Draft Recommendation Statement

Aspirin to Prevent Cardiovascular Disease and Cancer

This opportunity for public comment expires on October 12, 2015 at 8:00 PM EST

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Table of Contents

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Draft: Recommendation Summary

Population	Recommendation	Grade (What's This?)
Adults ages 50 to 59 years	The USPSTF recommends low-dose aspirin use for the primary prevention of cardiovascular disease (CVD) and colorectal cancer in adults ages 50 to 59 years who have a 10% or greater 10-year CVD risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years.	B
Adults ages 60 to 69 years	The decision to use low-dose aspirin to prevent CVD and colorectal cancer in adults ages 60 to 69 years who have a greater than 10% 10-year CVD risk should be an individual one. Persons who are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years are more likely to benefit. Persons who place a higher value on the potential benefits than the potential harms may choose to use low-dose aspirin.	C
Adults younger than age 50 years	The current evidence is insufficient to assess the balance of benefits and harms of aspirin use to prevent CVD and colorectal cancer in adults younger than age 50 years.	I
Adults age 70 years and older	The current evidence is insufficient to assess the balance of benefits and harms of aspirin use to prevent CVD and colorectal cancer in adults age 70 years and older.	I

Return to Table of Contents

Draft: Rationale

Importance

CVD and cancer are the leading causes of death in adults in the United States. In 2011, more than half of all deaths in the United States were caused by heart disease, cancer, or stroke.[1, 2]

Recognition of Risk Status

The primary risk factors for CVD include age, sex, race/ethnicity, abnormal lipid levels, high blood pressure, diabetes, and smoking.[3]

The USPSTF used a calculator derived from the American College of Cardiology/American Heart Association (ACC/AHA) pooled cohort equations to predict 10-year risk for first hard atherosclerotic CVD event (defined as nonfatal myocardial infarction [MI], coronary heart disease [CHD] death, and fatal or nonfatal stroke).[4] While concerns have been raised about the equations' potential to overpredict risk and their moderate discrimination, they are the only U.S.-based, externally-validated tool that reports risk as a combination of hard cerebrovascular and hard CHD events.

Risk factors for gastrointestinal (GI) bleeding with low-dose aspirin use include dose of aspirin used, history of GI ulcers or upper GI pain, bleeding disorders, renal failure, severe liver disease, and thrombocytopenia. Other factors that increase risk for GI or intracranial bleeding with low-dose aspirin use include concurrent anticoagulation therapy or nonsteroidal anti-inflammatory drug (NSAID) use, uncontrolled hypertension, male sex, and older age.[5]

Benefits of Aspirin Use

The USPSTF found adequate evidence that aspirin use to reduce risk for cardiovascular events (nonfatal MI and stroke) in adults ages 50 to 69 years who are at increased CVD risk is of moderate benefit. The magnitude of benefit can vary by age and 10-year CVD risk.

The USPSTF found adequate evidence that aspirin use reduces the incidence of colorectal cancer in adults after 10 years of use.

The USPSTF found inadequate evidence that aspirin use reduces risk for CVD events in adults who are at increased CVD risk and younger than age 50 years or older than age 69 years.

Harms of Aspirin Use

The USPSTF found adequate evidence that aspirin use in adults may increase risk for GI bleeding and hemorrhagic stroke. The USPSTF determined that the harms vary with individual risk but are small in adults age 59 years and younger and small to moderate in adults ages 60 to 69 years. The USPSTF found inadequate evidence to determine the harms of aspirin use in adults age 70 years and older.

USPSTF Assessment

In adults ages 50 to 69 years who are at increased CVD risk, the benefits of aspirin use include prevention of MI and ischemic stroke and, with long-term use, possible reduction in the incidence of colorectal cancer. Aspirin use may also result in small to moderate harms, including GI bleeding and hemorrhagic stroke.

The USPSTF concludes with moderate certainty that the net benefit of aspirin use to prevent CVD events and decrease colorectal cancer incidence in adults ages 50 to 59 years who are at increased risk for CVD but not bleeding is moderate.

