Selective Cyclooxygenase-2 Inhibition and Cardiovascular Effects

An Observational Study of a Medicaid Population

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Background: The differential effects of selective cyclooxygenase-2 (COX-2) inhibitors compared with nonspecific nonsteroidal anti-inflammatory agents (NSAIDs) on platelet aggregation and prostacyclin/thromboxane balance have led to concerns that COX-2 inhibitors may increase the risk for cardiovascular thrombotic events. Empirical studies have generally been limited to analyses of secondary end points with low event rates in clinical trials and single event rates in observational studies, all of which have come to conflicting conclusions. This observational cohort study examines the cardiovascular risk of COX-2 inhibitors compared with nonspecific NSAIDs in Maryland Medicaid enrollees, a high-risk population.

Methods: Medical and prescription claims were analyzed for noninstitutionalized Medicaid enrollees who received at least a 60-day supply of a COX-2 inhibitor or other prescription NSAID between June 2000 and June 2002 and who did not use these drugs for at least 6 months prior. Naproxen users were excluded. We developed a logistic model of propensity for treatment with COX-2 inhibitors and stratified patients by quintiles of their propensity score. The model adjusted for demographics, indications for COX-2 inhibitors, and cardiovascular risk factors.

Results: The study population comprised 1005 patients using COX-2 inhibitors and 5245 patients using a nonnaproxen NSAID. Of the 6250 patients, 70% were female, 50% were African American, and 30% were older than 50 years. Overall, 12% of the patients had at least 1 cardiovascular thrombotic event after treatment within the follow-up period. The propensity-adjusted odds ratio showed no significant effect of COX-2 inhibitor use on this percentage of patients (odds ratio, 1.09; 95% confidence interval, 0.90-1.33).

Conclusion: We did not find that COX-2 inhibitors increased cardiovascular risk over nonnaproxen NSAIDs in a high-risk Medicaid population.

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ELECTIVE CYCLOOXYGENASE-2 (COX-2) inhibitors have demonstrated improved gastrointestinal tract (GI) safety over traditional nonsteroidal anti-inflammatory drugs (NSAIDs). There is important evidence from clinical trials showing that, compared with traditional NSAIDs, COX-2 inhibitors are associated with a reduced rate of serious GI events such as bleeding, perforation and obstruction, and nuisance symptoms such as dyspepsia, as well as a reduced requirement for concomitant gastroprotective therapies such as proton pump inhibitors. This relative benefit may be related to a lack of COX-1-mediated inhibition of gastric mucous production and a lack of effect on platelet thromboxane production. However, the differential effects of COX-2 inhibitors compared with traditional NSAIDs on platelet aggregation, prostacyclin/thromboxane balance, and inflammatory mediators involved in the development of atherosclerosis have also led to concerns that there is a physiological basis for COX-2 inhibitors to increase the risk for thrombotic events.

Evidence from large prospective clinical trials on cardiovascular risks has been largely limited to secondary observations; those trials were designed to evaluate primarily GI end points. The VIOXX Gastrointestinal Outcomes Research Study (VIGOR) revealed an increased rate of thrombotic events in patients receiving rofecoxib or naproxen (0.4% vs 0.1%). Mukherjee and colleagues assessed the annualized myocardial infarction (MI) rates in the US Physicians Health Study,
the UK Doctors Study, the Thrombosis Prevention Trial, and the Hypertension Optimal Treatment Trial (n = 48,000 patients) and compared these results with the observations in the VIGOR study (n = 8000 patients) and the Celecoxib Long-term Arthritis Safety Study (CLASS) (n = 8000 patients). Their meta-analysis noted an annualized MI rate of 0.52% compared with a higher rate of 0.74% in the VIGOR study with rofecoxib (P = .04 compared with placebo) and 0.80% in the CLASS study with celecoxib (P = .02 compared with placebo). These authors indicated that caution should be used when prescribing COX-2 inhibitors in a population at risk for cardiovascular events.

