Dyslipidemia

CKT

KEY POINTS

Emphasize a heart-healthy lifestyle for all patients across their life span.

A discussion with the patient is the cornerstone of shared decision-making and should include the patient's 10-year risk of atherosclerotic cardiovascular disease according to the Pooled Cohort Equations, as well as risk-enhancing factors.

Statins are the foundation of pharmacologic therapy, to which ezetimibe and, if necessary, a proprotein convertase subtilisin/kexin type 9 inhibitor can be added to achieve lipid goals.

Special treatment algorithms are outlined for certain patient subgroups, such as certain ethnic groups, adults with chronic kidney disease, those with human immunodeficiency virus infection, and women.

The guidelines also award levels of evidence to their recommendations:

- Level A—high-quality evidence
- Level B-R—moderate-quality evidence from randomized controlled trials
- Level B-NR—moderate quality evidence from nonrandomized trials
- Level C-LD—limited data
- Level C-EO—expert opinion.

CLASSES OF RECOMMENDATION, LEVELS OF EVIDENCE

The guidelines award classes of recommendations, signifying the certainty of benefit compared with the estimated risk and the strength of the recommendation.

- Class I (strong)—benefit greatly exceeds risk; treatment is recommended
- Class IIa (moderate)—benefit exceeds risk; treatment is reasonable
- Class IIb (weak)—benefit equals or exceeds risk; treatment might be reasonable
- Class III: No benefit (moderate)—benefit equals risk; treatment is not recommended
- Class III: Harm (strong)—risk exceeds benefit.

Updates

- The American College of Cardiology (ACC) and American Heart Association (AHA) Task Force on Clinical Practice Guidelines published its most recent guidelines for cholesterol management in 2018,1 and followed it with guidelines for primary prevention of cardiovascular disease in 2019.

- The new guidelines have updated patient risk assessment and treatment options in primary and secondary prevention.

- In primary prevention, the guidelines provide clarity regarding decision-making in patients at intermediate risk of atherosclerotic cardiovascular disease (“intermediate” meaning a 7.5%–20% 10-year risk).

- In secondary prevention, the guidelines group patients according to their risk (high risk vs very high risk) and incorporate new non-statin therapies as add-on, evidence-based treatment options when low-density lipoprotein (LDL-C) remains above the 70 mg/dL threshold.

STATINS AND OTHER OPTIONS

Statin therapy is divided into 3 categories of intensity:

High-intensity, aiming for at least a 50% reduction in LDL-C. Examples:

- Atorvastatin 40–80 mg daily
- Rosuvastatin 20–40 mg daily.

Moderate-intensity, aiming at a 30% to 49% reduction in LDL-C. Examples:

- Atorvastatin 10–20 mg
- Fluvastatin 80 mg daily
- Lovastatin 40–80 mg
- Pitavastatin 1–4 mg daily
- Pravastatin 40–80 mg daily
- Rosuvastatin 5–10 mg
- Simvastatin 20–40 mg daily.

Low-intensity, aiming at a LDL-C reduction of less than 30%. Examples:

- Fluvastatin 20–40 mg daily
- Lovastatin 20 mg daily
- Pravastatin 10–20 mg daily
- Simvastatin 10 mg daily.

Non statin drugs

- The nonstatin LDL-lowering drugs such as ezetimibe and proprotein convertase subtilisin/ kexin type 9 (PCSK9) inhibitors can be added to statin therapy.
- Ezetimibe decreases cholesterol absorption and consequently lowers LDL-C levels by about 20%.
- PCSK9 inhibitors lower LDL-C by 50% to 60% by binding to PCSK9, inhibiting labeling of LDL receptors for degradation, thus prolonging LDL receptor activity at the cell membrane.

Primary preventive therapy in different patient subgroups

Severe hypercholesterolemia

Initiate high-intensity statin therapy immediately, irrespective of 10-year risk of atherosclerotic cardiovascular disease (ASCVD)

Adding ezetimibe is reasonable if low-density lipoprotein cholesterol (LDL-C) is ≥ 190 mg/dL or there is less than 50% reduction in LDL-C levels with maximal tolerated statins

Consider adding a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor in patients with heterozygous familial hypercholesterolemia or with LDL-C ≥ 220 mg/dL with maximally tolerated statins and ezetimibe

Diabetes mellitus in adults

Irrespective of 10-year ASCVD risk, initiate moderate-intensity statin therapy immediately

Aim for reduction of LDL-C by at least 50%

Adults age 40–75 with LDL-C levels 70–189 mg/dL

Before starting statins, engage in clinician-patient risk discussion, evaluating risk factors, 10-year ASCVD risk, risk enhancers (Table 2), patient's preference, costs, and adverse effects of statins

Use coronary artery calcium score to guide decision if risk is still unclear

Children and young adults

Assess risk factors in children age 0–19 years

Initiate statin therapy if patients have severely abnormal lipid profiles or clinical presentation of familial hypercholesterolemia and cannot be treated by 3 months lifestyle therapy

Ethnicity

Review racial and ethnic features that can influence ASCVD risk and intensity of treatment (Table 3)

Adults with chronic kidney disease

Starting moderate-intensity statin alone or in combination with ezetimibe can be useful

Adults with chronic inflammatory disorders and HIV

In adults age 40–75 with LDL-C 70–189 mg/dL with a 10-year ASCVD risk of over 5%, discuss moderate- or high-intensity statin therapy

Women

History of premature menopause (before age 40) or history of pregnancy-related disorders (hypertension, pre-eclampsia, gestational diabetes, small-for-gestational-age infants, and preterm deliveries) are risk-enhancing factors and should influence lifestyle and pharmacologic therapy decisions

If a patient age 20 to 75 has LDL-C ≥ 190 mg/dL, start high-intensity statin therapy right away

Adults age 40–75, without diabetes, with LDL-C levels 70–189 mg/dL

- Use the Pooled Cohort Equations, which are based on age, sex, race, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, and whether the patient is receiving treatment for high blood pressure, has diabetes, or smokes.
- This tool gives an estimate of the patient's risk of a cardiovascular event within the next 10 years, which the guidelines categorize as follows:
  - Low risk: < 5%
  - Borderline risk: 5%–7.5%
  - Intermediate risk: 7.5%–20%
  - High risk: > 20%.

Adults age 40–75, without diabetes, with LDL-C levels 70–189 mg/dL

- **Discuss the risk with the patient:** After evaluating 10-year risk, clinicians should discuss it with the patient before initiating statin therapy. Risk discussions are the cornerstone of the shared decision-making process.

- **Review risk-enhancing factors:** During the risk discussion, one should review not only the patient's 10-year risk according to the Pooled Cohort Equations, but also risk factors not included in the Pooled Cohort Equations.

  The guidelines describe these as "risk-enhancing factors".

