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Subgroup Analyses to Determine Cardiovascular Risk Associated With Nonsteroidal Antiinflammatory Drugs and Coxibs in Specific Patient Groups

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Abstract

Objective—To explore the extent to which clinical characteristics influence the association between cyclooxygenase 2 inhibitors (coxibs) and/or nonselective nonsteroidal antiinflammatory drugs (NSAIDs) and increased cardiovascular disease (CVD) risk in specific patient subgroups. There is substantial concern regarding the potential cardiovascular adverse effects of selective coxibs and nonselective NSAIDs, but many patients with arthritis experience important clinical benefits from these agents.

Methods—The study population consisted of Medicare beneficiaries also eligible for a drug benefits program for older adults during the years 1999–2004. We calculated the relative risk (RR) for CVD events (myocardial infarction [MI], stroke, congestive heart failure, and cardiovascular death) among users of coxibs or nonselective NSAIDs in the prior 6 months compared with nonusers. We assessed biologic interaction between these medication exposures and important patient characteristics.

Results—In the primary cohort, we identified 76,082 new users of coxibs, 53,014 new users of nonselective NSAIDs, and 46,558 nonusers. Compared with nonusers, the adjusted RR of CVD events for new users of each agent increased for rofecoxib (RR 1.22, 95% confidence interval [95% CI] 1.14, 1.30) and decreased for naproxen (RR 0.79, 95% CI 0.67, 0.93). Several patient characteristics were found to increase the risk of CVD events among users of some agents in both the primary and secondary cohorts, including age ≥80 years, hypertension, prior MI, prior CVD,

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AUTHOR CONTRIBUTIONS

Dr. Solomon had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study design. Solomon, Schneeweiss, Setoguchi, Avorn, Stürmer.

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rheumatoid arthritis, chronic renal disease, and chronic obstructive pulmonary disease. Rofecoxib and ibuprofen appeared to confer an increased risk in multiple patient subgroups.

Conclusion—Many nonselective NSAIDs and coxibs are not associated with an increased risk of CVD events. However, several patient characteristics identify important subgroups that may be at an increased risk when using specific agents.

INTRODUCTION

Since the withdrawal of rofecoxib and valdecoxib, concerns have been raised about the cardiovascular safety of other selective cyclooxygenase 2 inhibitors (coxibs) and the nonselective nonsteroidal antiinflammatory drugs (NSAIDs) (1–4). These concerns prompted the US Food and Drug Administration to require that a black-box warning be placed on all coxibs and nonselective NSAIDs, including warnings on over-the-counter agents (5). These agents are effective analgesics and are used by millions of patients for arthritis and other painful conditions. Few large, randomized controlled trials involving these agents have measured cardiovascular outcomes, leaving patients and physicians unsure of how dangerous these agents really are and whether all patients are at risk (6). It is possible that subgroups of patients are at a substantially increased risk for cardiovascular events when using these agents, while others are not. Such questions require a focused investigation into the effects of these agents within subgroups.

Subgroup analyses often meet with skepticism if the subgroups of interest are identified from the data without prior hypotheses. In contrast, although skepticism is reasonable, one can argue that the investigator has a responsibility to investigate and identify potentially important patient differences in susceptibility. Adverse effects of treatments may be concentrated in subgroups of patients who can be identified using clinical information. For example, information on the risk of adverse effects within subgroups classified according to age, sex, prior clinical conditions, or concomitant medications would likely be useful for patients and their doctors. Nevertheless, conducting subgroup analyses in the setting of a randomized controlled trial is problematic, as these studies are usually planned to estimate overall effects across all enrolled patients rather than to estimate effects within smaller subsets of patients. Thus, randomized trials usually provide estimates of effects within subgroups that are imprecise, i.e., have wide confidence intervals. In contrast, pharmacoepidemiologic databases drawn from health care utilization information comprise large populations that can provide more precise estimates within subgroups. Biases can be controlled by using available information about comorbid illnesses and concomitant medication use. The skepticism that often accompanies subgroup analyses is still appropriate for database studies, but in trials, much of the problem stems from the small size of subgroups, a problem that is mitigated in database studies. Nevertheless, as usual, it is reasonable to consider all subgroup findings tentative until evaluated with and confirmed by other data. Accordingly, we explored 2 pharmacoepidemiologic databases to evaluate the extent to which subgroups of older adults experience an increased risk of cardiovascular outcomes when using coxibs or nonselective NSAIDs.

