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Aspirin for the Primary Prevention of Cardiovascular Disease and Colorectal Cancer: A Decision Analysis for the U.S. Preventive Services Task Force

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Background: Evidence indicates that aspirin is effective for the primary prevention of cardiovascular disease (CVD) and colorectal cancer (CRC) but also increases the risk for gastrointestinal (GI) and cerebral hemorrhages.

Objective: To assess the net balance of benefits and harms from routine aspirin use across clinically relevant age, sex, and CVD risk groups.

Design: Decision analysis using a microsimulation model.

Data Sources: 3 systematic evidence reviews.

Target Population: Men and women aged 40 to 79 years with a 10-year CVD risk of 20% or less, and no history of CVD and without elevated risk for GI or cerebral hemorrhages that would contraindicate aspirin use.

Time Horizon: Lifetime, 20 years, and 10 years.

Perspective: Clinical.

Intervention: Low-dose aspirin (≤100 mg/d).

Outcome Measures: Primary outcomes are length and quality of life measured in net life-years and quality-adjusted life-years. Benefits include reduced nonfatal myocardial infarction, nonfatal ischemic stroke, fatal CVD, CRC incidence, and CRC mortality. Harms include increased fatal and nonfatal GI bleeding and hemorrhagic stroke.

Results of Base-Case Analysis: Lifetime net quality-adjusted life-years are positive for most adults initiating aspirin at ages 40 to 69 years, and life expectancy gains are expected for most men and women initiating aspirin at ages 40 to 59 years and 60 to 69 years with higher CVD risk. Harms may exceed benefits for persons starting aspirin in their 70s and for many during the first 10 to 20 years of use.

Results of Sensitivity Analysis: Results are most sensitive to the relative risk for hemorrhagic stroke and CVD mortality but are affected by all relative risk estimates, baseline GI bleeding incidence and case-fatality rates, and disutilities associated with aspirin use.

Limitations: Aspirin effects by age are uncertain. Stroke benefits are conservatively estimated. Gastrointestinal bleeding incidence and case-fatality rates account only for age and sex.

Conclusion: Lifetime aspirin use for primary prevention initiated at younger ages (40 to 69 years) and in persons with higher CVD risk shows the greatest potential for positive net benefit.

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Evidence for the effectiveness of aspirin in preventing recurrent complications from heart disease and stroke (secondary prevention) is strong (1, 2), but evidence for aspirin's net benefit in preventing cardiovascular disease (CVD) and cancer, including colorectal cancer (CRC), in healthy persons (primary prevention) has been mixed (2–8). Three recent systematic reviews conducted on behalf of the U.S. Preventive Services Task Force (USPSTF) investigated current evidence for the benefits and harms of aspirin for primary prevention of CVD, on all-cause mortality, for all types of cancer, and for CRC (9–14). These reviews reaffirm evidence of aspirin's effectiveness—no longer differing by sex—in preventing first-time myocardial infarction (MI) and ischemic stroke and find new evidence indicating its effectiveness in CRC prevention. However, the updated reviews also reaffirm aspirin's role in increasing the risk for major gastrointestinal (GI) bleeding and hemorrhagic stroke.

The central clinical dilemma in determining the appropriateness of aspirin for the primary prevention of CVD and CRC is an uncertain relationship between the benefits and harms of long-term aspirin use. Therefore, we conducted a decision analysis using simulation modeling to assess the expected net benefit of aspirin use for primary prevention across clinically relevant population groups defined by their age, sex, and underlying CVD risk characteristics. This study was initiated by the USPSTF to support the update (15) of its recommendations on using aspirin for primary prevention (3, 4).

Methods

Model Description

We conducted study analyses using the HealthPartners Institute ModelHealth: CVD microsimulation

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Context

Benefits and harms of routine aspirin use vary among individuals.

Contribution

This modeling study suggested that lifetime aspirin use for primary prevention of cardiovascular disease (CVD) and colorectal cancer (CRC) had potential net benefits for most men and women who did not have elevated bleeding risk and initiated aspirin use at ages 40 to 69 years. Overall benefits did not outweigh harms for persons in their 70s with a 10-year CVD risk of 20% or less.

Caution

Estimates of aspirin effects by age were uncertain.

Implication

Middle-aged men and women without elevated risk for gastrointestinal or cerebral hemorrhage should consider long-term aspirin use to prevent CVD and CRC.

model. This annual-cycle microsimulation model was parameterized to estimate the person-level natural history of cardiovascular risk factors and the lifetime incidence of CVD events in a cross-section representative of the U.S. population. A CRC incidence and case-fatality natural history module was added to our model for this study. A detailed description of the model, implemented by using Visual Basic 6.0 (Microsoft) and Microsoft Excel, can be found in the **Supplement** (available at www.annals.org).

Target Population

Aspirin for primary prevention was assessed independently for men and women across four 10-year age bands (40 to 49, 50 to 59, 60 to 69, and 70 to 79 years) and baseline 10-year CVD risk bands (ranging from 1% to 20%). Baseline 10-year CVD risk was rounded to the nearest integer and estimated using the American College of Cardiology/American Heart Association risk calculator for the first hard atherosclerotic CVD event (16). The calculation of CVD risk at baseline is independent from the event rates predicted by the model. For each age, sex, and baseline CVD risk band, simulated persons were randomly oversampled from population characteristics representative of the U.S. population. For men aged 60 to 79 years and women aged 70 to 79 years, 10-year low-risk bands that are rarely or never observed in NHANES (National Health and Nutrition Examination Survey) of the U.S. population were excluded.

Initial demographic characteristics were drawn from the U.S. Census (17). Initial body mass index, systolic blood pressure, high- and low-density lipoprotein cholesterol levels, and diabetes status were derived from the 2001 to 2010 NHANES data (18–22). Initial smoking status was derived from the 2007 National Health Interview Survey (23) and calibrated to projections from the Congressional Budget Office (24). All persons were assumed to be free of CVD and CRC and to have nonelevated bleeding risk at baseline (defined by the absence of any factors for which a clinical provider would deem aspirin unsafe, such as history of GI or intracranial bleeding or concurrent use of other medications that increase bleeding risk).

Study Perspective

Analyses were conducted from a clinical perspective with respect to health outcomes associated with aspirin use. Costs were not considered.

Time Horizon

The primary time horizon is over a lifetime, which we defined at the person level as the "age to death or age 100" in order to fully account for ongoing benefits and harms (25). Time horizons of 10 and 20 years are included for their practical relevance.

Choice of Intervention

Findings from the 3 coordinated, companion systematic evidence reviews were integral to the parameter assumptions and model design in this study (9–14). The reviews found evidence that daily aspirin use reduces the risk for nonfatal MI, nonfatal stroke, and 10-year (and greater) CRC incidence and mortality. Aspirin also was found to increase the risk for hemorrhagic stroke and major GI bleeding. The best balance of cardiovascular benefits and harms was reflected in aspirin doses of 100 mg/d or less (low dose). Benefits with respect to CRC incidence were not strongly correlated with dose or prior CVD status, and therefore higher aspirin dose and secondary prevention trials were included in deriving this parameter. No clear evidence was found that aspirin changes the relative risk (RR) for CVD death, fatal GI bleeding, all-cause mortality, or other types of cancer or that aspirin effects differ by age or, in contrast to prior USPSTF findings (4, 26), sex. Evidence reviews also informed baseline levels of GI bleeding risk and selection of the American College of Cardiology/American Heart Association risk calculator to specify baseline CVD risk in the model (16).

Intervention Effects

Effects from using aspirin for primary prevention were modeled as RR modifications to the annual probability of an event. The CVD and bleeding RRs were derived from 8 trials about low-dose aspirin for primary prevention (12, 27–34). The effect of aspirin on the RR for CRC incidence after 10 years of continuous use was estimated from 3 aspirin trials (13, 35, 36) (**Table 1**). Only a few low-dose aspirin trials independently reported ischemic stroke events (9); therefore, we used a combined stroke measure that included hemorrhagic stroke events to approximate the effect of aspirin on ischemic stroke, resulting in a conservative estimate of ischemic stroke benefits. All non-CRC benefits and harms with aspirin initiation are assumed to take effect immediately, and all RRs are assumed to return to 1.00 with aspirin discontinuation. Indirect effects of aspirin on disease incidence and mortality may arise when the

Table 1. Key Aspirin Benefit and Harm Parameter Values*

Parameter	RR				Reference
	Base Case	Worst Case	Best Case	Other Values	
Benefits					
CRC incidence (>10 y)	0.60	0.76	0.47	1.00	13, 35, 36
CVD death	1.00	1.00	0.85	0.97	12, 27–34
Nonfatal ischemic stroke	0.86	0.98	0.76		12, 27, 29–34
Nonfatal MI	0.83	0.94	0.74		12, 27–34
Harms					
Major GI bleeding	1.58	1.95	1.29		14, 27–29, 32, 33
Hemorrhagic stroke	1.27	1.68	1.00		14, 27–29, 31–34

CRC = colorectal cancer; CVD = cardiovascular disease; GI = gastrointestinal; MI = myocardial infarction; RR = relative risk.
* The other parameter values were used in 1-way sensitivity analyses. Uncertainty in aspirin's effect to reduce CVD mortality risk was included among the sensitivity analysis parameters because a plausible, but not statistically significant, effect was observed in the systematic review (9, 12). Parameter values for the RR of CVD mortality and hemorrhagic stroke were capped at 1.00 to maintain consistency in the directionality of aspirin benefits and harms. Findings include evidence on the effect of aspirin in the reduction of CRC incidence derived from non–low-dose aspirin (>100 mg/d) trial interventions (British Doctor's Trial and United Kingdom Transient Ischemic trial) (36) and on a CVD secondary prevention population (United Kingdom Transient Ischemic Attack trial) (36), but no apparent relationship with dose or prior CVD status for this effect has been identified (10, 13).

prevention or occurrence of an initial event alters the disease progression probabilities for subsequent events.