In contrast, large analyses by Konstam and colleagues have used the results of multiple clinical studies involving rofecoxib and have not demonstrated any increased risk for cardiovascular events comparing COX-2 inhibitors and nonnaproxen NSAIDs. In these analyses, naproxen stood out as being a unique NSAID in that its use was associated with reduced cardiovascular events compared with COX-2 inhibitors and other NSAIDs. Case-control studies have similarly found that naproxen is less likely to be associated with cardiovascular events compared with nonnaproxen NSAIDs. Observational studies have found mixed results when comparing select COX-2 inhibitors, NSAIDs, and naproxen and using acute MI (AMI) solely as an end point.

We elected to research this question with an observational retrospective cohort study of a Medicaid population, largely African American, at increased risk for cardiovascular events because of concomitant illness. Published studies incorporating pooled data analyses may include fewer higher-risk patients and thus are limited in their statistical power about this important subgroup. Many of the observational studies rely on case-control designs. In our cohort study, we evaluate the risk of cardiovascular events with COX-2 inhibitors vs conventional nonnaproxen NSAIDs, controlling for confounders by modeling the propensity to be prescribed a COX-2 inhibitor.

METHODS

POPULATION AND SUBJECT SELECTION

More than 400,000 Medicaid recipients not in institutions or eligible for Medicare are enrolled in 1 of 6 prepaid state-contracted managed care organizations. All encounter and prescription data for enrollees who received at least 1 prescription for an NSAID between January 1, 2000, and June 30, 2002, were retrieved for this study.

New patients with long-term use of COX-2 inhibitors or other NSAIDs were identified as those whose first (index) prescription came at least 6 months after data collection began and who were prescribed at least a 60-day supply over the study period. In the primary analysis, patients who took both a COX-2 inhibitor and another NSAID following their index prescription were classified as COX-2 inhibitor users. In a sensitivity analysis, those COX-2 inhibitor users who had first taken another NSAID were excluded altogether. Patients who had any use of the NSAID naproxen were also identified for separate analyses. The analysis was restricted to patients who were at least 18 years old on January 1, 2001.

STATISTICAL ANALYSIS

To judge the differential treatment effect of COX-2 inhibitors on cardiovascular risk, we must adjust for any differences in the risk profile of the COX-2 inhibitor users. For example, physicians may be more likely to prescribe COX-2 inhibitors to patients with comorbid conditions, especially when prior authorization procedures require such considerations. The differential risk profile may result in potential covariate imbalances attributed to nonrandomized treatment assignment. Such imbalance in covariates may confound the effect of the treatments, causing potential bias in the treatment effect estimates. To minimize bias, we applied the propensity score technique. A model was built to assess the propensity that a given patient will be assigned a COX-2 inhibitor or an NSAID. Because patients can have similar propensity scores but in fact receive different treatments, grouping people with similar scores can provide a basis to observe the treatment effect in individuals with similar risk profiles.

A history of at least 6 months was used to develop a logistic regression model to provide a propensity score for each patient and measure the likelihood of receiving a COX-2 inhibitor as a function of demographics (age, sex, and race), clinical indications, and cardiovascular risk factors. Covariates for clinical indications favoring COX-2 inhibitor use were history of GI problems, osteoarthritis, rheumatoid arthritis, back pain, or acute pain. Cardiovascular risk factors included as covariates were a diagnosis for hypertension, hyperlipidemia, obesity, diabetes, renal problems, and alcohol, tobacco, or other drug abuse. A prior occurrence of the primary outcome variable, a cardiovascular event, was also included. All diagnosis data were derived from the first 3 digits of the primary and secondary codes in the International Classification of Diseases, Ninth Revision (ICD-9) that were recorded in the medical encounter form. The date of diagnosis was taken as the first date of service for the earliest ICD-9 code that qualified the patient as having a given diagnosis (the qualifying ICD-9 codes used for each diagnosis are 531-537, 555-556, 562, 564, 569, and 578 for GI problems; 724-725 for back pain; 714 for rheumatoid arthritis; 715 for osteoarthritis; 716, 719, 726, 727, 729, 844, and 845 for acute pain; 230 for diabetes; 278 for obesity; 272 for hyperlipidemia; 291, 303, and 305 for tobacco, alcohol, or drug abuse; 401-404 for hypertension; and 581-585 for renal problems). Age interactions with each of these variables were also included in the model.

