Adrenal Insufficiency in Corticosteroids Use: Systematic Review and Meta-Analysis

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Objective: We aimed to estimate pooled percentages of patients with adrenal insufficiency after treatment with corticosteroids for various conditions in a meta-analysis. Secondly, we aimed to stratify the results by route of administration, disease, treatment dose, and duration.

Methods: We searched seven electronic databases (PubMed, MEDLINE, EMBASE, COCHRANE, CENTRAL, Web of Science, and CINAHL/Academic Search Premier) in February 2014 to identify potentially relevant studies. Original articles testing adult corticosteroid users for adrenal insufficiency were eligible.

Results: We included 74 articles with a total of 3753 participants. Stratified by administration form, percentages of patients with adrenal insufficiency ranged from 4.2% for nasal administration (95% confidence interval [CI], 0.5–28.9) to 52.2% for intra-articular administration (95% CI, 40.5–63.6). Stratified by disease, percentages ranged from 6.8% for asthma with inhalation corticosteroids only (95% CI, 3.8–12.0) to 60.0% for hematological malignancies (95% CI, 38.0–78.6). The risk also varied according to dose from 2.4% (95% CI, 0.6–9.3) (low dose) to 21.5% (95% CI, 12.0–35.5) (high dose), and according to treatment duration from 1.4% (95% CI, 0.3–7.4) (<28 d) to 27.4% (95% CI, 17.7–39.8) (>1 year) in asthma patients.

Conclusions: 1) Adrenal insufficiency after discontinuation of glucocorticoid occurs frequently; 2) there is no administration form, dosing, treatment duration, or underlying disease for which adrenal insufficiency can be excluded with certainty, although higher dose and longer use give the highest risk; 3) the threshold to test corticosteroid users for adrenal insufficiency should be low in clinical practice, especially for those patients with nonspecific symptoms after cessation. **(*J Clin Endocrinol Metab* 100: 2171–2180, 2015)**

Strengths and Limitations of the Study

- This is the first meta-analysis providing a broad view on the risk of adrenal insufficiency after use of various types of corticosteroids in several underlying diseases.
- Studies displayed heterogeneity in the type of corticosteroid used, underlying condition, treatment dose, treatment duration, and route of administration, thereby reflecting clinical practice. Our results were stratified by these factors.
- Because no individual data were available, risk stratification at the level of the individual patient was not possible.
- Many articles with high levels of bias were included in this meta-analysis because there were only a few articles with low levels of bias available. This may have affected the results.

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Abbreviation: CI, confidence interval.

Corticosteroids are widely used for the treatment of various inflammatory conditions and malignancies and after organ transplantation. Therapy with corticosteroids is targeted toward inhibition of an inflammatory response (1–3). However, the use of corticosteroids is associated with numerous side effects and is considered to be the most common cause of adrenal insufficiency (4, 5). Chronic use of corticosteroids inhibits the function of the hypothalamic-pituitary-adrenal axis by negative feedback, which may cause adrenal insufficiency also after the cessation of corticosteroid treatment (4, 6). Adrenal insufficiency is a serious, potentially life-threatening side effect of corticosteroid use. Therefore, patients may require glucocorticoid replacement therapy after chronic use of corticosteroids in periods of stress, such as trauma, surgery, or acute illness, until full recovery of adrenal function. In some cases, chronic replacement with physiological doses of glucocorticoid therapy is indicated (7–9).

Neither treatment dose and duration, nor administration form, nor random serum cortisol measurements seem to accurately predict the development of adrenal insufficiency after the use of corticosteroids (10, 11). The magnitude of the risk of developing this side effect is unclear. Given the high prevalence of corticosteroid users, it is of great clinical relevance to try to obtain knowledge about the risk of developing adrenal insufficiency.

Objective of the Study

The aim of this study is to perform a systematic review and meta-analysis of the percentage of patients that develops adrenal insufficiency after the use of corticosteroids. Secondary aims are to stratify the results by route of administration, underlying disease, treatment dose, and duration, and to perform a separate analysis for the studies that repeated the test for adrenal insufficiency.

