Primary Prevention of ASCVD and T2DM in Patients at Metabolic Risk: An Endocrine Society* Clinical Practice Guideline

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Objective: To develop clinical practice guidelines for the primary prevention of atherosclerotic cardiovascular disease (ASCVD) and type 2 diabetes mellitus (T2DM) in individuals at metabolic risk for developing these conditions.

Conclusions: Health care providers should incorporate regular screening and identification of individuals at metabolic risk (at higher risk for ASCVD and T2DM) with measurement of blood pressure, waist circumference, fasting lipid profile, and blood glucose. Individuals identified at metabolic risk should undergo 10-year global risk assessment for ASCVD or coronary heart disease to determine targets of therapy for reduction of apolipoprotein B–containing lipoproteins. Hypertension should be treated to targets outlined in this guideline. Individuals with prediabetes should be tested at least annually for progression to diabetes and referred to intensive diet and physical activity behavioral counseling programs. For the primary prevention of ASCVD and T2DM, the Writing Committee recommends lifestyle management be the first priority. Behavioral programs should include a heart-healthy dietary pattern and sodium restriction, as well as an active lifestyle with daily walking, limited sedentary time, and a structured program of physical activity, if appropriate. Individuals with excess weight should aim for loss of ≥5% of initial body weight in the first year. Behavior changes should be supported by a comprehensive program led by trained interventionists and reinforced by primary care providers. Pharmacological and medical therapy can be used in addition to lifestyle modification when recommended goals are not achieved. (***J Clin Endocrinol Metab*** **104: 3939–3985, 2019)**

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Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack; ARB, angiotensin II receptor blocker; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; DASH, Dietary Approaches to Stop Hypertension; DM, diabetes mellitus; DPP, Diabetes Prevention Program; DREAM, Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication; EVOO, extra virgin olive oil; FPG, fasting plasma glucose; HDL, high-density lipoprotein; HDL-C, HDL cholesterol; HOPE 3, Heart Outcomes Prevention Evaluation-3; hsCRP, high-sensitivity C-reactive protein; IDF, International Diabetes Federation; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IRS, insulin resistance syndrome; LDL, low density lipoprotein; LDL-C, LDL cholesterol; MI, myocardial infarction; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III; NHLBI, National Heart, Lung and Blood Institute; OGTT, oral glucose tolerance test; PREDIMED, Prevention With Mediterranean Diet; PROCAM, Prospective Cardiovascular Münster; RCT, randomized control trial; RR, relative risk; SPRINT, Systolic Blood Pressure Intervention Trial; T2DM, type 2 diabetes mellitus; TGL, triglyceride; USDA, United States Department of Agriculture; VFA, visceral fat area; VLDL, very low-density lipoprotein.

List of Recommendations

Definitions and diagnosis

1.1 In individuals aged 40 to 75 years in the office setting, we suggest providers screen for all five components of metabolic risk at the clinical visit. The finding of at least three components should specifically alert the clinician to a patient at metabolic risk (at higher risk for atherosclerotic cardiovascular disease and type 2 diabetes mellitus). (2⊕○○○).

Technical remark: The main components of metabolic risk as defined in this guideline are (i) elevated blood pressure, (ii) increased waist circumference, (iii) elevated fasting triglycerides, (iv) low high-density lipoprotein cholesterol, and (v) elevated glycemia. Elevated glycemia should be determined either by HbA1c, fasting glucose, or 2-hour glucose with a second test for confirmation using a new blood sample. Testing for additional biological markers (*e.g.,* high-sensitivity C-reactive protein) associated with metabolic risk should be limited to subpopulations. This recommendation is specifically for adults aged 40 to 75 years, those for whom the interventions have the greatest impact and evidence for efficacy. This does not restrict screening for appropriate individuals outside of this age range, especially those who are younger.

1.2 In individuals aged 40 to 75 years in the office setting who do not yet have atherosclerotic cardiovascular disease or type 2 diabetes mellitus and already have at least one risk factor, we advise screening every 3 years for all five components of metabolic risk as part of the routine clinical examination. (Ungraded Good Practice Statement)

1.3 To establish metabolic risk in the general population, we recommend that clinicians measure waist circumference as a routine part of the clinical examination. (1|⊕⊕⊕○)

Technical remark: This measurement does not replace the routine measurement of weight or calculation of body mass index but can provide more focused information regarding risk for atherosclerotic cardiovascular disease and type 2 diabetes mellitus. The Writing Committee agrees that the cutoffs for elevated waist circumference should be ≥102 cm for men and ≥88 cm for women in white, African, Hispanic, and Native American populations. The Writing Committee agrees that the cutoffs for waist circumference in Asian populations (both East Asian and South Asian) should be ≥90 cm for men and ≥80 cm for women.

1.4 In individuals previously diagnosed with prediabetes, we suggest testing at least annually for the presence of overt type 2 diabetes mellitus. (2|⊕⊕⊕○)

Technical remark: Prediabetes is defined in a variety of ways (fasting plasma glucose, 2-hour plasma glucose following a 75-g oral glucose tolerance test, or HbA1c) by different organizations in different countries, and the Writing Committee does not endorse preferential use of one definition over another.

1.5 We recommend that all individuals at metabolic risk in the office setting have their blood pressure measured annually and, if elevated, at each subsequent visit. (1|⊕⊕⊕⊕)

Technical remark: Blood pressure should be measured after 5 minutes of rest. Ambulatory and/or home blood pressure monitoring, when performed correctly, is recommended to confirm a diagnosis of hypertension after initial screening.

1.6 For individuals with elevated blood pressure >130 mm Hg systolic and/or >80 mm Hg diastolic who are not documented as having a history of hypertension, we recommend confirmation of elevated blood pressure on a separate day within a few weeks or with a home blood pressure monitor. (1|⊕⊕⊕⊕)

Lifestyle and behavioral therapy

2.1 In individuals at metabolic risk, we recommend that lifestyle modification be first-line therapy. (1|⊕⊕⊕⊕)

Technical remark: The Writing Committee believes that primary care providers, endocrinologists, geriatricians, and cardiologists should initiate discussions about the importance of adopting a healthy lifestyle with all individuals at metabolic risk. These and other relevant providers should encourage individuals to join comprehensive programs led by trained health professionals that support the adoption of healthy lifestyles, including diet and physical activity, aiming for moderate but sustained weight loss.

2.2 For individuals at metabolic risk with excess weight (defined by body mass index and/or waist circumference), we recommend that comprehensive programs to support the adoption of a healthy lifestyle should aim to achieve a weight loss of ≥5% of initial body weight during the first year. (1|⊕⊕⊕⊕)

Technical remark: Maintenance of weight loss by adoption of sustainable healthy behaviors should be encouraged with continuing support of primary providers and/or extended programs.

2.3 In individuals at metabolic risk, we recommend prescribing a cardiovascular-healthy diet. (1|⊕⊕⊕◯)
Technical remark: Providers can offer dietary recommendations based on common components of healthy cardiovascular dietary patterns to all individuals at metabolic risk. Specific dietary changes according to individual risk profiles could be supported with the help of a nutrition specialist in addition to the primary care provider.

2.4 In individuals at metabolic risk, we recommend prescribing daily physical activity, such as brisk walking, and reduction in sedentary time. (1|⊕⊕⊕◯)
Technical remark: Providers should encourage all individuals at metabolic risk to adopt an active lifestyle by walking and reducing the amount of time in sedentary activities. Structured activity programs may be added with the help of an exercise specialist for appropriate individuals.

Medical and pharmacological therapy

Risk assessment and evaluation

3.1 In individuals identified as having metabolic risk, we recommend global assessment of 10-year risk for either coronary heart disease or atherosclerotic cardiovascular disease to guide the use of medical or pharmacological therapy. (1|⊕⊕⊕◯)
Technical remark: Global risk assessment includes the use of one of the established cardiovascular risk equations. Elevated low-density lipoprotein is indicative of cardiovascular risk.

3.2 In individuals with low-density lipoprotein cholesterol ≥190 mg/dL (4.9 mmol/L) or triglycerides ≥500 mg/dL (<5.6 mmol/L), we recommend that, before considering the diagnosis of primary hyperlipidemia, practitioners should rule out secondary causes of hyperlipidemia. If a secondary cause can be excluded, primary hyperlipidemia should be suspected. (1|⊕⊕⊕◯)
Technical remark: Examples of secondary causes of hyperlipidemia include untreated hypothyroidism, nephrotic syndrome, renal failure, cholestasis, acute pancreatitis, pregnancy, polycystic ovarian disease, excess alcohol use, treatment with estrogens/oral contraceptives, antipsychotic agents, glucocorticoids, cyclosporine, protease inhibitors, retinoids, and beta blockers.

Cholesterol reduction

3.3 In individuals 40 to 75 years of age with low-density lipoprotein cholesterol ≥190 mg/dL (≥5.9 mmol/L), we recommend high-intensity statin therapy to achieve a low-density lipoprotein cholesterol reduction of ≥50%. (1|⊕⊕⊕◯)

3.4 In individuals 40 to 75 years of age with low-density lipoprotein cholesterol 70 to 189 mg/dL (1.8 to 4.9 mmol/L), we recommend a 10-year risk for atherosclerotic cardiovascular disease should be calculated. (1|⊕⊕⊕◯)

3.4.1 In individuals 40 to 75 years of age without diabetes and a 10-year risk ≥7.5%, we recommend high-intensity statin therapy either to achieve a low-density lipoprotein cholesterol goal <100 mg/dL (<2.6 mmol/L) or a low-density lipoprotein cholesterol reduction of ≥50%. (1|⊕⊕⊕◯)

3.4.2 In individuals 40 to 75 years of age without diabetes and a 10-year risk of 5% to 7.5%, we recommend moderate statin therapy as an option after consideration of risk reduction, adverse events, drug interactions, and individual preferences, to achieve either a low-density lipoprotein cholesterol goal <130 mg/dL (<3.4 mmol/L) or a low-density lipoprotein cholesterol reduction of 30% to 50%. (1|⊕⊕⊕◯)

3.4.3 In individuals with metabolic risk, without diabetes, on statin therapy, we suggest monitoring glycemia at least annually to detect new-onset diabetes mellitus. (2|⊕⊕⊕◯)

3.4.4 In individuals aged >75 years without diabetes and a 10-year risk ≥7.5%, we recommend discussing the benefits of statin therapy with the patient based on expected benefits vs possible risks/side effects. (1|⊕⊕⊕◯)

Technical remark: Decisions should be made on a case-by-case basis depending on estimates of likely benefits vs risks in individual patients. Statin therapy should be calibrated to reach the recommended low-density lipoprotein targets.

3.5 In individuals at metabolic risk who are taking statins with adequate low-density lipoprotein cholesterol reduction, elevated triglyceride levels [≥200 mg/dL (2.3 mmol/L)], and reduced high-density lipoprotein levels [≤50 mg/dL (1.3 mmol/L) in females, or ≤40 mg/dL (1.0 mmol/L) in males], we suggest considering fenofibrate adjunct therapy. (2|⊕⊕⊕◯)

Technical remark: Avoid gemfibrozil in this situation.

3.6 In individuals ≥40 years of age at metabolic risk with low-density lipoprotein cholesterol at target, an estimated 10-year atherosclerotic cardiovascular disease risk of >7.5%, and without clinical atherosclerotic cardiovascular disease or other atherosclerotic cardiovascular disease risk factors, we suggest treatment with a moderate-intensity statin. (2|⊕⊕⊕◯)

Blood pressure reduction

3.7 In individuals with blood pressure >130/80 mm Hg and a 10-year cardiovascular risk ≤10%, we suggest lifestyle management to lower blood pressure to <130/80 mm Hg and to reduce the risk for atherosclerotic cardiovascular disease. (2|⊕⊕⊕◯)

Technical remark: Because the 10-year risk is ≤10%, lifestyle intervention is appropriate and preferable to use of medications. Interventions include weight loss, healthy diet, sodium restriction, enhanced potassium intake, increased physical activity, and moderation of alcohol use.

3.8 In individuals without a history of atherosclerotic cardiovascular disease with metabolic risk who have a 10-year cardiovascular risk of >10% and blood pressure of >130/80 mm Hg, we suggest the use of blood pressure–lowering medication in addition to lifestyle modifications for primary prevention of atherosclerotic cardiovascular disease only when lifestyle modification alone has failed. (2|⊕⊕⊕◯)

Reducing progression to type 2 diabetes

3.9 In individuals with prediabetes, we recommend prescribing lifestyle modification before drug therapy to reduce plasma glucose levels. (1|⊕⊕⊕⊕)

3.10 In individuals with prediabetes who have limitations to physical activity or are not responding to lifestyle modifications, we recommend metformin as a first pharmacologic approach to reduce plasma glucose levels. (1|⊕⊕⊕◯)

Introduction

Importance of this topic and scope of guideline

The dramatic increase in the prevalence of individuals at risk for the development of atherosclerotic cardiovascular disease (ASCVD) and type 2 diabetes mellitus (T2DM) throughout the developed and developing world requires that physicians and other care providers are aware of the risk factors for these conditions and can identify individuals at risk to initiate treatment to prevent these diseases. The Endocrine Society has recognized the importance of identifying individuals who are at metabolic risk so that efforts can be instituted to prevent both ASCVD and T2DM.

Several risk factors for ASCVD and T2DM—hypertension, lipid abnormalities, hyperglycemia, and abdominal adiposity—tend to cluster together. This clustering was originally known as the insulin resistance syndrome (IRS) because it was thought that insulin resistance was its underlying cause. However, although insulin resistance may be associated with these risk factors, it may not always be present and does not fully explain the syndrome. The term IRS has been replaced by combinations of clinical criteria that are defined differently by various organizations and attempt to describe a clinical entity, the metabolic syndrome. The major purpose was to use clinical signs and symptoms to identify people who have a combination of risk factors that contribute to a higher long-term risk for ASCVD and T2DM than that in the general population.

This guideline addresses the population of individuals with components of the metabolic syndrome who do not yet have diagnosed ASCVD or T2DM and the steps that can be taken to prevent these two diseases. Physicians can screen for the key risk factors for ASCVD and T2DM at routine clinical visits when they obtain a patient's history and perform physical examinations.

This guideline also focuses on behavioral, nutritional, and medical management. Although surgical procedures have been found to be useful treatments for obesity, prediabetes, and T2DM (1–3), and are promising for prevention in observational studies, the Writing Committee did not discuss such interventions because more specific data on long-term prevention are needed and decisions on interventions and specific procedures are outside the scope of this document.

Summary of changes since the 2008 guideline

The differences between the 2008 guideline on this topic and this guideline are as follows:

1. This guideline is focused on measures to identify and reduce the risk of ASCVD and T2DM, rather than defining the metabolic syndrome as a clinical entity.
2. This guideline is more focused on adults between 40 and 75 years of age, for whom a higher quality of evidence exists than for other age groups, thus accruing the greatest impact.

3. HbA1c measurement is included as a measure of glycemia in the definition of metabolic risk.
4. For individuals with prediabetes, the recommended screening frequency for diabetes is increased to at least yearly.
5. Prediabetes is described more broadly and in a variety of ways to include definitions from different organizations in different countries.
6. Goals of therapy for elevated cholesterol are expressed both as absolute values and percentage reductions.
7. The American Heart Association (AHA)/American College of Cardiology (ACC) Pooled Cohort Equation was not available when the previous guideline was published. It is now included as a recommended means of calculating 10-year ASCVD risk.
8. The definitions of high (>7.5%) and moderate (5% to 7.5%) 10-year ASCVD risk as calculated with risk scoring have changed since the prior guideline, with correspondingly more intensive use of lipid-lowering agents. The previous guidelines defined moderate risk as <10% 10-year ASCVD risk.
9. Lower blood pressure (BP) levels are identified as targets of therapy to reduce ASCVD. The target of 140/90 mm Hg has been lowered to 130/80 mm Hg in accordance with more recent data from the Heart Outcomes Prevention Evaluation-3 (HOPE 3), Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication (DREAM), and Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack (ALLHAT) trials.
10. The recommendation for treatment with aspirin in this population has been eliminated due to a lack of sufficient evidence for its benefit. Subsequent data and a systematic review identified a relative risk (RR) reduction in nonfatal myocardial infarction (MI) but not in cardiovascular or all-cause mortality. The effects were modest and could be potentially outweighed by the risk of bleeding and other complications (4).
11. Dietary and exercise recommendations have been updated to correspond with more recent research data.

Systematic Review and Meta-Analyses

The Writing Committee commissioned the conduct of multiple systematic reviews to assess the effects of pharmacological interventions on preventing or delaying the onset of T2DM. The inclusion criteria focused on randomized controlled trials (RCTs) that evaluated a discrete list of medications suspected to affect the incidence of T2DM [diabetes medications, angiotensin II receptor blockers (ARBs), angiotensin-converting enzyme inhibitors, and statins]. The population of interest was individuals with metabolic risk factors but no known diabetes. Random-effects models were used for meta-analysis. A comprehensive search of several databases (from each database's earliest inclusive dates to 24 August 2017, in humans, in adults, and in any language) was conducted. The databases included MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Scopus. The search strategy was designed and conducted by an experienced librarian with input from the guideline methodologist. Controlled vocabulary supplemented with keywords was used to search for drug therapy for diabetes prevention, as well as to limit the search to RCTs and meta-analyses.

The results showed that metformin, α-glucosidase inhibitors, pioglitazone, and ARBs significantly reduced the incidence of diabetes and that statins increased the incidence of diabetes. The certainty in evidence was low due to limitations in study designs to evaluate the incidence of diabetes (inadequate washout period, brief period of follow-up, and varying definitions of T2DM) (5).

1. Definitions and Diagnosis

Growing evidence indicates that many individuals who develop ASCVD or T2DM have common antecedents of metabolic origin (6, 7). Although the pathophysiology underlying these antecedents is not fully understood, there is a strong overlap between cardiovascular risk factors and prediabetes in its various definitions [impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or at risk for diabetes with HbA1c above normal]. Accordingly, identification of a general condition called "metabolic risk" is reasonable.

