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CLINICAL RESEARCH STUDY

Celecoxib Versus Naproxen and Diclofenac in Osteoarthritis Patients: SUCCESS-I Study

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ABSTRACT

PURPOSE: To evaluate the efficacy and upper gastrointestinal (UGI) safety of celecoxib, compared with nonspecific nonsteroidal anti-inflammatory drugs (NSAIDs), among patients with osteoarthritis.

METHODS: A total of 13 274 osteoarthritis patients from 39 countries were randomly assigned to double-blind treatment with either celecoxib 100 mg twice daily (BID), celecoxib 200 mg BID, or nonselective NSAID therapy (diclofenac 50 mg BID or naproxen 500 mg BID) for 12 weeks. Standard validated measures were used to assess osteoarthritis efficacy. Serious UGI events were evaluated by 2 blinded, independent, gastrointestinal events committees.

RESULTS: Results from all primary efficacy assessments showed that both dosages of celecoxib were as effective as NSAIDs in treating osteoarthritis. Significantly more ulcer complications occurred within the nonselective NSAID group (0.8/100 patient-years) compared with the celecoxib group (0.1/100 patient-years) (odds ratio = 7.02; 95% confidence interval [CI], 1.46 to 33.80; $P = .008$). There were fewer ulcer complications in the celecoxib group compared with the NSAID group, both in patients taking concomitant aspirin and those not taking aspirin, but the difference reached statistical significance only in the latter comparison. The number of cardiovascular thromboembolic events was low and not statistically different between the groups (eg, myocardial infarction rates: celecoxib 10 events [0.55/100 patient-years] vs NSAIDs 1 event [0.11/100 patient-years], ($P = .11$), but the study was not powered to detect such differences.

CONCLUSIONS: In the treatment of osteoarthritis, celecoxib is as effective as the nonspecific NSAIDs naproxen and diclofenac, but has significantly fewer serious upper gastrointestinal events.

KEYWORDS: Celecoxib; Nonsteroidal anti-inflammatory agents; Osteoarthritis; Gastrointestinal events; Cardiovascular events; Rofecoxib; Naproxen; Diclofenac; NSAID gastropathy

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The gastrointestinal toxicity of nonsteroidal anti-inflammatory drugs (NSAIDs) is well recognized.[1] It has been estimated that serious gastrointestinal complications related to NSAID therapy result in approximately 103 000 hospitalizations and 16 500 deaths per year in the United States (US).[2] The cyclooxygenase-2 (COX-2)-specific inhibitors, which have demonstrated equivalent efficacy to nonspecific NSAIDs in the management of arthritis and pain,[3-7] may reduce these adverse events.[3,8-12]

CLINICAL SIGNIFICANCE

- Celecoxib 100 or 200 mg twice daily is as effective as diclofenac 50 mg BID and naproxen 500 mg BID in treating osteoarthritis.
- Significantly less ulcer complications occur with celecoxib as compared to NSAIDs both in patients taking concomitant aspirin and in those who are not.
- The number of cardiovascular thromboembolic events is low and not statistically different between the groups.

Three large, randomized, clinical trials compared the rates of serious upper gastrointestinal events in patients taking COX-2-specific inhibitors and nonspecific NSAIDs but came to different conclusions. The Vioxx Gastrointestinal Outcomes Research (VIGOR) trial, which compared rofecoxib with naproxen in rheumatoid arthritis patients, and the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), which compared lumiracoxib with naproxen and ibuprofen in osteoarthritis patients, found a significantly lower incidence of serious upper gastrointestinal events in patients treated with the COX-2-inhibitor compared with patients treated with nonspecific NSAIDs.[11,12] The Celecoxib Long-term Arthritis Safety Study (CLASS), which compared celecoxib with ibuprofen and diclofenac in patients with osteoarthritis and rheumatoid arthritis, did not conclusively demonstrate a significant reduction in the primary endpoint of upper gastrointestinal ulcer complications, although significant differences were observed when symptomatic ulcers were also considered with ulcer complications.[10] An unexpected finding from the VIGOR trial was a significantly increased risk of serious thromboembolic events in rofecoxib-treated patients compared with those taking naproxen;[11] no increased risk was seen with celecoxib in the CLASS trial or with lumiracoxib in the TARGET trial.[10,12]

Several questions remain about the safety advantage of COX-2-specific inhibitors compared with nonspecific NSAIDs, including whether they have a lower risk of serious gastrointestinal events and whether their potential gastrointestinal advantage is negated by an increased risk of thromboembolic complications. Additionally, the impact of concomitant low-dose aspirin use on gastrointestinal events is still uncertain. The VIGOR trial excluded all patients requiring concomitant aspirin,[11] and the CLASS and TARGET trials did not show any gastrointestinal safety advantage in the subgroup of patients taking concomitant aspirin.[10,12]

In an attempt to answer some of these questions, we present data from the SUccessive Celecoxib Efficacy and Safety Study-1 (SUCCESS-1), a large, multinational, "real-world," randomized, and controlled clinical trial in patients with osteoarthritis.

METHODS

Patients

The SUCCESS-1 study was specifically designed with inclusion and exclusion criteria that would yield a study population representative of osteoarthritis patients in community-based, outpatient, clinical practices in each of the participating countries. Eligible patients were aged 18 years or older; had osteoarthritis of the hip, knee, or hand (meeting American College of Rheumatology classification criteria) of at least 6 months duration before randomization; required daily anti-inflammatory agents or other analgesic therapy to control arthritis symptoms; and had a Functional Capacity Classification ranging from I to III.[13] Major exclusion criteria were a history of 2 or more episodes of active peptic ulceration; gastrointestinal bleeding, or recurrent gastric or duodenal ulcers; an esophageal, gastric, or duodenal ulcer within 30 days before randomization; or active gastrointestinal disease or any condition precluding NSAID therapy. Additional criteria for exclusion were intra-articular or intramuscular corticosteroid or intra-articular hyaluronic acid joint injection within 8 weeks before randomization; required daily use of anti-ulcer medications, including misoprostol, histamine H_2-receptor antagonists, proton-pump inhibitors, or antacids; or required daily acetaminophen or other analgesics (in addition to NSAID therapy) for arthritis pain relief. The use of other NSAIDs (except aspirin up to 325 mg daily for cardioprotection), oral corticosteroids, and disease modifying antirheumatic drugs were not permitted, and patients enrolled in the study were not thought to require these agents by their treating physician. The ethics committees or institutional review boards in all participating centers approved the study protocol, and all patients gave written informed consent.

