JAMA | US Preventive Services Task Force | EVIDENCE REPORT

Aspirin Use to Prevent Cardiovascular Disease and Colorectal Cancer
Updated Evidence Report and Systematic Review for the US Preventive Services Task Force

Janelle M. Guirguis-Blake, MD; Corinne V. Evans, MPP; Leslie A. Perdue, MPH; Sarah I. Bean, MPH; Caitlyn A. Senger, MPH

IMPORTANCE Low-dose aspirin is used for primary cardiovascular disease prevention and may have benefits for colorectal cancer prevention.

OBJECTIVE To review the benefits and harms of aspirin in primary cardiovascular disease prevention and colorectal cancer prevention to inform the US Preventive Services Task Force.

DATA SOURCES MEDLINE, PubMed, Embase, and the Cochrane Central Register of Controlled Trials through January 2021; literature surveillance through January 21, 2022.

STUDY SELECTION English-language randomized clinical trials (RCTs) of low-dose aspirin (≤100 mg/d) compared with placebo or no intervention in primary prevention populations.

DATA EXTRACTION AND SYNTHESIS Single extraction, verified by a second reviewer. Quantitative synthesis using Peto fixed-effects meta-analysis.

MAIN OUTCOMES AND MEASURES Cardiovascular disease events and mortality, all-cause mortality, colorectal cancer incidence and mortality, major bleeding, and hemorrhagic stroke.

RESULTS Eleven RCTs (N = 134 470) and 1 pilot trial (N = 400) of low-dose aspirin for primary cardiovascular disease prevention were included. Low-dose aspirin was associated with a significant decrease in major cardiovascular disease events (odds ratio [OR], 0.90 [95% CI, 0.85-0.95]; 11 RCTs [n = 134 470]; I^2 = 0%; range in absolute effects, −2.5% to −0.1%). Results for individual cardiovascular disease outcomes were significant, with similar magnitude of benefit. Aspirin was not significantly associated with reductions in cardiovascular disease mortality or all-cause mortality. There was limited trial evidence on benefits for colorectal cancer, with the findings highly variable by length of follow-up and statistically significant only when considering long-term observational follow-up beyond randomized trial periods. Low-dose aspirin was associated with significant increases in total major bleeding (OR, 1.44 [95% CI, 1.32-1.57]; 10 RCTs [n = 133 194]; I^2 = 4.7%; range in absolute effects, 0.1% to 1.0%) and in site-specific bleeding, with similar magnitude.

CONCLUSIONS AND RELEVANCE Low-dose aspirin was associated with small absolute risk reductions in major cardiovascular disease events and small absolute increases in major bleeding. Colorectal cancer results were less robust and highly variable.

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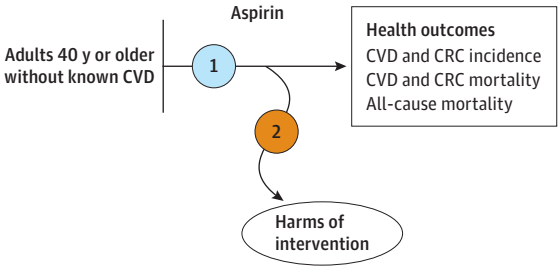
Author Affiliations: Kaiser Permanente Evidence-based Practice Center, Center for Health Research, Kaiser Permanente, Portland, Oregon (Guirguis-Blake, Evans, Perdue, Bean, Senger); Department of Family Medicine, University of Washington, Tacoma (Guirguis-Blake).

Corresponding Author: Janelle M. Guirguis-Blake, MD, Kaiser Permanente Evidence-based Practice Center, Department of Family Medicine, University of Washington, 521 Martin Luther King Jr Way, Tacoma, WA 98405 (jguirgui@u.washington.edu).

Cardiovascular disease (CVD) is the leading cause of death in the US.[1] Aspirin has long been a recommended therapy for primary CVD prevention in the US, and more recently it has also been considered for colorectal cancer (CRC) prevention.[2,3] In 2016, the US Preventive Services Task Force (USPSTF) issued age- and CVD risk–based recommendations for aspirin use for CVD and CRC prevention.[4] The USPSTF recommended initiating low-dose aspirin use for the primary prevention of CVD and CRC in adults aged 50 to 59 years who have a 10% or greater 10-year CVD risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years (B recommendation). The USPSTF concluded that the decision to initiate low-dose aspirin use for the primary prevention of CVD and CRC in adults aged 60 to 69 years who have a 10% or greater 10-year CVD risk should be an individual one (C recommendation). Also, the

Figure 1. Analytic Framework: Aspirin Use to Prevent Cardiovascular Disease and Colorectal Cancer



Key questions

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 between a priori subgroups defined by age, sex, 10-y cardiovascular risk, diagnosis of diabetes mellitus, or race and ethnicity?
b. Does the effect vary by dose or duration of aspirin use?

2 Does regular aspirin use increase major gastrointestinal bleeding, intracranial bleeding, or other serious harms?
a. Does the effect vary between a priori subgroups defined by age, sex, 10-y cardiovascular risk, diagnosis of diabetes mellitus, or race and ethnicity, or bleeding risk factors?
b. Does the effect vary by dose or duration of aspirin use?

Evidence reviews for the US Preventive Services Task Force (USPSTF) use an analytic framework to visually display the key questions that the review will address to allow the USPSTF to evaluate the effectiveness and safety of a preventive service. The questions are depicted by linkages that relate interventions and outcomes. CRC indicates colorectal cancer; CVD, cardiovascular disease

USPSTF determined that there was insufficient evidence for assessing the balance of benefits and harms of initiating aspirin use in adults younger than 50 years or in adults 70 years or older (I statement).

Since the publication of the 2016 recommendations, 3 new trials of aspirin for primary prevention have been published.[5-7] This systematic review updated the body of evidence on the CVD and CRC benefits and harms of aspirin in primary CVD prevention populations. This review was used in conjunction with a decision analysis[8,9] to update USPSTF recommendations.

