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Ten things to know about ten cardiovascular disease risk factors – 2022

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ABSTRACT

The American Society for Preventive Cardiology (ASPC) "Ten things to know about ten cardiovascular disease risk factors – 2022" is a summary document regarding cardiovascular disease (CVD) risk factors. This 2022 update provides summary tables of ten things to know about 10 CVD risk factors and builds upon the foundation of prior annual versions of "Ten things to know about ten cardiovascular disease risk factors" published since 2020. This 2022 version provides the perspective of ASPC members and includes updated sentinel references (i.e., applicable guidelines and select reviews) for each CVD risk factor section. The ten CVD risk factors include unhealthful dietary intake, physical inactivity, dyslipidemia, pre-diabetes/diabetes, high blood pressure, obesity, considerations of select populations (older age, race/ethnicity, and sex differences), thrombosis (with smoking as a potential contributor to thrombosis), kidney dysfunction and genetics/familial hypercholesterolemia. Other CVD risk factors may be relevant, beyond the CVD risk factors discussed here. However, it is the intent of the ASPC "Ten things to know about ten cardiovascular disease risk factors – 2022" to provide a tabular overview of things to know about ten of the most common CVD risk factors applicable to preventive cardiology and provide ready access to applicable guidelines and sentinel reviews.

1. Introduction

The American Society for Preventive Cardiology (ASPC) "Ten things to know about ten cardiovascular disease risk factors – 2022" is intended to help both primary care clinicians and specialists be informed about the latest advances in cardiovascular disease (CVD) prevention. This 2022 update summarizes ten things to know about ten important CVD risk factors, listed in tabular formats, and reflects updates by ASPC Fellowship in Training or Early Career section authors. These CVD risk factors include unhealthful dietary intake, physical inactivity, dyslipidemia, pre-diabetes/diabetes, high blood pressure, obesity, considerations of select populations, sex differences, and race/ethnicity,

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thrombosis (with smoking as a potential contributor to thrombosis), kidney dysfunction, and family history/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 a more detailed discussion of any of these CVD risk factors, this "Ten things to know about ten cardiovascular disease risk factors – 2022" also provides updated guidelines and other selected references in the applicable tables.

Within the individual, not all CVD risk factors share the same etiology. However, factor analyses and clinical experience supports that in many cases, the clustering of the most common metabolic diseases managed by clinicians is due to an underlying "common soil" causality. [1] The obesity epidemic and its adiposopathic consequences are leading contributors to major CVD risk factors such as type 2 diabetes mellitus, hypertension, and dyslipidemia that increase CVD risk, as well as other effects that directly increase CVD risk,[2, 3] Central adiposity is the only physical exam component of the metabolic syndrome.[4] A Scientific Statement from the American Heart Association states:

"Obesity contributes directly to incident cardiovascular risk factors, including dyslipidemia, type 2 diabetes, hypertension, and sleep disorders. Obesity also leads to the development of cardiovascular disease and cardiovascular disease mortality independently of other cardiovascular risk factors. More recent data highlight abdominal obesity, as determined by waist circumference, as a cardiovascular disease risk marker that is independent of body mass index [469]."

In some countries, increased adiposity has overtaken cigarette smoking as the leading cause of preventable death. [5] The two most common causes of non-accidental and non-infectious preventable deaths are CVD and cancer. It is therefore perhaps not surprising that CVD and cancer share similar modifiable risk factors, with cancer being a potential risk factor for CVD.[6] Recognition and examination of "adiposopathy" has emerged in the cancer literature, due to: "the tremendous growing implication of 'sick fat' in the initiation and development of important pathopysiological events in the human body, which result in severe (chronic) diseases and possible early mortality," including an important role in cancer and (cardio)metabolic diseases. [7] Regarding cardiovascular prevention, cardio-oncology is a subspecialty of cardiology originally created to address adverse cardiac effects of cancer treatments. An important component of global care within cardio-oncology is addressing the multiple risk factors shared by CVD and cancer, such as obesity and tobacco use, and other related risk factors. [8]

A focus on both CVD treatment and prevention is not unique to the cardio-oncologist. Many patients with CVD have multiple CVD risk factors, which requires a multifactorial management 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, this version of the "Ten Things to Know About Ten CVD Risk Factors" includes updates and different perspectives from different authors. Interested readers may elect to review prior versions of ASPC "Ten Things to Know About Ten CVD Risk Factors" publications for different perspectives on these same topics, and to see how thinking and priorities may have evolved. [9, 10]

1.1. Unhealthful dietary intake

1.1.1. Definition

Healthful nutrition is a cornerstone of CVD prevention; yet it is often among the most challenging of CVD risk factors to manage. Despite these challenges, even small targeted healthful changes in dietary intake have the potential to improve CV health. [11] The primary components of nutritional screening and medical nutrition therapy for CVD prevention include qualitative composition, energy content, and food consumption timing. A healthful nutrition plan is best crafted utilizing evidenced-based dietary patterns and shared decision-making between clinician and patient. [12] Considerations include social background, cultural applicability, cost, availability, and prioritization of nutritional goals as determined by the patient's health status (Figure 1) and the presence of metabolic diseases and cardiometabolic risk factors (e.g., high blood sugar, high blood pressure, dyslipidemia, and increased body fat). [12] The most healthful dietary strategy incorporates evidence-based nutrition and feeding patterns. [13] Dietary patterns most associated with reduced CVD risk are those that: [6, 7, 8, 9, 10]

- Prioritize:

  - 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:

  - Saturated fat, such as tropical oils, as well as ultra-processed meats preserved by smoking, curing, or salting or addition of chemical preservatives, such as bacon, salami, sausages, hot dogs, or processed deli or luncheon meats, which in addition to containing saturated fats, may also have increased sodium, nitrate, and other components which might account for an increase CVD risk compared to unprocessed red meat [14]
  - 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
  - Sugar-sweetened beverages
  - Alcoholic beverages [15, 16]
  - *Trans* fats

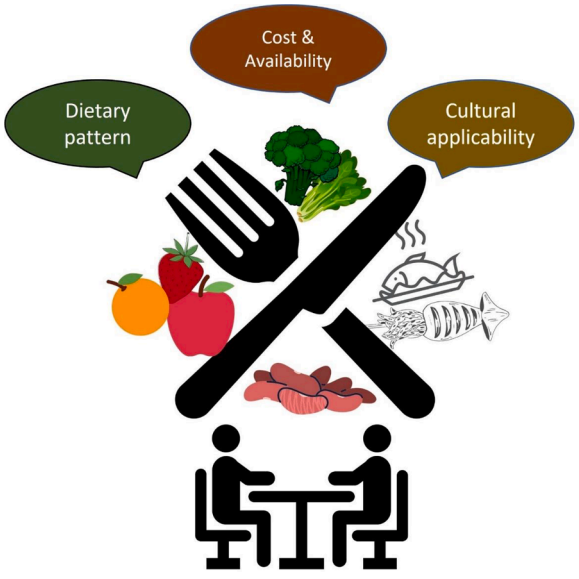

Figure 1. Adoption of healthful nutrition is a shared decision process between clinician and patient, with priorities based upon evidence-based dietary patterns, nutrition goals, cultural applicability, cost, and availability. While potentially counterintuive, patient preference is not consistently associated with improved health outcomes when implemeting medical nutrition therapy [17–19]. Healthful food choices made after medical nutrition therapy may differ from "preferred" food choices made before medical nutrition therapy.

1.1.2. Epidemiology

- From 2015–2018, 17.1% of U.S. adults > 20 years of age were on a "special diet" on a given day. More females were on a special diet than males, and more adults aged 40–59 and > 60 years of age 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.[20]
- Positive caloric balance and increased body fat increase the risk of CVD.[21]Atherosclerotic CVD (ASCVD) is rare among hunter-gatherers populations, whether the nutritional intake is higher or lower in fat, and irrespective of variations in plant vs meat intake. [22, 23, 24] Despite higher levels of physical activity, total energy expenditure among rural hunter-gatherers may be like adults living in European or US cities with high rates of obesity. [23] The reduced rate of CVD among hunter-gatherers may be attributable to lower body fat, with the BMI of hunter-gatherer populations typically being < 20 kg/m^2, [25] which is substantially below the BMI of many industrialized nations where CVD is the #1 cause of death. The reduced potential for adiposopathic consequences 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. [26] In addition to lower BMI, the reduction in CVD risk factors and reduction in CVD events among hunter-gatherer populations 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. [25]

1.1.3. Diagnosis and Treatment

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

1.2. PHYSICAL INACTIVITY

1.2.1. Definition and Physiology

Physical activity is any bodily movement produced by skeletal muscles that requires energy expenditure. [94, 95] 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_2 per kg body weight x minutes. [96] 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 clinical CVD. [97] Sedentary behavior refers to any waking activity with a low level of energy expenditure while sitting or lying down (1-1.5 METS).[98, 99]

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."* [94] 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).[94] Among two individuals of similar size, NEAT can be the single greatest inter-individual difference in daily energy expenditure, with variances of up to 2000 kcal per day; [100] the energy expenditure due to NEAT physical activity often exceeds the daily energy expenditure due to physical exercise.[101] Physical inactivity increases the risk of CVD, [102, 103] not unlike other risk factors such as cigarette smoking and dyslipidemia. [104]

Table 1
Ten things to know about nutrition and cardiovascular disease (CVD) prevention.

