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KRISTINA ISAND

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I. Ross Hamblin, Athanasios Fountas, Kirstie Lithgow, Paul Benjamin Loughrey, Efstathios Bonanos, Shah Khalid Shinwari, Kirsten Mitchell, Syed Shah, Lydia Grixti, Mike Matheou, **Kristina Isand**, David S McLaren, Ashutosh Surya, Hafiz Zubair Ullah, Katarina Klaucane, Anuradha Jayasuriya, Sumbal Bhatti, Akash Mavilakandy, Masato Ahsan, Susan Mathew, Ziad Hussein, Thijs Jansz, Wunna Wunna, James MacFarlane, John Ayuk, Prakash Abraham, William M Drake, Mark Gurnell, Antonia Brooke, Stephanie E Baldeweg, Amir H Sam, Niamh Martin, Claire Higham, Narendra Reddy, Miles J Levy, Rupa Ahluwalia, John Newell-Price, Joannis Vamvakopoulos, Amutha Krishnan, Andrew Lansdown, Robert D Murray, Aparna Pal, Karin Bradley, Yaasir Mamoojee, Tejpal Purewal, Janki Panicker, E Marie Freel, Faisal Hasan, Mohit Kumar, Biju Jose, Steven J Hunter, Niki Karavitaki, **Natural history of non-functioning pituitary microadenomas: results from the UK non-functioning pituitary adenoma consortium**, European Journal of Endocrinology, Volume 189, Issue 1, July 2023, Pages 87–95, https://doi.org/10.1093/ejendo/lvad070

II. **Kristina Isand**, Riccardo Pofi, Oliver Haermson, Melissa Vergis, Harishanthi Mahendran, John Ayuk, John Wass, Parag Yajnik, Karin Bradley, Niki Karavitaki, Aparna Pal, **Venous thromboembolism in patients with pituitary adenoma: UK multicentre cohort study**, European Journal of Endocrinology, Volume 193, Issue 2, August 2025, Pages 270–277, https://doi.org/10.1093/ejendo/lvaf139

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Contribution of Kristina Isand to the original publications:

Paper I: contributed to the material preparation, data collection, interpretation of the results, participating in draft writing and revision.

Papers II–IV: contributed to the study conception and design, material preparation, data collection, data analysis and interpretation of the results, writing of the draft and critical revision, submission and correspondence.

ABBREVIATIONS

ACTH	Adrenocorticotropic hormone
BMI	Body mass index
CD	Cushing's disease
CI	Confidence interval
CRH	Corticotropin-releasing hormone
CS	Cushing's syndrome
DOAC	Direct oral anticoagulant
DVT	Deep vein thrombosis
Endo-ERN	European reference network on rare endocrine conditions
ERCUSYN	European registry on Cushing's syndrome
FSH	Follicle-stimulating hormone
GH	Growth hormone
HDL	High-density lipoprotein
HPA	Hypothalamic–pituitary–adrenal
IGF-1	Insulin-like growth factor 1
IGT	Impaired glucose tolerance
INR	International normalised ratio
IPSS	Inferior petrosal sinus sampling
IQR	Interquartile range
LDDT	Low-dose dexamethasone test
LH	Luteinising hormone
LMWH	Low molecular weight heparin
LNSC	Late-night salivary cortisol
NFPA	Non-functioning pituitary adenoma
OR	Odds ratio
PAI-1	Plasminogen activator inhibitor-1
PE	Pulmonary embolism
PitNET	Pituitary neuroendocrine tumour
QoL	Quality of life
SD	Standard deviation
SfE	Society for Endocinology
TSH	Thyroid-stimulating hormone
TSS	Transsphenoidal surgery
UFC	Urinary free cortisol
UFH	Unfractionated heparin
VKA	Vitamin K antagonist
VTE	Venous thromboembolism

1. INTRODUCTION

The pituitary gland, often called the "master gland", regulates secretion of vital hormones. Pituitary adenomas are tumours originating in the anterior lobe, classified as functional (secreting hormones such as prolactin, growth hormone or adrenocorticotropic hormone) or non-functional (NFPAs) (Melmed, 2011; Tritos & Miller, 2023). Pituitary adenomas can also be classified on size: microadenomas <10 mm, macroadenomas >10 mm (Molitch, 2017). Functioning adenomas secrete hormones, leading to distinct clinical syndromes. Non-functioning adenomas (NFPAs) most often lack overt hormone secretion, but may also secrete hormones or hormone subunits; they are often detected due to mass effects or are incidental findings (Melmed et al., 2022). Prolactinomas are the most prevalent, followed by GH-secreting, ACTH-secreting, and non-functioning adenoma (Tritos & Miller, 2023). The natural history of pituitary adenomas varies, with some remaining stable while others grow, causing hormonal imbalances or compressive symptoms (Ntali & Wass, 2018; Raappana et al., 2010). Management depends on tumour type, size, and symptoms, with treatment options including medical therapy, surgery, and, in selected cases, radiotherapy (Yavropoulou et al., 2020). While first-line therapy is typically transsphenoidal surgery, prolactinomas are an exception, with bromocriptine or cabergoline being preferred treatments (Tritos & Miller, 2023).

Cushing's syndrome (CS) results from prolonged cortisol elevation, commonly due to exogenous steroid use or endogenous overproduction, as seen in ACTH-secreting pituitary adenomas (Cushing's disease). CS has a prevalence of 2–3 cases per million annually and leads to significant cardiovascular, metabolic, and thromboembolic complications (Gadelha et al., 2023; Reincke & Fleseriu, 2023). Diagnosis is challenging and often delayed, with common tests including late-night salivary cortisol, dexamethasone suppression tests, and 24-hour urinary free cortisol (Valassi, 2022; Varlamov et al., 2021). Several comorbidities remain even after patient remission, which can affect quality of life. Accurate and timely diagnosis and treatment are essential for mitigating chronic complications of excess glucocorticoids and improving patient quality of life (Gadelha et al., 2023).

Hypercoagulability is one highly important complication of CS. The incidence of venous thromboembolic events (VTE) in patients with endogenous CS is more than 10-fold higher versus those with non-functioning adenomas undergoing surgery (Stuijver et al., 2011a). The odds-ratio is 18-fold higher compared with the healthy population. VTE risk persists even months after CD surgery, indicating that hypercoagulability is not immediately reversible with cortisol normalization (Wagner et al., 2018a).

Data from retrospective studies suggests that extended thromboprophylaxis after surgery can decrease the incidence of VTE. Although the increased risk of VTE in patients with CS is clear, translating these data into clinical practice guidelines remains challenging (Manetti et al., 2010). 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 (Maria Fleseriu, Beverly MK Biller, Ashley Grossman, Brooke Swearingen and Shlomo Melmed on behalf of the Pituitary Society International Cushing Disease Workshop Task Force, n.d.). 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 (Isand et al., 2022a, 2023; van Haalen, Kaya, Pelsma, Dekkers, Biermasz, et al., 2022a).

2. REVIEW OF THE LITERATURE

2.1 Pituitary adenomas

The pituitary gland is located at the base of the brain, coming off the inferior hypothalamus, and weighs approximately half a gram. The pituitary gland is often referred to as the "master gland" and is the most important endocrine gland in the body because it regulates vital hormone secretion (Yeh & Chen, 1997). Anatomically, the pituitary gland is divided into three lobes: anterior, intermediate, and posterior. The anterior lobe is composed of several endocrine cells, such as lactotropes, somatotropes, and corticotropes, which synthesize and secrete specific hormones. The synthesis and release of these hormones are controlled by regulatory hormones secreted by the hypothalamus. Pituitary adenomas are located in the anterior lobe (*The Pituitary*, 2010).

The mean age at diagnosis of the pituitary adenoma is 39 years (interquartile range 27–58) with female to male ratio of 2,5 (Ntali & Wass, 2018; Raappana et al., 2010). The estimated prevalence of pituitary adenomas ranges from 14% to over 22%, with imaging studies frequently identifying more lesions than autopsies alone. Collectively, these data suggest that incidental pituitary adenomas may be present in up to one-quarter of individuals in the general population (Ezzat et al., 2004). However, most remain benign and asymptomatic throughout life. (Melmed et al., 2022). A small subset of pituitary tumours has been classified as aggressive pituitary tumours, based on resistance to medical treatment and multiple recurrences despite standard therapies combining surgical, medical and radiotherapy treatment approaches. The prevalence of aggressive tumours is not known (Raverot et al., 2018). Pituitary carcinomas, characterised by craniospinal and/or systemic metastases, are extremely rare and are estimated to comprise only 0.2% of all pituitary tumours (Raverot et al., 2014).

Pituitary adenomas are neoplasms of the pituitary that may hyper secrete hormones (including prolactin, growth hormone and adrenocorticotropic hormone, and rarely follicle-stimulating hormone, luteinizing hormone or TSH) or may be non-functional (Melmed, 2011; Tritos & Miller, 2023). Prolactinomas account for 32–66% of pituitary adenomas, GH-secreting tumours (acromegaly) accounts for 8–16% of pituitary tumours, ACTH-secreting pituitary tumour (Cushing's disease) account for 2–6%. Clinically non-functioning pituitary adenomas account for 15–54% of adenomas (Tabel 1). When it comes to the size of the adenoma, approximately 50% are microadenomas (<10 mm) and the remainder are macroadenomas (>10 mm) (Molitch, 2017).

Table 1. Pituitary adenoma prevalence (modified from (Molitch, 2017).

Type of pituitary adenoma	Prevalence (%)
Prolactin-secreting (Prolactinoma)	32–66
GH-secreting (acromegaly)	8–16
ACTH-secreting (Cushing's disease)	2–6
Non-functioning pituitary adenoma	15–54

All patients with pituitary tumours require endocrine evaluation for hormone hypersecretion. Patients with macroadenomas additionally require evaluation for hypopituitarism, and visual field testing. For those requiring treatment, first-line therapy is usually transsphenoidal pituitary surgery, except for prolactinomas, for which medical therapy, either bromocriptine or cabergoline, is usually first line (Tritos & Miller, 2023).

2.1.1 Non-functioning pituitary adenomas

Non-functioning pituitary adenomas (NFPAs) are benign pituitary tumours not associated with clinical manifestations secondary to hormonal hypersecretion. (Rogers et al., 2014). NFPAs are categorized based on size into non-functioning pituitary microadenomas (micro-NFPAs, with a maximum diameter of <1 cm) and macroadenomas (macro-NFPAs, with a diameter of >1 cm) (Ezzat et al., 2004). NFPAs account for 14–54% of pituitary adenomas, being the second most commonly found after prolactinomas and the commonest of all macroadenomas. The estimated prevalence of clinically relevant NFPAs is 7–41.3 cases per 100,000 of population (Ntali & Wass, 2018).

Recently, there has been a proposal to rename pituitary adenomas as pituitary neuroendocrine tumours (pitNETs)(Asa et al., 2017). However, this terminology has not been universally accepted among neuroendocrinologists. For consistency with the terminology used in the published articles forming the basis of this dissertation, the term pituitary adenoma is used throughout.

The clinical spectrum of NFPA varies from being completely asymptomatic to causing significant hypothalamic/pituitary dysfunction and visual field compromise due to their large size (Ntali & Wass, 2018). In a recent large (>200 participants), prospectively studied cohort of NFPA, the presentation was approximately 50% incidental and 50% due to tumour-related symptomatology (Freda et al., 2020).

Most symptoms of NFPA are associated with mass effects, including headaches, visual field defects, ophthalmoplegias, and hypopituitarism. Compression of the pituitary stalk may also lead to hyperprolactinemia (Drummond et al., 2019). Although rare, pituitary apoplexy can occur in NFPA; a retrospective study by Vargas et al. found that apoplexy was the initial presentation in 8% of 485 cases (Vargas et al., 2015).

Since NFPAs are not associated with hormonal hypersecretion, their diagnosis is often delayed and typically occurs only when compressive symptoms affect

surrounding tissues. At the time of diagnosis, approximately 67–90% of NFPAs are macroadenomas, with the median age of patients ranging between 51.5 and 65.5 years (Raappana et al., 2010).

The natural progression of unoperated NFPA varies greatly and is influenced by factors such as the tumour's initial size (microadenoma versus macroadenoma), the method of diagnosis (incidental versus non-incidental), and the clinical presentation (symptomatic versus asymptomatic). In contrast, the prognosis and outcomes for surgically managed NFPA are equally diverse, with potential risks including recurrence, tumour progression, hormone deficiencies, and worsening of visual field deficits (Yavropoulou et al., 2020).

2.1.1.1 Micro-non-functioning pituitary adenomas

Micro-NFPAs tend to be incidental findings, given their small size. There is a significant increase in the detection rates of "pituitary incidentalomas" over the years, the majority of which are NFPAs. One example can be the US population study by Watanabe et al, where the incidental detection of pituitary tumours has risen nearly 3-fold between 2004 and 2018 and similar trend has been seen in Northern Finland (Agustsson et al., 2015; Raappana et al., 2010; Watanabe et al., 2022).

To date, there are no uniformly used guidelines on the management of micro-NFPA's on the optimal length of follow-up or the frequency of biochemical and imaging surveillance. This, at least partly, is due to the fact that studies have been carried out on small sample size or looking at various pituitary adenomas as one cohort rather than only NFPA's.

2.2 Cushing's syndrome

Cushing syndrome (CS) results from prolonged elevation in plasma cortisol due to either exogenous steroid use or to excess endogenous cortisol production.

The latest registry data from the European Registry on Cushing's syndrome (ERCUSYN) report a female-to-male ratio of 4:1, and a mean age at diagnosis of 44 years (Valassi, 2022; Valassi et al., 2011).

The most common cause of CS is exogenous glucocorticoid use from any administration route (Reincke & Fleseriu, 2023).

Endogenous Cushing's syndrome comprises two groups: adrenocorticotropic hormone (ACTH)- dependent causes, which make up the majority (70–80% of cases) and ACTH-independent causes. Cushing's disease is the most common form of ACTH-dependent Cushing's syndrome (80–90%), in which a benign pituitary adenoma oversecretes ACTH Non-pituitary ACTH-secreting tumours (ectopic ACTH secretion) represent 10–20% of the ACTH-dependent forms (Tritos & Miller, 2023). Less than 1% of people with Cushing syndrome have a tumour that secretes corticotropin-releasing hormone (CRH) (Valassi et al., 2011).

The incidence of endogenous CS is approximately 2 to 3 per million people annually (Reincke & Fleseriu, 2023).

2.2.1 Clinical presentation and diagnosis

The clinical presentation of Cushing's syndrome varies depending on the severity and duration of cortisol excess. In cases of severe hypercortisolism, the signs and symptoms are typically clear and unmistakable. However, many of the features associated with Cushing's syndrome, such as hypertension and weight gain, are also common in the general population, and not all symptoms are present in every patient (Nieman, 2015). Clinical judgment and index of suspicion for CS are very important. Only patients with clinical features suspicious for hypercortisolaemia and patients with adrenal adenomas should be screened for CS (Reincke & Fleseriu, 2023). Signs and symptoms that occur in CS are listed in Table 2 (Modified from Nieman, 2015).

Table 2. Signs and symptoms of Cushing's syndrome (Modified from Nieman, 2015).

More Common	Less Common
Decreased libido	Atherosclerosis
Obesity/weight gain	Dorsal fat pad
Plethora	Oedema
Round face	Abnormal glucose tolerance/diabetes
Menstrual changes	Osteopenia/osteoporosis
Hirsutism	Headache
Hypertension	Backache
Easy bruising	Recurrent infections
Mood swings, depression	Abdominal Pain
Striae	Acne
Proximal muscle weakness	Female balding

Diagnosing Cushing's syndrome remains a real clinical challenge due to the wide spectrum of presentation, especially in milder or atypical cases. Another diagnostic difficulty arises in distinguishing between various causes of hypercortisolism (Bondugulapati & Lansdown, 2022). Data from ERCUSYN highlights a delay of two years between symptom onset and diagnosis, with multiple specialists often consulted before the correct diagnosis is made (Valassi, 2022).

There is no single preferred diagnostic test for CS, nor is there consensus on how to decide whether and when to test, despite attempts to develop a score for ease of diagnosis (Braun et al., 2019).