Methods

Scope of Review

Figure 1 shows the analytic framework and 2 key questions (KQs) that guided this review. Methodological details, additional analyses, findings from observational studies of bleeding harms, and detailed results in specific populations are available in the full evidence report.[10]

Data Sources and Searches

MEDLINE, PubMed (publisher-supplied records only), Embase, and the Cochrane Central Register of Controlled Trials were searched for relevant English-language articles published after the search dates for 3 parallel systematic reviews of aspirin previously conducted for the USPSTF (January 1, 2014, through January 14, 2021) (eMethods in the Supplement).[11-13] All studies in the prior reviews were also evaluated,[11-13] as well as reference lists of related systematic reviews. ClinicalTrials.gov was searched for relevant ongoing trials. Active surveillance was conducted through January 21, 2022, via article alerts and targeted journal searches to identify major studies that might affect the conclusions of the review or understanding of the evidence.

Study Selection

Two independent reviewers screened titles, abstracts, and full-text articles against a priori eligibility criteria (eTable 1 in the Supplement). Studies were eligible for inclusion if they were randomized clinical trials (RCTs), nonrandomized controlled intervention studies, or individual patient data meta-analyses and if they examined regular oral aspirin use (≥75 mg every other day for 12 months) compared with no treatment or a placebo. Eligible populations were adults 40 years or older without known CVD who were at average risk for CRC or were unselected for CRC risk. For KQ1 (benefits), outcomes of interest included a composite cardiovascular outcome and individual CVD outcomes including mortality, and CRC incidence and mortality. For KQ2 (harms), harms of interest were composite and site-specific bleeding events.

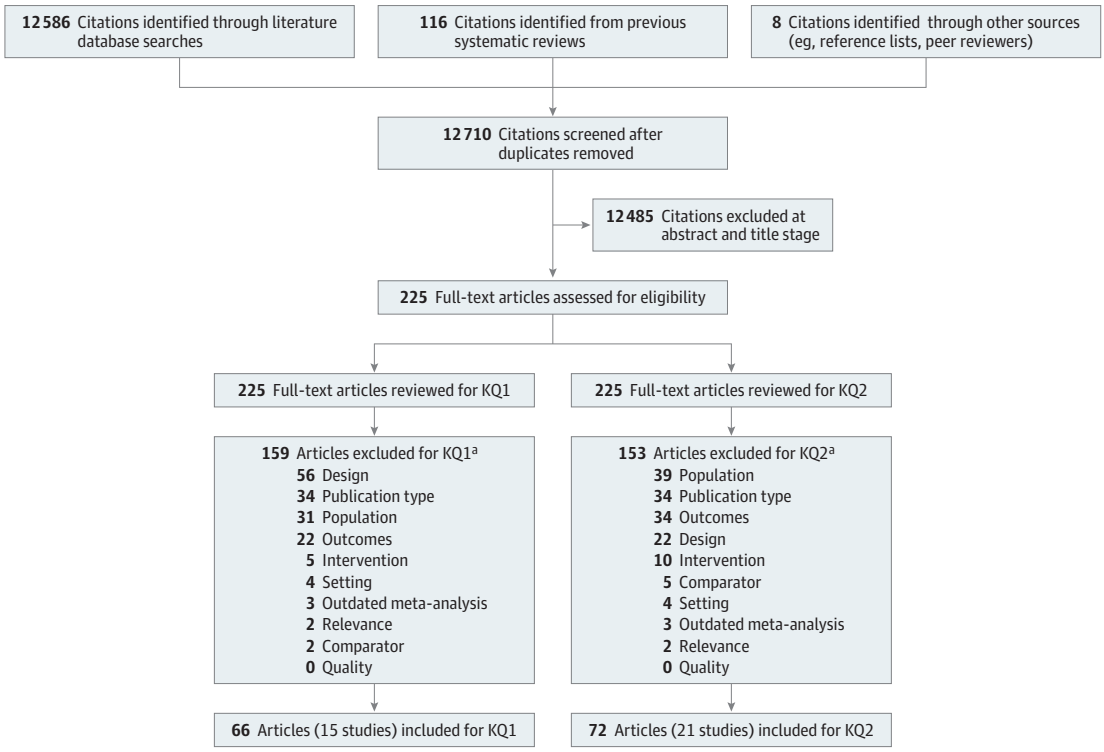
Data Extraction and Quality Assessment

Two reviewers independently applied USPSTF design-specific criteria to critically appraise each study (eTable 2 in the Supplement).[14] Each study was assigned a rating of "good," "fair," or "poor." Discordant ratings were resolved by consensus. Poor-quality studies—those with methodological shortcomings resulting in a high risk of bias—were excluded. One reviewer extracted data into standardized evidence tables and a second reviewer checked the tables for accuracy.

Data Synthesis and Analysis

The primary outcomes for CVD benefits (KQ1) were major CVD events (a composite of nonfatal myocardial infarction [MI], nonfatal stroke, and CVD mortality), total MI, total stroke (all types), total ischemic stroke, CVD mortality, and all-cause mortality. Nonfatal and fatal events were analyzed separately as secondary outcomes. Results for the secondary outcomes of nonfatal MI and nonfatal ischemic stroke, which appear in the companion decision analysis,[8,9] are reported here; results for other secondary outcomes are available in the full report.[10]

Figure 2. Literature Search Flow Diagram: Aspirin Use to Prevent Cardiovascular Disease and Colorectal Cancer



[a] Reasons for exclusion: Design: Study did not use an included design. Publication type: Publication was a conference abstract only. Population: Study was not conducted in an included population. Outcomes: Study did not report relevant outcomes. Intervention: Study did not use an included intervention. Setting: Study was not conducted in a country relevant to US practice or not conducted in, recruited from, or feasible for primary care or a health system. Outdated meta-analysis: Publication was an outdated meta-analysis that did not include recently published trials. Relevance: Study aim was not relevant. Comparator: Study did not use an included comparator. Quality: Study was poor quality. KQ indicates key question.

