Risk of Cardiovascular Events in Patients Receiving *Celecoxib*: A Meta-Analysis of Randomized Clinical Trials

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Some nonsteroidal anti-inflammatory drugs (NSAIDs), including cyclooxygenase-2 selective inhibitors, have been associated with increased cardiovascular (CV) events in recent clinical trials or observational studies. To determine whether the cyclooxygenase-2 selective inhibitor celecoxib affects CV risk, the incidence of CV events was analyzed in patients treated with celecoxib, placebo, or nonselective NSAIDs in the clinical trial database for celecoxib using defined Antiplatelet Trialists' Collaboration end points of nonfatal myocardial infarction, nonfatal stroke, and CV death. Patient data were derived from studies in osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, low back pain, and Alzheimer's disease. This meta-analysis included (1) 7,462 patients exposed to celecoxib 200 to 800 mg/day for 1,268 patient-years compared with 4,057 patients treated with placebo for 585 patient-years, and (2) 19,773 patients treated with celecoxib 200 to 800 mg/day for 5,651 patient-years compared with 13,990 patients treated with nonselective NSAIDs (diclofenac, ibuprofen, naproxen, ketoprofen, and loxoprofen) for 4,386 patient-years. CV events were adjudicated by a 3-member expert end point committee (WBW, JSB, PBG) blinded to treatment group and study. The incidence rates of the combined CV events were not significantly different between patients treated with celecoxib and placebo or between those treated with celecoxib and nonselective NSAIDs. Event rates were similar for adjudicated and nonadjudicated data. Dose of celecoxib, the use of aspirin, or the presence of CV risk factors did not alter these results. In conclusion, these analyses failed to demonstrate an increased CV risk with celecoxib relative to placebo and demonstrated a comparable rate of CV events with celecoxib treatment compared with nonselective NSAIDs. **(Am J Cardiol 2007;99:91–98)**

Substantial concerns exist about the cardiovascular (CV) effects of nonselective and cyclooxygenase-2 selective nonsteroidal anti-inflammatory drugs (NSAIDs).[1–11] In a previous pooled analysis involving >30,000 patients in 15 trials of celecoxib for the treatment of arthritis, no increases in CV events were observed compared with nonselective NSAIDs.[12] In the present study, we performed a more extensive assessment of CV events from 39 clinical trials involving >41,000 diverse patients. The focus of this analysis was on the incidence of primary CV events as defined by the Antiplatelet Trialists' Collaboration (APTC)[13] with celecoxib and its comparators (nonselective NSAIDs and placebo).

Methods

Clinical studies and protocol: The prespecified approach was to determine the incidence of primary CV events as defined by the APTC[13] (nonfatal myocardial infarction, nonfatal stroke, and CV death) for celecoxib, placebo, and the comparator NSAIDs (naproxen, diclofenac, ibuprofen, ketoprofen, and loxoprofen). All clinical studies from Pfizer's celecoxib drug safety database (Pfizer, Inc., New York, New York) meeting the following criteria were identified and included in the pooled analysis: (1) studies were randomized with a parallel group design; (2) 1 treatment arm was given celecoxib at doses of ≥200 mg/day; (3) 1 treatment arm was given a placebo comparator or a NSAID comparator; (4) the planned double-blind treatment period was ≥2 weeks, and (5) the final study report was completed by October 31, 2004. On the basis of these criteria, 41 studies that met the selection criteria were identified. Comparisons presented in this report include celecoxib versus placebo and celecoxib versus nonselective NSAIDs from a total of 39 studies. Two studies composed of only celecoxib and rofecoxib treatment groups were not included in the analyses presented herein. Open-label trials, studies designed to assess pharmacologic effects or drug–drug interactions rather than clinical outcomes, and single- or multiple-dose studies of celecoxib for acute pain were excluded from the meta-analysis. Because studies of spontaneous adenomatous colonic polyposis such as the Adenoma Prevention With Celecoxib (APC) trial[10] and the Prevention of Colorectal Sporadic Adenomatous Polyps (PreSAP) trial,[14] as well as the Alzheimer's Disease Anti-

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0002-9149/07/$ – see front matter
doi:10.1016/j.amjcard.2006.07.069

