INTRODUCTION

Salicylates have been used since antiquity to alleviate pain, fever, and inflammation. It was not until the mid 20th century, though, that physicians recognized aspirin’s antithrombotic properties and began to use aspirin to prevent myocardial infarction (MI).\(^1\) In...
the 1970s, insights into the cell biology of cancer led to the hypothesis that aspirin might also be an effective chemotherapeutic or chemopreventive agent. Following these observations, a number of landmark clinical trials have evaluated aspirin for both the prevention of cardiovascular disease and cancer.

Today, aspirin continues to be widely used, particularly for cardiovascular disease prevention. Among adults 45 to 75 in the United States, 52% report taking aspirin daily. Daily aspirin use is common even among those who do not have a history of heart disease (47%). Despite its popularity, aspirin for cardiovascular disease prevention has been controversial. In 2014, The Food and Drug Administration (FDA) advised that current evidence does not support the routine use of aspirin for primary prevention of heart attack or stroke. The statement cited weak evidence for benefit for cardiovascular disease prevention as well as potential for harm from bleeding.

In contrast, the US Preventive Services Task Force (USPSTF) recently issued guidelines endorsing aspirin’s use for primary prevention of cardiovascular disease and colorectal cancer in specific populations. The USPSTF is an independent committee composed of experts who regularly review the medical literature and compile evidence-based recommendations for preventive service use in primary care. In 2016, the USPSTF recommended low-dose aspirin for the prevention of colorectal cancer and cardiovascular disease among adults ages 50 to 59 who have 10-year risk of at least 10% for cardiovascular disease. The USPSTF stated that adults 60 to 69 who have 10-year risk of at least a 10% for cardiovascular disease may also benefit, but the decision to initiate aspirin in that age group should be individualized. The task force’s recommendations are summarized in Table 1.

To estimate 10-year cardiovascular risk, the USPSTF recommended using the American College of Cardiology/American Heart Association Atherosclerotic Cardiovascular Disease (ASCVD) risk calculator. The patient characteristics used to estimate cardiovascular risk are described in Box 1 and calculators are freely accessible online (http://tools.acc.org/ASCVD-Risk-Estimator). The risk calculator has several advantages including that it has been validated in US populations;

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<th>Population</th>
<th>Recommendation</th>
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<tr>
<td>Adults ages 50–59, ≥10% 10-y CVD risk</td>
<td>Initiate low-dose aspirin use.</td>
<td>B (The USPSTF recommends the service. There is moderate certainty that the benefit is moderate to substantial.)</td>
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<tr>
<td>Adults ages 60–69, ≥10% 10-y CVD risk</td>
<td>The decision to initiate low-dose aspirin use is an individual one.</td>
<td>C (At least moderate certainty that there is a small net benefit. USPSTF recommends selectively offering aspirin to individual patients based on professional judgment and patient preferences.)</td>
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<tr>
<td>Adults ages 40–49</td>
<td>No recommendation.</td>
<td>I (The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service).</td>
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<tr>
<td>Adults ages ≥ 70</td>
<td>No recommendation.</td>
<td>I (The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service.)</td>
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</table>

**Abbreviations:** CVD, cardiovascular disease; USPSTF, US Preventive Services Task Force.
provides age-, sex-, and race-specific estimates of cardiovascular risk; and includes ischemic stroke as an outcome. However, several studies suggest the calculator may overestimate the risk of cardiovascular disease in modern, diverse patient populations.\textsuperscript{5,10} Although it is the best available tool currently for estimating risk in US populations, clinicians should be aware of the limitations and imprecision of all such tools.

The task force also advised that aspirin should be avoided in adults who are at high risk of bleeding, who have a limited life expectancy, or who do not want to take a daily aspirin. The recommendation statement noted that there is insufficient evidence to recommend for or against initiating aspirin among adults 40 to 49 or adults 70 and older and that continuing aspirin in adults over age 70 is an individualized decision.\textsuperscript{6}

What informed the USPSTF’s recommendations and why did they differ from the FDA’s assessment of aspirin? One major difference between the 2 approaches is that the USPSTF considered aspirin’s role in preventing cardiovascular disease and cancer together, whereas the FDA considered only cardiovascular disease benefits. To evaluate aspirin’s benefits in 2 distinct disease areas (cancer and cardiovascular disease) as well as its harms, the USPSTF took a 2-step approach. First, the USPSTF commissioned 3 separate metaanalyses of available data on aspirin for the primary prevention of cardiovascular disease, prevention of cancer including colorectal cancer, and risk of major bleeding. Second, the task force commissioned a study that used data from these metaanalyses and other sources in a decision model designed to evaluate the net balance of benefits and harms of aspirin in different populations. In this review, we summarize the findings that informed the USPSTF’s recommendations and explore key areas of uncertainty in aspirin for primary prevention.

