

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

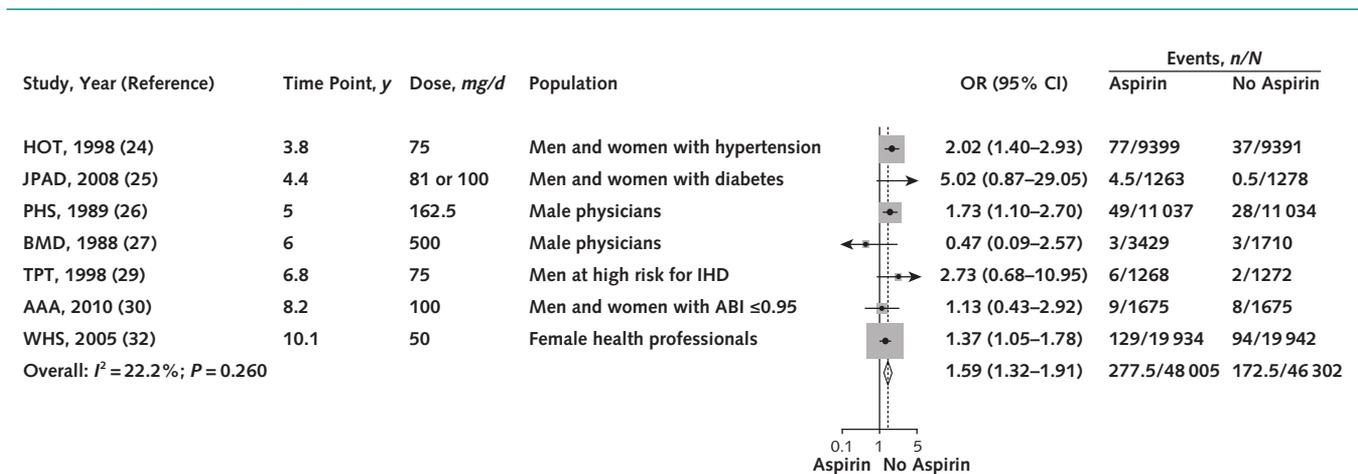
We reviewed all included and excluded studies in 4 relevant systematic reviews on aspirin-associated bleeding events (2, 6–8) and the 2 previous (9, 10) and updated USPSTF reviews (11, 12) to identify relevant literature. We supplemented this with newly identified studies found on PubMed, MEDLINE, and 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:

Related articles 777, 804, 814, 836
Editorial comment 846

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>I</i> ² = 22.2%	HOT, JPAD, PHS, BMD, TPT, AAA, WHS
	≤100 mg	5	67 097	1.58 (1.29-1.95); <i>I</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>I</i> ² = 0%	PPP, HOT, JPAD, JPPP, PHS, BMD, TPT, AAA, WHS
	≤100 mg	7	86 054	1.27 (0.96-1.68); <i>I</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>I</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>I</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

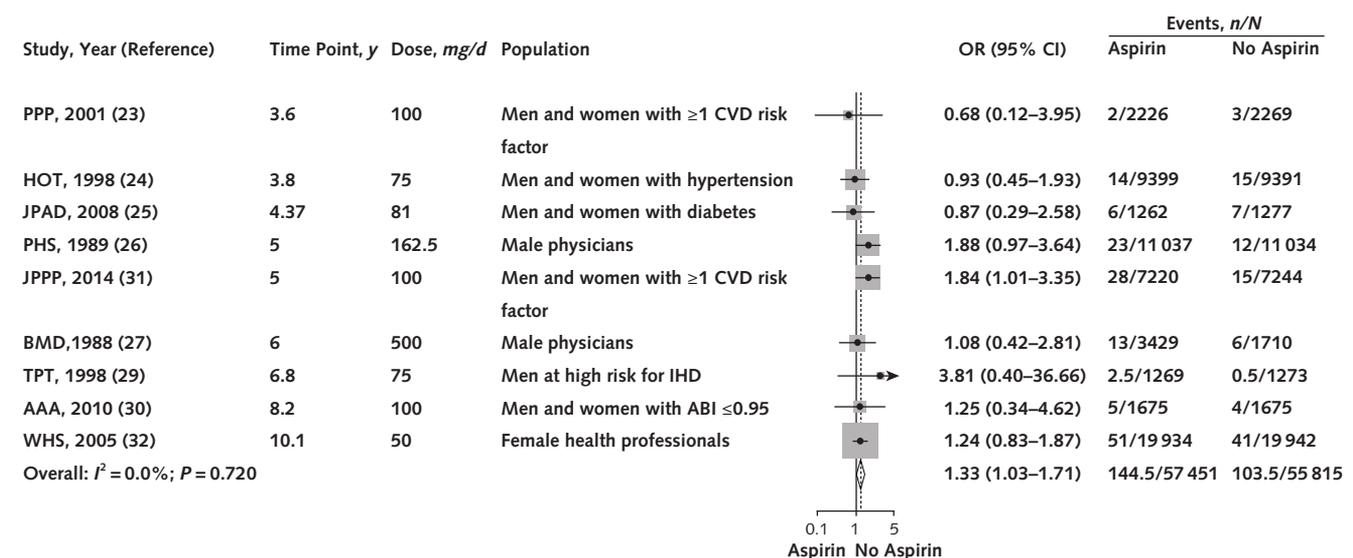
In both trial and cohort data, bleeding rates varied 2- to 4-fold at baseline among subgroups defined by increasing age, male sex, and selected cardiovascular risk factors (5). The largest and most consistent statistically significant differences in baseline bleeding risk oc-

