

Bleeding Risks With Aspirin Use for Primary Prevention in Adults: A Systematic Review for the U.S. Preventive Services Task Force

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Background: The balance between potential aspirin-related risks and benefits is critical in primary prevention.

Purpose: To evaluate the risk for serious bleeding with regular aspirin use in cardiovascular disease (CVD) primary prevention.

Data Sources: PubMed, MEDLINE, Cochrane Central Register of Controlled Trials (2010 through 6 January 2015), and relevant references from other reviews.

Study Selection: Randomized, controlled trials; cohort studies; and meta-analyses comparing aspirin with placebo or no treatment to prevent CVD or cancer in adults.

Data Extraction: One investigator abstracted data, another checked for accuracy, and 2 assessed study quality.

Data Synthesis: In CVD primary prevention studies, very-low-dose aspirin use (≤ 100 mg daily or every other day) increased major gastrointestinal (GI) bleeding risk by 58% (odds ratio [OR], 1.58 [95% CI, 1.29 to 1.95]) and hemorrhagic stroke risk by 27% (OR, 1.27 [CI, 0.96 to 1.68]). Projected excess bleeding events with aspirin depend on baseline assumptions. Estimated excess

major bleeding events were 1.39 (CI, 0.70 to 2.28) for GI bleeding and 0.32 (CI, -0.05 to 0.82) for hemorrhagic stroke per 1000 person-years of aspirin exposure using baseline bleeding rates from a community-based observational sample. Such events could be greater among older persons, men, and those with CVD risk factors that also increase bleeding risk.

Limitations: Power to detect effects on hemorrhagic stroke was limited. Harms other than serious bleeding were not examined.

Conclusion: Consideration of the safety of primary prevention with aspirin requires an individualized assessment of aspirin's effects on bleeding risks and expected benefits because absolute bleeding risk may vary considerably by patient.

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Although widely regarded as safe for patient-directed, over-the-counter use, aspirin is associated with a range of harms. They vary in type and severity with the dosage and duration of use and underlying patient risk factors. By inhibiting cyclooxygenase-1 enzyme activity, low-dose aspirin leads to mucosal damage to the gastrointestinal (GI) tract and causes erosions, ulcers, and bleeding (1). Cyclooxygenase-mediated antiplatelet effects also increase non-GI bleeding events that range from trivial to serious, including intracranial bleeding events and hemorrhagic strokes (2). The advisability of using aspirin for the primary prevention of cardiovascular disease (CVD) events, with or without considering potentially beneficial effects on cancer, depends on accurately estimating harms associated with a specific prevention regimen and the absolute and relative variability in harms for any individual or targeted subpopulation. We report serious bleeding-related harms from aspirin used for primary prevention. This review, along with 2 companion reviews (3, 4) on CVD and cancer benefits, was used to inform updated U.S. Preventive Services Task Force (USPSTF) recommendations. These reviews

all share a clinical focus on populations eligible for CVD primary prevention.

METHODS

Our full report describes our methods in detail (5).

Data Sources and Searches

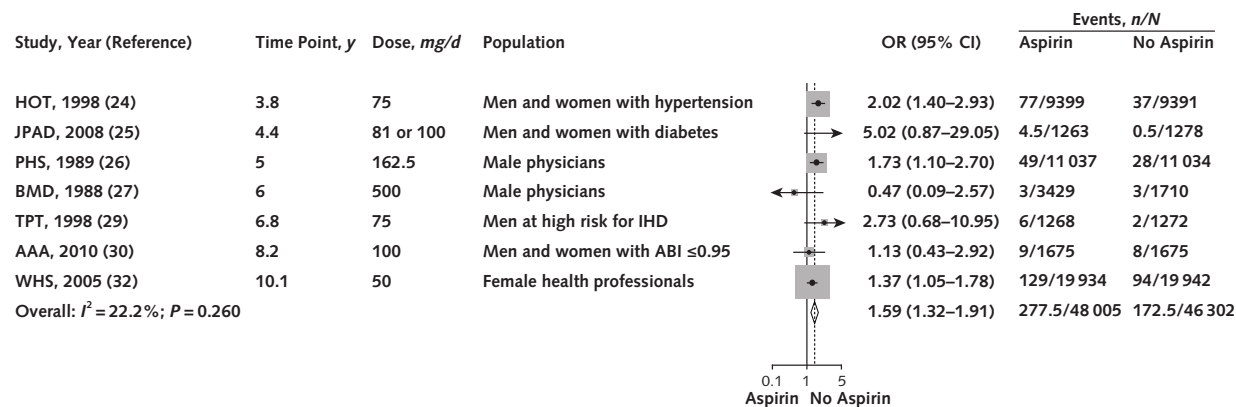
We reviewed all included and excluded studies in 4 relevant systematic reviews on aspirin-associated bleeding events (2, 6-8) and the 2 previous (9, 10) and updated USPSTF reviews (11, 12) to identify relevant literature. We supplemented this with newly identified studies found on PubMed, MEDLINE, and the Cochrane Central Registry of Controlled Trials from 1 January 2010 to 6 January 2015.

