CLINICAL—ALIMENTARY TRACT

A Combination of Esomeprazole and Aspirin Reduces Tissue Concentrations of Prostaglandin E_2 in Patients With Barrett's Esophagus

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BACKGROUND& AIMS: Proton pump inhibitors and nonsteroidal anti-inflammatory drugs might prevent esophageal adenocarcinoma in patients with Barrett's esophagus (BE), but there are limited data from clinical trials to support this concept. We conducted a randomized, double-blind, placebo-controlled, phase 2 trial to assess the effects of the combination of aspirin (3 different doses) and esomeprazole on tissue concentrations of prostaglandin (PG) E_2 in patients with BE with no dysplasia or low-grade dysplasia. **METHODS:** Participants were recruited through the multicenter Cancer Prevention Network and randomly assigned to groups that were given 40 mg esomeprazole twice daily in combination with an aspirin placebo once daily (arm A; n = 30), with 81 mg aspirin once daily (arm B; n = 47), or with 325 mg aspirin once daily (arm C; n = 45) for 28 days. We collected esophageal biopsy specimens before and after the intervention period to determine the absolute change in mean concentration of PGE_2 (the primary end point). **RESULTS:** Based on data from 114 patients, baseline characteristics were similar among groups. The absolute mean tissue concentration of PGE_2 was reduced by 67.6 ± 229.68 pg/mL in arm A, 123.9 ± 284.0 pg/mL in arm B ($P = .10$ vs arm A), and 174.9 ± 263.62 pg/mL in arm C ($P = .02$ vs arm A). **CONCLUSIONS: In combination with esomeprazole, short-term administration of higher doses of aspirin, but not lower doses or no aspirin, significantly reduced tissue concentrations of PGE_2 in patients with BE with either no dysplasia or low-grade dysplasia. These data support further evaluation of higher doses of aspirin and esomeprazole to prevent esophageal adenocarcinoma in these patients.** Clinical trial registration number NCT00474903.

Keywords: Esophageal Cancer; NSAIDs; Inflammation; Esophagus.

Barrett's esophagus (BE) is an acquired condition that affects approximately 1 in 20 adults in the United States.[1] Esophageal adenocarcinoma, which has become increasingly common in developed countries over the past 4 decades, is strongly associated with BE.[2] Based on currently available data, the annual incidence of esophageal adenocarcinoma in patients with BE is estimated to range from approximately 0.3% to 0.5%.[3–5] Unfortunately, the 5-year survival rate for patients with esophageal adenocarcinoma remains dismal (approximately 17%).[6]

Current strategies for improving clinical outcomes among patients with esophageal adenocarcinoma are largely focused on identifying malignant disease at an early, potentially curable stage. This could be accomplished through widespread adoption of endoscopic screening and/or surveillance programs. However, existing early detection guidelines endorsed by major subspecialty societies are inherently expensive, with a relatively limited evidence base.[5] Thus, further evaluation of novel approaches to esophageal cancer risk reduction among patients with BE is urgently needed.

Extensive preclinical data suggest that nonsteroidal anti-inflammatory drugs (NSAIDs), particularly aspirin, may play a protective role against the development of esophageal adenocarcinoma by inhibiting the cyclooxygenase 1 and 2 (COX-1 and COX-2) enzymes, which regulate production of prostaglandin (PG) E_2.[7–12] Up-regulation of PGE_2 has been associated with resistance to apoptosis, increased angiogenesis, and enhanced invasion in Barrett's mucosa and other gastrointestinal neoplasia, thereby providing a strong biologic rationale for assessing modulation of PGE_2 as a surrogate end point biomarker for phase 2 trials.[7–12]

Abbreviations used in this paper: BE, Barrett's esophagus; COX, cyclooxygenase; PPI, proton pump inhibitor.

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One proposed mechanism for BE-associated carcinogenesis is acid and/or bile salt–induced activation of COX-2 (with accompanying high levels of PGE_2 production), which would support the chemopreventive potential of a proton pump inhibitor (PPI) given in combination with aspirin. However, to date, the chemopreventive potential of PPI and/or NSAID therapy for BE-associated esophageal adenocarcinoma remains inconclusive,[5] and the combination approach has not been evaluated in a randomized clinical trial. For this multicenter, double-blind, placebo-controlled, phase 2 clinical trial, we hypothesized that a PPI plus higher-dose aspirin would be more effective for down-regulating PGE_2 than either a PPI alone or a PPI plus lower-dose aspirin in patients with BE.

Patients and Methods

All aspects of the study protocol were reviewed and approved by the appropriate institutional review board for human research at each participating site. Mayo Clinic in Rochester, Minnesota, served as the coordinating research base. The Data and Safety Monitoring Board of the Mayo Clinic Cancer Center reviewed safety data every 6 months and efficacy data within 6 months of the planned interim analysis.

General Overview

Participants were recruited at 12 Cancer Prevention Network member organizations: Cleveland Clinic in Cleveland, Ohio; Fox Chase Cancer Center in Philadelphia, Pennsylvania; Hines Veterans Administration in Hines, Illinois; Kaiser Permanente Medical Group in San Francisco, California; Kansas City VA Medical Center in Kansas City, Missouri; Massachusetts General Hospital in Boston, Massachusetts; Mayo Clinic in Scottsdale, Arizona, Jacksonville, Florida, and Rochester, Minnesota; St. Michael's Hospital in Toronto, Ontario, Canada; University Hospitals Case Medical Center in Cleveland, Ohio; and the University of Puerto Rico Cancer Center in San Juan, Puerto Rico. In total, 120 eligible participants were enrolled between May 2007 and January 2011.

Study Participants

The target population included adult patients (18 years or older) with histologically confirmed BE, defined as the presence of specialized columnar epithelium anywhere in the tubular esophagus with ≥2 cm of circumferential involvement and no evidence of high-grade dysplasia or cancer based on both clinical surveillance and additional research biopsy specimens. Participants were required to have documented intestinal metaplasia with goblet cells in ≥4 of 8 research biopsy samples (with ≥50% intestinal metaplasia) and could not have used aspirin, NSAIDs, or selective COX-2 inhibitors for ≥7 days during the 3-month period preceding a 28-day run-in phase. Women of childbearing potential were required to document a negative pregnancy test result before enrollment. General exclusion criteria were inability to abstain from aspirin, NSAID, or selective COX-2 inhibitor therapy for the duration of the trial; current or planned use of anticoagulants; prior fundoplication, bariatric surgery, or any other major upper gastrointestinal surgery (except cholecystectomy); history of confirmed esophageal high-grade dysplasia or cancer; history of cancer diagnosis ≤24 months (except nonmelanoma skin cancer or cervical carcinoma in situ) or cancer treatment ≤12 months (except hormone therapy) before run-in; receipt of other investigational agents ≤3 months before run-in (except compounds such as multivitamins, topically applied skin creams, and so on with no known interaction with the study agents); history of allergic reactions attributed to compounds of similar chemical or biologic composition to the study agents or rescue medication; history of endoscopically or radiographically diagnosed peptic ulcer disease (bleeding or nonbleeding); pregnant or lactating women; or comorbidities that might limit adherence to the study protocol.

