

## Research Article

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# A Randomized Placebo-Controlled Prevention Trial of Aspirin and/or Resistant Starch in Young People with Familial Adenomatous Polyposis

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## Abstract

Evidence supporting aspirin and resistant starch (RS) for colorectal cancer prevention comes from epidemiologic and laboratory studies (aspirin and RS) and randomized controlled clinical trials (aspirin). Familial adenomatous polyposis (FAP) strikes young people and, untreated, confers virtually a 100% risk of colorectal cancer and early death. We conducted an international, multicenter, randomized, placebo-controlled trial of aspirin (600 mg/d) and/or RS (30 g/d) for from 1 to 12 years to prevent disease progression in FAP patients from 10 to 21 years of age. In a 2 × 2 factorial design, patients were randomly assigned to the following four study arms: aspirin plus RS placebo; RS plus aspirin placebo; aspirin plus RS; RS placebo plus aspirin placebo; they were followed with standard annual clinical examinations including endoscopy. The primary endpoint was polyp number in the rectum and sigmoid colon (at the end of intervention), and the major secondary endpoint was size of the largest polyp. A total of 206 randomized FAP patients commenced intervention, of whom 133 had at least one follow-up endoscopy and were therefore included in the primary analysis. Neither intervention significantly reduced polyp count in the rectum and sigmoid colon: aspirin relative risk = 0.77 (95% CI, 0.54–1.10; versus nonaspirin arms); RS relative risk = 1.05 (95% CI, 0.73–1.49; versus non-RS arms). There was a trend toward a smaller size of largest polyp in patients treated with aspirin versus nonaspirin—mean 3.8 mm versus 5.5 mm for patients treated 1 or more years (adjusted  $P = 0.09$ ) and mean 3.0 mm versus 6.0 mm for patients treated more than 1 year ( $P = 0.02$ ); there were similar weaker trends with RS versus non-RS. Exploratory translational endpoints included crypt length (which was significantly shorter in normal-appearing mucosa in the RS group over time) and laboratory measures of proliferation (including Ki67). This clinical trial is the largest ever conducted in the setting of FAP and found a trend of reduced polyp load (number and size) with 600 mg of aspirin daily. RS had no clinical effect on adenomas. *Cancer Prev Res*; 4(5); 655–65. ©2011 AACR.

## Introduction

Somatic mutations in the adenomatous polyposis coli (*APC*) gene are found in most colorectal cancers (CRC) and many colorectal adenomas. Germline *APC* defects underlie

the disease familial adenomatous polyposis (FAP), which is characterized by the development of thousands of colorectal polyps beginning typically during puberty. Therefore, FAP patients represent a powerful model for CRC chemoprevention studies.

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**Note:** Investigators participating in CAPP1 are listed in Appendix. CAPP originally stood for Concerted Action Polyp Prevention of the European Union and now stands for Colorectal Adenoma/Carcinoma Prevention Programme.

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Consistent evidence of a protective effect of aspirin against colorectal neoplasia in 27 cohort or case-control studies (1, 2) contrasts with 4 randomized trials, which found only marginal evidence in favor of this benefit (3–6). In a study of 1,121 patients with a history of adenoma formation, Baron and colleagues (4) found that aspirin at 81 mg/d had a small protective effect [adenoma risk ratio (RR) = 0.81; 95% CI, 0.69–0.96], whereas aspirin at 325 mg/d did not (RR = 0.96; 95% CI, 0.81–1.13); the effect of the lower dose was greater on more advanced lesions (RR = 0.59; 95% CI, 0.38–0.92). A randomized placebo-controlled trial of aspirin (325 mg) by Sandler and colleagues (3) in 635 patients with a previous CRC found that adenomas developed in 17% of the aspirin group versus in 27% of the placebo group after 1 year ( $P = 0.004$ ). Benamouzig and colleagues (5) reported that lysine acetylsalicylate treatment resulted in an adenoma RR of 0.73 (95% CI, 0.52–1.04), with a greater effect of 300 mg versus 160 mg of lysine acetylsalicylate and a significantly reduced risk of advanced lesions ( $P = 0.01$ ). Most recently, Logan and colleagues (6) found that aspirin (300 mg/d) reduced adenoma risk (versus placebo; RR = 0.79; 95% CI, 0.63–0.99) in 939 people who had had an adenoma removed, again with evidence of a greater impact on advanced lesions.

Nine epidemiologic studies have investigated the relationship between starch intake and colorectal neoplasms, with higher starch intakes providing neoplasm reductions in the range of 25% to 50% (7). Cassidy and colleagues reported a significant negative correlation between population starch intakes and colon cancer incidence (8). Resistant starch (RS) is the sum of starch and the products of starch digestion not absorbed in the small intestine of healthy individuals (9); it undergoes colonic fermentation to short-chain fatty acids including butyrate (10). RS supplementation can improve a number of potential biomarkers of CRC risk including fecal concentrations of total and secondary bile acids, which it decreases (11, 12). The RS product butyrate reduces colonic neoplasia in azoxymethane-treated rats (13), and concentrations of physiologic butyrate suppress the *in vitro* growth of CRC cell lines and induce G<sub>1</sub> cell-cycle arrest, terminal differentiation, and apoptosis (14–17), probably reflecting its role as an inhibitor of histone deacetylase. Butyrate and nonsteroidal anti-inflammatory drugs (NSAID) differ radically in the transcriptome and proteome modifications they produce in tumor cells (17, 18).

The first trial conducted within the Colorectal Adenoma/Carcinoma Prevention Programme (CAPP), this study (CAPP1) was aimed to test aspirin and RS for preventing adenoma development in adolescents with FAP and for effects on mucosal crypt dimensions and cell proliferation, which are potential biomarkers of CRC chemoprevention.