1. Medical nutrition therapies most effective in reducing CVD are evidence-based, promote healthful qualitative and quantitative/caloric dietary intake, and conducive to long-term patient adherence [27] (Figure 1).
2. Regarding fats, increased saturated fat dietary 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 [28–31]. With isocaloric intake, CVD risk is reduced when saturated fats are replaced by unsaturated fats [32]. Although banned by the US Food and Drug Administration in 2019, trans fats are sometimes still reportedly found in foods such as cakes, pies, cookies, biscuits, microwavable breakfasts, stick margarine, crackers, microwave popcorn, doughnuts, and frozen pizza, especially when their polyunsaturated fat components are artificially hydrogenated into partially hydrogenated oils. Both saturated fats and trans-fats increase LDL-C levels, with trans-fat consumption most associated with increased CVD risk [32,33].
3. Regarding isocaloric carbohydrate intake, CVD risk is reduced when ultra-processed carbohydrates are replaced by fiber rich complex carbohydrates found in healthful whole foods including whole grains, vegetables, and fruits [32,34]. Ultra-processed carbohydrates promote weight gain and increase the risk of post-prandial hyperglycemia, hyperinsulinemia, hypertriglyceridemia, inflammation, endothelial dysfunction, sympathetic hyperactivity, and hypercoagulability, [35] all CVD risk factors [36,37].
4. The "diets" with the best evidence for CVD prevention are the Mediterranean Diet and "Dietary Approaches to Stop Hypertension" (DASH) [38]. Both dietary patterns prioritize vegetables, fruits, whole grains, fat-free or low-fat dairy products, fish, poultry, lean meats, nuts, seeds, legumes, and fiber.
5. Other evidence-based diets include vegetarian and Ornish diets [38]. 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 [39]. Higher plant protein intake may be associated with small reductions in risk of overall and CVD mortality [40]. While healthful plant-based diet (whole grains, fruits, vegetables, oils, tea, and coffee) may reduce CVD risk, unhealthful plant-based food intake (juices, sweetened beverages, ultra-refined grains, potatoes/fries, and sweets) may increase CVD risk [41]. In addition to genetics and other factors, a dietary intake of unhealthful non-meat, plant-based foods may help account for a relatively high rate of CVD among many vegetarians from India [42]. 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 [43,44].
6. The Ketogenic Diet is a very low carbohydrate diet (e.g., less than 50 grams per day) that discourages unhealthful ultra-processed and refined foods, discourages foods high in glycemic index/load, and discourages foods rich in *trans* fatty acids [27,45]. Ketogenic diets may promote short term weight loss in patients with pre-obesity or obesity, 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 and dietary cholesterol, then LDL-C levels may increase, which may prompt consideration of replacing saturated fats with monounsaturated and/or polyunsaturated fats and reducing dietary cholesterol intake [27,45–49]. If weight loss in a patient with metabolic disease is suspected to have promoted increased cholesterol intestinal absorption, then reducing dietary cholesterol intake and adding a cholesterol absorption inhibitor (e.g., ezetimibe) and a statin might be considered [27,50]. No long-term prospective clinical trial supports the ketogenic diet as reducing CVD. Just as the types of carbohydrates may help determine the effect of low-fat dietary consumption on CVD risk factors, CVD, and mortality, so it is likely the type of consumed fats may help determine the effect of long-term low carbohydrate diet on CVD risk and mortality [51].
7. A common weight reduction strategy in patients with pre-obesity and/or obesity involves portion control and caloric restriction to obtain a daily energy deficit (i.e., 500 – 750 kcal per day) [52]. This can be achieved by either continuous energy restriction or time-mediated caloric restriction (e.g., intermittent fasting, fasting-mimicking diets, and time restricted eating). Intermittent fasting may involve alternate day fasting or fasting 2 days per week (5:2). A fasting-mimicking diet may involve 5 days per week of low-calorie, low carbohydrate, proportionately higher fat nutritional intake [53]. Overall, intermittent fasting may reduce total caloric intake, facilitate weight reduction in patients with pre-obesity or obesity, improve cognitive function and improve CVD-related metabolic parameters (e.g. improve insulin sensitivity, blood pressure, lipids, and inflammatory markers) [53–55]. Weightreduction with intermittent fasting may be achieved while preserving resting metabolic rate and lean body mass, [27,56] especially if accompanied by routine physical activity. 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,

(*continued on next page*)

Table 1 (*continued*)

glucose tolerance, blood pressure, atherogenic lipids, and hepatic steatosis [57–59]. Prioritizing early in the day eating (i.e., breakfast) may promote greater diet-induced thermogenesis and relatively favorable effects on blood glucose and insulin concentrations compared to eating large evening meals. [60,61]. Some clinicians may have concerns that that fewer meals per day is less healthful than multiple small meals per day. However, in an isocaloric setting, greater meal frequency ("grazing" with multiple small meals and frequent snacks) may not afford clinically meaningful weight loss, anthropometric, energy balance, or other health advantages over 3 standard meals per day [62–65]. Conversely, neither intermittent fasting or TRE may promote greater weight loss than continuous energy restriction [66,67].

8. In patients without vitamin deficiency, [54] dietary supplements do not reduce CVD [68–70]. In fact, calcium supplementation may be associated with increased CVD risk [71]. Conversely, vitamin D and calcium intake in the form of healthful whole food consumption (e.g., fruits and vegetables) are associated with reduced risk of CVD [72]. 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 [73,74]. 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 [75–78].
9. Intake of foods rich in omega-3 fatty acids is associated with reduced CVD risk [79] and meta-analyses suggest supplements containing a combination of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) may also reduce CVD events [80,81]. A prospective clinical trial (i.e., Reduction of Cardiovascular Events with Icosapent-Ethyl Intervention Trial or REDUCE-IT) demonstrated reduced major adverse cardiac event with icosapent ethyl (purified EPA) among patients at high CVD risk and baseline hypertriglyceridemia [78]. In contrast to meta-analyses of non-prospective EPA and DHA supplement studies, the prospective, randomized Outcomes Study to Assess STatin Residual Risk Reduction With EpaNova in HiGh CV Risk PatienTs With Hypertriglyceridemia (STRENGTH) trial of a free fatty acid, omega-3 carboxylic acid preparation was stopped early for futility, suggesting that administration of concentrated capsules of EPA and DHA (beyond nutritional intake) does not reduce CVD events in patients with hypertriglyceridemia [82,83]. Thus, the potential CVD benefit of omega-3 fatty acid consumption may depend on baseline CVD risk, statin use, CVD outcomes studied, and the composition of the omega-3 fatty acid [84].
10. While genetics play a role in CVD risk, unhealthful dietary intake, 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 [85]. Barriers exist to healthful eating patterns, such as cost, convenience/preparation time, and family taste preferences. Clinicians should also be aware of challenges in food availability, education regarding healthful food preparation, and limitations of federal food assistance programs, which disproportionately affect low-income individuals [86,87]. Methods to implement healthful nutrition include educating patients regarding evidenced-based meal plans and dietary practice guidelines, [38] and referring patients to a dietitian nutritionist to implement medical nutrition therapy to help manage CVD risk factors and reduce CVD risk [88,89]. Other cost-effective patient advice includes suggesting no-salt fruits and vegetables, legumes (i.e., a low calorie, nutrient dense option associated with decreased all-cause mortality), milk, yogurt, carrot, cabbage, non-sweetened whole grain cereals and low sodium foods – which sometimes even if canned, may be cost effective nutrient dense options [90].

Sentinel Guidelines and References.
2021 Dietary Guidance to Improve Cardiovascular Health: A Scientific Statement From the American Heart Association [91].
2020 Dietary Guidelines for Americans 2020 – 2025 [92].
2019 A Clinician's Guide to Healthy Eating for Cardiovascular Disease Prevention [38].
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 [93].
2018 Clinician's Guide for Trending Cardiovascular Nutrition Controversies: Part II [21].

1.2.2. Epidemiology

- Only 50% of adults get sufficient physical activity to reduce the risk of many chronic diseases such as CVD [105]
- Roughly $117 billion in US healthcare costs yearly and 10% of premature mortality is associated with inadequate physical activity [105]
- Only 26% of US adult males and 19% of adult females obtain guideline-directed activity levels according to federal physical activity monitoring data. [106]
- Worldwide, approximately 3.9 million premature deaths annually might be prevented with adequate physical activity. [107]

1.2.3. 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). [108, 27, 109] Table 2 lists ten things to know about the diagnosis and treatment of physical inactivity and CVD prevention.

1.3. DYSLIPIDEMIA

1.3.1. 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. Increased cholesterol blood levels reflect the presence of increased atherogenic lipoproteins that may become entrapped within the subendothelial space, where they may undergo oxidation and scavenging by arterial macrophages, resulting in endothelial dysfunction, foam cells, fatty streaks, and atherosclerotic plaque formation. [129] 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 non-high density lipoprotein cholesterol (non-HDL-C) are predictors of ASCVD risk and superior to measuring the cholesterol carried by atherogenic lipoproteins low density lipoprotein (LDL-C) in predicting atherosclerotic CVD risk. [130] 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). [131] Because apo B and non-HDL cholesterol better reflect 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. [132, 133] This is especially true when atherogenic lipoprotein particle numbers are discordant with atherogenic lipoprotein cholesterol levels, [131] as may occur with diabetes mellitus or adiposopathic dyslipidemia. [27, 134]

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. While LDL-C can be measured directly, it is often reported as a calculated value according to the Friedewald formula (LDL-C = total cholesterol – HDL-C – triglyceride/5). The Friedewald calculation is less accurate when triglycerides are elevated (i.e., $\geq$ 400 mg/dL) or LDL-C levels are low (i.e., $<$ 70 mg/dL), and in these cases, LDL-C levels may be more accurately calculated using the Martin Hopkins equation. [135]

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, often do not correlate well with one another. [136] Measurement of remnant

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

1. In most cases, 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 [102,103,105].
2. Recommended physical activity for healthy adults includes at least 150 minutes of moderate-intensity physical activity per week, or ≥75 minutes of vigorous-intensity physical activity/week [93,109]. Physical activity above these recommendations may provide additional benefit [108,109]. Evidence supports benefits of muscle strengthening exercises (resistance training) of major muscle groups 2 – 3 times per week [98]. 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 [93]. A separate goal is to reduce sedentary behavior, even if replaced by light activity [27,93]. Mortality risk reduction can be achieved with even short periods of daily exercise [110].
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) [111]. Once a physical activity treatment plan is crafted by the clinician based upon patient history and physical exam, [83] 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) [112].
4. In patients with obesity (BMI ≥ 30 kg/m^2), diabetes mellitus, and well-controlled hypertension, resistance training ≥3 times/week may be beneficial to reduce CVD risk, improve insulin sensitivity, and reduce resting blood pressure [109]. While true it is best for patients to have blood pressure controlled before embarking on a strenuous resistance training program, it is also true that resistance training in patients with prehypertension or medication-controlled hypertension may reduce systolic and diastolic blood pressure [113].
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) [102,108,114]. 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 [27].
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 [103, 115–117].
7. Routine physical activity and exercise may help with weight loss maintenance (and possibly weight reduction itself), with favorable effects on adiposopathic endocrine and immune abnormalities that promote CVD. (See Obesity section) [27,118]. Individuals with decreased physical activity, immobility, and/or use of muscle wasting medications will often have a decrease in muscle mass. Patients with sarcopenia (i.e., often found in older individuals) [119] 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 [27,120,121].
8. Provided the guidance is patient-appropriate, adults ≥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 [106, 108].
9. In addition to physical exercise, non-exercise activity thermogenesis (NEAT) includes physical activities of daily living (e.g., fidgeting, standing, pacing, stair climbing), which often represents the highest percent of daily energy expenditure beyond resting metabolic rate, and may help account for the variation in body weight between individuals having similar caloric intake [27,122]. A common physical activity is walking, which has a dose-dependent, inverse relationship to adverse health outcomes [27]. Less than 5000 steps per day is considered sedentary; ≥10,000 steps per day is considered active [123]. While ≥10,000 steps per day may be optimal, any amount of physical activity above baseline has CVD benefits [124–125]. Brisk walking is a moderate intensity activity that most patients can do towards their recommended 150 minutes/week, and is an activity that confers CVD benefits similar to other types of moderate to vigorous activities [123,124,126]. While some consider walking as a component of NEAT, the Obesity Medicine Association considers steps ≥ 5000 steps per day as a minimum physical activity goal for patients with pre-obesity or obesity, and/or 150 – 300 minutes or more moderate-intensity aerobic activity per week or 75 – 150 minutes or more vigorous intensity aerobic activity per week [27].
10. Physical activity during pregnancy reduces the risk of pre-eclampsia, gestational hypertension, gestational diabetes, excessive gestational weight gain, delivery complications and postpartum depression, all which may be achieved without adverse fetal health outcomes such as stillbirth or adverse effects on birth weight [127]. Unless contraindicated, it is recommended regular physical activity be maintained throughout pregnancy, incorporating a variety of aerobic and muscle-strengthening activities. Those engaged in vigorous intensity aerobic activity or who were physically active before pregnancy can continue these activities during pregnancy and postpartum period, unless as before, clinical circumstances suggest it would be unhealthful to do so. Caveats would be the need to avoid physical activity in excessive heat and humidity, avoid dehydration by routine drinking of water, avoid physical contact, falls, or impaired oxygenation (i.e., high altitudes), avoid activities in supine position after the first trimester, and obtain general clinician education for "danger signs" when to stop or reduce physical activity and/or when to obtain specialist supervision for athletic competition [127].

