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## State-of-the-Art Review

### Ten things to know about ten cardiovascular disease risk factors

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## ABSTRACT

Given rapid advancements in medical science, it is often challenging for the busy clinician to remain up-to-date on the fundamental and multifaceted aspects of preventive cardiology and maintain awareness of the latest guidelines applicable to cardiovascular disease (CVD) risk factors. The “American Society for Preventive Cardiology (ASPC) Top Ten CVD Risk Factors 2021 Update” is a summary document (updated yearly) regarding CVD risk factors. This “ASPC Top Ten CVD Risk Factors 2021 Update” summary document reflects the perspective of the section authors regarding ten things to know about ten sentinel CVD risk factors. It also includes quick access to sentinel references (applicable guidelines and select reviews) for each CVD risk factor section. The ten CVD risk factors include unhealthy nutrition, physical inactivity, dyslipidemia, hyperglycemia, high blood pressure, obesity, considerations of select populations (older age, race/ethnicity, and sex differences), 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 CVD Risk Factors 2021 Update” to provide a succinct overview of things to know about ten common CVD risk factors applicable to preventive cardiology.

### What is already known?

- Since 2020, the “American Society for Preventive Cardiology (ASPC) Top Ten CVD Risk Factors” has summarized the clinical relevance of

ten important CVD risk factors towards the goal of preventing CVD events. [1]

- Among factors that increase the risk of CVD include unhealthy nutrition, physical inactivity, dyslipidemia, hyperglycemia, high blood

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pressure, obesity, considerations of select patient populations (older age, race/ethnicity and sex differences), thrombosis/smoking, kidney dysfunction, and genetics/familial hypercholesterolemia.

- Diagnosing and treating multiple CVD risk factors help prevent or reduce the risk of CVD.

### What is new?

- The “ASPC Top Ten CVD Risk Factors 2021 Update” summarizes ten important CVD risk factors from the perspective of section authors. This update reflects several new guidelines, and contains hundreds of new references, most of them from 2018–2020.
- 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 because a specialist in one aspect of preventive cardiology may not necessarily have expertise in all aspects of preventive cardiology.
- In addition to the “Top Ten” things to remember for each of ten sentinel CVD risk factors summarized in tabular form, updated sentinel citations are listed in the applicable tables to reflect the latest science and provide in-depth resources (e.g., illustrative guidelines and other selected references).

## 1. Introduction

The “American Society for Preventive Cardiology (ASPC) Top Ten Cardiovascular Disease (CVD) Risk Factors 2021 Update” is intended to help both primary care clinicians and specialists be better informed about the ever-increasing pace of advances in CVD prevention. The “ASPC Top Ten CVD Risk Factors 2021 Update” summarizes ten things to know about ten important CVD risk factors, listed in tabular formats, and updated by section authors. These CVD risk factors include unhealthy nutrition, physical inactivity, dyslipidemia, hyperglycemia, high blood pressure, obesity, considerations of select populations, sex differences, and race/ethnicity, thrombosis/smoking, kidney dysfunction, and genetics/familial hypercholesterolemia. The intent is not to create a comprehensive discussion of all aspects of 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 CVD Risk Factors 2021 Update” 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 CVD Risk Factors 2021 Update” 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. Additionally, many (most) patients with CVD have multiple CVD risk factors, which requires a multifactorial approach. Patients with CVD, or who are at risk for CVD, 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. Finally, compared to prior versions, this version includes updates and different perspectives from different authors. Interested readers may elect to review prior versions of “ASPC Top Ten CVD Risk Factors” publications for different perspectives on these same topics, and to see how thinking may have evolved. [1]

## 2. Unhealthy nutrition

### 2.1. Definition

The primary components of medical nutrition therapy for CVD prevention include qualitative composition, energy content, and food consumption timing. (Fig. 1) From 2015–2018, 17.1% of US adults  $\geq 20$  were on a “special diet” on a given day. More women were on a special diet than men, and more adults aged 40–59 and  $\geq 60$  were on a special diet than adults aged 20–39. The most common type of special diet reported among all adults was a weight loss or low-calorie diet. From 2007–2008 through 2017–2018, the percentage of adults on any special diet, weight loss or low-calorie diets, and low carbohydrate diets increased, while the percentage of adults on low-fat or low-cholesterol diets decreased. [2]

The most healthful dietary strategy incorporates evidence-based nutrition and feeding patterns. Dietary patterns most associated with reduced CVD risk are those that: [3–6]

- **Emphasize intake of:**
  - Vegetables, fruits, legumes, nuts, whole grains, seeds, and fish.
  - Foods rich in monounsaturated and polyunsaturated fatty acids such as fish, nuts, and non-tropical vegetable oils.
  - Soluble fiber.
- **Limit intake of:**
  - Saturated fat (e.g., ultra-processed red meats and tropical oils).
  - Excessive sodium.
  - Cholesterol, especially in patients at high risk for CVD with known increases in cholesterol blood levels with increased cholesterol intake.
  - Ultra-processed carbohydrates and meats
  - Sugar-sweetened beverages.
  - Alcoholic beverages [7,8].
  - *Trans* fats.

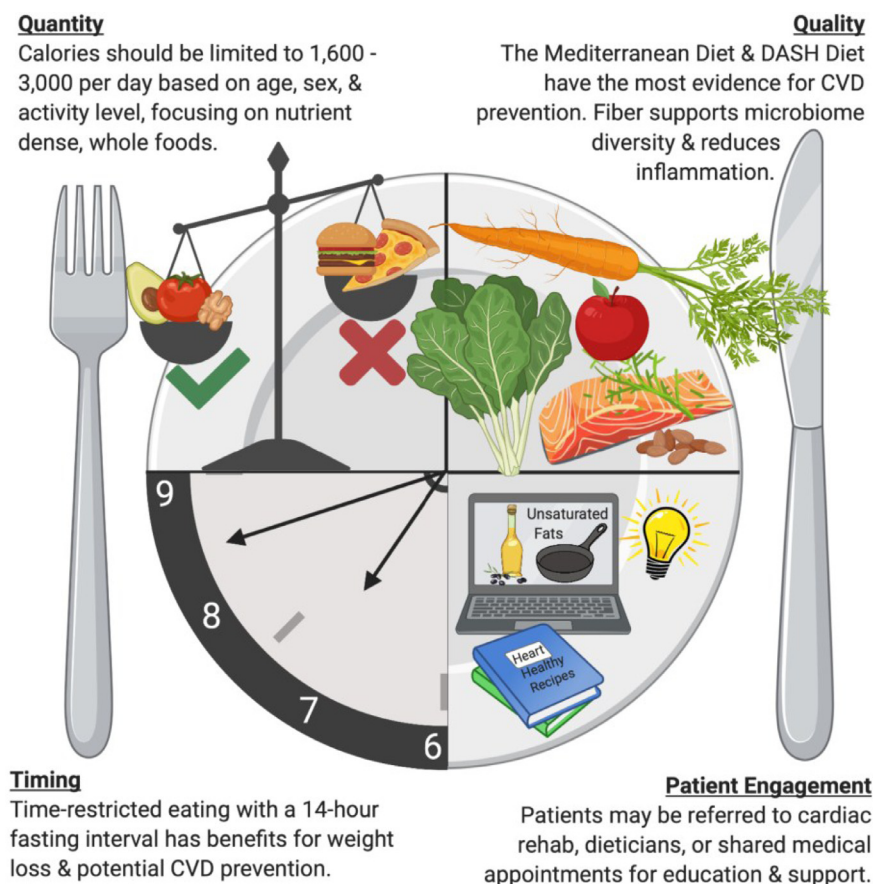
Positive caloric balance and increased body fat increase the risk of CVD.[3] One objective of healthful nutrition is to achieve a healthy body weight (see “Overweight and Obesity” section). This might best be achieved by medical nutrition therapy that incorporates qualitative dietary intake (e.g., avoiding ultra-processed foods, including sugar-sweetened foods), quantitative caloric restriction (e.g., avoiding energy dense foods), and possibly, temporal restriction of food. [13]

Food consumption can affect the microbiome. Lower microbiota diversity is associated with increased CVD risk. [14] Gut microbiota may generate short chain fatty acids, affect bile metabolism, and result in exposure to intestinal lipopolysaccharides that may stimulate proinflammatory signaling, potentially promoting obesity and metabolic disease. [5,14] Potentially pathogenic gut microbiota can generate trimethylamine-N-oxide (TMAO), which is a metabolite biomarker associated with increased atherosclerosis and thrombosis. [14,15] TMAO levels can potentially be reduced by replacing animal meats with plant-based foods. [16] Having said this, increased fish intake (generally thought healthful) can also increase TMAO, suggesting that concentration of TMAO alone cannot simply be interpreted as a marker of unhealthy food intake or unhealthy dietary pattern. [17]

Important to CVD prevention is that the microbiome can affect CVD drugs via metabolism, activation, deactivation, toxic metabolite production, modulation of transport, alteration in biliary excretion, with effects on the potential for therapeutic effect and drug toxicity. [18] No prospective CVD outcomes trial has yet demonstrated that altering the microbiome in humans reduces CVD risk or events.

### 2.2. Epidemiology

- Data from 2015–2016 suggests the prevalence of obesity (body mass index/BMI  $\geq 30$  kg/m<sup>2</sup>) was  $\sim 40\%$  of United States (US) adults. [19] Projections suggest that most of today’s children ( $\sim 60\%$ ) will



**Fig. 1.** Thinking outside the plate: CVD prevention via a focus on eating pattern quality, quantity, energy density, timing, and patient engagement. [9–12]

develop obesity at the age of 35 years, and roughly half of the projected prevalence will occur during childhood. [20]

- Positive caloric balance may result in enlargement of adipocytes and adipose tissue, resulting in adiposopathy (i.e., adipose tissue intracellular and intercellular stromal dysfunction leading to pathogenic adipose tissue endocrine and immune responses) that directly and indirectly contribute to metabolic diseases – most being major risk factors for CVD. [5,21] Some of the most common adiposopathic metabolic consequences of obesity are major CVD risk factors such as type 2 diabetes mellitus (T2DM) and hypertension. [5,22] Over the past decades, the rates of T2DM and hypertension have dramatically increased. [22]
- Concomitant with the increased prevalence of obesity and metabolic CVD risk factors is the intake of energy dense foods with low nutritional value, eating dealignment with circadian rhythms, [23] and consumption of fast foods. [24]

Positive caloric balance and increased body fat increase the risk of CVD. [5] Atherosclerotic CVD (ASCVD) is rare among hunter-gatherer populations, whether the nutritional intake is higher in fat or lower in fat. [25,26] While sometimes higher, total energy expenditure among rural hunter-gatherers may not always be substantially different from more industrialized populations. [26, 27] However, hunter-gatherer populations not only have reduced prevalence of CVD risk factors, but also low risk for CVD. This may be partially related to their preferential consumption of whole foods and fiber, as well as their dependence on daylight for feeding and, therefore, eating patterns better aligned with natural circadian rhythms. Where hunter-gatherers dramatically differ from more industrialized populations is BMI. The BMI of hunter-gatherer populations is typically < 20 kg/m<sup>2</sup>, [28] which is substantially below the BMI of many industrialized nations where CVD is the #1 cause of death among men and women. The reduced potential for adiposopathic consequences

leading to CVD risk factors and CVD helps explain why hunter-gatherer 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, [29] and an overall reduced rate of CVD.