## Materials and Methods

### Patient eligibility

Polyposis registry clinicians recruited young male and female patients who met the following major eligibility

criteria: age between 10 and 21 years and confirmed or a high likelihood of the presence of FAP. FAP status was determined by molecularly confirmed carriage of the FAP-associated APC mutation or by the determination of having a high probability of carrying the mutation on the basis of linked DNA markers or the presence of multiple colonic polyps, and/or multiple areas of congenital hypertrophy of retinal pigment epithelium in the context of a known FAP family history. Restricting eligibility to members of families manifesting classical FAP helped ensure homogeneity of disease in our study population. Current NSAID therapy, known aspirin sensitivity, major intercurrent illness, and pregnancy were grounds for exclusion. Advanced FAP was not a reason for exclusion unless surgery was planned within the next 12 months. The eligibility cutoff at 21 years was based on concerns that continuation beyond this age might risk delaying preventive surgery. All patients were required to provide written consent to participate in the trial; written consent was required from the parents of patients less than 16 years of age. They were advised strongly to avoid all products containing aspirin or other NSAIDs and to use paracetamol for pain relief.

### Trial design

We conducted an international, multicenter, double-blind, randomized trial with 4 arms: aspirin (600 mg as 2 tablets/d) plus matched placebo, RS [30 g as 2 sachets/d in a 1:1 blend of potato starch and high amylose maize starch (Hylon VII)] plus matched placebo, aspirin plus RS, and placebo plus placebo; this trial employed a 2 × 2 factorial design. All polyposis registries and clinics in Europe were invited to participate in the CAPP1 study. Our accrual goal was 208 patients, 52 in each of the 4 intervention arms.

Randomization was done centrally at Leeds University via a blocked randomization scheme with a block size of 16 so that each set of 16 recruits contained 4 persons within each of the 2 × 2 trial arms. The blocked randomization was stratified at the level of geographic regions recruiting sufficient number of participants to avoid confounding of trial results due to geographic differences (e.g., regional diet); the regional strata were as follows: United Kingdom, Scandinavia, northern Europe, and southern Europe. Last, if siblings were enrolled, we assigned each member of such family groups the same combination to remove the potential for package mix-ups within the family. The duration of intervention was from 1 to a potential maximum of 12 years, with a scheduled annual clinical examination including endoscopy. Patients were advised of their option to leave intervention after each annual examination but were invited to remain on intervention (up to and including age 21 years).

The primary trial endpoint was the proportion of patients with an increased polyp count in the rectum and sigmoid colon after intervention. A major secondary endpoint was size of the largest polyp, which was chosen as another quantifiable and objective measure of disease

severity. Given the multiple, international centers participating in this trial, it was not feasible to influence the clinical decision on whether the largest polyp was removed or left *in situ*, nor to tattoo any polyps for review at a later examination. We also assessed crypt dimensions. Secondary laboratory endpoints included proliferative-state assessments of (a) crypt-cell proliferation (CCP) measured by direct counting of mitoses and (b) indices of proliferation measured by using antibodies against proliferating-cell nuclear antigen (PCNA) and Ki67.

The RS dose was based on the maximum easily tolerated doses and doses used previously in short-term intervention studies with CRC biomarkers as endpoints (19, 20). Aspirin and its matched placebo were supplied by Bayer; the matched placebo was a lactose tablet (packaged at the pharmacy of Freeman Hospital in Newcastle). RS and its matched placebo were supplied by the National Starch and Chemical Company; the matched placebo was 30 g/d of digestible corn (maize) starch. Children less than 45 kg or less than 12 years of age took half doses.

The trial was conducted in accordance with principles of the Declaration of Helsinki, and each study center was required to get the protocol, including the final version of the patient information and informed consent form, approved by its ethics committee.

### Endpoint ascertainment

Endoscopists counted the actual number of polyps in the rectum and sigmoid colon if there were 10 or less and provided an estimate (11–15, 16–20, 21–30, 31–50, 51–100, >100) when more numerous. We also collected data on the total number of polyps (rectum and sigmoid, ascending, transverse, and descending colon), which presented a challenge because of differing endoscopy policies and the challenge of the total number of polyps in an FAP patient, which can run into the thousands. When the study was initiated, many centers used sigmoidoscopy under sedation to monitor young people with FAP and usually avoided polyp removal unless a polyp became very large or appeared to be advanced. Some centers relied on pediatric endoscopists who tended to prefer full colonoscopy under anesthetic. A diagrammatic form was used to clarify polyp count (actual or estimated) instructions and to invite the endoscopist to mark the maximum extent of examination. The size of the largest polyp was recorded on the form (estimated by comparing the polyp with open 5-mm biopsy forceps). We also requested all centers to record a withdrawal video of the rectum. If it was necessary to remove polyps, we asked that a recording be made before and after the removal. We specified rectal videos because we expected higher compliance among busy endoscopists with a rectal versus a more comprehensive, more time-consuming video. At least 2 withdrawal recordings in different perpendicular planes (i.e., at 90°) or with views taken from 10, 2, and 6 o'clock and starting at 20 cm from the anal verge were requested. At least twice during the recording, 5-mm forceps were opened near a polyp to assess the size of polyps and to provide a scale for the

views. Almost all endoscopists complied with the request for open-forcep reference images, but there was considerable variation in extent of recording, with some offering a full-withdrawal recording rather than only imaging the rectum. The video recordings were scored (better, worse, or same) by 2 experienced endoscopists (S.B. and R.K.S.P.) blinded to intervention and the time point of examination (baseline, first year, second year, etc.).

For assessing proliferative-state endpoints, six 5-mm mucosal biopsies were obtained from macroscopically normal mucosa from 5 to 15 mm from the anal verge; 2 biopsies were fixed in 75/25 absolute alcohol/glacial acetic acid for CCP, 2 were fixed in methacarn fixative (60 methanol:30 chloroform:10 glacial acetic acid) for PCNA immunostaining, and 2 in 10% neutral buffered formalin for determining Ki67 via MIB-1 immunostaining; these samples were transported to Newcastle University for processing. On receipt, CCP samples were transferred to 70% alcohol for long-term storage.

