Aspirin Use for the Primary Prevention of Cardiovascular Disease and Colorectal Cancer: U.S. Preventive Services Task Force Recommendation Statement

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Description: Update of the 2009 USPSTF recommendation on aspirin use to prevent cardiovascular disease (CVD) events and the 2007 recommendation on aspirin and nonsteroidal anti-inflammatory drug use to prevent colorectal cancer (CRC).

Methods: The USPSTF reviewed 5 additional studies of aspirin for the primary prevention of CVD and several additional analyses of CRC follow-up data. The USPSTF also relied on commissioned systematic 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.

Population: This recommendation applies to adults aged 40 years or older without known CVD and without increased bleeding risk.

Recommendation: The USPSTF recommends initiating low-dose aspirin use for the primary prevention of CVD and CRC in adults aged 50 to 59 years who have a 10% or greater 10-year CVD risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years. (B recommendation)

The decision to initiate low-dose aspirin use for the primary prevention of CVD and CRC in adults aged 60 to 69 years who have a 10% or greater 10-year CVD risk should be an individual one. 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 initiate low-dose aspirin. (C recommendation)

The current evidence is insufficient to assess the balance of benefits and harms of initiating aspirin use for the primary prevention of CVD and CRC in adults younger than 50 years. (I statement)

The current evidence is insufficient to assess the balance of benefits and harms of initiating aspirin use for the primary prevention of CVD and CRC in adults aged 70 years or older. (I statement)

The U.S. Preventive Services Task Force (USPSTF) makes recommendations about the effectiveness of specific preventive care services for patients without obvious related signs or symptoms.

It bases its recommendations on the evidence of both the benefits and harms of the service and an assessment of the balance. The USPSTF does not consider the costs of providing a service in this assessment.

The USPSTF recognizes that clinical decisions involve more considerations than evidence alone. Clinicians should understand the evidence but individualize decision making to the specific patient or situation. Similarly, the USPSTF notes that policy and coverage decisions involve considerations in addition to the evidence of clinical benefits and harms.

SUMMARY OF RECOMMENDATIONS AND EVIDENCE

The USPSTF recommends initiating low-dose aspirin use for the primary prevention of cardiovascular disease (CVD) and colorectal cancer (CRC) in adults aged 50 to 59 years who have a 10% or greater 10-year CVD risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years. (B recommendation)

The decision to initiate low-dose aspirin use for the primary prevention of CVD and CRC in adults aged 60 to 69 years who have a 10% or greater 10-year CVD risk should be an individual one. 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

See also:

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Figure. Aspirin use for the primary prevention of cardiovascular disease and colorectal cancer: clinical summary.

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Population	Adults aged 50 to 59 y with a ≥10% 10-y CVD risk	Adults aged 60 to 69 y with a ≥10% 10-y CVD risk	Adults younger than 50 y	Adults aged 70 y or older
Recommendation	Initiate low-dose aspirin use. Grade: B	The decision to initiate low-dose aspirin use is an individual one. Grade: C	No recommendation. Grade: I (insufficient evidence)	No recommendation. Grade: I (insufficient evidence)

