Glucocorticoid Use and Risk of Atrial Fibrillation or Flutter

A Population-Based, Case-Control Study

Christian Fynbo Christiansen, MD; Steffen Christensen, MD; Frank Mehnert, MSc; Steven R. Cummings, MD; Roland D. Chapurlat, MD, PhD; Henrik Toft Sørensen, MD, PhD, DMSc

Background: Glucocorticoid use is associated with increased risk of myocardial infarction, stroke, and heart failure, but data are limited on the risk of atrial fibrillation or flutter. We examined whether glucocorticoid use is associated with the risk of atrial fibrillation or flutter.

Methods: For this population-based, case-control study, we identified all patients with a first hospital diagnosis of atrial fibrillation or flutter from January 1, 1999, through December 31, 2005, in Northern Denmark (population, 1.7 million). For each case we selected 10 population controls matched by age and sex. We obtained data on glucocorticoid prescriptions within 60 days (current users) or longer before the index date (former users), comorbidity, and medications from medical databases. We used conditional logistic regression to compute odds ratios (ORs), controlling for potential confounders.

Results: Among 20,221 patients with atrial fibrillation or flutter, 1288 (6.4%) were current glucocorticoid users and 2375 (11.7%) were former users. Among 202,130 population controls, 5245 (2.6%) were current glucocorticoid users and 19,940 (9.9%) were former users. Current glucocorticoid use was associated with an increased risk of atrial fibrillation or flutter compared with never use (adjusted OR, 1.92; 95% CI, 1.79-2.06). Among new glucocorticoid users, the adjusted OR was 3.62 (95% CI, 3.11-4.22) and among long-term users it was 1.66 (95% CI, 1.53-1.80). The increased risk remained robust in patients with and without pulmonary and cardiovascular diseases. Former glucocorticoid use was not associated with increased risk (adjusted OR, 1.00; 95% CI, 0.96-1.06).

Conclusion: Current glucocorticoid use was associated with an almost 2-fold increased risk of atrial fibrillation or flutter.

Arch Intern Med. 2009;169(18):1677-1683
We conducted this population-based, case-control study in Northern Denmark, within a population of 1.7 million (approximately 30% of the Danish population). The Danish National Health Service provides free tax-funded medical care for all Danish residents and partially reimburses costs of most physician-prescribed drugs. Only a few cardiologists work outside public hospitals in Denmark, and most patients with atrial fibrillation or flutter have their conditions diagnosed during hospital admission or at hospital outpatient clinics. The unique civil registration number assigned to every Danish citizen and included in all Danish medical databases allowed us to electronically link several medical databases. For this study we used data from 3 different databases (the Danish National Registry of Patients [NRP], the prescription database of the region, and the Danish Civil Registration System [CRS]), merged into a research database at Aarhus University Hospital.

CASES OF ATRIAL FIBRILLATION OR FLUTTER

We used the NRP to identify all patients with an incident hospital diagnosis of atrial fibrillation or flutter from January 1, 1999, through December 31, 2005. We did not include patients with any earlier diagnosis of atrial fibrillation or flutter registered in the NRP. The NRP contains data with regard to all discharges from all nonpsychiatric hospitals since 1977 and with regard to emergency department and outpatient clinic visits since 1995. It includes information with regard to civil registration numbers of patients, dates of admission and discharge, and up to 20 discharge diagnoses, coded by physicians in accordance with the International Classification of Diseases, Eighth Revision (ICD-8),14 until the end of 1993 and the International Statistical Classification of Diseases, 10th Revision (ICD-10), thereafter.15

The ICD-8 codes used to identify patients with atrial fibrillation or flutter were 427.93 and 427.94, and the ICD-10 code was I48.9. The single ICD-10 code includes both atrial fibrillation and flutter; however, it has been reported that more than 90% of patients registered with atrial fibrillation and flutter have atrial fibrillation and 5% had atrial flutter only.16 We considered it appropriate to include both atrial fibrillation and flutter because they are often seen in the same patients and share risk factors and, to some extent, pathophysiologic factors.17,18 The positive predictive value of atrial fibrillation or flutter has been reported to be as high as 97% in the NRP.19 We also obtained data from the NRP with regard to hospital procedure codes of cardioversions (treatment code BEFA0 in the Danish treatment classification) within the year after diagnosis of atrial fibrillation or flutter.