Risk enhancers

Family history of premature atherosclerotic cardiovascular disease (in men age < 55 or in women age < 65)

Primary hypercholesterolemia
- Low-density lipoprotein cholesterol 160–180 mg/dL
- Non-high-density lipoprotein cholesterol 190–219 mg/dL

Metabolic syndrome: 3 or more of the following:
- Increased waist circumference by ethnically appropriate cut points
- Fasting triglyceride level > 150 mg/dL
- High blood pressure
- Elevated glucose
- Low high-density lipoprotein cholesterol (< 40 mg/dL in men, < 50 mg/dL in women)
- Chronic kidney disease (estimated glomerular filtration rate 15–59 mL/min/1.73 m^2)

Chronic inflammatory conditions (eg, psoriasis, rheumatoid arthritis, lupus, human immunodeficiency virus infection, acquired immunodeficiency syndrome)

History of premature menopause (age < 40) and history of pregnancy-associated conditions that increase later risk of atherosclerotic cardiovascular disease such as preeclampsia

High-risk ethnicity or race (eg, South Asian)

Lipids or biomarkers associated with elevated risk
- Persistently elevated hypertriglyceridemia (≥ 175 mg/dL nonfasting)
- Elevated high-sensitivity C-reactive protein (≥ 2.0 mg/L)
- Elevated lipoprotein (a) (≥ 50 mg/dL or ≥ 125 nmol/L)
  (relative indication for measurement: family history of premature atherosclerotic cardiovascular disease)
- Elevated apolipoprotein B (≥ 130 mg/dL)
  (relative indication for measurement: triglycerides ≥ 200 mg/dL)
- Ankle-brachial index < 0.9

Physicians should use additional risk-stratification tools for patients at borderline and intermediate risk

Adults age 40–75, without diabetes, with LDL-C levels 70–189 mg/dL

- For patients at borderline or intermediate risk, risk-enhancing factors are particularly useful to review during the risk discussion.
- By evaluating risk-enhancing factors, patients' risk can be revised, and preventive treatment prescribed only to those at higher risk, while avoiding over prescription for those at low risk.
- The guidelines give a class IIA recommendation to starting or intensifying statin therapy if risk-enhancing factors are present in borderline- and intermediate-risk adults.

Adults age 40–75, without diabetes, with LDL-C levels 70–189 mg/dL

- In unclear cases, consider coronary artery calcium measurement. If, in view of this evidence, the patient and clinician favor statin therapy, statins should be initiated at a moderate intensity to lower LDL-C by 30% to 49%.
- However, if the risk decision is still unclear even after reviewing the Pooled Cohort Equations and risk enhancers, the coronary artery calcium score can be added to guide decisions.
- A great body of research indicates that the coronary artery calcium score is an effective tool to stratify risk and improve risk estimation.
- If the score is 1 to 99, statin therapy is suggested, especially in patients older than 55.
- If the score is 100 or higher or patients are in the 75th percentile or higher for coronary artery calcium, statin therapy is clearly indicated.
- If the score is 0, statin therapy may be safely withheld unless the patient smokes or has premature cardiovascular disease

Adults age 40–75, without diabetes, with LDL-C levels 70–189 mg/dL

- Therapy recommendations for patients on either extreme of 10-year risk are more straightforward.
- For patients at low risk (< 5%), clinicians should still emphasize lifestyle changes to reduce risk modifiable factors.
- For patients at high risk (> 20%), clinicians should clearly recommend statin therapy aimed at lowering LDL-C by at least 50%.

Key points on secondary prevention[a]

Patient subgroup	Guideline recommendation
At very high risk[b]	If low-density lipoprotein cholesterol (LDL-C) levels are ≥ 70 mg/dL with the maximal tolerated statin therapy, it is reasonable to add ezetimibe
	If LDL-C level is ≥ 70 mg/dL on maximal tolerated statin and ezetimibe, it is reasonable to add a PCSK9 inhibitor
Not at very high risk	
Age ≤ 75	Goal is LDL-C reduction by 50%
	Use moderate-intensity statins if high-intensity statins are not tolerated
	If LDL-C ≥ 70 mg/dL on high-intensity statins, it is reasonable to add ezetimibe
Age > 75	Starting or continuing either moderate- or high-intensity statins is reasonable

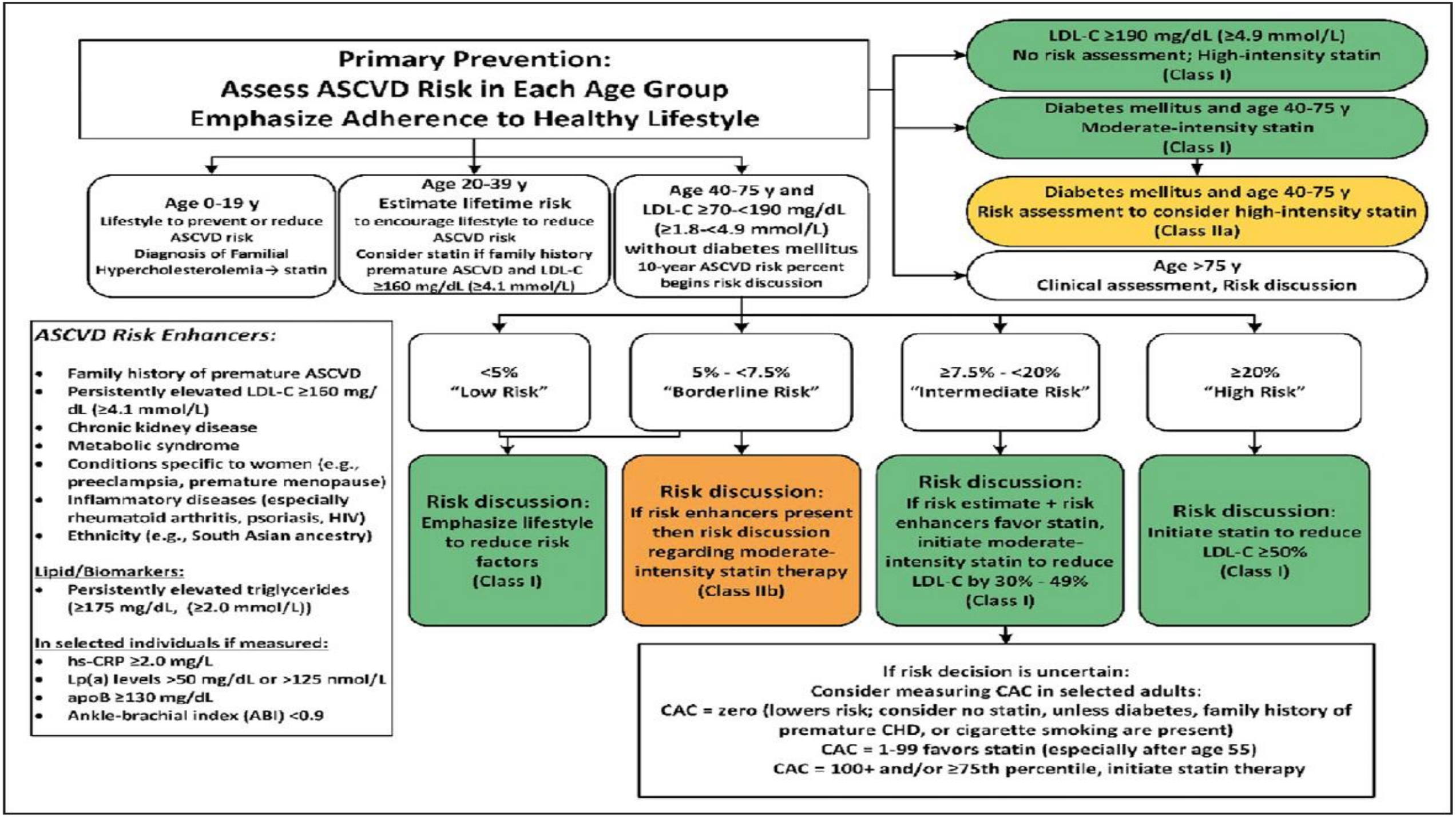
[a]Secondary prevention refers to patients with clinical atherosclerotic cardiovascular disease (ASCVD), ie, those with a history of acute coronary syndrome, myocardial infarction, stable or unstable angina, arterial revascularization, stroke, transient ischemic attack, or peripheral artery disease.