Baseline Evaluation and Run-in Phase

Following informed consent, willing participants completed a focused interview, brief questionnaire, physical examination, and peripheral blood draw for eligibility testing. Participants who met enrollment criteria entered a 28-day run-in phase, which included self-administration of esomeprazole 40 mg twice daily (ie, before breakfast and dinner). Eighty percent adherence with the run-in agent, based on an agent diary and follow-up telephone call at 14 (±3) days, was required for advancement to randomization. A repeat blood draw and baseline endoscopy were scheduled for 28 (±3) days after initiating the run-in phase.

Preintervention Endoscopy

The preintervention endoscopy examination was performed with a therapeutic endoscope (Olympus GIF-1T140 videoendoscope or equivalent; Olympus America, Center Valley, PA). Endoscopic landmarks, including the diaphragmatic hiatus, end of the tubular esophagus as marked by the proximal margin of gastric folds, and new squamocolumnar junction, were recorded. The extent of the circumferentially involved BE segment was determined using the Prague classification system.[13] Hiatal hernia size was measured by linear distance between the end of the tubular esophagus and the diaphragmatic hiatus. Short-segment BE was defined as specialized columnar epithelium lining <3 cm of the distal esophagus, whereas long-segment BE was defined as specialized columnar epithelium lining ≥3 cm of the distal esophagus.

Four-quadrant endoscopic surveillance biopsy specimens were obtained using Boston Scientific (Natick, MA) Radial Jaw 3 forceps at 2-cm intervals along the entire length of the Barrett's epithelium. Additional biopsy specimens were obtained from any ulcer, erosion, plaque, nodule, stricture, or other luminal irregularity. All surveillance biopsy specimens were assessed by local pathology review. Endoscopic research biopsy specimens (up to 8) were obtained with the same forceps from a 1-cm zone of Barrett's epithelium 1–2 cm above the level of the lower esophageal sphincter, just above the proximal margin of the gastric folds. Research biopsy specimens were washed for 5 seconds in phosphate-buffered saline and divided into 2 aliquots, which were snap frozen in liquid nitrogen or placed in 10% neutral buffered formalin at room temperature, respectively. All formalin-fixed research biopsy specimens were assessed by the study pathologist (T.C.S.). If high-grade dysplasia or cancer was detected in any research biopsy specimen, 2 additional gastrointestinal pathologists at Mayo Clinic in Rochester, Minnesota, were consulted. If the consensus diagnosis (including input from the local pathologist) was high-grade dysplasia or cancer, the participant was classified as a screen failure.

Findings of ulcer, erosion, plaque, nodule, stricture, or other luminal irregularity within the Barrett's segment; erosive esophagitis greater than Los Angeles class A; high-grade dysplasia or cancer; or inadequate Barrett's mucosa to satisfy the study end points (defined as <4 of 8 research samples with ≥50% intesti-

nal metaplasia by central pathology review) excluded further study participation.

Intervention Assignments and On-Study Monitoring

Willing, eligible participants were randomly assigned to receive a 28-day intervention with one of 3 study agent combinations (using a 1:1.5:1.5 schema to permit increased access to an active aspirin intervention): arm A (aspirin placebo + PPI), aspirin 81 mg placebo every day + aspirin 325 mg placebo every day + esomeprazole 40 mg twice daily (n = 30); arm B (lower-dose aspirin + PPI), aspirin 81 mg every day + aspirin 325 mg placebo every day + esomeprazole 40 mg twice daily (n = 47); and arm C (higher-dose aspirin + PPI), aspirin 81 mg placebo every day + aspirin 325 mg every day + esomeprazole 40 mg twice daily (n = 45). Esomeprazole was self-administered once in the morning and once in the evening, at least 1 hour before a meal. Aspirin or aspirin placebo (indistinguishable from the activate agent) was administered once in the morning with a meal. Adherence was defined as ≥80% ingestion of the protocol-defined doses. Antacid tablets (200 mg aluminum hydroxide, 200 mg magnesium hydroxide, and 25 mg simethicone per each tablet) were provided as rescue medication for acute symptoms of gastroesophageal reflux disease. Use of >12 antacid tablets per day and/or for >14 days was noted as a protocol deviation. Adverse events were classified and graded using NCI Common Toxicity Criteria, version 3.0 (available at www.ctep.cancer.gov). Attribution of agent-related adverse events was performed by the designated medical monitor (G.D.Z.), who was blinded to the intervention assignments.

Postintervention Evaluation

Participants returned at 28 (±3) days after randomization to assess adherence, concomitant medication use, and adverse events. A focused physical examination and peripheral blood draw were also performed. Postintervention endoscopy, research biopsies, and tissue handling were performed according to the standardized protocol applied at baseline.

Tissue Biomarkers

Research biopsy samples were shipped to Mayo Clinic Rochester for biomarker analyses. Tissue PGE_2 levels were assessed by a standardized method using enzyme immunoassay (Supplementary Materials and Methods).[12] The intra-assay/interassay coefficient of variance is <10%, with a specificity of 100% and a limit of detection of 15 pg/mL. PGE_2 levels were corrected for tissue weight and represented as nanograms per gram of tissue. Samples were run in 2 batches, with the preintervention and postintervention biopsy specimens obtained from a given participant run on the same plate.

Statistical Analyses

The primary end point was defined as absolute change in mean tissue PGE_2 concentration (postintervention mean PGE_2 level from up to 3 biopsy samples minus baseline mean PGE_2 level from up to 3 biopsy samples). Study participants were considered evaluable for the primary end point if they met eligibility criteria, and PGE_2 data were available from both the preintervention and postintervention evaluations. The 1:1.5:1.5 randomization schema was based on the Pocock–Simon dynamic allocation procedure,[14] which stratified by sex, length of Barrett's segment (<5 cm vs ≥5 cm of circumferential involvement), baseline dysplasia status (none versus low-grade or indefinite), and participating site. Assuming equal SDs of 50 pg/mL for all 3 intervention arms, the sample sizes were determined to be n = 38, n = 57, and n = 57 in the aspirin placebo + PPI, lower-dose aspirin + PPI, and higher-dose aspirin + PPI arms, respectively (N = 152 total). These sample sizes yielded 80% power to detect a difference of at least two-thirds of an SD in the mean PGE_2 concentration comparing each active aspirin arm with PPI alone, with a 2-sided α of 0.025 (adjusted for multiple comparisons). At least a two-thirds change in the SD was selected as the minimum threshold for a clinically significant change because it was consistent with the goals for end point modulation of phase 2 chemoprevention trials, and this value represented the consensus goal defined by the investigative team in conjunction with the study sponsor (Division of Cancer Prevention, National Cancer Institute) to strike a reasonable balance between subject recruitment and data interpretation.

