Aspirin for Primary Prevention of CVD

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LEARNING OBJECTIVES

1. Evaluate atherosclerotic cardiovascular disease (ASCVD) risk factors and tools to estimate short- and long-term ASCVD outcomes in various patient populations.
2. Analyze the benefit-risk of aspirin for the primary prevention of ASCVD.
3. Evaluate evidence-based literature to assess appropriate aspirin use for the primary prevention of ASCVD.
4. Using recommendations from various clinical practice guidelines, justify the use of aspirin for the primary prevention of ASCVD.

ABBREVIATIONS IN THIS CHAPTER

ASCVD	Atherosclerotic cardiovascular disease
CHD	Coronary heart disease
CKD	Chronic kidney disease
CVD	Cardiovascular disease
DM	Diabetes mellitus
MI	Myocardial infarction
RCT	Randomized controlled trial
T1DM	Type 1 diabetes
T2DM	Type 2 diabetes
USPSTF	U.S. Preventive Services Task Force

Table of other common abbreviations.

INTRODUCTION

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of morbidity and mortality globally. In the United States, ASCVD is also the leading cause of death for people of most racial groups, with an estimated cost of greater than $200 billion annually in health care services, medications, and lost productivity (Arnett 2019). Despite data suggesting a decline in mortality associated with cardiovascular disease (CVD), the burden associated with CVD remains high. More than 860,000 people die of CVD in the United States annually (Benjamin 2019). Much of this is attributable to suboptimal implementation of preventive strategies and uncontrolled ASCVD risk factors in many adults.

Globally, CVD can be categorized as altered perfusion (ischemia in the coronary, cerebral, and/or peripheral arteries), altered cardiac output, abnormal anatomy, and abnormalities of electrical conduction (Crouch 2010). This chapter will focus on ASCVD, which includes coronary heart disease (CHD), ischemic heart disease and ischemic stroke, and peripheral artery disease. In CHD, atherosclerotic plaques can cause narrowing in one or more of the coronary arteries that supply blood to the heart muscle. This damages the coronary arteries, and platelets can adhere to these damaged areas, causing ischemia. This can manifest as fatal or nonfatal myocardial infarction (MI), angina pectoris, and/or heart failure (Torpy 2009). Several risk factors increase a person's risk of developing ASCVD. Furthermore, several tools are available to assess a patient's ASCVD risk to determine whether preventive pharmacotherapy or lifestyle changes are warranted.

Cardiovascular Risk Factors

Often, the first ASCVD risk factor recognized is elevated serum cholesterol. Primary CVD prevention requires early lipid screening (Arnett 2019). The most pertinent component of a cholesterol panel

is the LDL because this is thought to be highly atherogenic; therefore, elevated LDL concentrations are associated with elevated CVD risk. In addition, assessing CVD risk includes screening for the presence of other risk factors, including age, sex, race, premature family history of ASCVD, diabetes, hypertension, and cigarette smoking.

The prevalence of CVD (CHD, heart failure, stroke, and hypertension) increases with age in those older than 20 in both men and women. Age 45 years or greater in men and 55 years or greater in women is a CV risk factor. The cardiovascular risk of women remains underestimated (Appleman 2015). At an equal age, women have greater CV risk than men, and some risk factor are more detrimental in women such as hypertension, smoking, and diabetes. Women are also exposed to hormonal factors (contraception, pregnancy and menopause) or other risk inducing situations (endometriosis, polycystic ovary syndrome, auto-immune diseases). The ASCVD age-adjusted death rates are 33% higher for blacks than for the overall U.S. population (Benjamin 2019). Blacks are almost twice as likely to have a first stroke and much more likely to die of stroke than whites. Several other minor risk factors are associated with ASCVD that are called risk-enhancing factors in the American College of Cardiology (ACC) and American Heart Association (AHA) primary prevention guideline (Box 1).

A premature family history of ASCVD increases an individual's CVD risk (Arnett 2019). The definition of a premature family history of ASCVD includes the occurrence of a CV event (e.g., MI, ischemic stroke, or transient ischemic attack) in a first-degree male relative younger than 55 or in a first-degree female relative younger than 65 A first-degree relative includes the individual's biological parents, siblings, and offspring. The main obstacle when assessing for this CVD risk factor is that it relies on subjective report, and family history may be unknown. Of note, none of the guideline-recommended risk assessment tools include family history of premature ASCVD as a variable because of wide variations in short- and long-term CVD risk in those with this risk factor.

The prevalence of CHD is increased in those with diabetes, even in the absence of cigarette smoking, hypertension, and lipid abnormalities. However, in those with additional risk factors, the incidence of CHD is markedly increased. Elevations in systolic and diastolic blood pressure are associated with a similar increase in CVD risk in those with and without diabetes, whereas cigarette smoking is associated with a significantly higher mortality rate in those with diabetes. Overall, individuals with diabetes and one or all of the three major risk factors appear to have a 2–4 times higher CVD death rate than those without diabetes (ADA 1989).

The question of whether diabetes itself should be a CHD risk equivalent came from a 1998 study that evaluated the impact of age at time of statin initiation on CVD risk in patients with diabetes, but the results were inconclusive (Haffner 1998). A second study evaluated the impact of diabetes on CVD risk and all-cause mortality in older men, analyzing the influence of age at onset, diabetes duration, and established and novel risk factors (Sattar 2013). The study showed that men who develop diabetes after age 60 and have an average diabetes duration of 1.9 years have a CHD risk of about one-half that of men of similar age who have an average diabetes duration of 16.7 years, with only the group having 16.7 years of diabetes having a risk similar to those with a previous MI and no diabetes. Earlier initiation of statin therapy and improved blood pressure control have likely reduced CVD risk in those with diabetes, but diabetes duration is important in determining the level of CVD risk. Typically, a diabetes duration of around 10 years for type 2 diabetes (T2DM) or 20 years for type 1 diabetes (T1DM) is considered a CHD risk equivalent. However, the diabetes duration is often unknown because patients presenting with T2DM symptoms may have had undiagnosed disease for years. Furthermore, CVD risk is increased as early as the prediabetes stage of this progressive condition, and increased vigilance and treatment of modifiable risk factors in this patient population is recommended (ADA 2019). In

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- General knowledge of the pathophysiology and risk factors that leads to the development of cardiovascular disease (CVD).
- Knowledge of aspirin's presumed role for primary prevention of CVD.
- Specific recommendations from current clinical practice guidelines for chronic disease states on the use of aspirin for primary prevention.
- Current clinical practice guidelines for the management of cholesterol and hypertension in adults.
- Familiarity with dosage forms and formulations of aspirin.

Table of common laboratory reference values.

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease. JACC 2019.
- USPSTF. 2016 Final Recommendation Statement on Aspirin.
- ADA. Cardiovascular disease and risk management: standards of medical care in diabetes. Diabetes Care 2019;42(suppl 1):S103-S123.

Box 1. Risk-Enhancing Factors for Clinician-Patient Risk Discussion

Family history of premature ASCVD (men < 55 yr; women < 65 yr)

Primary moderate hypercholesterolemia (LDL 160–189 mg/dL [4.1–4.8 mmol/L]; non–HDL 190–219 mg/dL [4.9–5.6 mmol/L])[a]

Metabolic syndrome (increased waist circumference [by ethnically appropriate cut points], elevated TG [> 150 mg/dL], elevated blood pressure, elevated glucose, and low HDL [< 40 mg/dL in men; < 50 mg/dL in women] are factors; a tally of 3 makes the diagnosis)

CKD (eGFR 15–59 mL/min/1.73 m^2 with or without albuminuria; not treated with dialysis or kidney transplantation)

Chronic inflammatory conditions such as psoriasis, rheumatoid arthritis, lupus, or HIV/AIDS

History of premature menopause (before age 40) and history of pregnancy-associated conditions that increase later ASCVD risk, such as preeclampsia

High-risk ethnicity (e.g., South Asian ancestry)

Lipids/biomarkers: associated with increased ASCVD risk

Persistently elevated[a] primary hypertriglyceridemia (≥ 175 mg/dL)

If measured:

1. Elevated high-sensitivity CRP (≥ 2.0 mg/L)
2. Elevated lipoprotein (a) (Lp(a)): A relative indication for its measurement is a family history of premature ASCVD. An Lp(a) ≥ 50 mg/dL or ≥ 125 nmol/L is a risk-enhancing factor, especially at higher Lp(a) concentrations
3. Elevated apoB (≥ 130 mg/dL): A relative indication for its measurement would be TG ≥ 200 mg/dL. A concentration ≥ 130 mg/dL corresponds to an LDL > 160 mg/dL and constitutes a risk-enhancing factor
4. ABI < 0.9

[a]Optimally, three determinations.

ABI = ankle-brachial index; apoB = apolipoprotein B; ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease.

Information from: Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease. JACC 2019;74:e177-232.

addition, proteinuria and low estimated GFR (eGFR less than 60 mL/minute/1.73 m^2) increase the CVD risk in those with diabetes, especially if present in combination.

The American Diabetes Association (ADA) recommends at least moderate-intensity statin therapy in patients with diabetes and additional ASCVD risk factors (ADA 2019). Evidence supports controlling individual CV risk factors to prevent or slow ASCVD in people with diabetes. Furthermore, larger risk reductions can be attained when several CV risk factors are addressed simultaneously. Under the current paradigm of aggressive risk factor modification in patients with diabetes, measures of 10-year CHD risk among U.S. adults with diabetes have improved significantly over the past decade, and ASCVD morbidity and mortality have decreased (ADA 2019).

In the United States, hypertension accounts for more ASCVD deaths than any other modifiable ASCVD risk factor (Arnette 2019). The prevalence among U.S. adults is higher in blacks compared to any other race and increases dramatically with increasing age. A meta-analysis of 61 prospective studies showed an increased ASCVD risk associated with higher systolic (> 20 mm Hg) and diastolic (> 10 mm Hg) blood pressure. In the presence of diabetes, hypertension is very common with prevalence rates of 30% in type 1 diabetes and 60% in type 2 diabetes (Leon 2015). In these patients, hypertension is associated with the development of diabetic nephropathy. The 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease recommends nonpharmacological therapy and blood pressure management in stage 1 hypertension and an estimated 10-year ASCVD risk ≥ 10%.

Cigarette smoking accounts for almost one-third of ASCVD-related deaths in those older than 35 (Benjamin 2019). Risk of CVD increases even in those with secondhand smoke exposure. There is no convincing evidence to date that smoking fewer cigarettes per day reduces the risk of CVD, though in several studies, a dose-response relationship has occurred among current smokers between the number of cigarettes smoked per day and the incidence of CVD (Benjamin 2019). Once patients can stop smoking altogether, their ASCVD risk decreases to that of a nonsmoking individual 10 years after smoking cessation. According to 2015 National Health Interview Survey data, most adult smokers (68.0%) wanted to quit smoking. Among them, 55.4% had tried in the past year, 7.4% had stopped recently, and 57.2% had received health care provider advice to quit. Receiving advice to quit smoking was lower in uninsured smokers and varied by race, with a lower prevalence in Asian (34.2%), American Indian/Alaska Native (38.1%), and Hispanic (42.2%) smokers than in white smokers (60.2%). In 2000–2015, there were significant increases in the prevalence of smokers who had tried to quit in the past year, had stopped recently, had a health professional recommend quitting, or had used cessation

counseling or medication. In 2015, less than 33% of smokers trying to quit used evidence-based therapies; 4.7% used both counseling and medication, 6.8% used counseling, and 29.0% used medication (16.6% nicotine patch, 12.5% gum/lozenges, 2.4% nicotine spray/inhaler, 2.7% bupropion, and 7.9% varenicline) (Benjamin 2019). Therefore, it is imperative to address smoking cessation at every patient encounter and offer evidence-based therapies.