Risk Assessment	Primary risk factors for CVD are older age, male sex, race/ethnicity, abnormal lipid levels, high blood pressure, diabetes, and smoking. Risk factors for GI bleeding with aspirin use include higher aspirin dose and longer duration of use, history of GI ulcers or upper GI pain, bleeding disorders, renal failure, severe liver disease, and thrombocytopenia. The USPSTF used a calculator derived from the ACC/AHA pooled cohort equations to predict 10-y risk for first atherosclerotic CVD event.			
Preventive Medication	Aspirin's anticlotting effect is useful for primary and secondary CVD prevention because it potentially decreases the accumulation of blood clots that form as a result of reduced blood flow at atherosclerotic plaques, thereby reducing hypoxic damage to heart and brain tissue. The mechanisms for inhibition of adenoma or colorectal cancer development are not yet well-understood but may result from aspirin's anti-inflammatory properties.			
Treatment and Dosage	A reasonable approach consistent with the evidence is to prescribe 81 mg/d (the most commonly prescribed dose in the United States), and assess CVD and bleeding risk factors starting at age 50 y and periodically thereafter, as well as when CVD and bleeding risk factors are first detected or change.			
Balance of Benefits and Harms	The benefits of aspirin use outweigh the increased risk for bleeding by a moderate amount.	The benefits of aspirin use outweigh the increased risk for bleeding by a small amount.	The evidence on aspirin use is insufficient and the balance of benefits and harms cannot be determined.	The evidence on aspirin use is insufficient and the balance of benefits and harms cannot be determined.
Other Relevant USPSTF Recommendations	The USPSTF has made recommendations on smoking cessation and promoting a healthful diet and physical activity, as well as screening for carotid artery stenosis, coronary heart disease, high blood pressure, lipid disorders, obesity, diabetes, peripheral artery disease, and colorectal cancer. These recommendations are available on the USPSTF Web site (www.uspreventiveservicestaskforce.org).			

For a summary of the evidence systematically reviewed in making this recommendation, the full recommendation statement, and supporting documents, please go to www.uspreventiveservicetaskforce.org.

ACC/AHA = American College of Cardiology/American Heart Association; CVD = cardiovascular disease; GI = gastrointestinal; USPSTF = U.S. Preventive Services Task Force.

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 initiate low-dose aspirin. (C recommendation)

The current evidence is insufficient to assess the balance of benefits and harms of initiating aspirin use for the primary prevention of CVD and CRC in adults younger than 50 years. (I statement)

The current evidence is insufficient to assess the balance of benefits and harms of initiating aspirin use for the primary prevention of CVD and CRC in adults aged 70 years or older. (I statement)

See the Clinical Considerations section for guidance on aspirin dosage.

See the **Figure** for a summary of the recommendations and suggestions for clinical practice.

Appendix Table 1 describes the USPSTF grades, and **Appendix Table 2** describes the USPSTF classification of levels of certainty about net benefit (both tables are available at www.annals.org).

RATIONALE
Importance
Cardiovascular disease and CRC are major causes of death among U.S. adults. In 2011, more than one 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 older age, male sex, race/ethnicity, abnormal lipid levels, high blood pressure, diabetes, and smoking (2).

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) (3). Although concerns have been raised about the equations' potential to overpredict risk and their moderate discrimination, they are the only U.S.-based, ex-

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ternally validated equations that report risk as a combination of cerebrovascular and CHD events.

Risk factors for gastrointestinal (GI) bleeding with aspirin use include higher dose and longer duration of use, 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 or nonsteroidal anti-inflammatory drug (NSAID) use, uncontrolled hypertension, male sex, and older age (4, 5).

This recommendation applies to adults who are at increased CVD risk and at average risk for CRC. Persons who are at increased CVD risk and are known to be at increased risk for CRC (for example, persons with a family or personal history of CRC or familial adenomatous polyposis) (6) should consult their health care provider.

Benefits of Aspirin Use

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

The USPSTF found adequate evidence that aspirin use reduces the incidence of CRC in adults after 5 to 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 are younger than 50 years or older than 69 years.

Harms of Aspirin Use

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

USPSTF Assessment

In adults aged 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, reduced incidence of CRC. Aspirin use may also result in small to moderate harms, including GI bleeding and hemorrhagic stroke.

The USPSTF concludes with moderate certainty that the benefit of aspirin use for the primary prevention of CVD events, combined with the reduced incidence of CRC, outweighs the increased risk for bleeding by a moderate amount in adults aged 50 to 59 years who have a 10-year CVD risk of 10% or greater.