### 2.3. Diagnosis and treatment

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

## 3. Physical inactivity

### 3.1. Definition and physiology

Physical activity is any bodily movement produced by skeletal muscles that requires energy expenditure. [68,69] The intensity of physical activity is defined in terms of metabolic equivalent units (METs). One MET is defined as the oxygen consumed while sitting at rest and is equal to 3.5 ml O<sub>2</sub> per kg body weight x minutes. [70] Light activity (e.g., slow walking) is 1.6–2.9 METs, moderate-intensity activity (e.g., moderate speed walking) is 3.0–5.9 METs and vigorous activity (e.g., moderate jogging) is ≥6 METs. As a frame of reference, patients who undergo cardiac stress testing and able to achieve ≥ 10 METs (e.g., high moderate to fast jogging) on a treadmill without ST-depression are generally at very-low risk for CVD. [71] Sedentary behavior refers to any waking activity with a low level of energy expenditure while sitting or lying down (1–1.5 METs). [72,73]

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.” [68] Physical activity also includes muscle activity during leisure time, for transportation, and as part of a person’s work – often termed non-exercise activity thermogenesis (NEAT). [68] Among two individuals of similar size, NEAT can be the single greatest

**Table 1**

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

1. Medical nutrition therapies most effective in reducing CVD are those that are evidence-based, promote healthful qualitative and quantitative/caloric dietary intake, and conducive to long-term patient adherence. [5] Saturated fat intake may promote atherogenesis via increased low-density lipoprotein cholesterol (LDL-C) levels, increased apolipoprotein B levels, increased LDL particle number, increase inflammation, and endothelial dysfunction. [30,31] In isocaloric settings, 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 such as vegetables and fruits.
2. Ultra-processed carbohydrates increase the risk of post-prandial hyperglycemia, hyperinsulinemia, hypertriglyceridemia, inflammation, endothelial dysfunction, sympathetic hyperactivity, and hypercoagulability, [32] all CVD risk factors.
3. The “diets” with the best evidence for CVD prevention are the Mediterranean Diet and “Dietary Approaches to Stop Hypertension” (DASH). [4] Both dietary patterns prioritize vegetables, fruits, whole grains, fat-free or low-fat dairy products, fish, poultry, lean meats, nuts, seeds, legumes, and fiber.
4. Other evidence-based diets include the vegetarian and Ornish diet. [4] A vegetarian meal plan includes plant-based foods such as vegetables, fruits whole grains, legumes, seeds, and nuts. Some “vegetarian diets” allow for eggs and milk. Animal meats are discouraged. [33] The Ornish Diet is illustrative of a highly fat-restricted nutritional intervention wherein macro and micronutrients are best eaten as natural whole food. The Ornish Diet includes vegetables, fruits, whole grains, legumes, and soy with limited amounts of green tea. [34,35]
5. The Ketogenic Diet is a carbohydrate-restricted intervention that discourages unhealthy ultra-processed and refined foods, discourages foods high in glycemic index/load, and discourages foods rich in *trans* fatty acids. [5] No long-term prospective clinical trial indicates that the ketogenic diet reduces CVD; however, ketogenic diets are often successful in promoting clinical weight loss in patients with overweight or obesity. The ketogenic diet may also lower postprandial glucose/insulin levels, lower blood pressure, lower triglyceride levels, and raise high density lipoprotein cholesterol (HDL-C) levels. Especially if the relatively high proportion of dietary fat with the ketogenic diet is composed of saturated fats, then LDL-C levels may increase, which may prompt consideration of replacing saturated fats with monounsaturated and/or polyunsaturated fats. [5,36–38] If the ketogenic diet is suspected to have promoted an increase in cholesterol intestinal absorption, then reduced dietary cholesterol and/or a cholesterol absorption inhibitor (e.g., ezetimibe) might be considered. [5,39]
6. Traditional guidelines for weight reduction in patients with overweight or obesity include continuous energy restriction, with a daily energy deficit of 500 – 750 kcal per day. [40] However, time-mediated caloric restriction is also a potential option, such as intermittent fasting, fasting-mimicking diets, and time restricted eating. Intermittent fasting [e.g., no food intake a certain number of days per week, such as alternate day fasting or fasting 2 days per week (5:2)] and fasting-mimicking diet (e.g., 5 days per week of low-calorie, low carbohydrate, proportionately higher fat nutritional intake), may facilitate weight reduction and improve CVD metabolic risk factors. [41] Specifically, intermittent fasting may reduce overall caloric intake, reduce body weight, and improve metabolic parameters [13] (e.g. improve insulin sensitivity, blood pressure, lipids, and inflammatory markers, even among patients with metabolic syndrome treated with statins and anti-hypertensive agents). This can often be achieved while preserving resting metabolic rate and lean body mass, [5,10] especially if accompanied by routine physical activity.
7. Time-restricted eating (TRE) can be defined as caloric consumption limited to a 6 – 10-hour period during the active day. In some patients, TRE can improve CVD risk factors such as body weight, glucose tolerance, blood pressure, atherogenic lipids, and hepatic steatosis. [9–11,42] (Figure 1) However, at least one prospective, randomized clinical trial demonstrated that compared to consistent meal timing (eating throughout the day, such as 3 meals per day and snacks), TRE had no significant effect on weight or metabolic markers, but did show a decrease in appendicular lean mass. [43] Prioritizing early in the day eating may promote greater diet induced thermogenesis and relatively favorable effects on blood glucose and insulin concentrations compared to eating large evening meals. [44,45] In an isocaloric setting, greater meal frequency (grazing with multiple small meals and frequent snacks) may not afford clinically meaningful metabolic advantages over 3 standard meals per day. However, food energy density / total daily caloric intake, food quality, food consumption times, and food knowledge and education may all play a role in affecting major CVD risk factors (hyperglycemia, high blood sugar, high blood lipids). (Figure 1)
8. In patients without vitamin deficiency, [13] dietary supplements do not reduce CVD, which includes supplementation with vitamin D. [46–48] Conversely, vitamin intake in the form of healthful whole food consumption (e.g., fruits and vegetables) are associated with reduced risk of CVD. [49] A notable example is the consumption of dairy products containing micro- and macronutrients (e.g., proteins, calcium, magnesium, potassium, vitamins) that may reduce inflammation and reduce CVD risk. [50,51] The balanced nutrients within “whole food” or “full fat” dairy consumption may help explain why dairy intake is often reported to have a neutral or favorable effect on CVD risk, even when some of the fatty acids in dairy foods are saturated fats. [52–55] While healthful plant-based foods (whole grains, fruits, vegetables, nuts, legumes, oils, tea, and coffee) may reduce CVD risk, unhealthy plant-based intake (juices, sweetened beverages, ultra-refined grains, potatoes/fries, and sweets) may increase CVD risk, [56] This (in addition to genetics and other factors) helps account for a relatively high rate of CVD among many vegetarians from India. [57]
9. Intake of foods rich in omega-3 fatty acids in general (i.e., cold water marine fish) is associated with reduced CVD risk, [58] and meta-analyses suggest supplements containing a combination of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) effectively may reduce CVD events. [59] Yet no prospective, randomized clinical trial data has yet proven this to be true. Conversely, prospective clinical outcomes data do support prescription icosapent ethyl (purified EPA) as reducing CVD events in patients at high CVD risk with baseline hypertriglyceridemia. [55] In contrast to the meta-analyses of non-prospective EPA and DHA supplement studies, early discontinuation due to futility of the prospective, randomized Outcomes Study to Assess STatin Residual Risk Reduction With Epanova in High CV Risk Patients With Hypertriglyceridemia (STRENGTH) trial of Epanova (a free fatty acid, omega-3 carboxylic acid prescription agent) suggests concentrated capsule EPA and DHA intake (beyond nutritional intake) does not reduce CVD events in patients with hypertriglyceridemia. [60,61]
10. While genetics play a role in CVD risk, unhealthy nutrition, physical inactivity, and cigarette smoking can also independently affect CVD risk. Favorable lifestyle adoption is associated with a nearly 50% lower relative risk of coronary artery disease than unfavorable lifestyle. [62] Barriers exist to healthful eating patterns, such as cost, convenience/preparation time, family taste preferences, and limitations of federal food assistance programs to low-income individuals. [63] Another barrier includes a lack of education regarding the purchase and preparation of healthful foods, which may be facilitated by shared culinary medical appointments (i.e., including nutrition and cooking lessons with cardiac rehabilitation appointments). [64] Methods to implement healthful nutrition include educating patients regarding evidenced-based meal plans and dietary practice guidelines, [4] and referring patients to a dietitian/nutritionist to implement medical nutrition therapy to help manage CVD risk factors and reduce CVD risk. [65,66]

**Sentinel guidelines and references**

2019 A Clinician's Guide to Healthy Eating for Cardiovascular Disease Prevention [4]

2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guideline [6]

2018 Clinician's Guide for Trending Cardiovascular Nutrition Controversies: Part II [3]

2017 Dietary Fats and Cardiovascular Disease: A Presidential Advisory From the American Heart Association [67]

inter-individual difference in daily energy expenditure, with variances of up to 2000 kcal per day; [74] the energy expenditure due to NEAT physical activity often exceeds the daily energy expenditure due to physical exercise. [75] Physical inactivity increases the risk of CVD, [76,77] not unlike other risk factors such as cigarette smoking and dyslipidemia. [78]

**3.2. Epidemiology**

- In the US one in two adults live with a chronic disease. Only 50% of adults get sufficient physical activity to reduce the risk of many chronic diseases such as CVD [79]
- Roughly \$117 billion in US healthcare costs yearly and 10% of premature mortality is associated with inadequate physical activity [79]



**Table 2**

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

1. Unless contraindicated, individuals derive health benefits from regular physical activity. Physical inactivity is a major risk factor for CVD, leading directly or indirectly to 10% increased premature mortality. [76,77,79]
2. Recommended physical activity for healthy adults includes at least 150 minutes of moderate-intensity physical activity per week, or  $\geq 75$  minutes of vigorous-intensity physical activity/week. [6,83] Physical activity above these recommendations may provide additional benefit. [82,83] Evidence supports benefits of muscle strengthening exercises (resistance training) of major muscle groups 2 – 3 times per week. [72] For patients unable to meet recommended physical activity goals, some moderate to vigorous physical activity (even less than recommended amounts) may help reduce CVD risk. [6] A separate goal is to reduce sedentary behavior, even if replaced by light activity. [5,6] Mortality risk reduction can be achieved with even short periods of daily exercise. [84]
3. Physical activity is an essential body function, which can be clinically measured, such as through physical activity vital sign assessment tools (i.e., questionnaires that assess physical activity). [85] Once a physical activity treatment plan is crafted by the clinician based upon patient history and physical exam, [61] and assessed through “physical activity vital signs,” it is common to find not all patients will adhere to physical activity guidance. For example, after 12 months from intervention, physical activity assessment and recommendations may result in 1 out of 12 sedentary adults meeting international recommended levels of physical activity (i.e., a number needed to treat of 12). [86]
4. In patients with obesity (BMI  $\geq 30$  kg/m<sup>2</sup>), diabetes mellitus, and well-controlled hypertension, resistance training  $\geq 3$  times/week may be beneficial to reduce CVD risk, improve insulin sensitivity, and reduce resting blood pressure. [83] Specifically, while true it is best for patients to have blood pressure controlled before embarking on a strenuous resistance training program, it is also true resistance training in patients with prehypertension or medication-controlled hypertension may reduce systolic and diastolic blood pressure. [87]
5. 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 HDL-C levels). [76,82,88] Prior to recommending resistance or dynamic training, patients benefit from an evaluation of their medical status, as well as a review of the planned physical activity. [5]
6. Beyond improvements in CVD risk factors, increased physical activity and routine physical exercise may benefit the cardiovascular system via: (a) enhanced myocardial muscle function (with amelioration of age-related loss of skeletal and cardiac muscle mass and strength), (b) reduced inflammation, (c) improved endothelial function, (d) cardio-protection against ischemia-reperfusion injury via increased myocardial oxygen utilization, (e) promotion of myocardial regeneration, (f) facilitated blood vessel dilatation capacity, (g) enhanced fibrinolysis, (h) improved autonomic balance, (i) decreased sympathetic tone, (j) reduced risk for cardiac dysrhythmias, and (k) reduced resting heart rate. [77,89–91]
7. 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. (See Obesity section) [5,92] Individuals with decreased physical activity, immobility, and/or muscle wasting medications will often have a decrease in muscle mass. Patients with sarcopenia (i.e., often found in older individuals) [93] may have a BMI in the normal weight range, but high percent body fat and 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. [5,94,95]
8. Provided the guidance is patient-appropriate, adults  $\geq 65$  years of age may benefit from multicomponent physical activity, including balance training of both dynamic (i.e., “aerobic training”) and muscle-strengthening (i.e., “resistance training”) activities to improve overall functional status (i.e., reduce pain of osteoarthritis, increase bone mineral density, reduce frailty, improve mobility, improve balance, and reduce the chances of injury) and reduce CVD risk. [80,82]
9. In addition to physical exercise, physical activity includes activities of daily living (e.g., fidgeting, standing, pacing, stair climbing), which often represents the second highest percent of daily energy expenditure (i.e., secondary to resting metabolic rate), and may help account for the variation in body weight between individuals having similar caloric intake. [5,96]
10. A common physical activity is walking, which has a dose-dependent, inverse relationship to adverse health outcomes. [5] Less than 5000 steps per day is considered sedentary;  $\geq 10,000$  steps per day is considered active. [97] While  $\geq 10,000$  steps per day may be optimal, any amount of physical activity above baseline has CVD benefits. [97–99] Brisk walking is a moderate intensity activity that most patients can do towards their recommended 150 minutes/week that confers CVD benefits similar to other types of moderate to vigorous activities. [98,97,100]

