Nonaspirin Nonsteroidal Anti-Inflammatory Drugs and Risk of Hospitalization for Intracerebral Hemorrhage

A Population-Based Case-Control Study

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Background and Purpose—Nonsteroidal anti-inflammatory drugs (NSAIDs) have effects on hemostasis and have been associated with an increased risk of bleeding. However, data relating the use of nonaspirin NSAIDs and risk of intracerebral hemorrhage (ICH) are sparse.

Methods—Using data from the County Hospital Patient Register and the Civil Registration System of North Jutland County, Denmark, we identified 912 cases of first-time ICH and 9059 sex- and age-matched population-based controls in the period of 1991 to 1999. All prescriptions for nonaspirin NSAIDs before the date of admission for ICH were identified through a population-based prescription database. Conditional logistic regression was used to adjust for potential confounding factors, including previous discharge diagnoses of hypertension, chronic bronchitis and emphysema, alcoholism, liver cirrhosis, diabetes mellitus, and prescriptions for insulin or oral hypoglycemic agents, antihypertensive agents, lipid-lowering agents, low-dose aspirin, high-dose aspirin, and oral anticoagulants.

Results—No overall association was found between prescription for nonaspirin NSAIDs in the preceding 30, 60, or 90 days and risk of ICH; ie, odds ratios ranged from 0.92 (95% CI, 0.70 to 1.21) to 1.13 (95% CI, 0.81 to 1.58). Furthermore, there was no increased risk of ICH associated with prescription for nonaspirin NSAIDs when the study population was stratified by age, sex, and a previous discharge diagnosis of hypertension.

Conclusions—Patients prescribed nonaspirin NSAIDs were not at an overall increased risk of being hospitalized for ICH. This reassuring finding was seen in all examined subgroups, including the elderly and patients with a previous discharge diagnosis of hypertension. (Stroke. 2003;34:387-391.)

Key Words: anti-inflammatory agents, nonsteroidal ■ case-control studies ■ epidemiology ■ intracerebral hemorrhage

Nonaspirin anti-inflammatory drugs (NSAIDs) are among the most commonly used medications worldwide. The use of NSAIDs has consistently been associated with an increased risk of bleeding, especially from the gastrointestinal tract.1,2 The increased risk is most likely due to a decreased synthesis of prostaglandins, which, among other consequences, lead to impairment of gastrointestinal mucosal integrity and platelet aggregation.1,3 Although most pronounced for aspirin, all NSAIDs affect platelet aggregation and bleeding time.4

The investigators of several randomized trials and observational studies have examined whether the use of NSAIDs increases the risk of intracerebral hemorrhage (ICH).5-9 A condition associated with high mortality and poor functional outcome.10,11 Most of these studies have focused on the use of aspirin,5-8 whereas limited data are available on the use of nonaspirin NSAIDs and risk of ICH. Because nonaspirin NSAIDs are widely used, even small risks of side effects, especially for serious conditions like ICH, may have considerable clinical and public health implications. Only 1 observational study has examined the association between NSAID use and risk of ICH. Although the study was based on >300 cases, several of the obtained risk estimates were statistically imprecise.9 Further information is needed, including data from subgroups of patients with an increased risk of ICH, eg, the elderly and hypertensive patients, before an increased risk of ICH associated with use of nonaspirin NSAIDs can be excluded.

We therefore conducted a population-based case-control study in Denmark to evaluate the risk of ICH among persons who received prescriptions for nonaspirin NSAIDs.
Subjects and Methods

The study was conducted within the population of North Jutland County, Denmark, which comprised ~490,000 inhabitants, ~9% of the total Danish population, during the study period of 1991 to 1999. The National Health Service provides tax-supported health care for all inhabitants, allowing free access to general practitioners, hospitals, and public clinics, and refunds a variable proportion of the costs of prescribed drugs. Through the use of the civil registry number, which is unique to every Danish citizen and encodes sex and date of birth, a complete hospital discharge and prescription history can be established for each individual, and unambiguous linkage between population-based registers can be performed.

Identification of Cases

The County Hospital Patient Register (HPR) of North Jutland County retains key information on all patients discharged from somatic hospitals in the county since 1977.12 The files of the HPR include information on the civil registry number of the patient, date of discharge, and up to 20 discharge diagnoses12 assigned exclusively by the physician at discharge according to the Danish version of the International Classification of Diseases, 8th revision (ICD-8) until the end of 1993 and 10th revision (ICD-10) thereafter.12

We identified all patients with a first diagnosis of ICH (ICD-8 codes 431.00, 431.08 to 431.90, 431.98, 431.99; ICD-10 codes I61.0 to I61.19) in the period of 1991 to 1999 (n=1086) using the HPR. Coding of the first episode as a recurrent, previous, or unconfirmed episode of ICH led to exclusion of 24 patients. Furthermore, patients with an address outside the county (n=131), those <18 years of age (n=3), and patients for whom no eligible controls could be identified (n=16) were excluded. In total, 912 cases were available for analyses.

