Hypertension

Effect of Celecoxib on Cardiovascular Events and Blood Pressure in Two Trials for the Prevention of Colorectal Adenomas

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Background—Cyclooxygenase-2 (COX-2) inhibitors have been shown to reduce colorectal adenomas but have been associated with increased cardiovascular risk.

Methods and Results—The Adenoma Prevention With Celecoxib (APC) trial studied celecoxib 200 mg twice daily and 400 mg twice daily and the Prevention of Spontaneous Adenomatous Polyps (PreSAP) trial used 400 mg once daily to test the efficacy and safety of celecoxib against placebo in reducing colorectal adenoma recurrence after polypectomy. An independent safety committee for both studies adjudicated and categorized serious cardiovascular events and then combined individual patient data from these long-term trials to improve the estimate of the cardiovascular risk and blood pressure changes associated with celecoxib compared with placebo. For adjudicated cardiovascular events, 77% and 54% in APC and PreSAP, respectively, had 37 months of follow-up. For APC and PreSAP combined, 83 patients experienced cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or heart failure. The hazard ratio for this prespecified composite end point was 2.6 (95% confidence interval [CI], 1.1 to 6.1) in patients taking 200 mg twice daily, 3.4 (95% CI, 1.5 to 7.9) in patients taking 400 mg twice daily in APC, and 1.3 (95% CI, 0.6 to 2.6) in patients taking 400 mg once daily in PreSAP (P for heterogeneity=0.13 comparing the combined doses in APC with the dose in PreSAP). The overall hazard ratio for this composite end point was 1.9 (95% CI, 1.1 to 3.1). Both dose groups in APC showed significant systolic blood pressure elevations at 1 and 3 years (200 mg twice daily: 1 year, 2.0 mm Hg; 3 years, 2.6 mm Hg; 400 mg twice daily: 1 year, 2.9 mm Hg; 3 years, 5.2 mm Hg); however, the 400 mg once daily group in PreSAP did not ($P<0.0001$ between studies).

Conclusions—Celecoxib at 200 or 400 mg twice daily or 400 mg once daily showed a nearly 2-fold–increased cardiovascular risk. The trend for a dose-related increase in cardiovascular events and blood pressure raises the possibility that lower doses or other dose intervals may be associated with less cardiovascular risk. (***Circulation***. 2006;114:1028-1035.)

Key Words: antiinflammatory agents, nonsteroidal ■ cyclooxygenase inhibitors ■ pharmacology

The confirmation of prior concerns of increased cardiovascular risk from rofecoxib in a randomized placebo-controlled trial led to the voluntary withdrawal of that cyclooxygenase (COX-2) inhibitor and intense scrutiny of other agents in the class.[1–4] We reported cardiovascular risk related to another COX-2 inhibitor, celecoxib, in a randomized placebo-controlled trial, Adenoma Prevention with Celecoxib (APC). That report also mentioned a preliminary analysis of a similar randomized placebo-controlled trial, Prevention of Spontaneous Adenomatous Polyps (PreSAP), which did not show a statistically significant increase in

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cardiovascular risk in patients receiving celecoxib 400 mg once daily but could not exclude a hazard ratio similar to that observed in APC.[5] These findings resulted in the suspension of study drug administration in both trials without interruption of patient follow-up for the primary study outcome, prevention of adenomas.[6]

The possibility of discrepancy between the effect of celecoxib on cardiovascular outcomes in APC and PreSAP raises an important question as to whether the different dose

regimens have different biological effects on the cardiovascular system. While the studies were proceeding, the National Cancer Institute and the Data Safety Monitoring boards of the studies established an independent cardiovascular safety committee to assess the effect of celecoxib on cardiovascular events. Before unblinding the data from either trial, the committee adjudicated serious cardiovascular events and categorized them into various composite end points. The use of uniform definitions and procedures provided an opportunity to synthesize data from both trials to obtain a combined estimate of risk. Both trials collected data on blood pressure at baseline and 1 and 3 years, allowing further exploration from randomized trial data of the cardiovascular effects of the different dosing regimens.

Methods

Patients

The APC and PreSAP trials both compared the efficacy and safety of celecoxib with placebo in reducing colorectal adenomas among patients with a high risk of colorectal adenoma recurrence over a 3-year surveillance period after endoscopic polypectomy. Patients in both trials underwent colonoscopy at 1 and 3 years after study entry. The APC trial, which enrolled patients in North America, the United Kingdom, and Australia, studied celecoxib at doses of 200 mg twice daily and 400 mg twice daily; the PreSAP trial, which enrolled patients from 32 countries, including the United States, on 6 continents, studied 400 mg celecoxib once daily. Patients were not excluded for preexisting cardiovascular disorders. Descriptions of each study design and results are presented elsewhere.[7,8]

Institutional review boards approved the study protocols, and all patients provided written informed consent. Patients were randomly assigned to treatment in a 1:1:1 ratio for the APC study and a 3:2 ratio of celecoxib to placebo in the PreSAP study. Each study stratified randomization by use or nonuse of low-dose aspirin at baseline. Randomization also was stratified by country in PreSAP and by center in APC. Both studies assessed baseline cardiovascular disease status and risk factors for cardiovascular disease.