POPULATION CONTROLS

For each atrial fibrillation or flutter case, we used the CRS to select 10 population controls matched on age and sex. The CRS is updated daily and contains data on civil registration number, residence, migration, vital status (dead or alive), and exact date of death for all Danish residents since 1968.11 The controls were selected by means of risk set sampling and assigned an index date identical to the hospital admission date for atrial fibrillation or flutter of the matched case.

GLUCOCORTICOID USE

All pharmacies in the region are equipped with electronic accounting systems, established to secure partial reimbursement of prescription expenses from the National Health Service.15 The prescription database contains information with regard to the civil registration numbers of customers, the type and amount of drugs prescribed (according to the Anatomic Therapeutic Chemical [ATC] classification system), and the prescription fill dates. We used the prescription database to identify any prescription for systemic glucocorticoids reimbursed before the date of admission for atrial fibrillation or flutter or index date. We included prednisolone, prednisone, methylprednisolone, dexamethasone, and hydrocortisone (the ATC codes are provided in the eAppendix, http://www.archinternmed.com), which are usually prescribed for oral administration for outpatient use. We did not include triamcinolone acetonide, triamcinolone hexacetonide, or betamethasone, which in Denmark are used only for local injections (eg, in the treatment of abscesses and pseudotumors).

We defined current users of glucocorticoids as patients who filled their most recent prescription for glucocorticoids within 60 days before the index date.20 Because some adverse effects may arise shortly after initiation of therapy, and because inclusion of prevalent users may underestimate these complications,21 we further categorized current users of glucocorticoids into 2 groups: new users, defined as having filled their first-ever prescription for glucocorticoids within 60 days before the index date, and long-term users, defined as current users who filled their first prescription more than 60 days before the index date. Patients who had filled their most recent prescription more than 60 days before the index date were defined as former users. Never users were defined as patients with no filled prescriptions for glucocorticoids registered in the prescription database.

Among users of prednisolone and prednisone, we examined a dose-response relation with the risk of atrial fibrillation or flutter. These drugs have clear indications and account for 80% of prescribed systemic glucocorticoids. We obtained data with regard to doses of tablets of prednisolone and prednisone prescribed most recently relative to the admission or index date and used these to compute odds ratios (ORs) for current low-dose use (2.5-mg or 5-mg tablets) and for current high-dose use (25-mg tablets).

COMORBIDITY

A number of risk factors for atrial fibrillation or flutter also may be associated with use of glucocorticoids. We therefore obtained data from the NRP on any previous hospital diagnosis since 1977 of cardiovascular diseases, COPD and asthma, diabetes, renal failure, inflammatory bowel disease, connective tissue disease and RA, liver disease and chronic pancreatitis, acute alcohol intoxication, alcoholism-related diseases, hyperthyroidism, and cancer. Associated ICD codes are provided in the eAppendix.

We used the prescription database to obtain data on ever use of antithyroid drugs, thyroid hormones, respiratory drugs, and cardiovascular drugs (with the inclusion of angiotensin-converting enzyme inhibitors, β-blocking agents, low-dose aspirin, statins, calcium antagonists, and other antihypertensives, diuretics, and nitrates) as markers of thyroid, pulmonary, or cardiovascular diseases. Any use of nonsteroidal anti-inflammatory drugs or selective cyclooxygenase 2 inhibitors was also included as a potential confounder. Their ATC codes are provided in the eAppendix. To identify patients with atrial fibrillation or flutter treated only by their general physician (and therefore not registered in the NRP), we obtained data with regard to previous use of digoxin and vitamin K antagonists by all study participants before their index dates.
STATISTICAL ANALYSIS

