

Five-Year Efficacy and Safety Analysis of the Adenoma Prevention with Celecoxib Trial

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Abstract

The Adenoma Prevention with Celecoxib Trial examined the efficacy and safety of the cyclooxygenase (Cox)-2 inhibitor, celecoxib, for sporadic colorectal adenoma prevention in patients at high risk for colorectal cancer. The trial randomized 2,035 subjects to receive either placebo, celecoxib 200 mg twice daily, or celecoxib 400 mg twice daily. The primary study safety and efficacy analyses involved 3 years of treatment. The results showed significant anti-tumor effect but also indicated increased cardiovascular adverse events in patients treated with celecoxib compared with placebo. A total of 933 patients participated in an extension of the Adenoma Prevention with Celecoxib Trial, with a planned total treatment and surveillance duration of 5 years. Study medication was stopped early, resulting in a median treatment duration of 3.1 years for those with a year 5 colonoscopy. Patients treated on the placebo arm had a cumulative adenoma incidence of 68.4% over 5 years of observation. This figure was 59.0% ($P < 0.0001$) for those receiving low-dose celecoxib, and 60.1% ($P < 0.0001$) for those receiving high-dose celecoxib. The cumulative incidence of advanced adenomas over 5 years was 21.3% of those taking placebo, 12.5% ($P < 0.0001$) of those taking low dose celecoxib and 15.8% ($P < 0.0001$) of those taking high-dose celecoxib. Investigator reported treatment emergent adverse events were similar across all treatment groups for categories including renal and hypertensive events and gastrointestinal ulceration and hemorrhage events. For a category composed of cardiovascular and thrombotic events, the risk relative to placebo was 1.6 (95% confidence interval, 1.0, 2.5) for those using 200 mg twice daily celecoxib and 1.9 (95% confidence interval, 1.2, 3.1) for those using 400 mg twice daily celecoxib. Secondary analysis showed an interaction between a baseline history of atherosclerotic heart disease and study drug use with respect to cardiovascular and thrombotic adverse events ($P = 0.004$). These results confirm the inhibitory effect of celecoxib on colorectal adenoma formation, and provide additional safety data indicating an elevated risk for cardiovascular and thrombotic adverse events, particularly for patients with preexisting atherosclerotic heart disease.

Although colorectal cancer (CRC) is a common cause of cancer mortality, the risk for this disease is reduced by as much as 90% after removal of premalignant adenomas by endoscopic polypectomy (1). Unfortunately, this procedure is uncomfort-

able and expensive, resulting in an unacceptably low level of use even among populations for whom health care access is not an issue (2). Chemoprevention using nonsteroidal anti-inflammatory drugs (NSAID) is a possible adjunct to endoscopic

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Investigator participants in the APC study are listed in the Appendix.

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polypectomy. Prospective randomized trials in patients with familial adenomatous polyposis found that both sulindac and celecoxib produced regression of existing adenomas (3, 4). NSAIDs have also been tested in large studies of patients at high risk of sporadic CRC because of a history of previously resected adenomas. These clinical trials documented significant reductions in adenoma recurrence for patients treated with aspirin (5, 6), sulindac (7), celecoxib (8), and rofecoxib (9). Important data for the field of chemoprevention were also obtained from large placebo-controlled trials of aspirin for cardiovascular protection. These studies, conducted in the United Kingdom, showed that CRC incidence was decreased by 40% among those randomized to aspirin, with a time point determined at 10 to 19 years from study randomization (10). This result is significant because these studies of preventive health care were conducted in a patient population with access to colonoscopy, suggesting that chemoprevention would have a major effect on cancer mortality for patients at risk who do not adhere to colon cancer screening guidelines.

Although recent randomized controlled trials showed that NSAIDs effectively prevented colorectal adenomas, they also raised significant safety concerns. Long-term aspirin use is associated with a 1.6- to 3.1-fold increased risk of serious gastrointestinal adverse events, including gastroduodenal ulcers and major gastrointestinal bleeding (11, 12). These events are even more common for other nonselective NSAIDs such as sulindac (12). Selective cyclooxygenase-2 (Cox-2) inhibitors, such as celecoxib and rofecoxib, are associated with fewer gastrointestinal toxicities due to their relative inactivity against Cox-1, the cyclooxygenase isoform responsible for protecting the gastric mucosa. Evidence for this comes from trials for arthritis patients, where selective Cox-2 inhibitors showed a better safety profile than nonselective NSAIDs (13–16). However, one arthritis study, the VIGOR trial, also found that patients treated with rofecoxib had greater numbers of serious cardiovascular adverse events than those receiving naproxen (14). An association with cardiovascular toxicity was also identified in two randomized colorectal adenoma prevention trials that compared rofecoxib to placebo (APPROVe Trial) and celecoxib to placebo [The Adenoma Prevention with Celecoxib (APC) Trial; refs. 17, 18].

The APC Trial was a randomized placebo-controlled trial of celecoxib for prevention of colorectal adenomas in patients at high risk for CRC because of a history of colorectal adenomas that were either large (≥ 6 mm diameter) or multiple. A total of 2,035 patients were randomized to receive placebo (679 patients), 200 mg celecoxib twice daily (685 patients), or 400 mg celecoxib twice daily (671 patients). The primary aim of the APC Trial was to assess the efficacy and safety of celecoxib for preventing colorectal adenomas over a 3-year treatment and surveillance interval. After completing the 3-year initial study period, patients were offered participation in a double-blind extension of the APC Trial allowing them to either remain on study medication for an additional 2 years or to participate in an off-treatment surveillance extension of the trial, with a final colonoscopy at study exit 5 years after randomization. Accrual to the APC Trial was completed in March, 2002. In late 2004, rofecoxib was withdrawn from the market due to recognition of its association with increased risk of serious cardiovascular adverse events. This led APC Trial investigators to conduct an independent adjudicated review of

selected cardiovascular safety end points at a time when the trial was still in progress. This analysis showed 2.6- and 3.4-fold increases in selected cardiovascular events compared with placebo in patients receiving celecoxib at doses of 200 and 400 mg twice daily, respectively (18). In response, all study medication use was discontinued on December 17, 2004, a date ~ 3 months before the final randomized patients were scheduled to complete the 3-year treatment interval. Although use of study medication was terminated, patients enrolled in the APC Trial extension study remained on study for the full 5 years, with continued collection of safety information and year 5 colonoscopic surveillance.

The primary efficacy and safety end points of the 3-year APC Trial have been reported previously (8, 18). Significant antitumor efficacy was identified. For patients on placebo, the incidence of newly detected adenomas by year 3 was 60.7%, confirming that the APC Trial included a high adenoma risk cohort. New adenoma detection during 3-year surveillance interval was reduced 33% for those on 200 mg celecoxib twice daily, and 45% for those on 400 mg celecoxib twice daily. Here, we report the results of the 5-year extension of the APC Trial.