Procedures

The study was a multicenter, multinational, randomized, double-blind, 3-arm, active-comparator trial. Patients were randomly assigned to receive either celecoxib (Celebrex; Pfizer, New York, New York) 100 mg twice daily; celecoxib 200 mg twice daily; or non-specific NSAID therapy (diclofenac [Voltaren; Novartis, Basel, Switzerland] 50 mg twice daily or naproxen [Naprosyn; Roche, Nutley, New Jersey] 500 mg twice daily) for 12 weeks. Naproxen was

administered to patients in the U.S. and Canada, and diclofenac was administered to patients in all other countries. Double-blind, central computer-generated, interactive voice response system (IVRS) randomization was in a 1:1:1 ratio, with block sizes of 3, using 2 randomization schedules: 1 for celecoxib treatment groups and naproxen, and the other for the celecoxib treatment groups and diclofenac. Study drug treatment was initiated either on the day of or the day following randomization, and no washout period was required before study drug administration.

The objectives of the study were to evaluate the overall efficacy, safety, and tolerability of celecoxib, as compared with nonspecific NSAIDs. At each visit (pretreatment, week 6, and week 12 [or final]), efficacy and safety were assessed and patients were queried as to what medications were taken. Efficacy was measured by: 1) Patient's Assessment of Arthritis Pain-Visual Analog Scale, graded on a scale of 0 mm (no pain) to 100 mm (very severe pain);[14] 2) Patient's Global Assessment of Arthritis, graded on a scale of 1 (very good) to 5 (very poor);[14] and 3) the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index, a 24-component patient assessment of osteoarthritis pain, joint stiffness, and physical function.[15] Patients with osteoarthritis of the hand also completed the WOMAC questionnaire, even though it has not been validated in patients with this disease classification. The primary efficacy analysis was a comparison of these endpoints among the treatment groups in prespecified countries or geographic sub-regions; an assessment of homogeneity of efficacy between various countries or geographic regions was also planned. The primary safety analysis included an adjudication of serious upper gastrointestinal events, as well as an overall evaluation of investigator-reported adverse events, including cardiovascular events.

Investigators were required to report any possible serious upper gastrointestinal adverse event, and to investigate those events according to local standard-of-care procedures, ie, there were no predetermined requirements for any gastrointestinal investigations, including endoscopy. Investigator-identified serious upper gastrointestinal events were reviewed and adjudicated to consensus by 2 independent committees (both blinded to patient randomization), using 2 different methodologies and definitions. The first committee used criteria that required endoscopic confirmation of all lesions ("adjudication based on endoscopic lesions"). Each case was classified as 1 of 5 distinct outcomes—categories 1 through 4 (perforations, ulcer bleeding, obstructions, and symptomatic ulcers, respectively) were upper gastrointestinal outcomes, and category 5 was "other" gastrointestinal events. Categories 1, 2 and 3 were designated "ulcer complications" and Categories 1 through 4 "significant upper gastrointestinal events" (Appendix A). The second committee (post hoc) used criteria based on clinical presentation, and did not always require endoscopic documentation of lesions ("adjudication based on clinical presentation"); patients were classified as having "complicated" or "confirmed" upper gastrointestinal outcomes (Appendix B).[16]

Statistical Analysis

All efficacy and safety analyses were conducted in the intention-to-treat cohort, defined as all patients who received at least 1 dose of study medication. The primary efficacy analysis was a comparison of efficacy in prespecified countries, groups of countries, or geographic regions. A treatment difference of ±9% (95% confidence interval [CI]) between the celecoxib and NSAID groups was anticipated. Clinical comparability was declared when the 95% CI of the difference in the mean treatment response between 2 treatments was ±10 mm on a 100-mm visual analog scale (VAS).[14] All prespecified efficacy analyses compared each dose of celecoxib with the combined NSAID group. Changes from baseline were compared using the Cochran-Mantel-Haenszel test for categorical variables and a general linear model for continuous variables. For continuous variables, the baseline value was included as a covariate. In addition, an assessment of homogeneity was performed to compare treatment effect across the different regions.[17]

All prespecified gastrointestinal safety analyses compared the combined celecoxib group with the combined NSAID group. Specifically concerning upper gastrointestinal safety, the prespecified power calculation required a comparison of the combined celecoxib and the combined NSAID groups. The rates of serious gastrointestinal events in the combined celecoxib group and in the combined NSAID group were compared using time-to-event analyses (log-rank test) and Fisher's exact test. A post hoc analysis of upper gastrointestinal safety according to aspirin use was also performed. Treatment differences in the incidence of adverse events were compared using the Fisher's exact test or the Cochran-Mantel-Haenszel test. Additionally, because of current interest, a post hoc analysis of cardiovascular event rates (which were investigator-reported) among the treatment groups was also performed. The odds ratio (OR) was calculated comparing events in the NSAID group to those in the celecoxib group. A significant P value of $\leq .05$ was designated for all assessments.

RESULTS

A total of 13 274 patients from 1142 study centers in 39 countries were randomized. Of these patients, 13 194 received at least 1 dose of study medication (intention-to-treat cohort): 4393 celecoxib 100 mg twice daily, 4407 celecoxib 200 mg twice daily, 905 naproxen 500 mg twice daily, and 3489 diclofenac 50 mg twice daily. Geographically, 6511 patients were from Europe and South Africa, 2873 from Latin America, 2736 from the U.S. and Canada, 681 from Asia, and 393 from Australia and New Zealand. Baseline characteristics were similar between the celecoxib and NSAID treatment groups, including cardiovascular history and risk factors for gastrointestinal events (Table 1). The majority of patients were Caucasian (80%) and women

Table 1 Baseline Characteristics of the 13 194 Randomized Participants, According to Treatment Group

