Technical Report

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

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road Rockville, Maryland 20850
www.ahrq.gov

Contract No. HHSA-290-2015-00007-I

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AHRQ Publication No. 21-05283-EF-2
October 2021

This report is based on research conducted by the HealthPartners Institute under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. HHSA-290-2015-00007-I, Subcontract Task Order No. 75Q80119F32009), via the Kaiser Permanente Evidence-based Practice Center. The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

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Acknowledgements

The authors gratefully acknowledge the following individuals for their contributions to this project: Howard Tracer, MD, at the Agency for Healthcare Research and Quality; current and former members of the U.S. Preventive Services Task Force who contributed to topic deliberations; Jack Cuzick, PhD, FRS, Vanessa Selak, PhD, and Steven M. Teutsch, MD, MPH, who provided expert review of the draft report; and Janelle M. Guirguis-Blake, MD, Corinne V. Evans, MPP, Leslie A. Perdue, MPH, Sarah I. Bean, MPH, Caitlyn A. Senger, MPH, MS, and Jennifer Lin, MD, with the Kaiser Permanente Evidence-based Practice Center for their collaboration.

Structured Abstract

Background. Evidence indicates that aspirin is effective for the primary prevention of cardiovascular disease (CVD) but regular use also increases risk for major gastrointestinal (GI) and cerebral hemorrhages.

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

Design. Decision analysis using a microsimulation model.

Data Sources. Relative risks of aspirin benefits and harms are sourced from an updated systematic evidence review.

Target Population. Men and women aged 40 to 79 years with 10-year CVD risk of 20 percent or less, no history of CVD, and non-elevated risk for major GI or cerebral hemorrhage.

Time Horizon. Lifetime and 10 years.

Perspective. Clinical.

Intervention. Daily use of low-dose aspirin (100mg or less). Lifetime use and stopping at 5-year age intervals between ages 65-85 years were considered as separate interventions.

Outcome Measures. Primary outcomes were net benefits in terms of quality-adjusted life years (QALYs) and life years. Aspirin benefits considered included reduction of non-fatal myocardial infarction and non-fatal ischemic stroke. Aspirin harms considered included increase in non-fatal major GI bleeding and intracranial hemorrhage. The potential for benefits of reduced CVD mortality and CRC incidence and the potential harm of increased fatal major GI bleeding were considered in sensitivity analyses.

Results of Base Case Analysis. When measured in QALYs, the lifetime net benefits from taking low-dose aspirin for primary prevention were positive for both men and women at ≥5% 10-year CVD risk levels when starting between ages 40-59 years and at ≥10% 10-year CVD risk levels when starting between ages 60-69 years. Lifetime gains in net QALYs with aspirin use ranged from 2.3 to 66.2 per 1,000 persons in these groups. Lifetime net benefits of starting aspirin measured in life years were positive for men at ≥5% and women at ≥10% 10-year CVD risk levels at ages 40-49 years, and they were positive for men at ≥7.5% and women at ≥15% 10-year CVD risk levels at ages 50-59 years. Lifetime gains in life years with aspirin use ranged from 0.4 to 52.4 net life years per 1,000 persons in these groups. Lifetime net life years were negative in most cases for persons starting aspirin between ages 60-69 years, and both measures of lifetime net benefit were generally negative for persons aged 70-79 years when starting aspirin. Stopping aspirin at 5-year intervals between ages 65-85 years showed little advantage compared to lifetime (or no) use. For most groups, aspirin harms realized in the first 10 years of use were expected to outweigh benefits realized in the first 10 years. For the groups that realized positive net benefit within 10 years of use, the net benefit was small.

Results of Sensitivity Analysis. Substantial variation in lifetime net QALYs and life years was found with alternative assumptions regarding aspirin's possible effect on CRC incidence, CVD mortality, and fatal major GI bleeding, though there was insufficient evidence of such effects using established USPSTF methods. Separate analyses that assumed aspirin i) reduces CRC incidence after 10 years of use or ii) reduces CVD mortality both showed moderate-to-large increases in lifetime net benefit relative to the base case analysis. When it was assumed that aspirin increases the risk of fatal major GI bleeding at the same proportion as non-fatal major GI bleeding, we found moderate reductions in estimated lifetime net benefit. Even small levels of disutility associated with routine use of aspirin led to moderate-to-large reductions in lifetime net QALYs.

Limitations. Sensitivity analyses demonstrate that findings are sensitive to uncertainty about aspirin's effects when used for primary prevention—particularly, whether aspirin reduces the risk for CRC incidence and affects fatal major GI bleeding risks. Some factors that may be correlated with CVD risk—such as blood pressure, current smoking, and diabetes—could not be accounted for in estimating major GI bleeding risks in a U.S. primary prevention population. Persons aged 40-49 and 70-79 years are not as well represented in primary prevention aspirin trials, making it less clear how aspirin use may affect these groups. Lack of validated prediction of CVD and bleeding risks by race/ethnicity limits the ability to report on these potentially important differences.

Conclusion. This updated decision analysis found many of the same population groups previously favored for aspirin initiation could expect positive lifetime net benefits of using aspirin for primary prevention. However, the quantitative margins for net benefit were generally much smaller in this updated decision analysis. This change in base case findings was driven by the removal of a beneficial effect of aspirin on CRC incidence, due to insufficient evidence for this outcome found by the updated systematic review. Uncertainty in influential factors related to net benefit notwithstanding, this decision analysis finds that men and women aged 40-59 and with ≥10% 10-year ASCVD risk were most likely to see lifetime benefit from using aspirin for primary prevention and that adults aged 70-79 with <= 20% 10-year ASCVD risk were most likely to experience net harm from starting aspirin.

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Chapter 1. Introduction

In any given year, approximately 720,000 Americans will suffer their first coronary attack, and 610,000 will suffer their first stroke [1]. African Americans are at higher risk for heart attacks than their female and male counterparts of other race-ethnicity groups, and are more likely to die following a heart attack [1]. Among cancers, colorectal cancer (CRC) is the third most common and deadly, accounting for about 8 percent of all new cases and deaths [2]. In economic terms, cardiovascular disease (CVD) and CRC account for more than $230 billion in direct medical costs annually, and the indirect costs from lost productivity and premature mortality are estimated to exceed $100 billion [1, 3, 4].

In 2016, the U.S. Preventive Services Task Force (USPSTF) recommended the initiation of low-dose aspirin use to prevent cardiovascular disease (CVD) and colorectal cancer (CRC) in adults aged 50-59 years (Grade: B) and 60-69 years (Grade: C) with ≥10% 10-year risk for first hard atherosclerotic CVD (ASCVD) event [5]. There was insufficient evidence to assess the initiation of aspirin use in adults aged <50 years or ≥70 years (Grade: I) [5]. The 2016 USPSTF aspirin recommendation for the prevention of CVD and CRC was supported by three separate systematic reviews [6-11] and a decision analysis [12, 13], with the systematic reviews informing key inputs to the decision analysis.

Since the release of the 2016 recommendation statement, findings from several large aspirin primary prevention trials have been published [14-16]. 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, informed by the systematic evidence review that has been conducted by the Kaiser Permanente Evidence Based Practice Center (EPC) [17], is designed to update estimates of the magnitude of the expected benefits and harms of using aspirin for primary prevention and support the USPSTF in updating their aspirin recommendation.

Chapter 2. Methods

This decision analysis uses microsimulation modeling to assess the net balance of harms and benefits from routine use of aspirin for the primary prevention of CVD for individuals with up to 20% risk of having a CVD event in the next ten years. The simulation uses evidence from the corresponding updated systematic evidence review conducted for the USPSTF [17]. Net benefits are assessed across three dimensions (sex, age, and baseline 10-year ASCVD risk) and two time horizons (lifetime and 10 years). Our decision analytic criterion was whether expected net benefit was positive (i.e., favoring aspirin use) or negative (i.e., indicating net harm and favoring aspirin non-use). Clinicians and patients may weigh the size of expected net benefit against uncertainty of the estimates to determine appropriateness of aspirin use.

Key Questions

The decision model addressed two key questions (KQ) and one contextual question (CQ) described below and summarized in **Table 1**.

KQ1: For clinically meaningful subgroups defined by age, sex, and 10-year ASCVD risk, what is the **lifetime net benefit** of starting aspirin for the primary prevention of CVD—assuming lifetime continuation or until adverse event or death—in terms of net quality-adjusted life years (primary outcome), life years, and events?
KQ2: For clinically meaningful subgroups defined by age, sex, and 10-year ASCVD risk, how does assuming aspirin will be discontinued prior to an adverse event or death (expressed as **5-year age intervals** for discontinuation) affect the lifetime benefit of starting aspirin for the primary prevention of CVD, in terms of quality-adjusted life years (primary outcome), net life years, and events?
CQ1: For clinically meaningful subgroups defined by age, sex, and 10-year ASCVD risk, what is the **10-year net benefit** of starting aspirin—assuming continuation until adverse event or death—for the primary prevention of CVD in terms of net quality-adjusted life years (primary outcome), life years, and events?

Model Design

Analyses in this study were conducted using the HealthPartners Institute ModelHealth™: Cardiovascular disease (ModelHealth: CVD) microsimulation model. ModelHealth: CVD also was used to conduct the 2016 decision analysis on aspirin for the USPSTF [12, 13]. This model was originally designed to assess the population health benefits and value of the USPSTF aspirin chemoprevention and CVD screening recommendations for the National Commission on Prevention Priorities [18, 19], but it has been broadly used for assessing disease prevention strategies in the U.S. population [20-23]. The model includes a CRC module capable of assessing primary prevention of either CRC cases or deaths directly. The model also includes detailed tobacco use microsimulation functions from the HealthPartners Institute ModelHealth™: Tobacco model [24, 25] to capture correlation of smoking risk between CVD and CRC at the level of individual patients. The **Technical Appendix** provides a detailed description of the microsimulation model used for this study.

ModelHealth: CVD is a discrete-event, annual-cycle microsimulation model parameterized to estimate the lifetime incidence of CVD events in a cross-section of individuals representative of the U.S. population. Modeled outcomes included incidence of myocardial infarction, ischemic stroke, intracranial hemorrhage, angina pectoris, congestive heart failure, intermittent claudication, diabetes, and CVD-related death. Variations in age, sex, and race/ethnicity were accounted for in the baseline prevalence of disease and in the distribution and progression of CVD risk factors. These included an individual's body mass index (BMI), systolic blood pressure (SBP), total cholesterol, high- and low-density lipoprotein cholesterol (HDL-C/LDL-C), diabetes status, and cigarette smoking status.

CVD incidence was modeled annually. CVD events were predicted by one-year risk equations estimated specifically for the model from long-term epidemiological data sourced from the Framingham Heart Study [26, 27]. Event risk was estimated based on a person's age, sex, BMI, blood pressure, cholesterol levels, smoking status, diabetes status, and previous history of CVD. CVD risk was not adjusted by race/ethnicity, but differences in cardiometabolic risk factors by race/ethnicity were accounted for in the model. **Technical Appendix Table 7** summarizes the risk equations for CVD outcomes and diabetes in ModelHealth: CVD.

The annual progression of continuous CVD risk factors was modeled in a two-step process (**Technical Appendix, Section 3.2**). First, the probability of an increase, decrease, or maintenance of a risk factor is determined given individual characteristics and the previous year's value. Second, if a risk factor changes, the amount of change was determined by a second set of equations using the same covariates. We estimated the equations that determine these probabilities using data from the Behavioral Risk Factor Surveillance System [28] and Framingham Heart Study [26, 27]. Tobacco cessation depended on a person's current smoking status, time in that state, and their demographic characteristics using probabilities derived from the National Health Interview Survey data [29] and published estimates from longitudinal studies of smoking relapse [30-34].

Screening and treatment for hypertension and dyslipidemia in the model were consistent with national clinical guidelines [35-39], and identification and adherence patterns are consistent with the rates observed within the National Health and Nutrition Examination Survey (NHANES) [40, 41] (**Technical Appendix, Sections 4.2 and 4.3**). The use of antihypertensive drugs and lipid-acting agents was modeled as an exogenous treatment effect that modifies these respective risk factors and alters disease risk accordingly. The use of aspirin may affect the relative risk of non-fatal myocardial infarction and ischemic stroke, CVD-related mortality, CRC incidence, major GI bleeding, and intracranial hemorrhage.

Rates of fatal and non-fatal major GI bleeding for persons not using aspirin and without elevated bleeding risks were obtained from a large New Zealand cohort study [42] (**Tables 2a** and **2b**). Major GI bleeding in these data was defined as gastrointestinal bleeds leading to hospitalization or death. The population without elevated bleeding risks was: aged 30-80 years; had no history of CVD, chronic kidney disease, and prior intracranial hemorrhage; had no history of aspirin, antiplatelet or anticoagulant use in the prior 6 months; and was not at high risk for bleeding based on comorbidities or co-treatments (non-aspirin nonsteroidal anti-inflammatory drugs, corticosteroids, or selective serotonin reuptake inhibitors in the prior 6 months).

CRC was modeled using an incidence and case-fatality rate approach, which tracks cancer incidence and mortality for each agent (**Technical Appendix, Section 3.6**). Baseline incidence and case-fatality rates by age, sex, and race/ethnicity were estimated from National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) data using SEER*Stat software version 8.3.8 [43]. Baseline incidence rates were adjusted according to smoking status using relative risks provided by the Smoking-Attributable Mortality, Morbidity, and Economic Costs (SAMMEC) as reported in the 2014 Surgeon General's Report on the Health Consequences of Smoking [44]. Baseline CRC incidence rates used in the model reflect contemporary use of screening technologies, such as colonoscopy, which can prevent CRC by the identification and removal of precursor adenomatous polyps or adenoma.

Patient Population

The key questions were assessed independently for men and women across four 10-year age bands (40-49, 50-59, 60-69, and 70-79 years old) and across baseline 10-year ASCVD risk bands that included 5%, 7.5%, 10%, 15%, and 20%, with each risk band defined by +/- 0.5% (1% bands). Baseline 10-year CVD risk was estimated using the American College of Cardiology/American Heart Association (ACC/AHA) Pooled Cohort risk equation for the first hard ASCVD event (non-fatal MI, non-fatal stroke, or coronary death) [45]. The calculation of ASCVD risk at baseline is independent from the event rates predicted by the model. Therefore, the model mirrors use of ASCVD risk identification in clinical practice where an individual's 10-year risk prediction does not necessarily correspond with future events. For each age, sex, and 1% baseline ASCVD risk band, simulated persons were randomly oversampled from population characteristics representative of the U.S. population to obtain a sample of 100,000 for each combination of age group, sex and 1% CVD risk band. For men aged 70-79 years, the 5% ASCVD 10-year risk band was excluded due to being rarely observed. To define the representative U.S. population from which the samples are drawn, initial demographic characteristics—including age, sex, and race/ethnicity—were obtained from the 2018 American Community Survey [46]. Initial CVD risk factors, including BMI, SBP, total cholesterol, LDL-C, HDL-C, BP treatment status, and diabetes status, were derived from the combined 2015-2018 NHANES surveys [40, 41]. Initial smoking status was derived from the combined 2017-2018 National Health Interview Surveys [47]. All persons for the decision analysis were free of CVD and CRC at baseline.

Summary of Model Updates From 2016 to 2021

A number of elements to the model design have been updated from the 2016 decision model [12, 13] for use in the current analysis. Population demographics by age, sex, and race ethnicity have been updated from the 2010 U.S. Census to estimates from the 2018 American Community Survey. Cardiometabolic risks have been updated from 2001-2010 to 2015-2018 data from NHANES. Smoking prevalence and transitions have been updated from 2007 to 2017-2018 data from the National Health Interview Survey. CRC incidence and case-fatality rates have been updated from data from SEER registry years 2001-2010 to years 2005-2017. Major GI bleeding incidence and fatality rates have been updated from an Italian cohort [48] and U.K. hospital data [49] with data from a large and more contemporary New Zealand cohort [42]. Death rates from causes other than CVD, CRC, and other smoking-attributable cancers have been updated from

2009-based life tables and mortality data to rates from 2017. Management of hypertension and high blood pressure in the model has been updated from following the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [50] and Adult Treatment Panel III [51] recommendations to be consistent with current USPSTF and ACC/AHA Task Force clinical practice guidelines [35-39]. The results will show that none of these model updates were a major factor in any key changes between findings of the 2021 and 2016 decision models.

Integration of Systematic Review Results Into the Model

Findings from an updated systematic evidence review on aspirin conducted on behalf of the USPSTF [17] were integral to the parameter assumptions and model design in this study. This review incorporated the latest evidence on aspirin's potential benefits and harms in the primary prevention of CVD and CRC. With an assessment of high confidence, the review found evidence that daily low dose (≤100 mg) aspirin use reduces the risk of non-fatal myocardial infarction (Odds Ratio [OR]=0.88, 95% confidence interval [CI]: 0.78-1.00) and non-fatal stroke (OR=0.88, 95% CI: 0.80-0.96) and increases the risk of major GI bleeding (OR=1.58, 95% CI: 1.38-1.80) and intracerebral hemorrhage (OR=1.31, 95% CI: 1.11-1.54). With an assessment of moderate confidence, the review found no to very small potential benefit for aspirin reducing risk of CVD mortality (OR = 0.95, 95% CI: 0.86-1.05). With an assessment of insufficient evidence, the review found that aspirin may, after 10 years of use, reduce CRC incidence (OR=0.64, 95% CI: 0.52-0.79). The best balance of cardiovascular benefits to harms was reflected in daily aspirin doses of 100mg or less. There was not clear or compelling evidence that aspirin changes risk for fatal major GI bleeds. Nor was there evidence that aspirin effects differ for specific populations defined by age, sex, race/ethnicity, diabetes status, or ASCVD risk. Evidence review findings also were used to inform the data source for baseline levels of major GI bleeding risk, the selection of the ACC/AHA Pooled Cohort risk equation [45] to determine baseline ASCVD risk in the model, and a lack of evidence to inform patient preferences regarding use of aspirin or the effect on quality of life. The systematic review did not assess the evidence for aspirin use in secondary prevention of CVD.

Aspirin Benefits and Harms

All aspirin effects were modeled as relative risk modifications to the annual probability of an event. Model parameters for aspirin's effects when used for primary prevention are summarized in **Table 3**. CVD and bleeding odds ratios from the updated systematic evidence review [17] were derived from primary prevention trials with aspirin dosing of 100mg of aspirin per day or less [14-16, 52-59]. Due to the updated systematic review finding very low strength of evidence to support a reduction in CRC incidence from any dose of aspirin [17], this effect was not included in the base case analysis. The odds ratios for non-fatal myocardial infarction, non-fatal stroke, non-fatal major GI bleeding, and intracranial hemorrhage were used to approximate relative risks in the simulation base case analysis. The odds ratio confidence intervals informed the low and high bounds of the sensitivity analyses. The updated systematic review also informed effects on reducing CVD mortality and increasing fatal major GI bleed risk in sensitivity analyses. All CVD 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 may arise when the prevention or occurrence of an initial event alters the disease progression probabilities for subsequent events, as determined by the Framingham-derived risk equations internal to the model (**Technical Appendix Table 7**). Effects of aspirin after experiencing a non-fatal CVD event were derived from secondary prevention trials (**Technical Appendix Table 18**). In sensitivity analysis, the effect of aspirin on the risk of developing colorectal cancer was estimated from 4 randomized clinical trials [60-62] identified by the systematic evidence review [17]. Based on the evidence review, the potential reduction in CRC incidence risk in sensitivity analysis was applied only after 10 years of continuous use and was assumed to persist for up to 10 years after stopping aspirin.

Quality-of-Life Weights

Health utilities for the major outcomes affected by aspirin use were estimated using literature sources [63-72] and are summarized in **Table 4**. Living without a CVD condition or CRC was given a health utility of 0.87. All other health utility weights were applied multiplicatively to that baseline. Disutilities from myocardial infarction and major GI bleeding events were applied only during the year an event occurs. Quality-of-life reductions for congestive heart failure were included because, as a major sequela to myocardial infarction, incidence may be indirectly affected by aspirin use in the model. In the base case analysis, no disutility was applied to taking aspirin daily, but two alternative scenarios with aspirin disutilities were simulated in sensitivity analysis.

Outcomes

Quality-adjusted life years (QALYs) and life years were the primary outcomes of the simulations, with QALYs selected as the leading measure because aspirin benefits and harms can affect both fatal and non-fatal outcomes. Simulated events included (benefits) non-fatal ischemic stroke, non-fatal myocardial infarction, combined non-fatal CVD events (non-fatal myocardial infarction, ischemic stroke, and congestive heart failure), CVD deaths (excluding those due to intracranial hemorrhage), CRC incidence, and CRC deaths and (harms) fatal and non-fatal major GI bleeding and intracranial hemorrhage. Net event totals were calculated as: (non-fatal CVD events + CVD deaths + CRC cases) – (major GI bleeding and intracranial hemorrhage events), with CRC cases included only in sensitivity analysis.

Time Horizon

To account for measurement of all relevant benefits and harms related to the decision to use aspirin for primary prevention, the primary time horizon was a person's lifetime (KQ1 and KQ2). A 10-year time horizon was included to address CQ1.

Decision Analysis Base Case

All analyses assessed outcomes of a simulated population initially without a history of CVD routinely using aspirin for the primary prevention compared to the same simulated population, all

else held equal, not using aspirin for primary prevention (**Figure 1**). For secondary prevention (e.g., after a major CVD event), aspirin was initiated at contemporary rates of adherence in both simulation arms. To align with common clinical practice, aspirin use was discontinued permanently in both arms after any major GI bleeding or an intracranial hemorrhage event. 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.

Uncertainty and Sensitivity Analysis

Two sources of uncertainty were considered in this study: stochastic heterogeneity resulting from the variability in outcomes experienced by a randomly selected sample population and parameter uncertainty resulting from the imprecision of model parameter estimates [73]. Confidence intervals reflecting stochastic heterogeneity were estimated by bootstrap resampling the simulated population for each stratified outcome 100,000 times with replacement. Deterministic (one-way) sensitivity analyses addressing uncertainty in key parameters were conducted by replicating simulations with all other parameters, probabilities, and population characteristics held equal.

Model Validation

Baseline rates of CVD events are generated by the combination of population characteristics at model initiation, the model's estimation of the natural progression of CVD risk factors as individuals age, and the model's risk equations for disease. **Tables 5a** and **5b** presents prevalence rates of myocardial infarction and ischemic stroke generated by the model for a birth cohort starting at age 40 and compares these values to corresponding rates observed in NHANES data [40, 41] as a benchmark for the external validity of the ModelHealth: CVD natural history engine.

Chapter 3. Results

Population Characteristics

Cardiometabolic risk factors among the U.S. population aged 40-79 years have shifted modestly in the data underlying the 2021 decision model compared to the 2016 decision model (**Table 6**). The 2016 model was sourced by population data from 2001-2010, whereas the 2021 model is sourced by population data from 2015-2018. Notable changes include an overall increase in BMI (from 29.0 kg/m^2 in the 2016 model to 30.1 kg/m^2 in 2021 model) and diabetes (from 17% prevalence in the 2016 model to 20% prevalence in the 2021 model) and reductions in smoking prevalence in most population groups. The corresponding prevalence in 10-year ASCVD risk by age and sex is shown in **Tables 7a** and **7b**.

These population attributes define the characteristics of the age, sex, and 10-year ASCVD risk strata used by the decision model (**Table 8**). Among younger ages, the high 10-year ASCVD risk groups tend to have very high prevalence of current smoking and diabetes, which are key risk factors for reflecting above-average 10-year ASCVD risk at these ages. In contrast, among older ages, a low 10-year ASCVD risk is difficult to achieve among persons who currently smoke or have diabetes.

Figure 2 shows how the event rates over 10 years predicted by the model compare the event rates predicted by the 10-year ASCVD risk score. Perfect concordance in 10-year event rates is not necessarily expected. For example, this may be true for persons with higher ASCVD risk scores, for whom contemporary trends in prevention activities (such as hypertension management, statin use, smoking cessation) incorporated within the model may abate risks to a greater degree than observed in the cohort used to derive the 10-year risk scores. Similar patterns have been seen in other comparisons to event rates predicted by the ACC/AHA 10-year ASCVD Pooled Cohort risk scores [74-77].

Effect of Model Updates on Baseline Event Rates

Shifts in cardiometabolic risk factors and other dynamic factors within the model, such as updates to reflect contemporary blood pressure and cholesterol treatment guidelines and medication use rates, can change the predicted event rates within a population strata even without changes to the event risk calculations within the model. **Table 9** shows the proportional change in baseline event rates between the 2016 and 2021 decision models. For most CVD events, changes were within +/- 10 percent. Changes in event rates were greater for CRC and major GI bleeding outcomes due to the change in incidence and case-fatality rates for these outcomes. Changes in baseline event rates can affect the absolute magnitude of aspirin's effects, even if the relative risk modification of taking aspirin remains the same.

KQ1: What Is the Lifetime Net Benefit of Aspirin?

In the base case analyses, the predicted lifetime net benefit from the routine use of aspirin for primary prevention of CVD was positive in terms of net QALYs for men and women aged 40-59 years (ranging from 1.9 net QALYs per 1000 women aged 50-59 with 5% 10-year ASCVD risk to 66.2 net QALYs per 1000 men aged 40-49 years with 20% 10-year ASCVD risk**, Table 10**), but mixed for net life years, depending on 10-year ASCVD risk (ranging from -18.7 net life years per 1000 women aged 50-59 with 5% 10-year ASCVD risk to 52.4 net life years per 1000 men aged 40-49 years with 20% 10-year ASCVD risk). For men and women aged 60-69 years, net QALYs were positive at and above the 10% 10-year ASCVD risk threshold (as high as 19.1 net QALYs per 1000 women with 20% 10-year ASCVD risk), but negative for nearly all groups in terms of net life years (as low as -23.5 net life years per 1000 women with 5% 10-year ASCVD risk). For men and women aged 70-79, lifetime net benefits were negative in terms of both net QALYs and life years for nearly all risk groups considered.

Tables 11 and **12** show the lifetime differences in net events that underlie the lifetime net QALY and life year estimates shown in **Table 10**. Prevented non-fatal MIs and ischemic strokes—along with downstream reductions in subsequent events and CVD deaths—balanced against non-fatal major GI bleeds and intracranial hemorrhage events. Due to differences in underlying event rates, more non-fatal MIs than non-fatal ischemic strokes were prevented for men; whereas, the reduction of these two types of events was more evenly balanced for women. Women also have a longer life expectancy, which corresponds to a longer average risk exposure during which aspirin can intervene.

KQ2: How Does Stopping Aspirin Use Between the Ages of 65 and 85 Years Modify Lifetime Net Benefit of Aspirin?

Tables 13 and **14** show lifetime net benefits of using aspirin for discrete intervals defined by stopping ages between 65-85 years. At older ages, the quantitative balance of 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 rates of major GI bleeding and intracranial hemorrhage. For men (**Table 13**), the trends in net benefit across stopping ages were generally monotonic, typically increasing with later stopping ages for men aged 40-59 years and decreasing in terms of net life years for men aged 60-69 years. The trends for women (**Table 14**) were generally similar, but there were some exceptions, such as for net life years among women aged 50-59 years with 20% 10-year ASCVD risk where slightly higher net benefit (+1.5 net life years per 1000 women) was found when stopping aspirin at age 80 years compared to lifetime use.

CQ1: What Is the 10-Year Net Benefit of Aspirin Use?

At the point of using aspirin for 10 years, the decision model predicted that aspirin will produce net harm for most population groups over this limited time horizon (**Table 15**). Net life years were negative for all groups considered over 10 years, and although net QALYs were positive for some groups, in no cases did net QALYs gained exceed 2 per 1,000 persons over this

interval. **Tables 16** and **17** show that over the first 10 years of aspirin use, although non-fatal MIs and ischemic strokes were prevented, the number of increased intracranial hemorrhage mortality exceeded that of the reduced CVD mortality and these led to the generally small or negative accumulation of net benefit over this period. It is important to note that these results describe the expected net benefits during the first 10 years of aspirin use and do not account for the full lifetime net benefits that could be expected with taking aspirin for 10 years and then stopping.

Summary Findings

Tables 18a-18d combine the estimates of net QALYs and life years across both time horizons and stopping scenarios, reflecting the results for KQ1, KQ2, and CQ1 together. These side-by-side results show that for KQ2, stopping aspirin at some point compared to lifetime use generally results in lower net benefit in terms of lifetime net QALYs and life years. There are some exceptions, such as women aged 50-59 with 20% 10-year ASCVD risk, where the lifetime net life years were 17.9 per 1,000 persons when stopping aspirin at age 85 versus 16.9 per 1,000 persons with lifetime aspirin use. However, as in this case, the margins were typically small in both absolute and relative scales. Another exception is when net benefits were negative for lifetime use (such as -18.7 net life years per 1000 women aged 50-59 years with 5% 10-year ASCVD risk when starting aspirin), but less negative if stopped sooner (such as -4.9 net life years for the same group of women who instead stopped aspirin at age 65). In these cases, initiating aspirin was typically found to produce negative net benefit no matter the duration of use.

Tables 19a-19d present a qualitative summary of the decision analytic criteria. Ignoring the magnitude and uncertainty of the base case estimates, predicted lifetime net QALYs were positive for all risk groups considered among men and women initiating aspirin at ages 40-59 years and for all groups with ≥10% 10-year ASCVD risk among men and women aged 60-69 years. Lifetime net life years were likewise positive for most risk groups among men aged 40-59 years, but this was only the case at higher risk thresholds (≥7.5% to ≥15% 10-year ASCVD risk) for women at these ages. For men and women aged 60-69 years, lifetime net QALYs were positive for persons with ≥10% 10-year ASCVD risk, but lifetime net life years were negative for most risk groups at this age. For men and women initiating aspirin at ages 70-79 years, lifetime net QALYs and life years were negative for nearly all scenarios considered.

Sensitivity Analyses

Tables 20-24 show sensitivity analysis findings for lifetime use of aspirin across 19 scenarios for each age, sex, and 10-year ASCVD risk group in terms of lifetime net QALYs and life years. Although magnitudes vary, the proportional differences across sensitivity scenarios were generally similar across the 10-year ASCVD risk groups shown separately in each table. The largest and most notable impact on net benefit resulted from assumptions on whether aspirin when used for primary prevention reduces risk of CRC incidence (Scenario 3), reduces risk of CVD mortality (Scenario 4), or increases the risk of fatal major GI bleeds (Scenario 7). For example, for persons with 10% 10-year ASCVD risk, the inclusion of a 34% reduction in CRC incidence risk increased lifetime net QALYs and life years by as much as 67.6 and 68.1 per 1000

persons (among women aged 40-49 years), respectively. The inclusion of a 5 percent reduction in CVD mortality risk increased lifetime net QALYs and life years by as much as 77.6 and 92.7 per 1,000 persons, respectively (again, with the largest change among women aged 40-49 years). Conversely, when it was assumed that aspirin increases fatal major GI bleeding at the same rate as non-fatal major GI bleeds, lifetime net QALYs and life years decreased by as much as 23.4 and 27.3, respectively, per 1,000 persons (among men aged 50-59 years). Also notable is that assuming even a very small (about 0.1%) reduction in health utility as a result of taking aspirin daily lifetime can reduce lifetime net QALYs by as much as 24.1 per 1,000 persons (among women aged 40-49 years with 5% 10-year ASCVD risk).

Tables 25a-25d show the effect of assuming aspirin reduces CRC incidence by 34% across both time horizons and all stopping scenarios. Lifetime net QALYs and life years were positive for all scenarios. Over 10 years, net QALYs and life years were positive for all groups but one: net life years for women aged 60-69 years with 10% 10-year ASCVD risk. **Tables 26** and **27** show how the addition of prevented CRC cases and deaths contributed to additional net QALYs and life years.

Tables 28a-28d show the effect of assuming aspirin reduces CVD mortality incidence by 5% (including death associated with MI and ischemic stroke, but excluding intracranial hemorrhage) across both time horizons and all stopping scenarios. Net QALYs and life years over a lifetime and 10-year horizon were positive for all scenarios under this assumption. **Tables 29** and **30** show how the addition of aspirin prevented CVD deaths contributed to additional net QALYs and life years.

Tables 31a-31d show the effect of assuming aspirin increases the risk of fatal major GI bleeds by the same amount (OR = 1.58) as non-fatal bleeds. While not as dramatic as the two prior examples, this assumption reduced estimated lifetime net QALYs and life years across the board, resulting in many more population groups predicted to experience net harm. **Tables 32** and **33** show how the addition of aspirin-caused major GI bleeding deaths reduced net QALYs and life years.

Chapter 4. Discussion

The updated systematic evidence review conducted on behalf of the U.S. Preventive Services Taskforce produced new estimates of the effectiveness of low-dose aspirin in preventing non-fatal MI and ischemic stroke when using aspirin for primary prevention; however, these benefits must be weighed against the added risk of major GI bleeding and intracranial hemorrhage. This decision analysis used simulation modeling to combine findings from the updated systematic review with various data sources in order to quantify the potential balance of benefits and harms across clinically meaningful subgroups defined by age, sex, and 10-year ASCVD risk.

We found that the estimated net lifetime benefit of low dose aspirin varied by starting age, sex, and 10-year ASCVD risk level and that positive or negative assessments sometimes differed between the net QALY and net life year outcomes (KQ1). Overall, we found that men and women aged 40-59 and with ≥10% 10-year ASCVD risk were most likely to see lifetime benefit from using aspirin for primary prevention and that adults aged 70-79 with <= 20% 10-year ASCVD risk were most likely to experience net harm from starting aspirin. We found that stopping aspirin at 5-year intervals between ages 65-85 years generally showed consistent trends in net benefit that approached the net benefit with lifetime use, whether net beneficial or net harmful (KQ2). We also found that for most groups, aspirin may generate net harm during the first 10 years of use and for the groups that showed net benefit over this time horizon, it was small in magnitude (CQ1).

Importantly, our sensitivity analyses showed that our findings can be quite sensitive on certain assumptions for which evidence is insufficient to determine aspirin's effect—especially, regarding aspirin's effects on CRC incidence and fatal major GI bleeding. Various scenarios showed potential to predict widespread net benefit—or net harm—depending on assumptions made. Among these was moderate-to-large increase in net benefits when aspirin was assumed to reduce the risk of CVD mortality by 5%. Although this outcome was not statistically significant in the updated systematic evidence review (OR=0.95, 95% CI: 0.86-1.05), the point estimate of this effect is lower and has a narrower confidence interval compared to the corresponding finding in 2016 (relative risk=0.97, 95% CI: 0.85-1.10) [7]. If new aspirin study results reveal a clearer reduction in CVD mortality, the assessment of balance between benefits and harms could be meaningfully altered. Also notable was that 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.

Comparison to 2016 Decision Analysis Findings

Table 34 compares the main findings of the 2016 and 2021 decision analyses. Although qualitatively similar in terms of assessment of positive or negative net benefit, the magnitudes of lifetime net QALYs and life years are substantially smaller with the 2021 update.

The evidence informing this analysis diverged from the 2016 decision analysis in two important ways. First, while the underlying evidence and meta-analysis were similar, the updated review

determined the available evidence was insufficient to have confidence in the effect of low-dose aspirin on CRC incidence when used for primary prevention. As noted in our sensitivity analysis findings, this difference makes a meaningful qualitative and quantitative difference in the assessment of net benefit favorable to aspirin nonuse. 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 are substantially lower.

The second major distinction was in the assessment of evidence regarding aspirin's effect on fatal major GI bleeding events. Aspirin was assumed to have the same effect of increasing non-fatal and fatal major GI bleeds in the 2016 decision analysis. In the 2021 update, the assessment of evidence did not support this assumption. The updated systematic evidence review was not able to assess this outcome directly due to the very low number of fatal major GI bleeds observed in the aspirin primary prevention trials, but analyses by others have suggested there is no differential effect with aspirin use on fatal major GI bleeding [78, 79]. 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.

Limitations

The results highlight the practical significance of some of the remaining uncertainty about aspirin's effects when used for primary prevention—particularly, whether aspirin reduces the risk for CRC incidence and affects fatal major GI bleeding risks. Risk of major GI bleeding has been shown to be correlated with some cardiometabolic risk factors, such as blood pressure, current smoking, and diabetes, but insufficient data were available to stratify risks in the model on these factors. Accounting for these factors in estimating major GI bleeding incidence may result in benefits and harms maintaining more consistent proportions across ASCVD risk strata. In addition, due to limited alternatives, we relied on estimates of major GI bleeding rates without aspirin use that were derived from a New Zealand population [42], and it is not known how these rates compare to the U.S. population. However, our sensitivity analyses (**Tables 20-24**, Scenarios 8-11) generally indicate that variation in major GI bleeding rates without aspirin do not substantially affect the lifetime net QALY and life year estimates when aspirin is assumed to only increase risk for non-fatal GI bleeds. 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) [80, 81] 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 evidence from randomized controlled trials insufficient to determine these relationships [17]. Although differences in cardiometabolic risk factors by race/ethnicity are accounted for within the model, lack of racial/ethnic-specific validated CVD event risk prediction and bleeding rates limits the ability to robustly assess these potentially important differences. The results from CQ1 best inform persons with a short planning horizon (such as persons with a life expectancy ≤10 years) because these analyses did not account for the additional benefits that may accrue after 10 years, regardless of whether continuing or stopping use of aspirin from that point in time. Men and women aged 40-49 years and 70-79 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 two new trials since 2016 did

include these younger (A Study of Cardiovascular Events in Diabetes, ASCEND [14]) and older age (Aspirin in Reducing Events in the Elderly, ASPREE [16]) groups. Findings depend in part on the natural history of cardiometabolic risk factors and event rates predicted by the model, which may inaccurately predict future outcomes for any given population group. Sensitivity analyses assuming systematically higher and lower baseline CVD event rates (**Tables 20-24**, Scenarios 5 and 6) are intended to inform how estimates would differ on this basis. While sensitivity analyses can help us understand the importance of limitations among model inputs and model validation provides assurance that the model structure is reasonable, replication in other models can further inform reliability of estimates.