The USPSTF concludes with moderate certainty that the benefit of aspirin use for the primary prevention of CVD events, combined with the reduced incidence of CRC, outweighs the increased risk for bleeding by a small amount in adults aged 60 to 69 years who have a 10-year CVD risk of 10% or greater.

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

CLINICAL CONSIDERATIONS

Patient Population Under Consideration

This recommendation applies to adults aged 40 years or older without known CVD (including history of MI or stroke) and without increased bleeding risk (for example, 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 reduced incidence of CRC. 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. An online version of the ACC/AHA risk calculator can be found at http://tools.acc.org/ASCVD-Risk-Estimator/.

CRC Prevention

Colorectal cancer prevention plays an important role in the overall health benefit of aspirin, but this benefit is not apparent until 10 years after aspirin therapy is started. Patients need to take aspirin for at least 5 to 10 years to realize this potential benefit (6, 7), and persons with shorter life expectancy are less likely to benefit. Thus, aspirin use is more likely to have an effect when it is started between the ages of 50 and 59 years. Because of the time required before a reduced incidence in CRC is seen, older persons (that is, 60 years or older) are less likely to realize this benefit than adults aged 50 to 59 years (8).

GI and Intracranial Bleeding

Evidence shows that risk for GI bleeding, with and without aspirin use, increases with age. For this recommendation, the USPSTF considered older age and male sex to be important risk factors for GI bleeding. Other risk factors include upper GI tract pain, GI ulcers, concurrent anticoagulation or NSAID use, and uncontrolled hypertension (4, 5). Nonsteroidal anti-inflammatory drug therapy combined with aspirin use increases the risk for serious GI bleeding compared with aspirin use alone (9). The rate of serious bleeding among aspirin users is about 2 to 3 times greater in

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Table 1. Lifetime Events in 10 000 Men Taking Aspirin*

CVD Risk	Nonfatal MIs Prevented	Nonfatal Ischemic Strokes Prevented	CRC Cases Prevented	Serious GI Bleeding Events Caused	Hemorrhagic Strokes Caused	Net Life-Years Gained	QALYs Gained
Aged 50-59 y							
10%	225	84	139	284	23	333	588
15%	267	86	121	260	28	395	644
20%	286	92	122	248	21	605	834
Aged 60-69 y							
10%	159	66	112	314	31	−20	180
15%	186	80	104	298	24	96	309
20%	201	84	91	267	27	116	318

CRC = colorectal cancer; CVD = cardiovascular disease; GI = gastrointestinal; MI = myocardial infarction; QALY = quality-adjusted life-year.
* A complete set of results are available in the decision analysis report (28).

patients with a history of GI ulcer (10). The risk for serious GI bleeding is 2 times greater in men than in women (10). These risk factors substantially increase the risk for bleeding and should be considered in the overall decision about whether to start or continue aspirin therapy. There is no evidence that enteric-coated or buffered formulations reduce the risk for serious GI bleeding (2, 4, 11).

Balance of Benefits and Harms

The USPSTF used a CVD microsimulation model to estimate cardiovascular event rates based on baseline risk factors and aspirin use. It used the AHA/ACC risk calculator to stratify findings of benefits and harms by 10-year CVD risk. The USPSTF also calculated estimates of CRC incidence and harms of bleeding to determine the net balance of benefits and harms across individuals with varying baseline CVD risk (8, 12).

Tables 1 and 2 present the USPSTF's estimated lifetime number of nonfatal MIs, ischemic strokes, and cases of CRC prevented, stratified by 10-year CVD risk level, age, and sex, among adults aged 50 to 69 years (the age range with evidence of net benefit from aspirin use). In addition, Tables 1 and 2 present the USPSTF's estimated lifetime number of GI bleeding events and hemorrhagic strokes. The USPSTF developed these estimates assuming that aspirin users are not taking NSAIDs and do not have other conditions that increase risk for GI bleeding. The USPSTF estimated life-years and quality-adjusted life-years (QALYs) saved as one part of its consideration of the balance of benefits and harms of these disparate clinical outcomes (see the Implementation section for more information on interpreting the results in Tables 1 and 2).

