CONSENSUS STATEMENT BY THE AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY ON THE MANAGEMENT OF DYSLIPIDEMIA AND PREVENTION OF CARDIOVASCULAR DISEASE ALGORITHM – *2020 EXECUTIVE SUMMARY*

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ABSTRACT

The treatment of lipid disorders begins with lifestyle therapy to improve nutrition, physical activity, weight, and other factors that affect lipids. Secondary causes of lipid disorders should be addressed, and pharmacologic therapy initiated based on a patient's risk for atherosclerotic cardiovascular disease (ASCVD). Patients at extreme ASCVD risk should be treated with high-intensity statin therapy to achieve a goal low-density lipoprotein cholesterol (LDL-C) of <55 mg/dL, and those at very high ASCVD risk should be treated to achieve LDL-C <70 mg/dL. Treatment for moderate and high ASCVD risk patients may begin with a moderate-intensity statin to achieve an LDL-C <100 mg/dL, while the LDL-C goal is <130 mg/dL for those at low risk. In all cases, treatment should be intensified, including the addition of other LDL-C-lowering agents (i.e., proprotein convertase subtilisin/kexin type 9 inhibitors, ezetimibe, colesevelam, or bempedoic acid) as needed to achieve treatment goals. When targeting triglyceride levels, the desirable goal is <150 mg/dL. Statin therapy should be combined with a fibrate, prescription-grade omega-3 fatty acid, and/or niacin to reduce triglycerides in all patients with triglycerides ≥500 mg/dL, and icosapent ethyl should be added to a statin in any patient with established ASCVD or diabetes with ≥2 ASCVD risk factors and triglycerides between 135 and 499 mg/dL to prevent ASCVD events. Management of additional risk factors such as elevated lipoprotein(a) and statin intolerance is also described.

Abbreviations:
AACE = American Association of Clinical Endocrinologists; **ACE** = American College of Endocrinology; **ACS** = acute coronary syndrome; **apo B** = apolipoprotein B; **ASCVD** = atherosclerotic cardiovascular disease; **BA** = bempedoic acid; **CAC** = coronary artery calcium; **CHD** = coronary heart disease; **CK** = creatine kinase; **CKD** = chronic kidney disease; **DHA** = docosahexaenoic acid; **EPA** = eicosapentaenoic acid; **FCS** = familial chylomicronemia syndrome; **FDA** = United States Food and Drug Administration; **FOURIER** = Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk; **HDL-C** = high-density lipoprotein cholesterol; **HeFH** = heterozygous familial hypercholesterolemia; **HoFH** = homozygous familial hypercholesterolemia; **hsCRP** = high-sensitivity C reactive protein; **IDL** = intermediate-density lipoproteins; **IMPROVE-IT** = Improved Reduction of Outcomes: Vytorin Efficacy International Trial; **IPE** = icosapent ethyl; **LDL-C** = low-density lipoprotein cholesterol; **Lp(a)** = lipoprotein a; **MACE** = major adverse cardiovascular events; **MI** = myocardial infarction; **OSA** = obstructive sleep apnea; **PCSK9** = proprotein convertase subtilisin/kexin type 9; **REDUCE-IT** = Reduction of Cardiovascular Events with EPA-Intervention Trial; **UKPDS** = United Kingdom Prospective Diabetes Study; **U.S.** = United States; **VLDL** = very-low-density lipoproteins

EXECUTIVE SUMMARY

This algorithm for the comprehensive management of dyslipidemia and prevention of cardiovascular disease (CVD) complements the 2017 American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) Guidelines for Management of Dyslipidemia and Prevention of Cardiovascular Disease (1) and provides clinicians with a practical guide that considers the whole patient, their spectrum of risks and complications, and evidence-based approaches to treatment. However, the algorithm has incorporated newer data that were not available when the 2017 guidelines were drafted but which are necessary for contemporary lipid management. Despite recent improvements in the overall rates of lipid disorders and heart disease, atherosclerotic cardiovascular disease (ASCVD) remains the leading cause of death throughout the world (2,3). In the United States (U.S.), coronary heart disease (CHD), heart failure, and stroke together affect 24.3 million people (9% of the population), and 29% and 26% of adults have elevations in low-density lipoprotein cholesterol (LDL-C) and triglycerides, respectively, putting them at risk of major adverse cardiovascular events (MACE) (3,4).

Controlling atherogenic cholesterol particle concentrations is fundamental to prevention of ASCVD, including CHD (5). However, only a small percentage of the U.S. population who clearly would benefit from a statin (i.e., hydroxymethylglutaryl-coenzyme A [HMG-CoA] reductase inhibitor) currently takes one (6). Moreover, the average LDL-C among U.S. adults, 112 mg/dL (3), is higher than the recommended LDL-C goal of <100 mg/dL for those with moderate ASCVD risk and well above the goals for people at high risk of ASCVD (1).

Risk factors for dyslipidemia, including obesity, chronic kidney disease (CKD), and diabetes, have risen steadily over recent decades and are expected to continue to increase (7-9). Most notably, 44% of U.S. adults now have obesity (defined by a body mass index [BMI] >30 kg/m^2), without any difference in the proportions of younger versus older adults (7). Early exposure to elevated lipids, prior to age 55 years, has a greater impact on CHD risk than do elevations later in life (10), indicating that careful management of patients with dyslipidemia is important across the lifespan.

This executive summary expands on the information in the Dyslipidemia and Prevention of Cardiovascular Disease Algorithm slides and provides the supporting refer-

ences. The algorithm is organized into discrete sections, as follows:

I. Dyslipidemic States
II. Secondary Causes of Lipid Disorders
III. Screening for and Assessing Lipid Disorders and ASCVD Risk
IV. ASCVD Risk Categories and Treatment Goals
V. Lifestyle Recommendations
VI. Treating LDL-C to Goal
VII. Managing Statin Intolerance and Safety
VIII. Management of Hypertriglyceridemia and the Role of Icosapent Ethyl
IX. Assessment and Management of Elevated Lipoprotein(a)
X. Profiles of Medications for Dyslipidemia

I. Dyslipidemic States

Dyslipidemia comprises a range of conditions, primarily defined by elevations in lipoprotein cholesterol, including LDL-C and non-high-density lipoprotein cholesterol (HDL-C), as well as elevated triglycerides (see Dyslipidemia and Prevention of Cardiovascular Disease Algorithm Slide I. Dyslipidemic States). All of these conditions independently increase the risk of ASCVD (11,12).

In the U.S., 38% of adults have a total cholesterol >200 mg/dL and 29% have LDL-C ≥130 mg/dL (3). Hypertriglyceridemia, defined as triglycerides ≥150 mg/dL, affects 26% of U.S. adults (4). Severe hypertriglyceridemia (triglycerides >500 mg/dL) increases the risk of acute pancreatitis and chylomicronemia syndrome (1,13). Lipoprotein(a), or Lp(a), is a low-density lipoprotein (LDL) particle with an apolipoprotein(a) attached to the apolipoprotein B (apo B) component. Approximately 20% of the population has increased levels of this pro-atherosclerotic particle (14).

Hypercholesterolemia and hypertriglyceridemia are frequently secondary to other medical conditions or medications (see Dyslipidemia and Prevention of Cardiovascular Disease Algorithm Slide II. Secondary Causes of Lipid Disorders), and there are also a wide variety of primary dyslipidemias. The most common primary dyslipidemias are elevated Lp(a) and mixed dyslipidemia, a combination of elevated levels of both cholesterol and triglycerides. This combination is also seen in 2 much less common states: familial combined hyperlipidemia and dysbetalipoproteinemia. Familial combined hyperlipidemia is defined as elevations in either cholesterol or triglycerides in ≥2 first-degree relatives (often occurring sequentially rather than simultaneously), along with a strong family history of premature ASCVD, and has an estimated population prevalence of 1 to 3% (3,15). Dysbetalipoproteinemia (type III dyslipidemia) consists of an excess of cholesterol enriched triglyceride-remnant lipoproteins. It is also associated with premature ASCVD but infrequently with a strong family history due to generally recessive inheritance.

Familial hypercholesterolemia is caused by major gene mutations affecting LDL receptor function with codominant inheritance, meaning the milder form is passed on by 1 parent (heterozygous familial hypercholesterolemia; HeFH) and the more severe form by both parents (homozygous familial hypercholesterolemia; HoFH). HeFH is associated with LDL-C levels of >190 mg/dL (>160 mg/dL in children) and HoFH with LDL-C >500 mg/dL in the absence of secondary causes (1). HeFH affects approximately 1 in 250 to 500 persons, whereas HoFH occurs at a rate of 1 to 4 per 1 million, although rates as high as 1/160,000 have been reported in some genetically isolated populations (1,16). Other rare genetic dyslipidemic syndromes include familial hypoalphalipoproteinemia, familial chylomicronemia syndrome (FCS), beta-sitosterolemia, lysosomal acid lipase deficiency, and lipodystrophy. Clinicians may refer patients to lipid specialists for further investigations and management as appropriate, including genetic testing.

II. Secondary Causes of Lipid Disorders

Once dyslipidemia has been diagnosed, secondary causes of the disorder must be excluded to rule out cases that could be treated or cured with approaches that do not involve cholesterol- or triglyceride-lowering medications (1,11,17,18).

Diagnosis of secondary causes should begin with a complete medical, family, and nutrition history. A physical examination must be undertaken to identify additional risk factors, including genetic features. Laboratory testing for glucose, thyroid, liver, and renal function should also be conducted. Finally, a list of all prescription and over the counter medications, as well as dietary supplements, should be compiled, as many of these affect lipids. Treating an underlying contributing disease or discontinuing a contributing medication, if medically appropriate, may ameliorate dyslipidemia.

In developed nations, the most common secondary cause of dyslipidemia is a sedentary lifestyle with lack of physical activity and a diet high in carbohydrates and/or simple sugars. A diet high in saturated fats and excessive alcohol intake may also lead to dyslipidemia. Other common secondary causes include medical conditions such as overweight or obesity and associated metabolic syndrome or prediabetes; uncontrolled diabetes; hypothyroidism; pregnancy; stage ≥3 CKD (ie, estimated glomerular filtration rate [eGFR] ≤59 mL/min/1.73 m^2), especially with albuminuria; nephrotic syndrome; cholestatic diseases of the liver; lipodystrophy; paraproteinemia (e.g., dysgammaglobulinemia, multiple myeloma); and chronic inflammatory conditions (e.g., rheumatoid arthritis, systemic lupus erythematosus) (1,18).