Screening and diagnostic tests for CS assess cortisol secretory status: abnormal circadian rhythm with late night salivary cortisol (LNSC), impaired glucocorticoid feedback with overnight 1-mg dexamethasone suppression test (DST) or low dose 2-day dexamethasone test (LDDT), and increased bioavailable cortisol with 24-hour urinary free cortisol (UFC). At least two or three samples

are needed for LNSC and UFC. Most patients require more than one test to establish a diagnosis of CS due to false positive and false-negative results (Fleseriu et al., 2021).

2.2.2 Complications of Cushing's syndrome

The management of patients with CS involves two equally important aspects: the prompt diagnosis and treatment of hypercortisolism, alongside the evaluation and management of associated comorbidities. Increased mortality in these patients is primarily driven by cardiovascular, thromboembolic, and infectious complications. While these risks are expected to decrease during disease remission, their incidence often temporarily rises postoperatively and does not fully return to normal in the long term (Varlamov et al., 2021). Cushing's comorbidities are summarized in Figure 1.

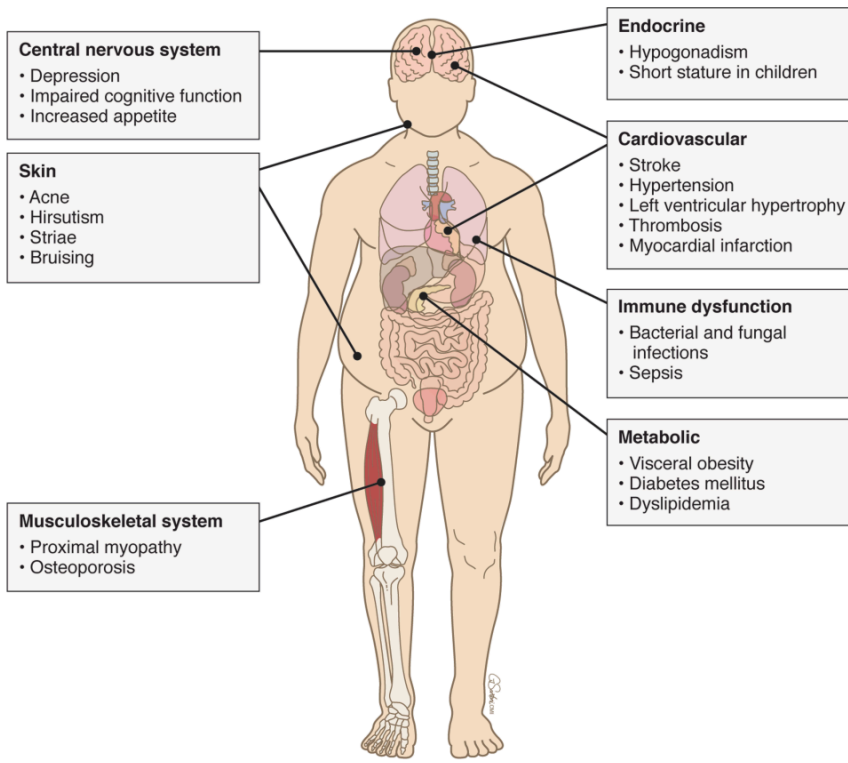

Figure 1. Clinical features of Cushing's disease (Adapted from Melmed et al., 2022 (Melmed et al., 2022), with permission from M. Fleseriu

2.2.2.1 Cardiovascular and metabolic complications

Cushing's syndrome significantly contributes to increased cardiovascular morbidity and mortality by heightening several CV risk factors, such as visceral obesity, insulin resistance, diabetes, hypertension and hyperlipidaemia compared to the general population, manifestation in a metabolic syndrome (Arnaldi et al., 2004; Varlamov et al., 2021). Cardiovascular disease remains the leading cause of death in patients with Cushing's disease, both during the active phase and after remission – highlighting the severe long-term risks of this condition. (Pivonello et al., 2016).

Hypertension, a condition observed in the majority of patients with Cushing's syndrome, is a critical risk factor. Remarkably, Harvey Cushing himself noted in 1932 that 9 out of his first 12 patients suffered from hypertension. Generally, the hypertension is slight to moderate but can, in some cases, be severe (Arnaldi et al., 2004). The main mechanisms involved in the pathogenesis of hypertension in Cushing's syndrome include the modification induced by glucocorticoid excess in the renin-angiotensin system, the mineralocorticoid activity, the sympathetic nervous system, and the vasoregulatory system (Pivonello et al., 2016). Remission from hypercortisolism can improve hypertension but it does not always normalise. In fact, Chihaoui et al found that 75% of patients had hypertension at diagnosis, and only 58% showed remission of hypertension one year after treatment (Chihaoui et al., 2023).

Central obesity, one of the most characteristic clinical signs of hypercortisolism is, by itself, a cardiovascular risk factor.

Hypercortisolism leads to hyperglycaemia and reduced glucose tolerance, determines insulin resistance, stimulates hepatic gluconeogenesis (Arnaldi et al., 2004). An impairment of glucose metabolism has been described in 27–87% of patients with Cushing's syndrome (Scaroni et al., 2017).

Dyslipidaemia in Cushing's syndrome is reported in 12–72% of patients and is commonly characterised by raised total and LDL cholesterol and triglyceride concentrations, and reduced HDL cholesterol concentrations. Dyslipidaemia may persist even one year after surgical remission in patients with pituitary or adrenal Cushing's syndrome (Sun et al., 2020).

Coagulation alterations represent another important factor of cardiovascular risk. About 10% of patients with CS present serious thromboembolic complications and CS is associated with a more than ten-fold increased risk of venous thromboembolism compared with people without Cushing's syndrome. These patients typically exhibit significant abnormalities in the haemostatic system, with a marked tendency towards a prothrombotic imbalance. (Arnaldi et al., 2004; Wagner et al., 2019). Hypercoagulability will be discussed in separate chapter.

2.2.2.2 Infections

CS leads to immunosuppression during its active phase, significantly increasing vulnerability to infections. Patients are nearly five times more likely to develop

infections compared to matched controls(Dekkers et al., 2013).The impairment of immune function associated with active Cushing's syndrome predisposing patients to infectious diseases, especially opportunistic infections. The increased risk of infection applies to virtually any microbial pathogen, but some infections are more common. Infections include opportunistic and commonly acquired bacterial infections (Staphylococcus, Streptococcus, Listeria, Nocardia, Legionella, Enterobacteriaceae, Mycobacterium) as well as fungal infections (Pneumocystis jirovecii, Candida, Aspergillus, and Cryptococcus) and protozoa (Toxoplasma) (Fareau & Vassilopoulou-Sellin, 2007; Lionakis & Kontoyiannis, 2003).

2.2.2.3 Osteopenia/osteoporosis

Bone health is significantly compromised in 64–100% of patients with Cushing's syndrome (Pivonello et al., 2016). Specifically, osteopenia is observed in 40–78% of cases, osteoporosis in 22–57%, and skeletal fractures in 11–76% of patients. Low-energy fractures are particularly common, with an increased incidence occurring within 2–3 years prior to diagnosis and treatment, which is suggestive of the delay in diagnosis (Pivonello et al., 2016).

2.2.2.4 Neuropsychiatric diseases

Psychiatric disorders are a prominent feature in patients with Cushing's syndrome (CS), especially during the active phase of hypercortisolism. Major depression is the most frequent and severe psychiatric manifestation and the prevalence in patients with CS is reported to be about 50–81% (Pivonello et al., 2015). Data from the ERCUSYN registry highlight that 35% of patients with CS experience depression, underscoring its significant contribution to impaired quality of life and delayed diagnosis. Also anxiety disorders and mania are also commonly observed in patients with CS (Valassi, 2022; Valassi et al., 2018).

Given the systemic and neuropsychiatric complications associated with hypercortisolism, it is unsurprising that patients with Cushing's syndrome experience a reduced quality of life (QoL). This has been confirmed using both generic and disease-specific questionnaires, with the Cushing QoL questionnaire being recognized as the most suitable tool for assessing QoL in these patients (Webb et al., 2008).

2.2.2.5 Reproductive and sexual disorders

Reproductive disorders are frequently observed in patients with CS. According to data from ERCUSYN, reduced libido was reported in 47% of cases, menstrual irregularities in 58% of women, and hypogonadism in 23% of men. Notably, menstrual irregularities were significantly more prevalent in pituitary-dependent cases compared to adrenal-dependent cases (Valassi, 2022). Reproductive disorders are frequently observed in patients with CS, contributing to significant challenges with fertility. In fact, infertility has been reported in up to 71% of female patients. (Abdelmannan & Aron, 2011).

2.3 Venous thromboembolism

Venous thromboembolism (VTE) primarily consists of two conditions: deep vein thrombosis (DVT) and pulmonary embolism (PE), but VTE can occur in virtually any venous district. While DVT involves the formation of blood clots in deep veins, typically in the legs, PE occurs when part of a clot detaches and obstructs the pulmonary arteries. VTE remains a significant public health concern due to its high morbidity and potential fatality. VTE is the third most common cardiovascular disorder, affecting up to 5% of individuals during their lifetime. PE accounts for up to 10% of in-hospital deaths, highlighting the need for early diagnosis and prevention of VTE. (Wells et al., 2018; R. H. White, 2003).

The annual incidence of VTE in Europe and the UK is estimated to be 1–2 cases per 1,000 individuals, though this varies based on risk factors (R. H. White, 2003). Risk factors that increase the likelihood of VTE are summarized in Table 2. Numerous risk stratification models have been developed to assist with clinical decision-making; however, there is no consensus on the most effective model. It is essential to assess patients for VTE risk factors and potential bleeding to mitigate these risks(*Overview | Venous Thromboembolism in over 16s*, 2018). Despite these efforts, some VTE events occur without any identifiable cause (Pastori et al., 2023).

The pathogenesis VTE is rooted in Virchow's triad, a concept introduced over 100 years ago and still relevant today. This triad describes three interdependent factors: hemodynamic imbalance, particularly blood stasis; damage to the endothelial vessel wall; and a local or systemic state of hypercoagulability. Venous thrombosis develops when these factors occur simultaneously (Figure 2). For instance, stasis in the deep veins of the legs, combined with heightened blood coagulability and endothelial injury, creates the ideal conditions for thrombus formation.(Blann & Lip, 2001; Kroegel & Reissig, 2003). (Blann & Lip, 2001).

The clinical presentation of VTE varies depending on its localisation. Patients with DVT often experience localised swelling, redness, and tenderness, and severe cases may result in limb discoloration. In contrast, PE symptoms range from sudden breathlessness and chest pain to hemodynamic instability. (Kroegel & Reissig, 2003; Wells et al., 2018).

Diagnostic tools for VTE include D-dimer tests, which help rule out VTE in low-risk patients, compression ultrasonography for diagnosing DVT, and computed tomography pulmonary angiography for diagnosing PE (Konstantinides et al., 2020; *Overview | Venous Thromboembolism in over 16s*, 2018).

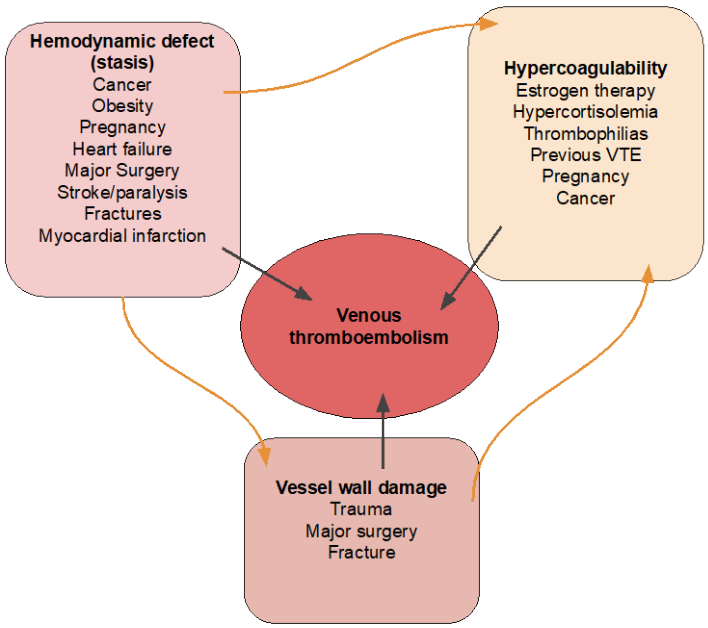

Figure 2. Pathogenic risk factors in VTE development (Virchow's triad). Modified from (Kroegel & Reissig, 2003)

2.3.1 Pharmacological prevention of VTE

Preventing VTE is a critical component of care for at-risk patients, particularly those hospitalised for medical conditions or undergoing surgical procedures. Effective prevention involves a combination of pharmacological and non-pharmacological interventions, guided by individual risk assessments.

Pharmacological prophylaxis is the cornerstone of VTE prevention. There are different anticoagulant medications available. Unfractionated heparin (UFH) that works by inhibition thrombin and factor Xa, is less commonly used today, but remains as a possible medication for some surgical procedures.

Low molecular weight heparins (LMWHs), such as enoxaparin and dalteparin, are widely used due to their more predictable pharmacokinetics and lower risk of complications. For example, enoxaparin is typically dosed at 40 mg subcutaneously once daily for general prophylaxis (Anderson et al., 2019).

Vitamin K antagonists (VKAs), such as warfarin, are another option for VTE prophylaxis, particularly for long-term use in patients with mechanical heart valves or atrial fibrillation. Warfarin works by inhibiting the synthesis of vitamin K-dependent clotting factors and requires close monitoring through the international normalized ratio (INR) to maintain therapeutic levels, usually between 2.0 and 3.0.

Direct oral anticoagulants (DOACs) represent a newer class of anticoagulants. These agents, which include factor Xa inhibitors like rivaroxaban and apixaban, as well as the direct thrombin inhibitor dabigatran, offer the advantage of ease of use without the need for routine monitoring. DOACs are increasingly used for prophylaxis in patients undergoing major orthopaedic surgeries or in acutely ill medical patients (Anderson et al., 2019; *Overview | Venous Thromboembolism in over 16s*, 2018).

For CS patients LMWH is preferred as 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. Data from routine thromboprophylaxis schemes across centres who provide care for patients with CS, shows that LMWH is considered the first choice (Isand et al., 2023; Maria Fleseriu, Beverly MK Biller, Ashley Grossman, Brooke Swearingen and Shlomo Melmed on behalf of the Pituitary Society International Cushing Disease Workshop Task Force, n.d.; van Haalen, Kaya, Pelsma, Dekkers, Endo-ERN Cushing and Thrombosis study group, et al., 2022).

2.3.2 Data on the risk of VTE in non-functioning pituitary adenomas and acromegaly

There is relatively little data on VTE risk in NFPA's and other pituitary adenomas compared to CS where the elevated risk is well known. Generally, patients with NFPA's are not considered to be at an elevated risk for VTE due to their pituitary condition, but there may be individual risk factors for VTE (including age, immobility, history of VTE) that should be taken into account (Stuijver et al., 2011a).

A study by Stuijver et al. analysed 473 patients who underwent transsphenoidal surgery (TSS), including 360 with ACTH-dependent pituitary Cushing's Syndrome and 113 with NFPAs. The findings indicated a higher rate of VTE within three months post-surgery in the Cushing's group (3.4%) compared to the NFPA group (0%), with the difference being statistically significant ($p = 0.01$) (Stuijver et al., 2011b).

The elevation in VTE risk in patients with acromegaly has been previously recognised: a Danish study investigated complications associated with acromegaly versus the general population and found the overall hazard ratio (HR) for VTE to be 2.3 (95% CI: 1.1–5.0), In the younger group (age < 50 years) the risk of VTE was higher (HR: 4.4 (95% CI: 1.5–12.9)), while in the older group, the HR for VTE was 1.7 (95% CI: 0.6–5.2) (Dal et al., 2016). The pathophysiology of elevated risk of VTE associated with increased GH and IGF-1 is unclear. Abnormalities in both coagulation and fibrinolytic systems in patients with acromegaly, such as elevated plasma fibrinogen, antithrombin III, tissue plasminogen activator (t-PA) and plasminogen activator inhibitor 1 (PAI-1) have been reported (Al Dahmani et al., 2015; C et al., 2008; Dal et al., 2016; Kyriakakis et al., 2020; Landin-Wilhelmsen et al., 1997).

