Coronary Disease, Screening and Primary Prevention

Basic Information

Terminology

- Coronary artery disease is a term used to describe atherosclerotic changes that occur in the blood vessels that supply the heart
- Coronary artery disease ranges from asymptomatic nonobstructive atherosclerosis and stable angina to acute coronary syndromes such as unstable angina, non–ST-elevation myocardial infarction, and ST-elevation myocardial infarction
- Screening for coronary artery disease refers to evaluation of asymptomatic and at-risk patients with the goal of identifying existing disease
- Primary prevention encompasses interventions undertaken with aim of preventing or delaying onset of coronary disease

Epidemiology

- Atherosclerotic cardiovascular disease remains the leading cause of mortality, morbidity, and overall health care costs globally despite significant improvement in outcomes in recent years[1-3]
- WHO reported that ischemic heart disease was responsible for approximately 9 million deaths worldwide in 2016[4]
- Currently, the estimated annual incidence of myocardial infarction in the United States is 605,000 new attacks and 200,000 recurrent attacks[5]
- Significant opportunity to improve clinician and patient participation in evidence-based screening and prevention remains

Etiology and Risk Factors

Etiology

- Coronary artery disease is a multifactorial inflammatory disease involving a complex interaction of genetic and environmental risk factors resulting in atherosclerosis
- The inciting event for atherosclerotic cardiovascular disease is generally endothelial injury or dysfunction resulting in an inflammatory response that leads to formation

of atherosclerotic plaque/atheroma consisting of inflammatory cells, cellular debris, smooth muscle cells, and varied amounts of cholesterol (ie, lipid core)[6,7,8]

Risk Factors

- Major risk factors[9,10]
  - Older age
  - Male sex
  - Hypertension
  - Diabetes
  - Dyslipidemia
  - Obesity
  - Smoking
- Additional risk factors
  - Low socioeconomic status has been linked to cardiovascular risk as a result of early and ongoing exposure to behavioral, educational, dietary, stress-related, and social risks that influence adherence to dietary, exercise, and pharmacological recommendations for heart health[10]
  - Poor quality sleep, short sleep duration (less than 6 hours), and poor sleep hygiene contribute to risk of hypertension, obesity, and adverse cardiovascular outcomes[10]

Risk Estimation

- Identifies the likelihood of future major cardiovascular events based on accurate assessment of medical, social, and family history using validated risk prediction calculators
- Risk assessment is the cornerstone of primary prevention and should be part of shared decision-making discussions between providers and patients to align goals of care and treatment strategies[10]
- Thorough evaluation of risk is essential to determine indications and potential benefits of lifestyle or pharmacological management of modifiable risk factors

Risk Assessment

- Assess medical and social history for:
  - Symptoms of angina or anginal equivalent
  - Level of physical activity: less than 150 minutes per week of moderate-intensity exercise[11-13]
  - Dietary habits: diet high in sugars, saturated and trans fats, low-fiber foods, and high-sugar drinks[14]
  - Smoking: more than 100 cigarettes in lifetime

- Alcohol use: more than 2 drinks per day[15]
- Family history of premature atherosclerotic disease: history of coronary artery disease in first-degree male relatives younger than 55 years and female relatives younger than 65 years

- Physical examination
  - Presence of xanthomas may indicate underlying lipid disorders
- Risk calculation
  - Several cardiovascular risk calculators are available; no single risk calculator is appropriate for all patients
  - Validated calculators include:
    - American College of Cardiology/American Heart Association ASCVD Risk Estimator[16] and pooled cohort equations
      - Most widely used in United States
      - Most reliable among US non-Hispanic White populations and non-Hispanic Black populations
      - May overestimate or underestimate risk in other populations
    - Framingham risk score[17]
      - Similar to American College of Cardiology/American Heart Association ASCVD Risk Estimator
    - Reynolds risk score[18,19]
      - More reliable for higher socioeconomic population
    - Joint British Societies (JBS3) Risk Estimator and QRISK[20]
      - More reliable for UK population
    - European Society of Cardiology SCORE (Systematic Coronary Risk Evaluation)[21,22]
      - Most reliable for European population
  - Some risk calculators provide 10-year atherosclerotic cardiovascular disease risk; others provide both 10-year as well as long-term/lifetime risk
    - Adults aged 20 to 59 years often have a low estimated 10-year risk but presence of only 1 major risk factor increases lifetime risk; therefore, consider calculation of a lifetime/30-year risk to reinforce adherence to lifestyle changes[10,16,23,24]
  - Use 10-year risk score to inform patient-centered discussions about initiation or escalation of lifestyle and pharmacological interventions aimed at reducing risk of adverse cardiovascular outcomes
    - Based on American College of Cardiology/American Heart Association ASCVD Risk Estimator scores, 10-year risk is classified as:[16]

    - Low risk: less than 5%
    - Borderline risk: 5% to 7.5%
    - Intermediate risk: 7.5% to 20%
    - High risk: more than 20%
- Risk-enhancing factors
    - Although risk calculators are powerful tools to predict population risk, they have limitations when applied to individuals
    - Presence or absence of additional risk-enhancing factors helps to further individualize risk prediction and guide management (eg, measuring coronary artery calcium score, initiating lipid-lowering medications) **(Figure 1)**
    - Risk-enhancing factors include:[25]
        - Family history of premature atherosclerotic cardiovascular disease (males younger than 55 years; females younger than 65 years)
        - Metabolic syndrome: presence of 3 of the following factors makes the diagnosis:
            - Increased waist circumference (by ethnically appropriate cut points)
            - Elevated triglyceride levels: higher than 150 mg/dL, nonfasting
            - Elevated blood pressure
            - Elevated glucose level
            - Low HDL-C: below 40 mg/dL in males; below 50 mg/dL in females)
        - Chronic kidney disease: estimated GFR 15 to 59 mL/minute/1.73 m^2
        - Chronic inflammatory conditions (eg, rheumatoid arthritis, lupus, HIV/AIDS, psoriasis)
        - High-risk race or ethnicity (eg, South Asian ancestry)
        - History of premature menopause (before age 40 years) or pregnancy-associated conditions (eg, preeclampsia)
        - Lipid-level or biomarker abnormalities
            - Hypertriglyceridemia: 175 mg/dL or higher, non-fasting
            - Elevated lipoprotein(a): 50 mg/dL or higher constitutes a risk-enhancing factor, especially at higher levels
                - Family history of premature atherosclerotic cardiovascular disease is a relative indication for measurement
            - Elevated apolipoprotein B: 130 mg/dL or higher corresponds to an LDL-C level higher than 160 mg/dL and constitutes a risk-enhancing factor
                - Triglyceride level of 200 mg/dL or higher is a relative indication for measurement
        - Abnormal ankle-brachial index: less than 0.9

- Recommendations for atherosclerotic cardiovascular disease risk estimation factor in sex, age, history, and comorbid conditions
  - For patients of any age with underlying conditions that predispose them to cardiovascular disease (eg, family history, current tobacco use, hypertension, obesity, hyperlipidemia), 2021 European Society of Cardiology guidelines recommend periodic cardiovascular risk assessment
  - Screening recommendations for younger adults with no known cardiovascular disease differ between organizations
    - 2019 American College of Cardiology/American Heart Association guidelines offer a moderate recommendation to assess patients aged 20 to 39 years with no established cardiovascular disease for traditional risk factors every 4 to 6 years to facilitate ongoing discussions about lifestyle modifications[10]
    - 2021 European Society of Cardiology guidelines *do not* recommend screening male patients younger than 40 years and female patients younger than 50 years with no known risk factors[22]
  - Both American College of Cardiology/American Heart Association and European Society of Cardiology recommend consideration of periodic assessment of cardiovascular risk factors and calculation of 10-year atherosclerotic cardiovascular disease risk for patients over 40 years
    - American College of Cardiology/American Heart Association recommends screening all patients aged 40 to 75 years using risk calculators[10,16,23]
    - European Society of Cardiology recommends considering screening male patients older than 40 years and female patients older than 50 years or post-menopausal[22]
  - American College of Cardiology/American Heart Association recommends:
    - Assessment of 30-year or lifetime risk for patients with low 10-year risk, particularly those younger than 59 years[10,16,23,24]
    - Use of risk-enhancing factors or coronary artery calcium score to guide risk discussion and decision about preventive intervention for adults at borderline risk or intermediate risk[10,25,26]
  - Reassess cardiovascular risk factors over time and engage in longitudinal shared decision-making discussions about risk assessment and preventive therapy[10]

