Background: In clinical trials, cyclooxygenase (COX)-2–selective nonsteroidal anti-inflammatory drugs (NSAIDs) were associated with an increased risk of thromboembolic events. We studied the association between NSAID use and risk of stroke in the prospective, population-based Rotterdam Study.

Methods: We followed 7636 persons free of stroke at baseline (1991-1993) for incident stroke until September 2004. Data on all filled prescriptions came from pharmacy records. With Cox regression models, we calculated crude and adjusted hazard ratios (HRs) of stroke for time-dependent current use, compared with never use, of NSAIDs grouped according to COX selectivity (COX-1 selective, nonselective, and COX-2 selective) and individual NSAIDs.

Results: At baseline, the mean age of the study sample was 70.2 years, and 61.3% were female. During 70 063 person-years of follow-up (mean, 9.2 years), 807 persons developed a stroke (460 ischemic, 74 hemorrhagic, and 273 unspecified). Current users of nonselective (HR, 1.72; 95% confidence interval [CI], 1.22-2.44) and COX-2–selective (HR, 2.75; 95% CI, 1.28-5.95) NSAIDs had a greater risk of stroke, but not users of COX-1–selective NSAIDs (HR, 1.10; 95% CI, 0.41-2.97). Hazard ratios (95% CIs) for ischemic stroke were 1.68 (1.05-2.69) for nonselective and 4.54 (2.06-9.98) for COX-2–selective NSAIDs. For individual NSAIDs, current use of the nonselective naproxen (HR, 2.63; 95% CI, 1.47-4.72) and the COX-2–selective rofecoxib (HR, 3.38; 95% CI, 1.48-7.74) was associated with a greater risk of stroke. Hazard ratios (95% CIs) for diclofenac (1.60 [1.00-2.57]), ibuprofen (1.47 [0.73-3.00]), and celecoxib (3.79 [0.52-27.6]) were greater than 1.00 but were not statistically significant.

Conclusions: In the general population, we found a greater risk of stroke with current use of nonselective and COX-2–selective NSAIDs. The risk of stroke was not limited to the use of COX-2–selective NSAIDs.
COX–2–selective NSAIDs or whether other pharmacological properties of NSAIDs could cause these detrimental effects.

We investigated the association between NSAID use and the risk of incident stroke in a large, prospective, population-based cohort study and whether any observed association was restricted to COX–2–selective NSAIDs.

**METHODS**

**STUDY POPULATION**

The Rotterdam Study is a prospective, population-based cohort study of age-related disorders. The medical ethics committee of the Erasmus Medical Center, Rotterdam, the Netherlands, approved the study. Between 1990 and 1993, all persons 55 years or older living in Ommoord, a district of Rotterdam, were invited to participate. Of the 10,275 eligible persons, 7,983 (77.7%) signed informed consent. Of these individuals, 7,722 were free of stroke at baseline. Follow-up examinations were conducted in 1993 to 1994, 1997 to 1999, and 2000 to 2004. In addition, the cohort was continuously monitored for major disease outcomes and death through linkage with records from the general practitioner and from information in the hospital including cerebrovascular disease, through automated linkage of the study database with files from general practitioners. Information on vital status was obtained at regular intervals from the municipal authorities in Rotterdam. When an event or death had been reported, additional information was obtained from the general practitioner and from information in the hospital records (including brain imaging) and discharge letters in the case of admittance or referral. In addition, nursing home physicians' files and files from general practitioners of participants who moved out of the district were scrutinized. Research physicians discussed information on all potential strokes and transient ischemic attacks with an experienced neurologist to verify all diagnoses while blinded to drug exposure. Subarachnoid hemorrhages were excluded. Subtyping of strokes in the Rotterdam Study has been extensively described previously. In brief, a stroke was subclassified as ischemic when a computed tomographic (CT) scan or magnetic resonance image (MRI) that was made within 4 weeks after the stroke occurred ruled out other diagnoses or when indirect evidence

**DRUG EXPOSURE**

Complete information on all filled prescriptions for all persons was obtained in automated format from the pharmacies. This included the product name, international nonproprietary name, Anatomical Therapeutic Chemical code, total number of delivered units (eg, tablets or capsules), prescribed daily number of units, date of delivery, and drug dosage. The duration of a prescription was calculated as the total number of delivered units divided by the prescribed daily number of units. Drug dosage was defined by the defined daily dose (DDD), the recommended daily dosage of a drug taken by adults for the main indication of the drug.