Our findings are not generalizable to all primary care patients. The simulation and systematic review on which it is based does not address aspirin use for secondary prevention of CVD. We also did not assess net benefits in patients with more than a 20% 10-year risk of a CVD event due to the limited number of aspirin trials reporting participants above this risk threshold. Furthermore, we did not assess net harms in individuals with recent use of non-aspirin nonsteroidal anti-inflammatory drugs, corticosteroids, or selective serotonin reuptake inhibitors, each of which may increase the risk of major GI bleeding or intracranial hemorrhage [48]. Finally, neither the systematic review [17] nor this decision analysis assessed the potential effect of aspirin on patients with high risk for CRC due to Lynch Syndrome [82].

Conclusions and Future Research Needs

These results indicate that several population groups may benefit from taking aspirin for the primary prevention of CVD, but magnitudes of net benefit were smaller in this update compared to the last USPSTF assessment of net benefits in 2016. Findings clearly suggest that the quality of life benefits from using aspirin may be considerably diminished among persons who dislike taking routine medications. Most challenging for decisions that policymakers, clinicians, and patients will make about use of aspirin for primary prevention is the substantial variation in net benefit found when varying key assumptions lack certainty with the current evidence. Future research should focus on further investigating aspirin's effect on CRC incidence and death, including the potential for delayed effects on these outcomes, and fatal major GI bleeding, as well as comprehensive risk assessment for major GI bleeding, similar to risk calculators for CVD risk. Additional evidence regarding whether or not aspirin effects differ by age, sex, 10-year CVD risk, diabetes status, and race/ethnicity may help identify patients who are more likely to benefit than be harmed by low-dose aspirin.

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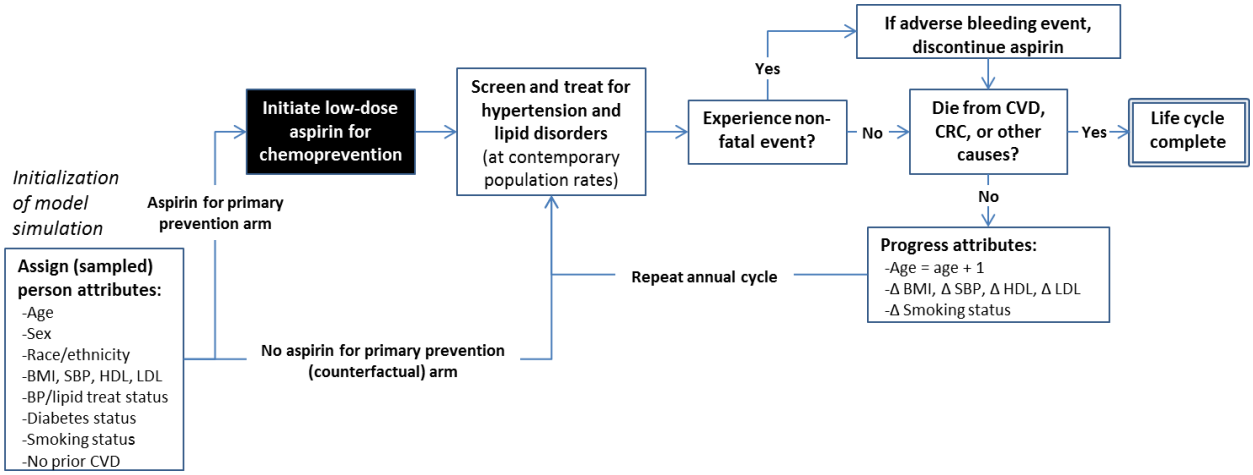
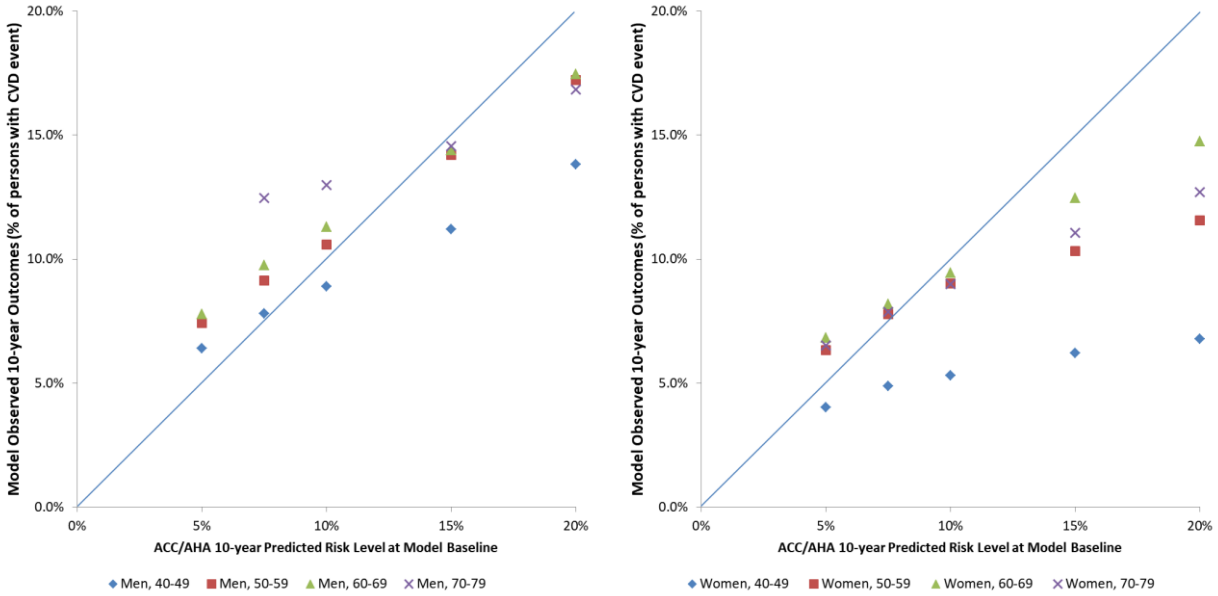
Figure 1. Decision Analysis Design



Notes: Figure adapted from Dehmer et al. [13]. BMI = body mass index; SBP = systolic blood pressure; HDL = high-density lipoprotein; LDL = low-density lipoprotein; BP = blood pressure; CVD=cardiovascular disease; CRC=colorectal cancer.

Figure 2. Comparison of 10-Year Model Outcomes With ASCVD 10-Year Risk Among Men and Women Aged 40-79



Notes: ASCVD = atherosclerotic cardiovascular disease. The y-axis represents the percent of persons observed having their first hard ASCVD event (non-fatal MI, non-fatal stroke, or coronary death) in a ModelHealth: CVD simulated cohort with a 10-year ACC/AHA baseline risk [45] specified in x-axis. The 45-degree line indicates perfect concordance in 10-year outcomes predicted by the ACC/AHA risk calculator and those observed in a simulated population. Points above the 45-degree line indicate that 10-year event rates simulated in the model are above the rate indicated by 10-year ACC/AHA risk; points below the 45-degree line indicate that 10-year event rates simulated in the model are below the rate indicated by 10-year ACC/AHA risk. Similar patterns have been seen in other comparisons [74-77].

Table 1. Summary of Key and Contextual Questions

Question	Example Clinical Scenario	Population	Outcomes	Outcome Time Horizon	Duration of Therapy or Stopping Age
KQ1	Patient: 55 year old female without prior CVD or elevated bleeding risk and a 10% risk of a hard atherosclerotic event in the next 10 years Question: If starting aspirin now, with a plan for continued lifetime use unless contraindicated, will the expected lifelong benefits exceed the harms?	Age: 40-49, 50-59, 60-69, and 70-79 years old Sex: female or male 10-year ASCVD risk: 5%, 7.5%, 10%, 15%, and 20%	QALYs§; Net life years; Events†	Lifetime	Lifetime therapy or until adverse event or death
KQ2	Patient: 55 year old female without prior CVD or elevated bleeding risk and a 10% risk of a hard atherosclerotic event in the next 10 years Question: If starting aspirin now, would the expected lifelong net benefit of using aspirin be higher or lower, compared to lifetime use, if planning to stop therapy at age 75?	Age: 40-49, 50-59, 60-69, and 70-79 years old Sex: female or male 10-year ASCVD risk: 5%, 7.5%, 10%, 15%, and 20%	QALYs§; Net life years; Events†	Lifetime	5-year future stopping age intervals from 65 to 85 years vs. lifetime therapy (or until adverse event or death)
CQ1	Patient: 55 year old female without prior CVD or elevated bleeding risk and a 10% risk of a hard atherosclerotic event in the next 10 years Question: If starting aspirin now, with a plan for continued lifetime use unless contraindicated, will the benefits exceed the harms within 10 years?	Age: 40-49, 50-59, 60-69, and 70-79 years old Sex: female or male 10-year ASCVD risk: 5%, 7.5%, 10%, 15%, and 20%	QALYs§; Net life years; Events†	10 years	First 10 years of lifetime therapy or until adverse event or death

§ Quality-adjusted life years (primary outcome)

†Non-fatal myocardial infarction, non-fatal ischemic stroke, hospitalization for congestive heart failure (as a major sequelae to MI), cardiovascular disease-related death (excluding due to intracranial hemorrhage), colorectal cancer cases, colorectal cancer death, gastrointestinal bleeding, gastrointestinal bleeding death, intracranial hemorrhage, intracranial hemorrhage death

Table 2a. Annual Fatal Major GI Bleeding Incidence Rates in Non-Aspirin Users

	Base Case[a]	Low Bound[b]	High Bound[c]
Men			
Age 40-49y	0.002%	0.000%	0.004%
Age 50-59y	0.007%	0.003%	0.011%
Age 60-69y	0.016%	0.007%	0.025%
Age 70-79y	0.021%	0.000%	0.041%
Age 80+y	0.041%[d]	0.021%[e]	0.082%[f]
Women			
Age 40-49y	0.001%	0.000%	0.003%
Age 50-59y	0.004%	0.001%	0.007%
Age 60-69y	0.008%	0.003%	0.014%
Age 70-79y	0.015%	0.000%	0.029%
Age 80+y	0.029%[d]	0.015%[e]	0.058%[f]

Notes: Baseline major GI bleeding risks are the probabilities of developing a major GI bleed, without aspirin, by age and sex. a) for ages 40-70 years, major GI bleeding incidence rates in the "nonmedication cohort" from Selak et al. [42]; b) for ages 40-79 years, lower threshold of 95% confidence interval; c) for ages 40-79 years, lower threshold of 95% confidence interval; d) based on the upper threshold of the 95% confidence interval for ages 70-79 years; e) assumes half the base case; f) assumes double the base rate; low and high bounds are for sensitivity analyses.

Table 2b. Annual Non-Fatal Major GI Bleeding Incidence Rates in Non-Aspirin Users

	Base Case[a]	Low Bound[b]	High Bound[c]
Men			
Age 40-49y	0.14%	0.12%	0.15%
Age 50-59y	0.16%	0.14%	0.18%
Age 60-69y	0.24%	0.21%	0.28%
Age70-79y	0.37%	0.28%	0.45%
Age 80+y	0.45%[d]	0.23%[e]	0.90%[f]
Women			
Age 40-49y	0.10%	0.08%	0.12%
Age 50-59y	0.13%	0.12%	0.15%
Age 60-69y	0.20%	0.17%	0.22%
Age 70-79y	0.29%	0.23%	0.36%
Age 80+y	0.36%[d]	0.18%[e]	0.72%[f]

Notes: Baseline major GI bleeding risks are the probabilities of developing a major GI bleed, without aspirin, by age and sex. a) for ages 40-70 years, major GI bleeding incidence rates in the "nonmedication cohort" from Selak et al. [42]; b) for ages 40-79 years, lower threshold of 95% confidence interval; c) for ages 40-79 years, lower threshold of 95% confidence interval; d) based on the upper threshold of the 95% confidence interval for ages 70-79 years; e) assumes half the base case; f) assumes double the base rate; low and high bounds are for sensitivity analyses.

Table 3. Effects of Using Low-Dose (≤100 mg/d) Aspirin for Primary Prevention

Parameter	Base case	Worst Case	Best Case	Other values	Source
Benefits					
CRC incidence (>10 years), odds ratio	1.00			0.64	[17]
CVD death, odds ratio	1.00			0.95	[17]
Non-fatal ischemic stroke, odds ratio	0.88	1.00	0.78		[17]
Non-fatal myocardial infarction, odds ratio	0.88	0.96	0.80		[17]
Harms					
Intracranial hemorrhage, odds ratio	1.31	1.54	1.11		[17]
Fatal major GI bleeding, odds ratio	1.00			1.58	Assumed, [17]
Non-fatal major GI bleeding, odds ratio	1.58	1.80	1.38		[17]

Notes: CRC=colorectal cancer; CVD=cardiovascular disease; GI=gastrointestinal.

Table 4. Health Utility Weights

	First year/new event	Ongoing quality-of-life	Source
Baseline health utility weight			
No CVD conditions		0.87	[63, 65-68]
Relative health utility weight			
Congestive heart failure	0.79	0.79	[64, 66-68, 72]
GI bleeding (major)	0.91	1.00	[72]
Hemorrhagic stroke	0.60	0.60	[63-67, 71, 72]
Ischemic stroke	0.77	0.77	[63-67, 72]
Myocardial Infarction	0.86	1.00	[63, 64, 66, 68, 72]
Taking aspirin daily, base case		1.00	Assumption
Relative health utility weights for sensitivity analysis scenarios			
Colorectal cancer	0.70	0.70	[69, 70]
Taking aspirin, sensitivity #1		0.999	Assumption
Taking aspirin, sensitivity #2		0.995	Assumption

Notes: CVD=cardiovascular disease; GI=gastrointestinal. All health utility weights are applied multiplicatively to the baseline health utility weight. The quality-of-life reduction for colorectal cancer is applied for up to five years in the case of non-fatal episodes. First year/new event health utility weights are applied during the year of an incidence event or first year of disease onset; ongoing health utilities are applied in subsequent years.

Table 5a. Comparison of ModelHealth: CVD Myocardial Infarction Event Rates With National Prevalence Estimates

	NHANES (2015-2018)	ModelHealth: CVD
Men		
Age 40-49	1.2%	2.2%
Age 50-59	5.0%	5.3%
Age 60-69	10.3%	10.3%
Age 70-79	16.8%	16.0%
Women		
Age 40-49	0.8%	1.0%
Age 50-59	2.9%	2.0%
Age 60-69	4.3%	3.9%
Age 70-79	4.8%	6.2%

Notes: NHANES=National Health and Nutrition Examination Survey; CVD=cardiovascular disease. This table compares myocardial infarction prevalence at various ages between NHANES 2015-2018 [40, 41] combined data and results from the ModelHealth: CVD model. Event rates indicate the percentage of the respective population with a history of event. The model run represented here is based on a birth cohort, starting at age 40, 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 datasets, outcomes are calculated for the age range from NHANES and the mid-point of the age range from the ModelHealth: CVD output; this methodological difference can explain some small discrepancies.

Table 5b. Comparison of ModelHealth: CVD Stroke Event Rates With National Prevalence Estimates

	NHANES (2015-2018)	ModelHealth: CVD
Men		
Age 40-49	1.7%	1.4%
Age 50-59	2.6%	2.0%
Age 60-69	6.2%	3.6%
Age 70-79	7.0%	6.5%
Women		
Age 40-49	1.4%	0.9%
Age 50-59	3.8%	1.5%
Age 60-69	3.7%	2.9%
Age 70-79	8.3%	5.6%

Notes: NHANES=National Health and Nutrition Examination Survey; CVD=cardiovascular disease. This table compares myocardial infarction prevalence at various ages between NHANES 2015-2018 [40, 41] combined data and results from the ModelHealth: CVD model. Event rates indicate the percentage of the respective population with a history of event. The model run represented here is based on a birth cohort, starting at age 40, 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 datasets, outcomes are calculated for the age range from NHANES and the mid-point of the age range from the ModelHealth: CVD output; this methodological difference can explain some small discrepancies.

Table 6. U.S. Population Cardiometabolic Risk Factors Used in 2021 and 2016 Aspirin Decision Models

	2016 Model	2021 Model
BMI (mean, kg/m^2)	29.0	30.1
% overweight	73%	77%
% obese	37%	44%
SBP (mean, mm Hg)	126.0	127.0
% hypertension	45%	49%
% over goal (≥140 mm Hg)	47%	44%
% using medications	30%	33%
Total cholesterol (mean, mg/dL)	206.0	197.4
LDL (mean, mg/dL)	121.4	117.3
HDL (mean, mg/dL)	53.9	55.2
% using medications	20%	25%
% with diabetes	17%	20%
% with previous CVD	11%	12%
% current smokers		
Men, 40-49y	26%	18%
Men, 50-59y	21%	20%
Men, 60-69y	19%	15%
Men, 70-79y	9%	9%
Women, 40-49y	21%	13%
Women, 50-59y	19%	16%
Women, 60-69y	15%	12%
Women, 70-79y	8%	8%

Notes: BMI = body mass index; overweight = BMI ≥ 25 kg/m^2; obese = BMI ≥ 25 kg/m^2; SBP = systolic blood pressure; LDL = low-density lipoprotein; HDL = high-density lipoprotein. Data are presented for adults aged 40-79 years. For the 2016 model, all data but smoking were derived from 2001-2010 NHANES [83-87] data, and smoking status was derived from 2007 NHIS data [88]. For the 2021 model, all data but smoking were derived from 20015-2018 NHANES data [40, 41], and smoking status was derived from 2017-2018 NHIS data [47].

Table 7a. Estimated Prevalence of 10-Year ASCVD Risk by Age Among Men

ACC/AHA 10-Year ASVD Risk %	Age 40-49y	Age 50-59y	Age 60-69y	Age 70-79y
0	0.7	<0.1	<0.1	<0.1
1	20.7	0.1	<0.1	<0.1
2	21.8	4.9	<0.1	<0.1
3	20.1	5.8	<0.1	<0.1
4	10.9	8.0	<0.1	<0.1
5	7.9	13.0	0.3	<0.1
6	3.9	11.0	1.0	<0.1
7	4.6	12.4	3.7	<0.1
8	1.9	6.4	7.1	0.3
9	1.9	8.1	7.4	<0.1
10	1.4	6.8	5.8	<0.1
11	0.2	4.6	6.4	0.3
12	0.2	2.6	4.5	0.5
13	0.6	2.6	8.4	2.9
14	0.2	1.6	6.6	2.2
15	<0.1	1.9	4.6	0.7
16	0.5	1.8	4.1	2.3
17	<0.1	1.3	4.0	4.5
18	0.1	0.6	4.0	4.4
19	0.7	0.5	2.8	3.4
20	0.2	0.8	3.3	4.9
0-20	98.8	94.7	74.1	26.2
7.5*	2.1	11.4	3.6	<0.1

Notes: ACC/AHA=American College of Cardiology/American Heart Association; ASCVD=atherosclerotic cardiovascular disease; CVD=cardiovascular disease; y=years. Data derived by applying the AHA/ACC risk calculator to 2015-2018 NHANES data [40, 41]. The 0-20% totals do not sum to 100% because some CVD-free persons have a risk greater than 20%. Risk levels are rounded to the nearest integer. * The 7.5% risk category is included among the decision analysis population groups and is calculated as 7-8% ACC/AHA 10-year risk.

Table 7b. Estimated Prevalence of 10-Year ASCVD Risk by Age Among Women

ACC/AHA 10-Year ASVD Risk %	Age 40-49y	Age 50-59y	Age 60-69y	Age 70-79y
0	29.0	0.7	<0.1	<0.1
1	45.6	25.0	<0.1	<0.1
2	11.8	26.1	7.3	<0.1
3	5.2	14.3	7.6	<0.1
4	1.8	10.1	7.9	<0.1
5	1.9	6.2	14.6	<0.1
6	1.2	3.3	9.0	0.8
7	0.5	3.1	11.1	1.4
8	1.0	1.8	8.4	1.0
9	0.4	2.7	4.7	3.8
10	0.3	1.1	4.8	1.7
11	0.2	0.9	5.3	2.2
12	<0.1	1.0	4.2	2.3
13	<0.1	0.1	1.9	2.2
14	0.4	0.8	1.6	6.7
15	<0.1	1.0	1.3	3.9
16	<0.1	0.1	1.3	3.5
17	0.1	0.2	2.7	3.3
18	<0.1	0.1	0.6	5.5
19	<0.1	0.4	1.0	4.8
20	0.3	0.2	0.6	7.7
0-20	99.8	99.2	96.0	50.8
7.5*	0.7	2.3	9.3	0.8

Notes: ACC/AHA=American College of Cardiology/American Heart Association; ASCVD=atherosclerotic cardiovascular disease; CVD=cardiovascular disease; y=years. Data derived by applying the AHA/ACC risk calculator to 2015-2018 NHANES data [40, 41]. The 0-20% totals do not sum to 100% because some CVD-free persons have a risk greater than 20%. Risk levels are rounded to the nearest integer. * The 7.5% risk category is included among the decision analysis population groups and is calculated as 7-8% ACC/AHA 10-year risk.

Table 8. Mean CVD Risk Characteristics by Age, Sex, and 10-Year ASCVD Risk Strata in Decision Model Population

	BMI (kg/m^2)	SBP (mmHg)	LDL (mg/dL)	HDL (mg/dL)	Treated BP (%)	Diabetes (%)	Current Smoking (%)
Men, Age 40-49y							
5% 10-year ASCVD risk	30.9	127.1	140.2	42.4	17%	18%	29%
7.5% 10-year ASCVD risk	31.5	128.8	142.5	41.2	25%	30%	51%
10% 10-year ASCVD risk	31.9	130.9	147.1	39.3	27%	37%	63%
15% 10-year ASCVD risk	32.7	133.6	151.3	37.6	39%	58%	78%
20% 10-year ASCVD risk	33.2	136.9	155.2	35.6	43%	76%	86%
Women, Age 40-49y							
5% 10-year ASCVD risk	35.2	129.3	136.8	42.3	35%	36%	61%
7.5% 10-year ASCVD risk	36.2	132.2	139.4	40.3	43%	50%	69%
10% 10-year ASCVD risk	36.9	134.6	140.8	39.2	49%	62%	70%
15% 10-year ASCVD risk	37.6	139.4	142.9	36.8	62%	76%	66%
20% 10-year ASCVD risk	37.8	143.7	143.8	35.6	70%	82%	64%
Men, Age 50-59y							
5% 10-year ASCVD risk	29.3	123.9	118.4	53.6	17%	3%	5%
7.5% 10-year ASCVD risk	30.0	128.8	127.9	48.6	24%	10%	15%
10% 10-year ASCVD risk	30.6	131.2	132.2	45.7	31%	19%	25%
15% 10-year ASCVD risk	31.7	135.7	137.1	41.3	40%	44%	38%
20% 10-year ASCVD risk	32.5	138.1	139.1	38.6	48%	64%	47%
Women, Age 50-59y							
5% 10-year ASCVD risk	32.0	133.3	136.4	54.8	40%	18%	39%
7.5% 10-year ASCVD risk	33.8	137.2	138.3	50.7	49%	44%	42%
10% 10-year ASCVD risk	34.6	140.0	139.4	49.1	56%	55%	47%
15% 10-year ASCVD risk	35.6	144.1	140.8	46.9	65%	69%	56%
20% 10-year ASCVD risk	36.4	147.1	141.2	45.7	72%	81%	56%
Men, Age 60-69y							
5% 10-year ASCVD risk	27.3	108.9	87.2	66.3	10%	0%	0%
7.5% 10-year ASCVD risk	28.0	118.7	101.6	58.8	17%	0%	3%
10% 10-year ASCVD risk	28.5	123.8	109.4	55.0	25%	2%	6%
15% 10-year ASCVD risk	29.3	130.8	118.9	50.2	41%	10%	16%
20% 10-year ASCVD risk	30.1	136.0	123.7	46.6	50%	28%	23%
Women, Age 60-69y							
5% 10-year ASCVD risk	30.1	127.4	120.0	63.5	30%	5%	3%
7.5% 10-year ASCVD risk	30.8	133.3	124.2	61.2	44%	10%	8%
10% 10-year ASCVD risk	31.7	136.8	125.6	59.3	53%	24%	12%
15% 10-year ASCVD risk	33.3	142.2	127.1	56.0	64%	52%	20%
20% 10-year ASCVD risk	34.2	145.6	128.0	54.2	72%	68%	28%
Men, Age 70-79y							
7.5% 10-year ASCVD risk	25.6	101.7	92.0	67.5	0%	0%	0%
10% 10-year ASCVD risk	26.1	107.8	91.8	66.7	3%	0%	0%
15% 10-year ASCVD risk	27.1	116.3	98.1	61.9	21%	1%	5%
20% 10-year ASCVD risk	27.8	124.8	106.0	57.5	35%	3%	8%
Women, Age 70-79y							
5% 10-year ASCVD risk	27.1	95.0	105.0	70.9	1%	0%	0%
7.5% 10-year ASCVD risk	28.0	108.9	118.7	66.1	12%	0%	0%
10% 10-year ASCVD risk	28.4	118.5	122.4	64.6	22%	0%	1%
15% 10-year ASCVD risk	29.2	130.2	127.5	62.7	49%	4%	4%
20% 10-year ASCVD risk	29.5	135.7	128.8	62.3	59%	11%	6%

Notes: BMI = body mass index; SBP = systolic blood pressure; LDL = low-density lipoprotein cholesterol; HDL = high-density lipoprotein cholesterol; BP = blood pressure; CVD = cardiovascular disease; ASCVD = atherosclerotic cardiovascular disease; y=years. All values are population means.

Table 9. Proportional Change in Base Model Event Rates With 2021 Updates Compared to 2016 Decision Model

	Life Years	QALYs	Non-fatal Myocardial Infarction	Non-fatal Ischemic Stroke	CVD	CVD Death	Hemorrhagic Stroke	Hemorrhagic Stroke Death	Colorectal Cancer	Colorectal Cancer Deaths	Major GI Bleeds	Major GI Bleed Death
Men, Initiation age 40-49y												
5% 10-yr ASCVD Risk	3%	3%	8%	6%	9%	11%	-7%	-7%	-8%	57%	16%	-7%
10% 10-yr ASCVD Risk	2%	2%	4%	3%	4%	8%	-12%	-11%	-9%	59%	13%	-4%
15% 10-yr ASCVD Risk	0%	0%	9%	8%	10%	13%	-6%	-5%	-6%	62%	8%	-20%
20% 10-yr ASCVD Risk	-1%	-1%	11%	8%	10%	13%	-13%	-11%	-9%	58%	15%	-6%
Women, Initiation age 40-49y												
5% 10-yr ASCVD Risk	3%	3%	-1%	-5%	-1%	-1%	-10%	-10%	-19%	22%	44%	-19%
10% 10-yr ASCVD Risk	3%	3%	-1%	-2%	0%	1%	-17%	-15%	-17%	33%	47%	-20%
15% 10-yr ASCVD Risk	2%	2%	1%	-3%	3%	1%	-21%	-21%	-16%	47%	40%	-28%
20% 10-yr ASCVD Risk	2%	2%	-3%	-3%	0%	1%	-17%	-17%	-16%	35%	43%	-21%
Men, Initiation age 50-59y												
5% 10-yr ASCVD Risk	4%	4%	3%	5%	6%	9%	-6%	-5%	-20%	30%	9%	-15%
10% 10-yr ASCVD Risk	4%	4%	-2%	-1%	1%	6%	-16%	-16%	-18%	45%	8%	-24%
15% 10-yr ASCVD Risk	3%	3%	1%	3%	3%	6%	-13%	-15%	-19%	46%	4%	-8%
20% 10-yr ASCVD Risk	3%	3%	1%	4%	4%	7%	-11%	-11%	-13%	61%	8%	-14%
Women, Initiation age 50-59y												
5% 10-yr ASCVD Risk	2%	2%	-9%	-11%	-8%	-9%	-11%	-12%	-21%	25%	28%	-36%
10% 10-yr ASCVD Risk	3%	3%	-8%	-8%	-3%	-2%	-17%	-17%	-26%	17%	33%	-34%
15% 10-yr ASCVD Risk	4%	5%	-9%	-8%	-5%	-4%	-20%	-20%	-23%	24%	36%	-24%
20% 10-yr ASCVD Risk	3%	3%	-5%	-4%	-2%	-3%	-21%	-20%	-23%	22%	38%	-12%
Men, Initiation age 60-69y												
5% 10-yr ASCVD Risk	7%	7%	5%	6%	7%	8%	-2%	-3%	-24%	36%	-1%	-33%
10% 10-yr ASCVD Risk	6%	6%	3%	4%	5%	5%	-10%	-10%	-24%	28%	-1%	-34%
15% 10-yr ASCVD Risk	4%	4%	-6%	0%	-2%	1%	-8%	-8%	-22%	34%	-1%	-27%
20% 10-yr ASCVD Risk	2%	3%	-2%	-2%	0%	2%	-12%	-13%	-20%	42%	-3%	-34%
Women, Initiation age 60-69y												
5% 10-yr ASCVD Risk	1%	2%	-10%	-8%	-9%	-7%	-14%	-17%	-25%	14%	23%	-43%
10% 10-yr ASCVD Risk	1%	1%	-12%	-11%	-8%	-8%	-16%	-17%	-25%	21%	25%	-36%
15% 10-yr ASCVD Risk	0%	0%	-7%	-9%	-4%	-4%	-21%	-20%	-21%	20%	22%	-39%
20% 10-yr ASCVD Risk	0%	0%	-6%	-4%	-2%	-3%	-24%	-24%	-21%	25%	19%	-45%
Men, Initiation age 70-79y												
10% 10-yr ASCVD Risk	4%	4%	-1%	2%	-1%	2%	-9%	-12%	-29%	27%	-8%	-54%
15% 10-yr ASCVD Risk	5%	6%	-1%	2%	0%	2%	-3%	-4%	-27%	23%	-8%	-48%
20% 10-yr ASCVD Risk	6%	6%	-1%	-3%	0%	2%	-3%	-3%	-29%	20%	-10%	-56%
Women, Initiation age 70-79y												
5% 10-yr ASCVD Risk	0%	0%	-5%	-7%	-7%	-5%	5%	-1%	-27%	4%	20%	-48%
10% 10-yr ASCVD Risk	2%	3%	-10%	-10%	-10%	-10%	-7%	-7%	-25%	11%	20%	-44%
15% 10-yr ASCVD Risk	0%	1%	-12%	-12%	-11%	-11%	-7%	-9%	-28%	5%	13%	-50%
20% 10-yr ASCVD Risk	-2%	-2%	-12%	-13%	-12%	-12%	-13%	-18%	-29%	6%	11%	-52%

Notes: QALYs = quality-adjusted life years, CVD = cardiovascular disease, GI = gastrointestinal, ASCVD = atherosclerotic cardiovascular disease, y = years. The table shows the proportional change in event rates in the 2021 decision model compared to the 2016 decision model.

Table 10. Lifetime Net Benefit of Aspirin for Men and Women With Lifetime Use (KQ1)

	Initiation Age 40-49y	Initiation Age Age 50-59y	Initiation Age Age 60-69y	Initiation Age Age 70-79y
Men, Net QALYs per 1000 persons (95% Confidence Interval)				
5% 10y ASCVD Risk	23.1 (15.8 to 30.4)	5.7 (-0.0 to 11.3)	-1.8 (-6.4 to 2.9)	N/A
7.5% 10y ASCVD Risk	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% 10y ASCVD Risk	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% 10y ASCVD Risk	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% 10y ASCVD Risk	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)
Men, Net Life Years per 1000 persons (95% Confidence Interval)				
5% 10y ASCVD Risk	10.6 (2.9 to 18.3)	-5.4 (-11.7 to 0.8)	-11.0 (-16.0 to -6.1)	N/A
7.5% 10y ASCVD Risk	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% 10y ASCVD Risk	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% 10y ASCVD Risk	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% 10y ASCVD Risk	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)
Women, Net QALYs per 1000 persons (95% Confidence Interval)				
5% 10y ASCVD Risk	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% 10y ASCVD Risk	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% 10y ASCVD Risk	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% 10y ASCVD Risk	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% 10y ASCVD Risk	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)
Women, Net Life Years per 1000 persons (95% Confidence Interval)				
5% 10y ASCVD Risk	-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% 10y ASCVD Risk	-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% 10y ASCVD Risk	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% 10y ASCVD Risk	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% 10y ASCVD Risk	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)

Notes: ASCVD=atherosclerotic cardiovascular disease; QALY=quality-adjusted life year; N/A=not applicable; y=years. The 10-year ASCVD risk levels are based on the ACC/AHA risk calculator and refer to a person's risk at model baseline/initiation. Risk levels are rounded to the nearest threshold (+/- 0.5%). Results reflect the difference between universal adoption of aspirin for primary prevention versus zero adoption. All else is held equal. Confidence intervals reflect stochastic heterogeneity and were calculated by bootstrap sampling with replacement 100,000 times from within the modeled population sample.

Table 11. Lifetime Net Events of Aspirin for Men With Lifetime Use (KQ1)

	Benefits from aspirin (Prevented events per 1,000 persons)						Harms from aspirin (Incurred events per 1,000 persons)				Net Balance (Benefits - harms)		
10-yr ASCVD Risk (%)	Myocardial infarction	Ischemic stroke	Non-fatal CVD Events	CVD Deaths	CRC Cases	CRC Deaths	Major GI Bleeds	Major GI Bleed Deaths	Intracranial Hemorrhage	Intracranial Hemorrhage Deaths	Net QALYs	Net Life Years	Net Events Prevented
Men, Initiation Age 40-49 years													
5	17.0	6.1	28.3	4.6	-	-	31.5	0.0	2.9	2.6	23.1	10.6	-4.2
7.5	19.6	6.6	32.4	4.7	-	-	30.3	0.0	2.5	2.3	29.1	16.2	1.9
10	20.5	7.0	34.0	5.2	-	-	29.7	0.0	2.3	2.0	48.0	36.1	5.1
15	22.5	8.0	37.6	5.5	-	-	27.1	0.0	2.5	2.3	52.3	37.9	11.1
20	24.9	7.7	40.3	6.2	-	-	24.7	0.0	2.4	2.2	66.2	52.4	16.9
Men, Initiation Age 50-59 years													
5	14.3	6.0	24.7	3.6	-	-	32.6	0.0	3.1	2.8	5.7	-5.4	-10.1
7.5	15.2	6.9	26.4	3.8	-	-	31.0	0.0	3.0	2.8	12.5	0.4	-6.6
10	15.5	7.3	28.2	4.1	-	-	29.8	0.0	2.8	2.5	18.0	4.2	-2.9
15	18.8	7.6	32.4	4.6	-	-	27.7	0.0	2.6	2.4	32.3	18.6	4.1
20	20.5	8.5	36.0	5.2	-	-	24.8	0.0	2.1	1.9	48.4	33.9	12.3
Men, Initiation Age 60-69 years													
5	10.1	6.0	19.0	2.7	-	-	32.9	0.0	3.0	2.7	-1.8	-11.0	-17.0
7.5	11.3	6.1	20.5	2.6	-	-	31.0	0.0	2.8	2.4	2.6	-6.7	-13.1
10	12.7	6.0	22.5	3.3	-	-	30.2	0.0	2.9	2.6	7.0	-3.0	-9.9
15	12.3	6.4	22.3	3.3	-	-	28.0	0.0	3.0	2.6	8.3	-2.2	-7.9
20	14.8	7.2	26.8	4.1	-	-	26.4	0.0	2.8	2.5	16.3	4.9	-0.8
Men, Initiation Age 70-79 years													
5	-	-	-	-	-	-	-	-	-	-	-	-	-
7.5	8.0	4.6	14.9	1.8	-	-	27.9	0.0	2.6	2.3	-4.6	-10.1	-16.1
10	8.9	5.1	16.4	2.2	-	-	28.2	0.0	2.6	2.2	-1.1	-6.9	-14.4
15	8.9	5.1	16.2	2.1	-	-	27.4	0.0	2.6	2.1	-1.9	-7.6	-13.7
20	9.7	5.5	17.6	2.0	-	-	25.7	0.0	2.6	2.1	0.9	-5.5	-10.9

Notes: ASCVD=atherosclerotic cardiovascular disease; CVD=cardiovascular disease; CRC=colorectal cancer; GI=gastrointestinal; QALY=quality-adjusted life year. The 10-year ASCVD risk levels are based on the ACC/AHA risk calculator and refer to a person's risk at model baseline/initiation. Risk levels are rounded to the nearest threshold (+/- 0.5%). Results reflect the difference between universal adoption of aspirin for primary prevention versus zero adoption; all else is held equal. MI and ischemic stroke events are non-fatal. The non-fatal CVD event column combines non-fatal 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: (Non-fatal CVD events + CVD deaths + CRC cases) – (Major GI bleeds + intracranial hemorrhage). In the base case, there was no effect of aspirin use on CRC incidence.

