Glucocorticoid-induced adrenal insufficiency

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I can do things you cannot, you can do things I cannot: together we can do great things.

— Mother Teresa

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ABSTRACT

Background: Glucocorticoids (GCs) are effective in treating many diseases and are widely used. However, glucocorticoid treatment can down-regulate the hypothalamic-pituitary-adrenal axis and lead to glucocorticoid-induced adrenal insufficiency. This thesis aimed to investigate the prevalence of oral GC prescriptions, related mortality, and the prevalence of GC-induced adrenal insufficiency during topical GC treatment and during intermittent high-dose GC therapy.

Methods: Individuals, living in Västra Götaland county, with prescriptions of prednisolone ≥5 mg/day (or equivalent dose of other GCs) for ≥21 days during 2007–2014 were identified in The Swedish Prescribed Drug Register. By using a personal identification number, patients were cross-linked with four other Swedish registries to collect information on indication for GC treatment, comorbidities, and cause-of death. To study if death was related to GC-induced adrenal insufficiency, medical records from 300 patients who died from sepsis were investigated. Twenty-seven patients with oral lichen planus receiving topical GC were studied and in a prospective study 10 adults with lymphoma receiving intermittent, high-dose GC were included.

Results: During 2007–2014, 14.1% of inhabitants (n=223 211) in Western Sweden received prescriptions for oral GCs at doses associated with risk of developing GC-induced adrenal insufficiency. GC users had a 2-fold overall risk of dying compared to controls (adjusted hazard ratio 2.1, 95% confidence interval 2.0–2.1). Under- and undiagnosed GC-induced adrenal insufficiency possibly contributed to the death in 47 of 300 (16%) patients considered to have died from sepsis. Approximately 20% of patients receiving chronic topical GCs in the oral cavity had GC-induced adrenal insufficiency. None of

the patients receiving intermittent high-dose GC therapy had GC-induced adrenal insufficiency.

Conclusion: Oral GC treatment is common and can lead to GC-induced adrenal insufficiency and increased mortality. GC-induced adrenal insufficiency is underdiagnosed and awareness is essential for the diagnosis and treatment.

Keywords: glucocorticoid, adrenal insufficiency, mortality

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SAMMANFATTNING PÅ SVENSKA

Bakgrund: Kortisonbehandling kan hämma den egna kortisolproduktionen och leda till binjurebarksvikt. Denna avhandling studerade prevalens av kortisonbehandling, dödlighet hos kortisonanvändare och om odiagnostiserad kortisonutlöst binjurebarksvikt kan leda till för tidlig död. I avhandlingen studerades även om munhålegel innehållande kortison, eller om högdos pulsbehandling med kortison kan orsaka binjurebarksvikt.

Metod: Samtliga individer, bosatta i Västra Götaland, som hämtat ut tabletter innehållande kortison (≥5 mg prednisolon/dag i minst 21 dagar) 2007-2014 inkluderades. Information om dödsorsak, sjuklighet och indikation for kortisonbehandling inhämtades från nationella register och den regionala vårddatabasen VEGA. För att studera om död var relaterad till odiagnostiserad kortisonutlöst binjurebarksvikt, granskades journaler från 300 patienter som hade blodförgiftning som registrerad dödsorsak. För att studera om munhålegel innehållande kortison kan orsaka binjurebarksvikt, studerades 27 patienter med oral lichen planus som stod på långvarig (>6 veckor) behandlades med munhålegel innehållande kortison. En prospektiv studie där 10 patienter som fick intermittent högdos kortisonbehandling studerades och binjurebarkfunktion kontrollerades regelbundet under behandlingen.

Resultat: Fjorton procent (n=223 211) av invånare i Västra Götaland hade hämtat ut kortisontabletter under studietiden. Dessa individer hade en dubblerad risk att dö (hazard ratio 2,1, 95 % konfidensintervall 2,0 till 2,1) jämfört med kontroller som inte hade hämtat ut kortisontabletter. Underbehandlad och odiagnostiserad kortisonutlöst binjurebarksvikt var sannolikt eller möjligen bidragande orsak till döden hos 47 (16%) av 300 patienter som hade blodförgiftning som registrerad dödsorsak. En femtedel av patienterna som använde kortison munhålegel hade kortisonutlöst binjurebarksvikt. Ingen av patienterna som fick intermittent högdos kortisonbehandling hade binjurebarksvikt.

Konklusion: Kortisonbehandling i tablettform är vanlig och kan leda till binjurebarksvikt och ökad dödlighet. Kortisonutlöst binjurebarksvikt är underdiagnostiserad och därför är medvetenhet avgörande för att diagnostisera och behandla sjukdomen.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Einarsdottir MJ, Ekman P, Trimpou P, Olsson DS, Johannsson G, Ragnarsson O. **High prescription rate of oral glucocorticoids in children and adults: a retrospective cohort study from Western Sweden.** Clin Endocrinol (Oxf). 2020;92(1):21-28.

II. Einarsdottir MJ, Ekman P, Molin M, Trimpou P, Olsson DS, Johannsson G, Ragnarsson O. **High mortality rate in oral glucocorticoid users: a population-based matched cohort study.** Front Endocrinol (Lausanne). 2022;13:918356.

III. Einarsdottir MJ, Trimpou P, Johannsson G, Ragnarsson O. **Undertreated and undiagnosed adrenal insufficiency as a premature cause of death in glucocorticoid users.** *Manuscript.*

IV. Einarsdottir MJ, Bankvall M, Robledo-Sierra J, Rödström PO, Bergthorsdottir R, Trimpou P, Hasséus B, Ragnarsson O. **Topical clobetasol treatment for oral lichen planus can cause adrenal insufficiency.** Oral Dis. 2023. Epub ahead of print.

V. Einarsdottir MJ, Kristjansdottir HL, Bergthorsdottir R, Johannssona G, Trimpou P, Lewerina C, Ragnarsson O. **Intermittent high-dose glucocorticoid treatment does not cause adrenal insufficiency in patients with diffuse large B-cell lymphoma - a prospective study.** Acta Haematol. 2023. Epub ahead of print.

CONTENTS

ABBREVIATIONS

ACTH	Adrenocorticotropic hormone
ANOVA	Analysis of variance
CBG	Cortisol-binding globulin
CD	Crohn's disease
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CRH	Corticotropin-releasing hormone
CYP3A4	Cytochrome P450 3A4
DDD	Defined daily dose
DHEA	Dehydroepiandrosterone
DHEA-S	Dehydroepiandrosterone sulfate
GC	Glucocorticoid
HPA	Hypothalamic-pituitary-adrenal
HR	Hazard ratio
ICD	International Classification of Diseases
RA	Rheumatoid arthritis
UC	Ulcerative colitis

1 INTRODUCTION

1.1 HISTORY OF GLUCOCORTICOIDS

Glucocorticoids (GCs) have been used as a medication for over 70 years (1). The first use of GCs was in September 1948 when Philip Hench treated a 29-year-old woman with severe rheumatoid arthritis (RA). She received GC injections every day, and on the third day, her morning stiffness was gone and joint swellings were markedly improved (2). Two years later, Hench, together with two chemists, Edward C. Kendall and Tadeus Reichstein received the Nobel Prize for their discovery relating to the hormones of the adrenal cortex (3). Since then, GCs (also known as corticosteroids) have assumed an essential role in treating inflammatory and immunological diseases (4-7). GCs are a highly effective treatment, but side effects are common (8). A wide range of adverse effects can be caused by GCs, ranging from mild mood changes to potentially fatal adrenal insufficiency and cardiovascular events (8-10). Other common adverse effects are insulin resistance, osteoporosis, hypertension, infections, and cataract formation (8, 11).

1.2 PREVALENCE OF GC USE

Oral GCs are prescribed to approximately 1% of the population (4, 5, 7, 12) (Table 1). The use of prescribed GCs is higher in people over the age of 80 years, with a prevalence of 3.5% in the USA and 10% in Denmark (4, 13). Prescriptions for short-term GC treatment are more common than for long-term use. A population-based cohort study from the USA showed that 21% received at least one prescription for short-term (≤30 days) use of oral GCs over a 3-year period (14). Studies on long-term (>3 months) GC use have shown a much lower prevalence (0.5%–0.7%) (5, 7). Long-term oral GC prescriptions have increased by 34% over the past 20 years despite new efficient alternative treatments for inflammatory diseases (6).

Table 1. Overview of studies investigating the prevalence of oral GC use.

Study	Population size	Country	Inclusion criteria	Study period	Prevalence
Walsh *et al.* 1996 (5)	65 786	UK	>3 months use	1992–1995	0.5% period prevalence
van Staa *et al.* 2000 (12)	244 235	UK	≥1 prescription	End of study Dec 1997 (mean 4.7 years)	0.9% point prevalence
Gudbjornsson *et al.* 2002 (7)	26 664	Iceland	>3 months use	1995–1996	0.7% period prevalence (2 years)
Fardet *et al.* 2011 (15)	4 518 753	UK	≥1 prescription	1989–2008	0.85% point prevalence
Overman *et al.* 2013 (4)	26 248	USA	Self-report of usage	1999–2008	1.2% weighted prevalence
Benard-Laribiere *et al.* 2017 (16)	382 572	France	≥1 prescription	2007–2014	14.7%–17.1% period prevalence (1 year)
Waljee *et al.* 2017 (14)	1 548 945	USA	≥1 prescription (treatment <30 days)	2012–2014	21.2% period prevalence (3 years)
Laugesen *et al.* 2017 (13)	5.6 million	Denmark	≥1 prescription (oral and injections)	1999–2015	3% in any given year

1.3 ADRENAL INSUFFICIENCY

The adrenal cortex consists of three layers: the zona glomerulosa, zona fasciculata, and zona reticularis. The zona glomerulosa produces mineralocorticoids (aldosterone, deoxycorticosterone), the zona fasciculata produces GCs (corticosterone and cortisol), and the zona reticularis produces androgens (mainly dehydroepiandrosterone [DHEA] and androstenedione) (17). The hypothalamus and pituitary gland regulate the production of cortisol (18). The hypothalamus releases corticotropin-releasing hormone (CRH), stimulating the pituitary gland to produce adrenocorticotropic hormone

(ACTH), which binds to receptors in the adrenal gland, resulting in cortisol production (Figure 1) (18).

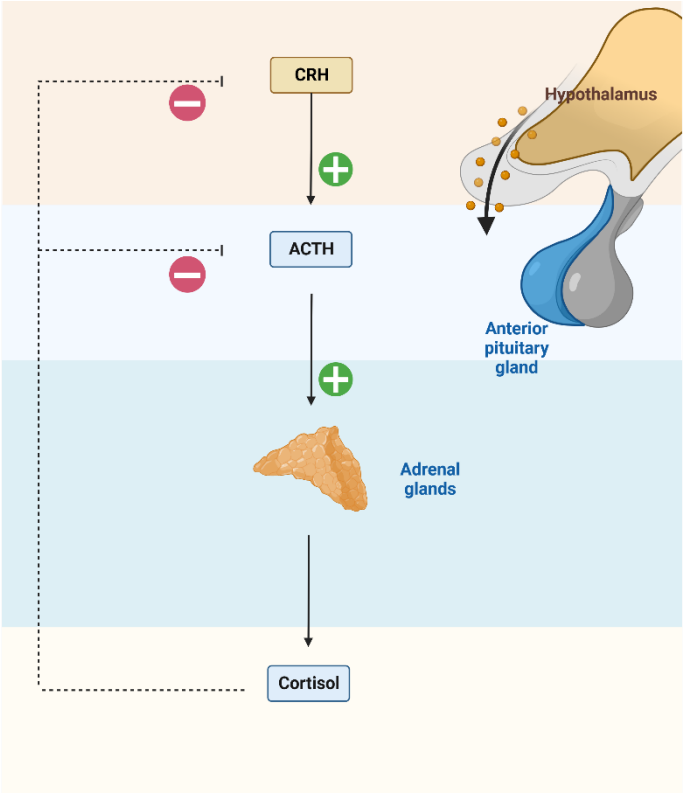

Figure 1. The physiology of the hypothalamic-pituitary-adrenal axis. ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone. Figure was created with BioRender.com.