Health utilities for outcomes affected by aspirin use were estimated using literature sources (37–46) (**Appendix Table 1**, available at www.annals.org). Living without a CVD condition or CRC was given a health utility of 0.872. All other health utility weights were applied multiplicatively to that baseline. Disutilities from MI and GI bleeding events were applied only during the year an event occurred. In the base-case analysis, no disutility was applied to taking aspirin daily, but 2 alternative scenarios with aspirin disutilities were considered in sensitivity analyses.

Analysis Design and Outcomes

All analyses compared outcomes of a simulated population routinely using aspirin for the primary prevention of CVD and CRC with the same population, all else held equal, not using aspirin for primary prevention (**Figure**). Primary outcomes are the net difference in undiscounted life-years and quality-adjusted life-years (QALYs), but all modeled benefits and harms were measured. Aspirin was initiated or continued at contemporary rates for secondary prevention in both simulation groups. It was discontinued permanently in both groups after any major GI bleeding or hemorrhagic stroke event. Model simulations were independently conducted with a 100 000-person sample for each age, sex, and baseline CVD risk group.

Baseline Event Rates and Model Validation

Baseline rates of CVD events are generated by the combination of population characteristics at model initiation, the natural progression of CVD risk factors as persons age, and the model's risk equations for disease. **Appendix Table 2** (available at www.annals.org) compares rates of MI and ischemic stroke generated by the model with corresponding rates observed in NHANES (18–22) for external validation of our model's natural history engine. Baseline rates of major GI bleeding in the nonelevated risk population (that is, among persons for whom aspirin use is not contraindicated) were estimated by using data from a large Italian population-based cohort study (47), with adjustments for the U.S. age and sex distribution (**Appendix Table 3**, available at www.annals.org). Case-fatality rates for GI bleeding, based on patients without complicating comorbidities, were derived from a prospective study conducted in the United Kingdom (48). Baseline CRC incidence rates used in the model are derived from U.S. data (49, 50) and reflect contemporary use of screening technologies, such as colonoscopy, which can prevent CRC by the identification and removal of cancer precursors.

Uncertainty and Sensitivity Analysis

Two sources of uncertainty were considered in this study: stochastic heterogeneity from the variability in outcomes experienced by a randomly selected sample population and parameter uncertainty from the imprecision of model parameter estimates (51). Confidence intervals reflecting stochastic heterogeneity were estimated by bootstrap resampling the simulated population for each stratified outcome 100 000 times with replacement. Deterministic (1-way) sensitivity analyses of key parameters were conducted with all other parameters, probabilities, and population characteristics held equal. **Table 1** and **Appendix Tables 1** and **3** present the alternative parameter values used in the deterministic analyses. Probabilistic sensitivity analyses can be found in our prior work (52).

Role of Funding Source

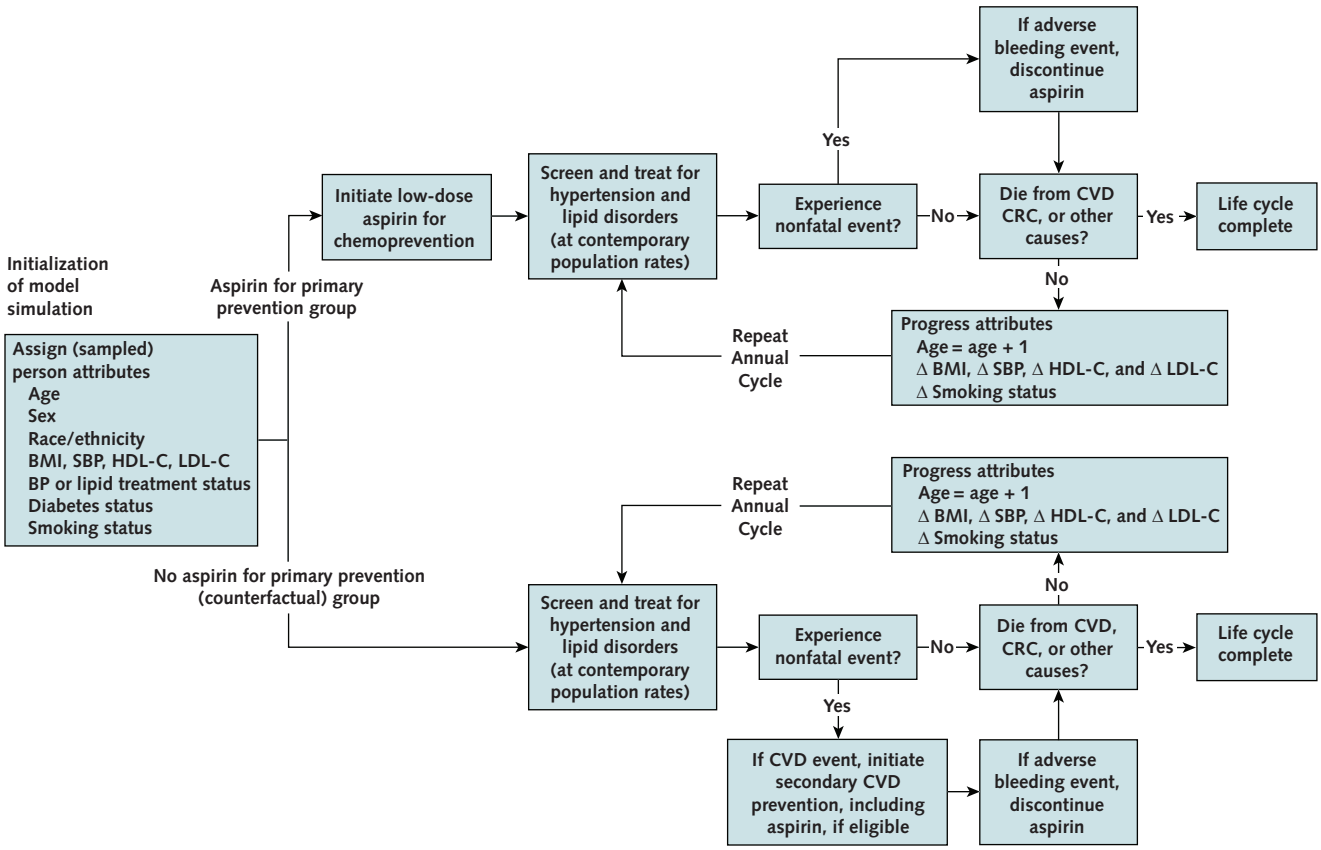
The Agency for Healthcare Research and Quality provided funding, project oversight, and review for this study. Four USPSTF members helped to resolve scope and methodological issues, and 4 peer reviewers provided feedback on draft findings. Final model results are the sole responsibility of the authors.

RESULTS

Lifetime Net Benefit

The estimated lifetime net difference in QALYs from using aspirin for primary prevention is positive for all sex and baseline CVD risk groups aged 40 to 69 years (range, 7.4 to 107.9 QALYs per 1000 persons) that we considered (**Table 2**). In our results, net life-years are positive for nearly all groups aged 40 to 59 years (range, 3.2 to 82.8 life-years per 1000 persons). For women aged 50 to 59 years with a 10-year CVD risk of 1% and both sexes aged 60 to 69 years with a 10-year CVD risk of 10% or less, net life-years are negative. Both net QALYs and life-years are negative for men and women of all considered risk levels aged 70 to 79 years. The magnitude of lifetime net life-years and

Figure. Simulation model and analysis design.



BMI = body mass index; BP = blood pressure; CRC = colorectal cancer; CVD = cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; SBP = systolic blood pressure.

QALYs is often similar for men and women and is generally greater the lower the age or the greater the 10-year CVD risk at initiation.

