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State-of-the-Art Review

Ten things to know about ten cardiovascular disease risk factors ("ASPC Top Ten – 2020")

Harold Edward Bays

Louisville Metabolic and Atherosclerosis Research Center, 3288, Illinois Avenue, Louisville, KY, 40213, USA

ABSTRACT

Preventive cardiology involves understanding and managing multiple cardiovascular disease (CVD) risk factors. Given the rapid advancements in medical science, it may be challenging for the busy clinician to remain up-to-date on the multifaceted and fundamental aspects of CVD prevention, and maintain awareness of the newest applicable guidelines. The "American Society for Preventive Cardiology (ASPC) Top Ten 2020" summarizes ten essential things to know about ten important CVD risk factors, listed in tabular formats. The ten CVD risk factors include unhealthful nutrition, physical inactivity, dyslipidemia, hyperglycemia, high blood pressure, obesity, considerations of select populations (older age, race/ethnicity, and gender), thrombosis/smoking, kidney dysfunction and genetics/familial hypercholesterolemia. For the individual patient, other CVD risk factors may be relevant, beyond the CVD risk factors discussed here. However, it is the intent of the "ASPC Top Ten 2020" to provide a succinct overview of things to know about ten common CVD risk factors applicable to preventive cardiology.

What is already known about this subject?

- Preventive cardiology necessitates understanding and managing multiple cardiovascular disease (CVD) risk factors.
- Among factors that increase the risk of CVD include unhealthful nutrition, physical inactivity, dyslipidemia, hyperglycemia, high blood pressure, obesity, considerations of select patient populations (older age, race/ethnicity and gender), thrombosis/smoking, kidney dysfunction, and genetics/familial hypercholesterolemia.
- Diagnosing and treating multiple CVD risk factors help prevent or reduce the risk of CVD.

What are the new findings in this manuscript?

- The "American Society for Preventive Cardiology (ASPC) Top Ten 2020" summarizes ten things to know about ten important CVD risk factors (listed in a tabular format) to provide a succinct overview of preventive cardiology.

- Primary care clinicians (family practice, internal medicine, nurse practitioners, physician assistants, obstetrics/gynecology, etc.) may benefit from an overview summary of multiple CVD risk factor identification and management. Specialists may benefit as well, because a specialist in one aspect of preventive cardiology may not necessarily have expertise in other aspects of preventive cardiology.
- In addition to the "Top Ten" things to remember summary for each of ten sentinel CVD risk factors, citations are listed in the applicable tables to provide the reader references to more in-depth resources (e.g., illustrative guidelines and other references).

Introduction

The intent of the "American Society for Preventive Cardiology (ASPC) Top Ten 2020" is to help both primary care clinicians and specialists keep up with the ever-increasing pace of advancements in cardiovascular disease (CVD) prevention. The "ASPC Top Ten 2020" summarizes ten things to know about ten important CVD risk factors, listed in tabular formats. These CVD risk factors include unhealthful nutrition, physical

Table 1

Ten things to know about nutrition and cardiovascular disease (CVD) prevention.

1. Medical nutrition therapy is most effective in reducing CVD when the dietary interventions are evidence-based, promote healthful quantitative and qualitative dietary intake, and when conducive to long-term patient adherence [3]

2. Saturated fat intake may promote atherogenesis via increased low-density lipoprotein cholesterol levels, increased apolipoprotein B levels, increased low density lipoprotein particle number, increase inflammation, and endothelial dysfunction [14,15]. Dairy products contain micro and macronutrients (e.g., proteins, calcium, magnesium, potassium, vitamins) that may reduce inflammation and reduce CVD risk [16]. Dairy products also contain short, medium, and long-chain saturated fatty acids, with differences in fatty acid size having different potential effects in promoting CVD risk [17]. The balanced nutrients within "whole food" dairy consumption may help explain why dairy intake is often reported to have a neutral or favorable effect on CVD risk [18,19], and why dairy consumption within the Mediterranean Diet does not increase, and may reduce CVD risk.

3. Ultra-processed carbohydrates increase the risk of post-prandial hyperglycemia, hyperinsulinemia, hypertriglyceridemia, inflammation, endothelial dysfunction, sympathetic hyperactivity, and hypercoagulability [20], all CVD risk factors. The nutrient comparator component in some clinical trials is a confounder in claims regarding the effects of saturated fats and ultra-processed carbohydrates on CVD risk. CVD risk is not reduced with isocalric substitution of saturated fats with unhealthful ultra-processed carbohydrates. CVD risk is not reduced with the isocaloric substitution of refined carbohydrates with saturated fats. CVD risk is reduced when saturated fats are replaced by unsaturated fats and when ultra-processed carbohydrates are replaced by fiber-rich complex carbohydrates found in healthful whole foods [21].

4. The "Dietary Approaches to Stop Hypertension" (DASH) diet has among the best evidence for prevention of CVD [2]. DASH diet meal planning includes vegetables, fruits, whole grains, fat-free or low-fat dairy products, fish, poultry, lean meats, nuts, seeds, legumes, fiber and the minerals calcium, potassium, and magnesium. Sodium is limited 1500–2300 mg per day, total fat is limited to ~27% of total daily calories, saturated fat is <6% of total daily calories, and cholesterol is limited to ≤150 mg per day for a 2100-Calorie eating plan. Among foods discouraged are red and processed meats, sugar-sweetened beverages, and foods with added sugars [22].

5. The Mediterranean Diet has among the best evidence for prevention of CVD [2]. Monounsaturated olive oil is a main source of fat, with other food components including vegetables, fruits, legumes, whole grains, nuts, and seeds, moderate intake of red wine, moderate consumption of seafood, fermented dairy products (cheese and yogurt), poultry, and eggs. Among foods discouraged are red meat, meat products, ultra-processed carbohydrates, and saturated fats (although lard and butter for cooking is found in some Mediterranean cuisine) [23].

6. The Vegetarian Diet has among the best evidence for CVD prevention [2]. A vegetarian diet meal plan includes foods that come mostly from plants such as vegetables, fruits whole grains, legumes, seeds, nuts, and may include eggs and milk. Animal meats are discouraged [24]. While healthful plant-based foods (whole grains, fruits, vegetables, nuts, legumes, oils, tea, and coffee) may reduce CVD risk, unhealthful plant-based intake (juices, sweetened beverages, ultra-refined grains, potatoes/fries, and sweets) may increase CVD risk [25], This (in addition to genetics and other factors) helps account for a relatively high rate of CVD among many vegetarians from India [26].

7. The Ketogenic Diet is a carbohydrate-restricted intervention that typically discourages unhealthful ultra-processed and refined foods, foods high in glycemic index/load, and foods rich in *trans* fatty acids. No long-term prospective clinical trial evidence supports the ketogenic diet as reducing CVD. Ketosis may reduce appetite and is often utilized for weight and CVD risk factor reduction in patients with overweight or obesity. In addition to reducing body weight, the ketogenic diet may lower postprandial glucose/insulin levels, lower blood pressure, lower triglyceride, and raise high density lipoprotein cholesterol levels. The ketogenic diet may increase low density lipoprotein cholesterol, which is an effect that may be somewhat mitigated by consumption of monounsaturated and/or polyunsaturated fats versus saturated fats [3,27–29].

8. The Therapeutic Lifestyle Change (TLC) diet is a relatively low-fat meal-plan originally recommended by the National Cholesterol Education Program, Adult Treatment Panel. While not as commonly used in clinical practice, the TLC diet continues to be a "diet" often used in lipid clinical trials. Total fat is 25–35%; polyunsaturated fats ≤10%; monounsaturated fat ≤20% of total daily calories. Carbohydrates are 50%–60% of total calories. Soluble fiber is increased to at least 5–10 g a day, preferably 10–25 g a day, as well as adding up to 2 g per day of plant stanols or sterols through foods or dietary supplements. Saturated fats are <7% daily calories; cholesterol is < 200 mg a day [30].

9. The Ornish Diet is illustrative of a fat-restricted nutritional intervention wherein macro and micronutrients are best eaten in their natural food form. The Ornish Diet includes vegetables, fruits, whole grains, legumes, and soy with limited amounts of green tea. Other recommendations are fish oil 3–4 g each day and small meals eaten frequently throughout the day. Dietary fat is limited to <10% of total daily calories and dietary cholesterol to ≤10 mg per day. Other nutrients

Table 1 (*continued*)

limited or best avoided include sugar, sodium, alcohol, animal products (red meat, poultry, and fish), caffeine (except green tea), refined carbohydrates and oils [31, 32].

10. Intermittent fasting may reduce overall caloric intake, reduce body weight, and improve metabolic parameters (e.g. improve insulin sensitivity, blood pressure, lipids, and inflammatory markers, even among patients with metabolic syndrome treated with statins and anti-hypertensive agents) often with preservation in resting metabolic rate and lean body mass [3,33].

<u>ILLUSTRATIVE GUIDELINE AND REFERENCE SECTION:</u>

[1] Clinician's Guide for Trending Cardiovascular Nutrition Controversies: Part II

[2] A Clinician's Guide to Healthy Eating for Cardiovascular Disease Prevention

[4] A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

[34] Dietary Fats and Cardiovascular Disease: A Presidential Advisory From the American Heart Association

inactivity, dyslipidemia, hyperglycemia, high blood pressure, obesity, considerations of select populations gender and race, thrombosis/smoking, kidney dysfunction, and genetics/familial hypercholesterolemia. The intent is not to create a comprehensive discussion of all things preventive cardiology. Instead, the intent is to focus on fundamental clinical considerations in preventive cardiology. For those wishing a more intensive discussion of any of these CVD risk factors, this "ASPC Top Ten 2020" also provides illustrative and updated guidelines and other selected references in the applicable tables, for the reader to access more detailed information.

The summary approach of the "ASPC Top Ten 2020" may benefit primary care clinicians (family practice, internal medicine, nurse practitioners, physician assistants, obstetrics/gynecology, etc.), who may welcome an overview of how CVD risk factors are best diagnosed and managed. Specialists may benefit, because a "specialist" in one aspect of preventive cardiology may not always have expertise in other basic aspects of preventive cardiology.