Materials and Methods

Study design

The APC Trial tested whether celecoxib would reduce the occurrence of endoscopically detected colorectal adenomas. Treatment consisted of either placebo, celecoxib 200 mg twice daily, or celecoxib 400 mg twice daily, with randomization stratified based on low-dose aspirin use (defined as doses of ≤ 325 or 162.5 mg orally every other day) and clinical site. The trial involved 91 clinical sites; 72 in the United States, 8 in Australia, 10 in Canada, and 1 in Great Britain. Each site received human subjects committee approval of the study protocol, and all patients provided written consent before study enrollment. During the treatment portion of the trial, an independent data and safety monitoring board reviewed safety data monthly and efficacy data semiannually.

Recruitment and randomization

Details of participant recruitment and randomization for the APC trial cohort have been published previously (8). APC Trial participants ranged from ages 31 to 88 years at enrollment and were considered to have a high risk of recurrent colorectal adenomas based on either multiple adenomas or removal of a single adenoma ≥ 6 mm in diameter. Within 3 mo before enrollment, eligible patients had a complete colonoscopy to the cecum with removal of all polyps, one or more of which was a histologically confirmed adenoma. Subjects were required to be willing to abstain from chronic use of all NSAIDs or Cox-2 inhibitors for the duration of the study. Chronic use of NSAIDs was defined as >21 days of use per year. Those using low-dose aspirin at baseline were required to continue using this medication, and those not using aspirin at baseline were required to abstain from aspirin use during the trial. Exclusion criteria included a history of familial adenomatous polyposis, hereditary nonpolyposis colon cancer, inflammatory bowel disease, or large bowel resection other than appendectomy. Other exclusions included a history of a renal or hepatic disorder, a significant bleeding disorder, or treatment for a gastrointestinal ulcer in the month before study entry. Patients were also ineligible if they used NSAIDs or high-dose aspirin at a frequency of more than or equal to three times per week during the 2 mo before randomization, or if they used oral or i.v. corticosteroids for >2 wk in the 6 mo before randomization.

Participants randomized to the APC trial who successfully completed the 3-year study interval were offered the option of continuing on an

extension study, allowing them to continue taking study medication in a blinded manner for an additional 2 y. In addition, participants not wishing to remain on study medication were allowed to continue in an additional 2-y surveillance arm. At 5 y after initial randomization, participants in the extension study underwent a colonoscopy for identification and removal of colorectal polyps.

Study treatment

Study medication was distributed in gelatin capsules containing 100 mg celecoxib for the 200 mg twice daily arm, 200 mg celecoxib for the 400 mg twice daily arm, or placebo, each identical in appearance. Subjects were provided medication at 6-mo intervals, and they were instructed to take two capsules with food in the morning and in the evening each day. Low-dose aspirin was supplied for subjects already taking this medication, and acetaminophen was supplied for the treatment of minor pain and febrile illnesses. Study medication use was discontinued for all APC Trial participants on December 17, 2004. Patients then returned to usual care, which entailed colonoscopic surveillance without chemoprevention. After this point, all participants wishing to do so remained on study for continued collection of safety data and completion of the year 5 colonoscopy.

End point assessment and follow-up

A complete physical examination, with determination of vital signs, complete blood count, serum chemistry studies, and urinalysis was done at baseline and 1, 3, and 5 y after randomization. Subjects on treatment were contacted every 2 mo by researchers at their study site to record concomitant medication use and report any adverse events. Subjects who were no longer using study medication were contacted by telephone every 6 to 12 mo for retrospective reporting of serious adverse events. During these discussions, patients were also counseled to avoid nonprotocol use of aspirin and NSAIDs.

A study investigator did a complete colonoscopy with visualization of the cecum and endoscopic removal of all polyps 1, 3, and 5 y after randomization. All polyps removed during these colonoscopies were reviewed by a central study pathologist. If the central study pathologist and institutional pathologist disagreed, polyps were reviewed by an adjudicating pathologist who was blinded to the previous histologic diagnosis and whose independent opinion resolved the discrepancy. Investigator-reported adverse events were classified according to MedRA 8.1 criteria.

Statistical analysis

All primary efficacy analyses were done on an intention-to-treat basis, with primary end points determined for all patients with follow-up colonoscopies regardless of whether the patient complied with study drug use. The primary efficacy end point was detection of an adenoma during a postrandomization colonoscopy. Secondary end points included detection of advanced adenomas, defined as those having any of the following characteristics: size of ≥ 1 cm by endoscopic measurement, villous or tubulovillous histology, high-grade dysplasia, intramucosal carcinoma, or invasive cancer.

The trial was designed with a statistical power of 96% to detect a 35% relative reduction in the proportion of subjects with adenomas detected over 3 y for celecoxib compared with placebo, independent of aspirin use. Power estimates assumed up to a 40% dropout rate, and adjusted for multiple comparisons (placebo versus celecoxib 200 mg twice daily and celecoxib 400 mg twice daily). Primary and secondary end points of adenoma and advanced adenomas, respectively, over time were compared for each treatment group using the Mantel-Cox test based on a life-table extension of the Mantel-Haenszel statistic with stratification for aspirin use at baseline (19–21). Subjects without follow-up colonoscopies were excluded from the analysis at both time points. A patient with a year 3 colonoscopy but with no colonoscopy at year 1 was included in the analysis at year 1 with the assumption that the patient had no adenoma at year 1, then included in the analysis at year 3 according to the findings of the year 3 colonoscopy.

A patient with an adenoma at the year 1 colonoscopy was not included in the year 3 analysis. A similar strategy was used for the year 5 analysis to determine the cumulative percent with adenomas or advanced adenomas over the 5 y. In addition the percentage of patients in the extension study with any adenoma detected at the year 5 colonoscopy were compared by treatment assignment and the relative risk for celecoxib compared with placebo was obtained.

Investigator-reported adverse events were analyzed in total and according to prespecified categories to describe renal/hypertensive disorders, gastrointestinal ulceration/hemorrhage, and cardiovascular and thromboembolic disorders. All events occurring after the first dose of study medication use up to 30 d after the last dose of study medication were included in these analyses. Homogeneity of treatment effect on the cardiovascular and thromboembolic disorders safety end point defined above was tested in subgroups defined by baseline aspirin use and cardiovascular risk factors: smoking, hyperlipidemia, diabetes, hypertension, age, arteriosclerosis, and cerebrovascular disease, as well as number of baseline risk factors (0, 1, 2, or more).

Results

Cohort characteristics and treatment

Baseline variables were similar across all treatment groups, and there were no significant differences for these values when the set of all patients randomized to the APC Trial were compared with those completing the year 5 colonoscopy (Table 1). Variables associated with risk of developing colorectal adenomas, such as age, CRC family history, and adenoma size and number were also balanced among treatment groups. Colonoscopic end points were assessed in 1,822 (89.5%) randomized subjects; 1,541 (75.7%) completed the year 3 examination and 639 (31.4%) completed the year 5 examination (Fig. 1). Reasons for patient withdrawal from the study before end point determination included withdrawal of consent for participation, withdrawal after an adverse event, and failure to respond to investigator's requests for follow-up (Fig. 1). Subjects who failed to complete the study were evenly distributed among the treatment groups. During the treatment interval, compliance with study medication use, as determined by pill count, was $>80\%$ in two-thirds of participants, with no significant difference among the treatment groups (8).

