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

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Abstract

Background: The balance between aspirin-related primary prevention of cardiovascular disease (CVD) and risk of bleeding varies by clinical and patient characteristics.

Purpose: Update the evidence base about the harms of aspirin in primary chemoprevention.

Data Sources: PubMed, MEDLINE, and the Cochrane Central Register of Controlled Trials and systematic reviews (January 1, 2010 through January 6, 2015).

Study Selection: Two investigators reviewed abstracts and full-text articles against pre-specified criteria.

Data Extraction: One investigator abstracted data; another checked for accuracy.

Data Synthesis: In CVD primary prevention studies, very low-dose aspirin use (≤100 milligrams daily or on alternate days) increased the risk of major gastrointestinal (GI) bleeding by 58% and hemorrhagic stroke by 27%. Based on annual bleeding rates expected in a community-based population, excess major bleeding events with very low-dose aspirin were projected to average 2 per 1,000 person-years for younger persons, females, and those with no other bleeding risk factors. Among older persons, males, and those with CVD risk factors that also increase bleeding risk, excess major bleeding events could be higher.

Limitations: We did not identify any externally validated tools for assessing major bleeding risks. More robust data are needed on the rate of harms with long-term low-dose aspirin use and the combined protective or harmful effects of common co-medications.

Conclusions: The risk of bleeding depends considerable on patient characteristics. Risks for aspirin primary chemoprevention are higher for community-dwelling candidates than among trial participants. Consideration of the safety and desirability of primary chemoprevention with

aspirin requires a qualitative assessment of aspirin's effects on bleeding risks and the expected benefits of primary chemoprevention.

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Introduction

Although widely regarded as a safe medication for patient-directed, over-the-counter use, aspirin is associated with a range of harms. These harms vary in type and severity with the dosage and duration of aspirin use as well as underlying patient risk factors. Through its inhibition of cyclooxygenase (COX)-1 enzyme activity, low-dose aspirin leads to mucosal damage to the gastrointestinal (GI) tract, causing erosions, ulcers, and bleeding (1). Through COX-mediated antiplatelet effects, low-dose aspirin also increases non-GI bleeding events that range from trivial to serious, including intracranial bleeds and hemorrhagic strokes (2). The advisability of taking aspirin for primary chemoprevention of cardiovascular disease (CVD) events, with or without considering the potentially beneficial cancer effects, depends on accurately estimating harms associated with a specific chemoprevention regimen and on the absolute and relative variability in harms for any individual or targeted subpopulation.

This report considers on the major bleeding-related harms of aspirin (3) in balancing the net benefit of aspirin in CVD primary prevention, as reported in two companion publications (4, 5). The perspective of these reviews these two reviews and this one, which were integrated through a clinical focus of a population eligible for primary prevention benefits, consider likely harms as well as potential additional benefits from preventing of colorectal and other cancers. These reviews were used to inform an updated U.S. Preventive Service Task Force (USPSTF) recommendation regarding low-dose aspirin for CVD primary prevention.

Methods

Our full report describes our methods in detail (3). After initial exploratory analyses (3) intended to identify the largest, most consistent, and applicable body of evidence for estimating

risks and rates of serious harms from aspirin use in clinical context, we focused on studies representing primary CVD chemoprevention with aspirin. We also considered how individual variability in the likelihood of harms would affect the choice to use aspirin for primary chemoprevention as well as the availability of valid tools to individualize harms assessments.

Data Sources and Searches

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

Study Selection

Two investigators independently reviewed abstracts and full-text articles against pre-specified criteria (3). We included trials and large longitudinal cohort studies conducted in adults with a mean age of ≥40 years that evaluated regular oral aspirin use (≥75 milligrams [mg] at least every other day) for ≥1 year for any indication compared to no treatment or placebo. We required studies to report serious GI or intracranial bleeding. Serious GI bleeding were those leading to death, those requiring hospitalization or transfusion, or those described by the trial investigator as serious. Intracranial bleeding included hemorrhagic stroke, intracerebral, subdural, and subarachnoid hemorrhage.

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 the majority of criteria and were downgraded to fair if not all criteria were met. Poor quality studies (i.e., >40% attrition, >20% attrition between groups, or other fatal flaws or the cumulative effects of multiple minor flaws or missing important information significant enough to limit confidence in the validity of results) were excluded.

Data Synthesis and Analysis

Aspirin exposure was inferred from the intended dosages and treatment duration in trials, without adjustment for actual adherence due to incomplete reporting. The average intended dose per day was calculated; an intended daily dose ≤325 mg was defined as low-dose aspirin use and that of ≤100 mg was defined as very low-dose. Since harms were often rare, we explored whether broadening bleeding definitions (i.e., any intracranial bleeding vs. hemorrhagic stroke alone) changed the results. Since the broader definition made little difference, we focused here on hemorrhagic stroke results for consistency with an individual patient data (IPD) meta-analysis (15) and our companion model (16). We used Peto's odds ratio (OR) for primary statistical analyses (17) due to rare events (i.e., control group event rate <1%). We stratified results by population (primary prevention of CVD, secondary prevention of CVD, and colorectal cancer [CRC] chemoprevention) and conducted sensitivity analyses by dose, frequency, and duration of the intended treatment. 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 [SSRIs] (18) and non-aspirin non-steroidal anti-inflammatory drugs [NSAIDs]) (19, 20). Other aspirin-related harms (e.g., age-related macular degeneration, ulcers) were addressed in our full report (3).

We calculated absolute treatment effects for bleeding outcomes to represent the range of control group event rates from the CVD primary prevention trials of very low-dose aspirin use. For each trial, we divided the number of events for each outcome by the person-years at risk (approximated by multiplying the same size of the control group by the mean follow-up years), and assume a constant risk value over time. We selected the minimum, median, and maximum control group event rates (excluding zeros and outliers) for each outcome and multiplied these by the pooled relative risks (RRs) for each outcome from the trials to calculate event rates with very low-dose aspirin use over 10 years. Excess cases were calculated by subtracting the event rate per 1,000 person-years for users from event rates in the control groups for each risk level. For bleeding outcomes, we contrasted excess cases based on control group rates from trials with results based on control group bleeding rates from the largest cohort study (21).

Role of Funding Source

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

Results

Although we considered a larger set of trials that reported on harms associated with aspirin use (3), this manuscript focuses on bleeding events through about 10 years of aspirin use in dosages and regimens intended for CVD primary prevention. We analyzed serious bleeding outcomes from 11 primary prevention CVD trials (22–32) which are discussed in detail in our companion manuscript (4). Ten of the 11 CVD primary prevention trials addressed one or more harms of aspirin use (22–25, 27–32), although harms outcomes were reported and defined

inconsistently. Some trials did not define bleeding site or severity and ascertainment methods were not always fully reported.

We also identified four recent fair- or good-quality cohort studies of aspirin clearly used (or presumed to be mostly used) for CVD primary prevention, which reported on bleeding risks after 3.9-12.5 years in individuals with and without low-dose aspirin use (**Table 1**) (21, 33–35). The majority of cohort data came from a single large good-quality cohort examining first hospitalizations for all major bleeding events (intracranial and extracranial) in a population of 372,850 community-dwelling individuals in Italy (186,425 new users of low-dose aspirin aged 30-95 years matched using propensity scoring to 186,425 never users). Bleeding rates reflected 1.6 million person-years of observations and a median follow-up of 5.7 years (interquartile range, 2.4-6.0 years). About one third of first episodes of hospitalizations for all major bleeding events were for intracranial bleeding (21). We also identified two IPD meta-analyses (8, 15) of included trials that reported harms that complement our findings.