Finally, many patients with CVD often have multiple CVD risk factors. As such, optimal CVD prevention usually requires a multifactorial approach. Patients with CVD, or who are at risk for CVD, most often benefit from global CVD risk reduction, with appropriate attention given to all applicable CVD risk factors. It may therefore be helpful for clinicians to have an overview of core principles applicable to the multiple CVD risk factors that often occur within the same patient who has CVD, or who is at risk for CVD.

Unhealthful nutrition

Definition and physiology

The potential impact of unhealthful nutritional on CVD is two-fold: qualitative and quantitative. Qualitatively, the most appropriate diet plan is one that is evidenced based. Among diet plans most associated with reduced CVD risk are those that [1–4]:

- Prioritize:
  - Vegetables, fruits, legumes, nuts, whole grains, seeds, and fish (preferably fish with higher contents of omega-3 fatty acids)
  - Soluble fiber
- Limit:
  - Saturated fat (best replaced with monounsaturated and polyunsaturated fats)
  - Excessive sodium intake
  - Excessive cholesterol consumption, especially in patients with hypercholesterolemia at increased CVD risk or patients known to increase cholesterol blood levels with increased cholesterol intake
  - Ultra-processed carbohydrates and meats
  - Sweetened beverages
  - No more than moderate intake of alcohol [5,6].
  - Avoid *trans* fats

Table 2
Ten things to know about physical inactivity and cardiovascular disease (CVD) prevention.

1. Physical inactivity is a major risk factor for CVD [37,38].
2. Increased physical activity and routine physical exercise often improve metabolic parameters that otherwise increase CVD risk (e.g., hyperglycemia, hyperinsulinemia, high blood pressure, hypertriglyceridemia, and reduced high-density lipoprotein cholesterol levels) [37,39,40].
3. Beyond improvements in CVD risk factors, increased physical activity and routine physical exercise may benefit the cardiovascular system via enhanced myocardial muscle function (with amelioration of age-related loss of skeletal and cardiac muscle mass and strength). Increased physical activity may reduce inflammation, improve endothelial function, provide cardioprotection against ischemia-reperfusion injury via increased myocardial oxygen utilization, promote myocardial regeneration, facilitate blood vessel dilatation capacity, enhance fibrinolysis, improve autonomic balance, decrease sympathetic tone, reduce cardiac dysrhythmias, reduce resting heart rate, and may possibly help generate a more healthful gut microbiota [38,41–43].
4. Routine physical activity and exercise may help with weight loss maintenance (and possibly weight loss itself), with favorable effects on adiposopathic endocrine and immune abnormalities that promote CVD. An essential principle is that even modest physical activity has health benefits, compared to physical inactivity [3,44].
5. Routine physical activity and exercise may improve body composition through increased muscle mass and decreased visceral and android fat. For the same body mass index, an individual with decreased physical activity and decreased muscle mass will have a higher percent body fat, and often an increase in visceral fat and android fat (i.e., abdominal subcutaneous adipose tissue plus visceral adipose tissue), which is a body composition profile associated with increased risk for CVD [3,45].
6. Provided the guidance is patient-appropriate, a balance of both dynamic (aerobic) and resistance (weightlifting) exercise training are recommended to improve myocardial function and reduce CVD risk [39].
7. In addition to physical exercise, physical activity that increases energy expenditure is dependent upon non-exercise activity thermogenesis (NEAT), which is physical activity beyond volitional sporting-like exercise. NEAT often represents the highest percent of daily energy expenditure beyond resting metabolic rate, and helps account for much of the variance in body weight between individuals having similar caloric intake [3,46].
8. A physical exercise prescription may help facilitate adherence to physical exercise program, and often includes frequency, intensity, time spent, type, and enjoyment (FITTE) [3,39].
9. For adults aged 18–64 years without health-related contraindications, common physical exercise recommendations include ≥150 min of moderate-intensity physical activity per week, or ≥75 min of vigorous-intensity physical activity per week [4]. Additional health benefits may be derived from increase moderate-intensity physical activity to 300 min per week, or equivalent. Muscle-strengthening activities are also recommended involving major muscle groups ≥2 days per week [35,39].
10. A common physical activity is walking. Less than 5000 steps per day is considered sedentary; ≥10,000 steps per day is considered active. While ≥10,000 steps per day may be optimal, advancing from minimal to some physical activity (incremental steps >2000 steps per day) may have CVD benefits [47]. Most cardiometabolic markers may especially be improved at > 7500 steps per day [48].

ILLUSTRATIVE GUIDELINE AND REFERENCE SECTION:
[4] A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines.
[37] Routine Assessment and Promotion of Physical Activity in Healthcare Settings: A Scientific Statement From the American Heart Association.
[39] Physical activity in the prevention of coronary heart disease: implications for the clinician.
[36] US Physical Activity Guidelines: Current state, impact and future directions.

Table 3
Ten things to know about lipids and cardiovascular disease (CVD) prevention.

1. Low density lipoprotein (LDL) cholesterol was the primary lipid treatment target for most CVD outcomes trials, and LDL cholesterol is the primary lipid treatment target according to most lipid guidelines [50,51]. However, compared to low density lipoprotein (LDL) cholesterol, apolipoprotein B, non-high density lipoprotein (non-HDL) cholesterol and LDL particle number may be better predictors of CVD risk for many patients with dyslipidemia, such as patients having hypertriglyceridemia, non-fasting blood samples, and those with very low LDL cholesterol levels [52–54].
2. Treatment terminology differs among cholesterol guidelines, often with lipid treatment "targets" being the lipid parameter being treated (e.g., LDL-cholesterol), lipid "goals" being the desired lipid parameter level, and "threshold" being the level by which if exceeded, may prompt the addition or intensification of lipid-pharmacotherapy (e.g., LDL cholesterol ≥ 70 for patients at very high CVD risk or ≥100 mg/dL for patients at high CVD risk) [50,51].
3. In most cases, elevated triglyceride (TG) levels are a risk factor for CVD, especially if the elevated TG levels represent an increase in atherogenic triglyceride-rich lipoproteins (e.g., very-low-density lipoproteins, intermediate density lipoproteins, remnant lipoproteins) [55].
4. Lipoprotein (a) is an LDL-like particle attached to apolipoprotein (a), which is thought to be atherogenic, possibly thrombogenic, and is a CVD risk factor. It is uncertain that lowering Lp(a) alone reduces CVD risk. Statins do not lower Lp(a); PCSK9 inhibitors lower Lp(a) [56,57].
5. Heterozygous Familial Hypercholesterolemia (HeFH) is the most common genetic disorder resulting in severe elevations in LDL-cholesterol (i.e., typically with LDL-cholesterol levels ≥ 190 mg/dL), with a reported prevalence of 1/200 to 1/500. Patients with FH are at high risk for premature CVD. Management of HeFH includes aggressive cholesterol lowering at an early age, usually involving statin therapy [58].
6. Statins are the most recommended drug treatment for hypercholesterolemia due to their cholesterol-lowering efficacy, safety, and CVD benefits supported by multiple cardiovascular outcomes trials [4]. In appropriate patients, "high intensity statins" (atorvastatin 40–80 mg or rosuvastatin 20–40 mg) may lower LDL cholesterol ≥ 50%, and are often recommended as first-line therapy in patients with CVD or at high risk for CVD [50,51]. Statin intolerance (e.g., statin-associated muscle symptoms or SAMS) may limit the dose or use of statins [59,60].
7. Ezetimibe modestly lowers LDL cholesterol levels ~18% and may modestly reduce CVD risk [61]. Bempedoic acid lowers LDL cholesterol ~ 20%, and when combined with ezetimibe in a fixed dose combination, lowers LDL cholesterol ~ 40%. A CVD outcome study with bempedoic acid is ongoing [62,63].
8. PCSK9 inhibitors are injectable agents that lower LDL cholesterol ≥50% and reduce CVD risk when added to high intensity or maximally tolerated statins [50,51].
9. Omega-3 fatty acids lower triglycerides and non-HDL cholesterol. Prescription icosapent ethyl is an eicosapentaenoic acid, ethyl ester agent that in a CVD outcomes trial, reduced the risk of CVD in patients at high CVD risk having triglyceride levels ≥150 mg/dL [64].
10. Fibrates are clinically used to lower triglyceride levels. However, no cardiovascular outcome study has yet reported that, as a primary endpoint, fibrates reduce CVD risk in patients specifically enrolled with high triglycerides. Post hoc analyses support that fibrates are most likely to reduce CVD in patients with baseline high triglycerides (and lower HDL cholesterol) [65].

ILLUSTRATIVE GUIDELINES AND/OR REFERENCES:
[4] A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines.
[50] AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Journal of the American College of Cardiology* 2018.
[51] 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk.

Epidemiology

Quantitatively, increases in positive caloric balance and body fat increase the risk of CVD [3]. One objective of healthful nutrition is to achieve a healthy body weight (see "Overweight and Obesity" section). Atherosclerotic CVD is rare among hunter-gatherers populations, whether the nutritional intake is higher in fat or lower in fat [7,8]. While sometimes higher, total energy expenditure among rural hunter-gathers may not always substantially differ from more industrialized populations [8,9]. Where hunter-gathers do substantially differ from more industrialized populations is body mass index (BMI). The BMI of hunter-gather populations is typically <20 kg/m² [10]. In stark contrast, data from 2015–2016 suggests the prevalence of obesity (BMI ≥ 30 kg/m²) was ~40% of US adults [11]. The lack of the adiposopathic consequences of increased body fat helps explain why hunter-gather populations not only have reduced CVD risk factors, but also minimum risk for CVD. Hunter-gatherers populations have lower blood pressure, and a total cholesterol level of ~100 mg/dL, compared to a total cholesterol level of ~200 mg/dL in adult Americans [12]. Conversely, US adults often have multiple CVD risk factors, accounting for CVD as the #1 cause of death [13].

Table 4

Ten things to know about diabetes mellitus and cardiovascular disease (CVD) prevention.