2.3.3 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 (Small et al., 1983). 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 (Stuijver et al., 2011a).

Babic et al reported in their retrospective analysis the risk for VTE being 2.6% after adrenalectomy for CS (Babic et al., 2019). 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 (Dekkers et al., 2013). A Swedish Nationwide study also reported an elevated risk for VTE compared to the general population (Papakokkinou et al., 2020). 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) (Papakokkinou et al., 2020). 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 (Wagner et al., 2019).

In a recent systematic review the pooled postoperative VTE incidence in patients after transsphenoidal surgery for CD was 2% (A. J. White et al., 2024).

2.3.4 Additional VTE risk factors

Risk factors other than hypercortisolaemia further elevate the risk for VTE. 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. Risk factors are summarised in Table 3. If any of these risks are present, thromboprophylaxis in CS 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)(Konstantinides et al., 2020; Ortel et al., 2020a; *Reducing the Risk of Thrombosis and Embolism during Pregnancy and the Puerperium (Green-Top Guideline No. 37a)*, n.d.).

Table 3. Risk factors for VTE

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
Surgery
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

2.3.5 Hypercortisolemia – related mechanisms of VTE

Mechanisms that are involved in the thromboembolic complications of hypercortisolism include endothelial dysfunction, hypercoagulability, and stasis (Virchow's triad)(Coelho et al., 2015). 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 (Alves Coelho et al., 2014) (Boscaro et al., 2002).

Patients with CS also present reduced plasma fibrinolytic capacity largely due to an increase in PAI-1, the plasminogen activator inhibitor type 1. The activated thromboplastin time (aPTT) is inversely correlated to levels of free urine cortisol and can be used as a clinical parameter (Arnaldi et al., 2004; Boscaro et al., 2002).

A hypercoagulable phenotype seems to persist even after surgical remission, further stressing the necessity for vigilant thromboprophylaxis (Manetti et al., 2010). Remarkably, most studies do not demonstrate a relation between severity of hypercortisolism, according to UFC values, and risk on VTE (Wagner et al., 2019).

2.3.6 The need for clear guidance for thromboprophylaxis for patients with CS

Although the increased risk of VTE in patients with CS is clear, translating these data into clinical practice guidelines has been challenging (Manetti et al., 2010; Trementino et al., 2010).

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 (Maria Fleseriu, Beverly MK Biller, Ashley Grossman, Brooke Swearingen and Shlomo Melmed on behalf of the Pituitary Society International Cushing Disease Workshop Task Force, n.d.). 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(Isand et al., 2022b, 2023; van Haalen, Kaya, Pelsma, Dekkers, Endo-ERN Cushing and Thrombosis study group, et al., 2022).

2.4 Summary of the literature review

Pituitary adenomas, arising from the anterior pituitary, are classified as functional or non-functional, with prolactinomas being the most common and NFPAs comprising 14–54% of cases. NFPAs are often incidentally detected, yet data on their natural history, particularly for microadenomas, remain limited.

Cushing's disease, a form of ACTH-secreting pituitary adenoma with a prevalence of 2–3 cases per million annually, is associated with significant metabolic and cardiovascular risks. Patients with CD have a markedly elevated risk of VTE. Although the literature underscores a tenfold or greater increase in VTE risk among patients with CS, thromboprophylaxis practices remain inconsistent, reflecting the lack of prospective data and uniform clinical guidelines.

Cohort studies suggest that VTE risk may vary by tumour subtype (e.g., functioning vs non-functioning) and remission status. However, comparative data across subtypes are limited, and existing thromboprophylaxis guidelines for general medical or surgical patients do not address the specific risks in pituitary adenoma patients – particularly those with hypercortisolism. Overall, these gaps in knowledge form the rationale for the studies presented in this dissertation.

3. AIMS OF THE STUDY

The aim of this dissertation is to investigate the clinical behaviour and thromboembolic risk associated with pituitary adenomas, with a particular focus on non-functioning microadenomas and Cushing's syndrome, in order to generate evidence to inform clinical decision-making and guideline development.

The specific aims were:

1. To generate evidence on the natural history of micro-NFPAs to support patient care (paper I).
2. To assess risk of VTE in patients with CD compared to functioning (acromegaly) NFPA pituitary adenomas (paper II).
3. To evaluate the prevalence of VTE in patients with Cushing's syndrome included in the European Registry of CS (ERCUSYN) and identify risk factors for VTE (paper III).

4. MATERIALS AND METHODS

The dissertation is based on three original studies including patients with pituitary adenomas. Study I included patients with CS. Study II included patients with CD, acromegaly and NFPA, study III included patients with NFPA. The main characteristics of the studies are described in Table 4.

Table 4. Overview of the studies

Study	Study cohort	Study aim	Study design
Study I	Patients with Micro-NFPA	To elucidate tumour behaviour, to generate care delivered to this group of patients	Retrospective
Study II	Patients with CD, Acromegaly, NFPA	To compare the prevalence of VTE's in CD, acromegaly, NFPA	Retrospective
Study III	Patients with CS from ERCUSYN	To evaluate the prevalence of VTE in CS and analyse risk factors for VTE	Retrospective

NFPA: non-functioning pituitary adenoma; CD: Cushing's disease; CS: Cushing's syndrome; ERCUSYN: European Registry on Cushing's syndrome; VTE: venous thromboembolism

4.1 Study approvals

The clinical trials were conducted in accordance with the Declaration of Helsinki.

Studies I (micro-NFPA study) and II (CD-acromegaly-NFPA) were retrospective in nature, and there was no intervention beyond routine delivery of patient care; they were registered with and approved as a clinical audit by the respective departments and there were patient consent waivers. Anonymised data were collected using a standardised proforma. For micro-NFPA study, the audit reference number for the co-ordinating centre was CARMS (Clinical Audit Registration and Management System) 16842 (University Hospitals Birmingham NHS Foundation Trust). For CD-acromegaly-NFPA study, the audit reference number for the co-ordinating centre was 7000 (Oxford University Hospitals).

The ERCUSYN study was approved by the ethics committee of the Hospital Sant Pau, Barcelona, Spain, which is the coordinating centre 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.

4.2 Patients and study design

4.2.1 Natural history of non-functioning pituitary microadenomas (study I)

Study I was a multi-centre, retrospective, cohort study involving 23 adult endocrine departments (UK NFPA consortium). Records of patients with the diagnosis of micro-NFPA followed up in the participating centres between January 1, 2008, and December 21, 2021, were reviewed. Diagnosis of micro-NFPA relied on the presence of a pituitary mass with imaging features consistent with an adenoma and maximum diameter <1 cm, and the absence of clinical and/or biochemical evidence of hormone hypersecretion. Cystic lesions considered to represent Rathke's cleft cysts were excluded. The frequency of assessment for hypopituitarism and of follow-up scanning was determined by the individual clinician based on their preference, local protocols, and/or the clinical picture of the patient.

4.2.2 Venous Thromboembolism and Pituitary Adenomas (Study II)

Study II was a retrospective observational cohort study was conducted across three endocrine centres in the United Kingdom (Oxford University Hospitals, Queen Elizabeth Hospital Birmingham, and the University Hospital Bristol). The study included all patients diagnosed with acromegaly, non-functioning adenomas (NFA), or Cushing's disease (CD) between 2010 and 2021. VTE events documented in patient records from four years prior to the diagnosis of the pituitary adenoma until the last follow-up was collected. If multiple VTE events occurred in a single individual, only the first event was analysed.

4.2.3 Prevalence of VTE across ERCUSYN patients (Study III)

Study III was a retrospective observational cohort study utilizing data from the ERCUSYN database, with data extraction performed on February 7, 2022. The database, created in 2008, includes retrospective data from patients diagnosed since January 1, 2000. At the time of analysis, 2174 patients from 57 centres across 26 European countries were included. Patients were included in the study if a follow-up visit reported a VTE event. Controls consisted of ERCUSYN patients without a VTE diagnosis. Additional data on VTE details and the centres' thromboprophylaxis protocols were requested for all VTE cases and obtained in 93% of cases.

4.3 Data collection

4.3.1 Natural history of non-functioning pituitary microadenomas (study I)

Clinical, pituitary imaging, and hormonal data at presentation and during monitoring were collected. The cases were identified from the databases of each centre. Secondary hypoadrenalism was confirmed by dynamic testing (either short Synacthen, insulin tolerance, or glucagon test according to local protocols). Secondary hypogonadism was defined as low, or inappropriately normal, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels coupled with a morning testosterone below the reference range in males, or low oestradiol and oligo/amenorrhoea in women of reproductive age, or as gonadotropins below the age reference in post-menopausal women. Secondary hypothyroidism was defined as low, or inappropriately normal, thyroid-stimulating hormone (TSH) paired with free thyroxine below the reference range. Growth hormone (GH) deficiency evaluation was not routinely performed due to specific criteria set by the UK National Institute of Clinical Excellence (NICE) for GH replacement. Medical and drug history were reviewed in detail for patients diagnosed with pituitary hormone deficits to identify potential confounding factors, such as opiate/opioid use, severe obesity, exogenous steroid use, low body mass index (BMI), and acute illness. Tumour size was defined by the largest diameter on MRI at detection and compared to sizes reported in subsequent MRIs. Total follow-up duration was defined from the date of tumour detection MRI to the last available imaging, or, in cases of surgical intervention, to the last imaging performed during conservative management.

4.3.2 Venous Thromboembolism and Pituitary Adenomas (Study II)

Demographic and clinical data were extracted from patient records, including sex, date and age at pituitary tumour diagnosis, date of pituitary tumour surgery, medical therapies used, treatment outcomes, and history of diabetes or impaired glucose tolerance (IGT), hypertension, osteoporosis, malignancy, dyslipidaemia, and coagulation disorders. Specific details about VTE events were also recorded, such as the type of VTE (deep vein thrombosis, pulmonary embolism, or other), number of VTEs per patient, date and age at VTE diagnosis, BMI, cortisol status in CD patients at the time of VTE, and the use of thromboprophylaxis during VTE management.

4.3.3 Prevalence of VTE across ERCUSYN patients (Study III)

Patient information analysed included sex, age at diagnosis, aetiology of CS, BMI, hypertension, DM, osteoporosis, smoking, cancer diagnosis, clinical status of CS, CS treatment options (surgical, medical, or both), and cortisol values. Remission status was assessed through biochemical tests, such as morning serum cortisol, 24-hour urinary free cortisol, and overnight 1-mg dexamethasone suppression tests, with centres providing both the hormone measurement values and diagnostic interpretations ("low," "normal," or "high") based on assay-specific ranges. For VTE patients, follow-up duration was recorded until the first visit reporting a VTE event, while for non-VTE patients, follow-up extended to the last available visit. Additional information collected included the type of VTE (e.g., pulmonary embolism or deep vein thrombosis), frequency of VTE events, anticoagulation details, antithrombotic stocking use, and routine anticoagulation practices in CS patients at the reporting centres.

4.4 Statistical methods

4.4.1 Natural history of non-functioning pituitary microadenomas (study I)

Percentages were estimated for categorical data and medians with interquartile (IQR) ranges for continuous variables. Micro-NFPA growth- and reduction-free curves were generated by the Kaplan–Meier method and the differences between outcomes in subgroups were explored by the log-rank test. Cox regression analysis was used to assess the effect of various factors on tumour growth and hazard ratios (HR) with 95% confidence intervals (CI) were calculated. There was no significant departure from proportional hazards assumptions for any of the variables. The level of significance was set at $p < 0.05$. Statistical analyses were performed by IBM SPSS Statistics for Windows, Version 20 (IBM Corp., Armonk, NY, US).

4.4.2 Venous Thromboembolism and Pituitary Adenomas (Study II)

Data are presented as mean ± standard deviation (SD) or median (interquartile range – IQR) according to the distribution of variables. The distribution of data was assessed by the Shapiro-Wilk test. A chi-square test of independence was performed to evaluate the odds of VTE events between groups (NFPA, acromegaly, and CD), and OR with 95% CI were calculated. In cases where an expected frequency in the contingency table was less than 5, Fisher's exact test was used.

Cox proportional hazards regression analysis was conducted to identify predictors of VTE events. As our objective was to examine causal associations between pituitary adenoma subtype and the risk of VTE, rather than to build a predictive model, confounder adjustment was applied in the multivariable Cox regression analysis. This approach is supported by guidance in the European Journal of Endocrinology.

Each covariate was individually tested in univariate analysis to determine its association with the time to VTE event. Given the limited number of VTE events (n = 20), we followed a cautious modelling strategy. Although the conventional recommendation is to include no more than one variable per 10 outcome events, recent literature supports the inclusion of more covariates in low-dimensional models when these are prespecified and clinically justified.

Our final multivariable model included four covariates: tumour subtype (exposure), diabetes/IGT (clinically relevant and statistically significant), sex, and age at diagnosis (both common confounders in VTE risk models). We explicitly acknowledge the risk of overfitting and interpret the results accordingly." The proportional hazards assumption was tested using log-minus-log plots. The level of significance was set at $p < 0.05$.

Statistical analyses were performed using SPSS (version 29, Chicago, IL, USA), and illustrations were prepared with GraphPad Prism 8.0 software package (GraphPad Software, Inc., La Jolla, CA, USA).

4.4.3 VTE across ERCUSYN patients (Study III)

Categorical data was expressed as percentages and quantitative data as means and SD (Gaussian distribution) and as median and interquartile range (q25-q75) (non-Gaussian distribution). We analysed data distribution using Shapiro-Wilk test. To compare differences in 24 h urine free cortisol levels between different aetiologies, 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 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 analyse 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)).

5. RESULTS

5.1 Study I

Data for 459 patients with micro-NFPA detected on MRI were retrieved. Median age at tumour identification was 44 years (IQR 31–57); 152 (33.1%) were males and 307 (66.9%) females, with females presenting at an earlier age than males (Table 5). The indications for imaging leading to micro-NFPA detection are shown in Table 6, with the most common being headaches (19.8%). The median maximum diameter of the tumour was 6 mm (IQR 4–8 mm).

Table 5. Patient demographics and tumour characteristics

	NFPA total
Age (years), median, (IQR)	44 (31–57)
Sex	
Males	152/459 (33.1%)
Females	307/459 (66.9%)
Size of micro-NFPA at detection (mm), median, (IQR)*	6 (4–8)
Micro-NFPAs with maximum diameter < 5 mm	125/426 (29.3%)
Micro-NFPAs with maximum diameter ≥ 5 mm	301/426 (70.7%)
Imaging follow-up duration (years), median, (IQR)**	3.5 (1.7–6.1)
Number of MRIs performed in those with imaging follow-up, median, (IQR) **	3 (2–4)

***** Data available for 426 patients

** Data available for 419 patients

IQR = Interquartile Range, micro-NFPA = non-functioning pituitary microadenoma, MRI =Magnetic Resonance Imaging, mm= millimetres

Table 6. Indication for imaging which led to micro-NFPA detection

Primary indication for imaging	Number of patients (%)
Headache	91 (19.8)
Neurological manifestations (excluding headache)	69 (15.0)
"Incidental" finding with no further details available	67 (14.6)
Hypogonadism	60 (13.1)
Hyperprolactinaemia (proved to be transient)	43 (9.4)
Visual disturbance	20 (4.4)
ENT problems *	20 (4.4)
Oligo-/Amenorrhea	16 (3.5)
Abnormal thyroid function tests	15 (3.3)
Screening**	12 (2.6)
Unknown	12 (2.6)
Galactorrhoea	11 (2.4)
Head injury	5 (1.1)
Hypoadrenalism	4 (0.9)
Hypopituitarism, not further specified	4 (0.9)
Pubertal delay/precocious puberty/short stature	3 (0.7)
Investigation for polyuria/polydipsia	2 (0.4)
Suspected Cushing's syndrome	2 (0.4)
Suspected acromegaly	1 (0.2)
Hyponatraemia	1 (0.2)
Obstructive sleep apnoea	1 (0.2)

ENT = Ear, Nose and Throat
** Tinnitus, anosmia, vertigo, otalgia, deafness, sinus or nasal septum or epiglottic problems, and during vestibular schwannoma surveillance*
*** For patients with Multiple Endocrine Neoplasia 1 (MEN1) or with history of cancer or of infiltrative/inflammatory disease*

5.1.1 Imaging outcomes during follow-up

In total, 419 patients had at least 2 MRIs. The median imaging monitoring period was 3.5 years (IQR 1.7–6.1 years). During this interval, acute pituitary apoplexy was diagnosed in one patient (0.2%) (female with an initial 7 mm micro-NFPA, with apoplexy presenting 16 months later and managed conservatively). Amongst the remaining 418 patients, in 49 (11.7%) the micro-NFPA enlarged, in 79 (18.9%) it reduced in size, and in 290 (69.4%) it remained stable.