Because of the discontinuation of study medication in December 2004, the colonoscopies conducted at 1 and 3 years after randomization reflected a period of maximal treatment exposure. For those who received a year 5 colonoscopy, the median duration of treatment exposure was just over 3 years, with an even distribution among treatment groups (Table 2). Approximately 5% of those having a year 5 colonoscopy received >4 years of study medication. Therefore, $>90\%$ of those receiving a year 5 colonoscopy had been off study medication for a year or more at the time of the final colonoscopy. Safety was assessed using investigator reported, treatment emergent data, including all patients receiving at least one dose of study drug. For this population, treatment duration was also balanced across the study arms, with a median treatment duration of ~ 2.95 years (range, 0.01–4.38 years; Table 2).

Adenoma prevention

The primary efficacy analysis considered adenomas detected at any time after randomization (Table 3). For the initial

Table 1. Baseline patient characteristics

Characteristic	Placebo twice daily <i>n</i> = 679	200 mg celecoxib twice daily <i>n</i> = 685	400 mg celecoxib twice daily <i>n</i> = 671
All APC trial participants			
Age (y) mean (range)	59 (31-88)	59 (35-83)	59 (34-87)
Male sex; no. (%)	473 (69.7)	460 (67.2)	454 (67.7)
Mean body mass index (kg/m ²)	28.8(M) 29.3 (F)	28.9 (M) 28.5 (F)	28.6 (M) 29.0 (F)
Race or ethnic group (%)			
Non-Hispanic White	624 (91.9)	632 (92.3)	607 (90.5)
Non-Hispanic Black	37 (5.4)	30 (4.4)	45 (6.7)
Hispanic	11 (1.6)	16 (2.3)	10 (1.5)
Asian, Pacific Islander, or other	7 (1.0)	7 (1.0)	9 (1.3)
CRC in a parent (%)	140 (20.6)	147 (21.5)	142 (21.2)
No of reported adenomas	2.0 ± 0.1	2.1 ± 0.1	2.1 ± 0.1
At least one adenoma ≥1 cm (%)	288 (42.4)	303 (44.2)	291 (43.4)
Multiple adenomas;no of patients (%)	374 (55.1)	375 (54.7)	363 (54.1)
Adenoma burden, (cm)*	1.48 ± 0.05	1.50 ± 0.05	1.47 ± 0.04
Use of low-dose aspirin (%) [†]	212 (31.2)	211 (30.8)	204 (30.4)
History of cardiovascular events(%) [‡]	99 (14.6)	94 (13.7)	99 (14.8)
History of hypertension (%)	280 (41.2)	290 (42.3)	264 (39.3)
History of diabetes (%)	61 (9.0)	67 (9.8)	66 (9.8)
Current cigarette smoker (%)	122 (18.0)	119 (17.4)	96 (14.3)
All APC trial extension study participants	<i>n</i> = 307	<i>n</i> = 311	<i>n</i> = 315
Age (y) mean (range)	59 (31-88)	59 (35-83)	59 (34-87)
Male sex (%)	222 (72.3)	221 (71.1)	215 (68.3)
Mean BMI (kg/m ²)	28.7 (M) 28.6 (F)	28.3 (M) 27.8 (F)	28.6 (M) 29.0 (F)
Race or ethnic group (%)			
Non-Hispanic White	289 (94.1)	291 (93.6)	287 (91.1)
Non-Hispanic Black	10 (3.3)	10 (3.2)	21 (6.6)
Hispanic	4 (1.3)	8 (2.6)	3 (1.0)
Asian, Pacific Islander, or other	4 (1.3)	2 (0.6)	4 (1.3)
APC trial extension study participants with year 5 colonoscopy results	<i>n</i> = 214	<i>n</i> = 207	<i>n</i> = 218
Age (y) mean (range)	59 (35-88)	59 (35-79)	59 (38-79)
Male sex (%)	148 (69.2)	152 (73.4)	155 (71.1)
Mean BMI (kg/m ²)	28.7 (M) 28.6 (F)	28.3 (M) 28.2 (F)	28.9 (M) 28.9 (F)
CRC in a parent (%)	57 (26.6)	45 (21.7)	48 (22.0)
No of reported adenomas at baseline, mean (SE)	2.2 (0.1)	2.1 (0.1)	2.1 (0.1)
At least one adenoma ≥1 cm at baseline (%)	82 (38.3)	88 (42.5)	74 (43.1)
Multiple adenomas at baseline (%)	120 (56.1)	115 (55.6)	119 (55.3)
Adenoma burden at baseline*, mean (SE)	1.51 (0.09)	1.51 (0.10)	1.47 (0.08)

*Defined as sum of diameter of all adenomas, in cm.

[†]Low-dose aspirin = ≤100 mg per day or 325 mg every other day.

[‡]Defined as a history of angina, myocardial infarction, coronary artery disease, congestive heart failure, or cerebrovascular disease.

3-year study period, the estimated cumulative incidence of one or more adenomas detected was 60.7%, 43.2%, and 37.5% for patients taking placebo, 200 and 400 mg of celecoxib twice daily, respectively (8). This corresponds to a risk ratio (RR) of 0.67 [95% confidence interval (95% CI), 0.59-

0.77] in the 200 mg twice daily users and 0.55 (95% CI, 0.48-0.64) in the 400 mg twice daily users. For the interval from randomization through the 5-year colonoscopy, the cumulative incidence of adenomas detected was 68.4% for placebo users, and 59.0% (RR, 0.71; 95% CI, 0.62-0.80), and

60.1% (RR, 0.62; 95% CI, 0.54-0.71) for patients taking 200 and 400 mg of celecoxib twice daily, respectively. This represents a significant reduction in adenoma incidence over 5 years compared with placebo for both treatment groups with 13.7% reduction for 200 mg twice daily celecoxib relative to placebo ($P < 0.0001$) and 12.1% reduction for 400 mg twice daily celecoxib relative to placebo ($P < 0.0001$). The rates of adenoma detection over 5 years for those without and with concomitant low-dose aspirin use were 58.6% and 59.7%, respectively, for the 200 mg celecoxib twice daily group and 60.4% and 59.7%, respectively, for the 400 mg celecoxib twice daily group. These values were also significantly lower than those of the placebo group, which were 69.2% and 66.9% for aspirin nonusers and users, respectively ($P \leq 0.01$ for all comparisons).

As a method of estimating the effect of drug withdrawal on adenoma incidence, we examined treatment-associated differences in adenomas detected for all patients undergoing a year 5 colonoscopy (Table 3; Fig. 2). At this individual time point for those on placebo, 36.9% had adenomas detected at year 5. This figure was 40.1% for those using 200 mg twice daily celecoxib (RR, 1.09; 95% CI, 0.85-1.38) and 41.3% for those using 400 mg twice daily celecoxib (RR, 1.11; 95% CI, 0.89-1.41).

