ORIGINAL ARTICLE

Celecoxib for the Prevention of Colorectal Adenomatous Polyps

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ABSTRACT

BACKGROUND

Overexpression of cyclooxygenase 2 (COX-2) has been associated with colorectal adenomatous polyps and cancer, prompting researchers to propose its inhibition as a chemopreventive intervention.

METHODS

The Prevention of Colorectal Sporadic Adenomatous Polyps trial was a randomized, placebo-controlled, double-blind study of the COX-2 inhibitor celecoxib given daily in a single 400-mg dose. At 107 centers in 32 countries, we randomly assigned 1561 subjects who had had adenomas removed before enrollment to receive celecoxib (933 subjects) or placebo (628 subjects) daily, after stratification according to the use or nonuse of low-dose aspirin. The primary outcome was detection of adenomas at either year 1 or year 3 by colonoscopy and was compared among the groups with the use of the Mantel–Cox test.

RESULTS

Colonoscopies were performed at year 1 on 88.7 percent of the subjects who had undergone randomization and at year 3 on 79.2 percent. Of the 557 subjects in the placebo group and the 840 subjects in the celecoxib group who were included in the efficacy analysis, 264 and 270, respectively, were found to have at least one adenoma at year 1, at year 3, or both. The cumulative rate of adenomas detected through year 3 was 33.6 percent in the celecoxib group and 49.3 percent in the placebo group (relative risk, 0.64; 95 percent confidence interval, 0.56 to 0.75; P<0.001). The cumulative rate of advanced adenomas detected through year 3 was 5.3 percent in the celecoxib group and 10.4 percent in the placebo group (relative risk, 0.49; 95 percent confidence interval, 0.33 to 0.73; P<0.001). Adjudicated serious cardiovascular events occurred in 2.5 percent of subjects in the celecoxib group and 1.9 percent of those in the placebo group (relative risk, 1.30; 95 percent confidence interval, 0.65 to 2.62).

CONCLUSIONS

The use of 400 mg of celecoxib once daily significantly reduced the occurrence of colorectal adenomas within three years after polypectomy. (ClinicalTrials.gov number, NCT00141193.)

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Colorectal cancer, the second most prevalent cancer in the developed world and the third most prevalent in developing nations,[1] is responsible worldwide for more than a million new cases of cancer and half a million deaths annually.[2] Recent annual reductions of 1.8 percent in the incidence in the United States are credited, in part, to increased screening and the removal of adenomatous polyps (adenomas).[3] Most cases of colorectal cancer are preceded by adenomas, which are characterized by an early accumulation of gene mutations.[4]

The regression and prevention of adenomas have become primary aims of investigators, who have used nonsteroidal antiinflammatory drugs (NSAIDs), including aspirin, to reduce the incidence and recurrence of adenomas.[5-7] Since being identified as distinct from the ubiquitous cyclooxygenase (COX) 1 isoform,[8] COX-2 has been shown to be overexpressed in colorectal cancers and adenomas in humans[9,10] and was demonstrated in knockout mice to be a controlling factor in the formation of adenomas.[11] Researchers have therefore sought to assess the effects of such selective COX-2 inhibitors as celecoxib on the formation of adenomas in hopes that these agents could overcome the gastrointestinal adverse events of nonselective NSAIDs that placed limits on effective therapy.

Three international, multicenter studies of the use of COX-2 inhibitors to prevent sporadic adenomas, including the present study, were launched in 1999 and 2000.[12,13] The randomized Adenoma Prevention with Celecoxib (APC) trial included 2035 patients in a study of two twice-daily doses of celecoxib, and the randomized Adenomatous Polyp Prevention on Vioxx (APPROVe) trial included 2586 patients in a study of rofecoxib. We undertook a randomized, placebo-controlled, double-blind study of 400 mg of celecoxib once daily in subjects who had undergone colonoscopy and polypectomy at baseline.

METHODS

STUDY DESIGN

We performed this randomized, placebo-controlled, double-blind study of three years of treatment with a once-daily dose of 400 mg of celecoxib (Celebrex, Pfizer). With guidance from the steering committee, the investigators developed the study protocol, which was approved by central and local ethics committees and overseen by an independent data and safety monitoring board. Investigators and an independent organization (Covance, Princeton, N.J.) collected data, Pfizer maintained the database, and a team consisting of both Pfizer and independent statisticians conducted the analyses. The cardiovascular safety committee independently reviewed and adjudicated all serious adverse events and performed an independent analysis. The authors vouch for the completeness and veracity of the data and data analyses.