The Writing Committee decided to define metabolic risk as reflecting an individual's predisposition for developing ASCVD and/or T2DM (see Appendix A for a full discussion of the choice of terminology). Individuals at metabolic risk often have (i) elevations of very low-density lipoproteins (VLDLs) with elevated triglycerides (TGLs), (ii) reduced levels of high-density lipoprotein cholesterol (HDL-C), (iii) increased plasma glucose levels, (iv) systemic hypertension, (v) enlarged waist circumference, (vi) a prothrombotic state, and (vii) a proinflammatory state. They can also have elevated apolipoprotein B–containing lipoproteins [primarily low-density lipoprotein (LDL), but also non-HDL lipoproteins such as VLDL, LDL, and chylomicrons], although this criterion applies more specifically to ASCVD

Table 1. Criteria Proposed for Clinical Diagnosis of the Metabolic Syndrome or Metabolic Risk

Clinical Measure	AHA/NHLBI[a] Revised NCEP ATP III	Original International Diabetes Federation[b]	Harmonized Definition[c]	Metabolic Risk (As Defined in This Guideline)
Age range	None	None	None	40–75 y
Selection criteria	Three of the five below	Start with elevated WC as below	Three of the five below	Three of the five below
Body weight/waist circumference	WC ≥102 cm in men or ≥88 cm in women (non-Asian origin)	WC ≥94 cm in men or ≥80 cm in women (Europids, sub-Saharan Africans, and Middle Eastern)	Population and country-specific definitions determined by local organizations	WC ≥102 cm in men or ≥88 cm in women (non-Asian origin)
	WC ≥90 cm in men or ≥80 cm in women (both East Asians and South Asians)	WC ≥90 cm in men or ≥80 cm in women (both East Asians and South Asians; South and Central Americans)		WC ≥90 cm in men or ≥80 cm in women (both East Asians and South Asians)
		WC ≥85 cm in men or ≥90 cm in women (Japanese)		
		plus any two of the following		
TGLs (fasting)	TGL ≥150 mg/dL (≥1.7 mmol/L) or on TGL Rx	TGL ≥150 mg/dL (≥1.7 mmol/L) or on TGL Rx	TGL ≥150 mg/dL (≥1.7 mmol/L) or on TGL Rx	TGL ≥150 mg/dL (≥1.7 mmol/L) or on TGL Rx
HDL-C	HDL-C <40 mg/dL (<1.0 mmol/L) in men or <50 mg/dL (<1.3 mmol/L) in women or on HDL-C Rx	HDL-C < 40 mg/dL (<1.0 mmol/L) in men or <50 mg/dL (<1.3 mmol/L) in women or on HDL-C Rx	HDL-C <40 mg/dL (<1.0 mmol/L) in men or <50 mg/dL (<1.3 mmol/L) in women or on HDL-C Rx	HDL-C <40 mg/dL (< 1.0 mmol/L) in men or <50 mg/dL (<1.3 mmol/L) in women or on HDL-C Rx
BP	≥130 mm Hg systolic or ≥85 diastolic or on hypertension Rx	≥130 mm Hg systolic or ≥85 diastolic or on hypertension Rx	≥130 mm Hg systolic or ≥85 diastolic or on hypertension Rx	≥130 mm Hg systolic or ≥80 diastolic or on hypertension Rx
Glycemia	Fasting glucose ≥100 mg/dL (5.6 mmol/L) or drug treatment for elevated glucose	Fasting glucose ≥100 mg/dL (5.6 mmol/L) (includes diabetes)	Fasting glucose >100 mg/dL (>5.6 mmol/L) or on drug treatment for elevated glucose	Fasting glucose ≥100 mg/dL (≥5.6 mmol/L) and <126 mg/dL (<7.0 mmol/L), *or* 2-h OGTT ≥140 mg/dL (≥7.8 mmol/L) and <200 mg/dL (<11.0 mmol/L), *or* HbA1c ≥5.7% to 6.4%, *or* on drug treatment for elevated glucose without diagnosis of DM

Abbreviation: NCEP ATP III, National Cholesterol Education Program - Adult Treatment Panel III Criteria for Metabolic Syndrome.

[Data derived from: Grundy, S. M., J. I. Cleeman, S. R. Daniels, K. A. Donato, R. H. Eckel, B. A. Franklin, D. J. Gordon, R. M. Krauss, P. J. Savage, S. C. Smith, Jr., J. A. Spertus, F. Costa, American Heart Association and National Heart Lung Blood Institute (2005). "Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement." Circulation 112(17): 2735–2752; Alberti, K. G., R. H. Eckel, S. M. Grundy, P. Z. Zimmet, J. I. Cleeman, K. A. Donato, J. C. Fruchart, W. P. James, C. M. Loria, S. C. Smith, Jr., E. International Diabetes Federation Task Force on, Prevention, L. National Heart, I. Blood, A. American Heart, F. World Heart, S. International Atherosclerosis and O. International Association for the Study of (2009). "Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity." Circulation 120(16): 1640–1645; and Alberti, K. G., P. Zimmet, J. Shaw and I. D. F. Epidemiology Task Force Consensus Group (2005). "The metabolic syndrome a new worldwide definition." Lancet 366(9491): 1059–1062.]

[a](8).

[b](9).

[c](10).

risk and is not included in the definition. The population of individuals with metabolic risk defined herein are those at risk for ASCVD and T2DM together but who have not yet been diagnosed with these conditions [Table 1 (8–10)].

These individuals can be identified by screening for the five components that have traditionally been used as indicators of the metabolic syndrome in the past. These are as follows:

1. Elevated fasting TGLs [≥150 mg/dL (≥1.7 mmol/L) or on medication]
2. Reduced HDL-C [<40 mg/dL (<1.0 mmol/L) in men and <50 mg/dL (<1.3 mmol/L) in women]
3. Elevated BP (≥130 mm Hg systolic or ≥85 mm Hg diastolic or on medication)
4. Elevated waist circumference (men ≥102 cm and women ≥88 cm; except for East and South Asian men ≥90 cm and women ≥80 cm)
5. Elevated glycemia (but not yet with T2DM) defined by cutoffs for prediabetes according to fasting blood glucose, oral glucose tolerance, and HbA1c. Specific cutoffs include:
   - fasting glucose ≥100 mg/dL (≥5.6 mmol/L) and <126 mg/dL (<7.0 mmol/L), or
   - 2-hour oral glucose tolerance test (OGTT) ≥140 mg/dL (≥7.8 mmol/L), and <200 mg/dL (<11.0 mmol/L), or
   - HbA1c ≥5.7% to 6.4%, or
   - currently on oral drug treatment for elevated glucose without diagnosis of diabetes mellitus (DM)

The cutoffs for waist circumference are adjusted for different ethnic populations, as East Asians and South Asians have increased risk at smaller waist circumferences (Table 1). The Writing Committee defines "metabolic risk" in this document to be consistent with certain definitions of the metabolic syndrome in individuals who are not yet diagnosed with ASCVD or T2DM. This guideline focuses on adults aged 40 to 75 years, for whom behavioral and medical intervention can have the greatest impact.

1.1 In individuals aged 40 to 75 years in the office setting, we suggest providers screen for all five components of metabolic risk at the clinical visit. The finding of at least three components should specifically alert the clinician to a patient at metabolic risk (at higher risk for ASCVD and T2DM) (2⊕○○○).

Technical remark: The main components of metabolic risk as defined in this guideline are (i) elevated BP, (ii) increased waist circumference, (iii) elevated fasting TGLs, (iv) low HDL-C, and (v) elevated glycemia (Table 1). Elevated glycemia should be determined either by HbA1c, fasting glucose, or 2-hour glucose with a second test for confirmation using a new blood sample. Testing for additional biological markers [*e.g.*, high-sensitivity C-reactive protein (hsCRP)] associated with metabolic risk should be limited to subpopulations. Additional biological markers have been associated with metabolic risk. Evidence that they provide an indication of metabolic risk beyond routine measurements is limited. Some measurements may have utility for determining the pattern or severity of metabolic risk but must be considered optional based on clinical judgment. Although these measures are not recommended for routine measurement, one or more of them may be measured according to physician discretion to confirm or clarify estimates of metabolic risk. This recommendation is specifically for adults aged 40 to 75 years, those for whom the interventions have the greatest impact and evidence for efficacy. This does not restrict screening for appropriate individuals outside of this age range, especially those who are younger.

1.2 In individuals aged 40 to 75 years in the office setting who do not yet have ASCVD or T2DM and already have at least one risk factor, we advise screening every 3 years for all five components of metabolic risk as part of the routine clinical examination (Fig. 1). (Ungraded Good Practice Statement)

Evidence

The suggested time frames for screening most of the components of metabolic risk are based on clinical consensus, without established evidence from controlled clinical studies. Importantly, the identification of individuals with prediabetes could allow those individuals to be treated with lifestyle modification to prevent the development of diabetes in the future (11, 12).

In the United States, ~35% of all adults and 50% of those ≥60 years of age are reported to have metabolic syndrome. In a Framingham Study cohort, 12.5% of women and 21.4% of men had metabolic syndrome without overt ASCVD or T2DM (or metabolic risk as defined in this document) according to the modified National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria (13, 14). When these individuals were reexamined 8 years later, the percentages increased to 23.6% for women and 33.9% for men (after direct adjustment to the baseline age), or by 47% and 56%, respectively (15). In the Diabetes Prevention Program (DPP) study, 53% of subjects with prediabetes met the NCEP ATP III criteria for metabolic syndrome at baseline, and 61% of those who initially did not meet the criteria in the placebo group met the criteria for

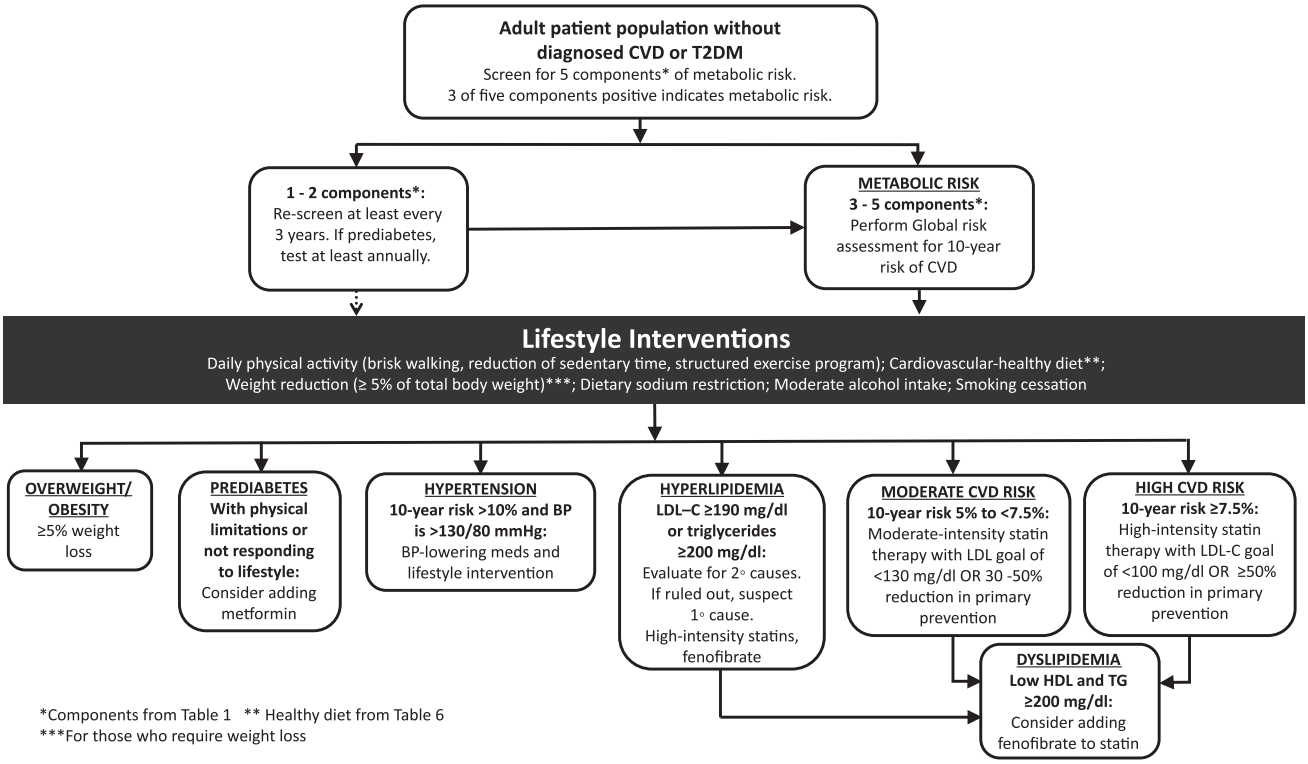

Figure 1. Flowchart for the assessment and treatment of metabolic risk.

metabolic syndrome after 3 years (16). Individuals with prediabetes defined by both HbA1c and fasting plasma glucose (FPG) criteria have a higher frequency of each of the metabolic syndrome components compared with those with prediabetes defined by either criterion alone (17).

Numerous analyses have established the ability of individual metabolic risk components to independently predict risk for ASCVD and T2DM; however, few analyses have studied the comparative effectiveness of individual risk components (18). The major difference between the 2005 AHA/National Heart, Lung and Blood Institute (NHLBI) definition (8) and the original International Diabetes Federation (IDF) definition of the metabolic syndrome (9) is that the former posited the presence of three out of five possible components, whereas the latter required that central obesity, as defined by waist circumference, be present first before examining for the other components (Table 1). Because some individuals at risk for ASCVD and T2DM do not have obesity and a substantial number of individuals with obesity may not be at higher risk, the AHA/NHLBI definition identifies a better population for further targeted screening for the risk for ASCVD and T2DM. Using the AHA/NHLBI definition, the metabolic syndrome is common and is associated with increased risk for T2DM and ASCVD in both sexes, accounting for up to half of new cases of T2DM and up to one-third of new ASCVD cases during 8 years of follow-up (15).

Many studies have evaluated the metabolic syndrome as a whole and its association with risk of ASCVD and mortality (6, 19, 20). The most recent of these (20) was a meta-analysis of 87 studies using various definitions of the metabolic syndrome. The metabolic syndrome was associated with an increased risk of ASCVD (RR, 2.35), ASCVD mortality (RR, 2.40), all-cause mortality (RR, 1.58), MI (RR, 1.99), and stroke (RR, 2.27). Very little difference in risk was found between each of the commonly used definitions of the metabolic syndrome, and the estimates of ASCVD risk were consistently higher in women than in men. When the outcomes were evaluated in the absence of T2DM (a situation analogous to our definition of metabolic risk), the metabolic syndrome was still associated with a high risk for ASCVD mortality. The prognostic value for ASCVD of adding T2DM to the other elements of the metabolic syndrome remains a subject of debate and needs further study. Additionally, more research is needed to determine whether the prognostic value of the metabolic syndrome exceeds the sum of its individual components.

The metabolic syndrome, in its various definitions, has a greater association with the development of T2DM than with ASCVD. When Framingham Offspring Study patients satisfying NCEP ATP III criteria for metabolic syndrome were followed for up to 11 years, metabolic syndrome criteria were found to increase the risk for developing diabetes by sixfold, regardless of the degree of insulin resistance (21).

A systemic review and meta-analysis (22) of 16 cohorts using six different definitions of the metabolic

syndrome reported the RR of incident diabetes ranging from 3.25 to 5.17, depending on the specific definition. The RR was substantially higher in individuals with four or more components of the metabolic syndrome than in those with three components. Although elevated glycemia is clearly a stronger predictor of diabetes than are the other four components (23), whether the metabolic syndrome provides any better prediction of diabetes than fasting glucose alone is yet to be established (24). However, others show that the metabolic syndrome provides additional prediction beyond that provided by IFG alone (23). As with ASCVD, more investigation is needed to determine whether the five components of the metabolic syndrome together provide better prediction of T2DM than when evaluated individually.

The concept of the metabolic syndrome has been, and continues to be, very useful to the medical community to enhance awareness of risk clustering and to promote thorough screening in individuals presenting with risk factors for ASCVD and/or T2DM. However, focusing on the metabolic syndrome should not divert attention from other established ASCVD and T2DM risk factors, such as smoking, LDL cholesterol (LDL-C), and family history, or from emerging risk factors, such as history of preeclampsia or gestational diabetes. Therefore, the concept of metabolic risk has maximal value when these additional clinical factors are considered by a physician.

Some combination of subclinical abnormalities related to insulin resistance/hyperinsulinemia/visceral obesity may signal a significant surplus of ASCVD risk that is not predicted by the classic risk calculators [including the ACC/AHA ASCVD risk calculator, the Framingham coronary heart disease (CHD) risk score, the United Kingdom Prospective Diabetes Study risk engine, and the Prospective Cardiovascular Münster (PROCAM) risk algorithm]. As long as the aim is to configure a "risk syndrome" (25), all that matters is the ability of its components to consistently and substantially contribute to the identification of those who may be at risk for ASCVD and T2DM. Although the currently available definitions of the metabolic syndrome are not yet fully validated as quantifiable predictors of risk, and more studies are necessary to test their ability to predict ASCVD and T2DM, these definitions can be used to identify more susceptible populations for more intensive screening (18).

Many different biomarkers of ASCVD and/or T2DM risk have been identified in addition to the five "classic" components of metabolic syndrome, including uric acid, apolipoprotein B, lipoprotein(a), adiponectin, leptin, fasting insulin or proinsulin, free fatty acids, homocysteine, the PAI-1 gene, fibrinogen, alanine aminotransferase as a marker of liver fat, hsCRP, inflammatory cytokines (*e.g.,* IL-6), homocysteine, liver or myocellular fat content by magnetic resonance spectroscopy, and microalbuminuria (in individuals without diabetes). Some of these have also been identified as markers of high diabetes risk (26). Emerging literature also suggests genomic markers to predict T2DM and ASCVD. However, the Writing Committee cannot recommend the measurement of these markers for routine clinical practice until further research has been completed (see "4. Further Research" below).