An unblinded preplanned variability assessment (without halting accrual) in the first 40 participants was performed. This analysis showed slightly higher than expected variation in the PGE_2 values, where the SD of the absolute change in PGE_2 values within each arm varied from a low of 63 pg/mL to a high of 112 pg/mL. Despite the increased variability observed, we retained the original sample size due to the slower than anticipated accrual rate. In addition, due to concerns of slow accrual, we added interim futility and efficacy analyses so that the study could potentially close early at the time of the interim analyses. This interim analysis was planned after 77 participants were evaluable for PGE_2 (n = 19, n = 29, and n = 29 in the aspirin placebo + PPI, lower-dose aspirin + PPI, and higher-dose aspirin + PPI arms), during which each active aspirin arm was compared with the aspirin placebo arm using a 2-sample *t* test (or nonparametric equivalent). Interim efficacy and futility boundaries were developed based on the O'Brien–Fleming method from the Lan–DeMets family[15] using EAST software developed by Cytel.[16] Each pairwise comparison decision was considered individually. If the 2-sided *P* value was found to be <.0008 in favor of the active treatment arm(s), then significant efficacy would be declared. If the 2-sided *P* value was >.634, then significant futility would be declared. The α and β spent at the interim look were 0.001 and 0.036, respectively, and at the final analysis, a *P* value <.0247 for either pairwise comparison in favor of the active treatment arm(s) would reject the null hypothesis and indicate that the active aspirin arm(s) was effective compared with the aspirin placebo arm, as per standard convention.[15]

Secondary end points included comparison of the percent change in PGE_2, baseline participant characteristics, agent adherence, and adverse events between intervention arms. Summary statistics and frequency tables were used to describe baseline subject characteristics, agent adherence, and adverse events. For participants who received more than the expected dose per protocol for any of the agents, we capped the percentage adherence numbers at 100%. Fisher exact test and Kruskal–Wallis test were used to test for associations between intervention arms and categorical and continuous data, respectively. Absolute and percent changes in PGE_2 were compared within each arm by the Wilcoxon signed rank procedure. The between-arm comparisons were performed using the Wilcoxon rank sum test. All statistical tests were performed 2 sided unless otherwise noted using SAS version 9.2 (SAS Institute, Inc, Cary, NC).

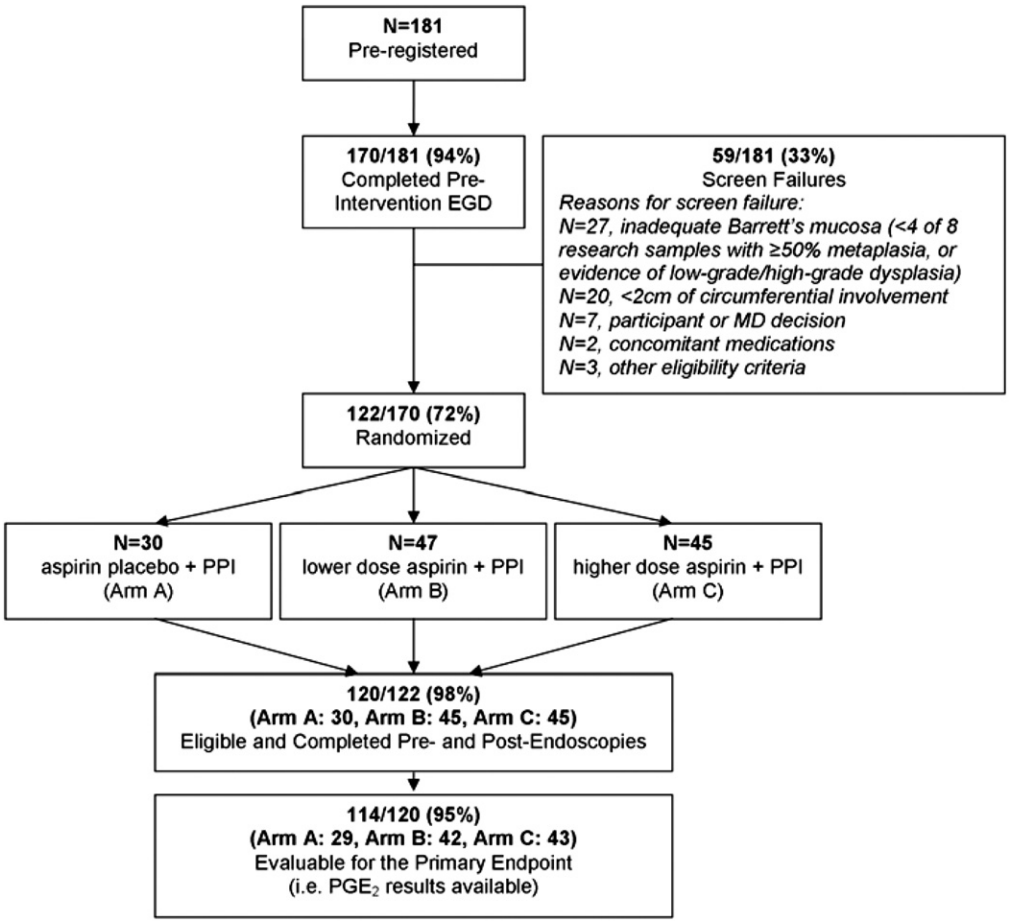

Figure 1. CONSORT diagram showing the number of participants who were preregistered, the number of screen failures, and the number of participants who were randomized and evaluable for the primary end point.

Results

Cohort Description

A CONSORT overview of participant recruitment is shown in Figure 1. A total of 181 unique participants provided informed consent and were preregistered for the baseline evaluation. A total of 59 participants were deemed screen failures. Reasons for screen failure included inadequate Barrett's mucosa (n = 27), <2 cm of circumferential BE (n = 20), participant or physician decision (n = 7), nonallowed concomitant medications (n = 2), and failure to meet other eligibility criteria (n = 3). Registered, ineligible participants, and intervention cohort participants were similar with respect to age, sex, smoking history, prior NSAID use, and lower-dose aspirin use ($P \geq .32$) (Table 1).

Because accrual was slower than anticipated, randomization was closed early before reaching the a priori accrual goal of 152 participants. In total, 122 participants were randomized. Two participants were withdrawn after randomization due to an inadequate number of surveillance biopsy specimens and a finding of high-grade dysplasia at the preintervention endoscopy examination, respectively. With respect to race/ethnicity, 118 of 120 randomized participants (98%) were self-identified as white (race status was missing/unknown for 2 additional participants), whereas 109 of 120 (91%) and 6 of 120 (5%) were self-identified as non-Hispanic and Hispanic/Latino, respectively (ethnicity status was missing/unknown for 5 additional participants). Within the randomized cohort, 6 participants were not evaluable for PGE_2 analyses because of sample-related issues (eg, improper temperature, lost or delayed samples), leaving 114 evaluable participants for the primary end point.

Intervention Arms, Adverse Events, and Agent Adherence

By design, intervention arms were evenly balanced with respect to sex ($P = .95$), length of BE ($P = .95$), and dysplasia status (no dysplasia vs low-grade dysplasia) at the preintervention evaluation ($P = 1.00$). Other baseline variables were similar between the intervention arms except for smoking history ($P = .005$) (Table 2).

Adverse events were reported in 26 of 120 trial participants (22%) after starting the assigned study intervention. Adverse event rates were similar across intervention arms (Table 2). Hiatal hernia erosions developed in one participant receiving aspirin placebo and one participant treated with lower-dose aspirin. Antral erosions developed in one participant in the aspirin placebo arm. One participant treated with higher-dose aspirin experienced an erosion at the gastroesophageal junction. No participants in any of the arms developed an ulcer. Agent adherence was

Table 1. Baseline Demographics by Trial Participation Status

	All registered (N = 181)	Ineligible or withdrawn (n = 61)	Intervention cohort (n = 120)	*P* value
Age (*y*)				.80[a]
Mean (SD)	59.9 (10.9)	60.4 (10.2)	59.7 (11.2)	
Median	60	61	60	
Range	32–86	35–84	32–86	
Sex, n (%)				1.00[b]
Female	28 (15.5)	9 (14.8)	19 (15.8)	
Male	153 (84.5)	52 (85.3)	101 (84.2)	
Smoking history, n (%)[c]				.32[b]
Current smoker	22 (12.2)	10 (16.7)	12 (10.0)	
Never smoked	80 (44.4)	23 (38.3)	57 (47.5)	
Quit/former smoker	78 (43.3)	27 (45.0)	51 (42.5)	
Prior history of chronic NSAID use, n (%)[c]				.62[b]
No	160 (88.9)	52 (86.7)	108 (90.0)	
Yes	20 (11.1)	8 (13.3)	12 (10.0)	
Prior history of lower-dose aspirin use, n (%)[c]				.47[b]
No	135 (75.0)	43 (71.7)	92 (76.7)	
Yes	45 (25.0)	17 (28.3)	28 (23.3)	

[a]Kruskal–Wallis test.
[b]Fisher exact test.
[c]Missing data from 1 participant who had unknown values (this participant was excluded from calculation of the *P* value).

excellent, with all participants receiving the majority of the assigned study doses, and was similar across the randomization arms ($P \geq .57$) (Table 2).

