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.

RESULTS: During 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) when compared with nonregular 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 women who used 2 to 5 tablets/week, 1.77 (95% CI, 1.44-2.18) for women who used 6 to 14 tablets/week, and 2.24 (95% CI, 1.66-3.03) for women who used more than 14 tablets/week (Ptrend = .001). Similar dose-response relationships were observed among short-term users (≤5 years; Ptrend < .001) and long-term users (>5 years; Ptrend < .001). In contrast, after adjustments were made for dose, increasing duration of use did not confer a greater risk of bleeding (Ptrend = .28).

CONCLUSION: Regular aspirin use is associated with gastrointestinal bleeding. Risk seems 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- and long-term users.

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KEYWORDS: Aspirin; Dose; Duration; Gastrointestinal bleeding; Long-term

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Conflict of Interest: Dr. Chan has served as a consultant to Bayer HealthCare.

Authorship: All authors had access to the data and played a role in writing this manuscript: study concept and design (ESH, WWH, ATC); acquisition of data (ESH, WWH, SSL, ATC); analysis and interpretation of data (ESH, LLS, ATC); drafting of the manuscript (ESH, LLS, WWH, SSL, ATC); critical revision of the manuscript for important intellectual content (ESH, LLS, WWH, SSL, ATC); statistical analysis (ESH, ATC); obtained funding (ATC); technical or material support (ATC); and study supervision (ATC). Dr Chan had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. An abstract of these data was presented at: the clinical plenary session of the American Gastroenterological Association/Digestive Disease Week, May 3, 2010, New Orleans, Louisiana. Requests for reprints should be addressed to Andrew T. Chan, MD, MPH, Gastrointestinal Unit, Massachusetts General Hospital, 55 Fruit Street, GRJ 722 Boston, MA 02114.
E-mail address: achan@partners.org.
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 2-fold higher risk of gastrointestinal bleeding among individuals regularly using aspirin compared with 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 2 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 (eg, 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 use and confounding risk factors.

On the basis of 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 more than 30 years.

### MATERIALS AND METHODS

#### Study Population

The NHS began in 1976 when 121,701 US female registered nurses, aged 30 to 55 years, returned a detailed health questionnaire. With a follow-up rate exceeding 92%, questionnaires subsequently have been mailed every 2 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

Previously, we have detailed our assessment of aspirin and nonsteroidal anti-inflammatory drug 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, they were asked to report 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 4 baby aspirin to 1 adult tablet. The major reasons for aspirin use as assessed in a subsample of the cohort taking 1 to 6 aspirin tablets/week and \(\geq 7\) aspirin tablets/week were headache (32% and 18%, respectively); arthritis/musculoskeletal pain (46% and 65%, respectively); cardiovascular disease prevention (9% and 8%, respectively); and other reasons (13% and 9%, respectively).\(^19\)

#### Ascertainment of Cases

In 2004, we asked participants to report episodes of gastrointestinal bleeding that 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 (\(P < .001\)); self-reported classification of upper (esophagus, stomach, and duodenum) and lower (colon or rectum) gastrointestinal bleeding had an accuracy of 94.5% (95% confidence interval [CI], 91.4-96.8). The cause of gastrointestinal bleeding was adjudicated on the basis of 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 (eg, diverticula).\(^20\)

#### Statistical Analysis

At baseline, we included women who returned the 1990 aspirin questionnaire. We excluded women with a history of gastrointestinal bleeding, cancer, peptic ulcer disease, or 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, whichever 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 re-

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**CLINICAL SIGNIFICANCE**

- The influence of aspirin dose and duration on the risk of gastrointestinal bleeding remains uncertain because of limitations of prior studies.
- Risk of gastrointestinal bleeding seems to be more strongly related to dose than duration of aspirin use.
- Bleeding risk can be minimized using the lowest effective dose among short- and long-term aspirin users.
ported ≥2 standard aspirin tablets/week were defined as regular users, whereas those who reported less were defined as nonregular users, consistent with prior analyses.\textsuperscript{17,22} We also grouped women according to previously described categories of the number of standard tablets used per week to estimate dosage of aspirin.\textsuperscript{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.\textsuperscript{17,22}

We used Cox proportional hazards modeling using time-varying variables with the most updated information for aspirin and other covariates before each 2-year interval to calculate relative risks (RRs) and 95% CIs.\textsuperscript{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 P < .05 was considered statistically significant.