**Sentinel Guidelines and References**

2020 Top 10 Things to Know about the Second Edition of the Physical Activity Guidelines for Americans [101]

2020 ESC Guidelines on sports cardiology and exercise in patients with cardiovascular disease: The Task Force on sports cardiology and exercise in patients with cardiovascular disease of the European Society of Cardiology (ESC) [83]

2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [6]

2018 The Physical Activity Guidelines for Americans [80]

2018 Physical Activity Guidelines Advisory Committee [72]

- Only 26% of US adult men and 19% of adult women obtain guideline-directed activity levels according to federal physical activity monitoring data. [80]
- Worldwide, approximately 3.9 million premature deaths annually might be prevented with adequate physical activity. [81]

**3.3. Diagnosis and treatment**

One example of clinically implementing physical activity is a physical exercise prescription that includes frequency, intensity, time spent, type, and enjoyment (FITTE). [5,82,83] Table 2 lists ten things to know about the diagnosis and treatment of physical inactivity and CVD prevention.

**4. Dyslipidemia****4.1. Definition and physiology**

Lipids include fats, steroids, phospholipids, steroids, triglycerides, and cholesterol that are important cellular components of body tissues and organs. Lipids are carried in the blood by lipoproteins. Except for

cholesterol carried by HDL particles (and in some cases, possibly chylomicrons), other lipoproteins that carry cholesterol are atherogenic. Atherogenic lipoproteins may become entrapped within the subendothelial space, where they may undergo oxidation and scavenging by arterial macrophages, resulting in foam cells, fatty streaks, and then atherosclerotic plaque formation. Progressive enlargement of the atherosclerotic plaque may produce chronic hemodynamically significant narrowing of the artery resulting in angina or claudication; acute plaque rupture may cause myocardial infarction and/or stroke.

Atherogenesis is promoted by increased numbers of atherogenic lipoproteins. Apolipoprotein B (apoB) levels and low-density lipoprotein (LDL) particle number are predictors of ASCVD risk and are superior to measuring the cholesterol carried by atherogenic lipoproteins (i.e., LDL) in predicting atherosclerotic CVD risk (i.e., LDL-C). This is especially true when atherogenic lipoprotein particle numbers are discordant with atherogenic lipoprotein cholesterol levels, [102] as may occur with diabetes mellitus or adiposopathic dyslipidemia. [5,103] However, largely because of convention, and because CVD outcomes trials of lipid-altering drugs have specified LDL-C as the primary lipid efficacy parameter, LDL-C remains the primary lipid treatment target in most dyslipidemia management guidelines.

Remnant lipoproteins are formed in the circulation via triglyceride-rich lipoproteins that undergo lipolysis by various lipases, such as chylomicrons and very-low-density lipoproteins (VLDL), leading to small VLDL and intermediate density lipoproteins (IDL). Lipoprotein remnant cholesterol is the cholesterol carried by lipoprotein remnants and is a marker of ASCVD risk. Remnant cholesterol is sometimes defined as blood cholesterol not contained in LDL and HDL particles. The methodology of measuring and reporting lipoprotein remnants vary, and often do not correlate well with one another. [104] Measurement of remnant lipoprotein cholesterol is not included in most major lipid management guidelines.

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 better reflects ASCVD risk (compared to LDL-C alone), measurement of these biomarkers may provide additional useful information regarding risk for CVD events and are sometimes included in lipid management guidelines and societal recommendations. [105,106]

Finally, regarding definitions, lipid treatment “targets” are often defined as the lipid parameter being treated (e.g., LDL-C), lipid “goals” are the desired lipid parameter level, and lipid “threshold” is the level by which if exceeded, may prompt the addition or intensification of lipid-lowering therapy (e.g., LDL-C  $\geq 70$  mg/dL for patients at very high CVD risk). [96,97] While some prior lipid guidelines were interpreted as suggesting lipid “goals” were no longer clinically justified, [107–109], many current inter-societal and international lipid guidelines have reaffirmed goals or thresholds in the management of patients with dyslipidemia. [110,111]

#### 4.2. Epidemiology

According to the US Centers for Disease Control: [112]

- Data reported from 2015–2016 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 US adults (55%, or 43 million) who could benefit, are taking cholesterol-lowering pharmacotherapy
- The number of US 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

#### 4.3. Diagnosis and treatment

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

### 5. Hyperglycemia

#### 5.1. Definition and physiology

Diabetes mellitus is a pathologic condition characterized by high blood glucose. Type 1 diabetes results from an absolute deficiency of insulin secretion. The early stages of T2DM are often characterized by insulin resistance, that when accompanied by an inadequate insulin secretory response, results in hyperglycemia. Among patients with T2DM, the relative degree of insulin resistance and insulin secretion can substantially vary. [135] Diabetes mellitus can be diagnosed [136] with one of the following measurements:

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

Diabetes mellitus contributes to both microvascular disease (e.g., retinopathy, nephropathy, neuropathy) and macrovascular disease. Hyperglycemia may contribute to atherosclerosis via direct and indirect mechanisms. Direct adverse effects of elevated circulating glucose levels include endothelial dysfunction, oxidative stress, heightened systemic inflammation, activation of receptors of advanced glycosylated end products, increased LDL oxidation, and endothelial nitric oxide synthase (eNOS) dysfunction. Indirect adverse effects of elevated glucose levels include platelet hyperactivity. While insulin resistance (i.e., as might be mediated by mechanisms involving adiposopathic responses associated with obesity) often leads to hyperglycemia, hyperglycemia may conversely contribute to insulin resistance via glucotoxicity. [137] Normalizing hyperglycemia and reduced glucotoxicity is one proposed mechanism how sodium glucose co-transporter 2 inhibitors may increase peripheral insulin sensitivity. [138] Insulin resistance may increase non-esterified circulating free fatty acids and worsen dyslipidemia, (e.g., increased very low-density lipoprotein hepatic secretion, reduced HDL-C levels, and increased small, more dense LDL particles). [139]

Women with prior history of gestational diabetes are at increased risk for T2DM. [140] 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 HDL-C, triglycerides  $\geq 250$  mg/dL). A history of gestational diabetes mellitus doubles the risk for CVD. [141] 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  $\geq 92$  mg/dL, or 2 h glucose levels  $\geq 153$  mg/dL. The diagnosis of GDM is also made when during an OGTT, the 1 h glucose levels is  $\geq 180$  mg/dL. [142]

#### 5.2. Epidemiology

T2DM is associated with double the risk for death and a 10-fold increase in hospitalizations for coronary heart disease. [143] According to the US Centers for Disease Control: [144]

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

#### 5.3. Diagnosis and treatment

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

### 6. High blood pressure

#### 6.1. Definition and physiology

Hypertension (HTN) can be defined as arterial blood pressure readings that, when persistently elevated above ranges established by medical organizations, adversely affect patient health. African Americans have a higher prevalence of HTN than Caucasians, helping to account for a higher rate myocardial infarction, stroke, chronic and end-stage kidney disease (ESKD), and congestive heart failure among African Americans. [159,160]

A challenge with diagnosis of HTN is ensuring accurate measurement: [161,162]

- Patients should avoid caffeine, physical exercise, stress, and/or smoking for 30 min prior to blood pressure measurement.
- Patients should have an 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.

**Table 3**

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

- LDL-C was the primary lipid treatment target for most CVD outcomes trials, and LDL-C is the primary lipid treatment target according to most lipid guidelines. [110,111] However, compared to LDL-C, apolipoprotein B, non-HDL-C and LDL particle number may be better predictors of CVD risk in select populations, such as patients with diabetes mellitus, obesity, hypertriglyceridemia, non-fasting blood samples, and those with low LDL-C levels. [113–115]
- A general principle of lipid management is that the most aggressive lipid-management is best directed at patients with the highest CVD risk. Ten year CVD risk can be assessed by various heart risk calculators, such as the ACC/AHA ASCVD Risk Calculator found at <http://tools.acc.org/ASCVD-Risk-Estimator-Plus/#/calculate/estimate/> that inputs CVD risk factors (i.e. < 5% = low risk; 5 – 7.4% = borderline risk; 7.5 – 19.9% = intermediate risk; ≥ 20% = high ten year CVD risk) or the MESA 10 year risk coronary heart disease (CHD) calculator found at <https://www.mesa-nhlbi.org/MESACHDRisk/MesaRiskScore/RiskScore.aspx> which among its 12 risk factors includes coronary artery calcification race/ethnicity and family history. It is recommended that patients with ASCVD initially receive high intensity statin therapy (i.e., atorvastatin 40 – 80 mg per day, or rosuvastatin 20 – 40 mg per day). The objective of lipid-altering therapy with statins is to achieve a ≥ 50% reduction in LDL-C and achieve an LDL-C < 70 mg/dL. In patients at very-high risk, achieving an LDL-C of < 55 mg/dL may also be appropriate, [111,116] with no apparent threshold below which further incremental risk reduction is not observed. Achieving lower levels of LDL-C often requires addition of other lipid-lowering drugs to statin therapy, such as ezetimibe, proprotein convertase subtilisin kexin (PCSK) 9 inhibitors, bempedoic acid, or bile acid binding resins.
- Lipoprotein (a) is an LDL-like particle conjugated to apolipoprotein (a). Lp(a) is both atherogenic and thrombogenic and is an established ASCVD risk factor. Statins do not lower Lp(a); PCSK9 inhibitors do lower Lp(a). [117,118] No CVD outcomes trials have yet shown that reducing Lp(a) levels reduces the risk of CVD events. However, such trials are ongoing. [119]
- Heterozygous Familial Hypercholesterolemia (HeFH) is the most common genetic disorder resulting in severe elevations in LDL-C (i.e., typically with LDL-C levels ≥ 190 mg/dL), with a reported U.S. prevalence of 1/200 to 1/500. Patients with FH are at high risk for premature CVD, attributable not only to the degree of elevation in atherogenic lipoprotein cholesterol levels, but also because of the cumulative lifetime exposure to increased LDL-C levels. [120] Management of HeFH includes aggressive cholesterol lowering at an early age, usually involving statin therapy. [121]
- Statin are the most recommended drug treatment for hypercholesterolemia due to their cholesterol-lowering efficacy, safety, and CVD benefits supported by numerous CVD outcomes trials. [6] In appropriate patients, “high intensity statins” (atorvastatin 40 – 80 mg or rosuvastatin 20 – 40 mg) may lower LDL-C ≥ 50%, and are often recommended as first-line therapy in patients with CVD or at high risk for CVD. [110,111] The most common clinical manifestation of statin intolerance is statin-associated muscle symptoms (SAMS), which may limit the dose or use of statins. [122,123] SAMS can sometimes be mitigated by rechallenging with the same statin at a lower dose, using different statins, or recommending statins be administered a few days per week, rather than daily. [123–125] Occasionally, the maximally tolerated dose of a statin is no statin, requiring use of other lipid-altering drugs to achieve clinically desirable LDL-C levels.
- Ezetimibe modestly lowers LDL-C levels ~ 18% and provides incremental risk reduction beyond statin therapy. [126] Bempedoic acid lowers LDL-C ~ 18%, and when combined with ezetimibe in a fixed dose combination, lowers LDL-C ~ 38%. A CVD outcome study with bempedoic acid is ongoing. [127,128]
- PCSK9 inhibitors are injectable agents that lower LDL-C ≥ 50% and reduce CVD risk when added to high intensity or maximally tolerated statins. [110,111]
- 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) [129], [104]
- Hypertriglyceridemia generally increases CVD risk, especially if triglycerides are ≥ 150 mg/dL (i.e., part of the diagnostic criteria for the metabolic syndrome). [110] In Europe, it is noted the risk for hypertriglyceride-induced pancreatitis is clinically significant at a severely elevated triglyceride level of 10 mmol/L (880 mg/dL). [111] In the US, very high triglyceride levels are typically defined as ≥ 500 mg/dL, [110] that may not only increase CVD risk, but also increase the risk of hypertriglyceride-induced pancreatitis – sometimes resulting in recurrent bouts of hypertriglyceride-induced pancreatitis. [130,131] Omega-3 fatty acids lower triglycerides and non-HDL-C. Prescription icosapent ethyl is an eicosapentaenoic acid, ethyl ester agent that reduces the risk of multiple CVD endpoints in patients at high CVD risk having triglyceride levels ≥ 150 mg/dL. [55]
- Fibrates are used to lower triglyceride levels. However, no CVD outcome study has yet shown that fibrates reduce CVD risk in patients with high triglycerides. Post hoc analyses support that fibrates may reduce CVD events in patients with high triglycerides (and low HDL-C levels). [132] A CVD outcome study of a selective peroxisome proliferator-activated receptor alpha modulator (pemaefibrate) is ongoing, with an entry criteria being patients with diabetes mellitus having hypertriglyceridemia and low HDL-C levels. [133,134]