Tissue PGE_2 Concentration

The primary objective was to compare preintervention and postintervention biopsy specimens within and between treatment arms based on PGE_2 concentrations in Barrett's mucosa. An interim analysis was performed after 77 participants were randomized (n = 19, n = 29, and n = 29 in the aspirin placebo, lower-dose aspirin, and higher-dose aspirin arms, respectively). The data were highly skewed, so the Wilcoxon rank sum test was used to compare the active aspirin arms with the aspirin placebo arm. The 2-sided *P* value was .0121 for the higher-dose aspirin arm versus aspirin placebo, which did not meet the interim analysis criteria to stop the trial for improved efficacy (2-sided *P* value <.0008 required) or futility (2-sided *P* value >.634 required). The 2-sided *P* value was .0550 for the lower-dose aspirin arm versus aspirin placebo, which did not meet the interim analysis criteria to stop the trial for improved efficacy (2-sided *P* value <.0008 required) or futility (2-sided *P* value >.634 required). As such, the study continued on until it was decided to close early due to slow accrual.

Of the 120 participants in the intervention cohort, 114 were evaluable for the primary end point (n = 29, n = 42, and n = 43 in the aspirin placebo + PPI, lower-dose aspirin + PPI, and higher-dose aspirin + PPI arms, respectively). All evaluable participants had at least 2 PGE_2 values available from the preintervention and postintervention endoscopy examinations (94% had 3 PGE_2 values). There was no statistically significant difference between the preintervention PGE_2 values across the 3 intervention arms ($P = .27$), but there was a statistically significant difference for the postintervention PGE_2 values ($P < .0001$) (Table 3). Both the lower-dose aspirin and higher-dose aspirin arms showed significant decreases in PGE_2 from baseline for both absolute and percent change (signed rank *P* value ≤.0004), whereas the aspirin placebo arm showed no significant change from baseline for absolute and percent change in PGE_2 values ($P \geq .27$). Based on the primary end point (absolute change in PGE_2), the higher-dose aspirin + PPI intervention resulted in a significant decrease in PGE_2 values as compared with the aspirin placebo + PPI arm ($P = .02$) (Table 3 and Figure 2). Higher-dose aspirin + PPI was also associated with a significant decrease in the percent change in PGE_2 values (secondary end point) compared with aspirin placebo + PPI ($P < .0001$) (Table 3 and Figure 3). Lower-dose aspirin + PPI versus aspirin placebo + PPI showed weaker results for absolute change ($P = .10$) (Table 3 and Figure 2), although there was still a trend toward a decrease in PGE_2 values. Based on percent change in PGE_2, lower-dose aspirin + PPI showed a significant decrease in the PGE_2 values as compared with aspirin placebo + PPI ($P = .0007$) (Table 3 and Figure 3). No significant difference was observed between the 2 active aspirin arms for absolute ($P = .26$) or percent change ($P = .45$) in PGE_2 values. The primary end point analyses were not appreciably altered after excluding outliers (data not shown).

Discussion

To our knowledge, we report the largest prospective chemoprevention trial in patients with BE conducted in North America. Data from this clinical trial provide the first demonstration of a statistically significant effect from the combination of esomeprazole 40 mg twice daily and aspirin 325 mg every day for 28 days on tissue PGE_2

Table 2. Baseline Demographics, Intervention Adherence, and Adverse Events by Intervention Arm

	Arm A (aspirin placebo + PPI) (n = 30)	Arm B (lower-dose aspirin + PPI) (n = 45)	Arm C (higher-dose aspirin + PPI) (n = 45)	Overall (N = 120)	*P* value
Age					.93[a]
Mean (SD)	60.1 (11.3)	59.7 (11.7)	59.3 (11.0)	59.7 (11.2)	
Median	61	59	59	60	
Range	(32–86)	(34–81)	(35–82)	(32–86)	
Sex, n (%)					.95[b]
Male	26 (86.7)	37 (82.2)	38 (84.4)	101 (84.2)	
Female	4 (13.3)	8 (17.8)	7 (15.6)	19 (15.8)	
ECOG performance score, n (%)					1.00[b]
0	29 (96.7)	44 (97.8)	44 (97.8)	117 (97.5)	
1	1 (3.3)	1 (2.2)	1 (2.2)	3 (2.5)	
Length of the Barrett's segment, n (%)					.95[b]
<5 cm of circumferential involvement	15 (50.0)	21 (46.7)	21 (46.7)	57 (47.5)	
≥5 cm of circumferential involvement	15 (50.0)	24 (53.3)	24 (53.3)	63 (52.5)	
Dysplasia status at preintervention, n (%)					1.00[b]
No dysplasia	26 (86.7)	38 (84.4)	38 (84.4)	102 (85.0)	
Low grade or indefinite for dysplasia	4 (13.3)	7 (15.6)	7 (15.6)	18 (15.0)	
Smoking history, n (%)					.005[b]
Current smoker	3 (10.0)	3 (6.7)	6 (13.3)	12 (10.0)	
Never smoked	9 (30.0)	31 (68.9)	17 (37.8)	57 (47.5)	
Quit/former smoker	18 (60.0)	11 (24.4)	22 (48.9)	51 (42.5)	
Prior history of chronic NSAID use, n (%)					.40[b]
No	29 (96.7)	40 (88.9)	39 (86.7)	108 (90.0)	
Yes	1 (3.3)	5 (11.1)	6 (13.3)	12 (10.0)	
Prior history of lower-dose aspirin use, n (%)					1.00[b]
No	23 (76.7)	35 (77.8)	34 (75.6)	92 (76.7)	
Yes	7 (23.3)	10 (22.2)	11 (24.4)	28 (23.3)	
Intervention adherence					
Esomeprazole					
No. of pills taken, median (range)	56 (37–64)	54 (44–69)	56 (37–75)	55 (37–75)	.63[a]
Adherence[c] (%), median (range)	100 (71–100)	100 (79–100)	100 (71–100)	100 (71–100)	.57[a]
Mean (SD)	98 (5.5)	99 (4.7)	98 (5.5)	98 (5.2)	
Aspirin/placebo 81 mg					
No. of pills taken, median (range)	28 (25–32)	27 (23–35)	28 (17–38)	28 (17–38)	.48[a]
Adherence[c] (%), median (range)	100 (84–100)	100 (84–100)	100 (61–100)	100 (61–100)	.99[a]
Mean (SD)	99 (3.0)	99 (2.7)	99 (6.0)	99 (4.3)	
Aspirin/placebo 325 mg					
No. of pills taken, median (range)	28 (25–32)	27 (23–35)	28 (23–38)	28 (23–38)	.61[a]
Compliance[c] (%), median (range)	100 (96–100)	100 (84–100)	100 (93–100)	100 (84–100)	.79[a]
Mean (SD)	100 (0.9)	99 (2.6)	99 (1.6)	99 (2.0)	
Treatment-emergent adverse events					
Any adverse event regardless of treatment relation or grade	5 (16.7)	8 (17.8)	13 (28.9)	26 (21.7)	.36[b]
Adverse events related to study medication	5 (16.7)	6 (13.3)	3 (6.7)	14 (11.7)	.39[b]
Grade 1 adverse events	6 (20.0)	7 (15.6)	10 (22.2)	23 (19.2)	.77[b]
Grade 2 adverse events	2 (6.7)	1 (2.2)	5 (11.1)	8 (6.7)	.27[b]
Grade 3 adverse events	0 (0.0)	1 (2.2)	1 (2.2)	2 (1.7)	1.00[b]

