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Long Term Use of Aspirin and the Risk of Gastrointestinal Bleeding

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Abstract

Background—In short-term trials, aspirin is associated with gastrointestinal bleeding. However, the effect of dose and duration of aspirin use on risk remains unclear.

Methods—We conducted a prospective study of 87,680 women enrolled in the Nurses' Health Study in 1990 who provided biennial data on aspirin use. We examined the relative risk (RR) of major gastrointestinal bleeding requiring hospitalization or blood transfusion.

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Results—Over a 24-year follow-up, 1537 women reported a major gastrointestinal bleeding. Among women who used aspirin regularly (≥2 standard [325-mg] tablets/week), the multivariate RR of gastrointestinal bleeding was 1.43 (95% confidence interval [CI], 1.29-1.59) compared with non-regular users. Compared with women who denied any aspirin use, the multivariate RRs of gastrointestinal bleeding were 1.03 (95% CI, 0.85-1.24) for women who used 0.5 to 1.5 standard aspirin tablets/week, 1.30 (95% CI, 1.07-1.58) for 2 to 5 tablets/week, 1.77 (95% CI, 1.44-2.18) for 6-14 tablets/week, and 2.24 (95% CI, 1.66-3.03) for >14 tablets/week (P_{trend}<.001). Similar dose-response relationships were observed among short-terms users (≤ 5 years; P_{trend}<.001) and long-term users (>5 years; P_{trend}<.001). In contrast, after adjustments were made for dose, increasing duration of use did not confer greater risk of bleeding (P_{trend}=0.28).

Conclusions—Regular aspirin use is associated with gastrointestinal bleeding. Risk appears more strongly related to dose than duration of aspirin use. Efforts to minimize adverse effects of aspirin therapy should emphasize using the lowest effective dose among both short-term and long-term users.

Keywords

Aspirin; dose; duration; long-term; gastrointestinal bleeding

Introduction

Many guidelines recommend long-term use of aspirin for prevention of cardiovascular events among patients with prior cardiovascular disease or multiple risk factors.1, 2 However, aspirin is associated with increased risk of major gastrointestinal bleeding.3-12 A recent meta-analysis found an approximately two-fold higher risk of gastrointestinal bleeding among individuals regularly using aspirin compared to placebo.9

Nonetheless, data regarding the influence of duration of use and dose of aspirin on bleeding risk are limited and conflicting. Some studies show that risk of aspirin-associated bleeding may diminish with continued exposure,13 whereas others suggest that the hazard accumulates over time.14 One meta-analysis found that increasing dose was associated with greater risk of gastrointestinal bleeding,10 whereas two others concluded that risk was not dose-dependent.8, 9 Most prospective data examining aspirin and gastrointestinal bleeding are based on secondary analysis of intervention trials or studies of prescription registries. However, trials are based on relatively infrequent bleeding events, are conducted within carefully selected trial populations (e.g. patients with coronary artery disease), and are only able to examine a limited number of doses over a short duration. Registry studies collect limited data on non-prescription aspirin usage and confounding risk factors.

Based on these limitations, we prospectively examined the effects of aspirin use on risk of major gastrointestinal bleeding among women enrolled in the Nurses' Health Study (NHS). This cohort has provided detailed and updated information regarding aspirin use across a wide range of intake for over 30 years.

Methods

Study Population

The NHS began in 1976 when 121,701 U.S. female registered nurses, aged 30 to 55 years, returned a detailed health questionnaire. With a follow-up rate of exceeding 92%, questionnaires subsequently have been mailed every two years to update information.15 Participants in the NHS were not selected on the basis of their health status, comorbid

conditions, or use of medications including aspirin.16 The institutional review board at the Brigham and Women's Hospital approved this study.