[b]Very high risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions (age ≥ 65, heterozygous familial hypercholesterolemia, history of coronary artery bypass surgery or percutaneous coronary intervention, diabetes mellitus, hypertension, chronic kidney disease, current smoking, persistently elevated LDL-C, or history of heart failure).

MONITORING RESPONSE

- TO LDL-C-LOWERING THERAPY As in the last guidelines, the current ones suggest assessing adherence and percentage response after initiating or changing the dose of LDL-C-lowering medications and lifestyle changes, with repeat lipid measurements 4 to 12 weeks after therapy is started.

- This can be repeated every 3 to 12 months as needed.


Primary Prevention:
Assess ASCVD Risk in Each Age Group
Emphasize Adherence to Healthy Lifestyle
LDL-C ≥190 mg/dL (≥4.9 mmol/L)
No risk assessment; High-intensity statin
(Class I)
Diabetes mellitus and age 40-75 y
Moderate-intensity statin
(Class I)
Diabetes mellitus and age 40-75 y
Risk assessment to consider high-intensity statin
(Class IIa)
Age >75 y
Clinical assessment, Risk discussion
Age 0-19 y
Lifestyle to prevent or reduce ASCVD risk
Diagnosis of Familial Hypercholesterolemia→ statin
Age 20-39 y
Estimate lifetime risk
to encourage lifestyle to reduce ASCVD risk
Consider statin if family history premature ASCVD and LDL-C ≥160 mg/dL (≥4.1 mmol/L)
Age 40-75 y and
LDL-C ≥70-<190 mg/dL (≥1.8-<4.9 mmol/L)
without diabetes mellitus
10-year ASCVD risk percent begins risk discussion
ASCVD Risk Enhancers:
Family history of premature ASCVD
Persistently elevated LDL-C ≥160 mg/dL (≥4.1 mmol/L)
Chronic kidney disease
Metabolic syndrome
Conditions specific to women (e.g., preeclampsia, premature menopause)
Inflammatory diseases (especially rheumatoid arthritis, psoriasis, HIV)
Ethnicity (e.g., South Asian ancestry)
Lipid/Biomarkers:
Persistently elevated triglycerides (≥175 mg/dL, (≥2.0 mmol/L))
In selected individuals if measured:
hs-CRP ≥2.0 mg/L
Lp(a) levels >50 mg/dL or >125 nmol/L
apoB ≥130 mg/dL
Ankle-brachial index (ABI) <0.9
<5%
"Low Risk"
5% - <7.5%
"Borderline Risk"
≥7.5% - <20%
"Intermediate Risk"
≥20%
"High Risk"
Risk discussion:
Emphasize lifestyle to reduce risk factors
(Class I)
Risk discussion:
If risk enhancers present then risk discussion regarding moderate-intensity statin therapy
(Class IIb)
Risk discussion:
If risk estimate + risk enhancers favor statin, initiate moderate-intensity statin to reduce LDL-C by 30% - 49%
(Class I)
Risk discussion:
Initiate statin to reduce LDL-C ≥50%
(Class I)
If risk decision is uncertain:
Consider measuring CAC in selected adults:
CAC = zero (lowers risk; consider no statin, unless diabetes, family history of premature CHD, or cigarette smoking are present)
CAC = 1-99 favors statin (especially after age 55)
CAC = 100+ and/or ≥75th percentile, initiate statin therapy

Familial Hypercholesterolemia

An individual may be labeled as having FH in one of two ways:

●DNA-based evidence of mutation in the LDLR, PCSK9, or APOB gene. Each of these genes influence LDL-C levels.

●Clinical characteristics that usually include a high LDL-C.

The following are three recognized diagnostic criteria schemes:

- ●Dutch Lipid Clinic
- ●Simon Broome

●American Heart Association criteria for the clinical diagnosis of FH: low density lipoprotein cholesterol (LDL-C) >190 mg/dL (>4.9 mmol/L) and either a first degree relative with LDL-C>190 mg/dL or with known premature coronary heart disease (55 years men; <60 years women)

Simon Broome Familial Hypercholesterolemia Register diagnostic criteria for familial hypercholesterolemia [1-3]

Criteria	Description
a	Total cholesterol concentration above 7.5 mmol/liter (290 mg/dL) in adults or a total cholesterol concentration above 6.7 mmol/liter (259 mg/dL) in children aged less than 16 years, or
	Low-density lipoprotein cholesterol concentration above 4.9 mmol/liter (189 mg/dL) in adults or above 4.0 mmol/liter (155 mg/dL) in children
b	Tendinous xanthomata in the patient or a first-degree relative
c	DNA-based evidence of mutation in the *LDLR, PCSK9,* or *APOB* gene
d	Family history of myocardial infarction before age 50 years in a second-degree relative or before age 60 years in a first-degree relative
e	Family history of raised total cholesterol concentration above 7.5 mmol/liter (290 mg/dL) in a first- or second-degree relative

A "definite" FH diagnosis requires either criteria *a* and *b*, or criterion *c*.
A "probable" FH diagnosis requires either criteria *a* and *d*, or criteria *a* and *e*.

FH: familial hypercholesterolemia.

Dutch Lipid Clinic Network diagnostic criteria for familial hypercholesterolaemia

Criteria	Points
1) Family history	
▪ First-degree relative with known premature (men: <55 years; women: <60 years) coronary or vascular disease, or ▪ First-degree relative with known LDL-C above the 95th percentile	1
▪ First-degree relative with tendinous xanthomata and/or arcus cornealis, or ▪ Children <18 years of age with LDL-C above the 95th percentile	2
2) Clinical history	
▪ Patient with premature (men: <55 years; women: <60 years) coronary artery disease	2
▪ Patient with premature (men: <55 years; women: <60 years) cerebral or peripheral vascular disease	1
3) Physical examination	
▪ Tendinous xanthomata	6
▪ Arcus cornealis before age 45 years	4
4) LDL-C levels	
▪ LDL-C ≥8.5 mmol/L (325 mg/dL)	8
▪ LDL-C 6.5 to 8.4 mmol/L (251-325 mg/dL)	5
▪ LDL-C 5 to 6.4 mmol/L (191-250 mg/dL)	3
▪ LDL-C 4 to 4.9 mmol/L (155-190 mg/dL)	1
5) DNA analysis	
▪ Functional mutation in the LDLR, apoB, or PCSK9 gene	8
Choose only one score per group, the highest applicable diagnosis (diagnosis is based on the total number of points obtained) ▪ A "definite" FH diagnosis requires >8 points ▪ A "probable" FH diagnosis requires 6 to 8 points ▪ A "possible" FH diagnosis requires 3 to 5 points	

FH: familial hypercholesterolaemia; LDL-C: low-density lipoprotein-cholesterol.
* Exclusive of each other (ie, maximum six points if both are present).

