AJKD

In the Literature

Does an Aspirin a Day Keep the Doctor Away?

Commentary on Bibbins-Domingo K; U.S. Preventive Services Task Force. Aspirin use for the primary prevention of cardiovascular disease and colorectal cancer: U.S. Preventive Services Task Force Recommendation Statement. Ann Intern Med. 2016;164(12):836-845.

Aspirin is an old and venerable medication. The antipyretic and analgesic effects of willow bark were known to the ancient Greeks, Assyrians, and Egyptians. Slowly, over centuries, the responsible compound was isolated and purified.[1] The first sample of pure acetylsalicylic acid was produced in Germany in 1897 and marketed in 1899 under the trademark of Aspirin, initially targeting treatment of pain in rheumatism.[2] With increasing clinical experience in the 1900s came observations of both harm, specifically bleeding, and benefit, specifically reductions in coronary events.

Subsequent research revealed the now well-known mechanism of cyclooxygenase-1 inhibition and downstream thromboxane A_2 generation that results in decreased platelet aggregation and clinical antithrombotic effect.[2] This led to clinical trials showing prevention of cardiovascular disease (CVD) events, followed by widespread uptake of aspirin use in the general population for CVD prevention. Over the years, many guideline groups have reviewed the evidence of benefit and risks with aspirin use and presented guidelines for clinical use, and in April 2016, the US Preventive Services Task Force (USPSTF) updated their guidelines[3] from previous ones in 2009[4] and 2007.[5] Although these updated guidelines discuss aspirin use for both CVD and colorectal cancer risk reduction, this editorial focuses on CVD risk reduction with aspirin and the specific implications for people with chronic kidney disease (CKD).

WHAT DOES THIS IMPORTANT REPORT SHOW?

Based on data from 3 new USPSTF-commissioned systematic reviews[6-8] and a decision analysis that evaluated potential net life-years and quality-adjusted life-years gained with aspirin use,[9] the USPSTF provided the following conclusions for low-dose aspirin use:

> The USPSTF concludes with moderate certainty that the benefit of aspirin use for the primary prevention of CVD events…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 (grade B)… [and] 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 (Grade C).
>
> The USPSTF concludes that the evidence on aspirin use in adults younger than 50 years or older than 69 years is insufficient to determine the balance of benefits and harms (Grade Insufficient evidence).

The 10-year CVD risk of ≥10% is based on the American College of Cardiology/American Heart Association (ACC/AHA) risk calculator.[10] Importantly, bleeding risk could be underestimated because it assumes that aspirin users do not take nonsteroidal anti-inflammatory drugs or have other conditions that increase the risk for bleeding.

The decision analysis by Dehmer et al[9] used a CVD microsimulation model to simulate a comparative study of aspirin users and nonusers aged 40 to 79 years. For external validation, baseline ischemic stroke and nonfatal myocardial infarction (MI) event rates generated in this model were similar to those observed in the National Health and Nutrition Examination Survey. Baseline gastrointestinal (GI) bleeding rates and mortality were estimated using studies from Italy and the United Kingdom. They note that the relative risk estimate for ischemic stroke with aspirin use likely underestimates benefits because it is derived from combined (ischemic and hemorrhagic) stroke data. Of note, none of the USPSTF-commissioned reviews mention including data for people with CKD.[8]

HOW DOES THIS REPORT COMPARE WITH PRIOR REPORTS?

The previous USPSTF guideline from 2009 for primary CVD prevention was substantially different (Table 1). Aspirin was recommended for men aged 45 to 79 years when the benefit from MI reduction outweighed the risk for GI bleeding and for women aged 55 to 79 years when the benefit from ischemic stroke reduction outweighed the risk for GI bleeding (Grade A).[4] They recommended against aspirin use in women younger than 55 years and men younger than 45 years (Grade D).