Materials and Methods

Eligibility criteria

Original studies assessing adrenal insufficiency in adult human corticosteroid users were eligible for inclusion. The diagnosis of adrenal insufficiency had to be established by one of the following tests: the insulin tolerance test, ACTH stimulation tests (0.5, 1, or 250 μg), CRH test, or metyrapone test. There were no restrictions in dose, duration, or type of corticosteroid therapy. Eligible administration forms of corticosteroids were oral, inhalation, topical, nasal, intra-articular injection, and im injection.

Articles were excluded if the examined population was not at risk of adrenal insufficiency secondary to the use of corticosteroids (eg, corticosteroid replacement therapy for primary or secondary adrenocortical failure, if not all patients used corticosteroids, or if patients included in the study were selected on the basis of having adrenal insufficiency). Articles were also excluded if no data or insufficient data were presented to analyze adrenal insufficiency after corticosteroid use.

Inclusion of articles was restricted to those in English and to articles that included at least 10 subjects to minimize the risk of selection bias. Articles containing the following populations were excluded: pregnant women, intensive care patients, and patients receiving corticosteroids perioperatively. Because we aimed to include studies in individuals aged 12 years or older, no dose corrections for body surface area were deemed necessary. If an article presented data for multiple study groups, of which some were eligible for inclusion, eligible study groups were included if the pertinent data could be extracted. Articles were also excluded if they were duplicates from already included articles or if they examined the same population as an already included article. Articles that were not retrievable online were requested by contacting the authors.

Definition of adrenal insufficiency

The cutoff value for serum cortisol used to define adrenal insufficiency was $\leq$ 500 nmol/L or higher (such as $\leq$ 550 nmol/L) to include as many articles as possible that have a low false-negative rate for adrenal insufficiency (12–14). Two articles were included that used a cutoff of 2 SD values below the cortisol value from a reference group within the study population, and one article was included that had a different cutoff value due to assay technique ($\leq$370 nmol/L). After using the metyrapone test, cortisol had to be at least 200 nmol/L (12). If no cutoff had been provided or if the cutoff used was not 500 nmol/L but individual data were presented, a cutoff of 500 nmol/L was employed to identify patients with adrenal insufficiency. A separate sensitivity analysis was performed for articles testing adrenal insufficiency at least 24 hours after the last use of corticosteroids (12).

Search strategy

In February 2014, PubMed, MEDLINE, EMBASE, COCHRANE, CENTRAL, Web of Science, and CINAHL/Academic Search Premier were searched in cooperation with a specialized librarian to identify potentially relevant articles (see Supplemental Data for complete search string). References of key articles were also assessed to identify potentially eligible articles. Only articles published from 1975 to the present were searched because RIA for cortisol became available shortly before the start of that year (15). Randomized controlled trials, cohort studies, and cross-sectional studies were considered, whereas case-control studies and case series are not suitable to estimate absolute risks (16).

Data extraction

All identified articles were entered in Reference Manager version 12 (Thomson Reuters) and were first screened on title and abstract. Potentially relevant articles were then reviewed in detail before inclusion into this meta-analysis. Two different reviewers performed both the screening of the title and abstract and the review in detail for potentially relevant articles. Articles containing more than one study group had multiple entries in this meta-analysis. The Meta-analysis Of Observa-

tional Studies in Epidemiology (MOOSE) guidelines were used for reporting (17).

Risk of bias assessment

Study elements that could potentially bias an association between corticosteroid use (exposure) and the development of adrenal insufficiency (outcome) were assessed for all included articles. Risk of selection bias was considered low if consecutive exposed patients or a random sample of exposed patients was included (thereby preventing selection bias) and if eligibility criteria were reported. Ascertainment of exposure to corticosteroids was considered adequate if this was done by protocol or medical record. Measurement of adrenal insufficiency was considered adequate if RIA was used for measuring cortisol concentrations (15). Loss to follow-up $< 5\%$ was considered a low risk of bias for randomized controlled trials and cohort studies. Studies not following these criteria harbor a higher risk of bias. We did not exclude these articles from analyses because this would result in a very low number of studies available for systematic review and meta-analyses.

