Use of Glucocorticoids and Risk of Venous Thromboembolism

A Nationwide Population-Based Case-Control Study

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Importance: Excess endogenous cortisol has been linked to venous thromboembolism (VTE) risk, but whether this relationship applies to exogenous glucocorticoids remains uncertain. Because the prevalence of glucocorticoid use and the incidence of VTE are high, an increased risk of VTE associated with glucocorticoid use would have important implications.

Background: To examine the association between glucocorticoid use and VTE.

Design: Population-based case-control study using nationwide databases.

Setting: Denmark (population 5.6 million).

Participants: We identified 38 765 VTE cases diagnosed from January 1, 2005, through December 31, 2011, and 387 650 population controls included through risk-set sampling and matched by birth year and sex. The VTE diagnosis date for the case was the index date for cases and matched controls.

Exposure: We classified individuals who filled their most recent glucocorticoid prescription 90 days or less, 91 to 365 days, and more than 365 days before the index date as present, recent, and former users, respectively. Present users were subdivided into new (first-ever prescription 90 days or less before the index date) and continuing users (others).

Main Outcomes and Measures: We used conditional logistic regression adjusted for VTE risk factors to estimate incidence rate ratios (IRRs) and 95% CIs for glucocorticoid users vs nonusers.

Results: Systemic glucocorticoids increased VTE risk among present (adjusted IRR, 2.31; 95% CI, 2.18-2.45), new (3.06; 2.77-3.38), continuing (2.02; 1.88-2.17), and recent (1.18; 1.10-1.26) users but not among former users (0.94; 0.90-0.99). The adjusted IRR increased from 1.00 (95% CI, 0.93-1.07) for a prednisolone-equivalent cumulative dose of 10 mg or less to 1.98 (1.78-2.20) for more than 1000 to 2000 mg, and to 1.60 (1.49-1.71) for doses higher than 2000 mg. New use of inhaled (adjusted IRR, 2.21; 95% CI, 1.72-2.86) and intestinal-acting (2.17; 1.27-3.71) glucocorticoids also increased VTE risk.

Conclusions and Relevance: The risk of VTE is increased among glucocorticoid users. Although residual confounding may partly explain this finding, we consider a biological mechanism likely because the association followed a clear temporal gradient, persisted after adjustment for indicators of severity of underlying disease, and existed also for noninflammatory conditions. Hence, our observations merit clinical attention.


Venous thromboembolism (VTE) is a common disease affecting more than 1 per 1000 persons each year in Western populations. Typically, it presents as deep venous thrombosis (DVT) of the legs and can result in pulmonary embolism (PE), a potentially fatal complication. Glucocorticoids are potent anti-inflammatory drugs widely used for various conditions, including chronic obstructive pulmonary disease as well as autoimmune and neoplastic disorders. In Denmark, 3.5% of the population redeemed a prescription for systemic glucocorticoids in 2010. Experimental studies show that glucocorticoids increase levels of clotting factors and fibrinogen. Also, Cushing syndrome has been linked to an increased VTE risk, possibly resulting from high endogenous glucocorticoid levels in these patients. Nevertheless, clinical data on the

See Editor’s Note at end of article

association between exogenous glucocorticoids and VTE are sparse, and comparison of available studies is hampered by their focus on specific patient populations.10-17 The only epidemiologic study18 conducted in the general population showed a 3-fold increased risk of VTE in current users of oral glucocorticoids compared with nonusers, decreasing with increasing duration of use. Because glucocorticoid use was not the primary exposure of interest, the study did not consider different routes of administration or equivalence dosages of glucocorticoid preparations. We examined the association between glucocorticoids and VTE in a nationwide population-based case-control study with prospectively collected data.

