AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS and the AMERICAN COLLEGE OF ENDOCRINOLOGY

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

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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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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.

V. Lifestyle Recommendations

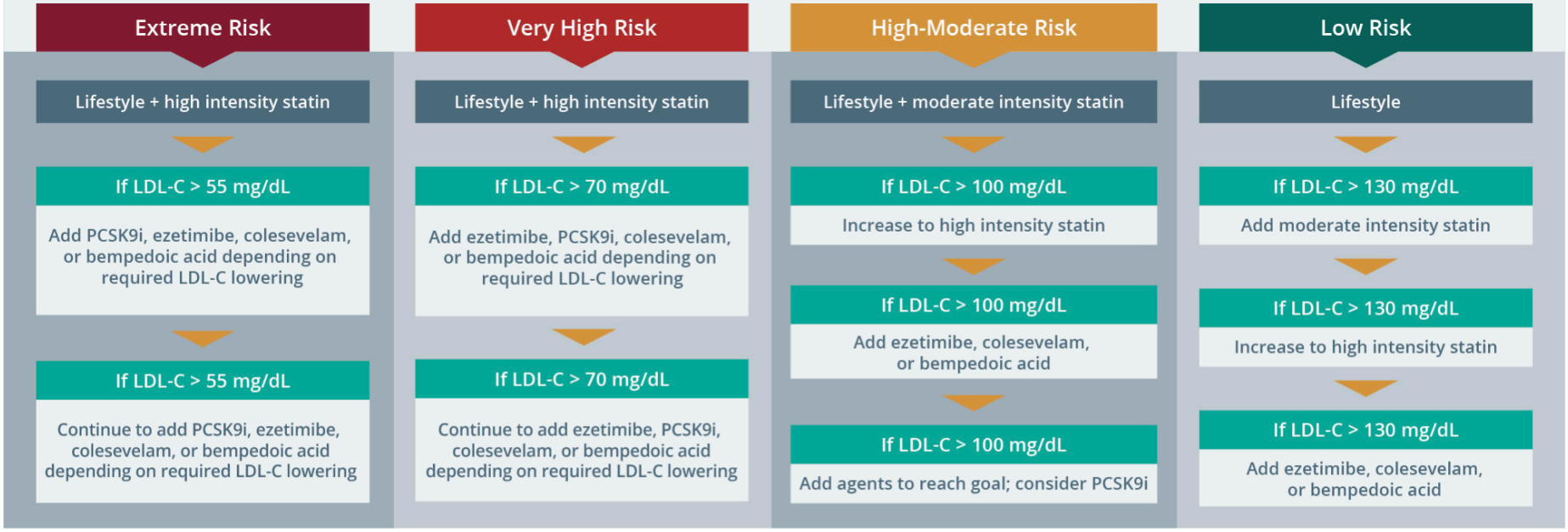
Intensity Stratified by Degree of CV Risk, Type of Dyslipidemia, and Related Complications

	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.

VI. TREATING LDL-C TO GOAL



CHECK LIPIDS EVERY 3 MONTHS OR MORE FREQUENTLY WHEN NECESSARY

HIGH-INTENSITY STATIN THERAPY	MODERATE-INTENSITY STATIN THERAPY				EZETIMIBE	PCSK9 INHIBITORS	COLESEVELAM	BEMPEDOIC ACID
Atorvastatin 40–80 mg	Rosuvastatin 5–10 mg	Atorvastatin 10–20 mg	Simvastatin 20–40 mg	Pitavastatin 2–4 mg	Ezetimibe 10 mg	Evolocumab 140 mg Q2W, 420 mg Q4W	Colesevelam 3.75 mg	Bempedoic Acid 180 mg
Rosuvastatin 20–40 mg	Fluvastatin XL 80 mg	Fluvastatin 40 mg BID	Pravastatin 40–80 mg	Lovastatin 40 mg		Alirocumab 75-150 mg Q2W		

When LDL-C goal is achieved, please refer to TG and Lp(a) slides.

