Pharmacotherapy 1

Dyslipidemia

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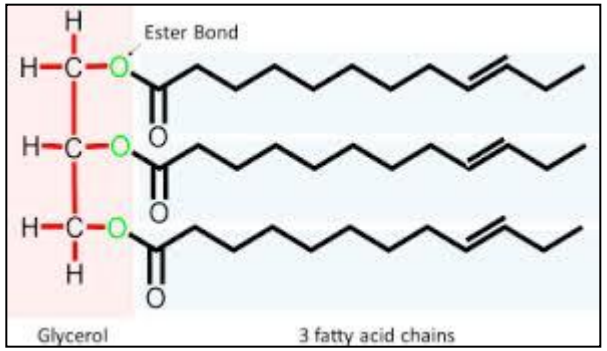
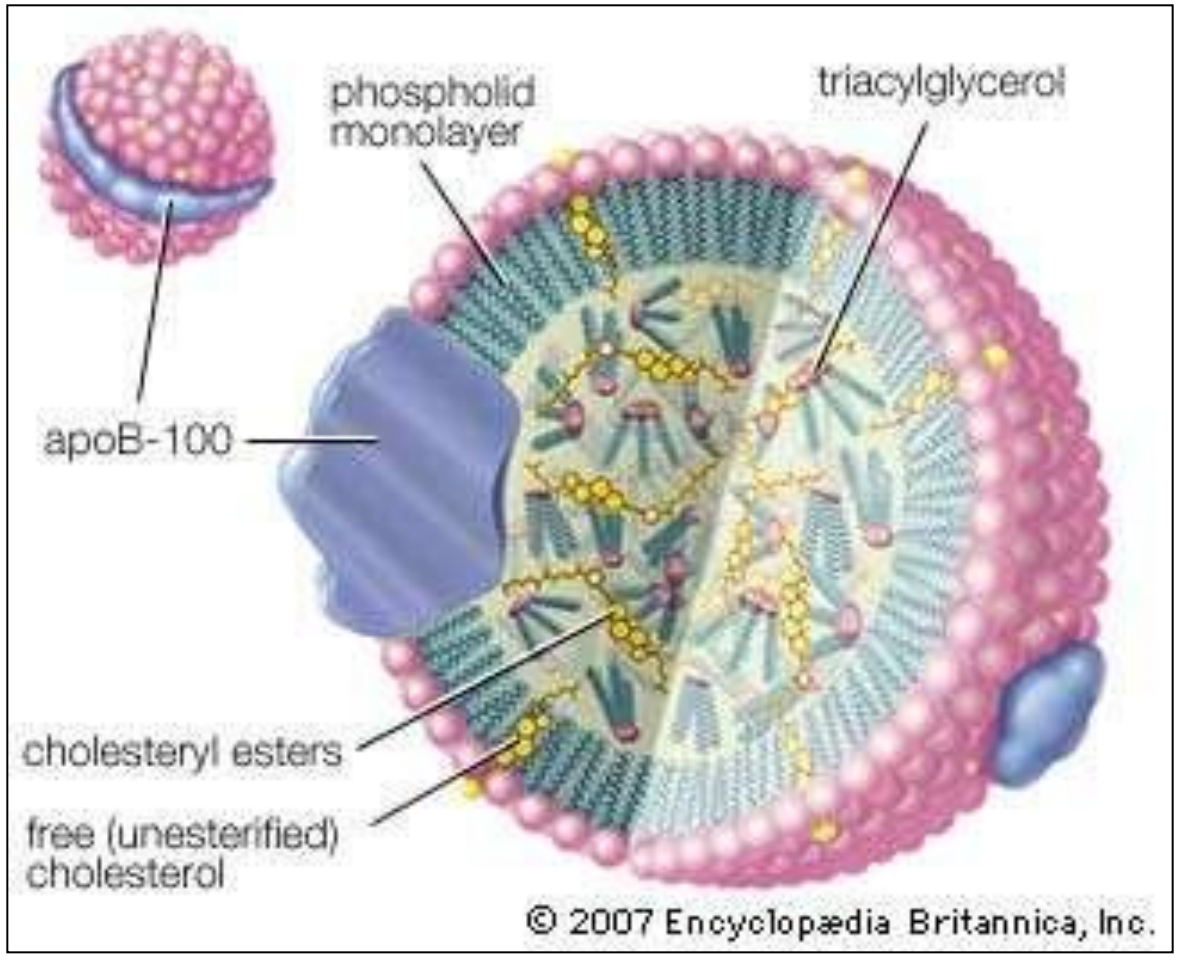
Dyslipidemia is elevated total cholesterol, LDL cholesterol, or triglycerides; low HDL cholesterol; or a combination of these abnormalities.

➢ Physiology and Pathophysiology

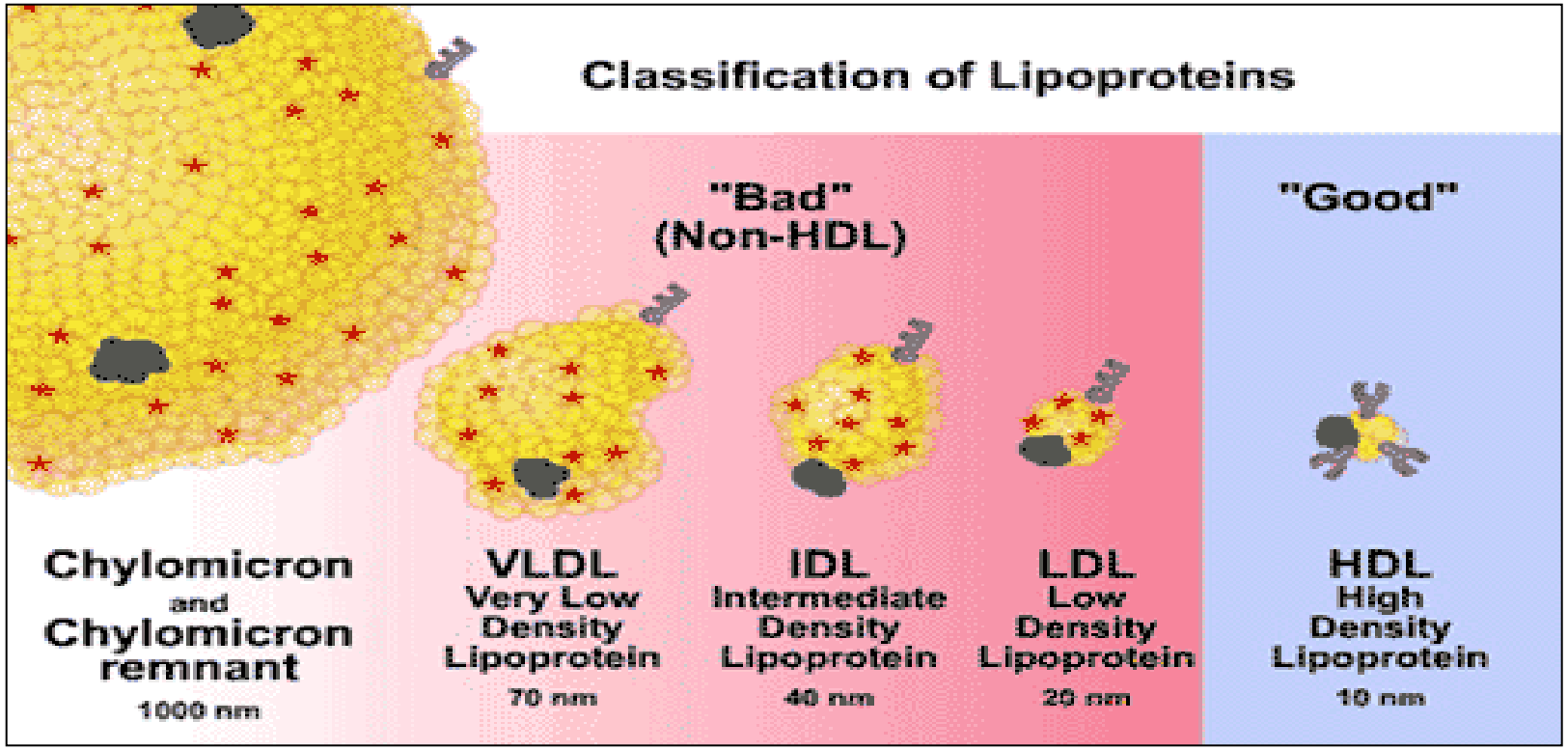
✓ Cholesterol, triglycerides, and phospholipids are transported in blood as complexes of lipids and proteins (lipoproteins).

✓ Plasma lipoproteins are spherical particles with surfaces that consist largely of phospholipid, free cholesterol, and protein, and cores that consist mostly of triglyceride and cholesterol ester.



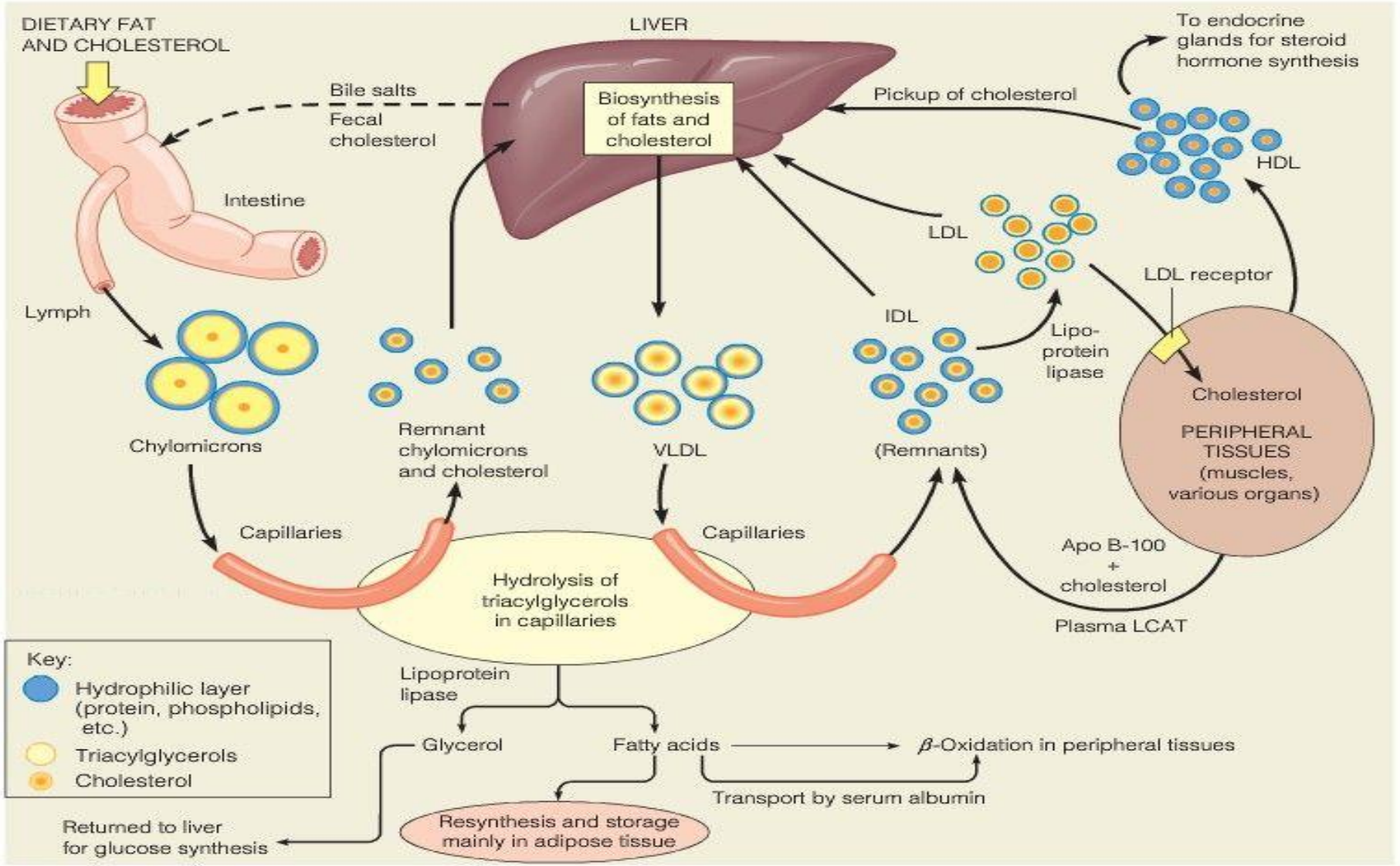


- ✓ The three major classes of lipoproteins found in serum are LDL, HDL, and VLDL.
- ✓ Abnormalities of plasma lipoproteins can result in a predisposition to coronary, cerebrovascular, and peripheral vascular arterial disease



%Protein:	1-2	6-10	18-22	45-55
%TG:	80- 95	55-80	5-15	5-10
%Cholesterol:	2-4	16-22	45-50	15-20

Normal Lipoprotein Metabolism



- ✓ **Primary or genetic lipoprotein disorders** are classified into six categories (Fredrickson-Levy-Lees Classification of Hyperlipoproteinemia):
  - I (chylomicrons) - rare
  - IIa (LDL) - **common**
  - IIb (LDL + VLDL) - **most common**
  - III (intermediate density lipoprotein) - rare
  - IV (VLDL) - **common**
  - V (VLDL + chylomicrons) - rare

- ✓ The primary defect in familial hypercholesterolemia is inability to bind LDL to the LDL receptor (LDL-R). This leads to a lack of LDL degradation by cells and unregulated biosynthesis of cholesterol.