Validity of ICH Diagnosis

Because hospital discharge data may vary in quality,13 we evaluated the positive predictive value of a discharge diagnosis of ICH in a random sample of 100 patients. The positive predictive value was calculated by dividing the number of patients with a confirmed ICH diagnosis after review of medical records, using the diagnostic criteria below as the gold standard, by the total number of patients evaluated. Medical records could be retrieved for 92% of the 100 patients. These medical records were reviewed by use of a standardized form.

The World Health Organization definition of stroke was used when reviewing these medical records, ie, an acute disturbance of cerebral function lasting >24 hours or leading to death of presumed vascular origin.14 ICH was defined as clinical symptoms of stroke combined with the presence of a CT- or MR-verified ICH or ICH established by autopsy and not preceded by a previous ischemic stroke in the same area.

The overall positive predictive value for ICH was 75.0% (95% CI, 65.4 to 83.0) among the 92 cases; ie, 69 of 92 cases had ICH when the above-mentioned criteria were used. A clear difference was seen when the predictive value was stratified according to availability of CT/MR scan at the treating hospital, ie, 89.7% (95% CI, 80.7 to 95.4; 61 of 68 cases) when imaging was available at the hospital compared with 33.3% (95% CI, 16.8 to 53.6; 8 of 24 cases) when imaging was not available at the hospital.

Of the 912 cases included in the study, 633 (69.4%) were discharged from hospital with easy access to brain imaging facilities.

Selection of Controls

Using the Civil Registration System, which has electronic records on all inhabitants in vital status, including change of address, date of emigration, and date of death for the entire Danish population since 1968, we planned to select 10 random controls for each case matched by age (same date of birth), sex, and place of residence (North Jutland County). The controls were selected with the incidence density sampling technique15; ie, the controls had to be alive and at risk of first ICH at the time the corresponding case was diagnosed. A small proportion of cases had <10 eligible controls, and for a few elderly patients (n=16), we found no controls who fulfilled the above-mentioned criteria. A total of 9059 controls were selected.

Data on Drug Use and Confounding Factors

The population-based Pharmaco-Epidemiologic Prescription Database of North Jutland County, initiated on January 1, 1989, with complete coverage from January 1, 1991, retains key information on prescriptions for refundable drugs dispensed from all 33 pharmacies in the county. This includes the civil registry number of the patient, type of drug prescribed according to the anatomical therapeutic chemical (ATC) classification system,16 and date of prescription (date the drug was dispensed). We identified all prescriptions for nonaspirin NSAIDs (ATC code M01A) among cases and controls before the date of hospital admission of cases through the Pharmaco-Epidemiologic Prescription Database. In Denmark, all nonaspirin NSAIDs except low-dose ibuprofen (200 mg per tablet) are available only by prescription. Although low-dose ibuprofen is available without prescription, pensioners and regular users of this drug, eg, patients with chronic diseases or pain requiring prolonged treatment, are presumably all registered in the Prescription Database because they receive a 50% refund when the ibuprofen is prescribed by a physician.

Data on potential confounding factors were collected from the HPR and the Pharmaco-Epidemiologic Prescription Database. Data from the HPR included discharge diagnoses of hypertension (ICD-8 codes 400 to 404, 410.09, 411.09, 412.09, 413.09, 414.09, 430.00, 430.01, 430.08, 430.09, 431.00, 431.01, 431.08, 431.09, 432.00, 432.01, 432.02, 432.08, 432.09, 433.09, 434.09, 435.09, 436.00, 436.01, 436.09, 437.00, 437.01, 437.08, 437.09, 438.09; ICD-10 code I10-I15), chronic bronchitis and emphysema (in proxy measure of smoking; ICD-8 codes 490, 491, 492; ICD-10 codes J40, J41, J42, J43, J44), alcoholism (ICD-8 code 303; ICD-10 code F10), liver cirrhosis (ICD-8 codes 571, 573; ICD-10 codes K70, K72, K74, K76), and diabetes mellitus (ICD-8 codes 249, 250; ICD-10 code E10-E14) registered either before or during the admission for ICH. Data from the Pharmaco-Epidemiologic Prescription Database included prescriptions for antihypertensive drugs (including angiotensin-converting enzyme inhibitors, β-blockers, calcium antagonists, diuretics, and angiotensin II receptor antagonists; ATC codes C02, C03, C07, C08, C09), insulin and oral hypoglycemic drugs (ATC codes A10A, A10B), lipid-lowering drugs (ATC code, C10), low-dose aspirin (75 to 150 mg; ATC code B01A C06), high-dose aspirin (100 to 500 mg; ATC codes N02B A01, N02B A51), and oral anticoagulants (warfarin, phenprocoumon; ATC codes B01A A03, B01A A04) redeemed before the date of ICH diagnosis.

