Five-Year Analysis of the Prevention of Colorectal Sporadic Adenomatous Polyps Trial

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OBJECTIVES: Subjects in the Prevention of Colorectal Sporadic Adenomatous Polyps (PreSAP) trial (PRESAP/ NCT00141193/ www.clinicaltrials.gov) were studied to determine effi cacy and safety at a year 5 assessment.

METHODS: In this randomized, placebo-controlled, double-blind trial, 1,561 subjects with diagnosed colorectal adenomas removed within 3 months of the study's initiation were assessed after ~ 3 years on celecoxib followed by 2 years off. Studied in 107 primary and secondary care settings, subjects were stratifi ed by cardioprotective aspirin use and randomized to receive orally 400 mg celecoxib (933 subjects) or placebo (628 subjects) once daily. Effi cacy was measured by colonoscopy at years 1, 3, and 5, and safety was measured by investigators for the on-treatment period and collected by subject self-report over 2 years post-treatment.

RESULTS: At year 5, the primary outcome measure was the rate of new adenomas measured cumulatively from baseline. This rate was statistically signifi cantly lower in the celecoxib group (51.4 %) than in the placebo group (57.5 % ; $P < 0.001$). Similarly, the cumulative rate of new advanced adenomas was signifi cantly lower in the celecoxib group (10.0 %) than in the placebo group (13.8 % ; $P = 0.007$). However, the year 5 interval measure, which was not cumulative and did not take the rates of previous years into account, showed that after 2 years off treatment, the celecoxib group (27.0 %) was 1.66 times more likely to have new adenomas than the placebo group (16.3 % ; $P < 0.0001$). Similarly, the percentage of patients with new advanced adenomas was signifi cantly higher in the celecoxib group (5.0 %) than in the placebo group (3.8 %) ($P = 0.0072$). The evaluation of safety from baseline through year 5 indicated that the risks of serious cardiac disorders (relative risk (RR) 1.66; 95 %confi dence interval (CI) 1.01 – 2.73), selected renal / hypertension events (RR 1.35; 95 % CI 1.09 – 1.68), and general vascular (RR 1.34; 95 %CI 1.08 – 1.68) and cardiac disorders (RR 1.59; 95 %CI 1.12 – 2.26) were higher in those taking celecoxib than in those on placebo.

CONCLUSIONS: The year 5 cumulative measures of the incidence of new and advanced adenomas were signifi cantly lower in the celecoxib group than in the placebo group, but the year 5 interval rates of these measures were signifi cantly lower in the placebo group than the celecoxib group, perhaps suggesting a release of cyclooxygenase-2 inhibition. Consistent with what has been previously reported, increased risk of renal / hypertension events and cardiac disorders associated with celecoxib therapy mandates caution in patient selection.

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INTRODUCTION

Chemoprevention of sporadic colorectal adenomatous polyps is a promising approach to controlling colorectal cancer and its attendant morbidity and mortality. Worldwide, the highest rates of colorectal cancer occur in Australia and its neighbor New Zealand, western Europe, southern Europe, and North America, refl ecting the fact that developed countries are home to almost 60 % of all diagnosed cases (1). Approximately 1.2 million cases of colorectal cancer occur annually, and the disease ranks as the third most common cancer in women (aft er cancers of the breast and cervix uteri) and the third most common in men (after cancers of the lung and prostate) (1). Poor adherence to screening guidelines and lack of endoscopic capacity, even in industrialized countries, jeopardizes early detection of adenomas as well as cancer (2). When cyclooxygenase-2 (COX-2) was found to be a determinative factor in adenoma formation in murine studies (3) and to be overexpressed in human adenomas and colorectal cancer (4,5), interest rose in using COX-2 inhibitors as chemopreventives. Th ree large trials were subsequently launched: the Adenoma Prevention with Celecoxib (APC) trial (6,7), the Adenomatous Polyp Prevention on Vioxx (APPROVe) trial (8), and the Prevention of Colorectal Sporadic Adenomatous Polyps (PreSAP) trial (9). All three demonstrated the utility of COX-2 inhibitors in preventing adenomatous polyps, but drug administration in all three was discontinued because of concerns over cardiovascular toxicity. Only in the PreSAP trial, a study of celecoxib (Celebrex; Pfi zer, New York, NY) (10) 400 mg once daily, was the risk of cardiovascular events relative to those with placebo found not to be statistically signifi cant at 3 years, although the number of events was small and the confi dence interval was wide (relative risk (RR) 1.3; 95 % confi dence interval (CI) 0.6 – 2.6) (11). Although not a selective nonsteroidal anti-infl ammatory drug like celecoxib and other COX-2 inhibitors, aspirin is a wellrecognized cardioprotective agent. Its emergence as a chemopreventive agent against colorectal cancer and its precursors through experimental (12 – 14) and observational studies (15), including cardiovascular disease studies (16,17), has been the subject of intensive scrutiny in the last decade (18–25). Th ese factors warranted attention to the use of cardioprotective aspirin in the design and analysis of the three large celecoxib trials. In the year 5 PreSAP study extension reported here, concluded 2 years aft er the last dose of study medication, our a priori objective was to evaluate the year 5 colonoscopy fi ndings in all subjects who completed the year 3 colonoscopy and to evaluate the off -treatment safety in all subjects enrolled in the 3-year blinded core phase of the study and any extension. Th at is, at the year 5 analysis, using methods similar to those used in the year 3 analysis, we wanted to determine if the celecoxib group had fewer new adenomas and fewer new advanced adenomas than the placebo group, to characterize the adenomas removed at the year 5 colonoscopy, and to determine the risk of serious adverse events (SAEs).

METHODS

Study design and study population Protocol and masking. Th e PreSAP trial was a randomized, placebo-controlled, double-blind study of celecoxib treatment in patients who had colorectal adenomas removed within 3 months of the study ’ s initiation. In all, at 107 centers in 32 countries on 6 continents, 1,561 subjects were randomized in a 3:2 ratio (celecoxib, 933; placebo, 628) using an interactive voice-response system to receive 400 mg celecoxib or identical-appearing placebo once daily for 3 years.

Assignment. Randomization was stratifi ed according to self-reported use of oral, low-dose cardioprotective aspirin (≤ 162.5 mg every day or 325 mg every other day). Eligibility criteria, randomization procedure, clinical settings, locations, and methods of statistical analysis are described elsewhere (9). Aft er prestudy baseline colonoscopy and polypectomy, colonoscopies were to be performed at years 1 and 3 of the study. When an independent data monitoring committee recommended

discontinuation of drug administration because of concerns regarding cardiovascular risk, all subjects were invited to enroll in a 2-year treatment-free follow-up, including a year 5 colonoscopy for subjects who completed the year 3 colonoscopy. Th is included those in a blinded on-treatment extension phase undertaken before drug discontinuation (celecoxib, 266 (mean total treatment duration, 3.28 years); placebo, 164 (mean total treatment duration, 3.27 years)). Th ose who agreed provided written consent before participation. Th e objectives of the follow-up study extension were to evaluate the effi cacy and safety following ~ 3 years on treatment and 2 years off treatment.