**Sentinel Guidelines and References**

2020 Handelsman Y. Consensus Statement By The American Association Of Clinical Endocrinologists And American College Of Endocrinology On The Management Of Dyslipidemia And Prevention Of Cardiovascular Disease [116]

2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [6]

2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. [111]

2018 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*. [110]

- 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 one minute, 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.
- Approximately 1 in 4 adults (24%) with HTN have their blood pressure under control.
- At least 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.

**6.2. Epidemiology**

According to the US Centers for Disease Control: [163]

- Uncontrolled HTN rates are rising in the US, with nearly half of adults in the US (108 million, or 45%) having HTN defined as a systolic blood pressure ≥ 130 mm Hg or a diastolic blood pressure ≥ 80 mm Hg or are taking medication for hypertension.

**6.3. Diagnosis and treatment**

Diagnosing HTN requires accurate assessment and measurement. In a medical office setting, blood pressure should be measured by a properly validated and calibrated BP measurement device, with proper cuff size, and taken by trained medical personnel. [6,164] Regarding blood pressure self-monitoring outside of a medical office setting (e.g., home, workplace), validated blood pressure measuring devices can be found at the US Blood Pressure Validated Listing (VDL™ at <https://www.validatebp.org>), which is an American Medical Association web-based independent review initiative that determines blood pressure measuring devices available in the US that meet the Validated

**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 unhealthful 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% or higher) 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 safely achieve despite diabetes self-management education, appropriate glucose monitoring, and especially if treated with multiple glucose-lowering agents including insulin. [145]
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). [146]
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. [110]
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, and depend on the specific anti-diabetes therapeutic agent. [147]
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 T2DM. While data support metformin in reducing CVD risk, the robustness of CVD outcomes data with metformin are lacking relative to some other anti-diabetes agents. Thus, metformin is considered as providing a potential benefit in reducing CVD. [148] 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 T2DM. [148] 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. [148]
6. In patients with T2DM, SGLT2 inhibitors reduce glucose levels and contribute to modest weight loss. [149] CVD outcomes trials in patients with T2DM support empagliflozin and canagliflozin as effective in reducing CVD events, and empagliflozin, canagliflozin, dapagliflozin, ertugliflozin as effective in preventing hospitalizations due to heart failure. [150] In patients with ischemic CVD or heart failure treated with comprehensive lifestyle intervention and metformin, SGLT2 inhibitors having CVD benefits should be considered as next line therapy. [6,148] Also, the management of CVD is often complicated by kidney disease, with kidney disease being a risk factor for CVD [151] In addition to their favorable CVD effects, SGLT2 inhibitors may reduce the progression of kidney disease. [151,152]
7. In patients with T2DM, GLP-1 receptor agonists have the potential to reduce CVD via glycemic control, improvement in lipid levels, reduction in body weight, reduction in blood pressure, and improvement in endothelial function. [153] Some GLP-1 receptor agonists have clinical trial evidence supporting a reduction in ischemic CVD (e.g., liraglutide, semaglutide, dulaglutide). [154] In patients with ischemic CVD treated with comprehensive lifestyle intervention and metformin, GLP-1 receptor agonists having CVD benefits should be considered as next line therapy. [6,148]
8. Sulfonylureas have neutral effects on CVD; however, sulfonylureas increase body weight and increase the risk of hypoglycemia. Severe hypoglycemia may promote cardiac dysrhythmias and increase the risk of sudden death. [155] 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. [148]
9. Regarding other oral anti-diabetes mellitus agents, in patients with CVD, pioglitazone has some data to support reduction in ischemic CVD; however, pioglitazone increases body weight and increases the risk of congestive cardiomyopathy. [156] Dipeptidyl peptidase-4 inhibitors have a neutral effect on body weight and atherosclerotic CVD; saxagliptin may increase the risk of hospitalization for heart failure. [148]
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. [148]

#### Sentinel Guidelines and References

- 2020 Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes [146]  
 2020 Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes [148]  
 2020 Cardiorenal Protection With the Newer Antidiabetic Agents in Patients With Diabetes and Chronic Kidney Disease A Scientific Statement From the American Heart Association [157]  
 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases. [158]  
 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease [6]

Device Listing Criteria. Most guidelines and scientific statements do not recommend the routine use of finger devices and wrist cuffs because of higher likelihood of efforts associated with incorrect positioning. [164]

Ambulatory blood pressure monitoring (ABPM) is often performed out of the office setting via a blood pressure cuff device that records blood pressure readings every 15–30 min intervals, typically for 24 to 48 h. Because of repeated blood pressure measurements over an extended time, ABPM is superior to a single office blood pressure measurement in the overall assessment of blood pressure, with implications regarding assessment of target organ damage and CVD risk. Some believe ABPM is the gold standard measurement for any patient with high blood pressure. Selected patients who may especially benefit from ABPM include patients with otherwise variable blood pressure readings or patients with suspected “white coat” or “masked” hypertension. [165]

Lowering blood pressure reduces CVD risk, reduces the progression of kidney disease, and reduces overall mortality among a range of patients otherwise at risk for CVD, including patients with and without high blood pressure. [161,166–170] Table 5 lists ten things to know about the diagnosis and treatment of HTN and CVD prevention.

## 7. Overweight and obesity

### 7.1. Definition and physiology

Overweight is defined as BMI > 25 and < 30 kg/m<sup>2</sup>. Obesity is defined as BMI ≥ 30 kg/m<sup>2</sup>. An increase in BMI is associated with an increase in coronary artery calcium, carotid intimal medial thickness, left ventricular thickness, [182,183] and increased lifetime CVD risk, [182,184] substantially mediated by obesity-promoted CVD risk factors. [5,185] Among patients with increased muscle mass (“body builders”), their increase in BMI might erroneously suggest an increase in body fat, while in patients with decreased muscle mass (sarcopenia), BMI might underestimate body fat. [5]

Obesity can be subcategorized into different classes: [186]

- Class I (BMI 30–34.9 kg/m<sup>2</sup>)
- Class II (BMI 35–39.9 kg/m<sup>2</sup>)
- Class III (or “severe;” BMI ≥40 kg/m<sup>2</sup>)

The adverse biomechanical aspects of obesity (“fat mass disease”) often compromise cardiac function via pericardial mechanical restraint, impaired left ventricular expansion, impaired left ventricular filling, and diastolic heart failure. [5] Obesity can also lead to adipocyte and adipose



**Table 5**

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

1. Self-monitoring ambulatory blood pressure measurements can be useful to confirm the diagnosis of HTN, which may especially be useful in patients with white coat HTN (elevated blood pressure only in the clinician setting/office) and masked HTN (elevated blood pressure only out of the clinician setting/office). [161,162] Self-monitoring of blood pressure can also help assess the effectiveness of HTN therapy. [164]
2. The American College of Cardiology / American Heart Association defines HTN as  $\geq 130/80$  mmHg, with a treatment goal of  $< 130/80$  mmHg. [161]
3. As long as the reduction in blood pressure does not result in adverse health experiences (i.e., signs, symptoms, or other evidence of hypotension or hypoperfusion), then among younger and healthier individuals, lower blood pressures reduce the risk of CVD. [169] Conversely, older individuals may experience signs and symptoms of hypotension if blood pressure is treated too aggressively, (i.e., with signs and symptoms of hypotension and potential decrease in myocardial perfusion with reduction in diastolic blood pressure  $< 70$  mmHg). [162]
4. HTN 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). [146]
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. [6,171]
6. Single pill combination antihypertensive therapy is often recommended for initial therapy (i.e., angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker combined with a calcium channel blocker or thiazide diuretic in the same pill.) [171,172]
7. Regarding diuretics, chlorthalidone and indapamide are “thiazide-like” diuretics with longer half-lives and achieve a greater blood pressure reduction over 24-hours than the thiazide hydrochlorothiazide. [173] Due to these effects and the results of CVD outcomes trials, the American College of Cardiology has recommended chlorthalidone as the preferred thiazide or thiazide-type diuretic. [161,174] Thiazide diuretics are often a first-line therapy for HTN. Loop diuretics (e.g., furosemide, torsemide, bumetanide, and azosemide) may be preferred in patients with heart failure (especially torsemide) and when estimated glomerular filtration rate is  $< 30$  ml/min. [161,175,176]
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. [161,177]
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 CCBs (e.g., verapamil and diltiazem) may cause bradycardia and heart block and should be avoided in patients with heart failure with reduced left ventricular ejection fraction. CCBs lower blood pressure and are first line antihypertensive agents. [161] Beta blockers 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 with other anti-hypertensive drug treatments. [178,179]
10. Community based approaches (e.g., churches, barbershops, neighborhood initiatives) and telemonitoring for HTN management may be beneficial for BP control beyond in-office practice alone. [180,181]

**Sentinel Guidelines and References**

2020 Self-Measured Blood Pressure Monitoring at Home: A Joint Policy Statement From the American Heart Association and American Heart Association [164]

2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease [6]

2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [6]

2018 ESC/ESH Guidelines for the management of arterial hypertension [162]

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 [161]

tissue dysfunction (“sick fat”). Adiposopathy is defined as pathogenic adipose tissue anatomic/functional disturbances promoted by positive caloric balance in genetically and environmentally susceptible individuals that result in adverse endocrine and immune responses that may directly promote CVD, and may cause or worsen metabolic disease. [21] Adiposopathy is analogous to cardiomyopathy, myopathy, encephalopathy, ophthalmopathy, retinopathy, enteropathy, nephropathy, neuropathy, and dermatopathy. Pathologic enlargement of heart cells and heart organ results in anatomic/functional abnormalities leading to “cardiomyopathy.” Pathogenic enlargement of fat cells and fat organ results in anatomic/functional abnormalities leading to “adiposopathy.” The dysfunction of adipose tissue (adiposopathy or “sick fat”) can be caused by positive caloric balance, physical inactivity, genetic predisposition, and environmental causes. Anatomic manifestations of adiposopathy include adipocyte hypertrophy, visceral, pericardial, perivascular, and other periorgan adiposity, growth of adipose tissue beyond its vascular supply, increased number of adipose tissue immune cells, and “ectopic fat deposition” in other body organs (e.g., liver, muscle, kidney). Pathophysiological manifestations of adiposopathy include impaired adipogenesis, pathological adipocyte organelle dysfunction (e.g., mitochondrial and endoplasmic reticulum “stress”), increased circulating free fatty acids, pathogenic adipose tissue endocrine responses (e.g., increased leptin, increased tumor necrosis factor- $\alpha$ , decreased adiponectin, and increased mineralocorticoids), and pathogenic adipose tissue immune responses (e.g., increased proinflammatory responses through increased tumor necrosis factor- $\alpha$  and decreased anti-inflammatory responses through decreased adiponectin). [5,26] Among the clinical manifestations of the adiposopathic consequences

of obesity include hyperglycemia, high blood pressure, dyslipidemia, metabolic syndrome, and fatty liver, which are associated with increased CVD risk. [5]

