Lower Risk of Thromboembolic Cardiovascular Events With Naproxen Among Patients With Rheumatoid Arthritis

Douglas J. Watson, PhD; Thomas Rhodes, MS; Bing Cai, MS; Harry A. Guess, MD, PhD

Background: Naproxen strongly inhibits platelet aggregation.

Objective: To examine the risk of acute thromboembolic cardiovascular events (TCEs) (myocardial infarction, sudden death, and stroke) with current naproxen use among patients with rheumatoid arthritis.

Methods: We studied patients aged 40 to 79 years with rheumatoid arthritis in the British General Practice Research Database, excluding those with a prior TCE and potentially confounding conditions. We matched up to 4 controls by sex, age, and site of medical practice to cases with first incident TCEs. The case diagnosis date was designated as the index date for each case and his or her controls. We categorized naproxen according to the most recent prescription prior to the index date as being current (≥30 days), past (>30 days but <365 days), or none (≥365 days before index date). Using conditional logistic regression, we conducted a matched case-control analysis with adjustment for potential confounders.

Results: We identified 809 cases. Current naproxen use was more common among controls (5.7%) than cases (3.2%). Adjusting for calendar year of treatment start, systemic corticosteroid use, diabetes, and comorbidity, we found that the odds ratio (95% confidence interval) for current naproxen use was 0.61 (0.39-0.94) while that for past use was 0.87 (0.65-1.16). Secondary and sensitivity analyses supported these results.

Conclusions: In this case-control study, patients with rheumatoid arthritis and a current prescription for naproxen had a reduced risk of acute major TCEs relative to those with no naproxen prescription in the past year. These results are consistent with the ability of naproxen to inhibit platelet aggregation.

Arch Intern Med. 2002;162:1105-1110

PLATELET AGGREGATION plays a central role in the pathophysiology of thromboembolic cardiovascular events (TCEs) such as myocardial infarction (MI) and stroke. Platelet activation and aggregation are mediated through the cyclooxygenase (COX) 1 isoform. Aspirin, an irreversible inhibitor of COX-1, profoundly inhibits platelet aggregation, prolongs bleeding time, and has been shown to reduce the incidence of serious TCEs in patients presenting with an acute coronary syndrome and in patients with a history of MI, angina pectoris, or stroke. Theoretically, some non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs), which are nonselective inhibitors of both COX-1 and COX-2, could also have an antithrombotic effect via inhibition of platelet activity. In particular, naproxen has been shown to confer clinically important levels of platelet inhibition. In addition, the product circular for naproxen in the United States and other countries states that naproxen reduces platelet aggregation, prolongs bleeding time, and is associated with a risk of bleeding.

For editorial comment see page 1091

The present study used a British population-based clinical database to estimate the risk of an acute major TCE in patients with rheumatoid arthritis (RA) using naproxen relative to those not using naproxen. Patients with RA were selected for study because of the likely high compliance with naproxen therapy.

RESULTS

A total 31614 patients met the study criteria for RA, of whom 14677 (46.4%) were excluded, leaving 16937 patients eligible for the analysis (Table 1). Of these, 809 had a first incident TCE (435 MIs, 27 sudden deaths, 347 cerebrovascular events) and comprised the cases for the analysis.
SUBJECTS AND METHODS

The General Practice Research Database (GPRD) represents a 6% sample of the population of England and Wales from general practices in Britain. Data are collected and recorded according to agreed-on standards and include demographic details, prescriptions, clinical diagnoses, and hospital referrals. Data concerning the use of over-the-counter medications are not available in the database. Data from a practice are incorporated in the GPRD only after that practice has been approved as “up-to-standard.” A number of studies have confirmed the validity of the diagnostic and prescription data contained in the GPRD. The scientific and ethical review group that oversees analyses using the GPRD approved the protocol for the present study.