Lifestyle Factors

The increased availability of affordable high-calorie food, decrease in physical activity, and overall sedentary lifestyle have resulted in the epidemic of obesity (Arnett 2019). Adults with a diagnosis of obesity (BMI 30 kg/m^2 or greater) or overweight (BMI 25–29.9 kg/m^2) are at a higher risk of ASCVD, heart failure, and atrial fibrillation than those with a normal BMI (18.5–24.9 kg/m^2). To prevent obesity, caloric intake must be balanced with caloric expenditure. The 2013 guideline for managing overweight and obesity in adults from the AHA, ACC, and The Obesity Society recommends that adults with obesity or overweight participate in comprehensive lifestyle programs for at least 6 months, which include a low-calorie diet (800–1500 kcal/day) and increased physical activity. Existing clinical guidance strongly recommends face-to-face or telephone-delivered weight-loss maintenance programs that provide no less than monthly contact with a trained interventionist to help participants engage in high levels of physical activity (200–300 minutes/week), monitor body weight at least weekly, and consume a reduced-calorie diet. Using FDA-approved pharmacologic therapies and bariatric surgery, adjunctive to complementary lifestyle interventions, may play a role in weight loss for select patients. The 2019 ACC/AHA guideline on the primary prevention of CVD encourages lifestyle interventions for overweight and obesity. Weight-loss interventions should be implemented cautiously and individualized to avoid harmful effects such as loss of lean muscle mass and nutritional deficiencies.

Using nutritious dietary patterns, maintaining a healthy weight, exercising regularly, and avoiding cigarette smoking have an important impact on ASCVD and its risk factors (Box 2). Following this lifestyle pattern can potentially reverse or reduce obesity, high cholesterol, diabetes, and hypertension (Arnett 2019). The literature on CV nutrition is limited by the lack of large-scale prospective randomized trials with ASCVD outcomes. Many observational studies have focused on the association of CVD mortality with dietary patterns, specifically the use of low-calorie sweeteners, high versus low-carbohydrate diets, refined grains, trans fat, saturated fat, sodium, and red meat.

Plant-based and Mediterranean diets include increased consumption of fruits, nuts, vegetables, legumes, and lean vegetables or animal protein (preferably fish). These diets have consistently been associated with a lower risk of all-cause mortality than standard diets in observational studies. The PREDIMED trial, which randomized participants to a Mediterranean diet supplemented with either extra-virgin olive oil or nuts, showed 30% and 28% reductions, respectively, in the combined end point (MI, stroke, or CV mortality). However, this was mainly driven by the reduction in stroke, with no significant improvement for mortality or MI. A comparison of plant and animal protein from the Adventist Health Study-2 cohort also indicated that using meat for protein was associated with a 61% increase in mortality rate, whereas replacing meat with nuts and seeds was associated with a 40% reduction in mortality. Finally, a 2019 study showed that a lower mortality rate was associated with replacing animal protein of different origins with plant protein (Arnett 2019).

Sugar-sweetened and artificially sweetened beverages have been correlated with increased rates of T2DM and ASCVD, with a 20% increase in the frequency of diabetes with one daily serving of these sweetened beverages (Arnett 2019). In large cohort studies, consumption of added sugar at greater than 10% of daily calories has been associated with an increased mortality rate. Adults who are habitually high consumers of sugar-sweetened beverages may use low-calorie sweetened beverages as a replacement strategy in the transition to water. In the REGARDS trial, the Southern dietary pattern substantially increased health risks, including a 56% higher risk of heart disease and a 30% higher risk of stroke. This pattern consisted of more fried food, added fats, organ and processed meats, and sugar-sweetened beverages. Consuming a diet with juices and sweetened beverages, refined grains, potatoes, and sweets resulted in a greater increase in coronary events than the increase with consumption of animal products. Given the additional risk associated with intake of these various food products, clinicians should

Box 2. Nutrition and Diet Recommendations from the 2019 ACC/AHA Guideline on the Primary Prevention of CVD

- A diet emphasizing intake of vegetables, fruits, legumes, nuts, whole grains, and fish is recommended to decrease ASCVD risk factors
- Replacement of saturated fat with dietary monounsaturated and polyunsaturated fats can reduce ASCVD risk
- A diet containing reduced amounts of cholesterol and sodium can decrease ASCVD risk
- As part of a healthy diet, it is reasonable to minimize the intake of processed meats, refined carbohydrates, and sweetened beverages to reduce ASCVD risk
- As part of a healthy diet, intake of trans fats should be avoided to reduce ASCVD risk

CVD = cardiovascular disease.

Information from: Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease. JACC 2019;74:e177-232.

counsel individuals about the associated harm and advise them to avoid these foods, when possible.

Furthermore, longstanding dietary patterns that focus on low intake of carbohydrates and high intake of animal fat and protein are associated with increased cardiac and noncardiac mortality rates. In a meta-analysis, low-carbohydrate diets were associated with a 31% higher risk of all-cause death, with an increased cardiac mortality rate (Beauchamp 2010). Population data from the ARIC study showed an 18% increase in mortality rate with low-carbohydrate diets using animal-derived protein and fat sources (e.g., lamb, beef, pork, chicken), but plant sources (e.g., vegetables, nuts, peanut butter, whole-grain breads) were associated with a lower mortality rate. In addition, the ARIC investigators noted a 23% increase in mortality rate associated with high-carbohydrate diets, with optimal carbohydrate intake of 50%–55%.

The take-home message that clinicians should relay to patients with high CV risk is to consume a healthy diet that highlights intake of vegetables, fruits, nuts, whole grains, lean vegetable or animal protein, and fish. Emphasize minimization of trans fats, red meat, and processed red meats; refined carbohydrates; and sweetened beverages. For adults with overweight and obesity, counseling and caloric restriction are recommended for achieving and maintaining weight loss (Arnett 2019).

There is a consistent inverse dose-response relationship between the amount of moderate to vigorous physical activity and incident ASCVD events and death (Wahid 2016) (Box 3). Clinicians should encourage all adults to engage in at least 150 minutes/week of accumulated moderate-intensity aerobic physical activity or 75 minutes/week of vigorous-intensity aerobic physical activity (or an equivalent combination of moderate and vigorous activity) to lower ASCVD risk. Shorter durations of exercise are perhaps as beneficial as longer ones (e.g., bouts of 10 minutes or more); hence, physical activity counseling should highlight the total accumulated amount. Additional reductions in ASCVD risk occur in those achieving a higher amount of aerobic physical activity (more than 300 minutes/week of moderate-intensity aerobic physical activity or 150 minutes/week of vigorous-intensity aerobic physical activity). Caution should be taken with recommending very high levels of physical activity because there is a diminishing additive benefit. Although there does not seem to be a lower limit on the quantity of moderate to vigorous physical activity at which benefits for ASCVD risk begin to accrue, all efforts should be made to promote achievement of the minimum recommended amount of physical activity by all adults. However, for individuals unable to achieve the minimum recommendation, encouraging at least some moderate to vigorous physical activity among those who are inactive (i.e., no moderate to vigorous physical activity), or increasing the amount in those who are insufficiently active, will still likely reduce ASCVD risk (Arnett 2019).

The Look AHEAD study was a randomized controlled trial (RCT) comparing an intensive lifestyle intervention (ILI) with a diabetes support and education (DSE) in overweight patients and patients with obesity and T2DM to track the incidence of CVD over time (Pi-Sunyer 2014). The ILI group focused on behavioral, nutrition, and activity themes, whereas the DSE group was invited to three group sessions in the first year that reviewed general information on diabetes management. A study goal was set for reducing the baseline body weight in the ILI group by 7.0%, with each individual's goal set at 10%. The Look AHEAD calorie goals were 1200–1500 kcal/day with 40–50 g of fat for those with an initial weight of 113 kg (250 lb). The diet goals included consuming less than 30% of calories from fat. The physical activity goal was 175 minutes/week of unsupervised exercise. Most subjects walked, but some jogged, swam, and biked. Some resistance exercise was encouraged. The trial was terminated after a median follow-up of 9.6 years. Although there was a differential effect on weight loss and fitness between the two groups, there was no effect on CV outcomes. There were many other health benefits of ILI, including improved biomarkers of glucose and lipid control, less sleep apnea, lower liver fat, less depression, improved insulin sensitivity, less urinary incontinence, less kidney disease, reduction in diabetes medications, maintenance of physical mobility, improved quality of life, and lower costs. Despite no difference in CVD event rates, the ILI group had many improvements to risk factors.

Box 3. Exercise and Physical Activity Recommendations from the 2019 ACC/AHA Guideline on the Primary Prevention of CVD

- Adults should routinely be counseled in health care visits to optimize a physically active lifestyle
- Adults should engage in at least 150 min/wk of accumulated moderate-intensity or 75 minutes/week of vigorous-intensity aerobic physical activity (or an equivalent combination of moderate and vigorous activity) to reduce ASCVD risk
- For adults unable to meet the minimum physical activity recommendations (at least 150 min/wk of accumulated moderate-intensity or 75 min/wk of vigorous-intensity aerobic physical activity), engaging in some moderate- or vigorous-intensity physical activity, even if less than this recommended amount, can reduce ASCVD risk
- Decreasing sedentary behavior in adults may be reasonable to reduce ASCVD risk

Information from: Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease. JACC 2019;74:e177-232.

CVD Risk Assessment

After obtaining a lipid profile and blood pressure reading and identifying all ASCVD risk factors, ASCVD risk can be estimated. The ASCVD risk prediction equations combine traditional risk factors with additional major risk factors to most

accurately estimate an individual's ASCVD risk (Benjamin 2019). The Framingham Heart Study developed the first ASCVD risk prediction equations. These equations were used to create the first risk score to be adopted as part of a national guideline, the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Grundy 2019). The 2013 ACC/AHA cholesterol guidelines further improved on these risk prediction equations. This race- and sex-specific pooled cohort equation (PCE) can estimate an asymptomatic individual's 10-year ASCVD risk and determine the ASCVD risk reduction of preventive interventions, as well as the patient's absolute risk. The PCE risk tool allows the clinician to maximize anticipated benefit and minimize potential harm from overtreatment.

Individuals at highest risk of CVD are those with clinical ASCVD. In assessing an individual's risk of an initial ASCVD event, the three main risk categories are as follows: those with severe hypercholesterolemia (LDL greater than 190 mg/dL), adults with diabetes, and adults age 40–75 with greater than a 20% ASCVD risk score (Grundy 2019). For individuals age 40–75 with or without diabetes, the 10-year ASCVD risk estimate is used to guide decision-making for many preventive interventions, including lipid and blood pressure management. The patient's ASCVD risk score should be introduced at the start of a patient-clinician discussion to promote risk-reducing strategies, including initiation of pharmacotherapy to control individual risk factors.