Major GI bleeding. Seven of the 11 CVD primary prevention trials reported major GI bleeding events after 3.8-10.1 years of daily or alternate day aspirin use (32, 36–41); events were rare (<1%) in both the aspirin and control groups. Major GI bleeding risk increased 59% among those taking 50-500 mg of aspirin daily (OR, 1.59 [95% confidence interval [CI], 1.32 to 1.91; I^2=22.2%) (**Table 2, Figure 1**). Estimated bleeding risks remained similar when limited to trials of very low-dose aspirin (k=5; OR, 1.58 [95% CI, 1.29 to 1.95]; I^2=28.6%), or when reported from an IPD examining a slightly different outcome (extracranial bleeding) from a slightly different set of six CVD primary prevention trials (rate ratio, 1.54 [95% CI, 1.30 to 1.82]) (15). The effects of aspirin on all major bleeding events in cohort data were very similar (incidence

rate ratio [IRR], 1.55 [95% CI, 1.48 to 1.63]), with similar effects sizes by bleeding site (GI IRR, 1.55; intracranial IRR, 1.54) (21).

Hemorrhagic stroke. Nine of 11 trials reported on hemorrhagic stroke over 3.6-10.1 years (22–25, 27, 29–32). Total hemorrhagic stroke events were far less common than ischemic strokes: 15.5% of total strokes reported in included trials were hemorrhagic. In all trials, the risk of hemorrhagic stroke was increased by about one-third (OR, 1.33 [95% CI, 1.03 to 1.71]; I^2=0%) (**Table 2, Figure 2**). The point estimate and its statistical significance varied slightly between pooled analyses, depending on the studies included, outcome definition, and perhaps dosage (3, 4). A single study, which was conducted in an older Japanese population with a hypertension prevalence of nearly 85%, showed a statistically significant increase in hemorrhagic stroke (OR, 1.84 [95% CI, 1.01 to 3.35]) (42). Due to rare events and between-study differences, all intracranial bleeding estimates were imprecise and depended more highly on which trials were included than is the case for GI bleeding (15). Cohort data suggested that intracranial bleeds contributed more prominently to bleeding-related hospitalizations in community settings and a 54% higher risk of bleeding which may reflect some secondary CVD prevention users (21).

How do estimated bleeding harms vary with patient-related factors?

For individuals with a very high baseline risk of bleeding or factors that greatly enhance aspirin-associated bleeding, aspirin may be relatively or absolutely contraindicated, as the number of excess bleeds becomes unacceptable regardless of potential benefits (3). To estimate the range of likely increase in absolute bleeding cases due to variability in baseline bleeding risk as well as aspirin-associated bleeding risk among potential aspirin chemoprevention candidates,

we examined baseline rates from trials and cohort studies. To best determine the independent risk factors, we emphasized results from IPD meta-analyses and multivariable analyses.

Baseline estimates of major bleeding risks (trial vs. cohort). In an IPD meta-analysis of control participants from six CVD primary prevention trials, mean extracranial bleeding rates were low (0.7 per 1,000 person-years) and hemorrhagic stroke rates even lower (0.3 per 1,000 person-years) (15) (**Table 3**). Across eight CVD primary prevention trials, the control group rates we approximated for major GI bleeding (0.23-1.04 per 1,000 person-years) or hemorrhagic stroke (0-1.26 per 1,000 person-years) were consistent with relatively uncommon events but illustrated some between-trial variability (**Table 4**). Substituting cohort rates of baseline bleeding created further variability; the estimated rate of hospitalization for extracranial bleeding among controls in the largest cohort study (21) was at least two times greater than the highest GI bleeding rate suggested by the trials (**Table 3**). Given a constant RR of GI bleeding associated with very low-dose aspirin use, excess cases of major GI bleeding varied substantially depending on whether they were estimated from median trial control group rates (0.28 [95% CI, 0.14 to 0.46] per 1,000 person-years) or from baseline rates suggested by the cohort data (1.39 [95% CI, 0.70 to 2.28] per 1,000 person-years). Similarly, 0.10 excess hemorrhagic strokes would be caused per 1,000 person-years of very low-dose aspirin use when using the median trial control group risk, while at least 0.32 would be expected using the baseline rate suggested by the cohort data.

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 (3). The largest and most consistent statistically significant differences in baseline bleeding risk occurred with increasing age (increasing 1.5-to-

2-fold in each subsequent decade greater than 50 years) and to a lesser extent, male sex (**Table 3**). Multivariable analyses of both trial and cohort data confirmed these findings (**Table 5**). In the cohort study, the highest rates of major bleeding events (12.0-14.0 per 1,000 person-years) occurred in those with a history of GI hospitalization with or without aspirin use (21). Even after adjustment for bleeding risk factors—including aspirin use—a history of GI hospitalization was the main factor that increased the relative incidence rate of hospitalizations for major bleeding (**Table 5**). Most trials, however, restricted patient enrollment to those without bleeding risk factors thus limiting risk and applicability.

Risk factors for increased major bleeding by site. Controlling for aspirin use, the effect of increasing age (per decade) had a greater effect on major GI or extracranial bleeding than on hemorrhagic stroke (**Table 5**). In addition to older age, male sex and diabetes mellitus increased the risk of serious bleeding, with possible variation in effect by site and imprecise magnitude. In an adjusted IPD meta-analysis of trial data (15), current smoking and mean systolic and diastolic blood pressure per 20 mm Hg were also independently associated with increased major extracranial bleeds. For hemorrhagic stroke, only increasing age, current smoking, and elevated mean blood pressure were clearly associated with increased risk. Relative risks associated with patient characteristics differed somewhat between the two major bleeding sites. Investigators noted that coronary heart disease risk factors associated with greater potential benefit from aspirin (i.e., age, male sex, diabetes, current smoking, mean blood pressure) were also associated with increased major bleeding risks for one or both outcomes, although somewhat more weakly (15).

A large good-quality cohort study reported on the influence of NSAIDS and other common medications on bleeding risk in never users and in current users of low-dose aspirin

(**Table 5**) (21). In adjusted analyses, NSAID use increased the baseline risk of bleeding (adjusted IRR, 1.10 [95% CI, 1.05 to 1.16]). Other co-medications not commonly used by primary CVD prevention candidates (e.g., anticoagulants and antiplatelets) increased major bleeding events by 31-42% (adjusted [data not shown]). Adjusted analyses suggested a protective effect of proton pump inhibitors (PPIs) and statins on bleeding risk.

While it was not always clear from reported data whether bleeding risk factors represented an increased baseline risk or an effect modification of aspirin use, the majority of the data suggested that the increased baseline bleeding risk was associated primarily with older age and male sex (without effect modification); the data were mixed or insufficient to examine effect modification in patients with diabetes mellitus and other CVD risk factors (3).

How do bleeding harms vary by aspirin regimen (dose, frequency, duration)?

We found very few within-trial direct comparisons of aspirin regimens within primary prevention populations. In addition, between-trial comparisons, including study level-stratified analyses by dosage, are of limited use due to potential confounding by other between-study differences (i.e., methodological and clinical heterogeneity). Cohort studies were similarly limited due to restrictions to a single low-dose regimen (35), lack of evaluation of dosage effects (21), or issues with exposure measurement (33, 34). In the two large U.S. cohorts, trend analyses strongly supported the effect of increasing cumulative weekly dosage on lower or upper GI bleeding in both short- and long-term users of aspirin (33, 34) particularly in women (33, 34) and for subarachnoid hemorrhages in men aged ≥55 years (43). In women, most bleeding cases (72.6%) in recent years (2000-2008) involved daily rather than less than daily use of aspirin (33).

