

ORIGINAL ARTICLE

Cardiovascular Risk Associated with Celecoxib in a Clinical Trial for Colorectal Adenoma Prevention

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ABSTRACT

BACKGROUND

Selective cyclooxygenase-2 (COX-2) inhibitors have come under scrutiny because of reports suggesting an increased cardiovascular risk associated with their use. Experimental research suggesting that these drugs may contribute to a prothrombotic state provides support for this concern.

METHODS

We reviewed all potentially serious cardiovascular events among 2035 patients with a history of colorectal neoplasia who were enrolled in a trial comparing two doses of celecoxib (200 mg or 400 mg twice daily) with placebo for the prevention of colorectal adenomas. All deaths were categorized as cardiovascular or noncardiovascular, and nonfatal cardiovascular events were categorized in a blinded fashion according to a prespecified scheme.

RESULTS

For all patients except those who died, 2.8 to 3.1 years of follow-up data were available. A composite cardiovascular end point of death from cardiovascular causes, myocardial infarction, stroke, or heart failure was reached in 7 of 679 patients in the placebo group (1.0 percent), as compared with 16 of 685 patients receiving 200 mg of celecoxib twice daily (2.3 percent; hazard ratio, 2.3; 95 percent confidence interval, 0.9 to 5.5) and with 23 of 671 patients receiving 400 mg of celecoxib twice daily (3.4 percent; hazard ratio, 3.4; 95 percent confidence interval, 1.4 to 7.8). Similar trends were observed for other composite end points. On the basis of these observations, the data and safety monitoring board recommended early discontinuation of the study drug.

CONCLUSIONS

Celecoxib use was associated with a dose-related increase in the composite end point of death from cardiovascular causes, myocardial infarction, stroke, or heart failure. In light of recent reports of cardiovascular harm associated with treatment with other agents in this class, these data provide further evidence that the use of COX-2 inhibitors may increase the risk of serious cardiovascular events.

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THE PROMISE OF A LOWER INCIDENCE of gastrointestinal side effects with the use of selective cyclooxygenase-2 (COX-2) inhibitors than with the use of nonselective nonsteroidal antiinflammatory drugs (NSAIDs) or aspirin has led to a marked increase in prescriptions for COX-2 inhibitors, despite the fact that they offer similar degrees of pain relief.¹⁻³ In addition, the identification of COX-2 as a promoter of intestinal tumorigenesis suggested that inhibiting this enzyme could prevent the formation of premalignant colorectal adenomas.⁴⁻⁸ Recently, however, this class of drugs has come under scrutiny because of clinical reports that they were associated with an increased risk of serious cardiovascular harm.⁹⁻¹¹ The mechanism of this effect is suggested in part by evidence that selective inhibition of COX-2 can block the production of prostacyclin without affecting the synthesis of thromboxane A₂,¹⁰ thereby potentially creating a prothrombotic state.

The observation of an increased incidence of death from cardiovascular causes, myocardial infarction, or stroke among patients receiving rofecoxib in the Adenomatous Polyp Prevention on Vioxx (APPROVe) trial and the associated voluntary withdrawal of this drug from the market prompted the data and safety monitoring board and steering committee of a similar ongoing trial of celecoxib to request a focused reassessment of data on cardiovascular safety by an independent committee, with the results presented at their scheduled meeting on December 10, 2004. The study was a prospective, randomized, double-blind, multicenter trial assessing the efficacy of celecoxib for the prevention of adenomatous polyps in patients who had undergone endoscopic polypectomy. Because neither prior clinical trials nor observational studies had reported a clearly increased risk of cardiovascular events with celecoxib use,^{2,5,12-16} this longer-term, placebo-controlled trial provided an important opportunity to evaluate the potential association. This report describes the findings of the independent cardiovascular safety committee.

METHODS

PATIENTS

The Adenoma Prevention with Celecoxib (APC) study compared the efficacy and safety of 200 mg of celecoxib twice daily, 400 mg of celecoxib twice daily, and placebo in reducing the occurrence of ad-

enomatous polyps in the colon and rectum one year and three years after endoscopic polypectomy. The trial was led by the Strang Cancer Prevention Center (New York) and cosponsored by the National Cancer Institute and Pfizer. Ninety-one sites participated (72 in the United States, 1 in the United Kingdom, 8 in Australia, and 10 in Canada). Participants ranged from 32 to 88 years of age and were considered to have a clinically significant risk of colorectal adenoma on the basis of a history of either multiple adenomas or a single adenoma that was at least 0.5 cm in diameter. All known adenomas were removed colonoscopically before drug treatment began.