Assessment of Aspirin Use

We have previously detailed our assessment of aspirin and non-steroidal antiinflammatory drugs (NSAID) use in the NHS cohort.17 Briefly, beginning in 1980, we asked women if they used aspirin in most weeks and if they answered yes, the number of pills or capsules per week and years of use. We updated this information biennially (except in 1986). Early in the study, most women used standard-dose 325-mg aspirin tablets;18 to reflect secular trends in consumption of low-dose, or baby aspirin, questionnaires after 1992 asked participants to convert intake of four baby aspirin to one adult tablet. The major reasons for aspirin use as assessed in a subsample of the cohort taking 1 to 6 aspirin/week and ≥ 7 aspirin/week were headache (32% and 18%, respectively); arthritis/musculoskeletal pain (46% and 65%); cardiovascular disease prevention (9% and 8%); and other reasons (13% and 9%).19

Ascertainment of Cases

In 2004, we asked participants to report episodes of gastrointestinal bleeding which required hospitalization or blood transfusion, a definition consistent with previous studies.11 Participants were asked to provide the site of their bleeding and the year of their bleed. As a validation, we verified accuracy of self-reports by reviewing medical records among a subsample of 351 women Two gastroenterologists, blinded to exposure, independently reviewed records. The correlation between self-reported date of diagnosis and confirmed date of diagnosis was 0.74 (*P* value<.001); self-reported classification of upper (esophagus, stomach, and duodenum) and lower (colon or rectum) gastrointestinal bleeding had an accuracy of 94.5% (95% CI, 91.4%-96.8%). The etiology of gastrointestinal bleeding was adjudicated based on review of the medical records, which documented active bleeding, stigmata of recent bleeding, or a lesion reasonably expected to result in recent hemorrhage in the absence of other causes (e.g. diverticula).20

Statistical Analysis

At baseline, we included women who returned the 1990 aspirin questionnaire. We excluded women with a prior history of gastrointestinal bleeding, cancer, peptic ulcer disease, bleeding related to cancer or polypectomy, or without a date of bleeding diagnosis. After these exclusions, 87,680 women were eligible for analysis. Person-time for each participant was calculated from the date of return of the baseline questionnaire to the date of first gastrointestinal bleeding, death from any cause or June 1, 2004, which ever came first.

As previously described, to reduce within-person variation, we used the cumulative average intake of aspirin as reported on all available questionnaires up to the start of each 2-year follow-up interval.21, 22 Women who reported ≥2 standard aspirin tablets/week were defined as regular users, where as those who reported less were defined as non-regular users, consistent with prior analyses.17, 22 We also grouped women according to previously described categories of number of standard tablets used per week to estimate dosage of aspirin.17, 22, 23 We examined duration of aspirin use according to the number of years of regular aspirin use reported in 1980 with updating of this variable every 2 years.17, 22

We used Cox proportional hazards modeling using time-varying variables with the most updated information for aspirin and other covariates prior to each 2-year interval to calculative relative risks (RR) and 95% CIs.24-28 We censored participants after any reports of cancer during follow-up. We evaluated interactions by assessing the statistical

significance of a cross-product interaction term. We used SAS version 9.1.3 (Cary, NC). All *P*-values were 2-sided and < 0.05 was considered statistically significant.

Results

Among 87,680 women, we documented 1537 major gastrointestinal bleeding events over 1,095,193 person-years. Compared to participants who reported no aspirin use, women reporting the highest levels of use were older, had a higher body mass index (BMI), were less apt to exercise, more likely to use non-steroidal anti-inflammatory drugs (NSAIDs), and more likely to have diabetes mellitus, hypercholesteremia, hypertension, coronary artery disease, or osteoarthritis (Table 1).

We found that regular aspirin users (≥ 2 standard [325 mg] tablets/week) had a significantly higher risk of developing gastrointestinal bleeding compared to nonregular users (age-adjusted RR, 1.56 ; 95% CI, 1.41-1.73)(Table 2). The relationship remained largely unchanged even after adjusting for other risk factors, (multivariate RR, 1.43; 95% CI, 1.29-1.59). Compared to non-regular use, the number needed to harm (NNH) associated with regular aspirin use was 1,169 for major gastrointestinal bleeding from any site, 2,120 for bleeding from upper tract, 4,210 for bleeding from the lower tract and 6,809 for bleeding from the small bowel or an unknown site. Regular aspirin use was associated with a multivariate RR of bleeding originating from the upper gastrointestinal tract of 1.70 (95% CI, 1.45-2.00). Although regular aspirin use was also significantly associated with risk of bleeding originating from the lower gastrointestinal tract, the effect appeared to be somewhat weaker (multivariate RR, 1.21; 95% CI, 1.03-1.41). Although we did not collect data on the precise etiology of gastrointestinal bleeding in all of the cases, we reviewed medical records in a subsample of 351 cases. The most common causes of upper gastrointestinal bleeding were ulcers (59.5%), inflammation (gastritis/duodenitis) (22.0%), and arteriovenous malformations (6.0%),. The most common causes of lower gastrointestinal bleeding were inflammation (colitis) (47.3%), diverticuli (43.5%), and arteriovenous malformation (3.8%).

