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Cardiovascular Outcomes in New Users of Coxibs and Nonsteroidal Antiinflammatory Drugs

High-Risk Subgroups and Time Course of Risk

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Objective. **Controversy persists regarding the cardiovascular risks of treatment with selective cyclooxygenase 2 inhibitors (coxibs) and nonselective nonsteroidal antiinflammatory drugs (NSAIDs). This study was undertaken to examine, in a large group of new users of coxibs and NSAIDs, the rate of cardiovascular events, their time course, and whether baseline cardiovascular risk modified the rate ratios (RRs) for future events.**

Methods. **This cohort study included Medicare beneficiaries who enrolled in a state-run prescription drug plan that fully covered NSAIDs and coxibs without restriction. All study patients started use of a coxib or NSAID after January 1, 1999. The primary composite end point was a hospital admission for either myocardial infarction or ischemic stroke. Predefined exposure groups included the 3 coxibs available in the US during the study period (celecoxib, rofecoxib, and valdecoxib), as well as oral formulations of diclofenac, ibuprofen, naproxen, and a composite of all other NSAIDs. We compared the rate of cardiovascular events associated with each of these agents with that in a reference group of patients who did not use NSAIDs or coxibs, but started other medications unrelated to cardiovascular risk. Daily exposure to all study drugs was assessed based on filled prescription data. A Cox proportional hazards model stratified on calendar year that included other baseline cardiovascular risk factors constituted the primary analysis.**

Results. **We identified 74,838 users of NSAIDs or coxibs, and 23,532 comparable users of other drugs comprised the reference group. Adjusted models demonstrated a significant elevation in the event rate for rofecoxib (RR 1.15, 95% confidence interval [95% CI] 1.06–1.25) and a significant reduction in the rate for naproxen (RR 0.75, 95% CI 0.62–0.92). No other coxib or NSAID was associated with a significant increase or decrease in cardiovascular event rate. The increased rate associated with rofecoxib was seen in the first 60 days of use (adjusted RR 1.14, 95% CI 1.01–1.29) and thereafter (adjusted RR 1.14, 95% CI 1.02–1.28). Kaplan-Meier event curves showed a similar pattern of risk (early and persistent separation of the event curves) among long-term rofecoxib users at low or high baseline cardiovascular risk.**

Conclusion. **We found an increased cardiovascular event rate among users of rofecoxib, and a decreased rate with naproxen use. Other coxibs and NSAIDs did not appear to be associated with a difference in event rate compared with users of other drugs. The increase in rate associated with rofecoxib was seen within the first 60 days and persisted. There was no important modification of the event rate based on the patient's baseline cardiovascular risk.**

Millions of elderly people take nonsteroidal antiinflammatory drugs (NSAIDs), selective and nonselective, because of their analgesic and antiinflammatory

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benefits (1). However, many questions remain about the cardiovascular safety of selective cyclooxygenase 2 inhibitors (coxibs) as well as nonselective NSAIDs, particularly in older adults. Despite a recent Food and Drug Administration requirement that the labels of all NSAIDs contain a boxed warning (2), few studies have estimated the cardiovascular risk of NSAIDs. The time course of cardiovascular events associated with coxibs is also controversial, and may reveal some information about their mechanism of cardiovascular risk. It is possible that the risk of cardiovascular events with these drugs may be based on a patient's underlying cardiovascular risk, but there is little published evidence on this. While appropriately designed randomized controlled trials would help answer these questions, results from such trials are not imminent. In the absence of trial data, nonexperimental epidemiologic studies provide the best alternative source of information for patients, doctors, and regulators.

Epidemiologic studies of drug safety can be conducted using previously collected, readily available data sources to allow for quicker and less expensive analyses than randomized controlled trials. These data sets contain information on patients with a broad range of comorbid conditions who use the drugs of interest in a typical manner; this may differ from the constrained patterns of use reflected in a clinical trial. However, nonexperimental studies of the cardiovascular safety of coxibs and NSAIDs have important potential limitations, including the nonrandom assignment of treatment, lack of information regarding important covariates such as aspirin use and body mass index, misclassification of drug exposure due to the availability of over-the-counter NSAIDs, and difficulty ascertaining the cause of out-of-hospital sudden death.

With these caveats in mind, we set out to examine the cardiovascular risk associated with the 3 coxibs marketed in the US during the study period—celecoxib, rofecoxib, and valdecoxib—and several commonly used NSAIDs, including diclofenac, ibuprofen, naproxen, and a combined group of other NSAIDs. The primary aims of these analyses were 1) to examine the risk of cardiovascular events in users of coxibs and NSAIDs compared with users of other drugs, 2) to assess the time course of risk, and 3) to determine whether baseline cardiovascular risk modifies the risk of future events. These study aims were pursued using a large health care utilization database with older at-risk adults, many of whom would not be included in trials but actually represent the target population for these medications.

METHODS

Role of the funding source. Personnel of 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.

Study design. We conducted a longitudinal cohort study consisting of new users of coxibs or NSAIDs. In the primary analysis, these groups were compared with subjects who did not use one of these agents, but who did initiate use of unrelated agents for the treatment of hypothyroidism or glaucoma (see Table 1 for list of all exposures). Exposure status was considered time-varying and was assessed on a daily basis from pharmacy dispensing records. Relative risks were calculated using Cox proportional hazards models that controlled for baseline demographic factors, cardiovascular risk factors, and health care utilization variables.

Study cohort. Subjects were beneficiaries of Medicare and a drug benefit program, the Pharmaceutical Assistance Contract for the Elderly (PACE), for low-to-moderate–income older adults residing in Pennsylvania. This drug benefit program pays for all medications, including coxibs and NSAIDs, with a copayment of $6–10. No restrictions on coxib use were in effect during the study period. Data obtained from the drug benefit program included drug name, dosage, days supply, 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. Linkage was made through unique health identification codes that were removed from the study database before analyses were conducted. Data use agreements are in place with PACE and the Center for Medicare and Medicaid Services. The Brigham and Women's Hospital Institutional Review Board approved the study protocol.