Statistical Analysis

We used conditional logistic regression to calculate odds ratios (ORs) for ICH among users and nonusers of nonaspirin NSAIDs. Initially, we conducted univariate analyses on the association between ICH and the use of nonaspirin NSAIDs and the potential confounding factors, ie, discharge diagnoses of hypertension, chronic bronchitis and emphysema, alcoholism, liver cirrhosis and diabetes mellitus, or prescriptions for antihypertensive drugs, insulin and hypoglycemic drugs, lipid-lowering drugs, low-dose aspirin, high-dose aspirin, and oral anticoagulants.

We then calculated ORs adjusted for the potential confounding factors, which were included in the models as dichotomous variables. Separate analyses were conducted with different exposure time windows, ie, medication prescribed within 30, 60, or 90 days before the date of admission for ICH. Furthermore, stratified analyses were performed according to sex, age, discharge diagnosis of hypertension, prescription of antihypertensive drugs, and availability of imaging at the discharging hospital.

Because cases had been hospitalized at least once by definition, data on cases may potentially have been more complete than for controls. Thus, we also performed analyses using only data on potential confounders obtained before the admission for ICH.

Estimation of 95% CIs for ORs was based on large sample theory for conditional maximum likelihood estimators. All analyses were done with SAS version 8.00 (SAS Institute Inc).
Results

Table 1 shows characteristics of the 912 cases and 9059 controls. A higher proportion of cases than controls had discharge diagnoses of hypertension, diabetes mellitus, chronic bronchitis and emphysema, alcoholism, and liver cirrhosis. Similarly, a higher proportion of cases than controls had redeemed prescriptions for antihypertensive drugs and insulin and hypoglycemic drugs. Low-dose aspirin and oral anticoagulants were also more frequently used among cases than controls.

Table 2 gives crude and adjusted ORs for ICH according to prescription for nonaspirin NSAIDs within 30, 60, or 90 days before the date of hospitalization for ICH. The proportion of cases and controls with a prescription for nonaspirin NSAIDs was virtually identical regardless of the time window used. Thus, for instance, 5.3% of cases and 4.2% of controls had received a prescription within 30 days before hospitalization, yielding a crude OR for ICH in this time window of 1.25 (95% CI, 0.91 to 1.70). After adjustment for potential confounding factors, the OR remained virtually unchanged at 1.13 (95% CI, 0.81 to 1.58). When restricting the analyses to the cases with ICH verified through record review (n=59) and their controls (n=589), we found a crude OR of 0.91 (95% CI, 0.21 to 3.96) for prescription of nonaspirin NSAIDs within 30 days before the date of ICH. Adjustment for potential confounding factors had only minor influence; ie, the OR was now 0.71 (95% CI, 0.13 to 3.94).

Changing the time window to 60 or 90 days before the date of hospitalization for ICH did not reveal any association between prescription for nonaspirin NSAID and risk of ICH.

To examine the relevance of our methodology, we also looked at the direction and magnitude of the ORs obtained for known risk factors for ICH in our analyses. The adjusted ORs for having been discharged from hospital with a diagnosis of hypertension or having redeemed a prescription for an antihypertensive drug or oral anticoagulants were 5.87 (95% CI, 4.82 to 7.14), 2.72 (95% CI, 2.30 to 3.22), and 2.15 (95% CI, 1.38 to 3.35), respectively, in our analyses.

To evaluate the possibility that prescription for nonaspirin NSAIDs might be associated with an increased risk of ICH in only certain subgroups of patients, we stratified our analyses according to sex, age, previous discharge diagnosis of hypertension, and previous prescription for an antihypertensive drug. No increased risk of ICH was found in any of the subgroups for nonaspirin NSAIDs prescriptions within 30 days before hospitalization (Table 3).