Statistical analysis

The main outcomes of this meta-analysis were the pooled percentages of patients with adrenal insufficiency after corticosteroid use, stratified by administration form, disease, treatment dose, and treatment duration. Percentages were pooled in a random-effects logistic regression model. A fixed logistic regression model was used when the number of studies in a particular subgroup was less than five. Analyses were performed with Stata version 12.1 (StataCorp).

Analysis stratified by administration form was based on administration forms used at the time of adrenal testing. If studies included patients using multiple types of corticosteroids (for example, use of inhalation corticosteroid next to oral corticosteroids), this was classified as multiple administration forms. Disease groups are: asthma (including chronic obstructive pulmonary disease) with only inhalation corticosteroids, asthma (including chronic obstructive pulmonary disease) with other administration forms (including multiple administration forms) of corticosteroids, allergic rhinitis and rhinosinusitis, dermatological disorders (psoriasis, atopic dermatitis, and lichen planus), rheumatic diseases (including osteoarthritis and rheumatoid arthritis), renal transplant, hematological cancers (including myeloma, lymphoma, acute lymphoblastic leukemia, and Hodgkin's disease), nasal polyposis, cystic fibrosis, and Crohn's disease. Diseases that were studied in one study only were not included in the analysis of adrenal insufficiency after the use of corticosteroids stratified by condition.

Treatment duration was categorized as follows: <1 month use, short term; 1 month to 1 year, medium term; and >1 year, long-term use. Treatment dose was categorized according to recommended doses, with the doses between the lower and upper bounds of the recommendation coded as medium dose, doses below the lower bound as low dose, and doses above the upper bound as high dose. Because the most used doses were supraphysiological, doses were not grouped according to physiological and supraphysiological dose. Limits used for the aim of categorization of dose groups and references can be found in Supplemental Table 1. For categorization, the average dose and duration were used. Studies not reporting treatment dose or duration could not be included in the respective stratified analysis. Not included in the treatment duration analysis were articles with multiple short courses of corticosteroids spread out over a period of time longer than 1 month. Analysis of the percentage of patients with adrenal insufficiency by treatment dose and by treatment duration was performed in asthma patients only, as opposed to the entire population of corticosteroids users, to provide a homogeneous patient population.

Separate analysis of study groups that performed repeated tests after discontinuation of corticosteroids was performed. Retesting 4 weeks after cessation of corticosteroid therapy was predominantly performed after a short-term, high-dose corticosteroid treatment regimen, whereas retesting 6 months after cessation of corticosteroid therapy predominantly occurred after long-term corticosteroid use in a medium-dose regimen. These two groups were therefore separated in the analysis. The percentage of patients with adrenal insufficiency at the retest was calculated as the number of patients with adrenal insufficiency at the retest divided by the total number of patients that were measured at time of the first test.

Sensitivity analyses were performed for studies using the ACTH 250-μg test only to exclude test heterogeneity and for studies using the RIA only because this is the preferred assay to detect cortisol. All sensitivity analyses were performed in asthma patients only, to minimize patient heterogeneity. No sensitivity analysis for insulin tolerance test use only was performed because there were only three studies using this test, and none of them included asthma patients.

Results

Study selection (Supplemental Figure 1)

The initial search provided 3600 unique articles. By assessment of references of key articles, another 16 articles were found, yielding a total of 3616 articles. After screening titles and abstracts, 365 articles remained for detailed review. Reasons for exclusion are shown in Supplemental Figure 1. Finally, 74 articles were included in this meta-analysis, containing a total of 136 study groups. Although in principle articles containing patients below the age of 12 years were excluded, two articles including patients from 9 to 11 years old were included because most the patients in these articles were above the age of 12. One article could not be retrieved even after contacting the first author (18).

