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Primary and Secondary Prevention of Coronary Artery Disease

OVERVIEW

Overview

Despite relatively recent declines in age-adjusted mortality, in 2013, cardiovascular disease (CVD) was the primary cause in nearly 801,000 deaths (30.8% of total deaths) in the United States. [1] In fact, CVD has been the leading cause of death in the United States for the past 100 years, except for 1918. [1] Although CVD age-adjusted death rates are reportedly declining in the United States, they are increasing in many developing countries, such that CVD is now the leading cause of death globally as well. [2] These developing countries and emerging market economies are succumbing to the epidemiologic transition that afflicted the United States (CVD-related mortality), posing a major challenge to these regions as they undergo social and economic development as emerging market economies. [3, 4, 5]

The most preventable form of CVD is coronary heart disease (CHD). In the United States, CHD annually results in over 370,000 deaths and 750,000 MIs, of which 550,000 are first infarctions and 200,000 are recurrent attacks. [1, 2] Black men and women die of heart disease at higher rates than other racial/ethnic groups (>39,000 in 2013 [2]), and heart disease continues to be the leading cause of death for women in the United States, accounting for more deaths in women than all forms of cancer, chronic lower respiratory disease, and diabetes mellitus combined. [1, 2]

An American Heart Association (AHA) policy statement concluded that

costs will rise to more than $1 trillion annually in the United States by the year 2030, thus suggesting the great need for preventative measures. [6]

About 15.4 million Americans aged 20 years or older have CHD (7.9% of US men, 5.1% of US women). [5] Asymptomatic disease is even more prevalent. By the year 2020, CHD is estimated to become the leading cause of death and disability worldwide. Despite this high prevalence, evidence increasingly suggests that the atherosclerotic process can be greatly slowed and its consequences markedly reduced by preventive measures. Primordial prevention usually refers to healthy lifestyle choices to prevent the development of coronary risk factors. [7] Primary prevention deals with delaying or preventing the onset of CVD (medical subject heading [MeSH] definition).

In a 4-decade Finnish population-based observational study (1972-2012) that evaluated how much changes in three major cardiovascular risk factors (smoking prevalence, serum cholesterol, and systolic blood pressure) may explain reduction in CHD mortality in 34,525 working-aged men and women who participated in the national FINRISK studies, Jousilahti et al found that in the first decade of the study, changes in these three target risk factors contributed to nearly 100% mortality reduction, whereas in the study's last decade, 66% (women) to 69% (men) of the mortality reduction could be attributed to changes in the three target risk factors. [8]

Many countries where CHD is on the rise have instituted counselling and educational methods to encourage people to reduce their risks for developing heart disease. A review examined 55 trials intended to reduce multiple risk factors; the trials lasted between 6 months and 12 years and were conducted in several countries over the course of 4 decades. The review suggested that intervention results in small reductions in risk factors, including blood pressure, cholesterol, and smoking, but has little or no impact on the risk of CHD mortality or morbidity. [9] This demonstrates that a different approach to behavior change is needed, particularly in developing countries where cardiovascular disease rates are rising.

A study by Pande et al suggests millions of US adults with peripheral arterial disease (PAD) are not receiving secondary prevention therapies. [10] PAD was defined as an ankle-brachial index of 0.90 or less. Of 7458 eligible participants aged 40 years or older, weighted PAD prevalence was 5.9±0.3%, corresponding to approximately 7.1 million US adults with PAD. Treatment with multiple therapies (statins, angiotensin converting enzyme [ACE] inhibitor/angiotensin receptor blockers [ARBs], and aspirin) is associated with reduced all-cause mortality.

Secondary prevention relies on early detection of disease process and application of interventions to prevent progression of disease (MeSH

definition). This article summarizes the guidelines for the primary and secondary prevention of CHD.

Risk Assessment and Primary Prevention

Risk factors and risk scores

Primary prevention reduces the risk of myocardial infarction (MI) and heart failure, decreases the need for coronary revascularization procedures, and extends and improves quality of life. In their 2013 guidelines, the American College of Cardiology (ACC) and the American Heart Association (AHA) devised a new score to estimate the 10-year risk of developing a first atherosclerotic cardiovascular disease (ASCVD) event, which was defined as nonfatal MI, coronary heart disease (CHD) death, or fatal or nonfatal stroke, over a 10-year period, in individuals who were initially free from ASCVD. [11, 12]

The new score provides sex- and race-specific estimates for the first ASCVD event for black and white men and women aged 40-79 years. Variables that merit inclusion in the risk assessment equations are age, total cholesterol, high-density lipoprotein cholesterol (HDL-C), systolic blood pressure (SBP) (including treated or untreated status), diabetes mellitus (diabetes), and current smoking status.

The ASCVD Risk Estimator is available at: http://tools.acc.org/ASCVD-Risk-Estimator/. [11, 12]

The recommendations for assessment of the 10-year risk for a first hard ASCVD event are as follows [11, 12] :

- Non-Hispanic black and non-Hispanic white individuals aged 40-79 years: The race- and sex-specific Pooled Cohort Equations to predict 10-year risk for a first hard ASCVD event should be used.

- Patients from populations other than black and non-Hispanic white groups: Use of the sex-specific Pooled Cohort Equations for non-Hispanic white individuals may be considered.

Updated guidelines advantages

The ACC/AHA indicate that two major advantages of these guidelines are the ability to not only estimate the risk for a broader-based ASCVD outcome that is more relevant to population groups (eg, women, black individuals) but also to provide risk estimates that are specific to black populations. [11, 12]

Screening guidelines

In 2015, the American College of Physicians (ACP) released guidelines on screening for CHD, including the following [13] :

- There is no evidence that cardiac screening improves patient outcomes in asymptomatic, low-risk adults.

- Potential harms of cardiac screening include false-positive results causing patients to undergo potentially unnecessary tests and procedures.