Review of Cardiovascular Safety

The Cardiovascular Safety Committee, formed at the request of the Data Safety Monitoring boards of both studies, was funded by the National Cancer Institute. The committee developed uniform end-point definitions as guidelines for adjudication and a statistical analysis plan, as previously described.[9] All serious adverse events were collected while the studies were ongoing, and the study sites were required to submit serious adverse events in a timely fashion, which were then investigated by study monitors. Each serious adverse event was reviewed by the Cardiovascular Safety Committee for consideration as a possible cardiovascular event. For all serious adverse events identified as cardiovascular, source documentation was reviewed by the Cardiovascular Safety Committee.

A hierarchical analysis was performed to explore the effect of celecoxib on various composite cardiovascular end points. Before simultaneous unblinding of the 2 trials, the Cardiovascular Safety Committee selected the composite end point of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or heart failure as the primary cardiovascular safety end point. Cox regression analysis, stratified by use or nonuse of low-dose aspirin, was used to estimate hazard ratios for each listed hierarchical outcome. The studies were both designed to have 37 months of follow-up for serious adverse events, which was 1 month longer than the planned period of study drug. For the purpose of the analyses of the adjudicated cardiovascular end points, patients were censored at the time of death, 37 months after randomization, or January 31, 2005, whichever came first. The choice of January 31, 2005, for the censoring of patients who had not completed the study arose from the decision to stop study medication on December 17, 2004, by the leadership of the 2

studies. Because not all patients would have stopped their medication on exactly December 17, January 31, 2005, represented a convenient cutoff date consistent with assigning each participant ≈1 month of follow-up. After the trials announced cessation of study medication, the study teams asked the site investigators to query each patient whose follow-up had not been regular regarding serious cardiovascular events. Under the censoring scheme described, both studies had follow-up information on >90% 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 person-time at risk.

Blood Pressure

In both studies, seated blood pressure was measured in all randomized patients at baseline. Follow-up seated blood pressure measurements were made at 1 and 3 years after randomization. Mean blood pressures and changes from baseline to 1 and 3 years were analyzed post hoc using all reported values. ANOVA was used to calculate differences between the changes for the celecoxib groups and their respective placebo groups, along with their associated 95% confidence intervals (CIs). The percentage of patients in each treatment group with rises in systolic blood pressure >10 and >15 mm Hg from baseline was calculated, and χ^2 tests were used to calculate the statistical significance of the differences.

Combined Analysis

A combined analysis not specified in either protocol was performed using the raw data from each of the 2 trials, stratifying by trial. All analyses compared each dose with its own placebo, and all statistical models included a term for baseline aspirin use. The first Cox model compared the 2 doses in the APC study. If the effect of these doses did not differ significantly, a Cox model combining both studies tested whether the effect of celecoxib differed by study. Because these 2 comparisons showed no difference among the celecoxib dose regimens, the analysis proceeded to combine the data with separate Cox models constructed for each trial. For each study, the natural log of the hazard ratio was estimated, along with its standard error. The 2 resulting log hazard ratios were combined by weighting each one by the inverse of its estimated variance. The SE of this combined log hazard ratio was calculated by standard methods, and the 95% CI was calculated. Finally, the hazard ratio and its confidence interval were calculated from the log hazard ratio. This process was used for each composite end point. Data are presented for the individual doses in each trial and for the pooled analysis. To assess the robustness of the estimates, a combined Cox model was constructed with terms for trial (APC or PreSAP) and celecoxib use (yes or no) to estimate the hazard ratio. A priori, we assumed that this model would produce estimates very close to those produced by the inverse variance method except for the end points of cardiovascular death and cardiovascular death plus myocardial infarction, which had <30 events in each trial.

Subgroup Analysis: Cardiovascular Risk and Aspirin Use

We used the full combined data set to determine whether patients with a history of prior cardiovascular (atherosclerotic or cerebrovascular) disease had a differential risk of adverse cardiovascular events when taking celecoxib. We constructed 2 Cox models, both stratified by study, baseline aspirin use, and history of cardiovascular disease. One model included a term for the interaction between history of cardiovascular disease and celecoxib; we used the difference between the −2log likelihoods from the model to assess the statistical significance of the interaction term. Analogous analyses were performed to examine whether the effect of celecoxib differed between those who did and did not take low-dose aspirin at baseline.

Independence From Sponsor and Statement of Responsibility

The Cardiovascular Safety Committee received baseline data for both the APC and PreSAP trials. The committee constructed a

TABLE 1.   Baseline Characteristics

	APC			PreSAP		
Baseline Characteristic	Placebo (n=679)	Celecoxib 200 mg BID (n=685)	Celecoxib 400 mg BID (n=671)	Placebo (n=628)	Celecoxib 400 mg QD (n=933)	P, PreSAP vs APC
Age (mean±SD), y	59±10	59±9	59±9	60±10	61±10	0.011
Male, %	70	67	68	65	67	0.2
Low-dose aspirin use, %	31	31	30	17	17	<0.0001
History of cardiovascular events, %*	14	13	14	11	14	0.4
Hypertension, %	41	42	39	35	39	0.02
Diabetes, %	9	10	10	11	10	0.5
Current cigarette smoker, %	18	17	14	24	23	<0.0001
Lipid-lowering drug use, %	38	38	38	17	17	<0.0001

*Baseline history of myocardial infarction, cerebrovascular disease, or angina.

database of the cardiovascular events, designed and performed all analyses completely independently of both sponsors, and presented the results of the initial analysis first to the Data Safety Monitoring boards of each study. The results of analyses in this article were reported directly to both sponsoring organizations on completion.