Table 12. Lifetime Net Events of Aspirin for Women With Lifetime Use (KQ1)

	Benefits from aspirin (Prevented events per 1,000 persons)						Harms from aspirin (Incurred events per 1,000 persons)				Net Balance (Benefits - harms)		
10-yr ASCVD Risk (%)	Myocardial infarction	Ischemic stroke	Non-fatal CVD Events	CVD Deaths	CRC Cases	CRC Deaths	Major GI Bleeds	Major GI Bleed Deaths	Intracranial Hemorrhage	Intracranial Hemorrhage Deaths	Net QALYs	Net Life Years	Net Events Prevented
Men, Initiation Age 40-49 years													
5	10.3	9.8	24.6	3.5	-	-	31.9	0.0	4.0	3.6	11.1	-10.6	-11.3
7.5	10.6	9.8	25.6	4.1	-	-	30.4	0.0	3.2	2.9	19.6	-2.6	-6.8
10	11.4	10.4	27.8	4.3	-	-	29.4	0.0	3.0	2.8	35.1	11.4	-3.1
15	11.7	10.7	28.8	4.6	-	-	29.3	0.0	2.9	2.6	43.0	17.7	-1.3
20	12.1	11.5	30.4	5.0	-	-	30.0	0.0	2.7	2.4	50.4	24.2	0.1
Men, Initiation Age 50-59 years													
5	8.4	9.9	22.3	3.1	-	-	30.9	0.0	4.0	3.4	1.9	-18.7	-12.8
7.5	9.0	10.4	24.1	3.5	-	-	28.9	0.0	3.8	3.4	10.4	-11.8	-8.3
10	9.2	11.1	24.8	4.1	-	-	28.0	0.0	3.5	3.2	17.1	-6.5	-5.8
15	10.5	11.9	28.1	3.9	-	-	26.9	0.0	3.1	2.8	30.8	7.5	-0.8
20	11.4	11.8	30.5	4.6	-	-	25.5	0.0	2.9	2.6	41.6	16.9	4.0
Men, Initiation Age 60-69 years													
5	5.7	7.9	16.2	2.1	-	-	30.4	0.0	4.0	3.5	-9.5	-23.5	-19.5
7.5	6.5	8.1	17.3	2.2	-	-	28.9	0.0	3.7	3.2	-5.8	-20.2	-16.3
10	6.4	9.1	18.8	2.6	-	-	27.7	0.0	3.6	3.2	2.3	-13.5	-12.9
15	7.2	10.6	22.0	3.1	-	-	25.8	0.0	3.3	2.9	11.6	-7.2	-6.9
20	8.0	11.6	24.5	3.6	-	-	25.1	0.0	3.3	2.8	19.1	-1.6	-3.1
Men, Initiation Age 70-79 years													
5	4.3	7.0	12.8	1.3	-	-	29.4	0.0	3.7	3.2	-11.7	-20.6	-22.2
7.5	4.7	6.9	13.4	1.3	-	-	28.3	0.0	3.3	2.7	-6.4	-15.4	-19.5
10	4.4	7.1	13.5	1.4	-	-	27.4	0.0	3.0	2.6	-6.1	-16.6	-18.0
15	5.0	7.7	14.8	1.6	-	-	24.8	0.0	3.4	2.9	-6.9	-17.9	-14.6
20	5.3	7.3	15.3	1.9	-	-	24.0	0.0	3.5	2.9	-4.4	-14.8	-13.2

Notes: ASCVD=atherosclerotic cardiovascular disease; CVD=cardiovascular disease; CRC=colorectal cancer; GI=gastrointestinal; QALY=quality-adjusted life year. The 10-year ASCVD risk levels are based on the ACC/AHA risk calculator and refer to a person's risk at model baseline/initiation. Risk levels are rounded to the nearest threshold (+/- 0.5%). Results reflect the difference between universal adoption of aspirin for primary prevention versus zero adoption; all else is held equal. MI and ischemic stroke events are non-fatal. The non-fatal CVD event column combines non-fatal 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: (Non-fatal CVD events + CVD deaths + CRC cases) – (Major GI bleeds + intracranial hemorrhage). In the base case, there was no effect of aspirin use on CRC incidence.

Table 13. Lifetime Net Benefit of Aspirin for Men for Various Stopping Ages (KQ2)

% 10-yr ASCVD Risk	Stop Aspirin Age 65 yr	Stop Aspirin Age 70 yr	Stop Aspirin Age 75 yr	Stop Aspirin Age 80 yr	Stop Aspirin Age 85 yr
Men, Initiation Age 40-49 years, Net QALYs per 1000 persons (95% Confidence Interval)					
5	13.1 (7.1 to 19.1)	18.8 (12.1 to 25.5)	20.9 (14.0 to 27.9)	22.2 (15.1 to 29.3)	23.6 (16.4 to 30.8)
7.5	17.4 (11.6 to 23.3)	22.1 (15.7 to 28.5)	25.0 (18.3 to 31.7)	27.4 (20.6 to 34.3)	28.7 (21.8 to 35.5)
10	35.1 (28.9 to 41.3)	40.3 (33.5 to 47.1)	43.6 (36.4 to 50.8)	46.2 (38.8 to 53.6)	47.1 (39.6 to 54.5)
15	40.8 (34.0 to 47.6)	46.2 (39.1 to 53.4)	49.8 (42.3 to 57.3)	50.5 (42.7 to 58.2)	52.1 (44.4 to 59.9)
20	50.2 (43.3 to 57.2)	56.4 (48.8 to 63.9)	61.3 (53.5 to 69.1)	64.4 (56.5 to 72.2)	65.5 (57.6 to 73.4)
Men, Initiation Age 40-49 years, Net Life Years per 1000 persons (95% Confidence Interval)					
5	7.5 (1.2 to 13.8)	11.7 (4.7 to 18.8)	11.7 (4.3 to 19.0)	11.3 (3.9 to 18.8)	11.6 (4.0 to 19.2)
7.5	10.0 (3.8 to 16.2)	13.3 (6.6 to 20.1)	14.8 (7.8 to 21.9)	15.9 (8.7 to 23.1)	16.4 (9.2 to 23.6)
10	28.8 (22.2 to 35.4)	32.2 (25.0 to 39.5)	34.3 (26.7 to 42.0)	35.7 (27.8 to 43.6)	35.7 (27.7 to 43.6)
15	32.4 (25.2 to 39.6)	36.2 (28.5 to 43.8)	38.0 (30.0 to 46.0)	37.2 (29.0 to 45.5)	38.3 (30.1 to 46.6)
20	42.3 (34.8 to 49.8)	45.8 (37.7 to 53.9)	49.4 (41.1 to 57.8)	51.8 (43.3 to 60.2)	52.1 (43.6 to 60.6)
Men, Initiation Age 50-59 years, Net QALYs per 1000 persons (95% Confidence Interval)					
5	2.0 (-2.2 to 6.2)	2.9 (-1.8 to 7.5)	4.0 (-1.2 to 9.3)	4.7 (-0.7 to 10.2)	5.7 (0.1 to 11.4)
7.5	5.5 (1.2 to 9.7)	9.2 (4.2 to 14.2)	10.7 (5.0 to 16.3)	11.6 (5.7 to 17.5)	12.1 (6.1 to 18.0)
10	9.1 (4.8 to 13.5)	12.3 (7.2 to 17.5)	15.2 (9.6 to 20.9)	16.2 (10.4 to 22.0)	17.6 (11.7 to 23.6)
15	17.2 (12.7 to 21.7)	24.5 (19.0 to 29.9)	28.7 (22.8 to 34.6)	31.0 (24.9 to 37.2)	31.7 (25.5 to 37.9)
20	26.1 (21.3 to 30.9)	35.4 (30.0 to 40.9)	41.5 (35.4 to 47.5)	45.4 (39.0 to 51.7)	47.2 (40.8 to 53.6)
Men, Initiation Age 50-59 years, Net Life Years per 1000 persons (95% Confidence Interval)					
5	-2.1 (-6.7 to 2.4)	-2.5 (-7.6 to 2.7)	-3.0 (-8.8 to 2.8)	-4.0 (-10.1 to 2.0)	-4.3 (-10.5 to 1.9)
7.5	2.4 (-2.3 to 7.0)	3.5 (-1.9 to 8.9)	2.7 (-3.4 to 8.9)	1.7 (-4.7 to 8.2)	0.6 (-5.9 to 7.1)
10	4.8 (0.1 to 9.6)	5.8 (0.1 to 11.4)	6.0 (-0.1 to 12.2)	4.4 (-1.9 to 10.7)	4.6 (-2.0 to 11.1)
15	11.8 (6.8 to 16.7)	16.5 (10.5 to 22.4)	18.2 (11.8 to 24.7)	19.1 (12.3 to 25.9)	18.5 (11.7 to 25.3)
20	20.2 (14.9 to 25.5)	26.6 (20.7 to 32.6)	30.2 (23.6 to 36.8)	32.6 (25.7 to 39.4)	33.4 (26.5 to 40.4)
Men, Initiation Age 60-69 years, Net QALYs per 1000 persons (95% Confidence Interval)					
5	N/A	N/A	-2.3 (-6.1 to 1.6)	-3.8 (-8.2 to 0.5)	-1.7 (-6.3 to 2.9)
7.5	N/A	N/A	-0.4 (-4.4 to 3.5)	1.6 (-2.6 to 5.8)	2.0 (-2.4 to 6.5)
10	N/A	N/A	3.7 (-0.4 to 7.8)	6.5 (1.9 to 11.1)	7.2 (2.4 to 11.9)
15	N/A	N/A	5.5 (1.5 to 9.5)	7.3 (2.9 to 11.7)	8.3 (3.6 to 12.9)
20	N/A	N/A	12.5 (8.5 to 16.6)	14.3 (9.6 to 18.9)	15.2 (10.3 to 20.0)
Men, Initiation Age 60-69 years, Net Life Years per 1000 persons (95% Confidence Interval)					
5	N/A	N/A	-6.7 (-10.8 to -2.7)	-10.1 (-14.7 to -5.4)	-9.8 (-14.7 to -5.0)
7.5	N/A	N/A	-5.5 (-9.7 to -1.3)	-5.3 (-9.7 to -0.8)	-6.4 (-11.2 to -1.7)
10	N/A	N/A	-2.1 (-6.4 to 2.2)	-1.3 (-6.2 to 3.5)	-2.0 (-6.9 to 3.0)
15	N/A	N/A	-0.6 (-4.8 to 3.7)	-0.9 (-5.6 to 3.8)	-1.3 (-6.3 to 3.7)
20	N/A	N/A	5.8 (1.6 to 10.0)	5.3 (0.5 to 10.2)	4.9 (-0.2 to 9.9)
Men, Initiation Age 70-79 years, Net QALYs per 1000 persons (95% Confidence Interval)					
5	N/A	N/A	N/A	N/A	N/A
7.5	N/A	N/A	N/A	N/A	-5.7 (-8.6 to -2.7)
10	N/A	N/A	N/A	N/A	-1.8 (-5.0 to 1.3)
15	N/A	N/A	N/A	N/A	-1.8 (-5.1 to 1.4)
20	N/A	N/A	N/A	N/A	1.3 (-1.6 to 4.1)
Men, Initiation Age 70-79 years, Net Life Years per 1000 persons (95% Confidence Interval)					
5	N/A	N/A	N/A	N/A	N/A
7.5	N/A	N/A	N/A	N/A	-9.5 (-12.6 to -6.3)
10	N/A	N/A	N/A	N/A	-6.2 (-9.6 to -2.8)
15	N/A	N/A	N/A	N/A	-6.3 (-9.8 to -2.8)
20	N/A	N/A	N/A	N/A	-3.8 (-6.9 to -0.6)

Notes: ASCVD=atherosclerotic cardiovascular disease; CVD=cardiovascular disease; QALY=quality-adjusted life year; N/A=not applicable; yr=years. The 10-year ASCVD risk levels are based on the ACC/AHA risk calculator and refer to a person's risk at model baseline/initiation. Risk levels are rounded to the nearest threshold (+/- 0.5%). Results reflect the difference between universal adoption of aspirin for primary prevention versus zero adoption. All else is held equal. Stopping age indicates the age at which persons in the aspirin for primary prevention arm stop aspirin. Confidence intervals reflect stochastic heterogeneity and were calculated by bootstrap sampling with replacement 100,000 times from within the modeled population sample.

Table 14. Lifetime Net Benefit of Aspirin for Women for Various Stopping Ages (KQ2)

% 10-yr ASCVD Risk	Stop Aspirin Age 65 yr	Stop Aspirin Age 70 yr	Stop Aspirin Age 75 yr	Stop Aspirin Age 80 yr	Stop Aspirin Age 85 yr
Women, Initiation Age 40-49 years, Net QALYs per 1000 persons (95% Confidence Interval)					
5	8.5 (2.5 to 14.4)	11.2 (4.5 to 17.9)	10.4 (3.4 to 17.4)	10.9 (3.5 to 18.4)	11.1 (3.6 to 18.6)
7.5	12.2 (6.3 to 18.2)	15.2 (8.8 to 21.6)	17.8 (11.2 to 24.5)	17.9 (10.9 to 24.9)	18.8 (11.8 to 25.9)
10	20.4 (14.3 to 26.6)	28.1 (21.2 to 35.0)	31.2 (23.8 to 38.6)	33.7 (26.0 to 41.3)	34.4 (26.6 to 42.2)
15	28.9 (22.3 to 35.5)	35.1 (28.2 to 42.0)	39.6 (32.5 to 46.6)	41.1 (33.7 to 48.4)	42.3 (34.8 to 49.8)
20	34.5 (27.6 to 41.3)	41.6 (34.2 to 49.0)	44.4 (36.6 to 52.3)	48.1 (40.1 to 56.1)	49.2 (41.0 to 57.3)
Women, Initiation Age 40-49 years, Net Life Years per 1000 persons (95% Confidence Interval)					
5	-1.0 (-7.2 to 5.3)	-1.5 (-8.4 to 5.3)	-5.0 (-12.3 to 2.3)	-7.4 (-15.1 to 0.4)	-8.8 (-16.7 to -1.0)
7.5	2.0 (-4.1 to 8.1)	1.6 (-5.0 to 8.2)	1.2 (-5.7 to 8.0)	-0.7 (-7.9 to 6.4)	-1.7 (-9.0 to 5.5)
10	7.9 (1.4 to 14.4)	12.6 (5.4 to 19.8)	12.6 (4.8 to 20.4)	12.9 (4.9 to 20.9)	11.9 (3.7 to 20.1)
15	14.9 (8.0 to 21.9)	17.2 (9.9 to 24.4)	19.5 (12.1 to 26.9)	18.4 (10.7 to 26.0)	18.1 (10.3 to 25.9)
20	19.4 (12.2 to 26.6)	23.2 (15.4 to 30.9)	23.6 (15.4 to 31.9)	24.9 (16.5 to 33.2)	24.2 (15.7 to 32.8)
Women, Initiation Age 50-59 years, Net QALYs per 1000 persons (95% Confidence Interval)					
5	1.0 (-3.5 to 5.6)	0.8 (-4.8 to 6.5)	1.3 (-4.9 to 7.5)	-14.6 (-21.3 to -8.0)	2.2 (-4.7 to 9.1)
7.5	5.7 (1.3 to 10.2)	8.3 (2.9 to 13.6)	10.9 (5.2 to 16.7)	-3.2 (-9.5 to 3.0)	10.5 (4.0 to 17.0)
10	8.9 (4.0 to 13.9)	13.7 (8.0 to 19.3)	16.9 (10.6 to 23.2)	2.8 (-3.8 to 9.5)	17.3 (10.4 to 24.1)
15	15.4 (10.8 to 20.0)	21.3 (15.9 to 26.8)	26.4 (20.4 to 32.4)	16.7 (10.5 to 22.8)	29.9 (23.6 to 36.3)
20	20.0 (15.0 to 25.0)	30.6 (24.9 to 36.4)	35.8 (29.6 to 42.1)	26.9 (20.3 to 33.4)	40.9 (34.1 to 47.6)
Women, Initiation Age 50-59 years, Net Life Years per 1000 persons (95% Confidence Interval)					
5	-4.9 (-9.7 to -0.1)	-8.5 (-14.5 to -2.5)	-11.9 (-18.5 to -5.3)	-34.5 (-41.4 to -27.5)	-16.6 (-23.8 to -9.5)
7.5	-1.7 (-6.3 to 2.9)	-3.5 (-9.1 to 2.1)	-4.6 (-10.6 to 1.5)	-23.5 (-30.1 to -16.9)	-10.1 (-16.9 to -3.3)
10	-0.3 (-5.5 to 4.9)	1.1 (-4.8 to 7.1)	0.6 (-6.0 to 7.2)	-19.2 (-26.1 to -12.3)	-4.9 (-12.0 to 2.2)
15	6.7 (1.9 to 11.5)	7.8 (2.2 to 13.5)	9.9 (3.7 to 16.1)	-4.6 (-11.0 to 1.8)	8.3 (1.7 to 14.9)
20	10.7 (5.4 to 16.0)	16.8 (10.8 to 22.8)	17.9 (11.4 to 24.4)	3.3 (-3.6 to 10.2)	17.9 (10.7 to 25.0)
Women, Initiation Age 60-69 years, Net QALYs per 1000 persons (95% Confidence Interval)					
5	N/A	N/A	-4.6 (-8.3 to -0.9)	-6.1 (-10.4 to -1.8)	-24.8 (-29.5 to -20.2)
7.5	N/A	N/A	-2.2 (-6.2 to 1.8)	-4.0 (-8.6 to 0.5)	-18.8 (-23.7 to -13.8)
10	N/A	N/A	1.6 (-2.4 to 5.6)	4.8 (0.2 to 9.4)	-7.8 (-12.7 to -2.9)
15	N/A	N/A	6.5 (2.6 to 10.5)	9.6 (5.3 to 13.9)	-1.3 (-5.9 to 3.4)
20	N/A	N/A	13.7 (9.7 to 17.6)	16.8 (12.3 to 21.3)	8.6 (3.8 to 13.5)
Women, Initiation Age 60-69 years, Net Life Years per 1000 persons (95% Confidence Interval)					
5	N/A	N/A	-10.5 (-14.3 to -6.7)	-15.6 (-20.0 to -11.3)	-39.5 (-44.3 to -34.8)
7.5	N/A	N/A	-9.2 (-13.5 to -5.0)	-14.7 (-19.4 to -9.9)	-33.6 (-38.8 to -28.3)
10	N/A	N/A	-5.9 (-10.1 to -1.6)	-6.5 (-11.3 to -1.8)	-23.5 (-28.6 to -18.5)
15	N/A	N/A	-3.0 (-7.3 to 1.2)	-4.0 (-8.6 to 0.7)	-19.7 (-24.8 to -14.7)
20	N/A	N/A	2.6 (-1.4 to 6.6)	1.0 (-3.8 to 5.7)	-11.9 (-17.0 to -6.8)
Women, Initiation Age 70-79 years, Net QALYs per 1000 persons (95% Confidence Interval)					
5	N/A	N/A	N/A	N/A	-9.3 (-12.5 to -6.1)
7.5	N/A	N/A	N/A	N/A	-3.1 (-6.4 to 0.2)
10	N/A	N/A	N/A	N/A	-5.0 (-8.2 to -1.8)
15	N/A	N/A	N/A	N/A	-4.8 (-8.3 to -1.3)
20	N/A	N/A	N/A	N/A	-2.7 (-6.2 to 0.9)
Women, Initiation Age 70-79 years, Net Life Years per 1000 persons (95% Confidence Interval)					
5	N/A	N/A	N/A	N/A	-15.3 (-18.6 to -12.0)
7.5	N/A	N/A	N/A	N/A	-9.3 (-12.6 to -6.0)
10	N/A	N/A	N/A	N/A	-13.0 (-16.2 to -9.9)
15	N/A	N/A	N/A	N/A	-13.2 (-16.9 to -9.6)
20	N/A	N/A	N/A	N/A	-10.5 (-14.2 to -6.9)

Notes: ASCVD=atherosclerotic cardiovascular disease; CVD=cardiovascular disease; QALY=quality-adjusted life year; N/A=not applicable; yr=years. The 10-year ASCVD risk levels are based on the ACC/AHA risk calculator and refer to a person's risk at model baseline/initiation. Risk levels are rounded to the nearest threshold (+/- 0.5%). Results reflect the difference between universal adoption of aspirin for primary prevention versus zero adoption. All else is held equal. Stopping age indicates the age at which persons in the aspirin for primary prevention arm stop aspirin. Confidence intervals reflect stochastic heterogeneity and were calculated by bootstrap sampling with replacement 100,000 times from within the modeled population sample.

Table 15. Net Benefit of Aspirin for Men and Women After 10 Years of Use (CQ1)

	Initiation Age 40-49y	Initiation Age Age 50-59y	Initiation Age Age 60-69y	Initiation Age Age 70-79y
Men, Net QALYs per 1000 persons (95% Confidence Interval)				
5% 10y ASCVD Risk	-0.6 (-1.1 to -0.0)	-1.3 (-1.9 to -0.7)	-2.1 (-2.9 to -1.4)	N/A
7.5% 10y ASCVD Risk	-0.5 (-1.1 to 0.0)	-0.6 (-1.2 to -0.0)	-1.8 (-2.6 to -1.1)	-3.4 (-4.3 to -2.6)
10% 10y ASCVD Risk	0.5 (-0.0 to 1.0)	-0.5 (-1.2 to 0.1)	-1.6 (-2.4 to -0.8)	-2.7 (-3.6 to -1.8)
15% 10y ASCVD Risk	0.7 (0.1 to 1.3)	0.2 (-0.6 to 1.1)	-1.9 (-2.9 to -0.9)	-3.2 (-4.3 to -2.2)
20% 10y ASCVD Risk	1.7 (1.0 to 2.5)	0.9 (0.1 to 1.8)	-0.8 (-1.9 to 0.3)	-1.9 (-2.8 to -1.0)
Men, Net Life Years per 1000 persons (95% Confidence Interval)				
5% 10y ASCVD Risk	-0.5 (-0.9 to -0.1)	-1.5 (-2.0 to -0.9)	-1.9 (-2.6 to -1.2)	N/A
7.5% 10y ASCVD Risk	-0.8 (-1.2 to -0.4)	-1.0 (-1.5 to -0.5)	-2.2 (-2.8 to -1.5)	-3.5 (-4.3 to -2.7)
10% 10y ASCVD Risk	-0.6 (-1.0 to -0.2)	-1.4 (-2.0 to -0.8)	-2.4 (-3.1 to -1.7)	-3.2 (-4.1 to -2.3)
15% 10y ASCVD Risk	-0.8 (-1.2 to -0.3)	-1.9 (-2.7 to -1.1)	-3.1 (-4.1 to -2.2)	-4.0 (-5.0 to -2.9)
20% 10y ASCVD Risk	-0.7 (-1.3 to -0.1)	-2.2 (-3.0 to -1.4)	-3.5 (-4.6 to -2.4)	-3.3 (-4.3 to -2.4)
Women, Net QALYs per 1000 persons (95% Confidence Interval)				
5% 10y ASCVD Risk	-0.4 (-0.8 to 0.1)	-1.4 (-2.1 to -0.7)	-1.9 (-2.6 to -1.1)	-2.3 (-3.0 to -1.7)
7.5% 10y ASCVD Risk	-0.3 (-0.7 to 0.2)	-1.1 (-1.8 to -0.3)	-1.6 (-2.3 to -0.8)	-1.5 (-2.2 to -0.8)
10% 10y ASCVD Risk	0.2 (-0.3 to 0.6)	0.0 (-0.8 to 0.8)	-1.8 (-2.8 to -0.8)	-2.0 (-3.0 to -1.1)
15% 10y ASCVD Risk	0.7 (0.1 to 1.2)	1.3 (0.7 to 2.0)	-0.8 (-1.8 to 0.2)	-3.1 (-4.2 to -2.0)
20% 10y ASCVD Risk	1.1 (0.5 to 1.6)	1.6 (0.8 to 2.5)	2.0 (1.0 to 2.9)	-3.1 (-4.3 to -2.0)
Women, Net Life Years per 1000 persons (95% Confidence Interval)				
5% 10y ASCVD Risk	-0.6 (-0.9 to -0.2)	-1.6 (-2.2 to -1.0)	-1.7 (-2.3 to -1.1)	-2.0 (-2.6 to -1.4)
7.5% 10y ASCVD Risk	-0.5 (-0.8 to -0.2)	-2.1 (-2.8 to -1.4)	-2.3 (-3.0 to -1.6)	-1.8 (-2.3 to -1.2)
10% 10y ASCVD Risk	-0.6 (-0.9 to -0.3)	-1.8 (-2.4 to -1.1)	-3.1 (-4.0 to -2.2)	-3.0 (-3.8 to -2.2)
15% 10y ASCVD Risk	-0.5 (-0.9 to -0.2)	-0.9 (-1.5 to -0.4)	-3.8 (-4.8 to -2.9)	-4.5 (-5.6 to -3.5)
20% 10y ASCVD Risk	-0.5 (-0.9 to -0.1)	-1.3 (-2.0 to -0.6)	-2.3 (-3.1 to -1.6)	-5.0 (-6.1 to -4.0)

Notes: ASCVD=atherosclerotic cardiovascular disease; QALY=quality-adjusted life year; N/A=not applicable; yr=years. The 10-year ASCVD risk levels are based on the ACC/AHA risk calculator and refer to a person's risk at model baseline/initiation. Risk levels are rounded to the nearest threshold (+/- 0.5%). Results reflect the difference between universal adoption of aspirin for primary prevention versus zero adoption. All else is held equal. Confidence intervals reflect stochastic heterogeneity and were calculated by bootstrap sampling with replacement 100,000 times from within the modeled population sample.

Table 16. Net Events of Aspirin for Men After 10 Years of Use (CQ1)

	Benefits from aspirin (Prevented events per 1,000 persons)						Harms from aspirin (Incurred events per 1,000 persons)				Net Balance (Benefits - harms)		
10-yr ASCVD Risk (%)	Myocardial infarction	Ischemic stroke	Non-fatal CVD Events	CVD Deaths	CRC Cases	CRC Deaths	Major GI Bleeds	Major GI Bleed Deaths	Intracranial Hemorrhage	Intracranial Hemorrhage Deaths	Net QALYs	Net Life Years	Net Events Prevented
Men, Initiation Age 40-49 years													
5	3.9	0.7	4.7	0.1	-	-	7.8	0.0	0.5	0.3	-0.6	-0.5	-3.9
7.5	4.8	0.9	5.8	0.0	-	-	8.0	0.0	0.5	0.2	-0.5	-0.8	-2.9
10	5.9	1.1	7.1	0.1	-	-	7.8	0.0	0.4	0.2	0.5	-0.6	-1.2
15	7.6	1.5	9.3	0.1	-	-	8.2	0.0	0.5	0.3	0.7	-0.8	0.5
20	9.2	2.0	11.6	0.2	-	-	7.8	0.0	0.5	0.3	1.7	-0.7	3.3
Men, Initiation Age 50-59 years													
5	3.9	1.1	5.1	0.0	-	-	10.2	0.0	0.8	0.5	-1.3	-1.5	-6.3
7.5	5.0	1.3	6.4	0.1	-	-	10.6	0.0	0.8	0.4	-0.6	-1.0	-5.2
10	5.5	1.5	7.2	0.1	-	-	10.6	0.0	0.8	0.5	-0.5	-1.4	-4.6
15	7.1	2.3	9.9	0.2	-	-	10.0	0.0	0.8	0.6	0.2	-1.9	-1.3
20	9.4	2.9	13.1	0.3	-	-	9.8	0.0	0.8	0.7	0.9	-2.2	2.1
Men, Initiation Age 60-69 years													
5	3.0	1.1	4.2	0.0	-	-	13.3	0.0	0.8	0.5	-2.1	-1.9	-10.4
7.5	3.8	1.5	5.5	0.1	-	-	13.3	0.0	1.0	0.7	-1.8	-2.2	-9.3
10	4.9	1.9	7.2	0.2	-	-	13.0	0.0	1.2	0.8	-1.6	-2.4	-7.6
15	5.7	2.3	8.5	0.3	-	-	14.3	0.0	1.3	1.0	-1.9	-3.1	-7.9
20	7.5	3.2	11.5	0.4	-	-	14.3	0.0	1.4	1.1	-0.8	-3.5	-4.9
Men, Initiation Age 70-79 years													
5	-	-	-	-	-	-	-	-	-	-	-	-	-
7.5	3.8	1.7	5.7	0.2	-	-	17.9	0.0	1.5	1.1	-3.4	-3.5	-14.6
10	4.1	2.2	6.6	0.2	-	-	17.5	0.0	1.3	1.1	-2.7	-3.2	-13.1
15	4.8	2.5	7.7	0.3	-	-	17.2	0.0	1.6	1.2	-3.2	-4.0	-12.0
20	5.7	2.8	9.1	0.3	-	-	17.0	0.0	1.6	1.2	-1.9	-3.3	-10.3

Notes: ASCVD=atherosclerotic cardiovascular disease; CVD=cardiovascular disease; CRC=colorectal cancer; GI=gastrointestinal; QALY=quality-adjusted life year. The 10-year ASCVD risk levels are based on the ACC/AHA risk calculator and refer to a person's risk at model baseline/initiation. Risk levels are rounded to the nearest threshold (+/- 0.5%). Results reflect the difference between universal adoption of aspirin for primary prevention versus zero adoption; all else is held equal. MI and ischemic stroke events are non-fatal. The non-fatal CVD event column combines non-fatal 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: (Non-fatal CVD events + CVD deaths + CRC cases) – (Major GI bleeds + intracranial hemorrhage). In the base case, there was no effect of aspirin use on CRC incidence.

Table 17. Net Events of Aspirin for Women After 10 Years of Use (CQ1)

	Benefits from aspirin (Prevented events per 1,000 persons)						Harms from aspirin (Incurred events per 1,000 persons)				Net Balance (Benefits - harms)		
10-yr ASCVD Risk (%)	Myocardial infarction	Ischemic stroke	Non-fatal CVD Events	CVD Deaths	CRC Cases	CRC Deaths	Major GI Bleeds	Major GI Bleed Deaths	Intracranial Hemorrhage	Intracranial Hemorrhage Deaths	Net QALYs	Net Life Years	Net Events Prevented
Women, Initiation Age 40-49 years													
5	2.0	1.0	3.1	0.0	-	-	6.5	0.0	0.5	0.2	-0.4	-0.6	-4.1
7.5	2.6	1.0	3.6	0.0	-	-	6.8	0.0	0.5	0.2	-0.3	-0.5	-3.9
10	2.9	1.3	4.4	0.0	-	-	6.5	0.0	0.4	0.2	0.2	-0.6	-2.7
15	3.2	1.7	5.1	0.1	-	-	6.2	0.0	0.4	0.2	0.7	-0.5	-1.6
20	3.3	2.0	5.4	0.0	-	-	6.5	0.0	0.3	0.2	1.1	-0.5	-1.5
Women, Initiation Age 50-59 years													
5	2.4	1.5	3.9	0.0	-	-	9.2	0.0	0.9	0.5	-1.4	-1.6	-6.6
7.5	2.8	2.3	5.3	0.1	-	-	9.4	0.0	1.0	0.6	-1.1	-2.1	-5.6
10	3.2	2.8	6.3	0.1	-	-	9.0	0.0	1.1	0.6	0.0	-1.8	-4.2
15	4.2	3.3	8.0	0.2	-	-	9.0	0.0	0.9	0.5	1.3	-0.9	-2.3
20	4.5	3.5	8.6	0.2	-	-	8.9	0.0	0.8	0.6	1.6	-1.3	-1.4
Women, Initiation Age 60-69 years													
5	1.9	1.8	3.8	0.1	-	-	11.7	0.0	1.1	0.6	-1.9	-1.7	-9.5
7.5	2.6	2.6	5.3	0.1	-	-	12.3	0.0	1.3	0.8	-1.6	-2.3	-8.9
10	2.6	2.8	5.8	0.2	-	-	12.5	0.0	1.4	1.0	-1.8	-3.1	-8.9
15	3.1	4.0	7.6	0.2	-	-	12.0	0.0	1.4	1.0	-0.8	-3.8	-6.7
20	4.0	5.3	10.0	0.4	-	-	12.1	0.0	1.3	0.9	2.0	-2.3	-3.9
Women, Initiation Age 70-79 years													
5	1.5	1.9	3.4	0.0	-	-	15.6	0.0	1.2	0.7	-2.3	-2.0	-14.2
7.5	1.8	2.4	4.3	0.1	-	-	15.3	0.0	1.1	0.7	-1.5	-1.8	-12.7
10	2.0	2.7	4.8	0.1	-	-	14.9	0.0	1.3	0.9	-2.0	-3.0	-12.1
15	2.4	3.6	6.2	0.2	-	-	14.4	0.0	1.8	1.2	-3.1	-4.5	-11.0
20	2.8	3.7	7.0	0.2	-	-	14.6	0.0	2.0	1.4	-3.1	-5.0	-10.7

Notes: ASCVD=atherosclerotic cardiovascular disease; CVD=cardiovascular disease; CRC=colorectal cancer; GI=gastrointestinal; QALY=quality-adjusted life year. The 10-year ASCVD risk levels are based on the ACC/AHA risk calculator and refer to a person's risk at model baseline/initiation. Risk levels are rounded to the nearest threshold (+/- 0.5%). Results reflect the difference between universal adoption of aspirin for primary prevention versus zero adoption; all else is held equal. MI and ischemic stroke events are non-fatal. The non-fatal CVD event column combines non-fatal 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: (Non-fatal CVD events + CVD deaths + CRC cases) – (Major GI bleeds + intracranial hemorrhage). In the base case, there was no effect of aspirin use on CRC incidence.

Table 18a. Net Benefit of Aspirin After 10 Years and Lifetime Net Benefit at Stopping Intervals and With Lifetime Use (KQ1, KQ2, CQ1), Initiation Age 40-49y

	10y use*	Stop at age 65y	Stop at age 70y	Stop at age 75y	Stop at age 80y	Stop at age 85y	Lifetime use
Men, Net QALYs per 1000 persons							
5% 10y ASCVD Risk	-0.6	13.1	18.8	20.9	22.2	23.6	23.1
7.5% 10y ASCVD Risk	-0.5	17.4	22.1	25.0	27.4	28.7	29.1
10% 10y ASCVD Risk	0.5	35.1	40.3	43.6	46.2	47.1	48.0
15% 10y ASCVD Risk	0.7	40.8	46.2	49.8	50.5	52.1	52.3
20% 10y ASCVD Risk	1.7	50.2	56.4	61.3	64.4	65.5	66.2
Men, Net Life Years per 1000 persons							
5% 10y ASCVD Risk	-0.5	7.5	11.7	11.7	11.3	11.6	10.6
7.5% 10y ASCVD Risk	-0.8	10.0	13.3	14.8	15.9	16.4	16.2
10% 10y ASCVD Risk	-0.6	28.8	32.2	34.3	35.7	35.7	36.1
15% 10y ASCVD Risk	-0.8	32.4	36.2	38.0	37.2	38.3	37.9
20% 10y ASCVD Risk	-0.7	42.3	45.8	49.4	51.8	52.1	52.4
Women, Net QALYs per 1000 persons							
5% 10y ASCVD Risk	-0.4	8.5	11.2	10.4	10.9	11.1	11.1
7.5% 10y ASCVD Risk	-0.3	12.2	15.2	17.8	17.9	18.8	19.6
10% 10y ASCVD Risk	0.2	20.4	28.1	31.2	33.7	34.4	35.1
15% 10y ASCVD Risk	0.7	28.9	35.1	39.6	41.1	42.3	43.0
20% 10y ASCVD Risk	1.1	34.5	41.6	44.4	48.1	49.2	50.4
Women, Net Life Years per 1000 persons							
5% 10y ASCVD Risk	-0.6	-1.0	-1.5	-5.0	-7.4	-8.8	-10.6
7.5% 10y ASCVD Risk	-0.5	2.0	1.6	1.2	-0.7	-1.7	-2.6
10% 10y ASCVD Risk	-0.6	7.9	12.6	12.6	12.9	11.9	11.4
15% 10y ASCVD Risk	-0.5	14.9	17.2	19.5	18.4	18.1	17.7
20% 10y ASCVD Risk	-0.5	19.4	23.2	23.6	24.9	24.2	24.2

Notes: ASCVD=atherosclerotic cardiovascular disease; QALY=quality-adjusted life year; N/A=not applicable; y=years. The 10-year ASCVD risk levels are based on the ACC/AHA risk calculator and refer to a person's risk at model baseline/initiation. Risk levels are rounded to the nearest threshold (+/- 0.5%). Results reflect the difference between universal adoption of aspirin for primary prevention versus zero adoption. All else is held equal. Stopping age indicates the age at which persons in the aspirin for primary prevention arm stop aspirin. * The "10y use" column indicates net benefit over 10 years of aspirin use. All other columns indicate net benefits over a lifetime horizon.