Table 1
Clinical trials included in the meta-analysis

Indication of Study Description	Sample Size	Duration of Trial (wks)	Celecoxib Total Daily Doses (mg)	Nonselective NSAID Comparator (mg)	Placebo Group
Osteoarthritis efficacy or safety studies					
Knee	874	12	200, 400	Naproxen 500 BID	+
Knee	282	6	200	0	+
Knee	317	6	200	Naproxen 500 BID	+
Knee	362	6	200	Naproxen 500 BID	+
Knee	316	6	200	Naproxen 500 BID	+
Knee	386	6	200	Ibuprofen 800 TID	+
Knee	958	4	200	Loxoprofen 60 TID	+
Knee	218	2	200, 400	0	+
Knee	956	12	200, 400	Naproxen 500 BID	+
Knee	684	6	200	0	+
Knee	715	6	200	0	+
Knee	598	6	200	Diclofenac 50 TID	+
Knee	123	6	200	0	+
Hip or knee	687	6	200	Diclofenac 50 BID	0
Hip or knee	353	6	200	0	+
Hip or knee (CAESAR trial)	916	52	200	Diclofenac 50 BID	0
Hip or knee	371	6	200	0	+
Hip/knee with HTN/type 2 diabetes	266	12	200	Naproxen 500 BID	0
Hip	845	12	200, 400	Naproxen 500 BID	+
Knee	301	4	200, 800	0	+
Hip or knee (SUCCESS trial)	13,194	12	200–400	Diclofenac 50 BID, naproxen 500 BID	0
Rheumatoid arthritis efficacy or safety studies					
Efficacy	247	4	400, 800	0	+
Efficacy and UGI safety	1,148	12	200, 400, 800	Naproxen 500 BID	+
Efficacy	1,102	12	200, 400, and 800	Naproxen 500 BID	+
Efficacy and UGI safety	655	24	400	Diclofenac SR 75 BID	0
Osteoarthritis and rheumatoid arthritis (mixed populations) studies					
Efficacy and UGI safety	89	12	200	Diclofenac 50 BID	0
GI safety outcomes (CLASS trial)	7,968	52–65	800	Ibuprofen 800 TID or diclofenac 75 BID	0
Efficacy and UGI safety	666	12	200	Diclofenac 50 BID	0
UGI safety	536	12	400	Naproxen 500 BID	0
Efficacy and UGI safety	125	12	200	Diclofenac 50 BID	0
UGI safety	1,097	12	400	Diclofenac 75 BID or ibuprofen 800 TID	0
Ankylosing spondylitis studies					
Efficacy	245	6	200	Ketoprofen 100 BID	+
Efficacy	611	12	200, 400	Naproxen 500 BID	+
Low back pain studies					
Efficacy	360	12	200	0	+
Efficacy	374	12	200	0	+
Efficacy	790	12	200, 400	0	+
Efficacy	881	4	200	Loxoprofen 60 TID	0
Alzheimer's disease studies					
Inhibition of disease progression	425	52	400	0	+
Efficacy	36	104	400	0	+

BID = twice daily; GI = gastrointestinal; HTN = hypertension; SUCCESS = Successive Celecoxib Efficacy and Safety Study; TID = thrice daily; UGI = upper gastrointestinal.

Inflammatory Prevention Trial (ADAPT),[15] were ongoing and blinded at the time of this analysis and data were not accessible to us from these studies, they could not be included in the meta-analysis.

The 39 studies constituting the meta-analysis are listed in Table 1. These studies included ambulatory adult patients diagnosed with osteoarthritis or rheumatoid arthritis evident for ≥3 months and patients with ankylosing spondylitis, low back pain, and Alzheimer's disease. Most of the trials were ≤26 weeks in duration; the exceptions included the Celecoxib Long-Term Arthritis Safety Study (CLASS),[1,16] the Alzheimer's disease treatment study, and the Celecoxib Study of Osteoarthritis in Elderly Patients: Long Term Safety and Pharmacoeconomic Aspects (CAESAR) trial.

In these trials, patients were randomly assigned to celecoxib 100 to 400 mg twice daily or 200 to 400 mg/day, comparator NSAIDs (ibuprofen 800 mg thrice daily, naproxen 500 mg twice daily, diclofenac 50 to 75 mg twice daily or 50 mg thrice daily, ketoprofen 100 mg twice daily, and loxoprofen 60 mg thrice daily), or placebo. The con-