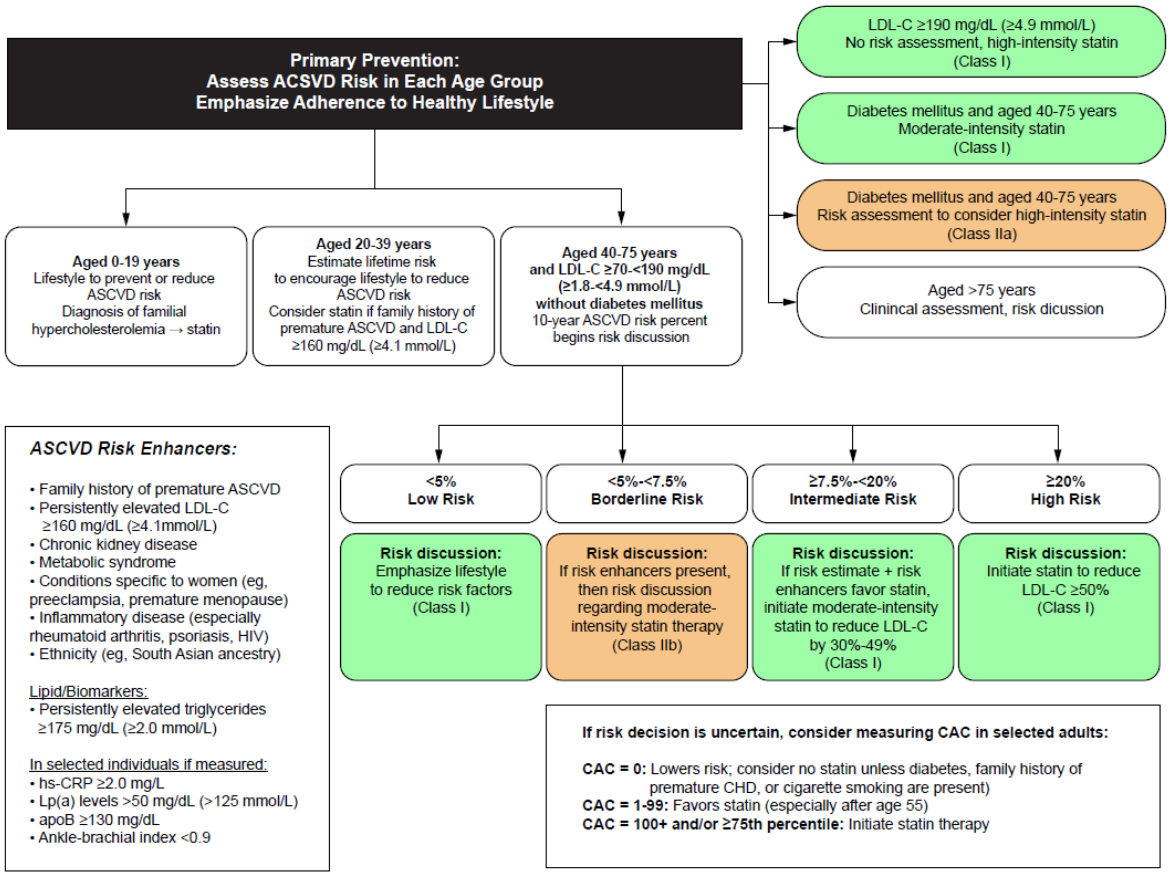

Figure 1. American College of Cardiology/American Heart Association algorithm for primary prevention of atherosclerotic cardiovascular disease.

Screening and Prevention

Screening

- Identifies existing disease in asymptomatic patients using invasive and noninvasive testing (eg, stress testing)
- Routine screening for coronary artery disease with stress testing in asymptomatic, low-risk adults is not recommended[27-29]
- Consider exercise stress testing using ECG in:[27]

- Asymptomatic male patients older than 45 years and female patients older than 55 years who:
  - Plan to start a vigorous exercise program
  - Are involved in occupations in which impairment may impact public safety (eg, pilots, bus drivers)
  - Are at high risk for coronary artery disease due to presence of peripheral arterial disease and chronic renal failure
- Patients with multiple risk factors to guide risk-reduction therapy

Prevention

- Shared decision-making between clinicians and patients for early identification and modification of risk factors is key to reducing morbidity and mortality associated with coronary artery disease
- American College of Cardiology/American Heart Association recommends team-based approach for control of risk factors associated with atherosclerotic cardiovascular disease[10]
- Socioeconomic and educational status is an important determinant of cardiovascular disease risk internationally[10]
  - Health care systems must consider various factors that can impact effective delivery of primary prevention (eg, housing and food insecurity, transportation difficulties, low health literacy, financial strain, inadequate social support)

Nutrition and Diet

- Diet emphasizing intake of vegetables, fruits, legumes, nuts, whole grains, and fish (ie, plant-based and Mediterranean diets) is recommended to decrease atherosclerotic cardiovascular disease risk factors and is associated with lower risk of all-cause mortality[10,22,30-34]
  - In the Adventist Health Study-2 cohort, using meat for protein was associated with 61% increase in mortality rate, whereas replacing meat with nuts and seeds was associated with 40% reduction in mortality rate[33]
- Replace saturated fat with dietary monounsaturated and polyunsaturated fats to reduce disease risk[10,22,35,36]
- Avoid intake of trans fat as it increases risk
  - Trans fats have an adverse effect on lipids and lipoproteins and promote endothelial dysfunction, insulin resistance, inflammation, and arrhythmias[35,37]
  - Trans fats have been associated with higher all-cause mortality rate in the REGARDS study[38]
- Reduce dietary sodium consumption as doing so has been shown to reduce blood pressure and cardiovascular events[10,22,39]

- Minimize sugar-sweetened and artificially sweetened beverages to less than 10% of total calories,[22] because they increase risk of type 2 diabetes and atherosclerotic cardiovascular disease[32,38,40]
    - Diet that includes juices, sweetened beverages, refined grains, potatoes or fries, and sweets resulted in a greater increase in coronary events than the increase seen with consumption of animal products[32]
- Minimize intake of refined carbohydrates and processed meats to reduce risk[10,38,41,42]
- Restrict alcohol consumption to less than 100 g per week[22]

Physical Activity and Exercise

- Physical activity is the cornerstone of maintaining and improving cardiovascular health
- Adults should engage in at least 150 minutes per week of moderate-intensity physical activity or at least 75 minutes per week of vigorous-intensity aerobic physical activity to reduce atherosclerotic cardiovascular disease risk[10,22,43-45]
    - Moderate-intensity physical activities include:
        - Brisk walking (2.4-4 mph)
        - Biking (5-9 mph)
        - Ballroom dancing
        - Active yoga
        - Recreational swimming
    - Vigorous-intensity physical activities include:
        - Jogging or running
        - Biking (more than 10 mph)
        - Singles tennis
        - Swimming laps
    - Short durations of exercise are as beneficial as longer ones, and total accumulated amount should be considered[46]
- Engaging in some moderate- or vigorous-intensity physical activity even if less than the recommended amount can be beneficial[10,22,43,44]
    - A consistent, strong inverse dose–response relationship exists between amount of physical activity and incident atherosclerotic cardiovascular disease events and death
- Sedentary behavior in adults is detrimental to atherosclerotic cardiovascular disease risk and should be minimized[10,22,47,48]
- Routinely assess physical activity and counsel patients at health care visits

Management of Obesity

- Calculate BMI annually or more frequently to identify patients who are overweight and obese[10]
- Both overweight and obesity increase atherosclerotic cardiovascular disease risk; therefore, weight loss is recommended in these patients to improve atherosclerotic cardiovascular disease risk profile[10,22,49]
- Weight loss should be achieved with comprehensive lifestyle modification that includes caloric restriction by monitoring food intake and regular physical activity[10,22,49-51]
    - Nutritional aspect of obesity revolves around balancing caloric intake with caloric expenditure
    - Adults who are overweight or obese are advised to participate in comprehensive lifestyle programs 6 months or longer in duration that help participants adhere to a low-calorie diet (800-1500 kcal/day) and increased physical activity
    - Comprehensive lifestyle intervention has been shown to produce weight loss comprising 5% to 10% of initial body weight in the short term (less than 6 months) and intermediate term (6-12 months) compared with usual care[49,51]
- Weight loss (5% of initial weight or greater) is associated with moderate improvements in blood pressure and LDL-C, triglyceride, and glucose levels and could delay onset of type 2 diabetes[49,50]
- Central adiposity, as measured by an increased waist circumference, has been associated with increased cardiometabolic and atherosclerotic cardiovascular disease risk and can be calculated to identify patients at higher cardiometabolic risk[10,52,53]
- FDA-approved pharmacological therapies **(Table 1)** and bariatric surgery are complementary to lifestyle interventions and have a role in weight loss for select patients[10,22,54,55]

Tobacco Use

- Smoking and smokeless tobacco (eg, chewing tobacco) are a leading cause of preventable disease, disability, and death in the United States[56]
- Cigarette smoking is a strong, independent risk factor for atherosclerotic cardiovascular disease events[57,58]
    - Even low levels of smoking increase risk of acute myocardial infarction, thus reducing the number of cigarettes per day does not totally eliminate risk
- Tobacco use must be evaluated and documented at every health care visit to facilitate tobacco cessation[59]