Table 18b. Net Benefit of Aspirin After 10 Years and Lifetime Net Benefit at Stopping Intervals and With Lifetime Use (KQ1, KQ2, CQ1), Initiation Age 50-59y

	10y use*	Stop at age 65y	Stop at age 70y	Stop at age 75y	Stop at age 80y	Stop at age 85y	Lifetime use
Men, Net QALYs per 1000 persons							
5% 10y ASCVD Risk	-1.3	2.0	2.9	4.0	4.7	5.7	5.7
7.5% 10y ASCVD Risk	-0.6	5.5	9.2	10.7	11.6	12.1	12.5
10% 10y ASCVD Risk	-0.5	9.1	12.3	15.2	16.2	17.6	18.0
15% 10y ASCVD Risk	0.2	17.2	24.5	28.7	31.0	31.7	32.3
20% 10y ASCVD Risk	0.9	26.1	35.4	41.5	45.4	47.2	48.4
Men, Net Life Years per 1000 persons							
5% 10y ASCVD Risk	-1.5	-2.1	-2.5	-3.0	-4.0	-4.3	-5.4
7.5% 10y ASCVD Risk	-1.0	2.4	3.5	2.7	1.7	0.6	0.4
10% 10y ASCVD Risk	-1.4	4.8	5.8	6.0	4.4	4.6	4.2
15% 10y ASCVD Risk	-1.9	11.8	16.5	18.2	19.1	18.5	18.6
20% 10y ASCVD Risk	-2.2	20.2	26.6	30.2	32.6	33.4	33.9
Women, Net QALYs per 1000 persons							
5% 10y ASCVD Risk	-1.4	1.0	0.8	1.3	2.8	2.2	1.9
7.5% 10y ASCVD Risk	-1.1	5.7	8.3	10.9	10.0	10.5	10.4
10% 10y ASCVD Risk	0.0	8.9	13.7	16.9	17.0	17.3	17.1
15% 10y ASCVD Risk	1.3	15.4	21.3	26.4	28.6	29.9	30.8
20% 10y ASCVD Risk	1.6	20.0	30.6	35.8	39.8	40.9	41.6
Women, Net Life Years per 1000 persons							
5% 10y ASCVD Risk	-1.6	-4.9	-8.5	-11.9	-14.2	-16.6	-18.7
7.5% 10y ASCVD Risk	-2.1	-1.7	-3.5	-4.6	-8.1	-10.1	-11.8
10% 10y ASCVD Risk	-1.8	-0.3	1.1	0.6	-2.7	-4.9	-6.5
15% 10y ASCVD Risk	-0.9	6.7	7.8	9.9	9.2	8.3	7.5
20% 10y ASCVD Risk	-1.3	10.7	16.8	17.9	18.4	17.9	16.9

Notes: ASCVD=atherosclerotic cardiovascular disease; QALY=quality-adjusted life year; N/A=not applicable; y=years. The 10-year ASCVD risk levels are based on the ACC/AHA risk calculator and refer to a person's risk at model baseline/initiation. Risk levels are rounded to the nearest threshold (+/- 0.5%). Results reflect the difference between universal adoption of aspirin for primary prevention versus zero adoption. All else is held equal. Stopping age indicates the age at which persons in the aspirin for primary prevention arm stop aspirin. * The "10y use" column indicates net benefit over 10 years of aspirin use. All other columns indicate net benefits over a lifetime horizon.

Table 18c. Net Benefit of Aspirin After 10 Years and Lifetime Net Benefit at Stopping Intervals and With Lifetime Use (KQ1, KQ2, CQ1), Initiation Age 60-69y

	10y use*	Stop at age 75y	Stop at age 80y	Stop at age 85y	Lifetime use
Men, Net QALYs per 1000 persons					
5% 10y ASCVD Risk	-2.1	-2.3	-3.8	-1.7	-1.8
7.5% 10y ASCVD Risk	-1.8	-0.4	1.6	2.0	2.6
10% 10y ASCVD Risk	-1.6	3.7	6.5	7.2	7.0
15% 10y ASCVD Risk	-1.9	5.5	7.3	8.3	8.3
20% 10y ASCVD Risk	-0.8	12.5	14.3	15.2	16.3
Men, Net QALYs per 1000 persons					
5% 10y ASCVD Risk	-1.9	-6.7	-10.1	-9.8	-11.0
7.5% 10y ASCVD Risk	-2.2	-5.5	-5.3	-6.4	-6.7
10% 10y ASCVD Risk	-2.4	-2.1	-1.3	-2.0	-3.0
15% 10y ASCVD Risk	-3.1	-0.6	-0.9	-1.3	-2.2
20% 10y ASCVD Risk	-3.5	5.8	5.3	4.9	4.9
Women, Net QALYs per 1000 persons					
5% 10y ASCVD Risk	-1.9	-4.6	-6.1	-8.5	-9.5
7.5% 10y ASCVD Risk	-1.6	-2.2	-4.0	-5.2	-5.8
10% 10y ASCVD Risk	-1.8	1.6	4.8	4.3	2.3
15% 10y ASCVD Risk	-0.8	6.5	9.6	10.9	11.6
20% 10y ASCVD Risk	2.0	13.7	16.8	18.3	19.1
Women, Net Life Years per 1000 persons					
5% 10y ASCVD Risk	-1.7	-10.5	-15.6	-20.6	-23.5
7.5% 10y ASCVD Risk	-2.3	-9.2	-14.7	-17.7	-20.2
10% 10y ASCVD Risk	-3.1	-5.9	-6.5	-9.2	-13.5
15% 10y ASCVD Risk	-3.8	-3.0	-4.0	-5.7	-7.2
20% 10y ASCVD Risk	-2.3	2.6	1.0	-0.4	-1.6

Notes: ASCVD=atherosclerotic cardiovascular disease; QALY=quality-adjusted life year; N/A=not applicable; y=years. The 10-year ASCVD risk levels are based on the ACC/AHA risk calculator and refer to a person's risk at model baseline/initiation. Risk levels are rounded to the nearest threshold (+/- 0.5%). Results reflect the difference between universal adoption of aspirin for primary prevention versus zero adoption. All else is held equal. Stopping age indicates the age at which persons in the aspirin for primary prevention arm stop aspirin. * The "10y use" column indicates net benefit over 10 years of aspirin use. All other columns indicate net benefits over a lifetime horizon.

Table 18d. Net Benefit of Aspirin After 10 Years and Lifetime Net Benefit at Stopping Intervals and With Lifetime Use (KQ1, KQ2, CQ1), Initiation Age 70-79y

	10y use*	Stop at age 85y	Lifetime use
Men, Net QALYs per 1000 persons			
5% 10y ASCVD Risk	N/A	N/A	N/A
7.5% 10y ASCVD Risk	-3.4	-5.7	-4.6
10% 10y ASCVD Risk	-2.7	-1.8	-1.1
15% 10y ASCVD Risk	-3.2	-1.8	-1.9
20% 10y ASCVD Risk	-1.9	1.3	0.9
Men, Net QALYs per 1000 persons			
5% 10y ASCVD Risk	N/A	N/A	N/A
7.5% 10y ASCVD Risk	-3.5	-9.5	-10.1
10% 10y ASCVD Risk	-3.2	-6.2	-6.9
15% 10y ASCVD Risk	-4.0	-6.3	-7.6
20% 10y ASCVD Risk	-3.3	-3.8	-5.5
Women, Net QALYs per 1000 persons			
5% 10y ASCVD Risk	-2.3	-9.3	-11.7
7.5% 10y ASCVD Risk	-1.5	-3.1	-6.4
10% 10y ASCVD Risk	-2.0	-5.0	-6.1
15% 10y ASCVD Risk	-3.1	-4.8	-6.9
20% 10y ASCVD Risk	-3.1	-2.7	-4.4
Women, Net Life Years per 1000 persons			
5% 10y ASCVD Risk	-2.0	-15.3	-20.6
7.5% 10y ASCVD Risk	-1.8	-9.3	-15.4
10% 10y ASCVD Risk	-3.0	-13.0	-16.6
15% 10y ASCVD Risk	-4.5	-13.2	-17.9
20% 10y ASCVD Risk	-5.0	-10.5	-14.8

Notes: ASCVD=atherosclerotic cardiovascular disease; QALY=quality-adjusted life year; N/A=not applicable; y=years. The 10-year ASCVD risk levels are based on the ACC/AHA risk calculator and refer to a person's risk at model baseline/initiation. Risk levels are rounded to the nearest threshold (+/- 0.5%). Results reflect the difference between universal adoption of aspirin for primary prevention versus zero adoption. All else is held equal. Stopping age indicates the age at which persons in the aspirin for primary prevention arm stop aspirin. * The "10y use" column indicates net benefit over 10 years of aspirin use. All other columns indicate net benefits over a lifetime horizon.

Table 19a. Decision Analytic Summary of Aspirin Use Scenarios (KQ1, KQ2, CQ1), Initiation Age 40-49y

	10y use*	Stop at age 65y	Stop at age 70y	Stop at age 75y	Stop at age 80y	Stop at age 85y	Lifetime use
Men, Net QALYs per 1000 persons							
5% 10y ASCVD Risk	–	+	+	+	+	+	+
7.5% 10y ASCVD Risk	–	+	+	+	+	+	+
10% 10y ASCVD Risk	+	+	+	+	+	+	+
15% 10y ASCVD Risk	+	+	+	+	+	+	+
20% 10y ASCVD Risk	+	+	+	+	+	+	+
Men, Net Life Years per 1000 persons							
5% 10y ASCVD Risk	–	+	+	+	+	+	+
7.5% 10y ASCVD Risk	–	+	+	+	+	+	+
10% 10y ASCVD Risk	–	+	+	+	+	+	+
15% 10y ASCVD Risk	–	+	+	+	+	+	+
20% 10y ASCVD Risk	–	+	+	+	+	+	+
Women, Net QALYs per 1000 persons							
5% 10y ASCVD Risk	–	+	+	+	+	+	+
7.5% 10y ASCVD Risk	–	+	+	+	+	+	+
10% 10y ASCVD Risk	+	+	+	+	+	+	+
15% 10y ASCVD Risk	+	+	+	+	+	+	+
20% 10y ASCVD Risk	+	+	+	+	+	+	+
Women, Net Life Years per 1000 persons							
5% 10y ASCVD Risk	–	–	–	–	–	–	–
7.5% 10y ASCVD Risk	–	+	+	+	–	–	–
10% 10y ASCVD Risk	–	+	+	+	+	+	+
15% 10y ASCVD Risk	–	+	+	+	+	+	+
20% 10y ASCVD Risk	–	+	+	+	+	+	+

Notes: ASCVD=atherosclerotic cardiovascular disease; QALY=quality-adjusted life year; N/A=not applicable; y=years. The 10-year ASCVD risk levels are based on the ACC/AHA risk calculator and refer to a person's risk at model baseline/initiation. Risk levels are rounded to the nearest threshold (+/- 0.5%). Cells with a "+" sign indicate net benefit was found to be positive in **Table 18a**, favoring aspirin use. Cells with a "–" sign indicate net benefit was found to be negative in **Table 18a**, favoring aspirin nonuse. * The "10y use" column indicates net benefit over 10 years of aspirin use. All other columns indicate net benefits over a lifetime horizon.

Table 19b. Decision Analytic Summary of Aspirin Use Scenarios (KQ1, KQ2, CQ1), Initiation Age 50-59y

	10y use*	Stop at age 65y	Stop at age 70y	Stop at age 75y	Stop at age 80y	Stop at age 85y	Lifetime use
Men, Net QALYs per 1000 persons							
5% 10y ASCVD Risk	–	+	+	+	+	+	+
7.5% 10y ASCVD Risk	–	+	+	+	+	+	+
10% 10y ASCVD Risk	–	+	+	+	+	+	+
15% 10y ASCVD Risk	+	+	+	+	+	+	+
20% 10y ASCVD Risk	+	+	+	+	+	+	+
Men, Net Life Years per 1000 persons							
5% 10y ASCVD Risk	–	–	–	–	–	–	–
7.5% 10y ASCVD Risk	–	+	+	+	+	+	+
10% 10y ASCVD Risk	–	+	+	+	+	+	+
15% 10y ASCVD Risk	–	+	+	+	+	+	+
20% 10y ASCVD Risk	–	+	+	+	+	+	+
Women, Net QALYs per 1000 persons							
5% 10y ASCVD Risk	–	+	+	+	+	+	+
7.5% 10y ASCVD Risk	–	+	+	+	+	+	+
10% 10y ASCVD Risk	+	+	+	+	+	+	+
15% 10y ASCVD Risk	+	+	+	+	+	+	+
20% 10y ASCVD Risk	+	+	+	+	+	+	+
Women, Net Life Years per 1000 persons							
5% 10y ASCVD Risk	–	–	–	–	–	–	–
7.5% 10y ASCVD Risk	–	–	–	–	–	–	–
10% 10y ASCVD Risk	–	–	+	+	–	–	–
15% 10y ASCVD Risk	–	+	+	+	+	+	+
20% 10y ASCVD Risk	–	+	+	+	+	+	+

Notes: ASCVD=atherosclerotic cardiovascular disease; QALY=quality-adjusted life year; N/A=not applicable; y=years. The 10-year ASCVD risk levels are based on the ACC/AHA risk calculator and refer to a person's risk at model baseline/initiation. Risk levels are rounded to the nearest threshold (+/- 0.5%). Cells with a "+" sign indicate net benefit was found to be positive in **Table 18b**, favoring aspirin use. Cells with a "–" sign indicate net benefit was found to be negative in **Table 18b**, favoring aspirin nonuse. * The "10y use" column indicates net benefit over 10 years of aspirin use. All other columns indicate net benefits over a lifetime horizon.

Table 19c. Decision Analytic Summary of Aspirin Use Scenarios (KQ1, KQ2, CQ1), Initiation Age 60-69y

	10y use*	Stop at age 75y	Stop at age 80y	Stop at age 85y	Lifetime use
Men, Net QALYs per 1000 persons					
5% 10y ASCVD Risk	–	–	–	–	–
7.5% 10y ASCVD Risk	–	–	+	+	+
10% 10y ASCVD Risk	–	+	+	+	+
15% 10y ASCVD Risk	–	+	+	+	+
20% 10y ASCVD Risk	–	+	+	+	+
Men, Net QALYs per 1000 persons					
5% 10y ASCVD Risk	–	–	–	–	–
7.5% 10y ASCVD Risk	–	–	–	–	–
10% 10y ASCVD Risk	–	–	–	–	–
15% 10y ASCVD Risk	–	–	–	–	–
20% 10y ASCVD Risk	–	+	+	+	+
Women, Net QALYs per 1000 persons					
5% 10y ASCVD Risk	–	–	–	–	–
7.5% 10y ASCVD Risk	–	–	–	–	–
10% 10y ASCVD Risk	–	+	+	+	+
15% 10y ASCVD Risk	–	+	+	+	+
20% 10y ASCVD Risk	+	+	+	+	+
Women, Net Life Years per 1000 persons					
5% 10y ASCVD Risk	–	–	–	–	–
7.5% 10y ASCVD Risk	–	–	–	–	–
10% 10y ASCVD Risk	–	–	–	–	–
15% 10y ASCVD Risk	–	–	–	–	–
20% 10y ASCVD Risk	–	+	+	–	–

Notes: ASCVD=atherosclerotic cardiovascular disease; QALY=quality-adjusted life year; N/A=not applicable; y=years. The 10-year ASCVD risk levels are based on the ACC/AHA risk calculator and refer to a person's risk at model baseline/initiation. Risk levels are rounded to the nearest threshold (+/- 0.5%). Cells with a "+" sign indicate net benefit was found to be positive in **Table 18c**, favoring aspirin use. Cells with a "–" sign indicate net benefit was found to be negative in **Table 18c**, favoring aspirin nonuse. * The "10y use" column indicates net benefit over 10 years of aspirin use. All other columns indicate net benefits over a lifetime horizon.

Table 19d. Decision Analytic Summary of Aspirin Use Scenarios (KQ1, KQ2, CQ1), Initiation Age 70-79y

	10y use*	Stop at age 85y	Lifetime use
Men, Net QALYs per 1000 persons			
5% 10y ASCVD Risk	N/A	N/A	N/A
7.5% 10y ASCVD Risk	–	–	–
10% 10y ASCVD Risk	–	–	–
15% 10y ASCVD Risk	–	–	–
20% 10y ASCVD Risk	–	+	+
Men, Net QALYs per 1000 persons			
5% 10y ASCVD Risk	N/A	N/A	N/A
7.5% 10y ASCVD Risk	–	–	–
10% 10y ASCVD Risk	–	–	–
15% 10y ASCVD Risk	–	–	–
20% 10y ASCVD Risk	–	–	–
Women, Net QALYs per 1000 persons			
5% 10y ASCVD Risk	–	–	–
7.5% 10y ASCVD Risk	–	–	–
10% 10y ASCVD Risk	–	–	–
15% 10y ASCVD Risk	–	–	–
20% 10y ASCVD Risk	–	–	–
Women, Net Life Years per 1000 persons			
5% 10y ASCVD Risk	–	–	–
7.5% 10y ASCVD Risk	–	–	–
10% 10y ASCVD Risk	–	–	–
15% 10y ASCVD Risk	–	–	–
20% 10y ASCVD Risk	–	–	–

Notes: ASCVD=atherosclerotic cardiovascular disease; QALY=quality-adjusted life year; N/A=not applicable; y=years. The 10-year ASCVD risk levels are based on the ACC/AHA risk calculator and refer to a person's risk at model baseline/initiation. Risk levels are rounded to the nearest threshold (+/- 0.5%). Cells with a "+" sign indicate net benefit was found to be positive in **Table 18d**, favoring aspirin use. Cells with a "–" sign indicate net benefit was found to be negative in **Table 18d**, favoring aspirin nonuse. * The "10y use" column indicates net benefit over 10 years of aspirin use. All other columns indicate net benefits over a lifetime horizon.

Table 20. Sensitivity Analysis Results for Persons With 5% ASCVD Baseline Risk (Lifetime Aspirin Use, Lifetime Follow-Up)

	Age 40-49				Age 50-59				Age 60-69				Age 70-79			
	Men		Women		Men		Women		Men		Women		Men		Women	
Scenario	**QALY**	**LY**	**QALY**	**LY**	**QALY**	**LY**	**QALY**	**LY**	**QALY**	**LY**	**QALY**	**LY**	**QALY**	**LY**	**QALY**	**LY**
(0) Base Case	23.1	10.6	11.1	-10.6	5.7	-5.4	1.9	-18.7	-1.8	-11.0	-9.5	-23.5	-	-	-11.7	-20.6
(1) ASA Disutility = 0.001	2.3	10.6	-13.0	-10.6	-11.9	-5.4	-17.0	-18.7	-16.7	-11.0	-25.5	-23.5	-	-	-24.8	-20.6
(2) ASA Disutility = 0.005	-80.9	10.6	-109.4	-10.6	-82.2	-5.4	-92.5	-18.7	-76.7	-11.0	-89.5	-23.5	-	-	-77.2	-20.6
(3) CRC OR = 0.64	82.9	69.7	69.8	47.5	58.8	45.9	53.1	31.0	50.0	38.8	33.8	18.0	-	-	21.1	9.2
(4) CVD Death OR = 0.95	100.4	101.9	79.5	70.9	77.1	78.8	67.0	59.1	51.3	51.6	40.2	35.5	-	-	23.1	20.4
(5) CVD Incidence Rates ↑10%	24.9	11.4	14.2	-9.0	11.1	-1.2	2.4	-17.5	-1.0	-10.8	-7.4	-22.0	-	-	-9.4	-18.7
(6) CVD Incidence Rates ↓10%	18.8	5.4	11.9	-9.5	3.1	-7.5	-1.4	-19.4	-2.1	-9.7	-10.4	-23.0	-	-	-13.6	-20.0
(7) Fatal GIB OR = 1.58	2.1	-13.9	-10.4	-35.6	-16.3	-30.9	-19.4	-43.5	-26.7	-39.9	-28.3	-45.4	-	-	-26.8	-38.2
(8) Fatal GIB Incidence Rate - High	22.7	10.2	10.9	-10.7	5.6	-5.4	1.8	-18.7	-1.8	-11.1	-9.6	-23.6	-	-	-11.5	-20.4
(9) Fatal GIB Incidence Rate - Low	23.2	10.6	11.3	-10.5	5.8	-5.3	2.0	-18.6	-1.7	-11.0	-9.5	-23.6	-	-	-11.7	-20.7
(10) Non-fatal GIB Incidence Rate - High	22.7	11.1	9.9	-10.8	4.6	-5.6	0.9	-18.5	-3.1	-11.1	-10.5	-23.3	-	-	-12.6	-19.9
(11) Non-fatal GIB Incidence Rate - Low	23.2	10.0	11.8	-10.7	6.6	-5.4	2.3	-19.1	-1.0	-11.0	-8.7	-23.8	-	-	-10.7	-20.7
(12) Non-fatal GIB OR = 1.38	24.0	10.5	12.2	-10.6	6.8	-5.3	2.9	-18.6	-0.8	-11.0	-8.6	-23.6	-	-	-10.8	-20.7
(13) Non-fatal GIB OR = 1.80	22.0	10.7	9.8	-10.7	4.3	-5.7	0.7	-18.8	-3.0	-11.2	-10.2	-23.3	-	-	-12.4	-20.3
(14) ICH OR = 1.11	45.5	34.7	40.2	20.3	29.5	10.6	29.5	10.6	17.8	10.1	12.4	-0.6	-	-	4.4	-4.0
(15) ICH OR = 1.54	-0.7	-15.0	-22.5	-45.3	-21.7	-35.0	-29.9	-52.7	-20.8	-31.5	-35.7	-50.8	-	-	-28.2	-37.7
(16) IS OR = 0.78	44.1	20.4	44.2	2.6	22.2	1.5	26.8	-9.5	9.3	-6.9	8.4	-17.2	-	-	-2.0	-18.0
(17) IS OR = 1.00	-0.2	0.4	-24.1	-23.9	-13.2	-13.7	-29.4	-30.4	-16.6	-16.7	-29.9	-29.6	-	-	-24.2	-23.5
(18) MI OR = 0.80	49.1	36.8	28.1	6.3	21.5	10.2	12.3	-8.6	7.5	-2.3	-4.0	-18.5	-	-	-9.5	-18.9
(19) MI OR = 0.96	-4.6	-17.9	-5.4	-26.8	-9.1	-19.9	-7.6	-27.6	-11.3	-20.2	-14.5	-28.0	-	-	-14.2	-22.7

Notes: ASCVD = atherosclerotic cardiovascular disease; ASA=acetylsalicylic acid (aspirin); CRC=colorectal cancer; OR=odds ratio; CVD=cardiovascular disease; GIB=major gastrointestinal bleeding; ICH=intracranial hemorrhage; IS=ischemic stroke; MI=myocardial infarction; QALY=net quality-adjusted life years; LY=net life years. Each numbered item represents a one-way sensitivity analysis with the parameter changed as described. Sensitivity ranges are described in **Tables 2**, **3**, and **4**.

Table 21. Sensitivity Analysis Results for Persons With 7.5% ASCVD Baseline Risk (Lifetime Aspirin Use, Lifetime Follow-Up)

	Age 40-49				Age 50-59				Age 60-69				Age 70-79			
	Men		Women		Men		Women		Men		Women		Men		Women	
Scenario	**QALY**	**LY**	**QALY**	**LY**	**QALY**	**LY**	**QALY**	**LY**	**QALY**	**LY**	**QALY**	**LY**	**QALY**	**LY**	**QALY**	**LY**
(0) Base Case	29.1	16.2	19.6	-2.6	12.5	0.4	10.4	-11.8	2.6	-6.7	-5.8	-20.2	-4.6	-10.1	-6.4	-15.4
(1) ASA Disutility = 0.001	9.4	16.2	-3.9	-2.6	-3.9	0.4	-7.6	-11.8	-11.5	-6.7	-20.7	-20.2	-14.9	-10.1	-19.0	-15.4
(2) ASA Disutility = 0.005	-69.5	16.2	-97.8	-2.6	-69.4	0.4	-79.4	-11.8	-67.8	-6.7	-80.2	-20.2	-55.9	-10.1	-69.5	-15.4
(3) CRC OR = 0.64	95.4	82.3	84.7	61.9	68.7	55.6	67.9	45.3	51.0	38.9	34.1	17.3	47.6	41.2	28.4	16.9
(4) CVD Death OR = 0.95	108.1	109.8	91.3	83.2	82.6	83.3	73.4	63.7	60.6	61.8	41.9	36.7	34.0	35.8	33.0	31.3
(5) CVD Incidence Rates ↑10%	38.6	26.9	31.4	9.3	15.1	2.4	18.7	-4.3	6.9	-3.6	-4.7	-20.8	-2.6	-8.9	-9.2	-19.1
(6) CVD Incidence Rates ↓10%	29.5	16.9	18.8	-4.4	12.2	0.0	3.7	-15.7	-0.9	-9.3	-4.7	-19.1	-4.1	-9.4	-8.3	-16.0
(7) Fatal GIB OR = 1.58	9.8	-6.2	1.5	-24.1	-10.2	-26.2	-6.2	-31.1	-19.2	-32.1	-21.8	-38.9	-18.3	-25.9	-23.5	-35.4
(8) Fatal GIB Incidence Rate - High	29.0	16.1	19.7	-2.5	12.5	0.4	10.1	-12.1	2.6	-6.7	-5.9	-20.3	-4.6	-10.0	-6.5	-15.4
(9) Fatal GIB Incidence Rate - Low	29.2	16.2	19.7	-2.6	12.4	0.3	10.6	-11.7	2.6	-6.7	-5.7	-20.2	-4.5	-10.0	-6.4	-15.5
(10) Non-fatal GIB Incidence Rate - High	28.5	16.3	18.8	-2.5	11.6	0.6	9.6	-11.3	1.5	-6.7	-6.4	-19.6	-5.9	-9.9	-7.1	-14.8
(11) Non-fatal GIB Incidence Rate - Low	29.6	15.9	21.0	-2.2	13.2	0.4	11.4	-11.6	3.3	-6.8	-5.1	-20.4	-3.4	-9.8	-5.6	-15.6
(12) Non-fatal GIB OR = 1.38	30.0	16.0	21.2	-2.1	13.7	0.7	11.7	-11.4	3.5	-6.8	-5.0	-20.3	-3.5	-9.8	-5.5	-15.3
(13) Non-fatal GIB OR = 1.80	28.2	16.2	18.6	-2.7	11.4	0.4	9.4	-11.7	1.7	-6.6	-6.6	-20.1	-5.6	-10.2	-7.3	-15.4
(14) ICH OR = 1.11	50.8	39.8	45.7	24.7	35.5	15.4	35.5	15.4	19.2	11.3	18.0	4.8	6.2	1.4	8.9	0.3
(15) ICH OR = 1.54	3.9	-10.8	-11.8	-36.2	-10.1	-24.3	-15.3	-39.1	-16.6	-27.4	-28.2	-43.5	-15.8	-22.2	-26.5	-36.5
(16) IS OR = 0.78	49.9	26.2	50.8	8.4	30.6	7.9	38.2	-1.1	14.9	-2.5	14.6	-12.8	3.9	-6.9	3.6	-13.2
(17) IS OR = 1.00	6.7	7.1	-16.0	-16.2	-7.7	-8.0	-24.6	-26.1	-12.6	-12.8	-27.0	-27.2	-12.4	-12.2	-20.1	-19.2
(18) MI OR = 0.80	58.2	45.7	40.4	17.8	32.6	20.4	22.3	-0.4	12.0	1.9	0.4	-14.7	0.6	-5.5	-3.5	-12.8
(19) MI OR = 0.96	1.3	-11.8	3.3	-18.4	-6.5	-18.7	-2.4	-24.6	-7.0	-16.0	-12.1	-26.0	-10.7	-15.6	-9.8	-18.4

Notes: ASCVD = atherosclerotic cardiovascular disease; ASA=acetylsalicylic acid (aspirin); CRC=colorectal cancer; OR=odds ratio; CVD=cardiovascular disease; GIB=major gastrointestinal bleeding; ICH=intracranial hemorrhage; IS=ischemic stroke; MI=myocardial infarction; QALY=net quality-adjusted life years; LY=net life years. Each numbered item represents a one-way sensitivity analysis with the parameter changed as described. Sensitivity ranges are described in **Tables 2**, **3**, and **4**.

Table 22. Sensitivity Analysis Results for Persons With 10% ASCVD Baseline Risk (Lifetime Aspirin Use, Lifetime Follow-Up)

	Age 40-49				Age 50-59				Age 60-69				Age 70-79			
	Men		Women		Men		Women		Men		Women		Men		Women	
Scenario	**QALY**	**LY**	**QALY**	**LY**	**QALY**	**LY**	**QALY**	**LY**	**QALY**	**LY**	**QALY**	**LY**	**QALY**	**LY**	**QALY**	**LY**
(0) Base Case	48.0	36.1	35.1	11.4	18.0	4.2	17.1	-6.5	7.0	-3.0	2.3	-13.5	-1.1	-6.9	-6.1	-16.6
(1) ASA Disutility = 0.001	29.0	36.1	12.2	11.4	2.3	4.2	-0.3	-6.5	-6.4	-3.0	-11.9	-13.5	-11.4	-6.9	-18.3	-16.6
(2) ASA Disutility = 0.005	-47.3	36.1	-79.4	11.4	-60.7	4.2	-70.0	-6.5	-60.0	-3.0	-68.8	-13.5	-52.4	-6.9	-67.2	-16.6
(3) CRC OR = 0.64	109.9	96.6	102.6	79.5	72.3	57.3	74.5	50.4	55.7	43.4	41.6	23.2	45.3	37.0	25.1	12.1
(4) CVD Death OR = 0.95	126.3	128.4	112.8	104.1	89.4	88.4	80.9	69.8	68.0	69.2	48.7	41.8	43.0	45.0	29.1	25.1
(5) CVD Incidence Rates ↑10%	53.1	40.9	46.0	20.2	21.8	9.2	24.3	1.6	7.1	-3.9	-0.7	-17.4	0.1	-6.7	-6.3	-16.8
(6) CVD Incidence Rates ↓10%	34.5	22.7	24.0	0.1	15.9	2.6	11.0	-9.4	1.6	-6.6	-2.3	-17.2	-0.7	-6.1	-7.0	-16.3
(7) Fatal GIB OR = 1.58	29.3	14.3	19.4	-7.1	-5.3	-23.0	-0.5	-26.8	-13.7	-27.2	-12.9	-31.4	-18.2	-26.7	-24.3	-38.0
(8) Fatal GIB Incidence Rate - High	47.7	35.8	35.1	11.3	17.8	4.1	16.9	-6.6	6.9	-3.1	2.3	-13.5	-1.0	-6.8	-6.0	-16.5
(9) Fatal GIB Incidence Rate - Low	48.2	36.2	35.3	11.5	17.7	4.0	17.0	-6.5	7.0	-3.0	2.3	-13.5	-1.2	-7.1	-6.3	-17.0
(10) Non-fatal GIB Incidence Rate - High	47.2	35.7	34.0	11.3	17.2	4.5	16.6	-5.9	5.5	-3.4	1.4	-13.3	-2.3	-6.6	-7.3	-16.4
(11) Non-fatal GIB Incidence Rate - Low	48.5	35.7	35.8	11.3	18.5	4.0	17.6	-7.0	7.7	-3.0	3.0	-13.7	-0.3	-7.0	-5.6	-17.2
(12) Non-fatal GIB OR = 1.38	49.1	36.2	36.4	11.7	18.8	4.1	17.8	-6.8	8.0	-2.8	3.3	-13.4	-0.3	-6.9	-5.6	-17.1
(13) Non-fatal GIB OR = 1.80	47.1	36.0	34.1	11.4	17.2	4.6	16.0	-6.5	5.6	-3.4	1.5	-13.6	-1.9	-6.8	-6.9	-16.6
(14) ICH OR = 1.11	66.4	56.1	58.3	36.7	41.4	19.9	41.4	19.9	22.5	13.7	21.8	6.9	9.9	4.9	8.4	-1.4
(15) ICH OR = 1.54	26.3	12.6	9.3	-16.4	-2.4	-18.1	-10.7	-37.0	-14.8	-26.7	-22.0	-39.7	-14.0	-20.9	-24.6	-35.8
(16) IS OR = 0.78	68.1	45.4	71.9	28.2	37.8	13.3	48.3	7.8	19.5	2.2	22.7	-7.0	7.4	-3.8	5.5	-13.5
(17) IS OR = 1.00	21.1	23.0	-7.9	-8.8	-3.9	-4.7	-22.5	-23.7	-9.6	-9.6	-22.8	-23.1	-10.5	-10.2	-20.5	-20.0
(18) MI OR = 0.80	80.6	69.3	57.9	34.4	38.1	24.2	31.4	7.7	18.9	8.6	8.4	-8.2	4.4	-1.9	-2.5	-13.4
(19) MI OR = 0.96	12.7	-0.6	14.2	-9.3	-1.4	-14.7	4.6	-18.5	-6.0	-15.8	-4.6	-20.1	-7.2	-12.7	-8.6	-18.6

Notes: ASCVD = atherosclerotic cardiovascular disease; ASA=acetylsalicylic acid (aspirin); CRC=colorectal cancer; OR=odds ratio; CVD=cardiovascular disease; GIB=major gastrointestinal bleeding; ICH=intracranial hemorrhage; IS=ischemic stroke; MI=myocardial infarction; QALY=net quality-adjusted life years; LY=net life years. Each numbered item represents a one-way sensitivity analysis with the parameter changed as described. Sensitivity ranges are described in **Tables 2**, **3**, and **4**.

Table 23. Sensitivity Analysis Results for Persons With 15% ASCVD Baseline Risk (Lifetime Aspirin Use, Lifetime Follow-Up)

	Age 40-49				Age 50-59				Age 60-69				Age 70-79			
	Men		Women		Men		Women		Men		Women		Men		Women	
Scenario	**QALY**	**LY**	**QALY**	**LY**	**QALY**	**LY**	**QALY**	**LY**	**QALY**	**LY**	**QALY**	**LY**	**QALY**	**LY**	**QALY**	**LY**
(0) Base Case	52.3	37.9	43.0	17.7	32.3	18.6	30.8	7.5	8.3	-2.2	11.6	-7.2	-1.9	-7.6	-6.9	-17.9
(1) ASA Disutility = 0.001	34.5	37.9	20.7	17.7	17.8	18.6	14.2	7.5	-3.8	-2.2	-1.6	-7.2	-11.9	-7.6	-18.2	-17.9
(2) ASA Disutility = 0.005	-36.4	37.9	-68.5	17.7	-40.2	18.6	-52.5	7.5	-52.3	-2.2	-54.6	-7.2	-52.1	-7.6	-63.4	-17.9
(3) CRC OR = 0.64	109.6	94.3	103.3	77.6	85.1	70.0	87.0	62.3	51.5	38.1	53.4	33.2	36.3	27.3	26.8	13.7
(4) CVD Death OR = 0.95	128.6	128.6	115.8	104.8	104.8	104.5	100.2	90.6	69.2	69.8	67.2	59.4	45.4	48.3	31.4	28.0
(5) CVD Incidence Rates ↑10%	55.3	42.0	52.9	28.2	40.7	25.6	37.3	13.6	10.8	1.3	13.4	-5.8	-1.0	-7.9	-3.6	-16.4
(6) CVD Incidence Rates ↓10%	44.2	29.9	42.9	17.7	25.6	13.4	23.2	-0.4	6.6	-4.5	10.1	-6.7	-3.4	-9.6	-7.5	-16.2
(7) Fatal GIB OR = 1.58	33.4	15.8	27.8	-0.3	15.1	-1.6	16.0	-9.8	-9.8	-23.3	-2.1	-23.1	-15.5	-23.4	-17.6	-30.4
(8) Fatal GIB Incidence Rate - High	51.9	37.7	42.7	17.4	31.9	18.2	30.9	7.6	8.1	-2.3	11.4	-7.3	-1.9	-7.6	-6.9	-17.9
(9) Fatal GIB Incidence Rate - Low	52.4	38.0	43.0	17.7	32.6	18.9	31.1	7.7	8.2	-2.3	11.7	-7.1	-1.9	-7.6	-6.8	-17.9
(10) Non-fatal GIB Incidence Rate - High	51.8	38.2	42.3	17.9	31.4	18.5	29.6	7.3	7.1	-2.2	10.4	-7.3	-3.5	-7.8	-7.9	-17.6
(11) Non-fatal GIB Incidence Rate - Low	53.6	38.8	43.9	17.9	33.3	18.8	32.0	8.1	9.0	-2.1	12.2	-7.4	-1.4	-7.9	-6.3	-18.2
(12) Non-fatal GIB OR = 1.38	54.0	38.8	44.2	18.0	33.5	18.9	32.1	8.0	9.0	-2.2	12.4	-7.3	-1.2	-7.6	-6.3	-18.1
(13) Non-fatal GIB OR = 1.80	51.0	37.7	41.9	17.7	31.2	18.3	29.9	7.5	7.4	-2.1	10.3	-7.6	-2.7	-7.6	-7.5	-17.8
(14) ICH OR = 1.11	72.5	60.3	66.6	43.1	54.9	33.7	54.9	33.7	24.3	15.0	30.1	13.1	8.7	3.8	9.4	-1.0
(15) ICH OR = 1.54	32.6	16.3	15.0	-12.5	12.4	-3.6	6.4	-18.8	-8.0	-19.5	-10.5	-30.9	-16.4	-23.2	-23.5	-35.5
(16) IS OR = 0.78	76.1	49.6	84.5	37.7	51.1	27.0	65.4	22.6	23.3	3.6	35.6	2.3	6.8	-4.9	5.6	-13.6
(17) IS OR = 1.00	21.7	21.9	-3.5	-3.5	4.5	3.6	-9.7	-11.2	-8.9	-9.4	-16.1	-17.0	-11.2	-11.0	-22.1	-21.8
(18) MI OR = 0.80	85.3	71.5	70.0	44.9	60.1	47.3	47.5	23.8	20.3	9.6	20.0	0.4	4.1	-1.9	-2.7	-14.0
(19) MI OR = 0.96	14.2	-0.6	20.0	-5.8	9.3	-4.4	13.7	-9.1	-2.9	-12.6	1.7	-16.9	-8.1	-13.3	-10.6	-21.3

Notes: ASCVD = atherosclerotic cardiovascular disease; ASA=acetylsalicylic acid (aspirin); CRC=colorectal cancer; OR=odds ratio; CVD=cardiovascular disease; GIB=major gastrointestinal bleeding; ICH=intracranial hemorrhage; IS=ischemic stroke; MI=myocardial infarction; QALY=net quality-adjusted life years; LY=net life years. Each numbered item represents a one-way sensitivity analysis with the parameter changed as described. Sensitivity ranges are described in **Tables 2**, **3**, and **4**.