We used conditional logistic regression to estimate ORs for atrial fibrillation or flutter among current and former users of glucocorticoids compared with never users, controlling for sex, age group, comorbidity, and drug use. Because we used risk set sampling of controls, the ORs are unbiased estimates of the incidence rate ratio. To not include patients with atrial fibrillation or flutter treated by their general physician without being previously hospitalized, we restricted the primary analyses to those cases and controls who had never before the index date filled a prescription for digoxin or a vitamin K antagonist. In a secondary analysis we included previous users of these agents. Another secondary analysis was limited to cases with atrial fibrillation or flutter recorded as the first listed diagnosis in the discharge summary and their controls. (The first listed diagnosis is the main reason for hospital admission or outpatient or emergency department visit.)

We repeated the analysis with the inclusion of only cases treated with cardioversion within 1 year after the index date and their controls, as a measure of severity of atrial fibrillation or flutter. To reduce potential confounding by indication, we also performed the analysis in prespecified subgroups of patients with and without cardiovascular diseases or cardiovascular drug use, COPD and asthma or respiratory drug use, and connective tissue disease and RA. We kept the matching in these subgroups and performed conditional logistic regression by means of only cases and controls with the subgroup disease.

To assess the impact of surveillance bias that stemmed from an increased number of hospitalizations among users of glucocorticoids, we repeated the analysis in subgroups defined by the number of hospital admissions in the year preceding the index date (0, 1, or ≥2 admissions). We also performed stratified analysis in age groups.

Statistical analyses were performed with SAS statistical software (version 9.1, SAS Institute Inc, Cary, North Carolina). The study was approved by the Danish Data Protection Agency (record 2004-41-4603) and the Aarhus University Registry Board.

SENSITIVITY ANALYSIS

We performed a sensitivity analysis to quantify the influence of potential unmeasured confounding on the observed association by means of a rule-out approach. We estimated how strongly a single unmeasured binary confounder would need to be associated with glucocorticoid use and atrial fibrillation or flutter to fully explain our findings and illustrated this association graphically. We assumed that the prevalence of such a confounder was as common as smoking (30.0% of the population) and that 2.5% of the population used glucocorticoids.

If atrial fibrillation or flutter began before the date of the first diagnosis, we would also expect an increased risk in patients who filled prescriptions of glucocorticoids more than 60 days before the index date compared with never users. To examine the sensitivity of the estimates to differences in exposure definition, we therefore repeated the analysis for exposure (filled glucocorticoid prescription) within 30, 60, 90, 120, and 180 days.

RESULTS

DESCRIPTIVE DATA

We identified 20 221 patients with an incident hospital diagnosis of atrial fibrillation or flutter and 202 130 population controls, with the exclusion from both groups of persons with previous prescriptions for digoxin or vitamin K antagonists (Table 1). Among the cases, 17 701 (8.76%) had atrial fibrillation or flutter diagnosed during hospital admission and 2520 (1.25%) at an outpatient clinic or emergency department.

Among the 20 221 cases, 1288 (6.4%) were current users of glucocorticoids (0 used dexamethasone, 41 [0.2%] used methylprednisolone, 845 [4.2%] used prednisolone, 397 [2.0%] used prednisone, and 5 [0.02%] used hydrocortisone). A total of 2375 cases (11.7%) were former glucocorticoid users. Among the 202 130 controls, 5245 (2.6%) were current glucocorticoid users, 19 940 (9.9%) were former users, and 176 945 (87.5%) were never users (Table 1).

Among the cases, 35.1% had been previously diagnosed as having cardiovascular diseases other than atrial fibrillation or flutter, compared with 18.5% of the controls. Use of cardiovascular drugs was, as expected, more frequent among the cases than among the controls (69.6% vs 49.9%). In addition, COPD and asthma, diabetes, hyperthyroidism, and connective tissue disease and RA were more common among the cases than among the population controls (Table 1).