In healthy individuals, cortisol secretion follows a circadian rhythm with the highest cortisol concentration in the early morning and the lowest at midnight (19). During stress (e.g., trauma, infection, critical illness), systemic cortisol availability is increased due to reduced circulating cortisol-binding proteins, decreased cortisol binding, reduced cortisol metabolism, and increased production of cortisol (20-23).

An insufficient production of cortisol is called adrenal insufficiency, which is a potentially fatal condition if left untreated (17, 24). Primary adrenal insufficiency is caused by adrenal disease and secondary adrenal insufficiency

is caused by pituitary diseases (25). Tertiary adrenal insufficiency is a condition where CRH is suppressed (25). GC use is the most common cause of tertiary adrenal insufficiency (26). GCs are a synthetic version of the cortisol hormone and down-regulate the hypothalamic-pituitary-adrenal (HPA) axis due to a negative feedback mechanism (Figure 2) (17). GCs inhibit the secretion of both CRH and ACTH (17). ACTH exerts trophic effects on the adrenal cortex and a lack of ACTH stimulation for a prolonged period of time can lead to adrenal atrophy (18). The terminology for this condition is confusing, as some scientific papers refer to the condition as secondary, tertiary, or iatrogenic adrenal insufficiency (27). The term *GC-induced adrenal insufficiency* will be used in this thesis.

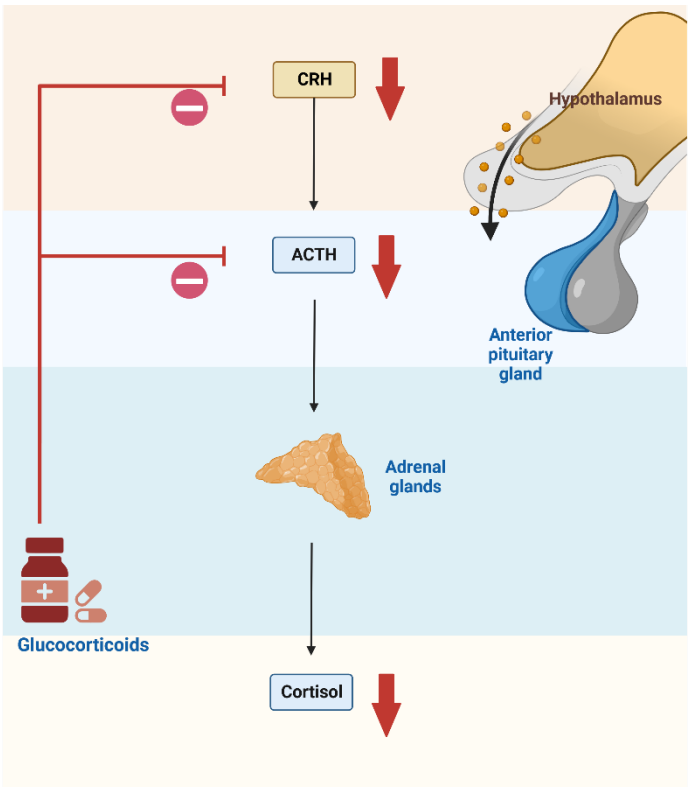

Figure 2. The physiology of GC-induced adrenal insufficiency. ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone. Figure was created with BioRender.com.

1.4 GC-INDUCED ADRENAL INSUFFICIENCY

The first case report describing GC-induced adrenal insufficiency was published in 1952, which is only 2 years after Hench, Kendall, and Reichstein were awarded the Nobel Prize (9). This first case was a 34-year old man with RA who had been treated with high-dose GC for 8 months. He was admitted to hospital and did not receive his GC treatment. Two days later, he underwent a hip operation and died of postoperative shock in spite of adequate shock therapy. Autopsy showed bilateral adrenal atrophy (9). It was suspected that adrenal atrophy might have decreased the body's ability to withstand stress and trauma (9).

This first case of GC-induced adrenal insufficiency well describes how adrenal insufficiency can lead to adrenal crisis, which is a life-threatening condition (24). During the last 70 years, several more fatal and near fatal cases of GC-induced adrenal insufficiency have been published (24, 28). In common, most of these cases have adrenal insufficiency that is insufficiently treated during infections or trauma, leading to adrenal crisis (9, 24, 28).

GC-induced suppression of the HPA axis may persist for a few days up to several months or years after the cessation of GC treatment (29, 30). In the recovery phase, initial activation of the HPA axis occurs with a measurable elevation of ACTH in serum (29). Later, basal cortisol secretion is recovered, which is often maintained by a compensatory elevation of ACTH. Last, there is recovery of adrenal stimulation during stress, infection, surgery, or other major physical trauma (23, 29, 31).

1.5 RISK OF GC-INDUCED ADRENAL INSUFFICIENCY

An individual's risk for developing GC-induced adrenal insufficiency cannot be accurately predicted but several factors affect the likelihood. The following factors are the most important.

1.5.1 GC DOSE AND DURATION OF TREATMENT

High GC doses and long treatment duration (>4 weeks) increase the risk of GC-induced adrenal insufficiency but no dose or duration is without a risk (10). Down-regulation of the HPA axis has been shown after low-dose (prednisolone 5 mg/day) treatment and has also been described after a short (≤2 weeks) duration of treatment (30, 32, 33). Patients who take GCs on alternate days have a lower risk of developing GC-induced adrenal insufficiency (34). Pulse therapy has also been associated with a lower risk of GC-induced adrenal insufficiency (35). Multiple daily split doses and bedtime administration affect circadian ACTH release and increase the risk of GC-induced adrenal insufficiency (36).

1.5.2 ROUTE OF ADMINISTRATION

The incidence of GC-induced adrenal insufficiency is highest for oral and intra-articular use but no route of administration is without a risk (10). A meta-analysis showed that 48.7% of oral GC users developed GC-induced adrenal insufficiency (Figure 3) (10). The lowest incidence was shown for topical and nasal use (10). Most studies that were included in the meta-analysis evaluated adrenal function during or around cessation of GCs (10). The time between the last GC dose and adrenal function testing was 0–30 days but most studies (50 out of 74 studies, information missing for 22 studies) conducted testing within 1 week after the last GC dose (10, 27).

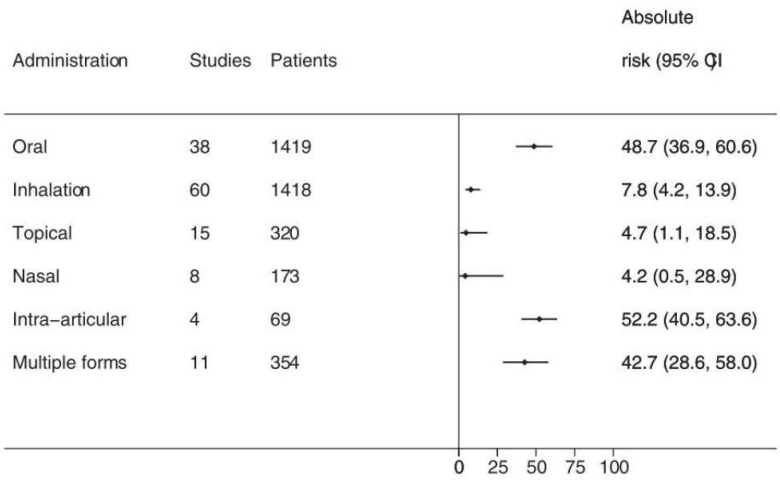

Figure 3. Risk of glucocorticoid-induced adrenal insufficiency stratified by route of administration. CI, confidence interval. Reproduced with permission from Oxford University Press (Journal of Clinical Endocrinology & Metabolism, Adrenal insufficiency in corticosteroids use: systematic review and meta-analysis. Broersen et al. 2015) (10).

1.5.3 TYPE OF GC

The type of GC can affect the risk of GC-induced adrenal insufficiency. Longer biological half-life and higher GC potency increase the risk (37). For example, betamethasone, due to its long half-life and strong binding to the GC receptor, suppresses the HPA axis more severely than prednisolone (38). Similarly, fluticasone propionate, which has a long half-life and high affinity for GC receptors, has been linked to most cases of GC-induced adrenal insufficiency in patients who use inhaled GCs (39-41).

1.5.4 DRUGS

Both drug interactions and concomitant use of other drugs can affect the risk of GC-induced adrenal insufficiency (37). GCs are metabolized by cytochrome P450 3A4 (CYP3A4) (42). CYP3A4 inhibitors (e.g., antifungal drugs, HIV protease inhibitors, clarithromycin, erythromycin, cyclosporine, diltiazem,

grapefruit juice, verapamil) increase the risk of GC-induced adrenal insufficiency (37, 43-45). On the other hand, CYP3A4 inducers decrease exposure to synthetic GCs and can lead to higher GC replacement dose or cause symptoms in patients with mild adrenal insufficiency. CYP3A4 inducers include various antiepileptic drugs, primidone, rifampicin, and St. John's wort (37, 45, 46).

1.5.5 OTHER POSSIBLE RISK FACTORS

Individual variation in susceptibility to GC-induced adrenal insufficiency is not fully understood and further research is warranted. Healthy male volunteers who have low cortisol levels following an overnight dexamethasone (0.5 mg) suppression test have been shown to have more suppressed adrenal function 1 week after withdrawal of GC treatment (47). The large individual variation in GC-induced adrenal insufficiency development might be due to differences in the sensitivity of the cortisol receptor. Several polymorphisms have been described in the cortisol receptor gene that might influence an individual's response to GC treatment (45, 48).

1.6 CLINICAL SYMPTOMS

Fatigue, weariness, feeling generally unwell, difficulty concentrating, nausea, anorexia, hyponatremia, and dizziness are common symptoms of GC-induced adrenal insufficiency (Figure 4) (27, 49). The condition can be dangerous and life-threatening but even subtle symptoms, such as fatigue, can negatively impact the patient's general health (50).

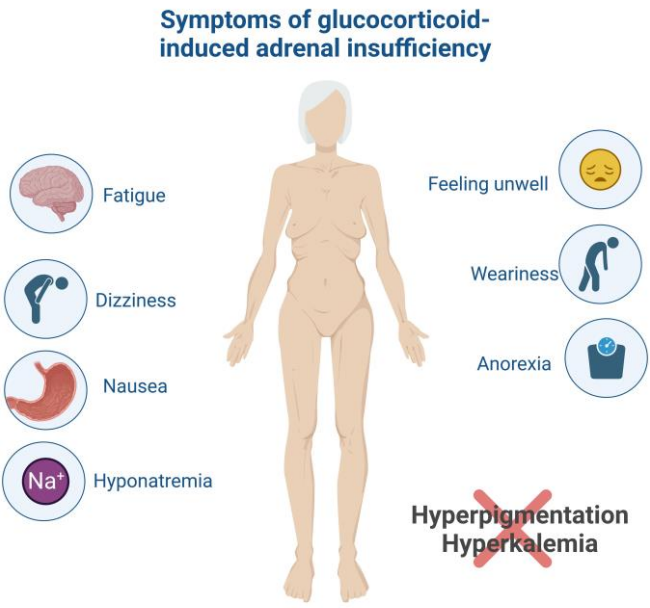

Figure 4. Symptoms of glucocorticoid-induced adrenal insufficiency. Figure was created with BioRender.com.

Patients with GC-induced adrenal insufficiency have no aldosterone deficiency, so hyperkalemia and salt cravings do not therefore present (25). The renin-angiotensin system is primarily responsible for aldosterone secretion and that is intact in GC-induced adrenal insufficiency (17). ACTH is not elevated in GC-induced adrenal insufficiency and hyperpigmentation does not therefore occur (25).

Symptoms of GC-induced adrenal insufficiency are often nonspecific and can easily be wrongly diagnosed as worsening of the underlying disease or GC withdrawal syndrome. GC withdrawal syndrome is related to the symptoms that occur in patients after withdrawal of supraphysiological GC doses (51). Patients with GC withdrawal syndrome have a normal response to an ACTH stimulation test and the condition does not predispose patients to adrenal crisis (52). All these three conditions (flare-up of underlying disease, GC-induced adrenal insufficiency, and GC withdrawal) resolve after patients resume the GC dose that had previously controlled their symptoms (52).