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-

yond 1 large cohort study to update a commonly cited baseline rate for major upper GI complications (that is, 1 per 1000 person-years) that was previously derived from a systematic review of observational studies (39) and is not specific for bleeding. In subsequent work, the same researchers emphasized potential variability of harms from aspirin with differences in baseline GI risk. They clarified that their original estimate should be revised slightly upward (1 to 2 major upper GI complications per 1000 person-years) but would still apply only to persons without significant risks (that is, men aged ≤ 60 years or women aged ≤ 70 years, all without history of GI pain, ulcers, and NSAID use) (40). This slightly increased range is consistent with another recent estimate of baseline risk for upper GI bleeding in aspirin nonusers with no CVD history (1.85 cases per 1000 person-years) (41). Although we found the average baseline GI bleeding rate to be slightly higher (approximately 2.4 cases per 1000 person-years) when using more recent cohort data, we believe these estimates are all reasonably similar (Table 2).

From a clinical perspective, factors that either increase the risk for baseline bleeding or enhance aspirin's effect on bleeding can increase absolute rates of bleeding events with aspirin use. Although we found little evidence of effect modification for aspirin-related bleeding effects by medications or other factors that would be commonly present in candidates for CVD primary prevention, baseline bleeding rates differed substantially across expected patient risk factors. Older age and male sex consistently had an increased baseline bleeding risk, and some evidence indicated increased bleeding risk with CVD risk factors, such as diabetes, current smoking, and elevated BP. Other researchers have determined that GI bleeding risk fac-

tors (that is, older age, male sex, history of GI ulcers or complications, and NSAID use) are relatively prevalent among aspirin users in the community (40), which suggests that substantial variability in cases of upper GI complications is to be expected among some users. These data are consistent with our findings, implying considerable potential variability in excess serious bleeding events with aspirin use because of risk factor differences among community-dwelling aspirin users.

We found no adequately validated tools for assessing bleeding risks associated with aspirin use in primary prevention. A single risk prediction tool for upper GI complications has been published and is publicly available (42). This tool has potential strengths but also deficiencies, including the incorporation of approaches to modifying the bleeding risk that are not empirically proven in a primary prevention population—for which caution clearly is warranted (43)—and insufficient external validation to confirm its readiness for clinical application (44). Therefore, selecting patients for aspirin prevention may be pragmatic through qualitative consideration of bleeding risk factors or candidate inclusion limited to those fitting trial selection criteria, which excludes those at increased risk (for example, previous ulcer or GI bleeding) and those with aspirin intolerance or contraindications (5).

A stepwise practical approach, outlined by the European Society of Cardiology (45), is to select candidates for aspirin prevention on the basis of minimizing potential harms in those most likely to benefit. First, the risk for major CVD events is determined (with no further consideration of aspirin use in those below a 10-year risk threshold of 10%). Second, safety is assessed by eliminating candidates with a history of bleeding without reversible causes or with concurrent use of other

Table 3. Absolute Events Caused or Prevented With Very-Low-Dose Aspirin Use for ≤ 10 y*

