Published online: 2021-12-24

Primary and Secondary Prevention of CAD: A Review

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Int J Angiol 2022;31:16–26.

Abstract

Coronary artery disease is the leading cause of death in both men and women, yet adequate control of risk factors can largely reduce the incidence and recurrence of cardiac events. In this review, we discuss various life style and pharmacological measures for both the primary and secondary prevention of coronary artery disease. With a clear understanding of management options, health care providers have an excellent opportunity to educate patients and ameliorate a significant burden of morbidity and mortality.

Keywords
- atherosclerosis
- coronary artery
- hypercholesterolemia
- hypertension
- myocardial infarction
- prevention
- aspirin

Coronary artery disease (CAD) continues to be the leading cause of death for both men and women globally, with over 17.9 million deaths attributed to CAD each year.[1,2] In the United States alone, more than 200 billion dollars are spent annually on CAD-related health services and medications.[3] However, unlike other disease processes, the development and progression of CAD can be largely attenuated through management of cardiovascular risk factors such as tobacco use, diet and activity, hypertension, diabetes, and dyslipidemia. This offers a tremendous opportunity for health care providers to positively impact the individual patient experience, as well as the global burden of disease. This article will review strategies for the primary and secondary prevention of cardiovascular disease (CVD).

Cardiac Risk Assessment for Primary Prevention

Those with known CVD are at the highest risk of a recurrent event and death. These patients need intense risk factor modification. However, it is also important to risk stratify those without CVD to tailor the intensity of preventive measures to reduce both individual risk and that of the population.

The recognition of heart-health risk represents the first step in determining the approach to individual patient management for primary prevention, and several tools have been developed to assist with this assessment. Some examples include the Framingham CVD risk score, the Reynolds risk score, and the QRISK3 assessment,[4] all of which can be used to estimate the future risk of a cardiac event (►**Tables 1–3**). The standard tool that is recommended by the American College of Cardiology (ACC) and American Heart Association (AHA) is the atherosclerotic cardiovascular disease (ASCVD) risk estimation tool (►**Table 4**). This risk estimator incorporates patient data and health conditions such as gender, age, race, cholesterol indices, blood pressure, presence of diabetes, and tobacco use in providing the 10-year risk of having a first cardiovascular event. The risk score not only helps individuals match the intensity of preventive measures to estimated risk, but also helps to maximize the benefits provided by these preventive measures while keeping the side effects and any potential harms to a minimum. On the basis of the estimated score, the individual is categorized into low, borderline, intermediate, or high risk,[4] with implication for starting either lifestyle modification or pharmacological therapy to further manage modifiable risk

published online
December 24, 2021

DOI https://doi.org/10.1055/s-0041-1729925.
ISSN 1061-1711.

Table 1 Framingham risk score

Risk factors—men			Points assigned		
Age (20–79 y)			−9 to +13		
Total cholesterol (<160 to >280 mg/dL)			0 to +11		
Tobacco use (yes or no, by age)			0 to +8		
HDL (>60 to <40 mg/dL)			−1 to +2		
Systolic blood pressure (<120 to >160 mm Hg)			0 to +3		
Risk Factors—women			**Points assigned**		
Age (20–79 y)			−7 to +16		
Total cholesterol (<160 to >280 mg/dL)			0 to +13		
Tobacco use (yes or no, by age)			0 to +9		
HDL (>60 to <40 mg/dL)			−1 to +2		
Systolic blood pressure (<120 to >160 mm Hg)			0 to +6		
Risk score (RS) and corresponding 10-year risk (%)					
RS	**%**	**RS**	**%**	**RS**	**%**
<9	<1			21	14
9–12	1	17	5	22	17
13–14	2	18	6	23	22
15	3	19	8	24	27
16	4	20	11	25+	>30

Abbreviation: HDL, high-density lipoprotein.
Source: Derived from the Adult Treatment Panel III, JAMA, 2001.[78]

factors. Of note, this tool is intended for use in adults aged 40 to 75 years due to the pooled cohort from which it was first validated in 2013.[5] Additionally, risk has been shown to be overestimated in Asian populations, particularly in Chinese[6] and South Asians,[7] and underestimated in patients with existing medical conditions associated with increased inflammation such as HIV,[8] autoimmune disorders,[5] and a history of radiation therapy.[9] To address this limitation, the revised AHA/ACC guideline on the primary prevention of CAD, published in 2019, has recommended the use of risk-

Table 2 Reynolds risk score

Risk factors assessed
Age
Smoking status
Systolic blood pressure
Total cholesterol
HDL
High sensitivity C-reactive protein
Family history CAD < 60 years old