The authors had full access to the data and take full responsibility for their integrity. All authors have read and agree to the manuscript as written.

Results

Baseline characteristics, including baseline medication use, for patients enrolled in APC and PreSAP were well balanced within each study (Table 1). Between studies, patients were similar with respect to age, distribution of gender, history of diabetes, and history of prior cardiovascular disease. Compared with APC patients, PreSAP patients had a lower prevalence of hypertension, a higher rate of cigarette smoking, and a lower use of aspirin and lipid-lowering drugs.

For the cardiovascular end points, all patients in APC had at least 2.6 years of follow-up, and 77% had 37 months of follow-up. In PreSAP, 83% had at least 2 years of follow-up,

and 54% had 37 months of follow-up. Individual component cardiovascular outcomes for the 2 studies are shown in Table 2. Event rates (per 1000 patient-years) and hazard ratios, relative to placebo, for each predefined composite end point are shown for each study in Table 3. Time to event is shown in Kaplan-Meier curves (Figure 1). As reported previously for APC,[6] the data showed a significantly increased hazard for the primary composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or heart failure in the patients taking celecoxib 200 mg twice daily (hazard ratio, 2.6; 95% CI, 1.1 to 6.1) and 400 mg twice daily (hazard ratio, 3.4; 95% CI, 1.5 to 7.9). In PreSAP, 400 mg once daily was not associated with a statistically significant increased risk of the primary cardiovascular composite outcome (hazard ratio, 1.3; 95% CI, 0.6 to 2.6); however, comparing the 2 celecoxib arms in APC and comparing the hazard ratios in APC and PreSAP did not show statistical evidence of heterogeneity among dose regimens with respect to increased cardiovascular risk (P for heterogeneity=0.7 for 2 APC doses; P=0.13

TABLE 2.   Patients With Individual Cardiovascular Events

	APC, n (%)			PreSAP, n (%)	
	Placebo (n=679)	200 mg BID (n=685)	400 mg BID (n=671)	Placebo (n=628)	400 mg QD (n=933)
Total cardiovascular deaths	1 (0.1)	5 (0.7)	6 (0.9)	4 (0.6)	4 (0.4)
Total noncardiovascular deaths	5 (0.7)	3 (0.4)	3 (0.4)	3 (0.5)	6 (0.6)
Total deaths	6 (0.9)	8 (1.2)	9 (1.3)	7 (1.1)	10 (1.1)
Fatal and nonfatal myocardial infarction	3 (0.4)	12 (1.8)	10 (1.5)	4 (0.6)	9 (1.0)
Fatal and nonfatal stroke	3 (0.4)	3 (0.4)	6 (0.9)	7 (1.1)	9 (1.0)
Nonfatal events					
Myocardial infarction	3 (0.4)	9 (1.3)	9 (1.3)	4 (0.6)	9 (1.0)
Stroke	3 (0.4)	3 (0.4)	5 (0.7)	5 (0.8)	9 (1.0)
Heart failure	2 (0.3)	1 (0.1)	4 (0.6)	0	3 (0.3)
Resuscitated sudden death	0	0	1 (0.1)	0	0
Thromboembolic event	1 (0.1)	3 (0.4)	4 (0.6)	1 (0.2)	0
Hospitalization for unstable angina	5 (0.7)	6 (0.9)	2 (0.3)	5 (0.8)	8 (0.9)
Arrhythmia	9 (1.3)	4 (0.6)	7 (1.0)	2 (0.3)	5 (0.5)
Cardiovascular procedure	7 (1.0)	10 (1.5)	7 (1.0)	2 (0.3)	9 (1.0)
Other cardiovascular	9 (1.3)	11 (1.6)	14 (2.1)	5 (0.8)	11 (1.2)