Characteristic	NSAID Groups (n = 4394)	Celecoxib Groups (n = 8800)	*P* Value*
	Number (%) or Mean ± SD		
Mean (SD) age (years)	62.2 (10.4)	62.2 (10.7)	.75
Sex			
Women	3351 (76.3)	6656 (75.6)	.43
Ethnic origin			
Caucasian	3506 (79.8)	7015 (79.7)	.92
Other	888 (20.2)	1785 (20.3)	.92
Index joint			
Knee	2787 (63.4)	5598 (63.6)	.83
Hip	796 (18.1)	1590 (18.1)	.95
Hand	811 (18.5)	1612 (18.3)	.85
Mean (SD) duration of osteoarthritis (years)	7.8 ± 7.5	7.8 ± 7.4	.75
Mean (SD) Visual Analog Scale Pain Score (mm)	56.0 ± 22.0	56.5 ± 22.0	.36
Risk factors			
Age ≥75 years	548 (12.5)	1125 (12.8)	.61
History of upper gastrointestinal bleeding	42 (1.0)	86 (1.0)	.91
History of ulcer	189 (4.3)	346 (3.9)	.31
History of diabetes mellitus	357 (8.1)	732 (8.3)	.70
History of hypertension	1667 (37.9)	3420 (38.9)	.30
History of congestive heart failure	70 (1.6)	167 (1.9)	.21
History of myocardial infarction	13 (0.3)	20 (0.2)	.46
History of coronary arteriosclerosis	5 (0.1)	22 (0.3)	.10
Aspirin use for cardioprophylaxis	315 (7.2)	622 (7.1)	.83

*All *P* values are from Exact methods, except for age, duration of osteoarthritis, and VAS pain scale, which are from the *t* test.

(76%). In both treatment groups, the mean age of patients was 62 years and the mean duration of osteoarthritis was 8 years. Results from all primary efficacy assessments showed that both dosages of celecoxib were as effective as NSAIDs in treating the signs and symptoms of osteoarthritis, including Patient's Assessment of Arthritis Pain – VAS (Table 2). Although in some instances the differences were statistically significant, they were not clinically significant according to the prespecified criteria (>10 mm difference on a 100-mm VAS). Homogeneity assessments also showed no difference in treatment response across the geographic areas. In addition, celecoxib 100 mg twice daily demonstrated efficacy similar to celecoxib 200 mg twice daily. Separate analyses of osteoarthritis of the hip, knee, or hand showed that all treatments were similarly efficacious in all joints.

The most commonly reported adverse events are shown in Table 3. Overall, a significantly smaller proportion of patients treated with celecoxib (37.2%) than with NSAIDs (40.3%) experienced at least 1 adverse event ($P < .001$). The most commonly reported events were abdominal pain and dyspepsia, both of which were experienced by significantly more NSAID patients than celecoxib patients. A total of 10 deaths were reported, 5 in the celecoxib group (0.06%) and 5 in the NSAID group (0.11%); the difference between groups was not statistically significant. In the investigators' opinions, 9 deaths were considered not related to study medication, and 1 was categorized as having an uncertain relationship to study medication. Adverse events requiring study withdrawal occurred in a smaller proportion of celecoxib-treated (9.2 %) than NSAID-treated patients (10.3%) ($P = .05$). The most common event leading to withdrawal was abdominal pain (2.1% in the celecoxib group and 2.8% in the NSAID group, $P = .02$).

Investigators identified 144 potential serious upper gastrointestinal events, and these were submitted for adjudication (Table 4). In the adjudication "by lesion" analysis, 36 events were judged as significant upper gastrointestinal events, including 9 events classified as "ulcer complications" (gastric or duodenal perforations, gastric outlet obstruction, or upper gastrointestinal bleeding, confirmed by endoscopy). Significantly more ulcer complications occurred within the NSAID group (0.8 per 100 patient-years) compared with celecoxib (0.1 per 100 patient-years) (OR = 7.02; 95% CI, 1.46 to 33.80; $P = .008$). In the adjudication "by clinical presentation" analysis, 37 events were judged as confirmed upper gastrointestinal events, including 12 events classified as complicated upper gastrointestinal events. Again, significantly more complicated upper gastrointestinal events were seen with the NSAID group (1.0 per 100 patient-years) compared with celecoxib (0.2 per 100 patient-years) (OR = 6.02; 95% CI, 1.50 to 34.57; $P = .004$). Figure 1 shows the time-to-event analysis for complicated upper gastrointestinal events, and Figure 2 shows a similar analysis for confirmed upper gastrointestinal events. Log-rank tests for comparison of celecoxib and the NSAID group were statistically significant for both analyses. SUCCESS-1 was not powered for comparisons between celecoxib and each of the two NSAIDs individually. However, a post hoc analysis showed that patients on celecoxib had numerically fewer events (2 events, 0.1/100 patient-years)

