CLINICAL—ALIMENTARY TRACT

Use of Aspirin or Nonsteroidal Anti-inflammatory Drugs Increases Risk for Diverticulitis and Diverticular Bleeding

LISA L. STRATE,[*,‡] YAN L. LIU,[§] EDWARD S. HUANG,[‖] EDWARD L. GIOVANNUCCI,[§,¶,#] and ANDREW T. CHAN[‖,#]

[*]University of Washington School of Medicine, Seattle, Washington; [‡]Division of Gastroenterology, Department of Medicine, Harborview Medical Center, Seattle, Washington; [§]Department of Nutrition, [¶]Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts; [‖]Gastrointestinal Unit, Massachusetts General Hospital, [#]Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts

This article has an accompanying continuing medical education activity on page e13. Learning Objective: Upon completion of this article and accompanying CME questions, successful learners will be able to recognize the influence of aspirin and NSAID use on the risk of diverticulitis and diverticular bleeding in individuals with diverticulosis.

Podcast interview: www.gastro.org/gastropodcast.

BACKGROUND & AIMS: Nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, have been implicated in diverticular complications. We examined the influence of aspirin and NSAID use on risk of diverticulitis and diverticular bleeding in a large prospective cohort. **METHODS:** We studied 47,210 US men in the Health Professionals Follow-up Study cohort who were 40–75 years old at baseline in 1986. We assessed use of aspirin, nonaspirin NSAIDs, and other risk factors biennially. We identified men with diverticulitis or diverticular bleeding based on responses to biennial and supplementary questionnaires. **RESULTS:** We documented 939 cases of diverticulitis and 256 cases of diverticular bleeding during a 22-year period of follow-up evaluation. After adjustment for risk factors, men who used aspirin regularly (≥2 times/wk) had a multivariable hazard ratio (HR) of 1.25 (95% confidence interval [CI], 1.05–1.47) for diverticulitis and a HR of 1.70 (95% CI, 1.21–2.39) for diverticular bleeding, compared with nonusers of aspirin and NSAIDs. Use of aspirin at intermediate doses (2–5.9 standard, 325-mg tablets/wk) and frequency (4–6 days/wk) were associated with the highest risk of bleeding (multivariable HR, 2.32; 95% CI, 1.34–4.02, and multivariable HR, 3.13; 95% CI, 1.82–5.38, respectively). Regular users of nonaspirin NSAIDs also had an increased risk of diverticulitis (multivariable HR, 1.72; 95% CI, 1.40–2.11) and diverticular bleeding (multivariable HR, 1.74; 95% CI, 1.15–2.64), compared with men who denied use of these medications. **CONCLUSIONS: Regular use of aspirin or NSAIDs is associated with an increased risk of diverticulitis and diverticular bleeding. Patients at risk of diverticular complications should carefully consider the potential risks and benefits of using these medications.**

Keywords: Side Effects; Toxicity; Colon Medication; Diverticular Disease.

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Nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, are a well-known cause of upper gastrointestinal tract complications. These medications also are implicated in lower gastrointestinal injury.[1–3] In randomized trials of patients with rheumatoid or osteoarthritis, 30%–50% of all serious gastrointestinal events associated with NSAIDs were localized to the lower gastrointestinal tract,[4–6] with diverticulitis and diverticular bleeding as the most common etiologies.[5,6] Although a number of case-control studies have shown a significantly higher prevalence of NSAID use among cases with complications of diverticular disease (diverticulitis and bleeding) compared with controls, risk estimates vary widely, with odds ratios ranging from 1.8 to 16.[7–12] In addition to the inherent biases in selection of controls and ascertainment of medication exposure associated with the case-control study design, these analyses also had limited data regarding medication type (NSAID vs aspirin), dose, timing, and duration of use.

Thus, to address these limitations, we prospectively examined the influence of aspirin and NSAIDs on risk of diverticular complications in a large cohort of men enrolled in the Health Professionals Follow-up Study, which provided long-term, detailed, and updated information on aspirin and NSAID use. In an earlier study of

Abbreviations used in this paper: CI, confidence interval; COX, cyclooxygenase; HR, hazard ratio; NSAID, nonsteroidal anti-inflammatory drug.