Subjects were eligible for the study cohort if they had been concomitant beneficiaries of both programs for at least 12 continuous months during the period 1999–2003. To be considered a user of a coxib or NSAID, a subject had to have 6 preceding months with no use of any coxib or NSAID. During these 6 months, the subject must have been an active system user, defined as filling at least 1 prescription and making at least 1 Medicare claim during this period. The date of the first coxib or NSAID prescription after fulfillment of this requirement was considered the index date. A similar definition was applied to the reference group; however, these subjects were required to have initiated use of a 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 impact on cardiovascular events. In secondary analyses, ibuprofen users were considered as the reference group since ibuprofen is one of the most common NSAIDs used worldwide and thus represents an important comparison group.

The use period ended with any of the following events: a gap between prescriptions for the drugs of interest of >30 days, initiation of treatment with another coxib or NSAID, a cardiovascular event, death, or loss of eligibility from PACE. Subjects were eligible for a second use period if they stopped

Table 1. Medication exposures

Selective cyclooxygenase 2 inhibitors	Nonselective NSAIDs*	Glaucoma medications	Thyroid hormones
Celecoxib	Diclofenac	Pilocarpine	Levothyroxine
Rofecoxib	Naproxen	Carbachol	Liothyronine
Valdecoxib	Ibuprofen	Physostigmine	
	Diflunisal	Demecarium bromide	
	Etodolac	Echothiophate iodide	
	Fenoprofen	Dorzolamide	
	Flurbiprofen	Brinzolamide	
	Indomethacin	Betaxolol	
	Ketoprofen	Levobunolol	
	Ketoralac	Metipranolol	
	Meclofenamate	Timolol	
	Mefenamic acid	Carteolol	
	Meloxicam	Dipivefrin	
	Nabumetone	Brimonidine	
	Oxaprozin	Apraclonidine	
	Piroxicam	Latanoprost	
	Sulindac	Unoprostone	
	Tolmetin	Epinephrine	

* Only oral formulations of nonsteroidal antiinflammatory drugs (NSAIDs) were included. Daily dosage categories were as follows: celecoxib low ≤200 mg, high >200 mg; rofecoxib low ≤25 mg, high >25 mg; valdecoxib low ≤20 mg, high >20 mg; and nonselective NSAIDs low ≤75% of the maximum antiinflammatory dosage, high >75%.

filling a medication of interest for at least 6 months but remained active system users.

Exposures of interest. Coxib use included the 3 coxibs available in the US during the study period (celecoxib, rofecoxib, and valdecoxib, as noted above). NSAID use included oral preparations of diclofenac, naproxen, ibuprofen, and a composite of all other available oral NSAIDs, excluding aspirin (see Table 1). Longitudinal exposure was assessed on a daily basis starting with the index date. Subjects were allowed to have a gap of up to 30 days between prescriptions to account for the intermittent use of coxibs and NSAIDs. The same gap was allowed between the prescriptions for thyroid hormones and glaucoma medication. (Sensitivity analyses allowed for a shorter [15-day] gap between prescriptions; the results of these analyses were very similar to results of the main analyses and are not presented.) Two duration-of-use categories were defined, short (≤60 days) and long (>60 days). Subjects contributed person-time in a continuous manner, such that a subject who used an NSAID for 70 days contributed the first 60 days to the short use category and the last 10 days to the long use category. Daily dosage categories were as follows: celecoxib low ≤200 mg, high >200 mg; rofecoxib low ≤25 mg, high >25 mg; valdecoxib low ≤20 mg, high >20 mg; and nonselective NSAIDs low ≤75% of the maximum antiinflammatory dosage, high >75%.

Cardiovascular events. The primary study outcome was a composite of acute cardiovascular events, e.g., hospitalization for myocardial infarction (MI) or for ischemic stroke. The coding algorithm for MI was a discharge diagnosis of acute MI (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code 410.XX) in the primary or secondary position for an acute-care hospitalization with a length of stay of <180 days but >3 days, unless the patient died. The coding algorithm for ischemic stroke was a diagnosis of acute stroke (ICD-9-CM code 433.XX or 434.XX) in the primary position for an acute-care hospitalization. Hemorrhagic stroke was not included in the primary outcome because of concerns about differential effects of coxibs and NSAIDs on platelets. Sensitivity analyses did include hemorrhagic stroke (ICD-9-CM code 431.XX in the primary position for an acute-care hospitalization), and the results were very similar and are not shown. MI and stroke can be accurately defined in a health care utilization database using claims algorithms; we have previously shown a positive predictive value for the MI codes in this data set of at least 94% using primary medical records, and others have shown similar accuracy for the stroke algorithm (3,4). The study composite outcome did not include out-of-hospital events that did not reach medical attention, such as out-of-hospital sudden death. MI and ischemic stroke were also considered separately in sensitivity analyses.

Covariates. We also considered important demographic and health care utilization information as well as the year of index date (first coxib or NSAID prescription) in all models. Individual cardiovascular covariates were studied, including prior diagnoses and/or treatments for MI, stroke, congestive heart failure, angina, diabetes, hypertension, coronary revascularization, carotid revascularization, peripheral vascular disease, use of a statin, and use of clopidogrel. A Charlson comorbidity score (5) and diagnoses of osteoarthritis, rheumatoid arthritis, malignant neoplasm, and chronic renal disease were added to all models. These covariates were defined based on data from the 6 months preceding each subject's index date. Use of data only from the prior 6 months excludes some available information, but it ensures equal ascertainment of data for all exposure groups.