Patients were stratified by quintiles of the distribution of their propensity score. The treatment effect within each stratum was then measured and averaged across strata to estimate the total effect of COX-2 inhibitor treatment on cardiovascular risk. Rosenbaum and Rubin have shown that within each stratum, the distribution of the covariates will be similar enough across treatment groups to remove about 90% of the bias due to the observed covariates. The goodness of fit of the propensity model was evaluated primarily by its ability to balance the covariates, using the standard χ² test, as well as by the logistic model's c and Hosmer-Lemeshow statistic.

The primary outcome for the baseline model was based on the end point first defined by the Antiplatelet Trialists' Collaboration (APTC) to measure the combined risk of cardiovascular and cerebral thrombotic events that may be affected by antiplatelet mechanisms. This end point was selected because it is a broad and validated means of screening that was used in previous studies. It includes cardiovascular, hemorrhagic, and unknown deaths; nonfatal MIs; and nonfatal strokes.

Secondary models allowed for varying the primary outcome. We added events of pulmonary and venous embolism or thrombosis to the APTC end point and, based on established criteria, ran the analysis on the more focused end points of AMI or stroke, respectively (the qualifying ICD-9 codes used for each end point are 410-411, 413-414, 433-438, and 798 for MI).
the combined APTC end point; 410-411, 413-413, 433-438, 452-453, and 798 for APTC + pulmonary and venous embolism or thrombosis; 410 for AMI; and 430-436 for stroke).

One-way sensitivity analyses were conducted to explore the robustness of results to different sample selection criteria regarding age and prior treatment use. We conducted separate analyses for rofecoxib and celecoxib. Despite the lack of data for over-the-counter drugs, specifically aspirin, we ran an analysis adjusting for the available data on prescription aspirin use in view of the evidence that ibuprofen use could attenuate the antiplatelet benefit of aspirin.1 All statistical analyses were performed with SAS version 8.2 software (SAS Institute, Cary, NC).

### RESULTS

#### SAMPLE CHARACTERISTICS

More than 97 000 patients had at least 1 prescription for an NSAID between January 1, 2000, and June 30, 2002. Of these, 64 053 had no use during the 6 months prior to June 15, 2000. Those 10 677 patients whose prescriptions totaled at least a 60-day supply prior to an occurrence of the primary outcome were retained for analysis. About 41% had taken at least some naproxen during the period and were set aside for separate analysis, leaving a net of 6250 nonnaproxen NSAID-treated patients for the primary analysis, 1005 of whom used a COX-2 inhibitor and 5245 of whom only used some other NSAID. Of the 6250 patients, 70% were female, 50% were African-American, and 30% were older than 50 years. The overall rate of cardiovascular thrombotic events was 12%.

Table 1 displays the baseline characteristics by the type of NSAID user. Both groups were at high risk for a variety of ailments, as would be expected from an adult population seeking chronic pain relief. Besides being predominantly female, adult Medicaid populations tend to have more morbidities, including cardiovascular disease, compared with the general population.26 For example, 56% of the COX-2 inhibitor users and 40% of other NSAID users had hypertension. Compared with the NSAID users, COX-2 inhibitor users tended to be older and twice as likely to have common indications in clinical practice for preferring COX-2 inhibitor use (eg, GI problems, osteoarthritis, back pain, or other acute pain). They were 7 times as likely to have rheumatoid arthritis; had about a 50% higher rate of prior cardiovascular risk factors of hypertension, diabetes, hyperlipidemia, obesity, and renal problems; and their rate of tobacco, alcohol, and drug abuse was lower—perhaps an association with their higher age profile.