1. The glucose treatment goal for most patients with diabetes mellitus is to achieve a hemoglobin A1c < 7% and avoid wide swings in blood glucose. Hemoglobin A1c goals may be higher or lower for individual patients depending on clinical presentation. For example, less stringent A1C goals (e.g., <8%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, or long-standing diabetes in whom the goal is difficult to achieve despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin [72].
2. Diabetes mellitus is a major risk factor for CVD, which warrants more aggressive treatment of other common CVD risk factors (e.g., overweight or obesity, high blood pressure, dyslipidemia, cigarette smoking) [73].
3. Patients with diabetes mellitus have more aggressive thresholds for implementing lipid therapy. Patients with diabetes mellitus 40–75 years of age benefit from at least moderate-intensity statin therapy, regardless of estimated 10-year atherosclerosis CVD (ASCVD) risk. Patients with diabetes mellitus with CVD or multiple CVD risk factors might best benefit from high intensity statins [50].
4. While some uncertainty exists in the degree by which glucose control alone reduces CVD, clinical trial evidence supports intensive glycemic control may significantly reduce coronary events without an increased risk of death; however, the optimum mechanism, speed, and extent of HbA1c reduction may differ with different populations [74].
5. Metformin has favorable effects on CVD risk factors (glucose, insulin, lipids, body weight, and possibly blood pressure), and is often a first line agent when treating type 2 diabetes mellitus. While data supports metformin in reducing CVD risk, the robustness of CVD outcomes data is lacking relative to some other anti-diabetes agents. Thus, metformin is considered as providing a potential benefit in reducing CVD [75]. A confounder is that metformin (and comprehensive lifestyle management) was commonly used as background therapy for CVD outcomes trials of other anti-diabetes agents that have demonstrated reduction in CVD risk. Thus, metformin and weight management and physical activity often remain first-line therapies for patients with type 2 diabetes mellitus [75]. Additional pharmacotherapy may include anti-diabetes mellitus agents known to have CVD outcomes benefits, [e.g., some sodium glucose transporter 2 (SGLT2) inhibitors and some glucagon like peptide-1 (GLP-1) receptor agonists], whose use should be considered independently of baseline hemoglobin A1c or individualized hemoglobin A1c goal [75].
6. SGLT2 inhibitors reduce glucose levels and contribute to modest weight loss. Clinical trials support empagliflozin and canagliflozin as effective in treating atherosclerotic CVD, and empagliflozin, canagliflozin, and dapagliflozin as effective in treating heart failure. In patients with atherosclerotic CVD or heart failure treated with comprehensive lifestyle intervention and metformin, SGLT2 inhibitors having CVD benefits should be considered as next line therapy [4,75].
7. Some GLP-1 receptor agonists have clinical trial evidence supporting a reduction in atherosclerotic CVD (e.g., liraglutide, semaglutide, dulaglutide). In patients with atherosclerotic CVD treated with comprehensive lifestyle intervention and metformin, GLP-1 receptor agonists having CVD benefits should be considered as next line therapy [4,75].
8. Sulfonylureas have neutral effects on CVD; but sulfonylureas increase body weight and increase the risk of hypoglycemia. Severe hypoglycemia may promote cardiac dysrhythmias and increase the risk of sudden death. In patients with CVD, or at risk for CVD, sulfonylureas are among the last anti-diabetes mellitus agents to consider, except perhaps when cost is a major barrier to use of other anti-diabetes agents for glucose control [75].
9. Regarding other oral anti-diabetes mellitus agents, pioglitazone has some data to support reduction in atherosclerotic CVD; however, pioglitazone increases body weight and increases the risk of congestive cardiomyopathy. Dipeptidyl peptidase-4 inhibitors have a neutral effect on body weight and atherosclerotic CVD; saxagliptin may increase the risk of hospitalization for heart failure [75].
10. Regarding other injectables (beyond GLP-1 receptor agonists), insulin increases the risk of weight gain, increases the risk of hypoglycemia, but generally has a neutral effect on atherosclerotic CVD and heart failure [75].

ILLUSTRATIVE GUIDELINE AND REFERENCE SECTION:

[4] A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines.

[66] Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2020

[73] Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes-2020

[75] Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2020

Table 5

Ten things to know about hypertension and cardiovascular disease (CVD) prevention.

1. Out of office (ambulatory) blood pressure measurements can be useful to confirm the diagnosis of hypertension, especially in patients with white coat hypertension (elevated blood pressure only in the clinician setting/office) and masked hypertension (elevated blood pressure only out of the clinician setting/office) [77, 78].
2. The American College of Cardiology/American Heart Association defines hypertension as ≥ 130/80 mmHg, with a treatment goal of <130/80 mmHg [77].
3. The European Society of Cardiology/European Society of Hypertension defines hypertension as ≥ 140/90 mmHg. Depending on clinical response and tolerability, the BP treatment goal is < 140/90 mmHg for everyone, < 130/80 mmHg in most patients, and 120–130/70-79 mmHg in patients with diabetes mellitus, CVD and stroke/transient ischemic attack. In patients with CVD, diastolic blood pressure should not be lowered to <70 mmHg (to avoid impairment of myocardial perfusion). For many older patients 65–80 years of age, the systolic blood pressure goal is 130–139 mmHg [78].
4. Hypertension is a major risk factor for CVD, which warrants more aggressive treatment of concomitant CVD risk factors (e.g., overweight or obesity, diabetes mellitus, dyslipidemia, cigarette smoking) [73].
5. Non-pharmacologic treatment of high blood pressure includes low-sodium diet (<2300 mg of sodium per day), adequate potassium intake, routine physical activity/exercise, attaining a healthy body weight, and no more than low to moderate alcohol intake [4,80].
6. Single pill combination antihypertensive therapy is often recommended for initial therapy (i.e., angiotensin-converting enzyme inhibitor/angiotensin-receptor blocker in same pill combination with a thiazide diuretic) [80,81] Sacubitril/valsartan is a combination neprilysin inhibitor/angiotensin receptor blocker that is a combination agent approved for the treatment of heart failure with reduced ejection fraction; it may also lower blood pressure [82].
7. Regarding diuretics, chlorthalidone is a thiazide-like diuretic with a longer half-life and often considered the preferred thiazide diuretic. Chlorthalidone reduces blood pressure more than hydrochlorothiazide, especially over a 24-h period of time, and has more robust data than hydrochlorothiazide to support reduction in CVD. Thiazide diuretics are a first-line therapy for hypertension. Loop diuretics (e.g., furosemide torasemide, bumetanide, azosemide may be preferred in patients with heart failure (especially torasemide) and when estimated glomerular filtration rate is < 30 ml/min [77,83,84].
8. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) are first line antihypertensive agents. In addition to lowering blood pressure, ACE inhibitors and ARBs are beneficial in treating heart failure and coronary artery disease. ACE inhibitors and ARBs should not be used together and should not be used in combination with direct renin inhibitors (i.e., aliskiren), largely due to questionable added benefits, and potential for hyperkalemia [77].
9. Calcium channel blocker (CCBs) may help treat angina and cardiac dysrhythmias; however, dihydropyridine CCBs (e.g., amlodipine, nifedipine) may cause edema and non-dihydropyridine CCB (e.g., verapamil and diltiazem) may cause bradycardia and heart block and should be avoided in patients with heart failure with reduced ejection fraction. CCB's lower blood pressure and are first line antihypertensive agents [77].
10. Beta blockers treatment reduce CVD in patients with reduced ejection fraction, are used to treat angina pectoris and cardiac dysrhythmias, and may reduce the risk of recurrent myocardial infarction after an acute myocardial infarction. However, the blood pressure lowering may be less than other anti-hypertensive drug treatments [85,86].

ILLUSTRATIVE GUIDELINE AND REFERENCE SECTION:

[4] A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines.

[77] 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults

[78] 2018 ESC/ESH Guidelines for the management of arterial hypertension

Diagnosis and treatment

Table 1 lists ten things to know about nutrition and CVD prevention.

Physical inactivity

Definition and physiology

Physical activity is any bodily movement produced by skeletal muscles that requires energy expenditure [35,36]. Physical exercise is a subcategory of physical activity that is *"planned, structured, repetitive, and aims to improve or maintain one or more components of physical fitness."* [35]

Table 6
Ten things to know about increased body fat and cardiovascular disease prevention.

1. CVD (and cancer) are the most common cause of mortality among patients with obesity [90–92]. Obesity directly increases the risk of CVD (e.g., via adiposopathic effects of epicardial fat), and indirectly increases the risk of CVD via the adiposopathic promotion of major CVD risk factors such as diabetes mellitus, high blood pressure, dyslipidemia, and thrombosis, as well as other conditions associated with increased CVD risk (e.g., sleep apnea, polycystic ovary disease, gestational diabetes, fatty liver) [3].
2. Weight reduction in patients with obesity often improves major CVD risk factors such as abnormalities in glucose, lipids, blood pressure and thrombosis, may have favorable effects on cardiac hemodynamics, and may reduce premature all-cause mortality [93–95]. Both weight reduction, and weight loss maintenance often present challenges in patients with overweight or obesity. Given that obesity is a multifactorial disease, overweight and obesity are best managed utilizing a multifactorial approach including nutrition, physical activity, motivational interviewing, behavior modification, pharmacotherapy, and possibly bariatric surgery [3].
3. No drug and dose having an indication to treat obesity has proven to reduce CVD events. Patients with obesity should undergo multifactorial CVD risk reduction (e.g., healthful nutrition and physical activity, smoking cessation, as well as optimal control of blood sugar, blood pressure, and blood lipids) [3].
4. Glucagon-like peptide 1 receptor agonists (GLP-1 RA) have clinical outcome trial evidence to support CVD benefits in patients with diabetes mellitus (e.g., liraglutide, semaglutide), with some anti-obesity agents being evaluated in CVD outcomes trials in patients with obesity [3].
5. Metformin and sodium glucose transporter (SGLT)-2 inhibitors decrease CVD among patients with diabetes mellitus. While they do not have an indication as anti-obesity agents, metformin and SGLT2 inhibitors modestly reduce body weight in patients with and without diabetes mellitus. When accompanied by weight loss, many anti-obesity drugs reduce CVD risk factors (i.e., orlistat, liraglutide, naltrexone/bupropion, and phentermine/topiramate are not contraindicated in patients with cardiovascular disease) [3].
6. Little evidence supports phentermine & topiramate combination anti-obesity agent as increasing or decreasing CVD risk among patients with obesity [96].
7. Phentermine is contraindicated in patients with CVD [3]
8. Among patients with obesity, CVD and type 2 diabetes mellitus without congestive cardiomyopathy, initial drug treatments to consider include metformin and GLP-1 RA (e.g., liraglutide, semaglutide), and SGLT-2 inhibitors (e.g., empagliflozin, canagliflozin) [3].
9. Among patients with obesity, CVD, type 2 diabetes mellitus with mild congestive cardiomyopathy, initial drug treatments to consider in include metformin and SGLT-2 inhibitors [3].
10. Among patients with obesity, CVD, and without type 2 diabetes mellitus and without congestive cardiomyopathy, initial treatments to consider include liraglutide [3].