Study Selection

Two investigators independently reviewed abstracts and full-text articles against prespecified criteria (5). We included trials and large longitudinal cohort studies conducted in adults with a mean age of 40 years or older that evaluated regular oral aspirin use (≥ 75 mg at least every other day) for 1 year or longer for any indication compared with no treatment or placebo. We required studies to report major GI or intracranial bleeding. Major GI bleeding included cases leading to death, those requiring hospitalization or transfusion, or those described by the trial investigator as serious. Intracranial bleeding included hemorrhagic stroke and intracerebral, subdural, and subarachnoid hemorrhage.

See also:

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Figure 1. Major GI bleeding in CVD primary prevention trials.

AAA = Aspirin for Asymptomatic Atherosclerosis; ABI = ankle brachial index; BMD = British Doctor's Trial; CVD = cardiovascular disease; GI = gastrointestinal; HOT = Hypertension Optimal Treatment; IHD = ischemic heart disease; JPAD = Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes; OR = odds ratio; PHS = Physicians' Health Study; TPT = Thrombosis Prevention Trial; WHS = Women's Health Study.

Data Extraction and Quality Assessment

One investigator abstracted data from the included studies; another checked data for accuracy. The same investigators assessed the quality of included studies using study design-specific criteria defined by the USPSTF (13) and supplemented with Newcastle-Ottawa Scale criteria for cohort studies (14). Good-quality studies met most criteria and were downgraded to fair if not all criteria were met. Poor-quality studies (those with >40% attrition, >20% attrition between groups, other fatal flaws, cumulative effects of multiple minor flaws, or missing information significant enough to limit confidence in the validity of results) were excluded (5).

Data Synthesis and Analysis

Aspirin exposure was inferred from the intended dosages and treatment duration in trials, without adjustment for actual adherence because of incomplete reporting. The average intended dose per day was calculated; 325 mg daily or less was defined as low-dose and 100 mg daily or less was defined as very-low-dose. Because harms were often rare, we explored whether broadening bleeding definitions (that is, any intracranial bleeding vs. hemorrhagic stroke alone) changed the results. The broader definition made little difference, so we focused on hemorrhagic stroke (or intracerebral hemorrhage) results for consistency with an individual-participant data (IPD) meta-analysis (15) and our companion model (16). We used the Peto odds ratio (OR) for primary statistical analyses (17) because of rare events (that is, a control group event rate <1%) and repeated analyses using the Mantel-Haenszel OR; in both methods, we used a 0.5 continuity correction (18) with no major differences in results (Appendix Table 1, available at www.annals.org). We stratified results by population (primary prevention of CVD, secondary prevention of CVD, and colorectal cancer prevention) and conducted sensitivity analyses by dose, frequency,

and duration of therapy. We also examined data by relevant a priori subgroups: age, sex, race/ethnicity, comorbidities (diabetes, liver disease, ulcer disease, and previous GI bleeding), and concurrent medication use (selective serotonin reuptake inhibitors and nonaspirin nonsteroidal anti-inflammatory drugs [NSAIDs]) (19–21). Some subgroup analyses (for example, proton-pump inhibitor or statin use) were not specified a priori. Other aspirin-related harms (for example, age-related macular degeneration and ulcers) were addressed in our full report (5).