Cumulative probability of tumour growth was 7.8% (95% CI 4.9%–8.1%), 14.5% (95% CI 10.2%–18.8%) and 18.3% (95% CI 13.0%–23.6%) at 3, 5 and 7 years, respectively (Figure 3, Table 7). Growth incidence was 2.7 (95% CI 2.0–3.5) per 100 person-years and where maximal tumour diameter data were provided (n=41), median increase was 2 mm (IQR 1–3). Median time until detection of first growth was 3 years (IQR 1.6–4.5), and a median number of three MRIs (range 2–6) were performed prior to this. Twenty-four (49%) of micro-NFPAs that grew became macroadenomas (23 of them were > 5 mm at first detection); in the patient with a starting tumour of < 5 mm, growth occurred during

pregnancy with subsequent reduction in size). In the group of 49 cases with tumour enlargement, five were operated on, 18 had no further radiological follow-up available and 26 had imaging monitoring for a median period of 2.1 years (1.3–3.8); in the last subgroup, 12 (48%) showed further increase in tumour size.

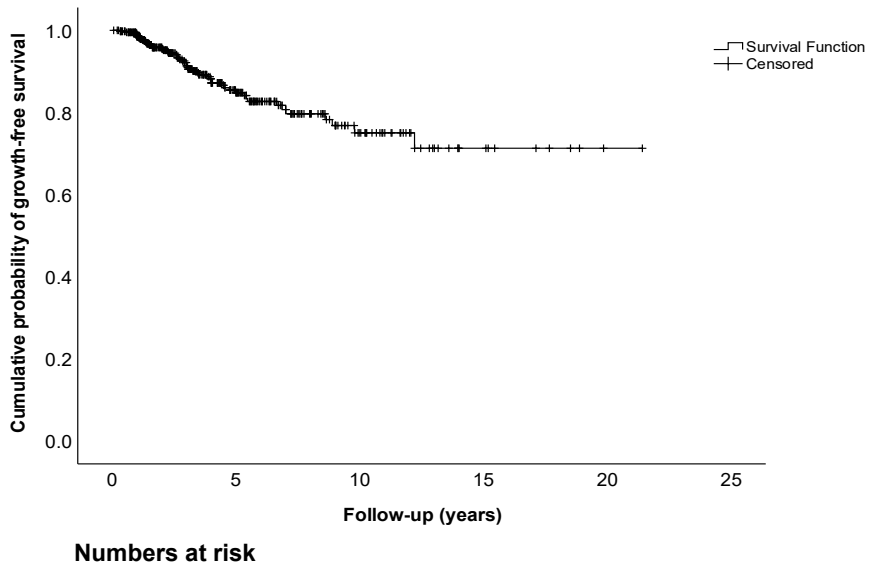

Figure 3. Cumulative probability of non-functioning pituitary microadenoma growth-free survival

During the whole monitoring period, eight patients with grown adenomas (first episode or after further increase) were managed by surgery (all had become macroadenomas, 1.9% of total cases). During the first 3 years of follow-up, one patient had transsphenoidal surgery [size at detection 9 mm – 21 months later, size 17 mm (optic chiasm clear) – operated due to growth]. Reasons for surgical intervention included development of visual field defects secondary to optic chiasm compression (n = 1), tumour abutting the optic chiasm but without visual deficit on neuro-ophthalmic assessment (n = 2), a wish for pregnancy (n = 1), or because of tumour growth alone (n = 4). Pathology showed pituitary adenoma (n = 6), "areas of necrosis and inflammation" (n = 1), or was unavailable (n = 1).

Cumulative probability of tumour shrinkage was 14.1% (95% CI 10.4–17.8%), 21.3% (95% CI 16.4–26.2%) and 26.0% (95% CI 20.1–31.9%) at 3, 5 and 7 years, respectively (Table 7). In the group of 79 cases with tumour shrinkage, 53 had no further follow-up available and 26 had imaging monitoring for a median of 2.1 years (IQR 1.7–3.5); in the last subgroup, nine (34.6%) had further reduction.

Age at micro-NFPA detection, sex, and size of micro-NFPA at time of detection (maximum diameter or size < 5 mm or ≥ 5 mm) were not predictors of enlargement or shrinkage (Table 8).

Table 7. Cumulative probability of tumour growth and reduction

	Cumulative probability of tumour growth (95% CI)		
	Total	**< 5 mm***	**≥ 5 mm***
1 year	1.3% (0.1–1.9)	0%	1.9% (0.3–3.5)
2 years	4.2% (2.0–6.4)	1.1% (0.0–3.3)	5.7% (2.8–8.6)
3 years	7.8% (4.9–8.1)	4.6% (0.0–9.9)	9.9% (8.0–11.8)
5 years	14.5% (10.2–18.8)	13.9% (3.7–24.1)	15.4% (10.1–20.7)
7 years	18.3% (13.0–23.6)	13.9% (3.7–24.1)	19.6% (13.1–26.1)
	Cumulative probability of tumour reduction (95% CI)		
	Total	**< 5 mm****	**≥ 5 mm****
1 year	3.0% (1.2–4.8)	4.7% (0.8–8.6)	2.3% (0.5–4.1)
2 years	9.6% (6.5–11.2)	9.4% (3.5–15.3)	10.2% (6.5–13.9)
3 years	14.1% (10.4–17.8)	15.4% (7.4–23.4)	14.8% (10.1–18.6)
5 years	21.3% (16.4–26.2)	28.8% (17.4–40.2)	20.6% (14.9–26.3)
7 years	26.0% (20.1–31.9)	36.0% (21.9–50.1)	25.3% (18.2–32.4)

* Log rank p=0.772 **Log rank p=0.446

Table 8. Hazard ratios for micro-NFPA growth and reduction

Variable	**Tumour growth Hazard Ratio (HR), 95% CI, *p* value**	**Tumour reduction Hazard Ratio (HR), 95% CI, *p* value**
Age at micro-NFPA detection	1.02 1.00–1.04 0.057	1.00 0.99–1.02 0.577
Sex	0.64 0.36–1.21 0.118	1.19 0.72–1.96 0.495
Tumour size (maximum diameter)	1.09 0.94–1.26 0.255	0.98 0.88–1.10 0.683
Tumour size (< 5 mm or ≥ 5 mm)	1.79 0.80–4.00 0.160	0.83 0.50–1.36 0.447

5.1.2 Pituitary function

At baseline, 33 (7.2%), 8 (1.7%), and 7 (1.5%) patients were reported to have secondary hypogonadism, hypothyroidism, and hypoadrenalism (without other documented factors associated with these findings), respectively (Table 9). Forty-one (85.4%) of those with pituitary hormone deficits had tumours ≥5 mm; the remaining seven (14.6%) had isolated hypogonadotropic hypogonadism and their tumour was <5 mm.

During follow-up, repeat assessment of the FSH/LH, TSH, and ACTH axes was performed in 325 (70.8%), 354 (77.0%), and 310 (67.5%) of patients, respectively. Two patients (0.6%) were diagnosed with new hypopituitarism during follow-up: secondary hypothyroidism in one (who already had hypogonadism and hypoadrenalism at baseline), and secondary hypogonadism, hypothyroidism, and hypoadrenalism in the other. In both patients, hypopituitarism was detected after tumour growth (both became macroadenomas).

Table 9. Prevalence of reported pituitary hormone deficits at time of micro-NFPA detection.

Pituitary hormone deficiency	Number of patients (%)
Isolated FSH/LH deficiency	26 (5.7)
Isolated TSH deficiency	3 (0.7)
Isolated ACTH deficiency	1 (0.2)
FSH/LH and TSH deficiency	1 (0.2)
FSH/LH and ACTH deficiency	2 (0.4)
FSH/LH, TSH and ACTH deficiency	4 (0.9)

5.2 Study II

5.2.1 Study Population

A total of 827 patients were included in the analyses: 107 with CD (12.9%), 502 with NFPA (60.7%), and 218 patients with acromegaly (26.4%). The overall median follow-up duration was 13.4 years (IQR 11.6–14.0), with similar durations across the diagnostic groups: 13.45 years (IQR 11.95–13.96) in patients with NFPA, 13.32 years (IQR 10.68–13.98) in those with CD, and 13.44 years (IQR 11.05–13.92) in patients with acromegaly. A Kruskal–Wallis's test showed no statistically significant difference in follow-up duration across groups ($p=0.412$), and Bonferroni-adjusted pairwise comparisons confirmed that all group differences were non-significant ($p > 0.74$ for all).

Of the 827 patients included, 400 (48.4%) were female and 427 (51.6%) were male. Sex and age distributions differed significantly among the three diagnostic groups. A Pearson Chi-square test revealed a significant difference in sex distribution ($\chi^2= 72.9$, $p < 0.001$), with females comprising 82.2% of the Cushing's disease group, 54.8% of the acromegaly group, and 38.4% of the NFPA group. Median age at diagnosis also differed significantly ($p < 0.001$). Median age was

lowest in patients with CD (43.0 years, IQR 31.0–53.0), intermediate in acromegaly (47.0 years, IQR 36.0–59.0), and highest in NFPA (59.0 years, IQR 49.0–69.0). Post-hoc Bonferroni-adjusted comparisons confirmed significant differences between all three groups ($p < 0.05$). These findings support the inclusion of sex and age as covariates in the adjusted regression model.

At least one TSS had been offered to 770 (92.9%) patients. Of these, 684 (88.8%) had one and 86 (11.2%) had two surgeries. Detailed characteristics of the patients are shown in Table 10. In the CD group, 67 (62.6%) patients were in remission after TSS. Twenty patients out of 107(18.7%) in the CD group received steroidogenesis inhibitors or other cortisol-lowering agents either as primary therapy or as an adjunct to surgery. Two out of 107 (1.78%) patients had undergone bilateral adrenalectomy; neither of them experienced a VTE event. In the acromegaly group, 110 (50.5%) patients achieved remission following TSS.

Table 10. Baseline characteristics of patients at last follow-up

	CD	**Acromegaly**	**NFPA**	**Total**
Sex n (%)				
female	88/107 (82.2)	119/218 (54.8)	193/502 (38.4)	400/827 (48.4)
male	19/107 (17.8)	99/218 (45.4)	309/502 (61.6)	427/827 (51.6)
Follow-up period (years, IQR)	13.32 (10.68–13.98)	13.44 (11.05–13.92	13.45 (11.95–13.96)	13.4 (11.6–14.0)
Age at diagnosis (median, years)	43 [31;53]	47 [36;59]	59 [49;69]	54 [42;67]
TSS n (%)	107/107 (100)	200/218 (91.7)	463/502 (92.2)	770/827 (93.1)
History of diabetes/IGT n (%)	22/73 (30.1)	55/217 (25.3)	117/483 (24.2)	194/773 (25.1)
Hypertension n (%)	37/107 (34.6)	92/216 (42.6)	155/357 (43.4)	284/680 (41.8)
Osteoporosis n (%)	11/98 (11.2)	8/82 (9.8)	49/484 (10.1)	68/664 (10.2)
Dyslipidaemia n (%)	22/72 (30.6)	59/216 (27.5)	134/483 (27.7)	215/771 (27.9)
Coagulation disorder n (%)	0/73 (0)	1/217 (0.5)	1/483 (0.2)	2/773 (0.3)

CD: Cushing's disease; NFPA: Non-functioning pituitary adenoma; TSS: Transsphenoidal surgery; IGT: Impaired glycose tolerance

5.2.2 VTE events

In total, 20 VTE events were documented (2.4%). During follow-up, 11.2% (12/107) of patients with CD experienced at least one VTE event, compared to 0.4% (2/502) in those with NFPA and 2.7% (6/218) in patients with acromegaly. Seventeen out of 20 (85.0%) patients had undergone TSS.

VTE events were more prevalent in patients with CD compared to those with acromegaly ($\chi 2$ 9.897; OR 4.48, 95% CI 1.63 to 12.30, p =0.002) or with NFPA ($\chi 2$ 41.477; OR 21.05, 95% CI 5.83 to 76.02, p < 0.001). Furthermore, patients with acromegaly had higher rate of VTE events compared to those with NFPA ($\chi 2$ 5.694; OR 4.70; 95% CI: 1.16 to 18.95, p=0.026) (Table 11).

Table 11. Risk of VTE across study groups

	OR	**95% CI**	***p*-value**
CD *vs* Acromegaly	4.48	1.63–12.30	0.002
CD *vs* NFPA	21.05	5.83–76.02	<0.001
Acromegaly *vs* NFPA	4.7	1.16–18.95	0.026

CD: Cushing's disease; NFPA: non-functioning pituitary adenoma; OR: odds ratio; 95% CI: 95% confidence interval

Details of VTEs occurring in patients with CD (4 males and 8 females) are provided in Table 2–3 and Figure 2–1. One patient experienced two VTEs, resulting in a total of 13 events. Of these, 8 were PE, 3 were DVT, one retinal vein thrombosis, and one right external jugular vein thrombosis. All patients had pituitary surgery, with 8 out of 12 having one and 4 more than one operation. Four VTEs occurred shortly after TSS, at 1-, 33-, 35-, and 45-days post-surgery; in this group, only one patient was on thromboprophylaxis. In total, 4 events presented within 3 to 24 months before, while 8 were recorded after the diagnosis of CD. Notably, 8 out of 12 events were detected within one year before or after the CD diagnosis. At the time of VTE diagnosis, 5 patients had active CD, as evidenced by serum cortisol levels after dexamethasone suppression testing, elevated 24-hour urine free cortisol, or elevated late-night salivary cortisol levels. Four patients were on hydrocortisone replacement therapy in the postoperative period, one patient had not yet been diagnosed with CD but likely had hypercortisolaemia, and two patients were in remission without glucocorticoid replacement for 31 and 47 months, respectively (Tables 12 and 13).

Table 12. Characteristics of VTE in Patients with CD

Patient	Diagnosis / Surgery	VTE Date	Sex	Age at VTE Diagnosis	BMI (kg/m²)	Active hyper-cortisolism	Type of VTE	VTE Details	Anti-coagulated at time of VTE?	Anticoagulation details
1	2018 / 2018	2017	F	60	Unknown	+	PE	Before the diagnosis of CD	No	Treated with Riva-roxaban for 3 months
2	2013 / 2013	2013	M	64	28	-	PE	Post-TSS, on hydrocortisone; active bowel infection	No	Treated with Warfarin for 1 year, stockings used
3	2013 / 2014	2013	F	63	33	+	PE	23 days after TSS; risk factors: diabetes, dyslipidemia, hypertension	No	Treated with Riva-roxaban for 4 months, stockings used for 1 year
4	2014 / 2015	2019	F	42	42	-	PE	Risk factors: malignancy (cervical carcinoma, 2014), diabetes; history of DVT 6 years prior	No	Treated with Warfarin for 6 months, then switched to lifelong Apixaban
5	2019 / 2019	2017	F	33	30	-	DVT	Diagnosed 2 years prior to CD; risk factors: diabetes	No	Treated with LMWH; stockings used lifelong
6	2021 / 2021	2020	F	74	24.5	++	PE	Risk factors: hyper-tension, diabetes	No	Lifelong Apixaban therapy
7	2013 / 2013	2013	F	35	32.8	-	Right external jugular vein thrombus	35 days post-TSS; risk factors: smoking	No	Treated with Enoxaparin

Patient	Diagnosis / Surgery	VTE Date	Sex	Age at VTE Diagnosis	BMI (kg/m²)	Active hyper-cortisolism	Type of VTE	VTE Details	Anti-coagulated at time of VTE?	Anticoagulation details
8	2012 / 2012	2015	F	48	26.1	-	DVT	Risk factors: diabetes	No	Treated with Enoxaparin
9	2014 / 2014	2014	M	51	22.5	++	Retinal vein thrombosis	35 days pre-TSS; risk factors: smoking, hyper-tension	No	Unknown
10	2018 / 2019	2019	M	46	60.4	-	PE	45 days post-TSS; risk factors: hypertension	No	Unknown
11	2020 / 2021	2021	F	53	27.4	-	PE	33 days post-TSS; risk factors: hypertension, diabetes	Yes	Treated with LMWH at the time of VTE
12	2020 / 2021	2020	M	62	Unknown	+	PE	Fournier's gangrene treated surgically in July 2020	No	Anticoagulation initiated post-VTE

CD: Cushing's disease; M: male; F: female; VTE: Venous Thromboembolism; PE: Pulmonary Embolism; DVT: Deep Vein Thrombosis; BMI: Body Mass Index; TSS: Transsphenoidal surgery; IPSS: Inferior Petrosal Sinus Sampling; LMWH: Low Molecular Weight Heparin; Active hypercortisolism: Presence (+), absence (-), severe (++).