Several risk assessment tools are available to estimate ASCVD risk in adults age 20–79 without established clinical ASCVD. These tools are available online and by mobile applications, which can be downloaded for easy and quick access during patient encounters. The ACC/AHA Risk Estimator app was developed to help clinicians and patients implement shared decision-making (Martin 2015). The app is widely available and easily accessed through computers, tablets, or smartphones. Increased accessibility compared with previous risk calculators was a critical step in facilitating use by patients and care providers. The app was also designed to be integrated into the electronic medical record for automatic calculation and display. The app not only facilitates estimation of 10-year ASCVD risk for those age 40–79 years, but also allows for lifetime risk estimation for those age 20-39. Using the app will facilitate linkage to lifestyle and obesity/overweight guideline recommendations because these are highlighted in the app. For example, the app's patient-oriented weight management section advises that "losing just 3–5% of body weight can improve blood pressure and cholesterol levels and reduce the risk for cardiovascular disease and diabetes."

All risk estimation tools have limitations. Therefore, population-based risk scores should be interpreted with caution, and patient-specific factors should not be overlooked. The PCE over-or underestimates the ASCVD risk for certain subgroups. Thus, after calculating the PCE, it is reasonable to use additional risk-enhancing factors to guide decisions about preventive interventions for patients at borderline or intermediate risk.

Risk Calculators

The Framingham Risk Score, originally published in 1998, was modified in 2002 by Adult Treatment Panel III (ATP III) to be used in the National Cholesterol Education Program (NCEP) ATP III guidelines (NCEP 2002). At this time, diabetes was removed from the equation because it was considered a CHD risk equivalent. This was the primary risk score used in the United States in 2002–2013. Guidelines recommended using the Framingham Risk Score in individuals with more than two CHD risk factors and without either ASCVD or a CHD risk equivalent. Those with a 10-year risk score of greater than 20% for death or MI are considered at high risk of CHD. Most participants in the Framingham study were white Americans, and this tool is most useful for risk assessment in white Americans and Asian Indians (Garg 2017). The Framingham Risk Score may overestimate the risk of CV events in Europeans and underestimate the CVD risk in Hispanic Americans and Asian Americans. This tool also only focuses on CHD and does not include stroke.

In 2007 and 2008, the Reynolds Risk Score was developed for women and men, respectively. This risk score adds the variables of family history and high-sensitivity CRP to its risk equation. Compared with the Framingham Risk Score, which tended to overestimate the CV risk in women, the Reynolds Risk Score better predicts the CV risk in this population (Cook 2012). Although the Reynolds Risk Score is not included in any guideline, it can further assess individual risk and perhaps educate specific individuals.

The 2013 ACC/AHA ASCVD risk calculator was the first model to include data from both a white population and an African American population (Table 1). This model is unique in including the risk of nonfatal stroke in its ASCVD risk estimation. The calculator tends to overestimate the 10-year risk of ASCVD in Mexican Americans and East-Asian Americans but underestimate the risk in Native Americans, South-Asian Americans, and Hispanics from Puerto Rico. Another potential limitation of this calculator is that it does not assess for a family history of premature CVD, which may underestimate the risk in patients with a significant family history of CV events. In addition, the calculator includes diabetes mellitus (DM) only as a yes or no question. Other factors that may affect CV risk in patients with DM include duration of DM, degree of severity in glycemic control, presence of enhancing risk factors, and whether the patient has T1DM or T2DM. In this 2013 ACC/AHA model, a 10-year risk of ASCVD is categorized as low risk (less than 5%), borderline risk (5% to less than 7.5%), intermediate risk (7.5% to less than 20%), and high risk (20% or greater).

Special Populations

For younger adults age 20–39 or individuals at low 10-year risk (less than 7.5%), lifetime or 30-year risk scores may better inform patient treatment decisions (Berry 2009). Knowing that a patient's lifetime ASCVD risk is greater than 50% may be useful for clinicians in encouraging lifestyle modifications.

Table 1. CV Risk Prediction Equations

Risk Calculator	Guideline	Outcome/Population Assessed
Framingham risk calculator	NCEP – ATP III and NLA	10-yr risk of MI or death Population: White American males
ASCVD risk calculator	ACC/AHA	10-yr risk and lifetime ASCVD risk (coronary death or nonfatal MI, or fatal or nonfatal stroke) Population: Inclusion of minorities
Reynolds Risk Score	N/A	10-, 20-, and 30-yr risk of MI, stroke, or revascularization Population: Inclusion of women

CV = cardiovascular; MI = myocardial infarction; N/A = not applicable; NLA = National Lipid Association.

Information from: Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease. JACC 2019;74:e177-232.

Although the incidence of CHD in individuals younger than 40 is low, those with a positive premature family history of CVD in a first-degree relative may require ASCVD risk assessment. In these younger individuals, simply rounding the person's age up to the minimum age required for use of the PCE may be done in practice to estimate the 10-year ASCVD risk, but the accuracy of this method is uncertain, and this practice is not endorsed in the current guidelines.

For individuals with an intermediate or borderline predicted 10-year ASCVD risk, coronary artery calcium measurement can help refine the risk assessment for preventive interventions (e.g., statin therapy). In these groups, coronary artery calcium measurement can reclassify risk upward (particularly if the coronary artery calcium score is 100 Agatston units or greater or 75th age/sex/race percentile or greater) or downward (if the coronary artery calcium score is zero) in many individuals. Sufficient evidence suggests that borderline- or intermediate-risk patients with elevated coronary artery calcium scores will have event rates that clearly exceed the benefit thresholds (e.g., 7.5% or more in 10 years) and that those with coronary artery calcium scores of zero will have event rates of less than 7.5%. This can help guide shared decision-making about statins. In observational data, the severity of coronary artery calcium is correlated with the likelihood of ASCVD risk reduction with statin therapy. Coronary artery calcium scoring has better discrimination and risk reclassification than other subclinical imaging markers or biomarkers. In the MESA trial, the coronary artery calcium score was strongly associated with the 10-year ASCVD risk in a graded manner across age, sex, and racial groups, independent of traditional risk factors. Coronary artery calcium may even refine ASCVD risk estimates among lower-risk women (less than a 7.5% 10-year risk), younger adults (younger than 45), and older adults (75 and older), but more data are needed to support its use in these subgroups. A coronary artery calcium score of zero identifies individuals at lower risk of ASCVD events and death over 10 years, who appear to derive little or no benefit from statins for ASCVD risk reduction. Thus, a coronary artery calcium score of zero can reclassify a patient into a lower-risk group for which preventive interventions (e.g., statins) can be postponed. Of note, the absence of coronary artery calcium does not rule out noncalcified plaque, and clinical judgment should be used when assessing a patient's overall ASCVD risk. Coronary artery calcium may also be considered in refining the risk of ASCVD in select low-risk adults (less than a 5% 10-year risk), such as those with a strong family history of premature CHD. Coronary artery calcium measurement is not intended as a screening test for all but may be used as a decision aid in select adults to facilitate the clinician-patient risk discussion.

Use of 10-year or lifetime risk estimates alone is not recommended in patients with familial hypercholesterolemia because this may underestimate the CVD risk (Grundy 2018). This population is typically treated with high-intensity statin therapy and additional LDL-lowering therapy as clinically appropriate. Risk estimators are not commonly used in young patients with T1DM, but by age 30, many will have had T1DM for 20 years or more. This places these patients at high risk of CVD, and risk factors should aggressively be managed in this population. Similarly, patients with T2DM who are younger than 40 are at high risk of CVD after 10 years or more of diabetes duration, and their risk factors necessitate aggressive management. In patients with diabetes younger than 40 with additional ASCVD risk factors, the patient and provider should consider using at least a moderate-intensity statin in addition to lifestyle therapy.

Existing evidence supporting statins for the primary prevention of CVD in those 65 and older does not include people older than 74, especially those older than 84 (Teng 2015; Savarese 2013; Konrat 2012). Similarly, patients older than

74 with T2DM were not included in trials evaluating the use and benefit of statins for primary prevention. A retrospective cohort study in Spain in 2006–2015 assessed whether statins were associated with a reduced incidence of ASCVD and mortality in older people initially free of CVD, by T2DM and age (Ramos 2018). This study found that in participants older than 74 without T2DM, statin treatment did not reduce ASCVD or all-cause mortality, even when the incidence of ASCVD was statistically significantly higher than the risk thresholds proposed for statin use. In patients with diabetes, statin use was statistically significantly associated with reductions in the incidence of ASCVD and all-cause mortality. This effect decreased after age 85 and disappeared in nonagenarians (90–99 years old). In real-world practice, a patient-clinician discussion should include the risk-benefit of primary preventive management, including lifestyle and medications.

Implications of CVD Risk Assessment

Identifying individual risk factors, applying ASCVD assessment tools, and initiating evidence-based pharmacotherapy permit clinicians to approach primary prevention effectively in high ASCVD risk individuals. Individuals at highest risk are those with an ASCVD risk greater than 20%, and those at lowest risk are those with ASCVD risk less than 5%. Even for those at lower ASCVD risk, clinicians should use clinical judgment and other tools to sufficiently assess ASCVD risk (e.g., assess family history, high-sensitivity CRP, coronary artery calcium). Primary prevention aims to prevent the onset of CVD by targeting the pathophysiology and risk factors. After a comprehensive CVD risk assessment, an in-depth discussion should occur. Clinicians should emphasize the importance of lifestyle modifications, including healthy eating and an adequate amount of physical activity, and apply guideline-recommended preventive medications, including statin therapy, CVD-reducing diabetes medications, and evidence-based hypertension and smoking cessation pharmacotherapy. For example, in an African American patient with an ASCVD risk greater than 20%, not receiving statin therapy, with an A1C greater than 10%, the first step would be to optimize control of underlying risk factors.

Aspirin for Primary Prevention of CVD

From 1897, when aspirin was first produced, to 1985, when aspirin was FDA approved for the secondary prevention of CVD, its benefit in reducing CVD morbidity and mortality in patients with occlusive CVD events, including subsequent CHD, has consistently been proven to outweigh the risks of major bleeding with long-term use. However, aspirin's role in primary prevention among apparently healthy people is less clear and necessitates meticulous evaluation and mutual decision-making to determine a realistic benefit-harm ratio. Because of the lack of a clear benefit-harm ratio from aspirin use for primary prevention, a consensus regarding its use also varies. Nonetheless, aspirin has been widely studied and used as one of the cornerstone pharmacologic interventions for the primary prevention of CVD. At low doses, aspirin exerts antiplatelet effects through selective inhibition of cyclooxygenase-1 (COX-1), which is required to produce thromboxane A_2, a powerful promoter of platelet aggregation. Inhibition of platelet aggregation prevents thrombus formation and progression of atherosclerosis, thereby reducing the risk of ASCVD. At higher doses, aspirin also exerts COX-2 inhibition, which may lead to adverse effects on blood pressure or renal function (Miner 2007).

Long-term aspirin therapy at lower doses of 75–100 mg daily has been associated with reduced CV events. Subgroup analyses from the 2002 Antithrombotic Trialists' Collaboration meta-analysis suggested that aspirin is as effective for preventing CVD at doses of 75–325 mg daily (ATTC 2002). Hence, for primary prevention, aspirin doses of 100 mg/day or less should be used to minimize the risk of bleeding, in congruence with the routine use of aspirin 81-mg dose in clinical practice.