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### Table 1. Descriptive Characteristics of 912 Cases With ICH and 9059 Controls (Matched on Age and Sex) From the County of North Jutland, Denmark, 1991–1999

<table>
<thead>
<tr>
<th>Category</th>
<th>Cases (n=912)</th>
<th>Controls (n=9059)</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR* (95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prescription of Drug</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonaspirin NSAIDs in previous 30 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>864</td>
<td>8674</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>48</td>
<td>385</td>
<td>1.25 (0.91–1.70)</td>
<td>1.13 (0.81–1.58)</td>
</tr>
<tr>
<td>Nonaspirin NSAIDs in previous 60 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>840</td>
<td>8366</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>72</td>
<td>893</td>
<td>1.03 (0.80–1.33)</td>
<td>0.92 (0.70–1.21)</td>
</tr>
<tr>
<td>Nonaspirin NSAIDs in previous 90 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>814</td>
<td>8199</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>98</td>
<td>860</td>
<td>1.15 (0.92–1.43)</td>
<td>1.04 (0.82–1.32)</td>
</tr>
</tbody>
</table>

*Adjusted for discharge diagnoses of hypertension, chronic bronchitis and emphysema, alcoholism, liver cirrhosis and diabetes mellitus, and prescriptions for insulin or oral hypoglycemic agents, antihypertensive agents, lipid-lowering agents, low-dose aspirin, high-dose aspirin, and oral anticoagulants before the date of admission for ICH.
Because of the apparent marked difference in the predictive value of the ICH diagnosis according to availability of brain imaging facilities at the discharging hospital, we also conducted analyses restricted to patients discharged from hospitals with easy access to CT/MR scanning. None of the results were materially altered. Finally, we performed analyses using only data on potential confounders obtained before the admission for ICH. The results of these analyses were almost identical to the original analyses; eg, the adjusted OR for receiving a prescription for nonaspirin NSAIDs 30 days before the ICH event was 1.15 (95% CI, 0.83 to 1.58).

Discussion

In this population-based case-control study, we found no substantial increase in the overall risk of being admitted to hospital for ICH among patients prescribed nonaspirin NSAIDs. The absence of an association was evident in all subgroups examined, including both men and women, elderly, and hypertensive patients.

The main strengths of our study are its large size, the uniformly organized healthcare system allowing a population-based design, our ability to adjust for conditions predisposing to ICH, and the use of data on exposures and confounding factors collected before the date of admission for ICH, which precluded any recall bias. The weaknesses include the use of routine hospital discharge diagnoses to ascertain case status and several potential confounding factors.

The validity of the ICH hospital discharge diagnosis has previously been reported to be high; however, there may be substantial variation in the predictive value between specialized and nonspecialized departments. We validated the register diagnosis of ICH in a random sample and found a high predictive value among patients discharged from departments with easy access to imaging facilities, ie, a CT or MR scanner, whereas a low predictive value was found for patients discharged from departments without easy access to such facilities. Including patients without ICH as cases in the study could reduce the possibility of finding an association between nonaspirin NSAIDs and ICH. However, limiting the analyses to verified cases only or to patients discharged from hospitals with easy access to imaging facilities did not change the results.

Focusing our study on hospitalized patients, we may have missed patients with very mild events or patients who died before they reached hospital. Likewise, elderly people living in nursing homes and other patients with a short life expectancy may have been less likely to be admitted to hospital. Thus, our findings may not necessarily be extended to all cases of ICH. However, as indicated by the age distribution in our study (mean age, 68 years; range, 19 to 98 years), even very old patients were hospitalized with ICH in the study area and hence were included in the study. Furthermore, studying hospitalized patients, ie, primarily patients with a medium grade of disease severity, would not hamper the generalizability of the findings unless having redeemed a prescription for nonaspirin NSAIDs was also a prognostic factor among ICH patients. This is not likely to be the case.

The overall credibility of the methodology used in our study was also supported by the fact that the risk estimates obtained for known risk factors for ICH, eg, a history of hypertension and treatment with oral anticoagulants, were in line with estimates from the existing literature.

We were unable to control for over-the-counter (OTC) use of nonaspirin NSAIDs and compliance or duration of actual use of the prescribed drugs; ie, redeeming a prescription was used as a proxy for actual use of a drug in our study, which is obviously not always a valid assumption. Both of these uncertainties could lead to misclassification of the exposure. In our study, however, OTC use of nonaspirin NSAIDs was limited to low-dose ibuprofen (200 mg per tablet) for which the sales constituted only 13.5% of the total nonaspirin NSAID sales in Denmark during the study period (personal communication, Janne Kampmann, Danish Medicines Agency, Copenhagen, Denmark, October 1, 2000).