In 2020, an illustrative clinical example of how obesity contributes to cardiopulmonary disease was the Severe Acute Respiratory Syndrome coronavirus (COVID-19) pandemic. In general, it was previously known that obesity increased the risk and severity of upper respiratory tract infections (URI). This was thought partially due to fat mass disease-mediated compromise of lung function with reduced tidal volume, reduced forced expiratory volume (FEV<sub>1</sub>), sleep apnea, day and nighttime hypoxia, as well as general debilitation and immobility. [5]

Additionally, “sick fat disease” adiposopathic responses were known to predispose to infection and worse outcomes due to disruption of innate and acquired immunity and exaggerated pro-inflammatory responses. With the onset of the COVID-19 pandemic, patients with obesity were among the most frequently affected, and most adversely affected. This was made more challenging because many patients feared exposure to the virus and thus limited their urgent and chronic medical care for obesity, metabolic diseases, and cardiovascular disease management – further worsening outcomes – especially among patients with obesity, diabetes, hypertension, and CVD. [187] Additional challenges included limited access to providers and temporary closure of many cardiac rehabilitation programs. In response, an ASPC Scientific Statement recommended: (1) expansion of telehealth visits; (2) enhanced self-monitoring of clinical signs and symptoms; (3) strategies towards medication adherence; (4) better utilization of team-based care; and (5) more aggressive adherence to lifestyle recommendations – including therapies directed at obesity management. [187]

While the adiposopathic manifestations of obesity result in immunopathies and endocrinopathies that indirectly increase CVD risk, obesity may also result in adiposopathic consequences that directly increase CVD risk. Epicardial and visceral fat share the same mesodermal embryonic origin, both are associated with increased CVD risk, and both are highly correlated with increased coronary calcification. Epicardial adipose tissue can directly contribute to heart failure (e.g., especially heart failure with preserved ejection fraction or HFpEF), atherosclerosis, cardiac dysrhythmias, fatty infiltration of the heart, and increased coronary calcium potentially related to pathogenic adipose tissue surrounding the heart, as well as pathogenic paracrine and vasocrine signaling and transmission of inflammatory factors, fatty acids, and possibly transport of atherogenic lipoproteins (i.e., “outside to in” model of atherosclerosis) [5]

In short, worsening obesity directly correlates with worsening impact on the cardiovascular system, with mortality, nonfatal coronary heart disease, and congestive heart failure increased among patients with severe obesity versus those with lesser classes of obesity. [188] The adverse effect of obesity on CVD can be both indirect through obesity-mediated development of major CVD risk factors (e.g. T2DM, HTN, and dyslipidemia) or direct via fat mass effects or adiposopathic epicardial immune and endocrine effects. [5,189,190]

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. Dual X-ray absorptiometry (DXA) is often 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, because an increase in waist circumference reflects adiposopathic dysfunction, which both directly and indirectly increases the risk of CVD. [5]

Another measure of potential clinical benefit is the waist-to-hip ratio. An elevated waist-to-hip ratio (> 0.9 in men; > 0.83 in women) may be a better predictor of myocardial infarction than an elevated BMI. [191,192] However, not all analyses support clinically meaningful differences between BMI, waist circumference, waist to hip ratio and weight to height ratio. [193] Also, BMI, waist circumference, waist to hip ratio and weight to height ratio are not direct measures of android or visceral adiposity, which are anthropometric measures most associated with CVD risk. Differences in android and visceral fat accumulation helps explain the differences in CVD risk between men and women, [194] can be measured by DXA for initial assessment, and then followed longitudinally by DXA to determine response to obesity treatment. [5]

The metabolic syndrome [195] is an LDL-C-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)]. Different waist circumference diagnostic criteria may apply to different races or ethnicities (e.g., Asian men  $\geq$  40 cm; Asian women  $\geq$  80 cm) [196]
- Elevated triglycerides  $\geq$  150 mg/dL (1.7 mmol/L), or use of medications for high triglycerides
- Reduced HDL-C (men  $<$  40 mg/dL (1.03 mmol/L); women  $<$  50 mg/dL (1.29 mmol/L), or use of medications for low HDL-C
- Elevated blood pressure ( $\geq$  130/85 mm Hg or use of medication for HTN)
- 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. [95]

## 7.2. Epidemiology

According to the US Centers for Disease Control: [19]

- The prevalence and severity of obesity in US adults has significantly increased from 1999–2000 through 2017–2018 [19]
- In 2017–2018, the age-adjusted prevalence of obesity (BMI  $\geq$  30 kg/m<sup>2</sup>) was  $\sim$  40% of US adults [19]
- In 2017–2018, non-Hispanic black adults (49.6%) - especially non-Hispanic black women (56.9%) - had the highest age-adjusted prevalence of obesity compared with other race and Hispanic-origin groups [19]
- In 2017–2018, the age-adjusted prevalence of severe obesity (BMI  $\geq$  40 kg/m<sup>2</sup>) was 9.2% of US adults [19]
- Complications of obesity include heart disease and stroke
- Other CVD-related complications of obesity include adiposopathic alterations in:[5]
  - CVD risk factors (e.g., diabetes mellitus, HTN, dyslipidemia).
  - Cardiovascular hemodynamics and heart function.
  - Heart, heart cells, and structure (which can result in electrocardiogram tracing abnormalities).
  - Atherosclerosis and MI.
  - Adiposopathic immunopathies that promote CVD risk factors and CVD.
  - Adiposopathic endocrinopathies that promote CVD risk factors and CVD.
  - Thrombosis.

While current antiobesity drug treatments can improve CVD risk factors, their use is limited to only  $\sim$  1% of eligible patients. [197] No current anti-obesity drug has CVD outcomes data to support anti-obesity drugs reduce CVD events. However, CVD outcomes trials are ongoing to determine if existing or future anti-obesity drugs reduce CVD events. [5,198]

Bariatric surgery continues to evolve as a treatment for obesity. [5] Bariatric surgery not only reduces CVD risk factors (i.e., T2DM, HTN and dyslipidemia, [199] but also reduces the risk of MI, stroke, and all-cause mortality. [200,201] Similar to anti-obesity drugs, bariatric surgery is performed in less than 1% of appropriate patients for which it is indicated. [202] Among the few medically eligible patients who receive treatment with bariatric surgery, significant disparities exist according to race, income, education level, and insurance type. [203]

## 7.3. Diagnosis and treatment

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

## 8. Considerations of selected populations (older age, race/ethnicity, sex differences)

### 8.1. Definition and physiology

#### 8.1.1. Older individuals

Older individuals (i.e., > 75 years of age) vary considerably in their future risk for CVD and life expectancy. This variance in CVD risk and mortality is largely dependent on underlying co-morbidities and degree of frailty. [216] Given the paucity of evidenced-based data among older individuals for the primary prevention of CVD, treatment recommendations are best determined by shared decision-making utilizing a patient-centered approach. [110,216] Clinicians should tailor discussions to individual CVD risk factors, complexity of concurrent illnesses, considerations of the quality of life, and cost issues related to polypharmacy. [216]

#### 8.1.2. Race

South Asians [217] may be at increased CVD risk largely due to increased prevalence of metabolic syndrome (even at a lower BMI), insulin

**Table 6**  
Ten things to know about increased body fat and cardiovascular disease (CVD) prevention

1. CVD (and cancer) are the most common causes of death among patients with obesity. [204–206] 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). [5]
2. Weight reduction in patients with obesity attenuates insulin resistance, 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. [207–209] 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. [5,210]
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).
4. Liraglutide is a GLP-1 receptor agonist that at a dose of 3.0 mg per day, is indicated as an anti-obesity agent, with metabolic benefits beyond weight loss alone. [5,211] In patients wherein the GLP-1 receptor agonist is being used to treat T2DM, liraglutide, semaglutide, and dulaglutide reduce the risk of CVD events. Anti-obesity agents (including GLP-1 receptor agonists alone or in combination with other molecular entities) are being evaluated in CVD outcomes trials. [5]
5. Among patients with obesity, CVD, and without T2DM and without congestive cardiomyopathy, initial treatments to consider include liraglutide, utilizing the dose indicated for treatment of obesity (i.e., subcutaneous injection of 3.0 mg per day). [5]
6. Metformin and 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. [212] 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 CVD). [5]
7. Among patients with obesity, CVD and T2DM without congestive cardiomyopathy, initial drug treatments to consider include metformin and GLP-1 receptor agonists (e.g., liraglutide, semaglutide, and dulaglutide), and SGLT-2 inhibitors (e.g., empagliflozin, dapagliflozin, and canagliflozin).
8. Among patients with obesity, CVD, T2DM with congestive cardiomyopathy, initial drug treatments to consider include metformin and SGLT-2 inhibitors. [5]
9. Little evidence supports phentermine & topiramate combination anti-obesity agent as increasing or decreasing CVD risk among patients with obesity. [213]
10. Phentermine is contraindicated in patients with CVD [5]

#### Sentinel Guidelines and References

2021 Obesity Algorithm eBook, presented by the Obesity Medicine Association.[5]

2020 Obesity in Adults: A Clinical Practice Guideline [214]

2015 Pharmacological Management of Obesity: An Endocrine Society Clinical Practice Guideline [215]

2013 AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults [186]

resistance and adiposopathic dyslipidemia (sometimes called “atherogenic dyslipidemia”), which can be defined as elevated triglycerides, reduced HDL-C levels, increased LDL particle number, with an increased prevalence of smaller, more dense LDL particles, and increased lipoprotein(a), all which may increase CVD risk. [26] Asians may also have increased risk of thrombosis as evidenced by increased plasminogen activator inhibitor, fibrinogen, lipoprotein (a), and homocysteine. Asians may have other factors that increase CVD risk such as impaired cerebrovascular autoregulation and sympathovagal activity, increased arterial stiffness, and endothelial dysfunction, [218] although it is uncertain if endothelial function of Asian Indians are inherently attenuated in comparison to Caucasians. [219]

Having South Asia heritage is considered an ASCVD risk enhancing factor [110] The “Mediators of Atherosclerosis in South Asians Living in America (MASALA)” was a longitudinal cohort of South Asians in the United States. This study supported South Asians as experiencing a disproportionately high burden of prevalent and incident T2DM compared with members of other race/ethnic groups. [220] The same applies to ASCVD. After adjusting for ASCVD risk factors, South Asians may have greater coronary artery calcification progression than Chinese, black, and Latino men but similar change to that of whites. [221]

South Asians make up over 20% of the world population. South Asians can be defined as those with ethnic roots originating from the Indian subcontinent (e.g., India, Pakistan, Sri Lanka, Nepal, and Bangladesh). Having said this, the term “South Asian” represents a heterogeneous population, with differences in diet, culture, and lifestyle among different South Asian populations and religions. Nonetheless, multiple studies have confirmed that South Asians have a 3- to 5-fold increase in the risk for myocardial infarction and cardiovascular death as compared with other ethnic groups. [222]

**African Americans** have among the highest CVD rates of any US ethnic or racial group. African Americans often have more favorable selected 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 HTN, left ventricular hypertrophy, obesity, T2DM, chronic kidney disease (CKD), and elevated lipoprotein (a) levels. [223]