OVERALL RISK OF ATRIAL FIBRILLATION OR FLUTTER

Current use of glucocorticoids was associated with an increased risk of hospitalization for atrial fibrillation or flutter, with an adjusted OR of 1.92 (95% CI, 1.79-2.06) (Table 2). Former glucocorticoid use was not associated with the risk of atrial fibrillation or flutter (adjusted OR, 1.00; 95% CI, 0.96-1.06). The approximately 2-fold risk increase was seen in all age groups except for the patients younger than 50 years, for whom the estimate was somewhat lower but imprecise (0-49 years: OR, 1.23; 95% CI, 0.63-2.43; 50-59 years: OR, 1.77; 95% CI, 1.24-2.50; 60-69 years: OR, 2.17; 95% CI, 1.82-2.60; 70-79 years: OR, 1.95; 95% CI, 1.74-2.19; ≥80 years: OR, 1.82; 95% CI, 1.63-2.04).

Inclusion of the 8100 cases with a history of digoxin or vitamin K antagonist use and their controls in the analysis had no major impact on the risk estimate for atrial fibrillation or flutter among current glucocorticoid users (OR, 1.74; 95% CI, 1.64-1.85). The adjusted OR for atrial fibrillation or flutter among the 9901 cases with atrial fibrillation or flutter listed as the first diagnosis in the discharge record was 1.60 (95% CI, 1.43-1.78).

FURTHER ANALYSIS

Among the new users of glucocorticoids, the adjusted OR was 3.62 (95% CI, 3.11-4.22), and among long-term users, the adjusted OR was 1.66 (95% CI, 1.53-1.80). Among current users of high-dose prednisolone or prednisone tablets, the adjusted OR was 4.03 (95% CI, 3.44-4.72), and the adjusted OR in current users of low-dose tablets was 1.78 (95% CI, 1.65-1.92), compared with never users of these drugs.

In the 1793 cases (8.9%) treated with cardioversion within the year after their first atrial fibrillation or flutter diagnosis, the adjusted OR for current glucocorticoid use was 1.86 (95% CI, 1.41-2.45). The risk of atrial
fibrillation or flutter among current users of glucocorticoids remained elevated in analyses restricted to cases and controls with and without COPD and asthma and cardiovascular diseases (Table 3). The risk was also increased among patients with connective tissue disease and RA, although the associated estimates were statistically imprecise. Stratification by the number of hospital admissions in the year before the index date had only a minor impact on the adjusted relative risk estimates (no admissions: OR, 1.81; 95% CI, 1.65-2.00; 1 admission: OR, 1.33; 95% CI, 0.93-1.89; and ≥2 admissions: OR, 1.71; 95% CI, 1.29-2.27).

Table 1. Characteristics of Cases With Atrial Fibrillation or Flutter and Controls From Northern Denmark, 1999-2005