One example of a widely debated marker is hsCRP (27). A high hsCRP level is indicative of a high ASCVD risk. The therapeutic consequence may be that general therapy to lower ASCVD risk should be initiated earlier than would be done without an elevated hsCRP level for a given Framingham risk score. In that case, measures might need to be taken to decrease LDL-C and BP to lower targets, but evidence to support specific lower targets has not yet been identified.

Studies have addressed the issue of whether hsCRP and other markers enhance the risk estimates of the well-known risk scores/engines (28). They conclude that adding hsCRP, or other novel risk markers, to more basic risk models does not improve the prediction of ASCVD risk, because most risk factors are interrelated and, by themselves, do not have good predictive value. Therefore, in a clinical setting, health care providers can rely on simple, less expensive measures, such as asking about family history, cigarette smoking, and measurements of BP and serum lipids. This will identify those individuals at highest ASCVD risk who will benefit the most from any medical intervention to lower that risk (29). Screening for high-sensitivity hsCRP may be beneficial in certain subpopulations, as recommended by the AHA/ACC guidelines (30), but it is not recommended routinely.

1.3 To establish metabolic risk in the general population, we recommend that clinicians measure waist circumference as a routine part of the clinical examination. (1l⊕⊕⊕○)

Technical remark: This measurement does not replace the routine measurement of weight or calculation of body mass index (BMI), but it can provide more focused information regarding risk for ASCVD and T2DM [Fig. 2 (31)]. The Writing Committee agrees that the cutoffs for elevated waist circumference should be ≥102 cm for men and ≥88 cm for women in white, African, Hispanic, and Native American populations (32). The Writing Committee agrees that the cutoffs for waist circumference in Asian populations (both East Asian and South Asian) should be ≥90 cm for men and ≥80 cm for women.

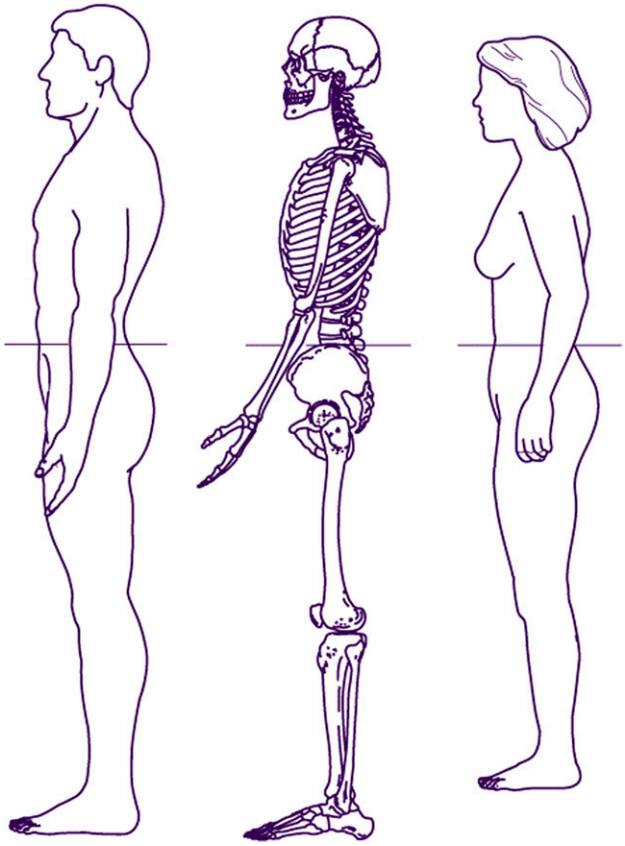

Figure 2. Measuring waist circumference according to National Health and Nutrition Examination Survey III protocol (31). [Reproduced from NHLBI Obesity Education Initiative Expert Panel on the Identification, Evaluation, and Treatment of Obesity in Adults (US). Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: The Evidence Report. Bethesda (MD): National Heart, Lung, and Blood Institute; 1998 Sep. Available at: http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=obesity.figgrp.237.]

Evidence

Numerous prospective observational studies have indicated that waist circumference and waist-to-hip ratio are better measures of central obesity and are better predictors of risk for ASCVD and diabetes than is weight or BMI (33). The Writing Committee advocates waist measurement because of its ease of use in the clinical setting when performed properly. Currently, waist circumference is rarely used by clinicians in the primary care setting. Increased use would help identify those individuals at higher risk who should receive further screening. However, it should not replace weight measurement or BMI, but should be complementary, because longitudinal measurement of weight is important for following up any major clinical interventions to treat obesity.

The Joint Interim Statement on metabolic syndrome (10) recognizes that the definition of elevated waist circumference is variable among different populations and suggests that for Europids (those of European descent), the threshold for increased waist circumference is ≥94 cm in men and ≥80 cm in women. For the US population, the AHA/NHLBI defines elevated waist circumference as ≥102 cm for men and ≥88 cm for women of non-Asian ethnicity and as ≥90 cm for men and ≥80 cm for women of South Asian and East Asian ethnicity [Table 2 (9, 34, 35)]. The "harmonized definition" of the metabolic syndrome, published in 2009, allowed for different ethnic waist circumference cutoffs based on different local guidelines without judging the relative merits.

Two important studies showed the rationale for using different cutoff points of waist circumferences in people of Asian descent. Tan *et al.* (36) found that a waist circumference cutoff of ≥90 cm in men and ≥80 cm in women seems to be comparable to that in US adults in terms of cardiometabolic risk. Alternatively, according to the reports from the examination committee of criteria for "obesity disease" in Japan, Japanese people with a visceral fat area (VFA) of >100 cm^2 have more than one obesity-related disorder, such as hyperglycemia, dyslipidemia, and hypertension. The correlation between VFA and waist circumference in men and women showed that a waist circumference of 85 cm in men and 90 cm in women corresponds to a VFA of 100 cm^2 (35). The Writing Committee recognizes heterogeneity within Asian populations (37, 38) and that East Asian and South Asian populations may have significant differences in lipid indices, fat mass as a proportion of BMI, and cardiovascular morbidity. More studies are necessary to clarify these differences before consensus on separate cutoffs for waist circumference might be established for these specific ethnic groups. Nevertheless, because of the considerable ethnicity-based variation in standard waist circumference, it is practical to use the ethnicity-specific values for waist circumferences in the 2005 AHA/NHLBI definition of the metabolic syndrome (8) until more specific data are available. There are potential limitations of waist circumferences, especially in people with BMI >35; however, these limitations may be less marked in Asian populations.

Practicality in the clinical setting is an important determinant of the use of waist circumference measurement. The Writing Committee places a high value on the need to identify risk for diabetes and ASCVD in ethnic populations where the incidence is increasing especially rapidly. Waist circumference can be easily measured in the clinical setting according to the National Health and Nutrition Examination Survey (NHANES) III protocol (39). This protocol directs health care providers to first identify and mark a bony landmark, the point at which waist circumference is measured. The subject stands and the examiner, positioned to the right of the subject, palpates the upper hip bone to locate the right iliac crest. Just above the uppermost lateral border of the right iliac crest, a horizontal mark is drawn and then crossed with a

vertical mark on the midaxillary line. The measuring tape is placed in a horizontal plane around the abdomen at the level of this marked point on the right side of the trunk. The plane of the tape is parallel to the floor, and the tape is snug but does not compress the skin. The measurement is made at a normal minimal respiration (Fig. 2). [Other methods of measuring waist circumference have been suggested (40) but are less widely adopted.]

1.4 In individuals previously diagnosed with prediabetes, we suggest testing at least annually for the presence of overt T2DM. (2|⊕⊕⊕◯)
Technical remark: Prediabetes is defined in a variety of ways (fasting plasma glucose, 2-hour plasma glucose following a 75-g OGTT, or HbA1c) by different organizations in different countries, and the Writing Committee does not endorse preferential use of one definition over another [Table 3 (41–44)].

Evidence

The natural history of prediabetes can be defined in terms of progression to T2DM. Most people with prediabetes will eventually progress to diabetes (45), particularly without appropriate lifestyle modifications. Early diagnosis of T2DM (with resulting earlier intervention) should result in a decrease in duration-dependent diabetes-related microvascular complications; however, direct data are not available to determine whether this decrease occurs. Published trials have not been sufficiently powered to show a reduction in these hard outcomes. However, the totality of evidence from the large number of diabetes prevention trials among people with IFG/IGT supports the hypothesis that early detection and treatment of prediabetes can reduce the rate of progression to diabetes and have beneficial effects on cardiovascular risk factors, metabolic syndrome, risk of retinopathy, kidney disease, quality of life, and health care costs.

FPG, 2-hour plasma glucose after a 75-g OGTT, and/or HbA1c can be used for identifying elevated glycemia, even though these tests may identify distinct and not fully overlapping populations of patients with undiagnosed diabetes and prediabetes.(46) The FPG test is automated and inexpensive but reflects the glycemic state at only a single time point. The OGTT is more sensitive but also more time-consuming, costly, and variable than the FPG test (47). However, some evidence suggests that the OGTT is a better predictor for cardiovascular and all-cause mortality than FPG (48, 49). HbA1c is a more long-term measure of glycemia with less sensitivity but also less variability than glucose tests and can be performed in the nonfasting state (50). There are also established international standardization programs for HbA1c laboratory assays. However, HbA1c is an indirect measure of average blood glucose. Marked discrepancies between measured HbA1c and plasma glucose levels may indicate HbA1c assay interference due to Hb variants (*i.e.*, hemoglobinopathies), and an assay without analytic interference should be used. In conditions associated with increased red blood cell turnover (*e.g.*, sickle cell disease or hemodialysis), plasma blood glucose criteria should be used to diagnose diabetes. Emerging data also suggest that genetic variants such as glucose-6-phosphate dehydrogenase deficiency, which increase the risk for hemolysis and are more common in some ethnic backgrounds, can have a significant impact on HbA1c levels (51). Nevertheless, there is a strong, continuous association between HbA1c and subsequent diabetes risk (52). Within the HbA1c spectrum of prediabetes, the yearly incidence of diabetes increases from ~3% with an HbA1c of 5.7% to ~9.5% with an HbA1c of 6.5%. According to

Table 2. Recommended Waist Thresholds to Define Abdominal Obesity

Region/Ethnicity[a]	Recommending Organization	Waist Circumference Threshold for Abdominal Obesity
United States	AHA/NHLBI	≥102 cm in men; ≥88 cm in women[b]
Europe/Europids	IDF	≥94 cm in men; ≥80 cm in women
Asia	AHA/NHLBI IDF	≥90 cm in men; ≥80 cm in women[c]

[Data derived from: Alberti, K. G., P. Zimmet, J. Shaw and I. D. F. Epidemiology Task Force Consensus Group (2005). "The metabolic syndrome—a new worldwide definition." Lancet 366(9491): 1059–1062; Grundy, S. M., J. I. Cleeman, C. N. Merz, H. B. Brewer, Jr., L. T. Clark, D. B. Hunninghake, R. C. Pasternak, S. C. Smith, Jr. and N. J. Stone (2004). "Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines." Circulation 110(2): 227–239; Examination Committee of Criteria for 'Obesity Disease' in Japan; Japan Society for the Study of Obesity. (2002). "New criteria for 'obesity disease' in Japan." Circ J 66(11): 987–992.]

[a]Data are not available for sub-Saharan Africans, Eastern Mediterranean and Middle East (Arab) populations, and ethnic South and Central Americans. The IDF suggests using waist thresholds for Europe/Europids for populations in these regions (9).

[b]AHA/NHLBI guidelines indicated that waist thresholds of ≥94 cm in men and ≥80 cm in women were optional in persons who show clinical evidence of insulin resistance (34).

[c]In Japan, national recommendations for waist circumference thresholds for abdominal obesity are ≥85 cm in men and ≥90 cm in women (35).

the American Diabetes Association, FPG, 2-hour plasma glucose following a 75-g OGTT, and HbA1c are equally appropriate to test for prediabetes or diabetes (41). Other organizations, such as the World Health Organization, also include HbA1c as an acceptable test for diabetes but not for prediabetes (42, 53). Based on these data, the Writing Committee suggests that people with prediabetes be screened for diabetes annually.

1.5 We recommend that all individuals at metabolic risk in the office setting have their BP measured annually and, when elevated, at each subsequent visit. (1l⊕⊕⊕⊕)
Technical remark: BP should be measured after 5 minutes of rest. Table 4 provides detailed BP measurement guidance. Ambulatory and/or home BP monitoring, when performed correctly, is recommended to confirm a diagnosis of hypertension after initial screening.

Evidence

Anyone >18 years of age at metabolic risk with stage 1 hypertension (130 to 139/85 to 89 mm Hg), individuals who are overweight or obese, and those of African American descent should be screened at least annually for hypertension. Screening should involve multiple readings and confirmation outside the office setting (54, 55). Either ambulatory or home BP measurement should be used to confirm a diagnosis of hypertension and to assess the presence of white-coat hypertension and masked hypertension (54–57).

1.6 For individuals with elevated BP >130 mm Hg systolic and/or >80 mm Hg diastolic who are not documented as having a history of hypertension, we recommend confirmation of elevated BP on a separate day within a few weeks or with a home BP monitor. (1l⊕⊕⊕⊕)

Evidence

Single BP readings are highly variable and depend on multiple factors in the methodology used to measure BP, in addition to the circumstance at the time of measurement (*e.g.*, rested, not rested, anxious). Out-of-office measurement of BP can be helpful for confirmation and management of hypertension. Among individuals with hypertension, self-monitoring of BP, without other interventions, has shown limited evidence for treatment-related BP reduction and achievement of BP control (58, 59). However, with the increased recognition of inconsistencies between office and out-of-office BPs and greater reduction in BP being recommended for hypertension control, increased attention is being paid to out-of-office BP readings, especially home BP monitoring (54).

There are specific guidelines for how to measure BP and these are summarized in the ACC/AHA 2017 guidelines on high BP (54) and elsewhere (60). The standards indicate that a process be undertaken that requires time and some diligence (Table 4). Office-based semiautomated oscillometric BP is the conventional approach for diagnosing

Table 3. Definitions of Prediabetes (Intermediate Glycemia)

	Prediabetes Category			
	IFG	IGT	High Risk for DM by A1c	
Organization	(Fasting Glucose)	(2-h OGTT)	(HgA1c)	Comments
ADA[a]	100–125 mg/dL (5.6–6.9 mmol/L)	140–199 mg/dL (7.8–11.0 mmol/L)	5.7%–6.4% (39–46 mmol/mol)	Any one of the three is sufficient
WHO 2011[b]	110-125 mg/dL (6.1–6.9 mmol/L)	140–199 mg/dL (7.8–11.0 mmol/L)		A1c is not recommended for diagnosis of intermediate glycemia
IEC 2003[c]	100–125 mg/dL (6.1–6.9 mmol/L)			FPG lower threshold was revised downward from previous 1997 report to include more individuals
IEC 2009[d]			6.0%–6.4% (42–46 mmol/mol)	Restricted to higher risk group than ADA definition for T2DM prevention

[Data derived from American Diabetes Association. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes. Diabetes Care 2019; 42(Suppl 1): S13–S28; World Health Organization. Use of glycated haemoglobin (HbA1c) in the diagnosis of diabetes mellitus: abbreviated report of a WHO consultation. 2011. www.who.int/diabetes/publications/diagnosis_diabetes2011/en/index.html; and The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Follow-up Report on the Diagnosis of Diabetes Mellitus Diabetes Care 2003 Nov; 26(11): 3160–3167. https://doi.org/10.2337/diacare.26.11.3160.]

[a](41).

[b](42).

[c](43).

[d](44).

hypertension using the methodology outlined in Table 4. An update to this approach evolved from both the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial (61) and the Systolic Blood Pressure Intervention Trial (SPRINT) (62). Automated office BP, an average of multiple readings (usually three to five) taken over a few minutes using a fully automated device, ideally while the individual rests quietly alone, was used in SPRINT (62, 63). If the patient is alone when the readings are taken, the approach is also useful for diagnosing white-coat hypertension. Automated office BP generates values 7 to 12 mm Hg lower than conventional office readings, and thus the results of trials using this technique cannot be directly applied to most office practices (64–66).

2. Lifestyle and Behavioral Therapy

2.1 In individuals at metabolic risk, we recommend that lifestyle modification be first-line therapy. (1|⊕⊕⊕⊕)

Technical remark: The Writing Committee thinks that primary care providers, endocrinologists, geriatricians, and cardiologists should initiate discussions about the importance of adopting a healthy lifestyle with all individuals at metabolic risk. These and other relevant providers should encourage individuals to join comprehensive programs led by trained health professionals that support the adoption of healthy lifestyles, including diet and physical activity, aiming for moderate but sustained weight loss.