Sentinel Guidelines and References
2020 World Health Organization Guidelines on Physical Activity and Sedentary Behavior [127]
2020 Top 10 Things to Know about the Second Edition of the Physical Activity Guidelines for Americans [128]
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) [109]
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 [93]
2018 Physical Activity Guidelines Advisory Committee [98]

lipoprotein cholesterol is not included in most major lipid management guidelines.

"Advanced lipid testing" may provide additional information regarding how circulating lipids and lipoproteins may impact ASCVD risk. As with apoB (a measure of atherogenic lipoprotein particle number), an increase in LDL particle number increases the risk for ASCVD. Smaller, more dense LDL particles are also associated with increased ASCVD risk; however, sole reliance on LDL particle size may be misleading, [137] and LDL particle size analyses are not recommended for ASCVD risk estimation. [131, 138, 139]

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" being the level by which if exceeded, may prompt the addition or intensification of lipid-lowering therapy. [31] While some prior lipid guidelines were interpreted as suggesting lipid "goals" were no longer clinically justified, [140, 141, 142], many current inter-societal and international lipid guidelines have reaffirmed goals or thresholds in the management of patients with dyslipidemia. [31, 139] For example, the 2018 ACC/AHA Lipid Guidelines recommend additional lipid-altering therapies when LDL-C ≥ 70 mg/dL for patients at very high ASCVD risk and ≥100 mg/dL for patients at high ASCVD risk). [31] The 2018 ESC/EAS guideline recommends an LDL-C goal of < 70 mg/dL for patients at high ASCVD risk, < 55 mg/dL in patients at very high ASCVD risk, and < 40 mg/dL in patients with second CVD event within 2 years.[139] Patients with Familial Hypercholesterolemia have marked elevations in cholesterol levels and represent a uniquely challenging patient population discussed in Section "10 Familial Hypercholesterolemia." No treatment goals exist for most other lipid parameters, such as high-density lipoprotein cholesterol and lipoprotein (a), with lipoprotein (a) discussed in sections "3 Dyslipidemia," "7 Selected Populations," and Section "10 Familial Hypercholesterolemia."

1.3.2. Epidemiology

According to the US Centers for Disease Control:[143]

- 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 U.S. adults (55%, or 43 million) who could benefit, are taking cholesterol-lowering pharmacotherapy
- The number of U.S. adults age 20 or older who have total cholesterol levels higher than 200 mg/dL is approximately 95 million, with nearly 29 million adult Americans having total cholesterol levels higher than 240 mg/dL

1.3.3. Diagnosis and Treatment

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

1.4. PRE-DIABETES/DIABETES

1.4.1. 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 leading to pre-diabetes or type 2 diabetes mellitus. Among patients with T2DM, the degree of insulin resistance and insulin secretion can substantially vary. [179] Diabetes mellitus can be diagnosed [180] with one of the following measurements:

- Hemoglobin A1c level $\geq$ 6.5%
- Fasting (at least 8 hours) plasma glucose $\geq$ 126 mg/dL on two successive measurements
- Random glucose level of $\geq$ 200 mg/dL in a patient with symptoms of hyperglycemia
- Oral glucose tolerance test (75 grams glucose in water) with 2-hour glucose value $\geq$ 200 mg/dL

Diabetes mellitus contributes to both microvascular disease (e.g., retinopathy, nephropathy, neuropathy) and macrovascular disease (e.g., cardiovascular disease and cardiovascular events). 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. [181] Similarly, hyperinsulinemia may be both the consequence and driver of insulin resistance. [182] Normalizing hyperglycemia and reducing glucotoxicity (without promoting insulin release) is one proposed mechanism how sodium glucose co-transporter 2 inhibitors (SGLT2 inhibitors) may increase peripheral insulin sensitivity. [183] 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). [184]

Females with a prior history of gestational diabetes are at increased risk for the development of T2DM. [185] 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 also doubles the risk for CVD. [186] Diagnosis of gestational diabetes mellitus (GDM) includes a 75-gram 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-hour glucose levels $\geq$ 153 mg/dl. The diagnosis of GDM is also made when during an OGTT,

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

1. LDL-C was the primary lipid treatment target for most ASCVD outcomes trials, and LDL-C is the primary lipid treatment target according to most lipid guidelines [31, 139]. However, compared to LDL-C, apolipoprotein B, non-HDL-C and LDL particle number may be better predictors of ASCVD risk in select populations, such as patients with diabetes mellitus, obesity, hypertriglyceridemia, non-fasting blood samples, and those with very-low LDL-C levels [144–146].
2. A general principle is that patients at the highest ASCVD risk require the most aggressive lipid-management. Ten year ASCVD risk for those 40 – 75 years of age can be assessed by inputting 10 CVD risk factors into the ACC/AHA ASCVD Risk Calculator found at http://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/ (as well as lifetime risk for those 20 – 59 years of age) [31].

Risk Category	10-Year ASCVD Risk
Low Risk	< 5%
Borderline Risk	5 – 7.4%
Intermediate Risk	7.5 – 19.9%
High Risk	$\geq$ 20%

The MESA 10 year risk coronary heart disease (CHD) calculator found at https://www.mesa-nhlbi.org/MESACHDRisk/MesaRiskScore/RiskScore.aspx has among its 12 CVD risk factors coronary artery calcification, race/ethnicity, and family history.

3. Once ASCVD risk is determined, it is generally 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 $\geq$ 50% reduction in LDL-C and achieve an LDL-C $\leq$ 70 mg/dL [31]. In patients at very-high risk, achieving an LDL-C of < 55 mg/dL may also be appropriate, [139,147] 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.
4. Imaging studies are another way to assess clinical ASCVD [93,148]. For example, computerized tomography coronary artery calcium (CAC) assessment can help stratify ASCVD risk and may be useful for patients at intermediate ASCVD risk, [149] when the decision to administer statin therapy is unclear [93]. Patients with CAC scores $\geq$ 400 AU are at high ASCVD risk [4,148,150], 150, 148, 150] Perhaps as importantly, a CAC score of zero suggests a low risk of CVD risk. [4] Patients with a CAC score of $\geq$ 1000 AU represent a phenotype of extreme coronary atherosclerosis with mortality like high CVD risk patients. [4, 151]
5. Lipoprotein (a) is an LDL-like particle conjugated to apolipoprotein (a). Lp(a) is both atherogenic and thrombogenic and is an established CVD risk factor which can help stratify ASCVD risk. Statins, nutritional intervention, and increased physical activity do not lower Lp(a); PCSK9 inhibitors do lower Lp(a). [152, 153] No CVD outcomes trials have yet shown that reducing Lp(a) levels reduces the risk of CVD events. However, Lp(a) levels can be reduced with lipoprotein apheresis and other pharmacotherapies in development (e.g., antisense oligonucleotides and small interfering ribonucleic acids). [154] The ongoing Lp(a) HORIZON cardiovascular outcome study is evaluating pelacarsen (i.e., antisense oligonucleotide targeting the LPA gene messenger RNA) regarding its effects upon major adverse cardiac events. [154, 155, 156] Until therapies that lower Lp(a) are proven to provide health benefits, a single accurate measure of Lp(a) may be sufficient to inform on CVD risk. [157]
6. Statins are the most recommended drug treatment for hypercholesterolemia due to their cholesterol-lowering efficacy, safety, and ASCVD benefits supported by numerous cardiovascular outcomes trials. [93] "High intensity statins" (atorvastatin 40 - 80 mg or rosuvastatin 20 – 40 mg) may lower LDL-C $\geq$ 50%, and are often recommended as first-line therapy in patients with ASCVD or at high risk for ASCVD. [31, 139] The most common clinical manifestation of statin intolerance is statin-associated muscle symptoms (SAMS), which may limit the dose or use of statins. [158, 159] 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. [160, 159, 161] 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. While some evidence exists regarding the objective presence of statin intolerance among some patients, [162] a small randomized crossover trial suggested that 90% of the side effects of a statin were also experience with a placebo. [163]
7. Common non-statin oral lipid-altering drugs include ezetimibe (an intestinal cholesterol absorption inhibitor) [164]and bempedoic acid (an adenosine triphosphate citrate lyase inhibitor that reduces hepatic cholesterol synthesis). [165] Ezetimibe modestly lowers LDL-C levels ~ 18% and provides incremental ASCVD risk reduction beyond statin therapy. [166] Bempedoic acid lowers LDL-C ~ 18%, and when combined with ezetimibe in a fixed dose combination, lowers LDL-C ~ 38%. A CVD outcome study of bempedoic acid in patients with statin intolerance is ongoing. [167, 168]

(continued on next page)

Table 3 (*continued*)

8. PCSK9 inhibitors are injectable agents that lower LDL-C ≥ 50% and reduce ASCVD risk when added to high intensity or maximally tolerated statins. [31, 139] Evolocumab [169] and alirocumab [170] are injectable fully humanized monoclonal antibodies that bind and inhibit PCSK9 and that are administered every 2 – 4 weeks. Inclisiran is an injectable small interfering (or silencing) ribonucleic acid agent that impairs hepatic PCSK9 synthesis and is administered every 6 months (twice a year). [171]Oral PCSK9 formulations are in development.
9. Hypertriglyceridemia (≥ 150 mg/dL) generally increases the risk for ASCVD (i.e., high triglycerides are part of the diagnostic criteria for the metabolic syndrome) [31] and especially increases ASCVD risk if the elevated triglyceride (TG) levels represent an increase in atherogenic triglyceride-rich lipoproteins (e.g., very-low-density lipoproteins, intermediate density lipoproteins, remnant lipoproteins) [172] and their remnants. [136] In Europe, the risk for hypertriglyceride-induced pancreatitis is thought clinically significant at a severely elevated triglyceride level of 10 mmol/L (880 mg/dL).[139] In the US, very high triglyceride levels are typically defined as ≥ 500 mg/dL, [31] and represent levels that may not only increase ASCVD risk, but also increase the risk of hypertriglyceride-induced pancreatitis – sometimes resulting in recurrent bouts of hypertriglyceride-induced pancreatitis. [173, 174]
10. Nutritional, physical activity, and pharmacotherapeutic interventions can reduce triglyceride levels. [175] 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 ASCVD risk having triglyceride levels ≥ 150 mg/dL. [78] 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 ASCVD events in patients with high triglycerides (and low HDL-C levels). [176] A CVD outcome study of a selective peroxisome proliferator-activated receptor alpha modulator (pemafibrate) in patients with diabetes mellitus having hypertriglyceridemia and low HDL-C levels [177, 178] was discontinued in 2022 for futility.