METHODS

SETTING

Denmark provides its entire population (5.6 million) with tax-supported health care and partial reimbursement for prescribed medications.19,20 A unique central personal registration number, assigned to all Danish residents, is used to record health services in various nationwide registries, allowing continuous population surveillance.19 The current study is based on information from such registries. The selection period for study participants, January 1, 2005, through December 31, 2011, was chosen based on the availability of prescription data.20

VENOUS THROMBOEMBOLISM

We used the Danish National Registry of Patients (DNRP)21 to identify all first-time primary and secondary inpatient and outpatient diagnoses of DVT or PE (International Classification of Diseases codes are reported in eTable 1; http://www.jamainternalmed.com). Patients with diagnoses of both PE and DVT were included only in the PE group. To reduce potential coding errors, we excluded patients who had an outpatient PE diagnosis without a subsequent inpatient VTE diagnosis within the following month. Emergency department diagnoses were excluded because of their low positive predictive value (31.3%).21 However, because patients referred to specialized wards after admission to an emergency department were coded as inpatient admissions, only approximately 6% of patients were recorded as emergency admissions.23

To further characterize the patients, we distinguished between (1) provoked VTE (patients with the following classic risk factors: surgery, major trauma or fracture, or pregnancy within 3 months preceding VTE and previous cancer or cancer within 3 months after VTE) and (2) unprovoked VTE (remaining cases). The date of VTE diagnosis was considered the index date for cases.

POPULATION CONTROLS

From the Danish Civil Registration System, which records daily changes in vital status for all Danish residents,22 we identified 10 population controls matched to each case by birth year and sex, using risk-set sampling without replacement. Persons eligible to be selected as controls had to be alive and at risk for a first VTE on the index date of the case with whom they were matched.24 Controls were assigned an index date identical to that of corresponding cases.

GLUCOCORTICOID USE

The Danish National Database of Reimbursed Prescriptions includes information on reimbursed medications redeemed at Danish community and outpatient pharmacies since January 1, 2004.20 Using the database, we identified all prescriptions of (1) systemic glucocorticoids, (2) inhaled glucocorticoids, and (3) glucocorticoids acting on the intestines redeemed by the cases and controls before their index date. Anatomical Therapeutic Chemical Classification System codes are provided in eTable 1. For each of the 3 types of glucocorticoids, we considered exclusive use of the relevant type. For example, for systemic glucocorticoids, we considered only individuals with no concomitant use of inhaled glucocorticoids or glucocorticoids acting on the intestines. We also differentiated between systemic glucocorticoid agents (betamethasone, methylprednisolone, prednisolone, prednisone, triamcinolone, and hydrocortisone). There were no dexamethasone prescriptions. Based on the prescription information, we then defined various exposure categories, as presented in Table 1. Nonusers (ie, individuals who filled no prescriptions for any glucocorticoids before the index date) constituted the reference group in all comparisons. Calculations of prednisolone-equivalent cumulative doses were based on methods used by Strensen et al.23

VTE RISK FACTORS

From the DNRP and prescription database, we identified the following comorbidities on the basis of the participants’ medical history before the index date: cardiovascular disease or treatment with cardiovascular drugs (angiotensin-converting enzyme inhibitors, angiotensin II receptor inhibitors, aspirin, β-blockers, calcium channel blockers, clopidogrel, diuretics, nitrates, and other antihypertensive drugs), chronic obstructive pulmonary disease or asthma, diabetes mellitus or antidiabetic treatment, liver disease, obesity, osteoporosis, renal failure, and any autoimmune disease.1,3,14,21,22-25 We also identified any infection or antibiotic treatment within 3 months before the index date and previous cancer or cancer diagnosed within 3 months after the index date.1,3,10,20,28

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To further account for potential unmeasured confounding from frailty and immobility, we included a variable for any inpatient admission (excluding the diseases listed in the previous sentences) within 3 months before the index date. Finally, we identified treatment with nonaspirin nonsteroidal anti-inflammatory drugs, hormone therapy, antipsychotics, statins, and vitamin K antagonists.\(^1,3,18,20\)

Glucocorticoids are used to treat various inflammatory conditions that by themselves may predispose to VTE, especially during flare-ups.\(^1,3,18,23,27,28\) To adjust for severity of the underlying disease, we accounted for treatment with immunomodulating agents (antitumor necrosis factor agents, methotrexate, cyclosporine, or azathioprine) within 90 days before the index date. All codes and exposure windows for comediations were provided in eTable 1.