Detailed benefit and harm outcomes are presented in Table 3 and Appendix Tables 4 and 5 (available at www.annals.org). Differences in lifetime net outcomes between men and women are explained by the differences in baseline incidence for MI (higher for men), ischemic stroke (higher for women), and GI bleeding (higher for men). Women also have a longer life expectancy, which corresponds to a longer average risk exposure during which aspirin can intervene. When comparing by age groups, we found that lifetime net CVD events and prevented CRC cases are at their lowest when aspirin is initiated at older ages. This corresponds to the decrease in person-years of risk exposure. In contrast, lifetime net harms are similar or greater among older age groups because of increases in baseline GI bleeding and hemorrhagic stroke risk with age. Persons with lower CVD risk often have greater expected reductions in CRC incidence and mortality because of longer life expectancy. Because of the complex interplay between benefits and harms of aspirin on the length or quality of life, the sign of net events does not always correspond with net life-years or net QALYs.

Net Benefit Over 10 and 20 Years

Over 20 years, the predicted net QALYs from aspirin remain positive for most CVD risk groups (men and women) aged 40 to 69 years (Table 2). However, the magnitude of net QALYs that is positive over 20 years is generally a small fraction of the lifetime net benefit (range, 0.1 to 23.6 QALYs per 1000 persons). In addition, net life-years are negative for nearly all groups over this time frame. Over 10 years, net life-years and QALYs are also negative, or are only marginally positive, for all groups. No CRC benefit is reflected in the 10-year results because of the delayed effect found in the systematic evidence review.

Sensitivity Analyses

One-way parameter sensitivity for men and women with baseline CVD risk of 10% over lifetime, 20-year, and 10-year horizons are compared in Appendix Tables 6 to 8 (available at www.annals.org), respectively. These tables show that the possibility for a direct reduction in the RR for CVD-related death from aspirin (cases 6 and 7) has the most potential to sway results; net life-years and QALYs would be positive for nearly all groups over all time horizons with only a 3% reduction in CVD mortality risk (case 7). The next most sensitive

Table 2. Net Life-Years and QALYs of Lifetime, 20-y, and 10-y Aspirin Use*

10-y CVD Risk, %	Initiation Age 40–49 y			Initiation Age 50–59 y			Initiation Age 60–69 y			Initiation Age 70–79 y		
	Lifetime	20 y	10 y	Lifetime	20 y	10 y	Lifetime	20 y	10 y	Lifetime	20 y	10 y
Men												
Net life-years per 1000 persons												
1	**28.0**	**−1.8**	**−0.5**	**13.2**	**−5.5**	**−1.0**	NA	NA	NA	NA	NA	NA
5	**48.9**	**−2.7**	**−0.7**	**15.3**	**−6.2**	**−1.8**	−5.7	**−11.0**	**−3.2**	NA	NA	NA
10	**71.0**	−1.9	**−1.1**	**33.3**	−2.8	**−2.1**	−2.0	**−10.0**	**−4.2**	**−15.0**	**−16.2**	**−6.5**
15	**82.8**	0.7	**−1.3**	**39.5**	−2.2	**−2.6**	**9.6**	**−5.3**	**−3.9**	**−18.0**	**−18.1**	**−6.1**
20	**80.1**	1.4	**−0.8**	**60.5**	**7.4**	**−1.1**	**11.6**	**−7.5**	**−5.1**	**−22.5**	**−22.3**	**−9.8**
Net QALYs per 1000 persons												
1	**51.7**	0.1	**−0.8**	**36.8**	0.1	**−1.1**	NA	NA	NA	NA	NA	NA
5	**74.1**	**4.2**	−0.1	**40.0**	**2.6**	**−1.4**	**16.1**	0.1	**−2.8**	NA	NA	NA
10	**97.2**	**8.7**	0.5	**58.8**	**10.1**	−0.4	**18.0**	1.9	**−2.9**	−1.0	**−4.7**	**−4.9**
15	**107.9**	**11.6**	0.7	**64.4**	**12.8**	0.0	**30.9**	**10.1**	**−1.3**	−3.1	**−5.7**	**−4.5**
20	**105.7**	**14.2**	**2.0**	**83.4**	**23.6**	**3.0**	**31.8**	**8.8**	**−1.7**	**−6.2**	**−8.4**	**−6.8**
Women												
Net life-years per 1000 persons												
1	3.2	**−1.7**	−0.3	**−9.6**	**−5.3**	**−0.9**	**−18.0**	**−7.9**	**−2.4**	NA	NA	NA
5	**41.7**	**−2.1**	**−0.7**	**10.0**	**−7.8**	**−2.2**	**−12.0**	**−10.0**	**−2.7**	**−23.4**	**−17.1**	**−3.4**
10	**59.0**	−1.2	**−0.6**	**21.9**	**−6.4**	**−2.5**	−1.2	**−10.0**	**−3.2**	**−25.1**	**−20.5**	**−5.0**
15	**57.3**	0.4	−0.3	**33.4**	**−3.6**	**−2.0**	1.7	**−11.0**	**−4.4**	**−22.0**	**−22.2**	**−6.6**
20	**67.7**	−0.6	**−0.7**	**46.3**	−2.6	**−2.3**	4.8	**−7.9**	**−4.9**	**−26.1**	**−24.3**	**−7.8**
Net QALYs per 1000 persons												
1	**36.6**	**1.4**	−0.3	**21.8**	−0.2	**−1.0**	**7.4**	−0.7	**−2.6**	NA	NA	NA
5	**78.4**	**5.2**	0.1	**45.0**	**4.2**	**−0.8**	**16.4**	2.2	**−1.5**	−4.4	**−6.1**	**−2.9**
10	**96.9**	**8.7**	**0.9**	**62.1**	**10.2**	0.1	**28.4**	**6.6**	−0.4	−4.4	**−6.1**	**−3.1**
15	**98.4**	**11.3**	**1.7**	**71.6**	**15.0**	**1.6**	**32.4**	**9.3**	0.1	−1.5	**−6.4**	**−4.0**
20	**106.5**	**10.3**	**1.2**	**83.3**	**16.8**	**1.5**	**36.0**	**13.0**	0.3	−2.7	**−5.5**	**−3.6**

CVD = cardiovascular disease; NA = not applicable; QALY = quality-adjusted life-year.
* The 10-y CVD risk levels are based on the American College of Cardiology/American Heart Association risk calculator and refer to a person's risk at model baseline. Risk levels are rounded to the nearest integer. Results reflect the difference between universal adoption of low-dose aspirin (≤100 mg/d) for primary prevention vs. no adoption. All else is held equal. Boldface values indicate that the CIs reflecting stochastic heterogeneity do not include 0 per bootstrap sampling with replacement 100 000 times from within the original modeled population sample. Findings include evidence on the effect of aspirin in the reduction of colorectal cancer incidence derived from non–low-dose aspirin (>100 mg/d) trial interventions (British Doctor's Trial and United Kingdom Transient Ischemic Attack trial) (36) and on a CVD secondary prevention population (United Kingdom Transient Ischemic Attack trial) (36), but no apparent relationship with dose or prior CVD status for this effect has been identified (10, 13).

parameter to both measures is the RR for hemorrhagic stroke (cases 13 and 14). Even a small disutility associated with taking aspirin routinely (cases 1 and 2) can dramatically decrease net QALYs. Aspirin's effect on reducing CRC incidence also has a considerable effect; not accounting for this effect reduces lifetime net QALYs by about 50% and lifetime net life-years by even more. Variation in GI bleeding incidence and case-fatality rates (cases 10 to 12) has a greater relative effect for persons initiating aspirin in their 60s and 70s.

Discussion

These estimates quantify the expected difference in benefits and harms from taking low-dose aspirin for the primary prevention of CVD and CRC by age, sex, and baseline 10-year CVD risk group as derived from a detailed microsimulation model. Overall, we find that aspirin is expected to improve overall quality of life (that is, reduce illness) for most men and women without elevated bleeding risk when aspirin is initiated at ages 40 to 69 years for lifetime use, unless otherwise contraindicated. Such use is also expected to improve life expectancy for most men and women who start aspirin at ages 40 to 59 years and for those at higher CVD risk who start aspirin at ages 60 to 69 years. Our primary results do not find overall benefits to outweigh harms for persons in their 70s with a 10-year CVD risk of 20% or less. The balance of benefits and harms from using aspirin over 10 and 20 years is far more tenuous for most population groups, and several limitations and considerations should be considered before translating any of these findings to practice.

This study incorporates important new evidence that has been published since the last USPSTF reviews (3, 4). One major difference is in our findings by sex. Aspirin was previously found to reduce the RR for MI in men by 32% and the RR for stroke in women by 17%; the current review finds that aspirin reduces the RR for MI by 17% and the RR for stroke by 14% (12) in both men and women. Another major difference is the new finding of lower risk for CRC after 10 years of aspirin use. This added benefit can account for more than half of the lifetime net benefit, in terms of life-years and QALYs, from routine aspirin use (case 3 in **Appendix Table 6**). Of note, the RR for GI bleeding with aspirin was previously 2.00 compared with 1.58 found in the updated review. The RR for hemorrhagic stroke was previously 1.69 compared with the substantially lower RR of 1.27 used in this study.