Evidence

During the past 30 years, many studies have examined the effects of weight reduction, through diet modification and increased physical activity, on the development of T2DM in high-risk individuals (67–71). These studies have been the subjects of numerous

Table 4. Checklist for Measuring BP Manually

Key Steps for Proper BP Measurements	Specific Instructions
Step 1: Properly prepare the patient	1. Have the patient relax, sitting in a chair (feet on floor, back supported) for >5 min. 2. The patient should avoid caffeine, exercise, and smoking for at least 30 min prior to measurement. 3. Ensure patient has emptied his/her bladder. 4. Neither the patient nor the observer should talk during the rest period or during the measurement. 5. Remove all clothing covering the location of cuff placement. 6. Measurements made while the patient is sitting or lying on an examining table do not fulfill these criteria.
Step 2: Use proper technique for BP measurements	1. Use a BP measurement device that has been validated and ensure that the device is calibrated periodically. 2. Support the patient's arm (*e.g.*, resting on a desk). 3. Position the middle of the cuff on the patient's upper arm at the level of the right atrium (the midpoint of the sternum). 4. Use the correct cuff size, such that the bladder encircles 80% of the arm and note if a larger or smaller than normal cuff size is used. 5. Either the stethoscope diaphragm or bell may be used for auscultatory readings.
Step 3: Take the proper measurements needed for diagnosis and treatment of elevated BP/hypertension	1. At the first visit, record BP in both arms. Use the arm that gives the higher reading for subsequent readings. 2. Separate repeated measurements by 1–2 min. 3. For auscultatory determinations, use a palpated estimate of radial pulse obliteration pressure to estimate SBP. Inflate the cuff 20–30 mm Hg above this level for an auscultatory determination of the BP level. 4. For auscultatory readings, deflate the cuff pressure 2 mm Hg per second and listen for Korotkoff sounds.
Step 4: Properly document accurate BP readings	1. Record SBP and DBP. If using the auscultatory technique, record SBP and DBP as onset of the first Korotkoff sound and disappearance of all Korotkoff sounds, respectively, using the nearest even number. 2. Note the time of most recent BP medication taken prior to measurements.
Step 5: Average the readings	1. Use an average based on ≥2 readings obtained on ≥2 occasions to estimate the individual's level of BP.
Step 6: Provide BP readings to patient	1. Provide patients the SBP/DBP readings both verbally and in writing.

See Whelton *et al.* (54).

Abbreviations: DBP, diastolic BP; SBP, systolic BP.

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reviews and meta-analyses (72). The landmark trials—the Da Qing Study (69), the Finnish Diabetes Prevention Study (71), and the DPP in the United States (11)—have all demonstrated that lifestyle interventions including diet and/or physical activity aiming at weight reduction in high-risk individuals significantly decrease the risk of progression to T2DM by 30% to 58% after 3 to 6 years of intervention. Longer-term follow-ups have also demonstrated reductions in the development of T2DM and ASCVD over decades after the end of the intervention periods (12, 73, 74).

In the Da Qing Study, the progression of IGT to diabetes during 6 years was significantly lower in all three intervention groups than in the control group: 44% in the diet-only group, 41% in the exercise-only group, and 46% in the combined diet and exercise group, compared with 68% in the control group. Long-term follow-up of the participants found that after 23 years of follow-up, 89.9% of the control group had developed diabetes compared with 72.6% in the intervention groups, demonstrating a long-term beneficial effect of lifestyle intervention programs (73). Additionally, ASCVD mortality was significantly reduced in the intervention groups, being 11.9% compared with 19.6% in the control group (73). This study provides convincing evidence for the long-term benefits of lifestyle modification programs in people with prediabetes to decrease the long-term risks of T2DM development and death due to ASCVD.

In the Finnish Diabetes Prevention Study (71), overweight individuals with IGT were randomized to usual care or to an individualized lifestyle modification program that emphasized weight reduction of ≥5% by reduced caloric intake, decreased intake of dietary fat and saturated fats, increased fiber intake, and the addition of 4 hours per week of moderate-intensity exercise. At 1 year, the intervention group had a mean weight loss of 4.2 kg (~5%) compared with only 0.8 kg (1%) in the control group. After a mean of 3.2 years of follow-up, the risk of developing T2DM was decreased by 58% in the intensive lifestyle modification group. Moreover, in subjects who exceeded the weight loss goal of 5%, the risk reduction was 74%, and in those who exceeded the exercise goal of 4 hours per week, the RR reduction was 80%. In follow-up studies performed 13 years after assignment to intervention, the risk of developing T2DM was still significantly reduced by almost 40% in individuals initially randomized to the intervention compared with that in the control group (74). Notably, the risk of developing T2DM was eliminated in the individuals who achieved all five lifestyle goals: none of these individuals developed T2DM during 7 years of follow-up (75, 76).

The DPP (11) randomized individuals with IGT to: (i) an intensive lifestyle modification intervention, (ii) treatment with metformin, or (iii) placebo. One of the goals for the group receiving the intensive lifestyle modification intervention was to lose ≥7% of body weight (77). Lifestyle modification emphasized reducing caloric intake, principally by reducing fat to <25% of energy, decreasing saturated fats, increasing dietary fiber, and increasing physical activity to at least 150 minutes per week of moderate-intensity exercise equivalent to brisk walking (16). After a mean study time of 2.8 years, the intensive lifestyle modification intervention group decreased the risk of developing diabetes by 58% compared with the placebo-treated control group. The intensive lifestyle modification intervention was also significantly more effective than treatment with metformin, which reduced the risk of diabetes by 31% (11, 78). No differences in the efficacy of the lifestyle or metformin programs were found among the various racial and ethnic groups or between men and women. However, the effectiveness of metformin was greatest in the younger age group and in those with a BMI >36 kg/m^2. Conversely, the lifestyle program was most effective in the older participants. Fifteen years of follow-up of DPP participants showed that the beneficial effects of metformin and lifestyle intervention were still significant compared with those of the control group, with reductions in the incidence of diabetes of 18% and 27%, respectively (12). Similar to the findings in the Da Qing Study and Finnish Diabetes Prevention Study, these results demonstrate the long-term benefits of lifestyle modification focusing on weight reduction, increased physical exercise, and a healthy diet to reduce the development of diabetes in high-risk populations.

In the DPP, 53% of subjects met the NCEP ATP III criteria for the metabolic syndrome at baseline. *Post hoc* analyses found that ~60% of the subjects in the control group who did not have metabolic syndrome at baseline developed the syndrome during 4 years. Metformin treatment reduced the risk by 17%, and the intensive lifestyle modification intervention decreased it by 41%. Furthermore, the intensive lifestyle modification intervention resulted in a reversal of metabolic syndrome in 38% of subjects who had metabolic syndrome at baseline, whereas reversal occurred in 18% of similar subjects in the control group (16).

The DPP report focusing on cardiovascular risk factors (79) found that hypertension was present in 30% of subjects at baseline. During 3 years, BP increased in the placebo- and metformin-treated groups

but significantly decreased in the group receiving the intensive lifestyle modification intervention. Serum TGLs decreased in all groups but to a significantly greater extent in the intensive lifestyle modification intervention group. This group also had significantly increased HDL-C levels and decreased small dense LDL-C. After 3 years, the quantity of medications used to control BP and dyslipidemia was reduced by 25% to 28% in the group receiving intensive lifestyle modification intervention. To date, the long-term effects of the DPP intensive lifestyle modification program or treatment with metformin on the incidence of cardiovascular events cannot be determined because of the low number of events.

2.2 For individuals at metabolic risk with excess weight (defined by BMI and/or waist circumference), we recommend that comprehensive programs to support the adoption of a healthy lifestyle should aim to achieve a weight loss of ≥5% of initial body weight during the first year. (1|⊕⊕⊕⊕)

Technical remark: Maintenance of weight loss by adoption of sustainable healthy behaviors should be encouraged with continuing support of primary providers and/or extended programs.

Evidence

Convincing evidence from well-conducted RCTs indicates that weight reduction of ≥5% of initial body weight in subjects who are overweight with metabolic risk is effective in decreasing the development of T2D and reducing multiple ASCVD risk factors, such as lowering BP and improving lipid profiles [Table 5 (69, 80–84)]. In general, weight loss programs included in diabetes prevention trials were designed to achieve a negative energy balance of 500 to 1000 kcal/d, causing a weight loss of 1 to 2 pounds/wk (0.5 to 1.1 kg/wk). In the DPP study, the lifestyle intervention group had a mean weight loss of ~7 kg at year 1 and then regained some weight, resulting in a mean weight loss of ~4 kg after 3 to 4 years of active intervention (77).

In DPP participants, weight loss was the most important predictor of reduction in diabetes incidence: for every kilogram of weight loss in DPP participants, there was a 16% reduction in risk of developing diabetes, adjusted for changes in diet and activity (85). The benefits for diabetes prevention of moderate weight loss in individuals with prediabetes have been shown in many trials of nonpharmacologic weight loss interventions, which have been summarized in previous systematic reviews (86). According to an NHLBI systematic review published in 2013, an average weight loss (and maintenance) of 2.5 to 5.5 kg over ≥2 years reduces the risk of developing T2DM by 30% to 60% in adults who are overweight and obese at high risk of diabetes (80). A recent systematic review of trials targeting primary prevention of ASCVD estimated that weight loss of 5% to 10% of initial weight during 12 to 24 months was associated with a reduction in fasting glucose of ~0.2 mmol/L and a reduction in HbA1c of ~0.6 percentage points (81).

Moderate weight loss has also consistently been shown to improve the lipid profile in individuals at metabolic risk. In the DPP study, weight loss during the first 2 years of intervention was the strongest predictor of improvement: for example, each kilogram of weight loss was associated with a reduction in TGL levels of 2.27 mg/dL (0.57 mmol/L) (87). The 2013 NHLBI systematic review stated that there is a dose-response relationship between the amount of weight loss achieved by lifestyle intervention and the improvement in lipid profile in individuals who are overweight or obese (80). Their assessment of the evidence highlighted the benefits of a reduction in TGLs (estimated at ~15 mg/dL or 0.17 mmol/L) with only 3 kg of weight loss, whereas weight loss of 5 to 8 kg was associated with a reduction in LDL (estimated at ~5 mg/dL or 0.13 mmol/L) and an increase in HDL (estimated at ~2 to 3 mg/dL or 0.5 to 0.8 mmol/L), leading to a more favorable cardiovascular profile. The recent systematic review of trials in primary prevention of ASCVD by Zomer *et al.* (81) reported a similar effect of moderate weight loss (5% to 10% during 12 to 24 months) on TGL levels (−16 mg/dL or 0.18 mmol/L) and a slightly greater impact on LDL (−10 mg/dL or 0.26 mmol/L) and total cholesterol (−17 mg/dL or 0.43 mmol/L). However, their meta-analysis reported a nonsignificant effect on HDL (+0.5 mg/dL or 0.13 mmol/L).

Moderate weight loss has a significant benefit on reductions in BP. In the DPP study, for every kilogram of weight loss during the 2 first years of intervention, systolic BP was reduced by 0.3 mm Hg (87). In the NHLBI systematic review, a 5% weight loss was associated with estimated reductions of 3 mm Hg in systolic BP and of 2 mm Hg in diastolic BP (80). The systematic review by Zomer *et al.* (81) provided similar effect estimates for studies of 6 to 12 months and slightly lower estimates for longer-term studies. In summary, ample evidence from multiple well-conducted RCTs, meta-analyses, and systematic reviews indicates that moderate weight loss of 5% or more results in significant benefits for diabetes prevention, reduction in hyperglycemia, reduction in BP, and improvement in lipid profiles associated with better cardiovascular health.

Maintenance of weight loss remains a challenge for many individuals. In the DPP and other diabetes prevention trials, a slow weight regain occurred after the first year of intervention, despite ongoing

Table 5. Effect of Lifestyle Components on Metabolic Parameters

Intervention	Glycemic/Diabetes Effect	BP Effect	Lipids Effect
Moderate weight loss ≥5% of initial weight (recommendation 2.2)	30%–60% reduction in diabetes incidence (80) Effect on glycemic indices (81): • Reduction in HbA1c ~0.6 U • Reduction in fasting glucose ~0.2 mmol/L (3.6 mg/dL)	BP reduction about 3/2 mm Hg (80, 81)	• Reduction in TGL (80, 81): 15–16 mg/dL (0.17–0.18 mmol/L) • Reduction in LDL (80, 81): 5–10 mg/dL (0.13–0.26 mmol/L) • Increase in HDL (80, 81): 4–31 mg/dL (0.1–0.8 mmol/L)
Healthy cardiovascular dietary patterns (recommendation 2.3)	Reduction 18%–40% in diabetes incidence (Mediterranean diet) (82)	BP reduction up to 6/3 mm Hg (based on DASH diet) (80)	*Trans* fat: repeatedly associated with adverse lipid profile (80) DASH diet: lower LDL and total cholesterol (80) Mediterranean diet: inconsistent findings (80)
Active lifestyle (recommendation 2.4)	Reduction of up to 65% in diabetes incidence (69, 83)	BP reduction about 2–5/1–4 mm Hg (80, 84)	Reduction in LDL ~3.0–6.0 mg/dL (0.08–0.16 mmol/L) (80)

Note that ranges are taken from systematic reviews and meta-analyses as listed below.

[Data derived from: Lifestyle Work Group (2013). Lifestyle Interventions to Reduce Cardiovascular Risk: Systematic Evidence Review from the Lifestyle Work Group, National Heart, Lung, and Blood Institute; Zomer, E., K. Gurusamy, R. Leach, C. Trimmer, T. Lobstein, S. Morris, W. P. James, and N. Finer (2016). "Interventions that cause weight loss and the impact on cardiovascular risk factors: a systematic review and meta-analysis." Obes Rev 17(10): 1001–1011; Salas-Salvado, J., M. Bullo, R. Estruch, E. Ros, M. I. Covas, N. Ibarrola-Jurado, D. Corella, F. Aros, E. Gomez-Gracia, V. Ruiz-Gutierrez, D. Romaguera, J. Lapetra, R. M. Lamuela-Raventos, L. Serra-Majem, X. Pinto, J. Basora, M. A. Munoz, J. V. Sorli and M. A. Martinez-Gonzalez (2014). "Prevention of diabetes with Mediterranean diets: a subgroup analysis of a randomized trial." Ann Intern Med 160(1): 1–10; Pan, X. R., G. W. Li, Y. H. Hu, J. X. Wang, W. Y. Yang, Z. X. An, Z. X. Hu, J. Lin, J. Z. Xiao, H. B. Cao, P. A. Liu, X. G. Jiang, Y. Y. Jiang, J. P. Wang, H. Zheng, H. Zhang, P. H. Bennett, and B. V. Howard (1997). "Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study." Diabetes Care 20(4): 537–544; Laaksonen, D. E., J. Lindstrom, T. A. Lakka, J. G. Eriksson, L. Niskanen, K. Wikstrom, S. Aunola, S. Keinanen-Kiukaanniemi, M. Laakso, T. T. Valle, P. Ilanne-Parikka, A. Louheranta, H. Hamalainen, M. Rastas, V. Salminen, Z. Cepaitis, M. Hakumaki, H. Kaikkonen, P. Harkonen, J. Sundvall, J. Tuomilehto, and M. Uusitupa (2005). "Physical activity in the prevention of type 2 diabetes: the Finnish diabetes prevention study." Diabetes 54(1): 158–165; and 2018 Physical Activity Guidelines Advisory Committee (2018). "2018 Physical Activity Guidelines Advisory Committee Scientific Report." Washington, DC: U.S. Department of Health and Human Services 2018.]

engagement with interventionists (11, 71, 86). In the DPP study, achieving the goal of 150 minutes per week of physical activity and dietary self-monitoring was associated with a greater chance of maintaining weight loss during the course of the active study (~3 years) (88). Successful weight loss and weight maintenance depend on high adherence to lifestyle intervention components, which include dietary changes, physical activity goals, consistent self-monitoring of targeted behaviors, and contacts with trained interventionists (individual and/or group sessions) (89). Strategies that improve adherence to lifestyle interventions for weight loss include (i) continuous support from health professionals and/or peers, (ii) teaching self-regulating skills through enhancement of self-monitoring, (iii) facilitating dietary routine by using meal replacements or interventions providing meals, and (iv) varying physical activity prescription in dose, intensity, or style (89). Ideally, comprehensive behavioral programs that support lifestyle changes in individuals at high metabolic risk should provide long-term support after the active phase of weight loss (usually 6 to 12 months); however, it is clearly costly and logistically challenging to do so. With or without long-term support from comprehensive programs, primary care providers should ensure regular support (during and after the weight loss phase) to monitor and set behavioral goals, reinforce positive behavioral changes, facilitate problem-solving when relapses occur, and reach out to other health care professionals, when appropriate, for support.

2.3 In individuals at metabolic risk, we recommend prescribing a cardiovascular-healthy diet. (1|⊕⊕⊕◯)

Technical remark: Providers can offer dietary recommendations based on common components of healthy cardiovascular dietary patterns [Table 6 (90)] to all individuals at metabolic risk. Specific dietary changes according to individual risk profiles could be supported with the help of a nutrition specialist in addition to the primary care provider.

Evidence

During the last few decades, the field of nutrition for prevention of ASCVD has moved from a macronutrient approach (*e.g.*, targeting only fats or carbohydrates)

toward promoting specific dietary patterns based on scientific evidence and with the hope of more effectively reaching the overall population, including health care providers. The United States Department of Agriculture (USDA)'s Nutrition Evidence Library conducted a series of systematic reviews and released their report in 2014 (90), providing evidence supporting the 2015 to 2020 Dietary Guidelines for Americans (91). Based on their systematic review, the USDA Nutrition Evidence Library concluded that "there is strong and consistent evidence that in healthy adults increased adherence to dietary patterns scoring ***high*** in fruits, vegetables, whole grains, nuts, legumes, unsaturated oils, low-fat dairy, poultry, and fish; ***low*** in red and processed meat, high-fat dairy, and sugar-sweetened foods and drinks; and ***moderate*** in alcohol is associated with decreased risk of fatal and nonfatal cardiovascular diseases, including CHD and stroke. (Grade: I – Strong)" (90). This dietary pattern is consistent with the definition of the Mediterranean diet pattern used in most studies but also includes many components of what has been defined as the "Healthy Eating Index" diet quality measurement tool (92).

One of the major trials that has helped advance the field of nutrition in cardiovascular primary prevention is the Prevention With Mediterranean Diet (PREDIMED) study. The initial trial results published in 2013 (93) were retracted for irregularities in the randomization process; however, the authors reanalyzed their data and provided revised results in 2018 (94). In its revised analysis, PREDIMED remains the first long-term multicenter RCT testing the impact of the Mediterranean diet on the incidence of ASCVD events in men and women at metabolic risk. The trial was conducted in Spain and tested the traditional diet consumed around the Mediterranean basin described as a frugal diet with most of the components listed in Table 6.