### Data and safety monitoring

Located in Newcastle University, the CAPP Operations Center housed the CAPP principal investigator (J.B.), study manager, research associate/recruiter, technician, and pharmacist, and coordinated the activities of the formal, independent CAPP Data Monitoring Committee (DMC) and the CAPP Steering Committee, which comprised multidisciplinary members to help in guiding the trial. The Operations Center staff coordinated day-to-day administration of the study, including dealing with study inquiries, distributing intervention packs, and collecting surveillance data including the hand-marked colorectal forms (which recorded the number and location of adenomatous polyps and size of the largest polyp in the examined colorectal segments), video recordings, and biopsy material for storage and processing. The Operations Center also offered study sites the option of genetic testing for the FAP-associated APC mutation in samples obtained from prospective patients. All trial data were transmitted by the study sites to the Operations Center, where they were entered into a computerized study database and transmitted ultimately to the trial Statistical Center at Leeds University for analysis; prior to the end of study, only randomization data were held at the CAPP Statistical Center in Leeds. The CAPP study manager and principal investigator visited study sites frequently on an ad hoc basis, conducting chart reviews and other procedures necessary to ensure the integrity of the data and safety of patients. The CAPP statistical team at Leeds University annually reported the trial data to the DMC, chaired by Professor Doug Altman (Cancer Research UK, London), for safety and efficacy review. The DMC was responsible for interrupting the trial if and when warranted by statistically significant preliminary results. All of these operational procedures were facilitated by the long-standing collaborative association of our sites as members of a trials consortium called the Leeds Castle Polyposis Group, 1 of the 2 research communities which

gave rise to the International Society for Gastrointestinal Tumours (InSiGHT; [www.insight-group.org](http://www.insight-group.org)).

### Compliance

To maintain interest in study participation, recruitment site personnel were asked to contact each study patient at least once every 6 months to coincide with a delivery of study tablets and sachets to the patient. Unused tablets and sachets were collected, counted, and recorded by the recruiters to assess compliance with study interventions. The Operations Center sent study tablets and sachets once a month to the study sites so as to maintain regular, monthly contact with the sites; the Center also provided patients with regular updates of study progress to maintain enthusiasm.

### Laboratory methods

We assayed proliferative states via 3 techniques (21) so as to assure reliable results for this important aberration. We used (a) a crypt-microdissection method in tissue fixed in alcohol/acetic acid to provide estimates of CCP because this method is technically robust and (b) 2 methods that applied antibodies to sections of formalin-fixed tissue for identifying dividing cells marked by the antibodies against PCNA and Ki67. As described earlier in text, 6 variously fixed biopsies were taken from normal mucosa near the anal verge at the baseline and annual examinations. When required for histologic analysis to determine CCP, samples were rehydrated, stained with Schiff's reagent, and microdissected to enable direct counts of total number (and location) of mitoses in whole crypts (22). The number of mitotic cells in each tenth of the crypt by length was recorded; crypt compartments were numbered from 1 (base) to 10 (luminal surface). Formalin-fixed biopsies were paraffin embedded and sectioned routinely prior to immunohistochemical staining by MIB1 to detect Ki67 (22) and by PC10 to detect PCNA.

Crypt width and length were measured in the microdissected specimens and formalin-fixed tissue sections via a graticule in the microscope eyepiece and were standardized via a reference slide. Results from 10 crypts were averaged for each biopsy assessed.

### Statistical methods

The study was designed to detect a statistically significant difference in the proportion of patients with an increased polyp number in the rectum and sigmoid colon in the aspirin (versus the nonaspirin) group or in the RS (versus the non-RS) group at the end of intervention (versus at baseline). The total number of polyps in the rectum and sigmoid colon (prior to any polypectomy) at all endoscopies subsequent to baseline was the outcome measure, that is, the dependent variable by a random effects model. Data for the total number of polyps seen in the rectum and sigmoid colon were available on all participants for all colonoscopies.

We included the secondary endpoint of total number of polyps throughout the colon (adjusted for the extent of

endoscopy to account for the variable completeness of endoscopy) so as to make more complete use of collected data. Variability in local policy over extent of endoscopy meant that polyps were counted, or estimated when too dense, in differing numbers of colorectal segments. We allowed for this variability by adjusting models for extent at all endoscopies subsequent to baseline, including it as an independent variable in the random effects models. Prior to the random effects modeling, linear regression was carried out so that total number of polyps at baseline endoscopy was the dependent variable and extent at baseline endoscopy was the independent variable. Adjusted values were calculated from the linear regression, that is, we computed the difference between the observed number of polyps at baseline and the average number of polyps for that extent at baseline endoscopy. This adjusted number of polyps at baseline was then included in the random effects model as an independent variable.

This was a  $2 \times 2$  factorial analysis that compared the 2 aspirin arms combined (aspirin plus RS and aspirin plus placebo) with the RS-plus-placebo and placebo-plus-placebo arms combined, and compared the 2 RS arms combined (RS plus aspirin and RS plus placebo) with the aspirin-plus-placebo and placebo-plus-placebo arms combined. We estimated an event rate of 40% in nonresponding patients, that is, 40% of the patients in that group would have an increased polyp number (rectum, sigmoid colon) at the end of intervention, and an intervention effect of 50% less patients (i.e., a total of 20%) developing an increased number in the responsive intervention group, based on the average effect recorded in the published observational studies (23). Because of the suggestion in some of these studies that the effect was greater with prolonged use, this study was designed to allow participants to remain on study for as long as they could tolerate the interventions. The final sample size estimate of 208 patients, 52 in each of the 4 arms of the factorial design, was based on early data indicating that almost all patients had detectable pathology and was designed to detect the anticipated intervention effect with an 80% power and  $\alpha$ -level of 0.025.

Major, prespecified secondary analyses included the size of the largest polyp at the end of intervention and assessed in the subset of patients who remained on study for more than 1 year; these patients were anticipated to be more likely to be fully compliant and to respond to an active intervention. Measurements of crypt length and width, hemicrypt cell count, and proliferation in normal mucosal biopsies also were secondary endpoints; these endpoints were considered exploratory because there were no prior data on potential effects on which to base power calculations.

Eight outcome measures were analyzed: 3 clinical endpoints [number of rectal and sigmoid polyps, largest polyp size (mm), and overall polyp number] and 5 exploratory translational endpoints (mean total CCP, crypt width, crypt length, the mean number of MIB1-positive cells per crypt, and the mean number of cells per hemicrypt).



All but the last variable were log transformed before analysis; for log-transformed outcome measures, the exponent of the intervention coefficient was taken to indicate the ratio of the outcome measure in treated to untreated patients; a ratio of 1.0 indicates no differences between treated and untreated patients.