Based on data from in vitro and clinical studies, NSAIDs were classified as COX–1 selective, nonselective, and COX–2 selective according to their relative selectivity for the COX–1 and COX–2 enzymes at therapeutic dosages (Table 1). For some NSAIDs, COX selectivity is unknown or equivocal (ie, benzydamine hydrochloride, tiaprofenic acid, tolmetin acid, phenylbutazone, tenoxicam, and aceclofenac).

Salicylates (ie, acetylsalicylic acid and carbamazepine calcium) are pharmacologically related to NSAIDs and inhibit platelet aggregation via COX–1; although, contrary to NSAIDs, their effects are irreversible. On these grounds, salicylates could be regarded as COX–1–selective NSAIDs; however, they are mostly prescribed at a low dose as platelet inhibitors for the prevention of cardiovascular disease and stroke. We did not include salicylates in the COX–1–selective NSAID group for the following reasons: (1) they are indicated for stroke prevention; (2) NSAID use is cautioned in persons already using salicylates because of the increased risk of gastrointestinal tract bleeding; and (3) some NSAIDs possibly antagonize the platelet inhibition induced by salicylates. This might obscure the protective effect of salicylates. Because of these potential sources of confounding by salicylates, all analyses were adjusted for the current use of salicylates, and the effect of salicylates on the association between NSAID use and stroke was studied through stratification.

**DIAGNOSIS OF STROKE**

A history of stroke at the time of enrollment into the Rotterdam Study was assessed by asking "did you ever suffer from a stroke, diagnosed by a physician?" Positive answers to this question were verified by reviewing the medical records. A history of transient ischemic attack was also assessed during the baseline interview. After enrollment into the Rotterdam Study, participants were continuously monitored for all major events, including cerebrovascular disease, through automated linkage of the study database with files from general practitioners. Information on vital status was obtained at regular intervals from the municipal authorities in Rotterdam. When an event or death had been reported, additional information was obtained from the general practitioner and from information in the hospital records (including brain imaging) and discharge letters in the case of admittance or referral. In addition, nursing home physicians' files and files from general practitioners of participants who moved out of the district were scrutinized. Research physicians discussed information on all potential strokes and transient ischemic attacks with an experienced neurologist to verify all diagnoses while blinded to drug exposure. Subarachnoid hemorrhages were excluded. Subtyping of strokes in the Rotterdam Study has been extensively described previously. In brief, a stroke was subclassified as ischemic when a computed tomographic (CT) scan or magnetic resonance image (MRI) that was made within 4 weeks after the stroke occurred ruled out other diagnoses or when indirect evidence
(eg, deficit limited to 1 limb or completely resolved within 72 hours and atrial fibrillation in absence of anticoagulants) indicated the ischemic nature of the stroke. Hemorrhagic stroke was diagnosed when a relevant hemorrhage was shown on a CT scan or MRI or when the patient permanently lost consciousness or died within hours after onset of focal signs. If a stroke could not be subclassified as ischemic or hemorrhagic as a consequence of a lack of the aforementioned data, it was classified as “unspecified.”

OTHER COVARIATES

Potential confounders were chosen a priori. Baseline covariates included age, sex, systolic blood pressure, body mass index, total serum cholesterol level, and smoking status. Time-dependent covariates included myocardial infarction; atrial fibrillation; heart failure; transient ischemic attacks; coronary artery bypass graft; percutaneous transluminal coronary angioplasty; diabetes mellitus; and use of antihypertensives, salicylates, and antithrombotics. Cardiovascular conditions were assessed at the baseline interview and follow-up examinations, together with a review of medical records. In addition, electrocardiography was performed to determine myocardial infarction and atrial fibrillation. Sitting blood pressure was measured on the right upper arm using a random-zero sphygmomanometer. In the analyses, the mean of 2 measurements, measured at 1 occasion, was used. Diabetes mellitus was defined as nonfasting serum glucose level exceeding 200 mg/dL (to convert to millimoles per liter, multiply by 0.0555) or the use of oral blood glucose-lowering drugs or insulin. Exposure to antihypertensives, salicylates, and antithrombotics was obtained from pharmacy records.