Potential Risks of Long-term Use

Bleeding risk

The adverse effect of most concern with aspirin is major bleeding, defined as bleeding that requires hospitalization with or without transfusion. The most common type of aspirin-associated bleeding is GI bleeding, which is rarely fatal. Inhibition of COX-1 increases the risk of upper GI bleeding; however, this risk is dose-dependent with aspirin therapy and can be minimized with the use of lower doses. The incidence of major bleeding is likely somewhat higher in the general population than in participants of randomized trials (Selak 2018). The U.S. Preventive Services Task Force (USPSTF) report on using aspirin for the primary prevention of CVD and cancer suggested that with increasing age, male sex, and diabetes, there is an increased risk of major bleeding with aspirin therapy (Whitlock 2016). According to the 2008 American College of Cardiology Foundation/American College of Gastroenterology/AHA guidelines, risk factors for GI toxicity from NSAIDs such as aspirin include a history of ulcer disease or ulcer complication; concurrent use of antiplatelet, anticoagulant, or glucocorticoid therapy; age 60 and older; and dyspepsia or gastroesophageal reflux disease symptoms. In patients who have an episode of major bleeding while taking aspirin for primary prevention, it should be determined whether the risk of recurrent bleeding outweighs the benefits of long-term use.

Aspirin Resistance

Aspirin resistance is a laboratory phenomenon that indicates the persistent presence of platelet COX-1 activity after aspirin treatment. Aspirin resistance is a controversial issue that lacks consensus and varies widely. Potential causes of aspirin resistance include genetic variability, obesity, advanced atherosclerosis, polymorphisms in the COX-1

gene, concurrent use of NSAIDs or proton pump inhibitors, increased platelet turnover, and use of enteric-coated formulations (Grosser 2013; Peace 2010). While evaluating the implications of aspirin resistance in clinical practice, remember that aspirin resistance identified in a laboratory may not translate to clinical resistance resulting in aspirin treatment failure. Current laboratory tests are not standardized or validated to predict the risk of future CVD events. Therefore, it is not recommended to routinely measure platelet function to identify potential evidence of aspirin resistance (Rocca 2012). Rather, patients who have had recurrence of CVD while taking aspirin should be reassessed for another underlying cause, including poor adherence and concurrent use of interacting medications. If resistance is truly the cause of CVD recurrence, an alternative to aspirin therapy should be considered.

Enteric-Coated Formulations

Whether enteric-coated formulations of aspirin should be used is one of the many uncertainties surrounding the long-term use of aspirin therapy. Indeed, the widely marketed theory about reduced bleeding risk with enteric-coated aspirin formulations has not been justified in the literature. Studies have shown that enteric-coated aspirin diminishes the risk of "topical" gastroduodenal epithelial injury but that this does not translate to a clinically relevant reduction in GI bleeding (McNeil 2018; Kelly 1996; Petroski 1993; Hawthorne 1991; Silvoso 1979). In fact, the USPSTF acknowledges that data analyses are limited to support the use of enteric-coated formulations of aspirin and states that "there is no evidence that enteric-coated or buffered formulations of aspirin reduce the risk for serious GI bleeding" (Bibbins-Domingo 2016). Furthermore, enteric coating has been identified as one of the potential causes of aspirin "resistance" or treatment failure. Enteric coating resulting in delayed absorption of aspirin results in an insufficient antithrombotic effect, certainly in the acute setting and possibly in chronic setting as well (Grosser 2013; Hennekens 2012; Peace 2010; Cox 2006; Ridker 1996). Given the lack of apparent gastroprotective effects and the possible increased potential for treatment failure with enteric-coated aspirin, clinicians should consider recommending non–enteric-coated aspirin.

Sensitivity

Patients who have sensitivity to aspirin products typically present with respiratory symptoms, including rhinitis and/or asthma. Urticaria or angioedema is less common, with an incidence of 7–20 per 10,000 individuals treated (Jenkins 2004; Stevenson 2004; Grattan 2003). Patients with aspirin sensitivity who are indicated for long-term aspirin use may be changed to an alternative antithrombotic agent or may undergo the aspirin desensitization process conducted by an allergist, when appropriate.

Colorectal Cancer

According to several meta-analyses, some evidence suggests a reduced incidence of colon cancer and mortality with aspirin over a 20-year follow-up , however, the data supporting this evidence was considered to be low-quality. Regarding prevention, evidence suggests that the benefit of aspirin is more apparent after only 10 years of follow-up (Cook 2013; Rothwell 2010; Flossmann 2007; Thrombosis prevention trial 1998; Farrell 1991; SALT 1991; Peto 1988). Evidence suggesting that long-term aspirin use reduces colorectal cancer mortality stems from post hoc analyses that have not been confirmed in appropriately designed RCTs and are not consistent with results from shorter follow-up trials (Rothwell 2010). Nor have more recent findings from two trials, ASCEND (A Study of Cardiovascular Events in Diabetes) and ARRIVE (The Aspirin to Reduce Risk of Initial Vascular Events), shown any significant difference in the incidence of GI tract cancer. However, of importance, the incidence of GI cancer was a secondary outcome in both of these trials. In the ASCEND trial with a mean follow-up of 7.4 years, the aspirin and placebo groups did not differ significantly in the incidence of GI tract cancer (2% in both groups). In the ARRIVE trial with a mean follow-up of 5 years, the rate of colon cancer was 0.22% and 0.10% in the aspirin and placebo groups, respectively. In the ASPREE trial over a mean follow-up of 5 years, the number of colorectal cancer deaths was higher in the aspirin group (0.8 vs. 0.5 deaths per 1000 person-years; HR 1.77; 95% CI, 1.02–3.06), but the authors acknowledged that in the context of several end points, the clinical importance of the between-group differences in death from any cause and cancer-related death is uncertain.

LANDMARK TRIALS FOR ASPIRIN USE FOR PRIMARY PREVENTION OF CVD

To implement evidence-based guideline recommendations in clinical practice, clinicians should evaluate practice-changing primary literature (Table 2). Starting in 1988, clinical trials sought to evaluate the potential benefit of aspirin for the primary prevention of CVD (Miedema 2016).

Several meta-analyses have collectively evaluated the outcomes of the major landmark trials published over the past 3 decades (1988–2018) to identify aspirin's benefits in primary prevention. The collated evidence from these trials, with follow-ups of 3.8–10 years, showed that aspirin therapy results in (1) none to a very small reduction in all-cause or CVD mortality (high-quality evidence), (2) a reduction in nonfatal MI over 10 years (moderate-quality evidence), and (3) none to a very small reduction in nonfatal stroke over 10 years (moderate-quality evidence). Table 3 lists the aggregate results for these specific outcomes. For comparative logistics and results of individual trials, see Table 2.

In general, the outcomes of major primary prevention studies include nonfatal MI, nonfatal stroke, and major GI bleed.

Patient Care Scenario

A.E., a 57-year-old African American woman, presents to the clinic for a diabetes follow-up. Her medical history is significant for T2DM (diagnosed 10 years ago), hypertension, hyperlipidemia, panic disorder, and anxiety. Her current medications include metformin 500 mg twice daily, insulin Basaglar 40 units daily, glipizide extended release 10 mg daily, losartan 100 mg daily, hydrochlorothiazide 25 mg daily, atorvastatin 40 mg daily, and bupropion extended release 150 mg daily. Her recent laboratory values are as follows: A1C 11.1%, TC 200 mg/dL, LDL 119 mg/dL, HDL 40 mg/dL, TG 206 mg/dL, SCr 0.73 mg/dL, and eGFR greater than 90 mL/minute/m^2; her comprehensive metabolic panel (CMP) and CBC are within normal limits. Her blood pressure in the office today is 136/70 mm Hg and heart rate is 84 beats/minute (blood pressure last visit 138/78 mm Hg, heart rate 79 beats/minute). She did not bring her glucometer today for evaluation; however, she states that her blood glucose readings are in the 200-mg/dL range (including fasting blood glucose and postprandial plasma glucose). Her blood glucose in the office was 198 mg/dL. She has no history of smoking. She is reluctant to take several medications if not absolutely necessary, despite previous discussions regarding CVD risk. Assess A.E.'s 10-year CVD risk and recommend primary preventive strategies appropriate to consider for her.

ANSWER

Risk Assessment:

Assess Modifiable and Nonmodifiable CVD Risk Factors:

A.E. is of African American ethnicity, and ASCVD risk tends to be greater in non-Hispanic African American females. She is older than 55, which also increases CVD risk. Her comorbidities include T2DM, which is currently poorly managed on the basis of A1C and self-monitored blood glucose values (diagnosed more than 10 years ago). Regarding hypertension, A.E. is currently near the goal of less than 130/80 mm Hg according to ADA recommendations. Regarding hyperlipidemia, she currently takes appropriate statin intensity on the basis of her 10-year ASCVD risk score.

Assess Bleeding Risk:

A.E. has no history of peptic ulcer disease, GI bleed, concurrent use of medications that increase bleeding risk, anemia, or renal disease and is not of advanced age. Her bleeding risk would be considered minimal, given the earlier information.

Calculate ASCVD 10-Year Risk Score:

A.E.'s 10-year ASCVD risk score is 19.7%, placing her at intermediate risk (7.5% to less than 20%). However, she is toward the upper limit of the range, closer to the high-risk category (greater than 20%).

Recommendations:

Regarding CVD risk factor optimization for T2DM, consider initiating a glucagon-like peptide 1 agonist or a sodium-glucose transporter protein-2 inhibitor according to the ADA guidelines. For hypertension, consider initiating calcium channel blocker therapy according to the ACC/AHA hypertension guidelines. For lifestyle modifications, educate the patient on dietary and physical activity recommendations. Regarding aspirin therapy for primary prevention, the ACC/AHA and ADA 2019 guidelines recommend aspirin for primary prevention in patients at increased risk of CVD, defined as a 10-year risk greater than 10%. Each guideline also recommends careful evaluation of the patient's bleeding risk associated with aspirin use. The recent trials ARRIVE and ASCEND showed an increased risk of major bleeding in patients with demographics similar to A.E.'s (age range, diabetes, 10-year CVD risk score).

1. Benjamin EJ, Muntner P, Alonso A, et al. Heart disease and stroke statistics-2019 update. Circulation 2019;139:e56-528.
2. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease. Circulation 2019;140:e596-e650.
3. American Diabetes Association (ADA). Cardiovascular Disease and Risk Management. Diabetes Care 2019;42:103-23.
4. ASCEND Study Collaborative Group. Effects of aspirin for primary prevention in persons with diabetes mellitus. N Engl J Med 2018;379:1529.
5. Gaziano JM, Brotons C, Coppolecchia R, et al. Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial. Lancet 2018;392:1036.

While evaluating the benefits of routine aspirin use in primary prevention, it is also important to evaluate the adverse effect profile of aspirin. The rarest but most serious site of aspirin-associated major bleeding is intracranial bleeding. In a 2016 meta-analysis, low-dose aspirin use (100 mg daily or less) was associated with a significantly increased risk of major GI bleeding of 58% (OR 1.58; 95% CI, 1.29–1.95) and nonsignificant increase in hemorrhagic stroke of 27% (OR 1.27; 95% CI, 0.96–1.68). This risk was somewhat higher when all doses of aspirin were considered (Whitlock 2016). Aspirin causes a significant 50% increase in major nonfatal extracranial bleeding over 10 years. In the ASCEND trial, major bleeding occurred in 4.1% in the aspirin group compared with 3.2% in the placebo group (RR 1.29; 95% CI, 1.09–1.52).