The USPSTF concludes with moderate certainty that the net benefit of aspirin use to prevent CVD events and decrease colorectal cancer incidence in adults ages 60 to 69 years who are at increased risk for CVD but not bleeding is at least small.

The USPSTF concludes that the evidence on aspirin use in adults younger than age 50 years or older than age 69 years is insufficient and the balance of benefits and harms cannot be determined.

Return to Table of Contents

Draft: Clinical Considerations

Patient Population Under Consideration

This recommendation applies to adults age 40 years and older without known CVD (including history of MI or stroke) and without increased bleeding risk (e.g., history of GI ulcers, recent bleeding, or use of medications that increase bleeding risk).

Assessment of the Balance of Benefits and Harms

The magnitude of the health benefits of aspirin use depends on an individual's baseline CVD risk and willingness to take aspirin for a sufficient duration to obtain the benefit of a reduction in the incidence of colorectal cancer. The magnitude of harms depends on the presence of risk factors for bleeding.

Baseline CVD Risk

The magnitude of the cardiovascular risk reduction with aspirin use depends on an individual's initial risk for CVD events. Risk assessment for CVD should include ascertainment of the following risk factors: age, sex, race/ethnicity, total cholesterol level, high-density lipoprotein cholesterol level, systolic blood pressure, hypertension treatment, diabetes, and smoking.

Colorectal Cancer Prevention

The prevention of colorectal cancer plays an important role in the overall health benefit of aspirin, but this benefit is not apparent until 10 years after starting aspirin. Patients need to take aspirin for at least 5 to 10 years to realize that potential benefit. Persons with shorter life expectancy are less likely to realize this benefit; thus, aspirin use is more likely to have an impact when it is started between the ages of 50 and 59 years.

GI and Intracranial Bleeding

Evidence shows that risk for GI bleeding, with and without aspirin use, increases with age. For the purposes of this recommendation, the USPSTF considered age and sex to be important risk factors for GI bleeding. Other risk factors include upper GI tract pain, GI ulcers, concurrent anticoagulation therapy or NSAID use, and uncontrolled hypertension.[5] NSAID therapy combined with aspirin use increases the risk for serious GI bleeding compared with aspirin alone.[6] The rate of serious bleeding in aspirin users is about 2 to 3 times greater in patients with a history of a GI ulcer.[7] Men have twice the risk for serious GI bleeding than women.[7] These risk factors increase the risk for bleeding substantially and should be considered in the overall decision about whether to start or continue aspirin therapy. Enteric-coated or buffered formulations do not clearly reduce the adverse GI effects of aspirin.

Balancing Benefits and Harms

The USPSTF used a cardiovascular disease microsimulation model to determine the probability of a cardiovascular event for individuals

based on risk factors present at baseline and the use of aspirin. The same risk factors were used to identify groups of individuals with similar risk of CVD events using the AHA/ACC risk calculator. Estimates of the probability of colorectal cancer and the harms of bleeding were also calculated to determine the net balance of benefits and harms across individuals with varying baseline risk factors for CVD.

Tables 1 and 2 present estimated lifetime number of MIs, strokes, and cases of colorectal cancer prevented according to 10-year CVD risk level, age, and sex in adults ages 50 to 69 years (the age range with evidence of net benefit from aspirin use). In addition, Tables 1 and 2 present estimated lifetime number of GI bleeding events and hemorrhagic strokes according to 10-year CVD risk level, age, and sex in adults ages 50 to 69 years. The estimates were developed assuming that individuals are not taking NSAIDs and do not have other conditions that increase risk for GI bleeding. Further, the decision about the level of risk at which the potential benefits outweigh potential harms is an individual one, but it is the judgment of the USPSTF that there is moderate certainty that the net benefit of aspirin use is at least moderate for adults ages 50 to 59 years who are at average risk for bleeding. Some adults may decide that avoiding an MI or stroke is of great value and that having a GI bleeding event is not as significant. This group would probably decide to take aspirin at a lower CVD risk level than those who are more concerned about GI bleeding. Adults who have a high likelihood of benefit with little potential for harm should be encouraged to consider aspirin use. Conversely, adults who have little potential of benefit or high risk for GI bleeding should be discouraged from aspirin use.