Early corneal arcus

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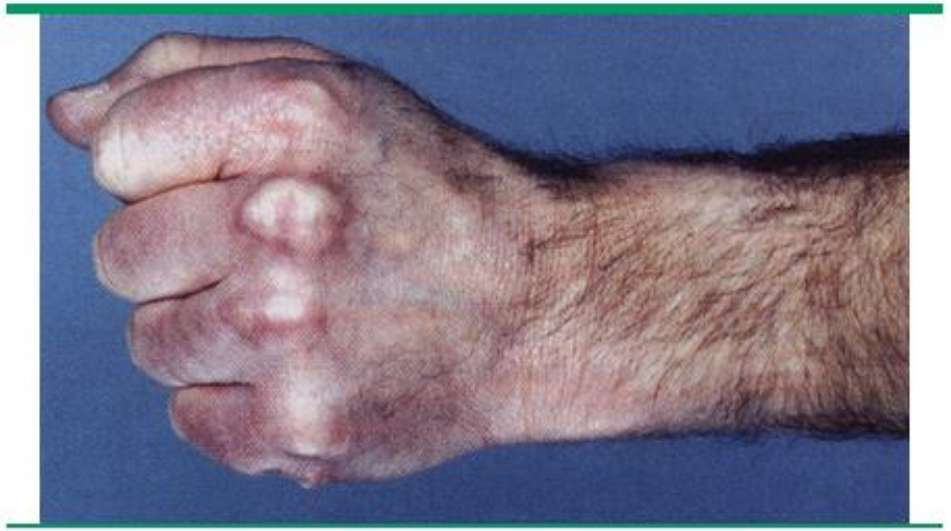
Tendon xanthomata



Tendon xanthomata on the dorsum of the hand in a patient with heterozygous familial hypercholesterolemia.

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Familial hypercholesterolemia

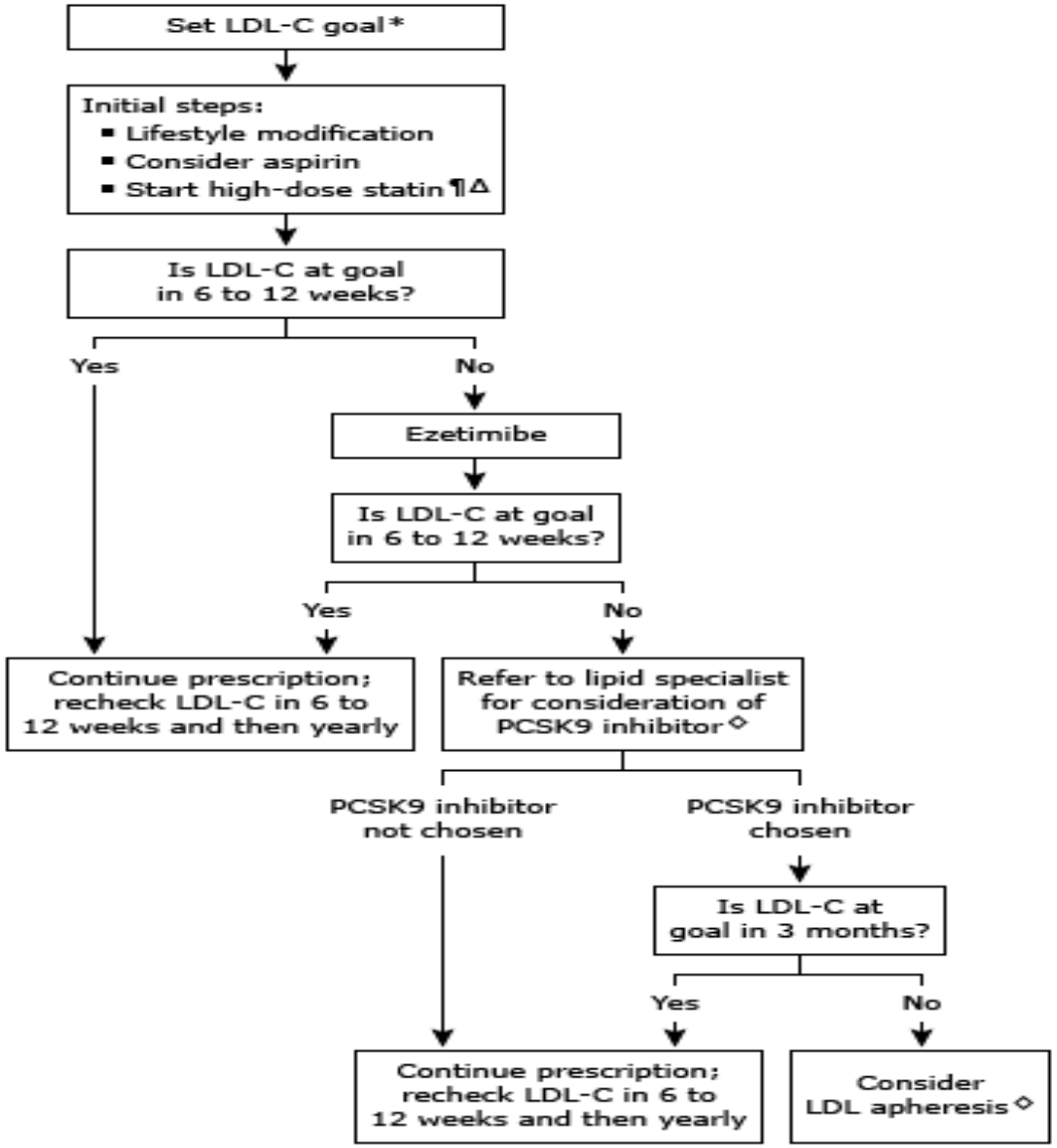
- Familial hypercholesterolemia (FH) is an autosomal dominant genetic disease caused by functional mutations at one of three genetic loci. In the absence of genetic testing, which confirms one of these mutations, FH is defined based on clinical criteria.

- Homozygous patients are rare and have an estimated prevalence of approximately 1:300,000 to 1:400,000. Heterozygous FH is estimated to occur in about 1 in 300 individuals in Europe and 1 in 200 to 250 individuals in the United States.