Although we adjusted for several potential confounding factors in the statistical analyses, our results may still be influenced by potential confounding factors not included in the analyses—eg, diet—or by residual confounding resulting from the use of proxy measures. Thus, discharge diagnoses of hypertension and chronic bronchitis and emphysema are not very sensitive measures for blood pressure and smoking, respectively. Moreover, information on the use of high-dose aspirin was probably not complete because a high proportion of the total high-dose aspirin sales in Denmark is OTC use (personal communication, Janne Kampmann, Danish Medicines Agency). However, OTC sales most likely constitute a smaller proportion in our study because a substantial proportion of the study population consisted of elderly persons who can obtain OTC drugs more cheaply by prescription.

Nonequivalence between cases and controls in the completeness and quality of the data on confounding factors

### TABLE 3. Crude and Adjusted ORs for ICH According to Prescription for Nonaspirin NSAIDs Within 30 Days Prior to the Date of Admission

<table>
<thead>
<tr>
<th></th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19–49 y</td>
<td>0.83 (0.20–3.53)</td>
<td>0.75 (0.15–3.84)</td>
</tr>
<tr>
<td>50–69 y</td>
<td>1.30 (0.78–2.19)</td>
<td>1.16 (0.65–2.06)</td>
</tr>
<tr>
<td>¿70 y</td>
<td>1.26 (0.84–1.88)</td>
<td>1.15 (0.76–1.76)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>1.50 (1.03–2.20)</td>
<td>1.32 (0.87–1.99)</td>
</tr>
<tr>
<td>Women</td>
<td>0.91 (0.53–1.56)</td>
<td>0.86 (0.48–1.53)</td>
</tr>
<tr>
<td><strong>Discharge diagnosis of hypertension</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.92 (0.24–3.59)</td>
<td>1.65 (0.35–7.91)</td>
</tr>
<tr>
<td>No</td>
<td>1.14 (0.79–1.64)</td>
<td>1.07 (0.74–1.56)</td>
</tr>
<tr>
<td><strong>Prescription for antihypertensive drugs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.36 (0.76–2.45)</td>
<td>1.46 (0.78–2.74)</td>
</tr>
<tr>
<td>No</td>
<td>1.13 (0.73–1.76)</td>
<td>1.08 (0.68–1.72)</td>
</tr>
</tbody>
</table>

*Adjusted for discharge diagnoses of hypertension (except when stratified by this variable), chronic bronchitis and emphysema, alcoholism, liver cirrhosis and diabetes mellitus and prescriptions for insulin or oral hypoglycemic agents, antihypertensive agents (except when stratified by this variable), low-dose aspirin, and oral anticoagulants before the date of admission for ICH.
based on hospital discharge diagnoses may have occurred because by definition cases had been hospitalized at least once. However, including only data on confounding factors obtained at discharges before the ICH event in the analyses did not change our findings. This indicates that nonequivalence of data available for cases and control may not have been a major problem in our study.

There are important differences in the effects of aspirin and nonaspirin NSAIDs on platelet aggregation and bleeding time. Aspirin inhibits platelet cyclooxygenase irreversibly, whereas the effect of nonaspirin NSAIDs is only temporary, although with considerable variability in extent and duration. Furthermore, the drugs may be used in different patient settings. Aspirin is often used as an antithrombotic agent, whereas nonaspirin NSAIDs are used as anti-inflammatory or analgesic agents. It is thus not obvious that results from studies on bleeding complications of aspirin use are applicable to users of nonaspirin NSAIDs. The results of the present study are consistent with those of a recent study by Thrift et al., who found no association between use of nonaspirin NSAIDs in the preceding fortnight and risk of ICH among 331 cases of ICH and 331 controls (OR, 0.85; 95% CI, 0.45 to 1.61). The 2 studies differed in several ways. Our study was based on prospectively collected population-based registry data and estimated the risk of ICH using different exposure time windows, whereas Thrift et al obtained detailed data using medical records and a questionnaire survey after the ICH event and focused on a predefined exposure time window. From this perspective, the almost identical risk estimates obtained in these 2 studies, indicating no substantially increased risk of ICH associated with use of nonaspirin NSAIDs, is striking and reassuring.

In conclusion, patients prescribed nonaspirin NSAIDs were not at an increased risk of being hospitalized for ICH. This finding was seen in all examined subgroups, including those with higher baseline risks for ICH, such as the elderly and patients with a previous discharge diagnosis of hypertension. Although an increased risk of ICH among users of nonaspirin NSAIDs cannot be ruled out, the reported data so far, including those from the present study, provide evidence that nonaspirin NSAIDs are not major contributors to the risk of ICH.

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References
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