\section*{RESULTS}
Among 87,680 women, we documented 1537 major gastrointestinal bleeding events during 1,095,193 person-years. Compared with participants who reported no aspirin use, women reporting the highest levels of use were older, had a higher body mass index, were less apt to exercise, were more likely to use nonsteroidal anti-inflammatory drugs, and were more likely to have diabetes mellitus, hypercholesterolemia, 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 with 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 with nonregular use, the number needed to harm associated with regular aspirin use was 1169 for major gastrointestinal bleeding from any site, 2120 for bleeding from upper tract, 4210 for bleeding from the lower tract, and 6809 for bleeding from the small bowel or an unknown site. Regular aspirin use was associated with a multivariate RR of 1.70 (95% CI, 1.45-2.00) for bleeding originating from the upper gastrointestinal tract. Although regular aspirin use also had a significant association with risk of bleeding originating from the lower gastrointestinal tract, the effect seemed to be somewhat weaker (multivariate RR 1.21; 95% CI, 1.03-1.41). Although we did not collect data on the precise cause 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%), diverticula (43.5%), and arteriovenous malformation (3.8%).

The apparent hazard associated with aspirin use was substantially greater with increasing dose (Table 3). Compared with 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\textsubscript{trend} < .001). Because women who reported regular use of higher doses may have used aspirin for longer periods, we further examined the influence of aspirin dose after also 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\textsubscript{trend} < .001).

\begin{table}[h]
\centering
\caption{Baseline Characteristics of the Study Cohort in 1990}
\begin{tabular}{|l|c|c|c|c|}
\hline
Characteristics & Aspirin Tablets (325 mg) per Week$^a$ & \\
& None (n = 18,570) & 0.5-1.5 (n = 36,923) & 2-5 (n = 16,392) & 6-14 (n = 11,666) & >14 (n = 4129) \\
\hline
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. (\%)$^c$ & 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) & 12,744 (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) & 13,817 (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/d & 4.94 (9.6) & 5.10 (9.4) & 5.51 (9.7) & 5.75 (10.4) & 5.47 (10.4) \\
\hline
\end{tabular}
\end{table}

\textsuperscript{a}One standard tablet is 325 mg of aspirin.

\textsuperscript{b}Body mass index is weight in kilograms divided by the square of the height in meters.

\textsuperscript{c}Current NSAID use is defined as regular intake of at least 2 tablets/week.

SD, Standard deviation; NSAID, nonsteroidal anti-inflammatory drug.
This effect of dose was observed for upper gastrointestinal bleeding (Multivariate RR 1.45 (95% CI, 1.12-1.89) <.001). However, after accounting for dose, the association of duration with risk of upper gastrointestinal bleeding was no longer significant (P trend = .74). For lower gastrointestinal bleeding, duration of use did not seem 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 myocardial infarction or coronary artery bypass grafting or had at least 2 cardiac risk factors (body mass index ≥ 30 kg/m², diabetes mellitus, hypertension, current smoking, or 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, nonsteroidal anti-inflammatory drug use, smoking, or alcohol use (Figure). In particular, the RR of bleeding was similar in women aged more than 60 years compared with younger women; however, the absolute risk of bleeding was higher among women aged more than 60 years, 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.