Abbreviations: CAD, coronary artery disease; HDL, high-density lipoprotein.
Note: For use in men and women without diabetes. Calculator available online at Reynoldsriskscore.org.[79]

Table 3 QRISK 3

Risk factors assessed
Age
Sex
Ethnicity
Smoking status
Diabetes
Chronic kidney disease
Atrial fibrillation
Systolic blood pressure
BMI
Migraines
Rheumatoid arthritis
Systemic lupus erythematous
Severe mental illness
Use of atypical antipsychotic
Routine steroid use
Erectile dysfunction
Cholesterol/HDL ratio
High sensitivity C-reactive protein
Family history CAD < 60 years old

Abbreviations: BMI, body mass index; CAD, coronary artery disease; HDL, high-density lipoprotein.
Note: Calculator available online at qrisk.org/three.[80]

Table 4 ASCVD risk estimator

Risk factors assessed	
Age	
Sex	
Ethnicity	
Blood pressure	
Total cholesterol	
HDL	
LDL	
Diabetes	
Smoking status	
Hypertension treatment status	
Statin therapy	
Aspirin therapy	
ASCVD risk assessment interpretation	
Low risk	<5%
Borderline risk	5–7.4%
Intermediate risk	7.5–19.9%
High risk	≥20%

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
Note: Calculator available online at tools.acc.org/ASCVD-Risk-Estimator-Plus.[81]

Table 5 Pharmacotherapy for smoking cessation

Stable CVD
1st line: Varenicline or combination nicotine replacement therapy
2nd line: Bupropion or single nicotine replacement product
3rd line: Nortriptyline
Insufficient response: Varenicline + bupropion, varenicline + single agent nicotine replacement therapy, or bupropion + single agent nicotine replacement therapy
ACS
1st line: Nicotine patch or combination nicotine replacement therapy in hospital, combination nicotine replacement therapy or varenicline at discharge
2nd line: Single nicotine replacement therapy product
3rd line: Bupropion

Abbreviations: ACS, acute coronary syndrome; CVD, cardiovascular disease.
Source: Derived from 2018 ACC Expert Consensus Decision Pathway on Tobacco Cessation Treatment: A Report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents by Rajat S. Barua et al.[82]

enhancing factors for further identification of those who may benefit from pharmacological therapy as a primary method.[4] Though some limitations remain, the use of such a tool is an excellent opportunity to begin a conversation with patients regarding their individual risk, and clinicians should routinely calculate the ASCVD score as part of a comprehensive approach to assessing risk.[4]

Smoking Cessation

Globally, tobacco smoking is accountable for millions of deaths annually, making it the leading preventable cause of death. Studies have shown that compared with nonsmokers, smokers have a reduction in life span of at least 10 years, with adverse effects on the cardiovascular system a frequent culprit. Among smoking-related deaths, one-third of cases are associated with CVD. Further, smoking even one cigarette per day is associated with a 40 to 50% increased risk of developing CVD.[10] Thus, it is of no surprise that smoking cessation reduces the risk of morbidity and mortality from CVD and is a cornerstone of both its primary and secondary prevention. Several atherosclerotic syndromes can be triggered by smoking cigarettes, including, but not limited to, stable angina, acute coronary syndrome (ACS), peripheral vascular disease, and stroke. These are due to two major effects of tobacco on the vascular system: vasomotor dysfunction and inflammation. Vasomotor dysfunction is a result of decreased nitric oxide, which normally drives the vasodilatory function of the endothelium and helps regulate platelet activation and thrombosis. The increased inflammatory response is the result of a rise in leukocytes and inflammatory markers, which ultimately manifests in the initiation and evolution of atherosclerosis.[11]

Smoking cessation strategies (►**Table 5**) should be provided to all smokers including the use of cessation pharmacotherapy. Studies have shown that nicotine replacement therapy (NRT), bupropion, varenicline, notriptyline, and cytisine were found superior to placebo. These agents help to reduce the physical withdrawal thus a more successful termination of nicotine use. Some strategies include combination treatment, extended use, reduce-to-quit protocols for smokers unready to quit, and treatment-matching via precision medicine.[12] Combination cessation pharmacotherapy can include nicotine patch combined with nicotine gum, bupropion, or varenicline. Extending the use of cessation therapy for 6 months or longer compared with the manufacturer-recommended 8 to 12 weeks may be helpful to prevent relapse. For those smokers who are unwilling to quit but are willing to reduce the amount of smoking, a reduce-to-quit strategy may be applied, which is initiating pharmacotherapy such as varenicline as a tool to facilitate abstinence.[12]