### ADJUSTMENT FOR CONFOUNDING

To adjust for comorbid conditions at baseline, a propensity model predicting COX-2 inhibitor treatment as a logistic function of all the covariates given in Table 1 was developed. Age was a continuous variable; all other variables were binary. All the COX-2 inhibitor indications were significant at the .05 level, as was age. Prior occurrence of a cardiovascular event had a P value of .10. The other variables and their interaction with age were retained to minimize bias in the coefficients. Two measures of goodness of fit were at acceptable levels: the c statistic, or area under the receiver operating characteristic curve, was 0.78, and the Homer-Lemeshow test had a P value of .24. The resulting model was used to compute an estimated probability of COX-2 inhibitor treatment for each individual—this is known as the propensity score.

Table 2 shows how the risk factors are distributed in our sample across treatment groups after they have been stratified by quintiles of the propensity score. Note that the covariates have largely been balanced across treatment within each stratum; thus, a stratified analysis would remove their confounding effect. For example, in stratum 5, 22% of the COX-2 inhibitor users and 20% of the other NSAID users had a prior qualifying cardiovascular event. In the lower strata (ie, those including patients who are less likely to be prescribed COX-2 inhibitors), a relatively smaller proportion of patients had a prior qualifying cardiovascular event. For example, in stratum 2, only 2% of the COX-2 inhibitor users and 1% of the NSAID users had such a prior cardiovascular event. The χ² tests of equality show significant differences (P<.05) only in 1 stratum each for age, rheumatoid arthritis, osteoarthritis, GI problems, and hyperlipidemia.

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Table 1. Baseline Characteristics by Type of NSAID User

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>COX-2 Inhibitor (n = 1005)</th>
<th>Other NSAID, Excluding Naproxen (n = 5245)</th>
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Abbreviations: APTC, Antiplatelet Trialists’ Collaboration; COX-2, selective cyclooxygenase-2; NSAID, nonsteroidal anti-inflammatory drug.

*Data are given as percentage of patients.
†Rows do not sum to 100% because patients can have multiple indications and cardiovascular risk factors. Percentages by age and race are mutually exclusive and add to 100%.
In each case, the difference is in the direction of higher baseline risk for the COX-2 inhibitor users.

### TREATMENT EFFECT

The propensity-adjusted treatment effect is given in Table 3, averaging the Mantel-Haenszel variance-weighted stratum-specific estimates (shown as “unadjusted rate of primary outcome” in Table 2). In our baseline model comparing nonnaproxen NSAID users receiving at least a 60 days’ supply of medication, COX-2 inhibitors do not significantly increase the risk of a cardiovascular event compared with other NSAIDs (odds ratio [OR], 1.09; 95% confidence interval [CI], 0.90-1.33). If the NSAID sample
is expanded to include those who also had previously used naproxen, the COX-2 inhibitor group's additional risk would then be slightly higher, but not statistically significant (OR, 1.14; 95% CI, 0.96-0.35).

Of the 1005 COX-2 inhibitor users who had not taken naproxen, 273 had taken more than a 59 days' supply of another NSAID, possibly counteracting a risk from COX-2 inhibitor use. When they are excluded from the analysis, there still is no significant difference in cardiovascular risk (OR, 1.11; 95% CI, 0.90-1.38), as shown in Table 3, indicating that the results are insensitive to the multiple exposure.

One-way sensitivity analyses varying the cardiovascular events included in the primary outcome were also performed. If the APTC definition of the primary end point was expanded to also include events of pulmonary and venous embolism or thrombosis, the estimated COX-2 inhibitor effect was similar and not significant (OR, 1.14; 95% CI, 0.94-1.36). We also found no significant differences when the definitions of the primary end point were narrowed to AMI (OR, 1.12; 95% CI, 0.67-1.85) or to stroke (OR, 1.15; 95% CI, 0.85-1.54).

When focusing on those with rofecoxib as their index drug, we did not find a statistically significant difference between rofecoxib and the other NSAIDs (OR, 0.99; 95% CI, 0.76-1.30). This was also true for celecoxib (OR, 1.19; 95% CI, 0.93-1.51). Excluding prescription aspirin use from the model, results were similarly not significant (OR, 1.10; 95% CI, 0.90-1.33).

The results were not sensitive to whether COX-2 inhibitor users had previously taken another NSAID, which is allowed in the baseline model. We also tried restricting the sample to those patients older than 40 years and found little effect on our conclusions (results not shown).