ANOVA and Pearson's  $\chi^2$  tests were carried out to compare baseline measures. Associations between the baseline measures and age and sex were tested by 2-sided *t* tests,  $\chi^2$  tests, and Spearman's correlations. Spearman's correlation coefficients were calculated for all pairwise combinations of the continuous baseline measures. Differences in final largest polyp size between the 4 intervention groups were investigated by linear regression. Modeling involved estimation of random effects, linear models, and generalized estimating equation logit models to identify main effects and possible interactions between intervention and time. The primary analyses compared the 2 arms containing aspirin with the 2 arms not containing aspirin and separately compared the 2 arms containing RS with the 2 arms not containing RS. The outcome measures in these models comprised all results obtained after entry endoscopy, and all models were adjusted for entry data and time on the intervention (years). In addition, the random-effects models for the total number of polyps were adjusted for age and extent, that is, the proportion of the colorectum examined. The total polyp number at entry was adjusted for the extent of endoscopy via adjusted values from linear regression; specifically, we computed the difference between the observed number of polyps and the average number of polyps for that extent of endoscopy. This residual number

formed the adjusted total of polyps at entry endoscopy. In analyses of numbers of polyps, the number of polyps which were removed at any endoscopy other than the last was added to the total number of polyps recorded at the following endoscopy.

We tested differences between interventions in results from video analysis with Fisher's exact test. All analyses were carried out by STATA version 8 (Stata Corporation), and probabilities less than 0.05 were considered significant.

## Results

### Patient characteristics

Recruitment to this trial took place in 12 international centers from June 1993 to April 2002. Initially 227 young people with intact colons were recruited into the study and 206 of these started the intervention (Fig. 1). Fifty-nine percent (133 of 227) had a baseline and at least one other endoscopy and were therefore eligible for data analyses. At baseline, age of these patients ranged from 10 to 21 years, with a mean age of 18 years, and half were female (Table 1). Patients were offered the option of leaving study at 1 year but were invited to remain on study after 1 year, some remaining on intervention for up to 7 years before the study ended. The study was approved by the relevant ethical committees in the participating countries. All recruits provided informed consent for their participation in the study and the provision of tissue samples.

Withdrawal rates in each intervention group were compatible with random loss [ $\chi^2(3) = 5.0, P = 0.3$ ]. For the 94

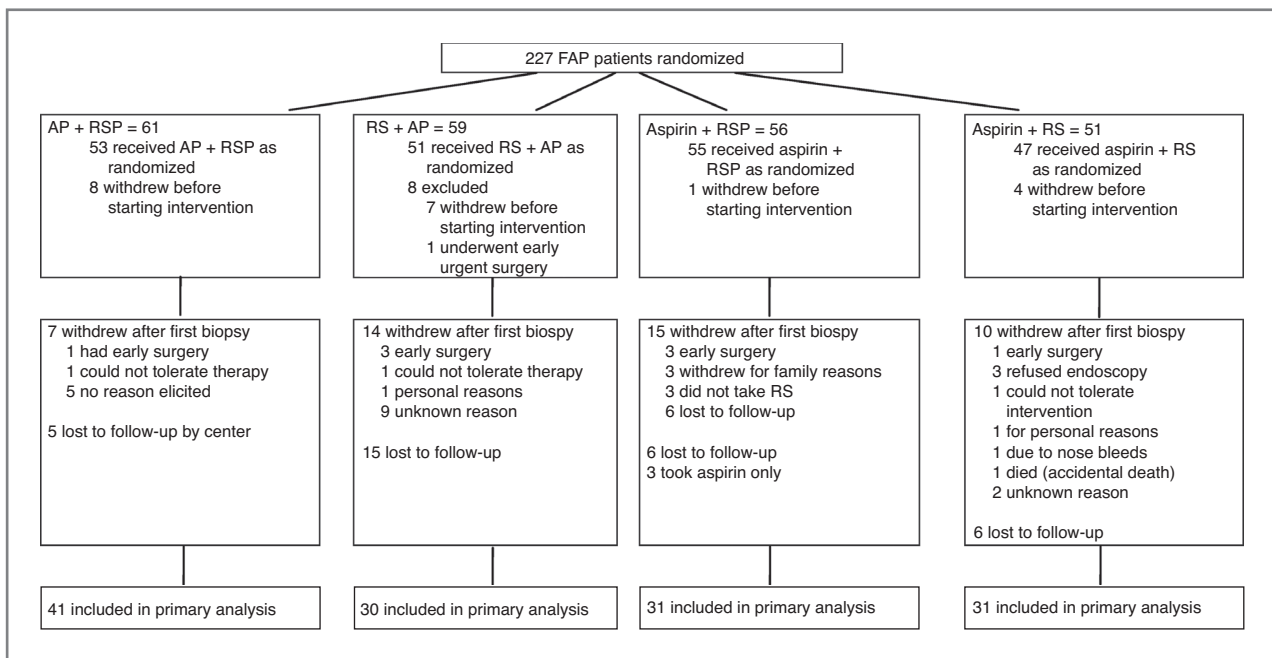


Figure 1. CAPP1 consort diagram. AP, aspirin placebo; RSP, RS placebo.

