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Aspirin Use to Prevent Cardiovascular Disease and Colorectal Cancer: An Evidence Update for the U.S. Preventive Services Task Force

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Structured Abstract

Background: Cardiovascular disease (CVD) is the leading cause of death and colorectal cancer (CRC) is the third leading cause of death in the United States.

Purpose: To systematically review evidence for the effectiveness of aspirin to prevent myocardial infarction (MI), stroke, cardiovascular death, and all-cause mortality in those without a history of CVD. In addition, to review evidence for CRC incidence and mortality associated with aspirin use in primary and secondary CVD populations. To further review harms associated with aspirin use.

Data Sources: We searched MEDLINE, PubMed, and the Cochrane Collaboration Registry of Controlled Trials to identify literature that was published between January 2014 and January 14, 2021. We supplemented our searches with reference lists from the previous review, relevant existing systematic reviews, suggestions from experts, and Clinicaltrials.gov to identify ongoing trials. We conducted ongoing surveillance for relevant literature through January 21, 2022.

Study Selection: Two investigators independently reviewed identified abstracts and full text articles against a set of a priori inclusion and quality criteria.

Data Analysis: One investigator abstracted data into an evidence table and a second investigator checked these data. We conducted Peto fixed effects meta-analyses to estimate the effect size of aspirin in preventing MI, stroke, CVD-related death and all-cause mortality, CRC incidence and mortality, major bleeding, major gastrointestinal (GI) bleeding, intracranial bleeding, hemorrhagic stroke, and extracranial bleeding. Additionally, we conducted sensitivity analyses using Mantel-Haenszel fixed effects and Restricted Maximum Likelihood random effects.

Results: We included 13 fair- to good-quality randomized, controlled trials (RCTs) (N=161,680) examining the effectiveness of aspirin for the primary prevention of CVD. Based on pooled analysis of 11 primary CVD prevention trials using aspirin ≤100 mg/day, low-dose aspirin reduces the risk of major CVD events (total MI, total stroke, CVD mortality) by 10 percent (k=11, N=134,470; Peto odds ratio [OR], 0.90 [95% confidence interval (CI), 0.85 to 0.95]), MI by 11 percent (k=11, N=134,470; Peto OR, 0.89 [95% CI, 0.82 to 0.96]), and ischemic stroke by 18 percent (k=5, N=79,334; Peto OR, 0.82 [95% CI, 0.72 to 0.92]) with no differences in CVD mortality (k=11, N=134,470; Peto OR, 0.95 [95% CI, 0.86 to 1.05]) or all-cause mortality (k=11, N=134,470; Peto OR 0.98 [95% CI, 0.93 to 1.03]). Absolute risk reductions in major CVD events in the trials ranged from 0.08 to 2.5 percent. Aspirin's benefits were similar when trials of all doses were pooled. Sensitivity analyses restricted to more recent trials where usual care includes aggressive risk factor modification including statin therapy show diminished effects of aspirin for major CVD events and total MI but larger effects for total ischemic stroke compared to older trials. A small subset of the trials reporting CVD outcomes also reported CRC outcomes. Based on 4 low-dose aspirin trials (N=86,137) recruiting primary CVD prevention populations, there was no statistically significant association between aspirin and CRC incidence when analyzing randomized trial periods (Peto OR 1.07 [95% CI, 0.92 to 1.24]; trial period 5-10 years). Analysis including post-trial observation periods up to 20 years and including trials with high-dose aspirin up to 500 mg/day (k=2; N=45,015) in primary prevention populations show

statistically significant reductions in CRC incidence (0.70 [95% CI, 0.50 to 0.98] and 0.82 [95% CI, 0.69 to 0.98]). Two low-dose aspirin RCTs (N=59,020) in primary CVD prevention populations report CRC mortality during the trial period (5-10 years) showing results concerning for possible harm with one trial demonstrating a statistically significant increase in CRC mortality in older adults. At 18 years of followup, including post-trial observational periods, three primary CVD prevention trials with mean daily aspirin doses ranging from 75 to 500 mg showed aspirin was associated with a decreased risk of CRC mortality (Peto OR 0.76 [95% CI, 0.62 to 0.94]). Low-dose aspirin is associated with a 31 percent increase in intracranial bleeding events (k=11; N=134,470; Peto OR, 1.31 [95% CI, 1.11 to 1.54]), and 53 percent increase in extracranial bleeding events (k=10; N=133,194; Peto OR 1.53 [95% CI, 1.39 to 1.70]). The absolute increases ranged from -0.2 to 0.4 percent for intracranial bleeding events and 0.2 to 0.9 percent for extracranial bleeding events. There is no compelling evidence to suggest that aspirin has a different relative CVD benefit or bleeding risk in specific populations defined by age, sex, race and ethnicity, diabetes status, or baseline 10-year CVD risk. Aspirin's CVD benefits appear to begin within the first 1-2 years of administration and the bleeding harms begin soon after aspirin initiation; there are limited data for more precise time increments or longer durations.

Limitations: Primary CVD prevention trials used different aspirin doses in heterogeneous populations with relatively short study followup, with duration mostly ranging from 4-6 years. Trials reporting CRC incidence and mortality outcomes are limited by short trial duration and multiple comparisons; observational followup of trials are limited by heterogeneity of aspirin doses, duration, indications, and populations with risk of biases and confounding. Estimates of rare bleeding harms are imprecise.

Conclusions: In primary prevention populations, low-dose aspirin reduces major CVD events, MI and ischemic stroke, but also increases major GI bleeding, extracranial bleeding, and intracranial bleeding. Our evidence suggests aspirin is associated with a possible long-term reduction in CRC incidence and mortality based on post-trial period observation, but the results are limited for low-dose aspirin among primary CVD prevention populations. More precise real-world U.S.-based estimates for bleeding events in the general population and specific populations with elevated CVD risk are necessary to accurately estimate the net benefit. Depending on CVD risk, this absolute CVD benefit in specific populations could potentially outweigh the bleeding risks. Models to identify these populations are needed.

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Chapter 1. Introduction

The 2016 U.S. Preventive Services Task Force (USPSTF) recommendation *Aspirin Use to Prevent Cardiovascular Disease and Colorectal Cancer*[1] considered data from multiple systematic reviews[2-4] and a decision analysis[5] in order to estimate the net benefits of aspirin use for the prevention of two highly prevalent diseases: cardiovascular disease (CVD) and colorectal cancer (CRC). This single systematic review summarizes the findings related to aspirin for the prevention of both conditions as well as bleeding risks associated with aspirin use for primary prevention.

Condition Definition

In the context of this systematic review, aspirin has been considered for the primary prevention of two conditions: CVD and CRC.

CVD refers to a class of diseases that affect the cardiovascular system. CVD can affect the heart, blood vessels, brain, kidneys, and arteries.[6] Atherosclerosis and hypertension are the most common underlying causes of CVD. Types of CVD include coronary heart disease, cardiomyopathy, hypertensive heart disease, heart failure, cardiac dysrhythmias, inflammatory heart diseases, valvular heart disease, stroke, cerebrovascular disease, and peripheral arterial disease.[6]

CRC is a cancer that originates in the large intestine and includes the following segments: the cecum, ascending colon, transverse colon, descending colon, sigmoid, and rectum.

Prevalence and Burden

Cardiovascular Disease

Cardiovascular disease is the leading cause of mortality in the United States for both sexes.[7, 8] Although the relative rate of CVD mortality steadily declined from 1980 to 2010, recent years have witnessed an increase in CVD mortality rates.[7] Researchers have posited that increases in rates of obesity, metabolic syndrome, and type 2 diabetes may be related to CVD mortality increases.[9, 10] In addition to high rates of mortality, 2015-2018 National Health and Nutrition Examination Survey (NHANES) data estimate that as many as 26.1 million adults in the United States live with the burden of a CVD diagnosis, defined as coronary heart disease (CHD), heart failure, or the consequences of a stroke.[7]

Each year, an estimated 605,000 Americans have a first heart attack and about 610,000 experience a first stroke.[7] High rates of CVD mortality and morbidity represent a significant economic burden to the health care system in the United States. The estimated direct and indirect cost of CVD for 2016 to 2017 was $363.4 billion.[11] While CVD impacts much of the population, the distribution of burden and risk factors varies among specific populations.

The prevalence of CVD increases progressively with age and is strongly influenced by the presence of risk factors. NHANES estimates from 2015-2018 show that while CVD is rare in males and females 20 to 39 years of age (1.1% and 1.2%, respectively), prevalence is highly common by the sixth or seventh decade (27.1% and 18.2% for males and females, respectively) (**Table 1**).[7] By the age of 45 years, the lifetime risk of CVD events in adults with optimal risk factor profiles (total cholesterol level <180 mg/dL, blood pressure <120/80 mm Hg, nonsmoking status, and nondiabetic status) compared to adults with one major risk factor varies greatly: 1.4 versus 39.6 percent among males and 4.1 versus 20.2 percent among females. Having two or more major risk factors further increases lifetime risk to 49.5 percent in males and 30.7 percent in females.[12] While males carry a higher overall burden of cardiovascular disease after age 60, females experience higher mortality from certain cardiovascular events, such as stroke.[7] Males tend to experience CVD events earlier in life. For myocardial infarction (MI), the mean age of first event is 65.6 years for males and 72.0 years for females.[7] In addition to age and sex differences, the burden of CVD also differs by race and ethnicity (**Table 2**). Among both sexes, Black Americans have the highest prevalence of CVD.[7] Differences in CVD prevalence by race and ethnicity are likely multifactorial with recent studies suggesting that disparities are more likely driven by nonbiologic and societal factors rather than genetic factors.[13, 14] Structural racism, socioeconomic inequality, environmental disparities, unequal access to care, and medication acceptance are all mechanisms contributing to inequities.[13]

Colorectal Cancer

CRC is the third leading cause of cancer death for both males and females[15]; it is estimated that 53,200 people in the United States will die from CRC in 2020.[16] Although death rates due to CRC have been falling on average 2.2 percent each year in the past decade, the burden of disease remains high. In 2020, CRC was estimated to represent 8.2 percent of incident cancers, with an estimated 147,950 people receiving a new diagnosis of CRC.

CRC incidence is higher for those who are male, older, and Black (**Figure 1**). Black males and females have the highest incidence of CRC among all racial/ethnic groups and also the highest CRC mortality: the annual CRC-related death rate overall is 16.3 deaths per 100,000 males and 11.5 deaths per 100,000 females of all races, but it is 22.5 deaths per 100,000 in Black males and 14.8 deaths per 100,000 in Black females.[16] While CRC is more common with increasing age, recent trends indicate CRC is increasing among those under 50 years of age.[17, 18] In 2018, 69 percent of U.S. adults 50 years and older were up to date with CRC screening and aspirin's role in CRC prevention may be lessened by increased screening rates.[19]

Risk Factors and Risk Assessment

Cardiovascular Disease

Risk factors for CVD are well established and include both modifiable and nonmodifiable components. Modifiable risk factors include high cholesterol, high blood pressure, diabetes, overweight and obesity, smoking, lack of physical activity, excessive alcohol use, and unhealthy diet. Nonmodifiable risk factors include age, sex, and family history of CVD.[20]

Cardiovascular risk can be estimated using multivariate equations that predict the risk of an event over 10 years. The Pooled Cohort Equations (PCE) are currently the standard of practice for risk assessment and provide sex- and race-specific estimates for Black and White males and females 40 to 79 years of age for 10-year risk of atherosclerotic cardiovascular disease events (CHD death, nonfatal MI, and fatal or nonfatal stroke).[21] In addition to sex and race, risk predictors include age, total cholesterol, high-density lipoprotein (HDL) cholesterol, systolic blood pressure (including treatment status), diabetes, and current smoking status. PCE risk thresholds are included in several recommendations from the USPSTF, including the prior aspirin recommendation and the recommendation for statins,[22, 23] and are also part of recommendations from other professional societies.[24] The 2019 American College of Cardiology/American Heart Association (ACC/AHA) primary prevention guidelines discuss the limitations of risk assessment scores, including known under- and overestimation in specific populations, and state that it may be reasonable to use additional risk-enhancing factors and then coronary artery calcium scores to guide decision-making for borderline risk (5 to <7.5% 10-year risk) or intermediate risk (≥7.5% to <20% 10-year risk) individuals if uncertainty remains.[24] Ongoing research gaps and areas needing clinical guidance involve risk estimation for Hispanic, Asian, and "American Indian" populations, for which there are not separate equations in the PCE. The original 2013 ACC/AHA guideline stated that the equations for nonHispanic White individuals could be considered for use in these groups, however, that risk may be overestimated for Hispanic and Asian populations and underestimated for "American Indian" men and women.[21] Further discussion of PCE limitations can be found in the Discussion section.

Based on NHANES 2015-2018 data, the vast majority of Americans aged 40 to 49 years have an estimated 10-year CVD risk of 10 percent or less using the PCE (96% of females and 92% of males).[25] For ages 50 to 59 years, 87 percent of females and 68 percent of males have estimated 10-year risk of 10 percent or less; at ages 60 to 69, 66 percent of females and 20 percent of males have estimated 10-year risk at this level. Estimated 10-year risk using the PCE is substantially different by race. For example, among Black males aged 50 to 59 years, 37 percent have an estimated 10-year risk less than 10 percent; this prevalence is 73 percent among White males.[25]

Colorectal Cancer

Many risk factors for CRC overlap with prominent risk factors also associated with CVD. Modifiable risk factors associated with higher incidence of CRC include excessive alcohol use, cigarette smoking, and physical inactivity.[26] Nonmodifiable risk factors include older age, history of adenomas, inflammatory bowel disease, family history of CRC or adenomas, and inherited conditions such as Lynch syndrome, Peutz-Jeghers syndrome, and MHY-associated polyposis.[27]

Risk assessment models for CRC are not routinely used in clinical practice, although many different risk models have been developed.[28] Risk factors commonly used in models include age, sex, family history (generally specified as first degree relatives), body mass index (BMI), and lifestyle factors (e.g., smoking, alcohol, diet, and exercise).

Mechanism of Action

Aspirin's mechanism of action to promote CVD prevention is well-known, but its role in CRC prevention is less understood. Aspirin, an irreversible cyclooxygenase (COX)-1 and -2 enzyme inhibitor, reduces the risk for atherothrombosis through the inhibition of platelet function (through COX-1 inhibition), and has been used widely for decades for the prevention of CVD events, particularly in secondary prevention populations.[29] The biomolecular mechanism for aspirin's possible anti-neoplastic effects are not well-understood nor widely accepted. The postulated mechanism includes both COX-dependent (increased cell apoptosis, reduced COX-catalyzed prostaglandin production), and non-COX dependent anti-cancer activity. Lower doses of aspirin preferentially inhibit COX-1 pathways while higher doses additionally inhibit COX-2 pathways; it has been postulated that aspirin's antineoplastic effects may be mediated through the COX-1 and COX-2 pathway along with modulation of oncogene-induced expression of transcription factors.[30]

The COX-1 enzyme is also responsible for producing a variety of prostaglandins with roles to protect the gastrointestinal (GI) mucosa.[31] By inhibiting this enzyme, aspirin use can promote GI bleeding.[32] At higher doses (≥300 mg/day), aspirin begins to inhibit COX-2 activity, taking on greater anti-inflammatory effects, but also increases the inhibition of prostaglandins produced by COX-1, further increasing the risk of GI bleeding.[32-34]

Recommendations of Others

Several guidelines have addressed aspirin's role in primary CVD prevention to accompany other CVD risk modification interventions including behavioral interventions for healthy eating, exercise and smoking cessation, blood pressure management, and statin therapy. Recommendations for aspirin for CVD primary prevention have focused on identifying primary prevention patients at sufficiently high CVD risk to outweigh bleeding harms. Recent U.S.-based recommendations by the ACC/AHA[24] and the American Diabetes Association (ADA)[35] recommend aspirin for selected patients, but neither recommend a specific PCE threshold for aspirin consideration **(Table 3)**. European recommendations[36-38] do not recommend the use of aspirin in primary prevention. The Cancer Council of Australia is the only organization advising consideration of aspirin for primary CRC prevention (**Table 4**), with other organizations recommending aspirin only for groups at increased risk of CRC.

Current U.S.-Based Clinical Practice

In the United States, aspirin use for the primary prevention of CVD is common and is often self-initiated rather than recommended by a physician. Data from the 2017 National Health Interview Survey (NHIS) found that 23.4 percent of adults age 40 or older and without CVD took aspirin for primary prevention and of these, 22.8 percent took aspirin without a physician's recommendation.[39] Older age, male sex, and the presence of CVD risk factors such as hypertension, high cholesterol, and diabetes, were associated with increased aspirin use. Among adults 50-59 years, 18.4 percent reported aspirin use; among adults 60-69 years, 34.7 percent

reported aspirin use. Nearly half of adults aged 70 or older reported aspirin use; this is an age range for which the USPSTF has an I recommendation (insufficient evidence to make a recommendation) and the ACC/AHA has a recommendation against.

Several organizations have recently recommended that aspirin be considered for the primary prevention of CRC.[40-42] There are no data currently available regarding physician practices for aspirin in the prevention of CRC in populations at average or high risk for CRC.

Chapter 2. Methods

Scope and Purpose

This review is a combined update of three reviews that supported the 2016 USPSTF recommendation[1] and decision model[43]: a review on aspirin to prevent CVD,[2] a review on aspirin to prevent CRC,[4] and a review on aspirin to prevent all cancers as well as the harms of aspirin.[3] Our update includes studies published since the previous reviews and studies from the previous reviews that met updated inclusion criteria. The most substantive changes in scope were to remove the outcomes of all cancer incidence, all cancer mortality, and colorectal adenomas. Only CRC incidence and mortality outcomes are carried forward in this review as previously it was the cancer outcome with the most evidence.

Analytic Framework and Key Questions

We followed USPSTF procedures and methods to define study inclusion and exclusion criteria (**Appendix A, Table 1**) and developed an analytic framework (**Figure 2**) with two Key Questions (KQs).

1. Does regular aspirin use in patients without known cardiovascular disease (CVD) reduce CVD- and colorectal cancer (CRC) incidence and mortality, or all-cause mortality?
   a. Does the effect vary in specific *a priori* populations defined by age, sex, 10-year cardiovascular risk, race and ethnicity, or diagnosis of diabetes mellitus?
   b. Does the effect vary by dose or duration of aspirin use?
2. Does regular aspirin use increase major GI bleeding, intracranial bleeding, or other serious harms?
   a. Does the effect vary in specific *a priori* populations defined by age, sex, 10-year cardiovascular risk, diagnosis of diabetes mellitus, race and ethnicity, or bleeding risk factors?
   b. Does the effect vary by dose or duration of aspirin use?

Data Sources and Searches

We considered all studies from the previous reviews on this topic for inclusion in the current review and performed a comprehensive search for new literature. We searched MEDLINE, PubMed (publisher-supplied only), Embase, and the Cochrane Collaboration Registry of Controlled Trials for relevant studies published between January 2014 and January 14, 2021. Studies included in the previous USPSTF review were evaluated for inclusion against the inclusion and exclusion criteria for the current review. A research librarian developed and executed the search, which was peer-reviewed by a second research librarian (**Appendix A**).

We also examined the reference lists of other previously published reviews, meta-analyses, and primary studies to identify additional potential studies for inclusion. We supplemented our

searches with suggestions from experts and articles identified through news and table-of-contents alerts. We also searched ClinicalTrials.gov (https://ClinicalTrials.gov/) for ongoing trials (**Appendix E**). Active surveillance was conducted after our searches through January 21, 2022 via article alerts and targeted journal searches to identify major studies that might affect the conclusions or understanding of the evidence. We managed all literature search results from these sources directly into EndNote® X9 (Thomson Reuters, New York, NY).

Study Selection

Detailed inclusion and exclusion criteria were developed to guide study selection (**Appendix A, Table 1**). Two reviewers independently reviewed the titles and abstracts of all identified articles to determine whether studies met these criteria. Two reviewers then independently evaluated the full text of potentially relevant studies. Disagreements regarding the abstract and/or full text review were resolved by discussion and consultation with a third reviewer if necessary. Excluded studies and reasons for exclusion are listed in **Appendix C**. We used DistillerSR (Evidence Partners, Ottawa, Canada) to conduct abstract and full-text review.

Population

We included populations age 40 years and older without known CVD and at average risk for CRC or unselected for CRC risk. Nongeneralizable populations such as those selected for genetic susceptibility syndromes, or a personal history of cancer, were excluded. For CRC outcomes only, populations with a history of CVD were also included for a prespecified sensitivity analysis. Studies needed to be conducted in countries categorized as "very high" on the 2017 Human Development Index, as defined by the United Nations Development Programme.[44]

Interventions and Comparators

We included studies examining any dose of regular oral aspirin use compared to no treatment or a placebo. We defined regular oral aspirin use as a minimum of 75 milligrams (mg) every other day for 12 months. Aspirin use for analgesic indication was not eligible as use patterns for this indication are likely more intermittent and inconsistent. We excluded interventions including nonaspirin antithrombotic medications, and aspirin as a cotreatment to another active intervention. Multifactorial trials including other eligible agents (e.g., vitamin E) or interventions (e.g., blood pressure reduction) were acceptable and results were combined for aspirin versus no aspirin arms. In a trial with additional randomization to warfarin or placebo,[45] we did not include any arms receiving warfarin, as we considered warfarin an excluded cotreatment.

Outcomes

For KQ1 (benefits), cardiovascular outcomes of interest included MI, stroke, death from MI or CHD, death from stroke, and composite outcomes of major CVD events. We also included colorectal cancer incidence, colorectal cancer mortality, and all-cause mortality. For KQ2 (harms), we were interested in hemorrhagic stroke, intracranial hemorrhage (ICH) and major

bleeding, defined as bleeding requiring a transfusion or hospitalization, or leading to death. This could include, but was not limited to, serious gastrointestinal bleeding. Other serious harms were also abstracted. Detailed definitions and the handling of composite outcomes are further described in the Data Analysis section.

Study Design

For both KQs, randomized controlled trials (RCTs), controlled clinical trials, and individual patient-data meta-analyses (IPD MA) were included. For KQ2 (harms), large observational studies were also considered. Eligible observational studies needed to report an aspirin group and non-aspirin control group. Case control studies, case series, and case reports were excluded. The inclusion of observational studies was limited to primary prevention CVD populations reporting major bleeding in an aspirin group and nonaspirin control group. Intent-to-treat (ITT) analyses from long-term observational followup from randomized trials were included (see additional details under Data Synthesis and Analysis).

Quality Assessment

Two reviewers applied USPSTF design-specific criteria[46] to assess the methodological quality of all eligible studies (**Appendix A, Table 2**). We assigned each study a quality rating of "good," "fair," or "poor." Discordant quality ratings were resolved by discussion or adjudicated by a third reviewer as needed. Studies rated as poor quality were not eligible for the review.

Good-quality RCTs were those that met all or nearly all of the specified quality criteria. Specifically, comparable groups were assembled initially and maintained throughout the study, followup was 90 percent or higher, assessment procedures were described and blinded if they involved direct interviews, randomization methods were described, and allocation was concealed. Fair-quality studies did not meet all criteria but did not have serious threats to their internal validity related to design, execution, or reporting. To be rated as poor quality, intervention studies generally have several important limitations, including at least one of the following risks of bias: very high attrition (generally >40%); differential attrition between intervention arms (generally >20%); lack of baseline comparability between groups without adjustment; or problematic issues in trial conduct, analysis, or reporting of results (e.g., possible selective reporting; inappropriate exclusion of participants from analyses; questionable validity of allocation or assessment procedures).

Data Abstraction

For all included studies, one reviewer extracted key elements into standardized abstraction forms in DistillerSR (Evidence Partners, Ottawa, Canada). Key elements included general characteristics of the study (e.g., author, year, study design), clinical and demographic characteristics of the sample and setting (e.g., age, race and ethnicity, baseline clinical characteristics, setting, country), intervention details (e.g., aspirin dose, duration) analytic

methods (e.g., adjustments), and outcomes relevant to KQ1 and KQ2. A second reviewer checked the data for accuracy.

Data Synthesis and Analysis

The primary outcomes of this review were:

- Major CVD events (nonfatal MI, nonfatal stroke, and CVD mortality)
- Total MI
- Total stroke
- Total ischemic stroke
- CVD mortality
- All-cause mortality
- CRC incidence
- CRC mortality
- Total major bleed
- Major GI bleed (GIB)
- Hemorrhagic stroke
- Intracranial hemorrhage
- Extracranial hemorrhage

Nonfatal and fatal events were also analyzed separately as secondary outcomes.

Cardiovascular Disease

Because of substantial heterogeneity in the primary composite outcomes defined by individual trials, and the fact that these composites often included outcomes that were not eligible for our review (i.e., angina, revascularization), trial-defined composite outcomes were not necessarily included as a primary outcome in our review. Instead, we constructed our own primary composite outcome—major CVD events—which was comprised of nonfatal MI, nonfatal stroke, and CVD mortality as a broad measure of CVD benefit. If an individual study did not report this outcome, we calculated it from individual outcomes. This approach may overestimate events if the reporting of separate outcomes included individuals with nonfatal events followed by a fatal event. For the outcomes of total MI and fatal MI, we included fatal coronary heart disease and sudden death in addition to MI events.

There was heterogeneity in the individual trials with regard to the outcomes contributing to CVD mortality. For several trials, CVD mortality was exclusively comprised of fatal MI (including CHD death and sudden death) and fatal stroke. In other trials, additional events such as aortic aneurysm, hypertensive heart disease, and pulmonary embolism were included. For comparability, we preferentially used the broader definition of CVD death because this was available from most trials. The narrower definition of fatal MI and fatal stroke was used when broader definitions were not reported.

Stroke

Where possible, our stroke outcomes are consistent with the 2013 definition of stroke from the AHA and the American Stroke Association (ASA).[47] Stroke outcomes were grouped into two categories by their mechanism—ischemia or hemorrhage. Hemorrhagic stroke includes neurological deficits as a result of intracerebral hemorrhage and subarachnoid hemorrhage. Intracranial bleeding encompasses intracerebral hemorrhage and subarachnoid hemorrhage as well as subdural hematoma (subdural hematoma is not considered a stroke). Intracranial bleeding does not necessarily have to manifest neurological deficits.

Colorectal Cancer

We included both CRC incidence and mortality, as reported by the trials. We also accepted the narrower outcomes of colon cancer as reported by the trials, with the knowledge that this could be underestimating cases in comparison to trials that looked for both colon and rectal cancer. We did not accept the broad category of GI cancer, as this could include other cancers of the GI tract, such as gastric cancer.

Major Bleeding

For harms (KQ2), we evaluated major bleeding, defined as bleeding requiring transfusion or hospitalization or leading to death. If a trial reported transfusions and death from bleeding separately, we added these events together. If a trial only reported deaths from bleeding, we used that number for major bleeding. If a trial reported bleeding without any mention of severity, we did not include it in our analysis. We further categorized major bleeding by location: GI (upper and lower), extracranial (inclusive of all bleeds except intracranial bleeds), and intracranial (inclusive of hemorrhagic stroke, subarachnoid hemorrhage, and subdural hemorrhage). If studies did not report these outcomes, we calculated them when data were available to calculate a composite. At times, studies only reported a subset of these bleeding locations and in those cases that subset was used in the pooled analysis for the larger category. For example, hemorrhagic stroke was substituted for intracranial hemorrhage if intracranial hemorrhage was not reported.

Analysis

We prespecified the following sensitivity analyses:

- Low-dose aspirin, defined as ≤100 mg/day.
- CRC incidence to include secondary CVD prevention populations in addition to primary CVD prevention.
- CRC incidence in studies that prespecified that outcome.
- Trials partly or fully conducted after Adult Treatment Panel (ATP) III (2001), a proxy for more widespread statin use. We hypothesize that there may be lower potential benefit of aspirin in contemporary trials because of greater statin use, more aggressive blood pressure (BP) control, lower smoking rates, and more pervasive CRC screening. Trial date was chosen as a proxy for statin use because only about half of primary prevention trials reported actual baseline statin use.

Because these studies were conducted in relatively healthy primary prevention populations, most outcomes were rare (i.e., generally <10% of participants experienced any given event, and <1% to 2% for some outcomes). Due to these rare events, we used the Peto fixed effects model for our primary statistical method.[48] Sensitivity analyses were conducted with the Mantel-Haenszel fixed effects model and the random effects restricted maximum likelihood (REML) model. We assessed the proportion of statistical heterogeneity using the I^2 statistic. We assessed small study bias using funnel plots and the Harbord test of bias for extracranial bleed, intracranial bleed, all-cause mortality, CVD mortality, and major CVD events. All analyses were conducted in Stata version 16 (StataCorp LP, College Station, TX).

Forest plots show calculated Peto odds ratios (OR) using the number of individuals with an event and the numbers of people analyzed in each randomized group. When events were reported as per unit of patient-years and the number of patient-years in each group was reported, we calculated the number of events in each group. We used first-event analyses when trials reported both first and total event analyses. We chose this more conservative approach because after a first event, patients are more likely to have a second event in the same category.

The range of absolute benefits or harms in the individual trials were calculated when the pooled outcomes showed statistically significant relative effects. These absolute benefits or harms do not represent pooled estimates. Absolute risk differences were not pooled due to rare events or differing event rates among studies; combined estimates of absolute risk differences typically have lower statistical power and result in more conservative confidence intervals.[48]

For CRC outcomes, IPD MAs were only used to obtain CRC incidence and mortality data for individual trials. We did not pool the results of IPD MAs with primary trials. Further, because these IPD MAs include only a subset of our included studies, we do not discuss their pooled results.

The handling of long-term observational followup from the randomized trials differed by outcome. We do not hypothesize a direct persistent effect of aspirin on CVD or bleeding outcomes for extended periods after discontinuation, thus, long-term observational followup for these outcomes are acknowledged in tables but were not pooled with randomized followup periods. In contrast, there could be persistent effects of aspirin on CRC incidence or mortality if aspirin prevents adenomas or adenoma progression and the randomized periods were too short to detect eventual reductions in CRC incidence or mortality. We report long-term observational followup for CRC outcomes in tables and pool estimates including long-term observational followup together. In addition to published results, Women's Health Study (WHS) investigators provided unpublished trial period and observational followup data for CRC incidence and mortality.[49]

For our subquestions on duration (KQ1b, KQ2b), we evaluated Kaplan-Meier curves as published in the primary literature. For each relevant outcome, we assessed if there were timepoints where Kaplan-Meier curves diverged, and whether separation of curves persisted.

Analysis Methods in Specific Populations

We prespecified analyses in specific populations defined by age, sex, 10-year cardiovascular risk, race and ethnicity, and diagnosis of diabetes mellitus to determine if there is evidence that the relative effects of aspirin differ in specific populations. During data abstraction we entered results for these subgroup analyses into our database and developed population-specific summary tables. In addition to outcomes, population-specific summary tables included information relevant to the credibility of each trial's subgroup analyses, including timing of the analysis and interaction testing for heterogeneity of treatment effect. Direct evidence from within-study comparisons was emphasized over across-study comparisons, which can be confounded by trial-level differences in populations and their risk factors.

During the data abstraction phase, we also catalogued the availability and characteristics of other subgroup analyses reported in the primary literature that we did not prespecify for our systematic review. This audit was used to assess whether additional post hoc formal subgroup analyses were warranted, based on the number of contributing studies and the credibility of subgroup analyses for each subpopulation of interest.

Because of trial-level heterogeneity in population recruitment, dose, duration, and recency, there are limitations to using trial-level analyses to investigate heterogeneity of treatment effect in specific populations, and we were unable to pool results. The most appropriate method for investigating a differential effect of aspirin in specific populations is with the use of individual patient-data meta-analyses. The 2009 Antithrombotic Trialists' (ATT) Collaboration IPD MA is a robust source for these data; however, it does not include the most recently published trials.[50] An update to this analysis is in progress and is expected in 2021.[51] In the absence of an updated IPD MA, we have prioritized within-trial analyses in our investigation of effects in specific populations.

For our subquestions KQ1a and KQ2a on whether the benefits or harms of aspirin vary in specific a priori identified populations, we constructed a population-specific credibility rating table to organize findings related to the credibility of subpopulation analyses and consistency of conclusions.

Grading the Strength of the Body of Evidence

The strength of evidence for each primary outcome as identified in the Data Analysis section was graded using an adaptation of the Evidence-based Practice Center approach,[52] which is based on a system developed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group.[53] This adaptation explicitly addresses four of the five Evidence-based Practice Center-required domains: consistency (similarity of effect direction and size), precision (degree of certainty around an estimate), reporting bias (potential for bias related to publication, selective outcome reporting, or selective analysis reporting), and study quality (i.e., study limitations, risk of bias). We do not evaluate the fifth domain—directness—as it is implied in the structure of the KQs (i.e., pertains to whether the evidence links the interventions directly to a health outcome).

Consistency was rated as reasonably consistent, inconsistent, or not applicable (e.g., single study). Precision was rated as reasonably precise, imprecise, or not applicable (e.g., no evidence). Reporting bias was rated as suspected, undetected, or not applicable (e.g., when there was insufficient evidence for a particular outcome). Study quality summarizes the quality ratings of the individual trials included for an outcome and indicates the degree to which the results are likely to have adequately low risk of bias. The limitations domain highlighted important restrictions in answering the overall KQ (e.g., lack of replication of interventions, nonreporting of outcomes important to patients or nonreporting of outcomes in some trials).

The overall strength of evidence was graded as "high," "moderate," "low," or "insufficient." "High" indicates high confidence that the evidence reflects the true effect and that further research is very unlikely to change our confidence in the estimate of effects. "Moderate" indicates moderate confidence that the evidence reflects the true effect and that further research may change our confidence in the estimate of effect and may change the estimate. "Low" indicates low confidence that the evidence reflects the true effect and that further research is likely to change our confidence in the estimate of effect and to change the estimate. A grade of "insufficient" indicates that evidence is either unavailable or does not permit estimate of an effect. At least two independent reviewers rated the overall strength of evidence for each intervention type. We resolved discrepancies through consensus discussion involving more reviewers.

Expert Review and Public Comment

A draft of the analytic framework, KQs, and inclusion/exclusion criteria was posted on the USPSTF website for public comment from January 30, 2020 to February 26, 2020. In response to public comment, analyses by race and ethnicity were added as *a priori* analyses for both key questions. In addition, the availability of other subgroup analyses, such as those based on CRC risk, was audited and addressed in the report according to USPSTF methods for analyses in specific populations. A final Research Plan was posted on the USPSTF website on May 14, 2020. The draft version of this report was reviewed by six invited experts and four individuals at USPSTF Federal Partner agencies. Experts were selected based on their expertise with both methodologic and content aspects of the review and were selected to obtain diverse informed perspectives. All expert comments were considered, and the report was updated to improve clarity, ensure accuracy, and address scientifically relevant concerns. The draft report was posted for public comment from October 5, 2021 to November 16, 2021. Based on public comment, text was edited for clarity and several references were added. All comments were shared with members of the USPSTF and the Agency for Healthcare Research and Quality (AHRQ).

USPSTF and AHRQ Involvement

The authors worked with USPSTF liaisons at key points throughout the review process to develop and refine the analytic framework and key questions and to resolve issues around scope for the final evidence synthesis.

AHRQ staff provided oversight for the project, coordinated the systematic review, reviewed the draft report, and assisted in an external review of the draft evidence synthesis.

Chapter 3. Results

Literature Search

We reviewed 12,710 abstracts and assessed 225 full-text articles for inclusion (**Appendix A Figure 1**). For all KQs, we included 23 studies (reported in 79 articles).[45, 54-131] For KQ 1, we included 15 trials (66 articles)[45, 49, 54-97, 99-105, 108-116, 125, 126, 129, 131] representing 165,492 people. For KQ 2, we included 21 studies (72 articles)[45, 54-91, 95-102, 104-109, 112-130]; these comprised 14 RCTs of 162,080 people and seven cohorts of 870,660 people. Three trials[55, 56, 101] and three cohorts[98, 106, 107] were newly identified in this update. In addition, two trials that were previously included published new data since the previous review: longer-term CVD followup from one trial,[57] new subpopulation analyses in one trial,[97] and CRC outcomes in two trials.[103, 108]

A list of included studies and a list of excluded studies with reasons for exclusion are available in **Appendix B** and **Appendix C**, respectively. We determined all included studies were of fair or good quality (**Appendix A, Table 2**).

KQ1. Does Regular Aspirin Use in Patients Without Known CVD Reduce CVD and CRC Incidence and Mortality, or All-Cause Mortality?
KQ1a. Does the Effect Vary in Specific a Priori Populations Defined by Age, Sex, 10-Year Cardiovascular Risk, Diagnosis of Diabetes Mellitus, or Race/Ethnicity?
KQ1b. Does the Effect Vary by Dose or Duration of Aspirin Use?

Summary of Results

There are three new trials[55, 56, 101] published since the previous reviews on this topic.[2-4]
Based on a meta-analysis of 13 primary prevention trials, aspirin at doses of 50 to 500 mg/day is associated with an11 percent reduction in major CVD events (k=13; N=161,680; Peto OR 0.89 [0.85 to 0.94]; I^2=0%) as well as a 14 percent reduction in MIs (k=13; N=161,680; Peto OR, 0.86 [95% CI, 0.80 to 0.92]; I^2=45.7%) and ischemic strokes (k=7; N=106,554; Peto OR, 0.86 [95% CI, 0.77 to 0.97]; I^2=16.0%) (**Table 5, Figure 3**). Aspirin does not appear to have a statistically significant effect on all-cause mortality or CVD mortality. In this group of trials with relatively healthy populations, the absolute major CVD event reductions ranged from 0.08 to 2.5 percent (**Table 6**). All 13 primary prevention trials were powered for composite outcomes, making it difficult to determine if the nonstatistically significant findings with some individual outcomes were attributable to lack of power. Each of the trials recruited participants from specific patient populations using a wide variety of aspirin doses, thereby making pooled estimates potentially less precise for specific clinical application.

Sensitivity analyses limited to low-dose aspirin, defined as ≤100 mg/day, show similar reductions in major CVD events (Peto OR 0.90 [95% CI, 0.85 to 0.95]), MI events (Peto OR 0.89 [0.82 to 0.96]), and ischemic strokes (Peto OR 0.82 [95% CI, 0.72 to 0.92]) compared to the main analyses with all aspirin doses (**Table 5, Figure 4**). All-cause mortality and CVD mortality remained nonstatistically significant in low-dose sensitivity analyses.

Findings for three stroke-related outcomes became statistically significant in low-dose sensitivity analyses. For all stroke types—ischemic and hemorrhagic combined— sensitivity analysis showed that low-dose aspirin was associated with a statistically significant reduction in total stroke (k=11, N=134,470; Peto OR, 0.91 [95% CI, 0.84 to 0.99]; I^2=0%) and nonfatal stroke (k=9, N=103,134; Peto OR, 0.88 [95% CI, 0.80 to 0.97]; I^2=0%). Likewise, nonsignificant findings in the main analysis for nonfatal ischemic stroke became statistically significant when only the low-dose trials were pooled, (k=5, N=54,947; Peto OR, 0.88 [95% CI, 0.78 to 1.00], p<0.05; I^2=0%) however less than half of the low-dose trials reported ischemic stroke.

Sensitivity analyses limited to trials partly or fully conducted since ATP III (2001)—a proxy for more widespread statin use—demonstrate smaller reductions in major CVD events and MI, but larger reductions in ischemic stroke. However, heterogeneity by dose and other population and trial characteristics may impact effects. Further exploration of data by trial completion dates did not reveal any consistent patterns.

Compared to the evidence for CVD outcomes, CRC data are far more sparse and findings for the effect of aspirin on CRC appear to vary based on the followup period considered. Aspirin at any dose does not appear to have a statistically significant effect on CRC incidence at 10 years or less (k=5, N=108,208; Peto OR, 1.08 [0.94 to 1.24]; I^2=16.7%) in pooled analysis of primary CVD prevention trials with events accrued during the randomized trial periods only.

However, two primary CVD prevention trials with extended observational followup both demonstrate that aspirin at any dose is associated with a decrease in CRC incidence at approximately 20 years of followup. A sensitivity analysis including one secondary prevention study showed similar CRC incidence results at long term post-trial observational followup. In the short term (5-10 years), one trial suggests a potential harm where aspirin use was associated with a statistically significant increased risk of CRC mortality; results were not significant in the other trial. At longer followup (approximately 20 years), aspirin use was associated with a statistically significant reduction in CRC mortality (k=3 all dose primary CVD prevention RCTs with observational followup periods, N=50,100; Peto OR, 0.76 [0.62 to 0.94]; I^2=0%). A sensitivity analysis including two secondary CVD prevention studies for all doses of aspirin showed similar CRC mortality results at long term post-trial observational followup. However, CRC mortality conclusions are limited by few CRC deaths. For both CRC incidence and mortality post-trial observation results, the pooled effects are heavily weighted by one large trial but results of other trials are consistent.

In the body of evidence for aspirin for the primary prevention of CVD, there is credible reporting for CVD outcomes for specific populations as defined by age and sex. Reporting is less robust, but still credible, for CVD outcomes by diabetes status and baseline CVD risk strata. Analyses by race and ethnicity are extremely sparse. For all subpopulation analyses examined, all-cause

mortality, CRC, and harms were reported less frequently than CVD outcomes. Findings consistently showed no difference in treatment effect across all specific populations evaluated and CVD outcomes, all-cause mortality, and CRC, with one notable exception. There was an inconsistent signal in analyses by age where the Women's Health Study and Physicians' Health Study reported statistically significant interaction testing with greater benefit in older age groups for MI. This finding was not consistent with findings for CVD composite outcomes in other trials and such suggestion of treatment effect modification was not confirmed in a prior IPD MA.[50]

In cases where time-to-event analyses suggest benefit for individual CVD outcomes, benefit generally accrues within the first 1-2 years. In one trial reporting statistically significant time-to-event analyses for composite CVD outcomes, benefit realized over the 9 years of maximum followup accrues within the first 5 years without further benefit seen beyond 5 years. For the CRC outcomes, followup rather than duration of use appeared to show a trend towards effects appearing after 10 years and continuing through approximately 17 to 20 years.

Detailed Results

Trial Characteristics

Thirteen RCTs (N=161,680)—three good-quality[59, 83, 101] and ten fair-quality[45, 55, 56, 64, 66, 69, 70, 81, 82, 91]—investigated the benefits of aspirin for the primary prevention of cardiovascular morbidity and mortality (**Table 7**). Seven[49, 56, 59, 81-83, 91, 92, 101, 103, 108, 112-114, 131] of these trials also reported CRC incidence (N=115,973) and three[45, 49, 82, 93, 101, 131] reported CRC mortality (N=64,159). As a sensitivity analysis for the CRC outcomes only, we included two additional trials[94, 111] examining the use of aspirin in secondary CVD prevention populations (N=3,812).

These thirteen primary prevention trials were conducted in the United Kingdom,[45, 55, 66, 69, 82] Italy,[64] Japan,[81, 91] the United States,[59, 83] or were multinational,[56, 70, 101] with two of these international trials including sites in the United States.[56, 101] Five trials[45, 59, 64, 70, 82] were conducted prior to the publication of ATP III in 2001,[132] a proxy for lower levels of background statin use, and 8 were conducted after 2001.[55, 56, 66, 69, 81, 83, 91, 101] Recent trials published since the last review for the USPSTF[2] focus on special populations with older age,[101] cardiovascular risk factors,[56] and diabetes.[55] Three of the 13 randomized control trials were open label: British Medical Doctors (BMD),[82] the Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD) trial,[81] and the Primary Prevention Project (PPP).[91] Six of the 13 trials included 2x2 factorial designs with cotreatments of vitamins/antioxidants[55, 59, 64, 66, 83] or warfarin.[45] Three of these 2x2 factorial trials reported no interaction between the cotreatment and aspirin,[45, 66, 83] and the remaining three cotreatment trials did not report interaction testing.[55, 59, 64] One trial, the Hypertension Optimal Treatment (HOT) trial, was a 3x2 factorial design wherein patients were initially randomized to one of three diastolic blood pressure targets, then each of the target blood pressure groups were randomized to aspirin or placebo.[70]

The 13 primary prevention RCTs randomized and analyzed a total of 161,680 participants with individual trial sizes ranging from 1,276[66] to 39,876[83] participants. The largest two trials were substantially larger than any other trials and both funded by the National Institutes of Health; WHS included more than 39,000 participants and its male counterpart, the PHS, included more

than 22,000 participants.[59, 83] Overall, trial duration ranged from 3.6 years[64] to 10.1 years[83] with extended followup after trial completion available for a mean of 10.3 and 26 years, in JPAD and WHS, respectively.[49, 81, 83] Further CRC incidence and/or mortality data were available for extended followup as abstracted and reported by separate IPD MA authors[92, 93] for three additional primary CVD prevention trials.[45, 59, 82] Three trials were terminated early: PHS (due to apparent aspirin benefit), PPP (because other trial publications supported aspirin benefit), and the Japanese Primary Prevention Project (JPPP), due to futility as sufficient power to find between group differences in primary endpoint would not be reached.[59, 64, 91]

The vast majority of primary CVD prevention trials (11 of 13) administered low-dose aspirin at ≤100 mg/day or every other day.[45, 55, 56, 64, 66, 69, 81, 83, 91, 101] In the two higher dose trials, one trial used 325 mg every other day,[59] and one used 300 or 500 mg daily.[82] The seven most recent trials used low-dose aspirin, so there may be interaction between aspirin dose, trial recency, and contemporary CVD risk management.[55, 56, 66, 69, 81, 91, 101] Five trials used enteric coated formulations;[56, 64, 69, 91, 101] the remainder administered non-enteric-coated, effervescent or unspecified formulations.[45, 55, 59, 66, 70, 81-83] Control groups received placebo in most studies except the three open label trials,[81, 82, 91] where control groups received nothing and/or were advised to avoid aspirin. Six trials were solely government sponsored,[59, 66, 81, 83, 91, 101] six trials were at least partially funded by pharmaceutical industry sponsorship;[55, 56, 64, 69, 70, 82] and one trial was funded by both government and a professional organization.[45]

Primary outcomes for all but one trial were study-defined composites of fatal and nonfatal CVD events or CVD mortality with highly variable definitions (**Appendix D, Table 1**). Aspirin in Reducing Events in the Elderly (ASPREE) was the only trial with a nonCVD focused primary composite endpoint of death, dementia, or persistent physical disability.[101] All trials were powered for these variably defined composites and in two trials, the composite definitions were altered after study design in order to increase power.[55, 56] Only four trials performed adjustments for confounders for their primary CVD outcomes,[59, 69, 83, 91] and only one trial performed adjustments for CRC outcomes.[81] Individual CVD-related events and bleeding harms were reported as secondary outcomes. Cancer (of any type) was identified as a pre-specified outcome for only four trials,[56, 59, 83, 91] although none of these trials were powered to detect a difference in colorectal cancer incidence or mortality between groups. With the exception of WHS—where participants self-reported colonoscopy or sigmoidoscopy screening—CRC screening rates were not reported in any of the trials. For WHS, endoscopy screening rates over the course of the followup were generally similar between aspirin and placebo groups; at the end of the trial (10.3 years), 51.4 percent of females in the aspirin group and 52.4 percent of females in the control group self-reported a screening endoscopy during the trial.

CVD-related events were ascertained using a combination of death certificates, national registries, hospital and outpatient records, autopsies (when available), and physician and patient questionnaires. Independent blinded endpoint committees confirmed events in all trials. Colorectal cancer incidence was confirmed by blinded committees with access to patient records, medial record review by a blinded assessor, or a combination of death and national cancer registries. One trial[56] did not report how CRC incidence was ascertained. All but two trials (ASPREE, WHS) reporting CRC mortality determined this outcome through national registries. In ASPREE, blinded assessors determined if the cause of death was colorectal cancer through a

review of medical records and death certificates.[101] WHS confirmed cancer deaths with medical record, death certificate, and/or National Death Index reports.[112]

Four trials had run-in periods ranging from 4 to 18 weeks.[55, 59, 83, 101] Two of these trials with run-in periods reported that 11 percent[101] and 36 percent[55] used aspirin prior to the run-in periods. Adherence with aspirin therapy in the intervention group was variably reported and wide-ranging, from 50 to 90 percent by trials' end (**Appendix D, Table 2**). Adherence was generally ascertained from participant questionnaires; pill counts were only performed in two trials.[45, 101] Most trials reported excellent followup of over 90 percent.[55, 59, 64, 66, 69, 70, 81, 83, 91, 101] High withdrawal rates were reported in two trials (Thrombosis Prevention Trial [TPT], Aspirin to Reduce Risk of Initial Vascular Events [ARRIVE]); ARRIVE reported 29 percent withdrawals in each group over 5 years and TPT reported 42 percent withdrawal rate at 5 years.[45, 56] All trials reported ITT analyses.

For the colorectal cancer outcomes, results were reported at various followup time periods (**Figure 5**). Four primary CVD prevention trials[56, 59, 83, 91, 108, 112, 114] report CRC incidence during the RCT stage of the study, with median followup ranging from 5 to 10 years. Two studies conducted an observational followup of the RCT (where intervention allocation was no longer maintained) and extended their average followup to 10.7[103] and 26[49, 112] years. Retention rates in the observational periods from those two trials were initially high, with 99.9 percent at 10 years for JPAD and 88.6 percent at 17.5 years for WHS. However, by 26 years of followup WHS retained 67 percent of the original randomized participants. Two studies[82 111]—one of which was a secondary CVD prevention study—had observational followup at 9 and 20 years that were completed by authors conducting an IPD meta-analysis.[92] CRC mortality was reported at the end of the two trials' randomized stages at approximately 5 and 10 years of followup[49, 101]; one trial additionally reported CRC mortality at extended observational followups at 17.5 and 26 years;[49] otherwise, for four studies[45, 82, 94, 111] (including two secondary CVD prevention populations) CRC mortality was measured through a median observational followup of 18 years by authors conducting an IPD meta-analysis.[93]

Participant Characteristics

The thirteen trials include a broad range of participants for whom primary prevention interventions are applicable, including higher risk populations. Nine trials included participants who would be considered at higher than average cardiovascular risk: patients with diabetes[55, 81]; patients with diabetes and ankle brachial index (ABI) ≤ 0.99[66]; patients with hypertension[70]; individuals with abnormal ABI ≤ 0.95[69]; individuals with at least one CVD risk factor[56, 64, 91]; or those at high risk for ischemic disease based on the Northwick Park Heart Study algorithm.[45] Estimated 10-year CVD or CHD risk based on well-known risk estimation scores such as the Pooled Cohort Equations or Framingham were reported in only two trials, and risk varied widely in these trials.[56, 83] The vast majority of participants in WHS had a very low CVD risk: 84 percent had an estimated 10-year CHD risk of <5 percent based on the Framingham CHD risk tool. ARRIVE, which specifically recruited high-risk participants, had mean 10-year CHD risk of 14 percent based on Framingham, and a mean 10-year CVD risk score of 17.4 percent based on the Pooled Cohort Equations. The annualized major CVD event rates in the control groups reflect the wide, greater than 10-fold variation in observed CVD risk and ranged from an

annualized rate of 0.26 percent in WHS to as high 3.09 percent in the Prevention of Progression of Arterial Disease and Diabetes (POPADAD) trial.[66, 83] Cumulative CRC incidence over the followup periods ranged from 0.1 percent at 5 years to 3.7 percent at 20 years.

The 13 primary prevention trials included a balanced number of males and females and reflected a broad distribution of ages. Three of the thirteen trials were conducted in healthy males only or among female-only health care professionals[59, 82, 83]; one additional trial solely recruited men,[45] and the remaining trials included both sexes. Overall, 52 percent of participants in the 13 primary prevention trials were women. Mean age was reported in all but one trial[82] and ranged from 53 years in PHS[59] to 74 years in ASPREE[101] which solely recruited older adults (**Figure 6**).

The largest two trials, PHS and WHS, had relatively young participants, with mean ages of 53 years and 54 years, respectively.[59, 83] Ninety percent of WHS participants were younger than 65 years and 75 percent of PHS participants were younger than 60 years. Five trials[55, 59, 82, 91, 101] reported the proportion of participants who were 70 or older: 7 percent in PHS, 14 percent in BMD (70-79 years), 24 percent in ASCEND, 55 percent in JPPP, and 97 percent in ASPREE. All studies excluded those taking current or regular aspirin therapy, as well as those with aspirin contraindications or allergies. Eight excluded those taking anticoagulants, antithrombotic, or other antiplatelet agents.[56, 59, 64, 69, 81, 83, 91, 101] Five trials excluded those with long term, current or regular non-steroidal anti-inflammatory drug (NSAID) use.[56, 59, 64, 83, 91] Eight of the trials specifically excluded those with a history of peptic ulcer disease,[45, 56, 59, 66, 69, 81, 82, 91] GI hemorrhage,[56] or severe indigestion.[66] Two secondary prevention trials were included for CRC sensitivity analyses only.[94, 111] Briefly, these trials recruited patients with a recent mild ischemic stroke, transient ischemic attack (TIA), or retinal artery occlusion (**Table 7**).

Participants in the thirteen primary prevention trials were overwhelmingly White when race was reported, and studies displayed an exceedingly wide range of prevalence of single CVD risk factors, such as smoking, BMI, diabetes, and hypertension (**Table 8**). Over 90 percent of participants were White in the four trials reporting race[55, 56, 83, 101]; ASPREE reported the highest rate of Black and Hispanic participants with 5 percent and 3 percent, respectively.[101] Percent of current smokers at baseline ranged from 4[101] to 41[45] percent. Mean BMI at baseline ranged from 24[81] to 31[55] kg/m^2 in nine trials.[45, 55, 56, 64, 66, 70, 81, 83, 91] ASPREE and ASCEND reported that 30 and 46 percent had BMIs >30, respectively.[55, 101] Eight trials reported the percent of participants with hypertension at baseline ranging from 10[82] to 85[91] percent, and one trial was exclusively in participants with hypertension.[70] Dyslipidemia was variably reported with mean total cholesterol levels over 200 mg/dL in six trials[45, 64, 66, 69, 70, 91]; one trial reported a mean of 161 mg/dL.[55] When reported, baseline statin use varied widely, ranging from 4[69] to 75[55] percent. All but one trial[45] reported diabetes comorbidity: one trial excluded participants with diabetes,[56] five trials included <10 percent of participants with diabetes at baseline,[59, 69, 70, 82, 83] three trials reported 11 to 34 percent with diabetes,[64, 91, 101] and three trials were exclusively conducted in those with diabetes.[55, 66, 81] HOT and BMD reported 9 and 12 percent of participants had a previous history of CVD, respectively,[70, 82] while the remaining trials had no participants with CVD[45, 56, 64, 69, 81, 83, 91, 101] or did not report prior CVD history.[55, 59, 66]

Detailed Results by Outcome

Effect of Aspirin on Major CVD Events

Pooled analysis from 13 trials (N=161,680) showed that aspirin use was associated with a decrease in major CVD events, defined as a composite of cardiovascular death, nonfatal MI, and nonfatal stroke of all types (Peto OR, 0.89 [95% CI, 0.85 to 0.94]; I^2=0%) (**Figure 7 and Table 9**). Absolute differences between intervention and control in CVD events ranged from -2.5 to -0.08 percent (**Table 6**). When restricted to low-dose studies for a sensitivity analysis, the association between aspirin and major CVD events was unchanged (k=11, N=134,470; Peto OR, 0.90 [95% CI, 0.85 to 0.95]; I^2=0%).

Effect of Aspirin on MI Events

Total MI events. Pooled analysis from 13 trials (N=161,680) demonstrated that aspirin is associated with a reduction in total MI events (Peto OR, 0.86 [95% CI, 0.80 to 0.92]; I^2=45.7%) (**Figure 8 and Table 10**). Absolute differences ranged from -1.9 to 1.2 percent (**Table 6**). Three trials showed large statistically significant benefit with point estimates ranging from 0.58 to 0.74.[59, 70, 91] Most trials showed point estimates less than 1 that were not statistically significant but 2 trials did have nonstatistically significant point estimates above 1.[66, 69] Sensitivity analyses by dose demonstrated a similar reduction in total MI events in the low-dose aspirin trials (k=11, N=134,470; Peto OR, 0.89 [95% CI, 0.82 to 0.96]; I^2=26.8%).

Fatal MI events. Pooled analysis from 13 trials (N=161,680) demonstrated no statistically significant effect on fatal MI/fatal coronary events (Peto OR, 0.91 [95% CI, 0.80 to 1.03]; I^2=18.0%) (**Figure 9 and Table 10**). Sensitivity analyses by dose showed similar nonsignificant results.

Nonfatal MI events. Results for nonfatal MI events paralleled the total MI event results. Pooled analysis from 13 trials (N=161,680) demonstrated that aspirin was associated with a reduction in nonfatal MI events (Peto OR 0.83 [95% CI, 0.76 to 0.90]; I^2=62.1%) (**Figure 10 and Table 10**). Absolute differences ranged from -2.0 to 0.2 percent (**Table 6**). Sensitivity analyses by dose demonstrated a similar and statistically significant reduction in nonfatal MI events in the low-dose aspirin trials (k=11, N=134,470; Peto OR, 0.88 [95% CI, 0.80 to 0.96]; I^2=44.2%).

Effect of Aspirin on Stroke

Total stroke. Pooled analysis of thirteen trials (N=161,680) showed that aspirin does not have a statistically significant effect on total stroke, including both ischemic and hemorrhagic (Peto OR, 0.94 [95% CI, 0.87 to 1.01]; I^2=0%) **(Figure 11 and Table 11**). The finding for total stroke became statistically significant in sensitivity analyses restricted to low-dose aspirin (k=11, N=134,470; Peto OR, 0.91 [95% CI, 0.84 to 0.99]; I^2=0%). The two higher dose trials of BMD and PHS had point estimates of 1.16 and 1.22, respectively, however confidence intervals crossed 1.[59, 82] In contrast, only 1 of 10 low-dose trials reporting this outcome showed a point estimate greater than 1.[56]

Fatal stroke. Pooled analysis of eleven trials (N=130,344) showed that aspirin does not have a statistically significant effect on fatal strokes, including both ischemic and hemorrhagic (Peto OR, 0.98 [95% CI, 0.78 to 1.22]; I^2=12.4%) (**Figure 12 and Table 11**). Sensitivity analysis likewise showed no statistically significant effect when stratified by dose.

Nonfatal stroke. Pooled analysis of eleven trials (N=130,344) showed that aspirin is associated with a nonstatistically significant effect on nonfatal strokes, including both ischemic and hemorrhagic (Peto OR, 0.92 [95% CI, 0.84 to 1.00], p>0.05; I^2=0%) (**Figure 13 and Table 11**). In contrast, sensitivity analysis restricted to low-dose aspirin trials shows that low-dose aspirin is associated with a statistically significant effect (k=9, n=103,134; Peto OR, 0.88 [95% CI, 0.80 to 0.97]; I^2=0%).

Ischemic stroke. Pooled analysis of seven trials (N=106,554) showed that aspirin is associated with a reduction in ischemic stroke (Peto OR, 0.86 [95% CI, 0.77 to 0.97]; I^2=16.0%) (**Figure 14 and Table 11**). Absolute differences ranged from -0.6 to 0.2 percent (**Table 6**). Sensitivity analysis pooling five low-dose aspirin trials resulted in a similar benefit (k=5, N=79,334; Peto OR, 0.82 [95% CI, 0.72 to 0.92]; I^2=0%).

Fatal ischemic stroke. Pooled analysis of six trials (N=65,414) showed no statistically significant effect on fatal ischemic stroke (Peto OR, 0.80 [95% CI, 0.50 to 1.29]; I^2=13.0%) (**Figure 15 and Table 11**). Events were rare as evidenced by five of six trials reporting fewer than ten events in each group. Due to this low event rate, sensitivity analysis by dose is limited.

Nonfatal ischemic stroke. Pooled analysis of seven trials (N=82,157) showed no statistically significant effect of aspirin on nonfatal ischemic stroke (Peto OR, 0.92 [95% CI, 0.82 to 1.03]; I^2=0%) (**Figure 16 and Table 11**). Results became statistically significant in sensitivity analyses limited to low-dose trials (k=5, N=54947; Peto OR, 0.88 [95% CI, 0.78 to 1.00], p<0.05; I^2=0%). Both higher dose trials showed point estimates above 1, although neither were statistically significant.[59, 82]

Effect of Aspirin on CVD Mortality

Cardiovascular deaths were variably defined across the primary prevention trials. In four trials, CVD mortality was comprised exclusively of fatal MI events and stroke.[66, 69, 81, 101] In other trials, definitions were broader and often included additional events such as deaths due to rheumatic fever, pulmonary embolism, abdominal aortic aneurysm, or hypertensive disease. Pooled analysis from 13 trials (N=161,680) demonstrated no statistically significant effect on CVD mortality (Peto OR, 0.95 [95% CI, 0.87 to 1.04]; I^2=4.3%) (**Figure 17 and Table 9**). Sensitivity analysis by dose yielded similar nonstatistically significant results.

Effect of Aspirin on All-Cause Mortality

Pooled analysis of 13 primary prevention trials (N=161,680) showed that aspirin is not associated with a change in all-cause mortality at 3.6 to 10.1 years (Peto OR, 0.97 [95% CI, 0.93 to 1.02]; I^2=0%) (**Figure 18 and Table 9**). ASPREE was the only individual trial with a statistically significant finding and reported higher all-cause mortality in the aspirin group.[101]

TPT reported a similar trend favoring the control group, but it was not statistically significant.[45] The remaining 11 trials all reported nonstatistically significant trends favoring the aspirin group. Sensitivity analyses by dose likewise yielded nonsignificant results.

Effect of Aspirin on CRC

CRC Incidence. Results for CRC incidence are highly variable by timing and length of followup. For events occurring within randomized periods only (k=5),[56, 59, 83, 91, 108, 112-114, 131] aspirin at all doses had no statistically significant association with CRC incidence at 5 to 10 years of followup (Peto OR, 1.08 [95% CI, 0.94 to 1.24]; I^2=16.7%) (**Figure 19 and Table 12**). None of the individual trials had individual relative comparisons that favored aspirin. A sensitivity analysis restricted to low-dose aspirin trials (k=4) produced similar results (Peto OR, 1.07 [(95% CI, 0.92 to 1.24]; I^2=36.0%).

Four primary CVD prevention studies (N=69,622) reported RCT or observational followup at approximately ten years; the pooled result did not show an association between aspirin use and CRC incidence (Peto OR, 0.98 [95% CI, 0.85 to 1.14]; I^2=0%) (**Figure 20**). Incorporating the secondary CVD prevention trial reporting CRC incidence at approximately ten years, United Kingdom Transient Ischaemic Attack (UK-TIA), did not change the pooled effect (Peto OR, 0.99 [95% CI, 0.86 to 1.14]).

Two primary CVD prevention studies reported observational followup at approximately 20 years; both showed that the group randomized during the trial period to aspirin experienced a lower incidence of CRC (k=2, N=45,015; Peto OR, 0.70 [95% CI, 0.50 to 0.98] and Peto OR, 0.82 [95% CI, 0.69 to 0.98] (**Figure 21**). Only one of these trials—WHS—used low-dose aspirin. The addition of the secondary CVD prevention study reporting CRC incidence at 20 years (UK-TIA) did not change the conclusions (k=3, N=47,464; pooled Peto OR, 0.79 [95% CI, 0.68 to 0.92]). Three primary prevention trials (BMD, PHS, WHS) and one secondary prevention trial (UK-TIA) provided post-trial observational data measured after 10 years and up to 19 years, not including incident CRC cases at earlier periods. This selected analysis showed a statistically significant reduction in CRC incidence in primary CVD prevention populations (Peto OR, 0.66 [95% CI, 0.53 to 0.82]; I^2=0%) (**Figure 22**), suggesting that the impact on CRC incidence does not occur until ten years after aspirin use has been initiated. Again, only one of these trials, WHS, used low-dose aspirin. The addition of the secondary CVD prevention observational study, UK-TIA, yielded similar results (Peto OR, 0.64 [95% CI, 0.52 to 0.79]). Further, WHS reported longer followup for CRC incidence through 26 years.[49] From 17.5 to 26 years, the group initially randomized to aspirin for 10 years of usage no longer experienced any reduction in CRC incidence (Peto OR, 1.16 [95% CI, 0.78 to 1.72]). When the entire followup period from baseline to 26 years was analyzed, aspirin use from 0-10 years continued to be associated with a decrease in CRC incidence, but the association was no longer statistically significant (Peto OR 0.87 [95% CI, 0.74 to 1.02]).

WHS contributed the largest proportion of participants and CRC cases to each of the previously mentioned pooled effects for CRC incidence and is heavily weighted in the statistically significant pooled 20-year effects (WHS N/total N=39,876/47,464 or 84.0%). It is also the only low-dose trial represented in studies reporting long-term observational followup. At 26 years,

WHS retained 67 percent of its participants for outcomes analysis; of these participants, 36 percent of participants were taking aspirin more than 3 days per month without any differences seen by original allocation.[49] While CRC-specific risk factors such as family history are not reported, WHS participants had the lowest observed CVD event rates and 90 percent of the trial population was less than 65 years. As such, WHS may reflect a generally healthy population. WHS is also the only trial that captured CRC screening using endoscopy (although it was self-reported). While participants reporting CRC screening were more likely to opt in to the post-trial followup, weighting by the inverse probability of opting in did not change the overall effects of aspirin on CRC incidence at 17.5 years. However, posttrial outside aspirin use was associated with cancer risk factors, and additional confounding during the posttrial followup cannot be ruled out.

CRC Mortality. Two RCTs reported CRC mortality during the trial phase (ASPREE[101] and WHS[49]). ASPREE reported that aspirin use was associated with statistically significantly higher CRC mortality at 4.7 years followup (Peto OR, 1.74 [95% CI, 1.02 to 2.95]). Although not statistically significant, WHS also reported an increase in CRC mortality for those taking aspirin at ten years (Peto OR, 1.14 [95% CI, 0.73 to 1.78]) (**Figure 23 and Table 12**). Observational followup at approximately 18 years was available for WHS[49] as well as two additional primary CVD prevention trials.[45, 82] These three studies showed that aspirin use for 6-10 years was associated with a lower risk of CRC mortality at long term followup, including both the trial and observational period events (Peto OR, 0.76 [95% CI, 0.62 to 0.94]; I^2=0%) (**Figure 24**). When two secondary CVD prevention trials were added to the analyses, the pooled long-term effect on CRC mortality did not differ (Peto OR, 0.74 [95% CI, 0.61 to 0.90]; I^2=0%). WHS also provided CRC mortality at 26 years; similar to CRC incidence, the effect from baseline to 26 years showed CRC mortality was reduced for the aspirin group, but the effect was attenuated from 17.5 to 26 years. Overall, among studies the number of deaths due to CRC were relatively low, and these studies were likely not powered to assess the effect of aspirin on CRC mortality. Further, these effects were not adjusted for CRC screening or CRC risk factors.

Sensitivity Analyses

Pooling Method

Primary analyses were conducted using the Peto OR fixed effects model because of rare events. Sensitivity analyses using the fixed effects Mantel-Haenszel model and the random effects REML model yielded similar results for all outcomes (**Table 5**).

Pre- and Post- Cholesterol Management Guidelines

We conducted sensitivity analyses to explore the potential influence of contemporary cardiovascular risk management, particularly background statin use, on the effect of aspirin. The publication of ATP III in 2001 was chosen as a proxy for statin use as only six of 13 primary prevention trials reported actual baseline statin use. Sensitivity analyses restricted to the eight trials conducted after ATP III[55, 56, 66, 69, 81, 83, 91, 101] showed diminished benefit for major CVD events and MI compared to trials conducted prior to ATP III[45, 59, 64, 70, 82] (**Table 5**). However, pooled estimates for ischemic and total stroke appear greater and became statistically significant

in these most contemporary trials compared to older trials. This finding may be influenced by dose because the highest ORs for these stroke outcomes occurred in PHS and BMD, high-dose trials conducted prior to ATP III. In contrast, statistical significance was lost for total MI events and nonfatal MI when restricted to post-ATP III trials. This loss of statistical significance is likely due to the removal of large older trials which reported moderate to large relative effect sizes for MI event outcomes. For example, three trials showed large statistically significant benefits for nonfatal MI with point estimates ranging from 0.58 to 0.64.[45, 59, 70] Further exploration of results by trial completion dates did not reveal any consistent patterns (analysis not shown).

Small-Study Effects

Funnel plots added little to our exploration of heterogeneity as this body of evidence is populated almost exclusively by large studies (**Appendix E**).

Duration of Aspirin Use

Eleven RCTs report time-to-event analyses for CVD benefits.[45, 55, 56, 64, 66, 69, 70, 81, 83, 91, 101] In cases where time-to-event analyses suggest benefit for individual outcomes, benefit generally accrues within the first 1-2 years. However, time-to-benefit analyses for primary composite CVD outcomes were significant only in ASCEND. When benefits are significant, there is no compelling evidence to suggest a delay in CVD benefit. ASCEND reports that composite CVD benefit realized over the 9 years of maximum followup accrues within the first 5 years without further benefit seen beyond 5 years.[55] Four trials reporting significant differences in time-to-event analyses for individual outcomes suggested that benefits appeared relatively soon after aspirin administration. These outcomes were MI in HOT,[70] CVD death in PPP,[64] ischemic heart disease in TPT,[45] and stroke in WHS.[83] For HOT and PPP, benefit began within the first year and continued throughout the trial, but their followup ended before 5 years.[64, 70] TPT showed nonfatal ischemic heart disease benefit within the first year continuing through 7 years.[45] WHS[83] showed that total stroke and ischemic stroke benefits were not seen until 1-2 years and continued until 7 or 8 years.

To further explore potential effects by duration, we sorted forest plots by duration of use. For CVD and mortality outcomes, no patterns were apparent by duration of aspirin use. However, in most of the trials, aspirin administration continued for only the 4 to 6-year trial duration, so it is difficult to make any conclusions about effect of aspirin on CVD outcomes for longer term use. For CRC incidence and mortality, followup rather than duration of use appeared to show a trend towards effects appearing after 10 years and continuing through 17.5 years.[103, 112 83] Furthermore, the longest followup available from WHS (26 years) indicates the effect on CRC is attenuated in the period between 17.5 and 26 years.