### Table 2: Relative Risk of Gastrointestinal Bleeding According to Regular Use of Aspirin

<table>
<thead>
<tr>
<th></th>
<th>Nonregular Users</th>
<th>Regular Users</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases/person-years</td>
<td>719/670,864</td>
<td>818/424,329</td>
<td></td>
</tr>
<tr>
<td>Incidence rate (case/1000 person-years)</td>
<td>1.07</td>
<td>1.93</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age-adjusted RR (95% CI)</td>
<td>1.0</td>
<td>1.56 (1.41-1.73)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Multivariate RR (95% CI)</td>
<td>1.0</td>
<td>1.43 (1.29-1.59)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Upper gastrointestinal bleeding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases/person-years</td>
<td>267/6,710,864</td>
<td>369/424,329</td>
<td></td>
</tr>
<tr>
<td>Incidence rate (case/1000 person-years)</td>
<td>0.40</td>
<td>0.87</td>
<td></td>
</tr>
<tr>
<td>Age-adjusted RR (95% CI)</td>
<td>1.0</td>
<td>1.89 (1.62-2.22)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Multivariate RR (95% CI)</td>
<td>1.0</td>
<td>1.70 (1.45-2.00)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Lower gastrointestinal bleeding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases/person-years</td>
<td>345/670,864</td>
<td>319/424,329</td>
<td></td>
</tr>
<tr>
<td>Incidence rate (case/1000 person-years)</td>
<td>0.51</td>
<td>0.75</td>
<td></td>
</tr>
<tr>
<td>Age-adjusted RR (95% CI)</td>
<td>1.0</td>
<td>1.29 (1.11-1.51)</td>
<td>.001</td>
</tr>
<tr>
<td>Multivariate RR (95% CI)</td>
<td>1.0</td>
<td>1.21 (1.03-1.41)</td>
<td>.017</td>
</tr>
<tr>
<td>Small bowel bleeding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases/person-years</td>
<td>107/670,864</td>
<td>130/424,329</td>
<td></td>
</tr>
<tr>
<td>Incidence rate (case/1000 person-years)</td>
<td>0.16</td>
<td>0.31</td>
<td></td>
</tr>
<tr>
<td>Age-adjusted RR (95% CI)</td>
<td>1.0</td>
<td>1.59 (1.23-2.06)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Multivariate RR (95% CI)</td>
<td>1.0</td>
<td>1.45 (1.12-1.89)</td>
<td>.005</td>
</tr>
</tbody>
</table>

CI = confidence interval; RR = relative risk.

aRegular aspirin use is defined as consumption of ≥ 2 tablets/week. Nonregular use is defined as consumption of < 2 tablets/week. RRs are compared with nonregular users as reference group.

bMultivariate 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/m²), physical activity (<1.7, 1.7-4.5, 4.6-10.5, 10.6-22.0, ≥22.1 mets/week), and alcohol intake (0, 0.1-4.9, 5-14.9, ≥15 g/day).

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

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

Includes 185 bleeding cases with unknown location of bleeding.

.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 gastrointestinal bleeding 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- 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 = .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 = .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 = .74). For lower gastrointestinal bleeding, duration of use did not seem to be strongly associated with bleeding risk.
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Table 3  Relative Risk of Gastrointestinal Bleeding According to Dose of Aspirin Use