The PREDIMED study participants had no previous episodes of ASCVD but were considered at high risk of ASCVD based on the presence of three or more risk factors (smoking, overweight or obesity, hypertension, dyslipidemia, and family history of early-onset ASCVD) or having T2DM. PREDIMED included 7447 subjects, and of these, ~70% had dyslipidemia, 80% had hypertension, and 50% had T2DM (94). Participants were randomized into one of three diet groups: (i) Mediterranean diet supplemented with extra-virgin olive oil (EVOO); (ii) Mediterranean diet supplemented with nuts; and (iii) control diet (advice on a low-fat diet).

The rate of new ASCVD events (MI, stroke, or death from ASCVD causes) was reduced in both Mediterranean diet arms by ~30% over a median time of 4.8 years of follow-up (93). The revised intention-to-treat analysis accounting for intracluster correlations or using propensity scores for adjustment in baseline variables (because of issues in randomization) demonstrated the same effect size of 30% reduction in risk (94). The Mediterranean diet prevented new ASCVD events equally in men and women, in older and younger individuals, in people with and without a family history of ASCVD, in smokers and nonsmokers, and in people with and without diabetes at baseline (93). The effect was greater in subgroups with hypertension, dyslipidemia, or BMI >30 kg/m^2 compared with the lesser risk categories at baseline.

Individuals who started PREDIMED fulfilling the metabolic syndrome diagnostic criteria (10) were more likely to reverse their metabolic syndrome status over a period of >4 years of follow-up when they were enrolled in one of the Mediterranean diet arms. This reversal was mainly driven by improvements in glycemia and waist circumference (95).

Dietary approach for diabetes prevention

In PREDIMED participants without diabetes at baseline, the Mediterranean diet with EVOO reduced the risk of developing T2DM by 40%, although the reduction in T2DM incidence was more modest in the Mediterranean diet with nuts (~18%) (83). This latter report from PREDIMED was not part of the USDA Nutrition Evidence Library review (released in early 2014), which concluded at the time that the evidence on dietary patterns and reduction in T2DM was still limited or inconsistent (90). Historically, both the DPP and the Finnish Diabetes Prevention Study used a diet with 25% of energy from fat (7% from saturated fats) and increased amounts of fiber. However, untangling the effect of specific dietary components from the overall lifestyle behavioral intervention and weight loss effect is difficult, especially because weight loss was the most important predictor of reduction in diabetes incidence (85).

Table 6. Components of Healthy Cardiovascular Dietary Patterns

Rich in	Moderate in	Low in
Vegetables	Alcohol	Red and processed meat
Fruits		High-fat dairy
Whole grains		Sugar-sweetened foods
Nuts		Sugar-sweetened drinks
Legumes		Sodium
Unsaturated oils		
Low-fat dairy		
Poultry		
Fish		

See United States Department of Agriculture (90).

Dietary approach for reduction in BP

According to the NHLBI systematic review, reducing sodium intake lowers BP independently of sex, age, and race, and it shows a greater effect in people with hypertension (80). The USDA and AHA recommend that sodium intake be limited to 2300 mg/d in most healthy individuals and 1500 mg/d in people with prehypertension or hypertension, which include most individuals at metabolic risk. Simply counseling individuals to reduce sodium intake leads to a reduction in BP by 3 to 4/1 to 2 mm Hg, empowering health care providers to talk about dietary sodium in their daily practice (80). Providers should remind their patients that adding salt to the food on their plate contributes only a small amount to their daily sodium intake. Even more sodium is intrinsically part of many prepared foods and conservation processes (*e.g.*, canned vegetables and soups, frozen meals). Sodium is found in high amounts in many foods, including pizza, tacos, burgers, sandwiches, soups, rice, and pasta dishes, as well as meat, poultry, seafood, condiments, and sauces.

A Dietary Approaches to Stop Hypertension (DASH) dietary pattern results in lower BP, and the evidence was summarized in both the NHLBI 2013 systematic review report (strength of evidence high) (80) and USDA Nutrition Evidence Library 2014 systematic review (grade 1, strong) (90). A dietary pattern consistent with the DASH diet is rich in fruits, vegetables, low-fat dairy, fish, whole grains, fiber, potassium, and other minerals at recommended levels and low in red and processed meat, sugar-sweetened foods and drinks, saturated fat, cholesterol, and sodium. The USDA review concluded that a DASH diet lowers systolic BP by ~5 to 6 mm Hg and diastolic BP by ~3 mm Hg compared with a typical American diet, benefiting both men and women, independently of age, race, and hypertensive status.

Adopting a Mediterranean dietary pattern may result in a small benefit on BP, mainly diastolic. In the PREDIMED study, after 4 years, the mean systolic and diastolic BP decreased in participants in all three groups, but the diastolic BP was slightly lower in the Mediterranean diet arms (~1.5 mm Hg lower for a Mediterranean diet plus EVOO and ~0.65 mm Hg lower for a Mediterranean diet plus nuts) (96). Inconsistent results regarding the impact of the Mediterranean diet on BP were reported in previous studies and systematic reviews (80, 90). Additional information on this topic is presented in recommendation 3.7 and see Table 10.

Dietary approach for reduction in lipids

USDA 2015 Dietary Guidelines (91) recommend limiting the amount of saturated fat intake (maximum 10% of total caloric intake) and avoiding *trans* fats (limiting to as low as possible). Saturated fats are found in animal products (*e.g.*, meat, dairy), and the main sources of saturated fats include mixed dishes, such as burgers, sandwiches, tacos, pizza, rice or pasta dishes, and meat, poultry, and seafood dishes. Artificial *trans*-fatty acids are produced by a process called hydrogenation and are used in some margarines, snack foods, and prepared desserts often as a replacement for saturated fatty acids. Although food manufacturers and restaurants have reduced the amounts of artificial *trans* fats in many foods in recent years, these fats can still be found in some processed foods, such as some desserts, microwave popcorn, frozen pizza, and coffee creamers. *Trans* fats have been repeatedly associated with the development of unfavorable lipid profiles and higher ASCVD risk (80, 97).

Numerous controlled feeding studies have assessed the impact of different fats and replacement by other macronutrients on lipid profiles (Table 7), as reported by the NHLBI 2013 systematic review (80). Overall, health care providers should recommend diets that are low in saturated and *trans* fats and rich in monounsaturated and polyunsaturated fatty acids and should choose carbohydrates classified as complex (whole grain, fiber-rich). However, this evidence is hard to translate into day-to-day practice and terms that individuals easily understand and can apply consistently in their daily life.

Evidence shows that a DASH diet lowers LDL compared with a typical American diet (80, 90). In contrast, the evidence related to the Mediterranean diet's impact on the classic clinical lipid profile is unclear. The NHLBI 2013 systematic review reported "no consistent effect on LDL, HDL, or TGL levels" from trials studying a Mediterranean diet. The USDA systematic review (March 2014) did not reach any conclusion concerning the effect of a Mediterranean diet on blood lipid levels (80, 90). Recent reports from the PREDIMED study reported a potential cardiovascular protective profile related to the size of HDL and LDL particles (98), function of HDL (99), and oxidative profile of LDL (100) after 1 year on a Mediterranean diet. However, in line with the NHLBI and USDA systematic reviews on clinical lipid profiles (80, 90), individuals in both Mediterranean diet arms of PREDIMED showed no significant improvements in hypertriglyceridemia or low HDL levels [defined as component criteria of the metabolic syndrome (10)] compared with those in the low-fat control diet arm (95).

2.4 In individuals at metabolic risk, we recommend prescribing daily physical activity, such as brisk walking, and reduction in sedentary time. (1|⊕⊕⊕◯)

Technical remark: Providers should encourage all individuals at metabolic risk to adopt an active lifestyle by walking and reducing the amount of time in sedentary activities. Structured activity programs may be added with the help of an exercise specialist for appropriate individuals.

Evidence

Physical activity and diabetes prevention

Among the diabetes prevention trials, the Da Qing Study directly compared exercise, diet, and a combination of diet and exercise (69). The exercise intervention (alone or in combination) mainly emphasized walking as a leisure activity and generally encouraged participants to increase their activity levels by at least "1 unit" per day, which was equivalent to 30 minutes of mild intensity (such as walking slowly, housecleaning), 20 minutes of moderate intensity (such as brisk walking, cycling), 10 minutes of strenuous activity (jogging, climbing stairs), or 5 minutes of very strenuous activity (jumping rope, basketball). The Da Qing Study showed a significant reduction of 46% in diabetes incidence during 6 years in the exercise-only arm, which was comparable to the other arms (a slightly greater reduction effect, yet not significantly greater than that of the other arms) (69).

In the US-based DPP study, participants in the lifestyle arm were encouraged to engage in physical activity of moderate intensity, such as brisk walking, for at least 150 minutes per week, and 74% of participants had achieved that goal at the end of the 24-week initial phase of intervention (11). The DPP lifestyle participants achieved a mean activity level of 208 minutes per week after 1 year and sustained a mean of 189 minutes per week at the end of the active intervention study period (median, 2.8 years). Although weight loss was the dominant predictor of diabetes risk reduction, DPP lifestyle participants with the highest levels of physical activity were more successful with long-term weight loss (85). Moreover, among the subgroup of lifestyle participants not meeting the weight loss goal after 1 year, those who achieved the physical activity goal of >150 minutes per week had 44% lower diabetes incidence (85).

Similarly, in the Finnish Diabetes Prevention Study, participants who met their physical activity goal but did not meet the weight loss goal had a significant reduction in diabetes incidence (71). Specifically, increases in moderate-to-vigorous leisure time physical activity and in strenuous, structured leisure time physical activity resulted in 63% to 65% reductions in diabetes risk, even after adjustment for changes in weight (83).

The recent *2018 Physical Activity Guidelines Advisory Committee Scientific Report* (84) also concludes that physical activity reduces diabetes risk and estimates that 150 to 300 minutes per week of moderate-to-vigorous physical activity leads to a 25% to 35% reduction in the risk of developing diabetes. The report noted that the relationship between activity level and diabetes risk reduction is a curvilinear slope, with greater benefits from increased physical activity being accrued by individuals who previously had low physical activity levels or who were considered inactive. No lower threshold for benefits was identified. Moreover, the report stated that increased time spent in sedentary behaviors is associated with a higher risk of developing type 2 diabetes (84).

Physical activity, BP, and lipids

Both the 2013 report from the NHLBI (80) and the *2018 Physical Activity Guidelines Advisory Committee Scientific Report* (84) provided "strong evidence" that physical activity lowers BP and reduces the risk of incident hypertension based on multiple systematic reviews and meta-analyses. In individuals with prehypertension, these meta-analyses reported a reduction of ~2 to 5 mm Hg for systolic BP and ~1 to 4 mm Hg for diastolic BP with regular physical activity. In individuals with

Table 7. Nutrient Action

Nutrient Action	LDL-C	HDL-C	TGLs
Replacing saturated fats with polyunsaturated or monounsaturated fatty acids	Lower	Higher	
Replacing saturated fats with polyunsaturated fatty acids			Lower
Replacing saturated fats with carbohydrates	Lower	Higher	Higher
Replacing *trans* fat with monounsaturated or polyunsaturated fatty acids	Lower	Higher	Lower
Replacing carbohydrates with monounsaturated or polyunsaturated fatty acids	Lower	Higher	Lower
Adding polyunsaturated fatty acids	Lower		Lower
Adding monounsaturated fatty acids		Higher	

See Lifestyle Work Group (80).

hypertension, the estimated effect is greater (~8.3/5.2 mm Hg lower) with aerobic exercise (84). The 2013 report from the NHLBI revealed that the typical interventions shown to be effective for lowering BP were of at least 12 weeks' duration, supporting three to four sessions of aerobic physical activity per week, lasting on average 40 minutes per session, and involving moderate- to vigorous-intensity physical activity (80). The 2018 NHLBI scientific report now highlights that aerobic and dynamic resistance exercise may be equally effective in reducing BP at a lower volume of physical activity. As with diabetes risk, the benefits to BP of increasing physical activity are greater in individuals starting at low levels of physical activity (84).

The 2013 NHLBI systematic review also reported that aerobic physical activity reduces LDL-C by an average of 2.5 to 6.0 mg/dL and non–HDL-C by an average of 6.0 mg/dL (80). In contrast, they reported that they did not find a consistent effect of aerobic activity on TGLs and HDL-C. Finally, the NHLBI reported that resistance training reduces LDL-C, TGLs, and non–HDL-C by 6 to 9 mg/dL on average and reported no consistent effect on HDL-C.

Additional information on this topic is presented in recommendation 3.7 and see Table 10.

Physical activity and ASCVD incidence

The *2018 Physical Activity Guidelines Advisory Committee Scientific Report* (84) stated that an increased amount of physical activity is associated with a lower incidence of ASCVD and lower ASCVD mortality. Based on the most updated evidence, the 2018 NHLBI scientific report continues to support the previously recommended levels of ≥150 minutes of at least moderate levels of physical activity. Individuals at an initially low level of physical activity receive greater benefits, with no lower (or upper) threshold. The benefits continue to accrue with additional physical activity, but there is no clear optimal amount. The report indicated that increased time spent in sedentary behavior is associated with a higher risk of incident ASCVD.

Gaps in physical activity research

This guideline Writing Committee, and other groups (80, 84, 101), have noticed a lack of high-quality interventional studies investigating the effect of physical activity in the primary prevention of ASCVD with long-term follow-up on actual ASCVD outcomes. Many interventional studies have investigated the inclusion of aerobic activity and/or resistance training as part of leisure time, but interventional studies are needed that will investigate other components of active behaviors such as transportation, occupational activities, and reductions or interruptions in (84) sedentary time. It is hoped such studies will include both intermediate risk factors and outcomes such as diabetes and ASCVD events.

Other lifestyle issues

Tobacco. Tobacco consumption is a well-established cause of ASCVD. Many observational prospective studies and meta-analyses of cohort studies have also supported a link between tobacco and the risk of developing diabetes (102, 103). Thus, primary prevention of ASCVD and diabetes should undoubtedly include counseling on smoking cessation and avoidance of tobacco. The 5As-type counseling approach has demonstrated positive outcomes (104). This approach delineates five counseling steps that a provider can complete in a few minutes: (i) Assess the risk behavior, (ii) Advise change, (iii) Agree on goals and an action plan via shared decision-making, (iv) Assist with treatment, and (v) Arrange follow-up (104). Providers should offer a combination of pharmacological and behavioral/psychological support to optimize the chance of success (105). Individuals can highly benefit from psychological support programs (105), currently offered by phone or online, when in-person formats are not available locally or are inconvenient for logistical reasons. Providers should inquire not only about cigarette consumption but also about other tobacco products (electronic cigarettes, cigarillos, chewing tobacco). Electronic cigarettes are currently a high priority for research on ASCVD prevention, and more data are needed (106–108).

Sleep disorders. Sleep disorders are emerging risk factors for many health conditions, and abnormal sleep patterns have been associated with risk of obesity, diabetes, and ASCVD (109, 110). Providers should screen individuals at metabolic risk and recommend diagnostic testing for sleep apnea when suspected, given that it is a frequent comorbid condition of obesity, diabetes, and ASCVD (109). Treatment of obstructive sleep apnea can reduce symptoms of daytime somnolence and improve quality of life (111)—which may help some individuals to have more energy to be more active physically—but strong evidence and long-term interventional studies supporting the benefits of the prevention of cardiovascular events is lacking (109, 111).

Stress. Stress has also been increasingly recognized as an important risk factor for predicting ASCVD events (112, 113). Stress management interventions—such as relaxation-based methods and cognitive behavioral techniques—have been included in secondary ASCVD prevention programs resulting in potential benefits (114). Nevertheless,

evidence is lacking regarding the efficacy of stress management interventions on the primary prevention of ASCVD and diabetes.

3. Medical and Pharmacological Therapy

Risk assessment and evaluation

3.1 In individuals identified as having metabolic risk, we recommend global assessment of 10-year risk for either CHD or ASCVD to guide the use of medical or pharmacological therapy. (1|⊕⊕⊕◯)

Technical remark: Global risk assessment includes the use of one of the established cardiovascular risk equations. Elevated LDL is indicative of cardiovascular risk.

Evidence

Several methodologies have been developed to assess 10-year cardiovascular risk status (115–117). The Framingham Heart Study CVD 10-year risk calculator (Framingham risk calculator) is a sex-specific algorithm that predicts the 10-year risk of having any cardiovascular event. The PROCAM risk algorithm calculates the risk of MI based on the 10-year follow-up of the PROCAM study. The Systematic Coronary Risk Evaluation (SCORE) risk charts, the European cardiovascular disease risk assessment model, are based on the results of 12 European cohort studies. These cardiovascular risk charts are based on sex, age, total cholesterol, systolic BP, and smoking status and are used to predict death due to MI. More recently, as part of two ACC/AHA guidelines that addressed assessment and treatment of cardiovascular risk (30, 118), a pooled cohort equation approach was developed (119, 120).

In comparison studies of the various guidelines, several reports have found that the pooled cohort equation offers better discrimination and net benefit regarding cardiovascular risk assessment. Although this method carries a risk for overestimation of risk, it was identified as the best available methodology to date by the US Preventive Service Task Force (121–124). Collectively, these risk calculation methods use easy-to-collect clinical parameters, such as age, use of cigarettes, BP, and serum lipid levels. Other risk calculators that are less widely used have also been published. The United Kingdom Prospective Diabetes Study risk engine has been developed with validated ASCVD risk estimates for people with T2DM (125, 126), although the population with previously diagnosed diabetes is outside the framework of the primary prevention population considered in this guideline. As other authors have published findings comparing the different algorithms, this Writing Committee made no attempt to undertake such comparisons among different population groups (127, 128). The Writing Committee recommends that 10-year risk for CHD be assessed for individuals using published algorithms that best pertain to the individuals from a particular population group. Clinical judgment or national or regional recommendations can be used for making these assessments.