Both trial and cohort data revealed that the risk of bleeding associated with low-dose aspirin use was apparent early on, likely persisted throughout usage, and probably quickly declined with discontinuation. In the Women's Health Study (WHS), the cumulative incidence of GI bleeding continued to increase in participants allocated to 100 mg of aspirin every other day compared to participants on placebo throughout the median 10.1 years of follow-up (44). In contrast, a stratified IPD meta-analysis suggested that the risk of major extracranial bleeding was most pronounced early on (i.e., 0-2.9 years, declining ≥3.0 years) (8). However, the risks of placebo also declined over time suggesting another mechanism for reduced bleeding events (such as unequal observation time) (3, 45). Cohort data addressed whether the magnitude of bleeding harms depends on the duration of aspirin use for different regimens. Two studies (33, 34) of regular users found that duration of use (<5 years or ≥5 years) did not alter the elevated bleeding risk. Thus, the limited data suggested that bleeding risks remain relatively constant with long-term use. The WHS which provided the sole study with information on discontinuation, observed rapid attenuation of excess GI bleeding risk after aspirin use ceased (44), but poor ascertainment of post-trial harms and high post-trial attrition limited complete confidence in this finding.

Discussion

Summary of Findings

We found the estimates from trial and cohort data of increased risk for serious bleeding with aspirin use in CVD primary prevention populations were relatively consistent. In both trials and cohort studies, increases in GI bleeding were quite consistently estimated with the best estimate for very low-dose aspirin use in CVD primary prevention populations through about 10 years being 1.58 ([95% CI, 1.29 to 1.95]; I^2=28.6%). In contrast, due to much rarer events, the

increased risk of hemorrhagic stroke was less precise; the best estimate for hemorrhagic stroke with very low-dose aspirin use for CVD primary prevention was 1.27 (95% CI, 0.96 to 1.68). This pooled estimate, which was not statistically significant, was likely due to fewer events when restricting to trials with very low-dose aspirin. Nonetheless, it was the estimate we provided for the companion model (16) based on *a priori* decisions to link harms estimates to the population and aspirin dosages used for estimating benefits. For both types of serious bleeding, our pooled estimates were not statistically heterogeneous or precise indicating inadequate power and less certainty of the average effect.

Factors that either increase the risk of baseline bleeding (e.g., age or previous medical history) or enhance aspirin's effect on bleeding (e.g., concurrent use of other medications) can increase bleeding harms on an absolute scale, making it difficult to distinguish between increased bleeding due to baseline factors and bleeding attributable to aspirin use alone (46). For example, it is well known that older age is associated with an increased risk of major GI bleeding (47–49). With a consistent RR increase for bleeding with aspirin use regardless of age, the absolute effect of aspirin on bleeding events (excess cases) will be greater in older adults. The effects of aspirin use on bleeding are further modified by co-use of other medications, increasing their absolute effects (50). Thus, co-medication use in a primary prevention population must be done cautiously. In contrast, most of the evidence we reviewed did not suggest effect modification of the RR of serious bleeding events—particularly upper GI bleeding—associated with low-dose aspirin use for CVD primary prevention across patients' socio-demographic subgroups. Nonetheless, baseline bleeding rates differed substantially across patient risk factors commonly present in populations that would be candidates for CVD primary prevention. Older age and male sex consistently demonstrated an increasing baseline bleeding risk, and some evidence

indicated increased bleeding risk with particular CVD risk factors. Most important, although RRs for GI bleeding (and to a lesser extent hemorrhagic stroke) were reasonably consistently estimated by both trials and cohort studies, these two study types provided substantially different estimates of baseline bleeding risks, with and without other risk factors present.

Anticipating and Estimating Individual Variability in Bleeding Risks with Aspirin Use

Beyond the variability in risk represented by age and sex (**Table 3**), individuals at increased risk of bleeding had limited or no representation in the CVD primary prevention trials (15). Thus, overall risk of bleeding at baseline were relatively low in participants not on aspirin in trials compared with cohort data (0.7 vs. 2.4 major extracranial bleeds per 1,000 person-years; 0.3 vs. 1.2 major intracranial bleeds per 1,000 person-years). Our simulations of excess bleeding cases with aspirin use (**Table 4**) showed that assumptions of the baseline bleeding rate are clearly important to avoid underestimation of risk that could occur from applying trial-based risks based on very selective patient groups to a more unselected general population. Previous research is consistent with a potential underestimation of baseline bleeding risk for a more general population when trial-based averages alone are used. For example, a previously derived and commonly cited baseline rate for major upper GI complications (i.e., 1 per 1,000 person-years) from observational studies (51) has been revised upward (1-2 per 1,000 person-years) and clarified to apply only to selected individuals without significant risks (i.e., men aged ≤60 years or women aged ≤70 years, all without prior history of GI pain, ulcer, and NSAID use) (47). A more recent average estimate is consistent; the baseline risk of upper GI bleeding in aspirin non-users considered to be the primary prevention cohort due to no CVD history was 1.85 cases per 1,000 person-years (52). The higher average baseline GI bleeding rate (2.4 per 1,000 person-

years) from cohort data in our simulations still resulted in a relatively modest excess cases (1.39 [95% CI, 0.70 to 2.28] per 1,000 person-years), suggesting that averages could underestimate risk. Thus, in the presence of bleeding risk factors, excess bleeding cases would be projected to increase beyond trial or cohort-based averages.

When excess cases of upper GI complications (presumed to represent bleeding primarily) among current aspirin users considered the prevalence of GI risk factors (i.e., age, male sex, history of GI ulcers or complications, and NSAID use), the average excess cases increased substantially to five excess cases of upper GI complications per 1,000 person-years (47). These estimates reflected relatively common bleeding risk factors among cardio-protective aspirin users from population-based databases and were based on age (79-88% aged ≥60 years), some degree of co-medication use (13-15% with other NSAID use), and medical history (5-8% with a past history of GI ulcers or complications). Excess cases, however, were projected to vary, increasing above this average when all potential risk factors were figured in. For example, almost no aspirin users aged ≥80 years would be expected to have ≤5 excess cases per 1,000 person-years. And, in those less than 80 years, excess cases would be expected to vary widely from 0.4-90 per 1,000 person-years with age being the major determinant within which additional risk factors operated. For individuals aged 60-80 years, only those with no more than 1 additional bleeding risk factor could expect below-average bleeding (≤5 excess cases) with aspirin use, while individuals less than 60 years would be largely protected from above-average excess cases unless ulcers were present (47). Thus, there is large potential variability of excess serious GI bleeding events with aspirin use due to risk factor differences among community-dwelling aspirin users. If intracranial or other extracranial sources of major bleeds were also considered, absolute excess cases and variability in case estimates would be further affected.

Determining Candidates for Primary Chemoprevention with Aspirin

Although a tool to predict bleeding risk could help clinicians and individuals make appropriate preventive medication decisions by helping identify those least likely to be harmed through bleeding, we found no adequately validated tools for assessing bleeding risks associated with aspirin for primary prevention of CVD or cancers. A single risk prediction tool for upper GI complications (primarily bleeding) has been published and is available in the public domain (53). This tool has potential strengths but also deficiencies, including the incorporation of approaches to modifying the bleeding risk (i.e., PPI use) that are not empirically proven in a primary prevention population and for which it is clear that more caution is needed (54). Most critically, this tool lacks sufficient external validation to allow its use in prospective risk prediction.