Outcome	Risk Level†	Baseline Risk for Outcome, events per 1000 person-years	Relative Risk (95% CI)	Events Caused per 1000 Person-Years (95% CI)‡
Major GIB§ (k = 5)	Low	0.23	1.58 (1.29 to 1.95)	0.13 (0.07 to 0.22)
	Median	0.49		0.28 (0.14 to 0.46)
	High	0.58		0.34 (0.17 to 0.55)
	Highest	1.04		0.60 (0.30 to 0.99)
ICH, including HS (k = 8)	Low	0.20	1.30 (1.00 to 1.68)	0.06 (0.00 to 0.14)
	Median	0.47		0.14 (0.00 to 0.32)
	High	0.59		0.18 (0.00 to 0.40)
	Highest	1.25		0.38 (0.00 to 0.85)
HS (k = 7)	Low	0.00	1.27 (0.96 to 1.68)	0.00 (0.00 to 0.00)
	Median	0.37		0.10 (−0.01 to 0.25)
	High	0.42		0.11 (−0.02 to 0.29)
	Highest	1.26		0.34 (−0.05 to 0.86)
Major bleeding event	Cohort	2.4 (GIB)	1.58 (1.29 to 1.95) (GIB)¶	1.39 (0.70 to 2.28) (GIB)
		1.2 (HS)	1.27 (0.96 to 1.68) (HS)¶	0.32 (−0.05 to 0.82) (HS)
		3.6 (total)		1.71 (0.65 to 3.10) (total)
		3.6	1.55 (1.48 to 1.63)	1.98 (1.73 to 2.27)

CVD = cardiovascular disease; GIB = gastrointestinal bleeding; HS = hemorrhagic stroke; ICH = intracranial hemorrhage.

* Very-low-dose aspirin use was defined as ≤ 100 mg/d. Data are from 8 CVD primary prevention trials. Boldface values represent events clearly caused by aspirin use (i.e., 95% CI does not include both caused and prevented events).

† Low (minimum), median, and high (maximum) control group rate for each outcome, excluding zeros and outliers from the set of CVD primary prevention trials. For major GIB and HS, "highest" indicates the maximum and "high" is the second highest.

‡ Negative values indicate cases prevented.

§ Data from companion systematic review on CVD primary prevention (11).

|| Baseline risk as reported by included cohort studies.

¶ Using cohort baseline risk and trial relative risks to estimate events caused or prevented.

Table 4. Relative Rate Ratios for Bleeding Among Subpopulations From Trials and Cohort Studies

Baseline Characteristic	Adjusted Incidence Rate Ratio (95% CI)		
	Major GI or Extracranial Bleeding*	Hemorrhagic Stroke†	Hospitalization for Major Bleeding Event‡
Age (per decade)	2.15 (1.93-2.39)	1.59 (1.33-1.90)	1.05 (1.05-1.05)§
Male sex (vs. female sex)	1.99 (1.45-2.73)	1.11 (0.52-2.34)	1.69 (1.61-1.79)
Diabetes (yes vs. no)	1.55 (1.13-2.14)	1.74 (0.95-3.17)	1.36 (1.28-1.44)
Current smoker (yes vs. no)	1.56 (1.25-1.94)	2.18 (1.57-3.02)	
Mean BP (per 20 mm Hg)	1.32 (1.09-1.58)	2.18 (1.62-2.87)	
Cholesterol level (per 1 mmol/L)	0.99 (0.90-1.08)	0.90 (0.77-1.07)	
BMI (per 5 kg/m ²):	1.24 (1.13-1.35)	0.85 (0.71-1.02)	
Previous GI hospitalization (yes vs. no)	-	-	2.87 (2.46-3.35)
Medication use (yes vs. no)			
NSAID	-	-	1.10 (1.05-1.16)
Aspirin (current vs. never)	-	-	1.61 (1.54-1.69)
Any antihypertensive	-	-	1.14 (1.08-1.19)
Statin	-	-	0.67 (0.62-0.71)
PPI	-	-	0.84 (0.80-0.88)

BMI = body mass index; BP = blood pressure; GI = gastrointestinal; NSAID = nonsteroidal anti-inflammatory drug; PPI = proton-pump inhibitor.

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

† Data from reference 15.

‡ Includes GI bleeding, intracranial hemorrhage, and hemorrhagic stroke. Data from reference 22.

§ Per year.

|| Mean of systolic and diastolic BPs combined.

medications that increase bleeding risk. Finally, for patients without safety concerns, aspirin is recommended for those with a clear CVD benefit or on a case-by-case basis by considering values, preferences, and other potential benefits when potential harms and benefits seem closely balanced.