Objectives and end points

The primary effi cacy objective of the extension phase was to determine the ability of celecoxib to prevent the occurrence of new colorectal adenomas as measured at colonoscopy and polypectomy aft er ~ 3 years on treatment and 2 years off treatment. New adenoma is defi ned as the fi rst on-study detection of an adenoma in subjects, all of whom had previously undergone colonoscopy and polypectomy. Th e primary end point was a cumulative estimate (mean ± s.d.) of the detection of new adenomas over a period of 5 years following a colonoscopy during which one or more adenomas had been removed. Th is estimate was based on multiple interval measures — that is, assessments at years 1, 3, and 5 of the percentage of evaluable subjects with new adenomas. Both the cumulative and the interval measures are reported. Secondary effi cacy end points included the new adenomas at year 5 in those without new adenomas and in those with or without previously detected new adenomas. Similar analyses were performed for advanced adenomas. Adenomas were characterized by three measures: the number of newly detected adenomas, the diameter of the largest adenoma, and the " adenoma burden " (a sum of the diameters of all adenomas excised from the patient). Th ose subjects eligible for evaluation at each end point are defi ned below under " Statistical Analysis. " Th e safety objective of the study extension was to collect and evaluate off - treatment safety data for 2 years aft er ending treatment. Records of SAEs were collected through annual telephone contacts during the treatment-free follow-up, and the severity of SAEs was graded based on the National Cancer Institute' s Common Terminology Criteria for Adverse Events (version 2) (26).

Assessments

Colonoscopies were performed at approximately year 1, year 3, and year 5. Polypectomy was performed as necessary. The protocol required photographic documentation that the colono scopist reached the cecum, the colon was clean, and the adenomas were of the size recorded. Aft er assessment by a local pathologist, any tissue removed was evaluated at a central pathology unit. Investigators or their representatives interviewed subjects by phone every 12 months aft er month 37 to collect information on SAEs.

Statistical analysis

Justifi cation of sample size and methods of statistical analysis for data collected through year 3 have been described elsewhere (9). Th e analyses performed through year 5 extended the ones for year 3, using the same methods. Th e eff ect of celecoxib in reducing the proportion of subjects in whom new adenomas were detected at year 1, year 3, or year 5 was estimated using the Mantel – Cox test, a life-table extension of the Mantel – Haenszel test (27 – 29), with stratifi cation for the use or nonuse of aspirin, calculating the relative risk by the method described by Kleinbaum et al. (30), as was used for the year 3 analysis (9). Th ose considered evaluable at years 1, 3, and 5 are described below and elsewhere (9). Th e number of adenomas, the size of the largest adenoma, and the total adenoma burden (defi ned as the sum of the diameters of each patient' s detected adenomas) detected during the 5 years were analyzed using van Elteren ' s test (31), an extension of the Wilcoxon rank-sum test, with subjects stratifi ed according to the use or nonuse of aspirin. Th e highest histopathological grade was analyzed using a

proportional odds ordinal regression model. All P values were two sided. Adverse events (AEs) were coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 8.1; Chantilly, VA) and summarized by system organ class and preferred term.

RESULTS

Participant fl ow and follow-up: subject disposition

In all, 1,043 (66.8 %) of the 1,561 randomized subjects enrolled in the 2-year study extension phase. Of these, 508 (54.4 %) of the celecoxib group and 347 (55.3 %) of the placebo group completed the year 5 colonoscopy (Figure 1). Th e remaining subjects either terminated early or were enrolled in the safety extension with colonoscopy. In the celecoxib group, 330 were without previously detected new adenomas and were considered evaluable for the year 5 primary analysis; in the placebo group, 184 had remained free of adenomas during the trial and were evaluable. An even larger group had remained free of advanced adenomas — 481 on celecoxib and 315 on placebo. All subjects randomized to the study and evaluated from baseline through year 3 are described elsewhere (9). Because all subjects underwent colonoscopy and polypectomy before study initiation, adenomas detected on study are referred to as new adenomas. The study, which opened in March 2001, ended follow-up in May 2007.

Demographic characteristics

Th e demographic characteristics of subjects participating in the 2-year extension (Table **1**) indicate that the celecoxib and placebo groups were similar in age, racial or ethnic origin, gender, and mean body mass index measures (the mean values of both groups indicated overweight) (32). Because similar balance was also seen between the celecoxib and placebo groups of subjects who remained free of adenomas and evaluable at year 5 as well as for celecoxib and placebo groups who participated in the safety extension, no additional analyses adjusting for covariates were undertaken.

Analysis — effi cacy

New adenomas. Table 2

reports two sets of year 5 fi ndings: cumulative rates that factor in measures since baseline and interval rates that measure rates at specifi c points (years 1, 3, or 5). Th e cumulative rate of new adenomas over 5 years, estimated by the Mantel – Cox method, was 51.4 % for the celecoxib group and 57.5 % for the placebo group (RR 0.75; 95 % CI 0.65 – 0.86; P <0.001; Table 2 and Figure 2; subjects with year 5 colonoscopy: celecoxib, 508/933; placebo, 347/628). The refore, over 5 years (after 3 years on treatment and 2 years off treatment), the cumulative RR of having a new adenoma detected was ~ 25 % lower in the celecoxib group overall. In contrast, in interval measures, adenomas were detected in a larger proportion in the celecoxib group (89 / 330 (27.0 %)) than in the placebo group (30 / 184 (16.3 %)) at year 5 (RR 0.75; 95 % CI 0.65 – 0.86; P < 0.0001; see Supplementary Figure S1 online for a summary of these fi ndings).

Advanced adenomas. Cumulative rates of newly detected advanced adenomas were signifi cantly lower in the celecoxib group (10.0 vs. 13.8 %; RR 0.64; 95 % CI 0.46 – 0.89; P = 0.007; Figure 3). In contrast, interval measures indicated that rates of newly detected advanced adenomas were signifi cantly higher in the celecoxib group than in the placebo group (5 vs. 3.8 %; RR 0.64; 95 % CI 0.45 – 0.89; P = 0.0072).