Findings in Specific Populations (KQ1a)

Age

Summary

Despite numerous prespecified analyses by age in this body of literature, few trials found a heterogeneity of treatment effect by age. In the few cases where interaction testing was significant, which occurred only in the largest trials, a greater benefit in older age groups was suggested. However, most subgroup analysis findings were inconsistent and not statistically significant. There are few trials reporting CRC incidence or mortality by age, showing conflicting results.

Trial Characteristics

Populations included in aspirin primary CVD prevention trials include a wide range of ages, and a new trial published since the last review, ASPREE, provides evidence in older populations that was previously lacking (**Figure 6**). Mean age was reported in all but one trial[82] and ranged from 53 years in PHS[59] to 74 years in ASPREE.[101] The largest two trials, PHS and WHS, had relatively young participants with mean ages of 53 years and 54 years, respectively.[59, 83] Ninety percent of WHS participants were younger than 65 years and 75 percent of PHS participants were younger than 60 years. Most trials' lower age limit was 40 to 50 years of age; JPAD had the widest age range for recruitment of 30 to 85 years.[81] ASPREE solely recruited older participants: ≥70 years or ≥65 among Black and Hispanic participants in the U.S.-based centers, so unsurprisingly this trial had the highest mean age at 74 years.[101] The upper age limit was specified in the inclusion criteria for six trials, ranging from 69 to 85 years.[45, 59, 69, 70, 81, 91] Five trials[55, 59, 82, 91, 101] reported the proportion of participants who were 70 or older: 7 percent in PHS, 14 percent in BMD (70-79 years), 24 percent in ASCEND, 55 percent in JPPP, and 97 percent in ASPREE.

Almost all primary CVD prevention trials (11 of 13) reported age-specific results (**Appendix D, Table 3**). Seven trials[55, 56, 69, 81, 83, 91, 101] reported a priori analyses by age for all-cause mortality or CVD outcomes with varying age strata: JPAD (<65 and ≥65 years), Aspirin for Asymptomatic Atherosclerosis (AAA) (<62 and ≥62 years), WHS (45 to 54, 55 to 64, and ≥65 years), JPPP (<70 and ≥70 years), ASCEND (<60, 60-69, ≥70 years), ASPREE (65-73, ≥74 years) and ARRIVE (<65 and ≥65 years). Four trials[45, 59, 66, 70] reported all-cause mortality or CVD outcomes by age, however, the timing of subanalyses are either post-hoc or unreported.

Results

Overall, nine trials reported trial-defined CVD composite outcomes by age and findings were inconsistent (**Appendix D, Table 4)**. Analyses were prespecified in seven trials[55, 56, 69, 81, 83, 91, 101] and interaction testing was performed in seven trials for CVD composites.[55, 56, 66, 81, 83, 91, 101] Only WHS reported statistically significant interaction testing supporting a differential effect of aspirin on composite CVD outcomes whereby benefit was greater in older compared to younger age groups (p for interaction=0.05) and was statistically significant only in those 65 or older

(relative risk [RR] 0.74 [95% CI, 0.59 to 0.92]).[83] JPAD and POPADAD followed this pattern, but without statistical significance.[66, 81] Several trials reported a greater benefit among younger compared to older age groups for composite CVD outcomes, although the interaction tests were not significant and the confidence intervals overlapped.[55, 56, 69, 70, 101] For example, ASPREE's prespecified age analysis for its CVD composite outcome showed a nonsignificant interaction test (65-73 years: hazard ratio [HR] 0.81 [95% CI, 0.65 to 1.01]; ≥74 years: HR 1.03 [95% CI, 0.88 to 1.20]); p for interaction=0.09).[101] Similarly, aspirin was not associated with a benefit for the CVD composite outcome for the overall population in ASPREE, of whom 97 percent were 70 or older (HR 0.95 [95% CI, 0.83 to 1.08]).[101] There was no suggestion of a differential effect of aspirin for all-cause mortality in three trials,[70, 91, 101] but only ASPREE reported prespecified analyses with interaction testing (p for interaction=0.66).

For MI, only the large WHS trial prespecified subanalyses by age (**Appendix D, Table 5**).[83] WHS and one other trial, PHS, reported interaction testing. Both trials reported greater MI benefit in older age groups (interaction testing p=0.03 for WHS and 0.02 for PHS).[59, 83] JPPP reported rare MI events (<1%) with apparently greater benefit in the older age group, however no statistical testing was performed.[91, 97] In HOT, the older and younger age groups had similar point estimates.[70, 79]

For stroke, only two trials[45, 91] reported interaction testing and only one trial[83] had prespecified analyses. There were with no consistent patterns emerging for effect of aspirin on stroke by age (**Appendix D, Table 6**).[45, 70, 83, 91, 101]

Three trials reported CRC outcomes for different age groups, showing mixed results (**Appendix D, Table 7**).[83, 101, 103, 131] ASPREE, which solely recruited older adults (≥70 years or ≥65 years in Hispanic and Black participants), reported no difference in CRC incidence at 4.7 years of followup (HR 1.02 [95% CI, 0.81 to 1.30]) but an increase in CRC mortality in the aspirin group compared to the control group, also at 4.7 years of followup (HR 1.77 [95% CI, 1.02 to 3.06]).[101, 131] Two trials, WHS and JPAD, reported CRC incidence by age strata for their extended observational period.[83, 103] In both studies it was unclear whether analyses by age were prespecified and only WHS conducted interaction testing. In both WHS and JPAD, aspirin use was associated with a statistically significant reduction in CRC incidence in the youngest age strata only (WHS: HR 0.71 [95% CI, 0.52 to 0.98] at 17.5 years in women 45-54 years; JPAD: 0.41 [95% CI, 0.15 to 0.97] at 10.7 years for adults <65 years). However, interaction testing in WHS was not statistically significant (p=0.28) and in both studies, confidence intervals overlapped among age strata. [81, 103]

Sex

Summary

Robust and credible trial-level data are available to evaluate whether there is a differential effect of aspirin by sex. These data offer no compelling evidence to support a differential treatment effect of aspirin on CVD composites, all-cause mortality, MI, stroke, or CRC outcomes. For within-study comparisons, interaction testing was not significant for any reported outcome when

conducted. In cases when interaction testing was not conducted, confidence intervals overlapped for estimates in males and females.

Trial Characteristics

All thirteen primary prevention trials provide within-study comparisons of CVD or mortality outcomes by sex or were conducted in a single sex (**Appendix D, Table 3**). Four trials included participants of only a single sex. The largest trial, WHS, recruited more than 39,000 female health professionals.[83] Three trials solely recruited men: PHS[59] and BMD[82] recruited healthy male health professionals and TPT recruited high CVD-risk men.[45] The remaining nine trials included both sexes, with females comprising 30 to 72 percent of participants. Six trials performed prespecified subanalyses by sex[55, 56, 69, 81, 91, 101] and three reported sex-specific analyses where it was unclear whether analyses were a priori or post hoc.[64, 66, 68, 70, 79] Interaction testing was performed in five trials.[55, 56, 66, 81, 101]

Results

Nine trials of both sexes and four single-sex trials report CVD composite outcomes by sex, providing no compelling evidence for a differential treatment effect by sex (**Appendix D, Table 8**). For within-study comparisons for composite CVD outcomes, interaction testing for heterogeneity of treatment effect was nonsignificant when conducted.[55, 56, 66, 81, 101] In cases when interaction testing was not conducted, confidence intervals overlapped for estimates in males and females.[64, 68-70, 79, 91] The only trial reporting statistically significant results for any sex-specific analysis of the primary CVD composite was ASCEND in males only (RR 0.86 [95% CI, 0.77 to 0.96]), however confidence intervals overlapped with analyses in females (RR 0.92 [95% CI, 0.78 to 1.09]) and again, interaction testing was not significant (p=0.49).[55]

Of the nine trials including both sexes, three reported all-cause mortality by sex.[54, 64, 68, 70, 79, 101] There was no evidence for a differential effect in these trials, either based on interaction testing[54, 101] or comparison of confidence intervals.[64, 68, 70, 79] For the four trials solely recruiting a single sex, no pattern emerges for aspirin's effect on CVD composite outcomes by sex. Point estimates for aspirin's relative effect ranged from 0.76 to 0.99 in the all-male trials and was 0.91 in the all-female trial; all confidence intervals overlapped. For all-cause mortality, point estimates for aspirin's relative effect ranged from 0.88 to 1.03 in the all-male trials and was 0.95 in WHS; again, all confidence intervals overlapped.

A smaller number of trials report MI outcomes by sex, but these data similarly offer no compelling evidence for modification of aspirin's effect by sex (**Appendix D, Table 9**). Two trials recruiting both sexes[64, 68, 70, 79] and the four single sex trials[45, 59, 82, 83] reported MI outcomes by sex. Neither of the trials with participants of both sexes performed prespecified analysis and neither reported formal interaction testing.[64, 68, 70, 79] Both HOT and PPP reported point estimates for MIs reflecting a greater benefit seen in males with HOT reporting a statistically significant reduction in MI only in men, however, confidence intervals overlapped with the results for women. For the trials recruiting a single sex, point estimates for aspirin's relative effect ranged from 0.56 to 0.96 in the three all-male trials and were statistically significant in two of three trials.[59, 82] In WHS, the point estimate was 1.02 and not statistically significant.[83] Given the low

MI event rates and overlapping confidence intervals, no conclusions can be made about aspirin's treatment effects on MI by sex.

Two trials including both sexes[64, 68, 70, 79] and the four single sex-trials[45, 59, 82, 83] reported total stroke and ischemic stroke outcomes by sex, and this evidence does not support a differential effect of aspirin on stroke by sex (**Appendix D, Table 10**). Neither of the trials with the participants of both sexes performed prespecified analysis or interaction testing.[64, 68, 70, 79] HOT and PPP reported point estimates for total stroke and ischemic stroke, respectively, reflecting a greater benefit in women, however, confidence intervals overlapped, event rates were very low (<1%), and results were not statistically significant for either males or females in these individual trials. For the four trials recruiting a single sex, point estimates for ischemic stroke varied widely. In the three all-male trials, relative effects for aspirin ranged from 0.56 to 1.45, and none were statistically significant.[45, 59, 82] In the one all-female trial, WHS, aspirin was associated with a statistically significant benefit (adjusted RR 0.76 [95% CI, 0.63 to 0.93]).[83] Similar patterns were seen for the total stroke outcome.

Evidence for CRC-related outcomes by sex is limited to the four single-sex trials, providing no compelling evidence for a differential treatment benefit of aspirin by sex (**Appendix D, Table 11**).[45, 59, 82, 83] For the randomized trial periods, none of the trials reported statistically significant results for CRC incidence and the point estimates were largely overlapping, with estimates of Peto OR 0.96 (95% CI, 0.76 to 1.21) in WHS (10.3 years randomized followup), and Peto OR 1.15 (95% CI, 0.80 to 1.65) in PHS (5 years randomized followup). With trial plus observational followup periods included in the analyses, both the all-female WHS (17.5 year followup) and all-male BMD (at 20 year followup) yielded statistically significant results with reasonably consistent point estimates for CRC incidence of 0.80 and 0.70, respectively. The CRC incidence effect in WHS was attenuated by the 26-year observational followup (Peto OR 0.87 [95% CI, 0.74 to 1.02]). The all-male PHS showed nonsignificant association of aspirin with CRC incidence at 12 years (IRR 1.03 [95% CI, 0.83 to 1.28]). CRC mortality at 17-18 years in WHS, BMD and TPT was reported with ORs of 0.86[49], 0.72[82] and 0.62[45] but only TPT showed a statistically significant benefit for their trial plus post-trial observational followup at 18.3 years (Peto OR 0.62 [95% CI, 0.41 to 0.94]). At 26 years of observational followup, WHS reported a nonstatistically significant effect on CRC mortality (Peto OR 0.96 [95% CI, 0.74 to 1.24])

Race and Ethnicity

Summary

Evidence for the effect of aspirin by race and ethnicity is very sparse, and these limited data suggest no differential effect. Only one trial, ASPREE, reported outcomes by race and ethnicity; these were prespecified analyses with interaction testing. For both composite CVD outcomes and all-cause mortality, confidence intervals were wide and overlapping for White, Black, and Hispanic participants, and individuals of other races with nonstatistically significant interaction testing. There are no trials reporting CRC outcomes by race. There are insufficient data to make conclusions about any differential effects of aspirin for CVD-related mortality or CRC outcomes based on race or ethnicity.

Trial Characteristics

Only four trials report participant race or ethnicity.[55, 56, 83, 101] In these trials, participants were almost exclusively White, with proportions ranging from 91 to 98 percent.

Results

ASPREE's prespecified analyses reported results by race and ethnicity, showing nonsignificant heterogeneity testing for both the CVD composite outcome (p for interaction=0.86) and all-cause mortality (p for interaction=0.19) (**Appendix D, Table 12)**.[54, 101]

Diabetes

Summary

There is no compelling evidence to suggest that aspirin has a differential effect on CVD outcomes based on diabetes status. Subgroup analyses were of limited credibility in that they were not prespecified in most trials, and few performed interaction testing. Moreover, results were conflicting in the rare presence of interaction testing. Confidence intervals consistently overlapped in estimates of aspirin's effect on outcomes in participants with and without diabetes, with estimates most commonly being nonsignificant in subgroup analyses. There is scant information from only a single trial in participants with diabetes showing that aspirin has no significant effect on CRC incidence in this population.

Trial Characteristics

All but one trial[45] reported diabetes comorbidity (**Table 8**). One trial excluded participants with diabetes,[56] five trials included <10 percent of participants with diabetes at baseline;[59, 69, 70, 82, 83] three trials reported 11 to 34 percent with diabetes comorbidity;[64, 91, 101] and three trials were exclusively conducted in those with diabetes.[55, 66, 81] One of these trials, ASCEND, is newly published since the last review.[55]

Trials providing analyses by diabetes status included the three trials solely recruiting participants with diabetes[55, 66, 81] and an additional 6 trials that performed subgroup analyses on patients with and without diabetes.[59, 64, 70, 83, 91, 101]

Results

Eight trials[55, 64, 66, 70, 80, 81, 83, 91, 101, 126] reported results for composite CVD outcomes or all-cause mortality for participants with diabetes (**Appendix D, Table 13**). Three of these trials solely recruited patients with diabetes,[55, 66, 81] three trials[83, 91, 101] reported diabetes as an a priori subanalysis and two trials had post-hoc or unclear timing of their analyses.[64, 70, 80, 126] Only two trials performed interaction testing,[64, 101] showing mixed results. One of these trials[64, 126] with post-hoc analysis reported a differential effect of aspirin on CVD mortality, where participants without diabetes had a statistically significant reduction (RR 0.32 [95% CI, 0.14 to 0.72]) and

results were not significant in participants with diabetes (RR 1.23 [95% CI, 0.49 to 3.10]; p for interaction=0.03).

In the other trial with interaction testing where analyses were prespecified,[101] there was no signal of effect modification by diabetes status for the primary CVD composite outcome (p for interaction=0.74). Of the three trials conducted solely in individuals with diabetes, only one[55] reported a statistically significant effect for their primary composite that included TIA (RR 0.88 [95% CI, 0.79 to 0.97]) however, when TIA was excluded, the results were no longer statistically significant. The remaining two trials in individuals with diabetes reported nonstatistically significant results for their study-defined primary CVD composites (POPADAD: HR 0.98 [95% CI, 0.76 to 1.26]; JPAD: HR 0.80 [95% CI, 0.58 to 1.10]).[66, 81] In all five trials reporting within-study comparisons of CVD composite outcomes by diabetes status, confidence intervals for aspirin effects in those with and without diabetes overlapped.[64, 70, 80, 83, 91, 101, 126] The three trials conducted solely in individuals with diabetes showed no statistically significant effect of aspirin on all-cause mortality.[55, 66, 81] Three trials reporting within-trial comparisons for all-cause mortality[54, 64, 70, 80, 101, 126] by diabetes status similarly showed no significant effect of aspirin for individuals with or without diabetes; confidence intervals overlapped for all within-study comparisons and interaction testing was nonsignificant in the one trial reporting this testing.[54, 101]

Seven trials[55, 59, 64, 66, 70, 81, 83] reported results for MI events for participants with diabetes (**Appendix D, Table 14**). Only one trial prespecified their subgroup analysis[83] and two trials reported interaction testing,[59, 83] with both finding no differential effect of aspirin on MI outcomes based on diabetes status (PHS: p for interaction=0.22; WHS: NS [value not reported]). Other trials reporting within-study comparisons of those with and without diabetes showed overlapping confidence intervals for the effect of aspirin.[64, 70, 80, 126] All trials solely recruiting individuals with diabetes reported nonsignificant effects of aspirin on MI with point estimates ranging from Peto ORs of 0.87 to 1.11.[55, 66, 81]

Six trials[55, 64, 66, 70, 80, 81, 83, 126] reported results for total stroke for participants based on diabetes status (**Appendix D, Table 15**). Only one trial[83] was a prespecified analysis and performed interaction testing; this trial reported nonsignificant interaction of effect by diabetes status (p for interaction =NS, value not reported). In WHS, there was a statistically significant reduction in stroke for participants with diabetes (RR 0.46 [95% CI, 0.25 to 0.85]) that was not significant for participants without diabetes (RR 0.87 [95% CI, 0.72 to 1.05]) but confidence intervals overlapped.[83]

JPAD, conducted exclusively in individuals with diabetes, reported CRC outcomes (**Appendix D, Table 16**).[81] This trial showed no significant effect of aspirin on CRC incidence at 5 years followup (HR 0.92 [95% CI, 0.55 to 1.55]).

Estimated CVD Risk

Summary

There is no compelling evidence to suggest that the relative effect of aspirin on CVD outcomes is modified by baseline CVD risk. Six trials provided evidence by estimated CVD risk strata; four

were prespecified analyses and five performed interaction testing. Each trial used a different CVD risk calculator and different risk thresholds. Interaction testing was nonsignificant for all outcomes, and confidence intervals by risk strata were consistently overlapping. These analyses have limited applicability in the context of current clinical practice in that no trials reported results for CVD risk strata defined by the Pooled Cohort Equations and one used a published Framingham CHD-only calculator; others were study-derived scores not available or validated for use in clinical practice.

Trial Characteristics

Populations included in aspirin primary prevention trials include a wide range of baseline CVD risk with several trials recruiting participants with one or more individual CVD risk factors or moderate-to-high 10-year CVD risk scores. Six trials[55, 56, 70, 77, 81, 83, 91, 95] reported results in populations defined by 5- to-10-year CVD risk strata (**Appendix D, Table 3).** These trials used a variety of risk calculators to define CVD risk. Most of the risk calculators were study-specific and not used in clinical practice; only one study[83] reported results by Framingham 10-year CHD-only risk score, and no studies reported risk strata using the Pooled Cohort Equations (**Appendix D, Table 17**). These analyses by CVD risk strata were prespecified in four trials, including WHS, which used Framingham.[55, 56, 83, 91] The timing of analyses in HOT and JPAD were unclear.[70, 77, 81, 95]

Results

Overall, six trials reported their primary composite CVD outcomes by CVD risk score strata (**Appendix D, Table 17**).[55, 56, 70, 77, 81, 83, 91, 95] The four prespecified[55, 56, 83, 91] and two unspecified[70, 77, 81, 95] subanalyses all reported overlapping confidence intervals for composite CVD outcomes. Interaction testing was not significant in all five trials conducting such analyses,[55, 56, 70, 77, 81, 83, 95] suggesting that aspirin has no differential treatment effect on composite CVD outcomes based on CVD risk score strata. The individual CVD outcomes of MI and stroke showed similar findings (**Appendix D, Tables 18 and 19**). One prespecified analysis[83] and one unspecified analysis[77] reported overlapping confidence intervals for MI based on CVD risk and nonsignificant interaction testing. Outcomes for stroke by risk strata are limited to WHS' prespecified analyses of total stroke and ischemic stroke, both showing overlapping confidence intervals and nonsignificant interaction testing.

Other Specific Populations

We audited the included trials for data addressing other specific populations and concluded that there was insufficient evidence for synthesis as only 1-2 trials reported CVD or CRC outcomes for any other specific populations.

KQ2. Does Regular Aspirin Use Increase Major Gastrointestinal Bleeding, Intracranial Bleeding, or Other Serious Harms?
KQ2a. Does the Effect Vary in Specific a Priori Populations Defined by Age, Sex, 10-Year Cardiovascular Risk, Diagnosis of Diabetes Mellitus, Race/Ethnicity, or Bleeding Risk Factors?
KQ2b. Does the Effect Vary by Dose or Duration of Aspirin Use?

Summary of Results

There are three new trials[55, 56, 101] and three new cohorts[98, 106, 107] published since the previous reviews on this topic.[2-4]

Aspirin at doses of 50 to 500 mg/day is associated with a 57 percent increase in major GI bleeding (k=12, N=146,340; Peto OR, 1.57 [95% CI, 1.37 to 1.78]; I^2=37.2%) (**Table 5**). Low-dose aspirin of 100 mg/day or less is associated with a similar increase in major GI bleeding (k=10, N=119,130; Peto OR, 1.58 [95% CI, 1.38 to 1.80]; I^2=25.5%). Aspirin at doses of 50 to 500 mg daily is also associated with a 22 percent increase in hemorrhagic stroke (k=12, N=160,404; Peto OR, 1.23 [95% CI, 1.01 to 1.48]; I^2=0), however sensitivity analyses restricted to low-dose trials did not yield a statistically significant association between low-dose aspirin and hemorrhagic stroke (k=10, N=133,194; Peto OR, 1.18 [95% CI, 0.97 to 1.45]; I^2=0.0%). Hemorrhagic strokes were rare events so there is uncertainty in estimates. Pooled estimates for intracranial hemorrhage—a broader outcome including subarachnoid hemorrhage and subdural hemorrhage in addition to hemorrhagic stroke—yielded a statistically significant 33 percent increase in events in the aspirin group for all doses and a similar statistically significant finding for low-dose aspirin ≤100 mg/day (k=11, N= 134,470; Peto OR 1.31 [95% CI, 1.11 to1.54]; I^2=0%).

Cohorts were included to explore whether harms associated with aspirin were similar in studies with broader populations and larger sample sizes, which may be better able to detect rare events for serious harms (**Table 13**). Similar to trial evidence, there was a wide range of absolute event rates of serious harm and similar relative increases in major gastrointestinal bleeding, intracranial hemorrhage and hemorrhagic stroke associated with aspirin. Exploration of observational studies by dose was limited because many of the studies reported bleeding harms for participants using a range of doses.

We also examined whether the relative effect of aspirin varied in prespecified specific populations or by the duration of use. There is no convincing data to suggest that aspirin has a differential bleeding risk based on age, sex, diabetes, estimated CVD risk, or race and ethnicity. Few trials report bleeding events in specific populations and due to the rare occurrence of total bleeding events in the trials, conclusions are limited by this scant evidence base. Regarding

duration of use, few trials (4 of 14) reported time-to-event analyses, limiting examination of harms by this variable. Examining Kaplan-Meier curves, it appears that the bleeding harms occur immediately or at about 1 year of aspirin use.

Detailed Results for Trials

Fourteen RCTs in CVD primary prevention populations reported one or more bleeding harms of interest: total major bleed (defined as a composite of intracranial hemorrhage, major GI bleeding, or major bleeding from other sites), major GI bleed (defined as a GI bleed that required a transfusion, hospital admission, or resulted in death), extracranial bleed (defined as major bleeding that was not intracranial), hemorrhagic stroke, and intracranial bleeding (defined as hemorrhagic stroke or other major intracranial bleeds).[45, 55, 56, 59, 64, 66, 69, 70, 81-83, 91, 101, 127, 130] These trials include the 13 primary prevention RCTs included for KQ1 and an additional pilot RCT that reported major GI bleeding. These trials used doses ranging from 100 mg every other day to 500 mg daily.

Effect of Aspirin on Total Major Bleed

Twelve trials (N=160,404) reported serious bleeding complications allowing calculation of total major bleeding events.[45, 55, 56, 59, 64, 69, 70, 81-83, 91, 101, 130] There was a statistically significant increase in total major bleeds associated with aspirin use (Peto OR, 1.45 [95% CI, 1.33 to 1.58]; I^2=12.1%) with similar results seen in the low-dose trials (k=10; N=133,194; Peto OR, 1.44 [95% CI, 1.32 to 1.57]; I^2=4.7%) (**Figure 25 and Table 5**). For the analysis using all doses, absolute differences ranged from -0.1 to 1.0 percent (**Table 6**). Although there was variation amongst the trials in what is included in this composite, in order to maximize number of trials pooled, we used any major bleeding events reported in those trials.

Effect of Aspirin on Extracranial Bleed

Twelve trials (N=160,404) reported serious bleeding complications allowing calculation of extracranial bleeding events.[45, 55, 56, 59, 64, 69, 70, 81-83, 91, 101, 130] There was a statistically significant increase in extracranial bleeds associated with aspirin use (Peto OR, 1.53 [95% CI, 1.39 to 1.69]; I^2=66.2%) with similar results seen in the low-dose trials (k=10; N=133,194; Peto OR, 1.53 [95% CI, 1.39 to 1.70]; I^2=67.4%) (**Figure 26 and Table 14**). For the analysis using all doses, absolute differences ranged from -0.1 to 0.9 percent (**Table 6**).

Effect of Aspirin on Major GI Bleed

Pooled analysis from 12 trials (N=146,340) showed that aspirin is associated with an increase in major GI bleeds (Peto OR, 1.57 [95% CI, 1.37 to 1.78]; I^2=37.2%) (**Figure 27 and Table 15**). Eleven of 12 trials report point estimates for GI bleeding associated with aspirin use that were greater than 1,[45, 55, 56, 59, 64, 69, 70, 81, 83, 91, 101] and seven were statistically significant.[55, 56, 64, 70, 81, 83, 101] Sensitivity analyses showed similar results for low-dose aspirin (k=10; N=119,130; Peto OR, 1.58 [95% CI, 1.38 to 1.80]; I^2=25.5%). However, the two high-dose trials had extremely rare events with four total events in BMD[82] and one event in PHS,[59] so estimates in the trials are

unstable. Five trials reported fatal GI bleeding, showing extremely rare outcomes so data were not pooled.[59, 70, 82, 83, 101]

Effect of Aspirin on Peptic Ulcer

Seven trials reported a consistently higher rate of upper GI ulcer events in the aspirin compared to the control groups, although the location and severity of the reported ulcer events varied (**Table 16**).[59, 69, 81-83, 91, 127] PHS and WHS reported statistically significantly higher upper GI ulcers or peptic ulcers in the aspirin compared to the control group while the other trials reported few ulcer events without statistical testing, but trends confirmed the PHS and WHS findings.

Effect of Aspirin on Intracranial Bleed

Pooled data from 13 trials (N=161,680) showed an increase in intracranial bleeds in the aspirin compared to the control group (Peto OR, 1.33 [95% CI, 1.13 to 1.56]; I^2=0%) (**Figure 28 and Table 17**). Sensitivity analysis of 11 low-dose trials (N=134,470) yielded similar results (Peto OR, 1.31 [95% CI, 1.11 to 1.54]; I^2=0%). For the analysis using all doses, absolute differences ranged from -0.2 to 0.4 percent (**Table 6**).

Effect of Aspirin on Total Hemorrhagic Stroke

Pooled analysis of 12 trials (N=160,404) showed that aspirin is associated with an increase in total hemorrhagic stroke (Peto OR, 1.23 [95% CI, 1.01 to 1.48]; I^2=0) (**Figure 29**). Individual trials reported wide confidence intervals all crossing 1.0, reflecting the rarity of hemorrhagic stroke events (0.13% to 0.55% in control groups). Five of the 12 trials showed point estimates less than 1 and seven trials showed estimates greater than 1 with no single trial reporting statistically significant results. Sensitivity analysis pooling 10 low-dose aspirin trials (N=133,194) did not yield statistically significant results (Peto OR, 1.18 [95% CI, 0.97 to 1.45]; I^2=0).

Effect of Aspirin on Fatal Hemorrhagic Stroke

Pooled analysis of nine trials (N=102,223) did not demonstrate a statistically significant association between aspirin and fatal hemorrhagic stroke (Peto OR, 1.06 [95% CI, 0.73 to 1.54]; I^2=0) (**Figure 30**). Likewise, sensitivity analyses using only low-dose aspirin trials did not yield statistically significant results. Event rates were exceedingly rare (0.02% to 0.47% in control groups) making estimates unstable.

Effect of Aspirin on Nonfatal Hemorrhagic Stroke

Pooled analysis of eight trials (N=100,947) showed that aspirin is associated with an increase in nonfatal hemorrhagic stroke (Peto OR, 1.38 [95% CI, 1.04 to 1.82]; I^2=0) (**Figure 31**). Sensitivity analysis remained statistically significant when restricting to six low-dose aspirin trials (N=73,737; Peto OR, 1.37 [95% CI, 1.01 to 1.85]; I^2=0.1%).

Sensitivity Analyses

Pre- and Post- Cholesterol Management Guidelines

The sensitivity analyses for trials conducted after ATP III in 2001, a proxy for more widespread statin use, suggested diminished harm for total major bleeding, extracranial bleeding, and major GI bleeding associated with aspirin compared to trials conducted prior to 2001 (**Table 5**). For example, aspirin was associated with a 48 percent relative increase in major GI bleeding in newer trials (k=6, N=92,905, Peto OR 1.48 [95% CI, 1.28 to 1.71]) but a 109 percent relative increase in older trials (k=6, N=53,435, Peto OR 2.09 [95% CI, 1.52 to 2.88]). In contrast, pooled estimates for intracranial bleeding were similar in both pre- and post-ATP III periods, but statistically significant only in later trials (pre-ATP III: k=5, N=53,035, Peto OR 1.32 [95% CI, 0.88 to 1.98]; post-ATP III: k=8, N=108,645, Peto OR 1.33 [95% CI, 1.12 to 1.58]). However, rare events and heterogeneity by dose limit conclusions of sensitivity analyses.

Pooling Method

Primary analyses were conducted using the Peto OR fixed effects model because of rare events. Sensitivity analyses using the fixed effects Mantel-Haenszel model and the random effects REML model yielded similar results for all outcomes.

Detailed Results for Observational Studies

Study Characteristics

We identified six observational cohorts (seven publications) reporting the rates of major bleeding in aspirin users (**Table 13**).[98, 106, 107, 117, 118, 120, 128] Populations in these observational studies varied widely. We attempted to identify studies evaluating primary prevention populations with primary CVD prevention as the indication for aspirin use. No study perfectly met these criteria, or studies were unclear on whether these aims were met. Thus, a slightly broader set of studies, where the vast majority of participants (>80%) had no CVD event history, were included as a complement to trial data.

Two of six cohorts were U.S.-based and both included health professionals, females in the Nurses' Health Study (NHS)[121] and males in the Health Professional Followup Study (HPFS).[120] Three studies were population-based cohorts: the Puglia, Italy cohort by De Berardis,[117] the Korean National Health Insurance database,[107] and the Taiwanese National Health Insurance Research Database.[98, 106] One study was from the Swedish National Diabetes Register.[118] Study size ranged from 13,455 in the Korean cohort[107] to 372,850 in the Italian cohort.[117] Half of the studies specifically aimed to identify new aspirin users.[106, 107, 117]

The studies reported a large range of aspirin doses: 75 mg daily,[118] 325 mg daily,[121] 75 to 325 mg daily,[106] 81 to 325 mg daily,[120] or ≤300 mg daily[117]; two studies reported nonspecific information about dosage and frequency ("low-dose"[107] or "average dose more than 14 defined daily doses per month."[106 117] Mean duration of aspirin use and followup ranged from 1 year[106] to 24

years.[121] Three studies were most likely to capture primary prevention populations as they excluded participants with previous CVD or a had very low proportion of participants with previous hospitalization for CVD: the Korean health insurance database,[107] the Swedish diabetes registry,[118] and the Italian population based cohort by De Berardis.[117]

The indications for aspirin use were sparsely reported and likely varied. The two U.S.-based observational studies examined indications for aspirin use in small subsets of the cohorts, reporting that 8 percent in NHS[121] and 58 percent in HPFS[120] used aspirin for CVD prevention. The Taiwanese database did not report the indication for aspirin use.[98, 106] In one analysis of this cohort, 0.11 percent had coronary artery disease and 0.02 percent had a history of ischemic stroke.[106] In the other analysis from this database, the proportion was much higher at 11 and 5 percent, respectively.[98] In the Italian and Korean cohorts, a primary prevention indication is assumed based on prescriptions that are available through national health insurance for CVD prevention[107, 117] or through explicit study aims.[118]

The participants recruited were as young as 20[98, 106] or 30 years[117, 118, 121] to as old as 90 years.[107] Mean age ranged from 41[106] to 71 years.[107] In the studies examining both sexes, approximately half of participants were female. Two studies specifically recruited participants with CVD risk factors: the Korean study[107] recruited individuals newly diagnosed with hypertension, diabetes, or dyslipidemia and the Swedish registry exclusively included those with diabetes.[118] In various analyses of the Taiwan health insurance database, participants with diabetes ranged from as low as 0.3 to 24 percent.[98, 106] Five percent of participants in NHS and HPFS had diabetes and these cohorts also included a large representation of participants with CVD risk factors—approximately 30 percent with hypertension and approximately 40 percent with hypercholesteremia in each cohort.[120, 121] The percent who were current smokers ranged from 5[120] to 18 percent[121] among reporting trials. Race and ethnicity were not reported in any study. Two cohorts were conducted in the United States,[120, 121] two in Europe,[117, 118] and two in Asia.[98, 106, 107]

Results by Outcome

Table 18 shows crude absolute incidence rates and relative risk for bleeding harms in aspirin and nonaspirin users in both cohorts and trials. Absolute rates in trials and cohorts were not pooled because of extremely variable event rates[48] and ranges are shown to explore whether the broader populations and larger sample sizes from cohort studies would show similar patterns to trials for rare harms events. Unlike for trials, relative bleeding rates associated with aspirin use were not pooled for cohorts because of heterogeneity of aspirin indication, exposure ascertainment, and wide range of duration. **Tables 19 and 20** show the bleeding harms in the individual cohort studies for KQ2.

Total Major Bleed

One large Italian population-based cohort (N=372,850) evaluating aspirin ≤300 mg with mean 5.7 year followup reported total major bleed. The absolute rates of total major bleeds in the aspirin group were 558 per 100,000 person-years (p-y) and 360 per 100,000 in the control group. These absolute rates corresponded to the higher end or above the range reported in the trials

which were 68 to 550 per 100,000 p-y in the aspirin group and 57 to 430 per 100,000 p-y in the no-aspirin group. This corresponded to a statistically significant 55 percent relative increase in total major bleeds in the aspirin group in this cohort study (incidence rate ratio [IRR]: 1.55 [95% CI, 1.48 to 1.63]). This relative increase was consistent with the pooled estimate for total major bleeds from trials (Peto OR 1.45 [95% CI, 1.33, 1.58]).

Major GIB

Six cohorts (N=852,014) report major GIB with absolute bleeding risk showing wide ranges in both the nonaspirin and aspirin groups. In the nonaspirin control group, rates ranged from 107/100,000 p-y[121] to 340/100,000 p-y[107] (**Table 19**). In the aspirin group, the absolute rate of major GIB ranged from 193/100,000 p-y[121] to 380/100,000 p-y.[117] In the trials, the absolute bleeding risk was generally similar to the cohorts, with smaller lower ranges, but wide ranges that overlapped those from the cohorts. In the trials, major GIB ranged from 0 to 230/100,000 in the nonaspirin group and 58 to 500/100,000 p-y in the aspirin group. The relative effect of aspirin on major GI bleeding ranged from an adjusted HR of 0.97 (95% CI, 0.77 to 1.16) for "low-dose" aspirin[107] to an adjusted RR of 1.67 (95% CI, 1.20 to 2.33) for aspirin in a dose of 325 mg daily compared to no aspirin[120]. Aside from the lowest estimate from the Korean database which was not statistically significant, showing a reduction in bleeding in the aspirin group, results from the other cohorts were all statistically significant, ranging from 1.43[121] to 1.67.[120] These were all within the confidence interval in the pooled analysis of major GI bleeding in trials (Peto OR 1.57 [95% CI, 1.37 to 1.78]).

Analyses by dose were limited because many cohorts reported wide ranges of doses. However, within-study comparisons from HPFS suggest that higher dose is associated with higher rates of major GI bleeding (81 mg/d: adjusted RR 1.17 [95% CI, 0.89 to 1.53]; 325 mg/d: adjusted RR 1.67 [95% CI, 1.20 to 2.33]).[120]
The Swedish National Diabetes Register[118] reported a higher number of ventricular ulcers in those taking aspirin (adjusted HR, 1.64 [95% CI, 1.06 to 2.53]).

Total Hemorrhagic Stroke

Three cohorts (N=119,781) reported hemorrhagic stroke outcomes.[107, 118, 121] The range of absolute hemorrhagic strokes in the nonaspirin control group in the cohorts was exceedingly wide, ranging from 15.8[121] to 470[107] per 100,000 p-y. This compares to a tighter range in the trials' control groups of 20[45] to 125[81] per 100,000 p-y. The range of absolute hemorrhagic stroke rates in the cohort aspirin groups was 13.2[121] to 360[107] per 100,000 p-y while the trials again reported a tighter range—25[64] to 114[101] per 100,000 p-y in the aspirin groups.

The relative effects of aspirin on hemorrhagic stroke in the three cohorts ranged from an adjusted HR of 0.85 (95% CI, 0.53 to 1.10)[107] to an adjusted HR of 1.26 (95% CI, 0.70 to 2.25).[118] Two cohorts reported hemorrhagic stroke point estimates similar to the trial evidence for all doses of aspirin,[118, 121] although unlike the pooled trial evidence, these estimates were not statistically significant (pooled trial estimate: Peto OR 1.23 [95% CI, 1.01 to 1.48]). The third cohort[107] reported fewer hemorrhagic strokes in the aspirin group, however, this also did not reach statistical significance (adjusted HR 0.85 [95% CI, 0.53 to 1.10]). Reflecting the low event rates,

the range of the confidence intervals for the cohorts was wide and overlapped with the pooled trial estimate.

Analyses by dose were limited because many cohorts reported wide ranges of doses. However, within-study comparisons suggest that increased days of aspirin per week are associated with a statistically significant trend for increased hemorrhagic stroke risk (p=0.02) (1-6 doses/week: IRR 0.84 [95% CI, 0.58 to 1.21]; 7-14 doses/week: adjusted RR 1.25 [95% CI, 0.76 to 2.05]; ≥15 doses/week adjusted RR 1.63 [95% CI, 0.93 to 2.86]).[121, 122]

Fatal Hemorrhagic Stroke

The Swedish diabetes registry (N=18,646) was the only cohort reporting fatal hemorrhagic stroke, showing a nonstatistically significant increase in fatal cerebral hemorrhage (adjusted HR 1.60 (95% CI, 0.51 to 6.05).[118]

Intracranial Hemorrhage

One large Italian population-based cohort (N=372,850) evaluating aspirin ≤300 mg with mean 5.7 year followup reported intracranial hemorrhage (**Table 20**).[117] The absolute rates of ICH in the aspirin group were 209.8 per 100,000 p-y and 122.1 per 100,000 in the control group. These absolute rates corresponded to the higher end of the range reported in the trials which were 26 to 250 per 100,000 p-y in the aspirin group and 20 to 170 per 100,000 p-y in the no-aspirin group. This corresponded to a statistically significant 54 percent relative increase in intracranial hemorrhages in the aspirin group in this cohort study (IRR: 1.54 [95% CI, 1.43 to 1.67]). This relative increase was consistent with the pooled estimate for intracranial hemorrhage from trials (Peto OR 1.33 [95% CI 1.13 to 1.56]).

Duration

Only 4 of 14 trials report time-to-event analyses for any bleeding harms.[56, 83, 91, 101] Using Kaplan-Meier curves, it appears that the bleeding harms occur immediately or at about 1 year. However, results are statistically significant in only two of four trials reporting time-to-event analyses.[56, 101] In these two trials, Kaplan-Meier curves diverge immediately for major hemorrhage,[101] GI bleeding[56, 101] and increased risk for these bleeding events persisted for the 6 year duration of trial followup. While the other two trials[83, 91] showed nonstatistically significant results for hemorrhagic stroke[83] and intracranial hemorrhage,[91] point estimates were above 1. When forest plots were sorted by duration of aspirin use, no patterns were apparent linking bleeding harms to duration of aspirin administration. Again, in most of the trials, aspirin administration continued for 4-6 years so it is difficult to make any conclusions about longer-term effects of aspirin on bleeding outcomes by duration of use.

In the cohorts, no pattern was revealed between duration of use and bleeding. For within-study comparisons, NHS and HPFS examined bleeding rates by duration of use (1-5, 6-10, >10, and >20 years continuous use) and the data did not suggest any difference in bleeding risk by duration of use.[120, 121]

Harms Findings in Specific Populations (KQ2a)

Summary

There is no convincing data to suggest that aspirin has a differential relative bleeding risk based on age, sex, diabetes, CVD risk, or race and ethnicity. Few trials report bleeding events in specific populations, and due to the rare occurrence of total bleeding harm events in the trials, conclusions are limited by this scant evidence base.

Age

There is no convincing data to suggest that aspirin has a differential relative bleeding risk based on age. Four trials[55, 70, 91, 101] report bleeding risk by age (**Appendix D, Table 20**). Analyses were prespecified in two trials[55, 101] and interaction testing was performed in three[55, 91, 101] of the four trials. ASPREE reported an interaction p-value of 0.05 for aspirin's effect on major hemorrhagic events by age, where the younger group had a greater risk of bleeding associated with aspirin use compared to the older group (65-73 years: HR 1.74 [95% CI, 1.31 to 2.31]; ≥74 years: HR 1.23 [95% CI, 1.01 to 1.49]).[101] However, the trial's post-hoc analyses for major hemorrhagic events with narrower age strata (65-69, 70-74, 75-84, ≥85 years) did not confirm this pattern and there were very few events in some age groups (nine total hemorrhagic events in participants 65-73 years), limiting power. ASPREE's prespecified major GI bleeding outcome also showed a trend with greater risk seen in the younger age groups, but interaction testing was nonsignificant (p=0.40) and confidence intervals overlapped for the age strata (65-74 years: HR 1.99 [95% CI, 1.32 to 3.02]; 75-79 years: HR 1.49 [95% CI, 0.95 to 2.34]; ≥80 years: 1.33 [95% CI, 0.85 to 2.08]).[130] Results for the composite of major hemorrhage in ASCEND[55] showed no consistent pattern by age and bleeding events in JPPP and HOT were too rare (<1%) in the age categories for conclusions.[70, 91]

Sex

Sex-specific data on harms are available from eight trials without any evidence to suggest a differential relative bleeding risk based on sex. Four trials were conducted either exclusively in males or females[45, 59, 82, 83] and four trials including both males and females[55, 64, 70, 101, 130] performed subanalyses by sex for bleeding harms (**Appendix D, Table 21**). Only two trials with both sexes prespecified their analysis and these same two trials performed interaction testing.[55, 101] For all major bleeding, ASPREE reported statistically significant increase in major bleeding in females only while ASCEND reported statistically significant results in males only, however, both trials reported nonsignificant interaction testing (ASCEND: p for interaction=0.79; ASPREE: p for interaction=0.1).[55, 101] HOT reported nonfatal major bleeding events by sex[70] with a higher crude risk seen with aspirin in males than females, but events were rare and statistical testing was not performed (men: 1.6 excess cases in the aspirin group per 1,000 p-y; women: 1.4 excess cases in the aspirin group per 1,000 p-y). In the trials recruiting a single sex, PHS reported a statistically significant increase in bleeding requiring transfusion or hospitalization (Adjusted RR: 1.71 [95% CI, 1.09, 2.69]).[59] TPT reported few events, making estimates unreliable.[45]

Within-study comparisons for the effect of aspirin on major GI bleeding in males and females are available in only one trial. ASPREE showed similar and statistically significant point estimates for the effect of aspirin on major GI bleeding for males and females with relative risks of 1.62 and 1.61, respectively, and nonsignificant interaction testing (p for interaction=0.98).[101, 130] For the single sex trials, WHS reported a statistically significant increase in GI bleeding requiring a transfusion (Peto OR 1.37 [95% CI, 1.05 to 1.78)].[83] For the male-only trials, GI bleeding events were exceedingly rare with imprecise estimates (BMD: Peto OR 0.15 [95% CI, 0.02 to 1.22]; TPT: Peto OR 2.73 (95% CI, 0.68 to 10.95]).[45, 59] Of note, the GI bleeding events in BMD were fatal only, and there were 4 total deaths from this cause; TPT reported a total of only eight major GI bleeding events.

Within-study comparisons for the effect of aspirin on hemorrhagic stroke in males and females are available in only one trial. PPP reported this outcome, but events were exceedingly rare with two total events in females and three total events in males, resulting in wide confidence intervals and unreliable point estimates.[64] Similarly, three male-only trials reported hemorrhagic stroke with rare events (<1%); so while point estimates were greater than 1 in all three trials, results were nonstatistically significant with wide confidence intervals. The all-male trial with the largest number of hemorrhagic strokes (45 total), reported an adjusted relative risk of 2.14 (95% CI, 0.96 to 4.77).[59] The only all-female trial, WHS, included 92 total hemorrhagic strokes, and aspirin was similarly associated with a nonstatistically significant increase in this outcome (RR 1.24 [95% CI, 0.82 to 1.87]).[83]

Race and Ethnicity

No trials report bleeding harms by race and ethnicity.

Diabetes

Because of rare harms events, there is limited data from which to evaluate a potential differential relative harm of aspirin in participants with and without diabetes. Prespecified within-trial comparisons from one study suggest no differential harm and only one of three trials conducted exclusively in participants with diabetes, ASCEND, had sufficient power to detect differences in aspirin-associated bleeding outcomes. Four trials[55, 66, 81, 101] reported bleeding risk in individuals with diabetes, with three of these trials solely recruiting participants with diabetes[55, 66, 81] and one trial, ASPREE,[101] performing a prespecified analysis with interaction testing (**Appendix D, Table 22**). ASCEND, recruiting solely participants with diabetes, reported statistically significant increases in major GI bleeding and a composite of major hemorrhage and a nonstatistically significant increase in total intracranial hemorrhage. JPAD and POPADAD, which also exclusively included those with diabetes, had small numbers of bleeding events, making estimates unstable. JPAD had 13 total hemorrhagic strokes and POPADAD had five total fatal hemorrhagic strokes. Within-study comparisons from ASPREE showed an increase in composite major hemorrhagic events and major GI bleeding which was not statistically significant in those with diabetes (HR 1.30 [95% CI, 0.81 to 2.10), N=2,057) but statistically significant in those without diabetes (HR 1.39 [95% CI, 1.17 to 1.64], N=17,057).[101] Point estimates were similar in the separate analyses, suggesting that limited power may have led to

nonstatistically significant results in those with diabetes. Eleven percent of ASPREE participants had diabetes at baseline.[101]

Estimated CVD Risk

No trials reported bleeding outcomes by CVD risk.

Other Specific Populations

We audited the included trials for data addressing other specific populations and concluded that there was insufficient evidence for synthesis as only 1-2 trials reported harms outcomes for any other specific populations.

Chapter 4. Discussion

Summary of Evidence

We conducted this review to support the USPSTF in updating its recommendation on aspirin to prevent CVD and CRC. We have included three new trials and three new cohort studies published since the previous review. Our meta-analyses of 11 low-dose primary CVD prevention trials show that aspirin reduces the risk of major CVD events by 10 percent, total MI by 11 percent and ischemic stroke by 18 percent, with no difference in CVD mortality or all-cause mortality (**Table 21**). CVD benefits were of similar magnitude when 13 primary prevention trials of all doses of aspirin were analyzed (**Table 22**). On the other hand, even with low-dose aspirin, we found a 31 percent increase in intracranial hemorrhage, and 53 percent in extracranial hemorrhage. These findings are remarkably similar to our previous CVD review[2] despite the addition of 47,170 participants from three new trials. Our findings are also consistent with those of several other recent meta-analyses.[133-137]

Thus, the small absolute CVD event reductions associated with aspirin use are closely matched by increases in major bleeding. Additional CRC benefit could potentially change the net benefit of aspirin. However, our systematic review found the evidence for CRC outcomes to be insufficient to very low strength because of limitations in the number of reporting trials, adequacy of followup duration, power, and reliance on observational followup (**Tables 21 and 22**). New CRC data published since the previous review[4] is available from two new trials[56, 101] and additional reporting from two older trials.[49, 103] With approximately 5 years of followup, the two new trials are too short in duration to expect a CRC incidence or mortality benefit to accrue, so the nonstatistically significant findings for CRC incidence in both trials are not surprising. However, in this same approximate 5-year period, ASPREE's findings of a statistically significant increase in CRC mortality—apparently due to a shift in greater late-stage cancers[131]—is concerning. The 10.7-year followup newly available from JPAD does not materially change prior CRC incidence estimates at 10-year followup because of the small and nearly equal number of incident CRC cases in the aspirin and control groups (27 and 31 cases, respectively). Longer-term results from WHS confirm that no CRC benefit is seen until 10 years after initiation, which may be plausible as the progression of an adenoma to CRC can take up to 10 years or longer. The CRC incidence benefit appears to be mitigated over time without continued aspirin use as unpublished results show that during the time period from years 17-26 years, the CRC incidence benefit is no longer seen [49]

Risk-Based Approach

The net benefit of aspirin for primary prevention is directly related to the risk of CVD events balanced by the risk of bleeding events. Baseline risk of both CVD and bleeding determine if the relative benefits and harms from aspirin translate into meaningful absolute differences. Limiting aspirin use to those populations more likely to see a greater relative benefit or lesser relative harms would be desirable. In our analyses of specific populations, there was no compelling evidence to suggest that the relative benefits or harms of aspirin differ in any of our a priori

identified populations defined by age, sex, race and ethnicity, diabetes status, and estimated CVD risk (**Appendix D, Table 23**). However, the strength of evidence for analyses in specific populations is insufficient to low in the absence of an updated IPD meta-analysis, which is the most appropriate source from which to conduct these analyses. Our conclusions are consistent with findings from a previous IPD meta-analysis,[50] which will likely be updated in 2021 and will include the most recent trials.[51] The one specific population previously understudied with newly available information was the older adult population. The new ASPREE trial[54, 101] suggests an overall harm of aspirin in the older population with an increase in all-cause mortality driven by higher cancer-related deaths. In the absence of evidence for differential treatment harms and benefits, aspirin's net benefit then hinges on the target population's baseline risk of CVD and bleeding.

Baseline CVD Risk Models

Given results from recent trials suggesting at most modest benefits from aspirin and harm in the ASPREE trial, many international guideline panels have recommended against routine aspirin use for primary prevention and instead have guidance to limit aspirin use to those with higher CVD risk and low GI bleeding risk (**Table 3**). The previous USPSTF recommendation[1] recommended low-dose aspirin for those 50-59 years with a 10 percent or greater CVD risk without an increased risk of bleeding (B recommendation) and for those 60-69 years with 10 percent or greater risk and no increased risk of bleeding as a shared decision (C recommendation). Because absolute benefit hinges on CVD risk, the selection of a specific CVD risk estimation tool has a substantive influence on for whom aspirin would be recommended. Inaccuracies in risk prediction could lead to over- or under-use of aspirin if a risk calculator systematically over or under predicts absolute CVD risk. The previous USPSTF aspirin recommendation uses the specific estimated 10-year CVD risk threshold of 10 percent from the PCE to guide decision-making.[22]

Concerns have been raised about potential inaccuracies with the PCE. These concerns have centered around model calibration, which is the agreement between observed and predicted outcomes.[138] While selected analyses have shown good calibration of the PCE in some external validation cohorts,[139] others have shown under- and overprediction in the PCE.[140-142] Reports of under- and overprediction are not unique to the PCE and have been observed in other risk tools that have been used in practice.[140, 143] Most commonly, external validation analyses show overprediction of the PCE in broad populations of men and women, in Black and White adults, and in older adults.[140, 141, 143, 144] One potential source of inaccuracy in the PCE is that risk equations are available for White and Black populations, but not for other racial and ethnic groups, who are recommended to use the equations for White participants.[21, 145] An analysis of a large and diverse primary care dataset (N=307,591), showed that overprediction also occurs in Asian, Pacific Islander, and Hispanic populations when the PCE equations for White men and women are used as recommended.[144] However, differences in outcome ascertainment and surveillance between the routine care database used for this validation cohort and prospectively collected outcomes for the derivation cohort limit the conclusions of this analysis. Analyses from the Multi-Ethnic Study of Atherosclerosis (MESA) cohort and Women's Health Initiative (WHI) similarly show overprediction in these racial and ethnic groups.[146, 147] Overestimation was

dramatically reduced when events from additional surveillance were included in sensitivity analyses in one[147] cohort but was not reduced in similar sensitivity analyses in the other cohort.[9] Another source of inaccuracy may be the use of dated cohorts in the development of the PCE.

Limited evidence suggests that there may be important differences in PCE performance by socioeconomic characteristics, where underprediction occurs in economically disadvantaged communities.[142, 148] If confirmed, such a finding would imply systematic under-initiation of aspirin as a preventive measure in disadvantaged communities which also experience higher event rates. However, another analysis of a large primary care dataset reported similar risk overestimation across socioeconomic status subgroups.[144] An external validation of the PCE conducted in a large New Zealand cohort found that socioeconomic deprivation was an independent and statistically significant predictor of CVD when added to the risk prediction equation.[149] Taken together, these findings suggest that the addition of socioeconomic status to CVD risk prediction tools may improve the identification of populations at high risk of adverse outcomes.

Despite the aforementioned shortcomings, the PCE is, to date, the only U.S.-based global CVD calculator that has published its external validations in other U.S.-based populations. Addition of nontraditional risk factors,[24, 150] recalibration, and other model revisions have been suggested to improve model fit, and such updates to the PCE may mitigate over- and underestimation concerns.[150-152] Some have specifically suggested the addition of coronary artery calcium (CAC) scoring to guide aspirin use.[153] However, this approach has not been evaluated in trials.

Bleeding Risk

Prognostic Models

Risk estimation models for major bleeding are far more limited compared to those for CVD. We identified no U.S.-based externally validated risk prediction tools for bleeding risks associated with low-dose aspirin for the primary prevention of CVD. Several well-known bleeding risk models have been developed to inform clinical decision-making, however most have been developed in patients with atrial fibrillation or venous thromboembolic events for anticoagulation candidacy (HAS-BLED, QBLEED, ATRIA, RIETE, OBRI).[154-158] In addition to population applicability concerns, these bleeding models either lack external validation or have shown poor predictive value.[156] Likewise, models differ in the type and severity of bleeding events predicted.

Two risk models[159, 160] may represent the most promising risk models that could be used for aspirin decision-making for primary CVD prevention, but both have limitations which preclude application to U.S.-based clinical practice. Selak et al. developed a prognostic major bleeding model among persons in whom aspirin might be considered for the primary prevention of CVD.[159] This group analyzed the New Zealand primary care PREDICT cohort (2007-2016) for model derivation (N=234,825) and a split-sample internal validation (N=143,675) in individuals ages 30-79 years not using aspirin. The multivariate model included a large number of predictors, including: demographic characteristics (age, ethnicity, and socioeconomic

deprivation), clinical measurements (systolic blood pressure and ratio of total-high-density lipoprotein cholesterol), family history of premature CVD, medical history (smoking, diabetes, bleeding, peptic ulcer, cancer, alcohol related condition, chronic liver disease or pancreatitis), and medication use (nonsteroidal anti-inflammatory agents, corticosteroids, and selective serotonin reuptake inhibitors). The non-parsimonious nature of the model has been criticized as presenting a barrier to routine use, with particular note that the social deprivation predictor is not transportable to other populations.[161] This risk prediction model has not been externally validated outside of New Zealand.

In an older paper with the aim of developing an easy-to-use score, DeGroot et al. developed a simple upper GI bleeding risk score for low-dose aspirin users without a history of prior GI bleed using a large Dutch health insurance database (2006-2010; N=235,531 aspirin users age ≥18 year).[160] External validation was conducted in a separate but similar Dutch insurance database of aspirin users identified via a nested case control approach (2005-2010; N=32,613 aspirin users, mean age 69 years). A limited set of candidate risk factors was considered based on plausibility, reliability, and distribution in the cohort and then the risk score was simplified to only 5 of the most important risk factors with backward stepwise elimination using likelihood ratio statistics. Risk factors were then assigned a point score based on the beta coefficient of the risk factor. Age >60 years, anemia, diabetes, other antiplatelet use, and anticoagulant use were the risk factors included in the final risk score. The authors reported modest accuracy in the validation cohort (C-statistic=0.63). While the tool was designed for easy implementation, other investigators have not externally validated the score and because of brief reporting, there is some uncertainty regarding the selection of risk factors.

Multivariate Analyses

In the absence of externally validated risk prediction models in clinically relevant populations, multivariate analyses identifying risk factors independently associated with increased bleeding risk could inform whether there are specific populations for whom bleeding risk is high enough to preclude aspirin use in the context of modest CVD benefit. We have compared risk factors identified in four multivariate analyses[50, 117, 159, 160] (**Appendix D, Table 24**). Risk factors consistently and independently associated with bleeding risk in these four analyses are older age, male sex, and diabetes. The three cohort analyses consistently showed that a history of GI issues, such as prior GI hospitalization, liver disease, alcohol disease, or peptic ulcer disease can increase the risk of bleeding. Further, concomitant medications including antiplatelets, NSAIDs, steroids, and anticoagulants can additionally increase the risk of bleeding. Only the New Zealand analysis by Selak et al[159] evaluated race, ethnicity, and socioeconomic status as predictors of bleeding risk. Both self-reported Maori and Pacific ethnicity were associated with a statistically significant elevated risk of major bleeding compared to those of European background. Socioeconomic deprivation was also statistically significantly associated with an increased risk of major bleeding in this analysis.[159]

The approach of limiting aspirin use in primary prevention to those patients without selected baseline bleeding risk factors including concomitant medications (NSAIDs, systemic steroids, anticoagulants, other antiplatelet agents) and medical conditions (history of GI bleeding,

coagulopathy, peptic ulcer disease, liver disease, alcohol related diseases) has been used in trials and suggested in guidelines.[1, 24]

Net Benefit Risk Calculators

Much attention has been given to net benefit assessment tools for aspirin use in primary prevention.[87, 162, 163] One model is currently being developed to inform the USPSTF deliberations.[25] A benefit to an integrated net benefit model—as opposed to use of separate CVD and bleeding risk calculators—is that several risk factors increase both CVD risk and bleeding risk.[50] Because the literature base on CVD risk prediction is more developed than that for GI bleeding risk, net benefit calculators emphasizing CVD risk may not fully account for bleeding risk factors. For example, certain risk factors which contribute to increased CVD risk also appear to elevate bleeding risk (age, sex, smoking, diabetes) while other CVD risk factors may not alter baseline bleeding risk (hyperlipidemia, family history of premature CVD). A calculator that includes risk factors such as smoking and diabetes (which increase CVD risk) for CVD estimation, but does not include these factors (which also increase GI bleeding risk) for GI bleeding risk estimation, may bias a calculator in favor of aspirin for persons at above average CVD risk levels by underestimating potential harms. However, critical limitations in the reporting of baseline GI bleeding estimates accounting for the presence of multiple risk factors, particularly in United States populations, presents limitations for the development of net benefit calculators. Because of the availability of a New Zealand-specific bleeding risk tool, Selak and colleagues were able to bring together their bleeding risk calculator along with updated pooled estimates of the effectiveness of aspirin to prevent CVD from a 2019 meta-analysis,[133] to develop individualized benefit-harm analyses available as an online net benefit calculator for clinical application (https://aspirinbenefitharmcalculator.shinyapps.io/calculator/).[164] Cancer outcomes are not incorporated into this model. This model calculates net benefit using two methods: assuming one CVD event was equivalent to one major bleed, and then assuming one CVD event was equivalent to two major bleeds. Assuming one CVD event is equivalent to one major bleed, 2.5 percent of females and 12.1 percent of males age 30-79 years without known CVD in this New Zealand cohort would achieve a net benefit from aspirin, with results highly dependent on baseline CVD and bleeding risk.

Ideally, shared decision-making related to aspirin initiation or discontinuation would be informed by user-friendly decision support tools including publicly available online net benefit risk calculators. In addition to the Selak calculator mentioned above, there are a few other such calculators available: https://asarisk.doctime.es/, http://www.aspiringuide.com/nav/3, and https://www.benefit-harm-balance.com/. The latter of these also offers estimates that include patient preferences. For application in the United States, these calculators do require updated CVD risk estimation with the PCE, updated meta-analysis estimates for the relative benefit and harm of aspirin in primary prevention populations, and contemporary estimates of absolute baseline bleeding risk rates.

Bleeding Risk Mitigation

Strategies to mitigate bleeding risk in those identified to be aspirin candidates may be to limit

aspirin dose, use an aspirin formulation with enteric coating, or coadminister aspirin with a proton pump inhibitor (PPI). Our review of primary CVD prevention trials did not provide sufficient evidence to make any conclusions about whether enteric coating mitigates bleeding risk, however, observational evidence does show that higher doses are associated with higher bleeding risk,[121] despite the similar bleeding risk for low-dose and all dose aspirin seen in our meta-analysis of only primary CVD prevention trials. There is evidence supporting the use of PPIs to reduce upper GI bleeding in low-dose aspirin users, although some concerns remain about osteoporosis,[165] B12 deficiency,[166] and enteric infections including *clostridium difficile* resulting from long term PPI use.[167] One meta-analysis of randomized trials (k=9, N=6,382) demonstrated that PPIs in primary and secondary CVD prevention populations are associated with a substantially decreased risk of peptic ulcers, bleeding ulcers, and erosive esophagitis.[168] One analysis from the United Kingdom primary care the Health Improvement Network (THIN) database analysis (N=199,049) found that aspirin users with concurrent PPI use had a 31 percent reduced risk of upper GI bleeding when the PPI was used for more than 1 month (OR 0.69 [95% CI, 0.54 to 0.88]) compared to aspirin users with past use of PPI.[169] Additionally, *h pylori* eradication has been proposed to mitigate aspirin-associated bleeding risk.[170]

Aspirin Discontinuation

Our analyses of primary CVD prevention trials suggest that CVD benefits accrue within the first 1-2 years and bleeding risks begin soon after initiation of aspirin. Unfortunately, limited specificity of the time points reported in trials' time-to-event analyses and Kaplan-Meier curves preclude more precise estimations of onset of these effects. These benefits and harms appear to persist while the participants continued to take aspirin during the trial duration, with cessation of CVD benefits and harms after aspirin has been discontinued. For example, in the long-term observational followup of WHS, CVD outcomes became null over long observational time points.[112] These primary trials do not provide precise estimates of temporal variations in bleeding risk over the duration of aspirin administration. It is unclear whether the risk of bleeding associated with aspirin use is especially high in the earliest period of administration. Nonetheless, assuming lifelong aspirin administration is likely unreasonable. Periodic re-assessment of net benefit is essential with decisions to discontinue aspirin use at some future time point after initiation.

Very little is known about any rebound thrombotic risks associated with aspirin discontinuation, although one cohort study has been published since the last review. A Swedish cohort study of over 600,000 adults evaluated the risk of cardiovascular events (hospitalization for MI, stroke, or CVD death) associated with discontinuation of long-term, low-dose aspirin therapy.[171] In the population taking aspirin for CVD primary prevention, discontinuation of aspirin was associated with a 28 percent increase (95% CI, 1.22 to 1.34) in cardiovascular events over a median of 3 years' followup. Until this study has been confirmed in another large primary prevention cohort, these findings should be considered with caution. This increase in risk associated with discontinuation is roughly similar to our pooled estimates of CVD risk reduction associated with aspirin initiation, so this limited evidence suggests that CVD risk returns to baseline after discontinuation without an excess rebound harm. Other research with intermediate platelet markers in animal models or in the secondary prevention literature is likewise scant.[172, 173] More

evidence is needed on this point, and an ongoing trial testing outcomes in aspirin withdrawal was also identified, but the estimated completion date is not until 2024.[174]

Statin Use

We examined how contemporary CVD risk factor management, especially widespread statin use, may impact aspirin's effectiveness on CVD outcomes with our sensitivity analyses examining trials conducted before and after the ATP III guideline release in 2001. Results were conflicting across outcomes. Consistent with other analyses[175, 176] comparing the effect of aspirin in the context of older versus contemporary CVD management,[175] we report that the major CVD event and MI benefits as well as most bleeding harms were diminished while ischemic stroke emerged as a statistically significant benefit in the post-ATP III pooled analysis. We believe these findings likely to be influenced by dose as contemporary trials solely use low-dose aspirin. The two higher dose trials—BMD (500 mg/day) and PHS (162.5 mg/day)—were published in the 1980s, prior to widespread statin use. Other sources of heterogeneity such as trial populations and duration may have further influenced aspirin's effect in these analyses. Three contemporary trials, ASCEND, ARRIVE, and ASPREE performed subgroup analyses by statin use finding no statistically significant interaction between aspirin and statins.[55, 56, 101] Nonetheless, statins have taken priority in the primary prevention clinical landscape due to recent aspirin trials generally showing null effects on CVD outcomes along with statins' well-established statistically significant relative risk reductions for cardiovascular disease events (25%), stroke events (22%), and mortality (14%) and favorable side effect profile.[177]

The recently published TIPS-3 trial (N=5,713) with a 2x2 factorial design evaluating a polypill and aspirin and recruiting patients with elevated CVD risk was not included in our results.[178] Nearly all countries represented were not high Human Development Index countries which we required for generalizability to the United States population by our inclusion criteria. However, inclusion of this trial would not have changed our overall conclusions. In this trial, aspirin reduced stroke (RR 0.58 [95% CI, 0.35 to 0.98]) but there was no statistically significant difference in CVD composite outcomes, CVD death, or MI between the aspirin and control groups.

CRC

Because this review was an update of prior reviews,[2-4] our scope included potential benefits from CVD as well as CRC. Our conclusions about the CRC benefits of aspirin are somewhat different than the previous review.[4] We conclude that there is insufficient evidence on the influence of low-dose aspirin on CRC incidence and CRC mortality in the primary CVD prevention trial evidence due to methodological limitations associated with the observational periods of trials. We have assessed that there is a very low strength of evidence supporting a reduction in CRC incidence from any dose of aspirin, including high doses above what would be considered appropriate in the context of primary CVD prevention. Our insufficient strength of evidence for CRC outcomes is supported by few included trials, many of which were small and reliant on post-trial observational results that are subject to biases (**Table 21**). Even ASPREE, which

showed a CRC mortality harm occurring within the first 5 years of randomized aspirin use, is limited by the short duration and large quantity of outcomes.

Our sensitivity analyses included trials of secondary CVD prevention[94, 111] and all doses of aspirin, as was done in the prior review (**Figures 20-22, 24**). These sensitivity analyses include broader post-trial observational data with consistent patterns of CRC incidence and mortality benefits, however there are still few overall studies with concerns about applicability and the biases associated with observational designs. Additionally, we recognize that there is a larger evidence base of observational studies addressing the association between aspirin use and CRC incidence or mortality. For example, a 2018 meta-analysis of 39 observational studies[179] reported an association between aspirin use and decreased colorectal cancer incidence (RR 0.79 [95% CI, 0.74 to 0.85]). In addition, a recent cohort study using the PLCO trial participants (n~146k) also reported a reduction in CRC incidence associated with aspirin use.[180] However, some of the surprising and substantial benefits reported bring into question the validity of observational data; for example, aspirin used only 1-3 times per month was associated with a large all-cause mortality benefit. Further, a pooled analysis[181] of two cohort studies indicated initiation of aspirin at 70 years or older was not associated with a lower risk of CRC, but did lower the risk of CRC for adults who initiated aspirin prior to age 70. The observational literature is further limited by heterogeneity of aspirin dosages, duration, indications, and populations. Observational data is also subject to numerous biases: selection bias (aspirin users may be healthier), misclassification bias (post-hoc CRC outcome measurement and aspirin exposures may not be accurate), recall bias (about reporting of true aspirin exposure), and confounding (particularly when indication and duration/dose vary or are unreported).

While not included in this update, the previous version of this systematic review[4] included evidence of the effect of aspirin on adenoma prevention. The previous review identified three RCTs among people with a history of adenomas, but the association of aspirin use with adenoma risk was inconsistent. Research conducted since the previous review also reported conflicting conclusions—with some suggesting aspirin had no effect on adenomas,[182, 183] or an effect only on adenomas in certain locations[184] (e.g., right-sided) or types of adenomas[185] (e.g., tubular adenomas).

Aspirin may also be useful in the prevention of CRC in people who are at higher risk of developing CRC, such as those with previous CRC, a history of adenomas, or genetic risk factors for CRC. One systematic review of RCTs recruiting people with previous colorectal neoplasia (CRC or advanced adenomas) found that low-dose aspirin was associated with a nonstatistically significant reduction in advanced neoplasia (k=3).[186] Another systematic review of five cohorts and one nested case-control study suggests that aspirin use after CRC diagnosis is associated with a lower risk of all-cause mortality, but the decreased risk in CRC-specific mortality was not statistically significant.[187] Many randomized controlled trials designed to assess the impact of aspirin on colorectal cancer are in progress. One trial—Add-Aspirin—is designed to determine if aspirin use after the diagnosis of an early-stage cancer (including colon/rectum, breast, gastrointestinal, and prostate cancers) can prevent the cancer from coming back (http://www.addaspirintrial.org/). Further studies have reported that among Lynch syndrome gene carriers, high-dose aspirin for 2 years was associated with a decreased risk of colorectal cancer.[188, 189]

While others have been interested in a possible benefit for other types of cancer,[190, 191] two recent study level meta-analyses did not find an association between aspirin and cancer. Overall cancer incidence and mortality outcomes were reported as exploratory outcomes in one review by Zheng (cancer incidence: 10 RCTs, N=124,523; cancer mortality: 12 RCTs, N=149,134), and no cancer outcome was statistically significant.[133] Similarly, the 2019 review by Haykal and colleagues focused on aspirin for the primary prevention of cancer (16 RCTs, N=104,018) found no statistically significant differences for any cancer outcome.[134]

Ongoing Trials

We identified a few ongoing primary prevention aspirin trials and related cohorts (**Appendix E**). A cohort study in Hong Kong (N=NR) will study the effectiveness of low-dose aspirin for the primary prevention of GI cancers (NCT04081831). A Korean trial of 4,118 participants is examining the effects of aspirin discontinuation on CVD events and is expected to publish in 2024 (NCT03757156). Finally, one in-progress cross sectional study (N=1,028) in Italy aims to examine patient preferences around benefit and harm trade-offs associated with of low-dose aspirin for primary and secondary prevention (NCT03603366). Further, ASCEND (NCT00135226) and ASPREE (ASPREE-XT) are following participants for long-term cancer outcomes.