A patient with GC-induced adrenal insufficiency may develop adrenal crisis after cessation of treatment or if GC dose is not increased when the patient is exposed to increased stress (infection, surgery, or trauma) (24). Symptoms of adrenal crisis in patients with GC-induced adrenal insufficiency have been described as severe weakness, dizziness, vomiting, hypotension, hypoglycemia, seizure, hyponatremia, impaired consciousness, and death (24, 53).

1.7 DIAGNOSIS

Routine screening for adrenal insufficiency in patients receiving GCs is not recommended in daily practice (54). Thus, diagnosis depends on the physician's awareness and clinical knowledge (27). Currently, morning plasma cortisol measurement (a blood test taken between 8 and 9 AM) is probably the best screening test (37, 55). For the vast majority of analytical methods used today, an unstressed morning cortisol level >350 nmol/L usually contradicts adrenal insufficiency (56). On the other hand, a morning cortisol level <140 nmol/L strongly suggests adrenal insufficiency (57).

If morning plasma cortisol is low, a dynamic test such as the ACTH stimulation test (also called corticotropin stimulation test, cosyntropin stimulation test, and short Synacthen test) is recommended (58). Patients are advised to undergo the dynamic test 24 hours after their last GC dose (37). If patients take GCs before providing a blood test, it can influence the results because of cross-reactivity from synthetic GCs in cortisol immunoassays (59). Early morning plasma cortisol correlates well with outcome on the ACTH stimulation test (60).

During the ACTH stimulation test, patients receive an injection of synthetic ACTH that stimulates the adrenal glands to release cortisol (61). Blood samples are taken 30 or 60 minutes after the injection to measure plasma cortisol (called the peak cortisol level). Patients with adrenal insufficiency have an inadequate peak cortisol level (58). The cut-off depends on the cortisol assay but, commonly, a cut-off of 450–500 nmol/L is used (56, 57, 62). Liquid chromatography-tandem mass spectrometry is considered the gold standard for cortisol measurement but immunoassays are more widely used due to cost, rapidity of results, and availability (61, 63). In Sweden, analytical methods

using specific monoclonal antibody immunoassays are commonly used, which have an approximately 20%–30% lower cut-off than polyclonal antibody assays (56, 64, 65). A repeated ACTH stimulation test is sometimes necessary to monitor the recovery of the HPA axis (37).

Measurement of serum DHEA sulfate (DHEA-S) concentration may provide additional information that can assist in improving the diagnosis of GC-induced adrenal insufficiency. However, further studies are needed (66).

1.7.1 TYPE OF DYNAMIC TEST

Both high-dose (250 µg) and low-dose (1 µg) ACTH stimulation tests have been used to diagnose adrenal insufficiency. The high-dose test was designed to diagnose primary adrenal insufficiency. Previously, the low-dose ACTH stimulation test was considered to offer better accuracy than the high-dose test in diagnosing secondary adrenal insufficiency (67, 68). Nevertheless, a meta-analysis based on 30 studies showed no difference in diagnostic accuracy between high- and low-dose ACTH stimulation tests (69).

There are other dynamic tests used to diagnose adrenal insufficiency, such as the insulin tolerance test, but it is uncomfortable for the patient and can have serious adverse effects (58). An ACTH stimulation test has comparable diagnostic accuracy to the insulin tolerance test and is the most widely used test to diagnose adrenal insufficiency (27, 70). The ACTH stimulation test is effective in ruling in, but not ruling out, secondary adrenal insufficiency (69). The overnight metyrapone test is considered by some to be more sensitive than the ACTH stimulation test for the diagnosis of secondary adrenal insufficiency (71). However, in patients with undiagnosed adrenal insufficiency, the overnight metyrapone test can potentially precipitate an acute adrenal crisis (72). The test is therefore rarely used and also because of the limited availability of 11-deoxycortisol assays (71, 72).

1.7.2 FACTORS INFLUENCING CORTISOL MEASUREMENTS AND DYNAMIC TESTS

In the circulation, >90% of circulating cortisol is bound: 80% is bound to cortisol-binding globulin (CBG) and 10%–15% to albumin (73, 74). Both bound and free components of cortisol are included in total cortisol measurement (75). Oral contraception and pregnancy increase the concentration of CBG, which increases total cortisol levels, and can give a falsely high cortisol concentration (76, 77). Similarly, conditions that lower CBG (e.g., nephrotic syndrome, critical illness, cirrhosis) reduce total circulating plasma cortisol (73, 75, 78).

The ACTH stimulation test evaluates the HPA axis at an adrenal level and, in acute ACTH deficiency, it can give a false normal response (61). Sleep and shift work also affect the secretory patterns of cortisol (79, 80). Morning cortisol levels can be low in healthy individuals after night shift work or short sleep duration (79, 80).

1.8 TREATMENT

1.8.1 GENERAL PRINCIPLES FOR TREATMENT OF ADRENAL INSUFFICIENCY

GC replacement therapy is essential for patients with adrenal insufficiency (57). Before Hench, Kendall, and Reichstein discovered GC, more than 80% of patients with primary adrenal insufficiency died within 2 years after diagnosis (81). Estimated endogenous daily production of cortisol is 9–11 mg/m^2/day in healthy men (82). A common GC replacement dose is hydrocortisone 15–25 mg daily in 2 or 3 divided doses (83). Hydrocortisone has a short half-life (1.5 hours) and the dosage therefore has to be divided throughout the day (83, 84). It is recommended that a greater portion of the daily dose be taken immediately upon awakening with smaller portions at lunchtime and in the late afternoon to mimic the physiological circadian rhythm of cortisol production (57, 62).

During stress (infection, trauma, surgery), the need for cortisol increases, which means that patients with adrenal insufficiency need to increase their oral hydrocortisone dose or, in severe stress, receive hydrocortisone injections (57, 62). If the hydrocortisone doses are not increased in these situations, it can lead to adrenal crisis (62). Every patient with adrenal insufficiency needs to be informed about this risk and it is important to educate the patient how to act in case of acute illness (57). These are called "sick day rules" and are rules about how and when to increase the hydrocortisone dose. For example, in case of fever >38°C, illness requiring bed rest, infection requiring antibiotics, or minor intervention under local anesthesia, the patient is advised to double the oral dose of hydrocortisone (57, 62). In some cases, the patient should triple the dose, such as with fever above 39°C (57). If the patient is unable to tolerate oral medication due to gastroenteritis or trauma, they need to be treated with hydrocortisone injections. In many countries, patients with adrenal insufficiency are equipped with steroid emergency cards to inform healthcare providers of the need for GC stress doses in the case of an emergency (Figure 5) (62).

Figure 5. The Swedish emergency steroid card (85). Figure reproduced with permission (Läkartidningen, ABC om Addisons sjukdom. Einarsdottir et al. 2022) (86).

1.8.2 PRINCIPLES FOR TREATMENT OF GC-INDUCED ADRENAL INSUFFICIENCY

The treatment principles mentioned previously are applicable to patients with GC-induced adrenal insufficiency as well as patients with secondary or primary adrenal insufficiency. Regarding treatment for patients with GC-induced adrenal insufficiency, some things are different from treatment for patients with primary and secondary adrenal insufficiency. The greatest difference is variable residual cortisol reserve and no aldosterone deficiency. Patients with GC-induced adrenal insufficiency also have a chance to recover their adrenal function. Replacement therapy is often only temporary until adrenal function has recovered. The treatment principle is GC replacement therapy with a slow tapering until recovery of the HPA axis. Hydrocortisone is a good replacement therapy due to its short half-life (57). Patients with primary adrenal insufficiency suffer from complete adrenal insufficiency but some patients with GC-induced adrenal insufficiency have only mild cortisol deficiency. These patients with mild GC-induced adrenal insufficiency may only require hydrocortisone when exposed to stress but do not need GC replacement daily (87, 88). Patients on low-dose GCs may need extra GCs during stress as more than one-third of patients on low-dose GCs have GC-induced adrenal insufficiency (89).

One of the biggest challenges in treating GC-induced adrenal insufficiency is a flare-up of the underlying disease. The GC tapering process is often postponed due to relapses of the underlying disease or GC withdrawal syndrome during the tapering phase, resulting in an increased GC requirement (52, 88).

1.9 PROGNOSIS AND RECOVERY OF GC-INDUCED ADRENAL INSUFFICIENCY

Patients with GC-induced adrenal insufficiency have a chance of recovery, and the recovery rate depends on the severity and duration of GC-induced adrenal insufficiency (90). The results of an ACTH stimulation test can be used to

predict the recovery of the HPA axis (90). Based on a retrospective study of 110 patients with GC-induced adrenal insufficiency, patients with delta cortisol (30-minute cortisol minus basal cortisol) <100 nmol/L on an ACTH stimulation test at baseline and a random cortisol level of <200 nmol/L at 1 year had no recovery of the HPA axis during 4 years of follow-up. (90). On the other hand, if delta cortisol was >100 nmol/L on an ACTH stimulation test at baseline, the 4-year recovery rate was 95% (90).

Patients with GC-induced adrenal insufficiency have a higher incidence of adrenal crisis compared to patients with primary and secondary adrenal insufficiency according to a retrospective Dutch cohort study including 458 patients with adrenal insufficiency (91). The study showed that the incidence rate of adrenal crisis per person-years was 5.2 for primary adrenal insufficiency, 3.6 for secondary adrenal insufficiency, and 15.1 for GC-induced adrenal insufficiency (91). The risk of adrenal crisis has been shown to be high after cessation of GC treatment. A retrospective cohort study showed that 7.1% of adrenal crises occurred within 30 days of cessation of GC treatment (92). In a cohort study from England, which included 183 patients with GC-induced adrenal insufficiency (74 of whom died during follow-up), infections were the most common cause of death (44.6%), while only 15.6% had adrenal insufficiency as their cause of death (93).

1.10 MORTALITY IN GC USERS

GC users have increased mortality compared to controls (Table 2) (93-101). Doses of prednisolone >5 mg/day have been associated with higher mortality (101) and doses of prednisolone <5 mg/day do not seem to increase mortality (99).

Table 2. Overview of studies investigating all-cause mortality in GC users.

Study	Country	Cases	Controls	Results
Schols *et al.* 2001 (94)	Holland	GC users (oral and inhalation) with COPD (n=290)	Patients with COPD without GC (n=44)	Doses of 10 mg prednisolone associated with mortality: RR: 3.3 (95% CI 1.76–6.18).
Sihvonen *et al.* 2006 (95)	Finland	Oral GC users with RA (n=395)	Patients with RA without GC (n=209)	>1 year treatment: HR 1.14 (95% CI 0.98–1.27). >10 years treatment: HR 1.69 (95% CI 1.12–2.56).
Lewis *et al.* 2008 (96)	USA	GC users with CD (n=1404); GC users with UC (n=1603)	Subjects without CD, UC, RA, COPD, asthma (n= 41 624)	Current GC use: CD; HR 2.48 (95% CI 1.85–3.31); UC; HR 2.81 (95% CI 2.26–3.50).
del Rincon *et al.* 2014 (97)	USA	Oral GC users with RA (n=386)	Patients with RA without GC (n=393)	Dose-dependent increase in death: HR 1.07 per mg of prednisone per day (95% CI 1.05–1.08).
Movahedi *et al.* 2016 (99)	UK	Oral GC users with RA (n=8395)	Patients with RA without GC (n=8367)	All-cause mortality: HR 1.97 (95 % CI 1.81–2.15).
Chester *et al.* 2016 (98)	USA	Prednisolone users with RA (n=3496)	Patients with RA without GC (n=2130)	Increased risk of death: HR 2.83 (95% CI 1.03–7.76).
Lee *et al.* 2019 (100)	Korea	Oral GC users with asthma (n=8334)	Patients with RA without GC (n=458 607)	All-cause mortality: HR 2.17 (95% CI 2.04–2.31).
Mebrahtu *et al.* 2019 (93)	UK	Oral GC users with chronic inflammatory diseases* (n=70 638)	Non-users (n=41 166)	Increase in HR for every increase of 5 mg prednisolone per day: 1.06 (95% CI 1.05–1.06).
Oh & Song 2020 (101)	South Korea	Chronic (≥30 days) oral GC users (n=3386)	General population (n=818 711)	Higher 5-year mortality: HR 1.41 (95% CI 1.28–1.55)

CD, Crohn's disease; CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; RA, rheumatoid arthritis; RR, relative risk; UC, ulcerative colitis.
*Inflammatory bowel disease, polymyalgia rheumatica, giant cell arteritis, rheumatoid arthritis, systemic lupus erythematosus, vasculitis.