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cases, No. (%) (n=20 221)</th>
<th>Population Controls, No. (%) (n=202 130)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
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<tr>
<td>Male</td>
<td>10 948 (54.1)</td>
<td>109 450 (54.1)</td>
</tr>
<tr>
<td>Female</td>
<td>9273 (45.9)</td>
<td>92 680 (45.9)</td>
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<tr>
<td>Age group, y</td>
<td></td>
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<tr>
<td>0-49</td>
<td>1157 (5.7)</td>
<td>11 618 (5.7)</td>
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<tr>
<td>50-59</td>
<td>2338 (11.6)</td>
<td>23 291 (11.5)</td>
</tr>
<tr>
<td>60-69</td>
<td>3969 (19.6)</td>
<td>39 894 (19.7)</td>
</tr>
<tr>
<td>70-79</td>
<td>6230 (30.8)</td>
<td>61 927 (30.6)</td>
</tr>
<tr>
<td>&gt;80</td>
<td>6527 (32.3)</td>
<td>65 400 (32.4)</td>
</tr>
<tr>
<td>Use of systemic glucocorticoids</td>
<td></td>
<td></td>
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<tr>
<td>Current use</td>
<td></td>
<td></td>
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<tr>
<td>Former use</td>
<td></td>
<td></td>
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<tr>
<td>Never use</td>
<td></td>
<td></td>
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<tr>
<td>Cardiovascular diseases</td>
<td></td>
<td></td>
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<tr>
<td>Previous hospital diagnosis, with the inclusion of hypertension</td>
<td>7100 (35.1)</td>
<td>37 314 (18.5)</td>
</tr>
<tr>
<td>Any use of cardiovascular drugs</td>
<td>14 072 (69.6)</td>
<td>100 915 (49.9)</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors</td>
<td></td>
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<td>β-Blockers</td>
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<tr>
<td>Low-dose aspirin</td>
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<td>Statins</td>
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<td>Calcium antagonants</td>
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<td>Diuretics</td>
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<td>Nitrates</td>
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<tr>
<td>Other antihypertensials</td>
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<tr>
<td>Renal failure</td>
<td></td>
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<tr>
<td>Diabetes mellitus, previous hospital diagnosis</td>
<td></td>
<td></td>
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<tr>
<td>COPD and asthma</td>
<td></td>
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<tr>
<td>Previous hospital diagnosis</td>
<td></td>
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<tr>
<td>Connective tissue disease and RA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any use of nonsteroidal anti-inflammatory drugs or cyclooxygenase 2 inhibitors</td>
<td>9954 (49.2)</td>
<td>89 125 (44.1)</td>
</tr>
<tr>
<td>Any use of nonsteroidal anti-inflammatory drugs or cyclooxygenase 2 inhibitors</td>
<td>179 (0.9)</td>
<td>1344 (0.7)</td>
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<tr>
<td>Cancer</td>
<td></td>
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<tr>
<td>Liver disease and chronic pancreatitis</td>
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<tr>
<td>Concurrent acute alcohol intoxication</td>
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<tr>
<td>Alcohol-related diseases</td>
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<tr>
<td>Hyperthyroidism</td>
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<tr>
<td>Any use of antithyroid drugs</td>
<td></td>
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<tr>
<td>Any use of thyroid hormones</td>
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</tbody>
</table>
| Abbreviations: COPD, chronic obstructive pulmonary disease; RA, rheumatoid arthritis.

Table 2. Association Between Glucocorticoid Use and Atrial Fibrillation or Flutter

<table>
<thead>
<tr>
<th>Glucocorticoid Use</th>
<th>No. of Cases/Controls</th>
<th>Odds Ratio (95% Confidence Interval)</th>
<th>Unadjusted</th>
<th>Adjusted a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never use</td>
<td>16 558/176 945</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Current use</td>
<td>1288/5245</td>
<td>2.66 (2.49-2.83)</td>
<td>1.92 (1.79-2.06)</td>
<td></td>
</tr>
<tr>
<td>New users</td>
<td>280/628</td>
<td>4.72 (4.09-5.46)</td>
<td>3.62 (3.11-4.22)</td>
<td></td>
</tr>
<tr>
<td>Long-term users</td>
<td>1008/4617</td>
<td>2.37 (2.21-2.55)</td>
<td>1.66 (1.53-1.80)</td>
<td></td>
</tr>
<tr>
<td>Former use</td>
<td>2375/19 940</td>
<td>1.28 (1.23-1.34)</td>
<td>1.00 (0.96-1.06)</td>
<td></td>
</tr>
</tbody>
</table>

a Adjusted for a previous diagnosis of cardiovascular diseases, chronic obstructive pulmonary disease and asthma, diabetes mellitus, renal failure, inflammatory bowel disease, connective tissue disease and rheumatoid arthritis, cancer, liver disease and chronic pancreatitis, acute alcohol intoxication, alcoholism-related diseases, hyperthyroidism, and use of nonsteroidal anti-inflammatory drugs or cyclooxygenase 2 inhibitors and cardiovascular, respiratory, and thyroid drugs.
SENSITIVITY ANALYSIS

