Corticosteroids and the Risk of Atrial Fibrillation

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Background: High-dose (pulse) corticosteroid therapy has been associated with the development of atrial fibrillation. This association, however, is mainly based on case reports.

Methods: To test the hypothesis that high-dose corticosteroid exposure increases the risk of new-onset atrial fibrillation, we performed a nested case-control study within the Rotterdam Study, a population-based cohort study among 7983 older adults. Cases were defined as persons with incident atrial fibrillation between July 1, 1991, and January 1, 2000. Their date of diagnosis was defined as the index date. All noncases within the Rotterdam Study who were alive and eligible on this index date were used as controls. Subsequently, we compared the proportion of cases and controls that received a corticosteroid prescription within 1 month preceding the index date. Corticosteroid exposure was categorized into high-dose exposure (oral or parenteral steroid at a daily dose ≥7.5 mg of prednisone equivalents) and low-intermediate–dose exposure (<7.5 mg of prednisone equivalents or inhaled corticosteroids).

Results: There were 385 eligible cases of new-onset atrial fibrillation during the study period. The risk of new-onset atrial fibrillation was significantly higher for persons who received a corticosteroid prescription within 1 month before the index date than for those without (odds ratio [OR], 3.75; 95% confidence interval [CI], 2.38-5.87). However, only high-dose corticosteroid use was associated with an increased risk (OR, 6.07; 95% CI, 3.90-9.42), whereas low-intermediate–dose use was not (OR, 1.42; 95% CI, 0.72-2.82). The association of atrial fibrillation with high-dose corticosteroid use was largely independent of the indication for corticosteroid therapy, since the risk of new-onset atrial fibrillation was not only increased in patients with asthma or chronic obstructive pulmonary disease (OR, 4.02; 95% CI, 2.07-7.81) but also in patients with rheumatic, allergic, or malignant hematologic diseases (OR, 7.90; 95% CI, 4.47-13.98).

Conclusion: Our findings strongly suggest that patients receiving high-dose corticosteroid therapy are at increased risk of developing atrial fibrillation.

Arch Intern Med. 2006;165:1016-1020

ARTIFICIAL FIBRILLATION (AF) IS the most common sustained rhythm disorder observed in clinical practice. Its clinical importance is highlighted by a high prevalence and serious clinical consequences such as hemodynamic impairment and ischemic stroke. The prevalence increases with age up to 4% in people older than 60 years and approximately 9% in people older than 80 years.1 Atrial fibrillation is associated with an increased risk (OR, 3.75; 95% CI, 2.38-5.87). However, only high-dose corticosteroid use was associated with an increased risk (OR, 6.07; 95% CI, 3.90-9.42), whereas low-intermediate–dose use was not (OR, 1.42; 95% CI, 0.72-2.82). The association of atrial fibrillation with high-dose corticosteroid use was largely independent of the indication for corticosteroid therapy, since the risk of new-onset atrial fibrillation was not only increased in patients with asthma or chronic obstructive pulmonary disease (OR, 4.02; 95% CI, 2.07-7.81) but also in patients with rheumatic, allergic, or malignant hematologic diseases (OR, 7.90; 95% CI, 4.47-13.98).

In addition, drugs have been associated with the onset of AF, but knowledge about the role of drugs in the development of AF is scarce.9 High-dose corticosteroid therapy has been associated with the development of AF, but this is mainly based on case reports.10-14 It is postulated that high doses of corticosteroids mediate potassium efflux via a direct effect on the cell membrane, which may induce arrhythmogenesis.15 To our knowledge, epidemiologic studies investigating the research hypothesis that corticosteroid therapy may induce AF have never been performed. Therefore, we performed a nested case-control study to test the hypothesis that corticosteroid use increases the risk of new-onset AF.
METHODS

SETTING

This study was conducted as part of the Rotterdam Study (RS), a prospective population-based cohort study on the occurrence and determinants of disease and disability in elderly persons. In 1990, all inhabitants of Ommoord, a suburb of Rotterdam in the Netherlands, who were 55 years or older and who had lived in the district for at least 1 year were invited to participate in the study. Of the 10,275 eligible persons, 7,983 (78%) participated. Participants gave informed consent and permission to retrieve information from medical records. At baseline, trained interviewers administered an extensive questionnaire during a home interview covering socioeconomic background and medical history, among other topics. During subsequent visits to the study center, additional interviewing, laboratory assessments, and clinical examinations were performed, including recording of electrocardiograms (ECGs). Follow-up examinations were carried out periodically (every 4 to 5 years). Data on all drug prescriptions dispensed to participants by automated pharmacies are routinely stored in a database. Information on vital status is obtained at regular time intervals from the municipal authorities in Rotterdam. The medical ethics committee of the Erasmus Medical Center, Rotterdam, the Netherlands, approved the study.