Table 2 Primary Efficacy Endpoints: Baseline to Week 12 Treatment Differences*

	Celecoxib 100 mg BID vs NSAID			Celecoxib 200 mg BID vs Celecoxib 100 mg BID		
	Mean Treatment Difference (95% Confidence Interval)					
Country/Region	Patient Assessment of Pain-VAS (mm)	Patient Global Assessment of Arthritis	Total WOMAC Score (mm)	Patient Assessment of Pain-VAS (mm)	Patient Global Assessment of Arthritis	Total WOMAC Score (mm)
United States	1.01 (−2.55 to 4.56)	.04 (−0.10 to 0.17)	−0.91 (−3.15 to 1.33)	−4.82 *(−8.34 to −1.29)*†	−0.12 (−0.25 to 0.01)	−1.31 (−3.53 to 0.91)
Canada	−0.37 (−3.32 to 2.58)	−0.03 (−0.14 to 0.08)	0.37 (−1.51 to 2.25)	1.30 (−1.65 to 4.24)	0.07 (−0.03 to 0.18)	0.38 (−1.49 to 2.26)
Benelux countries‡	2.33 (−1.85 to 6.51)	0.07 (−0.09 to 0.23)	0.50 (−2.23 to 3.22)	−1.72 (−5.92 to 2.47)	0.04 (−0.12 to 0.20)	−1.41 (−4.15 to 1.33)
Central Europe§	−1.73 (−4.86 to 1.39)	0.00 (−0.11 to 0.11)	0.11 (−1.99 to 2.21)	2.07 (−1.05 to 5.18)	0.04 (−0.07 to 0.15)	0.31 (−1.78 to 2.41)
Germany	−2.65 (−6.17 to 0.87)	−0.07 (−0.19 to 0.06)	−0.39 (−2.76 to 1.97)	3.19 (−0.33 to 6.72)	0.13 *(0.00 to 0.26)*	0.57 (−1.79 to 2.92)
Italy/Switzerland/Greece	4.15 (−0.48 to 8.78)	0.19 *(0.03 to 0.36)*	3.21 *(0.01 to 6.40)*	−1.35 (−5.93 to 3.24)	−0.07 (−0.23 to 0.09)	−0.48 (−3.66 to 2.70)
Nordic countries‖	0.79 (−3.52 to 5.10)	0.10 (−0.05 to 0.26)	3.72 *(0.89 to 6.56)*	−3.31 (−7.61 to 0.99)	−0.11 (−0.26 to 0.05)	−3.87 *(−6.67 to −1.07)*
Spain/Portugal	2.54 (−1.17 to 6.26)	0.13 (−0.01 to 0.26)	2.47 *(0.10 to 4.84)*	−1.14 (−4.84 to 2.56)	−0.12 (−0.26 to 0.01)	−0.10 (−2.46 to 2.26)
UK/Ireland	1.04 (−2.63 to 4.71)	0.10 (−0.03 to 0.23)	3.41 *(1.20 to 5.61)*	0.32 (−3.38 to 4.02)	0.00 (−0.13 to 0.14)	−1.39 (−3.61 to 0.82)
South Africa	3.63 (−1.91 to 9.18)	0.05 (−0.17 to 0.27)	−0.24 (−4.10 to 3.62)	−4.82 (−10.37 to 0.72)	−0.14 (−0.36 to 0.08)	−1.55 (−5.40 to 2.29)
Mexico	2.16 (−2.34 to 6.66)	0.09 (−0.07 to 0.24)	2.64 (−0.21 to 5.50)	−2.52 (−7.01 to 1.97)	−0.12 (−0.27 to 0.04)	−2.59 (−5.43 to 0.26)
Argentina/Chile	0.90 (−3.58 to 5.39)	0.00 (−0.16 to 0.17)	−0.72 (−3.37 to 1.94)	−1.16 (−5.65 to 3.33)	−0.04 (−0.20 to 0.13)	0.28 (−2.38 to 2.95)
Andean countries¶	3.82 (−1.11 to 8.75)	0.11 (−0.06 to 0.28)	2.84 (−0.39 to 6.07)	−2.28 (−7.20 to 2.63)	−0.15 (−0.32 to 0.02)	−1.23 (−4.45 to 1.98)
Brazil	0.94 (−2.95 to 4.83)	0.02 (−0.12 to 0.15)	2.02 (−0.40 to 4.44)	−0.95 (−4.83 to 2.93)	0.02 (−0.11 to 0.15)	−1.21 (−3.63 to 1.20)
Australia/New Zealand	0.36 (−5.69 to 6.40)	0.21 (−0.02 to 0.43)	0.97 (−2.67 to 4.62)	1.94 (−4.14 to 8.02)	−0.07 (−0.29 to 0.15)	0.82 (−2.84 to 4.49)
Asia#	5.02 *(1.20 to 8.85)*†	0.12 (−0.03 to 0.26)	Assessment not collected	−3.04 (−6.91 to 0.83)	−0.06 (−0.21 to 0.08)	Assessment not collected

*In the U.S. and Canada, celecoxib was compared with naproxen, and in all other countries, celecoxib was compared with diclofenac. BID = twice daily, NSAID = nonsteroidal anti-inflammatory drug. Patient global assessment of arthritis was based on a scale of 1-5. Confidence intervals (CIs) notated in italics represent a significant difference between groups. These differences were small and not clinically meaningful.

†Although the CI does not include 0, a difference of <10 mm on a VAS of 100 mm is clinically insignificant.

‡Belgium, Netherlands, Luxembourg.

§Czech Republic, Hungary, Poland, Slovakia.

‖Denmark, Finland, Norway, Sweden.

¶Colombia, Ecuador, Peru, Venezuela.

#Hong Kong, Malaysia, People's Republic of China, Philippines, Singapore, Taiwan, Thailand.

Table 3 Comparison of Adverse Events with ≥1% Incidence Between the Treatment Groups

Adverse Event	NSAID Groups (n = 4394) Number (%)	Celecoxib Groups (n = 8800) Number (%)	*P* Value
Any adverse event	1772 (40.3)	3274 (37.2)	<.001
Abdominal pain	274 (6.2)	423 (4.8)	<.001
Dyspepsia	259 (5.9)	423 (4.8)	.009
Diarrhea	164 (3.7)	307 (3.5)	>.2
Headache	148 (3.4)	263 (3.0)	>.2
Nausea	151 (3.4)	207 (2.4)	<.001
Upper respiratory infection	78 (1.8)	158 (1.8)	>.2
Dizziness	70 (1.6)	136 (1.5)	>.2
Peripheral edema	63 (1.4)	129 (1.5)	>.2
Flatulence	87 (2.0)	109 (1.2)	.001
Injury (accidental)	41 (0.9)	102 (1.2)	>.2
Rash	28 (0.6)	96 (1.1)	.012
Gastritis	49 (1.1)	84 (1.0)	>.2
Influenza-like symptoms	37 (0.8)	89 (1.0)	>.2
Bronchitis	32 (0.7)	90 (1.0)	>.1
Constipation	103 (2.3)	71 (0.8)	<.001
Anemia	51 (1.2)	69 (0.8)	.04
Insomnia	44 (1.0)	64 (0.7)	>.1
SGPT increased	59 (1.3)	44 (0.5)	<.001
Vomiting	50 (1.1)	47 (0.5)	<.001
Deaths	5 (0.11)	5 (0.06)	>.3

than either NSAID comparator (naproxen, 4 events [1.83/100 patient-years]; diclofenac, 3 events, [0.41/100 patient-years]). There was no statistically significant difference because of the small numbers, as anticipated.