In addition to considering these covariates separately, we combined them into a cardiovascular risk score, developed for the nonusers of coxibs and NSAIDs (6). All covariates were entered into a Cox proportional hazards model of the primary

Table 2. Baseline characteristics of study subjects during the 6 months before starting medication*

Characteristic	Celecoxib	Rofecoxib	Valdecoxib	Diclofenac	Ibuprofen	Naproxen	Other NSAIDs†	Nonusers‡
All patients included								
n	26,366	17,967	3,060	2,673	7,421	6,130	11,221	23,532
Age, mean ± SD years	80 ± 7	80 ± 7	79 ± 7	78 ± 7	78 ± 7	77 ± 7	78 ± 7	80 ± 7
Female	22,323 (85)	15,311 (85)	2,616 (85)	2,239 (84)	5,974 (81)	4,998 (82)	8,863 (79)	19,950 (85)
Race, white	24,970 (95)	17,145 (95)	2,929 (96)	2,474 (93)	6,406 (86)	5,455 (89)	10,360 (92)	22,062 (94)
Patients from 2003§								
n	2,903	2,413	1,615	325	1,092	982	1,504	4,266
Hospitalized	149 (5)	126 (5)	81 (5)	12 (4)	59 (5)	39 (4)	68 (5)	236 (6)
Nursing home residence	170 (6)	150 (6)	70 (4)	11 (3)	55 (5)	21 (2)	49 (3)	330 (8)
Physician visits, mean ± SD	5 ± 4	5 ± 4	5 ± 4	4 ± 4	4 ± 4	4 ± 4	5 ± 4	5 ± 4
No. of generic preparations taken, mean ± SD	7 ± 4	7 ± 4	7 ± 4	6 ± 4	7 ± 4	6 ± 4	7 ± 4	6 ± 4
Myocardial infarction	173 (6)	171 (7)	93 (6)	12 (4)	59 (5)	48 (5)	92 (6)	316 (7)
Congestive heart failure	787 (27)	660 (27)	416 (26)	71 (22)	251 (23)	202 (21)	426 (28)	1,199 (28)
Coronary revascularization	47 (2)	64 (3)	34 (2)	4 (1)	19 (2)	22 (2)	29 (2)	79 (2)
Angina	223 (8)	239 (9)	148 (9)	27 (8)	96 (9)	72 (7)	135 (9)	394 (9)
Diabetes	447 (15)	371 (15)	246 (15)	42 (13)	174 (16)	167 (17)	207 (14)	574 (13)
Hypertension	1,808 (62)	1,483 (61)	1,020 (63)	186 (57)	661 (61)	559 (57)	918 (61)	2,367 (55)
Statin use	892 (31)	756 (31)	517 (32)	106 (33)	359 (33)	317 (33)	482 (32)	1,156 (27)
Clopidogrel use	246 (8)	196 (8)	137 (8)	21 (6)	84 (8)	66 (7)	106 (7)	353 (8)
Peripheral vascular disease	313 (11)	255 (11)	151 (9)	36 (11)	106 (10)	84 (9)	126 (8)	473 (11)
Stroke	210 (7)	182 (8)	98 (6)	15 (5)	70 (6)	61 (6)	90 (6)	357 (8)
Carotid revascularization	6 (0.2)	7 (0.3)	3 (0.2)	0 (0)	2 (0.2)	2 (0.2)	2 (0.1)	13 (0.3)
Chronic renal disease	84 (3)	88 (4)	60 (4)	10 (3)	41 (4)	30 (3)	71 (5)	267 (6)
Rheumatoid arthritis	61 (2)	35 (1)	41 (3)	8 (2)	16 (1)	10 (1)	23 (2)	67 (2)
Osteoarthritis	747 (26)	590 (24)	502 (31)	61 (19)	169 (15)	160 (16)	315 (21)	572 (13)
Malignancy	75 (3)	76 (3)	36 (2)	5 (2)	39 (4)	20 (2)	32 (2)	132 (3)

* Except where indicated otherwise, values are the number (%).
† See Table 1 for list of other nonsteroidal antiinflammatory drugs (NSAIDs).
‡ Nonusers include new users of glaucoma medications and thyroid hormones.
§ Most baseline characteristics shown are for patients initiating use during 2003, because that is the only full year during the study when all medications were available.

end point. Parameter estimates were then applied to the individual covariates among the total study population to calculate a patient-specific risk score. Based on the cardiovascular risk score, subjects were stratified into 2 equal-sized groups: low-risk (2.9% with events) and high-risk (7.0% with events).

Data on several important covariates, such as smoking, aspirin use, body mass index, and educational attainment, were not available in our study database. Each of these factors has been associated with cardiovascular outcomes and may be related to the exposure status. Thus, there is the possibility for residual confounding bias not controlled for by adjusting for the covariates described above. To better understand this possibility, we examined data from the Medicare Current Beneficiary Survey, an in-home survey of ~10,000 beneficiaries conducted annually (7). We compared data on these potential confounders across the exposures of interest and calculated the potential residual bias caused by not adjusting for these factors, using methods we have previously developed (8).

Statistical analysis. All covariates were examined at baseline and then by year of index date. Person-time and cardiovascular events were calculated for each defined exposure, including nonusers. We then used Cox proportional hazards regression to estimate the rate ratio (RR) and 95% confidence interval (95% CI) for each study exposure. Because not every medication of interest was available during all study years (valdecoxib was only available during 2002 and 2003), the models were stratified by study year. We included all covariates in each model. To assess the proportionality of the hazard curves for each exposure, we examined the correlation between the Schoenfeld residuals and study time (9). None of the correlations were significant (all P values > 0.85); thus, the assumptions underlying the proportional hazards model were not violated.

Kaplan-Meier survival curves were examined for each drug of interest with sufficient long-term use. To address potential confounding, subjects were divided into 2 equal-sized groups, categorized as low-risk or high-risk for future cardiovascular events. Only the medications with at least 25 subjects followed up for at least 3 years were included in the plots. Using multiplicative interaction terms, we assessed for effect modification by duration of use and by baseline risk of cardiovascular events. All analyses were run with SAS version 8.0 (SAS Institute, Cary, NC).