The development of advanced adenomas was an important secondary efficacy analysis for this trial. Advanced adenomas are those ≥ 1 cm in diameter, containing villous or tubulovillous histology, high-grade dysplasia, carcinoma *in situ*, or invasive carcinoma. A total of 8 patients developed invasive CRC during the APC trial; 3 on the placebo arm and 5 on the 400 mg twice daily celecoxib arm. These cases were included in this analysis as having developed an advanced adenoma. During the initial 3-year treatment interval, the estimated cumulative incidence of advanced adenomas was 17.4% for patients taking placebo, 7.8% for those treated with celecoxib 200 mg twice daily and 6.3% for those treated with celecoxib 400 mg twice daily, corresponding to RRs of 0.43 (95% CI, 0.30-0.60) and 0.34 (95% CI, 0.23-0.50), respectively. The cumulative incidence of advanced adenomas over 5 years was 21.3% in the placebo users, compared with 12.5% of those taking celecoxib 200 mg twice daily and 15.8% of those taking celecoxib 400 mg twice daily ($P < 0.0001$). These values correspond to RRs of 0.48 (95% CI, 0.35-0.66) and 0.49 (95% CI, 0.35-0.67), respectively. When the results of the individual colonoscopy time point at year 5 were examined, not considering adenomas found at earlier time points, we found a trend toward more advanced adenomas in the high-dose treatment group, with a rate of 5.1% in placebo users and 10.1% in those

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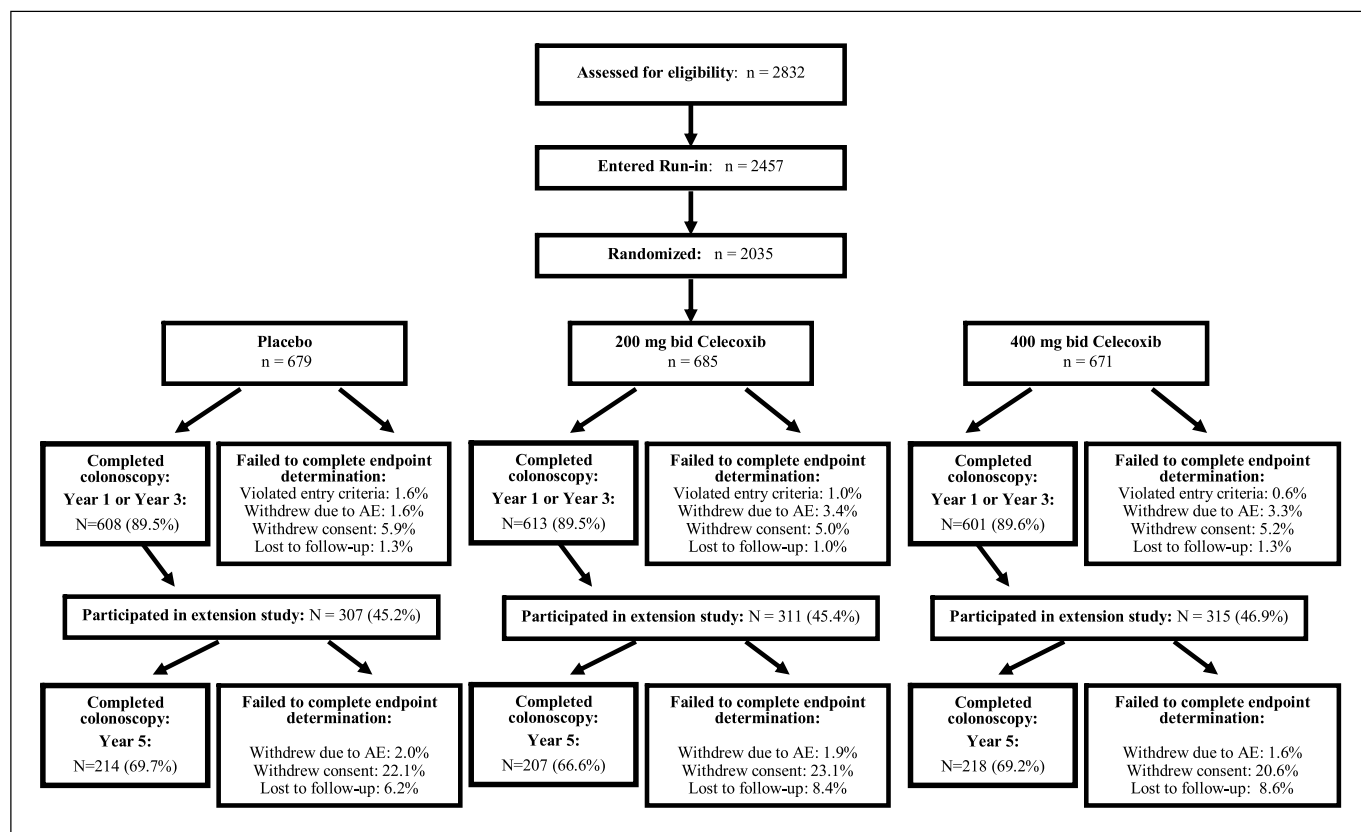


Fig. 1. APC trial CONSORT-E flowchart. Reasons for withdrawal from the study before efficacy end point determination were classified as follows: (a) Violation of study entry criteria, e.g., unable to confirm the presence of an adenoma on baseline colonoscopy; (b) withdrew after development of an adverse event (AE) or other medical reason; (c) withdrew consent for study participation, including all study withdrawal for nonmedical reasons, failed to complete a postrandomization colonoscopy for nonmedical reasons, or other protocol noncompliance; (d) lost to follow-up, i.e., investigators were unable to contact patient after randomization despite repeated attempts. Study sites reported the first and last days of medication use for each participant. Compliance with study medication use was calculated as the duration of study medication use in days, divided by 1,095 d. *Bid*, twice daily.

Table 2. Duration of treatment exposure

	Placebo twice daily	200 mg celecoxib twice daily	400 mg celecoxib twice daily
Efficacy Population*			
All randomized in both APC core and extension study (% out of total randomized)	679 (33.4)	685 (33.7)	671 (32.9)
Subjects (% of arm randomized) whose duration of treatment lasted:			
0-2 y	203 (29.9)	199 (29.0)	197 (29.4)
>2-3 y	220 (32.4)	220 (32.1)	176 (26.2)
>3-4 y	246 (36.2)	243 (35.5)	282 (42.0)
>4 y	10 (1.5)	23 (3.4)	16 (2.4)
Median y (range)	2.95 (0.002-4.22)	2.94 (0.01-4.34)	2.99 (0.02-0.439)
APC trial extension study participants with year 5 colonoscopy results (%)	214 (31.5)	207 (30.0)	218 (32.5)
APC trial extension study participants with year 5 colonoscopy results (%)	214 (31.5)	207 (30.0)	218 (32.5)
Subjects (% with Year 5 colonoscopy results) whose duration of treatment lasted:			
0-2 y	7 (3.3)	8 (3.9)	8 (3.7)
>2-3 y	74 (34.6)	64 (30.9)	60 (27.5)
>3-4 y	125 (58.4)	121 (58.5)	138 (63.3)
>4 y	8 (3.7)	14 (6.8)	12 (5.5)
Median (range) y	3.02 (0.76-4.22)	3.05 (0.14-4.33)	3.07 (0.02-4.38)
Safety population†			
All participants treated in both APC core and extension study (% out of total participants treated)	676 (33.3)	683 (33.7)	669 (33.0)
Subjects (%) whose duration of treatment lasted:			
0-2 y	200 (29.6)	197 (28.8)	195 (29.1)
>2-3 y	220 (32.5)	220 (32.2)	176 (26.3)
>3-4 y	246 (36.4)	243 (35.6)	282 (42.2)
>4 y	10 (1.5)	23 (3.4)	16 (2.4)
Median (range) y	2.95 (0.002-4.22)	2.94 (0.01-4.34)	2.99 (0.02-0.439)

*Efficacy was determined by comparing the cumulative incidence of adenoma detection over 5 y of surveillance.

