JAMA | US Preventive Services Task Force | MODELING STUDY

Aspirin Use to Prevent Cardiovascular Disease and Colorectal Cancer
Updated Modeling Study for the US Preventive Services Task Force

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IMPORTANCE The US Preventive Services Task Force (USPSTF) is updating its 2016 recommendation on the use of aspirin for the primary prevention of cardiovascular disease (CVD) and colorectal cancer (CRC).

OBJECTIVE To provide updated model-based estimates of the net balance in benefits and harms from routine use of low-dose aspirin for primary prevention.

DESIGN, SETTING, AND PARTICIPANTS Microsimulation modeling was used to estimate long-term benefits and harms for hypothetical US cohorts of men and women aged 40 to 79 years with up to 20% 10-year risk for an atherosclerotic CVD event and without prior history of CVD or elevated bleeding risks.

EXPOSURES Low-dose (≤100 mg/d) aspirin for lifetime use, unless contraindicated by a bleeding event, and with stopping ages in 5-year intervals from age 65 to 85 years.

MAIN OUTCOMES AND MEASURES Primary outcomes were lifetime net benefits measured in quality-adjusted life-years (QALYs) and life-years. Benefits included reduced nonfatal myocardial infarction and ischemic stroke. Harms included increased nonfatal major gastrointestinal bleeding and intracranial hemorrhage. Reduced CRC incidence was considered in sensitivity analysis.

RESULTS Estimated lifetime net QALYs were positive for both men and women at 5% or greater 10-year CVD risk when starting between ages 40 and 59 years and at 10% or greater 10-year CVD risk when starting between ages 60 and 69 years. These estimates ranged from 2.3 (95% CI, −2.7 to 7.4) to 66.2 (95% CI, 58.2 to 74.1) QALYs per 1000 persons. Lifetime net life-years were positive for men at 5% or greater and women at 10% or greater 10-year CVD risk starting aspirin at ages 40 to 49 years and for men at 7.5% or greater and women at 15% or greater 10-year CVD risk at ages 50 to 59 years. These estimates ranged from 0.4 (95% CI, −6.1 to 6.9) to 52.4 (95% CI, 43.9 to 60.9) life-years per 1000 persons. Lifetime net life-years were negative in most cases for persons starting aspirin between ages 60 and 79 years, as were lifetime net QALYs for persons aged 70 to 79 years. Stopping aspirin between ages 65 and 85 years generally showed little advantage compared with lifetime use. Sensitivity analyses showed lifetime net benefits may be higher if aspirin reduced CRC incidence or CVD mortality and lower if aspirin increased fatal major gastrointestinal bleeding or reduced quality of life with routine use.

CONCLUSIONS AND RELEVANCE This microsimulation study suggested that several population groups may benefit from taking aspirin for the primary prevention of CVD, primarily in persons starting at younger ages with higher 10-year CVD risk.

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Each year in the US, more than 1 million people will experience their first stroke or coronary attack and nearly 150 000 will develop colorectal cancer (CRC).[1,2] Aspirin has been identified as an agent with potential chemopreventive effects on both atherothrombosis and cancer, but these effects must be weighed against increased risks of serious bleeding.[3,4] In 2016, the US Preventive Services Task Force (USPSTF) published recommendations for the initiation of low-dose aspirin use to prevent first occurrence of cardiovascular disease (CVD) and CRC in adults for whom these benefits are expected to exceed harms.[5] These recommendations supported the initiation of low-dose aspirin use in adults aged 50 to 59 years (B recommendation) and 60 to 69 years (C recommendation), with 10% or greater 10-year risk for first hard atherosclerotic CVD (ASCVD) event.

Since 2016, findings from several new aspirin primary prevention trials have been published.[6-8] New evidence from these trials and other sources may alter the assessment of benefits and harms associated with using aspirin to prevent CVD and CRC. This decision analysis updated estimates of the net balance in benefits and harms of aspirin in primary CVD prevention populations. This decision analysis was used in conjunction with an updated systematic evidence review[9,10] to inform USPSTF recommendations.

Methods

Analyses in this study were conducted using the HealthPartners Institute ModelHealth: Cardiovascular Disease (ModelHealth: CVD) microsimulation model, which also was used to conduct the 2016 decision analysis on aspirin for the USPSTF.[11,12] The full report of this modeling study and its technical appendix contain additional detail on model methods, data sources, and validation, along with results from additional scenarios.[13]

Model Description

ModelHealth: CVD is a discrete-event, annual-cycle microsimulation model parameterized to estimate the lifetime incidence of CVD events in a cross-section of hypothetical individuals representative of the US population. The model was programmed in Visual Basic 6.0 (Microsoft). Variations in age, sex, and race and ethnicity were accounted for in the baseline prevalence of disease and in the distribution of CVD risk factors, including body mass index, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol and low-density lipoprotein cholesterol, diabetes status, and cigarette smoking status. Initial values of cardiometabolic risk factors were defined using combined 2015-2018 National Health and Nutrition Examination Survey (NHANES)[14,15] data and 2017-2018 National Health Interview Survey[16] data for smoking status. Cardiometabolic risk factors were updated with each annual cycle, and CVD events were predicted by 1-year risk equations estimated specifically for the model using Framingham Heart Study data (M.V.M., Biologic Specimen and Data Repository Information Coordinating Center restricted data set, 2010). Screening and treatment for hypertension and dyslipidemia and use of aspirin for secondary prevention were consistent with patient eligibility and dosing of national clinical guidelines,[17-22] and the probability of risk identification and treatment adherence were consistent with the rates observed within 2015-2018 NHANES data.[14,15]