RESULTS

We identified 74,838 new users of coxibs or NSAIDs. These subjects were compared with new users of thyroid hormones or glaucoma medications who were

Table 3. Cardiovascular events among all users of coxibs or NSAIDs*

		Myocardial infarction or stroke					
Treatment	n	Events	Person-years	Incidence rate per 100 person-years	Unadjusted rate difference	Unadjusted rate ratio (95% CI)	Adjusted rate ratio (95% CI)
Celecoxib	26,366	1,342	11,768	11.4	0.58 (−00.20, 1.37)	1.05 (0.98, 1.13)	0.99 (0.92, 1.07)
Rofecoxib	17,967	912	6,746	13.5	2.70 (1.69, 3.70)	1.25 (1.15, 1.35)	1.15 (1.06, 1.25)
Valdecoxib	3,060	112	985	11.4	0.55 (−1.61, 2.71)	1.05 (0.87, 1.27)	0.96 (0.78, 1.17)
Diclofenac	2,673	86	736	11.7	0.86 (−1.66, 3.38)	1.08 (0.87, 1.34)	1.10 (0.89, 1.37)
Ibuprofen	7,421	151	1,244	12.1	1.32 (−0.68, 3.31)	1.12 (0.95, 1.32)	0.96 (0.81, 1.14)
Naproxen	6,130	108	1,254	8.6	−2.21 (−3.91, 0.51)	0.80 (0.66, 0.97)	0.75 (0.62, 0.92)
Other NSAIDs†	11,221	292	2,615	11.2	0.34 (−1.03, 1.72)	1.03 (0.91, 1.17)	0.95 (0.84, 1.08)
Nonusers	23,532	1,847	17,067	10.8	Reference	Reference	Reference

* The rate difference was calculated as the difference in incidence rates between users of each selective cyclooxygenase 2 inhibitor (coxib) or nonsteroidal antiinflammatory drug (NSAID) and nonusers. Adjusted rate ratios were calculated from Cox proportional hazards models that included age, sex, race, hospitalizations, physician visits, number of other medications, nursing home residence, prior myocardial infarction, prior stroke, angina, congestive heart failure, peripheral vascular disease, revascularization procedures, diabetes, hypertension, use of a statin, use of clopidogrel, renal disease, rheumatoid arthritis, osteoarthritis, and malignancy. All models were stratified on the calendar year of the index date. 95% CI = 95% confidence interval.
† See Table 1 for list of other NSAIDs.

not new users of coxibs or NSAIDs (n = 23,532). Characteristics of these subjects are compared in Table 2. All groups were quite similar with respect to age, sex, and race distribution and most diagnoses. Users of ibuprofen and naproxen and the nonusers were less likely to have received a diagnosis of osteoarthritis.

The number of new use periods, person-time, and events are shown for all users of each coxib and NSAID in Table 3. There were large numbers of events for each drug. Table 3 displays the incidence rate, rate differences between users of each agent and glaucoma or thyroid drug users, and the unadjusted and adjusted rate ratios for cardiovascular events, comparing users of each drug with nonusers. Rofecoxib was associated with an increased rate difference and rate ratio, but the other 2 coxibs were not. This result was quite uniform across MI and stroke (Table 4). None of the NSAIDs was associated with an increased rate ratio, and naproxen was associated with a reduced rate ratio. Diclofenac did appear to be associated with an increased rate ratio of MI (Table 4), but not with the composite end point. In secondary analyses comparing each agent with ibuprofen as the reference group, the results were similar to those from the primary analyses (rofecoxib RR 1.19, 95% CI 1.00–1.41; celecoxib RR 1.03, 95% CI 0.87–1.22; valdecoxib RR 0.97, 95% CI 0.75–1.25; and naproxen (RR 0.79, 95% CI 0.62–1.01). The results obtained when the reference group included only glaucoma medication users (and not thyroid medication users) were also very similar (rofecoxib RR 1.27, 95% CI 1.11–1.44; celecoxib RR 1.09, 95% CI 0.96–1.24; valdecoxib RR 1.05, 95% CI 0.84–1.31; and naproxen RR 0.84, 95% CI 0.67–1.04).

As illustrated in Figure 1, the rate ratios observed in the first 60 days were very similar to those in the next

Table 4. Myocardial infarctions and strokes among users of coxibs or NSAIDs*

		Myocardial infarction			Stroke		
	n	Events	Person-years	Adjusted RR (95% CI)	Events	Person-years	Adjusted RR (95% CI)
Celecoxib	26,366	424	12,135	0.99 (0.87–1.13)	988	11,861	1.00 (0.92–1.09)
Rofecoxib	17,967	290	6,952	1.16 (1.01–1.34)	660	6,797	1.15 (1.04–1.26)
Valdecoxib	3,060	37	1,006	1.06 (0.75–1.50)	80	989	0.93 (0.74–1.18)
Diclofenac	2,673	34	751	1.43 (1.01–2.03)	56	739	0.98 (0.75–1.29)
Ibuprofen	7,421	47	1,253	1.02 (0.75–1.38)	111	1,247	0.95 (0.78–1.16)
Naproxen	6,130	28	1,272	0.67 (0.45–0.98)	89	1,257	0.83 (0.67–1.04)
Other NSAIDs†	11,221	72	2,667	0.77 (0.60–0.99)	229	2,625	1.02 (0.88–1.17)
Nonusers	23,532	622	17,935	Reference	1,339	17,370	Reference

* RR = rate ratio; 95% CI = 95% confidence interval.
† See Table 1 for list of other nonsteroidal antiinflammatory drugs (NSAIDs).