Overall, the USPSTF determined that the greatest net benefit to be gained is by adults aged 50 to 59 years whose 10-year CVD risk is 10% or greater. The USPSTF recommends that persons in this age and risk group start taking aspirin. Adults aged 60 to 69 years may also benefit from starting aspirin use, although the net benefit is smaller due to the increased risk for GI bleeding and decreased benefit in CRC prevention in this age group (8).

Further, the decision about the level of CVD risk at which the potential benefits outweigh potential harms is an individual one. Some adults may decide that

avoiding an MI or a stroke is very important and that having a GI bleeding event is not as significant. They may 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 for benefit or are at high risk for GI bleeding should be discouraged from it.

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 75 mg per day seems as effective as higher doses. The risk for GI bleeding may increase with the dosage. A pragmatic approach 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 approach 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 initiating aspirin use in adults younger than 50 years is limited. The potential benefit is probably lower than in adults aged 50 to 69 years because the risk for CVD events is lower (only a small percentage of adults younger than 50 years have a 10-year CVD risk ≥10%) (8). Adults younger than 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 initiating aspirin use in older adults is limited. Many adults aged 70 years or older are at increased risk for CVD because of their age. They have a high incidence of MI and stroke; thus, the potential benefit of aspirin could be substantial.

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Potential Harms

The relationship between older age and GI bleeding is well-established; thus, the potential harms for adults older than 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 of initiating aspirin use in this age group. In addition, aspirin use in adults older than 70 years results in smaller reductions in the incidence of CRC compared with younger adults.

Current Practice

Nearly 40% of U.S. adults older than 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 it or patients start it on their own. Among patients who were eligible for aspirin therapy and were at increased CHD risk (>10% 10-year risk), about 41% were told by a physician to take aspirin. Among patients aged 65 years or older who were told by a physician to take aspirin, 80% adhered to the recommendation (13).

Useful Resources

The USPSTF has made other recommendations on CVD prevention, 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. In addition, it has made recommendations on screening for CRC. 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 to prevent CVD for communities and health care organizations (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).

OTHER CONSIDERATIONS

Implementation

The decision to start or continue taking aspirin to prevent CVD and CRC is complex, with many important factors for clinicians and patients to consider. The most favorable balance of benefits and harms involves benefit for both CVD and CRC prevention and little potential for harm from bleeding. Persons who either are at low risk for CVD events or have a life expectancy too short to benefit from a reduced risk for CRC 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 4 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 long-term daily medication use are poor candidates for aspirin use.

• *Baseline CVD risk:* A 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 are near the 10% 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.

Table 2. Lifetime Events in 10 000 Women Taking Aspirin*

CVD Risk	Nonfatal MIs Prevented	Nonfatal Ischemic Strokes Prevented	CRC Cases Prevented	Serious GI Bleeding Events Caused	Hemorrhagic Strokes Caused	Net Life-Years Gained	QALYs Gained
Aged 50–59 y							
10%	148	137	139	209	35	219	621
15%	150	143	135	200	34	334	716
20%	152	144	132	184	29	463	833
Aged 60–69 y							
10%	101	116	105	230	32	−12	284
15%	110	129	93	216	34	17	324
20%	111	130	97	217	33	48	360

CRC = colorectal cancer; CVD = cardiovascular disease; GI = gastrointestinal; MI = myocardial infarction; QALY = quality-adjusted life-year.
* A complete set of results are available in the decision analysis report (28).

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• *Age 50 to 59 years:* Initiating aspirin in this age group has the largest average net benefit (**Tables 1** and **2**). 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 long-term daily medication. In addition, persons in this age range generally have sufficient life expectancy to benefit from a reduced risk for CRC.