Study characteristics

Study characteristics are shown in Supplemental Table 2. Included studies were published from 1975 to 2014. Of the 74 articles, 36 were clinical trials (19–54), 23 were cohort studies (1, 2, 8, 11, 55–73), and 15 were cross-sectional studies (10, 74–87). The 136 study groups contained a total of 3753 participants, of which 124 were healthy volunteers. There were 68 studies on asthma patients, eight studies on rhinitis or rhinosinusitis patients, 12 studies on patients with dermatological conditions (psoriasis, atopic dermatitis, and lichen planus), eight

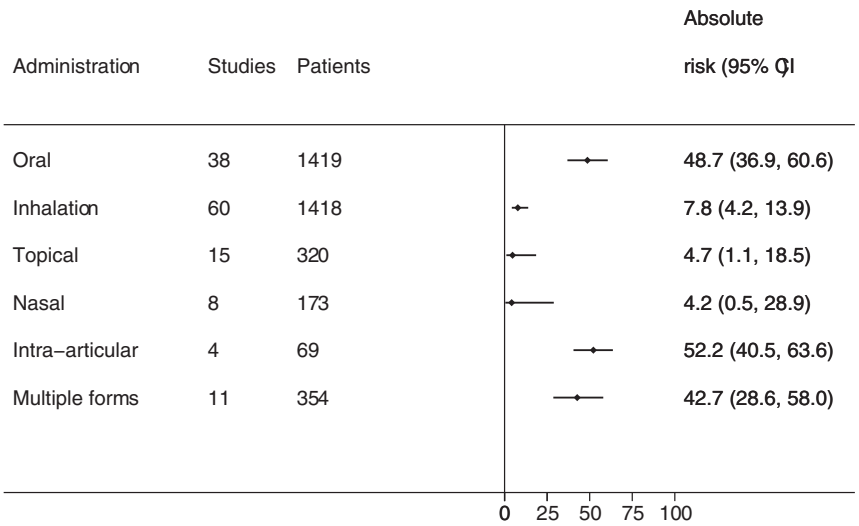

Figure 1. Meta-analysis, adrenal insufficiency after corticosteroids use by administration form.

studies on patients with rheumatological disorders (including rheumatoid arthritis and osteoarthritis), eight studies on renal transplant patients, four studies on patients with hematological malignancies, two studies on patients with nasal polyposis, three studies on patients with cystic fibrosis, two studies on patients with Crohn's disease, and one study each on patients with glaucoma, kidney and pancreas transplantation, bronchiectasis, various carcinomas, and giant cell arteritis, respectively. There were eight studies on patients with various conditions.

Risk of bias assessment

Inclusion of consecutive exposed patients or use of a random sample of exposed patients was explicitly stated in 17 articles (23%). Eligibility criteria were reported in 48 articles (65%). In 38 articles (51%), it was unclear how exposure to corticosteroids was ascertained. The remaining 36 articles did this by the use of a protocol or by retrieving data from medical records. In 14 articles (24%), loss to follow-up was reported. Reported loss to follow-up in these articles was 0 to 12.7%. Loss to follow-up exceeded 5% in one cohort study and two clinical trials. Details of risk of bias analysis at the level of individual studies are shown in Supplemental Table 3.

Study outcomes

Of the 3753 participants, 1190 were diagnosed with adrenal insufficiency. The ACTH 250-μg test was used by 103 study groups, and the time between the last dose of corticosteroids and the test for adrenal insufficiency was reported to be 24 hours or longer in 79 study groups. In seven study groups including 199 patients, use of other corticosteroids was allowed as co-medication. Details of study outcomes and tests used at the level of individual studies are shown in Supplemental Table 4.

Adrenal insufficiency and symptoms of adrenal insufficiency

In only 10 study groups, symptoms of adrenal insufficiency were reported. In total, 10 of 521 patients reported symptoms of adrenal insufficiency. Symptoms were not scored systematically in either of the articles. After testing, 98 patients appeared to have adrenal insufficiency within these study groups. Consequently, 88 patients would have been missed when only patients with symptoms of adrenal insufficiency had been tested.

Pooled analysis: adrenal insufficiency by administration form (Figure 1)

The percentage of adrenal insufficiency was 48.7% (95% confidence interval [CI], 36.9–60.6) after oral administration of corticosteroids. The results for other administration forms were: 7.8% (95% CI, 4.2–13.9) for inhalation, 4.7% (95% CI, 1.1–18.5) for topical administration, 4.2% (95% CI, 0.5–28.9) when administered intranasally, and 52.2% (95% CI, 40.5–63.6) in patients that used intra-articular corticosteroids. The use of multiple administration forms of corticosteroids resulted in a pooled percentage of adrenal insufficiency of 42.7% (95% CI, 28.6–58.0).