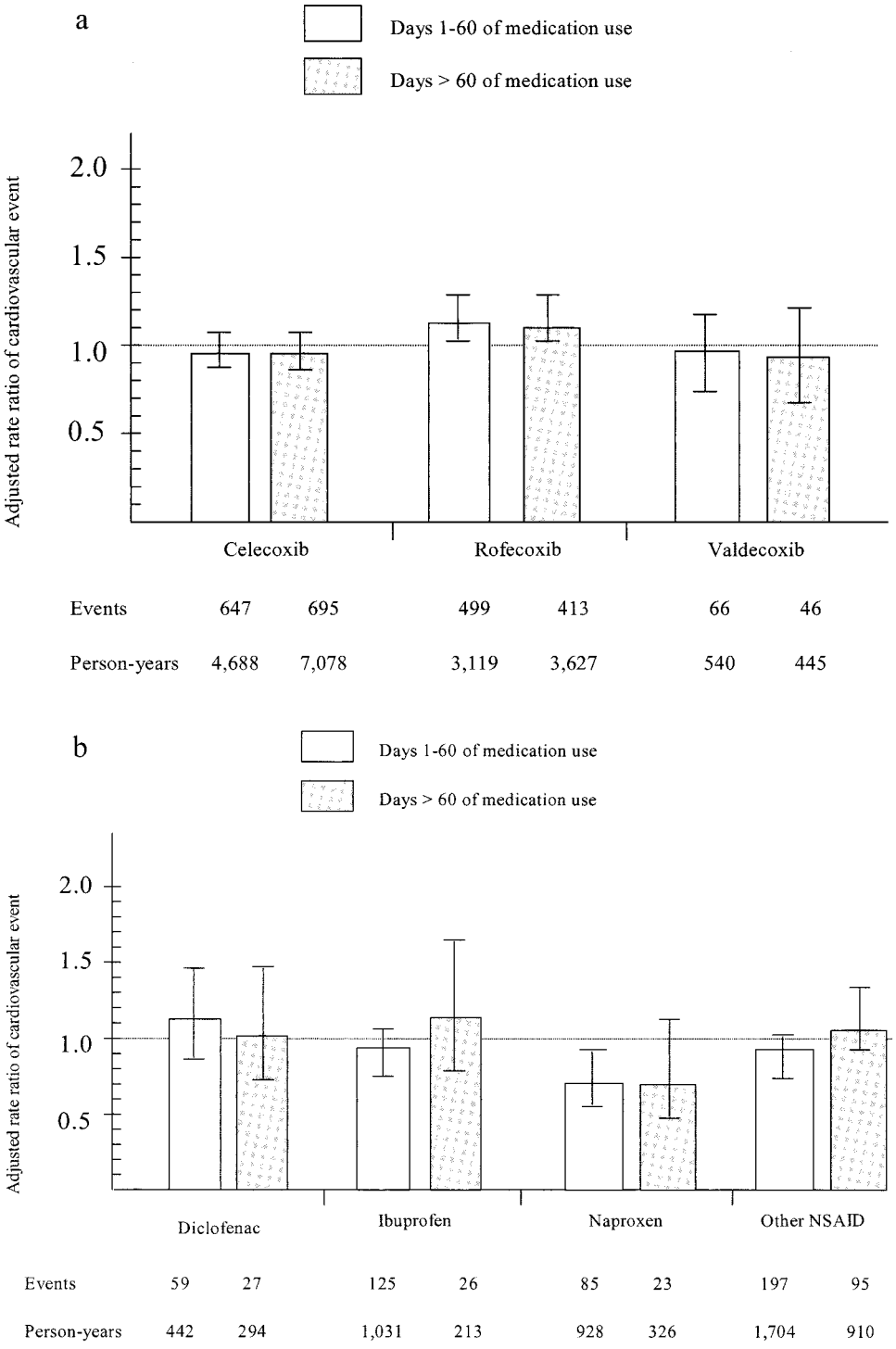

Figure 1. Adjusted rate ratio of myocardial infarction or ischemic stroke by duration of use of selective cyclooxygenase 2 inhibitors (**a**) or nonselective nonsteroidal antiinflammatory drugs (NSAIDs) (**b**). All estimates were derived from Cox proportional hazards models, stratified on year, that included age, sex, race, hospitalizations, physician visits, number of other medications, nursing home residence, prior myocardial infarction, prior stroke, angina, congestive heart failure, peripheral vascular disease, revascularization procedures, diabetes, hypertension, use of a statin, use of clopidogrel, renal disease, rheumatoid arthritis, osteoarthritis, and malignancy. The reference group was users of glaucoma or thyroid medications. Vertical lines show the 95% confidence intervals. No significant interactions between drug exposure and duration of medication use were observed (all P values > 0.8).