- Among adults at low risk, prevalence of CHD is low, and cardiac screening is of low predictive value. Therefore, cardiac screening is of low yield, and the probability that positive findings will influence therapeutic decision making is low.

- Clinicians should therefore emphasize strategies to reduce cardiovascular risk even further among low-risk adults by treating modifiable risk factors (smoking, diabetes, blood pressure [BP], hyperlipidemia, overweight, and exercise).

- Clinicians should not screen asymptomatic, low-risk adults for cardiac disease using resting or stress electrocardiography (ECG), stress echocardiography, or stress myocardial perfusion imaging.

- Clinicians should conduct cardiovascular risk assessment with a global risk score combining individual risk factor measurements into a single quantitative estimate of risk.

- The ACP recommendations do not apply to symptomatic patients or to screening athletes before participation in various events.

The 2013 ACC/AHA guidelines indicate that for patients aged 20-79 years who do not have existing clinical ASCVD, assess for clinical risk factors every 4-6 years. [11, 12] For patients with low 10-year risk (<7.5%), the guidelines recommend assessing 30-year or lifetime risk in patients aged 20-59 years.

Regardless of the patient's age, clinicians should communicate risk data to the patient and refer to the AHA/ACC lifestyle guidelines, which cover diet and physical activity. [14, 15] For patients with an elevated 10-year risk, clinicians should communicate risk data and refer to the AHA/ACC guidelines on blood cholesterol and obesity. [16, 17]

Hypercholesterolemia/dyslipidemia

The 2013 AHA/ACC guidelines on the management of elevated blood cholesterol no longer specify low-density lipoprotein (LDL-C) and non-HDL-C targets for the primary and secondary prevention of atherosclerotic CVD. The new guidelines identify four groups of primary- and secondary-

prevention patients in whom efforts should be focused to reduce cardiovascular disease events and recommend appropriate levels of statin therapy for these groups. [11, 16, 17]

Four statin-benefit groups

The 2013 AHA/ACC guidelines indicate that statin therapy is appropriate for the following individuals [16, 17, 18] :

- Those with clinical ASCVD (eg, previous MI, acute coronary syndrome [ACS], stable or unstable angina, stroke, transient ischemic attack [TIA] of atherosclerotic origin, peripheral arterial disease)

- Those with primary elevations of LDL-C of 190 mg/dL or greater (eg, familial hyperlipidemia)

- Those aged 40-75 years with diabetes and LDL-C levels of 70-89 mg/dL without clinical ASCVD

- Those without clinical ASCVD or diabetes aged 40-75 years who have LDL-C levels of 70-189 mg/dL as well as an estimated 10-year ASCVD risk of 7.5% or higher. This requires a clinician-patient discussion.

Initiation of statin therapy

Before therapy is initiated, the following potential secondary causes of dyslipidemia should be considered based on the associated dyslipidemia:

- High LDL: Hypothyroidism, [19, 20] nephrotic syndrome, primary biliary cirrhosis, [21] and anorexia nervosa [22, 23]

- Hypertriglyceridemia (triglyceride levels ≥500 mg/dL [5.65 mmol/L]) [18] : Diabetes mellitus, [24] chronic kidney disease, alcoholism, pregnancy, [25] hypothyroidism [19, 20]

- Low HDL: Diabetes mellitus, cigarette smoking, [26, 27] obesity [28]

The AHA/ACC expert panel found extensive and consistent evidence supporting the use of statins for the prevention of ASCVD in many higher-risk primary- and all secondary-prevention individuals [16, 17] without New York Heart Association (NYHA) class II-IV heart failure who were not receiving hemodialysis. [18] In the randomized controlled trials (RCTs) reviewed, initiation of moderate-intensity therapy (lowering LDL-C by approximately 30% to <50%) or high-intensity statin therapy (lowering LDL-C by approximately ≥50%) is a critical factor in reducing ASCVD events. [16, 17, 18] Moreover, statin therapy reduces ASCVD events across the spectrum of baseline LDL-C levels of 70 mg/dL or higher. In addition,

the relative reduction in ASCVD risk is consistent for primary and secondary prevention and for various patient subgroups. [16, 17, 18]

Of note, the absolute reduction in ASCVD events is proportional to baseline absolute ASCVD risk. Therefore, statin therapy is recommended for individuals at increased ASCVD risk who are most likely to experience a net benefit in terms of the potential for ASCVD risk reduction and the potential for adverse effects. [16, 17, 18]

Statin intensity recommendations in appropriate patients

High-intensity statin therapy (lowers LDL-C by approximately ≥50%) [16, 17, 18] :

- Atorvastatin 40-80 mg
- Rosuvastatin 20-40 mg

Moderate-intensity statin therapy (lowers LDL-C by approximately 30% to <50%)<ref>16</ref> [17, 18] :

- Atorvastatin 10-20 mg
- Rosuvastatin 5-10 mg
- Simvastatin 20-40 mg
- Pravastatin 40-80 mg
- Lovastatin 40 mg
- Fluvastatin XL 80 mg
- Fluvastatin 40 mg twice daily
- Pitavastatin 2-4 mg

Low-intensity statin therapy (lowers LDL-C by approximately <30%)<ref>16</ref> [17, 18] :

- Simvastatin 10 mg
- Pravastatin 10-20 mg
- Lovastatin 20 mg
- Fluvastatin 20-40 mg
- Pitavastatin 1 mg

Primary prevention recommendations

In considering statin therapy—for all patients, regardless of whether or not they fall into the statin-benefit groups—always keep in mind and discuss the potential clinical ASCVD risk-reduction benefits, adverse events, drug-drug interactions, and patient preferences. [16, 17, 18]

Adults aged 21 years and older with LDL-C levels of 190 mg/dL or greater [16, 17, 18] :

- Evaluate for secondary causes of hyperlipidemia (discussed above).

- Treat with statins (high-intensity agents, unless contraindicated; otherwise to maximum tolerated intensity).