Table 13. Cortisol status at the time of VTE event in patients with Cushing's disease

Cortisol Status at Time of VTE Event	Number of Patients
Active CD	5
Glucocorticoid dependent	4
Recovered HPA axis	2
Likely hypercortisolaemia (undiagnosed)	1

CD: Cushing's disease; HPA: hypothalamic–pituitary–adrenal

Patients classified as "Active CD" had biochemical evidence of hypercortisolaemia at the time of venous thromboembolism (VTE) diagnosis. "Glucorticoticoid dependent" refers to those on hydrocortisone replacement in the postoperative period. "Recovered HPA axis" refers to patients in long-term remission without glucocorticoid replacement therapy. "Likely hypercortisolaemia" refers to the period before the diagnosis of Cushing's disease.

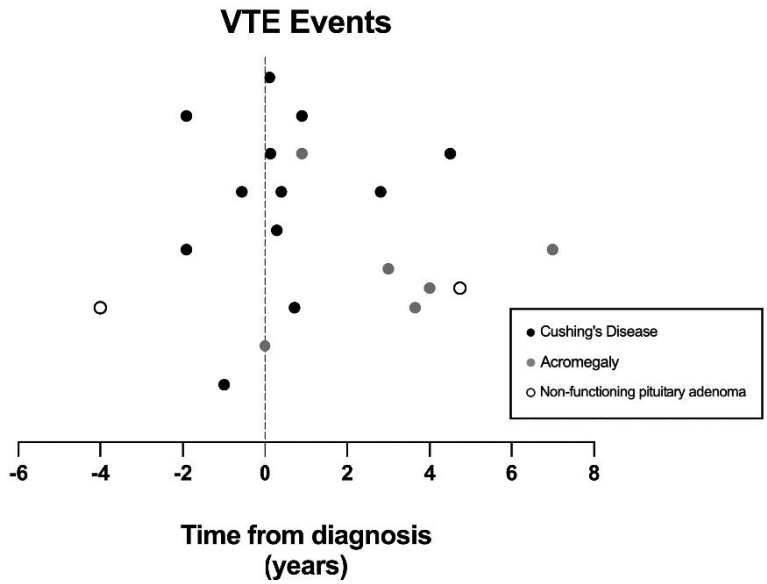

Figure 4. Time of venous thromboembolic event (VTE) in different aetiologies

VTE events in patients with NFPA were diagnosed over a time interval spanning from 4 years before to 4 years after the diagnosis of this tumour (Figure 4). In patients with acromegaly, 4 out of 6 VTE events presented between 3 to 20 years post-diagnosis, while two cases were reported within the first year of acromegaly diagnosis (Figure 4). Among all acromegaly cases with VTE, one event occurred when the patient had elevated IGF-1 levels.

5.2.3 Multivariable Cox Regression

In the univariable Cox regression analysis, a history of diabetes/IGT was associated with time to VTE (HR 4.24, 95% CI 1.71–10.54, p = 0.002) as opposed to sex, age at diagnosis, and cardiovascular risk factors. However, based on established clinical relevance and the observed differences in baseline characteristics across diagnostic groups, sex and age at diagnosis were retained in the multivariable model alongside diabetes/IGT and tumour subtype (see Methods and Table 14). In the adjusted analysis, patients with Cushing's disease had a markedly increased risk of VTE compared to those with NFPA (HR 46.87, 95% CI 11.38–192.98, p < 0.001), and patients with acromegaly also demonstrated a significantly elevated risk (HR 6.96, 95% CI 1.68–28.81, p = 0.007). Diabetes/IGT remained independently associated with VTE (HR 3.48, 95% CI 1.39–8.78, p = 0.008). Notably, neither sex (p = 0.30) nor age at diagnosis (p = 0.12) reached statistical significance in the multivariable model.

Table 14. Multivariate Cox regression analysis

	VTE HR	95% CI	P-value
NFA	reference		
Acromegaly	6.96	1.68–28.81	0.007
CD	46.87	11.38 – 192.98	< 0.001
Age at diagnosis	1.03	0.99 – 1.06	0.124
Female sex	0.58	0.21 – 1.60	0.298
Diabetes/IGT	3.48	1.39–8.78	0.008

5.3. Study III

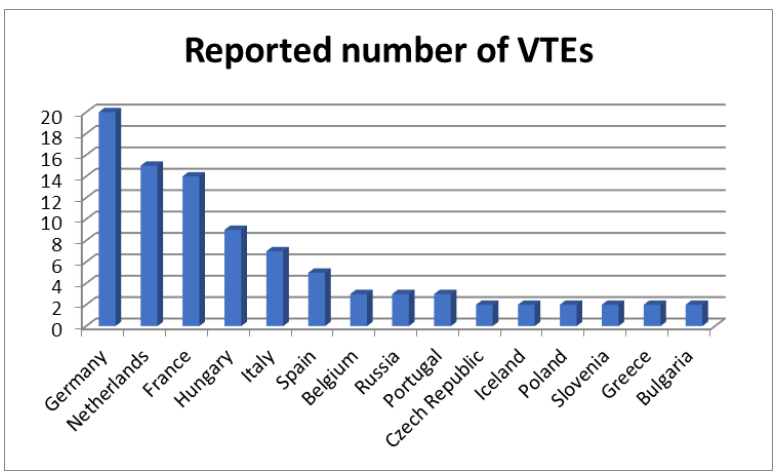

Figure 5. Reported number of venous thromboembolic events (VTE) per country.

VTE events were reported by 28 centres from 16 European countries (Figure 5).

5.3.1 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 15.

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 aetiology, 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 and/or 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.

Table 15. Baseline characteristics and univariate Cox regression of VTE risk factors

Risk Factor	Data available in	All patients	Patients without VTE	Patients with VTE	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)	<0.01
Age at diagnosis (years)	2169	44.9 (±14.3)	44.8 (±14.3)	46.9 (±14.4)	1.01 (0.999–1.03)	0.07
24h 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)	<0.01
Aetiology	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)	<0.05
Ectopic ACTH production		114 (6.1)	104 (5.9)	10 (10.5)	4.65 (2.04–10.62)	<0.01
Other		32 (1.7)	30 (1.7)	2 (2.1)	2.26 (0.51–10.03)	0.28
BMI (cm/kg^2)	1939	30.7 (±6.9)	30.7 (±6.9)	31.0 (±6.4)	1.01 (0.98–1.04)	0.63
Diabetes	1915	666 (34.8)	630 (34.6)	36 (38.3)	1.20 (0.79–1.81)	0.40
Hypertension	2170	1492 (68.8)	1420 (68.3)	72 (78.3)	1.71 (1.04–2.80)	<0.05
Smoking	1688	558 (33.1)	535 (33.1)	23 (31.9)	0.89 (0.55–1.42)	0.62
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)	<0.01
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)	0.03

VTE – venous thromboembolism

Number (%) of patients for categorical values, mean (±SD) for continuous variables with a Gaussian distripution, median (interquantile range) for continuous variables with a non-Gaussian distribution.

BMI-Body mass index; * UFC values were available for 48 patients.

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 6).

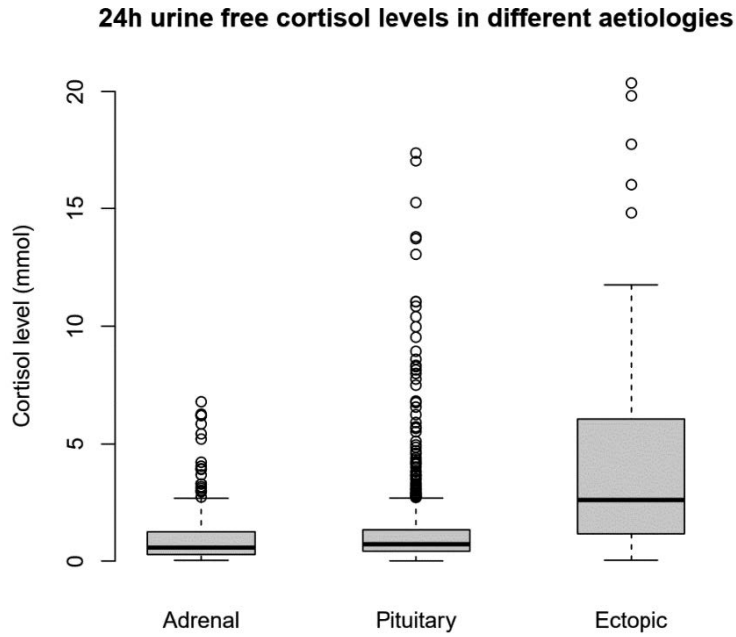

Figure 6. Urine free cortisol values in different Cushing's syndrome aetiologies.

Kruskal-Wallis's test revealed statistically significant difference between groups (P<.01). In post-hoc analysis Dunn's test with Bonferroni correction showed that UFC values between all three pairs of aetiologies 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 7).

Figure 7. 24-hour urinary free cortisol values by sex.

BMIs were similar in CS patients without VTE. The mean (±SD) BMI was 30.7 (±6.9) kg/m2 (range 14.8–58.8 kg/m2). 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, 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). 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, aetiology, hypertension, and the number of operations were included in multivariate Cox regression analysis (Table 16). The second operation was analysed 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.

Table 16. Time-dependent Cox multivariate regression analysis of VTE risk factors

	Hazard rate (95% confidence interval) of VTE on multivariate analysis	**p-value**
Sex		
Female	1	
Male	1.92 (1.17–3.13)	<0.01
Age at diagnosis	1.01 (0.99–1.03)	0.14
24h urine free cortisol (mmol)	1.06 (1.01–1.11)	<0.05
Aetiology		
Adrenal	1	
Pituitary	1.53 (0.77–3.05)	0.23
Ectopic ACTH production	2.16 (0.69–6.71)	0.18
Hypertension	1.13 (0.64–2.00)	0.66
Number of operations		
One	1	
Two or more	1.97 (1.17–3.34)	<0.05

VTE – venous thromboembolism

We also specifically analysed 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 8. 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 post-surgery is shown on a Kaplan-Meier curve for men and women (Figure 9).

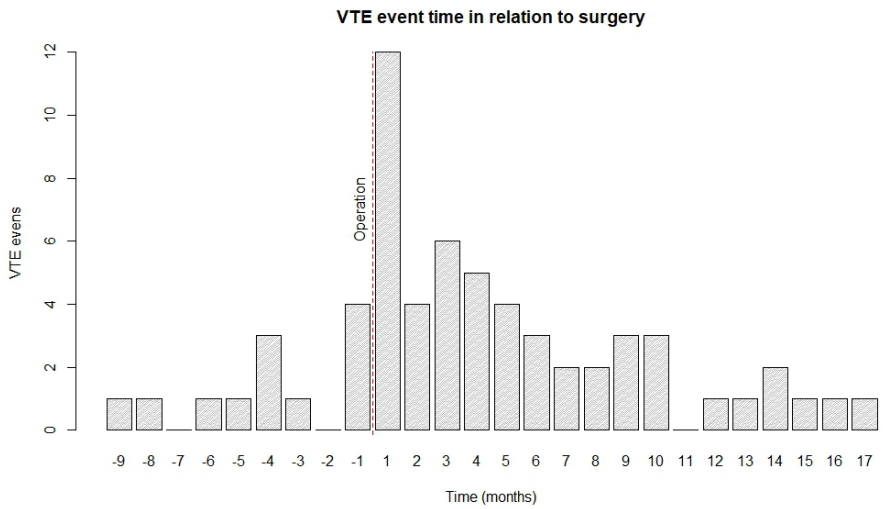

Figure 8. Venous thromboembolic event (VTE) time in relation to surgery.

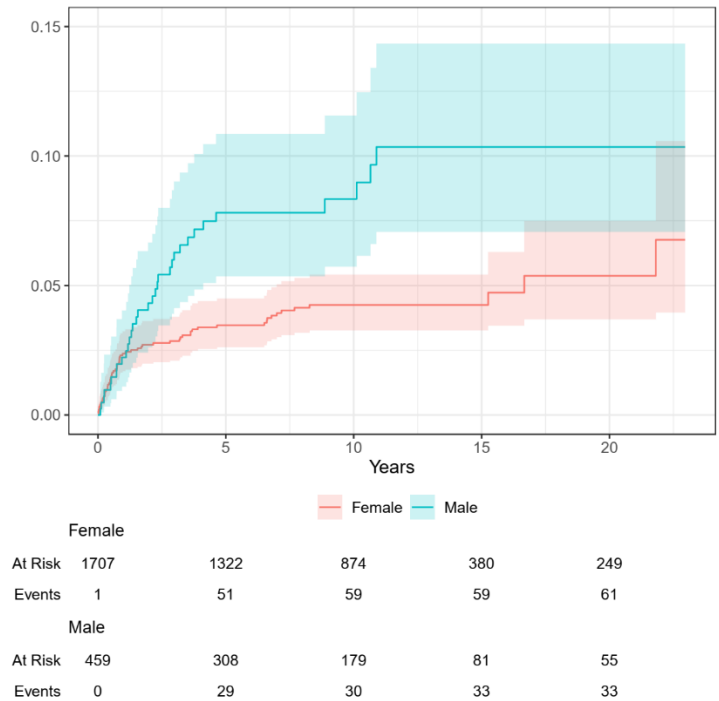

Figure 9. Kaplan-Meier curves showing cumulative incidence of VT.E after operation.

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 centres were contacted to see 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 tumour progression, one died of cardiac failure and for one patient the reason for death was not documented.

5.3.2 Additional information concerning VTEs requested from individual centres

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.

5.3.3 Centres routine thromboprophylaxis schemes

VTEs were reported by 28 centres of which 26 returned the survey. The results are summarized in Table 17.

Looking at the centre's routine thromboprophylaxis protocols, less than half (12/26, 46.2%) anticoagulated on a routine basis. Of the centres 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 aetiology.

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 centres also varied

Table 17. Thromboprophylaxis protocols in ERCUSYN centres with VTE positive cases

	Number of patients (%)
Routine anticoagulation (Total=26)	
YES	12 (46.2)
NO	14 (53.8)
Centres who provide thromboprophylaxis (Total=12)	
Aetiology	
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 centres)	
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 situation: high-risk patients, depending on comorbidities, only cancer patients, following VTE, once medical therapy for hypercortisolism started.

6. DISCUSSION

This dissertation investigates key aspects of managing pituitary adenomas in adults, focusing on the risk of VTE and thromboprophylaxis in CS, as well as the management of micro-NFPAs. Both topics have been marked by clinical uncertainty, with no clear guidance on thromboprophylaxis for patients with CS or follow-up regimens for micro-NFPAs. The findings of this dissertation contribute to knowledge regarding VTE events in CS, but also in acromegaly, and NFPA. Furthermore, clear guidance is now available for clinicians on thromboprophylaxis in CS patients. Additionally, this work offers valuable new insights into the management of micro-NFPAs.

6.1 Study I

To our knowledge, this is the largest study to date elucidating the outcomes of presumed micro-NFPAs in 23 participating endocrine departments (UK NFPA consortium). We have shown cumulative probability of tumour growth of 7.8% and 14.5%, at 3 and 5 years, respectively. The growth incidence was 2.7 per 100 person-years with only 1.9% of the total cases undergoing pituitary surgery during the follow-up period. Tumour size, age at micro-NFPA detection, and sex were not predictors of enlargement. Notably, extremely rare events were the diagnosis of new hypopituitarism (reported in only two patients, both of whom had tumour growth) and the development of acute pituitary apoplexy (in just one patient with an initial tumour size of 7 mm).