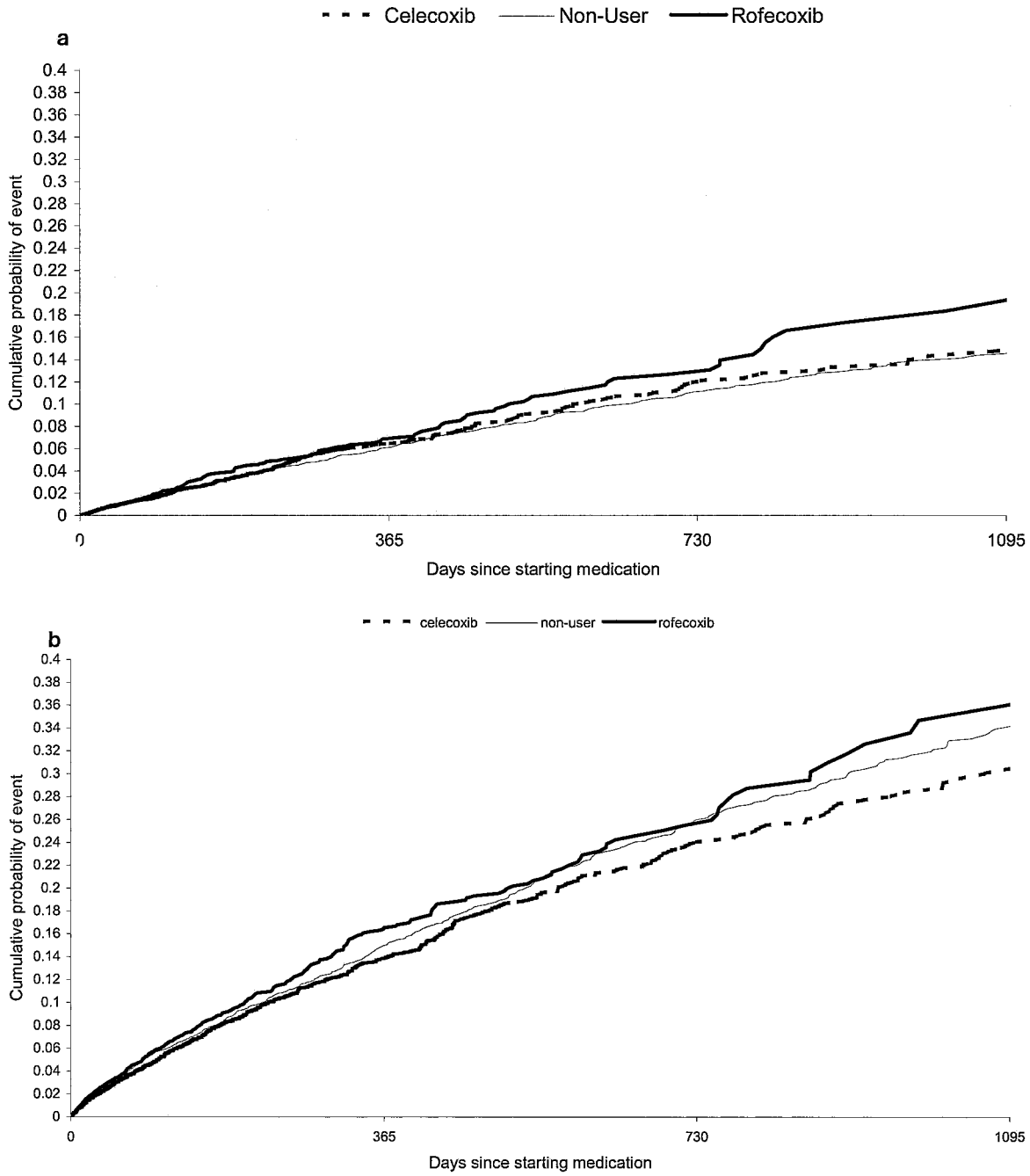

Figure 2. Kaplan-Meier survival curves illustrating the cumulative probability of a myocardial infarction or stroke during the first 3 years after starting treatment with a selective cyclooxygenase 2 inhibitor, among subjects who were at low risk (**a**) and subjects who were at high risk (**b**) of future cardiovascular events (see Methods for description of the different risk groups). Only drug exposures with at least 25 subjects followed up for at least 36 months were included in these analyses.

60 days for all medications. All interaction terms between the exposures of interest and the time receiving therapy were nonsignificant (all P values > 0.8). The time course of events was further explored in Kaplan-Meier survival analyses stratified on the cardiovascular disease risk score. Among the low-risk subgroup (Figure 2a), the probability of cardiovascular events rose within the first year for rofecoxib, but not celecoxib. This