Rates of fatal and nonfatal major gastrointestinal bleeding for persons not using aspirin—and without elevated bleeding risks, such as prior bleeding or use of medications that may increase bleeding risks—were obtained from a large New Zealand cohort study (eTable 1 in the Supplement).[23] The model includes a CRC module capable of assessing primary prevention of either CRC cases or deaths. CRC incidence in the model accounted for smoking status and reflected contemporary rates of screening. Health utilities for the major outcomes affected by aspirin use were estimated using literature sources and are summarized in eTable 2 in the Supplement. In the base case analysis, no disutility was applied to taking aspirin daily, but 2 alternative scenarios with aspirin disutilities were simulated in sensitivity analyses.

Target Population

Analyses were conducted independently for men and women—without prior history of CVD—across four 10-year age bands (40-49, 50-59, 60-69, and 70-79 years) and across 5 baseline 10-year CVD risk bands (5%, 7.5%, 10%, 15%, and 20%). Baseline 10-year CVD risk was estimated using the American College of Cardiology/American Heart Association Pooled Cohort risk equation for the first hard ASCVD event.[24] The prevalence of 10-year ASCVD risk in US adults and summary characteristics of the modeled population are presented in eTables 3 and 4, respectively, in the Supplement.

Intervention Strategies

Two strategies for low-dose aspirin use (≤100 mg/d) were modeled. In the first, aspirin was initiated at a specific age for lifetime daily use. In the second, aspirin was initiated at a specific age with a plan to stop at a predefined age, specified at 5-year age intervals from 65 to 85 years. In both strategies, aspirin was stopped permanently after a major gastrointestinal bleeding event or an intracranial hemorrhage event.

Effect estimates for the use of low-dose aspirin were taken from an updated systematic review that was conducted in coordination with this study to inform the USPSTF (**Table 1**).[9,10] The systematic review found routine use of low-dose aspirin was associated with a lower risk for nonfatal myocardial infarction (MI) and nonfatal ischemic stroke and higher risk for major gastrointestinal bleeding and intracranial hemorrhage. Although statistically significant associations with CRC incidence were found in selected analyses based on observational follow-up from a small number of studies, the systematic review found very low strength of evidence overall to support a reduction in CRC incidence from any dose of aspirin. Thus, in a change from the 2016 decision analysis,[11,12] the potential reduction in CRC incidence risk was considered only in sensitivity analysis. When included, the CRC effect was applied after 10 years of continuous use and assumed to persist for up to 10 years after stopping aspirin. A direct effect of aspirin on reducing CVD mortality risk was also considered in sensitivity analysis.

In all scenarios, non-CRC benefits and harms were assumed to take effect immediately, and relative risks were assumed to return to 1.00 with discontinuation of aspirin. Indirect effects of aspirin on CVD incidence and mortality could arise when the prevention or occurrence of an initial event altered the disease progression probabilities for subsequent events, as determined by the Framingham-derived risk equations internal to the model.

Table 1. Assumptions of Effects of Using Low-Dose (≤100 mg/d) Aspirin for Primary Prevention of CRC and CVD

Parameter	Relative risk			
	Base case[a]	Worst case[b]	Best case[b]	Other values[b]
Benefits				
Nonfatal myocardial infarction	0.88	0.96	0.80	
Nonfatal ischemic stroke	0.88	1.00	0.78	
CVD death	1.00			0.95
CRC incidence (>10 y)	1.00			0.64
Harms				
Intracranial hemorrhage	1.31	1.54	1.11	
Nonfatal major GI bleeding	1.58	1.80	1.38	
Fatal major GI bleeding	1.00			1.58

Abbreviations: CRC, colorectal cancer; CVD, cardiovascular disease; GI, gastrointestinal.

Source: Guirguis-Blake et al.[10]

[a] Values used in the primary analysis.

[b] Alternative assumptions used in the sensitivity analysis.

Outcomes

Primary outcomes were quality-adjusted life-years (QALYs) and life-years. QALYs were the preferred measure because aspirin benefits and harms can affect both fatal and nonfatal outcomes. Individual events were secondary outcomes and included benefits related to nonfatal ischemic stroke, nonfatal MI, combined nonfatal CVD events (nonfatal congestive heart failure, ischemic stroke, and MI), CVD deaths (excluding those due to intracranial hemorrhage), CRC incidence, CRC deaths, and harms related to fatal and nonfatal major gastrointestinal bleeding and intracranial hemorrhage. Net event totals were calculated as (non-fatal CVD events + CVD deaths + CRC cases) − (major gastrointestinal bleeding and intracranial hemorrhage events), with CRC cases included only in sensitivity analysis.