The apparent hazard associated with aspirin use was substantially greater with increasing dose (Table 3). Compared to participants who took no aspirin, women who took >14 tablets/week experienced the greatest risk (multivariate RR, 2.05; 95% CI, 1.53-2.74; P_{trend} <.001). Since women who reported regular use of higher doses may have used for longer periods, we further examined the influence of aspirin dose after additionally controlling for years of use. However, adjusted for duration of use, the effect of increasing aspirin dose remained strong (multivariate RR 2.24; 95% CI, 1.66-3.03 for >14 tablets/week; P_{trend} <.001). This effect of dose was observed for upper gastrointestinal bleeding (P_{trend} <.001) and lower gastrointestinal bleeding (P_{trend} =.004). Women who used >14 tablets/week had multivariate RRs of 3.61 (95% CI, 2.32-5.63) for upper and 1.45 (95% CI, 0.86-2.45) for lower gastrointestinal bleeding.

We examined whether aspirin dose influenced both short-term (≤5 years) and long-term (>5 years) users (Table 3). For both regular short-term and long-term users, increasing dose remained significantly associated with increasing risk of gastrointestinal bleeding. Among women who used >14 tablets/week, the multivariate RRs for gastrointestinal bleeding were 2.17 (95% CI, 1.51-3.12) for short-term users (P_{trend} <.001) and 1.94 (95% CI, 1.32-2.87) for long-term users (P_{trend}<.001). Duration of aspirin use did not significantly alter the association between aspirin dose and gastrointestinal bleeding risk ($P_{interaction}$=.15).

We also specifically assessed the effect of duration of regular use on risk of gastrointestinal bleeding. We observed a progressively greater risk of gastrointestinal bleeding with longer

duration of use, with the highest risk among women who used aspirin > 20 years (multivariate RR, 1.19; 95% CI, 0.86-1.63: P_{trend}=0.02) (Table 4). However, when we adjusted for the number of tablets/week, the effect of duration was no longer significant (multivariate RR for >20 years of aspirin, 0.79, 95% CI, 0.57-1.11; P_{trend}=0.28). We found similar associations for upper gastrointestinal bleeding, with increasing risk associated with longer duration of use. (P_{trend}=.004). However, after accounting for dose, the association of duration with risk of upper gastrointestinal bleeding was no longer significant (P_{trend}=0.74). For lower gastrointestinal bleeding, duration of use did not appear to be strongly associated with bleeding risk.

We considered the possibility that risk of gastrointestinal bleeding may vary according to underlying risk factors for which individuals may take aspirin. At the baseline assessment in 1990, 25,974 women had a history of prior myocardial infarction or coronary artery bypass grafting or had at least 2 cardiac risk factors (BMI ≥30 kg/m^2, diabetes mellitus, hypertension, current smoking, hypercholesterolemia). Among such women, regular aspirin use was associated with a multivariate RR of 1.55 (95% CI, 1.31-1.83) for gastrointestinal bleeding. We also did not find significant differences in the influence of aspirin in strata defined by age, body mass index, NSAID use, smoking, or alcohol use (Figure 1). In particular, the relative risk of bleeding was similar in women over age of 60 compared with younger women; however, the absolute risk of bleeding was higher among women over age 60 with an incidence rate of 1.97 per 1000 person-years compared with an incidence rate of 0.64 per 1000 person-years in the younger women.