Our results on tumour enlargement based on the monitoring of 419 cases are in accord with the findings of some (Fernández-Balsells et al., 2011; Han et al., 2022; Karavitaki et al., 2007), but not all studies (Arita et al., 2006; Sam et al., 2015). In our study, the cumulative probability of tumour reduction was 14.1% at 3 years with a speculative mechanism being ischaemic changes within the tumour.

Currently, for all micro-NFPAs, the Endocrine Society recommends MRI 1 year after detection, and if stable, every 1–2 years for 3 years, and less often thereafter(Freda et al., 2011). Similarly, the German Society for Endocrinology recommends annual MRI for 3 years, and if no change in tumour size, subsequent imaging is organised based on individual evaluation and discussion with the patient (Deutschbein et al., 2021). Others do not recommend further imaging surveillance for micro-NFPAs smaller than 5 mm at detection (Boguszewski et al., 2019; Galland et al., 2015). In a UK survey between 2021 and 2022, there was significant heterogeneity in the imaging monitoring practice adopted amongst clinicians. Interestingly 31% would perform pituitary MRI at 1 year, 18.3% at 1 and 2 years and 18.3% at 1, 2, and 3 years; in all approaches, the patient would be discharged if there was tumour stability (Hamblin et al., 2023). Our data challenge this approach and the existing guidelines, as the median increase during the whole follow-up period in the group of tumours that enlarged

was only 2 mm (IQR 1–3) and the probability of tumour growth in the first 3 years was low. Furthermore, only one patient was offered surgery during the first 3 years of monitoring (due to tumour growth rather than impact on the optic pathways). Consequently, extending the initial imaging interval to 3 years after micro-NFPA detection appears to be a safe, and arguably a more cost-effective approach to micro-NFPA surveillance.

We did not identify clinical predictors of tumour enlargement, particularly tumour size. It is of interest that there was a trend for older age to be associated with higher risk of micro-NFPA growth; larger studies would help clarify whether this is a true finding. In ours, as well as in other studies (Fernández-Balsells et al., 2011; Han et al., 2022; Pernik et al., 2022), the relatively short duration of follow-up has not allowed the establishment of the optimal timing for patient discharge. This short monitoring interval reflects real-world data, as most clinicians discharge the patients within 3 years of confirming tumour stability (Hamblin et al., 2023). Given the small-scale median increase in tumour size, it could be argued that elderly patients and particularly those with tumours <5 mm could be safely discharged after interval imaging at 3 years, or even at the time of the micro-NFPA detection. This would be after discussion with the patient explaining the rationale of this approach. During a median imaging follow-up period of 3.5 years, 1.9% of our cases were offered surgery with only three out of eight compressing or abutting the optic pathway. Whether a longer observation interval could result in a larger ratio of clinically significant tumour enlargement remains to be clarified. In a small subset of tumours that increased in size, growth continued; clarification of the clinical significance of this trend would require long-term surveillance.

The most frequent indication for imaging leading to tumour detection was headache (20% of cases), a symptom commonly reported in this group of patients (Constantinescu & Maiter, 2021; Han et al., 2022; Sanno et al., 2003).

Whether the micro-NFPA is indeed responsible for the headaches is difficult to establish, particularly for smaller lesions that do not trigger pain through dural tears or cavernous sinus invasion (Kreitschmann-Andermahr et al., 2013).

After micro-NFPA detection, a minority of patients were found with pituitary hormone deficits at baseline; 7.2% with secondary hypogonadism, 1.7% with secondary hypothyroidism, and 1.5% with secondary hypoadrenalism. Interestingly, in 15% of the cases, the tumour size was <5 mm. Whether the aetiology of the pituitary dysfunction correlates with pressure effects from the micro-NFPA in all cases is not clear and this could be particularly debated for small tumours or in the cases of reported isolated ACTH or TSH deficiency. Our results are in concordance with other series (Argan et al., 2021; Han et al., 2022; Kim et al., 2018; Lenders et al., 2016; Sanno et al., 2003) though exceptions include one study with loss of at least two hormonal axes in 50% (Yuen et al., 2008), and another with loss of one or more hormonal axes (most commonly LH/FSH and TSH deficiencies) in 42% of cases with micro-NFPAs (Sam et al., 2015). It should be highlighted that both studies had a small sample size (19 and 38 patients), and the possibility of clinical confounders in the patient groups cannot be excluded (eg,

in the study with a 50% rate of hypopituitarism, patients' mean BMI was 36.2 kg/m2) (Yuen et al., 2008). In our cohort, a considerable number of patients were screened for hypopituitarism in the absence of known tumour growth. This also featured in the UK survey, in which 47% of the respondents opted for annual pituitary function assessment (Yuen et al., 2008). We found that only 0.6% of the patients developed new hypopituitarism (detected after tumour growth which became macroadenoma). Our findings (also supported by the results of others (Fernández-Balsells et al., 2011; Han et al., 2022; Imran et al., 2016)), underpin the concept that there is little value in repeated hormonal screening in patients with stable imaging or no new clinical manifestations of hypopituitarism, as recommended by the Endocrine Society (Freda et al., 2011) and the French Society of Endocrinology guidelines (Galland et al., 2015).

The findings for this large, multi-centre study have further elucidated uncertainties over the natural history of conservatively managed micro-NFPAs and inform clinical practice. The low probability of tumour growth, especially during the first 3 years from micro-NFPA detection, combined with the absence of relevant clinical consequences, provides reassurance for both clinicians and patients. They also give ground to the argument for revising the current international imaging recommendations, as it has also been proposed in two smaller single-institution US reports (Han et al., 2022; Hordejuk et al., 2023). Delaying the first follow-up MRI to 3 years and reinforcing the need to avoid re-evaluation of pituitary function in the absence of tumour growth or of relevant clinical manifestations are important cost-effective approaches and, given the expanding detection rates of micro-NFPAs, could lead to considerable financial savings and spare significant resources for healthcare systems. In the absence of predictors of micro-NFPA growth, defining the group of patients requiring closer attention is challenging. Until longer-term follow-up studies are available, imaging at 3 years and if the tumour is stable, at 6 years from time of micro-NFPA detection would be a reasonable approach with an earlier scan dictated by a high index of suspicion of growth (eg, visual field deficits) or clinical signs of apoplexy.

6.2 Study II and Study III

In these studies, we demonstrate a significantly high risk of VTE in patients with CD and when compared to patients with acromegaly or NFPA. To our knowledge, this is the first study to analyse VTE prevalence in a sizeable cohort of patients with both functioning and non-functioning pituitary tumours over a median follow-up duration of 13.4 years.

VTE affects approximately 1–3% of the general population, and thromboprophylaxis is routinely used in patient groups with recognised elevated risk (Key et al., 2020). However, despite increasing evidence of VTE risk in CD, it is not yet standard practice to provide routine thromboprophylaxis in these patients. The Pituitary Society first highlighted this inconsistency in 2013, reporting that only 54% of surveyed centres provided perioperative thromboprophylaxis (Maria

Fleseriu, Beverly MK Biller, Ashley Grossman, Brooke Swearingen and Shlomo Melmed on behalf of the Pituitary Society International Cushing Disease Workshop Task Force, n.d.). More recent surveys have shown persistent variation: 74% in Endo-ERN centres, 46% in ERCUSYN centres, and 48% in Society for Endocrinology centres (Isand et al., 2022a, 2023; van Haalen, Kaya, Pelsma, Dekkers, Biermasz, et al., 2022a) indicating no clear improvement in practice despite growing evidence of elevated risk.

Our cohort confirms that patients with CD have a markedly elevated risk of VTE, with an 11.2% incidence rate, including a 47-fold higher risk than NFPA and a 7-fold higher risk than acromegaly. Notably, 33% of VTE events occurred within 45 days of transsphenoidal surgery (TSS), underlining the perioperative period as particularly vulnerable(Stuijver et al., 2011a; Wagner et al., 2019). Postoperative immobilisation and a sharp drop in cortisol may contribute to a pro-inflammatory, procoagulant state (Giraldi et al., 2011; van der Pas et al., 2012).

Although the majority of VTEs clustered around diagnosis and surgery, events occurred up to five years post-TSS, even in biochemically controlled patients. A nationwide study showed a 5-year HR of 3.53 for VTE in CD compared to matched controls but did not clarify the timing of events (Rudman et al., 2024). In the ERCUSYN cohort, VTEs were recorded up to 17 months post-surgery (Isand et al., 2023) and Dekkers et al showed that VTE risk peaks around diagnosis, diminishes after a year, but remains elevated long term (Dekkers et al., 2013).

Based on our findings and those of others, we recommend initiating thromboprophylaxis at diagnosis and continuing it for at least three months following biochemical remission. The optimal duration remains uncertain, but current proposals range from 1 to 6 months post-surgery, with some advocating longer use due to persistent coagulation abnormalities (Stuijver et al., 2011a; Suarez et al., 2020; Varlamov et al., 2021) (Vogel et al., 2023). Prospective randomised controlled studies could provide evidence for determining the optimal regimens. A recent Delphi panel consensus advises prophylactic LMWH for all patients with endogenous Cushing's syndrome at diagnosis and for three months post-remission, even if surgery is delayed (Isand et al., 2025).

The postoperative risk is particularly well documented: ERCUSYN registry data show 87% of VTEs occurred postoperatively, with nearly half within six months. A retrospective study comparing extended thromboprophylaxis with LMWH for 30 days plus elastic stockings versus a shorter duration found zero VTE cases in the extended group, compared to two cases in the shorter-duration group(Barbot et al., 2015). VTE incidence of 2%. A retrospective study found zero VTEs with 30-day LMWH + stockings vs. two VTEs with shorter prophylaxis (Barbot et al., 2015), and another study showed pharmacologic prophylaxis was safe, with only 1.5% haemorrhagic complications (McCormick et al., 2022).

In Study II, on multivariable analysis, diabetes mellitus/IGT emerged as an independent risk factor for VTE in patients with CD. This aligns with previous findings but remains difficult to interpret due to confounders such as obesity and

glycemic control (Bai et al., 2015; Ding et al., 2023; Gariani et al., 2016; Heit et al., 2016). A recent meta-analysis cited a modest increased risk by DM for developing VTE (OR 1.27) (Ding et al., 2023).

Acromegaly showed a comparatively lower VTE risk (HR 4.4 vs general population), though the underlying mechanism is unclear. GH hypersecretion may alter clot structure, with pilot data suggesting denser, more compact fibrin clots (Dal et al., 2016) (Kyriakakis et al., 2020).

Looking at patients with CS from the ERCUSYN cohort (Study III), the VTE prevalence was 4.4%, consistent with previous studies: 7.8% and 13.9% (Stuijver et al., 2011a; Suarez et al., 2020). At the same time van Zaane reported a wide range of VTE risk (1.9–56%) depending on timing. While pulmonary embolism was seen in 27.6% of cases, VTE-related fatality was uncommon. (Van Zaane et al., 2009). Male gender, higher UFC at diagnosis, and repeat surgery were significant predictors of VTE. Reoperation increased VTE risk (HR 2.18, 95% CI 1.38–3.45), highlighting the need for perioperative thromboprophylaxis in patients with refractory or recurrent disease. Our data also show that VTE risk peaks between 3–6 months post-op and remains elevated up to 10 months, declining thereafter. This may reflect not only surgical trauma but a rebound pro-inflammatory response from acute cortisol withdrawal, particularly after bilateral adrenalectomy (Lopes et al., 2023). We looked VTE's at any timepoint during CS lifespan, but a retrospective multicentre study by Stuijver at 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.

Hypertension was associated with VTE in univariate but not multivariate analysis, consistent with previous studies (Holst et al., 2010; Nazarzadeh et al., 2023). Meta-analyses have suggested a possible association in surgical patients (Huang et al., 2016).

Obesity was not an independent risk factor, with similar BMI distributions in patients with and without VTE. Ectopic CS, however, was clearly associated with higher VTE risk, likely due to its malignant etiology (Wagner et al., 2018b).

Cortisol levels at the time of VTE were normal or low in over half of patients, supporting the hypothesis that thrombotic risk persists despite biochemical remission. Still, patients who developed VTE had higher UFC at diagnosis than those who did not. VTEs were recorded up to 10 years after CS diagnosis, though some of these may be unrelated to prior hypercortisolism and instead due to age, malignancy, or infection (Suarez et al., 2020; Wagner et al., 2018b).

There remains considerable debate regarding optimal anticoagulation strategies in CS. While bleeding risk in neurosurgery is often raised as a concern, most data suggest the risk is low and largely limited to minor bleeding events (Alshehri et al., 2016; Capatina & Fleseriu, 2021). The Endo-ERN group found no increased surgical bleeding in CS patients undergoing adrenalectomy (Miyazato et al., 2011).

In our dataset, fewer than half of VTE patients received anticoagulation, likely reflecting the absence of clear guidelines and the understanding that CS alone is

not an indication for lifelong thromboprophylaxis. Duration and type of anticoagulation varied widely.

We mapped protocols across ERCUSYN centres reporting VTEs. Our survey had a 93% response rate (25/28 centres), the highest compared to previous audits (Endo-ERN 78%; Society for Endocrinology 39%) (Isand et al., 2022b; van Haalen, Kaya, Pelsma, Dekkers, Biermasz, et al., 2022b).

These data reflect wide variability in practice and highlight the lack of standardised guidance.

LMWH remains the most used agent, but this is at odds with current international guidelines (ASH, NICE), which recommend direct oral anticoagulants (DOACs) as first-line for most VTE indications due to convenience and cost-effectiveness (Ortel et al., 2020b; *Recommendations | Venous Thromboembolic Diseases*, 2020). Mechanical thromboprophylaxis (e.g. compression stockings) was used by 36% of Endo-ERN centres and 26% of Society for Endocrinology centres, but the Delphi panel recommends against routine use of stockings in CS.

These findings underscore the urgent need for prospective studies and clear, evidence-based guidelines to standardise thromboprophylaxis in Cushing's syndrome.

Most recently, a Delphi panel of international experts published the first formal position statement addressing this gap, which also serves as an umbrella document synthesising the collaborative work conducted as part of this thesis (Table 16 and Figure 10).

The consensus supports initiating prophylactic anticoagulation at the time of definitive CS diagnosis and recommends continuation for at least 3 months following biochemical remission, unless contraindicated. This guideline acknowledges the persistence of a hypercoagulable phenotype even after cortisol normalisation and advocates the use of standard weight-based low-molecular-weight heparin (LMWH) as the preferred agent. The panel reached consensus that patients with CS, regardless of aetiology, should receive thromboprophylaxis if no contraindications, and that mechanical prophylaxis (e.g. compression stockings) is not recommended. Importantly, the document also includes perioperative recommendations, reinforcing the role of LMWH in surgical settings and recommending reassessment of prophylaxis around inferior petrosal sinus sampling (IPSS).

This statement, based on structured multi-round consensus, offers the most up-to-date and comprehensive guidance available and is expected to help harmonise care across centres, reduce VTE incidence, and guide future audits and research.