Table 2
Characteristics of the patients at baseline used in the meta-analysis

Characteristic	Treatment Group			
	Placebo vs Celecoxib (200–800 mg)		Nonselective NSAIDs vs Celecoxib (200–800 mg)	
	Placebo (n = 4,057)	Celecoxib (n = 7,462)	NSAIDs (n = 13,990)	Celecoxib (n = 19,773)
Age				
Mean (yrs)	58.3 ± 13.4	58.6 ± 13.4	60.0 ± 12.2	60.3 ± 12.0
≥65 yrs, n (%)	1,447 (35.7)	2,685 (36.0)	5,357 (38.3)	7,789 (39.4)
Gender, n (%)				
Men	1,450 (35.7)	2,561 (34.3)	4,201 (30.0)	5,698 (28.8)
Women	2,607 (64.3)	4,901 (65.7)	9,789 (70.0)	14,075 (71.2)
Type of patient/study				
Osteoarthritis/rheumatoid arthritis	3,040 (74.9)	5,885 (78.9)	13,303 (95.1)	18,955 (95.9)
Low back pain	632 (15.6)	892 (12.0)	440 (3.1)	441 (2.2)
Ankylosing spondylitis	232 (5.7)	377 (5.1)	247 (1.8)	377 (1.9)
Alzheimer's disease	153 (3.8)	308 (4.1)	0 (0.0)	0 (0.0)
CV disease or risk factors at study baseline				
Hypertension, n (%)	1,481 (36.5)	2,719 (36.4)	3,433 (24.5)	3,866 (19.6)
Diabetes mellitus, n (%)	332 (8.2)	675 (9.0)	861 (6.2)	1,022 (5.2)
Hyperlipidemia, n (%)	808 (19.9)	1,380 (18.5)	2,167 (15.5)	2,677 (13.5)
Vascular disease, n (%)	243 (6.0)	479 (6.4)	667 (4.8)	814 (4.1)
Low-dose aspirin use, n (%)	530 (13.1)	996 (13.3)	1,635 (11.7)	2,174 (11.0)

comitant doses of aspirin permitted in all trials were 81 to 325 mg/day (for CV risk prophylaxis). Patients who began low-dose aspirin treatment during the course of the trial remained in the studies and in the analyses, but they were categorized as nonusers of aspirin.

Assessments for CV end points: The primary analysis in the present study was based on the APTC end points, excluding gastrointestinal hemorrhage.[13] These CV events were identified by extracting all serious adverse events reported by investigators using a World Health Organization Adverse Reactions Terminology dictionary.[17] This constituted the nonadjudicated data set, which was analyzed and compared with the results after adjudication. The CV events were assessed independently by a 3-member end point committee (WBW, JSB, PBG) with extensive expertise in cardiac and cerebrovascular end point assessment. All CV event adjudications were performed blinded to drug exposure and to type of study to determine if the CV events met the criteria for APTC end points. End points sought from the database included (1) nonfatal cardiac events (nonfatal myocardial infarction, myocardial ischemia, acute coronary syndrome, angina pectoris, resuscitated cardiac arrest, coronary revascularization); (2) deaths, including sudden or unexplained death or death more clearly attributable to cardiac causes; and (3) cerebrovascular events (ischemic or hemorrhagic stroke or transient ischemic attack).

The following definitions were used in the adjudicated diagnosis of an APTC end point. Acute myocardial infarction was defined as the presence of ≥2 of the following criteria: (1) chest pain, (2) abnormal cardiac enzyme concentrations of any magnitude (MB fraction of creatine phosphokinase and/or troponin), and (3) myocardial injury pattern or the development of Q waves in 2 contiguous electrocardiographic leads. Stroke was defined as ischemic or hemorrhagic stroke with an acute, focal neurologic event lasting >24 hours. Imaging studies (computed tomography or magnetic resonance imaging of the brain) were considered if available but were not required for adjudication of an event. CV death was defined as death that was sudden or unexplained or death associated with acute myocardial infarction, stroke, or pulmonary embolism.

If an event adjudicated by the end point committee differed in diagnosis from that assigned by the original reporter, the event was reclassified according to the committee's determination. If the data available were deemed insufficient by the committee to permit a definitive diagnosis, the original reporter's diagnosis was accepted. All events within 28 days of the last drug exposure were considered "exposure associated" and included in the analyses. When 2 events that were clinically linked occurred within 1 to 2 weeks of each other, only the more severe event was included; for example, if a patient had a hemorrhagic stroke followed by CV death 4 days later, only CV death was included in the analysis.

Statistical analyses: Analyses were performed by 1 investigator (SXP), and the results of the primary and secondary analyses reported here were independently evaluated and validated by statisticians in the Department of Biostatistics of the School of Public Health at the University of North Carolina at Chapel Hill, under the direction of 1 investigator (LML). The times to the APTC end points were analyzed in the entire cohort and in several subgroups described in the following. In any individual patient, the first event (nonfatal myocardial infarction, nonfatal stroke, or CV death) was used for the event-rate and time-to-event calculations. The intent-to-treat population was defined a priori in the various trial protocols as all patients who received ≥1 dose of assigned study medication and was used in all statistical analyses.