We calculated absolute treatment effects for bleeding outcomes to represent the range of control group event rates from the CVD primary prevention trials about aspirin use. For each trial, we divided the number of events for each outcome by the person-years at risk (approximated by multiplying the number of participants in the control group by the mean years of follow-up), assuming a constant risk over time. On the basis of the minimum, median, and maximum event rates (excluding outliers and zeros) for each outcome, we calculated a range of expected event rates after aspirin intervention using the pooled relative risks (RRs) from the included CVD primary prevention trials evaluating aspirin doses of 100 mg daily or less. Excess cases were calculated by subtracting the event rate per 1000 person-years for aspirin users from event rates in the control groups for each risk level. We contrasted excess cases based on control group event rates from trials with results based on control group bleeding rates from the largest cohort study (22).

Role of the Funding Source

Agency for Healthcare Research and Quality staff provided oversight for the project. The USPSTF liaisons helped resolve review scope issues but were not involved in the conduct of the review.

Table 1. Sensitivity Analyses for Bleeding in CVD Primary Prevention Trials

Study, Year (Reference)	Dose	Studies, k	Participants, n	Pooled OR (95% CI)	Included Trials
Major GI or extracranial bleeding					
Whitlock et al (main analysis), 2015 (5)*	Any	7	94 307	1.59 (1.32-1.91); $I^2 = 22.2\%$	HOT, JPAD, PHS, BMD, TPT, AAA, WHS
	≤100 mg	5	67 097	1.58 (1.29-1.95); $I^2 = 28.6\%$	HOT, JPAD, TPT, AAA, WHS
ATT Collaboration, 2009 (15)†	Any	6	95 456	1.54 (1.30-1.82)§; chi square = 3.1	BMD, PHS, TPT, HOT, PPP, WHS
De Berardis et al (cohort study), 2012 (22)*‡	≤300 mg	1	372 850	1.55 (1.46-1.65)	NA
Hemorrhagic stroke					
Guirguis-Blake et al (meta-analysis), 2015 (11)	Any	9	113 264	1.33 (1.03-1.71); $I^2 = 0\%$	PPP, HOT, JPAD, JPPP, PHS, BMD, TPT, AAA, WHS
	≤100 mg	7	86 054	1.27 (0.96-1.68); $I^2 = 0\%$	PPP, HOT, JPAD, JPPP, TPT, AAA, WHS
ATT Collaboration (IPD meta-analysis), 2009 (15)	Any	6	95 456	1.32 (1.00-1.75)§; chi square = 4.7	BMD, PHS, TPT, HOT, PPP, WHS
Intracranial hemorrhage, including hemorrhagic stroke					
Whitlock et al (main analysis), 2015 (5)	Any	10	114 540	1.34 (1.07-1.70); $I^2 = 0\%$	PPP, TPT, HOT, JPAD, PHS, JPPP, BMD, POPADAD, AAA, and WHS
	≤100 mg	8	87 330	1.30 (1.00-1.68); $I^2 = 0\%$	PPP, TPT, HOT, JPAD, JPPP, POPADAD, AAA, and WHS
De Berardis (cohort study), 2012 (22)‡	≤300 mg	1	372 850	1.54 (1.43-1.67)	NA

AAA = Aspirin for Asymptomatic Atherosclerosis; ATT = Antithrombotic Trialists; BMD = British Doctor's Trial; CVD = cardiovascular disease; GI = gastrointestinal; HOT = Hypertension Optimal Treatment; IPD = individual-participant data; JPAD = Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes; JPPP = Japanese Primary Prevention Project; NA = not applicable; OR = odds ratio; PHS = Physicians' Health Study; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; PPP = Primary Prevention Project; TPT = Thrombosis Prevention Trial; WHS = Women's Health Study.

* Major GI bleeding.

† IPD meta-analysis of GI or other major extracranial bleeding.

‡ Hospitalizations for first major bleeding event.

§ Year event rate ratio.

|| Incidence rate ratio.