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2021 ACC Expert Consensus Decision Pathway on the Management of ASCVD Risk Reduction in Patients With Persistent Hypertriglyceridemia [175]

2020 Consensus Statement By The American Association Of Clinical Endocrinologists And American College Of Endocrinology On The Management Of Dyslipidemia And Prevention Of Cardiovascular Disease [147]

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 [93]

2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. [139]

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*. [31]

the 1 hour glucose levels is ≥ 180 mg/dL.[187] Other complications of pregnancy that may increase CVD risk include preeclampsia, gestational hypertension, preterm delivery, small for gestational age, large for gestational age, placental abruption, miscarriage, or stillbirths. [188]

1.4.2. Epidemiology

T2DM is associated with double the risk for death and a 10-fold increase in hospitalizations for coronary heart disease. [189] According to the US Centers for Disease Control: [190]

- About 30.3 million US adults have diabetes mellitus; 1 in 4 may be unaware
- About 2% to 10% of yearly pregnancies in the United States are affected by gestational diabetes.
- Diabetes mellitus is the 7th 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

1.4.3. Diagnosis and Treatment

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

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 a hemoglobin A1c < 7% while simultaneously avoiding hypoglycemia and avoiding wide swings in blood glucose. Hemoglobin A1c goals may be higher or lower for individual patients depending on clinical presentation. For example, less stringent A1C goals (e.g., < 8% or higher) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, hypoglycemia unawareness extensive comorbid conditions, or long-standing diabetes in whom the goal is difficult to achieve despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin.
2. Diabetes mellitus is a major risk factor for CVD and increases the risk for CVD events. The presence of diabetes mellitus warrants more aggressive treatment of other common CVD risk factors (e.g., pre-obesity or obesity, high blood pressure, dyslipidemia, cigarette smoking). [191]
3. Patients with diabetes mellitus have more aggressive thresholds for implementing lipid therapy, and potentially more aggressive goals regarding the level of LDL-C achieved. For primary prevention, 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. [31] Patients with diabetes mellitus with ≥ one CVD risk factor are considered as very high CVD risk, and might best benefit from high intensity statins, with an LDL-C goal of < 70 mg/dL. [147, 139] Some "extremely high" CVD risk patients with diabetes mellitus having clinical ASCVD, multiple CVD risk factors, and end-organ damage (e.g., estimated glomerular filtration rate < 30 mL/min) may benefit from an LDL-C goal as low as <55 mg/dL. [147, 139]
4. While some uncertainty exists in the degree by which glucose control alone reduces CVD, clinical trial evidence supports intensive glycemic control as reducting 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. [192]
5. Metformin has favorable effects on CVD risk factors (glucose, insulin, lipids, body weight, and possibly blood pressure). Along with intensive lifestyle modifications through weight management and physical activity, metformin 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. 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, while first line treatment of type 2 diabetes mellitus "generally" includes metformin, [193] other additional or alternative drug treatments include pharmacotherapy 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]. [193] Decisions regarding the most appropriate first line anti-diabetes agent t depends upon comorbidities, patient-centered treatment factors (e.g., cost), glycemic needs, and anticipated health benefits. [193]
6. In patients with T2DM, SGLT2 inhibitors reduce glucose levels and contribute to modest weight loss. [194] 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. [195] In patients with ischemic CVD or heart failure, SGLT2 inhibitors with known CVD benefits should be considered as next line therapy concomitant with comprehensive lifestyle modification and metformin. [93, 193] Also, the management of CVD is often complicated by kidney disease, with kidney disease being a risk factor for CVD [196] In addition to their favorable CVD effects, SGLT2 inhibitors may reduce the progression of kidney disease. [197, 196]
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. [198] Some GLP-1 receptor agonists have clinical trial evidence supporting a reduction in ischemic CVD (e.g., liraglutide, semaglutide, dulaglutide). [199] 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. [93, 193] Tirzepatide (at the time of this writing) is in development for treatment of type 2 diabetes and obesity. Tirzepatide is considered a twincretin, in that it functions as a dual receptor agonist of GLP-1 and glucose-dependent insulinotropic polypeptide (GIP). Included in its development program is the SURPASS CVOT, which is a large phase 3 clinical trial evaluating the cardiovascular outcomes of tirzepatide versus dulaglutide among patients with type 2 diabetes mellitus.[200]
8. Sulfonylureas have neutral effects on CVD; however, sulfonylureas increase body weight and increase the risk of hypoglycemia. Severe hypoglycemia may promote

(*continued on next page*)

Table 4 (*continued*)

cardiac dysrhythmias and increase the risk of sudden death. [201] 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.

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. [202] Dipeptidyl peptidase-4 inhibitors have a neutral effect on body weight and atherosclerotic CVD; saxagliptin may increase the risk of hospitalization for heart failure.
10. Regarding other injectables (beyond GLP-1 receptor agonists), insulin promotes weight gain and increases the risk of hypoglycemia. Some studies suggest that in patients with stable coronary heart disease, insulin use may increase the risk of incident or recurrent major adverse cardiac events, and may also increase the risk of major adverse cardiac events in patients with acute coronary syndrome.[203] That said, the American Diabetes Association Standards of Care suggests that insulin has a neutral effect on atherosclerotic CVD and heart failure. [193]

Sentinel Guidelines and References

2022 Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes [191]
2022 Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes[193]
2021 Cardiorenal Protection With the Newer Antidiabetic Agents in Patients With Diabetes and Chronic Kidney Disease A Scientific Statement From the American Heart Association [204]
2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases. [205]
2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease [93]

1.5. HIGH BLOOD PRESSURE

1.5.1. Definition and Physiology

Hypertension (HTN) can be defined as arterial blood pressure (BP) readings that, when persistently elevated above ranges established by medical organizations, adversely affect patient health. African Americans have a higher prevalence of HTN than White individuals, helping to account for a higher rate myocardial infarction, stroke, chronic and end-stage kidney disease (ESKD), and congestive heart failure among African Americans. [206, 207]

A challenge with diagnosis of HTN is ensuring accurate BP measurement: [208, 209]

- Patients should avoid caffeine, physical exercise, stress, and/or smoking for 30 minutes prior to BP 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 minutes prior to BP measurement.
- BP should be obtained by properly validated and calibrated BP measurement device, with proper cuff size, and taken by trained medical personnel.
- On first measurement date, BP 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 BP measurement should be on the same arm previously recorded as having the highest BP measurement.

1.5.2. Epidemiology

According to the US Centers for Disease Control: [210]

- 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 BP $\geq$ 130 mm Hg or a diastolic BP $\geq$ 80 mm Hg or are taking medication for hypertension.
- Approximately 1 in 4 adults (24%) with HTN have their BP under control.
- At least half of adults (30 million) with BP $\geq$140/90 mm Hg who should be taking medication to control their BP are not prescribed or are not taking medication.

1.5.3. Diagnosis and Treatment

Diagnosing HTN requires accurate assessment and measurement. In a medical office setting, BP should be obtained by properly validated and calibrated BP measurement devices, with proper cuff size, and taken by trained medical personnel. [93, 211] Regarding BP self-monitoring outside of a medical office setting (e.g., home, workplace), validated BP measuring devices can be found at the US BP Validated Listing (VDL™ at https://www.validatebp.org), which is an American Medical Association web-based independent review initiative that determines which BP measuring devices available in the U.S. meet the Validated 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 incorrect positioning. [211]

Ambulatory BP monitoring (ABPM) is often performed out of the office setting via a BP cuff device that records BP readings every 15 – 30 minute intervals, typically for 24 to 48 hours. Because of repeated BP measurements over an extended time, ABPM is superior to a single office BP measurement in the overall assessment of BP, with implications regarding assessment of target organ damage and CVD risk. Some believe ABPM is the gold standard measurement for any patient with high BP. Selected patients who may especially benefit from ABPM include patients with otherwise variable BP readings or patients with suspected "white coat" or "masked" hypertension. [212]

Lowering BP reduces CVD risk, reduces the progression of kidney disease, and reduces overall mortality among a range of patients otherwise at risk for CVD. [213, 214, 215, 213, 214, 216, 217, 208] Table 5 lists ten things to know about the diagnosis and treatment of HTN and CVD prevention.

1.6. PRE-OBESITY AND OBESITY

1.6.1. Definition and Physiology

Overweight is defined as a body mass index (BMI) $\geq$ 25 and $<$ 30 kg/m^2. Obesity is defined as BMI $\geq$ 30 kg/m^2. An increase in BMI is associated with an increase in coronary artery calcium, carotid intimal medial thickness, left ventricular thickness, [236, 237] and increased lifetime CVD risk, [238, 236] all substantially mediated by obesity-promoted CVD risk factors. [239, 27] Obesity can be subcategorized into different classes, based upon BMI: [240]

- Class I (BMI 30-34.9 kg/m^2)
- Class II (BMI 35-39.9 kg/m^2)
- Class III (or "severe;" BMI $\geq$40 kg/m^2)

Overall, BMI is an acceptable criterion to assess adiposity for populations and most patients. BMI is often the first step in evaluating the patient with potential increased body fat. However, among individuals, relying upon BMI alone may be misleading. An increase in BMI among patients with increased muscle mass ("body builders") might erroneously suggest an increase in body fat. Conversely, a "normal" BMI in patients with decreased muscle mass (sarcopenia) might underestimate body fat. [27] Especially in the individual, percent body fat more accurately assesses body fat than BMI.

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 clinical body composition analysis, with other common clinical techniques to measure percent body fat including bioelectrical impedance analysis, air-displacement plethysmography, underwater weighing, and calipers. Other more research-oriented techniques to measure percent body fat include computerized tomography, magnetic resonance imaging, and deuterium dilution hyrometry [241]. Pre-obesity can be

Table 5
Ten things to know about hypertension and cardiovascular disease (CVD) prevention.