Table 3. Detailed Benefit and Harm Tradeoffs of Aspirin Use With a CVD Risk of 10%*

Variable	Benefits, *prevented events per 1000 persons*					
	MI†	Ischemic Stroke†	CVD Event†‡	CVD Death	CRC	CRC Death
Men						
Initiation age, 40–49 y						
Lifetime outcomes	28.1	8.0	43.6	4.6	15.4	3.7
20-y outcomes	16.8	3.5	21.6	0.8	4.7	0.8
10-y outcomes	8.2	1.3	9.8	0.1	0.0	0.0
Initiation age, 50–59 y						
Lifetime outcomes	22.5	8.4	37.2	4.1	13.9	3.0
20-y outcomes	16.4	4.6	23.1	1.4	6.8	1.2
10-y outcomes	8.0	1.8	10.1	0.2	0.0	0.0
Initiation age, 60–69 y						
Lifetime outcomes	15.9	6.6	26.6	3.3	11.2	2.6
20-y outcomes	13.0	4.7	19.5	1.4	7.4	1.4
10-y outcomes	6.6	2.1	9.0	0.2	0.0	0.0
Initiation age, 70–79 y						
Lifetime outcomes	11.9	6.1	21.6	2.7	7.9	2.1
20 year outcomes	10.9	5.4	18.8	2.0	6.6	1.6
10 year outcomes	5.7	2.3	8.7	0.4	0.0	0.0
Women						
Initiation age, 40–49 y						
Lifetime outcomes	15.9	12.3	35.4	4.1	16.2	4.1
20-y outcomes	8.2	4.4	13.6	0.3	3.9	0.7
10-y outcomes	4.1	1.7	6.0	0.0	0.0	0.0
Initiation age, 50–59 y						
Lifetime outcomes	14.8	13.7	35.8	3.9	13.9	3.6
20-y outcomes	9.9	7.7	19.6	1.2	6.1	1.2
10-y outcomes	5.2	3.1	8.7	0.1	0.0	0.0
Initiation age, 60–69 y						
Lifetime outcomes	10.1	11.6	26.7	3.1	10.5	2.7
20-y outcomes	7.9	8.1	18.4	1.4	6.0	1.1
10-y outcomes	4.3	3.6	8.4	0.2	0.0	0.0
Initiation age, 70–79 y						
Lifetime outcomes	7.1	8.8	19.1	2.0	7.9	2.3
20-y outcomes	6.1	7.1	15.2	1.3	5.6	1.6
10-y outcomes	3.4	3.2	7.1	0.2	0.0	0.0

CVD = cardiovascular disease; CRC = colorectal cancer; GI = gastrointestinal; MI = myocardial infarction; QALY = quality-adjusted life-year.
* The 10% 10-y CVD risk levels are based on the American College of Cardiology/American Heart Association risk calculator and refer to a person's risk at model baseline. Results reflect the difference between universal adoption of low-dose aspirin (≤100 mg/d) for primary prevention vs. no adoption. All else is held equal. Findings include evidence on the effect of aspirin in the reduction of CRC incidence derived from non–low-dose aspirin (>100 mg/d) trial interventions (British Doctor's Trial and United Kingdom Transient Ischemic Attack trial) (36) and on a CVD secondary prevention population (United Kingdom Transient Ischemic Attack trial) (36), but no apparent relationship with dose or prior CVD status for this effect has been identified (10, 13).
† Nonfatal.
‡ Includes nonfatal MI, ischemic stroke, and congestive heart failure (as major sequelae to MI).
§ Includes fatal and nonfatal events.
‖ Defined by the net of benefit and harm events or this equation: (nonfatal CVD events + CVD deaths + CRC cases) − (GI bleeding events + hemorrhagic strokes).

We also had many methodological differences (detailed in section 5.1 of the **Supplement**). The prior net benefit calculations were restricted to the first nonfatal events over 10 years (**Table 24** of the **Supplement**). In this analysis, we account for fatal and nonfatal events over a lifetime and provide life-years and QALYs as outcome measures. Our results reveal that the lifetime horizon is needed to ensure all important benefits and harms are captured and that the largest average net balance of benefits is realized with long-term aspirin use. Life-years are an important measure because they incorporate differences in the expected length of life that may come from increased prevalence of fatal bleeding episodes, which are balanced against indirect reductions in CVD or CRC mortality that arise from the prevention of nonfatal CVD and CRC incidence. Quality-adjusted life-years are an important measure because they incorporate both expected length- and quality-of-life effects, which balance all fatal and nonfatal benefits harms. In addition, the ratio of nonfatal to fatal events generally decreases with age; therefore, we find fewer preventable nonfatal MIs and ischemic strokes in older age groups in our competing risk framework. Calculations of harms also differ. Our analysis incorporates estimates of age-adjusted case-fatality associated with GI bleeding events. This can have a meaningful effect on net benefit calculations, particularly for men and women initiating aspirin in their 60s and 70s (case 10 in **Appendix Table 6**). In addition, hemorrhagic stroke rates vary by age and CVD risk groups, which means that both benefits and harms scale with baseline CVD risk in our analysis. The baseline hemorrhagic stroke rates generated by our model compare well with large U.S.-based cohort studies and

Table 3–Continued

Harms, *incurred events per 1000 persons*				Net Balance (Benefits − Harms)		
GI Bleeding§	Hemorrhagic Stroke§	GI Bleeding Death	Hemorrhagic Stroke Death	Net Events Prevented‖	Net Life-Years	Net QALYs
25.0	2.1	1.4	2.0	36.5	71.0	97.2
11.2	1.0	0.2	0.9	14.9	−1.9	8.7
5.0	0.5	0.1	0.3	4.3	−1.1	0.5
28.4	2.3	1.8	2.1	24.5	33.3	58.8
18.2	1.6	0.5	1.4	11.5	−2.8	10.1
8.5	0.8	0.2	0.6	1.0	−2.1	−0.4
31.4	3.1	2.2	2.7	6.7	−2.0	18.0
24.8	2.4	1.1	2.1	1.0	−10.7	1.9
12.4	1.3	0.3	0.9	−4.5	−4.2	−2.9
32.7	2.2	3.4	1.9	−2.6	−15.1	−1.0
30.6	2.0	3.1	1.7	−5.3	−16.2	−4.7
18.9	1.2	1.2	1.0	−11.1	−6.5	−4.9
20.8	3.0	1.3	2.7	32.0	59.0	96.9
7.5	1.1	0.1	0.8	9.2	−1.2	8.7
3.0	0.4	0.0	0.2	2.6	−0.6	0.9
20.9	3.5	1.4	3.1	29.3	21.9	62.1
12.3	2.2	0.3	1.8	12.4	−6.4	10.2
5.3	1.0	0.1	0.6	2.6	−2.5	0.1
23.0	3.2	2.1	2.8	14.1	−1.2	28.4
17.3	2.5	1.1	2.1	6.0	−10.5	6.6
9.2	1.2	0.3	0.8	−1.8	−3.2	−0.4
23.5	3.5	2.7	3.0	1.9	−25.1	−4.4
20.9	3.0	2.2	2.5	−1.7	−20.5	−6.1
12.0	1.4	0.7	1.0	−6.1	−5.0	−3.1

are generally much higher than assumed by the 2009 recommendation (**Table 25** of the **Supplement**).

A recent study (53) used long-term follow-up results from the Women's Health Study to develop competing risk prediction models to estimate absolute risk reduction among CVD, cancer, and GI bleeding. Despite differences in underlying evidence and methods, our results over 10 and approximately 15 years are generally similar (**Table 27** of the **Supplement**). Another recent study (54) used a population-based incidence model to estimate the net difference in event rates over 15 years with prophylactic aspirin use in the general U.K. population. For that which can be compared, findings are generally consistent between studies, with differences in net events attributable to differential baseline event rates between the U.S. and U.K. populations and by the combined-versus-separated approach to aspirin's effect on stroke type (**Table 28** of the **Supplement**). In addition, a cohort modeling study (55) examined the cost-effectiveness of aspirin for primary prevention of CVD and CRC in men. Findings are again generally similar, with differences in net QALYs largely explained by the inclusion of a disutility to taking aspirin in the study's base-case analysis.

The average effectiveness of aspirin is determined by randomized trials and may reflect cross-contamination if participants assigned to the control group chose to use aspirin or those assigned to the aspirin group chose not to use aspirin (nonadherence). It is not known what would be observed with typical adherence levels and a pure control group. We expect, however, that the effectiveness of aspirin reflected in our analysis should correspond with good adherence because the modeled population mirrors persons willing to participate in a clinical trial. Our findings may not be relevant to those with lower expected adherence patterns, especially if they are associated with disutility for taking aspirin.

The systematic reviews did not find compelling evidence of differential effects by age. It is not clear how robust the homogenous RR effects are for all population groups, particularly persons with low event rates in the trial populations (such as those in their early 40s). We extended aspirin effects for persons older than 80 years; however, we did not evaluate aspirin initiation for these persons (nor for those <40 years) because of limited representation at enrollment in aspirin trials. Results from the ongoing ASPREE (Aspirin in Reducing Events in the Elderly) trial (56) may help to fill data gaps among older populations.