PATIENTS AND METHODS

Study design

We examined the magnitude of interaction between patient characteristics and exposure to coxibs or nonselective NSAIDs. The effects of specific drugs within subgroups in one cohort (primary) were then investigated in a second cohort (secondary). Both cohorts were assembled, using identical methods, as longitudinal cohorts consisting of new users of coxibs or nonselective NSAIDs. As we have done previously (7), these exposure groups were compared with patients who did not use a coxib or nonselective NSAID, but who did initiate use of unrelated agents for the treatment of hypothyroidism or glaucoma. Using a comparator group with health-seeking characteristics similar to coxib and nonselective NSAID users improved the comparability of these groups. Exposure status was assessed on a daily basis from pharmacy dispensing records. We calculated incidence rates for cardiovascular disease (CVD) events in the total cohort and among specific subgroups. In addition, we estimated agent-specific rate ratios using Cox proportional hazards models that controlled for baseline demographic factors, cardiovascular risk factors, and health care utilization variables.

Study cohorts

Patients in the study cohorts were beneficiaries of US Medicare and 1 of 2 drug benefit programs: the Pharmaceutical Assistance Contract for the Elderly (PACE) in Pennsylvania (primary cohort) or the Pharmaceutical Assistance for the Aged and Disabled (PAAD) program in New Jersey (secondary cohort). Both drug benefit programs pay for all medications, including coxibs and nonselective NSAIDs, with a copayment between $6 and $10 (US dollars). No restrictions on coxib use were in effect during the study period until September 2004 when rofecoxib was voluntarily withdrawn from the market. Data obtained from the drug benefit programs included drug name, dose, days supplied, quantity dispensed, and date of dispensing. We linked these data to information from Medicare, including all inpatient and outpatient clinical encounters, diagnoses, procedure codes, and diagnosis-related groups. Linking was performed through unique health identification codes that were removed from the study database before analyses were conducted.

Patients were eligible for the study cohort if they had been concomitantly enrolled in Medicare and one of the pharmacy benefit programs for at least 12 continuous months during 1999–2003. To be considered a user of a coxib or nonselective NSAID, patients had to have 180 days prior to the study without use of any such agent. During this period and the 6 months before it, patients must have been active system users, defined as filling at least 1 prescription and making at least 1 Medicare claim during this baseline period. The date of the first coxib or nonselective NSAID prescription after fulfilling this requirement was considered the index date. A similar definition was applied to the comparison (reference) group, whose members were required to have initiated use of thyroid hormone or a medication for glaucoma. We required use of these other agents to ensure similar health care system use between the active drug users and the reference group. Neither treatment for hypothyroidism nor glaucoma medication was anticipated to have an important effect on cardiovascular events.

The period of initial use ended with any of the following events: a gap between prescriptions for the drugs of interest for >15 days, initiation of another coxib or nonselective NSAID, a CVD event, death, or loss of eligibility in PACE. Patients were eligible to initiate use again if they stopped filling a medication of interest for at least 6 months but remained active system users. Such cohort reentry was rare. When it occurred, we considered it a new observation with redefinition of covariates. Similar criteria were applied to the comparison group.

Data use agreements are in place with the PACE program, the PAAD program, and the Center for Medicare and Medicaid Services. The Brigham and Women's Hospital Institutional Review Board approved the study protocol.

Exposures of interest

Coxib use included the 3 coxibs available in the US during the study period: celecoxib, rofecoxib, and valdecoxib. Nonselective NSAID use included prescription oral preparations of diclofenac, ibuprofen, naproxen, and a composite of all other available oral NSAIDs, excluding aspirin. No information on over-the-counter medications, including aspirin, is available in either pharmacy database. We assessed longitudinal exposure for the agents of interest on a daily basis starting with the index date. We considered patients to be continuous users of a drug if there was no gap longer than 15 days between successive prescription periods for the same agent. Different doses of coxibs and nonselective NSAIDs were not considered in these analyses.