**Table 1.** Patient characteristics

Baseline measures (range of values)	N	Intervention <sup>a</sup> (n)				P
		RSP/AP (41)	RS/AP (30)	A/RSP (31)	A/RS (31)	
Age						
Mean (SD)		18.2 (7.8)	17.9 (10.8)	17.2 (6.9)	18.8 (7.9)	0.90
n	133	41	30	31	31	
Sex, n (%)						
Female	66	19 (46.3)	21 (70.0)	12 (41.4)	14 (45.2)	$\chi^2(3) = 6.2,$ $P = 0.10$
Male	65	22 (53.7)	9 (30.0)	17 (58.6)	17 (54.8)	
Total	131	41 (100)	30 (100)	29 (100)	31 (100)	
Number of endoscopies, n						
2	76	20	19	21	16	
3	30	12	3	3	12	
4	15	4	5	4	2	
5	8	4		3	1	
6	1	1				
7	2		2			
8	1		1			
Total	133	41	30	31	31	
Polyp data						
At least 1 polyp found, n (%)						
No	13	1 (2.4)	5 (17.9)	3 (10.0)	4 (13.3)	$\chi^2(3) = 4.8,$ $P = 0.18$
Yes	116	40 (97.6)	23 (82.1)	27 (90.0)	26 (86.7)	
Total	129	41 (100)	28 (100)	30 (100)	30 (100)	
Number of polyps in the rectum and sigmoid colon (0, 200)						
Mean (SD)		29.8 (43.0)	29.7 (52.5)	22.7 (32.3)	25.6 (44.4)	0.53 <sup>b</sup>
n	129	41	28	30	30	
Total number of polyps (0, 425)						
Mean (SD)		56.7 (86.4)	63.8 (115.6)	44.5 (90.5)	43.1 (76.2)	0.60 <sup>b</sup>
n	129	41	28	30	30	
Size of largest polyp (0.5, 50), mm						
Mean (SD)		6.1 (8.2)	4.2 (2.7)	4.0 (2.5)	4.3 (2.4)	0.63 <sup>b</sup>
n	110	38	21	27	24	
Crypts						
Crypt width (74.2, 199.7)						
Mean (SD)		121.5 (21.6)	110.7 (20.3)	116.8 (24.1)	111.5 (17.3)	0.16 <sup>b</sup>
n	113	35	24	25	29	
Crypt length (290.4, 765.1)						
Mean (SD)		499.4 (84.4)	467.3 (92.9)	494.8 (75.6)	498.6 (69.1)	0.27 <sup>b</sup>
n	112	35	24	25	28	
Mean total CCP (0.2, 37.9)						
Mean (SD)		5.3 (4.9)	6.1 (7.8)	7.5 (6.1)	6.1 (4.2)	0.27 <sup>b</sup>
n	113	35	24	25	29	

<sup>a</sup>Raw means presented.<sup>b</sup>Log-transformed measures used in the tests.

patients excluded from analysis, there was a nonsignificant difference in age at "dropout" between the 4 intervention groups (ANOVA,  $P = 0.06$ ). Of the patients included in the final analysis, 57% (76 of 133) had 2 colonoscopies, 23% (30 of 133) had 3, 11% (15 of 133) had 4, and 9% (12 of

133) had 5 to 8. No polyps were found in 15% of the colonoscopies; 57% of the colonoscopies went further than the sigmoid colon.

At baseline, the 4 intervention groups were well matched with regard to sex [ $\chi^2(3) = 6.2, P = 0.1$ ], age (ANOVA,

**Table 2.** Relative risks and 95% CIs from 12 univariate models estimating the effect of intervention by outcome measure

Outcome measures	No. of observations (no. of patients)	RS versus non-RS		Aspirin versus nonaspirin	
		Relative risk <sup>a</sup> (95% CI)	<i>P</i>	Relative risk (95% CI)	<i>P</i>
Total number of polyps in rectum and sigmoid	215 (116)	1.05 (0.73–1.49)	0.80	0.77 (0.54–1.10)	0.16
Crypt width	95 (58)	1.03 (0.93–1.13)	0.60	0.95 (–0.15 to 0.04)	0.28
Crypt length	95 (58)	1.01 (0.93–1.09)	0.86	1.08 (1.00–1.16)	0.04
Mean total CCP	95 (58)	1.28 (0.94–1.73)	0.12	1.37 (1.00–1.86)	0.05
Mean number of MIB1-positive cells <sup>b</sup>	116 (78)	1.02 (0.89–1.16)	0.82	0.99 (0.87–1.14)	0.93
Hemicrypt cells <sup>b,c</sup>	116 (78)	–0.82 (–5.05 to 3.42) <sup>c</sup>	0.71	3.67 (–0.55 to 7.90) <sup>c</sup>	0.09

NOTE: All models adjusted for first result and time on intervention (years).

<sup>a</sup>Estimated as the exponential coefficient of the intervention effect in the random effects model.

<sup>b</sup>Adjusted for calendar time to account for possible effect of differences in storage time of these samples before analysis; MIB1 is the antibody used in staining for Ki67.

<sup>c</sup>Variable not logged, coefficient not exponentiated.

$P = 0.90$ ), or any of the polyp and crypt parameters shown in Table 1. Younger patients tended to have more polyps at study entry (data not shown). At entry endoscopy, 41% of patients had 1 or more polyps removed; these patients tended to be older (mean age of 19 years) than those who did not have polyps removed (mean age of 16 years; 2-sided  $t$  test,  $P = 0.06$ ).

### Polyp assessments

After a median intervention period of 17 months (range 1–73 months), the risk of an increased polyp number in the rectum and sigmoid colon (primary endpoint) was not significantly reduced in either the aspirin or RS group (versus its counterpart group), with relative risks of 0.77 (aspirin; 95% CI, 0.54–1.10; versus nonaspirin) and 1.05 (RS; 95% CI, 0.73–1.49; versus non-RS group; Table 2). The diameter of the largest polyp (major secondary endpoint) detected by the endoscopist at the end of intervention tended to be smaller in the aspirin group ( $P = 0.05$  and 0.09 after adjusting for baseline measures; Table 3). The planned subgroup analyses of patients who elected to continue on study for more than 1 year found a significant reduction in the size of the largest polyp in the aspirin versus nonaspirin group ( $P = 0.02$ , adjusted for baseline; Table 3). We found an absence of polyps in the majority of our blinded review of rectal videos (both at baseline and during intervention), even though there were adenomas in the colon, so that most of the annual rectal videos in the 4 intervention categories received the same score as the baseline video. The risk of an increased total number of polyps in all examined segments of the colorectum (data not shown for this total number) was not reduced in either intervention group, with relative risks of 0.97 (aspirin; 95% CI, 0.65–1.43; versus nonaspirin) and 0.96 (RS; 95% CI, 0.65–1.42; versus non-RS).

### Crypt dimensions in macroscopically normal rectal mucosa

Relative risks of effects of intervention on crypt width and length are shown in Table 2. Mean crypt length decreased significantly over time on study in the 2 combined RS groups, compared with the 2 combined non-RS groups ( $P < 0.0001$  for interaction), in a model of the interaction between intervention and time (Fig. 2).

### Proliferation-state assessments (CCP, Ki67, PCNA)

Histologic examination of microdissected crypts from biopsies of apparently normal mucosa indicated increases in total CCP of 28% ( $P = 0.12$ ) in the RS versus non-RS group and 37% ( $P = 0.05$ ) in the aspirin versus nonaspirin group (Table 2). Ki67 results are also indicated in Table 2 (Number of MIB1-positive cells). Although both the microdissection-based method for CCP and the MIB1-staining method for Ki67 worked well during trial, the PCNA-based method proved to be unsuitable for a dispersed multicenter study such as CAPP1; the prolonged and variable immersion of samples in formalin due to differing durations of transport made PCNA recovery very problematic; and the PCNA results were considered to be too unreliable for analysis.