0016-5085/$36.00
doi:10.1053/j.gastro.2011.02.004

this cohort, we found that regular NSAID use, but not aspirin use, was associated positively with symptomatic diverticular disease[13]; however, that analysis was limited by the number of overall cases (n = 310), the short follow-up period (4 y), and the inability to evaluate medication dose and frequency or to differentiate diverticulitis or diverticular bleeding from gastrointestinal symptoms that arose in the setting of diverticulosis. In the present study, we offer results that include detailed data on aspirin and NSAID dose and frequency, encompassing 22 years of follow-up evaluation with 939 cases of diverticulitis and 256 cases of diverticular bleeding.

Materials and Methods

Study Population

The Health Professionals Follow-up Study is a prospective cohort of 51,529 male dentists, veterinarians, pharmacists, optometrists, osteopathic physicians, and podiatrists, age 40–75 years at baseline in 1986, who returned a detailed medical and dietary questionnaire. Medical information has been updated biennially and dietary information has been updated every 4 years via self-administered questionnaires.

Assessment of Diverticulitis and Diverticular Bleeding

The primary study end points were diverticulitis and diverticular bleeding. Beginning in 1990, men reporting newly diagnosed diverticulosis or diverticulitis on the biennial main study questionnaire were sent supplementary questionnaires to assess the date of diagnosis, procedures performed to confirm the diagnosis, symptoms or tests leading to the detection of diverticular disease, and treatment received. We defined cases of complicated diverticulitis as a report of a fistula, abscess, perforation, or obstruction. We defined cases of uncomplicated diverticulitis as reports of abdominal pain attributed to diverticular disease requiring antibiotics, hospitalization, or surgery; pain categorized as severe or acute; or abdominal pain presenting with fever, requiring medication, or evaluated with computed tomography. Diverticular bleeding was defined as rectal bleeding attributed to diverticulosis that required hospitalization, blood transfusions, intravenous fluids, surgery, angiography, tagged red blood cell scanning, or endoscopic hemostasis. We previously used these case definitions and have reported our methods for validation in detail.[14–16]

In addition, beginning in 2006, we updated the supplementary questionnaire to include a checklist of diverticular complications with definitions (diverticular bleeding; uncomplicated diverticulitis; and diverticular abscess, obstruction, perforation, and fistula) in addition to questions regarding diagnosis and treatment. In 2006, among all participants, we also inquired about gastrointestinal bleeding requiring hospitalization or blood transfusion, the location of the bleeding, and the date of onset. In a review of 239 cases, the self-reported date of diagnosis correlated with the medical record (correlation coefficient, 0.87; $P < .001$), and self-reported location of bleeding (upper vs lower) was correct in 93%. Therefore, patients who reported diverticular disease and gastrointestinal bleeding from the colon requiring hospitalization or blood transfusion in corresponding study periods were classified as having diverticular bleeding, and cases in addition to those documented via the supplementary questionnaire were included.

Assessment of Medication Use

We previously detailed our assessment of aspirin and NSAID use.[17] Briefly, since 1986, the biennial study questionnaire assessed regular use (defined as ≥2 times/wk) of aspirin ("eg, Anacin, Bufferin, Alka-Seltzer") and other anti-inflammatory drugs ("eg, Motrin, Indocin, Naprosyn, Dolobid"). In 1992, additional questions were added to assess the average number of aspirin tablets used per week and the frequency of aspirin use. Because of secular trends in the use of baby or low-dose aspirin, beginning in 1994 participants were instructed to convert baby aspirin to standard tablets (4 baby aspirin = 1 tablet). Indications for aspirin use were assessed on a 1993 supplementary questionnaire sent to 221 men who reported aspirin use since 1986. Indications for aspirin use included cardiovascular disease (25.4%), to decrease the risk of cardiovascular disease (58.4%), headaches (25.4%), joint or musculoskeletal pain (33%), and other (7%).[18] No participant reported taking aspirin for the relief of abdominal pain.