<table>
<thead>
<tr>
<th>Aspirin Tablets (325 mg) per Week</th>
<th>None</th>
<th>0.5-1.5</th>
<th>2-5</th>
<th>6-14</th>
<th>&gt;14</th>
<th>P trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>All casesb</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases/person-years</td>
<td>141/175,282</td>
<td>578/495,582</td>
<td>405/242,118</td>
<td>342/151,224</td>
<td>71/30,987</td>
<td></td>
</tr>
<tr>
<td>Age-adjusted RR (95% CI)</td>
<td>1.0</td>
<td>1.19 (0.99-1.43)</td>
<td>1.54 (1.27-1.86)</td>
<td>2.09 (1.71-2.54)</td>
<td>2.57 (1.93-3.43)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Multivariate RR (95% CI)</td>
<td>1.0</td>
<td>1.02 (0.85-1.23)</td>
<td>1.27 (1.05-1.55)</td>
<td>1.67 (1.36-2.04)</td>
<td>2.05 (1.53-2.74)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Multivariate RR + duration (95% CI)</td>
<td>1.0</td>
<td>1.03 (0.85-1.24)</td>
<td>1.30 (1.07-1.58)</td>
<td>1.77 (1.44-2.18)</td>
<td>2.24 (1.66-3.03)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Upper gastrointestinal bleedinga</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases/person-years</td>
<td>48/175,282</td>
<td>219/495,582</td>
<td>169/242,118</td>
<td>160/151,224</td>
<td>40/30,987</td>
<td></td>
</tr>
<tr>
<td>Age-adjusted RR (95% CI)</td>
<td>1.0</td>
<td>1.35 (0.99-1.85)</td>
<td>1.92 (1.39-2.65)</td>
<td>2.87 (2.08-3.97)</td>
<td>4.20 (2.75-6.41)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Multivariate RR (95% CI)</td>
<td>1.0</td>
<td>1.20 (0.87-1.64)</td>
<td>1.61 (1.16-2.24)</td>
<td>2.30 (1.65-3.20)</td>
<td>3.29 (2.14-5.04)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Multivariate RR + duration (95% CI)</td>
<td>1.0</td>
<td>1.20 (0.87-1.65)</td>
<td>1.65 (1.19-2.30)</td>
<td>2.45 (1.74-3.44)</td>
<td>3.61 (2.32-5.63)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Lower gastrointestinal bleedingf</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases/person-years</td>
<td>69/175,282</td>
<td>276/495,582</td>
<td>178/242,118</td>
<td>121/151,224</td>
<td>20/30,987</td>
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<tr>
<td>Age-adjusted RR (95% CI)</td>
<td>1.0</td>
<td>1.16 (0.89-1.52)</td>
<td>1.40 (1.05-1.85)</td>
<td>1.55 (1.15-2.09)</td>
<td>1.52 (0.92-2.50)</td>
<td>.003</td>
</tr>
<tr>
<td>Multivariate RR (95% CI)</td>
<td>1.0</td>
<td>0.96 (0.74-1.25)</td>
<td>1.13 (0.85-1.50)</td>
<td>1.23 (0.91-1.66)</td>
<td>1.23 (0.75-2.04)</td>
<td>.034</td>
</tr>
<tr>
<td>Multivariate RR + duration (95% CI)</td>
<td>1.0</td>
<td>0.97 (0.74-1.26)</td>
<td>1.18 (0.88-1.57)</td>
<td>1.37 (1.00-1.87)</td>
<td>1.45 (0.86-2.45)</td>
<td>.004</td>
</tr>
<tr>
<td>Short-term duration of use (≤5 y)g</td>
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<td></td>
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</tr>
<tr>
<td>No. of cases/person-years</td>
<td>141/175,282</td>
<td>578/495,582</td>
<td>339/198,924</td>
<td>223/91,725</td>
<td>39/15,860</td>
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</tr>
<tr>
<td>Age-adjusted RR (95% CI)</td>
<td>1.0</td>
<td>1.20 (0.99-1.44)</td>
<td>1.58 (1.29-1.92)</td>
<td>2.23 (1.80-2.76)</td>
<td>2.75 (1.93-3.93)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Multivariate RR (95% CI)</td>
<td>1.0</td>
<td>1.03 (0.85-1.24)</td>
<td>1.78 (1.43-2.21)</td>
<td>2.17 (1.51-3.12)</td>
<td>2.17 (1.51-3.12)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Long-term duration of use (&gt;5 y)g</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases/person-years</td>
<td>141/175,282</td>
<td>578/495,582</td>
<td>66/43,194</td>
<td>119/59,500</td>
<td>32/15127</td>
<td></td>
</tr>
<tr>
<td>Age-adjusted RR (95% CI)</td>
<td>1.0</td>
<td>1.19 (0.99-1.43)</td>
<td>1.36 (1.01-1.83)</td>
<td>1.84 (1.44-2.36)</td>
<td>2.40 (1.63-3.54)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Multivariate RR (95% CI)</td>
<td>1.0</td>
<td>1.02 (0.85-1.24)</td>
<td>1.18 (0.87-1.58)</td>
<td>1.52 (1.18-1.95)</td>
<td>1.94 (1.32-2.87)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