It is widely believed that aspirin reduces the risk for ischemic stroke but increases the risk for hemorrhagic

stroke. The latter was not found to be statistically significant in the systematic reviews, but we included this harm in our decision analysis because of its biological plausibility and the limited power to detect differences in this relatively rare event in study populations. In addition, our RR estimate for ischemic stroke underestimates benefits because it is derived from combined stroke data. This conservative approach may be appropriate given the imprecision in measuring the increased risk for hemorrhagic stroke.

By design, both CVD and CRC mortality risk may be affected indirectly by aspirin use in our model as a downstream effect of preventing nonfatal CVD events or CRC incidence, respectively. Low-dose aspirin trials indicate that there may be a small reduction in CVD mortality risk, but this finding is not statistically significant (12) and we did not include it in our base-case analysis. In contrast, evidence indicates that the RRs for CRC incidence and mortality are both reduced with aspirin use (13). To avoid double-counting, we modeled aspirin's effect on CRC incidence only and allowed the model's natural history of cancer to determine CRC deaths prevented. Nevertheless, we found that CVD mortality at 10 years and CRC mortality at 20 years in our model results align with rates observed in trials (**Table 29** of the **Supplement**).

The model accounts for a correlation between risk for CVD and CRC because of tobacco use. Hemorrhagic stroke risk also correlates with overall CVD risk. We did not, however, establish and incorporate GI bleeding risk equations that would account for a correlation between GI bleeding and CVD risk factors, such as tobacco use and diabetes.

These results naturally raise questions about whether there is an optimal age to stop aspirin use; however, evidence is lacking on the implications of discontinuing aspirin after long-term use. It could be misleading to use a model to inform discontinuation decisions without better data to support such analyses.

This analysis approached the decision to use aspirin from the perspective of a person's age, sex, and 10-year risk for CVD. Given the systematic evidence review findings of substantial benefit from aspirin in the prevention of CRC, persons with an elevated risk for CRC may consider using aspirin for this benefit alone. Stratifying net benefits by CRC risk was outside the scope of this analysis, but the detailed outcomes presented in **Table 3** and **Appendix Tables 4** and **5** may be helpful for those considering aspirin use for that reason.

These results apply to persons whose aspirin use is not absolutely contraindicated by a medical provider for such reasons as a history of GI or intracranial bleeding or concurrent use of medications that increase bleeding risk, which corresponds with the data we used to inform community-based bleeding risks (47). We did not account for heterogeneity in GI bleeding risks beyond age and sex. Case-fatality rates for GI bleeding events are not well-established in the literature. Aspirin primary prevention trials do not show a difference in GI bleeding mortality, but this may be due to the rarity of these events in highly selected trial populations. Our analysis uses observational GI bleeding mortality data (48), which indicate a large increase in case-fatality rates at older ages. Better estimates of how age, sex, aspirin, and other possible risk factors interact to affect GI bleeding and case-fatality rates may modify the net benefit findings, especially among older age groups (cases 10 to 12 in **Appendix Tables 6** to **8**).

These results indicate that several population groups may benefit from aspirin for the primary prevention of CVD and CRC. Nevertheless, discretion should be used when interpreting these results because sensitivity analyses reveal meaningful uncertainty about the magnitude of net benefit. Benefit and harm calculations are most sensitive to uncertainty about the effect of low-dose aspirin on the increased risk for hemorrhagic stroke and in the primary prevention of CVD mortality. Moreover, parameter estimates used in this study may not be reliable for populations underrepresented in the aspirin primary prevention trials. A better understanding of the effects of aspirin by age group and after discontinuation, additional studies that report aspirin's effect on ischemic stroke separately from hemorrhagic stroke, and the development of comprehensive risk equations for GI bleeding would increase confidence in and precision of the simulation results. Quality-of-life benefits from using aspirin may be considerably diminished among persons who dislike taking routine medications. Future research may identify additional benefits (such as protective effects against other types of cancer) or harms that may substantially alter these findings. These sources of uncertainty and patient preferences should be carefully considered in the shared decision-making process about the routine use of aspirin for primary prevention.

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Appendix Table 1. Health Utility Weights*

Parameter	First Year/ New Event	Ongoing Quality of Life	Reference
Baseline health utility weight			
No CVD conditions		0.872	38, 40–43
Relative health utility weight			
CRC	0.700	0.700	44, 45
Congestive heart failure	0.786	0.786	37, 39, 41–43
GI bleeding	0.907	1.000	37
Hemorrhagic stroke	0.600	0.600	37–42, 46
Ischemic stroke	0.771	0.771	37–42
MI	0.859	1.000	37–39, 41, 43
Taking aspirin daily, base case		1.000	Assumption
Taking aspirin daily, sensitivity 1		0.999	Assumption
Taking aspirin daily, sensitivity 2		0.995	Assumption

CRC = colorectal cancer; CVD = cardiovascular disease; GI = gastrointestinal; MI = myocardial infarction.
* All health utility weights are applied multiplicatively to the baseline health utility weight. The quality-of-life reduction for CRC is applied for ≤5 y in the case of nonfatal episodes. Quality-of-life reductions for congestive heart failure are included as major sequelae to MI. First-year/new-event health utility weights are applied during the year of an incident event or first year of disease onset; ongoing health utilities are applied in subsequent years.

Appendix Table 2. Comparison of Baseline Modeled CVD Event Rates With National Prevalence Estimates*

Age, y	Population With History of Event, %			
	MI		Ischemic Stroke	
	NHANES (2001–2010)	ModelHealth: CVD	NHANES (2001–2010)	ModelHealth: CVD
Men and women				
40–49	1.5	2.3	1.6	1.7
50–59	4.0	4.7	2.3	2.6
60–69	8.4	8.5	5.9	4.8
70–79	12.0	13.2	9.3	10.0
Men				
40–49	1.7	3.0	0.8	1.0
50–59	5.4	6.4	2.2	2.0
60–69	13.1	11.6	6.1	4.1
70–79	18.7	18.7	8.9	9.7
Women				
40–49	1.3	1.6	2.4	2.4
50–59	2.7	3.1	2.5	3.2
60–69	4.6	5.9	5.8	5.4
70–79	7.4	9.3	9.6	10.2

CVD = cardiovascular disease; MI = myocardial infarction; NHANES = National Health and Nutrition Examination Survey.
* This table compares CVD prevalence at various ages between NHANES 2001–2010 (18–22) combined data and results from the ModelHealth: CVD model. The model run represented here is based on a birth cohort (starting at age 40 y) with hypertension screening and treatment, cholesterol screening and treatment, and aspirin for primary and secondary prevention—all implemented and adopted at contemporary rates. For comparison purposes of the cross-sectional and longitudinal data sets, outcomes are calculated for the age range from NHANES and the midpoint of the age range from the ModelHealth: CVD output; this methodological difference can explain some small discrepancies.

Appendix Table 3. Baseline GI Bleeding and Case-Fatality Rate Parameter Values*

Parameter	Base Case	Sensitivity Value	Reference
GI bleeding, baseline risk (per year)			
Men, 40–49 y	0.05%	0.10%	47
Men, 50–59 y	0.12%	0.24%	47
Men, 60–69 y	0.21%	0.42%	47
Men, 70–79 y	0.39%	0.78%	47
Men, ≥80 y	0.61%	1.22%	47
Women, 40–49 y	0.03%	0.06%	47
Women, 50–59 y	0.07%	0.14%	47
Women, 60–69 y	0.13%	0.26%	47
Women, 70–79 y	0.23%	0.46%	47
Women, ≥80 y	0.36%	0.72%	47
GI bleeding, case-fatality rate			
Age 40–59 y	1%	0%, 0.5%	48
Age 60–79 y	3%	0%, 1.5%	48
Age ≥80 y	19%	0%, 9.5%	48

GI = gastrointestinal.
* Baseline GI bleeding risks are the probabilities of developing GI bleeding without aspirin by age and sex. GI bleeding case fatalities represent the probability of dying from GI bleeding by age. The other parameter values are used in 1-way sensitivity analyses and are intended to reflect analytically meaningful alternative values for these parameters rather than statistical uncertainty.