TABLE 3. Hazard Ratios Associated With Individual Doses and Combined Estimates

	APC			PreSAP		
	Placebo (n=679)	200 mg BID (n=685)	400 mg BID (n=671)	Placebo (n=628)	400 mg QD (n=933)	Combined HR, Any Celecoxib Dose
Death from cardiovascular causes, n (%)	1 (0.1)	5 (0.7)	6 (0.9)	4 (0.6)	4 (0.4)	
Rate/1000 patient-years	0.5	2.4	2.9	2.4	1.6	
HR relative to placebo (95% CI)		4.9 (0.6–42.2)	6.2 (0.7–51.4)		0.7 (0.2–2.7)	1.3 (0.4–4.0)
Death from cardiovascular causes or nonfatal myocardial infarction, n (%)	4 (0.6)	14 (2.0)	15 (2.2)	7 (1.1)	13 (1.4)	
Rate/1000 patient-years	1.9	6.7	7.4	4.2	5.3	
HR relative to placebo (95% CI)		3.5 (1.1–10.6)	3.9 (1.3–11.7)		1.3 (0.5– 3.2)	2.0 (1.0–4.0)
Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, n (%)	6 (0.9)	17 (2.5)	20 (3.0)	12 (1.9)	21 (2.3)	
Rate/1000 patient-years	2.9	8.2	9.9	7.2	8.6	
HR relative to placebo (95% CI)		2.8 (1.1–7.2)	3.4 (1.4–8.5)		1.2 (0.6–2.4)	1.7 (1.0–3.0)
Death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure, n (%)	7 (1.0)	18 (2.6)	23 (3.4)	12 (1.9)	23 (2.5)	
Rate/1000 patient-years	3.4	8.7	11.4	7.2	9.4	
HR relative to placebo (95% CI)		2.6 (1.1–6.1)	3.4 (1.5–7.9)		1.3 (0.6–2.6)	1.9 (1.1–3.1)
Death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, or unstable angina, n (%)	11 (1.6)	22 (3.2)	25 (3.7)	15 (2.4)	31 (3.3)	
Rate/1000 patient-years	5.3	10.6	12.4	9.1	12.7	
HR relative to placebo (95% CI)		2.0 (1.0–4.1)	2.3 (1.2–4.8)		1.4 (0.8–2.6)	1.7 (1.1–2.7)
Death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, unstable angina, or cardiovascular procedure, n (%)	17 (2.5)	30 (4.4)	32 (4.8)	17 (2.7)	37 (4.0)	
Rate/1000 patient-years	8.3	14.5	15.9	10.3	15.2	
HR relative to placebo (95% CI)		1.8 (1.0–3.2)	1.9 (1.1–3.5)		1.5 (0.8–2.7)	1.6 (1.1–2.5)
Any cardiovascular event,* n (%)	33 (4.9)	41 (6.0)	53 (7.9)	24 (3.8)	51 (5.5)	
Rate/1000 patient-years	16.3	20.1	26.7	14.6	21.2	
HR relative to placebo (95% CI)		1.2 (0.8–2.0)	1.6 (1.1–2.5)		1.5 (0.9–2.4)	1.4 (1.1–1.9)

HR indicates hazard ratio.

*Any cardiovascular event includes cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, unstable angina, cardiovascular procedure, or any other event deemed cardiovascular in nature.

for APC versus PreSAP). Therefore, we performed a combined analysis of APC and PreSAP, which overall demonstrated a significantly increased risk for the composite of cardiovascular death, myocardial infarction, stroke, or heart failure (hazard ratio, 1.9; 95% CI, 1.1 to 3.1; Figure 2).

In the combined analysis, adding other nonfatal cardiovascular outcomes, unstable angina, cardiovascular procedure, or other nonspecified cardiovascular event to this primary composite showed statistically significant hazard ratios, ranging from 1.4 to 1.7. The combined analysis did not show a differential effect of celecoxib among patients who were or were not taking low-dose aspirin, nor among patients with and without a history of prior cardiovascular disease, although the absolute risk was clearly higher in patients with history of prior cardiovascular disease (Table 4).

Blood Pressure Analysis

Blood pressure at baseline and 1 and 3 years and changes in blood pressure in both the APC and PreSAP studies are shown in Table 5. The percentage of people with blood pressure measurements at years 1 and 3 were 89% and 76%

in APC and 88% and 87% in PreSAP (Table 5). The APC trial showed a statistically significant increase in mean systolic blood pressure compared with placebo at 1 year in both the 200-mg (difference, 2.0 mm Hg; $P=0.04$) and the 400-mg (2.9 mm Hg; $P=0.005$) -twice-daily dose groups and in both dose groups at 3 years (200 mg, 2.6 mm Hg; $P=0.03$; 400 mg, 5.2 mm Hg; $P<0.001$; difference between doses, $P=0.02$). There was no difference in blood pressure between placebo and celecoxib 400 mg once daily in PreSAP at either 1 or 3 years. The differences between the changes between PreSAP and APC were highly significant ($P<0.0001$ for both 1 and 3 years). Similarly, the data showed dose-related increases in the percentage of patients with systolic blood pressure changes ≥ 10 and 15 mm Hg in APC that are significant at 3 years ($P<0.001$) but not in PreSAP (Table 5).

Discussion

Both the APC and PreSAP trials were designed with high statistical power to assess the efficacy of celecoxib in reducing the recurrence of colorectal adenomas. Although our
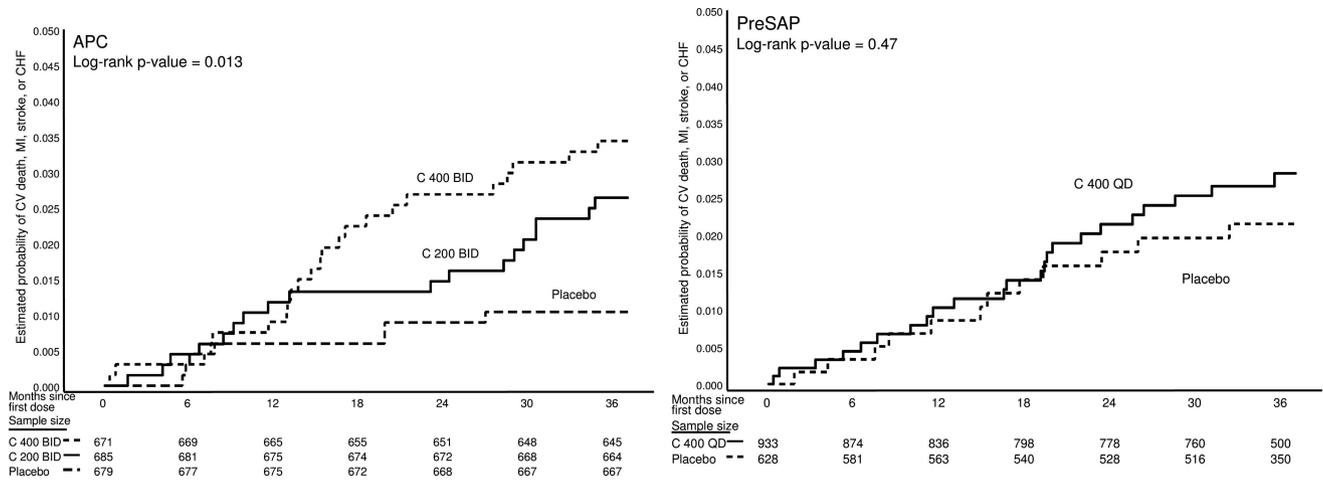
Figure 1. Kaplan-Meier curves showing time to the composite end point of death from cardiovascular causes, myocardial infarction, stroke, or heart failure among patients who received celecoxib or placebo.