STATISTICAL ANALYSIS

For all subjects, we calculated the duration of follow-up between the start of the study and the date of death, diagnosis of stroke, or end of the study period, whichever came first. We calculated the hazard ratios (HRs) (and 95% confidence intervals [CIs]) of stroke with a Cox proportional hazards model (SPSS 11.01 software; SPSS Inc, Chicago, Illinois), in which calendar time was used as the time axis. Separate analyses were performed for all strokes, ischemic strokes, and hemorrhagic strokes. All analyses were adjusted for age and sex (crude model). In a second model, we adjusted for other potential confounders as previously described (adjusted model).

During follow-up, at each time an event occurred, we determined the exposure to NSAIDs. Use of NSAIDs was classified as never, current, or past use of an NSAID and subsequently categorized into groups according to COX selectivity and as individual NSAIDs. Persons who had not used an NSAID before the date of an event were categorized as “never user.” Persons were considered current users of an NSAID if an event date fell between the start date and end date of a prescription. If a person had previously used an NSAID but no longer used the drug on an event date, they were considered a past user. Due to the initiation and cessation of prescribed drug use, persons can switch from the never to the current exposure category and from the current to the past exposure category or vice versa. Never use was the reference for all analyses. Simultaneous current use of 2 or more NSAIDs was rare (0.1%) and was excluded from the analyses.

For the individual NSAIDs, we investigated a dose-effect relationship by dichotomizing the mean dose of current use as 1 DDD or less and greater than 1 DDD.

We performed several subanalyses. First, we considered that noncompliance or a pharmacological “carryover” could affect the observed associations. Hence, in a sensitivity analysis we extended the risk window by 14 days after the end date of the prescription to see whether this altered our result. Second, the analysis was performed in a subcohort with a history of at least 1 NSAID prescription during follow-up to study the role of potential confounding by indication or contraindication. Third, previous studies have shown that COX-2–selective NSAIDs are preferentially prescribed to persons with substantial comorbidity. To investigate whether this played a role in our study population, we determined for all COX-selective NSAID groups whether a history of use was related to the risk of stroke. Finally, the effect of concomitant use of salicylates could affect our results for reasons described previously. We thus performed an analysis stratified by current use of salicylates.

RESULTS

Baseline characteristics of the cohort at risk are given in Table 2. At baseline, the mean age of the participants was 70.2 years, and the majority was female (61.3%). During 70,063 person-years of follow-up, 807 persons developed a stroke. Of these individuals, 460 were diagnosed as having an ischemic stroke and 74 as having a hemorrhagic stroke, while for 273 individuals the type of stroke could not be specified. The mean follow-up was 9.2 person-years. In our study population, 61 persons who experienced a stroke were current users of any NSAID at the time of the event, whereas 290 persons with a stroke had never used an NSAID during the study period.

As shown in Table 3, current use of any NSAID was associated with a greater risk of stroke compared with never use. Adjustment for confounders resulted in higher estimates. Associations were stronger if only ischemic strokes were considered. Use of any NSAID was related to the risk of hemorrhagic stroke (HR, 2.03; 95% CI, 0.81-5.11), albeit nonsignificant.

Table 3 also shows that current users of nonselective NSAIDs and of COX-2–selective NSAIDs had a higher risk of stroke compared with never users. We found no
 association for COX-1–selective NSAID use with the risk of stroke. Current use of NSAIDs with unknown COX selectivity on the index date was infrequent (0.02%) and thus not studied further. All associations were stronger if only ischemic strokes were considered (Table 3). There were no exposed cases in the class of COX-2–selective NSAIDs for hemorrhagic stroke precluding comparison of the effect of different NSAIDs on the risk of hemorrhagic stroke.

