at least one year, also  
30 potentially elevating the risk for VTE [25].

31

1 **Statement 4**

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

5 *Comment:*

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

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

19

20 **Statement 5**

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

23 *Comments:*

24 Thromboprophylaxis should be initiated in all patients with CS on  
25 admission regardless the reason for hospitalisation, and regardless of  
26 the biochemical severity of hypercortisolism, in the absence of clear  
27 contraindications[12], [22]. Immobilisation, whether due to severe  
28 illness, postoperative recovery, or reduced physical activity, exacerbates  
29 the risk of VTE in patients with CS [8]. Early mobilisation should be  
30 encouraged in parallel with thromboprophylaxis initiation  
31 [26].

32

33 **Statement 6:**

1 Patients with CS should receive thromboprophylaxis when they have at  
 2 least one of the following risk factors.  
 3 *Note: This list is not exhaustive, and clinicians may consider additional*  
 4 *risks.*

5

<b><i>Incident Risk Factors</i></b>
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

6

7

8

<b><i>Prevalent (Chronic/Persistent) Risk Factors</i></b>
Age over 60 years
Known thrombophilia (inherited or acquired)
Obesity (BMI > 30 kg/m <sup>2</sup> )
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

9

10

11 *Comments:*

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

1 long-term and are associated with a sustained increased risk of  
2 developing VTE over time.  
3 If any of these risks are present, thromboprophylaxis should not be  
4 delayed, but the distinction helps to decide if thromboprophylaxis is  
5 needed during high-risk periods (incident factors) or managing long-  
6 term risks (prevalent factors) [27][28].

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

10

### 11 **Statement 7**

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

15 *Comments:*

16 IPSS is an invasive procedure that carries certain risks, including  
17 brainstem injury, neurologic complications, and VTE [29][30][31][32]. If a  
18 patient with CS was not given thromboprophylaxis, it should be started  
19 around the time of IPSS and continued following the procedure to  
20 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.

- 1  
2 **Statement 8**  
3 Low molecular weight heparin (LMWH) in the standard weight-based  
4 prophylactic doses should be used for thromboprophylaxis in patients  
5 with CS.  
6 *Comments:*  
7 Local physicians should use the standard weight-based prophylactic  
8 doses of LMWH as recommended for their countries.  
9 There was a discussion in the panel regarding the use of direct oral  
10 anticoagulants (DOACs) as an alternative to LMWH for  
11 thromboprophylaxis in patients with CS. The use of DOACs in patients  
12 with CS is off-label. At present there are no data to support the safety of  
13 DOACs in CS patients indicating a critical area for further studies. One  
14 potential concern with DOACs is the higher reported bleeding risk  
15 compared to LMWH[33].

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

4

#### 5 **Statement 9**

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

8 *Comments:*

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

24

#### 25 **Perioperative thromboprophylaxis**

26

#### 27 **Statement 10**

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

31 *Comments:*

1 Perioperative thrombosis risk in CS is the most studied timeframe and it  
2 is one of the highest risk periods for VTE development. The results from  
3 the European Registries on Rare Endocrine Conditions (EuRRECa) and  
4 from Endo-ERN survey demonstrate the incidence rate of VTE in  
5 patients with CS who were receiving thromboprophylaxis was 10.2 (95%  
6 CI 2.6; 40.5) vs 25.6 (95% CI 6.5; 100.7) per 1000 person years without  
7 thromboprophylaxis[36]. Van Zaane et al. reported in a systematic  
8 review that the postoperative VTE risk increases from 0% to 5.6%, , with  
9 one outlier study, where the risk was considerably higher (20%).  
10 Importantly, it must be recognized that the observed risk only applied  
11 for in-hospital complications (mean length of stay, 5.5 d), whereas  
12 symptomatic VTE more commonly present after discharge. A cohort  
13 study by Manetti showed an improvement of coagulation parameters  
14 after successful surgery, but the normalisation may take up to one year  
15 [13], [39].  
16 In the ERCUSYN cohort, the hazard ratio (HR) for VTE is 2.18 (95% CI  
17 1.38-3.45) when a reoperation is performed[16].  
18

### 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]).

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**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

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

3

#### 4 **Statement 13**

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

8 *Comments:*

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

13

#### 14 **Statement 14**

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

18 *Comments:*

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

22

#### 23 **Considerations and contraindications to LMWH use in patients with CS**

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

32

1 When implementing thromboprophylaxis, it is crucial to also assess the  
 2 risk of bleeding. Factors that increase bleeding risk include active  
 3 bleeding, acquired bleeding disorders (e.g., liver failure), concurrent use  
 4 of other anticoagulants, acute stroke, thrombocytopenia (platelet count  
 5  $<75 \times 10^9/L$ ), uncontrolled hypertension (blood pressure  $>200$  mmHg  
 6 systolic or  $>120$  mmHg diastolic), untreated inherited bleeding disorders  
 7 (e.g., hemophilia or von Willebrand disease), and recent or planned  
 8 surgical procedures. Patients with a history of allergic reactions to  
 9 LMWH or those currently experiencing such reactions should be offered  
 10 an alternative form or preparation of thromboprophylaxis. The advice  
 11 should be sought from a hematologist ideally [28][46]

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**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
<b>Initiation of thromboprophylaxis for CS patients</b>			
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
<b>Perioperative thromboprophylaxis</b>			

<b>10</b>	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.	<b>94.1%</b>	<b>Round 2</b>
<b>11</b>	For optimal perioperative thromboprophylaxis management, LMWH is the preferred treatment option.	<b>100%</b>	<b>Round 2</b>
<b>12</b>	Postoperative laboratory testing should not include haemostatic parameters to guide clinical decision making.	<b>76.5%</b>	<b>Round 2</b>
<b>VTE Treatment</b>			
<b>13</b>	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.	<b>75%</b>	<b>Round 3</b>
<b>14</b>	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).	<b>78.4%</b>	<b>Round 3</b>

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

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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

2 **Table 2: Statements without >75% agreement**

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<i>Incident Risk Factors</i>
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

6

<i>Prevalent (Chronic/Persistent) Risk Factors</i>
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Age over 60 years
Known thrombophilia (inherited or acquired)
Obesity (BMI > 30 kg/m <sup>2</sup> )
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

1 **Table 3: Risks for VTE**

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4 **Mild CS and MACS**

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

13

14 **Preoperative laboratory testing for haemostatic parameters**

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

19

20 **Using DOACs as thromboprophylaxis**

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

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

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

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

13

14

### 15 **Next steps and areas of research**

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

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

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

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

9

## 10 **Conclusion**

11 In conclusion, the consensus statements developed through a Delphi  
12 method highlight the critical need for tailored thromboprophylaxis  
13 strategies in patients with CS. The consensus underscores the  
14 importance of initiating thromboprophylaxis at the time of diagnosis and  
15 continuing it at least until biochemical remission has been obtained.  
16 Additionally, LMWH is recommended due to its safety and efficacy  
17 profile.

18 The expert panel also identified key areas for future research, including  
19 the need for studies on the use of DOACs in patients with CS and for  
20 how long thromboprophylaxis should be continued after remission of  
21 hypercortisolism. Further research is also needed to refine the criteria  
22 for thromboprophylaxis in patients with mild CS and MACS, ensuring  
23 that the benefits outweigh the risks.

24 Overall, these consensus statements aim to standardise care practices  
25 and improve patient outcomes by providing clear guidelines for the  
26 management of thromboprophylaxis in patients with CS.

27

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