Table 3
Primary Antiplatelet Trialists' Collaborative end points by type of event: celecoxib versus placebo

Event	Celecoxib (200–800 mg) (n = 7,462)		Placebo (n = 4,057)		RR (95% CI), p Value
	Events	Rate/100 Patient-Yrs	Events	Rate/100 Patient-Yrs	
Adjudicated events					
APTC composite	18	1.42	7	1.20	1.11 (0.47–2.67), 0.81
CV deaths	8	0.63	3	0.51	1.26 (0.33–4.77), 0.74
Nonfatal MI	5	0.39	1	0.17	1.56 (0.21–11.90), 0.67
Nonfatal stroke	5	0.39	3	0.51	0.80 (0.19–3.31), 0.75
Nonadjudicated (investigator-reported) events					
APTC composite	23	1.81	8	1.37	1.26 (0.57–2.80), 0.57
CV deaths	11	0.87	3	0.51	1.74 (0.49–6.17), 0.39
Nonfatal MI	7	0.55	2	0.34	1.24 (0.27–5.76), 0.79
Nonfatal stroke	5	0.39	3	0.51	0.80 (0.19–3.31), 0.75

MI = myocardial infarction.

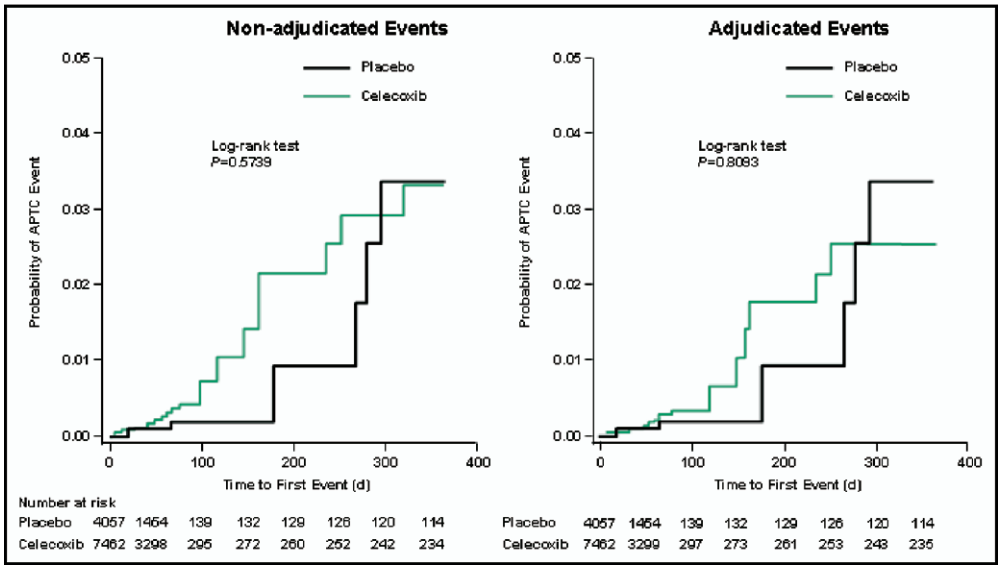

Figure 1. Time to APTC events with celecoxib (200 to 800 mg) versus placebo in all patients (nonadjudicated, investigator reported, and adjudicated are shown separately).

Analyses of serious CV events were performed from studies comparing celecoxib with placebo, from studies comparing celecoxib with combined nonselective NSAIDs (naproxen, ibuprofen, diclofenac, ketoprofen, and loxoprofen at any dose), and from studies comparing celecoxib with the individual NSAIDs (naproxen, ibuprofen, and diclofenac). For validation purposes, an additional meta-analysis including all patients randomized to either of the 3 treatment arms (celecoxib, placebo, or NSAIDs) in any clinical trial containing ≥2 of the 3 arms was also conducted.

Analyses of CV events were performed for all patients and for the following subgroups: (1) users versus nonusers of low-dose aspirin at baseline; (2) celecoxib dosage groups of 200, 400, and 800 mg/day as well as all doses combined; and (3) therapeutic indications of osteoarthritis and rheumatoid arthritis and the combined subgroup of patients with osteoarthritis and rheumatoid arthritis. In addition, analyses were performed for subgroups with or without CV risk factors ascertained by the investigators at baseline (hypertension, diabetes mellitus, hyperlipidemia, and history of vascular disease).

For the analysis of APTC CV events, the Cochran-Mantel-Haenszel test, stratified by study, was used to analyze differences in incidence rates (numbers of events per patient-year of treatment) between treatment groups. The relative risk (RR) of each respective event is expressed as the ratio of celecoxib to the comparator with 95% confidence intervals (CIs) and p values for statistical tests of the hypothesis that the RR equaled 1.0. When the estimated RR was <1, celecoxib had a more favorable CV event profile compared with the other treatment group; the reverse was true if the estimated RR was >1. Time-to-event data were compared using the log-rank test,[18] and the data were displayed graphically using the Kaplan-Meier method.[19] Events with onset >364 days were considered as having onset at day 364. All p values in this study were 2 sided, and all 95% CIs were 2 sided.