Treatment and Dosage

The optimal dose of aspirin to prevent CVD events is not known. Primary prevention trials have demonstrated benefits with various regimens, including doses of 75 and 100 mg per day and 100 and 325 mg every other day. A dose of about 75 mg per day seems as effective as higher doses. The risk for GI bleeding may increase with dose. A pragmatic approach that is consistent with the evidence is to prescribe 81 mg per day, which is the most commonly prescribed dose in the United States.

Although the optimal timing and frequency of discussions about aspirin therapy are unknown, a reasonable option may be to assess CVD and bleeding risk factors starting at age 50 years and periodically thereafter, as well as when CVD and bleeding risk factors are first detected or change.

Suggestions for Practice Regarding the I Statements

Potential Preventable Burden

Evidence from primary prevention trials on the benefits of aspirin use in adults younger than age 50 years is limited. The potential benefit of aspirin use in this age group is probably lower than in adults ages 50 to 69 years because the risk for CVD events is lower (only a small percentage of adults age <50 years have a ≥10% 10-year CVD risk). Adults younger than age 50 years who have an increased 10-year CVD risk may gain significant benefit from aspirin use; how much benefit is uncertain.

Evidence on the benefits and harms of aspirin use in older adults is limited. Many adults age 70 years and older are at increased risk for CVD based on their age. Adults in this age group have a high incidence of MI and stroke; thus, the potential benefit of aspirin could be substantial.

Potential Harms

The relationship between older age and GI bleeding is well-established; thus, the potential harms for adults older than age 70 years are significant. The complexity of risk factors, medication use, and concomitant illness make it difficult to assess the balance of benefits and harms in this age group. In addition, aspirin use in adults older than age 70 years results in smaller reductions in the incidence of colorectal cancer.

Current Practice

Nearly 40% of U.S. adults older than age 50 years use aspirin for the primary or secondary prevention of CVD.[5] A study of National Health and Nutrition Examination Survey data assessed how common aspirin use is for the primary prevention of CVD and whether physicians recommend aspirin use or patients start aspirin use on their own. Among patients eligible for aspirin therapy and at increased CHD risk (>10% 10-year risk), about 41% were told by a physician to take aspirin. Among adults age 65 years and older who were told by a physician to take aspirin, 80% adhered to the recommendation.[8]

Useful Resources

The USPSTF has made recommendations on other interventions for the primary and secondary prevention of CVD, including smoking cessation and promoting a healthful diet and physical activity, as well as screening for carotid artery stenosis, CHD, high blood pressure, lipid disorders, obesity, diabetes, and peripheral artery disease. These recommendations are available on the USPSTF Web site (www.uspreventiveservicestaskforce.org).

Additional Approaches to Prevention

Million Hearts® (millionhearts.hhs.gov) is a national initiative to prevent 1 million heart attacks and strokes by 2017. It aims to prevent heart disease and stroke by improving access to effective care, improving the quality of care for the “ABCS” (aspirin when appropriate, blood pressure control, cholesterol management, and smoking cessation), focusing clinical attention on the prevention of heart attack and stroke, and activating the public to lead a heart-healthy lifestyle.

The Community Preventive Services Task Force recommends several intervention strategies for communities and health care organizations to prevent CVD (available at www.thecommunityguide.org/cvd/). For health care systems, it recommends introducing clinical decision support systems to implement clinical guidelines at the point of care. For insurers and payers, it recommends reducing out-of-pocket costs to patients for medications to control high blood pressure and high cholesterol. For clinicians and health care organizations, it recommends incorporating multidisciplinary team-based care to improve blood pressure control, including patients, primary care providers, and other professionals such as nurses, pharmacists, dietitians, social workers, and community health workers.