1. Self-monitoring ambulatory BP measurements can be useful to confirm the diagnosis of HTN, especially in patients with white coat HTN (elevated BP only in the clinician setting/office) and masked HTN (elevated BP only out of the clinician setting/office). [208, 209] Self-monitoring of BP can also help assess the effectiveness of HTN therapy. [211]
2. The American College of Cardiology / American Heart Association defines HTN as ≥ 130/80 mmHg, with a treatment goal of < 130/80 mmHg. BP lowering medications is recommended for primary prevention in adults with an estimated 10-year atherosclerotic CVD risk of 10% or higher and an average systolic BP 130 mm Hg or higher or an average diastolic BP 80 mm Hg or higher. BP lowering medication is similarly recommended for secondary prevention of recurrent CVD events in patients with clinical CVD and an average systolic BP of 130 mm Hg or higher or an average diastolic BP of 80 mm Hg or higher. [208] The International Society of Hypertension recommends the diagnostic BP threshold for diagnosis of hypertension be an average of ≥ 140/90 mm Hg for office diagnosis of hypertension, ≥ 135/85 mm Hg for daytime ambulatory BP monitoring, and ≥ 130/80 mm Hg for 24-hour ambulatory BP monitoring. After starting anti-hypertensive medication, the blood pressure goals should be less than 140/90 mm Hg within three months, and after three months, less than 130/80 mm Hg in patients younger than 65 years. [218]
3. As long as the reduction in BP does not result in adverse health experiences (i.e., signs, symptoms, or other evidence of hypotension or hypoperfusion), then lower BPs reduce the risk of CVD.[216] Older individuals should be carefully monitored for signs and symptoms of hypotension [e.g., lightheadedness (potentially worsened with orthostatic changes), paleness to the skin with diaphoresis, syncope, blurred vision, impaired cognition, fatigue, nausea, depression, general felling of ill-health, and myocardial ischemic signs and symptoms suggestive of a potential decrease in myocardial perfusion with reduction in diastolic BP < 70 mmHg]. [209]
4. HTN is a risk factor for heart failure, coronary artery disease, stroke, peripheral artery disease chronic renal insufficiency and cardiac dysrhythmias, most commonly being atrial fibrillation. The presence of hypertension warrants more aggressive treatment of concomitant CVD risk factors (e.g., pre-obesity or obesity, diabetes mellitus, dyslipidemia, cigarette smoking). [191]
5. Non-pharmacologic, non-invasive treatment of high BP includes low-sodium diet (<2300 mg of sodium per day), salt substitute (i.e., 75% sodium chloride and 25% potassium chloride), adequate potassium intake, routine physical activity/exercise, and attaining a healthy body weight. [219, 93, 220] Adult males and females with elevated BP or hypertension who consume alcohol should drink no more than 2 and 1 standard drinks per day, respectively. [208] Invasive non-pharmacologic treatments for resistant hypertension may include renal denervation therapy. [221, 222]
6. Initiation of antihypertensive drug therapy with 2 first-line agents of different classes, either as separate agents or in a fixed-dose combination, is recommended for adults with an average BP more than 20/10 mm Hg above their BP target. [208] Specifically, single pill combination antihypertensive therapy is often recommended for initial therapy (i.e., angiotensin-converting enzyme inhibitor/angiotensin-receptor blocker in combination with a calcium channel blocker or thiazide diuretic in the same pill.) [219, 223]
7. Regarding diuretics, chlorthalidone and indapamide are "thiazide-like" diuretics with longer half-lives and achieve a greater BP reduction over 24-hours than the thiazide hydrochlorothiazide. [224] However, recommendations and data supporting chlorthalidone versus hydrochlorothiazide as the preferred thiazide or thiazide-type diuretic varies. [225, 208, 226] Thiazide diuretics are often a first-line therapy for HTN. Loop diuretics (e.g., furosemide, torasemide, bumetanide, and azosemide may be preferred in patients with heart failure (especially torasemide) and when estimated glomerular filtration rate is < 30 ml/min. [208, 227, 228] Steroidal mineralocorticoid receptor antagonists (MRA) such as spironolactone are often characterized as potassium sparing; however, especially in the presence of renal disease, spironolactone may cause hyperkalemia. Nonsteroidal MRA are in development for treatment of hypertension, heart failure, and to reduce the progression of renal disease (i.e., diabetes nephropathy) [229]. Finerenone is a nonsteroidal mineralocorticoid receptor antagonist (MRA) approved to reduce risk of estimated glomerular filter decline, end stage kidney disease, CVD death, non-fatal myocardial infarction, and hospitalization for heart failure in adult patients with chronic kidney disease associated with T2DM. (https://labeling.bayerhealthcare.com/html/products/pi/Kerendia_PI.pdf).
8. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) are first line antihypertensive agents. In addition to lowering BP, ACE inhibitors and ARBs are beneficial in treating heart failure and coronary artery disease. Sacubitril/valsartan is illustrative of a combination agent [combining an angiotensin receptor-neprilysin inhibitor (ARNI) with an angiotensin receptor blocker ACE inhibitors] with potential benefits in treating heart failure. [230] 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. [208, 231]
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 BP and are first line antihypertensive agents. [208] 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 BP lowering may be less than with other anti-hypertensive drug treatments. [232, 233]
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. [234, 235]

Sentinel Guidelines and References

2020 International Society of Hypertension Guideline [218]
2020 Self-Measured Blood Pressure Monitoring at Home: A Joint Policy Statement From the American Heart Association and American Heart Association [211]
2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease [93]
2018 ESC/ESH Guidelines for the management of arterial hypertension [209]
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 [208]

defined as a percent body fat of 30 – 34% for females and 25 – 29% for males, with obesity defined as ≥ 35% body fat for females and ≥ 30% body fat for males [241].

Although percent body fat assessment (via a reliable method) is more accurate than BMI alone in assessing body fat, percent body fat is more diagnostic than prognostic. From a cardio-preventive standpoint, at least since the 1940's, the risk of CVD is known to correlate to android fat. [1] Android fat includes the visceral adipose tissue (VAT) surrounding intra-abdominal body organs plus the abdominal subcutaneous adipose tissue (SAT). [242] Males described as having an "apple" distribution of body fat are at increased risk of CVD compared with females having a "pear" distribution of body fat. [1, 242] Increased waist circumference is the only physical finding criteria of the metabolic syndrome. The metabolic syndrome [243] is an LDL-C-independent clustering of CVD risk factors that include 3 or more of the following:

- Elevated waist circumference [males ≥ 40 inches (102 cm); females ≥ 35 inches (88 cm)]
- Different waist circumference diagnostic criteria may apply to different races or ethnicities (e.g., Asian males ≥ 40cm; Asian females ≥ 80 cm) [244]
- Elevated triglycerides ≥ 150 mg/dL (1.7 mmol/L), or use of medications for high triglycerides
- Reduced HDL-C (males < 40 mg/dL (1.03 mmol/L); females < 50 mg/dL (1.29 mmol/L), or use of medications for low HDL-C
- Elevated blood pressure (≥ 130/85 mm Hg or use of medication for HTN)
- Elevated fasting glucose ≥ 100 mg/dL (5.6 mmol/L) or use of medication for hyperglycemia (i.e., prediabetes or type 2 diabetes mellitus).

But just as with BMI and percent body fat, measuring waist circumference alone has its prognostic limitations. From a CVD perspective, it is the specific collection of visceral adipose tissue that is thought to most reflect the pathogenic state of increased adiposity. Both VAT and SAT can be pathogenic. [242] During positive caloric balance, if SAT is limited in its ability to store energy via adipocyte proliferation and differentiation, then energy overflow may occur with increased circulating fatty acid delivery to body organs, and potentially contributing to fatty muscle and liver (contributing to insulin resistance) and fatty heart. Energy overflow can also increase VAT, as well as epicardial

adipose tissue (EAT), with EAT considered the visceral fat of the heart. [242] Thus, central obesity is a clinical marker of adiposopathy and increased visceral adiposity is a surrogate marker for global fat dysfunction. [121] Assessment of visceral fat requires that it be measured, in ways beyond waist circumference alone. That is because the correlation of waist circumference with visceral adiposity is highly dependent on factors such as sex and ethnicity. [242, 245] Optimally, visceral fat should be < one pound and android fat < 3 pounds (as assessed by DXA for example). Values greater than these are associated with increased risk of cardiometabolic abnormalities such as increased blood glucose, increased blood pressure, and increased blood lipids. [241]

In short, increased body fat can result in "fat mass disease" and "sick fat disease." [246] Examples of the adverse biomechanical aspects of obesity ("fat mass disease") include compromise of cardiac function via pericardial mechanical restraint, impaired left ventricular expansion, impaired left ventricular filling, diastolic heart failure, sleep apnea, and immobility. [27] Additionally, an increase in body fat can also lead to adipocyte and adipose tissue dysfunction ("sick fat"). Adiposopathy is defined as pathogenic disturbance in adipose tissue anatomy and function that is 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. [2, 246, 241] Beyond the indirect increased CVD risk with obesity (e.g., promotion of metabolic diseases such as type 2 diabetes mellitus, hypertension, and dyslipidemia – all major CVD risk factors), [247, 248, 249] obesity may also result in adiposopathic consequences that directly increase CVD risk. [2] 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 through the physical increase in fat mass 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) [27]

1.6.2. *Epidemiology*

According to the US Centers for Disease Control: [250]

- Data from 2015~2016 suggests the prevalence of obesity (body mass index/BMI ≥ 30 kg/m^2) was ~ 40% of United States (US) adults. [250] Projections suggest that most of today's children (~ 60%) will develop obesity at the age of 35 years, and roughly half of the projected prevalence will occur during childhood. [251]
- 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 contribute to metabolic diseases – most being major risk factors for CVD. [2, 27] Some of the most common adiposopathic metabolic consequences of obesity are major CVD risk factors such as type 2 diabetes mellitus (T2DM) and hypertension. [27, 252] Over the past decades, along with the obesity epidemic, the rates of T2DM and hypertension have also dramatically increased. [252]
- 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, [253] and consumption of fast foods. [254]
- The prevalence and severity of obesity in US adults has significantly increased from 1999-2000 through 2017-2018 [250]
- In 2017~2018, the age-adjusted prevalence of obesity (BMI ≥ 30 kg/m^2) was ~ 40% of US adults [250]
- In 2017-2018, non-Hispanic Black adults (49.6%) - especially non-Hispanic Black females (56.9%) - had the highest age-adjusted prevalence of obesity compared with other race and Hispanic-origin groups [250]
- In 2017-2018, the age-adjusted prevalence of severe obesity (BMI ≥ 40 kg/m^2) was 9.2% of US adults [250]
- Complications of obesity include heart disease and stroke
- Other CVD-related complications of obesity include adiposopathic alterations in:[27]
  - 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 myocardioal infarction
  - 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 clinical use is limited to only ~ 1% of eligible patients. [255] Importantly, no current anti-obesity drug has CVD outcomes data to support the use of anti-obesity drugs to reduce CVD events. However, drugs such as GLP-1 receptor agonists have cardiovascular outcome study findings supporting a reduction in CVD among patients with diabetes mellitus, with most study participants having pre-obesity or obesity. [199] Higher doses of some of these same GLP-1 receptor agonists are approved for treatment of obesity (i.e., ligraglutide and semaglutide). Ongoing CVD outcomes trials are ongoing to determine if existing or future anti-obesity drugs will likewise reduce CVD events. [27, 256]

Bariatric surgery continues to evolve as a treatment for obesity. [27] Bariatric surgery not only reduces CVD risk factors (i.e., T2DM, HTN and dyslipidemia [257]), but also reduces the risk of MI, stroke, and all-cause mortality. [258, 259] Similar to anti-obesity drugs, bariatric surgery is performed in less than 1% of appropriate patients for which it is indicated. [260] Among the few medically eligible patients who receive treatment with bariatric surgery, significant disparities exist according to race, income, education level, and insurance type. [261]

1.6.3. *Diagnosis and Treatment*

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

1.7. *CONSIDERATIONS OF SELECTED POPULATIONS (OLDER AGE, RACE/ETHNICITY, SEX DIFFERENCES)*

1.7.1. *Definition and Physiology*

1.7.1.1. 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, genetic predisposition, and degree of frailty. [274] Given the limitation 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. [274, 31] 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.[274] (Chart 1)

Race/Ethnicity

1.7.2. *South Asian persons*

make up over 20% of the world population. South Asian persons can

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. [262, 263, 264] 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, hypertension, dyslipidemia, and thrombosis, as well as other conditions associated with increased CVD risk (e.g., sleep apnea, insulin resistance, polycystic ovary disease, gestational diabetes, non-alcoholic fatty liver disease). [27]
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. [265, 266, 267] Both weight reduction, and weight loss maintenance are often challenging in patients with pre-obesity or obesity. Given obesity is a multifactorial disease, pre-obesity and obesity are best managed utilizing a multifactorial approach including nutrition, physical activity, motivational interviewing, behavior modification, pharmacotherapy, and possibly bariatric surgery. [27, 268]
3. No drug and dose having an indication to treat obesity has yet 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. Semaglutide and liraglutide are indicated as both anti-diabetes and anti-obesity agents (albeit at different doses depending on the intended use), with metabolic benefits beyond weight loss alone. [269, 27] In patients wherein a GLP-1 receptor agonist is being used to treat T2DM, clinical outcomes studies support liraglutide, semaglutide, and dulaglutide as reducing the risk of CVD events. Anti-obesity agents are being evaluated in CVD outcomes trials. [27]
5. Among patients with obesity, CVD, and without T2DM and without congestive cardiomyopathy, initial treatments to consider include semaglutide and liraglutide, utilizing the dose indicated for treatment of obesity. [27]
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. [270] While no anti-obesity medication has yet demonstrated a reduction in CVD when used to treat obesity, when accompanied by weight loss, many anti-obesity drugs reduce CVD risk factors (i.e., semaglutide, liraglutide, naltrexone/bupropion, phentermine/topiramate, and orlistat are not contraindicated in patients with CVD). [27]
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. [27]
9. Little evidence supports the use of phentermine & topiramate combination anti-obesity agent as increasing or decreasing CVD risk among patients with obesity. [271]
10. Phentermine is contraindicated in patients with CVD [27]

