

## Clinical Practice Guideline

# Lipid Management in Patients with Endocrine Disorders: An Endocrine Society Clinical Practice Guideline

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**Abbreviations:** AACE, American Association of Clinical Endocrinologists; ACC, American College of Cardiology; ADA, American Diabetes Association; AHA, American Heart Association; ALT, alanine aminotransferase; AMP, adenosine monophosphate; AMPK, AMP-activated protein kinase; apo, apolipoprotein; apoA, apolipoprotein A; apoB, apolipoprotein B; apoE, apolipoprotein E; AST, aspartate aminotransferase; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CAC, coronary artery calcium; CAD, coronary artery disease; CETP, cholesteryl ester transfer protein; cIMT, carotid intima-media thickness; CHD, coronary heart disease; CK, creatine kinase; CKD, chronic kidney disease; COI, conflicts of interest; CRP, c-reactive protein; CT, computed tomography; CTT, Cholesterol Treatment Trialists; CV, cardiovascular; CVD, cardiovascular disease; CYP3A4, cytochrome P450 3A4; DHA, dosohexanoic acid; DPA, docosapentaenoic acid; EPA, eicosapentaenoic acid; ESRD, end-stage renal disease; FDA, U.S. Food and Drug Administration; FFA, free fatty acid; FH, familial hypercholesterolemia; FSH, follicle-stimulating hormone; GHD, growth hormone deficiency; GI, gastrointestinal; GLP-1, glucagon-like peptide; HbA1c, hemoglobin A1c; HCG, human chorionic gonadotropin; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; HR, hazards ratio; IGF-1, insulin-like growth factor 1; LT3, L-triiodothyronine; LT4, levothyroxine; LCAT, lecithin cholesterol acyltransferase; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; LH, luteinizing hormone; Lp(a), lipoprotein(a); LPL, lipoprotein lipase; MACE, major adverse cardiac event; MetS, metabolic syndrome; MI, myocardial infarction; NLA, National Lipid Association; NRI, net reclassification index; OCP, oral contraceptive; PCOS, polycystic ovary syndrome; PCSK9, proprotein convertase subtilisin/kexin type 9; RCT, randomized-controlled trial; RR, relative risk; RRR, relative risk reduction; RYGB, Roux-en-Y gastric bypass; SBGH, sex hormone-binding globulin; SCH, subclinical hypothyroidism; SCORE, Systemic Coronary Risk Evaluation; SG, sleeve gastrectomy; SGLT2, sodium-glucose co-transporter 2; T1D, type 1 diabetes; T2D, type 2 diabetes; TG, triglycerides; TSH, thyroid-stimulating hormone; ULN, upper limits of normal; VLDL, very low-density lipoprotein.

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## Abstract

**Objective:** This guideline will provide the practicing endocrinologist with an approach to the assessment and treatment of dyslipidemia in patients with endocrine diseases, with the objective of preventing cardiovascular (CV) events and triglyceride-induced pancreatitis. The guideline reviews data on dyslipidemia and atherosclerotic cardiovascular disease (ASCVD) risk in patients with endocrine disorders and discusses the evidence for the correction of dyslipidemia by treatment of the endocrine disease. The guideline also addresses whether treatment of the endocrine disease reduces ASCVD risk.

**Conclusion:** This guideline focuses on lipid and lipoprotein abnormalities associated with endocrine diseases, including diabetes mellitus, and whether treatment of the endocrine disorder improves not only the lipid abnormalities, but also CV outcomes. Based on the available evidence, recommendations are made for the assessment and management of dyslipidemia in patients with endocrine diseases.

**Freeform/Key Words:** endocrine diseases, lipids, triglycerides, cardiovascular disease, dyslipidemia, diabetes

## List of Recommendations

### 1. Screening and cardiovascular disease risk assessment

#### Measurement of lipids

- 1.1 In adults with endocrine disorders, we recommend a lipid panel for the assessment of triglyceride levels and for calculating low-density lipoprotein cholesterol. (1⊕⊕⊕O)

#### Technical Remarks:

- Non-fasting lipid panels are acceptable for initial screening.
- If triglyceride levels are elevated or if genetic dyslipidemia is suspected, repeat a fasting lipid panel.
- If lipoprotein(a) levels are measured, fasting or nonfasting samples can be obtained.

#### Cardiovascular risk assessment

- 1.2 In adults with endocrine disorders, we recommend conducting a cardiovascular risk assessment by evaluating traditional risk factors, including the calculation of 10-year atherosclerotic cardiovascular disease risk using a tool such as the Pooled Cohort Equations. (1⊕⊕⊕O)
- 1.3 In adults with endocrine disorders at borderline or intermediate risk (10-year atherosclerotic

cardiovascular disease risk 5%–19.9%), particularly those with additional risk-enhancing factors, in whom the decision about statin treatment and/or other preventive interventions is uncertain, we suggest measuring coronary artery calcium to inform shared decision making. (2⊕⊕⊕O)

#### Technical Remarks:

- Borderline and intermediate cardiovascular risk are defined as 5%–7.4% and 7.5%–19.9% 10-year atherosclerotic cardiovascular disease risk using the Pooled Cohort Equations.
- Risk-enhancing factors are additional features, including diseases, that enhance the risk of atherosclerotic cardiovascular disease beyond the risk associated with major risk factors and/or the calculated 10-year risk of atherosclerotic cardiovascular disease.
- In patients with additional risk-enhancing factors, including elevated lipoprotein(a), as described below, risk assessment should consider traditional 10-year atherosclerotic cardiovascular disease risk assessment and the presence of risk-enhancing factors. The coronary artery calcium score should be considered when risk assessment and treatment decisions remain uncertain.
- At present, we suggest measuring coronary artery calcium as the preferred tool for assessment of subclinical atherosclerosis. Other techniques to assess atherosclerotic burden are being developed.
- Coronary artery calcium = 0 marks very low risk of atherosclerotic cardiovascular disease. In patients with baseline coronary artery calcium = 0, evidence suggests

that it is reasonable to repeat a coronary artery calcium scan after 5 to 7 years in low-risk patients, 3 to 5 years in borderline-to-intermediate risk patients, and in 3 years for high-risk patients or those with diabetes.

- In patients without diabetes or atherosclerotic cardiovascular disease and with low-density lipoprotein >70 mg/dL (1.8 mmol/L), and 10-year atherosclerotic cardiovascular disease risk >7.5%, or 10-year atherosclerotic cardiovascular disease risk of 5% to 7.4% plus 1 or more risk-enhancing factors, or coronary artery calcium score over the 75<sup>th</sup> percentile for age, sex, and race, or coronary artery calcium score >100, the initiation of a statin, as adjunct to diet and exercise, is advised after a discussion of the risks/benefits with the patient.

- 1.4 In adult patients with a family history of premature atherosclerotic cardiovascular disease, or a personal history of atherosclerotic cardiovascular disease or a family history of high lipoprotein(a), we suggest measuring lipoprotein(a) to inform decision-making about short-term and lifetime atherosclerotic cardiovascular disease risk and the need to intensify low-density lipoprotein cholesterol-lowering therapy. (2⊕⊕OO)

**Technical Remarks:**

- Lipoprotein(a) ≥50 mg/dL (125 nmol/L) enhances the risk of atherosclerotic cardiovascular disease.
- Lipoprotein(a) testing does not need to be repeated if it has previously been measured (ie, in childhood or early adulthood).
- It is not yet known whether reducing lipoprotein(a) reduces atherosclerotic cardiovascular disease risk.

## 2. Hypertriglyceridemia

- 2.1 In adults with fasting triglyceride levels over 500 mg/dL (5.6 mmol/L), we recommend pharmacologic treatment as adjunct to diet and exercise to prevent pancreatitis. (1⊕OOO)

**Technical Remark:**

- Patients with triglyceride levels over 1000 mg/dL (11.3 mmol/L) often do not get an adequate response to medications and, therefore, control of diabetes, modification of diet, and weight loss are essential.

- 2.2 In patients with triglyceride-induced pancreatitis, we suggest against the use of acute plasmapheresis

as a first-line therapy to reduce triglyceride levels. (2⊕OOO)

**Technical Remark:**

- Plasmapheresis may be useful in those who do not respond to conventional methods of lowering triglycerides, such as individuals who have extraordinarily elevated triglyceride levels (eg, over 10 000 mg/dL [112.9 mmol/L]) or in extremely high-risk situations, such as pregnancy.

- 2.3 In patients without diabetes and who have triglyceride-induced pancreatitis, we suggest against the routine use of insulin infusion. (2⊕OOO)

**Technical Remark:**

- When uncontrolled diabetes is present, insulin therapy should be used to normalize glucose levels.

- 2.4 In adults who are on statins and still have moderately elevated triglyceride levels >150 mg/dL (1.7 mmol/L), and who have either atherosclerotic cardiovascular disease or diabetes plus 2 additional risk factors, we suggest adding eicosapentaenoic acid ethyl ester to reduce the risk of cardiovascular disease. (2⊕⊕⊕O)

**Technical Remarks:**

- Risk factors include traditional risk factors and risk-enhancing factors.
- The dose of eicosapentaenoic acid ethyl ester is 4 g/day.
- If eicosapentaenoic acid ethyl ester is not available or accessible, then it is reasonable to consider a fibrate.

- 2.5 In patients with elevated triglycerides (>150 mg/dL to 499 mg/dL [1.7 mmol/L to 5.6 mmol/L]), we suggest checking triglycerides before and after starting a bile acid sequestrant. (2⊕OOO)

**Technical Remark:**

- Bile acid sequestrants are contraindicated when triglycerides are above 500 mg/dL (5.6 mmol/L).

## 3. Type 2 diabetes mellitus

- 3.1 In adults with type 2 diabetes and other cardiovascular risk factors, we recommend

statin therapy in addition to lifestyle modification in order to reduce cardiovascular risk. (1⊕⊕⊕⊕)

**Technical Remarks:**

- High-intensity statins should be chosen in patients with atherosclerotic cardiovascular disease, or those with risk factors for atherosclerotic cardiovascular disease or risk-enhancing factors.
- Statins should not be used in women who are pregnant or trying to become pregnant.
- In patients over the age of 75, continuation of statin treatment or initiation of statin treatment depends upon atherosclerotic cardiovascular disease risk, prognosis, potential interacting medications, polypharmacy, mental health, and the wishes of the patient.

3.2 In adults with type 2 diabetes and other cardiovascular risk factors, we suggest lowering low-density lipoprotein cholesterol to achieve a goal of low-density lipoprotein cholesterol <70 mg/dL (1.8 mmol/L) in order to reduce cardiovascular risk. (2⊕○○○)

**Technical Remarks:**

- A statin should be added to lifestyle modifications if low-density lipoprotein cholesterol is >70 mg/dL (1.8 mmol/L).
- Low-density lipoprotein cholesterol should be <55 mg/dL (1.4 mmol/L) in patients with established cardiovascular disease or multiple risk factors.
- Additional low-density lipoprotein-lowering therapy (ezetimibe, proprotein convertase subtilisin/kexin type 9 inhibitor) may be needed if the low-density lipoprotein cholesterol goal is not reached with statins.
- Risk factors include traditional risk factors and risk-enhancing factors.

3.3 In adults with type 2 diabetes on a statin at low-density lipoprotein goal with residual triglycerides over 150 mg/dL (1.7 mmol/L) and with two additional traditional risk factors or risk-enhancing factors, we suggest adding eicosapentaenoic acid ethyl ester to reduce cardiovascular risk. (2⊕⊕⊕○)

**Technical Remarks:**

- Consider 4 g/day of eicosapentaenoic acid ethyl ester.
- If eicosapentaenoic acid ethyl ester is not available or accessible, then it is reasonable to consider a fibrate such as fenofibrate.

3.4 In adults with type 2 diabetes with chronic kidney disease stages 1–4 and postrenal transplant, we suggest statin therapy, irrespective of the cardiovascular risk score, to reduce cardiovascular risk. (2⊕○○○)

**Technical Remarks:**

- When selecting the statin, consider the renal clearance of the statin. Pitavastatin, pravastatin, and rosuvastatin all have at least partial clearance through the kidney, whereas atorvastatin, fluvastatin, lovastatin, and simvastatin are cleared via the liver.
- All statins require dose adjustments in chronic kidney disease, except for atorvastatin and fluvastatin.

3.5 In adults with type 2 diabetes and diabetic retinopathy, we suggest fibrates in addition to statins to reduce retinopathy progression. (2⊕○○○)

**Technical Remarks:**

- This recommendation applies regardless of triglyceride levels.
- The preferred fibrate is fenofibrate.

#### 4. Type 1 diabetes mellitus

4.1 In adults with type 1 diabetes, age 40 years and older and/or with duration of diabetes >20 years, and/or microvascular complications, we suggest statin therapy, irrespective of the cardiovascular risk score, to reduce cardiovascular risk. (2⊕○○○)

**Technical Remarks:**

- Low-density lipoprotein should be the primary target for lipid-lowering therapy.
- Consider therapy if low-density lipoprotein is over 70 mg/dl (1.8 mmol/L).
- Statins should not be used in women who are pregnant or trying to become pregnant.

4.2 In adults with type 1 diabetes with chronic kidney disease in stages 1–4, we suggest statin therapy, irrespective of the cardiovascular risk score, to reduce cardiovascular risk. (2⊕○○○)

**Technical Remarks:**

- Low-density lipoprotein should be the primary target for lipid-lowering therapy.

- Consider therapy if low-density lipoprotein is over 70 mg/dL (1.8 mmol/L).
- When selecting the statin, consider the renal clearance of the statin: pitavastatin, pravastatin, and rosuvastatin all have at least partial clearance through the kidney, whereas atorvastatin, fluvastatin, lovastatin, and simvastatin are cleared via the liver.
- All statins require dose adjustments in chronic kidney disease except for atorvastatin and fluvastatin.
- Ezetimibe can be added to the statin if required to lower low-density lipoprotein cholesterol further. No dose adjustments of ezetimibe are needed in chronic kidney disease.

4.3 In adults with type 1 diabetes with obesity, or with high triglycerides and low high-density lipoprotein cholesterol, we suggest statin therapy, irrespective of the cardiovascular risk score, to reduce cardiovascular risk. (2⊕○○○)

**Technical Remarks:**

- Low-density lipoprotein should be the primary target for lipid-lowering therapy.
- Consider therapy if low-density lipoprotein cholesterol is over 70 mg/dL (1.8 mmol/L).

4.4 In adults with type 1 diabetes and diabetic retinopathy, we suggest statin therapy, irrespective of the cardiovascular risk score, to reduce cardiovascular risk. (2⊕○○○)

**Technical Remarks:**

- Low-density lipoprotein should be the primary target.
- Consider therapy if low-density lipoprotein cholesterol is over 70 mg/dL (1.8 mmol/L).

## 5. Obesity

5.1 In individuals who have obesity, we advise assessment of components of the metabolic syndrome and body fat distribution to accurately determine the level of cardiovascular disease risk. (Ungraded Good Practice Statement)

**Technical Remarks:**

- Diagnosis of MetS requires the presence of *three* of the following criteria:
- Elevated triglycerides  $\geq 150$  mg/dL (1.7 mmol/L) or on triglyceride-lowering medication.
- Reduced high-density lipoprotein cholesterol  $< 50$  mg/dL (1.3 mmol/L) in women and  $< 40$  mg/dL (1.0 mmol/L) in men.

- Systolic blood pressure  $\geq 130$  mm Hg or diastolic blood pressure  $\geq 85$  mm Hg or on blood pressure medication.
- Elevated waist circumference (men  $\geq 40$  in [102 cm] and women  $\geq 35$  in [88 cm]), except for East and South Asian men ( $\geq 35$  in [90 cm]) and women ( $\geq 31.5$  in [80 cm]).
- Hyperglycemia (but not yet with type 2 diabetes) is defined by cutoffs for prediabetes according to fasting blood glucose, oral glucose tolerance, and/or hemoglobin A1c.
- Body fat distribution can be assessed in clinical practice by measuring the waist size or the waist/hip ratio.
- Waist size measurement in people with a body mass index greater than  $35 \text{ kg/m}^2$  has potential limitations.

5.2 In individuals who have obesity, we suggest lifestyle measures as the first-line treatment to reduce plasma triglycerides to lower cardiovascular and pancreatitis risk. (2⊕○○○)

**Technical Remarks:**

- Reductions in low-density lipoprotein cholesterol and increases in high-density lipoprotein cholesterol are modest compared to the decrease in triglycerides with lifestyle measures that produce weight loss.
- Lifestyle therapy-induced changes in the lipid profile in obesity have not been shown to reduce cardiovascular disease events.

5.3 In individuals who have obesity, we recommend the assessment of 10-year risk for atherosclerotic cardiovascular disease to guide the use of lipid-lowering therapy. (1⊕⊕⊕○)

**Technical Remarks:**

- Calculation of 10-year risk for atherosclerotic cardiovascular disease may be done using Pooled Cohort Equations.
- Elevated low-density lipoprotein cholesterol is predictive of cardiovascular risk.

5.4 In individuals who have obesity and are on pharmacological therapy for weight reduction, we suggest the reassessment of the lipid profile to evaluate the risk of cardiovascular disease and pancreatitis. (2⊕○○○)

**Technical Remark:**

- As there are no data on the timing of lipid measurements after weight loss, we suggest the reassessment of lipids after 5% weight loss and periodically thereafter and when the weight is stable.



5.5 In individuals with obesity, (body mass index >40 or >35 kg/m<sup>2</sup> with comorbidities) who undergo bariatric surgery, we suggest the measurement of the lipid profile after bariatric surgery to assess cardiovascular risk. (2⊕○○○)

**Technical Remarks:**

- Malabsorptive bariatric surgery procedures (eg, Roux-en-Y gastric bypass) are more effective than restrictive procedures (eg, banding, sleeve gastrectomy) in decreasing low-density lipoprotein cholesterol levels.
- Both restrictive and malabsorptive procedures decrease triglycerides.
- Reassess the lipid profile 1 to 3 months after bariatric surgery and periodically thereafter and when the weight is stable.

## 6. Thyroid disease

6.1 In patients with hyperlipidemia, we recommend ruling out hypothyroidism as the cause of the hyperlipidemia before treatment with lipid-lowering medications. (1⊕⊕⊕⊕)

**Technical Remark:**

- Hypothyroidism can elevate both cholesterol and triglyceride levels, which improve with treatment.

6.2 In patients with hyperthyroidism, we recommend re-evaluating the lipid panel after the patient becomes euthyroid. (1⊕⊕⊕⊕)

**Technical Remark:**

- Changes in low-density lipoprotein cholesterol have been observed as early as 3 months after the patient is euthyroid.

6.3 In patients with overt hypothyroidism, we suggest against treating hyperlipidemia until the patient becomes euthyroid in order to more accurately assess the lipid profile. (2⊕○○○)

6.4 In patients with subclinical hypothyroidism (thyroid-stimulating hormone <10 mIU/L) with associated hyperlipidemia, we suggest considering thyroxine treatment as a means of reducing low-density lipoprotein levels. (2⊕○○○)

**Technical Remark:**

- Take into consideration the patient's age and general health, the possibility of suppression of thyroid-stimulating hormone, and whether the patient has cardiovascular disease.

## 7. Excess glucocorticoids

7.1 In adult patients with Cushing syndrome, we recommend monitoring the lipid profile in order to identify cases of dyslipidemia. (1⊕⊕○○)

**Technical Remark:**

- Monitor lipid profile at the time of diagnosis and periodically afterwards at the discretion of the treating physician.

### Lipid-lowering therapy in Cushing syndrome

7.2 In adults with persistent endogenous Cushing syndrome, we suggest statin therapy, as adjunct to lifestyle modification, to reduce cardiovascular risk, irrespective of the cardiovascular risk score. (2⊕○○○)

**Technical Remarks:**

- Low-density lipoprotein cholesterol should be the primary target, and therapy should be considered if low-density lipoprotein cholesterol is over 70 mg/dL (1.8 mmol/L).
- Patients receiving mitotane therapy for Cushing syndrome commonly develop secondary dyslipidemia from therapy.
- Lipid-lowering therapy may not be appropriate for patients with limited life expectancy, such as those with an underlying malignancy.

7.3 In adults with cured Cushing syndrome, we advise the approach to cardiovascular risk assessment and treatment be the same as in the general population. (Ungraded Good Practice Statement)

### Lipid management in chronic glucocorticoid therapy

7.4 In adults receiving chronic glucocorticoid therapy above replacement levels, we suggest assessment and treatment of lipids and other cardiovascular risk factors because of the increased risk of cardiovascular disease. (2⊕○○○)

**Technical Remark:**

- Effects of glucocorticoid therapy on lipids and cardiovascular risk will vary based on the dose of glucocorticoid, duration of treatment, and underlying disease/indication.

**8. Disorders of growth hormone secretion****Adult growth hormone deficiency**

- 8.1 In adults with growth hormone deficiency, we recommend obtaining a lipid profile at diagnosis to assess for dyslipidemia. (1⊕⊕⊕O)
- 8.2 In adults with growth hormone deficiency associated with hypopituitarism, we suggest assessment and treatment of lipids and other cardiovascular risk factors. (2⊕OOO)

**Technical Remarks:**

- Low-density lipoprotein cholesterol should be the primary target.
  - Consider therapy if low-density lipoprotein cholesterol is over 70 mg/dL (1.8 mmol/L).
- 8.3 In adult patients with growth hormone deficiency, we recommend against using growth hormone replacement solely to lower low-density lipoprotein cholesterol to reduce cardiovascular risk. (1⊕⊕⊕O)

**Growth hormone excess (acromegaly)**

- 8.4 In adults with acromegaly, we suggest measurement of the usual lipid profile before and after treatment of growth hormone excess. (2⊕OOO)

**9. Polycystic ovary syndrome****Lipid abnormalities**

- 9.1 In women with polycystic ovary syndrome, we recommend obtaining a fasting screening lipid panel at diagnosis to assess cardiovascular risk. (1⊕⊕⊕O)

**Technical Remarks:**

- Polycystic ovary syndrome is associated with cardiovascular risk factors.
- Conduct lipid screening both before and intermittently during hormonal therapy.
- In polycystic ovary syndrome, hypertriglyceridemia is the most common lipid abnormality.

**Cardiovascular risk: effect of treatment of polycystic ovary syndrome on lipids**

- 9.2 In women with polycystic ovary syndrome, we suggest against using lipid-lowering therapies to treat hyperandrogenism or infertility. (2⊕OOO)

**10. Menopause and hormonal replacement**

- 10.1 In postmenopausal women, we recommend treating dyslipidemia with statin therapy, rather than hormone therapy. (1⊕⊕OO)

**Technical Remarks:**

- Hormone therapy increases the risk of cardiovascular disease, specifically venous thromboembolism and stroke. However, the absolute risk of cardiovascular disease is lower in younger compared to older postmenopausal women.
- Hormone therapy is described as estrogen ± progesterone/a progestin.

- 10.2 In postmenopausal women on hormone therapy and with other risk factors for cardiovascular disease, we recommend statin therapy to reduce cardiovascular risk. (1⊕⊕⊕⊕)

**Technical Remarks:**

- Hormone therapy increases the risk of cardiovascular disease, specifically venous thromboembolism and stroke. However, the absolute risk of cardiovascular disease is lower in younger compared to older postmenopausal women.
- Hormone therapy is described as estrogen ± progesterone/a progestin.
- Menopause may be associated with an increase in low-density lipoprotein cholesterol and a decrease in high-density lipoprotein cholesterol.
- Risk factors may be traditional risk factors or risk-enhancing factors.

- 10.3 In women who enter menopause early (<40 to 45 years old), we recommend assessment and treatment of lipids and other cardiovascular risk factors. (1⊕⊕⊕O)

**Technical Remarks:**

- Early menopause enhances cardiovascular disease risk.
- Atherosclerotic cardiovascular disease risk should be calculated and followed after menopause.

## 11. Hypogonadism and testosterone replacement and abuse

11.1 In patients with low testosterone levels, we suggest testosterone therapy as symptomatically indicated, and not as an approach to improve dyslipidemia or cardiovascular disease risk. (2⊕⊕OO)

11.2 In patients with low high-density lipoprotein (<30 mg/dL [0.8 mmol/L]), especially in the absence of hypertriglyceridemia, we advise clinical or biochemical investigation of anabolic steroid abuse. (Ungraded Good Practice Statement)

### Technical Remark:

- Supraphysiological doses of androgens will reduce high-density lipoprotein cholesterol levels.

## 12. Gender-affirming hormone therapy

12.1 In transwomen and transmen who have taken or are taking gender-affirming hormone therapy, we advise assessing cardiovascular risk by guidelines for nontransgender adults. (Ungraded Good Practice Statement)

### Technical Remark:

- There are no data to guide the selection of a gender marker in risk calculators for individuals on gender-affirming hormone therapy.

## Introduction

Hormones modulate every pathway involved in lipoprotein metabolism. This includes expression of lipoprotein receptors, production of apolipoproteins (apos), the activity of plasma lipoprotein-modifying enzymes, and the circulating levels of substrates such as fatty acids and glucose used for triglyceride (TG) synthesis. Therefore, it is anticipated that endocrine diseases might alter the lipid profile and enhance atherosclerotic cardiovascular disease (ASCVD) risk. However, with the exception of type 2 diabetes (T2D), many endocrine diseases are not mentioned, or not described in detail, in cholesterol management guidelines. The present guideline addresses this gap in information. The primary objectives are as follows:

- Describe lipid abnormalities and cardiovascular disease (CVD) risk in endocrine diseases.
- Assess whether treatment of the underlying endocrine disorder improves the lipid profile and/or lowers ASCVD risk.

- Assess the evidence for using lipid-lowering medications, as adjunct to diet and physical activity, in patients with these endocrine diseases.

Based upon the available evidence, recommendations are made for direct lipid treatment and endocrine disease treatment to manage dyslipidemia in endocrine diseases. The first part of the guideline addresses lipid measurement and ASCVD risk assessment. The second section addresses hypertriglyceridemia, dyslipidemia in type 1 diabetes (T1D) and T2D, obesity, thyroid disease, excess glucocorticoids, growth hormone deficiency (GHD) and excess, polycystic ovary syndrome (PCOS), menopause and hormonal replacement of menopause, testosterone replacement in hypogonadism, testosterone abuse, and gender-affirming hormone therapy. The last section of the guideline discusses implementation, including lifestyle therapy, and the efficacy and safety of lipid-lowering medications. In addition, this section provides a patient perspective on statin use. A summary of lipid metabolism and a discussion of other cholesterol management guidelines are provided in 2 appendices (see Appendix B and Appendix C, respectively).

## Commissioned Systematic Review

The Endocrine Society Writing Committee commissioned 2 systematic reviews, which were conducted by the Mayo Clinic Evidence-based Practice Center to support recommendations on the management of hyperlipidemia in patients with endocrine disorders.

The Writing Committee requested a first systematic review to investigate the impact of therapy for overt and subclinical hypo- and hyperthyroidism on serum lipids. The review summarized evidence from heterogeneous studies and suggested that treatment of overt but not subclinical hyperthyroidism was associated with worsening of lipid profile. Levothyroxine (LT4) therapy in both overt and subclinical hypothyroidism (SCH) led to improvement in the lipid profile, including lipoproteins, with the magnitude of improvement being larger for overt hypothyroidism (1).