Characteristics of detected adenomas. Th e characteristics of detected adenomas included the mean number detected, size of largest adenoma detected, and total adenoma burden (defi ned above). Th e cumulative data are in **Table 3**, and the interval data are in **Table 4**. Th e cumulative adenoma count through year 5 favored the celecoxib group. In the overall population, there was a signi fi cant diff erence in the count distribution because of the fact that celecoxib had a greater percentage of subjects without new adenomas (481/933, or 51.6 % vs. 263 / 628, or 41.9 %; P = 0.0004). In contrast, interval data in **Table 4** favor the placebo group: 41.6 % (261/628) of the placebo

group had no adenomas, whereas 34.5 % (322/933) of the celecoxib group had none. A signifi cantly higher mean number of newly detected adenomas was found in the celecoxib group: 1.8 ± 0.1 in the celecoxib group vs. 1.6 ± 0.1 in the placebo group (Wilcoxon rank-sum test stratifi ed by aspirin use, P = 0.0003). Also, the percentage of patients with one or more adenoma > 1 cm was higher in the celecoxib group (10/186, or 5.4 %) than in the placebo group (3/85, or 3.5 %). Colorectal cancer was detected in nine cases: fi ve were diagnosed at the year 1 colonoscopy (two cases, stage 0; three cases, stage 1), two at year 3 (stage 2A and stage 4), and two at the end of

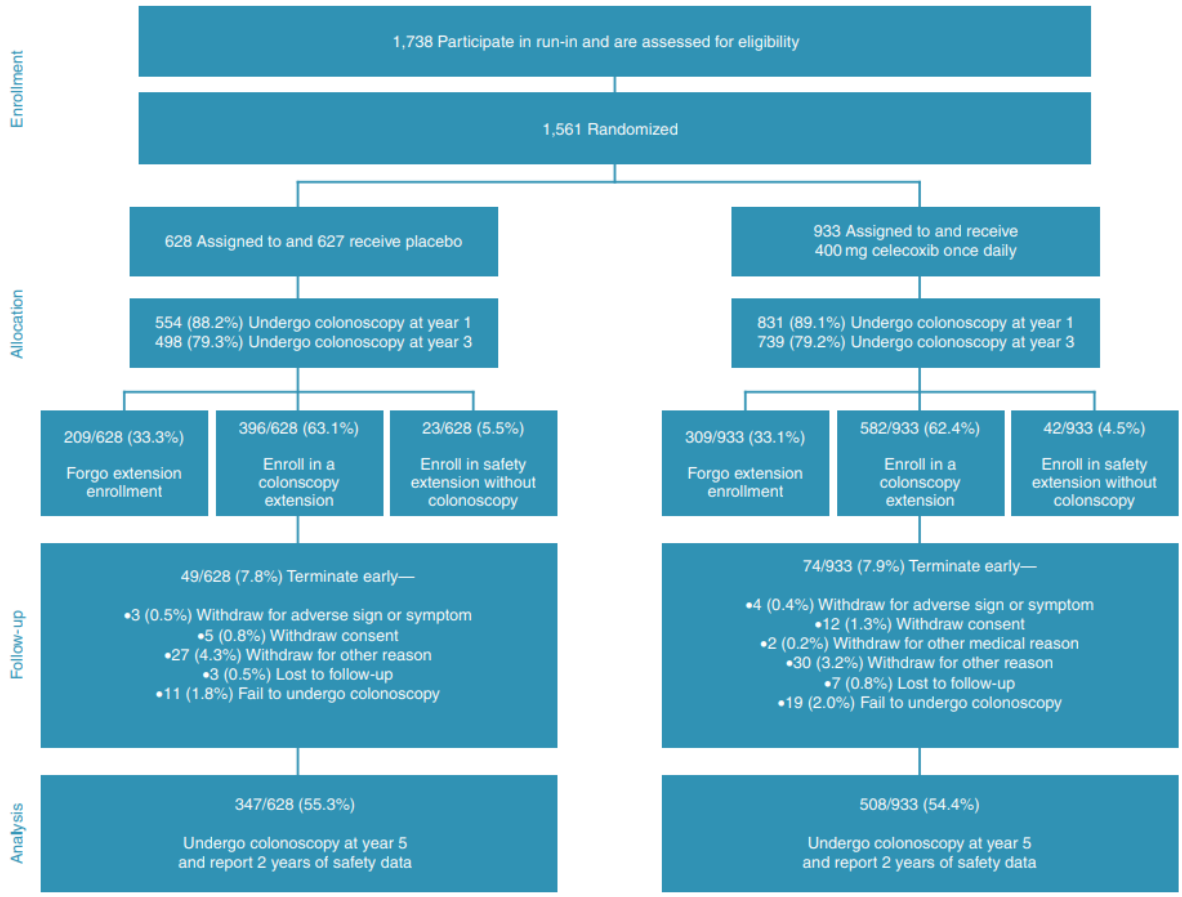

Figure 1. Of 1,738 who participated in a 1-month run-in, 1,561 were randomized, with 933 assigned to 400 mg celecoxib and 628 assigned to placebo daily. Enrollment was completed between March 2001 and March 2002. The last year 3 colonoscopy was performed in May 2005. After year 3, patients could enroll in one or more of four extension groups: three groups offered a colonoscopy at year 5 and one other, a safety extension phase, did not. In all, 209 (33.3 %) in the placebo group and 309 (33.1 %) in the celecoxib group declined enrollment in the study ' s extension phases. For those who enrolled, year 5 colonoscopies were concluded in 2007. Reasons for study discontinuation for patients undergoing the colonoscopy are reported here. Of the three patients in the placebo group who withdrew, one experienced a retrosigmoid junction perforation, one was diagnosed with prostate cancer, and one had increased levels of urea and creatinine. Of the six patients who withdrew in the celecoxib group, two had cerebrovascular accidents, one had pancreatitis, two had lung cancer, and one had an unknown serious adverse event (SAE). Disposition of subjects studied in the year 3 analysis was reported previously (9).

the extension phase at the year 5 colonoscopy (33). Of these, eight were in the celecoxib group (0.9%), and one was in the placebo group (0.2%). Analysis of highest histopathological grade indicated no statistically signifi cant diff erence between placebo and celecoxib groups for year 5 results, although the diff erence had been signifi cant **at year 3. Analysis — safety** **Table 5** reports AEs recorded over the length of the study from investigator reports during the

3-year treatment phase and self-reports of patients during the 2-year extension phase. Over the full study duration, 77.9 % of subjects in the celecoxib group (727/933) and 75.4 % of subjects in the placebo group (473/627) experienced an AE of any kind on treatment or off treatment. Analyzed within the MedDRA preferred term system, the AEs occurring most frequently were (celecoxib vs. placebo) gastrointestinal disorders (42.4 vs. 41.2%), infections and infestations (31.8 vs. 31.6%), musculoskeletal and connective tissue disorders (26.1 vs. 27.1 %), vascular disorders (20.6 vs. 15.3 %), and nervous system disorders (17.2 vs. 19.0%). Th e celecoxib group had signifi cantly higher rates of vascular disorders (RR 1.34; 95 % CI 1.08 – 1.68) and cardiac disorders (RR 1.59; 95% CI 1.12 – 2.26). Within the vascular disorder category, hypertension was the most common treatment-emergent AE, accounting for ~ 75 % of the events. All vascular and cardiac disorders are reported in detail in **Supplementary Tables S1 and S2 online.**