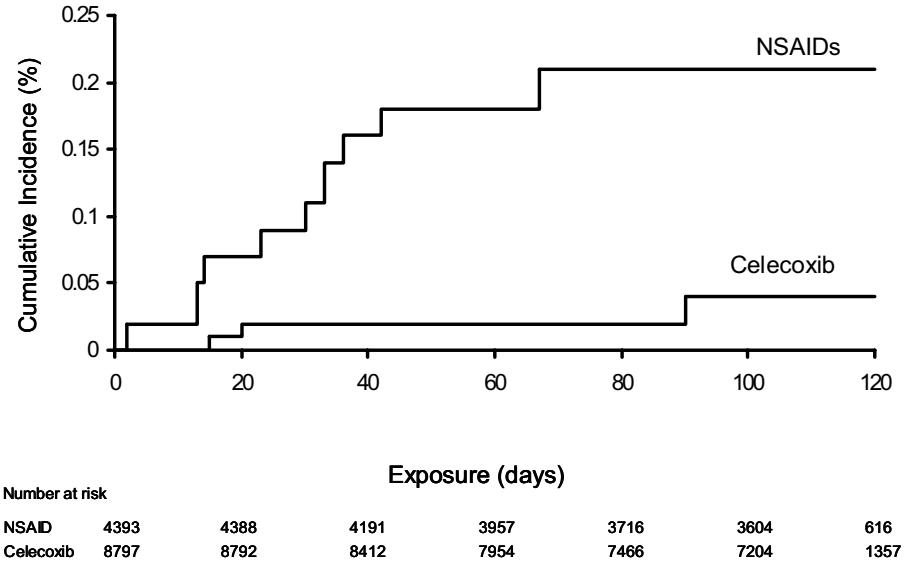
As shown in Table 5, a post hoc analysis of upper gastrointestinal events found that among nonaspirin users, the incidence of ulcer complications (adjudication "by lesion") was significantly higher in the NSAID group compared with the celecoxib group (OR = 12.05; 95% CI, 1.45 to 100.09). Among aspirin users (7% of the study population), the overall event rate was low. Although the incidence of ulcer complications was numerically lower in the celecoxib group than in the NSAID group, this difference was not statistically significant (OR = 1.98; 95% CI, 0.12 to 31.72). Similar results were obtained using the adjudication "by clinical presentation" endpoints.

The analysis of cardiovascular events was based upon investigator-reported events (ie, there was no preplanned adjudication). Investigators were masked to treatment assignment and all reported events were analyzed. There was no significant difference between celecoxib and the NSAID group in any cardiovascular adverse event rate, with the exception of investigator-reported cardiac failure (Table 6). The rate of cardiac failure was 0.22/100 patient-years with celecoxib and 1.00/100 patient-years with the NSAID group (OR = 4.51, 95% CI, 1.26 to 20.06, $P = .01$). The incidence of cerebrovascular disorders was low and statistically similar between the groups. A post hoc analysis of selected adverse events by treatment group across the geographic regions also showed no significant differences, except for the incidence of peripheral edema (celecoxib 100 mg twice daily 6.45/100 patient-years vs diclofenac 3.79/100 patient-

Table 4 Summary of Upper Gastrointestinal (UGI) Event Data Using Both Adjudication Methodologies

	NSAID Groups n = 4394 901.5 pt-years Number (Rate/100 Patient Years)	Celecoxib Groups n = 8800 1806.7 pt-years Number (Rate/100 Patient Years)	Odds Ratio (95% CI)	*P* Value*
Referred to adjudication (n = 144)	61 (6.7)	83 (4.8)	1.48 (1.04-2.09)	.026
Adjudication based on "lesion"				
Ulcer complications (n = 9)	7 (0.8)	2 (0.1)	7.02 (1.46-33.80)	.008
Significant UGI events (n = 36)	18 (2.0)	18 (1.0)	2.01 (1.04-3.86)	.049
Adjudication based on "clinical presentation"				
Complicated UGI events (n = 12)	9 (1.0)	3 (0.2)	6.02 (1.50-34.57)	.004
Confirmed UGI events (n = 37)	19 (2.1)	18 (1.0)	2.12 (1.05-4.28)	.023

*Fisher's exact test.



Number at risk

NSAID	4393	4388	4191	3957	3716	3604	616
Celecoxib	8797	8792	8412	7954	7466	7204	1357

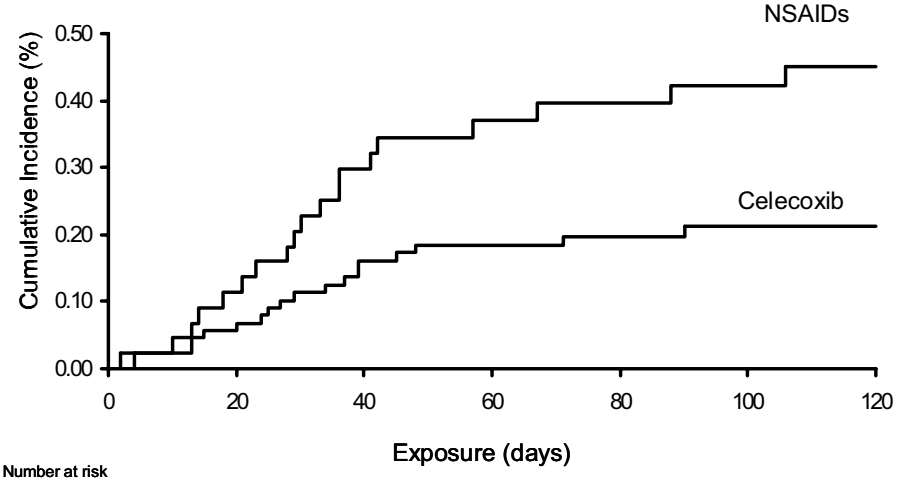
Figure 1 Cumulative probability of complicated upper gastrointestinal events in patients treated with celecoxib and nonsteroidal anti-inflammatory drugs (naproxen and diclofenac). Log-rank test for difference *P* value =.002.

years, *P* =.03). The risk of myocardial infarction (MI) was low and statistically similar among the treatment groups. The incidence of MI was 0.89/100 patient-years in the combined celecoxib 100 mg twice daily groups, 0.22/100 patient-years in the combined celecoxib 200 mg twice daily groups, and 0.61/100 patient-years for naproxen. There were no cases of MI in diclofenac users.