In comparison, the AHA, ACC Foundation, and America Diabetes Association in 2010 recommended low-dose aspirin for CVD prevention in men and women with increased CVD risk (Framingham risk calculator 10-year risk ≥ 10%).[11] The AHA and American Stroke Association (ASA) in their 2014

Address correspondence to Taimur Dad, MD, Tufts Medical Center, 800 Washington St, Box #391, Boston, MA 02111. E-mail: tdad@tuftsmedicalcenter.org

0272-6386
http://dx.doi.org/10.1053/j.ajkd.2016.10.012

Table 1. Guidelines Regarding Aspirin Use for Primary Prevention of CVD

Guideline	Recommendations in General Population	Recommendations in CKD	CVD Risk Equation Used
USPSTF 2016[3]	Low-dose aspirin for adults 50-59 y with 10-y CVD risk ≥ 10% without increased risk for bleeding (Grade B); low-dose aspirin for adults 60-69 y with 10-y CVD risk ≥ 10% without increased risk for bleeding (Grade C); no recommendation for adults <50 y and ≥70 y (Grade Insufficient)	Text mentions that "renal failure" is a risk factor for GI bleeding with aspirin use	AHA/ACC 2014 equation
AHA/ASA 2014[12]	Aspirin for adults with 10-y CVD risk > 10% (Class IIa; level of evidence A); individuals with asymptomatic carotid stenosis (Class I; level of evidence C for combined use of aspirin and statin)	Aspirin "might be considered" for prevention of first stroke in individuals with eGFRs < 45 but >30 mL/min/1.73 m^2 (Class IIb; level of evidence C)	AHA/ACC 2014 equation
AHA/ACCF/ADA 2010[11]	Low dose for adults with diabetes with 10-y CVD risk > 10% without increased risk for bleeding (ACCF/AHA Class IIa; level of evidence B. ADA level of evidence C)	Not mentioned	Framingham risk calculator
USPSTF 2009[4]	Aspirin for men 45-79 y when benefit of MI risk reduction outweighs risk for bleeding (Grade A); aspirin for women 55-79 y when benefit of ischemic stroke reduction outweighs risk for bleeding (Grade A); no aspirin for women < 55 y for stroke prevention or for men < 45 y for MI risk reduction (Grade D); no recommendation for men and women ≥ 80 y (Grade Insufficient)	Not mentioned	Framingham risk calculator for MI risk; Western States Stroke Consortium Stroke Calculator for ischemic stroke risk; different risk cutoffs provided within and between the men/women groups

Note: USPSTF: Grade A and B recommendations should be provided; Grade C should be provided to select patients; Grade D should be discouraged from use. AHA/ASA: Class I and IIa indicate benefit exceeds risk (ratio of benefit to risk higher for Class I than IIa). Level of evidence A indicates data from multiple randomized clinical trials/meta-analyses studying multiple populations; B, data from a single randomized clinical trial or nonrandomized trials studying limited populations; C, consensus/expert opinions, case studies, or standard of care from very limited populations. ADA: Level of evidence C: evidence from poorly controlled or uncontrolled studies.

Abbreviations: ACC(F), American College of Cardiology (Foundation); ADA, American Diabetes Association; AHA, American Heart Association; ASA, American Stroke Association; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; MI, myocardial infarction; USPSTF, United States Preventive Services Task Force.

guidelines state that aspirin prophylaxis for stroke prevention is reasonable for individuals whose 10-year risk is ≥10% (using the AHA/ACC CVD risk calculator), individuals with asymptomatic carotid stenosis, and individuals with estimated glomerular filtration rates (eGFRs) between 30 and 44 mL/min/1.73 m^2 (CKD stage 3b),[12] with the latter based on a post hoc analysis of the Hypertension Optimal Treatment (HOT) trial.

Most of these guidelines do not specifically address CKD because limited data regarding aspirin use and CVD prevention exist in these groups. One observational study from Korea using propensity score matching showed increased development of CVD without increased bleeding risk in patients with CKD and aspirin use,[13] whereas an observational study of aspirin prescription in maintenance hemodialysis patients, including patients from 7 countries, showed decreased risk for stroke but increased risk for any cardiac event including MI without increase in GI bleeding[14]; both these studies likely have significant residual indication bias. We reported an observational study also using propensity score matching in kidney transplant recipients that did not show a difference in CVD outcomes or mortality with aspirin use.[15] Another observational study of evaluating outcomes in patients with CKD with newly diagnosed atrial fibrillation who initiated anticoagulation therapy with aspirin, warfarin, or both showed a significant increased risk for bleeding associated with aspirin monotherapy in dialysis patients but not in patients with earlier stages of CKD.[16] In sum, limited information informing clinical practice can be extracted from these studies.

There are scant prospective randomized data for aspirin use in CKD populations, with a recent meta-analysis of aspirin use and CVD prevention in CKD finding only 3 trials.[17] The first was a prospective placebo-controlled study looking at simvastatin and