Discussion

In this prospective cohort, long-term, regular aspirin use (≥2 standard [325mg] tablets/week) was associated with increased risk of major gastrointestinal bleeding. We observed that the risk was dose-dependent with the greatest risk seen among women who used >14 tablets/week. The dose-response relationships were similar among short-term (≤5 years) and long-term (>5 years) aspirin users. In contrast, increasing duration of aspirin use was not significantly associated with risk of gastrointestinal bleeding after adjusting for aspirin dose. Controlling for other known or suspected risk factors did not alter these findings.

Our results are supported by previous randomized controlled trials which have demonstrated that aspirin use is associated with increased risk of gastrointestinal bleeding.3¯11 Consistent with our study, a recent meta-analysis estimated that aspirin use was associated with an odds ratio (OR) of 1.68 (95% CI, 1.51-1.88).8

Our findings that gastrointestinal bleeding risk is associated with increasing dose of aspirin are supported by several experimental studies. Mucosal prostaglandin synthesis are decreased at higher doses of aspirin.29, 30 In addition, experimental animal models have shown that gastric mucosal injury is highly dose-dependent. Results from several human studies are also consistent with our findings. First, a meta-analysis of 31 clinical trials with 192,036 patients observed the highest risk of gastrointestinal bleeding in those taking the highest doses (>200 mg daily) of aspirin.10 Second, in the CURE trial, the ORs for major bleeding risks were 1.52 (95% CI 1.00-2.31) for patients randomized to 101-199 mg of aspirin daily and 1.7 (95% CI, 1.22-2.59) for ≥200 mg of aspirin daily compared to patients taking ≤100 mg (P_{trend} <.001).31 Our findings do contrast with other meta-analyses of which did not observe a significant effect of dose.8, 9 However, these studies included trials with significant heterogeneity and reached discordant conclusions from many of the individual trials included within the meta-analyses.

Although an association between aspirin use and risk of upper gastrointestinal bleeding is well described, our results also support a modest relationship with lower gastrointestinal bleeding. This is consistent with observations that aspirin induces systemic changes to prostaglandin metabolism, leading to disruption of mucosal cell integrity and permeability in the distal gastrointestinal tract.[32, 33] Subsequently, luminal toxins and bacteria can induce inflammatory changes, producing erosions and ulcers.[34, 35] Other studies have suggested that NSAIDs generally increase the risk of lower gastrointestinal bleeding, but have been limited by their retrospective design, narrow ranges of doses and inability to separately analyze aspirin and non-aspirin NSAIDs.[13, 36-38]

Because the utilization of aspirin for chronic disease prevention requires long-term intake, most intervention trials have insufficient follow-up, ranging from 3 to 60 months, to evaluate the effects of duration on risk.[3, 4, 6, 7, 39-41] Our study, conducted over 24 years of follow-up, suggests that risk may not significantly increase with longer duration of use after accounting for aspirin dose. Several lines of evidence support these findings. In the UK-TIA trial, patients randomized to aspirin had the highest rates of gastrointestinal bleeding in the first 152 days of treatment.[13] This may be due to enhanced mucosal expression of nitric oxide synthase[42] and upregulation of mucosal cell growth with long-term aspirin use.[43]

Although previous studies have demonstrated the association between aspirin use and risk of gastrointestinal bleeding,[8-10] our study has several important strengths. First, we collected detailed, updated information on aspirin during the 24 years of follow-up across a broad range of intake. Thus, we were able to analyze the effects of aspirin across a wider range of doses and duration of use than would be feasible in a randomized controlled trial. Second, our cohort design avoided biases associated with poorly matched controls and differential data collection inherent in most case control studies. Such biases have previously led to widely varying risk estimates.[44] Finally, since all of our participants were nurses, the accuracy of self-reported aspirin use is likely to be high.