Appendix Table 4. Expanded Lifetime Benefit and Harm Tradeoffs of Aspirin Use for Men Aged 40–79 y*

10-y CVD Risk, %	Benefits, *events prevented per 1000 persons*						Harms, *events incurred per 1000 persons*				Net Balance (Benefits − Harms)		
	MI†	Ischemic Stroke†	CVD Event†‡	CVD Death	CRC	CRC Death	GI Bleeding§	Hemorrhagic Stroke§	GI Bleeding Death	Hemorrhagic Stroke Death	Net Events Prevented	Net Life-Years	Net QALYs
Initiation age, 40–49 y													
1	21.6	6.4	33.3	3.7	15.0	3.4	31.9	2.9	1.8	2.6	17.1	28.0	51.7
5	23.8	7.6	37.4	4.1	14.8	3.7	28.5	2.5	1.5	2.4	25.4	48.9	74.1
10	28.1	8.0	43.6	4.6	15.4	3.7	25.0	2.1	1.4	2.0	36.5	71.0	97.2
15	31.1	8.5	48.0	5.4	13.9	3.3	23.7	2.1	1.4	1.9	41.5	82.8	107.9
20	32.6	8.4	49.6	5.5	13.2	3.1	22.8	2.2	1.1	2.0	43.4	80.1	105.7
Initiation age, 50–59 y													
1	17.0	6.1	27.7	3.2	14.0	3.3	33.9	2.7	2.1	2.2	8.2	13.2	36.8
5	19.4	7.0	31.6	3.7	14.1	3.5	30.0	3.0	2.0	2.7	16.3	15.3	40.0
10	22.5	8.4	37.2	4.1	13.9	3.0	28.4	2.3	1.8	2.1	24.5	33.3	58.8
15	26.7	8.6	43.4	5.4	12.1	2.3	26.0	2.8	1.5	2.5	32.2	39.5	64.4
20	28.6	9.2	46.2	5.5	12.2	2.7	24.8	2.1	1.2	1.9	37.0	60.5	83.4
Initiation age, 60–69 y													
1	–	–	–	–	–	–	–	–	–	–	–	–	–
5	14.9	6.4	25.6	3.0	12.1	2.8	33.6	2.6	2.3	2.3	4.6	−5.7	16.1
10	15.9	6.6	26.6	3.3	11.2	2.6	31.4	3.1	2.2	2.7	6.7	−2.0	18.0
15	18.6	8.0	32.2	4.0	10.4	2.4	29.8	2.4	2.2	2.2	14.3	9.6	30.9
20	20.1	8.4	34.2	4.5	9.1	1.9	26.7	2.7	2.2	2.4	18.4	11.6	31.8
Initiation age, 70–79 y													
1	–	–	–	–	–	–	–	–	–	–	–	–	–
5	–	–	–	–	–	–	–	–	–	–	–	–	–
10	11.9	6.1	21.6	2.7	7.9	2.1	32.7	2.2	3.4	1.9	−2.6	−15.1	−1.0
15	12.8	6.5	22.5	2.5	6.9	1.7	30.6	2.3	3.3	2.0	−1.0	−18.0	−3.1
20	13.2	7.2	24.2	3.0	6.8	1.6	30.7	2.6	3.4	2.3	0.6	−22.5	−6.2

CRC = colorectal cancer; CVD = cardiovascular disease; GI = gastrointestinal; MI = myocardial infarction; QALY = quality-adjusted life-year.

* The 10-y CVD risk levels are based on the American College of Cardiology/American Heart Association risk calculator and refer to a person's risk at model baseline. Results reflect the difference between universal adoption of low-dose aspirin (≤100 mg/d) for primary prevention vs. no adoption. All else is held equal. Findings include evidence on the effect of aspirin in the reduction of CRC incidence derived from non–low-dose aspirin (>100 mg/d) trial interventions (British Doctor's Trial and United Kingdom Transient Ischemic Attack trial) (36) and on a CVD secondary prevention population (United Kingdom Transient Ischemic Attack trial) (36), but no apparent relationship with dose or prior CVD status for this effect has been identified (10, 13).

† Nonfatal.

‡ Includes nonfatal MI, ischemic stroke, and congestive heart failure (as major sequelae to MI).

§ Includes fatal and nonfatal events.

‖ Defined by the net of benefit and harm events or this equation: (nonfatal CVD events + CVD deaths + CRC cases) − (GI bleeding events + hemorrhagic strokes).

Appendix Table 5. Expanded Lifetime Benefit and Harm Tradeoffs of Aspirin Use for Women Aged 40–79 y*

10-y CVD Risk, %	Benefits, *events prevented per 1000 persons*						Harms, *events incurred per 1000 persons*				Net Balance (Benefits − Harms)		
	MI†	Ischemic Stroke†	CVD Events†‡	CVD Death	CRC	CRC Death	GI Bleeding§	Hemorrhagic Stroke§	GI Bleeding Death	Hemorrhagic Stroke Death	Net Events Prevented	Net Life-Years	Net QALYs
Initiation age, 40–49 y													
1	11.1	10.2	25.7	2.7	14.1	3.5	25.8	3.9	1.9	3.3	12.9	3.2	36.6
5	14.1	11.8	32.1	4.0	15.5	4.3	21.0	3.7	1.5	3.3	26.9	41.7	78.4
10	15.9	12.3	35.4	4.1	16.2	4.1	20.8	3.0	1.3	2.7	32.0	59.0	96.9
15	17.2	13.7	38.6	4.8	14.9	3.4	19.1	2.9	1.2	2.9	36.3	57.3	98.4
20	17.7	13.0	38.5	4.5	15.5	4.0	18.5	2.5	1.4	2.2	37.5	67.7	106.5
Initiation age, 50–59 y													
1	9.4	9.4	22.2	2.5	13.7	3.4	25.6	3.8	2.1	3.3	9.0	−9.6	21.8
5	12.2	11.3	28.7	3.6	14.1	3.6	23.9	3.6	1.8	3.3	18.9	10.0	45.0
10	14.8	13.7	35.8	3.9	13.9	3.6	20.9	3.5	1.4	3.1	29.3	21.9	62.1
15	15.0	14.3	36.7	4.7	13.5	3.4	20.0	3.4	1.3	3.1	31.5	33.4	71.6
20	15.2	14.4	36.6	4.4	13.2	3.6	18.4	2.9	1.4	2.6	33.1	46.3	83.3
Initiation age, 60–69 y													
1	7.2	8.8	18.4	1.8	12.5	3.5	27.2	4.2	2.5	3.6	1.2	−18.2	7.4
5	9.0	10.5	23.3	2.5	11.1	2.9	24.6	3.6	2.2	3.2	8.7	−12.7	16.4
10	10.1	11.6	26.7	3.1	10.5	2.7	23.0	3.2	2.1	2.8	14.1	−1.2	28.4
15	11.0	12.9	29.7	3.9	9.3	2.6	21.6	3.4	2.0	3.0	18.0	1.7	32.4
20	11.1	13.0	30.3	4.4	9.7	2.7	21.7	3.3	2.1	2.9	19.4	4.8	36.0
Initiation age, 70–79 y													
1	–	–	–	–	–	–	–	–	–	–	–	–	–
5	6.0	7.9	16.2	1.4	8.4	2.6	26.6	3.0	2.9	2.5	−3.6	−23.4	−4.4
10	7.1	8.8	19.1	2.0	7.9	2.3	23.5	3.5	2.7	3.0	1.9	−25.1	−4.4
15	7.5	9.8	20.5	2.0	7.3	2.4	22.9	3.2	2.7	2.7	3.7	−22.3	−1.5
20	8.6	10.6	22.8	2.5	7.2	2.1	21.4	3.3	2.8	3.0	7.8	−26.1	−2.7

CRC = colorectal cancer; CVD = cardiovascular disease; GI = gastrointestinal; MI = myocardial infarction; QALY = quality-adjusted life-year.
* The 10-y CVD risk levels are based on the American College of Cardiology/American Heart Association risk calculator and refer to a person's risk at model baseline. Results reflect the difference between universal adoption of low-dose aspirin (≤100 mg/d) for primary prevention vs. no adoption. All else is held equal. Findings include evidence on the effect of aspirin in the reduction of CRC incidence derived from non–low-dose aspirin (>100 mg/d) trial interventions (British Doctor's Trial and United Kingdom Transient Ischemic Attack trial) (36) and on a CVD secondary prevention population (United Kingdom Transient Ischemic Attack trial) (36), but no apparent relationship with dose or prior CVD status for this effect has been identified (10, 13).
† Nonfatal.
‡ Includes nonfatal MI, ischemic stroke, and congestive heart failure (as major sequelae to MI).
§ Includes fatal and nonfatal events.
|| Defined by the net of benefit and harm events or this equation: (nonfatal CVD events + CVD deaths + CRC cases) − (GI bleeding events + hemorrhagic strokes).