Abbreviations: BID = twice daily; LDL-C = low-density lipoprotein cholesterol; PCSK9i = proprotein convertase subtilisin/kexin type 9 inhibitor; Q2W once every 2 weeks; TG = triglyceride.

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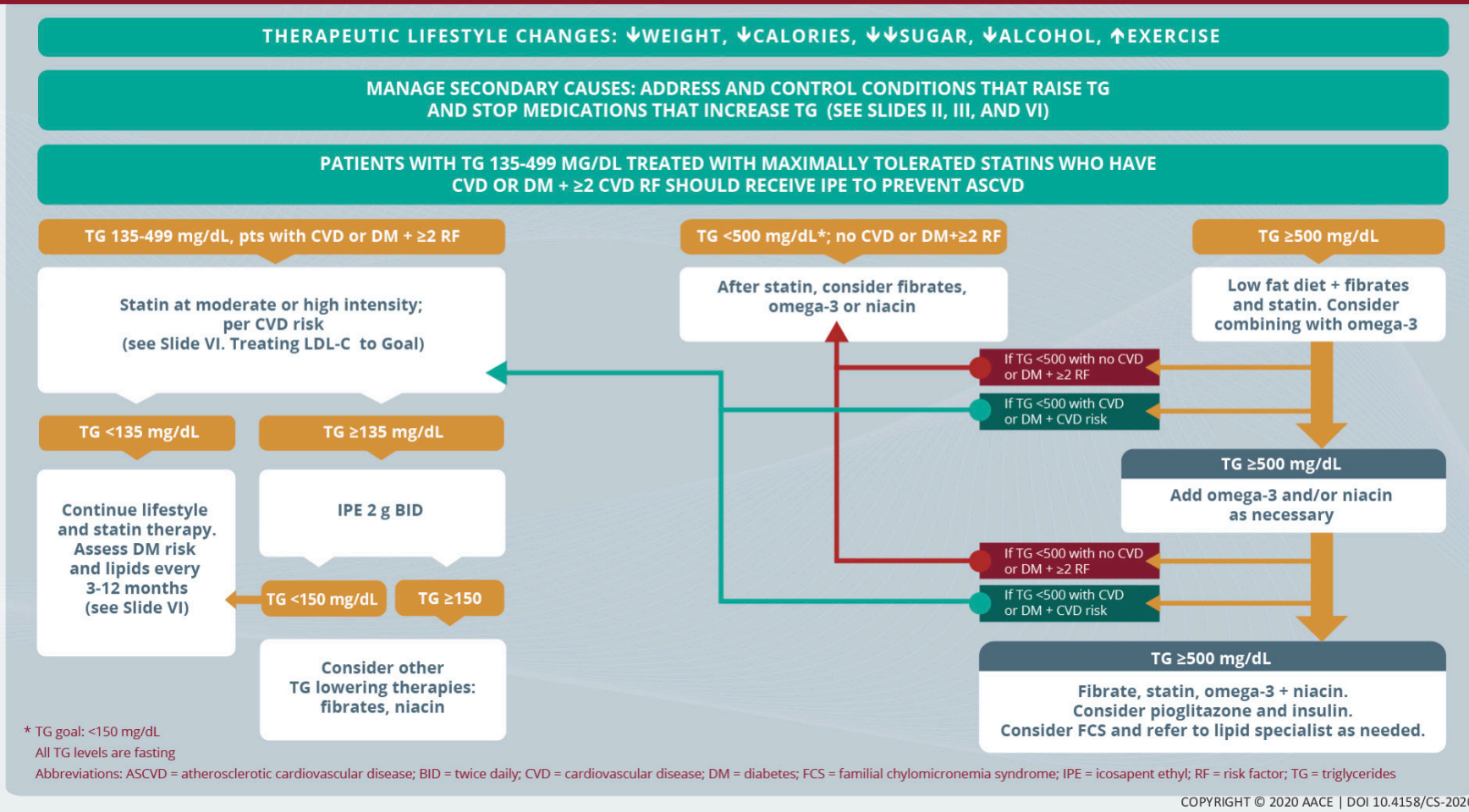
VII. Managing Statin Intolerance and Safety

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.

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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