  - To improve detection, ask “Have you smoked any tobacco product in the past 30 days, even a puff?” or “Have you vaped or used any other tobacco product in the past 30 days?”
- Strongly advise tobacco abstinence at every visit to reduce disease risk[57,60]
  - Tobacco users are more likely to quit after 6 months when clinicians strongly advise tobacco cessation than when clinicians give no advice or usual care
- Use a combination of behavioral interventions and pharmacotherapy to maximize cessation rates[10,22,60-62]
- Pharmacotherapy recommendations (see Table 1)[62]
  - First line: varenicline plus combination nicotine replacement therapy are first line for tobacco cessation, including in smokers with cardiovascular disease
    - Combination nicotine replacement therapy (comprising a nicotine patch plus patient’s choice of nicotine gum, lozenge, or inhaler or spray) is more effective than a single agent; adding a rapidly absorbed product (eg, gum) to patch therapy helps to control situational cravings
  - Second line: bupropion plus single nicotine replacement therapy are considered second line therapy for patients who are unable or unwilling to use first line choices
  - Use combination of agents as follows for smokers who have partial response or who do not achieve complete cessation with individual agents:
    - Varenicline plus single nicotine replacement therapy
    - Varenicline plus bupropion
    - Bupropion plus single nicotine replacement therapy
  - Bupropion lowers seizure threshold and is contraindicated in patients with history of seizure disorder
  - Neuropsychiatric adverse effects (eg, depression, psychosis, suicide) with varenicline and bupropion have been reported anecdotally but have not been observed or reported in large clinical trials and clinical cohort studies
    - Black box warnings about neuropsychiatric events have hence been removed by FDA[63,64]
- Consider having dedicated, trained staff to provide support for patients and to facilitate cessation[59]
- Advise all adults and adolescents to avoid secondhand smoke exposure to reduce risk[65]

Hypertension Management

- Hypertension is a well-established modifiable risk factor for atherosclerotic cardiovascular disease
- 2017 American College of Cardiology/American Heart Association guidelines recommend categorization of blood pressure levels for clinical decision[66]
  - Normal: systolic less than 120 mm Hg; diastolic less than 80 mm Hg
  - Elevated: systolic 120 to 129 mm Hg; diastolic less than 80 mm Hg
  - Stage 1 hypertension: systolic 130 to 139 mm Hg; diastolic 80 to 89 mm Hg
  - Stage 2 hypertension: systolic 140 mm Hg or higher; diastolic 90 mm Hg or higher
- European Society of Cardiology has a similar classification scheme but includes 6 categories of blood pressure
  - Optimal
  - Normal
  - High-normal
  - Grade 1
  - Grade 2
  - Grade 3
- Blood pressure targets for patients with hypertension[66]
  - For adults with confirmed hypertension and known cardiovascular disease or 10-year atherosclerotic cardiovascular disease risk of 10% or higher: less than 130/80 mm Hg is recommended
  - For adults with confirmed hypertension and no additional markers of increased cardiovascular risk: less than 130/80 mm Hg may be reasonable
- 2017 American College of Cardiology/American Heart Association guidelines provides the following framework for blood pressure management **(Figure 2)**. For patients with:
  - Normal blood pressure: promotion of healthy lifestyle behaviors and annual reassessment[66]
  - Elevated blood pressure: nonpharmacological therapy and blood pressure reassessment every 3 to 6 months[66]
  - Stage 1 and stage 2 hypertension: use 10-year atherosclerotic cardiovascular disease risk (as calculated by risk calculator) and stage of hypertension to guide therapy[66,67]
    - Adults with estimated 10-year risk of less than 10% and stage 1 hypertension: nonpharmacological therapies are recommended

    - Evaluate blood pressure every 3 to 6 months; if uncontrolled, initiate pharmacologic therapy (see Table 1)[67]
  - Adults with estimated 10-year risk of 10% or higher and stage 1 hypertension: initiation of blood pressure lowering medications is recommended in addition to nonpharmacologic therapies[66]
  - Adults with stage 2 hypertension: initiation of blood pressure lowering medications is recommended in addition to nonpharmacologic therapies regardless of risk[66]
- Nonpharmacological intervention
  - Maintenance of ideal body weight
    - Expect reduction of 1 mm Hg in blood pressure for every 1 kg reduction in body weight[68]
  - Healthy diet such as DASH (Dietary Approaches to Stop Hypertension) dietary pattern
    - Diet rich in vegetables, fruits, whole grains, and low-fat dairy products and with reduced amounts of total and saturated fat[39]
  - Reduced intake of dietary sodium
    - Optimal goal is less than 1500 mg/day but aim for at least 1000 mg/day reduction[66,69]
  - Increased intake of dietary potassium
    - Aim for 3500 to 5000 mg/day[66,70]
  - Physical activity
    - 90 to 150 minutes/week of aerobic activity or 90 to 150 minutes/week of dynamic resistance activity[66,71,72]
  - Moderation in alcohol intake
    - 2 drinks or less/day for males; 1 drink or less/day for females[66,73,74]
- Antihypertensive medications (see Table 1)
  - Pharmacological agents, in addition to lifestyle modifications, not only lower blood pressure but reduce risk of cardiovascular events and death[66]
  - First line agents: thiazide diuretics, dihydropyridine-calcium channel blockers, and ACE inhibitors or angiotensin receptor blockers[66,75-79]
    - High-quality randomized clinical trials have shown these classes of medications prevent cardiovascular disease as compared with placebo
    - For low-risk stage 1 hypertension, start with a single agent with dose titration and sequential addition of other agents to achieve blood pressure target

    - For adults with stage 2 hypertension, initiate 2 first line agents of different classes
  - ACE inhibitors or angiotensin receptor blockers are preferred first line agents for patients with chronic kidney disease or diabetes in presence of albuminuria[80-83]
  - Angiotensin receptor blockers are preferred in Black patients because of increased risk of angioedema with ACE inhibitors[75]
  - Evaluate adherence to antihypertensive medications and assess response to treatment as appropriate at monthly intervals until control is achieved[66,75,84,85]
  - Reduce polypharmacy (use single-pill combinations) and prescribe once-daily dosing regimen when possible to improve adherence[75]
  - For adults older than 65 years with hypertension, high burden of comorbidity, and limited life expectancy:
    - Use clinical judgment, patient preference, and team-based approach to assess risk or benefit regarding intensity of blood pressure lowering and choice of antihypertensive agent[66]

Statin Use

- Decision to initiate statin should be driven by age, 10-year atherosclerotic cardiovascular disease risk, and LDL-C levels
- 2019 American College of Cardiology/American Heart Association and 2021 European Society of Cardiology guidelines align on many recommendations. However, their approach differs slightly based on patient characteristics, guideline-specific risk-level assessments, and goals of therapy
  - Both organizations recommend aggressive management with highest tolerated dose of statin for patients with familial hypercholesterolemia and/or LDL-C of 190 mg/dL or higher[10,22,25,86,87]
- Patient age
  - European Society of Cardiology guidelines recommend aggressive lipid management for patients younger than 70 years
  - American College of Cardiology/American Heart Association extend recommendations to patients younger than 75 years[10,22]
- Target LDL-C goals
  - European Society of Cardiology guidelines provide a stepped approach to targeted LDL-C goals for specific patient risk categories in addition to recommendations to reduce baseline LDL-C percentages[22]
  - American College of Cardiology/American Heart Association does not provide specific target LDL-C goals but recommends percentage reduction from baseline according to comorbidity and risk level[10]

- Coronary artery calcium score
  - American College of Cardiology/American Heart Association incorporates specific recommendations for statin initiation based on coronary artery calcium score while European Society of Cardiology does not
  - American College of Cardiology/American Heart Association recommends coronary artery calcium score to determine need for statin for intermediate (7.5%-20%) and borderline (5%-7.5%) atherosclerotic cardiovascular disease risk patients[10,25,26,88]
    - Score of 0 reduces risk level to low risk and allows for deferral or delay in initiation of statin unless patient has diabetes, family history of coronary artery disease, or current tobacco use
    - Score of 1 to 99 favors initiation of statin, particularly in patients aged 55 years and older
    - Score greater than 100 and/or 75th percentile is a strong indicator to initiate statin
- Consider initiating statin in presence of other risk-enhancing factors as noted by 2018 American College of Cardiology/American Heart Association cholesterol guidelines[10,25]
- Treatment intensification should be conducted using a stepwise approach based on patient response to therapy and assessment of individual risks and benefits[22]
- Goals of care related to risks and benefits of initiating statin should be discussed with patients older than 70 years[10,25]

Aspirin Use

- Aspirin is not generally recommended for primary prevention of coronary heart disease but may be considered for certain subpopulations
- American College of Cardiology/American Heart Association recommends:[10,89-91]
  - Consideration of low-dose aspirin (75-100 mg) for patients aged 40 to 70 years who are at high atherosclerotic cardiovascular disease risk and low bleeding risk
  - Not initiating low-dose aspirin for primary prevention among patients at increased risk of bleeding, including those with:
    - History of gastrointestinal bleeding
    - Advanced age (older than 70 years)
    - Use of systemic corticosteroids or NSAIDs
    - Chronic conditions that predispose to increased bleeding (eg, coagulopathy, thrombocytopenia)

- US Preventive Services Task Force is more conservative in their recommendations than American College of Cardiology/American Heart Association, noting insufficient evidence to support use of aspirin for primary prevention among patients younger than 50 years and older than 70 years. They recommend:[89]
  - Consideration of low-dose aspirin for patients aged 50 to 59 years with 10-year atherosclerotic cardiovascular disease risk greater than 10%, life expectancy of 10 years or more, and no increased risk of bleeding
  - Selective use of aspirin for patients aged 60 to 68 years with same risk profile as above
- American Diabetes Association and European Society of Cardiology recommend:
  - Consideration of low-dose aspirin for primary prevention among patients with diabetes who have at least 1 major cardiovascular risk factor or are otherwise at high to very high risk of atherosclerotic cardiovascular disease with no increased risk of bleeding[22,92]