Pooled analysis: adrenal insufficiency per condition (Figure 2)

Pooled percentages of adrenal insufficiency per condition are presented in Figure 2 for conditions with at least two studies. Pooled percentages ranged from 6.8 to 60.0%. Asthma patients had an overall percentage adrenal insufficiency of 11.1% (95% CI, 6.8–17.7). This was lower for patients with asthma using inhaled corticosteroids (6.8%; 95% CI, 3.8–12.0), than for asthma patients using other administration forms including oral (43.7%; 95% CI, 27.3–61.6).

Adrenal insufficiency by treatment dose and treatment duration (Figure 3)

Analysis per treatment dose and treatment duration was performed in asthmatic patients only for reasons of population homogeneity. Use of corticosteroids in low, medium, or high doses resulted in a percentage of adrenal

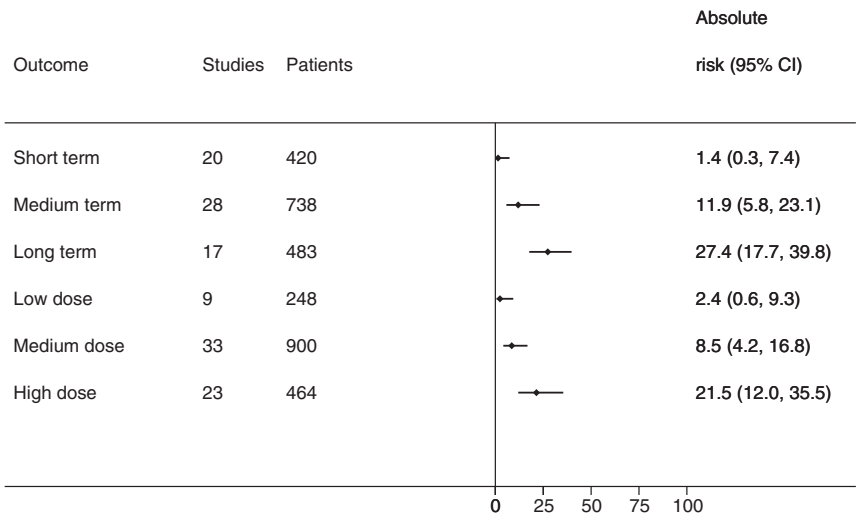

Figure 2. Meta-analysis, adrenal insufficiency after corticosteroids use per condition.

insufficiency of 2.4% (95% CI, 0.6–9.3), 8.5% (95% CI, 4.2–16.8), and 21.5% (95% CI, 12.0–35.5), respectively. Use of corticosteroids for a short, medium, or long term resulted in a percentage of adrenal insufficiency of 1.4% (95% CI, 0.3–7.4), 11.9% (95% CI, 5.8–23.1), and 27.4% (95% CI, 17.7–39.8), respectively.

If performed in asthma patients using inhaled corticosteroids only, the percentages of adrenal insufficiency in low, medium, and high doses were 1.5% (95% CI, 0.2–9.4), 5.4% (95% CI, 2.7–10.4), and 18.5% (95% CI, 8.7–35.2), respectively. In short-, medium-, and long-term treatment duration groups, percentages of adrenal insufficiency were 1.3% (95% CI, 0.2–7.2), 9.0% (95% CI, 4.3–17.9), and 20.3% (95% CI, 12.4–31.6), respectively (data not presented in figure).

Adrenal insufficiency after retesting (Figure 4)

Analysis of retests was split into studies that retested after 4 weeks, using mainly short-term, high-dose corticosteroids, and studies that retested after 6 months, using mainly long-term, medium-dose corticosteroids. Studies retesting after 4 weeks had a percentage of adrenal insufficiency after their first test of 38.7% (95% CI, 21.7–58.8). After 4 weeks, retesting showed a percentage of adrenal insufficiency of 14.9% (95% CI, 6.8–29.5). Studies retesting after 6 months had a percentage of adrenal insufficiency after their first test of 56.4% (95% CI, 38.2–72.9). After 6 months, the percentage of patients with adrenal insufficiency was still 25.3% (95% CI, 19.4–32.3).