The primary outcomes for CRC benefits (KQ1) were CRC incidence and CRC mortality. CRC outcomes occurring during randomized trial periods and those occurring during extended observational follow-up were reported separately.

The primary outcomes for harms (KQ2) were total major bleeding (bleeding requiring transfusion or hospitalization or leading to death), extracranial hemorrhage (inclusive of all bleeding except intracranial bleeding), major gastrointestinal bleeding, intracranial hemorrhage (inclusive of hemorrhagic stroke, subarachnoid hemorrhage, and subdural hemorrhage), and hemorrhagic stroke.

The Peto fixed-effects model was used as the primary statistical method for quantitative pooling because of the rarity of events.[15] Sensitivity analyses were conducted using the Mantel-Haenszel fixed-effects and restricted maximum likelihood random-effects models; results of these analyses are available in the full report.[10] The proportion of statistical heterogeneity was assessed using the I^2 statistic. When fewer than 3 studies were available for an analysis, the pooled outcome is shown for illustrative purposes only; such pooled results should be interpreted with caution, as they may not represent the true effect estimate.

Stata version 16 (StataCorp) was used for all quantitative analyses. All significance testing was 2-sided, and results were considered statistically significant at $P < .05$.

The aggregate strength of evidence was assessed for each KQ using the approach described in the Methods Guide for Effectiveness and Comparative Effectiveness Reviews,[16] based on the number, quality, and size of studies and the consistency and precision of results.

Results

Investigators reviewed 12 710 unique citations and 225 full-text articles for all KQs (**Figure 2**). Overall, 23 studies reported in 79 articles were included (N = 165 492 in RCTs; N = 870 660 in cohorts evaluating serious harms).[5-7,17-91] Three RCTs[5-7] and 3 cohorts[60,67,68] were newly identified in this update. The results from 2 high-dose RCTs,[21,44] 2 secondary prevention CVD RCTs reporting CRC outcomes in sensitivity analyses,[56,72] and 6 cohorts reporting serious harm[60,67,68,78,79,81,88] are not described here but are available in the full report.[10]

The 11 low-dose primary prevention RCTs (N = 134 470) and 1 pilot RCT (N = 400) included a broad range of participant populations, including populations with CVD risk factors (eTable 3 in the Supplement).[5-7,26,28,29,31,32,43,45,53,87] RCTs published since the prior reviews for the USPSTF[11-13] focused on special populations with older age,[7] cardiovascular risk factors,[6] and diabetes.[5]

Rates of major CVD events in the control groups varied widely, ranging from an annualized rate of 0.26%[45] to 3.09%.[29] Estimated 10-year CVD risk using the pooled cohort equations was reported in only 1 RCT, with a mean risk of 17.4%.[6] Overall, 63% of participants in the 11 low-dose primary prevention RCTs were women. The mean age of participants in these RCTs was 63 years and ranged from 55 years in the Women's Health Study (WHS)[45] to 74 years in the Aspirin in Reducing Events in the Elderly (ASPREE) trial,[7] which solely recruited older adults. Race and ethnicity were sparsely reported; in the 4 RCTs that reported race and ethnicity, more than 90% of participants were White.[5-7,45] CRC-specific risk factors such as family history of CRC were not reported in any RCT, and only 1 RCT[73] reported CRC screening rates (51.4% in the aspirin group and 52.4% in the placebo group self-reported receiving a screening endoscopy at any point during the 10.3 years of the RCT).

Trial characteristics are described in eTable 4 in the Supplement. The WHS[45] used an alternate-day dosing schedule of 100 mg every other day; the other trials used daily doses of 75 mg,[28,32] 81 mg,[43] or 100 mg.[5-7,26,29,31,53] Three of the 11 low-dose RCTs were conducted 2 or more decades ago, prior to the widespread use of statins.[26,28,32] Randomized trial periods ranged from 3.6 years[26] to 10.1 years.[45] New extended observational follow-up after randomized trial completion was available for the Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD) trial (10.3 years) and the WHS (26 years) (I.-M. Lee, ScD, Harvard Medical School, written communication, November 23, 2020).[43,45] Extended observational follow-up from the Thrombosis Prevention Trial (TPT) trial for CRC mortality data was collected by independent investigators at 18.3 years.[55] The primary outcomes for most RCTs were composite CVD events; these composites were defined inconsistently across trials. Cancer of any type was a prespecified outcome in only 3 low-dose aspirin RCTs.[6,45,53]

Benefits of Intervention

Key Question 1. Does regular aspirin use in patients without known CVD reduce CVD and CRC incidence and mortality, or all-cause mortality?

Eleven low-dose primary prevention CVD RCTs reported the effect of aspirin on CVD outcomes.[5-7,26,28,29,31,32,43,45,53] Six of these RCTs also reported CRC outcomes during the randomized period or extended observational follow-up.[6,55,64,69,73,91]

Cardiovascular and Mortality Outcomes

Major CVD Events, MI, Stroke | Pooled analyses from 11 RCTs (n = 134 470) showed that aspirin use was associated with a statistically significant decrease in major CVD events, MI (total and nonfatal), and total stroke, with odds ratio (OR) point estimates ranging from 0.88 to 0.91 for these outcomes (**Table 1**, **Figure 3**). Five RCTs reported total ischemic stroke (n = 79 334) or nonfatal ischemic stroke (n = 54 947); aspirin was associated with statistically significant relative risk reductions in both these outcomes (OR, 0.82 [95% CI, 0.72-0.92] for total ischemic stroke and OR, 0.88 [95% CI, 0.78-1.00] for nonfatal ischemic stroke). Absolute differences between aspirin and control groups in composite and individual CVD outcomes reported in the individual RCTs ranged from −2.5% to 1.2%.