ILLUSTRATIVE GUIDELINE AND REFERENCE SECTION:
[3] Obesity Algorithm eBook, presented by the Obesity Medicine Association. 2020

Physical activity also includes muscle activity during leisure time, for transportation, and as part of a person's work – often termed NEAT (non-exercise activity thermogenesis) [35]. Physical inactivity increases the risk of CVD [37,38].

Epidemiology

According to the US Centers for Disease Control:

- Only 50% of adults get sufficient physical activity to reduce the risk of many chronic diseases such as CVD
- Adequate physical activity could prevent 1 in 15 cases of CVD

Diagnosis and treatment

Table 2 lists ten things to know about the diagnosis and treatment of physical inactivity and CVD prevention.

Dyslipidemia

Definition and physiology

Lipids are organic molecules, such as fats, steroids, phospholipids, steroids, triglycerides, and cholesterol that are important cellular

Table 7
Ten things to know about select populations (older age, race/ethnicity, gender) and cardiovascular disease prevention.

1. CVD prevention recommendations vary among different guidelines regarding individuals over 65 years of age. CVD treatment decisions for older individuals are best based upon the individual presentation utilizing a patient-centered approach.
2. General principles of CVD prevention in older individuals include: (a) Blood pressure goal of< 140/90 mmHg, and perhaps lower depending upon the patient's clinical presentation (e.g., CVD, other CVD risk factors), or perhaps higher among those with poor life expectancy and risk for orthostatic hypotension and other side effects of lower blood pressure; (b) Unless accompanied by unacceptable side effects, statin therapy should be continued in older individuals, recommended to older individuals who experience CVD events or who are at high CVD risk, and offered as primary prevention to patients 75 years of age as primary prevention as part of patient centered, shared decision-making; (c) The degree of glucose control in older individuals should be based upon the underlying health and risks to the patient, with a priority to avoid hypoglycemia and hyperglycemia (i.e., hemoglobin A1c 7.5% or less in patients with 3 or more chronic illnesses and intact cognition, 8.0% or less in patients who are frail, with multiple chronic illnesses and/or moderate cognitive or functional impairment, and 9.0% or less in patients with very complex comorbidities, undergoing long-term assisted care, end-stage chronic illness, and/or moderate to severe cognitive or functional limitations; (d) Older individuals should avoid cigarette smoking that not only increases the risk of cancer, lung disease, and frailty, but also increases the risk of CVD and thrombosis. In patients with CVD treated with aspirin for anti-thrombotic effects, the benefits of continuing aspirin in older patients with CVD often exceed the risk of bleeding. Regarding primary prevention, the risk of bleeding in frail individuals over 80 years of age may exceed the potential benefits of preventing the first CVD event; and (e) Appropriate, patient-centered nutritional intervention and physical activity/exercise may not only have CVD benefits, but other CVD risk factor and anti-frailty health benefits in older individuals [50,97].
3. Compared to Caucasians, many Asian individuals are at increased CVD risk. Compared with Caucasians at the same statin dose, Asian individuals may have increased statin bioavailability, similar LDL-C lowering at lower statin doses, and thus lower approved statin doses among Asians [115].
4. In addition to healthful nutrition and physical activity generally applicable to all races, African Americans may be especially "salt sensitive" with regard to high blood pressure; with general recommendations that sodium be limited to less than 2300 mg per day in adults, and specifically less than 1500 mg per day among African Americans [116]. Guidelines for pharmacologic CVD prevention in African Americans are generally similar to other racial/ethnic groups, except regarding heart failure and hypertension. In African Americans, diuretics and calcium channel blockers may be preferred over angiotensin converting enzyme inhibitors and beta-blockers [99].
5. Recommendations to reduce CVD risk in Hispanics is like other races, with a substantial barrier often being effective CVD prevention communication to non-English speaking Hispanics [101].
6. Women typically have same rate of CVD onset 10 years later than men. However, this favorable cardioprotective effect diminishes among women with polycystic ovary syndrome and women entering the menopause. Women over 60 years of age often have less well controlled blood pressure, and higher prevalence of hypertension compared to men [106]. Any cardioprotective effect is mostly lost among women with type 2 diabetes mellitus (T2DM). Women with T2DM increase their risk of CVD three-fold, have higher risk of heart failure, stroke, claudication, and CVD mortality compared to men with T2DM [106]. While supporting CVD outcome data is more limited than men, statins appear to be equally effective for secondary CVD prevention in women, although women may have a greater likelihood of developing statin-associated diabetes mellitus and myalgias [106].
7. Chest pain is the most common symptom of acute coronary syndrome among both men and women. However, compared to men, women are more likely to present without chest pain (e.g. weakness, fatigue, nausea, dyspnea, and pain to neck, jaw, and back) [106].
8. Polycystic ovary syndrome (PCOS) often occurs in premenopausal women with overweight or obesity and is clinically characterized by androgen excess (hirsutism), amenorrhea or oligomenorrhea, and infertility [3]. PCOS increases CVD risk, largely because of accompanying cardiometabolic abnormalities such as insulin resistance, glucose intolerance, diabetes mellitus, hypertension, dyslipidemia (increased triglycerides and decreased high density lipoprotein cholesterol), metabolic syndrome, increased C-reactive protein, increased coronary artery calcium scores, increased carotid intima-medial thickness, and endothelial dysfunction [117]. As with other patients having increased CVD risk, women with PCOS should be aggressively treated with healthful nutrition and physical activity. Statin therapy may be indicated in many women with PCOS; however, statins may worsen insulin sensitivity in women with PCOS [118]. Conversely, statin therapy may lower testosterone in women with PCOS, with variable reports regarding effects on menstrual regularity, spontaneous ovulation, hirsutism, or acne [119,120]. Statin therapy combined with metformin therapy in women with PCOS may not only lower cholesterol, triglyceride, and testosterone

(continued on next page)

Table 7 (*continued*)

levels, but may also improve insulin resistance with improvement in menstrual regularity, hirsutism, acne, and spontaneous ovulation [121]. While the degree of possible teratogenic effects are unclear, statins are contraindicated in women who are pregnant, or who may become pregnant [122].

9. Regarding menopause, while premenopausal women may have some "protection" against CVD compared to men, this protection gap narrows after menopause. This increased CVD risk is partially because women entering the menopause are mostly older than premenopausal women. While perhaps more so in men than women, advancing age is also usually associated with an increase in percent body fat [123]. In women undergoing menopause, the loss of estrogens may have systemic effects such as worsening circulating lipids and lipoproteins and reduced central nervous system satiety effects of estrogens [124]. Taken together with age-related increase in body fat, women undergoing the menopause are at increased risk for insulin resistance, hypertension, and dyslipidemia – increasing CVD risk [125]. In some cases, menopausal hormone therapy (MHT) may increase the risk of CVD among menopausal women. If menopausal hormone therapy is to be used in menopausal women, it should be at the lowest effective dose, administered early (within 5 years) of menopause, and should not be prescribed for the purpose of preventing CVD [106].

10. Obesity, physical inactivity, and cigarette smoking may increase the risk of CVD more so in women than in men, indicating the need for aggressive management of these CVD risk factors among both women and men [106].

ILLUSTRATIVE GUIDELINE AND REFERENCE SECTION:

[50] AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Journal of the American College of Cardiology* 2018.

[99] American Heart Association Council on E, Prevention, Council on Cardiovascular Disease in the Y, Council on C, Stroke N, Council on Clinical C, Council on Functional G, Translational B, Stroke C. Cardiovascular Health in African Americans: A Scientific Statement From the American Heart Association.

[101] American Heart Association Council on E, Prevention, American Heart Association Council on Clinical C, American Heart Association Council on C, Stroke N. Status of cardiovascular disease and stroke in Hispanics/Latinos in the United States: a science advisory from the American Heart Association

[102] US Department of Health and Human Services Office of Minority Health. Minority Population Profiles.

[106] Cardiovascular Disease in Women: Clinical Perspectives

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components of body tissues and organs. Because they are insoluble in water, lipids such as cholesterol and triglycerides are carried in blood by lipoproteins [e.g., low density lipoproteins (LDL), very low-density lipoproteins (VLDL), chylomicrons, and high-density lipoproteins (HDL)]. Except for cholesterol carried by HDL particles (and possibly chylomicrons), other lipoproteins that carry cholesterol are atherogenic. Increased atherogenic lipoproteins may become entrapped within the arterial subendothelia, may undergo oxidation and subsequent inflammatory responses, resulting in plaque formation, plaque rupture, which is clinically manifest by myocardial infarction and stroke. One molecule of apolipoprotein (apo) B is found on each atherogenic lipoprotein. The collection of all cholesterol carried by atherogenic lipoproteins (i.e., except HDL cholesterol) is termed non-HDL cholesterol (calculation of non-HDL cholesterol = total cholesterol – HDL cholesterol). Because apo B and non-HDL cholesterol (and LDL particle number) better reflects underlying atherosclerotic risk (compared to LDL cholesterol alone), measurement of these biomarkers may provide additional useful information regarding risk for CVD.