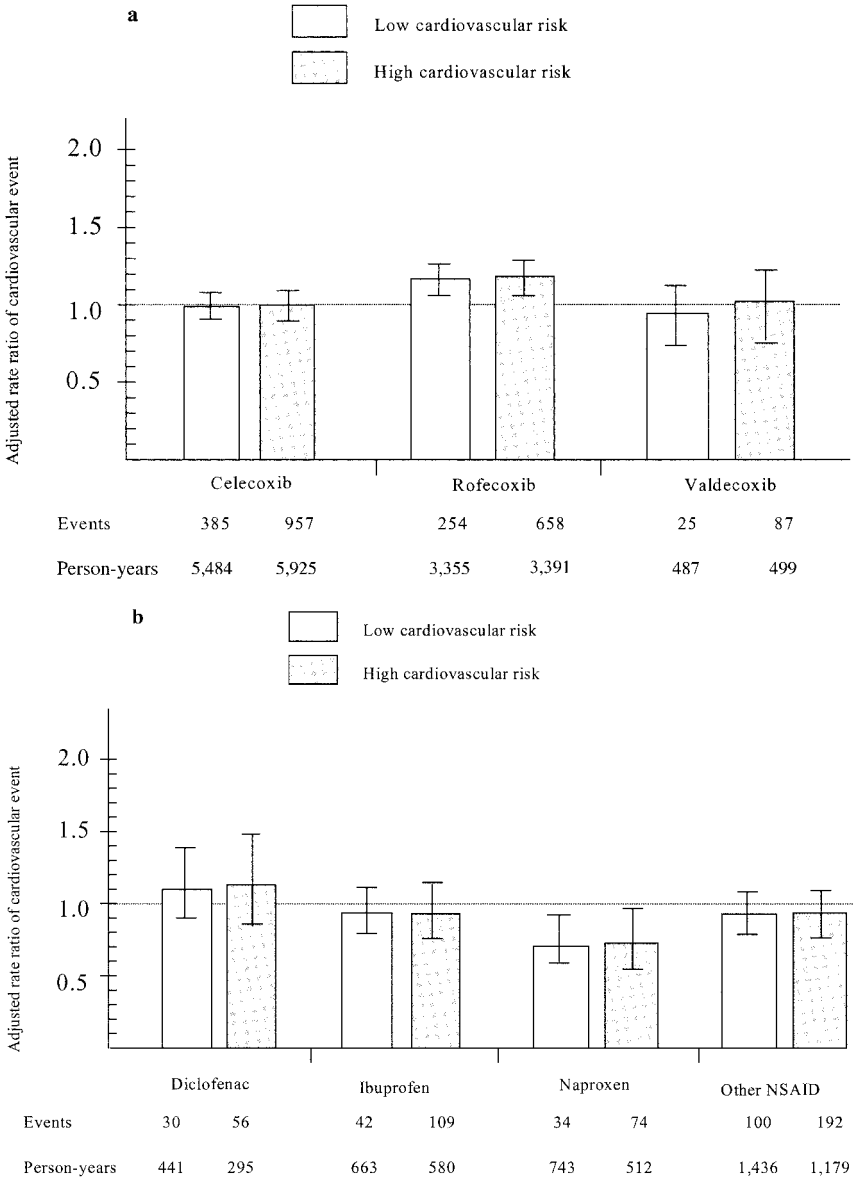

Figure 3. Adjusted rate ratio of myocardial infarction or ischemic stroke by baseline cardiovascular risk among users of selective cyclooxygenase 2 inhibitors (**a**) or nonselective nonsteroidal antiinflammatory drugs (NSAIDs) (**b**). All estimates were derived from Cox proportional hazards models, stratified on year, that included age, sex, race, hospitalizations, physician visits, number of other medications, nursing home residence, prior myocardial infarction, prior stroke, angina, congestive heart failure, peripheral vascular disease, revascularization procedures, diabetes, hypertension, use of a statin, use of clopidogrel, renal disease, rheumatoid arthritis, osteoarthritis, and malignancy. The reference group was users of glaucoma or thyroid medications. Vertical lines show the 95% confidence intervals. No significant interactions between drug exposure and baseline risk of cardiovascular disease were observed (all P values > 0.7).

elevation persisted throughout 3 years for rofecoxib users. The time course of events among high-risk patients (Figure 2b) was similar, but the probability of event was much higher. Celecoxib was not associated with an elevated probability of event in either low- or high-risk patients.

We then explored whether a patient's baseline cardiovascular risk modified the effects of a given agent (Figures 3a and b). None of the interaction terms for the exposures of interest and a baseline cardiovascular risk indicator were significant (all P values > 0.7). An elevated rate ratio with rofecoxib was observed in both

Table 5. Prevalence of potential unmeasured confounders in a separate survey of 9,501 Medicare beneficiaries*

	n	Female	Age, years		High school education or less	Obese (body mass index ≥30 kg/m^2)	Aspirin use	Smoking status		
			65–74	≥75				Current	Former	Never
Any coxib†	1,316	69.5	42.9	57.1	61.7	25.5	6.2	8.8	46.0	44.9
Celecoxib only	677	70.6	39.1	60.9	62.8	23.7	5.9	9.6	43.5	46.6
Rofecoxib only	488	66.8	46.3	53.7	59.8	27.5	6.4	6.6	50.7	42.2
Valdecoxib only	57	70.2	50.9	49.1	68.4	28.1	3.5	5.3	49.1	45.6
Nonselective NSAIDs only‡	702	59.1	53.9	46.2	63.1	25.1	9.8	10.1	49.6	40.1
Ibuprofen only	204	56.4	58.8	41.2	67.7	21.8	10.3	11.9	50.0	37.1
Naproxen only	210	56.7	54.3	45.7	61.4	26.8	12.9	11.0	50.7	38.3
Diclofenac only	51	62.8	43.1	56.9	60.8	34.0	2.0	4.0	56.0	40.0
Other NSAIDs only	252	61.5	50.8	49.2	62.7	24.4	8.7	8.8	48.0	43.2
Glaucoma or thyroid drugs only (nonusers)	1,272	71.1	32.5	67.5	40.4	18.4	5.4	6.2	46.6	47.1

* Data are from the Medicare Current Beneficiary Survey (7). Values are percents.
† All selective cyclooxygenase 2 inhibitor (coxib) categories include individuals who used a coxib with or without a nonsteroidal antiinflammatory drug (NSAID). If patients used >1 coxib, then these patients would be counted twice in the row "Any coxib" but would not be counted in the rows labeled "Celecoxib only," "Rofecoxib only," or "Valdecoxib only."
‡ Nonselective NSAIDs only categories exclude individuals who used any cyclooxygenase 2 inhibitors. If patients used >1 nonselective NSAID, then these patients would be counted twice in the row "Nonselective NSAIDs only" but would not be counted in the rows labeled "Ibuprofen only," "Naproxen only," "Diclofenac only," or "Other NSAIDs only."

low- and high-risk patients, while both low- and high-risk naproxen users experienced a reduction in cardiovascular events. We found a similar consistency of results among low- and high-dose users.

Because of concerns regarding unmeasured confounders in our study database, we examined educational attainment, smoking, body mass index, and aspirin use in a large survey of Medicare beneficiaries. As noted in Table 5, coxib users were more likely than nonusers to have had lower educational attainment, to be obese, and to be current smokers. These differences result in a small (2%) bias away from the null hypothesis in our primary health care utilization data analyses in which such factors were not considered. However, in the analyses with ibuprofen users as the reference group, the coxib analyses were biased up to 6% toward the null hypothesis.

DISCUSSION

In this study of patients ages 65 and older, we found that rofecoxib, but not celecoxib, valdecoxib, diclofenac, ibuprofen, or naproxen, was associated with an increased rate ratio of cardiovascular events compared with other medications. Naproxen was associated with a modest reduction in the rate ratio of cardiovascular events. The increased rate among rofecoxib users was observed in the first 60 days and persisted. Kaplan-Meier curves indicated that the risk with rofecoxib rose early and continued through 3 years. The rate ratio elevation was evident in patients at either low or high risk for future cardiovascular events.

While the rate ratios that we estimated for rofecoxib were smaller than those determined in several trials (10,11), the increase in cardiovascular event rate with rofecoxib in this study was somewhat higher than that observed in the Adenomatous Polyp Prevention on Vioxx (APPROVe) trial (10). In our study, rofecoxib was associated with an excess event rate of 2.70 per 100 patient-years compared with nonusers, while in the APPROVe trial there were 0.72 excess events per 100 patient-years (95% CI 0.19–1.25). One potential explanation for the smaller rate ratios we observed may be the greater cardiovascular risk of our study population, with a mean age of nearly 80 years; 7% had had an MI and 6% a stroke in the 6 months prior to starting the study medication. This is very different from findings in the APPROVe or Vioxx Gastrointestinal Outcomes Research (VIGOR) study trial populations (10,11). Others have noted that relative risks in high-risk groups often are lower than in low-risk groups (12,13). Most often this can be explained by the accumulation of competing risks, diminishing the relative effect of any one factor.