Within three months before enrollment, all subjects had undergone a colonoscopy, documented to the cecum, in which all polyps that were found were removed. Enrolled patients, all of whom had had adenomas detected and removed, received placebo during a single-blind, one-month run-in period. When the period ended, eligible subjects were stratified according to country and to the use or nonuse of low-dose aspirin, and then they were randomly assigned in a 3:2 ratio by an interactive voice-response system to receive 400 mg of celecoxib or placebo once daily. Colonoscopies were performed 12 months (year 1) and 36 months (year 3) after randomization. The investigators completed enrollment in one year (from March 2001 to March 2002) and performed the last colonoscopy in May 2005. Meetings of investigators before enrollment and site inspections for quality control during the trial were designed to promote uniform practice and quality assurance.

Safety evaluations during the study included physical examinations and clinical laboratory tests during the run-in period and at one and three years after enrollment. After they underwent randomization, subjects made return visits at 3, 6, 12, 18, 24, 30, 36, and 37 months for assessment of pill counts, as well as for reporting of concomitant medications and adverse events (which were also gauged during bimonthly telephone assessments). Safety data were reviewed every six months by the independent data and safety monitoring board, for whom an independent statistician issued unblinded reports for review. After reports in September 2004 of increased cardiovascular risk with the use of rofecoxib, the steering committee for the Prevention of Colorectal Sporadic Adenomatous Polyps (PreSAP) trial requested that an independent cardiovascular safety committee perform an analysis of cardiovascular events. Results from this analysis in December 2004 showed no significant increase in cardiovascular risk[14];

however, an increase detected in a similar, concurrent analysis of the APC trial by the same cardiovascular safety committee led to suspension of the administration of the study drug in the PreSAP trial on December 17, 2004.[13]

STUDY POPULATION

We enrolled 1738 subjects at 107 centers in 32 countries on six continents. Before study participation, all subjects provided written informed consent. Eligible subjects were 30 years of age or older and had undergone colonoscopy within three months before enrollment that showed either 1 adenoma that was at least 6 mm or 2 to 10 adenomas of any size. Inclusion criteria required photographic documentation that the cecum was reached, the colon was clean, and the adenomas that were removed were of the size charted. Subjects had to show 80 percent adherence to the 1-month run-in placebo medication and had to be willing to abstain from long-term use (defined as use for more than 21 days throughout the year) of all NSAIDs, including COX-2 inhibitors other than the blinded study drug but excluding cardioprotective doses of oral aspirin (≤162.5 mg daily or ≤325 mg every other day). Subjects were ineligible if they had a history of familial adenomatous polyposis, hereditary nonpolyposis colorectal cancer, inflammatory bowel disease, or invasive cancer within five years before enrollment. Also ineligible were subjects with renal, hepatic, or bleeding disorders; subjects hypersensitive to COX-2 inhibitors, NSAIDs, salicylates, or sulfonamides; subjects who had undergone large-bowel resection (excluding appendectomy); and subjects who had used NSAIDs, excluding cardioprotective doses of aspirin, three or more times a week within the 60 days before randomization.

STUDY END POINTS

The primary efficacy end point was detection by colonoscopy of at least one colorectal adenoma at year 1, at year 3, or both. All polyps removed during colonoscopies were submitted to local and central pathology laboratories for blinded review. An adjudicator resolved discrepancies in a blinded fashion.

Secondary efficacy end points one year and three years after enrollment included the number of colorectal adenomas, the size of the largest ones measured, and the total adenoma burden (the sum of the diameters of all the adenomas) over the three-year period. In addition, for consistency with the APC trial, end points included detection of advanced adenoma with any of the following characteristics: size of at least 1.0 cm according to measurements obtained endoscopically, villous or tubulovillous histologic features, high-grade dysplasia, intramucosal carcinoma, or invasive cancer.

Safety end points were based on investigator-reported adverse events, serious adverse events, laboratory measurements, and physical examinations. Adverse events were coded according to criteria from the Medical Dictionary for Regulatory Activities (MedDRA), version 8.1. Adjudicated cardiovascular end points were categorized as previously described.[15]

STATISTICAL ANALYSIS

The trial required 1500 subjects (900 in the celecoxib group and 600 in the placebo group) to ensure 90 percent power to detect at least a 35 percent relative reduction in the formation of adenomas in the celecoxib group as compared with the placebo group, assuming that 36 percent of subjects in the placebo group who were taking low-dose aspirin and 42 percent of subjects in the placebo group who were not taking low-dose aspirin would have newly detected adenomas at year 1, at year 3, or both. It was anticipated that 35 percent of the subjects would be taking low-dose aspirin. The sample size further allowed for subjects to withdraw from the study and assumed a two-sided type I statistical error of 0.05.