- ✓ **Secondary forms of dyslipidemia** also exist, and several drug classes may affect lipid levels (eg, progestins, thiazide diuretics, glucocorticoids, β-blockers, isotretinoin, protease inhibitors, cyclosporine, and sirolimus) → should be initially managed by correcting the underlying abnormality, including modification of drug therapy when appropriate.

Table 1: Secondary Causes of Lipoprotein Abnormalities	
Hypercholesterolemia	Hypothyroidism, Obstructive liver disease, Nephrotic syndrome Anorexia nervosa, Acute intermittent porphyria, Drugs: progestins, thiazide diuretics, glucocorticoids, beta-blockers, isotretinoin, protease inhibitors, cyclosporine, mirtazapine, sirolimus
Hypertriglyceridemia	Obesity, Diabetes mellitus, Lipodystrophy, Glycogen storage disease, Sepsis, Pregnancy, Acute hepatitis, Systemic lupus erythematous, Monoclonal gammopathy: multiple myeloma, lymphoma, Drugs: Alcohol, estrogens, isotretinoin, beta blockers, glucocorticoids, bile-acid resins, thiazides; asparaginase, interferons, azole antifungals, mirtazapine, anabolic steroids, sirolimus
Hypocholesterolemia	Malnutrition, Malabsorption, Myeloproliferative diseases, Chronic infectious diseases: AIDS, tuberculosis, Chronic liver disease
Low HDL	Malnutrition, Obesity, Drugs: beta-blockers, anabolic steroids, probucol, isotretinoin, progestins

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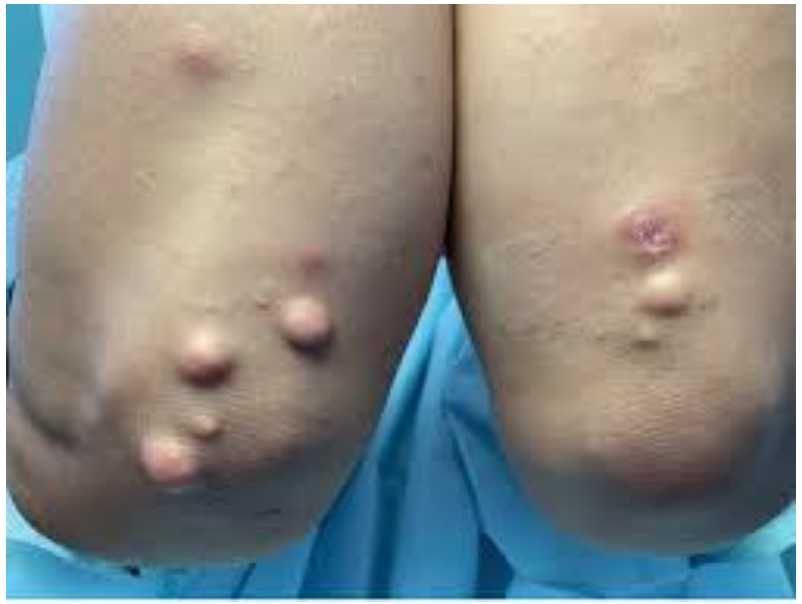
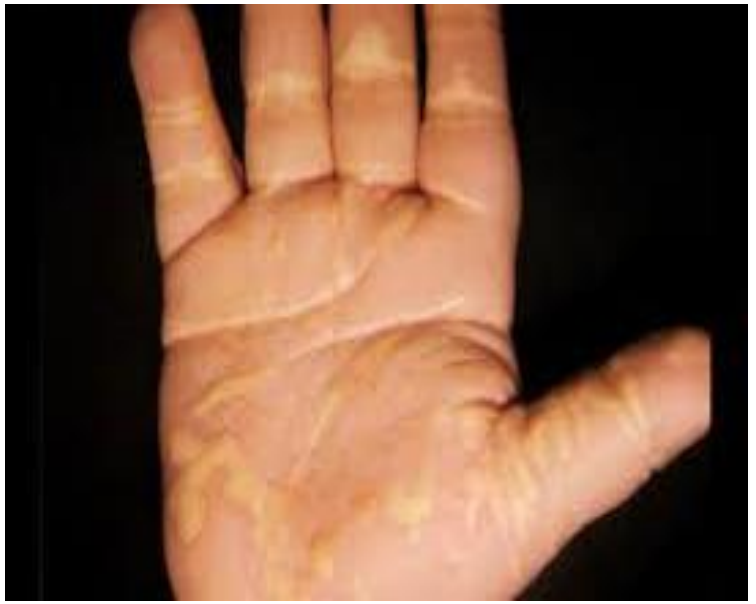




➢ Clinical Presentation

✓ <u>Symptoms</u>

- Most patients are asymptomatic for many years.
- Symptomatic patients may complain of chest pain, palpitations, sweating, anxiety, SOB, abdominal pain, or loss of consciousness or difficulty with speech or movement.

✓ <u>Signs</u>

None to abdominal pain, pancreatitis, eruptive xanthomas, peripheral polyneuropathy, high BP, BMI >30 kg/m^2, or waist size > 40 in (102 cm) in men (35 in [89 cm] in women).

✓ <u>Laboratory Tests</u>

Elevations in total cholesterol, LDL, triglycerides, ApoB, and hsCRP and low HDL.

Various screening tests for manifestations of vascular disease (ankle-brachial index, exercise testing) and diabetes (fasting glucose, oral glucose tolerance test, hemoglobin A1c).

Updated slide

➢ Patient Evaluation

- ✓ A fasting (12 hours or longer) lipoprotein profile should be measured in all adults 20 years of age or older at least once every 5 yrs.
- ✓ TG may be elevated in non-fasted individuals; total cholesterol is only modestly affected by fasting.
- ✓ VLDL = triglyceride/5
- ✓ LDL = total cholesterol - (VLDL + HDL).
- ✓ Total cholesterol is comprised of cholesterol derived from LDL, VLDL, and HDL
- ✓ If the profile is obtained in the nonfasted state, only total cholesterol and HDL-C will be usable because LDL-C is usually a calculated value; if total cholesterol is greater than or equal to 200 mg/dL, or if HDL-C is less than 40 mg/dL, a follow-up fasting lipoprotein profile should be obtained.
- ✓ Perform ASCVD risk assessment. When indicated, use the PREVENT-ASCVD Calculator.*

*Available at: https://professional.heart.org/en/guidelines-and-statements/prevent-calculator.

Updated slide

Table 12. Crosswalk Between 10-Year Risk ASCVD Estimates From PCE and PREVENT-ASCVD Equations

	Approximate Equivalent Ranges of 10-Year ASCVD Risk Estimates*	
Risk Group	**PCE**	**PREVENT-ASCVD**
Low	<5%	<3%
Borderline	5% to <7.5%	3% to <5%
Intermediate	7.5% to <20%	5% to <10%
High	≥20%	≥10%

* The PREVENT-ASCVD equations generally provide 10-year risk estimates that are 40% to 50% lower than the PCE estimates because the PCE calculator often overestimated the risk for adults.

ASCVD denotes atherosclerotic cardiovascular disease; and PCE, pooled cohort equations. Adapted from Khan et al.[1,3]

Given that the PREVENT-ASCVD equations accurately predict ASCVD risk, the threshold for consideration of LLT in primary prevention was set at a PREVENT-ASCVD 10-year risk estimate of ≥3%.

Table 2: Classification of Total-, LDL-, HDL-Cholesterol and Triglycerides in Adults		
Total Cholesterol	<200 mg/dL (<5.17 mmol/L) 200-239 mg/dL (5.17-6.20 mmol/L) ≥240 mg/dL (≥6.21 mmol/L)	Desirable Borderline high High
LDL Cholesterol	<100 mg/dL (<2.59 mmol/L) 100-129 mg/dL (2.59-3.35 mmol/L) 130-159 mg/dL (3.36-4.13 mmol/L) 160-189 mg/dL (4.14-4.90 mmol/L) ≥190 mg/dL (≥4.91 mmol/L)	Optimal Near or above optimal Borderline high High Very high
HDL Cholesterol	<40 mg/dL (<1.03 mmol/L) <50 mg/dL (≥1.3 mmol/L)	Low (men) Low (women)
Triglycerides	<150 mg/dL (<1.70 mmol/L) 150-199 mg/dL (1.70-2.25 mmol/L) 200-499 mg/dL (2.26-5.64 mmol/L) ≥500 mg/dL (≥5.65 mmol/L)	Normal Borderline high High Very high

For your reference

Table 3: Intensity of Statin Therapy by Drug and Dose

High-intensity Statin Therapy	**Moderate**-intensity Statin Therapy	**Low**-intensity Statin Therapy
Daily dose lowers LDL on average by ≥50%:	Daily dose lowers LDL on average by 30 to <50%:	Daily dose lowers LDL on average by <30%:
- Atorvastatin 40-80 mg **- Rosuvstatin 20-40 mg**	**- Atorvastatin 10-20 mg** **- Rosuvastatin 5-20 mg** **- Simvastatin 20-40 mg*** **- Pravastatin 40-80 mg** **- Lovastatin 40 mg** - Fluvastin XL 80 mg **- Fluvastatin 40 mg BID** - Pitavastatin 2-4 mg	- Simvastatin 10 mg **- Pravastatin 10-20 mg** **- Lovastatin 20 mg** - Fluvastatin 20-40 mg - Pitavastin 1 mg

*Simvastatin is not recommended by the FDA to be started at 80 mg/day due to increased risk of myopathy and rarely rhabdomyolysis .

Boldface type indicates medications that have CV outcome data from RCTs when given in the specified dose.

Use this table

TABLE 35-5

Intensity of Statin Therapy by Drug and Daily Dose

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Lowers LDL-C on average by ≥50%	Lowers LDL-C on average by 30% to <50%	Lowers LDL-C on average by <30%
Atorvastatin 40-80 mg[b] Rosuvastatin 20-40 mg[b]	Atorvastatin 10-20 mg[b] Rosuvastatin 5-10 mg[b] Simvastatin 20-40 mg[a,b] Pravastatin 40-80 mg Lovastatin 40 mg[b] Fluvastatin XL 80 mg Fluvastatin 40 mg BID[b] Pitavastatin 2-4 mg[b]	Simvastatin 10 mg Pravastatin 10-20 mg[b] Lovastatin 20 mg[b] Fluvastatin 20-40 mg Pitavastatin 1 mg

FDA, Food and Drug Administration; RCT, randomized clinical trials.

a Simvastatin is not recommended by the FDA to be initiated at 80 mg/day due to increased risk of myopathy and rhabdomyolysis.