- Previously undiagnosed heterozygous FH patients present with symptoms or signs of cardiovascular disease or adverse cardiovascular disease events in early middle age. Many patients will be identified by the finding of a low-density lipoprotein cholesterol (LDL-C) greater than the 90th percentile for age and sex when the test was performed for cardiovascular risk screening.

- Health care providers should recommend lipid profiles for all first-degree relatives of patients with FH in order to identify other individuals at risk.

Algorithm for low density lipoprotein cholesterol (LDL-C) lowering in patients with untreated heterozygous familial hypercholesterolemia



* LDL-C ≤70 to 100 mg or LDL-C ≤50% baseline.
¶ Atorvastatin titrated to 80 mg daily or rosuvastatin 40 mg daily.
Δ Patients who cannot tolerate statin will likely need early specialist referral.
◇ Discuss high burden of therapy with patient (ie, cost, subcutaneous injections).

Hypertriglyceridemia

DEFINITION: we categorize patients into three groups based on their fasting triglyceride level.

- Normal: <150 mg/dL (1.7 mmol/L)
- Moderate hypertriglyceridemia: 150 to 885 mg/dL (1.7 to 10 mmol/L)
- Severe hypertriglyceridemia: >885 mg/dL (≥10 mmol/L)

Management

All patients with hypertriglyceridemia should participate in nonpharmacologic lifestyle interventions such as weight loss in obese patients, aerobic exercise, and avoidance of concentrated sugars and medications that raise serum TG levels.

Excellent glycemic control in patients with diabetes should be first-line therapy. Other risk factors for ASCVD, such as hypertension and smoking, should also be addressed.

●All patients with hypertriglyceridemia should have an assessment of their low-density lipoprotein cholesterol level. If the patient is not at goal, statin therapy should be considered.

●For patients with TG levels persistently >885 mg/dL (10 mmol/L) after nonpharmacologic interventions, we suggest starting drug therapy to lower the risk of pancreatitis.

We start with a fibrate: Fenofibrate can be prescribed as a nanocrystal formulation (145 mg daily taken without regard to meals), as micronized capsules (200 mg daily taken with dinner), or as fenofibric acid (also called choline fenofibrate; 145 mg daily without regard to meals).

●For patients with TG levels between 150 mg/dL (1.7 mmol/L) and 885 mg/dL (10 mmol/L) taking statin therapy, we suggest adding a second lipid-lowering drug, for cardiovascular disease events.

We usually start with icosapent ethyl (fish oil) 4 g daily.

●For patients with hypertriglyceridemia not clearly associated with a secondary cause, we screen family members with a fasting TG level.

The following are the commonly used fibrates:

- Fenofibrate: Fenofibrate can be prescribed as a nanocrystal formulation (145 mg daily taken without regard to meals), as micronized capsules (200 mg daily taken with dinner), or as fenofibric acid (also called choline fenofibrate; 145 mg daily without regard to meals)

- Gemfibrozil: Gemfibrozil is prescribed at a dose of 600 mg twice daily and is given before breakfast and dinner. In patients with fenofibrate-induced increases in serum creatinine, gemfibrozil is a good alternative.

- Bezafibrate: Bezafibrate is prescribed in doses of 200 mg three times daily or a sustained-release daily dose of 400 mg daily.

- Nicotinic acid: Although nicotinic acid at doses of 1500 to 2000 mg daily can reduce TG levels by 15 to 25 percent

Adult dosing, major side effects, and drug interaction potential of lipid-lowering drugs

Drug class	Dose range*	Administration	Major side effects and drug interaction potentials
Statins			
Atorvastatin	10 to 80 mg/day	Take any time	Muscle-related (eg, myalgia, myopathy, myositis, rhabdomyolysis); headache; gastrointestinal (eg, nausea, constipation, dyspepsia, diarrhea); sleep disturbance; elevations in hepatocellular enzymes and alkaline phosphatase. Statins are dependent on CYP metabolism and/or transmembrane transporters (eg, OATP, BCRP) for clearance, subjecting them to a significant number of clinically relevant drug interactions. Coadministration of drugs that alter CYP metabolism or drug transporters often requires dose limitations or avoidance. The patient's medication list should be analyzed using a drug interaction database (Lexicomp drug interactions) whenever therapy is adjusted.
Fluvastatin	IR: 20 to 80 mg/day	IR: Take in the evening Divide dose twice per day (morning and evening) if dose >40 mg/day	
	XR: 80 mg/day	XR: Take any time	
Lovastatin	IR: 20 to 80 mg/day	IR: Take with evening meal Divide dose twice per day with meals if dose >20 mg/day	
	XR: 20 to 60 mg/day	XR: Take in the evening	
Pitavastatin	1 to 4 mg/day	Take any time	
Pravastatin	10 to 80 mg/day	Take in the evening¶	
Rosuvastatin	5 to 40 mg/day	Take any time	
Simvastatin	10 to 40 mg/day	Take in the evening	
Cholesterol absorption inhibitor			
Ezetimibe	10 mg/day	Take any time	Generally well tolerated; low risk for potential drug interactions. Increased transaminases may be observed with concurrent statin use; however, coadministration is common.
PCSK9 inhibitors			
Alirocumab	75 to 150 mg every 2 weeks or 300 mg every 4 weeks	Administer by subcutaneous injection into thigh, abdomen, or upper arm	Injection site reactions. Low risk for potential drug interactions.
Evolocumab	140 mg every 2 weeks or 420 mg every month Homozygous familial hypercholesterolemia: 420 mg every month to 420 mg every 2 weeks		

Adenosine triphosphate citrate lyase inhibitor			
Bempedoic acid	180 mg daily	Take any time	Hyperuricemia, acute gouty arthritis; myalgia, muscle spasms, arthralgias; increased aspartate aminotransferase. Potential for significant drug interactions; dose limitations for some statins are recommended during concurrent use. The patient's medication list should be analyzed using a drug interaction database (Lexicomp drug interactions) whenever therapy is adjusted.
Fibric acid derivatives			
Fenofibrate	Nanocrystal: 145 mg/day Micronized: 90 to 200 mg/day Nonmicronized: 120 to 160 mg/day Fenofibric acid: 105 to 135 mg/day	Multiple formulations exist with varying dosing and administration Some formulations must be administered with food	Increased serum transaminases, muscle-related (eg, myalgia, myositis, rhabdomyolysis), gastrointestinal (eg, dyspepsia, nausea, bloating, cramping). Potential for significant drug interactions; eg, increased risk of myopathy with statins, enhanced anticoagulant effect of warfarin. Gemfibrozil use with statins is not recommended. The patient's medication list should be analyzed using a drug interaction database (Lexicomp drug interactions) whenever therapy is adjusted.
Gemfibrozil	600 mg twice per day	Take 30 to 60 minutes before meals	
Bezafibrate (not available in the United States)	400 mg/day	Take with or after meals	
Bile acid sequestrants			
Cholestyramine	Powder: 4 to 24 g/day	Take within 30 minutes of a meal Administer granules or powder as prepared suspension Do not hold cholestyramine in mouth for prolonged periods (may cause tooth discoloration or enamel decay) Administer other oral medications ≥1 hour before or 4 to 6 hours after bile acid sequestrants	Nausea, bloating, cramping, and constipation; elevations in hepatic transaminases and alkaline phosphatase. Impaired absorption of fat soluble vitamins and coadministered medications. The patient's medication list should be analyzed using a drug interaction database (Lexicomp drug interactions) whenever therapy is adjusted.
Colestipol	Granules: 5 to 30 g/day Tablet: 2 to 16 g/day		
Colesevelam	Granules or tablet: 3.75 g/day		
Nicotinic acid (niacin)	IR: 250 mg to 6 g/day	Take with meals	Not recommended for use in most patients due to poor tolerability and lack of efficacy for clinical endpoints. Prostaglandin-mediated cutaneous flushing, headache, warm sensation, and pruritus; hyperpigmentation (particularly in intertriginous regions), acanthosis nigricans, and dry skin; nausea, vomiting, diarrhea; myositis; hyperglycemia, hyperuricemia; hypotension; increased risk of infection. Low risk for potential drug interactions.
	XR (Niaspan): 0.5 to 2 g/day	Take at bedtime after a low-fat snack or evening meal	