Medications that may contribute to dyslipidemia include oral estrogens and progestins, anabolic steroids, selective estrogen receptor modulators, highly active antiretroviral agents such as protease inhibitors for the treat-

ment of HIV, immunosuppressive medications (e.g., cyclosporine, mammalian target of rapamycin [mTOR] kinase inhibitor), glucocorticoids, retinoids, interferon, taxol derivatives, L-asparaginase, cyclophosphamide, atypical antipsychotic agents, beta-blockers, and thiazide diuretics. Although bile acid sequestrants are used mainly to reduce cholesterol, these agents may also increase triglyceride levels and should be used cautiously in patients with triglyceride elevations (1,18).

Monitoring of lipid levels should continue after a secondary cause of dyslipidemia has been diagnosed, as some conditions such as diabetes also increase the risk of ASCVD, and more aggressive lipid-lowering therapy is warranted. Simultaneous treatment of the secondary cause of dyslipidemia and the dyslipidemic state may be necessary.

III. Screening for and Assessing Lipid Disorders and ASCVD Risk

Screening for lipid disorders should be based on each patient's personal and family medical history, and assessments should include these findings as well as the results of a physical examination; laboratory evaluations; and diagnostic procedures as appropriate, including electrocardiograms and imaging. These results could be supplemented with an ASCVD risk calculator chosen based on the patient's individual characteristics. In particular, a coronary artery calcium (CAC) score is very useful for risk stratification.

Medical conditions that increase a patient's risk of dyslipidemia and/or ASCVD include impaired glucose tolerance, metabolic syndrome, diabetes, obesity, hypertension, prior cardiovascular or cerebrovascular events, CKD, nonalcoholic fatty liver disease (NAFLD) or nonalcoholic steatohepatitis (NASH), autoimmune or inflammatory disease (e.g., lupus, rheumatoid arthritis, psoriasis, periodontal disease), hepatitis C, a history of pancreatitis, and medications that alter lipids (e.g., steroids, retinoids, HIV therapy, antirejection medications; see Dyslipidemia and Prevention of Cardiovascular Disease Algorithm Slide II. Secondary Causes of Lipid Disorders). Behavioral factors include smoking, a sedentary lifestyle, and diets high in saturated fat (1). Patients whose family members have ASCVD, hypertension, or dyslipidemia should also be screened. A personal history or family history of tendon xanthomas, corneal arcus, or xanthelasma are clues suggesting hypercholesterolemia. Eruptive xanthomas and lipemia retinalis are suggestive of severe hypertriglyceridemia.

The physical examination should include each patient's height and weight (for calculation of BMI), waist circumference, blood pressure, and peripheral and carotid pulses. Further advanced evaluation may include a cardiac evaluation; vascular bruits; ankle-brachial index; and assessment of tendon xanthomas, eruptive xanthomas, lipemia retinalis, corneal arcus, and xanthelasma.

Laboratory evaluations include fasting levels of the lipid profile, including total cholesterol, HDL-C, triglycerides, LDL-C, and calculated non-HDL-C; a comprehensive medical panel, including uric acid (which is a cardiovascular risk factor); hemoglobin A1C (A1C); and thyroid-stimulating hormone. Assessment of apo B or LDL particles, Lp(a), and high-sensitivity C reactive protein (hsCRP) should also be considered based on individual patient clinical circumstances.

Diagnostic procedures may include resting electrocardiogram as well as treadmill, chemical, and/or nuclear stress tests, as appropriate. Beyond the CAC score, carotid ultrasound for plaque formation may be informative. Measurement of carotid intima-media thickness was used for predicting risk for years, but in the Multiethnic Study of Atherosclerosis (MESA), values above the 75th percentile did not predict risk of transient ischemic attack or stroke, whereas the presence of carotid plaques did (19).

The Framingham Risk Equation (https://framinghamheartstudy.org/fhs-risk-functions/cardiovascular-disease-10-year-risk/) was the first widely used risk calculator (20). More currently used risk calculators include the MESA risk calculator incorporating a CAC score (https://www.mesa-nhlbi.org/CAC-Tools.aspx), Reynold's Risk Score incorporating hsCRP (http://www.reynoldsriskscore.org), and the United Kingdom Prospective Diabetes Study Risk Engine for patients with diabetes (https://www.dtu.ox.ac.uk/riskengine/) (20-22). The recently enhanced American College of Cardiology/American Heart Association pooled-cohort ASCVD Risk Estimator (www.cvriskcalculator.com) is another option (23).

More detailed information on screening for lipid disorders and ASCVD risk can be found in the AACE/ACE 2017 Guidelines for Management of Dyslipidemia and Prevention of Cardiovascular Disease (1).

IV. ASCVD Risk Categories and Goals

In the clinical management of dyslipidemia, a reasonable goal is to strive for lipid levels in the normal range; however, more aggressive goals need to be set for higher-risk individuals. As shown in Table 1, AACE has defined 5 risk categories based on the number and severity of major risk factors (see Table 2). Each category has goals for LDL-C, non-HDL-C, and apo B levels, proportional to the degree of risk. A goal for triglyceride level is also offered (see Dyslipidemia and Prevention of Cardiovascular Disease Algorithm Slide IV. ASCVD Risk Categories and Goals) (1).

Individuals at extreme risk for ASCVD events include those already diagnosed with progressive ASCVD, including unstable angina after achieving an LDL-C <70 mg/dL; those with established clinical ASCVD plus diabetes, stage ≥3 CKD, or HeFH; or those with a history of premature ASCVD (age <55 years, male; <65 years, female).

Very-high-risk criteria include established or recent hospitalization for acute coronary syndrome (ACS) or for

coronary, carotid, or peripheral vascular disease with a 10-year ASCVD risk >20%. Individuals with diabetes who have 1 or more major risk factor(s) for ASCVD (Table 2), those with stage ≥3 CKD with albuminuria, or those with HeFH are also at very high risk.

Individuals at high risk include those with ≥2 risk factors and a 10-year risk between 10% and 20% or who have diabetes or stage ≥3 CKD with no other risk factors.

Moderate risk individuals have <2 risk factors and a 10-year risk <10%, and those at low risk have no ASCVD risk factors.

LDL-C has been, and remains, the main focus of efforts to improve lipid profiles in individuals at risk for ASCVD. Numerous LDL-C-lowering trials utilizing statins over many years have consistently demonstrated that lower LDL-C levels result in improved ASCVD outcomes (1). Outcomes trials with proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors in which achieved LDL-C levels were substantially lower than those in statin trials further reinforced the notion that "lower is better" (24,25). Thus, LDL-C goals range from <130 mg/dL for low-risk individuals to <55 mg/dL for those at extreme risk for ASCVD. The goal for the extreme risk category was derived from the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) trial, wherein lowering of LDL-C to 53 mg/dL with the addition of ezetimibe to simvastatin resulted in further ASCVD benefit (26). However, because an isolated focus on LDL-C is not always sufficient to prevent ASCVD in at-risk individuals or to treat existing atherosclerosis, goals for non-HDL-C, apo B, and triglycerides are also included in the risk assessment and goals. Non-HDL (total cholesterol minus HDL-C) reflects the total atherogenic burden, including particles contained within very-low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), and LDL as well as chylomicron remnants and Lp(a). The non-HDL-C goal is 25 to 30 mg/dL above the LDL-C goal (i.e., <80 mg/dL for extreme risk, <100 mg/dL for very high risk, <130 mg/dL for medium to high risk, and <160 mg/dL for low risk) and is a more precise indicator of ASCVD risk than LDL-C (1). Non-HDL-C reached a level of <65 mg/dL and apo B of <50 mg/dL in the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial, validating the non-HDL-C and apo B goals for patients at extreme risk (25).

The term apo B refers to the total plasma concentration of apo B-100, plus apo B-48. Apo B may be elevated in individuals with optimal LDL-C when small, dense

Table 1
ASCVD Risk Categories and Treatment Goals

Risk category	Risk factors and 10-year risk	Treatment goals (mg/dL)			
		LDL-C	Non-HDL-C	Apo B	TG
Extreme risk	• Progressive ASCVD including unstable angina • Established clinical ASCVD plus diabetes or CKD ≥3 or HeFH • History of premature ASCVD (<55 y, male; <65 y, female)	<55	<80	<70	<150
Very high risk	• Established clinical ASCVD or recent hospitalization for ACS, carotid, or peripheral vascular disease, or 10-year risk >20% • Diabetes with ≥1 risk factor(s) • CKD ≥3 with albuminuria • HeFH	<70	<100	<80	<150
High risk	• ≥2 risk factors and 10-year risk 10-20% • Diabetes or CKD ≥3 with no other risk factors	<100	<130	<90	<150
Moderate risk	• <2 risk factors and 10-year risk <10%	<100	<130	<90	<150
Low risk	• No risk factors	<130	<160	NR	<150

Abbreviations: ACS = acute coronary syndrome; Apo B = apolipoprotein B; ASCVD = atherosclerotic cardiovascular disease; CKD ≥3 = stage 3-5 chronic kidney disease (estimated glomerular filtration rate ≤59 mL/min/1.73 m^2); HeFH = heterozygous familial hypercholesterolemia; NR = not recommended; TG = triglycerides; y = years.
Adapted from Jellinger et al (1).