analysis of cardiovascular events was blinded and based on adjudicated prespecified outcomes, this safety analysis is based on few events and thus has limited statistical power. Although an increased cardiovascular risk was associated with both doses in APC, the similarly conducted PreSAP trial did not demonstrate a significant increase in cardiovascular risk associated with celecoxib 400 mg once daily; however, because of the small number of events and wide CIs, the data do not exclude a hazard ratio of the magnitude observed in APC.

Despite the low number of cardiovascular events, these trials in combination represent the most extensive long-term placebo-controlled experience with celecoxib, with a total of 10 500 patient-years of cumulative follow-up for cardiovascular events. This combined analysis, which showed a nearly 2-fold increased risk of cardiovascular death, myocardial infarction, stroke, or heart failure associated with celecoxib 400 mg daily or higher (Figure 2), uses individual patient data. This method has advantages over more traditional meta-analytic approaches by maintaining the randomization

structure of each study and using time-to-event data and the baseline strata to provide a more precise estimate of the hazard ratio. Moreover, we can assess more thoroughly whether celecoxib has a differential effect for patients with various baseline characteristics. Finally, access to the raw data allows presentation of the timing of individual events. Although the test for heterogeneity between trials was not statistically significant, suggesting that the pooling of these data is valid, a graded response in the 3 dose groups forces some caution in the interpretation of these results and reinforces the statistical uncertainty inherent in an analysis with few events.

The assessment of blood pressures provides another approach to evaluate whether the cardiovascular effect of celecoxib 400 mg once daily differs from 200 or 400 mg twice daily.[10] The blood pressure data, which are less encumbered by low statistical power, may provide biologically relevant support for the findings on outcomes. Some prior observational and short-term placebo-controlled data have suggested that celecoxib has less effect on blood pressure
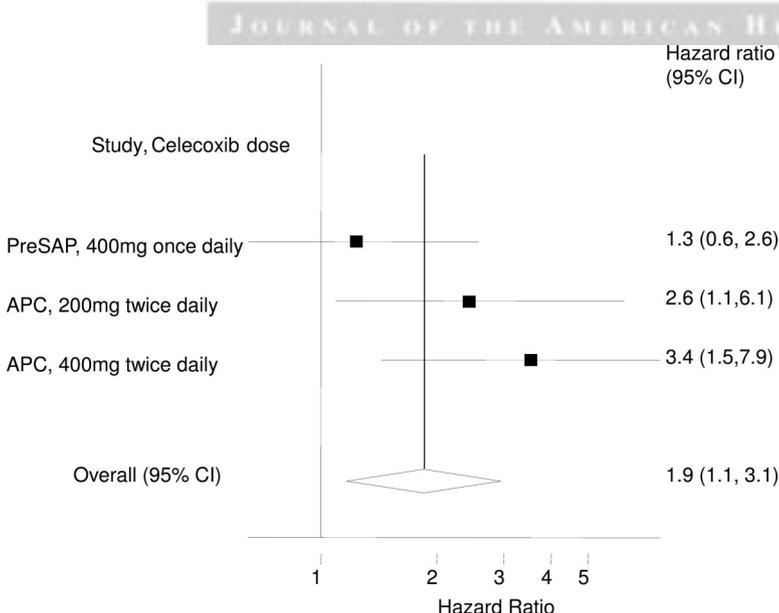

Figure 2. Combined analysis showing 3 separate dosing regimens in the PreSAP and APC studies.