†Safety analyses included all investigator-reported events occurring in the interval from first study drug use to 30 d after last study drug use.

on 400 mg celecoxib twice daily (RR, 1.95; 95% CI, 0.97-3.92; Table 3; Fig. 2).

Adverse effects associated with treatment

Previous reports described safety results from the initial 3-year treatment interval, providing data on an intention-to-treat basis (8, 18). The results of a separate adjudicated analysis of cardiovascular serious adverse events were also reported for the 3-year study interval (18). For this final 5-year safety analysis, we examined investigator reported, treatment emergent data, including any adverse event that occurred during the time from first study medication dose to 30 days after the last study medication dose. Because the majority of patients with year 5 study data had been off study medication for more than a year, we considered this treatment emergent safety analysis to be a more accurate reflection of drug-associated toxicity.

At least one adverse event was reported in 89.9% ($n = 608$) of placebo users, 93.9% ($n = 641$) of 200 mg twice daily celecoxib users, and 94.0% ($n = 629$) of 400 mg twice daily celecoxib users (Table 4). At least one serious adverse event was reported in 17.2% of those taking placebo, 18.3% of the 200 mg twice daily celecoxib users (RR, 1.1; 95% CI, 0.8-1.3; $P = 0.5$), and 21.2% of the 400 mg celecoxib twice daily users

(RR, 1.2; 95% CI, 1.0-1.5- $P = 0.06$). Only one subject experienced a serious complication as a result of a study colonoscopy. This patient on the control arm was successfully treated for a grade 3 postpolypectomy bleed. Prespecified analyses separately examined nonadjudicated investigator reports of renal/hypertensive disorders and gastrointestinal ulceration/hemorrhage events. No consistent dose-related trends toward increased incidence of renal/hypertensive disorders or gastrointestinal ulceration/hemorrhage events were observed.

Cardiovascular adverse events in APC Trial participants have been reported previously, using a prespecified analysis of adjudicated serious adverse events (18), and indicated increased risk of serious cardiovascular complications—defined as cardiovascular death, nonfatal myocardial infarction, stroke, or heart failure—among those using celecoxib, with RRs of 2.6 (95% CI, 1.1-6.1) and 3.4 (95% CI, 1.5-7.9) for the low- and high-dose cohorts, respectively. Adjudicated analyses of safety data were not planned or conducted for time points beyond the 3-year initial treatment trial. For the year 5 analysis, we examined investigator reported, treatment emergent cardiovascular and thrombotic adverse events, including in this category all events defined as myocardial infarction, cardiovascular therapeutic procedure,

Table 3. Risk of adenomas

Variable	Placebo twice daily	200 mg celecoxib twice daily	400 mg celecoxib twice daily
All subjects—detection of any adenoma	n = 679	n = 685	n = 671
Year 1 colonoscopy with any adenoma/total at risk (%)	271/608 (44.6)	186/613 (30.3)	137/601 (22.8)
Year 3 colonoscopy with any adenoma/total at risk (%)	83/286 (29.0)	66/357 (18.5)	76/400 (19.0)
Year 5 colonoscopy with any adenoma/total at risk (%)	16/81 (19.8)	33/119 (27.7)	54/149 (36.2)
Cumulative incidence of adenoma detection through year 3 (%; SE)	60.7 (2.1)	43.2 (2.1)	37.5 (2.1)
RR (95% CI)		0.67 (0.59-0.77)	0.55 (0.48-0.64)
P vs placebo		<0.0001	<0.0001
Cumulative incidence of adenoma detection through year 5 (%; SE)	68.4 (2.4)	59.0 (2.8)	60.1 (2.8)
RR (95% CI)		0.71 (0.62-0.80)	0.62 (0.54-0.71)
P vs placebo		<0.0001	<0.0001
Year 5 colonoscopy with any adenoma at year 5 colonoscopy/total with year 5 colonoscopy(%)	79/214 (36.9)	83/207 (40.1)	90/218 (41.3)
RR (95% CI)		1.09 (0.85-1.38)	1.11 (0.89-1.41)
P vs placebo		0.51	0.38
Subjects using aspirin	n = 212	n = 211	n = 204
Cumulative incidence of adenoma detection through year 5 (%; SE)	66.9 (4.2)	59.7 (5.1)	59.7 (5.0)
RR (95% CI)		0.75 (0.60-0.94)	0.63 (0.49-0.81)
P, vs placebo		0.01	0.0002
Year 5 colonoscopy with any adenoma at year 5 colonoscopy/total with year 5 colonoscopy(%)	21/71 (29.6)	30/67 (44.8)	32/71 (45.1)
RR (95% CI)		1.514 (0.97-2.37)	1.524 (0.98-2.37)
P vs placebo		0.066	0.057
Subjects not using aspirin	n = 467	n = 474	n = 467
Cumulative incidence of adenoma detection through year 5 (%; SE)	69.2 (3.0)	58.6 (3.3)	60.4 (3.4)
RR (95% CI)		0.69 (0.59-0.80)	0.61 (0.52-0.72)
P vs placebo		<0.0001	<0.0001
Year 5 colonoscopy with any adenoma at year 5 colonoscopy/total with year 5 colonoscopy(%)	58/143 (40.6)	53/140 (37.9)	58/147 (39.5)
RR (95% CI)		0.93 (0.7-1.3)	0.97 (0.73-1.28)
P vs placebo		0.64	0.81
All subjects—detection of advanced adenomas*	n = 679	n = 685	n = 671
Year 1 colonoscopy with advanced adenoma/total at risk (%)	68/608 (11.2)	26/613 (4.2)	17/601 (2.8)
Year 3 colonoscopy with advanced adenoma/total at risk (%)	32/458 (7.0)	18/487 (3.7)	18/503 (3.6)
Year 5 colonoscopy with advanced adenoma/total at risk (%)	8/171 (4.7)	10/194 (5.2)	21/207 (10.1)
Cumulative incidence of advanced adenoma through year 3 (%; SE)	17.4 (1.6)	7.8 (1.1)	6.3 (1.0)
RR (95% CI)		0.43 (0.31-0.61)	0.34 (0.24-0.50)
P vs placebo		<0.001	<0.001
Cumulative incidence of advanced adenoma through year 5 (%; SE)	21.3 (2.0)	12.5 (1.8)	15.8 (2.2)
RR (95% CI)		0.48 (0.35-0.66)	0.49 (0.35-0.67)
P vs placebo		<0.0001	<0.0001
Year 5 colonoscopy with any adenoma at year 5 colonoscopy/total with year 5 colonoscopy (%)	11/214 (5.1)	13/207 (6.3)	22/219 (10.1)
RR (95% CI)		1.21 (0.56-2.65)	1.95 (0.97-3.92)
P vs placebo		0.621	0.055

NOTE: A previous report of year 3 data failed to include one patient in the placebo group. The values provided here reflect this correction.
*Defined as adenomas ≥ 1 cm in diameter, containing villous or tubulovillous histology, high grade dysplasia, carcinoma *in situ*, or invasive carcinoma.