DISCUSSION

We found that celecoxib 100 mg twice daily was comparable to naproxen and diclofenac for relief of the signs and symptoms of osteoarthritis of the knee, hip, or hand. Additionally, celecoxib 100 mg twice daily and 200 mg twice daily were similar in efficacy. We found a significant reduction in serious upper gastrointestinal events in celecoxib-treated patients compared with patients on naproxen or diclofenac.

These results are important considering that differing conclusions with regard to serious upper gastrointestinal events were found in the CLASS, VIGOR, and TARGET trials.[10-12] The VIGOR trial showed that patients treated with rofecoxib 50 mg/day had a significantly lower risk of serious upper gastrointestinal complications compared with patients treated with naproxen 1000 mg per day.[11] Similar results were observed in the TARGET trial, which compared lumiracoxib 400 mg/day with either



Number at risk

NSAID	4393	4388	4191	3957	3716	3604	616
Celecoxib	8797	8792	8412	7954	7466	7204	1357

Figure 2 Cumulative Probability of Confirmed Upper Gastrointestinal Events in Patients Treated with Celecoxib and Nonsteroidal Anti-inflammatory Drugs (Naproxen and Diclofenac). Log-rank Test for Difference *P* Value =.019.

Table 5 Clinically Significant Upper Gastrointestinal Events (UGI) in Concurrent Users and Nonusers of Aspirin for Cardiovascular Protection

	NSAID Groups n = 315 61.0 pt-years	Celecoxib Groups n = 622 124.2 pt-years		
With Aspirin	number (rate/100 pt-yrs)		Odds Ratio (95% CI)	*P* Value
Referred to adjudication (n = 24)	11 (18.0)	13 (10.5)	1.70 (0.68-4.15)	.20
Adjudication based on lesion				
Ulcer complications (n = 2)	1 (1.6)	1 (0.8)	1.98 (0.12-31.72)	1.00
Significant UGI events (n = 7)	4 (6.6)	3 (2.4)	2.65 (0.59-11.93)	.23
Adjudication based on clinical presentation				
Complicated UGI events (n = 4)	2 (3.3)	2 (1.6)	1.98 (0.14-27.42)	.49
Confirmed UGI events (n = 8)	5 (8.2)	3 (2.4)	3.33 (0.64-21.53)	.08
Without Aspirin	n = 4079 840.4 pt-years	n = 8178 1682.4 pt-years		
Referred to adjudication (n = 120)	50 (6.0)	70 (4.2)	1.44 (0.98-2.10)	.05
Adjudication based on lesion				
Ulcer complications (n = 7)	6 (0.7)	1 (0.1)	12.05 (1.45-100.09)	.007
Significant UGI events (n = 29)	14 (1.7)	15 (0.9)	1.87 (0.90-3.89)	.11
Adjudication based on clinical presentation				
Complicated UGI events (n = 8)	7 (0.8)	1 (0.06)	14.06 (1.80-633.49)	.001
Confirmed UGI events (n = 29)	14 (1.7)	15 (0.9)	1.87 (0.84-4.17)	.09

naproxen or ibuprofen.[12] However, the CLASS trial failed to show a statistically significant difference between patients treated with celecoxib 800 mg/day and those treated with ibuprofen or diclofenac, although significant differences were observed when symptomatic ulcers were also considered with ulcer complications.[10] The reason(s) for these differences may be related to several factors, including study design and methodology of evaluating gastrointestinal outcomes, unexpectedly high withdrawal rates in the CLASS trial, or a higher than expected rate of aspirin use in the CLASS trial. It may also reflect a true difference in the gastrointestinal safety profiles of these agents; however, other studies show that this is unlikely.[3,18] Unlike the long-term CLASS, VIGOR, and TARGET trials,[10-12] the 12-week SUCCESS-1 study had a withdrawal rate of less than 20% and provides strong evidence of the upper gastrointestinal safety profile of celecoxib in a prospective, randomized, double-blinded, controlled setting.

There is no definitive consensus regarding the most appropriate methodology for evaluating upper gastrointestinal outcomes. In event trials with a high degree of monitoring

Table 6 Incidence of Selected Investigator-Reported Cardiovascular and Renal Events

	NSAID Groups (n = 4394) 901.5 pt-years	Celecoxib Groups (n = 8800) 1806.7 pt-years		
Event	Number (Rate/100 pt-yrs)		Odds Ratio (95%CI)	*P* Value
Coronary artery disorder	1 (0.11)	5 (0.28)	0.40 (0.05, 3.43)	.67
Angina pectoris	7 (0.78)	13 (0.72)	1.08 (0.43, 2.70)	.82
Myocardial infarction	1 (0.11)	10 (0.55)	0.20 (0.03, 1.56)	.11
Cerebrovascular disorders	6 (0.67)	14 (0.74)	0.86 (0.33, 2.23)	1.00
Cardiac failure	9 (1)	4 (0.22)	4.51 (1.39, 14.62)	.01
Peripheral edema	63 (6.99)	129 (7.14)	0.98 (0.73, 1.32)	.94
Hypertension	55 (6.1)	94 (5.2)	1.17 (0.84, 1.63)	.38

Odds ratios represent a comparison of the NSAID group with the celecoxib group.

(such as CLASS, VIGOR, and TARGET),[10-12] criteria requiring direct visualization of lesions may be appropriate, whereas in a more "real-world" study, the use of clinical criteria may be more suitable. Although SUCCESS-1 had a "real-world" design (few strict inclusion or exclusion criteria and little protocol-mandated monitoring in a broad range of patients worldwide under different healthcare systems), we used both evaluation criteria. The risk reduction seen with celecoxib compared with the NSAID group was consistent across both methodologies, thus reinforcing the robustness of our conclusions. Furthermore, the dose of diclofenac used (50 mg twice daily) is lower than the highest approved dose for osteoarthritis in the participating countries, and this would be expected to have biased the study against finding any safety advantage of celecoxib over the combined NSAID group (diclofenac n = 3489; naproxen, n = 905).