A detailed medical history, including baseline assessment of cardiovascular disease status and risk factors for cardiovascular disease, was obtained for each patient. The protocol was reviewed and approved by the appropriate institutional review boards, and all patients provided written informed consent before enrollment. Patients were randomly assigned to treatment with the use of a computer-generated randomization schedule. At the time of data review, 2035 patients had undergone randomization in a double-blind manner at a 1:1:1 ratio, after stratification according to the use or nonuse of aspirin for cardiovascular prophylaxis and the enrolling center. Enrollment began in November 1999 and concluded in March 2002. Compliance was assessed by means of both pill counts and standard monitoring of medical records every 6 to 12 weeks.

REVIEW OF CARDIOVASCULAR SAFETY

The cardiovascular safety committee developed endpoint definitions as guidelines for adjudication. The committee classified and adjudicated the end points by defining a hierarchy of composite end points (based on clinical importance and the prior findings with rofecoxib). These guidelines were designed specifically to assess cardiovascular safety (listed in the Supplementary Appendix, available with the full text of this article at www.nejm.org). An initial review identified all deaths and potential nonfatal cardiovascular adverse events. Two experienced independent assessors reviewed these events using medical records and narratives supplied by site investigators. Myocardial infarction was defined on the basis of either a clinical presentation characterized by typical symptoms, signs, or electrocardiographic changes associated with an elevation in the level of a cardiac marker or angiographic evi-

dence of coronary thrombosis. Stroke was defined as a persistent focal neurologic event whose onset was sudden and was not due to trauma or a tumor. Other cardiovascular events were categorized according to a preplanned schema. When this initial documentation was insufficient for adjudication, additional information was obtained from the investigative sites.

The entire cardiovascular safety committee was unaware of the patients' treatment assignments throughout the review process. For the purposes of this analysis, we evaluated a hierarchy of composite end points, including death from cardiovascular causes, myocardial infarction, stroke, heart failure, unstable angina, and the need for a cardiovascular procedure.

STATISTICAL ANALYSIS

Randomization codes were provided to Statistics Collaborative (Washington, D.C.). All analyses were performed according to the intention-to-treat principle, with data on each patient analyzed according to the original randomized treatment assignment. Log-rank tests were used to compare the time to a cardiovascular event in the three groups for each composite end point of interest. Cox models, with the treatment group as the only covariate, were used to estimate hazard ratios for the two celecoxib groups as compared with the placebo group. Although the randomization was stratified according to the baseline use or nonuse of aspirin and the center, the Cox models did not include these stratifying variables. Censoring was defined by assuming that a patient was followed for 37 months, until death, or until January 6, 2005 (the date defined for this analysis as the common close-out date) — whichever came first. At the time of this review, we had follow-up information for more than 97 percent of the patient-years at risk. Incidence rates were calculated for individual and composite cardiovascular events by dividing the number of patients with events by the number of patient-years at risk.

Important subgroups based on baseline characteristics were prespecified. To examine whether the effect of celecoxib varied between subgroups, we constructed Cox models with terms for treatment, subgroup, and the interaction between subgroup and treatment and evaluated the interaction terms for statistical significance.

Recommendations to the study's data and safety monitoring board were made on the basis of data

available at the time of the original analysis. This analysis contains data on three additional cardiovascular events that were not included in the original report.

RESULTS

At the time of the analysis, 77 percent of the 2035 patients had completed the study, and all of the remaining surviving patients had completed at least 2.8 years of follow-up (range, 2.8 to 3.1). The baseline characteristics were similar among the three groups (Table 1). The incidence of the prespecified composite cardiovascular end points, analyzed according to the time to the first event, and the associated hazard ratios are shown in Table 2. As compared with the placebo group, the group given 200 mg of celecoxib twice daily had a hazard ratio for death from cardiovascular causes, myocardial infarction, stroke, or heart failure of 2.3 (95 percent confidence interval, 0.9 to 5.5), and the group receiving 400 mg of celecoxib twice daily had a hazard ratio of 3.4 (95 percent confidence interval, 1.4 to 7.8). The results for the individual components of the composite end point are shown in Table 3.

There were six deaths in the placebo group, six in the group given 200 mg of celecoxib twice daily, and nine in the group given 400 mg twice daily, and one, three, and six of the deaths, respectively, were due to cardiovascular causes. The Kaplan–Meier curves for the combined end point of death from cardiovascular causes, myocardial infarction, stroke, or heart failure in the three groups are shown in Figure 1. The annualized incidence of death from cardiovascular causes, stroke, myocardial infarction, or heart failure was 3.4 events per 1000 patient-years in the placebo group, 7.8 events per 1000 patient-years in the group given 200 mg of celecoxib twice daily, and 11.4 events per 1000 patient-years in the group given 400 mg twice daily.