• *Age 60 to 69 years:* Adults in this age group with a higher CVD risk are most likely to have a favorable balance of benefits and harms, and younger adults are more likely to benefit from a reduced risk for CRC. Adults aged 60 to 69 years who are already taking aspirin as recommended by their clinician should continue use unless they develop new risk factors for bleeding. Adults who develop CVD should use aspirin, as directed by their clinician, to prevent future CVD events.

• *Age 70 years or older:* The USPSTF was unable to assess the balance of benefits and harms of initiating aspirin use in this age group. Adults aged 70 years or older who are currently taking aspirin should discuss with their clinician whether they should continue.

The time to benefit for CRC (that is, reduced CRC incidence and death) and time to harm are important considerations in assessing the benefits and harms of initiating aspirin use in older adults. The CVD prevention benefit begins within the first 5 years of use and continues as long as aspirin is used. The CRC prevention benefit is more complex. It takes at least 5 to 10 years of daily aspirin use to obtain a CRC benefit; however, due to a longer latent period, the benefit may take 10 to 20 years to appear. Therefore, older adults and those with shorter remaining life expectancy may receive less benefit. Meanwhile, bleeding harms may occur in the short term.

Tables 1 and **2** provide information to help clinicians understand the balance of benefits and harms of aspirin therapy, especially for adults in their 60s. The magnitude of net benefit is smaller at lower 10-year CVD risk levels and greater at higher levels. For both men and women, CRC benefits tend to be lower at higher CVD risk levels due to competing causes of mortality, including death from CVD.

Research Needs and Gaps

There are many important research gaps that, if filled, could identify populations that may benefit the most from using aspirin to prevent CVD and CRC. Cardiovascular disease prevention in subpopulations is a significant evidence gap. No data exist on the role of aspirin therapy in racial/ethnic groups. Additional evidence on benefits and harms in persons younger than 50 years or 70 years or older would help clarify who could potentially benefit from aspirin use. An updated version of the individual-patient data meta-analysis from the Antithrombotic Trialists' Collaboration 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. How the use of

proton-pump inhibitors with aspirin may change the balance of benefits and harms should be better understood. In addition, more information is needed to differentiate between aspirin's effect in reducing risk for ischemic stroke and increasing risk for hemorrhagic stroke.

The effect of aspirin use on CRC prevention in subpopulations is also an important research gap. The differential effects of sex, race/ethnicity, age, and genetic factors on risk for CRC and the effect 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 follow-up of CVD prevention trials that report cancer incidence and mortality outcomes would be helpful.

Additional research is needed to better estimate the harms of aspirin-induced GI bleeding. 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.

DISCUSSION

Burden of Disease

Cardiovascular disease and cancer are the leading causes of death among U.S. adults. Cardiovascular disease, 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 1 in 4 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 CRC (3).

Scope of Review

The USPSTF commissioned 3 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, 14). The systematic review on aspirin use to prevent CRC is an update of the 2007 USPSTF review (6, 7). The systematic review on aspirin use to prevent cancer other than CRC is new (4, 7). A review of potential harms was incorporated across all 3 systematic reviews (4, 5). The primary studies of interest for all reviews focused on primary prevention of CVD. Findings from the 3 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 (8, 12).

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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 (3). 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 for a first hard atherosclerotic CVD event, defined as nonfatal MI, CHD death, and fatal or nonfatal stroke. It was derived from participants in 4 community-based cohort studies sponsored by the National Heart, Lung, and Blood Institute. The tool accounts for various CVD outcomes, in contrast to many earlier tools that report only CHD outcomes. In addition, the cohorts from which it was derived allowed for 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 (15–25). Four of these studies were published since the last USPSTF review in 2009 (15–17, 25). The trials had a total of 118 445 participants; 3 were conducted exclusively in men and 1 exclusively in women. Participants' mean ages ranged from 55 to 65 years. Eight trials used an aspirin dose of 100 mg or less daily. Duration of follow-up was between 3 and 10 years (22).