We used a case-control study design among patients enrolled in up-to-standard GPRD practices. To avoid practices where data might be incompletely recorded, we excluded practices in which 20% or more of the patients had no recorded health care visits. Patients with 1 or more diagnoses consistent with RA and 1 or more prescriptions for an NSAID, a disease-modifying antirheumatic drug (DMARD), or a systemic corticosteroid were eligible for the study. We excluded patients younger than 40 or older than 79 years at study start, those with a previous TCE, and those with medical conditions that might confound the association of interest, including cancer (other than basal cell of the skin), vasculitis, coagulopathy, renal disease, liver failure, or alcohol or drug abuse at any time prior to study start. In addition, we excluded patients with a prescription for flurbiprofen (in-dobufen was not available in Britain during the years studied) or anticoagulants and/or antiplatelet agents (prescription for aspirin at any dosage, clopidogrel bisulfate, ticlopidine hydrochloride, dipyridamole, or heparin) during the year prior to study start. We also excluded patients with such prescriptions 30 days or less prior to their index date.

The primary end point was the first diagnosis of an acute TCE, defined as MI, sudden death, or cerebrovascular event. Cerebrovascular events included stroke, subarachnoid hemorrhage, and subdural hematoma but excluded transient ischemic attack. Since hemorrhagic and ischemic cerebrovascular events cannot always be distinguished clinically nor by the diagnoses in the database, we included both in the primary end point. The date of the first incident end point in a given patient was termed the index date. We matched up to 4 controls to cases by sex, age within 5 years, and medical practice. When no control could be matched within the same practice, we randomly selected controls matched on sex and age from other practices. A control’s index date was the same calendar date as the index date for the matched case.

We sent the general practitioners a questionnaire concerning all exposed cases and a 10% sample of both the unexposed cases and controls to verify the RA and TCE diagnoses in the database. Among the returned questionnaires, the RA diagnosis was confirmed in 80%, 74%, and 77% of the exposed cases, unexposed cases, and controls, respectively. The TCE diagnoses were confirmed in 80% of the exposed cases and in 78% of the unexposed cases.

Exposure to naproxen was based on the timing of prescriptions relative to the index date. Current naproxen use was defined as a prescription with a start date 30 days or less prior to the index date. Past naproxen use was defined as a prescription with an end date more than 30 days but 365 days or less prior to the index date, while no naproxen was no prescription with an end date more than 365 days prior to the index date. Use of NSAIDs other than naproxen was evaluated as a potential confounder in the primary analysis and was considered in secondary analyses as an exposure of interest.

We evaluated and controlled for potential confounders or effect modifiers other than the matching factors as needed in the analysis. These included the calendar year the patient started the study (1988-1991, 1992-1995, 1996-1999); smoking; prescription for DMARD, systemic portions of patients with past and no naproxen use were similar between cases and controls (Table 2). The distributions of age at study start and sex were similar for cases and controls. Cases were more likely to have an earlier study start date, to smoke, to have used systemic corticosteroids, and to have a positive CV risk score, diabetes, and/or other comorbidity.

We also examined the characteristics of patients with current naproxen use compared with those with no naproxen use in the past year. Among cases, current naproxen users were more likely to be 65 years or older (80.8% vs 65.9%) and to use DMARDs (50.0% vs 33.1%), and less likely to use steroids (26.9% vs 33.1%), have a positive CV risk score (46.2% vs 57.2%), or to have a comorbidity (3.9% vs 19.7%). Among controls, current naproxen users were more likely to use DMARDs (43.9% vs 32.5%), less likely to use steroids (18.5% vs 25.1%), and slightly less likely to have a positive CV risk score (40.8% vs 44.1%).

The odds ratios (ORs) (and 95% confidence intervals [CIs]) for current and past naproxen use matched on age, sex, and practice but without adjustment for other potential confounders were 0.57 (0.37-0.88) and 0.90 (0.68-1.19), respectively. The contribution of the 2-way