In addition to the increased risk of the prespecified composite end point of cardiovascular events, the point estimate of the number of venous thromboembolic events was also increased (though not significantly) among patients receiving celecoxib: four in the group given 400 mg of celecoxib twice daily and three in the group given 200 mg twice daily, as compared with one in the placebo group (hazard ratio for the two celecoxib groups combined, 3.5; 95 percent confidence interval, 0.4 to 28.5). There was no apparent increase in the risk of un-

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Placebo (N=679)	Celecoxib, 200 mg Twice Daily (N=685)	Celecoxib, 400 mg Twice Daily (N=671)
Age — yr	59.7±9.7	59.7±9.4	59.9±9.4
Male sex — no. (%)	473 (69.7)	460 (67.2)	454 (67.7)
History of cardiovascular events — no. (%)	321 (47.3)	335 (48.9)	307 (45.8)
Myocardial infarction	29 (4.3)	22 (3.2)	31 (4.6)
Cerebrovascular disease	14 (2.1)	20 (2.9)	13 (1.9)
Congestive heart failure	14 (2.1)	6 (0.9)	11 (1.6)
Angina	51 (7.5)	50 (7.3)	42 (6.3)
Hypertension	277 (40.8)	287 (41.9)	260 (38.7)
Diabetes — no. (%)†	61 (9.0)	66 (9.6)	64 (9.5)
Current smoker — no. (%)	122 (18.0)	119 (17.4)	96 (14.3)
Aspirin use — no. (%)	213 (31.4)	201 (29.3)	200 (29.8)
Use of lipid-lowering drug — no. (%)	184 (27.1)	188 (27.4)	191 (28.5)

* Plus-minus values are means ±SD. There were no significant differences among the groups.

† Data were missing for one patient in the placebo group.

stable angina, arrhythmia, or the need for a cardiovascular procedure. The hazard ratios associated with celecoxib use decreased when a broader class of cardiovascular events, including unstable angina and the need for a cardiovascular procedure, was added to the composite end point. The hazard ratio associated with celecoxib was not significantly affected by any of the baseline characteristics examined, including aspirin use at baseline (Table 4).

On December 16, 2004, on the basis of these findings, the advice of the cardiovascular safety committee, and previous findings with drugs in the same class, the data and safety monitoring board concluded that continued exposure to celecoxib placed patients at increased risk for serious cardiovascular events. On the basis of this recommendation, the steering committee stopped the use of study medication among the patients remaining in the trial. The trial remained blinded, and follow-up for the end point of adenoma continued. Three events that were documented after the study was stopped are included in the present analysis; their inclusion does not alter the overall conclusions of the report issued on December 16, 2004.

DISCUSSION

In a large, randomized, placebo-controlled, double-blind, multicenter trial, we found that twice-daily

treatment with 200 or 400 mg of celecoxib to prevent colorectal adenomas led to a dose-related increase in the risk of serious cardiovascular events, including death from cardiovascular causes, myocardial infarction, stroke, and heart failure. These results were consistent among the individual components of the composite end point. Because the use of other selective COX-2 inhibitors, including rofecoxib, valdecoxib, and parecoxib, has also been associated with an increased rate of cardiovascular events,^{17,18} our results heighten concern that this class of drug may be associated with increased cardiovascular risk. The cardiovascular safety committee also completed a preliminary review of cardiovascular safety in another study, the Prevention of Spontaneous Adenomatous Polyps (PreSAP) trial, which randomly assigned patients with a history of colorectal adenomas to receive either 400 mg of celecoxib once a day or placebo. The preliminary analysis did not show an increase in risk at this dose.

The reason for the apparent increase in cardiovascular risk associated with the use of COX-2 inhibitors is uncertain. One prominent hypothesis involves the effects of COX-2 inhibitors on two key prostanoids, prostacyclin and thromboxane A₂, which have a crucial role in vascular homeostasis.^{9,19,20} These prostanoids are generated by the action of the cyclooxygenase-1 (COX-1) and COX-2 isoenzymes on arachidonic acid.²¹ Thromboxane

Table 2. Incidence of and Hazard Ratios for the Composite End Points in the Celecoxib Groups Relative to the Placebo Group.