### Table 2. Characteristics of Patients With Any VTE or Unprovoked VTE and Population Controls in Denmark

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Any Cases (n = 38 765)</th>
<th>Any Controls (n = 38 7650)</th>
<th>Unprovoked Cases (n = 22 368)</th>
<th>Unprovoked Controls (n = 188 162)</th>
</tr>
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<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;55</td>
<td>10 220 (26.4)</td>
<td>102 200 (26.4)</td>
<td>6924 (31.0)</td>
<td>64 050 (34.0)</td>
</tr>
<tr>
<td>55-70</td>
<td>12 081 (31.2)</td>
<td>120 810 (31.2)</td>
<td>6684 (29.9)</td>
<td>57 688 (30.7)</td>
</tr>
<tr>
<td>&gt;70</td>
<td>16 464 (42.5)</td>
<td>164 640 (42.5)</td>
<td>8760 (39.2)</td>
<td>66 424 (35.3)</td>
</tr>
<tr>
<td>Age, median (IQR), y</td>
<td>67 (53-78)</td>
<td>67 (53-78)</td>
<td>65 (50-78)</td>
<td>63 (48-76)</td>
</tr>
<tr>
<td>Female sex</td>
<td>20 822 (53.7)</td>
<td>208 220 (53.7)</td>
<td>11 836 (52.9)</td>
<td>98 010 (52.1)</td>
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<tr>
<td>Classic risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cancer</td>
<td>9354 (24.1)</td>
<td>41 787 (10.8)</td>
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<td>.</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>249 (0.6)</td>
<td>972 (0.3)</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>Surgery</td>
<td>9165 (23.6)</td>
<td>23 029 (5.9)</td>
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<td>Trauma or fracture</td>
<td>3289 (8.5)</td>
<td>8635 (2.2)</td>
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<td>.</td>
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<td>Recent inpatient admission</td>
<td>11 445 (29.5)</td>
<td>17 646 (4.6)</td>
<td>3442 (15.4)</td>
<td>3600 (1.9)</td>
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<tr>
<td>Other comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Recent infection</td>
<td>12 960 (33.4)</td>
<td>47 600 (12.3)</td>
<td>6524 (29.2)</td>
<td>19 945 (10.6)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>23 944 (61.8)</td>
<td>198 679 (51.3)</td>
<td>12 803 (57.2)</td>
<td>85 124 (45.2)</td>
</tr>
<tr>
<td>COPD or asthma</td>
<td>4951 (12.8)</td>
<td>25 328 (6.5)</td>
<td>2646 (11.8)</td>
<td>10 547 (5.6)</td>
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<tr>
<td>Diabetes mellitus</td>
<td>3651 (9.4)</td>
<td>29 207 (7.5)</td>
<td>1914 (8.6)</td>
<td>12 335 (6.6)</td>
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<tr>
<td>Liver disease</td>
<td>673 (1.7)</td>
<td>2700 (0.7)</td>
<td>382 (1.7)</td>
<td>1117 (0.6)</td>
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<tr>
<td>Obesity</td>
<td>2415 (6.2)</td>
<td>10 919 (2.8)</td>
<td>1330 (5.9)</td>
<td>4877 (2.6)</td>
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<td>Osteoporosis</td>
<td>1834 (4.7)</td>
<td>13 247 (3.4)</td>
<td>885 (4.0)</td>
<td>5118 (2.7)</td>
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<td>Renal failure</td>
<td>1502 (2.7)</td>
<td>3911 (1.0)</td>
<td>462 (2.1)</td>
<td>1382 (0.7)</td>
</tr>
<tr>
<td>Any autoimmune disease</td>
<td>4119 (10.6)</td>
<td>26 306 (6.8)</td>
<td>2211 (9.9)</td>
<td>11 292 (6.0)</td>
</tr>
<tr>
<td>Comedicationse</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Statins</td>
<td>4779 (12.3)</td>
<td>52 212 (13.5)</td>
<td>2513 (11.2)</td>
<td>22 396 (11.9)</td>
</tr>
<tr>
<td>Hormone therapy</td>
<td>1747 (4.5)</td>
<td>17 772 (4.6)</td>
<td>1007 (4.5)</td>
<td>7412 (3.9)</td>
</tr>
<tr>
<td>Nonaspirin NSAIDs</td>
<td>5319 (13.7)</td>
<td>23 668 (6.1)</td>
<td>2837 (12.7)</td>
<td>10 565 (5.8)</td>
</tr>
<tr>
<td>Vitamin K antagonists</td>
<td>1516 (3.9)</td>
<td>11 133 (2.9)</td>
<td>751 (3.4)</td>
<td>4471 (2.4)</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>1539 (4.0)</td>
<td>7562 (2.0)</td>
<td>908 (4.1)</td>
<td>3423 (1.8)</td>
</tr>
<tr>
<td>Immunomodulating agents</td>
<td>203 (0.5)</td>
<td>728 (0.2)</td>
<td>110 (0.5)</td>
<td>310 (0.2)</td>
</tr>
</tbody>
</table>