Table 9. Recommendations for thromboprophylaxis in patients with Cushing's syndrome (CS) (Isand et al. 2025)

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 remission in the absence of obvious contraindications.	**82.4%**	**Round 2**
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 additional risk factors.	**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**

No	Statement	Agreement	Consensus conceived
	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**

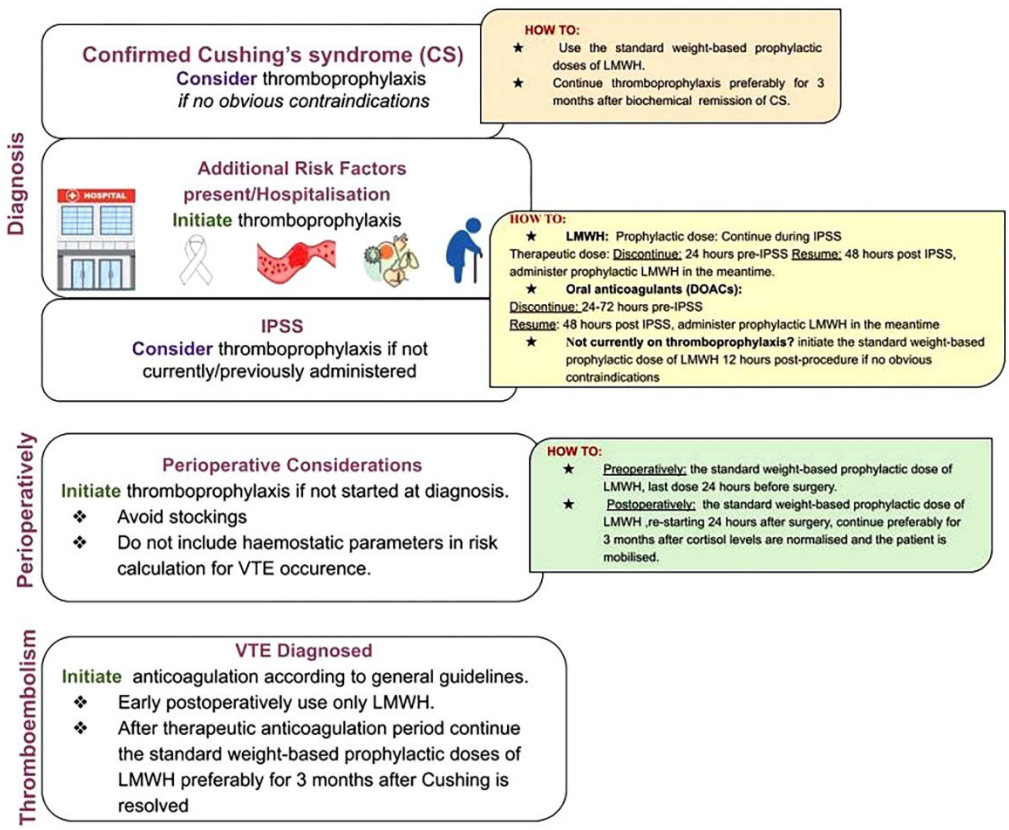

Figure 10. Recommended thromboprophylaxis strategy in patients with Cushing's syndrome (Isand 2025).

6.2.1 Strengths and limitations

In study I, the strengths include its large sample size and its multi-centre design with wide representation of UK endocrine departments, allowing the inclusion of more diverse groups of patients. Furthermore, those with hypopituitarism – either at baseline or diagnosed during follow-up – were carefully screened to clarify whether the hormonal deficits could be attributable to other confounding factors. Limitations include the lack of pathological confirmation of the diagnosis of adenoma which is, however, inherent to this study that aimed to investigate the outcomes of conservatively managed presumed micro-NFPAs. Variation in image interpretation amongst radiologists from participating centres needs to be considered and this could not be ameliorated due to the retrospective nature of the study; nonetheless, the findings represent "real- world" data reflecting daily clinical practice. GH deficiency was not routinely evaluated given the specific criteria for obtaining GH replacement set by the UK healthcare funding regulator (NICE), which includes fulfilling all 3 of the following criteria.

Firstly, severe GH deficiency, defined as a peak GH response of less than 9 mU/litre (3 ng/ml) during an insulin tolerance test or a cross-validated GH threshold in an equivalent test. Secondly, perceived impairment of quality of life (QoL), as demonstrated by a reported score of at least 11 in the disease-specific 'Quality of life assessment of growth hormone deficiency in adults' (QoL-AGHDA) questionnaire. Thirdly, a patient is already receiving treatment for any other pituitary hormone deficiencies as required ('Human Growth Hormone (Somatropin) in Adults with Growth Hormone Deficiency', n.d.). GH deficiency assessment would have added value in this context, as GH is typically among the earliest hormones to be affected by mass effect in NFPAs. This reflects the vulnerability of somatotroph cells, which are often the first to be compromised as the tumour expands. Early GH deficiency can signal evolving hypopituitarism, and its detection may serve as a sensitive marker for assessing pituitary damage. Furthermore, GH deficiency in adults has been associated with adverse metabolic and quality of life outcomes, underscoring its clinical relevance even if not life-threatening(Melmed et al., 2022).

The long interval covering this study, the wide geographical and organisational spread of the participating departments, as well as the variations and changes in the reporting practices may have introduced under-reporting of the micro-NFPAs in the databases of the centres. Finally, similarly to previous studies (Han et al., 2022; Karavitaki et al., 2007; Sam et al., 2015), the follow-up duration did not allow us to provide estimates of tumour behaviour in the longer term.

In study II, study has several strengths and limitations. It includes patients from three large pituitary referral centres, followed for a median of 13.4 years (IQR 11.6–14.0), and represents the largest cohort to date examining VTE prevalence in patients with CD compared to other pituitary tumours.

The retrospective design introduces the possibility of bias due to reliance on the accuracy and completeness of medical records. Additionally, we did not

collect data on oral contraceptive use, pregnancy, or family history of VTE, which may represent relevant confounding factors.

While the overall cohort was large, the number of VTE events was limited (n = 20), particularly in subgroup analyses, which constrained the complexity of multivariable modelling. We included four carefully selected covariates based on strong clinical rationale and previous literature. Although this exceeds the conventional threshold of 10 events per variable (EPV), prior studies support the validity of such models in low-dimensional settings2. Nonetheless, we acknowledge the potential for overfitting and interpret the findings with appropriate caution.

Despite these limitations, the size of the cohort and the long duration of follow-up enhance the study's value in evaluating VTE risk in patients with CD. To our knowledge, this is the first study to compare VTE prevalence across both functioning and non-functioning pituitary adenomas. Furthermore, we were able to review and analyse each individual VTE event to explore possible contributing factors.

In study III, the strengths include being 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. As we were able to analyse VTE's 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 is carried out, we cannot exclude the possibility that some of the VTE's were not reported and therefore missed, especially in countries where fewer VTE´s 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 centres were a VTE had been reported. Therefore, it only gives information about some centres and does not mirror the thromboprophylaxis schemes for all ERCUSYN centres.

6.2.2 Future perspective

There is a need to further study exact thromboprophylaxis details including the possibility of using DOACs. Another clinical question remains 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 (Fleseriu et al., 2023)). Furthermore, coagulation profile normalisation time remains uncertain.

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.

7. CONCLUSIONS

Overall, this dissertation highlights the heterogeneity of clinical behaviour and thromboembolic risk across pituitary adenoma subtypes and provides evidence to guide tailored patient management.

Main conclusions from the individual studies:

1. Non-functioning pituitary adenomas demonstrate low risk for clinically relevant growth or symptom development during long-term follow-up. This supports the safety of conservative management in selected patients.
2. Patients with Cushing's disease have a significantly higher risk of venous thromboembolism compared to patients with non-functioning adenomas or acromegaly, even during remission. These results affirm the need for tumour subtype-specific venous thromboembolism (VTE) risk evaluation.
3. Registry-based analysis of Cushing's syndrome patients across the European Registry for Cushing's syndrome (ERCUSYN) confirms elevated VTE prevalence, particularly around the time of diagnosis and surgical treatment. Although the risk remains elevated long-term, recent data now support evidence-based recommendations for extended thromboprophylaxis for 3 months after achieving biochemical remission in patients with CS.

A Delphi panel position statement was developed to provide structured guidance for thromboprophylaxis in endogenous Cushing's syndrome, bridging the previous gap in international clinical practice. This consensus supports systematic thromboprophylaxis based on patient- and disease-specific risk profiles.

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9. SUMMARY IN ESTONIAN

Mittefunktsioneerivate hüpofüüsi mikroadenoomide loomulik kulg ja venoosse trombemboolia esinemus hüpofüüsi adenoomi ja Cushingi sündroomiga patsientidel

Sissejuhatus:

Hüpofüüsi ehk ajuripatsi adenoomid on sagedased ajuripatsi eessagara kasvajad, mille levimus üldpopulatsioonis on hinnanguliselt kuni 22%. Need jagunevad funktsioneerivateks ja mittefunktsioneerivateks adenoomideks (NFPA-deks). Viimased ei põhjusta hormonaalset hüpersekretsiooni, kuid võivad avalduda kompressioonisümptomite kaudu (peavalu, nägemisväljade häired) või hüpopituitarismina. Suurusest lähtudes jagataks NFPA-d mikroadenoomideks (alla 1 cm diameetriga) ja makroadenoodenoomideks (üle 1 cm diameetriga). Mikroadenoomid on enamasti juhuleiud ja teadmised nende kasvutendentsi ja kulu kohta on endiselt piiratud.

Cushingi sündroom (CS) on kliiniline seisund, mis tekib organismi pikaajalisest kokkupuutest liigse kortisooliga. Kõige sagedasem hüperkortisoleemia põhjus on eksogeenne glükokortikoidide pikaajaline kasutamine.

Endogeensetest põhjustest on kõige sagedasem ACTH-toodav hüpofüüsi adenoom (Cushingi tõbi), harvematel juhtudel võib hüperkortisoleemia olla tingitud ka neerupealiste kasvajast või ektoopilisest ACTH tootmisest.

CS on haruldane ja tõsine endokriinhaigus, millega kaasneb suurenenud metaboolne, kardiovaskulaarne ja trombemboolia risk. Patsiendidel, kellel on CS, on oht venoosse trombemboolia (VTE) tekkeks oluliselt tõusnud ulatudes kuni kümnekordselt üle üldpopulatsiooni riski. Seni seletamatul põhjusel püsib kõrgenenud risk isegi aastaid pärast haiguse remissiooni. Siiani on puudunud ühtne lähenemine tromboprofülaktika rakendamisele CS-i patsientidel, kuigi uuringud on korduvalt rõhutanud selle vajalikkust. On ebaselge, kui suur on VTE risk erinevate ajuripatsikasvajate lõikes ning millised patsiendigrupid on enim ohustatud.

Eesmärgid

Doktoritöö üldine eesmärk oli hinnata erinevat tüüpi hüpofüüsi adenoomide loomulikku kulgu ja trombemboolia riski, eeskätt mittefunktsioneerivate hüpofüüsi mikroadenoomide ja Cushingi sündroomiga patsientidel, et toetada tõenduspõhiste jälgimisjuhiste ja otsustamisprotsesside väljatöötamist.

Töö spetsiifilised eesmärgid olid:

1. Selgitada mittefunktsioneerivate hüpofüüsi mikroadenoomide looduslikku kulgu ja jälgimisvajadust.
2. Võrrelda VTE esinemissagedust Cushingi tõve, akromegaalia ja mittefunktsioneerivate adenoomide vahel.
3. Hinnata Cushingi sündroomiga patsientide seas VTE levimust ja sellega seotud riskitegureid Euroopa registri ERCUSYN andmete põhjal.

Uuritavad ja meetodid:

Kõik uuringud olid retrospektiivsed mitmekeskuselised kohortuuringud.

Esimene uuring analüüsis kliinilist kulgu, pildidiagnostilisi ja hormonaalseid muutusi 459 mikro-NFPA diagnoosiga patsiendil 23 Ühendkuningriigi endokrinoloogia osakondades aastatel 2008–2021.

Teine uuring viidi läbi kolmes Suurbritannia keskuses ning hõlmas patsiente, kellel oli diagnoositud akromegaalia, mittefunktsioneeriv hüpofüüsi adenoom või Cushingi tõbi. Kokku kaasati uuringusse 827 patsiendi andmed (107 Cushing'i tõvega, 502 NFPA, 218 akromegaalia diagnoosiga), analüüsiti esmast VTE juhtumit ajavahemikus neli aastat enne endokriinhaiguse diagnoosi 2010 aastast kuni 2021 aastani, et leida ka VTE'd mis diagnoositi enne hüpofüüsi haiguse diagnoosi.

Kolmas uuring kasutas ERCUSYN registri retrospektiivseid andmeid, hõlmates 2174 patsienti 26 Euroopa riigist. VTE juhtumid tuvastati järelkontrolli käigus ning lisaks koguti infot tromboprofülaktika protokollide kohta keskustest, kus oli VTE'ga patsient esinenud. Uuringutesse kaasati ERCUSYNi registrisse kantud VTE-dokumenteeritud patsiendid ja neid võrreldi CS haigetega ERCUSYNis, kellel ei esinenud venoosse trombembooliat.

Tulemused ja järeldused:

Doktoritöö põhijäreldused olid:

1. Mittefunktsioneerivate hüpofüüsi mikroadenoomide loomulik kulg on üldjuhul healoomuline. Adenoomi kliiniliselt olulise edasise kasvu või uute sümptomite tekke risk on madal. Seega võib paljudel juhtudel rakendada konservatiivset jälgimisstrateegiat.
2. Cushingi tõvega patsientidel esineb märgatavalt suurem VTE risk võrreldes akromegaalia ja mittefunktsioneerivate adenoomidega. See toetab kasvaja alatüübi põhist tromboosiriski hindamist.

3. Euroopa Cushing'i sündroomi registri (ERCUSYN) andmetel on Cushingi sündroomi patsientidel märkimisväärne trombemboolia risk, eriti diagnoosimise ja operatsiooni-järgsel perioodil. Kõrgenenud risk püsib ka remissiooni järgselt ja seetõttu on soovitatav tromboprofülaktikat rakendada 3 kuud peale biokeemilise remissiooni saavutamist.

Lisaks koostati Delphi ekspertpaneeli põhjal rahvusvaheline seisukohavõtt tromboprofülaktika kohta Cushingi sündroomi puhul, mis täidab senise soovituste tühimiku ja aitab arstidel rakendada süstemaatilist riskipõhist lähenemist.

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PUBLICATIONS

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List of Publications:
Isand K, Pofi R, Haermson O, Vergis M, Mahendran H, Ayuk J, Wass J, Yajnik P, Bradley K, Karavitaki N, Pal A. Venous thromboembolism in patients with pituitary adenoma: UK multicentre cohort study. Eur J Endocrinol. 2025 Jul 31;193(2):270–277. doi: 10.1093/ejendo/lvaf139. PMID: 40608956..

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Jenkins GW, Kanatas A, Keohane S, Kerawala CJ, Keys W, King EV, Kong A, Lalloo F, Laws K, Leong SC, Lester S, Levy M, Lingley K, Madani G, Mani N, Matteucci PL, Mayland CR, McCaul J, McCaul LK, McDonnell P, McPartlin A, Mercadante V, Merchant Z, Mihai R, Moonim MT, Moore J, Nankivell P, Natu S, Nelson A, Nenclares P, Newbold K, Newland C, Nicol AJ, Nixon IJ, Obholzer R, O'Hara JT, Orr S, Paleri V, Palmer J, Parry RS, Paterson C, Patterson G, Patterson JM, Payne M, Pearson L, Poller DN, Pollock J, Porter SR, Potter M, Prestwich RJD, Price R, Ragbir M, Ranka MS, Robinson M, Roe JWG, Roques T, Rovira A, Sainuddin S, Salmon IJ, Sandison A, Scarsbrook A, Schache AG, Scott A, Sellstrom D, Semple CJ, Shah J, Sharma P, Shaw RJ, Siddiq S, Silva P, Simo R, Singh RP, Smith M, Smith R, Smith TO, Sood S, Stafford FW, Steven N, Stewart K, Stoner L, Sweeney S, Sykes A, Taylor CL, Thavaraj S, Thomson DJ, Thornton J, Tolley NS, Turnbull N, Vaidyanathan S, Vassiliou L, Waas J, Wade-McBane K, Wakefield D, Ward A, Warner L, Watson LJ, Watts H, Wilson C, Winter SC, Wong W, Yip CY, Yip K. Head and Neck Cancer: United Kingdom National Multidisciplinary Guidelines, Sixth Edition. J Laryngol Otol. 2024 Apr;138(S1):S1-S224. doi: 10.1017/S0022215123001615. Epub 2024 Mar 14. PMID: 38482835.

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K. Isand, J. Wass, J. Norris. I. Noor. Graves orbitopathy - Metastatic breast cancer presenting as orbitopathy, not previously recorded in the endocrine literature, case report, Endocrine Abstracts, 2021

Accepted posters and oral presentations:

Isand K, Pofi R, Haermson O, Vergis M, Mahendran H, Wass J, Yajnik P, Bradley K, Karavitaki N, Ayuk J, Pal A. Venous thromboembolism risk in Cushing's disease, acromegaly and non-functioning pituitary adenomas: insights from three UK tertiary centres. Oral Communication (OC7.3), SfE

BES 2025, 11 March 2025, Edinburgh. Session: Neuroendocrinology and Pituitary.