### Toxicity

No serious adverse effects were recorded. Some bloating was reported among RS takers. One participant in the aspirin/RS arm withdrew because of persistent nose bleeds. There were no other reports of bleeding or of cardiovascular or cerebrovascular events. The most common reason cited for withdrawal from study was difficulty in including starch in the habitual diet. There was no statistically significant difference between starch and its matching placebo or aspirin and its matching placebo in rates of withdrawal.

**Table 3.** Mean size of largest polyp by intervention group at baseline and at the end of intervention with aspirin (A) and/or RS

	Mean Size of largest polyp <sup>a</sup> (M)							
	Four intervention group comparison <sup>b</sup>				Aspirin comparison		Starch comparison	
	RSP/AP <sup>c</sup>	RS/AP	A/RSP	A/RS	Nonaspirin <sup>c</sup>	Aspirin	Non-RS <sup>c</sup>	RS
At baseline <sup>d</sup>	6.9 (31)	4.3 (20)	4.0 (25)	4.6 (19)	5.8 (51)	4.3 (44)	5.6 (56)	4.4 (39)
<i>P</i>		0.12	0.07	0.41		0.31		0.55
Final largest polyp size for all patients <sup>e</sup>	6.5 (31)	4.0 (20)	3.4 (25)	4.4 (19)	5.5 (51)	3.8 (44)	5.1 (56)	4.2 (39)
<i>P</i>		0.03	0.006	0.07		0.05		0.27
<i>P</i> adjusted for baseline		0.10	0.03	0.11		0.09		0.35
Final largest polyp size for patients treated for more than 1 year	6.5 (17)	4.6 (7)	2.9 (8)	3.1 (9)	6.0 (24)	3.0 (17)	5.4 (25)	3.8 (16)
<i>P</i>		0.26	0.03	0.02		0.01		0.17
<i>P</i> adjusted for baseline		0.42	0.09	0.03		0.02		0.19

Abbreviations: AP, aspirin placebo; RSP, RS placebo.

<sup>a</sup>Raw means presented, log-transformed measures used in tests.

<sup>b</sup>The *P* values are from linear regression for the following comparisons: RS/P versus P/P, A/P versus P/P, and A/RS versus P/P.

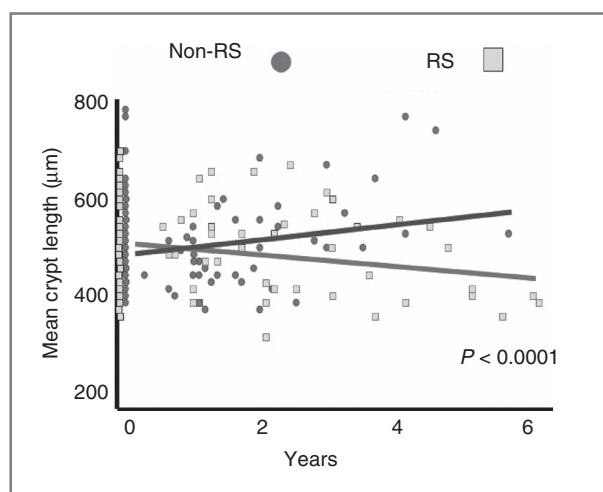
<sup>c</sup>Reference group in the linear regression models.

<sup>d</sup>Of 133 patients, 23 did not have polyps measured at baseline and 15 did not have polyps measured throughout the study. Numbers are based on patients who also have a result postbaseline.

<sup>e</sup>Numbers are based on patients who also have a baseline result.

## Discussion

This trial of aspirin (600 mg/d) and RS (30 g/d) in preventing adenoma occurrence in young people (mean age 18 years) with FAP is the largest clinical trial ever conducted in this setting. There was a nonsignificant trend



**Figure 2.** Mean length of microdissected crypts over time on study in patients of the RS group (RS plus aspirin placebo, RS plus aspirin) or of the non-RS group (aspirin plus RS placebo, aspirin placebo plus RS placebo). Crypts tended to lengthen with time on study for the non-RS group, whereas they shortened in the RS group (*P* for interaction < 0.0001).

of a reduced number of polyps in the rectum and sigmoid colon (primary endpoint) in the overall aspirin group (aspirin plus placebo and aspirin plus RS) versus the nonaspirin group at the end of intervention (Table 2). There also was evidence that the size of the largest polyp (secondary endpoint) was reduced in the overall aspirin versus the overall nonaspirin group (Table 3). Furthermore, among those treated for more than 1 year, the diameter of the largest polyp recorded in the aspirin group (3.0 mm) was only half that recorded in the nonaspirin group (6.0 mm; *P* = 0.02). Results of RS are discussed later.

Previous randomized trials (3–6,) support the view that long-term (1–3 years) aspirin ingestion (81–325 mg/d) results in a small but significant reduction in colonic adenoma formation in older persons with previous sporadic adenomatous polyps or CRC. In contrast, the CAPP2 study (which used interventions similar to those in this CAPP1 study) revealed no apparent beneficial impact on colorectal neoplasia (largely adenomatous polyps) of either aspirin at 600 mg or RS at 30 g/d in people with Lynch syndrome [hereditary nonpolyposis colorectal cancer (HNPCC)] after intervention for 29 months (24). Subsequent follow-up of participants in the CAPP2 study suggests an impact on subsequent cancers despite the lack of effect on adenoma formation (25). The modest efficacy of aspirin in intervention studies reported to date contrasts with the very substantial evidence from observational epidemiologic studies showing an approximately 50% reduction in risk of CRC among regular aspirin takers over



prolonged periods (26). These data suggest that aspirin may inhibit cancer in ways other than through inhibiting adenoma growth and development.