Time Horizon

All analyses in this study report outcomes over a lifetime (up to age 100 years) follow-up horizon. Outcomes over a 10-year horizon are in the full report.[13]

Analysis

Model simulations mimicked a randomized clinical trial with 2 otherwise identical synthetic cohorts distinguished by initiating or not initiating low-dose aspirin for primary prevention (**Figure**). Use of aspirin for secondary prevention (ie, after a major CVD event) and discontinuation due to contraindication was the same for both groups. All analyses compared estimated outcomes between these 2 groups. Positive net QALYs and life-years were deemed to favor aspirin use; negative net QALYs and life-years were deemed to favor aspirin nonuse. Model simulations were independently conducted with a sample population of 100 000 persons for each age, sex, and baseline ASCVD risk group. Confidence intervals were estimated by bootstrap resampling the simulated population for each stratified outcome 100 000 times with replacement. Model output was analyzed using R version 3.5.1 (R Project for Statistical Computing) and Stata version 16 (StataCorp).

Sensitivity Analyses

Sensitivity analyses addressing uncertainty in key parameters were conducted by replicating simulations with all other parameters, probabilities, and population characteristics held equal. Alternative values and assumptions considered in the sensitivity analysis can be found in Table 1 and eTables 1 and 2 in the Supplement.

Results

Compared with not using aspirin for primary prevention, the estimated lifetime net benefit from initiating aspirin for primary prevention of CVD in terms of both net QALYs and net life-years was more likely to be positive and of larger magnitude at earlier starting ages, at higher levels of 10-year ASCVD risk at initiation, and among men (**Table 2**). For men and women aged 40 to 49 years when starting aspirin, lifetime net QALYs were positive at all considered ASCVD risk levels ranging from 11.1 (95% CI, 3.5 to 18.6) to 66.2 (95% CI, 58.2 to 74.1) per 1000 persons, but lifetime net life-years were mixed, ranging from 10.6 (95% CI, 2.9 to 18.3) to 52.4 (95% CI, 43.9 to 60.9) per 1000 men and −10.6 (95% CI, −18.5 to −2.7) to 24.2 (95% CI, 15.7 to 32.7) per 1000 women (with positive values ≥10% 10-year ASCVD risk). For adults aged 50 to 59 years, the pattern was similar, with positive lifetime net QALYs ranging from 1.9 (95% CI, −5.1 to 8.8) to 48.4 (95% CI, 41.9 to 54.8) per 1000 persons and net life-years of smaller magnitude that were positive for men and women with 7.5% or greater and 15% or greater 10-year ASCVD risk, respectively. For adults aged 60 to 69 years, net QALYs were positive at 10% or greater 10-year ASCVD risk (as high as 19.1 [95% CI, 14.2 to 24.1] net QALYs per 1000 women with 20% 10-year ASCVD risk) but negative for nearly all groups in terms of net life-years. For men and women aged 70 to 79 years, lifetime net benefits were negative in terms of both net QALYs and life-years for nearly all risk groups considered.

Net QALYs and life-years depended on the net balance in individual benefit and harm events, as illustrated in **Table 3**. Prevented nonfatal MIs and ischemic strokes—along with downstream reductions in subsequent events and CVD deaths—balanced against nonfatal major gastrointestinal bleeds and intracranial hemorrhage events. Because of differences in underlying lifetime event rates (which extend beyond the estimated incidence of a first hard ASCVD event over 10 years), more nonfatal MIs than nonfatal ischemic strokes were prevented for men. In contrast, the reduction of these 2 events was more evenly balanced for women. Additional event-level results are reported in eTables 5 and 6 in the Supplement.

Stopping Scenarios

As individuals advance in age after many years of aspirin use, the quantitative balance of benefits and harms associated with

continued aspirin use can be unclear. Higher CVD event rates with age can generate additional potential benefits; however, these benefits can be partially or fully offset by higher underlying rates of major gastrointestinal bleeding and intracranial hemorrhage. Over most scenarios, when lifetime net benefits of using aspirin were estimated to be positive, net benefits were generally larger as the stopping age increased from 65 to 85 years at 5-year intervals, while negative lifetime net benefits generally became more negative with greater stopping age (eTable 7 in the Supplement).

In addition, the marginal increase (or decrease) in net benefit with stopping was smaller as stopping intervals approached lifetime use. For example, among men aged 40 to 49 years with 10% 10-year ASCVD risk, the highest lifetime net QALYs were predicted with lifetime use (48.0 per 1000 [95% CI, 40.6 to 55.5]); however, lifetime net QALYs were 12.9 per 1000 lower (35.1 per 1000 [95% CI, 28.9 to 41.3]) when stopping at age 65 years vs 0.9 per 1000 lower (47.1 per 1000 [95% CI, 39.6 to 54.5]) when stopping at age 85 years. In addition, there were cases—such as when aspirin was initiated for both men and women aged 50 to 59 years with 10% 10-year ASCVD risk—in which lifetime net QALYs were highest with lifetime use, but lifetime net life-years were greater at earlier stopping ages of 70 or 75 years. In such cases, excess risk for fatal bleeding events early on could later be offset by lower risk for fatal CVD events resulting from nonfatal CVD events that were prevented prior to stopping aspirin.