3.2 In individuals with LDL-C ≥190 mg/dL (4.9 mmol/L) or TGLs ≥500 mg/dL (<5.6 mmol/L), we recommend that, before considering the diagnosis of primary hyperlipidemia, practitioners should rule out secondary causes of hyperlipidemia. If a secondary cause can be excluded, primary hyperlipidemia should be suspected. (1|⊕⊕⊕◯)

Technical remark: Examples of secondary causes of hyperlipidemia include: untreated hypothyroidism, nephrotic syndrome, renal failure, cholestasis, acute pancreatitis, pregnancy, polycystic ovarian disease, excess alcohol use, treatment with estrogens/oral contraceptives, antipsychotic agents, glucocorticoids, cyclosporine, protease inhibitors, retinoids, and beta blockers.

Evidence

Elevated values of LDL-C (≥190 mg/dL) or TGLs (≥500 mg/dL) are likely to be due to primary hyperlipidemia from a genetic cause (known or unknown). However, before considering the diagnosis of primary hyperlipidemia, secondary causes of hyperlipidemia need to be ruled out. Because secondary hyperlipidemia is not rare, evaluation of underlying conditions that could be causing or exacerbating dyslipidemias is necessary before initiating or intensifying treatment as recommended in current guidelines (129–131). Secondary hyperlipidemia can occur as an isolated cholesterol elevation, an isolated TGL elevation, or as a combined pattern. Increased LDL-C levels (>190 mg/dL), high TGL levels (>500 mg/dL), xanthomas, a strong family history of hyperlipidemia, or a lack of an expected response to maximal therapeutic doses of lipid-lowering agents indicate primary hyperlipidemia. Secondary hyperlipidemia may result from different metabolic and endocrine conditions, liver or kidney disease, HIV, drug therapy, or dietary factors. As dyslipidemia may be an early indication, recognizing an underlying condition may alter subsequent treatment decisions. Furthermore, some dyslipidemias can appear to be refractory to drug treatment in the presence of an ongoing unrecognized secondary cause. For example,

untreated diabetes mellitus or excessive alcohol intake can render medical therapy for hypertriglyceridemia much less effective.

Cholesterol reduction

3.3 In individuals 40 to 75 years of age with LDL-C ≥190 mg/dL (≥5.9 mmol/L), we recommend high-intensity statin therapy to achieve an LDL-C reduction of ≥50% (Table 8). (1|⊕⊕⊕◯)

3.4 In individuals 40 to 75 years of age with LDL-C 70 to 189 mg/dL (1.8 to 4.9 mmol/L), we recommend a 10-year risk for ASCVD should be calculated. (1|⊕⊕⊕◯)

3.4.1 In individuals 40 to 75 years of age without diabetes and a 10-year risk ≥7.5%, we recommend high-intensity statin therapy either to achieve an LDL-C goal <100 mg/dL (<2.6 mmol/L) or an LDL-C reduction of ≥50% (Table 8). (1|⊕⊕⊕◯)

3.4.2 In individuals 40 to 75 years of age without diabetes and a 10-year risk of 5% to 7.5%, we recommend moderate statin therapy as an option after consideration of risk reduction, adverse events, drug interactions, and individual preferences, to achieve either an LDL-C goal <130 mg/dL (<3.4 mmol/L) or an LDL-C reduction of 30% to 50%. (1|⊕⊕⊕◯)

3.4.3 In individuals with metabolic risk, without diabetes, on statin therapy, we suggest monitoring glycemia at least annually to detect new-onset diabetes mellitus. (2|⊕⊕⊕◯)

3.4.4 In individuals aged >75 years without diabetes and a 10-year risk ≥7.5%, we recommend discussing the benefits of statin therapy with the patient based on expected benefits vs possible risks/side effects (Table 8). (1|⊕⊕⊕◯)

Technical remark: Decisions should be made on a case-by-case basis depending on estimates of likely benefits vs risks in individual patients. Statin therapy should be calibrated to reach the recommended LDL targets.

Evidence

Many large-scale clinical trials on statin use have documented a clear reduction in cardiovascular events by reduction in LDL-C level (34). This finding served as a foundation for recommendations and guidelines issued by the National Institutes of Health and the AHA, identifying treatment goals of LDL-C levels for individuals at varying degrees of cardiovascular risk. Although the risk factor role of LDL-C is well recognized, the most recent revision of cholesterol recommendations for the treatment of individuals at cardiovascular risk issued by the ACC/AHA has, to some extent, deviated from previous versions. Based on evidence from clinical trials, the guidelines recommend statin treatment of categories of individuals considered at increased metabolic risk (118). Treatment is recommended where a risk reduction outweighs the risk of adverse events. Those considered to be at risk include: (i) individuals of any age with high LDL-C, (ii) individuals >40 years of age who suffer from diabetes, and (iii) individuals without clinical ASCVD or diabetes with LDL-C levels of 70 to 189 mg/dL and an estimated 10-year risk for ASCVD of ≥7.5%. (For individuals ≥75 years of age, an assessment regarding benefit vs risk is appropriate.)

In these ACC/AHA guidelines, specific treatment goals for LDL-C are not emphasized, although reducing the

Table 8. Statin Therapy

Intensity	Definition	Dosage
Low	Daily dose lowers LDL-C by <30%, on average	Simvastatin 10 mg Pravastatin 10–20 mg Lovastatin 20 mg Fluvastatin 20–40 mg Pitavastatin 1 mg
Moderate	Daily dose lowers LDL-C by ~30% to ≥ 50%, on average	Atorvastatin 10–20 mg Rosuvastatin 5–10 mg Simvastatin 20–40 mg Pravastatin 40–80 mg Lovastatin 40 mg Fluvastatin extended release 80 mg Fluvastatin 40 mg twice a day Pitavastatin 2–4 mg
High	Daily dose lowers LDL-C by ≥50% or more, on average	Atorvastatin 40–80 mg Rosuvastatin 20–40 mg

plasma LDL-C level has been shown to significantly decrease the risk for cardiovascular disease with a 22% reduction rate in major vascular events with each reduction in LDL-C of 38.7 mg/dL (132). The ACC/AHA guidelines have stimulated an exchange of views in the literature with differing perspectives (133, 134) and, notably, Canadian guidelines recommend treatment to target rather than by therapy dose (135, 136).

Recently, the US Preventive Services Task Force updated their recommendation for screening for lipid disorders in adults based on a systematic review of the benefits and harms of statins (125, 137). The task force recommended the use of a low-to-moderate dose of a statin to prevent ASCVD events and mortality in adults aged 40 to 75 years with at least one ASCVD risk factor (*e.g.*, dyslipidemia, diabetes, hypertension, or smoking) and a calculated 10-year risk of cardiovascular events of ≥10%. Although the estimation of risk is acknowledged to be fraught with some degree of uncertainty, and the pooled cohort equations from the ACC/AHA guideline might overestimate risk, the tool was considered the best available at the time (120, 123, 124, 138, 139). The task force also concluded that direct evidence of whether different therapy doses or treatment-to-target strategies would affect clinical outcomes is extremely limited. A recent meta-analysis suggested that lower LDL-C levels were associated with a lower RR of major vascular events, underscoring that the issue of specific LDL-C targets remains unresolved (140, 141). Given this conundrum, some have advocated the incorporation of both LDL-C levels and ASCVD risk into treatment recommendations, as is the case for European guidelines (130, 142).

One concern in deemphasizing LDL-C goals is the risk of eliminating a potentially motivational tool for goal-directed behavior for patients and practitioners (143). Indeed, goal setting and goal-directed actions are long-standing practices in changing human behavior. Thus, it cannot be excluded that a lack of LDL-C treatment goals for any individual might reduce motivation and compliance as well as reduce awareness among treating physicians (144). Therefore, in deemphasizing LDL-C treatment goals, the 2013 ACC/AHA guidelines may have inadvertently eliminated a motivational tool for goal-directed behavior. Prior studies have shown generally poor adherence to statin therapy a year after initiation, even with the elimination of cost as a factor, which is of particular relevance for long-term treatment (145, 146). Alternatively, eliminating LDL-C targets may reduce polypharmacy with lipid-lowering medications and reduce the risk of medication side effects. However, on balance, LDL-C treatment goals may be useful in clinical practice, and a lack of these goals might adversely affect the individual's motivation and treatment adherence.

Owing to the wide adoption of statin treatment, data supporting an association between statin treatment and an increase in the incidence of new-onset T2DM has raised concerns (147–152). Meta-analyses have reported in aggregate a 9% increased risk for incident diabetes mellitus during statin treatment, with no clear difference among different statin drugs (153). However, the risk appears to be seen primarily with use of high-dose statins (124, 154, 155). As the benefits of statins for reduction in cardiovascular risk are well documented in individuals with or without diabetes, these risks should be taken carefully into consideration. Regular monitoring of glycemic status is warranted in individuals at high risk for the development of diabetes mellitus during statin therapy.

Other hypocholesterolemic agents

The first-line drug treatment of hypercholesterolemia is a statin. If the LDL target is not obtained with the optimal dose of a statin, additional treatment with ezetimibe or cholestyramine are options. In the case of confirmed statin intolerance after testing alternative statins at low doses, or in the case of any contraindication to statins, treatment alternatives are ezetimibe or cholestyramine. Anti-PCSK9 treatments are currently used in cases of severe familial hypercholesterolemia uncontrolled with statins.

Balance of benefits and harms

This recommendation was developed within the context of the sizable benefit to patients that derived from early preventive care in vulnerable populations. The Writing Committee thinks that this benefit outweighs the patient burden of early therapy with medications that lower BP and cholesterol. The Writing Committee also recognizes the added benefit of clinicians using a simple, easy-to-measure risk calculator in the clinical setting, despite the lack of data to compare the relative efficacy of the different risk scoring systems.

3.5 In individuals at metabolic risk who are taking statins with adequate LDL-C reduction, elevated TGL levels [≥200 mg/dL (2.3 mmol/L)], and reduced HDL levels [≤50 mg/dL (1.3 mmol/L) in females, or ≤40 mg/dL (1.0 mmol/L) in males], we suggest considering fenofibrate adjunct therapy. (2|⊕⊕⊕◯)

Technical remark: Statin treatment goals are identified in Table 9. Low HDL-C levels are defined in Table 1. Avoid gemfibrozil in this situation.

Evidence

Many individuals at metabolic risk have multiple lipid-based abnormalities, including elevations in TGLs,

reductions in HDL-C, and, in some cases, an increase in lipoprotein(a) (156–159). In recent years, more studies have documented a causal association between increases in TGLs as well as lipoprotein(a) levels and cardiovascular disease (158–163). Although epidemiological studies have well established that low HDL-C levels are associated with cardiovascular risk, it has been difficult to establish a causal relationship between decreased HDL-C and cardiovascular disease (164–166). Altogether, increases in TGL and lipoprotein(a) levels contribute to an increase in the level of cholesterol-carrying particles containing apolipoprotein B-100 (157, 159, 167). Elevations in apolipoprotein B–containing lipoproteins [LDL, VLDL, and lipoprotein(a)], characteristic of most individuals at metabolic risk, are associated with increased ASCVD risk (34, 168). A large number of randomized controlled clinical trials, many using statins, documented that lowering apolipoprotein B–containing lipoproteins reduces the risk for ASCVD (34).

The possible role of HDL-C in cardiovascular risk has attracted much interest. Although an increase in HDL-C levels would be expected to lower ASCVD risk, a number of recent randomized clinical trials focused on raising HDL-C levels using various agents/strategies have failed to show any beneficial effects on ASCVD outcomes (169–173). The Writing Committee thinks that there is insufficient evidence to indicate that an increase in HDL-C level *per se* would serve to reduce cardiovascular risk and that any recommendation regarding efforts to increase HDL-C levels would be premature.

In contrast to the case of HDL-C, Mendelian randomization studies have indicated a causal relationship between either TGLs or lipoprotein(a) and ASCVD (166, 174, 175). Many studies have provided support for a causative role of TGL and TGL-rich lipoproteins in ASCVD. This finding is relevant because of the common occurrence of increases in TGL levels among subjects at metabolic risk (176).

Non–HDL-C levels (representing cholesterol carried in atherogenic lipoproteins) have been considered important in guiding treatment to reduce cardiovascular risk (177–181). For this reason, for individuals at metabolic risk, attempts to reduce apolipoprotein B–containing lipoproteins by lowering non–HDL-C are prudent. This reduction may involve multiple avenues, including lifestyle modification addressing diet and exercise regimens as well as the use of TGL-lowering drugs such as fibrates, niacin, and ω-3 fatty acids (158, 159, 182). In both the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial and the Action to Control Cardiovascular Risk in Diabetes Lipid (ACCORD-Lipid) trial, fenofibrate alone or in combination with a statin significantly reduced the risk for major cardiovascular events in the subgroup of individuals with elevated TGLs and low HDL-C (61, 183). This finding was confirmed in a meta-analysis demonstrating a 35% reduction in the risk of major cardiovascular events with fibrates in individuals presenting with hypertriglyceridemia and low HDL-C (140, 184). Fibrates may be considered an add-on drug to statins (or LDL-C–lowering drugs) in individuals who persist with high TGLs and low HDL-C after LDL-C–lowering therapy (184). If a fibrate is used with the statin, fenofibrate is the drug of choice due to evidence of minimal interaction with statins and decreased risk of myopathy with this drug (185–187). Gemfibrozil should not be used in combination with statins due to an elevated risk for myopathy (188–190).

3.6 In individuals ≥40 years of age at metabolic risk with LDL-C at target, an estimated 10-year ASCVD risk of >7.5%, and without clinical ASCVD or other ASCVD risk factors, we suggest treatment with a moderate-intensity statin. (2|⊕⊕⊕◯)

Table 9. Treatment Recommendations and LDL-C Goals for Treatment

Primary Prevention	Statin Treatment	LDL-C Goal or % Reduction
• Adults with LDL-C ≥190 mg/dL (≥4.9 mmol/L)	High intensity	≥50% reduction of LDL-C
• Individuals 40–75 y of age without diabetes and LDL-C 70–189 mg/dL (1.8–4.9 mmol/L) • and a 10-y risk ≥7.5%	Moderate or high intensity	<100 mg/dL (<5.6 mmol/L) or ≥50% reduction of LDL-C
• Individuals 40–75 y of age without diabetes and LDL-C 70–189 mg/dL (1.8–4.9 mmol/L) • and a 10-y risk of 5% to <7.5%	Consider moderate intensity	<130 mg/dL (<3.4 mmol/L) or 30%–50% reduction of LDL-C
• Individuals aged >75 y without diabetes and LDL-C 70–189 mg/dL (1.8–4.9 mmol/L) • and a 10-y risk ≥7.5%	Consider first low intensity, after discussion with the patient	<130 mg/dL (< 3.4 mmol/L) or 30%–50% reduction of LDL-C

ASCVD risk factors include LDL-C ≥100 mg/dL (2.6 mmol/L), high BP, smoking, chronic kidney disease, albuminuria, and family history of premature ASCVD.

Evidence

Data from three exclusively primary prevention RCTs and a systematic review that included individuals with LDL-C levels <190 mg/dL and >70 mg/dL document the benefit of statin therapy (191–194). Estimates of expected 10-year ASCVD event rates were derived from the placebo groups and estimates of excess adverse events from the statin groups of meta-analyses of statin RCTs. The studies found high-level evidence for an ASCVD risk-reduction benefit from initiation of moderate- or high-intensity statin therapy in individuals 40 to 75 years old with a >7.5% estimated 10-year risk for ASCVD. The details of risk assessment calculation are presented in detail in the ACC/AHA blood cholesterol guidelines (118).

The reduction in ASCVD risk clearly outweighs the potential for adverse effects (118). Further support for this statement comes from the recent HOPE 3 study demonstrating that even people with low-to-intermediate cardiovascular risk had a clear mortality reduction with low-dose statin therapy (195). Thus, it is recommended that individuals 40 to 75 years of age, who are not already candidates for statin therapy, receive moderate-intensity statin therapy (Tables 8 and 9) when they have a >7.5% estimated 10-year risk for ASCVD and an LDL-C value of 70 to 189 mg/dL. This overall observation is further supported by the Cholesterol Treatment Trialists' 2010 meta-analysis that found a relative reduction in ASCVD events of similar magnitude across the spectrum of LDL-C levels >70 mg/dL (132). This recommendation is further reinforced by an overview of 12 systematic reviews of primary prevention with statins (194).

Blood pressure reduction

3.7 In individuals with BP >130/80 mm Hg and a 10-year cardiovascular risk ≤10%, we suggest lifestyle management to lower BP to <130/80 mm Hg to reduce the risk for ASCVD. (2|⊕⊕⊕◯)
Technical remark: Because the 10-year risk is ≤10%, lifestyle intervention is appropriate and preferable to use of medications. Table 10 (196–207) summarizes the relative impact of various behavioral and lifestyle changes on lowering of BP. These interventions include weight loss, healthy diet, sodium restriction, enhanced potassium intake, increased physical activity, and moderation of alcohol use.

Evidence

An overview of six systematic reviews of RCTs of BP-lowering therapy document a benefit of keeping BP <140 mm Hg systolic or to levels <130 mm Hg in high-risk individuals to maximally reduce ASCVD events (194, 208–212). The most comprehensive systematic reviews included 25 trials with 163,131 participants (213) and 27 trials with 108,297 participants (209, 214–217). The data from these analyses had a mean participant age ranging from 30 to 80 years, and the weighted mean age in the most comprehensive systematic review was 62 years.

In contrast, people at low or intermediate risk do not have the same magnitude of benefit of systolic BP reduction to levels <130 mm Hg. HOPE 3 was a placebo-controlled study examining whether further lowering of BP among those with a systolic BP <140 mm Hg and intermediate cardiovascular risk further reduced cardiovascular events. After a median follow-up of 5.6 years, treating a systolic BP <140 mm Hg had no significant effect on cardiovascular risk reduction, whereas treating that of ~140 mm Hg did (218).