Primary prevention trials consistently demonstrated effectiveness of aspirin in preventing nonfatal MI and stroke. Pooled analysis of 8 trials of low-dose aspirin (≤100 mg daily) showed a 17% reduction in nonfatal MI and coronary events (relative risk [RR], 0.83 [95% CI, 0.74 to 0.94]). Pooled analysis of 10 trials using any aspirin dose showed a 22% reduction.

Nonfatal strokes were also reduced when only low-dose aspirin trials were included in the analysis (RR, 0.86 [CI, 0.76 to 0.98]). Few fatal stroke events were reported in trials. Pooling the 11 trials showed a nonsignificant reduction in CVD mortality (RR, 0.94 [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 5% in participants taking low-dose aspirin (RR, 0.95 [CI, 0.89 to 1.01]). When trials using any aspirin dose were considered, the reduction was statistically significant (RR, 0.94 [CI, 0.89 to 0.99]) (14).

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, results were mixed. Evidence was not sufficient to support any sex-specific differences in CVD outcomes (14). 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 CRC mortality. Pooled data from primary and secondary CVD prevention trials with more than 10 years of follow-up suggest that a reduction in long-term cumulative CRC mortality is possible with aspirin use. The mortality benefit did not become apparent until 10 to 20 years after randomization (3). Aspirin dose in these trials ranged from 75 to 1200 mg per day, without clear evidence of a dose-related effect. The USPSTF evaluated 3 applicable primary and secondary CVD prevention trials that reported a 40% reduction in CRC incidence with aspirin use (RR, 0.60 [CI, 0.47 to 0.76]) 10 to 19 years after initiation (22, 26–28). 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 4 primary and secondary CVD prevention trials showed a similar but smaller reduction in CRC incidence (hazard ratio, 0.76 [CI, 0.63 to 0.94]) (29).

Although evidence of aspirin's effect on other types of cancer is evolving, it has not yet been seen in trial results. Total cancer mortality was not significantly reduced across 10 RCTs of primary CVD prevention (4). An analysis of 6 RCTs of primary CVD 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 the analyses differed from those reviewed by the USPSTF (for example, different groupings of studies, not a CVD primary prevention population, or higher doses of aspirin used) (4).

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 1 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 (30). The tool presumes a baseline incidence rate of upper GI complications of 1 event per 1000 person-years and is modified for 10-year age ranges starting at age 50 years. The tool uses Framingham sex-specific risk prediction equations for CHD and modifies bleeding risk with use of proton-pump inhibitors or *Helicobacter 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 data were insufficient 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 7 of the CVD primary prevention trials previously discussed (15, 17–19, 21–23). These trials reported major GI bleeding events, defined as GI bleeding requir-

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ing transfusion or hospitalization or leading to death. Aspirin dose ranged from 50 to 325 mg in all but 1 trial. Duration of use and follow-up ranged from 4 to 10 years. Major GI bleeding increased by 58% in aspirin users (odds ratio [OR], 1.58 [CI, 1.29 to 1.95]). Analyses of trials using the range of aspirin doses showed similar results. When all major primary and secondary CVD prevention trials were pooled (15 studies), the OR increased further to 1.65 (4). Cohort studies reported similar bleeding risk with aspirin use (10).

Hemorrhagic stroke was a rare event; 15.5% of total strokes reported in the trials were hemorrhagic. Across 9 primary CVD prevention trials, the rate of hemorrhagic stroke was 2.54 strokes per 1000 person-years in aspirin users and 1.95 strokes per 1000 person-years in nonusers. Pooled analyses of low-dose aspirin trials showed an increased risk for hemorrhagic stroke (OR, 1.27 [CI, 0.96 to 1.68]) (5). Pooled analyses of 9 trials of any dose showed a significant 33% increase in hemorrhagic stroke (OR, 1.33 [CI, 1.03 to 1.71]) (5).