The results of this analysis do not show a difference in the rate of cardiovascular events between COX-2 inhibitors and nonnaproxen NSAIDs. Given that the study population had higher baseline cardiovascular risk, these observations provide more confidence that the widespread use of COX-2 inhibitors will not be associated with an increase in thrombotic or coronary artery events. This is particularly important because NSAIDs are often used in older, higher-risk patients.

Our results do not contradict the large case-control studies that have identified long-term naproxen-treated patients as having a reduced rate of cardiovascular events compared with nonnaproxen-treated patients.12-14 An observational study of older Tennessee Medicaid enrollees, which compared those using any NSAID (whether naproxen or other) with those using none, found no difference in AMI and coronary heart disease death rates.27 A limitation of this study was the nondifferentiation between naproxen and other NSAIDs; therefore, the cardioprotective quality of naproxen was not assessed. In our study, we measured cardiovascular risk in the NSAID group with and without naproxen and found a near significant effect. The lack of a stronger protective effect for naproxen could be explained by the inclusion of inter-

In a follow-up to the Tennessee study, Ray et al15 compared AMI and heart disease rates of NSAID-treated patients with non-NSAID-treated patients. They found no increase in event rates per person-year for those who used each of the following: ibuprofen, naproxen, rofecoxib (dosed at ≤25 mg, the maximum recommended for >5 days of use), or celecoxib. They did, however, find a statistically significant increase for those receiving more than 25 mg of rofecoxib. Although they did not report NSAID-to-NSAID comparisons, their results are consistent with those in our study. The 2 studies complement each other in that their study defines more distinct levels of exposure, whereas we compare patients who are more similar to each other in that they all have been prescribed an NSAID. More recent observational studies of older adults have found mixed results—an elevated risk of AMI associated with rofecoxib17 or no increased risk of AMI with either COX-2 inhibitor.26

Our study is limited by the lack of data on over-the-counter use of aspirin, naproxen, or ibuprofen and by there being no prescription records for low dosages available over the counter. These over-the-counter users were not reimbursed by the state Medicaid program. From our data, we found relatively low aspirin use (0.7%) and no significant effect on cardiovascular risk. One previous study has specifically looked at whether over-the-counter use of NSAIDs (and smoking) biases models of MI risk and prescription NSAIDs.28 They found celecoxib users reporting less frequent aspirin use and concluded that the joint confounding effect of aspirin and smoking on the risk of MI would bias estimates of relative risk by no more than 6%.

We tested the sensitivity of the results to definitions expanded to include pulmonary and venous, embolic, or thrombotic events in addition to the combined APTC end point. We noted that the impact of the COX-2 inhibitors was not significant. Moreover, we obtained similar results when definitions were narrowed to AMI or stroke. We did not find a statistically significant difference between rofecoxib and celecoxib, though we may be limited in power by our sample size. Our results were insensitive as to whether COX-2 inhibitor users had previously taken another NSAID. Likewise, restricting our sample to those patients older than 40 years had little effect on our conclusions.

Our observational study adds to the evidence from clinical trials by analyzing a larger, higher-risk cohort in “real world” treatment. Despite the higher power resulting from the higher event rates, we still did not find cardiovascular risk associated with COX-2 inhibitor use. We add to the insights from other observational studies by adjusting for the propensity to be prescribed a COX-2 inhibitor.29 Compared with directly adjusting for the confounders in a single logistic model of risk, stratifying on quintiles of the propensity score allowed us to check for sufficient overlap between the treatment and control groups on the covariates to build an adequate model. Such overlap is necessary for either technique, but it is more transparent in the propensity method. Similar to pro-
penity scoring, another method is to first model a cardiovascular risk score as a function of several confounders and then use it as a single covariate in the final risk model. Propensity scores have the advantage of also including adjustment for variables related to treatment assignment (such as GI indications), which may also be related to the treatment outcome.

In conclusion, our observations of a high-risk cohort, which are adjusted for confounding by indication, provide additional information that COX-2 inhibitor use has no detrimental effect on the risk for cardiovascular events compared with nonnaproxen NSAIDs.

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