Long-term Use of Anti-inflammatory Drugs and Risk of Atrial Fibrillation

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Background: Previous reports have described an association between the use of corticosteroids (steroidal anti-inflammatory drugs [SAIDs]) and the risk of atrial fibrillation (AF). We sought to determine the existence of a similar association for non-SAIDs (NSAIDs).

Methods: We identified patients aged 40 to 89 years with a first-ever diagnosis of AF in 1996 in a United Kingdom primary care database and classified them as having paroxysmal or chronic AF. After validation with their primary care physicians, 1035 patients were confirmed as having incident chronic AF and 525 as having paroxysmal AF. Two separate nested case-control analyses estimated the risk of first-time chronic and paroxysmal AF among users of SAIDs and NSAIDs.

Results: We confirmed the previously reported association between current use of SAIDs and chronic AF (rate ratio [RR], 2.49; 95% confidence interval [CI], 1.56-3.97). However, we also found that the current use of NSAIDs was associated with an increased risk of chronic AF (RR, 1.44; 95% CI, 1.08-1.91). Such risk was further increased among long-term users with a treatment duration of longer than 1 year (RR, 1.80; 95% CI, 1.20-2.72). The increased risk of chronic AF was not explained by the occurrence of heart failure. The use of NSAIDs was not associated with paroxysmal AF.

Conclusions: The use of NSAIDs, as for SAIDs, is associated with an increased risk of chronic AF. Because the use of anti-inflammatory drugs in general is a marker for underlying inflammatory disorders, inflammation may be the common cause for the use of anti-inflammatory drugs and chronic AF.

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Atrial fibrillation (AF) is a common condition. It affects 0.4% of the general population but more than 6% of individuals older than 80 years. The prevalence of AF is increasing, even after adjustment for age. Atrial fibrillation reduces life expectancy. The most frequent pathoanatomical changes in AF are atrial fibrosis and loss of atrial muscle mass. Histological examination of atrial tissue of patients with AF has shown patchy fibrosis juxtaposed with normal atrial fibers, which may account for inhomogeneities of conduction. It is difficult to distinguish between changes due to AF and those due to associated heart disease, but fibrosis may precede the onset of AF. Atrial fibrosis may be caused by inflammation, as seen in cardiac sarcoidosis and autoimmune disorders. The coexistence of inflammatory diseases and AF, especially in the elderly, may be causal. The use of anti-inflammatory drugs may characterize a phenotype with an underlying inflammatory substrate. Because of this, we hypothesized the existence of an association between the consumption of anti-inflammatory drugs, of which nonsteroidal anti-inflammatory drugs (NSAIDs) represent the most common therapeutic class, and AF. Herein, we report on such an association and speculate on the possible underlying mechanisms.

Methods

Data Source

The United Kingdom (UK) General Practice Research Database (GPRD) contains computerized information entered by primary care physicians in the UK. The vast majority of the UK population is registered with a primary care physician. At the time of the study, approximately 1500 physicians were participating in the GPRD, covering a population of approximately 3 million individuals who are broadly representative of the UK population. The primary care physicians hold the complete medical record of registered individuals, including demographic data, all medical diagnoses, consultant and hospital referrals, and a record of all prescriptions issued. Prescriptions are generated directly from the primary care physician’s computer and entered into the patient’s computerized file.
All information is recorded by physicians during consultations in a standardized fashion, and individual practices regularly anonymize and send these data to the Medicines and Healthcare Products Regulatory Agency (UK Department of Health), which organizes them for use in research projects. Several validation studies have shown the accuracy and completeness of data on diagnoses, medical information, and prescriptions recorded in the GPRD. Previous studies have also confirmed the validity and utility of the GPRD for research on AF.

CASE ASCERTAINMENT

In previous studies, we identified patients aged 40 to 89 years with a first-ever recorded diagnosis of AF (International Classification of Diseases, Eighth Revision, 4163-4164) in 1996. Patients had to be registered with the general practitioner for at least two years, and individuals with a history of cancer or heart rhythm disorders were not included. For the purposes of the studies, patients whose arrhythmia persisted for more than 1 week were classified as having chronic AF. Those whose arrhythmia reverted to sinus rhythm within 1 week, either spontaneously or after treatment, were labeled as having paroxysmal AF. The AF diagnosis was validated through a questionnaire sent to primary care physicians, as detailed previously. In summary, primary care physicians were asked to confirm whether this AF episode was the first-ever diagnosis of AF for their patients and to provide information on diagnostic tests, procedures, and the etiology of the disorder, including details of drug therapies. Patient confidentiality was always preserved. We obtained valid responses in 93% of the 2040 patients who were originally identified with AF and for whom validation of diagnosis was requested, and in the end, 1035 patients were confirmed as having incident chronic AF and 525 as having paroxysmal AF.