Low-dose aspirin increases the risk of upper gastrointestinal complications.[19] Unlike the TARGET trial,[12] the SUCCESS-1 study was not stratified by aspirin use and did not have a prespecified sample size to study this issue. In our analysis of nonusers and users of aspirin, celecoxib was associated with a lower numerical rate of serious upper gastrointestinal events compared with NSAIDs. Although, the observed odds ratios were not significant in the aspirin subgroup, where the number of patients taking concomitant aspirin was too small (Table 5). Further controlled studies are required to more clearly define the benefit of COX-2-specific inhibitors compared with nonspecific NSAIDs in this population.

Concern has arisen regarding a potential increase in thromboembolic events in patients taking COX-2-specific inhibitors, as compared with those taking nonspecific NSAIDs.[20,21] The VIGOR trial showed that patients taking rofecoxib 50 mg daily had a fivefold increased risk of MI, compared with patients treated with naproxen.[11] More recently, the Adenomatous Polyp Prevention on Vioxx (APPROVe) study, which evaluated the incidence of adenomatous polyps in patients treated with rofecoxib 25 mg daily compared with placebo, showed a doubling of MI risk in the rofecoxib-treated patients.[22] In contrast to VIGOR, aspirin therapy was permitted in the APPROVe trial.[22] Following the release of these results, rofecoxib was voluntarily withdrawn from the worldwide market on September 30, 2004. In 2 studies of the investigational use of parecoxib/valdecoxib for postoperative pain relief following coronary artery bypass graft surgery, a significantly greater incidence of cardiovascular/thromboembolic events was detected in the parecoxib/valdecoxib treatment group compared with the placebo treatment group.[23,24] Subsequently, valdecoxib was voluntarily withdrawn from the worldwide market on April 7, 2005, based on its overall risk-benefit assessment. The data with other COX-2-specific inhibitors are mixed. In the TARGET study, patients treated for 1 year with lumiracoxib had a higher, but statistically nonsignificant, increased risk of MI compared with those taking naproxen.[12] Comparable results were also seen for etoricoxib in the Etoricoxib Diclofenac Gastrointestinal Evaluation (EDGE) trial, which had a follow-up of approximately 1 year.[25]

The data with celecoxib are controversial. As with other COX-2-specific inhibitors, there are no studies that were designed or powered to evaluate cardiovascular adverse events. In our 12- week study of average risk osteoarthritis patients, the incidences of cardiovascular adverse events, including hypertension, coronary artery disease, as well as stroke and transient ischemic attacks, were low, as expected, and similar between treatment groups (Table 6). In our post hoc analysis, we observed a higher, but nonsignificant difference in the incidence of MI in patients treated with celecoxib 100 mg twice daily compared with either naproxen or diclofenac. The incidence of MI in the celecoxib 200 mg twice daily group, however, was lower than that seen in patients on naproxen. Overall, there were few MI events in our study, and because of differences within the celecoxib group (ie, 4 times higher rate at the lower dose vs. the higher dose), it is difficult to draw robust conclusions from these data. Several studies of celecoxib (including the CLASS trial,[10,26] a pooled analysis of all celecoxib arthritis trials, which included SUCCESS[27] and several observational studies[28-30]) have not shown an increase in cardiovascular event rates with celecoxib. Some observational studies comparing celecoxib and rofecoxib have shown a dose-dependent increase in MI in patients treated with rofecoxib, but not celecoxib, thus suggesting a significant difference in the cardiovascular adverse event profile of these 2 drugs.[30-32] In a recent study on the use of celecoxib to prevent colon polyps (treatment duration 2.8-3.1 years), patients treated with celecoxib 400 mg twice daily had a 3.4 times greater risk of cardiovascular events compared with placebo, and the risk for patients treated with celecoxib 200 mg twice daily was 2.3 times greater than placebo.[33] In a similarly designed trial, with a similar treatment duration (average of 33 months), celecoxib 400 mg once daily did not show any significantly increased risk of serious cardiovascular events compared with placebo (preliminary data).[34] It is possible that the increased risk of MI is related to a long-term sustained suppression of the COX-2 enzyme, and thus is seen only in patients treated with high-dose celecoxib (400 mg) taken twice daily for a long period of time. Preliminary information from another long-term study, the Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT), showed an increased risk of thromboembolic events in naproxen-treated patients compared with placebo.[35] In this same trial, celecoxib was no different from placebo with regard to thromboembolic events.[35]

Other data have suggested that celecoxib may provide a beneficial cardiovascular effect by suppressing inflammation in vulnerable atherosclerotic plaques. A 2-week treatment with celecoxib improved endothelial function and reduced high-sensitivity C-reactive protein and oxidized low-density lipoproteins (LDL) in patients with coronary artery disease.[36] Another study found that rofecoxib and etori-

coxib, but not celecoxib, significantly increased LDL oxidation.[37] In light of concerns regarding COX-2-specific inhibitors and thromboembolic events, further studies in patients with higher cardiovascular risk are needed to elucidate the precise mechanism(s) involved and to evaluate whether true differences exist among the COX-2-specific inhibitors and nonspecific NSAIDs.

Because a limitation of our study is the short treatment duration (3 months), it can be argued that our results cannot be extrapolated to longer time periods. However, most previous studies, including the VIGOR and TARGET trials, have suggested that the risk of serious upper gastrointestinal complications with NSAIDs is linearly dependent on time, displaying a constant hazard function.[11,12,38-40] Thus, considering our large study population (>13 000 patients), it is probable that our conclusions can be extrapolated to longer time-periods.

In summary, our study shows that the COX-2-specific inhibitor celecoxib is as effective as the nonspecific NSAIDs naproxen and diclofenac but has significantly fewer serious upper gastrointestinal events. The number of cardiovascular thromboembolic events in our study was low, and, although numeric differences were noted, these did not reach statistical significance. Because current clinical osteoarthritis treatment guidelines vary in their recommendations regarding the appropriate therapeutic role of COX-2-specific inhibitors, clinicians should consider a number of factors, including the risk for upper gastrointestinal events, duration of therapy, as well as costs, before deciding upon individual patient treatment.