Table 24. Sensitivity Analysis Results for Persons With 20% ASCVD Baseline Risk (Lifetime Aspirin Use, Lifetime Follow-Up)

	Age 40-49				Age 50-59				Age 60-69				Age 70-79			
	Men		Women		Men		Women		Men		Women		Men		Women	
Scenario	**QALY**	**LY**	**QALY**	**LY**	**QALY**	**LY**	**QALY**	**LY**	**QALY**	**LY**	**QALY**	**LY**	**QALY**	**LY**	**QALY**	**LY**
(0) Base Case	66.2	52.4	50.4	24.2	48.4	33.9	41.6	16.9	16.3	4.9	19.1	-1.6	0.9	-5.5	-4.4	-14.8
(1) ASA Disutility = 0.001	49.4	52.4	28.3	24.2	34.8	33.9	25.4	16.9	5.0	4.9	6.6	-1.6	-8.5	-5.5	-14.9	-14.8
(2) ASA Disutility = 0.005	-17.5	52.4	-59.9	24.2	-19.5	33.9	-39.5	16.9	-39.9	4.9	-43.5	-1.6	-45.9	-5.5	-57.2	-14.8
(3) CRC OR = 0.64	120.0	105.2	118.9	94.0	104.7	89.8	99.2	74.3	60.3	46.4	55.3	32.5	35.0	25.4	23.1	9.6
(4) CVD Death OR = 0.95	149.2	151.2	125.4	114.1	119.6	119.0	110.9	100.0	72.0	71.5	70.8	60.5	42.7	44.1	32.4	28.9
(5) CVD Incidence Rates ↑10%	72.7	59.8	48.0	23.7	53.0	39.0	40.0	15.9	17.1	4.5	20.6	1.1	1.1	-6.5	-3.7	-15.0
(6) CVD Incidence Rates ↓10%	51.9	37.1	39.8	15.4	36.7	23.8	40.9	17.0	10.3	-0.5	18.7	1.1	-0.1	-7.4	-4.4	-15.7
(7) Fatal GIB OR = 1.58	50.9	34.6	35.1	6.2	33.7	16.9	25.2	-2.3	-1.7	-16.1	7.5	-15.5	-12.4	-20.8	-16.9	-29.3
(8) Fatal GIB Incidence Rate - High	65.7	51.9	50.2	24.0	48.3	33.9	41.0	16.2	16.3	5.0	18.8	-1.9	0.7	-5.7	-4.4	-14.8
(9) Fatal GIB Incidence Rate - Low	66.2	52.3	50.5	24.3	48.7	34.3	41.7	16.8	16.4	5.1	19.1	-1.7	0.9	-5.4	-4.4	-14.8
(10) Non-fatal GIB Incidence Rate - High	65.5	52.4	49.3	24.0	47.7	34.0	40.2	16.4	14.9	4.6	18.1	-1.4	-0.7	-5.9	-5.5	-14.5
(11) Non-fatal GIB Incidence Rate - Low	66.6	52.4	51.9	24.9	49.3	34.4	42.2	16.6	17.0	5.0	19.7	-1.8	1.7	-5.5	-3.6	-14.9
(12) Non-fatal GIB OR = 1.38	67.1	52.6	51.8	24.6	49.3	34.1	42.3	16.6	17.2	5.1	19.7	-1.8	1.8	-5.3	-3.7	-14.7
(13) Non-fatal GIB OR = 1.80	65.2	52.3	49.1	23.9	47.5	34.0	40.3	16.4	15.4	5.0	18.2	-1.7	-0.1	-5.7	-5.0	-14.5
(14) ICH OR = 1.11	83.3	71.3	73.4	49.3	64.4	41.7	64.4	41.7	31.8	22.0	36.3	17.0	11.4	5.8	10.4	0.6
(15) ICH OR = 1.54	46.5	30.6	24.8	-3.0	29.0	12.3	16.0	-11.3	-3.7	-17.2	1.3	-20.7	-12.3	-19.7	-21.6	-32.6
(16) IS OR = 0.78	92.5	66.6	86.6	40.4	69.8	44.5	77.7	33.5	33.5	13.8	45.4	9.1	10.5	-2.3	9.9	-11.3
(17) IS OR = 1.00	31.7	32.8	0.2	0.3	19.5	19.9	-3.9	-4.5	-2.2	-2.7	-12.6	-13.3	-9.1	-8.9	-20.4	-20.4
(18) MI OR = 0.80	108.1	95.6	80.0	54.3	77.8	64.2	64.0	39.7	31.2	19.3	30.5	9.4	7.6	0.7	-0.8	-11.9
(19) MI OR = 0.96	24.4	9.2	25.9	-0.8	17.7	2.6	20.4	-4.3	-0.1	-11.2	9.9	-10.3	-5.4	-11.3	-8.4	-18.0

Notes: ASCVD = atherosclerotic cardiovascular disease; ASA=acetylsalicylic acid (aspirin); CRC=colorectal cancer; OR=odds ratio; CVD=cardiovascular disease; GIB=major gastrointestinal bleeding; ICH=intracranial hemorrhage; IS=ischemic stroke; MI=myocardial infarction; QALY=net quality-adjusted life years; LY=net life years. Each numbered item represents a one-way sensitivity analysis with the parameter changed as described. Sensitivity ranges are described in **Tables 2**, **3**, and **4**.

Table 25a. Net Benefit of Aspirin After 10 Years and Lifetime Net Benefit at Stopping Intervals and With Lifetime Use (CRC OR = 0.64), Initiation Age 40-49y

	10y use*	Stop at age 65y	Stop at age 70y	Stop at age 75y	Stop at age 80y	Stop at age 85y	Lifetime use
Men, Net QALYs per 1000 persons							
5% 10y ASCVD Risk	2.4	60.9	72.9	79.2	81.6	83.3	82.9
7.5% 10y ASCVD Risk	2.8	73.2	82.9	89.3	93.2	94.9	95.4
10% 10y ASCVD Risk	3.8	85.9	96.8	103.3	107.7	108.9	109.9
15% 10y ASCVD Risk	4.1	87.7	98.1	104.9	107.3	109.4	109.6
20% 10y ASCVD Risk	5.6	97.0	107.1	114.0	117.9	119.3	120.0
Men, Net Life Years per 1000 persons							
5% 10y ASCVD Risk	1.4	55.5	65.9	69.7	70.2	70.7	69.7
7.5% 10y ASCVD Risk	1.1	66.4	74.5	79.2	81.5	82.4	82.3
10% 10y ASCVD Risk	1.3	79.2	88.1	93.0	95.9	96.2	96.6
15% 10y ASCVD Risk	1.3	78.9	87.5	92.5	93.3	94.7	94.3
20% 10y ASCVD Risk	1.8	88.7	96.1	101.3	104.4	104.8	105.2
Women, Net QALYs per 1000 persons							
5% 10y ASCVD Risk	2.2	52.4	61.1	65.3	68.6	69.8	69.8
7.5% 10y ASCVD Risk	2.9	61.8	71.1	79.5	82.3	83.8	84.7
10% 10y ASCVD Risk	3.1	72.6	88.0	95.5	100.0	101.8	102.6
15% 10y ASCVD Risk	4.1	75.7	88.2	96.6	100.4	102.4	103.3
20% 10y ASCVD Risk	4.7	90.2	103.1	110.3	116.1	117.6	118.9
Women, Net Life Years per 1000 persons							
5% 10y ASCVD Risk	0.9	43.3	48.4	49.8	49.9	49.2	47.5
7.5% 10y ASCVD Risk	1.3	52.1	57.6	62.8	63.3	62.8	61.9
10% 10y ASCVD Risk	1.2	61.3	73.8	77.9	80.1	79.9	79.5
15% 10y ASCVD Risk	1.3	62.1	70.5	76.6	77.5	77.9	77.6
20% 10y ASCVD Risk	1.4	77.0	86.5	91.1	94.4	94.0	94.0

Notes: CRC = colorectal cancer; OR = odds ratio; ASCVD=atherosclerotic cardiovascular disease; CVD=cardiovascular disease; QALY=quality-adjusted life year; N/A=not applicable; y=years. The 10-year ASCVD risk levels are based on the ACC/AHA risk calculator and refer to a person's risk at model baseline/initiation. Risk levels are rounded to the nearest threshold (+/- 0.5%). Results reflect the difference between universal adoption of aspirin for primary prevention versus zero adoption. All else is held equal. Stopping age indicates the age at which persons in the aspirin for primary prevention arm stop aspirin. This table presents results for a sensitivity analysis in which the risk for CRC incidence was 36% lower (OR = 0.64) with use of aspirin for at least 10 years. * The "10y use" column indicates net benefit over 10 years of aspirin use. All other columns indicate net benefits over a lifetime horizon.

Table 25b. Net Benefit of Aspirin After 10 Years and Lifetime Net Benefit at Stopping Intervals and With Lifetime Use (CRC OR = 0.64), Initiation Age 50-59y

	10y use*	Stop at age 65y	Stop at age 70y	Stop at age 75y	Stop at age 80y	Stop at age 85y	Lifetime use
Men, Net QALYs per 1000 persons							
5% 10y ASCVD Risk	3.6	33.9	49.9	54.8	57.2	58.7	58.8
7.5% 10y ASCVD Risk	4.1	36.5	58.4	65.1	67.7	68.3	68.7
10% 10y ASCVD Risk	5.4	35.8	59.5	67.0	69.9	71.9	72.3
15% 10y ASCVD Risk	6.1	45.3	71.9	79.6	83.2	84.4	85.1
20% 10y ASCVD Risk	8.5	56.2	86.3	95.9	101.5	103.5	104.7
Men, Net Life Years per 1000 persons							
5% 10y ASCVD Risk	1.5	29.7	43.8	46.6	46.9	47.0	45.9
7.5% 10y ASCVD Risk	1.8	34.0	52.6	56.6	57.0	55.9	55.6
10% 10y ASCVD Risk	2.3	31.2	52.5	57.0	57.0	57.6	57.3
15% 10y ASCVD Risk	1.8	40.0	63.3	68.3	70.1	69.9	70.0
20% 10y ASCVD Risk	3.1	50.8	77.6	84.4	88.3	89.3	89.8
Women, Net QALYs per 1000 persons							
5% 10y ASCVD Risk	2.4	23.1	39.9	47.7	52.7	53.3	53.1
7.5% 10y ASCVD Risk	4.2	31.3	56.1	64.0	66.3	67.7	67.9
10% 10y ASCVD Risk	5.4	37.2	61.4	69.9	73.0	74.5	74.5
15% 10y ASCVD Risk	6.5	40.7	69.0	79.0	83.7	86.0	87.0
20% 10y ASCVD Risk	7.1	43.7	78.6	90.0	96.6	98.4	99.2
Women, Net Life Years per 1000 persons							
5% 10y ASCVD Risk	0.4	16.8	29.8	33.6	34.6	33.0	31.0
7.5% 10y ASCVD Risk	1.3	24.7	45.0	48.6	48.1	46.8	45.3
10% 10y ASCVD Risk	1.6	29.3	49.4	53.5	53.1	51.9	50.4
15% 10y ASCVD Risk	2.2	32.3	55.1	61.5	63.3	63.1	62.3
20% 10y ASCVD Risk	2.1	34.8	65.3	72.3	75.2	75.2	74.3

Notes: CRC = colorectal cancer; OR = odds ratio; ASCVD=atherosclerotic cardiovascular disease; CVD=cardiovascular disease; QALY=quality-adjusted life year; N/A=not applicable; y=years. The 10-year ASCVD risk levels are based on the ACC/AHA risk calculator and refer to a person's risk at model baseline/initiation. Risk levels are rounded to the nearest threshold (+/- 0.5%). Results reflect the difference between universal adoption of aspirin for primary prevention versus zero adoption. All else is held equal. Stopping age indicates the age at which persons in the aspirin for primary prevention arm stop aspirin. This table presents results for a sensitivity analysis in which the risk for CRC incidence was 36% lower (OR = 0.64) with use of aspirin for at least 10 years. * The "10y use" column indicates net benefit over 10 years of aspirin use. All other columns indicate net benefits over a lifetime horizon.

Table 25c. Net Benefit of Aspirin After 10 Years and Lifetime Net Benefit at Stopping Intervals and With Lifetime Use (CRC OR = 0.64), Initiation Age 60-69y

	10y use*	Stop at age 75y	Stop at age 80y	Stop at age 85y	Lifetime use
Men, Net QALYs per 1000 persons					
5% 10y ASCVD Risk	5.1	45.5	46.9	50.1	50.0
7.5% 10y ASCVD Risk	5.1	41.9	48.8	50.2	51.0
10% 10y ASCVD Risk	6.1	44.9	54.7	55.9	55.7
15% 10y ASCVD Risk	6.7	38.0	49.8	51.4	51.5
20% 10y ASCVD Risk	8.0	43.1	57.6	59.1	60.3
Men, Net QALYs per 1000 persons					
5% 10y ASCVD Risk	3.0	39.9	39.0	40.0	38.8
7.5% 10y ASCVD Risk	2.1	35.0	39.5	39.0	38.9
10% 10y ASCVD Risk	2.6	37.8	44.8	44.5	43.4
15% 10y ASCVD Risk	2.4	30.8	39.0	38.9	38.1
20% 10y ASCVD Risk	2.1	35.2	46.3	46.2	46.4
Women, Net QALYs per 1000 persons					
5% 10y ASCVD Risk	2.7	28.4	35.3	34.5	33.8
7.5% 10y ASCVD Risk	4.3	25.1	34.1	34.5	34.1
10% 10y ASCVD Risk	3.7	24.3	42.5	43.4	41.6
15% 10y ASCVD Risk	6.5	31.4	50.0	52.5	53.4
20% 10y ASCVD Risk	8.5	35.4	51.6	54.3	55.3
Women, Net Life Years per 1000 persons					
5% 10y ASCVD Risk	1.0	22.0	24.4	20.8	18.0
7.5% 10y ASCVD Risk	1.4	17.2	21.6	19.7	17.3
10% 10y ASCVD Risk	-0.1	15.6	29.1	27.4	23.2
15% 10y ASCVD Risk	1.0	21.6	35.4	34.7	33.2
20% 10y ASCVD Risk	1.7	23.9	34.1	33.7	32.5

Notes: CRC = colorectal cancer; OR = odds ratio; ASCVD=atherosclerotic cardiovascular disease; CVD=cardiovascular disease; QALY=quality-adjusted life year; N/A=not applicable; y=years. The 10-year ASCVD risk levels are based on the ACC/AHA risk calculator and refer to a person's risk at model baseline/initiation. Risk levels are rounded to the nearest threshold (+/- 0.5%). Results reflect the difference between universal adoption of aspirin for primary prevention versus zero adoption. All else is held equal. Stopping age indicates the age at which persons in the aspirin for primary prevention arm stop aspirin. This table presents results for a sensitivity analysis in which the risk for CRC incidence was 36% lower (OR = 0.64) with use of aspirin for at least 10 years. * The "10y use" column indicates net benefit over 10 years of aspirin use. All other columns indicate net benefits over a lifetime horizon.

Table 25d. Net Benefit of Aspirin After 10 Years and Lifetime Net Benefit at Stopping Intervals and With Lifetime Use (CRC OR = 0.64), Initiation Age 70-79y

	10y use*	Stop at age 85y	Lifetime use
Men, Net QALYs per 1000 persons			
5% 10y ASCVD Risk	N/A	N/A	N/A
7.5% 10y ASCVD Risk	10.7	45.6	47.6
10% 10y ASCVD Risk	9.8	43.5	45.3
15% 10y ASCVD Risk	7.9	35.6	36.3
20% 10y ASCVD Risk	9.5	33.3	35.0
Men, Net QALYs per 1000 persons			
5% 10y ASCVD Risk	N/A	N/A	N/A
7.5% 10y ASCVD Risk	7.2	41.1	41.2
10% 10y ASCVD Risk	5.5	37.0	37.0
15% 10y ASCVD Risk	3.5	28.0	27.3
20% 10y ASCVD Risk	4.7	25.5	25.4
Women, Net QALYs per 1000 persons			
5% 10y ASCVD Risk	3.8	23.0	21.1
7.5% 10y ASCVD Risk	5.1	31.4	28.4
10% 10y ASCVD Risk	4.9	25.6	25.1
15% 10y ASCVD Risk	5.0	26.4	26.8
20% 10y ASCVD Risk	4.8	21.3	23.1
Women, Net Life Years per 1000 persons			
5% 10y ASCVD Risk	1.7	14.4	9.2
7.5% 10y ASCVD Risk	2.2	22.8	16.9
10% 10y ASCVD Risk	1.4	15.3	12.1
15% 10y ASCVD Risk	0.8	16.2	13.7
20% 10y ASCVD Risk	0.1	11.1	9.6

Notes: CRC = colorectal cancer; OR = odds ratio; ASCVD=atherosclerotic cardiovascular disease; CVD=cardiovascular disease; QALY=quality-adjusted life year; N/A=not applicable; y=years. The 10-year ASCVD risk levels are based on the ACC/AHA risk calculator and refer to a person's risk at model baseline/initiation. Risk levels are rounded to the nearest threshold (+/- 0.5%). Results reflect the difference between universal adoption of aspirin for primary prevention versus zero adoption. All else is held equal. Stopping age indicates the age at which persons in the aspirin for primary prevention arm stop aspirin. This table presents results for a sensitivity analysis in which the risk for CRC incidence was 36% lower (OR = 0.64) with use of aspirin for at least 10 years. * The "10y use" column indicates net benefit over 10 years of aspirin use. All other columns indicate net benefits over a lifetime horizon.

Table 26. Lifetime Net Events of Aspirin for Men With Lifetime Use (CRC OR = 0.64)

	Benefits from aspirin (Prevented events per 1,000 persons)						Harms from aspirin (Incurred events per 1,000 persons)				Net Balance (Benefits - harms)		
10-yr ASCVD Risk (%)	Myocardial infarction	Ischemic stroke	Non-fatal CVD Events	CVD Deaths	CRC Cases	CRC Deaths	Major GI Bleeds	Major GI Bleed Deaths	Intracranial Hemorrhage	Intracranial Hemorrhage Deaths	Net QALYs	Net Life Years	Net Events Prevented
Men, Initiation Age 40-49 years													
5	16.3	5.8	26.6	3.4	10.4	4.3	31.8	0.0	3.0	2.7	82.9	69.7	2.9
7.5	18.9	6.2	30.4	3.2	11.3	4.7	30.6	0.0	2.6	2.4	95.4	82.3	9.4
10	19.8	6.7	32.0	3.7	11.4	4.6	30.0	0.0	2.3	2.1	109.9	96.6	12.5
15	21.8	7.6	35.8	3.9	10.5	4.3	27.4	0.0	2.6	2.3	109.6	94.3	17.7
20	24.1	7.3	37.9	4.5	10.2	4.1	25.1	0.0	2.5	2.3	120.0	105.2	22.7
Men, Initiation Age 50-59 years													
5	13.8	5.7	23.2	2.5	10.6	4.1	33.0	0.0	3.2	2.8	58.8	45.9	-2.7
7.5	14.6	6.5	24.7	2.5	10.9	4.7	31.3	0.0	3.1	2.8	68.7	55.6	0.7
10	15.1	7.0	26.5	2.7	10.7	4.5	30.2	0.0	2.9	2.6	72.3	57.3	4.2
15	18.2	7.3	30.8	3.2	10.4	4.3	28.1	0.0	2.7	2.5	85.1	70.0	11.2
20	19.7	8.0	33.5	3.5	10.6	4.5	25.2	0.0	2.2	1.9	104.7	89.8	18.2
Men, Initiation Age 60-69 years													
5	9.7	5.7	17.4	1.5	11.0	4.6	33.2	0.0	3.1	2.7	50.0	38.8	-9.2
7.5	10.9	5.9	19.3	1.5	10.9	4.7	31.4	0.0	2.8	2.5	51.0	38.9	-5.0
10	12.2	5.7	21.1	2.2	11.1	4.7	30.6	0.0	3.1	2.7	55.7	43.4	-2.0
15	11.8	6.1	20.9	2.2	10.7	4.0	28.3	0.1	3.0	2.6	51.5	38.1	-0.3
20	14.3	7.0	25.3	3.0	10.5	4.2	26.7	0.0	2.9	2.6	60.3	46.4	6.8
Men, Initiation Age 70-79 years													
5	-	-	-	-	-	-	-	-	-	-	-	-	-
7.5	7.5	4.4	13.4	0.5	11.4	6.1	28.3	0.0	2.6	2.4	47.6	41.2	-8.0
10	8.5	4.7	14.9	1.0	11.7	5.4	28.5	0.0	2.7	2.3	45.3	37.0	-5.9
15	8.5	5.0	15.2	1.2	10.5	4.6	27.6	0.0	2.6	2.2	36.3	27.3	-5.5
20	9.3	5.3	16.7	1.3	10.0	4.0	25.9	0.0	2.6	2.2	35.0	25.4	-2.8

Notes: ASCVD=atherosclerotic cardiovascular disease; CVD=cardiovascular disease; CRC=colorectal cancer; GI=gastrointestinal; QALY=quality-adjusted life year. The 10-year ASCVD risk levels are based on the ACC/AHA risk calculator and refer to a person's risk at model baseline/initiation. Risk levels are rounded to the nearest threshold (+/- 0.5%). Results reflect the difference between universal adoption of aspirin for primary prevention versus zero adoption; all else is held equal. MI and ischemic stroke events are non-fatal. The non-fatal CVD event column combines non-fatal 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: (Non-fatal CVD events + CVD deaths + CRC cases) – (Major GI bleeds + intracranial hemorrhage). This table presents results for a sensitivity analysis in which the risk for CRC incidence was 36% lower (OR = 0.64) with use of aspirin for at least 10 years.

Table 27. Lifetime Net Events of Aspirin for Women With Lifetime Use (CRC OR = 0.64)

	Benefits from aspirin (Prevented events per 1,000 persons)						Harms from aspirin (Incurred events per 1,000 persons)				Net Balance (Benefits - harms)		
10-yr ASCVD Risk (%)	Myocardial infarction	Ischemic stroke	Non-fatal CVD Events	CVD Deaths	CRC Cases	CRC Deaths	Major GI Bleeds	Major GI Bleed Deaths	Intracranial Hemorrhage	Intracranial Hemorrhage Deaths	Net QALYs	Net Life Years	Net Events Prevented
Women, Initiation Age 40-49 years													
5	10.0	9.4	23.2	2.6	10.4	3.9	32.1	0.0	4.0	3.6	69.8	47.5	-3.6
7.5	10.2	9.5	24.1	3.0	11.0	4.3	30.6	0.0	3.2	2.9	84.7	61.9	1.3
10	11.0	9.9	25.6	2.9	11.3	4.8	29.6	0.0	3.1	2.9	102.6	79.5	4.2
15	11.3	10.2	27.0	3.6	10.6	4.1	29.6	0.0	2.9	2.6	103.3	77.6	6.0
20	11.8	10.8	28.3	3.6	10.6	4.3	30.3	0.0	2.8	2.5	118.9	94.0	6.9
Women, Initiation Age 50-59 years													
5	8.2	9.5	21.2	2.4	10.3	4.1	31.1	0.0	4.1	3.5	53.1	31.0	-5.0
7.5	8.8	10.0	22.9	2.5	10.4	4.3	29.1	0.0	3.8	3.4	67.9	45.3	-0.6
10	8.9	10.5	23.0	3.0	11.1	4.3	28.3	0.0	3.6	3.3	74.5	50.4	1.9
15	10.1	11.4	26.3	2.5	10.8	4.3	27.3	0.0	3.2	2.9	87.0	62.3	6.2
20	11.1	11.2	28.3	3.0	10.8	4.4	25.8	0.0	2.9	2.7	99.2	74.3	10.7
Women, Initiation Age 60-69 years													
5	5.5	7.6	15.2	1.4	9.5	4.0	30.7	0.0	4.1	3.5	33.8	18.0	-12.1
7.5	6.4	7.9	16.5	1.6	9.2	3.6	29.2	0.0	3.8	3.2	34.1	17.3	-8.9
10	6.3	8.9	17.9	2.0	9.4	3.7	27.8	0.0	3.7	3.2	41.6	23.2	-5.4
15	7.0	10.2	20.6	2.2	9.4	3.9	26.1	0.0	3.3	2.9	53.4	33.2	-0.2
20	7.8	11.3	23.5	2.7	8.6	3.5	25.4	0.0	3.3	2.8	55.3	32.5	3.2
Women, Initiation Age 70-79 years													
5	4.2	6.8	12.1	0.9	8.7	3.4	29.6	0.0	3.8	3.2	21.1	9.2	-14.8
7.5	4.6	6.7	12.6	0.7	8.8	3.7	28.5	0.0	3.3	2.7	28.4	16.9	-12.5
10	4.2	6.9	12.8	1.0	8.2	3.3	27.5	0.0	3.0	2.7	25.1	12.1	-11.2
15	4.9	7.5	13.9	1.1	8.5	3.7	24.9	0.0	3.5	2.9	26.8	13.7	-7.8
20	5.2	7.2	14.8	1.6	8.0	3.0	24.2	0.0	3.5	3.0	23.1	9.6	-6.3

Notes: ASCVD=atherosclerotic cardiovascular disease; CVD=cardiovascular disease; CRC=colorectal cancer; GI=gastrointestinal; QALY=quality-adjusted life year. The 10-year ASCVD risk levels are based on the ACC/AHA risk calculator and refer to a person's risk at model baseline/initiation. Risk levels are rounded to the nearest threshold (+/- 0.5%). Results reflect the difference between universal adoption of aspirin for primary prevention versus zero adoption; all else is held equal. MI and ischemic stroke events are non-fatal. The non-fatal CVD event column combines non-fatal 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: (Non-fatal CVD events + CVD deaths + CRC cases) – (Major GI bleeds + intracranial hemorrhage). This table presents results for a sensitivity analysis in which the risk for CRC incidence was 36% lower (OR = 0.64) with use of aspirin for at least 10 years.

Table 28a. Net Benefit of Aspirin After 10 Years and Lifetime Net Benefit at Stopping Intervals and With Lifetime Use (CVD Death OR = 0.95), Initiation Age 40-49y

	10y use*	Stop at age 65y	Stop at age 70y	Stop at age 75y	Stop at age 80y	Stop at age 85y	Lifetime use
Men, Net QALYs per 1000 persons							
5% 10y ASCVD Risk	2.5	54.5	69.1	81.6	91.8	97.5	100.4
7.5% 10y ASCVD Risk	3.6	63.0	77.7	89.9	100.1	105.5	108.1
10% 10y ASCVD Risk	5.5	84.1	98.7	109.6	117.0	123.2	126.3
15% 10y ASCVD Risk	6.4	90.4	106.0	116.7	121.7	127.1	128.6
20% 10y ASCVD Risk	8.1	102.9	120.4	134.3	142.4	146.0	149.2
Men, Net Life Years per 1000 persons							
5% 10y ASCVD Risk	3.1	56.0	71.0	83.1	93.4	98.9	101.9
7.5% 10y ASCVD Risk	3.9	63.8	79.2	91.7	102.0	107.4	109.8
10% 10y ASCVD Risk	5.1	86.4	100.9	112.0	119.1	125.5	128.4
15% 10y ASCVD Risk	5.8	91.1	106.9	117.3	121.7	127.3	128.6
20% 10y ASCVD Risk	6.7	104.8	121.8	136.1	144.5	147.8	151.2
Women, Net QALYs per 1000 persons							
5% 10y ASCVD Risk	1.3	39.6	52.0	61.1	70.3	75.5	79.5
7.5% 10y ASCVD Risk	2.1	47.6	61.6	73.7	80.2	86.5	91.3
10% 10y ASCVD Risk	3.4	62.0	80.9	92.6	103.0	108.1	112.8
15% 10y ASCVD Risk	3.5	65.4	82.3	95.8	104.4	110.8	115.8
20% 10y ASCVD Risk	4.3	74.0	92.1	104.0	114.4	119.9	125.4
Women, Net Life Years per 1000 persons							
5% 10y ASCVD Risk	1.4	35.8	46.7	55.1	63.0	67.8	70.9
7.5% 10y ASCVD Risk	2.2	44.2	57.1	67.8	73.7	79.2	83.2
10% 10y ASCVD Risk	3.1	57.3	75.2	85.7	95.8	99.9	104.1
15% 10y ASCVD Risk	2.8	58.4	73.6	86.7	94.1	100.1	104.8
20% 10y ASCVD Risk	3.2	66.5	83.5	94.8	104.3	109.0	114.1

Notes: CVD=cardiovascular disease; OR = odds ratio; ASCVD=atherosclerotic cardiovascular disease; QALY=quality-adjusted life year; N/A=not applicable; y=years. The 10-year ASCVD risk levels are based on the ACC/AHA risk calculator and refer to a person's risk at model baseline/initiation. Risk levels are rounded to the nearest threshold (+/- 0.5%). Results reflect the difference between universal adoption of aspirin for primary prevention versus zero adoption. All else is held equal. Stopping age indicates the age at which persons in the aspirin for primary prevention arm stop aspirin. This table presents results for a sensitivity analysis in which the risk for CVD mortality was 5% lower (OR = 0.95) with aspirin use. * The "10y use" column indicates net benefit over 10 years of aspirin use. All other columns indicate net benefits over a lifetime horizon.

Table 28b. Net Benefit of Aspirin After 10 Years and Lifetime Net Benefit at Stopping Intervals and With Lifetime Use (CVD Death OR = 0.95), Initiation Age 50-59y

	10y use*	Stop at age 65y	Stop at age 70y	Stop at age 75y	Stop at age 80y	Stop at age 85y	Lifetime use
Men, Net QALYs per 1000 persons							
5% 10y ASCVD Risk	3.7	29.1	43.8	56.5	66.5	72.6	77.1
7.5% 10y ASCVD Risk	5.2	29.0	45.8	59.2	71.0	78.0	82.6
10% 10y ASCVD Risk	6.3	36.6	52.2	67.2	77.3	85.6	89.4
15% 10y ASCVD Risk	8.9	46.9	69.3	84.2	94.8	100.7	104.8
20% 10y ASCVD Risk	10.4	57.0	80.4	96.0	109.0	115.3	119.6
Men, Net Life Years per 1000 persons							
5% 10y ASCVD Risk	4.3	29.6	45.5	58.6	68.6	74.4	78.8
7.5% 10y ASCVD Risk	5.7	30.1	46.6	60.0	71.8	78.5	83.3
10% 10y ASCVD Risk	6.6	36.9	52.5	67.3	76.4	84.7	88.4
15% 10y ASCVD Risk	8.3	46.7	69.5	83.9	94.6	100.3	104.5
20% 10y ASCVD Risk	8.9	56.8	80.1	95.2	108.4	114.8	119.0
Women, Net QALYs per 1000 persons							
5% 10y ASCVD Risk	3.1	21.9	32.2	45.1	55.0	61.9	67.0
7.5% 10y ASCVD Risk	3.4	25.5	39.1	51.3	60.2	67.5	73.4
10% 10y ASCVD Risk	5.8	30.8	48.3	61.0	69.3	75.1	80.9
15% 10y ASCVD Risk	8.0	41.2	61.7	76.7	88.3	94.8	100.2
20% 10y ASCVD Risk	9.1	47.1	69.4	85.4	96.8	104.1	110.9
Women, Net Life Years per 1000 persons							
5% 10y ASCVD Risk	3.6	19.8	28.8	40.3	48.0	54.5	59.1
7.5% 10y ASCVD Risk	3.0	21.8	33.3	43.8	51.9	58.1	63.7
10% 10y ASCVD Risk	4.9	25.7	42.4	53.2	59.8	64.1	69.8
15% 10y ASCVD Risk	6.9	37.7	56.2	70.2	80.9	86.0	90.6
20% 10y ASCVD Risk	7.5	43.2	63.2	77.4	86.8	93.8	100.0

Notes: CVD=cardiovascular disease; OR = odds ratio; ASCVD=atherosclerotic cardiovascular disease; QALY=quality-adjusted life year; N/A=not applicable; y=years. The 10-year ASCVD risk levels are based on the ACC/AHA risk calculator and refer to a person's risk at model baseline/initiation. Risk levels are rounded to the nearest threshold (+/- 0.5%). Results reflect the difference between universal adoption of aspirin for primary prevention versus zero adoption. All else is held equal. Stopping age indicates the age at which persons in the aspirin for primary prevention arm stop aspirin. This table presents results for a sensitivity analysis in which the risk for CVD mortality was 5% lower (OR = 0.95) with aspirin use. * The "10y use" column indicates net benefit over 10 years of aspirin use. All other columns indicate net benefits over a lifetime horizon.

Table 28c. Net Benefit of Aspirin After 10 Years and Lifetime Net Benefit at Stopping Intervals and With Lifetime Use (CVD Death OR = 0.95), Initiation Age 60-69y

	10y use*	Stop at age 75y	Stop at age 80y	Stop at age 85y	Lifetime use
Men, Net QALYs per 1000 persons					
5% 10y ASCVD Risk	3.2	26.7	35.5	45.3	51.3
7.5% 10y ASCVD Risk	5.7	34.9	47.0	54.1	60.6
10% 10y ASCVD Risk	7.6	40.8	54.3	62.5	68.0
15% 10y ASCVD Risk	9.4	42.2	54.2	63.3	69.2
20% 10y ASCVD Risk	11.3	45.4	60.1	66.8	72.0
Men, Net QALYs per 1000 persons					
5% 10y ASCVD Risk	4.3	27.4	36.3	45.6	51.6
7.5% 10y ASCVD Risk	6.6	36.1	48.3	55.1	61.8
10% 10y ASCVD Risk	8.4	41.6	55.2	63.4	69.2
15% 10y ASCVD Risk	10.0	42.6	54.4	63.6	69.8
20% 10y ASCVD Risk	10.7	45.0	60.0	66.5	71.5
Women, Net QALYs per 1000 persons					
5% 10y ASCVD Risk	3.8	22.3	29.5	34.2	40.2
7.5% 10y ASCVD Risk	4.2	20.9	29.4	36.2	41.9
10% 10y ASCVD Risk	4.9	23.7	36.1	43.1	48.7
15% 10y ASCVD Risk	9.0	36.3	49.8	59.2	67.2
20% 10y ASCVD Risk	10.6	38.9	54.0	63.7	70.8
Women, Net Life Years per 1000 persons					
5% 10y ASCVD Risk	5.0	21.4	26.5	30.1	35.5
7.5% 10y ASCVD Risk	4.4	18.2	25.2	31.6	36.7
10% 10y ASCVD Risk	4.8	20.5	30.9	37.1	41.8
15% 10y ASCVD Risk	7.7	32.5	44.2	52.2	59.4
20% 10y ASCVD Risk	7.8	33.1	45.8	54.1	60.5

Notes: CVD=cardiovascular disease; OR = odds ratio; ASCVD=atherosclerotic cardiovascular disease; QALY=quality-adjusted life year; N/A=not applicable; y=years. The 10-year ASCVD risk levels are based on the ACC/AHA risk calculator and refer to a person's risk at model baseline/initiation. Risk levels are rounded to the nearest threshold (+/- 0.5%). Results reflect the difference between universal adoption of aspirin for primary prevention versus zero adoption. All else is held equal. Stopping age indicates the age at which persons in the aspirin for primary prevention arm stop aspirin. This table presents results for a sensitivity analysis in which the risk for CVD mortality was 5% lower (OR = 0.95) with aspirin use. * The "10y use" column indicates net benefit over 10 years of aspirin use. All other columns indicate net benefits over a lifetime horizon.

Table 28d. Net Benefit of Aspirin After 10 Years and Lifetime Net Benefit at Stopping Intervals and With Lifetime Use (CVD Death OR = 0.95), Initiation Age 70-79y

	10y use*	Stop at age 85y	Lifetime use
Men, Net QALYs per 1000 persons			
5% 10y ASCVD Risk	N/A	N/A	N/A
7.5% 10y ASCVD Risk	6.4	24.2	34.0
10% 10y ASCVD Risk	7.1	32.6	43.0
15% 10y ASCVD Risk	9.4	37.1	45.4
20% 10y ASCVD Risk	11.0	34.2	42.7
Men, Net QALYs per 1000 persons			
5% 10y ASCVD Risk	N/A	N/A	N/A
7.5% 10y ASCVD Risk	8.0	25.9	35.8
10% 10y ASCVD Risk	8.2	34.3	45.0
15% 10y ASCVD Risk	10.9	39.7	48.3
20% 10y ASCVD Risk	11.8	35.3	44.1
Women, Net QALYs per 1000 persons			
5% 10y ASCVD Risk	2.6	16.4	23.1
7.5% 10y ASCVD Risk	5.5	26.0	33.0
10% 10y ASCVD Risk	5.0	21.6	29.1
15% 10y ASCVD Risk	5.9	23.4	31.4
20% 10y ASCVD Risk	6.4	23.1	32.4
Women, Net Life Years per 1000 persons			
5% 10y ASCVD Risk	3.8	14.8	20.4
7.5% 10y ASCVD Risk	6.4	25.2	31.3
10% 10y ASCVD Risk	5.3	18.4	25.1
15% 10y ASCVD Risk	6.2	20.7	28.0
20% 10y ASCVD Risk	6.3	20.1	28.9

Notes: CVD=cardiovascular disease; OR = odds ratio; ASCVD=atherosclerotic cardiovascular disease; QALY=quality-adjusted life year; N/A=not applicable; y=years. The 10-year ASCVD risk levels are based on the ACC/AHA risk calculator and refer to a person's risk at model baseline/initiation. Risk levels are rounded to the nearest threshold (+/- 0.5%). Results reflect the difference between universal adoption of aspirin for primary prevention versus zero adoption. All else is held equal. Stopping age indicates the age at which persons in the aspirin for primary prevention arm stop aspirin. This table presents results for a sensitivity analysis in which the risk for CVD mortality was 5% lower (OR = 0.95) with aspirin use. * The "10y use" column indicates net benefit over 10 years of aspirin use. All other columns indicate net benefits over a lifetime horizon.