### STATISTICAL ANALYSIS

First, we characterized the study population using descriptive statistics. Next, we used conditional logistic regression to estimate unadjusted odds ratios (ORs) and 95% CIs for the association between glucocorticoid use and VTE. Given risk-set sampling used for sampling of controls, the ORs are unbiased estimates of the underlying incidence rate ratios (IRRs).\(^24\) We then fitted a multiple logistic regression model with adjustment for all risk factors listed in Table 2. We examined systemic glucocorticoids, inhaled glucocorticoids, glucocorticoids acting on the intestine, and individual systemic glucocorticoids. In the analysis using prednisolone-equivalent cumulative doses, we assessed systemic glucocorticoids according to 7 categories (\( \leq 10 \), >10-50, >50-100, >100-500, >500-1000, >1000-2000, and >2000 mg), on the basis of dose distribution in the study population. To examine whether the association depended on VTE subtype, we repeated all analyses for unprovoked VTE, DVT, and PE. We also stratified the overall results for systemic glucocorticoids by route of administration (injection or oral) after excluding patients with connective tissue diseases, as these patients most likely received their prescriptions for intra-articular treatment.

Using conventional logistic regression, while adjusting for the matching factors, we performed subgroup analyses according to age (<55, 55-70, and >70 years); sex; presence or absence of cancer, trauma or fracture, diabetes mellitus, cardiovascular disease, chronic obstructive pulmonary disease, asthma, obesity, recent inpatient admission, recent infection, and any autoimmune disease; and recent treatment with immunomodulating agents.

Abbreviations: COPD, chronic obstructive pulmonary disease; ellipsis, not applicable; IQR, interquartile range; NSAIDs, nonsteroidal anti-inflammatory drugs; VTE, venous thromboembolism.

\(^a\) Prescribing cancer or a cancer diagnosis within 3 months after the index date.

\(^b\) Any hospital admission within 3 months before the index date.

\(^c\) Any inpatient or outpatient admission for infection or redemption of a prescription for antibiotics within 3 months before the index date.

\(^d\) Any hospital admission since 1977 or any redeemed prescription since 2004.

\(^e\) Prescription redemption within 60 days (antipsychotics and NSAIDs) or 90 days (hormone therapy, vitamin K antagonists, and immunomodulating agents) before the index date.
This analysis was performed for present use of systemic glucocorticoids and the outcomes of overall VTE, DVT, and PE.