Several studies since the CAPP1 study was initiated lend support to the chosen interventions; the large cohort study European Prospective Investigation into Cancer and Nutrition (27, 28) showed a lower CRC risk in people with a higher dietary fiber intake. It is probable that a higher fiber intake is associated with a higher intake of RS. The NSAID celecoxib has been shown to inhibit adenoma development in patients with previous adenomas (29, 30), although concurrent low-dose aspirin use had no additional impact. A study involving one of our senior authors (R.K.S.P.) drew on early experience from CAPP1 and showed an inhibitory effect of celecoxib on adenoma development in FAP (31). One of the potential limitations of the CAPP1 study was that data on polyp numbers and sizes were collected by multiple endoscopists at several centers during a period of substantial improvements in endoscopy performance. These issues likely increased the variation in estimates of polyp burden and so reduced the ability to detect effects of the interventions. The study by Steinbach and colleagues (31) avoided these problems by using only 2 specialist endoscopy teams.

Assuming that more compliant patients would volunteer to remain on study after the first planned exit opportunity (at 1 year), we planned secondary analyses of patients who remained on study for more than 1 year. These analyses revealed a significantly beneficial effect of aspirin on polyp size (Table 3). The impact of aspirin in reducing the recorded size of the largest polyp is a finding of potential clinical importance because it would imply an effect on disease progression rather than initiation. There has been considerable focus on cyclooxygenase 2 (COX-2) inhibition as a mechanism for CRC prevention, but the COX inhibitory properties of aspirin are largely against COX-1. Aspirin has effects on other pathways of importance in tumorigenesis; however, Stark and colleagues (32), for example, showed that aspirin suppresses NF- $\kappa$ B-driven transcription and enhances apoptosis. We have shown *in vitro* inhibition of new blood vessel formation by physiologic concentrations of salicylate (33). Such effects might prevent small adenomas from progressing to malignancy; even a modest reduction in the volume of large polyps will reduce the number of cells exposed to subsequent genetic alterations leading to malignant transformation. The evidence of an aspirin impact on the progression of neoplasia is in keeping with protective effects against colon cancer more than a decade after aspirin therapy stopped in cardiovascular prevention trials of the 1980s; these findings were extended by recent analyses of cardiovascular trials of low-dose aspirin that revealed a similar, but smaller, delayed effect on CRC incidence and cancer death (34).

There was no detectable effect of RS on number of polyps in the rectum and sigmoid colon in the primary analysis.

Secondary findings indicated that longer-term use of RS was associated with a significant reduction in crypt length in normal-appearing mucosa. This discovery is of biological interest and may provide an independent indicator of compliance with the intervention. There was no evidence that RS supplementation had any adverse effect on adenoma risk. Epidemiologic studies suggest that higher-starch diets (richer in RS) are associated with reduced CRC risk, and there is strong evidence for antineoplastic effects of butyrate, a major short-chain fatty acid produced in the colon from bacterial degradation of RS. There have been reports, however, of increased neoplastic risk in rodents given very large RS doses (much greater than those used in human studies; ref. 17). Although we assessed both aspirin and RS for effects on the total number of polyps in all examined segments of the colorectum, multicenter and international variability in the extent of colon examined beyond the sigmoid segment made results of these analyses highly variable and difficult to interpret despite our rigorous efforts to account for this variability.

The CAPP1 study in isolation does not provide sufficient evidence to recommend long-term use of aspirin in FAP patients. It might be argued, however, that seen in the light of recent publications suggesting a long-term benefit in cancer prevention (34), aspirin is worthy of further evaluation in FAP patients who retain segments of the colorectum, particularly in the context of concern over the potential side effects of selective COX-2 inhibitors.

Although aspirin and RS had limited (or no) demonstrable effect in CAPP1 on polyp formation in FAP, it remains to be established whether these agents are effective in other settings. The CAPP2 study tested the effect of similar interventions in an older, genetically susceptible population with pathologic mutations in mismatch repair genes (Lynch syndrome or HNPCC). After 29 months of intervention, there was no significant effect of either intervention agent on colorectal neoplasia (largely adenomatous polyps). Recent results from long-term follow-up, however, suggest effects on carcinoma occurrence after cessation of the intervention. These results are consistent with the conclusion that the antineoplastic effects of aspirin intervention may take many years to appear.

The CAPP1 study successfully recruited and retained 113 participants with FAP, but many challenges have made this low-cost international approach based on FAP registries less attractive than was originally hoped. These challenges include the young age of the group under investigation; variable clinical practices in different countries meaning that colonoscopies were highly variable in terms of the extent of colonic investigation; and successful follow-up when working with so many different clinical groups, each of which could recruit only limited number of participants because of the low prevalence of the disease. Nevertheless, the genetically susceptible population must remain of primary interest given their capacity to provide a model system for disease processes usually too lengthy to be studied in the prevention setting.

## Appendix

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## Disclosure of Potential Conflicts of Interest

J. Burn is a consultant with Bayer Schering Pharma. Bayer, Leverkusen supplied Aspirin and placebo. In this trial the role of the funding sources was strictly financial. They had no input into the study design, data collection, analysis, and interpretation in writing of the report and in the decision to submit the paper for publication. The other authors did not disclose any potential conflicts of interest.