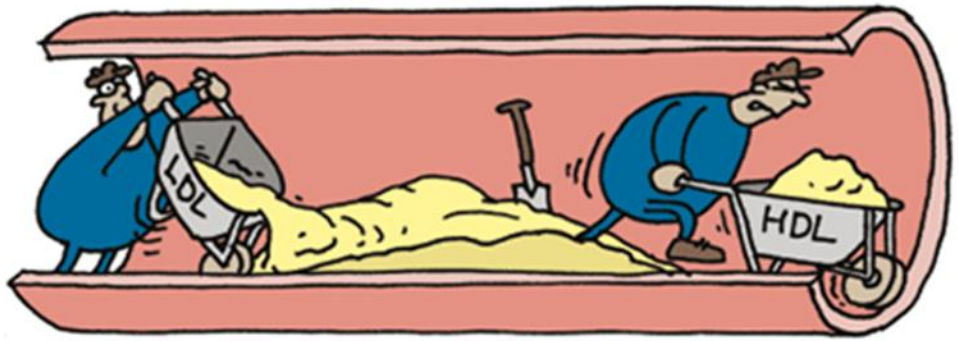
b Evidence of improved cardiovascular outcomes based on at least one RCT when given in the specified dose.

➢ Treatment

<u>Desired Outcomes</u>

- ✓ The primary goal is reduce the risk of first or recurrent events such as MI, angina, HF, ischemic stroke, or PAD.

- ✓ The goals of therapy expressed as LDL-C levels are surrogate endpoints.



➢ Nonpharmacologic Therapy

- ✓ Ideally, TLC including reduced intake of saturated fats and cholesterol, increased stanol/sterol (occur naturally in small amounts in many grains, vegetables, fruits, legumes, nuts, and seeds) and fiber intake, weight reduction, and increased physical activity should be used to attain lower LDL-C and to achieve reductions in CHD risk.
- ✓ In general, physical activity of moderate intensity 30 minutes per day for most days of the week should be encouraged.
- ✓ All patients should also be counselled to stop smoking.
- ✓ TLC may prevent the need for drug therapy, augment LDL-lowering drug therapy, and allow for lower doses.
- ✓ Many persons should be given a three-month trial (two visits spaced 6 weeks apart) of dietary therapy and TLC before advancing to drug therapy unless patients are at very high risk (severe hypercholesterolemia, known CHD, CHD risk equivalents, multiple risk factors, and strong family history) → involve all family members, especially if the patient is not the primary person preparing food.

✓Total daily fiber intake should be about 20 to 30 g/d, with about 25% or 6 g/d, being soluble fiber (oat bran, pectins, and psyllium products) →little or no effect on HDL-C or TG

✓Each 20 gm per day ingestion of fish lowers CHD risk by 7% and eating fish once weekly or more should reduce CHD mortality.

✓Fish oil supplementation provides an increased amount of the omega-3 polyunsaturated fatty acids (eicosapentaenoic acid and docosahexaenoic acid).

✓ Fish oil supplementation has a large effect in reducing triglycerides and VLDL-C, but it either has no effect on total and LDL-C or may cause elevations in these fractions.

- ✓Smoking, obesity, a sedentary life-style and drugs such as β-blockers lower HDL.
- ✓HDL may be elevated by moderate alcohol ingestion (less than two drinks per day), physical exercise, smoking cessation, weight loss, oral contraceptives, phenytoin, and terbutaline.
- ✓If all recommended dietary changes were instituted, the estimated average reduction in LDL would range from 20% to 30%.
- ✓Drug therapy is indicated following an adequate trial of TLC changes.

Use this table

TABLE 35-4

Nonpharmacologic Therapy to Improve Lipid Levels and ASCVD Risk

Recommendations to Modify Select Lipid Parameters	
Lower LDL cholesterol	• Increase soluble fiber intake • Phytosterol (2 g/day) supplementation
Increase HDL cholesterol	• Increase physical activity • Smoking cessation
Lower triglycerides	• Lose weight (5%-10% body weight loss) • Increase physical activity • Abstain from alcohol • Reduce intake of refined carbohydrates and sugars
Recommendations to Reduce ASCVD Risk	
Nutrition and diet	• Avoid eating *trans* fats • Increase intake of vegetables, fruits, legumes, nuts, whole grains, and fish • Replace foods containing saturated fats with unsaturated (monounsaturated and polyunsaturated) fats • Minimize intake of processed meat products, refined carbohydrate foods, and sweetened beverages • Reduce intake of cholesterol and sodium-containing foods • For patients who are overweight or obese, reduce daily calories to achieve and maintain weight loss of 5%-10%
Physical activity	• Obtain at least 150 min/wk of moderate-intensity or 75 minutes of vigorous-intensity physical activity • Decrease sedentary behaviors
Other lifestyle factors	• Smoking cessation and avoiding tobacco products • Avoid secondhand smoke exposure

Table 4: Macronutrient Recommendations for the TLC Diet	
Component*	Recommended Intake
Total fat	25%-35% of total calories
Saturated fat	Less than 7% of total calories
Polyunsaturated fat	Up to 10% of total calories
Monounsaturated fat	Up to 20% of total calories
Carbohydrates#	50%-60% of total calories
Cholesterol	<200 mg/day
Dietary Fiber	20-30 grams/d
Plant sterols	2 grams/d
Protein	Approximately 15% of total calories
Total calories	To achieve and maintain desirable body weight

*: Calories from alcohol not included.

#: Carbohydrates should derive from foods rich in complex carbohydrates such as whole grains, fruits, and vegetables.

New Slide

➢Updated Pharmacological Guidelines

- ✓ 2026 Updated ACC/AHA dyslipidemia guidelines shift toward *earlier*, *personalized*, and *target-driven* lipid lowering using *additional biomarkers* and *faster* escalation *beyond statins* to reduce *lifetime* ASCVD risk.
- ✓ Start statin based on risk, aim for LDL targets, and add nonstatin therapy (escalate) early if goals are not achieved to reduce ASCVD risk (Lower LDL = lower ASCVD risk).
- ✓ The 2018 ACC/AHA Blood Cholesterol Guideline identified statin benefit groups where the data from RCT demonstrate clear evidence that the benefit of statin therapy outweighs the potential risks. It identifies groups of patients who qualify for treatment with statins to reduce the 10-year risk of ASCVD in secondary and primary intervention. Ten-year risk should be calculated beginning at age 40 in patients without ASCVD or LDL-C ≥ 190 mg/ dL. Lifetime risk may be calculated in patients age 20– 39 and patients age 40– 59 with a 10-year risk < 7.5% to inform decisions regarding lifestyle modification.

New Slide

✓ Major differences (Summary: treat EARLY, treat to TARGET, ESCALATE FAST)

Feature	2018	2026
Framework	Statin benefit groups	Continuous risk-based approach
Decision trigger	Group membership (Statin eligible groups)	Risk + LDL target
Risk tool	Pooled cohort	PREVENT
Age focus	≥40 yrs	≥30 yrs
Targets	Not emphasized (Max/max-tolerated dose)	Core component (Not just max dose but reach goal)
Approach	Stepwise (Prolonged over months) Sequential escalation after titrating to full statin trial	Earlier + aggressive (Reach LDL goal FAST) Add nonstatin Tx early (after first check) instead of prolonged titration, do not delay until multiple visits

✓ Steps summary:

1. Assess risk
2. Set LDL goal
3. Start statin
4. Reassess (4–12 weeks)
5. Add ezetimibe if needed
6. Escalate further if needed

New Slide

✓ Risk Assessment (age + tools)

❖ Age-based approach:

- 20 - 39 yrs (young patients = low short-term risk but high long-term risk)

- Focus on **lifetime risk (**Risk of developing ASCVD over remaining life**)**
- Consider statin if:
  - LDL ≥160 mg/dL
  - Strong family history

- 40 - 75 yrs: Use 10-year risk + lifetime risk (use it when age 40 - 59 with low 10-year risk (<7.5%))

❖ Risk categories (using PREVENT):

- Low (< 3%)
- Borderline (3 - 5%)
- Intermediate (5 - 10%)
- High (≥ 10%)

New Slide

❖ Assess risk enhancers:

- Lp(a): measure once in all adults (genetic risk marker → not modified by lifestyle)
- ApoB: selective use (esp. if high TG/DM/CKM syndrome)
- CAC score: if unsure (to reclassify borderline/intermediate risk)

✓ **LDL Targets by risk:**

❖ Very high-risk ASCVD → **< 55 mg/dL & (Non-HDL-C goal < 85 mg/dL**

❖ High risk (primary prevention) → **< 70 mg/dL & (Non-HDL-C goal < 100 mg/dL)**

❖ Moderate risk (Borderline/intermediate risk) → **< 100 mg/dL & (Non-HDL-C goal < 130 mg/dL)**

New Slide

✓ Statin

❖ High-intensity (↓ LDL ≥ 50%):

- Use in:

  - ASCVD
  - LDL ≥ 190

❖ Moderate-intensity (↓ LDL 30 - 49%):

- Use in:

  - Diabetes
  - Primary prevention

New Slide

✓ Diabetes

- ❖ Age 40 - 75 → **ALL** get statin
- ❖ Intensity depends on risk:
  - Moderate-intensity: **most** patients
  - High-intensity if multiple risk factors: Long duration (> 10 y T2DM), Albuminuria, eGFR < 60, Retinopathy/neuropathy, Age > 50
- ❖ Target: usually **< 70 mg/dL**

✓ Reassess

- ❖ Check lipids in **4 - 12 weeks** after starting/changing therapy then periodically (every 3 - 12 months)
- ❖ Evaluate: goal attainment & % LDL reduction
- ❖ If not at goal after initial check, do not wait months and do not keep increasing statin only

New Slide

✓ When to add ezetimibe

- ❖ If LDL above goal after first reassessment
- ❖ Do NOT wait for multiple statin titrations
- ❖ Early if: ASCVD, LDL ≥ 190, high baseline LDL

✓ When to add PCSK9 / other drugs

- ❖ Add PCSK9 inhibitor if:
  - Still above goal after statin + ezetimibe
  - Very high-risk ASCVD
- ❖ Add bempedoic acid (inhibits cholesterol synthesis with less muscle toxicity) when:
  - Statin intolerance
  - Need additional LDL lowering
  - Prefer oral option
- ❖ Add inclisiran when:
  - Poor adherence to injections
  - Want infrequent dosing (every 6 months)

New Slide

✓ Risk Enhancers:

❖ Use in borderline/intermediate risk (5–20%, 10-yr ASCVD risk)

❖ Key enhancers:

- Family history of premature ASCVD
- LDL ≥ 160
- CKD
- Metabolic syndrome

✓ **Specific markers** (more use of biomarkers + imaging):

❖ **Lp(a)**

- Measure once in all adults
- Use if: family history, premature ASCVD
- High = ↑ risk → treat more aggressively

❖ **ApoB**

- Use when: high TG, DM, obesity
- Reflects atherogenic particle number

New Slide

✓ CAC* (to guide uncertain cases)

❖ Use when:

- Borderline/ Intermediate risk (5–20%, 10-yr ASCVD risk) → mainly used when risk is not clearly low or high
- Decision about statin is uncertain

❖ Interpretation:

- CAC = 0 AU → Can defer statin (except high-risk)
- CAC 1 – 99 AU → Consider statin
- CAC ≥ 100 AU → Start statin

❖ "When unsure" means:

- Patient hesitant
- Borderline risk
- Conflicting risk factors

*: CAC, coronary artery calcium; AU, Agatston units;

New Slide

Lp(a) is an LDL-like particle that has an extra protein called **apolipoprotein(a)** attached to it. It is:

- Genetically determined (mostly inherited)

- Strongly atherogenic (causes plaque)

- Pro-thrombotic (increases clot risk)

- It increases risk of CAD and stroke

- Measure **once in a lifetime**

- Not significantly changed by diet or lifestyle

- Often elevated in patients with family history of early ASCVD and premature heart disease

New Slide

ApoB is a protein found on all atherogenic lipoproteins (LDL, VLDL, IDL, Lp(a))

- ApoB = total number of atherogenic particles

- ApoB is helpful (**better marker of CV risk)** when TG is high, metabolic syndrome, DM, or obesity

- Higher ApoB = more atherogenic particles = higher ASCVD risk

- Used to refine risk assessment, decide on earlier or more aggressive therapy, guide intensification beyond LDL alone

➢ Pharmacological Therapy

✓ Generally speaking, for every 1% reduction in LDL, there is a 1% reduction in CHD event rates.