Limitations of the Literature

There are several limitations to this literature. As mentioned previously, the 13 primary prevention studies are clinically heterogeneous in terms of aspirin dose, duration, populations, and baseline CVD risk. Additionally, most trials were powered for variably-defined composite CVD outcomes rather than any individual CVD outcomes. In these primary prevention populations, individual CVD outcomes were rare enough that findings of nonstatistical significance could potentially be due to lack of power. While some of this lack of power can be overcome with meta-analysis, the trials are further limited by short trial durations and lack of comparable time-to-event data reporting, so we could not precisely determine the minimum time-to-benefit for CVD outcomes. We could also not determine if CVD benefits persist at a constant rate beyond 5 to 10 years of use.

Overall, there were few trials reporting CRC outcomes and they were of too short duration to expect CRC incidence or mortality benefits to accrue. Thus, we included observational periods after trial completion, recognizing that the data collection after the randomized stage is similar to an observational study and is potentially subject to bias or confounding. We also included trials recruiting secondary CVD prevention populations; since CRC and CVD share many risk factors, these populations may have increased CRC risk when compared to a general population. The timing of the CRC outcomes were inconsistent among studies, and some were captured post-hoc by a separate research group conducting an IPD MA. With the exception of WHS, trials did not collect CRC screening rates. For most studies, we also do not know the proportion of participants who continued their assigned allocation at daily or every other day dosing beyond the 5-10 year randomized phase.

Because of rare event rates for bleeding harms, estimates in this meta-analysis are imprecise for some bleeding outcomes. We therefore expanded our study design to include observational studies for harms but little detail about specific dosing and indication were available, thus little could be concluded about the harms specific to daily low-dose aspirin. We acknowledge that these cohort studies themselves have limitations, such as self-reporting of aspirin exposure,[120, 121] and incomplete reporting of dose and indication for use.[98, 106, 107] In some studies, regular use was defined as >2 tablets per week, which is less use than would be seen in every other day dosing trials and may reflect indication for analgesia.[120, 121] Other cohorts reported use in excess of what would be typically used for primary prevention of CVD, also suggesting the indication was not for CVD prevention.

One additional unanswered clinical question is whether GI bleeds associated with aspirin use are more fatal, less fatal, or have similar case fatality compared to GI bleeds occurring in nonaspirin users. We did not pool fatal GI bleeding events in our meta-analysis of included trials because of an exceedingly small number of fatal bleeding events in reporting trials, and inconsistent reporting among trials. Other systematic reviews have chosen to combine primary and secondary CVD prevention trials and present data using these very small event rates, showing conflicting results.[192-194]

Little has been published about quality of life (QOL) outcomes with aspirin for primary prevention or patient preferences with aspirin use. While ASPREE's primary outcome was disability-free survival with results showing no difference in this QOL-related outcome in the aspirin group,[102, 105] there were no other trials reporting QOL outcomes. Shared decision-making tools would ideally incorporate any QOL effects along with patient preferences; one in-progress cross sectional study (N=1,028) in Italy aims to examine patient preferences around the risks and benefits and harms of low-dose aspirin for primary and secondary prevention (NCT03603366).

Limitations of Our Review

Our primary analyses focused on primary CVD prevention literature for all outcomes including CVD benefits, bleeding harms, and CRC effects. We did not include secondary prevention populations for the bleeding outcomes because those with CVD often have higher bleeding risk either due to risk factors (smoking, uncontrolled hypertension) or co-medication with anticoagulants. In contrast, we did pool primary and secondary CVD prevention trials for our CRC outcome analyses because there were very few primary prevention trials reporting CRC outcomes; we reported results from the post-trial observational period but did not include a wider literature of observational studies examining aspirin use and CRC outcomes. In order to maximize the number of trials pooled for CVD and bleeding outcomes, we accepted narrower or broader outcome definitions as reported by trials. For some trials we calculated our primary composite outcomes of major CVD events from individual outcomes. This approach may overestimate events if the reporting of separate outcomes included individuals with nonfatal events followed by a fatal event.

Future Research Needs

The literature related to CVD risk estimation is far more developed than for GI bleeding risk. The next generation of aspirin net benefit calculators will require more precise estimates of GI bleeding, including fatal bleeding, that account for additional risk factors beyond age, sex, and history of aspirin use (e.g., race/ethnicity, socioeconomic status, comorbidities). Ideally, these data would be available in a large US-based cohort and could serve as the underlying data for an externally validated GI bleeding risk calculator.

For both CVD and bleeding outcomes, the forthcoming ATT IPD meta-analysis update is likely to provide the more definitive analyses on whether there is differential benefit or harm for CVD and bleeding outcomes in specific populations.

Finally, a large, long-term, low-dose aspirin trial examining CRC effects at 20 years would be ideal to examine the marginal effects of aspirin in the context of contemporary screening practices. It could also be useful to conduct a shorter trial among the general population to assess the impact of aspirin on adenomas, although that could be resource intensive and require a large number of colonoscopies. At minimum, the CVD prevention trials already conducted could link their trial participants to registries that track CRC diagnoses or deaths. However, this type of observational design would have the same limitations as those in the extended followup studies previously described. Any future trials should account for all modalities of CRC screening as well as CRC risk factors, as most of the CVD prevention trials do not address these potential confounders. Further, there are exceedingly scant data available to date to inform the role of aspirin used for primary prevention in Black, Hispanic, Asian and Native populations.

Conclusions

This updated systematic review included three new trials (N=47,170) and three new cohort studies (N=358,495). Despite this accrual of new evidence, findings for CVD outcomes and bleeding harms were remarkably similar to our prior review.[2] In both low-dose and all-dose analyses, aspirin was associated with statistically significant relative risk reductions and small absolute risk reductions of up to 2.5 percent for major CVD events in primary prevention populations. These benefits were offset by statistically significant relative risk increases and small absolute increases of up to 1.0 percent for major bleeding harm. While there was little new evidence about CRC effects, ASPREE's findings of potentially increased rates of later stage cancers in older adults puts into question potential CRC benefits. Moreover, aspirin's potential role in CRC prevention could be diminished by increases in CRC screening in recommended ages. The role of aspirin in primary prevention for CVD will continue to evolve based on the closely matched magnitude of CVD benefit and bleeding risks in the context of declining smoking rates, increasing statin use, and more aggressive hypertension management.

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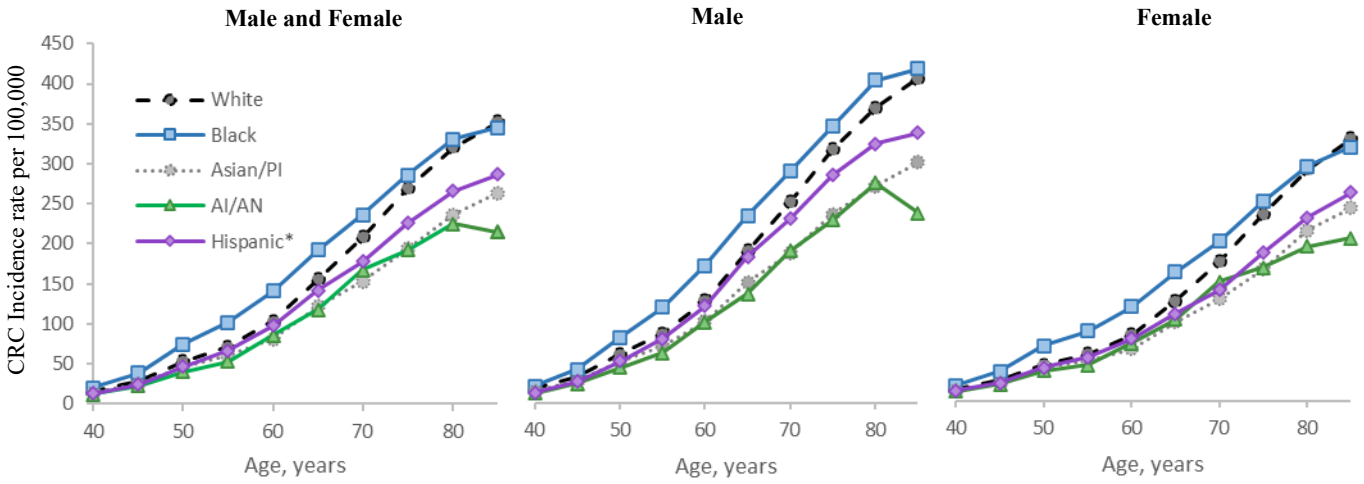
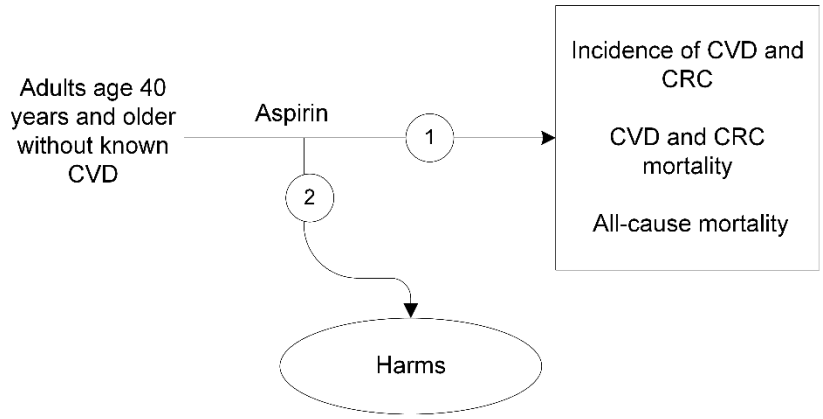
Figure 1. Age-Specific Colorectal Cancer Incidence Rates/100,000 by Race and Ethnicity, United States, 1999-2014



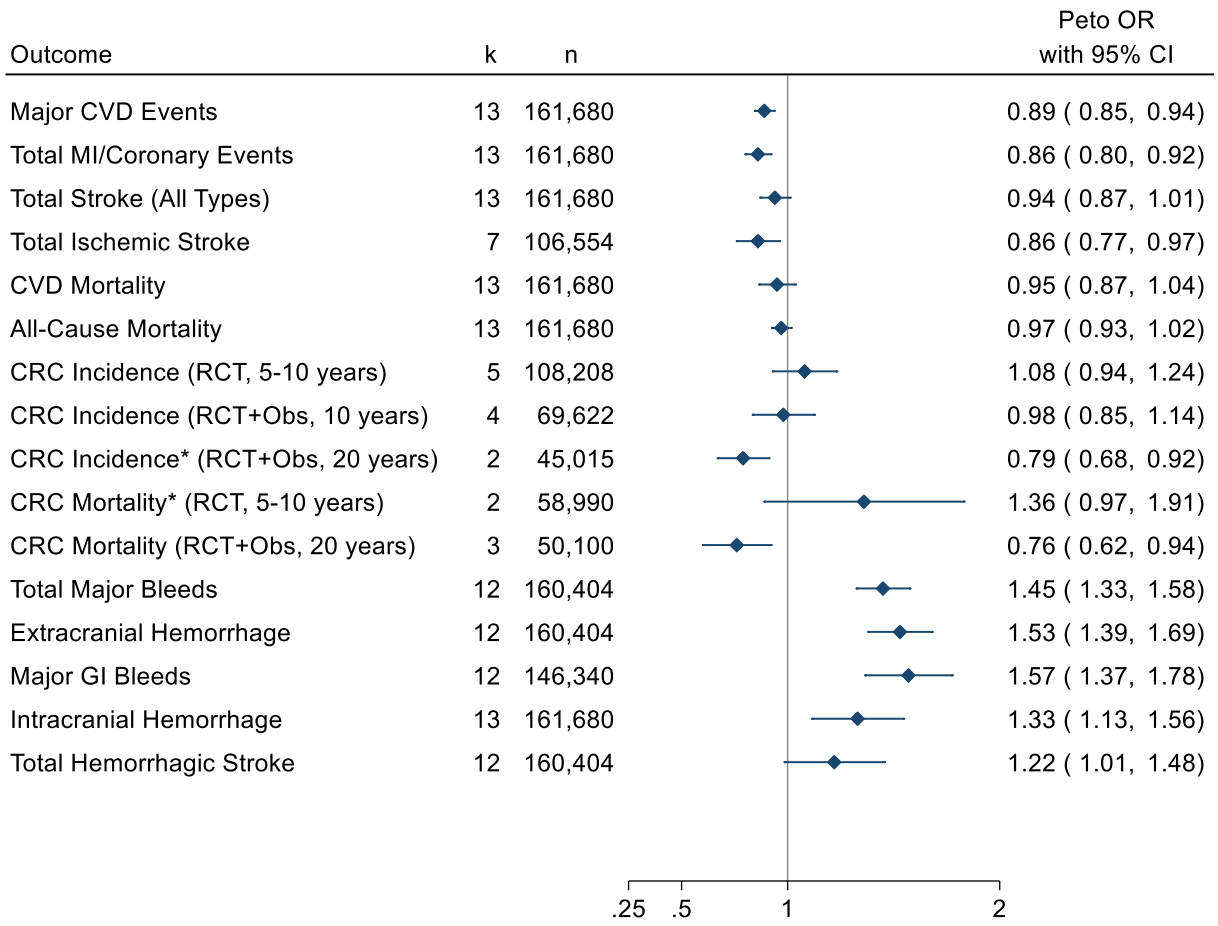
Note: Data combined from the Center for Disease Control and Prevention National Program of Cancer Registries and the National Cancer Institute Surveillance, Epidemiology and End Results Program.[195]
* Not mutually exclusive from race categories
Abbreviations: AI = American Indian; AN = Alaska Native; CRC = colorectal cancer; PI = Pacific Islander

Figure 2. Analytic Framework



Abbreviations: CRC = Colorectal cancer; CVD = cardiovascular disease

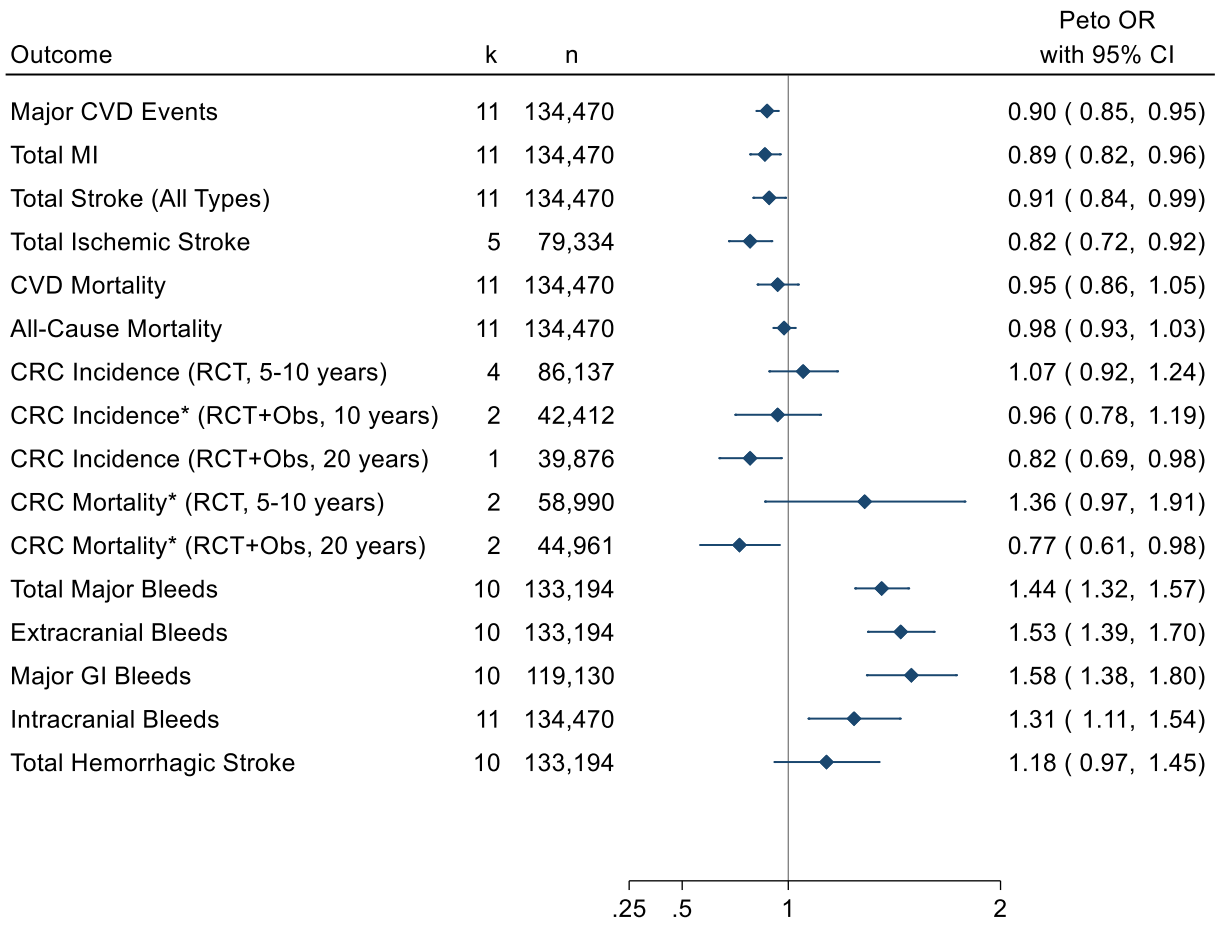
Figure 3. Pooled Analyses for KQ 1 and KQ 2 Outcomes



* Pooled results for outcomes with only 2 trials are shown only for illustrative purposes. Individual trial results are consistent with the pooled results.

Abbreviations: CI = confidence interval; CRC = colorectal cancer; CVD = cardiovascular disease; GI = gastrointestinal; K = number of studies; N = number of participants; Obs = observational; OR = odds ratio; RCT = randomized controlled trial

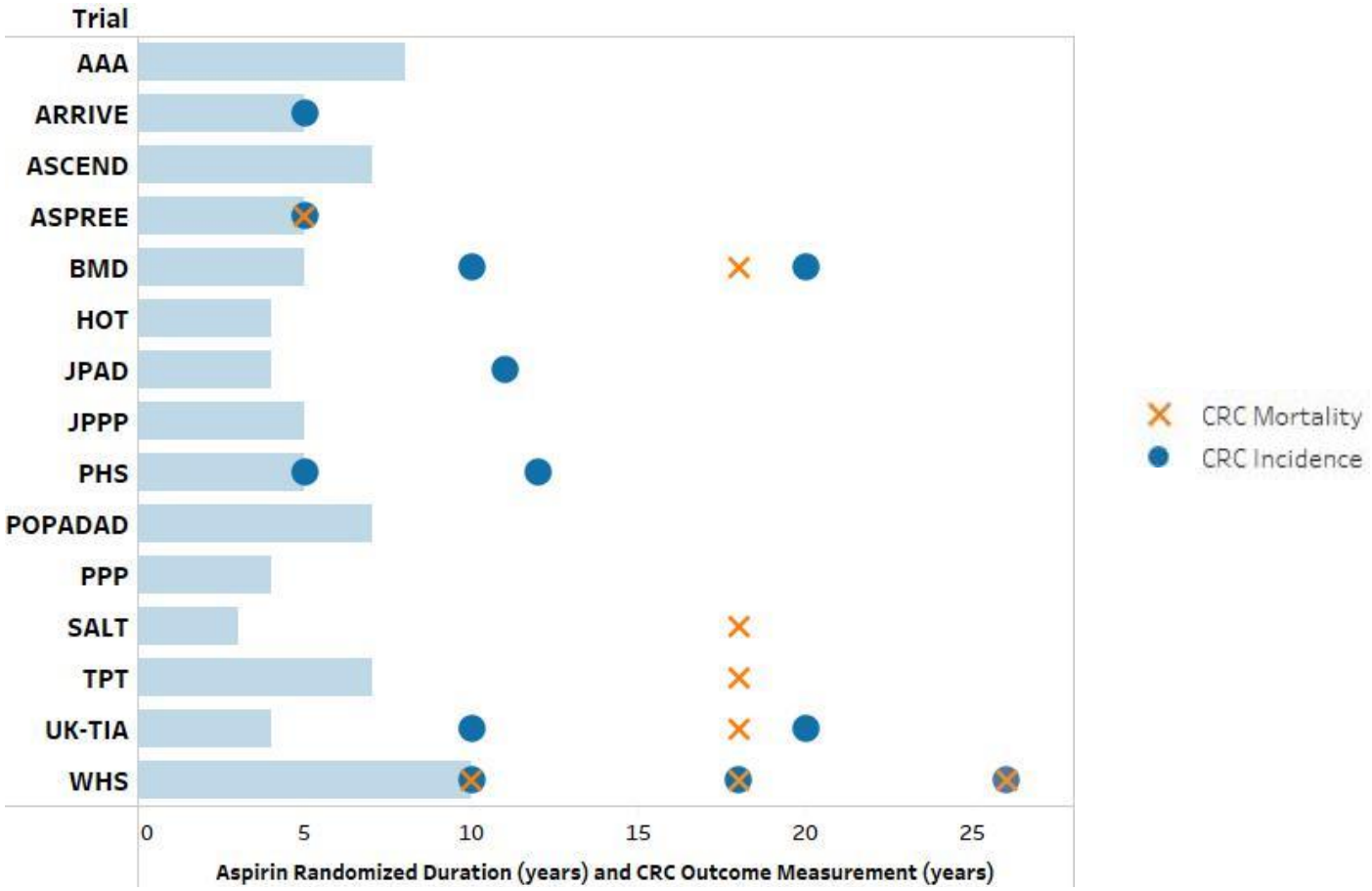
Figure 4. Pooled Analyses for KQ 1 and KQ 2 Outcomes, Daily Aspirin Dose of 100 mg or Less



* Pooled results for outcomes with only 2 trials are shown only for illustrative purposes. Individual trial results are consistent with the pooled results.

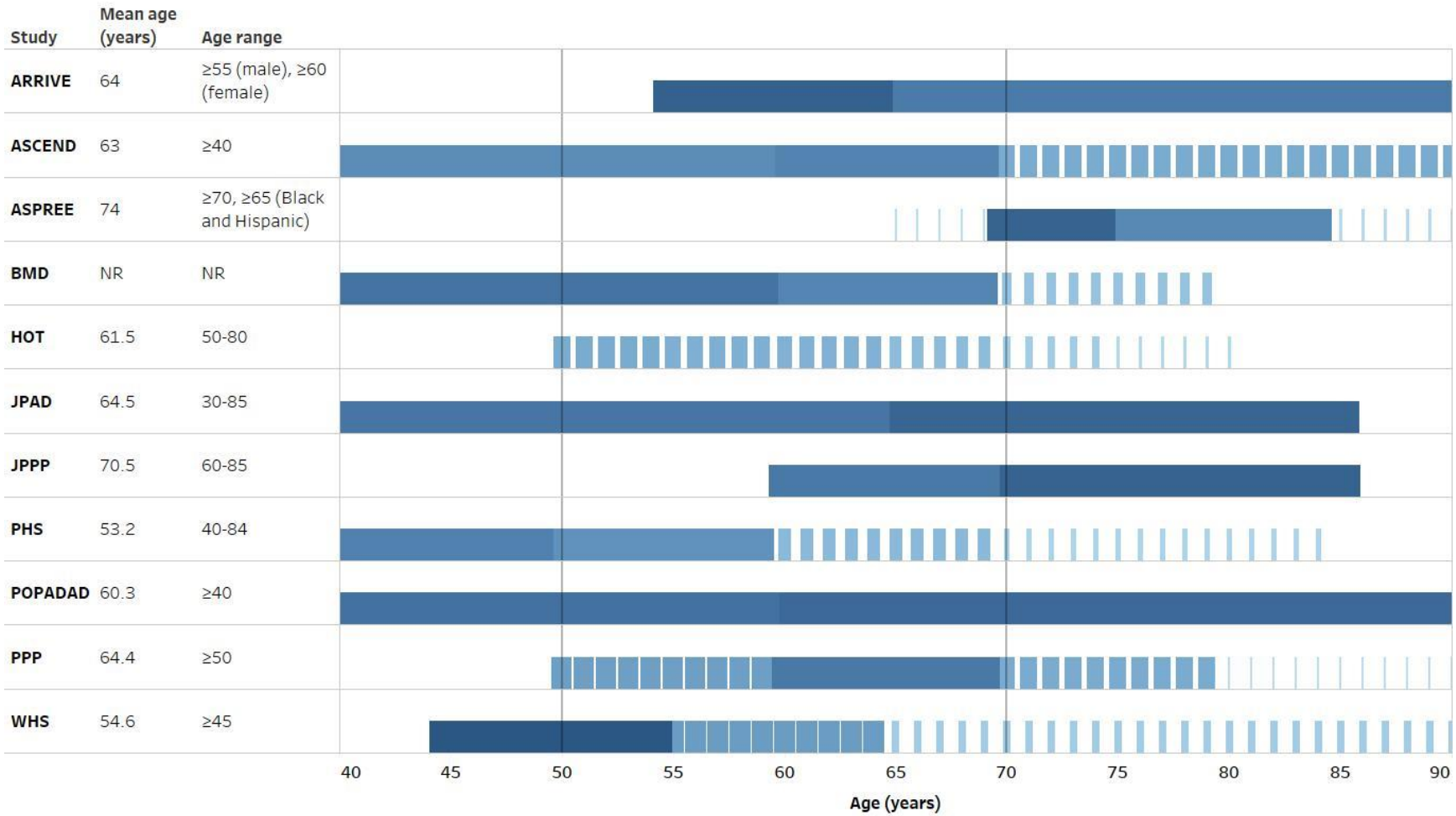
Abbreviations: CI = confidence interval; CRC = colorectal cancer; CVD = cardiovascular disease; GI = gastrointestinal; k = number of studies; n = number of participants; Obs = observational; OR = odds ratio; RCT = randomized controlled trial

Figure 5. Duration of Randomized Aspirin Use and Timepoints for CRC Incidence and Mortality



Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis; ARRIVE = Aspirin to Reduce Risk of Initial Vascular Events; ASA = aspirin; ASCEND = A Study of Cardiovascular Events in Diabetes; ASPREE = Aspirin in Reducing Events in the Elderly; BMD = British Male Doctors; CRC = colorectal cancer; HOT = Hypertension Optimal Treatment Study; JPAD = Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; JPPP = Japanese Primary Prevention Project; PHS = Physician's Health Study; POPADAD = The Prevention of Progression of Arterial Disease and Diabetes trial; PPP = Primary Prevention Project; SALT = Swedish Aspirin Low-dose Trial; TPT Thrombosis Prevention Trial; UK-TIA = United Kingdom Transient Ischaemic Attack; WHS = Women's Health Study

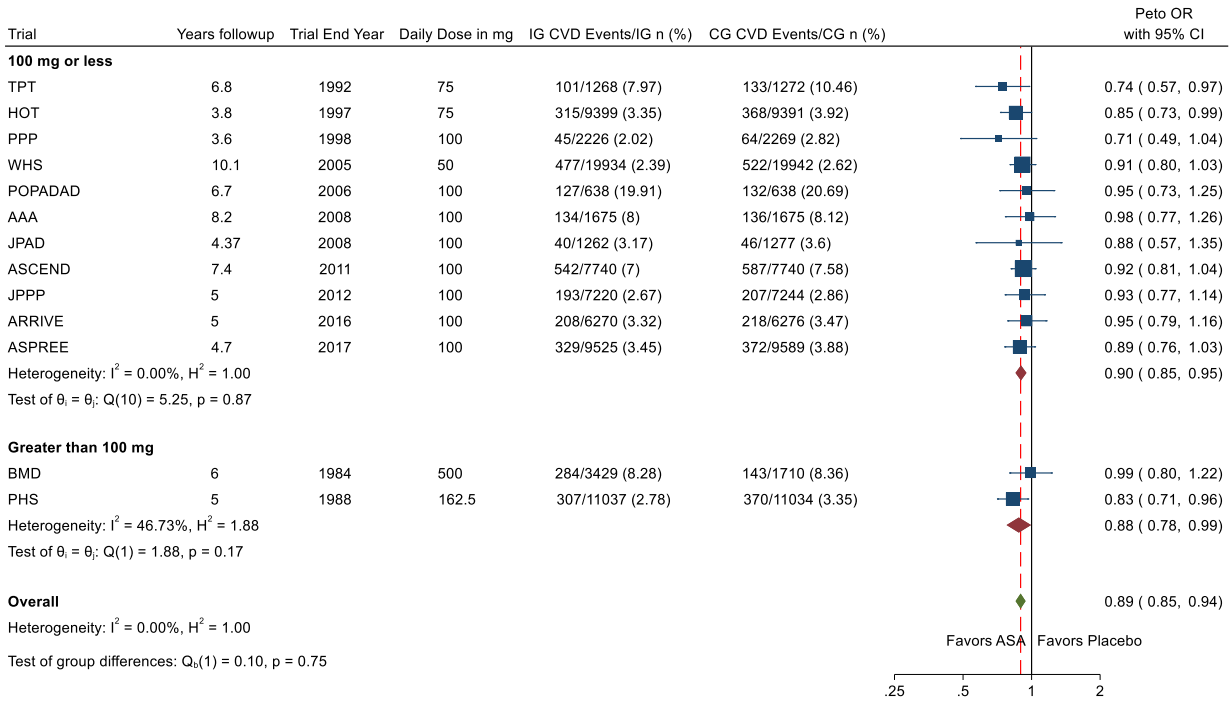
Figure 6. Age Distribution for the Primary CVD Prevention Aspirin Trials



Note: Lighter shading and thinner bars both indicate a smaller proportion of the sample in that age group.

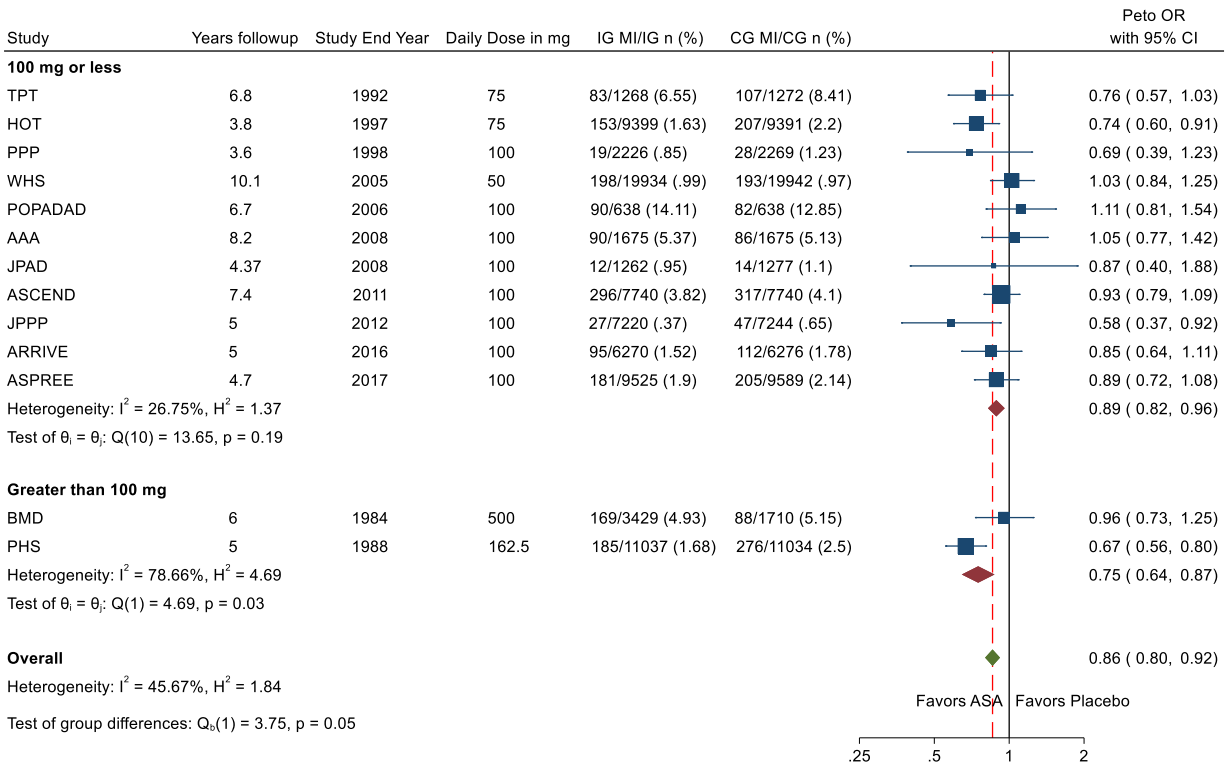
Abbreviations: ARRIVE = Aspirin to Reduce Risk of Initial Vascular Events; ASCEND = A Study of Cardiovascular Events in Diabetes; ASPREE = Aspirin in Reducing Events in the Elderly; BMD = British Male Doctors; CVD = cardiovascular disease; HOT = Hypertension Optimal Treatment Study; JPAD = Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; JPPP = Japanese Primary Prevention Project; PHS = Physician's Health Study; POPADAD = The Prevention of Progression of Arterial Disease and Diabetes trial; PPP = Primary Prevention Project; WHS = Women's Health Study

Figure 7. Key Question 1: Pooled Analysis of Major CVD Event (CVD Mortality, Nonfatal Stroke, or Nonfatal MI) Risk, Aspirin Compared With Placebo, Stratified by Daily Dose and Sorted by Trial End Year



Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis; ARRIVE = Aspirin to Reduce Risk of Initial Vascular Events; ASA = aspirin; ASCEND = A Study of Cardiovascular Events in Diabetes; ASPREE = Aspirin in Reducing Events in the Elderly; BMD = British Male Doctors; CG = control group; CI = confidence interval; CVD = cardiovascular disease; HOT = Hypertension Optimal Treatment Study; IG = intervention group; JPAD = Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; JPPP = Japanese Primary Prevention Project; mg = milligram; MI = myocardial infarction; n = number of participants; OR = odds ratio; PHS = Physician's Health Study; POPADAD = The Prevention of Progression of Arterial Disease and Diabetes trial; PPP = Primary Prevention Project; TPT Thrombosis Prevention Trial; WHS = Women's Health Study

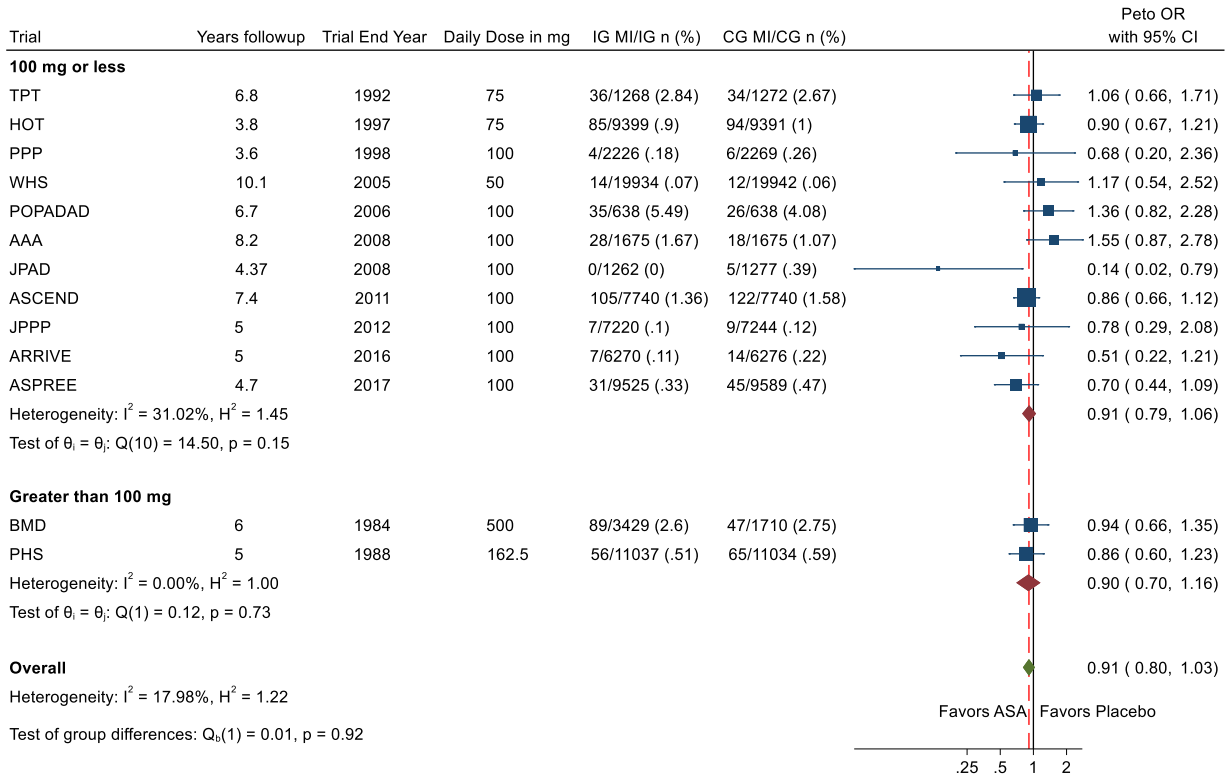
Figure 8. Key Question 1: Pooled Analysis of Total MI* Risk, Aspirin Compared With Placebo, Stratified by Daily Dose and Sorted by Trial End Year



***** Includes fatal coronary heart disease and sudden death in addition to MI events.

Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis; ARRIVE = Aspirin to Reduce Risk of Initial Vascular Events; ASA = aspirin; ASCEND = A Study of Cardiovascular Events in Diabetes; ASPREE = Aspirin in Reducing Events in the Elderly; BMD = British Male Doctors; CG = control group; CI = confidence interval; HOT = Hypertension Optimal Treatment Study; IG = intervention group; JPAD = Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; JPPP = Japanese Primary Prevention Project; mg = milligram; MI = myocardial infarction; n = number of participants; OR = odds ratio; PHS = Physician's Health Study; POPADAD = The Prevention of Progression of Arterial Disease and Diabetes trial; PPP = Primary Prevention Project; TPT Thrombosis Prevention Trial; WHS = Women's Health Study

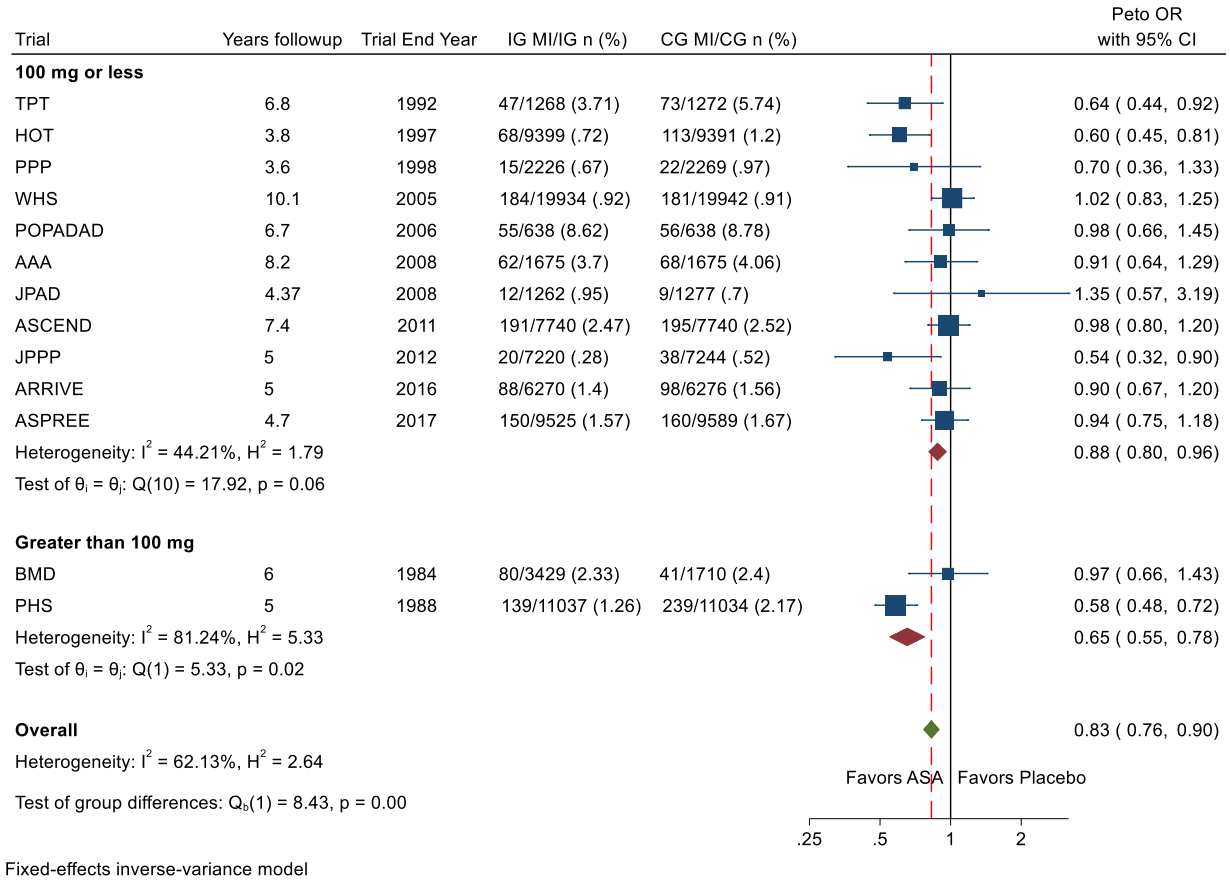
Figure 9. Key Question 1: Pooled Analysis of Fatal MI* Risk, Aspirin Compared With Placebo, Stratified by Daily Dose and Sorted by Trial End Year



***** Includes fatal coronary heart disease and sudden death in addition to MI events.

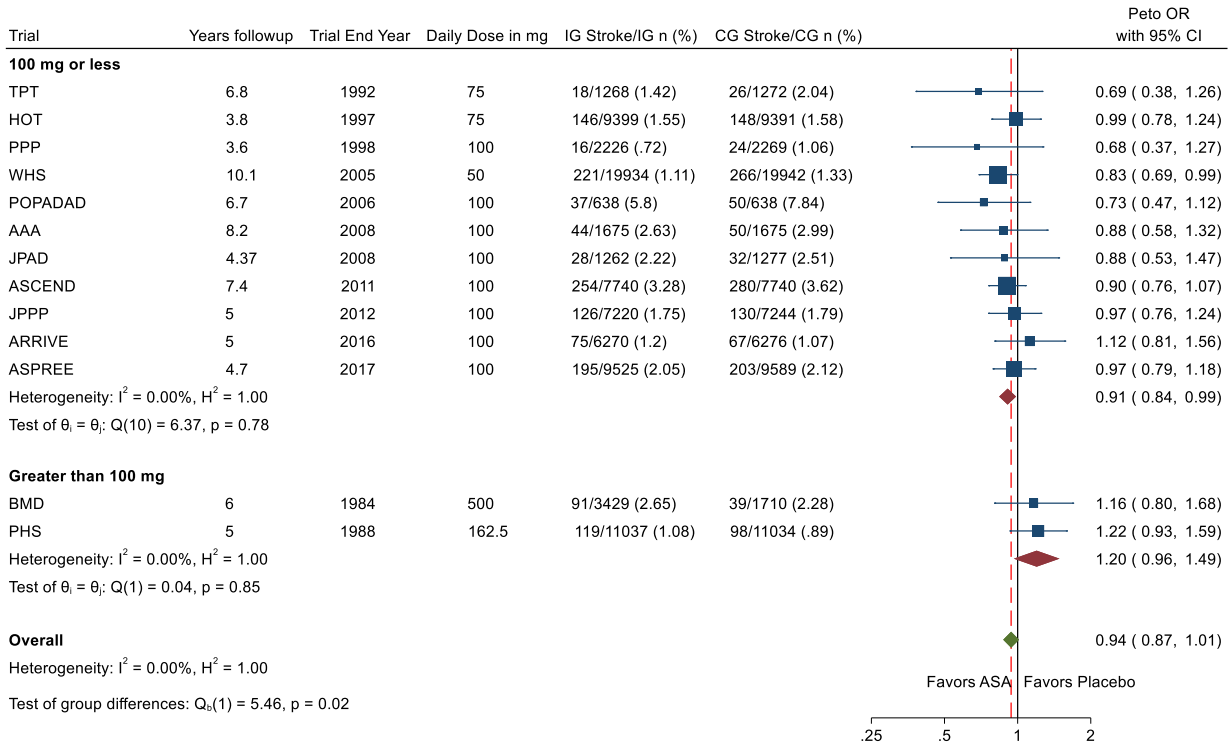
Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis; ARRIVE = Aspirin to Reduce Risk of Initial Vascular Events; ASA = aspirin; ASPREE = Aspirin in Reducing Events in the Elderly; BMD = British Male Doctors; CG = control group; CI = confidence interval; HOT = Hypertension Optimal Treatment Study; IG = intervention group; JPAD = Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; JPPP = Japanese Primary Prevention Project; mg = milligram; MI = myocardial infarction; n = number of participants; OR = odds ratio; PHS = Physician's Health Study; POPADAD = The Prevention of Progression of Arterial Disease and Diabetes trial; PPP = Primary Prevention Project; TPT Thrombosis Prevention Trial; WHS = Women's Health Study

Figure 10. Key Question 1: Pooled Analysis of Nonfatal MI Risk, Aspirin Compared With Placebo, Stratified by Daily Dose and Sorted by Trial End Year



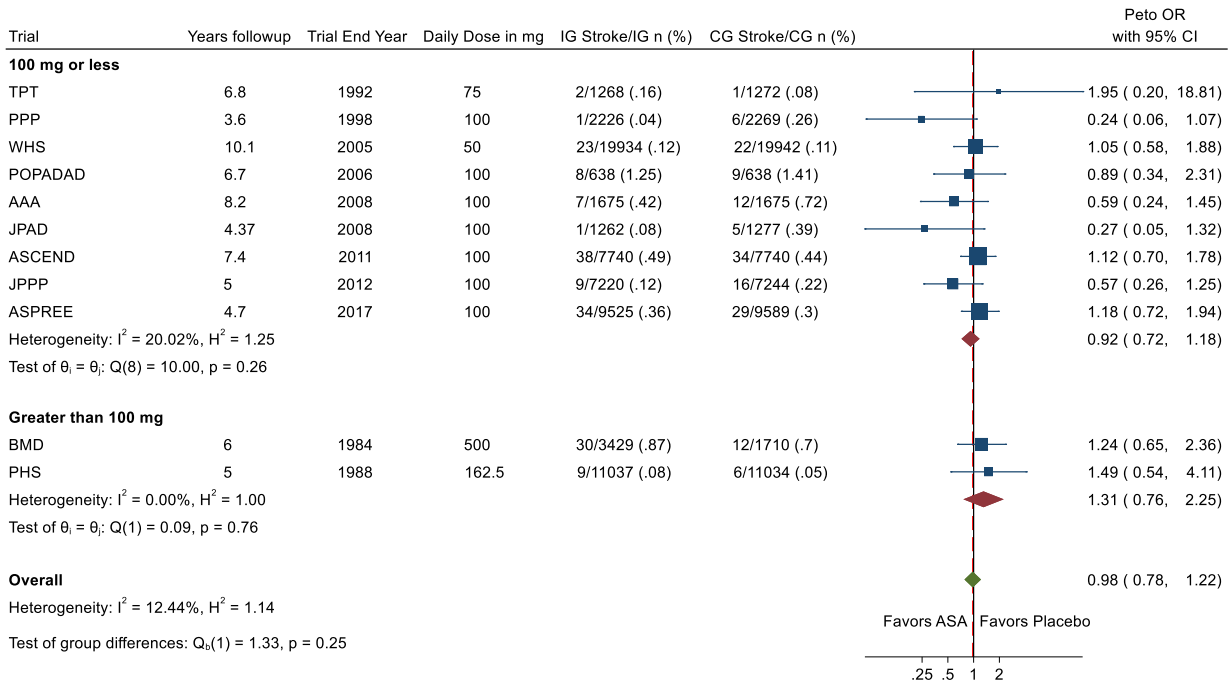
Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis; ARRIVE = Aspirin to Reduce Risk of Initial Vascular Events; ASA = aspirin; ASPREE = Aspirin in Reducing Events in the Elderly; BMD = British Male Doctors; CG = control group; CI = confidence interval; CVD = cardiovascular disease; HOT = Hypertension Optimal Treatment Study; IG = intervention group; JPAD = Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; JPPP = Japanese Primary Prevention Project; mg = milligram; MI = myocardial infarction; n = number of participants; OR = odds ratio; PHS = Physician's Health Study; POPADAD = The Prevention of Progression of Arterial Disease and Diabetes trial; PPP = Primary Prevention Project; TPT Thrombosis Prevention Trial; WHS = Women's Health Study

Figure 11. Key Question 1: Pooled Analysis of Total All-Type Stroke (Fatal and Nonfatal) Risk, Aspirin Compared With Placebo, Stratified by Dose and Sorted by Trial End Year



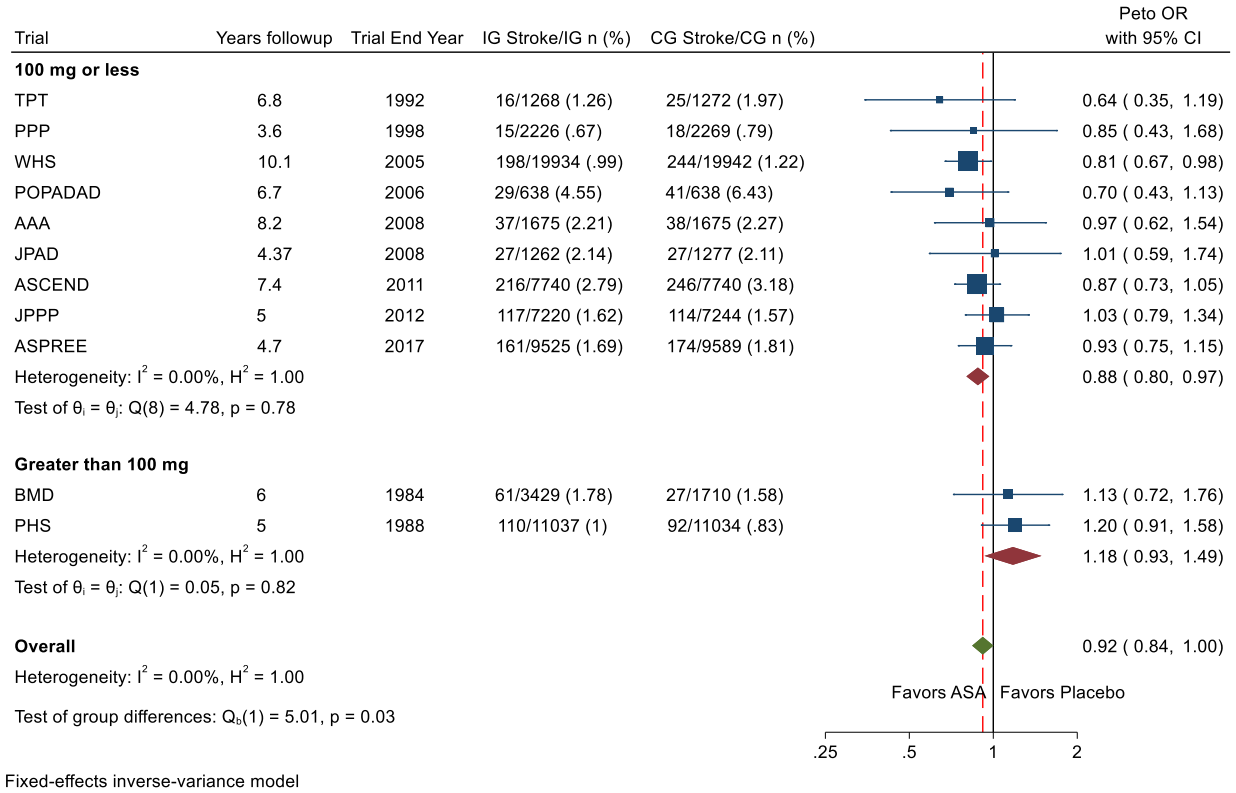
Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis; ARRIVE = Aspirin to Reduce Risk of Initial Vascular Events; ASA = aspirin; ASCEND = A Study of Cardiovascular Events in Diabetes; ASPREE = Aspirin in Reducing Events in the Elderly; BMD = British Male Doctors; CG = control group; CI = confidence interval; F/U = followup; HOT = Hypertension Optimal Treatment Study; IG = intervention group; JPAD = Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; JPPP = Japanese Primary Prevention Project; mg = milligram; n = number of participants; OR = odds ratio; PHS = Physician's Health Study; POPADAD = The Prevention of Progression of Arterial Disease and Diabetes trial; PPP = Primary Prevention Project; TPT Thrombosis Prevention Trial; WHS = Women's Health Study

Figure 12. Key Question 1: Pooled Analysis of Fatal All-Type Stroke Risk, Aspirin Compared With Placebo, Stratified by Daily Dose and Sorted by Trial End Year



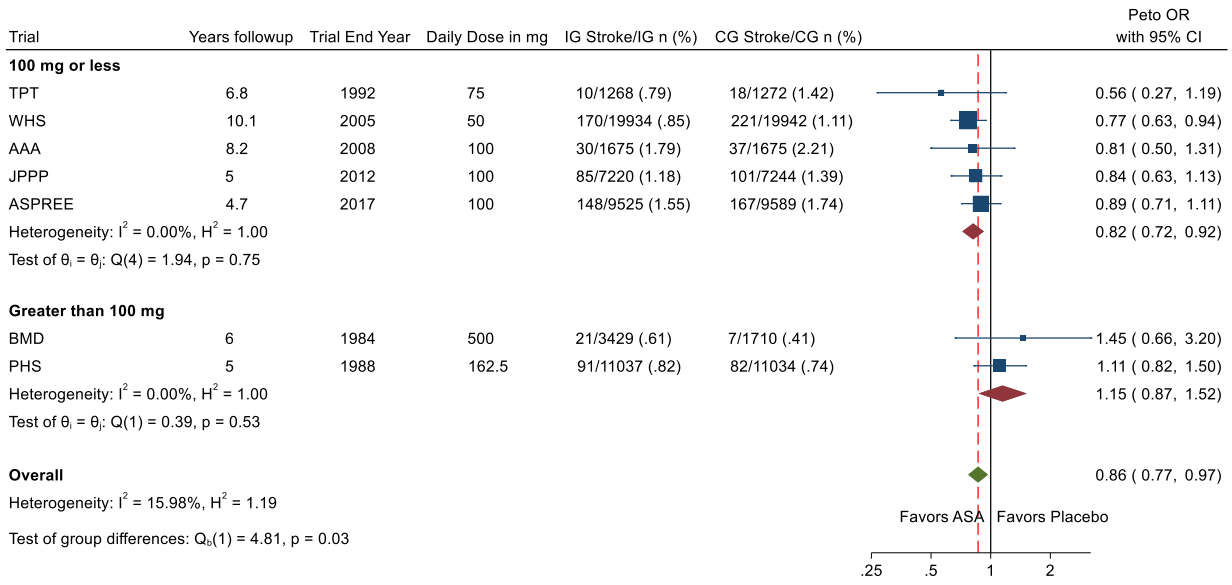
Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis; ASA = aspirin; ASCEND = A Study of Cardiovascular Events in Diabetes; ASPREE = Aspirin in Reducing Events in the Elderly; BMD = British Male Doctors; CG = control group; CI = confidence interval; IG = intervention group; JPAD = Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; JPPP = Japanese Primary Prevention Project; mg = milligram; n = number of participants; OR = odds ratio; PHS = Physician's Health Study; POPADAD = The Prevention of Progression of Arterial Disease and Diabetes trial; PPP = Primary Prevention Project; TPT Thrombosis Prevention Trial; WHS = Women's Health Study

Figure 13. Key Question 1: Pooled Analysis of Nonfatal All-Type Stroke Risk, Aspirin Compared With Placebo, Stratified by Daily Dose and Sorted by Trial End Year



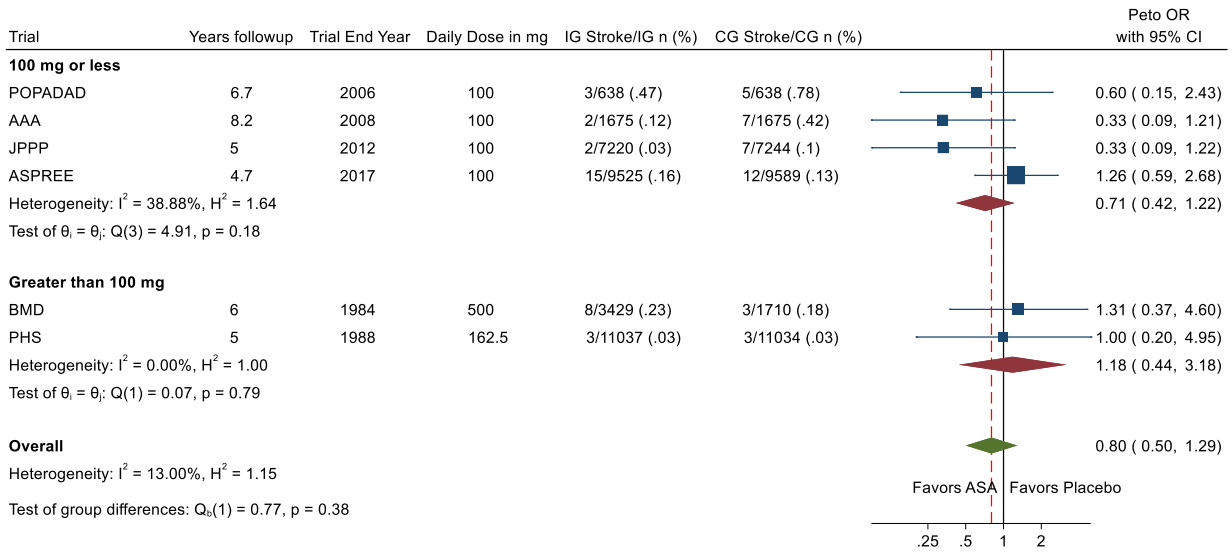
Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis; ASA = aspirin; ASCEND = A Study of Cardiovascular Events in Diabetes; ASPREE = Aspirin in Reducing Events in the Elderly; BMD = British Male Doctors; CG = control group; CI = confidence interval; IG = intervention group; JPAD = Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; JPPP = Japanese Primary Prevention Project; mg = milligram; n = number of participants; OR = odds ratio; PHS = Physician's Health Study; POPADAD = The Prevention of Progression of Arterial Disease and Diabetes trial; PPP = Primary Prevention Project; TPT Thrombosis Prevention Trial; WHS = Women's Health Study

Figure 14. Key Question 1: Pooled Analysis of Total Ischemic Stroke (Fatal and Nonfatal) Risk, Aspirin Compared With Placebo, Stratified by Daily Dose and Sorted by Trial End Year



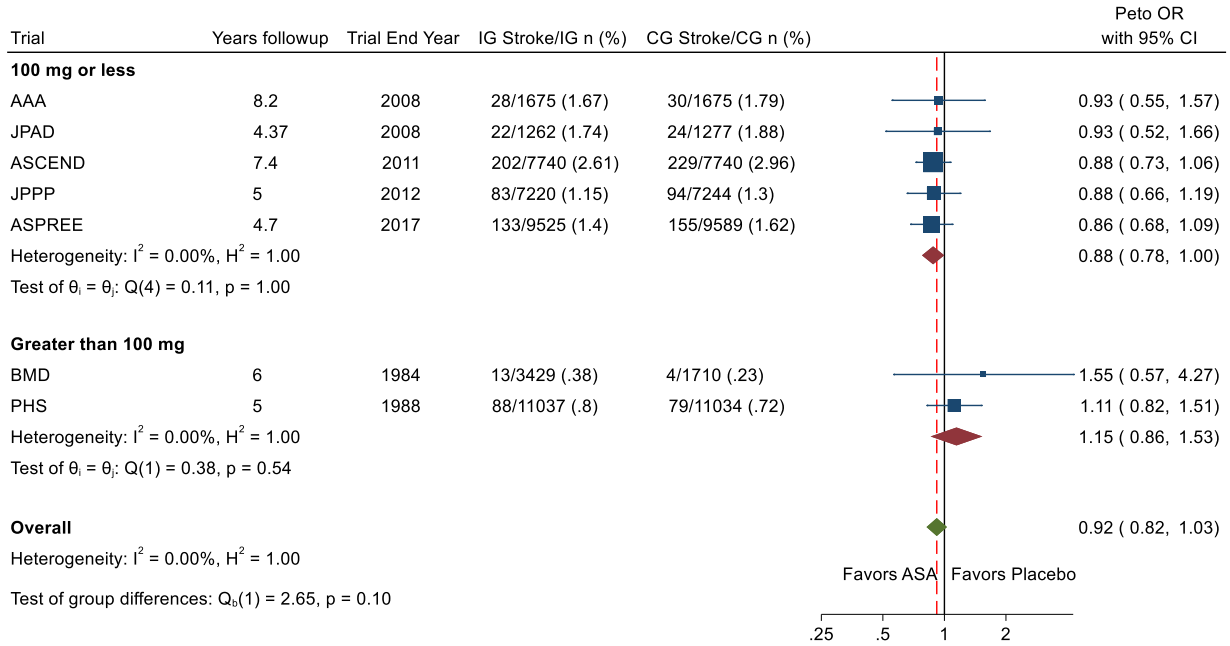
Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis; ASA = aspirin; ASPREE = Aspirin in Reducing Events in the Elderly; BMD = British Male Doctors; CG = control group; CI = confidence interval; IG = intervention group; JPPP = Japanese Primary Prevention Project; mg = milligram; n = number of participants; OR = odds ratio; PHS = Physician's Health Study; TPT Thrombosis Prevention Trial; WHS = Women's Health Study

Figure 15. Key Question 1: Pooled Analysis of Fatal Ischemic Stroke Risk, Aspirin Compared With Placebo, Stratified by Dose and Sorted by Trial End Year



Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis; ASA = aspirin; ASPREE = Aspirin in Reducing Events in the Elderly; BMD = British Male Doctors; CG = control group; CI = confidence interval; IG = intervention group; JPPP = Japanese Primary Prevention Project; mg = milligram; n = number of participants; OR = odds ratio; PHS = Physician's Health Study; POPADAD = The Prevention of Progression of Arterial Disease and Diabetes trial

Figure 16. Key Question 1: Pooled Analysis of Nonfatal Ischemic Stroke Risk, Aspirin Compared With Placebo, Stratified by Dose and Sorted by Trial End Year



Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis; ASA = aspirin; ASCEND = A Study of Cardiovascular Events in Diabetes; ASPREE = Aspirin in Reducing Events in the Elderly; BMD = British Male Doctors; CG = control group; CI = confidence interval; IG = intervention group; JPAD = Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; JPPP = Japanese Primary Prevention Project; mg = milligram; n = number of participants; OR = odds ratio; PHS = Physician's Health Study

Figure 17. Key Question 1: Pooled Analysis of CVD Mortality Risk, Aspirin Compared With Placebo, Stratified by Dose and Sorted by Trial End Year

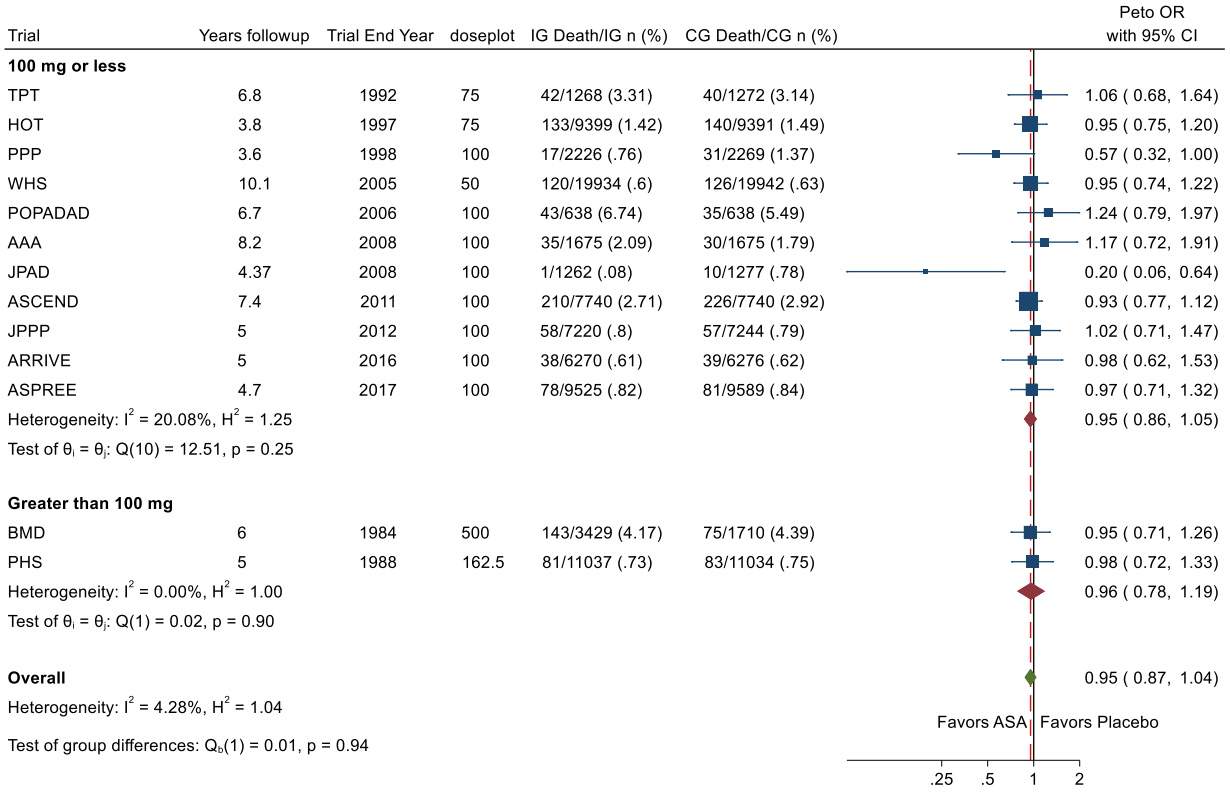


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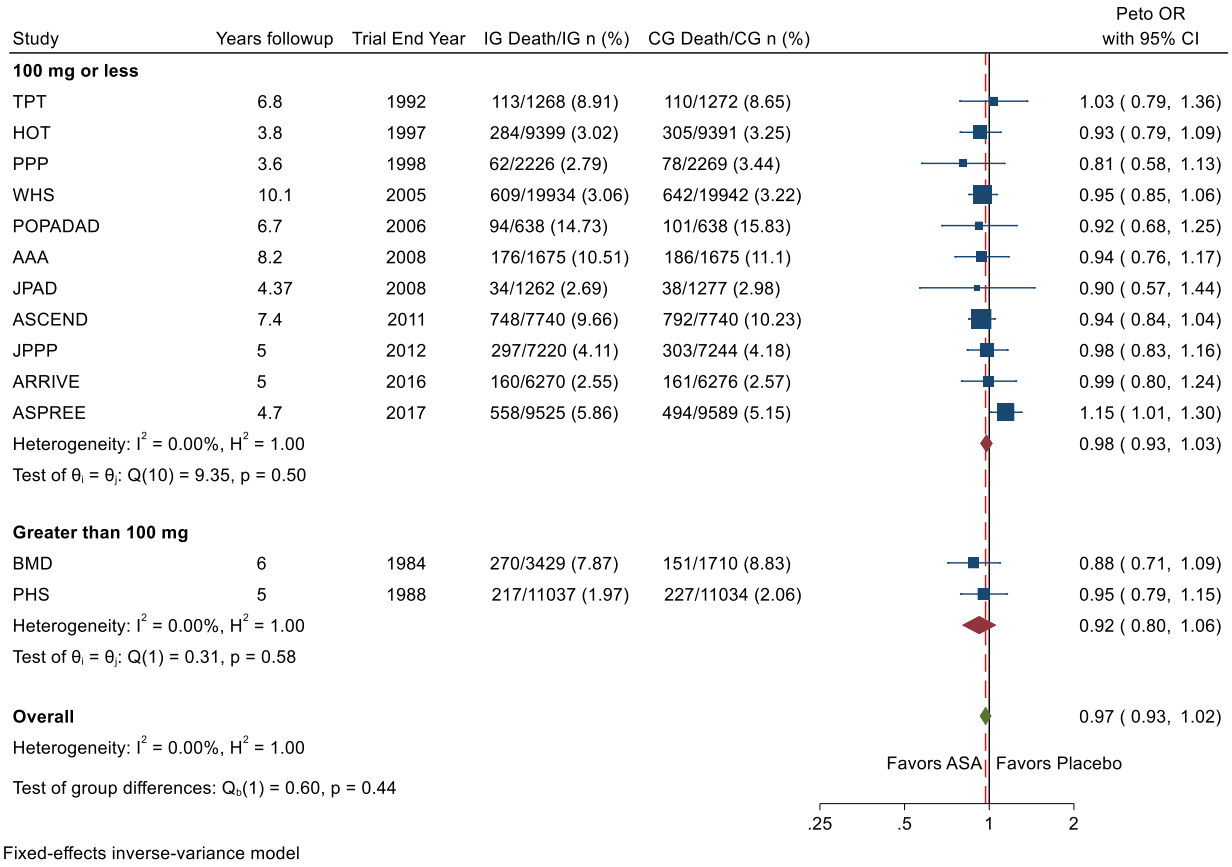
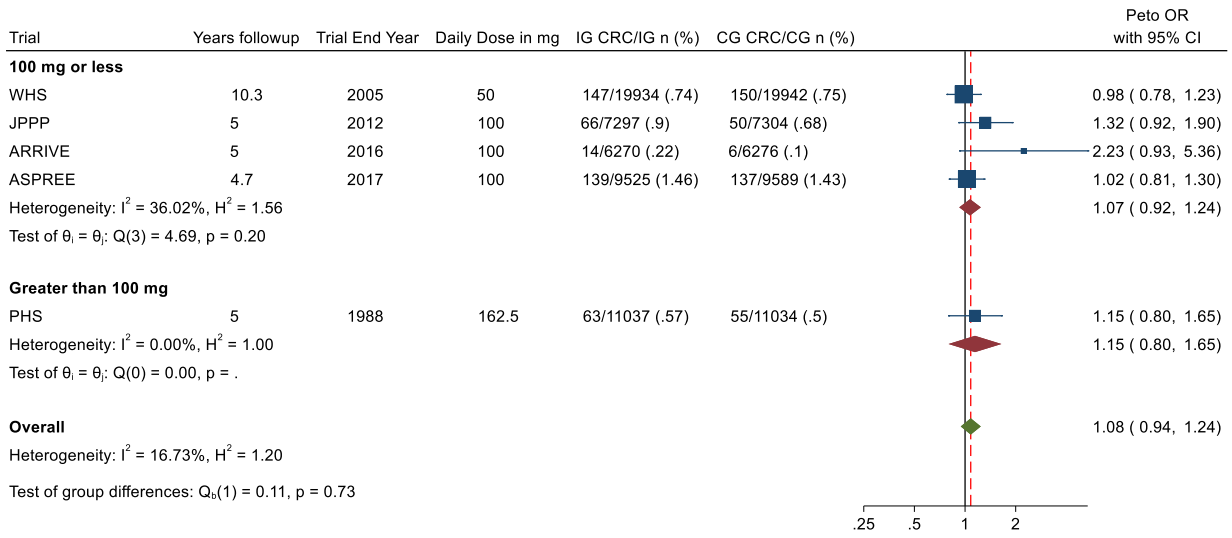
Figure 18. Key Question 1: Pooled Analysis of All-Cause Mortality Risk, Aspirin Compared With Placebo, Stratified by Daily Dose and Sorted by Trial End Year