We performed several secondary analyses. First, to reduce potential misclassification by left censoring, we repeated the dose analysis among patients with at least 3 years of prescription history. Second, we used a rule-out approach to illustrate how strongly a single unmeasured binary confounder would have to be associated with glucocorticoids and VTE to fully explain our findings, assuming a confounder prevalence of 30% and glucocorticoid prevalence of 10%. Third, to assess confounding by indication, we performed a before-and-after analysis comparing the VTE rate within 90 days after vs before a first-time prescription for injectable glucocorticoids. We assumed the remaining potential confounders to remain constant during these time periods. Outside the hospital, injectable glucocorticoids are prescribed primarily for treatment of allergy (which is not a known VTE risk factor) and for intra-articular treatment of inflammatory connective tissue diseases. To limit the analysis to patients with allergy or connective tissue disease and glucocorticoid injection treatment only, we excluded patients with connective tissue disease and previous or concomitant use of the other glucocorticoid administration forms. We also repeated the analysis after excluding individuals with any inpatient admission (except VTE) within the year before prescription, since treatment might have been initiated during that earlier admission. Last, we estimated the absolute incidence rate differences using a back-calculation method described previously. Briefly, we extrapolated the exposure distribution among the controls to the person-years of the general population (obtained from the Danish Civil Registration System for 2003-2011 and stratified by age, sex, and calendar year) to calculate the VTE incidence among users and nonusers and standardized the difference to the age and sex distribution among the whole population. We then compared this mean excess incidence rate to the mean incidence rate in the exposed group and determined the population attributable risk fraction (PARF). The PARF was calculated as the proportion of the difference in incidence rates attributable to the exposure. This analysis was performed for present use of systemic glucocorticoids and the outcomes of overall VTE, DVT, and PE.

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VTE cases. We performed all analyses using commercial software (SAS, version 9.2; SAS Institute, Inc).

RESULTS

DESCRIPTIVE DATA

Table 2 presents the characteristics of 38,765 VTE cases and 387,650 population controls included in the study. Among the VTE cases, 57.7% had unprovoked VTE, 61.2% had DVT, and 38.8% had PE. The median age was 67 years (interquartile range, 53-78 years) and 53.7% were women. All other covariates, except for the use of statins and hormone therapy, were more prevalent among cases than among controls.

VENOUS THROMBOEMBOLISM

The magnitude of the association between glucocorticoid use and VTE depended on the administration form (Table 3). For systemic glucocorticoids, present use was associated with the greatest risk increase (adjusted IRR, 2.31; 95% CI, 2.18-2.45). New use was associated with a higher VTE risk (3.06; 2.77-3.38) than continuing use (2.02; 1.88-2.17). The adjusted IRR was 1.18 (95% CI, 1.10-1.26) and 0.94 (0.90-0.99) for recent and former use, respectively. Oral glucocorticoids were associated with higher risks compared with the injectable forms (eTable 3). The adjusted IRR was 1.00 (95% CI, 0.93-1.07) for a cumulative dose of 10 mg or less, 1.98 (1.78-2.20) for a cumulative dose greater than 1000 to 2000 mg, and 2.90 (2.77-3.03) for a cumulative dose greater than 5000 mg.
mg, and 1.60 (1.49-1.71) for doses higher than 2000 mg (Table 3 and Figure). All systemic glucocorticoids, including hydrocortisone, were associated with increased VTE risk, with particularly high estimates for prednisolone use and new use of prednisone (Table 4). For inhaled glucocorticoids, only new use was associated with an increased VTE risk (adjusted IRR, 2.21; 95% CI, 1.72-2.86). Present use of glucocorticoids acting on the intestines increased the risk both among new users (adjusted IRR, 2.17; 95% CI, 1.27-3.71) and continuing users (1.76; 1.22-2.56).

In general, the results for unprovoked VTEs were similar to the overall results (Tables 3 and 4). However, we detected a tendency toward higher estimates for PE than for DVT, which was evident for systemic glucocorticoids (Table 5).

The subgroup analysis revealed an increased risk across all subgroups examined (Table 6). There was no substantial difference by sex or age group. However, all comorbidities, except asthma (with regard to PE) and cancer, demonstrated a consistent pattern, with higher estimates among individuals in whom the disease was absent. The overall adjusted IRR for VTE was 3.37 (95% CI, 1.92-5.93) among recent users of immunomodulating agents and 2.30 (2.17-2.42) among those without recent use of these agents.