For the present study, all participants were observed from baseline until they had incident AF, died, or reached the end of the study period on January 1, 2000, whichever came first. Because we had pharmacy dispensing records as of January 1, 1991, that included a medication history of at least 6 months, all cases of incident AF before July 1, 1991, were excluded from the analyses.

CASES AND CONTROLS

Three methods were used to assess new cases of atrial fibrillation. In the first method, ECGs were recorded at baseline and during follow-up examinations at the research center with an ACTA electrocardiograph (Esaote Biomedica, Florence, Italy), stored digitally, and subsequently analyzed by the modular ECG analysis system (MEANS).11,12 The reported sensitivity and specificity of the MEANS program in coding arrhythmias is high (96.6% and 99.5%, respectively).13 To verify the diagnosis of AF, all ECGs indicating a diagnosis of AF or atrial flutter or any other rhythm disorder were recoded independently by 2 physicians who were blinded to the MEANS diagnosis. The judgment of a cardiologist was asked and taken as decisive in case of persistent disagreement.

For the second method, general practitioners participating in the RS sent computerized information on selected diseases to the researchers of the RS on a weekly basis. Specially trained interviewers administered an extensive questionnaire during a home interview covering socioeconomic background and medical history, among other topics. During subsequent visits to the study center, additional interviewing, laboratory assessments, and clinical examinations were performed, including recording of electrocardiograms (ECGs). Follow-up examinations were carried out periodically (every 4 to 5 years). Data on all drug prescriptions dispensed to participants by automated pharmacies are routinely stored in a database. Information on vital status is obtained at regular time intervals from the municipal authorities in Rotterdam. The medical ethics committee of the Erasmus Medical Center, Rotterdam, the Netherlands, approved the study.

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EXPOSURE DEFINITION

In the research area, there were 7 fully computerized pharmacies linked to 1 network. During the study, all participants filled 98% of their prescriptions in 1 of these 7 pharmacies. Data on all dispensed drugs from January 1, 1991, were available in a computerized format on a day-to-day basis. The data included the date of prescribing, the total amount of drug units per prescription, the prescribed daily number of units, and product name.

Persons who received a corticosteroid prescription for oral, rectal, parenteral, or inhaled use within 1 month before the index date were defined as exposed; all others were considered nonexposed. Corticosteroid exposure was categorized as high-dose exposure (oral, parenteral, or rectal steroids with daily dose equivalent to \( \geq 7.5 \) mg of prednisone; ie, supraphysiologic doses) and low-intermediate–dose exposure (oral, parenteral, or rectal steroids with daily doses equivalent to \(< 7.5 \) mg of prednisone or inhaled corticosteroids; ie, approximately equivalent to or less than the physiologic range of endogenous glucocorticoid secretion).14 Exposed persons were further categorized as new users (first prescription) and prior users to compare the risk for developing AF between new users and persons who had used steroids before.

To study potential confounding or effect modification by asthma and/or chronic obstructive pulmonary disease (asthma/COPD) status, stratified analyses were conducted for presence or absence of asthma/COPD as proxied by the dispensing of more than 2 bronchodilator prescriptions prior to the index date.

COFACTORS

The following patient characteristics were individually assessed as potential confounders: age (on index date), sex, hypertension, heart failure, myocardial infarction, diabetes mellitus, body mass index (calculated as weight in kilograms divided by the square of height in meters), smoking status (current, former, or never), total serum cholesterol level, hyperthyroidism, and prevalence of left ventricular hypertrophy on the ECG. Hypertension was defined as systolic blood pressure higher than 160 mm Hg and diastolic blood pressure higher than 100 mm Hg or use of any antihypertensive drug. Criteria for prevalent and incident myocardial infarction and heart failure have been described in detail elsewhere.21-23 Diabetes mellitus was defined as a random or postload glucose level of 200 mg/dL or higher (\( \geq 11.1 \) mmol/L) and/or use of blood glucose lowering medication prior to the index date.

Data on use of other medications within 1 month before the index date, such as antiplatelet drugs, diuretics, \( \beta \)-blockers, calcium antagonists, and angiotensin-converting enzyme inhibitors and antiasthmatic agents (other than inhaled corticosteroids) were obtained from pharmacy records and analyzed as potential confounders.
During the follow-up period, we identified 435 cases of new-onset AF after July 1, 1991. After exclusion of 50 cases of AF for which the date of onset was unknown or AF was discovered coincidentally, 385 cases were eligible for this study. Table 1 lists the baseline characteristics for cases and controls. Cases were on average older than controls, more often male, and had on average a higher body mass index. Also, cases were more likely to have hypertension, prior myocardial infarction, heart failure, diabetes mellitus, and left ventricular hypertrophy on ECG and were more likely to be current or former smokers at baseline, after adjustment for age and sex.