Return to Table of Contents

Draft: Other Considerations

Implementation

The decision to start or continue taking aspirin to prevent CVD and colorectal cancer is complex, with a number of important factors for clinicians and patients to consider. The most favorable balance of benefits and harms involves benefit for both CVD and colorectal cancer

prevention and little potential for harm from bleeding. Persons who are either at low risk for CVD events or who have a life expectancy that is too short to benefit from a reduction in risk for colorectal cancer will receive significantly less benefit; thus, the balance of benefits and harms will likely not be favorable.

The balance of benefits and harms of aspirin use is contingent on four main factors: risk for bleeding, preferences about taking aspirin, baseline CVD risk, and age.

- **Risk for bleeding:** Aspirin use is likely to do more harm than good in persons who are at increased risk for GI or intracranial bleeding.
- **Preferences about taking aspirin:** Persons who place a high value on avoiding daily medication use are poor candidates for aspirin use.
- **Baseline CVD risk:** The CVD risk threshold of 10% should prompt a discussion about aspirin use. Persons who are at higher risk will benefit more from aspirin use than those who just meet the threshold. Although persons who are at lower risk may still receive benefit, they are less likely to have a favorable balance of benefits and harms.
- **Age:** The best time for adults to discuss initiation of aspirin is during ages 50 to 59 years. Persons in this age range generally have a remaining life expectancy that is long enough to expect benefit from a reduction in risk for colorectal cancer, and a CVD risk threshold of 10% will identify patients for whom the benefits outweigh the harms, provided they are not at increased risk for bleeding and are willing to take a daily medication. For adults ages 60 to 69 years, those who are younger are more likely to benefit from a reduction in risk for colorectal cancer, and those with a higher CVD risk are most likely to have a favorable balance of benefits and harms. Adults ages 60 to 69 years who develop CVD should use aspirin for secondary prevention; those already taking aspirin who meet the risk threshold should continue its use unless they develop new bleeding risks.

The time to benefit for colorectal cancer and time to harm are important considerations in assessing the benefits and harms of aspirin use in older adults. It takes at least 5 to 10 years of daily aspirin use to see a benefit for colorectal cancer (i.e., reduction in colorectal cancer incidence and death), and that benefit may not appear for 10 to 20 years after beginning aspirin use. Therefore, older adults at advanced ages and those with shorter remaining life expectancy may receive less benefit. Meanwhile, bleeding harms may occur in the short term.

Research Needs and Gaps

There are a number of important research gaps that, if filled, could identify populations who may benefit the most from using aspirin to prevent CVD and colorectal cancer. CVD prevention in subpopulations is a significant evidence gap. No data exist on the role of aspirin chemoprevention in racial/ethnic groups. Additional evidence on benefits and harms in persons younger than age 50 years or age 70 years and older would help clarify who could potentially benefit from aspirin use. An updated version of the Antithrombotic Trialists' individual patient data meta-analysis that accounts for confounders would be helpful in understanding the effect of aspirin in subpopulations.

More information is needed to determine the interactions between statins and aspirin. A better understanding is needed of how the use of proton pump inhibitors with aspirin may change the balance of benefits and harms. Additionally, more information is needed to differentiate between aspirin's effect in reducing risk for ischemic stroke and in increasing risk for hemorrhagic stroke.

The effect of aspirin use on colorectal cancer prevention in subpopulations is also an important research gap. The differential effects of sex, race/ethnicity, age, and genetic factors on risk for colorectal cancer and the impact of screening require additional research. More research is also needed to determine the best dosing strategies, the long-term effects in persons with previous adenoma and on adenoma prevention, and the durability of benefits after aspirin is discontinued. Longer-term followup of CVD prevention trials that reports cancer incidence and mortality outcomes would be helpful.

Development of an externally-validated risk assessment tool for bleeding that could be used at the point of care would be helpful. A tool that considers both CVD risk and GI bleeding risk would be useful to clinicians and patients when deciding whether to start or continue aspirin use for primary prevention.