IR: immediate release; XR: extended release; PCSK9 inhibitors: proprotein convertase subtilisin kexin type 9 inhibitors; LDL-C: low density lipoprotein cholesterol.

* Dose ranges provided are total daily doses for oral administration (except PCSK9 inhibitors) in adult patients with normal organ function. Statin dose ranges include low-, moderate-, and/or high-intensity LDL-C-lowering therapy, depending on specific statin. For indications and doses, refer to the relevant clinical topic reviews and Lexicomp drug information monographs included within UpToDate.
¶ Per United States labeling, may be taken any time of day; however, UpToDate contributors prefer evening administration due to pravastatin's short half-life.

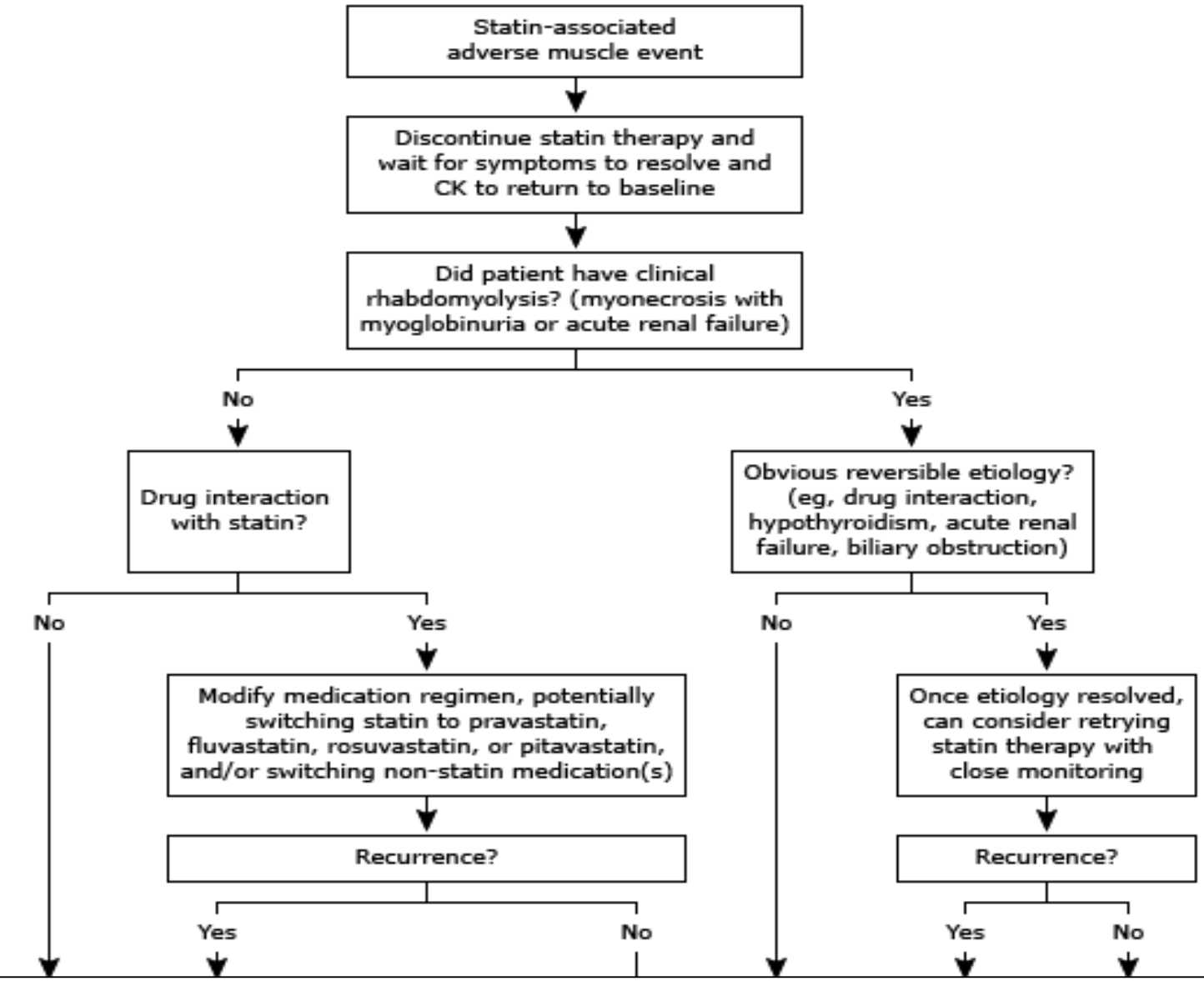
Monitoring

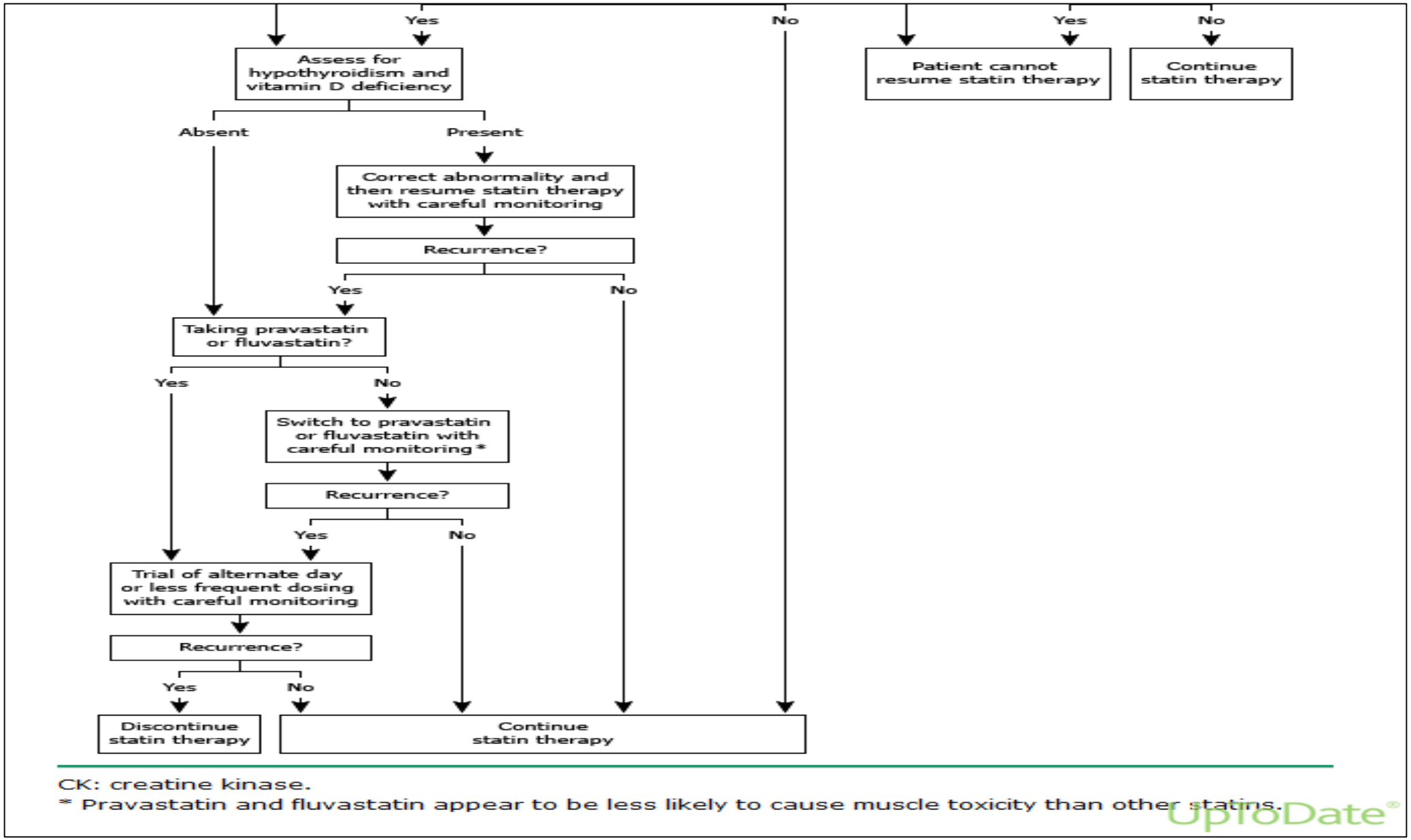
- Routine monitoring of serum creatine kinase (CK) levels is not recommended in patients on statins, but it is useful to obtain a baseline CK level for reference purposes prior to starting statin therapy.
- Patients treated with statins should be alerted to report the new onset of myalgias or weakness
- We check baseline aminotransferase levels prior to initiating statin therapy; we do not routinely monitor these levels in patients on statins.

The choice of statin

- Rosuvastatin, atorvastatin, and simvastatin cause the greatest percentage change in LDL cholesterol; they are preferred in patients who require a potent statin because of high cardiovascular risk or who require >35 percent reduction in LDL cholesterol.
- In patients with severe renal impairment, we suggest treatment with atorvastatin or Fluvastatin. These medications do not require dose adjustment.
- In patients with chronic liver disease who require a statin because of high cardiovascular risk, we suggest complete abstinence from alcohol and the use of pravastatin at a low dose
- We suggest not routinely monitoring serum creatine kinase (CK), but it is useful to obtain a baseline CK level for reference purposes prior to starting statin therapy. Patients treated with statins should be alerted to report the new onset of myalgias or weakness.
- We suggest checking baseline aminotransferase levels prior to initiating statin therapy; routine monitoring of these levels is not necessary for patients on statins.
- We suggest checking a thyroid-stimulating hormone level prior to initiating statin therapy.

Management of statin myopathy





CK: creatine kinase.

* Pravastatin and fluvastatin appear to be less likely to cause muscle toxicity than other statins.

Table 3 New recommendations, and new and revised concepts

New recommendations
Cardiovascular imaging for assessment of ASCVD risk
Assessment of arterial (carotid and/or femoral) plaque burden on arterial ultrasonography should be considered as a risk modifier in individuals at low or moderate risk.
Cardiovascular imaging for assessment of ASCVD risk
CAC score assessment with CT may be considered as a risk modifier in the CV risk assessment of asymptomatic individuals at low or moderate risk.
Lipid analyses for CVD risk estimation