- Untreated patients: Intensify statin therapy to achieve a minimum 50% LDL-C reduction; once the maximum intensity of statin therapy is achieved, add a non-statin agent for further LDL-C reduction.

Diabetic adults aged 40-75 years with LDL-C levels of 70-189 mg/dL (1.81-4.90 mmol/L) [16, 17, 18]:

- Initiate/continue moderate-intensity statin therapy.

- If the estimated 10-year ASCVD risk is 7.5% or greater, treat with high-intensity statin therapy, unless contraindicated.

Nondiabetic adults aged 40-75 years without clinical ASCVD but have LDL-C levels of 70-189 mg/dL (1.81-4.90 mmol/L) [16, 17, 18]:

- Use the Pooled Cohort Risk Calculator to estimate the 10-year ASCVD risk and guide initiation of statins (see http://my.americanheart.org /cvriskcalculator or http://www.cardiosource.org/science-and-quality/practice-guidelines-and-quality-standards/2013-prevention-guideline-tools.aspx).

- If the estimated 10-year ASCVD risk is 7.5% or greater, treat with moderate- to high-intensity statin therapy.

- If the estimated 10-year ASCVD risk is 5% up to 7.5%, treat with moderate-intensity statin therapy.

BP control

Hypertension is a well-established risk factor for adverse cardiovascular outcomes, including CHD. SBP is at least as powerful a coronary risk factor as the diastolic BP (DBP). Isolated systolic hypertension has been established as a major hazard for CHD. Compelling data from meta-analyses indicate that a reduction of DBP by 5-6 mm Hg results in a reduction of stroke risk by 42% and CHD events by 15%. [29]

The self-management of hypertension, which includes BP self-monitoring and self-titration of antihypertensive drugs, along with telemonitoring of home BP measurements, is an important addition to the control of hypertension in primary care. Patients who self-manage hypertension have experienced a decrease in SBP compared to those who sought usual care. [30] The Clinical Evaluation of Remote Notification to Reduce Time to Clinical Decision (CONNECT) trial found that wireless remote monitoring with automatic clinician alerts significantly reduced the time to a clinical decision in response to clinical events as well as reduced the length of

hospital stay. [31]

In patients with mild hypertension (SBP 140-159 mm Hg or DBP 90-99 mm Hg), the following is noted:

- Despite side effects and cost of antihypertensive medications, the beneficial effects of treatment may outweigh the risks, even in low-risk patients.

- Treatment, if necessary, is initiated with a low-dose of a once-a-day antihypertensive drug in an attempt to minimize future cardiovascular risk after a prolonged trial of nonpharmacologic therapy.

- One such antihypertensive medication that is used worldwide is hydrochlorothiazide (HCTZ). A daily dose of 12.5-25 mg was measured in head-to-head studies using ambulatory BP measurement (ABPM) and was shown to be consistently inferior to all other drug classes. Because data is lacking for dosing, HCTZ is an inappropriate first-line drug for the treatment of hypertension. [32]

In individuals with high-normal BP (SBP 130-139 mm Hg and/or DBP 85-89 mm Hg), the following is noted:

- These persons have an increased risk of cardiovascular events over time compared with those who have optimal BP.

- Antihypertensive drug therapy should be considered among such patients if diabetes or end-organ damage is present.

- Treatment, particularly with an angiotensin-converting enzyme (ACE) inhibitor or, if not tolerated, an angiotensin-II receptor blocker (ARB), is also warranted in patients with renal insufficiency, diabetes mellitus, or heart failure to slow the progression of the underlying disease.

Alcohol

Moderate alcohol consumption (1-2 drinks per day is associated with a reduced overall and CHD-related mortality compared with both abstinence and heavy drinking. [33, 34]

However, alcohol raises HDL-C (by stimulating the hepatic production of apolipoprotein [apo] A-I and A-II), [35, 36, 37] stimulates fibrinolysis, [38, 39, 40] reduces fibrinogen levels, [41, 42] reduces inflammation, [43] and inhibits platelet activation. [44] Moreover, the personal and social risks of alcohol intake (eg, violence, trauma, car accidents, binge drinking) appear to be higher in younger individuals. [45]

In the United States, additional antioxidant effects have been attributed to red wine, but the consumption of other alcoholic beverages is associated with a somewhat lower or similar reduction in CHD risk, [46, 47] and the pattern and amount of alcohol intake appears to be more important than the type.

Antioxidants

Although several observational studies and 1 randomized, controlled secondary prevention trial (CHAOS) [48] found reduced CVD in those taking large amounts of antioxidant vitamins, no benefit for 400 and 300 IU/d of vitamin E, respectively, was found in the Heart Outcomes Prevention Evaluation (HOPE) [49] Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevention, [50] and Heart Protection Studies (HPS). [51]

A meta-analysis of available data suggests no benefit for antioxidant vitamins. [52]

Herbals

An estimated 40% of the US population uses herbal remedies, and at least $15 billion is spent annually in North America on alternative forms of health care. Inquiry about the use of herbals is a component of good medical care, especially in cardiovascular medicine.

Alternative medicine approaches to cholesterol lowering include garlic, policosanol, gugulipid, and red rice yeast extracts, the latter of which contains 3-hydroxy-3-methylglutaryl coenzyme-A (HMG-CoA) reductase inhibitors. Garlic modestly lowers cholesterol (approximately 3%) and may lower BP and inhibit platelet aggregation. Fermented red rice yeast extracts contain statins and lower cholesterol 13-26%. [53] Ephedra-containing herbals, often used as anorexics, are associated with hypertension and stroke and have been banned in the United States. [54, 55]

Aspirin

Two meta-analyses showed that aspirin use (75-162 mg/d) decreases the occurrence of primary MI by 25-33% and has also been shown to decrease death due to vascular causes; these benefits are not gender specific. [56, 57] However, all benefits have to be balanced against the risk of gastrointestinal bleeding.