Table 2
Major Atherosclerotic Cardiovascular Disease Risk Factors

Major risk factors	Additional risk factors	Nontraditional risk factors
Advancing age[a,b,c,d] ↑Total serum cholesterol level[a,b,d] ↑Non–HDL-C[d] ↑LDL-C[a,d] Low HDL-C[a,d,e] Diabetes mellitus[a,b,c,d] Hypertension[a,b,c,d] Chronic kidney disease 3,4[h] Cigarette smoking[a,b,c,d] Family history of ASCVD[a,d,g]	Obesity, abdominal obesity[c,d] Family history of hyperlipidemia[d] ↑Small, dense LDL-C[d] ↑Apo B[d] ↑LDL particle concentration Fasting/postprandial hypertriglyceridemia[d] PCOS[d] Dyslipidemic triad[f]	↑Lipoprotein (a) ↑Clotting factors ↑Inflammation markers (hsCRP; Lp-PLA_2) ↑Homocysteine levels Apo E4 isoform ↑Uric acid ↑TG-rich remnants

Abbreviations: apo = apolipoprotein; ASCVD = atherosclerotic cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; hsCRP = high sensitivity C-reactive protein; LDL = low-density lipoprotein; LDL-C = low-density lipoprotein cholesterol; Lp-PLA_2 = lipoprotein-associated phospholipase; PCOS = polycystic ovary syndrome.
[a]Risk factors identified in the Framingham Heart study.
[b]Risk factors identified in the MRFIT study (Multiple Risk Factor Intervention Trial).
[c]Risk factors identified in the INTERHEART study.
[d]Risk factors identified in guidelines and position statements (National Cholesterol Education Program Adult Treatment Panel III, American Association of Clinical Endocrinologists Polycystic Ovary Syndrome Position Statement, American Association of Clinical Endocrinologists Insulin Resistance Syndrome Position Statement, American Diabetes Association Standards of Care, American Diabetes Association/American College of Cardiology Consensus Statement on Lipoprotein Management in Patients with Cardiometabolic Risk, National Lipid Association, Clinical Utility of Inflammatory Markers and Advanced Lipoprotein Testing).
[e]Elevated high-density lipoprotein cholesterol is a negative risk factor.
[f]Hypertriglyceridemia; low high-density lipoprotein cholesterol; and an excess of small, dense low-density lipoproteins.
[g]Definite myocardial infarction or sudden death before 55 years of age in father or other male first-degree relative or before 65 years of age in mother or other female first-degree relative.
[h]Based on a pooled analysis of community-based studies (N = 22,634).
Reprinted with permission from Jellinger et al (1).

LDL particles are present. This often occurs in individuals with insulin resistance who manifest hypertriglyceridemia, diabetes, metabolic syndrome, or obesity (12,27-31). Apo B-100 measurement may provide a more accurate assessment of atherogenicity because all atherogenic particles (i.e., VLDL, IDL, and LDL) contain 1 apo B-100 molecule. AACE supports an apo B goal of <90 mg/dL for individuals at risk of ASCVD, including those with diabetes, and of <80 mg/dL for those with established ASCVD or diabetes plus ≥1 additional risk factor (12,31). An apo B goal <70 mg/dL is recommended for patients in the extreme risk category and should be considered in clinical situations characterized by persistent ASCVD. Furthermore, measurement of apo B is useful in assessing the success of lipid-lowering therapy, since apo B may remain above goal after achieving the LDL-C goal.

Goal triglyceride levels are <150 mg/dL; levels ranging from 150 to 199 mg/dL are classified as borderline high; levels 200 to 499 mg/dL are high, and levels ≥500 mg/dL are considered very high (11). Several studies including the long-term follow up of the Helsinki Heart Study, the Japan EPA Lipid Intervention Study, and the Reduction of Cardiovascular Events with EPA-Intervention Trial (REDUCE-IT), showed that treating patients with elevated triglycerides significantly improved cardiovascular outcomes and/or lowered the ASCVD mortality rate (32-34). Additionally, a subgroup analysis of several triglyceride-lowering trials utilizing fibrates demonstrated improved ASCVD outcomes when baseline triglycerides are >200 mg/dL and HDL-C is <40 mg/dL (32,35-37).

Low HDL-C (HDL-C <40 mg/dL in men and <50 mg/dL in women, without accompanying hypertriglyceridemia) is not included as a factor in the risk category table. However, epidemiologic evidence and findings from the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial study support a cardioprotective role of HDL-C (1,38,39). Increasing HDL-C pharmacologically utilizing fibrates or niacin, however, has not demonstrated a primary ASCVD benefit. Therefore, AACE recommends that, after aggressive lifestyle interventions to raise HDL-C as high as possible, the focus should be on reducing LDL-C by pharmacologic therapy, especially if HDL-C levels are low and other risk factors are present (including borderline elevated LDL-C levels, a family history of premature ASCVD, or a personal history of ASCVD) (1).

V. Lifestyle Recommendations

The management of dyslipidemia requires a comprehensive strategy to control lipid levels and address associated metabolic abnormalities and modifiable risk factors. Managing individuals with lipid disorders begins with

implementation of lifestyle changes including medical nutrition therapy, physical activity, smoking cessation, and assessment of sleep and mental health issues. The intensity of these interventions should be stratified by the degree of cardiovascular risk, type of dyslipidemia, and related complications.

Diet can have a substantial effect on lipid levels and is an important determinant of ASCVD risk. Experts have yet to reach consensus on what is the optimal diet for prevention and treatment of ASCVD. Several dietary patterns, however, appear to be beneficial, including the Mediterranean and Dietary Approaches to Stop Hypertension (DASH), which improve cardiovascular outcomes (40,41). A single dietary pattern may not be optimal for all populations, and logistic feasibility and cultural appeal of specific diets vary widely among the many regions of the world. Even though medical nutrition therapy continues to be a challenging area, there are certain commonalities between diets which have shown benefit.

Nutritional guidelines for the reduction of cardiovascular risk usually recommend diets rich in fruits and vegetables, whole grains, legumes, and high soluble fiber, and avoiding processed foods, with a reduction in total calories. The Mediterranean and DASH diets support these principles. Generally, reduced fat dairy products, fish, lean meats, and skinless poultry are preferable to traditional high fat alternatives, and salt intake should be decreased (41,42). Soluble fiber lowers LDL-C with reductions of 8 to 24%. Sources of insoluble fiber (such as whole wheat) are also associated with low ASCVD risk. The recommendation for a total fat intake of 25 to 35% of calories comes from the observation that a low-fat diet can lead to elevations of triglycerides and lowering of HDL-C, especially when excessive simple carbohydrates or alcohol are consumed. Paradoxically, studies have shown that limiting fat intake to ~10% of calories is associated with ASCVD regression and decreased ASCVD events (43,44). In the European Prospective Investigation into Cancer and Nutrition (EPIC)–Oxford study, mortality from ischemic heart disease was lower in vegetarians than in nonvegetarians (45). Studies looking at the incidence of stroke have revealed a benefit to whole-food, plant-based, high-fiber diets with little or no animal products (46). One mechanism might be that meat and dairy cause higher levels of trimethylamine N-oxide, which has been associated with development and progression of atherosclerosis, primarily by altering the gut microbiome (47).

Physical activity is associated with improvements in risk factors such as obesity, waist circumference, glucose intolerance, hypertension, and dyslipidemia. Specific lipid-level improvements associated with regular exercise include reduced triglyceride and VLDL-C levels, increased HDL-C, reductions in hsCRP, and in some individuals, decreased LDL-C levels (1). Exercise programs generally should include 150 to 300 minutes weekly of moderate-intensity physical activity (48). Daily physical activity goals may be met in a single session or multiple sessions throughout the course of a day (10 minutes minimum); for some individuals, breaking activity up throughout the day may help improve adherence to physical activity programs (49). Additional studies also suggest that weight and resistance training may be beneficial to some individuals with the insulin resistance syndrome, independent of body fat or aerobic fitness (50). Therefore, in addition to aerobic activity, muscle-strengthening activity is recommended at least 2 days a week (51).

Individuals who are nonadherent to regular physical activity should be repeatedly encouraged, and practitioners should apply a variety of strategies as necessary to improve adherence. Strategies may include individually tailored advice, identification of adherence barriers, referral to instructor-led exercise classes, and routine follow-up and consultation.

Evidence supports an association of 6 to 8 hours of sleep per night with a reduction in cardiometabolic risk factors, whereas sleep deprivation aggravates insulin resistance, hypertension, hyperglycemia, and dyslipidemia, and increases inflammatory cytokines (52-57). Daytime drowsiness, a frequent symptom of sleep disorders such as sleep apnea, is associated with an increased risk of accidents, errors in judgment, and diminished performance. Basic sleep hygiene recommendations should be provided to all patients with potential cardiovascular problems. The most common type of sleep apnea, obstructive sleep apnea (OSA), is caused by physical obstruction of the airway during sleep. The resulting lack of oxygen causes the patient to awaken and snore, snort, and grunt throughout the night. The awakenings may happen hundreds of times per night, often without the patient's awareness. OSA is more common in males, the elderly, and persons with obesity. People with suspected OSA should be referred for a home study in lower risk settings or to a sleep specialist for formal evaluation and treatment in higher-risk settings.

Evidence supports an association between ASCVD and mental health issues. Depression is an independent risk factor, as well as more prevalent, in patients with ASCVD. Other mental health issues, such as schizophrenia, bipolar disorder, anxiety, and post-traumatic stress disorder have been found to increase the risk for ASCVD. The association is unclear but may be on the basis of genetic, environmental, psychologic, or other mechanisms (58). Having a positive outlook, in contrast, has been associated with improved ASCVD outcomes (59). This has been referred to as a happiness factor but emphasizes the importance of a close social structure and community involvement.

Although some meta-analyses have shown decreased cardiovascular outcomes in persons who drink limited quantities of alcohol compared to abstainers (60,61), drinking alcohol is not recommended as an intervention due to potential adverse effects. Drinking too much alcohol can

raise triglycerides. Increases in HDL-C may occur, but in not the HDL-C subfraction associated with a cardioprotective effect. Excess alcohol can also lead to hypertension, cardiomyopathy, and atrial fibrillation with subsequent strokes (62). Substance abuse with cocaine has also been associated with both acute cardiovascular events (e.g., hypertension and arrhythmias) and atherosclerosis and cardiomyopathy in the long-term (63).

Smoking is a major risk factor for ASCVD and may triple the risk of death due to atherosclerosis. Fortunately, smoking cessation mitigates the risk rapidly and significantly. One year of abstinence will decrease the risk of heart attacks significantly, and 5 years will decrease the risk of stroke to a level comparable to that of nonsmokers (3,64). Smoking cessation is perhaps the most important component of lifestyle therapy and involves avoidance of all tobacco products. Transient nicotine replacement therapy and other pharmacologic interventions (e.g., sustained release bupropion and varenicline) should be considered in patients having difficulty with smoking cessation. Structured programs should be recommended for patients unable to stop smoking on their own (1).