High cumulative GC doses have been associated with higher risk of death (99). GC users have increased morbidity and mortality from cardiovascular disease and heart failure (97, 102). According to previous research, GC use has been associated with increased all-cause mortality as well as cardiovascular mortality among patients with RA. Both a longer treatment duration as well as higher dosages are associated with a worse outcome (95, 97, 98).

There is evidence that not only GC treatment itself but also the period following the cessation of GC treatment may increase mortality. In a study of 70 638 oral GC users, there was an increase in mortality rate during the first 2 months after the discontinuation of oral GC treatment followed by a decrease in mortality after the first 3 months (93). This increased mortality raises the concern that the patients are dying from undertreated or undiagnosed GC-induced adrenal insufficiency caused (37).

1.11 GAPS OF KNOWLEDGE

Although GCs have been used as medication for over 70 years, many questions regarding GC treatment still remain unanswered. The prevalence of GC use has been investigated but most previous studies have focused on the prevalence of GC treatment rather than its indications. Information on the prevalence and indications for oral GC treatment in children is also limited.

Many well-known side effects of GC treatment may lead to increase mortality. However, most previous mortality studies have not examined all patients using GCs, only those suffering from a particular disease such as RA.

Regarding GC-induced adrenal insufficiency, it is still unclear if it contributes to premature mortality in GC users. In addition, GC-induced adrenal insufficiency may have a larger clinical burden than we are aware of. Our hypothesis is that GC-induced adrenal insufficiency remains underdiagnosed and can contribute to increased mortality in GC users.

2 AIMS

Paper I: To estimate the prevalence of GC use at doses associated with a risk of GC-induced adrenal insufficiency.

Paper II: To investigate all-cause mortality and disease-specific mortality in a large population-based cohort of oral GC users.

Paper III: To investigate if GC-induced adrenal insufficiency is an underestimated cause of death among oral GC users.

Paper IV: To determine the prevalence of GC-induced adrenal insufficiency in patients with oral lichen planus treated with a topical GC (clobetasol propionate) in the oral cavity.

Paper V: To investigate the incidence of GC-induced adrenal insufficiency in patients receiving short-term, high-dose oral GC treatment.

An overview of each paper is shown in Table 3.

Table 3. Overview of each paper.

	Paper I	***Paper II***	***Paper III***	***Paper IV***	***Paper V***
Study design	Retrospective cohort study	Retrospective matched cohort study	Retrospective cohort study	Cross-sectional study	Prospective study
Aim	Estimate the prevalence and indication for GC use	Investigate mortality in oral GC users	Investigate if adrenal insufficiency is an underestimated cause of death among oral GC users	Determine the prevalence of adrenal insufficiency in patients using topical GCs	Investigate the incidence of adrenal insufficiency in patients receiving GC pulse treatment
Population	223 211 oral GC users	223 211 oral GC users	300 oral GC users who died from sepsis	27 patients with oral lichen planus	10 patients with diffuse large B-cell lymphoma
Study period	2007–2014	2007–2014	2007–2014	2017–2021	2018–2020
Methods	Cross-linkage of national registries	Cross-linkage of national registries	Review of medical records	Evaluation of adrenal function (morning plasma cortisol)	Evaluation of adrenal function (Synacthen test)
Main outcomes	14.1% of all inhabitants in Västra Götaland county who had received a prescription for oral GCs during the study period	Oral GC users have increased mortality compared to the background population (adjusted HR 2.1; 95% CI 2.0–2.1)	11 patient deaths (3.7%) were probably due to undiagnosed and untreated GC-induced adrenal insufficiency	Approximately 20% had GC-induced adrenal insufficiency	None of the patients developed GC-induced adrenal insufficiency

CI, confidence interval; GC, glucocorticoid; HR, hazard ratio.

3 PATIENTS AND METHODS

3.1 STUDY DESIGN, SUBJECTS, AND METHODS

Papers I, *II*, and *III* were based on registry data. Five large registries were used to collect data on GC users in Western Sweden (Figure 6). These registries were:

1. *The Swedish Prescribed Drug Register* which has information on all prescriptions dispensed in Swedish pharmacies since 1 July 2005 (103).
2. *The Swedish National Patient Register* that includes information on all inpatient care in Sweden since 1987 and information on outpatient visits since 2001 (104). Information on primary care is not provided in the register.
3. *The Swedish Cancer Register* that includes data on cancer diagnosis since 1958 (105).
4. *The Västra Götaland Regional Healthcare Database* has information from inpatient, primary, and private healthcare for inhabitants in Västra Götaland county since 2000.
5. *The Swedish Cause-of-Death Registry* that includes information on all deaths in Sweden since 1961 (106).

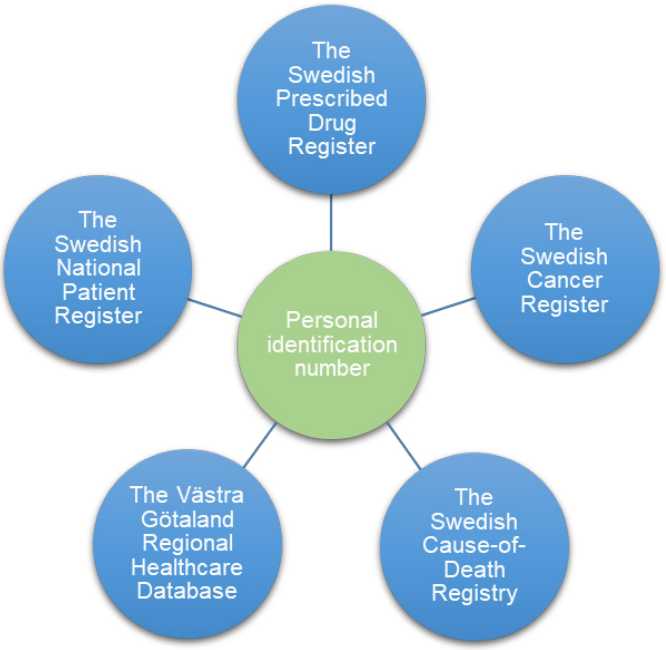

Figure 6. In Papers I, II, and III, information was collected from five large Swedish registries.

3.1.1 PREVALENCE OF GC USE – *PAPER I*

Paper I was a retrospective cohort study. To identify patients at risk of developing GC-induced adrenal insufficiency, a search was conducted in *The Swedish Prescribed Drug Register* using the Anatomical Therapeutic Chemical codes for oral GCs (prednisolone H02AB06, hydrocortisone H02AB09, betamethasone H02AB01, and dexamethasone H02AB02). All inhabitants in Västra Götaland County, Sweden, with dispensed oral GCs (prednisolone ≥5 mg or equivalent doses of hydrocortisone, betamethasone, or dexamethasone for ≥21 days) from 1 January 2007 to 31 December 2014 were included (Table 4).

Table 4. Criteria used in Paper I to identify patients in The Swedish Prescribed Drug Register.

Type of glucocorticoid	Anatomical Therapeutic Chemical code	Dose during maximum 21 days
Prednisolone	H02AB06	105 mg
Hydrocortisone	H02AB09	420 mg
Betamethasone	H02AB01	10.5 mg
Dexamethasone	H02AB02	10.5 mg

The following data were retrieved from *The Swedish Prescribed Drug Register*:

- Number of dispensed prescriptions;
- Number of tablets per prescription;
- Number of defined daily doses (DDDs) per prescription.

In the registry, DDD is defined according to the World Health Organization (WHO) definition (7). DDD for betamethasone and dexamethasone is 1.5 mg, prednisolone 10 mg, and hydrocortisone 30 mg.

The date of first dispensed prescription of oral GC was defined as the index date. Patients were cross-linked with three other Swedish registries using their personal identification number. These registries (*The Swedish National Patient Register, The Swedish Cancer Register*, and *The Västra Götaland Regional Healthcare Database*) were used to collect information on the indication for GC treatment and comorbidities using International Classification of Diseases 10th Revision (ICD-10) codes. Information on comorbidities was collected for a 2-year period before the index date, and indication for treatment 6 months before and 6 months after the index date. Information on the size of the population living in the area during the time of the study was retrieved from Statistics Sweden (107).

Based on the duration of oral GC treatment, the patients were divided into four groups:

1. Single-occasion users (received one prescription over the study period);

2. Occasional users (received more than one prescription but less than 300 tablets per year);
3. Medium-term users (received more than one prescription and more than 300 tablets per year for up to 2 consecutive years);
4. Long-term users (received more than one prescription and more than 300 tablets per year for at least 2 consecutive years).

3.1.2 MORTALITY IN GC USERS – *PAPER II*

Paper II was a retrospective matched cohort study using the same cohort as in *Paper I*. Information on causes of death was collected from *The Swedish Cause-of-Death Registry*. For each case, one control subject from *Västra Götaland's Population Register (Västfolket)* matched for age and sex was included. Controls with dispensed oral or injectable GCs during the study period were excluded.

The patients, defined as cases, were divided into four groups according to GC dose received in the previous 3-month period:

1. Non-users (0 DDDs per day);
2. Low-dose users (more than 0 DDDs per day but lower than 0.5 DDDs per day);
3. Medium-dose users (0.5–1.5 DDDs per day);
4. High-dose users (more than 1.5 DDDs per day).

Depending on the previous 3-month period, a case could be moved between the DDD groups at any time during the study. For example, a case may have been classified as a high user at the beginning of the study and as a non-user at a later time depending on the GC dose dispensed during the previous 3 months. The term "non-user" refers to a case who meets the inclusion criteria and has been dispensed at least one GC prescription but has not been dispensed GCs within the previous 3 months.

3.1.3 GC-INDUCED ADRENAL INSUFFICIENCY AS A PREMATURE CAUSE OF DEATH – *PAPER III*

This was retrospective cohort study using the same cohort as in *Papers I* and *II*. Patients who died from sepsis within 6 months from a dispensed prescription of oral GCs were included in *Paper III* (n=665). A total of 300 randomly selected medical records were reviewed to investigate the cause of death and to determine if it was possible or probable that the death could have been related to undiagnosed GC-induced adrenal insufficiency. A random number generator in Microsoft Excel 2016 (Microsoft Corporation, Redmond, Washington, USA) was used to provide the random sample.

Following data were collected from medical records:

- Previous medical history;
- Duration of GC use;
- Indication for GC use;
- GC use before and during hospital stay;
- Symptoms and signs before death;
- Results of blood tests before death.

One investigator conducted the initial review and estimated if it was unlikely, possible, or probable that the death could have been related to undiagnosed and undertreated GC-induced adrenal insufficiency. This initial reviewer considered 51 deaths possibly or probably linked to GC-induced adrenal insufficiency. Thereafter, three additional investigators reviewed the medical records independently: one investigator reviewed all 51 cases, and two reviewed 26 and 25 cases, respectively. The investigators did not know each other's gradings during the review process. The grading of unlikely, possible, or probable death due to adrenal insufficiency required consensus between two reviewers.

3.1.4 TOPICAL GC TREATMENT FOR ORAL LICHEN PLANUS – *PAPER IV*

This paper was a clinical cross-sectional study. Adult patients with oral lichen planus receiving long-term (>6 weeks) topical GC treatment were included. The patients were identified at the Department of Oral Medicine, Sahlgrenska University Hospital. Patients using other medications containing GCs (such as nasal spray, tablets, ointments, inhalations, and injections) and patients with a history of adrenal insufficiency were excluded.

Thirty patients participated in the study (Figure 7). Adrenal function was assessed by measuring serum cortisol between 8 and 9 AM after a withdrawal of GC treatment for 48 hours. For patients with serum cortisol concentrations <280 nmol/L, an ACTH stimulation test (Synacthen test) was performed. Plasma cortisol concentrations were measured by radioimmunoassay (Roche Cobas, Cortisol-II).