Efficacy analyses included all subjects who had undergone randomization. The effect of celecoxib in reducing the proportion of subjects in whom adenomas were detected at year 1, at year 3, or both was estimated with the use of the Mantel–Cox test, a life-table extension of the Mantel–Haenszel test,[16-18] with stratification for the use or nonuse of aspirin. The method for calculating relative risk was described by Kleinbaum et al.[19] Subjects considered at risk at year 1 included those who underwent colonoscopy at year 1, as well as those who underwent colonoscopy only at year 3 and who were classified as having had no adenomas detected at year 1. Subjects considered at risk at year 3 were those who had undergone colonoscopy at year 3 and in whom no adenomas were identified before year 3. The occurrence of advanced adenomas was analyzed according to the same method. Separate analyses of the occurrence of adenomas at year 1 and at year 3 were per-

Table 1. Baseline Characteristics of the Subjects.*

Characteristic	Placebo (N=628)	Celecoxib (N=933)
Age — yr		
Median	61	61
Range	30–87	31–92
Male sex — no. (%)	406 (64.6)	629 (67.4)
Race or ethnic group — no. (%)†		
White	557 (88.7)	835 (89.5)
Black	18 (2.9)	16 (1.7)
Hispanic or Latin American	14 (2.2)	21 (2.3)
Asian	36 (5.7)	60 (6.4)
Native American	3 (0.5)	1 (0.1)
Body-mass index		
Men	27.3±0.2	27.4±0.2
Women	26.6±0.3	27.2±0.3
Blood pressure — mm Hg‡		
Diastolic	80.6±0.40	81.4±0.31
Systolic	134.6±0.70	135.3±0.54
Colorectal cancer in a parent — no. (%)	109 (17.4)	145 (15.5)
Use of low-dose aspirin — no. (%)§	107 (17.0)	155 (16.6)
Findings during colonoscopy at baseline		
No. of reported adenomas	1.9±0.1	1.9±0.0
Adenoma ≥1 cm — no. (%)	295 (47.0)	448 (48.0)
Adenoma burden — cm¶	1.72±0.06	1.73±0.04

formed with the use of a Mantel–Haenszel test, stratified according to the use or nonuse of aspirin. The number of adenomas, the size of the largest adenoma, and the total adenoma burden detected during the three years were analyzed with van Elteren's test,[20] an extension of the Wilcoxon rank-sum test, stratified according to the use or nonuse of aspirin. There were no interim analyses of efficacy. All reported P values are two sided.

Investigator-reported adverse events were summarized for all treated subjects, regardless of adherence to study protocol. Additional summaries were provided for prespecified categories of adverse events. Serious adverse cardiovascular events were adjudicated and categorized as previously described.[13]

RESULTS

BASELINE CHARACTERISTICS

Baseline demographic characteristics, colonoscopic findings, cardiovascular risk factors, and body-mass index were similar in the groups (Table 1). The proportion of subjects with a history of cardiovascular events (atherosclerotic or cerebrovascular disease) was 11.1 percent in the placebo group and 13.7 percent in the celecoxib group.

SUBJECT DISPOSITION

Of 1738 subjects screened for eligibility, 1561 underwent randomization, 628 to the placebo group and 933 to the celecoxib group; 107 (17.0 percent) in the placebo group and 160 (17.1 percent) in the celecoxib group took low-dose aspirin. In the placebo group, 554 subjects (88.2 percent) completed the colonoscopy at year 1 and 498 (79.3 percent) completed the colonoscopy at year 3; in the celecoxib group, 831 subjects (89.1 percent) completed the year 1 colonoscopy and 739 (79.2 percent) completed the year 3 colonoscopy (Fig. 1). In all, 495 subjects in the placebo group (78.8 percent) and 727 in the celecoxib group (77.9 percent) received the study medication for 80 percent or more of the study period.

Table 1. (Continued.)