In the context of secondary prevention of CAD, it can be assumed that a similar strategy for smoking cessation to that used in healthy participants should be utilized, though data in this population are still somewhat limited. One large meta-analysis sought to evaluate the effect of various interventions on smoking cessation in patients with chronic and acute CVD, including counseling, NRT, varenicline, and bupropion.[13] While inpatient counseling did not seem to show a benefit, telephone counseling was 50% more efficacious than usual care, and in-person counseling was 68% better than usual care. The benefit was shown in both those with acute and chronic CVD, and underscores the importance

of behavioral interventions in this population. The use of NRT and bupropion both yielded inconclusive results in this meta-analysis, but varenicline was found to be highly efficacious. Of note, its use was only evaluated in one study, which included stable CVD patients without ACS. In this meta-analysis and additional trials, there is a difference in observed effectiveness of medical therapy for smoking cessation between those presenting with acute versus chronic CVD. For instance, only one included trial evaluated the effect of bupropion in patients with stable CVD, and it was found to be efficacious. Alternatively, the studies assessing bupropion in acute CVD patients found no significant benefit overall.[13] This lack of benefit seen in patients with acute presentations of CVD may be attributed in part to the intrinsic motivation for change, which occurs after an acute event and renders a patient more willing to consider smoking cessation regardless of intervention used. Such acute events or "teachable moments" have been well described in the context of smoking cessation, including among those with a recent hospitalization or new disease diagnosis.[14] Such a phenomenon may lessen the effect of medication by comparison. However, there may be a true pathophysiological difference in the effect of bupropion versus varenicline in patients presenting with ACS, as additional trials have gone on to show increased smoking abstinence in patients using varenicline after ACS.[15]

Though additional trials are needed to further assess the efficacy of medical treatment for smoking cessation in patients with CVD, the safety of NRT, bupropion, and varenicline has been well documented. Like other tobacco products, the nicotine in NRT can still exert negative effects on the coronary arteries, which contribute to CVD.[16] Fortunately, NRT still appears to be an acceptable and safe option for those with underlying disease. One trial found no increase in the rate of death, myocardial infarction (MI), or hospitalization for a cardiac cause in patients with known CVD who were assigned to NRT and studied over a total of 14 weeks.[17] Similarly, no short- or long-term increase in mortality was observed in patients who were given NRT while hospitalized with ACS.[18] Bupropion and varenicline use in those with known CVD have shown no increase in untoward cardiovascular events, including those presenting with ACS,[19,20] and should therefore be offered to patients. Overall, given the safety profile and effectiveness of various therapies, the ACC/AHA recommends varenicline or combination NRT as first-line therapy for those with chronic or acute presentations of CVD. Bupropion or a single NRT product should be used as a second-line therapy in those with stable CVD, while single-agent NRT but not bupropion is recommended as second-line therapy for those with ACS, as bupropion has yet to show benefit in this population.

Diet/Physical Activity

Variation in macronutrients, such as carbohydrates, fat, and protein, and the number of calories consumed have been shown to directly correlate with cardiovascular health[21] and therefore play a significant role in the primary and secondary prevention of CVD, which are addressed here in the same manner (►**Table 6**). Despite the importance of a healthy diet, it is difficult to follow a nutrition intervention long term to assess cardiac events and mortality due to adherence challenges and resource limitations. Further, assessing the effect of particular macronutrients on cardiovascular health presents a challenge as foods tend to be eaten in combination. Therefore, many studies seek to evaluate the effect of diet on shorter-term outcomes, such as lipid profile, or choose to evaluate outcomes associated with overall dietary patterns. For instance, the AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk provides an assessment of the effect of several dietary patterns and macronutrients on blood pressure and serum lipids rather than overall CVD events or mortality. Assessment of the Mediterranean diet, a dietary pattern with high intake of vegetables, fruits, herbs, nuts, beans, and whole grains, is associated with decrease in blood pressure of 6 to 7/2 to 3 mm Hg in middle-aged and elderly adults with type 2 diabetes or three CVD risk factors. This diet did show any particular improvement in serum low-density lipoprotein (LDL), high-density lipoprotein (HDL), or triglyceride levels, though it notes limitations in available data.[22] The same group also reviewed the effect of Dietary Approaches to Stop Hypertension (DASH) diet, which aims to restrict sodium intake to less than 2,300 mg a day, and encourage consumption of potassium, calcium, and magnesium. They found an overall decrease in blood pressure of approximately 5 to 6/3 mm Hg when compared with a typical American diet. The average LDL cholesterol was decreased by 11 mg/dL and HDL cholesterol was reduced by 4 mg/dL, and there was no effect on triglycerides.[22] Other popular diet patterns include those restrictive of certain food groups and those that seek to increase intake of a particular micronutrient. For instance, one large observational study in the Japanese population found that replacement of animal proteins with those from fish or plants reduced CAD-related mortality.[23] Alternatively, certain patterns of consumption have been found to have deleterious effects on health, particularly those with high consumption of red meat, processed meat, sodium, and sugary beverages, which have been associated with increased CAD mortality.[24] The Southern diet exemplifies this pattern, and is frequently composed of fried food, processed meat, high fat intake, and sugary drinks. Studies have associated this diet in particular with a 56% increased risk of CAD.[25]