Table 1. Characteristics of subjects enrolled in 2-year extension

Characteristics	All extension participants				Extension participants with Y5 colonoscopy			
	Placebo		Celecoxib		Placebo		Celecoxib	
	N=419	%	*N*=624	%	*N*=347	%	*N*=508	%
Men	278	66.3	411	65.9	232	66.9	340	66.9
Women	141	33.7	213	34.1	115	33.1	168	33.1
Age								
18–44	38	9.1	41	6.6	36	10.4	33	6.5
45–64	252	60.1	370	59.3	213	61.4	309	60.8
≥65	129	30.8	213	34.1	98	28.2	166	32.7
Mean±s.e.	59.2	±0.49	60.5	0.39	58.4	±0.53	59.9	0.42
Race and ethnicity								
Asian	28	6.7	47	7.5	28	8.1	46	9.1
Black	7	1.7	9	1.4	7	2.0	6	1.2
Non-Hispanic white	371	88.5	553	88.6	303	87.3	442	87.0
Hispanic	13	3.1	14	2.2	9	2.6	13	2.6
Native American	0	0.0	1	0.2	0	0.0	1	0.2
Body mass index (mean)								
Men	27.2±0.24		27.5±0.20		27±0.27		27±0.20	
Women	26.2±0.42		27.4±0.35		26±0.39		27±0.36	
Aspirin users	66	15.8	99	15.9	47	13.5	73	14.4
Non-aspirin users	353	84.2	525	84.1	300	86.5	435	85.6

Not all subjects participating in the off-treatment extension underwent the year 5 (Y5) colonoscopy. Some reported only safety information.

In three selected analyses defi ned before unblinding — examining renal or hypertensive disorders, gastrointestinal ulceration or hemorrhage, and cardiovascular thromboembolic events (see **Table 5** footnotes for event descriptions) — incidence, 2 years aft er treatment ended, was signifi cantly diff erent between study arms only for the renal / hypertension events. More common in the celecoxib group overall (21.3 vs. 15.8%; RR 1.35; 95% CI 1.09 –1.68), these events included elevated serum creatinine levels, fl uid retention, edema, hypertension, proteinuria, and renal failure. Neither rates of gastrointestinal ulceration or hemorrhage nor rates of cardiovascular thromboembolic events diff ered signifi cantly between the two groups. SAEs aff ected more than one-fi ft hof patients in each group. Rates were higher in the celecoxib group overall (23.9 vs. 20.6%). Overall, 17 subjects (1.8%) in the celecoxib arm and 8 subjects (1.3%) in the placebo arm died, but this diff erence was not statistically signifi cant (RR 1.44; 95% CI 0.62–3.35). Of SAEs

classifi ed according to the MedDRA system organ class name and preferred term, rates of serious vascular disorders, although higher in the celecoxib group (2.0 vs. 1.4 %; RR 1.42; 95 % CI 0.65 – 3.12), were not statistically signifi cantly diff erent; however, rates of serious cardiac disorders were signifi cantly higher in the celecoxib group than in the placebo group (5.6 vs. 3.4 % ; RR 1.66; 95 % CI 1.01 – 2.73). In the 2 years off treatment, very few SAEs classifi ed as cardiac disorders were reported (celecoxib, 1.4 % ; placebo, 1.0 %).

Analysis by aspirin use or nonuse — effi cacy

New adenomas. In those taking aspirin, the cumulative rate of new adenomas was lower in the placebo group (54.9 %) than in the celecoxib group (58.4 % ; RR 0.80; 95 % CI 0.57 – 1.13; P = 0.197; **Table 2**). In those not taking aspirin, the cumulative rate was signifi cantly lower in the celecoxib group (50.2%) than in the placebo group (58.0% ; RR 0.73; 95% CI 0.64 – 0.86; P < 0.001). Interval rates at year 5 were uniformly lower in subjects taking placebo than in those taking celecoxib, both for those taking aspirin (7.7 vs. 37.3%) and for those not (17.7 vs. 25.1%), and the diff erence was signifi cant in the group not taking aspirin. Th e results indicated that diff erences between the placebo and celecoxib groups were not signifi cantly diff erent for those taking aspirin.

Advanced adenomas. Cumulative rates of advanced adenomas were lower in the celecoxib group, whether subjects were taking aspirin or not, but interval results were mixed: results in those taking aspirin favored the celecoxib group, whereas measures in those not taking aspirin favored those in the placebo group.

Table 2. Detection of new adenomas

Detection of any adenoma and advanced adenomas	Placebo (*N*=628)	Celecoxib (*N*=933)	Relative risk (95% confidence interval)	*P* value
		Cumulative rates		
Any adenoma detected at colonoscopy through year 5 (%±s.e.)				
All subjects	57.5±2.3	51.4±2.0	0.75 (0.65–0.86)	<0.001
Subjects taking aspirin	54.9±5.6	58.4±5.2	0.80 (0.57–1.13)	0.197
Subjects not taking aspirin	58.0±2.5	50.2±2.2	0.73 (0.64–0.86)	<0.001
Advanced adenomas detected at colonoscopy through year 5 (%±s.e.)[a]				
All subjects	13.8±1.6	10.0±1.2	0.64 (0.46–0.89)	0.007
Subjects taking aspirin	18.4±4.6	10.4±3.1	0.52 (0.24–1.13)	0.093
Subjects not taking aspirin	12.9±1.7	9.9±1.3	0.67 (0.46–0.96)	0.030
		Interval rates		
Any new adenoma detected at colonoscopy at year 5—number with new adenomas/evaluable (%)				
All subjects	16.3% (30/184)	27.0% (89/330)	0.75 (0.65–0.86)	<0.0001
Subjects taking aspirin	7.7% (2/26)	37.3% (19/52)	0.80 (0.57–1.13)	0.1969
Subjects not taking aspirin	17.7% (28/158)	25.1% (70/279)	0.74 (0.64–0.86)	<0.0001
Advanced adenomas detected at colonoscopy at year 5—number with advanced adenoma/evaluable (%)[a]				
All subjects	3.8% (12/315)	5.0% (24/481)	0.64 (0.45–0.89)	0.0072
Subjects taking aspirin	6.7% (3/45)	4.5% (3/66)	0.52 (0.24–1.13)	0.0934
Subjects not taking aspirin	3.3% (9/270)	5.1% (21/415)	0.67 (0.46–0.96)	0.0296

[a]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 subjects had undergone colonoscopy and polypectomy within 3 months of study initiation; therefore, *new adenomas* refers to the first on-study adenomas detected in these subjects. Subjects considered evaluable 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 evaluable 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. Year 3 colonoscopy had to be conducted on days 995–1,196 to be included. Subjects considered evaluable at year 5 included those who underwent colonoscopy at year 5, including those considered at risk and undergoing colonoscopy at year 3 and not having any adenomas detected at year 3.