Cardiovascular disease events

The primary study outcome was a composite of CVD events: hospitalization for myocardial infarction (MI), stroke, or congestive heart failure (CHF), or out-of-hospital death attributable to CVD. We created a composite outcome because all of these individual end points represent important clinical events that have been shown to be potentially related to coxibs or nonselective NSAIDs. MI and stroke can be accurately defined in a health care utilization database using claims algorithms; we have previously shown a positive predictive value of at least 94% for the MI codes used in this study using primary medical records, and other researchers have shown similar accuracy for the stroke and CHF algorithms (8–10).

We developed the coding algorithm for out-of-hospital death attributable to CVD in a substudy in which we compared the patient's cause of death from the death certificate with information from a variety of coding algorithms based on health care claims. We chose a coding algorithm for use in this study that required patients to have had a hospital diagnosis or outpatient diagnosis for CVDs including coronary artery disease, CHF, hypertensive heart disease, cardiac valve disease, or cardiomyopathy within 6 months of death. Patients were not allowed to have had a diagnosis of cancer or human immunodeficiency virus within 1 month of death. This algorithm had a specificity of 95% and a sensitivity of 75%.

Subgroups and covariates

Before the analyses, we identified a group of patient characteristics that might define important subgroups in which the effects of coxibs and/or nonselective NSAIDs on CVD

events may be modified. Factors tested as potential subgroups included age, sex, prior MI, prior CHF, prior stroke, prior CVD (including MI, CHF, and stroke), hypertension, diabetes, any CVD risk factor (including hypertension, diabetes, or hyperlipidemia), chronic renal disease, rheumatoid arthritis (RA), chronic obstructive pulmonary disease (COPD), use of a statin, and use of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker. These subgroups were chosen based on a review of the literature regarding coxibs, nonselective NSAIDs, and CVD (11,12). These same patient characteristics were also considered as covariates in multivariable regression models. Other covariates included in regression modeling included health care utilization information, the year of index date (first coxib or nonselective NSAID prescription), coronary revascularization, carotid revascularization, peripheral vascular disease, and use of clopidogrel. We included an adaptation of the Charlson comorbidity index (13) and diagnoses for osteoarthritis and malignant neoplasm in all models. These subgroups and covariates were defined based on data from the 6 months preceding each patient's index date. Restricting these baseline values to what was available during these 6 months omitted some available information, but ensured equal ascertainment of data for all patients.

Statistical analyses

All analyses were initially conducted in the primary cohort and then repeated in the secondary cohort. We began by assessing characteristics of patients by exposure status during the 6-month baseline period. The end points were then defined, allowing us to calculate person-years and event rates for each exposure group. The event rates were not constant but were proportional by exposure and assessed graphically. Thus, we used Cox proportional hazards regression to estimate the relative risk (RR) of CVD events as the hazard ratio (HR) and 95% confidence interval (95% CI) for each study exposure in the total population of patients. The Cox regression accounted for the amount of time a patient was treated with a drug by only comparing groups of patients with similar exposure periods. Because valdecoxib was only available during 2002 and 2003, we stratified models by study year. This helped control for temporal trends in prescribing. We included all covariates in each model. No adjustments were made for multiple comparisons because these analyses were exploratory in nature and we had no joint hypothesis (14–16).