Assessment of Other Potential Risk Factors

We also assessed dietary fiber, fat, red meat, corn, popcorn, and nut intake; physical activity; and obesity as potential confounders.[14–16,19–23] Nutritional information was assessed every 4 years using a food-frequency questionnaire. Physical activity was assessed on biennial questionnaires, and expressed in metabolic equivalent hours per week. Body mass index (kg/m^2) was calculated from self-reported body weight that was updated biennially, and height, which was reported at baseline in 1986. The validity and reproducibility of the dietary questionnaires, body measurements, and physical activity assessment have been shown previously.[24–26]

Statistical Analysis

We excluded from the analysis men who reported a diagnosis of diverticulosis, diverticulitis or diverticular bleeding, cancer (except nonmelanoma skin cancer), or inflammatory bowel disease on the baseline questionnaire. In addition, we excluded men who did not return the baseline food-frequency questionnaire or provided implausible dietary data (men with average daily intakes outside the range of 800–4300 kcal). The remaining baseline population included 47,210 men. Men contrib-

uted person-time from the date of return of the baseline questionnaire in 1986 to the date of the first diagnosis of diverticular complications, the date of death, or December 31, 2008, whichever came first. Men who reported a new diagnosis of gastrointestinal cancer, diverticulosis, diverticulitis, diverticular bleeding, or inflammatory bowel disease were censored at the date of diagnosis.

We examined the association between regular use of aspirin and NSAIDs and the incidence of diverticulitis and diverticular bleeding using simple updating (the medication use reported on the questionnaire immediately preceding the follow-up interval of interest). Consistent with prior analyses, regular use was defined as 2 or more times per week, and nonregular use was defined as less than 2 times per week.[17,18] For this analysis, regular users of aspirin only, NSAIDs only, and both aspirin and NSAIDs were compared separately with nonusers of both aspirin and NSAIDs. Frequency of aspirin use also was evaluated according to the average number of days aspirin was used per week in categories. In addition, we assessed the relationship between aspirin dose and the risk of diverticular complications. Dose was estimated and categorized according to the number of standard dose (325 mg) tablets used per week. We evaluated the cumulative updated dose to account for variation in dose over the study period using time-varying covariates. In this analysis, each participant contributed person-time according to data they provided on each biennial questionnaire. Last, we examined the risk of diverticular complications according to the duration of aspirin and NSAID use. Duration was calculated in years of regular use beginning in 1986 with updating every 2 years and accounting for interruptions in use.

We divided the number of new cases of diverticulitis and diverticular bleeding by the number of person-years in each use category to calculate incidence rates. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for each end point using a Cox proportional hazards model. Men in each category of use were compared with men in the reference category (nonregular users).[27] Age-adjusted models were stratified by age in 1-year intervals and study period in 2-year intervals. Multivariable models adjusted for age and study period as well as body mass index (6 categories); dietary intake (quintiles) of fat; fiber, red meat, nut, corn, and popcorn consumption; total caloric intake; and physical activity (quintiles). We used the most recent information available for each covariate. We excluded NSAID users from the analyses of aspirin use, and aspirin users from the analyses of NSAID use to better isolate the effect of each drug individually. We assessed statistical interaction of aspirin and NSAID use by including cross-product terms in our models and assessing their significance using the Wald test.

All analyses were performed using SAS software, version 9.1.3 (SAS Institute Inc, Cary, NC). Tests for linear trend were performed by treating the median value of each of the measurement categories as a continuous variable.[28] All tests were 2-sided and a P value of less than .05 was considered statistically significant. Return of the self-administered study questionnaire was regarded as informed consent. The institutional review boards of the Harvard School of Public Health approved the study protocol.

Results

During 859,164 person-years of follow-up evaluation, we documented 939 incident cases of diverticulitis, and 256 incident cases of diverticular bleeding. Baseline characteristics of the cohort are summarized in Table 1

Table 1. Baseline Characteristics of the Study Cohort in 1986 According to Regular Use of Aspirin and NSAIDs