Sensitivity Analyses

Table 4 shows key results from the sensitivity analyses; additional results from all sensitivity analyses are reported in eTables 8-12 in the Supplement. When a benefit of aspirin in reducing CRC incidence by 36% after 10 years of use (scenario 3) was included, lifetime net benefit estimates were substantially higher, and in many cases, changed negative assessments to positive. For example, lifetime net QALYs for women aged 40 to 49 years with 10% 10-year ASCVD risk when starting aspirin were estimated to be 102.6 (95% CI, 92.5 to 112.7) per 1000 with the CRC benefit compared with 35.1 (95% CI, 27.3 to 43.0) per 1000 without, and for similar women in their 70s, lifetime net QALYs were 25.1 (95% CI, 20.5 to 29.6) per 1000 with the CRC benefit compared with −6.1 (95% CI, −10.5 to −3.4) per 1000 without. Additional results are reported in eTables 13-15 in the Supplement.

When aspirin was predicted to reduce the risk of CVD death by 5% (scenario 4), an increase in net benefit larger than with the CRC benefit was found (eTables 16-18 in the Supplement). In contrast, when aspirin was predicted to increase fatal major gastrointestinal bleeding at the same rate of nonfatal major gastrointestinal bleeding (scenario 5), net benefit estimates were substantially lower. For example, lifetime net QALYs and life-years were about half compared with the base case estimate for men and women with 10% 10-year risk starting aspirin in their 40s, and lifetime net QALYs and life-years were both negative for men and women starting aspirin at ages 50 to 79 years with 10% 10-year ASCVD risk (eTables 19-21 in the Supplement).

Even very small (0.1% or 0.5%) reductions in quality of life (ie, disutility) with daily aspirin use were estimated to substantially reduce lifetime net QALYs (scenarios 1 and 2). For example, women aged 40 to 49 years with 10% 10-year ASCVD risk when starting aspirin would expect 35.1 (95% CI, 27.3 to 43.0) lifetime net QALYs

Figure. Decision Analysis Design

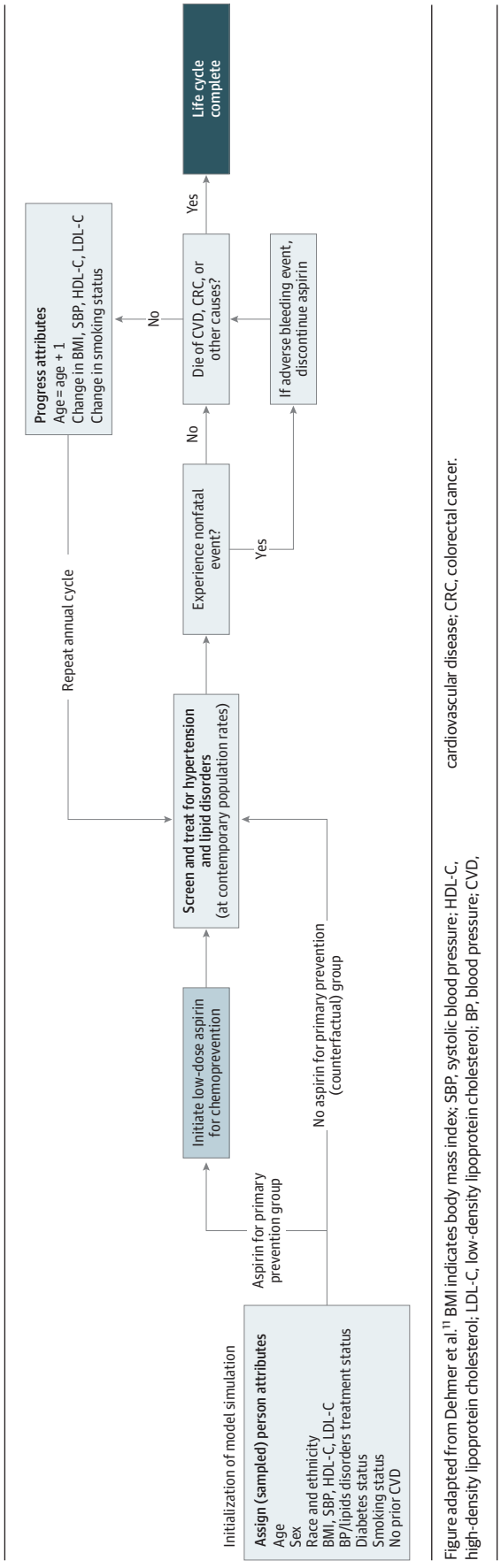

Figure adapted from Dehmer et al.[11] BMI indicates body mass index; SBP, systolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; BP, blood pressure; CVD, cardiovascular disease; CRC, colorectal cancer.

Table 2. Estimated Lifetime Net Benefit of Aspirin With Lifetime Use by Initiation Age