End Point*	Celecoxib, 200 mg Twice Daily (N=685)		Celecoxib, 400 mg Twice Daily (N=671)		Both Celecoxib Groups (N=1356)		Placebo (N=679)		Celecoxib, 200 mg Twice Daily (N=685)		Celecoxib, 400 mg Twice Daily (N=671)		Both Celecoxib Groups (N=1356)	
	number of patients	(percent)	number of patients	(percent)	rate/1000 patient-years	rate/1000 patient-years	rate/1000 patient-years	rate/1000 patient-years	hazard ratio (95% confidence interval)	hazard ratio (95% confidence interval)	hazard ratio (95% confidence interval)			
Death from cardiovascular causes	1 (0.1)	3 (0.4)	6 (0.9)	9 (0.7)	0.5	1.4	2.9	2.2	3.0 (0.3–28.6)	6.1 (0.7–50.3)	4.5 (0.6–35.5)			
Death from cardiovascular causes or non-fatal MI	4 (0.6)	12 (1.8)	15 (2.2)	27 (2.0)	1.9	5.8	7.4	6.6	3.0 (1.0–9.3)	3.8 (1.3–11.5)	3.4 (1.2–9.7)			
Death from cardiovascular causes, non-fatal MI, or stroke	6 (0.9)	15 (2.2)	20 (3.0)	35 (2.6)	2.9	7.3	9.9	8.6	2.5 (1.0–6.4)	3.4 (1.4–8.5)	2.9 (1.2–7.0)			
Death from cardiovascular causes, non-fatal MI, stroke, or heart failure	7 (1.0)	16 (2.3)	23 (3.4)	39 (2.9)	3.4	7.8	11.4	9.6	2.3 (0.9–5.5)	3.4 (1.4–7.8)	2.8 (1.3–6.3)			
Death from cardiovascular causes, non-fatal MI, stroke, heart failure, or angina	11 (1.6)	18 (2.6)	25 (3.7)	43 (3.2)	5.4	8.7	12.5	10.6	1.6 (0.8–3.4)	2.3 (1.1–4.7)	2.0 (1.0–3.8)			
Death from cardiovascular causes, non-fatal MI, stroke, heart failure, or angina or need for a cardiovascular procedure	17 (2.5)	26 (3.8)	31 (4.6)	57 (4.2)	8.4	12.7	15.5	14.1	1.5 (0.8–2.8)	1.9 (1.0–3.3)	1.7 (1.0–2.9)			

* MI denotes myocardial infarction.

Table 3. Incidence of Individual Cardiovascular and Fatal Events.

End Point	Placebo (N=679)	Celecoxib, 200 mg Twice Daily (N=685)	Celecoxib, 400 mg Twice Daily (N=671)	Both Celecoxib Groups (N=1356)
	<i>number of patients (percent)</i>			
Death from any cause	6 (0.9)	6 (0.9)	9 (1.3)	15 (1.1)
Death from cardiovascular causes	1 (0.1)	3 (0.4)	6 (0.9)	9 (0.7)
Death from noncardiovascular causes	5 (0.7)	3 (0.4)	3 (0.4)	6 (0.4)
Nonfatal cardiovascular events				
Myocardial infarction	3 (0.4)	9 (1.3)	9 (1.3)	18 (1.3)
Stroke	3 (0.4)	3 (0.4)	5 (0.7)	8 (0.6)
Heart failure	2 (0.3)	1 (0.1)	4 (0.6)	5 (0.4)
Thromboembolic event	1 (0.1)	3 (0.4)	4 (0.6)	7 (0.5)
Resuscitation after sudden cardiac arrest	0	0	1 (0.1)	1 (0.1)
Hospitalization for unstable angina	5 (0.7)	4 (0.6)	2 (0.3)	6 (0.4)
Arrhythmia	9 (1.3)	4 (0.6)	7 (1.0)	11 (0.8)
Cardiovascular procedure	7 (1.0)	9 (1.3)	6 (0.9)	15 (1.1)
Other	9 (1.3)	11 (1.6)	14 (2.1)	25 (1.8)

A₂, which promotes platelet aggregation, vasoconstriction, and smooth-muscle proliferation, is synthesized primarily in platelets, which express only COX-1. Conversely, prostacyclin, which has antiaggregative, antiproliferative, and vasodilatory actions, is the main prostanoid product of endothelial cells, synthesized as a result of the action of COX-2.²²

Whereas nonselective NSAIDs inhibit both COX-1 and COX-2, selective COX-2 inhibitors act primarily on COX-2.⁹ The selective COX-2 inhibitors may therefore suppress vascular production of prostacyclin without affecting the synthesis of platelet-derived thromboxane A₂. This imbalance may promote thrombosis and increase the risk of cardiovascular events.¹⁰ Nonaspirin, nonselective NSAIDs may also not sufficiently reduce thromboxane A₂ synthesis long enough to prevent platelet aggregation and atherosclerotic events.¹⁰ Other potentially detrimental effects of COX-2 inhibitors have been suggested, including elevated blood pressure, though some reports have indicated that these drugs may have beneficial effects on vascular health.²³