Lp(a) measurement should be considered at least once in each adult person's lifetime to identify those with very high inherited Lp(a) levels >180 mg/dL (>430 nmol/L) who may have a lifetime risk of ASCVD equivalent to the risk associated with heterozygous familial hypercholesterolaemia.
Drug treatments of patients with hypertriglyceridaemia
In high-risk (or above) patients with TG between 1.5 and 5.6 mmol/L (135 - 499 mg/dL) despite statin treatment, n-3 PUFAs (icosapent ethyl 2 × 2g/day) should be considered in combination with statins.
Treatment of patients with heterozygous FH
In primary prevention, for individuals with FH at very-high risk, an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) should be considered.

Treatment of dyslipidaemias in older people

Treatment with statins is recommended for primary prevention, according to the level of risk, in older people aged ≤75.

Treatment of dyslipidaemias in older people

Initiation of statin treatment for primary prevention in older people aged >75 may be considered, if at high risk or above.

Treatment of dyslipidaemias in DM

In patients with T2DM at very-high risk, an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.4 mmol/L (<55mg/dL) is recommended.

In patients with T2DM at high risk, an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.8 mmol/L (<70 mg/dL) is recommended.

Statins are recommended in patients with T1DM who are at high or very-high risk.

Treatment of dyslipidaemias in DM

Intensification of statin therapy should be considered before the introduction of combination therapy.

If the goal is not reached, statin combination with ezetimibe should be considered.

Treatment of dyslipidaemias in DM

Statin therapy is not recommended in pre-menopausal patients with DM who are considering pregnancy or not using adequate contraception.

Lipid-lowering therapy in patients with ACS

For patients who present with an ACS, and whose LDL-C levels are not at goal despite already taking a maximally tolerated statin dose and ezetimibe, adding a PCSK9 inhibitor early after the event (if possible, during hospitalization for the ACS event) should be considered.

Drug treatments of hypertriglyceridaemia

Statin treatment is recommended as the first drug of choice for reducing CVD risk in high-risk individuals with hypertriglyceridaemia [TG >2.3 mmol/L (200 mg/dL)].

Treatment of patients with heterozygous FH

For FH patients with ASCVD who are at very-high risk, treatment to achieve at least a 50% reduction from baseline and an LDL-C <1.4 mmol/L (<55 mg/dL) is recommended. If goals cannot be achieved, a drug combination is recommended.

Treatment of patients with heterozygous FH

Treatment with a PCSK9 inhibitor is recommended in very-high-risk FH patients if the treatment goal is not achieved on maximal tolerated statin plus ezetimibe.

Treatment of dyslipidaemias in older people

It is recommended that the statin is started at a low dose if there is significant renal impairment and/or the potential for drug interactions, and then titrated upwards to achieve LDL-C treatment goals.