### ASPIRIN AND PRIMARY PREVENTION OF CARDIOVASCULAR DISEASE

#### Nonfatal Myocardial Infarction

Nearly 30 years ago, the British Doctors Trial first evaluated whether aspirin can prevent MI. The trial, which randomized healthy male physicians to aspirin, reported a nonsignificant 3% reduction in the rate of nonfatal MI.\textsuperscript{11} One year later, though, the Physicians’ Health Study, an analogous but larger trial conducted in the United States, reported a significant reduction in nonfatal MI (hazard ratio, 0.59; 95% confidence interval [CI], 0.47–0.74).\textsuperscript{12}

Since those early studies, a total of 10 high-quality trials have evaluated aspirin for the primary prevention of MI.\textsuperscript{13} Echoing the pattern of those initial studies, the
USPSTF’s metaanalysis found substantial heterogeneity among these trials ($I^2$ 62%). Overall, however, the metaanalysis reported a reduction in the relative risk (RR) of nonfatal MI among those taking aspirin (RR, 0.78; 95% CI, 0.71–0.87). Three of the 4 largest trials included in the metaanalysis demonstrated benefit, and the fourth demonstrated benefit among older participants. Taken together, these results suggest that aspirin does reduce the risk of nonfatal MI.

Although these findings support aspirin’s efficacy, aspirin’s absolute benefit in reducing nonfatal MI is modest. Given the typical rates of MI seen among patients enrolled in primary prevention trials, low-dose aspirin would prevent about 4 to 5 nonfatal heart attacks for every 1000 people treated with aspirin for 10 years. Aspirin’s cardiovascular disease benefits appear early on after initiating use, likely within the first 1 to 5 years of use.

**Nonfatal Stroke**

Aspirin’s antiplatelet properties suggest that aspirin may both lower the risk of ischemic stroke and increase the risk of hemorrhagic stroke. The USPSTF’s metaanalysis examined 10 trials that reported both ischemic and hemorrhagic stroke outcomes. Across aspirin trials, hemorrhagic stroke accounted for only about 16% of strokes. Combining these 10 trials, there was no evidence that aspirin reduced stroke risk (RR, 0.95; 95% CI, 0.85–1.06). Among the 7 trials that used only low-dose aspirin (<100 mg/d), however, the metaanalysis found a reduction in the risk of nonfatal stroke (RR, 0.86; 95% CI, 0.76–0.98). In primary prevention trials, aspirin did seem to increase the risk of hemorrhagic stroke (odds ratio [OR], 1.33; 95% CI, 1.03–1.71). Even low-dose aspirin may increase the risk of hemorrhagic stroke, although the estimate from the USPSTF metaanalysis did not attain statistical significance (OR, 1.27; 95% CI, 0.96–1.68).

As with prevention of MI, the absolute risk reduction in stroke is modest. Given the typical stroke rates seen in primary prevention trials, low-dose aspirin would prevent about 4 nonfatal strokes for every 1000 people treated for 10 years.

**Cardiovascular Death**

Across 11 trials, a pooled analysis did not demonstrate a statistically significant reduction in risk of cardiovascular death (RR, 0.94; 95% CI, 0.86–1.03).

**Special Populations and Effect Modification**

Is aspirin especially beneficial in any particular population? Aspirin prevents more cardiovascular events among patients who are more likely to have cardiovascular events. Thus, the greater the underlying risk, the greater the absolute benefit. For example, among patients enrolled in primary prevention trials, there was a near 10-fold difference in the estimated absolute benefit, depending on baseline risk. For those with the lowest cardiovascular disease risk, aspirin prevented approximately 0.15 nonfatal MIs per 1000 person-years compared with and 1.43 MIs per 1000 person-years in the highest risk populations.

The benefits of aspirin may vary with age, and in particular, the RR reduction for MI may increase with age. Three trials that reported results by age demonstrated larger RR reductions for MI at older ages, although not all trials reported significant interactions. Several trials also evaluated stroke rates with aspirin use by age and did not show significant differences, although event rates were low in subgroup analyses.