As shown in Table 4, for individual NSAIDs, current use of the nonselective NSAID naproxen and the COX-2–selective rofecoxib were associated with a greater risk of stroke. All but 1 person among the COX-2–selective users, who experienced an event, used rofecoxib. Although HRs for current use of diclofenac (HR, 1.60; 95% CI, 1.00-2.57), ibuprofen (adjusted HR, 1.47; 95% CI, 0.73-3.00), and celecoxib (adjusted HR, 3.79; 95% CI, 0.52-27.6) were greater than 1.00, none of them reached the level of conventional statistical significance. The low number of events for celecoxib (n = 1), as well as for all other individual NSAIDs, prohibited further investigation of these exposure categories. There was no clear dose-response effect, since doses of 1 DDD or less and greater than 1 DDD were both associated with a greater risk of stroke. However, analyses were compromised by low case numbers and unequal distribution of exposed cases across dosage categories.

As for our subanalyses, the extension of the risk window by 14 days after the cessation of drug use attenuated the risk estimates (adjusted HRs [95% CIs] of stroke for current use of any current NSAID, 1.61 [1.20-2.16]; for COX-1–selective NSAIDs, 1.01 [0.37-2.72]; for nonselective NSAIDs, 1.55 [1.11-2.16]; and for COX-2–selective NSAIDs, 2.71 [1.26-5.86]. If we performed the analysis in a subcohort with at least 1 NSAID prescription during follow-up (517 events), we observed little change in HRs compared with the analyses in which never use was defined as the reference (data not shown). Past use of COX-2–selective NSAIDs compared with never use was associated with a greater risk of stroke (adjusted HR, 2.04; 95% CI, 1.34-3.09); no such association was observed for a history of any NSAID use (HR, 1.13; 95% CI, 0.95-1.35) or for the other COX-selective groups (COX-1–selective NSAIDs, [HR, 1.13; 95% CI, 0.94-1.35]; and nonselective

### Table 3. Hazard Ratios for All Strokes and Ischemic Strokes With Current Use of Any NSAID and NSAIDs Grouped According to COX Selectivity

<table>
<thead>
<tr>
<th>Drug Exposure</th>
<th>All Strokes</th>
<th>Ischemic Strokes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases, HR (95% CI), Crude</td>
<td>Cases, HR (95% CI), Adjusted</td>
</tr>
<tr>
<td>Never use</td>
<td>290 [Reference]</td>
<td>156 [Reference]</td>
</tr>
<tr>
<td>Use of:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any NSAID</td>
<td>61 1.58 (1.19-2.08)</td>
<td>34 1.74 (1.20-2.53)</td>
</tr>
<tr>
<td>Nonselective NSAID</td>
<td>48 1.58 (1.16-2.15)</td>
<td>24 1.58 (1.02-2.44)</td>
</tr>
<tr>
<td>COX-1–selective NSAID</td>
<td>5 0.95 (0.38-2.31)</td>
<td>2 0.78 (0.19-3.16)</td>
</tr>
<tr>
<td>COX-2–selective NSAID</td>
<td>7 2.40 (1.12-5.14)</td>
<td>7 4.20 (1.93-9.13)</td>
</tr>
</tbody>
</table>

### Table 4. Hazard Ratios of All Strokes and Ischemic Strokes With Current Use of Individual NSAIDs

<table>
<thead>
<tr>
<th>Drug Exposure</th>
<th>All Strokes</th>
<th>Ischemic Strokes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases, HR (95% CI), Crude</td>
<td>Cases, HR (95% CI), Adjusted</td>
</tr>
<tr>
<td>Never use</td>
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</tr>
<tr>
<td>Use of:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonselective NSAIDs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diclofenac use</td>
<td>20 1.35 (0.86-2.13)</td>
<td>12 1.61 (0.89-2.90)</td>
</tr>
<tr>
<td>Ibuprofen use</td>
<td>11 1.32 (0.72-2.42)</td>
<td>3 0.76 (0.24-2.40)</td>
</tr>
<tr>
<td>Naproxen use</td>
<td>15 2.67 (1.58-4.48)</td>
<td>7 2.37 (1.15-5.06)</td>
</tr>
<tr>
<td>COX-2–selective NSAIDs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rofecoxib use</td>
<td>6 3.24 (1.42-7.37)</td>
<td>6 5.73 (2.48-13.2)</td>
</tr>
</tbody>
</table>