TABLE 4. Hazard Ratio for Cardiovascular Death, Nonfatal Myocardial Infarction, Stroke, or Heart Failure in Patients Who Are or Are Not Taking Low-Dose Aspirin and in Patients With and Without a History of Prior Cardiovascular Disease for the combined APC and PreSAP Data

	Placebo, n/N (%)	Celecoxib, n/N (%)	Hazard Ratio (95% CI)	P for Interaction
Low-dose aspirin users				
Yes	7/319 (2.2)	25/570 (4.4)	2.1 (0.9–5.0)	0.8
No	12/988 (1.2)	39/1719 (2.3)	1.8 (1.0–3.5)	
History of cardiovascular events				
Yes	6/167 (3.6)	26/314 (8.3)	2.3 (0.9–5.6)	0.6
No	13/1140 (1.1)	38/1975 (1.9)	1.8 (0.9–3.3)	

than do other agents in this class.[11,12] Schwartz et al[13] reported that 14 days of treatment with celecoxib 200 mg twice daily increased systolic blood pressure (4.3 mm Hg) by an amount similar to rofecoxib 25 mg once daily (3.4 mm Hg) and naproxen 500 mg twice daily (3.1 mm Hg) compared with placebo (−1.3 mm Hg). Conversely, a much larger study recently found that neither celecoxib 200 mg once daily nor naproxen 500 mg twice daily increased blood pressure, whereas rofecoxib 25 mg once daily did.[14]

We observed a graded response on systolic blood pressure in the 2 trials, with no change on average with 400 mg QD and a dose-related increase with 200 to 400 mg BID. Although in a prior study, no increase in blood pressure was observed at the time of expected trough plasma levels during once daily dosing, an increase in blood pressure of a magnitude similar to that seen in APC has been seen at peak dosing.[15] Thus, the timing of blood pressure measurements related to the dosing of celecoxib may be important for the interpretation of these results, and it is conceivable that once-daily dosing simply results in a less sustained blood pressure effect than twice-daily dosing. This hypothesis is supported by ambulatory blood pressure data suggesting that there was a 2– to 4–mm Hg increase in systolic blood pressure over the 4 hours after dosing of celecoxib.[16] Alternatively, the relatively short half-life of celecoxib is a potential explanation for the apparent differential blood pressure response between the 2 trials; however, this hypothesis has not been rigorously tested.[17,18] The suggestion of

TABLE 5. Blood Pressure Values and Changes at Baseline and at 1- and 3-Year Follow-Up

	APC			PreSAP	
	Placebo (n=678)	200 mg BID (n=683)	400 mg BID (n=665)	Placebo (n=626)	400 mg QD (n=933)
BP					
Baseline, mm Hg	131.7 ±17.2/80.0±9.6	131.6 ±15.9/79.2±8.8	130.5 ±15.9/78.7±9.4	134.6 ±17.4/80.6±10.0	135.4 ±16.6/81.4±9.3
1 y, mm Hg (n)	132.2 ±17.4/78.8±10.5 (603)	134.5 ±18.0/79.3±10.3 (608)	133.7 ±17.7/78.8±9.5 (598)	133.1 ±16.7/80.1±9.9 (553)	135.3 ±17.4/80.8±10.0 (823)
3 y, mm Hg (n)	130.7 ±17.2/77.3±10.1 (506)	133.0 ±17.0/78.2±9.9 (518)	134.2 ±18.5/77.9±9.8 (516)	131.8 ±16.1/79.1±9.6 (547)	133.6 ±16.3/79.9±9.4 (807)
Change in BP¹ from baseline compared to change in placebo,* mm Hg (95% CI)					
At 1 y	…	2.0 (0.1–4.0)/1.2 (−0.1–2.4)	2.9 (0.9–4.9)/1.2 (−0.1–2.4)	…	0.9 (−1.0–2.7)/0.0 (−1.2–1.1)
At 3 y	…	2.6 (0.2–4.9)/1.8 (0.4–3.3)	5.2 (2.9–7.6)/2.1 (0.6–3.5)	…	0.6 (−1.3–2.4)/0.0 (−1.1–1.1)
Patients with change in systolic BP on follow-up,† %					
At 1 y					
≥10 mm Hg	26±1.8	31±1.9	32±1.9	20±1.7	22±1.4
≥15 mm Hg	18±1.5	22±1.7	23±1.7	13±1.4	14±1.2
At 3 y					
10 mm Hg	24±1.9	31±2.0	36±2.1	22±1.8	23±1/5
≥15 mm Hg	16±1.6	21±1.8	27±2.0	14±1.5	15±1.3

BP indicates blood pressure.

*Means are compared with study-specific placebo means. The difference between the changes in systolic blood pressure at 3 years in the 200 and 400 mg BID groups in APC is statistically significant (P=0.02). The difference between the changes in systolic blood pressure between PreSAP and APC are highly significant (P<0.0001 for both 1 and 3 years). The analyses are based on ANOVA for systolic and diastolic blood pressure with study, dose, and aspirin use at baseline as the independent variables.

†Because of pronounced digit preference, the observations were smoothed using a 3-point rectangular smoother to obtain more accurate estimates of means and of percentages >10 and 15 mm Hg. To assess the robustness of the results, we tested the raw data and other smoothing strategies; all produced similar effect sizes. At 1 year, all probability values are >0.01 for differences at 1 year between any 2 doses within trials and the differences between changes from placebo to any dose between APC and PreSAP. At 3 years, the probability comparing differences between the 400 mg BID and placebo doses in APC are <0.001 for both 10 and 15 mm Hg. The probabilities associated with the differences with placebo between the 400 mg BID dose in APC and the 400 mg QD dose in PreSAP are 0.005 and 0.002 for 10 and 15 mm Hg, respectively. No other comparison at 3 years (200 mg BID vs APC placebo, 200 vs 400 mg BID, 400 mg QD vs PreSAP placebo, or difference between effect of 400 mg QD in PreSAP and 200 mg BID in APC) has a probability value <0.01.

short-lived inhibition of endothelial COX-2 and subsequent recovery of that enzyme during once-daily dosing[17] needs to be tested prospectively. Nevertheless, the low number of overall events in these studies, the fact that these studies of polyp prevention did not define a protocol for measuring blood pressure, and the fact that earlier blood pressure measurements were not recorded limit our ability to determine whether blood pressure elevations underlie the cardiovascular risks observed.