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 (31). 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 that 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 (10).

Estimate of Magnitude of Net Benefit

The USPSTF used a microsimulation model to estimate the magnitude of net benefit (8, 12). The model incorporated findings from the 3 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 numbers of nonfatal MIs and ischemic strokes prevented, CRC cases prevented, and serious GI bleeding events caused by aspirin, the USPSTF also considered net life-years and net QALYs 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 unless contraindicated by an adverse bleeding event results in the greatest gain in net life-years (range, 219 to 463 life-years in women and 333 to 605 life-years in men) and net QALYs (range, 621 to 833 QALYs in women and 588 to 834 QALYs in men). Initiating aspirin use during ages 60 to 69 years and continuing unless contraindicated by an adverse bleeding event results in smaller gains in net life-years (range, −12 to 48 life-years in women and −20 to 116 life-years in men) and net QALYs (range, 284 to 360 QALYs in women and 180 to 318 QALYs in men). 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 QALYs gained from aspirin use is moderate in adults aged 50 to 59 years. Adults aged 60 to 69 years gain fewer net life-years and QALYs because of the increased harms from bleeding that come with older age and the reduced potential for CRC benefits (that is, direct reduction in 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 aged 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 also increased).

How Does Evidence Fit With Biological Understanding?

Aspirin is an 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. Its anticlotting effect is useful for primary and secondary prevention of cardiovascular events because it can potentially decrease the accumulation of blood clots that form as the result of reduced blood flow at atherosclerotic plaques, thereby reducing hypoxic damage to heart and brain tissue (32).

Aspirin is an irreversible cyclooxygenase (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 (33).

The mechanisms for inhibition of adenoma or CRC development are not yet well-understood. Cyclooxygenase-dependent and -independent pathways have been proposed. Cyclooxygenase-dependent pathways may rely on aspirin's anti-inflammatory properties to reduce tumorigenesis (3).

Response to Public Comment

A draft version of this recommendation statement was posted for public comment on the USPSTF Web site from 15 September 2015 to 12 October 2015. Many comments requested clarification about initiating and continuing aspirin use, especially for persons in their 60s and 70s. The USPSTF added language throughout the recommendation statement to clarify its focus on initiating aspirin use and enhanced the "Implementation" section to provide guidance on continuing aspirin use. Several comments asked for clarification on the use of aspirin to prevent CRC in persons who are not at increased CVD risk. The USPSTF clarified that its recommendation is based on the combined benefit of CVD and CRC reduction, and only at 10-year CVD risk levels of 10% or greater is there certainty that the benefits exceed the harms of low-dose aspirin use. Several comments found the tables difficult to interpret or

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asked to include additional age and risk levels. The USPSTF considered other presentations of the data, but the tables represent the results from the decision-analysis model that are most relevant to its estimation of net benefits. Therefore, the tables only include the age and sex ranges for which the USPSTF found moderate certainty of small or moderate net benefit. More detailed tables can be found in the decision analysis report (8).

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 CRC. To update these recommendations, the USPSTF reviewed 5 additional studies of aspirin for the primary prevention of CVD and several additional analyses of CRC follow-up 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.

RECOMMENDATIONS OF OTHERS

The AHA and the American Stroke Association (34) 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 50 years or most women younger than 60 years who have low CVD risk because the risk for bleeding outweighs the potential benefits of aspirin treatment (35).

Previous recommendations from the American Academy of Family Physicians about aspirin use for the primary prevention of CVD and CRC have been consistent with those of the USPSTF (36). The American College of Chest Physicians suggests that patients older than 50 years without symptomatic CVD use low-dose aspirin for primary CVD prevention (37).

No organizations recommend aspirin use for the primary prevention of CRC in average-risk adults. The American Cancer Society recognizes that long-term regular aspirin use has both harms and benefits, including reduced risk for CRC, but has not formally reviewed the evidence and does not currently have recommendations for or against aspirin use. The American Gastroenterological Association and the National Comprehensive Care Network limit their recommendations to patients who are at increased risk for CRC (6).