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**Abbreviations:** CI, confidence interval; COX, cyclooxygenase; HR, hazard ratio; NSAID, nonsteroidal anti-inflammatory drug.

*Sex and age adjusted.

*Additionally adjusted for systolic blood pressure, body mass index, total serum cholesterol level, and smoking status. Time-dependent covariates included myocardial infarction; atrial fibrillation; heart failure; transient ischemic attacks; coronary artery bypass graft; percutaneous transluminal coronary angioplasty; diabetes mellitus; and use of antihypertensives, salicylates, and antithrombotics.

*Results are shown for analyses with 5 or more current exposed cases for the all strokes outcome.

*Sex and age adjusted.

*Additionally adjusted for systolic blood pressure, body mass index, total serum cholesterol level, and smoking status. Time-dependent covariates included myocardial infarction; atrial fibrillation; heart failure; transient ischemic attacks; coronary artery bypass graft; percutaneous transluminal coronary angioplasty; diabetes mellitus; and use of antihypertensives, salicylates, and antithrombotics.
NSAIDs, [HR, 1.16; 95% CI, 0.91-1.48]). Notably, almost all users of COX-2–selective NSAIDs had used other types of NSAIDs earlier during follow-up and were, in general, long-term users of NSAIDs.

Only 2 cases were current concomitant users of salicylates and NSAIDs; hence, stratification on concomitant use of salicylates could not be performed.

**COMMENT**

In the general population, we found an overall greater risk of stroke with use of NSAIDs, especially in the categories of nonselective NSAIDs and COX-2–selective NSAIDs. The risk of stroke was most pronounced with COX-2–selective NSAID use.

Strengths of our study design included its prospective design, large number of participants, long follow-up period, and a general population-based setting, which makes selection bias unlikely. Information bias was prevented by prospectively collected and complete automated pharmacy records of all filled prescriptions and blinded adjudication of cerebrovascular events. Certain limitations of our study, however, deserve comment. First, as with most of the clinical trials and observational studies performed to date, inferences must be interpreted in the context of small numbers despite a mean follow-up of more than 9 years. Second, although in the Netherlands long-term use of NSAIDs was fully reimbursed until the beginning of 2004, some miscategorization might have occurred owing to intermittent use of “over-the-counter” NSAIDs. If this biased our results, however, it will have led us to underestimate an effect rather than overestimate the risk of stroke. Finally, “preferential prescribing” might have played a role in the COX-2–selective NSAIDs group, since we observed a higher risk of stroke for past users of COX-2–selective NSAIDs. This channeling bias with COX-2–selective NSAIDs has been described previously in another Dutch patient population setting. However, since the risk estimates were higher for current use of COX-2–selective NSAIDs than for past use, this type of confounding cannot fully explain the greater risk of stroke.

Our results are largely in agreement with the currently available data from randomized clinical trials. In the Alzheimer Disease Anti-inflammatory Prevention Trial (ADAPT), use of naproxen was associated with a similar 2-fold increased risk of stroke compared with placebo, which is in striking accordance with the results of the present study. This same study did not report an effect of celecoxib on the risk of stroke. In our study, no statistically significant effect was found for celecoxib either, although the effect size was similar to that of rofecoxib. Because of low numbers, however, an effect of celecoxib on the risk of stroke cannot be excluded. The similar occurrence of ischemic cerebrovascular events for the rofecoxib and the naproxen treatment arms of the Vioxx GI Outcomes Research (VIGOR) study corresponds with our finding of a greater risk of stroke for both these NSAIDs. However, because VIGOR did not include a placebo treatment, it does not provide evidence for the direction of the association. More compelling data consistent with an increase in the risk of stroke with rofecoxib use are provided by the results of the “Adenomatous Polyp Prevention on Vioxx trial,” in which a 2-fold increased risk for cerebrovascular events was observed compared with placebo after 36 months of follow-up.