Primary prevention of CVD and colorectal cancer

Initiate low-dose aspirin for individuals aged 50-59 years who have the following features (grade B recommendation) [58] :

- Have a 10-year ASCVD risk 10% or greater
- Are not at increased bleeding risk
- Have a life expectancy of 10 years or longer
- Are willing to take daily low-dose aspirin for at least 10 years

Individualize treatment for individuals aged of 60-69 years with a 10-year ASCVD risk of 10% or greater (grade C recommendation). The use of aspirin is likely to benefit this age group who share the features of those listed in the 50-59 years age population. [58] Those who place a higher value on the potential benefits than the potential harms may choose to initiate low dose aspirin.

For adults younger than 50 years or older than 70 years, there is insufficient evidence evaluate the benefits/risks of initiating low-dose aspirin. [58]

Lifestyle Management

Primary prevention should start with lifestyle modification, including smoking cessation, weight management, diet, and physical activity. Hormone therapy increases cardiovascular events in postmenopausal women. Estrogen alone increases stroke, but it does not alter coronary heart disease (CHD) events.

Smoking cessation

Of all the lifestyle modifications recommended to prevent cardiovascular disease (CVD), smoking cessation is the most important. Tobacco use prematurely kills more than 480,000 Americans annually. [59] Smoking cessation is the most cost-effective preventive measure, estimated at $220 to $5050 per year of life saved (LYS) in 1993 to $490 to $15,280 LYS in 2006. [60] Individuals aged 30 years gain 3-5 years of life by stopping smoking, and the mortality benefit was shown to be equally impressive in elderly populations. [61, 62] The most effective smoking cessation programs involve programmatic and/or group support and the use of nicotine substitutes and antidepressants, such as bupropion. Varenicline is a more recent addition to the smoking cessation armamentarium and has been found to be superior to bupropion in this respect. [63, 64, 65]

Smoking is a risk factor for CVD in women and men; however, a systemic review and meta-analysis by Huxley and Woodward suggested that in some countries, smoking by women has risen; the study suggested that proper counseling and nicotine addiction programs should focus on young women. [66]

Smoking cessation counseling with supportive contact after a patient with acute myocardial infarction is discharged is potentially cost-effective and

may reduce the incidence of smoking and further adverse health events. [67]

The goal is complete cessation and no exposure to environmental tobacco smoke. The following "5 A's" are a common approach to assess patients' smoking behavior [68] :

- Ask the patient about tobacco use status at every visit.

- Advise every patient who uses tobacco to quit.

- Assess the patient's willingness to quit using tobacco

- Assist the patient by counseling and developing a plan for quitting.

- Arrange follow-up, referral to special programs, or pharmacotherapy (including nicotine replacement and bupropion).

In addition, urge the patient to avoid exposure to environmental tobacco smoke at work and home.

Diet

Dietary recommendations from the 2013 American Heart Association (AHA)/American College of Cardiology (ACC) guideline on lifestyle management to reduce cardiovascular are summarized below. [14]

Adults who would benefit from a reduction in LDL-C

Adults who fall into this group should emphasize intake of foods including vegetables, fruits, whole grains, legumes, low-fat diary products, poultry, fish and nontropical vegetable oils. Limit the intake of sweets, sugar-sweetened beverages, and red meats. Adults can achieve this type of diet by following plans such as the DASH (Dietary Approaches to Stop Hypertension) diet (see below), AHA diet, or US Department of Agriculture (USDA) food patterns. (Level of evidence [LOE]: A)

In addition, limiting the amount of calories from saturated fat to 5%-6% as well as reducing the percentage of calories from trans fat are recommended. (LOE: A)

Adults who would benefit from reduction in blood pressure (BP)

Adults who fall into this group should follow the same dietary emphasis as those who would benefit from LDL-C reduction (eg, vegetables, fruits, whole grains, legumes, DASH diet), as well as combine the DASH diet with a reduction in sodium intake. (LOE: A)

Guidance in reducing sodium intake include not consuming more than 2,400 mg of sodium daily; an associated greater reduction in BP with

further reduction to 1500 mg/day; and achieving a lower BP with reduction of sodium intake by at least 1000 mg daily. (LOE: B)

DASH dietary pattern

The DASH dietary pattern is high in vegetables, fruits, whole grains, low-fat/fat-free dairy products, poultry, fish, beans, nuts, and nontropical vegetable oils, as well as rich in potassium, magnesium, calcium, protein, and fiber. [14, 15, 69] It is low in sweets, sugar-sweetened beverages, sodium, and red meats, as well as saturated fat, total fat, and cholesterol. This dietary pattern aims for a daily maximum target of 2,000 calories.

Compared to a typical American diet of the 1990s, the DASH dietary pattern reduced the following [14, 15] :

- BP by 5-6/3 mm Hg in adults with BP 120-159/80-95 mm Hg, for both women and men, black and non-black adults, older and younger adults, and hypertensive and nonhypertensive adults

- LDL-C by 11 mg/dL and HDL-C by 4 mg/dL, with no effect on triglycerides, in adults with total cholesterol levels below 260 mg/dL and LDL-C levels below 160 mg/dL, including black and non-black adults, as well as hypertensive and non-hypertensive adults

Alcohol intake

Light-to-moderate alcohol consumption (5-25 g/d) has been significantly associated with a lower incidence of cardiovascular and all-cause mortality in patients with CVD. [70] A meta-analysis by Costanzo et al found J-shaped curves for alcohol consumption and mortality, with a significant maximal protection against cardiovascular mortality with consumption of approximately 26 g/d and maximal protection against mortality from any cause in the range of 5-10 g/d. [70]

Physical activity

Reduced physical activity is a major risk factor for CVD. In elderly individuals, walking 30 minutes daily reduces the risk of MI by as much as 50%. [71, 72] The Cooper Center Longitudinal Study found that low fitness in mid-life was associated with a higher lifetime risk for CVD death, [73] and a study evaluating the relationship between physical activity and CVD risk among 44,551 men (age, 40-75 y) found that vigorous- and moderate-intensity activity were associated with a lower risk of CVD and major chronic disease. [74]

The 2013 AHA/ACC lifestyle management guidelines recommendation for physical activity to reduce LDL-C, non HDL-C, and BP is 3-4 sessions each week that last an average of 40 minutes per session and involve

moderate-to-vigorous intensity physical activity. [14]

Abnormal heart rate recovery (HRR) has been demonstrated to be prognostic factor for mortality. [75] In attempting to determine whether HRR (defined as heart rate at peak exercise and exactly 1 minute into the recovery period) could be improved with cardiac rehabilitation, findings by Jolly et al suggest that patients with abnormal HRR at baseline could normalize HRR with exercise. The mortality rate of these patients was similar to that of individuals with baseline normal HRR. [75]

The following general principles should be considered when recommending increased physical activity to patients:

- Increased physical activity begins with increasing lifestyle activities, such as walking.