	Mean (95% CI)			
	Initiation age 40-49 y	Initiation age 50-59 y	Initiation age 60-69 y	Initiation age 70-79 y
Women				
Net QALYs per 1000 persons				
10-y ASCVD risk, %[a]				
5	11.1 (3.5 to 18.6)	1.9 (−5.1 to 8.8)	−9.5 (−14.4 to −4.6)	−11.7 (−15.2 to −8.1)
7.5	19.6 (12.3 to 26.8)	10.4 (3.9 to 16.9)	−5.8 (−10.9 to −0.7)	−6.4 (−10.0 to −2.8)
10	35.1 (27.3 to 43.0)	17.1 (10.2 to 24.0)	2.3 (−2.7 to 7.4)	−6.1 (−9.4 to −2.7)
15	43.0 (35.4 to 50.5)	30.8 (24.5 to 37.2)	11.6 (6.9 to 16.4)	−6.9 (−10.7 to −3.0)
20	50.4 (42.3 to 58.5)	41.6 (34.8 to 48.5)	19.1 (14.2 to 24.1)	−4.4 (−8.1 to −0.7)
Net life-years per 1000 persons				
10-y ASCVD risk, %[a]				
5	−10.6 (−18.5 to −2.7)	−18.7 (−26.0 to −11.5)	−23.5 (−28.4 to −18.5)	−20.6 (−24.3 to −16.9)
7.5	−2.6 (−10.0 to 4.7)	−11.8 (−18.7 to −5.0)	−20.2 (−25.6 to −14.9)	−15.4 (−19.0 to −11.8)
10	11.4 (3.2 to 19.7)	−6.5 (−13.6 to 0.7)	−13.5 (−18.7 to −8.4)	−16.6 (−20.0 to −13.2)
15	17.7 (9.8 to 25.5)	7.5 (0.9 to 14.1)	−7.2 (−12.3 to −2.1)	−17.9 (−21.9 to −14.0)
20	24.2 (15.7 to 32.7)	16.9 (9.7 to 24.1)	−1.6 (−6.8 to 3.6)	−14.8 (−18.6 to −11.0)
Men				
Net QALYs per 1000 persons				
10-y ASCVD risk, %[a]				
5	23.1 (15.8 to 30.4)	5.7 (0.0 to 11.3)	−1.8 (−6.4 to 2.9)	NA
7.5	29.1 (22.3 to 36.0)	12.5 (6.5 to 18.5)	2.6 (−1.9 to 7.2)	−4.6 (−7.7 to −1.5)
10	48.0 (40.6 to 55.5)	18.0 (12.0 to 24.0)	7.0 (2.2 to 11.8)	−1.1 (−4.4 to 2.2)
15	52.3 (44.5 to 60.1)	32.3 (26.2 to 38.5)	8.3 (3.5 to 13.0)	−1.9 (−5.4 to 1.6)
20	66.2 (58.2 to 74.1)	48.4 (41.9 to 54.8)	16.3 (11.4 to 21.1)	0.9 (−2.2 to 3.9)
Net life-years per 1000 persons				
10-y ASCVD risk, %[a]				
5	10.6 (2.9 to 18.3)	−5.4 (−11.7 to 0.8)	−11.0 (−16.0 to −6.1)	NA
7.5	16.2 (9.0 to 23.5)	0.4 (−6.1 to 6.9)	−6.7 (−11.5 to −1.9)	−10.1 (−13.4 to −6.8)
10	36.1 (28.1 to 44.1)	4.2 (−2.3 to 10.8)	−3.0 (−8.0 to 1.9)	−6.9 (−10.5 to −3.4)
15	37.9 (29.6 to 46.2)	18.6 (11.7 to 25.4)	−2.2 (−7.2 to 2.9)	−7.6 (−11.3 to −3.9)
20	52.4 (43.9 to 60.9)	33.9 (26.9 to 40.9)	4.9 (−0.1 to 10.0)	−5.5 (−8.8 to −2.2)

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; NA, not applicable; QALY, quality-adjusted life-year.

[a] Risk levels correspond to the 10-year ASCVD risk, which is based on the American College of Cardiology/American Heart Association risk calculator and refers to a person's risk at model baseline/initiation. Risk levels are rounded to the nearest threshold (±0.5%). NA indicates that the 10-year ASCVD risk level was not feasible or very unlikely within the population group. Results reflect the difference between universal adoption of aspirin for primary prevention vs zero adoption. All else is held equal.

per 1000 with no disutility associated with daily aspirin use, 12.2 (95% CI, 4.3 to 20.1) per 1000 with a 0.1% disutility, and −79.4 (95% CI, −87.3 to −71.5) per 1000 with a 0.5% disutility.

Discussion

This decision analysis used simulation modeling to combine findings from the updated systematic review[9,10] with various data sources to quantify the potential balance of lifetime benefits and harms across clinically meaningful subgroups defined by age, sex, and 10-year ASCVD risk. The estimated net lifetime benefit of low-dose aspirin varied by starting age, sex, and 10-year ASCVD risk level, and positive or negative net benefit sometimes differed between the net QALY and net life-year outcomes. Overall, men and women aged 40 to 59 years and with 10% or greater 10-year ASCVD risk were most likely to see lifetime benefit from starting aspirin for primary prevention, and adults aged 70 to 79 years with 20% or less 10-year ASCVD risk were most likely to experience net harm. Stopping aspirin at 5-year intervals between ages 65 to 85 years generally showed consistent patterns in net benefit that approached the net benefit with lifetime use, whether net beneficial or net harmful. However, small marginal differences between an earlier stopping age and lifetime use, as well as instances in which certain net benefits could be higher at earlier stopping ages, suggest it may be reasonable for some patients to consider using aspirin for primary prevention for a fixed interval rather than a lifetime.