**Hispanic/Latino individuals** often have elevated triglyceride and reduced HDL-C levels, and increased risk for insulin resistance. A “Hispanic Mortality Paradox” is sometimes described wherein the Hispanic/Latino population is reported as having a lower overall risk of mortality than non-Hispanic Whites and non-Hispanic Blacks (albeit higher risk of mortality than Asian Americans). [224] Nonetheless, CVD is the leading cause of death among Hispanics and the “Hispanic Paradox” may not apply to all Hispanic/Latino subpopulations. [225] Thus, to reduce CVD risk, Hispanic/Latino individuals should undergo diagnosis and treatment of CVD risk factors similar to other ethnicities / races. [226]

**Native Americans** are defined as members of indigenous peoples of North, Central, and South America, with American Indians and Alaskan Natives often residing in North America. [227] In 2018, American Indians / Alaska Natives were 50% more likely to be diagnosed with CVD compared to non-Hispanic Whites, which may be related to a higher prevalence of CVD risk factors such as obesity, diabetes mellitus, HTN, and higher rates of cigarette smoking. [227] 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, T2DM, higher triglyceride levels, reduced HDL-C levels, and higher prevalence of metabolic syndrome).[228] Older literature suggests incident CVD events among Pima Indians may not be as high as predicted. [229] This is, in part, because in some cases compared to Caucasians, untreated LDL-C levels may be lower among Pima men older than 30 and in women older than 25 years of age. [228] 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.[230]

**Women** with CVD risk factors are at increased risk for CVD events, directionally similar to men. CVD is the leading cause of mortality among women.[231] CVD causes ~ 4 times as many deaths in women

compared to breast cancer.[232] Compared to men, women are at higher risk for bleeding after invasive cardiac procedures, and are more predisposed to autoimmune/inflammatory disease, and fibromuscular dysplasia, potentially predisposing to myocardial infarction in the absence of atherosclerotic obstructive coronary arteries - especially among younger women. [233] According to the 2018 American Heart Association, American College of Cardiology Guideline on the Management of Blood Cholesterol, premature menopause and hypertensive disorders of pregnancy (i.e., preeclampsia) are CVD risk enhancers. [110] Gestational diabetes and preterm delivery are also recognized as increasing lifetime CVD risk.

## 8.2. Epidemiology

- Due to insufficient data (many CVD outcomes trials excluded older patients), the treatment recommendations for primary CVD risk reduction in individuals > 75 years old often have less scientific support than treatment recommendations for younger age groups. Also, due to the population makeup of the supporting databases, CVD 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 ACC/AHA ASCVD Risk Calculator includes an age range of 40–79 years. [234]
- Many CVD risk calculators do not take into full account the influence of race on CVD risk. The ACC/AHA ASCVD Heart Risk Calculator is limited to the races of “Other” and African Americans. [234] Conversely, the Multi-Ethnic Study of Atherosclerosis (MESA) 10-year CHD risk tool includes Caucasians, Chinese, African Americans, and Hispanics 45–85 years of age as data input, along with coronary artery calcification. [235]
- CVD is the leading cause of death for women and men of most racial and ethnic groups in the US, accounting for ~20% of deaths per year. [236]
- 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. [237]
- Compared to Caucasians, Hispanics/Latinos 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/Latinos, foreign-born Hispanics/Latinos have about half as much heart disease; 29% less high blood pressure; and 45% more high total cholesterol. [238]
- Compared to Caucasian adults, American Indians/Alaska Native adults have a higher prevalence of CVD risk factors such as obesity, high blood pressure, and current cigarette smoking. In 2018, American Indians/Alaska Natives had a 50 percent greater risk for coronary heart disease compared to non-Hispanic Whites.[227]
- Heart disease is the leading cause of death for African American and Caucasian women in the US. Among American Indian and Alaska Native women, heart disease and cancer cause roughly the same number of deaths each year. [239]
- Age and sex are important risk factors for stroke. One in 5 US women between 55–75 years of age will have a stroke in her lifetime. Stroke kills twice as many women as breast cancer. [240] Greater longevity in women helps account for strokes occurring more frequently in women than men; however, women may also have sex-specific stroke risk factors (e.g., endogenous hormones, exogenous hormones, and pregnancy-related exposures). [241]

## 8.3. 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.

## 9. Thrombosis and smoking

### 9.1. Definition and physiology

Thrombosis is the intravascular (arterial or venous) coagulation of blood, resulting in a “blood clot” which may cause local or downstream obstruction of a vessel (thromboembolism). Atherosclerosis may lead to chronic luminal narrowing that obstructs on-demand blood flow, resulting in angina or claudication. Thromboembolic acute obstruction of a femoral vein may lead to an acute deep vein thrombosis; an acute obstruction of a coronary artery may lead to a myocardial infarction; and an acute obstruction to a carotid artery may lead to a stroke. [259]

Risk factors for thrombosis include older age, atrial fibrillation, cigarette smoking, prosthetic heart valves, blood clotting disorders, trauma/fractures, physical inactivity (including prolonged bed rest / immobility), obesity, diabetes mellitus, HTN, dyslipidemia, certain drug treatments (estrogens), pregnancy, and cancer. Finally, a prior CVD event increases the risk of a future CVD event, often involving a thromboembolic component. Thus, patients with an 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 CVD morbidity and mortality.[260] Tobacco cigarette smoking increases CVD risk via promoting thrombosis, inflammation, free radical formation, carbon monoxide-mediated increases 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 LDL-C. [260]

Vaping devices (electronic cigarettes or “e-cigarettes”) are battery-operated nicotine (as well as flavoring and other chemicals) delivery devices that generate an aerosol that is intended to be 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 an acute increase in the sympathetic nervous system, increase in blood pressure, decrease in coronary blood flow, increase in myocardial remodeling/fibrosis, promotion of dysrhythmias and promotion of thrombosis, with longer-term adverse effects on endothelial function, inflammation, lipid levels (reduced high density lipoprotein and increased LDL-C levels), blood pressure, and insulin resistance.[261]

### 9.2. Epidemiology

According to the US Centers for Disease Control: [262–266]

- Stroke is a leading cause of serious long-term disability, reducing mobility in more than half of stroke survivors age 65 and over.
- In the US, stroke is responsible for 1 out of 20 deaths.
- About 90% of all strokes are ischemic strokes.
- The 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.
- Smoking is a leading cause of preventable death, accounting for 480,000 deaths a year.
- In 2018, 13.7% of all adults (34.2 million people) smoked cigarettes: 15.6% of men and 12.0% of women.
- Cigarette smoking has a dose-response relationship with stroke. [267]
- E-cigarettes are the most frequently used tobacco product among youths. Roughly 5% of middle school students and 20% of high school students report using e-cigarettes. [266]

### 9.3. Diagnosis and treatment

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



**Table 7**

Ten things to know about select populations (older age, race/ethnicity, sex differences) and cardiovascular disease (CVD) prevention.

1. CVD prevention recommendations vary among different guidelines regarding individuals over 75 years of age. CVD treatment decisions for older individuals are best based upon the individualized patient-centered approach.
2. General principles of CVD prevention in older individuals include: (a) Blood pressure goal of at least < 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, risk for orthostatic hypotension, falls, and other side effects of lower blood pressure or polypharmacy; (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 may be a reasonable goal in some patients with 3 or more chronic illnesses and intact cognition). Less stringent hemoglobin A1c (8.0% or less) may be considered in patients who are frail, with multiple chronic illnesses, advanced cognitive or functional impairment, limited life expectancy, or long-standing diabetes mellitus in whom more aggressive blood sugar control potentially contributes to an unacceptable risk of hypoglycemia. Some have further suggested extending the hemoglobin A1c goal to 8.5 or 9.0% for patients with very complex comorbidities, undergoing long-term assisted care, end-stage chronic illness, and advanced cognitive or functional limitations; [216] (d) Older individuals should avoid cigarette smoking which 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.[110,216]
3. Compared to Caucasians, many Asian Americans 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 the approved statin doses are often lower among Asian individuals.[242]
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 recommendation that in individuals with HTN, the optimal goal is < 1500 mg of sodium per day, [6] which may be especially important among African Americans.[243] Guidelines for pharmacologic CVD prevention in African Americans are generally similar to other racial/ethnic groups, except regarding heart failure and HTN. In African Americans, diuretics and calcium channel blockers may be preferred over angiotensin converting enzyme inhibitors and beta-blockers.[223]
5. Recommendations to reduce CVD risk in Hispanics/Latinos is like other races, with ineffective CVD prevention communication being a substantial barrier to non-English speaking Hispanics. [226] Important factors in effective CVD prevention among minorities are sustainable interventions that adequately address communication barriers, and that both acknowledge and address the impact of race/ethnic culture in discussions regarding behavioral and other treatment recommendations. Effective patient communication may [244] or may not [245] be influenced by the race/ethnicity of the provider. Clinician decision making may be influenced by integrating themes regarding race, patient-levels issues, system-level issues, bias and racism, patient values, and communication. [246] On a patient level, practical interventions to potentially improve understanding and adherence to treatment among minorities may generally include instilling confidence in the minority patient communication abilities, and specifically facilitating the simple asking and answering of clinically applicable questions. [247,248]
6. Women typically have the same rate of CVD onset 10 years later than men. However, this favorable cardioprotective effect diminishes among women with polycystic ovary syndrome, cigarette smoking and women entering menopause. Women over 60 years of age often have lower rates of controlled HTN and higher prevalence of HTN compared to men. [231] Any cardioprotective effect is mostly lost among women with T2DM. Women with T2DM have a three-fold increased risk of CVD, with a higher risk of heart failure, stroke, claudication, and CVD mortality compared to men with T2DM. [231] While supporting CVD outcome data are 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. [231]
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). [231]
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. [5] PCOS increases CVD risk, largely because of accompanying cardiometabolic abnormalities such as insulin resistance, glucose intolerance, diabetes mellitus, HTN, dyslipidemia (increased triglycerides and decreased HDL-C), metabolic syndrome, increased C-reactive protein, increased coronary artery calcium scores, increased carotid intima-medial thickness, and endothelial dysfunction.[249] 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. [250] Conversely, statin therapy may lower testosterone in women with PCOS, with variable reports regarding effects on menstrual regularity, spontaneous ovulation, hirsutism, or acne. [251,252] Statin therapy combined with metformin therapy in women with PCOS may not only lower cholesterol, triglyceride, and testosterone levels, but may also improve insulin resistance with improvement in menstrual regularity, hirsutism, acne, and spontaneous ovulation. [253] While the degree of possible teratogenic effects are unclear, statins are contraindicated in women who are pregnant, or who may become pregnant. [254]
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. [255] In women going through 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. [256] Taken together with age-related increase in body fat, women undergoing menopause are at increased risk for insulin resistance, HTN, and dyslipidemia – increasing CVD risk. [257] In some cases, hormone replacement therapy primarily used to treat menopausal symptoms 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. [231]
10. Obesity, physical inactivity, T2DM, 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. [231]

**Sentinel Guidelines and References**

2020 The Use of Sex-Specific Factors in the Assessment of Women's Cardiovascular Risk [110,258]

2020 US Department of Health and Human Services Office of Minority Health. Minority Population Profiles. [227]

2017 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. [223]

2016 Cardiovascular Disease in Women: Clinical Perspectives [231]

2014 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 [226]

**Table 8**

Ten things to know about thrombosis and smoking and cardiovascular disease (CVD) prevention