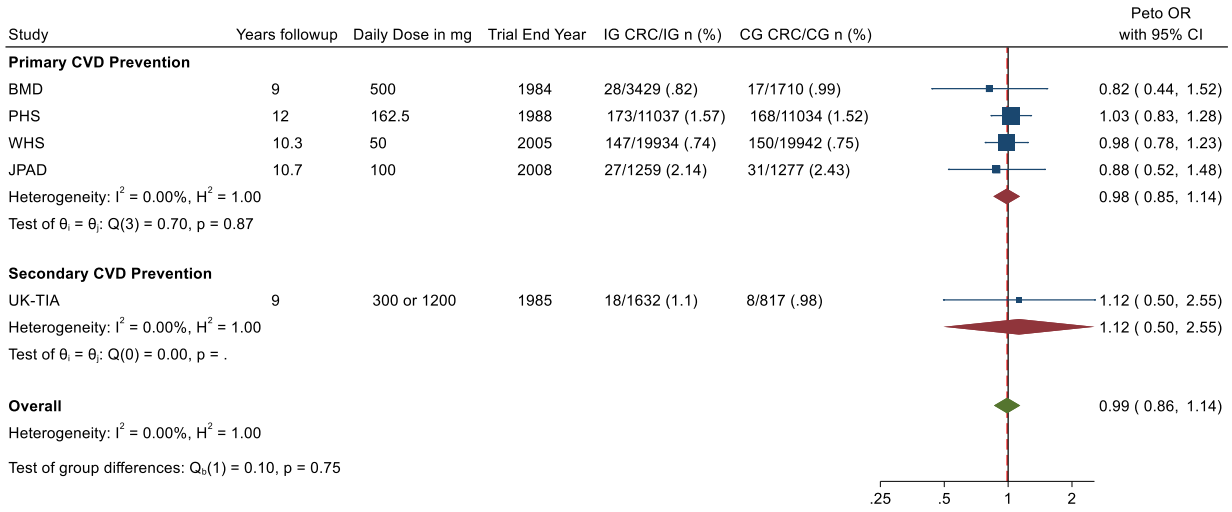
Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis; ARRIVE = Aspirin to Reduce Risk of Initial Vascular Events; ASA = aspirin; ASCEND = A Study of Cardiovascular Events in Diabetes; ASPREE = Aspirin in Reducing Events in the Elderly; BMD = British Male Doctors; CG = control group; CI = confidence interval; HOT = Hypertension Optimal Treatment Study; IG = intervention group; JPAD = Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; JPPP = Japanese Primary Prevention Project; mg = milligram; n = number of participants; OR = odds ratio; PHS = Physician's Health Study; POPADAD = The Prevention of Progression of Arterial Disease and Diabetes trial; PPP = Primary Prevention Project; TPT Thrombosis Prevention Trial; WHS = Women's Health Study

Figure 19. Key Question 1: Pooled Analysis of CRC Incidence Risk During the Trial Phase of Primary CVD Prevention RCTs From 5 to 10 Years, Aspirin Compared With Placebo, Stratified by Dose and Sorted by Trial End Year



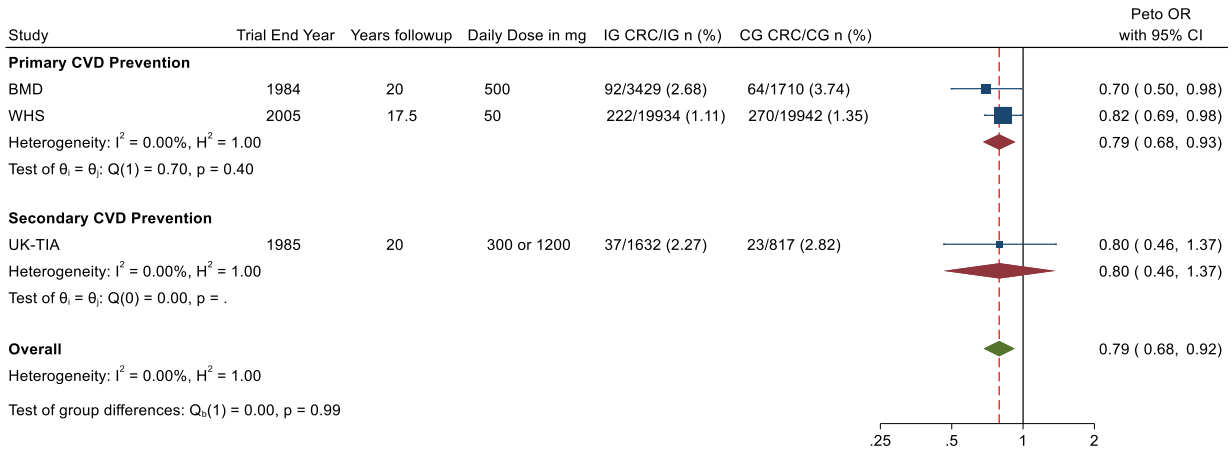
Abbreviations: ARRIVE = Aspirin to Reduce Risk of Initial Vascular Events; ASPREE = Aspirin in Reducing Events in the Elderly; CG = control group; CI = confidence interval; CRC = colorectal cancer; IG = intervention group; JPPP = Japanese Primary Prevention Project; mg = milligram; n = number of participants; OR = odds ratio; PHS = Physician's Health Study; WHS = Women's Health Study

Figure 20. Key Question 1: Pooled Analysis of CRC Incidence Risk During the Trial or Observational Phases of Primary and Secondary CVD Prevention Studies at Approximately 10 Years' Followup, Aspirin Compared With Placebo, Stratified by Dose and Sorted by Trial End Year



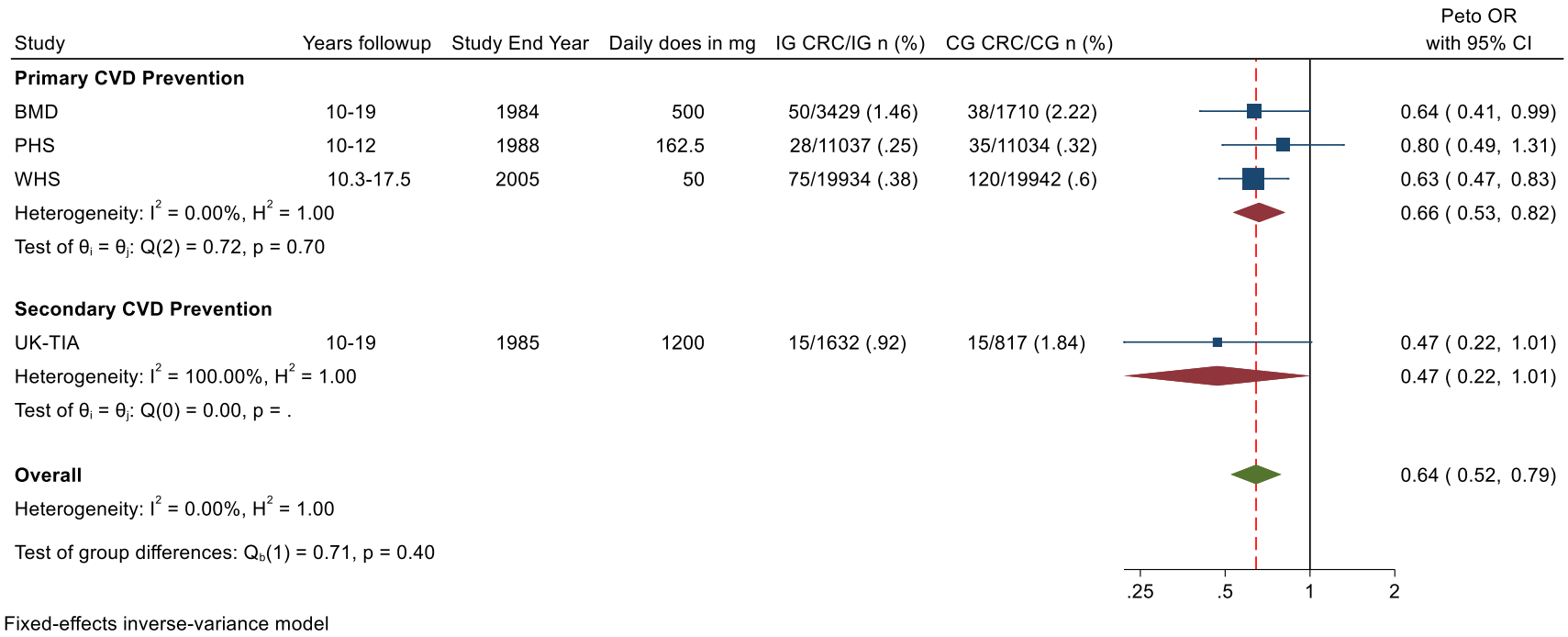
Abbreviations: BMD = British Male Doctors; CG = control group; CI = confidence interval; CRC = colorectal cancer; IG = intervention group; JPAD = Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; mg = milligram; n = number of participants; OR = odds ratio; PHS = Physician's Health Study; UK-TIA = United Kingdom Transient Ischaemic Attack; WHS = Women's Health Study

Figure 21. Key Question 1: Pooled Analysis of CRC Incidence Risk During the Trial and Observational Phases of Primary and Secondary CVD Prevention Studies Up to 20 Years, Aspirin Compared With Placebo, Stratified by Dose and Sorted by Trial End Year



Abbreviations: BMD = British Male Doctors; CG = control group; CI = confidence interval; CRC = colorectal cancer; IG = intervention group; mg = milligram; n = number of participants; OR = odds ratio; UK-TIA = United Kingdom Transient Ischaemic Attack; WHS = Women's Health Study

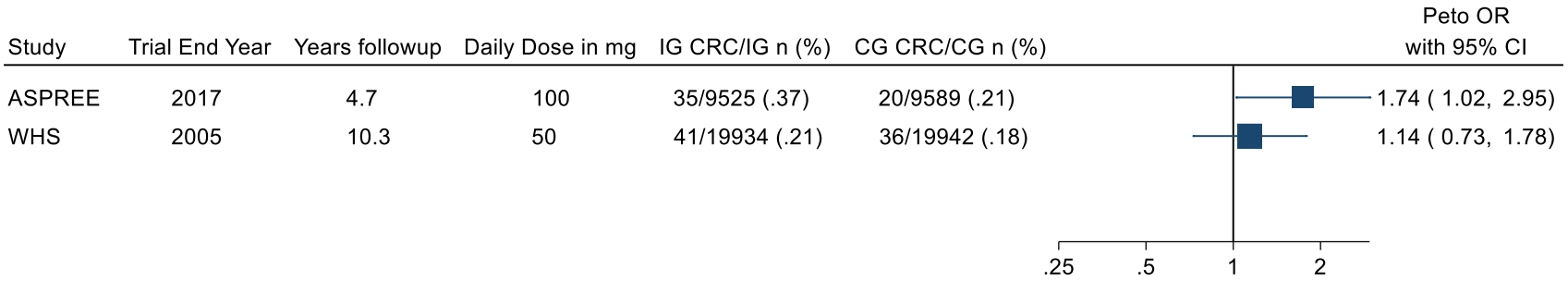
Figure 22. Key Question 1: Pooled Analysis of CRC Incidence Risk During the Observational Phases of Primary and Secondary CVD Prevention Studies From 10 to 19 Years,* Aspirin Compared With Placebo, Stratified by Dose and Sorted by Trial End Year



* Does not include any CRC cases that occurred prior to 10 years of followup.

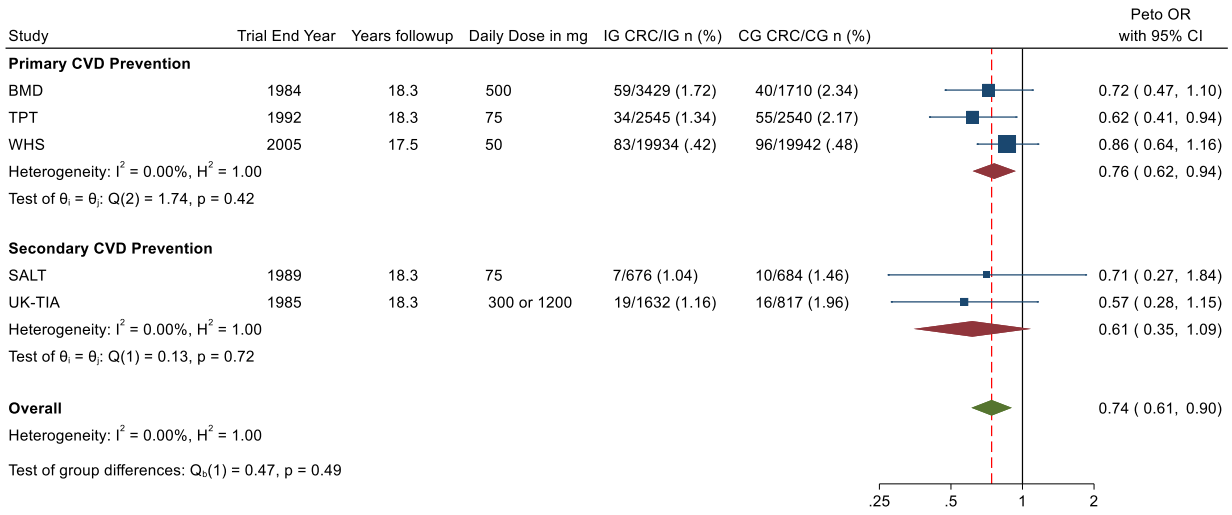
Abbreviations: BMD = British Male Doctors; CG = control group; CI = confidence interval; CRC = colorectal cancer; IG = intervention group; mg = milligram; n = number of participants; OR = odds ratio; PHS = Physician's Health Study; UK-TIA = United Kingdom Transient Ischaemic Attack; WHS = Women's Health Study

Figure 23. Key Question 1: Pooled Analysis of CRC Mortality Risk During the Trial Phase of Primary CVD Prevention Studies From 5 to 10 Years, Aspirin Compared With Placebo, Stratified by Dose and Sorted by Trial End Year



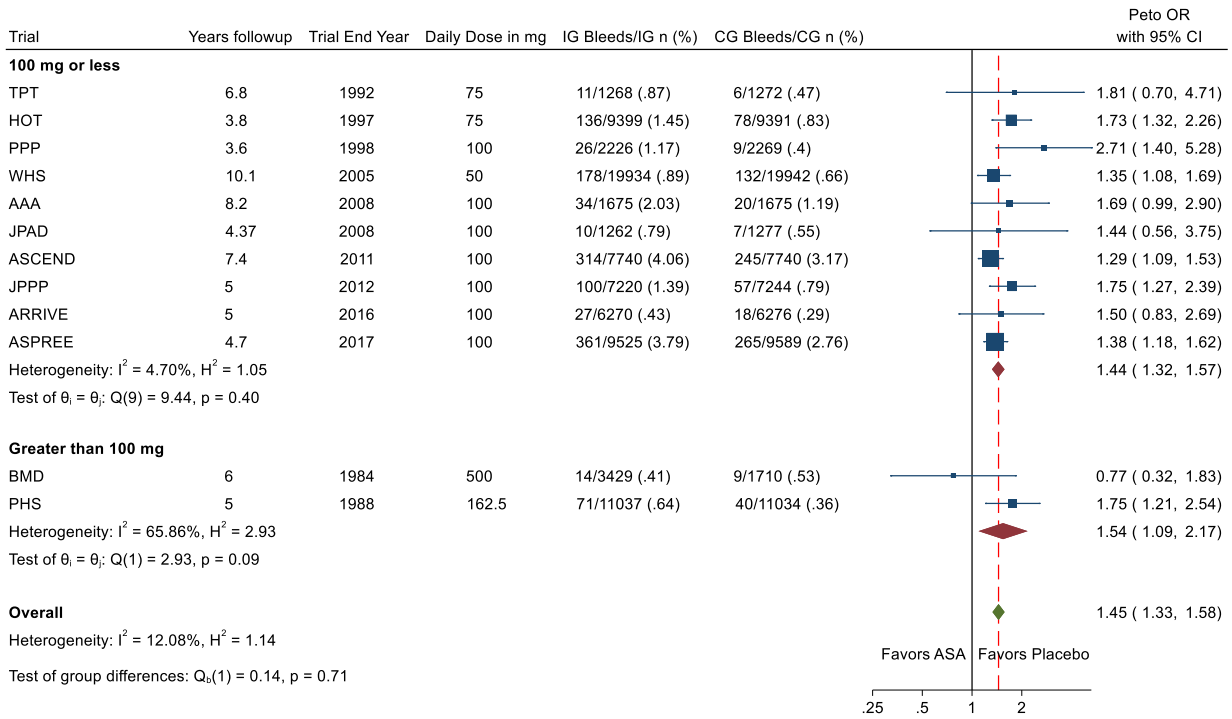
Abbreviations: ASPREE = Aspirin in Reducing Events in the Elderly; CG = control group; CI = confidence interval; CRC = colorectal cancer; IG = intervention group; mg = milligram; n = number of participants; OR = odds ratio; WHS = Women's Health Study

Figure 24. Key Question 1: Pooled Analysis of CRC Mortality Risk During the Trial and Observational Phases of Primary and Secondary CVD Prevention Studies Up to 18 Years, Aspirin Compared With Placebo, Stratified by Dose and Sorted by Trial End Year



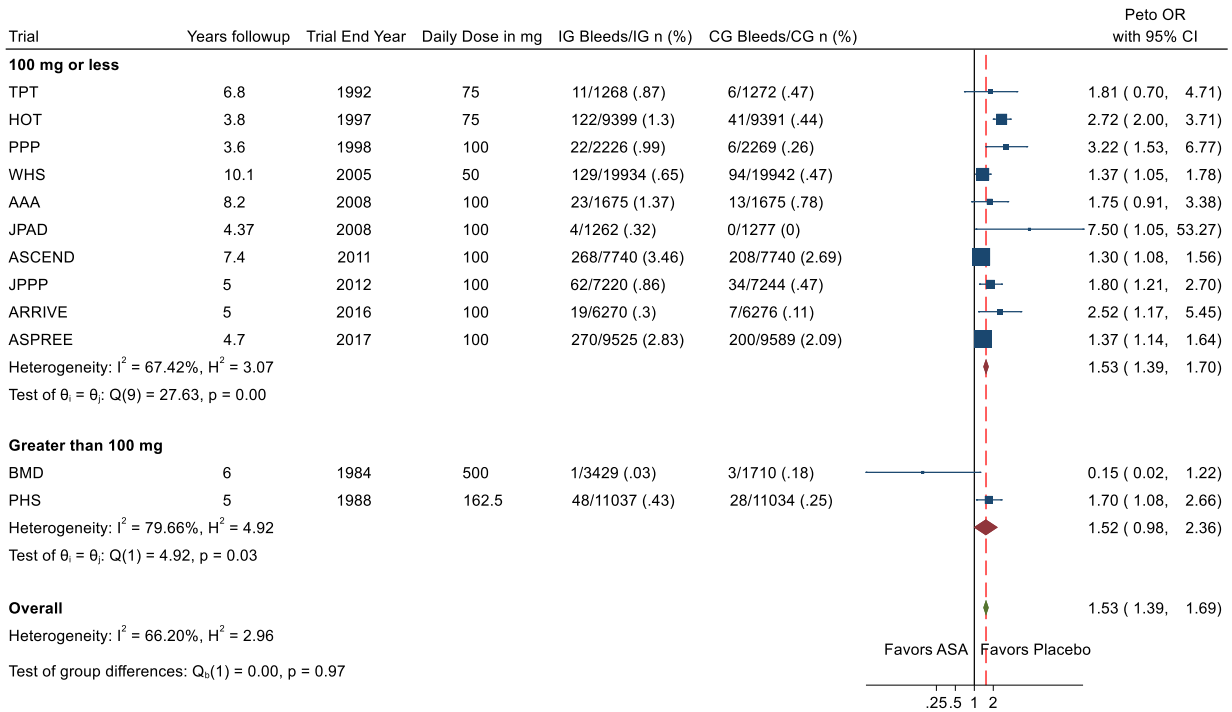
Abbreviations: BMD = British Male Doctors; CG = control group; CI = confidence interval; CRC = colorectal cancer; IG = intervention group; mg = milligram; n = number of participants; OR = odds ratio; SALT = Swedish Aspirin Low-dose Trial; TPT Thrombosis Prevention Trial; UK-TIA = United Kingdom Transient Ischaemic Attack; WHS = Women's Health Study

Figure 25. Key Question 2: Pooled Analysis of Total Major Bleed Risk, Aspirin Compared With Placebo, Stratified by Daily Dose and Sorted by Trial End Year



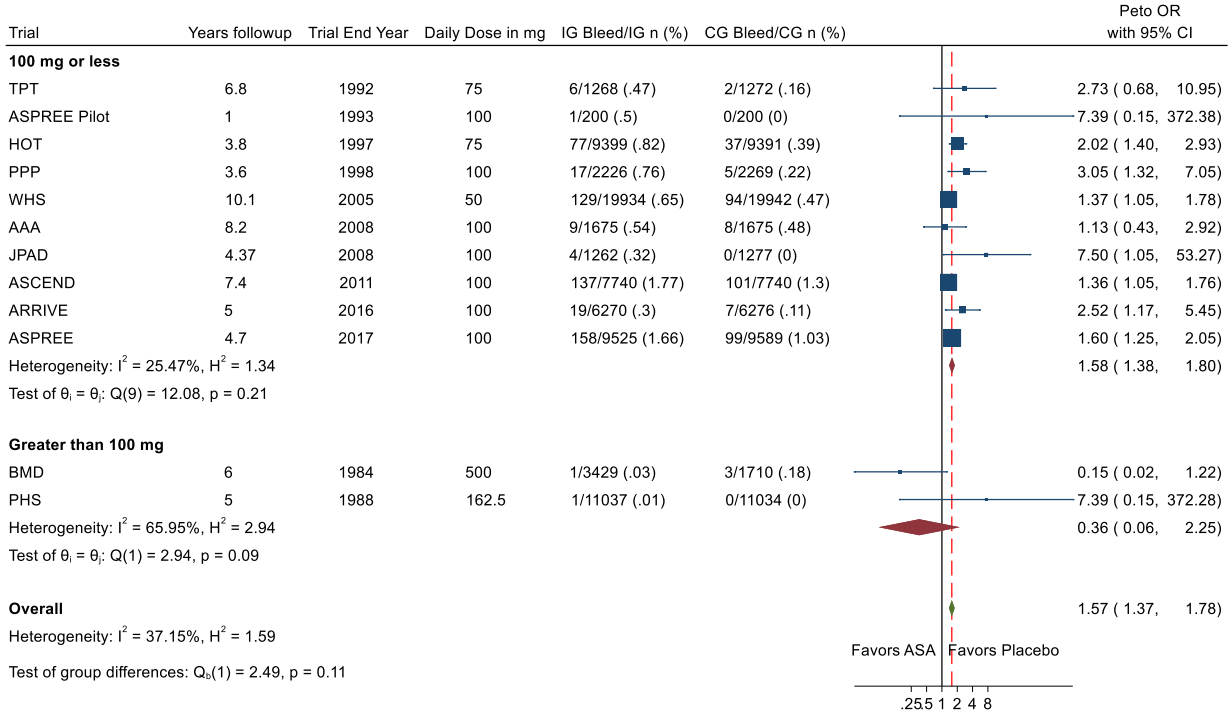
Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis; ARRIVE = Aspirin to Reduce Risk of Initial Vascular Events; ASA = aspirin; ASCEND = A Study of Cardiovascular Events in Diabetes; ASPREE = Aspirin in Reducing Events in the Elderly; BMD = British Male Doctors; CG = control group; CI = confidence interval; HOT = Hypertension Optimal Treatment Study; IG = intervention group; JPAD = Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; JPPP = Japanese Primary Prevention Project; mg = milligram; n = number of participants; OR = odds ratio; PHS = Physician's Health Study; PPP = Primary Prevention Project; TPT Thrombosis Prevention Trial; WHS = Women's Health Study

Figure 26. Key Question 2: Pooled Analysis of Extracranial Bleed Risk, Aspirin Compared With Placebo, Stratified by Daily Dose and Sorted by Trial End Year



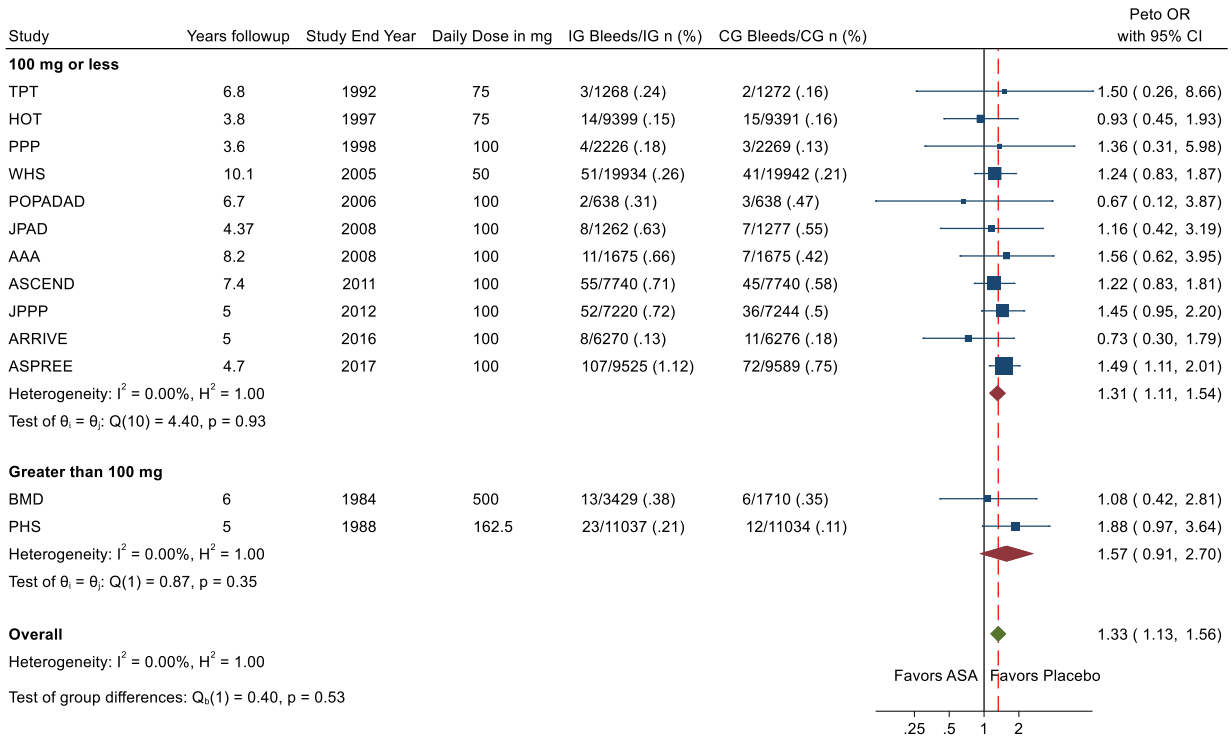
Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis; ARRIVE = Aspirin to Reduce Risk of Initial Vascular Events; ASA = aspirin; ASCEND = A Study of Cardiovascular Events in Diabetes; ASPREE = Aspirin in Reducing Events in the Elderly; BMD = British Male Doctors; CG = control group; CI = confidence interval; HOT = Hypertension Optimal Treatment Study; IG = intervention group; JPAD = Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; JPPP = Japanese Primary Prevention Project; mg = milligram; n = number of participants; OR = odds ratio; PHS = Physician's Health Study; PPP = Primary Prevention Project; TPT Thrombosis Prevention Trial; WHS = Women's Health Study

Figure 27. Key Question 2: Pooled Analysis of Major GI Bleed Risk, Aspirin Compared With Placebo, Stratified by Daily Dose and Sorted by Trial End Year



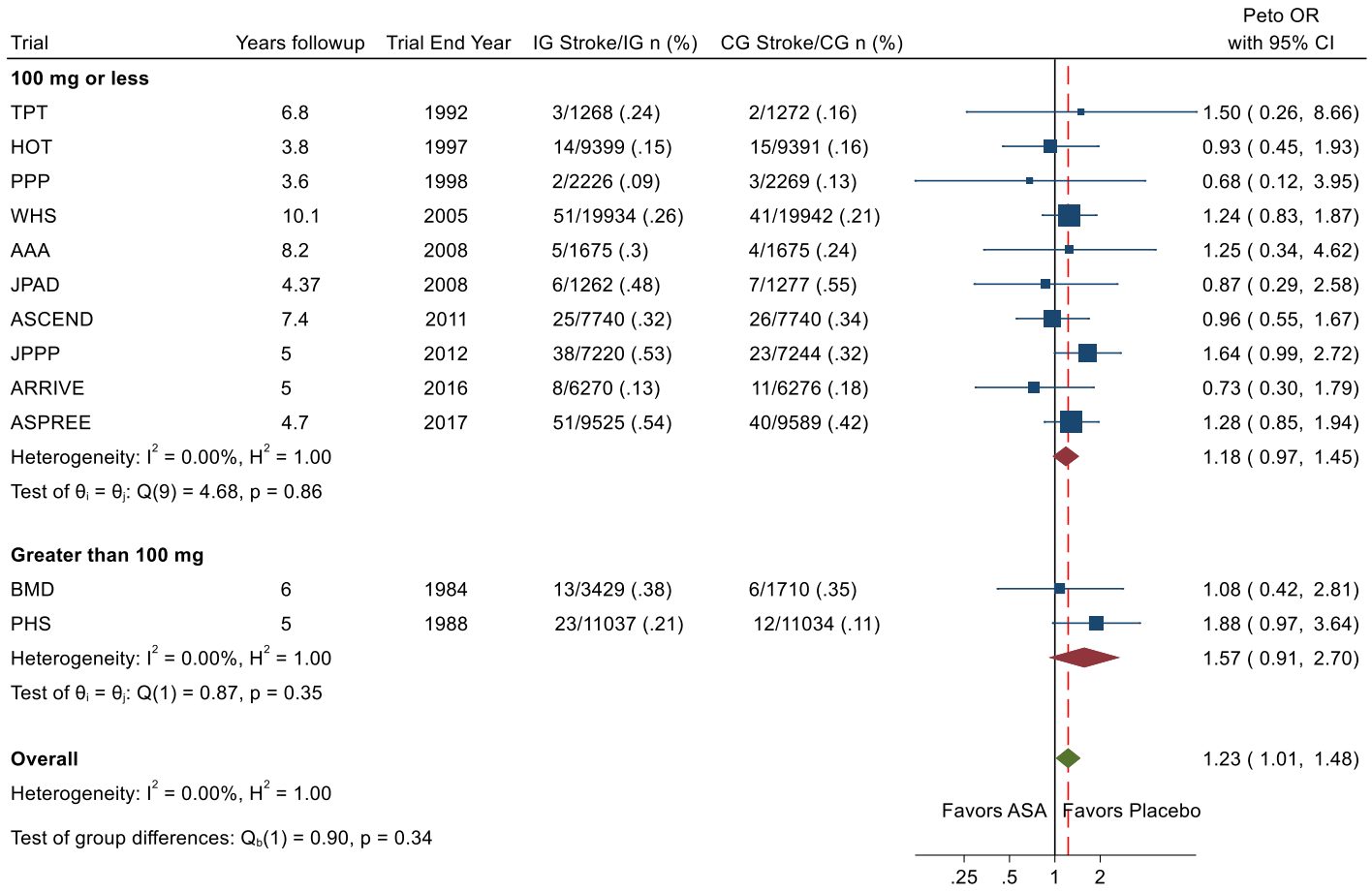
Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis; ARRIVE = Aspirin to Reduce Risk of Initial Vascular Events; ASA = aspirin; ASCEND = A Study of Cardiovascular Events in Diabetes; ASPREE = Aspirin in Reducing Events in the Elderly; BMD = British Male Doctors; CG = control group; CI = confidence interval; GI = gastrointestinal; HOT = Hypertension Optimal Treatment Study; IG = intervention group; JPAD = Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; JPPP = Japanese Primary Prevention Project; mg = milligram; n = number of participants; OR = odds ratio; PHS = Physician's Health Study; PPP = Primary Prevention Project; TPT Thrombosis Prevention Trial; WHS = Women's Health Study

Figure 28. Key Question 2: Pooled Analysis of Total Intracranial Bleed Risk, Aspirin Compared With Placebo, Stratified by Dose and Sorted by Trial End Year



Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis; ARRIVE = Aspirin to Reduce Risk of Initial Vascular Events; ASA = aspirin; ASCEND = A Study of Cardiovascular Events in Diabetes; ASPREE = Aspirin in Reducing Events in the Elderly; BMD = British Male Doctors; CG = control group; CI = confidence interval; HOT = Hypertension Optimal Treatment Study; IG = intervention group; JPAD = Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; JPPP = Japanese Primary Prevention Project; mg = milligram; n = number of participants; OR = odds ratio; PHS = Physician's Health Study; POPADAD = The Prevention of Progression of Arterial Disease and Diabetes trial; PPP = Primary Prevention Project; TPT Thrombosis Prevention Trial; WHS = Women's Health Study

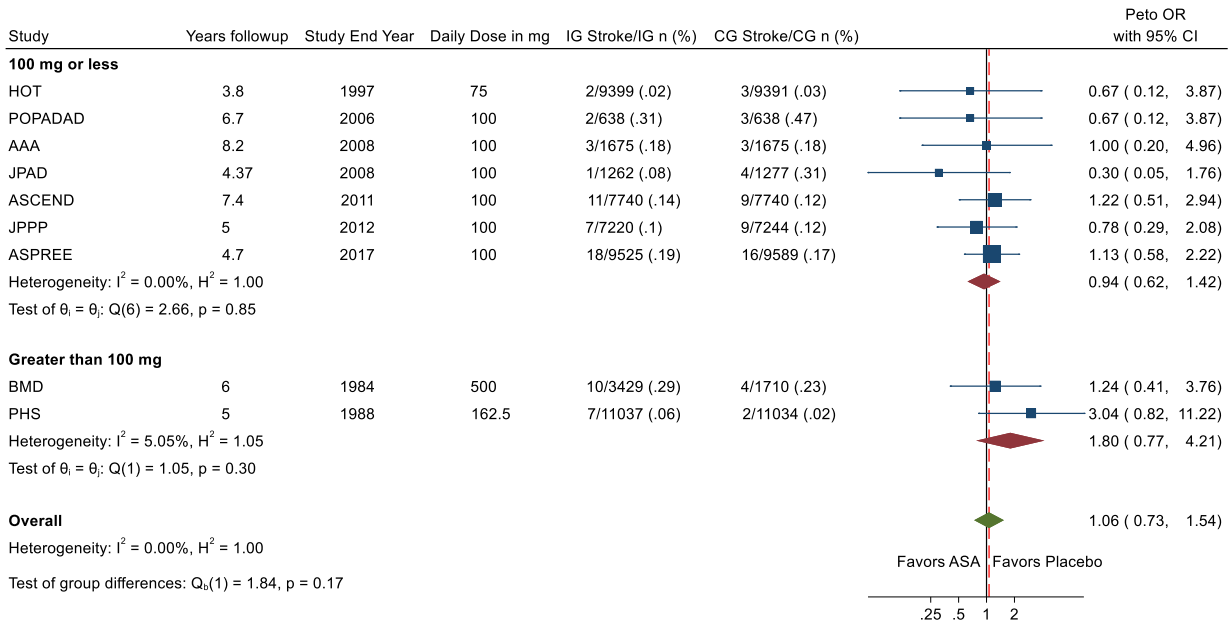
Figure 29. Key Question 2: Pooled Analysis of Total Hemorrhagic Stroke* Risk, Aspirin Compared With Placebo, Stratified by Daily Dose and Sorted by Trial End Year



***** Includes neurological deficits as a result of intracerebral hemorrhage and subarachnoid hemorrhage.

Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis; ARRIVE = Aspirin to Reduce Risk of Initial Vascular Events; ASA = aspirin; ASCEND = A Study of Cardiovascular Events in Diabetes; ASPREE = Aspirin in Reducing Events in the Elderly; BMD = British Male Doctors; CG = control group; CI = confidence interval; HOT = Hypertension Optimal Treatment Study; IG = intervention group; JPAD = Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; JPPP = Japanese Primary Prevention Project; mg = milligram; n = number of participants; OR = odds ratio; PHS = Physician's Health Study; PPP = Primary Prevention Project; TPT Thrombosis Prevention Trial; WHS = Women's Health Study

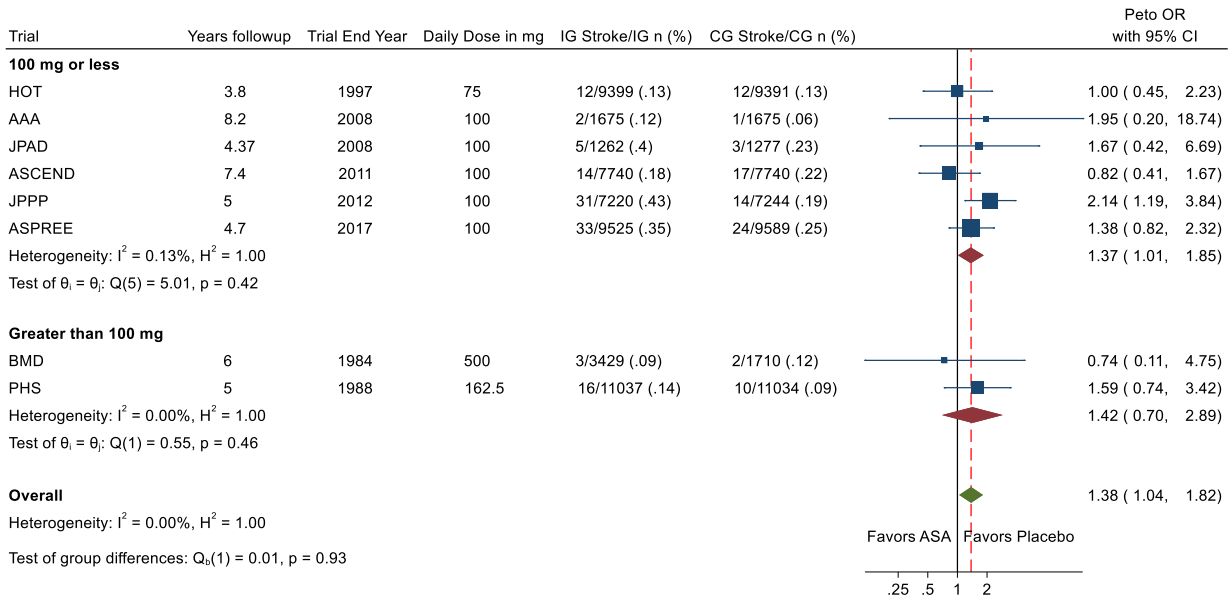
Figure 30. Key Question 2: Pooled Analysis of Fatal Hemorrhagic Stroke* Risk, Aspirin Compared With Placebo, Stratified by Dose and Sorted by Trial End Year



***** Includes neurological deficits as a result of intracerebral hemorrhage and subarachnoid hemorrhage.

Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis; ASA = aspirin; ASCEND = A Study of Cardiovascular Events in Diabetes; ASPREE = Aspirin in Reducing Events in the Elderly; BMD = British Male Doctors; CG = control group; CI = confidence interval; CVD = cardiovascular disease; HOT = Hypertension Optimal Treatment Study; IG = intervention group; JPAD = Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; JPPP = Japanese Primary Prevention Project; mg = milligram; n = number of participants; OR = odds ratio; PHS = Physician's Health Study; POPADAD = The Prevention of Progression of Arterial Disease and Diabetes trial

Figure 31. Key Question 2: Pooled Analysis of Nonfatal Hemorrhagic Stroke* Risk, Aspirin Compared With Placebo, Stratified by Daily Dose and Sorted by Trial End Year



***** Includes neurological deficits as a result of intracerebral hemorrhage and subarachnoid hemorrhage.

Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis; ASA = aspirin; ASCEND = A Study of Cardiovascular Events in Diabetes; ASPREE = Aspirin in Reducing Events in the Elderly; BMD = British Male Doctors; CG = control group; CI = confidence interval; CVD = cardiovascular disease; HOT = Hypertension Optimal Treatment Study; IG = intervention group; JPAD = Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; JPPP = Japanese Primary Prevention Project; mg = milligram; n = number of participants; OR = odds ratio; PHS = Physician's Health Study

Table 1. Prevalence of CVD (CHD, HF, and Stroke) by Age From NHANES 2015-2018[7]

Age, years	Males, %	Females, %
20-39	1.1	1.2
40-59	8.6	8.4
60-79	27.1	18.2
80+	42.9	31.3

Abbreviations: CHD = coronary heart disease; CVD = cardiovascular disease; HF = heart failure; NHANES = National Health and Nutrition Examination Survey

Table 2. Age-Adjusted Prevalence of CVD (CHD, HF, and Stroke) in Adults Age ≥20 Years by Race and Ethnicity From NHANES 2015-2018[7]

Race and Ethnicity	Males, %	Females, %
All	10.4	8.4
Non-Hispanic White	10.4	7.8
Black	11.0	11.5
Hispanic	8.7	8.1
Asian	6.8	4.2
American Indian/Alaska Native	Not reported	Not reported

Abbreviations: CHD = coronary heart disease; CVD = cardiovascular disease; HF = heart failure; NHANES = National Health and Nutrition Examination Survey

Table 3. Recommendations of Others for the Primary Prevention of CVD Using Aspirin

Organization/Professional Society	Year	Recommendation
American Diabetes Association (ADA)[196]	2020	Aspirin therapy (75–162 mg/day) may be considered as a primary prevention strategy in those with diabetes who are at increased cardiovascular risk, after a comprehensive discussion with the patient on the benefits versus the comparable increased risk of bleeding. Recommendations for using aspirin as primary prevention include both men and women aged ≥50 years with diabetes and at least one additional major risk factor (family history of premature ASCVD, hypertension, dyslipidemia, smoking, or chronic kidney disease/albuminuria) who are not at increased risk of bleeding (e.g., older age, anemia, renal disease). Noninvasive imaging techniques such as coronary calcium scoring may potentially help further tailor aspirin therapy, particularly in those at low risk. For patients over the age of 70 years (with or without diabetes), the balance appears to have greater risk than benefit. Thus, for primary prevention, the use of aspirin needs to be carefully considered and may generally not be recommended. Aspirin may be considered in the context of high cardiovascular risk with low bleeding risk, but generally not in older adults. Aspirin therapy for primary prevention may be considered in the context of shared decision-making, which carefully weighs the cardiovascular benefits with the fairly comparable increase in risk of bleeding.
American College of Cardiology/American Heart Association (ACC/AHA)[24]	2019	Low-dose aspirin (75 to 100 mg/day) might be considered for the primary prevention of ASCVD among select adults 40 to 70 years of age at higher CVD risk but not at increased bleeding risk. Low-dose aspirin use is not recommended on a routine basis for primary prevention of CVD in adults over 70 years, or among adults of any age who are at increased risk of bleeding.
NICE Clinical Knowledge Summaries[36]	2018	Do not routinely prescribe antiplatelet treatment for the primary prevention of CVD. Consider prescribing aspirin in people with a high risk of stroke or myocardial infarction.
American Academy of Family Physicians (AAFP)[197]	2016	Previous and current recommendations from the AAFP regarding aspirin use reflect those of the USPSTF.
Scottish Intercollegiate Guidelines Network (SIGN)[38]	2017	Aspirin is not recommended for primary prevention of cardiovascular disease.
European Guidelines on CVD Prevention in Clinical Practice[37]	2016	Antiplatelet therapy is not recommended in individuals without CVD due to the increased risk of major bleeding. Antiplatelet therapy (e.g. with aspirin) is not recommended for people with DM who do not have CVD.

Abbreviations: ASCVD = atherosclerotic cardiovascular disease; CVD = cardiovascular disease; mg = milligram; DM = diabetes mellitus; USPSTF = United States Preventive Services Task Force

Table 4. Recommendations of Others for the Primary Prevention of CRC Using Aspirin

Organization/Professional Society	Year	Recommendation
American College of Gastroenterology (ACG)[41]	2021	Low-dose aspirin in individuals between ages 50–69 years with a cardiovascular disease risk of ≥10% over the next 10 years, who are not at an increased risk for bleeding and willing to take aspirin for at least 10 years may be considered to reduce the risk of CRC. Aspirin as a substitute for CRC screening is not recommended.
American Gastroenterological Association (AGA)[42]	2021	In individuals at average risk for CRC who are 1) younger than 70 years with a life expectancy of at least 10 years, 2) have a 10-year cardiovascular disease risk of at least 10%, and 3) not at high risk for bleeding, clinicians should use low-dose aspirin to reduce CRC incidence and mortality. In individuals with a history of CRC, clinicians should consider using aspirin to prevent recurrent colorectal neoplasia. In individuals at average risk for CRC, clinicians should not use non-aspirin NSAIDs to prevent colorectal neoplasia because of a substantial risk of cardiovascular and gastrointestinal adverse events.
American Cancer Society (ACS)[198, 199]	2019	The ACS has not formally reviewed evidence or released an official guideline advocating for or against aspirin use but has publicly acknowledged that long-term regular aspirin use has both harms and benefits, including reducing risk for CRC.
Cancer Council of Australia (CCA)[40]	2019	For all people aged 50–70 years who are at average risk of colorectal cancer, aspirin should be actively considered to prevent colorectal cancer. A low dose (100–300 mg per day) is recommended for at least 2.5 years, commencing at age 50 to 70 years. The benefit may extend to older ages with longer duration of use. Benefit for cancer prevention (though shorter for cardiovascular risk) is evident only 10 years after initiation so a life expectancy of at least 10 years should be taken into consideration in the advice to use aspirin. The choice to take aspirin should be personalized based on age, sex and potential reduction in cardiovascular events, cerebrovascular events and thrombotic stroke. The individual should take into account the potential risks of taking aspirin. Aspirin should be avoided in patients with current dyspepsia, any history of peptic ulcer, aspirin allergy, bleeding diathesis, an increased risk of gastrointestinal hemorrhage (such as associated with use of oral anticoagulants or antiplatelet agents), or renal impairment. The benefit in colorectal cancer risk reduction in women over 65 is less clear cut. However, based on limited data available, older women with cardiovascular risk factors may derive a greater overall benefit than harm. People who are at high risk of colorectal cancer due to Lynch Syndrome carrier status should be advised to begin aspirin from the commencement of their colonoscopy screening (usually at age 25 years). Non-syndromic familial cancer patients should be actively considered for aspirin, bearing in mind the possibility of adverse events. 600 mg/day has been shown to be effective, but lower dose (100 mg/day) may be as effective and is recommended based on the data available at the time of the systematic review.
National Institute for Health and Care Excellence (NICE)*[200]	2020	Patients diagnosed with Lynch Syndrome should begin daily aspirin therapy to reduce risk of CRC. No statement regarding aspiring for CRC prevention in other populations has been made.
National Comprehensive Care Network (NCCN)	2015	Aspirin should only be used for patients at increased risk of CRC.

*****Update in progress

Abbreviations: CRC = colorectal cancer; mg = milligram

Table 5. Pooled Estimates for KQ1 and KQ2 Outcomes for Primary and Sensitivity Analyses

Outcome	Analysis	k	n	Peto Fixed Effects OR (95% CI)	I^2	Mantel-Haenszel Fixed Effects RR (95% CI)	I^2	Restricted Maximum Likelihood Random Effects (95% CI)	I^2
Major CVD events (nonfatal MI, nonfatal stroke, CVD mortality)	All	13	161,680	0.89 (0.85, 0.94)	0	0.90 (0.86, 0.94)	0	0.90 (0.86, 0.95)	0
	≤100 mg	11	134,470	0.90 (0.85, 0.95)	0	0.90 (0.86, 0.95)	0	0.90 (0.86,0.95)	0
	Prior statins	5	55,574	0.84 (0.77, 0.92)	0	0.85 (0.78, 0.93)	1.9	0.85 (0.78, 0.93)	0
	Statin use	8	106,106	0.92 (0.87, 0.98)	0	0.93 (0.87, 0.98)	0	0.93 (0.87, 0.98)	0
Total MI Events	All	13	161,680	0.86 (0.80, 0.92)	45.7	0.86 (0.81, 0.92)	47.0	0.86 (0.78, 0.95)	47.8
	≤100 mg	11	134,470	0.89 (0.82, 0.96)	26.8	0.89 (0.83, 0.96)	28.0	0.89 (0.81, 0.97)	26.1
	Prior statins	5	53,035	0.75 (0.67, 0.83)	16.6	0.75 (0.67, 0.84)	23.6	0.76 (0.66, 0.87)	31.8
	Statin use	8	108,645	0.94 (0.86, 1.02)	6.0	0.94 (0.86, 1.02)	6.8	0.94 (0.86, 1.02)	0
Fatal MI Events	All	13	161,680	0.91 (0.80, 1.03)	18.0	0.91 (0.81, 1.03)	3.7	0.92 (0.81, 1.04)	0
	≤100 mg	11	134,470	0.91 (0.79, 1.06)	31.0	0.92 (0.79, 1.06)	18.8	0.92 (0.80, 1.07)	0
	Prior statins	5	53,035	0.92 (0.77, 1.09)	0	0.92 (0.77, 1.09)	0	0.92 (0.77, 1.09)	0
	Statin use	8	108,645	0.90 (0.75, 1.08)	49.5	0.91 (0.76, 1.08)	40.2	0.93 (0.72, 1.21)	33.8
Nonfatal MI Events	All	13	161,680	0.83 (0.76, 0.90)	62.1	0.83 (0.77, 0.90)	62.3	0.82 (0.72, 0.94)	60.5
	≤100 mg	11	134,470	0.88 (0.80, 0.96)	44.2	0.88 (0.81, 0.96)	43.9	0.86 (0.75, 0.98)	44.4
	Prior statins	5	53,035	0.64 (0.56, 0.74)	28.4	0.64 (0.56, 0.74)	32.4	0.66 (0.55, 0.80)	36.4
	Statin use	8	108,645	0.95 (0.86, 1.05)	0	0.95 (0.86, 1.05)	0	0.95 (0.86, 1.05)	0
Total Stroke (all types)	All	13	161,680	0.94 (0.87, 1.01)	0	0.94 (0.87, 1.01)	0	0.94 (0.87, 1.01)	0
	≤100 mg	11	134,470	0.91 (0.84, 0.99)	0	0.91 (0.84, 0.99)	0	0.91 (0.84, 0.99)	0
	Prior statins	5	53,035	1.03 (0.89, 1.20)	26.3	1.03 (0.89, 1.20)	25.6	1.03 (0.88, 1.21)	7.4
	Statin use	8	108,645	0.91 (0.83, 0.99)	0	0.91 (0.84, 0.99)	0	0.91 (0.84, 0.99)	0
Fatal Stroke	All	11	130,344	0.98 (0.78, 1.22)	12.4	0.98 (0.78, 1.22)	1.1	1.00 (0.80, 1.25)	0

Table 5. Pooled Estimates for KQ1 and KQ2 Outcomes for Primary and Sensitivity Analyses

Outcome	Analysis	k	n	Peto Fixed Effects OR (95% CI)	I^2	Mantel-Haenszel Fixed Effects RR (95% CI)	I^2	Restricted Maximum Likelihood Random Effects (95% CI)	I^2
(all types)	≤100 mg	9	103,134	0.92 (0.72, 1.18)	20.0	0.92 (0.72, 1.18)	10.2	0.95 (0.74, 1.21)	0
	Prior statins	4	34,245	1.10 (0.67, 1.81)	36.1	1.10 (0.67, 1.83)	19.1	1.18 (0.70, 2.01)	0
	Statin use	7	96,099	0.95 (0.74, 1.22)	6.9	0.95 (0.74, 1.22)	0	0.96 (0.75, 1.24)	0
Nonfatal Stroke (all types)	All	11	130,344	0.92 (0.84, 1.00)	0	0.92 (0.84, 1.00)	0	0.92 (0.84, 1.01)	8.2
	≤100 mg	9	103,134	0.88 (0.80, 0.97)	0	0.88 (0.80, 0.97)	0	0.88 (0.80, 0.97)	0
	Prior statins	4	34,245	1.06 (0.86, 1.31)	19.8	1.06 (0.86, 1.31)	18.8	1.04 (0.81, 1.33)	17.6
	Statin use	7	96,099	0.89 (0.81, 0.98)	0	0.89 (0.81, 0.98)	0	0.89 (0.81, 0.98)	0
Total Ischemic Stroke	All	7	106,554	0.86 (0.77, 0.97)	16.0	0.86 (0.77, 0.97)	14.7	0.87 (0.77, 0.98)	10.1
	≤100 mg	5	79,334	0.82 (0.72, 0.92)	0	0.82 (0.72, 0.93)	0	0.82 (0.72, 0.93)	0
	Prior statins	3	29,750	1.05 (0.81, 1.37)	42.5	1.05 (0.81, 1.37)	41.1	1.01 (0.67, 1.53)	34.0
	Statin use	4	76,804	0.82 (0.73, 0.94)	0	0.83 (0.73, 0.94)	0	0.83 (0.73, 0.94)	0
Fatal Ischemic Stroke	All	6	65,414	0.80 (0.50, 1.29)	13.0	0.80 (0.50, 1.29)	8.4	0.80 (0.45, 1.40)	14.5
	≤100 mg	4	38,204	0.71 (0.42, 1.22)	38.9	0.71 (0.41, 1.23)	37.6	0.61 (0.27, 1.39)	40.6
	Prior statins	2	27,210	1.18 (0.44, 3.18)	0	1.19 (0.43, 3.29)	0	1.18 (0.43, 3.29)	0
	Statin use	4	38,204	0.71 (0.42, 1.22)	38.9	0.71 (0.41, 1.23)	37.6	0.61 (0.27, 1.39)	40.6
Nonfatal Ischemic Stroke	All	7	82,157	0.92 (0.82, 1.03)	0	0.92 (0.82, 1.03)	0	0.92 (0.82, 1.03)	0
	≤100 mg	5	54,947	0.88 (0.78, 1.00) *[Note: p<0.05]*	0	0.88 (0.78, 1.00) *[Note: p<0.05]*	0	0.88 (0.78, 1.00)	0
	Prior statins	2	27,210	1.15 (0.86, 1.53)	0	1.15 (0.86, 1.53)	0	1.14 (0.85, 1.53)	0
	Statin use	5	54,947	0.88 (0.78, 1.00) *[Note: p<0.05]*	0	0.88 (0.78, 1.00) *[Note: p<0.05]*	0	0.88 (0.78, 1.0)	0
CVD Mortality	All	13	161,680	0.95 (0.87, 1.04)*	4.3	0.95 (0.87, 1.04)	0	0.96 (0.88, 1.05)	0
	≤100 mg	11	134,470	0.95 (0.86, 1.05)	20.1	0.95 (0.87, 1.04)	0	0.96 (0.87, 1.06)	0

Table 5. Pooled Estimates for KQ1 and KQ2 Outcomes for Primary and Sensitivity Analyses

Outcome	Analysis	k	n	Peto Fixed Effects OR (95% CI)	I^2	Mantel-Haenszel Fixed Effects RR (95% CI)	I^2	Restricted Maximum Likelihood Random Effects (95% CI)	I^2
	Prior statins	5	53,035	0.93 (0.81, 1.08)	0	0.94 (0.81, 1.08)	0	0.94 (0.81, 1.8)	0
	Statin use	8	108,645	0.97 (0.86, 1.08)	22.4	0.97 (0.86, 1.08)	0	0.97 (0.87, 1.09)	0
All-cause Mortality	All	13	161,680	0.97 (0.93, 1.02)†	0	0.97 (0.93, 1.02)	0	0.97 (0.92, 1.02)	14.2
	≤100 mg	11	134,470	0.98 (0.93, 1.03)	0	0.98 (0.93,1.03)	0	0.98 (0.92, 1.03)	18.6
	Prior statins	5	53,035	0.93 (0.84, 1.02)	0	0.93 (0.85, 1.02)	0	0.93 (0.85, 1.02)	0
	Statin use	8	108,645	0.99 (0.93, 1.04)	6.0	0.99 (0.94, 1.04)	5.5	0.99 (0.92, 1.05)	26.9
CRC incidence (RCT only, 5 or 10 years f/u)	1° prevention, all doses	5	108,208	1.08 (0.94, 1.24)	16.7	1.08 (0.94, 1.24)	14.7	1.08 (0.94, 1.24)	0
	1° prevention, ≤100 mg	4	86,137	1.07 (0.92, 1.24)	36.0	1.07 (0.92, 1.24)	34.2	1.07 (0.92, 1.24)	0
	1° and 2° prevention, all doses	NA	NA	NA	NA	NA	NA	NA	NA
CRC incidence (RCT+obs, 10-year f/u)	1° prevention, all doses	4	69,622	0.98 (0.85, 1.14)	0	0.98 (0.85, 1.14)	0	0.98 (0.85, 1.14)	0
	1° prevention, ≤100 mg	2	42,412	0.96 (0.78, 1.19)	0	0.96 (0.78, 1.19)	0	0.96 (0.78, 1.19)	0
	1° and 2° prevention, all doses	5	72,071	0.99 (0.86, 1.14)	0	0.99 (0.85, 1.14)	0	0.99 (0.86, 1.14)	0
CRC incidence (RCT+obs, 20-year f/u)	1° prevention	2	45,015	0.79 (0.68, 0.93)	0	0.80 (0.68, 0.93)	0	0.80 (0.68, 0.93)	0
	1° prevention, ≤100 mg	1	39,876	0.82 (0.69, 0.98)	NA	0.82 (0.69, 0.98)	NA	0.82 (0.69, 0.98)	NA
	1° and 2° prevention, all doses	3	47,464	0.79 (0.68, 0.92)	0	0.80 (0.69, 0.92)	0	0.80 (0.69, 0.92)	0
CRC incidence (obs, 10+ years only)	1° prevention, all doses	3	67,086	0.66 (0.53, 0.82)	0	0.66 (0.54, 0.82)	0	0.66 (0.54, 0.82)	0
	1° prevention, ≤100 mg	1	39,876	0.63 (0.47, 0.83)	NA	0.63 (0.54, 0.82)	NA	0.63 (0.54, 0.82)	NA
	1° and 2° prevention, all doses	4	69,535	0.64 (0.52, 0.79)	0	0.65 (0.53, 0.80)	0	0.65 (0.53, 0.79)	0

Table 5. Pooled Estimates for KQ1 and KQ2 Outcomes for Primary and Sensitivity Analyses

Outcome	Analysis	k	n	Peto Fixed Effects OR (95% CI)	I^2	Mantel-Haenszel Fixed Effects RR (95% CI)	I^2	Restricted Maximum Likelihood Random Effects (95% CI)	I^2
CRC mortality (RCT only, 5 or 10 years f/u)	1° prevention, all doses	2	58,990	1.36 (0.97, 1.91)	30.2	1.36 (0.96, 1.92)	31.4	1.37 (0.90, 2.10)	31.3
	1° prevention, ≤100 mg	2	58,990	1.36 (0.97, 1.91)	30.2	1.36 (0.96, 1.92)	31.4	1.37 (0.90, 2.10)	31.3
	1° and 2° prevention, all doses	NA	NA	NA	NA	NA	NA	NA	NA
CRC mortality (RCT+obs, 18-year f/u)	1° prevention, all doses	3	50,100	0.76 (0.62 to 0.94)	0	0.76 (0.62 to 0.94)	0	0.76 (0.62, 0.94)	0
	1° prevention, ≤100 mg	2	44,961	0.77 (0.61, 0.98)	39.9	0.77 (0.61, 0.98)	39.4	0.76 (0.55, 1.05)	39.4
	1° and 2° prevention, all doses	5	53,909	0.74 (0.61 to 0.90)	0	0.75 (0.62 to 0.90)	0	0.75 (0.62, 0.90)	0
Total Major Bleeding	All	12	160,404	1.45 (1.33, 1.58)	12.1	1.44 (1.32, 1.57)	16.7	1.47 (1.32, 1.63)	17.9
	≤100 mg	10	133,194	1.44 (1.32, 1.57)	4.7	1.43 (1.31, 1.56)	9.6	1.46 (1.31, 1.62)	18.2
	Prior statins	5	53,035	1.74 (1.42, 2.11)	22.1	1.75 (1.43, 2.14)	27.0	1.74 (1.42, 2.13)	0
	Statin use	7	107,369	1.39 (1.26, 1.53)	0	1.38 (1.26, 1.52)	0	1.38 (1.26, 1.51)	0
Extracranial Bleeding	All	12	160,404	1.53 (1.39, 1.69)	66.2	1.53 (1.39, 1.69)	64.9	1.73 (1.39, 2.16)	66.6
	≤100 mg	10	133,194	1.53 (1.39, 1.70)	67.4	1.53 (1.38, 1.69)	67.2	1.80 (1.40, 2.31)	73.1
	Prior statins	5	53,035	2.30 (1.82, 2.90)	61.8	2.40 (1.87, 3.09)	59.9	2.22 (1.47, 3.36)	42.9
	Statin use	7	107,369	1.40 (1.26, 1.56)	23.2	1.40 (1.25, 1.56)	12.0	1.39 (1.25, 1.55)	0
Major GI Bleeding	All	12	146,340	1.57 (1.37, 1.78)	37.2	1.57 (1.37, 1.79)	25.8	1.57 (1.35, 1.84)	9.5
	≤100 mg	10	119,130	1.58 (1.38, 1.80)	25.5	1.58 (1.38, 1.80)	17.5	1.59 (1.36, 1.87)	14.1
	Prior statins	6	53,435	2.09 (1.52, 2.88)	36.2	2.12 (1.51, 2.97)	17.8	2.14 (1.51, 3.03)	0
	Statin use	6	92,905	1.48 (1.28, 1.71)	15.9	1.48 (1.28, 1.71)	0	1.47 (1.27, 1.70)	0
Intracranial Bleeding	All	13	161,680	1.33 (1.13, 1.56)	0	1.33 (1.13, 1.56)	0	1.33 (1.13, 1.56)	0
	≤100 mg	11	134,470	1.31 (1.11, 1.54)	0	1.31 (1.11, 1.54)	0	1.31 (1.10, 1.54)	0

Table 5. Pooled Estimates for KQ1 and KQ2 Outcomes for Primary and Sensitivity Analyses

Outcome	Analysis	k	n	Peto Fixed Effects OR (95% CI)	I^2	Mantel-Haenszel Fixed Effects RR (95% CI)	I^2	Restricted Maximum Likelihood Random Effects (95% CI)	I^2
	Prior statins	5	53,035	1.32 (0.88, 1.98)	0	1.32 (0.87, 1.99)	0	1.31 (0.86, 1.98)	0
	Statin use	8	108,645	1.33 (1.12, 1.58)	0	1.33 (1.13, 1.56)	0	1.33 (1.12, 1.58)	0
Total Hemorrhagic Stroke	All	12	160,404	1.23 (1.01, 1.48)	0	1.23 (1.01, 1.49)	0	1.22 (1.01, 1.48)	0
	≤100 mg	10	133,194	1.18 (0.97, 1.45)	0	1.18 (0.97, 1.45)	0	1.18 (0.96, 1.45)	0
	Prior statins	5	53,035	1.27 (0.84, 1.91)	0	1.27 (0.84, 1.92)	0	1.25 (0.81, 1.93)	0
	Statin use	7	107,369	1.21 (0.98, 1.50)	0	1.21 (0.98, 1.50)	0	1.21 (0.98, 1.50)	0
Fatal Hemorrhagic Stroke	All	9	102,223	1.06 (0.73, 1.54)	0	1.06 (0.73, 1.54)	0	1.06 (0.73, 1.55)	0
	≤100 mg	7	75,013	0.94 (0.62, 1.42)	0	0.94 (0.62, 1.42)	0	0.96 (0.63, 1.45)	0
	Prior statins	3	46,000	1.50 (0.70, 3.21)	2.4	1.51 (0.69, 3.34)	0.5	1.45 (0.63, 3.32)	0
	Statin use	6	56,223	0.96 (0.63, 1.46)	0	0.96 (0.63, 1.46)	0	0.98 (0.61, 1.50)	0
Nonfatal Hemorrhagic Stroke	All	8	100,947	1.38 (1.04, 1.82)	0	1.38 (1.04, 1.83)	0	1.36 (1.01, 1.84)	6.8
	≤100 mg	6	73,737	1.37 (1.01, 1.85)	0.1	1.37 (1.01, 1.86)	0.6	1.35 (0.93, 1.95)	20.5
	Prior statins	3	46,000	1.22 (0.71, 2.07)	0	1.22 (0.71, 2.07)	0	1.21 (0.71, 2.07)	0
	Statin use	5	54,947	1.44 (1.04, 2.00)	7.3	1.38 (1.04, 1.83)	8.3	1.43 (0.93, 2.21)	27.8

* REML model: RR, 0.96 (95% CI, 0.88 to 1.05)
† REML model: RR, 0.97 (95% CI, 0.92 to 1.02)
Abbreviations: 1° = primary; 2° = secondary**;** CI = confidence interval; CRC = colorectal cancer; CVD = cardiovascular disease; ECH = extracranial hemorrhage; F/U = followup; GI = gastrointestinal; ICH = intracranial hemorrhage; k = number of studies; mg = milligrams; MI = myocardial infarction; n = number of participants; obs = observational; OR = odds ratio; RCT = randomized controlled trial

Table 6. Range in Absolute Estimates for Statistically Significant Relative Effects

Outcome	Analysis	k	n	Peto Fixed Effects OR (95% CI)	Range in absolute effects, %
Major CVD events (nonfatal MI, nonfatal stroke, CVD mortality)	All	13	161,680	0.89 (0.85, 0.94)	-2.5 to -0.08
	≤100 mg	11	134,470	0.90 (0.85, 0.95)	-2.5 to -0.1
Total MI Events	All	13	161,680	0.86 (0.80, 0.92)	-1.9 to 1.2
	≤100 mg	11	134,470	0.89 (0.82, 0.96)	-1.9 to 1.2
Nonfatal MI Events	All	13	161,680	0.83 (0.76, 0.90)	-2.0 to 0.2
	≤100 mg	11	134,470	0.88 (0.80, 0.96)	-2.0 to 0.2
Total Stroke (all types)	All	13	161,680	0.94 (0.87, 1.02)	-2.0 to 0.4
	≤100 mg	11	134,470	0.91 (0.84, 0.99)	-2.0 to 0.1
Nonfatal Stroke (all types)	All	11	130,344	0.92 (0.84, 1.00)	-1.9 to 0.2
	≤100 mg	9	103,134	0.88 (0.80, 0.97)	-1.9 to 0.05
Total Ischemic Stroke	All	7	106,554	0.86 (0.77, 0.97)	-0.6 to 0.2
	≤100 mg	5	79,334	0.82 (0.72, 0.92)	-0.6 to -0.2
Nonfatal Ischemic Stroke	All	7	82,157	0.92 (0.82, 1.03)	-0.3 to 0.1
	≤100 mg	5	54,947	0.88 (0.78, 1.00) *[Note: p<0.05]*	-0.3 to -0.1
CRC incidence (RCT+obs, 20-year f/u)	1° prevention, all doses	2	50,100	0.79 (0.68, 0.93)	-1.1 to -0.2
	1° prevention, ≤100 mg	1	39,876	0.82 (0.69, 0.98)	-0.2
	1° and 2° prevention, all doses	3	47,464	0.79 (0.68, 0.92)	-1.1 to -0.2
CRC incidence (obs, 10+ years only)	1° prevention, all doses	3	67,086	0.66 (0.53, 0.82)	-0.8 to -0.06
	1° prevention, ≤100 mg	1	39,876	0.63 (0.47, 0.83)	-0.2
	1° and 2° prevention, all doses	4	69,535	0.64 (0.52, 0.79)	-0.9 to -0.06
CRC mortality (RCT+obs, 18-year f/u)	1° prevention, all doses	3	50,100	0.76 (0.62 to 0.94)	-0.8 to -0.06
	1° prevention, ≤100 mg	2	44,961	0.77 (0.61, 0.98)	-0.8 to -0.06
	1° and 2° prevention, all doses	5	53,909	0.74 (0.61 to 0.90)	-0.8 to -0.06
Total Major Bleeding	All	12	160,404	1.45 (1.33, 1.58)	-0.1 to 1.0
	≤100 mg	10	133,194	1.44 (1.32, 1.57)	0.1 to 1.0
ECH	All	12	160,404	1.53 (1.39, 1.69)	-0.1 to 0.9
	≤100 mg	10	133,194	1.53 (1.39, 1.70)	0.2 to 0.9
Major GI Bleeding	All	12	146,340	1.57 (1.37, 1.78)	-0.1 to 0.6