Management of Diabetes

- Diabetes is a major risk factor for cardiovascular disease, which remains the most common cause of death for adults with type 2 diabetes[93]
- American College of Cardiology/American Heart Association, American Diabetes Association, and European Society of Cardiology support lifestyle modification to prevent cardiovascular disease in this population[10,22,92-94]
  - Lifestyle management
    - Physical activity: 150 minutes/week or more moderate-intensity exercise (50%-70% maximum predicted heart rate) over 3 or more days/week with no more than 2 consecutive days without exercise
      - Studies have shown that exercise leads to improvements in cardiovascular risk factors (eg, blood pressure, dyslipidemia, body composition), but no clinical trial has demonstrated a reduction in major cardiovascular endpoints or mortality[95,96]
    - Nutrition: a heart-healthy diet is a key intervention in diabetes treatment to improve glycemic control and improve atherosclerotic cardiovascular disease risk factors[30,97]
    - Weight management: counsel patients with overweight or obesity that lifestyle changes can lead to 30% rate of weight loss and clinically meaningful health benefits[10,92,94]
    - Smoking: advise all patients to not use tobacco products and provide smoking cessation counseling[10,92,94]
  - Glycemic control

- Type 2 diabetes is associated with 2- to 4-fold increased risk of cardiovascular disease with event rates correlating with the degree of hyperglycemia[93]
- 1% increase in hemoglobin A1C was associated with 21% increased risk of macrovascular disease (eg, cardiovascular disease events, including myocardial infarction) and 37% increased risk of microvascular disease (eg, retinopathy, nephropathy)[98,99]
- However, 3 major randomized clinical trials of diabetes and macrovascular disease comparing intensive glycemic control (with hemoglobin A1C of 6.4%-6.9%) versus standard glycemic control (with hemoglobin A1C of 7%-8.4%) failed to demonstrate a benefit on macrovascular outcomes with intensive therapy[100-102]
- Current American College of Cardiology/American Heart Association, American Diabetes Association, and European Society of Cardiology recommendations for glycemic control emphasize individualization of glycemic goals with the following targets:[22,92,94,103]
    - For most patients, hemoglobin A1C lower than 7% is a reasonable target to reduce risk of microvascular disease
    - Hemoglobin A1C lower than 6.5% may be considered for patients with diabetes of short duration, long life expectancy, and no significant cardiovascular disease if it can be achieved safely
    - Hemoglobin A1C lower than 8% for patients with severe or frequent hypoglycemic events, limited life expectancy, or comorbid conditions
- Choice of glucose-lowering agents (see Table 1)
    - Metformin is first line agent to improve glycemic control and reduce atherosclerotic cardiovascular disease risk[104]
    - Consider sodium-glucose cotransporter 2 inhibitors or a glucagon-like peptide-1 receptor agonist in patients that require glucose-lowering therapy despite initial lifestyle modifications and use of metformin and who have additional risk factors for cardiovascular disease[105-110]

- Additional risk factor management
    - Blood pressure[66,92,94]
        - Goal of less than 130/80 mm Hg is reasonable
        - Pharmacotherapy should include ACE inhibitors or angiotensin receptor blockers
    - Cholesterol[10,25,92,94,111,112]

- Patients with diabetes aged 40 to 75 years with LDL-C 70 to 189 mg/dL should receive at least moderate-intensity statin
- If aged 40 to 75 years with additional atherosclerotic cardiovascular disease risk factors, high-intensity statin is recommended

- Aspirin[92,94]
  - Low-dose aspirin is reasonable for patients with diabetes with at least 1 or more cardiovascular risk factors and no increased risk of bleeding

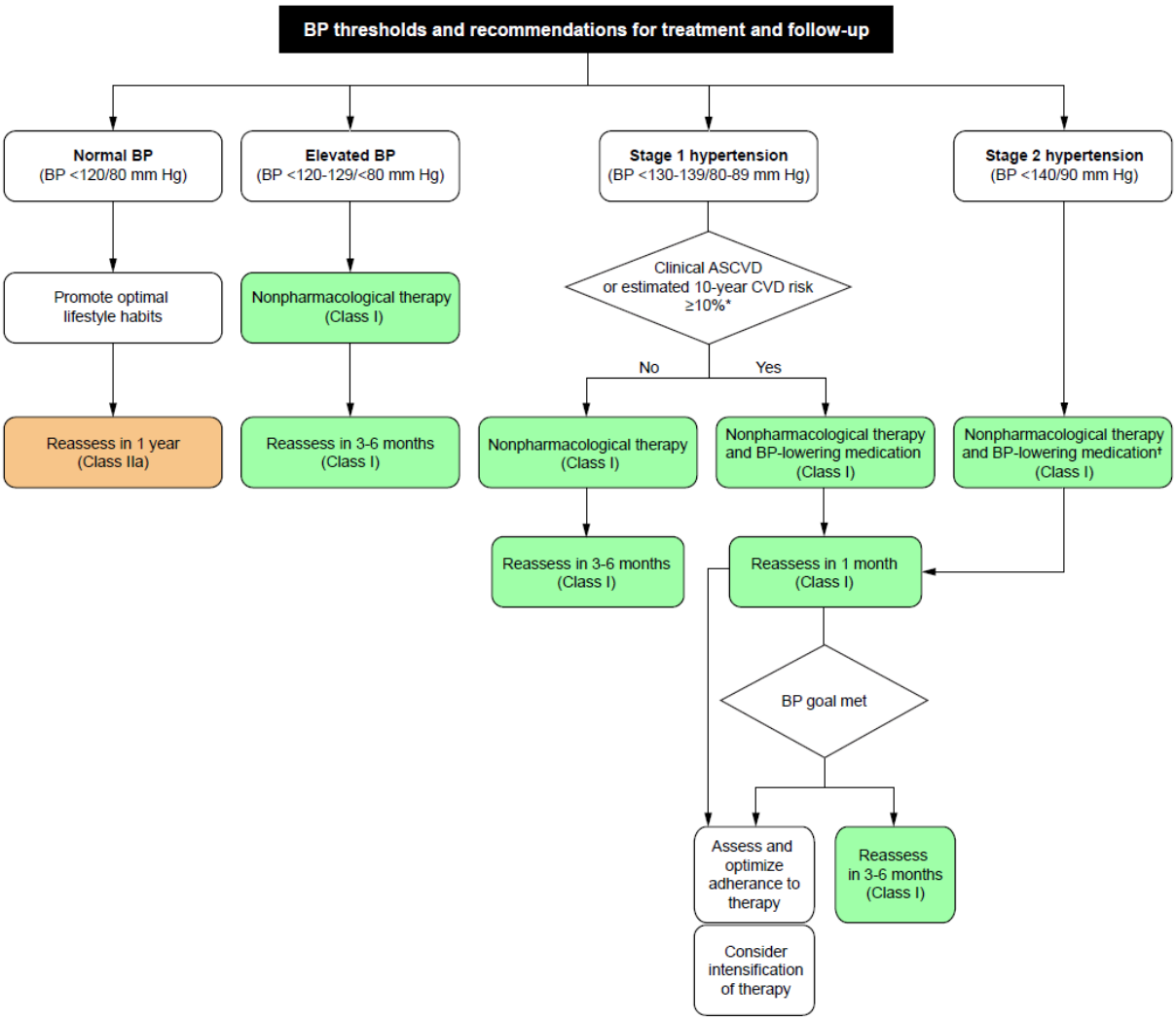

Figure 2. American College of Cardiology/American Heart Association blood pressure management recommendations.

Table 1. Drug Therapy: Coronary disease, screening and primary prevention.

Medication	Therapeutic use	Dosage	Safety concerns	Notable adverse reactions	Special considerations
Antidiabetic agents					
Biguanides					
Metformin, immediate release	First line in patients with T2DM to improve glycemic control and reduce ASCVD risk[D1,D2]	Initial dose: 500 mg PO twice daily or 850 mg PO once daily[D3] Increase by 500 mg/week or 850 mg every 2 weeks as needed[D3] Max dose: 2550 mg/day PO divided twice daily; use doses >1000 mg/day with caution in older patients[D3,D4] Adjust dose for eGFR 30-45 mL/minute/1.73 m^2 [D3]	**BOXED WARNING:** risk of lactic acidosis in high-risk patients[D3] Contraindicated in patients with eGFR <30 mL/minute/1.73m^2 or acute or chronic metabolic acidosis[D3] Do not initiate in patients with eGFR 30-45 mL/minute/1.73 m^2 [D3] Avoid use in patients older than 80 years and in patients with hepatic impairment[D3,D4] Drug interactions:	Diarrhea Lactic acidosis Nausea Vitamin B_{12} deficiency[D3]	Doses above 2000 mg/day may be better tolerated given 3 times daily[D3] GI intolerance can be mitigated by gradual dose titration[D2] Monitor renal function at baseline and at least annually[D3] Monitor hematologic parameters annually and vitamin B_{12} at 2-3 year intervals[D3]

			may need to avoid or adjust dosage of certain drugs[D3]		
Metformin, extended-release	First line in patients with T2DM to improve glycemic control and reduce ASCVD risk[D1,D2]	Initial dose: 500-1000 mg PO once daily[D3,D5] Increase by 500 mg/week as needed[D3,D5] Max dose: 2500 mg PO once daily; use doses >1000 mg/day with caution in older patients[D3-D5] Adjust dose for eGFR 30-45 mL/minute/1.73 m^2 [D3]	**BOXED WARNING:** risk of lactic acidosis in high-risk patients[D3] Contraindicated in patients with eGFR <30 mL/minute/1.73m^2 or acute or chronic metabolic acidosis[D3] Do not initiate in patients with eGFR 30-45 mL/minute/1.73 m^2 [D3] Avoid use in patients older than 80 years and in patients with hepatic impairment[D3,D4] Drug interactions: may need to avoid or adjust dosage of certain drugs[D3]	Diarrhea Lactic acidosis Nausea Vitamin B_{12} deficiency[D3]	If glycemic control is not achieved at maximum dose, consider dividing into 2 daily doses[D3] GI intolerance can be mitigated by gradual dose titration[D2] Monitor renal function at baseline and at least annually[D3] Monitor hematologic parameters annually and vitamin B_{12} at 2- to 3-year intervals[D3]

