180-day mortality may favor the use of CPAP until more evidence becomes available. The FIRST-ABC trial provides helpful information on preferred approaches to respiratory management in the PICU, although uncertainty still dominates clinical decision-making involving optimal respiratory support following extubation for pediatric patients.

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Should Patients Take Aspirin for Primary Cardiovascular Prevention? Updated Recommendations From the US Preventive Services Task Force

Allan S. Brett, MD

**The US Preventive Services Task Force (USPSTF)** issued its first Guide to Clinical Preventive Services in 1989.¹ That initial monograph included a recommendation to “consider” aspirin prophylaxis for primary cardiovascular prevention in men 40 years or older with coronary risk factors and low bleeding risk. The sole basis for that recommendation was 2 randomized trials in which study participants were exclusively male physicians.

Since then, the USPSTF has updated its position on aspirin for primary prevention on multiple occasions, and the trajectory has been tortuous. In 1996, after further deliberation, the USPSTF reconsidered the evidence and concluded that the balance of harms and benefits was too close to justify a general recommendation.² But in 2002, after publication of 3 more trials with more representative study populations, the task force recommended strongly that clinicians discuss aspirin chemoprevention with people at increased risk for coronary disease and suggested that decisions be informed by risk calculators and tables with estimated benefits and harms.³ Notably, the wording “strongly recommend” referred only to having discussions with patients and not to routine aspirin use.

In 2009, the USPSTF went further when it strongly and specifically recommended aspirin prophylaxis be encouraged
A new stage in aspirin therapy for cardiovascular disease prevention

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for a broad range of adults (men aged 45-79 years; women aged 55-79 years) according to estimated 10-year risk for myocardial infarction, stroke, and gastrointestinal bleeding; those estimates were detailed in age- and sex-specific tables. But in 2016, the USPSTF changed its recommendation. It narrowed the age range of eligible candidates for aspirin prophylaxis and explicitly recommended that aspirin be considered only for those whose 10-year cardiovascular risk exceeded 10%, whose life expectancy exceeded 10 years, and who were not at increased risk for bleeding. The 2016 Recommendation Statement also mentioned—for the first time—prevention of colorectal cancer as a potential benefit.

In this issue of JAMA, the USPSTF reports its newest Recommendation Statement, and the pendulum has swung further away from aspirin prophylaxis for primary prevention: The guideline does not recommend routine preventive aspirin for anyone. This iteration specifically advises against initiating aspirin in people 60 years or older (a D recommendation in the USPSTF grading system). However, for those aged 40 to 59 years with 10-year cardiovascular risk 10% or greater, the guideline advises clinicians and patients to make individualized decisions about initiating aspirin prophylaxis. This is a C recommendation, defined as “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.”

The basis for these new recommendations is an updated review that included 11 randomized trials of low dose aspirin (dose of 100 mg/d or less) for primary prevention. The review demonstrated a 10% relative reduction in major cardiovascular events (but no reduction in mortality) and a 44% relative increase in major bleeding events, over 4 to 10 years of aspirin use. However, absolute differences across trials in composite and individual cardiovascular outcomes ranged from 2.5 fewer to 1.2 more events per 100 aspirin users; for composite and individual major bleeding events, absolute differences ranged from 0.07 fewer events to 1.0 more events per 100. The USPSTF also reviewed colorectal cancer outcomes and found that evidence was inadequate to include prevention of colorectal cancer in the benefit-harm assessment.

An important development between the 2016 and current versions was the publication in 2018 of 3 large placebo-controlled randomized clinical trials of primary prevention with aspirin that involved a total of more than 47,000 patients with 5 to 7 years of follow-up. ARRIVE included people 55 years or older with multiple risk factors (but not diabetes) and estimated 10-year cardiovascular risk of 17%; it found no evidence of cardiovascular benefit and a small statistically significant increase in gastrointestinal bleeding. ASCEND exclusively included people with diabetes (40 years or older); it found a 1 percentage-point decrease in cardiovascular events and a 1 percentage-point increase in major bleeding. ASCEND additionally included people with diabetes (40 years or older); it found a 1 percentage-point decrease in cardiovascular events and a 1 percentage-point increase in major bleeding. Arguably, these 3 recent trials, which were included among the 11 trials that informed the new Recommendation Statement, should have special weight. Compared with older trials, these trials were performed in more contemporary populations with likely better control of blood pressure and lipids and a lower prevalence of smoking. Taken together, these more recent trials cast doubt about net benefit for aspirin prophylaxis in current practice.