VI. Treating LDL-C to Goal

As described in Section IV, ASCVD Risk Categories and Goals, AACE has established LDL-C goals ranging from <55 mg/dL to <130 mg/dL according to individuals' ASCVD risk based on a large body of evidence of numerous outcomes trials with statins, ezetimibe, and PCSK9 inhibitors (1,24-26). The findings from these trials consistently demonstrate that ASCVD risk decreases with LDL-C along a continuum, supporting a "lower is better" approach. In a meta-analysis of 26 prospective statin trials involving close to 170,000 participants by the Cholesterol Treatment Trialists group (CTT), each 38 mg/dL (1 mmol/L) reduction in LDL-C led to a 29% decrease in major vascular events (nonfatal myocardial infarction [MI] or ASCVD death) when baseline LDL-C was <77 mg/dL and a 37% reduction when baseline was <70 mg/dL. There was a 19% reduction in coronary revascularizations and a 16% reduction in cerebrovascular accident (65). Another meta-analysis of 8 major statin trials demonstrated that those individuals achieving an LDL-C <50 mg/dL, a non-HDL-C <75 mg/dL, and apo B <50 mg/dL have the lowest ASCVD events (66).

A statin should be used as first-line cholesterol-lowering therapy, unless contraindicated; current evidence supports a moderate- to high-intensity statin (1,65,67). However, considerable residual risk often persists even after aggressive statin monotherapy in primary prevention patients with multiple cardiovascular risk factors and in secondary prevention patients with stable clinical ASCVD or ACS (30,67,68). Statin intolerance (see Section VII, Managing Statin Intolerance and Safety) or the inability to reach LDL-C goal may limit the use of intensive statin therapy in some patients (69). Due to these limitations, some patients may require the addition of other agents to achieve LDL-C goals, and the evidence from recent combination therapy studies have proven that reducing LDL-C by any means leads to ASCVD event reductions. In the IMPROVE-IT trial, which involved 18,144 patients with ACS, an LDL-C of 53 mg/dL achieved with the combination of ezetimibe plus moderate-dose statin significantly reduced the risk of MACE (a composite of cardiovascular death, nonfatal MI, unstable angina requiring rehospitalization, coronary revascularization, or nonfatal stroke) compared with an LDL-C of 70 mg/dL achieved with the statin alone, with the most pronounced benefits in patients with diabetes and those older than 75 years (26). The FOURIER and Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab Study (ODYSSEY Outcomes) trials also showed that reducing LDL-C to low levels with combination therapy improves outcomes over high-intensity statin alone (24,25). In the FOURIER trial, evolocumab added to high-intensity statin therapy reduced LDL-C to 30 mg/dL (59% difference from the statin-only group), which after 2.2 years was associated with a 15% decrease in a composite of cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization (25). As individual endpoints, MI, stroke, and coronary revascularization were reduced by 27%, 21%, and 22%, respectively. Likewise, after 4 years of therapy in ODYSSEY Outcomes, LDL-C levels were 55% lower with alirocumab plus a high-intensity statin than with statin alone (66 mg/dL versus 103 mg/dL), and this reduction was associated with a statistically significant 15% decrease in a composite of death from CHD, nonfatal MI, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization (24). MI, ischemic stroke, and unstable angina were reduced as individual events by 14%, 27%, and 39%, respectively. Post-hoc analysis of prespecified groups in FOURIER suggests a progressive composite MACE benefit with progressive LDL-C reductions to very low levels (70).

To date, cardiovascular outcomes trials (CVOTs) with colesevelam or bempedoic acid (BA) have not been published, but the CVOTs with statins plus ezetimibe or a PCSK9 inhibitor suggest that further LDL-C lowering with any combination of agents would confer ASCVD benefits. On this basis, the algorithm advocates progressively increasing the intensity of therapy to achieve LDL-C goals.

Lifestyle management is the foundation of all lipid-reduction regimens, and statin therapy should be started in low-risk patients unable to maintain LDL-C <130 mg/dL on lifestyle therapy and given to all patients at moderate to extreme risk regardless of their initial LDL-C level. Lipids should be checked every 3 months or more frequently when necessary. The table at the bottom of Slide VI lists the dosages of the different LDL-C-lowering options

recommended in each ASCVD risk column, and the range of LDL-C reductions in primary hyperlipidemia or familial hypercholesterolemia reported in the prescribing information for each agent appear in Table 3 (71-82).

If patients are not at goal, address adherence to therapy first. When intensification is necessary, the order of agents listed indicates the AACE preference for consideration. For example, treatment for patients at extreme risk should begin with lifestyle therapy plus a high-intensity statin (atorvastatin 40 to 80 mg or rosuvastatin 20 to 40 mg, or the highest tolerated statin dose) to achieve an LDL-C goal of <55 mg/dL. If LDL-C remains above goal after 3 months, a PCSK9 inhibitor, ezetimibe, colesevelam, or BA should be added, depending on required LDL-C lowering, and a third agent should be added if the combination fails to achieve the goal. Because the cost of ezetimibe is low, it may be preferred over PCSK9 inhibitors as second-line therapy to achieve an LDL-C <70 mg/dL for patients who require no more than 15 to 20% further reduction to reach goals. For patients at moderate or high risk, lipid management should begin with a moderate-intensity statin and be increased to a high-intensity statin before adding a second lipid-lowering medication to reach an LDL-C <100 mg/dL.

VII. Managing Statin Intolerance and Safety

For the great majority of patients, statins are safe and well-tolerated, and for those at heightened risk of ASCVD, the ASCVD benefit far outweighs the likelihood of adverse effects. Nevertheless, statin intolerance may occur in a significant subset of statin-treated patients.

Statin-associated muscle symptoms are the most common reason for statin intolerance, and may include pain, weakness, cramps, or stiffness. Observational studies and experience in clinical practice have suggested an incidence ranging from ~5 to >20%, although placebo-controlled clinical trials have reported the risk to be much lower. Assessment is based on the temporal association of symptoms with onset of treatment, cessation upon statin discontinuation, and if not severe, recurrence of symptoms following re-challenge with the same and/or up to 2 other statins. An elevated creatine kinase (CK) level is not required for establishing the diagnosis, although it may be corroborated by CK ≥4 times the upper limit of normal. More severe myopathy leading to rhabdomyolysis, with CK >10 times the upper limit of normal, is rare (~1 per 10,000 patient-years) and requires immediate statin cessation, hydration, and monitoring of renal

Table 3
Effects of LDL-C Lowering Agents[a]

Agent	LDL-C reductions
Moderate-intensity HMG-CoA reductase inhibitors (statins)	
Lovastatin 40 mg	–31% to –42%
Pravastatin 40-80 mg	–34% to –37%
Fluvastatin 40 mg BID	–36%
Fluvastatin XL 80 mg	–35%
Pitavastatin 2-4 mg	–38% to –45%
Simvastatin 20-40 mg	–29% to –41%
Atorvastatin 10-20 mg	–29% to –33%
Rosuvastatin 5-10 mg	–45% to –52%
High-intensity HMG-CoA reductase inhibitors (statins)	
Atorvastatin 40-80 mg	–50% to –60%
Rosuvastatin 20-40 mg	–55% to –63%
Cholesterol absorption inhibitor: ezetimibe[b]	–12% to –17%
PCSK9 inhibitors	
Evolocumab 140 mg Q2W or 420 mg Q4W[b]	–63% to –71%
Alirocumab 75-150 mg Q2W[b]	–48% to –58%
Bile acid sequestrant: colesevelam[b]	–8% to –16%
ACL inhibitor: bempedoic acid[b]	–17% to –18%

Abbreviations: ACL = adenosine triphosphate-citrate lyase; BID = twice daily; HMG-CoA = hydroxymethylglutaryl-coenzyme A; LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9; Q2W = once every 2 weeks; Q4W = once every 4 weeks; XL = extended release.
[a]Refer to references 71 to 82.
[b]In combination with statin therapy.

function. Its occurrence is a contraindication for future statin therapy (83-85).

Physicians should be aware of the factors that may increase the risk for statin-induced myopathy. These include female sex, small body size, age >65 years, frailty, East Asian ancestry, a personal or family history of myopathy, poorly controlled hypothyroidism, subnormal vitamin D, and the use of medications that raise circulating levels of statins and/or their active metabolites (e.g., erythromycin, fluconazole). In such cases consider using smaller statin doses and/or less potent statins with lower incidence of myopathy (e.g., pitavastatin, extended-release fluvastatin), along with cautious up-titration of dose. It is important to advise patients to report muscle symptoms of any severity that occur with initiation of statin, increase in dose, or change to a different statin type, and to stop treatment if these are deemed to be clinically significant. Once symptoms resolve, therapy may be resumed as a trial, with consideration of a lower dose of the same statin, an alternate statin such as those noted above, or others with relatively low lipid solubility (pravastatin, rosuvastatin). Other approaches to consider for alleviating symptoms include less frequent dosing (e.g., 1 to 3 per week), and/or a trial of coenzyme Q10 therapy, with addition or substitution of nonstatin lipid lowering medications as needed (86).

Statins may accelerate hyperglycemia progression minimally as an on-target effect (average A1C increase of ~0.1%), leading to onset of diabetes in those already at highest diabetes risk. Overall, the incidence of statin-associated diabetes is ~10% greater than that with placebo over the usual 2- to 6-year time course of clinical trials (87). However, in view of the demonstrated benefits of statin therapy for prevention of ASCVD, the leading cause of death in patients with diabetes, the risk for new onset diabetes or modest worsening of glycemic control in established diabetes does not justify withholding statins in patients with significant ASCVD risk (88,89).

Statin use may be suspected of triggering less common adverse symptoms in individual patients, and, as for muscle symptoms, a trial of discontinuation and resumption of statin therapy can help in assessing the likelihood that such symptoms are statin related. However, there is no convincing clinical trial evidence for a significant risk of hemorrhagic stroke, arthritis, tendonitis, or cataracts, or for adverse effects on cognition or liver or kidney function (87).