---

**Table 1. Patient Accounting**

<table>
<thead>
<tr>
<th>No. (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Meeting study criteria for rheumatoid arthritis</td>
<td>31 614 (100.0)</td>
</tr>
<tr>
<td>Total exclusions*</td>
<td>14 677 (46.4)</td>
</tr>
<tr>
<td>Age &lt;40 or &gt;79 y</td>
<td>5385</td>
</tr>
<tr>
<td>Prior thromboembolic event</td>
<td>2088</td>
</tr>
<tr>
<td>Other medical exclusions</td>
<td>2803</td>
</tr>
<tr>
<td>Flurbiprofen, antiplatelet agent, or anticoagulant use</td>
<td>1817</td>
</tr>
<tr>
<td>Patients from practices with &gt;20% no visits</td>
<td>2633</td>
</tr>
<tr>
<td>Other exclusions†</td>
<td>9326</td>
</tr>
<tr>
<td>Eligible for analysis</td>
<td>16 937 (53.6)</td>
</tr>
<tr>
<td>Cases</td>
<td>809 (4.9)‡</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>435</td>
</tr>
<tr>
<td>Sudden death</td>
<td>27</td>
</tr>
<tr>
<td>Cerebrovascular event</td>
<td>347</td>
</tr>
<tr>
<td>Matched controls</td>
<td>2285 (13.5)‡</td>
</tr>
</tbody>
</table>

*Exclusions are not mutually exclusive; patients may have had more than 1 of the listed exclusion criteria.
†For example, missing date of birth, died before study start, problem with study start or end date.
‡Percentage of 16 937 patients eligible for the analysis.

A total of 2285 controls were matched to the 809 cases for the primary analysis. Current naproxen use was seen in 26 cases (3.2%) vs 130 controls (5.7%), while the pro-

---

©2002 American Medical Association. All rights reserved.
The associations of the other drug therapies with all TCEs and MI specifically among patients who did not have prescriptions for naproxen.

To corroborate the results, we repeated the analyses for all TCEs and for MI using a prospective cohort study design. We used similar methods to those in the case-control approach to identify the study cohort and determine the study start and stop dates for each subject. We identified courses of naproxen therapy. We defined the start of a course as the date the prescription was written and the end of a course as the sum of the start date plus the duration of the prescription plus 15 days. For patients with missing data on duration of a prescription, we assigned the median value for the entire study population. We considered a patient to be a current user from the start date for a given course until the earliest of the end date for that course or end of follow-up. If another prescription for naproxen was given before either of these dates, we counted the course of therapy as continuing until the earliest of the end date of the last course without a new prescription or end of follow-up.

Patients may have had more than 1 period of current naproxen use. Following the end of a course of naproxen, we considered a patient a past user until a new course of naproxen began or the end of follow-up, whichever came first. We classified patients without a naproxen prescription from study start until end of follow-up as not exposed to naproxen, and these patients served as the control group for the analysis. For the controls, we assessed the same potential confounders and effect modifiers, as determined by their presence during the year prior to study start, as in the case-control analysis. We conducted a survival analysis using Cox regression models, selecting covariates for analysis and eligibility in the final models in the same manner as in the case-control analysis. We included current naproxen use (yes, no) in the model as a time-dependent variable. We estimated both unadjusted and adjusted risk ratios for current naproxen vs never use, and used a likelihood ratio test to test the null hypothesis that the hazard ratio for current use was 1.0.

The survival analysis in the cohort study yielded similar results, although with some loss of precision. The hazard ratio (95% CI) for the crude association of current naproxen with all TCEs was 0.55 (0.28-1.11); in the final adjusted model it was 0.53 (0.22-1.28). The crude association (95% CIs) of current naproxen use with MI was 0.26 (0.06-1.04); in the final adjusted model it was 0.38 (0.10-1.54).

The results of this study suggest that patients with RA currently using naproxen have a lower risk for TCEs related...
The negative association of TCEs with naproxen use is in the expected direction based on preclinical and pharmacologic data suggesting that naproxen has a strong antiplatelet effect. The present study also did not show an effect of current use of naproxen, nor did it show an effect of current use of diclofenac, which have a less profound effect on platelet activity, nor did it show an effect of current use of non-naproxen NSAIDs combined among patients not using naproxen.

It is possible that the finding of a lower risk of MI with current naproxen use is due to a lower baseline risk of events. We examined the distributions of baseline characteristics of current naproxen users compared with non-
users, and did not find any major differences in baseline risk. Nevertheless, it is possible that there could be residual confounding due to factors not fully accounted for in our analysis.