✓ Lipid-lowering drugs can be broadly divided into agents that:

a. decrease the synthesis of VLDL and LDL
b. agents that enhance VLDL clearance
c. agents that enhance LDL catabolism
d. agents that decrease cholesterol absorption
e. agents that elevate HDL
f. or some combination of these characteristics

- **Primary hypercholesterolemia** (familial hypercholesterolemia and familial combined hyperlipidemia) is treated with HMG Co-A reductase inhibitors (statins), bile acid resins, niacin or eztimibe.

❖ **HMG-CoA Reductase (statins)**

✓ Of the above choices, statins are first choice because they are the most potent total and LDL cholesterol-lowering agents and among the best tolerated.

✓ Statins interrupt the conversion of HMG-CoA to mevalonate, the rate-limiting step in de novo cholesterol biosynthesis, by inhibiting HMG-CoA reductase.

✓ Currently available products include rosuvastatin, atorvastatin, pitavastatin, simvastatin, lovastatin, pravastatin, and fluvastatin.

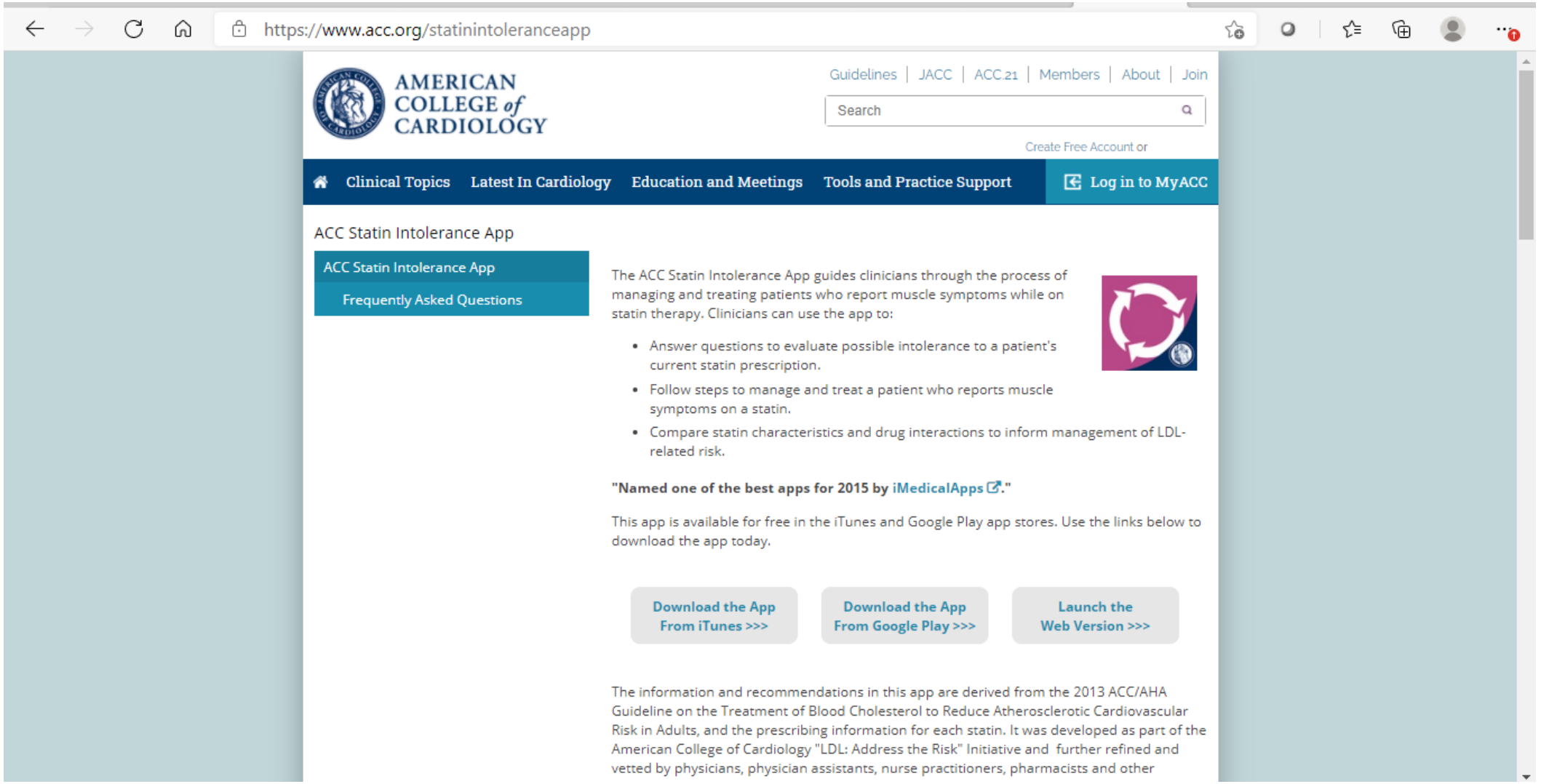
✓ Total and LDL-C are reduced in a dose-related fashion by 30% or more on average when added to dietary therapy. ↓ LDL 20-60%, ↓ 10-29% TG, ↑ HDL 6-12%

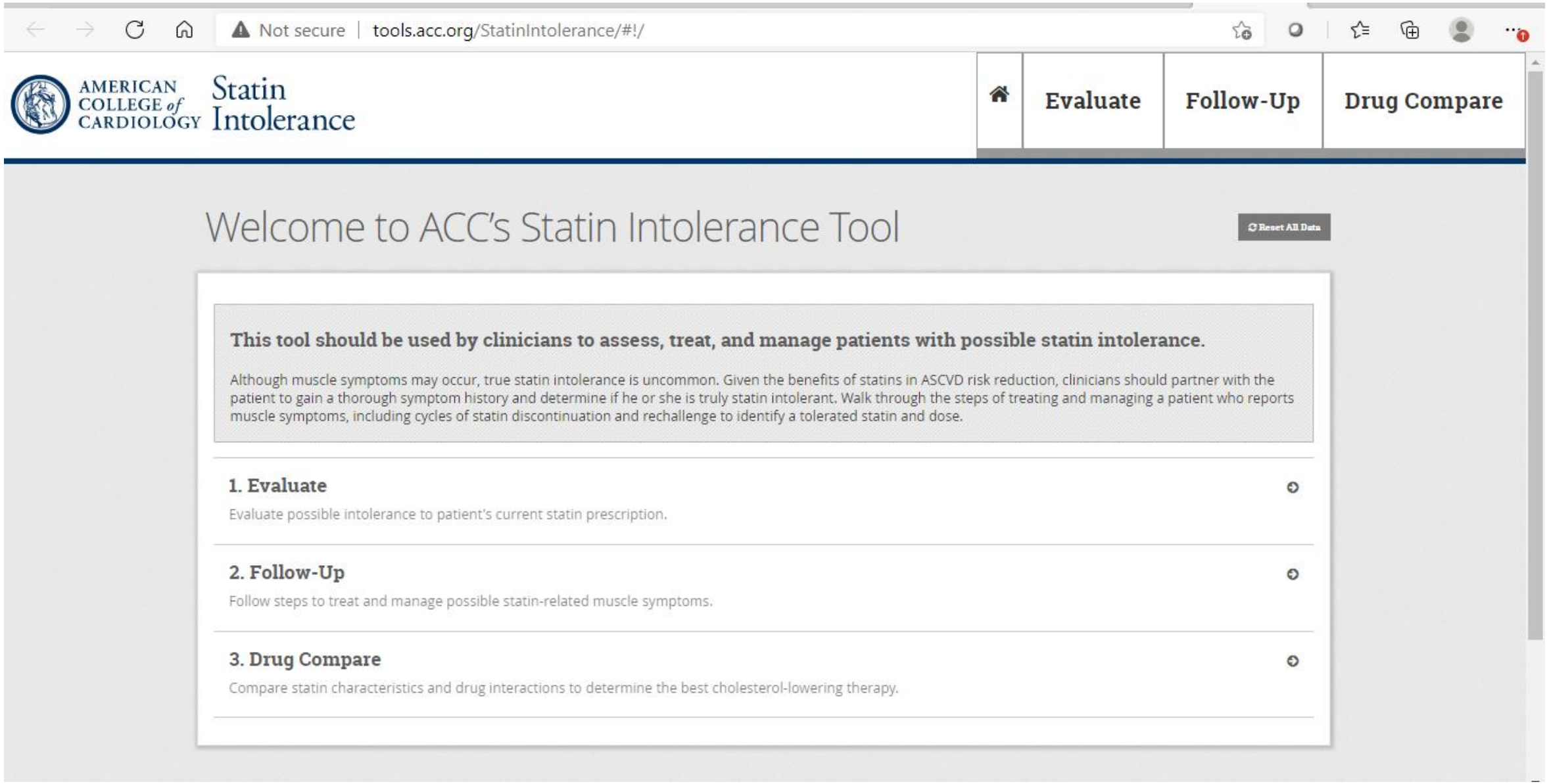
✓ The reductions in LDL-C are dose-dependent and log-linear, so that with each doubling of the dose of statin, LDL-C levels fall by about 6 percent.