In the absence of robust risk calculators for bleeding risks, the selection of patients for aspirin chemoprevention may be based pragmatically through qualitative consideration of bleeding risk factors or through limiting candidates to those fitting trial selection criteria. In terms of safety, besides previous ulcers or GI bleeding, aspirin intolerance or contraindications, and some medications (e.g., antiplatelets or anticoagulants) may be considered absolute or relative contraindications to aspirin use for primary chemoprevention due to their consistent association with very elevated bleeding risk (47, 50, 50, 55) and the exclusion of such patients from most trials (3). NSAIDs and other medications increase bleeding risk but less significantly so, and they may be added by patients at some point during a long-term aspirin regimen even when absent at initiation (56). 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 avoiding unnecessary harm.

A stepwise practical approach outlined by the European Society of Cardiology to select candidates for aspirin chemoprevention is based on minimizing potential harms in those most likely to benefit (57). In the first step, the 10-year risk of major CVD events (with no further consideration of aspirin use in those under 10% risk) is determined. Second, safety is assessed by eliminating candidates with a history of bleeding without reversible causes or with concurrent use of other medications that increase bleeding risk. And finally, for patients without safety concerns, aspirin is recommend for those with a clear CVD benefit or, when potential harms and benefits appear closely balanced; values, preferences, and other potential benefits (i.e., CRC) are considered on a case-by-case basis. For example, in initially healthy female participants in the WHS, competing risk models for individualized prediction of 15-year absolute risk reduction (fatal and non-fatal CVD, cancer, and major GI bleeding combined) suggested that only ~2% would experience ≥1% overall absolute risk reduction across all events (number need to treat, 100) (58). Among this ~2%, most (54%) were aged ≥65 years with a baseline 10-year CVD risk of approximately 18% and a major GI bleeding risk of 1.94 per 1,000 person-years. Although age 65 years was preferred to identify women with a clear net benefit, approximately 20% of 65-year-olds would be projected into the negative overall treatment group, while another 70% would experience a very modest net benefit (<1% absolute risk reduction).

A patient's willingness and ability to take a daily medication must also be considered in selecting good candidates, particularly for broader prevention effects beyond CVD. On the basis of current data, most investigators agree that achieving cancer benefits requires continuing aspirin use for 4-5 years (3, 59) and perhaps longer for lower dosages or less than daily use (58). Primarily due to the differing timeframes over which risks and benefits might be expected to occur (early on and throughout active use for bleeding risks and CVD events (11) but delayed

10-20 years for CRC effects), life expectancy may also affect considerations. Future research clarifying the timing and persistence of the risks and benefits observed during and beyond different durations of low-dose aspirin use could change considerations in identifying the individuals most likely to obtain net health benefits.

Caveats

Overall approach. Clinical context influenced our approach to analyzing the bleeding harms associated with aspirin. Our primary results came from analyses of 11 CVD primary prevention trials (11) because we sought to estimate additional cancer benefits in a CVD primary prevention population taking low-dose aspirin. Consistent with the USPSTF approach in 2009 (60) and research by others (61), we intended for our outcome estimates to reflect the minimal possible dosage shown to achieve CVD benefits in CVD primary prevention populations, in order to minimize potential harms. Thus, we included alternate-day and daily aspirin studies and focused on very low dosage uses (≤100 mg). As reported elsewhere, these approaches have demonstrated CVD benefits (11) and have proved proving feasible for reducing longer-term impact on cancer incidence (3).

Our original analytic plan to use the same or similar aspirin regimens in applicable populations to estimate the effect of aspirin use on all established outcomes (i.e., bleeding harms, as well as CVD and cancer benefits) resulted in our emphasizing results from a more limited set of trials. This approach may have introduced imprecision due to lack of power. Nonetheless, given the known differences between these two populations in relative causes of death (3) and other factors—including baseline bleeding risk (52) or proportional impact of hemorrhagic

versus ischemic strokes (15)—emhasizing data from primary prevention populations is prudent to avoid faulty conclusions or extrapolations from secondary prevention populations,

Precision and breadth of harms estimations. Excess bleeding events are relatively rare and are not consistently captured. The bleeding sites most uniformly reported are major upper GI or intracerebral sites; other major bleeding sites (lower GI bleeding) or related issues (e.g., diverticular disease complications) (62–64) may be affected by low-dose aspirin use as well. Similarly, minor bleeding issues are not well-reported. Hemorrhagic strokes and ischemic strokes are often not reported separately, and other types of intracranial bleeds are generally missing. Reported data on ulcers are even sparser and therefore were not factored into our analyses, although other investigators have included ulcers and dyspepsia alongside bleeding in their estimates of upper GI complications (although bleeding alone was 80% of events) (47, 49). We did not cover the effects of daily use of aspirin on quality of life issues (65) but it may be important to consider when recommending use of a long-term chemopreventive agent in an asymptomatic population.

While trial-based rates potentially underestimate the risks for clinical practice, cohort estimates may over-estimate baseline bleeding risks. Estimates from community-dwelling individuals using very low-dose aspirin alone (or with clearly documented co-medication use) for CVD primary prevention remain sparse, since clear data on exposure can be difficult to capture for a ubiquitous and primarily over-the-counter medication.

Future Research

More robust and comprehensive trial data are needed on the entire set of related outcomes for low-dose aspirin use such as cancer-specific incidence and mortality, bleeding and other

harms, CVD events, other benefits such as preventing cognitive decline, and cause-specific and all-cause mortality. Clear consideration of the dosage, timing, and duration of effects within the same primary prevention populations that would be offered aspirin for prevention is needed to better assess the relative harms and benefits. Multiple trials underway (66–69) and planned additional IPD meta-analysis of existing trials by the Non-Vascular outcomes on Aspirin (NoVA) collaboration will provide some of this essential information (70).

Rare events make large applicable studies for the range of consistently defined bleeding harms with low-dose aspirin a priority. Given the emerging evidence for prolonged use to achieve a range of health outcomes, there is a need for information on continuous (i.e., 5-15 years) use of very low-dose aspirin alongside common co-medications. Particularly important co-medications may be those with on- or off-target effects on platelets or the coagulation system (71), affect multiple outcomes similar to aspirin (e.g., statins effects on CVD, bleeding, cancer) (21, 49, 72), or are common or synergistic with aspirin in potential high-benefit/high-risk populations, such as SSRIs in the elderly (73). Statin co-use is particularly important, since 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 (and other medications) is documented alongside detailed clinical assessment of outcomes and related health care events will complement ongoing trials.

Since bleeding is the major known harm of aspirin use, some of the proposed approaches to prevent bleeding need large-scale RCTs to determine the magnitude of risk reduction and any unintended consequences on the desired beneficial outcomes. Measures to reduce cerebral bleeding attributable to aspirin, particularly by detecting and adequately treating hypertension (74), are of high priority. Data on *Helicobactor pylori* eradication has been conducted primarily

to prevent re-bleeding in patients on aspirin or NSAIDS and should be considered in the primary prevention context or prophylactically for ulcer and bleeding prevention, such as the ongoing *Helicobactor* Eradication Aspirin Trial (75). Studying the use of PPIs in the primary prevention context may be worth investigating for reducing GI effects, particularly if *H. pylori* eradication is not a good approach.

Conclusions

Even at low- or very low-doses, aspirin increases the risk of bleeding and other harms. Major GI bleeding risk increases by about 58% and hemorrhagic stroke by about 27% among participants in very low-dose aspirin trials, but absolute bleeding events will vary depending on individual bleeding risks. Age is the strongest independent risk factor for increased bleeding which is followed by male sex and selected CVD risks factors that vary by bleeding site. A history of previous GI bleeding or ulcers increases the risk of bleeding the most, but individuals with these risks have been excluded from trials. Because no tools for predicting the risk of bleeding in this clinical scenario have been validated, pinpointing the balance between the benefits and harms of low-dose aspirin use, particularly considering the first 10 years of regular use, will depend on qualitative assessment of the baseline risk for bleeding and CVD benefits.