CVD Mortality | Cardiovascular deaths were inconsistently defined across the 11 primary prevention RCTs. In 4 RCTs, CVD mortality was composed exclusively of fatal MI events and stroke.[7,29,31,43] In other RCTs, definitions were broader, including additional events such as deaths due to rheumatic fever, pulmonary embolism, abdominal aortic aneurysm, or hypertensive disease. Pooled analysis from the 11 RCTs (n = 134 470) demonstrated no statistically significant association of aspirin use with CVD mortality (OR, 0.95 [95% CI, 0.86-1.05]; I^2 = 20.1%) (Figure 3).

All-Cause Mortality | A pooled analysis of the 11 primary prevention RCTs (n = 134 470) showed that aspirin was not significantly associated with a difference in all-cause mortality at 3.6 to 10.1 years (OR, 0.98; [95% CI, 0.93-1.03]; I^2 = 0%) (Figure 3). The ASPREE (Aspirin in Reducing Events in the Elderly) trial, a new RCT conducted exclusively in older adults, was the only trial with a statistically significant finding; this trial reported higher all-cause mortality in the aspirin group than the control group at 4.7 years (5.86% in the aspirin group, 5.15% in the control group; OR, 1.15 [95% CI, 1.01-1.30]).[7]

Sensitivity Analyses

Sensitivity analyses showed that for the outcomes of total and nonfatal MI only, RCTs that were partly or fully conducted prior to 2001, when Adult Treatment Panel III (ATP III) guidelines were published and statin use became more widespread, showed larger relative risk reductions than RCTs conducted after 2001; confidence intervals of these relative risk estimates did not overlap. Additionally, only RCTs published since 2001 showed a statistically significant benefit from aspirin for ischemic stroke, although confidence intervals overlapped with those of the older RCTs. Detailed results are available in the full report.[10]

CRC Outcomes

CRC Incidence | Studies reporting the association of aspirin with CRC incidence had highly variable results by length of follow-up, duration of use, and timing of outcome measurement (eFigure 1 in the Supplement). For events occurring within RCT periods only (4 studies),[6,53,69,73,91] low-dose aspirin had no statistically significant association with CRC incidence at 5 to 10 years of follow-up (n = 86 137; OR, 1.07 [(95% CI, 0.92-1.24]; I^2 = 36.0%) (Figure 3). No single RCT reported a statistically significant beneficial association between low-dose aspirin and CRC incidence (eFigure 2 in the Supplement). Two low-dose primary CVD prevention studies (n = 42 412) reported RCT or observational follow-up at approximately 10 years; the pooled result (presented for illustrative purposes only) did not show a statistically significant association between aspirin use and CRC incidence (OR, 0.96 [95% CI, 0.78-1.19]; I^2 = 0%) (Figure 3).Neither RCT had an individual relative comparison that statistically favored aspirin (OR, 0.88 [95% CI, 0.52-1.48] and OR, 0.98 [95% CI, 0.78-1.23]) (eFigure 3 in the Supplement).

In contrast, 1 low-dose primary CVD prevention RCT, the WHS, reported observational follow-up at approximately 20 years and results suggested a benefit of aspirin for CRC incidence.[73] In the WHS, the group randomized to aspirin during the trial period experienced a significantly lower incidence of CRC at approximately 20 years (n = 39 876; OR, 0.82 [95% CI, 0.69-0.98]) (Figure 3). The point estimate for reductions in CRC incidence was even greater in

Table 1. Ranges of Study-Level Absolute Estimates for Relative Effects Found Statistically Significant in Meta-analysis of Low-Dose Aspirin Trials in Primary CVD Prevention Populations

Outcome	No. Studies	No. Participants	OR (95% CI)	Range of absolute effects, %
Major CVD events (nonfatal MI, nonfatal stroke, CVD mortality)	11	134 470	0.90 (0.85 to 0.95)	−2.5 to −0.1
MI events				
Total	11	134 470	0.89 (0.82 to 0.96)	−1.9 to 1.2
Nonfatal	11	134 470	0.88 (0.80 to 0.96)	−2.0 to 0.2
Stroke (all types)				
Total	11	134 470	0.91 (0.84 to 0.99)	−2.0 to 0.1
Nonfatal	9	103 134	0.88 (0.80 to 0.97)	−1.9 to 0.05
Ischemic stroke				
Total	5	79 334	0.82 (0.72 to 0.92)	−0.6 to −0.2
Nonfatal[a]	5	54 947	0.88 (0.78 to 1.00)	−0.3 to −0.1
CRC				
Incidence				
RCT + observational, 20-y follow-up	1	39 876	0.82 (0.69 to 0.98)	−0.2
Observational, 10- to 20-y follow-up	1	39 876	0.63 (0.47 to 0.83)	−0.2
Mortality	2	44 961	0.77 (0.61 to 0.98)	−0.8 to −0.06
RCT + observational, 18-y follow-up				
Bleeding				
Total major	10	133 194	1.44 (1.32 to 1.57)	0.1 to 1.0
Extracranial	10	133 194	1.53 (1.39 to 1.70)	0.2 to 0.9
Major GI	10	119 130	1.58 (1.38 to 1.80)	0.06 to 0.6
Intracranial	11	134 470	1.31 (1.11 to 1.54)	−0.2 to 0.4
Hemorrhagic stroke				
Total	10	133 194	1.18 (0.97 to 1.45)	−0.07 to 0.2
Nonfatal	6	73 737	1.37 (1.01 to 1.85)	−0.04 to 0.2

Abbreviations: CRC, colorectal cancer; CVD, cardiovascular disease; GI, gastrointestinal; MI, myocardial infarction; OR, odds ratio; RCT, randomized clinical trial.