One important way in which this analysis diverged from the 2016 decision analysis was in considering the effect of aspirin on

Table 3. Estimated Lifetime Net Events of Initiating Aspirin for Lifetime Use Among Persons With 10% 10-Year ASCVD Risk

Population group	Mean (95% CI)										
	Benefits, prevented events per 1000 persons				Harms, incurred events per 1000 persons				Net balance (benefits - harms)		
	MI	Ischemic stroke	Nonfatal CVD events	CVD deaths	GI bleeds	GI bleed deaths	ICH	ICH deaths	Net QALYs	Net life-years	Net events prevented
Women											
Initiation age, y											
40-49	11.4 (10.7 to 12.1)	10.4 (9.8 to 11.1)	27.8 (26.4 to 29.1)	4.3 (3.9 to 4.7)	29.4 (28.3 to 30.4)	0.0 (0.0 to 0.0)	3.0 (2.6 to 3.3)	2.8 (2.1 to 3.5)	35.1 (27.3 to 43.0)	11.4 (3.2 to 19.7)	−0.3 (−3.1 to 1.0)
50-59	9.2 (8.5 to 9.8)	11.1 (10.3 to 11.8)	24.8 (23.5 to 26.1)	4.1 (3.7 to 4.5)	28.0 (26.9 to 29.0)	0.0 (0.0 to 0.0)	3.5 (3.2 to 3.9)	3.2 (2.6 to 3.9)	17.1 (10.2 to 24.0)	−6.5 (−13.6 to 0.7)	−2.6 (−5.8 to −1.7)
60-69	6.4 (5.9 to 7.0)	9.1 (8.5 to 9.8)	18.8 (17.7 to 20.0)	2.6 (2.3 to 2.9)	27.7 (26.7 to 28.7)	0.0 (0.0 to 0.0)	3.6 (3.2 to 4.0)	3.2 (2.6 to 3.7)	2.3 (−2.7 to 7.4)	−13.5 (−18.7 to −8.4)	−9.9 (−12.9 to −9.2)
70-79	4.4 (3.9 to 4.8)	7.1 (6.6 to 7.6)	13.5 (12.6 to 14.4)	1.4 (1.2 to 1.6)	27.4 (26.3 to 28.4)	0.0 (0.0 to 0.0)	3.0 (2.7 to 3.3)	2.6 (2.2 to 3.0)	−6.1 (−9.4 to −2.7)	−16.6 (−20.0 to −13.2)	−15.5 (−18.0 to −14.7)
Men											
Initiation age, y											
40-49	20.5 (19.5 to 21.6)	7.0 (6.4 to 7.6)	34.0 (32.4 to 35.6)	5.2 (4.8 to 5.7)	29.7 (28.7 to 30.7)	0.0 (0.0 to 0.0)	2.3 (2.0 to 2.6)	2.0 (1.0 to 3.1)	48.0 (40.6 to 55.5)	36.1 (28.1 to 44.1)	7.2 (5.1 to 9.7)
50-59	15.5 (14.7 to 16.4)	7.3 (6.7 to 7.9)	28.2 (26.8 to 29.5)	4.1 (3.7 to 4.5)	29.8 (28.8 to 30.9)	0.0 (0.0 to 0.0)	2.8 (2.4 to 3.1)	2.5 (1.7 to 3.4)	18.0 (12.0 to 24.0)	4.2 (−2.3 to 10.8)	−0.3 (−2.9 to 1.3)
60-69	12.7 (12.0 to 13.4)	6.0 (5.5 to 6.5)	22.5 (21.3 to 23.7)	3.3 (3.0 to 3.7)	30.2 (29.2 to 31.3)	0.0 (0.0 to 0.0)	2.9 (2.6 to 3.3)	2.6 (1.9 to 3.3)	7.0 (2.2 to 11.8)	−3.0 (−8.0 to 1.9)	−7.3 (−9.9 to −6.0)
70-79	8.9 (8.2 to 9.5)	5.1 (4.6 to 5.5)	16.4 (15.5 to 17.4)	2.2 (1.9 to 2.5)	28.2 (27.2 to 29.2)	0.0 (0.0 to 0.0)	2.6 (2.3 to 2.9)	2.2 (1.6 to 2.9)	−1.1 (−4.4 to 2.2)	−6.9 (−10.5 to −3.4)	−12.2 (−14.4 to −10.9)

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CVD, cardiovascular disease; GI, gastrointestinal; ICH, intracranial hemorrhage; MI, myocardial infarction; QALY, quality-adjusted life-year.

Myocardial infarction and ischemic stroke events are nonfatal. The nonfatal CVD event column combines nonfatal MIs, ischemic strokes, and congestive heart failure (as a major sequela to MI). Net events prevented are defined by the net of benefit and harm events, or (nonfatal CVD events + CVD deaths) − (major GI bleeds + intracranial hemorrhage). In the base case, there was no assumed effect of aspirin use on CRC incidence.