- Regarding the use of aspirin for CVD primary prevention, randomized clinical trials suggest the risks of bleeding outweigh the health benefits, even among most patients with diabetes mellitus. [6,268–275] Aspirin may be beneficial in primary prevention for select patients with diabetes mellitus who are at high risk for CVD and who are at low risk for bleeding, but only after a patient-centered evaluation and discussion. [146,276,277] Coronary artery calcium (CAC) assessment can help inform the clinical use of aspirin in primary prevention, with those having a CAC score of  $\geq 100$  Agatston Units (AU) having a favorable risk/benefit estimation from the use of aspirin, while those with zero CAC are estimated to have net harm from aspirin. [278]
- The standard of care for managing thrombotic risk in secondary prevention (preventing recurrent ischemic events after an 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). [279]
- Aspirin is the first drug of choice in secondary prevention after a myocardial infarction and should be continued indefinitely unless contraindicated or adverse experiences occur. [280] 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 (i.e., less bleeding) and higher doses having greater CVD risk reduction. [281] Aspirin doses of 75 – 100 mg per day may offer the optimal benefit/risk ratio in chronic prevention of recurrent atherothrombosis in patients with an acute coronary syndrome [280] (i.e., 81 mg “baby aspirin”).
- Acutely, aspirin is beneficial in patients with unstable coronary artery disease, acute myocardial infarction, and unstable angina. [282–284] Aspirin platelet inhibition is fastest with chewable aspirin, which has a more rapid onset of action than soluble aspirin, which has a more rapid onset of action than whole solid aspirin, which has a more rapid onset of action than enteric-coated aspirin. [285] After calling 9-1-1 for emergency phone help, patients undergoing an acute myocardial infarction are advised to chew one 325 mg aspirin slowly, preferably within 30 minutes of the onset of symptoms. [286] Chronic administration of aspirin is recommended to prevent recurrent ischemic stroke. Administration of aspirin is *NOT* recommended for acute stroke, due to the potential of worsening of a hemorrhagic stroke. [286,287]
- In patients experiencing an acute coronary syndrome, unless side effects occur or contraindications exist, DAPT should be continued for at least 12 months after the CVD event. After a patient-centered discussion, DAPT for longer than 12 months may be considered if the net potential benefit it thought to outweigh the potential risk (i.e., bleeding). [288]
- The “5 A’s” framework (as adapted for other CVD risk factor management, such as counseling for obesity [289]) can help engage patients in a discussion about smoking cessation. The 5 A’s include: (a) *A*sk patients about tobacco use; (b) *A*dvice smokers to quit tobacco; (c) *A*ssess a smoker’s readiness to quit; (d) *A*ssist smokers to quit; (e) *A*rrange follow-up. [289–291]
- To reduce the risk of thrombosis, CVD, cancer, and other ill effects of tobacco cigarette smoking, [6] patients who smoke cigarettes may benefit from a *A*sk, *A*dvice, and *R*eferral (*AAR*) approach to a behavioral support program. Referral program utilization is enhanced with patient agreement to be contacted (*A*sk, *A*dvice, and *C*ontact or *AAC*) for a behavior support appointment, as opposed to simply being referred. [292] If upon initial patient-centered discussions, the patient declines referral for behavior support, then this offer should be repeated on subsequent clinician encounters, as the willingness of the patient to quit smoking may change over time.
- Antismoking pharmacotherapy can act synergistically with behavior therapy and enhance the chances the patient will stop cigarette smoking. FDA approved anti-smoking medications include nicotine patch, lozenge, gum, inhaler, nasal spray, varenicline, and bupropion. Many of these medications can be used in combination. Clinicians should be aware of the dosing, precautions, and inform the patient of potential side effects of these therapies. [293,294]
- The aerosol from e-cigarettes typically does not contain all the contaminants in tobacco smoke. Short-term use of e-cigarettes in healthy individuals may not adversely affect vascular function. [261,295] However, most e-cigarettes contain nicotine, which is highly addictive and may increase the long-term risk of CVD.
- While potentially safer than traditional tobacco cigarettes, the Centers for Disease Control (CDC) and Food and Drug Administration recommend that tetrahydrocannabinol (THC)-containing and/or nicotine-containing e-cigarettes should not be used by youths and young adults, women who are pregnant, or adults who do not currently use tobacco products. [264] Those choosing to use e-cigarettes as an alternative to cigarettes should completely switch from cigarettes to e-cigarettes, and not use both products concomitantly. [264] While reasonable to use e-cigarettes as a part of a bridging smoking cessation strategy in certain populations, the data on such an approach remain unclear. [296] The FDA has not approved e-cigarettes as a smoking cessation aid, and more research is needed to better understand the long term health effects of e-cigarettes and their role in helping smokers to stop tobacco smoking. [261,297]

**Sentinel Guidelines and References**

2020 Centers for Disease Control. Smoking & Tobacco Use. Electronic cigarettes [264]  
 2020 Smoking Cessation. A Report from the Surgeon General [298]  
 2020 Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes-[146]  
 2020 Heart Disease and Stroke Statistics-Update: A Report from the American Heart Association [299]  
 2018 ACC Expert Consensus Decision Pathway on Tobacco Cessation Treatment [300]

**10. Kidney dysfunction***10.1. Definition and physiology*

According to the “Kidney Disease: Improving Global Outcomes” (KDIGO) guidelines, [301] CKD is defined as greater than 3 months of a reduced estimated glomerular filtration rate (eGFR), beginning at a moderate reduction of  $< 60$  mg/min/1.73 m<sup>2</sup> and/or increase in urine protein excretion [i.e., albuminuria, beginning at a moderate increase in the albumin creatinine ratio  $\geq 30$  mg/g ( $\geq 3$  mg/mmol)]. [302] 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), CKD is an independent risk factor for CVD, likely due to endothelial dysfunction, accelerated atherosclerosis, [303] increased inflammation, vascular calcification and other vasculopathies. [304] Other non-traditional CVD risk factors often found in patients with CKD include left ventricular hypertrophy, anemia, abnormal calcium-phosphate metabolism, and elevated urate levels. [305]

Over 2/3<sup>rd</sup> of patients over 65 years with CKD have concomitant CVD. [306] Both eGFR  $< 60$  mg/min/1.73 m<sup>2</sup> and albuminuria are independent predictors of CVD events and CVD mortality. [307] CVD

is inversely related to eGFR. Generally, CKD and ESKD are associated with a 5–10 fold higher risk for developing CVD compared to aged matched controls. [308] Specifically, patients with CKD having eGFR 15–60 mg/min/1.73 m<sup>2</sup> have about two to three times higher risk of CVD mortality, compared to patients without CKD. [307,309] As such, CKD is considered a “risk enhancing factor” that places patients at high risk for CVD. [110]

*10.2. Epidemiology*

According to the US Centers for Disease Control and The Heart Disease and Stroke Statistics 2020 Update from the American Heart Association: [310,311]

- 15% of US adults are estimated to have CKD.
- The prevalence of CVD increases with age, with about 1/3 of patients over 60 years of age having CVD.
- 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 mellitus and high blood pressure are the main reported causes of ESKD and the prevalence of

CKD is about 37% of adults with diabetes mellitus and 31% among adults with high blood pressure. [157]

- In US children and adolescents younger than 18 years, polycystic kidney disease and glomerulonephritis (inflammation of the kidneys) are the main causes of ESKD.
- CKD is often associated with low rates of standard preventive therapies directed towards CVD risk reduction (e.g., adequate control of glucose, blood pressure, and cholesterol). [312] For example, in an analysis of patients with CKD evaluated from 2003–2007, only 50% were taking statins, and 42% who had statins recommended were not taking them. [313] In summary, patients with CKD are often not treated with statins. When treated, patients with CKD rarely achieve LDL-C treatment goals. [314]

### 10.3. Diagnosis and treatment

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

## 11. Genetic abnormalities / familial hypercholesterolemia

### 11.1. Definition and physiology

Among the more common inherited causes of CVD in younger individuals include genetic abnormalities leading to vasculopathies, aneurysmal disorders, cardiomyopathies, and coagulopathies. [190,352] Genetic abnormalities can also lead to CVD risk factors such as diabetes mellitus [353] and hypertension. [354] Other genetic abnormalities leading to CVD includes inherited dysrhythmia syndromes and genetic dyslipidemias. [355]

Within the clinical practice of preventive cardiology, genetic dyslipidemia is the most common treatable cause of inherited premature coronary heart disease. [190] Laboratory diagnosis of inherited dyslipidemias may involve sequencing the entire human genome or custom sequencing of one or more genes. In some countries, it is common for patients with marked elevations in LDL-C levels to undergo genetic evaluation for Familial Hypercholesterolemia (FH) to identify pathogenic variants of the LDL receptor (LDLR, most common), apolipoprotein B (APOB), or proprotein convertase subtilisin/kexin type 9 (PCSK9). [356,357] However, in addition to laboratory genetic testing, the diagnosis of Familial Hypercholesterolemia can also be made clinically. In the US, FH is more commonly assessed via one or more clinical diagnostic criteria for FH such as The American Heart Association, Simon Broome, and/or Dutch Lipid Clinic Network criteria (see Tables 10a–10c). [358–362]

Among patients without FH, an elevated lipoprotein (a) [Lp(a)] level is an independent CVD risk factor [117] and the most common monogenic cause of atherosclerotic CVD. The European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) Guidelines for the Management of Dyslipidemias suggest that Lp(a) measurement should be considered at least once in each adult person's lifetime to identify those with very high inherited Lp(a) levels >180 mg/dL (>430 nmol/L), who may have a lifetime risk of ASCVD equivalent to the risk associated with heterozygous familial hypercholesterolemia. [111] Measurement of Lp(a) is superior to genetic testing for an LPA variant, as current genetic testing for this variant is not a reliable predictor of elevated Lp(a) levels in all ethnic groups. In addition to identification of monogenic disorders, genetic testing may allow for the calculation of a "polygenic risk score" to complement clinical risk scores used to predict ASCVD events. [356,363,364] However, the role of these "polygenic risk scores" in primary and secondary prevention of CVD is still evolving.

### 11.2. Epidemiology

- In the US, heterozygous FH (as defined by the Dutch Lipid Clinic criteria) occurs in approximately 1:250 individuals, [366] with an in-

creased rate among those having Lebanese, South African Afrikaner, South African (Ashkenazi) Jewish, South African Indian, French Canadian, Finland, Tunisia, and Denmark population backgrounds. [367]

- The risk of premature coronary heart disease (CHD) is increased by 20 fold among untreated FH patients [368] and CHD typically occurs before age 55 and 60 among women and men with FH respectively. [362]
- Myocardial infarction occurs about 20 years earlier among those with FH compared to those without FH, [369] and occurs in up to 1 in 7 of patients having acute coronary syndrome < 45 years of age. [370]
- Beyond atherosclerotic CVD, among the more common inherited causes of other forms of CVD among younger individuals include genetic abnormalities leading to vasculopathies, aneurysmal disorders, and coagulopathies. [371]

### 11.3. Diagnosis and treatment

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

## 12. Conclusion

The "ASPC Top Ten CVD Risk Factors 2021 Update" summarizes ten things to know about ten CVD risk factors, accompanied by sentinel references for each section. The ten CVD risk factors include unhealthy nutrition, physical inactivity, dyslipidemia, hyperglycemia, high blood pressure, obesity, considerations of select populations (older age, race/ethnicity, and sex differences), 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 CVD Risk Factors 2021 Update" 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.[6]

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Section authors reviewed and edited their respective sections. Dr. Peter Toth reviewed and edited the entire manuscript. All authors reviewed and approved responses to journal peer reviewer comments. Dr. Harold Bays served as medical writer, coordinated the input of authors, and submitted the manuscript.