Table 6. Range in Absolute Estimates for Statistically Significant Relative Effects

Outcome	Analysis	k	n	Peto Fixed Effects OR (95% CI)	Range in absolute effects, %
	≤100 mg	10	119,130	1.58 (1.38, 1.80)	0.06 to 0.6
ICH	All	13	161,680	1.33 (1.13, 1.56)	-0.2 to 0.4
	≤100 mg	11	134,470	1.31 (1.11, 1.54)	-0.2 to 0.4
Total Hemorrhagic Stroke	All	12	160,404	1.23 (1.01, 1.48)	-0.07 to 0.2
	≤100 mg	10	133,194	1.18 (0.97, 1.45)	-0.07 to 0.2
Nonfatal Hemorrhagic Stroke	All	8	100,947	1.38 (1.04, 1.82)	-0.04 to 0.2
	≤100 mg	6	73,737	1.37 (1.01, 1.85)	-0.04 to 0.2

Abbreviations: 1º = primary; CI = confidence interval; CVD = cardiovascular disease; ECH = extracranial hemorrhage; F/U = followup; GI = gastrointestinal; ICH = intracranial hemorrhage; k = number of studies; mg = milligram; MI = myocardial infarction; n = number of participants; obs = observational; OR = odds ratio; RCT = randomized controlled trial

Table 7. Characteristics of Included Trials

Study name Author, year	Quality	Country	Study design, cotreatment	N relevant	Brief Population Description	ASA dose Formulation	Control group	ASA duration Mean followup, years
Primary CVD prevention								
AAA Fowkes, 2010[69]	Fair	UK	RCT	3,350	Males and females age 50-75 years old with ABI ≤0.95	100 mg QD, enteric-coated	Placebo QD	8.2
ARRIVE Gaziano, 2018[56]	Fair	Multi-site*	RCT	12,546	Males age ≥55 years with 2-4 CVD risk factors and females aged ≥60 years with 3+ CVD risk factors	100 mg QD, enteric-coated	Placebo QD	5 (median)
ASCEND ASCEND Study Collaborative, 2018[55]	Fair	UK	2x2 RCT, omega-3 fatty acid supplements	15,480	Males and females age ≥40 years with diabetes	100 mg QD, unspecified	Placebo QD	7.4
ASPREE McNeil, 2018[101]	Good	US, Australia	RCT	19,114	Males and females age ≥70 years (≥65 years of age among Black and Hispanic populations in the United States)	100 mg QD, enteric-coated	Placebo QD	4.7
BMD Peto, 1988[82]	Fair	UK	RCT	5,139	Male physicians (age range NR)	500 mg QD (300 mg enteric coated aspirin could be requested as an alternate to 500 mg soluble or effervescent aspirin)	No placebo tablets used. Told to avoid aspirin and use paracetamol if analgesics were needed	6
HOT Hanson, 1998[70]	Fair	Multi-site†	3x2 RCT, HTN treatment goals	18,790	Males and females age 50-80 with hypertension	75 mg QD, unspecified	Placebo	3.8
JPAD Ogawa, 2008[81]	Fair	Japan	RCT	2,539	Males and females age 30-85 years with diabetes	81 mg or 100 mg QD, not enteric coated	Nonaspirin details not reported	4.37 (median)‡
JPPP Ikeda, 2014[91]	Fair	Japan	RCT	14,658	Males and females age 60-85 years with hypertension, dyslipidemia, or diabetes	100 mg QD, enteric-coated	No ASA	5.02 (median)
PHS Physician's Health Study, 1989[59]	Good	US	2x2 RCT, Beta-carotene	22,071	Male physicians age 40-84 years	325 mg QOD, not enteric coated§	Placebo	5
POPADAD Belch, 2008[66]	Fair	Scotland	2x2 RCT, Antioxidant	1,276	Males and females age ≥40 years with diabetes and ABI ≤0.99	100 mg QD, not enteric coated	Placebo QD	6.7 (median)
PPP Rongaclioni, 2001[64]	Fair	Italy	2x2 RCT, Vitamin E	4,495	Males and females age ≥50 years with ≥1 risk factor for CVD	100 mg QD, enteric coated tablet	No ASA	3.6

Table 7. Characteristics of Included Trials

Study name Author, year	Quality	Country	Study design, cotreatment	N relevant	Brief Population Description	ASA dose Formulation	Control group	ASA duration Mean followup, years
TPT The Medical Research Council's General Practice Research Framework, 1998[45]	Fair	UK	2x2 RCT, Warfarin	2,540	Males age 45-69 years at high risk for ischemic heart disease	75 mg QD, controlled release capsule	Placebo QD	6.8 (median)
WHS Ridker, 2005[83]	Good	US	2x2 RCT, Vitamin E	39,876	Female health professionals age ≥45 years	100 mg QOD, not enteric coated	Placebo QOD	10.1‖
Secondary CVD prevention								
SALT The SALT Collaborative Group, 1991[94]	Fair	Sweden	RCT	1,363	Males and females age 50-79 years old with history of TIA, minor ischemic stroke, or retinal artery occlusion in prior 3 months	75 mg QD	Placebo QD	2.7
UK-TIA UK-TIA Study Group, 1990[111]	Fair	UK	RCT	2,449	Males and females age >40 years with recent TIA or minor ischemic stroke	IG1: 300 mg (two 150 mg aspirin tablets in the morning and two placebo tablets in the evening), unspecified IG2: 1200 mg (two 300 mg aspirin tablets twice a day), unspecified	IG1: Placebo (two tablets twice a day) IG2: Placebo (two tablets twice a day)	4.4

* US, UK, Germany, Ireland, Italy, Poland, Spain
† UK, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Greece, Israel, Italy, the Netherlands, Norway, Spain, Sweden, Switzerland, China
‡ 10.7 year extended followup
§ 624 participants in IG requested enteric-coated preparation and 16 requested Ecotrin
‖ 26-year extended followup

Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis; ABI = Ankle-brachial Index; ARRIVE = Aspirin to Reduce Risk of Initial Vascular Events; ASA = aspirin; ASCEND = A Study of Cardiovascular Events in Diabetes; ASPREE = Aspirin in Reducing Events in the Elderly; BMD = British Male Doctors; CVD = cardiovascular disease; F/U = followup; g = grams; HOT = Hypertension Optimal Treatment Study; HTN = hypertension; IG = intervention group; JPAD = Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; JPPP = Japanese Primary Prevention Project; mg = milligrams; NR = not reported; PHS = Physician's Health Study; POPADAD = The Prevention of Progression of Arterial Disease and Diabetes trial; PPP = Primary Prevention Project; QD = every day; QOD = every other day; Rand = randomized; RCT = randomized controlled trial; SALT = Swedish Aspirin Low-dose Trial; TIA = transient ischemic attack; TPT Thrombosis Prevention Trial; tx = treatment; UK-TIA = United Kingdom Transient Ischaemic Attack; US = United States; WHS = Women's Health Study

Table 8. Baseline Characteristics of Included Randomized, Controlled Trials

Study name, Author, Year	N rand	Mean age, years	% Female	% HTN	SBP/ DBP mm Hg, mean	TC LDL HDL mg/dL, mean	% DM	% Statin use	% Current smokers	Mean BMI	BMI >30	Calculated CVD Risk	% Prior CVD	Control group CVD event rate per year, %*
Primary CVD prevention														
AAA Fowkes, 2010[69]	3,350	62	72	NR	148/84	238 NR NR	3	4	33	NR	NR	NR	0	0.99
ARRIVE Gaziano, 2018[56]	12,546	64	30	65†	145/NR	NR	0	NR	29	28.4	NR	14.0% (mean 10 year Framingham CHD risk score); 17.4% (mean ACC/AHA 10 year CVD risk score)	0	0.69
ASCEND ASCEND Study Collaborative, 2018[55]	15,480	63	37	62	136/77	161 NR 49	100	75	8	31	46	Vascular risk score‡ (5 year risk of serious vascular event w/o aspirin or n-3 acids): low (<5%): 40%, moderate (5% - <10%): 42%, high (> or = 10%): 17%.	NR	1.02
ASPREE McNeil, 2018[101]	19,114	74	56	74	NR	NR	11	34	4	BMI, %: UW, <20: 2 Norm, 20-24: 24 OW, 25-29: 44	30	NR	0	0.82
BMD Peto, 1988[82]	5,139	NR	0	10	136/NR	NR	2	NR	<20 cigs/day: 7; >=20 cigs/day: 6	NR	NR	NR	Heart disease (excluding MI): 6.2, Other vascular disease: 3.6, TIA: 2.6	1.39
HOT Hanson, 1998[70]	18,790	62	47	100	170/105	236 NR NR	8	NR	16	28	NR	NR	9§	1.03
JPAD Ogawa, 2008[81]	2,539	64	45	58	135/76	NR NR 55	100	26	21	24	NR	NR	0	0.82

Table 8. Baseline Characteristics of Included Randomized, Controlled Trials

Study name, Author, Year	N rand	Mean age, years	% Female	% HTN	SBP/ DBP mm Hg, mean	TC LDL HDL mg/dL, mean	% DM	% Statin use	% Current smokers	Mean BMI	BMI >30	Calculated CVD Risk	% Prior CVD	Control group CVD event rate per year, %*
JPPP Ikeda, 2014[91]	14,658	71	58	85	137/78	203 120 58	34	72	13	24	NR		0	0.57
PHS Physician's Health Study, 1989[59]	22,071	53.2	0	NR	SBP, %: <109: 3.2§ 110-129: 52.6§ 130-149: 39.7§ ≥150: 4.5§ DBP, mm Hg, %: ≤69: 5.9§ 70-79: 31.4§ 80-89:52.4§ ≥90: 10.4§	TC, %: <159: 10.0§ 160-209: 39.1§ 210-259: 36.4§ ≥260: 14.6§ NR NR	2	NR	11	BMI (kg/m2), %: ≤23.0126: 25.7§ 23.0127-24.4075: 24.1§ 24.4076-26.3865: 25.1§ ≥ 26.3866: 25.0§	NR	NR	0	0.67
POPADAD Belch, 2008[66]	1,276	60	56	NR	145/79	212 120 46	100	NR	31	29	NR	NR	0	3.09
PPP Rongaclioni, 2001[64]	4,495	64	58	68	145/85	236 151 54	17	16	15	28	23	NR	0	0.78
TPT The Medical Research Council's General Practice Research Framework, 1998[45]	2,540	58	0	NR	139/NR	248 NR NR	NR	NR	41	27	NR	All participants in top 20% or 25% (if in high IHD region) according to risk assessment tool derived from Northwick Park Heart Study variables.	0	1.54

Table 8. Baseline Characteristics of Included Randomized, Controlled Trials

Study name, Author, Year	N rand	Mean age, years	% Female	% HTN	SBP/ DBP mm Hg, mean	TC LDL HDL mg/dL, mean	% DM	% Statin use	% Current smokers	Mean BMI	BMI >30	Calculated CVD Risk	% Prior CVD	Control group CVD event rate per year, %*
WHS Ridker, 2005[83]	39,876	55	100	26	SBP/ DBP, mm Hg, %: <120/<75 : 33 120-29/75-84: 32 130-39/85-89: 19 ≥140/≥90 : 16	NR	3	NR	13	26	18	10-year risk of CHD (Framingham), %: <5.0%: 84 5.0-9.9%: 12 ≥10.0%: 4	0 (CHD)	0.26
Secondary CVD prevention‖														
SALT The SALT Collaborative Group, 1991[94]	1,360	67	34	42.5† 4.7¶	NR	NR	12.8	NR	27.0	NR	NR	NR	Angina: 17.6 MI: 11.4 CHF: 5.2 Previous TIA: 9.5 Previous stoke: 9.1	
UK-TIA UK-TIA Study Group, 1990[111]	2,435	60	27	27†	151/88	NR	4††	0.4	53	NR	NR	NR	Past MI: 9.9% Angina: 14.7% Cardiac failure: 1.3% A fib: 2.0% Cardiac valvular disease: 2.3% Previous non-disabling stroke: 3.3%	

*Calculated as the percentage with major cardiovascular events (fatal and nonfatal stroke, fatal and nonfatal myocardial infarction, and CVD death) in the control group divided by the years of follow-up
†Taking HTN medication
‡Vascular risk score is from an internal study model, not a published risk score.
§ Calculated
‖ Secondary prevention trials included for CRC sensitivity analyses only
¶ Known untreated HTN
†† Treated diabetes

Table 8. Baseline Characteristics of Included Randomized, Controlled Trials

Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis; ABI = Ankle Brachial Index; ACC/AHA = American College of Cardiology/American Heart Association; ARRIVE = Aspirin to Reduce Risk of Initial Vascular Events; ASCEND = A Study of Cardiovascular Events in Diabetes; ASPREE = Aspirin in Reducing Events in the Elderly; BMD = British Doctor's Trial; BMI = Body Mass Index; CHD = Coronary heart disease; CHF = Coronary Heart Failure; Cigs = cigarettes; CVD = Cardiovascular Disease; DBP = Diastolic Blood Pressure; dL = deciliter; DM = diabetes mellitus; HDL = High Density Lipoprotein; HOT = Hypertension Optimal Treatment; HTN = Hypertension; IHD= Ischemic Heart Disease; JPAD = Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes; JPPP= Japanese Primary Prevention Project; kg = kilogram; LDL = Low Density Lipoprotein; m2 = square meter; MI = Myocardial Infarction; mg = milligram; mmHg = millimeters mercury; N = number; Norm = Normal weight; NR = not reported; OW = overweight; PAD = Peripheral Arterial Disease; PHS = Physician's Health Study; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; PPP = Primary Prevention Project; Rand = randomized; SALT = Swedish Aspirin Low Dose Trial; SBP = Systolic Blood Pressure; TC = Total Cholesterol; TIA = Transient Ischemic Attack; TPT = Thrombosis Prevention Trial; UK = United Kingdom; UK-TIA = United Kingdom Transient Ischemic Attack; UW = Underweight; WHS = Women's Health Study; W/o = without

Table 9. Key Question 1: Effect of Aspirin on Major Cardiovascular Events (Total Stroke, Total MI, CVD Mortality), Cardiovascular-Related Mortality, and All-Cause Mortality

Study name Author, year	Mean F/U, years	Outcome	IG n/n analyzed	CG n/n analyzed	Peto OR (95% CI)
AAA Fowkes, 2010[69]	8.2	Major CVD events	134/1675	136/1675	0.98 (0.77, 1.26)
		CVD-related mortality	35/1675	30/1675	1.17 (0.72, 1.91)
		All-cause mortality	176/1675	186/1675	0.94 (0.76, 1.17)
ARRIVE Gaziano, 2018[56]	5 (median)	Major CVD events	208/6270	218/6276	0.95 (0.79, 1.16)
		CVD-related mortality	38/6270	39/6276	0.98 (0.62, 1.53)
		All-cause mortality	160/6270	161/6276	0.99 (0.80, 1.24)
ASCEND ASCEND Study Collaborative, 2018[55]	7.4	Major CVD events	542/7740	587/7740	0.92 (0.81, 1.04)
		CVD-related mortality	210/7740	226/7740	0.93 (0.77, 1.12)
		All-cause mortality	748/7740	792/7740	0.94 (0.84, 1.04)
ASPREE McNeil, 2018[101]	4.7	Major CVD events	329/9525	372/9589	0.89 (0.76, 1.03)
		CVD-related mortality	78/9525	81/9589	0.97 (0.71, 1.32)
		All-cause mortality	558/9525	494/9589	1.15 (1.01, 1.30)
BMD Peto, 1988[82]	6	Major CVD events	284/3429	143/1710	0.99 (0.80, 1.22)
		CVD-related mortality	143/3429	75/1710	0.95 (0.71, 1.26)
		All-cause mortality	270/3429	151/1710	0.88 (0.71, 1.09)
HOT Hanson, 1998[70]	3.8	Major CVD events	315/9399	368/9391	0.85 (0.73, 0.99)
		CVD-related mortality	133/939	140/9391	0.95 (0.75, 1.20)
		All-cause mortality	284/9399	305/9391	0.93 (0.79, 1.09)
JPAD Ogawa, 2008[81]	4.37 (median)	Major CVD events	40/1262	46/1277	0.88 (0.57, 1.35)
		CVD-related mortality	1/1262	10/1277	0.20 (0.06, 0.64)
		All-cause mortality	34/1262	38/1277	0.90 (0.57, 1.44)
JPPP Ikeda, 2014[91]	5 (median)	Major CVD events	193/7220	207/7244	0.93 (0.77, 1.14)
		CVD-related mortality	58/7220	57/7244	1.02 (0.71, 1.47)
		All-cause mortality	297/7220	303/7244	0.98 (0.83, 1.16)
PHS Physician's Health Study, 1989[59]	5	Major CVD events	307/11037	370/11034	0.83 (0.71, 0.96)
		CVD-related mortality	81/11037	83/11034	0.98 (0.72, 1.33)
		All-cause mortality	217/11037	227/11034	0.95 (0.79, 1.15)
POPADAD Belch, 2008[66]	6.7 (median)	Major CVD events	127/638	132/638	0.95 (0.73, 1.25)
		CVD-related mortality	43/638	35/638	1.24 (0.79, 1.97)
		All-cause mortality	94/638	101/638	0.92 (0.68, 1.25)
PPP	3.6	Major CVD events	45/2226	64/2269	0.71 (0.49, 1.04)

Table 9. Key Question 1: Effect of Aspirin on Major Cardiovascular Events (Total Stroke, Total MI, CVD Mortality), Cardiovascular-Related Mortality, and All-Cause Mortality

Study name Author, year	Mean F/U, years	Outcome	IG n/n analyzed	CG n/n analyzed	Peto OR (95% CI)
Rongaclioni, 2001[64]		CVD-related mortality	17/2226	31/2269	0.57 (0.32, 1.00)
		All-cause mortality	62/2226	78/2269	0.81 (0.58, 1.13)
TPT The Medical Research Council's General Practice Research Framework, 1998[45]	6.8 (median)	Major CVD events	101/1268	133/1272	0.74 (0.57, 0.97)
		CVD-related mortality	42/1268	40/1272	1.06 (0.68, 1.64)
		All-cause mortality	113/1268	110/1272	1.03 (0.79, 1.36)
WHS Ridker, 2005[83]	10.1	Major CVD events	477/19934	522/19942	0.91 (0.80, 1.03)
		CVD-related mortality	120/19934	126/19942	0.95 (0.74, 1.22)
		All-cause mortality	609/19934	642/19942	0.95 (0.85, 1.06)

Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis; ARRIVE = Aspirin to Reduce Risk of Initial Vascular Events; ASCEND = A Study of Cardiovascular Events in Diabetes; ASPREE = Aspirin in Reducing Events in the Elderly; BMD = British Male Doctors; CG = control group; CI = confidence interval; CVD = cardiovascular disease; F/U = followup; HOT = Hypertension Optimal Treatment Study; IG = intervention group; JPAD = Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; JPPP = Japanese Primary Prevention Project; PHS = Physician's Health Study; n = number of participants; OR = odds ratio; p-y = person-years; POPADAD = The Prevention of Progression of Arterial Disease and Diabetes trial; PPP = Primary Prevention Project; TPT = Thrombosis Prevention Trial; WHS = Women's Health Study

Table 10. Key Question 1: Effect of Aspirin on MI*

Study name Author, year Quality	Mean F/U, yrs	Outcome	IG n/n analyzed	CG n/n analyzed	Peto OR (95% CI)
AAA Fowkes, 2010[69] Fair	8.2	MI - Total	90/1675	86/1675	1.05 (0.77, 1.42)
		MI - Fatal	28/1675	18/1675	1.55 (0.87, 2.78)
		MI - Nonfatal	62/1675	68/1675	0.91 (0.64, 1.29)
ARRIVE Gaziano, 2018[56] Fair	5 (median)	MI - Total	95/6270	112/6276	0.85 (0.64, 1.11)
		MI - Fatal	7/6270	14/6276	0.51 (0.22, 1.21)
		MI - Nonfatal	88/6270	98/6276	0.90 (0.67, 1.20)
ASCEND ASCEND Study Collaborative, 2018[55] Fair	7.4	MI - Total	296/7740	317/7740	0.93 (0.79, 1.09)
		MI - Fatal	105/7740	122/7740	0.86 (0.66, 1.12)
		MI - Nonfatal	191/7740	195/7740	0.98 (0.80, 1.20)
ASPREE McNeil, 2018[101] Good	4.7	MI - Total	181/9525	205/9589	0.89 (0.72, 1.08)
		MI - Fatal	31/9525	45/9589	0.70 (0.44, 1.09)
		MI - Nonfatal	150/9525	160/9589	0.94 (0.75, 1.18)
BMD Peto, 1988[82] Fair	6	MI - Total	169/3429	88/1710	0.96 (0.73, 1.25)
		MI - Fatal	89/3429	47/1710	0.94 (0.66, 1.35)
		MI – Nonfatal	80/3429	41/1710	0.97 (0.66, 1.43)
HOT Hanson, 1998[70] Fair	3.8	MI - Total	153/9399	207/9391	0.74 (0.60, 0.91)
		MI - Fatal	85/9399	94/9391	0.90 (0.67, 1.21)
		MI - Nonfatal	68/9399	113/9391	0.60 (0.45, 0.81)
JPAD Ogawa, 2008[81] Fair	4.37 (median)	MI - Total	12/1262	14/1277	0.87 (0.40, 1.88)
		MI - Fatal	0/1262	5/1277	0.14 (0.02, 0.79)
		MI - Nonfatal	12/1262	9/1277	1.35 (0.57, 3.19)
	10.3† (median)	MI - Total	28/1262	29/1277	0.98 (0.58, 1.65)
		MI - Fatal	3/1262	6/1277	0.52 (0.14, 1.92)
		MI - Nonfatal	25/1262	23/1277	1.10 (0.62, 1.95)
JPPP Ikeda, 2014[91] Fair	5 (median)	MI - Total	27/7220	47/7244	0.58 (0.37, 0.92)
		MI - Fatal	7/7220	9/7244	0.78 (0.29, 2.08)
		MI - Nonfatal	20/7220	38/7244	0.54 (0.32, 0.90)
PHS Physician's Health Study, 1989[59] Good	5	MI - Total	185/11037	276/11034	0.67 (0.56, 0.80)
		MI - Fatal	56/11037	65/11034	0.86 (0.60, 1.23)
		MI - Nonfatal	139/11037	239/11034	0.58 (0.48, 0.72)

Table 10. Key Question 1: Effect of Aspirin on MI*

Study name Author, year Quality	Mean F/U, yrs	Outcome	IG n/n analyzed	CG n/n analyzed	Peto OR (95% CI)
POPADAD Belch, 2008[66] Fair	6.7	MI - Total	90/638	82/638	1.11 (0.81, 1.54)
		MI - Fatal	35/638	26/638	1.36 (0.82, 2.28)
		MI - Nonfatal	55/638	56/638	0.98 (0.66, 1.45)
PPP Rongaclioni, 2001[64] Fair	3.6	MI - Total	19/2226	28/2269	0.69 (0.39, 1.23)
		MI - Fatal	4/2226	6/2269	0.68 (0.20, 2.36)
		MI - Nonfatal	15/2226	22/2269	0.70 (0.36, 1.33)
TPT The Medical Research Council's General Practice Research Framework, 1998[45] Fair	6.8 (median)	MI - Total	83/1268	107/1272	0.76 (0.57, 1.03)
		MI - Fatal	36/1268	34/1272	1.06 (0.66, 1.71)
		MI - Nonfatal	47/1268	73/1272	0.64 (0.44, 0.92)
WHS Ridker, 2005[83] Good	10.1	MI - Total	198/19934	193/19942	1.03 (0.84, 1.25)
		MI - Fatal	14/19934	12/19942	1.17 (0.54, 2.52)
		MI - Nonfatal	184/19934	181/19942	1.02 (0.83, 1.25)
	17.5†	MI - Total	Events: 320/19934	Events: 323/19942	HR: 0.98 (0.84, 1.15)

* Includes fatal coronary heart disease and sudden death in addition to MI events.

† Observational followup

Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis; ARRIVE = Aspirin to Reduce Risk of Initial Vascular Events; ASCEND = A Study of Cardiovascular Events in Diabetes; ASPREE = Aspirin in Reducing Events in the Elderly; BMD = British Male Doctors; CG = control group; CI = confidence interval; F/U = followup; HOT = Hypertension Optimal Treatment Study; IG = intervention group; JPAD = Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; JPPP = Japanese Primary Prevention Project; MI = myocardial infarction; n = number of participants; OR = odds ratio; p-y = person-years; PHS = Physician's Health Study; POPADAD = The Prevention of Progression of Arterial Disease and Diabetes trial; PPP = Primary Prevention Project; TPT Thrombosis Prevention Trial; WHS = Women's Health Study; yrs = years

Table 11. Key Question 1: Effect of Aspirin on Stroke

Study name Author, year	Mean F/U, years	Outcome	IG n/n analyzed	CG n/n analyzed	Peto OR (95% CI)
AAA Fowkes, 2010[69]	8.2	Ischemic stroke - total	30/1675	37/1675	0.81 (0.50, 1.31)
		Ischemic stroke - fatal	2/1675	7/1675	0.33 (0.09, 1.21)
		Ischemic stroke - nonfatal	28/1675	30/1675	0.93 (0.55, 1.57)
		All-type stroke - total	44/1675	50/1675	0.88 (0.58, 1.32)
		All-type stroke - fatal	7/1675	12/1675	0.59 (0.24, 1.45)
		All-type stroke - nonfatal	37/1675	38/1675	0.97 (0.62,1.54)
		Unknown stroke - fatal	2/1675	2/1675	NR
		Unknown stroke - nonfatal	7/1675	7/1675	NR
ARRIVE Gaziano, 2018[56]	5 (median)	Total stroke	75/6270	67/6276	1.12 (0.81, 1.56)
ASCEND ASCEND Study Collaborative, 2018[55]	7.4	Ischemic stroke - nonfatal	202/7740	229/7740	0.88 (0.73, 1.06)
		All-type stroke	254/7740	280/7740	0.90 (0.76, 1.07)
		All-type stroke - fatal	38/7740	34/7740	1.12 (0.70, 1.78)
		All-type stroke - nonfatal	216/7740	246/7740	0.87 (0.73, 1.05)
ASPREE McNeil, 2018[101]	4.7	Ischemic stroke – total*	148/9525	167/9589	0.89 (0.71, 1.11)
		Ischemic stroke - fatal	15/9525	12/9589	1.26 (0.59, 2.68)
		Ischemic stroke - nonfatal	133/9525	155/9589	0.86 (0.68, 1.09)
		All-type stroke	195/9525	203/9589	0.97 (0.79, 1.18)
		All-type stroke - fatal	34/9525	29/9589	1.18 (0.72, 1.94)
		All-type stroke - nonfatal	161/9525	174/9589	0.93 (0.75, 1.15)
		Unknown stroke - total	2/9525	1/9589	NR
		Unknown stroke - fatal	1/9525	1/9589	NR
BMD Peto, 1988[82]	6	Ischemic stroke - total	21/3429	7/1710	1.45 (0.66, 3.20)
		Ischemic stroke - fatal	8/3429	3/1710	1.31 (0.37, 4.60)
		Ischemic stroke - nonfatal†	13/3429	4/1710	1.55 (0.57, 4.27)
		All-type stroke	91/3429	39/1710	1.16 (0.80, 1.68)
		All-type stroke - fatal	30/3429	12/1710	1.24 (0.65, 2.36)
		All-type stroke - nonfatal†	61/3429	27/1710	1.13 (0.72, 1.76)
		Unknown stroke - fatal	12/3429	5/1710	NR
		Unknown stroke - nonfatal†	45/3429	21/1710	NR
HOT Hanson, 1998[70]	3.8	All-type stroke	146/9399	148/9391	0.99 (0.78,1.24)
JPAD Ogawa, 2008[81]	4.37 (median)	Ischemic stroke - nonfatal	22/1262	24/1277	0.93 (0.52, 1.66)
		All-type stroke	28/1262	32/1277	0.88 (0.53, 1.47)
		All-type stroke - fatal	1/1262	5/1277	0.27 (0.05, 1.32)

Table 11. Key Question 1: Effect of Aspirin on Stroke

Study name Author, year	Mean F/U, years	Outcome	IG n/n analyzed	CG n/n analyzed	Peto OR (95% CI)
		All-type stroke - nonfatal	27/1262	27/1277	1.01 (0.59, 1.74)
	10.3** (median)	Ischemic stroke - nonfatal	38/1262	46/1277	HR: 0.85 (0.55, 1.31)
		All-type stroke - fatal	10/1262	8/1277	HR: 1.31 (0.52, 3.43)
JPPP Ikeda, 2014[91]	5 (median)	Ischemic stroke - total	85/7220	101/7244	0.84 (0.63, 1.13)
		Ischemic stroke - fatal	2/7220	7/7244	0.33 (0.09, 1.22)
		Ischemic stroke - nonfatal	83/7220	94/7244	0.88 (0.66, 1.19)
		All-type stroke	126/7220	130/7244	0.97 (0.76, 1.24)
		All-type stroke - fatal	9/7220	16/7244	0.57 (0.26, 1.25)
		All-type stroke - nonfatal	117/7220	114/7244	1.03 (0.79, 1.34)
		Unknown stroke - nonfatal	3/7220	5/7244	NR
PHS Physician's Health Study, 1989[59]	5	Ischemic stroke - total	91/11037	82/11034	1.11 (0.82, 1.50
		Ischemic stroke - fatal‡	3/11037	3/11034	1.0 (0.20, 4.95)
		Ischemic stroke - nonfatal	88/11037	79/11034	1.11 (0.82, 1.51)
		All-type stroke §	119/11037	98/11034	1.22 (0.93, 1.59)
		All-type stroke - fatal‡	9/11037	6/11034	1.49 (0.54, 4.11)
		All-type stroke - nonfatal	110/11037	92/11034	1.20 (0.91, 1.58)
		Unknown stroke - total§	5/11037	4/11034	NR
		Unknown stroke - fatal‡	0/11037	2/11034	NR
POPADAD Belch, 2008[66]	6.7 (median)	Ischemic stroke - fatal	3/638	5/638	0.60 (0.15, 2.43)
		All-type stroke	37/638	50/638	0.73 (0.47, 1.12)
		All-type stroke - fatal	8/638	9/638	0.89 (0.34, 2.31)
		All-type stroke - nonfatal	29/638	41/638	0.70 (0.43, 1.13)
		Unknown stroke - fatal	3/638	1/638	NR
PPP Rongaclioni, 2001[64]	3.6	All-type stroke‖	16/2226	24/2269	0.68 (0.37, 1.27)
		All-type stroke - fatal	1/2226	6/2269	0.24 (0.06, 1.07)
		All-type stroke - nonfatal	15/2226	18/2269	0.85 (0.43, 1.68)
TPT The Medical Research Council's General Practice Research Framework, 1998[45]	6.8 (median)	Ischemic stroke - total	10/1268	18/1272	0.56 (0.27, 1.19)
		All-type stroke	18/1268	26/1272	0.69 (0.38, 1.26)
		All-type stroke - fatal	2/1268	1/1272	1.95 (0.20, 18.81)
		All-type stroke - nonfatal	16/1268	25/1272	0.64 (0.35, 1.19)
		Unknown stroke	5/1268	6/1272	NR

Table 11. Key Question 1: Effect of Aspirin on Stroke

Study name Author, year	Mean F/U, years	Outcome	IG n/n analyzed	CG n/n analyzed	Peto OR (95% CI)
WHS Ridker, 2005[83]	10.1	Ischemic stroke - total¶	170/19934	221/19942	0.77 (0.63, 0.94)
		All-type stroke	221/19934	266/19942	0.83 (0.69, 0.99)
		All-type stroke - fatal	23/19934	22/19942	1.05 (0.58, 1.88)
		All-type stroke - nonfatal	198/19934	244/19942	0.81 (0.67, 0.98)
	17.5**	Ischemic stroke - total	Events: 306/19934	Events: 372/19942	HR: 0.81 (0.70, 0.95)
		All-type stroke	Events: 391/19934	Events: 438/19942	HR: 0.88 (0.77, 1.01)

* Includes 9 ischemic strokes with hemorrhagic transformation in 9 participants (6 aspirin and 3 placebo). Ischemic stroke only includes stroke events adjudicated as ischemic (does not include uncertain type).
† Nonfatal occurrences of a particular disease exclude occurrences in patients who later died of that disease
‡ Includes all deaths regardless of previous nonfatal events
§ First events only.
‖ 3 strokes deemed disabling in the IG and 4 in the CG
¶ 4 unclassified strokes in CG
** Observational followup

Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis; ARRIVE = Aspirin to Reduce Risk of Initial Vascular Events; ASCEND = A Study of Cardiovascular Events in Diabetes; ASPREE = Aspirin in Reducing Events in the Elderly; BMD = British Male Doctors; CG = control group; CI = confidence interval; F/U = followup; HOT = Hypertension Optimal Treatment Study; IG = intervention group; JPAD = Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; JPPP = Japanese Primary Prevention Project; n = number of participants; OR = odds ratio; p-y = person-years; PHS = Physician's Health Study; POPADAD = The Prevention of Progression of Arterial Disease and Diabetes trial; PPP = Primary Prevention Project; TPT Thrombosis Prevention Trial; WHS = Women's Health Study

Table 12. Key Question 1: Effect of Aspirin on CRC Incidence and CRC-Related Mortality

Study name Author, year	Outcome	Mean F/U, years	IG n/n analyzed	CG n/n analyzed	Peto OR (95% CI)
ARRIVE Gaziano, 2018[56]	CRC incidence	5 (median)	14/6270	6/6276	2.23 (0.93, 5.36)
ASPREE McNeil, 2018[101, 131]	CRC incidence	4.7	139/9525	137/9589	1.02 (0.81, 1.30)
	CRC-related mortality		35/9525	20/9589	1.74 (1.02, 2.95)
BMD Peto, 1988[82, 92, 93]	CRC incidence	9	28/3429	17/1710	0.82 (0.44, 1.52)
		10-19	50/3429	38/1710	0.64 (0.41, 0.99)
		20	92/3429	64/1710	0.70 (0.50, 0.98)
	CRC-related mortality	18.3	59/3429	40/1710	0.72 (0.47, 1.10)
JPAD Ogawa, 2008[81, 103]	CRC incidence	10.7 (median)	27/1259	31/1277	0.88 (0.52, 1.48)
JPPP Ikeda, 2014[91, 108]	CRC incidence	5 (median)	66/7297	50/7304	1.32 (0.92, 1.90)
PHS Physician's Health Study, 1989[59, 113, 114]	CRC incidence	5	63/11037	55/11034	1.15 (0.80, 1.65)
		6-12	97/11037	94/11034	1.03 (0.78, 1.37)
		10-12	28/11037	35/11034	0.80 (0.49, 1.31)
		12	173/11037	168/11034	1.03 (0.83, 1.28)
SALT The SALT Collaborative Group, 1991[93, 94]	CRC-related mortality	18.3	7/676	10/684	0.71 (0.27, 1.84)
TPT The Medical Research Council's General Practice Research Framework, 1998[45, 93]	CRC-related mortality	18.3 (median)	34/2545	55/2540	0.62 (0.41, 0.94)
UK-TIA UK-TIA Study Group, 1990[93, 111]	CRC incidence	9	18/1632	8/817	1.12 (0.50, 2.55)
		10-19	15/1632	15/817	0.47 (0.22, 1.01)
		20	37/1632	23/817	0.80 (0.46, 1.37)
	CRC-related mortality	18.3	300 mg/d: 8/811	16/817	0.51 (0.23, 1.15)
			1200 mg/d: 11/821		0.68 (0.32, 1.46)
			300 or 1200 mg/d: 19/1632		0.57 (0.28, 1.15)
WHS Ridker, 2005[49, 83, 112]	CRC-related mortality	0-10.3	41/19934	36/19942	1.14 (0.73, 1.78)
		0-17.5	83/19934	96/19942	0.86 (0.64, 1.16)
		0-26	114/19934	119/19942	0.96 (0.74, 1.24)
		10.3-17.5	42/19934	60/19942	0.70 (0.48, 1.04)

Table 12. Key Question 1: Effect of Aspirin on CRC Incidence and CRC-Related Mortality

Study name Author, year	Outcome	Mean F/U, years	IG n/n analyzed	CG n/n analyzed	Peto OR (95% CI)
		17.5-26	31/19934	23/19942	1.35 (0.79, 2.30)
	CRC incidence	0-10.3	147/19934	150/19942	0.98 (0.78, 1.23)
		0-17.5	222/19934	270/19942	0.82 (0.69, 0.98)
		0-26	274/19934	315/19942	0.87 (0.74, 1.02)
		10.3-17.5	75/19934	120/19942	0.63 (0.47, 0.83)
		17.5-26	52/19934	45/19942	1.16 (0.78, 1.72)

Abbreviations: ARRIVE = Aspirin to Reduce Risk of Initial Vascular Events; ASPREE = Aspirin in Reducing Events in the Elderly; BMD = British Male Doctors; CG = control group; CI = confidence interval; CRC = colorectal cancer; F/U = followup; IG = intervention group; JPAD = Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; JPPP = Japanese Primary Prevention Project; n = number of participants; OR = odds ratio; PHS = Physician's Health Study; SALT = Swedish Aspirin Low-dose Trial; TPT Thrombosis Prevention Trial; United Kingdom Transient Ischaemic Attack; WHS = Women's Health Study

Table 13. Key Question 2: Characteristics of Cohorts Included for Harms

Study name, Author, year, Quality rating	Country	Mean F/U	Population inclusion and exclusion	N	Mean age (range), years	% Female	% DM	% Current smokers	ASA Dose & Duration	Indication
De Berardis, 2012[117] Good	ITA	5.7	Included: New users of low-dose ASA (≤300 mg) during the index period; aged ≥30 years on index date with no prescription for ASA in the past year; current users those who had the last ASA prescription filled ≤75 days before hospitalization for major bleeding events Excluded: Aged <30 years or >95 years, former ASA user (i.e., last ASA prescription ≥75 days before event) and those with DM treated prior to cohort entry but without antidiabetic prescription during study period	372,850	69 (30-95)	53	15	NR	≤300 mg 5.7 (median)	ASA for the prevention of CVD is available to all citizens at high CVD risk only by prescription and is free of charge so assuming CVD prevention indication.
HPFS Huang, 2010[120] Fair	US	11.4	Included: Male health professionals who returned 1994 questionnaire on ASA use Excluded: Males with a prior history of GIB, cancer or peptic ulcer disease	32,989	61 (NR)	0	5	5	81-325 mg QD* NR	Assessed only in subsample of 211 men. Indications were CVD, 25.4%; to decrease risk for CVD, 58.4%; headaches, 25.4%; joint or musculoskeletal pain, 33.0%; and other reasons, 7.0%.
Korean National Health Insurance Service-Senior Cohort Jung, 2020[107] Fair	KOR	7.8	Included: Males and females; aged 60–90 years; newly diagnosed with HTN, type 2 DM, or dyslipidemia Excluded: Patients with a history of IHD, stroke, or heart failure before their index dates; patients with a history of hemorrhagic events, coagulation defects; peptic ulcer diseases, or severe diseases, including end-stage renal disease or end-stage liver disease before enrollment	13,455	71 (60-90)	58	18	4	NR ("low-dose") 4.8 years	Newly started receiving ASA based on prescribing records, ASA prescriptions were given to those with CVD risk factors and authors state that this prescription was covered through national health insurance, so assuming CVD prevention indication.
NHIRD Chen, 2017[106] Fair	TWN	1	Included: New low-dose ASA (75-325 mg daily) users age ≥20 years Excluded: Active GIB at enrollment; malignant tumor of the GI tract; disease associated with alcohol; inflammatory bowel disease radiation gastroenteritis or colitis; intestinal vascular insufficiency; coagulopathy before low-dose ASA use†	322,830	41 (20-80+)	49	0.3	NR	75-325 mg daily 1 year	Unclear

Table 13. Key Question 2: Characteristics of Cohorts Included for Harms

Study name, Author, year, Quality rating	Country	Mean F/U	Population inclusion and exclusion	N	Mean age (range), years	% Female	% DM	% Current smokers	ASA Dose & Duration	Indication
NHIRD Luo, 2019[98] Fair	TWN	10 (mean 2.55 years; range 0.08-10.96 years)	Included: Males and females age >20 years, taking ASA with an average dose more than 14 defined daily dose per month Excluded: Malignancy of the GI tract, alcohol-related diseases, inflammatory bowel disease, coagulopathy, vascular insufficiency of the intestine, gastroenteritis or colitis due to radiation, and nonvariceal UGIB‡	22,210	64 (20+)	47	24	NR	"Average dose more than 14 defined daily dose per month." 2.55 years	Unclear
NHS Huang, 2011[121] Fair	US	24	Included: Female registered nurses, aged 30-55 years in 1976 who returned in 1990 ASA questionnaire Excluded: Prior history of GIB, cancer, peptic ulcer disease, bleeding related to cancer or polypectomy, or without a date of bleeding diagnosis	87,680	57 (NR)	100	5	18	325 mg QD§ 24 years	Assessed only in subsample of the cohort taking 1 to 6 ASA/wk and ≥7 ASA/wk: headache (32% and 18%, respectively); arthritis/musculoskeletal pain (46% and 65%); CVD prevention (9% and 8%); and other reasons (13% and 9%).
SNDR Ekstrom, 2013[118] Fair	SWE	3.9	Included: Patients with type 2 DM, age 30–80 years, and with data available for all analyzed variables at baseline in 2006 Excluded: History of CVD, cancer or bleeding; taking ASA dose other than 75 mg/day; BMI <18 and/or plasma Cr >150 umol/L; incomplete records; taking other anticoagulant drugs (except ASA), cardiac glycosides, or organic nitrates, history of CHD, CABG, PCI, stroke including cerebral bleeding, CHF, AFib, PVD, amputation, renal failure, GI ulcer; ventricular, respiratory, other bleeding	18,646	62 (30-80)	45	100	15	75 mg QD >12 months	Assumed primary prevention based on study aims, use of national prescription data for ASA, and a DM quality assurance register

* Regular users defined as 2 or more times per week

† ICD9-CM codes: Active GIB at enrollment; malignant tumor of the GI tract (150.xx, 151.xx, 152.xx, 153.xx, 154.xx); disease associated with alcohol (291.xx, 303.xx, 305.xx, 571.0, 571.1, 571.2, 571.3); inflammatory bowel disease (556.x, 555.x); radiation gastroenteritis or colitis (558.1); intestinal vascular insufficiency (557.xx); coagulopathy (286.xx) before low-dose ASA use

‡ ICD9-CM codes: Malignancy of the GI tract (150.xx, 151.xx, 152.xx, 153.xx, and 154.xx); alcohol-related diseases (291.xx, 303.xx, 305.xx, 571.0, 571.1, 571.2, and 571.3); inflammatory bowel disease ((556.x and 555.x); coagulopathy ((286.xx); vascular insufficiency of the intestine (557.xx); gastroenteritis or colitis due to radiation (558.1); and nonvariceal UGIB (530.7, 530.82, 531.0, 531.00, 531.01, 531.2531.2x, 531.4, 531.4x, 531.6531.6x, 532.0, 532.00, 532.01, 532.2532.2x, 532.4, 532.4x, 32.6532.6x, 533.0, 533.00, 533.01, 33.2533.2x, 533.4, 533.4x, 533.6533.6x, 534.0, 534.00, 534.01, 534.2534.2x, 534.4, 534.4x, 534.6534.6x, 535.x1, 537.83, 537.84, and 578.0.)

§ Early in the study most participants used 325 mg tablets; based on changes in secular trends, questionnaires after 1992 asked participants to convert intake of 4 baby aspirin into one tablet

Table 13. Key Question 2: Characteristics of Cohorts Included for Harms

Abbreviations: Afib = atrial fibrillation; ASA = aspirin; BMI = Body Mass Index; CABG = coronary artery bypass grafting; CHD = Coronary heart disease; CHF = Coronary Heart Failure; CM = Clinical Modification; Cr = creatine; CVD = Cardiovascular Disease; D = day; DM = diabetes mellitus; F/U = followup; g = grams; GI = gastrointestinal; GIB = gastrointestinal bleeding; HPFS = Health Professionals Followup Study' HTN = hypertension; ICD = International Classification of Diseases; IHD= Ischemic Heart Disease; ITA = Italy; KOR = Korea; mg = milligrams; n = number of participants; NHIRD = National Health Insurance Research Database; NHS = Nurses' Health Study; NR = not reported; PCI = percutaneous coronary intervention; PVD = peripheral vascular disease; Q = every; SNDR = Swedish National Diabetes Register; SWE = Sweden; UGIB = upper GI bleeding; umol/L = micromole per liter; US = United States; TWN = Taiwan; wk = week

Table 14. Key Question 2: Effect of Aspirin on Extracranial Bleeding as Variably Defined in Randomized, Controlled Trials

Study name Author, year	Mean F/U, years	Outcome	IG n/n analyzed	CG n/n analyzed	Peto OR (95% CI)
AAA Fowkes, 2010[69]	8.2	Extracranial hemorrhage	23/1675	13/1675	1.75 (0.91, 3.38)
ARRIVE Gaziano, 2018[56]	5 (median)	Total GI bleed	19/6270	7/6276	2.52 (1.17, 5.45)
ASCEND ASCEND Study Collaborative, 2018[55]	7.4	Extracranial hemorrhage	268/7740	208/7740	1.30 (1.08, 1.56)
ASPREE McNeil, 2018[101]	4.7	Extracranial hemorrhage	270/9525	200/9589	1.37 (1.14, 1.64)
BMD Peto, 1988[82]	6	Total GI bleed	1/3429	3/1710	0.15 (0.02, 1.22)
HOT Hanson, 1998[70]	3.8	Extracranial hemorrhage	122/9399	41/9391	2.72 (2.00, 3.71)
JPAD Ogawa, 2008[81]	4.37 (median)	GI bleeding requiring transfusion	4/1262	0/1277	7.50 (1.05, 53.27)
JPPP Ikeda, 2014[91]	5 (median)	Extracranial bleeding requiring transfusion or hospitalization	62/7220	34/7244	1.80 (1.21, 2.70)
PHS Physician's Health Study, 1989[59]	5	Bleeding requiring transfusion or hospitalization	48/11037	28/11034	1.70 (1.08, 2.66)
PPP Rongaclioni, 2001	3.6	Extracranial hemorrhage	22/2226	6/2269	3.22 (1.53, 6.77)
TPT The Medical Research Council's General Practice Research Framework, 1998[45]	6.8 (median)	Total major bleeds	11/1268	6/1272	1.81 (0.70, 4.71)
WHS Ridker, 2005[83]	10.1	Total GI bleed	129/19934	94/19942	1.37 (1.05, 1.78)

Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis; ARRIVE = Aspirin to Reduce Risk of Initial Vascular Events; ASCEND = A Study of Cardiovascular Events in Diabetes; ASPREE = Aspirin in Reducing Events in the Elderly; BMD = British Male Doctors; CG = control group; CI = confidence interval; F/U = followup; HOT = Hypertension Optimal Treatment Study; IG = intervention group; JPAD = Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; JPPP = Japanese Primary Prevention Project; PHS = Physician's Health Study; n = number of participants; OR = odds ratio; PPP = Primary Prevention Project; TPT Thrombosis Prevention Trial; WHS = Women's Health Study

Table 15. Key Question 2: Effect of Aspirin on Major GI Bleeding in Randomized, Controlled Trials

Study name Author, year	Mean F/U, years	Outcome	IG n/n analyzed	CG n/n analyzed	Peto OR (95% CI)
AAA Fowkes, 2010[69]	8.2	Major GI bleed	9/1675	8/1675	1.13 (0.43, 2.92)
ARRIVE Gaziano, 2018[56]	5 (median)	Major GI bleed	19/6270	7/6276	2.52 (1.17, 5.45)
ASCEND ASCEND Study Collaborative, 2018[55]	7.4	Major GI bleed	137/7740	101/7740	1.36 (1.05, 1.76)
ASPREE McNeil, 2018[101]	4.7	Major GI bleed	158/9525	99/9589	1.60 (1.25, 2.05)
ASPREE Pilot Silagy, 1993[127]	1	Major GI bleed	1/200	0/200	7.39 (0.15, 372.38)
BMD Peto, 1988[82]	6	Fatal GI bleed*	1/3429	3/1710	0.15 (0.02, 1.22)
HOT Hanson, 1998[70]	3.8	Major GI bleed	77/9399	37/9391	2.02 (1.40, 2.93)
JPAD Ogawa, 2008[81]	4.37 (median)	Major GI bleed	4/1262	0/1277	7.50 (1.05, 53.27)
PHS Physician's Health Study, 1989[59]	5	Fatal GI bleed	1/11037	0/11034	7.39 (0.15, 372.28)
PPP Rongaclioni, 2001	3.6	Major GI bleed	17/2226	5/2269	3.05 (1.32, 7.05)
TPT The Medical Research Council's General Practice Research Framework, 1998[45]	6.8 (median)	Major GI bleed	6/1268	2/1272	2.73 (0.68, 10.95)
WHS Ridker, 2005[83]	10.1	Major GI bleed	129/19934	94/19942	1.37 (1.05, 1.78)

***** Includes fatal gastric hemorrhage and fatal hemorrhagic peptic. Does not include perforated ulcer.

Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis; ARRIVE = Aspirin to Reduce Risk of Initial Vascular Events; ASCEND = A Study of Cardiovascular Events in Diabetes; ASPREE = Aspirin in Reducing Events in the Elderly; BMD = British Male Doctors; CG = control group; CI = confidence interval; F/U = followup; GI = gastrointestinal; HOT = Hypertension Optimal Treatment Study; IG = intervention group; JPAD = Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; PHS = Physician's Health Study; n = number of participants; OR = odds ratio; p-y = person-years; PPP = Primary Prevention Project; TPT Thrombosis Prevention Trial; WHS = Women's Health Study

Table 16. Key Question 2: Effect of Aspirin on Peptic Ulcers in Randomized, Controlled Trials

Study name Author, year	Mean F/U, years	Outcome	IG n/n analyzed	CG n/n analyzed	Relative Comparison (95% CI)
AAA Fowkes, 2010[69]	8.2	GI ulcer	14/1675	8/1675	NR
ASPREE (pilot) Silagy, 1993[127]	1	Duodenal ulcer	2/200	0/200	NR
		Deep bleeding duodenal ulcer	1/200	0/200	NR
BMD Peto, 1988[82]	6	Fatal hemorrhagic peptic ulcer	0.0/10,000 p-y	3.2/10,000 p-y	NR
		Nonfatal peptic ulcer	46.8/10,000 p-y	29.6/10,000 p-y	NR; p<0.05
		Fatal perforated peptic ulcer	2/3429	0/1710	NR
JPAD Ogawa, 2008[81]	4.37 (median)	Nonhemorrhagic duodenal ulcer	1/1262	1/1277	NR
		Nonhemorrhagic gastric ulcer	17/1262	3/1277	NR
		Hemorrhagic gastric ulcer	5/1262	3/1277	NR
JPPP Ikeda, 2014[91]	5 (median)	Gastroduodenal ulcer	191/7323	91/7335	NR
PHS Physician's Health Study, 1989[59]	5	Hemorrhagic ulcer	38/11037	22/11034	Adj RR: 1.77 (1.07, 2.94); p=0.04
	5	Upper GI ulcer	169/11037	138/11034	Adj RR: 1.22 (0.98, 1.53); p=0.08
WHS Ridker, 2005[8]	10.1	Peptic ulcer	542/19934	413/19942	Adj RR: 1.32 (1.16, 1.50); p<0.001

Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis; adj = adjusted; ASPREE = Aspirin in Reducing Events in the Elderly; BMD = British Male Doctors; CI = confidence interval; F/U = followup; GI = gastrointestinal; JPAD = Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; JPPP = Japanese Primary Prevention Project; p-y = person-years; PHS = Physician's Health Study; SNDR = Swedish National Diabetes Register; WHS = Women's Health Study

Table 17. Key Question 2: Effect of Aspirin on Intracranial Bleeding in Randomized, Controlled Trials

Study name Author, year Quality	Mean F/U, years	Outcome	IG n/n analyzed	CG n/n analyzed	Peto OR (95% CI)
AAA Fowkes, 2010[69]	8.2	Intracranial bleeding	11/1675	7/1675	1.08 (0.42, 2.81)
ARRIVE Gaziano, 2018[56]	5 (median)	Total hemorrhagic stroke*	8/6270	11/6276	1.88 (0.97, 3.64)
ASCEND ASCEND Study Collaborative, 2018[55]	7.4	Total intracranial hemorrhage	55/7740	45/7740	1.50 (0.26, 8.66)
ASPREE McNeil, 2018[101]	4.7	Intracranial bleeding	107/9525	72/9589	0.93 (0.45, 1.93)
BMD Peto, 1988[82]	6	Total hemorrhagic stroke*	13/3429	6/1710	1.36 (0.31, 5.98)
HOT Hanson, 1998[70]	3.8	Total hemorrhagic stroke*	14/9399	15/9391	1.24 (0.83, 1.87)
JPAD Ogawa, 2008[81]	4.37 (median)	Intracranial bleeding	8/1262	7/1277	0.67 (0.12, 3.87)
JPPP Ikeda, 2014[91]	5 (median)	Total intracranial hemorrhage	52/7220	36/7244	1.16 (0.42, 3.19)
PHS Physician's Health Study, 1989[59]	5	Total hemorrhagic stroke*	23/11037	12/11034	1.56 (0.62, 3.95)
POPADAD Belch, 2008[66]	6.7 (median)	Fatal hemorrhagic stroke*	2/638	3/638	1.22 (0.83, 1.81)
PPP Rongaclioni, 2001[64]	3.6	Intracranial bleeding	4/2226	3/2269	1.45 (0.95, 2.20)
TPT The Medical Research Council's General Practice Research Framework, 1998[45]	6.8 (median)	Total hemorrhagic stroke*	3/1268	2/1272	0.73 (0.30, 1.79)
WHS Ridker, 2005[83]	10.1	Total hemorrhagic stroke*	51/19934	41/19942	1.49 (1.11, 2.01)

* Includes neurological deficits as a result of intracerebral hemorrhage and subarachnoid hemorrhage.

Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis; ARRIVE = Aspirin to Reduce Risk of Initial Vascular Events; ASCEND = A Study of Cardiovascular Events in Diabetes; ASPREE = Aspirin in Reducing Events in the Elderly; BMD = British Male Doctors; CG = control group; CI = confidence interval; F/U = followup; HOT = Hypertension Optimal Treatment Study; IG = intervention group; JPAD = Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; JPPP = Japanese Primary Prevention Project; PHS = Physician's Health Study; n = number of participants; OR = odds ratio; POPADAD = The Prevention of Progression of Arterial Disease and Diabetes trial; PPP = Primary Prevention Project; TPT Thrombosis Prevention Trial; WHS = Women's Health Study

Table 18. Key Question 2: Crude Absolute Incidence Rates and Relative Rates of Bleeding Harms in Aspirin and Nonaspirin Users as Reported in Trials and Cohort Studies

Outcome	K (N)	Aspirin Crude absolute rates per 100k p-y Range		No Aspirin* Crude absolute rates per 100k p-y Range		Relative Comparison of Aspirin vs No Aspirin (95% CI)	
		Trials†	Cohorts	Trials†	Cohorts	Trials Pooled Peto OR for all doses (95% CI)	Cohorts IRR, HR, or RR (95% CI)
Total major bleed	RCTs: 12 (160,404) Cohorts: 1 (372,850)	68 to 550	558	57 to 430	360	1.45 (1.33, 1.58)	1.55 (1.48, 1.63)
Major gastrointestinal bleeding	RCTs: 12 (146,340) Cohorts: 5 (852,014)	58 to 500	193 to 380	0 to 230	107 to 340	1.57 (1.37, 1.78)	0.97 (0.77, 1.16) to 1.67 (1.20, 2.33)‡
Hemorrhagic stroke	RCTs: 12 (160,404) Cohorts: 3 (119,781)	25 to 114	13.2 to 360	20 to 125	15.8 to 470	1.23 (1.01, 1.48)	0.85 (0.53, 1.10) to 1.26 (0.70, 2.25)
Intracranial hemorrhage	RCTs: 13 (161,680) Cohorts: 1 (372,850)	26 to 250	209.8§	20 to 170	122.1§	1.33 (1.13, 1.56)	1.54 (1.43, 1.67)

***** In cohorts, controls were propensity-score matched or relative risks were adjusted for population characteristics

† When event rates and person-years were not reported, we calculated the event rate using the people with an event and the median followup time. We assumed that each person contributed the same median followup time.

‡ An additional cohort reports upper and lower gastrointestinal bleeding separately and these relative risks are not included in this range, but are reasonably consistent

§ Calculated using 603,797 p-y in aspirin group and 980,166 p-y in no aspirin group

Abbreviations: Adj. = adjusted; GI = gastrointestinal; HR = hazard ratio; IRR = incidence rate ratio; K = number of studies; NR = not reported; OR = odds ratio; p-y; person years; RR = relative risk

Table 19. Key Question 2: Effect of Aspirin on Major GI Bleeding in Cohort Studies

Study name Author, year	Mean F/U, years	Dose and duration	Outcome	Population	IG N with events/N analyzed Events per 100,000 p-y	CG N with Events/N analyzed Events per 100,000 p-y	Results (95% CI)
NHIRD Luo, 2019[98]	2.55	>14 defined daily doses per month (75-325 mg daily) 2.55 years	Major upper GI bleeding	Total	379/11105 p-y NR	326/11105 p-y NR	Adj HR: 1.48 (1.28, 1.72)
NHIRD Chen, 2017[106]	1	75-325 mg daily 1 year	Major lower GI bleeding	Total	108*/53805 p-y NR	161*/269025 p-y NR	Adj HR: 2.75 (2.06, 3.65)
			Major lower GI bleeding	<75 years	89*/52242 p-y NR	131*/261263 p-y NR	Adj HR: 2.62 (1.92, 3.58)
			Major lower GI bleeding	≥75 years	21*/1547 p-y NR	22*/7755 p-y NR	Adj HR: 3.95 (2.13, 7.32)
Korean National Health Insurance Service-Senior Cohort Jung, 2020[107]	7.8	"Low-dose" (not further specified) Mean 4.8 (minimum ≥6 months, IQR 2.7-7.3 years)	Major GI bleeding	Total	85/3366 300/100,000 p-y	288/10089 340/100,000 p-y	Adj HR: 0.97 (0.77, 1.16)
De Berardis, 2012[117]	5.7	≤300 mg (frequency NR) Median 5.7 (IQR 2.4-6.0)	Major GI bleeding	Total	2294/186425 380†/100,000 p-y	2193/186425 220†/100,000 p-y	IRR: 1.55 (1.46, 1.65)
HPFS Huang, 2010[120]	14	81-325 mg NR	Major GI bleeding	Total (regular users defined as ≥2/wk)	463/18230 231/100,000 p-y	244/14759 138/100,000 p-y	Adj RR: 1.32 (1.12, 1.55)
			Major GI bleeding	1-5 years continuous regular use	241/NR 232/100,000 p-y	244/14759 138/100,000 p-y	Adj RR: 1.19 (0.95, 1.48)¶
			Major GI bleeding	6-10 years continuous regular use	130/NR 229/100,000 p-y	244/14759 138/100,000 p-y	Adj RR: 1.18 (0.91, 1.53)¶

Table 19. Key Question 2: Effect of Aspirin on Major GI Bleeding in Cohort Studies

Study name Author, year	Mean F/U, years	Dose and duration	Outcome	Population	IG N with events/N analyzed Events per 100,000 p-y	CG N with Events/N analyzed Events per 100,000 p-y	Results (95% CI)
			Major GI bleeding	>10 years continuous regular use	92/NR 230/100,000 p-y	244/14759 138/100,000 p-y	Adj RR: 1.01 (0.75, 1.35)¶
			Major GI bleeding	81 mg daily use	94/NR 271/100,000 p-y	139/NR 196/100,000 p-y	Adj RR: 1.17 (0.89, 1.53)
			Major GI bleeding	325 mg daily use	52/NR 347/100,000 p-y	139/NR 196/100,000 p-y	Adj RR: 1.67 (1.20, 2.33)
			Major GI bleeding	≤60 years, regular users	64/NR 120/100,000 p-y	66/NR 87/100,000 p-y	NR#
			Major GI bleeding	>60 years, regular users	399/NR 270/100,000 p-y	178/NR 176/100,000 p-y	NR#
			Major lower GI bleeding	Total (regular users defined as ≥2/wk)	193/18230 96/100,000 p-y	110/14759 62/100,000 p-y	Adj RR: 1.22 (0.95, 1.56)
			Major lower GI bleeding	1-5 years continuous regular use	102/NR 98/100,000 p-y	110/14759 62/100,000 p-y	Adj RR: 1.20 (0.86, 1.68)**
			Major lower GI bleeding	6-10 years continuous regular use	49/NR 86/100,000 p-y	110/14759 62/100,000 p-y	Adj RR: 1.05 (0.70, 1.57)**
			Major lower GI bleeding	>10 years continuous regular use	42/NR 105/100,000 p-y	110/14759 62/100,000 p-y	Adj RR: 1.10 (0.71, 1.70)**
			Major upper GI bleeding	Total (regular users defined as ≥2/wk)	204/18230 102/100,000 p-y	99/14759 56/100,000 p-y	Adj RR: 1.49 (1.16, 1.92)
			Major upper GI bleeding	1-5 years continuous regular use	101/NR 0.97/1,000 p-y	99/14759 0.56/1,000 p-y	Adj RR: 1.18 (0.84, 1.66)††
			Major upper GI bleeding	6-10 years continuous regular use	61/NR 107/100,000 p-y	99/14759 56/100,000 p-y	Adj RR: 1.33 (0.90, 1.96)††
			Major upper GI bleeding	>10 years continuous regular use	42/NR 105/100,000 p-y	99/14759 56/100,000 p-y	Adj RR: 1.11 (0.71, 1.71)††

Table 19. Key Question 2: Effect of Aspirin on Major GI Bleeding in Cohort Studies

Study name Author, year	Mean F/U, years	Dose and duration	Outcome	Population	IG N with events/N analyzed Events per 100,000 p-y	CG N with Events/N analyzed Events per 100,000 p-y	Results (95% CI)
NHS Huang, 2011[121]	24	325 mg	Major GI bleeding	Total (regular users defined as ≥2/wk)	818/32187 193/100,000 p-y	719/55493 107/100,000 p-y	Adj RR: 1.43 (1.29, 1.59)
			Major GI bleeding	1-5 years continuous regular use	302/NR 162/100,000 p-y	1015/NR 129/100,000 p-y	Adj RR: 0.99 (0.87, 1.13)‡‡
			Major GI bleeding	6-10 years continuous regular use	119/NR 183/100,000 p-y	1015/NR 129/100,000 p-y	Adj RR: 0.98 (0.81, 1.20)‡‡
			Major GI bleeding	11-20 years continuous regular use	61/NR 207/100,000 p-y	1015/NR 129/100,000 p-y	Adj RR: 0.98 (0.74, 1.28)‡‡
			Major GI bleeding	>20 years continuous regular use	40/NR 151/100,000 p-y	1015/NR 129/100,000 p-y	Adj RR: 0.79 (0.57, 1.11)‡‡
			Major GI bleeding	≤60 years	146/NR 94/100,000 p-y	158/NR 50/100,000 p-y	NR§§
			Major GI bleeding	>60 years	672/NR 270/100,000 p-y	561/NR 176/100,000 p-y	NR§§
			Major GI bleeding	High CVD risk‖ ‖	NR/NR	NR/NR	Adj RR: 1.55 (1.31, 1.83)
			Major upper GI bleeding	Total (regular users defined as ≥2/wk)	369/32187 87/100,000 p-y	267/55493 40/100,000 p-y	Adj RR: 1.70 (1.45, 2.00)
			Major upper GI bleeding	1-5 years continuous regular use	123/NR 66/100,000 p-y	406/NR 52/100,000 p-y	Adj RR: 0.97 (0.79, 1.19)¶¶
			Major upper GI bleeding	6-10 years continuous regular use	58/NR 89/100,000 p-y	406/NR 52/100,000 p-y	Adj RR: 1.13 (0.85, 1.51)¶¶
			Major upper GI bleeding	11-20 years continuous regular use	31/NR 105/100,000 p-y	406/NR 52/100,000 p-y	Adj RR: 1.09 (0.74, 1.61)¶¶
			Major upper GI bleeding	>20 years continuous regular use	18/NR 68/100,000 p-y	406/NR 52/100,000 p-y	Adj RR: 0.76 (0.46, 1.26)¶¶

Table 19. Key Question 2: Effect of Aspirin on Major GI Bleeding in Cohort Studies

Study name Author, year	Mean F/U, years	Dose and duration	Outcome	Population	IG N with events/N analyzed Events per 100,000 p-y	CG N with Events/N analyzed Events per 100,000 p-y	Results (95% CI)
			Major lower GI bleeding	Total (regular users defined as ≥2/wk)	319/32187 75/100,000 p-y	345/55493 51/100,000 p-y	Adj RR: 1.21 (1.03, 1.41)
			Major lower GI bleeding	1-5 years continuous regular use	127/NR 68/100,000 p-y	460/NR 58/100,000 p-y	Adj RR: 0.98 (0.80, 1.20)##
			Major lower GI bleeding	6-10 years continuous regular use	41/NR 63/100,000 p-y	460/NR 58/100,000 p-y	Adj RR: 0.82 (0.59, 1.14)##
			Major lower GI bleeding	11-20 years continuous regular use	23/NR 78/100,000 p-y	460/NR 58/100,000 p-y	Adj RR: 0.97 (0.62, 1.51)##
			Major lower GI bleeding	>20 years continuous regular use	13/NR 49/100,000 p-y	460/NR 58/100,000 p-y	Adj RR: 0.70 (0.39, 1.26)##

*Ns calculated from percents
†Calculated using 603,797 p-y in aspirin group and 980,166 p-y in no aspirin group
¶p-value for trend by duration: 0.749; multivariate analyses for adjustment minus dose available
#p-value for interaction 0.81; HR displayed in figure but data not reported (for ≤60 years; estimate to the right of 1.0, 95% CI appears to cross 1.0; for >60 years, estimate to the right of 1.0, 95% CIs appear to not cross 1.0)
**p-value for trend=0.932; multivariate analysis adjusted for everything minus dose available
††p-value for trend=0.641; multivariate analysis adjusted for everything minus dose available
‡‡p-value for trend=0.280
§§P-value for interaction 0.15. HR shown in graph, but data not reported (for ≤60 years, estimate appears to be to the right of 1.0, with CIs not crossing the line; for >60 years, appears to be to the right of 1.0, with CIs not crossing the line.
‖‖High CVD risk defined as participants with history of prior MI or coronary artery bypass grafting or had at least 2 cardiac risk factors (BMI ≥30 kg/m2, DM, HTN, current smoking, hypercholesterolemia)
¶¶p-value for trend=0.744
##p-value for trend=0.212

Abbreviations: Adj = adjusted; BMI = body mass index; CG = control group; CI = confidence interval; CVD = Cardiovascular Disease; DM = diabetes mellitus; F/U = followup; g = grams; GI = gastrointestinal; HPFS = Health Professionals Followup Study; HR = hazard ratio; HTN = hypertension; IG = intervention group; IQR = interquartile range; mg = milligrams; n = number of participants; NHIRD = National Health Insurance Research Database; NHS = Nurses' Health Study; NR = not reported; p-y = person-years; RR = relative risk; SNDR = Swedish National Diabetes Register; wk = week

Table 20. Key Question 2: Effect of Aspirin on Intracranial Bleeding in Cohort Studies

Study name Author, year	F/U, mean years	Dose and duration, years	Outcome	Population	IG N with events/N analyzed Events per 100,000 p-y	CG N with events/N analyzed Events per 100,000 p-y	Results (95% CI)
Korean National Health Insurance Service-Senior Cohort Jung, 2020[107]	7.8	"Low-dose" (not further specified) Mean 4.8 (minimum ≥6 months IQR 2.7-7.3 years)	Hemorrhagic stroke - total	Total	101/3366 360/100,000 p-y	397/10089 470/100,000 p-y	Adj HR: 0.85 (0.53, 1.10)
De Berardis, 2012[117]	5.7	≤300 mg (frequency NR) 5.7 (IQR 2.4-6) years	Intracranial hemorrhage - total	Total	1267/186425 209.8*/100,000 p-y	1197/186425 122.1*/100,000 p-y	IRR: 1.54 (1.43, 1.67)
SNDR Ekstrom, 2013[118]	3.9	75 mg QD >12 months	Cerebral hemorrhage - total	Total	NR/4608	NR/14038	Adj HR: 1.26 (0.70, 2.25)†
			Cerebral hemorrhage - total	Male	NR/2585	NR/7721	Adj HR: 1.13 (0.54, 2.38)‡
			Cerebral hemorrhage - total	Female	NR/2023	NR/6317	Adj HR: 1.42 (0.57, 3.58)§
			Cerebral hemorrhage - fatal	Total	NR/4608	NR/14038	Adj HR: 1.60 (0.51, 6.05)‖
			Cerebral hemorrhage - fatal	Female	NR/2023	NR/6317	Adj HR: 1.26 (0.11, 14.3)¶
			Cerebral hemorrhage - fatal	Male	NR/2585	NR/7721	Adj HR: 1.68 (0.46, 6.15)#
NHS Huang, 2011[121, 122]	14	325 mg per aspirin NR	Hemorrhagic stroke - total	1-6 aspirin per week	53/35960 13.2/100,000 p-y	61/19233 15.8/100,000 p-y	Unadj IRR: 0.84 (0.58, 1.21)**
			Hemorrhagic stroke - total	7-14 aspirin per week	22/7900 21.4/100,000 p-y	61/19233 15.8/100,000 p-y	Adj RR: 1.25 (0.76, 2.05)**
			Hemorrhagic stroke - total	≥15 aspirin per week	16/4694 30.0/100,000 p-y	61/19233 15.8/100,000 p-y	Adj RR: 1.63 (0.93, 2.86)**
			Subarachnoid hemorrhagic stroke - total	1-6 aspirin per week	38/35960 9.5/100,000 p-y	37/19233 9.6/100,000 p-y	Unadj IRR: 0.99 (0.63 to 1.56)**

Table 20. Key Question 2: Effect of Aspirin on Intracranial Bleeding in Cohort Studies

			Subarachnoid hemorrhagic stroke - total	7-14 aspirin per week	13/7900 12.7/100,000 p-y	37/19233 9.6/100,000 p-y	Adj RR: 1.28 (0.67, 2.43)**
			Subarachnoid hemorrhagic stroke - total	≥15 aspirin per week	12/4694 22.5/100,000 p-y	37/19233 9.6/100,000 p-y	Adj RR: 2.02 (1.04, 3.91)**

*Calculated using 603,797 p-y in aspirin group and 980,166 p-y in no aspirin group
†59 events in all participants total; not reported by group. 90 events per 100,000 p-y overall.
‡36 events in all males total; not reported by group. 100 events per 100,000 p-y overall.
§23 events in all females total; not reported by group. 80 events per 100,000 p-y overall.
‖14 events in all participants total; not reported by group. 20 events per 100,000 p-y overall.
¶3 events in all females total; not reported by group. 10 events per 1000 p-y overall.
#11 events in all males total; not reported by group. 30 events per 1000 p-y overall.
**p-value for trend by aspirin frequency=0.02 (for both outcomes)

Abbreviations: Adj=adjusted; CG=control group; CI=confidence interval; CVD=cardiovascular disease; F/U=followup; HR=hazard ratio; IG=intervention group; IQR=interquartile range; IRR=incidence rate ratio; ITA=Italy; NHS=Nurses' Health Study; NR=not reported; p-y=person-years; KOR=Korea; RR=relative risk; SNDR=Swedish National Diabetes Register; SWE=Sweden

Table 21. Summary of Evidence for Low-Dose Aspirin (≤100 mg/d)

Outcome	Studies (K) Study design Observations (N)	Summary of findings*	Consistency and precision	Overall SOE	Body of evidence limitations	Applicability
KQ1						
Major CVD events (total MI, total stroke, CVD death)	K=11 RCTs N=134,470	Peto OR (95% CI): 0.90 (0.85, 0.95) Range of absolute effects, %: -2.5 to -0.1	Consistent, precise	HIGH for benefit	**CVD outcomes:** Substantial clinical heterogeneity in populations, recency as a proxy for optimal CVD risk factor management, and trial duration. Trials mostly 4-6 years with one trial as long as 10 years. Trials may have insufficient followup for potential long-term CVD mortality benefit. Trials powered for composite CVD outcomes of varying severity (fatal and nonfatal outcomes with some trials including angina, revascularization in composite CVD outcome). Low event rates for stroke (1 to 2% for total stroke in control groups; <1% to 2% ischemic stroke events in control groups) limit precision for these outcomes. Studies infrequently adjusted for confounders.	Broadly appliable to primary prevention populations, including those with comorbidities.
Total MI	K=11 RCTs N=134,470	Peto OR (95% CI): 0.89 (0.82, 0.96) Range of absolute effects, %: -1.9 to 1.2	Consistent, precise	HIGH for benefit		
Total stroke	K=11 RCTs N=134,470	Peto OR (95% CI): 0.91 (0.84, 0.99) Range of absolute effects, %: -2.0 to 0.1	Reasonably consistent, precise	MODERATE for benefit		
Total ischemic stroke	K=5 RCTs N=79,334	Peto OR (95% CI): 0.82 (0.72, 0.92) Range of absolute effects, %: -0.6 to -0.2	Consistent, precise	MODERATE for benefit		
CVD mortality	K=11 RCTs N=134,470	Peto OR (95% CI): 0.95 (0.86, 1.05)	Reasonably consistent, imprecise	MODERATE for no benefit		
All-cause mortality	K=11 RCTs N=134,470	Peto OR (95% CI): 0.98 (0.93, 1.03)	Reasonably consistent, reasonably precise	MODERATE for no benefit		
CRC incidence (based on trial evidence only)	K=4 N=86,137	Peto OR (95% CI): 1.07 (0.92, 1.24)	Inconsistent, imprecise	INSUFFICIENT	**CRC outcomes:** Most trials have inadequate RCT followup period of ~5 years for cancer outcomes; only WHS has a randomized period of 10 years. Very few cases and wide confidence intervals. Long-term followup collected in an observational design where allocation to aspirin or control was no longer	Broadly applicable to primary prevention populations, but for longest-term F/U some analyses available for females only (WHS) or males only (TPT). TPT is an older trial
CRC incidence (based on long-term observational evidence only in primary prevention populations)	K=1 (WHS) N=39,876	WHS 17.5 years: Peto OR 0.82 (0.69 to 0.98) WHS 26 years: Peto OR 0.87 (0.74, 1.02)	NA (1 study: WHS), imprecise	INSUFFICIENT		

Table 21. Summary of Evidence for Low-Dose Aspirin (≤100 mg/d)

Outcome	Studies (K) Study design Observations (N)	Summary of findings*	Consistency and precision	Overall SOE	Body of evidence limitations	Applicability
CRC mortality (based on trial only evidence)	K=2 N=59,020	2 trials: Peto ORs 1.74 (1.02, 2.95) and 1.14 (0.73, 1.78)	Reasonably consistent, imprecise	INSUFFICIENT	randomized. Adherence and cross-over increased over time. Observational data for some trials collected by outside investigators.	where 41% were current smokers.
CRC mortality (based on long-term observational evidence only in primary prevention populations)	K=2 N=44,961	17-18 years F/U: 2 trials, not pooled: Peto ORs 0.86 (0.64, 1.16) and 0.62 (0.41, 0.94)	Consistent, imprecise	INSUFFICIENT		
KQ2						
Total major bleed	K=10 RCTs N=133,194	Peto OR (95% CI): 1.44 (1.32, 1.57) Range of absolute effects, %: 0.1 to 1.0	Consistent, precise	HIGH for harm	**Harms outcomes:** Rare event rates for bleeding harms limit precision, particularly for hemorrhagic stroke. Substantial clinical heterogeneity in populations, recency, and trial duration. Ascertainment methods of GI bleeding events rarely reported in trials. Dose analyses very limited in cohorts because many cohorts reported a wide range of doses.	Broadly appliable to primary prevention populations, including those with comorbidities.
Extracranial hemorrhage	K=10 RCTs N=133,194	Peto OR (95% CI): 1.53 (1.39, 1.70) Range of absolute effects, %: 0.2 to 0.9	Consistent, reasonably precise	MODERATE to HIGH for harm		
Major gastrointestinal bleeding	K=10 RCTs N=119,130 Cohort K=1 (HPFS) N=32,989	Peto OR (95% CI): 1.58 (1.38, 1.80) Range of absolute effects, %: 0.06 to 0.6 Cohort: Within-study comparisons from 1 cohort suggest that higher dose is associated with higher rates of major GI bleeding (81 mg/d: adjusted RR 1.17 [95% CI, 0.89 to 1.53]; 325 mg/d: adjusted RR 1.67 [95% CI, 1.20 to 2.33]).	Consistent, reasonably precise	MODERATE for harm		
Intracranial hemorrhage	K=11 RCTs N=134,470	Peto OR (95% CI): 1.31 (1.11, 1.54) Range of absolute effects, %: -0.2 to 0.4	Consistent, imprecise	MODERATE for harm		
Total hemorrhagic stroke	K=10 RCTs N=133,194 Cohort K=1 (NHS)	Peto OR (95% CI): 1.18 (0.97, 1.45) Cohort: within-study comparisons from 1 cohort suggest that increased days of aspirin/ week are	Inconsistent, imprecise	LOW for harm		

Table 21. Summary of Evidence for Low-Dose Aspirin (≤100 mg/d)

Outcome	Studies (K) Study design Observations (N)	Summary of findings*	Consistency and precision	Overall SOE	Body of evidence limitations	Applicability
	N=87,680	associated with a statistically significant trend for increased risk (p=0.02) (1-6 doses/week: IRR 0.84 [95% CI, 0.58 to1.21]; 7-14 doses/week adjusted RR 1.25 [95% CI, 0.76 to 2.05]; ≥15 doses/week adjusted RR 1.63 [95% CI, 0.93 to 2.86].				