Appendix Table 6. Comparisons in Lifetime Net Benefit of Taking Aspirin for Men and Women With a CVD Risk of 10%*

Cases	Net LYs or QALYs per 1000 persons															
	Initiation Age, 40–49 y				Initiation Age, 50–59 y				Initiation Age, 60–69 y				Initiation Age, 70–79 y			
	Men		Women		Men		Women		Men		Women		Men		Women	
	LYs	QALYs	LYs	QALYs	LYs	QALYs	LYs	QALYs	LYs	QALYs	LYs	QALYs	LYs	QALYs	LYs	QALYs
(0) Base case	71.0	97.2	59.0	96.9	33.3	58.8	21.9	62.1	−2.0	18.0	−1.2	28.4	−15.1	−1.0	−25.1	−4.4
(1) ASA disutility = 0.005	71.0	0.5	59.0	−18.1	33.3	−19.4	21.9	−25.3	−2.0	−47.4	−1.2	−44.1	−15.1	−52.1	−25.1	−66.3
(2) ASA disutility = 0.001	71.0	77.4	59.0	73.5	33.3	42.7	21.9	44.2	−2.0	4.5	−1.2	13.6	−15.1	−11.6	−25.1	−17.1
(3) CRC benefit = none	32.7	50.0	10.5	41.2	5.4	22.7	−11.7	21.0	−21.5	−8.0	−21.2	2.6	−25.5	−15.6	−37.3	−20.6
(4) CRC RR = 0.47	81.7	110.8	72.7	113.1	43.0	71.0	31.8	74.4	3.8	26.0	5.3	36.6	−11.3	4.2	−19.9	2.0
(5) CRC RR = 0.76	55.7	78.4	40.1	75.2	21.9	43.9	10.0	46.8	−10.3	7.2	−9.4	17.8	−19.2	−6.6	−29.8	−10.6
(6) CVD death RR = 0.85	345.3	329.9	322.7	317.3	287.4	273.7	264.0	264.6	194.1	183.8	196.1	193.2	122.6	115.2	111.0	110.1
(7) CVD death RR = 0.97	123.0	141.4	114.6	143.7	77.6	96.3	72.1	104.1	34.6	48.8	38.0	61.3	12.4	22.2	5.8	21.8
(8) GIB RR = 1.29	77.4	103.8	67.5	105.2	42.4	67.8	30.6	70.3	7.9	27.8	8.1	37.5	−1.8	11.7	−13.3	6.7
(9) GIB RR = 1.95	62.5	88.6	49.5	87.8	23.2	48.7	13.2	53.4	−17.1	3.3	−13.4	16.8	−32.5	−17.5	−41.7	−19.8
(10) GIB death = none	84.5	108.7	73.1	108.9	49.4	72.6	36.5	74.5	15.9	33.3	18.2	45.1	10.6	20.9	−2.7	14.6
(11) GIB death = 50%	78.8	103.8	65.1	102.2	41.3	65.7	29.1	68.3	7.0	25.7	8.6	36.9	−3.0	9.2	−15.0	4.2
(12) GIB incidence rate = double	60.7	85.8	47.3	84.7	18.3	42.6	7.1	46.8	−21.9	−2.2	−19.8	10.2	−39.9	−25.2	−51.5	−29.3
(13) HS RR = 1.00	101.6	125.1	98.8	134.0	61.9	85.1	66.3	102.6	27.6	45.4	30.1	57.8	0.7	13.7	1.3	20.6
(14) HS RR = 1.68	25.1	55.0	−11.8	31.8	−17.7	12.0	−38.5	6.1	−44.1	−21.1	−57.0	−23.5	−37.6	−22.0	−64.8	−42.2
(15) IS RR = 0.76	80.1	118.2	73.9	130.9	40.7	76.4	36.1	96.3	1.8	29.6	7.3	51.8	−12.3	6.8	−20.0	8.6
(16) IS RR = 0.98	57.8	70.2	39.3	54.5	23.9	37.4	9.1	26.3	−7.9	3.3	−12.3	0.8	−19.0	−10.6	−29.2	−19.2
(17) MI RR = 0.74	102.9	129.1	81.9	119.7	55.9	81.6	39.1	79.3	9.3	29.7	6.8	37.1	−9.6	5.1	−21.9	−0.5
(18) MI RR = 0.94	29.2	56.1	30.6	68.8	8.3	33.0	0.0	39.5	−15.9	3.9	−12.3	16.3	−23.4	−9.9	−29.8	−9.9
(19) Discounted (3%, base case)	24.2	38.5	19.1	37.3	12.2	26.7	6.0	27.7	−4.2	7.8	−3.7	13.9	−11.5	−2.4	−16.7	−3.9

ASA = acetylsalicylic acid (aspirin); CRC = colorectal cancer; CVD = cardiovascular disease; GIB = gastrointestinal bleeding; HS = hemorrhagic stroke; IS = ischemic stroke; LY = life-year; MI = myocardial infarction; QALY = quality-adjusted life-year; RR = relative risk.

* Results reflect the difference (sensitivity) in lifetime net outcomes compared with the base-case analysis, averaged across all age, sex, and baseline CVD groups. Each numbered item represents a 1-way sensitivity analysis with the parameter changed as described. Case 4 CRC benefit = none is equivalent to setting the CRC RR = 1. Case 10 GIB death = none is equivalent to setting the case-fatality rates from GI bleeding to 0%. Case 12 GIB incidence rate = double is equivalent to doubling the baseline probabilities of GI bleeding. See **Table 1** and **Appendix Tables 1** and **3** for additional detail. Findings include evidence on the effect of aspirin in the reduction of CRC incidence derived from non–low-dose aspirin (>100 mg/d) trial interventions (British Doctor's Trial and United Kingdom Transient Ischemic Attack trial) (36) and on a CVD secondary prevention population (United Kingdom Transient Ischemic Attack trial) (36), but no apparent relationship with dose or prior CVD status for this effect has been identified (10, 13). Outcome sensitivity is proportionally similar for groups with other 10-y CVD risk thresholds.

Appendix Table 7. Comparisons in Net Benefit of Taking Aspirin Over 20 y for Men and Women With a CVD Risk of 10%*

Cases	Net LYs or QALYs per 1000 persons															
	Initiation Age, 40–49 y				Initiation Age, 50–59 y				Initiation Age, 60–69 y				Initiation Age, 70–79 y			
	Men		Women		Men		Women		Men		Women		Men		Women	
	LYs	QALYs	LYs	QALYs	LYs	QALYs	LYs	QALYs	LYs	QALYs	LYs	QALYs	LYs	QALYs	LYs	QALYs
(0) Base case	−1.9	8.7	−1.2	8.7	−2.8	10.1	−6.4	10.2	−10.7	1.9	−10.5	6.6	−16.2	−4.7	−20.5	−6.1
(1) ASA disutility = 0.005	−1.9	−60.4	−1.2	−65.1	−2.8	−52.8	−6.4	−56.0	−10.7	−55.5	−10.5	−54.0	−16.2	−53.2	−20.5	−62.4
(2) ASA disutility = 0.001	−1.9	−5.2	−1.2	−6.1	−2.8	−2.7	−6.4	−3.1	−10.7	−9.8	−10.5	−5.7	−16.2	−14.7	−20.5	−17.6
(3) CRC benefit = none	−4.4	2.6	−3.9	3.0	−6.7	1.2	−10.6	1.5	−15.3	−8.0	−14.7	−1.9	−21.5	−14.0	−25.8	−14.7
(4) CRC RR = 0.47	−1.1	10.5	−0.7	10.0	−1.2	13.2	−5.5	12.9	−9.2	5.0	−9.4	9.0	−14.3	−1.5	−18.3	−2.9
(5) CRC RR = 0.76	−3.0	6.2	−2.4	6.2	−4.3	6.5	−8.0	6.8	−12.6	−2.0	−12.1	3.3	−18.2	−8.2	−22.4	−9.3
(6) CVD death RR = 0.85	63.7	65.2	47.1	50.1	96.3	94.8	75.2	79.5	98.8	95.0	86.8	88.7	91.3	86.2	73.8	73.6
(7) CVD death RR = 0.97	10.0	18.9	9.3	17.8	13.0	23.5	12.1	25.8	10.8	20.1	9.3	23.3	4.8	13.1	0.5	11.7
(8) GIB RR = 1.29	−1.3	9.7	−0.6	9.5	−0.6	12.8	−5.4	11.7	−7.7	5.5	−7.4	10.1	−6.8	4.6	−12.8	1.3
(9) GIB RR = 1.95	−2.4	7.6	−1.8	7.7	−4.6	7.6	−7.4	8.7	−16.4	−4.4	−14.3	2.3	−29.2	−17.3	−31.2	−16.4
(10) GIB death = none	−0.4	9.9	−0.5	9.3	1.0	13.4	−3.9	12.4	−4.5	7.3	−3.9	12.2	2.3	11.1	−6.4	5.9
(11) GIB death = 50%	−0.9	9.5	−1.0	8.9	−0.8	11.9	−5.0	11.5	−7.8	4.4	−7.3	9.3	−7.4	2.8	−14.3	−0.9
(12) GIB incidence rate = double	−2.0	7.6	−1.7	7.5	−7.0	4.9	−9.5	6.6	−19.4	−7.8	−16.2	0.3	−34.3	−22.9	−38.7	−23.8
(13) HS RR = 1.00	4.7	15.7	3.4	14.6	7.4	20.5	7.0	24.1	4.7	17.0	4.5	21.8	−4.7	6.3	−3.7	10.5
(14) HS RR = 1.68	−11.2	−1.3	−10.4	−2.2	−21.8	−9.0	−23.7	−8.3	−32.5	−19.5	−35.6	−18.6	−33.1	−21.0	−46.7	−32.2
(15) IS RR = 0.76	−1.4	12.8	−0.9	13.4	−2.0	15.6	−5.1	19.9	−10.2	7.3	−9.0	16.9	−14.7	0.9	−18.3	1.8
(16) IS RR = 0.98	−2.4	3.7	−1.4	2.8	−4.5	3.2	−7.7	−0.5	−12.0	−4.8	−13.0	−5.9	−18.2	−11.4	−22.0	−15.6
(17) MI RR = 0.74	−0.8	11.5	−0.2	10.4	1.1	15.2	−5.1	12.6	−8.0	5.6	−9.0	8.9	−13.2	−0.9	−18.9	−4.0
(18) MI RR = 0.94	−3.9	4.8	−1.8	6.9	−6.0	4.9	−9.0	6.4	−14.4	−2.8	−12.7	3.0	−20.4	−9.9	−22.5	−9.0
(19) Discounted (3%, base case)	−1.5	5.6	−0.9	5.7	−2.4	6.2	−4.8	6.4	−7.8	0.5	−7.5	4.1	−12.0	−4.3	−14.3	−4.7