Three aspects of the new USPSTF recommendation statement are worth additional comment. First, the recommendations explicitly refer to initiation of aspirin. Clinicians are thus left without explicit guidance about management of the many patients already taking aspirin for primary prevention. This omission is unfortunate, given that an estimated 28% of adults 40 years or older (and 46% of those 70 years or older) were using aspirin for primary prevention as recently as 2019, according to a nationally representative survey. In a brief statement, the USPSTF authors indicate that “for patients who have initiated aspirin use...it may be reasonable to consider stopping aspirin use around age 75 years,” according to microsimulation modeling. Although unstated, the authors presumably are referring to people who initiated aspirin before age 60. But consider 2 people with identical cardiovascular-risk and bleeding-risk profiles at age 55: One patient begins aspirin and the other does not, and they both present to a clinician for further advice when they are age 60. Given that the guideline recommends against starting aspirin at age 60 because there is no net benefit beyond that age, it is unclear why the first person should continue aspirin until age 75 while the second person should not start aspirin therapy.

Second, the decision to start aspirin therapy in people aged 40 to 59 years is heavily dependent on 10-year risk for cardiovascular events, as estimated in the widely used calculator associated with the American College of Cardiology and American Heart Association (ACC/AHA). The USPSTF authors acknowledge that in several external validation studies the calculator overpredicts cardiovascular risk, and they appropriately remind clinicians that cardiovascular risk prediction is “imprecise and imperfect at the individual level.” This source of uncertainty is in obvious tension with the guideline’s specific use of the 10% threshold for cardiovascular risk and presents a challenge in individualizing decisions to initiate aspirin use. Plugging data into the ACC/AHA calculator and generating a specific percent probability creates a sense of precision for clinicians and patients that is misleading, although alluring in its apparent objectivity.

Third, the process of individualizing decisions should include understandable estimates of absolute benefit and harm (with acknowledgment of their imprecision). Those estimates, briefly described above, are detailed in the separate Evidence Review (in Table 2) but not in the Recommendation Statement. Instead, the Recommendation Statement includes a table (Table 2 in the article) derived from a decision analytic model, showing net benefits of aspirin therapy expressed as life-years and quality-adjusted life-years (QALYs) gained per 1000 persons, according to age, sex, and 10-year risk. This expression of net benefit has the advantage of collapsing cardiovascular and bleeding outcomes into a single quality-of-life metric. However, for discussions with
individual patients, expressing outcomes as QALYs per 1000 persons may be problematic.

How should clinicians use this new Recommendation Statement? For patients 60 years or older, clinicians should not initiate aspirin for primary prevention; clinician-initiated discussions about aspirin prophylaxis are unnecessary, except for inquiring whether patients are already taking aspirin based on their own decisions. The 3 randomized trials from 20189-11 also provide indirect support for stopping aspirin in patients in this age group who are already taking it for primary prevention. For patients aged 40 to 59 years, the definition of the C recommendation is key. In stating that C interventions can be recommended, the USPSTF allows clinicians latitude in whether and when to initiate discussions about aspirin prophylaxis for patients in this age group.

When those discussions occur, what does “individualizing” the decision entail? Patients whose general philosophy of medical care is “don’t prescribe medication for me unless there is strong evidence to support it” should not start aspirin prophylaxis, whereas those who favor preventive interventions even in borderline cases could reasonably opt for taking aspirin. Other patients have no strong general preferences on taking (or not taking) medications purely for prevention and are not interested in lengthy deliberation; such patients often ask a trusted clinician to decide for them. But for still other patients, individualized decision-making implies detailed discussion and an expectation that clinicians can confidently predict whether a specific patient will experience net benefit from aspirin. However, that goal is illusory, and clinicians should not pretend otherwise. For such patients, the best approach is for clinicians to be knowledgeable about the data on primary prevention with aspirin.15 Close reading of the new USPSTF guideline and its companion Evidence Review, and becoming familiar with the 3 more recent aspirin trials, is a good way to prepare for these clinical encounters.

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