Table 4
Primary Antiplatelet Trialists' Collaborative end points by type of event: celecoxib versus nonselective NSAIDs

Event	Celecoxib (200–800 mg) (n = 19,773)		Nonselective NSAIDs (n = 13,990)		RR (95% CI), p Value
	Events	Rate/100 Patient-yrs	Events	Rate/100 Patient-yrs	
Adjudicated events					
APTC composite	54	0.96	49	1.12	0.90 (0.60–1.33), 0.59
CV deaths	12	0.21	19	0.43	0.57 (0.28–1.14), 0.11
Nonfatal MI	32	0.57	15	0.34	1.76 (0.93–3.35), 0.08
Nonfatal stroke	10	0.18	15	0.34	0.51 (0.23–1.10), 0.09
Nonadjudicated (investigator-reported) events					
APTC composite	57	1.01	54	1.23	0.86 (0.59–1.26), 0.44
CV deaths	15	0.27	19	0.43	0.72 (0.37–1.39), 0.33
Nonfatal MI	35	0.62	19	0.43	1.49 (0.82–2.70), 0.19
Nonfatal stroke	7	0.12	16	0.36	0.33 (0.14–0.78), 0.01

Abbreviation as in Table 3.

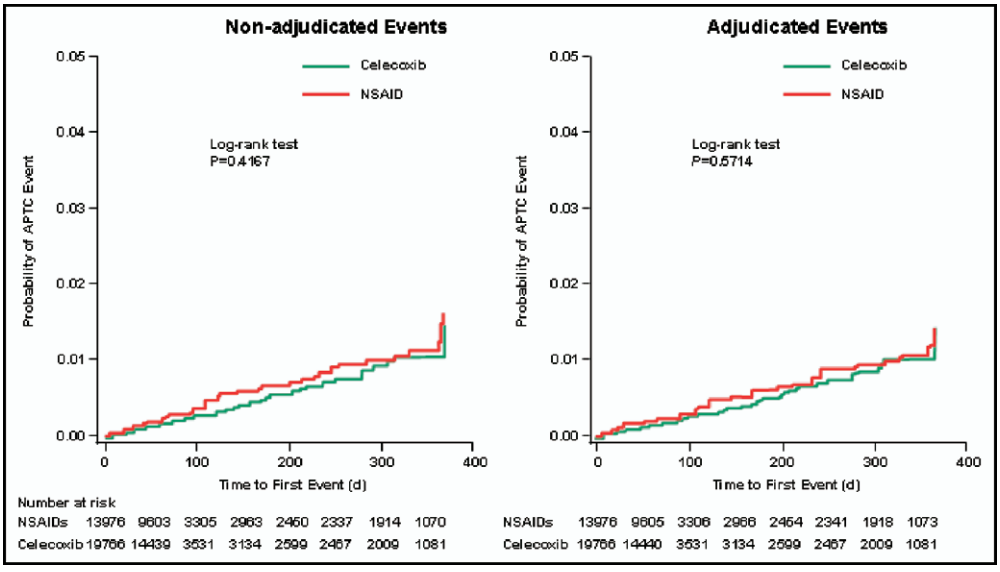

Figure 2. Time to APTC events with celecoxib (200 to 800 mg) versus nonselective NSAIDs in all patients (nonadjudicated, investigator reported, and adjudicated are shown separately).

Results

Baseline characteristics of the treatment groups: As listed in Table 1, 41,077 patients were included in this meta-analysis: 23,030 patients were randomized to celecoxib (total dose 200 to 800 mg/day), 4,057 to placebo, and 13,990 to nonselective NSAIDs (including 2,953 to naproxen, 2,484 to ibuprofen, 7,639 to diclofenac, 90 to ketoprofen, and 824 to loxoprofen). Most trials were 12 weeks in duration; those notably longer in duration were the NSAID-controlled trials CAESAR (52 weeks, 916 patients), the CLASS trial (≥26 weeks, 7,968 patients), and the placebo-controlled Alzheimer's disease trial (52 weeks, 425 patients) and its 2-year placebo-controlled extension (2 years, 36 patients). For placebo-controlled studies, about 90% of the patients were exposed to short- or intermediate-term (4 to 12 weeks) study drug administration. Because of the large and longer term CLASS trial,[1,16] drug exposure for celecoxib compared with diclofenac and ibuprofen was longer than comparisons between celecoxib and naproxen.

Clinical characteristics of the patients according to treatment groups (celecoxib, placebo, or nonselective NSAIDs) are listed in Table 2. Baseline patient characteristics in the comparisons between celecoxib (200 to 800 mg) and placebo and between celecoxib (200 to 800 mg) and the nonselective NSAIDs were similar for age, gender, therapeutic indications, and aspirin use (11% to 13% in each group). Similar proportions of the patients in the celecoxib (200 to 800 mg) versus placebo treatment groups and in the celecoxib (200 to 800 mg) versus nonselective NSAIDs treatment groups had the CV risk factor of hypertension, diabetes, hyperlipidemia, or vascular disease at baseline (Table 2).