Table 2. Summary of Outcomes of the Major Primary Prevention Studies of ASA

Study Study Logistics Year Study Design ASA Dose/day Duration	Study Population Country Total n No. of Women Age Range	Annual Events (%/year), ASA vs. Control Rate Ratio [CI] Nonfatal MI	Nonfatal Ischemic Stroke	Major GI Bleed
BDT 1988 RCT, DB, PC 500 mg 5.8 yr	UK 5139 0 60–79	104 (0.54%) vs. 90 (0.47%) 1.15 [0.73–1.79]	61 (0.30%) vs. 27 (0.26%) 1.13 [0.72–1.77]	20 (0.10%) vs. 20 (0.10%) 1.00 [0.37–2.70]
PHS 1989 R, OL 325 mg 5 yr	United States 22,071 0 40–84	**129 (0.24%) vs. 213 (0.39%)** **0.61 [0.46–0.81]**	110 (0.20%) vs. 92 (0.17%) 1.20 [0.91–1.59]	48 (0.09%) vs. 30 (0.05%) 1.59 [0.89–2.84]
TPT 1998 2 x 2 factorial, DB, PC 75 mg 6.8 yr	UK 5085 0 45–69	**96 (0.58%) vs. 37 (0.83%)** **0.70 [0.50–0.98]**	18 (0.21%) vs. 25 (0.29%) 0.64 [0.34–1.20]	20 (0.12%) vs. 13 (0.08%) 1.54 [0.63–3.77]
HOT 1998 2 x 2 factorial, DB, PC 75 mg 3.8 yr	Multi-national 18,790 8883 50–80	**68 (0.19%) vs. 114 (0.32%)** **0.60 [0.41–0.88]**	146 (0.41%) vs. 148 (0.42%) 0.98% (0.78–1.24)	**114 (0.32%) vs. 62 (0.18%)** **1.81 [1.22–2.66]**
PPP 2001 R, OL, 2 x 2 factorial 100 mg 3.6 yr	Italy 4495 2583 50–80	15 (0.18%) vs. 21 (0.25%) 0.72 (0.31–1.71)	15 (0.19%) vs. 18 (0.23%) 0.84 [0.42–1.07]	6 (0.07%) vs. 3 (0.04%) 1.98 [0.36–11.02]
WHS 2005 R, DB, PC 100 mg every other day 10.1 yr	United States 39,876 39,876 > 45	184 (0.09%) vs. 181 (0.09%) 1.02 [0.78–1.33]	**198 (0.10%) vs. 244 (0.12%)** **0.81 [0.85–0.97]**	127 (0.06%) vs. 91 (0.05%) 1.39 [0.98–1.97]
POPADAD 2008 R, DB, PC 100 mg 6.7 yr	Scotland 1276 713 > 40	55 (1.29%) vs. 56 (1.31%) 0.98 [0.69–1.40]	29 (0.68%) vs. 41 (0.96%) 0.71 [0.45–1.12]	28 (0.66%) vs. 31 (0.73%) 0.89 [0.53–1.50]
JPAD 2008 R, OL 81–100 mg 4.4 yr	Japan 2539 1153 30–85	12 (0.22%) vs. 9 (0.16%) 1.35 [0.57–3.19]	22 (0.49%) vs. 24 (0.48%) 1.01 [0.60–1.72]	10 (0.18%) vs. 7 (0.13%) 1.45 [0.55–3.81]
AAA 2010 R, DB 100 mg 8.2 yr	Scotland 3350 72 50–80	62 (0.45%) vs. 68 (0.50%) 0.91 [0.65–1.28]	37 (0.27%) vs. 38 (0.28%) 0.97 [0.62–1.52]	9 (0.07%) vs. 8 (0.06%) 1.13 [0.43–2.92]

(*Continued*)

Table 2. Summary of Outcomes of the Major Primary Prevention Studies of ASA (*Continued*)

Study Study Logistics Year Study Design ASA Dose/day Duration	Study Population Country Total n No. of Women Age Range	Annual Events (%/year), ASA vs. Control Rate Ratio [CI] Nonfatal MI	Nonfatal Ischemic Stroke	Major GI Bleed
JPPP 2013 R, OL, PC 100 mg 6.5 yr	Japan 14,464 8341 60–85	**20 (0.06%) vs. 38 (0.10%)** **0.53 [0.31–0.91]**	117 (0.30%) vs. 114 (0.30%) 1.00 [0.77–1.31]	**103 (0.28%) vs. 31 (0.08%)** **3.33 [2.22–4.98]**
ARRIVE 2018 R, DB, PC 100 mg 5 yr	Multi-nation 12,546 3708 Men > 55 with 2-4 CVD risk factors Women > 60 + > 3 risk factors	88 (0.28%) vs. 98 (0.31%) 0.90 [0.67–1.20]	75 (0.24%) vs. 67 (0.21%) 1.12 [0.80–1.55][a]	**61 (0.19%) vs. 29 (0.09%)** **2.11 [1.35–3.28]**
ASCEND 2018 R, DB, PC 100 mg 7.4 yr	UK 15,480 5796 > 40 yr with diabetes but without CVD before enrollment	191 (0.33%) vs. 195 (0.34%) 0.98 [0.80–1.19]	227 (0.40%) vs. 244 (0.43%) 0.93 [0.77–1.12][b]	**137 (0.24%) vs. 101 (0.18%)** **1.36 [1.05–1.75]**
ASPREE 2018 R, DB, PC, multicenter 100 mg 4.7 yr	US; Australia 19,114 10,704 ≥ 70 yr; ≥ 65 yr in US & black or Hispanic w/o CVD, dementia, or disability	171 (0.40%) vs. 184 (0.43%) 0.93 [0.76–1.15]	148 (0.35%) vs. 167 (0.39%) 0.89 [0.71–1.11]	**361 (0.86%) vs. 265 (0.62%)** **1.38 [1.18–1.62]**[c]

Bolding = significant outcomes.

[a]Fatal and nonfatal.

[b]Hemorrhagic and ischemic.

[c]Major hemorrhage (hemorrhagic stroke, symptomatic intracerebral hemorrhage, or extracranial hemorrhage leading to transfusion, hospitalization, surgery, or death.

ASA = aspirin; DB = double-blind; NNT = number needed to treat; OL = open-label; PC = placebo-controlled; RCT = randomized controlled trial.

Information from: Peto R, Gray R, Collins R, et al. Randomised trial of prophylactic daily aspirin in British male doctors. Br Med J (Clin Res Ed) 1998;296:313-6; Steering Committee of the Physicians' Health Study Research Group. Final report on the aspirin component of the ongoing Physicians' Health Study. N Engl J Med 1989;321:129-35; Thrombosis prevention trial: randomised trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk. Lancet 1998;351:233-41; Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. Lancet 1998;35:1755-62; De Gaetano G, Collaborative Group of the Primary Prevention Project. Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomised trial in general practice. Collaborative Group of the Primary Prevention Project. Lancet 2001;357:89-95; Ridker PM, Cook NR, Lee IM, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. N Engl J Med 2005;352:1293-304; Belch J, MacCuish A, Campbell I, et al. The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo

Table 2. Summary of Outcomes of the Major Primary Prevention Studies of ASA (*Continued*)

controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. BMJ 2009; 337:a1840; Ogawa H, Nakayama M, Morimoto T, et al. Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial. JAMA 2008;300:2134-41; Fowkes FG, Price JF, Stewart MC, et al. Aspirin for prevention of cardiovascular events in a general population screened for a low ankle brachial index: a randomized controlled trial. JAMA 2010;303:841-8; Ikeda Y, Shimada K, Teramoto T, et al. Low-dose aspirin for primary prevention of cardiovascular events in Japanese patients 60 years or older with atherosclerotic risk factors: a randomized clinical trial. JAMA 2014;312:2510-20; Gaziano JM, Brotons C, Coppolecchia R, et al. Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial. Lancet 2018;392:1036; ASCEND Study Collaborative Group. Effects of aspirin for primary prevention in persons with diabetes mellitus. N Engl J Med 2018;379:1529; McNeil JJ, Nelson MR, Woods RL, et al. Effect of aspirin on all-cause mortality in the healthy elderly. N Engl J Med 2018;379:1519.

Table 3. ASA (75–100 mg) vs. Placebo in the Primary Prevention of CVD

Outcomes	No. of Patients	Certainty of Evidence	Relative Effect (RR - 95% CI)	Absolute Anticipated Risks over 10 Yr (P) Risk with placebo (A) Risk with ASA[a]	
Total mortality	161,660	Moderate	0.97 (0.93–1.02)	P - 83 per 1000[b] A - 2 fewer per 1000	
MI (nonfatal)	142,566	High	0.83 (0.76–0.90)	Low risk[c]	P - 27 per 1000[d] A - 5 fewer per 1000
				Moderate risk	P - 83 per 1000 A - 14 fewer per 1000
				High risk	P - 136 per 1000 A - 23 fewer per 1000
Stroke (nonfatal ischemic and hemorrhagic strokes)	127,433	Moderate	0.95 (0.85–1.06)	Low risk[c]	P - 23 per 1000[d] A - 1 fewer per 1000
				Moderate risk	P - 65 per 1000 A - 3 fewer per 1000
				High risk	P - 108 per 1000 A - 5 fewer per 1000

[a]The risk difference in the aspirin group (and its 95% CI) is based on the estimated risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b]Control group risk estimate for 10-yr mortality applies to a 60-yr-old person (male or female) and comes from population-based data from Statistics Norway. Mortality increases with age (e.g., 50-yr-old man; 40 deaths per 1000 in 10 yr) and is lower in females than in males (e.g., 2.5% in women age 50 yr vs. 4% in men age 50 yr).

[c]Risk groups correspond to low (5%), medium (15%), and high risk (25%) according to the Framingham score (or other risk tool) to estimate 10-yr risk.

[d]Control group risk estimates in low, moderate, and high CV risk groups are based on the Framingham score. We have used data from an individual patient data meta-analysis to provide estimated risks for patient-important outcomes not covered by the Framingham Risk Score. We have also adjusted for 20% overestimation associated with the Framingham Risk Score.

Information from: Guirguis-Blake JM, Evans CV, Senger CA, et al. Aspirin for the Primary Prevention of Cardiovascular Events: A Systematic Evidence Review for the US Preventive Services Task Force: Evidence Synthesis No. 131. AHRQ Publication No. 13-05195-EF-1. Agency for Healthcare Research and Quality, 2015; ASCEND Study Collaborative Group. Effects of aspirin for primary prevention in persons with diabetes mellitus. N Engl J Med 2018;379:1529; McNeil JJ, Nelson MR, Woods RL, et al. Effect of aspirin on all-cause mortality in the healthy elderly. N Engl J Med 2018;379:1519; Gaziano JM, Brotons C, Coppolecchia R, et al. Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial. Lancet 2018;392:1036.

In the ARRIVE trial, GI bleeding events occurred in 0.97% of the aspirin group and 0.47% of the placebo group (HR 2.11; 95% CI, 1.36–3.28). In the ASPREE trial, the rates of major hemorrhage were 8.6 and 6.2 events per 1000 person-years (HR 1.38; 95% CI, 1.18–1.62) in aspirin and placebo groups, respectively.