Sentinel Guidelines and References
2022 Anti-Obesity Medications and Investigational Agents: An Obesity Medicine Association Clinical Practice Statement [470].
2020 Obesity in Adults: A Clinical Practice Guideline [272]
2015 Pharmacological Management of Obesity: An Endocrine Society Clinical Practice Guideline [273]
2013 AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults [240]

Chart 1
Primary CVD prevention recommendations of statin use and diagnostic testing for adults ≥ 75 years of age: [31]

75 years or older	If LDL-C $_{70}$ – 189 mg/dL, then it may be reasonable to start with a moderate-intensity statin. If patients have demonstrable functional decline, multimorbidity, frailty, or reduced life-expectancy, then it may be reasonable to stop statin therapy in some cases
75 – 80 years	If LDL-C 70 – 189 mg/dL, then it may be reasonable to measure coronary calcium to potentially reclassify those with CAC of zero to a lower ASCVD risk to potentially avoid statin therapy

be defined as those with ethnic roots originating from the Indian subcontinent (e.g., India, Pakistan, Sri Lanka, Nepal, and Bangladesh). [275] That said, persons included in the term "South Asians" 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 Asian persons have a 3- to 5-fold increase in the risk for myocardial infarction and cardiovascular death as compared with other ethnic groups. [276, 277] South Asian persons may be at increased CVD risk, largely due to increased prevalence of metabolic syndrome (even at a lower BMI), insulin 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. [1] (See Chart 2) Those of Asian descent may also have increased risk of thrombosis as evidenced by increased plasminogen activator inhibitor, fibrinogen, lipoprotein (a), and homocysteine. Asian persons may have other factors that increase CVD risk such as impaired cerebrovascular autoregulation and sympathovagal activity, increased arterial stiffness, and endothelial dysfunction, [278, 279]

Having South Asia heritage is considered an ASCVD risk enhancing factor. [31] The "Mediators of Atherosclerosis in South Asians Living in America (MASALA)" evaluated a longitudinal cohort of South Asian persons in the United States. This study showed a disproportionately higher prevalent and incidence of T2DM in South Asian persons compared with other ethnic groups. [280] The same applies to ASCVD. After adjusting for ASCVD risk factors, South Asian persons may have greater coronary artery calcification progression than Chinese, Black males and Latino males but similar change to that of White males. [281]

1.7.3. 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 White 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, (including young African American females), [284] left ventricular hypertrophy, obesity, T2DM, chronic kidney disease (CKD), and elevated lipoprotein (a) levels. [285]

1.7.4. 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

Chart 2
Metrics for cardiovascular disease prevention in South Asian persons* [282, 283]

Metrics: physical exam and biomarkers	Desirable goal
Hemoglobin A1c	< 6%
Waist circumference	Female: < 31 inches (<80cm) Male: < 35 inches (< 90 cm)
Body mass index	< 23 kg/m^2
Lipoprotein (a)	< 100 nmol/L
Total cholesterol	< 160 mg/dL
Low density lipoprotein cholesterol	High risk: < 70 mg/dL Very high risk: <50 mg/dL Extreme risk: < 30 mg/dL
High density lipoprotein cholesterol (HDL-C)	Females: > 50 mg/dL Males: > 40 mg/dL
Triglycerides	< 150 mg/dL
Non-HDL-C	High risk: <100 mg/dL Very high risk: < 80 mg/dL Extreme risk: < 60 mg/dL

* While the listed metrics are considered "desirable," the cardiovascular disease benefits of drug therapy to improve some of these metrics await cardiovascular outcomes trials.

reported as having a lower overall risk of mortality than non-Hispanic Whites and non-Hispanic Black persons (albeit higher risk of mortality than Asian Americans). [286] Nonetheless, CVD is the leading cause of death among Hispanics and the "Hispanic Paradox" may not apply to all Hispanic/Latino subpopulations. [287] Thus, to reduce CVD risk, Hispanic/Latino individuals should undergo diagnosis and treatment of CVD risk factors similar to other ethnicities / races. [288]

1.7.5. 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. [289] In 2018, American Indians / Alaska Natives were 50% more likely to be diagnosed with CVD compared to White individuals, which may be related to a higher prevalence of CVD risk factors such as obesity, diabetes mellitus, HTN, and higher rates of cigarette smoking. [289] Pima (Akimel O'odham or "river people") Indians are a subset of American Indians located in southern Arizona and northern Mexico. Pima Indians are reported to 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).[290] Older literature suggests incident CVD events among Pima Indians may not be as high as predicted. [291] This is, in part, because in some cases compared to White individuals, untreated LDL-C levels may be lower among Pima males older than 30 and in females older than 25 years of age. [290] Despite a potential lower CVD risk compared to White persons, heart disease remains a major cause of mortality among Pima Indians, especially among those with concomitant renal failure.[292]

1.7.6. Females

with CVD risk factors are at increased risk for CVD events, directionally similar to males. CVD is the leading cause of mortality among females.[293] CVD accounts for up to 4 times as many deaths in females compared to breast cancer.[294] Compared to males, females are at higher risk for bleeding after invasive cardiac procedures, and are more predisposed to autoimmune/inflammatory disease, and fibromuscular dysplasia. This may potentially predispose females to myocardial infarction in the absence of atherosclerotic obstructive coronary arteries - especially among younger females. [295] 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. [31] Gestational diabetes and preterm delivery are also recognized as increasing lifetime CVD risk.

1.7.7. Epidemiology

- Due to insufficient data (many CVD outcomes trials excluded older patients), the treatment recommendations for primary CVD risk reduction in individuals $\geq$ 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. [296]
- 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. [296] Conversely, the Multi-Ethnic Study of Atherosclerosis (MESA) 10-year CHD risk tool includes Caucasians/Whites, Chinese, African Americans, and Hispanics individuals 45–85 years of age as data input, along with coronary artery calcification. [297]
- CVD is the leading cause of death for females and males across most racial and ethnic groups in the US, accounting for ~20% of deaths per year. [298]
- 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. [299]
- Compared to Whites , Hispanic/Latino individuals 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 Hispanic/Latino individuals have about half as much heart disease; 29% less high blood pressure; and 45% more high total cholesterol. [300]
- Compared to White 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.[289]
- Heart disease is the leading cause of death for African American and White females in the US. Among American Indian and Alaska Native females, heart disease and cancer cause roughly the same number of deaths each year. [301]
- Age and sex are important risk factors for stroke. One in 5 US females between 55 – 75 years of age will have a stroke in their lifetime. Stroke kills twice as many females as breast cancer. [302] Greater longevity in females helps account for strokes occurring more frequently in females than males; however, females may also have sex-specific stroke risk factors (e.g., exogenous hormones, and pregnancy-related hormone exposures). [303]

1.7.8. Diagnosis and Treatment

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

1.8. THROMBOSIS

1.8.1. 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 (i.e., 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 and potential pulmonary embolism. Plaque rupture and acute thrombus formation obstructing a coronary artery may lead to a myocardial infarction; acute obstruction of a carotid artery may lead to a stroke. [322]

Risk factors for thrombosis include cigarette smoking, older age, atrial fibrillation, prosthetic heart valves, blood clotting disorders, trauma/fractures, physical inactivity (including prolonged bed rest / immobility), obesity, diabetes mellitus, HTN, dyslipidemia, certain drug treatments, [323] pregnancy, and cancer. Due to higher hormonal components, older oral contraceptives were associated with increased risk of thrombotic stroke. But even current combination oral contraceptives may somewhat increase the risk of myocardial infarction and stroke, especially oral contraceptives containing $>$ 50 micrograms of estrogens. [324] Similarly, while the risk is small with currently recommended doses, long-term hormone therapy (i.e., estrogen with or without progestins) may mildly increase the risk of thromboembolism. [325] Anabolic androgenic steroid use for athletic "body building" increases the risk of increase of erythrocytes and hemoglobin concentration, thromboembolism, intracardiac thrombosis, stroke, cardiac dysrhythmias, atherosclerosis, concentric left-ventricular myocardial hypertrophy with impaired diastolic function and sudden cardiac death. [326] The data regarding stroke risk with testosterone replacement therapy in hypogonadal males is inconsistent, and thus the relationship of testosterone replacement therapy to stroke is unclear. [327]

One of the most common preventable contributors to thrombosis is tobacco cigarette smoking, [328]which is a well-known, major contributor to overall CVD morbidity and mortality, not just due to

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 ≥ 75 years of age. CVD treatment decisions for older individuals are best based upon an individualized patient-centered approach.
2. General principles of CVD prevention in older individuals include: (a) the BP goal for the vast majority of older adults is <130 mm Hg, [304], 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 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, hypoglycemia unawareness, limited life expectancy, or long-standing diabetes mellitus in whom more aggressive blood sugar control potentially contributes, or has contributed to an unacceptable risk for 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; [274] (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 from aspirin in many frail individuals over 80 years of age likely exceeds 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.[274, 31]
3. Compared to Whites, many Asian Americans are at increased CVD risk, especially those of South Asian descent. Compared with Whites 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.[305]
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, [93] which may be especially important among African Americans.[306] Guidelines for pharmacologic CVD prevention in African Americans are 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.[285]
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 Hispanic individuals. [288] 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 [307] or may not [308] be influenced by the race/ethnicity of the clinician . Clinician decision making may be influenced by integrating themes regarding race, patient-levels issues, system-level issues, bias and racism, patient values, and communication. [309] On a patient level, practical interventions to potentially improve understanding and adherence to treatment among minorities may include instilling confidence in the minority patient communication abilities, and facilitating the simple asking and answering of clinically applicable questions. [310, 311]
6. Females typically have the same rate of CVD onset 10 years later than males. However, this favorable cardioprotective effect diminishes among females with polycystic ovary syndrome, cigarette smoking and females entering menopause. Females over 60 years of age often have lower rates of controlled HTN and higher prevalence of HTN compared to males. [293] Any cardioprotective effect is mostly lost among females with T2DM. Females with T2DM have a three-fold increased risk of CVD, with a higher risk of heart failure, stroke, claudication, and CVD mortality compared to males with T2DM. [293] While supporting CVD outcome data are more limited than males, statins appear to be equally effective for secondary CVD prevention in females, although females may have a greater likelihood of developing statin-associated diabetes mellitus and myalgias. [293]
7. Chest pain is the most common symptom of acute coronary syndrome among both males and females. However, compared to males, females are more likely to present without chest pain (e.g., weakness, fatigue, nausea, dyspnea, and pain to neck, jaw, and back). [293]
8. Polycystic ovary syndrome (PCOS) often occurs in premenopausal females with pre-obesity or obesity and is clinically characterized by androgen excess (hirsutism), amenorrhea or oligomenorrhea, and infertility. [27] 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.[312] As with other patients at increased CVD risk, females with PCOS should be aggressively treated with healthful nutrition and physical activity. Statin therapy may be indicated in many females with PCOS; however, statins may worsen insulin sensitivity in females with PCOS. [313] Conversely, statin therapy may lower testosterone in females with PCOS, with variable reports regarding effects on menstrual regularity, spontaneous ovulation, hirsutism, or acne. [314, 315] Statin therapy combined with metformin therapy in females 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. [316] Because the degree of possible teratogenic effects of statins were unclear, statins were previously contraindicated in females who are pregnant, or who may become pregnant. [317] In 2021, the Food and Drug Administration requested removal of the strongest warning against using statins during pregnancy, but still advised most pregnant patients stop taking statins. (https://www.fda.gov/drugs/drug-safety-and-availability/fda-requests-removal-strongest-warning-against-using-cholesterol-lowering-statins-during-pregnancy#:~:text=FDA%20is%20requesting%20that%20manufacturersthey%20learn%20they%20are%20pregnant).
9. Regarding menopause, while premenopausal females may have some "protection" against CVD compared to males, this protection gap narrows after menopause. This increased CVD risk is partially because females entering the menopause are mostly older than premenopausal females. Advancing age is also usually associated with an increase in percent body fat. [318] In females 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. [319] Taken together with age-related increase in body fat, females undergoing menopause are at increased risk for insulin resistance, HTN, and dyslipidemia – increasing CVD risk. [320] In some cases, hormone replacement therapy primarily used to treat menopausal symptoms may increase the risk of (thrombotic) CVD among menopausal females. If menopausal hormone therapy is to be used in menopausal females, 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. [293]
10. Obesity, physical inactivity, T2DM, and cigarette smoking may increase the risk of CVD more so in females than in males, indicating the need for aggressive management of multiple CVD risk factors among both females and males. [293]