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## References

- Cuzick J, Otto F, Baron JA, Brown PH, Burn J, Greenwald P, et al. Aspirin and non-steroidal anti-inflammatory drugs for cancer prevention: an international consensus statement. *Lancet Oncol* 2009;10:501-7.
- Din FV, Theodoratou E, Farrington SM, Tenesa A, Barnetson RA, Cetnarskyj R, et al. Effect of aspirin and NSAIDs on risk and survival from colorectal cancer. *Gut* 2010;59:1670-9.
- Sandler RS, Halabi S, Baron JA, Budinger S, Paskett E, Keresztes R, et al. A randomized trial of aspirin to prevent colorectal adenomas in patients with previous colorectal cancer. *N Engl J Med* 2003;348:883-90.
- Baron JA, Cole BF, Sandler RS, Haile RW, Ahnen D, Bresalier R, et al. A randomized trial of aspirin to prevent colorectal adenomas. *N Engl J Med* 2003;348:891-9.
- Benamouzig R, Deyra J, Martin A, Girard B, Jullian E, Piednoir B, et al. Daily soluble aspirin and prevention of colorectal adenoma recurrence: one-year results of the APACC trial. *Gastroenterology* 2003;125:328-36.
- Logan RFA, Grainge MJ, Shepherd VC, Armitage NC, Muir KR. Aspirin and folic acid for the prevention of recurrent colorectal adenomas. *Gastroenterology* 2008;134:29-38.
- Young G, Le Leu RK. Resistant starch and colorectal cancer. *J AOAC Int* 2004;87:775-86.
- Cassidy A, Bingham SA, Cummings JH. Starch intake and colorectal cancer risk: an international comparison. *Br J Cancer* 1994;69:937-42.
- Asp NG, van Amelsvoort JM, Hautvast JG. Nutritional implications of resistant starch. *Nutr Res Rev* 1996;9:1-31.
- Scheppach W, Fabian C, Sachs M, Kasper H. Effect of starch malabsorption on fecal short-chain fatty acid excretion of man. *Scand J Gastroenterol* 1988;23:755-9.
- Hylla S, Gostner A, Dusel G, Anger H, Bartram HP, Christl SU, et al. Effects of resistant starch on the colon in healthy volunteers: possible implications for cancer prevention. *Am J Clin Nutr* 1998;67:136-42.
- Grubben MJ, van den Braak CC, Essenberg M, Olthof M, Tangerman A, Katan MB, et al. Effect of resistant starch on potential biomarkers for colonic cancer risk in patients with colonic adenomas. *Dig Dis Sci* 2001;46:750-6.
- D'Argenio G, Cosenza V, Delle Cave M, Iovino P, Delle Valle N, Lombardi G, et al. Butyrate enemas in experimental colitis and protection against large bowel cancer in a rat model. *Gastroenterology* 1996;110:1727-34.
- Hague A, Manning AM, Hanlon KA, Huschtscha LI, Hart D, Paraskeva C. Sodium butyrate induces apoptosis in human colonic tumour cell lines in a p53-independent pathway: Implications for the possible role of dietary fibre in the prevention of large-bowel cancer. *Int J Cancer* 1993;55:498-505.
- Heerdts B, Houston M, Augenlicht L. Potentiation by specific short-chain fatty acids of differentiation and apoptosis in human colonic carcinoma cell lines. *Cancer Res* 1994;54:3288-93.
- Siavoshian S, Segain JP, Komprobst M, Bonnet C, Cherbut C, Galmiche JP, et al. Butyrate and trichostatin A effects on the proliferation/differentiation of human intestinal epithelial cells: induction of cyclin D3 and p21 expression. *Gut* 2000;46:507-14.
- Mariadason JM, Corner GA, Augenlicht LH. Genetic reprogramming in pathways of colonic cell maturation induced by short chain fatty acids: comparison with trichostatin A, sulindac, and curcumin and implications for chemoprevention of colon cancer. *Cancer Res* 2000;60:4561-72.
- Williams EA, Coxhead JM, Mathers J. Anti-cancer effects of butyrate: use of micro-array technology to investigate mechanisms. *Proc Nutr Soc* 2003;62:107-15.
- van Munster IP, Tangerman A, Nagengast FM. Effect of resistant starch on colonic fermentation, bile acid metabolism, and mucosal proliferation. *Dig Dis Sci* 1994;39:834-42.
- Grubben MJ, van den Braak CC, Essenberg M, Olthof M, Tangerman A, Katan MB, et al. Effect of resistant starch on potential biomarkers for colonic cancer risk in patients with colonic adenomas: a controlled trial. *Dig Dis Sci* 2001;46:750-6.
- Goodlad RA, Levi S, Lee CY, Mandir N, Hodgson H, Wright NA. Morphometry and cell proliferation in endoscopic biopsies: evaluation of a technique. *Gastroenterology* 1991;101:1235-41.
- Mills SJ, Mathers JC, Chapman PD, Burn J, Gunn A. Colonic crypt cell proliferation state assessed by whole crypt microdissection in sporadic neoplasia and familial adenomatous polyposis. *Gut* 2001;48:41-6.
- Giannucci E, Egan KM, Hunter DJ, Stampfer MJ, Colditz GA, Willett WC, et al. Aspirin and the risk of colorectal cancer in women. *N Engl J Med* 1995;333:609-14.

24. Burn J, Bishop DT, Mecklin JP, Macrae F, Mösllein G, Olschwang S, et al. Effect of aspirin or resistant starch on colorectal neoplasia in the Lynch syndrome. *N Engl J Med* 2008;359:2567–78.
25. Burn J, Gerdes AM, Mecklin J-P, et al. Aspirin prevents cancer in Lynch syndrome. *Eur J Cancer Suppl* 2009;7:320–21.
26. U.S. Preventive Services Task Force. Routine aspirin or nonsteroidal anti-inflammatory drugs for the primary prevention of colorectal cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2007;146:361–4.
27. Bingham SA, Day NE, Luben R, Ferrari P, Slimani N, Norat T, et al. Dietary fibre in food and protection against colorectal cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC): an observational study. *Lancet* 2003;361:1496–501.
28. Bingham S. The fibre-folate debate in colo-rectal cancer. *Proc Nutr Soc* 2006;65:19–23.
29. Bertagnolli MM, Eagle CJ, Zauber AG, Redston M, Solomon SD, Kim K, et al. Celecoxib for the prevention of sporadic colorectal adenomas. *N Engl J Med* 2006;355:873–84.
30. Bertagnolli MM, Eagle CJ, Zauber AG, Redston M, Breazna A, Kim K, et al. Five-year efficacy and safety analysis of the Adenoma Prevention with Celecoxib Trial. *Cancer Prev Res* 2009;2:310–21.
31. Steinbach G, Lynch PM, Phillips RK, Wallace MH, Hawk E, Gordon GB, et al. The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. *N Engl J Med* 2000;342:1946–52.
32. Stark LA, Dunlop MG. Nucleolar sequestration of RelA (p65) regulates NF-kappaB-driven transcription and apoptosis. *Mol Cell Biol* 2005;25:5985–6004.
33. Borthwick GM, Johnson AS, Partington M, Burn J, Wilson R, Arthur HM. Therapeutic levels of aspirin and salicylate directly inhibit a model of angiogenesis through a Cox-independent mechanism 10.1096/fj.06–5987com. *FASEB J* 2006;20:2009–16.
34. Rothwell PM, Wilson M, Elwin C-E, Norrving B, Algra A, Warlow CP, et al. Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials. *Lancet* 2010;376:1741–50.

# Cancer Prevention Research

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