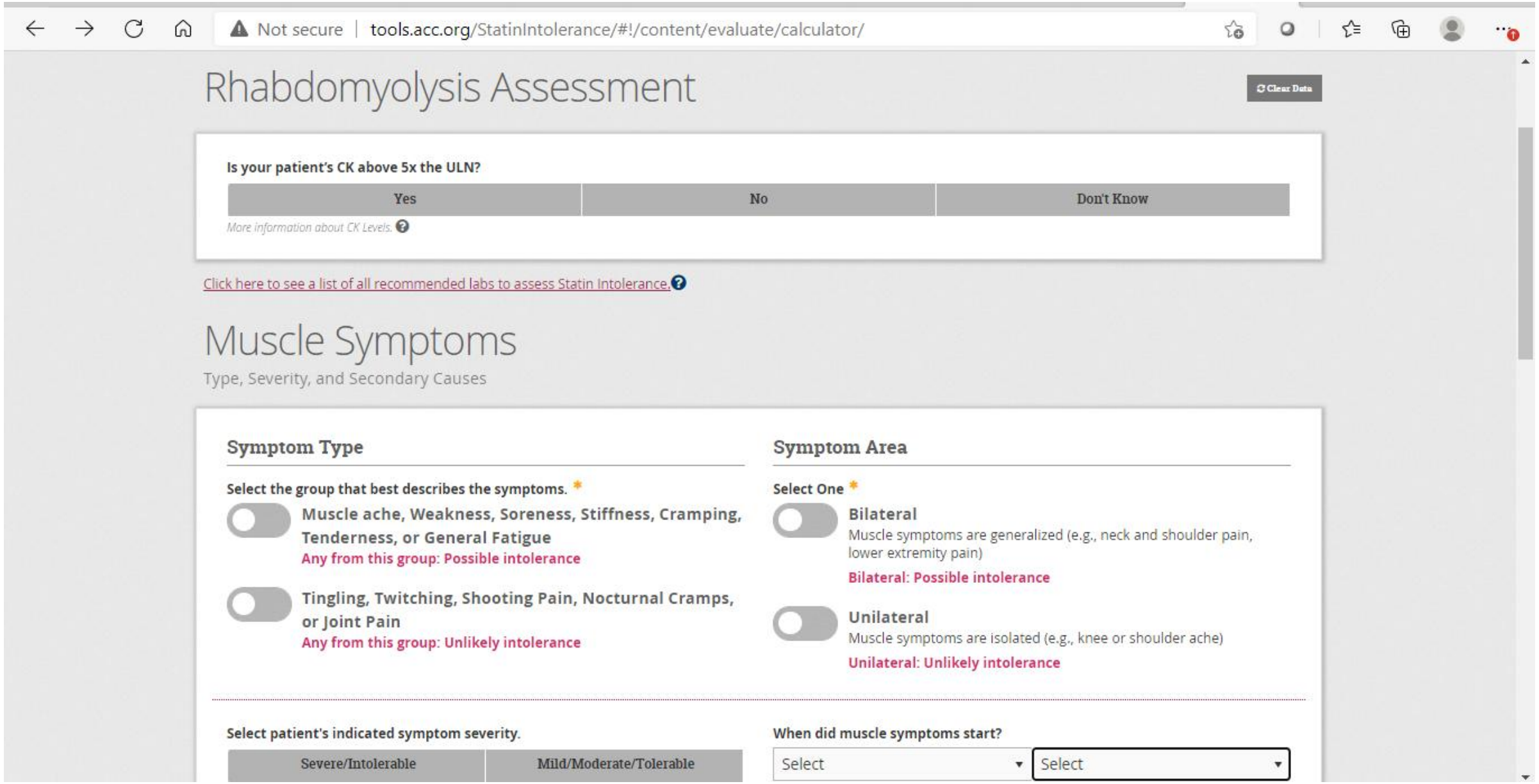
- ✓ The statins are generally administered with the evening meal or at bedtime (greater LDL-C reductions occur when they are administered at night than in the morning).
- ✓ Atorvastatin & its metabolites have very long $t_{1/2}$ (morning administration is equally effective).
- ✓ Rosuvastatin has a $t_{1/2}$ of 20 to 30 hours and can be taken at any time of the day. Statins with a short $t_{1/2}$ (<4 hours) such as fluvastatin, lovastatin, simvastatin, and others should be taken in the evening since hepatic cholesterol synthesis is maximal between midnight and 2:00 AM.
- ✓ The lipid-lowering effect of statins appears within the first week of use and becomes stable after approximately 4 weeks of use.
- ✓ Common S/Es (5%– 10% of patients): GI upset (e.g., abdominal pain, diarrhea, bloating, constipation) and muscle pain or weakness, which can occur without creatine kinase elevations.
- ✓ Elevation of serum transaminase levels (primarily ALT) to greater than 3X the upper limit of normal occurs in ~ 1.3% of patients on moderate to high doses of statins and serious muscle toxicity occurs in < 0.6% of patients (a low risk of abnormal ALT or CK).

- ✓ Statin-associated muscle symptoms (SAMS) are reported by 10% to 25% of statin users and are frequently reported by patients as a reason for statin discontinuation.
- ✓ Certain risk factors are known to increase the risk of developing SAMS and these include advanced age, female gender, low BMI, frequent heavy exercisers, comorbidities (eg, kidney disease, hypothyroidism), and increased serum statin concentrations due to D-DIs.
- ✓ STD CK level: Males 18+ : 52-336 U/L Females 18+: 38-176 U/L
- ✓ Statin-induced myalgias are likely to resolve within 2 months of discontinuing the drug.
- ✓ If symptoms resolve, the same or lower dose of the statin can be reintroduced.
- ✓ If symptoms recur, use a low dose of a different statin and increase as tolerated.
- ✓ If the cause of symptoms is determined to be unrelated, restart the original statin.

A Statin Intolerance App (available at: http://www.acc.org/statinintoleranceapp) created by the ACC is a helpful resource that can be used to determine the possibility of SAMS and provide guidance on managing patients with possible SAMS.




Not secure | tools.acc.org/StatinIntolerance/#!/
AMERICAN COLLEGE of CARDIOLOGY
Statin Intolerance
Evaluate
Follow-Up
Drug Compare
Welcome to ACC's Statin Intolerance Tool
Reset All Data
This tool should be used by clinicians to assess, treat, and manage patients with possible statin intolerance.
Although muscle symptoms may occur, true statin intolerance is uncommon. Given the benefits of statins in ASCVD risk reduction, clinicians should partner with the patient to gain a thorough symptom history and determine if he or she is truly statin intolerant. Walk through the steps of treating and managing a patient who reports muscle symptoms, including cycles of statin discontinuation and rechallenge to identify a tolerated statin and dose.
1. Evaluate
Evaluate possible intolerance to patient's current statin prescription.
2. Follow-Up
Follow steps to treat and manage possible statin-related muscle symptoms.
3. Drug Compare
Compare statin characteristics and drug interactions to determine the best cholesterol-lowering therapy.


Not secure | tools.acc.org/StatinIntolerance/#!/content/evaluate/calculator/
Rhabdomyolysis Assessment
Clear Data
Is your patient's CK above 5x the ULN?
Yes
No
Don't Know
More information about CK Levels.
Click here to see a list of all recommended labs to assess Statin Intolerance.
Muscle Symptoms
Type, Severity, and Secondary Causes
Symptom Type
Select the group that best describes the symptoms. *
Muscle ache, Weakness, Soreness, Stiffness, Cramping, Tenderness, or General Fatigue
Any from this group: Possible intolerance
Tingling, Twitching, Shooting Pain, Nocturnal Cramps, or Joint Pain
Any from this group: Unlikely intolerance
Symptom Area
Select One *
Bilateral
Muscle symptoms are generalized (e.g., neck and shoulder pain, lower extremity pain)
Bilateral: Possible intolerance
Unilateral
Muscle symptoms are isolated (e.g., knee or shoulder ache)
Unilateral: Unlikely intolerance
Select patient's indicated symptom severity.
Severe/Intolerable
Mild/Moderate/Tolerable
When did muscle symptoms start?
Select
Select

Likelihood of Statin-Related Muscle Symptoms with Current Prescription

Statin: Atorvastatin (Lipitor®) Dose: 10 *(20)* mg | Frequency: Once daily

		Statin-Related Muscle Symptoms	
Value	**Result**	**Possible**	**Unlikely**
Symptom timing allows for statin intolerance	Yes		
Symptom Type	Muscle ache, Weakness, Soreness, Stiffness, Cramping, Tenderness General Fatigue	✔	
Symptom Location	Bilateral	✔	
Sex	Female predisposes to statin adverse effects. May need lower dose or alternate statin.	✔	
Age	40-74		
Race/Ethnicity	White		
CK Elevated > 5x ULN?	No		
Risk Factors for Statin Symptoms	Identified / **1**	✔	
Non-Statin Causes	Identified / **3**		✔

Next Steps

1. **Conduct any labs needed** to establish risk factors or secondary causes.
2. If symptoms were determined to arise from non-statin cause or if the predisposing condition has been treated, you may resume statin therapy at original dose

❖ Bile Acid Resins (BARs)

- ✓ Their primary action is to bind bile acids in the intestinal lumen, and markedly increasing excretion of acidic steroids in the feces (stimulates hepatic synthesis of bile acids from cholesterol).
- ✓ The increase in hepatic cholesterol biosynthesis may be paralleled by increased hepatic VLDL production and, consequently, bile acid resins may aggravate hypertriglyceridemia in patients with combined hyperlipidemia. ↓ LDL 15-30%, no effect or ↑ TG, ↑ HDL 3-5%
- ✓ These agents should not be used as monotherapy in patients with triglyceride levels > 250 mg/dL. They may be combined with nicotinic acid or statins.
- ✓ GI complaints of constipation, bloating, epigastric fullness, nausea, and flatulence are most commonly reported.
- ✓ The adverse effects can be managed by increasing the fluid intake, modifying the diet to increase bulk, and using stool softeners.
- ✓ The other major limiting complaint is the gritty texture and bulk; these problems may be minimized by mixing the powder with orange drink or juice.

- ✓ Other potential adverse effects: impaired absorption (with high doses) of fat-soluble vitamins A, D, E, and K; hypernatremia and hyperchloremia; GI obstruction; and reduced bioavailability of acidic drugs as coumarin anticoagulants, nicotinic acid, thyroxine, acetaminophen, hydrocortisone, hydrochlorothiazide, loperamide, and possibly iron.

- ✓ Drug interactions may be avoided by alternating administration times with an interval of 6 hours or greater between the bile acid resin and other drugs.

- ✓ Colestipol may have better palatability because it is odorless and tasteless.

- ✓ BARs are increasingly used in combination with other drugs, as low doses are tolerated well and they work in a complementary fashion with other agents.

- ✓ Currently available BARs include the following:
  - Cholestyramine: 4– 24 g/ d PO in divided doses before meals.
  - Colestipol: tablets, 2– 16 g/ d PO; granules, 5– 30 g/ d PO in divided doses before meals.
  - Colesevelam: 625 mg tablets, three tablets PO bid or six tablets PO daily (maximum of seven tablets daily) with food, or one packet of oral suspension daily.

❖ Niacin

- ✓ Niacin (nicotinic acid) may also be used in primary hypercholesterolemia in combination with bile acid resins (complementary action) or as monotherapy for this disorder.
- ✓ Niacin reduces the hepatic synthesis of VLDL, which, in turn, leads to a reduction in the synthesis of LDL. ↓ LDL 5-25%, ↓ 20-50% TG, ↑ HDL 15-35%
- ✓ Niacin also increases HDL by reducing its catabolism.
- ✓ The principal use of niacin is for mixed hyperlipemia or as a second-line agent in combination therapy for hypercholesterolemia.
- ✓ It is also considered to be the first-line agent or an alternative for hypertriglyceridemia treatment.
- ✓ Nicotinic acid is usually administered in two or three doses a day, with the exception of the extended release product Niaspan®, which is administered as a single dose at bedtime.

- ✓ Niacin has many adverse drug reactions that occur commonly.
- ✓ Cutaneous flushing and itching appear to be prostaglandin mediated and can be reduced by aspirin 325 mg given shortly before niacin ingestion. Concomitant alcohol and hot drinks may magnify flushing and pruritus with niacin and they should be avoided at the time of ingestion.
- ✓ Flushing seems to be related to rising plasma concentrations of niacin; taking the dose with meals and slowly titrating the dose upward may minimize these effects.
- ✓ Sustained release products may minimize these complaints in some patients.
- ✓ Potentially important laboratory abnormalities occurring with niacin therapy include elevated liver function tests, hyperuricemia, and hyperglycemia.
- ✓ Recent experience with niacin in diabetes suggests that some diabetic patients do not have worsened glycemic control with dose-titration and sustained-release products.

- ✓ With less than 3 grams per day, the degree of liver function test elevation is generally not marked and often transient, and a temporary reduction in dosage frequently corrects the problem (contraindicated in patients with active liver disease).

- ✓ Niacin-associated hepatitis is more common with sustained-release preparations (more expensive), and their use should be restricted to patients intolerant of regular-release products (should always be used first).

- ✓ Preexisting gout and diabetes may be exacerbated by niacin; these patients should be monitored more closely and their medication titrated appropriately.

- ✓ Dry eyes and other ophthalmologic complaints are also occasionally noted.

- ✓ Niacin may magnify the hypotensive effects of vasodilators.

❖ Ezetimibe

- ✓ Ezetimibe is currently the only available cholesterol-absorption inhibitor.
- ✓ Ezetimibe may provide an additional 25% mean reduction in LDL-C when combined with a statin and provides an approximately 18% decrease in LDL-C when used as monotherapy.
- ✓ The recommended dosing is 10 mg PO once daily. No dosage adjustment is required for renal insufficiency and mild hepatic impairment or in elderly patients.
- ✓ SEs are infrequent: GI symptoms (e.g., diarrhea, abdominal pain) and myalgias.
- ✓ A clinical outcome trial showed decreased reduction of CV events with the combination of simvastatin and ezetimibe compared with placebo in patients with chronic renal failure.
- ✓ It is useful in patients with FH who do not achieve adequate LDL-C reductions with statin therapy alone.

- **Combined hyperlipoproteinemia** may be treated with statins, niacin, or fibrates **combinations** to lower LDL-C without elevating VLDL and triglycerides.