VIII. Management of Hypertriglyceridemia and the Role of Icosapent Ethyl

In 2001, the Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program suggested a level of <150 mg/dL as the therapeutic goal for triglycerides (90). Although this threshold was not very well validated, it is generally thought to be a reasonable goal for triglyceride reduction and has been adopted by AACE, the National Lipid Association (NLA), and others. Triglycerides may be measured fasting or nonfasting, and optimum levels are considered to be well below 100 mg/dL (91).

The prevalence of hypertriglyceridemia, defined as triglyceride levels exceeding 150 mg/dL, is approximately 26% in the U.S. (4). Combinations of genetic defects and environmental effects contribute to the development of hypertriglyceridemia; increased production of triglycerides occurs in obesity, insulin resistance, and diabetes, whereas various genetic conditions cause decreased clearance of triglycerides. Hypertriglyceridemia may present with increased numbers or concentrations of atherogenic small, dense LDL particles and apo B-100-associated triglyceride-rich lipoprotein remnant cholesterol particles, which increase ASCVD risk (92).

Prior to publication of REDUCE-IT, only a few studies with inconsistent results supported lowering triglycerides to reduce ASCVD events (32,35-37), whereas several large-scale clinical trials failed to prove that managing triglycerides reduces ASCVD (93,94). No medication that lowers triglycerides was approved by the United States Food and Drug Administration (FDA) to reduce ASCVD until 2019, when icosapent ethyl (IPE), a highly purified, nonoxidized formulation of eicosapentaenoic acid (EPA), received an indication to prevent ASCVD morbidity and mortality in patients with triglycerides ≥150 mg/dL and established ASCVD or diabetes with ≥2 ASCVD risk factors on maximally tolerated statins (95). The indication was granted on the strength of the REDUCE-IT results; however, because the triglyceride decrease in the trial was only 18%, the cardiovascular outcome does not seem to be related to this reduction. Therefore, in the discussion below, we separate the role of managing high triglycerides with lifestyle and medications (including IPE and other omega-3 fatty acids) from the role of IPE to prevent cardiovascular events, which appears to be largely, if not entirely independent of its effect on triglycerides. This represents a paradigm shift in the management of people with established ASCVD or those with diabetes at high risk for ASCVD: preventing the next event rather than simply further controlling traditional cardiovascular risk biomarkers.

Management of hypertriglyceridemia should begin with lifestyle modification, including weight reduction and/or macronutrient modification (i.e., restricted intake of simple carbohydrates, fat, and alcohol) and increased physical activity (see Section V. Lifestyle Recommendations) (1). Secondary causes of hypertriglyceridemia, including medical conditions such as diabetes and medications that increase triglycerides, should be addressed first.

Pharmacologic agents used to reduce triglycerides include fibrates, omega-3 fatty acids, and nicotinic acid (niacin). Along with their primary LDL-C-lowering effects, statins and PCSK9 inhibitors also moderately reduce triglycerides, and ezetimibe may have a mild triglyceride-lowering effect (see Section X. Profiles of Medications for Dyslipidemia).

Fibrates are generally considered the most potent triglyceride-lowering agents, with reductions of 45 to 55% (1,35,96,97). Fibrates bind to and activate hepatic peroxisome proliferator-activated receptor alpha, which complexes with the retinoid X receptor to regulate gene expression involved with activation of beta-oxidation of fatty acids, thus reducing the availability of free fatty acids for triglyceride synthesis for the formation of VLDL (98). Subgroup analyses from various fibrate trials such as ACCORD, FIELD, and others, though nonsignificant, suggest fibrates may confer cardiovascular benefits in patients with triglycerides ≥200 mg/dL and HDL-C ≤40 mg/dL (1,32,35).

Prescription-grade omega-3 fatty acids, which include formulations of EPA alone or in combination with docosahexaenoic acid (DHA), are approved to treat triglyceride elevations ≥500 mg/dL. These agents reduce triglycerides by approximately 20 to 45%, depending on baseline triglyceride levels (34,95,99,100). Prescription-grade omega-3 fatty acids also demonstrated anti-inflammatory, antioxidant, and antiplatelet mechanisms; reduced platelet activity; and reduced thrombosis, and EPA seems to also improve plaque stability (1,101).

Niacin, or nicotinic acid, reduces triglyceride by 20 to 30% in a dose-dependent fashion (1). Niacin likely reduces triglycerides by reducing lipolysis and thereby decreasing the supply of free fatty acids, which depresses triglyceride synthesis in the liver. Niacin may also reduce the hepatic synthesis of apo CIII, thus removing a potent inhibitor of lipoprotein lipase activity. This leads to increased lipoprotein lipase hydrolysis and clearance of triglycerides, VLDL, IDL, and chylomicrons (102,103).

For patients with hypertriglyceridemia who do not have established ASCVD or diabetes with ≥2 risk factors, a triglyceride level of <150 mg/dL is the goal. If this cannot be achieved with statin therapy, then a fibrate, omega-3 fatty acid, or niacin may be considered.

To reduce the risk of acute pancreatitis, a fibrate, prescription-grade omega-3 fatty acid (IPE, EPA, or EPA-DHA formulation), and/or niacin should be given to all patients with severe hypertriglyceridemia (>500 mg/dL), with the goal of reducing triglycerides to well below 500 mg/dL (1,91,104,105). The higher the baseline triglyceride level, the greater the percent and absolute triglyceride lowering, but the less likely any single agent will sufficiently reduce triglycerides to goal. One may add one agent at a time or combinations of agents depending on the degree of triglyceride lowering required (1,91,104). In patients with diabetes, pioglitazone and/or insulin can also be utilized in an additive fashion to reduce triglycerides (1,88,89,105).

Aggressive triglyceride lowering is also required to treat chylomicronemia, which usually presents with triglycerides >880 mg/dL. This condition may be a sign of lipoprotein lipase activity deficiency, a manifestation of FCS. FCS can be identified by the inability of combinations of triglyceride-lowering agents to substantially reduce triglycerides. Although rare, this disorder is also associated with an increased incidence of acute and chronic pancreatitis; affected individuals should be referred to a lipid specialist.

Management of ASCVD risk in people with triglycerides >150 mg/dL should begin with statin therapy, which yields triglyceride reductions of up to 35% (1,106-108). Moderate- to high-intensity statin therapy should be initiated according to ASCVD risk category (see Section VI. Treating LDL-C to Goal). Based on the REDUCE-IT findings (34), AACE recommends adding IPE to prevent ASCVD if triglycerides are between 135 and 499 mg/dL on maximally tolerated statin therapy in patients who have ASCVD (secondary prevention cohort of REDUCE-IT) or diabetes plus ≥2 cardiovascular risk factors (primary prevention cohort). In REDUCE-IT, IPE 2,000 mg twice daily was evaluated in patients who had triglycerides of 135 to 499 mg/dL and LDL-C of 41 to 100 mg/dL on a stable statin dose with or without ezetimibe. At a median 4.9 years of follow-up, an 18% reduction from baseline triglycerides in the IPE group was associated with a profoundly significant 25% relative risk reduction and a 4.8% absolute risk reduction in the primary composite endpoint of cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina. Relative risk of the key secondary 3-point composite hard endpoints of cardiovascular death, nonfatal MI, or nonfatal stroke was reduced by 26%, and absolute risk of these endpoints by 3.6% (34). Overall, there was a remarkable 30% reduction in total ASCVD events (109). The mechanism behind the IPE benefits is not clear, as neither its triglyceride-lowering capabilities, its reduction of inflammation, nor its mild effect on platelets can explain the remarkable benefits observed at the end of the trial (34). A prespecified substudy indicates that the benefits were strongly related to serum levels of EPA. After 1 year, IPE significantly increased serum EPA levels by 386% from baseline. The on-treatment levels correlated strongly with reductions in cardiovascular death, MI, stroke, coronary revascularization, unstable angina, sudden cardiac death, cardiac arrest, new heart failure, and all-cause mortality (110).

Patients whose triglycerides are <150 mg/dL on a statin plus IPE should continue lifestyle and statin therapy, as indicated, and triglycerides and other lipids should be monitored every 3 to 12 months, along with diabetes risk, which is increased in patients with high triglycerides (1,89). If the patient's triglycerides remain >150 mg/dL on the statin-IPE regimen, a fibrate or niacin may be considered. Over-the-counter fish oil dietary supplements are not FDA-approved for lowering triglycerides and are not recommended for this purpose because they contain very low amounts of polyunsaturated omega-3 fatty acids as well as trans fatty acids and saturated fat (111-113).

IX. Assessment and Management of Elevated Lipoprotein(a)

Increased Lp(a) is the most common genetic dyslipidemia, with a prevalence in the general population of 20%, and is an independent, genetic, and causal risk factor for ASCVD (MI, stroke, peripheral arterial disease, recurrent events, and calcific aortic stenosis) (14,114-116). It possesses homology with the fibrin-binding domains of plasminogen and plasmin with prothrombotic and antifibrinolytic effects, as well as the oxidized phospholipids that are pro-inflammatory. A Lp(a) level >50 mg/dL is associated with increased risk of recurrent events in patients on statin therapy (117).

Measurement of Lp(a) in patients should be considered in the following settings:

- All patients with clinical ASCVD, especially premature or recurrent ASCVD despite LDL-C lowering;
- Individuals with a family history of premature ASCVD and/or increased Lp(a);
- Individuals with South Asian or African ancestry, especially with a family history of ASCVD or increased Lp(a);
- Individuals with a 10-year ASCVD risk ≥10% (primary prevention setting), in order to stratify risk;
- Patients with a personal or family history of aortic valve stenosis;
- Patients with refractory elevations of LDL-C despite aggressive LDL-C-lowering therapy (i.e., statin resistance).

No medications are FDA approved to lower Lp(a). Agents that have been demonstrated to reduce Lp(a) levels include PCSK9 inhibitors, niacin, oral estrogen, and aspirin (118-121). Outcomes trials focusing on selective lowering of Lp(a) by an antisense oligonucleotide are underway. Lipoprotein apheresis, although infrequently performed today, can be considered in extreme cases (122). Currently, recommended treatment of patients with elevated Lp(a) is aggressive lowering of LDL-C, which mitigates the risk associated with the Lp(a) elevation (1).