- A complete exercise program includes stretching, aerobic exercise, and resistance training.

- More frequent exercise, optimally daily, provides more benefit.

- More strenuous exercise, such as jogging, provides more benefit. A good goal is 75% of the age-predicted maximal heart rate (220 − age of individual).

- Excellent benefit can be derived from 40 minutes of daily exercise.

- Studies have also shown that even 15 minutes daily or 90 minutes weekly of moderate-intensity exercise may be beneficial. [76]

- European studies suggest that increased waist circumference and physical inactivity are associated with an increased risk of CHD. [77]

Weight management

The goal of weight management is a body mass index (BMI) of 18.5-24.9 kg/m^2 for men and women, as well as a waist circumference less than 40 inches in men and below 35 inches in women. [78] The 2011 AHA/ACCF (ACC Foundation) guideline for secondary prevention and risk reduction therapy for patients with CVD and other atherosclerotic vascular disease include the following weight management strategies [79, 80] :

- Assess BMI and/or waist circumference on each visit; consistently encourage weight maintenance/reduction with an appropriate balance of physical activity/structured exercise, caloric intake, and formal behavioral programs to maintain/achieve a BMI of 18.5-24.9 kg/m^2.

- Measure horizontal waist circumference at the iliac crest; if it is at

least 35 inches (≤89 cm) in women and at least 40 inches (≤102 cm) in men, intensify lifestyle changes, focusing on weight management.

- Aim for an initial weight-loss goal of about a 5%-10% reduction from baseline; when this goal is achieved, assess if further weight loss is indicated.

The Aerobics Center Longitudinal Study found that maintaining or improving fitness was associated with a lower risk of all-cause and CVD mortality in men. [81] Healthcare providers should encourage men to exercise regularly, regardless of age and BMI change, as it is important for longevity. [81]

Summary of general nutritional recommendations

Achieve and maintain ideal body weight by limiting foods high in calories and low in nutrition, including those high in sugar, (eg, soft drinks, candy).

Eat a variety of fruits, vegetables, legumes, nuts, soy products, low-fat dairy products, and whole grain breads, cereals, and pastas.

Consume baked/broiled fish at least twice per week.

Choose oils and margarines low in saturated fat and high in omega-3 fat (eg, canola, soybean, walnut, and flaxseed oils, including those fortified with stanols and sterols).

Avoid foods high in saturated and trans-fats (eg, red meat, whole milk products, pastries).

Limit alcohol consumption to no more than 2 drinks daily for men or 1 drink daily for women.

Take in less than 6 g of salt or less than 2400 mg/d of sodium.

Secondary prevention (after development of CHD)

Several large observational studies, all of which had at least 5 years of follow-up and a meta-analysis including these studies, showed a substantial reduction in mortality (relative risk [RR]: 0.64 (I: 0.58-0.71)] in patients with a history of MI, coronary artery bypass grafting (CABG), angioplasty, or known CHD, who quit smoking compared with patients who continued to smoke. [82, 83] The overall mortality risk of smokers who quit decreased by 50% in the first couple of years and had a tendency to approach that of nonsmokers in approximately 5-15 years of cessation of smoking.

Secondary Prevention Goals and Management

For secondary prevention, individuals aged 75 years and younger with clinical atherosclerotic cardiovascular disease (ASCVD) should be started on high-intensity statin therapy unless contraindicated. [18] In individuals with clinical ASCVD with contraindications to high-intensity statin therapy but who would otherwise benefit from it, or in persons who are predisposed to statin-associated adverse effects, a second-line option is moderate-intensity statin therapy, if tolerated.

When considering moderate- or high-intensity statin therapy in those older than 75 years with clinical ASCVD, assess the potential risk-reduction benefits, adverse effects, drug-drug interactions, and patient preferences. Continue statin therapy if tolerated. [18]

Patients covered by current guidelines include those with established coronary and other atherosclerotic vascular disease, including peripheral arterial disease, atherosclerotic aortic disease, and carotid artery disease. Treatment for patients whose only manifestation of cardiovascular risk is diabetes will be the topic of a separate AHA scientific statement.

The 2011 American Heart Association (AHA)/American College of Cardiology Foundation (ACCF) update of their guideline for secondary prevention and risk reduction therapy for patients with CVD and other atherosclerotic vascular disease can be found at: http://circ.ahajournals.org/content/124/22/2458.long. [79, 80] The recommendations are outlined below.

Blood pressure control

The goal is blood pressure (BP) below 140/90 mm Hg, or below 130/80 mm Hg if the patient has diabetes or chronic kidney disease. [79, 80]

For all patients, initiate or maintain lifestyle modification, weight control, increased physical activity, alcohol moderation, sodium reduction, and increased consumption of fresh fruits, vegetables, and low-fat dairy products.