*Pooled estimates presented where quantitative pooling was conducted; absolute effects calculated only when relative effects were statistically significant

Abbreviations: ACM = all-cause mortality; CI=confidence interval; CRC = colorectal cancer; CVD=cardiovascular disease; d = day; F/U = followup; GI = gastrointestinal; HPFS = Health Professionals' Followup Study; IPD = individual patient data; K=number of studies; KQ = Key Question; MA = meta-analysis; mg = milligram; N=number of participants; NA = not applicable; NHS = Nurses' Health Study; OR=odds ratio; PHS = Physicians' Health Study; RCT=randomized controlled trial; SOE = strength of evidence; TPT = Thrombosis Prevention Trial; US = United States; WHS = Women's Health Study

Table 22. Summary of Evidence for All Aspirin Doses and Sub-Key Questions (KQ1a/b, KQ2 a/b)

Outcome	Studies (K) Study design Observations (N)	Summary of findings*	Consistency and precision	Overall SOE	Body of evidence limitations	Applicability
KQ1						
Major CVD events	K=13 N=161,680	Peto OR (95% CI): 0.89 (0.85, 0.94) Range of absolute effects, %: -2.5 to -0.08	Consistent, precise	HIGH for benefit	**CVD outcomes:** Substantial clinical heterogeneity in populations, recency as a proxy for optimal CVD risk factor management, and trial duration. Trials mostly 4-6 years with one trial as long as 10 years. Trials powered for composite CVD outcomes of varying severity (fatal and nonfatal outcomes with some trials including angina, revascularization in composite CVD outcome). Low event rates for stroke (1 to 2% for total stroke in control groups; <1% to 2% ischemic stroke events in control groups) limit precision for these outcomes. Studies infrequently adjusted for confounders.	Broadly appliable to primary prevention populations, including those with comorbidities. Most trials (11 of 13) used low-dose aspirin which is the most clinically relevant in current practice.
Total MI	K=13 N=161,680	Peto OR (95% CI): 0.86 (0.80, 0.92) Range of absolute effects, %: -1.9 to 1.2	Consistent, precise	HIGH for benefit		
Total stroke	K=13 N=161,680	Peto OR (95% CI): 0.94 (0.87, 1.01) Range of absolute effects, %: -2.0 to 0.4	Reasonably consistent, reasonably precise	LOW for no benefit		
Total ischemic stroke	K=7 N=106,554	Peto OR (95% CI): 0.86 (0.77, 0.97) Range of absolute effects, %: -0.6 to 0.2	Consistent, precise	MODERATE for benefit		
CVD mortality	K=13 N=161,680	Peto OR (95% CI): 0.95 (0.87, 1.04)	Reasonably consistent, imprecise	MODERATE for no benefit		
All-cause mortality	K=13 N=161,680	Peto OR (95% CI): 0.97 (0.93, 1.02)	Reasonably consistent, reasonably precise	MODERATE for no benefit		
CRC incidence (based on trial only evidence)	K= 5 N=108,208	Peto OR (95% CI): 1.08 (0.94, 1.24)	Inconsistent, imprecise	INSUFFICIENT	**CRC outcomes:** Most trials have inadequate RCT followup period of ~5 years for cancer outcomes; only WHS has a randomized period of 10 years. Very few cases and wide confidence intervals. Long-term followup collected in an observational design where allocation to aspirin or control was no longer randomized.	Broadly applicable to primary prevention populations, but for longest-term F/U some analyses available for females only (WHS) or males only (TPT). TPT is an older trial where
CRC incidence (based on long-term observational evidence only in primary	K= 2 N=45,015	2 trials, up to 20 years F/U: Peto ORs 0.70 (0.50 to 0.98) and 0.82 (0.69, 0.98) Range of absolute effects, %: -1.1 to -0.2	Consistent, imprecise	VERY LOW for benefit		

Table 22. Summary of Evidence for All Aspirin Doses and Sub-Key Questions (KQ1a/b, KQ2 a/b)

Outcome	Studies (K) Study design Observations (N)	Summary of findings*	Consistency and precision	Overall SOE	Body of evidence limitations	Applicability
prevention populations)					Adherence and cross-over increased over time. Observational data for some trials collected by outside investigators.	41% were current smokers.
CRC mortality (based on trial only evidence)	K=2 N=59,020	2 trials: Peto ORs 1.74 (1.02, 2.95) and 1.14 (0.73, 1.78)	Reasonably consistent, imprecise	INSUFFICIENT		
CRC mortality (based on long-term observational evidence only in primary prevention populations)	K=3 N=50,100	Up to 18 years F/U: Peto OR 0.76 (0.62, 0.94) Range of absolute effects, %: -0.8 to -0.06	Consistent, imprecise	INSUFFICIENT		
KQ2						
Total major bleed	K=12 N=160,404 Cohort K=1 N=372,850	Peto OR (95% CI): 1.45 (1.33, 1.58) Range of absolute effects from trials, %: -0.1 to 1.0 Cohort: IRR 1.55 (1.48 to 1.63)	Consistent, precise	HIGH for harm	**Harms outcomes:** Rare event rates for bleeding harms limit precision. Substantial clinical heterogeneity in populations, recency, and trial duration. Ascertainment methods of GI bleeding events rarely reported in trials. Dose analyses very limited in cohorts because many cohorts reported a wide range of doses.	Broadly appliable to primary prevention populations, including those with comorbidities. Most trials (11 of 13) used low-dose aspirin which is the most clinically relevant in current practice.
Extracranial hemorrhage	K=12 N=160,404	Peto OR (95% CI): 1.53 (1.39, 1.69) Range of absolute effects from trials, %: -0.1 to 0.9	Consistent, reasonably precise	MODERATE for harm		
Major gastrointestinal bleeding	K=12 N=146,340 Cohort K=5 N=852,014	Peto OR (95% CI): 1.57 (1.37, 1.78) Range of absolute effects from trials, %: -0.1 to 0.6 Cohorts: Relative comparisons ranged from 0.97 (0.77, 1.16) to 1.67 (1.20, 2.33)	Consistent, reasonably precise	MODERATE for harm		
Intracranial hemorrhage	K=13 N=161,680 Cohort K=1 N=372,850	Peto OR (95% CI): 1.33 (1.13, 1.56) Range of absolute effects from trials, %: -0.2 to 0.4 Cohort: IRR 1.54 (1.43, 1.67) in 1 cohort	Consistent, imprecise	MODERATE for harm		

Table 22. Summary of Evidence for All Aspirin Doses and Sub-Key Questions (KQ1a/b, KQ2 a/b)

Outcome	Studies (K) Study design Observations (N)	Summary of findings*	Consistency and precision	Overall SOE	Body of evidence limitations	Applicability
Total hemorrhagic stroke	K=12 N=160,404 Cohort K=3 N=119,781	Peto OR (95% CI): 1.23 (1.01, 1.48) Range of absolute effects from trials, %: -0.07 to 0.2 Cohorts: Relative comparisons ranged from 0.85 (0.53, 1.10) to 1.26 (0.70, 2.25)	Inconsistent, imprecise	LOW for harm		
Subquestions for differences in treatment effect in specific a priori populations and analyses by duration						
KQ1/2a. Differences in treatment effect for CVD outcomes, CRC, and harms in a priori identified subpopulations defined by age, sex, race and ethnicity, diabetes, and CVD risk	See specific population credibility table (Appendix D, Table 23) for details	In the body of evidence for aspirin for the primary prevention of CVD, there is robust and credible reporting for CVD outcomes for subpopulations as defined by age and sex. Reporting is less robust, but still credible, for CVD outcomes by diabetes status and baseline CVD risk strata. Analyses by race and ethnicity are extremely sparse. For all subpopulation analyses examined, ACM, CRC and harms were reported less frequently than CVD outcomes. Findings consistently showed no difference in treatment effect across all subpopulations evaluated and CVD outcomes, all-cause mortality, CRC, and harms, with one notable exception. There was an inconsistent signal in analyses by age where WHS and PHS reported statistically significant interaction testing with greater benefit in older age groups for MI. This finding was not consistent with findings in other trials for CVD composite outcomes and such suggestion of treatment effect modification was not confirmed in a prior 2009 IPD MA.	See specific population credibility table (Appendix D, Table 23) for details	INSUFFICIENT to LOW	No updated IPD MA that includes 3 trials published since previous review. IPD MA is more appropriate for evaluation of potential heterogeneity of treatment effect than trial-level analyses. For analyses by baseline CVD risk, each trial used a different CVD risk calculator and different risk thresholds Adjustments for confounders were generally not performed in subgroup analyses and in a few cases it was unclear if they were performed Limited reporting for ACM, CRC, harms.	For analyses by age, sex, and diabetes status, broad applicability across primary prevention populations In the 1 reporting trial for race and ethnicity, only 13% of participants were from the US. No trials reported CVD risk subgroups defined by the Pooled Cohort Equations; others were study-derived scores not available or validated for use in clinical practice.

Table 22. Summary of Evidence for All Aspirin Doses and Sub-Key Questions (KQ1a/b, KQ2 a/b)

Outcome	Studies (K) Study design Observations (N)	Summary of findings*	Consistency and precision	Overall SOE	Body of evidence limitations	Applicability
KQ1/2b. Differences in treatment effect for CVD outcomes, CRC, and harms by treatment duration	CVD outcomes K=11 N=137,653 CRC K=1 N=39,876 Harms K=4 N=86,224	In cases where time-to-event analyses suggest benefit for individual CVD outcomes, benefit generally accrues within the first 1-2 years. For CRC incidence, followup rather than duration of use appeared to show a trend towards effects appearing after 10 years and continuing through approximately 17 to 20 years, however the results are driven by the large WHS trial. Only 4 of 14 trials report time-to-event analyses for any bleeding harms. Using Kaplan-Meier curves, it appears that the bleeding harms occur immediately or at about 1 year. However, results are statistically significant in only 2 of 4 trials reporting time-to-event analyses.	CVD: consistent and reasonably precise CRC: consistency NA and precise HARMS: consistent and reasonably precise	MODERATE that CVD benefit accrues in 1-2 years and continues for at least 4-6 years INSUFFICIENT for CRC outcomes MODERATE that bleeding harm accrues soon after aspirin initiation	In most trials, aspirin administration continued for only the 4-6 year trial duration so it is difficult to make any conclusions about effect of aspirin on CVD outcomes for longer term use. Most trials reported time-to-event analyses for study-defined CVD composite outcomes and there was variation in the definition for these composites. Analyses limited by very rare harms events.	Broadly appliable to primary prevention populations, including those with comorbidities. CRC duration analyses limited 1 study in females only

*Pooled estimates presented where quantitative pooling was conducted; absolute effects calculated only when relative effects were statistically significant

Abbreviations: ACM = all-cause mortality; CI=confidence interval; CRC = colorectal cancer; CVD=cardiovascular disease; F/U = followup; GI = gastrointestinal; HPFS = Health Professionals' Followup Study; IPD = individual patient data; K=number of studies; KQ = Key Question; MA = meta-analysis; MOD = moderate; N=number of participants; NA = not applicable; NHS = Nurses' Health Study; OR=odds ratio; PHS = Physicians' Health Study; RCT=randomized controlled trial; SOE = strength of evidence; TPT = Thrombosis Prevention Trial; US = United States; WHS = Women's Health Study

Literature Search Strategies for Primary Literature

Key:
/ = MeSH subject heading
$ = truncation
ti = word in title
ab = word in abstract
pt = publication type
* = truncation
kw = keyword
sb = subset
pdat = publication date
fs = floating subheading

MEDLINE

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R)

1 Colorectal Neoplasms/
2 Colonic Neoplasms/
3 Sigmoid Neoplasms/
4 Colorectal Neoplasms, Hereditary Nonpolyposis/
5 Rectal Neoplasms/
6 Anus Neoplasms/
7 Anal Gland Neoplasms/
8 Colonic Polyps/
9 (colorectal or colon or colonic or rectal or rectum or rectosigmoid$).ti,ab.
10 (cancer$ or carcinoma$ or malignan$ or tumor$ or tumour$ or neoplas$ or polyp$).ti,ab.
11 9 and 10
12 or/1-8,11
13 Aspirin/
14 Salicylates/
15 aspirin.ti,ab.
16 acetylsalicylic.ti,ab.
17 salicylate$.ti,ab.
18 or/13-17
19 12 and 18
20 limit 19 to (english language and yr="2014 -Current")
21 Cardiovascular Diseases/
22 Heart Diseases/
23 Heart Arrest/
24 Death, Sudden, Cardiac/
25 Out-of-Hospital Cardiac Arrest/
26 Myocardial Ischemia/
27 Acute Coronary Syndrome/

28 Angina Pectoris/
29 Angina, Stable/
30 Angina, Unstable/
31 Angina Pectoris, Variant/
32 Microvascular Angina/
33 Coronary Disease/
34 Coronary Artery Disease/
35 Coronary Occlusion/
36 Coronary Stenosis/
37 Coronary Restenosis/
38 Coronary Thrombosis/
39 Myocardial Infarction/
40 Anterior Wall Myocardial Infarction/
41 Inferior Wall Myocardial Infarction/
42 No-Reflow Phenomenon/
43 Shock, Cardiogenic/
44 Myocardial Reperfusion Injury/
45 Myocardial Stunning/
46 Vascular Diseases/
47 Stroke/
48 Brain Infarction/
49 Brain Stem Infarctions/
50 Lateral Medullary Syndrome/
51 Cerebral Infarction/
52 Infarction, Anterior Cerebral Artery/
53 Infarction, Middle Cerebral Artery/
54 Infarction, Posterior Cerebral Artery/
55 Stroke, Lacunar/
56 cardiovascular disease$.ti,ab.
57 heart disease$.ti,ab.
58 myocardial infarction.ti,ab.
59 heart arrest.ti,ab.
60 myocardial ischemia.ti,ab.
61 myocardial ischaemia.ti,ab.
62 coronary artery disease.ti,ab.
63 heart attack$.ti,ab.
64 stroke.ti,ab.
65 cerebrovascular disease$.ti,ab.
66 cerebrovascular disorder$.ti,ab.
67 cardiac arrest.ti,ab.
68 acute coronary syndrome.ti,ab.
69 angina pectoris.ti,ab.
70 stable angina.ti,ab.
71 unstable angina.ti,ab.

72 microvascular angina.ti,ab.
73 coronary occlusion.ti,ab.
74 coronary disease.ti,ab.
75 coronary thrombosis.ti,ab.
76 coronary stenosis.ti,ab.
77 coronary restenosis.ti,ab.
78 myocardial stunning.ti,ab.
79 no-reflow phenomenon.ti,ab.
80 cardiogenic shock.ti,ab.
81 myocardial reperfusion.ti,ab.
82 vascular disease$.ti,ab.
83 brain infarction$.ti,ab.
84 brain stem infarction$.ti,ab.
85 artery infarction$.ti,ab.
86 cerebral infarction$.ti,ab.
87 lateral medullary syndrome.ti,ab.
88 or/21-87
89 (clinical trial or adaptive clinical trial or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or equivalence trial or pragmatic clinical trial or Meta-Analysis).pt.
90 clinical trials as topic/ or adaptive clinical trials as topic/ or clinical trials, phase i as topic/ or clinical trials, phase ii as topic/ or clinical trials, phase iii as topic/ or clinical trials, phase iv as topic/ or controlled clinical trials as topic/ or non-randomized controlled trials as topic/ or randomized controlled trials as topic/ or equivalence trials as topic/ or intention to treat analysis/ or pragmatic clinical trials as topic/ or meta-analysis as topic/
91 control groups/ or double-blind method/ or single-blind method/ or control groups/ or random allocation/ or placebos/
92 (randomized or randomised or placebo or randomly or phase iii or phase 3).ti,ab.
93 (RCT or placebo or sham or dummy or single blind$ or double blind$ or allocated or allocation or triple blind$ or treble blind$ or random$).ti,ab.
94 ((control$ or clinical) adj3 (study or studies or trial$ or group$)).ti,ab.
95 (Nonrandom$ or non random$ or non-random$ or quasi-random$ or quasirandom$).ti,ab.
96 allocated.ti,ab.
97 ((open label or open-label) adj5 (study or studies or trial$)).ti,ab.
98 ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial$)).ti,ab.
99 (pragmatic study or pragmatic studies).ti,ab.
100 ((pragmatic or practical) adj3 trial$).ti,ab.
101 ((quasiexperimental or quasi-experimental) adj3 (study or studies or trial$)).ti,ab.
102 (metaanaly$ or meta analy$).ti,ab.
103 or/89-102
104 18 and 88 and 103
105 limit 104 to (english language and yr="2014 -Current")
106 remove duplicates from 105

107 Mortality/
108 Morbidity/
109 Death/
110 Hemorrhage/
111 Gastrointestinal Hemorrhage/
112 Stroke/
113 Intracranial Hemorrhages/
114 Cerebral Hemorrhage/
115 safety.ti,ab.
116 harm$.ti,ab.
117 mortality.ti,ab.
118 toxicity.ti,ab.
119 (adverse adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab.
120 gastrointestinal.ti,ab.
121 bleed$.ti,ab.
122 hemorrhag$.ti,ab.
123 haemorrhag$.ti,ab.
124 stroke$.ti,ab.
125 adverse effects.fs.
126 toxicity.fs.
127 or/107-126
128 18 and 103 and 127
129 Animals/ not (Humans/ and Animals/)
130 128 not 129
131 limit 130 to (english language and yr="2014 -Current")
132 cohort studies/ or longitudinal studies/ or follow-up studies/ or prospective studies/ or evaluation study/
133 cohort.ti,ab.
134 longitudinal.ti,ab.
135 (follow-up or followup).ti,ab.
136 prospective$.ti,ab.
137 (comparison group$ or control group$).ti,ab.
138 observational.ti,ab.
139 database$.ti,ab.
140 (nonrandomi$ or non-randomi$).ti,ab.
141 population$.ti,ab.
142 Registries/
143 (registr$ or register$).ti,ab.
144 cross-sectional studies/
145 cross-sectional.ti,ab.
146 multivariate analysis/ or chi-square distribution/ or logistic models/
147 multivariate.ti,ab.
148 comparative study/

149 or/132-148
150 18 and 127 and 149
151 Animals/ not (Humans/ and Animals/)
152 150 not 151
153 limit 152 to (english language and yr="2014 -Current")
154 20 or 106 or 131 or 153

PUBMED *[publisher supplied references only]*

1. Aspirin[tiab] OR acetylsalicylic[tiab] OR Salicylate*[tiab]

2. ((colorectal[tiab] OR colon[tiab] OR colonic[tiab] OR rectal[tiab] OR rectum[tiab] OR rectosigmoid*[tiab]) AND (cancer[tiab] OR cancers[tiab] OR cancerous[tiab] OR carcinoma*[tiab] OR malignan*[tiab] OR tumor[tiab] OR tumoro*[tiab] OR tumors[tiab] OR tumour*[tiab] OR neoplasm*[tiab] OR polyp OR polypo* OR polyps[tiab]))

3. stroke[tiab] OR cerebrovascular disease*[tiab] OR cerebrovascular disorder*[tiab] OR brain infarction*[tiab] OR cerebral infarction*[tiab] OR artery infarction*[tiab] OR “coronary thrombosis”[tiab] OR “coronary occlusion”[tiab] OR “cardiogenic shock”[tiab] OR “myocardial reperfusion”[tiab] OR “myocardial stunning”[tiab] OR “lateral medullary syndrome”[tiab]

4. cardiovascular disease*[tiab] OR heart disease*[tiab] OR coronary disease*[tiab] OR vascular disease*[tiab] OR "myocardial infarction"[tiab] OR “cardiac arrest”[tiab] OR "heart arrest"[tiab] OR heart attack*[tiab] OR "myocardial ischemia"[tiab] OR "myocardial ischaemia"[tiab] OR "coronary artery disease"[tiab] OR “acute coronary syndrome”[tiab] OR angina[tiab] OR “coronary restenosis”[tiab] OR “coronary stenosis”[tiab]

5. #1 AND (#2 OR #3 OR #4) AND publisher[sb] AND (2014:2020[pdat])) Filters: English

Cochrane Central Register of Controlled Clinical Trials (CENTRAL)

#1 (Aspirin or acetylsalicylic or Salicylate*):ti,ab,kw
#2 (colorectal or colon or colonic or rectal or rectum or rectosigmoid):ti,ab,kw
#3 (cancer* or carcinoma* or malignan* or tumor* or tumour* or neoplas* or polyp*):ti,ab,kw
#4 #2 AND #3
#5 (coronary or angina or myocardial or "cardiac arrest" or "cardiac death" or "heart arrest"):ti,ab,kw
#6 (heart near attack*):ti,ab,kw
#7 (Cardiovascular next Disease*):ti,ab,kw
#8 (Heart next Disease*):ti,ab,kw
#9 (vascular next disease*):ti,ab,kw
#10 stroke:ti,ab,kw

#11 (brain next infarction*):ti,ab,kw
#12 ("brain stem" near infarction*):ti,ab,kw
#13 "Lateral Medullary Syndrome":ti,ab,kw
#14 (Cerebral near infarction*):ti,ab,kw
#15 (Cerebrovascular next disease*):ti,ab,kw
#16 (Cerebrovascular next disorder*):ti,ab,kw
#17 {OR #4-#16}
#18 #1 AND #17 with Publication Year from 2014 to 2020, in Trials
#19 #18 NOT (clinicaltrials or trialsearch):so

Embase

#1 'rectum tumor'/exp/mj OR 'colon tumor'/exp/mj
#2 colorectal:ti,ab OR colon:ti,ab OR colonic:ti,ab OR rectal:ti,ab OR rectum:ti,ab OR rectosigmoid*:ti,ab
#3 cancer*:ti,ab OR carcinoma*:ti,ab OR malignan*:ti,ab OR tumor*:ti,ab OR tumour*:ti,ab OR neoplas*:ti,ab OR polyp*:ti,ab
#4 #2 AND #3
#5 #1 OR #4
#6 'acetylsalicylic acid'/mj
#7 aspirin:ti,ab OR acetylsalicylic:ti,ab OR salicylate*:ti,ab
#8 #6 OR #7
#9 #5 AND #8
#10 'cardiovascular disease'/exp/mj
#11 'cardiovascular disease*':ti,ab OR 'heart disease*':ti,ab OR 'myocardial infarction':ti,ab OR 'heart arrest':ti,ab OR 'myocardial ischemia':ti,ab OR 'myocardial ischaemia':ti,ab OR 'coronary artery disease':ti,ab OR 'heart attack*':ti,ab OR stroke:ti,ab OR 'cerebrovascular disease*':ti,ab OR 'cerebrovascular disorder*':ti,ab OR 'cardiac arrest':ti,ab OR 'acute coronary syndrome':ti,ab OR 'angina pectoris':ti,ab OR 'stable angina':ti,ab OR 'unstable angina':ti,ab OR 'microvascular angina':ti,ab OR 'coronary occlusion':ti,ab OR 'coronary disease':ti,ab OR 'coronary thrombosis':ti,ab OR 'coronary stenosis':ti,ab OR 'coronary restenosis':ti,ab OR 'myocardial stunning':ti,ab OR 'no-reflow phenomenon':ti,ab OR 'cardiogenic shock':ti,ab OR 'myocardial reperfusion':ti,ab OR 'vascular disease*':ti,ab OR 'brain infarction*':ti,ab OR 'brain stem infarction*':ti,ab OR 'artery infarction*':ti,ab OR 'cerebral infarction*':ti,ab OR 'lateral medullary syndrome':ti,ab
#12 #10 OR #11
#13 #8 AND #12
#14 'clinical trial'/de OR 'controlled clinical trial'/de OR 'randomized controlled trial'/exp OR 'randomization'/exp OR 'single blind procedure'/de OR 'double blind procedure'/de OR 'crossover procedure'/de OR 'placebo'/de OR 'randomized controlled trial (topic)'/de OR 'clinical trial (topic)'/de OR 'controlled clinical trial (topic)'/de OR 'meta analysis'/exp OR 'meta analysis (topic)'/de
#15 trial:ti OR compare:ti OR compared:ti OR comparison:ti
#16 (evaluated:ab OR evaluate:ab OR evaluating:ab OR assessed:ab OR assess:ab) AND (compare:ab OR compared:ab OR comparing:ab OR comparison:ab)

#17 (open NEXT/1 label):ti,ab
#18 ((double OR single OR doubly OR singly) NEXT/1 (blind OR blinded OR blindly)):ti,ab
#19 (parallel NEXT/1 group*):ti,ab
#20 crossover:ti,ab OR 'cross over':ti,ab
#21 ((assign* OR match OR matched OR allocation) NEAR/6 (alternate OR group OR groups OR intervention OR interventions OR patient OR patients OR subject OR subjects OR participant OR participants)):ti,ab
#22 assigned:ti,ab OR allocated:ti,ab
#23 volunteer:ti,ab OR volunteers:ti,ab
#24 'phase iii':ti,ab OR 'phase 3':ti,ab
#25 rct:ti,ab OR placebo:ti,ab OR sham:ti,ab OR dummy:ti,ab OR 'single blind*':ti,ab OR 'double blind*':ti,ab OR allocated:ti,ab OR allocation:ti,ab OR 'triple blind*':ti,ab OR 'treble blind*':ti,ab OR random*:ti,ab
#26 ((control* OR clinical) NEAR/3 (study OR studies OR trial* OR group* OR design)):ti,ab
#27 ((equivalence OR superiority OR 'non inferiority' OR noninferiority) NEAR/3 (study OR studies OR trial*)):ti,ab
#28 'pragmatic study':ti,ab OR 'pragmatic studies':ti,ab
#29 ((pragmatic OR practical) NEAR/3 trial*):ti,ab
#30 ((quasiexperimental OR 'quasi experimental') NEAR/3 (study OR studies OR trial*)):ti,ab
#31 metaanaly*:ti,ab OR 'meta analy*':ti,ab
#32 #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31
#33 #9 OR #13
#34 #32 AND #33 AND [humans]/lim AND [english]/lim AND [2014-2020]/py AND ([young adult]/lim OR [adult]/lim OR [middle aged]/lim OR [aged]/lim OR [very elderly]/lim)
#35 'mortality'/exp/mj OR 'morbidity'/exp/mj OR 'death'/exp/mj OR 'bleeding'/exp/mj OR 'cerebrovascular accident'/exp/mj OR 'adverse event'/exp/mj OR 'toxicity'/exp/mj
#36 safety:ti,ab OR harm*:ti,ab OR mortality:ti,ab OR toxicity:ti,ab OR gastrointestinal:ti,ab OR bleed*:ti,ab OR hemorrhag*:ti,ab OR haemorrhag*:ti,ab OR stroke*:ti,ab
#37 #35 OR #36
#38 #8 AND #32 AND #37
#39 'longitudinal study'/exp OR 'prospective study'/de OR 'cohort analysis'/de OR 'follow up'/de OR 'register'/de OR 'cross-sectional study'/de
#40 cohort*:ti,ab OR longitudinal:ti,ab OR 'follow up':ti,ab OR followup:ti,ab OR prospective*:ti,ab OR 'comparison group*':ti,ab OR 'control group*':ti,ab OR observational:ti,ab OR database*:ti,ab OR nonrandomi*:ti,ab OR population*:ti,ab OR registr*:ti,ab OR register*:ti,ab OR 'cross-sectional':ti,ab
#41 'multivariate analysis'/exp OR 'chi square distribution'/de
#42 multivariate:ti,ab
#43 'comparative study'/de
#44 #39 OR #40 OR #41 OR #42 OR #43
#45 #8 AND #37 AND #44
#46 #38 OR #45

#47 (#38 OR #45) AND ([young adult]/lim OR [adult]/lim OR [middle aged]/lim OR [aged]/lim OR [very elderly]/lim) AND [humans]/lim AND [english]/lim AND [2014-2020]/py
#48 #34 OR #47

Appendix A Table 1. Inclusion and Exclusion Criteria

	Inclusion	Exclusion
Aim	Primary prevention of CVD, CRC, and/or all-cause mortality	Secondary and tertiary prevention of CVD or CRC
Populations	Adults age ≥40 years without known CVD and at average risk for CRC or unselected for CRC risk*	Other selected nongeneralizable populations (e.g., those with genetic susceptibility syndromes or personal history of cancer)
Interventions	Regular oral aspirin use (at least 75 mg every other day) for 12 months	Coadministration with other nonaspirin antithrombotic medications (e.g., warfarin)
Comparisons	Placebo or no treatment	Any active substance or intervention
Outcomes	**KQ 1:** Myocardial infarction, stroke, death from myocardial infarction or stroke, CRC incidence, CRC mortality, and all-cause mortality **KQ 2:** Major bleeding, defined as bleeding requiring transfusion or hospitalization or leading to death (including but not limited to gastrointestinal bleeding), hemorrhagic stroke, or other serious harms	**KQ 1:** Intermediate markers of CVD (e.g., calcium scores, intimal medial thickness, or asymptomatic electrocardiography findings); intermediate markers of platelet function or clotting **KQ 2:** Postoperative or minor bleeding
Study Designs	**All KQs:** Good- and fair-quality studies, according to USPSTF criteria **KQ 1:** Randomized, controlled trials; controlled clinical trials; and individual patient data meta-analyses **KQ 2:** Randomized, controlled trials; controlled clinical trials; individual patient data meta-analyses; and large observational studies	**All KQs:** Poor-quality studies, according to USPSTF criteria **KQ 1:** Observational studies **KQ 2:** Case control studies, case series, case reports, narrative reviews, commentaries, or editorials
Setting	Studies conducted in countries categorized as "very high" on the 2017 Human Development Index, as defined by the United Nations Development Programme†	

***** For CRC outcomes only, populations with and without a history of CVD will be included.

† Andorra, Argentina, Australia, Austria, Bahamas, Bahrain, Barbados, Belarus, Belgium, Brunei Darussalam, Bulgaria, Canada, Chile, Croatia, Cyprus, Czechia, Denmark, Estonia, Finland, France, Germany, Greece, Hong Kong, Hungary, Iceland, Ireland, Israel, Italy, Japan, Kazakhstan, Korea (Republic of), Kuwait, Latvia, Liechtenstein, Lithuania, Luxembourg, Malaysia, Malta, Montenegro, Netherlands, New Zealand, Norway, Oman, Poland, Portugal, Qatar, Romania, Russian Federation, Saudi Arabia, Singapore, Slovakia, Slovenia, Spain, Sweden, Switzerland, UK, United Arab Emirates, Uruguay, US. Taiwan is not incorporated into HDI calculations for the People's Republic of China and will be considered very high HDI based on calculations from Taiwan's government.

Abbreviations: CRC = colorectal cancer; CVD = cardiovascular disease; KQ = key question; mg = milligram; USPSTF = United States Preventive Services Task Force

Appendix A Table 2. Quality Assessment Criteria*

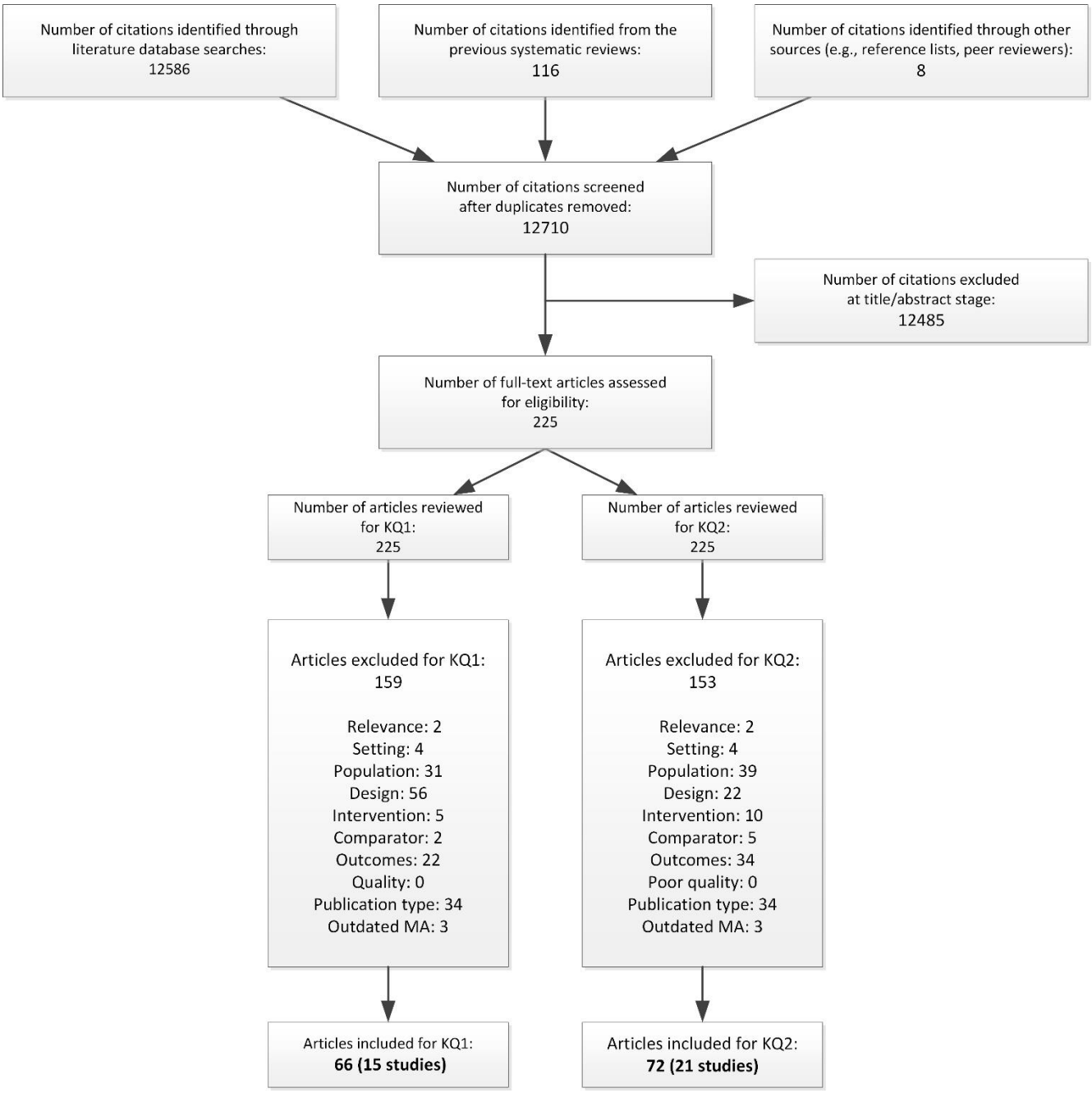
Study Design	Adapted Quality Criteria
Cohort studies, adapted from Newcastle-Ottawa Scale[201]	**Bias arising in randomization process or due to confounding** • Balance in baseline characteristics • No baseline confounding • No time-varying confounding **Bias in selecting participants into the study** • No evidence of biased selection of sample • Start of followup and start of intervention coincide **Bias due to departures form intended interventions** • Participant intervention status is clearly and explicitly defined and measured • Classification of intervention status is unaffected by knowledge of the outcome or risk of the outcome **Bias in classifying interventions** • Fidelity to intervention protocol • Participants were analyzed as originally allocated **Bias from missing data** • Outcome data are reasonably complete and comparable between groups • Confounding variables that are controlled for in analysis are reasonably complete • Reasons for missing data are similar across groups • Missing data are unlikely to bias results **Bias in measurement of outcomes** • Blinding of outcome assessors • Outcomes are measured using consistent and appropriate procedures and instruments across treatment groups • No evidence of biased use of inferential statistics **Bias in reporting results selectively** • No evidence that the measures, analyses, or subgroup analyses are selectively reported

Appendix A Table 2. Quality Assessment Criteria*

Study Design	Adapted Quality Criteria
Randomized clinical trials, adapted from U.S. Preventive Services Task Force Manual[46]	**Bias arising in the randomization process or due to confounding** • Valid random assignment/random sequence generation method used • Allocation concealed • Balance in baseline characteristics **Bias in selecting participants into the study** • CCT only: No evidence of biased selection of sample **Bias due to departures from intended interventions** • Fidelity to the intervention protocol • Low risk of contamination between groups • Participants were analyzed as originally allocated **Bias from missing data** • No, or minimal, post-randomization exclusions • Outcome data are reasonably complete and comparable between groups • Reasons for missing data are similar across groups • Missing data are unlikely to bias results **Bias in measurement of outcomes** • Blinding of outcome assessors • Outcomes are measured using consistent and appropriate procedures and instruments across treatment groups • No evidence of biased use of inferential statistics **Bias in reporting results selectively** • No evidence that the measures, analyses, or subgroup analyses are selectively reported

* All randomized clinical trials were classified as good, fair, or poor according to the USPSTF Procedure Manual[46]

Appendix A Figure 1. Literature Flow Diagram



Abbreviations: KQ = key question; MA = meta-analysis

Below is a list of included studies and their ancillary publications (indented below main results publication):

Key Question 1:

1. Ascend Study Collaborative Group, Bowman L, Mafham M, et al. Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus. N Engl J Med. 2018;379(16):1529-39. PMID: 30146931. https://dx.doi.org/10.1056/NEJMoa1804988
    a. Aung T, Haynes R, Barton J, et al. Cost-effective recruitment methods for a large randomised trial in people with diabetes: A Study of Cardiovascular Events iN Diabetes (ASCEND). Trials [Electronic Resource]. 2016;17(1):286. PMID: 27296091. https://dx.doi.org/10.1186/s13063-016-1354-9
    b. Wolfe R, Murray AM, Woods RL, et al. The aspirin in reducing events in the elderly trial: Statistical analysis plan. International Journal of Stroke. 2018;13(3):335-8. PMID: 29111960. https://dx.doi.org/10.1177/1747493017741383

2. Belch J, MacCuish A, Campbell I, 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 (Clinical research ed). 2008;337:a1840. PMID: 18927173.

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    a. Flossmann E, Rothwell PM, British Doctors Aspirin T, et al. Effect of aspirin on long-term risk of colorectal cancer: consistent evidence from randomised and observational studies. Lancet (London, England). 2007;369(9573):1603-13. PMID: 17499602. https://dx.doi.org/10.1016/S0140-6736(07)60747-8
    b. Rothwell PM, Wilson M, Elwin CE, et al. Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials. Lancet (London, England). 2010;376(9754):1741-50. PMID: 20970847. https://dx.doi.org/10.1016/S0140-6736(10)61543-7

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c. Cook NR, Cole SR, Hennekens CH. Use of a Marginal Structural Model to Determine the Effect of Aspirin on Cardiovascular Mortality in the Physicians' Health Study. American Journal of Epidemiology. 2002;155(11):1045-53. PMID: 12034583.
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e. Kurth T, Glynn RJ, Walker AM, et al. Inhibition of Clinical Benefits of Aspirin on First Myocardial Infarction by Nonsteroidal Antiinflammatory Drugs. Circulation. 2003;108(10):1191-5. PMID: 12939216.
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5. Fowkes FG, Price JF, Stewart MC, 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(9):841-8. PMID: 20197530.

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7. Hansson L, Zanchetti A, Carruthers SG, 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 (London, England). 1998;351(9118):1755-62. PMID: 9635947.
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    b. Hansson L, Zanchetti A. The Hypertension Optimal Treatment (HOT) Study: 12-month data on blood pressure and tolerability. With special reference to age and gender. Blood Press. 1995;4(5):313-9. PMID: 8535554
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the Elderly (ASPREE) trial. Contemporary Clinical Trials Communications. 2018;11:30-6. PMID: 30023457. https://dx.doi.org/10.1016/j.conctc.2018.05.015

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15. The Medical Research Council's General Practice Research Framework. 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. Lancet (London, England). 1998;351(9098):233-41. PMID: 9457092.
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    b. Rothwell PM, Wilson M, Elwin CE, et al. Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials. Lancet (London, England). 2010;376(9754):1741-50. PMID: 20970847. https://dx.doi.org/10.1016/S0140-6736(10)61543-7

Key Question 2:

1. Ascend Study Collaborative Group, Bowman L, Mafham M, et al. Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus. N Engl J Med. 2018;379(16):1529-39. PMID: 30146931. https://dx.doi.org/10.1056/NEJMoa1804988
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    b. Wolfe R, Murray AM, Woods RL, et al. The aspirin in reducing events in the elderly trial: Statistical analysis plan. International Journal of Stroke. 2018;13(3):335-8. PMID: 29111960. https://dx.doi.org/10.1177/1747493017741383

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Health Study. American Journal of Epidemiology. 2002;155(11):1045-53. PMID: 12034583.
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    c. Saito Y, Morimoto T, Ogawa H, et al. Low-dose aspirin therapy in patients with type 2 diabetes and reduced glomerular filtration rate: subanalysis from the JPAD trial. Diabetes care. 2011;34(2):280-5. PMID: 21270185.
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Appendix C. Excluded Studies

Code	Exclusion
E1	Study relevance
E2	Setting (not a very high index country)
E3	Population
E3a	Population: Patients with existing cardiovascular disease diagnosis or history
E3b	Population: Patients with a-fib, familial hypercholesterolemia, or hypercoagulable disorders
E3c	Population: Children or adults less than 40 years of age
E3d	Population: Observational study with less than 10,000 patients
E4	Study design: Not a randomized controlled trial or clinical control trial (Key Question 1 only)
E5	Intervention: Not relevant intervention/agent
E5a	Intervention: Duration less than 1 year
E5b	Intervention: Dose - Aspirin dose less than 75 milligrams every other day, dose not reported, or irregular or occasional use
E5c	Intervention: Non-oral or non-tablet forms of aspirin
E5d	Intervention: Aspirin as a co-treatment
E6	Comparisons: Any active substance or intervention
E7	Outcomes
E8	Study quality
E9	Non-English publication
E10	Publication type (i.e., conference abstracts)

Reference	Code
Allison, Matthew, Garland, Cedric, et al. The association between aspirin use and the incidence of colorectal cancer in women. Am J Epidemiol. 164(6): 567-575. 2006. PMID: 16847042. https://dx.doi.org/10.1093/aje/kwj250	KQ1E4 KQ2E7
Almas A, Ghazni MS, Hashmani S, Mushtaq Z. Aspirin in Primary Prevention of Myocardial Infarction/Angina and Stroke in Hypertensive Patients. Jcpsp, Journal of the College of Physicians & Surgeons - Pakistan. 28(7): 574. 2018. PMID: 29950269. https://dx.doi.org/10.29271/jcpsp.2018.07.574	KQ1E2 KQ2E2
Aspirin in coronary heart disease. The Coronary Drug Project Research Group. Circulation. 62(6 Pt 2): V59-62. 1980. PMID: 7002353.	KQ1E3a KQ2E3a

Reference	Code
Aspirin in coronary heart disease. The Coronary Drug Project Research Group. J Chronic Dis. 29(10,0021-9681 (Print),0021-9681 (Linking): 625-642. 1976. PMID: None.	KQ1E3a KQ2E3a
Aspirin Myocardial Infarction Study: design, methods and baseline results. US Department of Health and Human Services, Public Health Services, National Institutes of Health, 1980. 1980. PMID: None.	KQ1E3a KQ2E3a
At Chan, P Gibbs, S Orchard, J Lockery, et al. Effect of initiating aspirin on cancer events in the healthy elderly: Primary results from the aspree randomized controlled trial. Gastroenterology. Conference: 2019 DDW. United States. 156(6 s1): S-78-s-79. 2019. PMID: None.	KQ1E10 KQ2E10

Appendix C. Excluded Studies

Reference	Code
Baigent, C, Blackwell, L, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet. 373(9678): 1849-60. 2009. PMID: 19482214. https://dx.doi.org/10.1016/s0140-6736(09)60503-1	KQ1E11 KQ2E11
Barker AL, McNeil JJ, Seeman E, Ward SA, et al. A randomised controlled trial of low-dose aspirin for the prevention of fractures in healthy older people: protocol for the ASPREE-Fracture substudy. Injury Prevention. 22(4): 297-301. 2016. PMID: 26002770. https://dx.doi.org/10.1136/injuryprev-2015-041655	KQ1E7 KQ2E7
Baron, JA, Cole, BF, et al. A randomized trial of aspirin to prevent colorectal adenomas. N Engl J Med. 348(10): 891-899. 2003. PMID: 12621133. https://dx.doi.org/10.1056/NEJMoa021735	KQ1E3 KQ2E3
Bavry AA, Thomas F, Allison M, Johnson KC, et al. Nonsteroidal anti-inflammatory drugs and cardiovascular outcomes in women: results from the women's health initiative. Circ Cardiovasc Qual Outcomes. 7(4): 603-10. 2014. PMID: 25006185. https://dx.doi.org/10.1161/CIRCOUTCOMES.113.000800	KQ1E5 KQ2E5
Becattini, C, Agnelli, G, et al. Aspirin for preventing the recurrence of venous thromboembolism.. N Engl J Med. 366(21): 1959-1967. 2012. PMID: 22621626.	KQ1E3 KQ2E3
Belcaro G, Cesarone MR, Scipione C, Scipione V, et al. Delayed progression of atherosclerosis and cardiovascular events in asymptomatic patients with atherosclerotic plaques: 3-year prevention with the supplementation with Pycnogenol R+Centellicum R. Minerva Cardioangiol. 68(1): 15-21. 2020. PMID: 31625707. https://dx.doi.org/10.23736/S0026-4725.19.05051-5	KQ1E1 KQ2E1
Benamouzig R, Uzzan B, Deyra J, Martin A, et al. Prevention by daily soluble aspirin of colorectal adenoma recurrence: 4-year results of the APACC randomised trial. Gut. 61(2): 255-61. 2012. PMID: 21890814. https://dx.doi.org/10.1136/gutjnl-2011-300113	KQ1E3 KQ2E3
Benamouzig, R, Deyra, J, et al. Daily soluble aspirin and prevention of colorectal adenoma recurrence: one-year results of the APACC trial. Gastroenterology. 125(2): 328-36. 2003. PMID: 12891533. https://dx.doi.org/10.1016/s0016-5085(03)00887-4	KQ1E3 KQ2E3
Benamouzig, R, Yoon, H, et al. APACC, a French prospective study on aspirin efficacy in reducing colorectal adenoma recurrence: design and baseline findings. Eur J Cancer Prev. 10(4,0959-8278 (Print),0959-8278 (Linking): 327-335. 2001. PMID: 11535875. https://dx.doi.org/10.1097/00008469-200108000-00006	KQ1E3 KQ2E3
Bernard-Hardy, JM, Cunha, L, et al. European Stroke Prevention Study 2: baseline data. J Neurol Sci. 131(Suppl): 1-58. 1995. PMID: 7500119.	KQ1E3a KQ2E3a
Bouget, J, Balusson, F, et al. Major bleeding risk and mortality associated with antiplatelet drugs in real-world clinical practice. A prospective cohort study. PLoS One. 15(8): e0237022. 2020. PMID: 32764775. https://dx.doi.org/10.1371/journal.pone.0237022	KQ1E7 KQ2E4
Bowman L, Mafham M, Wallendszus K, Stevens W, et al. Effects of aspirin for primary prevention in persons with diabetes mellitus: the ASCEND Study Collaborative Group. J Vasc Surg. 69(1): 305. 2019. PMID: None. https://dx.doi.org/10.1016/j.jvs.2018.10.072	KQ1E10 KQ2E10

Appendix C. Excluded Studies

Reference	Code
Brasky TM, Liu J, White E, Peters U, et al. Non-steroidal anti-inflammatory drugs and cancer risk in women: results from the Women's Health Initiative. Int J Cancer. 135(8): 1869-83. 2014. PMID: 24599876. https://dx.doi.org/10.1002/ijc.28823	KQ1E4 KQ2E7
Brasky, TM, Potter, JD, et al. Non-steroidal anti-inflammatory drugs and cancer incidence by sex in the VITamins And Lifestyle (VITAL) cohort. Cancer Causes Control. 23(3): 431-44. 2012. PMID: 22212612. https://dx.doi.org/10.1007/s10552-011-9891-8	KQ1E4 KQ2E7
Brighton, TA, Eikelboom, JW, et al. Low-dose aspirin for preventing recurrent venous thromboembolism. N Engl J Med. 367(21): 1979-1987. 2012. PMID: 23121403. https://dx.doi.org/10.1056/NEJMoa1210384	KQ1E3 KQ2E3
Cea Soriano L, Gaist D, Soriano-Gabarro M, Bromley S, et al. Low-dose aspirin and risk of intracranial bleeds: An observational study in UK general practice. Neurology. 89(22): 2280-2287. 2017. PMID: 29093065. https://dx.doi.org/10.1212/WNL.0000000000004694	KQ1E4 KQ2E4
Cea Soriano L, Gaist D, Soriano-Gabarro M, Garcia Rodriguez LA. Incidence of intracranial bleeds in new users of low-dose aspirin: a cohort study using The Health Improvement Network. Journal of Thrombosis & Haemostasis. 15(6): 1055-1064. 2017. PMID: 28371181. https://dx.doi.org/10.1111/jth.13686	KQ1E4 KQ2E6
Cea Soriano L, Gaist D, Soriano-Gabarró M, García Rodríguez LA. The importance of validating intracranial bleeding diagnoses in The Health Improvement Network, United Kingdom: Misclassification of onset and its impact on the risk associated with low-dose aspirin therapy. Pharmacoepidemiol Drug Saf. 28(2): 134-139. 2019. PMID: 29806168. https://dx.doi.org/10.1002/pds.4561	KQ1E4 KQ2E4
Cea Soriano L, Lanas A, Soriano-Gabarro M, Garcia Rodriguez LA. Incidence of Upper and Lower Gastrointestinal Bleeding in New Users of Low-Dose Aspirin. Clinical Gastroenterology & Hepatology. 17(5): 887-895.e6. 2019. PMID: 29908361. https://dx.doi.org/10.1016/j.cgh.2018.05.061	KQ1E4 KQ2E6
Cea Soriano L, Soriano-Gabarroé M, Lanas A, Garciéa Rodriéguez LA. New use of low-dose aspirin and risk of upper and lower gastrointestinal bleeding: Associations by case-fatality, hospitalisation status, bleeding location, aspirin dose and duration in a large observational study in the united kingdom. United European Gastroenterology Journal. 5(5): A136-A137. 2017. PMID: None. https://dx.doi.org/10.1177/2050640617725668	KQ1E10 KQ2E10
Cea Soriano L, Vora P, Soriano-Gabarro M, Garcia Rodriguez LA. The effect of low-dose aspirin on colorectal cancer prevention and gastrointestinal bleeding according to bodyweight and body mass index: Analysis of UK primary care data. Int J Cardiol. 297: 135-139. 2019. PMID: 31515060. https://dx.doi.org/10.1016/j.ijcard.2019.08.001	KQ1E4 KQ2E4
Chan, AT, Giovannucci, EL, et al. Aspirin dose and duration of use and risk of colorectal cancer in men. Gastroenterology. 134(1): 21-8. 2008. PMID: 18005960. https://dx.doi.org/10.1053/j.gastro.2007.09.035	KQ1E4 KQ2E7
Chan, AT, Giovannucci, EL, et al. Long-term use of aspirin and nonsteroidal anti-inflammatory drugs and risk of colorectal cancer. JAMA. 294(8): 914-923. 2005. PMID: 16118381. https://dx.doi.org/10.1001/jama.294.8.914	KQ1E4 KQ2E5b

Appendix C. Excluded Studies

Reference	Code
Chan, AT, McNeil, J. Aspirin and Cancer Prevention in the Elderly: Where Do We Go From Here?. Gastroenterology. 156(3): 534-538. 2019. PMID: 30529298. https://dx.doi.org/10.1053/j.gastro.2018.11.063	KQ1E10 KQ2E10
Chiang C, Chen TC, Yeh YC, Chen YY. Aspirin as a primary prevention of cardiovascular disease in high-risk new diabetes patients: A retrospective cohort study in Taiwan. Neurology. 92(15). 2019. PMID: None.	KQ1E10 KQ2E10
Chowdhury EK, Nelson MR, Ernst ME, Margolis KL, et al. Factors associated with treatment and control of hypertension in a healthy elderly population free of cardiovascular disease: a cross-sectional study. Am J Hypertens. 33(4):350-361. 2020. PMID: 31807750. https://dx.doi.org/10.1093/ajh/hpz192	KQ1E7 KQ2E7
Cloud G, Donnan G, Williamson J, Eaton C, et al. The effect of aspirin on ischemic stroke sub-types in the healthy elderly. European Stroke Journal. 4: 69. 2019. PMID: None. https://dx.doi.org/10.1177/2396987319845560	KQ1E10 KQ2E10
Cote, R, Battista, RN, et al. Lack of effect of aspirin in asymptomatic patients with carotid bruits and substantial carotid narrowing. The Asymptomatic Cervical Bruit Study Group. Ann Intern Med. 123(9): 649-655. 1995. PMID: 7574219. https://dx.doi.org/10.7326/0003-4819-123-9-199511010-00002	KQ1E3a KQ2E3a
DAMAD Study Group. Effect of aspirin alone and aspirin plus dipyridamole in early diabetic retinopathy. A multicenter randomized controlled clinical trial. The DAMAD Study Group. Diabetes. 38(4): 491-498. 1989. PMID: 2647556.	KQ1E3 KQ2E3
de Groot NL, Hagenaars MP, Smeets HM, Steyerberg EW, et al. Primary non-variceal upper gastrointestinal bleeding in NSAID and low-dose aspirin users: development and validation of risk scores for either medication in two large Dutch cohorts. J Gastroenterol. 49(2): 245-53. 2014. PMID: 23609946. https://dx.doi.org/10.1007/s00535-013-0817-y	KQ1E4 KQ2E4
Design of a multicenter randomized trial for the Stroke Prevention in Atrial Fibrillation Study. The Stroke Prevention in Atrial Fibrillation Investigators. Stroke. 21(4,0039-2499 (Print),0039-2499 (Linking): 538-545. 1990. PMID: 2183405. https://dx.doi.org/10.1161/01.str.21.4.538	KQ1E3b KQ2E3b
Diener, HC. European Stroke Prevention Study 2. Efficacy and safety data. J Neurol Sci. 151(Suppl 1): S1-S77. 1997. PMID: 9276859. https://dx.doi.org/10.1016/s0022-510x(97)86566-5	KQ1E3a KQ2E3a
Dumbleton JS, Avery AJ, Coupland C, Hobbs FD, et al. The Helicobacter Eradication Aspirin Trial (HEAT): A Large Simple Randomised Controlled Trial Using Novel Methodology in Primary Care. EBioMedicine. 2(9): 1200-4. 2015. PMID: 26501118. https://dx.doi.org/10.1016/j.ebiom.2015.07.012	KQ1E5 KQ2E5
Effects of aspirin treatment on diabetic retinopathy. Ophthalmology. 98(5 Suppl): 757-765. 1991. PMID: 2062511.	KQ1E3 KQ2E3
ETDRS Investigators. Aspirin effects on mortality and morbidity in patients with diabetes mellitus. Early treatment Diabetic Retinopathy Study report 12. ETDRS Investigators. JAMA. 268(10): 1292-1300. 1992. PMID: 1507375. https://dx.doi.org/10.1001/jama.1992.03490100090033	KQ1E3 KQ2E3

Appendix C. Excluded Studies

Reference	Code
ETDRS Investigators. Aspirin effects on mortality and morbidity in patients with diabetes mellitus. Early Treatment Diabetic Retinopathy Study report 14. ETDRS Investigators. JAMA. 268(10): 1292-1300. 1992. PMID: 1507375. https://dx.doi.org/10.1001/jama.1992.03490100090033	KQ1E3 KQ2E3
ETDRS Investigators. Early Treatment Diabetic Retinopathy Study design and baseline patient characteristics. ETDRS report number 7. Ophthalmology. 98(5 Suppl): 741-756. 1991. PMID: 2062510. https://dx.doi.org/10.1016/s0161-6420(13)38009-9	KQ1E3 KQ2E3
Fasey, N, BRENNAN, PJ, et al. Thrombosis prevention trial: follow-up study of practical implications. Br J Gen Pract. 52(476): 208-209. 2002. PMID: 12030663.	KQ1E7 KQ2E7
Fernandez-Jimenez R, Latina J, Hajjar R, Fuster V, et al. Low dose aspirin for primary prevention of cardiovascular disease: Use patterns and impact across race in the southern community cohort study. J Am Coll Cardiol. 71(11 Suppl): A1892. 2018. https://dx.doi.org/10.1016/S0735-1097(18)32433-1	KQ1E4 KQ2E7
Friis, S, Poulsen, AH, et al. Aspirin and other non-steroidal anti-inflammatory drugs and risk of colorectal cancer: a Danish cohort study. Cancer Causes Control. 20(5): 731-40. 2009. PMID: 19122977. https://dx.doi.org/10.1007/s10552-008-9286-7	KQ1E4 KQ2E7
Galli M, Andreotti F, D'Amario D, Vergallo R, et al. Aspirin in Primary Prevention of Cardiovascular Disease in the Elderly. Eur Heart J Cardiovasc Pharmacother. 2019. PMID: 31504373. https://dx.doi.org/10.1093/ehjcvp/pvz046	KQ1E4 KQ2E4
Garcia Rodriguez LA, Lanas A, Soriano-Gabarro M, Cea Soriano L. Low-dose aspirin and risk of upper/lower gastrointestinal bleeding by bleed severity: a cohort study with nested case-control analysis using primary care electronic health records from the United Kingdom. Ann Med. 51(2): 182-192. 2019. PMID: 31025592. https://dx.doi.org/10.1080/07853890.2019.1591635	KQ1E4 KQ2E4
Garcia Rodriguez LA, Soriano-Gabarro M, Cea Soriano L. Incidence of colorectal cancer in new users and non-users of low-dose aspirin for primary prevention of cardiovascular or cerebrovascular disease in the United Kingdom. Eur Heart J. 37(1 Suppl): 634. 2016. PMID: None. https://dx.doi.org/10.1093/eurheartj/ehw433	KQ1E10 KQ2E10
Garcia Rodriguez LA, Soriano-Gabarro M, Gaist D, Cea Soriano L. New use of low-dose aspirin and risk of intracerebral haemorrhage, subdural haematoma and subarachnoid haemorrhage: Associations by sex, case-fatality and trauma status in a large observational study. Eur Heart J. 38: 645. 2017. PMID: None. https://dx.doi.org/10.1093/eurheartj/ehx502.3107	KQ1E10 KQ2E10
García Rodríguez, LA, Vora, P, et al. Bleeding associated with low-dose aspirin: Comparison of data from the COMPASS randomized controlled trial and routine clinical practice. Int J Cardiol. 318: 21-24. 2020. PMID: None.https://dx.doi.org/10.1016/j.ijcard.2020.06.048	KQ1E3a KQ2E3a

Appendix C. Excluded Studies

Reference	Code
Garcia-Rodriguez L, Gabarró MS, Vora P, Soriano LC. THE EFFECT OF LOW-DOSE ASPIRIN ON COLORECTAL CANCER PREVENTION AND GASTROINTESTINAL BLEEDING ACCORDING TO BODYWEIGHT AND BODY MASS INDEX: ANALYSIS OF PRIMARY CARE DATA FROM THE UNITED KINGDOM. Gastroenterology. 156(6): S-742. 2019. PMID: None. https://dx.doi.org/10.1016/S0016-5085(19)38790-6	KQ1E4 KQ2E4
Garcia-Rodriguez L, Lanas A, Gabarró MS, Soriano LC. Risk of Both upper and Lower Gastrointestinal Bleeding Associated with Low-Dose Acetylsalicylic Acid and Proton Pump Inhibitors Among Nearly 400,000 Individuals in Routine General Practice in the United Kingdom. Gastroenterology. 154(6): S-136-S-137. 2018. PMID: None. https://dx.doi.org/10.1016/S0016-5085(18)30882-5	KQ1E10 KQ2E10
Goicoechea, M, De Vinuesa, MSG, et al. Aspirin treatment in primary cardiovascular prevention and renal disease progression in CKD patients: A randomized clinical trials (AASER study). J Am Soc Nephrol. 28: B5. 2017. PMID: None.	KQ1E10 KQ2E10
Guo, CG, Zhang, F, et al. 340 PREDICTING TREND OF UPPER AND LOWER GASTROINTESTINAL BLEEDING BASED ON POPULATION PRESCRIPTION OF ASPIRIN AND PROTON PUMP INHIBITORS. Gastroenterology. 158(6): S-59. 2020. PMID: None. https://dx.doi.org/10.1016/S0016-5085(20)30829-5	KQ1E10 KQ2E10
H Soejima, T Morimoto, S Okada, M Sakuma, et al. 44 % of patients with myocardial infarction are silent manifestation in diabetics. Circulation. 134. 2016.	KQ1E10 KQ2E10
Hall KT, Kessler T, Buring JE, Passow D, et al. Genetic variation at the coronary artery disease risk locus GUCY1A3 modifies cardiovascular disease prevention effects of aspirin. Eur Heart J. 40(41): 3385-3392. 2019. PMID: 31228190. https://dx.doi.org/10.1093/eurheartj/ehz384	KQ1E4 KQ2E4
Hirsch, C. Daily aspirin for primary prevention increased risk for major GI bleeding in healthy older adults. Ann Intern Med. 05(): 05. 2021. PMID: 19122977. https://dx.doi.org/10.7326/ACPJ202101190-004	KQ1E10 KQ2E10
Hsu J, Donnelly JP, Chaudhary NS, Moore JX, et al. Aspirin use and long-term rates of sepsis: A population-based cohort study. PLoS ONE [Electronic Resource]. 13(4): e0194829. 2018. PMID: 29668690. https://dx.doi.org/10.1371/journal.pone.0194829	KQ1E7 KQ2E7
Huang WY, Daugherty SE, Shiels MS, Purdue MP, et al. Aspirin Use and Mortality in Two Contemporary US Cohorts. Epidemiology. 29(1): 126-133. 2018. PMID: 28863047. https://dx.doi.org/10.1097/EDE.0000000000000746	KQ1E4 KQ2E7
I Hammami, M Mafham, J Armitage, S Parish. Risk of major gastrointestinal bleed in relation to vascular disease risk in 0.5M UK Biobank participants. Eur Heart J. 40(1 Suppl): 265. 2019. PMID: None. https://dx.doi.org/10.1093/eurheartj/ehz747.0263	KQ1E10 KQ2E10
Iwamoto, J, Murakami, M, et al. Current states of prevention of drug-induced gastroduodenal ulcer in real clinical practice: A cross-sectional study. J Clin Biochem Nutr. 66(2): 158-162. 2020. PMID: 32231413. https://dx.doi.org/10.3164/jcbn.19-66	KQ1E4 KQ2E3d