[a]Kruskal–Wallis test.
[b]Fisher exact test.
[c]Percent compliance = 100 · ([Total Number of Pills Taken]/([Number of Days Pills Taken] · [Scheduled Number of Pills per Day]).

values in participants with BE, as compared with esomeprazole 40 mg twice daily without active aspirin. Although lower-dose aspirin (81 mg every day) + PPI did not significantly alter tissue PGE_2 concentration, this finding was likely influenced by our relatively small sample size. Of note, a significant difference relative to the aspirin placebo + PPI group was observed when the percent decrease in PGE_2 levels was compared. These results support further evaluation of 325 mg aspirin administered together with twice-daily esomeprazole as a potential chemoprevention strategy for patients with BE in larger, more definitive phase 3 trials.

Esophageal adenocarcinoma is a lethal disease with a 5-year survival rate of approximately 17%.[6] Survival is stage dependent, and early spread before the onset of symptoms is characteristic of this tumor. Currently, the best hope for improved survival of patients with esophageal adenocarcinoma is detection of cancer at an early and

Table 3. PGE_2 Summary in All 114 Evaluable Participants

PGE_2 measurement	Arm A (aspirin placebo + PPI) (n = 29)	Arm B (lower-dose aspirin + PPI) (n = 42)	Arm C (higher-dose aspirin + PPI) (n = 43)
Preevaluation[a]			
Mean (SD)	210.9 (244.18)	178.3 (249.4)	204.2 (265.53)
Median (range)	149.9 (12.5 to 1024.6)	63.4 (2.0 to 1019.1)	110.8 (2.4 to 1140.2)
Postevaluation[a]			
Mean (SD)	143.3 (129.51)	54.3 (148.9)	29.3 (35.33)
Median (range)	92.3 (12.9 to 518.0)	13.6 (1.5 to 916.7)	17.0 (1.6 to 182.3)
Absolute change			
Mean (SD)	−67.6 (229.68)	−123.9 (284.0)	−174.9 (263.62)
Median (range)	0.0 (−745.2 to 454.7)	−47.3 (−976.6 to 789.0)	−93.1 (−1113.6 to 75.3)
Within-arm signed rank *P* value	.27	<.0001	<.0001
Wilcoxon rank sum *P* value[b]		vs aspirin placebo *P* = .0955[b]	vs aspirin placebo *P* = .0204[b]
		lower-dose vs higher-dose aspirin *P* = .26	
Percent change			
Mean (SD)	45.0 (183.03)	−24.5 (143.1)	−58.9 (63.05)
Median (range)	0.0 (−86.8 to 717.8)	−77.6 (−98.2 to 618.1)	−83.6 (−98.7 to 242.1)
Within-arm signed rank *P* value	.68	.0004	<.0001
Wilcoxon rank sum *P* value	—	vs aspirin placebo *P* = .0007	vs aspirin placebo *P* < .0001
		lower-dose vs higher-dose aspirin *P* = .45	

NOTE. All values are expressed as picograms per milliliter unless otherwise noted.
[a]PGE_2 values were similar at pre-evaluation (*P* = .27) and significantly different at postevaluation (*P* < .0001).
[b]The nominal significance level was .0247 after adjusting for the interim analysis and multiple comparisons.

potentially curable stage. To accomplish this, current strategies have focused on identifying more patients at risk, namely those with BE, in conjunction with widespread endoscopic surveillance of patients with known BE. Both strategies, however, are inherently flawed, expensive, and impractical. Furthermore, there are no prospective clinical data to confirm either approach is effective. Although observational studies have shown surveillance to be associated with cancer down-staging with improved 5-year survival, the relevance of these studies is markedly limited by the risk of lead-time bias.[17,18] In this context, alternative intervention strategies such as chemopreven-

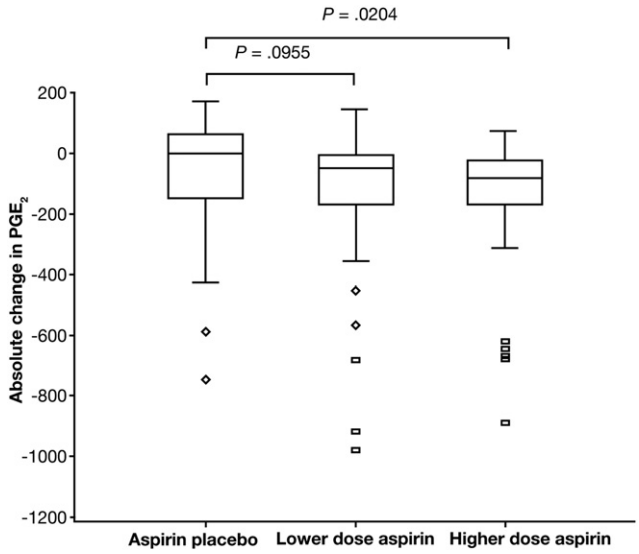

Figure 2. Box plots for the absolute change in PGE_2 by intervention arm. After adjusting for the interim analysis and multiple comparisons, the nominal significance level was .0247. As shown, the higher-dose aspirin + PPI intervention resulted in a significant decrease in PGE_2 values as compared with aspirin placebo + PPI (*P* = .020), whereas the lower-dose aspirin + PPI intervention did not differ significantly from aspirin placebo + PPI (*P* = .096).