Glucagon-like peptide-1 (GLP-1) receptor agonists					
Liraglutide	Second line in patients with T2DM to improve glycemic control and reduce CVD risk[D1] Recommended as part of the glucose-lowering regimen in patients at high risk of ASCVD regardless of HbA1C[D1,D2]	Initial dose: 0.6 mg subcutaneously once daily for 1 week, then 1.2 mg once daily [D6] Max dose: 1.8 mg subcutaneously once daily[D6] 0.6 mg dose is for dose titration and is not effective for glycemic control[D6]	**BOXED WARNING:** risk of thyroid C-cell tumors in rodents; human relevance not determined[D6] Contraindicated in patients with a personal/family history of medullary thyroid carcinoma or in patients with multiple endocrine neoplasia syndrome type 2[D6]	Acute kidney injury Cholelithiasis Cholecystitis Diarrhea Nausea Pancreatitis Serious hypersensitivity reactions Vomiting[D6]	Monitor renal function with dosage escalations in patients reporting severe GI adverse reactions[D6]
Semaglutide	Second line in patients with T2DM to improve glycemic control and reduce CVD risk[D1] Recommended as part of glucose-	Initial dose: 0.25 mg subcutaneously once weekly for 4 weeks, then 0.5 mg once weekly[D7] May increase to 1 mg once weekly after 4 weeks[D7] Max dose: 1 mg subcutaneously once	**BOXED WARNING:** risk of thyroid C-cell tumors in rodents; human relevance not determined[D7] Contraindicated in patients with a personal/family history of medullary thyroid carcinoma or	Acute kidney injury Diarrhea Nausea Pancreatitis Serious hypersensitivity reactions Vomiting[D7]	Monitor renal function at baseline and with dosage escalations in patients reporting severe GI adverse reactions[D7] Monitor for worsening

	lowering regimen in patients at high risk of ASCVD regardless of HbA1C[D1,D2]	weekly[D7] 0.25 mg dose is for dose titration and is not effective for glycemic control[D7]	in patients with multiple endocrine neoplasia syndrome type 2[D7]		diabetic retinopathy in patients with a history of diabetic retinopathy[D7]
Sodium-glucose cotransporter 2 (SGLT2) inhibitors					
Canagliflozin	Second line in patients with T2DM to improve glycemic control and reduce CVD risk[D1] Recommended as part of glucose-lowering regimen in patients at high risk of ASCVD regardless of HbA1C[D1,D2]	Initial dose: 100 mg PO once daily[D8] Max dose: 300 mg PO once daily[D8] Adjust dose for eGFR 30-59 mL/minute/1.73m^2 [D8] Do not initiate in patients with eGFR <30 mL/minute/1.73 m^2 unless albuminuria >300 mg/day, then may continue 100 mg PO once daily[D8]	Contraindicated in patients on dialysis[D8] Do not use in patients with severe hepatic impairment; use has not been studied in this population[D8] Drug interactions: may need to avoid or adjust dosage of certain drugs[D8]	Acute kidney injury Bone fractures Fournier gangrene GU infections Hypotension Ketoacidosis LDL-C increased[D8]	Correct volume depletion before initiating therapy[D8] Monitor patients for infection, new pain or tenderness, and sores or ulcers involving lower limbs[D8] Monitor renal function at baseline and periodically thereafter[D8] SGLT2 inhibitors increase urinary glucose excretion,

					leading to positive urine glucose tests[D8]
Empagliflozin	Second line in patients with T2DM to improve glycemic control and reduce CVD risk[D1] Recommended as part of glucose-lowering regimen in patients at high risk of ASCVD regardless of HbA1C[D1,D2]	Initial dose: 10 mg PO once daily[D9] Max dose: 25 mg PO once daily[D9] Do not initiate in patients with eGFR <45 mL/minute/1.73 m^2 and discontinue if eGFR falls persistently <45 mL/minute/1.73 m^2 [D9]	Contraindicated in patients with severe renal impairment, ESRD, or dialysis[D9] Do not use for treatment of diabetic ketoacidosis[D9]	Acute kidney injury Fournier gangrene GU infections Hypotension Ketoacidosis LDL-C increases[D9]	Correct volume depletion before initiating therapy[D9] Monitor renal function at baseline and periodically thereafter[D9] SGLT2 inhibitors increase urinary glucose excretion, leading to positive urine glucose tests[D9]
Antihypertensive agents					
Angiotensin-converting enzyme inhibitors (ACEI)					
Benazepril	First line in patients with stage 1 hypertension (BP 130-139/80-89 mm Hg) and	Initial dose: 5-10 mg PO once daily[D11] Usual dose: 10-40 mg/day PO in 1-2 doses[D10]	Contraindicated in patients with history of angioedema[D11] Use with caution in patients with renal	Agranulocytosis Angioedema Cough Hepatoxicity Hyperkalemia Hypotension	Monitor blood pressure, renal function, serum potassium, and WBC closely

	an estimated ASCVD risk of ≥10% and in those with stage 2 hypertension (BP ≥140/90 mm Hg)[D1,D10]	Max dose: 40 mg/day PO[D11] Adjust dose for GFR <30 mL/minute/1.73m^2 [D11]	impairment, renal artery stenosis, or obstruction in outflow tract of left ventricle (ie, aortic stenosis, hypertrophic cardiomyopathy)[D11,D12] Patients whose renal function is dependent on the renin-angiotensin system (eg, those with heart failure) may be at risk of developing renal dysfunction[D11] Drug interactions: may need to avoid or adjust dosage of certain drugs[D11]	Nephrotoxicity Neutropenia[D11,D13]	during therapy[D11,D13]
Lisinopril	First line in patients with stage 1 hypertension (BP 130-139/80-89 mm Hg) and	Initial dose: 10 mg PO once daily[D10,D12] Usual dose: 10-40 mg PO once daily[D10]	Contraindicated in patients with history of angioedema[D12] Use with caution in patients with renal	Agranulocytosis Angioedema Cough Hepatoxicity Hyperkalemia Hypotension	Monitor blood pressure, renal function, serum potassium, and WBC closely

	an estimated ASCVD risk of ≥10% and in those with stage 2 hypertension (BP ≥140/90 mm Hg)[D1,D10]	Max dose: 40 mg PO once daily[D12] Adjust dose for CrCl ≤30 mL/minute[D12]	impairment, renal artery stenosis, or obstruction in outflow tract of left ventricle (ie, aortic stenosis, hypertrophic cardiomyopathy)[D12] Patients whose renal function is dependent on the renin-angiotensin system (eg, those with heart failure) may be at risk of developing renal dysfunction[D12] Drug interactions: may need to avoid or adjust dosage of certain drugs[D12]	Nephrotoxicity Neutropenia[D12,D13]	during therapy[D12,D13]
Angiotensin receptor blockers (ARB)					
Losartan	First line in patients with stage 1 hypertension (BP 130-139/80-	Initial dose: 50 mg PO once daily[D10,D14] Usual dose: 50-100 mg/day PO in 1-2	Has not been studied in patients with severe hepatic impairment[D14]	Hyperkalemia Hypotension Nephrotoxicity[D14]	Monitor blood pressure, renal function, and serum potassium closely during