Primary CV events (composite) for placebo-controlled trials: For the primary analysis, results are reported on the basis of adjudicated APTC end points and nonadjudicated APTC end points. The RRs and 2-sided 95% CIs based on the Cochran-Mantel-Haenszel test are listed in

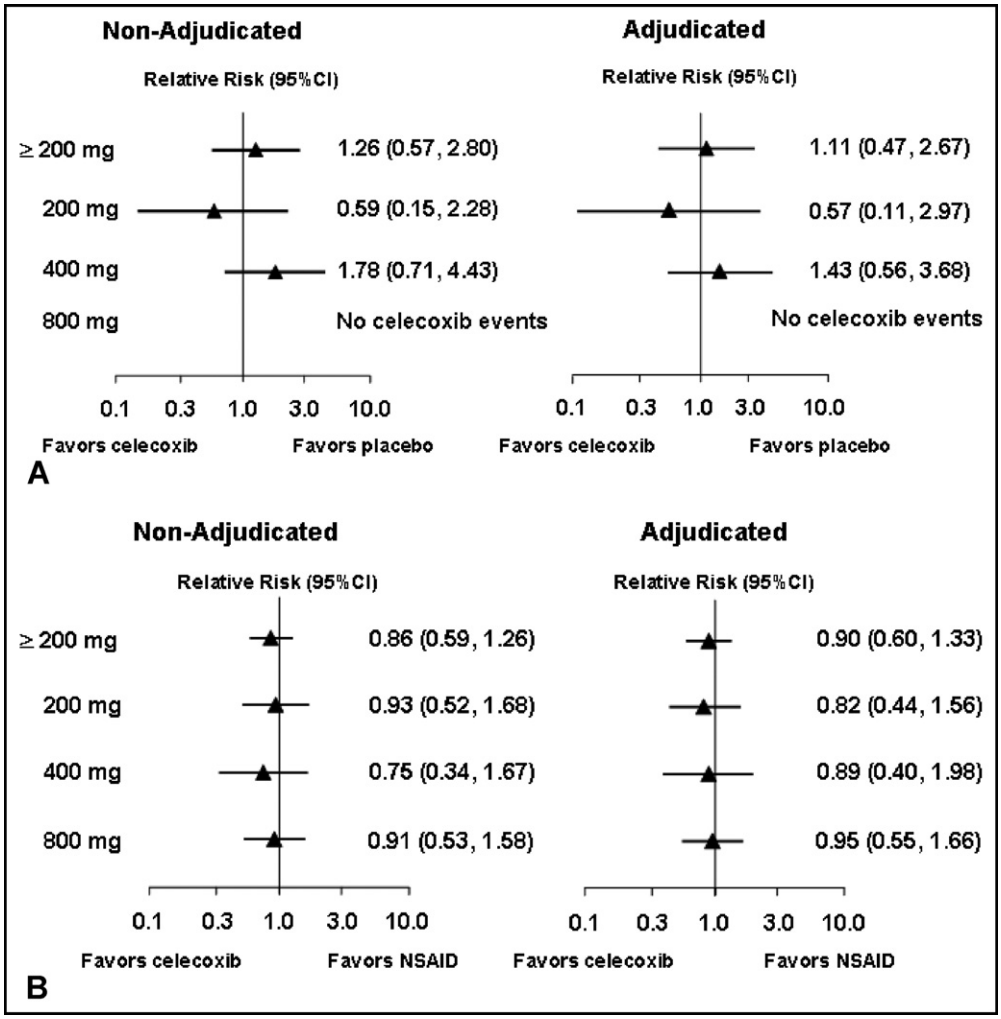

Figure 3. Pooled analysis of APTC end points by dose of celecoxib (total dose 200, 400, or 800 mg/day): RRs *(solid triangles)* and 2-sided 95% CIs *(bars)* for celecoxib versus placebo *(A)* and celecoxib versus nonselective NSAIDs *(B)*.

Table 3. A Kaplan-Meier plot of time to first APTC end point is presented in Figure 1. A total of 23 APTC events were reported by investigators in 7,462 patients randomized to celecoxib (1,268.3 patient-years) and 8 APTC events in 4,057 patients randomized to placebo (584.5 patient-years). For the celecoxib versus placebo adjudicated events comparison, no significant treatment difference was evident (RR 1.11, 2-sided 95% CI 0.47 to 2.67, p = 0.81). Similarly, the RR for the nonadjudicated events was 1.26, with a 2-sided 95% CI of 0.57 to 2.80 (p = 0.57). The adjudicated celecoxib APTC event rate was 1.42/100 patient-years, compared with a placebo rate of 1.20/100 patient-years.