✓ Niacin is the most effective agent and may be combined with a bile acid resin.

✓ Bile acid resins alone in this disorder may elevate VLDL and triglycerides, and their use as single agents for treating combined hyperlipoproteinemia should be avoided.

✓ Ezetimibe could also be used in combination therapy in Type IIb.

❖ **Fibrates**

✓ Fibric acid (gemfibrozil, fenofibrate) monotherapy is effective in reducing VLDL.

↓ LDL 5-20%, ↓ 20-50% TG, ↑ HDL 10-35%

✓ Fibrates reduce the synthesis of VLDL and with a concurrent increase in the rate of removal of triglyceride-rich lipoproteins from plasma.

✓ Fenofibrate may have fewer drug interactions than gemfibrozil but fenofibrate has been reported to worsen renal function.

- ✓ Fibrates may potentiate the effects of oral anticoagulants and INR should be monitored very closely with this combination.

- ✓ Enhanced hypoglycemic effects are reported to occur when a fibrate is given to patients on sulfonylurea compounds, but the mechanisms for these interactions are not well understood.

- ✓ A myositis syndrome of myalgia, weakness, stiffness, malaise, and elevations in CPK and AST is seen with the fibrates, and it seems to be more common in patients with renal insufficiency.

- **Hypertriglyceridemia (**lipoprotein pattern types I, III, IV, and V)

- ✓ Dietary fat restriction (10%-20% of calories as fat), weight loss, alcohol restriction, and treatment of the coexisting disorder are the basic elements of management.

- ✓ Drugs useful in hypertriglyceridemia include gemfibrozil or fenofibrate, niacin, and higher potency statins (atorvastatin, rosuvastatin, pitvastatin, and simvastatin).

- ✓ Gemfibrozil or fenofibrate are the preferred drugs in diabetics because of the effect of niacin on glycemic control unless the newer ER forms are used.

- ✓ Fenofibrate may be preferred in combination with statin therapy since it does not impair statin metabolism and minimizes potential drug interactions.

- ✓ Statins may also be used, because they provide modest reductions in triglycerides and modest elevations in HDL.

- ✓ Very high triglycerides are associated with pancreatitis.

- ✓ The effects of fish oil on lipoprotein metabolism are mediated through a reduction in VLDL production and suppression of VLDL apolipoprotein B.

- ✓ Fish oil supplementation may be most useful in patients with hypertriglyceridemia; however, its role in treatment is not well defined.

- ✓ Potential complications of fish oil supplementation as thrombocytopenia and bleeding disorders, have been noted, especially with high doses (eicosapentaenoic acid 15 to 30 g/d); and well-controlled trials are needed to determine if fish oils are safe and effective before their use may be broadly recommended.

- **Low HDL cholesterol**

✓ Low HDL-C is a strong independent risk predictor of ASCVD.

✓ Specified goal for HDL-C raising is not available.

✓ Low HDL-C may be a consequence of insulin resistance, physical inactivity, diabetes, cigarette smoking, very high carbohydrate intake, and certain drugs.

✓ Niacin has the potential for the greatest increase in HDL.

✓ Due to the lack of pharmacological agents demonstrating an improvement in clinical outcomes by focusing on raising HDL-C, lifestyle modification remains the preferred approach.

✓ Although alcohol consumption has been shown to increase HDL-C, it is not acceptable to recommend this to patients who do not already consume alcohol.

Combination Therapy

- ✓ Two or three lipoprotein profiles at 6-week intervals should confirm lack of response prior to initiation of combination therapy.
- ✓ In general, a statin and a BAR or niacin with a BAR provide the greatest reduction in total and LDL cholesterol.
- ✓ In particular, familial hypercholesterolemia patients often require combination therapy (two or three drugs) and are managed with surgical therapy (partial ileal bypass), plasmapheresis (LDL-apheresis), and liver transplantation (to replace LDL receptors).
- ✓ Familial combined hyperlipidemia may respond better to a fibrate and a statin than to a fibrate and a BAR.

- **Diabetic Dyslipidemia**

✓ Characterized by hypertriglyceridemia, low HDL-C, and LDL-C that is minimally elevated.

✓ Small, dense LDL (pattern B) in diabetes is more atherogenic than larger, more buoyant forms of LDL (pattern A).

✓ Because the primary target is **LDL-C** in diabetic dyslipidemia, statins are considered by many to be initial drugs of choice.

✓ Although the effect of statins on triglycerides and HDL-C abnormalities commonly seen in diabetes is less than with fibrates, studies suggest that they reduce CHD risk significantly.

- **Pregnancy**

✓ Cholesterol and triglyceride levels rise progressively throughout pregnancy. Drug therapy is not instituted nor is it usually continued during pregnancy.

✓ If the pregnant patient is very high risk, a bile acid resin may considered since there is no systemic drug exposure.

✓ Statins are contraindicated.

✓ Dietary therapy is the mainstay of treatment, with emphasis on maintaining a nutritionally balanced diet as per the needs of pregnancy.

➢ Other agents

Mipomersen is an oligonucleotide inhibitor of apolipprotein B-100 synthesis.

- ✓ It is indicated as an adjunct to lipid lowering medications and diet to reduce LDL-C, apolipoprotein B, total cholesterol and non-HDL-C in patients with homozygous familial hypercholesterolemia.
- ✓ The average reduction in LDL-C is ~25% with the most common adverse events being injection site pain (~10%). Mild to moderate elevations in liver enzymes have been reported.

Lomitapide oral capsule is a microsomal triglyceride transfer protein (MTP) inhibitor.

- ✓ Inhibiting MTP reduces the level of cholesterol that the liver and intestines assemble and secrete into the circulation.
- ✓ The average decrease in LDL-C beyond baseline is ~40%.
- ✓ Hepatic steatosis associated with lomitapide may be a risk factor for progressive liver disease including steatohepatitis and cirrhosis. Mild to moderate elevations in liver enzymes have been reported.

Alirocumab and evolocumab: A new category of LDL lowering therapy was approved by the FDA in 2015.

- ✓ Their mechanism of action is to inhibit proprotein convertase subtilisin/kexin type 9 (PCSK9).
- ✓ PCSK9 promotes intracellular degradation of hepatic LDL receptor and reduces LDL clearance from the circulation (therefore the drug lower LDL concentrations significantly).
- ✓ Alirocumab and evolocumab are given by SC injection.
- ✓ The typical LDL reduction ranges from about 40% to over 60% with both drugs.
- ✓ The most common adverse effect reported in clinical trials is injection site pain.

Table 5: Effects of Drug Therapy on Lipids			
Drug	Mechanism of Action	Effects	Comment
Cholestyramine, colestipol and colesevelam	↑ LDL catabolism ↓ cholesterol absorption	↓ Cholesterol	Problem with compliance; binds many co-administered acidic drugs
Niacin	↓ LDL and VLDL ↓ synthesis	↓ Triglyceride ↓ cholesterol ↑ HDL	Problems with patient acceptance; good in combination with bile acid resins; extended release niacin causes less flushing and is less hepatotoxic than sustained release
Gemfibrozil, fenofibrate, clofibrate	↑ VLDL clearance ↓ VLDL synthesis	↓ Triglyceride ↓ cholesterol ↑ HDL	Clofibrate causes cholesterol gall stones; modest LDL lowering; raises HDL; gemfibrozil inhibits the metabolism (glucuronidation) of simvastatin, lovastatin and atorvastatin

Table 5: Effects of Drug Therapy on Lipids			
Drug	Mechanism of Action	Effects	Comment
Simvastatin, Atorvastatin Rosuvastatin	↑ LDL catabolism; inhibit LDL synthesis	↓ Cholesterol	Highly effective in heterozygous familial hypercholesterolemia and in combination with other agents
Ezetimibe	Blocks cholesterol absorption across the intestinal border	↓ Cholesterol	Few adverse effects; effects additive to other drugs
Mipomerson	Inhibitor of Apolipoprotein B-100	↓ Cholesterol	Increase in transaminases, risk of hepatosteatosis and hepatotoxicity; must be given by SQ injection. Only indicated for familial hypercholesterolemia. To be used along with other lipid lowering therapies (statins)

Table 5: Effects of Drug Therapy on Lipids			
Drug	Mechanism of Action	Effects	Comment
Lomitapide	Microsomal triglyceride transfer protein inhibitor	↓ Cholesterol	Hepatotoxicity must be monitored via Juxtapid Risk Evaluation and Mitigation Strategy program. Only indicated for familial hypercholesterolemia. To be used along with other lipid lowering therapies (statins)
Alirocumab **Evolocumab**	PCSK9 inhibitor	↓ Cholesterol, ↓ Lpa	Given by SQ injection, injection site pain, low risk of hepatoxicity

➢ Evaluation of Therapeutic Outcomes

- ✓ In patients treated for secondary intervention, symptoms of atherosclerotic CVD as angina or intermittent claudication, may improve over months to years.
- ✓ If patients have xanthomas, these lesions should regress with therapy.
- ✓ Lipid measurements should be obtained in the fasted state to minimize interference from chylomicrons, and once the patient is stable, monitoring is needed at intervals of 6 months to 1 year.
- ✓ Use of diet diaries enable information about diet to be collected in a systematic fashion and may improve patient adherence to dietary recommendations.
- ✓ Patients on resin therapy should have a fasting lipid profile (FLP) panel checked every 4 to 8 weeks until a stable dose; triglycerides should be checked at stable dose to insure they have not increased.

- ✓ Niacin requires baseline LFT, uric acid and glucose; repeat tests are appropriate at doses of 1,000 to 1,500 mg per day.
- ✓ Symptoms myopathy or diabetes-like symptoms should be investigated and may require CK or glucose determinations; more frequent monitoring in diabetics may be necessary.
- ✓ A FLP 4 to 8 weeks after the initial dose or dose changes with statins is appropriate.
- ✓ LFTs should be obtained at baseline and periodically thereafter based on package insert information; recognized experts believe that monitoring for hepatotoxicity and myopathy should be symptom triggered.
- ✓ In particular, older patients are more likely to have constipation (bile acid resins), skin and eye changes (niacin), gout (niacin), gallstones (fibrates), and bone/joint disorders (fibrates, statins).
- ✓ Therapy (in elderly) should be started with lower doses and titrated up slowly to minimize adverse effects.

CLASS (STRENGTH) OF RECOMMENDATION

CLASS I (STRONG) — **Benefit >>> Risk**

Suggested phrases for writing recommendations:
- Is recommended
- Is indicated/useful/effective/beneficial
- Should be performed/administered/other
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is recommended/indicated in preference to treatment B
  - Treatment A should be chosen over treatment B

CLASS IIa (MODERATE) — **Benefit >> Risk**

Suggested phrases for writing recommendations:
- Is reasonable
- Can be useful/effective/beneficial
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is probably recommended/indicated in preference to treatment B
  - It is reasonable to choose treatment A over treatment B

CLASS IIb (WEAK) — **Benefit ≥ Risk**

Suggested phrases for writing recommendations:
- May/might be reasonable
- May/might be considered
- Usefulness/effectiveness is unknown/unclear/uncertain or not well established

CLASS III: No Benefit (MODERATE) — **Benefit = Risk**
(Generally, LOE A or B use only)

Suggested phrases for writing recommendations:
- Is not recommended
- Is not indicated/useful/effective/beneficial
- Should not be performed/administered/other

CLASS III: Harm (STRONG) — **Risk > Benefit**

Suggested phrases for writing recommendations:
- Potentially harmful
- Causes harm
- Associated with excess morbidity/mortality
- Should not be performed/administered/other

LEVEL (QUALITY) OF EVIDENCE‡

LEVEL A
- High-quality evidence‡ from more than 1 RCTs
- Meta-analyses of high-quality RCTs
- One or more RCTs corroborated by high-quality registry studies

LEVEL B-R — **(Randomized)**
- Moderate-quality evidence‡ from 1 or more RCTs
- Meta-analyses of moderate-quality RCTs

LEVEL B-NR — **(Nonrandomized)**
- Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies
- Meta-analyses of such studies

LEVEL C-LD — **(Limited Data)**
- Randomized or nonrandomized observational or registry studies with limitations of design or execution
- Meta-analyses of such studies
- Physiological or mechanistic studies in human subjects

LEVEL C-EO — **(Expert Opinion)**

Consensus of expert opinion based on clinical experience

COR and LOE are determined independently (any COR may be paired with any LOE).