In contrast to our findings, most of the earlier clinical trials of selective COX-2 inhibitors in patients with arthritis did not appear to show an increase in cardiovascular risk.^{2,5,14,24} These trials,

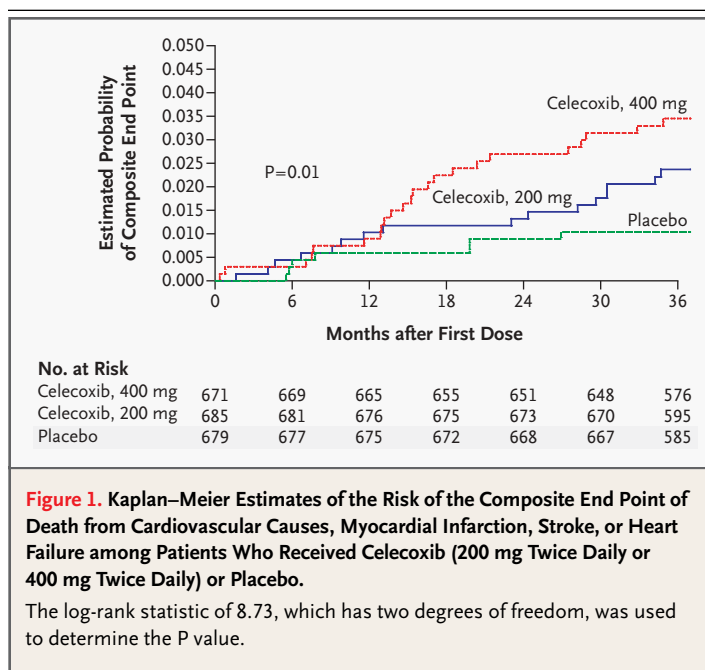
however, were generally short-term studies designed to assess the use of this class of drug for pain relief and to evaluate associated adverse gastrointestinal events. They included a relatively small proportion of patients at high risk for cardiovascular events or excluded such patients, despite the fact that many patients who are taking these drugs or who are considered candidates for this therapy are at high cardiovascular risk.²⁵ Consequently, the studies lacked adequate statistical power to confirm or refute a cardiovascular hazard related to the use of COX-2 inhibitors.¹¹ The use of active rather than placebo controls in many of these studies also made the findings difficult to interpret.

The results of the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial³ and a subsequent study, APPROVe,²⁶ raised questions about the safety of rofecoxib. The VIGOR trial, which compared a nine-month course of 50 mg of rofecoxib per day (a larger dose than that usually recommended for the long-term treatment of arthritis) with naproxen in patients with rheumatoid arthritis, reported a higher risk of myocardial infarction among the patients receiving rofecoxib.²⁷ Some have attributed these findings to the potentially cardioprotective effects of naproxen,^{28,29} although this interpretation has been a source of contention.^{18,20}

More recently, the APPROVe trial, a randomized, placebo-controlled trial designed to evaluate the efficacy of rofecoxib for preventing colorectal polyps in patients with a history of colorectal adenomas, was terminated early because of an increased risk of cardiovascular events.^{10,26} These results prompted voluntary withdrawal of rofecoxib from the market. Topol has reported that another controlled trial also showed an increased risk of cardiovascular events with treatment with 12.5 mg of rofecoxib per day, as compared with nabumetone or placebo.³⁰

The results of other studies have aroused concern about the safety of selective COX-2 inhibitors. In a placebo-controlled trial of pain relief after coronary-artery bypass surgery, the use of the parenteral COX-2 inhibitor parecoxib followed by oral treatment with its active metabolite valdecoxib, or treatment with placebo followed by valdecoxib, was associated with a significantly increased risk of cardiovascular thromboembolic events.³¹ In this issue of the *Journal*, Nussmeier et al. report a second trial showing a significant increase in cardiovascular events when parecoxib and valdecoxib were used in the immediate postoperative period after coronary-artery bypass surgery.³² The Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET) also showed a nonsignificant increase in the risk of cardiovascular events with lumiracoxib therapy,¹⁰ as compared with naproxen or ibuprofen therapy, but only among patients who were not taking aspirin.