Table 6 Dietary recommendations

1.	Emphasize intake of vegetables, fruits, legumes, nuts, whole grains, and fish
2.	Replace saturated fat with monosaturated fat and polysaturated fat
3.	Avoid trans fats
4.	Reduce cholesterol and sodium intake
5.	Minimize the intake of sweetened beverages, refined carbohydrates, and processed meats

Source: Derived from Arnett et al.[83]

In addition to healthy eating habits, a moderate amount of physical activity has been associated with improved cardiovascular health in both the primary and secondary prevention settings. The AHA/ACC recommends aerobic exercise performed for at least 150 minutes per week at a moderate intensity, or for 75 minutes per week at a vigorous level (►**Table 7**).[4] Some examples of exercises that are of moderate intensity include brisk walking, biking, ballroom dancing, active yoga, and recreational swimming. These activities are equivalent to 3.0 to 5.9 metabolic equivalents (METs). Exercises of vigorous intensity include jogging/running, fast-paced biking, singles tennis, and swimming laps, and they are greater than 6 METs. Aquatic therapy is beneficial in patients with comorbidities such as morbid obesity or arthritis, which would otherwise limit exercise capacities.[26] Resistance exercises are beneficial as well, and confer improved physical functioning and better glycemic control.[4]

Overall, patients looking to achieve the primary or secondary prevention of CVD through lifestyle improvements should target a goal body mass index (BMI) of 18.5 to 24.9 kg/m^2, and those who are overweight should aim for a reduction of body weight equivalent to 3 to 10% using diet and exercise, with a goal of 150 minutes of physical activity or more per week. The ideal diet should seek to increase vegetables, nuts, poultry, fish, and whole grains, while reducing trans and saturated fats, sugar-sweetened beverages and foods, and sodium.[27]

Hypertension

More than a quarter of the world's adult population have been identified to have hypertension, and it is a leading cause of mortality and reduction in disability-adjusted life-years.[28] Further, hypertension accounts for more deaths from CVD than any other modifiable risk factor,[29] making healthy blood pressure a prime treatment target for physicians and patients. Stage 1 hypertension is defined as a systolic blood pressure of 130 to 139 mm Hg or a diastolic blood pressure of 80 to 89 mm Hg, while stage 2 hypertension is defined as systolic blood pressure of 140 mm Hg or greater or diastolic blood pressure of 90 mm Hg or greater. All patients with hypertension should develop healthy lifestyle habits to decrease blood pressure, but those with stage 1 hypertension as well as an ASCVD risk score greater than 10% or diabetes, and those with stage 2 hypertension should also receive pharmacotherapy[4] (►**Table 8**). Lifestyle interventions remain a vital component in treating hypertension at either stage due to their proven effectiveness. It has been proposed that physical activity can lead to a reduction in body weight, which decreases inflammation, and ultimately causes a reduction in vascular resistance due to lower oxidative stress, sympathetic activity, vascular responsiveness to adrenergic- and endothelin-receptor stimulation, renin–angiotensin system activity, and intima–media thickness.[30] The benefit of maintaining a healthy weight in the prevention of hypertension has been demonstrated in several observational studies, including one that identified an incremental increase in the development of hypertension with increasing basal metabolic index, even among those with a BMI in the normal range.[31] In addition to maintaining a healthy weight, lifestyle interventions include eating a diet high in fruits, vegetables, low-fat dairy products and low in sodium, drinking a modest amount of alcohol, avoiding nonnarcotic analgesics, and taking supplemental folic acid.[32]