Characteristic	Placebo (N=628)	Celecoxib (N=933)
Cardiovascular risk factors — no. (%)‖	398 (63.4)	601 (64.4)
Hypertension**	221 (35.2)	361 (38.7)
Hyperlipidemia††	107 (17.1)	162 (17.4)
Atherosclerotic heart disease	58 (9.2)	105 (11.3)
Diabetes‡‡	70 (11.2)	89 (9.5)
Current smoker	153 (24.4)	215 (23.0)
Cerebrovascular disorder	14 (2.2)	32 (3.4)
Cardiovascular events — no. (%)§§	70 (11.1)	128 (13.7)

* Plus–minus values are means ±SE. Body-mass index is the weight in kilograms divided by the square of the height in meters.
† Race or ethnic group was identified by the physician or subject and recorded by the physician.
‡ Data on baseline values for blood pressure were missing from two subjects in the placebo group.
§ Low-dose aspirin was defined as 162.5 mg or less daily or 325 mg or less every other day.
¶ The adenoma burden was defined as the sum of the diameters of all adenomas reported during colonoscopy at baseline.
‖ Cardiovascular risk factors included a baseline history of hypertension, hyperlipidemia, atherosclerotic heart disease (i.e., angina, myocardial infarction, or cardiac revascularization procedure), diabetes, current smoking, or cerebrovascular disorder. Data on cardiovascular history were missing for one subject in each group.
** Subjects with hypertension were defined as those who had terms on the medical records corresponding to clinic visits at screening or baseline that matched verbatim the terms with the diagnostic codes of the *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM) for essential hypertension (code 401.x), hypertensive heart disease (code 402.x), hypertensive renal disease (code 403.x), hypertensive heart and renal disease (code 404.x), and secondary hypertension (code 405.x).
†† Subjects with hyperlipidemia were defined as those who had terms on the medical records corresponding to clinic visits at screening or baseline that matched verbatim the terms with the diagnostic codes of the ICD-9-CM codes for disorders of lipid metabolism (code 272.x).
‡‡ Data on diabetes history were missing for one subject in the celecoxib group.
§§ Subjects included those with a history of cardiovascular events (i.e., atherosclerotic or cerebrovascular disease).

Forty-two percent of subjects who underwent colonoscopy at year 3 did so after administration of the drug was suspended on December 17, 2004; 93 percent of those colonoscopies were performed within three months after suspension. Total treatment exposure was 2331 patient-years (mean, 2.49 years) for celecoxib and 1570 patient-years (mean, 2.50 years) for placebo, reflecting the 3:2 ratio of randomization.

EFFICACY

Of the 557 subjects in the placebo group and the 840 subjects in the celecoxib group who were included in the efficacy analysis, 264 and 270, respectively, were found to have at least one adenoma at year 1, at year 3, or both (Table 2). Overall, the three-year estimated cumulative rate of adenomas, calculated on the basis of the Mantel–Cox method, was 33.6 percent for subjects receiving celecoxib and 49.3 percent for subjects receiving placebo (relative risk, 0.64; 95 percent confidence interval, 0.56 to 0.75; P<0.001) (Table 2). The results were similar for subjects taking low-dose aspirin at baseline (relative risk, 0.61; 95 percent confidence interval, 0.43 to 0.88; P=0.007), as well as for those not taking low-dose aspirin at baseline (relative risk, 0.65; 95 percent confidence interval, 0.55 to 0.76; P<0.001). Fifty-six subjects in the placebo group and 42 in the celecoxib group were found to have advanced adenomas as follows: 40 in the placebo group and 25 in the celecoxib group at year 1, and 16 in the placebo group and 17 in the celecoxib group at year 3. The estimated cumulative proportion of subjects with advanced adenomas at year 3 was 5.3 percent in the celecoxib group and 10.4 percent in the placebo group (relative risk, 0.49; 95 percent confidence interval, 0.33 to 0.73; P<0.001). Among subjects who had any new adenoma detected, the mean size of the largest adenoma and the mean adenoma burden were significantly lower in the celecoxib group than in the placebo group; the difference in the mean number of adenomas was not significant (Table 2).