In terms of safety, some medications (for example, antiplatelet or anticoagulant drugs) may be considered absolute or relative contraindications to aspirin use for primary prevention because of their association with elevated bleeding risk (40, 46, 47). The NSAIDs and other medications used commonly in CVD primary prevention populations (for example, selective serotonin reuptake inhibitors) also increase bleeding risk, but less significantly so (47), and our review found limited data on their use with aspirin. Clinicians should remain aware that these medications may be added at some point during an aspirin regimen, even when absent at initiation (48). Thus, clinicians must remain alert to potential drug interactions with long-term aspirin use. Using the lowest possible dosage for the appropriate duration to gain the desired benefit is a prudent approach to avoid unnecessary harm.

A patient's willingness and ability to use a daily medication is another consideration for selecting good candidates, particularly for broader prevention effects beyond CVD. On the basis of current data, most investigators agree that achieving cancer benefits requires continuous aspirin use for 4 to 5 years (5, 49) and perhaps longer for lower dosages or less than daily use (50). Primarily due to the differing time frames over which risks and benefits might be expected to occur (early and throughout active use for bleeding risks and CVD events [11] but delayed 10 to 20 years for potential colorectal cancer effects), life expectancy may also affect considerations. Future research that clarifies the minimal duration, timing, and persistence of benefits

and the risks with low-dose aspirin use could alter considerations of who is likely to benefit.

Our review had limitations. By excluding CVD secondary prevention populations, we had reduced power resulting in imprecision, particularly for rare bleeding events. Nonetheless, given the known differences between CVD primary and secondary prevention populations in relative causes of death (5) and other factors, including baseline bleeding risk (41) and the proportional effect of hemorrhagic versus ischemic strokes (15), we emphasized data from low-dose aspirin use in primary prevention populations to avoid inappropriate extrapolation or faulty conclusions. Because of limitations in study reporting, some types of serious bleeding (for example, lower GI) are not adequately represented in our results. Total bleeding events (including less serious bleeding that may be important to patients) are clearly increased (2) but were too variably reported to summarize. Data on other harms, such as ulcers, and other potential issues (for example, diverticular disease complications) (51-53) that may be affected by low-dose aspirin use were too limited to incorporate because of our restricted focus and limitations in study reporting.

Further research is critically important to better specify the broad range of potential benefits and harms with aspirin in CVD primary prevention populations, with clear consideration of the minimum dosage, timing, and duration of effects across important outcomes within these populations. More robust and comprehensive trial data involving representative patient samples on low-dose aspirin use for primary prevention should address all-cause mortality; CVD and cancer incidence and mortality; bleeding and other major harms; and emerging potential benefits, such as preventing cognitive decline. Multiple ongoing trials (54-57) and a planned additional IPD meta-analysis of existing trials

by the Non-Vascular outcomes on Aspirin collaboration will provide some of this essential information (58). Large applicable studies are needed to examine the range of relatively rare bleeding events and other harms from low-dose aspirin, particularly because the population for whom chemoprevention could be recommended is potentially very large. Given the emerging evidence for prolonged aspirin use to achieve some health outcomes, more information is needed about the continuous use (that is, 5 to 15 years) of very-low-dose aspirin with common co-medications. Important co-medications may be those with on- or off-target effects on platelets or the coagulation system (59); those that affect several outcomes similar to aspirin (for example, statins' effects on CVD, bleeding, and cancer) (22, 60, 61); or those that are common or synergistic with aspirin in potential high-benefit and high-risk populations, such as selective serotonin reuptake inhibitors in elderly persons (62). Concurrent use of statins is important because it may modify bleeding risk in a protective way but also reduce the potential benefits from aspirin. Large-scale, population-based, observational studies in which the uptake, continuation, and discontinuation of aspirin prophylaxis are documented alongside detailed clinical assessment of outcomes and related health care events would complement ongoing trials.

Because bleeding is the major known harm of aspirin use, others have proposed clinical approaches to reduce harms associated with chemoprevention. For example, *Helicobacter pylori* eradication has been conducted primarily to prevent recurrent bleeding in patients receiving aspirin or NSAIDs and needs investigation in the prophylactic, primary prevention context, such as in the ongoing *Helicobacter* Eradication Aspirin Trial (63). Investigating the use of proton-pump inhibitors for reducing GI effects in the primary prevention context may be worthwhile, particularly if *H pylori* eradication is not a good approach and concerns about any increase in CVD risks (43) are allayed. Large-scale randomized, controlled trials are required to determine the effect of such strategies on overall prevention, including the magnitude of risk reduction and any unintended consequences, especially on desired beneficial outcomes. Measures to reduce intracerebral bleeding attributable to aspirin, such as by detecting and adequately treating hypertension (64), are high priority.