	Aspirin		NSAIDs	
	Nonregular users (n = 33,336)	Regular users (n = 13,874)	Nonregular users (n = 44,633)	Regular users (n = 2577)
Age, mean (SD), y	53 (9.7)	56 (9.7)	54 (9.7)	55 (9.9)
Body mass index, mean (SD), kg/m^2	24.9 (5.0)	25.1 (5.2)	24.9 (5.0)	25.5 (5.6)
Physical activity, mean (SD), MET, h/wk	21 (29.5)	21 (28.8)	21 (29.3)	21 (29.5)
Coronary heart disease, %	4	12	6	6
Osteoarthritis, %	7	11	7	36
Current smoking, %	9	10	10	10
Dietary intake, mean (SD)				
Calories, kcal/day	1973 (617)	2018 (623)	1984 (619)	2017 (623)
Fiber, g/day	21 (7.0)	21 (7.0)	21 (7.1)	21 (6.7)
Fat, g/day	72 (14.0)	71 (14.1)	71 (14.1)	72 (13.7)
Red meat, servings/day	4.3 (3.2)	4.3 (3.1)	4.3 (3.2)	4.5 (3.2)
Alcohol, g/day, mean	11 (15.0)	13 (16.3)	11 (15.4)	13 (16.7)
Current NSAID use, %	5	7	–	–
Current aspirin use, %	–	–	29	39

NOTE. All variables except for age are age-standardized. Regular use was defined as at least 2 times per week. Nonregular use was defined as less than 2 times per week.
MET, metabolic equivalent.

Table 2. Aspirin and NSAID Use and Risk of Diverticulitis and Diverticular Bleeding

	Nonusers of aspirin and NSAIDs	Regular use of aspirin only	Regular use of NSAIDs only	Regular use of aspirin and NSAIDs
Person-years	367,223	273,233	96,726	120,609
Diverticulitis				
Incident cases	288	313	148	190
Age-adjusted HR (95% CI)[a]	1.0	1.32 (1.12–1.55)	1.87 (1.52–2.29)	1.85 (1.53–2.42)
Multivariate HR (95% CI)[b]	1.0	1.25 (1.05–1.47)	1.72 (1.40–2.11)	1.65 (1.36–2.01)
Diverticular bleeding				
Incident cases	58	93	40	65
Age-adjusted HR (95% CI)[a]	1.0	1.90 (1.36–2.65)	1.92 (1.27–2.91)	2.45 (1.69–3.53)
Multivariate HR (95% CI)[b]	1.0	1.70 (1.21–2.39)	1.74 (1.15–2.64)	2.02 (1.38–2.96)

NOTE. Regular use was defined as at least 2 times per week. Nonregular use was defined as less than 2 times per week.
[a]Age-adjusted HRs adjusted for age (in years) and study period in 2-year intervals.
[b]Multivariate HR adjusted for age; study period; body mass index; dietary fat, fiber, red meat, nut, corn, and total caloric intake; and physical activity.

according to regular use of aspirin and NSAIDs and standardized for age. Approximately 29% of participants reported regular aspirin use (≥2 times/wk) and 5% reported regular NSAID use. On average, regular users of aspirin were more likely to have a history of coronary heart disease than nonusers, and users of aspirin and NSAIDs were more likely to have osteoarthritis and to consume more alcohol than nonusers.

After controlling for other potential risk factors for diverticular complications, we observed a significantly higher risk of diverticulitis among regular users of NSAIDs (multivariable HR, 1.72; 95% CI, 1.40–2.11), and to a lesser degree among regular users of aspirin (multivariable HR, 1.25; 95% CI, 1.05–1.47) when compared with men who denied use of either drug (Table 2). In analyses according to subtypes of diverticulitis, we observed that regular NSAID use appeared to be associated more strongly with risk of complicated diverticulitis (multivariable HR, 2.55; 95% CI, 1.32–4.95) than uncomplicated diverticulitis (multivariable HR, 1.65; 95% CI, 1.32–2.05) compared with nonuse of either NSAIDs or aspirin. For both subtypes, we found comparable risk estimates for regular aspirin use, with a multivariable HR of 1.13 (95% CI, 0.61–2.10) for complicated diverticulitis and 1.24 (95% CI, 1.04–1.47) for uncomplicated diverticulitis.