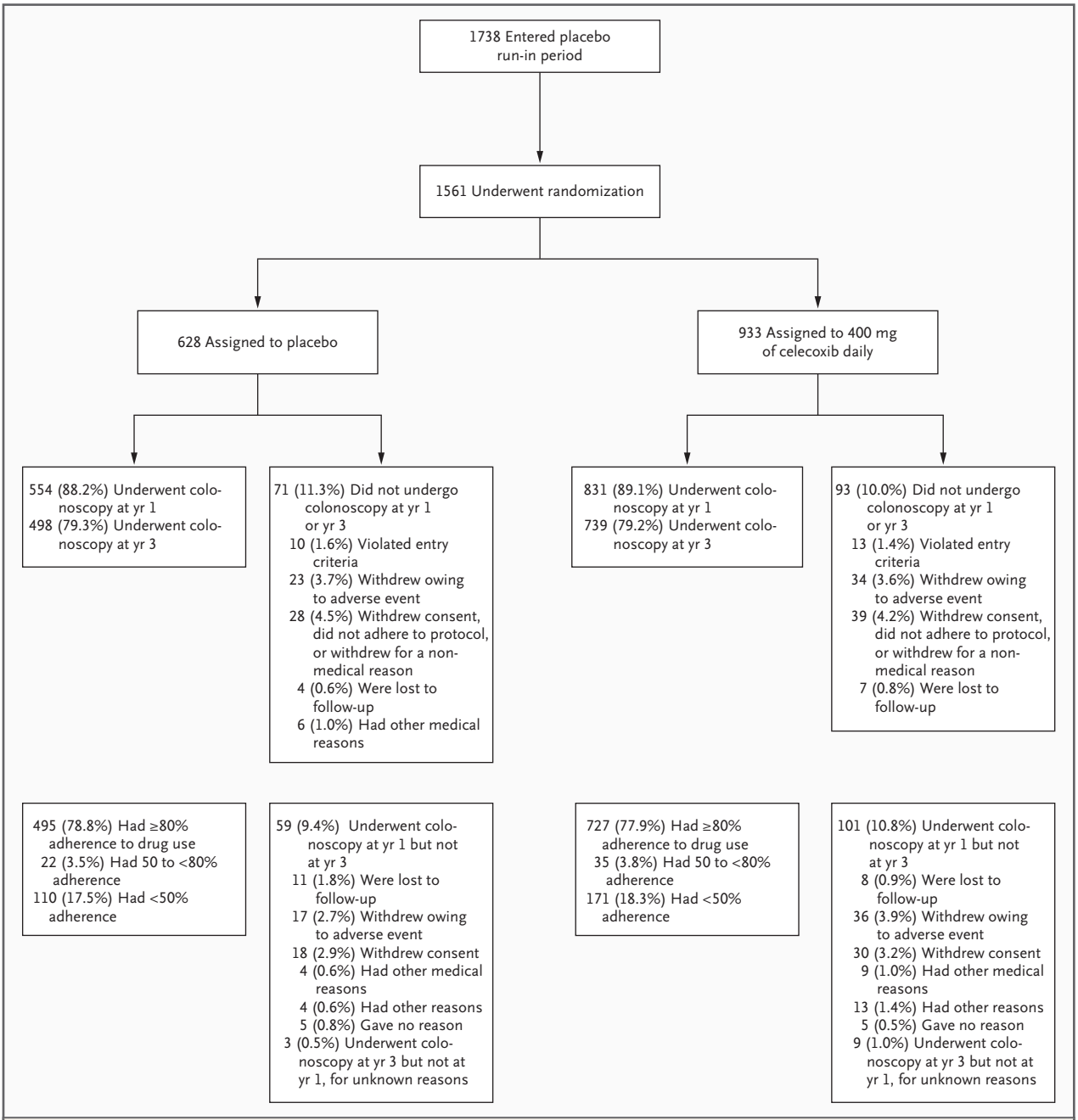

Figure 1. Enrollment and Disposition of Subjects.

SAFETY

In the placebo group, the only adverse events related to colonoscopy were three cases of bleeding and one case of hypotension. All four occurred at baseline. Adverse events related to colonoscopy reported in the celecoxib group were 10 cases of bleeding, 2 perforations, 3 cardiovascular complications (tachycardia and bradycardia), and 1 vasovagal episode. Eleven occurred at baseline, four at year 1, and one at year 3.