Epidemiology

According to the US Centers for Disease Control [49]:

- Data reported from 2015 to 2016 suggests that more than 12% of adults age 20 and older had total cholesterol higher than 240 mg/dL
- Only slightly more than half of U.S. adults (55%, or 43 million) who could benefit, are taking cholesterol-lowering pharmacotherapy
- The number of U.S. adults age 20 or older who have total cholesterol levels higher than 200 mg/dL is approximately 95 million, with nearly 29 million adult Americans having total cholesterol levels higher than 240 mg/dL

Table 8

Ten things to know about thrombosis and smoking and cardiovascular disease prevention.

1. Polymer-free and durable polymer drug-eluting stents may reduce the risk of stent thrombosis [132].

2. In primary prevention, the risk of aspirin (i.e., bleeding) may exceed the beneficial reduction in CVD events in most patients, even among patients with diabetes mellitus [4,133–135]. Possible exceptions might include select diabetes mellitus patients not at increased bleeding risk, who are: (1) 40–70 years of age at high CVD risk [136]; (2) < 70 years of age at intermediate to high CVD risk (>5% 10 year CVD risk) [137], (3) ≥ 50 years with diabetes plus one additional major CVD risk factor (family history of premature atherosclerotic CVD, hypertension, dyslipidemia, smoking, or chronic kidney disease/albuminuria) [73].

3. The standard of care for patients at thrombosis risk in secondary prevention (preventing recurrent ischemic events after acute coronary syndrome and to prevent stent thrombosis after percutaneous coronary intervention) includes dual antiplatelet therapy (DAPT). DAPT is typically defined as aspirin plus the use of a P2Y12 receptor inhibitor (clopidogrel, ticagrelor, or prasugrel) [138].

4. Aspirin is the first drug of choice in lifelong administration in secondary prevention after a myocardial infarction [139]. Aspirin coated preparations may reduce gastrointestinal bleeding. The coated aspirin dose of 100 mg per day may help reduce CVD, death (and cancer), with lower doses being better tolerated (less bleeding) and higher doses having greater CVD risk reduction [140]. Aspirin doses of 75–100 mg per day may offer the optimal benefit:risk ratio in chronic prevention of recurrent thrombosis in patients with acute coronary syndrome [139] (81 mg "baby aspirin").

5. Acutely, older data supported aspirin as beneficial in patients with unstable coronary artery disease, acute myocardial infarction, and unstable angina [141–143]. Subsequent data supported aspirin platelet inhibition being fastest with chewable aspirin, which is faster-acting than soluble aspirin, which is faster-acting than whole solid aspirin, which is faster-acting than enteric-coated aspirin [144]. After calling 9-1-1 for emergency phone help, patients undergoing an acute myocardial infarction are often advised to chew one 325 mg aspirin slowly, preferably within 30 min of the onset of symptoms [145]. Acute administration of aspirin in patients with acute stroke is not recommended due to the potential of worsening a hemorrhagic stroke [145].

6. Chronically, aspirin is recommended as initial treatment to prevent recurrent ischemic (not hemorrhagic) stroke [146].

7. In patients with acute coronary syndrome, DAPT or aspirin may continue to reduce CVD risk beyond one year, with the continued recommendation of DAPT or aspirin mostly dependent upon safety (i.e., risk of bleeding) [147].

8. Tobacco cigarette smoking increases CVD risk via promoting thrombosis, inflammation, free radical formation, carbon monoxide-mediated increase in carboxyhemoglobin formation, increase in sympathetic activity (with increased myocardial oxygen demand and potential promotion of dysrhythmias), reduced nitric oxide with endothelial dysfunction, and oxidation of low density lipoprotein cholesterol [148].

9. To reduce the risk of thrombosis, CVD, cancer, and other ill effects of tobacco cigarette smoking [4], patients, families, and caregivers may benefit from an online resource regarding prevention and cessation of cigarette smoking and control of tobacco use [149].

10. The aerosol from vaping e-cigarettes typically does not contain all the contaminants in tobacco smoke. Short-term use of vaping e-cigarettes in health individuals may not adversely affect vascular function [127,150]. However, most e-cigarettes deliver nicotine, which is highly addictive and has many effects that may increase the long-term risk of CVD. While potentially safer from a CVD standpoint compared to tobacco smoking, the Centers for Disease Control (CDC) and Food and Drug Administration recommend that tetrahydrocannabinol (THC)-containing and/or nicotine-containing vaping e-cigarettes never be used by youths and young adults, or women who are pregnant, and not started by adults who do not currently use tobacco products [131]. Those choosing to use e-cigarettes as an alternative to cigarettes should completely switch from cigarettes to e-cigarettes, and not use both products [131]. Adults using nicotine-containing e-cigarette, or vaping, products as an alternative to cigarettes should not go back to tobacco-based cigarette smoking [131]. While much is unknown [151], vaping e-cigarettes may be a reasonable stepwise treatment for tobacco cigarette smokers who have failed smoking cessation, and plan to utilize vaping e-cigarettes as a path towards discontinuing all smoking products [127].

ILLUSTRATIVE GUIDELINE AND REFERENCE SECTION:

[4] A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines.

[73] Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes-2020

[149] Cigarette Smoking: Health Risks and How to Quit [Physician Data Query (PDQ): Patient Version

[131] Centers for Disease Control. Smoking & Tobacco Use. Electronic cigarettes

Table 9

Ten things to know about kidney disease and cardiovascular disease prevention.

1. An estimated glomerular filtration rate (eGFR) glomerular filtration rate < 60 mg/min/1.73 m^2 increases the risk of death, CVD events, and hospitalizations [152] Among patients with coronary heart disease, an eGFR < 30 mg/min/1.73 m^2 substantially increases the risk of CVD mortality and all-cause mortality [157].

2. Treatment of chronic kidney disease (CKD) often includes management of major CVD risk factors (e.g., diabetes mellitus, hypertension, cigarette smoking) [152, 158].

3. Among the anti-diabetes mellitus drugs having the most favorable renal effects include glucagon-like peptide-1 receptor agonists and sodium glucose cotransporter type 2 inhibitors [159]. With the possible exception of glucagon-like receptor agonists and thiazolidinediones, virtually all antidiabetes medication classes have representative drugs that require dosing adjustment, depending upon eGFR [160]. Many antidiabetes medications are not recommended and/or have lack of data in patients with severe renal insufficiency.

4. Preferred antihypertensive agents in patients with CKD (but not dialysis) include: (a) angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers ARBs); (b) diuretics; (c) dihydropyridine calcium channel blockers; and (d) mineralocorticoid receptor blockers. Preferred antihypertensive agents in patients undergoing dialysis include (a) beta adrenergic blockers (e.g., atenolol); (b) dihydropyridine calcium channel blockers; (c) angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers; (d) direct vasodilators [161]. The benefit:risk ratio of ACE inhibitors and ARBs is unclear in patients with eGFR < 30 mg/min/1.73 m^2. This helps for account for why, as a class, ACE inhibitors and ARBs are more commonly discontinued with eGFR <30 mg/min/1.73 m^2, compared to patients with higher eGFR [162]. In non-dialysis patients with eGFR < 30 mg/min/1.73 m^2, loop diuretics are preferred over thiazide diuretics. Torsemide generally has more predictable bioavailability compared to furosemide [163]. Dialysis patients with some urine output may benefit from continued loop diuretics [164]. In renal insufficiency, dihydropyridine calcium channel blockers (amlodipine, felodipine, nicardipine, nifedipine) may be preferred over non dihydropyridine channel blockers (i.e., verapamil, diltiazem) due to potentially less drug interactions with common medications (e.g., statins) and less potential for atrioventricular conduction delays and heart block when used together with betablockers [161]. Beta blockers in patients with end stage renal disease may reduce the risk of heart failure, hypertension, and cardiac dysrhythmias [165]. Direct vasodilators (hydralazine and minoxidil) are usually one of the last line therapies for hypertension and renal failure [161]. Virtually all anti-hypertensive medications classes have representative drugs that require dosing adjustment, depending upon eGFR [166].

5. Statin therapy may reduce CVD risk among patients with mild to moderate renal insufficiency (not dialysis) [167]. Statin therapy may not reduce kidney failure, but may modestly reduce proteinuria and rate of eGFR decline [168]. With exception of atorvastatin, other statins (as well as many other lipid-altering drugs) require dosing adjustment in patients with CKD [169]. While no dosing adjustment is needed for patients with mild or moderately impaired renal function, little to no data exists regarding the use of proprotein subtilisin/kexin 9 inhibitors in patients with severe CKD [170].

6. In addition to increasing the risk of CVD and other adverse health outcomes, cigarette smoking may be an independent risk factor for CKD [171]. Antiplatelet therapy in patients with CKD may reduce the risk of myocardial infarction, but increase the risk of bleeding. The risk of bleeding in patients with CKD is compounded with the use of dual antiplatelet therapy [172].

7. In addition to potentially contributing to ischemia, anemia can also contribute to cardiac hypertrophy potentially leading to heart failure and sudden cardiac death. Patients with end stage kidney disease may require higher amounts of erythropoiesis-stimulating therapies, especially before dialysis initiation, given that CVD events are highest during the first week after dialysis initiation [173].

8. Many recommended nutritional interventions in patients with CKD at risk for CVD are similar to patients with CVD alone (e.g., limited sodium intake, limited ultra-processed carbohydrates, limited simple sugars, limited saturated fats with preference for omega-3 and omega-9 polyunsaturated fatty acids). Additional considerations include limiting total proteins (with relative higher amounts of protein consumption acceptable in patients undergoing dialysis) and high fiber fruits and vegetables that are lower in potassium [174,175].