Several limitations also exist in our study. First, aspirin intake was self-selected in our cohort, which may introduce biases to our results because women who took aspirin may have more co-morbidities than those who do not. However, we adjusted for these baseline differences to minimize this bias. Second, we cannot assess the relationship of bleeding risk to more refined categories of dose. However, most women over the time period of our study used standard 325-mg aspirin tablets, and we accounted for the use of lower dose (81 mg) by asking women to convert intake into standard dose equivalents. Our assessment of dose according to standard tablets/week is a relevant measure of a range of aspirin intake that has been previously associated with other dose-related outcomes in this cohort.[17, 19, 22] Third, since our cohort did not specifically query the aspirin formulation used, we were unable to address the difference between enteric coated versus plain aspirin. However, substantial evidence suggests that the influence of enteric coating on bleeding risk is not significant.[45] Fourth, because we collected updated data on aspirin use biennially, we were unable to examine day-to-day variation in use within each two-year time period. However, this would likely lead to non-differential misclassification of exposure, resulting in an underestimate of the association. Fifth, our study population consisted of female health professionals, which may limit the generalizability to other population. However, there is little biological reason to expect that differences in the association of aspirin with bleeding would differ by occupation or gender.

In summary, our results have potential implications for long-term aspirin use in the prevention of chronic disease. Specifically, the risk of gastrointestinal bleeding appears more strongly related to dose than duration of aspirin use. These results suggest that the

adverse effects of aspirin therapy can be minimized by using the lowest effective dose among both short-term and long-term users.

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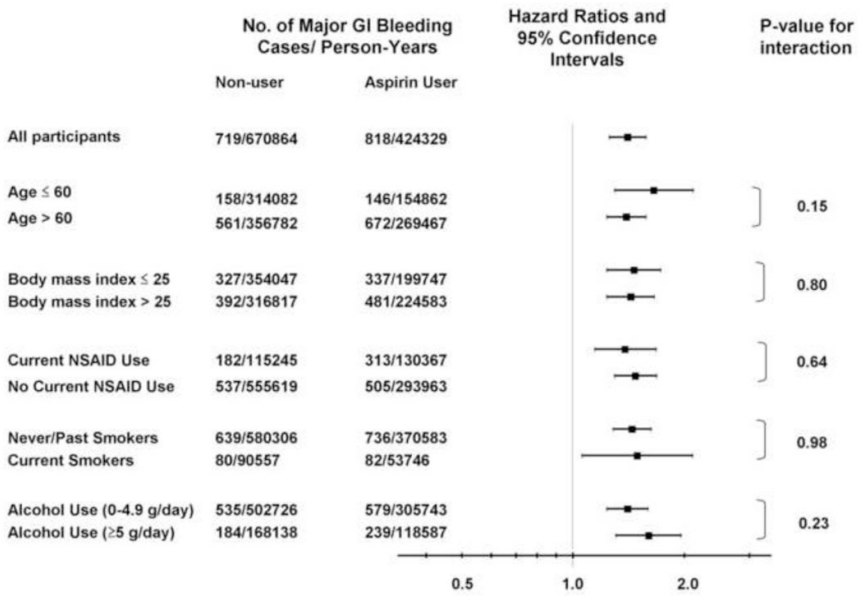

Figure 1.

Multivariate-adjusted Stratified Analyses of Gastrointestinal Bleeding Risk According to Aspirin Use. Multivariate hazard ratios are adjusted for age (years), NSAID use (yes or no), smoking status (never, past, current), body mass index (<21, 21-22.9, 23-24.9, 25-29.9, ≥30 kg/m^2), physical activity (<1.7, 1.7-4.5, 4.6-10.5, 10.6-22.0, ≥22.1 mets/week), alcohol (0, 0.1-4.9, 5-14, ≥15 g/day). For each stratified analysis, the stratification variable was omitted from the model.