Lipid-lowering therapy in patients with ACS

If the LDL-C goal is not achieved after 4 - 6 weeks despite maximal tolerated statin therapy and ezetimibe, addition of a PCSK9 inhibitor is recommended.

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Lipid analyses for CVD risk estimation

ApoB analysis is recommended for risk assessment, particularly in people with high TG, DM, obesity or metabolic syndrome, or very low LDL-C. It can be used as an alternative to LDL-C, if available, as the primary measurement for screening, diagnosis, and management, and may be preferred over non-HDL-C in people with high TG, DM, obesity, or very low LDL-C.

Pharmacological LDL-C lowering

If the goals are not achieved with the maximum tolerated dose of statin, combination with ezetimibe is recommended.

Pharmacological LDL-C lowering

For secondary prevention, patients at very-high risk not achieving their goal on a maximum tolerated dose of statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended.

For very-high-risk FH patients (that is, with ASCVD or with another major risk factor) who do not achieve their goals on a maximum tolerated dose of statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended.

Five definitions of the metabolic syndrome

Parameters	NCEP ATP3 2005*	IDF 2009	EGIR 1999	WHO 1999	AACE 2003
Required			Insulin resistance or fasting hyperinsulinemia (ie, in top 25% of the laboratory-specific reference range)	Insulin resistance in top 25%[Δ]; fasting glucose ≥6.1 mmol/L (110 mg/dL); 2-hour glucose ≥7.8 mmol/L (140 mg/dL)	High risk of insulin resistance[◇] or BMI ≥25 kg/m^2 or waist ≥102 cm (men) or ≥88 cm (women)
Number of abnormalities	**≥3 of:**	**≥3 of:**	**And ≥2 of:**	**And ≥2 of:**	**And ≥2 of:**
Glucose	Fasting glucose ≥5.6 mmol/L (100 mg/dL) or drug treatment for elevated blood glucose	Fasting glucose ≥5.6 mmol/L (100 mg/dL) or diagnosed diabetes	Fasting glucose 6.1 to 6.9 mmol/L (110 to 125 mg/dL)		Fasting glucose ≥6.1 mmol/L (110 mg/dL); ≥2-hour glucose 7.8 mmol/L (140 mg/dL)
HDL cholesterol	<1.0 mmol/L (40 mg/dL) (men); <1.3 mmol/L (50 mg/dL) (women) or drug treatment for low HDL cholesterol[§]	<1.0 mmol/L (40 mg/dL) (men); <1.3 mmol/L (50 mg/dL) (women) or drug treatment for low HDL cholesterol	<1.0 mmol/L (40 mg/dL)	<0.9 mmol/L (35 mg/dL) (men); <1.0 mmol/L (40 mg/dL) (women)	<1.0 mmol/L (40 mg/dL) (men); <1.3 mmol/L (50 mg/dL) (women)
Triglycerides	≥1.7 mmol/L (150 mg/dL) or drug treatment for elevated triglycerides[§]	≥1.7 mmol/L (150 mg/dL) or drug treatment for high triglycerides	or ≥2.0 mmol/L (180 mg/dL) or drug treatment for dyslipidemia	or ≥1.7 mmol/L (150 mg/dL)	≥1.7 mmol/L (150 mg/dL)
Obesity	Waist ≥102 cm (men) or ≥88 cm (women)[¥]	Waist ≥94 cm (men) or ≥80 cm (women)	Waist ≥94 cm (men) or ≥80 cm (women)	Waist/hip ratio >0.9 (men) or >0.85 (women) or BMI ≥30 kg/m^2	
Hypertension	≥130/85 mmHg or drug treatment for hypertension	≥130/85 mmHg or drug treatment for hypertension	≥140/90 mmHg or drug treatment for hypertension	≥140/90 mmHg	≥130/85 mmHg

NCEP: National Cholesterol Education Program; IDF: International Diabetes Federation; EGIR: Group for the Study of Insulin Resistance; WHO: World Health Organization; AACE: American Association of Clinical Endocrinologists; HDL: high-density lipoprotein; CVD: cardiovascular disease; BMI: body mass index.

Therapeutic goals for management of metabolic syndrome

	Goals
Lifestyle risk factors	
Abdominal obesity	Year 1: Reduce body weight 7 to 10 percent
	Continue weight loss thereafter with ultimate goal BMI <25 kg/m^2
Physical inactivity	At least 30 min (and preferably ≥60 min) continuous or intermittent moderate intensity exercise 5 times per week, but preferably daily
Atherogenic diet	Reduced intake saturate fat, trans fat, cholesterol
Metabolic risk factors	
Dyslipidemia	
Primary target elevated LDL cholesterol	High risk*: <100 mg/dL (2.6 mmol/>L); optional <70 mg/dL
	Moderate risk: <130 mg/dL (3.4 mmol/L)
	Lower risk: <160 mg/dL (4.9 mmol/L)
Secondary target elevated non-HDL cholesterol	High risk*: <130 mg/dL (3.4 mmol/L); optional <100 mg/dL (2.6 mmol/L) very high risk
	Moderate risk: <160 mg/dL (4.1 mmol/L)
	Lower risk: <190 mg/dL (4.9 mmol/L)
Tertiary target reduced HDL cholesterol	Raise to extent possible with weight reduction and exercise
Elevated blood pressure	Reduce to at least <140/90 (<130/80 if diabetic)
Elevated glucose	For IFG, encourage weight reduction and exercise
	For type 2 DM, target A1C <7 percent
Prothrombotic state	Low-dose aspirin for high-risk patients
Proinflammatory state	Lifestyle therapies; no specific interventions

LDL: low-density lipoprotein; HDL: high-density lipoprotein; DM: diabetes mellitus; IFG: impaired fasting glucose.
* High-risk: diabetes, known coronary artery disease.

Definitions of metabolic syndrome in children and adolescents

Parameters	Modified ATP III	IDF (10 to 16 years)	NHANES III
Required			
Waist circumference		≥90th percentile*	≥90th percentile
Number of abnormalities	≥3	≥2	All
Triglyceride	>95th percentile	≥150 mg/dL (1.7 mmol/L)	≥110 mg/dL (1.24 mmol/L)
HDL	<5th percentile	<40 mg/dL (1.03 mmol/L)	≤40 mg/dL (1.03 mmol/L)
BP	Either	Either	≥90th percentile
Systolic	>95th percentile	>130 mmHg	
Diastolic	>95th percentile	≥85 mmHg	
Glucose	Impaired glucose tolerance	≥100 mg/dL (5.6 mmol/L)	Fasting ≥110 mg/dL (6.1 mmol/L)

ATP III: Adult Treatment Panel; IDF: International Diabetes Federation; NHANES: National Health and Nutrition Examination Survey; HDL: high-density lipoprotein; BP: blood pressure.
* Ethnic-specific waist circumference (see Fernandez JR, Redden DT, Pietrobelli A, et al. Waist circumference percentiles in nationally representative samples of African-American, European-American, and Mexican-American children and adolescents. J Pediatr 2004; 145:439).