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Reference	Code
J Armitage, G Santulli. In diabetes with no CVD, aspirin reduced serious vascular events but increased major bleeding at 7.4 years. Ann Intern Med. 169(12): Jc67-. 2018. PMID: 30557420. https://dx.doi.org/10.7326/ACPJC-2018-169-12-067	KQ1E10 KQ2E10
J Ryan, E Storey, A Murray, R Woods, et al. A randomized controlled trial of the effect of aspirin versus placebo on incident dementia and probable alzheimer's disease. Alzheimer's & dementia. 15(7): P1277-p1278. 2019. PMID: None. https://dx.doi.org/10.1016/j.jalz.2019.06.3671	KQ1E10 KQ2E10
Jacobs, EJ, Thun, MJ, et al. A large cohort study of long-term daily use of adult-strength aspirin and cancer incidence. J Natl Cancer Inst. 99(8): 608-15. 2007. PMID: 17440162. https://dx.doi.org/10.1093/jnci/djk132	KQ1E4 KQ2E7
Jaspers Focks J, Tielemans MM, van Rossum LG, Eikendal T, et al. Gastrointestinal symptoms in low-dose aspirin users: a comparison between plain and buffered aspirin. Netherlands Heart Journal. 22(3): 107-12. 2014. PMID: 24522950. https://dx.doi.org/10.1007/s12471-014-0522-3	KQ1E4 KQ2E6
Juul-Moller, S, Edvardsson, N, et al. Double-blind trial of aspirin in primary prevention of myocardial infarction in patients with stable chronic angina pectoris. The Lancet. 340(8833): 1421-1425. 1992. PMID: 1360557. https://dx.doi.org/10.1016/0140-6736(92)92619-q	KQ1E3a KQ2E3a
Kim J, Lee J, Shin CM, Lee DH, et al. Risk of gastrointestinal bleeding and cardiovascular events due to NSAIDs in the diabetic elderly population. BMJ Open Diabetes Research & Care. 3(1): e000133. 2015. PMID:3 26719806. https://dx.doi.org/10.1136/bmjdrc-2015-000133	KQ1E4 KQ2E5
Kim TG, Kim SH. Analysis of the Occurrence of Major Hemorrhagic Incidents in Patients with Low-Dose Aspirin Usage in Korean Populations - Does Low-Dose Aspirin Really Increase the Risk of Bleeding?. Neurointervention. 15(1): 52-54. 2020. PMID: 32070087. https://dx.doi.org/10.5469/neuroint.2019.00297	KQ1E10 KQ2E10
Kim YJ, Choi NK, Kim MS, Lee J, et al. Evaluation of low-dose aspirin for primary prevention of ischemic stroke among patients with diabetes: a retrospective cohort study. Diabetol Metab Syndr. 7: 8. 2015. PMID: 25733983. https://dx.doi.org/10.1186/s13098-015-0002-y	KQ1E4 KQ2E7
Kronmal, RA, Hart, RG, et al. Aspirin use and incident stroke in the cardiovascular health study. CHS Collaborative Research Group. Stroke. 29(5,0039-2499 (Print),0039-2499 (Linking): 887-894. 1998. PMID: 9596230. https://dx.doi.org/10.1161/01.str.29.5.887	KQ1E4 KQ2E3d
Kurata, JH, Abbey, DE. The effect of chronic aspirin use on duodenal and gastric ulcer hospitalizations. J Clin Gastroenterol. 12(3,0192-0790 (Print),0192-0790 (Linking)): 260-266. 1990. PMID: 2193980. https://dx.doi.org/ 10.1097/00004836-199006000-00005	KQ1E3a KQ2E3a
Larsson, SC, Giovannucci, E, et al. Long-term aspirin use and colorectal cancer risk: a cohort study in Sweden. Br J Cancer. 95(9): 1277-9. 2006. PMID: 17060932. https://dx.doi.org/10.1038/sj.bjc.6603442	KQ1E4 KQ2E7
Lee WA, Cheng CL, Yang YHK. Risk of age-related macular degeneration in aspirin uses. Pharmacoepidemiol Drug Saf. 27: 79. 2018. https://dx.doi.org/10.1002/pds.4629	KQ1E10 KQ2E10

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Reference	Code
Lee WJA, Cheng CL, Yang YHK. Association of aspirin use and age-related macular degeneration in Taiwan. Pharmacoepidemiol Drug Saf. 25: 283. 2016. https://dx.doi.org/10.1002/pds.4070	KQ1E10 KQ2E10
Lee WJA, Cheng CL, Yang YHK. Does aspirin use increase the risk of age-related macular degeneration: A population-based comparative cohort study. Pharmacoepidemiol Drug Saf. 28: 340-341. 2019. https://dx.doi.org/10.1002/pds.4864	KQ1E4 KQ2E4
Leung, WY, So, WY, et al. Lack of benefits for prevention of cardiovascular disease with aspirin therapy in type 2 diabetic patients--a longitudinal observational study. Cardiovasc Diabetol. 8: 57. 2009.	KQ1E4 KQ2E3d
Lin BM, Curhan SG, Wang M, Eavey R, et al. Duration of Analgesic Use and Risk of Hearing Loss in Women. Am J Epidemiol. 185(1): 40-47. 2017. PMID: 27974293. https://dx.doi.org/10.1093/aje/kww154	KQ1E4 KQ2E5b
Lin KJ, De Caterina R, Garcia Rodriguez LA. Low-dose aspirin and upper gastrointestinal bleeding in primary versus secondary cardiovascular prevention: a population-based, nested case-control study. Circ Cardiovasc Qual Outcomes. 7(1): 70-7. 2014. PMID: 24254886. https://dx.doi.org/10.1161/CIRCOUTCOMES.113.000494	KQ1E4 KQ2E4
Lin, HMD, Vora, P, et al. Association between Low-Dose Aspirin Use and Colorectal Cancer Incidence in Taiwan. JAMA Network Open. 3(11):e2026494-e2026494. 2020. https://dx.doi.org/10.1001/jamanetworkopen.2020.26494	KQ1E4 KQ2E7
Lockery JE, Collyer TA, Abhayaratna WP, Fitzgerald SM, et al. Recruiting general practice patients for large clinical trials: lessons from the Aspirin in Reducing Events in the Elderly (ASPREE) study. Med J Aust. 210(4): 168-173. 2019. PMID: 30835844. https://dx.doi.org/10.5694/mja2.12060	KQ1E7 KQ2E7
Lockery, JE, Ernst, ME, et al. Prescription Medication Use in Older Adults Without Major Cardiovascular Disease Enrolled in the Aspirin in Reducing Events in the Elderly (ASPREE) Clinical Trial. Pharmacotherapy. 40(10): 1042-1053. 2020. https://dx.doi.org/10.1002/phar.2461	KQ1E7 KQ2E7
Logan, RF, Grainge, MJ, et al. Aspirin and folic acid for the prevention of recurrent colorectal adenomas. Gastroenterology. 134(1): 29-38. 2008.	KQ1E3 KQ2E3
M Riaz, J Ryan, A Huq, R Woods, et al. ASPREE: cohort stratification by APOE genotype. Twin research and human genetics. 21(5): 405-406. 2019. https://dx.doi.org/10.1017/thg.2018.51	KQ1E10 KQ2E10
Mahady S, Woods R, Polekhina G, Chan A, et al. Factors associated with aspirin-related upper gastrointestinal bleeding in the elderly: Data from a randomized controlled trial of 19 114 people. J Gastroenterol Hepatol. 34: 176. 2019. https://dx.doi.org/10.1111/jgh.14803	KQ1E10 KQ2E10
Mayor S. Long term NSAIDs are associated with lower colorectal cancer risk, study shows. BMJ. 351: h4599. 2015. PMID: 26306535. https://dx.doi.org/10.1136/bmj.h4599	KQ1E10 KQ2E10
McNeil J, Grimm R, Nelson M, Murray A, et al. The aspirin in reducing events in the elderly trial (ASPREE): Progress report. Glob Heart. 9(1): e215. 2014. https://dx.doi.org/10.1016/j.gheart.2014.03.2003	KQ1E10 KQ2E10

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Reference	Code
Meade, TW, WILKES, HC, et al. Randomized controlled trial of low dose warfarin in the primary prevention of ischaemic heart disease in men at high risk: design and pilot study. Eur Heart J. 9(8): 836-843. 1988. PMID: 3053176.	KQ1E7 KQ2E7
Modjtahedi BS, Fong DS, Jorgenson E, Van Den Eeden SK, et al. The Relationship Between Nonsteroidal Anti-inflammatory Drug Use and Age-related Macular Degeneration. Am J Ophthalmol. 188: 111-122. 2018. PMID: 29360460. https://dx.doi.org/10.1016/j.ajo.2018.01.012	KQ1E5 KQ2E5
Okada S, Morimoto T, Ogawa H, Sakuma M, et al. Does long-term use of low-dose aspirin develop proteinuria in diabetic patients?. Diabetes. 64: A414. 2015. PMID: . https://dx.doi.org/	KQ1E10 KQ2E10
Okada S, Morimoto T, Ogawa H, Sakuma M, et al. Is Long-Term Low-Dose Aspirin Therapy Associated with Renal Dysfunction in Patients with Type 2 Diabetes? JPAD2 Cohort Study. PLoS ONE [Electronic Resource]. 11(1): e0147635. 2016. PMID: 26808136. https://dx.doi.org/10.1371/journal.pone.0147635	KQ1E7 KQ2E7
Okada, S, Morimoto, T, et al. Association Between Statins and Cancer Incidence in Diabetes: a Cohort Study of Japanese Patients with Type 2 Diabetes. J Gen Intern Med. 36:632-639. 2020. https://dx.doi.org/10.1007/s11606-020-06167-5	KQ1E5 KQ2E5
Orchard, SG, Lockery, JE, et al. Cancer history and risk factors in healthy older people enrolling in the ASPREE clinical trial. Contemp Clin Trials. 96:106095. 2020. https://dx.doi.org/10.1016/j.cct.2020.106095	KQ1E7 KQ2E7

Reference	Code
Orkaby AR, Yang L, Dufour AB, Travison TG, et al. Long-term aspirin use is associated with a lower prevalence of mobility limitation in older men. Circulation. 138(1 Suppl):A12007-A12007. 2018.	KQ1E10 KQ2E10
Palaniappan M, Selvarajan S, George M, Subramaniyan G, et al. Pattern of Adverse Drug Reactions Reported with Cardiovascular Drugs in a Tertiary Care Teaching Hospital. Journal of Clinical and Diagnostic Research JCDR. 9(11): FC01-4. 2015. PMID: 26675485. https://dx.doi.org/10.7860/JCDR/2015/13810.6704	KQ1E2 KQ2E2
Persantine-aspirin reinfarction study. Design, methods and baseline results. By the persantine-aspirin reinfarction study research group. Circulation. 62(3 Pt 2,0009-7322 (Print),0009-7322 (Linking)): II1-42. 1980.	KQ1E3a KQ2E3a
Petersen, P, Boysen, G, et al. Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation. The Copenhagen AFASAK study. Lancet. 1(8631): 175-179. 1989.	KQ1E3b KQ2E3b
Preliminary report of the Stroke Prevention in Atrial Fibrillation Study. N Engl J Med. 322(12,0028-4793 (Print),0028-4793 (Linking): 863-868. 1990.	KQ1E3b KQ2E3b
Robman LD, Guymer RH, Woods R, Hodgson L, et al. The role of aspirin in age-related macular degeneration: The ASPREE-AMD randomized controlled trial. Invest Ophthalmol Vis Sci. 59(9): 5539. 2018.	KQ1E10 KQ2E10
Rodriguez LG, Gaist D, Soriano-Gabarró M, Soriano LC. New use of low-dose aspirin is not associated with a significantly increased risk of intracranial bleeds: Results from a population-based nested case-control study in the united kingdom. Circulation. 134(1 Suppl):A12926. 2016.	KQ1E10 KQ2E10

Appendix C. Excluded Studies

Reference	Code
Rothwell PM, Cook NR, Gaziano JM, Price JF, et al. Effects of aspirin on risks of vascular events and cancer according to bodyweight and dose: analysis of individual patient data from randomised trials. Lancet. 392(10145): 387-399. 2018. https://dx.doi.org/10.1016/S0140-6736(18)31133-4	KQ1E11 KQ2E11
Rothwell PM, Fowkes FG, Belch JF, Ogawa H, et al. Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials. Lancet. 377(9759): 31-41. 2011. PMID: 21144578. https://dx.doi.org/10.1016/S0140-6736(10)62110-1	KQ1E7 KQ2E7
Rothwell PM, Price JF, Fowkes FG, Zanchetti A, 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. 379(9826): 1602-12. 2012. PMID: 22440946. https://dx.doi.org/10.1016/S0140-6736(11)61720-0	KQ1E7 KQ2E7
RUDNICKA, AR, MT-ISA, S, et al. Associations of plasma fibrinogen and factor VII clotting activity with coronary heart disease and stroke: prospective cohort study from the screening phase of the Thrombosis Prevention Trial. Journal of Thrombosis and Haemostasis. 4(11): 2405-2410. 2006. PMID: 17002654.	KQ1E7 KQ2E7
Rydberg DM, Holm L, Mejyr S, Loikas D, et al. Sex differences in spontaneous reports on adverse bleeding events of antithrombotic treatment. Eur J Clin Pharmacol. 70(1): 117-26. 2014. PMID: 24096684. https://dx.doi.org/10.1007/s00228-013-1591-8	KQ1E4 KQ2E4
Sasso FC, Marfella R, Pagano A, Porta G, et al. Lack of effect of aspirin in primary CV prevention in type 2 diabetic patients with nephropathy: results from 8 years follow-up of NID-2 study. Acta Diabetol. 52(2): 239-47. 2015. PMID: 25109286. https://dx.doi.org/10.1007/s00592-014-0623-x	KQ1E4 KQ2E4
Sato, H, Ishikawa, K, et al. Low-dose aspirin for prevention of stroke in low-risk patients with atrial fibrillation: Japan Atrial Fibrillation Stroke Trial. Stroke. 37(2): 447-451. 2006.	KQ1E3b KQ2E3b
Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. EAFT (European Atrial Fibrillation Trial) Study Group. Lancet. 342(8882): 1255-62. 1993. PMID: 7901582.	KQ1E3a KQ2E3a
Seidu S, Kunutsor SK, Sesso HD, Gaziano JM, et al. Aspirin has potential benefits for primary prevention of cardiovascular outcomes in diabetes: updated literature-based and individual participant data meta-analyses of randomized controlled trials. Cardiovasc Diabetol. 18(1): 70. 2019. PMID: 31159806. https://dx.doi.org/10.1186/s12933-019-0875-4	KQ1E11 KQ2E11
Selak V, Jackson R, Poppe K, Kerr A, et al. Are the benefits of aspirin likely to exceed the risk of major bleeds among people in whom aspirin is recommended for the primary prevention of cardiovascular disease?. N Z Med J. 131(1484): 19-25. 2018. PMID: 30359352.	KQ1E4 KQ2E4
Selak V, Jackson R, Poppe K, Wu B, et al. Personalized Prediction of Cardiovascular Benefits and Bleeding Harms From Aspirin for Primary Prevention: A Benefit-Harm Analysis. Ann Intern Med. 171(8):529-542. 2019. https://dx.doi.org/10.7326/M19-1132	KQ1E4 KQ2E4

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Reference	Code
Selak V, Jackson R, Poppe K, Wu B, et al. Predicting Bleeding Risk to Guide Aspirin Use for the Primary Prevention of Cardiovascular Disease: A Cohort Study. Ann Intern Med. 170(6): 357-368. 2019. https://dx.doi.org/10.7326/M18-2808	KQ1E4 KQ2E4
Selak V, Kerr A, Poppe K, Wu B, et al. Annual Risk of Major Bleeding Among Persons Without Cardiovascular Disease Not Receiving Antiplatelet Therapy. JAMA. 319(24): 2507-2520. 2018. https://dx.doi.org/10.1001/jama.2018.8194	KQ1E6 KQ2E6
Selvaraj S, Bhatt D, Claggett B, Djousse L, et al. Heart failure is not associated with increased cancer incidence among participants in the physicians' health study. Circulation. 136(1 Suppl): A13644. 2017.	KQ1E10 KQ2E10
Seshasai, SR, Wijesuriya, S, et al. Effect of aspirin on vascular and nonvascular outcomes: meta-analysis of randomized controlled trials. Arch Intern Med. 172(3): 209-216. 2012.	KQ1E4 KQ2E4
Sirois C, Moisan J, Poirier P, Gregoire JP. Myocardial infarction and gastro-intestinal bleeding risks associated with aspirin use among elderly individuals with type 2 diabetes. Ann Med. 46(5): 335-40. 2014. PMID: 24785356. https://dx.doi.org/10.3109/07853890.2014.902636	KQ1E4 KQ2E4
Slattery, J, Warlow, CP, et al. Risks of gastrointestinal bleeding during secondary prevention of vascular events with aspirin--analysis of gastrointestinal bleeding during the UK-TIA trial. Gut. 37(4,0017-5749 (Print),0017-5749 (Linking): 509-511. 1995.	KQ1E7 KQ2E3a
Soriano LC, Gaist D, Soriano-Gabarró M, Rodríguez LAG. Incidence of intracranial bleeds in new users and non-users of low-dose aspirin in the UK. Pharmacoepidemiol Drug Saf. 25: 570. 2016. https://dx.doi.org/10.1002/pds.4070	KQ1E10 KQ2E10
Soriano LC, Soriano-Gabarro M, Lanas A, Rodríguez LAG. Incidence of upper and lower gastrointestinal bleeds in new users and non-users of low-dose aspirin in the UK. Pharmacoepidemiol Drug Saf. 26: 392-393. 2017. https://dx.doi.org/10.1002/pds.4275	KQ1E10 KQ2E10
Soriano LC, Soriano-Gabarró M, Rodríguez LAG. Protection against colorectal cancer with use of low-dose aspirin: Selection bias is unlikely based on results using three different study designs. Pharmacoepidemiol Drug Saf. 25: 561. 2016. https://dx.doi.org/10.1002/pds.4070	KQ1E4 KQ2E7
Stampfer, MJ, Buring, JE, et al. The 2 x 2 factorial design: its application to a randomized trial of aspirin and carotene in U.S. physicians. Stat Med. 4(2): 111-116. 1985.	KQ1E7 KQ2E7
Stocks NP, Gonzalez-Chica DA, Woods RL, Lockery JE, et al. Quality of Life for 19,114 participants in the ASPREE (ASPirin in Reducing Events in the Elderly) study and their association with sociodemographic and modifiable lifestyle risk factors. Qual Life Res. 28(4): 935-946. 2019. PMID: 30411180. https://dx.doi.org/10.1007/s11136-018-2040-z	KQ1E4 KQ2E4
Stroke Prevention in Atrial Fibrillation Study. Final results. Circulation. 84(2): 527-539. 1991.	KQ1E3b KQ2E3b
Sundstrom J, Hedberg J, Thuresson M, Aarskog P, et al. Low-Dose Aspirin Discontinuation and Risk of Cardiovascular Events: A Swedish Nationwide, Population-Based Cohort Study. Circulation. 136(13): 1183-1192. 2017. https://dx.doi.org/10.1161/CIRCULATIONAHA.117.028321	KQ1E4 KQ2E4
Sung J, Tsoi KKF. Comparing mortality of colorectal cancer and gastrointestinal bleeding among patients with long-term use of low dose aspirin: A population-based study of 689,209 patients. J Clin Oncol. 35(4). 2017.	KQ1E10 KQ2E10

Appendix C. Excluded Studies

Reference	Code
Sung JJY, Tsoi KK. Risk of gastrointestinal bleeding and benefit from colorectal cancer reduction. A 10-year population-based study for long-term use of low dose aspirin. United European Gastroenterology Journal. 4(5): A62. 2016. https://dx.doi.org/10.1177/2050640616663688	KQ1E10 KQ2E10
Takada M, Fujimoto M, Hosomi K. Difference in risk of gastrointestinal complications between users of enteric-coated and buffered low-dose aspirin. Int J Clin Pharmacol Ther. 52(3): 181-91. 2014.	KQ1E6 KQ2E6
The Persantine-Aspirin Reinfarction Study Research Group. Persantine and aspirin in coronary heart disease. The Persantine-Aspirin Reinfarction Study Research Group. Circulation. 62(3): 449-461. 1980.	KQ1E3a KQ2E3a
Thorat MA, Cuzick J. Prophylactic use of aspirin: systematic review of harms and approaches to mitigation in the general population. Eur J Epidemiol. 30(1): 5-18. 2015. PMID: 25421783. https://dx.doi.org/10.1007/s10654-014-9971-7	KQ1E4 KQ2E4
Tsoi KK, Chan FC, Hirai HW, Sung JJ. Risk of gastrointestinal bleeding and benefit from colorectal cancer reduction from long-term use of low-dose aspirin: A retrospective study of 612 509 patients. J Gastroenterol Hepatol. 33(10): 1728-1736. 2018. PMID: 29665624. https://dx.doi.org/10.1111/jgh.14261	KQ1E4 KQ2E3
Uchiyama S. Aspirin for primary stroke prevention in elderly patients with vascular risk factors. Journal of General and Family Medicine. 18(6): 331-335. 2017. PMID: 29264061. https://dx.doi.org/10.1002/jgf2.102	KQ1E10 KQ2E10
UK-TIA Study Group. United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: interim results. BMJ. 296(6618): 316-320. 1988.	KQ1E3a KQ2E3a
van Kruijsdijk RC, Visseren FL, Ridker PM, Dorresteijn JA, 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. 101(5): 369-76. 2015. PMID: 25475110. https://dx.doi.org/10.1136/heartjnl-2014-306342	KQ1E4 KQ2E4
Ward SA, Raniga P, Ferris NJ, Woods RL, et al. ASPREE-NEURO study protocol: A randomized controlled trial to determine the effect of low-dose aspirin on cerebral microbleeds, white matter hyperintensities, cognition, and stroke in the healthy elderly. International Journal of Stroke. 12(1): 108-113. 2017. PMID: 27634976. https://dx.doi.org/10.1177/1747493016669848	KQ1E7 KQ2E7
Warle-van Herwaarden MF, Koffeman AR, Valkhoff VE, t Jong GW, et al. Time-trends in the prescribing of gastroprotective agents to primary care patients initiating low-dose aspirin or non-steroidal anti-inflammatory drugs: a population-based cohort study. Br J Clin Pharmacol. 80(3): 589-98. 2015. PMID: 25777983. https://dx.doi.org/10.1111/bcp.12626	KQ1E1 KQ2E1
Wu IC, Hsieh HM, Wu MT. A short-term risk-benefit analysis of occasional and regular use of low-dose aspirin in primary prevention of vascular diseases: a nationwide population-based study. BMJ Open. 5(1): e006694. 2015. PMID: 25575876. https://dx.doi.org/10.1136/bmjopen-2014-006694	KQ1E4 KQ2E5a
Wu IC, Lin MY, Yu FJ, Hsieh HM, et al. A short-term effect of low-dose aspirin on major hemorrhagic risks in primary prevention: a case-crossover design. PLoS ONE [Electronic Resource]. 9(5): e98326. 2014. PMID: 24879431. https://dx.doi.org/10.1371/journal.pone.0098326	KQ1E4 KQ2E5a

Appendix C. Excluded Studies

Reference	Code
Wu S, Han J, Qureshi AA. Use of aspirin, non-steroidal anti-inflammatory drugs, and acetaminophen (paracetamol), and risk of psoriasis and psoriatic arthritis: a cohort study. Acta Derm Venereol. 95(2): 217-23. 2015. PMID: 24691893. https://dx.doi.org/10.2340/00015555-1855	KQ1E4 KQ2E7
Wu, Y, Yang, J, et al. Bleeding Risk in Randomized Controlled Trials Comparing Aspirin, Clopidogrel, and Vitamin K Antagonists: A Network Meta-analysis of 204,989 Patients. Am J Ther. 28(1): e156-e162. 2021. PMID: 33369919. https://dx.doi.org/https://dx.doi.org/10.1097/MJT.0000000000001003	KQ1E7 KQ2E3
Xu, Y, Wang, C, et al. PCV9 A 5-YEAR REAL WORLD PATIENT LEVEL ANALYSIS OF LOW-DOSE ASPIRIN PRIMARY PREVENTION BENEFIT AND RISK ANALYSIS BASED ON A MULTI-HOSPITAL EMR DATABASE. Value in Health. 23: S91. 2020. https://dx.doi.org/10.1016/j.jval.2020.04.114	KQ1E2 KQ2E2

Reference	Code
Y Saito, S Okada, H Ogawa, H Soejima, et al. The long-term therapy with low-dose aspirin did not reduce cardiovascular events in patients with type 2 diabetes in primary prevention setting: 10-year follow-up of a randomized controlled trial. Circulation. 134(1 Suppl): A13428. 2016.	KQ1E10 KQ2E10
Yusuf, S, Joseph, P, et al. Polypill with or without Aspirin in Persons without Cardiovascular Disease. N Engl J Med. 384(3): 216-228. 2020. https://dx.doi.org/10.1056/NEJMoa2028220	KQ1E2 KQ2E2
Zhang, SM, Cook, NR, et al. Low-dose aspirin and breast cancer risk: results by tumour characteristics from a randomised trial. Br J Cancer. 98(5,0007-0920 (Print),0007-0920 (Linking): 989-991. 2008.	KQ1E7 KQ2E7
Zhou, Z, Ofori-Asenso, R, et al. Association of Statin Use With Disability-Free Survival and Cardiovascular Disease Among Healthy Older Adults. J Am Coll Cardiol. 76(1): 17-27. 2020. https://dx.doi.org/10.1016/j.jacc.2020.05.016	KQ1E5 KQ2E5

Appendix D Table 1. Primary and Secondary Outcomes in Included Trials

Study name Author, year	Primary endpoint	Secondary endpoint
Primary CVD prevention		
AAA Fowkes, 2010[69]	Composite outcome: initial (earliest) fatal or nonfatal coronary event or stroke or revascularization	1) All initial vascular events, defined as a composite outcome: primary end point event or angina, intermittent claudication, or TIA; 2) ACM
ARRIVE Gaziano, 2018[56]	Composite outcome of time to first occurrence of cardiovascular death, MI, unstable angina, stroke, or transient ischemic attack. Safety endpoints were hemorrhagic events and incidence of other adverse events, and were analyzed in the intention-to-treat population.	Composite of the time to first occurrence of cardiovascular death, MI, or stroke; time to individual components of this composite secondary outcome; time to first occurrence of unstable angina; time to first occurrence of transient ischemic attack; and time to and incidence of ACM. All cancers excluding non-melanoma skin cancer (*all cancers will be reported elsewhere)
ASCEND ASCEND Study Collaborative, 2018[55]	First serious vascular event (i.e., MI, stroke or transient ischemic attack, or death from any vascular cause, excluding any confirmed intracranial hemorrhage). The primary safety outcome was the first major bleeding event (i.e., intracranial hemorrhage, sight-threatening bleeding event in the eye, gastrointestinal bleeding, or other serious bleeding	Gastrointestinal tract cancer overall and excluding those occurring during the first 3 years of follow-up) and the composite of any serious vascular event or any arterial revascularization procedure
ASPREE McNeil, 2018[101]	Composite of death, dementia, or persistent physical disability	Major hemorrhage and cardiovascular disease (defined as fatal coronary heart disease, nonfatal MI, fatal or nonfatal stroke, or hospitalization for heart failure)
BMD Peto, 1988[82]	Mortality from stroke, MI, or other vascular conditions	Nonfatal vascular and nonvascular events: MI, CVA, TIA, bleeding, other vascular conditions and nonfatal malignant neoplasms, respiratory events, cataracts, migraines, musculoskeletal disorders
HOT Hanson, 1998[70]	Composite of major CV events: fatal and nonfatal MI, fatal and nonfatal stroke, and death due to CVD	Fatal and nonfatal MI or stroke, CVD mortality, total mortality, death from kidney failure, change in eGFR, major and minor hemorrhage
JPAD Ogawa, 2008[81]	Composite of any atherosclerotic event: sudden death; death from coronary, cerebrovascular, or aortic causes; nonfatal acute MI; unstable angina; newly developed exertional angina; nonfatal ischemic and hemorrhagic stroke; TIA; or nonfatal aortic and peripheral vascular disease	Each primary end point and combinations of primary end points and death from any cause; adverse events: reported GI events, any hemorrhagic events other than CVA
JPPP Ikeda, 2014[91]	Composite of death from cardiovascular causes (MI, stroke, and other cardiovascular causes), nonfatal stroke (ischemic or hemorrhagic, including undefined cerebrovascular events), and nonfatal MI	Composite included the same events as the primary end point, plus TIA, angina pectoris, and arteriosclerotic disease requiring surgery or intervention. Other secondary end points were death from cardiovascular disease, death from noncardiovascular causes, nonfatal stroke (ischemic or hemorrhagic), nonfatal MI, TIA, angina pectoris, arteriosclerotic disease requiring surgery or intervention, and serious extracranial hemorrhage requiring transfusion or hospitalization

Appendix D Table 1. Primary and Secondary Outcomes in Included Trials

Study name Author, year	Primary endpoint	Secondary endpoint
PHS Physician's Health Study, 1989[59]	CVD mortality	MI events (fatal and nonfatal), strokes (fatal and nonfatal), ACM
POPADAD Belch, 2008[66]	Death from CHD or stroke, nonfatal MI or stroke, above ankle amputation for critical limb ischemia; Death from CHD or stroke	ACM, nonfatal MI, and occurrence of other vascular events
PPP Rongaclioni, 2001[64]	Composite outcome: cumulative rate of CV death, nonfatal MI, and nonfatal stroke	CV death, total death, nonfatal MI, total CV events: CV deaths, total deaths, total CV events (defined as nonfatal MI, nonfatal stroke, angina, TIA, PAD, revascularization procedures)
TPT The Medical Research Council's General Practice Research Framework, 1998[45]	All IHD: coronary death and fatal and nonfatal MI; Fatal IHD: coronary death and fatal MI	Stroke (thrombotic and hemorrhagic)
WHS Ridker, 2005[83]	Composite outcome: major CV event, defined as a nonfatal MI, nonfatal stroke, or CVD death	MI, stroke, CVD mortality, ACM
Secondary prevention trials		
SALT The SALT Collaborative Group, 1991[94]	N/A - CRC followup outcomes only (Study reports first event in the composite outcome of stroke (minor or major) or death from any cause)	N/A - (Study reports stroke (Fatal, nonfatal); stroke or two or more TIAs within a week of each other necessitating a change of treatment; or MI)
UK-TIA UK-TIA Study Group, 1990[111]	N/A - CRC followup outcomes only (Study reports non-fatal MI, non-fatal major stroke, vascular death, or non-vascular death)	

Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis; ACM = all-cause mortality; ARRIVE = Aspirin to Reduce Risk of Initial Vascular Events; ASCEND = A Study of Cardiovascular Events in Diabetes; ASPREE = Aspirin in Reducing Events in the Elderly; BMD = British Male Doctors; CHD = cardiovascular heart disease; CRC = colorectal cancer; CVA = cerebrovascular accident; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; HOT = Hypertension Optimal Treatment Study; HTN = hypertension; IHD = ischemic heart disease; JPAD = Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; JPN = Japan; JPPP = Japanese Primary Prevention Project; MI = myocardial infarction; N/A = not applicable; PAD = PHS = Physician's Health Study; POPADAD = The Prevention of Progression of Arterial Disease and Diabetes trial; PPP = Primary Prevention Project; SALT = Swedish Aspirin Low-dose Trial; TIA = transient ischemic attack; TPT Thrombosis Prevention Trial; UK-TIA = United Kingdom Transient Ischaemic Attack; WHS = Women's Health Study

Appendix D Table 2. Adherence and Crossover in Included Trials

Study name Author, year	N rand	Mean F/U, years	Adherence & crossover
Primary CVD prevention			
AAA Fowkes, 2010[69]	3350	8.2 years	Adherence methods=diary Patients took (ASA) study med for 60% of person years of followup. More than 85% took (ASA) study med for at least 6 months. At 5 yrs, those taking their medication did so for 88% of person-yrs throughout trial and those classified as not taking, did so for 24% person-years Cross overs: ASA physician or self-prescribed at 5 years IG: 16.4%; CG 15.0%
ARRIVE Gaziano, 2018[56]	12546	5 years (median)	NR
ASCEND ASCEND Study Collaborative, 2018[55]	15480	7.4 years	Mean adherence (weighted according to person-years for a serious vascular event) was 70% in the IG and 70% in the CG. The estimated mean between-group difference in the rate of use of trial aspirin or nontrial aspirin or other antiplatelet treatment was 69%.
ASPREE McNeil, 2018[101]	19144	4.7 years	Adherence assessed annually by means of tablet counts on returned bottles of aspirin or placebo. In the final 12 months of the trial, 62% of the participants in the aspirin group and 64% of those in the placebo group were still taking the assigned trial intervention.
BMD Peto, 1988[82]	5139	6 years	In IG, 19.5% stopped at year 1 and 24.8% stopped at year 6. In CG, 1.8% started ASA at year 1 and 9.2% started at year 6. However, in table 2 which details adherence, the denominator used for year five is 2738 (N randomized = 3429). No details are provided about where this number comes from (lost of followup, deaths, etc). It would seem that adherence was at either 76% or 60% depending on how it was calculated.
HOT Hanson, 1998[70]	18790	3.8 years	% of participants taking ASA in IG: NR
JPAD Ogawa, 2008[81]	2539	4.37 years (median)*	For original 4.37 years median F/U: In IG, 1,139 (90.3%) took ASA through completion of original F/U. In CG 0.5% had taken ASA and 0.2% had taken other anti-platelet meds. At the end of the initial F/U period, patients were administered ASA according to the decision of each physician. For extended F/U period: 2160 (85%) retained their original allocation. 270 in IG stopped taking ASA and 109 in CG initiated ASA.
JPPP Ikeda, 2014[91]	14658	5.02 years (median)	% of participants taking ASA: 88.9% reported that they were adherent in year 1; 76.0% in year 5. In the CG the proportion of patients who started to take daily ASA increased from 1.5% in year 1 to 9.8% in year 2. Use of antiplatelet or anticoagulant agents was 10.5% in the ASA group and 10.4% in the no ASA group at 5 yrs.

Appendix D Table 2. Adherence and Crossover in Included Trials

Study name Author, year	N rand	Mean F/U, years	Adherence & crossover
PHS Physician's Health Study, 1989[59]	22071	5 years	% of participants taking ASA or other antiplatelet drugs: At 5 years, 85.71% in IG and 14.23% in CG The 12-year F/U for CRC includes 5 years of randomized treatment and then self-selection of aspirin use from years 5-12. After the end of the randomized period (which was terminated early because of aspirin benefit) participants could choose to receive aspirin or placebo. Overall, 71% chose to take aspirin regularly on 3 or more days of the week. Table 4 (Sturmer) shows that 45% person-years of the regular aspirin users post-trial were originally allocated to the CG and 39% person-years of irregular aspirin users post-trial were originally allocated to the IG.
POPADAD Belch, 2008[66]	1276	6.7 years (median)	At 1 year, 14% of participants stopped taking trial drugs (aspirin or placebo, also included AntiOx participants) At 5 yrs: 50% (cumulative) of patients withdrew from trial therapy (unclear how adherence ascertained)
PPP Rongaclioni, 2001[64]	4495	3.6 years	% of Participants no longer taking ASA At the end of year 1: 19.2% At the end of surveillance: 19.3% (7.9% in the IG discontinued due to AEs) Crossover: 7.2% (% in CG taking ASA)
TPT The Medical Research Council's General Practice Research Framework, 1998[45]	5499	6.8 years (median)	% of participants taking ASA: About 2% of tablets (warfarin or aspirin) were missed according to tablet counts at followup visits. Serum salicylate measured in a subsample of 378 men; 6.8% in aspirin groups (including warfarin) had serum levels indicating no recent ASA use and 5.4% in no aspirin groups had levels suggesting recent ASA use
WHS Ridker, 2005[83]	39876	10.1 years†	% of participants taking ASA: Compliance was defined as use on at least 120 days per year: Year 1: 88%Year 5: 76% Year 10: 67% Trial average: 73% Compliance was slightly, but significantly lower in IG vs CG, averaging about 1% lower from year 2 onward. Outside ASA use for 4 or more days per month averaged 12% over the length of FU with NS diff by randomized ASA assignment. For the long-term observational followup, the IG and CG had similar post-trial aspirin use; approximately 36% of participants reported aspirin use of more than 3 days per month at 26 years.
Secondary CVD prevention			
	1363	2.7 years	
UK-TIA UK-TIA Study Group, 1990[111]	2449	4.4 years	

* 10.7 year extended f/u for CVD outcomes
† 17.5 year extended f/u for CVD outcomes and 26 year f/u for CRC outcomes

Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis; AntiOx = antioxidants; ARRIVE = Aspirin to Reduce Risk of Initial Vascular Events; ASA = aspirin; ASCEND = A Study of Cardiovascular Events in Diabetes; ASPREE = Aspirin in Reducing Events in the Elderly; BMD = British Male Doctors; CG = control group; CRC = colorectal cancer; CVD = cardiovascular disease; D = day; F/U = followup; GBR = United Kingdom; HOT = Hypertension Optimal Treatment Study; HTN

Appendix D Table 2. Adherence and Crossover in Included Trials

= hypertension; IG = intervention group; ITA = Italy; JPAD = Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; JPN = Japan; JPPP = Japanese Primary Prevention Project; mg = milligrams; MI = myocardial infarction; N = number of participants; N/A = not applicable; NR = not reported; O = other; PHS = Physician's Health Study; POPADAD = The Prevention of Progression of Arterial Disease and Diabetes trial; PPP = Primary Prevention Project; Q = every; RCT = randomized controlled trial; SALT = Swedish Aspirin Low-dose Trial; SWE = Sweden; TPT Thrombosis Prevention Trial; tx = treatment; UK-TIA = United Kingdom Transient Ischaemic Attack; US = United States; WHS = Women's Health Study; yrs = years

Appendix D Table 3. Landscape of Included Trials' Reporting Analyses in Specific Populations

A *priori* specific population from Research Plan	Study is population- specific	Study reports a priori subgroup analysis	Study reports post hoc subgroup analysis	Study reports subgroup analysis and the specification of the analysis is unclear
Age	ASPREE (≥70 or older, ≥65 in US Black and Latinx populations)	AAA (<62, ≥62) ARRIVE (<65, ≥65) ASCEND (<60, ≥60, <70, ≥70) ASPREE (younger vs older than median) JPAD (<65, ≥65) JPPP (<70, >70)* WHS (45-54, 55-64, ≥65)		HOT (<65, ≥65) PHS (40-49, 50-59, 60-69, 70-84) POPADAD (<60, ≥60) TPT (45-49, 50-54, 55-59, 60-64, 65-69)
Sex	BMD – Men PHS – Men TPT - Men WHS - Women	AAA ARRIVE ASCEND ASPREE JPAD JPPP		POPADAD HOT[79] PPP
Race/ Ethnicity		ASPREE (White, Black, Latinx, Other)		
Estimated CVD Risk	ARRIVE (10-yr CHD risk of 10-20%/10-yr CVD risk 20-30%) TPT – Top 20% risk (by Northwick Park Heart Study algorithm)	ARRIVE (CVD risk ≤10.5%, 10.5-15.1, 15.1-21.6, >21.6) ASCEND (5-year risk estimated from study-derived risk score) JPPP (study-derived risk score where participants received a score based on the sum of risk factors [male +1, ≥70 +1, smoker +3, HTN +1, diabetes +1.5]) WHS (<5%, 5%-9.9%, ≥10%)		HOT (5-20%, >20%)[77] JPAD
Diabetes	ASCEND JPAD POPADAD	ASCEND (duration of DM) ASPREE JPPP WHS	AAA (without DM only) PPP	HOT[80] PHS

* Primary composite outcome only prespecified

Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis; ARRIVE = Aspirin to Reduce Risk of Initial Vascular Events; ASCEND = A Study of Cardiovascular Events in Diabetes; ASPREE = Aspirin in Reducing Events in the Elderly; BMD = British Male Doctors; CVD = cardiovascular disease; DM = diabetes mellitus; HOT = Hypertension Optimal Treatment Study; HTN = hypertension; JPAD = Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; JPPP = Japanese Primary Prevention Project; PHS = Physician's Health Study; POPADAD = The Prevention of Progression of Arterial Disease and Diabetes trial; PPP = Primary Prevention Project; RCT = randomized controlled trial; TPT Thrombosis Prevention Trial; WHS = Women's Health Study

Appendix D Table 4. Key Question 1: Effect of Aspirin on Major CVD Events by Age

Study name Author, year	Mean F/U, yrs	Type of analysis	Outcome	Group	IG n/n analyzed IG event rate/p-y	CG n/n analyzed CG event rate/p-y	Results (95% CI)	P-value for interaction
AAA Fowkes, 2010[69]	8.2	A priori	Primary composite outcome (Fatal or nonfatal coronary event or stroke of revascularization)	<62 years	57/NR 8.6/1000	70/NR 10.2/1000	HR: 0.85 (0.60, 1.20)	NR
				≥62 years	124/NR 18.8/1000	106/NR 16.6/1000	HR: 1.13 (0.87, 1.47)	
ARRIVE Gaziano, 2018[56]	5	A priori	Primary composite outcome (MI, stroke, CVD death, unstable angina, or TIA)	<65 years	NR/NR	NR/NR	HR: 0.86 (0.67, 1.11)	0.2681
				≥65 years	NR/NR	NR/NR	HR: 1.04 (0.84, 1.30)	
ASCEND ASCEND Study Collaborative, 2018[55]	7.4	A priori	Primary composite outcome (nonfatal MI, nonfatal stroke, TIA, death from vascular cause) or revascularization	<60 years	190/2795	238/2795	RR: 0.79 (0.66, 0.96)	0.15
				60-69 years	319/3123	359/3124	RR: 0.87 (0.75, 1.02)	
				≥70 years	324/1822	339/1821	RR: 0.95 (0.81, 1.10)	
ASPREE McNeil, 2018[101]	4.7	NA	CVD secondary composite outcome (Fatal CHD, nonfatal MI, fatal or nonfatal stroke [including hemorrhagic stroke], or hospitalization for heart failure)	Total (≥70 years)	448/9525 10.7/1000	474/9589 11.3/1000	HR: 0.95 (0.83, 1.08)	NA
		A priori	CVD secondary composite outcome (Fatal CHD, nonfatal MI, fatal or nonfatal stroke [including hemorrhagic stroke], or hospitalization for heart failure)	65-73 years	Events: 141/4719 6.8/1000	Events: 177/4823 8.4/1000	HR: 0.81 (0.65, 1.01)	0.09
				≥74 years	Events: 307/4806 14.4/1000	Events: 297/4766 14.1/1000	HR: 1.03 (0.88, 1.20)	
		Post-hoc	CVD secondary composite outcome (Fatal CHD, nonfatal MI, fatal or nonfatal stroke [including hemorrhagic stroke], or hospitalization for heart failure)	65-69 years	Events: 10/NR 9.5/1000	Events: 9/NR 8.8/1000	HR: 1.10 (0.44, 2.70)	0.37
				70-74 years	Events: 160/NR 6.9/1000	Events: 201/NR 8.5/1000	HR: 0.81 (0.66, 1.00)	
				75-84 years	Events: 230/NR 14.3/1000	Events: 220/NR 13.8/1000	HR: 1.04 (0.86, 1.25)	
				≥85 years	Events: 48/NR 30.7/1000	Events: 44/NR 31.2/1000	HR: 0.99 (0.66, 1.49)	
		NA	Composite of major adverse CVD events (Fatal CHD (excluding death from heart failure), nonfatal MI, or fatal or nonfatal ischemic stroke)	Total (≥70 years)	329/9525 7.8/1000	372/9589 8.8/1000	HR: 0.89 (0.77, 1.03)	NA

Appendix D Table 4. Key Question 1: Effect of Aspirin on Major CVD Events by Age

Study name Author, year	Mean F/U, yrs	Type of analysis	Outcome	Group	IG n/n analyzed IG event rate/p-y	CG n/n analyzed CG event rate/p-y	Results (95% CI)	P-value for interaction
		A priori	Composite of major adverse CVD events (Fatal CHD (excluding death from heart failure), nonfatal MI, or fatal or nonfatal ischemic stroke)	65-73 years	Events: 110/4719 5.3/1000	Events: 148/4823 7.0/1000	HR: 0.76 (0.59, 0.97)	0.11
				≥74 years	Events: 219/4806 10.2/1000	Events: 224/4766 10.6/1000	HR: 0.97 (0.81, 1.17)	
		Post-hoc	Composite of major adverse CVD events (Fatal CHD (excluding death from heart failure), nonfatal MI, or fatal or nonfatal ischemic stroke)	65-69 years	Events: 8/NR 7.6/1000	Events: 7/NR 6.8/1000	HR: 1.12 (0.41, 3.10)	0.5
				70-74 years	Events: 112/NR 5.2/1000	Events: 162/NR 6.8/1000	HR: 0.77 (0.61, 0.97)	
				75-84 years	Events: 166/NR 10.3/1000	Events: 175/NR 10.9/1000	HR: 0.94 (0.76, 1.16)	
				≥85 years	Events: 33/NR 20.8/1000	Events: 28/NR 19.7/1000	HR: 1.06 (0.64, 1.76)	
		NA	Death from IHD or stroke	Total (≥70 years)	78/9525 1.8/1000	81/9589 1.9/1000	HR: 0.97 (0.71, 1.33)	NA
			All-cause mortality	Total (≥70 years)	558/9525 12.7/1000	494/9589 11.1/1000	HR: 1.14 (1.01, 1.29)	
		A priori	All-cause mortality	65-73 years	154/4719 7.2/1000	145/4823 6.6/1000	HR: 1.09 (0.87, 1.36)	0.66
				≥74 years	404/4806 18.0/1000	349/4766 15.6/1000	HR: 1.15 (1.00, 1.33)	
HOT Hansson, 1998[70, 79]	3.8	Unclear	Primary composite outcome (CVD death, MI, and stroke)	<65 years	NR/6425 6.5/1000	NR/6378 8.2/1000	RR: 0.79 (0.64, 0.98)	NR
				≥65 years	NR/2974 14.4/1000	NR/3013 15.6/1000	RR: 0.92 (0.74, 1.15)	
			CVD-related mortality	<65 years	NR/6425 2.1/1000	NR/6378 2.6/1000	RR: 0.80 (0.55, 1.16)	NR
				≥65 years	NR/2974 7.4/1000	NR/3013 6.8/1000	RR: 1.08 (0.79, 1.48)	
			All-cause mortality	<65 years	NR/6425 4.9/1000	NR/6378 5.5/1000	RR: 0.90 (0.70, 1.15)	NR
				≥65 years	NR/2974 14.7/1000	NR/3013 15.3/1000	RR: 0.96 (0.77, 1.19)	
JPAD Ogawa, 2008[81]	4.37	Prespecified	Primary composite outcome (Fatal or nonfatal IHD, fatal or nonfatal stroke, and PAD)	<65 years	23/543	27/633	HR: 1.0 (0.57, 1.70)	0.27
				≥65 years	45/719	59/644	HR: 0.68 (0.46, 0.99)	
JPPP Ikeda, 2014[91, 97]	5	A priori for primary composite outcome, post-hoc	Primary composite outcome (CVD death, nonfatal stroke [ischemic or hemorrhagic], and nonfatal MI)	<70 years	52/3234	53/3259	Adj HR: 1.00 (0.68, 1.46)	0.745
				≥70 years	141/3986	154/3985	Adj HR: 0.92 (0.73, 1.16)	

Appendix D Table 4. Key Question 1: Effect of Aspirin on Major CVD Events by Age

Study name Author, year	Mean F/U, yrs	Type of analysis	Outcome	Group	IG n/n analyzed IG event rate/p-y	CG n/n analyzed CG event rate/p-y	Results (95% CI)	P-value for interaction
		for other outcomes	CVD-related mortality	<70 years	10/3234	10/3259	NR	0.968
				≥70 years	48/3986	47/3985	NR	
			All-cause mortality	<70 years	76/3234	72/3259	NR	NR
				≥70 years	221/3986	231/3985	NR	
POPADAD Belch, 2008[66]	6.7	Unclear	Primary composite outcome (Death from CHD, nonfatal MI or stroke, or above the ankle amputation for critical leg ischemia)	<60 years	38/297	36/315	HR: 1.11 (0.70, 1.75)	0.44
				≥60 years	78/341	81/323	HR: 0.89 (0.65, 1.21)	
			CVD-related mortality	<60 years	10/297	10/315	HR: 1.07 (0.44, 2.56)	0.77
				≥60 years	33/341	25/323	HR: 1.24 (0.74, 2.09)	
WHS Ridker, 2005[83]	10.1	A priori	Primary composite outcome (CVD death, nonfatal MI, nonfatal stroke)	45-54 years	163/12010	161/12015	RR: 1.01 (0.81, 1.26)	0.05
				55-64 years	183/5876	186/5878	RR: 0.98 (0.80, 1.20)	
				≥65 years	131/2048	175/2049	RR: 0.74 (0.59, 0.92)	

Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis; ARRIVE = Aspirin to Reduce Risk of Initial Vascular Events; ASCEND = A Study of Cardiovascular Events in Diabetes; ASPREE = Aspirin in Reducing Events in the Elderly; BMD = British Doctor's Trial; CG = control group; CHD = Coronary heart disease; CI = confidence interval; CVD = Cardiovascular Disease; F/U = followup; HOT = Hypertension Optimal Treatment; HR = Hazard ratio; IHD= Ischemic Heart Disease; IG = intervention group; JPAD = Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes; JPPP= Japanese Primary Prevention Project; MI = Myocardial Infarction; NA = not applicable; NR = not reported; PAD = Peripheral Arterial Disease; PHS = Physician's Health Study; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; PPP = Primary Prevention Project; p-y = person years; TIA = Transient Ischemic Attack; TPT = Thrombosis Prevention Trial; WHS = Women's Health Study

Appendix D Table 5. Key Question 1: Effect of Aspirin on Myocardial Infarction by Age

Study name Author, year	Mean F/U, years	Type of analysis	Outcome	Group	IG n/n analyzed IG event rate/p-y	CG n/n analyzed CG event rate/p-y	Results (95% CI)	P-value for interaction
ASPREE McNeil, 2018[101]	4.7	NA	MI - total	Total (≥70 years)	171/9525	184/9589	HR: 0.93 (0.76, 1.15)	NA
HOT Hanson, 1998[70, 79]	3.8	Unclear	MI - total	<65 years	NR/6425 2.2/1000	NR/6378 3.4/1000	RR: 0.66 (0.47, 0.93)	NR
				≥65 years	NR/2974 2.5/1000	NR/3013 4.1/1000	RR: 0.62 (0.38, 0.98)	
JPPP Ikeda, 2014[91, 97]	5	Post-hoc	MI - total	<70 years	10/3234	12/3259	NR	NR
				≥70 years	17/3986	35/3985	NR	
PHS Physician's Health Study, 1989[59]	5	Unclear	MI - total	40-49 years	27/4527	24/4524	Adj RR: 1.12 (NR, NR)	0.02
				50-59 years	51/3725	87/3725	Adj RR: 0.58 (NR, NR)	
				60-69 years	39/2045	84/2045	Adj RR: 0.46 (NR, NR)	
				70-84 years	22/740	44/740	Adj RR: 0.49 (NR, NR)	
WHS Ridker, 2005[83]	10.1	A priori	MI - total	45-54 years	69/12010	56/12015	RR: 1.23 (0.87, 1.75)	0.03
				55-64 years	88/5876	75/5878	RR: 1.17 (0.86, 1.59)	
				≥65 years	41/2048	62/2049	RR: 0.66 (0.44, 0.97)	

Abbreviations: ASPREE = Aspirin in Reducing Events in the Elderly; CG = control group; CI = confidence interval; F/U = followup; HOT = Hypertension Optimal Treatment; HR = Hazard ratio; IG = intervention group; JPPP= Japanese Primary Prevention Project; MI = Myocardial Infarction; NA = not applicable; NR = not reported; PHS = Physician's Health Study; p-y = person years; WHS = Women's Health Study

Appendix D Table 6. Key Question 1: Effect of Aspirin on Stroke by Age

Study name Author, year	Mean F/U, years	Type of analysis	Outcome	Group	IG n/n analyzed IG event rate/p-y	CG n/n analyzed CG event rate/p-y	Results (95% CI)	P-value for interaction
ASPREE McNeil, 2018[101]	4.7	NA	Total stroke	Total (≥70 years)	195/9525 Events: 209/9525	203/9589 Events: 215/9589	Peto OR: 0.97 (0.79, 1.18)	NA
			Ischemic stroke - total	Total (≥70 years)	148/9525	167/9589	HR: 0.89 (0.71, 1.11)	NA
HOT Hanson, 1998[70, 79]	3.8	Unclear	Total stroke	<65 years	NR/6425 3.0/1000	NR/6378 2.7/1000	RR: 1.14 (0.82, 1.60)	NR
				≥65 years	NR/2974 6.6/1000	NR/3013 7.5/1000	RR: 0.87 (0.64, 1.19)	
JPPP Ikeda, 2014[91, 97]	5	Post-hoc	Ischemic stroke - total	<70 years	25/3234	29/3259	NR	NR
				≥70 years	60/3986	72/3985	NR	
			Total stroke - nonfatal	<70 years	35/3234	34/3259	NR	0.970
				≥70 years	82/3986	80/3985	NR	
TPT The Medical Research Council's General Practice Research Framework, 1998[45, 65]	6.8	Unclear	Total stroke	45-49 years	0/1447 p-y 0.0/1000	1/1502 p-y 0.7/1000	Adj RR: NA	0.85
				50-54 years	3/1905 p-y 1.6/1000	0/1899 p-y 0.0/1000	Adj RR: NA	
				55-59 years	4/1663 p-y 2.4/1000	11/1812 p-y 6.1/1000	Adj RR: 0.40 (NR, NR)	
				60-64 years	7/1811 p-y 3.9/1000	9/1756 p-y 5.1/1000	Adj RR: 0.99 (NR, NR)	
				65-69 years	4/1279 p-y 3.1/1000	5/1102 p-y 4.5/1000	Adj RR: 0.59 (NR, NR)	
WHS Ridker, 2005[83]	10.1	A priori	Ischemic stroke - total	45-54 years	57/12010	71/12015	RR: 0.80 (0.57, 1.14)	NR
				55-64 years	60/5876	75/5878	RR: 0.80 (0.57, 1.12)	
				≥65 years	53/2048	75/2049	RR: 0.70 (0.49, 1.00)	
			Total stroke	45-54 years	77/12210	90/12015	RR: 0.85 (0.63, 1.16)	NR
				55-64 years	76/5876	90/5878	RR: 0.84 (0.62, 1.14)	
				≥65 years	68/2048	86/2049	RR: 0.78 (0.57, 1.08)	

Abbreviations: Adj = adjusted; ASPREE = Aspirin in Reducing Events in the Elderly; CG = control group; CI = confidence interval; F/U = followup; HOT = Hypertension Optimal Treatment; HR = Hazard ratio; IG = intervention group; JPPP= Japanese Primary Prevention Project; NA = not applicable; NR = not reported; p-y = person years; TPT = Thrombosis Prevention Trial; WHS = Women's Health Study

Appendix D Table 7. Key Question 1: Effect of Aspirin on Colorectal Cancer by Age

Study name Author, year	Mean F/U, years	Type of analysis	Outcome	Group	IG n/n analyzed IG event rate/p-y	CG n/n analyzed CG event rate/p-y	Results (95% CI)	P-value for interaction
ASPREE McNeil, 2018[101, 130]	4.7	NA	CRC-related mortality	Total (≥70 years)	35/9525 0.8/1000	20/9589 0.5/1000	HR: 1.77 (1.02, 3.06)	NA
			CRC incidence		139/9525 3.3/1000	137/9525 3.2/1000	HR 1.02 (0.81, 1.30)	NA
JPAD Ogawa, 2008[81, 103]	10.7	Unclear	CRC incidence	<65 years	6/543 1.29/1000	18/633 3.26/1000	HR: 0.41 (0.15, 0.97)	NR
				≥65 years	21/719 3.70/1000	13/644 2.53/1000	HR: 1.50 (0.76, 3.08)	
WHS[112]	17.5	Unclear	CRC incidence	45-54 years	68/12010	95/12015	HR: 0.71 (0.52, 0.98)	0.28
				55-64 years	76/5876	99/5878	HR: 0.76 (0.56, 1.02)	
				≥65 years	58/2048	55/2049	HR: 1.04 (0.72, 1.50)	

Abbreviations: ASPREE = Aspirin in Reducing Events in the Elderly; CG = control group; CI = confidence interval; CRC = colorectal cancer; F/U = followup; HR = Hazard ratio; IG = intervention group; JPAD = Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes; NA = not applicable; NR = not reported; p-y = person years

Appendix D Table 8. Key Question 1: Effect of Aspirin on Major CVD Events by Sex

Study name Author, year	Mean F/U, years	Type of analysis	Outcome	Group	IG n/n analyzed IG event rate/p-y	CG n/n analyzed CG event rate/p-y	Results (95% CI)	P-value for interaction
AAA Fowkes, 2010[69]	8.2	Prespecified	Primary composite outcome (fatal or nonfatal coronary event or stroke or revascularization)	Female	85/1194 8.8/1000 p-y	93/1202 9.6/1000 p-y	HR: 0.92 (0.68, 1.23)	NR
				Male	96/481 27.4/1000 p-y	83/473 23.9/1000 p-y	HR: 1.15 (0.86, 1.54)	
ARRIVE Gaziano, 2018[56]	5	Prespecified	Primary composite outcome (MI, stroke, CVD death, unstable angina, TIA)	Female	NR/1851	NR/1857	HR: 0.85 (0.60, 1.20)	0.4342
				Male	NR/4419	NR/4419	HR: 0.99 (0.82, 1.20)	
ASCEND ASCEND Study Collaborative, 2018[55]	7.4	A priori	Primary composite outcome or revascularization (Nonfatal MI, nonfatal ischemic stroke or TIA, death from vascular cause, excluding intracranial hemorrhage, or revascularization)	Female	260/2897	278/2899	RR: 0.92 (0.78, 1.09)	0.49
				Male	573/4843	658/4841	RR: 0.86 (0.77, 0.96)	
ASPREE McNeil, 2018[101]	4.7	Prespecified	Primary composite outcome (Fatal CHD, nonfatal MI, fatal or nonfatal stroke, hospitalization for heart failure)	Female	211/5373 8.8/1000 p-y	203/5410 8.4/1000 p-y	HR: 1.04 (0.86, 1.26)	0.21
				Male	237/4152 13.2/1000 p-y	271/4179 15.0/1000 p-y	HR: 0.88 (0.74, 1.05)	
			All-cause mortality	Female	244/5373 9.7/1000 p-y	225/5410 8.9/1000 p-y	HR: 1.09 (0.91, 1.30)	0.46
				Male	314/4152 16.6/1000 p-y	269/4179 14.1/1000 p-y	HR: 1.19 (1.01, 1.40)	
BMD Peto, 1988[82]	6	NA	CVD-related mortality	Total (all males)	143/3429	75/1710	Peto OR: 0.95 (0.71, 1.25)	NA
			CVD composite (MI, stroke, CVD mortality)		284/3429	143/1710	Peto OR: 0.99 (0.80, 1.22)	NA
			All-cause mortality		270/3429 143.5/10000 p-y	151/1710 159.5/10000 p-y	Peto OR: 0.88 (0.71, 1.09)	NA
HOT	3.8	Unclear		Female	NR/4437	NR/4446	RR: 1.06 (0.72, 1.59)	NR

Appendix D Table 8. Key Question 1: Effect of Aspirin on Major CVD Events by Sex

Study name Author, year	Mean F/U, years	Type of analysis	Outcome	Group	IG n/n analyzed IG event rate/p-y	CG n/n analyzed CG event rate/p-y	Results (95% CI)	P-value for interaction
Hansson, 1998[70, 79]			CVD-related mortality		3.0/1000 p-y	2.8/1000 p-y		
				Male	NR/4962 4.4/1000 p-y	NR/4945 5.0/1000 p-y	RR: 0.89 (0.66, 1.19)	
			Primary composite outcome (CVD death, MI, stroke)	Female	NR/4437 6.5/1000 p-y	NR/4446 8.0/1000 p-y	RR: 0.81 (0.63, 1.04)	NR
				Male	NR/4962 11.2/1000 p-y	NR/4962 12.8/1000 p-y	RR: 0.87 (0.72, 1.05)	
			All-cause mortality	Female	NR/4437 6.6/1000 p-y	NR/4446 5.9/1000 p-y	RR: 1.12 (0.86, 1.47)	NR
				Male	NR/4962 9.2/1000 p-y	NR/4962 11.1/1000 p-y	RR: 0.83 (0.68, 1.02)	
JPAD Ogawa, 2008[81]	4.37	Unclear	Primary composite outcome (Fatal or nonfatal IHD, fatal or nonfatal stroke, and PAD)	Female	28/556	35/596	HR: 0.88 (0.53, 1.44)	NR, NS
				Male	40/706	51/681	HR: 0.74 (0.49, 1.12)	
JPPP Ikeda, 2014[91]	5	A priori	Primary composite outcome (CVD death, nonfatal stroke, and nonfatal MI)	Female	94/4165	93/4176	Adjusted HR: 1.03 (0.77, 1.37)	NR
				Male	99/3055	114/3068	Adjusted HR: 0.87 (0.67, 1.14)	
PHS Physician's Health Study, 1989[59]	5	NA	Primary composite outcome (Nonfatal MI, nonfatal stroke, CVD death)	Total (all males)	307/11037	370/11034	Adjusted RR: 0.82 (0.70, 0.96)	NA
			CVD-related mortality		81/11037	83/11034	Adjusted RR: 0.96 (0.60, 1.54)	NA
			All-cause mortality		217/11037	227/11034	Adjusted RR: 0.96 (0.80, 1.14)	NA
POPADAD Belch, 2008[66]	6.7	Unclear	CVD-related mortality	Female	17/352	16/361	HR: 1.09 (0.55, 2.16)	0.68
				Male	26/286	19/277	HR: 1.33 (0.73, 2.40)	
			Primary composite outcome (Death from CHD or stroke, nonfatal MI or stroke, above ankle amputation for critical leg ischemia)	Female	48/352	55/361	HR: 0.89 (0.60, 1.31)	0.54
				Male	68/286	62/277	HR: 1.04 (0.74, 1.47)	
PPP	3.6	Unclear		Female	17/1277	26/1306	OR: 0.66 (0.36, 1.23)	NR

Appendix D Table 8. Key Question 1: Effect of Aspirin on Major CVD Events by Sex

Study name Author, year	Mean F/U, years	Type of analysis	Outcome	Group	IG n/n analyzed IG event rate/p-y	CG n/n analyzed CG event rate/p-y	Results (95% CI)	P-value for interaction
Roncaglioni, 2001[64]			Primary composite outcome (CVD mortality, nonfatal MI, nonfatal stroke)	Male	28/949	38/963	OR: 0.74 (0.45, 1.22)	
			CVD-related mortality	Female	6/1277	15/1306	OR: 0.41 (0.16, 1.05)	NR
				Male	11/949	16/963	OR: 0.69 (0.32, 1.50)	
			All-cause mortality	Female	20/1277	34/1306	OR: 0.60 (0.34, 1.04)	NR
				Male	42/949	44/963	OR: 0.97 (0.63, 1.49)	
TPT The Medical Research Council's General Practice Research Framework, 1998[45]	6.8	NA	CVD-related mortality	Total (all males)	42/1268	40/1272	Peto OR: 1.06 (0.68, 1.64)	NA
			All-cause mortality		113/1268 13.6/1000 p-y	110/1272 13.1/1000 p-y	Peto OR: 1.03 (0.79, 1.36)	NA
WHS Ridker, 2005[83]	10.1	NA	Primary composite outcome (Nonfatal MI, nonfatal stroke, CVD death)	Total (all females)	477/19934	522/19942	Adjusted RR: 0.91 (0.80, 1.03)	NA
			CVD-related mortality		120/19934	126/19942	Adjusted RR: 0.95 (0.74, 1.22)	NA
			All-cause mortality		609/19934	642/19942	Adjusted RR: 0.95 (0.85, 1.06)	NA

Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis; ARRIVE = Aspirin to Reduce Risk of Initial Vascular Events; ASCEND = A Study of Cardiovascular Events in Diabetes; ASPREE = Aspirin in Reducing Events in the Elderly; BMD = British Doctor's Trial; CG = control group; CHD = Coronary heart disease; CI = confidence interval; CVD = Cardiovascular Disease; F/U = followup; HOT = Hypertension Optimal Treatment; HR = Hazard ratio; IHD= Ischemic Heart Disease; IG = intervention group; JPAD = Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes; JPPP= Japanese Primary Prevention Project; MI = Myocardial Infarction; NA = not applicable; NR = not reported; NS = not significant; OR = odds ratio; PAD = Peripheral Arterial Disease; PHS = Physician's Health Study; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; PPP = Primary Prevention Project; p-y = person years; RR = relative risk; TIA = Transient Ischemic Attack; TPT = Thrombosis Prevention Trial; WHS = Women's Health Study

Appendix D Table 9. Key Question 1: Effect of Aspirin on Myocardial Infarction By Sex

Study name Author, year	Mean F/U, years	Type of analysis	Outcome	Group	IG n/n analyzed IG event rate/p-y	CG n/n analyzed CG event rate/p-y	Results (95% CI)	P-value for interaction
BMD Peto, 1988[82]	6	NA	MI - total	Total (all male)	169/3429	88/1710	Peto OR: 0.96 (0.73, 1.25)	NA
HOT Hansson, 1998[70, 79]	3.8	Unclear	MI - total	Female	NR/4437 1.7/1000 p-y	NR/4446 2.1/1000 p-y	RR: 0.81 (0.49, 1.31)	NR
				Male	NR/4962 2.9/1000 p-y	NR/4945 5.0/1000 p-y	RR: 0.58 (0.41, 0.81)	
PHS Physician's Health Study, 1989[59]	5	NA	MI - total	Total (all male)	139/11037 254.8/100000 p-y	239/11034 439.7/100000 p-y	Adjusted RR: 0.56 (0.45, 0.70)	NA
			MI/Coronary Events - total		185/11037	276/11034	Peto OR: 0.67 (0.56, 0.80)	NA
PPP Roncaglioni, 2001[64, 68]	3.6	Unclear	MI - total	Female	8/1277	6/1306	OR: 1.37 (0.47, 3.95)	NR
				Male	11/949	22/963	OR: 0.50 (0.24, 1.04)	
TPT The Medical Research Council's General Practice Research Framework, 1998[45]	6.8	NA	MI - total	Total (all male)	69/1268 8.5/1000 p-y	98/1272 12.1/1000 p-y	Peto OR: 0.69 (0.51, 0.95)	NA
			MI/Coronary Events - total		83/1268 10.2/1000 p-y	107/1272 13.3/1000 p-y	Peto OR: 0.76 (0.57, 1.03)	NA
WHS Ridker, 2005[83]	10.1	NA	MI - total	Total (all female)	198/19934	193/19942	Adjusted RR: 1.02 (0.84, 1.25)	NA

Abbreviations: BMD = British Doctor's Trial; CG = control group; CI = confidence interval; F/U = followup; HOT = Hypertension Optimal Treatment; IG = intervention group; MI = Myocardial Infarction; n = number of participants; NA = not applicable; NR = not reported; OR = odds ratio; PHS = Physician's Health Study; PPP = Primary Prevention Project; p-y = person years; RR = relative risk; TPT = Thrombosis Prevention Trial; WHS = Women's Health Study