Event rates were very low (<1 event/100 patient-years) for comparisons of 2,478 patients receiving nonselective NSAIDs (335.0 patient-years) with 2,035 placebo-treated patients (237.5 patient-years). For the placebo versus nonselective NSAID adjudicated events comparison of APTC events, no difference was observed (RR 1.10, 2-sided 95% CI 0.17 to 7.21, p = 0.92).

Primary CV events (composite) for nonselective NSAID-controlled trials: Adjudicated APTC end points and nonadjudicated APTC end points are listed in Table 4 and shown in Figure 2. A total of 57 APTC events were reported by investigators in 19,773 patients randomized to celecoxib (5,651.2 patient-years) and 54 APTC events in 13,990 patients randomized to any nonselective NSAID (4,386.4 patient-years). Comparisons of celecoxib versus nonselective NSAIDs demonstrated no difference in adjudicated event rates (RR 0.90, 2-sided 95% CI 0.60 to 1.33, p = 0.59) or for nonadjudicated event rates (RR 0.86, 2-sided 95% CI 0.59 to 1.26, p = 0.44). The rate for adjudicated events in celecoxib-treated patients was 0.96/100 patient-years, compared with a rate of 1.12/100 patient-years for patients treated with nonselective NSAIDs. Assessment of individual types of adjudicated CV events indicated a higher RR for myocardial infarction (RR 1.76, 2-sided 95% CI 0.93 to 3.35, p = 0.08) with celecoxib compared with the nonselective NSAIDs and a lower RR for stroke with celecoxib compared with the nonselective NSAIDs (RR 0.51, 2-sided 95% CI 0.23 to 1.10, p = 0.09).

CV event rates according to CV risk factors at baseline: Risk factors recorded at baseline included the use of low-dose aspirin and the presence of hypertension, diabetes mellitus, hyperlipidemia, and/or a history of vascular dis-

ease. Adjudicated and nonadjudicated event rates were higher in patients with baseline CV risk factors than in those without baseline CV risk. No significant increases in RRs for APTC events were found in patients treated with celecoxib relative to placebo or relative to nonselective NSAIDs in patients with CV risk factors. In users of aspirin, the RR for APTC events for celecoxib relative to NSAIDs was 1.25 (95% CI 0.68 to 2.30, p = 0.47). For nonusers of aspirin, the RR for APTC events for celecoxib relative to NSAIDs was 0.68 (95% CI 0.40 to 1.16, p = 0.16). Of note, in nonusers of aspirin, adjudicated CV death rates with celecoxib were significantly lower than with nonselective NSAIDs (0.16 events/100 patient-years vs 0.45 events/100 patient-years, RR 0.43, 2-sided 95% CI 0.19 to 0.95, p = 0.04).

Adjusting for CV risk factors at baseline did not significantly affect the RR for CV events. For example, the hazard ratio for celecoxib versus placebo controlling for study and CV risk at baseline (no risk factors, 1 risk factor, or 2 risk factors) was 1.07 (95% CI 0.45 to 2.58, p = 0.876) for adjudicated events and 1.20 (95% CI 0.54 to 2.70, p = 0.653) for nonadjudicated events. The hazard ratio for celecoxib versus NSAIDs controlling for study and CV risk at baseline was 0.89 (95% CI 0.60 to 1.31, p = 0.548) for adjudicated events and 0.85 (95% CI 0.58 to 1.24, p = 0.406) for nonadjudicated events.

CV events according to other factors: The RRs for adjudicated and nonadjudicated APTC end points of CV death, nonfatal myocardial infarction, and nonfatal stroke did not vary according to doses of 200, 400, and 800 mg/day for celecoxib versus placebo or versus nonselective NSAIDs (Figure 3). In addition, there were no significant differences in CV event rates with celecoxib versus nonselective NSAID comparators in patients with osteoarthritis or rheumatoid arthritis. For the 1 small Alzheimer's disease study that compared celecoxib 400 mg/day with placebo for ≤52 weeks and its 2-year placebo-controlled extension (36 patients), the RR was 1.71 (95% CI 0.57 to 5.19, p = 0.34) for the nonadjudicated APTC composite end point.