The sensitivity analysis revealed that an unmeasured confounder that is 4 times more frequent among users than nonusers of glucocorticoids would need to increase the risk of atrial fibrillation or flutter by a factor of 9 or more to explain fully our finding of an adjusted OR of 1.92 (95% CI, 1.79-2.06), if no increased risk actually existed (Figure). The risk estimates decreased only slightly as a result of increasing the exposure time window (30 days: adjusted OR, 2.01; 95% CI, 1.85-2.19; 60 days: adjusted OR, 1.92; 95% CI, 1.79-2.06; 90 days: adjusted OR, 1.76; 95% CI, 1.65-1.88; 120 days: adjusted OR, 1.69; 95% CI, 1.58-1.80; 120 days, adjusted OR, 1.59; 95% CI, 1.50-1.69).

In this large, population-based, case-control study, we found that use of systemic glucocorticoids was associated with an almost doubled risk of atrial fibrillation or flutter. The risk was 4 times higher among new users of glucocorticoids compared with never users, and the finding was robust in patients with and without COPD or asthma and cardiovascular diseases.

Our findings extend the data from the 2 previous case-control studies with regard to glucocorticoid use and risk of atrial fibrillation. Van der Hooft et al\(^9\) analyzed 385 new cases of atrial fibrillation and 6364 controls in a case-control study nested within The Rotterdam Study, a prospective cohort study of persons 55 years and older. Beforehand, 50 patients (11%) were excluded because of a missing index date or because atrial fibrillation was discovered coincidently. Current glucocorticoid use was as-
associated with a markedly increased risk of atrial fibrillation (adjusted OR, 3.75; 95% CI, 2.38-5.87). The association was stronger among new users and users of high-dose glucocorticoids, especially among those with indications other than COPD and asthma. The associations were not studied among former users, for whom the indication for glucocorticoid treatment may be the same.

By means of the UK General Practice Research Database, Huerta et al included 468 cases with atrial fibrillation. Use of oral glucocorticoids was associated with an increased risk of atrial fibrillation even after adjustment for comorbidity, with the inclusion of COPD and asthma exacerbation during the previous year (adjusted OR, 1.9; 95% CI, 1.4-2.6). However, the study included only COPD patients, and the results may not hold for other patient categories.

The main strengths of our study include its population-based design within the setting of a free tax-supported universal health care system, which largely removes referral and selection biases. The study population was large and yielded robust and consistent estimates in subanalyses. The positive predictive value of the atrial fibrillation or flutter diagnosis in the NRP has been reported to be as high as 97%, which implies that coding errors should have had only a minor influence on our results. We were unable to separate atrial fibrillation and flutter. Because only 5% of cases are expected to have atrial flutter, our results are driven by atrial fibrillation, but the association is not necessarily the same for flutter.

Glucocorticoid users may have higher hospitalization rates than nonusers and thus an increased likelihood of being diagnosed as having asymptomatic atrial fibrillation; however, we found virtually the same risk estimates regardless of the number of hospital contacts within 1 year before the index date and in the cases with atrial fibrillation or flutter listed as the main reason for hospitalization. Thus, any surveillance bias is unlikely to fully explain our findings.

Data in the prescription databases are complete. Although we had to use redemption of a prescription as a proxy for actual glucocorticoid use, the direct beneficial effects of glucocorticoids on a wide range of symptoms, as well as copayment requirements, increased the likelihood of compliance. Any noncompliance most likely was independent of subsequent atrial fibrillation or flutter and would attenuate the relative risk estimates toward the null.

Patients with any previous prescription for digoxin or vitamin K antagonists were not included in the primary analysis, and we may thus have missed patients with severe heart failure, deep venous thrombosis, pulmonary embolism, and artificial cardiac valves. However, this factor is unlikely to bias our results because inclusion of these patients in a secondary analysis left the overall risk estimates virtually unchanged.