To assess the possibility of an increased risk of CVD events among specific patient subgroups using specific coxibs and/or nonselective NSAIDs, we examined the interaction between patient characteristics and these agents. We assessed (positive) biologic interaction, considered to be an excess over additivity of effects, by calculating the attributable proportion of risk from interaction, hereafter referred to as the attributable proportion (AP) (17,18). The AP refers to the proportion of risk for a given outcome among patients with both exposures of interest (one of the drugs of interest and one of the patient characteristics) that is due to the interaction between exposures. The AP is calculated as the relative excess risk from the interaction divided by the RR in persons with both exposures of interest: $AP = [RR_{AB} - (RR_A + RR_B - 1)]/RR_{AB}$, where A and B are 2 patient characteristics. Values close to zero suggest no interaction, values above zero suggest a positive interaction, and values below zero suggest a negative interaction (19); these analyses focus on positive interactions only. We first assessed the AP for each patient subgroup using a coxib or nonselective

NSAID in the primary cohort and then repeated these calculations in the secondary cohort. Interactions in which the AP values were in the top tertile in both cohorts were considered important. The patient subgroups forming these important interactions were further examined by calculating the subgroup-specific incidence rates for CVD events. We also examined statistical interaction, an excess over a multiplicative relationship of relative effects, using full Cox proportional hazards regression models with 1 interaction term added per model. All analyses were run in SAS software, version 8.0 (SAS Institute, Cary, NC).

RESULTS

We identified 76,082 new users of coxibs, 53,014 new users of nonselective NSAIDs, and 46,558 nonusers in the primary cohort (Table 1). There were no substantial differences between patients who used one of these agents and nonusers, except that nonusers were generally less likely to have been diagnosed with osteoarthritis or RA. The mean age of the cohort was 80 years, and most were white women. Cardiovascular comorbid conditions were common across all exposure groups. The baseline characteristics of the secondary cohort were quite similar (data not shown).

The primary cohort experienced 7,262 CVD events during the 64,136 person-years of followup (Table 2). The incidence rates for these events varied substantially across exposure groups, with rofecoxib users experiencing the highest rates (14.7 per 100 person-years), naproxen users experiencing the lowest rates (8.5 per 100 person-years), and nonusers midway between the 2 (11.2 per 100 personyears). The adjusted HRs from Cox proportional hazards models also showed this pattern: rofecoxib associated with an elevated risk (HR 1.22, 95% CI 1.14, 1.30) and naproxen with a reduced risk (HR 0.79, 95% CI 0.67, 0.93) compared with nonusers. This pattern was similar in the secondary cohort (data not shown).

We calculated the AP of risk from interaction in the primary and secondary cohorts. We found 7 patient characteristics for which the point estimate of the AP was in the upper tertile in both cohorts (the confidence intervals for some of these APs typically extended below the upper tertile). These patient characteristics included age ≥80 years (AP with ibuprofen 0.22; 95% CI 0.05, 0.39), hypertension (AP with nonselective NSAIDs 0.13; 95% CI −0.05, 0.31), prior MI (AP with ibuprofen 0.25; 95% CI −0.02, 0.53), prior CVD (AP with ibuprofen 0.22; 95% CI 0.01, 0.43), RA (AP with valdecoxib 0.12; 95% CI −0.53, 0.77), chronic renal disease (AP with other nonselective NSAIDs 0.28; 95% CI 0.09, 0.46), and COPD (AP with ibuprofen 0.19; 95% CI −0.04, 0.41) (see Appendix A).

We then compared the incidence rates by agent for each of these patient subgroups (Table 3). Rofecoxib and ibuprofen users in many of the subgroups experienced substantial increments in CVD events compared with nonusers. For example, among patients age ≥80 years, rofecoxib users experienced 4.8 more events per 100 personyears and ibuprofen users experienced 3.4 more CVD events than nonusers. Among patients with a prior MI, rofecoxib users sustained 9.4 more CVD events and ibuprofen users 11.4 more events per 100 person-years compared with nonusers. As expected, many factors associated with a relatively strong interaction in the primary cohort were associated with a weaker interaction in the secondary cohort.

DISCUSSION

We examined the extent to which the cardiovascular risk associated with coxibs and/or nonselective NSAIDs is elevated in specific patient subgroups. In studying 2 separate epidemiologic cohorts of older adults starting treatment with these agents, we found that age ≥80 years, hypertension, prior MI, prior CVD, RA, chronic renal disease, and COPD identified subgroups of patients with an elevated risk for cardiovascular events when using certain coxibs or nonselective NSAIDs. These interactions were relatively specific between given agents and patient characteristics, and the increment in absolute risk was large among specific patient subgroups. Agents that appeared to confer consistently higher risks across a variety of subgroups included rofecoxib and ibuprofen. As expected, and illustrating the utility of having a secondary cohort, we found that many of the interaction effects that were strong in the primary cohort were much weaker in the secondary cohort.