For diverticular bleeding, the associations of regular use of NSAIDs and aspirin were similar (multivariable HR, 1.74; 95% CI, 1.15–2.64; and multivariable HR, 1.70; 95% CI, 1.21–2.39, respectively). Combined use of aspirin and NSAIDs was associated with a multivariable HR for diverticulitis of 1.65 (95% CI, 1.36–2.01) and for bleeding of 2.02 (95% CI, 1.38–2.96). A formal test of whether the concurrent use of aspirin and NSAIDs was associated with a greater risk than use of each drug alone was not statistically significant for diverticulitis ($P = .06$) or for bleeding ($P = .145$).

The association between aspirin use and diverticular complications did not display a linear dose-relationship in the multivariable analyses excluding NSAID users ($P = .28$ for trend for diverticulitis and $P = .10$ for trend for diverticular bleeding) (Table 3). However, we observed

Table 3. Dose of Aspirin and Risk of Diverticulitis and Diverticular Bleeding

	Tablets/wk, 325 mg				
	None	0.1–1.9	2–5.9	≥6	*P* for trend
Person-years	127,213	107,535	98,505	47,467	
Diverticulitis					
Incident cases	124	110	128	58	
Age-adjusted HR (95% CI)[a]	1.0	1.09 (0.83–1.41)	1.35 (1.05–1.73)	1.21 (0.88–1.66)	.09
Multivariate HR (95% CI)[b]	1.0	1.02 (0.78–1.33)	1.26 (0.97–1.62)	1.11 (0.81–1.52)	.28
Diverticular bleeding					
Incident cases	19	34	47	16	
Age-adjusted HR (95% CI)[a]	1.0	1.81 (1.02–3.21)	2.75 (1.60–4.71)	2.02 (1.04–3.95)	.02
Multivariate HR (95% CI)[b]	1.0	1.58 (0.88–2.82)	2.32 (1.34–4.02)	1.65 (0.84–3.26)	.10

NOTE. Analyses limited to non-NSAID users. Regular use was defined as at least 2 times per week. Nonregular use was defined as less than 2 times per week. Dose was analyzed using cumulative updating.
[a]Age-adjusted HRs adjusted for age (in years) and study period in 2-year intervals.
[b]Multivariate HRs adjusted for age; study period; body mass index; dietary fat, fiber, red meat, nut, corn, and total caloric intake; and physical activity.

Table 4. Frequency of Aspirin Use and Risk of Diverticulitis and Diverticular Bleeding

	Days per week					
	None	<2	2–3.9	4–6	Daily	*P* for trend
Person-years	220,303	50,674	21,787	40,153	71,418	
Diverticulitis						
Incident cases	194	50	24	54	102	
Age-adjusted HR (95% CI)[a]	1.0	0.94 (0.68–1.31)	1.05 (0.69–1.61)	1.30 (0.94–1.78)	1.52 (1.18–1.95)	<.001
Multivariate HR (95% CI)[b]	1.0	0.88 (0.64–1.23)	0.99 (0.65–1.53)	1.24 (0.90–1.71)	1.46 (1.13–1.88)	.002
Diverticular bleeding						
Incident cases	43	9	5	24	36	
Age-adjusted HR (95% CI)[a]	1.0	1.20 (0.57–2.55)	1.35 (0.53–3.46)	3.49 (2.05–5.96)	1.87 (1.19–2.95)	<.001
Multivariate HR (95% CI)[b]	1.0	1.08 (0.51–2.30)	1.21 (0.47–3.11)	3.13 (1.82–5.38)	1.57 (0.98–2.51)	.003

NOTE. Analyses limited to non-NSAID users. Regular use was defined as at least 2 times per week. Nonregular use was defined as less than 2 times per week.

[a]Age-adjusted HRs adjusted for age in 1-year intervals and study period in 2-year intervals.

[b]Multivariate HRs adjusted for age; study period; body mass index; dietary fat, fiber, red meat, nut, corn, and total caloric intake; and physical activity.

that men who took intermediate doses of aspirin (2–5.9 standard [325-mg] tablets/wk) had the highest risk of diverticular bleeding (multivariable HR, 2.32; 95% CI, 1.34–4.02) when compared with men who reported no aspirin use.