The second systematic review requested by the Writing Committee was to estimate the magnitude of change in lipid parameters associated with weight loss in adults. This review summarized data from multiple randomized trials and presented the change of lipid parameters associated either with losing 1 kg or 1 unit of body mass index (BMI) by means of lifestyle interventions, pharmacologic interventions, and bariatric surgery, at 6 and 12 months. Another finding from the systematic review was that low-carbohydrate diets resulted in reductions in TG and



increases in high-density lipoprotein cholesterol (HDL-C), whereas low-fat diets resulted in reductions across the lipid panel, including high-density lipoprotein (HDL). Results for surgery were consistent across malabsorptive and restrictive surgery (2).

The Writing Committee suggested that data from these 2 systematic reviews can support shared decision-making and help with recommending treatment for hyperlipidemia.

## 1. Screening and cardiovascular disease risk assessment

### Measurement of lipids

- 1.1 In adults with endocrine disorders, we recommend a lipid panel for the assessment of TG levels and for calculating low-density lipoprotein cholesterol (LDL-C). (1⊕⊕⊕O)

#### Technical Remarks:

- Nonfasting lipid panels are acceptable for initial screening.
- If TG levels are elevated or if genetic dyslipidemia is suspected, repeat a fasting lipid panel.
- If lipoprotein(a) [Lp(a)] levels are measured, fasting or nonfasting samples can be obtained.

#### Evidence and discussion

In adults, the long-standing standard clinical approach for lipid assessment uses blood obtained after an 8- to 10-hour fast overnight, allowing only water and noncaffeinated beverages. The lipid panel consists of plasma or serum concentrations of total cholesterol, TG, HDL-C, and a calculated value of LDL-C. Table 1 shows typical changes in lipid and lipoprotein levels, including Lp(a) in the endocrine and metabolic disorders discussed in this guideline. HDL-C, and TG have normal ranges based upon population distribution. LDL-C does not have a normal range because “optimal” LDL-C concentrations vary according to the degree of ASCVD risk of the individual.

The initial classification of hyperlipidemia proposed by Fredrickson in 1967 introduced a system for identifying lipoprotein disorders and arbitrarily required 12 to 16 hours of fasting (3, 4). The Friedewald formula, subsequently introduced in the 1970s, has been widely used to estimate LDL-C by subtracting the sum of HDL-C and very low-density lipoprotein (VLDL) cholesterol (estimated by TG/5) from total cholesterol, and used fasting data (5). This equation uses a fixed ratio of 5:1 between TG and

VLDL cholesterol. With the development of standardized, automated, high throughput enzymatic analyses in the 1980s, rapid measurement of serum cholesterol and TG has been possible. The Friedewald formula is generally considered accurate within serum TG levels under 150 mg/dL (1.7 mmol/L) and LDL-C levels of at least 70 mg/dL (1.8 mmol/L) (6). In people with high TG, estimated low LDL-C, diabetes, or obesity, apolipoprotein B (apoB) or non-HDL-C may be useful for assessment of ASCVD risk.

Since it has become evident that the Friedewald formula underestimates LDL-C as serum TG levels increase above 150 mg/dL (1.7 mmol/L) or with LDL-C levels under 70 mg/dL (1.8 mmol/L), new and more accurate approaches to estimate LDL-C have been developed. The Martin-Hopkins formula is gaining wider use for calculation of LDL-C and uses an adjustable correction factor based on TG and non-HDL-C levels. It appears to have greater accuracy in both fasting and nonfasting samples as well as in settings of low LDL-C and high TG (7, 8). The Martin-Hopkins equation reduces the need for routine, direct measurement of LDL-C and is gaining wider use. Recently, in 2020, a new equation developed from the NIH proposes LDL-C estimation that can be used in patients with TG up to 800 mg/dL (9.0 mmol/L) (9).

#### Fasting versus nonfasting lipid testing

In the past decade, there has been a push toward nonfasting measurements of lipids because of convenience and practicality. Nonfasting blood samples simplify the process for patients, laboratories, and clinicians and are likely to improve patient follow-through with lipid testing. There is some evidence that nonfasting lipid panels may improve cardiovascular (CV) risk prediction (10–12). A meta-analysis of 68 prospective studies in over 300 000 individuals, from the Emerging Risk Factors Consortium (13) suggests that lipid assessment in vascular disease can be simplified by measurement of either total cholesterol, HDL-C, or apos from nonfasting samples without regard to TG. In the 20 studies that used nonfasting blood samples, the strength of the association between plasma lipid concentrations and incident CV events was preserved. Nonfasting non-HDL-C and nonfasting calculated LDL-C were superior to fasting measurements for predicting CV risk ( $n = 103\ 354$ ; number of events 3829). A nonfasting TG level of 175mg/dL (2.0 mmol/L) has been suggested as a cutoff point to identify CV risk (14). However, a pooled study of 2 large cohorts showed an increase in CV risk even in the 89–176 mg/dL (1.0–2.0 mmol/L) range for nonfasting TG (15). Further, almost all clinical trials with lipid-lowering drugs have used fasting lipid samples. Limited data suggests that for the same individual, fasting and nonfasting lipid levels are similarly associated with CV

**Table 1.** Lipids and lipoproteins in select endocrine disorders

Disease	LDL-C	HDL-C	TG	Lp(a)
Type 2 diabetes	No change or ↑	Normal or ↓	↑	–
Type 1 diabetes	No change or ↑	Normal or ↓	↑	–
Obesity	No change or ↑	↓	↑	–
Hypothyroidism	No change or ↑	Normal or ↑	Normal or ↑	Normal or ↑
Subclinical hypothyroidism	No change or ↑	Normal or ↓	Normal	Normal
Hyperthyroidism	↓	Normal or ↓	Normal or ↑	↓
Cushing's syndrome/disease	No change or ↑	Normal or ↓	↑	Normal or ↑
Chronic glucocorticoid therapy	No change or ↑	Normal or ↑	Normal or ↑	–
Adult growth hormone deficiency	↑	Normal or ↓	Normal or ↑	Normal
Acromegaly	No change or ↑	Normal or ↓	↑	↑
Polycystic ovary syndrome	No change or ↑	↓	↑	↑
Menopause vs premenopause	↑	Normal or ↓	Normal	Normal or ↑
Oral HRT for menopause	↓	↑	↑	↓
Male hypogonadism	↑	Normal or ↓	↑	Normal or ↑
Testosterone replacement for male hypogonadism	No change or ↓	Normal or ↓	Normal or ↓	↓
Anabolic steroid abuse	↑	↓	Normal or ↑	↓
Gender affirming hormone therapy: transmen	↑	↓	↑	–
Gender affirming hormone therapy: transwomen	–	–	↑	–

Abbreviations: CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; HRT, hormone replacement therapy; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a), TG, triglycerides.

The normal range for HDL-C is  $\geq 40$  mg/dL (1.0 mmol/L) in men and  $\geq 50$  mg/dL (1.3 mmol/L) in women. The normal range for TG is 0–150 mg/dL (0–1.7 mmol/L). Lp(a)  $\geq 50$  mg/dL (125 mmol/L) is considered a CVD risk-enhancing factor. Evidence is limited on the effects of transgender hormone therapy on lipids.

↓, decreased; ↑, increased; Normal, indicates within the normal range; –, data insufficient.

events (16); however, no randomized outcomes trials have been conducted using nonfasting TG as a key biomarker.

### Cardiovascular risk assessment

1.2 In adults with endocrine disorders, we recommend conducting CV risk assessment by evaluating traditional risk factors, including calculation of 10-year ASCVD risk using a tool such as the Pooled Cohort Equations. (1⊕⊕⊕⊕)

1.3 In adults with endocrine disorders at borderline or intermediate risk (10-year ASCVD risk 5–19.9%), particularly those with additional risk-enhancing factors, in whom the decision about statin treatment and/or other preventive interventions is uncertain, we suggest measuring coronary artery calcium (CAC) to inform shared decision-making. (2⊕⊕⊕⊕)

#### Technical Remarks:

- Borderline and intermediate CV risk are defined as 5% to 7.4% and 7.5% to 19.9% 10-year ASCVD risk using the Pooled Cohort Equations.
- Risk-enhancing factors are additional features, including diseases, that enhance the risk of ASCVD beyond the risk

associated with major risk factors and/or the calculated 10-year risk of ASCVD.

- In patients with additional risk-enhancing factors, including elevated Lp(a), as described below, risk assessment should consider traditional 10-year ASCVD risk assessment and the presence of risk-enhancing factors. The CAC score should be considered when risk assessment and treatment decisions remain uncertain.
- At present, we suggest measuring CAC as the preferred tool for assessment of subclinical atherosclerosis. Other techniques to assess atherosclerotic burden are being developed.
- CAC = 0 marks very low risk of ASCVD. In patients with baseline CAC = 0, evidence suggests that it is reasonable to repeat a CAC scan after 5 to 7 years in low-risk patients, 3 to 5 years in borderline-to-intermediate risk patients, and in 3 years for high-risk patients or those with diabetes.
- In patients without diabetes or ASCVD and with LDL-C  $> 70$  mg/dL (1.8 mmol/L) and 10-year ASCVD risk  $> 7.5\%$ , or 10 year ASCVD risk 5% to 7.4% plus 1 or more risk-enhancing factors, or CAC score over the 75<sup>th</sup> percentile for age, sex, and race, or CAC score  $> 100$ , the initiation of a statin, as adjunct to diet and exercise, is advised after a discussion of the risks/benefits with the patient.

- 1.4 In adult patients with a family history of premature ASCVD, or a personal history of ASCVD or family history of high Lp(a), we suggest measuring Lp(a) to inform decision-making about short-term and lifetime ASCVD risk and the need to intensify LDL-C-lowering therapy. (2⊕⊕OO)

#### Technical Remarks:

- Lp(a)  $\geq$ 50 mg/dL (125 nmol/L) enhances risk of ASCVD.
- Lp(a) testing does not need to be repeated if it has previously been measured (ie, in childhood or early adulthood).
- It is not yet known whether reducing Lp(a) reduces ASCVD.

#### Evidence and discussion

Clinical risk assessment is critical for matching the intensity of treatment to the degree of absolute CV risk. There is a rich amount of literature on advanced risk assessment in CV medicine (17). Previously, studies assessed whether a single new marker might “add” to traditional risk factors for risk stratification; new studies increasingly compare multiple markers to each other and assess advanced metrics such as area under the receiver operating curve and net reclassification index (NRI) (18). Through this process, a hierarchy has emerged of tests that add the most to global risk discrimination and those that add the least. Current expert consensus in the field is summarized below.

The first step in risk prediction is the calculation of 10-year risk using a clinical risk tool, which in the United States should be the American College of Cardiology (ACC)/American Heart Association (AHA) Pooled Cohort Equations (<http://static.heart.org/riskcalc/app/index.html#!/baseline-risk>), derived from the following cohorts: Framingham Heart and Framingham Offspring, Coronary

Artery Risk Development in Young Adults (CARDIA), Atherosclerosis Risk in Community (ARIC), and the Cardiovascular Health Study (CHS) (19, 20). This risk algorithm uses traditional risk factors, including age, sex, race, systolic blood pressure, treatment for hypertension, total cholesterol, HDL-C, smoking, and diabetes, for the calculation of 10-year risk of myocardial infarction (MI), stroke, and CV death. Additional risk-enhancing factors include family history of premature coronary artery disease (CAD), metabolic syndrome (MetS), chronic kidney disease (CKD), chronic inflammatory conditions such as rheumatoid arthritis, history of early menopause, or preeclampsia, and high-risk race/ethnicities, including South Asian ancestry. Risk assessment is described in Table 2.

Novel risk assessment tools that can be added to traditional risk assessment and risk-enhancing factors are generally grouped into 4 categories: genetic, lipid, other serum biomarkers, and imaging.

Genetic tests for risk stratification, such as polygenic risk scores (21), may modestly improve risk prediction. However, these are not currently available in clinical practice.

Advanced lipid testing can include direct serum measurement of apoB, fractionation of conventional lipid subclasses (eg, differentiation of small, dense LDL-C from larger, more buoyant particles), direct measurement of lipoprotein particle number, and measurement of Lp(a) (22, 23). Current evidence suggests that some of these tests may be helpful in further characterizing lipid abnormalities, including diagnosis of underlying genetic dyslipidemias. However, multiple expert panels and guidelines have concluded that these tests add little to risk prediction beyond the standard lipid profile (19, 23). In particular, non-HDL-C (total cholesterol – HDL-C), which can be calculated from a standard fasting or nonfasting lipid panel, predicts risk similarly

**Table 2.** Assessment of ASCVD risk in patients with endocrine diseases

#### Suggested Steps in Risk Assessment

- Determine if the patient has established ASCVD or long-standing diabetes. If not, proceed with risk assessment.
- Calculate the 10-year risk using the Pooled Cohort Equations (<http://static.heart.org/riskcalc/app/index.html#!/baseline-risk>)
- Assess for presence of additional risk-enhancing factors.
- The Endocrine Society considers persistent Cushing syndrome and Cushing disease, high-dose chronic glucocorticoid therapy, and possibly adult GHD, acromegaly, and hypothyroidism as risk-enhancing factors.
- In borderline-to-intermediate risk patients (10-year ASCVD risk of 5% to 19.9%), consider a coronary artery calcium score, particularly when risk enhancing factors are present.
- Conduct a clinician–patient risk discussion, including discussion of lifetime risk and lifetime lipid-lowering treatment benefit, along with patient preferences.

to apoB testing or other advanced lipid testing (23, 24). ApoB  $\geq 130$  mg/dL (1.3 g/L) or non-HDL  $>190$  mg/dL (4.9 mmol/L) should be considered risk-enhancing factors.

### Measurement of lipoprotein(a)

Lp(a) is a modified low-density lipoprotein (LDL)-like particle in which apolipoprotein a (apo[a]), a large protein with structural similarity to plasminogen, is covalently bound to apoB. Circulating Lp(a) levels are primarily determined by the apo(a) genotype, without significant dietary or environmental influences (25). Epidemiological studies, Mendelian randomization studies, and genome-wide association studies all show increased CVD risk in individuals with elevated Lp(a) (25–28), but clinical trial data showing CV benefit of lowering Lp(a) are lacking. Inhibitors of Lp(a) production (ie, apo[a] antisense oligonucleotides and siRNA) are currently in development (29). Standardized immunoassays for Lp(a) are now widely available (30). Values are reported as nmol/L or mg/dL; the nmol/L level being roughly 2 to 3 times greater than the mg/dL level. Lp(a) appears to be unaffected by fasting status and can be measured in fasting or nonfasting states.

Lp(a) levels can be very helpful for assessment of familial risk. In cases of early advanced atherosclerosis, Lp(a) testing may also be useful to explain less-than-expected LDL-C reduction with statins, since statins do not lower Lp(a) levels, but when these are elevated, the cholesterol content of Lp(a) contributes significantly to calculated and directly measured LDL-C. However, this test adds little in terms of global risk assessment across the general population and thus does not have characteristics of a good screening test (19, 23). However, some experts believe that every patient should have Lp(a) measured once, perhaps in childhood or early adulthood during routine lipid screening (31). In appropriately selected patients with familial risk, elevated Lp(a)  $\geq 50$  mg/dL or  $\geq 125$  nmol/L should be considered a risk-enhancing factor that may drive more aggressive treatment or the need for advanced risk assessment. Evidence from the Women's Health Study and the Women's Health Initiative suggest that elevated Lp(a) only predicts ASCVD in women with total cholesterol above 220 mg/dL (5.7 mmol/L) (32).

Multiple serum biomarkers have been proposed for advanced risk assessment that test for inflammation, oxidative stress, endothelial dysfunction, thrombosis, and other important pathways (19). In general, although widely available, serum markers suffer from higher intertest variability. At this time, even multiple biomarker panels have been shown to add little to global risk assessment (33, 34). Only elevated high-sensitivity C-reactive protein (hsCRP)  $\geq 2.0$  mg/L (19.0 nmol/L), a serum biomarker of inflammation supported by robust risk-prediction literature, should be used as a risk-enhancing factor that may drive more

aggressive treatment or the need for advanced risk assessment (35).

### Measurement of coronary artery calcium

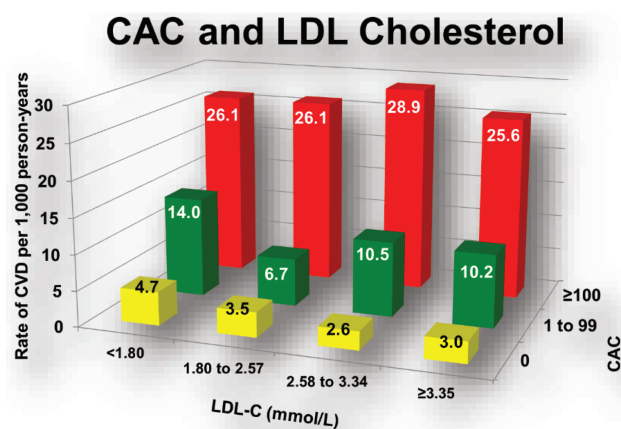
Common imaging tests for advanced risk assessment are aimed at directly assessing the burden of subclinical atherosclerosis. Most notable among these are carotid ultrasound tests for carotid intima-media thickness (cIMT) and carotid plaque, and cardiac-gated computed tomography (CT) scans for the assessment of CAC. These tests have the advantage of directly assessing end-organ damage, thus integrating a variety of risk exposures and personalizing this assessment to the individual patient in a particular vascular bed of interest, such as the coronary arteries (36). A drawback of these tests can be the subsequent management of incidental findings, for example of small nodules identified in the lung fields.

Many studies directly compare the performance of multiple advanced risk assessment strategies (37, 38). The most promising tests have been hsCRP, to test for subclinical inflammation and CAC, and carotid ultrasound to test for subclinical atherosclerosis. In comparative effectiveness analysis, there is consensus that the single best test for improving risk assessment is the CAC score (39). The CAC score leads to the largest improvements in area under the receiver operating curve over traditional risk factors (C-statistic change  $\sim 0.05$ ) and the largest NRI values ( $\sim 0.60$  in intermediate risk patients). Furthermore, the CAC score outperforms carotid ultrasound in head-to-head comparative effectiveness analysis (40).

CAC can be performed on any modern multidetector CT scanner in about 10 to 15 minutes with about 1 mSv of radiation (approximately similar to a bilateral mammogram). When the CAC score is zero (CAC = 0), patients are low risk and can be reclassified into lower-risk groups with less aggressive lipid therapies (41). When the CAC score is elevated (CAC  $>100$  or  $>75^{\text{th}}$  percentile for age, sex, and race), patients can be moved into higher-risk categories and treated more aggressively, using statins with or without nonstatin therapies to achieve lower LDL-C levels (42). There is good evidence that CAC can identify select patients with severe lipid disorders but who have no detectable (calcified) coronary atherosclerosis and who are, therefore, at relatively low risk (43) (Fig. 1).

The 2017 guidelines from the Society of Cardiovascular Computed Tomography (SCCT) defined 2 broad groups that might benefit from CAC testing for advanced risk assessment: (1) those with a 10-year ASCVD risk of 5% to 20%, and (2) those with a 10-year risk  $<5\%$ , with a family history of premature CAD or with another risk condition (44). The 2018 AHA/ACC Cholesterol Guidelines also endorse CAC, with an IIA recommendation in patients at borderline-to-intermediate risk (10-year ASCVD risk 5–19.9%) and in highly selected lower-risk patients with risk-enhancing





**Figure 1.** CVD events per 1000 person-years by strata of CAC and LDL-C. CAC predicts ASCVD risk independent of LDL-C. Patients with lower LDL-C but higher CAC remain high risk, while patients with higher LDL-C but CAC = 0 remain low risk. Abbreviations: CAC, coronary artery calcium; CVD, cardiovascular disease; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol. Reproduced with permission from Martin SS, Blaha M, Blankenstien R, et al. "Dyslipidemia, coronary artery calcium, and incident atherosclerotic cardiovascular disease: implications for statin therapy from the multi-ethnic study of atherosclerosis." *Circulation*, 2014;129(1):77–86. (43)

factors (35). According to the AHA/ACC guidelines, risk-enhancing factors that can be used to justify CAC scanning include MetS, inflammatory disorders (eg, rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis), HIV, hypertriglyceridemia, South Asian ancestry, history of premature menopause (before age 40 years), and pregnancy-related complications such as preeclampsia. The present Endocrine Society guideline identifies additional disorders that enhance ASCVD risk: Cushing syndrome, Cushing disease, high-dose chronic glucocorticoid therapy, and possibly adult GHD, acromegaly, and hypothyroidism.

Table 3 shows a general approach to using CAC to inform initial lipid-lowering therapy. In patients with an initial CAC of zero, a repeat CAC test should be considered to re-assess the CAC score and therefore possible risk (and treatment) reclassification; recent data from an analysis of CAC scores and coronary events in Multi-Ethnic Study of Atherosclerosis supports the following schedule: low-risk patient (10-year ASCVD risk <5%, 5 to 7 years), borderline-to-intermediate risk patient (10-year ASCVD risk 5% to 19.9%, 3 to 5 years), high-risk patient (10-year ASCVD risk ≥20%, 3 years) or patient with diabetes (3 years) (45, 46). Coronary artery calcium should generally not be repeated in already aggressively treated patients, as it is not designed to be a measure of lipid-lowering treatment efficacy.

Caution must be taken when applying CAC scoring to patients with high risk, such as genetically proven familial hypercholesterolemia (FH). As CAC identifies only the calcified component of coronary plaque (as seen first in a type 4 atheroma), early noncalcified plaque can be missed. In young patients with high risk, genetically proven FH or

other atherogenic endocrine conditions that might have been present from a young age (eg, severe obesity, diabetes), such early plaque is indicative of the need for continued aggressive lipid lowering, and CAC should not be used as the only deciding factor about the intensity of lipid-lowering therapy. In limited scenarios, CT angiography can be used to detect early noncalcified plaque, although such testing is generally reserved for symptomatic patients. Caution also is advised in interpreting CAC as zero in active smokers, who have additional thrombotic risk beyond their burden of atherosclerosis.

There is now excellent evidence that CAC reclassifies risk in patients with MetS and T2D. For example, Malik et al studied 1738 participants with MetS and 881 participants with T2D from the National Institutes of Health/National Heart, Lung, and Blood Institute-funded Multi-Ethnic Study of Atherosclerosis (48). After a mean 11.1 years of follow-up, the NRI for CAC in MetS was 0.22, and the NRI for CAC in diabetes was 0.23, indicating good risk reclassification of these groups. Participants with MetS and T2D with CAC of zero had low event rates, and CAC ≥400 was associated with a 3.2- and 3.5-fold increased risk of ASCVD, respectively. The CAC score predicted risk even after controlling for diabetes duration of 10 years or longer at baseline, insulin use, and glycemic control. CAC scoring also predicts risk in T1D (49).

### Values and preferences

This guideline places a high value on the shared decision-making process (the clinician–patient risk discussion). Additional risk information is considered highly important in carrying out an effective clinician–patient risk discussion regarding individualization of preventive therapies. For example, a general discussion of lifetime ASCVD risk, and accordingly, lifetime treatment benefit, may be an important part of the clinician–patient risk discussion in younger adults. When a patient is unwilling or unable to take medication or prefers taking preventive medication at any level of risk, there is little value in advanced risk stratification beyond the standard traditional risk factor assessment.

## 2. Hypertriglyceridemia

2.1 In adults with fasting TG levels over 500 mg/dL (5.6 mmol/L), we recommend pharmacologic treatment as adjunct to diet and exercise to prevent pancreatitis. (1⊕000)

### Technical Remark:

- Patients with TG levels over 1000 mg/dL (11.3 mmol/L) often do not get an adequate response to medications; therefore, control of diabetes, modification of diet, and weight loss are essential.



**Table 3.** Proposed decision-making approach to selective use of coronary artery calcium measurement for risk prediction

Using 10-year ASCVD Risk Estimate plus CAC Score to Guide Statin Therapy					
Patient's 10-year ASCVD risk estimate	<5%	5–7.4%	7.5–19.9%	≥20%	
Consulting ASCVD risk estimate alone	Statin not recommended	Consider statin	Recommend statin	Recommend statin	
Consulting ASCVD risk estimate + CAC	If CAC score = 0	Statin not recommended	Statin generally not recommended	Statin generally not recommended	Recommend statin
	If CAC score >0	Statin may be considered	Recommend statin	Recommend statin	Recommend statin
Does CAC score modify treatment plan?	X CAC less effective for this population	✓ CAC can reclassify risk up or down	✓ CAC can reclassify risk up or down	X CAC not effective for this population	

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium.

CAC = 0 should not be used as sole justification for use of lifestyle alone, to the exclusion of pharmacotherapy in familial hypercholesterolemia, advanced diabetes, and/or active smoking.

From Greenland P, Blaha MJ, Budoff MJ, Erbel R, Watson KE. "Coronary Calcium Score and Cardiovascular Risk." *J Am Coll Cardiol*. 2018; 72(4): 434–447. (47)

### Evidence and discussion

Although the relationship between severe hypertriglyceridemia and incident acute pancreatitis is well established, the lack of randomized-controlled trials (RCTs) testing whether TG reduction does prevent pancreatitis has led some to question whether the relationship is causal (50). In patients with marked hypertriglyceridemia, it is important to assess medications, and if possible, discontinue those such as estrogen and bile acid sequestrants that contribute to TG elevations. A more extensive list is in the section on "Considerations for Implementation of the Guidelines." Medications such as statins, fibrates, and omega-3 fatty acids, as adjunct to lifestyle modification, can adequately reduce TG in patients with TG 500 to 1000 mg/dL (5.6 to 11.3 mmol/L), and thereby reduce the risk of pancreatitis. However, in patients with severely elevated TG above 1000 mg/dL (11.3 mmol/L), these medications may not adequately lower TG and, therefore, a very low fat diet, weight loss, avoidance of alcohol, and glycemic control in people with diabetes may be needed to prevent pancreatitis. Recently, however, volanesorsen, an investigational antisense oligonucleotide to apoC3, has been reported to dramatically reduce TG levels in patients with severe TG elevation (fasting chylomicronemia syndrome) due to homozygous lipoprotein lipase (LPL) deficiency (51, 52). However, safety considerations include thrombocytopenia, which can be severe and is unpredictable. The New Drug Application for volanesorsen was not approved by the US Food and Drug Administration (FDA); however, volanesorsen has been approved for use in the European Union.

2.2 In patients with TG-induced pancreatitis, we suggest against the use of acute plasmapheresis as first-line therapy to reduce TG levels. (2⊕000)

### Technical Remark:

- Plasmapheresis may be useful in those who do not respond to conventional methods of lowering TG, such as individuals who have extraordinarily elevated TG levels (eg, over 10 000 mg/dL [112.9 mmol/L]) or in extremely high-risk situations such as pregnancy.

### Evidence and discussion

Plasmapheresis has been suggested to be useful for the acute management of TG-induced pancreatitis (53–58). However, for most cases of TG-induced pancreatitis, there is no evidence to support its superiority over cessation of oral fat intake, after which TG levels fall rapidly if no additional chylomicrons enter the circulation. Moreover, plasmapheresis only improves TG levels temporarily without addressing the underlying cause (59). In 1 single site study, outcomes from TG-induced pancreatitis were not improved when a plasmapheresis protocol was introduced (60). Use of plasmapheresis should be considered an option only in patients who do not respond to conventional methods or who have extraordinarily elevated TG levels (eg, over 10 000 mg/dL [112.9 mmol/L]). In addition, plasma exchange to supply apolipoprotein CII is beneficial in the extremely rare patients with apolipoprotein CII deficiency.