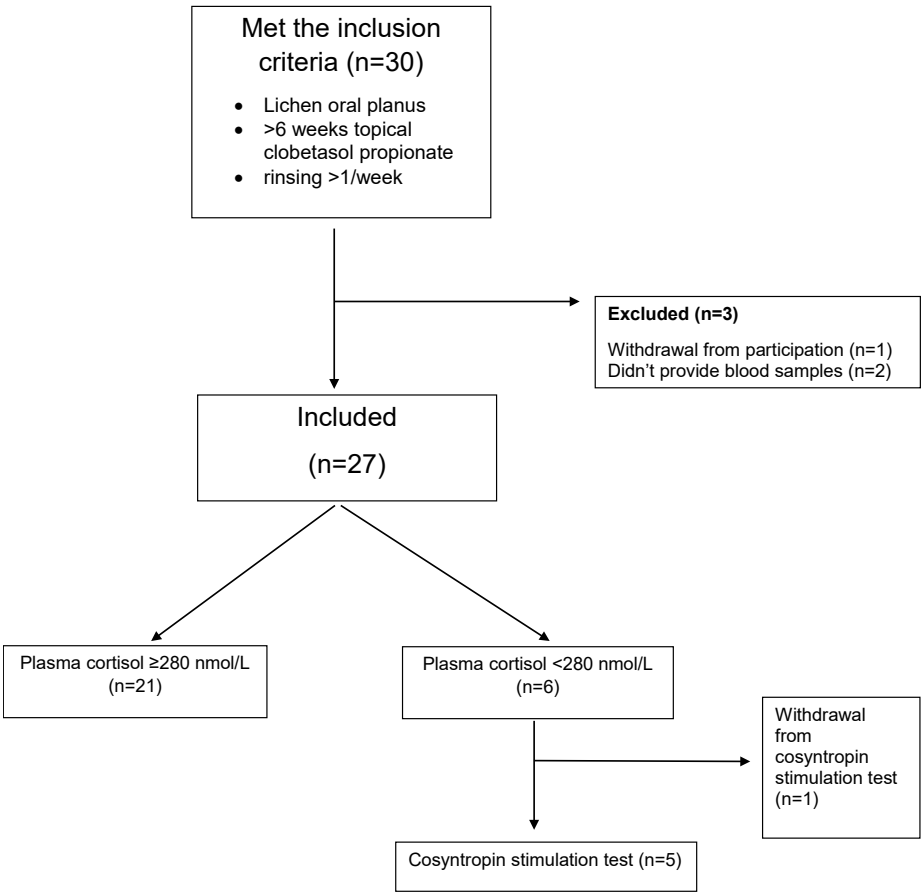

Figure 7. Flowchart of inclusion, exclusion, and study process for Paper IV. The figure is reproduced with permission from John Wiley and Sons (Oral Diseases, Topical clobetasol treatment for oral lichen planus can cause adrenal insufficiency. Einarsdottir et al. 2023) (108).

3.1.5 INTERMITTENT HIGH-DOSE GC TREATMENT – *PAPER V*

Paper V was a prospective study. Patients with newly diagnosed diffuse large B-cell lymphoma receiving short-term, high-dose oral GC therapy as an adjuvant to their chemotherapy were identified at the Department of Hematology, Sahlgrenska University Hospital. All subjects using GCs (oral,

injection, inhalation, nasal spray, ointment), with adrenal metastasis, or having a previous history of adrenal insufficiency were excluded from the study. ACTH stimulation tests (Synacthen test) were performed at study entry and before the 5th cycle of chemotherapy, and 3 months after the last cycle of chemotherapy (Figure 8). All the Synacthen tests were performed at 8–9 AM after an overnight fast. Normal adrenal function was defined as morning plasma cortisol >280 nmol/L and peak plasma cortisol (30 or 60 minutes after injection of cosyntropin) >450 nmol/L. Plasma cortisol concentration was measured with a radioimmunoassay (Roche Cobas, Cortisol-II).

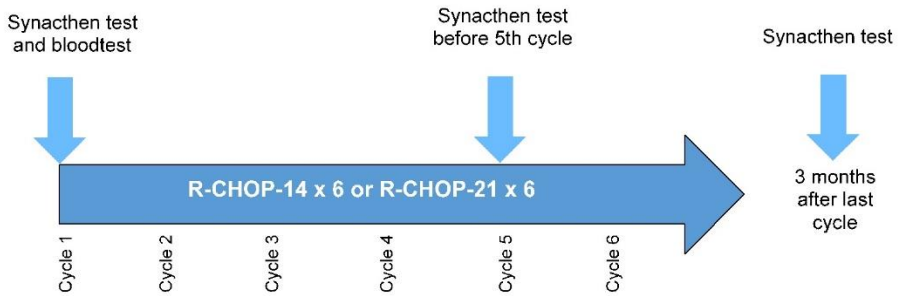

Figure 8. Study design of *Paper V*. *R-CHOP-14, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone treatment with 14-day interval between cycles; R-CHOP-21, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone treatment with 21-day interval between cycles.*

3.2 STATISTICAL ANALYSIS

3.2.1 PREVALENCE OF GC USE – *PAPER I*

Period prevalence for the study period 2007–2014 was calculated using the mean population size during the study period as a denominator. Population size data stratified by age and gender was obtained from Statistics Sweden (107) and used to calculate age- and gender-specific period prevalence. Age was defined as age at the first GC-dispensed prescription.

3.2.2 MORTALITY IN GC USERS – *PAPER II*

In *Paper II*, mortality was calculated using Cox proportional hazard models. The hazard ratio with a 95% confidence interval (CI) was calculated for mortality in GC users compared to controls. The log-rank test was used to determine the difference in survival. In order to assess mortality by DDD groups, time-dependent Cox proportional hazards models were used, which provided hazard ratios with 95% CIs and p-values. Both unadjusted hazard ratio and hazard ratio adjusted for age, sex, and comorbidities were calculated. The comorbidities used were diabetes (ICD-10 codes E10–E14), deep vein thrombosis (I80–I82), pulmonary embolism (I26), hypertension (more than 2 dispensed prescription of antihypertensive drugs), stroke (I64), ischemic heart disease (I20–I25), heart failure (I50), pneumonia (J12–J18), and malignant neoplasm (C00–C97) diagnosed from 2 years prior to inclusion.

3.2.3 *PAPERS III, IV,* AND *V*

Descriptive data were presented as mean ± standard deviation and median (range). For the comparison of groups, Student's *t*-test was used for continuous variables with normal distribution and the Mann-Whitney *U*-test for non-normally distributed data. The Chi-square test or Fisher's exact test was used for differences in proportions. In *Paper V,* repeated measure analysis of variance (ANOVA) was used to investigate significant differences in measurements (morning cortisol, peak cortisol, plasma sodium, plasma ACTH, systolic blood pressure, and body mass index) at baseline, before the 5th cycle, and 3 months after the last cycle.

All analyses in *Papers I* and *II* were conducted by a statistician who used SAS® version 9.4 (Cary, NC, USA). Analysis in *Papers III, IV,* and *V* were performed using IBM SPSS Statistics for Windows, version 25 (IBM Corp, Armonk, NY, USA). A p-value of <0.05 was considered statistically significant in all *Papers*.

3.3 METHODOLOGICAL CONSIDERATIONS

3.3.1 PREVALENCE OF GC USE AND MORTALITY – *PAPERS I* AND *II*

Papers I and *II* are based on registry data and the quality of the registries is the key to ensure reliable results. *The Swedish National Cause-of-Death Registry*, *The Swedish Prescribed Drug Register*, *The Swedish Cancer Register*, and *The Swedish National Patient Register* are held by *National Board of Health and Welfare* which guarantees high data quality. By law, all hospitals in Sweden are required to report all in-patient care to *The Swedish Patient Registry* (109). Validation of *The Swedish National Patient Register* has shown that 85%–95% of diagnoses in the database are valid (109). *The Swedish National Cause-of-Death Registry* has fewer than 1% of deaths without a recorded cause of death (110).

The definition of the GC-user group is not the same in *Papers I* and *II*. In *Paper I*, there are four groups according to the duration of GC treatment. After the publication of *Paper I*, a mortality study including the same cohort (*Paper II*) was designed. While preparing the statistical analysis, we discovered that the same group classification would potentially create an immortal time bias (111). In an observational study, immortal time bias may occur if exposure status is determined by an event occurring after baseline. There is a possibility that this bias can lead to overestimations or underestimations of an effect (111). In *Paper I*, we define groups based on what happened after baseline. All long-term users survive >2 years according to definition and, if their survival is shorter, they are classified as medium-term users. If we suppose, we conduct a mortality study and use the same classification as in *Paper I*. No deaths occurred among long-term users during the first 2 years of follow-up (because the patients have to survive >2 years to be classified as long-term users). As a result, there is an immortality time in the long-term users' follow-up since death cannot occur during the first two years of follow-up. In contrast to the control group, in which deaths can occur during these first two years of follow-up. This type of design of the mortality analysis would underestimate the risk of death in long-term users. We therefore changed the group classification. In *Paper II*, we divided patients into four groups based on DDD use in the previous 3-month period.

The *Swedish Prescribed Drug Register* contains information on DDD for every prescription made in Sweden. The DDD used in the registry is the WHO definition of DDD (112). This definition differs from the GC equivalent dose used in inclusion criteria in *Papers I* and *II*. The WHO definition of 1 DDD is betamethasone 1.5 mg, dexamethasone 1.5 mg, prednisolone 10 mg, and hydrocortisone 30 mg (112). According to this definition prednisolone 5 mg is equivalent to hydrocortisone 15 mg but the most commonly used definition is that prednisolone 5 mg is equivalent to hydrocortisone 20 mg (27) and that is used in the inclusion criteria.

In *Papers I* and *II*, we relied on a prescription registry that only provided information on dispensed prescriptions; thus, compliance and actual use can only be assumed. Another option had been to send questionnaires to patients and ask about GC use but such methods also have limitations such as recall bias.

In *Paper I*, the indication for GC treatment was a pertinent indication, i.e., the indication listed is probably the actual indication but it cannot be definitively stated.

3.3.2 GC-INDUCED ADRENAL INSUFFICIENCY AS A PREMATURE CAUSE OF DEATH – *PAPER III*

It is a methodological challenge to conduct a study to determine whether the recorded cause of death is correct. Our hypothesis was that GC-induced adrenal insufficiency is an underestimated cause of death in GC users. We did not have blood samples from these patients who had already died, so it was impossible to measure cortisol levels in plasma. To test our hypothesis, we decided to examine the medical records of patients who had sepsis as the recorded cause of death. We chose sepsis as the cause of death because sepsis and adrenal crisis share many symptoms and infection is one of the most common factors leading to adrenal crisis (113). This method has limitations

because it cannot be determined with 100% certainty whether the death was caused by adrenal insufficiency or not.

3.3.3 *PAPERS IV* AND *V*

In *Papers IV* and *V*, a high-dose (250 µg) ACTH stimulation test was used to evaluate adrenal function. Previously, a low-dose test was considered to have higher sensitivity in the diagnosis of secondary adrenal insufficiency (67, 68). However, meta-analysis has not shown any difference in diagnostic accuracy between high- and low-dose ACTH stimulation tests (69). The low-dose ACTH stimulation test has been shown to increase the risk of false positive results due to technical problems (dilution of the synthetic ACTH, adsorption to the plastic infusion tube) (114, 115).

In *Papers IV* and *V*, a morning cortisol concentration of 280 nmol/L was used as a cut-off value for dynamic testing. This cut-off value is debatable. A recent review article recommended a cortisol cut-off value of 270 nmol/L when determining whether further investigation with dynamic testing was indicated in patients with suspected GC-induced adrenal insufficiency (37). Furthermore, a morning cortisol concentration ≥270 nmol/L is not associated with withdrawal symptoms or adrenal crisis in patients recovering after adrenalectomy for Cushing syndrome (116).

In *Papers IV* and *V,* all patients who used any other medications containing GCs (ointments, tablets, nasal spray, inhalations, and injections) were excluded from participation since other forms of GC can suppress the HPA axis and can affect morning plasma cortisol. Information on current medication was also collected in *Paper IV* and *V* because some medications (e.g., oral contraceptives) can influence plasma cortisol concentration (76).

3.4 ETHICAL CONSIDERATIONS

The Ethical Regional Board of Gothenburg approved all the studies included in this thesis: *Papers I, II,* and *III* (Dnr 773-14), *Paper IV* (Dnr 670-17), and

Paper V (Dnr 750-17). The studies were conducted in accordance with the World Medical Association Declaration of Helsinki.