[a] $P < .05$ for intervention vs control.

an analysis examining only CRC events occurring during the post-trial observational period (≥10 years from the beginning of the trial) (OR, 0.63 [95% CI, 0.47-0.83]) (Figure 3). These analyses suggest that the potential effect of aspirin on CRC incidence may not occur until 10 years after aspirin use has been initiated. However, additional WHS follow-up from 17.5 to 26 years showed no significant difference in CRC incidence between the group initially randomized to aspirin for 10 years of usage and the control group (OR, 1.16 [95% CI, 0.78-1.72]) (I.-M. Lee, ScD, Harvard Medical School, written communication, November 23, 2020). When the entire follow-up period from baseline to 26 years was analyzed, there was not a statistically significant association of 10 years of randomized aspirin use with a lower CRC incidence (OR, 0.87 [95% CI, 0.74-1.02]).

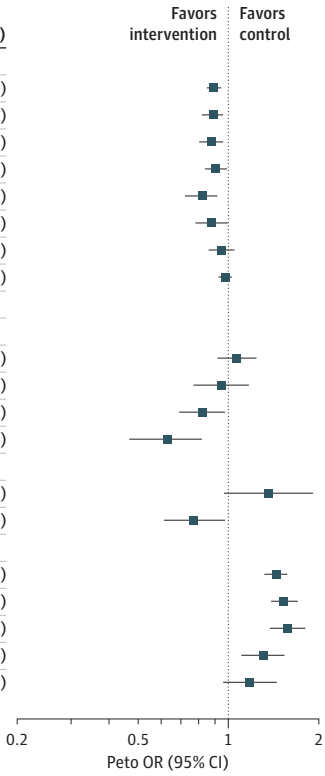
The WHS contributed the largest proportion of participants and CRC cases to each of the pooled effects for CRC incidence reported above and was the only contributing study with follow-up beyond 20 years. At 26 years, the WHS retained 67% of its participants for outcomes analysis; of these participants, 36 percent of participants were taking aspirin more than 3 days per month without any differences in aspirin use based on original study group allocation (I.-M. Lee, ScD, Harvard Medical School, written communication, November 23, 2020). Posttrial aspirin use during the observational period in both the aspirin and placebo groups was associated with cancer risk factors, and additional confounding during the post-trial follow-up cannot be ruled out.

CRC Mortality | Results for CRC mortality were highly variable, potentially because of differences in duration of aspirin use, timing of outcome measurements, and length of follow-up. Two RCTs, ASPREE and the WHS, reported CRC mortality during the trial periods. Pooled analyses of these 2 RCTs (presented for illustrative purposes only) showed that aspirin use for 5 to 10 years was associated with a point estimate in the direction of higher risk of CRC mortality at 5 to 10 years, although this result was not statistically significant (OR, 1.36 [95% CI, 0.97-1.91]) (Figure 3). Both trials showed an OR point estimate greater than 1; ASPREE reported that aspirin use was associated with statistically significantly higher CRC mortality at 4.7 years follow-up (OR, 1.74 [95% CI, 1.02-2.95]),[7] but in the WHS there was not a statistically significant association at 10 years (OR, 1.14 [95% CI, 0.73-1.78]) (I.-M. Lee, ScD, Harvard Medical School, written communication, November 23, 2020).

In contrast to results from the trial periods, results from longer-term observational follow-up suggested a CRC mortality benefit. Observational follow-up at approximately 18 years was available for the WHS (I.-M. Lee, ScD, Harvard Medical School, written communication, November 23, 2020) and TPT trials.[28,55] Pooled analyses

Figure 3. Meta-analysis Results for Effect of Low-Dose Aspirin on CVD, CRC, and Harms Outcomes in CVD Primary Prevention Populations

Outcome	No. of studies	No. of participants	No./total (%)		Peto OR (95% CI)
			Intervention	Control	
Cardiovascular disease					
Major CVD events	11	134 470	2511/67 157 (3.7)	2785/67 313 (4.1)	0.90 (0.85-0.95)
Total MI	11	134 470	1244/67 157 (1.9)	1398/67 313 (2.1)	0.89 (0.82-0.96)
Nonfatal MI	11	134 470	892/67 157 (1.3)	1013/67 313 (1.5)	0.88 (0.80-0.96)
Total stroke (all types)	11	134 470	1160/67 157 (1.7)	1159/67 313 (1.7)	0.91 (0.84-0.99)
Total ischemic stroke	5	79 334	443/39 622 (1.1)	544/39 722 (1.4)	0.82 (0.72-0.92)
Nonfatal ischemic stroke	5	54 947	468/27 422 (1.7)	532/27 525 (1.9)	0.88 (0.78-1.00)
CVD mortality	11	134 470	586/67 157 (0.9)	815/67 313 (1.2)	0.95 (0.86-1.05)
All-cause mortality	11	134 470	3135/67 157 (4.7)	3210/67 313 (4.8)	0.98 (0.93-1.03)
Colorectal cancer					
CRC incidence					
RCT, 5- to 10-y follow-up	4	86 137	366/43 026 (0.9)	343/43 111 (0.8)	1.07 (0.92-1.24)
RCT + observational, 10-y follow-up[a]	2	42 412	174/21 193 (0.8)	181/21 219 (0.9)	0.96 (0.78-1.19)
RCT + observational, 20-y follow-up	1	39 876	222/19 934 (1.1)	270/19 942 (1.4)	0.82 (0.69-0.98)
Observational, 10- to 20-y follow-up	1	39 876	75/19 934 (0.4)	120/19 942 (0.6)	0.63 (0.47-0.83)
CRC mortality					
RCT, 5- to 10-y follow-up[a]	2	58 990	76/29 459 (0.3)	56/29 531 (0.2)	1.36 (0.97-1.91)
RCT + observational, 20 -y follow-up[a]	2	44 961	117/22 479 (0.5)	151/22 482 (0.7)	0.77 (0.61-0.98)
Harms					
Total major bleeding	10	133 194	1197/66 519 (1.8)	837/66 675 (1.3)	1.44 (1.32-1.57)
Extracranial bleeding	10	133 194	930/66 519 (1.4)	609/66 675 (0.9)	1.53 (1.39-1.70)
Major GI bleeding	10	119 130	557/59 499 (0.9)	353/59 631 (0.6)	1.58 (1.38-1.80)
Intracranial bleeding	11	134 470	315/67 157 (0.5)	242/67 313 (0.4)	1.31 (1.11-1.54)
Total hemorrhagic stroke	10	133 194	203/66 519 (0.3)	172/66 675 (0.3)	1.18 (0.97-1.45)



Proportions do not correspond directly to pooled ORs, as weighting in meta-analysis models differs from this approach. CRC indicates colorectal cancer; CVD, cardiovascular disease; GI, gastrointestinal; RCT, randomized clinical trial; MI, myocardial infarction; OR, odds ratio.