Subgroup analyses are potentially valuable to the extent that they can inform clinicians about how study results apply to particular types of patients. However, because subgroup analyses necessarily involve fewer data than an overall analysis of a study, they lead to estimates that are less precise and inferences that are more error prone than an overall analysis. The present results, like nearly all analyses of interactions, should be viewed as tentative. We did, however, specify the groups of interest a priori, and we sought estimates from 2 separate cohorts in an attempt to balance the limitations of subgroup analyses. Both cohorts were heavily weighted with frail, elderly patients, and thus our findings may not apply to younger and healthier adults.

We used the AP as the primary measurement of interaction (19). This measure estimates the proportion of the combined effect of the 2 primary factors that represents an excess over additivity of their separate effects (on either a relative or absolute scale). Excess over additivity corresponds more closely to a biologic measure of interaction than does the traditional statistical interaction term, which is a departure from multiplicative effects (17,20). Unlike the usual product terms in multiplicative models, the AP has a real interpretation (i.e., the proportion of disease burden caused by interaction between the factors).

Several important limitations are inherent in our methods. The data set comprised information from older, low-income adults, many of whom are frail. Although their results may not generalize to all patient populations, coxibs and nonselective NSAIDs are widely used in older adults who are frail from arthritis. We were not able to determine what medications, including over-the-counter nonselective NSAIDs and aspirin, patients used on a daily basis because we relied on pharmacy claims information. There may have been some patients who filled prescriptions but did not use the medications or patients who obtained drugs from other sources without filling prescriptions in the database. Additionally, we did not have information on important potential confounders, such as aspirin use, tobacco use, and body mass index. It is possible that the elevated cardiovascular risk we observed between ibuprofen use and prior CVD may be due to the negation of the benefits of aspirin among continuous ibuprofen users (21). Without information on aspirin, we were unable to explore this possibility. Confounders may substantially bias results in nonrandomized study

designs such as ours. Based on prior work on this topic, we believe that this bias is small and in the direction of the null (22). By choosing a comparison group comprising new users, we were able to control indirectly for health system utilization.

We also chose not to pursue dose-specific analyses among subgroups. This decision was based on an overarching concern to conduct as few comparisons as possible in the context of this project, which, by its nature, involved multiple comparisons. Furthermore, there were few patients receiving high doses of coxibs, i.e., only 42 patients received >400 mg of celecoxib per day. Dose comparisons, however, may be interesting for future subgroup analyses. In addition, we focused solely on positive interactions to further reduce the number of results that would have to be compared.

Our findings have potential clinical relevance. The additive interaction and stratified analyses suggest that rofecoxib and ibuprofen are the only agents consistently associated with an increased risk for CVD events among specific patient subgroups. While the interaction measures were imprecise enough to preclude conclusive inferences, the estimated magnification of risk among patients with RA taking rofecoxib in the primary cohort is particularly interesting in light of prior findings from the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial (23). The fact that we did not observe a similar concentration in risk among subgroups of patients using many of the other agents may be of even greater relevance. These results should bolster physicians' and patients' confidence that most coxibs and nonselective NSAIDS are not associated with an elevated risk of CVD events in many patient subgroups using typical doses.

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Pfizer reviewed and commented on the research protocol and a draft of the manuscript. Otherwise, they had no role in this work. The authors had full access to all of the study data.