Sentinel Guidelines and References

2020 The Use of Sex-Specific Factors in the Assessment of Women's Cardiovascular Risk [321, 31]

2020 US Department of Health and Human Services Office of Minority Health. Minority Population Profiles. [289]

2017 Cardiovascular Health in African Americans: A Scientific Statement From the American Heart Association. [285]

2016 Cardiovascular Disease in Women: Clinical Perspectives [293]

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 [288]

thrombosis alone.[329] Tobacco cigarette smoking increases CVD risk via 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. [329] Tobacco and tobacco-related products may also trigger pro-thrombotic processes, such as inflammation, oxidative stress, platelets reactivity, coagulation, and adverse effects upon the vascular endothelium. [328]

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 (i.e., reduced high density lipoprotein and increased LDL-C levels), blood pressure, and insulin resistance.[330]

Regarding primary prevention, it is uncertain if the benefits of aspirin exceed its risks. Guidelines recommend low-dose aspirin in select adults 40 – 70 years of age at high ASCVD risk, but not at increased risk of bleeding. [93] Regarding secondary prevention, 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. As a component of comprehensive cardiovascular secondary prevention, aspirin 81 – 325 mg per day is often beneficial and indicated for patients with history of CVD, stroke, or peripheral artery disease. [331] In addition to aspirin, a second anti-platelet agent may be warranted (i.e., dual antiplatelet therapy or DAPT). Overriding concepts and recommendations for DAPT cited by the "2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease" [332] include:

- Unless contraindicated or otherwise not tolerated, aspirin therapy should be continued indefinitely in patients with coronary artery disease. Lower daily doses of aspirin, including in patients treated with DAPT, are associated with lower bleeding complications and comparable ischemic protection than higher doses of aspirin. The recommended daily dose of aspirin in patients treated with DAPT is 81 mg (range, 75 mg to 100 mg).
- The addition of a P2Y12 inhibitor to aspirin monotherapy, as well as prolongation of DAPT, necessitates a fundamental tradeoff between decreasing ischemic risk and increasing bleeding risk.
- Shorter-duration DAPT can be considered for patients at lower ischemic risk with high bleeding risk; longer-duration DAPT may be reasonable for patients at higher ischemic risk with lower bleeding risk. In most clinical settings, DAPT is recommended for at least 6–12 months after a coronary artery event.

1.8.2. Epidemiology

According to the US Centers for Disease Control: [333, 334, 335, 336, 337]

- 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 Black as for White persons, and Black patients 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 males and 12.0% of females.
- Cigarette smoking has a dose-response relationship with stroke. [338]
- 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. [337]

1.8.3. Diagnosis and Treatment

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

Table 8
Ten things to know about thrombosis and cardiovascular disease (CVD) prevention

1. Regarding the use of aspirin for CVD primary prevention, randomized clinical trials suggest the risks of bleeding outweigh the health benefits. [339, 340, 341, 342, 343, 344, 345, 346, 93] The benefits of aspirin for primary prevention in patients with diabetes mellitus may be counterbalanced by bleeding hazard. [347, 348] Aspirin may be beneficial in primary prevention for select patients at high risk for CVD and who are at low risk for bleeding, but only after a patient-centered evaluation and discussion. [349, 191, 350] 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. [351, 352, 353]
2. The standard of care for managing thrombotic risk in secondary prevention (i.e., preventing recurrent ischemic events after an acute coronary syndrome and to prevent stent thrombosis after percutaneous coronary intervention) includes DAPT. DAPT is typically defined as aspirin plus the use of a P2Y12 receptor inhibitor (e.g., clopidogrel, ticagrelor, or prasugrel). [354]
3. Aspirin is the first antithrombotic drug of choice in secondary prevention after a myocardial infarction and should be continued indefinitely unless contraindicated or adverse experiences occur. [355] 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. [356] 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 [355] (i.e., 81 mg "baby aspirin"). [331]
4. Acutely, aspirin is beneficial in patients with unstable coronary artery disease, acute myocardial infarction, and unstable angina.[357, 358, 359] 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. [360] After calling 9-1-1 for emergency phone help, patients undergoing an acute myocardial infarction are often advised to chew one 325 mg aspirin slowly, preferably within 30 minutes of the onset of symptoms. [361] 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. [361, 362]
5. 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, regardless of stent implantation. After a patient-centered discussion, DAPT for longer than 12 months may be considered if the net potential benefit if thought to outweigh the potential risk (i.e., bleeding). [363] Conversely, shorter duration DAPT may be reasonable for patients at high bleeding risk. [364, 365]
6. The "5 A's" framework (as adapted for other CVD risk factor management, such as counseling for obesity [366]) can help engage patients in a discussion about smoking cessation. The 5 A's include: (a) ***A***sk patients about tobacco use; (b) ***A***dvise smokers to quit tobacco; (c) ***A***ssess a smoker's readiness to quit; (d) ***A***ssist smokers to quit; (e) ***A***rrange follow-up. [366, 367, 368]
7. To reduce the risk of thrombosis, CVD, cancer, and other ill effects of tobacco cigarette smoking, [93] patients who smoke cigarettes may benefit from a Ask, Advise, and Refer (AAR) approach to a behavioral support program. Referral program utilization is enhanced with patient agreement to be contacted (Ask, Advise, and Contact or AAC) for a behavior support appointment, as opposed to simply being referred. [369] 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.
8. Antismoking pharmacotherapy can act synergistically with behavior therapy and enhance the chances the patient will stop cigarette smoking. FDA approved antismoking 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. [370, 371]
9. 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. [372, 330] However, most e-cigarettes contain nicotine, which is highly addictive and likely increases the long-term risk of CVD. Also, some analyses suggest use of e-cigarettes may not be effective regarding success in stopping smoking or to prevent relapse of smoking. [373]
10. 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, females who are pregnant, or adults who do not currently use tobacco products. [335] 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. [335] While

(*continued on next page*)

Table 8 (*continued*)

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. [374] 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. [375, 330]

Sentinel Guidelines and References

2022 Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes [191]
2020 Smoking Cessation. A Report from the Surgeon General [376]
2020 Heart Disease and Stroke Statistics-Update: A Report From the American Heart Association [377]
2018 ACC Expert Consensus Decision Pathway on Tobacco Cessation Treatment [378]
2016: 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease [332]

1.9. KIDNEY DYSFUNCTION

1.9.1. Definition and Physiology

According to the "Kidney Disease: Improving Global Outcomes" (KDIGO) guidelines, [379] chronic kidney disease (CKD) is defined as persistently elevated urine albumin excretion [≥30 mg/g (≥3mg/mmol) creatinine], persistently reduced estimated glomerular filtration rate (eGFR <60 ml/min per 1.73 m^2), or both, for greater than 3 months . [380]

A bidirectional relationship exists between CVD and CKD, with each worsening the status of the other. Both have similar "traditional" risk factors such as hypertension, diabetes mellitus, obesity, and cigarette smoking. Beyond these shared risk factors, CKD remains an independent risk factor for CVD. This is likely due to the CKD-mediated adverse effects on the cardiovascular system, such as worsened endothelial dysfunction, accelerated atherosclerosis,[381] increased inflammation, vascular calcification and other vasculopathies, [382] left ventricular hypertrophy, anemia, abnormal calcium-phosphate metabolism, and increased systemic toxins such as elevated urate levels (i.e., uremia). [383]

Over 2/3rd of patients over 65 years with CKD have concomitant CVD. [384] Both eGFR < 60 mg/min/1.73 m^2 and albuminuria are independent predictors of CVD events and CVD mortality. [385] CVD incidence 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. [386] Specifically, patients with CKD having eGFR 15-60 mg/min/1.73 m^2 have about two to three times higher risk of CVD mortality, compared to patients without CKD. [385, 387] As such, CKD is considered a "risk enhancing factor" that places patients at high risk for CVD. [31]

1.9.2. Epidemiology

According to the US Centers for Disease Control and The Heart Disease and Stroke Statistics 2021 Update from the American Heart Association: [388, 389, 390]

- Generally, more than 1 in 7 (approximately 15% of US adults or 37 million people) are estimated to have CKD. Specifically, the overall prevalence of chronic kidney disease (estimated glomerular filtration rate <60 mL•min−1•1.73 m−2 or albumin-to-creatinine ratio ≥30 mg/g) was 14.8% in 2013–2016.
- As many as 9 in 10 adults with CKD do not know they have CKD.
- About 2 in 5 adults with severe CKD do not know they have CKD.
- CKD is more common in people aged 65 years or older (38%) than in people aged 45–64 years (12%) or 18–44 years (6%).
- CKD is more common in non-Hispanic Black adults (16%) than in non-Hispanic White adults (13%) or non-Hispanic Asian adults (13%).
- About 14% of Hispanic adults have CKD.
- Incidence of end-stage kidney disease in the United States is projected to increase 11% to 18% through 2030.
- 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. [204]
- 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 may be associated with an increased risk of heart failure. The excess risk of heart failure is especially increased African American and Hispanic individuals. [391]
- Creatinine-based estimated glomerular filtration rate (eGFR) and/or albuminuria (either by semi-quantitative dipstick for proteinuria or albumin-to-creatinine ratio) may improve cardiovascular risk classification. [392]
- 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). [393] 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. [394] Even when treated with statins, patients with CKD rarely achieve LDL-C treatment goals. [395]

1.9.3. Diagnosis and Treatment

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

1.10. FAMILY HISTORY, GENETIC ABNORMALITIES, AND FAMILIAL HYPERCHOLESTEROLEMIA

1.10.1. Definition and Physiology

Obtaining a family history of cardiovascular disease helps identify and stratify CVD risk. Beyond atherosclerotic CVD, among the more common inherited causes of other forms of CVD among younger individuals include genetic abnormalities leading to vasculopathies, valvulopathies, aneurysmal disorders, and coagulopathies. [437] Regarding atherosclerosis, underlying genetic disorders may contribute to atherosclerotic CVD. 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. [438]Management of HeFH includes aggressive cholesterol lowering at an early age, usually involving statin therapy. [439]