In these studies, all 3 doses of celecoxib examined were effective in reducing the number of adenomatous polyps and higher-grade histological lesions.[7,8] Whether lower doses would be effective for this purpose is unknown, although a trend for a reduction in polyps in a smaller study of patients with familial adenomatous polyposis has been observed with a dose of 100 mg twice daily.[19] Most patients exposed to celecoxib take the drug for pain relief. The usual dose of celecoxib for arthritis pain relief (average daily dose, 200 mg) is lower than the doses tested in APC and PreSAP. The cardiovascular risk associated with usual analgesic doses is unknown and cannot be reliably estimated from the available small, short-term, placebo-controlled trials or the many observational studies with their inherent limitations. Moreover, we cannot reliably extrapolate our data to short-term use of celecoxib because these studies do not have sufficient power to allow assessment of the true time course of the cardiovascular risk. Nevertheless, physicians must recognize the increased potential for cardiovascular risk compared with placebo when considering celecoxib for pain relief.

We undertook this comprehensive analysis of cardiovascular safety only after substantial public concern had been raised about the safety of rofecoxib. Moreover, neither APC nor PreSAP was designed or powered to assess cardiovascular risk. Thus, the results of this analysis are limited by the statistical uncertainty arising from the small total number of events. Indeed, a potential explanation for the smaller relative risk associated with celecoxib in PreSAP compared with APC is the higher placebo event rate in that trial (7.2 of 100 patient-years in PreSAP compared with 3.4 of 1000 patient-years in APC), although these rates are based on only 7 and 12 placebo events, respectively. Thus, chance is a possible explanation for the apparently discrepant hazard related to celecoxib in the 2 trials. Finally, the data in this article differ minimally from the data originally presented to the 2 Data Safety Monitoring boards and from original report describing the cardiovascular end points in APC[6] because, during the year from stopping the study to closing the database, some baseline data were updated, and a few additional cardiovascular events were identified.

Conclusions

In summary, we observed a nearly 2-fold increased risk of the composite end point of cardiovascular death, myocardial infarction, stroke, or heart failure when combining all doses of celecoxib tested in 2 similar placebo-controlled, long-term cancer prevention trials. The observed dose-related increase in cardiovascular events and blood pressure raises the possibility that even lower once-daily dose regimens may be associated with lower overall cardiovascular hazard. Further research is needed to determine whether lower doses of celecoxib would provide pain relief and adenomatous polyp prevention with a clinically acceptable level of cardiovascular risk.

References

1. 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;96:272–277.
2. Bombardier C, Laine L, Reicin A, Shapiro D, Burgos-Vargas R, Davis B, Day R, Ferraz MB, Hawkey CJ, Hochberg MC, Kvien TK, Schnitzer TJ, for the VIGOR Study Group. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis: VIGOR Study Group. *N Engl J Med*. 2000;343:1520–1528.
3. Bresalier RS, Sandler RS, Quan H, Bolognese JA, Oxenius B, Horgan K, Lines C, Riddell R, Morton D, Lanas A, Konstam MA, Baron JA, for the Adenomatous Polyp Prevention on Vioxx (APPROVe) Trial Investigators. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N Engl J Med*. 2005;352:1092–1102.
4. Nussmeier NA, Whelton AA, Brown MT, Langford RM, Hoeft A, Parlow JL, Boyce SW, Verburg KM. Complications of the COX-2 inhibitors parecoxib and valdecoxib after cardiac surgery. *N Engl J Med*. 2005;352:1081–1091.
5. Food and Drug Administration. Joint meeting with the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee. Available at: http://www.fda.gov/ohrms/dockets/ac/05/slides/2005–4090s1.htm. Accessed July 18, 2006.
6. Solomon SD, McMurray JJ, Pfeffer MA, Wittes J, Fowler R, Finn P, Anderson WF, Zauber A, Hawk E, Bertagnolli M, for the Adenoma Prevention with Celecoxib (APC) Study Investigators. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. *N Engl J Med*. 2005;352:1071–1080.
7. Bertagnolli MM, Eagle CJ, Zauber AG, Redston M, Solomon SD, Kim K, Tang J, Rosenstein RB, Wittes J, Corle D, Hess TM, Woloj M, Boisserie F, Anderson WF, Viner JF, Bagheri D, Gordon GB, Burn J, Chung DC, Dewar T, Folwy TR, Hoffman N, Macrae F, Pruitt RE, Salzman JR, Salzberg B, Tylwestrowicz T, Hawk ET, for the APC Study Investigators. Celecoxib for the prevention of sporadic colorectal adenomas. *N Engl J Med*. 2006;355:873–884.
8. Arber N, Eagle C, Spicak J, Racz I, Dite P, Hajer J, Zavoral M, Lechuga MJ, Gerletti P, Tang J, Rosenstein RB, Macdonald K, Bhadra P, Fowler R, Wittes J, Zauber AG, Solomon SD, Levin B, for the Prevention of Sporadic Adenomatous Polyps (PreSAP) Investigators. Celecoxib for the prevention of colorectal adenomatous polyps. *N Engl J Med*. 2006;355:885–895.
9. Solomon SD, McMurray JJ, Pfeffer MA, Wittes J, Fowler R, Finn P, Anderson WF, Zauber A, Hawk E, Bertagnolli M, for the Adenoma Prevention with Celecoxib (APC) Study Investigators. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. *N Engl J Med*. 2005;352:1071–1080.
10. Messerli FH, Sichrovsky T. Does the pro-hypertensive effect of cyclooxygenase-2 inhibitors account for the increased risk in cardiovascular disease? *Am J Cardiol*. 2005;96:872–873.
11. Solomon DH, Schneeweiss S, Levin R, Avorn J. Relationship between COX-2 specific inhibitors and hypertension. *Hypertension*. 2004;44:140–145.
12. Whelton A, White WB, Bello AE, Puma JA, Fort JG, for the SUCCESS-VII Investigators. Effects of celecoxib and rofecoxib on blood pressure and edema in patients ≥65 years of age with systemic hypertension and osteoarthritis. *Am J Cardiol*. 2002;90:959–963.