Return to Table of Contents

Draft: Discussion

Burden of Disease

CVD and cancer are the leading causes of death in adults in the United States. CVD, including heart attack and stroke, is responsible for 30% of all deaths in the United States.[1] More than 26 million adults have been diagnosed and are living with heart disease. Nearly 8 million adults have a history of MI and 6 million have a history of stroke. The costs of caring for persons with CVD were estimated at $315 billion in 2010.[2]

Cancer accounts for one in four deaths in the United States. Colorectal cancer is the third most common cancer in the United States. In 2014, there were an estimated 137,000 new cases and 50,000 deaths due to colorectal cancer.[3]

Scope of Review

The USPSTF commissioned three systematic evidence reviews and a decision analysis model to develop its recommendation on aspirin use to prevent CVD and cancer. The systematic review on aspirin use to prevent CVD is an update of the 2009 USPSTF review.[2] The systematic review on aspirin use to prevent colorectal cancer is an update of the 2007 USPSTF review.[3] The systematic review on aspirin use to prevent cancer other than colorectal cancer is new.[5] A review of potential harms was incorporated across all three systematic reviews.[5] The primary studies of interest for all reviews focused on primary prevention of CVD. Findings from the three coordinated systematic reviews were integral to determining the parameters and assumptions used in the decision analysis model, which was used to estimate net benefit for the recommendation.

Effectiveness of Risk Assessment and Preventive Medication

The USPSTF used a calculator derived from the 2013 ACC/AHA pooled cohort equations to estimate CVD risk thresholds.[4] The USPSTF selected this tool because of its broader focus on CVD outcomes (combining both cerebrovascular and cardiovascular outcomes), its external validation in various U.S. populations, and its reasonable performance in studies. The calculator predicts 10-year risk of a first hard atherosclerotic CVD event, defined as nonfatal MI, CHD death, and fatal or nonfatal stroke. It was derived from participants in four community-based cohort studies sponsored by the National Heart, Lung, and Blood Institute. The tool accounts for a variety of CVD outcomes, in contrast to many earlier tools that report only CHD outcomes. In addition, the cohorts from which it was derived allowed the development of sex- and race-specific equations.

The USPSTF focused its review of the evidence on studies of the primary prevention of CVD. It considered 11 randomized, controlled trials (RCTs) that evaluated the benefits of aspirin for the primary prevention of cardiovascular events.[9-19] Four of these studies were published since the last USPSTF review in 2009.[9-11, 19] The trials had a total of 118,445 participants; three were conducted exclusively in men and one exclusively in women. Participants' mean ages ranged from 55 to 65 years. Eight trials used doses of aspirin of 100 mg or less daily. Duration of followup was between 3 and 10 years.[20]

Primary prevention trials consistently demonstrated effectiveness of aspirin in preventing MI and stroke. Pooled analysis of 10 trials showed a 22% reduction in MI and coronary events (relative risk [RR], 0.78 [95% confidence interval (CI), 0.71 to 0.87]). When pooled analysis was restricted to eight trials that used low-dose aspirin (≤100 mg daily), the reduction remained significant. Nonfatal strokes were also reduced when only low-dose aspirin trials were included in the analysis (RR, 0.86 [95% CI, 0.76 to 0.98]). Few fatal stroke events were reported in trials. Pooling of the 11 trials showed a nonsignificant reduction in CVD mortality (RR, 0.94 [95% CI, 0.86 to 1.03]); results were similar when analysis was restricted to studies of low-dose aspirin. Reduction in all-cause mortality was not significant in any of the trials reporting it. However, when trial results were pooled, all-cause mortality risk was reduced by 6% in participants taking aspirin (RR, 0.94 [95% CI, 0.89 to 0.99]). A sensitivity analysis of eight low-dose trials resulted in a similar relative risk (RR, 0.95 [95% CI, 0.89 to 1.01]).[20]

Subpopulation analyses evaluated effect modification of aspirin by age, sex, and diabetes status. Analysis supports the likelihood that older age groups have greater MI benefit than younger age groups; however, the results were mixed. There was not sufficient evidence to support any sex-specific differences in CVD outcomes.[20] This differs from the 2009 analysis, in which sex-specific outcome differences were apparent. This was likely due to the predominance of findings from the Women's Health Study, with its relatively young and healthy study population. There were also no clear differences in outcomes based on diabetes status.