	89 mm Hg) and an estimated ASCVD risk of ≥10% and in those with stage 2 hypertension (BP ≥140/90 mm Hg)[D1,D10]	doses[D10] Max dose: 100 mg PO once daily[D14] Adjust dose for mild to moderate hepatic impairment[D14]	Patients whose renal function is dependent on the renin-angiotensin system (eg, those with heart failure) may be at risk of developing renal dysfunction[D14] Drug interactions: may need to avoid or adjust dosage of certain drugs[D14]		therapy[D14] Patients with ACEI-induced angioedema can receive an ARB 6 weeks after the ACEI is discontinued[D10]
Olmesartan	First line in patients with stage 1 hypertension (BP 130-139/80-89 mm Hg) and an estimated ASCVD risk of ≥10% and in those with stage 2 hypertension (BP ≥140/90 mm Hg)[D1,D10]	Initial dose: 20 mg PO once daily[D15] Usual dose: 20-40 mg PO once daily[D10,D15] Max dose: 40 mg PO once daily[D15]	Has not been studied in patients with severe hepatic impairment[D15] Patients whose renal function is dependent on the renin-angiotensin system (eg, those with heart failure) may be at risk of developing renal dysfunction[D15] Drug interactions:	Hyperkalemia Hypotension Nephrotoxicity Sprue-like enteropathy[D15]	Monitor blood pressure, renal function, and serum potassium closely during therapy[D15] Patients with ACEI-induced angioedema can receive an ARB 6 weeks after the ACEI is discontinued[D10]

			may need to avoid or adjust dosage of certain drugs[D15]		
Valsartan	First line in patients with stage 1 hypertension (BP 130-139/80-89 mm Hg) and an estimated ASCVD risk of ≥10% and in those with stage 2 hypertension (BP ≥140/90 mm Hg)[D1,D10]	Initial dose: 80-160 mg PO once daily[D16] Usual dose: 80-320 mg PO once daily[D10] Max dose: 320 mg PO once daily[D16]	Has not been studied in patients with severe hepatic impairment[D16] Patients whose renal function is dependent on the renin-angiotensin system (eg, those with heart failure) may be at risk of developing renal dysfunction[D16] Drug interactions: may need to avoid or adjust dosage of certain drugs[D16]	Hyperkalemia Hypotension Nephrotoxicity[D16]	Monitor blood pressure, renal function, and serum potassium closely during therapy[D16] Patients with ACEI-induced angioedema can receive an ARB 6 weeks after the ACEI is discontinued[D16]
Calcium channel blockers (CCB)					
Dihydropyridines					
Amlodipine	First line in patients with stage 1 hypertension (BP 130-139/80-	Initial dose: 5 mg PO once daily[D17] Usual dose: 2.5-10 mg PO once daily[D10]	Avoid in patients with HFrEF; amlodipine is preferred if a dihydropyridine CCB	Hypotension Peripheral edema[D17]	Edema more common in females than males[D10]

	89 mm Hg) and an estimated ASCVD risk of ≥10% and in those with stage 2 hypertension (BP ≥140/90 mm Hg)[D1,D10]	Max dose: 10 mg PO once daily[D17]	is required[D10] Use with caution in patients with hepatic failure or severe aortic stenosis[D17]		
Nifedipine, extended-release	First line therapy in in patients with stage 1 hypertension (BP 130-139/80-89 mm Hg) and an estimated ASCVD risk of ≥10% and in those with stage 2 hypertension (BP ≥140/90 mm Hg)[D1,D10]	Initial dose: 30-60 mg PO once daily[D18,D19] Usual dose: 30-90 mg PO once daily[D10] Max dose: 90-120 mg PO once daily[D18,D19]	Contraindicated in patients with cardiogenic shock[D18] Avoid in patients with HFrEF[D10] Use with caution in patients with hepatic impairment, aortic stenosis, altered GI anatomy, or hypomotility disorders[D18,D19] Drug interactions: may need to avoid or adjust dosage of certain drugs[D18]	GI obstruction/ulceration Hypotension Peripheral edema[D18]	Edema is more common in females than males[D10]
Nondihydropyridines					

Diltiazem, extended-release	First line in patients with stage 1 hypertension (BP 130-139/80-89 mm Hg) and an estimated ASCVD risk of ≥10% and in those with stage 2 hypertension (BP ≥140/90 mm Hg)[D1,D10]	Usual dose: 120-360 mg PO once daily[D10] Max dose: 480 mg PO once daily[D20]	Contraindicated in patients with second- or third-degree heart block, sick sinus syndrome, hypotension, or acute MI and pulmonary congestion[D20] Do not use in patients with HFrEF[D10] May worsen heart failure[D20] Use with caution in patients with renal impairment and hepatic impairment[D20] Drug interactions: may need to avoid or adjust dosage of certain drugs[D20]	AV block Bradycardia Constipation Hepatic enzymes increased Hypotension Rash[D20]	Monitor renal and hepatic function at regular intervals[D20] Maximum antihypertensive effect occurs by day 14 of therapy[D20]
Verapamil, extended-release	First line in patients with stage 1	Usual dose: 120-360 mg PO in 1-2 doses[D10]	Contraindicated in patients with severe left ventricular	AV block Bradycardia Constipation	Monitor hepatic function periodically[D21]

	hypertension (BP 130-139/80-89 mm Hg) and an estimated ASCVD risk of ≥10% and in those with stage 2 hypertension (BP ≥140/90 mm Hg)[D1,D10]	Max dose: 480 mg PO once daily[D21]	dysfunction, second- or third-degree heart block, sick sinus syndrome, hypotension, cardiogenic shock, WPW, or Lown-Ganong-Levine syndrome[D21] Do not use in patients with HFrEF[D10] May worsen heart failure[D21] Use with caution in patients with renal impairment, hepatic impairment, myasthenia gravis, or Duchenne muscular dystrophy[D21] Drug interactions: may need to avoid or adjust dosage of certain drugs[D21]	Hepatic enzymes increased Hypotension[D21]	
Thiazide diuretics					

Chlorthalidone	First line in patients with stage 1 hypertension (BP 130-139/80-89 mm Hg) and an estimated ASCVD risk of ≥10% and in those with stage 2 hypertension (BP ≥140/90 mm Hg)[D1,D10] Preferred thiazide diuretic based on prolonged half-life and proven trial reduction of CVD[D10]	Usual dose: 12.5-25 mg PO once daily[D10] Max dose: 100 mg PO once daily[D22]	Contraindicated in anuric patients and those with sulfonamide hypersensitivity[D22] Potential for exacerbation or activation of systemic lupus erythematosus[D22] Use with caution in patients with severe renal disease, hepatic impairment, progressive liver disease, or gout[D10,D22]	Cholesterol/triglycerides increased Electrolyte depletion Hyperglycemia Hyperuricemia Hypovolemia[D22,D23]	Monitor electrolytes and uric acid levels periodically[D10] Low risk of cross-sensitivity with sulfonamide allergy[D24] Appears to retain effectiveness at GFR <30 mL/minute/1.73m[2] [D25]
Hydrochlorothiazide	First line in patients with stage 1 hypertension (BP 130-139/80-89 mm Hg) and an estimated ASCVD risk of ≥10% and in	Usual dose: 25-50 mg PO once daily[D10] Max dose: 50 mg PO once daily[D23]	Contraindicated in anuric patients and those with sulfonamide hypersensitivity[D23] Potential for exacerbation or activation of	Acute myopia Cholesterol/triglycerides increased Electrolyte depletion Hyperglycemia Hyperuricemia Hypovolemia Secondary angle-closure glaucoma[D23]	Monitor electrolytes and uric acid levels periodically[D10] Low risk of cross-sensitivity with sulfonamide allergy[D24]

	those with stage 2 hypertension (BP ≥140/90 mm Hg)[D1,D10]		systemic lupus erythematosus[D23] Use with caution in patients with severe renal disease, hepatic impairment, progressive liver disease, or gout[D10,D23]		Does not appear to retain effectiveness at GFR <30 mL/minute/1.73m[2] [D25]
Lipid-lowering agents					
Hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors					
Atorvastatin	ASCVD risk reduction[D1] Initiate high-intensity therapy in patients with LDL-C ≥190 mg/mL[D1,D26] Initiate moderate-intensity therapy in patients aged 40-75 years with diabetes and LDL-C 70-189	High-intensity dose: 80 mg PO once daily; down titrate to 40 mg if unable to tolerate 80 mg dose[D26] Moderate-intensity dose: 10-20 mg PO once daily[D6]	Contraindicated in patients with active liver disease or unexplained persistent transaminase elevations[D27] Use with caution in patients with recent stroke or TIA[D27] Drug interactions: may need to avoid or adjust dosage of certain drugs[D27]	Blood glucose/HbA1C increased Hepatoxicity Myopathy Rhabdomyolysis[D27]	Monitor lipid levels at 4-12 weeks after initiation or dose adjustment and then every 3-12 months as necessary[D6] Monitor liver function at baseline and if signs or symptoms of hepatic injury occur[D27]

	mg/dL; progress to high-intensity therapy as necessary[D1,D26] Initiate moderate-intensity therapy in patients aged 40-75 years without diabetes and with LDL-C 70-189 mg/dL at high risk (≥20%) to reduce LDL-C ≥50%[D1,D26] Consider moderate-intensity therapy in patients aged 40-75 years without diabetes and with LDL-C 70-189 mg/dL at borderline (5%				

	to <7.5%) to intermediate (7.5% to <20%) risk to reduce LDL-C by 30%-49%[D1,D26] Consider therapy in patients aged 20-39 years if family history of premature ASCVD and LDL-C ≥160 mg/mL[D1,D26] Risk-enhancing factors favor initiation or intensification of statin therapy[D26]				
Rosuvastatin	ASCVD risk reduction[D1] Initiate high-intensity therapy in patients with LDL-C ≥190	High intensity dose: 20-40 mg PO once daily[D26] Moderate intensity dose: 5-10 mg PO once daily[D26] Consider a lower starting dose and careful up	Contraindicated in patients with active liver disease or unexplained persistent transaminase elevations[D28]	Blood glucose/HbA1C increased Hepatoxicity Myopathy Rhabdomyolysis[D28]	Monitor lipid levels at 4-12 weeks after initiation or dosage adjustment and then every 3-12 months as