The definition of RA for this study was based on general practitioner–recorded GPRD codes related to diagnoses and clinical findings commonly found in RA. We validated the RA diagnosis in a sample of the subjects and found that the diagnosis was confirmed in 80%, 74%, and 77% of the exposed cases, unexposed cases, and controls, respectively. In addition, the accuracy of the diagnosis data in the GPRD has been studied previously and found to be acceptable for research purposes.12,13 On repeating the analysis using a more restrictive list of RA diagnoses, we obtained similar results (data not shown), suggesting that the results were not sensitive to the choice of RA diagnostic codes.

Data on actual use of medications and compliance with dosing instructions are not available in the GPRD. However, patients with RA often require long-term daily therapy for pain and inflammation and thus are more likely to be compliant with NSAID regimens than other patients. In addition, we defined current naproxen therapy as a prescription within 30 days, and the use of short prescription time reduces misclassification error.16 The fact that current exposure to naproxen in this study showed a stronger protective effect than did past exposure would seem to corroborate this approach.

The end points in this study were recorded diagnoses related to MI, sudden death, or cerebrovascular events. We validated the end point diagnosis in 80% of the exposed cases and in 78% of the unexposed cases.

Table 5. Conditional Logistic Regression Results of Matched Case-Control Analysis of the Association of Naproxen and Other Drug Therapies With Myocardial Infarction

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naproxen (vs none)†</td>
<td>0.57 (0.31-1.06)</td>
<td>.07</td>
</tr>
<tr>
<td>Past</td>
<td>0.90 (0.60-1.34)</td>
<td>.59</td>
</tr>
<tr>
<td>Naproxen (vs current non-naproxen NSAIDs)‡</td>
<td>0.40 (0.13-1.20)</td>
<td>.10</td>
</tr>
<tr>
<td>Current</td>
<td>1.47 (1.00-2.16)</td>
<td>.05</td>
</tr>
<tr>
<td>Past</td>
<td>1.55 (1.08-2.24)</td>
<td>.02</td>
</tr>
<tr>
<td>Ibuprofen (vs none)‡</td>
<td>0.74 (0.35-1.55)</td>
<td>.41</td>
</tr>
<tr>
<td>Current</td>
<td>0.80 (0.47-1.35)</td>
<td>.42</td>
</tr>
<tr>
<td>Diclofenac (vs none)†</td>
<td>1.68 (1.14-2.49)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Past</td>
<td>1.32 (0.94-1.85)</td>
<td>.10</td>
</tr>
</tbody>
</table>

*Except for comparison of current naproxen use to none, and of naproxen use to non-naproxen (NSAID) use, these analyses were done among patients who were not using naproxen. CI indicates confidence interval.
†Adjusted for calendar year of patient start, systemic corticosteroid use, cardiovascular risk score, and comorbidity.
‡Adjusted for smoking and cardiovascular risk score.
§Adjusted for smoking and systemic corticosteroid use.
¶Adjusted for calendar year of patient start, diabetes mellitus, and comorbidity.

Table 6. Results of Survival Analysis of Prospective Cohort Analysis of the Association of Naproxen Use With All Thromboembolic Events

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naproxen use (vs none)</td>
<td>0.53 (0.22-1.28)</td>
<td>.16</td>
</tr>
<tr>
<td>Past</td>
<td>1.26 (0.88-1.81)</td>
<td>.21</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.57 (0.47-0.69)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age, y (vs age &lt;65 y)</td>
<td>0.40-54</td>
<td>0.22 (0.16-0.29)</td>
</tr>
<tr>
<td>55-64</td>
<td>0.62 (0.50-0.76)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Smoking (vs no)</td>
<td>1.50 (1.22-1.84)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Systemic corticosteroid use (vs none)†</td>
<td>1.37 (1.12-1.67)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>DMARD use (vs none)‡</td>
<td>1.23 (1.02-1.49)</td>
<td>.03</td>
</tr>
<tr>
<td>Positive CV risk score (vs =0)¶</td>
<td>1.76 (1.46-2.13)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*Each factor in the model is adjusted for all others shown. CI indicates confidence interval.
†Patients were classified as using systemic corticosteroids or disease-modifying antirheumatic drugs (DMARD) if they received a prescription 90 days or less but more than 30 days prior to their index date.
‡See the “Subjects and Methods” section for determination of cardiovascular (CV) risk score.
¶See the “Subjects and Methods” section for determination of cardiovascular (CV) risk score.