There is evidence of a potential long-term benefit on colorectal cancer mortality. Pooled data from a small selected set of primary and secondary CVD prevention trials suggest that a reduction in long-term cumulative colorectal cancer mortality is possible with aspirin use. The mortality benefit did not become apparent until 10 to 20 years after randomization.[3] Doses in these trials ranged from 75 to 1,200 mg per day, without clear evidence of a dose-related effect. The applicability of these results to a broader CVD primary prevention trial of low-dose aspirin use only is uncertain. The USPSTF evaluated three more clearly applicable primary and secondary CVD prevention trials that reported a 40% reduction in colorectal cancer incidence with aspirin use (RR, 0.60 [95% CI, 0.47 to 0.76]) 10 to 19 years after initiation.[16, 21-23] These studies suggest that at least 5 to 10 years of aspirin use is required to achieve this reduction. A previously published individual patient data meta-analysis of four primary and secondary CVD prevention trials showed a similar but smaller reduction in colorectal cancer incidence (hazard ratio, 0.76 [95% CI, 0.63 to 0.94]).[24]

While there is evolving evidence of aspirin's effect on other types of cancer, it has not yet been seen in trial results. Total cancer mortality was not significantly reduced across 10 RCTs of CVD primary prevention.[5] An analysis of six RCTs of CVD primary prevention also showed no reduction in total cancer incidence. Other published reports have demonstrated reductions in total cancer mortality and incidence, but the RCTs included in those analyses differed from those reviewed by the USPSTF (e.g., different groupings of studies, not a CVD primary prevention population, or higher doses of aspirin used).[5]

Potential Harms of Preventive Medication

Using aspirin for the primary prevention of CVD variably increases risk for major GI and intracranial bleeding and hemorrhagic stroke, depending on the patient's medical history and other factors, such as concurrent medication use.

The USPSTF found only one risk prediction tool for bleeding based on a systematic review of risk estimates and incidence of upper GI bleeding and CHD with low-dose aspirin use.[25] The tool presumes a baseline incidence rate of upper GI complications of 1 event per 1,000 person-years, and is modified for 10-year age ranges starting at age 50 years. The tool uses Framingham CHD sex-specific risk prediction equations and modifies bleeding risk with use of proton pump inhibitors or *Heliobacter pylori* eradication, neither of which has been tested for net benefit as part of a comprehensive prevention regimen. Two retrospective validation studies were conducted, but there are insufficient data to support its use for prospective prediction in a clinical setting.

To evaluate the risk for GI bleeding, the most common serious harm of aspirin use, the USPSTF considered seven of the CVD primary prevention trials previously discussed .[9, 11-13, 15-17] These trials reported major GI bleeding events defined as GI bleeding requiring transfusion or hospitalization or leading to death. Aspirin dosages ranged from 50 to 325 mg in all but one trial. Duration of use and followup ranged from 4 to 10 years. Major GI bleeding increased by 59% in aspirin users (Peto odds ratio [OR], 1.59 [95% CI, 1.32 to 1.91]). Analyses that were restricted to trials using low-dose aspirin (≤100 mg per day) showed similar results. When all major primary and secondary CVD prevention trials were pooled (15 studies), the OR increased further to 1.65.[5] Cohort studies reported similar bleeding risk with aspirin use.[7]

Hemorrhagic stroke was a rare event; 15.5% of total strokes reported in the trials were hemorrhagic. Across nine CVD primary prevention trials, the rate of hemorrhagic stroke was 2.54 strokes per 1,000 person-years in aspirin users and 1.95 strokes per 1,000 person-years in nonusers. Pooled analysis of nine trials showed a significant 33% increase in hemorrhagic stroke (OR, 1.33 [95% CI, 1.03 to 1.71]).[26] When analyses were restricted to low-dose aspirin trials, risk for hemorrhagic stroke tended to decrease (Peto OR, 1.27 [95% CI, 0.96 to 1.68]) (data unpublished).