- 2.3 In patients without diabetes who have TG-induced pancreatitis, we suggest against the routine use of insulin infusion. (2⊕○○○)

**Technical Remark:**

- When uncontrolled diabetes is present, insulin therapy should be used to normalize glucose levels.

**Evidence and discussion**

There is little data to support the use of insulin infusion in TG-induced pancreatitis. In nonhyperglycemic patients, low-dose insulin (1 to 2 units per hour) is usually sufficient to block adipose tissue lipolysis, reduce circulating free fatty acid (FFA) levels, and theoretically reduce TG production by the liver. Insulin also can increase LPL activity, which may accelerate the clearance of TG from plasma. Although a reduction in TG after insulin infusion in individuals without diabetes who have TG-induced pancreatitis has been reported in several case studies (61–65), whether similar changes would have occurred simply by restricting oral intake without the use of insulin is unclear (66). A single study of chylomicronemia associated with uncontrolled diabetes demonstrated that fasting plus insulin infusion led to more rapid TG lowering than insulin alone (66). This is likely due to a reduction in adipose tissue lipolysis leading to reduced hepatic TG synthesis; plasma FFAs are normally reduced with very low doses of insulin. Given there is no clear evidence and only small studies in which possible efficacy cannot be ruled out, judicious use of low-dose insulin could be considered.

The use of high doses of insulin, such as the amounts routinely used for diabetic ketoacidosis (>0.1 units/kg), increases the risk of acute hypoglycemia. When used with concomitant glucose infusion to prevent hypoglycemia, it is likely to lead to carbohydrate-induced increase in TG production, which would be counterproductive.

- 2.4 In adults who are on statins and still have moderately elevated TG levels >150 mg/dL (1.7 mmol/L), and who have either ASCVD or diabetes plus 2 additional risk factors, we suggest adding eicosapentaenoic acid (EPA) ethyl ester to reduce the risk of CVD. (2⊕⊕⊕○)

**Technical Remarks:**

- Risk factors include traditional risk factors and risk-enhancing factors.
- The dose of EPA ethyl ester is 4 g/day.
- If EPA ethyl ester is not available or accessible, then it is reasonable to consider a fibrate.

**Evidence and discussion**

The relationship between hypertriglyceridemia and increased CV risk has been known for nearly 50 years. This association was found in several epidemiology studies and was stronger in women (67). Within the last decade, a number of genetic analyses implicated genes that modulate TG levels to be causal in the pathophysiology of atherosclerosis and CVD (68–70), and they have confirmed that heterozygous deletion and other types of mutations of LPL increase CVD risk (71).

The VA-HIT trial in men with coronary disease, low HDL-C, mild elevation in TG (mean TG 160 mg/d [1.8 mmol/L]) and mean LDL-C 112 mg/dL (2.9 mmol/L) found a significant reduction in the composite primary endpoint of nonfatal MI or coronary death in subjects randomized to gemfibrozil versus placebo (72). This trial was conducted before the widespread use of statins in people with ASCVD. Subsequently, studies of fibrates have been interpreted as showing reduced CV events in post hoc analyses in patients with increased TG levels and low HDL levels; however, the overall benefit of these drugs in statin-treated patients has not been shown. Although a series of fenofibrate studies, including ACCORD, which was confined to subjects with T2D, have shown no overall CV benefit in statin-treated patients, subgroup analyses of those patients with TG levels over 200 mg/dL (2.3 mmol/L) and low levels of HDL (<40 mg/dL [1.0 mmol/L]) showed benefit (73). These subgroup analyses were not prespecified, with the exception of the ACCORD trial. These results are statistically imperfect, as they involved subgroups merged for a meta-analysis. An ongoing CV outcome study of a PPAR alpha agonist, PROMINENT, is confined to individuals with hypertriglyceridemia (TG 200–499 mg/dL [2.3–5.6 mmol/L]) and low HDL-C (<40 mg/dL [1.0 mmol/L] in men and women) and will, for the first time, provide a valid test of the important question of CVD effects of a fibrate added to a statin in the setting of high TG.

Multiple trials have failed to show any CVD benefit of 1 g/d of mixed EPA + dososahexanoic acid (DHA), generally as omega-3 acid ethyl esters (O3AEE) (74, 75). In contrast, in a double blind RCT, REDUCE-IT, in a high-risk statin treated population with LDL-C below 100 mg/dL (2.6 mmol/L) and elevated fasting TG up to 500 mg/dL (5.6 mmol/L), EPA ethyl ester 4 g daily reduced CVD events (relative risk reduction [RRR] 25%) (76). The study population consisted of patients with either ASCVD, or T2D and 2 additional risk factors. Although the inclusion criteria specified that patients with diabetes have at least 1 additional risk factor, analysis of the actual trial population revealed that most patients with diabetes had at least 2 other risk factors

(77). The latter were either traditional risk factors or factors that would be considered risk-enhancing factors: hsCRP > 3 mg/L; creatinine clearance >30 and <60 mL/min; and retinopathy, microalbuminuria, and ankle brachial index <0.9 (78). The reduction in ASCVD events did not appear to be related either to the degree of baseline TG elevation or to the on-treatment TG levels <150 vs >150 mg/dL (<1.7 vs >1.7 mmol/L) (76). Further, a prespecified subgroup analysis of those patients with or without T2D showed similar benefits.

REDUCE-IT was not the first randomized CVD outcomes trial to show benefit with pure EPA. CVD benefit was reported in a randomized but open-label trial of pure EPA, using 1.8 g/d of an ethyl-ester preparation essentially identical to EPA ethyl ester, in a population of Japanese patients, but this trial was open label, which could introduce bias. The CVD benefit seen in REDUCE-IT does not apply to other omega-3 fatty acids, particularly those with a mix of EPA and DHA. STRENGTH was the first trial of a mix of EPA plus DHA at full dose (4 g/d) in patients recruited for elevated TG (200–499 mg/dL [2.3–5.6 mmol/L], along with low HDL-C (<40 mg/dL [1.0 mmol/L] in men and <45 mg/dL [1.2 mmol/L] in women). Participants did not have a history of CVD events but were at high risk of CVD. The trial was discontinued by the data monitoring board due to its low likelihood of success. No data are yet available to support the use of supplements containing both EPA and DHA to reduce ASCVD risk.

2.5 In patients with elevated TG (>150 mg/dL to 499 mg/dL [1.7 mmol/L to 5.6 mmol/L]), we suggest checking TG before and after starting a bile acid sequestrant. (2⊕○○○)

**Technical Remark:**

- Bile acid sequestrants are contraindicated when TG are > 500 mg/dL (5.6 mmol/L).

**Evidence**

Although bile acid sequestrants are seldom used today for the treatment of hypercholesterolemia, they are used on occasion in people with diabetes because they also lower hemoglobin A1c (HbA1c) (79). Use of bile acid sequestrants can lead to an increase in plasma TG due to an increase in VLDL production rates, although this effect is variable (80). Individuals with high baseline levels of TG (>500 mg/dL [5.6 mmol/L]) can reach very high levels after treatment with bile acid sequestrants (81). As a result, it has been suggested that hypertriglyceridemia is a relative contraindication to the use of this class of drugs (81). In a meta-analysis, TG were also shown to

increase significantly after the use of a newer bile acid sequestrant, colesevelam (82). Due to the variability of the response, we suggest checking plasma TG before starting and again several weeks after initiating a bile acid sequestrant.

### 3. Type 2 diabetes mellitus

3.1 In adults with T2D and other CV risk factors, we recommend statin therapy in addition to lifestyle modification in order to reduce CV risk. (1⊕⊕⊕⊕)

**Technical Remarks:**

- High-intensity statins should be chosen in patients with ASCVD, or those with risk factors for ASCVD, or risk enhancing factors.
- Statins should not be used in women who are pregnant or trying to become pregnant.
- In patients over the age of 75, continuation of statin treatment or initiation of statin treatment depends upon ASCVD risk, prognosis, potential interacting medications, polypharmacy, mental health, and the wishes of the patient.

**Evidence and discussion**

Dyslipidemia in T2D is characterized by hypertriglyceridemia, low levels of HDL-C, and average or borderline elevations of LDL-C (83). LDL particles are typically small and dense (83). Total apoB levels are elevated (84), reflecting an increase in the number of TG-rich lipoprotein and small, dense LDL particles. Similar lipid abnormalities are often observed in MetS in the absence of overt diabetes (85).

There is consensus that ASCVD risk is increased 2- to 4-fold in T2D (86, 87), the magnitude of the increased risk varying between studies. Some have considered T2D to be a “CVD risk equivalent” (88) (ie, as strong a risk factor as established CVD). Others suggest that the risk is less strong than established CVD (89), but there is no disagreement that CVD risk is indeed increased in T2D. A population-based retrospective cohort study showed the transition to a high-risk category for CVD at a younger age for people with diabetes than for those without (mean difference 14.6 years). Men and women with diabetes entered the high-risk category for acute MI, stroke, or death from any cause at ages 47.9 and 54.3 years, respectively (90). This study also found that the protective effect of female sex on CVD was attenuated by diabetes. The age-adjusted hazards ratio (HR) for acute MI in people without diabetes was 2.56 (95%

confidence interval [CI]: 2.53–2.60) in men compared with women, and in people with diabetes 1.40 (CI: 1.36–1.43) in men compared with women, and lower when adjusted for sociodemographic factors, comorbidities, and use of health care services. Individuals with diabetes (and MetS) often have several CVD risk factors, including hyperglycemia, hypertension, nephropathy, and cigarette use, in addition to dyslipidemia. It is difficult to apportion the extent that each risk factor contributes to overall CVD risk. However, in an analysis of risk factors in the UK Prospective Diabetes Study (UKPDS), LDL-C was the strongest predictor of CVD events (91). This observation is supported by strong evidence that CVD risk is reduced to a greater extent by lowering LDL-C levels than by treatment of other risk factors.

Dyslipidemia often improves following the initiation of all modalities of glucose-lowering therapy. In particular, the initiation of insulin often leads to TG reduction. Metformin, which often is the first drug used for treatment of T2D, can lower TG and lead to small improvements in HDL-C (92, 93). How much of these changes is due to glucose lowering versus weight reduction is unclear. Other glucose-lowering drugs associated with beneficial changes in the lipid profile include glucagon-like peptide (GLP-1) receptor agonists (94, 95) and thiazolidinediones (93, 95). Sodium-glucose co-transporter 2 (SGLT2) inhibitors (96, 97) can modestly increase LDL-C levels (98, 99). The relative contribution of glucose control, specific actions of the drug, and weight loss is difficult to assess. Sulfonylureas, dipeptidyl peptidase-4 inhibitors, meglitinides, and  $\alpha$ -glucosidase inhibitors are generally considered to be lipid neutral (93, 95, 100).

UKPDS found that intensive diabetes treatment resulted in a 16% nonsignificant risk reduction for MI (101). However, significant risk reductions for MI and death from any cause were observed during the 10 years of post-trial follow-up (102). In UKPDS 34, which analyzed diabetes endpoints and CVD outcomes in 342 overweight patients allocated intensive treatment with metformin or conventional therapy, the metformin group had a significantly lower risk of mortality and of MI compared with subjects in the conventional therapy group (103). Tight glycemic control failed to improve CV outcomes in 3 large studies of intensive insulinization (104–106). In ACCORD, intensive insulin treatment for 3.5 years resulted in the expected target reduction in HbA1c, yet mortality increased and major CV events were not significantly reduced (104). In ADVANCE, in which various strategies to lower blood glucose achieved a target HbA1c of 6.5%, the intensity of glucose control did not significantly change major macrovascular events, death from CV causes, or death from any cause after 5 years of follow-up (105). In the VADT

study, intensive glucose control in patients with poorly controlled T2D had no significant effect on the rates of major CV events or death after a follow-up period of 5.6 years (106). Pioglitazone in Pro-Active (107); the GLP-1 receptor agonists liraglutide in the LEADER trial (108), dulaglutide in REWIND (109), and albiglutide in HARMONY OUTCOMES (110); the SGLT2 inhibitors empagliflozin in EMPA REG OUTCOMES (111); canagliflozin in the CANVAS trial (112); and dapagliflozin in DECLARE-TIMI 58 (113) have all been reported to reduce CVD outcomes, although the role of glucose lowering per se is unclear.

Of the various therapies to prevent or treat CVD in T2D, the most successful to date has been statins, which act mainly by inhibiting HMG-CoA reductase, the rate-limiting enzyme in cholesterol synthesis, thereby upregulating LDL receptors and lowering plasma LDL-C levels. Even though LDL-C levels are not usually elevated in diabetes, the benefit of statins was first demonstrated in the Heart Protection Study, an RCT comparing 40 mg simvastatin daily to placebo (114). In a prespecified secondary analysis of participants with diabetes randomized to simvastatin 40 mg, the rate of first major vascular events (eg, major coronary events, strokes, revascularizations) was reduced by 22% (95% CI: 13–30) over 5 years (115). Subsequent events were also reduced (115). In those with diabetes who did not have a history of vascular events at entry into the study, there was a significant 33% (95% CI: 17–46) reduction in the rate of vascular events.

In CARDS, 10 mg atorvastatin daily, in comparison to placebo, over 3.9 years, reduced the risk of first CV events, including stroke, by 37% (95% CI: -52 to -17,  $P = 0.001$ ) in patients with T2D, without high LDL-C levels and with no history of CVD (116). However, these findings were not confirmed in the ASPEN trial, albeit this trial had several design problems (117). Nonetheless, meta-analyses that include more than 100 000 subjects (118) strongly support the beneficial effect of statins in CVD prevention in T2D. Statins have purported pleiotropic effects other than lipid lowering effects, so it is conceivable that some of these pleiotropic effects might have contributed to the prevention of CVD events. However, the meta-analyses (of statin RCTs) indicate that CVD events decrease by about 20% and mortality by about 10% for every 40-mg/dL (1.0 mmol/L) reduction in LDL-C in people with diabetes (118, 119), suggesting that lipid lowering plays a much greater role in CVD prevention than possible pleiotropic effects. In the Cholesterol Treatment Trialists (CTT) meta-analysis of people with diabetes in 14 randomized trials of statins, with a mean treatment duration of 4.3 years, similar reductions in MI or coronary death (0.78, 0.69–0.87;  $P < 0.0001$ ), coronary revascularization (0.75, 0.64–0.88;  $P < 0.0001$ ), and stroke (0.79, 0.67–0.93;  $P = 0.0002$ )



were observed in people with and without diabetes (118). Moreover, in clinical trials in subjects without diabetes, the strong relationship between in-trial LDL-C levels and CVD events independent of the modality of cholesterol lowering (120–122) suggests that LDL-C reduction is a major mechanism of lowering ASCVD risk.

3.2 In adults with T2D and other CV risk factors, we suggest lowering LDL-C to achieve a goal of LDL-C <70 mg/dL (1.8 mmol/L) in order to reduce CV risk. (2⊕000)

#### Technical Remarks:

- A statin should be added to lifestyle modifications if LDL-C is >70 mg/dL (1.8 mmol/L).
- LDL-C should be <55 mg/dL (1.4 mmol/L) in patients with established CVD or multiple risk factors.
- Additional LDL-lowering therapy (ezetimibe, proprotein convertase subtilisin/kexin type 9 inhibitor) may be needed if the LDL-C goal is not reached with statins.
- Risk factors include traditional risk factors and risk-enhancing factors.

#### Evidence and discussion

Considerable evidence from RCTs of statins, and trials of statins in combination with ezetimibe or monoclonal antibodies to PCSK9, conducted in patients with and without ASCVD and in subgroups including patients with diabetes, demonstrates that the greater the reduction in LDL-C levels, the greater the reduction in the risk of CV events (123, 124). This benefit depends upon the absolute reduction in LDL-C and the baseline risk of ASCVD (125). The CTT individual participant data meta-analysis of 26 statin trials found that for every 1 mmol/L (39 mg/dL) reduction in LDL-C, there was a 22% RRR in major ASCVD events (HR 0.78; 95% CI: 0.76–0.80;  $P < 0.0001$ ).

In the PROVE-IT TIMI 22 trial, conducted in very high-risk patients with acute coronary syndrome, there was a progressive reduction in risk (death, MI, stroke, recurrent ischemia, revascularization), as LDL-C levels fell from 80 to 100 mg/dL (2.1 to 2.6 mmol/L) through 60 to 80 mg/dL (1.6 to 2.1 mmol/L), through 40 to 60 mg/dL (1.0 to 1.6 mmol/L), and <40 mg/dL (1.0 mmol/L) (126). In the TNT trial in patients with stable coronary heart disease (CHD), reduction in LDL-C to 77 mg/dL (2.0 mmol/L) provided greater ASCVD benefit (CHD death, nonfatal MI, fatal or nonfatal stroke, resuscitation after cardiac arrest) compared with the reduction in LDL-C to 101 mg/dL (2.6 mmol/L) (127). Further, in the CTT meta-analysis of individual participant data from 5 statin trials comparing more intensive to less intensive statin treatment,

more intensive treatment led to a significant 15% (95% CI: 11–18,  $P < 0.001$ ) additional reduction in major vascular events, with separately significant reductions in coronary death or nonfatal MI of 13%, in ischemic stroke of 16%, and in coronary revascularization of 19% (123). Today, very low LDL-C levels can be achieved with either a combination of statins plus ezetimibe, or PCSK9 inhibitors with or without statins and/or ezetimibe. The addition of ezetimibe to statin therapy after acute coronary syndromes resulted in the incremental lowering of LDL-C and improved CV outcomes (120), including in the 27% of the study population with diabetes. The mean LDL-C in the ezetimibe plus statin group was 53 mg/dL (1.4 mmol/L), which is below previous LDL-C target levels.

Injectable PCSK9 antibodies have been available since 2015. They trap PCSK9 in plasma, thereby preventing PCSK9 from binding to LDL receptors at the hepatocyte surface. As a result, LDL receptors are targeted for recycling to the cell surface rather than for lysosomal degradation. Because of the resulting increase of LDL receptors at the cell surface, PCSK9 antibodies lower LDL-C levels beyond those usually achievable with statins with or without ezetimibe (128, 129). Two secondary prevention trials of PCSK9 antibodies on a background of statin therapy, FOURIER (129) and in patients with ASCVD ODYSSEY OUTCOMES (130) in patients with ACS, both achieved very low in-trial LDL-C levels (30 mg/dL [0.8 mmol/L] and 53 mg/dL [1.4 mmol/L] on treatment, respectively), which were lower than previous guidelines. Both studies showed a CVD benefit from this additional LDL lowering and in prespecified analyses, similar RRR in the primary composite CV endpoint in patients with diabetes compared with those without diabetes. In FOURIER, 11 031 of 27 564 patients (40%) had T2D. Evolocumab significantly reduced the relative risk (RR) of the primary composite endpoint (CVD death, MI, stroke, coronary revascularization, or hospital admission for unstable angina) in patients with diabetes by 17% (HR 0.83 (95% CI: 0.75–0.93;  $P = 0.0008$ ) over 3 years (131). In ODYSSEY OUTCOMES, 5444 of 18 924 patients (28.8%) had diabetes, 8246 (43.6%) had prediabetes, and 5234 (27.7%) were normoglycemic (132). Alirocumab significantly reduced the RR of the primary composite endpoint in patients with diabetes by 16% (HR 0.84, 95% CI: 0.74–0.97) over 2.8 years, and the RRR was similar among patients with diabetes, prediabetes, or normoglycemia. In view of the very high risk of CVD in people with T2D, we suggest targeting the lower LDL-C levels achieved in these newer trials, with a practical goal of <70 mg/dL (1.8 mmol/L). Because the data from these clinical trials demonstrate additional benefit at even lower levels of LDL-C, we suggest that those patients with



diabetes who are at the highest risk (ie, those with established CVD or multiple risk factors) achieve LDL-C levels even lower than 70 mg/dL (1.8 mmol/L).

### Benefits and risks/harms

The benefits of achieving very low cholesterol levels are a reduction in CVD events (fatal and nonfatal MI, ischemic stroke, coronary revascularization procedures) and mortality. Whether low LDL-C levels confer a risk to the patient has been addressed by data from numerous RCTs of statins, meta-analyses of the RCTs, and, more recently, RCTs of PCSK9 inhibitors. These trials have found that low LDL-C levels, including LDL-C as low as 10 to 20 mg/dL (0.3 to 0.5 mmol/L) in patients taking PCSK9 inhibitors, are not associated with an increase in serious adverse events. Observational studies in 1989 and 1994 reported an association of high cholesterol with thromboembolic or nonhemorrhagic stroke but, in contrast, an inverse relationship between cholesterol and intracerebral hemorrhage (133–135). However, subsequent large outcome trials of statins did not confirm this. Individual trials and meta-analyses of these RCTs, which included about 170 000 subjects followed for a mean of 4 years, found that, in people without a history of stroke, LDL-C reduction reduced ischemic stroke and did not increase hemorrhagic stroke (118). However, 1 RCT, SPARCL, in a secondary stroke/transient ischemic attack population that was not included in the CTT meta-analyses, showed a small increase in hemorrhagic stroke events (55 vs 33) in participants randomized to atorvastatin 80 mg daily compared with placebo but, importantly, a significant reduction in total stroke and ischemic stroke (136, 137). Additional analyses showed that the risk of hemorrhage was higher in those with a hemorrhagic stroke as an entry event but was not associated with baseline or treated LDL-C (138). A subsequent RCT compared the effect of LDL-C reduction, using statins and (as needed) ezetimibe, to a goal below 70 mg/dL (1.8 mmol/L) and a goal of 90 to 110 mg/dL (2.3 to 2.8 mmol/L) in individuals with a history of ischemic stroke or TIA (139). Cardiovascular events, including ischemic stroke, were significantly reduced in the group randomized to the lower LDL-C goal, but intracerebral hemorrhage was numerically increased (18 vs 13 events), although not statistically significant. The implications of these data are not clear because the trial ended early due to a loss of funding, and therefore, the prespecified number of patients to be enrolled was not achieved. Also, without a placebo group, causality could not be determined. Analysis of stroke in ODYSSEY OUTCOMES, a trial of alirocumab, targeting LDL-C levels of 25 to 50 mg/dL, found a significant decrease in ischemic stroke, without an increase in

hemorrhagic stroke (140). A prospective cohort study of 27 937 women who were enrolled in the Women's Health Study (WHS) showed 0.8% of women with LDL-C levels of 70 mg/dL (1.8 mmol/L) or lower had suffered a hemorrhagic stroke, double the rate of women with LDL-C levels between 100 mg/dL (2.6 mmol/L) and 130 mg/dL (3.4 mmol/L), although this study did not provide any data regarding the effect of lipid-lowering therapy on stroke (141).

In several clinical trials and meta-analyses, statins produced a small increase in HbA1c of the magnitude of 0.1%, which seems unlikely to significantly change CVD risk (142). Statins, however, increase the risk of developing diabetes (143), with an absolute increase of 0.2% per year in major statin RCTs (142), but the benefit/risk ratio is favorable because of the significant reduction in the high risk of MI and stroke in diabetes (144, 145). The risk of newly diagnosed diabetes is especially increased in those taking high doses of potent statins and individuals predisposed to diabetes, such as those with MetS (146). These findings are consistent with Mendelian Randomization studies that show an association between low LDL-C and diabetes risk (147–149). However, the PCSK9 antibody evolocumab, in the FOURIER trial (131), and alirocumab in ODYSSEY OUTCOMES (132) did not increase the risk of new-onset diabetes or worsen glycemia in patients with diabetes, although these studies were relatively short term and, therefore, cannot be considered definitive.

3.3 In adults with T2D on a statin at LDL goal with residual TG over 150 mg/dL (1.7 mmol/L) and with 2 additional traditional risk factors or risk-enhancing factors, we suggest adding EPA ethyl ester to reduce CV risk. (2⊕⊕⊕O)

### Technical Remarks:

- Consider 4g/day of EPA ethyl ester.
- If EPA ethyl ester is not available or accessible, then it is reasonable to consider a fibrate, such as fenofibrate.

### Evidence and discussion

Omega-3 fatty acids are effective at lowering elevated TG levels (150). Some data suggests that EPA ethyl ester, a highly purified EPA ethyl ester, reduces selected inflammatory markers in patients with elevated TG (151) and may have other biological effects that could play a role in reducing atherosclerosis (152). In the placebo-controlled trial REDUCE-IT, in 8179 subjects, a high dose (4 g/day) of EPA ethyl ester, lowered major adverse cardiac events (MACE) by an additional 25% in statin-treated subjects, with residual fasting hypertriglyceridemia (median at baseline in

the EPA ethyl ester group, 216.5 mg/dL (2.4 mmol/L) (Q1 176.5 [2.0 mmol/L], Q3 272 mg/dL [3.1 mmol/L]) and either established ASCVD or T2D and 2 additional risk factors (76,77). The RRR for the composite primary endpoint was 25% (95% CI: 0.68–0.83);  $P < 0.001$ . However, the benefit did not appear to relate to either baseline TG levels or the change in TG. In addition, the use of an essentially identical agent, ethyl icosapentate, at a dose resulting in a comparable on-treatment EPA level, showed a comparable 19% CVD reduction in JELIS, an open-label, randomized, blinded endpoint trial (153). Other studies have failed to show a similar benefit of omega-3 fatty acids, including in subjects with diabetes (74, 154, 155), again, possibly because not all subjects were hypertriglyceridemic, or possibly due to inadequate doses of omega-3 fatty acids, or because a combination of both EPA and DHA was used. The STRENGTH trial of a mixed EPA and DHA formulation in hypertriglyceridemic subjects at a high risk of CVD has been discontinued by the data monitoring board due to a low likelihood of success.

The hallmark of diabetic dyslipidemia is hypertriglyceridemia. Several medications reduce hypertriglyceridemia in patients with T2D. As exemplified by the ACCORD study, TG levels fall significantly in response to fenofibrate in patients with diabetes (156). The VA-HIT trial in men with coronary disease, low HDL-C, and mild elevations in TG found that gemfibrozil given without a statin significantly reduced coronary events (72). Subsequent clinical trials have, to date, failed to provide definitive evidence for a benefit on CVD outcomes of fibrate therapy, either alone or in combination with statins, although post hoc analysis of several fibrate studies indicate that CVD benefit is confined to those with elevated TG and low HDL-C levels (156–158). The lack of evidence for CVD benefit is likely due in part to the fact that these trials have not been limited to subjects with hypertriglyceridemia (156–158). The PROMINENT trial, which will test the effect of fibrate treatment on CV endpoints in hypertriglyceridemic subjects with diabetes, is due for completion in 2022.

Based on the small number of clinical trials of omega-3 fatty acids with CV endpoints, positive results, which were confined to EPA ethyl esters, and because the benefits of fibrates are limited to post hoc analyses, the guideline writing committee suggests the use of icosapentaenoic acid ethyl ester at 4 g per day in statin-treated patients with T2D and residual hypertriglyceridemia. If this is not available or not accessible, fibrates may be considered, although the evidence for benefit is currently limited to post hoc analyses.

3.4 In adults with T2D with CKD stages 1–4 and postrenal transplant, we suggest statin therapy, irrespective of the CV risk score, to reduce CV risk. (2⊕000)

#### Technical Remarks:

- When selecting the statin, consider the renal clearance of the statin. Pitavastatin, pravastatin, and rosuvastatin all have at least partial clearance through the kidney, whereas atorvastatin, fluvastatin, lovastatin, and simvastatin are cleared via the liver.
- All statins require dose adjustments in CKD except for atorvastatin and fluvastatin.