CI = confidence interval; RR = relative risk.

aRRs are compared with non-users as reference group.

bIncludes 237 bleeding cases with unknown or unspecified location.

bMultivariate 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/m2), physical activity (<1.7, 1.7-4.5, 4.6-10.5, 10.6-22.0, ≥22.1 mets/wk), and alcohol intake (0, 0.1-4.9, 5-14.9, ≥15 g/d).

bMultivariate RR model is adjusted for aforementioned variables and aspirin duration (continuous use in years).

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

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

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

DISCUSSION

In this prospective cohort, long-term, regular aspirin use (≥2 standard [325-mg] 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 demonstrating 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 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 is 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 also are 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 Clopidogrel in Unstable angina to prevent Recurrent Events trial, the odds ratios for major bleeding risks were 1.52 (95% CI, 1.00-2.31) for patients randomized to 101 to 199 mg of aspirin daily and 1.7 (95% CI, 1.22-
Patients randomized to ≥ 200 mg of aspirin daily, compared with patients taking ≤ 100 mg (P_{trend} < .001). Our findings contrast with other meta-analyses that did not reach discordant conclusions from many of the individual trials included within the meta-analyses. 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. Finally, because 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 comorbidities 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 a lower dose (81 mg) by asking women to convert intake into standard dose equiv-