X. Profiles of Medications for Dyslipidemia

The pharmacologic management of dyslipidemia requires a comprehensive strategy to control lipid levels and more importantly reduce cardiovascular events. This field is constantly evolving as new studies are published and new agents are developed.

Statins (i.e., HMG-CoA reductase inhibitors) are the initial medication of choice for LDL-C reduction. The best-studied class of lipid lowering medications, they significantly and consistently improve ASCVD outcomes, not just lipid values. Statins have a relatively low side effect profile and have been studied across all ages and comorbidities. Currently available options include atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin. Numerous large clinical trials have established the efficacy and safety profile of statins, which decrease plasma LDL-C in a dose-dependent fashion by 20 to 55%, triglycerides by up to 35%, and raise HDL-C by 2 to 10% (1). As mentioned, a 2010 meta-analysis by the CTT strongly confirmed the benefit of LDL-C lowering with a statin. Robust event reduction correlated with the degree of LDL-C lowering (123).

Statin therapy is associated with a modestly increased risk of increased glucose levels and new-onset diabetes (87,124,125). However, any increases in glucose levels that occur are not enough to offset the benefits of reduced cardiovascular morbidity and mortality. Despite initial observations of elevated liver enzymes in clinical trials, the FDA has concluded that statins as a class do not have negative impacts on the liver, and liver monitoring is not necessary (126). However, statins are contraindicated in active liver disease (127). See Section VII, Managing Statin Intolerance and Safety, for a discussion of other side effects such as statin intolerance and myalgias.

The unique characteristics of various statins emerge from differences in their metabolism, bioavailability, potency, and duration of action. For example, some statins are potent inhibitors of cytochrome P450, which can lead to interactions with other agents such as cyclosporin, rifampin, protease inhibitors, and other agents. For more details, see the AACE/ACE 2017 Guidelines for Management of Dyslipidemia and Prevention of Cardiovascular Disease (1).

Cholesterol absorption inhibitors primarily reduce LDL-C by 10 to 25% and may also have beneficial effects on triglycerides, apo B, and HDL-C. These effects are often synergistic in combination therapy with statins, colesevelam, or BA. Ezetimibe is the only member of this drug class; it acts by reducing cholesterol absorption at the brush border of enterocytes via cholesterol transporter interference (1). The IMPROVE-IT trial demonstrated a significant reduction in the ASCVD endpoints in individuals treated with ezetimibe plus simvastatin versus simvastatin alone (26). Ezetimibe has minimal adverse effects and a strong safety profile (1).

Alirocumab and evolocumab are monoclonal antibodies that inhibit PCSK9, a protein that regulates the recycling of LDL, thereby reducing LDL-C up to 71% when added to maximum statin therapy or given as monotherapy (1,73,74). Given by subcutaneous injection every 2 to 4 weeks, they have a favorable safety and tolerability profile. They have demonstrated favorable ASCVD outcomes, especially in high-risk patients (24,25), although high cost and need for injections have limited their use.

At full dosage, bile acid sequestrants reduce LDL-C by 15 to 25% and increase HDL-C by 4 to 11%. In patients with elevated triglycerides, they may further increase triglycerides. In fact, colesevelam is contraindicated in patients with triglycerides >500 mg/dL. One agent, colesevelam, is approved for glucose-lowering therapy in

adults with type 2 diabetes. They can be added to a cholesterol absorption inhibitor to achieve LDL-C reductions comparable to moderate-dose statins. However, there are no outcomes data as of this time. Important side effects are bloating, constipation, and interference with absorption and action of other medications such as thyroid hormone (1).

BA is a novel LDL-C-lowering agent that is effective in combination with statins and with ezetimibe, acting in a fashion that potentiates statin action. In clinical trials, BA reduced LDL-C by 15 to 24% (128-131). When given as a fixed-dose combination, BA plus ezetimibe reduced LDL-C by 36% compared with a 2% increase with placebo (132). No evidence is, as yet, available on cardiovascular outcomes benefit. BA does not lead to increases in glucose concentrations or the development of diabetes (131). Uric acid was increased in 26% of treated patients versus 10% of placebo; 11% of persons having a past history of gout versus 2% of placebo had an acute gout episode, which in the total trial population was 1.5% on BA versus 0.4% on placebo. Another infrequent but noteworthy complication is tendon rupture. Tendon rupture in the rotator cuff, biceps tendon, or Achilles tendon may occur more often in people who are older, have CKD, or have been treated with glucocorticoids or with fluoroquinolone antibiotics. BA is contraindicated in combination with simvastatin >20 mg and pravastatin >40 mg (71).

IPE, a purified formulation of the omega-3 fatty acid EPA, is indicated to reduce cardiovascular risk among patients with elevated triglyceride levels as an add-on to maximally tolerated statin therapy, as established by REDUCE-IT. In this trial, IPE reduced the risk of cardiovascular events (cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina) by 25% and cardiovascular death by 20%, which corresponded to absolute risk reductions of 4.8% and 0.9%, respectively, at 4.9 years in patients with hypertriglyceridemia who were treated with IPE and maximally tolerated statins (see Section VIII. Management of Hypertriglyceridemia and the Role of Icosapent Ethyl) (34). In clinical trials, IPE was associated with muscle and joint pain, swelling of the extremities, constipation, gout, increased bleeding, and increased risk of atrial fibrillation or flutter (1).

Both IPE and combination omega-3-acid ethyl esters, in which EPA is coupled with DHA, are indicated as adjuncts to diet for the reduction of triglyceride levels in adults with severe (≥500 mg/dL) hypertriglyceridemia. It should be noted that these effects are for prescription strength omega-3 fatty acids and not over-the-counter supplements (1).

Fibrates are effective for treating individuals with severe hypertriglyceridemia and for individuals at risk of ASCVD who have elevated triglycerides and low HDL-C levels as their primary lipid abnormality. Currently available fibrates are gemfibrozil, fenofibrate, micronized fenofibrate, and fenofibric acid. Fibrates lower triglycerides by up to 55% and increase HDL-C by 6 to 18% (1,35,96,97). Outcomes studies with fibrates have had mixed results, especially in statin-treated populations and in individuals treated with fibrates who have less severe triglyceride and HDL-C abnormalities (32,35,39,93). Maximum dosages of certain statin-fibrate combinations such as simvastatin with fenofibrate and other statins with gemfibrozil need to be considered. There is a small but significant increase in creatinine with fibrates (1). However, despite initially and reversibly increasing serum creatinine, fenofibrate reduced albuminuria and slowed eGFR loss over 5 years (133).

Niacin is a potent LDL-C- and triglyceride-lowering medication that also substantially increases HDL-C. Niacin lowers LDL-C by up to 20% in a dose-dependent manner. In combination with statins or bile acid sequestrants, niacin has been associated with angiographic evidence of reduced progression and some regression of atheromatous plaques (1). However, large-scale clinical trials such as Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides (AIM-HIGH) have not demonstrated cardiovascular benefit with niacin when individuals are well-controlled on statin therapy, and in some instances, the combination may increase the side effect profile (134,135).

Blood glucose elevations have been associated with higher dosages of niacin, particularly in individuals with diabetes, but these are mild and temporary. Flushing may occur, especially at the beginning of niacin therapy; however, this effect often diminishes with continued use. Flushing occurs less frequently with extended-release niacin and can be ameliorated by pretreating with aspirin or a nonsteroidal anti-inflammatory agent and by slowly titrating the dosage upward. Hepatoxicity is associated with sustained release niacin. Increases in uric acid and gout can occur, along with an increased possibility of statin muscle toxicity (1). Niacin has been shown to decrease Lp(a), although the clinical impact of this is unknown and may only occur with certain phenotypic expression (136).

Lomitapide, a microsomal triglyceride transfer protein (MTP) inhibitor, is a treatment option for HoFH. This agent, which may be associated with hepatotoxicity, is available with restricted distribution and may be useful for individuals with HoFH not responsive to PCSK9 inhibitor therapy (137). It is usually only utilized by lipid experts. Another HoFH treatment, mipomersen (an antisense apo B oligonucleotide), was recently withdrawn from the U.S. market. Treatment of HoFH is outside the scope of this algorithm.

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Yehuda Handelsman, MD, FACP, FNLA, MACE: Amarin, BI-Lilly, Sanofi, consultant and/or speaker; Amgen, Applied Therapeutics, AstraZeneca, BMS, Gan & Lee, Novo Nordisk, Sanofi, research grant support.

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AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS and the AMERICAN COLLEGE OF ENDOCRINOLOGY

AACE/ACE MANAGEMENT OF DYSLIPIDEMIA AND PREVENTION OF CARDIOVASCULAR DISEASE ALGORITHM

2020

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Please refer to the Executive Summary for full details, including evidence citations, supporting each slide in the algorithm.

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Table of Contents—Dyslipidemia and Prevention of Cardiovascular Disease Algorithm

Abbreviations: ASCVD = atherosclerotic cardiovascular disease; IPE = icosapent ethyl; LDL-C = low-density lipoprotein cholesterol.

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I. Dyslipidemic States

- Hypercholesterolemia
  - Defined relative to risk; see Slide IV
- Hypertriglyceridemia
  - TG >150 mg/dL; severe, TG >500 mg/dL
- Familial combined (mixed) hyperlipidemia
- Familial hypercholesterolemia
  - Heterozygous: associated with LDL-C >190 mg/dL (>160 mg/dL in children); prevalence 1 in 250
  - Homozygous: LDL-C >500 mg/dL; prevalence 1 in 1 million
- Elevated Lp(a)
- Familial chylomicronemia syndrome (FCS)
- Other rare genetic conditions
  - Familial hypoalphalipoproteinemia
  - Familial dysbetalipoproteinemia
  - Hypoalphalipoproteinemia
  - Beta-sitosterolemia
  - Lysosomal acid lipase deficiency
  - Lipodystrophy

Abbreviations: LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein(a); TG = triglyceride.