9. As with CVD, routine physical activity reduces the risk of morbidity and mortality in patients with CKD [176]. Additionally, patients with CKD with deteriorating renal function may likewise have a deterioration in their physical activity, cardiorespiratory fitness, and muscle mass, with full recovery not achieved even with renal transplant [177]. The combination of physical inactivity, uremia, and possible decrease in protein intake contributes to loss of muscle mass. Regular physical activity has cardiometabolic benefits, as well as neuromuscular, cognitive, and renoprotective benefits [177].

10. Due to the marked increased CVD risk and other complications of CKD, referral to a nephrology specialist should be considered for patients with eGFR <30 mg/min/1.73 m^2, albuminuria ≥300 mg per 24 h, or rapid decline in eGFR [178].

Table 9 (*continued*)

ILLUSTRATIVE GUIDELINE AND REFERENCE SECTION:

[152] Unraveling Cardiovascular Risk in Renal Patients
[160] Therapeutic Considerations for Antihyperglycemic Agents in Diabetic Kidney Disease
[161] Clinical Pharmacology of Antihypertensive Therapy for the Treatment of Hypertension in CKD
[178] Chronic Kidney Disease Diagnosis and Management: A Review.

Table 10a

Simon Broome diagnostic criteria for Familial Hypercholesterolemia [181,182].

Definite Familial Hypercholesterolemia:
- Adult with total cholesterol levels ≥ 290 mg/dL (> 7.5 mmol/L) or LDL-C ≥ 190 mg/dL (> 4.9 mmol/L)
- Child < 16 years of age with total cholesterol levels ≥ 260 mg/dL (> 6.7 mmol/L) or LDL-C ≥ 155 mg/dL (> 4.0 mmol/L)

PLUS EITHER
- Tendon xanthomas, or tendon xanthomas in a first degree relative (parent, sibling or child) or second degree relative (grandparent, aunt, or uncle)

OR
- Deoxynucleic acid (DNA)-based evidence of an LDL receptor mutation, familial defective apo B-100, or a PCSK9 mutation

Possible Familial Hypercholesterolemia:
- Adult with total cholesterol levels ≥ 290 mg/dL (> 7.5 mmol/L) or LDL-C ≥ 190 mg/dL (> 4.9 mmol/L)
- Child < 16 years of age with total cholesterol levels ≥ 260 mg/dL (> 6.7 mmol/L) or LDL-C ≥ 155 mg/dL (> 4.0 mmol/L)

PLUS FAMILY HISTORY OF AT LEAST ONE OF THE FOLLOWING:
- Family history of myocardial infarction in first degree relative < age 60 years or second-degree relative < age 50 years
- Family history of an adult first- or second-degree relative with elevated total cholesterol ≥ than 290 mg/dL (> 7.5 mmol/L) or child, brother or sister aged < 16 years with total cholesterol ≥ than 260 mg/dL (> 6.7 mmol/L)

Table 10b

Dutch Lipid Clinic Network diagnostic criteria for Familial Hypercholesterolemia [181–183].

Criteria	Points
Family history	
First-degree relative with known premature* coronary and vascular disease, OR	1
First-degree relative with known LDL-C level above the 95th percentile	
First-degree relative with tendinous xanthomata and/or arcus cornealis, OR	2
Children aged less than 18 years with LDL-C level above the 95th percentile	
Clinical history	
Patient with premature* coronary artery disease	2
Patient with premature* cerebral or peripheral vascular disease	1
Physical examination	
Tendinous xanthomata	6
Arcus cornealis prior to age 45 years	4
Untreated cholesterol levels mg/dL (mmol/liter)	
LDL-C ≥ 330 mg/dL (≥8.5)	8
LDL-C 250–329 mg/dL (6.5–8.4)	5
LDL-C 190–249 mg/dL (5.0–6.4)	3
LDL-C 155–189 mg/dL (4.0–4.9)	1
DNA analysis	
Functional mutation in the *LDLR, apo B or PCSK9* gene	8
Diagnosis (diagnosis is based on the total number of points obtained)	
Definite Familial Hypercholesterolemia	>8
Probable Familial Hypercholesterolemia	6–8
Possible Familial Hypercholesterolemia	3–5
Unlikely Familial Hypercholesterolemia	<3

LDL-C = low - density lipoprotein cholesterol.

DNA = Deoxynucleic acid.

LDL-R = low - density lipoprotein receptor.

Apo B = apolipoprotein B.

PCSK9 = Proprotein convertase subtilisin/kexin type 9.

* Premature coronary and vascular disease = < 55 years in men; < 60 years in women.

Table 10c

Make Early Diagnosis to Prevent Early Dealths (MEDPED) diagnostic criteria for Heterozygous Familial Hypercholesterolemia [181,182].

Familial Hypercholesterolemia (FH) is diagnosed if total cholesterol exceeds these cutpoints in mg/dL (mmol/L)*			
Age (years)	First degree relative with FH	Second degree relative with FH	Third degree relative with FH	General population
<20	220 (5.7)	230 (5.9)	240 (6.2)	270 (7.0)
20–29	240 (6.2)	250 (6.5)	260 (6.7)	290 (7.5)
30–39	270 (7.0)	280 (7.2)	290 (7.5)	340 (8.8)
≥ 40	290 (7.5)	300 (7.8)	310 (8.0)	360 (9.3)

* The total cholesterol cutpoints for FH is dependent upon the confirmed cases of FH in the family. If FH is not diagnosed in the family, then the cutpoint for diagnosis is as per general population.

Diagnosis and treatment

Table 3 lists ten things to know about the diagnosis and treatment of dyslipidemia and CVD prevention.

Hyperglycemia

Definition and physiology

Diabetes mellitus is a pathologic condition characterized by high blood glucose. Diabetes mellitus can be diagnosed [66] with one of the following:

- Hemoglobin A1c level ≥ 6.5%
- Fasting plasma glucose ≥ 126 mg/dL on two successive measurements
- Random glucose level of ≥200 mg/dL
- Oral glucose tolerance test with 2-h glucose value ≥ 200 mg/dL

Hyperglycemia may contribute to atherosclerosis via direct and indirect mechanisms. Direct adverse effects of elevated circulating glucose levels include endothelial dysfunction, oxidative stress, LDL oxidation, and endothelial nitric oxide synthase (eNOS) dysfunction. Indirect adverse effects of elevated glucose levels include platelet hyperactivity and associated insulin resistance, which may increase non-esterified circulating free fatty acids and worsen dyslipidemia, (e.g., increased very low-density lipoprotein hepatic secretion, reduced HDL cholesterol levels, and increased small, more dense LDL particles) [67].

Many risk factors for CVD are also risk factors for gestational diabetes (e.g., increased body fat, physical inactivity, increased age, nonwhite race, hypertension, reduced high-density lipoprotein cholesterol triglycerides > 250 mg/dL). A history of gestational diabetes mellitus doubles the risk for CVD [68], and might be considered a CVD risk factor. Diagnosis of gestational diabetes mellitus (GDM) includes a 75-g oral glucose tolerance test (OGTT) performed at 24–28 weeks of gestation. GDM is diagnosed when fasting glucose levels are ≥92 mg/dL, or 2-h glucose levels ≥153 mg/dL. The diagnosis of GDM is also made when during an OGTT, the 1 h glucose levels is ≥ 180 mg/dL [69].

Epidemiology

Type 2 diabetes mellitus is associated with double the risk for death and a 10-fold increase in hospitalizations for coronary heart disease [70]. According to the US Centers for Disease Control [71]:

- About 30.3 million US adults have diabetes; 1 in 4 may be unaware
- Diabetes mellitus is the 7th leading cause of death in the United States
- Diabetes is the most common cause of kidney failure, lower-limb amputations, and adult blindness
- In the last 20 years, the number of adults diagnosed with diabetes mellitus has more than doubled

Diagnosis and treatment

Table 4 lists ten things to know about the diagnosis and treatment of diabetes mellitus and CVD prevention.

High blood pressure

Definition and physiology

Hypertension is defined as blood pressure readings that exceed acceptable ranges for patient health, as established by medical organizations. High blood pressure is a major risk factor for CVD. African Americans have a higher prevalence of hypertension than Caucasians, helping to account for a higher rate of stroke, end-stage renal disease and congestive heart failure [76].

A major challenge with diagnosis of high blood pressure is ensuring accurate measurement [77,78]:

- Patients should avoid caffeine, physical exercise, stress, and/or smoking for 30 min prior to blood pressure measurement.
- Patients should have empty bladder, have clothing removed from the arm, be seated with feet flat on the floor, relaxed and quiet for 5 min prior to blood pressure measurement.
- Blood pressure should be obtained by properly validated and calibrated blood pressure measurement device, with proper cuff size, and taken by trained medical personnel.
- On first measurement date, blood pressure should be measured in both arms by repeated values separated by at least 1 min, with a record of the values and respective arms (left and right).
- Longitudinally, future blood pressure measurement should be on the same arm previously recorded as having the highest blood pressure measurement.

Epidemiology

According to the US Centers for Disease Control [79]:

- Nearly half of adults in the United States (108 million, or 45%) have hypertension defined as a systolic blood pressure ≥ 130 mm Hg or a diastolic blood pressure ≥ 80 mm Hg or are taking medication for hypertension.
- Only about 1 in 4 adults (24%) with hypertension have their condition under control.
- Half of adults (30 million) with blood pressure ≥140/90 mm Hg who should be taking medication to control their blood pressure are not prescribed or are not taking medication.

Diagnosis and treatment

Table 5 lists ten things to know about the diagnosis and treatment of high blood pressure and CVD prevention.

Table 10d

Ten things to know about genetics/familial hypercholesterolemia and cardiovascular disease prevention.