Increased harms may result from factors that either increase bleeding risk or enhance the bleeding effect of aspirin. An adjusted individual patient data meta-analysis found that older age (per decade), male sex, and diabetes increased risk for serious bleeding.[27] Smoking and increased blood pressure were also associated with increased major extracranial bleeding. A large cohort study of rates of hospitalization for major bleeding events also suggested older age, male sex, and diabetes had effects on increasing bleeding risk. Statin and proton pump inhibitor use may decrease the likelihood of hospitalization from a major bleeding event.[7]

Estimate of Magnitude of Net Benefit

The USPSTF used a microsimulation model to estimate the magnitude of net benefit.[28] The model incorporated findings from the three systematic reviews to inform its parameters and assumptions. Results were stratified by age decade, sex, and 10-year CVD risk. When combined with primary trial data and meta-analyses, the model provides an additional analytic basis to assess the balance of benefits and harms of aspirin use. In addition to the number of MIs and ischemic strokes prevented, the number of colorectal cancer cases prevented, and the number of serious GI bleeding events caused by aspirin, the USPSTF also considered net life-years and net quality-adjusted life-years gained (or lost) over a lifetime as a result of aspirin use (Tables 1 and 2).

Initiating aspirin use during ages 50 to 59 years and continuing its use unless contraindicated by an adverse bleeding event results in the greatest gain in net life-years (range, 21.9 to 46.3 in women and 33.3 to 60.5 in men) and net quality-adjusted life-years (range, 62.1 to 83.3 in women and 58.8 to 83.4 in men). Both CVD and bleeding risk represent a continuum of risk estimation. The USPSTF chose the 10% 10-year CVD risk threshold as the point at which the tradeoff of benefits and harms reaches an adequate level of certainty. The benefits for an individual patient may shift above or below the threshold depending on individual risk assessment.

The USPSTF determined with moderate certainty that the net benefit in life-years and quality-adjusted life-years gained from aspirin use is moderate in adults ages 50 to 59 years. Adults ages 60 to 69 years gain fewer net life-years and quality-adjusted life-years because of the increased harms from bleeding that come with older age and the reduced potential for colorectal cancer benefits (direct reduction of incidence and indirect reduction in mortality), which require at least 10 years to become apparent. The USPSTF concluded with moderate certainty that the net benefit from aspirin use is small in adults ages 60 to 69 years. In both age groups, persons with higher CVD risk will have a greater net benefit (provided their bleeding risk is not increased).

How Does Evidence Fit With Biological Understanding?

Aspirin is a NSAID. It is one of the most commonly used drugs, and is used mostly to relieve pain. Over the past 30 years, its platelet and clotting effects have become better understood. Aspirin's anticlotting effect is useful for primary and secondary prevention of cardiovascular events because it can potentially decrease the accumulation of blood clots that form due to reduced blood flow at atherosclerotic plaques, thereby reducing hypoxic damage to heart and brain tissue.[29]

Aspirin is an irreversible cyclo-oxygenase (COX) inhibitor. The COX-1 enzyme is responsible for producing the prostaglandins that protect the gastric mucosa. Inhibition of the COX-1 enzyme leaves the mucosa susceptible to damage and GI bleeding. This negative effect increases at higher doses of aspirin.[30]

The mechanisms for inhibition of adenoma or colorectal cancer development are not yet well-understood. COX-dependent and COX-independent pathways have been proposed. COX-dependent pathways may rely on aspirin's anti-inflammatory properties to reduce tumorigenesis.[3]

Return to Table of Contents

Draft: Update of Previous USPSTF Recommendation

This recommendation updates the 2009 USPSTF recommendation on aspirin use to prevent CVD events and the 2007 recommendation on aspirin and NSAID use to prevent colorectal cancer. To update these recommendations, the USPSTF reviewed four additional studies of aspirin for the primary prevention of CVD and several additional analyses of colorectal cancer followup data. The USPSTF also relied on reviews of all-cause mortality and total cancer incidence and mortality and a comprehensive review of harms. The USPSTF then used a microsimulation model to systematically estimate the balance of benefits and harms.