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Nowak E, Fleseriu M, Zhang Q, Ma Z, Yuen K, Gilis-Januszewska A, Hanzu F, Matikainen N, Minasyjan M, Pichler R, Araujo-Castro M, Arvat E, Bioletto F, **Isand K**, Wass J, Reincke M. Cycle characterisation and treatment outcome in cyclic Cushing's syndrome: a multicenter case series. Poster, ENDO 2024, Boston.

Isand K, Volke V, Webb S, Santos A, Wass J, Valassi E. Venous thrombotic events (VTE) across ERCUSYN: do centres anticoagulate on a routine basis and details of these VTE events. Poster, ECE 2023 (Oral communication), Istanbul.

Isand K, Volke V, Webb S, Santos A, Wass J, Valassi E. High prevalence of venous thrombotic events in Cushing's syndrome: data from ERCUSYN. Poster, ENDO 2023, Chicago.

Isand K, Plummer Z, Volke V, Newell-Price J, Wass JAH, Pal A. Anticoagulation practice in patients with Cushing's syndrome – an SfE audit across centres in the UK. Poster, SfE 2022, Harrogate.

ELULOOKIRJELDUS

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Haridus

2021–2025	Tartu Ülikool, Meditsiiniteaduste valdkond, doktoriõpe
2015–2022	Tartu Ülikool, residentuur endokrinoloogia erialal
2008–2015	Tartu Ülikool, Arstiteaduskond
2005–2008	Nõo Reaalgümnaasium, Nõo, Eesti
2004–2005	Mart Reiniku Gümnaasium
1996–2003	Ülenurme Gümnaasium, Ülenurme, Eesti

Praegused ametikohad

August 2024 –	Oxfordi Ülikooli Haiglad, teadur
Aprill 2025 –	Põhja-Eesti Regionaalhaigla, Tallinn, endokrinoloog
Juuli 2022 – märts 2025	Ida-Tallinna Keskhaigla, Endokrinoloogiakeskus, Tallinn, konsultant-endokrinoloog
Juuli 2022 –	Läänemaa Haigla, Haapsalu. Konsultant-endokrinoloog
Detsember 2022 –	Health Clinic, Tallinn, konsultant-endokrinoloog
September 2022 –	Tartu Ülikool, Tartu, nooremteadur

Töökogemus:

Veebruar 2018 – juuni 2022	Ida-Tallinna Keskhaigla, Endokrinoloogiakeskus, Tallinn, arst
November 2016 – august 2020	Tallinna Linnakliinik, arst
September 2015 – august 2020	Põhja-Eesti Regionaalhaigla, Tallinn, valvearst
November 2020 – august 2021	Oxfordi Ülikooli Haiglad, Oxford, clinical and research fellow, prof. John Wassi uurimisrühm, teadur
Juuni 2013 – august 2015	Ida-Tallinna Keskhaigla, Tallinn, arst-resident
Jaanuar 2014 – mai 2015	Põhja-Eesti Regionaalhaigla, arst-resident
Oktoober 2014 – detsember 2014	Tartu Ülikooli Kliinikum, Kopsu intensiivravi osakond, intensiivõde
Mai 2008 – august 2008	OÜ Alatskivi Perearst, õendusabi töötaja

Peamine uurimisvaldkond: hüpofüüsi haigused

Erialased kuuluvused:
European Society of Endocrinology (ESE, kongressikomitee liige)
Society for Endocrinology (SfE)
Endocrine Society (ES)
Pituitary Society
Eesti Endokrinoloogia Selts (EES, juhatuse liige, EESi president)
European Thyroid Association

Publikatsioonid:
Isand K, Riccardo Pofi, Oliver Haermson, Melissa Vergis, Harishanthi Mahendran, John Wass, Parag Yajnik, Karin Bradley, Niki Karavitaki, John Ayuk, Aparna Pal. Venous Thromboembolism in patients with pituitary adenoma: UK multicentre cohort study. European journal of endocrinology, accepted manuscript.

Fountas A, Lithgow K, Loughrey PB, Bonanos E, Shinwari SK, Mitchell K, Mavilakandy A, Ahsan M, Matheou M, **Isand K**, Hamblin R, McLaren DS, Ullah HZ, Grixti L, MacFarlane J, Jayasuriya A, Bhatti S, Wunna W, Shah S, Hussein Z, Mathew S, Klaucane K, Ayuk J, Toogood A, Tsermoulas G, Ahmed S, Paluzzi A, Batra R, Vamvakopoulos J, Krishnan A, Higham C, Abraham P, Baldeweg SE, Purewal T, Panicker J, Martin N, Drake WM, Ahluwalia R, Newell-Price J, Gurnell M, Mamoojee Y, Brooke A, Lansdown A, Murray RD, Bradley K, Pal A, Reddy N, Levy MJ, Freel EM, Jose B, Hunter SJ, Karavitaki N. Conservatively managed non-functioning pituitary macroadenomas – cohort study from the UK Non-functioning Pituitary Adenoma Consortium. Eur J Endocrinol. 2025;192(5):680–690. doi:10.1093/ejendo/lvaf091.

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A, Lalloo F, Laws K, Leong SC, Lester S, Levy M, Lingley K, Madani G, Mani N, Matteucci PL, Mayland CR, McCaul J, McCaul LK, McDonnell P, McPartlin A, Mercadante V, Merchant Z, Mihai R, Moonim MT, Moore J, Nankivell P, Natu S, Nelson A, Nenclares P, Newbold K, Newland C, Nicol AJ, Nixon IJ, Obholzer R, O'Hara JT, Orr S, Paleri V, Palmer J, Parry RS, Paterson C, Patterson G, Patterson JM, Payne M, Pearson L, Poller DN, Pollock J, Porter SR, Potter M, Prestwich RJD, Price R, Ragbir M, Ranka MS, Robinson M, Roe JWG, Roques T, Rovira A, Sainuddin S, Salmon IJ, Sandison A, Scarsbrook A, Schache AG, Scott A, Sellstrom D, Semple CJ, Shah J, Sharma P, Shaw RJ, Siddiq S, Silva P, Simo R, Singh RP, Smith M, Smith R, Smith TO, Sood S, Stafford FW, Steven N, Stewart K, Stoner L, Sweeney S, Sykes A, Taylor CL, Thavaraj S, Thomson DJ, Thornton J, Tolley NS, Turnbull N, Vaidyanathan S, Vassiliou L, Waas J, Wade-McBane K, Wakefield D, Ward A, Warner L, Watson LJ, Watts H, Wilson C, Winter SC, Wong W, Yip CY, Yip K. Head and Neck Cancer: United Kingdom National Multidisciplinary Guidelines, Sixth Edition. J Laryngol Otol. 2024 Apr; 138(S1):S1-S224. doi: 10.1017/S0022215123001615. Epub 2024 Mar 14. PMID: 38482835.

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Aktsepteeritud abstraktid poster ja suuliste ettekanntena:

Isand K, Pofi R, Haermson O, Vergis M, Mahendran H, Wass J, Yajnik P, Bradley K, Karavitaki N, Ayuk J, Pal A. Venous thromboembolism risk in Cushing's disease, acromegaly and non-functioning pituitary adenomas: insights from three UK tertiary centres. Oral Communication (OC7.3), SfE

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Isand K, Volke V, Webb S, Santos A, Wass J, Valassi E. High prevalence of venous thrombotic events in Cushing's syndrome: data from ERCUSYN. Poster, ENDO 2023, Chicago.

Isand K, Plummer Z, Volke V, Newell-Price J, Wass JAH, Pal A. Anticoagulation practice in patients with Cushing's syndrome – an SfE audit across centres in the UK. Poster, SfE 2022, Harrogate.

DISSERTATIONES MEDICINAE UNIVERSITATIS TARTUENSIS

1. **Heidi-Ingrid Maaroos**. The natural course of gastric ulcer in connection with chronic gastritis and *Helicobacter pylori*. Tartu, 1991.
2. **Mihkel Zilmer**. Na-pump in normal and tumorous brain tissues: Structural, functional and tumorigenesis aspects. Tartu, 1991.
3. **Eero Vasar**. Role of cholecystokinin receptors in the regulation of behaviour and in the action of haloperidol and diazepam. Tartu, 1992.
4. **Tiina Talvik**. Hypoxic-ischaemic brain damage in neonates (clinical, biochemical and brain computed tomographical investigation). Tartu, 1992.
5. **Ants Peetsalu**. Vagotomy in duodenal ulcer disease: A study of gastric acidity, serum pepsinogen I, gastric mucosal histology and *Helicobacter pylori*. Tartu, 1992.
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7. **Hele Everaus**. Immuno-hormonal interactions in chronic lymphocytic leukaemia and multiple myeloma. Tartu, 1993.
8. **Ruth Mikelsaar**. Etiological factors of diseases in genetically consulted children and newborn screening: dissertation for the commencement of the degree of doctor of medical sciences. Tartu, 1993.
9. **Agu Tamm**. On metabolic action of intestinal microflora: clinical aspects. Tartu, 1993.
10. **Katrin Gross**. Multiple sclerosis in South-Estonia (epidemiological and computed tomographical investigations). Tartu, 1993.
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12. **Viiu Tuulik**. The functional disorders of central nervous system of chemistry workers. Tartu, 1994.
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14. **Rein Kolk**. Atrial versus ventricular pacing in patients with sick sinus syndrome. Tartu, 1994.
15. **Toomas Podar**. Incidence of childhood onset type 1 diabetes mellitus in Estonia. Tartu, 1994.
16. **Kiira Subi**. The laboratory surveillance of the acute respiratory viral infections in Estonia. Tartu, 1995.
17. **Irja Lutsar**. Infections of the central nervous system in children (epidemiologic, diagnostic and therapeutic aspects, long term outcome). Tartu, 1995.
18. **Aavo Lang**. The role of dopamine, 5-hydroxytryptamine, sigma and NMDA receptors in the action of antipsychotic drugs. Tartu, 1995.
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21. **Reet Mändar**. Vaginal microflora during pregnancy and its transmission to newborn. Tartu, 1996.
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33. **Janika Kõrv**. Incidence, case-fatality and outcome of stroke. Tartu, 1998.
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38. **Allen Kaasik**. Thyroid hormone control over β-adrenergic signalling system in rat atria. Tartu, 1998.
39. **Vallo Matto**. Pharmacological studies on anxiogenic and antiaggressive properties of antidepressants. Tartu, 1998.
40. **Maire Vasar**. Allergic diseases and bronchial hyperreactivity in Estonian children in relation to environmental influences. Tartu, 1998.
41. **Kaja Julge**. Humoral immune responses to allergens in early childhood. Tartu, 1998.

42. **Heli Grünberg**. The cardiovascular risk of Estonian schoolchildren. A cross-sectional study of 9-, 12- and 15-year-old children. Tartu, 1998.
43. **Epp Sepp**. Formation of intestinal microbial ecosystem in children. Tartu, 1998.
44. **Mai Ots**. Characteristics of the progression of human and experimental glomerulopathies. Tartu, 1998.
45. **Tiina Ristimäe**. Heart rate variability in patients with coronary artery disease. Tartu, 1998.
46. **Leho Kõiv**. Reaction of the sympatho-adrenal and hypothalamo-pituitary-adrenocortical system in the acute stage of head injury. Tartu, 1998.
47. **Bela Adojaan**. Immune and genetic factors of childhood onset IDDM in Estonia. An epidemiological study. Tartu, 1999.
48. **Jakov Shlik**. Psychophysiological effects of cholecystokinin in humans. Tartu, 1999.
49. **Kai Kisand**. Autoantibodies against dehydrogenases of α-ketoacids. Tartu, 1999.
50. **Toomas Marandi**. Drug treatment of depression in Estonia. Tartu, 1999.
51. **Ants Kask**. Behavioural studies on neuropeptide Y. Tartu, 1999.
52. **Ello-Rahel Karelson**. Modulation of adenylate cyclase activity in the rat hippocampus by neuropeptide galanin and its chimeric analogs. Tartu, 1999.
53. **Tanel Laisaar**. Treatment of pleural empyema — special reference to intrapleural therapy with streptokinase and surgical treatment modalities. Tartu, 1999.
54. **Eve Pihl**. Cardiovascular risk factors in middle-aged former athletes. Tartu, 1999.
55. **Katrin Õunap**. Phenylketonuria in Estonia: incidence, newborn screening, diagnosis, clinical characterization and genotype/phenotype correlation. Tartu, 1999.
56. **Siiri Kõljalg**. *Acinetobacter* – an important nosocomial pathogen. Tartu, 1999.
57. **Helle Karro**. Reproductive health and pregnancy outcome in Estonia: association with different factors. Tartu, 1999.
58. **Heili Varendi**. Behavioral effects observed in human newborns during exposure to naturally occurring odors. Tartu, 1999.
59. **Anneli Beilmann**. Epidemiology of epilepsy in children and adolescents in Estonia. Prevalence, incidence, and clinical characteristics. Tartu, 1999.
60. **Vallo Volke**. Pharmacological and biochemical studies on nitric oxide in the regulation of behaviour. Tartu, 1999.
61. **Pilvi Ilves**. Hypoxic-ischaemic encephalopathy in asphyxiated term infants. A prospective clinical, biochemical, ultrasonographical study. Tartu, 1999.
62. **Anti Kalda**. Oxygen-glucose deprivation-induced neuronal death and its pharmacological prevention in cerebellar granule cells. Tartu, 1999.
63. **Eve-Irene Lepist**. Oral peptide prodrugs – studies on stability and absorption. Tartu, 2000.

64. **Jana Kivastik**. Lung function in Estonian schoolchildren: relationship with anthropometric indices and respiratory symptomas, reference values for dynamic spirometry. Tartu, 2000.
65. **Karin Kull**. Inflammatory bowel disease: an immunogenetic study. Tartu, 2000.
66. **Kaire Innos**. Epidemiological resources in Estonia: data sources, their quality and feasibility of cohort studies. Tartu, 2000.
67. **Tamara Vorobjova**. Immune response to *Helicobacter pylori* and its association with dynamics of chronic gastritis and epithelial cell turnover in antrum and corpus. Tartu, 2001.
68. **Ruth Kalda**. Structure and outcome of family practice quality in the changing health care system of Estonia. Tartu, 2001.
69. **Annika Krüüner**. *Mycobacterium tuberculosis* – spread and drug resistance in Estonia. Tartu, 2001.
70. **Marlit Veldi**. Obstructive Sleep Apnoea: Computerized Endopharyngeal Myotonometry of the Soft Palate and Lingual Musculature. Tartu, 2001.
71. **Anneli Uusküla**. Epidemiology of sexually transmitted diseases in Estonia in 1990–2000. Tartu, 2001.
72. **Ade Kallas**. Characterization of antibodies to coagulation factor VIII. Tartu, 2002.
73. **Heidi Annuk**. Selection of medicinal plants and intestinal lactobacilli as antimicrobil components for functional foods. Tartu, 2002.
74. **Aet Lukmann**. Early rehabilitation of patients with ischaemic heart disease after surgical revascularization of the myocardium: assessment of health-related quality of life, cardiopulmonary reserve and oxidative stress. A clinical study. Tartu, 2002.
75. **Maigi Eisen**. Pathogenesis of Contact Dermatitis: participation of Oxidative Stress. A clinical – biochemical study. Tartu, 2002.
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77. **Tõnu Rätsep**. Aneurysmal subarachnoid haemorrhage: Noninvasive monitoring of cerebral haemodynamics. Tartu, 2002.
78. **Marju Herodes**. Quality of life of people with epilepsy in Estonia. Tartu, 2003.
79. **Katre Maasalu**. Changes in bone quality due to age and genetic disorders and their clinical expressions in Estonia. Tartu, 2003.
80. **Toomas Sillakivi**. Perforated peptic ulcer in Estonia: epidemiology, risk factors and relations with *Helicobacter pylori*. Tartu, 2003.
81. **Leena Puksa**. Late responses in motor nerve conduction studies. F and A waves in normal subjects and patients with neuropathies. Tartu, 2003.
82. **Krista Lõivukene**. *Helicobacter pylori* in gastric microbial ecology and its antimicrobial susceptibility pattern. Tartu, 2003.

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