Table 29. Lifetime Net Events of Aspirin for Men With Lifetime Use (CVD Death OR = 0.95)

	Benefits from aspirin (Prevented events per 1,000 persons)						Harms from aspirin (Incurred events per 1,000 persons)				Net Balance (Benefits - harms)		
10-yr ASCVD Risk (%)	Myocardial infarction	Ischemic stroke	Non-fatal CVD Events	CVD Deaths	CRC Cases	CRC Deaths	Major GI Bleeds	Major GI Bleed Deaths	Intracranial Hemorrhage	Intracranial Hemorrhage Deaths	Net QALYs	Net Life Years	Net Events Prevented
Men, Initiation Age 40-49 years													
5	16.0	5.5	25.6	9.1	-0.3	0.2	32.0	0.0	3.0	2.6	100.4	101.9	-3.2
7.5	18.6	5.9	29.3	9.3	-0.4	0.2	30.8	0.0	2.7	2.4	108.1	109.8	2.3
10	19.3	6.5	30.9	9.5	-0.2	0.1	30.2	0.0	2.4	2.1	126.3	128.4	5.5
15	21.3	7.3	34.2	9.4	-0.4	0.2	27.6	0.1	2.6	2.3	128.6	128.6	10.7
20	23.3	7.0	36.1	10.3	-0.4	0.2	25.2	0.0	2.6	2.3	149.2	151.2	15.8
Men, Initiation Age 50-59 years													
5	13.6	5.5	22.5	8.3	-0.2	0.1	33.1	0.0	3.2	2.9	77.1	78.8	-8.5
7.5	14.3	6.5	23.9	8.5	-0.2	0.1	31.5	0.0	3.2	2.9	82.6	83.3	-5.4
10	14.6	6.8	25.3	8.8	-0.2	0.1	30.2	0.0	2.9	2.6	89.4	88.4	-1.9
15	17.8	7.0	29.4	9.0	-0.2	0.1	28.2	0.0	2.8	2.5	104.8	104.5	4.5
20	19.1	7.9	32.2	9.5	-0.3	0.2	25.3	0.1	2.2	1.9	119.6	119.0	11.8
Men, Initiation Age 60-69 years													
5	9.7	5.6	17.4	7.5	-0.2	0.1	33.3	0.0	3.2	2.8	51.3	51.6	-14.7
7.5	10.7	5.6	18.5	7.2	-0.1	0.0	31.6	0.0	2.8	2.5	60.6	61.8	-11.2
10	12.1	5.6	20.5	8.4	-0.2	0.1	30.7	0.0	3.1	2.7	68.0	69.2	-7.7
15	11.5	6.0	20.1	8.5	-0.2	0.1	28.5	0.1	3.1	2.7	69.2	69.8	-5.8
20	13.8	6.7	24.2	8.9	-0.2	0.2	26.9	0.0	2.9	2.6	72.0	71.5	0.6
Men, Initiation Age 70-79 years													
5	-	-	-	-	-	-	-	-	-	-	-	-	-
7.5	7.7	4.3	13.5	6.5	-0.2	0.1	28.2	0.1	2.6	2.3	34.0	35.8	-13.5
10	8.4	4.7	14.9	7.2	-0.1	0.1	28.6	0.0	2.7	2.3	43.0	45.0	-11.5
15	8.3	4.7	14.5	7.3	-0.1	0.0	27.8	0.0	2.7	2.1	45.4	48.3	-10.8
20	9.2	5.2	16.0	6.9	-0.2	0.1	26.1	0.0	2.7	2.2	42.7	44.1	-8.2

Notes: ASCVD=atherosclerotic cardiovascular disease; CVD=cardiovascular disease; CRC=colorectal cancer; GI=gastrointestinal; QALY=quality-adjusted life year. The 10-year ASCVD risk levels are based on the ACC/AHA risk calculator and refer to a person's risk at model baseline/initiation. Risk levels are rounded to the nearest threshold (+/- 0.5%). Results reflect the difference between universal adoption of aspirin for primary prevention versus zero adoption; all else is held equal. MI and ischemic stroke events are non-fatal. The non-fatal CVD event column combines non-fatal 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: (Non-fatal CVD events + CVD deaths + CRC cases) – (Major GI bleeds + intracranial hemorrhage). This table presents results for a sensitivity analysis in which the risk for CVD mortality was 5% lower (OR = 0.95) with aspirin use.

Table 30. Lifetime Net Events of Aspirin for Women With Lifetime Use (CVD Death OR = 0.95)

	Benefits from aspirin (Prevented events per 1,000 persons)						Harms from aspirin (Incurred events per 1,000 persons)				Net Balance (Benefits - harms)		
10-yr ASCVD Risk (%)	Myocardial infarction	Ischemic stroke	Non-fatal CVD Events	CVD Deaths	CRC Cases	CRC Deaths	Major GI Bleeds	Major GI Bleed Deaths	Intracranial Hemorrhage	Intracranial Hemorrhage Deaths	Net QALYs	Net Life Years	Net Events Prevented
Women, Initiation Age 40-49 years													
5	9.9	9.3	22.5	7.5	-0.2	0.1	32.3	0.0	4.1	3.6	79.5	70.9	-10.3
7.5	10.1	9.2	23.0	8.2	-0.2	0.1	30.8	0.0	3.3	3.0	91.3	83.2	-6.2
10	10.9	9.8	25.1	8.4	-0.2	0.1	29.7	0.0	3.0	2.8	112.8	104.1	-2.2
15	11.2	10.1	26.0	8.8	-0.2	0.1	29.7	0.0	3.0	2.7	115.8	104.8	-0.7
20	11.6	10.7	27.6	9.0	-0.2	0.1	30.3	0.0	2.8	2.5	125.4	114.1	0.8
Women, Initiation Age 50-59 years													
5	8.0	9.4	20.4	7.5	-0.2	0.1	31.4	0.0	4.1	3.4	67.0	59.1	-11.2
7.5	8.6	9.9	21.9	7.9	-0.2	0.1	29.2	0.0	3.8	3.4	73.4	63.7	-6.9
10	8.8	10.5	22.5	8.4	-0.1	0.1	28.3	0.0	3.6	3.3	80.9	69.8	-4.5
15	10.0	11.2	25.5	8.2	-0.2	0.1	27.2	0.0	3.2	2.9	100.2	90.6	0.2
20	10.8	11.2	27.9	9.1	-0.2	0.2	25.9	0.0	3.0	2.7	110.9	100.0	5.2
Women, Initiation Age 60-69 years													
5	5.5	7.7	15.1	6.4	-0.1	0.0	30.8	0.0	4.1	3.5	40.2	35.5	-16.9
7.5	6.2	7.6	15.5	6.3	-0.1	0.0	29.1	0.0	3.8	3.2	41.9	36.7	-14.4
10	6.2	8.6	17.3	6.8	-0.1	0.1	27.9	0.0	3.7	3.2	48.7	41.8	-10.9
15	6.9	10.0	19.6	7.5	-0.2	0.1	26.2	0.0	3.3	2.9	67.2	59.4	-5.5
20	7.6	11.0	22.1	7.9	-0.1	0.1	25.5	0.0	3.4	2.8	70.8	60.5	-1.8
Women, Initiation Age 70-79 years													
5	4.1	6.7	11.9	5.0	0.0	0.0	29.6	0.0	3.8	3.2	23.1	20.4	-19.8
7.5	4.4	6.6	12.2	5.7	-0.1	0.0	28.5	0.0	3.3	2.7	33.0	31.3	-16.8
10	4.2	6.9	12.6	5.3	-0.1	0.1	27.5	0.0	3.1	2.6	29.1	25.1	-15.4
15	4.8	7.4	13.6	5.6	0.0	0.0	24.9	0.0	3.5	2.9	31.4	28.0	-12.1
20	5.1	7.0	14.2	6.1	-0.1	0.0	24.3	0.0	3.6	2.9	32.4	28.9	-10.7

Notes: ASCVD=atherosclerotic cardiovascular disease; CVD=cardiovascular disease; CRC=colorectal cancer; GI=gastrointestinal; QALY=quality-adjusted life year. The 10-year ASCVD risk levels are based on the ACC/AHA risk calculator and refer to a person's risk at model baseline/initiation. Risk levels are rounded to the nearest threshold (+/- 0.5%). Results reflect the difference between universal adoption of aspirin for primary prevention versus zero adoption; all else is held equal. MI and ischemic stroke events are non-fatal. The non-fatal CVD event column combines non-fatal 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: (Non-fatal CVD events + CVD deaths + CRC cases) – (Major GI bleeds + intracranial hemorrhage). This table presents results for a sensitivity analysis in which the risk for CVD mortality was 5% lower (OR = 0.95) with aspirin use.

Table 31a. Net Benefit of Aspirin After 10 Years and Lifetime Net Benefit at Stopping Intervals and With Lifetime Use (GIB Death OR=1.58), Initiation Age 40-49y

	10y use*	Stop at age 65y	Stop at age 70y	Stop at age 75y	Stop at age 80y	Stop at age 85y	Lifetime use
Men, Net QALYs per 1000 persons							
5% 10y ASCVD Risk	-1.2	2.0	3.6	3.7	3.9	3.5	2.1
7.5% 10y ASCVD Risk	-1.5	5.8	8.1	9.6	10.4	10.0	9.8
10% 10y ASCVD Risk	-0.4	22.5	25.3	27.6	29.6	28.9	29.3
15% 10y ASCVD Risk	-0.1	29.9	32.3	33.9	33.2	34.0	33.4
20% 10y ASCVD Risk	0.7	40.7	44.7	48.2	50.8	50.9	50.9
Men, Net Life Years per 1000 persons							
5% 10y ASCVD Risk	-1.2	-5.5	-5.9	-8.4	-10.0	-11.8	-13.9
7.5% 10y ASCVD Risk	-1.9	-3.5	-2.8	-3.0	-3.8	-5.3	-6.2
10% 10y ASCVD Risk	-1.6	14.1	14.7	15.7	16.4	14.5	14.3
15% 10y ASCVD Risk	-1.8	19.7	20.0	19.5	17.1	17.2	15.8
20% 10y ASCVD Risk	-1.8	31.1	32.2	34.1	36.0	35.1	34.6
Women, Net QALYs per 1000 persons							
5% 10y ASCVD Risk	-0.9	-2.9	-2.4	-7.2	-7.4	-9.1	-10.4
7.5% 10y ASCVD Risk	-0.7	3.6	4.1	4.0	2.7	2.0	1.5
10% 10y ASCVD Risk	-0.3	13.8	19.9	20.0	21.1	19.9	19.4
15% 10y ASCVD Risk	0.1	21.5	26.0	28.3	28.1	28.2	27.8
20% 10y ASCVD Risk	0.6	27.6	32.2	32.7	34.8	34.6	35.1
Women, Net Life Years per 1000 persons							
5% 10y ASCVD Risk	-1.2	-14.2	-17.4	-25.6	-28.8	-32.5	-35.6
7.5% 10y ASCVD Risk	-1.0	-8.3	-11.8	-15.4	-18.9	-21.8	-24.1
10% 10y ASCVD Risk	-1.1	0.2	2.9	-0.5	-1.8	-5.1	-7.1
15% 10y ASCVD Risk	-1.2	6.1	6.4	6.1	3.0	1.3	-0.3
20% 10y ASCVD Risk	-1.2	11.3	12.1	9.8	9.1	7.0	6.2

Notes: GIB=major gastrointestinal bleeding; OR=odds ratio; ASCVD=atherosclerotic cardiovascular disease; CVD=cardiovascular disease; QALY=quality-adjusted life year; N/A=not applicable; y=years. The 10-year ASCVD risk levels are based on the ACC/AHA risk calculator and refer to a person's risk at model baseline/initiation. Risk levels are rounded to the nearest threshold (+/- 0.5%). Results reflect the difference between universal adoption of aspirin for primary prevention versus zero adoption. All else is held equal. Stopping age indicates the age at which persons in the aspirin for primary prevention arm stop aspirin. This table presents results for a sensitivity analysis in which the risk for major GI mortality was 58% higher (OR = 1.58) with aspirin use. * The "10y use" column indicates net benefit over 10 years of aspirin use. All other columns indicate net benefits over a lifetime horizon.

Table 31b. Net Benefit of Aspirin After 10 Years and Lifetime Net Benefit at Stopping Intervals and With Lifetime Use (GIB Death OR=1.58), Initiation Age 50-59y

	10y use*	Stop at age 65y	Stop at age 70y	Stop at age 75y	Stop at age 80y	Stop at age 85y	Lifetime use
Men, Net QALYs per 1000 persons							
5% 10y ASCVD Risk	-3.0	-8.3	-10.6	-12.3	-14.3	-14.9	-16.3
7.5% 10y ASCVD Risk	-3.3	-5.5	-5.5	-9.1	-8.8	-9.5	-10.2
10% 10y ASCVD Risk	-3.0	-0.4	-2.5	-3.4	-4.2	-4.6	-5.3
15% 10y ASCVD Risk	-1.9	9.0	13.7	15.3	16.1	15.1	15.1
20% 10y ASCVD Risk	-1.0	20.0	26.2	29.8	33.0	33.2	33.7
Men, Net Life Years per 1000 persons							
5% 10y ASCVD Risk	-3.4	-14.1	-18.0	-21.9	-26.0	-28.1	-30.9
7.5% 10y ASCVD Risk	-4.1	-10.5	-13.7	-20.4	-22.2	-24.6	-26.2
10% 10y ASCVD Risk	-4.2	-6.3	-11.6	-15.7	-19.4	-21.4	-23.0
15% 10y ASCVD Risk	-4.4	2.2	3.9	2.6	1.7	-0.9	-1.6
20% 10y ASCVD Risk	-4.4	13.1	15.9	16.6	18.1	17.1	16.9
Women, Net QALYs per 1000 persons							
5% 10y ASCVD Risk	-3.2	-6.3	-10.5	-14.1	-14.6	-17.5	-19.4
7.5% 10y ASCVD Risk	-2.5	-0.4	0.1	0.1	-3.2	-4.6	-6.2
10% 10y ASCVD Risk	-1.6	2.3	4.4	4.9	2.8	1.1	-0.5
15% 10y ASCVD Risk	-0.1	9.1	13.6	16.4	16.7	16.0	16.0
20% 10y ASCVD Risk	0.4	15.3	23.3	24.8	26.9	25.7	25.2
Women, Net Life Years per 1000 persons							
5% 10y ASCVD Risk	-3.7	-13.4	-21.7	-29.8	-34.5	-39.5	-43.5
7.5% 10y ASCVD Risk	-3.8	-8.8	-12.9	-17.2	-23.5	-27.6	-31.1
10% 10y ASCVD Risk	-3.7	-7.9	-9.6	-13.4	-19.2	-23.6	-26.8
15% 10y ASCVD Risk	-2.7	-0.6	-1.2	-1.8	-4.6	-7.9	-9.8
20% 10y ASCVD Risk	-2.8	5.1	8.2	5.0	3.3	0.1	-2.3

Notes: GIB=major gastrointestinal bleeding; OR=odds ratio; ASCVD=atherosclerotic cardiovascular disease; CVD=cardiovascular disease; QALY=quality-adjusted life year; N/A=not applicable; y=years. The 10-year ASCVD risk levels are based on the ACC/AHA risk calculator and refer to a person's risk at model baseline/initiation. Risk levels are rounded to the nearest threshold (+/- 0.5%). Results reflect the difference between universal adoption of aspirin for primary prevention versus zero adoption. All else is held equal. Stopping age indicates the age at which persons in the aspirin for primary prevention arm stop aspirin. This table presents results for a sensitivity analysis in which the risk for major GI mortality was 58% higher (OR = 1.58) with aspirin use. * The "10y use" column indicates net benefit over 10 years of aspirin use. All other columns indicate net benefits over a lifetime horizon.

Table 31c. Net Benefit of Aspirin After 10 Years and Lifetime Net Benefit at Stopping Intervals and With Lifetime Use (GIB Death OR=1.58), Initiation Age 60-69y

	10y use*	Stop at age 75y	Stop at age 80y	Stop at age 85y	Lifetime use
Men, Net QALYs per 1000 persons					
5% 10y ASCVD Risk	-6.1	-19.5	-24.4	-24.3	-26.7
7.5% 10y ASCVD Risk	-5.3	-14.4	-15.4	-18.8	-19.2
10% 10y ASCVD Risk	-4.7	-8.1	-9.2	-12.0	-13.7
15% 10y ASCVD Risk	-5.5	-5.3	-6.2	-8.1	-9.8
20% 10y ASCVD Risk	-5.1	0.0	0.0	-1.5	-1.7
Men, Net QALYs per 1000 persons					
5% 10y ASCVD Risk	-6.3	-26.8	-33.9	-36.1	-39.9
7.5% 10y ASCVD Risk	-6.2	-21.7	-25.1	-30.7	-32.1
10% 10y ASCVD Risk	-6.0	-15.9	-19.6	-24.3	-27.2
15% 10y ASCVD Risk	-7.3	-13.2	-16.7	-20.5	-23.3
20% 10y ASCVD Risk	-8.4	-8.9	-11.5	-14.8	-16.1
Women, Net QALYs per 1000 persons					
5% 10y ASCVD Risk	-4.0	-14.2	-19.7	-24.8	-28.3
7.5% 10y ASCVD Risk	-3.8	-9.7	-14.8	-18.8	-21.8
10% 10y ASCVD Risk	-3.7	-4.3	-3.8	-7.8	-12.9
15% 10y ASCVD Risk	-2.7	0.1	0.4	-1.3	-2.1
20% 10y ASCVD Risk	-0.0	8.0	9.0	8.6	7.5
Women, Net Life Years per 1000 persons					
5% 10y ASCVD Risk	-4.1	-21.7	-31.5	-39.5	-45.4
7.5% 10y ASCVD Risk	-4.9	-18.0	-27.4	-33.6	-38.9
10% 10y ASCVD Risk	-5.3	-13.0	-16.6	-23.5	-31.4
15% 10y ASCVD Risk	-6.0	-10.5	-14.7	-19.7	-23.1
20% 10y ASCVD Risk	-4.6	-4.0	-8.3	-11.9	-15.5

Notes: GIB=major gastrointestinal bleeding; OR=odds ratio; ASCVD=atherosclerotic cardiovascular disease; CVD=cardiovascular disease; QALY=quality-adjusted life year; N/A=not applicable; y=years. The 10-year ASCVD risk levels are based on the ACC/AHA risk calculator and refer to a person's risk at model baseline/initiation. Risk levels are rounded to the nearest threshold (+/- 0.5%). Results reflect the difference between universal adoption of aspirin for primary prevention versus zero adoption. All else is held equal. Stopping age indicates the age at which persons in the aspirin for primary prevention arm stop aspirin. This table presents results for a sensitivity analysis in which the risk for major GI mortality was 58% higher (OR = 1.58) with aspirin use. * The "10y use" column indicates net benefit over 10 years of aspirin use. All other columns indicate net benefits over a lifetime horizon.

Table 31d. Net Benefit of Aspirin After 10 Years and Lifetime Net Benefit at Stopping Intervals and With Lifetime Use (GIB Death OR=1.58), Initiation Age 70-79y

	10y use*	Stop at age 85y	Lifetime use
Men, Net QALYs per 1000 persons			
5% 10y ASCVD Risk	N/A	N/A	N/A
7.5% 10y ASCVD Risk	-7.5	-17.4	-18.3
10% 10y ASCVD Risk	-7.4	-16.4	-18.2
15% 10y ASCVD Risk	-6.7	-13.7	-15.5
20% 10y ASCVD Risk	-5.9	-9.3	-12.4
Men, Net QALYs per 1000 persons			
5% 10y ASCVD Risk	N/A	N/A	N/A
7.5% 10y ASCVD Risk	-8.1	-23.0	-25.9
10% 10y ASCVD Risk	-8.6	-23.0	-26.7
15% 10y ASCVD Risk	-8.0	-20.1	-23.4
20% 10y ASCVD Risk	-8.0	-16.0	-20.8
Women, Net QALYs per 1000 persons			
5% 10y ASCVD Risk	-5.1	-21.3	-26.8
7.5% 10y ASCVD Risk	-5.6	-17.9	-23.5
10% 10y ASCVD Risk	-6.1	-20.0	-24.3
15% 10y ASCVD Risk	-5.5	-13.0	-17.6
20% 10y ASCVD Risk	-6.6	-12.6	-16.9
Women, Net Life Years per 1000 persons			
5% 10y ASCVD Risk	-5.1	-29.2	-38.2
7.5% 10y ASCVD Risk	-6.5	-26.7	-35.4
10% 10y ASCVD Risk	-7.7	-30.6	-38.0
15% 10y ASCVD Risk	-7.3	-22.7	-30.4
20% 10y ASCVD Risk	-9.0	-22.1	-29.3

Notes: GIB=major gastrointestinal bleeding; OR=odds ratio; ASCVD=atherosclerotic cardiovascular disease; CVD=cardiovascular disease; QALY=quality-adjusted life year; N/A=not applicable; y=years. The 10-year ASCVD risk levels are based on the ACC/AHA risk calculator and refer to a person's risk at model baseline/initiation. Risk levels are rounded to the nearest threshold (+/- 0.5%). Results reflect the difference between universal adoption of aspirin for primary prevention versus zero adoption. All else is held equal. Stopping age indicates the age at which persons in the aspirin for primary prevention arm stop aspirin. This table presents results for a sensitivity analysis in which the risk for major GI mortality was 58% higher (OR = 1.58) with aspirin use. * The "10y use" column indicates net benefit over 10 years of aspirin use. All other columns indicate net benefits over a lifetime horizon.

Table 32. Lifetime Net Events of Aspirin for Men With Lifetime Use (Major GI Bleeding Death OR=1.58)

	Benefits from aspirin (Prevented events per 1,000 persons)						Harms from aspirin (Incurred events per 1,000 persons)				Net Balance (Benefits - harms)		
10-yr ASCVD Risk (%)	Myocardial infarction	Ischemic stroke	Non-fatal CVD Events	CVD Deaths	CRC Cases	CRC Deaths	Major GI Bleeds	Major GI Bleed Deaths	Intracranial Hemorrhage	Intracranial Hemorrhage Deaths	Net QALYs	Net Life Years	Net Events Prevented
Men, Initiation Age 40-49 years													
5	17.2	6.2	28.9	5.1	-	-	33.3	1.7	2.9	2.6	2.1	-13.9	-6.5
7.5	19.9	6.7	32.9	5.1	-	-	31.8	1.6	2.5	2.3	9.8	-6.2	-0.1
10	20.8	7.2	34.6	5.7	-	-	31.3	1.5	2.3	2.0	29.3	14.3	3.3
15	22.7	8.0	38.3	6.0	-	-	28.5	1.6	2.5	2.2	33.4	15.8	9.4
20	25.2	7.8	40.9	6.5	-	-	26.1	1.2	2.4	2.2	50.9	34.6	15.4
Men, Initiation Age 50-59 years													
5	14.4	6.1	25.2	4.1	-	-	34.4	1.9	3.1	2.8	-16.3	-30.9	-12.8
7.5	15.4	7.0	27.0	4.3	-	-	32.8	1.8	3.0	2.7	-10.2	-26.2	-9.1
10	15.9	7.5	29.0	4.6	-	-	31.7	1.9	2.8	2.5	-5.3	-23.0	-5.3
15	19.0	7.8	33.1	5.0	-	-	29.4	1.5	2.6	2.4	15.1	-1.6	2.1
20	20.6	8.6	36.4	5.6	-	-	26.3	1.4	2.1	1.9	33.7	16.9	10.3
Men, Initiation Age 60-69 years													
5	10.2	6.0	19.4	3.2	-	-	34.9	2.2	3.0	2.6	-26.7	-39.9	-20.1
7.5	11.5	6.2	21.1	3.0	-	-	32.7	2.1	2.7	2.4	-19.2	-32.1	-15.8
10	12.9	6.1	23.1	3.7	-	-	32.4	2.1	2.9	2.6	-13.7	-27.2	-13.1
15	12.4	6.6	22.9	3.7	-	-	29.7	1.9	3.0	2.6	-9.8	-23.3	-10.5
20	15.0	7.4	27.7	4.7	-	-	28.2	1.8	2.7	2.4	-1.7	-16.1	-2.9
Men, Initiation Age 70-79 years													
5	-	-	-	-	-	-	-	-	-	-	-	-	-
7.5	8.1	4.7	15.1	2.1	-	-	30.0	1.8	2.5	2.3	-18.3	-25.9	-19.3
10	9.0	5.2	17.0	2.7	-	-	30.2	2.1	2.6	2.2	-18.2	-26.7	-17.3
15	9.1	5.2	16.7	2.5	-	-	29.3	1.7	2.5	2.1	-15.5	-23.4	-16.4
20	9.9	5.6	18.0	2.3	-	-	27.7	1.8	2.6	2.1	-12.4	-20.8	-13.8

Notes: ASCVD=atherosclerotic cardiovascular disease; CVD=cardiovascular disease; CRC=colorectal cancer; GI=gastrointestinal; QALY=quality-adjusted life year. The 10-year ASCVD risk levels are based on the ACC/AHA risk calculator and refer to a person's risk at model baseline/initiation. Risk levels are rounded to the nearest threshold (+/- 0.5%). Results reflect the difference between universal adoption of aspirin for primary prevention versus zero adoption; all else is held equal. MI and ischemic stroke events are non-fatal. The non-fatal CVD event column combines non-fatal 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: (Non-fatal CVD events + CVD deaths + CRC cases) – (Major GI bleeds + intracranial hemorrhage). This table presents results for a sensitivity analysis in which the risk for major GI mortality was 58% higher (OR = 1.58) with aspirin use.

Table 33. Lifetime Net Events of Aspirin for Women With Lifetime Use (Major GI Bleeding Death OR=1.58)

	Benefits from aspirin (Prevented events per 1,000 persons)						Harms from aspirin (Incurred events per 1,000 persons)				Net Balance (Benefits - harms)		
10-yr ASCVD Risk (%)	Myocardial infarction	Ischemic stroke	Non-fatal CVD Events	CVD Deaths	CRC Cases	CRC Deaths	Major GI Bleeds	Major GI Bleed Deaths	Intracranial Hemorrhage	Intracranial Hemorrhage Deaths	Net QALYs	Net Life Years	Net Events Prevented
Women, Initiation Age 40-49 years													
5	10.4	9.9	25.1	3.8	-	-	33.2	1.5	4.0	3.5	-10.4	-35.6	-13.3
7.5	10.7	10.1	26.3	4.5	-	-	31.7	1.5	3.1	2.8	1.5	-24.1	-8.3
10	11.4	10.6	28.2	4.6	-	-	30.5	1.2	3.0	2.8	19.4	-7.1	-4.7
15	11.7	10.8	29.3	5.0	-	-	30.3	1.2	2.9	2.6	27.8	-0.3	-2.6
20	12.2	11.6	30.9	5.3	-	-	31.5	1.2	2.7	2.4	35.1	6.2	-1.5
Women, Initiation Age 50-59 years													
5	8.4	10.0	22.7	3.4	-	-	32.3	1.7	4.0	3.4	-19.4	-43.5	-15.2
7.5	9.0	10.5	24.6	3.9	-	-	30.4	1.4	3.8	3.4	-6.2	-31.1	-10.5
10	9.2	11.1	25.0	4.4	-	-	29.6	1.4	3.5	3.2	-0.5	-26.8	-8.2
15	10.5	12.0	28.4	4.2	-	-	28.1	1.3	3.1	2.8	16.0	-9.8	-2.5
20	11.5	12.0	31.0	4.9	-	-	26.7	1.3	2.9	2.6	25.2	-2.3	2.4
Women, Initiation Age 60-69 years													
5	5.8	8.0	16.7	2.5	-	-	32.0	1.8	4.0	3.5	-28.3	-45.4	-22.0
7.5	6.5	8.3	17.7	2.4	-	-	30.4	1.7	3.7	3.2	-21.8	-38.9	-18.8
10	6.5	9.3	19.3	2.9	-	-	29.4	1.6	3.5	3.1	-12.9	-31.4	-15.5
15	7.2	10.7	22.2	3.4	-	-	27.4	1.5	3.2	2.8	-2.1	-23.1	-9.4
20	8.1	11.7	25.1	4.0	-	-	26.6	1.2	3.3	2.8	7.5	-15.5	-4.8
Women, Initiation Age 70-79 years													
5	4.3	7.0	13.1	1.5	-	-	31.1	1.7	3.7	3.2	-26.8	-38.2	-25.0
7.5	4.8	7.0	13.8	1.6	-	-	30.2	1.9	3.3	2.7	-23.5	-35.4	-22.6
10	4.5	7.2	14.0	1.7	-	-	29.0	2.1	3.0	2.5	-24.3	-38.0	-20.8
15	5.1	7.8	15.1	1.7	-	-	26.4	1.3	3.4	2.9	-17.6	-30.4	-17.1
20	5.4	7.4	15.6	2.1	-	-	25.7	1.6	3.5	2.9	-16.9	-29.3	-15.9

Notes: ASCVD=atherosclerotic cardiovascular disease; CVD=cardiovascular disease; CRC=colorectal cancer; GI=gastrointestinal; QALY=quality-adjusted life year. The 10-year ASCVD risk levels are based on the ACC/AHA risk calculator and refer to a person's risk at model baseline/initiation. Risk levels are rounded to the nearest threshold (+/- 0.5%). Results reflect the difference between universal adoption of aspirin for primary prevention versus zero adoption; all else is held equal. MI and ischemic stroke events are non-fatal. The non-fatal CVD event column combines non-fatal 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: (Non-fatal CVD events + CVD deaths + CRC cases) – (Major GI bleeds + intracranial hemorrhage). This table presents results for a sensitivity analysis in which the risk for major GI mortality was 58% higher (OR = 1.58) with aspirin use.

Table 34. Comparison of 2016 and 2021 Decision Analysis Main Findings, Lifetime Aspirin Use and Time Horizon

	Initiation Age 40-49y		Initiation Age 50-59y		Initiation Age 60-69y		Initiation Age 70-79y	
	2016	2021	2016	2021	2016	2021	2016	2021
Men, Net QALYs per 1000 persons								
5% 10y ASCVD Risk	74.1	23.1	40	5.7	16.1	-1.8	N/A	N/A
7.5% 10y ASCVD Risk	N/A	29.1	N/A	12.5	N/A	2.6	N/A	-4.6
10% 10y ASCVD Risk	97.2	48	58.8	18	18	7	-1	-1.1
15% 10y ASCVD Risk	107.9	52.3	64.4	32.3	30.9	8.3	-3.1	-1.9
20% 10y ASCVD Risk	105.7	66.2	83.4	48.4	31.8	16.3	-6.2	0.9
Men, Net Life Years per 1000 persons								
5% 10y ASCVD Risk	48.9	10.6	15.3	-5.4	-5.7	-11	N/A	N/A
7.5% 10y ASCVD Risk	N/A	16.2	N/A	0.4	N/A	-6.7	N/A	-10.1
10% 10y ASCVD Risk	71	36.1	33.3	4.2	-2	-3	-15	-6.9
15% 10y ASCVD Risk	82.8	37.9	39.5	18.6	9.6	-2.2	-18	-7.6
20% 10y ASCVD Risk	80.1	52.4	60.5	33.9	11.6	4.9	-22.5	-5.5
Women, Net QALYs per 1000 persons								
5% 10y ASCVD Risk	78.4	11.1	45	1.9	16.4	-9.5	-4.4	-11.7
7.5% 10y ASCVD Risk	N/A	19.6	N/A	10.4	N/A	-5.8	N/A	-6.4
10% 10y ASCVD Risk	96.9	35.1	62.1	17.1	28.4	2.3	-4.4	-6.1
15% 10y ASCVD Risk	98.4	43	71.6	30.8	32.4	11.6	-1.5	-6.9
20% 10y ASCVD Risk	106.5	50.4	83.3	41.6	36	19.1	-2.7	-4.4
Women, Net Life Years per 1000 persons								
5% 10y ASCVD Risk	41.7	-10.6	10	-18.7	-12	-23.5	-23.4	-20.6
7.5% 10y ASCVD Risk	N/A	-2.6	N/A	-11.8	N/A	-20.2	N/A	-15.4
10% 10y ASCVD Risk	59	11.4	21.9	-6.5	-1.2	-13.5	-25.1	-16.6
15% 10y ASCVD Risk	57.3	17.7	33.4	7.5	1.7	-7.2	-22	-17.9
20% 10y ASCVD Risk	67.7	24.2	46.3	16.9	4.8	-1.6	-26.1	-14.8

Notes: ASCVD=atherosclerotic cardiovascular disease; QALY=quality-adjusted life year; N/A=not applicable; y=years. The 10-year ASCVD risk levels are based on the ACC/AHA risk calculator and refer to a person's risk at model baseline/initiation. Risk levels are rounded to the nearest threshold (+/- 0.5%). Results reflect the difference between universal adoption of aspirin for primary prevention versus zero adoption. All else is held equal. 2016 decision analysis findings are from Dehmer et al. [13].

1 Model Overview

The decision analysis was conducted using the HealthPartners Institute ModelHealth™: Cardiovascular disease microsimulation model (ModelHealth: CVD). ModelHealth: CVD is a dynamic, discrete event, annual-cycle microsimulation model parameterized to estimate the lifetime incidence of CVD events in a cohort of individuals representative of the U.S. population. This model was originally designed to assess the population health benefits and value of the U.S. Preventive Services Task Force (USPSTF) aspirin chemoprevention and CVD screening recommendations for the National Commission on Prevention Priorities [1, 2], but it has been broadly used for assessing disease prevention strategies in the U.S. population [3-8]. The version of the model used for this analysis also incorporates three cancer groupings to conduct sensitivity analysis of the potential impact of aspirin use on colorectal cancer (CRC) and to better account for competing risks of smokers. Herein, the adapted model used for this study is referred to as ModelHealth: CVD.

ModelHealth: CVD is implemented using Visual Basic 6 and Microsoft Excel. The primary unit of observation is a hypothetical person who takes on a variety of detailed attributes (such as age, sex, race/ethnicity, BMI, systolic blood pressure, disease status, etc.). The lifetime progression of these characteristics is simulated over time. Epidemiological data sourced from the Framingham Heart Study—a major cardiovascular disease surveillance study ongoing since 1948—plays an important role in this model's construction. Although the mechanics of ModelHealth: CVD center on individuals—i.e., through microsimulation—policy relevance is achieved through aggregating individuals representative of a policy-relevant group, such as the U.S. population. Policy interventions are evaluated by simulating the same population twice—once with the policy intervention of interest, such as a clinical preventive service, imposed, and once without it. In practice, this evaluation approach is comparable to a randomized clinical trial (RCT) design, with the treatment and the placebo being applied to the same hypothetical research population.

2 Model Description

Initialization

Technical Appendix Figure 1 illustrates the process flow of ModelHealth: CVD. Simulating an individual's health trajectory first involves initializing a hypothetical person at a specific age (e.g., 40), with individual characteristics (such as sex and race/ethnicity) and initial health parameters (such as cholesterol and blood pressure levels and BMI) all drawn from U.S.-representative distributions. Thereafter, ModelHealth: CVD simulates the hypothetical person's lifespan and the natural history of cardiovascular disease in annual cycles.

Intervention and Background Preventive Services

At the beginning of each annual cycle, the model determines whether the simulated individual receives a specified intervention of interest or a background preventive service. The intervention in this analysis is aspirin for primary prevention. Background preventive services in ModelHealth: CVD are screening for hypertension and initiating statin use for the primary

prevention of CVD, as recommended by the U.S. Preventive Services Task Force [9, 10]. Eligibility for preventive services may be dictated by the parameters of a policy intervention—such as aspirin use among all persons older than age 40 without prior history of major GI bleeding or intracranial hemorrhage in the treatment arm—or by contemporary adoption patterns of background preventive services (i.e., applied to both policy arms) observed in the population. Upon receiving a preventive service, the model determines whether the individual is eligible for treatment (e.g., taking statins for treating high cholesterol). Pharmacological treatment criteria for dyslipidemia and hypertension are implemented to be consistent with U.S. Preventive Services Task Force and American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [9-13].

Treatment

The effect of treatment for high cholesterol or high blood pressure is realized through its impact on cholesterol or systolic blood pressure (SBP), respectively. For example, an individual with high cholesterol could be treated with a statin and see a 30 percent reduction in low-density lipoprotein (LDL), but taking a statin does not translate to a direct reduction in the individual's risk of a myocardial infarction. Instead, these changes in risk factors will translate to lowered disease risk, as determined by the model's risk engine described in Section 3.4. In contrast, taking aspirin on a daily basis directly alters the relative risk of having an event (such as a myocardial infarction or a gastrointestinal bleed).