Sensitivity analysis

For the sensitivity analysis, we combined all studies with asthma patients, which resulted in a percentage of adrenal insufficiency of 11.1% (95% CI, 6.8–17.7) as a reference group. When only studies were included that explicitly tested for adrenal insufficiency at least 24 hours after the last corticosteroid dose, the percentage of adrenal insufficiency was slightly lower (6.6%; 95% CI, 2.2–18.3). When performed on studies using the ACTH 250-μg test only, a percentage of 8.5% (95% CI, 4.7–14.8) was found. When performed on studies using RIA

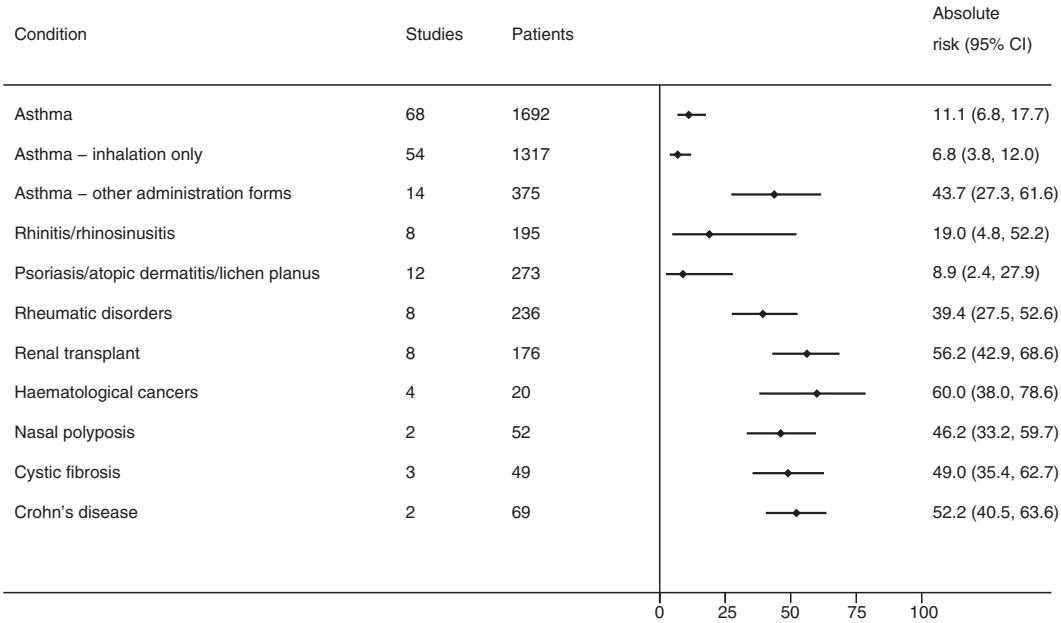

Figure 3. Meta-analysis, adrenal insufficiency per dose and duration in asthma patients.