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Table 1

Baseline characteristics of study participants from Pennsylvania (primary cohort) during the 6 months prior to initiating medication *

Patient characteristics	Celecoxib	Rofecoxib	Valdecoxib	Diclofenac	Ibuprofen	Naproxen	Other nsNSAIDs†	Nonusers‡
No.	40,865	27,675	7,542	4,141	11,796	10,228	26,849	46,558
Age, mean ± SD years	80 ±7	80 ± 7	80 ± 7	78 ± 7	78 ± 7	78 ± 7	80 ± 7	80 ± 7
Female sex	86	87	87	85	83	83	82	86
White race	95	96	96	93	87	90	93	94
Hospitalized	21.3	22.8	17.6	15.4	20.7	15.5	16.5	24.1
Nursing home resident	5.8	6.0	4.4	2.8	4.5	2.7	3.2	6.9
Physician visits, mean ± SD	5 ± 4	5 ± 4	5 ± 4	5 ± 4	5 ± 4	4 ± 4	5 ± 4	5 ± 4
Different medications, mean ± SD	7 ± 4	7 ± 4	7 ± 4	6 ± 4	7 ± 4	6 ± 4	7 ± 4	6 ± 4
Myocardial infarction	4.9	4.9	4.4	3.9	4.6	3.9	4.9	6.4
Congestive heart failure	5.1	5.2	3.8	2.9	4.3	3.1	4.4	6.5
Coronary revascularization	0.8	0.9	0.6	0.7	1.0	0.7	0.8	1.3
Angina	7.7	7.7	5.9	7.2	7.6	6.6	7.1	7.9
Diabetes	13.4	13.4	14.9	12.8	14.7	14.0	15.8	13.1
Hypertension	56.9	56.9	61.5	54.8	56.2	55.9	58.7	53.0
Hyperlipidemia	36.7	37.6	47.4	38.7	36.4	40.7	39.9	40.8
Statin use	25.6	26.7	32.0	25.9	26.5	28.8	28.4	25.2
Clopidogrel use	5.9	6.6	8.6	4.1	5.4	5.2	5.7	6.7
Peripheral vascular disease	8.3	8.3	8.2	6.6	7.1	6.6	7.6	9.0
Stroke	5.5	5.7	6.7	3.5	4.9	4.8	5.3	7.3
Carotid revascularization	0.2	0.2	0.2	0.1	0.2	0.2	0.2	0.2
Chronic renal disease	2.6	2.9	2.9	1.7	2.8	2.4	3.6	5.0
Rheumatoid arthritis	2.4	1.7	2.5	1.6	1.1	1.0	1.4	1.7
Osteoarthritis	22.0	20.2	26.5	18.4	12.4	12.3	13.6	13.9
Malignancy	2.1	2.2	1.7	1.4	2.8	1.9	1.7	2.5
Comorbid conditions, mean ± SD	2 ± 2	1 ± 2	2 ± 2	2 ± 2	1 ± 2	2 ± 2	1 ± 2	2 ± 2

* Values are the percentage unless otherwise indicated. nsNSAIDs = nonselective nonsteroidal antiinflammatory drugs.

† Other nsNSAIDs include diflunisal, etodolac, fenoprofen, flurbiprofen, indomethacin, ketoprofen, ketorolac, meclofenamate, mefenamic acid, meloxicam, nabumetone, oxaprozin, piroxicam, sulindac, and tolmetin.

‡ Nonusers include new users of glaucoma medications and thyroid hormones.

Table 2

Cardiovascular outcomes among Pennsylvania Medicare beneficiaries (primary cohort) who recently initiated a selective cyclooxygenase 2 inhibitor or nsNSAID*

	Events†	Person-years	Incidence rate per 100 person-years (95% CI)	Adjusted hazard ratio (95% CI)‡
Celecoxib	1,630	15,242	10.7 (10.2, 11.2)	0.89 (0.83, 0.94)
Rofecoxib	1,314	8,936	14.7 (13.9, 15.5)	1.22 (1.14, 1.30)
Valdecoxib	215	2,317	9.3 (8.1, 10.6)	0.86 (0.75, 0.99)
Diclofenac	92	987	9.3 (7.5, 11.4)	0.91 (0.74, 1.13)
Ibuprofen	209	1,784	11.7 (10.2, 13.4)	0.96 (0.83, 1.10)
Naproxen	162	1,904	8.5 (7.2, 9.9)	0.79 (0.67, 0.93)
Other nsNSAID§	533	5,122	10.4 (9.5, 11.3)	0.87 (0.79, 0.96)
Nonusers	3,107	27,844	11.2 (10.8, 11.6)	Reference

*nsNSAID = nonselective nonsteroidal antiinflammatory drug; 95% CI = 95% confidence interval.