Papers I and *II* were register studies and all of the data was not traceable to a particular individual. In *Paper III*, the National Board of Health and Welfare Sweden provided personal identification numbers and we stored them securely and password-protected.

Papers IV and *V* were studies with participants who gave written informed consent prior to participation. Participation was voluntary and patients could stop or withdraw their consent at any time.

Participation in research studies can be directly beneficial. Five patients in *Paper IV* were diagnosed with GC-induced adrenal insufficiency and received treatment that can increase their quality of life and decrease mortality during intercurrent illness.

The patients in *Paper V* received chemotherapy that is physically and psychologically demanding. The participation rate in the study was low and was terminated after the inclusion 10 patients since none of these had biochemically verified adrenal insufficiency.

4 RESULTS

4.1 PREVALENCE OF GC USE – *PAPER I*

A total of 223 211 individuals were included in the study, which was 14.1% of inhabitants in Västra Götaland County at the time of the study. Mean age was 48 ± 24 (range 0.1–107) years. Women were 55.6% and dominated in all age groups except in the 0–9 year age group (Figure 9).

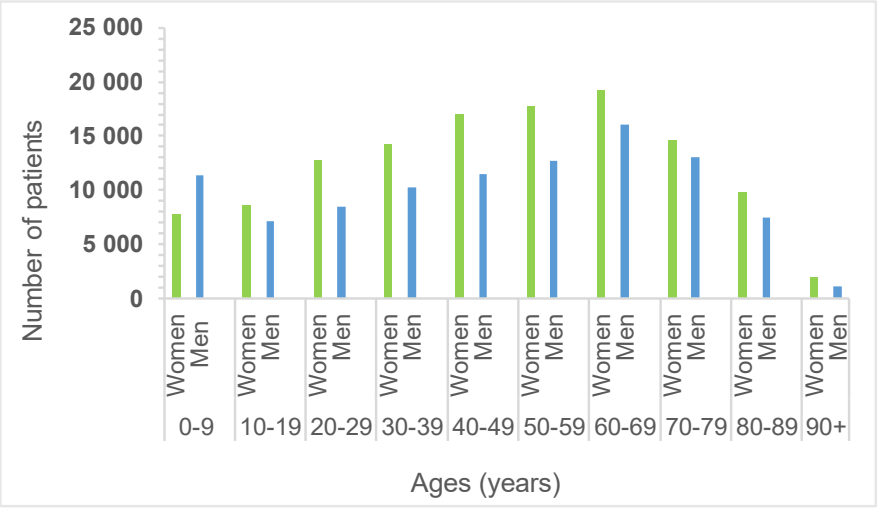

Figure 9. Age and sex distribution of the patients in Paper I.

Most GC users were single-occasion users (53.1%) followed by occasional users (30.9%), medium-term users (12.5%), and long-term users (3.5%).

The most common indications for GC treatment in the cohort were chronic obstructive pulmonary disease and asthma (17.2%), allergy (12.5%), and malignant neoplasms (11.5%). In children and adolescents, allergy was the most frequent indication (20.5%) followed by asthma (16.2%). Betamethasone was the most frequently used GC in the whole cohort but prednisolone was the most commonly used GC among long-term and medium-term users (Figure 10).

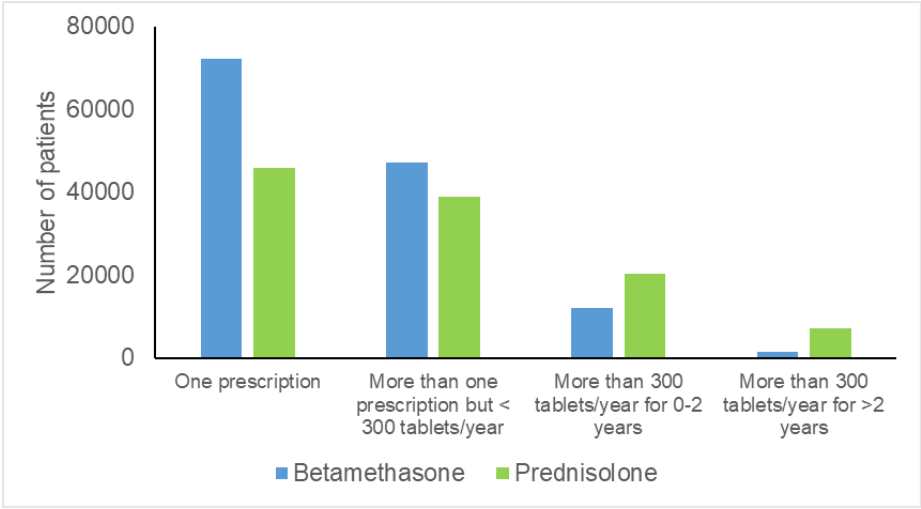

Figure 10. The type of glucocorticoid used in Paper I stratified by the four subgroups.

The highest prevalence of oral GC use was seen in the 80–89 year age group, where every fourth individual received oral GC treatment (Figure 11). The prevalence was 7.5%, 4.4%, 1.8%, and 0.5% for single-occasion, occasional, medium-term, and long-term users, respectively.

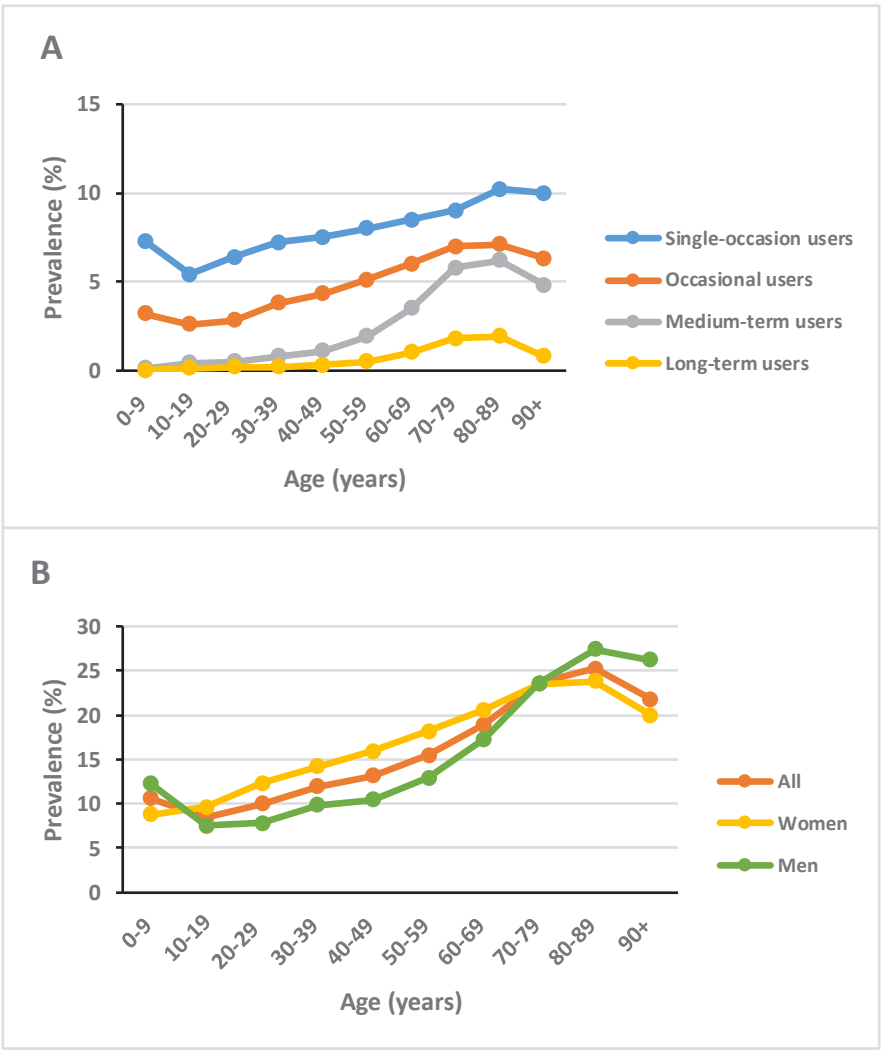

Figure 11. Prevalence of glucocorticoid use in Västra Götaland County 2007–2014 stratified by (A) the length of treatment, and (B) age and gender. Reproduced with permission from John Wiley and Sons (Clinical Endocrinology, High prescription rate of oral glucocorticoids in children and adults: a retrospective cohort study from Western Sweden. Einarsdottir et al. 2020) (117).

4.2 MORTALITY IN GC USERS – *PAPER II*

Mortality analysis on the same cohort as in *Paper 1* showed a 2-fold overall risk of dying during follow-up compared to controls (hazard ratio adjusted for age, sex, and comorbidities was 2.1 (95% CI 2.0–2.1). Disease-specific mortalities are illustrated in Figure 12. The adjusted hazard ratio was 2.5 (95% CI 2.2–2.9) for pulmonary embolism and 2.1 (95% CI 1.9–2.3) for sepsis. The highest adjusted disease-specific hazard ratios were observed in high-dose users for deaths from heart failure 2.4 (95% CI 2.0–2.9), pneumonia 3.8 (95% CI 3.1–4.7), sepsis 6.7 (95% CI 5.1–8.8), and pulmonary embolism 7.8 (95% CI 5.7–10.7).

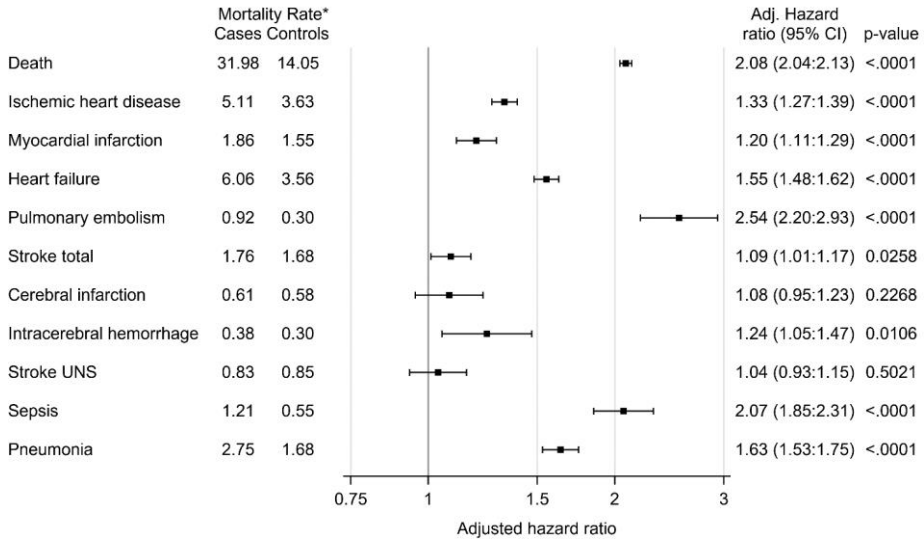

*Figure 12. All-cause mortality and disease-specific mortality in glucocorticoid users (cases) compared to age- and sex-matched controls. *Number of deaths per 1000 patient-years. Reproduced under the term of creative commons licence (CC BY) (Frontiers in Endocrinology. High mortality rate in oral glucocorticoid users: a population-based matched cohort study. Einarsdottir et al. 2022) (118).*

4.3 GC-INDUCED ADRENAL INSUFFICIENCY AS A PREMATURE CAUSE OF DEATH – *PAPER III*

Further analysis of the same cohort as in *Papers I* and *II* showed that 665 patients died from sepsis within 6 months from the last dispensed prescription of oral GC. A random sample of 300 patients (121 women, 40%) who died in hospital were included in the study. Mean age was 76 ± 12 years (range 30–99 years) and the mean duration of treatment was 13.9 ± 17.9 months (range 0.1–78 months). After review of medical records, GC-induced adrenal insufficiency was considered to have possibly or probably contributed to death in 47 patients (16%). These patients had lower GC dose ($p=0.002$), more often gastrointestinal symptoms ($p=0.003$) and hypoglycemia ($p<0.001$), and had lower systolic blood pressure on admission ($p=0.018$) when compared to the group of 253 patients in which adrenal insufficiency was not considered to have contributed to their death. The death of 11 patients (4%) was considered to have probably been due to untreated and undiagnosed GC-induced adrenal insufficiency. Five of these 11 patients did not receive GCs during their hospital stay because GC treatment had been mistakenly discontinued. Under- and undiagnosed GC-induced adrenal insufficiency was considered a possible cause of death in 36 patients (12%).