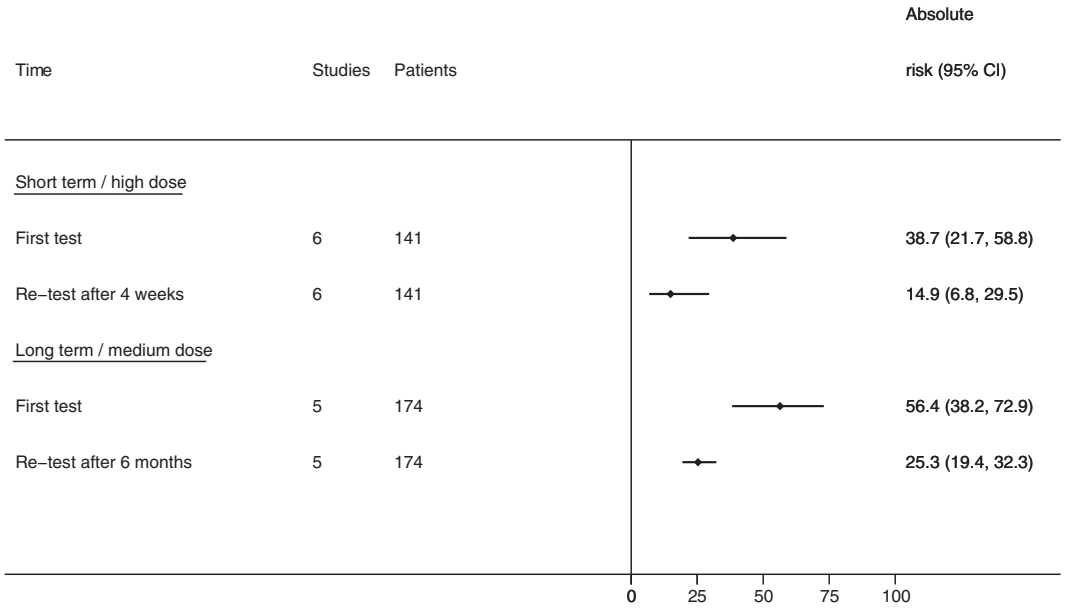

Figure 4. Meta-analysis, adrenal insufficiency after corticosteroids use by time of test.

only, a percentage of 14.7% (95% CI, 7.1–27.9) was found.

Discussion

We performed a systematic review and meta-analysis to estimate the percentage of patients that develop adrenal insufficiency after the use of corticosteroids. Depending on administration form, the percentage of patients with adrenal insufficiency varied from 4.2% for nasal corticosteroids to 52.2% for intra-articular corticosteroids. Stratified by disease, percentages ranged from 6.8% for asthma patients with inhalation corticosteroids only to 60.0% for patients with hematological malignancies. According to dose, the percentage of adrenal insufficiency varied from 2.4% (low dose) to 21.5% (high dose), and according to treatment duration from 1.4% (<28 d) to 27.4% (>1 y) in asthma patients. This means that there is no administration form, disease, dose group, or treatment duration for which the risk of adrenal insufficiency can be safely excluded. Although the percentage of patients with adrenal insufficiency after corticosteroids use declines over time, a substantial number of patients remained adrenal insufficient after 6 months.

This is the first meta-analysis providing a broad view on the risk of adrenal insufficiency after use of various types of corticosteroids for several diseases. To the best of our knowledge, only one meta-analysis (88) has been published on appropriately tested adrenal insufficiency in asthma, reporting percentages of adrenal insufficiency ranging from 5.5 to 13.3%. In the current meta-analysis, we found a percentage of 6.8% of adrenal insufficiency in asthmatic patients using inhaled corticosteroids, which is in line with results from the meta-analysis mentioned.

Included studies displayed heterogeneity in the type of corticosteroid used, underlying condition, treatment dose, treatment duration, and route of administration. It is important to consider that this heterogeneity reflects clinical practice. It should also be kept in mind that condition, treatment dose, treatment duration, and route of administration are clearly related. In our stratified analysis, we did not adjust for all mutually dependent factors, mainly because these factors are related in clinical practice as well, but also because meta-regression techniques would fall short in the absence of individual patient level data to disentangle these clearly related factors. Differences in the percentage of patients with adrenal insufficiency per condition may partly be explained by treatment dose and duration, partly by administration form, and partly by the nature of the disease. Higher treatment dose and longer treatment duration give higher systemic levels of corticosteroids, and therefore higher percentages of adrenal insufficiency (89). This might explain the low risk of adrenal insufficiency in nasal corticosteroids use and the high risk of adrenal insufficiency in rheumatic diseases, after renal transplant, in hematological malignancies, and when multiple administration forms are used. The use of oral corticosteroids results in higher systemic levels of corticosteroids than in cases of inhalation, topical, and nasal corticosteroids use, and consequently leads to higher percentages of adrenal insufficiency (32). The use of nasal as well as oral and inhalation corticosteroids in rhinitis and rhinosinusitis patients might have contributed to the higher percentage of adrenal insufficiency than in patients