A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

* The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).

† For comparative-effectiveness recommendations (COR I and IIa; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

‡ The method of assessing quality is evolving, including the application of standardized, widely used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.

COR indicates Class of Recommendation; EO, expert opinion; LD, limited data; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.

Updated slide

TABLE 35-6

Pharmacokinetic Properties of Statins

Statin	Half-Life (hours)	CYP Enzyme Metabolism	Lipophilic?	Renal Excretion (%)
Atorvastatin	14	CYP3A4	Yes	<2
Fluvastatin	3	CYP2C9	Yes	5
Lovastatin	2-3	CYP3A4	Yes	10
Pitavastatin	12	CYP2C9	Moderately	15
Pravastatin	2	None	No	20
Rosuvastatin	19	CYP2C9	No	10
Simvastatin	2	CYP3A4	Yes	13

Updated slide

TABLE 35-7

Safety of Lipid-Lowering Therapies

Lipid-Lowering Drug Class	Adverse Effects		Contraindications
	Common/Possible (1%-10%)	Rare/Unlikely (<1%)	
Statins	• Statin-associated muscle symptoms (myalgia/myopathy) • New-onset diabetes mellitus • Transient, mild elevation in transaminase levels	• Rhabdomyolysis • Severe hepatotoxicity	• Pregnancy *in most patients* • Breastfeeding • Decompensated cirrhosis • Acute liver failure
Cholesterol absorption inhibitors	• GI adverse effects • Myalgias (when used with statin) • Elevated transaminase levels (when used with statin)	• Thrombocytopenia	• Pregnancy/breastfeeding • Acute liver failure
Bile acid sequestrants	• GI adverse effects and/or obstruction • Impaired absorption of fat-soluble vitamins • Reduced bioavailability of select drugs	• Ileus • Cholecystitis • Severe hypertriglyceridemia	• History of bowel obstruction • Fasting TG are 300 mg/dL or higher
ACL inhibitors	• Hyperuricemia • Cholelithiasis	• Increased risk of tendon rupture • Increased risk of benign prostate hyperplasia	
PCSK9 mAbs	• Injection-site reactions • Flu-like symptoms post-injection		• Hypersensitivity reaction to alirocumab or evolocumab

Updated slide

Table 35-7
Safety of Lipid-Lowering Therapies

Fibrates	• GI adverse effects • Transient elevation in transaminases • Myalgias (especially when used with statin) • Mild increase in serum creatinine	• Increased risk of gallstones	• Preexisting gallbladder disease • CrCl of 30 mL/min (0.5 mL/s) or lower
Omega-3 PUFA	• GI adverse effects • Eructation • Increased risk of bleeding when used with antiplatelets or anticoagulants • Increased risk of atrial fibrillation or flutter		• Caution in patients with allergy or sensitivity to fish and/or shellfish
Niacin	• Dermatologic effects (flushing/itching) • Increased transaminases • Hyperuricemia • Hyperglycemia	• Increased risk of atrial fibrillation or flutter • Rhabdomyolysis (with statin) • Hepatotoxicity (with statin)	• Active peptic ulcer • Arterial hemorrhage • Persistently elevated transaminase levels
Inclisiran	• Injection-site reactions		• Pregnancy/breastfeeding
Evinacumab	• Infusion-site pruritus • Influenza-like reactions • Rhinorrhea		• Pregnancy/breastfeeding

ACL, adenosine triphosphate-citrate lyase; CrCl, creatinine clearance; mAbs, monoclonal antibodies; PUFA, polyunsaturated fatty acids; SAMS, statin-associated muscle symptoms.

For your reference

Lipoprotein Goals for ASCVD Risk Reduction

Patient population	LDL-C <100 mg/dL (2.6 mmol/L) Non–HDL-C <130 mg/dL (3.4 mmol/L)	LDL-C <70 mg/dL (1.8 mmol/L) Non–HDL-C <100 mg/dL (2.6 mmol/L)	LDL-C <55 mg/dL (1.4 mmol/L) Non–HDL-C <85 mg/dL (2.2 mmol/L)
Primary prevention	PREVENT-ASCVD <10% • If TG ≥150 mg/dL to 499 mg/dL, apoB goal: <90 mg/dL	PREVENT-ASCVD ≥10% • If TG ≥150 mg/dL to 499 mg/dL, apoB goal: <70 mg/dL	N/A
Severe hypercholesterolemia	**Without** FH, ASCVD risk factors, and subclinical atherosclerosis	**With** FH, ASCVD risk factors, or subclinical atherosclerosis	Severe hypercholesterolemia or HeFH with clinical ASCVD
Diabetes	**Without** ASCVD risk factors or diabetes-specific risk modifiers • apoB goal: <90 mg/dL	**With** ASCVD risk factors or diabetes-specific risk factors • apoB goal: <70 mg/dL	N/A
Subclinical atherosclerosis	CAC = 1–99 AU and <75th percentile for age, sex, and race	• CAC ≥100 to 299 AU or ≥75th percentile for age, sex, race • CAC ≥300 to 999 AU ◦ Optional goal: LDL-C <55 mg/dL, non–HDL-C <85 mg/dL and consider apoB goal <55 mg/dL	CAC ≥1000 AU
Hypertriglyceridemia	<50 y old with no additional risk enhancers	• With clinical ASCVD not at very high risk ◦ apoB goal: <70 mg/dL • Age 40–75 y with ≥1 ASCVD risk factor ◦ apoB goal: <70 mg/dL	With clinical ASCVD at very high risk • apoB goal: <55 mg/dL
Clinical ASCVD	N/A	Not at very high risk • Optional goal: LDL-C <55 mg/dL, non–HDL-C <85 mg/dL and consider apoB goal <55 mg/dL	• At very high risk ◦ apoB goal: <55 mg/dL • With CKD

2026 Dyslipidemia

Figure 1. Lipoprotein Goals for ASCVD Risk Reduction.

apoB indicates apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; AU, Agatston units; CAC, coronary artery calcium; CKD, chronic kidney disease; FH, familial hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; and TG, triglycerides.

What Is New?

All slides of this table are for your reference

New or Revised	Section Title	2018 Recommendation	2026 Recommendation
New	3.3. Measurement of ApoB	N/A	COR 2a: In adults on LLT, particularly those with ASCVD, CKM syndrome, type 2 diabetes, and/or elevated TG, measurement of apoB is reasonable to guide decisions regarding further therapeutic intensification once LDL-C and/or non–HDL-C goals are achieved.
New	3.4. Measurement of Lp(a)	N/A	COR 1: In all adults, measurement of Lp(a) concentration is recommended at least once for ASCVD risk assessment.
New	4.1.5. Dietary Supplements	N/A	COR 3: In individuals with dyslipidemia, the use of dietary supplements is not recommended to lower LDL-C or TG based on limited and inconsistent data and/or limited benefits in lipid-lowering and reduction in ASCVD risk.
New	4.1.6. When to Refer to a Registered Dietitian Nutritionist	N/A	COR 1: In individuals with fasting TG ≥1000 mg/dL (11.3 mmol/L) referral to an RDN is recommended to create an individualized treatment plan aimed at reducing TG and the risk of pancreatitis.
New	4.2.3.2. PREVENT-ASCVD Equations	N/A	COR 1: In adults aged 30 to 79 y without ASCVD or subclinical atherosclerosis and with an LDL-C level between 70 and 189 mg/dL (1.8-4.9 mmol/L), the PREVENT-ASCVD equations should be used to estimate 10-y ASCVD risk, with categorization as having low (<3%), borderline (3% to <5%), intermediate (5% to <10%), or high (≥10%) risk.

What Is New?

New or Revised	Section Title	2018 Recommendation	2026 Recommendation
Revised	4.2.3.3. Risk Enhancers	COR 2b: In patients at borderline risk, in risk discussion, the presence of risk-enhancing factors may justify initiation of moderate-intensity statin therapy.	COR 2a: In adults without ASCVD with a borderline 10-y ASCVD risk estimate (3% to <5%) by the PREVENT-ASCVD equations, consideration of risk enhancers is reasonable to personalize risk assessment and the potential benefit of initiating LLT as an adjunct to lifestyle management to reduce ASCVD risk.
New	4.2.3.3. Risk Enhancers	N/A	COR 2a: In adults without ASCVD with a borderline 10-y ASCVD risk estimate (3% to <5%) by the PREVENT-ASCVD equations, if hsCRP is measured and is ≥2 mg/L on 2 successive occasions with no identifiable underlying cause of hsCRP elevation, high-intensity statin therapy can be useful to reduce the risk of ASCVD events.
New	4.2.3.4. Reproductive Risk Markers	N/A	COR 2a: In adults without ASCVD, consideration of reproductive risk markers, such as early menopause (<45 y old) and history of adverse pregnancy outcomes (gestational hypertension, preeclampsia, gestational diabetes, preterm delivery) is reasonable to personalize ASCVD risk assessment when considering the potential benefit of initiating LLT as an adjunct to lifestyle management for primary ASCVD prevention.
Revised	4.2.3.6. Selective Imaging of Subclinical Atherosclerosis	COR 2a: In intermediate-risk or selected borderline-risk adults, if the decision about statin use remains uncertain, it is reasonable to use a CAC score in the decision to withhold, postpone, or initiate statin therapy.	COR 1: In adults at intermediate risk and select adults at borderline risk with no prior ASCVD, if the decision regarding LLT remains uncertain, a CAC score should be used for further risk stratification and to guide the decision to withhold, postpone, or initiate therapy.

What Is New?

New or Revised	Section Title	2018 Recommendation	2026 Recommendation
New	4.2.3.7. Management in Primary Prevention in Adults 30 to 79 Years of Age With LDL-C Levels 70 to 189 mg/dL	N/A	COR 1: In adults at low (<3%) 10-y estimated risk for ASCVD who have an LDL-C <160 mg/dL (4.1 mmol/L) and a 30-y risk estimate of <10% (for those aged 30-59 y), counseling on health behaviors is recommended to reduce LDL-C and risk for ASCVD.
New	4.2.3.7. Management in Primary Prevention in Adults 30 to 79 Years of Age With LDL-C Levels 70 to 189 mg/dL	N/A	COR 2a: In adults at low (<3%) 10-y estimated risk for ASCVD but with an LDL-C of 160 to 189 mg/dL (4.1-4.9 mmol/L) or a 30-y ASCVD risk ≥10% (for those aged 30-59 y), a moderate-intensity statin is reasonable to reduce cumulative exposure to atherogenic lipoproteins.
New	4.2.3.7. Management in Primary Prevention in Adults 30 to 79 Years of Age With LDL-C Levels 70 to 189 mg/dL	N/A	COR 2a: In adults at borderline (3% to <5%) 10-y estimated risk for ASCVD risk in whom a decision is made to initiate statin therapy for primary prevention, a moderate-intensity statin is reasonable to achieve ≥30% to 49% LDL-C reduction and to reduce ASCVD risk.
New	4.2.3.7. Management in Primary Prevention in Adults 30 to 79 Years of Age With LDL-C Levels 70 to 189 mg/dL	N/A	COR 1: In adults at intermediate (5% to <10%) 10-y estimated risk for ASCVD, at least a moderate-intensity statin is recommended to achieve ≥30% to 49% LDL-C reduction and to reduce ASCVD risk; for those in the higher end of this risk range, a high-intensity statin is beneficial to further reduce LDL-C by ≥50% and reduce ASCVD risk.

What Is New?