13. Schwartz JI, Vandormael K, Malice MP, Kalyani RN, Lasseter KC, Holmes GB, Gertz BJ, Gottesdiener KM, Laurenzi M, Redfern KJ, Brune K. Comparison of rofecoxib, celecoxib, and naproxen on renal function in elderly subjects receiving a normal-salt diet. *Clin Pharmacol Ther.* 2002;72:50–61.

14. Sowers JR, White WB, Pitt B, Whelton A, Simon LS, Winer N, Kivitz A, van Ingen H, Brabant T, Fort JG, for the Celecoxib Rofecoxib Efficacy and Safety in Comorbidities Evaluation Trial (CRESCENT) Investigators. The effects of cyclooxygenase-2 inhibitors and nonsteroidal anti-inflammatory therapy on 24-hour blood pressure in patients with hypertension, osteoarthritis, and type 2 diabetes mellitus. *Arch Intern Med.* 2005;165:161–168.

15. Izhar M, Alausa T, Folker A, Hung E, Bakris GL. Effects of COX inhibition on blood pressure and kidney function in ACE inhibitor-treated blacks and Hispanics. *Hypertension.* 2004;43:573–577.

16. White WB, Kent J, Taylor A, Verburg KM, Lefkowith JB, Whelton A. Effects of celecoxib on ambulatory blood pressure in hypertensive patients on ACE inhibitors. *Hypertension.* 2002;39:929–934.

17. Grosser T, Fries S, FitzGerald GA. Biological basis for the cardiovascular consequences of COX-2 inhibition: therapeutic challenges and opportunities. *J Clin Invest.* 2006;116:4–15.

18. Carothers AM, Moran AE, Cho NL, Redston M, Bertagnolli MM. Development of resistance to selective cyclooxygenase-2 inhibition in C57BL/6J-Min/+ (Min/+) mice. *Cancer Res.* 2006;66:6432–6438.

19. Steinbach G, Lynch PM, Phillips RK, Wallace MH, Hawk E, Gordon GB, Wakabayashi N, Saunders B, Shen Y, Fujimura T, Su LK, Levin B. The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. *N Engl J Med.* 2000;342:1946–1952.

CLINICAL PERSPECTIVE

Cyclooxygenase-2 (COX-2) inhibitors have been associated with increased cardiovascular risk. This study reports the results of a comprehensive cardiovascular risk analysis from 2 randomized placebo-controlled trials of celecoxib for the prevention of adenomatous polyps. The effects of 3 dose regimens of celecoxib—400 mg once daily, 200 mg twice daily, and 400 mg twice daily—on cardiovascular events and blood pressure compared with placebo were assessed. There was an increased risk of cardiovascular death, myocardial infarction, stroke, or heart failure in patients taking celecoxib 200 mg twice daily (hazard ratio, 2.6; 95% confidence interval [CI], 1.1 to 6.1) or 400 mg twice daily (HR, 3.4; 95% CI, 1.5 to 7.9) but not in patients receiving celecoxib 400 mg once daily (hazard ratio, 1.3; 95% CI, 0.6 to 2.6). Combining all dose regimens in a pooled analysis yielded an overall hazard ratio for this composite end point of 1.9 (95% CI, 1.1 to 3.1). Elevations in blood pressure at 3 years were observed in patients receiving 200 mg twice daily (2.6 mm Hg) and in patients receiving 400 mg twice daily (5.2 mm Hg) but not in patients receiving 400 mg once daily. These data suggest an overall nearly doubling of cardiovascular risk in patients receiving celecoxib in these dosing regimens. Clinicians need to be aware that the data suggest a dose-related increase in cardiovascular risk associated with celecoxib use. The apparent dose-related increase in both cardiovascular events and blood pressure observed in this analysis raises the possibility that lower once-daily dosing regimens may be associated with lower cardiovascular hazard, although this hypothesis requires prospective testing.

Circulation

Effect of Celecoxib on Cardiovascular Events and Blood Pressure in Two Trials for the Prevention of Colorectal Adenomas

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