RESULTS

Although we considered a larger set of trials that reported on harms associated with aspirin use (5), this review focuses on bleeding events from 10 of 11 CVD primary prevention trials in adults (mean age, 53.2 to 70.1 years) that addressed 1 or more serious bleeding events due to aspirin use (23-32). Trial details are reported in our companion article (3). We also identified 2 IPD meta-analyses (8, 15) of included trials that reported harms analyses complementing our trial-level results and 4 recent fair- or good-quality cohort studies (22, 33-35) of bleeding risks in persons with or without extended low-dose aspirin use; these studies were clearly or presumed for CVD primary prevention (Appendix Table 2, available at www.annals.org). Most relevant cohort data came from a large good-quality Italian study examining hospitalizations for all major bleeding events (intracranial and extracranial) after a median follow-up of 5.7 years in a population of 372 850 community-dwelling adults (186 425 new users of low-dose aspirin matched using propensity scoring with 186 425 never users; mean age, 69.4 years [range, 30 to 95 years]).

Major GI Bleeding

Seven CVD primary prevention trials of aspirin, 50 to 500 mg daily or every other day, used over 3.8 to 10.1 years (24-27, 29, 30, 32), showed a 59% increased risk for major GI bleeding (OR, 1.59 [95% CI, 1.32 to

1.91]; $I^2 = 22.2\%$) (Figure 1). Estimated bleeding risks remained similar when limited to trials of very-low-dose aspirin or when reported from an IPD meta-analysis examining a slightly different outcome (extracranial bleeding) of 6 CVD primary prevention trials (Table 1) (15). In cohort data, the effect of aspirin on hospitalizations for major GI bleeding events was similar (incidence rate ratio, 1.55 [CI, 1.46 to 1.65]) (22).

Hemorrhagic Stroke

Nine trials of aspirin, 50 to 500 mg daily or every other day, used for 3.6 to 10.1 years (23-27, 29-32) showed an increased risk for hemorrhagic stroke by about one third (OR, 1.33 [CI, 1.03 to 1.71]; $I^2 = 0\%$), regardless of dose (Figure 2 and Table 1). The point estimate and its statistical significance varied slightly between pooled analyses depending on the studies included and whether the outcome included any cases of intracranial hemorrhage (3, 5, 15). The only study with a statistically significant increase in hemorrhagic stroke (OR, 1.84 [CI, 1.01 to 3.35]) was conducted in an older hypertensive Japanese population (31). Cohort data suggested that hospitalizations for intracranial bleeding events may contribute more prominently to bleeding-related hospitalizations in community settings (incidence rate ratio, 1.54 [CI, 1.43 to 1.64]) (22), representing about one third of hospitalizations for all major bleeding events (22).

Baseline Estimates of Major Bleeding Risks (Trial vs. Cohort)

Mean major bleeding rates among control group participants from 6 CVD primary prevention trials were low (0.7 extracranial bleeding event and 0.3 hemorrhagic stroke per 1000 person-years) based on an IPD meta-analysis (15) (Table 2). In contrast, hospitalization rates for GI bleeding among control participants in the cohort study (22) were much higher (2.4 per 1000 person-years) than the highest GI bleeding rate suggested by the trials, with substantial variability by age (Table 2). The effect of baseline bleeding rate assumptions on calculations of excess bleeding events is illustrated in Table 3. Given a constant increase in the RR for bleeding associated with very-low-dose aspirin use, excess cases of major GI bleeding would vary considerably, depending on assumptions of the baseline rate (for example, 0.28 excess major GI bleeding event per 1000 person-years based on median trial control group rates compared with 1.39 excess cases per 1000 person-years based on cohort control group rates) (Table 3). For excess hemorrhagic strokes, variability is less extreme because baseline bleeding rates remain relatively rare whether estimated from trials or cohorts and some trials included participants with higher baseline bleeding risks.