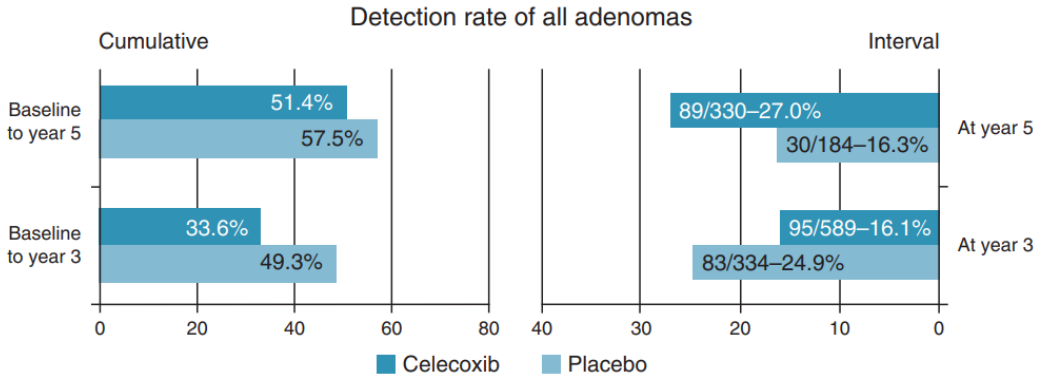

Figure 2. In the cumulative assessments (left), the percentage of subjects with new adenomas was signifi cantly lower in the celecoxib group at year 3 and 5 assessments (both periods, P < 0.001). In the interval assessments (right), detection of new adenomas was signifi cantly lower in the celecoxib group at years 1 and 3 (treatment phase) but signifi cantly higher in the celecoxib group at year 5 (off-treatment phase; all periods, P < 0.0001).

As with new adenomas, interval results indicated that for those taking aspirin, diff erences between the placebo and celecoxib groups were not signifi cantly diff erent. Th e number of subjects with the year 5 colonoscopy taking aspirin was small (celecoxib, 73; placebo, 47); thus, it was even smaller in the advanced adenoma subset (celecoxib, 66; placebo, 45).

Characteristics of detected adenomas. Comparisons of adenoma characteristics between the group taking aspirin and the group not taking aspirin were signifi cantly diff erent only on the measure of the number of new adenomas detected in both cumulative (see **Table 3**) and interval analyses (see **Table 4**). Findings generally mirrored those of the general subject population, but aspirin

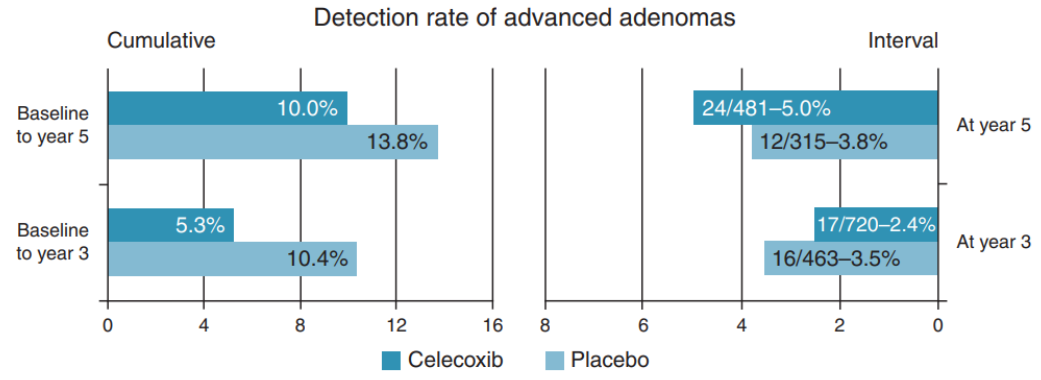

Figure 3. In the cumulative assessments (left) , the percentage of subjects with new advanced adenomas was signifi cantly lower in the celecoxib group at years 3 (P < 0.001) and 5 (P = 0.007). In the interval assessments at years 3 and 5 (right) , detection of new advanced adenomas was signifi cantly lower in the celecoxib group than the placebo group at year 3 (treatment phase; P = 0.0003) but higher in the celecoxib group at year 5 evaluation (off-treatment phase; P = 0.0072).

intake moderated values. For example, top-of-range values of the number of new adenomas (16), the largest adenoma (30.0 mm), and the highest adenoma burden (30.3 mm) were all higher in the celecoxib group that did not take aspirin; however, these same measurements in subjects who took celecoxib and aspirin were reduced by as much as 95 % .

Analysis by aspirin use or nonuse — safety

The rates of AEs were generally higher in the celecoxib group, whether subjects were taking aspirin or not (Table **5**), but diff erences were generally not signifi cantly diff erent. However, signifi cantly higher rates of selected renal / hypertensive events were found in celecoxib subjects not taking aspirin (21.0 vs. 13.9 % (RR 1.51; 95 % CI 1.17 – 1.95)) than in the placebo subset not taking aspirin. Diff erences were most dramatic between the celecoxib and placebo groups in subjects taking aspirin for rates of gastrointestinal ulceration and hemorrhage events (14.4 vs. 9.4 %) and cardiovascular thromboembolic events (18.8 vs. 13.1 %), but neither of these diff erences was signifi cant. Overall, of the 25 subjects who died, 19 were not aspirin users. Also, of the nine with colorectal cancer, eight were not aspirin users.

Analysis of all subjects, with or without new adenomas — effi cacy

Assessment of all subjects who underwent colonoscopy at year 5, whether or not we had detected adenomas in them previously at year 1 or year 3, indicated a pattern consistent with that seen in the subjects in whom we had found no adenomas: a lower percentage of new adenomas at year 3 in the celecoxib group than in the placebo group and a reversal of that pattern at year 5 aft er 2 years off treatment (Table **6**). Th is pattern was also true for the subgroups. However, at year 5 in aspirin users, in whom diff erences had not been signifi cant in the analysis limited to those without new adenomas, rates in the celecoxib group were signifi cantly higher than those in the placebo group, and the relative risk of new adenomas was twice as high (RR 2.189; 95 % CI 1.20 – 4.00; P = 0.0052). At year 3 in this same group, rates favored those taking celecoxib (19.2 vs. 23.4 %), but no signifi cant diff erence was found.

Table 3. Characteristics of adenomas: cumulative rates through year 5

Characteristics	Placebo	Celecoxib	*P* value
	Cumulative		
Number of adenomas (mean cm±s.e.)[a]			
All subjects	2.3±0.1	2.3±0.1	0.0004
Subjects without adenomas	41.9% (263/628)	51.6% (481/933)	
Subjects taking aspirin	2.2±0.2	2.5±0.3	0.4311
Subjects without adenomas	42.1% (45/107)	47.7% (74/155)	
Subjects not taking aspirin	2.3±0.1	2.3±0.1	0.0004
Subjects without adenomas	41.8% (218/521)	52.3% (407/778)	
Largest adenoma size (mean cm±s.e.)			
All subjects	0.7±0.0	0.7±0.1	0.0767
Subjects taking aspirin	0.6±0.0	0.5±0.0	0.6576
Subjects not taking aspirin	0.7±0.0	0.7±0.1	0.0815
Adenoma burden (mean cm±s.e.)[b]			
All subjects	1.2±0.1	1.2±0.1	0.1841
Subjects taking aspirin	1.0±0.1	1.0±0.1	0.6345
Subjects not taking aspirin	1.2±0.1	1.2±0.1	0.2141

[a]Calculations for number of adenomas in year 5, unlike in core phase, considered all values, including 0.
[b]Adenoma burden was calculated by adding the diameters of all detected adenomas.
Subjects considered evaluable 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 evaluable 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. Year 3 colonoscopy had to be conducted on days 995–1,196 to be included. Subjects considered evaluable at year 5 included those who underwent colonoscopy at year 5, including those considered at risk and undergoing colonoscopy at year 3 and not having any adenomas detected at year 3.