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II. Secondary Causes of Lipid Disorders

Recommendation: manage secondary cause(s) and treat lipid disorders as appropriate

Undesirable lifestyle conditions

- Excessive alcohol intake
- Lack of physical activity
- Fat-dense diet (primarily saturated fat)
- High carbohydrate/high sugar intake
- Malnutrition

Medical conditions

- Overweight/obesity/metabolic syndrome/prediabetes
- Uncontrolled diabetes
- Hypothyroidism
- Pregnancy
- CKD ≥3, especially with albuminuria
- Nephrotic syndrome
- Cholestatic diseases of the liver
- Lipodystrophy
- Paraproteinemia (dysgammaglobulinemia; MM)
- Chronic inflammatory conditions (RA, SLE)

Medications

- Progestins
- Oral estrogens
- Anabolic steroids
- Selective estrogen receptor modulators
- Protease inhibitors (for treatment of HIV)
- Immunosuppressive drugs (eg, cyclosporine, mTOR kinase inhibitor)
- Glucocorticoids
- Retinoids
- Interferon
- Taxol derivatives
- L-asparaginase
- Cyclophosphamide
- Atypical antipsychotic drugs
- Beta-blockers
- Thiazide diuretics
- Bile acid sequestrants[a]

[a]Bile acid sequestrants lower LDL-C but may increase triglycerides.

Abbreviations: CKD = chronic kidney disease; HIV = human immunodeficiency viruses; LDL-C = low-density lipoprotein cholesterol; MM = multiple myeloma; mTOR = mammalian target of rapamycin; RA =rheumatoid arthritis; SLE = systemic lupus erythematosus.

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III. Screening for and Assessing Lipid Disorders and ASCVD Risk

History	**Personal:** smoking, diet, physical activity, impaired glucose tolerance, metabolic syndrome, diabetes, obesity, hypertension, dyslipidemia, cardiovascular or cerebrovascular events, CKD, NAFLD/NASH, autoimmune/ inflammatory disease (e.g., lupus, rheumatoid arthritis, psoriasis), hepatitis C, history of pancreatitis, medications that alter lipids (e.g., steroids, retinoids, HIV therapy, anti-rejection medications) **Family:** cardiovascular disease, hypertension, dyslipidemia
Exam	Height, weight, BMI, waist circumference, BP, cardiac evaluation, peripheral and carotid pulses, vascular bruits, ABI, tendon xanthomas, eruptive xanthomas, lipemia retinalis, corneal arcus, xanthelasma
Laboratory	Lipid profile + calculated non-HDL-C, CMP + uric acid, HbA1c, TSH; consider apo B or LDL-P number, Lp(a), hsCRP, microalbuminuria, albuminuria
Diagnostic procedures	ECG: resting, stress tests (treadmill, chemical, nuclear) as appropriate Imaging: CAC scoring; consider carotid ultrasound and/or CIMT
Risk calculators	MESA Risk Calculator, Reynold's Risk Score, Framingham Risk Score, ACC/AHA ASCVD Risk Estimator, UKPDS Risk Engine (if diabetes)

Abbreviations: ABI = ankle-brachial index; ACC = American College of Cardiology; AHA = American Heart Association; apo B = apolipoprotein B; ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index; BP = blood pressure; CAC = coronary artery calcium; CIMT = carotid intima-media thickness; CKD = chronic kidney disease; CMP = comprehensive metabolic panel; ECG = electrocardiogram; HbA1c = hemoglobin A1c; HDL-C = high-density lipoprotein cholesterol; HIV = human immunodeficiency viruses; hsCRP = high sensitivity C reactive protein; LDL-P = low density lipoprotein particle; Lp(a) = lipoprotein(a); MESA = Multiethnic Study of Atherosclerosis; NAFLD = nonalcoholic fatty liver disease; NASH = nonalcoholic steatohepatitis; TSH = thyroid stimulating hormone; UKPDS = United Kingdom Prospective Diabetes Study.

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IV. ASCVD Risk Categories and Treatment Goals

Risk category	Risk factors[a] and 10-year risk	Treatment goals (mg/dL)			
		LDL-C	Non-HDL-C	Apo B	TG
Extreme risk	• Progressive ASCVD including unstable angina • Established clinical ASCVD plus diabetes or CKD ≥3 or HeFH • History of premature ASCVD (<55 years, male; <65 years, female)	<55	<80	<70	<150
Very high risk	• Established clinical ASCVD or recent hospitalization for ACS, carotid, or peripheral vascular disease, or 10-year risk >20% • Diabetes with ≥1 risk factor(s) • CKD ≥3 with albuminuria • HeFH	<70	<100	<80	<150
High risk	• ≥2 risk factors and 10-year risk 10-20% • Diabetes or CKD ≥3 with no other risk factors	<100	<130	<90	<150
Moderate risk	• <2 risk factors and 10-year risk <10%	<100	<130	<90	<150
Low risk	• No risk factors	<130	<160	NR	<150

[a]Major risk factors: advancing age, elevated non-HDL-C, elevated LDL-C, low HDL-C, diabetes, hypertension, CKD, cigarette smoking, family history of ASCVD.

Abbreviations: ACS = acute coronary syndrome; apo B = apolipoprotein B; ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; HDL-C = high-density lipoprotein cholesterol; HeFH = heterozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; NR = not recommended; TG = triglyceride.

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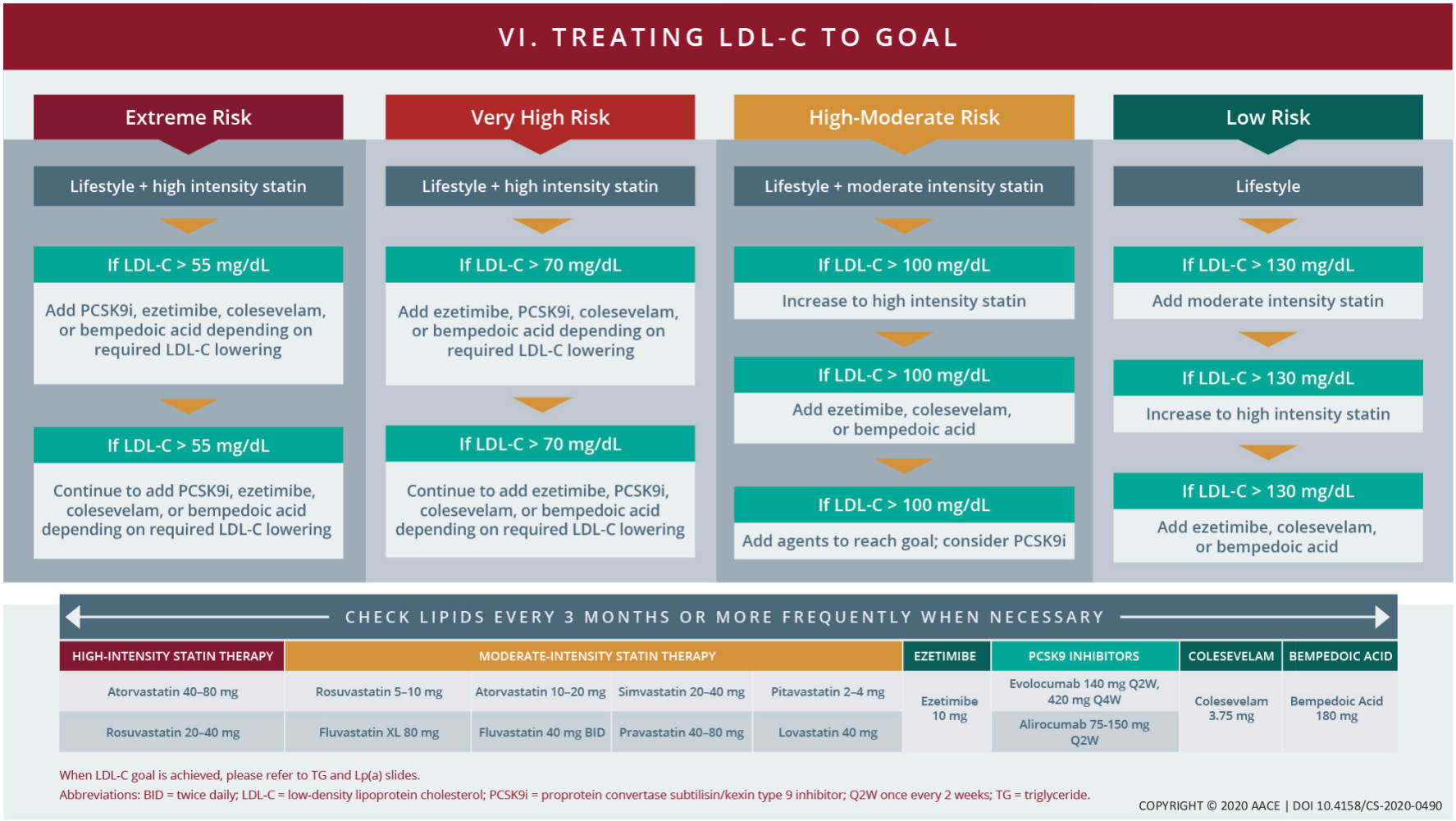
V. Lifestyle Recommendations

Intensity Stratified by Degree of CV Risk, Type of Dyslipidemia, and Related Complications

	General recommendations	Initial considerations	Implementation
Nutrition	Whole-food, plant-based, Mediterranean, and DASH diets recommended	Nuts, seeds, and avocado OK if no adiposity. If animal products consumed, order of preference: fish (especially fatty fish); lean meat and skinless poultry; limit processed foods	Focus on whole grains, legumes, vegetables, and fruits Avoid added sugars, salt, and fat Limit low-fiber grains and potatoes ("white starches"), fried foods, fast foods, and alcohol (especially if high triglycerides) Limit calories for 5-10% weight reduction[a] (if overweight/obesity)
Physical activity	Physical activity ≥3 times/week Reduce/break up prolonged sitting	Start with low duration and intensity of activity and increase slowly until activity goals are met	150-300 minutes/week of moderate-intensity or 75-150 minutes/week of high-intensity activity Resistance training ≥2 times/week
Sleep	Sleep duration 6-8 hours/night	Screen for and treat sleep apnea	Lifestyle modification with weight loss as needed Avoid sleeping pills
Mental health	Assess for depression, anxiety, and substance abuse	Lifestyle modification Address substance abuse Refer to mental health professionals as needed	Encourage community involvement (community centers, charitable organizations, schools, houses of worship, etc) and use of support services
Smoking	No tobacco or nicotine related products	Avoid passive exposure to tobacco smoke	Nicotine in any formulation is associated with atherosclerosis

[a] See AACE/ACE Comprehensive Clinical Practice Guidelines for Medical Care of Patients with Obesity and AACE/ACE Treatment Algorithm for the Medical Care of Patients With Obesity.