For patients with BP of 140/90 mm Hg or greater (or ≥130/80 mm Hg for individuals with chronic kidney disease or diabetes), as tolerated, add BP medication, treating initially with beta-blockers and/or angiotensin-converting enzyme (ACE) inhibitors, with addition of other drugs, such as thiazides, as needed to achieve goal BP. [79, 80]

Lipid management

The goal is achieving low-density lipoprotein cholesterol (LDL-C) levels below 100 mg/dL; if triglyceride levels are 200 mg/dL or above, non-HDL-C (non-high-density lipoprotein cholesterol) levels should be below 130 mg/dL. (Non-HDL-C = total cholesterol − HDL-C.) [79, 80]

The following measures should be taken for all patients [79, 80] :

- Start dietary therapy; reduce the intake of saturated fats (to <7% of total calories), trans-fatty acids (<7% of total calories), and cholesterol (to

- Adding plant stanols/sterols (2 g/d) and viscous fiber (>10 g/d) will further lower the LDL-C level.

- Promote daily physical activity and weight management.

- Encourage increased consumption of omega-3 fatty acids in the form of fish or in capsule form (1 g/d) for risk reduction. (Pregnant and lactating women should limit their intake of fish to minimize exposure to methylmercury.)

- For treatment of elevated triglyceride levels, higher doses are usually necessary for risk reduction.

  In addition, to encourage treatment compliance, particularly with cardiovascular medications in secondary prevention, clinicians should provide clear discussions about the risk of disease recurrence and medication-specific information at the start of pharmacotherapy, and they should ease the transition between primary and secondary care. [84]

  Assess fasting lipid profile in all patients and within 24 hours of hospitalization for those with an acute cardiovascular or coronary event. For hospitalized patients, before discharge, initiate lipid-lowering medication as recommended below, according to the following schedule [79, 80] :

  - LDL-C level should be below 100 mg/dL, and further reduction of LDL-C level to less than 70 mg/dL is reasonable.

  - If the baseline LDL-C level is 100 mg/dL, initiate LDL-C-lowering drug therapy.

  - If the patient is on treatment and the LDL-C level is 100 mg/dL, intensify LDL-C-lowering drug therapy (may require LDL-C-lowering drug combination [standard dose of statin with ezetimibe, bile acid sequestrant, or niacin]).

  - If the baseline LDL-C level is 70-100 mg/dL, treating to an LDL-C level below 70 mg/dL is reasonable.

  - If the triglyceride levels are 200-499 mg/dL, non-HDL-C levels should be below 130 mg/dL, and further reduction of non-

HDL-C levels to below 100 mg/dL is reasonable.

Therapeutic options to reduce non-HDL-C level include the following [79, 80]:

- More intense LDL-C-lowering therapy

- Niacin (after LDL-C-lowering therapy)

- Fibrate therapy (after LDL-C-lowering therapy)

If triglyceride levels are 500 mg/dL, fibrate or niacin is a therapeutic option to prevent pancreatitis before initiating LDL-C-lowering therapy. In addition, treat the LDL-C level to goal after triglyceride-lowering therapy. Achieve a non-HDL-C level below 130 mg/dL, if possible. Note the following [79, 80]:

- Patients with very high triglyceride levels should not consume alcohol.

- The use of bile acid sequestrants is relatively contraindicated when triglyceride levels are above 200 mg/dL.

- The risk for severe myopathy can be increased when the combination of a high-dose statin plus a fibrate is used. Therefore, maintain relatively low statin doses with this treatment combination.

- Do not substitute dietary supplement niacin for prescription niacin.

In 2011, The National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH) stopped a clinical trial studying a blood lipid treatment that was adding high-dose, extended-release niacin to statin treatment in people with heart and vascular disease. [85] The study was stopped because the treatment did not reduce the risk of cardiovascular events, including heart attacks and stroke. The Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM HIGH) study selected patients at risk for cardiovascular events despite well-controlled LDL-C. Participants who took high-dose, extended-release niacin and statin treatment had increased HDL-C and lower triglyceride levels compared to participants who took a statin alone. However, the combination treatment did not reduce fatal or nonfatal heart attacks, strokes, hospitalizations for acute coronary syndrome, or revascularization procedures to improve blood flow in the arteries of the heart and brain. [85]

Furthermore, the AIM HIGH investigators concluded that patients

with atherosclerotic CVD and LDL-C levels below 70 mg/dL (1.81 mmol/L) experienced no incremental clinical benefit from the addition of niacin to statin therapy, despite significant improvements in HDL-C and triglyceride levels. [86]

A study by Mills et al suggested that intensive statin dosing reduces the risk of nonfatal events (coronary heart disease and nonfatal myocardial infarction [MI]) and may have a role in reducing mortality. [87] However, the benefits of high-dose statins must be weighed against the risk of myopathy, including rhabdomyolysis, at high doses.

When LDL-C-lowering medications are used, obtain at least a 30-40% reduction in LDL-C levels. If LDL-C below 70 mg/dL is the chosen target, consider drug titration to achieve this level to minimize side effects and cost. When the goal of LDL-C below 70 mg/dL is not achievable because of high baseline LDL-C levels, it generally is possible to achieve LDL-C reductions of over 50% by either statin therapy or LDL-C-lowering drug combinations.

RVX-208, the first oral agent designed to enhance apolipoprotein (apo) A-I synthesis, has been shown to increase apoA-I, HDL-C, and concentrations of large HDL particles, as well as elevate liver enzymes. [88]

Lowering LDL-C with statin regimens may have an effect in people with moderate-to-severe kidney disease. [89] The Study of Heart and Renal Protection (SHARP) trial suggests simvastatin (20 mg) plus ezetimibe (10 mg) daily safely reduces the incidence of major atherosclerotic events in a wide range of patients with advanced chronic kidney disease.

Secondary prevention trials in older persons with coronary artery disease and hypercholesterolemia have demonstrated that statin drugs reduced all-cause mortality, cardiovascular mortality, coronary events, coronary revascularization, stroke, and intermittent claudication. Statin therapy significantly decreases cardiovascular events and all-cause mortality in women and men. [90]

Raal et al found that lipid-lowering therapy is associated with delayed cardiovascular events and prolonged survival in patients with homozygous familial hypercholesterolemia. [91]

Diabetes management

The goal of diabetes management is to maintain a glycosylated hemoglobin (HbA1c) concentration below 7%. Consider the following [79, 80]:

- Initiate lifestyle and pharmacotherapy to achieve near-normal HbA1c levels.