Disease Events

The next step in each annual cycle (following prevention/treatment) is to determine whether the individual experiences any non-fatal disease events during that year. Specifically, a person may: (1) have a myocardial infarction, (2) have an ischemic stroke, (3) have a intracranial hemorrhage, (4) experience angina pectoris, (5) develop congestive heart failure, (6) develop intermittent claudication, (7) develop diabetes, (8) experience a gastrointestinal bleed, (9) develop CRC, and/or (10) develop another type of cancer. The annual risks of (1)-(7) are determined by equations derived specifically for this model using data from the Framingham Heart Study [14, 15]. If a person has a cardiovascular event—that is, one or more of (1)-(6)—and survives, that person becomes eligible for secondary prevention. Because insufficient evidence was found with respect to aspirin's effect on cancers other than CRC the role of these cancers in the model, described in detail in Section 3.7, is limited to their contribution as a competing smoking-related mortality risk. Treatment for dyslipidemia and hypertension for secondary prevention are similarly based on national guidelines [11, 12] . Men and women who have a non-fatal myocardial infarction or ischemic stroke are also eligible for aspirin chemoprophylaxis.

Each year a person also faces a risk of dying from cardiovascular disease, a gastrointestinal bleed, a fatal case of cancer, or from other causes. The annual risk of death from CVD-related causes is based on a study-specific equation derived from the Framingham Heart Study. The risk of death from gastrointestinal bleed is literature-based. The probability that a cancer episode is fatal is derived from Surveillance, Epidemiology, and End Results Program (SEER) cancer registry data. The probability of dying from a cause other than CVD or cancer is derived from U.S. life tables. A person who dies of any cause—or reaches the age of 100—exits the model,

lifecycle complete. Model input details and sources are provided below.

Aging and Progression of Natural History

Finally, when a person survives a cycle, that individual's health status and parameters must be transitioned for the next cycle. Each cycle is annual, and therefore, the individual's age will simply increment by one. Biological cardiovascular risk factors—namely, high-density lipoprotein (HDL), LDL, SBP, and body mass index (BMI)—naturally progress over time, and annual transitions are modeled by a two-step process. First, it is determined whether the individual's risk factor increases, decreases, or stays the same. These probabilities are based on a multinomial logistic equation (which accounts for age, previous values, and other individual characteristics). Second, if a specific risk factor is determined to increase or decrease, a secondary set of equations determines the size of this change. The process repeats itself until the simulated person dies (or reaches age 100). Cigarette smoking initiation and cessation probabilities were derived from National Health Interview Survey data. Relapse rates after cessation was derived from longitudinal studies.

3 Model Data Sources and Parameters

A computational model with the degree of detail contained within ModelHealth: CVD requires a considerable amount of data and scientific evidence to specify all necessary parameters and inform the key transitional mechanisms. This lengthy section describes the many data sources and assumptions required for model computations.

3.1 Population Characteristics

The population modeled for this study was defined at baseline (i.e., prior to any simulation within the model) and stratified by 10-year age group (40-49 years, 50-59 years, 60-69 years, and 70-79 years), sex (men and women), and 10-year CVD risk (5%, 7.5%, 10%, 15%, and 20%). The demographic distribution by year of age and race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, or other) within each 10-year age and sex group was derived from 2018 American Community Survey data[16]. Initial biological CVD risk factors, including BMI, SBP, LDL, and HDL, medication use rates for blood pressure and cholesterol, and diabetes status—all among persons without a history of CVD—were derived from the combined 2015-2018 National Health and Nutrition Examination Survey (NHANES) surveys[17, 18]. Current smoking status (current, former, or never cigarette smoker) was derived from combined 2017 and 2018 National Health Interview Survey [19]. Baseline 10-year CVD risk was rounded to the nearest threshold (+/- 0.5%) and estimated using the ACC/AHA risk calculator for the first hard atherosclerotic cardiovascular disease (ASCVD) event (non-fatal MI, non-fatal stroke, or coronary death) [20]. The calculation of 10-year CVD risk at baseline is independent from the model's risk engine and mirrors 10-year CVD risk calculation as it may be practiced in clinical settings. Persons meeting the characteristics of each strata are oversampled from the characteristics of the general U.S. population. **Technical Appendix Tables 1a** and **1b** shows how 10-year CVD risk in the U.S. population is distributed by age and sex groups.

Technical Appendix Table 2 summarizes mean CVD risk characteristics for the age, sex, and

10-year ASCVD risk strata used for the aspirin decision analysis. As made clear in **Technical Appendix Tables 1a** and **1b**, no one stratification group in **Technical Appendix Table 2** is representative of the U.S. population, and some groups are decidedly unrepresentative. For example, for a 40-49 year old woman to have a 10-year CVD risk of 20 percent, she would need to have particularly elevated risk factors. Likewise, for a woman in her 70s to have only a 5 percent 10-year risk of a CVD event, she would need to have risk factors apart from age that are on the opposite end of the spectrum. However, persons within each age, sex, and 10-year CVD risk strata were sampled to be representative of persons meeting the criteria of that strata in the U.S. population (e.g., men aged 40-49 with a 5% 10-year risk of having a CVD event).

When assessing CVD risk, clinicians are likely to use the ACA/AHA or a similar 10-year risk calculator in daily practice. Because the risk calculator is separate from the model's risk engine, there is imperfect correlation between a simulated person's baseline 10-year risk categorization and their CVD events as determined by the model. This parallels the imperfect correlation between baseline risk as predicted by a calculator in clinical decision-making and the realized patient experience with CVD over time. **Technical Appendix Figure 2** illustrates this imperfect correlation and reflect patterns similar to those shown in other comparisons of the difference between observed outcomes and those predicted by the ACC/AHA risk calculator [21-24]. Despite the imperfect correlation, baseline event rates predicted by our model validate reasonably well to U.S. population event rates observed in NHANES data as shown further below in **Technical Appendix Table 27**.

3.2 Progression of Biological Risk Factors

After each annual cycle in ModelHealth: CVD, an individual's time-dependent attributes must be transitioned to reflect the age progression and natural history of biological cardiovascular disease risk factors over one's lifetime. A person's age simply increments by one, but the remaining risk factors (BMI, HDL, LDL, and SBP) transition according to a two-step process. Change in smoking status is described in Section 3.3.

Step 1: Determine probability that a risk factor changes

In the first step of the process, a person faces a probability of increasing, decreasing, or staying the same in a particular risk factor. For LDL, HDL, and BMI, staying the same is defined as a change of less than or equal +/-1 percent for the year. Due to the greater variability in measuring blood pressure, staying the same in SBP is classified as being within +/-3.5 percent for the year. In all cases, these probabilities were estimated using multinomial logistic regression. HDL, LDL, and SBP were estimated using annualized Framingham Heart Study data adjusting for age, sex, and BMI [14, 15]. BMI was estimated from Behavioral Risk Factor Surveillance System (BRFSS) survey data (from current weight and previous year recall) adjusting for age, sex, and race/ethnicity [25].

For year-to-year BMI transitions, the increasing or decreasing cases were split in two additional sub-cases. Specifically, one allows for small changes or "drifting" (i.e., an increase or decrease of 1 to 5 percent), and the other accommodates larger changes (i.e., an increase or decrease of 5 percent or more). Our analysis of Framingham Heart Study and BRFSS data indicate that these

weight-change modalities reflect what people typically experience in real life, and the probabilities of each modality shift as we age. For example, a typical male may be most at risk for significant weight gain in his 20s, be more likely to have his BMI drift up in his 30s and 40s, and then face a stronger tendency towards weight stabilization in his 50s and 60s.

Step 2: Determine size of risk factor change

Once a person's transition modality has been determined, the second step is to determine the size of the change. Age, sex, and (in the case of BMI) race/ethnicity-specific equations were estimated for each of these cases. Whereas the first step in the process is stochastically determined in each cycle (i.e., facing a probability of each scenario), the second step is deterministic, with the transition applied as a percentage change (or zero change, in the case that a risk factor remains stable from the previous year). **Technical Appendix Table 3** summarizes the details of this two-step process of year-on-year transitions of risk factors.

3.3 Modeling Smoking Behavior

Overview

Individuals may be in one of three smoking states: never smoker, current smoker, or former smoker. The probability that an individual is in a given smoking state at introduction into the model is determined by multivariate risk equations that account for age, sex, race/ethnicity, and the lifetime educational attainment. Similarly, the likelihood that an agent who is currently in the never-smoker state begins smoking within a given cycle is conditioned on his/her age, sex, and race/ethnicity, using the simulation model's race/ethnicity categories of white non-Hispanic, black non-Hispanic, Hispanic, and all other.

Initial smoking status

A multinomial logistic regression with outcomes corresponding to three smoking states (never, current, former) was estimated in SAS 9.4 to determine the likelihood of an individual having an initial smoking status given his/her age, sex, and race/ethnicity. Estimates of smoking risk equations combined data from the 2017 and 2018 National Health Interview Survey, the most current two years available at the time of the estimation [19]. Probabilities of being in each smoking state at model baseline are the mean SAS predicted values for each strata, where strata are defined by single year of age, sex and race/ethnicity category.

Standard definitions of smoking status are used, with the usual definitional prerequisite of having smoked at least 100 cigarettes in their lifetime was applied to exclude experimental smoking.:

Never smoker:	Having smoked fewer than 100 cigarettes in their lifetime
Current smoker:	Having smoked at least 100 cigarettes in their lifetime and having smoked in the last week
Former smoker:	Having smoked at least 100 cigarettes in their lifetime and having quit for 4 or more years

The results of the estimation are contained in **Technical Appendix Table 4**.

Time since quit for initial former smokers

Time in state (i.e., the number of years since quitting) determines the probability of relapse. To determine the distribution of time since quit for individuals assigned as former smokers at model baseline we reviewed years since quit in combined 2015-18 National Health Interview Survey data (expanding the years of survey beyond the years used for baseline smoking status due to the small number of former smokers in each year's sample in some age groups) [26]. We examined quits that were self-reported to have occurred within the most recent 10 years separately from quits 11 or more years ago because the simulation's relapse rates are zero starting in the 11th year (see below). While there may be a weak pattern toward decreasing frequency of having quit with longer time since quit, the pattern is obscured by the heaping of self-reported values at 5-year intervals with corresponding lower values between. The proportion of former smokers who reported quitting more than 11 or more years ago increases with age at the time of survey (e.g., fewer former smokers reported quitting within the first 10 years as age increases). There were no clear differences by sex or race/ethnicity.

Therefore, we first estimated the probability that a simulated person who was assigned to be a former smoker at model baseline quit 13 or more years ago by 10 year age bands using combined 2015-18 National Health Interview Survey data (ages 49-49, 4.9%; 50-59, 66.0%; 60-69 74.9%; 70-79, 84.7%, 80+, 90.1%). Individuals were assigned a zero probability of relapse. Other former smokers were assigned an equal probability of having quit within each of the most recent 12 years (e.g., uniformly distributed). We used 12 years since quit to delineate these two steps (rather than the 10-year mark that delineated a positive vs zero probability of relapse; see below) to allow the heaped responses for 10 years since quit to be distributed over both earlier and later years. Consistent with the relapse function, base-year former smokers who are assigned 11 or 12 years since quit are assigned a zero probability of relapse.

Lifetime smoking behavior

An individual's "risk" of changing smoking status (i.e., transitioning to another smoking state), is determined by current state, time in that state, and demographic characteristics. Individuals who have never smoked remain in the never smoker state because smoking initiation after the simulation's lowest age (40 years) is very rare. A current smoker can remain in the current smoker state or quit and transition to the former state. A former smoker either relapses into the current smoker state or remains in the former smoker state.

Logistic regression was used to determine the risk of smoking initiation or the probability of cessation from combined 2015-18 National Health Interview Survey data [26]. We identified quitters as those indicating they had ceased cigarette use within the last 12 months with no indication of relapse at the time of the survey. **Technical Appendix Table 5** contains the results of these estimations.

Relapse after quitting tobacco use is time-sensitive. The longer a person has successfully quit smoking, the less likely he or she is to relapse. We used published longitudinal studies to

estimate relapse probabilities for each year since quit, conditional on having not relapsed in a prior year. We recorded relapse rates from available years from five longitudinal studies [27-31], and fit a log-linear line to obtained a smoothed function of conditional relapse probability as a function of time since quit [relapse probability = 0.18901 -0.08038*ln(time since quit)], with years 11+ assigned a relapse probability of zero. The relapse rates obtained from literature for the first year were chosen to align as closely as possible with the simulation's definition of cessation with regard to how long an average smoker had quit before at the time of survey administration (see above). **Technical Appendix Table 6** shows the annual relapse rates based on this function.

3.4 Risk of Cardiovascular Disease Events

Published risk calculators for cardiovascular disease—such as PROCAM [32], SCORE [33], QRisk [34], or those derived from the Framingham Heart Study [35]—generally estimate an individual's 10-year risk of disease. These are difficult to translate to a microsimulation model with annual cycles. In addition, existing risk profiles commonly combine outcomes (such as chronic heart disease or cardiovascular disease, generally, compared to myocardial infarction or ischemic stroke, specifically—for example, see [36]).. They may also exclude potentially policy-relevant risk factors (such as differentiating current smokers from former smokers), and/or include clinical risk factors that may not be salient to population-level policy evaluation (such as evidence of left ventricular hypertrophy in the risk of stroke—for example, see [37]). For these reasons, we used data from the Framingham Heart Study to derive and develop customized 1-year risk equations for use in ModelHealth: CVD.

We developed risk equations for eight outcomes: non-fatal myocardial infarction (MI), non-fatal ischemic stroke, intracranial hemorrhage, angina pectoris, congestive heart failure, intermittent claudication, non-specific cardiovascular disease-related death, and diabetes. The risk analysis uses the Original Cohort (beginning in 1948 with 5,209 attendees) and the Offspring (beginning in 1971 with 5,124 attendees) arms of the Framingham Heart Study. Data were sourced from the National Heart, Lung, and Blood Institute's Biologic Specimen and Data Repository Information Coordinating Center, with approval and human subjects oversight from the HealthPartners Institute for Education and Research's Institutional Review Board [14, 15]. Statistical survival analysis was performed using Stata, Version 11 (Statacorp, College Station, TX).

To use as much of this rich data source as possible, allow for time-varying covariates, and provide for a direct estimate of annual risk, we adopted a parametric over the more common semi-parametric Cox proportional hazard approach in our analysis. Similar parametric methods have been previously explored and validated by Framingham Heart Study researchers [38]. Age, BMI, HDL, LDL, SBP, and one's disease history are all included as potential time-varying covariates in the analyses.

Because age accounts for time within a single person's life and because we do not have strong evidence with respect to the impact of secular time trends, we estimated an individual's risk using the exponential proportional hazards model (which has a time independent or "memoryless" property). Specifically, estimation was conducted using the *streg* command in Stata. Time independence is particularly important when estimating annual risk (i.e., $t = 1$), because the additional information in the shape parameter (i.e., embodied in the so-called

accelerated failure time metric) is never appropriately used and may otherwise systematically over-or under-estimate risk in a one year context. The resulting exponential model is estimated with a person j likelihood function of the risk of an event $(d_j \in \{0,1\})$ between t_{0j} and t_j is

$$L_j = \left[\frac{e^{\left(-e^{\beta_0 + x_j\beta}\right)t_j}}{e^{\left(-e^{\beta_0 + x_j\beta}\right)t_{0j}}}\right]\left(e^{-e^{\beta_0 + x_j\beta}}\right)^{d_j}$$

with an individual's probability of an event in the next year equal to $F(1) = 1 - e^{\left(-e^{\beta_0 + x_j\beta}\right)}$.

3.5 Baseline Risk of Fatal and Nonfatal Major GI Bleeding Events

The model simulates the incidence of fatal and nonfatal major GI bleeding as separate events. The evidence from aspirin primary prevention trials shows that aspirin increases the risk of non-fatal bleeds (OR = 1.58, 95% CI: 1.38 to 1.80), while a reliable pooled estimate of the impact of aspirin on fatal events could not be obtained due to rare fatal events in reporting trials and inconsistent reporting across trials [39].

Baseline fatal and nonfatal events rates were obtained from a large New Zealand cohort study conducted by Selak et al. [40]. Unlike other cohort studies, Selak et al. provide age- and sex-specific baseline rates for nonfatal and fatal major GI bleeding in a large cohort of nonaspirin users. Control groups in trial data could not be used to provide reliable baseline rates due to low and highly variable rates of major GI bleeding, low number of fatal major GI bleeding events, and sparsity of trials reporting fatal-only major GI bleeds. We used rates from 240,000 nonaspirin users reported by Selak et al. (the nonmedication cohort) as summarized in **Technical Appendix Table 8**. Because the cohort included only those ages 30 to 80, we apply the upper threshold of the 95% confidence interval for ages 70-79 year as reported by Selak et al. to the simulation model's 80+ year old cohort.

3.6 Modeling Colorectal Cancer Incidence and Fatality for Sensitivity Analysis

Colorectal cancer (CRC) was modeled using an incidence and case-fatality rate approach. Baseline incidence of malignant CRC by age, sex, and race/ethnicity for CRC was estimated from combined 2013-17 Surveillance, Epidemiology, and End Results (SEER) using the "Incidence - SEER Research Limited-Field Data with Delay-Adjustment, 21 Registries, Malignant Only, Nov 2019 Sub (2000-2017)" dataset, accessed and analyzed using SEER*Stat software version 8.3.8 [41]. Incidence rates are delay-adjusted but were not age-adjusted so that they represent the current U.S. population. Incidence rates were obtained from this source by 5-year age group, sex and race/ethnicity. These baseline incidence rates were parsed into rates for never, current and former smokers through standard population attributable fraction calculations [42-44] using the baseline smoking status probabilities described above and relative risks for smoking-attributable mortality in Smoking-Attributable Mortality, Morbidity, and Economic Costs (SAMMEC) as reported in the 2014 Surgeon General's Report on The Health Consequences of Smoking [45].

Case-fatality rates were calculated from 10-year survival rates that we estimated in SEER*Stat using the database "Incidence - SEER Research Data, 18 Registries, Nov 2019 Sub (2000-2017)" [41]. Survival rates for malignant CRC cases were estimated using methods that underlie SEER program reported 5-year survival rates [46]. Specifically, period survival calculation methods were used to leverage most recent data, and 3 years of data were used per survival cohort to provide increase sample. We used relative survival, which factors-out SEER estimates of mortality from other causes and thereby allows the resulting case-fatality rates to be employed in the simulation alongside probabilities for deaths from other causes. Case-fatality rates are not specific to smoking status. Rather, relative risks of smoking attributable mortality [45] are applied to incidence rates, which results in both incidence and mortality probabilities being specific to smoking status in the simulation.

CRC incidence and case-fatality rates used in the simulations are listed in **Technical Appendix Tables 9 and 10**. For both incidence and survival calculations, race/ethnicity categories were created in SEER*Stat to match those of the simulation model rather than using pre-defined SEER*Stat categories. However, misclassification in cancer data is likely greater for race/ethnicity categories other than white and black, both irrespective of Hispanic origin [47].

3.7 Modeling Cancer Competing Risks for Smokers

The simulation embeds higher mortality rate for CVD among smokers, and with the inclusion of CRC cancers above, it also embeds higher mortality rate for CRC. While effects on CRC are only shown in sensitivity analysis when the relative risk of CRC from using aspirin is changed from 1.0, the differential risk of CRC for smokers and non-smokers operates in all scenarios. This directly modifies the competing risks of CVD deaths and in doing so also modifies the number of years for which smokers are alive and at risk for CVD events. Although the scope for the current evidence review excludes cancers other than CRC, we maintain the model's prior estimates of differential impact of smoking on other cancers in the current version of the model to capture the differential competing risks of death posed by other smoking-attributable cancers. **Technical Appendix Tables 11-13** present these inputs by sets of cancers for which different relative risks are provided by SAMMEC [45], including relative risks of 1.0 for cancers that have not been determined to have increased risk from smoking.

3.8 Impact of Disease on Duration and Quality of Life (Morbidity)

Health utilities for the major outcomes affected by aspirin use are summarized in **Technical Appendix Table 14** as estimated by averaging across literature sources. To achieve better inter-condition consistency among utility estimates, only health utilities from studies that derived utilities weights for multiple conditions were included. However, these estimates are consistent with the results of systematic reviews of CVD utility values that included a wide range of study types[48-50]. No sources were identified that separately reported on intracranial hemorrhage along with health utilities for multiple other CVD conditions. To estimate the disutility for intracranial hemorrhage, we applied the marginal health utility difference between intracranial hemorrhage and ischemic stroke from a study comparing quality-of-life between stroke types [51] to the health utility for ischemic stroke that was derived across multiple sources [52-57]. We

identified only one estimate of health utilities from major GI bleeds within a study of multiple condition.[57] The estimate is nearly identical to that from a study focused on major GI bleeds [58] (the only other estimate of major GI bleed health utilities that we identified). Health utility while living with CRC varies greatly by stage of disease, treatment, and time since diagnosis. We did not incorporate a full stage progression model for our sensitivity analysis of the potential impact of aspirin use on CRC. Therefore, from systematic reviews [59, 60] we chose a single health utility value to represent the average health utility over the course of illness.

In the simulation, final health utility weights are derived as multiplicative reductions for multiple simultaneous health states. This includes living without one of the simulated conditions which was given a health utility of 0.87. [52, 53, 55, 56, 61] For example, a condition that is assigned a healthy utility value of .80 relative to an otherwise healthy individual results in a positive utility of 0.872*0.80 = 0.698. Any additional conditions that are present in the same year result in an additional multiplication of each condition's utility value to obtain the total positive utility for the year. The input utilities shown in **Technical Appendix Table 14** are derived from the referenced studies such that the average reduction in utility compared to ideal health (=1.0 – 0.87) is not double counted during simulation.

Reduced utilities from myocardial infarction and major GI bleeding events are applied only during the year in which an event occurs and were annualized based on an average acute burden period of 3 months from the incident event. Data on ongoing quality-of-life reductions, independent of sequela and subsequent events, after acute recovery from a non-fatal MI are lacking. As such, quality-of-life reductions for congestive heart failure were included because, as a major sequela to myocardial infarction, incidence may be indirectly affected by aspirin use in the model.

Quality of life reductions for cancer cases are assumed to persist for 5 years in long-term survivors or until death for fatal cancer cases. The average time until death for fata cases is assigned as 2.3 years of CRC, 2.0 years for trachea, lung and bronchus cancers, and 4.7 years for all other smoking-attributable cancers [62].

3.9 Risk of Death from Other Causes

The probability of dying from a cause other than CVD or cancer was derived from U.S. life tables [63] with deaths from CVD or cancer netted out using compressed mortality data in the CDC Wonder database [64]. These probabilities are summarized in **Technical Appendix Table 15**.

4 Clinical Preventive Services for CVD

In addition to aspirin, U.S. Preventive Services Task recommends screening for hypertension and initiating stating therapy when indicated among persons without history of CVD [9, 10]. The American College of Cardiology and American Heart Association also has convened expert panels to produce clinical practice guidelines for the prevention and management of cardiometabolic risk factors [11-13]. Primary and secondary prevention activities, consistent

with these guidelines and contemporary rates of adoption, are included in the model for setting the appropriate context and background rate of CVD events for evaluating the potential net benefits of using aspirin for primary prevention.

4.1 Aspirin Use

Aspirin for Primary Prevention (Decision Analysis)

To assess the potential net benefit (or harm) of using aspirin for primary prevention, two parallel simulations were conducted: one in which all agents initiate aspirin for primary prevention and another (the counterfactual) in which all agents do not use aspirin for primary prevention. All other factors between these simulations were held equal. To align with common clinical practice, aspirin use was discontinued permanently in both simulations after any major GI bleeding or intracranial hemorrhage event. CVD and bleeding relative risks were derived from eight low-dose (defined as 100mg per day or less) primary prevention trials identified by the systematic evidence review [39, 65-75]. All CVD benefits and harms are assumed to take effect immediately after initiating aspirin use, and all relative risks are assumed to return to 1.00 after discontinuing use of aspirin. The updated systematic review rated the evidence for the potential effect of aspirin on the relative risk of developing CRC to be low, and therefore this effect was included only for sensitivity analyses. When the CRC effect was included, we assumed based on data from three trials that the effect was realized beginning after 10 years of continuous aspirin use and would persist for up to 10 years following stoppage. The trials informing aspirin's effect on benefits and harms for primary prevention are summarized in **Technical Appendix Table 16** and the relative risk parameters are summarized in **Technical Appendix Table 17**.

Aspirin for Secondary Prevention

In both the intervention and counterfactual simulations of the aspirin primary prevention decision analysis, aspirin may be initiated following a non-fatal CVD event for the purposes of reducing the risk of subsequent events (secondary prevention). A meta-analysis of 16 secondary prevention aspirin trials indicates a 31 percent reduction in MI risk (95% Rate Ratio [RR] CI: 0.60-0.80) and a 22 percent reduction in ischemic stroke risk (95% RR CI: 0.61-0.99) [81]. Due to the relative rarity of intracranial hemorrhage and major GI bleeding and the smaller sample sizes of participants in secondary trials and insufficient evidence to distinguish clear differences between men and women in risk for intracranial hemorrhage and major GI bleeding, we calculated a combined unadjusted odds ratio from primary prevention trials to estimate the risk of these adverse events associated with aspirin use [39]. Similar to primary prevention trials, secondary preventive use of aspirin does not show a statistically significant reduction in CVD-related or all-cause mortality. A summary of the aspirin treatment effects when used for secondary prevention of CVD is given in **Technical Appendix Table 18**.

Use of Aspirin for Model Event Validation

When validating events in the model (**Technical Appendix Figure 2 and Table 27**), we implemented aspirin use for primary prevention in at contemporary use rates based on National Health and Nutrition Examination Survey (2015-2018) data. Observed population use of aspirin

for primary prevention does not necessarily align with the 2016 U.S. Preventive Services Taskforce guidelines, but it is correlated with ASCVD risk and age. We estimated the probability of aspirin use for primary prevention for analyses outside of the decision analysis using the logistic equation described in **Technical Appendix Table 19**.

4.2 Screening for Hypertension

Risk Assessment and Treatment Criteria

The model follows the 2017 American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines for treating high blood pressure [11] and assumes that providers will consider initiating drug therapy when systolic blood pressure ≥130 mm Hg for persons with history of CVD, diabetes, a10-year ASCVD risk ≥10%, or aged ≥65 years and when systolic blood pressure ≥140 mm Hg for all other persons. The therapeutic goal is systolic blood pressure < 130 mm Hg in all cases. The model applies contemporary rates of adherence to these guidelines, as derived from National Health and Nutrition Examination Survey (2015-2018) data and described in **Technical Appendix Table 20**.

Screening Frequency

The model follows the U.S. Preventive Services Task Force recommendation of annual blood pressure screening for persons aged ≥40 years [10]. Although screening is frequent, it is well documented that many patients are not aware of their elevated blood pressure [82]. To account for this, the model requires awareness of hypertension before treatment may be offered as derived from 2015-2018 National Health and Nutrition Examination Survey data and described in **Technical Appendix Table 21**.

Medication Use

We derived use rates of antihypertensives for primary and secondary prevention from 2015-2018 National Health and Nutrition Examination Survey data [17, 18]. Specifically, antihypertensive use rates for primary prevention were estimated by the weighted proportion of the sample of those with no self-reported history of CVD (i.e., not told of prior MI, congestive heart failure, angina pectoris, or stroke) who report having been told to use a antihypertensive by a medical care provider and are currently following that advice. Likewise, antihypertensive use rates for secondary prevention were estimated by the weighted proportion of the sample of those with self-reported history of CVD (i.e., previously told of prior MI, congestive heart failure, angina pectoris, or stroke) who report having been told to use an antihypertensive medication by a medical care provider and are currently following that advice. The medication use rates for blood pressure medications are presented in **Technical Appendix Table 22**.

Treatment Effects

We used meta-analyses/reviews of antihypertensive therapy to identify major (of 1,000 or more persons) randomized controlled trials comparing blood pressure reduction associated with drug therapy to a placebo [83-91]. We included trials—accounting for a total of 54,863 subjects— that

had a follow-up period of at least 52 weeks, involved subjects for primary or secondary prevention, were subject-blinded (at a minimum), and reported changes in SBP as an outcome. In addition, due to the considerable heterogeneity in blood pressure medication strategies—including differences in first-line drugs, doses, and combinations [92]—we included only studies with a stepped therapy treatment (and preferably matched stepped therapy of a placebo in the control arm). Trials were excluded if additional (open label) blood pressure lowering drugs were allowed for use in the placebo group unless observed at rates lower than 10 percent. The trials included in our analysis are summarized in **Technical Appendix Table 23**.

To accommodate diverse treatment strategies with respect to baseline blood pressure relative to goal, we estimated treatment effects on blood pressure levels using a simple weighted ordinary least squares regression, with baseline SBP levels (respectively) as the only predictor:

$$Effect_{SBP} = \beta_0 + (BaselineSBP)\beta_{BaselineSBP}$$

To assign person-specific effect sizes of the impact of drug therapy on SBP, we constructed a triangle distribution centered on the mean effect size described above, with upper and lower limits defined by the standard deviation in a subset of antihypertensive trials that reported this measure [94, 100, 101]. Average blood pressure lowering effects of antihypertensive drugs used in ModelHealth: CVD are summarized in **Technical Appendix Table 24**.

4.3 Statin Use

Risk Assessment and Treatment Criteria

The model follows the U.S. Preventive Services Task Force recommendation to initiate use of low-to-moderate dose statins in adults aged 40-70 years without a history of CVD or who have ≥1 CVD risk factors—which include dyslipidemia (low-density lipoprotein cholesterol >130 mg/dL or high-density lipoprotein <40 mg/dL), diabetes, hypertension, or smoking—and who have a 10-year ASCVD risk ≥10% [9]. The Task Force recommends selectively offering low-to-moderate dose to patients with ≥1 CVD risk factors and a 10-year ASCVD risk 7.5%-10%. The Task Force guidelines do not apply to persons with a history of CVD or low-density lipoprotein cholesterol >190 mg/dL. For these persons, the model follows the 2018 American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines for the management of blood cholesterol, which recommends initiating a high-dose statin for these persons with higher CVD risk [12]. The model applies contemporary rates of adherence to these guidelines, as derived from National Health and Nutrition Examination Survey (2015-2018) data and described in **Technical Appendix Table 25**.

Screening Frequency

The model follows the U.S. Preventive Services Task Force suggestion to screen for risk factors that indicate statin use every 5 years [9].

Medication Use

We derived use rates of statins for primary and secondary prevention from 2015-2018 National Health and Nutrition Examination Survey data [17, 18]. Specifically, statin use rates for primary prevention were estimated by the weighted proportion of the sample of those with no self-reported history of CVD (i.e., not told of prior MI, congestive heart failure, angina pectoris, or stroke) who report having been told to use a cholesterol lowering medication by a medical care provider and are currently following that advice. Likewise, statin use rates for secondary prevention were estimated by the weighted proportion of the sample of those with self-reported history of CVD (i.e., previously told of prior MI, congestive heart failure, angina pectoris, or stroke) who report having been told to use statin by a medical care provider and are currently following that advice. The medication use rates for statins are presented in **Table 26**.

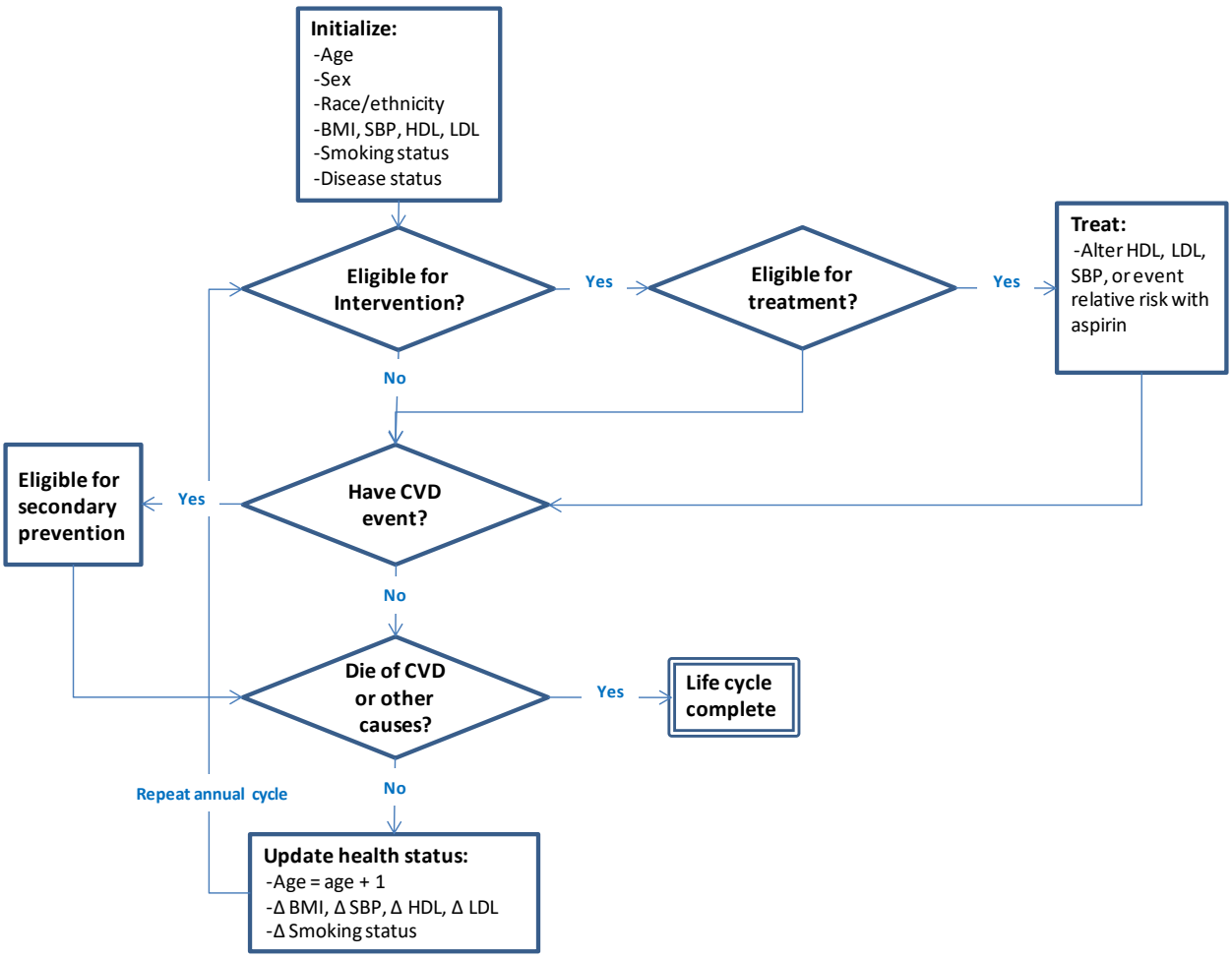
Treatment Effects

The model follows the evidence summarized by the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines for the management of blood cholesterol indicating that on average a low-to-moderate dose statin reduces low-density lipoprotein cholesterol by 30% and a high-dose statin reduces low-density lipoprotein cholesterol by 50% [12]. The model assumes no effect of statin use on high-density lipoprotein cholesterol.

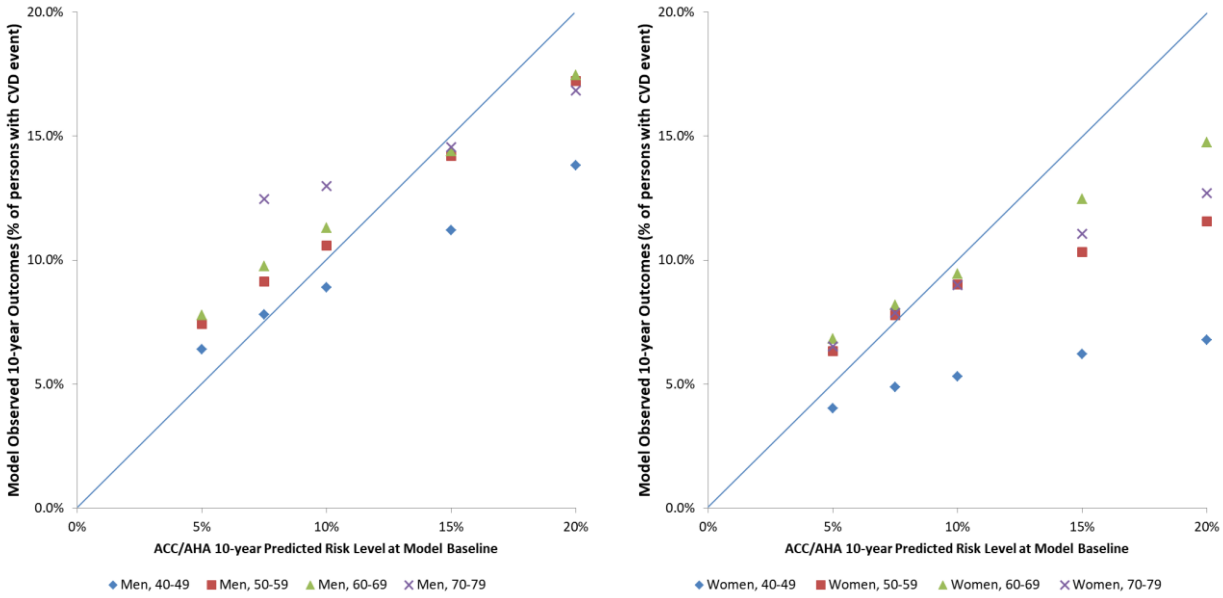
5 Model Validation

Baseline rates of CVD events are generated by the combination of population characteristics at model initiation, the model's estimation of the natural progression of CVD risk factors as individuals age, and the model's risk equations for disease. **Technical Appendix Tables 27a** and **27b** present prevalence rates of MI and ischemic stroke generated by the model for a birth cohort starting at age 40 and compares these values to corresponding rates observed in 2015-2018 National Health and Nutrition Examination Survey data [17, 18] for external validation of the ModelHealth: CVD natural history engine.