1. Among the more common inherited causes of CVD among younger individuals include genetic abnormalities leading to vasculopathies, aneurysmal disorders, and coagulopathies [190]. Within the clinical practice of preventive cardiology, genetic dyslipidemia is the most common treatable cause of inherited premature coronary heart disease [190].
2. Heterozygous Familial Hypercholesterolemia (HeFH) is most commonly an autosomal dominant genetic metabolic disorder resulting in extreme elevations of low-density lipoprotein (LDL) cholesterol levels (i.e., typically $\geq$ 190 mg/dL in adults), and a 10–17 fold increased risk of atherosclerotic CVD in untreated patients with HeFH, and 8–15 fold increase in patients treated with statins. The residual CVD risk among statin-treated patients suggests under-treatment with statins and other lipid-altering drugs, and/or delay of introduction of lipid-altering too late in life [183].
3. In a patient with a FH phenotype, a negative DNA genetic testing does not exclude a diagnosis of FH [179]. Many lipid center clinicians believe 10–50% of DNA FH testing negative patients still having an unidentified FH mutation. This helps account for why many clinicians utilize clinical diagnosis over DNA genetic blood testing to diagnose FH [191].
4. While tendon xanthomas can rarely be associated with increases in non-cholesterol sterol concentration (i.e., sitosterolemia) [192], tendon xanthomas are the physical exam finding most pathognomonic for FH, and the physical exam finding most included in FH diagnostic criteria (see Table 10 a – b). Aortic stenosis is also often found in patients with FH, potentially detected by heart murmur upon auscultation of the heart, and whose onset and severity are dependent lifetime exposure to increased cholesterol levels [193].
5. Cascade (family) screening for FH is recommended in individuals and families with very high LDL-C levels [194].
6. High intensity statin (atorvastatin 80 mg or 40 mg per day, or rosuvastatin 40 or 20 mg per day) is the drug treatment of first choice for patients with FH [50].
7. Commonly cited lipid goals in patients with HeFH are a low-density lipoprotein cholesterol level of <100 mg/dL and <70 mg/dL being a goal for HeFH patients having CVD and/or other CVD risk factors placing them at very high risk [50]. Lipoprotein (a) is an additional lipid parameter that should be assessed in patients with HeFH [57].
8. Largely due to very high baseline LDL cholesterol levels, and high rate of atherosclerotic CVD, it is common that patients with FH do not achieve their LDL-cholesterol treatment goals with statins alone. Patients with FH who do not achieve their LDL cholesterol treatment goals with maximally tolerated high intensity statins may benefit from adding proprotein convertase subtilisin kexin 9 inhibitors, bempedoic acid, ezetimibe (alone or combined with bempedoic acid), or other lipid-altering drugs (e.g., bile acid sequestrants such as colesevelam HCl) [50,58,62,63,188,195,196].
9. The increase in atherosclerotic CVD risk is not only dependent upon the degree of increased LDL cholesterol blood levels, but also the lifetime exposure/burden of elevated LDL cholesterol. The threshold age for onset of clinical coronary heart disease can be extended by earlier administration of statin therapy. Thus, statin treatment should strongly be considered in patients with HeFH, beginning at 8–10 years of age [183].
10. Lipoprotein apheresis is another treatment option for patients with FH who are unable to achieve LDL cholesterol treatment goals with nutrition, physical activity, and lipid-altering drug therapy [197].

ILLUSTRATIVE GUIDELINE AND REFERENCE SECTION:

[198] Current management of children and young people with heterozygous familial hypercholesterolaemia - HEART UK statement of care.

[50] AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines.

[58] Familial hypercholesterolemia treatments: Guidelines and new therapies.

[199] NICE's [National Institute for Health and Care Excellence (UK) Updates Team] Familial hypercholesterolaemia: identification and management: Evidence reviews for case-finding, diagnosis and statin monotherapy

[194] Cascade Screening for Familial Hypercholesterolemia and the Use of Genetic Testing

Overweight and obesity

Definition and physiology

Overweight is defined as body mass index (BMI) $\geq$ 25 and < 30 kg/m^2. Obesity is defined as $\geq$ 30 kg/m^2. An increase in BMI is generally associated with increase CVD risk, substantially mediated by obesity-promoted CVD risk factors [87]. In patients with increased muscle mass ("body builders"), an increase in BMI might erroneously suggest an increase in body fat. In patients with decreased muscle mass (sarcopenia), BMI might underestimate body fat [3].

Percent body fat more accurately assesses body fat than BMI. However, while percent body fat analysis may provide diagnostic clarity, measures of percent body fat differ in their accuracy and reproducibility, with dual x-ray absorptiometry (DXA) considered a "gold standard" for body composition analysis. Currently, the cut-off points for percent body fat are largely based on subjective opinion. Conversely, much data supports waist circumference and assessment of android/visceral fat as correlating to CVD risk. That is likely because an increase in waist circumference reflects adiposopathic dysfunction, which both directly and indirectly increases the risk of CVD [3].

The metabolic syndrome [88] is an LDL cholesterol-independent clustering of CVD risk factors that include 3 or more of the following:

- Elevated waist circumference (men $\geq$ 40 inches (102 cm); women $\geq$ 35 inches (88 cm),
- Elevated triglycerides $\geq$ 150 mg/dL (1.7 mmol/L),
- Reduced high density lipoprotein cholesterol (men < 40 mg/dL (1.03 mmol/L); women < 50 mg/dL (1.29 mmol/L),
- Elevated blood pressure ($\geq$ 130/85 mm Hg or use of medication for hypertension)
- Elevated fasting glucose $\geq$ 100 mg/dL (5.6 mmol/L) or use of medication for hyperglycemia.

An increase in waist circumference is the only anatomic abnormality listed in defining metabolic syndrome and reflects the importance of adiposopathic endocrine and immune abnormalities leading to CVD risk factors and CVD itself [3,89].

Epidemiology

According to the US Centers for Disease Control [11]:

- In 2015–2016, the prevalence of obesity (BMI $\geq$ 30 kg/m^2) was ~40% of US adults [11].
- Complications of obesity include heart disease and stroke
- Other CVD-related complications of obesity include adiposopathic alterations in [3]:
  - CVD risk factors (e.g., diabetes mellitus, hypertension, dyslipidemia)
  - Heart function and cardiovascular hemodynamics
  - Heart, heart cells, and structure (which can result in electrocardiogram tracing abnormalities)
  - Atherosclerosis and myocardial infarction
  - Immunopathies that promote CVD risk factors and CVD
  - Endocrinopathies that promote CVD risk factors and CVD
  - Thrombosis

Diagnosis and treatment

Table 6 lists ten things to know about the diagnosis and treatment of increased body fat and CVD prevention.

Considerations of selected populations (older age, race/ethnicity, gender)

Definition and physiology

Older individuals

Older individuals have a wide variance in the future risk for CVD and life expectancy. This variance in CVD risk and mortality is largely dependent on underlying diseases and degree of frailty [97]. Given the variance in clinical presentation, the relative absence of evidenced-based treatment data among older individuals, complexity of concurrent

illnesses, considerations of the quality of life and cost issues related to polypharmacy, treatment recommendations to older individuals are best determined by shared decision-making utilizing a patient-centered approach [50,97].

Race. **Asians** (particularly South Asians) may sometimes be at increased CVD risk, largely due to increased prevalence of metabolic syndrome, insulin resistance, elevated lipoprotein (a), adiposopathic dyslipidemia (sometimes called "atherogenic dyslipidemia"), which can be defined as elevated triglyceride levels, reduced high density lipoprotein cholesterol levels, increased low density lipoprotein (LDL) particle number, and an increased prevalence of smaller, more dense LDL particles, all which may increase CVD risk [8]. Asians may also have increased risk of thrombosis as evidenced by increased plasminogen activator inhibitor, fibrinogen, lipoprotein (a), and homocysteine. Finally, Asians may have other factors that increase CVD risk such as impaired cerebrovascular autoregulation and sympathovagal activity, increased arterial stiffness, and endothelial dysfunction [98].

 African Americans have among the highest CVD rates of any US ethnic or racial group. African Americans often have more favorable isolated lipid parameters compared with Caucasian Americans (e.g., higher HDL-C levels and lower triglyceride levels), and lower coronary artery calcium (CAC) than whites. Conversely, African Americans have a higher prevalence of hypertension, left ventricular hypertrophy, obesity, type 2 diabetes mellitus and elevated lipoprotein (a) levels [99].

 Hispanic individuals often have elevated triglyceride and reduced HDL cholesterol levels, and increased risk for insulin resistance. A "Hispanic Mortality Paradox'' describes how Hispanics are sometimes.

 reported to have a lower overall risk of mortality than non-Hispanic Whites and non-Hispanic Blacks (albeit higher risk of mortality than Asian Americans) [100]. Nonetheless, CVD is the leading cause of death among Hispanics. Thus, to reduce CVD risk, Hispanic individuals should undergo diagnosis and treatment of CVD risk factors similar to other ethnicities/races [101].

 Native Americans can be defined as members of indigenous peoples of North, Central, and South America, with American Indians and Alaskan Natives often residing in North America.

 Many American Indians/Alaska Natives have a higher risk for CVD, which may be related to increased CVD risk factors such as obesity, diabetes mellitus, high blood pressure and cigarette smoking [102]. Pima (Akimel O'odham or "river people") Indians are a subset of American Indians located in southern Arizona and northern Mexico. Pima Indians have a high rate of CVD risk factors (e.g., high prevalence of obesity, insulin resistance, type 2 diabetes mellitus, higher triglyceride levels, reduced high-density lipoprotein cholesterol levels, and higher rate of metabolic syndrome) [103]. Based upon the increased prevalence of CVD risk factor, older literature suggests CVD risk among Pima Indians may not be as high as anticipated [104]. This is possibly, in part, because in some cases, untreated low-density lipoprotein cholesterol levels may be lower among Pima men older than 30 and in women older than 25 years of age [103]. Despite a potential lower CVD risk compared to Caucasians, heart disease remains a major cause of mortality among Pima Indians, especially among those with concomitant renal failure [105].

 Women with CVD risk factors have increased CVD risk, directionally similar to men. CVD is the leading cause of mortality among women [106]. CVD causes ~ 4 times as many deaths in women compared to breast cancer [107]. Compared to men, women are at higher risk for bleeding after invasive procedures, and are more predisposed to autoimmune/inflammatory disease, pre-eclampsia, and fibromuscular dysplasia, potentially predisposing to myocardial infarction in the absence of atherosclerotic obstructive coronary arteries - especially among younger women [108]. According to the 2018 American Heart Association, American College of Cardiology Guideline on the Management of Blood Cholesterol, premature menopause and preeclampsia are CVD risk enhancers, with gestational diabetes and preterm delivery also

recognized as increasing lifetime CVD risk [50].