4.4 TOPICAL GC TREATMENT FOR ORAL LICHEN PLANUS – *PAPER IV*

Twenty-seven patients were included in the study. Twenty-one (78%) had morning cortisol ≥280 nmol/L (range 280–570 nmol/L) and six (22%) <280 nmol/L (range 13–260 nmol/L) (Figure 13). Five of these six patients underwent dynamic testing with cosyntropin stimulation that showed severe adrenal insufficiency in two patients (cortisol peak 150 and 210 nmol/L, respectively) and mild adrenal insufficiency in three patients (cortisol peak 350–388 nmol/L).

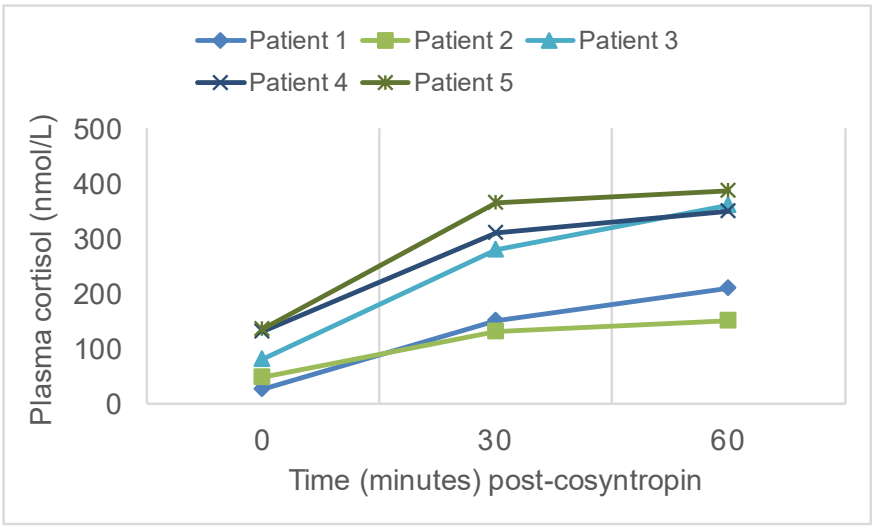

Figure 13. Plasma cortisol before, and 30 and 60 minutes after injection of synthetic adrenocorticotropic hormone (cosyntropin). Reproduced with permission from John Wiley and Sons (Oral Diseases, Topical clobetasol treatment for oral lichen planus can cause adrenal insufficiency. Einarsdottir et al. 2023) (108).

4.5 INTERMITTENT HIGH-DOSE GC TREATMENT – *PAPER V*

Ten patients (4 women and 6 men) were included in the study. Mean age was 61 years (range 40–78 years). Mean prednisone dose was 95 mg/day (range 75–100 mg/day). All patients had normal morning plasma cortisol and normal response to ACTH stimulation at baseline and during follow-up (Figure 14). Morning cortisol, peak cortisol, and plasma ACTH did not differ significantly between baseline, before the 5th cycle, or 3 months after the last cycle ($p=0.607$, $p=0.247$, and $p=0.198$, respectively).

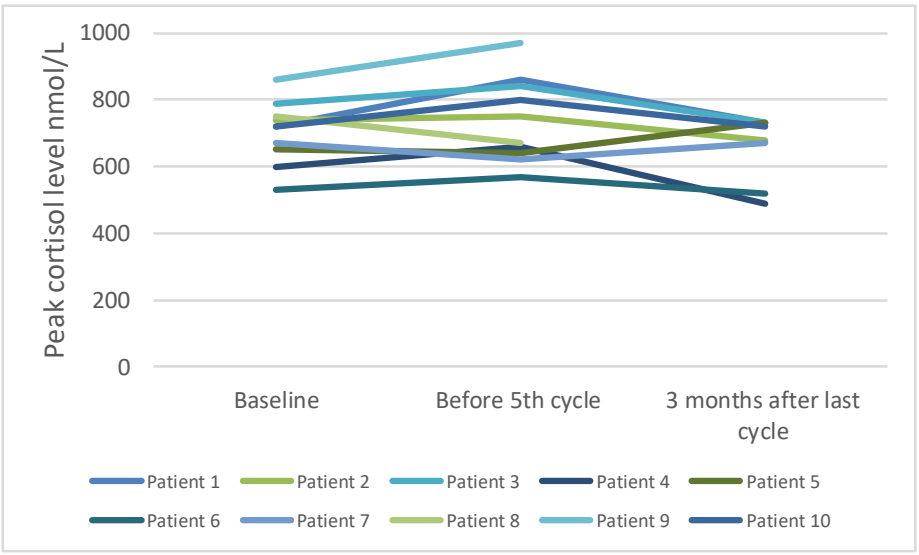

Figure 14. Results from the cosyntropin stimulation tests performed at baseline, before the 5th cycle, and 3 months after the last cycle of chemotherapy. Patients 8 and 9 did not undergo the 3rd cosyntropin stimulation test because of the coronavirus pandemic.

5 DISCUSSION

5.1 PREVALENCE OF GC TREATMENT AND PRESCRIPTION PATTERN

GCs have been used for more than 70 years. Our study showed that GCs are still frequently prescribed at doses associated with risk of GC-induced adrenal insufficiency in both pediatric and adult patients (*Paper I*). Although short-term treatment is most common, the prevalence of long-term oral GC use was 0.5%. This is similar to previous studies which have demonstrated prevalence of 0.5%-0.7% for long-term (>3 months) GC use (5, 7). The number of new GC users did not change over the study period 2007–2014 but previous studies have shown that the prescription pattern of oral GC may be changing. During a 20-year period (1989–2008) in the UK, the number of prescriptions for long-term oral GCs increased by 34%. However, patients with newly diagnosed RA, Crohn's disease, or ulcerative colitis were less likely to receive long-term GC prescriptions than those with a long history of these diseases (6). The use of new antirheumatic and disease-modifying drugs can explain this. However, despite these new drugs, GCs are still an essential treatment for these diseases and are often used in combination with these newer disease-modifying drugs in the treatment of RA (119-121).

In our study, the highest prevalence was seen in patients >80 years of age, with the highest prevalence in men ages 80–89 years. Studies from the USA and Denmark have reported similar findings (4, 13).

During the study period, one of ten children used oral GCs, illustrating the importance of being aware of the potential risk for GC-induced adrenal insufficiency in pediatric patients. Fatal GC-induced adrenal insufficiency has in fact been described in children (122).

Betamethasone was the most commonly prescribed oral GC (54%) followed by prednisolone (45%) (*Paper I*). This high prescription rate of betamethasone seems to be specific for Sweden. The UK and the USA use prednisolone more frequently with prescription rates of 90% and 77%, respectively (4-6, 12). In Denmark, prednisolone accounted for 50% of all GC prescriptions (oral and injections) in 2015 (13). This high prescription rate of betamethasone in our

study is interesting in terms of GC-induced adrenal insufficiency. Betamethasone suppresses the HPA axis more severely than prednisolone (38). Common use of betamethasone may also have implications for long-term outcomes as prednisolone has a shorter half-life and has mineralocorticoid activity, unlike betamethasone (123).

The strength of *Paper I* is the access to large databases. We had information on all prescriptions at all Swedish pharmacies and we only used dispensed prescriptions. The information on underlying disease was obtained from hospitals, primary care, and private clinics, which is unique since most previous studies do not include data from at least one of these settings. Furthermore, we investigated oral GC use in adults and children while previous studies focused on adult GC use. One limitation of *Paper I* is that we only included patients treated with oral GCs. Therefore, patients using other routes of administration, such as inhalation, injection, and topical, are not included. The number of people at risk of developing GC-induced adrenal insufficiency is probably higher than our findings indicate because other administration forms of GC can cause adrenal suppression (10).

5.2 MORTALITY IN GC USERS

Paper II, which included 223 211 oral GC users in a matched cohort, revealed that oral GC users are at a doubled risk of death during follow-up compared to matched controls. The risk of death, after adjustment for comorbidities and other possible confounders, from pulmonary embolism, pneumonia and sepsis was increased.

Previous studies have shown that GC users with one specific underlying disease (asthma, Crohn's disease, ulcerative colitis, or RA) have an approximately doubled risk of death compared to non-users (96, 99, 100). A population-based study has shown that chronic (≥30 days) GC users were 1.4 times more likely to die from all causes compared to controls (101).

We report an increased mortality risk from pulmonary embolism in GC users. This is a novel finding because previous studies have not focused on pulmonary embolism as a specific cause of death in patients receiving GC

treatment (97, 99-101). The results of our study are in accordance with the increased incidence of thromboembolism among patients with endogenous hypercortisolism, who are at 10-fold greater risk of venous thromboembolism (124-127). An approximately 2-fold increased incidence rate of pulmonary embolism and deep vein thrombosis has also been reported in GC users in a population-based case-control study from Denmark (128). Similarly, strong dose-dependent relationships have been found between oral GC use and thromboembolism in children (129).

GC treatment increases the susceptibility to infections (130, 131). In our study, high-dose users were at a 6-fold increased risk of death from sepsis and a 3-fold increased risk of death from pneumonia. These findings are similar to mortality studies in patients with endogenous hypercortisolism (132, 133). In patients with Cushing disease, 11% of all deaths are related to infections and half of them to pneumonia (133). One-third of all deaths in patients with Cushing's syndrome are from infections (132). One possible explanation for increased mortality in GC users from infections might be that undiagnosed adrenal crisis contributes to increased mortality. This hypothesis was further investigated in *Paper III*.

Our findings are of importance because, as we have shown in *Paper I,* GC treatment is common and can contribute to increased mortality. Clinicians should be aware of this increased risk of death in GC users and provide appropriate treatment, such as antibiotics or anticoagulants, if indicated.

A key strength of *Paper II* is the ability to evaluate mortality in oral GC users using a large population-based cohort, as opposed to prior studies that focused on mortality in GC users with a particular disease (94, 96, 99, 100). However, it is difficult to uncover whether the use of oral GCs is causally related to mortality because a number of confounders are involved, including the underlying disease itself and its severity (95, 97). Further research on this topic is therefore needed.

5.3 GC-INDUCED ADRENAL INSUFFICIENCY AND PREMATURE MORTALITY

Paper III shows that GC-induced adrenal insufficiency is an important and neglected cause of death in GC users and underlines the importance of awareness of the disorder during intercurrent illness and following cessation of GC treatment. If the healthcare provider is unaware of the current treatment for GC, hospitalization may pose a danger to the patient. Although the patients in *Paper III* had high levels of comorbidity, their survival should not be adversely affected by undiagnosed or undertreated GC-induced adrenal insufficiency. Awareness and knowledge about GC-induced adrenal insufficiency is essential and can potentially be life-saving in this population. It is necessary to educate patients to prevent adrenal crises during intercurrent illness. Patients need to be informed to double or triple their GC dose and to take GCs every 6–8 hours (Figure 15) (134, 135). It is also important to initiate stress dose administration at the onset of stress.