#### Evidence and discussion

CVD is the leading cause of death in individuals with CKD, which is defined as a sustained reduction in kidney function in which the glomerular filtration rate remains below 60 mL per minute or the urine albumin-to-creatinine ratio is >30 mg of albumin/g creatinine for >3 months. End-stage renal disease (ESRD) is defined as total and permanent kidney failure typically requiring either dialysis or transplantation. ESRD is associated with very high risk for CVD events. Diabetes is the leading cause of both CKD and ESRD. Several studies have evaluated the effect of statin therapy in patients with CKD and ESRD. The SHARP study, which examined the effect of LDL-C lowering by a statin (simvastatin) plus ezetimibe on CVD outcomes in patients with moderate-to-severe CKD, showed a reduction in MACE associated with LDL lowering, especially in those with high baseline LDL-C levels (159). However, the prognostic value of on-treatment LDL-C appears to be less in those with CKD due to diabetic kidney disease than other causes (160). The event reduction appeared to be decreased if not absent in those on dialysis. Cholesterol lowering by statins failed to reduce CVD endpoints in patients with ESRD on dialysis in either the 4D (161) or AURORA trials (162). After renal transplantation, statin treatment significantly reduced cardiac death and nonfatal MI but not the primary CVD endpoint in the ALERT trial (163). However, the extension trial did find a significant reduction in risk of cardiac death, nonfatal MI, and cardiac interventional procedures (164). Based on this small number of clinical trials, we suggest initiating statins to prevent CVD outcomes in patients with early-to-moderate CKD independent of other risk factors but not in patients with ESRD on dialysis. Continuation of statin treatment in a patient whose CKD progresses to requiring dialysis can be left to clinical judgement.

3.5 In adults with T2D and diabetic retinopathy, we suggest fibrates in addition to statins to reduce retinopathy progression. (2⊕000)

**Technical Remarks:**

- This recommendation applies regardless of TG levels.
- The preferred fibrate is fenofibrate.

**Evidence and discussion**

Although the primary CV endpoint was not statistically significant in the placebo-controlled FIELD study of fenofibrate in patients with T2D, a surprising finding was the reduction of retinopathy requiring laser treatment in the fenofibrate group compared with the placebo group (165). Fenofibrate also delayed progression of retinopathy in the ACCORD trial, in which tight glycemic control but not blood pressure control had a beneficial effect on retinopathy (166). Also, in a retrospective, matched cohort study in people with T2D, treatment with fibrates (largely bezafibrate and fenofibrate, but also ciprofibrate, gemfibrozil, and, in 1 patient, clofibrate) was independently associated with a reduced progression to a first diagnosis of diabetic retinopathy (167). Based on these studies, we suggest using a fibrate to reduce retinopathy progression in persons with T2D. Fenofibrate is preferred to gemfibrozil because fenofibrate was studied in RCTs, and because gemfibrozil in combination with a statin is associated with increased risk of myopathy.

#### 4. Type 1 diabetes mellitus

4.1 In adults with T1D age 40 years and older and/or with duration of diabetes > 20 years, and/or microvascular complications, we suggest statin therapy, irrespective of the CV risk score, to reduce CV risk. (2⊕000)

**Technical Remarks:**

- LDL should be the primary target for lipid-lowering therapy.
- Consider therapy if LDL is over 70 mg/dl (1.8 mmol/L).
- Statins should not be used in women who are pregnant or trying to become pregnant.

**Evidence and discussion**

Individuals with T1D have participated in several randomized, controlled CV outcome studies of statins. Statins appear to be equally effective in lipid lowering for patients with T1D vs T2D and those without diabetes. For example, in the Heart Protection Study, the reduction in CVD events was not significantly different in 615 subjects with T1D compared with 5348 subjects with T2D, albeit the CIs were

wide (115). Hero and colleagues used a Swedish registry to assess the effects of lipid-lowering therapy in 24 230 individuals with T1D without known CVD included in the 2006–2008 registry (overall mean age 39.4 years). They were followed until the end of 2012; 5387 were treated with lipid-lowering medications (97% statins) and 18 843 were not treated with lipid-lowering medications. After a mean follow-up of 6 years, the HRs for treated versus untreated were CVD death, 0.6; all-cause death, 0.56; fatal/nonfatal stroke, 0.56; fatal/nonfatal MI, 0.78; fatal/nonfatal CHD, 0.85; and fatal/nonfatal CVD, 0.77 (168). A meta-analysis of statin use in 18 686 subjects with diabetes (1466 of whom had T1D) in 14 randomized trials of statins reported a 21% reduction in major CVD events and a 13% reduction in vascular mortality for every 1.0 mmol/L (approximately 40 mg/dL) drop in LDL during a mean follow-up of 4.3 years (118).

There is a paucity of data regarding the age at which to start statin therapy in subjects with T1D. A 2019 report found that in individuals participating in the T1D exchange clinic registry, statin use increased from 2% in subjects aged 10 to 17 years to 4% in subjects age 18 to 25 years and to 21% in subjects age 25 to 39 years. Most subjects on statin therapy had LDL <100 mg/dL (2.6 mmol/L); regardless of statin use, subjects with LDL >100 mg/dL (2.6 mmol/L) were more likely to have at least 1 additional CVD risk factor compared with those with LDL <100 mg/dL (2.6 mmol/L) (169). The Pittsburgh Epidemiology of Diabetes Complications study reported CVD event rates at 0.98% per year in young adults (age 28 to 38 years) with T1D, with an increase to 3% per year in adults over 55 years, with CVD accounting for 40% of all deaths in individuals with T1D >20 years' duration (170). A recent study by Rawshani et al demonstrates that age of T1D onset has a significant impact on CVD risk, with greatest risk in those with earliest onset of T1D (defined as <10 years old) (171). Thus, although specific evidence is lacking to guide which age and/or diabetes duration to initiate therapy, there is good evidence that duration of diabetes predicts increased CVD risk, and statin therapy reduces CVD risk in subjects with T1D.

4.2 In adults with T1D with CKD in stages 1 to 4, we suggest statin therapy, irrespective of the CV risk score, to reduce CV risk. (2⊕000)

**Technical Remarks:**

- LDL should be the primary target for lipid-lowering therapy.
- Consider therapy if LDL is over 70 mg/dL (1.8 mmol/L).
- When selecting the statin, consider the renal clearance of the statin: pitavastatin, pravastatin, and rosuvastatin all have at least partial clearance through the kidney,

whereas atorvastatin, fluvastatin, lovastatin, and simvastatin are cleared via the liver.

- All statins require dose adjustments in CKD except for atorvastatin and fluvastatin.
- Ezetimibe can be added to the statin if required to lower LDL-C further. No dose adjustments of ezetimibe are needed in CKD.

### Evidence and discussion

The presence of renal disease in diabetes increases CVD risk, but, even in the absence of renal disease, T1D confers increased CVD risk (172, 173). However, although renal disease is a CVD risk factor, especially in T1D, there is no evidence that statins (or any other lipid-lowering agents) improve renal outcomes; thus, the use of lipid-lowering therapy is aimed at reducing CVD risk, not CKD risk. The SHARP study found that lipid-lowering therapy in patients with diabetes with CKD stages 1–4 decreased CVD risk; however, this study did not distinguish between T1D and T2D (159). Furthermore, although several studies have not shown any benefit to initiation of lipid-lowering therapy in patients with CKD stage 5 (dialysis), there is no evidence of any harm (161, 162, 174), albeit none of these studies were conducted specifically in T1D. The ALERT study found a benefit of statin therapy in individuals postrenal transplant (175, 176). Thus, although evidence suggests that initiation of lipid-lowering therapy in CKD stage 5 is likely of no benefit, there is no evidence to guide the management of lipid-lowering therapy in patients with CKD who progress to stage 5. We suggest that lipid-lowering therapy should be initiated in patients with T1D with CKD stages 1–4 or postrenal transplant; if a patient progresses to stage 5, the lipid-lowering therapy may be continued, but it should not be initiated in a patient in stage 5 CKD.

- 4.3 In adults with T1D with obesity, or with high TG and low HDL-C, we suggest statin therapy, irrespective of the CV risk score, to reduce CV risk. (2⊕○○○)

#### Technical Remarks:

- LDL should be the primary target for lipid-lowering therapy.
- Consider therapy if LDL-C is over 70 mg/dL (1.8 mmol/L).

### Evidence and discussion

The treatment of hyperglycemia reduces TG levels. The SEARCH for Diabetes in Youth study found that improved glycemic control over a 2-year period led to improvements in lipid profiles, albeit improved glycemic control alone was not

sufficient to meet lipid goals (177). Observational studies suggest that intensive glycemic control reduces CVD events (178, 179). Furthermore, as shown in the DCCT/EDIC study in T1D (179), even a relatively short period of good glycemic control is associated with decreased CVD events years later, termed a “legacy effect.” However, those that gained excessive weight with intensive therapy appear to have less benefit than those who gained less weight (180). Analyses of the DCCT/EDIC study over a 30-year follow-up period found that age and sex were not the dominant predictors of CVD risk factors; rather, HbA1c and lipid measurements (TG and LDL levels) had the strongest longitudinal associations. Furthermore, weight was predictive of blood pressure, heart rate, and lipid profile levels (181). The timing of the impact of weight gain on CVD risk appeared delayed: for the first 13 years of EDIC, those who gained the most weight had increased CVD risk factors but no increase in CVD events, possibly due to their increased use of blood pressure and lipid-lowering therapy. However, after 14 years of follow-up, the group with greatest weight gain had increased CVD events (180).

Thus, individuals with T1D who develop features of MetS (central obesity, high TG, and low HDL-C) appear to be at increased CVD risk and should be treated with lipid-lowering therapy, in addition to diet and increased physical activity. Early addition of blood pressure and/or lipid-lowering therapy may help reduce the risk associated with increased weight gain, but there is no data to support the timing of additional therapy.

- 4.4 In adults with T1D and diabetic retinopathy, we suggest statin therapy, irrespective of the CV risk score, to reduce CV risk. (2⊕○○○)

#### Technical Remarks:

- LDL should be the primary target.
- Consider therapy if LDL-C is over 70 mg/dL (1.8 mmol/L).

### Evidence and discussion

A meta-analysis of 20 studies of 19 234 patients with T1D (n = 4438) or T2D (n = 14 896) found that the presence of any degree of diabetic retinopathy increased all-cause mortality and CVD events compared with those without diabetic retinopathy. The RR was greater for those with T1D than for those with T2D and remained significant even after adjusting for traditional CVD risk factors (182).

## 5. Obesity

- 5.1 In individuals who have obesity, we advise assessment of the components of the MetS and body fat distribution to accurately determine



the level of CVD risk. (Ungraded Good Practice Statement)

#### Technical Remarks:

- Diagnosis of MetS requires the presence of 3 of the following criteria:
  - Elevated TG  $\geq$  150 mg/dL (1.7 mmol/L) or on TG-lowering medication.
  - Reduced HDL-C  $<$ 50 mg/dL (1.3 mmol/L) in women and  $<$ 40 mg/dL (1.0 mmol/L) in men.
  - Systolic blood pressure  $\geq$  130 mm Hg or diastolic blood pressure  $\geq$  85 mm Hg or on blood pressure medication.
  - Elevated waist circumference (men  $\geq$  40 in [102 cm] and women  $\geq$  35 in [88 cm]), except for East and South Asian men  $\geq$  35 in (90 cm) and women  $\geq$  31.5 in (80 cm).
  - Hyperglycemia (but not yet with T2D) is defined by cutoffs for prediabetes according to fasting blood glucose, oral glucose tolerance, and/or HbA1c.
- Body fat distribution can be assessed in clinical practice by measuring the waist size or the waist/hip ratio.
- Waist size measurement in people with a BMI  $>$ 35 kg/m<sup>2</sup> has potential limitations.

#### Evidence and discussion

Obesity is frequently associated with MetS, which is a risk-enhancing factor for ASCVD, and is treated initially by lifestyle modifications, including a healthy diet and physical activity. Lipid abnormalities in MetS include elevated TG, low HDL-C, and increased non-HDL-C. Although LDL-C may not be above the threshold considered appropriate for initiating statin treatment, apoB and small dense LDL-C may be increased (183).

Dyslipidemia in obesity is similar to that of MetS, with increased TG and FFAs, decreased HDL-C, and, in many patients, increased apoB and slightly increased LDL-C, with increased small, dense LDL. The increase in apoB is partly due to hepatic overproduction of apoB-containing lipoproteins (184–186). Postprandial hyperlipidemia is more frequent in obesity, leading to accumulated circulating atherogenic remnants (186–188).

Most epidemiological studies define obesity based on BMI, which has been shown to be a strong predictor of CVD mortality. Limitations of BMI have been noted (189). Anthropometric methods such as waist circumference and waist/hip ratio have been demonstrated to be better measures of central obesity (190) and better predictors of risk for ASCVD and diabetes than weight or BMI (186, 191, 192).

Increased waist circumference has been associated with increased mortality within each BMI category (193–195).

Reduction in waist circumference by diet and/or exercise improves cardiometabolic risk factors regardless of weight loss (196–201). Measurement of waist circumference is relatively simple and can be done either at the iliac crest or midway between the level of the last rib and the iliac crest (202). Normal values vary by sex and by ethnicity. A 2020 Consensus Statement of the IAS (International Atherosclerosis Society) and the ICCR (International Chair on Cardiovascular Risk) Working Group concluded that BMI and waist circumference identify high risk better than either measurement alone (202). The consensus statement recommended the routine measurement of waist circumference in clinical practice as another vital sign that will help determine the efficacy of diet and exercise.

- 5.2 In individuals who have obesity, we suggest lifestyle measures as the first-line treatment to reduce plasma TG to lower CV and pancreatitis risk. (2⊕000)

#### Technical Remarks:

- Reductions in LDL-C and increases in HDL-C are modest compared with the decrease in TG with lifestyle measures that produce weight loss.
- Lifestyle therapy-induced changes in the lipid profile in obesity have not been shown to reduce CVD events.

#### Evidence and discussion

Weight loss can be achieved and maintained with calorie restriction, healthy diet, behavioral interventions, and physical activity. A loss of  $>$ 5% of body weight is associated with amelioration of some of the comorbidities associated with obesity. Weight loss has a greater effect on TG than LDL-C (203). The 2013 National Heart, Lung, and Blood Institute Systematic Review noted a dose–response relationship between the amount of lifestyle-related weight loss and improvement in the lipid profile in people with overweight or obesity (204). Weight loss of 3 kg was associated with TG reductions of approximately 15 mg/dL (0.17 mmol/L), whereas weight loss of 5 to 8 kg was associated with LDL-C reduction of 5 mg/dL (0.13 mmol/L) and an increase in HDL-C of 2 to 3 mg/dL (0.5 to 0.8 mmol/L). A systematic review of clinical trials in patients without ASCVD observed a similar effect of moderate weight loss (5 to 10% over 12 to 24 months) on TG levels (-16 mg/dL or 0.18 mmol/L) and a slightly greater impact on LDL (-10 mg/dL or 0.26 mmol/L) and total cholesterol (-17 mg/dL or 0.43 mmol/L), but a nonsignificant effect on HDL (+0.5 mg/dL or 0.13 mmol/L) (205).



In the LOOK AHEAD trial in patients with T2D, the intensive lifestyle intervention (including a behavioral weight-loss program,  $\geq 10\%$  group weight loss goal, calorie restriction, and increased physical activity) was compared with diabetes support and education (control group) (206). Analysis of the data over 4 years showed statistically significant differences among the intensive lifestyle and control groups in weight loss (6.2 kg and 0.9 kg, respectively), TG reduction (25.6 mg/dL and 19.75 mg/dL, respectively), and HDL-C increase (3.7 mg/dL and 2.0 mg/dL, respectively) (207). LDL-C, adjusted for medications, was reduced by about 9 mg/dL in both groups. Intensive lifestyle therapy did not reduce CVD events (HR, 0.95; 95% CI: 0.83–1.09), the primary endpoint of LOOK AHEAD, and the trial was stopped early on the basis of a futility analysis (206).

The Endocrine Society designed a protocol for a meta-analysis to assess changes in lipids and lipoproteins in adults with overweight or obesity after 6 to 12 months of weight-reducing interventions: lifestyle, pharmacotherapy (US FDA drugs approved for weight reduction plus metformin), or bariatric surgery. The meta-analysis was conducted by the Evidence Practice Center, Mayo Clinic and included 73 RCTs enrolling 32 496 patients (2). The most favorable effect of weight loss on lipids was observed in TG (Table 4). With diet, exercise, or a combination of the 2, TG were reduced by about 4 mg/dL (0.05 mmol/L) per kg of weight loss, whereas the reduction in LDL-C was -1.3 mg/dL (0.03 mmol/L) per kg of weight loss. HDL-C increases at 12 months were 0.5 mg/dL (0.01 mmol/L) per kg of weight loss.

5.3 In individuals who have obesity, we recommend the assessment of 10-year risk for ASCVD to guide the use of lipid-lowering therapy. (1 $\oplus\oplus\oplus\oplus$ )

#### Technical Remarks:

- Calculation of 10-year risk for ASCVD may be done using the Pooled Cohort Equations.
- Elevated LDL-C is predictive of CV risk.

#### Evidence and discussion

RCTs have clearly demonstrated that LDL-C reduction with statins significantly decreases major ASCVD events. Subgroup analyses consistently show that the efficacy and safety of statin therapy are similar in patients with and without obesity (123). Cholesterol management guidelines recommend statin therapy as the first pharmacological choice, and in most guidelines LDL-C is the primary target (see the “Summary of Cholesterol Treatment Guidelines” section) (31). As the decision to initiate statin treatment as adjunct to diet and exercise depends upon the 10-year risk of ASCVD, we recommend the calculation of 10-year risk in people with obesity.

5.4 In individuals who have obesity and are on pharmacological therapy for weight reduction, we suggest reassessment of the lipid profile to evaluate the risk of CVD and pancreatitis. (2 $\oplus\oplus\oplus$ )

#### Technical Remark:

- As there are no data on the timing of lipid measurements after weight loss, we suggest reassessment of lipids after 5% weight loss and periodically thereafter, when the weight is stable.

#### Evidence and discussion

Medications indicated for weight reduction, in combination with diet and exercise, have variable effects on lipids. The

**Table 4.** Change in lipids and lipoproteins (mg/dL per 1-kg weight loss) by intervention

Group	TC	95% CI	I <sup>2</sup>	TG	95% CI	I <sup>2</sup>	HDL	95% CI	I <sup>2</sup>	LDL	95% CI	I <sup>2</sup>
Lifestyle (diet, exercise, or combined)												
6 mo	-0.60	-1.17, -0.02	84.8%	-3.18	-2.19, -4.17	93.1%	0.46	0.29, 0.63	89.3%	-0.35	-0.83, 0.13	93.1%
12 mo	-1.66	-2.83, -0.50	97.4%	-4.00	-5.24, -2.77	95.3%	0.46	0.19, 0.71	91.7%	-1.28	-2.19, -0.37	95.5%
Pharmacotherapy												
6 mo	-3.29	-3.86, -2.73	41.1%	-3.54	-4.84, -2.25	99.5%	0.04	-0.21, 0.28	99.4%	-2.57	-3.73, -1.41	99.8%
12 mo	-1.69	-2.77, -0.61	95.1%	-1.25	-2.94, 0.43	83.5%	0.37	0.23, 0.52	92.9%	-1.67	-2.28, -1.06	97.3%
Bariatric surgery												
6 mo	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	-0.66 <sup>a</sup>	N/A	N/A
12 mo	-0.61	-1.04, -0.19	76.2%	-2.47	-3.14, -1.80	70.9%	0.42	0.37, 0.47	0.0%	-0.33	-0.77, 0.10	81.3%

<sup>a</sup> Insufficient data for meta-analysis. I<sup>2</sup> is a measure of heterogeneity.

Abbreviations: CI, confidence interval; HDL, high-density lipoprotein, HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.

To convert mg/dL to mmol/L for total cholesterol, LDL-C and HDL-C, divide mg/dL by 38.7. To convert mg/dL to mmol/L for TG, divide mg/dL by 88.6.

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magnitude of lipid reduction in clinical trials of 12-months duration is shown in Table 5. These data are from the meta-analysis by Hasan et al. A commonly prescribed medication, phentermine, is only approved for short-term use (up to 12 weeks) and, therefore, is not included in the table.

Medications indicated for weight management have varying contraindications and adverse effects, which must be taken into account in order to be prescribed safely (208–212). All are contraindicated in pregnancy. Contraindications, warnings, and common side effects are summarized in Table 1 in Appendix D.

With the exception of orlistat, these medications act in the central nervous system, particularly the hypothalamus. Orlistat decreases intestinal absorption of fat, thus reducing chylomicron production and TG in chylomicronemia. Case studies have reported that orlistat reduces TG in patients with monogenic LPL deficiency (213).

To date, there is no evidence that medications at the doses approved for weight reduction reduce CV mortality or morbidity in individuals with obesity. LEADER, a noninferiority, placebo, controlled trial of liraglutide that used the lower doses approved for diabetes, found that liraglutide, median dose 1.78 mg, reduced the rate of major CV events (HR 0.87, 95% CI: 0.78–0.97), with statistical significance for superiority as well as noninferiority (108). However, there is no evidence that higher-dose (3.0 mg/d) liraglutide has the same effect in patients with obesity who

do not have diabetes. Dulaglutide and semaglutide, both GLP1-receptor agonists approved for glycemic control in T2D, are both known (and indicated) to reduce CVD, as well as to cause modest weight loss, although neither is officially approved for the latter indication. A randomized CV outcome trial called SELECT is currently ongoing in patients with obesity but without diabetes, with semaglutide (2.4 mg/wk), a once-weekly GLP-1 analog (clinicaltrials.gov Identifier: NCT03574597). SGLT2, primarily indicated for glycemic control in T2D, also cause weight loss, although none is indicated for this use. Empagliflozin (111), canagliflozin (112, 214), and dapagliflozin (113) significantly reduced CV morbidity and mortality in RCTs of patients with diabetes who had or were at risk of ASCVD.

5.5 In individuals with obesity (BMI >40 or >35 kg/m<sup>2</sup> with comorbidities), who undergo bariatric surgery, we suggest measurement of the lipid profile after bariatric surgery to assess CV risk. (2⊕000)

#### Technical Remarks:

- Malabsorptive bariatric surgery procedures (eg, Roux-en-Y gastric bypass [RYGB]) are more effective than restrictive procedures (eg, banding, sleeve gastrectomy [SG]) in decreasing LDL-C levels.
- Both restrictive and malabsorptive procedures decrease TG.

**Table 5.** FDA-approved medications for long-term weight management: change in lipids (mg/dL) per 1 kg of weight loss in randomized controlled trials

Drug	Mechanism of Action	No. Trials	No. Active Treatments	Daily Dose, mg	Mean Change mg/dL per kg Weight Loss, 6 and 12 months			
					Follow-up	TG	LDL-C	HDL-C
Orlistat	Intestinal lipase inhibitor	19	3313	360	6 mo	-4.85	-2.89	-0.04
					12 mo	-1.63	-1.94	0.24
Phentermine/topiramate <sup>a</sup>	Sympathomimetic amine anorectic/antiseizure with monoamine oxidase inhibitor unknown	2	2246	3.75/23 7.5/46 15/92	12 mo	-0.83	-0.88	0.22
Naltrexone/bupropion	Opioid antagonist/norepinephrine-dopamine reuptake inhibitor	4	3088	16/360 32/360	6 mo	-1.38	-0.70	0.19
					12 mo	-2.91	-0.94	0.78
Liraglutide <sup>b</sup>	Glucagon-like-1 receptor agonist, increases satiety by action in central nervous system	2	3121	3.0, 1.8	12 mo	-1.94	-0.28	0.49

To convert mg/dL to mmol/L for total cholesterol, LDL-C and HDL-C, divide mg/dL by 38.7. To convert mg/dL to mmol/L for TG, divide mg/dL by 88.6.

<sup>a</sup> Phentermine/topiramate 15/92 mg was evaluated in 1507 subjects, 7.5/46 mg in 498 subjects, and 3.75/23 mg dose in 241 subjects.

<sup>b</sup> Liraglutide 3.0 mg is approved for weight management and was evaluated in 2910 subjects in 2 trials. Liraglutide 1.8 mg is approved for management of type 2 diabetes and was evaluated in 211 subjects in 1 trial.

Abbreviations: FDA, US Food and Drug Administration; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides. Reproduced with permission from Hasan B, Nayfeh T, Alzuabi M, et al. "Weight loss and serum lipids in overweight and obese adults: a systematic review and meta-analysis." *J Clin Endocrinol Metab.* 2020;105(12) (2)

- Reassess lipid profile 1 to 3 months after bariatric surgery and periodically thereafter and when weight is stable.

### Evidence and discussion

Guidelines recommend consideration of bariatric surgery in people with BMI  $\geq 40$  kg/m<sup>2</sup> or BMI  $\geq 35$  kg/m<sup>2</sup> and 1 or more weight-related comorbidities, who have not achieved sufficient weight loss following lifestyle and behavioral treatment, with or without pharmacotherapy (203). In the observational Swedish Obese Subjects (SOS) study, bariatric surgery was associated with significant reductions in CV death (HR, 0.47;  $P = 0.002$ ) and CV events (MI or stroke; HR, 0.67;  $P < 0.001$ ), respectively (215). In a matched, observational cohort of people with obesity and T2D in Sweden, RYGB was associated with a reduction in the risk of fatal and nonfatal MI by 49% (HR, 0.51; 95% CI: 0.29–0.91) and CV death by 59% (HR, 0.41; 95% CI: 0.19–0.90) (216). A meta-analysis has confirmed that bariatric surgery is associated with significantly reduced CV-related mortality (217, 218).

SG and RYGB lead to significant body-weight reduction and improvement of metabolic comorbidities, including dyslipidemia. Improvement in the lipid profile is not related to the amount of weight loss but rather to the type of surgery (219). Although SG and RYGB decrease TG and increase HDL-C to a similar extent, reduction in plasma LDL-C is more pronounced after a malabsorptive procedure (RYGB, biliopancreatic diversion) than a restrictive (SG, gastric banding) procedure (220, 221). The effect of malabsorptive surgery on LDL-C reduction was confirmed in the meta-analysis designed by the Endocrine Society (Table 6). These clinical observations suggest that the underlying cellular and

molecular mechanisms that modulate LDL-C metabolism may differ between bariatric procedures (222).

A prospective observational study of 1156 patients with severe obesity found a large weight loss (mean 35 kg) at 12 years in 418 patients who had undergone RYGB surgery and remission of diabetes in 51% of 84 patients (223). Mean reductions in LDL-C and TG from baseline in the surgical group were 11.0 mg/dL (0.28 mmol/L) and 62.8 mg/dL (0.71 mmol/L), respectively, at 12 years. HDL-C increased by 12.9 mg/dL (0.33 mmol/L). These changes in lipid parameters are consistent with the 1-year data (mg/dL change per kg of weight loss) in the Endocrine Society meta-analysis (Table 6).