Epidemiology

- Due to insufficient data (many CVD outcomes trials excluded older patients), the treatment recommendations to reduce CVD risk often have less scientific support than treatment recommendations for younger adults. Also, due to the population makeup of the supporting databases, CVD risk scores risk scores are only validated for individuals at or below 65, 75, or 80 years of age, depending upon the CVD risk assessment calculator. For example, the American College of Cardiology/American Heart Association (ACC/AHA) Heart Risk Calculator includes an age range of 40–79 years [109].
- Many CVD risk calculators do not take into full account the influence of race on CVD risk. The ACC/AHA CVD Risk Calculator is limited to the races of "Other" and African Americans [109]. Conversely, the Multi-Ethnic Study of Atherosclerosis (MESA) 10-year atherosclerotic CVD risk tool includes Caucasians, Chinese, African Americans, and Hispanics 45–85 years of age as data input, along with coronary artery calcification [110].
- Cardiovascular heart disease are a leading cause of death for people of most racial and ethnic groups in the United States, accounting for ~20% of deaths per year [13].
- African Americans ages 35–64 years are 50% more likely to have high blood pressure than whites. African Americans ages 18–49 are 2 times as likely to die from heart disease than whites [111].
- Compared to whites, Hispanics have 35% less heart disease, but a 50% higher death rate from diabetes, 24% more poorly controlled high blood pressure, and 23% more obesity.
- Compared with US-born Hispanics, foreign-born Hispanics have about half as much heart disease; 29% less high blood pressure; and 45% more high total cholesterol [112].
- Compared to white adults, American Indians/Alaska Native adults have greater CVD risk factors such as obesity, high blood pressure, and cigarette smoking, and in 2018, American Indians/Alaska Natives had a 50% greater risk for coronary heart disease [102].
- Heart disease is the leading cause of death for African American and white women in the United States. Among American Indian and Alaska Native women, heart disease and cancer cause roughly the same number of deaths each year [113].
- Age is an important risk factor for stroke. Greater longevity in women helps account for strokes occurring more often in women than men. One in 5 women in the United States will have a stroke in her lifetime. Stroke kills twice as many women as breast cancer [114].

Diagnosis and treatment

Table 7 lists ten things to know about the diagnosis and treatment of patients of older age, different races/ethnicities, and women.

Thrombosis and smoking

Definition and physiology

Risk factors for thrombosis include older age, atrial fibrillation, cigarette smoking, prosthetic heart valves, blood clotting disorders, trauma/fractures, prolonged bed rest/immobility, certain drug treatments (estrogens), pregnancy, and cancer. CVD risk factors that increase the risk of thrombosis include diabetes mellitus, hypertension, hyperlipidemia, poor nutrition, physical inactivity, and obesity. Finally, a prior CVD event increases the risk of a future CVD event, often involving a thrombosis component. Thus, patients with acute coronary syndrome benefit from well-managed anti-thrombotic therapy as secondary prevention to reduce the risk of future CVD events.

Tobacco cigarette smoking is a well-known, major contributor to cardiovascular morbidity and mortality [126]. Vaping devices (electronic

cigarettes) are battery-operated nicotine (as well as flavoring and other chemicals) delivery devices that generates an aerosol that is inhaled. Vitamin E acetate, an additive in some tetrahydrocannabinol (THC) -containing e-cigarette, or vaping, products, is strongly linked to "E-cigarette or Vaping product use-associated Lung Injury" (EVALI). Nicotine alone has the potential to adversely affect the cardiovascular system, via acute increase in the sympathetic nervous system, increase in blood pressure, decrease in coronary blood flow, increase in myocardial remodeling/fibrosis, promotion of dysrhythmias, promotion of thrombosis, with longer-term adverse effects on endothelial function, inflammation, lipid levels (reduced high density lipoprotein and increased low density lipoprotein cholesterol levels), blood pressure, and insulin resistance [127].

Thromboembolic conditions are a leading cause of mortality and represent both arterial and venous thrombotic conditions. Ischemic heart disease and ischemic stroke comprise major arterial thromboses; deep-vein thrombosis and pulmonary embolism comprise venous thromboembolism [128].

Epidemiology

According to the US Centers for Disease Control [129–131]:

- In the US, stroke is responsible for 1 out of 20 deaths.
- Nearly 1 of 4 strokes are in people who have had a previous stroke
- About 90% of all strokes are ischemic strokes
- Stroke is a leading cause of serious long-term disability, reducing mobility in more than half of stroke survivors age 65 and over.
- Risk of having a first stroke is nearly twice as high for blacks as for whites, and blacks have the highest rate of death due to stroke.
- High blood pressure, high cholesterol, smoking, obesity, and diabetes mellitus are leading causes of stroke.
- Smoking is the leading cause of preventable death.
- In 2018, 13.7% of all adults (34.2 million people) currently smoked cigarettes: 15.6% of men, 12.0% of women.

Diagnosis and treatment

Table 8 lists ten things to know about the diagnosis and treatment of thrombosis and smoking and CVD prevention.

Kidney dysfunction

Definition and physiology

Chronic kidney disease can be defined as a glomerular filtration rate < 60 mg/min/1.73 m^2 and/or increase in urine protein excretion (i.e., albuminuria with albumin creatinine ratio ≥ 30 mg/g (≥ 3 mg/mmol)]. In addition to the accompanying major CVD risk factors that promote and/or worsen kidney function (e.g., high blood pressure, diabetes mellitus, cigarette smoking), chronic kidney disease itself is an independent major CVD risk factor, likely due to endothelial dysfunction, accelerated atherosclerosis [152], increased inflammation, vascular calcification and other vasculopathies [153]. Other non-traditional CVD risk factors often found in patients with CKD include left ventricular cardiac hypertrophy, low hemoglobin and serum albumin, and elevated phosphate and urate [154]. Chronic kidney disease is a "risk enhancing factor" that places patients at high risk for CVD [50].

Epidemiology

According to the US Centers for Disease Control [155,156]:

- 15% of US adults are estimated to have chronic kidney disease (CKD)
- Most (9 in 10) adults with CKD do not know they have CKD

- African Americans are about 3 times more likely than whites to develop end stage kidney disease (ESKD)
- In US adults aged 18 years or older, diabetes and high blood pressure are the main reported causes of ESKD.
- In US children and adolescents younger than 18 years, polycystic kidney disease and glomerulonephritis (inflammation of the kidneys) are the main causes of ESKD.

Diagnosis and treatment

Table 9 lists ten things to know about the diagnosis and treatment of kidney dysfunction and CVD prevention.

Genetic abnormalities/familial hypercholesterolemia

Definition and physiology

CVD risk factors have pathogenic effects that lead to CVD events. Underlying genetic disorders may also contribute to phenotypically expressed CVD. Diagnosis of inherited dyslipidemias can be via laboratory testing for genetic disorders and may involve sequencing the entire human genome or custom sequencing of one or more genes. Genome wide association studies (GWAS) may reveal nucleotide polymorphisms, defined as two or more alleles at one locus having gene sequences coding for biological mechanisms or traits. For example, it is common in some countries that patients with marked elevations in LDL cholesterol levels undergo genetic evaluation of Familial Hypercholesterolemia (FH) via identifying pathogenic variants of LDL receptor (most common), apolipoprotein B, and proprotein convertase subtilisin/kexin type 9 (PCSK9) [179]. In the US, FH is more commonly assessed via one or more clinical diagnostic criteria for FH such as Simon Broome, Dutch Lipid Clinic Network, and Make Early Diagnosis to Prevent Early Deaths (MEDPED) [180].

Epidemiology

- In the US, heterozygous FH (as defined by the Dutch Lipid Clinic criteria) occurs in approximately 1:250 individuals [184], with an increased rate among those having Lebanese, South African Afrikaner, South African (Ashkenazi) Jewish, South African Indian, French Canadian, Finland, Tunisia, and Denmark population backgrounds [185].
- The risk of premature coronary heart disease is increased by 20 fold among untreated FH patients [186], and occurs in up to 1 in 7 of patients having acute coronary syndrome < 45 years of age [187].
- The onset of CVD events in patients with heterozygous FH have a wide variance, with onset of myocardial infarction about 20 years earlier than those without FH [188], and typically before age 55 and 60 years among men and women respectively [183].
- Especially if untreated, patients with heterozygous FH may experience a myocardial infarction between 30 and 40 years of age – with higher risk among men versus women, those with concurrent cigarette smoking, and FH patients having elevated lipoprotein (a) levels [189].

Diagnosis and treatment

Table 10d lists ten things to know about the diagnosis and treatment of genetics/familial hypercholesterolemia and CVD prevention.

Conclusion

The "American Society for Preventive Cardiology (ASPC) Top Ten 2020" summarizes ten things to know about ten important CVD risk factors, accompanied by sentinel references for each section. The ten CVD risk factors include unhealthful nutrition, physical inactivity,

dyslipidemia, hyperglycemia, high blood pressure, obesity, considerations of select populations (older age, race/ethnicity, and gender), thrombosis/smoking, kidney dysfunction and genetics/familial hypercholesterolemia. Primary care clinicians may benefit from a summary of the basics regarding diagnosis and management of CVD risk factors, which is fundamental to preventive cardiology. Specialists may benefit because not all specialists in one area of preventive cardiology will be a specialist in all aspects of preventive cardiology. Finally, the field of preventive cardiology is undergoing rapid growth. Those beginning in preventive cardiology may benefit from an overview of essentials in diagnosis and management of CVD risk factors. The "ASPC Top Ten 2020" represents a starting point for those interested in a multifactorial approach CVD prevention, with preventive cardiology best implemented via a team-based approach that depending on the situation, may include clinicians, nurses, dietitians, pharmacists, educators, front-desk personnel, social workers, community health workers, psychologists, exercise physiologists, and other health providers [4].

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Disclosures

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