A previous metaanalysis examined effects of aspirin on stroke and MI risk by sex and reported larger reductions in MI for men and greater reductions in stroke risk for women with aspirin use, although the study did not assess for sex-specific...
interactions specifically. These sex-specific differences were largely driven by findings from the Women's Health Study, which reported a reduction in stroke but not MI with aspirin use in women. Overall, though, owing to inconsistency across trials, lack of subgroup prespecification, and lack of formal interaction testing, the USPSTF concluded there was not sufficient evidence to support differences in the effect of aspirin by sex for the combined outcome of cardiovascular disease.

A number of trials have evaluated aspirin’s specific cardiovascular effects in patients with diabetes. Results from these trials did not suggest effect modification for risk of stroke or MI among patients with diabetes.

ASPIRIN AND CANCER

In addition to its antiplatelet effects, aspirin has recognized antineoplastic properties. A number of dedicated trials have demonstrated aspirin’s effectiveness in reducing colonic adenomas, although these trials focused on precancerous lesions. Reanalysis of cardiovascular disease prevention trials has provided some insight into aspirin’s effect on the development of colorectal cancer and death from colorectal cancer.

Data from cardiovascular disease prevention trials suggest that regular aspirin use reduces the incidence of colorectal cancer by about 40% (RR, 0.60; 95% CI, 0.47–0.76). This benefit is seen between 10 and 20 years after initiating aspirin. Within 10 years of initiation, aspirin has little benefit (RR, 0.99; 95% CI, 0.85–1.15). The minimum duration of aspirin use needed to reduce the risk of cancer is not well-established, but some data suggest that longer use is associated with greater benefit. Given typical rates of cancer in the United States, and given the time required to see benefit, for every 1000 adults treated from age 50 onward, an estimated 12 to 14 cases of colorectal cancer could be prevented. When used consistently for several years, aspirin also seems to reduce the risk of death from colorectal cancer (hazard ratio, 0.51; 95% CI, 0.35–0.74), although benefits only accrue after 10 to 20 years of initiation.

In addition to colorectal cancer, the USPSTF evaluated aspirin’s effect on incidence of all cancers. The metaanalysis examined 6 trials of aspirin for cardiovascular disease prevention and did not find a benefit (RR, 0.98; 95% CI, 0.93–1.04). When restricted to trials with a median intended duration of use of at least 4 years, there was a marginally statistically significant reduction in incidence of all cancers (RR, 0.86; 95% CI, 0.74–0.99). A metaanalysis of individual patient data from studies of aspirin for primary prevention reported a reduction in incidence of all cancers (hazard ratio, 0.88; 95% CI, 0.80–0.98), with benefits seen 3 to 4 years after randomization. This metaanalysis, however, included studies that only reported fatal cancers and also included studies of aspirin and warfarin coadministration.

The USPSTF metaanalysis also examined whether aspirin use reduces mortality from all cancers. In considering 10 trials that evaluated aspirin for primary prevention of cardiovascular disease, the metaanalysis did not demonstrate a reduction in cancer deaths (RR, 0.96; 95% CI, 0.87–1.06). A previous metaanalysis had demonstrated a reduction in cancer death after at least 4 years of use (hazard ratio, 0.82; 95% CI, 0.70–0.95), although that analysis excluded trials of alternate day dosing and included trials of high-dose aspirin unlikely to be used for primary prevention of cardiovascular disease.

ASPIRIN AND BLEEDING COMPLICATIONS

Although aspirin’s antithrombotic properties reduce heart attack and ischemic stroke, those same properties can promote bleeding, including disabling or life-threatening
central nervous system bleeding. In addition, aspirin promotes gastric ulcer formation, which, in turn, creates additional risk for bleeding.

The USPSTF commissioned a metaanalysis specifically to synthesize evidence on bleeding risks, particularly gastrointestinal (GI) bleeding and hemorrhagic stroke, the most serious forms of bleeding. The metaanalysis found that, overall, GI bleeding is rare, with less than 1% of those on aspirin affected. Still, aspirin is associated with GI bleeding (OR, 1.59; 95% CI, 1.32–1.91) and even low-dose aspirin seems to increase risk (OR, 1.58; 95% CI 1.29–1.95). Although these point estimates were similar, observational studies suggest that higher doses are associated with a higher risk of GI bleeding. Depending on the underlying risk of bleeding, aspirin might be expected to contribute between 1 and 6 cases of GI bleeding for every 1000 adults treated for 10 years.