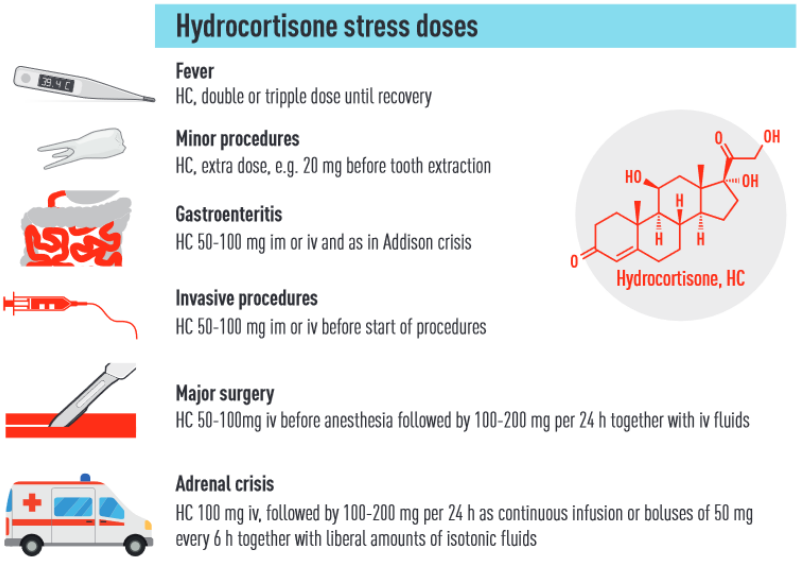

Figure 15. Hydrocortisone (HC) stress dose recommendations for patients with adrenal insufficiency. Figure reproduced with permission from Elsevier (Pituitary Tumors: A Comprehensive and Interdisciplinary Approach. Chapter 9 - Endocrinological Diagnosis and Replacement Therapy for Hypopituitarism. Esposito et al. 2021) (136)

The cases we classified as probable deaths from undiagnosed or undertreated adrenal insufficiency are similar to previously published cases. Considering the first described case of GC-induced adrenal insufficiency, the patient was hospitalized and did not receive GC during hospital stay and died of postoperative shock (9). This case was published in 1952, and 70 years later, it appears that long-term GC users may still be at risk of adrenal crisis during hospitalization and stress.

The patients that were considered to have possibly or probably died from GC-induced adrenal insufficiency had significantly lower GC dose than the group whose death was considered unrelated to their GC-induced adrenal insufficiency. A previous study has shown that more than one-third of patients on low-dose prednisolone treatment for RA had adrenal insufficiency (89). These patients have an inadequate GC dose when they are exposed to increased stress and it is therefore essential to give them a stress GC dose.

The strength of *Paper III* was that four endocrinologists reviewed the medical records in a blinded process; however, the methodology has limitations. It was a retrospective study with a large amount of missing data but it was probably the most effective way of investigating premature mortality, even though it is not possible to determine with 100% certainty that the death was caused by adrenal insufficiency.

5.4 PREVALENCE OF GC-INDUCED ADRENAL INSUFFICIENCY IN PATIENTS USING TOPICAL GC IN THE ORAL CAVITY

In *Paper IV*, 18.5% of patients receiving chronic topical GCs treatment for oral lichen planus had biochemically verified GC-induced adrenal insufficiency. Physicians and dentists need to be aware of this potential risk and know how to diagnose and treat adrenal insufficiency.

Previous studies on this topic have shown that 4% of those who used clobetasol as maintenance treatment had a suppressed HPA axis (137) and a more recent study showed that one of 15 patients on clobetasol as maintenance treatment developed HPA axis suppression (138). In these previous studies, maintenance treatment was defined as topical GC treatment on alternate days. However, in our study, some patients used clobetasol daily, possibly explaining the high prevalence of GC-induced adrenal insufficiency. GC use on alternate days has been associated with a decreased risk of adrenal suppression (34). The high prevalence of GC-induced adrenal insufficiency can also be explained by the timing of topical GC use. The patients in our studies used clobetasol in the evening and that has been associated with a higher risk of adrenal suppression (36).

In *Paper IV*, patients with GC-induced adrenal insufficiency had significantly lower DHEA-S concentrations compared to patients with a normal morning cortisol level. Further investigation is needed to determine if DHEA-S could be used as a screening tool for GC-induced adrenal insufficiency. Some research indicates that a normal age- and gender-specific serum DHEA-S level makes the diagnosis of adrenal insufficiency extremely unlikely (139).

The main strength of *Paper IV* is that all patients were on maintenance treatment and used the same type of clobetasol propionate (gel 0.025%). Dynamic testing was used to diagnose GC-induced adrenal insufficiency, which is a strength. Unfortunately, we had no information on morning cortisol levels before the start of clobetasol treatment.

5.5 SHORT-TERM, HIGH-DOSE GC TREATMENT AND GC-INDUCED ADRENAL INSUFFICIENCY

Paper V was a prospective study showing that short-term, high-dose GC treatment does not seem to down-regulate the HPA axis. There were only 10 patients included in the study. These patients were receiving chemotherapy, and participating in medical studies, which involve additional testing and appointments, and is therefore an additional burden. Consequently, we stopped

the study when 10 patients were included and none had adrenal insufficiency. Our results differ from previous studies (140, 141). A study including 10 patients with diffuse large B-cell lymphoma receiving R-CHOP-21 showed three patients to have adrenal insufficiency (140). The adrenal insufficiency was temporary and recovered 3–5 weeks after the last cycle in all patients (140). Another study included 15 patients with diffuse large B-cell lymphoma and three of them developed adrenal insufficiency after the 5th cycle (141). Our results may differ because of differences in the methods used in these studies. Both of the previous studies used a low-dose ACTH stimulation test and, in the study by Owattanapanich *et al*. (140), the adrenal insufficiency was defined as peak cortisol <497 nmol/L after a low-dose cosyntropin stimulation, which is a quite high cut-off (115). If the peak cortisol cut-off value had been set at 450 nmol/L (as in our study) only two patients would have met the definition of adrenal insufficiency with marginally low cortisol (386 and 440 nmol/L, respectively).

Our results agree with studies on patients receiving pulse methylprednisolone therapy for Graves' ophthalmopathy. Twelve patients were included and treated with intravenous methylprednisolone 500 mg/wk weekly for 6 weeks followed by 250 mg/wk for an additional 6 weeks. None of the patients had adrenal insufficiency on a high-dose ACTH stimulation test before the final dose of methylprednisolone (35).

Our findings show that adrenal insufficiency does not seem to be common after short-term, high-dose GC treatment. Nevertheless, our results do not exclude that transient adrenal insufficiency might happen. Awareness of GC-induced adrenal insufficiency is important and, in case of symptoms, it is critical to investigate and treat appropriately. Although the prospective study design in *Paper V* was a major strength, the low number of participants was a significant disadvantage.

In summary, this thesis highlights that GC-induced adrenal insufficiency is a clinical problem which is probably often undiagnosed and undertreated. Good treatment is available and the need for education is urgent because patients with adrenal insufficiency are still dying due to lack of knowledge (142). Hopefully, the results of this thesis will contribute to a better understanding of GC-induced adrenal insufficiency as well as improved patient care.

6 CONCLUSIONS

During 2007–2014, 14.1% of inhabitants in Western Sweden received prescriptions for oral GC at doses associated with the risk of developing GC-induced adrenal insufficiency.

Users of oral GCs have an increased mortality rate compared to the background population. The risk of death from sepsis, pulmonary embolism, and heart failure is increased in GC users compared to controls.

Under- and undiagnosed GC-induced adrenal insufficiency is likely to be a significant cause of death among GC users.

Topical GC used in the oral cavity can cause GC-induced adrenal insufficiency.

Short-term, high-dose oral GC treatment, commonly used as adjuvant treatment in patients with malignant diseases, does not seem to cause GC-induced adrenal insufficiency.

It is essential to be aware of GC-induced adrenal insufficiency and, importantly, to educate patients regarding stress GC doses during intercurrent illness.

7 ONGOING RESEARCH AND FUTURE PERSPECTIVES

The prevalence of GC use will likely continue to be high. For example, in Sweden, there is a 5-fold increase in the use of inhaled glucocorticoids (143). Moreover, new indications for GC treatment are still growing. GCs became highly used during the COVID-19 pandemic because dexamethasone use decreased mortality in COVID-19 patients requiring respiratory support (144). Therefore, it is highly expected that GCs will continue to be a commonly used medication during the coming decades. Thus, the adverse effects of GCs and GC-induced adrenal insufficiency will continue to challenge clinicians.

There is a growing awareness of GC-induced adrenal insufficiency. Since 2021, at least four extensive review articles about this condition have been published (27, 37, 88, 145). The need for clinical guidelines is urgent and the evidence on indications for hydrocortisone replacement treatment is lacking (27). Two randomized trials are ongoing in Denmark to investigate the effect of hydrocortisone compared to placebo (88). One of these trials is a randomized, double-blind clinical trial to compare the effect of hydrocortisone and placebo in patients with partial adrenal insufficiency (146). The other trial is a multicenter, randomized, double-blind, placebo-controlled clinical trial to investigate the effect of supplemental hydrocortisone during stress in patients with GC-induced adrenal insufficiency (147). Hopefully, the results of these trials will assist us in determining when and how to treat patients suffering from GC-induced adrenal insufficiency.

The awareness of stress GC doses is also increasing. In 2020, the European Society of Endocrinology published guidance on stress doses for GC users during the COVID-19 pandemic (148). Such guidance is strongly needed and a study has shown that 71% of respondents (93 physicians and 7 specialist nurses) changed their management after being directed to the guidelines (149).

These recommendations can be confusing for the patient. To simplify this stress dose administration, the French consensus on adrenal insufficiency patient education has recommended standard stress doses administered at 6- to 8-hour intervals initiated at the onset of the stress (134, 135). Other forms of education, such as standardized group education programs or active learning

with opportunities to work through scenarios, could improve patient knowledge on the prevention of adrenal crises (135, 150).

In the UK, individuals who use GCs for more than 3 weeks are recommended to carry a special steroid treatment wallet card (151) (Figure 16). The card is a reminder to patients of the risks of abruptly discontinuing GC therapy and is also an alert to healthcare providers. Results of surveys conducted in 1992, 1998, and 2010 showed that about 50% of long-term GC users have steroid treatment cards in the UK (152-154). If similar wallet card would be used in more countries, it could improve safety for GC users. Similarly, for hospitalized GC users, a warning signal that appears in an electronic medication management system when a physician interrupts long-term GC treatment prescription would be helpful.

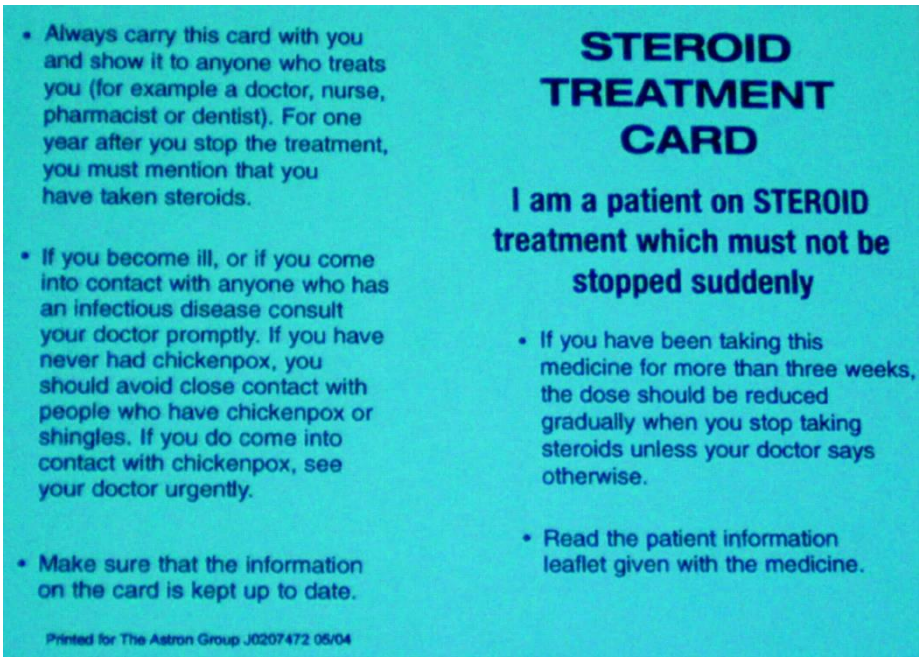

Figure 16. Steroid treatment card. Reproduced with permission from BMJ Publishing Group Ltd. (BMJ, ABC of chronic obstructive pulmonary disease. Pharmacological management--oral treatment, Currie, G. P. et al) (155).

Lastly, prospective studies are required to characterize further risk factors for GC-induced adrenal insufficiency, the predictive chance for adrenal gland recovery, and investigation of individual variation.

We plan to conduct a prospective study to investigate if a 6-week treatment course with topical clobetasol suppresses adrenal function in patients with oral lichen planus. Morning cortisol level will be measured at baseline, at 3 and 6 weeks, and at 6 weeks after the last clobetasol dose. The aim is to investigate when adrenal suppression starts and to study if 6 weeks is sufficient time for the adrenal gland to recover.

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