ASA = acetylsalicylic acid (aspirin); CRC = colorectal cancer; CVD = cardiovascular disease; GIB = gastrointestinal bleeding; HS = hemorrhagic stroke; IS = ischemic stroke; LY = life-year; MI = myocardial infarction; QALY = quality-adjusted life-year; RR = relative risk.

* Results reflect the difference (sensitivity) in 20-y net outcomes compared with the base-case analysis, averaged across all age, sex, and baseline CVD groups. Each numbered item represents a 1-way sensitivity analysis with the parameter changed as described. Case 4 CRC benefit = none is equivalent to setting the CRC RR = 1. Case 10 GIB death = none is equivalent to setting the case-fatality rates from GI bleeding to 0%. Case 12 GIB incidence rate = double is equivalent to doubling the baseline probabilities of GI bleeding. See **Table 1** and **Appendix Tables 1** and **3** for additional detail. Findings include evidence on the effect of aspirin in the reduction of CRC incidence derived from non–low-dose aspirin (>100 mg/d) trial interventions (British Doctor's Trial and United Kingdom Transient Ischemic Attack trial) (36) and on a CVD secondary prevention population (United Kingdom Transient Ischemic Attack trial) (36), but no apparent relationship with dose or prior CVD status for this effect has been identified (10, 13). Outcome sensitivity is proportionally similar for groups with other 10-y CVD risk thresholds.

Appendix Table 8. Comparisons in Net Benefit of Taking Aspirin Over 10 y for Men and Women With a CVD Risk 10%*

Cases	Net LYs or QALYs per 1000 persons															
	Initiation Age, 40–49 y				Initiation Age, 50–59 y				Initiation Age, 60–69 y				Initiation Age, 70–79 y			
	Men		Women		Men		Women		Men		Women		Men		Women	
	LYs	QALYs	LYs	QALYs	LYs	QALYs	LYs	QALYs	LYs	QALYs	LYs	QALYs	LYs	QALYs	LYs	QALYs
(0) Base case	−1.1	0.5	−0.6	0.9	−2.1	−0.4	−2.5	0.1	−4.2	−2.9	−3.2	−0.4	−6.5	−4.9	−5.0	−3.1
(1) ASA disutility = 0.005	−1.1	−39.1	−0.6	−39.8	−2.1	−38.7	−2.5	−38.9	−4.2	−39.9	−3.2	−38.1	−6.5	−39.4	−5.0	−39.8
(2) ASA disutility = 0.001	−1.1	−7.4	−0.6	−7.2	−2.1	−8.0	−2.5	−7.7	−4.2	−10.3	−3.2	−8.0	−6.5	−11.8	−5.0	−10.4
(3) CRC benefit = none	−1.1	0.5	−0.6	0.9	−2.1	−0.4	−2.5	0.1	−4.2	−2.9	−3.2	−0.4	−6.5	−4.9	−5.0	−3.1
(4) CRC RR = 0.47	−1.1	0.5	−0.6	0.9	−2.1	−0.4	−2.5	0.1	−4.2	−2.9	−3.2	−0.4	−6.5	−4.9	−5.0	−3.1
(5) CRC RR = 0.76	−1.1	0.5	−0.6	0.9	−2.1	−0.4	−2.5	0.1	−4.2	−2.9	−3.2	−0.4	−6.5	−4.9	−5.0	−3.1
(6) CVD death RR = 0.85	13.5	13.3	10.1	10.2	22.4	20.7	17.9	17.6	26.0	22.9	21.8	20.7	26.5	23.2	20.6	18.8
(7) CVD death RR = 0.97	1.3	2.7	1.9	3.1	1.7	2.9	2.7	4.6	2.0	2.4	2.0	4.0	−0.1	0.5	0.4	1.6
(8) GIB RR = 1.29	−1.0	0.9	−0.6	1.1	−1.7	0.3	−2.3	0.5	−3.4	−1.7	−2.6	0.4	−4.4	−2.5	−3.6	−1.5
(9) GIB RR = 1.95	−1.2	0.2	−0.6	0.7	−2.4	−1.1	−2.7	−0.3	−5.7	−4.8	−3.8	−1.5	−9.3	−8.3	−6.9	−5.3
(10) GIB death = none	−0.8	0.8	−0.6	0.9	−1.5	0.1	−2.0	0.6	−2.7	−1.6	−1.9	0.6	−2.6	−1.6	−2.8	−1.2
(11) GIB death = 50%	−0.9	0.7	−0.6	0.9	−1.8	−0.1	−2.3	0.3	−3.6	−2.3	−2.5	0.1	−4.7	−3.4	−4.1	−2.3
(12) GIB incidence rate = double	−0.9	0.3	−0.7	0.6	−3.4	−2.2	−3.2	−0.9	−6.4	−5.8	−4.0	−1.8	−10.0	−9.4	−7.9	−6.6
(13) HS RR = 1.00	−0.1	2.0	0.0	2.0	−0.3	1.9	−0.1	3.2	−1.0	0.9	−0.6	2.9	−3.2	−1.4	−1.9	0.7
(14) HS RR = 1.68	−2.5	−1.4	−1.9	−1.1	−5.8	−5.0	−5.5	−4.2	−8.7	−8.2	−8.6	−7.2	−10.0	−9.0	−11.0	−10.1
(15) IS RR = 0.76	−1.1	1.3	−0.6	1.9	−2.0	1.0	−2.5	2.5	−4.2	−1.5	−3.1	2.2	−6.4	−3.6	−4.8	−1.3
(16) IS RR = 0.98	−1.2	−0.6	−0.6	−0.4	−2.2	−1.9	−2.6	−2.3	−4.3	−4.5	−3.3	−3.4	−6.6	−6.7	−5.0	−5.4
(17) MI RR = 0.74	−1.1	1.2	−0.5	1.3	−1.8	0.4	−2.5	0.5	−4.1	−2.4	−3.1	−0.1	−6.2	−4.2	−4.8	−2.7
(18) MI RR = 0.94	−1.2	−0.4	−0.6	0.5	−2.1	−1.3	−2.7	−0.6	−4.5	−3.8	−3.3	−1.1	−6.8	−5.8	−5.1	−3.5
(19) Discounted (3%, base case)	−0.9	0.5	−0.5	0.8	−1.7	−0.3	−2.1	0.1	−3.5	−2.4	−2.6	−0.3	−5.4	−4.2	−4.1	−2.6

ASA = acetylsalicylic acid (aspirin); CRC = colorectal cancer; CVD = cardiovascular disease; GIB = gastrointestinal bleeding; HS = hemorrhagic stroke; IS = ischemic stroke; LY = life-year; MI = myocardial infarction; QALY = quality-adjusted life-year; RR = relative risk.

* Results reflect the difference (sensitivity) in 10-y net outcomes compared with the base-case analysis, averaged across all age, sex, and baseline CVD groups. Each numbered item represents a 1-way sensitivity analysis with the parameter changed as described. Case 4 CRC benefit = none is equivalent to setting the CRC RR = 1. Case 10 GIB death = none is equivalent to setting the case-fatality rates from GI bleeding to 0%. Case 12 GIB incidence rate = double is equivalent to doubling the baseline probabilities of GI bleeding. See **Table 1** and **Appendix Tables 1** and **3** for additional detail. Findings include evidence on the effect of aspirin in the reduction of CRC incidence derived from non–low-dose aspirin (>100 mg/d) trial interventions (British Doctor's Trial and United Kingdom Transient Ischemic Attack trial) (36) and on a CVD secondary prevention population (United Kingdom Transient Ischemic Attack trial) (36), but no apparent relationship with dose or prior CVD status for this effect has been identified (10, 13). Outcome sensitivity is proportionally similar for groups with other 10-y CVD risk thresholds.