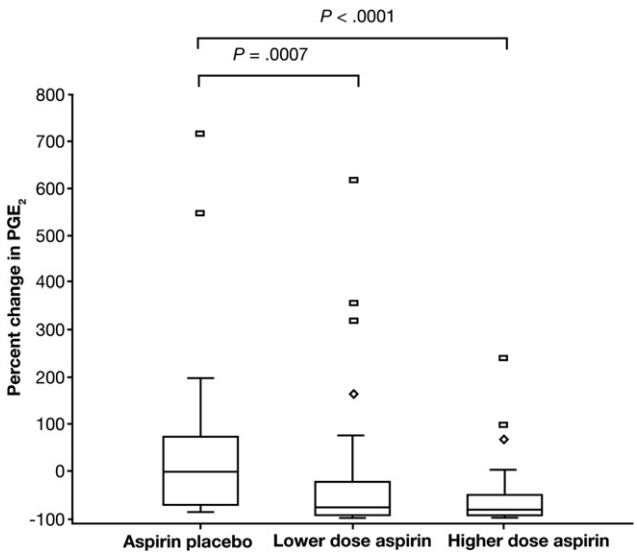

Figure 3. Box plots for the percent change in PGE_2 by intervention arm. As shown, the higher-dose aspirin + PPI and lower-dose aspirin + PPI interventions resulted in significant decreases in PGE_2 values as compared with aspirin placebo + PPI (*P* < .001).

tion are worthy of consideration, specifically during the early stages of neoplastic transformation.[5]

It is widely accepted that chronic injury and resulting inflammation play a major role in the development of several cancers, including esophageal adenocarcinoma.[9,19–23] The catalysis of arachidonic acid to PGE_2 by COX enzymes is believed to be critically involved in injury- or inflammation-induced esophageal carcinogenesis. Low pH, as well as exposure to caustic bile salts, can induce COX-2 expression in both ex vivo culture models of BE and in esophageal adenocarcinoma cell lines.[24,25] COX-2 expression increases concomitantly with neoplastic progression in BE, thereby supporting the association of the arachidonic acid pathway with the development of esophageal adenocarcinoma.[26] Moreover, higher PGE_2 levels have been reported in Barrett's epithelium compared with normal squamous mucosa.[27] PGE_2 induces the proliferation of Barrett's epithelial cells, whereas PGE_2 inhibition reduces their proliferation.[19] In addition, PGE_2 is known to diminish tumor surveillance by inhibiting natural killer cell activity.[28] Recent animal studies further show that inhibition of PGE_2 production with the use of selective and nonselective COX-2 inhibitors can decrease the rate of esophageal adenocarcinoma development.[19] Thus, chronic induction of PGE_2 appears to stimulate esophageal carcinogenesis through multiple mechanisms.

A number of candidate chemoprevention agents have been proposed for patients with BE, including PPIs, selective and nonselective COX inhibitors (including aspirin), lyophilized black raspberries, antioxidants, green tea, retinoids, ursodeoxycholic acid, statins, and curcumin.[10,29–31] Most attention has been directed toward the use of aspirin and other NSAIDs, which appear to lower the risk of esophageal cancer by favorably affecting COX-related pathways that are up-regulated by excess exposure to acid and/or bile salts. Although observational studies suggest that PPI therapy is associated with a decreased risk for the development of high-grade dysplasia and adenocarcinoma, the chemopreventive potential of PPIs, by suppressing acid and bile salt reflux, appears to be marginal when used as monotherapy.[32–34] There are a variety of possible explanations for this marginal effect, including the inability of PPIs to completely eliminate acid/bile salt reflux or activation of gastrin-cholecystokinin-COX-2–mediated procarcinogenic signaling pathways. It is therefore logical to use a PPI agent in combination with NSAIDs to determine if the combination more effectively targets intermediate markers of Barrett's-associated carcinogenesis.

Unfortunately, selective COX-2 inhibitors have been shown to increase the risk of thrombotic cardiovascular events, making their widespread use for cancer chemoprevention problematic. An alternate approach is to use aspirin with a PPI, as was performed in our study. Aspirin decreases the risk of thrombotic cardiovascular events and is frequently recommended for patients at increased risk for myocardial infarction. In addition, PPIs may make aspirin a more useful and safer chemopreventive agent by minimizing aspirin-induced mucosal injury. Given the age-related increase in risk of gastrointestinal bleeding associated with NSAID use, this is a real concern for any chemoprevention strategy among patients with BE, who tend to be of older age.[35] Although PPIs, by targeting the root cause of the problem, may prevent chronic esophageal injury and decrease inflammation, aspirin use could control any COX-2 activation that may result from breakthroughs in acid suppression or gastrin activation by PPIs.

Clinical trial data regarding the potential chemopreventive effects of aspirin and other NSAIDs in patients with BE are currently limited. One clinical trial examined the effect of celecoxib given for 48 weeks in participants with low-grade and high-grade dysplasia and found no difference in the proportion of biopsy samples with dysplasia between participants treated with celecoxib compared with placebo.[36] Another small crossover study showed that esomeprazole 40 mg twice daily in conjunction with aspirin at a dosage of 325 mg daily administered for 10 days resulted in lower esophageal mucosal PGE_2 content in participants with BE, whereas esomeprazole alone or in combination with rofecoxib did not reduce PGE_2 production.[34] To our knowledge, no additional clinical trial data have yet been reported on the potential effects of different doses of aspirin, in combination with PPI therapy, as a potential esophageal cancer chemopreventive strategy. The rationale for the use of the lower and higher dose of aspirin was to define if the smaller dose of aspirin was equally effective in decreasing tissue PGE_2 concentrations in patients with BE compared with the higher dose. Another reason to undertake such a dose-ranging study is that the higher dose of aspirin in one colon cancer prevention study appeared to be less effective than lower-dose aspirin.[37]

Strengths of the current study design included the avoidance of recruitment of participants with intestinal metaplasia of the cardia, the requirement for confirmation of intestinal metaplasia with goblet cells, and a detailed interview to make sure patients were not unwittingly using aspirin or other NSAIDs before randomization. Thus, careful steps were taken to ensure a homogeneous group of study participants with histologically confirmed BE. Although our trial was conducted at multiple, geographically disparate sites, the relatively limited racial/ethnic diversity of our randomized cohort makes it unlikely that ethnopharmacology had any appreciable influence on our findings. Although a significant difference was noted in the higher-dose aspirin arm versus the aspirin placebo arm, no such difference could be detected in the lower-dose aspirin arm, despite a trend in that direction. The lack of a significant effect in the lower-dose aspirin + esomeprazole arm may have been due to a lack of power and not a true lack of efficacy. The inability to achieve the a priori sample size, the lack of a sample size adjustment for the increased variability in PGE_2, and the use of planned nonparametric tests (instead of the parametric tests that the sample size was based on) all may have contributed to the study being

underpowered to detect a significant effect for the lower-dose aspirin + esomeprazole arm. As such, we cannot conclude from our data that a combination of lower-dose aspirin + esomeprazole does not provide chemopreventive benefits for patients with BE.

There are a number of factors that make BE studies challenging to conduct. Importantly, many patients with BE already take aspirin or NSAIDs, which makes any such longer-term clinical trial difficult to perform. Also, PGE_2 levels represent a surrogate end point for more direct clinical end points, such as progression to high-grade dysplasia and adenocarcinoma. There is no simple study design for assessing these more clinically relevant, yet substantially less common end points without considerable resource investment.

Our rationale to use PGE_2 as a surrogate biomarker of NSAID-related chemoprevention is based on its direct role in carcinogenesis in Barrett's mucosa through up-regulation of proliferation, resistance to apoptosis, and angiogenesis. Furthermore, PGE_2 biosynthesis is a downstream target of several oncogenic signals and can be down-regulated by tumor suppressors.[38–40] The findings that carcinogenic bile salts in a pH-dependent manner up-regulate PGE_2 biosynthesis along with increased expression of key regulators of PGE_2 by DNA damage and by aberrant p53 expression[41] further support that the effect of genetic or epigenetic gains or losses that promote neoplasia could be inferred through a mechanistically relevant composite biochemical readout such as PGE_2 synthesis.