### Table 4 Relative Risk of Gastrointestinal Bleeding According to Duration of Regular Aspirin Use

<table>
<thead>
<tr>
<th>Duration of Continuous Use (y)</th>
<th>None</th>
<th>1-5</th>
<th>6-10</th>
<th>11-20</th>
<th>&gt;20</th>
<th>P trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cases(^b)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases/person-years</td>
<td>1015/788,056</td>
<td>302/186,218</td>
<td>119/66,855</td>
<td>61/29,512</td>
<td>40/26,553</td>
<td></td>
</tr>
<tr>
<td>Age-adjusted RR (95% CI)</td>
<td>1.0</td>
<td>1.08 (0.95-1.23)</td>
<td>1.19 (0.98-1.44)</td>
<td>1.33 (1.03-1.73)</td>
<td>1.20 (0.87-1.65)</td>
<td>.010</td>
</tr>
<tr>
<td>Multivariate RR (95% CI)(^c)</td>
<td>1.0</td>
<td>1.06 (0.93-1.21)</td>
<td>1.15 (0.95-1.40)</td>
<td>1.29 (1.00-1.68)</td>
<td>1.19 (0.86-1.63)</td>
<td>.023</td>
</tr>
<tr>
<td>Multivariate RR + dose (95% CI)(^d)</td>
<td>1.0</td>
<td>0.99 (0.87-1.13)</td>
<td>0.98 (0.81-1.20)</td>
<td>0.98 (0.74-1.28)</td>
<td>0.79 (0.57-1.11)</td>
<td>.280</td>
</tr>
<tr>
<td>Upper gastrointestinal bleeding(^a)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases/person-years</td>
<td>406/788,056</td>
<td>123/186,218</td>
<td>58/66,855</td>
<td>31/29,512</td>
<td>18/26,553</td>
<td></td>
</tr>
<tr>
<td>Age-adjusted RR (95% CI)</td>
<td>1.0</td>
<td>1.10 (0.89-1.34)</td>
<td>1.44 (1.09-1.90)</td>
<td>1.61 (1.12-2.33)</td>
<td>1.33 (0.83-2.14)</td>
<td>.003</td>
</tr>
<tr>
<td>Multivariate RR (95% CI)(^c)</td>
<td>1.0</td>
<td>1.08 (0.88-1.32)</td>
<td>1.41 (1.06-1.86)</td>
<td>1.60 (1.11-2.31)</td>
<td>1.32 (0.82-2.12)</td>
<td>.004</td>
</tr>
<tr>
<td>Multivariate RR + dose (95% CI)(^d)</td>
<td>1.0</td>
<td>0.97 (0.79-1.19)</td>
<td>1.13 (0.85-1.51)</td>
<td>1.09 (0.74-1.61)</td>
<td>0.76 (0.46-1.26)</td>
<td>.744</td>
</tr>
<tr>
<td>Lower gastrointestinal bleeding(^f)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases/person-years</td>
<td>460/788,056</td>
<td>127/186,218</td>
<td>41/66,855</td>
<td>23/29,512</td>
<td>13/26,553</td>
<td></td>
</tr>
<tr>
<td>Age-adjusted RR (95% CI)</td>
<td>1.0</td>
<td>1.03 (0.85-1.26)</td>
<td>0.93 (0.68-1.29)</td>
<td>1.17 (0.77-1.79)</td>
<td>0.88 (0.51-1.53)</td>
<td>.952</td>
</tr>
<tr>
<td>Multivariate RR (95% CI)(^c)</td>
<td>1.0</td>
<td>1.02 (0.83-1.24)</td>
<td>0.89 (0.64-1.22)</td>
<td>1.11 (0.73-1.69)</td>
<td>0.86 (0.49-1.49)</td>
<td>.699</td>
</tr>
<tr>
<td>Multivariate RR + dose (95% CI)(^d)</td>
<td>1.0</td>
<td>0.98 (0.80-1.20)</td>
<td>0.82 (0.59-1.14)</td>
<td>0.97 (0.62-1.51)</td>
<td>0.70 (0.39-1.26)</td>
<td>.212</td>
</tr>
</tbody>
</table>

**Notes:**
- CI = confidence interval; RR = relative risk.
- aRRs are compared with those without any continuous aspirin use as reference group.
- \(^b\)Includes 237 bleeding cases with unknown or unspecified location.
- \(^c\)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), and alcohol intake (0, 0.1-4.9, 5-14.9, >15 g/d).
- \(^d\)Multivariate RR model is adjusted for aforementioned variables and aspirin dose (continuous use in tablets per week).
- \(^e\)Upper gastrointestinal bleeding is defined as bleeding presumed to originate from the esophagus, stomach, or duodenum.
- \(^f\)Lower gastrointestinal bleeding is defined as bleeding presumed to originate from the colon or rectum.

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**References:**
1. Huang et al Long-Term Aspirin Use and Bleeding Risk
Our assessment of dose according to standard tablets/week is a relevant measure of a range of aspirin intake that has been associated with other dose-related outcomes in this cohort.17,19,22 Third, because 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 2-year time period. However, this would likely lead to nondifferential 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 populations. However, there is little biological reason to expect that differences in the association of aspirin with bleeding would differ by occupation or gender.

CONCLUSIONS

Our results have potential implications for long-term aspirin use in the prevention of chronic disease. Specifically, the risk of gastrointestinal bleeding seems 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- and long-term users.

ACKNOWLEDGMENTS

The authors acknowledge the continued dedication of the participants in the NHS; Gideon Aweh, MS (Channing Laboratory, Brigham and Women’s Hospital, Boston, Mass), for programming assistance; Karen Corsano, MA (Channing Laboratory, Brigham and Women’s Hospital), for programming assistance; and Barbara Egan, BS (Channing Laboratory, Brigham and Women’s Hospital), for assistance in medical records collection.

References

Huang et al. Long-Term Aspirin Use and Bleeding Risk