	mg/mL[D1,D26] Initiate moderate-intensity therapy in patients aged 40-75 years with diabetes and LDL-C 70-189 mg/dL; progress to high-intensity therapy as necessary[D1,D26] Initiate moderate-intensity therapy in patients aged 40-75 years without diabetes and with LDL-C 70-189 mg/dL at high risk (≥20%) to reduce LDL-C ≥50%[D1,D26] Consider	titration in Asian patients[D26,D28] Adjust dose for CrCl <30 mL/minute/1.73m^2 [D28]	Drug interactions: may need to avoid or adjust dosage of certain medications[D28]		necessary[D26] Monitor liver function at baseline and if signs or symptoms of hepatic injury occur[D28]

	moderate-intensity therapy in patients aged 40-75 years without diabetes and with LDL-C 70-189 mg/dL at borderline (5% to <7.5%) to intermediate (7.5% to <20%) risk to reduce LDL-C by 30%-49%[D1,D26] Consider therapy in patients aged 20-39 years if family history of premature ASCVD and LDL-C ≥160 mg/mL[D1,D26] Risk-enhancing factors favor initiation or				

	intensification of statin therapy[D26]				
Cholesterol absorption inhibitors					
Ezetimibe	Add-on therapy to maximally tolerated statin when LDL-C remains ≥70 mg/dL[D26]	10 mg PO once daily[D26]	Contraindicated in patients with active liver disease or unexplained persistent transaminase elevations[D29] Avoid in patients with moderate to severe hepatic impairment[D29] Use with caution in patients with moderate to severe renal impairment[D29] Drug interactions: may need to avoid or adjust dosage of certain medications[D29]	Arthralgia Diarrhea Sinusitis Upper respiratory tract infection[D29]	Generally well-tolerated[D26] Monitor liver function at baseline and if signs or symptoms of hepatic injury occur[D29] Monitor lipid levels at 4-12 weeks after initiation or dosage adjustment and repeat every 3-12 months as necessary[D26] LDL-C reduction when used with high-intensity statin: 65%[D30]
Platelet inhibitors					

Salicylates					
Aspirin	Consider in patients aged 40-70 years who are high risk for ASCVD but not at high risk for bleeding[D1]	Usual dose: 81 mg PO once daily[D1]	Contraindicated in patients with the syndrome of asthma, rhinitis, and nasal polyps[D31] Avoid use in patients with risk of bleeding, active peptic ulcer disease, or severe hepatic insufficiency[D1,D31]	Bleeding Gastric ulceration[D31]	
Tobacco cessation therapies					
Nicotine replacement therapy (NRT)					
Nicotine, gum	First line for tobacco cessation as combination NRT to reduce ASCVD risk; second line as single NRT[D1,D32] Combination NRT is more effective than single NRT; add a rapidly	If first cigarette ≤30 minutes of waking: 4 mg every hour as needed[D1,D32] If first cigarette >30 minutes of waking: 2 mg every hour as needed[D1,D32] Max dose: 24 pieces/day[D33] Use ≥3 months, until	Use with caution in patients with dental work, sodium restriction, hypertension, stomach ulcers, or history of seizures[D32,D33] Drug interactions: may need to avoid or adjust dosage of certain drugs[D33]	Heartburn Hiccups Jaw soreness Local irritation Nausea Palpitations Tachycardia[D1,D32,D33]	May be difficult with dentures[D32] Avoid food and beverage for 15 minutes before and after use[D33] Use ≥9 pieces/day for first 6 weeks to improve outcomes[D33] Sodium content

	absorbed product (eg, gum) to patch therapy to cover situational cravings*[D32] Combination NRT has similar efficacy to varenicline[D32] Single NRT may be used in combination with varenicline or bupropion in patients who do not achieve abstinence with monotherapy[D32]	patient is confident that they will not return to smoking[D32]			per 2 mg piece = 11 mg[D33] Sodium content per 4 mg piece = 13 mg[D33]
Nicotine, patch	First line for tobacco cessation as combination NRT to reduce ASCVD risk; second line as single NRT[D1,D32]	CPD ≥10: 21 mg patch/day transdermally[D1,D32] CPD <10: 14 mg patch/day transdermally[D1,D32] After 6 weeks, continue	Avoid in patients with skin disorders[D1] Use with caution in patients with hypertension, stomach ulcers, or history of seizures[D34]	Abnormal dreams Insomnia Local irritation Palpitations Tachycardia[D1,D32,D34]	May start patch before or on quit date; continue even if a slip occurs[D32] Easiest NRT to use; compliance is greatest with

	Combination NRT is more effective than single NRT; add a rapidly absorbed product (eg, gum) to patch therapy to cover situational cravings*[D32] Combination NRT has similar efficacy to varenicline[D32] Combination therapy with a nicotine patch and bupropion is more effective than single NRT[D32] Single NRT may be used in combination with varenicline or bupropion in	original dosage or taper to lower doses every 2 weeks[D32] Use ≥3 months, until patient is confident that they will not return to smoking[D32]	Drug interactions: may need to avoid or adjust dosage of certain drugs[D34]		patch[D32] Provides a steady nicotine concentration[D32] Remove at bedtime if sleep disturbances occur[D34]

	patients who do not achieve abstinence with monotherapy[D32]				
Nicotinic receptor partial agonist					
Varenicline	First line for tobacco cessation to reduce ASCVD risk[D1,D32] Relieves nicotine withdrawal and blocks reward of smoking[D32] Similar efficacy to combination NRT[D32] More effective than single NRT or bupropion[D32] May be used in combination with single NRT or bupropion in patients who do	0.5 mg PO once daily for 3 days, then 0.5 mg PO twice daily for 4 days, then 1 mg PO twice daily[D1,D32] Use for 3-6 months[D1,D32] Adjust dose for CrCl <30 mL/minute[D35]	Use with caution in patients with acute coronary syndrome[D32] Drug interactions: may need to avoid or adjust dosage of certain drugs[D35]	Abnormal dreams Angioedema Erythema multiforme Headache Insomnia Nausea Neuropsychiatric reactions Seizures Somnambulism Stevens-Johnson syndrome[D32,D35]	Initiate therapy 1-4 weeks (up to 3 months) before quit date[D32] Combination with NRT resulted in a high discontinuation rate of varenicline due to adverse events during clinical trials[D35] Neuropsychiatric reactions are no more common than other tobacco cessation medications[D32] Administer with food and water to

	not achieve abstinence with monotherapy[D32]				minimize nausea[D1,D32]
Aminoketone antidepressants					
Bupropion, extended-release	Second line for tobacco cessation to reduce ASCVD risk[D1,D32] Combination therapy with a nicotine patch is more effective than bupropion monotherapy[D32] Similar efficacy to NRT[D32] May be useful in patients with depression[D32] May be used in combination with varenicline or single NRT in patients who do	150 mg PO once daily for 3 days, then 150 mg PO twice daily[D1,D32] Max dose: 300 mg PO twice daily[D36] Use 3-6 months[D32] Adjust dose for moderate to severe hepatic impairment (Child-Pugh 7-15)[D36] Consider dosage adjustment in mild hepatic impairment (Child-Pugh 5-6) or renal impairment (GFR <90 mL/minute)[D36]	**BOXED WARNING:** risk of suicidal ideation and behavior children and young adults[D36] Contraindicated in patients with seizure disorders or current/prior diagnosis of anorexia nervosa or bulimia[D36] Use with caution in patients with bipolar disorder or angle-closure glaucoma[D36] Drug interactions: may need to avoid or adjust dosage of certain drugs[D36]	Dry mouth Headache Hypertension Insomnia Neuropsychiatric reactions[D32,D36]	Initiate therapy 1-2 weeks before quit date[D32] May lessen post-cessation weight gain during drug therapy[D32]

	not achieve abstinence with monotherapy[D32]				
Weight loss agents					
Gastrointestinal lipase inhibitors					
Orlistat	Adjunct to lifestyle interventions in select patients to achieve weight loss and reduce ASCVD risk[D1] May be considered for patients with BMI ≥30 kg/m^2 or BMI ≥27 kg/m^2 with ≥1 obesity-associated comorbidity[D37,D38] Recommended in patients with cardiovascular disease[D37]	Usual dose: 120 mg PO 3 times daily[D39]	Contraindicated in patients with chronic malabsorption syndrome or cholestasis[D39] Exclude organic causes of obesity (eg, hypothyroidism) before initiation[D39] Use with caution in patients with renal impairment or history of hyperoxaluria or calcium oxalate nephrolithiasis[D39] Drug interactions: may need to avoid or adjust dosage of certain drugs[D39]	Cholelithiasis Fecal incontinence Fecal urgency Flatulence Hepatotoxicity Steatorrhea[D9]	Nonsystemic[D37] Also available OTC (60 mg PO 3 times daily)[D40] Administer during or up to 1 hour after each main meal containing fat[D39] Supplement with a daily multivitamin containing vitamin A, D, E, and K and beta-carotene at least 2 hours before or after dose[D39] Patients should be on a balanced