Abbreviations: CV = cardiovascular; DASH = Dietary Approaches to Stop Hypertension.



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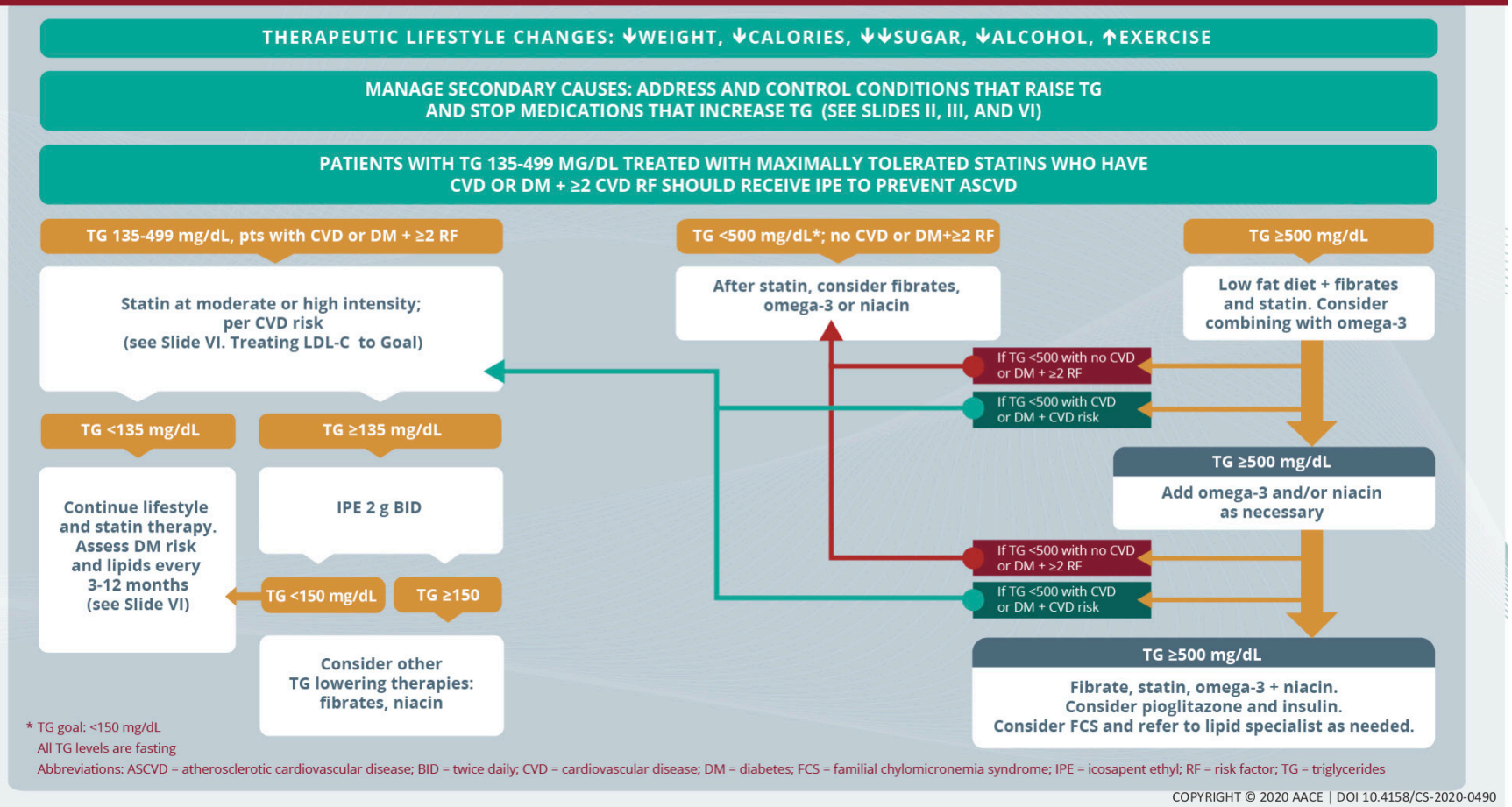
VII. Managing Statin Intolerance and Safety

Statin-Associated Muscle Symptoms	
Definition	Bilateral muscle symptoms (eg, pain, weakness, cramps, stiffness) with onset of statin use, relief with discontinuation, and recurrence with rechallenge with same and/or 2 other statins
Incidence	5-20% in clinical studies; rhabdomyolysis (CK >10 ULN) rare: ~1/10,000 patient-years
Risk factors	Older (>75 years), female, low BMI, East Asian, history of muscle symptoms, impaired renal and/or hepatic function, diabetes, HIV, some medications (eg, fibrates, erythromycin, fluconazole), statin type and dose, low vitamin D, hypothyroidism, acute infection
Prevention	Assess pre-existing symptoms, reinforce that benefits of statins outweigh the risks Consider lower doses in patients at risk
Treatment	• Acknowledge patient's symptoms and, if considered significant, stop the statin • When symptoms resolve, if myopathy not severe, rechallenge; may try lower dose, less frequent dosing (1-3/week); different statin (at least 2; consider pitavastatin or fluvastatin) • Consider normalizing a low vitamin D and/or adding CoQ10 • As needed add nonstatin therapies
Other Disorders	
Increased risk of new onset diabetes	Statins may minimally increase hyperglycemia but not enough to offset the benefits of reduced cardiovascular morbidity and mortality
No risk	No evidence of effects on liver, kidney, cognition, or eyes

Abbreviations: BMI = body mass index; CK = creatine kinase; CoQ10; coenzyme Q10; ULN = upper limit of normal.

VIII. MANAGEMENT OF HYPERTRIGLYCERIDEMIA AND THE ROLE OF IPE



* TG goal: <150 mg/dL
All TG levels are fasting

Abbreviations: ASCVD = atherosclerotic cardiovascular disease; BID = twice daily; CVD = cardiovascular disease; DM = diabetes; FCS = familial chylomicronemia syndrome; IPE = icosapent ethyl; RF = risk factor; TG = triglycerides

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IX. Assessment and Management of Elevated Lipoprotein(a)

Elevated Lp(a) is an independent genetic causal risk factor for ASCVD and aortic valve stenosis

Measure Lp(a) in patients in the following settings:

- Family history of premature ASCVD and/or increased Lp(a)
- All patients with premature or recurrent ASCVD despite LDL-C lowering

Treatment of patients with elevated Lp(a)

- Intensive lowering of LDL-C

Agents that reduce Lp(a) (↓ ~20-30%)[a]

- PCSK9 inhibitors
- High dose niacin
- Estrogen
- Aspirin, 80-160 mg

Lp(a) apheresis (↓ 50-80%)

- Refer to lipid specialist for assessment

[a]No agents are FDA approved for Lp(a) lowering.

Abbreviations: ASCVD = atherosclerotic cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein(a); PCSK9 = proprotein convertase subtilisin/kexin type 9.

X. Profiles of Medications for Dyslipidemia

Class	HMG-CoA Reductase Inhibitors (Statins)	Cholesterol Absorption Inhibitor	PCSK9 Inhibitors	Bile Acid Sequestrants	ACL Inhibitor	Omega-3 Fatty Acids	Fibric Acid Derivatives	Niacin
Agents	Atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin	Ezetimibe	Alirocumab, evolocumab	Cholestyramine, colestipol, colesevelam	Bempedoic acid	IPE, omega-3 acid ethyl esters (EPA + DHA)	Fenofibrate, fenofibric acid, gemfibrozil	Immediate, slow, extended release
LDL-C effect	↓ to ↓↓↓	↓ to ↓↓	↓↓↓ to ↓↓↓↓	↓ to ↓↓	↓ to ↓↓	IPE: — EPA + DHA: ↑	↑↓	↓ to ↓↓
Triglyceride effect	↓ to ↓↓	—	– to ↓	↑	—	↓ to ↓↓	↓↓↓	↓↓ to ↓↓↓
Non-HDL-C effect	↓↓	↓	↓↓↓	– to ↓	↓ to ↓↓	IPE: ↓↓ EPA + DHA: ↓	↓↓	↓↓ to ↓↓↓
CV outcome	++ to +++	+	++	– to +	—	IPE: ++ to +++ EPA + DHA: —	– to +	– to +
Glucose intolerance/ diabetes risk	↑	—	—	↓ to ↓↓	↓	—	—	↑
Muscle effect	↑ to ↑↑	—	—	—	—	—	– to ↑	—
Liver effect	—	—	—	—	—	—	—	↑ to ↑↑
Kidney effect	—	—	—	—	↑	—	Fenofibrate ↑creatinine	—
GI effect	—	Mild diarrhea	—	Bloating, constipation	—	Dyspepsia	Possible cholelithiasis, hepatitis	Abdominal pain, dyspepsia, jaundice
Brain effect	↑↓	—	—	—	—	—	—	—
Other effects	—	—	Injection site reaction, – to ↑	—	Tendon rupture, ↑ uric acid	Atrial fibrillation ↑ bleeding ↑	Fenofibrate may improve diabetic retinopathy	Flushing, pruritus, ↑ uric acid, gout
Interactions	CYP450i (eg, cyclosporin, rifampin, protease inhibitors; mycins)	—	—	↓ Absorption of thyroid hormones; vitamins A, D, E, K; other medications	Avoid with simvastatin >20 mg and pravastatin >40 mg	—	May potentiate anticoagulant effects; gemfibrozil ↑↑statin muscle toxicity	↑ Statin muscle toxicity

Abbreviations: ACL = ATP-citrate lyase; CV = cardiovascular; CYP450i = cytochrome P450 inhibitor; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; GI = gastrointestinal; HMG-CoA = hydroxymethylglutaryl-coenzyme A; IPE = icosapent ethyl; LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9.

Few adverse events or possible benefits | Potential for adverse effects | Neutral

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