Table 1

Baseline Characteristics of the Study Cohort in 1990

	Aspirin Tablets (325 mg) per week †				
Characteristics	**None (n=18570)**	**0.5-1.5 (n=36923)**	**2-5 (n=16392)**	**6-14 (n=11666)**	**>14 (n=4129)**
Age, mean (SD), y	56.5 (7.3)	55.9 (7.1)	56.8 (7.1)	57.8 (7.0)	58.8 (6.9)
Body mass index, mean (SD), kg/m^2‡	25.0 (6.3)	24.9 (6.1)	25.4 (6.2)	25.6 (6.5)	26.3 (6.9)
Current NSAID use, No. (%)§	1957 (10.5)	4796 (13.0)	3309 (20.2)	3085 (26.4)	1364 (33.0)
Physical activity, mean (SD), mets/wk	15.3 (20.7)	15.7 (22.5)	15.5 (22.5)	15.2 (20.6)	14.1 (18.8)
Diabetes mellitus, No. (%)	993 (5.4)	1471 (4.0)	844 (5.2)	771 (6.6)	284 (6.9)
Hypercholesterolemia, No. (%)	6169 (33.2)	12744 (34.5)	6416 (39.1)	4899 (42.0)	1759 (42.6)
Hypertension, No. (%)	5086 (27.4)	9665 (26.2)	5490 (33.5)	4560 (39.1)	1866 (45.2)
Coronary artery disease, No. (%)	238 (1.3)	380 (1.0)	447 (2.7)	363 (3.1)	113 (2.7)
Osteoarthritis, No. (%)	4615 (24.9)	9982 (27.0)	6123 (37.4)	5907 (50.6)	2750 (66.6)
Smoking status					
Past, No. (%)	6750 (36.4)	13817 (37.4)	6529 (39.8)	4729 (40.5)	1571 (38.1)
Current, No. (%)	3682 (19.8)	6171 (16.7)	2813 (17.2)	1969 (16.9)	780 (18.9)
Mean alcohol use, mean (SD), g/day	4.94 (9.6)	5.10 (9.4)	5.51 (9.7)	5.75 (10.4)	5.47 (10.4)

† One standard table is 325 mg of aspirin.

‡ Body mass index is weight in kilograms divided by the square of the height in meters.

§ Current NSAID use is defined as regular intake of at least 2 tablets per week.

Table 2

Relative Risk of Gastrointestinal Bleeding According to Regular Use of Aspirin†

	Non-Regular users	Regular users	*P* Value
All Cases			
No of cases/Person-years	719/670864	818/424329	
Incidence Rate (Case/1000 person-years)	1.07	1.93	
Age-adjusted RR (95% CI)	1.0	1.56 (1.41-1.73)	<.001
Multivariate RR (95% CI)‡	1.0	1.43 (1.29-1.59)	<.001
Upper Gastrointestinal Bleeding*			
No of cases/Person-years	267/6710864	369/424329	
Incidence Rate (Case/1000 person-years)	0.40	0.87	
Age-adjusted RR (95% CI)	1.0	1.89 (1.62-2.22)	<.001
Multivariate RR (95% CI)‡	1.0	1.70 (1.45-2.00)	<.001
Lower Gastrointestinal Bleeding**			
No of cases/Person-years	345/670864	319/424329	
Incidence Rate (Case/1000 person-years)	0.51	0.75	
Age-adjusted RR (95% CI)	1.0	1.29 (1.11-1.51)	0.001
Multivariate RR (95% CI)‡	1.0	1.21 (1.03-1.41)	0.017
Small Bowel Bleeding***			
No of cases/Person-years	107/670864	130/424329	
Incidence Rate (Case/1000 person-years)	0.16	0.31	
Age-adjusted RR (95% CI)	1.0	1.59 (1.23-2.06)	<.001
Multivariate RR (95% CI)‡	1.0	1.45 (1.12-1.89)	0.005

†Regular aspirin use is defined as consumption of ≥ 2 tablets per week. Non-regular use is defined as consumption of < 2 tablets per week.

Relative risks (RR) are compared to non-regular users as reference group.

‡Multivariate RR model is adjusted for age, NSAID use (yes or no), smoking status (never, past, current), body mass index (<21, 21-22.9, 23-24.9, 25-29.9, ≥30 kg/m^2), physical activity (<1.7, 1.7-4.5, 4.6-10.5, 10.6-22.0, ≥22.1 mets/week), alcohol (0, 0.1-4.9, 5-14.9, ≥15 g/day)

*Upper gastrointestinal bleeding is defined as bleeding presumed to originate from the esophagus, stomach, or duodenum.