- Begin vigorous modification of other risk factors (eg, physical activity, weight management, BP control, cholesterol management) as discussed earlier.

- Coordinate diabetic care with the patient's primary care physician or endocrinologist.

In December 2016, the US Food and Drug Administration (FDA) approved a new indication for empagliflozin (Jardiance) for reducing the risk of CV death in adults with type 2 diabetes and CVD. [92] The approval was based on findings from the EMPA-REG OUTCOME trial involving 7,020 patients in which empagliflozin produced a 38% relative risk reduction in CV mortality and a 32% risk reduction in all-cause mortality compared with placebo among the patients with type 2 diabetes, all of whom had established CVD and were already being treated with statins, ACE inhibitors, and aspirin. [93]

In August 2017, the FDA has approved a new indication for liraglutide (Victoza) to reduce the risk of major adverse CV events (CV death, nonfatal MI, or nonfatal stroke) in adults with type 2 diabetes and established CVD. [94] Liraglutide is the second drug approved for glucose lowering in type 2 diabetes that has gained an additional indication for CV benefit based on results from FDA-mandated CV outcomes trials.

The approval is based on the results from the LEADER trial, which demonstrated that liraglutide statistically significantly reduced the risk of cardiovascular death, non-fatal heart attack or nonfatal stroke by 13% versus placebo, when added to standard of care, with an absolute risk reduction of 1.9%.The overall risk reduction was derived from a statistically significant 22% reduction in cardiovascular death with liraglutide treatment versus placebo, with an absolute risk reduction of 1.3%, and non-significant reductions in nonfatal heart attack and nonfatal stroke. [95]

Antiplatelet agents and anticoagulants

Note the following [79, 80]:

- Start aspirin 75-162 mg/day, and continue indefinitely in all patients unless contraindicated. For patients undergoing coronary artery bypass grafting, initiate aspirin therapy (100-325 mg/day) within 6 hours after surgery to reduce saphenous vein graft closure. Doses above 162 mg/day can be continued for up to 1 year.

- Start and continue clopidogrel 75 mg/day in combination with aspirin for up to 12 months in patients after acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) with stent placement (at least 1 month, but ideally 12 months, for bare metal stent; at least 12 months for drug-eluting stents). Patients who have undergone PCI with stent placement should initially receive higher-dose aspirin at 162-325 mg/d for 1 month for bare metal stent, 3 months after sirolimus-eluting stent, 6 months after paclitaxel-eluting stent, after which daily long-term aspirin use should be continued indefinitely at a dose of 75-162 mg. [96]

- Manage warfarin to an international normalized ratio (INR) of 2.0-3.0 for paroxysmal or chronic atrial fibrillation or flutter, and in post–MI patients when clinically indicated (eg, atrial fibrillation, left ventricular [LV] thrombus).

- Closely monitor use of warfarin in conjunction with aspirin and/or clopidogrel as this regimen is associated with an increased bleeding risk.

A nationwide cohort study has suggested that treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) duration in patients with prior MI, whether short term or long term, is associated with increased risk of death and recurrent MI in patients with prior MI and is not recommended for this population. [97] NSAID use should be limited from a cardiovascular safety point of view.

Renin, angiotensin, and aldosterone system blockers

Consider the following regarding ACE inhibitors [79, 80] :

- Unless contraindicated, initiate and continue ACE inhibitor therapy indefinitely in all patients with an LV ejection fraction (LVEF) of 40% or below; in those with hypertension, diabetes, or chronic kidney disease; and consider for all other patients.

- ACE inhibitors may be considered optional for lower-risk patients with normal LVEF in whom cardiovascular risk factors are well controlled and revascularization has been performed.

Consider the following regarding angiotensin receptor blockers (ARBs) [79, 80] :

- Use ARBs in patients who are intolerant of ACE inhibitors, as well as in those with heart failure or have had an MI with an LVEF of 40% or below.

- Consider ARBs in combination with ACE inhibitors in those with systolic dysfunction heart failure.

Aldosterone blockade are used in post-MI patients without significant renal dysfunction (creatinine level should be >2.5 mg/dL in men and >2.0 mg/dL in women) or hyperkalemia (potassium level should be 79</ref> [80] One study has suggested that higher dietary potassium intake is associated with lower rates of stroke and may reduce the risk of CHD. [98]

Beta-blockers

Start and continue beta-blockers indefinitely in all patients who have had MI, ACS, or LV dysfunction, with or without heart failure symptoms, unless contraindicated. [79, 80]

Consider chronic therapy for all other patients with coronary or other vascular disease or diabetes, unless contraindicated.

Influenza vaccination

Patients with CVD should receive an influenza vaccination every year. [79, 80]

Women and Coronary Artery Disease

In the United States, coronary heart disease (CHD) is the leading cause of death in men and women, claiming more lives than cancer, accidents, and diabetes combined. [99, 100] Although breast cancer may be more feared, age-adjusted death rates from cardiovascular disease (CVD) in women are 4 times higher in white women and 6 times higher in black women than the death rates for breast cancer.