NESTED CASE-CONTROL ANALYSES

Two separate case-control analyses were performed to estimate the risk of first-time chronic AF and paroxysmal AF among users of NSAIDs. We included all patients with confirmed chronic AF and paroxysmal AF, and the date of their initial diagnosis was the index date. We assigned a random date to all members of the study cohort where AF cases were ascertained, and randomly sampled 2 groups of 5000 controls from the pool of eligible members: one for the set of chronic AF cases and the other for the set of paroxysmal AF cases. The random date was used as the index date.

EXPOSURE DEFINITION

Exposure to NSAIDs and SAIDs was categorized as current when the supply of the most recent prescription lasted until the index date or ended in the month before it; as recent when it ended between 1 and 6 months before the index date; as past when it ended more than 6 months before the index date; and as nonuse when there was no recorded use ever before the index date. The effect of daily dose and treatment duration was examined among current users.

Regarding oral SAIDs, prednisolone doses up to 5 mg/d were classified as low, doses up to 10 mg/d as medium, and doses higher than 10 mg/d as high. The corresponding cutoff values were 20 and 40 mg/d for hydrocortisone, 0.8 and 1.5 mg/d for dexamethasone, and 25 and 50 mg/d for cortisone. Regarding NSAIDs, specific cutoff values for doses, in milligrams, were as follows: acemetacin, 120; azapropazole, 600; diclofenac, 100; diflunisal, 1500; etodolac, 400; fenbufen, 900; fenoprofen, 1200; flurbiprofen, 150; ibuprofen, 1200; indomethacin, 75; ketorolac, 150; ketorolac, 30; mefenamic acid, 1000; meloxicam, 7.5; nabumetone, 1000; naproxen, 750; piroxicam, 10; sulindac, 200; tenoxicam, 10; and tiaprofenic acid, 600. Doses less than or equal to the cutoff value were grouped under low-medium doses, and doses greater than the cutoff value were considered high doses. Duration of use was computed among current users summing the days included in the time interval of “consecutive” prescriptions and categorized into 3 groups: use for less than 1 month, use between 1 month and 1 year, and use for more than 1 year.

STATISTICS

We used unconditional logistic regression to compute multivariate estimates of odds ratios and 95% confidence intervals (CIs) of AF associated with SAID or NSAID use as well as the dose and duration response. All estimates were adjusted by age, sex, and other risk factors, including smoking status; body mass index; alcohol consumption; prior health care visits; presence of diabetes, hypertension, heart failure, ischemic heart disease, or valvular heart disease; and use of digoxin, anticoagulants, aspirin, and non-SAIDs.

Table 1. Rate Ratio (RR) of Chronic Atrial Fibrillation (AF) According to Use, Treatment Duration, and Daily Dose of Steroidal Anti-inflammatory Drugs (SAIDs)*

<table>
<thead>
<tr>
<th>SAID Exposure</th>
<th>Controls (n=5000)</th>
<th>Chronic AF Cases (n=1035)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Timing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonuse</td>
<td>4594</td>
<td>882</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Current use</td>
<td>69</td>
<td>52</td>
<td>2.49 (1.56-3.97)</td>
</tr>
<tr>
<td>Recent use</td>
<td>109</td>
<td>42</td>
<td>1.51 (0.89-2.57)</td>
</tr>
<tr>
<td>Past use</td>
<td>228</td>
<td>59</td>
<td>0.84 (0.60-1.18)</td>
</tr>
<tr>
<td><strong>Timing, d</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤30</td>
<td>18</td>
<td>18</td>
<td>4.73 (2.01-11.16)</td>
</tr>
<tr>
<td>&gt;30</td>
<td>51</td>
<td>34</td>
<td>1.90 (1.09-3.31)</td>
</tr>
<tr>
<td>31-365</td>
<td>25</td>
<td>19</td>
<td>1.58 (0.76-3.25)</td>
</tr>
<tr>
<td>&gt;365</td>
<td>26</td>
<td>15</td>
<td>2.46 (1.06-5.69)</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>30</td>
<td>21</td>
<td>1.95 (0.95-4.02)</td>
</tr>
<tr>
<td>Medium</td>
<td>14</td>
<td>6</td>
<td>1.93 (0.61-6.10)</td>
</tr>
<tr>
<td>High</td>
<td>25</td>
<td>25</td>
<td>3.41 (1.68-6.90)</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.