Return to Table of Contents

Draft: Recommendations of Others

The AHA and the American Stroke Association[31] recommend the use of low-dose aspirin for cardiovascular (including but not specific to stroke) prophylaxis in adults whose risk is sufficiently high for the benefits to outweigh the risks associated with treatment; they suggest that a 10-year CVD risk of 6% to 10% is sufficient.

The American Diabetes Association suggests low-dose aspirin therapy for primary prevention in patients with type 1 or 2 diabetes who have an increased CVD risk (>10% 10-year CVD risk) and are not at increased risk for bleeding. It does not recommend aspirin therapy in men younger than age 50 years or most women younger than age 60 years who have a low CVD risk because the risk for bleeding outweighs the potential benefits of aspirin treatment.[32]

The U.S. Food and Drug Administration recently denied the primary prevention of MI as an indication for aspirin use in any risk group. In a consumer bulletin, it noted the risks for GI and intracranial bleeding and suggested the benefits of primary prevention have not been well-established.[33]

The American Academy of Family Physicians' recommendations are consistent with the 2009 USPSTF recommendations.[34] The American College of Chest Physicians suggests that patients older than age 50 years without symptomatic CVD use low-dose aspirin for CVD primary prevention.[35]

No organizations recommend aspirin use for the primary prevention of colorectal cancer in average-risk adults. The American Cancer Society recommends against the use of aspirin and other NSAIDs as a colorectal cancer prevention strategy.[36] The American Gastroenterological Association and the National Comprehensive Care Network limit their recommendations to patients who are at increased risk for colorectal cancer.[3]

Return to Table of Contents

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Draft: Table 1. Lifetime Events* in Women Taking Aspirin

CVD Risk	MIs Prevented	Ischemic Strokes Prevented	CRC Cases Prevented	Serious GI Bleeding Caused	Hemorrhagic Strokes Caused	Net Life-Years Gained	Quality-Adjusted Life-Years Gained
Ages 50 to 59 years							
10%	14.8	13.7	13.9	20.9	3.5	21.9	62.1
15%	15.0	14.3	13.5	20.0	3.4	33.4	71.6
20%	15.2	14.4	13.2	18.4	2.9	46.3	83.3
Ages 60 to 69 years							
10%	10.1	11.6	10.5	23.0	3.2	-1.2	28.4
15%	11.0	12.9	9.3	21.6	3.4	1.7	32.4
20%	11.1	13.0	9.7	21.7	3.3	4.8	36.0

Note: A complete set of results are available in the decision analysis report.[28]
* Per 1,000 persons.
Abbreviations: CVD=cardiovascular disease; CRC=colorectal cancer; GI=gastrointestinal; MI=myocardial infarction.

Return to Table of Contents

Draft: Table 2. Lifetime Events* in Men Taking Aspirin

CVD Risk	MIs Prevented	Ischemic Strokes Prevented	CRC Cases Prevented	Serious GI Bleeding Caused	Hemorrhagic Strokes Caused	Net Life-Years Gained	Quality-Adjusted Life-Years Gained
Ages 50 to 59 years							
10%	22.5	8.4	13.9	28.4	2.3	33.3	58.8
15%	26.7	8.6	12.1	26.0	2.8	39.5	64.4
20%	28.6	9.2	12.2	24.8	2.1	60.5	83.4
Ages 60 to 69 years							
10%	15.9	6.6	11.2	31.4	3.1	-2.0	18.0
15%	18.6	8.0	10.4	29.8	2.4	9.6	30.9
20%	20.1	8.4	9.1	26.7	2.7	11.6	31.8

Note: A complete set of results are available in the decision analysis report.[28]
* Per 1,000 persons.
Abbreviations: CVD=cardiovascular disease; CRC=colorectal cancer; GI=gastrointestinal; MI=myocardial infarction.

Return to Table of Contents

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