## 6. Thyroid disease

Hypothyroidism is characterized by the relative or absolute reductions in serum levels of thyroxine (T4). Serum levels of total or free triiodothyronine (T3), however, are not reliable markers of hypothyroidism. Thyroid-stimulating hormone (TSH) is elevated in primary hypothyroidism. However, TSH is typically low or inappropriately normal in central hypothyroidism, which may be caused by pituitary disease (secondary hypothyroidism) or hypothalamic disorders (tertiary hypothyroidism). Patients with nonthyroidal chronic illness can have decreased serum levels of T3, T4, and TSH, and generally lack hypothyroid symptoms. Patients with generalized thyroid hormone resistance usually have high concentrations of T3 and T4, with inappropriately normal or elevated TSH and variable degrees of hypothyroid and hyperthyroid symptoms. Subclinical hypothyroidism is characterized by normal T3

**Table 6.** Serum lipid changes (mg/dL) per 1-kg weight loss according to bariatric procedure

Group	TC	95% CI	I <sup>2</sup>	TG	95% CI	I <sup>2</sup>	HDL	95% CI	I <sup>2</sup>	LDL	95% CI	I <sup>2</sup>
Banding												
12 mo	-0.75	-1.97, 0.47	N/A	-6.03	-8.31, -3.76	N/A	0.43	0.18, 0.68	N/A	0.89	-0.42, 2.19	N/A
Sleeve gastrectomy												
12 mo	0.02	-0.46, 0.51	N/A	-2.43	-3.44, -1.42	N/A	0.46	0.35, 0.58	N/A	0.17	-0.30, 0.64	N/A
Malabsorptive bariatric surgery (RYBP + BPD)												
6 mo	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	-0.66 <sup>a</sup>	N/A	N/A
12 mo	-0.73	-1.21, -0.26	77.2%	-2.13	-2.72, -1.54	58.4%	0.41	0.36, 0.47	0.0%	-0.54	-1.02, -0.07	82.3%
RYBP												
6 mo	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	-0.66 <sup>a</sup>	N/A	N/A
12 mo	-0.62	-1.17, -0.07	75.1%	-2.23	-3.04, -1.43	66.7%	0.42	0.36, 0.48	0.0%	-0.38	-0.83, 0.07	74.8%
BPD												
12 mo	-1.12	-1.51, -0.72	N/A	-2.01	-2.64, -1.39	N/A	0.38	0.25, 0.50	N/A	-1.12	-1.56, -0.68	N/A

Abbreviations: BPD, biliopancreatic diversion; CI, confidence interval; HDL, high-density lipoprotein, HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; RYBP, Roux-en-Y gastric bypass; TG, triglycerides.

<sup>a</sup> Data not sufficient for meta-analysis. I<sup>2</sup> is a measure of heterogeneity. To convert mg/dL to mmol/L for total cholesterol, LDL-C and HDL-C, divide mg/dL by 38.7. To convert mg/dL to mmol/L for TG, divide mg/dL by 88.6.

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and T4, with an elevated TSH (<10 mIU/L) and few, if any, symptoms attributable to hypothyroidism.

Complicating these diagnoses are data suggesting that euthyroid elderly patients have higher TSH values that continue to rise with increasing age and are especially notable as patients reach and continue through their 9<sup>th</sup> decade (224). The significance of this is unclear, but there may be a genetic component, since children of nonagenarians with elevated TSH have higher TSH levels than age-matched controls (225).

Thyroid dysfunction has major effects on lipoprotein metabolism. Hypothyroidism is associated with reduced LDL receptors, reduced cholesterol 7 alpha-hydroxylase, low cholesterol ester transfer protein, and decreased lipoprotein lipase, which, together, may lead to an elevation in total cholesterol, TG, LDL-C, and apoB. High-density lipoprotein cholesterol has been reported to increase, remain unchanged, or decrease. One study found increased HDL-C in hypothyroid patients, but reduced cholesterol efflux (226). Increased LDL oxidation has also been demonstrated (227–229). Hypothyroid patients often have elevated Lp(a) and apoB. These lipid abnormalities, along with reduced endothelial function and hypercoagulability, may contribute to an increased risk of atherosclerosis in patients with hypothyroidism (230).

In overt hyperthyroidism, total cholesterol and LDL-C are decreased, while TG are normal and HDL-C is unchanged or decreased (see Table 1). The effects of thyroid hormone on lipid metabolism have been reviewed (231). Thyroid hormone stimulates hepatic clearance of cholesterol by increasing biliary secretion (232). The increase in bile acids reduces the cholesterol in the liver, which results in compensatory increase in hepatic cholesterol synthesis and the uptake of cholesterol to restore hepatic cholesterol. Thyroid hormone diminishes the intestinal absorption of dietary cholesterol (233), increases LDL receptor number (234), and increases HMGCoA mRNA, protein, and activity (235, 236). Thyroid hormone also stimulates LDL receptor gene synthesis (237) and increases the activity of enzymes that metabolize lipoproteins, including hepatic lipase, LPL, cholesteryl ester transfer protein (CETP), and lecithin cholesterol acyltransferase (LCAT) (238–242).

6.1 In patients with hyperlipidemia, we recommend ruling out hypothyroidism as the cause of the hyperlipidemia before treatment with lipid lowering medications. (1⊕⊕⊕⊕)

**Technical Remark:**

- Hypothyroidism can elevate both cholesterol and TG levels, which improve with treatment.

6.2 In patients with hyperthyroidism, we recommend re-evaluating the lipid panel after the patient becomes euthyroid. (1⊕⊕⊕⊕)

**Technical Remark:**

- Changes in LDL-C have been observed as early as 3 months after the patient is euthyroid.

**Evidence and discussion**

Hyperthyroidism, unless transient, such as in thyroiditis, results in decreased levels of total and LDL-C (231) as well as reduced HDL-C, Lp(a), apoA-1, and apoB (243). The effects on TG are variable (231). Thyroid hormones affect lipid metabolism by several mechanisms, as addressed earlier. The Endocrine Society performed a meta-analysis of the results of 23 randomized and 144 nonrandomized clinical trials that evaluated cholesterol and TG concentrations in patients with thyroid disorders before and after treatment. In patients with overt hyperthyroidism, treatment with antithyroid medication, surgery, or radioiodine significantly increased total and LDL-C and HDL-C, but the increase in TG was not statistically significant (Table 7) (1). Treatment of subclinical hyperthyroidism did not alter lipid parameters. Recent studies suggest that control of hyperthyroidism may lead to BMI values that exceed premonitory levels. Therefore, it is prudent to re-assess not only the lipid profile, but other factors that increase CV risk at that point (244, 245).

6.3 In patients with overt hypothyroidism, we suggest against treating hyperlipidemia until the patient becomes euthyroid in order to more accurately assess the lipid profile. (2⊕○○○)

**Evidence and discussion**

Abundant data dating back over a century demonstrate that overt hypothyroidism is associated with dyslipidemia. Descriptive and randomized controlled studies show that LT4 treatment is effective in lowering elevated serum lipid levels (246). However, few studies examined the time course of this association regarding either the development or the recovery of dyslipidemia with the development or the correction of hypothyroidism.

Some data suggest that coronary disease is more likely in patients with hypertension and hypothyroidism than in patients with hypertension who are euthyroid (230). In elderly patients living in nursing homes, a study found a higher rate of clinical coronary disease in patients with hypothyroidism compared with euthyroid controls (247). Whether this observation is due to dyslipidemia, the associated

autoimmunity, or other effects of hypothyroidism could not be determined. Conversely, the clinical effects of hypothyroidism in patients with coronary disease are complex. Hypothyroidism decreases cardiac work and oxygen demand but decreases cardiac contractility, often resulting in worsened angina. However, classic studies more than a half-century ago found evidence that general surgery can be safely performed in patients with hypothyroidism.

In patients with hyperlipidemia, several studies have shown the prevalence of preexisting overt hypothyroidism to be between 1.4% and 13%. In a retrospective chart review of over 4000 patients with newly diagnosed hyperlipidemia and who had a serum TSH determined, 3% had moderate elevations of TSH (>5 mIU/L) and 1.7% had a TSH over 10 mIU/L (248). The Cardiovascular Health Study, however, found no association of subacute or overt hypothyroidism with either increased CV outcomes or with mortality (249).

In the Endocrine Society-planned meta-analysis of clinical trials that evaluated the effects of treatment of thyroid disease on lipid parameters, total cholesterol, LDL-C, HDL-C, and TG decreased in patients with overt hypothyroidism

treated with LT4 (Table 8) but were not significantly changed in patients treated with a combination of LT4 and T3 (1).

6.4 In patients with SCH (TSH <10 mIU/L) with associated hyperlipidemia, we suggest considering thyroxine treatment as a means of reducing LDL levels. (2⊕000)

#### Technical Remark:

- Take into consideration the patient's age and general health, the possibility of suppression of TSH, and whether the patient has CVD.

#### Evidence and discussion

Prior clinical trials of people with SCH (TSH 4 to 10 mIU/L) treated with T4 compared with placebo and a meta-analysis of these trials have failed to show any benefit in terms of thyroid-related symptoms, fatigue, depressive symptoms, and/or quality of life (250). However, the meta-analysis performed for this guideline showed an 11 mg/dL reduction in LDL-C in patients with SCH treated with T4. The impact of T4 replacement on long-term CV outcomes is unknown. Among

**Table 7.** Effect of treatment of overt hyperthyroidism on lipid parameters

Lipid Parameter	Baseline Lipid Parameter Mean, mg/dL (95% CI)	Postintervention Change in Lipids Mean, mg/dL (95% CI)	Number of Studies
Total cholesterol	158.7 (153.6, 163.9)	44.4 (37.7, 51.0)	31
LDL-C	89.2 (76.7, 101.6)	31.1 (24.3, 37.9)	29
HDL-C	46.5 (43.0, 49.9)	5.5 (1.5, 9.6)	32
TG	110.1 (99.7, 120.4)	7.3 (−0.5, 15.1)	30

Treatment includes antithyroid medication, surgery, or radioiodine. To convert mg/dL to mmol/L for total cholesterol, LDL-C, and HDL-C, divide mg/dL by 38.7. To convert mg/dL to mmol/L for TG, divide mg/dL by 88.6.

Abbreviations: CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.

From Kotwal A, Cortes T, Genere N, et al. "Treatment of thyroid dysfunction and serum lipids: a systematic review and meta-analysis." *J Clin Endocrinol Metab.* 2020;105(12) (1)

**Table 8.** Effect of thyroxine replacement on lipid parameters in overt and subclinical hypothyroidism

Population	Lipid Parameter	Baseline Lipid Parameter, mg/dL (95% CI)	Postintervention Change in Lipids, mg/dL (95% CI)	Number of Studies
Overt hypothyroidism	Total cholesterol	260.3 (252.8, 267.7)	−58.4 (−64.7, −52.1)	72
	LDL-C	168.8 (161, 176.5)	−41.1 (−46.5, −35.7)	55
	HDL-C	54.3 (51.5, 57.1)	−4.1 (−5.7, −2.6)	57
	TG	147.3 (139.4, 155.3)	−27.3 (−36.6, −17.9)	60
Subclinical hypothyroidism	Total cholesterol	217.4 (212.1, 222.6)	−12.0 (−14.5, −9.6)	79
	LDL-C	139.5 (134.3, 144.7)	−11.1 (−13.1, −9.0)	74
	HDL-C	51.8 (50.1, 53.5)	0.15 (−0.89, 1.9)	76
	TG	124.5 (115.8, 133.1)	−4.5 (−7.9, −1.2)	76

To convert mg/dL to mmol/L for total cholesterol, LDL-C and HDL-C, divide mg/dL by 38.7. To convert mg/dL to mmol/L for TG, divide mg/dL by 88.6.

Abbreviations: CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.

From Kotwal A, Cortes T, Genere N, et al. "The effect of treatment of hyper- and hypothyroidism on serum lipids: a systematic review and meta-analysis." *J Clin Endocrinol Metab.* 2020;105(12) (1)



the studies included in the meta-analysis, 82% defined SCH as normal T4 and TSH 5–10 mIU/L. In 18% of the studies, T4 was normal and TSH levels were in the range of 10 to 20 mIU/L.

Descriptive studies of populations with SCH generally support the concept that such patients have lipid abnormalities, although the data are not uniform. Several groups have reported higher levels of total cholesterol and LDL-C in individuals with SCH compared with euthyroid subjects and even in patients with TSH values <10 mIU/L (251–253). However, other studies find elevations only in those with TSH >10 mIU/L (254). Generally, lipid levels decrease after treatment with LT4, although the time course of improvement is not stated.

In the Endocrine Society meta-analysis of patients with SCH, total cholesterol, LDL-C, and TG were reduced after LT4 treatment, but the magnitude of these changes was less in comparison to patients with overt hypothyroidism (Table 8). In patients with SCH who were not treated with LT4, lipids did not change over time.

The relationship of SCH and other indices of CVD risk and clinical events have been studied with varying results based on age and degree of TSH elevation. A retrospective study found fewer ischemic events in patients younger than 70 years of age with SCH and who had their TSH levels normalized, but not in older patients (255).

The risk of MI was found to be increased in postmenopausal women with SCH (256). A 2017 meta-analysis found increased CV events in patients with TSH values >10 mIU/L and a nonstatistically significant increase in patients with TSH >7 mIU/L (257). A meta-analysis of almost 3500 adults with SCH (TSH 4.5 to 19.9 mIU/L) found no increased risk of stroke vs age- and sex-adjusted pooled HRs across all groups, but did find a significant increased risk in people younger than 65 years of age (258). In a comparison of subgroups with TSH 4.5 to 6.9 mIU/L, 7 to 9.9 mIU/L, and 10–19.9 mIU/L, fatal stroke increased with higher TSH levels but the trend was not significant. A meta-analysis of individual participant data from 11 prospective studies in 55 287 adults (over a half-million person-years) including 3450 adults with SCH found an increased risk of CVD in patients with TSH 10 to 19.9 mIU/L but not in those with lower levels of TSH (259). CHD mortality was increased in patients with TSH 10 to 19.9 mIU/L and 7 to 9.9 mIU/L, although only statistically significant in the higher TSH group (259). Several, generally small, studies of SCH have also found higher levels of c-reactive protein (CRP), Lp(a), and cIMT when compared with age- and gender-matched controls (260, 261).

The precise clinical value of L-triiodothyronine (LT3) treatment in reducing elevated lipids remains unclear. Daily therapy with LT3 alone reduced total cholesterol

in doses that did not normalize TSH. A cross-over study of LT4 versus LT3 therapy continued to normalization of TSH found lower cholesterol levels in the LT3 arm (262). Nevertheless, The American Thyroid Association guidelines do not recommend targeting high-normal T3 levels or low-normal TSH levels in people with hypothyroidism who also have dyslipidemia (263). An RCT of moderate vs weight-related higher LT4 doses combined with LT3 found that higher levels of serum-free T4 were associated with lower total and LDL-C (264).

The American Thyroid Association guidelines do not recommend the routine use of combinations of LT4 and LT3 therapy specifically to improve the lipid profile. Likewise, genetic testing is not currently recommended for clinical identification of patients with type 2 deiodinase gene polymorphisms to guide possible combination therapy. Nor is there a recommendation for monotherapy with LT3 in hypothyroid patients with significant dyslipidemia (263).

## 7. Excess Glucocorticoids

- 7.1 In adult patients with Cushing syndrome, we recommend monitoring the lipid profile in order to identify cases of dyslipidemia. (1⊕⊕OO)

### Technical Remark:

- Monitor lipid profile at the time of diagnosis and periodically afterwards at the discretion of the treating physician.

### Evidence and discussion

Dyslipidemia is a common metabolic abnormality in Cushing syndrome, although precise estimates of the prevalence are difficult to obtain because the definitions and cutoffs for dyslipidemia vary across studies, and the criteria also vary across lipid guidelines over time. Patient cohorts reported in Cushing studies are relatively small, and the reference populations used for comparison may or may not be matched for BMI (265). Estimates for the prevalence of dyslipidemia in active Cushing disease range from 38% to 71% (266). The dyslipidemia in Cushing syndrome is characterized by elevated plasma total cholesterol and TG due to increased circulating VLDL and LDL particles (267), and variable levels of HDL-C (268, 269). Dyslipidemia severity can be influenced by the severity and duration of hypercortisolemia, presence of diabetes, and degree of visceral obesity.

The pathophysiology of dyslipidemia in glucocorticoid excess is complex and incompletely understood, involving both direct and indirect effects of glucocorticoids on liver

and adipose tissue (267). Patients with Cushing syndrome have increased hepatic synthesis and secretion of VLDL and also demonstrate increased visceral fat distribution compared with controls (270, 271). Although short-term increases in glucocorticoids stimulate lipolysis, proadipogenic effects are more prominent in chronic hypercortisolism. Glucocorticoids stimulate preadipocyte differentiation and inhibit adenosine monophosphate (AMP)-activated protein kinase (AMPK) in visceral adipose tissue, leading to increased lipogenesis and fat storage. Glucocorticoids stimulate AMPK in the liver, promoting fatty acid and cholesterol synthesis, and contributing to development of hepatic steatosis (272).

Patients who achieve successful remission of Cushing syndrome after treatment do experience improvement in dyslipidemia and other CV risk factors such as obesity, hypertension, and diabetes (273). However, these risk factors persist after cure in a significant proportion of patients (274). Therefore, patients may require monitoring and treatment for dyslipidemia after successful biochemical remission of Cushing disease.

### Lipid-lowering therapy in Cushing syndrome

7.2 In adults with persistent endogenous Cushing syndrome, we suggest statin therapy, as adjunct to lifestyle modification, to reduce CV risk irrespective of the CV risk score. (2⊕○○○)

#### Technical Remarks:

- LDL-C should be the primary target, and therapy should be considered if LDL-C is over 70 mg/dL (1.8 mmol/L).
- Patients receiving mitotane therapy for Cushing syndrome commonly develop secondary dyslipidemia from therapy.
- Lipid-lowering therapy may not be appropriate for patients with limited life expectancy, such as those with an underlying malignancy.

7.3 In adults with cured Cushing syndrome, we advise the approach to CV risk assessment and treatment be the same as in the general population. (Ungraded Good Practice Statement)

### Evidence and discussion

Chronic hypercortisolism due to Cushing syndrome is associated with the development of MetS with hypertension, insulin resistance, dyslipidemia, a prothrombotic state, and visceral obesity, which may increase the risk of ASCVD. Patients with active Cushing disease have a high prevalence of hypertension (55% to 85%), obesity (32% to 41%), and diabetes mellitus (20% to 47%) (266). A long-term follow-up study and meta-analysis of patients with Cushing disease

demonstrated that overall mortality is 2.2-fold greater than in the general population (275). CVD (MI, stroke) is the most common cause of death in Cushing syndrome (276). In a cohort study of 343 patients with Cushing syndrome evaluated over the pre- and postdiagnosis and treatment periods, the risk of MI (HR, 3.7; 95% CI, 2.4–5.5) and stroke (HR, 2.0; 95% CI, 1.3–3.2) were increased (277). Patients with Cushing syndrome who achieve remission generally have much better outcomes compared with those with persistent disease, with a standardized mortality ratio of 1.2 (95% CI: 0.45, 3.18) compared with 5.50 (95% CI: 2.69, 11.26) in those with persistent disease (275). A small study of patients younger than 45 years of age who achieved long-term remission of Cushing syndrome had evidence of subclinical coronary atherosclerosis on cardiac CT imaging (30%, 3/10,  $P = 0.01$ ) compared with age- and gender-matched controls (0%, 0/20) (278).

Several medications used for the treatment of Cushing syndrome have important effects on lipids. Ketoconazole is an imidazole derivative that inhibits several key enzymes in cortisol biosynthesis. Ketoconazole is also an inhibitor of cholesterol biosynthesis, and treatment can lead to an approximately 25% reduction in apoB and LDL-C levels (267). Importantly, ketoconazole is a potent inhibitor of cytochrome P450 3A4 (CYP3A4) and can markedly increase plasma levels of certain statins, specifically simvastatin, lovastatin, and, to a lesser extent, atorvastatin. This can significantly increase the risk of myotoxicity from statin therapy. Therefore, statins not metabolized by the CYP3A4 system (including fluvastatin, pravastatin, and rosuvastatin) should be used when cholesterol-lowering therapy is required in the setting of ketoconazole therapy.

Mifepristone, a glucocorticoid-receptor antagonist, has been shown to improve glycemic control, diastolic blood pressure, and weight in patients with endogenous Cushing syndrome. After 24 weeks of mifepristone treatment, mean HDL-C was significantly reduced by  $14.2 \pm 11.9$  mg/dL ( $0.37 \pm 0.31$  mmol/L) from a mean baseline of  $62.3 \pm 27.8$  mg/dL ( $1.6 \pm 0.72$  mmol/L); there were no statistically significant changes in LDL-C or TG (279). Weight loss achieved with mifepristone treatment persisted for 2 additional years in patients who remained on therapy (280).

Pasireotide, a somatostatin analogue, has been shown to significantly decrease cortisol levels in Cushing disease. A phase 3 double-blind trial of pasireotide administered subcutaneously twice daily in patients with Cushing disease reported significant reductions in systolic and diastolic blood pressure, weight, and LDL-C ( $-15$  mg/dL [ $-0.4$  mmol/L]; 95% CI,  $-23$  to  $-8$  mg/dL [ $-0.6$  to  $-0.2$  mmol/L]) (281). Another phase 3 trial of a longer acting formulation of pasireotide, administered once a month, also found a reduction in blood pressure and weight, but LDL-C levels were not reported (282). In both studies, the use of pasireotide

was associated with a significant increase in hyperglycemia, HbA1c, and in some cases new diabetes.

Mitotane, a diphenylmethane derivative that acts as a mitochondrial toxin in adrenal tissue, has been used for the treatment of adrenal cortical carcinoma and refractory Cushing syndrome. The drug also inhibits cortisol synthesis through the inhibition of multiple enzymes (283). Mitotane use commonly causes an increase in cholesterol and TG levels, with maximal changes in cholesterol occurring 1 to 5 months after drug initiation (284). Mitotane can increase cholesterol levels by over 60%, but this can be successfully managed with statin therapy (265). Mitotane is a lipophilic agent that binds to lipoproteins in serum, and such binding inhibits the activity of mitotane in vivo, suggesting that the lipoprotein-free fraction is the more active form. It has been suggested that statins, by decreasing the lipoprotein-bound fraction, might increase mitotane efficacy in patients with adrenocortical carcinoma (284).

### Values and preferences

The advice to offer statin therapy to reduce CV risk in adult patients with persistent Cushing syndrome places higher value on the consistent evidence of excess CV morbidity and mortality in Cushing syndrome, and the long-term safety and efficacy of LDL-lowering therapy with statins in the general population of patients with dyslipidemia, hypertension, diabetes, and obesity. There are no RCTs of statins or other lipid-lowering therapies evaluating CV outcomes specifically in patients with persistent Cushing syndrome or cured Cushing syndrome. As with treatment of CV risk factors in general, performing an individualized risk assessment with shared decision-making is prudent for determining the most appropriate treatment for individual patients.

### Lipid management in chronic glucocorticoid therapy

7.4 In adults receiving chronic glucocorticoid therapy above replacement levels, we suggest the assessment and treatment of lipids and other CV risk factors because of the increased risk of CVD. (2⊕000)

#### Technical Remark:

- Effects of glucocorticoid therapy on lipids and CV risk will vary based on the dose of glucocorticoid, duration of treatment, and underlying disease/indications.

### Evidence and discussion

The literature on the prevalence of glucocorticoid therapy-induced dyslipidemia (elevated total and LDL-C and TG) is conflicting, with 1 large study demonstrating no clear

association (285) and another in patients with hypopituitarism on glucocorticoid replacement demonstrating a dose-dependent effect on total cholesterol, LDL, and TG levels (286). The effects of exogenous glucocorticoid therapy on lipid metabolism are influenced by many factors, including dose and route of administration, duration of therapy, underlying medical conditions, and concurrent medications.

Several observational studies have found a significant association between chronic glucocorticoid therapy and the risk of ASCVD. A cohort study of patients in the United Kingdom compared people who were prescribed systemic glucocorticoids and who also had a diagnosis of iatrogenic Cushing syndrome (n = 547) with those prescribed glucocorticoids without a diagnosis of iatrogenic Cushing syndrome (n = 3231) and those not prescribed systemic glucocorticoids (n = 3282) (287). A multivariate analysis adjusted for age, sex, intensity of glucocorticoid use, underlying disease, smoking status, anticoagulant use, and therapies for diabetes, hypertension, and dyslipidemia showed a strong relationship between iatrogenic Cushing syndrome and CV events: adjusted HR, 2.27 (95% CI, 1.48–3.47) for CHD and 3.77 (95% CI, 2.41–5.90) for heart failure. A nested case-control study of over 50 000 patients with at least 1 prescription for oral or non-systemic glucocorticoid therapy found an increased risk of ischemic heart disease (OR, 1.20; 95% CI, 1.11–1.29) (288). However, it is unclear if the estimated increased risk was clinically important, given the nested case-control design. A second cohort study with over 68 000 glucocorticoid users compared with over 82 000 nonusers showed a risk-adjusted RR of CV events of 2.56 (CI, 2.18–2.99) in patients receiving high-dose glucocorticoids (289). Another nested case-control analysis of a large cohort found that users of higher dose glucocorticoids (equivalent to >10 mg of prednisolone per day) had a greater risk of acute MI compared to nonusers (OR, 2.15; 95% CI, 1.45–3.14) (290). Robust tools for estimating ASCVD event risk related to chronic glucocorticoid therapy are lacking. However, the QRISK3 10-year CV risk prediction algorithm developed in the United Kingdom has recently incorporated corticosteroid use as a clinical variable in its risk prediction algorithm (291).

The effects of glucocorticoid-replacement therapy regimens on CV risk factors have also been explored in patients with adrenal insufficiency (292). A study of 2424 patients with hypopituitarism found a dose-dependent increase in mean serum total cholesterol, TG, LDL-C, and BMI in patients receiving glucocorticoid doses equivalent to ≥20 mg per day of hydrocortisone, compared with patients without central adrenal insufficiency and those receiving doses equivalent to <20 mg per day of hydrocortisone (286). The

risks of overreplacement of glucocorticoids are becoming better appreciated. However, there are currently no studies that clearly delineate the optimal glucocorticoid regimen in terms of metabolic profile and ASCVD risk.

### Values and preferences

There are a lack of high-quality clinical outcome studies evaluating the effect of lipid therapy on ASCVD outcomes specifically in Cushing syndrome as well as in patients taking glucocorticoids chronically. Evaluating CV risk associated with chronic glucocorticoid therapy is complicated by the wide variability in the CV risks of the underlying conditions that are being treated with glucocorticoid therapy, dose and duration of glucocorticoid therapy, and the presence of other ASCVD risk factors in the population. The advice to assess and treat dyslipidemia and other risk factors places higher value on the observational evidence that chronic glucocorticoid therapy is a relevant marker of increased CV risk and should be a consideration when engaging patients in shared decision-making regarding the benefits and risks of lipid-lowering therapy.

## 8. Disorders of growth hormone secretion

### Adult growth hormone deficiency

Adult GHD is a distinct syndrome and may be the result of prior childhood GHD, structural lesions, trauma, or idiopathic in etiology. GHD is the most common endocrine abnormality in patients with hypopituitarism. Hypopituitarism with complete or partial failure of secretion of 1 or more pituitary hormones may arise from specific gene mutations or may be related to sellar tumors, such as pituitary neoplasms or craniopharyngioma, or infiltrative/inflammatory disorders, radiation, or traumatic brain injury. Adult-onset hypopituitarism is generally permanent and heterogeneous, requiring replacement.