*aRate ratio adjusted for age, sex, smoking, body mass index, alcohol use, health care visits, ischemic heart disease, heart failure, valvular disease, hypertension, diabetes, and use of digoxin, anticoagulants, aspirin, and non-SAIDs.

PROSTATE CANCER RISK OF CHRONIC AF ACCORDING TO USE, TREATMENT DURATION, AND DAILY DOSE OF SAIDs

We found that use of SAIDs is associated with an increased risk of chronic AF (RR, 2.49; 95% CI, 1.56-3.97 for current use, and RR, 1.51; 95% CI, 0.89-2.57 for recent use), confirming previous findings (Table 1). When we grouped low and medium doses in 1 category, the estimate of RR was 1.95 (95% CI, 1.05-3.60), and the cor-
chronic AF. The increased RR occurred for all NSAIDs, were different from each other in their relationship with medium and high (Table 2).

1.20-2.72) (Table 2). We found no dose-response effect in the association when we divided daily use into low-

1.57 (95% CI, 1.15-2.15), and the RR was highest for the use of NSAIDs for more than 1 year (RR, 1.80; 95% CI, 1.57-2.15) (Table 2). We found no dose-response effect in the association when we divided daily use into low-

1.00; 95% CI, 0.78-1.30).

RISK OF PAROXYSMAL AF ACCORDING TO USE, TREATMENT DURATION, AND DAILY DOSE OF NSAIDs

We found that the current use of NSAIDs was associated with an RR of 1.44 (95% CI, 1.08-1.91) for chronic AF. The increased risk tended to disappear with time elapsing since last NSAID use (Table 2). The RR associated with the use of NSAIDs for more than 30 days was 1.57 (95% CI, 1.15-2.15), and the RR was highest for the use of NSAIDs for more than 1 year (RR, 1.80; 95% CI, 1.20-2.72) (Table 2). We found no dose-response effect in the association when we divided daily use into low-

1.00; 95% CI, 1.11-2.71) (Table 3).

INTERACTION BETWEEN USE OF NSAIDs AND ANTECEDENTS OF HEART FAILURE IN THE RELATIONSHIP WITH CHRONIC AF

Because it is conceivable that the long-term use of NSAIDs becomes associated with AF owing to the known association of NSAIDs with increased risk of myocardial infarction, thereby causing more heart failure (HF), which in turn causes a higher rate of AF among NSAIDs users,
we hypothesized that the association is present only in individuals with HF and absent in individuals without HF. Among patients with HF, however, there was no major increased risk of chronic AF in current NSAID users (RR, 0.93; 95% CI, 0.38-2.27). Conversely, among patients without HF, there was an increased risk of AF in NSAID users (RR, 1.49; 95% CI, 1.10-2.02) (Table 4). This finding indirectly speaks against a major role for HF in mediating the association between the use of NSAIDs and increased risk of chronic AF.

COMMENT

We found that the current use of NSAIDs is associated with a statistically significant 44% increase in the risk of chronic AF, while no similar association was found regarding paroxysmal AF. We also confirmed previous findings regarding the association of the use of SAIDs with an increased risk of chronic AF.

Several drugs have been associated with an increased risk of AF, but knowledge about the role of drugs in the development of AF is scarce. In a comprehensive review article that was published in 2004, corticosteroids were included among the several drug categories for which such an association had been reported. Indeed, several case reports and small-series observational studies, as well as 1 case-control study, had reported on such an association. Such findings were confirmed in an extensive series based on the Rotterdam Study, a population-based cohort study involving 7983 older adults. Several hypotheses were raised at that time to explain the association: (1) high-dose corticosteroids mediate (local) potassium efflux via a direct effect on the cell membrane, which may induce arrhythmias; (2) the mineral corticosteroid effect of high doses of glucocorticosteroids can cause retention of sodium and fluid, which in turn may cause hypertension, left atrial enlargement, and congestive heart failure—all known risk factors for AF; and (3) corticosteroids may favor the development of late potentials and occasionally cause profound peripheral vasodilatation and anaphylactic reactions. However, there is as yet no conclusive evidence for any of these mechanisms, and it was concluded then that high-dose corticosteroid therapy may act as a trigger rather than as a single cause for AF, in line with the earlier-described trigger-substrate relationship in drug-induced AF. The present report confirms those earlier observations. Current and recent use of SAIDs (mostly because of chronic obstructive pulmonary disease and rheumatic diseases) was associated with a higher risk of AF with a clear dose-response relationship.