Table 4. Sensitivity Analysis, Estimated Lifetime Net Benefits of Aspirin With Lifetime Use Among Persons With 10% 10-Year ASCVD Risk

	Mean (95% CI)							
	Initiation age 40-49 y		Initiation age 50-59 y		Initiation age 60-69 y		Initiation age 70-79 y	
Scenario[a]	Net QALYs	Net life-years	Net QALYs	Net life-years	Net QALYs	Net life-years	Net QALYs	Net life-years
Women								
0: Base case	35.1 (27.3 to 43.0)	11.4 (3.2 to 19.7)	17.1 (10.2 to 24.0)	−6.5 (−13.6 to 0.7)	2.3 (−2.7 to 7.4)	−13.5 (−18.7 to −8.4)	−6.1 (−9.4 to −2.7)	−16.6 (−20.0 to −13.2)
1: ASA disutility = 0.001	12.2 (4.3 to 20.1)	11.4 (3.2 to 19.7)	−0.3 (−7.2 to 6.6)	−6.5 (−13.6 to 0.7)	−11.9 (−16.9 to −6.9)	−13.5 (−18.7 to −8.4)	−18.3 (−21.6 to −14.9)	−16.6 (−20.0 to −13.2)
2: ASA disutility = 0.005	−79.4 (−87.3 to −71.5)	11.4 (3.2 to 19.7)	−70.0 (−76.9 to −63.1)	−6.5 (−13.6 to 0.7)	−68.8 (−73.8 to −63.7)	−13.5 (−18.7 to −8.4)	−67.2 (−70.6 to −63.9)	−16.6 (−20.0 to −13.2)
3: CRC RR = 0.64	102.6 (92.5 to 112.7)	79.5 (68.6 to 90.4)	74.5 (65.4 to 83.5)	50.4 (40.6 to 60.1)	41.6 (35.0 to 48.1)	23.2 (16.4 to 30.1)	25.1 (20.5 to 29.6)	12.1 (7.3 to 17.0)
4: CVD death RR = 0.95	112.8 (101.1 to 124.4)	104.1 (91.2 to 116.9)	80.9 (71.4 to 90.4)	69.8 (59.1 to 80.4)	48.7 (41.5 to 55.9)	41.8 (33.7 to 49.9)	29.1 (23.9 to 34.2)	25.1 (19.4 to 30.7)
5: GI bleed death RR = 1.58	19.4 (10.8 to 28.0)	−7.1 (−16.2 to 2.1)	−0.5 (−8.2 to 7.3)	−26.8 (−35.1 to −18.6)	−12.9 (−18.5 to −7.2)	−31.4 (−37.4 to −25.3)	−24.3 (−28.9 to −19.8)	−38.0 (−42.9 to −33.0)
Men								
0: Base case	48.0 (40.6 to 55.5)	36.1 (28.1 to 44.1)	18.0 (12.0 to 24.0)	4.2 (−2.3 to 10.8)	7.0 (2.2 to 11.8)	−3.0 (−8.0 to 1.9)	−1.1 (−4.4 to 2.2)	−6.9 (−10.5 to −3.4)
1: ASA disutility = 0.001	29.0 (21.5 to 36.4)	36.1 (28.1 to 44.1)	2.3 (−3.7 to 8.2)	4.2 (−2.3 to 10.8)	−6.4 (−11.2 to −1.7)	−3.0 (−8.0 to 1.9)	−11.4 (−14.7 to −8.0)	−6.9 (−10.5 to −3.4)
2: ASA disutility = 0.005	−47.3 (−54.8 to −39.9)	36.1 (28.1 to 44.1)	−60.7 (−66.7 to −54.7)	4.2 (−2.3 to 10.8)	−60.0 (−64.8 to −55.3)	−3.0 (−8.0 to 1.9)	−52.4 (−55.7 to −49.1)	−6.9 (−10.5 to −3.4)
3: CRC RR = 0.64	109.9 (100.8 to 118.9)	96.6 (86.7 to 106.5)	72.3 (64.2 to 80.4)	57.3 (48.3 to 66.3)	55.7 (49.0 to 62.4)	43.4 (36.2 to 50.6)	45.3 (39.9 to 50.7)	37.0 (31.2 to 42.8)
4: CVD death RR = 0.95	126.3 (115.9 to 136.6)	128.4 (116.9 to 139.9)	89.4 (80.2 to 98.6)	88.4 (78.0 to 98.8)	68.0 (60.8 to 75.1)	69.2 (61.1 to 77.2)	43.0 (37.7 to 48.2)	45.0 (39.0 to 51.1)
5: GI bleed death RR = 1.58	29.3 (20.8 to 37.8)	14.3 (4.9 to 23.6)	−5.3 (−12.5 to 1.8)	−23.0 (−31.0 to −15.0)	−13.7 (−19.5 to −8.0)	−27.2 (−33.5 to −20.9)	−18.2 (−22.4 to −13.9)	−26.7 (−31.4 to −22.1)

Abbreviations: ASA, acetylsalicylic acid (aspirin); ASCVD, atherosclerotic cardiovascular disease; CRC, colorectal cancer; CVD, cardiovascular disease; GI, gastrointestinal; QALY, quality-adjusted life-years; RR, relative risk.

[a] Each numbered item represents a 1-way sensitivity analysis with the parameter changed as described.

