

# A Propsective Study of Aspirin Use and the Risk of Gastrointestinal Bleeding in Men

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**Purpose:** Data regarding the influence of dose and duration of aspirin use on risk of major gastrointestinal (GI) bleeding are limited and conflicting. The aim of this study is to examine the long-term effects of dose and duration of aspirin use on GI bleeding in a large prospective cohort.

**Methods:** We conducted a prospective study of 32,989 men enrolled in the Health Professionals Follow-up Study (HPFS) without history of GI bleeding, ulcer or cancer in 1994 who each provided data on aspirin use and other risk factors biennially. We biennially collected updated data on aspirin use and other risk factors. In 2006 and 2008, we asked participants to report episodes of GI bleeding which required hospitalization or blood transfusions, site of bleed and date of the event. Among a subsample of 239 men, two gastroenterologists reviewed medical records and validated accuracy of self-reports. Person-time for each participant was calculated from date of return of the 1994 questionnaire to the date of their first GI bleed, death from any cause or January 1, 2008, whichever came first. We used Cox proportional hazards modeling to control for multiple bleeding risk factors and to calculate the 95% confidence interval (CI). We used the most updated information for aspirin use and other covariates prior to each 2-year interval.

**Results:** During 14 years of follow-up, 707 men reported an episode of major gastrointestinal bleeding over 377,231 person-years. After adjusting for risk factors, regular aspirin use ( $\geq 2$  times/week) had a multivariate relative risk (RR) of gastrointestinal bleeding of 1.32 (95% confidence interval [CI], 1.12-1.55) compared to non-regular use. The association was particularly evident for bleeding originating from the upper tract (multivariate RR, 1.49; 95% CI, 1.16-1.92). Compared to men who denied any aspirin use, the multivariate RRs of upper gastrointestinal bleeding were 1.05 (95% CI 0.71-1.52) for men who used 0.5-1.5 standard tablets per week, 1.31 (95% CI 0.88-1.95) for 2-5 aspirin per week, 1.63 (95% CI, 1.15-2.32) for 6-14 aspirin per week and 2.40 (95% CI, 1.10-5.22) for  $>14$  aspirin per week ( $P_{\text{trend}} < 0.001$ ). The overall risk also appeared to be dose-dependent among short-term users ( $< 5$  years;  $P_{\text{trend}} < .001$ ) and long-term users ( $\geq 5$  years;  $P_{\text{trend}} = 0.015$ ) (**Table 1**). In contrast, after controlling for dose, increasing duration of use did not appear to be associated with risk ( $P_{\text{trend}} = 0.749$ ).

**Conclusion:** Regular aspirin use increases the risk of gastrointestinal bleeding, especially from the upper tract. However, the risk of bleeding appears to be more strongly related to dose than to duration of use. Risk of bleeding should be minimized by using the lowest effective dose among short-term and long-term aspirin users.

**Table 1.** Relative Risk of Gastrointestinal Bleeding According to Aspirin Dose†

	Aspirin Tablets (325 mg) per week					<i>P</i> trend**
	None	0.5-1.5	2-5	6-14	>14	
Upper GI Cases						
No of cases/Person-years	66/117664	48/76621	47/65721	134/111974	8/5736	
Age-adjusted RR (95% CI)	1.0	1.07 (0.73-1.56)	1.30 (0.89-1.90)	1.68 (1.24-2.29)	2.41 (1.14-5.09)	<.001
Multivariate RR (95% CI) ‡	1.0	1.04 (0.71-1.52)	1.30 (0.89-1.91)	1.61 (1.18-2.20)	2.36 (1.11-5.00)	<.001
Multivariate RR + Duration(95% CI)§	1.0	1.05 (0.71-1.54)	1.31 (0.88-1.95)	1.63 (1.15-2.32)	2.40 (1.10-5.22)	<.001
Short-Term Users (<5 years)¶						
No of cases/Person-years	163/117552	104/63007	57/44449	154/53167	7/2250	
Age-adjusted RR (95% CI)	1.0	1.17 (0.91-1.50)	0.95 (0.70-1.30)	1.59 (1.26-2.01)	2.33 (1.08-5.06)	<.001
Multivariate RR (95% CI)‡	1.0	1.15 (0.89-1.48)	0.95 (0.70-1.29)	1.52 (1.20-1.93)	2.16 (0.99-4.70)	<.001
Long-Term Users (≥5 years)¶						
No of cases/Person-years	163/117552	33/13508	34/21219	147/58601	8/3479	
Age-adjusted RR (95% CI)	1.0	1.45 (0.98-2.14)	1.12 (0.77-1.64)	1.43 (1.13-1.82)	1.47 (0.71-3.04)	0.008
Multivariate RR (95% CI) ‡	1.0	1.42 (0.96-2.09)	1.14 (0.78-1.66)	1.39 (1.09-1.78)	1.49 (0.72-3.09)	0.015

†Relative Risk (RR) are compared to those without any continuous aspirin use as reference group

\*\*P trend calculated using median aspirin dose of each category as continuous variable.

‡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<sup>2</sup>, exercise (<1.7, 1.7-4.5, 4.6-10.5, 10.6-22.0,

$\geq 22.1$  mets/week), alcohol (0, 0.1-4.9, 5-14.9,  $\geq 15$  g/day).

¶Duration analyses include all bleeding cases.

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