When it comes to treating hypertension in patients who already have established CVD, the lowering of blood pressure overall is more important than the selection of a particular drug class.[33] However, some classes of drugs have shown particular benefits relevant to those who have established CVD. Beta blockers have heterogeneous effects depending on the agent selected, and while they are not the most effective antihypertensive agents, they are standard of care for patients experiencing angina and in those with heart failure (specifically carvedilol, metoprolol, and bisoprolol).[34] Angiotensin-converting enzyme inhibitors should be considered for blood pressure control in all patients after an MI as they can improve heart failure[35] and have been shown to decrease cardiovascular death, MI, and stroke.[36] Aldosterone antagonists have protective effects in patients with left ventricular function following MI, and their use should be considered for this reason.[37] While calcium channel blockers can be used as an alternative to β blockers for treating angina, they are not recommended overall for secondary prevention since they do not have any benefit in preventing heart failure as other classes of antihypertensives do.[33] Individual patient characteristics should be considered when selecting among the various choices of antihypertensives available, with an overall goal of maintaining blood pressure at 130/80 mm Hg or below.

Diabetes Mellitus

Known as the CAD risk equivalent,[38] type 2 diabetes mellitus (T2DM) is one of the most important risk factors for the development and progression of CVD. T2DM is defined as having hemoglobin A1c level of more than 6.5%. Lifestyle modification via diet and exercise is recommended for all patients with diabetes, including those patients with prediabetes (defined as hemoglobin A1c level of 5.7–6.4%).[4] As glycemic control is the main treatment goal, diets such as the Mediterranean, DASH, and vegetarian/vegan along with portion control have proven beneficial in preventing hyperglycemia. Avoiding refined carbohydrates and replacing them with fiber-rich whole grains is the mainstay of these diets.[39] As a reduction in hemoglobin A1c has been seen with weight loss, a combination exercise regimen including both aerobic and resistance training has shown to be effective in managing both weight and hyperglycemia (►**Table 9**).[40]

As patients reach the maximal benefits from both diet and exercise without arriving at the optimal hemoglobin A1c, the first line of pharmacologic therapy recommended is the introduction of metformin,[4] which tends to be well tolerated. It appears that the addition of this agent may lead to a significant reduction in MI and all-cause mortality.[41] Two classes of glycemic control agents that have recently shown clear cardiovascular benefits are the glucagon-like peptide 1 (GLP-1) agonists and sodium–glucose cotransporter (SGLT-2) receptor inhibitors. These drugs are reported to reduce

Table 7 Exercise recommendations

1.	Adults should be routinely encouraged to maintain a physically active lifestyle
2.	Each week adults should perform 150 min of moderate-intensity exercise, or 75 minutes of high-intensity exercise, or a combination of the two
3.	Any amount of physical activity in those unable to meet the recommended amount is still beneficial
4.	Decrease sedentary factor

Source: Derived from Arnett et al.[83]

major adverse cardiovascular events without causing major episodes of hypoglycemia.[42,43] Given the cardioprotective benefits brought on by these two classes of medications, they should be considered as reasonable agents to manage T2DM while preventing the development or progression of CVD.

The management of T2DM in the setting of secondary prevention of CVD does not differ from that employed in the primary prevention setting. A similar approach to lifestyle management with diet and exercise, followed by pharmacotherapy with metformin, GLP-1 agonists, and SGLT-2 receptor inhibitors, as needed, is recommended in those with established CVD. Of note, the DAPA-HF trial[44] and EMPEROR-Reduced trial[45] showed that SGLT-2 inhibition reduced the combined risk of cardiovascular death and hospitalization for heart failure in patients with heart failure with reduced ejection fraction, regardless of diabetes status. Therefore, it seems reasonable to give special consideration to SGLT-2 inhibitors in patients who have already experienced a CVD event with resultant reduction in left ventricular dysfunction.

Lipid-Lowering Therapy

Reduction in LDL is a pivotal aspect of the prevention of clinical ASCVD. In the primary prevention setting, adults between the ages of 20 and 39 years should focus on a healthy lifestyle to decrease LDL values. Initiation of drug therapy can be considered in this age group if the LDL is at least 160 mg/dL.[4] For adults between the ages of 40 and 75 years, a calculation of the 10-year ASCVD risk helps with risk stratification as patients with higher risk scores benefit from higher therapy intensity and vice versa (►**Table 10**). The following groups of patients require initiation of drug therapy owing to their intermediate risk for ASCVD events regardless of ASCVD score: those with LDL level of at least 190 mg/dL (require high-intensity therapy) and those diagnosed with diabetes between the ages of 40 and 75 years (moderate-intensity therapy).[4] The decision to initiate or maintain treatment therapy in patients who are older than 75 years should only be reached after a risk–benefit discussion between physicians and the patient.[46] Statins are first-line therapy, and require monitoring of liver enzymes 12 weeks after initiation of therapy and with any change in dose.[47]