Investigator-reported serious adverse events occurred in less than 20 percent of either group (Table 3). Thirty-five subjects died of cardiovascular causes or had myocardial infarction, stroke, or

Table 2. Primary and Secondary End Points and Characteristics of Adenomas.*

Variable	Placebo (N=628)	Celecoxib (N=933)	Relative Risk (95% CI)	P Value
Detection of any adenoma at colonoscopy†				
All subjects				
Year 1 — no. with adenoma/total no. at risk (%)	181/557 (32.5)	175/840 (20.8)	—	—
Year 3 — no. with adenoma/total no. at risk (%)	83/334 (24.9)	95/589 (16.1)	—	—
Cumulative rate of adenomas detected through year 3 — %	49.3±2.2	33.6±1.7	0.64 (0.56–0.75)	<0.001
Subjects taking aspirin				
Cumulative rate of adenomas detected through year 3 — %	51.1±5.4	33.7±4.1	0.61 (0.43–0.88)	0.007
Subjects not taking aspirin				
Cumulative rate of adenomas detected through year 3 — %	48.9±2.4	33.6±1.8	0.65 (0.55–0.76)	<0.001
Detection of advanced adenomas at colonoscopy‡				
All subjects				
Year 1 — no. with advanced adenoma/total no. at risk (%)	40/557 (7.2)	25/840 (3.0)	—	—
Year 3 — no. with advanced adenoma/total no. at risk (%)	16/463 (3.5)	17/720 (2.4)	—	—
Cumulative rate of advanced adenomas detected through year 3 — %	10.4±1.3	5.3±0.79	0.49 (0.33–0.73)	<0.001
Characteristics of adenomas§				
No. of adenomas identified	2.0±0.1	1.8±0.1	—	0.15
Size of largest adenoma — cm	0.6±0.0	0.5±0.0	—	0.002
Adenoma burden — cm¶	1.0±0.1	0.8±0.0	—	0.005

* Plus–minus values are means ±SE. CI denotes confidence interval, and dashes not applicable.
† Subjects considered at risk at year 1 included those who underwent colonoscopy at year 1, as well as those who did not undergo colonoscopy at year 1 but did undergo colonoscopy at year 3. The latter were classified as having had no adenomas detected at year 1. Subjects considered at risk at year 3 included subjects who underwent colonoscopy at year 3 and either had no adenomas at year 1 or did not undergo colonoscopy at year 1 and were therefore assumed to have had no adenomas at year 1.
‡ Advanced adenomas were defined as adenomas that were at least 1 cm or had villous or tubulovillous histologic features, high-grade dysplasia, intramucosal carcinoma, or invasive carcinoma.
§ All three P values for these characteristics are based on van Elteren's test, stratified according to the use or nonuse of aspirin.
¶ The adenoma burden was defined as the sum of the diameters of all adenomas detected.

congestive heart failure adjudicated by the cardiovascular safety committee; these consisted of 2.5 percent of the celecoxib group (23 of 933) and 1.9 percent of the placebo group (12 of 628) (relative risk, 1.30; 95 percent confidence interval, 0.65 to 2.62), with estimated rates of 9.4 and 7.2 events per 1000 patient-years for celecoxib and placebo, respectively. Of these 35 subjects, 12 came from a subgroup of 198 with a history of cardiovascular or cerebrovascular events (relative risk, 1.55; 95 percent confidence interval, 0.42 to 5.76), and 23 from a subgroup of 1363 without a medical history of cardiovascular or cerebrovascular events (relative risk, 1.14; 95 percent confidence interval, 0.49 to 2.65; P for interaction=0.59), indicating no significant difference in relative risk between subjects with and those without a history of previous cardiovascular events.

Three quarters of all subjects who received at least one dose of study medication had at least one adverse event (74.0 percent in the placebo group and 77.1 percent in the celecoxib group) (Table 3). Investigator-reported renal and hypertensive adverse events were more common in the celecoxib group than in the placebo group (relative risk, 1.35; 95 percent confidence interval, 1.08 to 1.69) overall. Of investigator-reported adverse events occurring in 5 percent or more of subjects, only hypertension was significantly more common in the celecoxib group than in the placebo group (15.5 percent vs. 10.7 percent of subjects; relative risk, 1.45; 95 percent confidence interval, 1.11 to 1.91). Nevertheless, mean (±SE) systolic and diastolic blood pressures fell slightly in both treatment groups from baseline to the end of treatment for all subjects (systolic, –2.3±0.78 mm Hg in the pla-