3.8 In adults without a history of ASCVD with metabolic risk who have a 10-year cardiovascular risk of >10% and BP of >130/80 mm Hg, we suggest the use of BP-lowering medication in addition to lifestyle modifications for primary prevention of ASCVD only when lifestyle modification alone has failed. (2|⊕⊕⊕◯)

Evidence

Only a few studies address appropriate BP management for primary prevention of ASCVD events in people with metabolic syndrome who have neither diabetes nor diagnosed ASCVD. Thus, other than lifestyle management (Table 10), the optimal antihypertensive approach is not clear. A *post hoc* analysis of SPRINT notes that lower BP levels among those with metabolic syndrome provided similar cardiovascular risk reduction to those without the metabolic syndrome (219). Guideline recommendations (54) should be followed for lowering BP in both groups. Note that beta-blockers should be avoided for hypertension treatment in individuals who are overweight or obese, due to the risk of weight gain (220, 221). Current guidelines recommend initial therapy with either a calcium channel blocker, renin angiotensin system inhibitor, or thiazide diuretic (54).

Three studies evaluated people with metabolic syndrome who were at elevated cardiovascular risk. These trials include HOPE 3, DREAM, and ALLHAT. Additionally, a meta-analysis and systematic review of trials that compared more intensive to standard BP reduction (222) reported that more intense lowering of BP reduces the risk of stroke, coronary events, major cardiovascular events, and cardiovascular mortality. In a

Table 10. Best Proven Nonpharmacologic Interventions for Prevention and Treatment of Hypertension

Nonpharmacologic Intervention		Dose	Approximate Impact on Systolic BP		
			Hypertension	Normotension	References
Weight loss	Weight/body fat	Best goal is ideal body weight but aim for at least a 1 kg reduction in body weight for most adults who are overweight. Expect ~1 mm Hg for every 1 kg reduction in body weight.	−5 mm Hg	−2/3 mm Hg	(196)
Healthy diet	DASH dietary pattern	Consume a diet rich in fruits, vegetables, whole grains, and low-fat dairy products with reduced content of saturated and total fat.	−11 mm Hg	−3 mm Hg	(197, 198)
Reduced intake of dietary sodium	Dietary sodium	Optimal goal is < 1500 mg/d but at least 1000 mg/d reduction in most adults	−5/6 mm Hg	−2/3 mm Hg	(199, 200)
Enhanced intake of dietary potassium	Dietary potassium	3500–5000 mg/d, preferably by consumption of a diet rich in potassium	−4/5 mm Hg	−2 mm Hg	(201)
Physical activity	Aerobic	• 90–150 min/wk • 65%–75% heart rate reserve	−5/8 mm Hg	−2/4 mm Hg	(202, 203)
	Dynamic resistance	• 90–150 min/wk • 50%–80% one rep maximum • Six exercises, three sets per exercise, 10 repetitions per set	−4 mm Hg	−2 mm Hg	(202)
	Isometric resistance	• Four for 2 min (hand grip), 1 min rest between exercises, 30%– 40% maximum voluntary contraction, three sessions per wk • 8–10 wk	−5 mm Hg	−4 mm Hg	(204, 205)
Moderation in alcohol intake	Alcohol consumption	In individuals who drink alcohol, reduce alcohol[a] to: • Men: two or fewer drinks daily • Women: less than one drink daily	−4 mm Hg	−3 mm Hg	(203, 206, 207)

The type, dose, and expected impact on BP in adults with a normal BP and with hypertension are shown.

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[a]In the United States, one "standard" drink contains roughly 14 g of pure alcohol, which is typically found in 12 oz of regular beer (usually about 5% alcohol), 5 oz of wine (usually about 12% alcohol), and 1.5 oz of distilled spirits (usually about 40% alcohol).

stratified analysis of these data, using three different systolic BP cutoffs (150, 140, and 130 mm Hg), achieving an additional 10 mm Hg reduction in systolic BP reduced ASCVD risk in all of the outcomes mentioned above. However, in this meta-analysis, many individuals had established hypertension, and in HOPE 3, there was no reduced risk of CV events among those <140/90 mm Hg (218).

In the DREAM trial (223), the primary outcomes were newly diagnosed diabetes or death, and the mean systolic BP at baseline was 136.1 mm Hg. The results showed no difference in the primary endpoints.

In the ALLHAT trial, 31,512 adults, ≥55 years or age, with hypertension and at least one other risk factor for CHD were stratified into IFG (n = 1399) and normoglycemic (n = 17,012) groups. Participants were randomly assigned to double-blind first-step treatment with chlorthalidone, amlodipine besylate, or lisinopril. The primary outcome was the composite of fatal CHD or nonfatal MI, total mortality, and other clinical complications. There was no significant difference in RR for the primary outcome among those with IFG or normoglycemia irrespective of randomized drug.

Use of thiazide diuretics and/or beta-blockers in people with metabolic syndrome can increase insulin resistance, dyslipidemia, and hyperuricemia and worsen glucose intolerance. However, these metabolic changes have not translated into a reduced cardiovascular benefit. Indeed, as shown in the follow-up of ALLHAT, long-term diuretic use was associated with an increase in fasting glucose levels among those with IFG. This increase in glucose into the diabetes range was not associated with increased ASCVD risk after a 12-year follow-up, as long as the diabetes was treated (224). Additionally, *post hoc* analysis of nearly two-thirds of participants in ALLHAT who met the criteria for metabolic syndrome revealed that chlorthalidone was similar to lisinopril or amlodipine in regard to reducing ASCVD risk (225, 226).

Use of traditional beta-blockers may lead to deterioration of glucose tolerance, dyslipidemia, and inability to lose weight. Several large clinical trials documented a 15% to 29% increased risk of developing diabetes as a result of traditional beta-blocker therapy (227, 228).

However, newer vasodilating beta-blockers (*e.g.*, carvedilol and nebivolol) have shown neutral or favorable effects on metabolic profiles compared with traditional beta-blockers and might be a practical option for the treatment of hypertension in the metabolic syndrome (229–231). The novel vasodilator beta-blocker nebivolol has a very good metabolic profile among beta-blockers but has never been tested for cardiovascular outcomes except in older people (231, 232). Nebivolol has been evaluated in older people with heart failure with and without diabetes, but there are no outcome data in people with metabolic syndrome (233). Notably, a diuretic or beta-blocker, when used alone in individuals who are overweight or obese with IFG, will increase the risk for diabetes development (229, 234, 235). In many cases, diabetes is reversible but not always (236).

Reducing progression to type 2 diabetes

3.9 In individuals with prediabetes, we recommend prescribing lifestyle modification before drug therapy to reduce plasma glucose levels. (1|⊕⊕⊕⊕)

3.10 In individuals with prediabetes who have limitations to physical activity or are not responding to lifestyle modifications, we recommend metformin as a first pharmacologic approach to reduce plasma glucose levels. (1|⊕⊕⊕◯)

Evidence

Clinical trial evidence indicates that the risk for diabetes can be markedly reduced by lowering plasma glucose levels in individuals with prediabetes (as defined in recommendation 1.4). Glucose concentrations can be reduced by either lifestyle intervention (as described in "2. Lifestyle and Behavioral Therapy" above) or drug therapy. In the DPP, both metformin and troglitazone were shown to delay the conversion of prediabetes to diabetes (11, 237). Metformin reduced the risk of developing diabetes by 31% over ~4 years (during randomized blinded active phase of DPP trial) and 18% during 10 and 15 years of follow-up (based of DPP Outcomes Study open follow-up) (238). At the 15-year follow-up, both metformin and lifestyle interventions prevented microvascular events in the DPP Outcomes Study participants (238). Moreover, metformin was estimated to be a cost-saving intervention when prescribed for diabetes prevention (238). Two clinical trials have assessed the effect of thiazolidinediones in diabetes prevention, the Troglitazone in the Prevention of Diabetes (TRIPOD) trial using troglitazone (239) and the DREAM trial using rosiglitazone (223). However, evidence of potential harmful effects related to thiazolidinediones has decreased clinical use in recent years, and careful assessment of the potential harms-to-benefits ratio must be undertaken for each individual before considering treatment with this class (240). Insulin is a highly efficacious drug for lowering glucose: in the Outcome Reduction With Initial Glargine Intervention (ORIGIN) trial, basal insulin treatment with glargine insulin during a period of 6.2 years resulted in a 28% RR

reduction in the development of diabetes in high-risk individuals (241).

α-Glucosidase inhibitors have also been demonstrated to reduce the progression to diabetes in people with prediabetes and are commonly used in populations consuming an Asian diet. In the Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) multinational study, acarbose was progressively increased to 100 mg three times daily as tolerated during a mean follow-up period of 3.3 years. This dosage resulted in a 25% RR reduction for conversion to diabetes and a 49% RR reduction for the development of cardiovascular events (242). In a Japanese study, treatment with voglibose at a dosage of 0.3 mg three times daily reduced the risk of progression to diabetes by 40%, but the study was not adequately powered to evaluate the effects on cardiovascular events (243).

Overall, the Writing Committee suggests metformin as the first pharmacological approach (with the exception of patients for whom it is contraindicated) because metformin has been shown to reduce the risk of diabetes by 31% during ~4 years of active treatment in DPP (11), and to have a long-term effect on diabetes prevention and a reduction in microvascular events (238). Furthermore, metformin is relatively low in cost, is generally well tolerated, has a good safety profile, and its oral administration is largely acceptable to patients. Acarbose is also recommended for its efficacy as long as patients can tolerate the gastrointestinal effects (up to three-fourths of individuals experience flatulence and approximately one-third report diarrhea).

A meta-analysis including 42 trials commissioned by the guideline Writing Committee found some evidence that α-glucosidase inhibitors, angiotensin-converting enzyme inhibitors, ARBs, metformin, orlistat, phentermine-topiramate, and pioglitazone significantly reduced the risk of biochemical conversion to T2DM, whereas statins and nateglinide increased that risk. Of these, metformin is the most sensible first-line agent purely for diabetes prevention, given its efficacy, safety, and tolerability (low risk profile of severe side effects) and protective effect shown in RCTs. Others of these agents have specific benefits for treating individual components of metabolic risk, such as hypertension and obesity, but they do not have enough evidence to support their use for diabetes prevention (5).

4. Further Research

Current gaps in science

1. Our understanding of the various factors affecting the underlying pathogenesis of metabolic syndrome and its risk for ASCVD or T2DM has expanded. More research is needed, however, especially related to the role of increased inflammation as seen in the liver and in blood vessels and the connection to insulin resistance, atherosclerosis, and β-cell failure. More studies are needed on the relationship between the metabolic syndrome and nonalcoholic fatty liver disease and nonalcoholic steatohepatitis and on how this relationship affects new medical therapies for these conditions. Better understanding is needed of the extent to which reduction in liver fat, by medications or otherwise, eventually reduces ASCVD.
2. Does the addition of one or more of the newer biomarkers (as described in section 1.1) that correlate with metabolic risk enhance the predictive power of these simple equations for ASCVD or T2DM, and do they affect the therapeutic intervention? The estimation of the risk of an ASCVD event will determine whether an intervention is required to lower that risk. When the marker is causally related to the disease process, then it will also determine which therapeutic intervention is indicated.
3. More research is needed on the relative weighting of each of the components of metabolic risk.
4. Prediabetes and diabetes are essentially part of a continuum of elevated glycemia, and it is often difficult to distinguish whether medical efforts to treat glycemia are truly decreasing the incidence of T2DM or treating early diabetes. This distinction may not be important clinically, but future studies need a focus on the prevention of ASCVD, diabetic microvascular complications, mortality, and patient-important outcomes as opposed to focusing purely on biochemical conversion to T2DM.
5. Further identification and analysis of genetic markers for metabolic risk and their relationship to ASCVD and T2DM are required (see discussion below).
6. We need to better understand how to use these genetic markers to guide the choice of preventive therapy using a personalized approach (see discussion below).
7. Medications in certain classes for the treatment of T2DM, such as SGLT-2 inhibitors and GLP-1 agonists, may have cardiovascular benefits and potential use in the primary prevention of both ASCVD and T2DM; however, evidence is lacking (5). More controlled trials to assess their benefit in this area are needed (244).

8. Studies indicate that certain bariatric surgical procedures can be beneficial for the treatment of individuals with severe obesity and T2DM. Further studies to determine the risks and benefits of these procedures for the prevention of ASCVD and T2DM are needed.
9. More studies are needed on metabolic risk and noninvasive tests of vascular dysfunction to determine whether these can improve the prediction of ASCVD and T2DM.
10. More research is needed regarding new approaches in the public health sphere for population-based efforts to prevent ASCVD and T2DM. Treatment of this problem cannot be restricted to the medical office setting.

Future perspectives on personalized medicine in primary prevention of ASCVD and diabetes

Genomics markers in primary prevention of ASCVD and diabetes

The advent of the Human Genome Project has raised hope that genomics would offer personalized medicine for the prediction, diagnosis, and treatment of a large spectrum of diseases, including ASCVD and T2DM. With the rapid advances in knowledge and technology, a large number of genetic variants are now known to be associated with T2DM and with ASCVD (245), and these numbers will likely continue to increase. Given the large number of risk variants now identified, their additive (small) effects can be aggregated into "scores" representing the genetic burden of currently known loci for T2DM or ASCVD.

Such "genetic burden scores" derived from risk variants associated with ASCVD predict ASCVD events in prospective studies but initially added little to prediction algorithms containing traditional risk factors and family history (246). More recently, however, scores that aggregated a larger number of ASCVD loci showed slightly better predictive performance on top of current traditional clinical factors such as the Framingham risk score or the ACC/AHA score (247, 248). Similarly, aggregated scores of T2DM genetic risk variants can predict who will develop T2DM in prospective studies, but genetic information adds little to prediction model performance once they include demographics and classic risk factors, such as those included in the definition of metabolic risk (BMI/waist circumference, lipids, glycemia) (249–251). However, correct implementation of polygenic risk scores for ASCVD/T2DM prediction is rarely seen in clinical practice, likely because there is a lack of data showing that this knowledge will truly change clinical decisions, individual behaviors, and ASCVD/T2DM outcomes.

Observational studies have shown that adopting a healthy lifestyle is associated with a reduced risk of ASCVD at any level of genetic risk and further suggest that a healthy lifestyle (no current smoking, no obesity, regular physical activity, and a healthy diet) is associated with a risk reduction in ASCVD of up to 50% in individuals considered at "high genetic risk" based on a polygenic aggregated risk score (252).

In the context of diabetes prevention, individuals at high risk based on their genotypes benefit from intensive lifestyle interventions as much or perhaps to a greater extent than individuals not considered at high genetic risk (251). This has been shown for genetic risk attributed to a single genetic variant, such as *TCF7L2* (253, 254), which is the T2DM risk locus with the largest effect size per risk allele identified to date and has been the most replicated across studies, and for genetic risk estimated on aggregate risk constructed from multiple known T2DM risk loci (255, 256). For example, in the DPP, participants with the highest genetic risk (top quartile of the aggregate genetic risk score) clearly benefited from intensive lifestyle intervention: in this subgroup, diabetes incidence was 12 cases per 100 person-years in the placebo arm vs 5 cases per 100 person-years in the lifestyle arm ($P < 0.001$) (255). Moreover, the lifestyle intervention significantly increased the chance of regression to normoglycemia in DPP participants with a higher T2DM genetic burden (255).

Evidence of interactions between genetic variants and response to intensive lifestyle intervention is emerging. For example, a combined analysis from the DPP and Action for Health in Diabetes (Look AHEAD) trials found that a variant of the *MTIF3* obesity allele modified the effects of lifestyle interventions on weight loss and that there was no similar effect in the control arms (257). A meta-analysis suggested that individuals carrying the *FTO* obesity risk allele—the most replicated obesity risk locus—may lose more weight with diet and exercise interventions than do noncarriers (258, 259).

The field of nutrigenomics has also exploded in recent years, raising the hope that this field may contribute to the prevention of ASCVD, T2DM, and metabolic diseases (260). For example, high adherence to the Mediterranean diet in the PREDIMED trial reduced or inhibited the association between glycemic/ASCVD outcomes with selected genetic risk variants at known T2DM loci such as *TCF7L2* or known obesity loci such as *FTO* (261). However, the field is still challenged by many observational studies reporting interactions between certain genetic risk variants and specific food or dietary components, but replication is lacking (260).