** Lower gastrointestinal bleeding is defined as bleeding presumed to originate from the colon or rectum.

*** Include 185 bleeding cases with unknown location of bleeding

Table 3

Relative Risk of Gastrointestinal Bleeding According to Dose of Aspirin Use[†]

	Aspirin Tablets (325 mg) per week					
	None	**0.5-1.5**	**2-5**	**6-14**	**>14**	***P* trend**
All Cases[§]						
No of cases/Person-years	141/175282	578/495582	405/242118	342/151224	71/30987	
Age-adjusted RR (95% CI)	1.0	1.19 (0.99-1.43)	1.54 (1.27-1.86)	2.09 (1.71-2.54)	2.57 (1.93-3.43)	<.001
Multivariate RR (95% CI)[‡]	1.0	1.02 (0.85-1.23)	1.27 (1.05-1.55)	1.67 (1.36-2.04)	2.05 (1.53-2.74)	<.001
Multivariate RR + Duration (95% CI)[§]	1.0	1.03 (0.85-1.24)	1.30 (1.07-1.58)	1.77 (1.44-2.18)	2.24 (1.66-3.03)	<.001
Upper Gastrointestinal Bleeding[*]						
No of cases/Person-years	48/175282	219/495582	169/242118	160/151224	40/30987	
Age-adjusted RR (95% CI)	1.0	1.35 (0.99-1.85)	1.92 (1.39-2.65)	2.87 (2.08-3.97)	4.20 (2.75-6.41)	<.001
Multivariate RR (95% CI)[‡]	1.0	1.20 (0.87-1.64)	1.61 (1.16-2.24)	2.30 (1.65-3.20)	3.29 (2.14-5.04)	<.001
Multivariate RR + Duration (95% CI)[§]	1.0	1.20 (0.87-1.65)	1.65 (1.19-2.30)	2.45 (1.74-3.44)	3.61 (2.32-5.63)	<.001
Lower Gastrointestinal Bleeding[**]						
No of cases/Person-years	69/175282	276/495582	178/242118	121/151224	20/30987	
Age-adjusted RR (95% CI)	1.0	1.16 (0.89-1.52)	1.40 (1.05-1.85)	1.55 (1.15-2.09)	1.52 (0.92-2.50)	0.003
Multivariate RR (95% CI)[‡]	1.0	0.96 (0.74-1.25)	1.13 (0.85-1.50)	1.23 (0.91-1.66)	1.23 (0.75-2.04)	0.034
Multivariate RR + Duration (95% CI)[§]	1.0	0.97 (0.74-1.26)	1.18 (0.88-1.57)	1.37 (1.00-1.87)	1.45 (0.86-2.45)	0.004
Short-Term Duration of Use (≤5 years) [//]						
No of cases/Person-years	141/175282	578/495582	339/198924	223/91725	39/15860	
Age-adjusted RR (95% CI)	1.0	1.20 (0.99-1.44)	1.58 (1.29-1.92)	2.23 (1.80-2.76)	2.75 (1.93-3.93)	<.001
Multivariate RR (95% CI)[‡]	1.0	1.03 (0.85-1.24)	1.78 (1.43-2.21)	2.17 (1.51-3.12)	2.17 (1.51-3.12)	<.001
Long-Term Duration of Use (>5 years)[//]						
No of cases/Person-years	141/175282	578/495582	66/43194	119/59500	32/15127	
Age-adjusted RR (95% CI)	1.0	1.19 (0.99-1.43)	1.36 (1.01-1.83)	1.84 (1.44-2.36)	2.40 (1.63-3.54)	<.001
Multivariate RR (95% CI)[‡]	1.0	1.02 (0.85-1.24)	1.18 (0.87-1.58)	1.52 (1.18-1.95)	1.94 (1.32-2.87)	<.001

[†] Relative risks (RR) are compared to non-users as reference group.

[§] Includes 237 bleeding cases with unknown or unspecified location

[‡] Multivariate RR model is adjusted for age, NSAID use (yes or no), smoking status (never, past, current), body mass index (<21, 21-22.9, 23-24.9, 25-29.9, ≥30 kg/m^2), physical activity (<1.7, 1.7-4.5, 4.6-10.5, 10.6-22.0, ≥22.1 mets/week), alcohol (0, 0.1-4.9, 5-14.9, ≥15 g/day)

[§] Multivariate RR model is adjusted for aforementioned variables as well as aspirin duration (continuous use in years).