Major trials that provide clear evidence include the British Doctors Trial (BDT), the Physicians' Health Study (PHS), the Thrombosis Prevention Trial (TPT), the Hypertension Optimal Treatment (HOT) study, the Primary Prevention Project (PPP), and the Women's Health Study (WHS). These were prospective RCTs that showed significant reductions in transient ischemic attack but no reduction in MI (BDT), significant relative risk reduction in fatal and nonfatal MI (PHS), and significant reductions in ischemic heart disease and MI (TPT and HOT). Of note, the PPP, TPT, and HOT trials targeted a population at greater CVD risk. The WHS found no significant reduction in CV events or MI; however, the study targeted women at very low CVD risk (primary outcome of major CVD events was less than 3% over 10 years). After stratification by age, women older than 65 did have a significant reduction in major CVD events (HR 0.74 [95% CI, 0.59–0.92]), including a reduction in nonfatal MI (HR 0.66 [95% CI, 0.44–0.97]). There was also a 17% decrease in the risk of stroke (HR 0.83 [95% CI, 0.69–0.99] p=0.04).

The original 1997 AHA guidelines did not include aspirin use for primary prevention because of the lack of sufficient data. Not until 2002 did USPSTF and AHA endorsed the use of low-dose aspirin for primary prevention. This change occurred primarily because of results from the PHS, TPT, and HOT trials. Aspirin at doses of 75–325 mg/day reduced the risk of nonfatal MI by 44%, 30%, and 40% in the PHS, TPT, and HOT trials, respectively. Although the risk of major GI bleeding was not increased in the PHS and TPT trials, it was significantly increased in HOT trial. The only trial to show a significant reduction in fatal MI was the PHS (10 vs. 26, 0.02 vs. 0.05%/year; RR 0.34 [0.15–0.75]).

In 2009, the USPSTF guidelines updated the recommendations specific to age and sex according to the 2005 WHS study and a 2006 sex-specific meta-analysis (Berger 2006; Ridker 2005). The WHS provided evidence to support the use of aspirin in women to reduce rates of stroke, including nonfatal stroke, whereas the meta-analysis supported the use of aspirin to reduce MI in men and ischemic stroke in women younger than 65. In women older than 65, evidence supported the benefit of aspirin in both stroke and MI reduction. In 2016, the USPSTF recommendations were updated to be more specific but now allow for more clinical judgment and benefit-risk analysis, given that the results from more recent trials, including POPADAD (Prevention of Progression of Arterial Disease and Diabetes), JPAD (Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes), AAA (Aspirin for Asymptomatic Atherosclerosis), and JPPP (The Japanese Primary Prevention Project), showed no clear benefits.

The three most recent trials published in 2018 (ARRIVE, ASCEND, and ASPREE) are more reflective of modern preventive practices, including blood pressure control, smoking cessation, and cholesterol reduction. In the upcoming ACCEPT-D trial (Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes), patients older than 50 with diabetes who were taking simvastatin were randomized to low-dose aspirin versus placebo. Outcomes from this trial may help clarify the effects of modern preventive strategies on aspirin's efficacy and further value.

The ARRIVE study enrolled 12,546 patients 55 and older (men) or 60 and older (women) at a moderate risk of CHD (three or more CV risk factors: dyslipidemia, current smoking, high blood pressure, positive family history of CVD). Baseline characteristics included mean age 64 years, 30% female, BMI 28.5 kg/m^2, and 97.9% white. In ARRIVE, aspirin use in the intermediate-risk population (around 15% in 10 years) did not reduce the composite outcome of first MI, stroke, CV death, unstable angina, or transient ischemic attack, whereas GI bleeding events were more than twice as likely with aspirin use. After a median follow-up of 5 years, the risk of any death was 2.55% and 2.57%, respectively (HR 0.99; 95% CI, 0.80–1.24). However, there was no significant difference in the rates of CV death (HR 0.97). Because of a low aspirin adherence rate of 61%, a per-protocol analysis was conducted that showed a reduction in fatal and nonfatal MI by 47%. The ARRIVE trial was designed robustly; however, it had several limitations. External validity was limited because most patients were white males, and patients with diabetes were excluded. In addition, the average 10-year ASCVD risk score of subjects was 17%, so the study's findings may not be applied to patients with a high ASCVD risk of greater than 20%.

The 2018 ASCEND trial enrolled 15,480 patients with diabetes, age older than 40, and no known CVD. Baseline characteristics included mean age 63.3 years, 62.5% male, 95.5% white, BMI 30.6 kg/m^2, current smoker 8.3%, former smoker 45.5%, hypertension 61.6%, systolic blood pressure 136.2 mm Hg, T2DM 94.1%, DM duration 7 years, 12% with A1C greater than 8% and 30% with A1C 6.5%–8%, and statin use 74.9%. In ASCEND, aspirin use in patients with diabetes led to a 12% relative reduction in nonfatal MI, stroke, transient ischemic attack, or vascular death, excluding intracerebral hemorrhage, whereas major bleeds were 29% more likely. Around one-half the excess of bleeding was in the GI tract, with around one-third in the upper GI tract. Despite the known gastroprotective benefits of routine use of proton pump inhibitors in aspirin users, only around 25% of patients in the study were receiving proton pump inhibitors. Perhaps routine use of proton pump inhibitors in patients requiring aspirin therapy could mitigate the risk of upper GI tract bleeding. The number needed to treat was 91 to prevent

one serious vascular event, and the number needed to harm was 112 to cause one major bleed. The authors deemed that these intention-to-treat analyses underestimated the benefits as well as the risks of aspirin use because of lack of adherence to the regimen during the trial. The risk of death from any cause was 9.7% versus 10.2% (RR 0.94; 95% CI, 0.85–1.04) during a mean follow-up of 7.4 years. However, aspirin did not significantly reduce the risk of vascular death (2.7% vs. 2.9%; RR 0.93; 95% CI, 0.77–1.12). Over 80% of patients were at a low to moderate risk (less than 10% risk within 5 years) of a CVD event, with only 17% patients with an ASCVD risk score greater than 10%. Most participants had well-treated diabetes with an average baseline A1C of less than 8%, around 75% were receiving statin therapy, and the average systolic blood pressure was around 136 mm Hg. As a result, the findings of this study cannot be applied to high-risk patients with poorly controlled diabetes. In addition, most of the study participants were white residing in the UK, which limits the external validity.

The ASPREE trial enrolled 19,114 healthy older adults (older than 70, older than 65 in Hispanic or black patients) without a history of CVD, cerebrovascular disease, dementia, or any other chronic condition that would likely limit survival to less than 5 years. Baseline characteristics included median age 74 years, 54% female, BMI 28.1 kg/m^2, HDL 61.5 mg/dL, SCr 0.9 mg/dL, eGFR 73 mL/minute/m^2, and systolic blood pressure 139 plus 17 mm Hg, and diastolic blood pressure 77 plus 10 mm Hg. Findings of this study support the current USPSTF approach to not using aspirin for primary prevention in most individuals older than 70. In ASPREE, aspirin use in healthy older adult patients did not reduce MI or ischemic strokes, but there was a substantial, progressive increase in major hemorrhage. In addition, there was an increase in all-cause death in the aspirin group, mainly because of increased cancer deaths. After a median of 4.7 years of follow-up, the risk of death from any cause was 12.7 and 11.1 events per 1000 person-years (HR 1.14; 95% CI, 1.01–1.29). The risk of fatal CVD was similar in the aspirin and placebo groups (1.8 vs. 1.9 events per 1000 person-years; HR 0.97; 95% CI, 0.71–1.33). Of note, the CVD risk in ASPREE participants was greater than 10% over 10 years, so adults 70 and older were technically high risk; nevertheless, they had no CVD-related benefit from aspirin. Therefore, the question remains unanswered regarding whether aspirin may benefit higher-risk younger populations (those younger than 70).

Of note, contemporary practice has provided better lifetime risk factor control to patients in ASPREE than to trial patients from the 1980s. Thus, patients in ASPREE or other recent trials have a lower likelihood of reducing their already low risk of thrombotic events than trial participants from the 1980s. According to findings from the recent trials, clinicians should think twice before initiating aspirin for primary prevention in older individuals and those at low to moderate CVD risk. In fact, it would also be reasonable to discontinue aspirin in patients who only have a primary prevention indication. Aspirin therapy may not be a cornerstone CVD preventive strategy for all patients, with modern-day randomized trial evidence building against its routine use.

RECOMMENDATIONS FOR INITIATING ASPIRIN FOR PRIMARY PREVENTION OF CVD

All major CV health organizations have made relatively similar recommendations for the use of aspirin in secondary prevention, but the consensus regarding aspirin use in primary prevention varies. The FDA has remained consistent in its stance and does not recommend aspirin for primary prevention despite emerging evidence from clinical trials over the past 30 years. In 2003, Bayer HealthCare (BHC) submitted a citizen petition requesting to add aspirin 75- to 325-mg/day dosing for the primary prevention of MI in patients with a CHD risk greater than 10% for over 10 years or a positive benefit-risk ratio as assessed by their health care provider. However, in 2014, the FDA concluded that data are insufficient to support the inclusion of primary prevention of MI as an indication in the professional labeling of aspirin and subsequently denied BHC's petition. Recommendations from various guidelines have evolved over the past 2 decades (Table 4).

A recently published viewpoint in *JAMA* describes a practical stepwise approach that involves shared decision-making about initiating, continuing, or discontinuing aspirin for primary prevention (Box 4).

CONCLUSION

After 3 decades of studying reductions in various CV events in several different populations with varying levels of CVD risk, investigators have better data to identify individuals who may not be appropriate candidates for use of aspirin for primary prevention of CVD. Shared decisions about initiating, continuing, and discontinuing aspirin for primary prevention should focus on individual patient risks and preferences, which in turn will improve patient satisfaction given the ambiguity presented by aspirin. The most recent data and guideline recommendations support a risk-based approach that limits the use of aspirin for the primary prevention of CVD to individuals age 40–79 at moderate or high CV risk with clear benefit-harm ratio. However, data are still lacking to confirm benefits and harms of aspirin use in patients with the highest CVD risk (greater than 20%), those of African American descent, and those with uncontrolled comorbidities that increase CVD risk. Therefore, more research is needed to identify patients at high CVD risk and acceptable bleeding risk for whom a once-daily affordable therapy such as low-dose aspirin is worth considering. Outcomes of current trials, such as the ongoing ACCEP-D trial will provide further evidence for or against aspirin for primary prevention in the modern world.