Composite analysis: Data from all patients in the 39 celecoxib clinical trials were combined for a single meta-analysis of the composite APTC end point comparing the 3 treatment groups. For patients taking any dose of celecoxib (n = 23,966), 66 events were observed, compared with 7 events in patients taking placebo (n = 4,057) and 49 events in those taking nonselective NSAIDs (n = 13,976). Hazard ratios for celecoxib versus placebo were 0.78 (95% CI 0.36 to 1.72, p = 0.538) for adjudicated events and 0.76 (95% CI 0.36 to 1.58, p = 0.461) for nonadjudicated events. Hazard ratios for celecoxib versus nonselective NSAIDs were 0.95 (95% CI 0.65 to 1.37, p = 0.771) for adjudicated events and 0.95 (95% CI 0.67 to 1.35, p = 0.765) for nonadjudicated events.

Discussion

In analyses of clinical trials involving >41,000 patients, no significant increase in CV events (nonfatal myocardial infarction, nonfatal stroke, and CV death) was found when patients treated with the cyclooxygenase-2 selective inhibitor celecoxib were compared with patients who received nonselective NSAIDs or placebo. In addition, although overall event rates were higher in patients with increased CV risk factors or in those who were users of aspirin at baseline, we found no differences in APTC event rates among the celecoxib, nonselective NSAID, or placebo treatment groups. Also, there were no increases in APTC event rates according to dose of celecoxib, from 200 to 800 mg/day (Figure 3).

All reported nonfatal myocardial infarction, nonfatal stroke, and mortal events were adjudicated by an expert committee blinded to treatment allocation and to the type of study, including indication. Although CV event rates were relatively similar for the adjudicated versus nonadjudicated events, there was an important adjustment in the case of nonfatal stroke (Table 4). On the basis of nonadjudicated stroke events, there were significantly fewer nonfatal strokes with celecoxib compared with nonselective NSAIDs (RR 0.33, p = 0.01). Because the adjudication process diagnosed clinical stroke events in some patients with transient ischemic attack, the event rate was found to be slightly higher in patients taking celecoxib (0.18 events/100 patient-years for adjudicated strokes vs 0.12 events/100 patient-years for nonadjudicated strokes), and the RR for stroke with celecoxib compared with nonselective NSAIDs was no longer statistically significant. It is also noteworthy that our adjudication process did not remove APTC events to the extent that statistical trends were altered in a meaningful way (Tables 3 and 4).

The CV event rates in the present meta-analysis are similar to those published in our first analysis[12] for the comparisons between celecoxib and the nonselective NSAIDs in the osteoarthritis and rheumatoid arthritis population and slightly higher for the populations involved in comparisons between celecoxib and placebo. In the present meta-analysis, we have extended our findings with a more comprehensive assessment of celecoxib safety that included patients with low back pain, ankylosing spondylitis, and Alzheimer's disease. The difference for the placebo event rate in the present meta-analysis compared with the previous one was due to the inclusion of the single long-term Alzheimer's disease study, in which a higher CV event rate was observed, probably attributable to the advanced age and CV co-morbidities in the population.

Before using standardized and adjudicated APTC events for these meta-analyses, clinical trials such as CLASS[1,16] used regulatory definitions and coded diagnoses that are based on investigator-reported diagnoses and clinical terms or language in case report forms. Differences in CV event rates between coded adverse event terms and the present analysis are not unexpected. The identification of serious adverse events by investigators was not necessarily based on the same criteria as the APTC diagnostic criteria used in our analysis; no prespecified or uniform event criteria were used by the investigators or clinical coordinators.

The studies included in our meta-analysis were not originally designed to assess the relative effects of celecoxib versus nonselective NSAIDs or placebo on CV risk. Fortunately, baseline demographics, including age, proportion of patients with underlying CV risk factors, and the use of low-dose aspirin were recorded and were similar among the drug treatment groups (Table 2). The other major potential

concern is that although our sample size was quite large, most trials were of relatively short durations, so the patient-years of exposure were relatively small, particularly for the placebo group. Thus, the description of absolute risk for celecoxib relative to placebo must be interpreted with caution. However, as noted previously, the event rates in our placebo-controlled trials were not dissimilar from those in recently reported placebo-controlled trials in patients with spontaneous adenomatous polyps.[9,10] Our data relating celecoxib to the nonselective NSAIDs are more robust but still have the limitation that none of the comparator trials exceeded 1 year of patient follow-up (with the exception of the small 2-year Alzheimer's disease study). In the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial,[2] the separation of CV events occurred within 4 to 6 months of exposure to rofecoxib versus naproxen, but in the Adenomatous Polyp Prevention on Vioxx (APPROVe)[9] and APC[10] trials, increased CV events were not observed in the cyclooxygenase-2 selective inhibitor treatment groups relative to placebo until well after 12 months of drug exposure.

Our study represents the largest "patient-level" meta-analysis of celecoxib to date. The results of this analysis fail to demonstrate a difference in the incidence of CV events compared with nonselective NSAIDs or compared with placebo up to 1 year of treatment exposure.

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