Reference List

(1) **Iwamoto J, Saito Y, Honda A, Matsuzaki Y. Clinical features of gastroduodenal injury associated with long-term low-dose aspirin therapy. World J Gastroenterol. 2013;19:1673-1682.**

(2) **Seshasai SR, Wijesuriya S, Sivakumaran R, Nethercott S, Erqou S, Sattar N et al. Effect of aspirin on vascular and nonvascular outcomes: meta-analysis of randomized controlled trials. Arch Intern Med. 2012;172:209-216. [PMID: 22231610]**

(3) **Whitlock EP, Williams S, Burda BU, Feightner A, Beil T. Aspirin use in adults: total cancer, all-cause mortality and harms. Rockville, MD: Agency for Healthcare Research and Quality; 2014. [PMID: None]**

(4) **Guirguis-Blake JM, Evans CV, Senger CA, O'COnnor EA, Whitlock EP. Aspirin for the primary prevention of cardiovascular events: a systematic evidence review for the U.S. Preventive Services Task Force. Annals of Internal Medicine. 2015;**

(5) **Chubak J, Whitlock EP, Williams SB, Kaminemi A, Burda BU, Buist DSM et al. Aspirin for the prevention of cancer: systematic evidence reviews for the U.S. Preventive Services Task Force. Annals of Internal Medicine. 2015;**

(6) **Lanas A, Wu P, Medin J, Mills EJ. Low doses of acetylsalicylic acid increase risk of gastrointestinal bleeding in a meta-analysis. Clin Gastroenterol Hepatol. 2011;9:762-768. [PMID: 21699808]**

(7) **Valkhoff VE, Sturkenboom M, Hill C, Veldhuyzen van ZS, Kuipers EJ. Low-dose acetylsalicylic acid use and the risk of upper gastrointestinal bleeding: A meta-analysis of randomized clinical trials and observational studies. Can J Gastroenterol. 2013;27:159-167. [PMID: 23516680]**

(8) **Rothwell PM, Price JF, Fowkes FG, Zanchetti A, Roncaglioni MC, Tognoni G et al. Short-term effects of daily aspirin on cancer incidence, mortality, and non-vascular death: analysis of the time course of risks and benefits in 51 randomised controlled trials. Lancet. 2012;379:1602-1612. [PMID: 22440946]**

(9) **Dube C, Rostom A, Lewin G, Tsertsvadze A, Barrowman N, Code C et al. The use of aspirin for primary prevention of colorectal cancer: a systematic review prepared for the U.S. Preventive Services Task Force. Ann Intern Med. 2007;146:365-375. [PMID: 17339622]**

(10) **Wolff T, Miller T, Ko S. Aspirin for the primary prevention of cardiovascular events: an update of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med. 2009;150:405-410. [PMID: 19293073]**

(11) Guirguis-Blake JM, Evans CV, Rowland MG, Senger CA, O'COnnor EA, Whitlock EP. Aspirin for the primary prevention of cardiovascular events: a systematic evidence review for the U.S. Preventive Services Task Force. Rockville, MD: Agency for Healthcare Research and Quality; 2014. [PMID: None]

(12) Chubak J, Kamineni A, Buist D, Anderson M, Brandzel S, Shulman L et al. Aspirin use for the prevention of colorectal cancer: an evidence update for the U.S. Preventive Services Task Force. Rockville, MD: Agency for Healthcare Research and Quality; 2014. [PMID: None]

(13) Harris RP, Helfand M, Woolf SH, Lohr KN, Mulrow CD, Teutsch SM et al. Current methods of the US Preventive Services Task Force: a review of the process. Am J Prev Med. 2001;20:21-35. [PMID: 11306229]

(14) Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analysis 2014. Accessed at http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp on 21 January 2014. [PMID: None]

(15) Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, Peto R et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet. 2009;373:1849-1860. [PMID: 19482214]

(16) Maciosek MV, Dehmer SP, Flottemesch TJ. Aspirin use to prevent CVD and cancer: decision analysis. Washington, D.C.: Agency for Healthcare Research and Quality; 2015. [PMID: None]

(17) Fu R, Gartlehner G, Grant M, Shamliyan T, Sedrakyan A, Wilt TJ et al. Conducting quantitative synthesis when comparing medical interventions: AHRQ and the Effective Health Care Program. J Clin Epidemiol. 2011;64:1187-1197. [PMID: 21477993]

(18) Targownik LE, Bolton JM, Metge CJ, Leung S, Sareen J. Selective serotonin reuptake inhibitors are associated with a modest increase in the risk of upper gastrointestinal bleeding. Am J Gastroenterol. 2009;104:1475-1482. [PMID: ajg2009128 [pii];10.1038/ajg.2009.128 [doi]]

(19) de Abajo FJ, Gil MJ, Bryant V, Timoner J, Oliva B, Garcia-Rodriguez LA. Upper gastrointestinal bleeding associated with NSAIDs, other drugs and interactions: a nested case-control study in a new general practice database. Eur J Clin Pharmacol. 2013;69:691-701.

(20) Hreinsson JP, Kalaitzakis E, Gudmundsson S, Bjornsson ES. Upper gastrointestinal bleeding: incidence, etiology and outcomes in a population-based setting. Scand J Gastroenterol. 2013;48:439-447.

(21) de Berardis G, Lucisano G, D'Ettorre A, Pellegrini F, Lepore V, Tognoni G et al. Association of aspirin use with major bleeding in patients with and without diabetes. JAMA. 2012;307:2286-2294. [PMID: 22706834]

(22) de Gaetano G. Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomised trial in general practice. Collaborative Group of the Primary Prevention Project. Lancet. 2001;357:89-95. [PMID: 11197445]

(23) Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. Lancet. 1998;351:1755-1762. [PMID: 9635947]

(24) Ogawa H, Nakayama M, Morimoto T, Uemura S, Kanauchi M, Doi N et al. Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial. JAMA. 2008;300:2134-2141. [PMID: 18997198]

(25) Final report on the aspirin component of the ongoing Physicians' Health Study. N Engl J Med. 1989;321:129-135. [PMID: 2664509]

(26) Aspirin effects on mortality and morbidity in patients with diabetes mellitus. Early treatment Diabetic Retinopathy Study report 12. ETDRS Investigators. JAMA. 1992;268:1292-1300. [PMID: 1507375]

(27) Peto R, Gray R, Collins R, Wheatley K, Hennekens C, Jamrozik K et al. Randomised trial of prophylactic daily aspirin in British male doctors. Br Med J (Clin Res Ed). 1988;296:313-316. [PMID: 3125882]

(28) Belch J, MacCuish A, Campbell I, Cobbe S, Taylor R, Prescott R et al. The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. BMJ. 2008;337:a1840. [PMID: 18927173]

(29) Thrombosis Prevention Trial: randomised trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk. The Lancet. 1998;351:233-241. [PMID: 9457092]

(30) Fowkes FG, Price JF, Stewart MC, Butcher I, Leng GC, Pell AC et al. Aspirin for prevention of cardiovascular events in a general population screened for a low ankle brachial index: a randomized controlled trial. JAMA. 2010;303:841-848. [PMID: 20197530]

(31) Ikeda Y, Shimada K, Teramoto T, Uchiyama S, Yamazaki T, Oikawa S et al. Low-dose aspirin for primary prevention of cardiovascular events in Japanese patients

60 years or older with atherosclerotic risk factors: a randomized clinical trial. JAMA. 2014;312:2510-2520.