Importantly, however, our report now extends those earlier observations to the therapeutic group of NSAIDs, which are mostly devoid of the above-reported postulated proarrhythmogenic properties of SAIDs but share with SAIDs the indication as treatment for chronic inflammatory conditions. We found, in particular, that the current use of NSAIDs was associated with a significant 44% increased risk of chronic AF, with the risk tending to disappear after the NSAID treatment was discontinued. The increased risk was present irrespective of treatment duration, although our data are compatible with a greater risk associated with long-term use. We found no apparent dose-relationship when we divided daily use into low-medium and high. In essence, the use of NSAIDs, irrespective of the dosing, appeared to coincide with a higher risk of AF. At the same time, we found no overall association between use of NSAIDs and the risk of paroxysmal AF, although long-term NSAIDs users also presented an increased risk of paroxysmal AF.

The use of cyclooxygenase-2 inhibitors, both selective (coxibs) and traditional NSAIDs, has been found to be associated with an increased risk of acute myocardial infarction, largely currently interpreted as attributable to an increased risk of thrombosis after the impairment of prostacyclin production, which is mainly cyclooxygenase-2 dependent. This increased risk of thrombosis might translate into an increased risk of late HF, in turn explaining the higher risk of AF compared with patients with no previous myocardial infarction. However, such a hypothesis does not seem to be compatible with our data. When we stratified the analysis according to antecedents of HF, we found that the increased risk of chronic AF associated with the use of NSAIDs was actually present in patients without HF but absent in those with prior HF.

However, the association of increased risk of AF with the use of NSAIDs does not imply a cause-and-effect relationship. Indeed, a likely explanation for our findings is the existence of an underlying inflammatory condition, increasing the risk of AF on the one hand and prompting the use of NSAIDs on the other. Underlying inflammatory conditions could favor the onset or maintenance of AF. Atrial fibrosis is the most frequent pathoanatomical change found in AF. Patchy fibrosis in close proximity with normal atrial fibers may account for conduction inhomogeneities, and it has been argued that fibrosis precedes the onset of AF. Atrial fibrosis is cur-
rently the main structural target for the proposed use of drugs inhibiting the renin-angiotensin system in AF\textsuperscript{15,16} and may be caused by inflammation,\textsuperscript{14} as seen in cardiac sarcoidosis\textsuperscript{15} and autoimmune disorders.\textsuperscript{16} Inflammation, possibly also through the production of thromboxane \(A_2\) and prostaglandin \(F_{2\alpha}\), has recently been shown to cause inflammatory tachycardia.\textsuperscript{47} It is possible, and we would like to propose, that conditions presenting systemic inflammation, such as autoimmune and rheumatic disorders, represent an independent risk factor for atrial fibrillation and subsequently for an increased risk of onset or persistence of AF. Consequently, the use of anti-inflammatory drugs may be a proxy for an underlying inflammatory substrate favoring AF. We believe that this hypothesis deserves further investigation.

We acknowledge a few limitations of our study. The diagnosis of chronic AF is not in keeping with the currently used distinction between AF that is amenable to cardioversion ("persistent" AF) and AF for which cardioversion is deemed unsuitable ("permanent" AF)\textsuperscript{48} but was the only one available at the time of the entry of data in our primary care database, in which the duration of AF was the only distinctive criterion between paroxysmal and chronic AF. Most likely, our definition of chronic AF includes all cases of currently defined permanent AF cases and a certain proportion of persistent AF cases. Confirmatory analyses of more recent databases should clarify this better. The possibility of unknown confounders underlying the relationship cannot be totally discarded. Also, we have no clear explanation for the stronger association of NSAID use with chronic AF than with paroxysmal AF. One possibility is that the underlying atrial fibrosis, caused by inflammation—for the presence of which the use of anti-inflammatory agents is a marker—is a condition that predisposes more to perpetuating than to actually causing AF. Another possibility, however, is the smaller sample size of paroxysmal AF cases (\(n = 525\)) compared with chronic AF cases (\(n = 1035\)). Indeed, the estimates of risk associated with paroxysmal AF and chronic AF were overlapping; actually—when analyzing the long-term use of NSAIDs defined as continuous use for more than 1 year—the estimates were quite similar (RR, 1.74; 95\% CI, 1.11-2.71 vs RR, 1.80; 95\% CI, 1.20-2.72). All such issues need to be addressed in future analyses. Furthermore, future studies on the association of SAIDs or NSAIDs with AF should ideally include a description of left ventricular function, atrial size and/or function, and inflammatory markers, which would help to make the association more biologically plausible.

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