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**Table 9**

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

1. An estimated glomerular filtration rate (eGFR) < 60 mg/min/1.73 m<sup>2</sup> increases the risk of death, CVD events, and hospitalizations [303] Among patients with coronary heart disease, an eGFR < 30 mg/min/1.73 m<sup>2</sup> substantially increases the risk of CVD mortality and all-cause mortality. [315] CVD is a leading cause of death among patients with CKD. [299] In patients without CKD (who are often younger), cancer and CVD are the two most common causes of death. Among patients with CKD, CVD is the most common cause of death, with increasing risk of CVD death inversely related to the eGFR. [316]
2. Treatment of CKD often includes management of major CVD risk factors (e.g., diabetes mellitus, HTN, cigarette smoking). [303,317,318]
3. Anti-diabetes mellitus drugs having the most favorable renal effects include SGLT2 inhibitors and GLP-1 receptor agonists. [319] In patients with T2DM, both SGLT2 inhibitors and GLP-1 receptor agonists reduce CVD events.[320] SGLT2 inhibitors may reduce the progression of renal disease by 45% in those with or without CVD. GLP-1 receptor agonists can reduce urinary albumin excretion, slow kidney disease progression, and reduce CV events. [318,321] While both reduce the risk of CVD, compared to GLP-1 receptor agonists, SGLT2 inhibitors have a more marked effect on preventing hospitalization for heart failure and reducing kidney disease progression. [320] With the exception of thiazolidinediones and GLP-1 receptor agonists, virtually all anti-diabetes medication classes have representative drugs that require dosing adjustment, depending upon eGFR.[322] Many anti-diabetes medications are not recommended and/or have lack of data regarding their safety and efficacy in patients with severe renal insufficiency.
4. Adults with CKD and HTN should be treated to a blood pressure goal of < 130/80 mmHg. [161] especially in the presence of proteinuria. [323,324] 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. [325] The benefit:risk ratio of ACE inhibitors and ARBs is unclear in patients with eGFR < 30 mg/min/1.73 m<sup>2</sup>. This helps account for why, as a class, ACE inhibitors and ARBs are more commonly discontinued with eGFR < 30 mg/min/1.73 m<sup>2</sup>, compared to patients with higher eGFR. [326] Having said this, discontinuing ACE inhibitors or ARB's after hospitalization specifically for acute kidney injury may be associated with a higher risk of post discharge mortality. [327,328] In non-dialysis patients with eGFR < 30 mg/min/1.73 m<sup>2</sup>, loop diuretics are preferred over thiazide diuretics. Torsemide generally has more predictable bioavailability compared to furosemide.[329] Dialysis patients with some urine output may benefit from continued loop diuretics.[330] In patients with renal insufficiency, dihydropyridine calcium channel blockers (amlodipine, felodipine, nifedipine, 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. [325] Beta blockers in patients with ESKD may reduce the risk of heart failure, HTN, and cardiac dysrhythmias. [331] Direct vasodilators (hydralazine and minoxidil) are usually one of the last line therapies for HTN and renal failure. [325] Virtually all anti-hypertensive medications classes have representative drugs that require dosing adjustment, depending upon eGFR. [332]
5. Meta-analyses support statin therapy as reducing CVD events in primary prevention among patients with mild to moderate renal insufficiency (not on dialysis); [333] however, the relative risk reduction in major vascular event risk diminishes as eGFR declines.[334–336] Statin therapy may not reduce kidney failure, but may modestly reduce proteinuria and rate of eGFR decline. [337] With the exception of atorvastatin, other statins (as well as many other lipid-altering drugs) require dosing adjustment in patients with CKD. [338] Clinical trial evidence supports ezetimibe plus simvastatin combination as reducing the incidence of major atherosclerotic events in patients with a wide range of patients with advanced CKD. [339] Moderate intensity statin (with or without ezetimibe) is recommended in adults with CKD not on dialysis, who have a 10-year ASCVD risk of 7.5% or higher. [110,340] 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. [341]
6. In addition to increasing the risk of CVD and other adverse health outcomes, cigarette smoking may be an independent risk factor for CKD. [342] 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. [343]
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 ESKD 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. [344]
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 allowed in patients undergoing dialysis) and restricting high fiber fruits and vegetables high in potassium to those lower in potassium. [345,346] Regarding body weight, an obesity paradox is sometimes described in patients with CKD wherein those with increased adiposity have a survival advantage. Potential explanations include (a) CKD due to obesity may progress less aggressively compared to kidney disease due to other causes; (b) patients with CKD related to obesity may have less intense inflammation, circulatory cytokines, and endotoxin-lipoprotein interactions compared to other inflammatory causes of CKD; (c) obesity may allow for increased sequestration of uremic toxins in adipose tissue; (d) patients at lower BMI may be undernourished with protein-muscle-energy wasting; and (e) patients at lower BMI may have worsened hemodynamic stability. [5] However, among patients with CKD, patients with obesity have a higher risk for CKD progression, with or without accompanying metabolic abnormalities. [347] Bariatric surgery in patients with CKD may reduce eGFR decline, reduce incidence of kidney failure, and improve access for possible kidney transplantation.[5,348]
9. Cardiovascular fitness and healthy lifestyle choices are associated with lower risk of incident CKD.[299] As with CVD, routine physical activity reduces the risk of morbidity and mortality in patients with CKD. [349] 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. [350] 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. [350]
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<sup>2</sup>, albuminuria ≥ 300 mg per 24 hours, or rapid decline in eGFR. [351]

**Sentinel Guidelines and References**

2020 Heart Disease and Stroke Statistics – Update: A Report from the American Heart Association [299]

2020 Cardiorenal Protection With the Newer Antidiabetes Agents in Patients with Diabetes and Chronic Kidney Disease: A Statement from the American Heart Association [157]

2019 Clinical Pharmacology of Antihypertensive Therapy for the Treatment of Hypertension in CKD [325]

2019 Chronic Kidney Disease Diagnosis and Management: A Review. [351]

2019 Primary and Secondary Prevention of Cardiovascular Disease in Patients with Chronic Kidney Disease [318]

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**Table 10a**American Heart Association *Clinical Criteria for the Diagnosis of Heterozygous FH* [359]

- Low density lipoprotein cholesterol (LDL-C)  $\geq 190$  mg/dL (5 mmol/L) among adults or LDL-C  $\geq 160$ mg/dL (4 mmol/L) among children

PLUS EITHER

- First degree relative with LDL-C  $\geq 190$  mg/dL

OR

- First degree relative with known premature coronary heart disease (<55 years among men; <60 years among women)

OR

- First degree relative with positive genetic testing for an LDL-C-raising gene defect (LDL receptor, apoB, or PCSK9)

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**Table 10d**

Ten things to know about genetics/familial hypercholesterolemia and cardiovascular disease (CVD) prevention

1. Genetic dyslipidemia is the most common treatable cause of inherited premature atherosclerotic coronary heart disease. [371] Heterozygous Familial Hypercholesterolemia (HeFH) is most commonly an autosomal dominant genetic metabolic disorder resulting in marked elevations of LDL-C levels (i.e., typically  $\geq 190$  mg/dL in adults), a 10 – 17 fold increased risk of atherosclerotic CVD in untreated patients, and an 8 – 14 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 delayed introduction of lipid-altering drugs. [362]
2. In a patient with a FH phenotype, negative DNA genetic testing [to identify pathogenic variants of LDLR (most common), APOB, or PCSK9] does not exclude a diagnosis of FH. [356] It is likely that patients with phenotypic FH who have negative genetic testing for FH may have an unidentified FH mutation. Thus, many clinicians choose to utilize clinical diagnostic criteria based upon AHA, Simon Broome, and/or Dutch Lipid Clinic Network criteria over genetic testing to diagnose FH (Tables a – c). [359,360,362,372]
3. While tendon xanthomas can rarely be associated with increases in non-cholesterol sterol concentration (i.e., sitosterolemia), [373] tendon xanthomas are the physical exam finding most strongly associated with FH, and the physical exam finding most included in FH diagnostic criteria (see Tables 10 b – c). 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 on lifetime exposure to increased LDL-C levels. [374]
4. Cascade (family) screening for FH is recommended in individuals and families with very high LDL-C levels. [375]
5. High intensity statin (atorvastatin 80 mg or 40 mg per day, or rosuvastatin 40 or 20 mg per day) is first-line treatment for patients with FH. [110]
6. Commonly cited lipid goals in patients with HeFH are a LDL-C level of < 100 mg/dL and < 70mg/dL being a goal for HeFH patients having CVD and/or other CVD risk factors placing them at very high risk. [110] Lipoprotein (a) is an additional lipid parameter that should be assessed in patients with HeFH. [118]
7. Largely due to high baseline LDL-C levels and high rate of atherosclerotic CVD, it is common that patients with FH do not achieve their LDL-C treatment goals with maximally tolerated statins alone. These patients may benefit from adding ezetimibe, PCSK 9 inhibitors, bempedoic acid and/or other lipid-altering drugs (e.g., bile acid sequestrants such as colesevelam HCl). [110,121,127,128,369,376,377]
8. The reduction in atherosclerotic CVD risk is not only dependent upon the degree of LDL-C lowering, but also when lipid treatment is implemented. Earlier statin treatment may reduce the lifetime exposure/burden of elevated LDL-C, with the age for onset of coronary heart disease delayed by earlier administration of statin therapy. Statin treatment should strongly be considered in patients with HeFH beginning at 8 – 10 years of age. [362]
9. Lipoprotein apheresis is another treatment option for patients with FH who are unable to achieve LDL-C treatment goals with nutrition, physical activity, and lipid-altering drug therapy alone.[378]
10. Among patients without FH, elevated Lipoprotein (a) [Lp(a)] is the most common monogenic cause of ASCVD, and should be considered at least once in each adult person's lifetime to identify those with very high inherited Lp(a) levels. [111] Measuring Lp(a) is superior to genetic testing for an LPA variant, as current genetic testing for this variant is not a reliable predictor of elevated Lp(a) in all ethnic groups. Genetic testing may allow for the calculation of a "polygenic risk score" to complement clinical risk scores used to predict ASCVD events. The role of these "polygenic risk scores" in primary and secondary prevention of CVD is still evolving. [356,363,364]

**Sentinel Guidelines and References**

2020 Genetic Testing in Dyslipidemia: A Scientific Statement from the National Lipid Association [357]

2018 Clinical Genetic Testing for Familial Hypercholesterolemia: JACC Scientific Expert Panel [356]

2018 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. [110]

2018 Familial hypercholesterolemia treatments: Guidelines and new therapies. [121]

2017 Cascade Screening for Familial Hypercholesterolemia and the Use of Genetic Testing [375]

**Table 10b**

Simon Broome diagnostic criteria for Familial Hypercholesterolemia [360,365]

**Definite Familial Hypercholesterolemia:**

- Adult with total cholesterol levels  $\geq 290$  mg/dL (> 7.5 mmol/L) or LDL-C  $\geq 190$  mg/dL (> 4.9 mmol/L)
- Child < 16 years of age with total cholesterol levels  $\geq 260$  mg/dL (> 6.7 mmol/L) or LDL-C  $\geq 155$  mg/dL (> 4.0 mmol/L)

PLUS EITHER

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

OR

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

**Possible Familial Hypercholesterolemia:**

- Adult with total cholesterol levels  $\geq 290$  mg/dL (>7.5 mmol/L) or LDL-C  $\geq 190$  mg/dL (>4.9 mmol/L)
- Child < 16 years of age with total cholesterol levels  $\geq 260$  mg/dL (>6.7 mmol/L) or LDL-C  $\geq 155$  mg/dL (>4.0 mmol/L)

PLUS 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  $\geq 290$  mg/dL (>7.5 mmol/L) or a child, brother or sister aged < 16 years with total cholesterol  $\geq 260$  mg/dL (> 6.7 mmol/L)

**Table 10c**

Dutch Lipid Clinic Network diagnostic criteria for Familial Hypercholesterolemia [360,362,365]

Criteria	Points
Family history	
First-degree relative with known premature* coronary and vascular 1 disease, OR	
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	
<b>Clinical history</b>	
Patient with premature* coronary artery disease	2
Patient with premature* cerebral or peripheral vascular disease	1
<b>Physical examination</b>	
Tendinous xanthomata	6
Arcus cornealis prior to age 45 years	4
<b>Untreated Cholesterol levels mg/dl (mmol/liter)</b>	
LDL-C $\geq$ 330 mg/dL ( $\geq$ 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
<b>DNA analysis</b>	
Functional mutation in the <i>LDLR</i> , <i>apo B</i> or <i>PCSK9</i> gene	8
<b>Diagnosis (diagnosis is based on the total number of points obtained)</b>	
Definite Familial Hypercholesterolemia	>8
Probable Familial Hypercholesterolemia	6 – 8
Possible Familial Hypercholesterolemia	3 – 5
Unlikely Familial Hypercholesterolemia	<3

\* Premature coronary and vascular disease = < 55 years in men; < 60 years in women LDL-C = low - density lipoprotein cholesterol DNA = Deoxy nucleic acid LDL-R = low - density lipoprotein receptor Apo B = apolipoprotein B PCSK9 = Proprotein convertase subtilisin/kexin type 9

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