(32) Ridker PM, Cook NR, Lee IM, Gordon D, Gaziano JM, Manson JE et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. N Engl J Med. 2005;352:1293-1304. [PMID: 15753114]

(33) Huang ES, Strate LL, Ho WW, Lee SS, Chan AT. A prospective study of aspirin use and the risk of gastrointestinal bleeding in men. PLoS ONE. 2010;5:e15721. [PMID: 21209949]

(34) Huang ES, Strate LL, Ho WW, Lee SS, Chan AT. Long-term use of aspirin and the risk of gastrointestinal bleeding. Am J Med. 2011;124:426-433. [PMID: 21531232]

(35) Ekstrom N, Cederholm J, Zethelius B, Eliasson B, Fharm E, Rolandsson O et al. Aspirin treatment and risk of first incident cardiovascular diseases in patients with type 2 diabetes: an observational study from the Swedish National Diabetes Register. BMJ Open. 2013;3:2013. [PMID: 23604419]

(36) Fowkes FG, Price JF, Stewart MC, Butcher I, Leng GC, Pell AC et al. Aspirin for prevention of cardiovascular events in a general population screened for a low ankle brachial index: a randomized controlled trial. JAMA. 2010;303:841-848. [PMID: 20197530]

(37) Ogawa H, Nakayama M, Morimoto T, Uemura S, Kanauchi M, Doi N et al. Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial. JAMA. 2008;300:2134-2141. [PMID: 18997198]

(38) Peto R, Gray R, Collins R, Wheatley K, Hennekens C, Jamrozik K et al. Randomised trial of prophylactic daily aspirin in British male doctors. Br Med J (Clin Res Ed). 1988;296:313-316. [PMID: 3125882]

(39) Final report on the aspirin component of the ongoing Physicians' Health Study. New England Journal of Medicine. 1989;321:129-135. [PMID: 2664509]

(40) Thrombosis Prevention Trial: randomised trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk. The Lancet. 1998;351:233-241. [PMID: 9457092]

(41) Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. Lancet. 1998;351:1755-1762. [PMID: 9635947]

(42) Ikeda Y, Shimada K, Teramoto T, Uchiyama S, Yamazaki T, Oikawa S et al. Low-dose aspirin for primary prevention of cardiovascular events in Japanese patients

60 years or older with atherosclerotic risk factors: a randomized clinical trial. JAMA. 2014;312:2510-2520.

(43) Iso H, Hennekens CH, Stampfer MJ, Rexrode KM, Colditz GA, Speizer FE et al. Prospective study of aspirin use and risk of stroke in women. Stroke. 1999;30:1764-1771. [PMID: 10471421]

(44) Cook NR, Lee IM, Zhang SM, Moorthy MV, Buring JE. Alternate-day, low-dose aspirin and cancer risk: long-term observational follow-up of a randomized trial. Ann Intern Med. 2013;159:77-85. [PMID: 23856681]

(45) Patrono C. Low-dose aspirin in primary prevention: cardioprotection, chemoprevention, both, or neither? Eur Heart J. 2013;34:3403-3411. [PMID: eht058 [pii];10.1093/eurheartj/eht058 [doi]]

(46) Hallas J, Lauritsen J, Villadsen HD, Gram LF. Nonsteroidal anti-inflammatory drugs and upper gastrointestinal bleeding, identifying high-risk groups by excess risk estimates. Scand J Gastroenterol. 1995;30:438-444. [PMID: 7638569]

(47) Hernandez-Diaz S, Garcia Rodriguez LA. Cardioprotective aspirin users and their excess risk of upper gastrointestinal complications. BMC Med. 2006;4:22. [PMID: 16987411]

(48) Garcia Rodriguez LA, Hernandez-Diaz S, de Abajo FJ. Association between aspirin and upper gastrointestinal complications: systematic review of epidemiologic studies. Br J Clin Pharmacol. 2001;52:563-571. [PMID: 1476 [pii]]

(49) Garcia Rodriguez LA, Lin KJ, Hernandez-Diaz S, Johansson S. Risk of upper gastrointestinal bleeding with low-dose acetylsalicylic acid alone and in combination with clopidogrel and other medications. Circulation. 2011;123:1108-1115. [PMID: 21357821]

(50) Lanas A, Garcia-Rodriguez LA, Arroyo MT, Gomollon F, Feu F, Gonzalez-Perez A et al. Risk of upper gastrointestinal ulcer bleeding associated with selective cyclo-oxygenase-2 inhibitors, traditional non-aspirin non-steroidal anti-inflammatory drugs, aspirin and combinations. Gut. 2006;55:1731-1738. [PMID: gut.2005.080754 [pii];10.1136/gut.2005.080754 [doi]]

(51) Hernandez-Diaz S, Rodriguez LA. Incidence of serious upper gastrointestinal bleeding/perforation in the general population: review of epidemiologic studies. J Clin Epidemiol. 2002;55:157-163. [PMID: 11809354]

(52) Lin KJ, De CR, Garcia Rodriguez LA. Low-dose aspirin and upper gastrointestinal bleeding in primary versus secondary cardiovascular prevention: a population-based, nested case-control study. Circulation. 2014;Cardiovascular:70-77. [PMID: 24254886]

(53) Lanas A, Polo-Tomas M, Casado-Arroyo R. The aspirin cardiovascular/gastrointestinal risk calculator--a tool to aid clinicians in practice. Aliment Pharmacol Ther. 2013;37:738-748. [PMID: 23413984]

(54) Shah NH, LePendu P, Bauer-Mehren A, Ghebremariam YT, Iyer SV, Marcus J. Proton pump inhibitor usage and the risk of myocardial infarction in the general population. PLoS ONE. 2015;10:e0124653.

(55) Shiotani A, Kamada T, Haruma K. Low-dose aspirin-induced gastrointestinal diseases: past, present, and future. [Review] [76 refs]. J Gastroenterol. 2008;43:581-588.

(56) Hedberg J, Sundstrom J, Thuresson M, Aarskog P, Oldgren J, Bodegard J. Low-dose acetylsalicylic acid and gastrointestinal ulcers or bleeding--a cohort study of the effects of proton pump inhibitor use patterns. J Intern Med. 2013;274:371-380. [PMID: 23800296]

(57) Halvorsen S, Andreotti F, Ten Berg JM, Cattaneo M, Coccheri S, Marchioli R et al. Aspirin therapy in primary cardiovascular disease prevention: a position paper of the European Society of Cardiology working group on thrombosis. J Am Coll Cardiol. 2014;64:319-327. [PMID: S0735-1097(14)02579-0 [pii];10.1016/j.jacc.2014.03.049 [doi]]

(58) van Kruijsdijk RC, Visseren FL, Ridker PM, Dorresteijn JA, Buring JE, van der Graaf Y et al. Individualised prediction of alternate-day aspirin treatment effects on the combined risk of cancer, cardiovascular disease and gastrointestinal bleeding in healthy women. Heart. 2014;

(59) Brotons C, Benamouzig R, Filipiak KJ, Limmroth V, Borghi C. A Systematic Review of Aspirin in Primary Prevention: Is It Time for a New Approach? Am J Cardiovasc Drugs. 2014;

(60) Aspirin for the prevention of cardiovascular disease: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2009;150:396-404. [PMID: 19293072]

(61) Campbell CL, Smyth S, Montalescot G, Steinhubl SR. Aspirin dose for the prevention of cardiovascular disease: a systematic review. [Review] [61 refs]. JAMA. 2007;297:2018-2024. [PMID: 17488967]

(62) Strate LL. Lower GI bleeding: epidemiology and diagnosis. Gastroenterol Clin North Am. 2005;34:643-664.

(63) Lanas A, Garcia-Rodriguez LA, Polo-Tomas M, Ponce M, Alonso-Abreu I, Perez-Aisa MA et al. Time trends and impact of upper and lower gastrointestinal bleeding and perforation in clinical practice. Am J Gastroenterol. 2009;104:1633-1641.