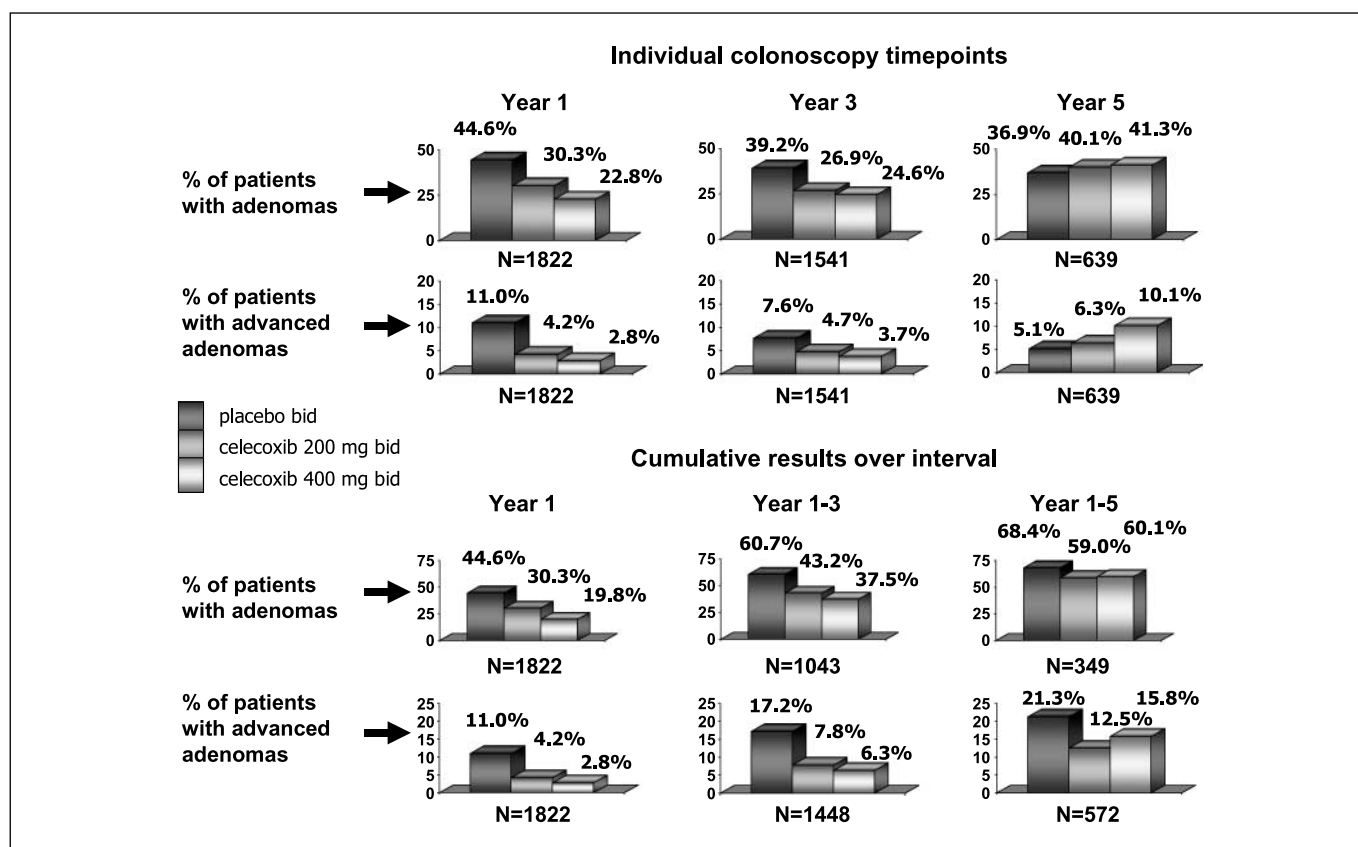


Fig. 2. Adenomas detected during study observation period. The top six figures represent colonoscopy results for individual time points. The year 1 and year 3 results include only patients who did not have an adenoma detected on previous colonoscopies. The year 5 result depicts the results for all individuals receiving a year 5 colonoscopy, irrespective of whether or not one or more adenomas had been detected at previous colonoscopies. The bottom six figures report the cumulative results over 5 y observation period. The year 1 and year 3 colonoscopy results correspond to the time of planned study drug use. By the year 5 colonoscopy, ~94% of subjects had been off study drug for at least 1 y.

cerebrovascular disease, peripheral vascular disease, peripheral vascular therapeutic procedure, venous thrombosis or thromboembolism, and death or circulatory collapse due to cardiovascular causes (see Supplementary Data online for more details). In the 2 years off treatment, very few serious cardiovascular or thrombotic events occurred (1.3%, placebo; 2.6%, 200 mg twice daily celecoxib; 1.9%, 400 mg twice daily celecoxib). In the treatment-emergent analysis, 3.8% of placebo users experienced one or more cardiovascular and thrombotic adverse events, compared with 6.0% (RR, 1.6; 95% CI, 1.0-2.5) and 7.5% (RR, 1.9; 95% CI, 1.2-3.1) for those using celecoxib 200 and celecoxib 400 mg twice daily, respectively (Table 4). These values were higher in aspirin users than in aspirin nonusers. The absolute magnitude of risk was greatest for patients with cardiovascular risk factors at baseline, defined as those reporting a history of atherosclerotic heart disease, age >65 years, smoking, hypertension, or hyperlipidemia. Patients with no baseline risk factors comprised only 15.4% of those randomized, and had a cardiovascular and thrombotic event rate per 100 of 0.9 if using placebo, 3.9 if using celecoxib 200 mg twice daily, and 1.9 if using celecoxib 400 mg twice daily (Table 5). These rates were 2.2, 3.7, and 4.9, respectively, for the 35% of patients with one cardiovascular risk factor at baseline, and 5.9, 8.2, and 11.2, respectively, for those with two or more baseline risk factors ($P_{\text{interaction}} =$

0.51). When individual risk factors were examined, the only factor significantly associated with celecoxib dose and event risk was a baseline history of atherosclerotic heart disease ($P_{\text{interaction}} = 0.004$).