The importance of reducing LDL for the secondary prevention of CVD has been underscored by recent guideline

Table 8 Hypertension recommendations

1.	Adults with hypertension adopt nonpharmacological interventions including weight loss, a heart-healthy dietary pattern, sodium reduction, potassium supplementation, increased physical activity, and limited alcohol intake
2.	In patients with a 10-year ASCVD risk score of 10% or higher, or with hypertension and diabetes, and with BP of 130/80 mm Hg or higher, BP lowering medications should be initiated
3.	In adults with hypertension and CKD, diabetes, or 10-year ASCVD risk score of 10% or higher, a target BP $<$ 130/80 mm Hg should be used
4.	In patients with a 10-year ASCVD risk score of 10% or lower, BP lowering meds should be initiated at BP $>$ 140/90 mm Hg
5.	In adults without additional ASCVD risk factors, targeting a BP of 130/80 mm Hg may be reasonable

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CKD, chronic kidney disease.
Source: Derived from Arnett et al.[83]

changes calling for lower absolute serum values in patients who have already experienced clinical ASCVD. Though prior and current iterations of the AHA/ACC Multisociety Guideline on the Management of Blood Cholesterol have recommended an absolute reduction in serum LDL of 50% or greater, the contemporary guideline both defines an absolute target LDL value and recommends additional therapeutic modalities in a designated subset of patients with clinical ASCVD felt to be "very high risk."[47] Specifically, all patients with clinical ASCVD should be initiated on high-intensity statin, with a moderate-intensity statin reserved for those who cannot tolerate higher dosing. While the primary goal of statin therapy in this regard is to lower the LDL level by 50% (the expected effect of a high-intensity statin, by definition), those who continue to have an LDL level above the goal of 70 mg/dL should receive additional therapy with ezetimibe. For those who fall into the very high-risk category, a proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitor should be considered in addition to statin and ezetimibe to reach the therapeutic goal of 70 mg/dL or less. The push for lower targeted LDL values comes in the wake of several large meta-analyses showing that patients with prior ASCVD on more intensive statin regimens experience fewer vascular events when compared with those on more conservative statin therapy.[48–50] In one meta-analysis by the Cholesterol Treatment Trialists' Collaboration comparing patients with prior ASCVD on high-intensity statin to those on moderate- or low-intensity statin, the high-intensity statin group benefitted from an overall reduction in coronary death and nonfatal MI of 13% and a reduction in coronary revascularization of 19%.[48] Thus, patients and clinicians should continue to closely monitor serum LDL values, with a plan to step up therapy as indicated if goal values are not met.

Antiplatelet Agents

For several decades, aspirin use for the primary prevention of CVD was encouraged following promising results from multiple studies; however, its overall benefit has been challenged in more recent years, and appears nuanced. Aspirin is an irreversible inhibitor of cyclooxygenase (COX), an enzyme required for the synthesis of prostaglandins. The decrease in prostaglandins resulting from aspirin administration is responsible for its antipyretic and analgesic effects, which are temporary until cells can regenerate new COX. In platelets, the inhibition of COX prevents platelet activation and aggregation, and is irreversible due to the lack of nuclei preventing new synthesis.[51] Aspirin is cheap, over-the-counter, and taken once per day, and does not require dosing titration or routine laboratory follow-up—all factors that support ease of use. A pivotal and supportive early trial of the 1980s, the Physicians' Health Study, evaluated the effectiveness of aspirin 325 mg versus placebo every other day over a follow-up period of approximately 5 years. While there was no mortality benefit identified in the aspirin group, there was a significant 44% risk reduction in the development of MI. Further analysis revealed that the risk reduction was predominantly in those over 50 years of age, and was greatest in those with low levels of cholesterol.[52] The Collaborative Group of the Primary Prevention Project studied the effects of daily low-dose aspirin in those specifically with cardiac risk factors, and found a decreased risk of cardiac death and total cardiac events (►**Table 11**).[53]