The U.S. Food and Drug Administration recently denied a manufacturer's request to add 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 that the benefits of primary prevention have not been well-established (38).

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APPENDIX: U.S. PREVENTIVE SERVICES TASK FORCE MEMBERS

Members of the USPSTF at the time this recommendation was finalized† are Kirsten Bibbins-Domingo, PhD, MD, MAS (University of California, San Francisco, San Francisco, California); David C. Grossman, MD, MPH (Group Health Research Institute, Seattle, Washington); Susan J. Curry, PhD (University of Iowa, Iowa City, Iowa); Karina W. Davidson, PhD, MASc (Columbia University, New York, New York); John W. Epling Jr., MD, MSEd (State University of New York Upstate Medical University, Syracuse, New York); Francisco A.R. García, MD, MPH (Pima County Department of Health, Tucson, Arizona); Matthew Gillman, MD, SM (Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, Massachusetts); Diane M. Harper, MD, MPH, MS (University of Louisville, Louisville, Kentucky); Alex R. Kemper, MD, MPH, MS (Duke University, Durham, North Carolina); Alex H. Krist, MD, MPH (Fairfax Family Practice, Fairfax, and Virginia Commonwealth University, Richmond, Virginia); Ann E. Kurth, PhD, CNM, MSN, MPH (Yale School of Nursing, West Haven, Connecticut); C. Seth Landefeld, MD (University of Alabama at Birmingham, Birmingham, Alabama); Carol M. Mangione, MD, MSPH (University of California, Los Angeles, Los Angeles, California); William R. Phillips, MD, MPH (University of Washington, Seattle, Seattle, Washington); Maureen G. Phipps, MD, MPH (Brown University, Providence, Rhode Island); and Michael P. Pignone, MD, MPH (University of North Carolina, Chapel Hill, North Carolina). Immediate Past Chair Albert L. Siu, MD, MSPH, and former USPSTF members Douglas K. Owens, MD, MS, and Michael L. LeFevre, MD, MSPH, also contributed to the development of this recommendation statement.

† For a list of current USPSTF members, go to www.uspreventiveservicestaskforce.org/Page/Name/our-members.

Appendix Table 1. What the USPSTF Grades Mean and Suggestions for Practice

Grade	Definition	Suggestions for Practice
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.	Offer/provide this service.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.	Offer/provide this service.
C	The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.	Offer/provide this service for selected patients depending on individual circumstances.
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.
I statement	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	Read the Clinical Considerations section of the USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

Appendix Table 2. USPSTF Levels of Certainty Regarding Net Benefit

Level of Certainty*	Description
High	The available evidence usually includes consistent results from well-designed, well-conducted studies in representative primary care populations. These studies assess the effects of the preventive service on health outcomes. This conclusion is therefore unlikely to be strongly affected by the results of future studies.
Moderate	The available evidence is sufficient to determine the effects of the preventive service on health outcomes, but confidence in the estimate is constrained by such factors as: the number, size, or quality of individual studies; inconsistency of findings across individual studies; limited generalizability of findings to routine primary care practice; and lack of coherence in the chain of evidence. As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion.
Low	The available evidence is insufficient to assess effects on health outcomes. Evidence is insufficient because of: the limited number or size of studies; important flaws in study design or methods; inconsistency of findings across individual studies; gaps in the chain of evidence; findings that are not generalizable to routine primary care practice; and a lack of information on important health outcomes. More information may allow an estimation of effects on health outcomes.

* The USPSTF defines *certainty* as "likelihood that the USPSTF assessment of the net benefit of a preventive service is correct." The net benefit is defined as benefit minus harm of the preventive service as implemented in a general primary care population. The USPSTF assigns a certainty level on the basis of the nature of the overall evidence available to assess the net benefit of a preventive service.

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