Discussion

The APC Trial was designed to identify the relationship between celecoxib dose, antitumor efficacy, and treatment safety for patients at risk for CRC because of a history of adenomas. In the initial 3-year study interval, we found that a celecoxib dose of 200 mg twice daily was associated with a 33% reduction in adenoma detection, with a 57% reduction in advanced adenomas. For this dose, analysis of a selected category of treatment-emergent, investigator reported cardiovascular and thrombotic events indicated a 1.5-fold increase in risk, from a rate of 4.4% to 6.6% of those treated. In comparison, the 400 mg twice daily celecoxib dose achieved somewhat higher benefit (45% reduction in adenomas, 66% reduction in advanced adenomas) but also at a higher cardiovascular risk of 1.8-fold (8.1% incidence; ref. 8). A second randomized trial, the Pre-SAP Trial, showed that 400 mg of celecoxib once daily for 3 years produced a 36% reduction in adenoma detection, a 51% decrease in advanced adenoma detection, and no statistically significant increase in cardiovascular serious

adverse events (7). These data led us to conclude that celecoxib at 400 mg twice daily is not an acceptable adenoma chemoprevention regimen for sporadic disease, whereas the lower, and once daily dose, may be considered in patients at high risk for sporadic CRC and low risk for cardiovascular complications. In addition, for patients with familial adenomatous polyposis whose high cancer risk may justify a 400 mg twice daily regimen, those with a history of cardiovascular disease should avoid celecoxib use and consider surgery or a nonselective NSAID such as sulindac.

The current analysis expands the results of the APC Trial in two important ways. First, it provides treatment-emergent safety data for the patients who continued on treatment beyond 3 years, extending the median treatment duration to

~3.0 years across all study arms. Consistent with the 3-year data, this extended analysis showed no consistent treatment-associated increase in adverse events categorized as renal/hypertensive disorders or gastrointestinal ulceration and hemorrhage (Table 4). The cardiovascular and thrombotic risks continued to be evident, with a 1.6-fold increased risk for the 200 mg twice daily cohort and 1.9-fold risk for the 400 mg twice daily cohort. This expanded data set also allowed us to explore baseline factors that indicate an increased risk of cardiovascular complications. We found a significant interaction between celecoxib treatment and cardiovascular and thrombotic events for those reporting a baseline history of atherosclerotic heart disease. From these results, we conclude that the celecoxib regimens studied should not be

Table 4. Incidence of adverse events after randomization

Adverse event*	Placebo twice daily	200 mg celecoxib twice daily	400 mg celecoxib twice daily
All serious adverse events—subjects experiencing event (%)	116 (17.2)	125 (18.3)	142 (21.2)
RR (95% CI)		1.1 (0.8,1.3)	1.2 (1.0,1.5)
Deaths	7 (1.04)	9 (1.32)	13 (1.94)
RR (95% CI)		1.3 (0.5-3.4)	1.9 (0.8-4.7)
Any adverse event—subjects with AE/subjects in cohort (%)	608/676 (89.9)	641/683 (93.9)	629/669 (94.0)
RR (95% CI)		1.0 (1.0-1.1)	1.0 (1.0-1.1)
Renal/hypertensive disorders [†]	119/676 (17.6)	149/683 (21.8)	122/669 (18.2)
RR (95% CI)		1.2 (1.0-1.5)	1.0 (0.8-1.3)
Gastrointestinal ulceration and hemorrhage [‡]	70/676 (10.4)	73/683 (10.7)	63/669 (9.4)
RR (95% CI)		1.0 (0.8-1.4)	0.9 (0.7-1.3)
Cardiovascular and thromboembolic disorders [§]	26/676 (3.8)	41/683 (6.0)	50/669 (7.5)
RR (95% CI)		1.6 (1.0-2.5)	1.9 (1.2-3.1)
Aspirin users—any adverse event—subjects with AE/subjects using aspirin (%)	201/219 (91.8)	193/205 (94.1)	198/211 (93.8)
RR (95% CI)		1.0 (1.0-1.1)	1.0 (1.0-1.1)
Renal/hypertensive disorders	39/219 (17.8)	54/205 (26.3)	33/211 (15.6)
RR (95% CI)		1.5 (1.0-2.1)	0.9 (0.6-1.3)
Gastrointestinal ulceration and hemorrhage	20/219 (9.1)	27/205 (13.2)	26/211 (12.3)
RR (95% CI)		1.4 (0.8-2.5)	1.3 (0.8-2.3)
Cardiovascular and thromboembolic disorders	15/219 (6.8)	20/205 (9.8)	18/211 (8.5)
RR (95% CI)		1.4 (0.7-2.7)	1.2 (0.6-2.4)
Nonaspirin users—any adverse event—subjects with AE/subjects not using aspirin (%)	409/457 (89.5)	450/478 (94.1)	436/458 (95.2)
RR (95% CI)		1.0 (1.0-1.1)	1.1 (1.0-1.1)
Renal/hypertensive disorders	80/457 (17.5)	95/478 (19.9)	89/458 (19.4)
RR (95% CI)		1.1 (0.9-1.5)	1.1 (0.8-1.5)
Gastrointestinal ulceration and hemorrhage	50/457 (10.9)	46/478 (9.6)	37/458 (8.1)
RR (95% CI)		0.9 (0.6-1.3)	0.7 (0.5-1.1)
Cardiovascular and thromboembolic disorders	11/457 (2.4)	21/478 (4.4)	32/458 (7.0)
RR (95% CI)		1.8 (0.9-3.7)	2.9 (1.5-5.7)

*Treatment-emergent adverse events included were those that occurred during the time after the first dose of study medication to 30 d after the last dose of study medication.

[†]Category includes reports of elevated creatinine, fluid retention/edema, hypertension, proteinuria, and renal failure.

[‡]Category includes anemia, gastrointestinal bleeding, gastritis/duodenitis, upper or lower gastrointestinal ulceration, and other hemorrhage.

[§]Category includes angina, myocardial infarction, cardiovascular therapeutic procedure, cerebrovascular disease, peripheral vascular disease, peripheral vascular therapeutic procedure, venous thrombosis or thromboembolism, and death or circulatory collapse due to cardiovascular causes.

Table 5. Selected cardiovascular and thrombotic events according to baseline risk factors

	Placebo twice daily	200 mg celecoxib twice daily	400 mg celecoxib twice daily	P value for interaction
No risk factors at baseline				
Patients with no baseline risk factors (%)*	108 (15.9)	102 (14.9)	103 (15.4)	
Patients experiencing event (%)	1 (0.9)	4 (3.9)	2 (1.9)	
One risk factor at baseline				
Patients with one baseline risk factor (%)	228 (33.7)	241 (35.3)	244 (36.5)	
Patients experiencing event (%)	5 (2.2)	9 (3.7)	12 (4.9)	
Two or more risk factors at baseline				
Patients with ≥ 2 baseline risk factors (%)	340 (50.3)	340 (49.8)	322 (48.1)	
Patients experiencing event (%)	20 (5.9)	28 (8.2)	36 (11.2)	
Association between number of risk factors and events				0.515
Association between events and individual baseline risk factors				
Smoking (%)	20 (4.9)	28 (6.5)	32 (7.9)	0.514
Hyperlipidemia (%)	15 (5.8)	17 (6.6)	29 (11.5)	0.210
Diabetes (%)	5 (8.2)	7 (10.4)	10 (15.2)	0.385
Hypertension (%)	16 (5.7)	21 (7.3)	24 (9.2)	0.864
Atherosclerotic heart disease (%)	7 (8.2)	14 (18.4)	18 (21.4)	0.004
Cerebrovascular disease (%)	2 (13.3)	4 (16.7)	3 (18.8)	0.828
Age >65 y (%)	9 (2.0)	18 (3.8)	26 (5.5)	0.779

NOTE: Risk factors: cigarette smoking, hypertension, hyperlipidemia, atherosclerotic heart disease, cerebrovascular disease, diabetes.