To better assess the effect of consistency of use on the risk of diverticular complications, we also examined frequency of regular aspirin use in non-NSAID users (Table 4). Compared with nonregular users, men who used aspirin daily had a significantly higher risk of diverticulitis (multivariable HR, 1.46; 95% CI, 1.13–1.88; $P = .002$ for trend). Similar to the findings for aspirin dose, we found that moderately frequent use of aspirin was associated strongly with the risk of diverticular bleeding. Men who reported aspirin use 4–6 days per week had a multivariable HR of 3.13 (95% CI, 1.82–5.38) when compared with men who denied aspirin use.

In addition, we found that increasing duration of regular aspirin and NSAID use was associated with greater risk of diverticular complications among nonusers of NSAIDs and aspirin, respectively. Ten years or more of aspirin use was associated with a multivariable HR of 1.51 (95% CI, 1.13–2.03; $P = .01$ for trend) for diverticulitis, and 2.53 (95% CI, 1.43-4.46; $P = .003$ for trend) for bleeding compared with nonregular use. Likewise, after 10 years of NSAID use the HR of diverticulitis was 1.80 (95% CI, 1.30–2.51; $P < .001$ for trend), and of diverticular bleeding was 2.17 (95% CI, 1.23–2.85; $P = .006$ for trend).

To address the possibility of confounding by comorbid illness, we additionally adjusted our analyses for cardiovascular disease and osteoarthritis, the 2 most common indications for aspirin use in this cohort. In this analysis, the relationships between aspirin and NSAID use and diverticulitis remained largely unchanged (multivariable HR, 1.20; 95% CI, 1.01–1.42 for aspirin; multivariable HR, 1.64; 95% CI, 1.33–2.02 for NSAIDs). For diverticular bleeding, the association with aspirin use was not materially altered (multivariable HR, 1.66; 95% CI, 1.18–2.33), but the association with NSAIDs was somewhat attenuated (multivariable HR, 1.42; 95% CI, 0.92–2.18).

Discussion

In this large prospective study of men, we observed that regular use of aspirin or NSAIDs was associated with an increased risk of diverticulitis and diverticular bleeding. The magnitude of the increased risk of bleeding was similar for regular aspirin and NSAID users. The highest risk of diverticular bleeding was observed in men who used aspirin with moderately high frequency (4–6 days/wk) and in moderately high doses (2–5.9 standard [325-mg] tablets/wk). For diverticulitis, the risk appeared somewhat greater for regular NSAID users than for regular aspirin users, and the risk increased with frequency of aspirin use but not with higher doses.

Several previous case-control studies and one prospective cohort study have observed similar associations between aspirin and/or NSAID use and diverticular complications.[7–13] Our study expanded on these findings in several notable ways. First, we distinguished diverticulitis from diverticular bleeding and studied a spectrum of complications. In contrast, aside from one small study of diverticular bleeding,[12] prior studies have focused on perforated diverticulitis,[8–10] a severe manifestation, or combined diverticulitis and diverticular bleeding.[7,11,13] This differentiation is important because diverticulitis and diverticular bleeding likely have distinct biologic mechanisms, and it is not known whether aspirin or NSAIDs serve to initiate or promulgate complications. Second, we were able to examine separately the effects of aspirin and NSAID use, whereas most prior studies used a combined exposure measure.[7,8,10,11] Third, we collected detailed data on aspirin use during 22 years of prospective follow-up evaluation, which enabled us to disentangle the specific effects of dose, frequency, duration, and

timing of medication use in relation to diverticular complications. Last, we were able to adjust for many important known potential confounders of diverticular complications including diet, body mass index, and physical activity.

There are several potential mechanisms by which aspirin and NSAIDs may promote diverticular complications. NSAIDs, including aspirin, are thought to damage the colon via direct topical injury and/or impaired prostaglandin synthesis, which compromise mucosal integrity, increase permeability, and enable the influx of bacteria and other toxins.[29] Diverticulitis is defined by the presence of microperforation or macroperforation leading to abscess formation, and is believed to be the result of an impaired mucosal barrier and increased intracolonic pressure.[30] Diverticular bleeding occurs when a nutrient artery ruptures into the colon lumen, and commonly involves local mucosal ulceration in the absence of inflammation.[31,32] In addition, NSAIDs, including aspirin, likely promote blood loss from existing lesions via inhibition of platelet aggregation.