Table 3. Incidence of Adverse Events.*

Adverse Event	Placebo (N=628)	Celecoxib (N=933)	Relative Risk (95% CI)†
All serious adverse events — no. of subjects (%)‡	106 (16.9)	186 (19.9)	1.18 (0.95–1.46)
Death from any cause	7 (1.1)	11 (1.2)	1.06 (0.41–2.71)
Investigator-reported cardiovascular disorders (nonadjudicated)§	18 (2.9)	41 (4.4)	1.53 (0.89–2.64)
Adjudicated death from cardiovascular causes, myocardial infarction, stroke, or congestive heart failure¶	12 (1.9)	23 (2.5)	1.30 (0.65–2.62)‖
Investigator-reported colorectal cancers	1 (0.2)	6 (0.6)	4.03 (0.48–33.41)
Investigator-reported adverse events**			
All subjects who had adverse events — no. of subjects (%)	464 (74.0)	719 (77.1)	1.04 (0.98–1.10)
Renal or hypertensive disorders††	96 (15.3)	193 (20.7)	1.35 (1.08–1.69)
Gastrointestinal ulceration or hemorrhage ‡‡	65 (10.4)	113 (12.1)	1.17 (0.88–1.56)
Cardiovascular disorders (nonadjudicated)§	30 (4.8)	70 (7.5)	1.57 (1.03–2.38)
Subjects taking aspirin who had adverse events — no./total no. (%)	86/107 (80.4)	131/160 (81.9)	1.02 (0.90–1.15)
Renal or hypertensive disorders††	27/107 (25.2)	37/160 (23.1)	0.92 (0.60–1.41)
Gastrointestinal ulceration or hemorrhage ‡‡	10/107 (9.3)	23/160 (14.4)	1.54 (0.76–3.10)
Cardiovascular disorders (nonadjudicated)§	13/107 (12.1)	26/160 (16.3)	1.34 (0.72–2.48)
Subjects not taking aspirin who had adverse events — no./total no. (%)	378/520 (72.7)	588/773 (76.1)	1.05 (0.98–1.12)
Renal or hypertensive disorders††	69/520 (13.3)	156/773 (20.2)	1.52 (1.17–1.97)
Gastrointestinal ulceration or hemorrhage ‡‡	55/520 (10.6)	90/773 (11.6)	1.10 (0.80–1.51)
Cardiovascular disorders (nonadjudicated)§	17/520 (3.3)	44/773 (5.7)	1.74 (1.01–3.01)

* The analyses of investigator-reported adverse events excluded one subject who was randomly assigned to the placebo group but never received study drug. Events summarized are those beginning or intensifying from any time after the first dose of study drug to up to three years after the first dose of study drug, regardless of the date of the last dose of the study drug.

† CI denotes confidence interval.

‡ Rates of other serious adverse events not included in this table were similar in the two groups and are reported in Supplementary Appendix 2.

§ This category was prespecified to include angina, cardiac or peripheral vascular therapeutic procedures, cerebrovascular disease, myocardial infarction or ischemia, peripheral vascular disease, death or circulatory collapse (excluding noncardiovascular deaths and events attributable to other cardiovascular disorders), or venous thrombosis or thromboembolism.

¶ The adjudicated analysis included one subject who was randomly assigned to the placebo group but never received study drug. All serious adverse events were adjudicated on the basis of the intention-to-treat occurrence, defined as beginning or intensifying any time after the first dose of study drug up to 3 years and 30 days after the first dose of study drug, regardless of the date that treatment with the study drug was completed or withdrawn. This analysis includes only serious adverse events that were considered to be cardiovascular by an independent cardiovascular safety committee whose members were unaware of subjects' randomized treatment assignments. Nonfatal serious adverse events considered to be cardiovascular were categorized in a blinded fashion according to a prespecified scheme.

‖ The relative risks (adjudicated events) were estimated from Cox models with treatment group and use or nonuse of aspirin as covariates.

** This category includes both serious and nonserious adverse events.

†† Renal or hypertensive disorders were prespecified as elevated creatinine, fluid retention, edema, hypertension, proteinuria, or renal failure.

‡‡ This category was prespecified as gastrointestinal bleeding, gastritis or duodenitis, upper or lower gastrointestinal ulceration, or other hemorrhage.

cebo group and –1.9±0.64 mm Hg in the celecoxib group; diastolic, –1.5±0.49 mm Hg in the placebo group and –1.5±0.38 mm Hg in the celecoxib group) and in both aspirin strata.

Investigator reports of gastrointestinal ulceration or hemorrhage were similar (celecoxib group, 12.1 percent; placebo group, 10.4 percent), and no significant difference was seen in hemoglobin and hematocrit laboratory values over the three-year period (mean hematocrit values in the placebo and the celecoxib groups were 43.9 and 43.8, respectively, at year 1, and 44.2 and 44.1, respectively, at year 3) (see Supplementary Appendix 1, available with the full text of this article at www.nejm.org).