The risk of new-onset AF was significantly higher for corticosteroid users than for those who were unexposed (OR, 3.75; 95% CI, 2.38-5.87). The risk of new-onset AF was dose dependent in that exposure to low or intermediate daily doses was associated with a nonsignificant risk increase (OR, 1.42; 95% CI, 0.72-2.82), while high-dose exposure was associated with a more than 6-fold increased risk (OR, 6.07; 95% CI, 3.90-9.42) (Table 2). Newly exposed persons had a somewhat higher risk for AF than persons who had received corticosteroids before (OR, 6.0; 95% CI, 2.2-16.2 vs OR, 3.49; 95% CI, 2.17-5.62), but this difference was not statistically significant (Table 2).

The association of AF with high-dose corticosteroid use was largely independent of the indication for corticosteroid therapy, since the risk of new-onset AF was significantly higher both in patients with asthma/COPD (OR, 4.02; 95% CI, 2.07-7.81) and in patients with rheumatic, allergic, or malignant hematologic diseases (OR, 7.90; 95% CI, 4.47-13.98) (Table 3).

Since most of the high-dose corticosteroid users had other known risk factors for AF, we performed 2 extra analyses. In an age- and sex-adjusted analysis including the sum score as a continuous variable, the measures of association became stronger. For the high-dose group, the OR became 6.43 (95% CI, 4.38-9.45), while it was 6.07 (95% CI, 3.90-9.42) in the multivariate analysis. For the high-dose asthma/COPD group, the OR became 4.33 (95% CI, 2.27-8.27), while it was 4.02 (95% CI, 2.07-7.81) in the multivariate analysis. For the high dose in other diseases group, the OR became 9.88 (95% CI, 5.72-17.07), while it was 7.90 (95% CI, 4.47-13.98) in the multivariate analysis. Second, we performed an extra analysis in which we categorized the study population in 2 mutually exclusive groups: individuals with 0 to 2 risk factors for AF and individuals with 3 or more risk factors (we stratified on the median number of risk factors in the study population). In both groups, we found a similar risk for AF in high-dose corticosteroid users (adjusted for age, sex, and number of risk factors). In the stratum with 0 to 2 risk factors, the OR was 7.09 (95% CI, 3.62-13.90), while in the stratum with 3 to 8 risk factors, the OR was 6.09 (95% CI, 3.81-9.76).
This population-based study shows that current use of high-dose corticosteroids is associated with an increased risk of new-onset AF. This association was found in patients with and without asthma/COPD.

Wei et al\textsuperscript{20} recently reported an increased risk of hospitalization for cardiovascular disease (myocardial infarction, heart failure, and ischemic stroke) in high-dose corticosteroid users. The researchers explained this finding among others by the (long-term) cardiovascular adverse effects of corticosteroids, such as hypertension, diabetes mellitus, and obesity, which are independent risk factors for cardiovascular disease. In our study, the finding of an increased risk of AF, especially in new, high-dose users, suggests that there is also a potential direct arrhythmogenic effect. Arrhythmogenic effects (including life-threatening arrhythmias) following corticosteroid pulse therapy have been described before in case reports\textsuperscript{10,14,24-26} and in a recent case-control study.\textsuperscript{27} Several mechanisms are likely to be involved in the development of AF in patients treated with (high-dose) corticosteroids. First, it has been postulated that high-dose corticosteroids mediate (local) potassium efflux via a direct effect on the cell membrane, which may induce arrhythmogenesis.\textsuperscript{15} Second, high doses of glucocorticosteroids can have mineralocorticosteroid effects, such as retention of sodium and fluid, which may cause hypertension, left atrial enlargement, and congestive heart failure—all known risk factors for AF.\textsuperscript{28} Other proposed mechanisms are development of late potentials, profound peripheral vasodilatation, and anaphylactic reactions.\textsuperscript{29,30} However, there is yet no conclusive evidence for any of these mechanisms. In our study population, there were few cases with AF without any underlying cardiovascular risk factor. Therefore, we think that high-dose corticosteroid therapy may act as a trigger rather than as a single cause for AF, which would be in line with the earlier described trigger-substrate relation in drug-induced AF.\textsuperscript{9}

In a recent case-control study, Huerta et al\textsuperscript{27} reported a positive association between short-term oral corticosteroid therapy and cardiac arrhythmias (including AF) in persons with asthma/COPD. The association was not investigated in persons without asthma/COPD. Consequently, confounding by indication could not be excluded. However, in our study we found an association in patients with and without asthma/COPD.