†Includes the cardiovascular outcomes such as myocardial infarction, stroke, congestive heart failure, and out-of-hospital death attributable to cardiovascular disease.

‡Adjusted hazard ratios from Cox proportional hazards models including all variables in Table 1.

§Other nsNSAIDs are listed in Table 1.

Table 3

Cardiovascular disease event rates for patient subgroups of interest among the primary cohort*

	Age ≥ 80 years	Hypertension	Prior myocardial infarction	Prior cardiovascular disease†	Rheumatoid arthritis	Chronic renal disease	Chronic obstructive pulmonary disease
Celecoxib	13.5 (12.7, 14.3)	11.4 (10.7, 12.1)	25.5 (21.8, 29.6)	20.6 (18.7, 22.6)	9.7 (7.0, 13.2)	27.3 (21.9, 33.6)	17.2 (15.6, 18.8)
Rofecoxib	19.2 (18.0, 20.5)	16.7 (15.5, 17.8)	42.0 (35.8, 49.1)	30.9 (27.9, 34.1)	18.9 (12.9, 26.6)	40.6 (32.6, 50.1)	21.9 (19.7, 24.3)
Valdecoxib	12.6 (10.6, 14.8)	10.9 (9.2, 12.7)	36.2 (24.9, 51.3)	21.3 (16.5, 27.2)	13.3 (5.8, 26.3)	37.3 (22.6, 57.2)	16.2 (12.7, 20.4)
Diclofenac	12.5 (9.3, 16.4)	10.8 (8.1, 14.1)	16.9 (6.1, 36.3)	20.2 (12.6, 30.6)	10.3 (1.3, 38.0)	33.5 (12.2, 72.6)	17.3 (11.9, 24.3)
Ibuprofen	17.8 (14.9, 21.0)	13.1 (10.9, 15.5)	44.0 (30.6, 61.7)	29.8 (23.4, 37.5)	8.5 (1.0, 28.9)	23.3 (10.6, 43.8)	20.5 (16.0, 25.9)
Naproxen	12.8 (10.4, 15.7)	9.0 (7.3, 11.1)	21.5 (11.8, 36.1)	20.1 (14.9, 26.7)	7.9 (1.0, 28.9)	23.3 (10.6, 43.8)	12.2 (8.7, 16.5)
Other nsNSAID‡	13.4 (12.0, 15.0)	12.1 (10.8, 13.4)	37.8 (30.3, 46.4)	25.4 (21.8, 29.4)	7.5 (3.0, 15.5)	48.4 (37.9, 60.8)	16.4 (13.9, 19.3)
Nonusers	14.4 (13.8, 15.0)	12.9 (12.3, 13.4)	32.6 (29.9, 35.6)	23.4 (22.0, 24.9)	10.0 (7.2, 13.5)	35.8 (32.3, 39.6)	18.0 (16.8, 19.2)

*Values are the incidence rate per 100 person-years (95% confidence interval). nsNSAID = nonselective nonsteroidal antiinflammatory drug.

†Cardiovascular disease events include hospitalized myocardial infarction, stroke, or congestive heart failure and out-of-hospital cardiovascular death.

‡See Table 1 for a list of other nsNSAIDs.

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Appendix A

Interaction between coxib or nsNSAID use and patient subgroups among the primary and secondary cohorts*