A number of individual risk factors affect bleeding risk (Box 2). Trials of aspirin for cardiovascular disease prevention have identified a number of risk factors including age, male sex, diabetes, hypertension, tobacco use, and obesity as risk factors for bleeding. A number of other conditions, including advanced liver and renal disease and concurrent use of other anticoagulants, can also increase the risk of bleeding. Trials have generally not compared doses of aspirin, but observational data suggest that risk of both GI and central nervous system bleeding increases with dose. Although there are known risk factors for bleeding that may help to qualitatively risk stratify patients, there have been no prospectively validated tools for predicting bleeding risk among those taking aspirin.

MODELING TO UNDERSTAND THE BENEFITS AND HARMs OF ASPIRIN

Should we recommend aspirin for primary prevention to our patients? Aspirin reduces nonfatal MI, ischemic stroke, and mortality from colorectal cancer but increases GI and intracranial bleeding. Weighing these benefits and harms, however, may not be straightforward, especially when the risks and benefits may vary according to population and time frame. One way to quantitatively evaluate the net benefit of aspirin is to use decision modeling.

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**Box 2**

Risk factors for bleeding when considering aspirin initiation

- **Demographics**
  - Older age
  - Male sex

- **Medical history**
  - Diabetes mellitus
  - Hypertension
  - Liver disease
  - Renal disease
  - Previous hospitalization for gastrointestinal problem or history of abdominal pain
  - Thrombocytopenia or underlying coagulopathy
  - Obesity

- **Aspirin properties and medication interactions**
  - Dose and duration of use
  - Use of nonsteroidal antiinflammatory drugs
  - Anticoagulant use
  - Tobacco use
Decision models are a methodologic approach for estimating the effects of interventions on health outcomes in different populations over time. Modeling is especially useful for a treatment like aspirin, in which risks and benefits vary by patient and where risks and benefits appear at different time points. A related advantage of modeling is that it allows us to quantify aspirin’s overall impact on quantity and quality of life. Even if we knew the number of patients who might be expected to benefit or be harmed by aspirin, comparing those outcomes is difficult if each has a different severity and impact on quality of life. Modeling addresses this by translating outcomes into a single measure, the quality-adjusted life-year, which incorporates both duration and quality of life. Because the main effect of aspirin is on nonfatal events, which can substantially decrease quality of life, the use of QALYs is particularly helpful for assessing the usefulness of aspirin.

Using this approach, investigators working with the USPSTF developed a decision model of aspirin for the primary prevention of colorectal cancer and cardiovascular disease. The main modeling results are reported in Table 2. The analysis found that benefits generally outweighed harms and were greatest for men and women who initiate aspirin in their 50s and continue until death or an adverse event. Benefits increased as risk of cardiovascular disease increased. For example, men in their 50s with a 10-year risk of 10% of cardiovascular disease would gain a net 58.8 QALYs per 1000 adults treated over a lifetime, whereas men with a 20% risk of cardiovascular disease would gain 83.4 QALYs.

One final advantage of modeling is its ability to ask “what if” questions that build on the literature, but are not directly addressed in any clinical trial. For example, the modeling study addressed whether starting aspirin at a younger age, between 40 and 49 years, is beneficial. The model results suggested initiating aspirin in this age range provides the greatest benefit, although these results rely on extrapolating aspirin’s benefits to this younger population, because this younger population has not been the focus of clinical trials. The USPSTF did not recommend aspirin use in younger patients because of the lack of empirical evidence.

The results from the modeling study should be interpreted with an understanding of the strengths and limitations of modeling. First, models rely on the best available estimates of effect from the literature. A strength of this analysis is that the model incorporated results from the 3 comprehensive metaanalyses discussed herein and from additional evidence. However, if there are unidentified biases in these estimates from the literature, they will be reflected in the model results. Second, models require making choices about which benefits and harms to include, and those choices can affect the model’s estimates. For example, in the accompanying metaanalysis, risk of hemorrhagic stroke with low-dose aspirin was not statistically significant (OR, 1.27; 95% CI, 0.96–1.68), but was still incorporated in the main model, largely because the authors felt that the point estimate represented a real effect. A sensitivity analysis excluding this risk favored aspirin more strongly. Readers should appreciate that all models require simplifying a complex reality through a set of choices and these choices can influence the model’s findings. The substantial advantage of modeling is that it provides an approach for estimating net benefit when there are complex benefits and harms.