Our nonrandomized study may be vulnerable to unmeasured and uncontrolled confounding, in particular, by the underlying diseases that lead to glucocorticoid use. Former glucocorticoid use was not associated with an increased risk of atrial fibrillation or flutter, whereas the highest risk occurred among new users and users of high-dose tablets. Despite this evidence of a dose-response relationship, we cannot rule out at least some influence of disease severity because new users and high-dose users may have more severe underlying disease. However, we found a consistently elevated risk of atrial fibrillation or flutter among glucocorticoid users in analyses stratified by indications for glucocorticoid use.

We had incomplete data on lifestyle factors, with the inclusion of smoking and obesity; however, adjustment for COPD and asthma and ischemic heart disease accounted for at least some of the effects of these factors. The sensitivity analysis showed that the increased risk of atrial fibrillation or flutter associated with glucocorticoid use could not be explained by even a strong single unmeasured confounder. Furthermore, risk of atrial fibrillation or flutter was not elevated in former users of glucocorticoids expected to have lifestyles similar to the current users.

We do not have data with regard to the mechanism that underlies our finding. Long-term glucocorticoid use is associated with increased risk of atherosclerosis, diabetes mellitus, hypertension, heart failure, and ischemic heart disease, which are well-known risk factors for atrial fibrillation. However, our finding of the highest risk among new users of glucocorticoids indicates either a short-term adverse effect (eg, development of hypertension within a few days after commencement of glucocorticoid treatment) or an effect associated with the severity of the underlying disease (eg, inflammation). Glucocorticoids may also increase plasma volume and induce hypokalemia by mineralocorticoid-like action, and it has been suggested that even a subclinical fluctuation of serum potassium level from a local cellular potassium efflux owing to a direct effect on the cell membrane may induce arrhythmias. In conclusion, this large, population-based, case-control study showed that current use of systemic glucocorticoids is associated with increased risk of atrial fibrillation or flutter.

Accepted for Publication: June 19, 2009.

Correspondence: Christian Fynbo Christiansen, MD, Department of Clinical Epidemiology, Aarhus University Hospital, Olof Palmes Alle 43-45, DK-8200 Aarhus N, Denmark (cc@dce.au.dk).

Author Contributions: Study concept and design: Christiansen, Christensen, Mehnert, and Sørensen. Analysis and interpretation of data: Christiansen, Christensen, Mehnert, Cummings, Chapurlat, and Sørensen. Drafting of the manuscript: Christiansen, Christensen, and Chapurlat. Critical revision of the manuscript for important intellectual content: Mehnert, Cummings, Chapurlat, and Sørensen. Statistical analysis: Mehnert. Study supervision: Christiansen and Sørensen.

Financial Disclosure: Dr Cummings is a consultant to Merck and Novartis. Drs Christiansen, Christensen, Chapurlat, and Sørensen and Mr Mehnert did not report receiving any fees, honoraria, grants, or consultancies that would constitute a conflict of interest with the current study. The Department of Clinical Epidemiology, Aarhus University Hospital, receives funding for other
studies from companies in the form of research grants to (and administered by) Aarhus University. None of these studies have any relation to the present study.

**Funding/Support:** The Danish Medical Research Council grant 271-05-0511 and the Clinical Epidemiological Research Foundation, Denmark, funded this study.

**Role of the Sponsor:** Neither sponsor had a role in the design, conduct, analysis, or reporting of this study.

**Previous Presentation:** This study was presented at the 24th International Conference on Pharmacoepidemiology and Therapeutic Risk Management; August 18, 2008; Copenhagen, Denmark.

**Additional Information:** The eAppendix is available at http://www.archinternmed.com.

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**REFERENCES**


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(Reprinted) Arch Intern Med/Vol. 169 (No. 18), Oct. 12, 2009

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