Several other observational studies also investigated the use of NSAIDs on the risk of ischemic stroke. Our finding of an overall greater risk of ischemic stroke with current use of NSAIDs corresponds with the case-control study by Bak et al. However, direct information on potential confounders was not available in this study, and only concomitant drug use could be used as proxy for the presence of confounding conditions. Andersohn et al found a greater risk of ischemic stroke for rofecoxib, etoricoxib, and diclofenac but not for celecoxib. The higher risk was most pronounced with COX-2–selective NSAID use, which corresponds with our observations. In our study we observed similar odds ratios for celecoxib and rofecoxib. However, celecoxib was not introduced in the Netherlands until 2001, and the use among persons in our cohort was limited, precluding definite conclusions. Like Andersohn et al, our results also put forward a higher risk of stroke with the use of diclofenac, although statistical significance was not reached. These observational studies, including our own, suggest that an effect of NSAIDs on the risk of ischemic stroke is not restricted to the COX-2–selective compounds.

The classification of COX selectivity used in the present study complies with the generally accepted labeling of NSAID selectivity. Nevertheless, some debate exists regarding the COX-selective properties of, mainly, diclofenac, celecoxib, and naproxen. Some have argued that diclofenac is COX-2 selective, since diclofenac would not differ much from celecoxib in terms of its ability to inhibit COX-2. However, therapeutically relevant COX-2 selectivity will be difficult to attain, since the concentration of diclofenac necessary to achieve 80% inhibition of COX-2 is expected to cause a similar inhibition of COX-1. For naproxen, relative selectivity for COX-1, and hence a cardioprotective effect, has been suggested, since naproxen causes near-maximal inhibition of platelet aggregation similar to aspirin. However, clinical evidence does not suggest that relative COX-1 selectivity is achieved. Despite the alleged differences in COX selectivity of these compounds, we found higher risks of stroke for both diclofenac and naproxen and also for celecoxib and rofecoxib. These findings do not necessarily exclude the possibility of an effect through a COX-related mechanism. Because selective inhibition of COX-2 causes platelet aggregation, use of COX-2–selective NSAIDs could, as suggested previously, cause a prothrombotic state. However, since both COX-1 and COX-2 are involved in vascular homeostasis, any pharmacological inhibition of the COX enzymes could be expected to disturb the thrombotic equilibrium, which would explain our observations. In addition, other COX–mediated processes relevant to the pathophysiologic mechanisms of cerebrovascular events might be involved, such as inflammatory response and renovascular physiology. This could provide an alternative explanation for the cerebrovascular risk not being restricted to COX-2–selective NSAIDs.
In conclusion, our study suggests that the greater risk of stroke is not limited to the use of COX-2–selective NSAIDs. Our risk estimates are in line with estimates from the literature. The existing knowledge regarding the effects of pharmacological interference of COX is currently incomplete. Evaluation of COX activity in vivo, together with postmarketing surveillance and observational studies, will be essential to elucidate the potential mechanisms underlying the cerebrovascular effects associated with these drugs.

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Author Contributions: Dr Stricker had full access to all data in the study and had final responsibility for the decision to submit for publication. Study concept and design: Haag, Hofman, Breteler, and Stricker. Acquisition of data: Bos and Stricker. Analysis and interpretation of data: Haag, Bos, Koudstaal, Breteler, and Stricker. Drafting of the manuscript: Haag and Stricker. Critical revision of the manuscript for important intellectual content: Haag, Bos, Hofman, Koudstaal, and Breteler. Statistical analysis: Breteler and Stricker. Obtained funding: Hofman, Breteler, and Stricker. Administrative, technical, and material support: Bos. Study supervision: Hofman, Koudstaal, Breteler, and Stricker.

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