Table 4. Summary of Guideline Changes on Low-Dose ASA in Primary CV Prevention

Organization	Older Recommendations ("Then")	Latest Recommendations ("Now")
USPSTF	**2002 -** Patients with 5-yr CHD risk > 3% (account for patient preference) **2009 (age- and gender-specific)** • Men age 45–79 whose potential benefit because of reduction in MI outweighs the potential harm (grade A) • Women age 55–79 whose potential benefit because of reduction in ischemic stroke outweighs the potential harm (grade A)	**2016 (age- and risk-specific)** • Adults age 50–59 with a 10-yr CVD risk ≥ 10%: Recommend ASA for prevention of CVD if patient is not at increased risk of bleeding and has a life expectancy of at least 10 yr (grade B) • Adults age 60–69 with a 10-yr CVD risk ≥ 10%: Decision to initiate ASA therapy should be individualized (grade C)
ACC/AHA	**2002 -** Patients with 5-yr CHD risk > 3% (account for patient preference)	**2019** • Adults age 40–70 at higher risk of CVD but not at increased risk of bleeding ("higher" CVD risk ≥ 10% 10 year ASCVD risk) • Adults > 70 or any age with increased risk of bleeding: Routine ASA use is not recommended. Increased risk of bleeding is defined as a history of GI bleeding, peptic ulcer disease, bleeding at other sites, age > 70, thrombocytopenia, coagulopathy, CKD, and concurrent use of other medications that increase bleeding risk such as NSAIDs, steroids, DOACs, and warfarin
ASA	**2011 -** Patients with a 10-yr CHD risk of 6%–10% (if benefits outweigh risks)	**2014 -** Patients with a 10-yr ASCVD risk > 10% (if benefits outweigh risks)
ADA	**2009** Adults > 40 with T1DM or T2DM at high CVD risk + additional risk factors (family history of CVD, hypertension, smoking, dyslipidemia, or albuminuria) **2010** Adults > 50 with T1DM or T2DM who have at least one additional major risk factor (family history of premature ASCVD, hypertension, dyslipidemia, smoking, or albuminuria) and are not at increased risk of bleeding	**2019** Adults with diabetes > 50 yr with T1DM or T2DM who have at least **one** additional major risk factor (family history of premature ASCVD, hypertension, dyslipidemia, smoking, or albuminuria), if patient is in agreement after a discussion on the benefits vs. increased risk of bleeding (older age, anemia, renal disease)
ACCP CHEST	**2008** Patients with moderate risk of a coronary event (grade 1A) • For women < 65 who are at risk of an ischemic stroke and in whom the concomitant risk of major bleeding is low (grade 2A) • For women ≥ 65 at risk of ischemic stroke or MI and in whom the concomitant risk of major bleeding is low (grade 2B)	**2012** Adults > 50 without symptomatic CVD (not recommended if patient is receiving anticoagulation therapy) (grade 2B)
European Society of Cardiology (ESC)	**2012** ASA may be considered in patients with hypertension and reduced renal function or at high CVD risk (grade 2B) ASA is not recommended for people with diabetes who do not have clinical ASCVD (grade 3A)	**2016** Antiplatelet therapy is not recommended in individuals without CVD because of the increased risk of major bleeding (grade 3B)

Table 4. Summary of Guideline Changes on Low-Dose ASA in Primary CV Prevention (*Continued*)

Organization	Older Recommendations ("Then")	Latest Recommendations ("Now")
AAFP		**2016** • Adults age 50–59 with a 10-yr ASCVD risk ≥ 10%: Recommend ASA for prevention of CVD if patient is not at increased risk of bleeding and has a life expectancy of at least 10 yr (grade B) • Adults age 60–69 with a 10-yr CVD risk ≥ 10%: Decision to initiate ASA therapy should be individualized (grade C) • Adults < 50 and > 70: ASA use is not recommended

ASCVD = atherosclerotic cardiovascular disease; CHD = coronary heart disease; CKD = chronic kidney disease; DOAC = direct oral anticoagulant; T1DM = type 1 diabetes; T2DM = type 2 diabetes.

Information from: U.S. Preventive Services Task Force. Aspirin for the prevention of cardiovascular disease: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2002;136:157-60; U.S. Preventive Services Task Force. Aspirin for the prevention of cardiovascular disease: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2009;150:396-404; Wolff T, Miller T, Ko S. Aspirin for the primary prevention of cardiovascular events: an update of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med 2009;150:405; Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease. Circulation 2019;140:e596-e650; Goldstein LB, Bushnell CD, Adams RJ, et al.; American Heart Association Stroke Council; Council on Cardiovascular Nursing; Council on Epidemiology and Prevention; Council for High Blood Pressure Research; Council on Peripheral Vascular Disease, and Interdisciplinary Council on Quality of Care Outcomes Research. Guidelines for the primary prevention of stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2011;42:517-84; Meschia JF, Bushnell C, Boden-Albala B, et al. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2014;45:3754; American Diabetes Association (ADA). Standards of Medical Care in Diabetes. Diabetes Care 2009;32:31; American Diabetes Association (ADA). Standards of Medical Care in Diabetes. Diabetes Care 2010;33:32; American Diabetes Association (ADA). Cardiovascular Disease and Risk Management. Diabetes Care 2019;42:103-23; Patrono C, Baigent C, Hirsh J, et al. Antiplatelet drugs: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133:199S-233S; Vandvik PO, Lincoff AM, Gore JM, et al. Primary and secondary prevention of cardiovascular disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:e637S; You JJ, Singer DE, Howard PA, et al. Antithrombotic therapy for atrial fibrillation: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:e531S; Perk J, De Backer G, Gohlke H, et al. European guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Eur Heart J 2012;33:1635; Piepoli MF, Hoes AW, et al. 2016 European guidelines on cardiovascular disease prevention in clinical practice: the Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Atherosclerosis 2016;252:207-74.

Box 4. Practical Approach to Low-Dose Aspirin Use for Primary Prevention

Step 1: Assess the patient's baseline level of understanding about role of aspirin in heart health and interest in learning more to tailor information to meet the patient's needs

Step 2: Educate on the key conditions to facilitate a patient-specific conversation. Estimation of CVD risk and a review of individual CVD risk factors can personalize and refine risk

Review of potential benefits and harms:

Benefits

- Reduced CVD mortality
- Reduced myocardial infarction risk
- Reduced stroke occurrence
- Reduced colorectal cancer mortality

Harms

- Intracranial bleeding
- Major and minor GI bleeding
- Nuisance bleeding and bruising
- Increased costs and follow-up visits

Step 3: Assess patient preferences regarding long-term use of a medication, concerns of heart conditions, and adverse effects of aspirin to identify what matters to the patient most

Information from: Chiang KF, Shah SJ, Stafford RS. A practical approach to low-dose aspirin for primary prevention. JAMA 2019 Jun 28. [Epub ahead of print]

Practice Points

Atherosclerotic cardiovascular disease remains the leading cause of morbidity and mortality globally. Early CV risk factor assessment and implementation of preventive strategies can significantly reduce ASCVD risk in all patients, regardless of their respective 10-year risk score classification.

- **Lifestyle risk factors, traditional risk factors, and risk-enhancing factors should be screened for in addition to assessing for ASCVD risk using an appropriate validated risk assessment tool for each patient.**
- **Other modifiable ASCVD risk factors, including cholesterol, blood pressure, diabetes, and lifestyle management, should be prioritized before considering aspirin for primary prevention.**
- **Evidence from early trials failed to provide a clear benefit-harm ratio regarding aspirin use for primary prevention in various patient populations.**
- **Over the past 2 decades, major advances in CVD risk reduction strategies, including smoking cessation, use of statin therapy, and optimization of hypertension management, have become cornerstones of the primary prevention approach.**
- **Data analyses from three large RCTs in 2018 (ARRIVE, ASCEND, and ASPREE) suggest little or no benefit of aspirin in primary prevention and have even reported net harm.**
- **Findings of the ARRIVE, ASCEND, and ASPREE trials may be extrapolated to individuals at moderate CVD risk, those with diabetes, and those who are considered "healthy" older adults, respectively. These RCTs found no significant reduction in the risk of ASCVD compared with placebo but found an increased risk of major bleeding with aspirin use.**
- **Current recommendations from the ACC/AHA and ADA consider the findings of these recent landmark trials and encourage a meticulous evaluation of the benefit-harm ratio when using aspirin as a modality for primary prevention.**
- **CVD risk scores should continually be updated and validated to account for ongoing interventions known to reduce CVD risk in the short and long term.**

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Self-Assessment Questions

Questions 1 and 2 pertain to the following case.

T.J. is a 60-year-old African American woman with a medical history of type 2 diabetes (T2DM) (diagnosed 2 years ago). She presents to the clinic for a follow-up. Her in-office blood pressure is 142/88 mm Hg (last visit 148/80 mm Hg), heart rate is 80 beats/minute, and BMI is 24 kg/m^2. A recent lipid panel shows LDL 110 mg/dL, HDL 40 mg/dL, TG 148 mg/dL, and TC 180 mg/dL. T.J.'s comprehensive metabolic panel (CMP) is within normal limits, A1C is 6.8%, and urine albumin/creatinine ratio is 10 mg/g. She denies cigarette smoking and reports an overall active lifestyle. T.J.'s home drugs include metformin 1000 mg twice daily and a multivitamin.

1. In addition to lifestyle modifications, which one of the following is best to add to T.J.'s daily regimen for the primary prevention of cardiovascular disease (CVD)?

   A. Lisinopril 5 mg daily and atorvastatin 20 mg daily
   B. Aspirin 81 mg and atorvastatin 40 mg daily
   C. Atorvastatin 20 mg daily
   D. Aspirin 81 mg daily

2. Which one of the following best evaluates T.J.'s risk of CVD?

   A. Framingham Risk Score more than 10%
   B. Framingham Risk Score less than 5%
   C. Atherosclerotic cardiovascular disease (ASCVD) risk score less than 10%
   D. ASCVD risk score greater than 10%

3. A 50-year-old Hispanic woman with a medical history significant for T2DM, hypertension, and current smoking (½ pack/day for 30 years) presents for an initial visit for chronic disease management. Her blood pressure is 128/78 mm Hg, heart rate is 70 beats/minute, and BMI is 22 kg/m^2. The patient's father died of his first coronary heart disease (CHD) event at age 65; her mother is living and healthy with no pertinent medical history. The patient's recent lipid panel shows LDL 100 mg/dL, HDL 38 mg/dL, TG 158 mg/dL, and TC 170 mg/dL. Her A1C, CMP, and CBC are within normal limits, and her urine albumin/creatinine ratio is 43 mg/g. The patient's home drugs include lisinopril 20 mg daily, hydrochlorothiazide 25 mg daily, Lantus 20 units daily, metformin 1000 mg twice daily, and atorvastatin 40 mg daily (increased 2 weeks ago by her primary care physician). The patient values heart health, especially given her family history of CHD. Which one of the following best evaluates the use of aspirin for primary prevention of CVD in this patient?

   A. Risk of bleeding outweighs the benefit of aspirin.
   B. Risk of CVD outweighs the risk of bleeding.
   C. Patient is not a candidate for aspirin for primary prevention.
   D. Calculated 10-year ASCVD risk score indicates aspirin therapy.

4. A 55-year-old man from Puerto Rico has a medical history of hypertension, T2DM (diagnosed 12 years ago), and erectile dysfunction. Which one of the following best evaluates the use of CVD risk tools in this patient?

   A. Framingham risk tool may accurately assess the risk of CVD.
   B. Framingham risk tool may overestimate the risk of CVD.
   C. ASCVD 10-year risk tool may accurately assess the risk of CVD.
   D. ASCVD 10-year risk tool may underestimate the risk of CVD.

5. A 40-year-old African American man with a new diagnosis of T2DM presents to the clinic. He has no other significant medical history or pertinent family history. His vital signs are blood pressure 118/68 mm Hg, heart rate 70 beats/minute, and BMI 23 kg/m^2. Both his CMP and his CBC are within normal limits. Lipid panel shows TC 162 mg/dL, LDL 90 mg/dL, HDL 40 mg/dL, and TG 160 mg/dL. Which one of the following risk prediction models is best to use to estimate this patient's risk of CVD?