(64) Kvasnovsky CL, Papagrigoriadis S, Bjarnason I. Increased diverticular complications with nonsteriodal anti-inflammatory drugs and other medications: a systematic review and meta-analysis. Colorectal Disease. 2014;16:O189-O196.

(65) Thiagarjan P, Jankowski JA. Tipping the balance: benefits and risks of aspirin in chemoprevention of colorectal cancers. Curr Colorectal Cancer Reports. 2013;9:1-8. [PMID: None]

(66) Armitage JM. ASCEND: A Study of Cardiovascular Events iN Diabetes 2014. Accessed at http://clinicaltrials.gov/ct2/show/NCT00135226?term=cardiovascular+events+prevention+trial+in+diabetes&rank=4. [PMID: None]

(67) de Berardis G, Sacco M, Evangelista V, Filippi A, Giorda CB, Tognoni G et al. Aspirin and simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes (ACCEPT-D): design of a randomized study of the efficacy of low-dose aspirin in the prevention of cardiovascular events in subjects with diabetes mellitus treated with statins. Trials. 2007;8:21. [PMID: 17725825]

(68) Study design of ASPirin in Reducing Events in the Elderly (ASPREE): A randomized, controlled trial. Contemp Clin Trials. 2013;36:555-564. [PMID: 24113028]

(69) A study to assess the efficacy and safety of enteric-coated acetylsalicylic acid in patients with moderate risk of cardiovascular disease (ARRIVE). 2013. Accessed at http://clinicaltrials.gov/show/NCT00501059 on 8 May 2013. [PMID: None]

(70) Henderson N, Smith T. Aspirin for the next generation. Ecancermedicalscience. 2013;7:300. [PMID: 10.3332/ecancer.2013.300 [doi];can-7-300 [pii]]

(71) Freedman JE. Appreciating and mitigating bleeding risk. Circulation. 2012;125:e548-e550. [PMID: 125/14/e548 [pii];10.1161/CIRCULATIONAHA.112.104224 [doi]]

(72) Gazzerro P, Proto MC, Gangemi G, Malfitano AM, Ciaglia E, Pisanti S et al. Pharmacological actions of statins: a critical appraisal in the management of cancer. Pharmacol Rev. 2012;64:102-146. [PMID: pr.111.004994 [pii];10.1124/pr.111.004994 [doi]]

(73) de Abajo FJ. Effects of selective serotonin reuptake inhibitors on platelet function: mechanisms, clinical outcomes and implications for use in elderly patients. Drugs Aging. 2011;28:345-367. [PMID: 2 [pii];10.2165/11589340-000000000-00000 [doi]]

(74) Elwood PC, Almonte M, Mustafa M. Is there enough evidence for aspirin in high-risk groups? Curr Colorectal Cancer Reports. 2013;9:9-16.

(75) Hawkey CJ. Helicobactor Eradication Aspirin Trial (HEAT) 2014. Accessed at https://clinicaltrials.gov/ct2/show/NCT01506986. [PMID: None]

Table 1. Brief description of included cohort studies and individual patient-data meta-analysis

Author, Year Quality	Design	Country	Mean Follow-up (Years)	Population	N	Mean Age and Range (years)	% Female	% Diabetes	% Current Smokers	ASA Dose and Frequency
de Berardis, 2012 (21) Good	Cohort, Retrospective	Italy	5.7*	Males and females aged ≥ 30 years, new aspirin users vs. never users	372,850	69.4 (30-95)	53.1	15	NR	≤ 300 mg with most recent prescription filled ≥ 75 days prior to bleeding event
Ekstrom, 2013 (SNDR) (35) Fair	Cohort, Prospective	Sweden	3.9	Males and females w/ diabetes	18,646	62.3 (30-80)	44.7	100	15.4	75 mg qd
Huang, 2010 (HPS) (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/week
Huang, 2011 (NHS) (34) Fair	Cohort, Prospective	United States	12.5	Female nurses	87,680	56.6 (30-55)	100	5	17.6	325 mg ≥ 2 tablets/week
ATT Colla-boration, 2009 (15)	IPD meta-analysis	Multi-national	3.7-10.0	Primary CVD prevention populations	k=6†, 95,459	56 (NR)	54	4	16	50-500 mg qd
Rothwell, 2012 (8)	IPD meta-analysis	Multi-national	3.6-8.2	Primary CVD prevention populations	k=6‡, 35,535	61.5 (NR)	44.1	NR	21.9	75-100 mg qd

*Median

†Included primary CVD prevention trials: Women's Health Study (WHS), British Medical Doctors (BMD), Thrombosis Prevention Trial (TPT), Hypertension Optimal Treatment (HOT), Primary Prevention Project (PPP), and the Physician's Health Study (PHS)

‡Included primary CVD prevention trials: Thrombosis Prevention Trial (TPT), Hypertension Optimal Treatment (HOT), Primary Prevention Project (PPP), Prevention of Progression of Arterial Disease and Diabetes (POPADAD), Aspirin for Asymptomatic Atherosclerosis (AAA), Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD)

Abbreviations: ASA= acetylsalicylic acid; mg= milligrams; NR= not reported; qd= daily; w/= with

Table 2. Sensitivity analyses for bleeding in CVD primary prevention trials

Source	Dose	k	n	Pooled OR (95% CI)	Included Trials
Major GI or extracranial bleeding					
Main analysis*	Any dose	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 (IPD meta-analysis)† (15)	Any dose	6	95,456	1.54 (1.30, 1.82)§, χ^2=3.1	BMD, PHS, TPT, HOT, PPP, WHS
de Berardis et al., (cohort study)‡ (21)	≤ 300 mg	1	372,850	1.55 (1.48, 1.63)‖	NA
Hemorrhagic stroke					
Meta-analysis (11)	Any dose	9	113,264	1.33 (1.03, 1.71), I^2=0.0%	PPP, HOT, JPAD, JPPP, PHS, BMD, TPT, AAA, WHS
	≤ 100 mg	7	86,054	1.27 (0.96, 1.68), I^2=0.0%	PPP, HOT, JPAD, JPPP, TPT, AAA, WHS
ATT Collaboration, 2009 (IPD meta-analysis) (15)	Any dose	6	95,456	1.32 (1.00, 1.75)§, , χ^2=4.7	BMD, PHS, TPT, HOT, PPP, WHS
Intracranial hemorrhage including hemorrhagic stroke					
Main analysis	Any dose	10	114,540	1.34 (1.07, 1.70), I^2=0.0%	PPP, TPT, HOT, JPAD, PHS, JPPP, BMD, POPADAD, AAA, WHS
	≤ 100 mg	8	87,330	1.30 (1.00, 1.68), I^2=0.0%	PPP, TPT, HOT, JPAD, JPPP, POPADAD, AAA, WHS

*Major GI bleeding
†GI or other major extracranial bleeding
‡Hospitalizations for first major bleeding event (extracranial or intracranial)
§Year event rate ratio
‖Incidence rate ratio

Table 3. Absolute bleeding rates among no-ASA control groups, overall and by subpopulations, from trials and cohort studies

Baseline Characteristic	**Major GI/extracranial bleeding‡** from ATT Collaboration, 2009 (15); events per 1,000 person-years	**Hemorrhagic stroke** from ATT Collaboration, 2009 (15); events per 1,000 person-years	**Hospitalizations for major bleeding event§** from cohort studies (de Berardis (21)); events per 1,000 person-years (95% CI)
All control group participants	0.7	0.3	3.60 (3.48 to 3.72) Major extracranial bleeding (approx..): 2.40 Major intracranial bleeding (approx.): 1.20
Age subgroups	< 65 years: 0.5 65+ years: 1.7	--	< 50 years: 0.61 (0.41 to 0.91) 50-59 years: 1.40 (1.24 to 1.58) 60-69 years: 2.58 (2.40 to 2.77) 70-79 years: 4.61 (4.39 to 4.85) 80+ years: 6.93 (6.51 to 7.38)
Sex subgroups	Male: 1.0 Female: 0.5	--	Male: 4.50 (4.3 to 4.70) Female: 2.86 (2.72 to 3.01)