Baseline Estimates of Major Bleeding Risks, by Subgroup

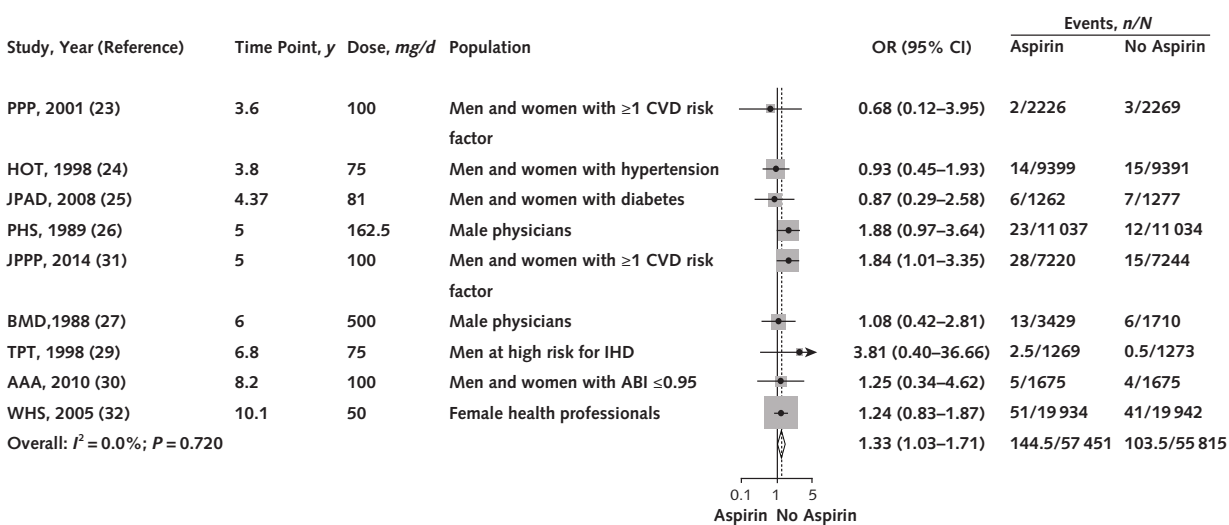
In both trial and cohort data, bleeding rates varied 2- to 4-fold at baseline among subgroups defined by increasing age, male sex, and selected cardiovascular risk factors (5). The largest and most consistent statistically significant differences in baseline bleeding risk oc-

curred with increasing age (increasing 1.5- to 2-fold in each subsequent decade after 50 years) and, to a lesser extent, male sex (Table 2). Multivariable analyses of both trial and cohort data suggested that age, sex, and other common factors independently modify baseline bleeding risks (Table 4). However, many trials restricted enrollment to participants without clear bleeding risk factors. After adjustment for bleeding risk factors—including aspirin use—a history of GI hospitalization was associated with the largest relative incidence rate of hospitalizations for major bleeding in cohort data (Table 4).

Risk Factors for Increased Major Bleeding, by Site

The RRs associated with participant characteristics differed somewhat between the 2 major bleeding sites. When analyses controlled for aspirin use, increasing age (per decade) had a greater effect on major GI or extracranial bleeding than on hemorrhagic stroke (Table 4). In addition to older age, male sex and diabetes mellitus increased the risk for serious bleeding, with possible variation in effect by site and due to imprecise magnitude. In an adjusted IPD meta-analysis of trial data (15), current smoking and mean blood pressure (BP) per 20 mm Hg were also independently associated with increased major extracranial bleeding events. For hemorrhagic stroke, only increasing age, current smoking, and elevated mean BP were clearly associated with increased risk, with elevated BP more strongly associated with hemorrhagic stroke than GI bleeding risk. Investigators noted that coronary heart disease risk factors associated with greater potential benefit from aspirin (that is, age, male sex, diabetes, current smok-

Figure 2. Hemorrhagic stroke in CVD primary prevention trials.



AAA = Aspirin for Asymptomatic Atherosclerosis; ABI = ankle brachial index; BMD = British Doctor's Trial; CVD = cardiovascular disease; HOT = Hypertension Optimal Treatment; IHD = ischemic heart disease; JPAD = Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes; JPPP = Japanese Primary Prevention Project; OR = odds ratio; PHS = Physicians' Health Study; PPP = Primary Prevention Project; TPT = Thrombosis Prevention Trial; WHS = Women's Health Study.

Table 2. Absolute Bleeding Rates Among Nonaspirin Control Groups, Overall and by Subpopulations*

Baseline Characteristic	Major GI or Extracranial Bleeding*, events per 1000 person-years	Hemorrhagic Stroke†, events per 1000 person-years	Hospitalization for Major Bleeding Event (95% CI)‡, events per 1000 person-years
All control participants	0.7	0.3	3.60 (3.48-3.72) Major extracranial bleeding (approximately): 2.40 Major intracranial bleeding (approximately): 1.20
Age subgroups	<65 y: 0.5 ≥65 y: 1.7	-	<50 y: 0.61 (0.41-0.91) 50-59 y: 1.40 (1.24-1.58) 60-69 y: 2.58 (2.40-2.77) 70-79 y: 4.61 (4.39-4.85) ≥80 y: 6.93 (6.51-7.38)
Sex subgroups	Men: 1.0 Women: 0.5	-	Men: 4.50 (4.30-4.70) Women: 2.86 (2.72-3.01)

GI = gastrointestinal.