Even at low or very low doses, aspirin increases the risk for bleeding events but absolute excess bleeding events will vary depending on individual baseline bleeding risks. Depending on the bleeding site, age is the strongest common risk factor for increased baseline bleeding, along with male sex, co-medications, and specific CVD risk factors. A history of GI bleeding or ulcers also greatly increases the baseline risk for bleeding, which explains why persons with these risks have been excluded from trials. Because no validated tools for predicting bleeding risk are available in this clinical scenario, pinpointing the balance between the benefits and harms of aspirin use, particularly considering the first 10 years of regular use, will depend on qualitative

assessment of the baseline risk for bleeding alongside CVD benefits.

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Appendix Table 1. Comparison of Different Meta-analytic Approaches: CVD Primary Prevention Trials

Outcome	Aspirin Dose	Peto OR (95% CI)	Mantel-Haenszel OR (95% CI)
Major GI bleeding	Any	1.59 (1.32–1.91); $I^2 = 22.2\%$	1.60 (1.32–1.97); $I^2 = 21.8\%$
	≤100 mg	1.58 (1.29–1.95); $I^2 = 28.6\%$	1.60 (1.29–1.97); $I^2 = 27.1\%$
Hemorrhagic stroke	Any	1.33 (1.03–1.71); $I^2 = 0\%$	1.33 (1.03–1.72); $I^2 = 0\%$

CVD = cardiovascular disease; GI = gastrointestinal; OR = odds ratio.

Appendix Table 2. Brief Description of Included Cohort Studies and IPD Meta-analysis

Study, Year (Reference) Quality	Design	Country	Mean Follow-up, y	Population	Participants, n	Mean Age (Range), y	Women, %	Diabetes, %	Current Smokers, %	Aspirin Dose and Frequency Co-medication Use, %
De Berardis et al, 2012 (22) Good	Cohort, retrospective	Italy	5.7*	Men and women aged ≥ 30 y, new aspirin users vs. never-users	372 850	69.4 (30-95)	53.1	15	NR	≤ 300 mg with most recent prescription filled ≥ 75 d before bleeding event NSAIDs: 34.8 PPIs: 45.5 Statins: 24.6
Elkström et al (SNDR), 2013 (35) Fair	Cohort, prospective	Sweden	3.9	Men and women with diabetes	18 646	62.3 (30-80)	44.7	100	15.4	75 mg/d NSAIDs: 0 PPIs: NR Statins: 35.7
Huang et al (HPFS), 2010 (33) Fair	Cohort, prospective	United States	11.4	Male health professionals	32 989	60.9 (NR)	0	5.4	5.2	Any dose ≥ 2 times/wk NSAIDs: 12.6 PPIs: NR Statins: NR
Huang et al (NHS), 2011 (34) Fair	Cohort, prospective	United States	12.5	Female nurses	87 680	56.6 (30-55)	100	5	17.6	325 mg ≥ 2 tablets/wk NSAIDs: 16.5 PPIs: NR Statins: NR
ATT Collaboration, 2009 (15)	IPD meta-analysis	Multinational	3.7-10.0	Primary CVD prevention populations	k = 6†, 95 459	56 (NR)	54	4	16	50-500 mg/d NSAIDs: NR PPIs: NR Statins: NR
Rothwell et al, 2012 (8)	IPD meta-analysis	Multinational	3.6-8.2	Primary CVD prevention populations	k = 6‡, 35 535	61.5 (NR)	44.1	NR	21.9	75-100 mg/d NSAIDs: NR PPIs: NR Statins: NR

AAA = Aspirin for Asymptomatic Atherosclerosis; ATT = Antithrombotic Trialists; BMD = British Doctor's Trial; CVD = cardiovascular disease; HOT = Hypertension Optimal Treatment; HPFS = Health Professionals Follow-up Study; IPD = individual-participant data; JPAD = Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes; NHS = Nurses' Health Study; NR = not reported; NSAID = nonsteroidal anti-inflammatory drug; PHS = Physicians' Health Study; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; PPI = proton-pump inhibitor; PPP = Primary Prevention Project; SNDR = Swedish National Diabetes Register; TPT = Thrombosis Prevention Trial; WHS = Women's Health Study.

* Median.

† Included primary CVD prevention trials: WHS, BMD, TPT, HOT, PPP, and PHS.

‡ Included primary CVD prevention trials: TPT, HOT, PPP, POPADAD, AAA, and JPAD.