The 2010 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) report on assessment of cardiovascular risk in asymptomatic adults includes the recommendation that for all adult women and men, global risk scoring should be performed and a family history of cardiovascular disease should be obtained for cardiovascular risk assessment. [101]

Compared with men, levels of low-density lipoprotein cholesterol (LDL-C) is lower and high-density lipoprotein cholesterol (HDL-C) is higher in women before menopause. Although women have lower rates of hypertension and cigarette smoking than men, rates for obesity and diabetes mellitus are higher. Diabetes mellitus is a particularly serious risk factor in women, tripling the risk of cardiovascular death and causing diabetic women to have the same frequency of CVD as diabetic men. [102,

[103, 104] HDL-C and triglyceride levels are more predictive of CVD in women than in men. [105] Women have been noted to have similar or slightly higher prevalence of stable angina as compared to men. [106]

It is now recognized that women tend to present more commonly with unstable angina as compared to men, the reverse of which is true for myocardial infarction (MI). However, when women do present with MI, they are more likely to have Q wave rather than non-Q wave MIs. [107, 108] Mortality rates of MI and coronary artery bypass grafting (CABG) are about 50% higher in women, mostly related to older age of onset. Lipid lowering has shown similar efficacy in women and men in the angiographic progression and event trials. Cardioprotective agents, including aspirin, beta-blockers, and angiotensin-converting enzyme (ACE) inhibitors, appear to have similar efficacy in men and women. [109, 110, 111]

Hormone therapy is no longer recommended to prevent coronary events in postmenopausal women with or without established CHD. Although hormone therapy improves LDL-C and HDL-C levels, [112, 113] it also increases coagulation and inflammation (as measured by C-reactive protein [CRP]) and decreases LDL-C particle size. [5, 114] Treatment rates for risk factors in women tend to be even lower than in men, as are rates for coronary angiography and coronary artery revascularization following presentation with chest pain.

Women who may have had radiotherapy through the mid-1980s to treat breast cancer are also at an increased risk of mortality from CVD. The concern is even greater if the woman was treated for a left-sided breast cancer with contemporary tangential breast or chest wall radiotherapy. [115]

Finally, it must be emphasized that although the guidelines detailed above represent best practice, their formulation is often a blend of science and art. Therefore, guideline interpretation should always occur alongside good clinical judgment.

Questions & Answers

Overview

How many lives can be saved with primary prevention of cardiovascular disease (CVD)?

Which factors contribute to a decline in the mortality of coronary heart disease (CHD)?

What is the efficacy of statin therapy for the prevention of coronary artery disease (CAD)?

What is the American College of Cardiology (ACC) and the American Heart Association (AHA) risk score for atherosclerotic cardiovascular disease (ASCVD)?

What are improvements in the ACC/AHA updated guidelines for the assessment of cardiovascular risk?

What are American College of Physicians (ACP) screening guidelines for coronary heart disease (CHD)?

What are AHA/ACC treatment guidelines for elevated blood cholesterol for the primary and secondary prevention of coronary artery disease (CAD)?

According to the AHA/ACC guidelines, when is statin therapy indicated in the prevention of coronary artery disease?

What are considerations prior to initiation of statin therapy for the prevention of coronary artery disease (CAD)?

What are the AHA/ACC guidelines for statin therapy intensity to prevent coronary artery disease (CAD)?

What are the AHA/ACC guidelines for statin therapy as primary prevention of coronary artery disease (CAD) in specific patient groups?

What is the role of hypertension management in the prevention of coronary artery disease (CAD)?

Which treatments for mild hypertension aid in the prevention of coronary heart disease (CAD)?

Which treatments for high-normal hypertension aid in the prevention of coronary heart disease (CAD)?

What is the role of alcohol consumption in the prevention of coronary artery disease (CAD)?

What is the role of antioxidants in the prevention of coronary artery disease (CAD)?

What is the role of herbal remedies in the prevention of coronary artery disease (CAD)?

What is the role of aspirin in the prevention of coronary artery disease (CAD)?

What is the role of lifestyle modification in the primary prevention of coronary artery disease (CAD)?

What is the role of smoking cessation in the prevention of coronary artery disease (CAD)?

What are the 2013 American Heart Association (AHA)/American College of Cardiology (ACC) dietary recommendations to reduce cardiovascular risks and prevent coronary artery disease (CAD)?

What is the DASH dietary pattern for prevention of coronary artery disease (CAD)?

What are role of light-to-moderate alcohol consumption in the prevention of coronary artery disease (CAD)?

AHA/ACC lifestyle management guidelines for physical activity to prevent coronary artery disease (CAD)?

What are general principles of increased physical activity in the prevention of coronary artery disease (CAD)?

What is the role of weight management the prevention of coronary artery disease?

What are the general nutritional recommendations for prevention of coronary artery disease (CAD)?

What is the estimated reduction in mortality from coronary heart disease (CHD) attributed to smoking cessation?

What are American Heart Association (AHA)/American College of Cardiology Foundation (ACCF) guidelines for secondary prevention of coronary artery disease (CAD)?

What is the role of blood pressure control in the secondary prevention of coronary artery disease (CAD)?

What is the role of lipid management in the secondary prevention of coronary artery disease (CAD)?

What are American Heart Association (AHA)/American College of Cardiology Foundation (ACCF) recommendations for assessing and treating high levels of LDL-C for secondary prevention of coronary artery disease (CAD)?

What are therapeutic options to reduce the non-HDL-C level in the secondary prevention of coronary artery disease (CAD)?

What is the role of fibrate or niacin in the secondary prevention of coronary artery disease (CAD)?

What is the efficacy of intensive statin dosing for secondary prevention of coronary artery disease (CAD)?

What is the efficacy of lowering LDL-C with statin regimens for the secondary prevention of coronary artery disease (CAD)?

What is the role of diabetes management in the secondary prevention of coronary artery disease?

What is the role of empagliflozin (Jardiance) in the secondary prevention of coronary artery disease (CAD)?

What is the role of antiplatelet agents and anticoagulants in the secondary prevention of coronary artery disease (CAD)?

What is the role of ACE inhibitors in the secondary prevention of coronary artery disease (CAD)?

What is the role of angiotensin receptor blockers (ARBs) in the secondary prevention of coronary artery disease (CAD)?

What is the role of beta-blockers in the secondary prevention of coronary artery disease (CAD)?

What is the role of influenza vaccination in the secondary prevention of coronary artery disease (CAD)?

What are recommendations for the assessment of cardiovascular risk in asymptomatic adults with coronary artery disease (CAD)?

What are the treatment guidelines for coronary artery disease in women?