Table 4. Characteristics of adenomas: interval rates at year 5

Characteristics	Placebo		Celecoxib		*P* value
	Measure of adenoma characteristic		Measure of adenoma characteristic		
	Mean±s.e.	Median (range)	Mean±s.e.	Median (range)	
	Interval				
Number of adenomas[a]					
All subjects	1.6±0.1	1.0 (1.0–5.0)	1.8±0.1	1.0 (1.0–16.0)	0.0003
Subjects without adenomas	261/628 (41.6%)		322/933 (34.5%)		
Subjects taking aspirin	1.9±0.4	1.5 (1.0–5.0)	1.8±0.2	2.0 (1.0–5.0)	0.0063
Subjects without adenomas	37/107 (34.6%)		39/155 (25.2%)		
Subjects not taking aspirin	1.6±0.1	1.0 (1.0–5.0)	1.8±0.1	1.0 (1.0–16.0)	0.0053
Subjects without adenomas	224/521 (43.0%)		283/778 (36.4%)		
Largest adenoma size (cm)					
All subjects	0.6±0.1	0.5 (0.2–3.7)	0.8±0.2	0.4 (0.1–30.0)	0.4590
Subjects taking aspirin	0.6±0.1	0.6 (0.2–1.0)	0.6±0.1	0.55 (0.2–1.5)	0.7227
Subjects not taking aspirin	0.6±0.1	0.5 (0.2–3.7)	0.8 ± 0.2	0.4 (0.1–30.0)	0.3493
Adenoma burden (cm)[b]					
All subjects	0.8±0.1	0.6 (0.2–4.5)	1.1±0.2	0.6 (0.1–30.3)	0.7227
Subjects taking aspirin	0.9±0.2	0.7 (0.2–2.6)	0.9±0.1	0.8 (0.2–2.0)	0.7895
Subjects not taking aspirin	0.8±0.1	0.6 (0.2–4.5)	1.1±0.3	0.6 (0.1–30.3)	0.6271

[a]The calculation of the number of adenomas for year 5, unlike in the core phase, considered all values, including 0.

[b]Adenoma burden was calculated by adding the diameters of all detected adenomas.

Subjects considered evaluable 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 evaluable 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. Year 3 colonoscopy had to be conducted on days 995–1,196 to be included. Subjects considered evaluable at year 5 included those who underwent colonoscopy at year 5, including those considered at risk and undergoing colonoscopy at year 3 and not having any adenomas detected at year 3.

DISCUSSION

This randomized, double-blind, placebo-controlled study of 400 mg of celecoxib (once daily) studied subjects aft er ~ 3 years on and 2 years off treatment. Th e cumulative rates of new adenomas and the rates of advanced adenomas for those in the celecoxib group were signifi cantly lower than those in the placebo group, a residual eff ect from the strongly signifi cant lowering of risk during the study' s fi rst 3 years. In contrast, the interval rates of new adenomas and new advanced adenomas aft er 2 years off treatment were found to be signifi cantly higher in the celecoxib group than in the placebo group, an eff ect that may be because of loss of inhibition by celecoxib. As mentioned above, new adenomas refers to the fi rst on-study adenomas detected in these subjects, all of whom had undergone colonoscopy and polypectomy within 3 months of study initiation. Adenoma characteristics studied included the mean number of newly detected adenomas, the mean size of the largest adenoma detected, and the overall adenoma burden, but analysis indicated signifi cant diff erences between groups only in the number of newly detected adenomas. Th ese were, however, signifi cant for both cumulative and interval measures, although in opposite directions. Although the study was not designed specifi cally to measure post-treatment recurrence, the higher values in the trial ' s celecoxib group for year 5 may indicate fi ndings similar to the discovery by Baron et al. (34) of a higher risk of small adenomas in the year following therapy cessation in subjects who were treated with rofecoxib, an eff ect characterized as protective against larger adenomas. Although this explanation is not our own, it seems possible that a truncated "natural" process might resume in an "unnatural" or overcompensatory manner. Investigators reason that when an intervention is associated with greater numbers of small adenomas or with lower rates of development of advanced adenomas rather than other lesions, the mechanism at work may be a constraint on the adenoma-to-carcinoma progression responsible for advancing small adenomas to villous or larger adenomas

(18,34,35). In our study, however, at year 5 we found measures of all three adenoma characteristics (the number of new adenomas, the diameter of the largest adenoma, and the sum of all diameters of all adenomas excised from the patient) to be higher in the off - treatment celecoxib group than in the off - treatment placebo group. Although it is true that there were no statistically signifi cant diff erences found between the celecoxib and placebo groups in largest adenoma size or adenoma burden, whether measured cumulatively or at intervals, there were dramatic diff erences between the two groups on the breadth of the range of values: in the celecoxib

Table 5. Adverse events

Events	Placebo		Celecoxib		Relative risk (95% confidence interval)
	N	%	*N*	%	
Adverse events[a]					
All subjects	473/627	75.4	727/933	77.9	1.03 (0.98–1.09)
Subjects taking aspirin	88/107	82.2	133/160	83.1	1.01 (0.90–1.13)
Subjects not taking aspirin	385/520	74.4	594/773	76.8	1.03 (0.97–1.11)
Vascular disorders[b]	96/627	15.3	192/933	20.6	1.34 (1.08–1.68)
Cardiac disorders[c]	41/627	6.5	97/933	10.4	1.59 (1.12–2.26)
Selected adverse events[d]					
Renal/hypertension events[e]					
All subjects	99/627	15.8	199/933	21.3	1.35 (1.09–1.68)
Subjects taking aspirin	27/107	25.2	37/160	23.1	0.92 (0.60–1.41)
Subjects not taking aspirin	72/520	13.9	162/773	21.0	1.51 (1.17–1.95)
Gastrointestinal ulceration and hemorrhage events[f]					
All subjects	69/627	11.0	116/933	12.4	1.13 (0.85–1.50)
Subjects taking aspirin	10/107	9.4	23/160	14.4	1.54 (0.76–3.10)
Subjects not taking aspirin	59/520	11.4	93/773	12.0	1.06 (0.78–1.44)
Cardiovascular thromboembolic events[g]					
All subjects	40/627	6.4	82/933	8.8	1.38 (0.96–1.98)
Subjects taking aspirin	14/107	13.1	30/160	18.8	1.43 (0.80–2.58)
Subjects not taking aspirin	26/520	5.0	52/773	6.7	1.35 (0.85–2.13)
Serious adverse events					
All subjects	129/627	20.6	223/933	23.9	1.16 (0.95–1.41)
Subjects taking aspirin	35/107	32.7	57/160	35.6	1.09 (0.77–1.53)
Subjects not taking aspirin	94/520	18.1	166/773	21.5	1.19 (0.95–1.49)
Death from any cause	8/627	1.3	17/933	1.8	1.44 (0.62–3.35)
Colorectal cancers	1/627	0.2	8/933	0.9	5.38 (0.67–42.87)
Vascular disorders[h]	9/627	1.4	19/933	2.0	1.42 (0.65–3.12)
Cardiac disorders[i]	21/627	3.4	52/933	5.6	1.66 (1.01–2.73)

[a]These adverse events were recorded anytime throughout the 5-year study but were events that occurred initially after the first dose of study medication or were an intensification of an event with initial onset before the first dose.