‡Resulting in hospitalization, transfusion or death

§Combined GI bleeding and intracranial bleeding

Abbreviations: ATT = Antithrombotic Trialists; CI = confidence interval; GI = gastrointestinal

Table 4. Absolute events *caused* or prevented with very low-dose aspirin use (≤ 100 mg per day) up to 10 years, CVD primary prevention trials

Outcome	Risk Level‡	Baseline Risk of Outcome, Events per 1,000 person-years	Relative Risk (95% CI)‖	Events *Caused* or Prevented** per 1,000 person-years (95% CI)
Aspirin dose ≤ 100 mg per day (k=8)				
Major GI bleeding* (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 hemorrhagic stroke (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)***
Hemorrhagic stroke (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 events	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)***

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

†Using cohort baseline risk and trial relative risks to estimated events caused or prevented

‡Lowest (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 GI bleeding and hemorrhagic stroke, highest indicates the maximum while high is the second highest.

§Baseline risk as reported by included cohort studies

‖Based on ≤ 100 mg/day in primary CVD prevention trials

**Negative sign indicates cases prevented

Bolding represents events clearly caused or prevention (i.e., 95% CI does not include both caused and prevented events); *caused events are italicized*

Abbreviations: CI = confidence interval; CVD = cardiovascular disease; GI = gastrointestinal; ICH = intracranial hemorrhage; mg = milligram(S); MI = myocardial infarction

Table 5. Relative rate ratios for bleeding among sub-populations from trials and cohort studies

Baseline Characteristic	**Major GI/extracranial bleeding‡** from ATT Collaboration, 2009 (15) *Adjusted Rate Ratio (95% CI)*	**Hemorrhagic stroke** from ATT Collaboration, 2009 (15) *Adjusted Rate Ratio (95% CI)*	**Hospitalizations for major bleeding event§** from cohort study (de Berardis (21)) *Adjusted Incidence Rate Ratio (95% CI)*
Age	2.15 (1.93 to 2.39) per decade	1.59 (1.33 to 1.90) per decade	1.05 (1.05 to 1.05) per year
Male sex (vs. female)	1.99 (1.45 to 2.73)	1.11 (0.52 to 2.34)	1.69 (1.61 to 1.79)
Diabetes (yes vs. no)	1.55 (1.13 to 2.14)	1.74 (0.95 to 3.17)	1.36 (1.28 to 1.44)
Current Smoker (yes vs. no)	1.56 (1.25 to 1.94)	2.18 (1.57 to 3.02)	
Mean BP (per 20 mm Hg)	1.32 (1.09 to 1.58)	2.18 (1.62 to 2.87)	
Cholesterol (per 1 mmol/L)	0.99 (0.90 to 1.08	0.90 (0.77 to 1.07)	
BMI (per 5 kilograms):	1.24 (1.13 to1.35)	0.85 (0.71 to 1.02)	
Previous GI hospitalization (yes vs no)	---	---	2.87 (2.46 to 3.35)
Medication use (yes vs no):			
NSAIDS			1.10 (1.05 to 1.16)
ASA			1.61 (1.54 to 1.69)‖
Any antihypertensive			1.14 (1.08 to 1.19)
Statins			0.67 (0.62 to 0.71)
PPI			0.84 (0.80 to 0.88)

‡Resulting in hospitalization, transfusion or death

§Combined GI bleeding and intracranial hemorrhage/hemorrhagic stroke

‖Adjusted incidence rate ratio (current vs. never)

Abbreviations: ASA = acetylsalicylic acid; BMI = body mass index; CI = confidence interval; GI = gastrointestinal; mmol/L = millmoles per liter; mm Hg = millimeters of mercury; NSAID = nonsteroidal anti-inflammatory drugs; PPI = proton pump inhibitor; vs = versus

Figure 1. Forest plot of major GI bleeding , CVD primary prevention trials

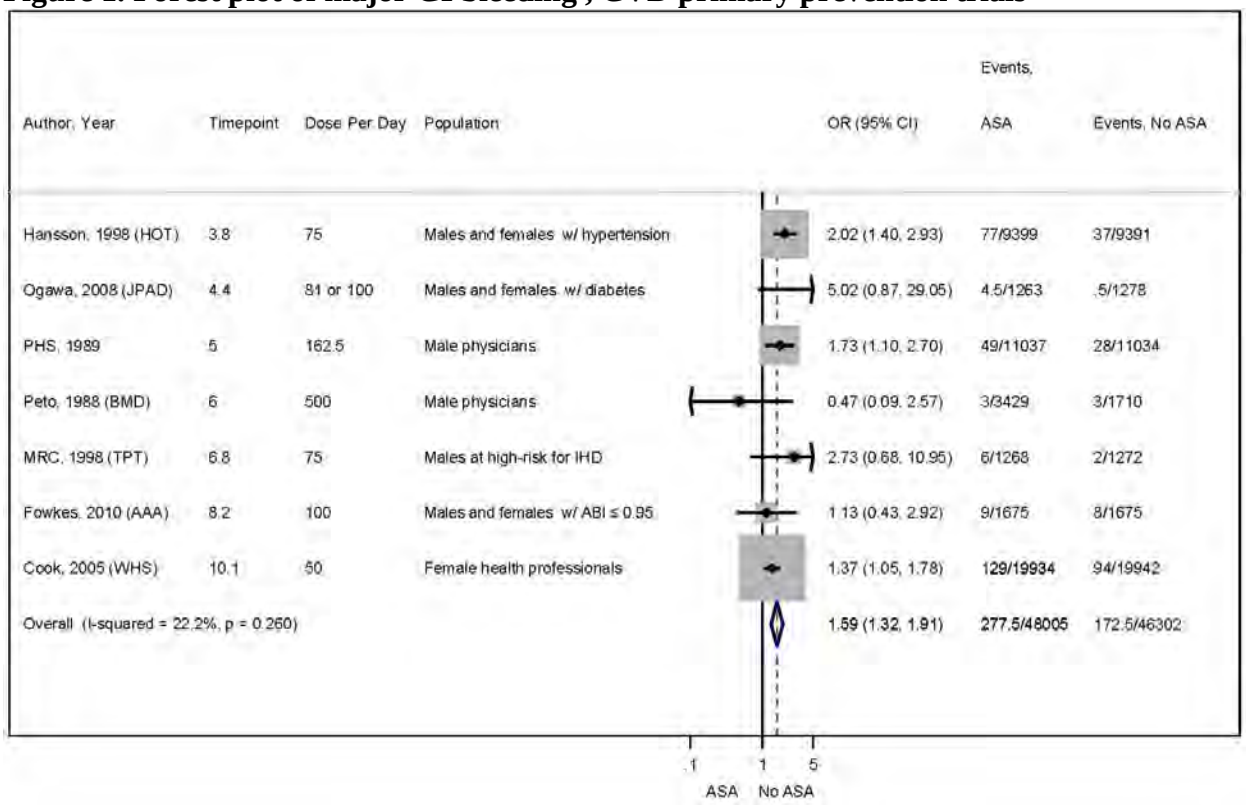

Figure 2. Forest plot of hemorrhagic strokes, CVD primary prevention trials