Our results indicate that NSAID use is associated more strongly with diverticulitis than aspirin use. In fact, the HR of combined NSAID and aspirin use was similar to the risk of NSAID use alone. This result is supported by several other studies in which aspirin and NSAID use were evaluated independently. In an earlier analysis of the Health Professionals Follow-up cohort, NSAID use was associated significantly with symptomatic diverticular disease whereas aspirin use was not.[13] In a case-control study, Morris et al[9] found that NSAID use, but not aspirin use, was associated with perforated diverticulitis. We also found a stronger association between NSAIDs and complicated diverticulitis. Although the association with NSAIDs remained significant when excluding individuals with complicated disease, the study questionnaires did not explicitly denote complications before 2006, and it is possible that the observed associations are largely owing to complicated diverticulitis. The greater effect of NSAIDs vs aspirin in diverticulitis may be owing in part to the fact that low-dose aspirin is absorbed primarily in the stomach and duodenum, limiting topical injury to the colon.[29]

We found that men in the moderately high-dose and frequency categories of aspirin use were at a somewhat higher risk of diverticular bleeding than men in the highest categories. The antiplatelet effects of aspirin may account for these findings. At low and moderate doses of aspirin the predominant effect is on the cyclooxygenase (COX)-1 isoenzyme leading to thromboxane A2–mediated platelet inhibition.[33] However, at higher doses aspirin preferentially may inhibit the COX-2 isoenzyme, which promotes thrombosis and vasoconstriction rather than bleeding.[33] Indeed, several studies have suggested that higher aspirin doses are associated with somewhat greater risk of thrombotic cardiovascular events.[34–36]

Our study had several limitations. Diverticular complications and medication use were self-reported. However, study participants were well-educated health care professionals who likely accurately report their diagnoses and medication use. Moreover, we confirmed self-reported outcomes via chart review in a subset of individuals and self-reported aspirin and NSAID use in this cohort previously have been associated with several disease outcomes that have been validated separately.[16,26] Any misclassification bias is likely to be nondifferential, resulting in an underestimate of any true association between NSAID and aspirin use and diverticular complications. Given the observational nature of our study, we cannot exclude the possibility of residual confounding. Nonetheless, controlling for purported risk factors for diverticular complications including diet and lifestyle did not appreciably alter our results. In addition, our results are consistent with previous investigations and have clear biologic plausibility. We were unable to examine the impact of NSAID dose and frequency or COX-2 selective inhibitor use because of the limited follow-up evaluation (NSAID dose and duration were assessed since 2000 and COX-2 selective use was assessed since 2004). Finally, our study cohort consisted of male health professionals, which may limit the generalizability of our results to other populations. However, we would not expect the association of aspirin with bleeding to differ by occupation.

In conclusion, we observed significantly increased risks of diverticulitis and diverticular bleeding among users of aspirin and NSAIDs. These findings have important clinical and public health implications given the prevalence of diverticular disease and NSAID use particularly in the elderly.[37,38] Analgesia should be selected carefully in individuals with diverticulosis, especially those with prior complications. Future studies are needed to better identify individuals at risk of diverticular complications, and to develop strategies to mitigate the lower gastrointestinal toxicity of NSAIDs.

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Received October 4, 2010. Accepted February 4, 2011.

Reprint requests

Address requests for reprints to: Lisa L. Strate, MD, MPH, Harborview Medical Center, 325 Ninth Avenue, Box 359773, Seattle, Washington 98104. e-mail: lstrate@u.washington.edu; fax: (206) 744-8698.

Conflicts of interest

The authors disclose no conflicts.

Funding

This project was funded by a grant from the National Institutes of Health (CA55075); Dr Chan is a Damon Runyon Cancer Research Foundation Clinical Investigator; and Dr Huang is supported by an American Gastroenterological Association Fellow to Faculty Transition Award.

The content is solely the responsibility of the authors and does not necessarily represent the official views of the Damon Runyon Cancer Research Foundation, National Cancer Institute, or the National Institutes of Health. The funding sources had no role in the design, conduct, or reporting of this study.