[a] Pooled results with only 2 studies are shown for illustrative purposes only.

(presented for illustrative purposes only) from these 2 RCTs showed that aspirin use for 7 to 10 years was associated with a significantly lower risk of CRC mortality at long-term follow-up, including both trial and observational period events (OR, 0.77 [95% CI, 0.61-0.98]; I^2 = 39.9%) (Figure 3). The individual results from the TPT were statistically significant (OR, 0.62 [95% CI, 0.41-0.94), but the individual results from the WHS were not (OR, 0.86 [95% CI, 0.64-1.16]). The WHS also provided data on CRC mortality at 26 years, showing no statistically significant reduction in CRC mortality (OR, 0.96 [95% CI, 0.74-1.24]) (I.-M. Lee, ScD, Harvard Medical School, written communication, November 23, 2020).

Overall, among included 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 risk factors.

Sensitivity Analyses

For all CRC outcomes, results were similar in sensitivity analyses including studies of secondary CVD prevention populations (eFigures 2-12 in the Supplement).

Harms of Intervention

Key Question 2. Does regular aspirin use increase major gastrointestinal bleeding, intracranial bleeding, or other serious harms?

Twelve RCTs of low-dose aspirin in primary prevention populations reported 1 or more major bleeding harms.[5-7,26,28,29,31,32,43,45,53,87] These include the 11 RCTs described above reporting CVD outcomes and an additional pilot RCT (n = 400) that reported major gastrointestinal bleeding.[87]

In pooled analyses, low-dose aspirin was significantly associated with increases in all bleeding events examined, except for total hemorrhagic stroke (Table 1, Figure 3). Statistically significant OR point estimates ranged from 1.31 to 1.58, with absolute differences ranging from −0.2% to 1.0% in individual RCTs. The nonsignificance of the increase in total hemorrhagic stroke may be due to low event rates (0.13% to 0.55% in control groups) and wide confidence intervals.

Sensitivity Analyses

For the outcome of extracranial bleeding, RCTs that were partly or fully conducted prior to 2001 (when the ATP III guidelines led to widespread statin use) showed larger increases in bleeding risk than RCTs conducted after 2001, with confidence intervals that did not overlap. Detailed results of sensitivity analyses are available in the full report.[10]

Key Questions 1a and 2a. Does the effect vary in specific a priori populations defined by age, sex, 10-year cardiovascular risk, diagnosis of diabetes mellitus, or race and ethnicity?

Specific Populations | For CVD, CRC, and bleeding outcomes, synthesis and critical appraisal of subanalyses did not provide strong evidence to suggest effect modification in different population groups—by age, sex, diabetes status, baseline CVD risk strata, or race and ethnicity.[10]

Key Questions 1b and 2b. Does the effect vary by dose or duration of aspirin use?

Dose | For all CVD, CRC, and bleeding outcomes, sensitivity analyses showed similar pooled results for trials administering any dose of aspirin vs trials administering low-dose aspirin only (eFigures 2-12 in the Supplement).

Duration | Most trials reported time-to-event analyses for CVD outcomes.[5-7,26,28,29,31,32,43,45,53] In cases in which time-to-event analyses suggested benefit for individual CVD outcomes, benefit generally accrued within the first 1 to 2 years.[26,28,32,45] For CRC outcomes, follow-up period rather than aspirin duration was more suggestive of benefit. Specifically, aspirin was only associated with a significant reduction in CRC incidence in analyses of about 20 years of follow-up or in highly selected analyses including only years 10 to 20 of follow-up (Figure 3). However, these data are from 1 study using observational follow-up, and data are too limited to determine whether there is a minimum duration of use needed for CRC benefit. For bleeding outcomes, few trials reported time-to-event analyses, limiting examination of harms by duration of use.[6,7,45,53] Among the few trials with Kaplan-Meier curves, bleeding harms appeared to occur immediately or at about 1 year of aspirin use. Detailed results by duration are available in the full report.[10]

Discussion

This systematic review of 11 RCTs of low-dose aspirin for primary CVD prevention found that aspirin use was significantly associated with reduction in the odds of CVD events, including major CVD events, total MI, and ischemic stroke, although there were no significant reductions in CVD mortality or all-cause mortality at up to 10 years of follow-up (**Table 2**). Low-dose aspirin was significantly associated with increases in bleeding harms, including intracranial and extracranial hemorrhage. Thus, the findings of this meta-analysis are consistent with those of the previous systematic review conducted for the USPSTF[11] as well as several other recent meta-analyses, in demonstrating that small absolute CVD event reductions associated with aspirin use are closely matched by increases in major bleeding.[92-96]

Use of aspirin for primary CVD prevention is widespread in the US, with more than one-third of adults 50 years or older taking aspirin for this purpose when surveyed in 2017-2018.[97] However, many international guideline panels have recently recommended against routine aspirin use for primary CVD prevention and instead recommended judicious use in those with relatively high CVD risk and low gastrointestinal bleeding risk.[98-102] There are no US-based externally validated risk prediction tools for bleeding risks associated with low-dose aspirin use for the primary prevention of CVD. Risk factors consistently and independently associated with bleeding risk in multivariable analyses include older age, male sex, diabetes, liver disease, alcohol disease, peptic ulcer disease, and history of gastrointestinal issues, such as prior gastrointestinal hospitalization.[78,103-105]