using nasal corticosteroids only. The use of only topical corticosteroids in patients with psoriasis, atopic dermatitis, or lichen planus may explain the low percentage of patients with adrenal insufficiency. The different administration forms in asthma patients may largely explain the low percentage of adrenal insufficiency in patients with asthma using only inhalation corticosteroids and the high percentage of adrenal insufficiency in asthma patients using other administration forms of corticosteroids. Intra-articular corticosteroids are administered at high doses and are known to suppress serum cortisol levels within 24–48 hours, recovering only after 1–4 weeks (90). This might explain the high percentage of adrenal insufficiency after the use of intra-articular corticosteroids. The high rate of adrenal insufficiency is probably also a reflection of the fact that these injections are depot formulations. The presence of adrenal insufficiency in such situations may in part be due to the continued presence of corticosteroids in the body, whereas reduction of steroid levels will be gradual rather than abrupt. Most studies did not provide data on treatment adherence, and assessing the impact of (non-)adherence on risk of adrenal insufficiency was therefore not possible. Because all included studies were observational, the results of our meta-analyses are likely to reflect clinical practice.

Included studies also showed heterogeneity in cortisol assay and in the type of cortisol tests performed. The sensitivity analysis did not reveal any material difference in overall percentage of adrenal insufficiency if only articles using a RIA were included, or if only articles using the ACTH 250-μg test were included. Although the diagnostic performance of RIA in the routine evaluation of adrenocortical function is considered superior to other competitive protein-binding analytical methods, like fluorimetry (91, 92), the chemiluminescence immunoassay seems to have comparable diagnostic performance and accuracy to RIA (93). It should be kept in mind that test criteria for adrenal insufficiency available in clinical practice have a high sensitivity rather than a high specificity, and therefore the number of false-positive test results is not negligible. None of the studies retrieved by our literature search used the more modern tandem mass spectrometry (94).

Several pathophysiological pathways may be involved in the development of adrenal insufficiency after the use of corticosteroids. It is certainly relevant to disentangle these different pathways and address the question of whether differences in dosage, treatment duration, and type of corticosteroid differentially affect the activity of the hypothalamic-pituitary-adrenal axis. However, in our review we aimed to evaluate the effect of corticosteroids on adrenal function in clinical practice instead of disentangling the exact mechanisms of adrenal insufficiency.

There was no sensitivity analysis performed for low risk of bias articles only, because there was only one article with low risk of bias (based on the inclusion of patients and loss to follow-up) within the group of studies with asthma patients only. If only studies with a time gap of at least 24 hours between the last dose of corticosteroids and the test for adrenal insufficiency were included, the percentage of adrenal insufficiency decreased only slightly. In our main analyses, we included articles irrespective of the time between last corticosteroid use and time of test. It is important to keep in mind that the percentage of patients with adrenal insufficiency would have been slightly higher than estimated in this meta-analysis had all articles used a time gap of at least 24 hours between the last dose of corticosteroids and the time of the test.

Corticosteroids are used by at least 1% of the population (3). The risk of developing adrenal insufficiency in these patients is 1.4 to 60.0%, and symptoms of mild to moderate adrenal insufficiency, like fatigue and abdominal discomfort, are nonspecific and therefore difficult to ascribe to adrenal insufficiency. In addition, accurate predictors are not available to distinguish between the patients that will become adrenal insufficient and those that will not. Also there is insufficient evidence to prove any withdrawal scheme after steroid use to be efficient or safe (95). Therefore, we recommend that all patients with unexplained symptoms after steroid withdrawal be tested for possible adrenal insufficiency. In case of insufficient response, treatment should be initiated with physiological doses of hydrocortisone.

In conclusion, this study demonstrates that all patients using corticosteroid therapy are at risk for adrenal insufficiency. This implies that clinicians should: 1) inform patients about the risk and symptoms of adrenal insufficiency; 2) consider testing patients after cessation of high-dose or long-term treatment with corticosteroids; and 3) display a low threshold for testing, especially in those patients with nonspecific symptoms after cessation.

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Transparency Declaration: L.H.A.B. is guarantor.

The manuscript is an honest, accurate, and transparent account of the study being reported; no important aspects of the study have been omitted; any discrepancies from the study as planned have been explained.

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