In contrast, to our knowledge, neither pharmacoepidemiologic studies nor randomized, controlled trials have reported clear evidence of an increased cardiovascular risk associated with celecoxib. The failure of pharmacoepidemiologic studies to show an increased risk may be due in part to the lower doses and shorter duration of use in these studies than in clinical trials and in part to the potential for selection bias in nonrandomized studies. Nevertheless, the Celecoxib in Long-term Arthritis Safety Study (CLASS),² which used the same dose of celecoxib (400 mg twice daily) that was given to one group in the APC study and compared celecoxib with two nonselective NSAIDs, did not show an increased rate of cardiovascular events.² CLASS differed from the VIGOR study in several important ways. A short-term study not designed for systematic and formal assessment of cardiovascular events, CLASS enrolled relatively low-risk patients and allowed the use of aspirin for cardiovascular protection. In addition, FitzGerald has suggested that CLASS did not completely refute evidence of



an increased cardiac risk associated with celecoxib use in non-aspirin users, as compared with those taking ibuprofen (but not diclofenac).²⁰ Moreover, the results of a randomized, controlled clinical trial of celecoxib in patients with Alzheimer’s disease, reported to the Food and Drug Administration, demonstrated an increase in cardiovascular events among patients receiving celecoxib.³³

Although we found that patients with an increased cardiovascular risk at baseline appeared to have a higher absolute rate of events than those with no increase in cardiovascular risk at baseline, formal statistical tests of interaction showed no differential effect of celecoxib with respect to baseline cardiovascular risk. One prespecified subgroup included users of cardioprotective aspirin at baseline. Although the overall absolute risk appeared to be higher among such patients, analysis of the data on aspirin users in this study shows that they had a higher frequency of cardiovascular risk factors at baseline than did nonusers.

The cardiovascular findings with regard to celecoxib use in the APC study are consistent with those identified for rofecoxib use in the APPROVe trial. In contrast, preliminary analyses from the PreSAP trial, which involved a daily dose of 400 mg of celecoxib, showed no apparent increase in cardiovascular risk. The differences in the dosing regimens between these two trials — twice daily in the APC study, as

Table 4. Incidence of Death from Cardiovascular Causes, Myocardial Infarction, Stroke, or Heart Failure According to Baseline Characteristics.

Subgroup	No. of Patients	Placebo	Both Celecoxib Groups	Hazard Ratio (95% CI)*	P Value for Interaction
		<i>no./total no. (%)</i>			
Age					0.61
<60 yr	1078	4/372 (1.1)	14/706 (2.0)	1.8 (0.6–5.6)	
≥60 yr	957	3/307 (1.0)	25/650 (3.8)	4.0 (1.2–13.2)	
Sex					0.55
Female	648	2/206 (1.0)	8/442 (1.8)	1.9 (0.4–8.7)	
Male	1387	5/473 (1.1)	31/914 (3.4)	3.2 (1.3–8.3)	
Baseline cardiovascular risk factors					0.44
Yes	963	4/321 (1.2)	28/642 (4.4)	3.5 (1.2–10.1)	
No	1072	3/358 (0.8)	11/714 (1.5)	1.8 (0.5–6.6)	
Diabetes					0.86
Yes	191	1/61 (1.6)	5/130 (3.8)	2.3 (0.3–19.9)	
No	1843	6/617 (1.0)	34/1226 (2.8)	2.9 (1.2–6.8)	
Aspirin use					0.63
Yes	614	2/213 (0.9)	14/401 (3.5)	3.8 (0.9–16.6)	
No	1421	5/466 (1.1)	25/955 (2.6)	2.4 (0.9–6.4)	
Use of lipid-lowering drug					0.79
Yes	563	3/184 (1.6)	15/379 (4.0)	2.4 (0.7–8.4)	
No	1472	4/495 (0.8)	24/977 (2.5)	3.1 (1.1–8.8)	

* CI denotes confidence interval.

compared with once daily in the PreSAP study — support the hypothesis that sustained inhibition of prostacyclin may contribute to the increase in cardiovascular risk. Other potential differences in the trials, including geographic differences, differences in the patient population, and differences in use of concomitant medications, may have contributed to the disparity in the preliminary findings.

The increased cardiovascular risk in the APC trial was based on a small number of events in a trial that was not designed or statistically powered to evaluate cardiovascular risk. Although we believe we have identified all adverse cardiovascular events, we cannot rule out the possibility that some events remained unreported. Our results must therefore be interpreted with caution.

Still, in the context of the results of the other trials reviewed involving agents in the same class, these data suggest that there may be a real increase in cardiovascular risk associated with the use of celecoxib in particular and the class of selective COX-2 inhibitors in general. If correct, this interpretation

has substantial implications for public health,^{11,34} patient education,³⁵ and drug regulation.^{36,37} Given the experience with COX-2 inhibitors, we support the call for regulatory agencies to consider requesting a formal evaluation of long-term cardiovascular outcomes of any new drug with a mechanism of action that could augment the risk of cardiac and vascular events, especially if many patients who are likely to use the new agent are prone to cardiovascular disease.²⁵ This category may include nonselective NSAIDs (other than aspirin), as discussed earlier. More broadly, this experience underscores both the need for long-term, placebo-controlled trials to assess safety as well as efficacy and the need to improve methods for assessing potential adverse cardiovascular outcomes in studies with noncardiovascular primary end points.