In addition, others have used similar MI diagnosis lists and confirmed a similar percentage.17 The cause of sudden death, although often not documented, is usually CV disease, and this diagnosis is frequently included in CV outcome studies. The cerebrovascular end points included both ischemic and hemorrhagic diagnoses, despite the fact that an antiplatelet effect of naproxen might protect against the former and increase the hazard for the latter. We included both types because it is sometimes difficult to distinguish the 2 types clinically, and because most such events are ischemic. Nevertheless, we performed a sensitivity analysis restricting cerebrovas-
cular diagnoses to those most likely on inspection of diagnostic codes to reflect an ischemic etiology, and this analysis yielded similar results (data not shown).

Currently, there are a few published studies of a potential antithrombotic effect of naproxen. In a case-control study, Rahme et al18 examined the association of naproxen use and hospitalization for acute MI among elderly Canadian men and women. They found the risk of hospitalization for acute MI to be lower among long-term users of naproxen than among long-term users of other non-aspirin NSAIDs (OR, 0.65; 95% CI, 0.48-0.97). Solomon et al19 performed a case-control study of NSAID use and MI and found that although use of any NSAID was not associated with the outcome, use of naproxen was associated with a reduction in the risk of MI compared with nonusers (OR, 0.84; 95% CI, 0.72-0.98). In a cohort study of new users of nonaspirin NSAIDs, Ray et al20 found that the risk of acute MI among current users of naproxen was essentially the same as among nonusers (RR, 1.03; 95% CI, 0.98-1.08), but somewhat lower than among current users of ibuprofen (RR, 0.83; 95% CI, 0.69-0.98).

In summary, the present study found that patients with RA aged 40 to 79 years who had recently received a prescription for naproxen had a lower risk of TCEs than patients who had not had a prescription for naproxen in the prior year. These results are consistent with the antiplatelet effect of naproxen. Sensitivity analyses, including a cohort analysis, were generally consistent with, but less precise than, the primary results.

Accepted for publication February 14, 2002.

This study was funded by Merck & Co Inc, Whitehouse Station, NJ.

This study was presented at the American College of Rheumatology Annual Scientific Meeting, San Francisco, Calif, November 14, 2001.

Corresponding author and reprints: Douglas J. Watson, PhD, Department of Epidemiology, Merck Research Laboratories, 10 Sentry Pkwy (BL1-7), Blue Bell, PA 19422 (e-mail: watsond@merck.com).

REFERENCES

condition, the major bleeding rate is 6.5% as shown in the ESSENCE study.\(^5\)

Make sure you find out about all ADEs associated with a given drug. Pharmaceutical representatives are delighted to expound the advantages of their products but are reluctant to describe all of the ADEs. In today’s marketplace, all drugs in a class may be assumed to have the same pharmacodynamics, but their individual pharmacokinetics and ADEs are their distinguishing characteristics. If unsure about all of the ADEs, consult with USP Drug Information or ASHP Drug Information, the 2 noncommercial drug data sources that contain information not contained in the drug's labeling.

Richard S. Blum, MD
East Hills, NY
(e-mail: pharmboy@optonline.com)

Dr Blum is affiliated with St Francis Hospital, Roslyn, NY; Long Island University, C. W. Post Campus, New York, NY; and US Pharmacopoeia, Rockville, Md.


Error in Definition. In the Original Investigation by Watson et al titled “Lower Risk of Thromboembolic Cardiovascular Events With Naproxen Among Patients With Rheumatoid Arthritis” in the May 27 issue of the ARCHIVES (2002; 162:1105-1110), the term no naproxen was incorrectly defined. On page 1106, in the third paragraph of the right-hand column of the “Subjects and Methods” section, the correct definition should have read “...no naproxen was no prescription with an end date less than 365 days prior to the index date.”