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APPENDIX A

Gastrointestinal Events Committee Classification of Serious Upper Gastrointestinal Events for Adjudication Based on Endoscopic Lesions*

Classification	Description of Primary Diagnosis
1	UGI perforation: An opening in the wall of the stomach or duodenum requiring surgery or laparoscopic repair, but only if the evidence was unequivocal (free air, peritoneal irritation signs, etc.).
2	UGI bleeding: 1 of 7 traditional clinical presentations (2a-2d4).
2a	Hematemesis with gastric or duodenal ulcer or large erosion proven by endoscopy or UGI barium radiograph.
2b	A gastric or duodenal ulcer or large erosion proven by endoscopy with evidence of active bleeding or stigmata of a hemorrhage (visible vessel or attached clot to base of an ulcer).
2c	Melena with a gastric or duodenal ulcer or large erosion proven by endoscopy or UGI barium radiograph.
2d-1	Hemoccult positive stools with a gastric or duodenal ulcer or large erosion proven by endoscopy or UGI barium radiograph and with bleeding as evidenced by a fall in hematocrit of ≥5% or a reduction of hemoglobin of >1.5 g/dL from baseline.
2d-2	Hemoccult positive stools with a gastric or duodenal ulcer or large erosion proven by endoscopy or UGI barium radiograph and with bleeding as evidenced by orthostasis (changes to postural vital signs; increase in pulse rate of ≥20 beats/min or a decrease in systolic blood pressure of ≥20 mmHg or diastolic blood pressure of ≥10 mmHg).
2d-3	Hemoccult positive stools with a gastric or duodenal ulcer or large erosion proven by endoscopy or UGI barium radiograph and with bleeding as evidenced by a need for blood transfusion of 2 or more units.
2d-4	Hemoccult positive stools with a gastric or duodenal ulcer or large erosion proven by endoscopy or UGI barium radiograph and with bleeding as evidenced by blood in the stomach as determined by endoscopy or nasogastric aspiration.
3	Gastric Outlet Obstruction: Opinion of clinician with endoscopic or UGI barium radiograph documentation. Endoscopic evidence would include tight edematous pylorus with an ulcer in the pyloric channel, inability to pass the endoscope tip into the duodenal bulb or descending duodenum, or retained fluid/food in the stomach. UGI barium radiograph evidence of obstruction would include: (1) a dilated stomach, (2) a slowly emptying stomach in a patient with clinical evidence of outlet obstruction, and in some instances, with an ulcer seen in the channel or duodenal bulb or (3) severe narrowing and edema obstructing the outlet of the stomach.
4	Other UGI Event: Symptomatic ulcers documented by endoscopy or UGI barium radiograph and with no evidence of GI bleeding were summarized separately as were other symptomatic UGI complaints.

*UGI = upper gastrointestinal. Categories 1, 2 and 3 were designated "ulcer complications" and included perforations, ulcer bleeding, and obstruction. Category 4 was symptomatic ulcers and other UGI events. Categories 1 through 4 were designated "significant upper gastrointestinal events."

APPENDIX B

Gastrointestinal Events Committee Classification of Serious Upper Gastrointestinal Events for Adjudication Based on Clinical Presentation (adapted)[16]

Event	Criteria for Confirmed Event	Criteria for Complicated Event
Gastric or duodenal perforation due to active gastric ulcer or duodenal ulcer	Report of gastric or duodenal perforation (excluding perforation caused by a malignant ulcer) confirmed by one or more of the following: 1. Endoscopy 2. Surgery 3. Unequivocal radiographic results consistent with free intraperitoneal air or extravasation of contrast media 4. Autopsy	All gastric or duodenal perforations are classified as complicated.
Obstruction due to active gastric ulcer or duodenal ulcer	Postprandial nausea and vomiting lasting for at least 24 hours AND evidence of narrowing of the distal stomach, pylorus, or duodenum due to a nonmalignant ulcer documented by: 1. Endoscopy 2. Surgery 3. Radiography 4. Autopsy	All obstructions are classified as complicated.
Development of active gastric ulcer or duodenal ulcer	Report of gastric ulcer or duodenal ulcer confirmed by one or more of the following: 1. Endoscopy 2. Surgery 3. Unequivocal radiological evidence of active gastric ulcer or duodenal ulcer on upper gastrointestinal series with contrast 4. Autopsy	Gastric ulcer or duodenal ulcer associated with a confirmed upper gastrointestinal hemorrhage as defined under Development of Upper Gastrointestinal Hemorrhage, criteria 1, 2, or 3.
Development of upper gastrointestinal (esophageal, gastric, or duodenal) hemorrhage	Report of upper gastrointestinal hemorrhage fulfilling one or more of the following: 1. Healthcare provider documented frank hematemesis (distinguished from blood tinged or streaked emesis), including coffee-grounds vomitus, OR healthcare provider-witnessed frank blood or coffee grounds by gastric aspiration or lavage (distinguished from scant coffee-grounds that clear rapidly). 2. Healthcare provider documented frank melena (distinguished from other dark stool eg, that due to bismuth salts). 3. Active upper gastrointestinal bleeding documented by endoscopy, angiography, or surgery. 4. Heme-positive stool associated with a documented upper gastrointestinal lesion judged by the healthcare provider to be the source of the bleeding AND associated with either of the following: a) Significant bleeding/volume loss b) Stigmata of recent bleeding (visible vessel, pigmented spot or clot on ulcer base) on endoscopy. 5. Patient reported hematemesis or melena associated with a documented upper gastrointestinal lesion judged by the healthcare provider to be the source of the bleeding AND associated with one or more of the following: a) Significant bleeding/volume loss b) Stigmata of recent bleeding (visible vessel, pigmented spot or clot on ulcer base) on endoscopy.	1. Upper gastrointestinal hemorrhage associated with significant bleeding/volume loss.*

*Criteria for significant bleeding/volume loss: One or more of the following (a, b, c, or d) is temporally related to the event: a. Decrease in hemoglobin $\geq$2 gm/dL (or $\geq$6% decrease in hematocrit if hemoglobin not available). b. Evidence of orthostatic (sitting to standing, or lying to sitting) changes; one or more of: i) pulse rate increase of $>$20 beats/minute, ii) decrease in systolic blood pressure $>$20 mmHg, iii) decrease in diastolic blood pressure $>$10 mmHg. c. Other evidence of significantly reduced circulatory volume (eg, significant hypotension corrected by volume replacement). d. Transfusion of blood or packed red blood cells.

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