8.1 In adults with GHD, we recommend obtaining a lipid profile at diagnosis to assess for dyslipidemia. (1⊕⊕⊕⊕)

### Evidence and discussion

GHD adversely affects the lipid profile (293–296). Adults with GHD commonly develop dyslipidemia characterized by elevated plasma total cholesterol and LDL-C; effects on TG and HDL-C are variable (293, 297–301). Increased small dense LDL-C particles have been observed (299, 302) and, in 1 study, increased postprandial remnant lipoproteins, which decreased after GH replacement (303). There are no consistent alterations in apoB, apoA-1, or Lp(a) levels (293, 297, 299).

GH increases the expression of hepatic LDL receptors and reduces PCSK9 expression (304–306); GH treatment of GHD adults has been shown to decrease plasma LDL-C levels by increasing clearance of LDL and apoB-100 (307–309) and VLDL. GHD results in body composition changes with decreased lean body mass and increased visceral adiposity, a phenotype associated with increased insulin resistance and dyslipidemia (296). Insulin resistance is considered a low-grade inflammatory state, and increased CRP levels and interleukin-6 levels have been observed in GHD (310).

8.2 In adults with GHD associated with hypopituitarism, we suggest assessment and treatment of lipids and other CV risk factors. (2⊕○○○)

### Technical Remarks:

- LDL-C should be the primary target.
- Consider therapy if LDL-C is over 70 mg/dL (1.8 mmol/L).

### Evidence and discussion

Hypopituitarism is associated with an increased risk of premature mortality when compared to age- and sex-matched controls (311–315). Mortality is increased in both men and women with adult GHD, but rates are higher in women (312, 316, 317). Age is also a risk factor, with standardized mortality ratios higher in younger individuals compared with older adults. Evidence suggests that patients with adult GHD have an increased risk of CV morbidity and mortality. Hypopituitarism with deficiency of GH and other pituitary hormones is associated with a reduced life expectancy, and a 2-fold higher risk of CV death compared with healthy individuals (315, 318). Observational studies have found increased MI and CV mortality in patients with hypopituitarism on conventional replacement therapy (314, 319). Increased coronary artery calcifications and cIMT have been observed in patients with GHD (320, 321). GHD may have direct adverse effects on the myocardium and endothelium, and indirect effects mediated through increased CV risk factors, hypercoagulability, decreased exercise performance, and/or reduced pulmonary capacity (322). Although GHD has been hypothesized as a contributor to the excess CV mortality in hypopituitarism, the exact mechanisms remain unclear.

The technical remark to consider lipid-lowering therapy if LDL-C is above 70 mg/dL is a suggestion. There are no RCTs showing a reduction in ASCVD events in patients with GHD and associated hypopituitarism. However, as discussed previously, evidence from numerous RCTs of statins shows that ASCVD benefit is based upon the absolute amount of LDL-C reduction and the baseline risk



of the patient. Trials of statins in combination with either ezetimibe or PCSK9 antibodies show that reduction in LDL-C to 55 mg/dL and to 40 mg/dL is beneficial in patients at high risk of ASCVD.

- 8.3 In adult patients with GHD, we recommend against using GH replacement solely to lower LDL-C to reduce CV risk. (1⊕⊕⊕O)

#### Evidence and discussion

Long-term GH replacement improves the lipid profile in patients with GHD, with a decrease in total cholesterol and LDL-C, no change or increase in HDL-C, and no change in TG levels (300, 323–330). The reduction in LDL-C is much smaller than that achieved with statin therapy, and LDL particle size may remain unchanged (302). Treatment with GH increases apoA and Lp(a) levels (331–334).

In observational studies GH replacement is associated with improvement in cIMT (335, 336). There is no evidence to suggest that GH-replacement therapy decreases mortality in men and women (337). One study in GHD patients on long-term GH-replacement therapy observed a decreased risk of nonfatal stroke in both men and women (338). Small non-randomized studies have observed decreased CV events in individuals on GH-replacement therapy (319, 339), strong data are lacking.

A single observational study has shown that the addition of GH to statin therapy in hypopituitary patients is associated with an additive LDL-C reduction (340). Whether the increase in Lp(a) levels that occurs with GH therapy enhances CVD risk is unknown.

In summary, GH replacement results in a small reduction in LDL-C, which is of a much lower magnitude compared with the reduction observed with statins. There is insufficient evidence to show that GH replacement has a beneficial effect on ASCVD outcomes. Therefore, we do not recommend GH replacement solely for reducing LDL-C or ASCVD risk in patients with GHD. Assessment of ASCVD risk and therapy should be based on ASCVD risk factors.

#### Growth hormone excess (acromegaly)

- 8.4 In adults with acromegaly, we suggest measurement of the usual lipid profile before and after treatment of GH excess. (2⊕OOO)

#### Evidence and discussion

Acromegaly is characterized by chronic GH hypersecretion, commonly due to a somatotroph pituitary adenoma. Exposure to excess GH is associated with 2- to 3-fold increase in mortality and morbidity (341) manifested as

hypertrophic cardiomyopathy, diastolic and systolic dysfunction, hypertension, arrhythmias, valvular diseases, and/or accelerated atherosclerosis. Metabolic complications such as T2D and associated dyslipidemia can also occur. Whether the risk of ASCVD in acromegaly is increased needs further investigation.

GH exerts an overall lipolytic effect, inducing the hydrolysis of TG to FFAs and glycerol. GH inhibits hepatic lipase and LPL activity, and lipid abnormalities in GH excess may be related to decreased activity of these lipases (342, 343). GH also modulates tissue response to insulin, and insulin resistance and glucose intolerance may be seen in acromegaly. These alterations can contribute to hypertriglyceridemia in patients with acromegaly. Increased CETP activity has been observed in active acromegaly (343), whereas decreased CETP and LCAT activity were demonstrated in another small cohort (344). The most common lipid abnormality in acromegaly is mild-to-moderate hypertriglyceridemia (342, 344). Effects of GH excess on plasma cholesterol levels are variable (345). Increased small, dense LDL particles can occur despite lower LDL-C levels (343, 346). HDL-C levels may be unchanged or reduced. One study showed increased apolipoprotein E (apoE) or apoA-1 levels compared with controls (347), whereas another found no differences in apoA-1 or apoB levels (348).

Several studies have examined changes in lipids after surgical and medical treatment of acromegaly. After surgery, TG returned to normal, and total and LDL-C remained unchanged (349–351). Treatment of acromegaly with octreotide reduced TG and LDL-C and increased HDL-C (346, 352), but had no effect on plasma lipids when administered after surgery (353). Even incomplete biochemical improvement (characterized by inadequate GH suppression after oral glucose tolerance test or absence of normalization of insulin-like growth factor 1 levels) appeared to be sufficient to improve total cholesterol, LDL-C, TG, and Lp(a) levels compared with pretreatment levels (354). GH-receptor antagonist therapy with pegvisomant increased TG levels in healthy men (355) and increased total and LDL-C levels in patients with acromegaly (356, 357).

Elevated levels of Lp(a) are associated with an increased risk of ASCVD. Lp(a) levels may be higher in individuals with acromegaly compared with controls without acromegaly, and may decrease after surgical treatment or somatostatin analog therapy (346–349, 358, 359). A study of patients with acromegaly found that mean Lp(a) was significantly reduced from 39.5 mg/dL before surgery to 28 mg/dL after surgery in patients who achieved remission (350). However, in the group of patients with persistent acromegaly after surgery, mean Lp(a) (52 mg/dL before surgery) did not significantly change after surgery.



## 9. Polycystic ovary syndrome

PCOS is a complex phenotypically heterogeneous disorder in women of reproductive age characterized by hyperandrogenism, ovulatory dysfunction, and/or polycystic ovarian morphology. Metabolic abnormalities, primarily insulin resistance and compensatory hyperinsulinemia, are evident in many affected women (360–362).

### Lipid abnormalities

- 9.1 In women with PCOS, we recommend obtaining a fasting screening lipid panel at diagnosis to assess CV risk. (1⊕⊕⊕O)

#### Technical Remarks:

- PCOS is associated with CV risk factors.
- Conduct a lipid screening both before and intermittently during hormonal therapy.
- In PCOS, hypertriglyceridemia is the most common lipid abnormality.

#### Evidence and discussion

Dyslipidemia is very common in women with PCOS and occurs in up to 70% of US women with this diagnosis (363). Lipid metabolism in PCOS is altered by a multitude of factors and is not fully explained by visceral obesity alone (364, 365). Several patterns of dyslipidemia have been described, but women with PCOS often exhibit an atherogenic lipid profile, similar to that in diabetes and MetS, characterized by increased TG, low HDL-C, and normal or increased LDL-C; qualitative alterations include increased small, dense LDL particles (365–375). These characteristic lipid changes occur throughout the reproductive span from early adulthood, persist after menopause, and appear to be driven by visceral adiposity, insulin resistance (374, 376, 377), hyperandrogenism (378–380), and/or genetic and environmental factors (373, 381, 382). Studies have found no alterations in apoB levels in women with PCOS, reduced apo A-1 levels (368), higher concentrations of Lp(a), especially in nonobese women with PCOS (369, 383, 384), and decreased cholesterol efflux capacity (385).

Women with ovulatory PCOS show a milder atherogenic lipid profile or normal lipids compared with those with anovulatory PCOS (384, 386). Lean women with PCOS may have only low HDL-C levels, whereas those with obesity also have elevations in TG (387). The prevalence of elevated LDL-C levels above 100 mg/dL (2.6 mmol/L) ranges between 24% and 40% (365, 388, 389) and occurs irrespective of body weight (373).

### Cardiovascular risk

ASCVD risk in women with PCOS has been hard to characterize and is potentially conferred by the existence of metabolic dysfunction driven primarily by underlying insulin resistance. Women with PCOS often have ASCVD risk factors, such as abdominal obesity, and components of MetS with underlying insulin resistance. Insulin resistance may occur independently of obesity and is usually severe in women with hyperandrogenism and chronic anovulation. In the United States, up to 80% of women with PCOS are obese (390); however, outside of the United States, the prevalence of obesity is estimated to be 50% (391). MetS is also more common in women with PCOS compared with BMI-comparable women without PCOS, and has been shown to be 2- to 5-fold higher in women with PCOS than without (374). Based on the National Cholesterol Education Program Adult Treatment Panel III criteria, 34% to 46% of US Caucasian women with PCOS have MetS (392). Several studies have evaluated CVD risk factors. Early reports suggested that women with PCOS might have an increased CVD risk (393), but subsequent small studies have not confirmed this (394–396). There are no long-term prospective studies assessing CVD risk in PCOS, and evidence for increased CVD morbidity and mortality in women with PCOS remains inconclusive (397).

Based on existing data, our recommendation is to screen all women with PCOS with a lipid profile at the time of diagnosis. Additional screening for CV risk factors, such as family history of premature or early CVD, cigarette smoking, impaired glucose tolerance/T2D, hypertension, or obstructive sleep apnea is important to stratify risk in these women (389, 398).

### Effect of treatment of PCOS on lipids

Lifestyle changes in women with PCOS, recommended as the first line of therapy, result in improvements in body composition, hyperandrogenism, insulin resistance, and ovulation but, overall, appears to have minimal to no impact on lipids (399–402). The effect of metformin on lipid levels in women with PCOS appears to be variable. Oral contraceptives (OCPs) containing estrogen increase TG levels. This increase may be substantial in genetically susceptible individuals who may have high TG before taking OCPs and may lead to pancreatitis. Estrogen is also associated with an increase in HDL-C and a decrease in LDL-C ranging from 5% to 20% (403).

In women who do not desire conception, statin therapy may be considered based on risk factors, with lower LDL-C

goals in those with MetS, T2D, or overt vascular or renal disease (389).

- 9.2 In women with PCOS, we suggest against using lipid-lowering therapies to treat hyperandrogenism or infertility. (2⊕○○)

#### Evidence and discussion

Large-scale clinical studies of statins in women with PCOS, either as monotherapy or in combination with other therapies, are very limited. Statins are effective in decreasing total cholesterol and LDL-C in women with PCOS, with no evidence of effect on HDL-C when compared with placebo or OCPs (404–408). Significant TG reduction has been observed in all these studies. There are currently no long-term studies evaluating the effect of statins on CV outcomes in women with PCOS.

There is a small but increasing body of evidence that statins may improve testosterone levels in women with PCOS. Treatment with atorvastatin has been shown to decrease biochemical hyperandrogenism in these women (404, 405, 409), but the evidence is not sufficient to recommend the use of statins for reducing androgens. In addition, statins are contraindicated in pregnancy, and adequate contraception is essential for women of reproductive age taking statins. Small studies have evaluated the use of metformin in combination with simvastatin or placebo and found similar reductions in testosterone and luteinizing hormone (LH) levels (410, 411). Treatment with simvastatin alone has been shown to be more effective in decreasing testosterone levels, hirsutism, menstrual irregularity, and ovarian volume compared with the use of metformin alone or in combination therapy with simvastatin (412, 413). Antiandrogenic effects have not been demonstrated with ezetimibe (414). Inhibition of ovarian theca-interstitial cell proliferation and steroidogenesis in vitro due to reduced availability of testosterone precursors thought to be related to statin therapy have been proposed as possible mechanisms (415–417).

Data on the effects of statins on insulin sensitivity and glucose tolerance in women with PCOS are conflicting. Several, although not all, studies demonstrated a worsening of insulin resistance in women treated in the statin arm (405, 408, 418). Therefore, because PCOS is already a risk factor for diabetes, we suggest not using statin therapy to decrease androgen levels in women with PCOS until clear evidence is available.

There is limited to no evidence for use of statins as adjunct therapy during in vitro fertilization procedures; therefore, it is not recommended (419).

## 10. Menopause and hormonal replacement

- 10.1 In postmenopausal women, we recommend treating dyslipidemia with statin therapy rather than hormone therapy. (1⊕⊕○○)

#### Technical Remarks:

- Hormone therapy increases the risk of cardiovascular disease, specifically venous thromboembolism and stroke. However, the absolute risk of cardiovascular disease is lower in younger compared to older postmenopausal women.
- Hormone therapy is described as estrogen ± progesterone/a progestin.

#### Evidence and discussion

Estrogen has a role in the metabolism of TG, cholesterol, and fatty acids in the liver through a variety of mechanisms. Estrogen has been shown to increase VLDL synthesis, upregulate the LDL receptor, and improve insulin sensitivity in the liver (420). The changes in lipid and lipoprotein levels across menopause are relatively small, and variable results are reported in different studies. In general, there is a shift towards a more atherogenic profile with a predominance of smaller, denser LDL particles, decreases in HDL-C, and increases in total cholesterol levels postmenopause compared to premenopause. Surgically-induced menopause triggers an abrupt drop in estrogen levels (421–423). The increase in LDL-C levels postmenopause may be due to increases in PCSK9 (424), although any possible clinical or pathophysiological significance of this is unknown, and postmenopausal women have not been described to have any uniquely strong response to PCSK9-inhibitory monoclonal antibodies.

The treatment of postmenopausal symptoms may involve the use of estrogen with or without progesterone or a progestin. Oral estrogen therapy increases HDL-C by up to 15% and decreases LDL-C by up to 20%. Transdermal estrogen has similar effects on lipid levels but generally less of a change in lipid levels compared with oral estrogen. Progestins tend to decrease HDL-C levels, thus the use of combined estrogen and progesterone (required for the prevention of adverse endometrial effects) tends to blunt lipid changes compared with estrogen alone (425, 426).

Estrogen may dramatically increase TG levels in patients with an underlying predisposition to hypertriglyceridemia, which could trigger acute pancreatitis. This risk of postmenopausal hormone therapy-induced pancreatitis appears to be limited. A population-based case-control study examining postmenopausal hormone therapy use and pancreatitis found no significant increase in the risk of pancreatitis among current or former users of estrogen

or combined estrogen/progestins compared to nonusers (427); however, there are many reports of estrogen-induced hypertriglyceridemia and pancreatitis (428, 429).

For years, observational and case-control studies suggested that hormone therapy for menopause reduced CVD; however, 2 large RCTs (HERS [430] and WHI [431] concluded that hormone therapy, specifically oral conjugated equine estrogens 0.625 mg plus medroxyprogesterone acetate 2.5 mg, or oral conjugated equine estrogens 0.625 mg alone, increased CVD (CHD events and nonfatal MI as well as venous thromboembolism and stroke), especially when given to older women (>10 years after age of menopause) (432, 433). In the WHI trials of conjugated equine estrogen (CEE), either alone or in combination with medroxyprogesterone acetate (MPA), increased CHD (nonfatal MI or coronary death) risk was found with CEE + MPA at one year (HR 1.80; 95% CI, 1.08–2.99), but was lower or neutral with time. In post-intervention follow up, CHD events were elevated with CEE + MPA, and reduced with CEE compared to placebo, but not statistically significant (433). In both trials, in the intervention phase, stroke (usually ischemic), deep vein thrombosis, and total cardiovascular events were significantly increased, although the risk was lower in younger women (433). Thus, hormone therapy increases the risk of CVD, especially if started late (>age 60 years or >10 years postmenopause).

A meta-analysis found that hormone therapy significantly reduces CVD in younger, but not older women (434). A Cochrane Database systematic review concluded that hormone therapy in postmenopausal women has no benefit on CVD risk and potential harm (largely due to the risk of thromboembolic events and stroke) (435). We do not recommend the use of hormone therapy to treat dyslipidemia. Although this guideline focuses on treatment of lipid disorders to reduce CVD risk, and does not make recommendations regarding HT for postmenopausal women, the literature suggests that HT may be appropriate for treatment of menopausal symptoms such as hot flashes, night sweating, and disrupted sleep, especially in relatively healthy younger postmenopausal women.

10.2 In postmenopausal women on hormone therapy and with other risk factors for CVD, we recommend statin therapy to reduce CV risk. (1⊕⊕⊕⊕)

**Technical Remarks:**

- Hormone therapy increases the risk of cardiovascular disease, specifically venous thromboembolism and stroke. However, the absolute risk of cardiovascular disease is lower in younger compared to older postmenopausal women.

- Hormone therapy is described as estrogen ± progesterone/a progestin.
- Menopause may be associated with an increase in LDL-C and a decrease in HDL-C.
- Risk factors may be traditional risk factors or risk-enhancing factors.

**Evidence and discussion**

Although postmenopausal hormone therapy appears to increase CVD risk when started >10 years after menopause, it decreases that risk when started <10 years postmenopause. The use of statins in postmenopausal women has beneficial effects on CVD risk, including women both using and not using hormone therapy (436). A post hoc analysis of the HERS trial found that statin use was associated with lower rates of CVD events (437). Furthermore, a nested case-control study suggested that statin use may attenuate the increased thromboembolic risk seen with hormone replacement therapy in menopause (438). It is important to note that a large share of even newly postmenopausal women have sufficient CVD risk to warrant serious consideration of statin therapy. Further, prior or concurrent initiation of statin treatment appears to blunt or even eliminate the trend towards increased CVD soon after the initiation of estrogen therapy, and it appears to potentiate any beneficial CVD effect associated with hormone therapy (439). Thus, in women using hormone therapy, we recommend the use of lipid-lowering therapy to reduce CVD risk.

10.3 In women who enter menopause early (<40 to 45 years old), we recommend assessment and treatment of lipids and other CV risk factors. (1⊕⊕⊕⊕)

**Technical Remarks:**

- Early menopause enhances CVD risk.
- ASCVD risk should be calculated and followed after menopause.

**Evidence and discussion**

Several studies have reported that a younger age at menopause predicts CVD independently of traditional risk factors (440–443). Kryczka and colleagues report that adding early menopause (≤3 years from onset) to the 10-year atherosclerotic disease risk estimator and to the systematic coronary risk evaluation (SCORE) model significantly improves their predictive value (444). In an analysis of pooled individual data from 15 observational studies in 5 countries, the risk of ASCVD, including MI, angina, and stroke, was 1.5-fold higher in women with premature menopause (<40 years) and 1.3-fold higher in women with early

menopause (40 to 44 years) compared with women who experienced menopause at age 50 to 51 years (443). These data are consistent with another study of pooled individual participant data, which found an inverse relationship between age at menopause and coronary heart disease events (445). Thus, we recommend the assessment of lipids and other CVD risk factors and use of lipid-lowering therapy to reduce CVD risk in women who enter menopause early, defined as younger than age 40–45 years.

## 11. Hypogonadism and testosterone replacement and abuse

The lipid profile in men with hypogonadism may show increased LDL-C and TG, and low HDL-C (150, 446, 447). Replacement doses of testosterone have minor effects on circulating lipids in men with low testosterone (448). Men with hypogonadism, however, have increased CVD risk, but the reasons for this may be multiple. Low levels of testosterone are associated with low levels of HDL-C and elevated TG, as well as insulin resistance, increased waist circumference, increased FFAs, and other features of the MetS. Testosterone replacement has been shown to improve insulin sensitivity (449–451). In contrast to the doses of testosterone used for replacement, higher-dose androgens, often used to increase muscle mass, lead to profound effects on circulating lipids. Although testosterone therapies to improve well-being or athletic performance are often done illicitly, some patients will have such treatments prescribed by their doctors.

- 11.1 In patients with low testosterone levels, we suggest testosterone therapy as symptomatically indicated, and not as an approach to improve dyslipidemia or CVD risk. (2⊕⊕OO)

### Evidence and discussion

The effects of androgens on circulating lipoproteins levels have been studied in the setting of replacement therapies and with the use of illicit body building and athletic-enhancing drugs. Replacement doses of testosterone have been found to have either minimal effects on lipids (reduction in LDL-C and TG, or decrease in HDL-C) or no effect (448). One study comparing different forms of replacement found no change in circulating lipids (452).

Pending the results of additional long-term studies, the potential adverse effects of testosterone replacement on CVD are concerning. The use of these agents, which have limited but beneficial effects on sexual function and mood (453), should alert the clinician to more aggressively control other risk factors and consider a lower goal for LDL reduction.

- 11.2 In patients with low HDL (<30 mg/dL [0.8 mmol/L]), especially in the absence of hypertriglyceridemia, we advise clinical or biochemical investigation of anabolic steroid abuse. (Ungraded Good Practice Statement)

### Technical Remark:

- Supraphysiological doses of androgens will reduce HDL-C levels.

### Evidence and discussion

Effects of androgens on lipids are most evident with supraphysiologic hormone usage. Exuberant use of androgens, often taken for athletic enhancement, lowered HDL by >50% to a mean level of 23 mg/dL (0.6 mmol/L) and raised LDL >50% to 188 mg/dL (4.9 mmol/L) (454). These effects were shown to reverse several months after the discontinuation of anabolic steroids (454–456). Other effects of androgenic anabolic steroids include increased apoB, and decreased Lp(a) (457).

Androgens, especially testosterone, are activators of hepatic lipase, an enzyme that hydrolyzes phospholipids in HDL, assists with the clearance of small VLDL and converts LDL into small, dense LDL. For this reason, anabolic steroids markedly suppress HDL-C levels and sometimes also raise TG (150, 458).

## 12. Gender-affirming hormone therapy

- 12.1 In transwomen and transmen who have taken or are taking gender-affirming hormone therapy, we advise assessing CV risk by guidelines for nontransgender adults. (Ungraded Good Practice Statement)

### Technical Remark:

- There are no data to guide the selection of a gender marker in risk calculators for individuals on gender-affirming hormone therapy.

### Evidence and discussion

Studies of lipid changes in transgender individuals are limited. Several studies of testosterone therapy for transgender males reported a reduction in HDL and an increase in TG levels (150, 457, 459). Similarly, a meta-analysis found significant increases in TG and LDL-C, significant reductions in HDL-C, and no change in total cholesterol in transmen taking hormonal therapy (460). The estimated increase in TG was 9 and 21 mg/dL (0.1 and 0.2 mmol/L) at 3 to 6 months and ≥24 months of therapy, respectively, and the increase in LDL-C was 11 and 17.8 mg/dL (0.3 and



0.5 mmol/L) at 12 and  $\geq 24$  months, respectively. HDL-C was reduced at all time points (-6.5 mg/dL [-0.2 mmol/L], -8.1 mg/dL [-.2 mmol/L], and -8.5 mg/dL [-0.2 mmol/L]). These estimates were associated with wide 95% CIs and only a small number of studies had data at the earliest and latest time points. In transwomen, the only lipid parameter with a significant change was TG, which increased by an estimated 31.9 mg/dL (0.4 mmol/L) (95% CI, 3.9–59.9) at  $\geq 24$  months. Triglycerides were increased in transwomen taking oral estrogens, but not in transwomen treated with transdermal estrogen.

There is a paucity of data evaluating CVD and CVD risk in transmen and transwomen. In the meta-analysis described above, there were too few CV events to make an assessment (460). Although it appears that mortality is increased in individuals taking gender-affirming hormone therapy compared with the general population, the increased mortality is due in part to suicides, acquired immunodeficiency syndrome (AIDS), and drug abuse. CVD death was increased only in current but not past users of ethinyl estradiol (461). In the absence of any further data, we suggest assessing ASCVD risk per usual guidelines. The choice of which gender flag to use in the risk assessment is unknown.

### 13. Considerations for implementation of the guidelines

This section provides a brief overview of lifestyle measures and the efficacy and safety of medications for hypercholesterolemia and hypertriglyceridemia.

#### Lifestyle therapy

A healthy diet and physical activity are essential components of a treatment plan for dyslipidemia to prevent or reduce ASCVD (35, 462, 463). Information on lifestyle modifications for the reduction of LDL-C and TG can be found in the 2013 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk (464). Food groups for a healthy diet include vegetables, fruits, legumes (lentils, beans, peas, chickpeas), whole grain cereals, bread, low fat dairy products (skimmed milk, low-fat yogurt), low-fat poultry without skin, lean and oily fish without the skin, nontropical vegetable oils, and nuts. The dietary components may be modified for individuals with diabetes or other disorders that benefit from nutrition therapy, and the calories may be adjusted for maintenance of weight loss or for weight reduction. Calories from saturated fat should constitute no more than 5% to 6% of the total calorie count and should avoid trans-fat. Sodium restriction

**Table 9.** Statins: LDL-C reduction by dose and major drug interactions

Statin	Estimated Percent of LDL-C Reduction by Dose			Major Drug Interactions <sup>a</sup>
	High intensity, $\geq 50\%$	Moderate intensity, 30–50%	Low intensity, $< 30\%$	
Atorvastatin	<b>40 mg, 80 mg</b>	<b>10 mg, 20 mg</b>	–	Gemfibrozil should be avoided in all statins
Rosuvastatin <sup>b</sup>	<b>20 mg, 40 mg</b>	<b>5 mg, 10 mg</b>	–	Clarithromycin, itraconazole, colchicine, cyclosporine, niacin
Simvastatin	–	<b>20 mg, 40 mg</b>	10 mg	Cyclosporine, darolutamide, niacin
Pravastatin	–	<b>40 mg, 80 mg</b>	<b>10 mg, 20 mg</b>	Verapamil, diltiazem, amlodipine, macrolide antibiotics, amiodarone, dronedarone, antifungal azoles, nefazadone, danazol, ranolazine, colchicine, cyclosporine, daptomycin, niacin
Pitavastatin	–	<b>1 mg, 2 mg, 4 mg</b>	–	Macrolide antibiotics, colchicine, cyclosporine
Lovastatin	–	<b>40 mg, 80 mg</b>	<b>20 mg</b>	Erythromycin, rifampin, colchicine, niacin
Fluvastatin	–	<b>40 mg BID</b>	20 mg, 40 mg	Verapamil, diltiazem, amiodarone, dronedarone, macrolide antibiotics, antifungal azoles, nefazadone, danazol, ranolazine, colchicine, cyclosporine, niacin

Bold font represent drugs and doses specifically studied in CVD outcome trials that demonstrated significant reduction in vascular events (123, 467)

Abbreviations: CVD, cardiovascular disease, HIV, human immunodeficiency virus; LDL-C, low-density lipoprotein cholesterol.