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 FH to identify pathogenic variants of the LDL receptor (i.e., most common), apolipoprotein B (APOB), or proprotein convertase subtilisin/kexin type 9 (PCSK9). [440, 441] 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–b, 10c). [442, 443, 444, 445, 446]

Among patients without FH, an elevated lipoprotein (a) [Lp(a)] level is an independent CVD risk factor [152] and a prominent monogenic cause of atherosclerotic CVD, with 70 - > 90% of interindividual heterogeneity being genetically determined. [447] The worldwide prevalence of elevated Lp(a) levels is estimated at approximately 20%, is independent of nutrition or physical activity (i.e., elevated Lp(a) levels are often described as > 50 mg/dL or >125 nmol/L), [448] and remains

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^2 increases the risk of death, CVD events, and hospitalizations [381] Among patients with coronary heart disease, an eGFR < 30 mg/min/1.73 m^2 substantially increases the risk of CVD mortality and all-cause mortality. [396]In younger patients without CKD , 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 [377,397].
2. Treatment of CKD often includes management of major CVD risk factors (e.g., diabetes mellitus, HTN, cigarette smoking). [381, 398, 399]
3. Anti-diabetes mellitus drugs having the most favorable renal effects include SGLT2 inhibitors and GLP-1 receptor agonists. [400] In patients with T2DM, both SGLT2 inhibitors and GLP-1 receptor agonists reduce CVD events.[401] 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. [402, 399] 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. Cardiologists are 3 times more likely than endocrinologists to see patients with both type 2 diabetes and cardiovascular disease. Clinicians focused on cardiovascular disease prevention share responsibility with primary care clinicians for recommending SGLT-2 inhibitor and GLP-1 receptor agonists. This may require coordinated and multifaceted interventions engaging clinicians, patients, payers, professional societies, and health systems to incentivize adoption of these medications as part of routine cardiovascular prevention and kidney care. [403, 401] 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.[404] 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, [208] especially in the presence of proteinuria. [405, 406] 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. [407] The benefit:risk ratio of ACE inhibitors and ARBs is unclear in patients with eGFR < 30 mg/min/1.73 m^2. This helps account for why, as a class, ACE inhibitors and ARBs are more commonly discontinued with eGFR < 30 mg/min/1.73 m^2, compared to patients with higher eGFR. [408] 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. [409, 410] In non-dialysis patients with eGFR < 30 mg/min/1.73 m^2, loop diuretics are preferred over thiazide diuretics. Torsemide generally has more predictable bioavailability compared to furosemide.[411] Dialysis patients with some urine output may benefit from continued loop diuretics.[412] In patients with renal insufficiency, dihydropyridine calcium channel blockers (amlodipine, felodipine, nicardipine, nifedipine) may be preferred over non dihydropyridine channel blockers (i.e., verapamil, diltiazem) due to potentially less drug interactions with common medications (e.g., statins) and less potential for atrioventricular conduction delays and heart block when used together with betablockers. [407] Beta blockers in patients with ESKD may reduce the risk of heart failure, HTN, and cardiac dysrhythmias. [413] Direct vasodilators (hydralazine and minoxidil) are usually one of the last line therapies for HTN and renal failure. [407] Virtually all anti-hypertensive medications classes have representative drugs that require dosing adjustment, depending upon eGFR. [414] Future study results will better determine if nonsteroidal mineralocorticoid receptor antagonists (e.g., esaxerenone, apararenone, and KBP-5074) will improve renal outcomes in high-risk individuals. [229, 415] Existing data suggests that finerenone may delay the progression of diabetes nephropathy and reduce cardiovascular morbidity in patients with diabetes nephropathy. [416, 417]
5. Meta-analyses support statin therapy as reducing CVD events in primary prevention among patients with mild to moderate renal insufficiency (not on dialysis); [418] however, the relative risk reduction in major vascular event risk diminishes as eGFR declines.[419, 420, 421] Statin therapy may not reduce kidney failure, but may modestly reduce proteinuria and rate of eGFR decline. [422] With the exception of atorvastatin, other statins (as well as many other lipid-altering drugs) require dosing adjustment in patients with CKD. [423] 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. [424] 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. [425, 31] While no dosing adjustment is needed for patients with mild or moderately impaired renal function, little data exists regarding the use of proprotein subtilisin/kexin 9 inhibitors in patients with severe CKD. [426]
6. In addition to increasing the risk of CVD and other adverse health outcomes, cigarette smoking may be an independent risk factor for CKD. [427] 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. [428]
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. [429]
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 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. [430, 431] 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. [27] However, among patients with CKD, patients with obesity have a higher risk for CKD progression, with or without accompanying metabolic abnormalities. [432] Bariatric surgery in patients with CKD may reduce eGFR decline, reduce incidence of kidney failure, and improve access for possible kidney transplantation.[433, 27]
9. Cardiovascular fitness and healthy lifestyle choices are associated with lower risk of incident CKD.[377] As with CVD, routine physical activity reduces the risk of morbidity and mortality in patients with CKD. [434] 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. [435] 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. [435]
10. Due to the marked increased CVD risk and other complications of CKD, referral to a nephrology specialist should be considered for patients with eGFR < 30 mg/min/1.73 m^2, albuminuria ≥ 300 mg per 24 hours, or rapid decline in eGFR. [436]

Sentinel Guidelines and References
2021 Heart Disease and Stroke Statistics – Update: A Report from the American Heart Association [377, 390]
2020 Cardiorenal Protection With the Newer Antidiabetes Agents in Patients with Diabetes and Chronic Kidney Disease: A Statement from the American Heart Association [204]
2019 Clinical Pharmacology of Antihypertensive Therapy for the Treatment of Hypertension in CKD [407]
2019 Chronic Kidney Disease Diagnosis and Management: A Review. [436]
2019 Primary and Secondary Prevention of Cardiovascular Disease in Patients with Chronic Kidney Disease [399]

Table 10a
American Heart Association *Clinical* Criteria for the Diagnosis of Heterozygous FH [443]

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

PLUS EITHER

- First degree relative with LDL-C ≥190 mg/dL

OR

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

OR

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

Table 10b
Simon Broome diagnostic criteria for Familial Hypercholesterolemia [451, 444]

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

PLUS EITHER
- Tendon xanthomas 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 ≥ 290 mg/dL (>7.5 mmol/L) or LDL-C ≥ 190 mg/dL (>4.9 mmol/L)
- Child < 16 years of age with total cholesterol levels ≥ 260 mg/dL (>6.7 mmol/L) or LDL-C ≥ 155 mg/dL (>4.0 mmol/L)

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

Table 10c
Dutch Lipid Clinic Network diagnostic criteria for Familial Hypercholesterolemia [451, 446, 444, 446]

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

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

stable over a patient's lifetime. [152, 447] 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. [139] Table 3 summarizes current therapeutic considerations for elevated Lp (a) levels.

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. [449, 450, 440] However, the role of these "*polygenic risk scores*" in primary and secondary prevention of CVD is still evolving.

1.10.2. Epidemiology

- The worldwide prevalence of FH is estimated as 1:313 among subjects in the general population, 10-fold higher among those with ischemic heart disease (IHD), 20-fold higher among those with premature IHD, and 23-fold higher among those with severe hypercholesterolemia. [452]
- In the US, heterozygous FH (as defined by the Dutch Lipid Clinic criteria) occurs in approximately 1:250 individuals, [453] with an increased rate among those having Lebanese, South African Afrikaner, South African (Ashkenazi) Jewish, South African Indian, French Canadian, Finland, Tunisia, and Denmark population backgrounds. [454]
- The risk of premature coronary heart disease (CHD) is increased by 20 fold among untreated FH patients [455] and CHD typically occurs before age 55 and 60 among females and males with FH respectively. [446]
- Myocardial infarction occurs about 20 years earlier among those with FH compared to those without FH,[456] and occurs in up to 1 in 7 of patients having acute coronary syndrome < 45 years of age. [457]

1.10.3. Diagnosis and Treatment

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

1.10.4. Conclusion

The American Society of Preventive Cardiology (ASPC) "Ten things to know about ten cardiovascular disease risk factors – 2022" summarizes ten things to know about ten CVD risk factors, accompanied by sentinel references for each section. The ten CVD risk factors include unhealthful dietary intake, physical inactivity, dyslipidemia, prediabetes/diabetes, high blood pressure, obesity, considerations of select populations (older age, race/ethnicity, and sex differences), thrombosis (with smoking as a potential contributor to thrombosis), kidney dysfunction and family history/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 "Ten things to know about ten cardiovascular disease risk factors – 2022" 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 clinicians.[93]

TABLE 10d
Ten things to know about family history/genetics/familial hypercholesterolemia and cardiovascular disease (CVD) prevention

1. Genetic dyslipidemia is the most common treatable cause of inherited premature atherosclerotic coronary heart disease. [437] Heterozygous Familial Hypercholesterolemia (HeFH) is most commonly an autosomal dominant genetic metabolic disorder resulting in marked elevations of LDL-C levels (i.e., typically ≥ 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. [446]
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. [440] 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). [458, 443, 444, 446]
3. While tendon xanthomas can rarely be associated with increases in non-cholesterol sterol concentration (i.e., sitosterolemia), [459] tendon xanthomas are the physical exam finding most strongly associated with FH, and a sentinel physical exam finding 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. [460]
4. Cascade (family) screening for FH is recommended in individuals and families with very high LDL-C levels. [461]
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. [31]
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. [31] Lipoprotein (a) is an additional lipid parameter that is often assessed in patients with HeFH. [153]
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). [31, 462, 439, 456, 167, 168, 463]
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. [446]
9. Drug treatment options for patients with homozygous FH include statins, PCSK9 monoclonal antibodies, angiopoietin-like 3 monoclonal antibodies,[464, 465] and lomitapide, as well as potentially inclisiran.[466], ezetimibe, bempedoic acid, and bile acid sequestrants. [467] 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.[468]
10. Among patients without FH, elevated Lipoprotein (a) [Lp(a)] is a prominent 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. [139, 447] 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. [449, 450, 440]

Sentinel Guidelines and References
2020 Genetic Testing in Dyslipidemia: A Scientific Statement from the National Lipid Association [441]
2018 Clinical Genetic Testing for Familial Hypercholesterolemia: JACC Scientific Expert Panel [440]
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. [31]
2018 Familial hypercholesterolemia treatments: Guidelines and new therapies. [439]
2017 Cascade Screening for Familial Hypercholesterolemia and the Use of Genetic Testing [461]

Transparency

This manuscript was edited and updated from "Ten Things to Know About Ten Cardiovascular Disease Risk Factors – 2021." [10] Beginning in 2020, the American Society of Preventive Cardiology has published this "Ten Things to Know About Ten Cardiovascular Disease Risk Factors" via yearly updates from invited authors.

Author Contributions

HEB served as the medical writer and editor for all sections. The following authors primarily updated the following sections: PS (Nutrition), AI (Physical Inactivity), RD (Dyslipidemia), AT (Pre-diabetes/diabetes), MAR (High Blood Pressure), AM (Obesity), AT & YAS (Special Populations), CG (Thrombosis with smoking as a potential contributor to thrombosis), AN (Kidney Dysfunction), AK & SS (Family history/genetics/familial Hypercholesrerolemia), PPT reviewed and/or commented on all sections.

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Evidence

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Ethics Review

This review submission was not a report of an original investigation of human test subjects or volunteers and therefore did not require review by an Institutional Review Board.

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