   A. Reynolds risk
   B. Framingham risk
   C. ASCVD 10-year risk
   D. ASCVD lifetime risk

6. A 68-year-old Hispanic man presents to the clinic for an initial visit. His medical history is significant for T2DM (diagnosed 12 years ago), hypertension, dyslipidemia, and a history of several GI bleeds requiring hospitalization in the past 5 years (most recent event was within the past year). He does not smoke or drink alcohol. His vital signs for the most recent three consecutive visits are blood pressure less than 130/80 mm Hg and BMI 20–24 kg/m^2; all of his laboratory values are within normal limits. His current medications include Lantus 25 units daily, liraglutide (Victoza) 1.8 mg daily, metformin 1000 mg twice daily, atorvastatin 40 mg daily, lisinopril 40 mg daily, hydrochlorothiazide 25 mg daily, and aspirin 81 mg daily. His most recent ASCVD 10-year risk is 11%. Which one of the following is best to recommend for this patient?

   A. Make no change in therapy.
   B. Initiate famotidine therapy.
   C. Discontinue aspirin therapy.
   D. Increase aspirin to 162 mg daily.

7. A 64-year-old white woman presents to the clinic for a follow-up. She has a history of hypertension, T2DM, hyperlipidemia, chronic kidney disease (CKD) (eGFR 50 mL/minute/1.73 m^2), and anemia. Her vital signs include blood pressure 122/70 mm Hg, heart rate 80 beats/minute, and BMI 24 kg/m^2. Her most recent A1C is at 7.2%, and her lipid panel shows TC 172 mg/dL, LDL 95 mg/dL, HDL 42 mg/dL, and TG 175 mg/dL. Her CBC shows Hgb 10.5 g/dL, Hct 33.5%, and Plt 210,000/mm^3. She currently takes lisinopril 10 mg daily, metformin extended release 1000 mg daily, atorvastatin 10 mg daily, and ferrous sulfate 325 mg daily. She has also taken aspirin 81 mg daily for several years. However, she is concerned because she recently heard that aspirin may cause more harm than good in patients with diabetes and a history of bleeding. Her father died of a myocardial infarction (MI) at age 62. The patient does not smoke or drink alcohol. According to the ASCEND trial, which one of the following is best to recommend regarding the use of aspirin for the primary prevention of ASCVD in this patient?

   A. Continue low-dose aspirin because she is at high risk of CVD and would benefit from risk reduction of MI, as shown in the trial.
   B. Discontinue low-dose aspirin therapy because she is at moderate risk of CVD, and her risk of an upper GI bleed outweighs the benefits of CVD risk reduction.
   C. Continue aspirin therapy, but change to an enteric-coated formulation to mitigate the risk of GI bleed that was increased in the trial.
   D. Discontinue aspirin therapy because the trial showed an increased risk of colorectal cancer in patients using long-term aspirin therapy.

Questions 8–11 pertain to the following case.

G.H. is a 71-year-old African American man with a medical history significant for resistant hypertension, hyperlipidemia, current smoker (1 pack/day for the past 40 years), and gout. He presents to your clinic for a follow-up. The patient currently takes amlodipine 5 mg daily, valsartan/hydrochlorothiazide 160 mg/12.5 mg daily, spironolactone 25 mg daily, metoprolol tartrate 50 mg twice daily, atorvastatin 20 mg daily, aspirin 81 mg daily, and allopurinol 100 mg daily. G.H.'s blood pressure control has been improving and is in the 120/80-mm Hg range at home as well as during clinic visits. Today, his blood pressure in the clinic is 122/80 mm Hg. G.H.'s most recent laboratory test results show CMP within normal limits and lipid panel as follows: TC 222 mg/dL, HDL 60 mg/dL, LDL 130 mg/dL, and TG 160 mg/dL.

8. Which one of the following best evaluates G.H.'s 10-year ASCVD risk score?

   A. Less than 10%
   B. 10%–14%
   C. 15%–19%
   D. Greater than 20%

9. Which one of the following risk factor(s), if optimized, would be most likely to reduce G.H.'s CVD risk by 10%?

   A. Smoking
   B. Blood pressure
   C. HDL
   D. TC

10. Results from which one of the following landmark trials would be best to extrapolate to G.H.'s treatment?

   A. ASCEND
   B. ASPREE
   C. ARRIVE
   D. WHS

11. G.H. asks if you would recommend discontinuing or continuing aspirin on the basis of a randomized trial's results. Which one of the following is best to recommend for G.H.?

   A. Discontinue aspirin because the ASCEND trial found an increased incidence of cancer-related deaths in patients older than 70 and those without a history of cancer.
   B. Continue aspirin because the ARRIVE trial found significant reductions in MI or ischemic strokes in African American male patients.
   C. Discontinue aspirin because the ASPREE trial found that, compared with placebo, aspirin did not reduce the risk of CVD events and increased the risk of major hemorrhage.
   D. Continue aspirin because the ASPREE trial found that aspirin provides survival free of dementia and physical disability.

12. In which one of the following patients would it be best to consider discontinuing low-dose aspirin to mitigate bleeding risk? (Assume systolic blood pressure 120 mm Hg, HDL 60 mg/dL, and TC 180 mg/dL, controlled and on treatment for hypertension and hyperlipidemia.)

   A. 65-year-old African American man – current smoker with controlled diabetes [ASCVD 23.7% – high risk)
   B. 52-year-old white man – current smoker, controlled diabetes, taking rivaroxaban for pulmonary embolism (ASCVD 12.4% – moderate risk)
   C. 60-year-old African American woman – nonsmoker with controlled diabetes (ASCVD 11.3% – moderate risk)
   D. 69-year-old white man – nonsmoker (ASCVD 15.3% – moderate risk)

13. An 80-year-old African American woman has a medical history that includes atrial fibrillation, hyperlipidemia, T2DM, mild anemia, and breast cancer. She presents to the anticoagulation clinic to discuss the costs and pill burden of her medications. She currently takes apixaban 5 mg twice daily, simvastatin 10 mg daily, metformin 500 mg twice daily, metoprolol succinate 25 mg daily, ferrous sulfate 325 mg daily, a multivitamin daily, and aspirin

81 mg daily. The patient is concerned about the high copay of apixaban and would like to change to warfarin therapy for cost-savings. She also feels overwhelmed with the number of medications she currently takes, especially given her "good" health status at her advanced age. Her most recent blood pressure in the office was 109/60 mm Hg, and she has never required medications for high blood pressure. Her CMP, CBC, and current iron concentrations are within normal limits. Her current A1C is 6.5%, LDL is 80 mg/dL, HDL is 81 mg/dL, TC is 173 mg/dL, and TG is 62 mg/dL. She states that she has been taking the aspirin dose only three times weekly to reduce her pill burden and because she is unclear about aspirin's benefits. She asks you to consult her physician about discontinuing aspirin if it is not necessary. Which one of the following is best to recommend for this patient?

A. Discontinue aspirin because the patient is not benefiting from its cardioprotective effect.
B. Continue aspirin therapy, given the patient's ASCVD risk score.
C. Discontinue aspirin therapy because of the benefit-harm ratio.
D. Continue aspirin therapy according to the ADA guidelines.

14. A 59-year-old African American woman (height 64 inches, weight 79 kg) presents for a medication management visit. Her medical history is significant for T2DM, hyperlipidemia, hypertension, gastroesophageal reflux disease, and anemia. Her blood pressure today is 138/88 mm Hg (previous office blood pressure 134/76 mm Hg) and heart rate is 87 beats/minute. Laboratory values (dated 8 months ago) show A1C 7.4%, urine albumin/creatinine 9.7 mg/g (7.9 mg/g 11 months ago), electrolytes normal, SCr 0.81 mg/dL, eGFR greater than 90 mL/minute/1.73 m^2, CBC normal, TC 174 mg/dL, LDL 83 mg/dL, HDL 53 mg/dL, and TG 188 mg/dL. Her current medications include metformin 1000 mg twice daily, Januvia 100 mg daily, glipizide 5 mg twice daily, losartan 100 mg daily, lovastatin 20 mg daily, aspirin 81 mg daily, and omeprazole 20 mg daily. The patient reports she does not smoke or drink alcohol, is nonadherent to lovastatin because she does not have elevated cholesterol, and does not want to take aspirin because it will cause a stomach bleed. She ran out of Januvia 2 weeks ago. Which one of the following is best to recommend to reduce this patient's ASCVD risk?

A. Assess her family history of premature ASCVD to determine whether she should continue aspirin therapy for primary prevention of ASCVD.
B. Explain the benefit of an appropriate-intensity statin for high ASCVD risk, change lovastatin 20 mg daily to atorvastatin to 40 mg daily, and discontinue aspirin 81 mg daily.
C. Explain the benefits of an appropriate-intensity statin for intermediate ASCVD risk, change lovastatin 20 mg daily to atorvastatin 20 mg daily, and continue aspirin 81 mg daily.
D. Explain the benefits of an appropriate-intensity statin for intermediate ASCVDrisk, repeat the fasting lipid panel, and continue aspirin 81 mg daily.

15. A 70-year-old African American man has a medical history that includes T2DM, hypertension, hyperlipidemia, peripheral neuropathy, stage 3 CKD, anemia, and benign prostatic hyperplasia. He presents to the clinic for a follow-up with his primary care physician. The physician asks if you can help with medication reconciliation because the patient wants to know whether he needs to take all of his medications. The patient's blood pressure is 148/80 mm Hg (last visit 130/70 mm Hg), heart rate is 78 beats/minute, and BMI is 40 kg/m^2. Laboratory values include SCr 1.38 mg/dL, eGFR 58 mL/minute/1.73 m^2, Hgb 10.2 g/dL, Hct 30.4%, Plt 300,000/mm^3, A1C 8.5%, TC 154 mg/dL, LDL 91 mg/dL, HDL 42 mg/dL, and TG 103 mg/dL. Self-monitoring of blood glucose shows fasting plasma glucose slightly above target with one episode of hypoglycemia (blood glucose 56 mg/dL) and mostly above goal for postprandial plasma glucose (three of nine readings have been at target). He confirms documentation of no allergies/intolerances, no smoking, and no alcohol. His current medications include Lantus 30 units daily, Januvia 50 mg daily, metoprolol extended release 100 mg daily, clonidine 0.3 mg three times daily, minoxidil 2.5 mg twice daily, furosemide 40 mg daily, lovastatin 40 mg daily, aspirin 81 mg daily, gabapentin 300 mg three times daily, and tamsulosin 0.4 mg daily. He also reports taking naproxen OTC for joint aches/pain. He does not currently engage in any physical activity and does not follow a healthy diet (high in carbohydrates, restaurant food, and fried foods). Which one of the following is best to recommend to reduce this patient's ASCVD risk?

A. Underlying modifiable risk factors for ASCVD are not optimized and require immediate interventions to reduce his ASCVD risk, and his bleeding risk outweighs the benefit of aspirin therapy.
B. Underlying modifiable risk factors are optimized, given his age and comorbidities, and his bleeding risk does not outweigh the benefit of aspirin therapy.
C. Underlying modifiable risk factors for ASCVD are optimized, and his bleeding risk outweighs the benefit of aspirin therapy for primary prevention.
D. Underlying modifiable risk factors for ASCVD are not optimized and require immediate interventions to reduce his ASCVD risk, and his ASCVD risk outweighs the bleeding risk of aspirin therapy.