In summary, a blinded review of cardiovascular events in a large, randomized, controlled study of two doses of celecoxib for the prevention of colorectal adenomas showed a dose-related risk of such events, including death from cardiovascular causes,

myocardial infarction, stroke, and heart failure. In light of other recent reports of the adverse cardiovascular effects of other agents in this class, these data provide further evidence that long-term use of COX-2 inhibitors may increase the risk of serious cardiovascular events. These risks will need to be weighed against any potential benefits of celecox-

ib in preventing colorectal neoplasia and in relieving pain.

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Drs. McMurray, Pfeffer, and Zauber report having received consulting fees from Pfizer. Drs. Solomon, McMurray, and Pfeffer report having received lecture fees from Pfizer. Dr. Wittes reports having received consulting fees from Merck within the past two years.

APPENDIX

The following persons participated in the APC Study: **Steering Committee:** M.M. Bertagnolli, E. Hawk, C. Eagle; **Statistical Team:** A. Zauber, K.M. Kim, D. Corle, R. Rosenstein, J. Tang, T. Hess, A. Wilton; **Medical Monitors:** W. Anderson, L. Doody; **Central Pathology Review:** M. Redston; **Project Directors:** M. Woloj, D. Bagheri, A. Crawford, M. Schietrum, V. Ladouceur; **Data and Safety Monitoring Board:** S. Rosen (chair), L. Friedman, R. Makuch, R. Phillips, P. Taylor; **Principal Investigators:** **United States:** S. Auerbach (California Professional Research, Newport Beach), C.F. Barish (Wake Research Associates, Raleigh, N.C.), T. Barringer (Carolinas Medical Center, Charlotte, N.C.), R.W. Bennetts (Northwest Gastroenterology Clinic, Portland, Ore.), M. Blitstein (Associates in Gastroenterology and Liver Disease, Lake Forest, Ill.), J. Bruggen (Wake Forest University Baptist Medical Center, Winston-Salem, N.C.), P. 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REFERENCES

- Marnett LJ, Rowlinson SW, Goodwin DC, Kalgutkar AS, Lanzo CA. Arachidonic acid oxygenation by COX-1 and COX-2: mechanisms of catalysis and inhibition. *J Biol Chem* 1999;274:22903-6.
- Silverstein FE, Faich G, Goldstein JL, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomized controlled trial. *JAMA* 2000;284:1247-55.
- Bombardier C, Laine L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *N Engl J Med* 2000;343:1520-8.
- Marnett LJ, Kalgutkar AS. Cyclooxygenase 2 inhibitors: discovery, selectivity and the future. *Trends Pharmacol Sci* 1999;20:465-9.
- Steinbach G, Lynch PM, Phillips RKS, et