<sup>a</sup> Some of the drugs listed require a reduction in statin dose of some statins and should be avoided in others. Macrolide antibiotics include clarithromycin, erythromycin and telithromycin. Azole antifungals include itraconazole, ketoconazole, posaconazole, and voriconazole. All statins have varying interactions with HIV protease inhibitors and other antiretroviral medications, and hepatitis C protease inhibitors (142). For more information on interactions and dose limitations, see product labeling and Newman et al. 2019 “Statin Safety and Associated Adverse Events: A Scientific Statement from the American Heart Association” (142).

<sup>b</sup> Due to increased rosuvastatin plasma concentrations in Asian patients, initiation with the 5 mg dose is suggested.

From the prescribing information of Parke-Davis Div of Pfizer, Inc. 2020, SciGen Pharmaceuticals 2020, NuCare Pharmaceuticals, Inc. 2020, PD-Rx Pharmaceuticals, Inc. 2020, Kowa Pharmaceuticals America, Inc. 2009, Teva Pharmaceuticals USA, Inc. 2020, Mylan Pharmaceuticals, Inc. 2020 (468–474).



to 2 g daily is recommended for those with high blood pressure. The DASH diet and the AHA diet use this general approach. Reductions in TG are usually greater than reductions in LDL-C. Reduced risk of ASCVD has been demonstrated with the Mediterranean diet supplemented with extra virgin olive oil or nuts in the PREDIMED randomized trial in high-risk subjects with no history of ASCVD (465).

US government guidelines recommend a total of 150 to 300 minutes a week of moderate intensity aerobic physical activity, or 75 to 150 minutes a week of vigorous exercise, as well as resistance training at least twice a week for adults (466). These recommendations also apply to older adults, who should add balance training. Studies of the effects of physical activity on lipids are inconsistent (466). The 2018 Physical Activity Guidelines Advisory Committee concluded, from a review of meta-analyses and individual studies, that physical activity decreased LDL-C by 2.5 to 6.0 mg/dL (0.1 to 0.2 mmol/L) but had no consistent effect on TG (466).

#### Pharmacological treatment for LDL-C reduction: statins

Statins are the first line of pharmacological treatment as adjunct to diet and exercise to reduce LDL-C (Table 9). Statins reduce LDL-C by inhibiting HMG-Co A reductase, which controls the rate-limiting step in the cholesterol synthesis pathway, thereby reducing LDL-C synthesis, which leads to upregulation of LDL receptors. Numerous long-term RCTs of a median duration of 5.1 years, and meta-analyses of these trials have proven that statins reduce atherosclerotic vascular events in patients with and without ASCVD by 22% per mmol/L (38.6 mg/dL) reduction in LDL-C (123). The decision to start a statin depends upon the LDL-C level and the ASCVD risk of the patient, taking into account risk-enhancing factors, potential risks and benefits, and patient preference. Assessment of 10-year ASCVD risk in adults with an LDL-C of 70 to 190 mg/dL (1.8 to 4.9 mmol/L) and without a history of ASCVD should be done by the AHA/ACC Pooled Cohort Equations calculator. The choice of a moderate or high-intensity statin is dependent upon the ASCVD risk of the patient and the baseline LDL-C. In many guidelines, LDL-C is the target of therapy. Specific goals for LDL-C (<130 mg/dL [3.4 mmol/L], <100 mg/dL [2.6 mmol/L], <70 mg/dL [1.8 mmol/L], <55 mg/dL [1.4 mmol/L]), which are risk dependent, are recommended in some guidelines (462, 463, 475, 476). However, the 2018 ACC/AHA guideline for cholesterol management recommends monitoring the percentage of the reduction in LDL-C and specifies a threshold for LDL-C in high-risk patients (LDL-C 70 mg/dL [1.8 mmol/L]), which, when exceeded, warrants intensification of statin treatment and possibly the addition of a nonstatin drug (35).

The use of statins in patients over the age of 75 years has been debated. Data published in 2019 from a participant-level meta-analysis of 28 RCTs (median duration 4.9 years) in 186 854 participants (including 14 483 older than 75 years at randomization) found a significant 21% RR reduction in major vascular events per every 1.0 mmol/L (38.7 mg/dL) reduction in LDL-C in adults older than 75 years at randomization (477). This RR reduction did not differ among the 6 subgroups by age ( $\leq 55$ , 56 to 60, 61 to 65, 66 to 70, 71 to 75, and >75 years). These data suggest a benefit in continuing statin therapy in adults over the age of 75 who have an intermediate or high risk of ASCVD, and the consideration of using a moderate intensity statin at a lower dose, or a low intensity statin. Factors to consider in older patients are polypharmacy, potential drug interactions, mental health, the prognosis of other diseases, and the wishes of the patient.

#### Non-statin LDL-C-lowering medications

Nonstatin medications (Table 10) are useful when, despite lifestyle changes and maximally tolerated statin therapy, more LDL-C reduction is needed.

The first medication to consider as adjunct to statin treatment is ezetimibe 10 mg, which is an inhibitor of the critical mediator of cholesterol absorption in the intestine, the Niemann-Pick-C1-like 1 receptor. This receptor is also expressed in the liver. Ezetimibe is generally used with a statin.

For additional LDL-C reduction in patients taking a statin, subcutaneous injection (every 2 weeks or once a month) of monoclonal antibodies to PCSK-9 (alirocumab and evolocumab) may be used either with the statin or with the statin plus ezetimibe. These medications block the effects of PCSK9 (a proprotein convertase) on degradation of LDL receptors in the liver. They are indicated as adjunct to diet, and either alone or in combination with other lipid lowering medications, for reducing CV events in people with ASCVD, and for reducing LDL-C in patients with FH (eg, heterozygous FH). Evolocumab also has an indication as adjunct to diet and lipid-lowering medications for treatment of homozygous FH. The cost of PCSK9 inhibitors may be prohibitive for some patients.

If more LDL-C reduction is desired in patients taking maximally tolerated statin therapy and ezetimibe, and cost or intolerance of injections prevent the use of monoclonal antibodies to PCSK9, a bile acid sequestrant may be added provided that TG are below 500 mg/dL (5.6 mmol/L). Bile acid-binding resins include colestipol, cholestyramine, and colesevelam, which are generally used in combination with a statin or a statin and ezetimibe. Bile acid sequestrants lower cholesterol by binding to bile acids in the gastrointestinal (GI) tract, preventing their absorption, thereby

**Table 10.** Medications for additional LDL-C reduction in patients taking statins (maximal tolerated doses)

Medication	Mechanism of Action	Dose for LDL-C Reduction	LDL-C Reduction	Major Drug Interactions
Ezetimibe	Binds to Nieman Pick N1L1 receptor and prevents absorption of cholesterol from GI tract	10 mg daily	15–20%	Cyclosporine, fenofibrate, fibrates, cholestyramine
Alirocumab <sup>a</sup>	Prevents degradation of LDL receptor by inhibiting PCSK9	75 mg every 2 wks or 300 mg every 4 wks	56–61% on background of statin	None known
Evolocumab <sup>a</sup>	Prevents degradation of LDL receptor by inhibiting PCSK9	140 mg @ 2 wks subcutaneously or 420 mg subcutaneously once monthly	63–71% on a background of a statin; 41–45% on background of statin + ezetimibe	None known
Cholestyramine	Bile acid sequestrant	8–16 g daily in divided doses, once or twice a day starting with 4 g	12–25%	When given concomitantly with warfarin, thiazide diuretics, thyroxine, estrogens and progestins, tetracycline, phenobarbital, penicillin G, acetaminophen, phosphate supplements
Colesevelam	Bile acid sequestrant	1250–1875 mg by mouth two times daily	15–18%	When given concomitantly with oral contraceptives, levothyroxine, warfarin, glimepiride, glipizide, phenytoin
Bempedoic acid	ATP citrate lyase inhibitor, inhibitor of cholesterol synthesis	180 mg by mouth daily	18% on a background of a statin	Limit simvastatin to 20 mg, pravastatin limit to 40 mg, cyclosporine

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; ATP, adenosine triphosphate; CVD, cardiovascular disease; FH, familial hypercholesterolemia; GI, gastrointestinal; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; N1L1, N1-linker 1; PCSK9, proprotein convertase subtilisin/kexin type 9.

<sup>a</sup> Alirocumab and evolocumab are indicated to reduce the risk of ASCVD events in patients with established CVD. They are also indicated as adjunct to diet alone, or in combination with other lipid-lowering therapies to reduce LDL-C in patients with primary hyperlipidemia (eg, heterozygous FH). Evolocumab is also approved alone in combination with other lipid-lowering therapies in patients with homozygous FH who require additional lowering of LDL-C. The other medications in this table are not indicated to reduce ASCVD events.

From the prescribing information for NuCare Pharmaceuticals, Inc. 2020, Esperion Therapeutics 2020, Ohm Laboratories Inc. 2020, Sanofi-Aventis, U.S. LLC 2018, Amgen Inc. 2017, Eon Labs 2020, Daiichi Sankyo 2020 (470, 478–483). All medications are to be used as adjunct to diet and exercise.

increasing hepatic synthesis of bile acids, which reduces the amount of cholesterol in the liver. Reduced hepatic cholesterol leads to the upregulation of LDL receptors.

Bempedoic acid is an adenosine-triphosphate citrate lyase inhibitor approved by the US FDA in 2020 for use as an adjunct to diet and maximally tolerated statin therapy in adults with heterozygous FH or established ASCVD, who require additional reduction in LDL-C (478). The effect of bempedoic acid on CV morbidity and mortality has not been determined but is under investigation.

### Treatment for hypertriglyceridemia

In patients with elevated TG, initial management includes the identification and treatment of secondary factors that raise TG, and the initiation or adjustment of lifestyle therapy. Secondary factors include endocrine

diseases discussed in this guideline, chronic liver and kidney disease, and medications (estrogens, glucocorticoids, mitotane, tamoxifen, raloxifene, bile acid resins, protease inhibitors, retinoids, hydrochlorothiazide, propranolol, metoprolol, cyclosporine, tacrolimus, phenothiazine, aripiprazole, olanzapine, quetiapine, and risperidone). For patients with persistent elevation in TG up to 500 mg/dL (5.6 mmol/L) per day, statins are the first choice of pharmacological therapy as adjunct to lifestyle changes. A fibrate may also be used with the caution that the combination of a fibrate and a statin increases the risk of myopathy. This risk is more common with gemfibrozil compared with fenofibrate (see “Hypertriglyceridemia: Fibrates” section). In addition, as noted in this guideline, EPA ethyl ester is recommended to reduce ASCVD risk in statin-treated patients with TG of 150–499 mg/dL

(1.7–5.6 mmol/L), and either ASCVD or T2D and 2 additional risk factors (76).

The risk of pancreatitis increases with TG > 500 mg/dL (5.6 mmol/L) and is even greater as TG rise to 1000 mg/dL (11.3 mmol/L) or higher. Diet and exercise, and the treatment of secondary factors, may lower TG. However, if TG reduction is not sufficient, pharmacological therapy (statin, fibrates, or omega-3 fatty acids) should be considered.

Patients with TG levels of about 1000 mg/dL (11.3 mmol/L) or greater may have 1 or multiple genetic mutations, and a greater sensitivity to medications and other secondary factors that increase TG. Monogenetic hypertriglyceridemia, such as LPL deficiency, is rare and is often diagnosed in childhood or adolescence. For such extreme elevations in TG, a diet with very low-fat content, as little simple sugar as possible, and no alcohol may reduce TG. The addition of fibrates or omega-3 fatty acids may be useful. Niacin also reduces TG but has safety concerns (see “Hypertriglyceridemia: Niacin” section).

## Safety of lipid-lowering medications

### Hypercholesterolemia

#### Statins

When using any medication, the possibility of adverse events must be considered. The safety of the statin class of medications has been reviewed (125, 142, 484). Therefore, the most serious safety considerations will be described here.

#### Myopathy/rhabdomyolysis

The hallmark serious adverse effect of statins is myopathy (incidence <0.1%), defined here and in the prescribing information for most statins as unexplained muscle pain or weakness (or other muscle symptoms such as stiffness or cramping), with creatine kinase (CK) elevation >10 times the upper limits of normal (ULN) (142, 485). As women generally have lower CK levels than men (486, 487), if a sex-adjusted normal range is not used, myopathy may present in women at lower-fold elevations in CK. African American women have similar CK levels compared with non-Hispanic white men, and African American men have higher CK levels compared with non-Hispanic white men.

The time from initiation of statin treatment to myopathy varies and may occur years after statin initiation. When CK levels are extremely high, such as above 10 000 IU/L or greater than 40 times ULN, rhabdomyolysis, which is a severe form of myopathy, should be considered.

Rhabdomyolysis may be associated with renal impairment, including acute renal failure and myoglobinuria, but not in all cases. This is a medical emergency. Information on the presentation and treatment of statin-induced rhabdomyolysis can be found in *Endocrine and Metabolic Medical Emergencies: A Clinician's Guide, Second Edition* (488). Myopathy is rare, with incidence <0.1% for most statins and 1% for simvastatin 80 mg, a dose no longer used (489). The incidence of rhabdomyolysis is even lower at <0.01%.

Possible risk factors for myopathy/rhabdomyolysis include older age (490, 491), female sex, diabetes, Chinese ancestry (490), renal insufficiency, pre-existing muscle disease, hypothyroidism, and drug interactions. The mechanism of myopathy is not known.

In a patient with unexplained muscle symptoms, CK levels will distinguish nonserious muscle symptoms from myopathy. In patients with myopathy, discontinuation of the statin usually results in resolution of muscle symptoms within days, and reduction in CK, which returns to normal within 2 to 3 weeks. If rhabdomyolysis is suspected, intensive hydration is usually effective in preventing renal failure (492). Other causes or precipitating factors of myopathy should be considered and interacting medications discontinued, if possible (488).

About 10% of patients stop statin use because of adverse symptoms, not necessarily caused by the statin, and are often labeled statin intolerant (493, 494). The most common symptoms are muscle weakness or pain, and these are usually not accompanied by increases in CK. Statin-associated muscle symptoms are caused by the statin in <1% of patients, as demonstrated by large, long-term, placebo, controlled CVD outcome trials (495, 496) and meta-analyses of these trials (125, 497). In the 2016 meta-analysis of 12 statin CVD outcome studies in 97 000 subjects, myalgia or muscle ache occurred in 5162 (11.7%) participants allocated statins versus 5015 (11.4%) participants allocated placebo ( $P = 0.10$ ) (125). In 4 double-blind, placebo-controlled, randomized trials of statins that specifically queried muscle symptoms, none found a statistically significant difference in muscle symptoms between statin and placebo groups, using the intention-to-treat analyses (496, 498–500). In an electronic database review, 90% of statin-intolerant patients tolerated the same or a different statin when re-challenged (494), and, in 2 RCTs, in patients labeled statin intolerant (493, 501), the vast majority could tolerate a statin under double-blind conditions. These data taken together suggest that the intolerance is not pharmacologic in most patients.

Members of the Writing Committee sought to incorporate the patient's voice into this guideline by developing and administering a brief survey about CVD and statin

use in collaboration with a patient advocacy organization who helped us identify members with diabetes. Although the response rate to the survey was low, some of the information was of interest. Of 348 patients who answered the survey, 67% were female, the majority were age 50 years and older, 62% were affected with T1D and 38% with T2D, and approximately 6% recorded that they had a history of heart attack. Nearly two-thirds were taking a statin as prescribed, but an additional one-quarter of these patients were not taking a statin, although it had been recommended by their doctor. The reasons for not taking a statin were largely related to concerns about side effects, including muscle aches and muscle disease, memory loss, and liver disease. Of patients taking a statin as prescribed, about one-third reported side effects, largely muscle aches. These data are consistent with the medical literature but should be interpreted with caution because they are observational and from a survey with a low response rate.

#### New-onset diabetes

Randomized-controlled trials and meta-analyses of RCTs show that statins increase the risk of newly diagnosed diabetes mellitus (143, 144, 502, 503), most commonly in patients with multiple risk factors for diabetes (146, 503), with an absolute risk of about 0.2% per year depending upon the baseline risk of the population (143, 144). The mechanisms are not fully known. Despite the increased risk of newly diagnosed diabetes, statins still have a favorable benefit/risk ratio, even in patients predisposed to develop diabetes, and are usually continued in those patients who develop new diabetes (see Section 3, “Type 2 Diabetes Mellitus”).

#### Hepatic adverse events

Statins, which act in the liver, cause confirmed, dose-related, asymptomatic elevations in hepatic transaminases greater than 3 times ULN, with elevation in alanine aminotransferase (ALT) greater than aspartate aminotransferase (AST), in up to 1% of patients in clinical trials (127, 504), but these patients usually do not develop severe liver disease (505). Studies including an RCT in patients with chronic liver disease, show that statins are safe in patients with nonalcoholic fatty liver disease, including those with modest elevations in transaminases (<3 times ULN) (506, 507). Therefore, statins may be safely initiated when needed for LDL-C and/or CV risk reduction in individuals with transaminase elevations up to 3 times ULN and/or other evidence of hepatic steatosis.

Severe liver injury (hepatotoxicity) is extremely rare (508–510), estimated to occur in about 1 in 100 000 patients

(509) and not detectable in clinical trials. Monitoring of ALT and AST does not prevent severe liver disease (505).

#### Steroidogenesis

Although statins inhibit HMG-CoA reductase, the rate-limiting enzyme in the cholesterol synthesis pathway, studies of lovastatin, simvastatin, and pravastatin show that these statins do not have a clinically significant effect on steroid hormone synthesis, although some evidence suggests that statins reduce androgen levels in patients with PCOS, as discussed previously. Hormones evaluated include cortisol, adrenocorticotropic hormone (511–513), basal or human chorionic gonadotropin (HCG)-stimulated testosterone, free testosterone index, sex hormone-binding globulin (SHBG), LH, or follicle-stimulating hormone (FSH) (514). In 1 small trial, simvastatin 80 mg, a dose no longer recommended, reduced bioavailable testosterone in 81 men by 10% compared with placebo, but not total or free testosterone, FSH, LH, SHBG, or the response to HCG (513).

Because statins are contraindicated in pregnancy and recommended for use in women of reproductive age only if they use contraception and are very unlikely to conceive, few studies have examined the effect of statins on gonadal function in women. Simvastatin 40 mg compared with placebo in a double-blind RCT in normal cycling premenopausal women had no effect on the menstrual cycle or progesterone synthesis (515).

#### Nonstatin therapies

##### Monoclonal antibodies to proprotein convertase subtilisin/kexin type 9

The most common adverse effect of evolocumab and alirocumab is injection site reaction, which occurs in about 2% to 4% of patients (129). Severe hypersensitivity reactions are rare, as are other allergic reactions, including urticaria, nummular eczema, and hypersensitivity vasculitis. Available data show no effect on steroidogenesis and lipid-soluble vitamins (516).

##### Ezetimibe

Elevated transaminases have been observed but are rare in patients taking ezetimibe, and likely not caused by ezetimibe. However, the drug should not be used in patients with moderate or severe liver disease.

Randomized-controlled trial data during 6 years of follow-up found no evidence that ezetimibe caused myopathy/rhabdomyolysis, more than a 3-fold elevation in hepatic transaminases, gallbladder problems (including cholecystectomy), or cancer (517). Ezetimibe increases



plasma levels of cyclosporine; therefore, levels of cyclosporine should be monitored.

### Bile acid-binding resins

Adverse effects of bile acid-binding resins include constipation, abdominal pain, bloating, flatulence, and increased hepatic transaminases. Of the medications in this class, colesevelam seems to be the best tolerated. Bile acid binding decreases the absorption of folic acid and fat-soluble vitamins and a variety of medicines. To prevent this, medications should be taken 2 to 4 hours before or 4 to 6 hours after the bile acid-binding resin. Colesevelam appears to cause fewer GI side-effects, and so is likely the best-tolerated agent in this class. Further, it has greater selectivity for bile acids and so seems less likely to interfere with absorption of other medications and nutrients. Bile acid resins may cause a 10% to 20% increase in TG (81, 518) in individuals with TG levels above 500 mg/dL (5.6 mmol/L), and so are contraindicated in this setting.

### Bempedoic acid

Bempedoic acid was approved by the FDA in 2020, and therefore safety data were limited at the time of writing this guideline. Drug interactions of bempedoic acid with simvastatin and pravastatin increase concentrations of these statins, which could increase the risk of myopathy (478). Therefore, concomitant simvastatin should be limited to a dose of 20 mg, and pravastatin to a dose of 40 mg. Bempedoic acid increases uric acid levels, and gout was observed in 1.5% of patients taking bempedoic acid in clinical trials compared with 0.4% of patients on placebo. The placebo-corrected incidence of other adverse effects in clinical trials were benign prostatic hyperplasia in about 1% of patients and tendon rupture in 0.5% of patients. An increase in hemoglobin of  $\geq 2$  g/dL in 3% of patients, an increase in platelet counts of 5% and transient elevations of AST and/or ALT to above 3 times the upper limit of normal in about 1% of patients usually resolved or improved with continued treatment or after discontinuation of treatment.

## Hypertriglyceridemia

### Fibrates

Fenofibrate is much less likely than gemfibrozil to induce myopathy when administered with a statin (156). For this reason, the recommendation in statin labels is to avoid gemfibrozil. In an evaluation of the US Adverse Event Reporting System, of 3 519 000 prescriptions for fenofibrate and a statin, 4.5 cases of rhabdomyolysis were reported per million prescriptions (519). In contrast, for 6 750 000 prescriptions of gemfibrozil and a statin, 87 cases of rhabdomyolysis were reported per million prescriptions (519). In

a large randomized double-blind CVD outcome trial (over 5000 patients) evaluating fenofibrate and placebo on a background of simvastatin, with duration of follow-up of about 5 years, the incidence of CK elevations more than 10 times ULN was 0.4% in the fenofibrate group and 0.3% in the placebo group (156).

### Omega-3 fatty acids (prescription)

Omega-3 fatty acids, which can be a combination of eicosapentanoic acid (EPA) and docosapentaenoic acid or EPA alone, reduce the production of very low density lipoproteins in the liver, which are TG-rich and may also increase the clearance of TG-rich lipoproteins by increasing LPL activity. The REDUCE-IT trial compared CV outcomes in participants with high ASCVD risk, randomized to eicosapentaenoic acid ethyl ester or placebo (76). A significant reduction in ASCVD events was found and the risk/benefit was favorable. However, there were more hospitalizations for atrial fibrillation/flutter (3.1% vs 2.1%) and more events of serious bleeding (2.7% vs 2.1%) in the EPA ethyl ester group.

Omega-3-acid-ethyl-esters (combination of EPA and DHA), which are indicated to lower the risk of pancreatitis in patients with TG  $>500$  mg/dL (5.6 mmol/L), but do not have evidence for reduction in ASCVD risk, have been associated with an increase in atrial fibrillation and bleeding.

### Niacin

Niacin reduces TG, total cholesterol and LDL-C, and increases HDL-C. Prescription niacin is no longer available in Europe because of its adverse safety profile. The most common adverse events are flushing and pruritis. Niacin also increases plasma glucose and worsens glycemic control (520), and it is associated with an increased risk of newly diagnosed diabetes (521). Other serious adverse effects of niacin identified in the AIM High (522) and HPS2-THRIVE clinical trials (523) include hepatotoxicity (which is rare), infection, GI bleeding, and myopathy. The latter trial, with a follow-up period of about 4 years, did not show a benefit on ASCVD of adding niacin-laropiprant to a statin. This result and the safety hazards associated with niacin treatment suggest that niacin should have limited use today (524) and should probably not be used in people with diabetes or impaired glucose tolerance.

## Method of development of evidence-based clinical practice guidelines: participants

### Participants

The Writing Committee consisted of 10 content experts representing expertise in lipid disorders, endocrinology, diabetes, preventive cardiology, and clinical epidemiology.



**Table 11.** GRADE classification of guideline recommendations

Quality of Evidence		High Quality	Moderate Quality	Low Quality	Very Low Quality
Description of Evidence		Well-performed RCTs	RCTs with some limitations	RCTs with serious flaws	Unsystematic clinical observations
		Very strong evidence from unbiased observational studies	Strong evidence from unbiased observational studies	Some evidence from observational studies	Very indirect evidence observational studies
Strength of Recommendation	Strong (1): “We recommend...” Benefits clearly outweigh harms and burdens and vice versa	1⊕⊕⊕⊕	1⊕⊕⊕○	1⊕⊕○○	1⊕○○○
	Conditional (2): “We suggest...” Benefits closely balanced with harms and burdens	2⊕⊕⊕⊕	2⊕⊕⊕○	2⊕⊕○○	2⊕○○○

One of the committee members brought an international perspective to this guideline topic. The Writing Committee also included a clinical practice guideline methodologist who led the team of comparative effectiveness researchers that conducted the systematic reviews and meta-analyses.

#### Guideline development process

The Endocrine Society’s guideline development process combines elements of the GRADE framework (525) with an approach that was felt to be more appropriate for the rare endocrine disease space where scientific evidence is limited or nonexistent. The Society applies the steps in the GRADE framework to research questions for which there is an ample body of knowledge of low-to-moderate quality or higher (see Table 11 for descriptions of low and moderate quality evidence). In these situations, GRADE provides methodological and statistical rigor, which results in robust recommendations, which are classified using quality of evidence and strength of recommendation, as described in by Guyatt et al (526) and are represented graphically in Table 11.

Where evidence is extremely limited and/or not systematically analyzed, we provide recommendations based on an expert review of the limited data. This process is less systematic than the GRADE methodological framework; however, these recommendations are also clearly classified using the GRADE classification system.

Some of the Society’s clinical practice guidelines also include Ungraded Good Practice Statements (527). This unclassified clinical guidance can include expert opinion statements on good practice, references to recommendations made in other guidelines, and observations on preventive care and shared decision-making.

Guideline recommendations include the relevant population, intervention, comparator, and outcome. When further clarification on implementation is needed, we include

a Technical Remarks section. These provide supplementary information such as timing, setting, dosing regimens, and necessary expertise. All recommendations are followed by a synopsis of the evidence that underpins it. Authors may also include short statements on patients’ values and preferences, the balance of benefits and harms, and minority opinions, where relevant.

It should be noted that the Society’s guideline development process is currently instituting new approaches and processes.

#### Internal and External Review

Approximately 18 months into the development process, Endocrine Society clinical practice guidelines undergo a Comment Review Period of 1 month, where there is an opportunity for internal and external stakeholders to review the guidelines draft and provide comments. These stakeholders include Endocrine Society members, the Society’s Clinical Guidelines Committee (CGC), representatives of any co-sponsoring organizations, a representative of Council, and an Expert Reviewer. Following revisions to the guideline manuscript in response to Comment Review Period comments, it is returned to CGC, the Council Reviewer, and the Expert Reviewer for a second review and ballot. Finally, the guidelines manuscript is subject to the *Journal of Clinical Endocrinology & Metabolism*’s publisher’s review prior to publication. This review is undertaken by an individual with expertise in the topic, without relevant conflicts of interest, and external to the guideline writing committee, CGC, and Council.