**SECONDARY ANALYSES**

Restricting the dose analysis to patients with at least 5 years of prescription history did not affect the results substantially (eTables 4 and 5). Using the rule-out approach, we estimated that, for an unmeasured confounder to fully explain our estimates, this confounder would have to be 5 times more prevalent among present users of systemic glucocorticoids than among nonusers and would itself have to increase the VTE risk by 18 times; only under such extreme conditions could the results be explained (eFigure). Supporting the overall results, the before-and-after analysis showed an IRR of 2.15 (95% CI, 1.55-2.98) and 3.69 (2.46-6.39) after also excluding patients with recent hospital admission. Rate differences, obtained from back-calculations, are presented in Table 7.

**COMMENT**

We found that glucocorticoid users had an increased risk of VTE, particularly PE. Systemic glucocorticoids were associated with the greatest risk. Patients initiating treatment with systemic glucocorticoids within 90 days before the index date had a 3-fold increased risk, corroborated by the back-calculations. However, the results were sensitive to the inclusion of immunosuppressants as comorbidities, and the estimates were substantially higher among patients with recent immunosuppressant use (eTable 6). The findings were consistent across different subgroups, and the results were robust to adjustment for other risk factors, comorbidities, and comedications.
sponding to 11 extra VTE cases per 1000 new users of systemic glucocorticoids annually. The risk increased with increasing cumulative dose. New use of inhaled glucocorticoids and present use of glucocorticoids acting on the intestines also increased VTE risk.

Previous epidemiologic studies reported an association between glucocorticoids and VTE among surgical patients and patients with specific diseases, for example, multiple myeloma, multiple sclerosis, inflammatory bowel disease, systemic lupus erythematosus, or nephrotic syndrome.6,10-13,17 Furthermore, glucocorticoids have been shown to predict VTE in the outpatient setting (OR, 2.2 for women and 2.1 for men)14 and admission for DVT within 60 days after hospital discharge (OR, 4.1).16

To our knowledge, there has been only one previous study on glucocorticoid use and VTE risk in the general population.18 Using the British General Practice Research Database to identify 6550 VTE cases, the investigators showed that, compared with nonusers, current users of oral glucocorticoids had an OR of 3.1; the OR was 4.7 for 0 to 30 days’ duration of use, decreasing to 2.0 for more than 1 year of use. Past use (termed former use in our study) was associated with an OR of 1.2. Thus, although not substantially different, their point estimates were higher than ours. However, our study has several advantages: we included 6 times as many cases, adjusted for more VTE risk factors, and relied on filled prescriptions rather than written prescriptions.33 Furthermore, we investigated the association according to different administration routes, types of agents, and cumulative doses.

The temporality of the association (ie, the strongest effect at initiation of therapy and the absence of an effect after discontinuation) is in line with an effect on coagula-

Table 6. Any VTE, Deep Venous Thrombosis, and Pulmonary Embolism Associated With Present Use of Systemic Glucocorticoids

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Any VTE Adjusted Incidence Rate Ratio (95% CI)</th>
<th>Deep Venous Thrombosis</th>
<th>Pulmonary Embolism</th>
</tr>
</thead>
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<tr>
<td>Sex</td>
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</tr>
<tr>
<td>Male</td>
<td>2.32 (2.13-2.52)</td>
<td>1.94 (1.73-2.18)</td>
<td>2.82 (2.49-3.19)</td>
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<td>Female</td>
<td>2.28 (2.13-2.45)</td>
<td>2.01 (1.82-2.22)</td>
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<td>Age, y</td>
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<td>&lt;55</td>
<td>2.36 (2.01-2.78)</td>
<td>2.03 (1.66-2.48)</td>
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<td>55-70</td>
<td>2.62 (2.36-2.90)</td>
<td>2.07 (1.80-2.38)</td>
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<td>&gt;70</td>
<td>2.19 (2.05-2.35)</td>
<td>1.98 (1.79-2.18)</td>
<td>2.44 (2.21-2.69)</td>
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<td>Cancer</td>
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</tr>
<tr>
<td>Yes</td>
<td>2.90 (2.64-3.19)</td>
<td>2.56 (2.24-2.93)</td>
<td>3.23 (2.81-3.70)</td>
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<td>No</td>
<td>2.05 (1.92-2.19)</td>
<td>1.78 (1.63-1.95)</td>
<td>2.44 (2.20-2.69)</td>
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Abbreviations: COPD, chronic obstructive pulmonary disease; VTE, venous thromboembolism.