[b]The vascular disorders in this category included the serious vascular disorders listed below plus aortic atherosclerosis, arterial disorder, arteriopathic disease, arteriosclerosis, atherosclerosis, atherosclerosis obliterans, deep vein thrombosis, diastolic hypertension, essential hypertension, flushing, hematoma, hot flush, hyperemia, infarction, intermittent claudication, labile blood pressure, lymphedema, peripheral coldness, peripheral ischemia, peripheral vascular disorder, phlebitis, phlebitis superficial, Raynaud's phenomenon, secondary hypertension, thrombophlebitis, superficial thrombophlebitis, varicophlebitis, varicose vein, vein disorder, venous insufficiency, and venous stasis.

[c]The cardiac disorders in this category included the serious cardiac disorders listed below and supraventricular arrhythmia, atrial flutter, atrial tachycardia, complete atrioventricular block, bradycardia, cardiogenic shock, cardiomyopathy, carditis, coronary artery atherosclerosis, extrasystoles, hypertensive heart disease, mitral valve incompetence, mitral valve prolapse, palpitations, sinus bradycardia, sinus tachycardia, tachycardia, ventricular arrhythmia, ventricular extrasystoles, and ventricular hypertrophy.

[d]These categories, defined before unblinding, included serious and nonserious events. Only in the 3-year core phase and the blinded extension were nonserious events counted.

[e]The renal or hypertensive disorders category was specified before unblinding and included elevated creatinine level, fluid retention, edema, hypertension, proteinuria, or renal failure.

[f]The gastrointestinal ulceration and hemorrhage category was specified before unblinding and included gastrointestinal bleeding, gastritis or duodenitis, upper or lower gastrointestinal ulceration, or other hemorrhage.

[g]The cardiovascular disorders category was specified before unblinding and included 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.

[h]The serious vascular disorders included angiopathy, aortic aneurysm, aortic thrombosis, arterial rupture, circulatory collapse, hemorrhage, hypertension, hypertensive crisis, hypotension, orthostatic hypotension, peripheral artery aneurysm, thrombosis, varicose ulceration, and venous thrombosis.

[i]The serious cardiac disorders included acute myocardial infarction, angina pectoris, unstable angina, aortic valve stenosis, arrhythmia, atrial fibrillation, atrioventricular block, cardiac disorder, cardiac failure, congestive cardiac failure, cardiogenic shock, coronary artery disease, myocardial infarction, myocardial ischemia, palpitations, and sick sinus syndrome.

These adverse events were reported by investigators and coded according to criteria from the Medical Dictionary for Regulatory Activities, version 8.1. An adverse event that occurred more than once in the same subject was only counted once; however, if a subject had two or more adverse events, that subject contributed once for each different adverse event to the count. Data do not include reports from one subject who, although assigned to the placebo group, never received study drug.

Table 6. Detection of new adenomas in all subjects with year 5 colonoscopy with or without previous new adenoma

Subjects	Placebo		Celecoxib		Relative risk (95% confidence interval)	*P* value
	N	%	*N*	%		
Year 5						
All subjects in a colonoscopy extension	396	63.1	582	62.4		
All subjects with year 5 colonoscopy	347	55.3	508	54.4		
With new adenoma at year 3	105	30.4	110	21.7	0.712 (0.57–0.90)	0.0039
With new adenoma at year 5	86	24.8	186	36.6	1.476 (1.19–1.83)	0.0003
Aspirin users with year 5 colonoscopy	47	43.9	73	47.1		
With new adenoma at year 3	11	23.4	14	19.2	0.819 (0.41–1.65)	0.5795
With new adenoma at year 5	10	21.3	34	46.6	2.189 (1.20–4.00)	0.0052
Non-aspirin users with year 5 colonoscopy	300	57.6	435	55.9		
With new adenoma at year 3	94	31.5	96	22.1	0.700 (0.55–0.89)	0.0041
With new adenoma at year 5	76	25.3	152	34.9	1.38 (1.09–1.74)	0.0057

All subjects had undergone colonoscopy and polypectomy within 3 months of study initiation; therefore, the term *new adenomas* refers to the first on-study adenomas detected in these subjects. Population includes all subjects who had year 5 colonoscopy, even if they had one or more new adenomas detected at any time after baseline.

group in the post-treatment period, as many as 16 new adenomas were detected at colonoscopy (placebo, 5 was maximum); adenomas were as large in diameter as 30 mm (placebo, 3.7 mm), and adenoma burden was as high as 30.3 mm (placebo, 4.5 mm). Th is was not true in the subgroup taking aspirin, a nonsteroidal antiinfl ammatory drug that has not been associated with unusual post-treatment recurrence (23). Although having more new adenomas in the celecoxib group than in the placebo group may be attributable to the cessation of the COX-2 inhibition, determining the cause will require further study. More than three-quarters of those participating in the extension study (76.9 %) experienced AEs of any type, and 22.5 % experienced AEs that were classifi ed as serious. Patients enrolled in the trial were vulnerable: more than a fourth of the patients enrolled in this trial were ≥ 65 years of age, and at baseline 472 (50.6 %) of the celecoxib group and 297 (47.3 %) of the placebo group had a signifi - cant medical history or a current abnormality related to cardiovascular disease. Over the full study duration, including ~ 2 years off treatment, celecoxib, compared with placebo, was associated with an increased risk of serious and general cardiac disorders, serious selected renal / hypertensive events, and general vascular disorders, providing additional evidence of an association between COX-2 inhibition and such AEs. Th e seriousness of this risk is a critical consideration in determining the appropriate use of celecoxib to prevent colorectal adenomas. Colorectal cancer was detected in nine cases: fi ve were diagnosed at the year 1 colonoscopy, two at year 3, and two at year 5. Of these, eight were in the celecoxib group (0.9 %), and one was in the placebo group (0.2 %). Th e fi ve cases diagnosed at year 1 are thought to represent either incomplete excision or disease undetected at baseline colonoscopy. If either was the explanation, these cases were well established before patients received the fi rst dose of celecoxib and did not represent a target for chemoprevention but for treatment. Medical history was not favorable: all cases were in patients who had previously had polyps removed and 3 were in patients who had a parent with colorectal cancer. Dosing and duration of therapy may be factors that could be manipulated to achieve benefi t with less risk. Once-daily dosing with 400 mg has its merits. In comparison with the twice-daily dosing in the APC trial, once-daily dosing was associated in years 1, 3, and 5 with lower incidence of new adenomas and with lower cumulative measures for both new and advanced adenomas; furthermore, the adjudicated evaluation of cardiovascular events when treatment ended found rates in the celecoxib group in the PreSAP study not to be signifi cantly diff erent from those of the placebo group (6,7,9,11). Defi nitive effi cacy