Technical Appendix Figure 1. ModelHealth: CVD Flow Diagram



Technical Appendix Figure 2: 10-yr Model Outcomes Compared With ACC/AHA 10-yr Risk for Men Aged 40-79



Notes: ACC/AHA=American College of Cardiology/American Heart Association. The y-axis represents the percent of persons observed having their first hard atherosclerotic cardiovascular disease (ASCVD) event (non-fatal MI, non-fatal stroke, or coronary death) in a ModelHealth: CVD simulated cohort with a 10-year ACC/AHA baseline risk specified in x-axis [20]. The 45-degree line indicates perfect concordance in 10-year outcomes predicted by the ACC/AHA risk calculator and those observed in a simulated population. Points above the 45-degree line indicate that 10-year event rates simulated in the model are above the rate indicated by 10-year ACC/AHA risk; points below the 45-degree line indicate that 10-year event rates simulated in the model are below the rate indicated by 10-year ACC/AHA risk. Similar patterns have been seen in other comparisons [21-24].

Technical Appendix Table 1a. Distribution of Estimated ACC/AHA 10-Year ASCVD Risk in CVD-Free, Among Men Aged 40 to 79 Years in the United States

ACC/AHA 10-Year ASVD Risk %	Age 40-49y	Age 50-59y	Age 60-69y	Age 70-79y
0	0.7	<0.1	<0.1	<0.1
1	20.7	0.1	<0.1	<0.1
2	21.8	4.9	<0.1	<0.1
3	20.1	5.8	<0.1	<0.1
4	10.9	8.0	<0.1	<0.1
5	7.9	13.0	0.3	<0.1
6	3.9	11.0	1.0	<0.1
7	4.6	12.4	3.7	<0.1
8	1.9	6.4	7.1	0.3
9	1.9	8.1	7.4	<0.1
10	1.4	6.8	5.8	<0.1
11	0.2	4.6	6.4	0.3
12	0.2	2.6	4.5	0.5
13	0.6	2.6	8.4	2.9
14	0.2	1.6	6.6	2.2
15	<0.1	1.9	4.6	0.7
16	0.5	1.8	4.1	2.3
17	<0.1	1.3	4.0	4.5
18	0.1	0.6	4.0	4.4
19	0.7	0.5	2.8	3.4
20	0.2	0.8	3.3	4.9
0-20	98.8	94.7	74.1	26.2
7.5*	2.1	11.4	3.6	<0.1

Notes: ACC/AHA=American College of Cardiology/American Heart Association; ASCVD=atherosclerotic cardiovascular disease; CVD=cardiovascular disease; y=years. Data derived by applying the AHA/ACC risk calculator to 2015-2018 NHANES data [17, 18]. The 0-20% totals do not sum to 100% because some CVD-free persons have a risk greater than 20%. Risk levels are rounded to the nearest integer. * The 7.5% risk category is included among the decision analysis population groups and is calculated as 7-8% ACC/AHA 10-year risk.

Technical Appendix Table 1b: Distribution of Estimated ACC/AHA 10-Year ASCVD Risk in CVD-Free, Among Non-Pregnant Women Aged 40 to 79 Years in the United States

ACC/AHA 10-Year ASVD Risk %	Age 40-49y	Age 50-59y	Age 60-69y	Age 70-79y
0	29.0	0.7	<0.1	<0.1
1	45.6	25.0	<0.1	<0.1
2	11.8	26.1	7.3	<0.1
3	5.2	14.3	7.6	<0.1
4	1.8	10.1	7.9	<0.1
5	1.9	6.2	14.6	<0.1
6	1.2	3.3	9.0	0.8
7	0.5	3.1	11.1	1.4
8	1.0	1.8	8.4	1.0
9	0.4	2.7	4.7	3.8
10	0.3	1.1	4.8	1.7
11	0.2	0.9	5.3	2.2
12	<0.1	1.0	4.2	2.3
13	<0.1	0.1	1.9	2.2
14	0.4	0.8	1.6	6.7
15	<0.1	1.0	1.3	3.9
16	<0.1	0.1	1.3	3.5
17	0.1	0.2	2.7	3.3
18	<0.1	0.1	0.6	5.5
19	<0.1	0.4	1.0	4.8
20	0.3	0.2	0.6	7.7
0-20	99.8	99.2	96.0	50.8
7.5*	0.7	2.3	9.3	0.8

Notes: ACC/AHA=American College of Cardiology/American Heart Association; ASCVD=atherosclerotic cardiovascular disease; CVD=cardiovascular disease; y=years. Data derived by applying the AHA/ACC risk calculator to 2015-2018 NHANES data [17, 18]. The 0-20% totals do not sum to 100% because some CVD-free persons have a risk greater than 20%. Risk levels are rounded to the nearest integer. * The 7.5% risk category is included among the decision analysis population groups and is calculated as 7-8% ACC/AHA 10-year risk.

Technical Appendix Table 2. Mean CVD Risk Characteristics by Age, Sex, and 10-Year CVD Risk Strata

	BMI (kg/m^2)	SBP (mmHg)	LDL (mg/dL)	HDL (mg/dL)	Treated BP (%)	Diabetes (%)	Current Smoking (%)
Men, Age 40-49y							
5% 10-year ASCVD risk	30.9	127.1	140.2	42.4	17%	18%	29%
7.5% 10-year ASCVD risk	31.5	128.8	142.5	41.2	25%	30%	51%
10% 10-year ASCVD risk	31.9	130.9	147.1	39.3	27%	37%	63%
15% 10-year ASCVD risk	32.7	133.6	151.3	37.6	39%	58%	78%
20% 10-year ASCVD risk	33.2	136.9	155.2	35.6	43%	76%	86%
Women, Age 40-49y							
5% 10-year ASCVD risk	35.2	129.3	136.8	42.3	35%	36%	61%
7.5% 10-year ASCVD risk	36.2	132.2	139.4	40.3	43%	50%	69%
10% 10-year ASCVD risk	36.9	134.6	140.8	39.2	49%	62%	70%
15% 10-year ASCVD risk	37.6	139.4	142.9	36.8	62%	76%	66%
20% 10-year ASCVD risk	37.8	143.7	143.8	35.6	70%	82%	64%
Men, Age 50-59y							
5% 10-year ASCVD risk	29.3	123.9	118.4	53.6	17%	3%	5%
7.5% 10-year ASCVD risk	30.0	128.8	127.9	48.6	24%	10%	15%
10% 10-year ASCVD risk	30.6	131.2	132.2	45.7	31%	19%	25%
15% 10-year ASCVD risk	31.7	135.7	137.1	41.3	40%	44%	38%
20% 10-year ASCVD risk	32.5	138.1	139.1	38.6	48%	64%	47%
Women, Age 50-59y							
5% 10-year ASCVD risk	32.0	133.3	136.4	54.8	40%	18%	39%
7.5% 10-year ASCVD risk	33.8	137.2	138.3	50.7	49%	44%	42%
10% 10-year ASCVD risk	34.6	140.0	139.4	49.1	56%	55%	47%
15% 10-year ASCVD risk	35.6	144.1	140.8	46.9	65%	69%	56%
20% 10-year ASCVD risk	36.4	147.1	141.2	45.7	72%	81%	56%
Men, Age 60-69y							
5% 10-year ASCVD risk	27.3	108.9	87.2	66.3	10%	0%	0%
7.5% 10-year ASCVD risk	28.0	118.7	101.6	58.8	17%	0%	3%
10% 10-year ASCVD risk	28.5	123.8	109.4	55.0	25%	2%	6%
15% 10-year ASCVD risk	29.3	130.8	118.9	50.2	41%	10%	16%
20% 10-year ASCVD risk	30.1	136.0	123.7	46.6	50%	28%	23%
Women, Age 60-69y							
5% 10-year ASCVD risk	30.1	127.4	120.0	63.5	30%	5%	3%
7.5% 10-year ASCVD risk	30.8	133.3	124.2	61.2	44%	10%	8%
10% 10-year ASCVD risk	31.7	136.8	125.6	59.3	53%	24%	12%

Technical Appendix Table 2. Mean CVD Risk Characteristics by Age, Sex, and 10-Year CVD Risk Strata

	BMI (kg/m^2)	SBP (mmHg)	LDL (mg/dL)	HDL (mg/dL)	Treated BP (%)	Diabetes (%)	Current Smoking (%)
15% 10-year ASCVD risk	33.3	142.2	127.1	56.0	64%	52%	20%
20% 10-year ASCVD risk	34.2	145.6	128.0	54.2	72%	68%	28%
Men, Age 70-79y							
7.5% 10-year ASCVD risk	25.6	101.7	92.0	67.5	0%	0%	0%
10% 10-year ASCVD risk	26.1	107.8	91.8	66.7	3%	0%	0%
15% 10-year ASCVD risk	27.1	116.3	98.1	61.9	21%	1%	5%
20% 10-year ASCVD risk	27.8	124.8	106.0	57.5	35%	3%	8%
Women, Age 70-79y							
5% 10-year ASCVD risk	27.1	95.0	105.0	70.9	1%	0%	0%
7.5% 10-year ASCVD risk	28.0	108.9	118.7	66.1	12%	0%	0%
10% 10-year ASCVD risk	28.4	118.5	122.4	64.6	22%	0%	1%
15% 10-year ASCVD risk	29.2	130.2	127.5	62.7	49%	4%	4%
20% 10-year ASCVD risk	29.5	135.7	128.8	62.3	59%	11%	6%

Notes: BMI = body mass index; SBP = systolic blood pressure; LDL = low-density lipoprotein cholesterol; HDL = high-density lipoprotein cholesterol; BP = blood pressure; CVD = cardiovascular disease; ASCVD = atherosclerotic cardiovascular disease; y=years. All values are population means.

Technical Appendix Table 3: ModelHealth: CVD Annual Progression of Risk Factors

Step	Case	Source	Controlled Factors	Estimator
1	P(BMI Change)	BRFSS [25]	Age, sex, race/ethnicity, previous BMI	Multinominal Logit
1	P(HDL Change)	Framingham [14, 15]	Age, sex, BMI, previous HDL	Multinominal Logit
1	P(LDL Change)*	Framingham [14, 15]	Age, sex, BMI, previous LDL	Multinominal Logit
1	P(SBP Change)	Framingham [14, 15]	Age, sex, BMI, previous SBP	Multinominal Logit
2	Q(BMI Change)	BRFSS [25]	Age, sex, race/ethnicity, previous BMI	OLS
2	Q(HDL Change)	Framingham [14, 15]	Age, sex, BMI, previous HDL	Random Effects
2	Q(LDL Change)*	Framingham [14, 15]	Age, sex, BMI, previous LDL	Random Effects
2	Q(SBP Change)	Framingham [14, 15]	Age, sex, BMI, previous SBP	Random Effects

Notes: P() = probability. Q() = quantity. OLS = Ordinary least squares regression. BRFSS = Behavioral Risk Factor Surveillance System. *In actuality, the progression of LDL is more complex than indicated in the table and text. LDL was not measured with the same regularity as HDL and total cholesterol in the Framingham Heart Study; therefore, transitions in LDL were modeled in additional two steps. First, the probability and quantity of change in total cholesterol was modeled as described above. Second, HDL and total cholesterol were used in a prediction equation—derived from NHANES with high explanatory power (i.e., $R^2 > 0.9$)—to estimate a corresponding LDL level. Although not included in the prediction equations, estimations related to changes in cholesterol and blood pressure controlled for treatment.

Technical Appendix Table 4. Results of Multinomial Estimation Predicting Initial Smoking Status

Variable name	Current Smoker	Former Smoker
Ref. Category	-6.1201	-4.1504
Male	2.2808	4.1662
Age	0.1829	0.0908
Age Squared	-0.00172	-0.00055
Black non-Hispanic	-0.1435	-0.6481
Hispanic	-0.6270	-0.5607
Other race, non-Hispanic	-0.5772	-0.6452
Male * Age interaction	-0.0735	-0.1438
Male * Age Squared interaction	0.00682	0.00133

Source: National Health Interview Survey[19]. Table values represent coefficients in a multinomial logistic regression equation. Reference group is White non-Hispanic, female, never smoker.

Technical Appendix Table 5. Results of Logistic Regressions Predicting Adult Smoking Cessation

Variable name	Coefficient
Reference group	0.5159
Male	1.0320
Age	-0.1105
Age Squared	0.000949
Black, non-Hispanic	-0.2056
Hispanic	0.1008
Other race, non-Hispanic	0.1405
Male * Age interaction	-0.0390
Male * Age Squared interaction	0.000348

Source: National Health Interview Survey [26]. Table values represent coefficients in a logistic regression equation. Reference group = non-Hispanic white females.

Technical Appendix Table 6. Baseline Smoking Tobacco Relapse Rates

Years Since Quit	Probability of Relapse
1	0.189
2	0.133
3	0.101
4	0.078
5	0.060
6	0.045
7	0.033
8	0.022
9	0.012
10	0.004
11+	0.000

Source: Log-linear equation based upon longitudinal studies [27-31].

Technical Appendix Table 7. Summary of Risk Equation Hazard Ratios Derived From Framingham Heart Study Data

Risk Factor	MI	Ischemic Stroke	Intracranial Hemorrhage	Congestive Heart Failure	Angina Pectoris	Intermittent Claudication	Diabetes	CVD-related Death
Age (per year)	1.039	1.067	1.049	1.074	1.024	1.039	1.064	1.069
Sex (female)	0.380				0.587	0.619		0.495
BMI (per kg/m^2)			0.904	1.024			1.108	
HDL (per mg/dL)	0.986	0.988		0.986	0.989	0.993	0.968	
LDL (per mg/dL)	1.005				1.006	1.007		1.004
SBP (per mm Hg)	1.013	1.023	1.020	1.015	1.011	1.015	1.004	1.009
Current smoking	1.698		1.497	1.401		2.871		1.589
Diabetes	1.889	1.913		2.176		2.237		1.590
Previous any CVD, or	2.784	2.005	1.568		2.750	2.529		
Previous MI				3.885				1.455
Previous IS								1.759
Previous ICH								57.313
Previous CHF								9.27
Previous Other CVD				1.838				1.93

Notes: CVD = cardiovascular disease; MI = myocardial infarction; IS = ischemic stroke; ICH = intracranial hemorrhage; CHF = congestive heart failure. Estimations are based on the exponential proportional hazards model. Myocardial infarction and ischemic stroke risks are for non-fatal events; risks for other CVD outcomes include fatal and non-fatal events. Congestive heart failure risk is for a hospitalized event. Risks for angina pectoris, intermittent claudication, and diabetes reflect incidence of these conditions. All continuous variables used in ModelHealth: CVD are natural log transformed; however, hazard ratios of non-log variables are presented here instead for easier interpretation. Source is authors' analysis of data from the Framingham Heart Study [14, 15].

Technical Appendix Table 8. Risk for Major GI Bleeding Events Without Aspirin

Outcome	Sex	Age 40-49y	Age 50-59y	Age 60-69y	Age 70-79y	Age 80y+*
Annual Probability of Nonfatal Major GI Bleed	Men	0.14%	0.16%	0.24%	0.37%	0.45%
	Women	0.10%	0.13%	0.20%	0.29%	0.36%
Annual Probability of Fatal Major GI Bleed	Men	0.00%	0.01%	0.02%	0.02%	0.04%
	Women	0.00%	0.00%	0.01%	0.02%	0.03%

Source: Selak et al. [40]. Notes: y=years. Major GI bleeding incidence rates in the "nonmedication cohort". *For ages 80+ rates are based on the upper threshold of the 95% confidence interval for ages 70-79 years.

Technical Appendix Table 9. Colorectal Cancer Incidence Rates per 100,000 Persons

	Women			Men		
	Never smoker	Current smoker	Former smoker	Never smoker	Current smoker	Former smoker
Non-Hispanic White						
40-44 years	16.4	28.5	22.2	20.5	26.3	25.5
45-49 years	25.5	44.3	34.7	35.5	45.4	44.0
50-54 years	42.3	73.5	57.5	62.6	80.2	77.7
55-59 years	42.9	79.8	56.2	61.7	128.3	78.9
60-64 years	54.5	101.3	71.4	81.3	169.1	104.1
65-69 years	68.3	160.5	101.8	112.1	230.8	141.2
70-74 years	89.5	210.3	133.3	145.4	299.4	183.2
75-79 years	129.2	281.7	188.6	190.4	367.4	241.8
80-84 years	165.6	360.9	241.7	240.5	464.2	305.5
85+ years	184.2	401.6	269.0	246.2	536.7	359.5
Non-Hispanic Black						
40-44 years	18.3	31.8	24.9	21.5	27.5	26.6
45-49 years	31.7	55.1	43	39.8	50.9	49.4
50-54 years	61.1	106.3	83.1	80.4	103	99.7
55-59 years	61.4	114.3	80.5	91.6	190.5	117.3
60-64 years	81.4	151.3	106.6	121.8	253.4	156
65-69 years	98.2	230.7	146.3	164.9	339.6	207.7
70-74 years	116.9	274.8	174.2	191.5	394.5	241.3
75-79 years	136.7	297.9	199.5	241.5	466	306.7
80-84 years	166.8	363.5	243.5	279.3	539.1	354.8
85+ years	170	370.6	248.2	232.5	506.8	339.4
Hispanic						
40-44 years	14	24.4	19.1	15	19.2	18.6
45-49 years	21.6	37.6	29.4	25.1	32.1	31.1
50-54 years	41.3	71.9	56.2	52.7	67.4	65.3
55-59 years	44	81.8	57.6	64.3	133.7	82.2
60-64 years	61.6	114.5	80.7	89.8	186.7	114.9
65-69 years	72.4	170.1	107.8	127.3	262.2	160.4
70-74 years	88.2	207.2	131.4	153.7	316.7	193.7
75-79 years	108.4	236.2	158.2	184.6	356.2	234.4
80-84 years	130.9	285.4	191.1	219.7	424.1	279.1
85+ years	146.2	318.7	213.4	226.7	473.8	326.4
Other						
40-44 years	12	22	16.6	15.8	20.2	19.6
45-49 years	22.9	39.9	31.2	30.6	39.1	37.9
50-54 years	42.9	74.6	58.3	63	80.6	78.1
55-59 years	40.1	74.6	52.5	68.1	141.6	87.2
60-64 years	55.2	102.7	72.3	93.2	193.8	119.3
65-69 years	68.4	160.7	101.9	119.1	245.4	150.1
70-74 years	79.7	187.2	118.7	137.3	282.8	173
75-79 years	98.7	215.2	144.1	164.5	317.6	209
80-84 years	131.8	287.4	192.5	190.5	367.7	241.9
85+ years	151.7	330.8	221.5	193.8	422.4	282.9

Sources: [41, 45].

Technical Appendix Table 10. Colorectal Cancer Case-Fatality Rates

	Women	Men
Non-Hispanic White		
40-44 years	0.33	0.37
45-49 years	0.37	0.41
50-54 years	0.30	0.35
55-59 years	0.36	0.40
60-64 years	0.35	0.42
65-69 years	0.37	0.41
70-74 years	0.41	0.42
75-79 years	0.41	0.47
80-84 years	0.48	0.52
85+ years	0.55	0.52
Non-Hispanic Black		
40-44 years	0.43	0.49
45-49 years	0.41	0.45
50-54 years	0.35	0.41
55-59 years	0.43	0.49
60-64 years	0.44	0.48
65-69 years	0.45	0.47
70-74 years	0.44	0.53
75-79 years	0.55	0.64
80-84 years	0.56	0.59
85+ years	0.72	0.82
Hispanic		
40-44 years	0.39	0.43
45-49 years	0.38	0.48
50-54 years	0.34	0.37
55-59 years	0.36	0.43
60-64 years	0.41	0.43
65-69 years	0.37	0.44
70-74 years	0.51	0.47
75-79 years	0.52	0.58
80-84 years	0.61	0.65
85+ years	0.73	0.67
Other		
40-44 years	0.38	0.37
45-49 years	0.35	0.38
50-54 years	0.27	0.25
55-59 years	0.32	0.35
60-64 years	0.33	0.33
65-69 years	0.31	0.36
70-74 years	0.40	0.42
75-79 years	0.37	0.52
80-84 years	0.57	0.53
85+ years	0.73	0.67

Source: [41].

Technical Appendix Table 11. Cancer Incidence and Case-Fatality Rates of Trachea, Lung, and Bronchus

Outcome	Sex	Smoking status	40-44y	45-49y	50-54y	55-59y	60-64y	65-69y	70-74y	75-79y	80-84y	85y+
Incidence (per 100,000 adults)	Men	Never smoker	2.2	5.6	12.5	20.6	43.3	65.7	98.5	141.2	152.7	145.2
		Current smoker	31.5	80.5	179.2	391.1	824.3	1859.1	2785.9	3177.5	3437.2	3267.4
		Former smoker	9.7	24.7	55	93.9	198	511.9	767.1	911.9	986.4	937.7
	Women	Never smoker	2.4	5.9	11.4	14.1	27.3	42.3	54.6	63.5	59.4	48.2
		Current smoker	32.2	78.8	152.2	267.4	518.3	1001.2	1291.6	1465.3	1370.4	1112.8
		Former smoker	6.4	15.6	30.2	70.6	136.7	287.9	371.4	405.1	378.8	307.6
Mortality (case-fatality rate)	Men	Any	0.53	0.58	0.59	0.59	0.6	0.56	0.56	0.55	0.57	0.62
	Women	Any	0.46	0.48	0.51	0.51	0.52	0.51	0.53	0.56	0.61	0.7

Sources: [41, 45].

Technical Appendix Table 12. Incidence and Case-Fatality of Other Cancers With Smoking-Attributable Risk

Outcome	Sex	Smoking status	40-44y	45-49y	50-54y	55-59y	60-64y	65-69y	70-74y	75-79y	80-84y	85y+
Incidence (per 100,000 adults)	Men	Never smoker	51.1	107.9	207.5	334.0	526.4	747.4	998.9	1228.7	1369.8	1402.5
		Current smoker	89.0	187.7	361.0	621.3	979.0	1756.4	2347.4	2678.6	2986.1	3057.5
		Former smoker	69.5	146.7	282.1	437.6	689.5	1113.6	1488.4	1793.9	1999.8	2047.7
	Women	Never smoker	53.2	87.0	141.7	179.8	279.3	443.6	578.2	696.3	757.6	759.1
		Current smoker	68.1	111.4	181.3	373.9	580.9	913.8	1191.1	1343.9	1462.1	1465.0
		Former smoker	66.0	107.9	175.7	230.1	357.5	558.9	728.6	884.3	962.1	964.0
Mortality (case-fatality rate)	Men	Any	0.29	0.34	0.36	0.40	0.41	0.40	0.40	0.41	0.43	0.49
	Women	Any	0.25	0.31	0.32	0.36	0.39	0.39	0.42	0.45	0.48	0.57

Sources: [41, 45].

Technical Appendix Table 13. Incidence and Case-Fatality of Other Cancers With No Smoking-Attributable Risk

Outcome	Sex	40-44y	45-49y	50-54y	55-59y	60-64y	65-69y	70-74y	75-79y	80-84y	85y+
Incidence (per 100,000 adults)	Men	62.7	132.9	256.6	415.1	635.7	927.9	1218.6	1478.1	1625.4	1621.3
	Women	59.0	96.8	159.2	233.4	353.4	531.2	694.5	840.1	919.6	904.6
Mortality (case-fatality rate)	Men	0.29	0.34	0.36	0.40	0.41	0.40	0.40	0.41	0.43	0.49
	Women	0.25	0.31	0.32	0.36	0.39	0.39	0.42	0.45	0.48	0.57

Source: [41].

Technical Appendix Table 14. Health Utility Weights

	First year/new event	Ongoing quality-of-life	Source
Baseline health utility weight			
No CVD conditions		0.87	[52, 53, 55, 56, 61]
Relative health utility weight			
Congestive heart failure	0.79	0.79	[54-57, 61]
GI bleeding	0.91	1.00	[57]
Hemorrhagic stroke	0.60	0.60	[51-57]
Ischemic stroke	0.77	0.77	[52-57]
Myocardial Infarction	0.86	1.00	[52, 54, 55, 57, 61]
Taking aspirin daily, base case		1.00	Assumption
Relative health utility weights for sensitivity analysis scenarios			
Colorectal cancer	0.70	0.70	[59, 60]
Taking aspirin, sensitivity #1		0.999	Assumption
Taking aspirin, sensitivity #2		0.995	Assumption

Notes: CVD=cardiovascular disease; GI=gastrointestinal. All health utility weights are applied multiplicatively to the baseline health utility weight. The quality-of-life reduction for colorectal cancer is applied for up to five years in the case of non-fatal episodes. Quality-of-life reductions for congestive heart failure are included as a major sequela to MI. First year/new event health utility weights are applied during the year of an incidence event or first year of disease onset; ongoing health utilities are applied in subsequent years.

Technical Appendix Table 15. Summary of Annual Mortality Risk From Causes Other Than CVD and Cancer

Age	Men	Women
40-49 years	0.23%	0.15%
50-59 years	0.44%	0.30%
60-69 years	0.82%	0.60%
70-79 years	1.88%	1.49%
80-89 years	4.58%	3.51%
90-100 years	14.96%	12.68%

Source: [63, 64] w. Notes: CVD = cardiovascular disease. Mortality risk is based on annual probabilities by age and sex in the U.S. life tables [63] with CVD and cancer mortality subtracted out using underlying cause-of-death mortality data in the CDC Wonder database [64]. Causes for CVD mortality included ICD-10 codes I10-I25, I30-I51, and I60-I69, and causes for cancer mortality included the ICD-10 codes for the following smoking-attributable cancers: lip, oral cavity, and pharynx (C00-C14), esophagus (C15), stomach (C16), colon and rectum (C18-C20), pancreas (C25), larynx (C32), trachea, lung, bronchus (C33–C34), cervix uteri (C53), kidney and renal pelvis (C64-65), urinary bladder (C67), and acute myeloid leukemia (C92.0).

Technical Appendix Table 16. Summary of Aspirin Trials Informing Treatment Effect Parameters

Study Name	Year Published	N	Dose, schedule	Age Range (years)	Mean Age (years)	Mean Follow-up (years)	Model Parameters Informed
AAA [65]	2010	3,350	100 mg, daily	50-75	62.0	8.2	CVD death, GIB, ICH, IS, MI
ARRIVE [73]	2018	12,546	100 mg, daily	≥55	64.0	*5.0	CVD death, GIB, ICH, MI
ASCEND [74]	2018	15,480	100 mg, daily	≥40	63.0	7.4	CVD death, GIB, ICH, IS, MI
ASPREE [75]	2018	19,144	100 mg, daily	≥65	74.0	4.7	CVD death, GIB, ICH,IS, MI
BMD [76]	1988	5,139	500 mg, daily	N/R	61.6	6	CRC incidence
HOT [66]	1998	18,790	75 mg, daily	50-80	61.5	3.8	CVD death, GIB, ICH, MI
JPAD [67]	2008	2,539	100 mg, daily	30-85	64.5	*4.4	CVD death, GIB, ICH, IS, MI
JPPP [72]	2014	14,658	100 mg, daily	60-85	70.5	*5	CVD death, ICH, IS, MI
PHS [77]	1989	22,071	325 mg, QOD	40-84	53.2	5	CRC incidence
POPADAD [68]	2008	1,276	100 mg, daily	≥40	60.3	*6.7	CVD death, ICH, MI
PPP [69]	2001	4,495	100 mg, daily	≥50	64.4	3.6	CVD death, GIB,ICH, MI
TPT [70]	1998	2,540	75 mg, daily	45-69	57.5	*6.8	CVD death, GIB, ICH, MI
UK-TIA [76]	1990	2,449	300mg or 1200mg, daily	≥40	60.3	4,4	CRC incidence
WHS [71, 78]	2005	39,876	100 mg, QOD	≥45	54.6	10.1	CVD death, CRC Incidence, GIB, ICH, MI

Notes: N = study population size at randomization; AAA = Aspirin for Asymptomatic Atherosclerosis Study; ARRIVE=Aspirin to Reduce Risk of Initial Vascular Events Study; ASCEND = A Study of Cardiovascular Events in Diabetes; ASPREE = Aspirin in Reducing Events in the Elderly Study; BMD = British Medical Doctors Study; HOT = Hypertension Optimal Treatment Study; JPAD = Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes Study; JPPP = Japanese Primary Prevention Project Study; POPADAD = Prevention of Progression of Arterial Disease and Diabetes Study; PHS=Physician's Health Study; PPP = Primary Prevention Project Study; TPT = Thrombosis Prevention Trial; UK-TIA = UK Transient Ischaemic Attack Aspirin Trial; WHS = Women's Health Study; QOD = every other day; CVD = cardiovascular disease; CRC = colorectal cancer; GIB = relative risk for major gastrointestinal bleeding; ICH = intracranial hemorrhage; IS = relative risk for ischemic stroke; MI = relative risk for myocardial infarction. The mean age is at study enrollment. An asterisk (*) denotes a median value. The BMD,UK-TIA and, PHS trials involved aspirin doses greater than 100 mg. but these studies were included in the derivation of aspirin's effect on CRC incidence because evidence suggests the effect is not related to dose [79, 80]. All studies included in this table are CVD primary prevention trials, except for UK-TIA, which enrolled persons with prior transient ischemic attack or stroke and is only used here for the derivation of aspirin's effect on CRC incidence.

Technical Appendix Table 17: Summary of Aspirin Treatment Effects for Primary Prevention of CVD and CRC

Parameter	Base case	Worst Case	Best Case	Other values	Source
Benefits					
CRC incidence (>10 years), odds ratio	1.00			0.64	[39]
CVD death, odds ratio	1.00			0.95	[39]
Non-fatal ischemic stroke, odds ratio	0.88	1.00	0.78		[39]
Non-fatal myocardial infarction, odds ratio	0.88	0.96	0.80		[39]
Harms					
Intracranial hemorrhage, odds ratio	1.31	1.54	1.11		[39]
Fatal major GI bleeding, odds ratio	1.00			1.58	Assumed, [39]
Non-fatal major GI bleeding, odds ratio	1.58	1.80	1.38		[39]

Sources: [39, 65-75]. Notes: CRC = colorectal cancer; CVD = cardiovascular disease. For informing trial details, see **Technical Appendix Table 16**. Best and worst cases are based on 95% confidence intervals. The "other value" for CVD-related death is based on the mean (but not statistically significant) found among primary prevention trials. The "other value" for CRC is based on assuming no CRC benefit from long-term aspirin use.

Technical Appendix Table 18. Summary of Aspirin Treatment Effects for Secondary Prevention of CVD

Condition	Relative risk	Source
Relative Risk of Myocardial Infarction	0.69	[81]
Relative Risk of Ischemic Stroke	0.78	[81]
Relative Risk of Intracranial Hemorrhage	1.31	[39]
Relative Risk of CVD-related Death	1.00	[81]
Relative Risk of Major GI Bleed	1.58	[39]

Technical Appendix Table 19: Estimation of Aspirin Use for Primary Prevention for Validation Analyses

Logistic Parameter	Coefficient		ASCVD risk group	Use of aspirin for primary prevention
Age	0.332		5% 10-year risk	20%
10-yr ASCVD risk	0.009		7.5% 10-year risk	31%
Constant	-0.272		10% 10-year risk	33%
			15% 10-year risk	40%
			20% 10-year risk	61%

Notes: ASCVD = atherosclerotic cardiovascular disease; yr = year. Source: National Health and Nutrition Examination Survey (2015-2018) [17, 18].

Technical Appendix Table 20. BP Medication Initiation Offer Rates Based on Clinical Criteria

Population	BP Threshold for Treatment	BP Medication Initiation Offer Rate
History of CVD	130 mm Hg systolic BP	95%
Diabetes, 10-year ASCVD risk ≥10%, or age ≥ 65 years	130 mm Hg systolic BP	95%
No prior CVD or diabetes and 10-year ASCVD risk <10%	140 mm Hg systolic BP	75%

Notes: ASCVD = atherosclerotic cardiovascular disease Source: National Health and Nutrition Examination Survey (2015-2018) [17, 18]. Notes: Values are rounded to the nearest 5%.

Technical Appendix Table 21. Hypertension Awareness Rates

Population	Hypertension Awareness
No history of CVD	
Age 40-49 years	60%
Age 50-59 years	65%
Age 60-69 years	75%
Age ≥70 years	70%
History of CVD	
Age 40-49 years	90%
Age 50-59 years	90%
Age 60-69 years	90%
Age ≥70 years	85%

Source: National Health and Nutrition Examination Survey (2015-2018) [17, 18]. Notes: Values are rounded to the nearest 5%.

Technical Appendix Table 22. Summary of Antihypertensive Medication Use Rates

Parameter	Medication use rate
No history of CVD (primary prevention)	
Age 40-64 years	75%
Age ≥65 years	90%
History of CVD (secondary prevention)	
Age 40-64 years	85%
Age ≥65 years	90%

Source: National Health and Nutrition Examination Survey (2015-2018) [17, 18]. Notes: Values are rounded to the nearest 5%.

Technical Appendix Table 23. Summary of Antihypertensive Drug Trials Included in Estimation of Treatment Effects

Trial	Subjects	Ages (years)	Baseline SBP (mm Hg)	Mean ↓ SBP (mm Hg)
FEVER	9,711	50 – 79	154.3	4.5
HYVET	3,845	80+	173.0	13.0
MRC-1	17,354	35 – 64	161.5	10.5
MRC-2	4,396	65 – 74	173.0	15.5
PROGRESS	6,105	30 – 90	147.0	9.0
SHEP	4,736	60+	170.3	14.0
STOP	1,627	70 – 84	195.0	22.0
Syst-China	2,394	60+	170.5	9.1
Syst-Eur	4,695	60+	174.0	13.0

Sources: FEVER [93]; HYVET [94]; MRC-1[95], MRC-2[96]; PROGRESS[97]; SHEP[98]; STOP [99]; Syst-China[100]; Sys-Eur [101]. Notes: SBP = systolic blood pressure.

Technical Appendix Table 24. Summary of Antihypertensive Drug Treatment Effects

	*β*0	*βBaselineSBP*	Std. Dev.
Antihypertensive Drug Effect (reduction) on SBP (mm Hg)	-40.101	0.310	16.90

Notes: SBP = systolic blood pressure. Source: Analysis of clinical trials described in **Technical Appendix Table 23**.

Technical Appendix Table 25. BP Statin Initiation Offer Rates Based on Clinical Criteria

Population			Statin Medication Initiation Offer Rate
No prior CVD	LDL < 190 mg/dL, ≥ 1 CVD risk, and 10-yr ASCVD ≥10%	Age 40-49 years	30%
		Age 50-59 years	45%
		Age 60-69 years	50%
		Age 70-75 years	60%
	LDL ≥ 190 mg/dL	Age 40-49 years	15%
		Age 50-59 years	30%
		Age 60-69 years	45%
		Age 70-75 years	60%
Prior CVD		Age 40-49 years	45%
		Age 50-59 years	65%
		Age 60-69 years	80%
		Age 70-75 years	75%
		Age ≥76 years	75%

Source: National Health and Nutrition Examination Survey (2015-2018) [17, 18]. Notes: Values are rounded to the nearest 5%.

Table 26. Summary of Statin Use Rates

Population	Medication use rate
No history of CVD (primary prevention)	
Age 40-49 years	0.50%
Age 50-59 years	0.55%
Age 60-69 years	0.80%
Age ≥70 years	0.75%
History of CVD (secondary prevention)	
Age 40-49 years	0.65%
Age 50-59 years	0.80%
Age 60-69 years	0.85%
Age ≥70 years	0.90%

Source: National Health and Nutrition Examination Survey (2015-2018) [17, 18]. Notes: Values are rounded to the nearest 5%.

Technical Appendix Table 27a. Comparison of ModelHealth: CVD Myocardial Infarction Event Rates With National Prevalence Estimates

	NHANES (2015-2018)	ModelHealth: CVD
Men		
Age 40-49	1.2%	2.2%
Age 50-59	5.0%	5.3%
Age 60-69	10.3%	10.3%
Age 70-79	16.8%	16.0%
Women		
Age 40-49	0.8%	1.0%
Age 50-59	2.9%	2.0%
Age 60-69	4.3%	3.9%
Age 70-79	4.8%	6.2%

Notes: NHANES = National Health and Nutrition Examination Survey; CVD = cardiovascular disease. This table compares CVD prevalence at various ages between NHANES 2015-2018 [17, 18] combined data and results from the ModelHealth: CVD model. The model run represented here is based on a birth cohort, starting at age 40, 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 datasets, outcomes are calculated for the age range from NHANES and the mid-point of the age range from the ModelHealth: CVD output; this methodological difference can explain some small discrepancies. Similar patterns have been seen in other comparisons [21-24].

Technical Appendix Table 27b. Comparison of ModelHealth: CVD Stroke Event Rates With National Prevalence Estimates

	NHANES (2015-2018)	ModelHealth: CVD
Men		
Age 40-49	1.7%	1.4%
Age 50-59	2.6%	2.0%
Age 60-69	6.2%	3.6%
Age 70-79	7.0%	6.5%
Women		
Age 40-49	1.4%	0.9%
Age 50-59	3.8%	1.5%
Age 60-69	3.7%	2.9%
Age 70-79	8.3%	5.6%

Notes: NHANES = National Health and Nutrition Examination Survey; CVD = cardiovascular disease. This table compares CVD prevalence at various ages between NHANES 2015-2018 [17, 18] combined data and results from the ModelHealth: CVD model. The model run represented here is based on a birth cohort, starting at age 40, 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 datasets, outcomes are calculated for the age range from NHANES and the mid-point of the age range from the ModelHealth: CVD output; this methodological difference can explain some small discrepancies. Similar patterns have been seen in other comparisons [21-24].

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