We believe that data from the current phase 2 trial provide strong support for a larger, more definitive phase 3 trial to further clarify the role of aspirin and esomeprazole in esophageal cancer chemoprevention among patients with BE. Indeed, our study represents the largest chemoprevention trial in BE to date and has the advantage of examining a geographically diverse patient population. The ongoing multicenter phase 3 AspECT trial, which is being conducted in the United Kingdom and elsewhere in Europe, is also examining aspirin and esomeprazole as a combination chemopreventive intervention for patients with BE,[42] with results that should serve to complement these findings.

In conclusion, data from this multicenter, prospective, phase 2 trial show that twice-daily esomeprazole in combination with higher-dose (325 mg) daily aspirin therapy can favorably affect tissue PGE_2 levels in patients with BE. Although lower-dose aspirin (81 mg) was not found to significantly reduce PGE_2 levels as compared with esomeprazole alone based on the primary end point analysis, data from our secondary analyses suggest that esomeprazole twice per day in combination with 81 mg aspirin per day may also provide some chemopreventive benefits for patients with BE. As such, a larger trial is recommended to more fully investigate the aspirin dose effect to see what dose of aspirin is optimal. Given the importance of PGE_2 and related molecular pathways in Barrett's-associated carcinogenesis, this dual regimen of aspirin and esomeprazole warrants further evaluation as a novel chemoprevention strategy for an increasingly common disease with potentially devastating clinical outcomes.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org and at http://dx.doi.org/10.1053/j.gastro.2012.06.044.

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Conflicts of interest

The authors disclose the following: Dr Limburg served as a consultant for Genomic Health, Inc, from August 12, 2008, to April 19, 2010. Mayo Clinic has licensed Dr Limburg's intellectual property to Exact Sciences, and he and Mayo Clinic have contractual rights to receive royalties through this agreement. Dr Romero receives funding from AstraZeneca for Mayo Clinic Barrett's esophagus registry and tissue bank. The remaining authors disclose no conflicts.

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Supplementary Materials and Methods

Esophageal tissue was snap frozen, stored at −70°C, weighed, and homogenized in 1 mL buffer containing 10 μmol/L indomethacin and 3 μmol AA-861 (a lipoxygenase inhibitor) using a Polytron homogenizer (PRO Scientific Inc, Monroe, CT). Two milliliters of methanol was added immediately afterward to precipitate proteins and extract prostanoids. Samples were then centrifuged at 3000*g* for 10 minutes at 4°C. Supernatants were diluted with 15% ethanol/acetate buffer and added to a Sep-Pak C18 column (Millipore, Bedford, MA) preconditioned with 5 mL methanol.

After loading the sample, the Sep-Pak was washed with 5 mL water and then 5 mL hexane, and prostanoids were eluted with 4 mL ethyl acetate containing 1% methanol. The Sep-Pak extract was then evaporated using a Speed-Vac concentrator (Savant, Holbrook, NY) and the residue brought up in 0.5 mL immunoassay buffer. The samples were assayed at 1/1, 1/2, 1/10, and 1/50 dilution using enzyme immunoassay kits from Cayman Chemical (Ann Arbor, MI).

The enzyme immunoassay is based on a competition between the PG contained in the supernatant and the PG-acetylcholinesterase conjugate (tracer) for a limited amount of monoclonal antibody after 18 hours of incubation at 4°C. Two hundred microliters of Ellman's reagent was used as the substrate for acetylcholinesterase. The proportion of the bound tracer was determined spectroscopically, and the concentration of PGE_2 was determined using standard curves from known concentrations.

Is 325 mg of Prevention Worth a Pound of Cure?

See "A combination of esomeprazole and aspirin reduces tissue concentrations of prostaglandin E_2 in patients with Barrett's esophagus," by Falk GW, Buttar NS, Foster NR, et al, on page 917.

This issue of GASTROENTEROLOGY presents a study that provides the scientific basis to justify conduct of a clinical trial to determine whether aspirin prevents esophageal adenocarcinoma among patients with Barrett's esophagus.[1] This topic is timely and important because the prevalence of Barrett's esophagus and incidence of esophageal adenocarcinoma continues to rise, and the survival of patients who develop esophageal adenocarcinoma is dismal.[2] Moreover, current management includes surveillance endoscopy with targeted and random biopsies to detect dysplasia and early cancer; however, surveillance is inefficient owing to the rare incidence of esophageal adenocarcinoma among patients undergoing surveillance and the fact that the vast majority of patients who develop esophageal adenocarcinoma were not previously identified as having Barrett's esophagus and therefore were not enrolled in surveillance.[3] Radiofrequency ablation is recommended for patients with dysplasia, but seems to require repeated application to maintain remission from dysplasia and metaplasia.[4] The end result is that current management of patients with Barrett's esophagus is expensive and does not guarantee mortality reduction from cancer. For these reasons, chemoprevention of cancer is an attractive alternative strategy.

This study was a randomized, double-blind, placebo-controlled clinical trial that compared the effect of 2 dose levels of aspirin in combination with esomeprazole on tissue prostaglandin E_2 (PGE2) concentration. One hundred twenty patients with Barrett's esophagus with no dysplasia or low-grade dysplasia were enrolled in this 28-day trial. The results revealed that 325 mg aspirin daily, but not 81 mg, resulted in significantly lower tissue PGE2 concentration compared with placebo. What does this answer mean and how will this knowledge impact the health of patients with Barrett's esophagus? Regarding the primary outcome variable, PGE2 concentration is elevated in esophageal tissue consisting of intestinal metaplasia compared with squamous epithelium.[5] Increases in PGE2 are associated with features of malignancy such as angiogenesis, invasion, and reduced apoptosis; moreover, up-regulation of PGE2 induces Barrett's proliferation, whereas inhibition of PGE2 reduces proliferation.[6] For these reasons PGE2 concentration can be considered a surrogate that indicates the malignant potential of Barrett's esophagus, and this study is an essential step toward defining the role of aspirin for chemoprevention.

Does this mean that all patients with Barrett's esophagus should be on full-dose aspirin to prevent esophageal adenocarcinoma? Currently the answer is no. The results of this trial, although encouraging, are not sufficiently conclusive to alter current clinical care. Several issues need addressing before adopting such a clinical strategy. Unfortunately, this is not the first time we have seen data supporting a role for nonsteroidal anti-inflammatory drugs to reduce esophageal adenocarcinoma incidence. In a set of experiments similar to those supporting aspirin chemoprevention, the molecular mechanisms supporting the rationale for targeting cyclo-oxygenase-2 (COX-2) to prevent a variety of cancers have been extensively developed.[7] COX-2 expression was noted to be significantly increased in human Barrett's esophagus tissue compared with normal esophageal mucosa, and a selective COX-2 inhibitor could attenuate tissue COX-2 expression.[5] Even more convincingly, selective COX-2 inhibitors have been demonstrated to reduce the development of esophageal adenocarcinoma compared with placebo in an animal model.[6] Despite these convincing pilot data, however, a rigorously conducted randomized, placebo-controlled, clinical trial of a selective COX-2 inhibitor failed to demonstrate clinical benefit.[8] In this study, participants with Barrett's esophagus and low- or high-grade dysplasia were randomized to receive celecoxib (200 mg twice daily) or placebo. After 48 weeks of therapy, there was no difference between active and placebo treated groups in the median change in the proportion of esophageal biopsies with dysplasia or cancer. Moreover, secondary endpoints, including changes in the total surface area of Barrett's mucosa, tissue prostaglandin levels, methylation of tumor suppressor gene (p16, adenomatous polyposis coli, and E-cadherin), did not differ between COX-2–treated and placebo participants. A variety of factors potentially undermining the efficacy of COX-2 inhibition may have been responsible for these negative results. It may have been that the dose of celecoxib was inadequate to induce the intended effect, or the duration of the trial was too short to observe benefit, or that dysplasia is simply too far advanced to have allowed celecoxib to reverse the natural history of esophageal adenocarcinoma. Regardless, the promise of COX-2 inhibition to reduce cancer was not delivered, despite the volume of pilot data that supported this hypothesis.