Appendix D Table 10. Key Question 1: Effect of Aspirin on Stroke by Sex

Study name Author, year	Mean F/U, years	Type of analysis	Outcome	Group	IG n/n analyzed IG event rate/p-y	CG n/n analyzed CG event rate/p-y	Results (95% CI)	P-value for interaction
BMD Peto, 1988[82]	6	NA	Ischemic stroke - total	Total (all male)	21/3429	7/1710	Peto OR: 1.45 (0.66, 3.20)	NA
			Total stroke		91/3429	39/1710	Peto OR: 1.16 (0.80, 1.68)	NA
HOT Hansson, 1998[70, 79]	3.8	Unclear	Total stroke	Female	3.2/1000 p-y	4.0/1000 p-y	RR: 0.78 (0.54, 1.12)	NR
				Male	5.0/1000 p-y	4.3/1000 p-y	RR: 1.16 (0.86, 1.56)	
PHS Physician's Health Study, 1989[59]	5	NA	Ischemic stroke – total	Total (all male)	91/11037	82/11034	Adjusted RR: 1.11 (0.82, 1.50)	NA
			Total stroke		119/11037	98/11034	Adjusted RR: 1.22 (0.93, 1.60)	NA
PPP Roncaglioni, 2001[64, 68]	3.6	Unclear	Ischemic stroke - total	Female	6/1277	9/1306	OR: 0.68 (0.24, 1.92)	NR
				Male	8/949	7/963	OR: 1.16 (0.42, 3.22)	
			Total stroke	Female	6/1277	11/1306	OR: 0.56 (0.21, 1.51)	NR
				Male	10/949	13/963	OR: 0.78 (0.34, 1.78)	
TPT The Medical Research Council's General Practice Research Framework, 1998[45]	6.8	NA	Ischemic stroke - total	Total (all male)	10/1268 1.2/1000 p-y	18/1272 2.2/1000 p-y	Peto OR: 0.56 (0.27, 1.19)	NA
			Total stroke		18/1268 2.2/1000 p-y	26/1272 3.2/1000 p-y	Peto OR: 0.69 (0.38, 1.26)	NA
WHS Ridker, 2005[83]	10.1	NA	Ischemic stroke - total	Total (all female)	170/19934	221/19942	Adjusted RR: 0.76 (0.63, 0.93)	NA
			Total stroke		221/19934	266/19942	Adjusted RR: 0.83 (0.69, 0.99)	NA

Abbreviations: BMD = British Doctor's Trial; CG = control group; CI = confidence interval; F/U = followup; HOT = Hypertension Optimal Treatment; IG = intervention group; n = number of participants; NA = not applicable; NR = not reported; OR = odds ratio; PHS = Physician's Health Study; PPP = Primary Prevention Project; p-y = person years; RR = relative risk; TPT = Thrombosis Prevention Trial; WHS = Women's Health Study

Appendix D Table 11. Key Question 1: Effect of Aspirin on Colorectal Cancer by Sex

Study name Author, year	Mean F/U, years	Type of analysis	Outcome	Group	IG n/n analyzed IG event rate/p-y	CG n/n analyzed CG event rate/p-y	Results (95% CI)	P-value for interaction
BMD Peto, 1988[82, 92, 93]	9	NA	CRC incidence	Total (all male)	28/3429	17/1710	Adjusted HR: 0.82 (0.45, 1.49)	NA
	10-19				50/3429	38/1710	Adjusted HR: 0.64 (0.42, 0.97)	NA
	20				92/3429	64/1710	Adjusted HR: 0.70 (0.51, 0.97)	NA
	13.3		CRC-related mortality		59/3429	40/1710	Adjusted OR: 0.73 (0.49, 1.10)	
PHS Physician's Health Study, 1989[59, 113, 114]	1	NA	CRC incidence	Total (all male)	12/11037	6/11034	Adjusted RR: 2.00 (0.75, 5.32)	NA
	2				25/11037	17/11034	NR	NA
	3				39/11037	28/11034	NR	NA
	4				53/11037	42/11034	NR	NA
	5				63/11037	55/11034	Adjusted RR: 1.15 (0.80, 1.65)	NA
	6-12				97/11037	94/11034	OR: 1.03 (0.78, 1.37)	NA
	10-12				28/11037	35/11034	OR: 0.80 (0.49, 1.31)	NA
	12				173/11037	168/11034	IRR: 1.03 (0.83, 1.28)	NA
TPT The Medical Research Council's General Practice Research Framework, 1998[45, 93]	18.3	NA	CRC-related mortality	Total (all male)	34/2545	55/2540	OR: 0.61 (0.40, 0.94)	NA
WHS Ridker, 2005[83, 112]	10.3	NA	CRC incidence	Total (all female)	144/19934	150/19942	Adjusted HR: 0.96 (0.76, 1.20)	NA
	10.3-17.5				58/19934	99/19942	Adjusted HR: 0.58 (0.42, 0.80)	NA
	17.5				202/19934	249/19942	Adjusted HR: 0.80 (0.67, 0.97)	NA

Abbreviations: BMD = British Doctor's Trial; CG = control group; CI = confidence interval; F/U = followup; HOT = Hypertension Optimal Treatment; IG = intervention group; n = number of participants; NA = not applicable; NR = not reported; OR = odds ratio; PHS = Physician's Health Study; PPP = Primary Prevention Project; p-y = person years; RR = relative risk; TPT = Thrombosis Prevention Trial; WHS = Women's Health Study

Appendix D Table 12. Key Question 1: Effect of Aspirin on Major CVD Events by Race/Ethnicity

Study name Author, year	Mean F/U, years	Type of analysis	Outcome	Group	IG n/n analyzed IG event rate/p-y	CG n/n analyzed CG event rate/p-y	Results (95% CI)	P-value for interaction
ASPREE McNeil, 2018[101]	4.7	Prespecified	CVD composite outcome*	White (AUS)	384/NR 10.7/1000 p-y	400/NR 11.1/1000 p-y	HR: 0.96 (0.84, 1.11)	0.86
				White (US)	25/NR 8.9/1000 p-y	34/NR 12.0/1000 p-y	HR: 0.74 (0.44, 1.24)	
				Black	23/451 13.0/1000 p-y	24/450 13.9/1000 p-y	HR: 0.94 (0.53, 1.67)	
				Hispanic	11/NR 11.4/1000 p-y	9/NR 9.2/1000 p-y	HR: 1.17 (0.48, 2.83)	
				Other race	5/NR 9.1/1000 p-y	7/NR 11.1/1000 p-y	HR: 0.83 (0.26, 2.61)	
			Composite of major adverse CVD events†	White (AUS)	282/NR 7.8/1000 p-y	320/NR 8.9/1000 p-y	HR: 0.88 (0.75, 1.04)	0.99
				White (US)	18/NR 6.4/1000 p-y	20/NR 7.0/1000 p-y	HR: 0.91 (0.48, 1.72)	
				Black	17/451 9.6/1000 p-y	19/450 11.0/1000 p-y	HR: 0.88 (0.46, 1.69)	
				Hispanic	8/NR 8.3/1000 p-y	8/NR 8.2/1000 p-y	HR: 1.00 (0.37, 2.66)	
				Other race	4/NR 7.2/1000 p-y	5/NR 7.9/1000 p-y	HR: 0.93 (0.25, 3.48)	
			All-cause mortality	White (AUS)	486/NR 13.0/1000 p-y	410/NR 10.9/1000 p-y	HR: 1.20 (1.05, 1.36)	0.19
				White (US)	29/NR 9.7/1000 p-y	35/NR 11.5/1000 p-y	HR: 0.84 (0.52, 1.38)	
				Black	24/451 12.0/1000 p-y	30/450 15.3/1000 p-y	HR: 0.78 (0.45, 1.33)	
				Hispanic	10/NR 9.0/1000 p-y	14/NR 12.3/1000 p-y	HR: 0.72 (0.32, 1.61)	
				Other race	9/NR 15.3/1000 p-y	5/NR 7.3/1000 p-y	HR: 2.05 (0.69, 6.13)	

*Fatal CHD, nonfatal MI, fatal or nonfatal stroke (including hemorrhagic stroke), or hospitalization for heart failure

†Fatal CHD (excluding death from heart failure), nonfatal MI, fatal or nonfatal ischemic stroke

Abbreviations: ASPREE = Aspirin in Reducing Events in the Elderly; AUS = Australia; CG = control group; CHD = Coronary heart disease; CI = confidence interval; CVD = Cardiovascular Disease; F/U = followup; HR = Hazard ratio; IHD= Ischemic Heart Disease; IG = intervention group; MI = Myocardial Infarction; n = number of participants; p-y = person years; US = United States

Appendix D Table 13. Key Question 1: Effect of Aspirin on Major CVD Events by Diabetes Mellitus

Study name Author, year	Mean F/U, years	Type of analysis	Outcome	Group	IG n/n analyzed IG event rate/p-y	CG n/n analyzed CG event rate/p-y	Results (95% CI)	P-value for interaction
ASCEND ASCEND Study Collaborative, 2018[55]	7.4	NA	Primary composite outcome (Nonfatal MI, nonfatal ischemic stroke or TIA, death from any vascular cause, excluding confirmed intracranial hemorrhage)	Total (All DM)	658/7740	743/7740	RR: 0.88 (0.79, 0.97)	NA
			Primary composite outcome excluding TIA (Nonfatal MI, nonfatal ischemic stroke, death from any vascular cause, excluding confirmed intracranial hemorrhage)		542/7740	587/7740	RR: 0.92 (0.82, 1.03)	NA
			CVD-related mortality		210/7740	226/7740	RR: 0.93 (0.77, 1.12)	NA
			All-cause mortality		748/7740	792/7740	RR: 0.94 (0.85, 1.04)	NA
ASPREE McNeil, 2018[101]	4.7	Prespecified	CVD composite outcome (Fatal CHD, nonfatal MI, fatal or nonfatal stroke, hospitalization for heart failure)	DM	54/1027 12.8/1000 p-y	55/1030 12.7/1000 p-y	HR: 1.01 (0.69, 1.47)	0.74
				Without DM	394/8498 10.5/1000 p-y	419/8559 11.1/1000 p-y	HR: 0.94 (0.82, 1.08)	
			Composite of major adverse CVD events (Fatal CHD [excluding death from heart failure], nonfatal MI, fatal or nonfatal ischemic stroke)	DM	41/1027 9.7/1000 p-y	47/1030 10.8/1000 p-y	HR: 0.90 (0.59, 1.36)	0.98
				Without DM	288/8498 7.6/1000 p-y	325/8559 8.6/1000 p-y	HR: 0.89 (0.76, 1.04)	
			All-cause mortality	DM	87/1027 19.4/1000 p-y	68/1030 15.0/1000 p-y	HR: 1.33 (0.97, 1.82)	0.31
				Without DM	471/8498 11.9/1000 p-y	426/8559 10.7/1000 p-y	HR: 1.11 (0.98, 1.27)	
HOT Hanson, 1998[70, 80]	3.8	Unclear	Primary composite outcome (Fatal and nonfatal MI, all fatal and nonfatal strokes, other CVD deaths)	DM	47/752 17.0/1000 p-y	54/749 19.6/1000 p-y	RR: 0.87 (0.59, 1.28)	NR
				Without DM	268/8647 8.3/1000 p-y	314/8642 9.7/1000 p-y	RR: 0.85 (0.72, 1.00)	
			CVD-related mortality	DM	23/752	26/749	RR: 0.89 (0.51, 1.57)	NR

Appendix D Table 13. Key Question 1: Effect of Aspirin on Major CVD Events by Diabetes Mellitus

Study name Author, year	Mean F/U, years	Type of analysis	Outcome	Group	IG n/n analyzed IG event rate/p-y	CG n/n analyzed CG event rate/p-y	Results (95% CI)	P-value for interaction
					8.2/1000 p-y	9.2/1000 p-y		
				Without DM	110/8647 3.2/1000 p-y	114/8642 3.5/1000 p-y	RR: 0.96 (0.74, 1.25)	
			All-cause mortality	DM	40/752 14.2/1000 p-y	36/749 12.7/1000 p-y	RR: 1.12 (0.72, 1.76)	NR
				Without DM	244/8647 7.4/1000 p-y	269/8642 8.2/1000 p-y	RR: 0.90 (0.76, 1.07)	
JPAD Ogawa, 2008[81]	4.37	NA	Primary composite outcome (Sudden death, death from coronary, cerebrovascular, and aortic causes, nonfatal MI, unstable angina, newly developed exertional angina, nonfatal ischemic and hemorrhagic stroke, TIA, nonfatal aortic and peripheral vascular disease)	Total (All DM)	68/1262 13.6/1000 p-y	86/1277 17.0/1000 p-y	HR: 0.80 (0.58, 1.10)	NA
	10.3				167/1262 16.5/1000 p-y	171/1277 16.3/1000 p-y	Adjusted HR: 0.94 (0.76, 1.17)	NA
	4.37		All-cause mortality		34/1262	38/1277	HR 0.90 (0.57, 1.14)	NA
JPPP Ikeda, 2014[91]	5	A priori	Primary composite outcome (Death from CVD, nonfatal stroke [ischemic or hemorrhagic], and nonfatal MI)	DM	86/2445	98/2458	Adj. HR: 0.89 (0.66, 1.18)	NR
				Without DM	107/4775	109/4786	Adj. HR: 0.99 (0.76, 1.30)	
POPADAD Belch, 2008[66]	6.7	NA	Primary composite outcome (Death from CHD or stroke, nonfatal MI or stroke, or above ankle amputation for critical limb ischemia)	Total (All DM)	116/638	117/638	HR: 0.98 (0.76, 1.26)	NA
			CVD-related mortality		43/638	35/638	HR: 1.23 (0.79, 1.93)	NA
			All-cause mortality		94/638	101/638	HR: 0.93 (0.71, 1.24)	NA
PPP Rongaclioni, 2001[64, 126]	3.7	Post-hoc	Primary composite outcome (CVD death, stroke, MI)	DM	20/519	22/512	RR: 0.90 (0.50, 1.62)	NR
				Without DM	30/1832	51/1921	RR: 0.59 (0.37, 0.94)	

Appendix D Table 13. Key Question 1: Effect of Aspirin on Major CVD Events by Diabetes Mellitus

Study name Author, year	Mean F/U, years	Type of analysis	Outcome	Group	IG n/n analyzed IG event rate/p-y	CG n/n analyzed CG event rate/p-y	Results (95% CI)	P-value for interaction
			CVD-related mortality	DM	10/519	8/512	RR: 1.23 (0.49, 3.10)	0.03
				Without DM	8/1832	25/1921	RR: 0.32 (0.14, 0.72)	
			All-cause mortality	DM	25/519	20/512	RR: 1.23 (0.69, 2.19)	NR
				Without DM	42/1832	61/1921	RR: 0.70 (0.47, 1.04)	
WHS Ridker, 2005[83]	10.1	A priori	Primary composite outcome (Nonfatal MI, nonfatal stroke, death from CVD)	DM	58/NR	62/NR	RR: 0.9 (0.63, 1.29)	NR
				Without DM	418/NR	460/NR	RR: 0.9 (0.79, 1.03)	

Abbreviations: ASCEND = A Study of Cardiovascular Events in Diabetes; ASPREE = Aspirin in Reducing Events in the Elderly; CG = control group; CHD = Coronary heart disease; CI = confidence interval; CVD = Cardiovascular Disease; DM = diabetes mellitus; F/U = followup; HOT = Hypertension Optimal Treatment; HR = Hazard ratio; IHD= Ischemic Heart Disease; IG = intervention group; JPAD = Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes; JPPP= Japanese Primary Prevention Project; MI = Myocardial Infarction; n = number of participants; NA = not applicable; NR = not reported; OR = odds ratio; PAD = Peripheral Arterial Disease; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; PPP = Primary Prevention Project; p-y = person years; RR = relative risk; TIA = Transient Ischemic Attack; WHS = Women's Health Study

Appendix D Table 14. Key Question 1: Effect of Aspirin on Myocardial Infarction by Diabetes Mellitus

Study name Author, year	Mean F/U, years	Type of analysis	Outcome	Group	IG n/n analyzed IG event rate/p-y	CG n/n analyzed CG event rate/p-y	Results (95% CI)	P-value for interaction
ASCEND ASCEND Study Collaborative, 2018[55]	7.4	NA	MI/Coronary Events - total	Total (All DM)	296/7740	317/7740	Peto OR: 0.93 (0.79, 1.09)	NA
HOT Hansson, 1998[70, 80]	3.8	Unclear	MI - total	DM	11/752 3.9/1000 p-y	18/749 6.4/1000 p-y	RR: 0.61 (0.29, 1.29)	NR
				Without DM	71/8647 2.2/1000 p-y	109/8642 3.4/1000 p-y	RR: 0.65 (0.48, 0.87)	
JPAD Ogawa, 2008[81]	4.37	NA	MI/coronary events - total	Total (All DM)	12/1262	14/1277	Peto OR: 0.87 (0.40, 1.88)	NR
	10.3				28/1262	29/1277	NR	NR
POPADAD Belch, 2008[66]	6.7	NA	MI/coronary events - total	Total (All DM)	90/638	82/638	Peto OR: 1.11 (0.81, 1.54)	NR
PHS Physician's Health Study, 1989[59]	5	Unclear	MI - total	DM	11/275	26/258	Adjusted RR: 0.39 (NR)	0.22
				Without DM	128/10750	213/10763	Adjusted RR: 0.60 (NR)	
PPP Rongaclioni, 2001[64, 126]	3.7	Post-hoc	MI - total	DM	5/519	10/512	RR: 0.49 (0.17, 1.40)	NR
				Without DM	15/1832	22/1921	RR: 0.69 (0.36, 1.35)	
WHS Ridker, 2005[83]	10.1	A priori	MI - total	DM	36/NR	24/NR	RR: 1.48 (0.88, 2.49)	NR, NS
				Without DM	162/NR	169/NR	RR: 0.96 (0.77, 1.18)	

Abbreviations: ASCEND = A Study of Cardiovascular Events in Diabetes; CG = control group; CI = confidence interval; DM = diabetes mellitus; F/U = followup; HOT = Hypertension Optimal Treatment; IG = intervention group; JPAD = Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes; JPPP= Japanese Primary Prevention Project; MI = Myocardial Infarction; n = number of participants; NA = not applicable; NR = not reported; OR = odds ratio; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; PPP = Primary Prevention Project; p-y = person years; RR = relative risk; WHS = Women's Health Study

Appendix D Table 15. Key Question 1: Effect of Aspirin on Stroke by Diabetes Mellitus

Study name Author, year	Mean F/U, years	Type of analysis	Outcome	Group	IG n/n analyzed IG event rate/p-y	CG n/n analyzed CG event rate/p-y	Results (95% CI)	P-value for interaction
ASCEND ASCEND Study Collaborative, 2018[55]	7.4	NA	Ischemic stroke - nonfatal	Total (All DM)	202/7740	229/7740	RR: 0.88 (0.73, 1.06)	NA
			Total stroke		254/7740	280/7740	Peto OR: 0.09 (0.76, 1.07)	NA
HOT Hansson, 1998[70, 80]	3.8	Unclear	Total stroke	DM	20/752 7.2/1000 p-y	22/749 7.9/1000 p-y	RR: 0.91 (0.50, 1.67)	NR
				Without DM	126/8647 3.9/1000 p-y	126/8642 3.9/1000 p-y	RR: 1.00 (0.78, 1.27)	
JPAD Ogawa, 2008[81]	4.37	NA	Total stroke	Total (All DM)	28/1262	32/1277	Peto OR: 0.88 (0.53, 1.47)	NA
			Ischemic stroke - nonfatal		22/1262 4.4/1000 p-y	24/1277 4.6/1000 p-y	HR: 0.93 (0.52, 1.66)	NA
	10.3		Ischemic stroke - nonfatal		38/1262 3.8/1000 p-y	46/1277 4.4/1000 p-y	HR: 0.85 (0.55, 1.31)	NA
POPADAD Belch, 2008[66]	6.7	NA	Total stroke		37/638	50/638	Peto OR: 0.73 (0.47, 1.12)	NA
PPP Rongaclioni, 2001[64, 126]	3.7	Post-hoc	Total stroke	DM	9/519	10/512	RR: 0.89 (0.36, 2.17)	NR
				Without DM	11/1832	19/1921	RR: 0.59 (0.28, 1.25)	
WHS Ridker, 2005[83]	10.1	A priori	Ischemic stroke - total	DM	13/NR	29/NR	RR: 0.42 (0.22, 0.82)	NR, NS
				Without DM	157/NR	192/NR	RR: 0.81 (0.66, 1.00)	
			Total stroke	DM	15/NR	31/NR	RR: 0.46 (0.25, 0.85)	NR, NS
				Without DM	206/NR	235/NR	RR: 0.87 (0.72, 1.05)	

Abbreviations: ASCEND = A Study of Cardiovascular Events in Diabetes; CG = control group; CI = confidence interval; DM = diabetes mellitus; F/U = followup; HOT = Hypertension Optimal Treatment; HR: hazard ratio; IG = intervention group; JPAD = Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes; n = number of participants; NA = not applicable; NR = not reported; NS = not significant; OR = odds ratio; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; PPP = Primary Prevention Project; p-y = person years; RR = relative risk; WHS = Women's Health Study

Appendix D Table 16. Key Question 1: Effect of Aspirin on Colorectal Cancer by Diabetes Mellitus

Study name Author, year	Mean F/U, years	Type of analysis	Outcome	Group	IG n/n analyzed IG event rate/p-y	CG n/n analyzed CG event rate/p-y	Results (95% CI)	P-value for interaction
JPAD Ogawa, 2008[81]	5	NA	CRC incidence	Total (All DM)	27/1259 2.61/1000 p-y	31/1277 2.91/1000 p-y	HR: 0.92 (0.55, 1.55)	NR

Abbreviations: CG = control group; CI = confidence interval; DM = diabetes mellitus; F/U = followup; HR: hazard ratio; IG = intervention group; JPAD = Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes; n = number of participants; NA = not applicable; NR = not reported; p-y = person years

Appendix D Table 17. Key Question 1: Effect of Aspirin on Major CVD Events by CVD Risk

Study name Author, year	Mean F/U, years	Type of analysis	Outcome	Group	IG n/n analyzed IG event rate/p-y	CG n/n analyzed CG event rate/p-y	Results (95% CI)	P-value for interaction
ARRIVE Gaziano, 2018[56]	5	A priori	Primary composite outcome (MI, stroke, CVD death, unstable angina, or TIA)	≤10.5% CVD risk*	NR/NR	NR/NR	HR: 0.58 (0.35, 0.97)	0.0920
				10.5-15.1% CVD risk*	NR/NR	NR/NR	HR: 0.99 (0.69, 1.42)	
				15·1 to ≤21·6% CVD risk*	NR/NR	NR/NR	HR: 0.87 (0.63, 1.20)	
				>21.6% CVD risk*	NR/NR	NR/NR	HR: 1.18 (0.91, 1.53)	
ASCEND ASCEND Study Collaborative, 2018[55]	7.4	A priori	Primary composite outcome or revascularization (MI, stroke, or TIA, CVD death, excluding intracranial hemorrhage, and revascularization)	Low CVD risk (<5% 5-year) †	179/3128	208/3136	RR: 0.86 (0.71, 1.05)	0.47
				Moderate CVD Risk (5-<10% 5-year) †	384/3294	431/3254	RR: 0.86 (0.75, 0.99)	
				High CVD risk (≥10% 5-year) †	270/1318	297/1350	RR: 0.94 (0.80, 1.11)	
HOT Hansson, 1998[70, 77]	3.8	Unclear	Primary composite outcome (Fatal and nonfatal MI, all fatal and nonfatal stroke, other CVD death)	15-20% 10-year CV Risk‡	114/4700 6.4/1000	113/4700 6.4/1000	RR: 1.00 (0.77, 1.30)	NR, NS
				≥20% 10-year CV Risk‡	201/4699 11.5/1000	252/4691 14.7/1000	RR: 0.78 (0.65, 0.94)	
JPAD Ogawa, 2008[81, 95]	4.37	Unclear	Primary composite outcome (Death from coronary, cerebrovascular, and aortic causes, nonfatal MI, unstable angina, new exertional angina, nonfatal stroke, TIA, and nonfatal aortic and PAD)	Low CVD risk§	8/314 6.3/1000	19/414 11.4/1000	Adj HR: 0.53 (0.23, 1.21)	0.26
				High CVD risk§	60/945 16.2/1000	66/859 19.5/1000	Adj HR: 0.78 (0.55, 1.11)	
JPPP Ikeda, 2014[91]	5	A priori	Primary composite outcome (Death from CVD, nonfatal stroke [ischemic or hemorrhagic], nonfatal MI)	Risk score <4‖	NR/NR	NR/NR	HR 1.09 (0.72, 1.63)	NR
				Risk score ≥4‖	NR/NR	NR/NR	HR 0.90 (0.72, 1.13)	
WHS	10.1	A priori		<5% 10-year CHD risk¶	152/NR	175/NR	RR: 0.86 (0.69, 1.07)	NR, NS

Appendix D Table 17. Key Question 1: Effect of Aspirin on Major CVD Events by CVD Risk

Study name Author, year	Mean F/U, years	Type of analysis	Outcome	Group	IG n/n analyzed IG event rate/p-y	CG n/n analyzed CG event rate/p-y	Results (95% CI)	P-value for interaction
Ridker, 2005[83]			Primary composite outcome (Nonfatal MI, nonfatal stroke, death from CVD)	5.0%-9.9% 10-year CHD risk¶	96/NR	97/NR	RR: 0.96 (0.72, 1.27)	
				≥10% 10-year CHD risk¶	61/NR	60/NR	RR: 1.06 (0.74, 1.52)	

* Risk estimation conducted through a study-specific equation
†5-year risk estimation conducted through a study-specific equation
‡ Risk stratification as follows: low risk: <15%, medium: 15-20%, high: 20-30%, very high: >30%. No participants in HOT were low-risk. Categorizations based on 1999 WHO-International Society of Hypertension Guidelines[202] where categorization is based on blood pressure level and number of CVD risk factors. 10-year risk is not calculated with an equation, but groups are described as having risk levels typically in the stated range.
§ Low CVD Risk: Males over age 50 and females over age 60 without additional risk factors, or males below age 50 and females below age 60 with or without additional risk factors. High risk: Males over age 50 and females over age 60 who had 1 or more additional CVD risk factors. Additional CVD risk factors (in addition to diabetes) defined as current smoking, HTN, family history of CAD, and proteinuria.[95]
‖ Study-derived risk score where participants received a score based on the sum of risk factors (male +1, ≥70 +1, smoker +3, HTN +1, diabetes +1.5)
¶Calculated using Framingham CHD risk score among those with blood specimens (28,345 total)

Abbreviations: Adj = adjusted; ARRIVE = Aspirin to Reduce Risk of Initial Vascular Events; ASCEND = A Study of Cardiovascular Events in Diabetes; CAD = coronary artery disease; CG = control group; CHD = coronary heart disease; CI = confidence interval; CV = cardiovascular; CVD = Cardiovascular Disease; F/U = followup; HOT = Hypertension Optimal Treatment; HR: hazard ratio; HTN = hypertension; IG = intervention group; JPAD = Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes; MI = Myocardial Infarction; n = number of participants; NA = not applicable; NR = not reported; NS = not significant; p-y = person years; RR = relative risk; TIA = Transient Ischemic Attack; WHS = Women's Health Study

Appendix D Table 18. Key Question 1: Effect of Aspirin on MI by CVD Risk

Study name Author, year	Mean F/U, years	Type of analysis	Outcome	Group	IG n/n analyzed IG event rate/p-y	CG n/n analyzed CG event rate/p-y	Results (95% CI)	P-value for interaction
HOT Hansson, 1998[70, 77]	3.8	Unclear	MI - total	15-20% 10-year CV Risk*	32/4700 1.8/1000 p-y	49/4700 2.8/1000 p-y	RR: 0.65 (0.42, 1.01)	NR, NS
				≥20% 10-year CV Risk*	50/4699 2.8/1000 p-y	78/4691 4.5/1000 p-y	RR: 0.64 (0.45, 0.91)	
JPAD Ogawa, 2008[81, 95]	4.37	Unclear	CHD event - total	Low CVD risk†	2/314	11/414	NR	NA
WHS Ridker, 2005[83]	10.1	A priori	MI - total	<5% 10-year CHD risk‡	59/NR	59/NR	RR: 0.99 (0.69, 1.42)	NR, NS
				5.0%-9.9% 10-year CHD risk‡	36/NR	45/NR	RR: 0.78 (0.50, 1.20)	
				≥10% 10-year CHD risk‡	32/NR	23/NR	RR: 1.48 (0.86, 2.53)	

*Risk stratification as follows: low risk: <15%, medium: 15-20%, high: 20-30%, very high: >30%. No participants in HOT were low-risk. Categorizations based on 1999 WHO-International Society of Hypertension Guidelines[202] where categorization is based on blood pressure level and number of CVD risk factors. 10-year risk is not calculated with an equation, but groups are described as having risk levels typically in the stated range.

†Low CVD Risk: Males over age 50 and females over age 60 without additional risk factors, or males below age 50 and females below age 60 with or without additional risk factors[95]

‡Calculated using Framingham CHD risk score among those with blood specimens (28,345 total)

Abbreviations: CG = control group; CHD = coronary heart disease; CI = confidence interval; CV = cardiovascular; CVD = Cardiovascular Disease; F/U = followup; HOT = Hypertension Optimal Treatment; IG = intervention group; JPAD = Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes; MI = Myocardial Infarction; n = number of participants; NA = not applicable; NR = not reported; NS = not significant; p-y = person years; RR = relative risk; WHS = Women's Health Study

Appendix D Table 19. Key Question 1: Effect of Aspirin on Stroke by CVD Risk

Study name Author, year	Mean F/U, years	Type of analysis	Outcome	Group	IG n/n analyzed IG event rate/p-y	CG n/n analyzed CG event rate/p-y	Results (95% CI)	P-value for interaction
WHS Ridker, 2005[83]	10.1	A priori	Ischemic stroke - total	<5% 10-year CHD risk*	54/NR	76/NR	RR: 0.70 (0.50, 1.00)	NR, NS
				5.0%-9.9% 10-year CHD risk*	35/NR	37/NR	RR: 0.92 (0.58, 1.46)	
				≥10% 10-year CHD risk*	16/NR	29/NR	RR: 0.57 (0.31, 1.04)	
			Total stroke	<5% 10-year CHD risk*	78/NR	97/NR	RR: 0.80 (0.59, 1.07)	NR, NS
				5.0%-9.9% 10-year CHD risk*	48/NR	42/NR	RR: 1.11 (0.74, 1.68)	
				≥10% 10-year CHD risk*	17/NR	32/NR	RR: 0.54 (0.30, 0.98)	

*Calculated using Framingham CHD risk score among those with blood specimens (28,345 total)

Abbreviations: CG = control group; CHD = coronary heart disease; CI = confidence interval; CVD = Cardiovascular Disease; F/U = followup; IG = intervention group; n = number of participants; NR = not reported; NS = not significant; p-y = person years; RR = relative risk; WHS = Women's Health Study

Appendix D Table 20. Key Question 2: Effect of Aspirin on Serious Harms by Age

Study name Author, year	Mean F/U, years	Type of analysis	Outcome	Group	IG n/n analyzed IG event rate/p-y	CG n/n analyzed CG event rate/p-y	Results (95% CI)	P-value for interaction
ASCEND ASCEND Study Collaborative, 2018[55]	7.4	A priori	Composite of major hemorrhage	<60 years	84/2795	79/2795	RR: 1.07 (0.79, 1.45)	0.26
				60-69 years	113/3123	80/3124	RR: 1.41 (1.07, 1.87)	
				≥70 years	117/1822	86/1821	RR: 1.37 (1.04, 1.80)	
ASPREE McNeil, 2018[101]	4.7	NA	Death from major hemorrhage	Total (≥70 years)	28/9525 0.7/1000	24/9589 0.6/1000	HR: 1.18 (0.68, 2.03)	NA
			Hemorrhagic stroke	Total (≥70 years)	43/9525 1.0/1000	34/9589 0.8/1000	HR: 1.27 (0.81, 2.00)	NA
			Hemorrhagic stroke and subarachnoid hemorrhagic stroke	Total (≥70 years)	51/9525	40/9589	Peto OR: 1.28 (0.85 to 1.94)	NA
			Major hemorrhage (non-stroke) - total	Total (≥70 years)	325/9525	233/9589	NR	NA
			Composite of major hemorrhagic events	Total (≥70 years)	361/9525 8.6/1000	265/9589 6.2/1000	HR: 1.38 (1.18, 1.62)	NA
		Prespec	Composite of major hemorrhagic events	65-73 years	Events:127/4719 6.2/1000	Events: 75/4823 3.5/1000	HR: 1.74 (1.31, 2.31)	0.05
				≥74 years	Events: 234/4806 11.0/1000	Events:190/4766 8.9/1000	HR: 1.23 (1.01, 1.49)	
		Post-hoc	Composite of major hemorrhagic events	65-69 years	Events: 3/NR 2.8/1000	Events: 6/NR 5.8/1000	HR: 0.49 (0.12, 1.95)	0.08
				70-74 years	Events: 147/NR 6.3/1000	Events: 88/NR 3.7/1000	HR: 1.72 (1.32, 2.24)	
				75-84 years	Events: 181/NR 11.2/1000	Events: 145/NR 9.0/1000	HR: 1.25 (1.00, 1.55)	
				≥85 years	Events: 30/NR 19.0/1000	Events: 26/NR 18.2/1000	HR: 1.04 (0.61, 1.76)	
		NA	Intracranial bleeding	Total (≥70 years)	107/9525 2.5/1000	72/9589 1.7/1000	HR: 1.50 (1.11, 2.02)	NA
			Major GI bleeding	Total (≥70 years)	158/9525 3.7/1000	99/9589 2.3/1000	Adj HR: 1.62 (1.25, 2.10)	NA

Appendix D Table 20. Key Question 2: Effect of Aspirin on Serious Harms by Age

Study name Author, year	Mean F/U, years	Type of analysis	Outcome	Group	IG n/n analyzed IG event rate/p-y	CG n/n analyzed CG event rate/p-y	Results (95% CI)	P-value for interaction
		Prespec	Major GI bleeding	65-74 years	66/NR 2.7/1000	34/NR 1.4/1000	HR: 1.99 (1.32, 3.02)	0.40
				75-79 years	47/NR 4.1/1000	31/NR 2.7/1000	HR: 1.49 (0.95, 2.34)	
				≥80 years	45/NR 7.0/1000	34/NR 5.2/1000	HR: 1.33 (0.85, 2.08)	
HOT Hanson, 1998[70, 79]	3.8	Unclear	Fatal bleeding events*	<65 years	NR/6425 0.2/1000	NR/6378 0.2/1000	NR, p=NS	NR
				≥65 years	NR/2974 0.3/1000	NR/3013 0.4/1000	NR, p=NS	
			Major Bleed - nonfatal	<65 years	NR/6425 3.0/1000	NR/6378 1.7/1000	NR, p=0.002	NR
				≥65 years	NR/2974 4.3/1000	NR/3013 2.6/1000	NR, p=0.034	
JPPP Ikeda, 2014[91, 97]	5	Post-hoc for outcome other than primary composite	Extracranial bleeding requiring transfusion or hospitalization	<70 years	27/3234	16/3259	NR	0.748
				≥70 years	35/3986	18/3985	NR	
			Total hemorrhagic stroke	<70 years	11/3234	4/3259	NR	NR
				≥70 years	27/3986	19/3985	NR	

*****15 events total; NR by group

Abbreviations: ASCEND = A Study of Cardiovascular Events in Diabetes; ASPREE = Aspirin in Reducing Events in the Elderly; CG = control group; CI = confidence interval; F/U = followup; GI = gastrointestinal; HOT = Hypertension Optimal Treatment; HR: hazard ratio; IG = intervention group; JPPP= Japanese Primary Prevention Project; NA = not applicable; NR = not reported; NS = not significant; OR = odds ratio; Prespec = prespecified; p-y = person years; RR = relative risk;

Appendix D Table 21. Key Question 2: Effect of Aspirin on Serious Harms by Sex

Study name Author, year	Mean F/U, years	Type of analysis	Outcome	Group	IG n/n analyzed IG event rate/p-y	CG n/n analyzed CG event rate/p-y	Results (95% CI)	P-value for interaction
ASCEND ASCEND Study Collaborative, 2018[55]	7.4	A priori	Composite of major hemorrhage	Female	111/2897	89/2899	RR: 1.25 (0.95, 1.65)	0.79
				Male	203/4843	156/4841	RR: 1.31 (1.06, 1.61)	
ASPREE McNeil, 2018[54]	4.7	Prespecified	Major GI bleeding	Female	82/5373 3.4/1000 p-y	51/5410 2.1/1000 p-y	HR: 1.62 (1.14, 2.30)	0.98
				Male	76/4152 4.2/1000 p-y	48/4179 2.6/1000 p-y	HR: 1.61 (1.12, 2.31)	
			Composite of major hemorrhage	Female	190/5373 7.9/1000 p-y	121/5410 5.0/1000 p-y	HR: 1.58 (1.26, 1.99)	0.1
				Male	171/4152 9.5/1000 p-y	144/4179 7.9/1000 p-y	HR: 1.21 (0.97, 1.51)	
BMD Peto, 1988[82]	6	NA	Major GI bleeds	Total (all men)	1/3429 0.5/10000 p-y	3/1710 3.2/10000 p-y	Peto OR: 0.15 (0.02, 1.22)	NA
			Hemorrhagic stroke - total		13/3429	6/1710	Peto OR: 1.08 (0.42, 2.81)	NA
HOT Hansson, 1998[70, 79]	3.8	Unclear	Fatal bleeding events	Female	NR/4437 0.1/1000 p-y	NR/4446 0.2/1000 p-y	NR	NR
				Male	NR/4962 0.3/1000 p-y	NR/4945 0.2/1000 p-y	NR	
			Nonfatal major bleeding events	Female	NR/4437 2.7/1000 p-y	NR/4446 1.3/1000 p-y	NR	NR
				Male	NR/4962 4.1/1000 p-y	NR/4945 2.5/1000 p-y	NR	
PHS Physician's Health Study, 1989[59]	5	NA	Bleeding requiring transfusion or hospitalization	Total (all men)	48/11037	28/11034	Adjusted RR: 1.71 (1.09, 2.69)	NA
			GI hemorrhage - fatal		1/11037	0/11034	Peto OR: 7.39 (0.15, 372.28)	NA
			Hemorrhagic stroke – total		23/11037	12/11034	Adjusted RR: 2.14 (0.96, 4.77)	NA
PPP Rongaclioni, 2001[68 64]	3.6	Unclear	Other serious bleeding	Female	9/1277	2/1306	OR: 4.63 (1.00, 21.46)	NR
				Male	15/949	4/963	OR: 3.85 (1.27, 11.64)	
			Hemorrhagic stroke - total	Female	0/1277	2/1306	OR: 0.20 (0.01, 4.23)	NR
				Male	2/949	1/963	OR: 2.03 (0.18, 22.44)	
TPT The Medical Research Council's	6.8	NA	Major GI bleeds	Total (all men)	6/1268	2/1272	Peto OR: 2.73 (0.68, 10.95)	NA
			Total major bleeds		11/1268	6/1272	Peto OR: 1.81 (0.70, 4.71)	NA
			Hemorrhagic stroke - total		3/1268 0.3/1000 p-y	2/1272 0.2/1000 p-y	Peto OR: 1.50 (0.26, 8.66)	NA

Appendix D Table 21. Key Question 2: Effect of Aspirin on Serious Harms by Sex

Study name Author, year	Mean F/U, years	Type of analysis	Outcome	Group	IG n/n analyzed IG event rate/p-y	CG n/n analyzed CG event rate/p-y	Results (95% CI)	P-value for interaction
General Practice Research Framework, 1998[45]{								
WHS Ridker, 2005[83]	10.1	NA	Major GI bleeds	Total (all women)	129/19934	94/19942	Peto OR: 1.37 (1.05, 1.78)	NA
			Hemorrhagic stroke - total		51/19934	41/19942	RR: 1.24 (0.82, 1.87)	

Abbreviations: ASCEND = A Study of Cardiovascular Events in Diabetes; ASPREE = Aspirin in Reducing Events in the Elderly; BMD = British Medical Doctors; CG = control group; CI = confidence interval; F/U = followup; GI = gastrointestinal; HOT = Hypertension Optimal Treatment; HR: hazard ratio; IG = intervention group; NA = not applicable; NR = not reported; OR = odds ratio; PHS = Physician's Health Study; PPP = Primary Prevention Project; p-y = person years; RR = relative risk; TPT = Thrombosis Prevention Trial; WHS = Women's Health Study

Appendix D Table 22. Key Question 2: Effect of Aspirin on Serious Harms by Diabetes Mellitus

Study name Author, year	Mean F/U, years	Type of analysis	Outcome	Group	IG n/n analyzed IG event rate/p-y	CG n/n analyzed CG event rate/p-y	Results (95% CI)	P-value for interaction
ASCEND ASCEND Study Collaborative, 2018[55]	7	NA	Hemorrhagic stroke - total	Total (All DM)	25/7740	26/7740	RR: 0.96 (0.55, 1.66)	NA
			Total intracranial hemorrhage		55/7740	45/7740	RR: 1.22 (0.82, 1.81)	NA
			Major GI bleeding		137/7740	101/7740	RR: 1.36 (1.05, 1.75)	NA
			Composite of major hemorrhage		314/7740	245/7740	RR: 1.29 (1.09, 1.52)	NA
ASPREE McNeil, 2018[54]	4.7	Prespecified	Composite of major hemorrhagic events (Hemorrhagic stroke, symptomatic intracranial bleeding, extracranial bleeding leading to transfusion, hospitalization, surgery, or death)	DM	38/1027 9.0/1000 p-y	30/1030 6.9/1000 p-y	HR: 1.30 (0.81, 2.10)	0.81
				Without DM	323/8498 8.6/1000 p-y	235/8559 6.2/1000 p-y	HR: 1.39 (1.17, 1.64)	
			Major GI bleeding	DM	15/1027 3.5/1000 p-y	9/1030 2.1/1000 p-y	HR: 1.71 (0.75, 3.90)	0.89
				Without DM	143/8498 3.7/1000 p-y	90/8559 2.3/1000 p-y	HR: 1.61 (1.23, 2.09)	
JPAD Ogawa, 2008[81]	4.37	NA	Hemorrhagic stroke - total	Total (All DM)	6/1262	7/1277	Peto OR: 0.87 (0.29, 2.58)	NA
			Major-GI bleeding requiring transfusion		4/1262	0/1277	NR	NA
			Composite of hemorrhagic stroke and severe GI bleeding		10/1262	7/1277	NR	NA
	10.3	NA	Hemorrhagic stroke - total	Total (All DM)	11/1262	15/1277	Adj. HR: 0.71 (0.32, 1.55)	NA
POPADAD Belch, 2008[66]	6.7	NA	Hemorrhagic stroke - fatal	Total (All DM)	2/638	3/638	Peto OR: 0.67 (0.12, 3.87)	NA

Abbreviations: Adj = adjusted; ASCEND = A Study of Cardiovascular Events in Diabetes; ASPREE = Aspirin in Reducing Events in the Elderly; CG = control group; CI = confidence interval; DM = diabetes mellitus; F/U = followup; GI = gastrointestinal; HR: hazard ratio; IG = intervention group; NA = not applicable; NR = not reported; OR = odds ratio; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; p-y = person years; RR = relative risk

Appendix D Table 23. Credibility Rating for Evidence in Specific Populations

Specific population	Outcome	K reporting specific population of interest	N Randomized	K with prespecified analyses in specific populations	K reporting interaction testing	Consistency of conclusions
Age	CVD*	11/13 (11 within-study)	Within-study: 155,229	7/11	9/11	**Inconsistent** **Within-study comparisons:** WHS and PHS report statistically significant interaction testing showing greater benefit for MI in older age groups and WHS further reported an interaction p-value of 0.05 for composite CVD outcomes but other trials showed nonsignificant interaction tests for composite CVD outcomes and overlapping confidence intervals for age strata. Prior 2009 ATT IPD MA did not confirm significant differential effect
	ACM	3/13 (3 within-study)	Within-study: 52,592	1/3	1/3	**Consistent for no difference in treatment effect** **Within-study comparisons:** 1 trial with interaction testing showed no differential effect and the other reporting trials had similar rates in older and younger age groups
	CRC	3/13 (2 within-study, 1 in older adults)	Within-study: 22,473 Older adults: 19,114	0/2	1/2	**Consistent for no difference in treatment effect** **Within-study comparisons:** JPAD and WHS report statistically significant reduction in CRC incidence in their youngest age strata only, but interaction testing in WHS was not significant and confidence intervals overlapped among age strata in both studies **Older adult trials:** Statistically significant increase in CRC mortality in ASPREE trial of older adults, but nonsignificant effect of aspirin on CRC incidence
	Harms	4/13 (4 within-study)	Within-study: 68,072	2/4	3/4	**Consistent for no difference in treatment effect** **Within-study comparisons:** ASPREE reported an interaction p-value of 0.05 for aspirin's effect on major hemorrhagic events by age where the younger group had a greater risk of bleeding associated with aspirin use compared to the older group. The pattern for major GI bleeding was similar in ASPREE but interaction testing was not significant. ASCEND showed no consistent pattern of major hemorrhage by age and events were rare in other reporting trials.
Sex	CVD*	13/13 (9 within-study, 4 single-sex)	Within-study: 92,278 Single-sex: 72,585	6/9	5/9	**Consistent for no difference in treatment effect** **Within-study comparisons:** interaction testing for heterogeneity of treatment effect was nonsignificant for any outcome when conducted. In cases when interaction testing was not conducted, confidence intervals overlapped for estimates in men and women. **Single-sex trials:** point estimates for men and women have similar range and confidence intervals overlap

Appendix D Table 23. Credibility Rating for Evidence in Specific Populations

Specific population	Outcome	K reporting specific population of interest	N Randomized	K with prespecified analyses in specific populations	K reporting interaction testing	Consistency of conclusions
	ACM	7/13 (3 within-study, 4 single-sex)	Within-study: 42,429 Single-sex: 72,585	1/3	1/3	**Consistent for no difference in treatment effect** **Within-study comparisons:** no evidence for a differential effect either based on interaction testing or comparison of confidence intervals. **Single-sex trials:** point estimates have a similar range for men and women and confidence intervals overlap
	CRC	4/13 (4 single-sex)	Within-study: NA Single-sex: 72,585	NA	NA	**Insufficient** **Within-study comparisons:** no reporting trials **Single-sex trials:** For most time periods, point estimates have a similar range for men and women and confidence intervals overlap
	Harms	8/13 (4 within-study, 4 single-sex)	Within-study: 57,909 Single-sex: 72,585	2/4	2/4	**Consistent for no difference in treatment effect** **Within-study comparisons:** Nonsignificant interaction testing in the 2 reporting trials; other 2 trials have very rare events with overlapping confidence intervals where reported **Single-sex trials:** No suggestion of differential effect by sex with most harms outcomes showing increased risk for bleeding in both men and women; some outcomes have extremely low event rates and wide confidence intervals
Race/Ethnicity	CVD*	1/13 (1 within-study)	Within-study: 19144 Single-sex: NA	1	1	**Cannot be determined - 1 trial** **Within-study comparisons:** Confidence intervals wide for all racial/ethnic groups and overlapping with nonstatistically significant interaction testing
	ACM	1/13 (1 within-study)	Within-study: 19144 Single-sex: NA	1	1	**Cannot be determined - 1 trial** **Within-study comparisons:** Confidence intervals wide for all racial/ethnic groups and overlapping with nonstatistically significant interaction testing
	CRC	0	NA	NA	NA	Not applicable
	Harms	0	NA	NA	NA	Not applicable

Appendix D Table 23. Credibility Rating for Evidence in Specific Populations

Specific population	Outcome	K reporting specific population of interest	N Randomized	K with prespecified analyses in specific populations	K reporting interaction testing	Consistency of conclusions
Diabetes	CVD*	8/13 (5 within-study, 3 diabetes-only)	Within-study: 96,963 Diabetes-only: 19,295	3/5	2/5	**Reasonably consistent for no difference in treatment effect** **Within-study comparisons:** Mixed results from 2 trials performing interaction testing. A post-hoc analysis reported a differential effect of aspirin on CVD mortality, where only those without diabetes had a statistically significant reduction (p for interaction=0.03). In the other trial where analyses were prespecified, there was no signal of effect modification for the primary CVD composite outcome (p for interaction=0.74). All 5 trials reporting CVD composite outcomes had overlapping confidence intervals for those with and without diabetes. **Diabetes-only:** Consistent point estimates of nonsignifcant small relative benefit from aspirin
	ACM	6/13 (3 within-study, 3 diabetes-only)	Within-study: 82,305 Diabetes-only: 19,295	1/3	1/3	**Consistent for no difference in treatment effect** **Within-study comparisons:** Confidence intervals overlapped for all within-study comparisons and interaction testing was nonsignificant in the one trial reporting this testing. **Diabetes-only:** Consistent point estimates of nonsignifcant small relative benefit from aspirin
	CRC	1/13 (1 diabetes-only)	Diabetes-only: 2,539	NA	NA	**Cannot be determined - 1 trial** **Diabetes-only:** nonsignificant effect of aspirin on CRC incidence but only 5 years followup
	Harms	4/13 (1 within-study, 3 diabetes-only)	Within-study: 19,144 Diabetes-only: 19,295	1/1	1/1	**Consistent for no difference in treatment effect** **Within-study:** 1 prespecified analysis showed nonsignificant interaction testing with similar harm magnitude in those with and without diabetes **Diabetes-only:** In ASCEND, the 1 trial with adequate power for bleeding events, statistically significant increased harm in those with diabetes. Two other trials in those with diabetes have extremely limited numbers of bleeding events with odds ratios less than 1 but wide confidence intervals
Estimated CVD Risk	CVD*	6/13 (6 within-study)	Within-study: 103,889	4/6	5/6	**Consistent for no difference in treatment effect** **Within-study:** All trials reported overlapping confidence intervals for varying risk strata and interaction testing was not significant in all trials conducting such analyses
	ACM	0	NA	NA	NA	Not applicable
	CRC	0	NA	NA	NA	Not applicable
	Harms	0	NA	NA	NA	Not applicable

*Any CVD outcome with preference given to trial primary composite CVD outcomes

Appendix D Table 23. Credibility Rating for Evidence in Specific Populations

Abbreviations: ACM = all-cause mortality; ASCEND = A Study of Cardiovascular Events in Diabetes; ASPREE = Aspirin in Reducing Events in the Elderly; ATT = Antithrombotic Trialists' Collaboration; CRC = colorectal cancer; CVD = cardiovascular disease; JPAD = Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes; IPD MA = Individual Participant-Level data meta-analysis; K=number of studies; N=number of participants; NA = not applicable; PHS = Physician's Health Study; WHS = Women's Health Study

Appendix D Table 24. Selected Multivariate Analyses Reporting Risk Factors Associated With Major GI Bleeding

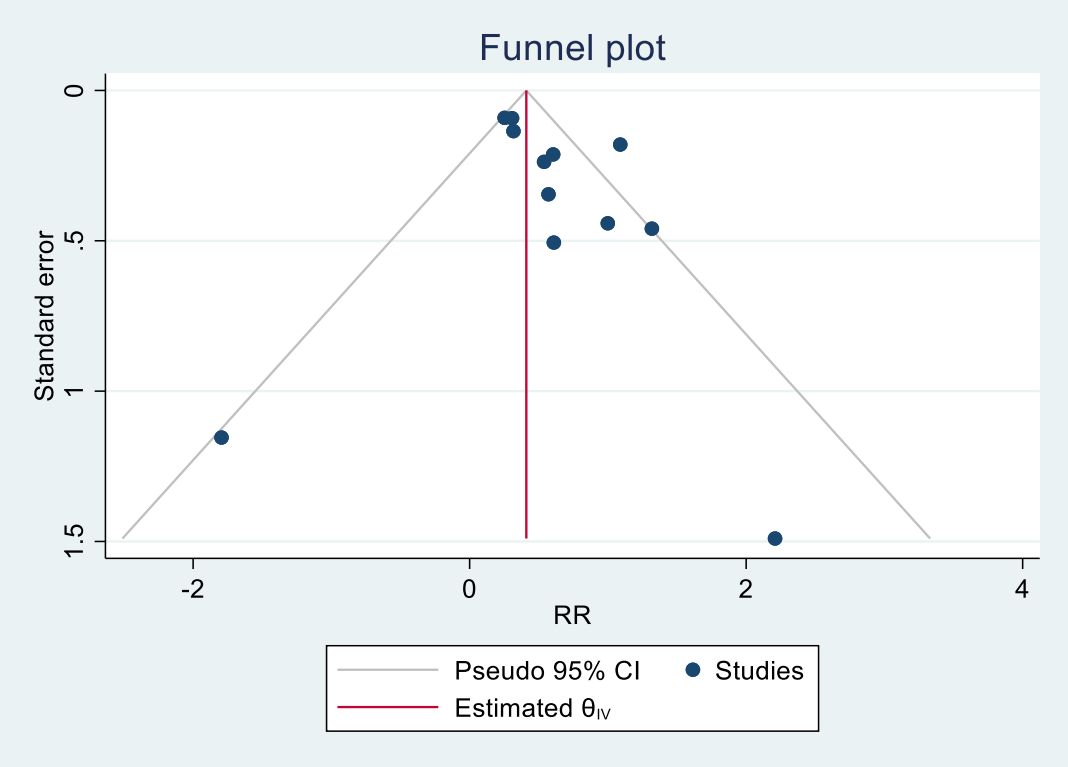
Risk factor	ATT Collaboration[50] Major extracranial bleed Rate ratio (95% CI)	DeBerardis et al.[117] Major bleed Adjusted IRR (95% CI)	DeGroot et al.[160] Upper GI Bleed Adjusted HR (95% CI)	Selak et al.[159] Major bleed Adjusted HR (95% CI)[50]
	IPD meta-analysis of 6 aspirin primary prevention trials	Italian population-based cohort of new aspirin users (≤300 mg/d) and matched controls	Dutch health insurance database of new "low-dose" aspirin users (dose NR) and matched controls	New Zealand primary CVD prevention cohort not dispensed aspirin in prior 6 months
Age	Per decade: 2.15 (1.93-2.39)	Per year: 1.05 (1.05-1.05)	60-70 years (compared to 18-60 year reference group): 1.6 (1.3, 1.9) >70 years (compared to 18-60 year reference group): 2.2 (1.9-2.6)	Per year: 1.04 (1.03-1.04)
Male sex	1.99 (1.45-2.73)	1.69 (1.61-1.79)	1.3 (1.1-1.4)	Separate analyses in males and females
Diabetes status	1.55 (1.13-2.14)	1.36 (1.28-1.44)	1.4 (1.1-1.7)	Males: 1.19 (1.04-1.37) Females: 1.20 (1.03-1.40)
Current smoking	1.56 (1.25-1.94)	NR	NR	Males: 1.47 (1.33-1.62) Females: 1.64 (1.44-1.87)
Blood pressure	Per 20 mm Hg increase: 1.32 (1.09-1.58)	Use of anti-HTN medications: 1.14 (1.08-1.19)	NR	Not statistically significant for per mm Hg increase in SBP Use of BP meds: Males: 1.23 (1.10-1.37) Females: 1.15 (1.03-1.29)
Lipid levels	Cholesterol (per 1 mmol/L): 0.99 (0.90-1.08)	NR	NR	Ratio of total:HDL cholesterol: Males: 0.95 (0.92-0.98) Females:1.00 (0.96-1.05)
GI comorbidities	NR	Previous hospitalization for GI problems: 2.87 (2.46-3.35)	Peptic ulcer disease: 3.9 (1.4-10.4) Cirrhosis: 5.3 (2.3-11.9) Anemia 2.3 (1.9-2.8)	Prior bleed: Males: 3.13 (2.73-3.59) Females: 3.18 (2.70-3.75) Alcohol-related condition: Males: 1.96 (1.54-2.51) Females: 2.59 (1.81-3.70) Liver disease: Males: 2.17 (1.54-3.06) Females: 2.66 (1.66-4.27)
Steroid use	NR	NR	2.3 (1.5-3.5)	Males: 1.42 (1.23-1.64)

Appendix D Table 24. Selected Multivariate Analyses Reporting Risk Factors Associated With Major GI Bleeding

Risk factor	ATT Collaboration[50] Major extracranial bleed Rate ratio (95% CI)	DeBerardis et al.[117] Major bleed Adjusted IRR (95% CI)	DeGroot et al.[160] Upper GI Bleed Adjusted HR (95% CI)	Selak et al.[159] Major bleed Adjusted HR (95% CI)[50]
				Females: 1.39 (1.19-1.62)
NSAID use	NR	1.10 (1.05-1.16)	2.7 (1.6-4.5)	Males: 1.19 (1.08-1.31) Females: 1.11 (0.99-1.25)
Anticoagulant use	NR	1.31 (1.21-1.43)	14.6 (5.6-22.1)	Excluded from cohort if used in prior 6 months
Use of other antiplatelets	NR	1.42 (1.29-1.56)	2.2 (1.8-2.7)	Excluded from cohort if used in prior 6 months
PPI	NR	0.84 (0-80-0.88)	Hx PPI use: 1.2 (1.1-1.4)	Peptic ulcer disease med: Males: 1.44 (1.29-1.60) Females: 1.45 (1.29-1.63)
Statins	NR	0.67 (0.62-0.71)	NR	Not statistically significant
Cancer	NR	NR	NR	Males: 1.76 (1.52-2.02) Females: 1.35 (1.16-1.57)
SSRI	NR	NR	1.5 (1.1-2.1)	Males: 1.34 (1.12-1.60) Females: 1.18 (1.00-1.39)

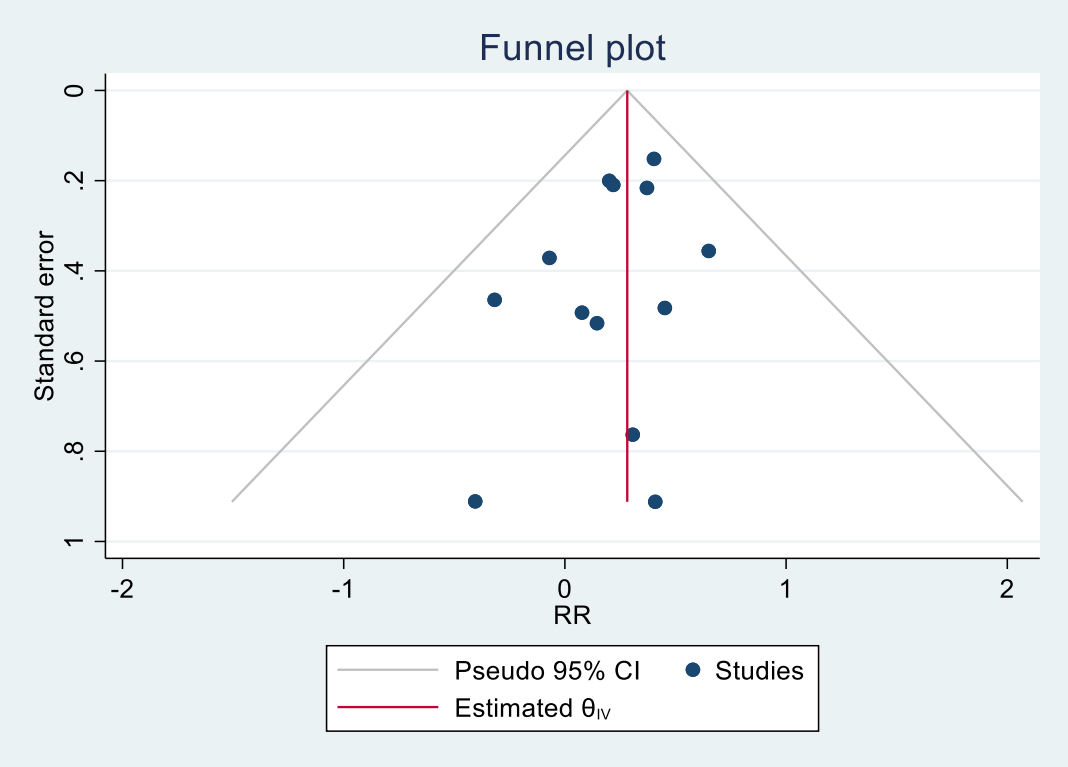
Abbreviations: ATT = Antithrombotic Trialists; CI = confidence interval; CVD = cardiovascular disease; DBP = diastolic blood pressure; GI = gastrointestinal; HR = hazard ratio; Hx = history; HTN = hypertension; IPD MA = Individual Participant-Level data meta-analysis; NR = not reported; NSAID = nonsteroidal anti-inflammatory drugs; PPI = protein pump inhibitor; SBP = systolic blood pressure; SSRI = Selective Serotonin Reuptake Inhibitor

Appendix E Figure 1. Extracranial Bleeds Funnel Plot



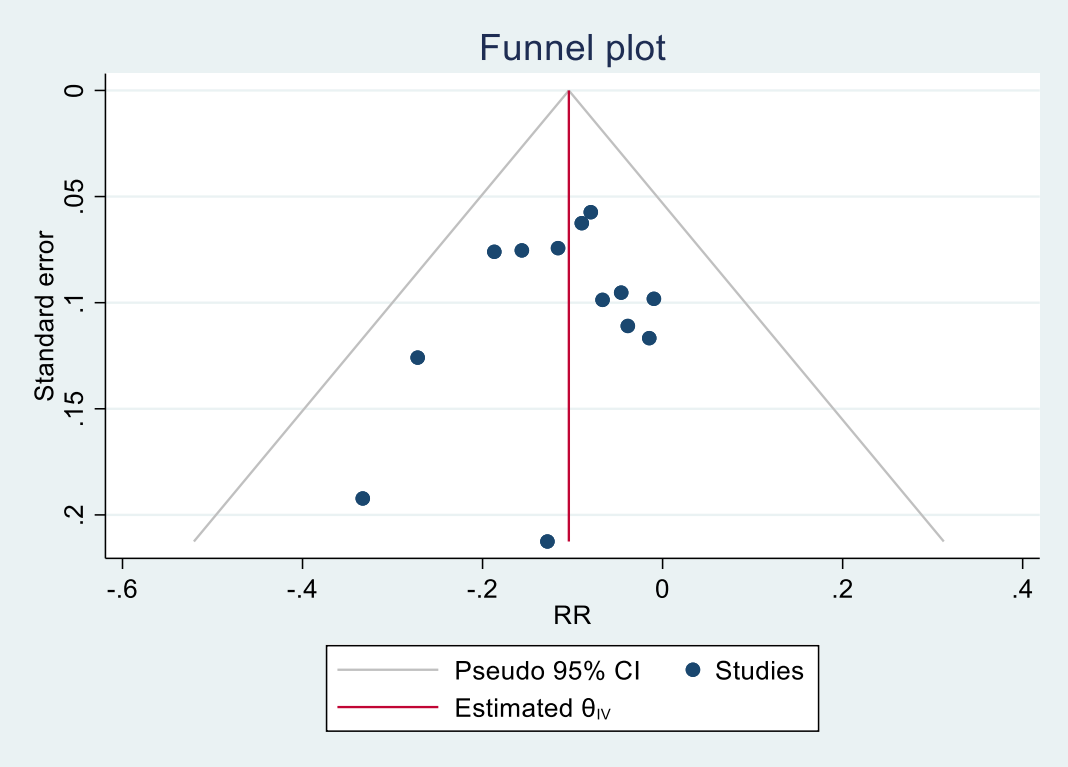
Harbord test for small study effects p=0.02

Appendix E Figure 2. Intracranial Bleed Funnel Plot



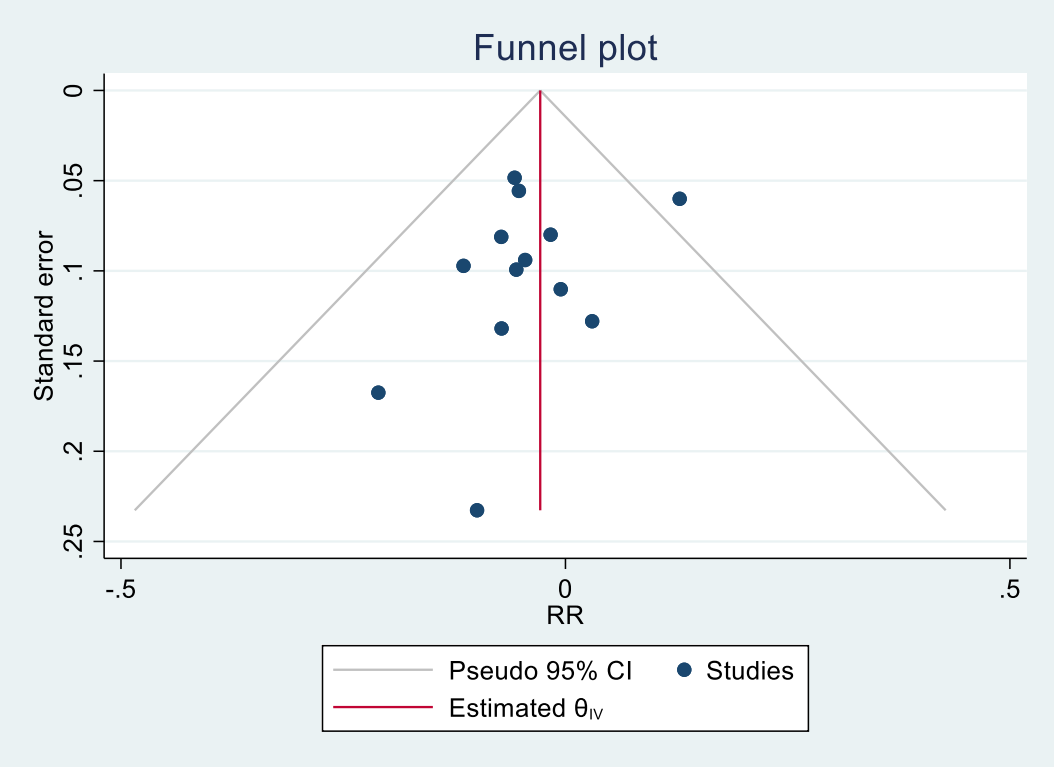
Harbord test for small study effects p=0.35

Appendix E Figure 3. Major CVD Events Funnel Plot



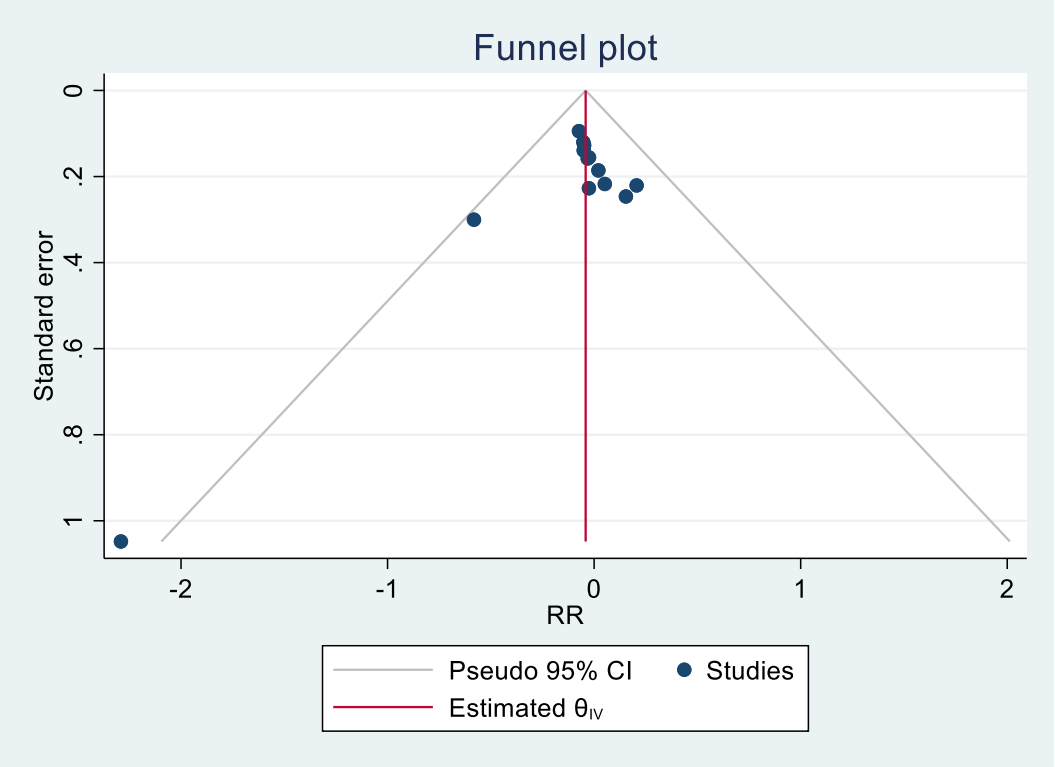
Harbord test for small study effects p=0.61

Appendix E Figure 4. All-Cause Mortality Funnel Plot



Harbord test for small study effects p=0.37

Appendix E Figure 5. CVD Mortality Funnel Plot



Harbord test for small study effects p=0.19

Appendix F. Ongoing Studies

Trial	Location	N	Duration (years)	Intervention	Relevant outcomes	Trial registry no.	Est. completion date
Aspirin Withdrawal and Clinical Outcome in Patients With Moderate to High Cardiovascular Risk But Without Cardiovascular Disease	Korea	4,118	5	Aspirin (dose NR)	CVD events	NCT03757156	November 2024
ASPREE Cancer Endpoints Study (ACES)	US	14,500	NR	Low-dose aspirin (100 mg/day)	Incidence or recurrence of cancer	NCT01968798	April 2024
ASCEND Cancer Long Term Followup	UK	15,480	NR	Low-dose aspirin (100 mg/day)	Incidence of cancer	NCT00135226	Long-term completion NR
ENgAGE-HK (cohort)	Hong Kong	NR	NR	Low-dose aspirin (details NR)	Incidence of colorectal, gastric, and esophageal cancer; related mortality	NCT04081831	November 2019
Patient-centered Benefit-risk Observational Study of Low-dose Aspirin for CVD and CRC Prevention	Italy	1,028	NR	Low-dose aspirin (details NR)	Patient risk/benefit trade off; change in likelihood of adverse events; preferences of aspirin use in specific populations	NCT03603366	October 2019

Abbreviations: ACCEPT-D = Aspirin and simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes; CVD = cardiovascular disease; CRC = colorectal cancer; ENgAGE-HK = Effectiveness of Low-dose Aspirin in Decreasing Chance of Getting Stomach and Intestine cancer – Hong Kong; Est = estimated; ICH = intracranial hemorrhage; ISRCTN = International Standard Randomised Controlled Trial Number; mg/day = milligrams per day; MI = myocardial infarction; N = number of participants; NCT = National Clinical Trial number; no = number; NR = not reported; UK = United Kingdom; US = United States