**AREAS OF UNCERTAINTY AND FUTURE CONSIDERATIONS**

**Dose**

Of the 11 cardiovascular disease primary prevention trials, 8 included in the USPSTF metaanalysis used a dose of 100 mg of aspirin or less. A dose of 81 mg is commonly
<table>
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<th>CVD Risk&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Nonfatal MIs Prevented</th>
<th>Nonfatal Ischemic Strokes Prevented</th>
<th>Colorectal Cancer Cases Prevented</th>
<th>Serious GI Bleeding Events Caused</th>
<th>Hemorrhagic Strokes Caused</th>
<th>Net Life-Years Gained</th>
<th>QALYs Gained</th>
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Abbreviations: CVD, cardiovascular disease; GI, gastrointestinal; MI, myocardial infarction; QALY, quality-adjusted life-year.

<sup>a</sup> The 10-y CVD risk is based on the American College of Cardiology/American Heart Association risk calculator estimate.

prescribed in the United States. There are no trials, though, that specifically compare doses head-to-head for primary prevention, although studies are underway.\textsuperscript{13}

Is low-dose aspirin preferable? Bleeding may be lower with lower doses. Although there are very few direct comparisons of dose for primary prevention, observational data suggest a higher risk of both GI and intracranial bleeding with increased doses.\textsuperscript{26,27} Second, the reduction in ischemic stroke is based on trials with dosages of less than 100 mg.\textsuperscript{13} In contrast, some evidence suggests higher doses have a more potent antineoplastic effect.\textsuperscript{24} The available evidence seems to suggest that a dose of less than 100 mg/d provides the best balance of risk and benefit for primary prevention.\textsuperscript{6}

Age

Most trials of aspirin for primary prevention of cardiovascular disease included participants in their 50s and 60s. Although some trials did include older and younger patients, these trials either did not report age-specific findings, were not powered to detect age-specific effects, or did not look at the extremes of age.\textsuperscript{12,32,33} Although the USPSTF modeling study suggested that taking aspirin beginning at that younger age may produce the greatest benefit, the direct evidence underlying this result is sparse. Similarly, there is no randomized trial evidence to guide aspirin initiation among adults over the age of 70, although aspirin use is quite common in this population. Although cardiovascular disease risk increases with advancing age, bleeding risk also increases, and the balance of risks and benefits is less clear. There is ongoing research to evaluate the benefit of initiating aspirin in adults over the age of 70.\textsuperscript{34}

Other Cancers

Previous metaanalyses have suggested that aspirin may indeed reduce incidence and death from cancers other than colorectal cancer.\textsuperscript{24,25} These metaanalyses, however, included studies that are difficult to generalize to a primary prevention population. For example, the metaanalyses included studies that used higher doses of aspirin, excluded studies of every-other-day dosing or coadministered aspirin and warfarin. Despite this uncertainty, these metaanalyses offer some evidence that aspirin may have a role in reducing risk from cancers other than colorectal cancer.

SUMMARY

Current evidence supports initiating aspirin for primary prevention in selected higher risk populations. In particular, adults in their 50s who are at increased risk of cardiovascular disease and are not at increased risk of bleeding are most likely to benefit. Adults in their 60s may also benefit, although the risk of harm increases with age. Older populations are also less likely to benefit from colorectal cancer risk reduction, as this benefit takes years to manifest. In general, treatment decisions should involve an assessment of the individual’s risk of cardiovascular disease, bleeding risk, and life expectancy. Incorporating patient preferences is also critical in deciding whether to initiate aspirin for primary prevention.

When evaluating an intervention with complex benefits and harms such as aspirin, decision modeling provides a useful approach. The modeling integrated evidence about the effect of aspirin on cardiovascular and colorectal cancer outcomes. Based on the evidence reviews and modeling, the USPSTF concluded that aspirin’s benefits outweigh its harms in specific populations. These conclusions differ from the FDA’s recommendations, in part because the USPSTF considered the benefits of aspirin
for both cardiovascular disease and cancer, whereas the FDA focused on cardiovascular benefits alone.

Decades of research on aspirin have refined our understanding of its benefits and risks. Current evidence supports the use of aspirin for primary prevention in specific populations. Ongoing studies will likely help further define the optimal dose of aspirin, its use in broader age groups, and its role in prevention of other cancers.

REFERENCES