and safety comparisons, of course, require randomized trials. Th is study, one in the vanguard of placebo-controlled colorectal cancer chemoprevention trials with a COX-2 inhibitor, demonstrates in cumulative measures that the celecoxib group has lower rates of recurrent and advanced adenomatous polyps aft er 3 years on therapy and 2 years off therapy. Associated increased RRs in cardiac disorders, vascular disorders, and renal / hypertension events and the increases in adenoma measures aft er therapy discontinuation signifi cantly limit the potential use of this compound to those at high risk for colorectal neoplasia and without signifi cant risk for cardiovascular sequelae and aff ect therapy duration. In the APC follow-up study, Bertagnolli et al. (7) reported signifi cant dosedependent reductions in advanced adenomas and adverse renal, gastrointestinal, and cardiovascular eff ects of celecoxib at doses of 200 mg twice daily and 400 mg twice daily. As observed by others and as indicated in our results, prevention of advanced adenomas appears to be a particularly appropriate target for celecoxib, as demonstrated by the ability of celecoxib to reduce the number of colorectal polyps in patients with familial adenomatous polyposis (36), its ability in this trial to reduce sporadic advanced adenoma rates by 50 % in the fi rst year of treatment (9), its abi lity to be eff ective over time against such adenomas, and its ability to control adenoma size and burden. However, the occurrence of larger adenomas aft er treatment cessation at year 5 draws attention to the need to consider AEs aft er drug withdrawal. It should be pointed out that this study has intrinsic limitations in terms of known clinical outcomes. Such uncertainty is among the reasons that no calculation of the possible reduction in colorectal cancer-mediated morbidity and mortality is undertaken here. Another fundamental reason is that calculations of that sort were never conceived to be part of the PreSAP trial analysis. It must be remembered that adenoma formation is only a surrogate marker of colon cancer and that the vast majority of adenomas do not progress to cancer. On the other hand, cardiac and vascular disorders are associated with signifi cant morbidity and mortality, with cardiovascular disease claiming more lives worldwide every year than any other cause (37). Statistically signifi cantly increased risk of cardiac disorders and renal / hypertension sequelae in this extension phase of the PreSAP trial make apparent just how personalized the practice of medicine may need to become if chemopreventives carrying associated risks are to be utilized. On a clinical level, currently, celecoxib serves what has been termed a “niche ” population — those with familial adenomatous polyposis — and proposals have pondered mixing and matching clinical factors (age, cardiovascular risk and therapies, and gastrointestinal risk and therapies) for consideration (38). On a molecular level, in the Health Professionals Follow-up Study and the Nurses’ Health Study, aspirin use failed to reduce the risk of colorectal cancers in those in whom COX-2 expression was low or absent but statistically signifi cantly reduced risk in those in whom COX-2 expression was high (39). Highly individualized adenoma risk profi les were demonstrated in the Aspirin / Folate Polyp Prevention Study (40). In this randomized trial of aspirin treatment in a population with a history of colorectal adenoma occurrence, investigators found that two COX-2 single-nucleotide polymorphisms were associated with statistically signifi cant increased risk for adenoma recurrence, and evidence suggested that in a specifi c genotype the protective eff ect of an 81-mg daily dose of aspirin was modifi ed (41). A prespecifi ed study conducted aft er the APC trial closed investigated whether there was an association between a higher risk of synchronous advanced or recurrent adenomas and the number or presence of nondysplastic aberrant crypt foci, but none was found (42); nonetheless, these types of trials are those that are expected eventually to identify reliable surrogate end point biomarkers. Such fi ndings indicate that physicians will have to be adept in assessing risk – benefi t ratios while designing new clinical trials and pursuing other tools,

including enhanced patient characterization and molecular profi ling of adenomas. Meanwhile, investigators may also need to revisit dosing schedules, study therapy duration, and create combinations of active agents (43) to serve those patients who have the least vulnerability to cardiovascular and renal / hypertensive risk and the most to gain from eff ective chemoprevention.

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Worldwide, 1.2 million cases of colon cancer occur annually.
- ✓ The occurrence of adenomatous polyps, colon cancer's precursors, can be reduced with celecoxib, a cyclooxygenase-2 inhibitor; however, concern over the drug's cardiovascular safety forced discontinuation of randomized trials and relegated its use to cases of familial adenomatous polyposis.

WHAT IS NEW HERE

- ✓ Reported here are new data for the 2-year off-treatment follow-up following drug discontinuation in the Prevention of Colonic Sporadic Adenomatous Polyps trial.
- ✓ Findings show that celecoxib's strong control of new adenomas at years 1 and 3 allowed cumulative rates at year 5 of new adenomas to be lower in the celecoxib group than the placebo group, whereas interval rates indicated a lower rate of new adenomas in the placebo group than in the celecoxib group. The same pattern was found in advanced adenomas.
- ✓ Although the trial was not designed to evaluate specific adenoma characteristics after 2 years off treatment, at year 5, adenomas detected in patients in the celecoxib group were more numerous and larger than those found in the placebo group, an effect that may be because of loss of inhibition by celecoxib.
- ✓ Risk of serious cardiac disorders (relative risk (RR) 1.66; 95% confidence interval (CI) 1.01–2.73) and overall cardiac disorders (RR 1.59; 95% CI 1.12–2.26) were significantly higher in the celecoxib group than the placebo group at year 5. Also, significantly higher in the celecoxib group were selected renal/hypertension events (RR 1.35; 95% CI 1.09–1.68).
- ✓ In aspirin users, cumulative measures taken across 5 years indicated that the mean number of new adenomas was lower in the placebo group (54.9±5.6) than in the celecoxib group (58.4±5.2), but this measure was not statistically significant (P=0.197). Interval measures showed the same pattern: a lower percentage of new adenomas in the placebo group (7.7%) than in the celecoxib group (37.3%), but no statistically significant difference (P=0.1969).
- ✓ Aspirin users in the placebo group were less likely than those in the celecoxib group to experience gastrointestinal ulceration and hemorrhage events (9.4 vs. 14.4%), cardiovascular thromboembolic events (13.1 vs. 18.8%), or any serious adverse event (32.7 vs. 35.6%), but none of these differences was statistically significant.

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