Table 11. Related Guideline Content

Recommendation Number	Guideline Title	Organization	Publication Year
1.2, 3.1	Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB Sr, Gibbons R, Greenland P, Lackland DT, Levy D, O'Donnell CJ, Robinson JG, Schwartz JS, Shero ST, Smith SC, Jr., Sorlie P, Stone NJ, Wilson PW ***2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines*** Journal of the American College of Cardiology 2014;63:2935–2959	ACC/AHA	2014
1.4	American Diabetes Association ***Standards of Medical Care in Diabetes 2019*** Diabetes Care 2019 Jan;42(Suppl 1)	ADA	2019
1.5, 1.6, 3.8	Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P, Ovbiagele B, Smith SC Jr, Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams KA Sr, Williamson JD, Wright JT Jr ***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: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines*** Hypertension 2018;71:1269–1324	ACC/AHA/AAPA/ ABC/ACPM/AGS/ APhA/ASH/ASPC/ NMA/PCNA	2017
2.3	Health and Human Services Office of Disease Prevention and Health Promotion and US Department of Agriculture Center for Nutrition Policy Promotion ***2015–2020 Dietary Guidelines for Americans. 8th ed.*** https://health.gov/dietaryguidelines/2015/guidelines	HHS/USDA	2015
2.4	2018 Physical Activity Guidelines Advisory Committee ***2018 Physical Activity Guidelines Advisory Committee Scientific Report*** Washington, DC: US Department of Health and Human Services; 2018	HHS	2018
2.4	Qaseem A, Holty JE, Owens DK, Dallas P, Starkey M, Shekelle P ***Management of obstructive sleep apnea in adults: a clinical practice guideline from the American College of Physicians*** Annals of Internal Medicine 2013;159(7):471-483	ACP	2013
3.1, 3.3 - 3.4, 3.6	Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC Jr, Watson K, Wilson PW ***2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines*** Journal of the American College of Cardiology 2014;63:2889–2934	ACC/AHA	2014
3.2	Genest J, McPherson R, Frohlich J, Anderson T, Campbell N, Carpentier A, Couture P, Dufour R, Fodor G, Francis GA, Grover S, Gupta M, Hegele RA, Lau DC, Leiter L, Lewis GF, Lonn E, Mancini GB, Ng D, Pearson GJ, Sniderman A, Stone JA, Ur E ***2009 Canadian Cardiovascular Society/Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in the adult—2009 recommendations*** Canadian Journal of Cardiology 2009;25:567–579	CCS	2009
3.3 - 3.4	Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, Hoes AW, Jennings CS, Landmesser U, Pedersen TR, Reiner Z, Riccardi G, Taskinen MR, Tokgozoglu L, Verschuren WM, Vlachopoulos C, Wood DA, Zamorano JL ***2016 ESC/EAS guidelines for the management of dyslipidaemias: the Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR)*** Atherosclerosis 2016;253:281–344	ESC/EAS	2016

(*Continued*)

Table 11. Related Guideline Content (Continued)

Recommendation Number	Guideline Title	Organization	Publication Year
3.3 - 3.4, 3.8	Anderson TJ, Gregoire J, Hegele RA, Couture P, Mancini GB, McPherson R, Francis GA, Poirier P, Lau DC, Grover S, Genest J, Jr., Carpentier AC, Dufour R, Gupta M, Ward R, Leiter LA, Lonn E, Ng DS, Pearson GJ, Yates GM, Stone JA, Ur E ***2012 Update of the Canadian Cardiovascular Society guidelines for the diagnosis and treatment of dyslipidemia for the prevention of cardiovascular disease in the adult*** Canadian Journal of Cardiology 2013;29:151–167	CCS	2013
3.5	Berglund L, Brunzell JD, Goldberg AC, Goldberg IJ, Sacks F, Murad MH, Stalenhoef AF ***Evaluation and treatment of hypertriglyceridemia: an Endocrine Society clinical practice guideline*** Journal of Clinical Endocrinology & Metabolism 2012;97(9):2969–2989	Endocrine Society	2012

Some hypothesized that if a patient knew that they had an increased genetic susceptibility to T2DM, this might motivate them to implement lifestyle strategies such as changes in diet or increased physical activity. Unfortunately, observational and interventional trial data do not bear out this hypothesis or support the use of genetic susceptibility testing and knowledge of personal genetic risk for T2DM in implementing behavioral changes, either by personal initiative or within a structured lifestyle intervention similar to DPP, even when supported by a genetic counselor (262–265).

In the context of statin use for primary prevention, one clinical trial showed that incorporation of a genetic risk score into shared decision-making sessions led by genetic counselors with individuals at intermediate risk for CHD and health care providers resulted in a modest increase in statin utilization in individuals with high genetic risk (266). Future studies are needed to assess the impacts on actual outcomes and to determine whether this approach is generalizable to various practice settings.

In summary, genetic information can predict ASCVD and T2DM, but clinical prediction algorithms have not yet incorporated this information in current clinical practice. Adopting a healthy lifestyle reduces the risk of ASCVD and T2DM at any level of genetic risk and may have slightly greater benefits for individuals at higher genetic risk. However, at this time, there are no data supporting the hypothesis that patients' knowledge of their genetic risk profile leads to greater behavioral changes to adopt and maintain a healthier lifestyle, although emerging data suggest a potential usefulness for pharmacologic decisions. Genomics integration may become more promising in primary prevention of ASCVD and T2DM if genetic determinants are identified of the degree of response to lifestyle interventions (such as degree of weight loss or changes in glycemia/lipids) or to specific aspects of behavioral changes (better response to physical activity, specific response to dietary components) to tailor our future interventions).

5. Related Guidelines and Statements

Numerous existing guidelines and statements on T2DM and ASCVD have been developed by other medical societies and associations. Certain recommendations and content in these other guidelines align with the work of this Writing Committee. In Table 11, we point the reader to the most notable of these guidelines and list the recommendations in this guideline with which they align.

Methodology

Participants

The Writing Committee consisted of seven content experts representing the following specialties: endocrine disorders, nephrology, and hypertension. Several members of the committee brought an international perspective to this guideline topic. The Writing Committee also included a clinical practice guideline methodologist who led the team of comparative effectiveness researchers that conducted the systematic review and meta-analysis. The methodologist also supervised application of the GRADE methodological framework for each recommendation, including quality of evidence assessments and strength of recommendation designations.

Guideline development process

The Endocrine Society's guideline development process follows the GRADE framework (267, 268) and includes special considerations unique to rare endocrine diseases where scientific evidence is limited or nonexistent. The GRADE framework is described in Table 12.

Some of the Society's clinical practice guidelines also include Ungraded Good Practice Statements (269). This unclassified clinical guidance can include expert opinion statements on good practice, references to recommendations made in other guidelines, and observations on preventive care and shared decision-making.

Guideline recommendations include the relevant population, intervention, comparator, and outcome. When further clarification on implementation is needed, the Writing Committee included technical remarks. These provide supplemental information such as timing, setting, dosing regimens, and necessary expertise. All recommendations are followed by a synopsis of the evidence on which they are based. Authors may also include short statements on patients' values and preferences, the balance of benefits and harms, and minority opinions, where relevant.

Internal and external review

Approximately 18 months into the development process, Endocrine Society clinical practice guidelines undergo a comment review period of 1 month when there is an opportunity for internal and external stakeholders to review the guideline draft and provide comments. These stakeholders include Endocrine Society members, the Society's Clinical Guidelines Subcommittee (CGS), representatives of any cosponsoring organizations, a representative of Council, and an expert reviewer. Following revisions to the guideline manuscript in response to comment review period comments, it is returned to the CGS, the Council reviewer, and the expert reviewer for a second review and ballot. Finally, the guideline manuscript is subject to *Journal of Clinical Endocrinology & Metabolism* publisher's review prior to publication. This review is undertaken by an individual with expertise in the topic, without relevant conflicts of interest, and external to the guideline Writing Committee, CGS, and Council.

Disclaimer

The Endocrine Society's clinical practice guidelines are developed to be of assistance to endocrinologists by providing guidance and recommendations for particular areas of practice. The guidelines should not be considered inclusive of all proper approaches or methods, or exclusive of others. The guidelines cannot guarantee any specific outcome, nor do they establish a standard of care. The guidelines are not intended to dictate the treatment of a particular patient. Treatment decisions must be made based on the independent

Table 12. GRADE Classification of Guideline Recommendations

QUALITY OF EVIDENCE		High Quality	Moderate Quality	Low Quality	Very Low Quality
Description of Evidence		• *Well-performed RCTs* • *Very strong evidence from unbiased observational studies*	• *RCTs with some limitations* • *Strong evidence from unbiased observational studies*	• *RCTs with serious flaws* • *Some evidence from observational studies*	• *Unsystematic clinical observations* • *Very indirect evidence observational studies*
STRENGTH OF RECOMMENDATION	**Strong (1): "We recommend…"** *Benefits clearly outweigh harms and burdens, or vice versa*	**1|⊕⊕⊕⊕**	**1|⊕⊕⊕O**	**1|⊕⊕OO**	**1|⊕OOO**
	Conditional (2): "We suggest…" *Benefits closely balanced with harms and burdens*	**2|⊕⊕⊕⊕**	**2|⊕⊕⊕O**	**2|⊕⊕OO**	**2|⊕OOO**

judgement of healthcare providers and each patient's individual circumstances.

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Conflicts of interest

The Endocrine Society's conflict of interest (COI) policy specific to the development of clinical practice guidelines can be requested from the Society. In summary, the rules are as follows:

1. To be considered for membership of a Writing Committee, nominees are required to disclose all relationships with industry for the 12-month period prior to guideline Writing Committee initiation. This is consistent with the reporting time frame for the National Institutes of Health and the Food and Drug Administration.
2. Potential COIs that should be declared include all relationships with commercial, noncommercial, institutional, and patient/public organizations that are (or may be) pertinent to the scope of the guideline.
3. The Chair of the Clinical Guidelines Subcommittee reviews all disclosed relationships and determines whether they are relevant to the topic of the guideline and present a potentially relevant COI.
4. The Chair of the Clinical Guidelines Subcommittee selects Writing Committee Chairs and Co-Chairs based on COI information and the individuals' clinical expertise and other skills. The Endocrine Society Council reviews and endorses the nominees or makes appropriate changes. The three Chairs then select and appoint Writing Committee members.
5. The Chair and Co-Chair of the Writing Committee must be free of any COI or other biases that could undermine the integrity or credibility of the work.
6. Most (≥50%) of the Writing Committee members must be free of relevant COIs.
7. Writing Committee members with relevant COIs are required to declare the situation and recuse themselves from any relevant discussions, votes, and from drafting recommendations.
8. All Writing Committee members must refrain from adding new relevant industry relationships throughout the guideline development process.
9. If a member is aware of another person who might have a conflict and has not declared it for some reason, they are obliged to bring this to the Writing Committee Chair's attention.
10. Staff, Writing Committee Chairs, and members must be alert for situations which might present a potential or perceived COI.

Appendix A. Choice of Terminology

In this guideline, the Writing Committee focuses on a specific set of risk factors for ASCVD and T2DM. The term "metabolic syndrome" has been used to describe a set of clinical features clustered in individuals, most of whom have abdominal adiposity, conferring an increased risk for ASCVD andT2DM. There are various definitions of the metabolic syndrome; they all include a subset of the relevant risk factors for ASCVD and T2DM. Although these risk factors (high TGL/low HDL, increased small dense LDL, elevated BP, elevated plasma glucose, abdominal obesity, insulin resistance, and inflammatory and thrombotic markers) tend to occur together in the same individuals, the etiology is not fully understood. Furthermore, because these definitions do not contain all ASCVD risk factors and dichotomize the population into those with and without the metabolic syndrome, it should not be used as an indicator of absolute, short-term risk for ASCVD. The occurrence of multiple metabolic risk factors in one individual, nonetheless, does indicate the presence of a higher long-term risk for both ASCVD and T2DM.

The concept that insulin resistance clusters with glucose intolerance, dyslipidemia, and hypertension to enhance ASCVD risk was proposed by Reaven in 1988 (270). At that time, it was presumed that the various clinical characteristics were linked by an overriding pathophysiological mechanism tied to insulin resistance, hence the term "insulin resistance syndrome." In IRS, the primacy of insulin resistance is posited on the grounds that insulin resistance is an effective transducer of environmental influences, with obesity (especially visceral) (10), cardiorespiratory fitness (271), and stress (272) being the most important ones. On the effector side, insulin exerts potent actions not only in pathways of glucose homeostasis, but also on lipid turnover, BP control, and vascular reactivity. Moreover, chronic hyperinsulinemia—the *in vivo* adaptive response to insulin resistance—has been shown to have pathogenic potential in its own right [*e.g.*, by downregulating insulin action (273), strengthening anti-natriuresis (274), or by stimulating the adrenergic nervous system (275)], thereby creating reinforcement circuits in the network (276). These facts are supported by a wealth of experimental and clinical investigation (277). Importantly, however, note that just as insulin resistance alone is insufficient to alter glucose tolerance—for which some degree of β-cell dysfunction is required—insulin resistance/hyperinsulinemia is neither strictly necessary nor sufficient to alter lipid metabolism, BP, or vascular function. Each of these homeostatic systems is under the control of multiple factors. Also, each of these systems is redundant, with plenty of interactions.

More recently, the pathophysiological IRS has been replaced by combinations of clinical criteria, defined by various organizations, which attempt to describe a clinical entity, the metabolic syndrome. The major purpose initially was to use clinical signs and symptoms to identify people with a clustering of risk factors, with a higher risk for ASCVD and T2DM than the general population.

In fact, hyperinsulinemia predicts diabetes, dyslipidemia (278), and, to a lesser extent, hypertension (279), and it is an independent, when weak, ASCVD predictor (280). Measuring insulin resistance directly (by the hyperinsulinemic–euglycemic clamp technique or by glucose tolerance testing) is too difficult for practical clinical use. Using fasting plasma insulin levels as a proxy for insulin resistance introduces confounding, owing to the partly different physiology of hyperinsulinemia and insulin resistance (281) as well as lack of measurement standardization across studies.

These practical hurdles have prompted the search for practical, easily measured surrogates of insulin resistance, among which the waist girth or the waist-to-hip ratio seemed

best in certain epidemiological studies (282). Thus, anthropometric measures have tended to replace insulin resistance in various definitions of the syndrome, such as those from the AHA/NHLBI (8), World Health Organization (283), NCEP ATP III (284), IDF (9), European Group for the Study of Insulin Resistance (285), and the American Association of Clinical Endocrinologists (286). These varying definitions have adopted mixtures of anthropometric, pathophysiological, and clinical criteria. Predictors (waist girth, insulin, TGLs) and outcomes (diabetes, hypertension) have been dichotomized (thresholds rather than continuous variables), assembled (any two of three or three of five criteria), and even prioritized (*e.g.*, waist girth first, then any two of three) as a result of clinical consensus, without hard evidence for their usefulness.

The stability of the metabolic syndrome over time is ill-defined: it may display a relatively high rate of spontaneous regression (as is the case with IGT). In the only relevant study (287), the prevalence of the metabolic syndrome did not increase in Mexico City from 1990 to 1992 and 1997 to 1999 despite increasing central obesity. The metabolic syndrome by itself offers little substantial advantage in ASCVD risk prediction over available algorithms (*e.g.*, the Framingham score). However, a careful meta-analysis has shown that, depending on the definition (and modifications thereof), sample size, subject selection, duration of follow-up, outcome event, and type of statistical analysis, using the metabolic syndrome as a predictor may provide some improvement in risk assessment (288). To predict diabetes, alternatively, the current definitions of metabolic syndrome do not offer any significant advantage over other algorithms (289, 290) although they efficiently detect IGT (21), which is an important antecedent of diabetes. Which component of the syndrome carries what weight has not been established.

For the metabolic syndrome to be a better predictor of risk for ASCVD and T2DM, its criteria must be unambiguously defined (291). Physiological parameters should not be dichotomized unless independent evidence proves the existence of a threshold in their relationship to risk. Modeling should explore nonlinearities and weighting, and established predictors (*e.g.*, age, familial diabetes, premature ASCVD) should be included in the model.

In this document, the term "metabolic risk" is used so as not to favor one term over another. One reason for avoiding the use of "metabolic syndrome," the most popular term, is that major organizations that have produced guidelines for the metabolic syndrome allow its diagnosis to be extended to individuals with T2DM. The Endocrine Society recognizes T2DM as a separate disease entity, for which other guidelines specific to diabetes are applicable. Therefore, to avoid any confusion, metabolic risk is restricted to individuals who do not manifest clinical diabetes. It does not, however, exclude prediabetes from the category of metabolic risk.

Appendix B. Conflicts of Interest

Task Force Member	Employment	Uncompensated Memberships	Uncompensated Leadership	Personal Financial	Organizational Financial	Spousal/ Family Info
James L. Rosenzweig, MD (Chair)	Hebrew Rehabilitation Hospital, Boston, MA	None declared	None declared	None declared	- Novo Nordisk, Quintiles External Endpoint Adjudication Committee	None declared
George L. Bakris, MD	University of Chicago Medicine, Chicago, IL	None declared	- National Kidney Foundation Board of Directors	• AbbVie, Steering Committee • Amgen Inc., Consultant • AstraZeneca Pharmaceuticals LP, Consultant • Bayer HealthCare Pharmaceuticals, Inc., Consultant • -Boehringer Ingelheim, Consultant • Janssen Pharmaceuticals, Steering Committee and Consultant • Medtronic Vascular, Inc., Consultant • Merck Sharp & Dohme, Consultant • Novo Nordisk, Consultant • Relypsa, Consultant • Theravance Biopharma, Consultant • Am J Nephrology, Section Editor • Diabetes Care, Associate Editor • - UpToDate, Editor	- Bayer, Principal Investigator	None declared
Lars F. Berglund, MD, PhD	University of California, Davis	None declared	-NIH Reviewer	• Boston Scientific, Stock Ownership • Gilead Sciences, Stock Ownership • Johnson & Johnson, Stock Ownership • Medtronic, Stock Ownership • Novo Nordisk, stock ownership • - Pfizer, Stock Ownership	- NIH, Co-investigator on research grants	None declared
Marie-France Hivert, MD, MSc	Harvard Pilgrim, Health Care Institute, Harvard Medical School, Boston, MA	- American Heart Association, Member of Leadership Lifestyle Council	None declared	• - American Diabetes Association, Awardee of research/career grant	- NIH, Principle Investigator/ Co-investigator on research grants	None declared

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Appendix B. Conflicts of Interest (Continued)

Task Force Member	Employment	Uncompensated Memberships	Uncompensated Leadership	Personal Financial	Organizational Financial	Spousal/ Family Info
Edward S. Horton, MD	Harvard Medical School, Boston, MA	None declared	- NIH, Publications and Presentations Committee for two trials	• Theracos, Data Safety Monitoring Board • Polymer Technology Systems, Inc., Consultant • - Takeda Pharmaceuticals USA, Inc., Consultant	None declared	None declared
Rita R. Kalyani, MD, MHS	Johns Hopkins University School of Medicine, Baltimore, MD	None declared	- Diabetes Sisters, Board of Directors	None declared	- NIH, Primary Investigator/ Co-investigator on research grants	None declared
M. Hassan Murad, MD, MPH	Mayo Clinic Knowledge and Evaluation Research Unit, Rochester, MN	None declared	None declared	None declared	None declared	None declared
Bruno L. Vergès, MD, PhD	Centre Hospitalier Universitaire Dijon Bourgogne, Dijon, France	None declared	None declared	• Novartis, Advisory Board • Novo Nordisk, Advisory Board • - Servier, Advisory Board	None declared	None declared

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Disclosure Summary: See Appendix B.

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