*Incidence rate ratios computed with conventional logistic regression adjusted for age, sex, classic risk factors, other comorbidities, and use of comediations, as listed in Table 2. Present users were individuals who filled their most recent prescription for glucocorticoids within 90 days before the index date.

Within the 90 days before the index date.

search Database to identify 6550 VTE cases, the investigators showed that, compared with nonusers, current users of oral glucocorticoids had an OR of 3.1; the OR was 4.7 for 0 to 30 days’ duration of use, decreasing to 2.0 for more than 1 year of use. Past use (termed former use in our study) was associated with an OR of 1.2. Thus, although not substantially different, their point estimates were higher than ours. However, our study has several advantages: we included 6 times as many cases, adjusted for more VTE risk factors, and relied on filled prescriptions rather than written prescriptions.33 Furthermore, we investigated the association according to different administration routes, types of agents, and cumulative doses.

The temporality of the association (ie, the strongest effect at initiation of therapy and the absence of an effect after discontinuation) is in line with an effect on coagula-
tion. Also, it is parallel to the epidemiologic effects of oral contraceptives on VTE risk, which are also coagulation-mediated.33 In fact, experimental studies show a rapid effect of glucocorticoids on clotting factor levels.6,8 In a study of 24 healthy men randomized to receive either dexamethasone 3 mg twice daily or placebo for 5 days, Brotman et al29 found an increase in clotting factor and fibrinogen levels in the treatment arm. However, glucocorticoids may also inhibit platelet aggregation and tissue factor–mediated leukocyte procoagulant activity,6 which over time could overshadow the initial procoagulant effects.

We found an effect of inhaled glucocorticoids and glucocorticoids acting on the intestines. Despite their limited bioavailability, they are associated with clinically significant systemic absorption36,37 as supported by our results. Oral glucocorticoids were associated with a higher risk than the injectable form. A possible explanation is that some injections were used for intra-articular treatment, which has lower bioavailability,28 although we tried to reduce this proportion by excluding patients with connective tissue diseases. The increased VTE risk among hydrocortisone users was rather unexpected, since hydrocortisone is used for replacement therapy in pituitary or adrenal insufficiency with the aim of mimicking physiologic glucocorticoid levels.39 Our observation may be interpreted with caution, since the hydrocortisone estimates were imprecise.

We found a greater risk of PE than of DVT. This paradox has previously been observed for pulmonary conditions such as chronic obstructive pulmonary disease and may result from local phenomena in the lungs rather than represent a complication of DVT.43 However, whether a similar explanation exists for glucocorticoids is unclear.

Several issues should be considered when interpreting our study. There are some limitations of the Danish National Database of Reimbursed Prescriptions.20 First, the database includes no information on adherence.20 Second, use of glucocorticoids during hospitalization and outpatient clinic visits (eg, intra-articular treatment) is not recorded.20 However, copayment requirements increase our confidence that filled prescriptions reflect use. Second, the database is relatively new, possibly introducing left censoring of our exposure information.20 Nevertheless, our sensitivity analysis among individuals with at least 5 years of prescription history showed no evidence of substantial left censoring. Third, use of glucocorticoids during hospitalization and outpatient clinic visits (eg, intra-articular treatment) is not recorded.20

The discharge data we used to identify cases and comorbidities have high validity.44,45 Nevertheless, a validation study of VTE diagnoses registered in the DNRP found that approximately 20% of patients with an inpatient VTE diagnosis did not fulfill the researchers’ strict clinical criteria.22 Emergency department diagnoses had particularly low validity. Our study excluded these diagnoses, which somewhat limits misclassification. Finally, surveillance bias by increased diagnostic suspicion is unlikely because of unawareness of the association between systemic glucocorticoids and VTE. Nevertheless, patients with respiratory diseases may have less respiratory capacity to compensate for a PE, potentially resulting in a falsely increased PE risk among users of inhaled glucocorticoids.