* Resulting in hospitalization, transfusion, or death. Data from reference 15.

† Data from reference 15.

‡ Includes GI and intracranial bleeding. Data from reference 22.

ing, and mean BP) were also associated with increased major bleeding risks for 1 or both outcomes, although somewhat more weakly (15). The influence of co-medications was assessed in the cohort study only (Table 4) (22); in adjusted analyses, NSAID use further increased the risk for bleeding (adjusted incidence rate ratio, 1.10 [CI, 1.05 to 1.16]), with a possible protective effect on bleeding risk from proton-pump inhibitor and statin use.

Bleeding Events, by Aspirin Regimen

We found very few within-trial direct comparisons of aspirin regimens for primary prevention, and between-trial comparisons were potentially confounded by other between-study differences. Cohort studies were similarly uninformative because of restrictions to a single low-dose regimen (35), lack of evaluation of dosage effects (22), or issues with exposure measurement (33, 34). In the 2 large U.S. cohorts (33, 34), trend analyses strongly supported the effect of increasing the cumulative weekly aspirin dosage on lower or upper GI bleeding in both short- and long-term aspirin users, particularly women, and subarachnoid hemorrhages in men aged 55 years or older (36). Most bleeding cases (72.6%) involved daily, rather than less frequent, use of aspirin (33).

Using available trial and cohort data, we found that the risk for bleeding associated with low-dose aspirin use probably persists throughout use but declines with discontinuation. In the Women's Health Study, the cumulative incidence of GI bleeding did not plateau in very-low-dose aspirin users compared with placebo recipients throughout 10 years of follow-up (37). In contrast, a time point-stratified IPD meta-analysis suggested that the risk for major extracranial bleeding seen in early years decreased after 3 years (8). Because bleeding risks with placebo also declined with time, however, another mechanism for reduced bleeding events (such as unequal observation time) could have driven this observation (5, 38). Two cohort studies found that bleeding risk in regular aspirin users did not vary by duration of use (<5 years or ≥5 years) (33, 34). Weak evidence from the Women's Health Study suggested that excess GI bleeding risk rapidly attenuates after stopping aspirin (37).

DISCUSSION

We found relatively consistent estimates of increased risk for serious bleeding events with aspirin use in CVD primary prevention populations, whether based on trial or cohort data. For major GI bleeding, the best estimate with very-low-dose aspirin use in CVD primary prevention populations was an RR of 1.58 (CI, 1.29 to 1.95; $I^2 = 28.6\%$). Although studies varied in the duration of aspirin use and data were sparse and somewhat mixed on whether risk remains consistent throughout aspirin use, we believe that current empirical data suggest a constant risk throughout use. In contrast, due in part to rarer events and smaller effect size, the increased RR of hemorrhagic stroke was not statistically significant, with a best estimate of 1.27 (CI, 0.96 to 1.68) for very-low-dose aspirin use in CVD primary prevention. These are the estimates we provided for the companion model (16) based on a priori decisions to link harms estimates to the same population and aspirin dosages used for estimating benefits. For both types of bleeding, our pooled estimates were not statistically heterogeneous; their imprecision may reflect inadequate power because of rare events and reduced certainty of an average effect.

Estimates of baseline bleeding risk are critical for accurately assessing the absolute risk for bleeding with aspirin use and determining net benefit. Control group trial participants had much lower average risks for bleeding than those from cohort studies (Table 2). This probably reflects the fact that, beyond the variability in risk represented by age and sex, participants at increased risk for bleeding had limited or no representation in the CVD primary prevention trials (15). Our simulations illustrating a range of projected excess bleeding cases with very-low-dose aspirin use (Table 3) showed that assumptions about baseline bleeding rate are clearly important to avoid the underestimation of risk that could occur from applying trial-based averages based on selective patient groups to a more unselected general population.

Nonetheless, the research basis for appropriately establishing community-based rates of serious bleeding remains insufficient, despite a long-standing interest in this issue. For example, we found little data be-

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