- al. The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. *N Engl J Med* 2000;342:1946-52.
6. Giardiello FM, Yang VW, Hylind LM, et al. Primary chemoprevention of familial adenomatous polyposis with sulindac. *N Engl J Med* 2002;346:1054-9.
 7. Baron JA. Epidemiology of non-steroidal anti-inflammatory drugs and cancer. *Prog Exp Tumor Res* 2003;37:1-24.
 8. Hawk ET, Viner J, Richmond E, Umar A. Non-steroidal anti-inflammatory drugs (NSAIDs) for colorectal cancer prevention. *Cancer Chemother Biol Response Modif* 2003;21:759-89.
 9. FitzGerald GA, Patrono C. The coxibs, selective inhibitors of cyclooxygenase-2. *N Engl J Med* 2001;345:433-42.
 10. FitzGerald GA. Coxibs and cardiovascular disease. *N Engl J Med* 2004;351:1709-11.
 11. Topol EJ, Falk GW. A coxib a day won't keep the doctor away. *Lancet* 2004;364:639-40.
 12. White WB, Faich G, Borer JS, Makuch RW. Cardiovascular thrombotic events in arthritis trials of the cyclooxygenase-2 inhibitor celecoxib. *Am J Cardiol* 2003;92:411-8.
 13. Mamdani M, Juurlink DN, Lee DS, et al. Cyclo-oxygenase-2 inhibitors versus non-selective non-steroidal anti-inflammatory drugs and congestive heart failure outcomes in elderly patients: a population-based cohort study. *Lancet* 2004;363:1751-6.
 14. Solomon DH, Schneeweiss S, Glynn RJ, et al. Relationship between selective cyclooxygenase-2 inhibitors and acute myocardial infarction in older adults. *Circulation* 2004;109:2068-73.
 15. Ray WA, Stein CM, Daugherty JR, Hall K, Arbogast PG, Griffin MR. COX-2 selective non-steroidal anti-inflammatory drugs and risk of serious coronary heart disease. *Lancet* 2002;360:1071-3.
 16. Mamdani M, Rochon P, Juurlink DN, et al. Effect of selective cyclooxygenase 2 inhibitors and naproxen on short-term risk of acute myocardial infarction in the elderly. *Arch Intern Med* 2003;163:481-6.
 17. Furberg CD, Psaty BM, FitzGerald GA. Parecoxib, valdecoxib, and cardiovascular risk. *Circulation* 2005;111:249.
 18. Juni P, Nartey L, Reichenbach S, Sterchi R, Dieppe PA, Egger M. Risk of cardiovascular events and rofecoxib: cumulative meta-analysis. *Lancet* 2004;364:2021-9.
 19. Crofford LJ, Lipsky PE, Brooks P, Abramson SB, Simon LS, van de Putte LB. Basic biology and clinical application of specific cyclooxygenase-2 inhibitors. *Arthritis Rheum* 2000;43:4-13.
 20. FitzGerald GA. COX-2 and beyond: approaches to prostaglandin inhibition in human disease. *Nat Rev Drug Discov* 2003;2:879-90.
 21. McAdam BF, Catella-Lawson F, Mardini IA, Kapoor S, Lawson JA, FitzGerald GA. Systemic biosynthesis of prostacyclin by cyclooxygenase (COX)-2: the human pharmacology of a selective inhibitor of COX-2. *Proc Natl Acad Sci U S A* 1999;96:272-7. [Erratum, *Proc Natl Acad Sci U S A* 1999;96:5890.]
 22. Brock TG, McNish RW, Peters-Golden M. Arachidonic acid is preferentially metabolized by cyclooxygenase-2 to prostacyclin and prostaglandin E2. *J Biol Chem* 1999;274:11660-6.
 23. Chenevard R, Hurlimann D, Bechir M, et al. Selective COX-2 inhibition improves endothelial function in coronary artery disease. *Circulation* 2003;107:405-9.
 24. Farkouh ME, Kirshner H, Harrington RA, et al. Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), cardiovascular outcomes: randomised controlled trial. *Lancet* 2004;364:675-84.
 25. Zhao SZ, Burke TA, Whelton A, von Allmen H, Henderson SC. Comparison of the baseline cardiovascular risk profile among hypertensive patients prescribed COX-2-specific inhibitors or nonspecific NSAIDs: data from real-life practice. *Am J Manag Care* 2002;8:Suppl:S392-S400.
 26. Bresalier RS, Sandler RS, Quan H, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N Engl J Med* 2005;352.
 27. Mukherjee D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. *JAMA* 2001;286:954-9.
 28. Weir MR, Sperling RS, Reicin A, Gertz BJ. Selective COX-2 inhibition and cardiovascular effects: a review of the rofecoxib development program. *Am Heart J* 2003;146:591-604.
 29. Konstam MA, Weir MR, Reicin A, et al. Cardiovascular thrombotic events in controlled, clinical trials of rofecoxib. *Circulation* 2001;104:2280-8.
 30. Topol EJ. Rofecoxib, Merck, and the FDA. *N Engl J Med* 2004;351:2877-8.
 31. Ott E, Nussmeier NA, Duke PC, et al. Efficacy and safety of the cyclooxygenase 2 inhibitors parecoxib and valdecoxib in patients undergoing coronary artery bypass surgery. *J Thorac Cardiovasc Surg* 2003;125:1481-92.
 32. Nussmeier NA, Whelton AA, Brown MT, et al. Complications of the COX-2 inhibitors parecoxib and valdecoxib after cardiac surgery. *N Engl J Med* 2005;352.
 33. Celecoxib. PhRMA IQ5-97-02-001. (Accessed February 7, 2005, at http://www.clinicalstudyresults.org/documents/company-study_76_0.pdf.)
 34. Topol EJ. Failing the public health — rofecoxib, Merck, and the FDA. *N Engl J Med* 2004;351:1707-9.
 35. Dieppe PA, Ebrahim S, Martin RM, Juni P. Lessons from the withdrawal of rofecoxib. *BMJ* 2004;329:867-8.
 36. Josefson D. FDA warns Merck over its promotion of rofecoxib. *BMJ* 2001;323:767.
 37. Mukherjee D, Topol EJ. Pharmaceutical advertising versus research spending: are profits more important than patients? *Am Heart J* 2003;146:563-4.

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