*Percent of those with the risk factor who experienced an event in the time interval from first dose of study medication to 30 d after last dose of study medication.

used for adenoma prevention in patients with a history of atherosclerosis.

The second important contribution of this study is that it provides data concerning the effect on disease incidence and severity associated with withdrawal of an effective chemopreventive agent. At the time of the year 5 colonoscopy, >90% of the participants had been off study medication for a year or more. Adenomas develop over time, with an estimated rate of progression to malignant disease of from 10 to 20 years (22). Studies of repeated colonoscopy with polypectomy show that the rate of new adenoma detection decreases over time as patients with a lower risk of adenoma development drop out of the denominator (1). One of the concerns over use of chemoprevention is that, rather than preventing disease progression, the drug would merely inhibit development of low-grade lesions, allowing those with higher malignant potential to continue to progress. A manifestation of this could be drug-associated reduction in adenoma size but not severity, therefore preventing colonoscopic detection and removal of the more significant disease. If so, it follows that withdrawal of drug would result in reemergence of disease at an accelerated rate compared with those without drug. However, the year 5 colonoscopy results for the APC Trial indicate that this was not the case for celecoxib chemoprevention. The rates of adenoma detection at the year 5 colonoscopy were similar across all treatment groups (Fig. 2). At the low celecoxib dose, we observed a comparable result when disease severity was examined, with advanced adenomas detected in 5.1% and 6.3% of participants using placebo and 200 mg twice daily celecoxib, respectively. Interestingly, we did find a trend toward

more advanced adenomas at year 5 in patients using celecoxib 400 mg twice daily (Table 3; Fig. 2).

Aspirin prevents colorectal adenomas and reduces the incidence of CRC (6, 10, 23). A significant number of patients randomized on the APC trial (31%) were using low-dose aspirin at the time of study entry, and were required to remain on this treatment for the duration of the trial. Entry into the study required recent detection and removal of adenomas; therefore, the aspirin user subset provided an important cohort of patients who developed colorectal adenomas while using low-dose aspirin. Comparison of year 5 efficacy results between users and nonusers of aspirin showed similar rates of disease detected during surveillance for the placebo arm (66.9% versus 69.2%, respectively; Table 3). The effect of celecoxib was also comparable for both groups, with a 37% reduction in adenomas for aspirin users and a 39% reduction in aspirin nonusers with the 400 mg twice daily celecoxib dose. This relationship was observed for all surveillance intervals and indicates that celecoxib mediates adenoma suppression in individuals resistant to chemoprevention with low-dose aspirin.

In summary, the APC Trial showed that celecoxib prevents sporadic colorectal adenomas in patients at high risk for CRC. This effect was particularly strong with respect to the detection of advanced adenomas, and significant benefit was achieved even in patients who entered the study having developed adenomas while routinely using low-dose aspirin. Because the APC Trial was initiated before the cardiovascular risks of NSAIDs were appreciated, the study was not designed to test cardiovascular end points. As a result, the event numbers in the selected cardiovascular and thrombotic category are small,

and the confidence intervals are wide. The extended safety data presented here continue to show an increased risk for cardiovascular toxicity, particularly for the 400 mg twice daily celecoxib dose and for patients with a history of atherosclerotic heart disease. We conclude that chemoprevention efficacy of the magnitude seen in the APC and Pre-SAP Trials would have a major effect on CRC incidence and mortality, but this regimen cannot be recommended for routine use in sporadic patients due to safety concerns. Additional Cox-2 inhibitor trials should therefore be conducted so that treatment risks and benefits can be adequately quantified for patients at high CRC risk.

Disclosure of Potential Conflicts of Interest

M.M. Bertagnolli, M. Redston: Grant support for the APC Trial from Pfizer, Inc., under a Clinical Trials Agreement with Brigham & Women's Hospital. C.J. Eagle, A. Breazna, R.B. Rosenstein, J. Tang, N. Collins, N. Dengler, J. Sanocki: Employees of Pfizer, Inc. C.J. Eagle, A. Breazna, R.B. Rosenstein, J. Tang, N. Collins: Owner of shares in Pfizer, Inc. F. Macrae: Grant support for clinical trials from Pfizer, Inc. The other authors disclosed no potential conflicts of interest.

Appendix

The following persons participated in the APC Study: Steering Committee: M.M. Bertagnolli, E.T. Hawk, C.J. Eagle, G.B. Gordon; Statistical Team: A.G. Zauber, A. Brezna, K.M. Kim, D. Corle, R.B. Rosenstein, J. Tang, T. Hess, A. Wilton, J. Sanocki; Medical Monitors: W. Anderson, L. Doody; Central Pathology Review: M. Redston; K. Geisinger, C. Compton; Project Directors: N. Collins, G. M. Woloj, D. Bagheri, A. Crawford, M. Schietrum, V. Ladouceur, N. Dengler; 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, NC), T. Barringer (Carolinas Medical Center, Charlotte, NC), R.W. Bennetts (Northwest Gastroenterology Clinic, Portland, OR), M. Blitstein (Associates in Gastroenterology and Liver Disease, Lake Forest, IL), J. Bruggen (Wake Forest University Baptist Medical Center, Winston Salem, NC), P. Carricaburu (Veterans Affairs Hospital, Sheridan, WY), D. Chung (Massachusetts General Hospital, Boston, MA), F. Colizzo (Pentucket Medical Associates, Haverhill, MA), R. Curtis (Newton Wellesley Hospital, Newton, MA), T. Dewar (Harris Methodist Hospital Fort Worth, Ft. Worth, TX), R. DuBois (Vanderbilt University Medical Center, Nashville, TN), T. Feinstat (Gastroenterology Consultants of Sacramento, Roseville, CA), T.R. Foley (Regional Gastroenterology Associates of Lancaster, Lancaster, PA), D. Gabbazadeh (Huntington Research Group, Huntington Station, NY), J. Geenen (Wisconsin Center for Advanced Research, Milwaukee, WI), F. Giardiello (Johns Hopkins Hospital, Baltimore, MD), A. Goetsch (nTouch Research, Huntsville, AL), M. Goldberg (Regional Gastroenterology Associates of Lancaster, Evanston, IL), J.L. Goldstein (University of Illinois at Chicago, Chicago, IL), W. Harlan, III (Asheville Gastroenterology Associates, Asheville, NC), R. Hogan (Gastrointestinal Associates, Jackson, MS), M. Kamionkowski (Gastroenterology Associates of Cleveland, Mayfield Heights, OH), M. Kelfer (Fallon Clinic, West Boylston, MA), B. Kerzner (Health

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