Strategies to mitigate bleeding risk in individuals identified to be aspirin candidates may include limiting aspirin dose, using an aspirin formulation with enteric coating, or co-administering aspirin with a proton pump inhibitor (PPI). This review of primary CVD prevention trials did not provide sufficient evidence to make any conclusions about how enteric coating or dose adjustments may mitigate bleeding risk; however, observational evidence has shown that higher doses are associated with higher bleeding risk.[82] There is also evidence supporting the use of PPIs to reduce upper gastrointestinal tract bleeding in aspirin users,[106-108] although long-term PPI use has been associated with osteoporosis[109]; vitamin B_{12} deficiency[110]; and enteric infections, including *Clostridioides difficile*.[111] Additionally, *Helicobacter pylori* eradication has been proposed to mitigate aspirin-associated bleeding risk.[112]

A decision analysis was developed to inform USPSTF recommendations.[8] This decision analysis assessed the overall net benefit of aspirin for primary prevention of CVD using effect estimates of the benefits and harms of aspirin from the present review, estimated 10-year CVD risk from the pooled cohort equations,[113] CVD event rates from risk equations in the decision analysis simulation model, and bleeding risk estimates by age and sex from a large New Zealand cohort.[114] The model estimated that expected lifetime net benefits of aspirin use may be positive or negative depending on an individual's age, sex, and CVD risk status. Bleeding risk estimates by age and sex in the US population in aspirin nonusers are not available, nor are data on bleeding risk in any population that also accounts for other bleeding risk factors such as smoking and diabetes; such data would further inform future decision analyses.

Contemporary CVD risk factor management, especially widespread statin use, may alter the relative importance of aspirin as a primary prevention agent. Sensitivity analyses performed in this review demonstrated conflicting results across outcomes between RCTs conducted before and after the ATP III guideline release in 2001. Consistent with a prior analysis comparing pre–ATP III and post–ATP III trials,[115] the sensitivity analyses showed that major CVD event and MI benefits, as well as most bleeding harms, were diminished in post–ATP III trials, while ischemic stroke emerged as a statistically significant benefit in post–ATP III pooled analyses. These findings are likely influenced by additional sources of heterogeneity such as aspirin dose and trial population characteristics. Three contemporary trials—A Study of Cardiovascular Events in Diabetes (ASCEND), Aspirin to Reduce Risk of Initial Vascular Events (ARRIVE), and ASPREE—performed subgroup analyses by statin use and found no statistically significant interaction between aspirin use and statin use.[5-7] Nonetheless, statins have taken priority in the CVD primary prevention clinical landscape because of their well-established CVD and mortality benefits and favorable adverse effect profile.[116]

Despite robust reporting of subanalyses in many specific populations, there was no compelling evidence to suggest effect modification in different population groups by age, sex, diabetes status, baseline CVD risk strata, or race and ethnicity. This finding was consistent with a 2009 individual patient data meta-analysis.[103] An updated individual patient data meta-analysis is anticipated in 2022.

Table 2. Summary of Evidence for Low-Dose Aspirin (≤100 mg/d)

Outcome	No. of studies (participants)	Summary of findings[a]	Consistency and precision	Overall strength of evidence	Body of evidence limitations	Applicability
KQ1: Benefits of regular aspirin use						
Major CVD events (total MI, total stroke, CVD death)	11 RCTs (n = 134 470)	OR, 0.90 (95% CI, 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 (a proxy for optimal CVD risk factor management), and trial duration Trials mostly 4-6 y, with 1 trial lasting 10 y Trials may have insufficient follow-up to evaluate long-term CVD mortality benefit Trials powered for composite CVD outcomes of varying severity (fatal and nonfatal outcomes, with some trials including angina and revascularization in the composite outcome) Low event rates for stroke (1% to 2% for total stroke in control groups; <1% to 2% for ischemic stroke events in control groups) limit precision for these outcomes Studies infrequently adjusted for confounders	Broadly applicable to primary prevention populations, including those with comorbidities
Total MI	11 RCTs (n = 134 470)	OR, 0.89 (95% CI, 0.82-0.96) Range of absolute effects, −1.9% to 1.2%	Consistent, precise	High for benefit		
Total stroke	11 RCTs (n = 134 470)	OR, 0.91 (95% CI, 0.84-0.99) Range of absolute effects, −2.0% to 0.1%	Reasonably consistent, precise	Moderate for benefit		
Total ischemic stroke	5 RCTs (n = 79 334)	OR, 0.82 (95% CI, 0.72-0.92) Range of absolute effects, −0.6% to −0.2%	Consistent, precise	Moderate for benefit		
CVD mortality	11 RCTs (n = 134 470)	OR, 0.95 (95% CI, 0.86-1.05)	Reasonably consistent, imprecise	Moderate for no benefit		
All-cause mortality	11 RCTs (n = 134 470)	OR, 0.98 (95% CI, 0.93-1.03)	Reasonably consistent, reasonably precise	Moderate for no benefit		
CRC incidence (based on trial evidence only)	4 RCTs (n = 86 137)	OR, 1.07 (95% CI, 0.92-1.24)	Inconsistent, imprecise	Insufficient	CRC outcomes: Most trials had inadequate RCT durations of ≈5 y for cancer outcomes; only WHS had a randomized duration of 10 y Very few cases and wide confidence intervals Long-term follow-up was collected in an observational design in which allocation to aspirin or control was no longer randomized Adherence decreased and crossover increased over time Observational data for some trials were collected by outside investigators	Broadly applicable to primary CVD prevention populations, but for longest-term follow-up some analyses only available for females (WHS) or males (TPT) TPT is an older trial in which 41% of participants were current smokers
CRC incidence (based on long-term observational evidence only in primary CVD prevention populations)	1 study (n = 39 876)	WHS 17.5-y follow-up: OR, 0.82 (95% CI, 0.69-0.98) WHS 26-y follow-up: OR, 0.87 (95% CI, 0.74-1.02)	NA (1 study), imprecise	Insufficient		
CRC mortality (based on trial evidence only)	2 RCTs (n = 58 990)	ASPREE OR, 1.74 (95% CI, 1.02-2.95) WHS OR, 1.14 (95% CI, 0.73-1.78)	Reasonably consistent, imprecise	Insufficient		
CRC mortality (based on long-term observational evidence only in primary CVD prevention populations)	2 studies (n = 44 961)	17-y to 18-y follow-up: WHS OR, 0.86 (95% CI, 0.64-1.16) TPT OR, 0.62 (95% CI, 0.41-0.94)	Consistent, imprecise	Insufficient		
KQ2: Harms of regular aspirin use						
Total major bleeding	10 RCTs (n = 133 194)	OR, 1.44 (95% CI, 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	Broadly applicable to primary CVD prevention populations, including individuals with comorbidities
Extracranial hemorrhage	10 RCTs (n = 133 194)	OR, 1.53 (95% CI, 1.39-1.70) Range of absolute effects, 0.2% to 0.9%	Consistent, reasonably precise	Moderate to high for harm		
Major GI bleeding	10 RCTs (n = 119 130)	OR, 1.58 (95% CI, 1.38-1.80) Range of absolute effects, 0.06% to 0.6%	Consistent, reasonably precise	Moderate for harm		
Intracranial hemorrhage	11 RCTs (n = 134 470)	OR, 1.31 (95% CI, 1.11-1.54) Range of absolute effects, −0.2% to 0.4%	Consistent, imprecise	Moderate for harm		
Total hemorrhagic stroke	10 RCTs (n = 133 194)	OR, 1.18 (95% CI, 0.97-1.45)	Inconsistent, imprecise	Low for harm		