However, numerous studies published after the early 2000s showed limited or no overall benefit from aspirin for primary prevention, including in those with diabetes mellitus, asymptomatic peripheral artery disease, and those over 60 years with cardiovascular risk factors.[54–57] Three large trials published in 2018—the ASCEND trial, the ASPREE trial, and the ARRIVE trial—sought to assess the effect of aspirin for primary prevention and address prior data limitations in specific patient populations: those with diabetes mellitus, the elderly, and those at moderate risk for CVD, respectively. The ASCEND trial[58] found a significant reduction in primary CVD events (MI, stroke, transient ischemic attack [TIA], or all-cause mortality) from 9.6 to 8.5% over a mean follow-up of 7 years in those with diabetes mellitus, but with an increase in bleeding events in those randomized to aspirin (4.1 vs. 3.2%). The ASPREE trial[59] evaluated the effect of aspirin in the elderly on the development of a composite of death, dementia, and physical disability, and found no difference from placebo. Further, there was an increased risk of bleeding and all-cause mortality in the treatment group, the latter of which seemed to be due to an increased risk of cancer. The ARRIVE trial[60] showed no significant difference in a composite end point of cardiovascular death, MI, unstable angina, TIA, or stroke between the aspirin and placebo groups in those with CVD risk factors over a median follow-up of 5 years. There was an increased risk of gastrointestinal bleeding in the aspirin group (0.97 vs. 0.46%), with most bleeding events considered mild. Of note, though the ARRIVE trial had sought to enroll a group of individuals felt to be at moderate risk of CVD with three or more risk factors (active tobacco use, hypertension, dyslipidemia, and family history of CVD), the overall event rate was approximately one-third of what was anticipated. Though it is speculative, this may have been due to concomitant improvement in control of other risk factors such as hypertension and diabetes over the course of the study. The results of these trials show that the benefit of aspirin for primary prevention is nuanced, and individual risks of bleeding and the presence of other cardiovascular risk factors should be taken into consideration.

The role of aspirin in the secondary prevention of CAD has been well established and supported by numerous randomized controlled trials. The International Study of Infarct Survival-2 trial randomized over 17,000 patients with an acute MI to receive streptokinase infusion over 1 hour, aspirin for 1 month, or placebo. The aspirin group had a significant reduction in vascular death compared with those given placebo after just 5 weeks (9.4 vs. 11.8%).[61] Another trial found that among those who had experienced either an acute

Table 9 Diabetes mellitus recommendations

1.	Each week adults should perform 150 min of moderate-intensity exercise, or 75 minutes of high-intensity exercise, to improve glycemic control and achieve weight loss
2.	At the time of diagnosis, initiate lifestyle therapies as well as metformin as first-line therapy
3.	For those with additional ASCVD risk factors who require further glucose lowering therapy, it is reasonable to initiate SGLT-2 inhibitor or GLP-1R agonist

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; GLP-1R, glucagon-like peptide-1 receptor; SGLT-2, sodium–glucose cotransporter.
Source: Derived from Arnett et al.[83]

Table 10 Statin intensity

High intensity	Atorvastatin 40–80 mg
	Rosuvastatin 20–40 mg
Moderate intensity	Atorvastatin 10–20 mg
	Fluvastatin 40 mg twice daily
	Lovastatin 40 mg
	Pravastatin 40–80 mg
	Pitavastatin 2–4 mg
	Rosuvastatin 5–10 mg
	Simvastatin 20–40 mg
Low intensity	Fluvastatin 20–40 mg
	Lovastatin 20 mg
	Pravastatin 10–20 mg
	Pitavastatin 1 mg
	Simvastatin 20–40 mg

Source: Derived from 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines by NJ Stone et al.[84]

or prior event (unstable angina, MI, cerebrovascular accident (CVA), peripheral artery disease (PAD)), the addition of an antiplatelet reduced the risk of any serious vascular event by approximately one-third, without an adverse effect on other causes of death.[62] In light of multiple trials consistently showing this benefit, the ACC/AHA recommends aspirin 81 to 162 mg per day indefinitely for the secondary prevention of CVD.[63]

All patients who experience an ACS should receive a second antiplatelet agent in addition to aspirin for a year. Acceptable agents include the P2Y12 receptor blockers clopidogrel, ticagrelor, or prasugrel, though the first two are preferred in patients who do not undergo percutaneous coronary intervention (PCI). In those who do undergo PCI, any of the three agents may be used, and the P2Y12 inhibitor should be maintained for at least 1 month in those who receive a bare metal stent and for 1 year in those who receive a drug-eluting stent.[27]

Miscellaneous Treatments

Fish Oil

Fish oil, or long-chain omega-3 fatty acids, has been the subject of interest for several decades after early trials showed lower rates of stroke, MI, and death in those with prior CVD. Fish oil supplementation is widely commercially available, and most frequently composed of 1 g or less of a mixture of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Although the exact mechanism by which fish oil might reduce CVD events has yet to be determined, there is a suggestion for a reduction in inflammation with administration.[64] With numerous small studies showing mixed results, a large 2018 meta-analysis composed of 77,917 individuals was conducted by the AHA, but it failed to show any benefit of fish oil in the primary prevention of CAD.[65] However, the analysis was repeated the following year with the addition of three new trials, which increased the number of participants by more than 60%. Reanalysis with the larger dataset showed that fish oil supplementation did indeed decrease the risk of MI, CAD, and CAD death, with greater risk reduction linearly related to the dose of fish oil administered.[66]