We had no explicit information on lifestyle factors but included various underlying diseases as proxies for lifestyle. It is possible that our results present some overestimation of inflammatory conditions that might lead to
VTE because of confounding by disease severity. We tried to mitigate this effect by multivariable analyses, including recent treatment with immunomodulating agents as a proxy for disease severity. In addition, we presented a separate analysis for systemic hydrocortisone use in which the underlying condition, pituitary or adrenal insufficiency, is not by itself associated with VTE. Similarly, the before-and-after analysis, which excluded patients with connective tissue disease, supported our overall results. Last, on the basis of our rule-out sensitivity analysis, we can reasonably conclude that there was no confounder capable of explaining away the findings, because disease severity or chronic severe inflammation would not have such strong independent effects on VTE. These results and the consistency across VTE subtypes and individual glucocorticoids, as well as the temporality of the effect, increase our confidence that the results reflect a true biological effect.

In conclusion, glucocorticoid users had an increased risk of VTE, especially PE. The effect was strongest for new users of systemic glucocorticoids but persisted (albeit less prominently) among users of inhaled glucocorticoids and glucocorticoids acting on the intestines. Although residual confounding might partially explain the results, clinicians should be aware of this association.

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Author Contributions: Ms Johannesdottir had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Johannesdottir, Horváth-Puhó, Dekkers, Jørgensen, and Sørensen. Acquisition of data: Pedersen and Sørensen. Analysis and interpretation of data: Johannesdottir, Horváth-Puhó, Dekkers, Cannegieter, Ehrenstein, Vandenbroucke, Pedersen, and Sørensen. Drafting of the manuscript: Johannesdottir, Jørgensen. Critical revision of the manuscript for important intellectual content: Johannesdottir, Horváth-Puhó, Dekkers, Cannegieter, Ehrenstein, Vandenbroucke, Pedersen, and Sørensen. Administrative, technical, and material support: Sørensen. Study supervision: Jørgensen, Vandenbroucke, and Sørensen.

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REFERENCES

Weighing Benefits and Risks

Glucocorticoids and Thromboembolism

Glucocorticoids are one of the most widely prescribed medications. They are effective for a large and diverse set of illnesses ranging from asthma to systemic lupus erythematosus. Unfortunately, their efficacy is accompanied by many adverse effects, including increased infection risk, hyperglycemia, hypertension, and mania.

But does glucocorticoid use also cause venous thromboembolism? This is not a simple question to answer because some of the illnesses that are treated with glucocorticoids may themselves cause venous thromboembolism (eg, autoimmune diseases) or may result in immobility that predisposes to venous thromboembolism.

This population-based case-control study provides strong evidence that glucocorticoids are associated with an increased risk of venous thromboembolism. The increased risk was found not only for systemic glucocorticoids but also for inhaled glucocorticoids and glucocorticoids acting on the intestines. Since this is an observational study, residual confounding cannot be eliminated as a possible explanation for the association between glucocorticoids and venous thromboembolism. However, a causal link is strengthened by the risk being stronger with new users and with higher doses in an analysis that adjusts for a number of potential confounders.

Given the already known serious adverse effects of glucocorticoids, establishing an elevated risk for venous thromboembolism with this study does not change the indications for glucocorticoids, but it should remind us to always make sure that the potential benefits of treatment outweigh the risks (eg, does this patient’s asthma require an inhaled corticosteroid?) and to be prepared to diagnose and treat thromboembolism.

Mitchell H. Katz, MD