New or Revised	Section Title	2018 Recommendation	2026 Recommendation
New	4.2.3.7. Management in Primary Prevention in Adults 30 to 79 Years of Age With LDL-C Levels 70 to 189 mg/dL (1.8-4.9 mmol/L)	N/A	COR 2a: In adults at borderline (3% to <5%) or intermediate (5% to <10%) 10-y estimated risk for ASCVD in whom statin therapy is initiated, it is reasonable to treat to a goal of LDL-C <100 mg/dL (2.6 mmol/L) and non–HDL-C <130 mg/dL (3.4 mmol/L) to reduce ASCVD risk.
New	4.2.3.7. Management in Primary Prevention in Adults 30 to 79 Years of Age With LDL-C Levels 70 to 189 mg/dL (1.8-4.9 mmol/L)	N/A	COR 1: In adults at high (≥10%) 10-y risk for ASCVD in whom LLT is initiated for primary prevention, high-intensity statin therapy is recommended to achieve an LDL-C reduction of ≥50% to reduce the risk of ASCVD.
New	4.2.3.7. Management in Primary Prevention in Adults 30 to 79 Years of Age With LDL-C Levels 70 to 189 mg/dL (1.8-4.9 mmol/L)	N/A	COR 2a: In adults at high (≥10%) 10-y risk for ASCVD in whom a decision to initiate statin therapy is made, it is reasonable to treat to a goal of LDL-C <70 mg/dL (1.8 mmol/L) and non–HDL-C <100 mg/dL (2.6 mmol/L) to reduce ASCVD risk.
New	4.2.3.7. Management in Primary Prevention in Adults 30 to 79 Years of Age With LDL-C Levels 70 to 189 mg/dL	N/A	COR 2a: In adults at high (≥10%) 10-y estimated risk for ASCVD on maximally tolerated statin, it is reasonable to add ezetimibe if a goal LDL-C <70 mg/dL (1.8 mmol/L) and non–HDL-C <100 mg/dL (2.6 mmol/L) is not achieved.

What Is New?

New or Revised	Section Title	2018 Recommendation	2026 Recommendation
Revised	4.2.4.3. Severe Hypercholesterolemia With LDL-C ≥190 mg/dL (4.9 mmol/L)	COR 2a: In patients 20 to 75 years of age with an LDL-C level of 190 mg/dL or higher (4.9 mmol/L) who achieve less than a 50% reduction in LDL-C while receiving maximally tolerated statin therapy and/or have an LDL-C level of 100 mg/dL or higher (2.6 mmol/L), ezetimibe therapy is reasonable.	COR 1: In adults with severe hypercholesterolemia with an LDL-C ≥190 mg/dL (4.9 mmol/L) and without clinical ASCVD, additional ASCVD risk factors, HeFH, or subclinical atherosclerosis who are on maximally tolerated statin therapy, the addition of ezetimibe, a PCSK9 mAb and/or bempedoic acid is recommended to achieve a goal of LDL-C <100 mg/dL (2.6 mmol/L) and a non–HDL-C goal of <130 mg/dL (3.4 mmol/L) and to reduce ASCVD risk.
Revised	4.2.4.3. Severe Hypercholesterolemia With LDL-C ≥190 mg/dL (4.9 mmol/L)	COR 2b: In patients 30 to 75 y of age with heterozygous FH and with an LDL-C level of 100 mg/dL or higher (2.6 mmol/L) while taking maximally tolerated statin and ezetimibe therapy, the addition of a PCSK9 inhibitor may be considered.	COR 1: In adults with severe hypercholesterolemia with LDL-C ≥190 mg/dL (4.9 mmol/L) without clinical ASCVD but with clinical or genetic confirmation of HeFH, additional ASCVD risk factors, or documented coronary calcification, who are on maximally tolerated statin therapy, the addition of ezetimibe, a PCSK9 mAb and/or bempedoic acid to achieve a goal of LDL-C <70 mg/dL (1.8 mmol/L) and non–HDL-C <100 mg/dL (2.4 mmol/L) is recommended to lower LDL-C and reduce ASCVD risk.
New	4.2.4.3. Severe Hypercholesterolemia With LDL-C ≥190 mg/dL (4.9 mmol/L)	N/A	COR 1: In adults with severe hypercholesterolemia with LDL-C ≥190 mg/dL (4.9 mmol/L) with clinical ASCVD, who are on maximally tolerated statin therapy, the addition of ezetimibe, a PCSK9 mAb, or bempedoic acid is recommended to achieve a goal of LDL-C <55 mg/dL (1.4 mmol/L) and non–HDL-C <85 mg/dL (2.2 mmol/L) to lower LDL-C and reduce ASCVD risk.
New	4.2.4.3. Severe Hypercholesterolemia With LDL-C ≥190 mg/dL (4.9 mmol/L)	N/A	COR 2a: In adults with severe hypercholesterolemia with or without clinical ASCVD and LDL-C ≥100 mg/dL (2.6 mmol/L) despite maximally tolerated statin with or without ezetimibe therapy, treatment with inclisiran is reasonable to lower LDL-C.

What Is New?

New or Revised	Section Title	2018 Recommendation	2026 Recommendation
Revised	4.2.5. Diabetes in Adults Without Established ASCVD	COR 1: In adults 40 to 75 y of age with diabetes, regardless of estimated 10-year ASCVD risk, moderate-intensity statin therapy is indicated.	COR 1: In adults 40 to 75 y of age with diabetes and without clinical ASCVD, moderate-intensity statin therapy is indicated to achieve ≥30% to 49% reduction in LDL-C and a goal of LDL-C <100 mg/dL (2.6 mmol/L) and non–HDL-C <130 mg/dL (3.4 mmol/L) to reduce ASCVD risk.
Revised	4.2.5. Diabetes in Adults Without Established ASCVD	COR 2a: In adults with diabetes who have multiple ASCVD risk factors, it is reasonable to prescribe high-intensity statin therapy with the aim to reduce LDL-C levels by 50% or more.	COR 2a: In adults 40 to 75 y of age with diabetes who have multiple ASCVD risk factors, it is reasonable to prescribe high-intensity statin therapy to achieve ≥50% reduction in LDL-C and a goal of LDL-C <70 mg/dL (1.8 mmol/L) and non–HDL-C <100 mg/dL (2.6 mmol/L) to reduce ASCVD risk.
Revised	4.2.6. Secondary ASCVD Prevention	COR 1: In patients who are 75 y of age or younger with clinical ASCVD, high-intensity statin therapy should be initiated or continued with the aim of achieving a 50% or greater reduction in LDL-C levels.	COR 1: In adults with clinical ASCVD who are not at very high risk, high-intensity statin therapy should be initiated to achieve ≥50% reduction in LDL-C and a goal of LDL-C <70 mg/dL (1.8 mmol/L) and non–HDL-C <100 mg/dL to reduce the risk of recurrent ASCVD events.
New	4.2.6. Secondary ASCVD Prevention	N/A	COR 2a: In adults with clinical ASCVD who are not at very high risk and on maximally tolerated statin therapy, it is reasonable to add ezetimibe, a PCSK9 mAb, or bempedoic acid (selected based on the degree of LDL-C lowering needed and patient preference) to achieve a goal LDL-C <55 mg/dL (1.4 mmol/L) and non–HDL-C <85 mg/dL (2.2 mmol/L) and to reduce the risk of ASCVD events.

What Is New?

New or Revised	Section Title	2018 Recommendation	2026 Recommendation
New	4.2.6. Secondary ASCVD Prevention	N/A	COR 2a: In adults with clinical ASCVD who are at very high risk and on maximally tolerated statin therapy, ezetimibe and/or a PCSK9 mAb should be added (selected based on the degree of LDL-C lowering needed and patient preference) to achieve a goal of LDL-C <55 mg/dL (1.4 mmol/L) and non–HDL-C <85 mg/dL (2.2 mmol/L) and to reduce risk of ASCVD events.
New	4.2.6. Secondary ASCVD Prevention	N/A	COR 2a: In adults with clinical ASCVD who are at very high risk on maximally tolerated statin therapy, it is reasonable to add bempedoic acid to a statin, with or without ezetimibe and/or PCSK9 mAb, to reach an LDL-C goal <55 mg/dL (1.4 mmol/L) and non–HDL-C <85 mg/dL (2.2 mmol/L) to reduce the risk of ASCVD events.
New	4.2.6. Secondary ASCVD Prevention	N/A	COR 2a: In adults with clinical ASCVD who are at very high risk and on maximally tolerated statin therapy with or without ezetimibe, it is reasonable to add inclisiran in those unable to tolerate or obtain evolocumab or alirocumab or have a strong preference for less frequent dosing to achieve an LDL-C goal <55 mg/dL (1.4 mmol/L) and non–HDL-C <85 mg/dL (2.2 mmol/L).
New	4.2.8.4. Management of Dyslipidemia in Persons Planning Pregnancy, During Pregnancy, or While Lactating	N/A	COR 2a: In pregnant individuals with severe fasting hypertriglyceridemia (TG ≥500 mg/dL [5.7 mmol/L]), the use of fibrates (after the first trimester) or high-dose omega-3 ethyl esters is reasonable as an adjunct to lifestyle management to lower TG levels and reduce the risk of pancreatitis.

What Is New?

New or Revised	Section Title	2018 Recommendation	2026 Recommendation
New	4.2.8.8. Adults With CKD—Stage 3 or Higher	N/A	COR 1: In adults with CKD stage 3 or higher and clinical ASCVD, LLT with high-intensity statin therapy with or without ezetimibe and/or a PCSK9 mAb is recommended to achieve a ≥50% reduction in LDL-C levels and a goal of LDL-C <55 mg/dL (1.4 mmol/L) and non–HDL-C <85 mg/dL (2.2 mmol/L) to reduce ASCVD risk.
New	4.2.8.9. Persons Living With HIV	N/A	COR 1: In people living with HIV aged 40 to 75 on stable combination antiretroviral therapy, statin therapy is recommended to reduce risk of a first ASCVD event and reduce the rate of coronary atherosclerosis progression.
New	4.2.8.10. Adults With Cancer or History of Cancer	N/A	COR 1: Adult cancer survivors with life expectancy of at least 2 y who otherwise qualify for LLT should be treated similarly to people without history of cancer to reduce the risk of ASCVD events.
New	4.2.9. Management of Hypertriglyceridemia	N/A	COR 1: In adults with clinical ASCVD and LDL-C ≥55 mg/dL (1.4 mmol/L) and non–HDL-C ≥85 mg/dL on maximally tolerated statin with persistently elevated TG levels ≥150 to 999 mg/dL (1.7–11.3 mmol/L), intensification of LDL-C–lowering therapy is recommended to reduce ASCVD risk.

What Is New?

New or Revised	Section Title	2018 Recommendation	2026 Recommendation
New	4.2.9. Management of Hypertriglyceridemia	N/A	COR 1: In adults with familial chylomicronemia syndrome and fasting TG ≥1000 mg/dL (11.3 mmol/L), olezarsen (an apoC3 inhibitor) is recommended, as an adjunct to diet, to lower TG levels and reduce the risk of pancreatitis.
New	4.2.9. Management of Hypertriglyceridemia	N/A	COR 1: In adults aged 40 to 75 y without a history of ASCVD or diabetes who have persistently elevated TG levels ≥150 to 499 mg/dL (≥1.7–5.6 mmol/L), it is recommended to estimate 10-y ASCVD risk by the PREVENT equations to guide a benefit-risk discussion regarding further optimization of diet and lifestyle management as well as the potential initiation of statin therapy to reduce ASCVD risk.
New	4.2.10. Approach to Patients With Elevated Lp(a)	N/A	COR 1: In all individuals with elevated Lp(a) (≥125 nmol/L or ≥50 mg/dL), optimal early control of modifiable cardiovascular risk factors is recommended to reduce ASCVD risk.
New	4.2.10. Approach to Patients With Elevated Lp(a)	N/A	COR 1: In individuals with clinical ASCVD and elevated Lp(a) who have not achieved LDL-C and non–HDL-C treatment goals on maximally tolerated statin therapy, the addition of a PCSK9 mAb with proven cardiovascular benefit is recommended to achieve treatment goals and reduce ASCVD risk.

Thank You