[*] Upper gastrointestinal bleeding is defined as bleeding presumed to originate from the esophagus, stomach, or duodenum.

[**] Lower gastrointestinal bleeding is defined as bleeding presumed to originate from the colon or rectum.

[//] Duration of use is summation of years of regular aspirin users (≥2 standard tablets/week) based on each biennial questionnaire. Non-regular users (<2 standard tablets/week) were included as referent categories for both short and long-term duration analyses.

Table 4

Relative Risk of Gastrointestinal Bleeding According to Duration of Regular Aspirin Use[†]

	Duration of Continuous Use (years)					
	None	**1-5**	**6-10**	**11-20**	**>20**	***P* trend**
All Cases[§]						
No of cases/Person-years	1015/788056	302/186218	119/64855	61/29512	40/26553	
Age-adjusted RR (95% CI)	1.0	1.08 (0.95-1.23)	1.19 (0.98-1.44)	1.33 (1.03-1.73)	1.20 (0.87-1.65)	0.010
Multivariate RR (95% CI)[‡]	1.0	1.06 (0.93-1.21)	1.15 (0.95-1.40)	1.29 (1.00-1.68)	1.19 (0.86-1.63)	0.023
Multivariate RR + Dose (95% CI)[§]	1.0	0.99 (0.87-1.13)	0.98 (0.81-1.20)	0.98 (0.74-1.28)	0.79 (0.57-1.11)	0.280
Upper Gastrointestinal Bleeding[*]						
No of cases/Person-years	406/788056	123/186218	58/64855	31/29512	18/26553	
Age-adjusted RR (95% CI)	1.0	1.10 (0.89-1.34)	1.44 (1.09-1.90)	1.61 (1.12-2.33)	1.33 (0.83-2.14)	0.003
Multivariate RR (95% CI)[‡]	1.0	1.08 (0.88-1.32)	1.41 (1.06-1.86)	1.60 (1.11-2.31)	1.32 (0.82-2.12)	0.004
Multivariate RR + Dose (95% CI)[§]	1.0	0.97 (0.79-1.19)	1.13 (0.85-1.51)	1.09 (0.74-1.61)	0.76 (0.46-1.26)	0.744
Lower Gastrointestinal Bleeding[**]						
No of cases/Person-years	460/788056	127/186218	41/64855	23/29512	13/26553	
Age-adjusted RR (95% CI)	1.0	1.03 (0.85-1.26)	0.93 (0.68-1.29)	1.17 (0.77-1.79)	0.88 (0.51-1.53)	0.952
Multivariate RR (95% CI)[‡]	1.0	1.02 (0.83-1.24)	0.89 (0.64-1.22)	1.11 (0.73-1.69)	0.86 (0.49-1.49)	0.699
Multivariate RR + Dose (95% CI)[§]	1.0	0.98 (0.80-1.20)	0.82 (0.59-1.14)	0.97 (0.62-1.51)	0.70 (0.39-1.26)	0.212

[†] Relative risks (RR) are compared to those without any continuous aspirin use as reference group.

[§] Includes 237 bleeding cases with unknown or unspecified location

[‡] Multivariate RR model is adjusted for age, NSAID use (yes or no), smoking status (never, past, current), body mass index (<21, 21-22.9, 23-24.9, 25-29.9, ≥30 kg/m^2), physical activity (<1.7, 1.7-4.5, 4.6-10.5, 10.6-22.0, ≥22.1 mets/week), alcohol (0, 0.1-4.9, 5-14.9, ≥15 g/day)

[§] Multivariate RR model is adjusted for aforementioned variables as well as aspirin dose (continuous use in tablets per week).

[*] Upper gastrointestinal bleeding is defined as bleeding presumed to originate from the esophagus, stomach, or duodenum.

[**] Lower gastrointestinal bleeding is defined as bleeding presumed to originate from the colon or rectum.