					diet that contains 30% calories from fat[D39]
Glucagon-like peptide-1 (GLP-1) receptor agonist					
Liraglutide	Adjunct to lifestyle interventions in select patients to achieve weight loss and reduce ASCVD risk[D1] May be considered for patients with BMI ≥30 kg/m^2 or BMI ≥27 kg/m^2 with ≥1 obesity-associated comorbidity[D37,D38]	Initial dose: 0.6 mg subcutaneously once daily for 1 week[D41] Increase dose by 0.6 mg weekly[D41] Target dose: 3 mg subcutaneously once daily[D41]	**BOXED WARNING:** risk of thyroid C-cell tumors in rodents; human relevance not determined[D41] Contraindicated in patients with personal/family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2[D41] May increase risk of suicidal ideation or behavior[D41]	Acute kidney injury Cholelithiasis Cholecystitis Diarrhea Heart rate increased Nausea Pancreatitis Serious hypersensitivity reactions Vomiting[D41]	Generally well-tolerated[D37] Discontinue if 4% weight loss is not achieved by 16 weeks[D41]
Opioid antagonist/aminoketone antidepressant combination					
Naltrexone/bupropion	Adjunct to lifestyle interventions in select patients to achieve	Week 1: 1 tablet (8 mg/90 mg naltrexone/bupropion) PO once daily	**BOXED WARNING:** risk of suicidal ideation and behavior children and young adults[D42]	Anxiety Blood pressure increased Constipation Dizziness	Monitor blood pressure and heart rate at baseline and periodically

	weight loss and reduce ASCVD risk[D1] May be considered for patients with BMI ≥30 kg/m^2 or BMI ≥27 kg/m^2 with ≥1 obesity-associated comorbidity[D37,D38]	Week 2: 1 tablet PO twice daily Week 3: 2 tablets PO every morning and 1 tablet PO every evening Week 4: 2 tablets PO twice daily[D42] Adjust dose for moderate to severe renal impairment or moderate hepatic impairment[D42]	Contraindicated in patients with uncontrolled hypertension, seizure disorders, anorexia nervosa, bulimia, chronic opioid use, or acute opioid withdrawal[D42] Not recommended in patients with ESRD or severe hepatic impairment[D42] Use with caution in patients with bipolar disorder or angle-closure glaucoma[D42] Drug interactions: may need to avoid or adjust dosage of certain drugs[D42]	Headache Heart rate increased Hepatotoxicity Insomnia Nausea Neuropsychiatric reactions Seizures Vomiting[D42]	during therapy[D42] Discontinue if ≥5% weight loss is not achieved by 12 weeks[D42]
Sympathomimetic amine anorectic/antiepileptic combination					
Phentermine/topiramate	Adjunct to lifestyle interventions in	Initial dose: 3.75 mg/23 mg (phentermine/topiramat	Contraindicated in patients with glaucoma or	Cognitive impairment Constipation Dizziness	Avoid evening dosing due to possibility of

	select patients to achieve weight loss and reduce ASCVD risk[D1] May be considered for patients with BMI ≥30 kg/m^2 or BMI ≥27 kg/m^2 with ≥1 obesity-associated comorbidity[D37,D38] Not recommended in patients with uncontrolled hypertension or history of cardiovascular disease[D37]	e) PO once daily for 14 days, then 7.5 mg/46 mg PO once daily for 10 weeks[D43] If <3% weight loss at 12 weeks, discontinue or increase dose to 11.25 mg/69 mg PO once daily for 14 days, then 15 mg/92 mg PO once daily for an additional 10 weeks[D43] Max dose: 15 mg/92 mg PO once daily[D43] Adjust dose for CrCl <50 mL/minute or moderate hepatic impairment (Child-Pugh 7-9)[D43]	hyperthyroidism[D43] Avoid in patients with ESRD on dialysis or severe hepatic impairment[D43] Use with caution in patients with history of depression or other mood disorders[D43] May increase risk of suicidal ideation or behavior[D43] Drug interactions: may need to avoid or adjust dosage of certain medications[D43]	Dry mouth Dysgeusia Headache Heart rate increased Hypokalemia Insomnia Metabolic acidosis Mood disorders Paresthesias[D43]	insomnia[D43] Monitor heart rate and basic metabolic profile at baseline and periodically during treatment[D43] Discontinue if ≥5 % weight loss is not achieved after 10 weeks on maximum dose[D43] Discontinue 15 mg/92 mg gradually by taking a dose every other day for at least 1 week to reduce risk of seizure[D43]

ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, ASCVD = atherosclerotic cardiovascular disease, AV = atrioventricular, BP = blood pressure, CCB = calcium channel blocker, CrCl = creatinine clearance, CPD = cigarettes per day, CVD = cardiovascular disease, eGFR = estimated glomerular filtration rate, ESRD = end-stage renal disease, GI = gastrointestinal, GLP-1 = glucagon-like peptide-1, GU = genitourinary, HbA1c = hemoglobin A1c, HFrEF = heart failure with reduced ejection fraction, HMG-

CoA = hydroxymethylglutaryl coenzyme A, LDL-C = low-density lipoprotein cholesterol, MI = myocardial infarction, NRT = nicotine replacement therapy, SGLT2 = sodium-glucose cotransporter 2, T2DM = type 2 diabetes mellitus, TIA = transient ischemic attack, WPW = Wolff-Parkinson-White.

*Base choice of rapidly absorbed product (eg, gum, lozenge, spray, inhaler) on patient preference.[D32]

Special Considerations

Screening in Patients With Diabetes

- Although diabetes confers an increased risk for cardiovascular events independent of other traditional risk factors, several prospective randomized trials have shown no significant improvement in outcomes among patients who underwent routine screening for coronary artery disease[92,113-117]
- Routine screening for coronary artery disease in asymptomatic patients with diabetes is not recommended[92,113-117]

Screening in Patients on Dialysis

- Patients with chronic kidney disease have a greater burden of cardiovascular disease, which impacts prognosis and management[118]
- Screen patients on dialysis with 12-lead ECG annually[118]
- Screen selected potential renal transplant recipients with stress testing[118]

Primary Prevention in Females

- Menopause is associated with development of cardiovascular risk factors in females
- Despite observational data supporting use of hormone replacement therapy for prevention of cardiovascular disease, large randomized clinical trials have failed to demonstrate a benefit[119,120]
- Based on recommendations from North American Menopause Society, American College of Endocrinology, and US Preventive Services Task Force, menopause hormone therapy is currently not recommended for preventing or reducing cardiovascular disease for females of any age[121-123]

Follow-up

Referral

- Consider referral to cardiologist for primary prevention or screening for patients with:
  - Strong family history of premature coronary artery disease
  - Significant cholesterol disorders (eg, familial hypercholesterolemia, hypertriglyceridemia, or hyperlipidemia) that are resistant to standard treatment
  - Multiple uncontrolled risk factors

Summary

Key Points

- Promote a healthy lifestyle throughout life to prevent atherosclerotic cardiovascular disease[10]
- Work in partnership with patients to evaluate risk of disease, assess readiness for lifestyle improvements, and evaluate social determinants that may hinder their progress[10]
- Risk estimation is cornerstone of primary prevention; all adults aged 40 to 75 years should undergo 10-year atherosclerotic cardiovascular disease risk estimation[10,16,23-25]
- Tobacco avoidance is critically important for atherosclerotic cardiovascular disease prevention
    - Assess all adults for tobacco use and strongly advise cessation at every health care visit[10,57,62]
- All adults should consume a heart-healthy diet rich in fruits, vegetables, whole grains, nuts, and lean protein (eg, fish, poultry, legumes) while minimizing intake of trans fats, added sugars, red meat, sodium, and saturated fats[10,30-42]
- All adults should engage in regular, brisk physical activity (at least 150 minutes/week of moderate intensity or 75 minutes/week of vigorous intensity)[10,43-48]
- For adults who are overweight or obese, recommend caloric restriction to achieve and maintain weight loss[10,49-51]
- For all adults with elevated blood pressure or hypertension, target blood pressure lower than 130/80 mm Hg using lifestyle modification and pharmacologic treatment where indicated[10,66]
- For patients with type 2 diabetes, a combination of lifestyle modifications and aggressive risk-factor management is important to reduce cardiovascular disease risk[10,92-94]
- Aspirin is not routinely recommended for primary prevention of atherosclerotic cardiovascular disease because of absence of benefit[10,89-92]
- Statin therapy is indicated for primary prevention of atherosclerotic cardiovascular disease in patients with elevated LDL-C of 190 mg/dL or higher, with diabetes, aged 40 to 75 years, and determined to be at sufficient disease risk after partnered discussion[10,22,25,86,87,92,111,112,124]
- Routine screening for coronary artery disease of asymptomatic adults at low risk for cardiovascular disease is not recommended[27-29]

Alarm Signs and Symptoms

- Any patient with onset of symptoms such as chest pain, dyspnea on exertion, syncope, or sudden cardiac arrest must undergo further evaluation and no longer falls under the umbrella of asymptomatic patients

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Figure Legends

Figure 1. American College of Cardiology/American Heart Association algorithm for primary prevention of atherosclerotic cardiovascular disease.

apoB, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; CHD, coronary heart disease; hs-CRP, high-sensitivity C-reactive protein; Lp(a), lipoprotein a.

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Figure 2. American College of Cardiology/American Heart Association blood pressure management recommendations.

ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CVD, cardiovascular disease.

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