Unlike prior studies, which evaluated the effects of standard dose combinations of EPA and DHA, the REDUCE-IT trial assessed the efficacy of 4 g of pure EPA (brand name Vascepa) in preventing CVD events. The study population included those with elevated triglyceride levels despite statin use, with approximately 30% of patients assessed for primary prevention and 70% for secondary prevention.[67] The study group experienced a significant reduction in CVD events, which led to the FDA's approval of Vascepa as a secondary therapy for the reduction of CVD events in those with two or more cardiac risk factors, diabetes mellitus or established CVD, and triglyceride levels of 150 mg/dL or higher.[68] Overall, fish oil—whether used in a potent, purified, prescription form for a specific population, or in its usual and easily accessible form—shows promise for both the primary and secondary prevention of CAD events. However, supplements undergo far less regulation by the Federal Drug Administration, and there are no current guidelines to recommend its routine use. Ongoing research to clarify which subgroups may experience the greatest benefit from supplementation is still needed, but recommendations may be made on an individual basis in the interim.

Vitamin D

Vitamin D, another widely available supplement, has been studied for the prevention of CVD but with less promising results. Early trials[69,70] indicated a possible correlation

Table 11 Antiplatelet agents

Agent		Class
Primary prevention		
Aspirin	Low-dose aspirin can be considered for primary prevention in adults age 40–70 y with an elevated risk for clinical ASCVD without increased bleeding risk	IIb
	Low-dose aspirin should not be given routinely in those > 70 y	III
	Low-dose aspirin should not be given for primary prevention to any adult at increased risk of bleeding	III
Secondary prevention		
Aspirin	Low-dose aspirin should be given to those with CAD unless contraindicated	I
	For patients undergoing coronary bypass grafting, aspirin 100–325 mg daily should be started within 6 h	I
P2Y12	Clopidogrel 75 mg can be used for those with CAD who are intolerant or allergic to aspirin	I
P2Y12 or aspirin	For patients with TIA, CVA, or symptomatic PAD, aspirin 75–325 mg or clopidogrel 75 mg should be taken daily	I
P2Y12 + aspirin	If the risk of bleeding from thienopyridine after stent placement outweighs the benefit, it is reasonable to stop before 12 mo	IIa

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; CVA, cerebrovascular accident; PAD, peripheral artery disease; TIA, transient ischemic attack.
Source: Derived from Smith et al.[63,85]

between low serum levels of vitamin D and cardiovascular events. Additionally, vitamin D has been shown to have beneficial effects on inflammatory markers,[71] insulin sensitivity,[72] and the renin–angiotensin system,[73] triggering an interest in supplementation for CVD prevention. The VITAL trial assessed the effect of daily supplementation of 2,000 IU of vitamin D_3 in a primary prevention cohort including 25,871 individuals over approximately 5 years. Unfortunately, no benefit was found for the prevention of CVD, nor did it lead to an improvement in inflammatory markers or lipid profiles in participants over the study period.[74] At this time, there is no large trial or meta-analysis to suggest a benefit for supplementation for either the primary or secondary prevention of CVD.

Folic Acid

With some epidemiologic studies showing a lower incidence of CVD in those with lower serum homocysteine levels, there has been an interest in folic acid supplementation for CVD risk reduction. Trials have shown that daily supplementation with 0.5 to 5 mg of folic acid leads to a 25% reduction in plasma homocysteine levels,[75] but studies assessing the effect on CVD development have been mixed. One large meta-analysis showed a 10% lower risk of stroke, with a 4% lower risk of CVD development. A greater benefit was seen in those with lower plasma folate levels at initiation, as well as in those who had no pre-existing CVD.[76] Although further research is needed, there is some indication that folic acid supplementation is beneficial, especially for use in primary prevention and in those with low plasma folate levels.

Conclusion

Overall, CVD is responsible for significant morbidity and mortality worldwide, but with appropriate management of risk factors through lifestyle interventions and pharmacotherapies, there is a great opportunity to impact millions of lives. Although medical therapies and their proper application continue to improve over time, data show that only around two-thirds of patients are adherent to treatment, even in the secondary prevention setting.[77] This highlights the excellent opportunity and important role health care providers can provide with ongoing patient education and encouragement.

Conflicts of Interest
None declared.

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