The fact that we found an association only in patients receiving high-dose steroid exposure is in line with the study by Huerta et al,\textsuperscript{27} who also found no association with the use of inhaled corticosteroids (low-dose steroid exposure) and cardiac arrhythmias. We also found an increased risk for AF in recent new corticosteroid users as well as in persons who used corticosteroids before, supporting the hypothesis that corticosteroids have a potential direct arrhythmogenic effect (Table 2). That new corticosteroid users seem to have an even higher risk to develop AF than persons who also used corticosteroids before might be explained by the fact that all new users who developed AF (n=4) were high-dose users. The more long-term users who developed AF (n=39) included a mix of high-dose (n=25) and low-intermediate-dose users (n=14). The higher relative risk in patients with rheumatic, allergic, or malignant hematologic diseases than in patients with asthma/COPD (Table 3) could be explained by the fact that the prescribed steroid doses are usually highest in the first patient group.

Several aspects of validity need to be discussed. Selection bias is unlikely because cases and controls were derived from a prospective, population-based cohort study, and controls came from the same study base as cases. Information bias is unlikely because data on drug use were prospectively gathered. Since corticosteroids are only available by prescription, pharmacy records provide complete coverage. Compliance with systemic corticosteroid regimens is usually good because such patients are often seriously ill. Misclassification of the diagnosis of AF is unlikely and would be random because the outcome was assessed independently of the exposure.

Diagnosis bias is a potential problem: patients who are ill and need corticosteroids may undergo more ECGs. However, we think that diagnosis bias is negligible in our study because we excluded all cases of AF that were discovered by screening, protocol, or standard hospitalization ECGs. We restricted the analyses to symptomatic cases who presented themselves spontaneously. Misclassification of the index date is possible, because the date of diagnosis is not always the same as the date of onset of AF. To decrease the degree of misclassification of index date, we excluded AF cases with an unknown date of onset. In our study, it is unlikely that confounding explains our results because we were able to adjust for many important potential confounders. Moreover, confounding by indication is not likely to explain the association. We were able to study the association in persons with

\textbf{Table 3. New-Onset Atrial Fibrillation and Corticosteroid Therapy in Different Patient Groups}

<table>
<thead>
<tr>
<th>Corticosteroid</th>
<th>Cases, No. (n = 385)</th>
<th>OR† (95% CI)</th>
<th>OR‡ (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>and/or COPD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>43</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Low-intermediate dose</td>
<td>13</td>
<td>1.46 (0.78-2.76)</td>
<td>1.40 (0.73-2.70)</td>
</tr>
<tr>
<td>High dose</td>
<td>13</td>
<td>4.71 (2.51-8.81)</td>
<td>4.02 (2.07-7.81)</td>
</tr>
<tr>
<td>Diseases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>299</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Low-intermediate dose</td>
<td>1</td>
<td>0.78 (0.11-5.55)</td>
<td>0.57 (0.08-4.24)</td>
</tr>
<tr>
<td>High dose</td>
<td>16§</td>
<td>10.78 (6.50-17.83)</td>
<td>7.90 (4.47-13.98)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; OR, odds ratio.

*In the 30 days before the index date.  \footnote{Adjusted for age and sex.} \footnote{Adjusted for age, sex, myocardial infarction, heart failure, body mass index, user status, and use of antihypertensives in the month before the index date.} \footnote{Steroid indication: polymyalgia rheumatica, rheumatoid arthritis, (acute) bronchitis, allergic skin reaction, multiple myeloma, and non-Hodgkin lymphoma.}
asthma/COPD and in those with other indications for corticosteroid therapy. This makes it highly unlikely that the indications asthma or COPD and who developed AF (n=16) received corticosteroid therapy for various indications: polymyalgia rheumatica (n=6), rheumatoid arthritis (n=1), (acute) bronchitis (n=4), allergic skin reaction (n=1), as concomitant therapy for multiple myeloma (n=1) and non-Hodgkin lymphoma (n=1), and unknown indications (n=2). As these indications are so heterogeneous, we do not expect that these diseases confounded our results. Moreover, the strong risk increases make residual confounding unlikely.

In conclusion, our findings suggest that patients receiving high-dose corticosteroid therapy are at increased risk of developing AF. Therefore, careful monitoring of these patients by clinical examination and by performing an ECG before and after high-dose (pulse) therapy could increase the chance to diagnose and treat this serious arrhythmia as early as possible. Because persons who develop AF are at increased risk of serious cardiovascular complications such as heart failure and ischemic stroke and have a chance to develop chronic AF, early detection of AF is essential.

Accepted for Publication: December 23, 2005.
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Financial Disclosure: None.

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