With regard to the current study, it is imperative that we carefully consider the role of tissue PGE2 concentration as a surrogate for clinical outcomes. Using the cau-

tion we have learned from the COX-2 studies, it is not possible to assume that the prostaglandin data presented from this study will manifest as cancer prevention for patients with Barrett's esophagus. For example, the absolute difference in prostaglandin concentration achieved statistical significance in this study; however, it is unknown whether these results represent a clinically relevant difference that will be associated with significant reductions in cancer incidence. It would be useful to identify the absolute and relative changes in PGE2 levels that are clinically relevant so that this surrogate may be converted to an expected reduction in dysplasia or cancer incidence. For this reason, a human trial testing aspirin chemoprevention with relevant outcomes including dysplasia and cancer incidence should be performed.

The American Gastroenterological Association guidelines for the management of patients with Barrett's esophagus called for studies of cancer chemoprevention.[2] The phase II study published herein is an answer to that request and adds much to the existing literature. Because one function of pilot studies is to identify proper dosing of drugs in a clinical trial, however, it was unfortunate that the reduction in PGE2 levels associated with 81 mg aspirin was not significant. As the authors point out, this result may have been owing to a type II error, meaning that there is inability to observe a significant difference when one actually exists and a larger trial could yet reveal a role for low-dose of aspirin. As it stands, the options for going forward include conducting yet another pilot study to confirm the dose necessary to achieve the desired therapeutic effects, conducting the full-scale study with full-dose aspirin, or conducting the full-scale study using 2 doses, which would greatly increase the sample necessary to demonstrate efficacy. Indeed, the difficulty of enrollment into the current trial gives pause to consideration of the latter; a study of clinical outcomes requires more participants followed for a much longer period of time.

One caveat regarding this study is that aspirin is not the only drug examined. The effect of acid suppression, specifically with proton pump inhibitors (PPIs), may possess an independent effect on neoplastic progression. PGE2 levels trended lower in the PPI plus placebo arm. Although not significant, the sample was small and just as may have been the case with low-dose aspirin, the lack of significance may also represent a type II error. Prior studies support the effect of PPI on reducing dysplasia and cancer incidence in Barrett's esophagus.[9–11] It is acknowledged, however, that because the vast majority of Barrett's esophagus patients are already on a PPI, the clinical importance of this question is less compelling than the aspirin component.

Finally, because the cost of aspirin is negligible the barrier for its use is the incidence of adverse events. In this study, adverse events were not different from placebo, with the caveat that this was a comparatively small sample with limited follow-up. A complete randomized, controlled trial of duration sufficient to detect clinical outcomes will also need to be powered to exclude significant adverse events with aspirin use. PPIs may mitigate the gastrointestinal complications of aspirin use, but other hazards exist. Although I am generally inclined to provide an evidence basis for my arguments, I highlight a personal anecdote to highlight my point. Some years ago, I was called by a friend to inform me that his spouse was "having trouble signing her name." After conducting a mini-mental status examination over the phone it was evident that this was least of her problems: Her myriad of symptoms included a Broca's (expressive) aphasia. Fearing the worst (ie, a stroke or brain tumor) I was somewhat relieved to learn that she had a subdural hematoma, which was successfully evacuated. Upon further questioning it was revealed that she had fallen while playing tennis a few days earlier, but this had not been particularly bothersome and she and her playing partners had not recalled any head trauma. The most disturbing fact, however, was that she had been taking 81 mg of aspirin daily "because someone told her it was good for her." Note that apart from age, she had no risk factors that warranted aspirin prophylaxis for any disease state. Take-home message? Anyone can have a bad day on aspirin.

So what have we learned from this study? There is a good scientific basis supporting the role of aspirin plus PPI in reducing tissue concentrations of a marker for malignant potential among patients with Barrett's esophagus without high-grade dysplasia. This effect was significant for full-dose (325 mg) but not confirmed for low-dose (81 mg) daily aspirin. Adverse events were not increased in the aspirin compared with the placebo arm. These results support the conduct of properly powered, randomized, controlled trials testing the hypothesis that aspirin plus PPI reduces esophageal adenocarcinoma incidence among patients with Barrett's esophagus. The AspECT study being performed in the UK is an example of just such a trial, for which results will hopefully provide the rationale for change in the clinical management of patients with Barrett's esophagus.[12,13] Aspirin plus PPI chemoprophylaxis, if effective and safe, could greatly reduce the health and economic burden associated with this cancer. Until the results of trials using clinical endpoints are published, however, it is premature to recommend aspirin solely on the basis of chemoprevention of esophageal adenocarcinoma.

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Data to Guide the "Test and Treat Era" of Hepatitis C

See "Predicted effects of treatment for HCV infection vary among European countries," by Deuffic–Burban S, Deltenre P, Buti M, et al, on page 974.

Health leaders around the world are facing critical questions regarding how to combat a rising tide of hepatitis C virus (HCV)-associated liver disease. Worldwide, an estimated 130–170 million persons are living with chronic HCV infection, and HCV causes 1 in 4 cases of cirrhosis and 170,000 deaths per year.[1] Persons living with HCV are often unaware they are infected, reflecting the relatively asymptomatic nature of HCV infection until late in the course of disease and the often decades-long latency between acquisition of HCV and the development of end-stage liver disease and death. Many HCV-infected persons were infected decades ago, before the discovery of the virus in the late 1980s and the advent of blood bank screening and other prevention measures. As time passes and HCV has a longer opportunity to cause progressive liver damage, the number of HCV-infected persons developing end-stage liver disease (hepatocellular carcinoma and liver cirrhosis) is increasing at an accelerating rate.[2] For example, in the United States, the number of persons dying from HCV-associated conditions recently surpassed the number of deaths from HIV/AIDS. The US Centers for Disease Control and Prevention (CDC) estimate that HCV-related cirrhosis and morbidity will continue to increase year over year into the next decade and beyond.[3,4]

Fortunately, health officials are not empty handed in facing this looming crisis. A growing arsenal of direct-acting antiviral agents can clear HCV from the body (ie, achieve virologic cure). The addition of 1 of 2 commercially available protease inhibitors to treatment regimens can increase rates of sustained virologic response (ie, viral eradication after completion of treatment) to 63%–75%.[5,6] Other compounds under study in clinical trials may increase rates of viral eradication even further.[7] Achieving a sustained virologic response is important, because persons successfully clearing virus after HCV therapy have lower rates of hepatocellular carcinoma and all-cause mortality.[8,9]

The opportunity created by these new therapies is compromised by the lack of quality information that can be used to target case identification and treatment efforts. Insufficient public health surveillance systems that track HCV disease, mortality, and access to testing and medical care hinder health leaders from recognizing the growing threat of chronic hepatitis C and the potential benefits that accompany HCV testing, care, and treatment.[10] Seeking to fill this information gap, Deuffic–Burban et al