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## Additional Information

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**Disclosure Summary:** The Endocrine Society maintains a rigorous conflict-of-interest review process for developing clinical practice guidelines. The following conflict-of-interest policy, which was in place at the time of guideline initiation, was employed throughout the guideline-development process. All Guideline Writing Committee members must declare any potential conflicts of interest by completing a conflict-of-interest form. The Clinical Guidelines Committee reviews all conflicts of interest before the Society's Board approves the members to participate on the Writing Committee and periodically during the development of the guideline. All others participating in the guideline's development must also disclose any conflicts of interest in the matter under study, and most of these participants must be without any conflicts of interest. The Clinical Guidelines Committee and the Writing Committee have reviewed all disclosures for this guideline and resolved or managed all identified conflicts of interest.

Conflicts of interest are defined as remuneration in any amount from commercial interests; grants; research support; consulting fees; salary; ownership interests [eg, stocks and stock options (excluding diversified mutual funds)]; honoraria and other payments for participation in speakers' bureaus, advisory boards, or boards of directors; and all other financial benefits. Specific details regarding the disclosures of the Writing Committee members for this guideline can be found in Appendix A.

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**Data Availability:** All data generated or analyzed during this study are included in this published article or in the data repositories listed in the References.

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**Appendix A.** Lipid Management Guideline Writing Committee Conflict of Interest Table

Task Force Member	Employment	Uncompensated Memberships	Uncompensated Leadership	Personal Financial	Organizational Financial	Spousal / Family Information
Connie Newman (Chair)	Adjunct Professor, New York University School of Medicine	The Obesity Society	American Heart Association: Chair, Scientific Statement, Statin Associated Adverse Events	None declared	None declared	None declared
	Consultant Physician, New York Harbor Veterans Administration Hospital	National Lipid Association	American Medical Women Association: President (2018–2019)			
		American Association of Clinical Endocrinologists				
		American Heart Association				
Michael Blaha	Director of Clinical Research, Johns Hopkins	None declared	American Heart Association, Committee Member/Grantee	Norvartis, Advisory Board	National Institutes of Health; National Heart, Lung, and Blood Institute	None declared
	Member, Endocrinologic and Metabolic Drug Advisory Committee (Food and Drug Administration)			- Amgen, Advisory Board	American Heart Association	
				Aralez, Advisory Board	Aetna Foundation	
				Medimmune, Advisory Board	Amgen Foundation	
				Novo Nordisk, Advisory Board	Food and Drug Administration	
				Akcea, Advisory Board		
				Sanofi, Advisory Board		
				Regeneron, Advisory Board		
				Siemens, Consulting Fee		
Jeffrey Boord	Parkview Health System	American Diabetes Association	None declared	None declared	None declared	None declared
		American Heart Association				
		American College of Physicians				



## Appendix A. Continued

Task Force Member	Employment	Uncompensated Memberships	Uncompensated Leadership	Personal Financial	Organizational Financial	Spousal / Family Information
Bertrand Cariou	Chu Nantes - Universite De Nantes, Professor of Endocrinology	None declared	None declared	Amgen, Speaker Bureau, Advisory Board Pierre Fabre, Speaker Bureau MSD (Merck), <i>Speaker Bureau</i> <i>realtu</i> Novo-Nordisk, Speaker Bureau and Advisory Board Sanofi-Aventis, Speaker Bureau and Advisory Board Regeneron, Advisory Board Akcea, Advisory Board Genfit, Consultant MedImmune	Sanofi-Aventis Regeneron	None declared
Alan Chait	Professor of Medicine, University of Washington	None declared	None declared	MedImmune	MedImmune	None declared
Henry Fein	Attending Physician & Faculty, Sinai Hospital of Baltimore	None declared	None declared	Expert Witness	None declared	None declared
Henry Ginsberg	Professor of Medicine, Columbia University	None declared	None declared	Merck & Co., Inc., Consultant Sanofi, SA, Consultant Regeneron Pharmaceuticals, Inc., Consultant Amgen, Inc., Consultant Resverlogix Corp., Consultant Akcea, Consultant Kowa, Consultant Esperion Therapeutics, Consultant	MedImmune	None declared None declared None declared
Ira Goldberg (Co-chair)	Professor, New York University School of Medicine, Division Director, Langone Medical Center	None declared	None declared	Amgen, Inc., Consultant Akcea, Consultant	None declared	None declared
Savitha Subramanian	Associate Professor, University of Washington	None declared	None declared	Biohead, Consultant Kowa, Consultant Akcea, Consultant Sanofi, Consultant Regeneron, Consultant	None declared	None declared

**Appendix A. Continued**

Task Force Member	Employment	Uncompensated Memberships	Uncompensated Leadership	Personal Financial	Organizational Financial	Spousal / Family Information
Lisa Tannock	Professor, University of Kentucky	American Heart Association	American Heart Association: Committee Member; Member Scientific Statement, Study Section Member/Chair	National Institutes of Health, Peer Review	None declared	None declared
	Division Chief, University of Kentucky Academic Medical Center	American Association of Clinical Endocrinologists	Postgraduate Medicine, Editorial Board			
	Staff Physician, Lexington Veterans Affairs Medical Center	American Diabetes Association	Veterans Affairs, Peer Review			
			American Heart Association, Peer Review			
			Endocrine Self-Assessment Program, peer review			

**Appendix B: Lipid Metabolism**

Two major classes of circulating lipids, TG and cholesterol, are transported as the core components of lipoproteins. The apolipo-proteins on the surface of lipoproteins allow these particles to be soluble in a water environment and interact with enzymes and cell surface receptors, thus controlling their ability to supply lipids to tissues.

Triglycerides are the major storage forms of energy and are derived from dietary fat and from synthesis in the liver. In the small intestine, TG are assembled into chylomicrons, which enter the circulation via the thoracic duct. Chylomicrons are normally not found in fasting plasma. The liver synthesizes and secretes TG in the form of VLDL, which contains TG synthesized from fatty acids that are recycled from the adipose tissue, obtained from lipoproteins, or synthesized from glucose and/or amino acids. Lipolysis of TG from TG-rich lipoproteins is performed primarily by interaction with LPL, which is associated with the luminal surface of capillaries, and results in the release of fatty acids from their glycerol backbone, thereby supplying lipids for energy or storage by muscles and adipose tissue. The lipoproteins resulting from this reaction are either chylomicron or VLDL remnants, because TG, but not cholesterol or cholesteryl ester, are removed from the particles. With further loss of TG, VLDL remnants generate low-density LDL, which are removed from the circulation primarily by liver LDL receptors. All the chylomicron remnants and some of the VLDL remnants are cleared in the liver by both the LDL receptor and at least 1 other pathway mediated by LRP. High-density lipoprotein has a distinct metabolic pathway that includes its production from the liver and gut, the addition and removal of lipids in the circulation, and clearance mainly in the liver. A more complete review of lipoprotein physiology can be found in standard texts, and an illustrative figure of endogenous and exogenous pathways of lipid metabolism in a 2019 review on lipid management (528).

The clinical approach to abnormal levels of plasma lipids focuses on abnormal circulating levels of lipoproteins. Primary disorders of lipoprotein metabolism must be separated from the effects of endocrine disorders and disorders of other organ systems on lipids. Monogenic primary disorders are rare. Other primary disorders are mostly polygenic and common, and easily influenced by multiple factors including environmental factors such as diet, exercise, and medications. Routinely normal levels of TG and other biomarkers are based on population distributions; however, clinicians may be better served by the concepts of “optimal” and “elevated,” which can be used to indicate thresholds for clinical action. Various guidelines and scientific statements have denoted TG levels above 150 mg/dL (1.7 mmol/L), 170 mg/dL (1.9 mmol/L), or 200 mg/dL

(2.3 mmol/L) as elevated (35, 529, 530). While extremely high levels of TG can cause acute (and recurrent/chronic) pancreatitis (with the risk increasing above a fasting TG of 500 mg/dL [5.6 mmol/L]) (531), the pathophysiologic imperative to treat less dramatic elevations (such as 150–500 mg/dL [1.7–5.6 mmol/L]) until recently were not supported by clear-cut clinical trial data. This changed with the REDUCE-IT trial (76), which is discussed in these guidelines. For hypercholesterolemia, the realization that average cholesterol increased CV risk prompted a different metric: what had been average cholesterol levels became abnormal, as they were associated with increased ASCVD. Further support came from studies that showed that reducing LDL-C decreased ASCVD (123, 124, 129, 130, 159).

Increased plasma levels of TG occur only in the setting of increased circulating levels of VLDL and/or chylomicrons. Because TG lipolysis of these 2 lipoproteins has a common pathway via LPL, very-elevated levels of VLDL can saturate this pathway, reducing and delaying lipolysis of chylomicrons, leading to their accumulation even in fasting plasma. This tends to occur as TG levels begin to exceed 500 mg/dL (5.6 mmol/L). Higher TG levels, above 1000 mg/dL (11.3 mmol/L), are always associated with fasting chylomicronemia. In addition to being larger than VLDL, and therefore more buoyant, chylomicrons contain a shortened form of the major structural protein, apoB48, so named because it is 48% of apoB100, which is the form of apoB in VLDL and LDL and the main ligand for the LDL receptor.

The major cholesterol-carrying lipoproteins are LDL and HDL, and hypercholesterolemia is usually due to increased LDL concentration. In most clinical situations and in most large research studies, LDL-C levels are estimated by the Friedewald method, subtracting HDL-C and TG/5 (an estimate of VLDL cholesterol) from the total cholesterol. With TG levels >150 mg/dL (1.7 mmol/L), this estimate is inaccurate; it is also inaccurate at very low levels of LDL-C (<70 mg/dL [1.8 mmol/L]).

Two conditions can cause both increased TG and increased cholesterol. One is “combined hyperlipidemia,” characterized by increased VLDL and LDL levels. The other is the rare disorder dysbetalipoproteinemia (formerly known as Type III hyperlipidemia in the Frederickson classification), with increased levels of circulating remnant particles that contain both comparable amounts of TG and cholesterol, such that VLDL has a TG-to-cholesterol ratio of 3 or less instead of the typical ratio of 5. Dysbetalipoproteinemia usually results from homozygosity of apoE2, 1 of the 3 isoforms of apoE, plus 1 or more other poorly understood factors. The E2/E2 genotype

may be expressed as dysbetalipoproteinemia because of secondary disorders that alter lipid metabolism, including obesity, diabetes, and hypothyroidism. When an individual has the E2/E2 genotype on the background of other genes predisposing to hyperlipidemia, dysbetalipoproteinemia occurs largely because apoE2 binding to the LDL receptor is defective, decreasing the hepatic catabolism of apoE2-containing VLDL.

## Appendix C

### Cholesterol Treatment Guidelines

In 2013, the AHA and the ACC published new guidelines for the “treatment of blood cholesterol to reduce atherosclerotic CV risk in adults” (532). Those guidelines were dramatically different than prior National Institutes of Health–sponsored guidelines, written under the umbrella of the Adult Treatment Panel (533–535). The 2013 AHA/ACC guidelines (532), which were the 4<sup>th</sup> version of the Adult Treatment Panel guidelines, removed goals or targets for LDL-C, which had been a central component of the prior Adult Treatment Panel guidelines published in 1988, 1993, and 2001, as well as updates published in 2004 and 2006 (536). The 2006 update, titled “AHA/ACC Guidelines for Secondary Prevention for Patients with Coronary and Other Atherosclerotic Vascular Disease,” was based on 13 RCTs and recommended the strongest LDL goals to that time.

By 2013, health professionals were well educated in the use of LDL-C for both the initiation of treatment for hypercholesterolemia and for setting goals. The 2013 AHA/ACC guidelines altered the paradigm to be used by health care providers to identify, treat, and follow patients who needed cholesterol lowering by eliminating LDL-C goals (533–536). Patients were followed by assessing the percentage of reduction in LDL-C.

The guidelines defined high-risk patient management groups (history of ASCVD, diabetes mellitus, severe elevation in LDL-C) that required lipid-lowering medication as adjunct to diet and lifestyle therapies, without assessment of the 10-year ASCVD risk score. They also defined, based upon the 10-year risk of ASCVD, primary prevention groups that would be likely to benefit from statin therapy. The 10-year risk of ASCVD was calculated from the ACC/AHA Pooled Cohort Equations. Statins were grouped by intensity of LDL-C reduction, and high-intensity statins, which reduced LDL-C by 50% or more, were recommended for the highest risk patients. Patients were followed by assessing the percentage of reduction in LDL-C.

**2018 AHA/ACC cholesterol clinical practice guidelines**

In 2018, new guidelines were published by the AHA/ACC (35). These guidelines defined high-risk patient groups for treatment with high-intensity statin therapy, as well as groups who would benefit from moderate-intensity statins. They acknowledged new CV endpoint data for ezetimibe and PCSK9-inhibiting monoclonal antibodies by formally endorsing these statin adjuncts. They also recommended calculation of the 10-year risk in patients with diabetes and no history of ASCVD. In addition, these guidelines recommended the consideration of risk-enhancing factors and CAC scoring to further define risk and/or aid decisions about the initiation of statin treatment or intensification of therapy. The guideline's "Top 10 Take-Home Messages" are:

1. In all individuals, emphasize a heart-healthy lifestyle across the life course.
2. In patients with clinical ASCVD, reduce LDL-C with high-intensity statin therapy or maximally tolerated statin therapy.
3. In very high-risk ASCVD, use an LDL-C threshold of 70 mg/dL (1.8 mmol/L) to consider the addition of nonstatins to statin therapy.
4. In patients with severe primary hypercholesterolemia (LDL-C level  $\geq 190$  mg/dL [4.9 mmol/L]), without calculating 10-year ASCVD risk, begin high-intensity statin therapy.
5. In patients 40 to 75 years of age with diabetes mellitus and LDL-C  $\geq 70$  mg/dL (1.8 mmol/L), start moderate-intensity statin therapy without calculating the 10-year ASCVD risk.
6. In adults 40 to 75 years of age evaluated for primary ASCVD prevention, have a clinician-patient risk discussion before starting statin therapy.
7. In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels  $\geq 70$  mg/dL (1.8 mmol/L), at a 10-year ASCVD risk of  $\geq 7.5\%$ , start a moderate intensity statin if a discussion of treatment options favors statin therapy.
8. In adults 40 to 75 years of age without diabetes mellitus and a 10-year risk of 7.5% to 19.9% (intermediate risk), risk-enhancing factors favor the initiation of statin therapy.
9. In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels  $\geq 70$  mg/dL to 189 mg/dL (1.8 to 4.9 mmol/L), at a 10-year ASCVD risk of  $\geq 7.5\%$  to 19.9%, if a decision about statin therapy is uncertain, consider measuring CAC.

10. Assess adherence and the percentage response to LDL-C-lowering medication and lifestyle changes with repeat lipid measurement 4 to 12 weeks after statin initiation or dose adjustment, repeated every 3 to 12 months, as needed.

The guideline also states that in patients with a 10-year risk of ASCVD at 5% to 7.5% (borderline risk), risk-enhancing factors may favor statin therapy.

The 2018 ACC/AHA guidelines on cholesterol management are compared (and provided in chronological order below) to existing guidelines from other organizations in the United States, Canada, and Europe.

**National Lipid Association Recommendations for Patient-Centered Management of Dyslipidemia: Part 1 – Full Report (2015)**

These guidelines, the first published post-2013, stressed treatment goals, noting that the authors did not agree with the AHA/ACC 2013 guidelines (23). The National Lipid Association (NLA) report utilized 4 risk categories, and in sharp contrast with the AHA/ACC 2013 guidelines, recommended treatment goals for each category.

The NLA guidance also differed from the 2013 AHA/ACC guidelines by using levels of non-HDL-C as the primary treatment goal and both LDL-C and apoB levels as secondary goals. For low-, moderate-, and high-risk groups, the primary goal was non-HDL-C  $< 130$  mg/dL (3.4 mmol/L), with secondary goals of  $< 100$  mg/dL (2.6 mmol/L) for LDL-C and  $< 90$  mg/dL (0.002 mmol/L) for apoB. For the very high-risk group, NLA recommended a non-HDL-C goal of  $< 100$  mg/dL (2.6 mmol/L), with LDL-C and apoB goals of  $< 70$  mg/dL (0.001 mmol/L) and  $< 80$  mg/dL (0.002 mmol/L), respectively. The NLA guideline combined populations with T1D and T2D together regardless of age, duration of disease, or presence or absence of microangiopathy. The NLA participated in the development and publication of the 2018 AHA/ACC guidelines and supported them fully, although some features of the 2015 NLA guidelines were not addressed in the new 2018 AHA/ACC guidelines (35).

**2016 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult**

This is an update of their 2012 guidelines, and the major recommendations include CVD risk assessment every 5 years for adults ages 40–75 years using a Framingham Risk Score modified by family history or a Cardiovascular



Life Expectancy Model, which estimates CV age (476). These differ from the Pooled Cohort Equations risk score used in the AHA/ACC guidelines. They proposed LDL-C as the primary target for therapy and non-HDL or apoB as alternative targets, which is different from the AHA/ACC 2018 and from the NLA 2015 guidelines. For all secondary prevention and high-risk primary prevention, the Canadian Cardiovascular Society recommends a target of LDL-C <2.0 mmol/L (about <80 mg/dL), or a >50% reduction in LDL-C, an apoB <80 mg/dL, or a non-HDL-C <2.6 mmol/L (about <100 mg/dL). They also recommend even more aggressive therapy for individuals with recent acute coronary syndromes and established CAD with an LDL-C target of <1.8 mmol/L (about <70 mg/dL) or >50% reduction. Such therapy might require the combination of nonstatin agents like ezetimibe with a maximally tolerated statin. Overall, the Canadian recommendations have some differences from the 2018 AHA/ACC guidelines, such as the use of target levels of LDL-C, apoB, and non-HDL-C, although the 2018 guidelines are much closer to the Canadian guidelines than were the 2013 AHA/ACC guidelines. They differ from those of the NLA by choosing LDL-C rather than non-HDL-C goals and by suggesting a >50% LDL-C reduction as an alternative to an LDL-C of 70 mg/dL in the highest-risk group. However, as noted, the NLA has now aligned itself with the 2018 AHA/ACC guidelines.

#### 2017 American Association of Clinical Endocrinologists and American College of Endocrinology Guidelines for Management of Dyslipidemia and Prevention of Cardiovascular Disease

This is an update of the American Association of Clinical Endocrinologists (AACE) 2012 guidelines and defines 5 risk categories accompanied by LDL-C, non-HDL-C, and apoB goals (475). Extreme risk is defined as progressive ASCVD, including unstable angina after achieving an LDL-C goal of <70 mg/dL (1.8 mmol/L), established ASCVD in individuals with diabetes mellitus, CKD, heterozygous FH, or premature ASCVD occurring at ages <55 years for males and <65 years for females. For the extreme risk group, the treatment goals are the most aggressive of any previous guideline: LDL-C <55 mg/dL (1.4 mmol/L), non-HDL-C <80 mg/dL (2.1 mmol/L), or apoB <70 mg/dL (0.7 g/L). For adults with very high risk (defined as acute coronary syndrome, coronary or carotid artery disease, or peripheral vascular disease, or 10-year risk >20%, diabetes or chronic renal disease stages 3 or 4 with >1 additional risk factor, or heterozygous FH), treatment goals are LDL-C <70 mg/dL (1.8 mmol/L), non-HDL-C <100 mg/dL (2.6 mmol/L), and

apoB <80 mg/dL (0.8 g/L). Lower treatment goals, with LDL-C <100 mg/dL (2.6 mmol/L), non-HDL-C <130 mg/dL (3.2 mmol/L), and apoB <90 mg/dL (0.9 g/L) are recommended for individuals with high risk or moderate risk. For individuals with low CVD risk (defined as zero risk factors), the LDL-C goal is <130 mg/dL (3.4 mmol/L). Although LDL-C is the primary goal parameter, the AACE recommends using non-HDL-C first when TG levels are between 200 and 500 mg/dL (2.3 and 5.6 mmol/L).

#### 2019 European Society of Cardiology and European Atherosclerosis Society Guidelines for the Management of Dyslipidemia

This is an update of the 2016 guidelines from these 2 major European societies. They identify 4 patient groups as having very high or high total CV risk: (1) documented CVD, (2) T1D or T2D, (3) very high levels of risk factors generating a 10-year cumulative risk score of >10% for a first fatal CV event using a calculated SCORE assessment tool, and (4) CKD (462). Individuals with lower levels of risk are categorized using their SCORE: 5% to 10% for high risk, 1% to 5% for moderate risk, and <1% for low risk. The use of SCORE for predicting fatal events is unique to the ESC/EAS and is based on their belief that such an approach eliminates bias and misdiagnosis. Low-density lipoprotein cholesterol has been designated as the treatment goal lipid biomarker, with non-HDL-C used as a secondary goal after the LDL-C goal has been reached. Apolipoprotein B is recommended as a potential secondary target, similar to non-HDL-C, if an assay for apoB is readily available. The ESC/EAS recommends treatment goals based on CV risk: very high CV risk, whether secondary or primary prevention, LDL-C goal of <1.4 mmol/L (55 mg/dL), and LDL-C reduction of >50% from baseline; high CV risk, LDL-C goal of <1.8 mmol/L (70 mg/dL) and a reduction of at least 50% if the baseline LDL-C is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL); for moderate risk, LDL-C of <2.6 mmol/L (100 mg/dL); for low risk, an LDL-C <3.0 mmol/L (116 mg/dL). For individuals with ASCVD who have a second vascular event within 2 years while taking maximal tolerated doses of a statin, ESC/EAS guidelines suggest consideration of an LDL-C goal of <1.0 mmol/L (40 mg/dL). Secondary goals are non-HDL-C 0.8 mmol/L (30 mg/dL) higher than for LDL-C, and apoB <65 mg/dL, <80 mg/dL, and <100 mg/dL for very high-risk, high-risk, and moderate-risk groups, respectively.

Overall, the ESC/EAS guidelines differ from others by having more levels of LDL-C goals depending on risk, and also a suggestion for reducing LDL-C to <40 mg/dL (1.0 mmol/L) for people with ASCVD and recent vascular

events. Another difference is the use of fatal ASCVD events as the target of prevention, but this is not critical to the function of the guidelines.

#### **2019 Endocrine Society Clinical Practice Guideline: Primary Prevention of ASCVD and T2DM in Patients at Metabolic Risk**

This guideline provides recommendations for the management of lipids, blood pressure, blood glucose, and excess weight or increased waist circumference in patients with increased metabolic risk (defined in the guideline), who have not developed ASCVD or T2D (463). Lifestyle and behavioral therapies, and medical and pharmacologic management are discussed. High-intensity statin treatment is recommended for people ages 40 to 75 with increased metabolic risk and LDL-C of 190 mg/dL (4.9 mmol/L) or greater to achieve a  $\geq 50\%$  reduction in LDL-C, and also for individuals ages 40 to 75 with increased metabolic risk who have a 10-year ASCVD risk  $\geq 7.5\%$  to either achieve an LDL-C goal of  $< 100$  mg/dL (2.6 mmol/L), or a  $\geq 50\%$  reduction in LDL-C. In individuals with increased metabolic risk and a 10-year ASCVD risk of 5.0% to 7.5%, moderate-intensity statin therapy is recommended to achieve an LDL-C goal of  $< 130$  mg/dL (3.4 mmol/L) or a 30% to 50% reduction in LDL-C. In individuals with increased metabolic risk who are older than 75 years and have a 10-year risk  $\geq 7.5\%$ , the guideline recommends discussion with the patient of the risks/benefits for statin therapy on an individualized basis in order to reach a decision about statin treatment.

#### **American Diabetes Association Standards of Medical Care in Diabetes – 2020: Lipid Management**

The ADA updates their guidelines for diabetes management annually, and the 2020 update (537) aligned their recommendations for statin treatment with the 2018 AHA/ACC guidelines for the management of blood cholesterol.

In contrast to prior American Diabetes Association (ADA) Standards of Medical Care, recommendations for lipid management in adults with diabetes were individualized based upon the presence of ASCVD, or risk for ASCVD, diabetic kidney disease, or heart failure. Lifestyle modification is recommended for all patients with diabetes. For patients of all ages with diabetes and ASCVD, high-intensity statin therapy as adjunct to lifestyle is recommended. For patients with ASCVD and LDL-C  $\geq 70$  mg/dL (1.8 mmol/L) on maximally tolerated statin therapy, the ADA suggests consideration of additional LDL-C lowering therapy, with either ezetimibe (possibly preferred because of lower cost) or a PCSK9 inhibitor. In individuals with diabetes and without ASCVD but older than 40 years of age, moderate-intensity statins are recommended (as adjunct to lifestyle), with consideration of high-intensity statin treatment for those with multiple ASCVD risk factors or in the age range of 50 to 70 years, and consideration of the addition of ezetimibe to maximally tolerated statin therapy in adults with a 10-year ASCVD risk of 20% or greater.

In people older than 75 years and with diabetes, and who are not taking a statin, the ADA suggests considering statin treatment after a discussion about the potential risks/benefits. For younger adults with diabetes, in the age range of 20–39 years, the ADA suggests consideration of statin therapy in those with other ASCVD risk factors.

The authors of the 2020 Standards of Care had the opportunity to consider the results of the REDUCE-IT trial (76), which showed a CVD benefit of the omega-3 fatty acid, EPA ethyl ester, 4 g daily, when added to statin therapy in adults with elevated TG up to 500 mg/dL (5.6 mmol/L) and either ASCVD or T2D with additional risk factors. Based on these data, the ADA recommended consideration of EPA ethyl ester to reduce ASCVD risk in statin-treated adults with diabetes and TG levels between 135 and 499 mg/dL (1.5 and 5.6 mmol/L).

**Appendix D. Safety of Medications for Weight Reduction in Obesity Table**

Medication	Contraindications	Warnings	Common Adverse Reactions
Orlistat	Chronic malabsorption, cholestasis, pregnancy	Reduced levels of fat-soluble vitamins, interaction with cyclosporine (reduced cyclosporine levels), severe liver injury, worsening of renal function in patients with chronic kidney disease, increased gastrointestinal side effects if high-fat diet	Steatorrhea, oily spotting, flatulence with discharge, fecal urgency, incontinence
Phentermine/topiramate	Use with monoamine oxidase inhibitors, hyperthyroidism, glaucoma, pregnancy	Increased heart rate, suicidal behavior, acute myopia and secondary angle closure glaucoma, mood and sleep disorders, cognitive impairment, metabolic acidosis, increased creatinine	Paresthesia, dizziness, insomnia, dysgeusia, constipation, dry mouth
Naltrexone/bupropion	Uncontrolled hypertension, seizure disorders, anorexia, bulimia, abrupt discontinuation of alcohol, benzodiazepines, or barbiturates, pregnancy	Suicidal ideation and behavior, neuropsychiatric adverse events during smoking cessation, risk of seizure, increased blood pressure and heart rate, angle closure glaucoma in patients with untreated narrow angle, hepatitis, liver dysfunction	Nausea, constipation, vomiting, diarrhea, headache, dizziness, insomnia, dry mouth
Liraglutide, 3 mg	Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2, pregnancy	Thyroid C cell tumors, acute pancreatitis, acute gallbladder disease, severe hypoglycemia when used with sulfonyleurea or other glucose secretagogue, increased heart rate, impaired renal function, suicidal behavior or ideation	Nausea, vomiting, diarrhea, constipation, abdominal pain, headache, decreased appetite, fatigue, dizziness, increased lipase

From prescribing information Roche Laboratories Inc. 1999, Novo Nordisk 2020, VIVUS 2012, Nalpropion Pharmaceuticals 2020 (209–211, 538).