In addition, we observed that the risk associated with rofecoxib began early after initiation of treatment, unlike what has been suggested based on data from the APPROVe trial (10). A crucial advantage of our study is the superior power for detecting small differences. We observed 499 events in the first 60 days of rofecoxib use,

whereas in the APPROVe trial there were only 46 events observed in the full 3 years, and perhaps 20 in the first 18 months. Furthermore, rofecoxib 50 mg daily was associated with increased cardiovascular risk compared with naproxen 500 mg twice daily in the 12 months of the VIGOR trial (11).

It is important to place our findings in the context of earlier studies. In 2 randomized controlled trials, valdecoxib was found to be associated with a 2–4-fold increased risk of cardiovascular events compared with placebo, immediately after coronary artery bypass graft surgery (14,15). In relatively short-term trials among patients with arthritis, valdecoxib was not associated with an increased risk of MI or stroke compared with placebo or with nonselective NSAIDs (16). Rofecoxib at 25 mg and 50 mg daily for 1–3 years was found to be associated with a 2-fold increased risk of thrombotic cardiovascular events compared with placebo or naproxen (10,11). Several, but not all, observational studies have shown a similar increase in risk associated with rofecoxib (17–20). In one study, celecoxib at 200 mg and 400 mg twice daily was associated with a 2.5–3.5-fold increased risk of cardiovascular events compared with placebo (21), whereas most observational studies have shown no increased cardiovascular risk with low- or high-dose celecoxib (17–20).

There are no long-term randomized controlled trials comparing NSAIDs with placebo with regard to cardiovascular outcomes. However, results of several nonexperimental studies have suggested a reduced cardiovascular risk associated with naproxen compared with other agents (22–24). Ibuprofen may block the cardioprotective benefits of aspirin (25), and several (but not all) observational studies have suggested that ibuprofen may be associated with increased cardiovascular risk in patients taking aspirin (26–29). There are even fewer data regarding other specific NSAIDs and cardiovascular risk.

The lack of cardiovascular risk associated with valdecoxib or celecoxib in this study is notable. In contrast to the Adenoma Prevention with Celecoxib (APC) trial (21), in which an increased risk of cardiovascular events was observed among subjects taking twice-daily doses of celecoxib 200 mg or 400 mg, very few patients in our study (70 of 26,366 users of celecoxib) took $\geq$400 mg daily. In addition, our study population was primarily female (84%), whereas two-thirds of the members of the APC trial cohort were men. The 2 randomized trials that showed a cardiovascular risk associated with short-term valdecoxib use were conducted in patients who had just undergone coronary artery bypass grafting (14,15), a period when the endothelium is highly thrombophilic (30). In the present study, few new users of valdecoxib had undergone coronary or carotid revascularization in the 6 months prior to starting treatment (37 of 3,060 users of valdecoxib), making our study population unlike that of either the Coronary Artery Bypass Grafting study I (CABG I) or the CABG II (14,15).

Much of the current debate about coxibs and NSAIDs focuses on their use among specific patient groups, raising the question of whether there are subgroups of patients in which their use is especially dangerous or safe. Our results do not support the contention that the rate ratio of any of these agents differs by baseline cardiovascular risk. However, these analyses were exploratory, and more work is needed to determine whether there are differences in risk among certain patient groups.

It is important to note the limitations of our study methods. Observational drug studies are plagued by the potential for channeling of certain types of patients to use specific drugs. These patient characteristics may themselves influence cardiovascular risk, and thus could cause confounding bias if not controlled for in the analyses. Our analyses did control for many important factors such as age, sex, race, prior cardiovascular events, angina, congestive heart failure, hypertension, and use of relevant medications. However, large health care utilization databases do not contain information on other potential confounders, including smoking, aspirin use, body mass index, and socioeconomic status. These unmeasured factors could introduce bias into our analyses. We examined the potential bias (Table 5) and found that the comparisons between coxib users and nonusers may have caused minimal bias against coxibs, while the comparisons between coxib users and ibuprofen users may have produced bias against ibuprofen.

Another potential limitation is the lack of information on out-of-hospital sudden cardiac death, which was not included in our study end point. Only if this were to occur differentially across exposure groups would it lead to bias. Many NSAIDs are available over the counter, and thus there may be some misclassification of exposure. This is less problematic among low-income elderly persons with a complete drug benefit, for whom most NSAIDs are likely obtained through prescriptions with very small copayments. Some may consider the old age of our population (mean 79 years) as a limitation. Since older adults are the target population for coxibs, however, they are a very relevant study population.

Strengths of this study include the new use design (31), the definition of exposure in a time-varying manner, the large size and relative heterogeneity of the study sample, and the examination of how confounders may have biased our results. It is also important to note that the numbers of events we observed among the coxib users (n = 2,366) is 8 times larger than what has been observed in all long-term coxib clinical trials combined (n = 295) (32).

In this observational study, we have confirmed the findings of prior studies that showed an increased rate of cardiovascular events associated with rofecoxib and a decreased rate associated with naproxen. Celecoxib, valdecoxib, diclofenac, and ibuprofen were not associated with an increased rate of cardiovascular events in these analyses. The Kaplan-Meier curves, as well as the multivariable models, suggest that rofecoxib users have an increased rate of cardiovascular events soon after starting treatment. The elevated rate of events with rofecoxib appears to persist and is observed in both low and high cardiovascular risk groups. Our data do not focus on the potential cause of this increased cardiovascular risk, but the early divergence in the risk curves suggests that abrupt elevations in blood pressure, thrombosis, and/or vasoconstriction all might contribute. These analyses support the contention that most of these agents are not associated with a significant increase in cardiovascular risk in typical clinical settings.

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