A summary of the number of patients with serious adverse events categorized by the MedDRA systems organ class is provided in Supplementary Appendix 2. Those systems organ classes with the most patients were gastrointestinal disorders; cardiac disorders; benign, malignant, and unspecified neoplasms; surgical and medical procedures; and nervous system disorders. Within the systems organ classes, there were no significant differences in incidence between the celecoxib and the placebo groups.

DISCUSSION

In this randomized, placebo-controlled, double-blind clinical trial, 400 mg of celecoxib once daily was associated with a relative risk of 0.64 for adenomas detected during a three-year period. A reduced risk was apparent at the first follow-up colonoscopy (year 1) and persisted at the second (year 3). Likewise, the cumulative rate of detection of advanced adenomas was lower in the celecoxib group, which had a relative risk of 0.49. The size of the largest adenoma and the adenoma burden were significantly lower in the celecoxib group, but the mean number of adenomas among those with any adenoma was not significantly different between the groups. The relative risk of adenomas during the three years among subjects who took low-dose aspirin was 0.61, which was similar to the relative risk among all subjects.

Celecoxib may be effective against existing adenomas perhaps missed on an index colonoscopy and against the formation of new adenomas, as evidenced by reductions in the newly diagnosed adenomas at year 1 and year 3. This effect is consistent with experimental evidence in animals and humans and with epidemiologic data.

The study did not directly address whether celecoxib affects the risk of a first adenoma or progression to invasive cancer. Colorectal cancer was diagnosed in six subjects in the celecoxib group (0.6 percent) and one subject in the placebo group (0.2 percent) (Table 3). Because five of these seven cases were diagnosed at the year 1 colonoscopy (stage 0 in two subjects and stage 1 in three), these five cases might represent either incomplete excision or disease that was undetected at the index colonoscopy. The remaining two cases of colorectal cancer were diagnosed at year 3 (stage 2A and stage 4). Three of the seven cases were in subjects whose mothers had colorectal cancer.

Delineation of clinical benefit requires further research. As the type of adenoma that responds to celecoxib becomes characterized, treatment with celecoxib may be found to reduce the frequency of colonoscopy necessary in certain subjects prone to adenomas. Also, determining the persistence of the effect of celecoxib on the prevention of adenomas and advanced adenomas is expected to be an especially important aspect of the follow-up of these subjects. Celecoxib may also have effects on other enzymes, such as 15-lipoxygenase-1,[21] which could mediate its biologic effects. Further assessment of the relative risks and benefits of celecoxib in patients with adenomas is expected not only to promote greater safety for patients but also to encourage greater patient–physician dialogue, thus improving overall patient care.

Neither gastrointestinal adverse events nor changes in the laboratory values of hemoglobin were significantly different between groups. Cardiovascular safety results, however, need to be considered with those previously reported for the APC trial.[13] A significant increase in adjudicated serious cardiovascular events with the use of celecoxib in the APC trial (an increase in risk by a factor of two or three for a composite end point of myocardial infarction, stroke, congestive heart failure, or cardiovascular-related death)[13] prompted suspension of the administration of celecoxib in both the APC trial and our study. In our study, the relative risk of such events with the use of celecoxib as compared with placebo was 1.30 (95 percent confidence interval, 0.65 to 2.62).

The relative risk of renal or hypertensive adverse events associated with celecoxib was 1.35 (95 percent confidence interval, 1.08 to 1.69). Nevertheless, once-daily celecoxib was not associated with an increase in mean blood pressure, a finding in

contrast to the results in the APC trial reported by Bertagnolli et al. elsewhere in this issue of the *Journal*.[22]

In our study, subjects came from six continents and the study protocol required photographic documentation of polyp size and cecal intubation to ensure conformity across clinical sites. The simplicity of once-daily dosing may have promoted enrollment and sustained adherence to the regimen of study medication. Subjects required documentation of adenomas at baseline and were at high risk for further adenomatous polyps. Because this study included a diverse population, our findings probably have broad applicability.

In conclusion, we found that celecoxib significantly reduced the risk of colorectal adenomas. These findings, which are consistent with other evidence linking COX-2 with colorectal neoplasia, indicate that selective inhibition of COX-2 may reduce colorectal tumorigenesis. Deriving specific recommendations for the clinical use of this treatment approach requires further investigation.

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APPENDIX

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