CRC incidence through a sensitivity analysis rather than the main analysis, based on the findings of the updated systematic review.[9,10] With this effect included in the 2016 decision analysis base case, but excluded from the 2021 decision analysis base case, the net benefits of aspirin estimated with the 2021 update were substantially lower. This distinction adds uncertainty to our findings, because although observational studies have suggested strong CRC prevention benefits with aspirin,[25-27] there is insufficient evidence from randomized clinical trials to support this finding, in part because few trials have prespecified and followed up this outcome beyond 10 years, when biological plausibility of an effect is hypothesized.[9,10] Future trials could address limitations in the CRC evidence base; however, trials of 10 to 20 years' duration may be challenging to conduct, and no such findings are imminently expected. In addition, a recent aspirin trial in older adults, ASPREE, found a significant increase in CRC mortality over 5 years, further complicating assessments of the available evidence.[28]

A second major change from the 2016 decision analysis was in the assessment of evidence regarding the effect of aspirin on fatal major gastrointestinal bleeding events, where aspirin was previously assumed to have the same effect of increasing nonfatal and fatal major gastrointestinal bleeds. In the 2021 update, the assessment of evidence did not support this assumption. The updated systematic evidence review was not able to assess the effect of aspirin on fatal gastrointestinal bleeding because of the low number of fatal major gastrointestinal bleeds observed in the aspirin primary prevention trials, but analyses by others have suggested there is no adverse effect of aspirin use on fatal major gastrointestinal bleeding.[29,30] This change in methods generated higher estimated net benefits for aspirin and partially offset the reduction generated by the removal of the CRC incidence benefit.

The updated systematic review confirmed no significant association of low-dose aspirin with CVD mortality (odds ratio, 0.95 [95% CI, 0.86-1.05])[9,10]; however, the point estimate was lower and had a narrower confidence interval compared with the corresponding finding in 2016 (relative risk, 0.97 [95% CI, 0.85-1.10]).[31] The sensitivity analysis results from this study indicate that if aspirin was associated with a small direct reduction in CVD mortality, net benefit estimates would be meaningfully altered in the direction of favoring aspirin use. However, the model did account for CVD deaths that were indirectly prevented or delayed because of the prevention of an earlier nonfatal CVD event resulting from low-dose aspirin use.

This analysis predicted outcomes for groups of similar patients, but individual assessments may include different priorities among outcomes and treatment strategies. Net QALY assessments showed strong adverse influence from small disutilities associated with aspirin use, suggesting that aspirin chemoprevention may not be well-suited to persons with no history of CVD who dislike routine use of medications.

Limitations

This study has several limitations. First, results from the sensitivity analysis highlight the practical significance of some of the remaining uncertainty about the effects of aspirin when used for primary prevention—particularly, whether aspirin reduces the risk for CRC incidence and affects fatal major gastrointestinal bleeding risks. Risk of major gastrointestinal bleeding may be correlated with some cardiometabolic risk factors, such as blood pressure, current smoking, and diabetes,[32,33] but insufficient data were available to stratify bleeding risks in the model on these factors. Accounting for these factors in estimating major gastrointestinal bleeding incidence may result in more precisely estimated harms across 10-year ASCVD risk levels. Second, also because of insufficient data, it was assumed that aspirin-associated bleeding risks were constant over time, but lifetime net benefits of aspirin would be higher if these relative risks decreased the longer aspirin was used (or would be lower if these risks increased with longer use).

Third, because of limited alternatives, this study relied on estimates of major gastrointestinal bleeding rates without aspirin use that were derived from a New Zealand population,[23] and it is not known how these rates compare with those for the US population. Fourth, observational studies have found associations between aspirin use and lower rates of incidence and mortality in CRC and other cancers (including breast, esophageal, gastric, pancreatic, and prostate),[25-27] which could substantially affect the assessment of using aspirin for primary prevention; however, the decision analysis follows the conclusions of the updated evidence review, which found the observational data subject to potential biases that complicate causal inference and the evidence from randomized clinical trials insufficient to determine these relationships.[9,10]

Fifth, event prediction data were insufficient to robustly assess potentially important differences in net benefits by race and ethnicity. Sixth, men and women aged 40 to 49 years and 70 to 79 years are not as well-represented in the primary prevention aspirin trials, making it less clear how well the aspirin effects translate to these groups, but 2 new trials since 2016 included these younger (ASCEND[6]) and older (ASPREE[8]) age groups.

Seventh, findings depend in part on the natural history of cardiometabolic risk factors and event rates predicted by the microsimulation model, which may inaccurately predict future outcomes for any given population group. Replication in other simulation models can further inform reliability of estimates.

Eighth, findings are not generalizable to all primary care patients. The decision analysis and updated systematic review[9,10] did not address aspirin use for secondary prevention of CVD. This study also did not assess net benefits in patients with more than a 20% 10-year risk of a CVD event because of the historical consideration of more than 20% 10-year ASCVD risk as a risk-equivalent for the presence of CVD[34] and the limited reporting by aspirin trials on the ASCVD risk levels of participants.[9,10] Furthermore, this study did not assess net harms in individuals with recent use of nonaspirin nonsteroidal anti-inflammatory drugs, corticosteroids, or selective serotonin reuptake inhibitors, each of which may increase the risk of major gastrointestinal bleeding or intracranial hemorrhage.[32] In addition, neither the updated systematic review[10] nor this decision analysis assessed the potential effect of aspirin on patients with high risk for CRC due to Lynch Syndrome.[35]

Conclusions

This microsimulation study suggested that several population groups may benefit from taking aspirin for the primary prevention of CVD, primarily in persons starting at younger ages with higher 10-year CVD risk.

ARTICLE INFORMATION

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Author Contributions: Dr Dehmer 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: Dehmer, Guirguis-Blake, Maciosek.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Dehmer, Maciosek.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Dehmer, O'Keefe, Guirguis-Blake, Maciosek.
Obtained funding: Maciosek.
Administrative, technical, or material support: Evans, Perdue, Maciosek.
Supervision: Dehmer.

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