Drug exposure	Patient subgroup based on data from prior 6 months	Primary cohort AP (95% CI) (n = 175,654)	Secondary cohort AP (95% CI) (n = 174,050)
Valdecoxib	Cardiovascular risk factors	0.32 (0.01, 0.62)	−0.09 (−0.48, 0.31)
Rofecoxib	Rheumatoid arthritis	0.30 (0.03, 0.57)	−0.16 (−0.80, 0.49)
Valdecoxib	Myocardial infarction	0.30 (0.03, 0.56)	−0.20 (−0.65, 0.26)
Valdecoxib	Female sex	0.30 (−0.13, 0.72)	−0.30 (−0.75, 0.15)
Other nsNSAID†	Chronic renal disease	0.28 (0.09, 0.46)‡	0.19 (−0.04, 0.43)‡
Ibuprofen	Congestive heart failure	0.26 (0.05, 0.47)	0.06 (−0.27, 0.38)
Ibuprofen	Myocardial infarction	0.25 (−0.02, 0.53)‡	0.24 (−0.10, 0.57)‡
Rofecoxib	Diabetes mellitus	0.25 (0.15, 0.36)	0.08 (−0.08, 0.24)
Valdecoxib	Hypertension	0.25 (−0.01, 0.5)	0.08 (−0.19, 0.34)
Diclofenac	COPD	0.24 (−0.07, 0.55)	0.03 (−0.47, 0.52)
Other nsNSAID†	Myocardial infarction	0.24 (0.06, 0.42)‡	0.20 (−0.01, 0.41)‡
Diclofenac	Chronic renal disease	0.23 (−0.39, 0.86)	−1.01 (−3.32, 1.29)
Other nsNSAID†	Cardiovascular risk factors	0.22 (0.02, 0.42)	0.08 (−0.18, 0.34)
Ibuprofen	Age ≥80 years	0.22 (0.05, 0.39)‡	0.15 (−0.07, 0.37)‡
Ibuprofen	Cardiovascular disease	0.22 (0.01, 0.43)‡	0.19 (−0.05, 0.42)‡
Valdecoxib	Chronic renal disease	0.21 (−0.16, 0.57)	−0.20 (−0.74, 0.35)
Rofecoxib	Congestive heart failure	0.19 (0.09, 0.30)‡	0.11 (−0.03, 0.25)‡
Valdecoxib	COPD	0.19 (−0.04, 0.41)	−0.24 (−0.58, 0.10)
Other nsNSAID†	Congestive heart failure	0.19 (0.04, 0.34)‡	0.26 (0.11, 0.40)‡
Ibuprofen	COPD	0.19 (−0.04, 0.41)‡	0.32 (0.11, 0.53)‡
Other nsNSAID†	Cardiovascular disease	0.16 (0.016, 0.31)‡	0.18 (0.03, 0.33)‡
Rofecoxib	Age ≥80 years	0.16 (0.07, 0.24)‡	0.13 (0.03, 0.23)‡
Valdecoxib	Cardiovascular disease	0.16 (0.07, 0.24)	0.01 (−0.22, 0.25)
Rofecoxib	Cardiovascular risk factors	0.15 (0.02, 0.24)	0.03 (−0.15, 0.21)
Diclofenac	Statin use	0.14 (−0.29, 0.57)	0.01 (−0.55, 0.57)
Ibuprofen	ACE inhibitor or ARB use	0.13 (−0.08, 0.35)	−0.04 (−0.36, 0.27)
Diclofenac	Hypertension	0.13 (−0.26, 0.52)	−0.08 (−0.63, 0.48)
Naproxen	Cardiovascular disease	0.13 (−0.14, 0.40)‡	0.11 (−0.17, 0.38)‡
Other nsNSAID†	Hypertension	0.13 (−0.05, 0.31)‡	0.13 (−0.07, 0.34)‡
Valdecoxib	Rheumatoid arthritis	0.12 (−0.53, 0.77)‡	0.23 (−0.44, 0.89)‡

*nsNSAID = nonselective nonsteroidal antiinflammatory drug; 95% CI = 95% confidence interval; COPD = chronic obstructive pulmonary disease; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker.

†Other nsNSAIDs include diflunisal, etodolac, fenoprofen, flurbiprofen, indomethacin, ketoprofen, ketorolac, meclofenamate, mefenamic acid, meloxicam, nabumetone, oxaprozin, piroxicam, sulindac, and tolmetin.

‡The table consists of the top tertile of attributable proportions (AP) for the primary cohort and is organized from largest to smallest AP. The 13 APs with an ‡ were found to be in the top tertile for both the primary and secondary cohorts.