Abbreviations: CRC, colorectal cancer; CVD, cardiovascular disease; GI, gastrointestinal; KQ, key question; MI, myocardial infarction; NA, not applicable; OR, odds ratio; RCT, randomized clinical trial; TPT, Thrombosis Prevention Trial; WHS, Women's Health Study.

[a] Pooled estimates presented when quantitative pooling was conducted; absolute effects calculated only when relative effects were statistically significant.

While additional benefits for CRC prevention could potentially change the net benefit of aspirin use, there was insufficient evidence of the effect of low-dose aspirin on CRC outcomes to reach this conclusion because of limitations in the number of reporting trials, adequacy of follow-up duration, power, and reliance on observational follow-up. New CRC data published since the previous review[13] are now available from 2 new trials,[6,91] and additional reporting is available from 3 older trials (I.-M. Lee, ScD, Harvard Medical School, written communication, November 23, 2020).[64,69] With approximately 5 years of follow-up, the 2 new trials, which report null effects, are too short in duration to expect a CRC incidence or mortality benefit to accrue. However, one of these trials, ASPREE, found a concerning and statistically significant increase in CRC mortality for aspirin users over this 5-year period, apparently due to a shift in greater late-stage cancers.[91]

Sensitivity analyses for CRC outcomes included trials of secondary CVD prevention[56,72] and all doses of aspirin.[21,44] These sensitivity analyses examining different indications and doses of aspirin included broader posttrial observational data, finding positive effects of aspirin use on CRC incidence for up to approximately 20 years, despite an expectation that benefits would diminish over time as aspirin use converges (ie, individuals randomized to placebo potentially initiate aspirin and those randomized to aspirin use potentially discontinue aspirin). These findings are consistent with a larger evidence base of observational studies finding an association between aspirin use and CRC incidence or mortality,[117,118] although this observational literature is limited by heterogeneity of aspirin dosages, duration of use, indications, and populations studied. There are still relatively few studies showing these patterns, and the study designs raise concerns about applicability and biases associated with observational designs, including selection bias, misclassification bias, recall bias, and confounding. While others have raised the possibility that aspirin may be protective for other types of cancer,[119,120] 2 recent study-level meta-analyses failed to find an association between aspirin and cancer.[92,93] A large low-dose aspirin trial examining CRC effects at 20 years after randomization would be ideal to examine the marginal effects of aspirin use in the context of contemporary CRC screening practices. Future trials should also account for baseline CRC screening as well as CRC risk factors, potential confounders not addressed in most of the CVD prevention trials included in this review.

Limitations

There are several limitations to this systematic review. First, the main analyses focused on primary CVD prevention literature for all outcomes, including CVD benefits, bleeding harms, and CRC effects; secondary prevention populations were not included in analyses for the bleeding outcomes because individuals with established CVD often have higher bleeding risk either due to risk factors (smoking, uncontrolled hypertension) or co-medication with anticoagulants. Second, to maximize the number of trials pooled for CVD and bleeding outcomes, trials with variable outcome definitions were pooled; specific outcome definitions are available in the full report.[10] Third, for some trials primary composite outcomes of major CVD events were calculated from individual outcomes for the purposes of this systematic review, potentially overestimating events as a given individual could have experienced a nonfatal and then fatal event. Fourth, USPSTF requirements to include only very high Human Development Index countries precluded inclusion of the recently published TIPS-3 trial.[121] However, inclusion of this trial would not have changed the conclusions of the review.

Conclusions

Low-dose aspirin was associated with small absolute risk reductions in major cardiovascular disease events and small absolute increases in major bleeding. Colorectal cancer results were less robust and highly variable.

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Author Contributions: Dr Guirguis-Blake had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Guirguis-Blake, Evans, Perdue, Bean.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Guirguis-Blake, Evans, Perdue, Bean.
Critical revision of the manuscript for important intellectual content: Guirguis-Blake, Evans, Perdue, Senger.
Statistical analysis: Guirguis-Blake, Perdue.
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