CARE MODEL: Pharmacologic Management of Dyslipidemia in Adults

Clinical ASCVD*

Yes → Secondary Prevention (age > 18 y)

Very high risk# ASCVD
LDL goal < 55 mg/dL
→ High intensity or maximally tolerated statin
→ If LDL ≥ **55 mg/dL,** add ezetimibe and/or PCSK9-I mAb^
→ Consider adding bempedoic acid if LDL not at goal

ASCVD <u>not</u> at very high risk
LDL goal < 70 mg/dL
→ High intensity or maximally tolerated statin
→ If LDL ≥ **70 mg/dL,** add ezetimibe, PCSK9-I mAb^, and/or bempedoic acid
→ Can consider lower LDL goal of **< 55 mg/dL** based on age and clinical judgement

No → Primary Prevention (30-79 y)

LDL ≥ 190 mg/dL†
LDL goal < 100 mg/dL
→ High intensity or maximally tolerated statin
→ If LDL ≥ **100 mg/dL,** add ezetimibe, PCSK9-I mAb^, and/or bempedoic acid
→ LDL goal **< 70 mg/dL if HeFH or additional risk factors present**

LDL < 190 mg/dL
→ **Diabetes**

Yes

<u>20-39 y</u>: may consider moderate intensity statin based on risk

<u>40-75 y</u>: moderate intensity statin, LDL goal < **100 mg/dL**.

If 10-year risk ≥ 10% *or* risk enhancers present, high intensity statin, LDL goal **< 70 mg/dL**

No → Assess 10-year PREVENT-ASCVD Risk & Have Discussion w/Patient

< 3 %
LDL goal not specified
→ **<u>30-59 y</u>:** consider moderate intensity statin if LDL 160-189 *or* 30-year risk ≥ 10%

3 - < 5 %
LDL goal < 100 mg/dL
→ Consider moderate intensity statin if risk enhancer(s) present

5 - < 10%
LDL goal < 100 mg/dL
→ Moderate intensity statin. Consider high intensity statin if risk nearing 10%

≥ 10%
LDL goal < **70** mg/dL
→ High intensity statin. If LDL ≥ **70 mg/dL,** add ezetimibe. Can add PCSK9-I mAb or bempedoic acid if LDL not at goal

*Consists of acute coronary syndromes, hx of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, TIA, PAD

#History of ≥ 2 major ASCVD events *or* 1 major ASCVD event and ≥2 high-risk features (age ≥ 65 y, prior CABG or PCI, DM, HTN, currently smoking, hx of HF, persistently elevated LDL ≥ 100 mg/dL despite maximally tolerated statin and ezetimibe

^If unable to tolerate, obtain, or adhere to PCSK9-I mAb, consider inclisiran as an alternative. Do not use PCSK9-I mAb and inclisiran in combination

†Consider genetic testing for familial hypercholesterolemia

Primary Prevention Risk Enhancers: family history of premature ASCVD, persistently elevated LDL ≥ 160 mg/dL, non-HDL ≥ 190, or apoB ≥ 120 mg/dL, T2DM, CKD 3+, HTN, metabolic syndrome, pre-eclampsia, premature menopause [< 40 y], gestational DM or HTN, inflammatory disease (e.g., lupus, psoriasis, RA, HIV), ancestry (e.g., South Asian, Filipino), persistently elevated TG ≥ 175 mg/dL, Lp(a) ≥ 50 mg/dL or ≥ 125 nmol/L, hsCRP ≥ 2 mg/L

Labs & Monitoring

<u>Screening - Primary Prevention</u>
- **Begin at age 19;** if unremarkable, rescreen at least every 5 years
- Earlier if concern for familial hypercholesterolemia (9-11 years old)

<u>Lipid Panel</u>
- **Recheck 4-12 wks after statin initiation/dose change,** then q 6-12 mo
- **No LDL is too low** – LDL < 20 mg/dL did not ↑ adverse event risk
- Fasting lipid panel not necessary **unless TG are elevated** – standard panel can't calculate LDL if TG > 400 mg/dL
  - To avoid issue, order as "**lipid panel w/reflex direct LDL**"

<u>LFTs</u>
- **Obtain prior to statin initiation;** not necessary thereafter unless symptoms of hepatotoxicity
- CMP obtained 3-6 months prior to initiation can be used as baseline

<u>Lp(a)</u>
- Genetically determined – **minimally affected by lifestyle; measure once in adult life**
- Elevated Lp(a) (≥ 50 mg/dL or ≥ 125 nmol/L) associated w/↑ ASCVD risk and all-cause mortality

Myalgia likely to be statin-attributed if:

- Bilateral
- Involves proximal muscles
- Onset within weeks to months of initiation or dose increase

If statin-attributed muscle symptoms (SAMS) present:

- <u>D/c statin until symptoms resolve</u> (usually 1-2 weeks, up to 2 months)
- Management options:
  - **Rechallenge at reduced dose**
  - **Switch to a different statin** at comparable or lower dose
  - **Use alternative dosing regimen** (every other day, q3 days, weekly) with titration to max tolerated dose
  - **Consider other agents** – ezetimibe, bempedoic acid, PCSK9-I mAb
- <u>Extensive history of intolerance</u> – check Vit D / TSH level
  - If low, replace, and reintroduce low intensity statin
- CoQ10 – not effective, guideline recommends against use

High-Intensity (↓ LDL ≥ 50%)	
Atorvastatin 40-80 mg	Rosuvastatin 20-40 mg
Moderate-Intensity (↓ LDL ≥ 30-49%)	
Atorvastatin 10-20 mg Fluvastatin 40 mg BID, 80 mg XL QD Lovastatin 40 mg Pitavastatin 1-4 mg	Pravastatin 40-80 mg Rosuvastatin 5-10 mg Simvastatin 20-40 mg

apoB indicates apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; CABG, coronary artery bypass grafting; CKD, chronic kidney disease; DM, diabetes mellitus; FH, familial hypercholesterolemia; HeFH, heterozygous familial hypercholesterolemia; HF, heart failure; hsCRP, high-sensitivity C-reactive protein; HTN, hypertension; LDL, low-density lipoprotein; Lp(a), lipoprotein(a); mAb, monoclonal antibody; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; PCSK9-I, proprotein convertase subtilisin/kexin type 9 inhibitor; PREVENT, Preventing Risk of Cardiovascular Disease EVENTs; TIA, transient ischemic attack; and TG, triglycerides.

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CLASS	DRUGS	ADVANTAGES	DISADVANTAGES/COMMENTS	COST
Recommended Lipid Lowering Therapies				
HMG-CoA Reductase Inhibitors (statins) ↓ hepatic cholesterol synthesis	Atorvastatin (Lipitor) Fluvastatin (Lescol) Lovastatin (Mevacor) Pitavastatin (Livalo) Pravastatin (Pravachol) Rosuvastatin (Crestor) Simvastatin (Zocor)	**↓ LDL 20-55%,** ↓ TG 10-30%, ↑ HDL 5-15% **↓ CV event risk** Pravastatin: ↓ myopathy risk but less potent Pleotropic effects: improve endothelial function, inhibit platelet aggregation, ↓ LDL oxidation, ↓ vascular inflammation, and stabilize atherosclerotic plaque	With each doubling of statin dose, expect only ~6% added LDL ↓ Myalgias, arthralgias, myopathy (1-5% risk) **Avoid use in pregnancy and while lactating** (exceptions: high risk ASCVD, FH) Can ↑ glucose and risk of new onset DM – **benefit of statin outweighs risk** LFT elevations usually transient and resolve without intervention; no link between statin and life-threatening liver damage **Fluvastatin, lovastatin, & simvastatin** – must be dosed in the evening d/t short $t_{1/2}$ **Simvastatin & lovastatin** – many drug interactions; use of alternative statins preferred	¢-$$
Cholesterol Absorption Inhibitor ↓ dietary & biliary cholesterol absorption	Ezetimibe (Zetia)	**↓ LDL 18%** (alone), **25%** (w/statin), ↓ TG 5-10%, ↑ HDL 1-3% **↓ CV event risk** in combo w / moderate intensity statin (IMPROVE-IT); not proven to ↓ CV events when used alone Generic available – inexpensive, well-tolerated	Diarrhea Myopathy (less risk than statin alone); increased risk if used w / statin	$
PCSK9 Inhibitor: Monoclonal Antibodies ↑ hepatocyte degradation of LDL	Alirocumab (Praluent) Evolocumab (Repatha)	**↓ LDL 45-64%,** ↓ TG 12-17%, ↑ HDL 4-7%, **↓ Lp(a) ~15-30%** **↓ CV event risk** (FOURIER & ODESSEY) & all-cause mortality Few drug interactions	COST – brand name only Subcutaneous injection every 2-4 weeks Alternative for high-risk statin-intolerant pts	$$$$
ATP Citrate Lyase Inhibitor ↓ hepatic cholesterol synthesis (upstream from statins)	Bempedoic acid (Nexletol)	**↓ LDL 21-24%** (alone in pts w / SAMS), **17-18%** (w / max. tolerated statin), ↓ TG < 2%, **↓ HDL 4-6%** **↓ CV event risk** (CLEAR Outcomes)	COST – brand name only Alternative for high-risk statin-intolerant pts – no muscle side effects when used alone No effect on glucose or risk of DM **Can ↑ SCr, BUN, and uric acid** (caution in pts w / gout or hyperuricemia) ↑ risk of tendon rupture and kidney stones **Avoid use w / pravastatin ≥ 40 mg/day & simvastatin ≥ 20 mg/day;** caution w / fibrates	$$$$
Other Lipid Lowering Therapies				
PCSK9 Inhibitor: Small Interfering RNA (siRNA) Inhibits hepatic synthesis of PCSK9	Inclisiran (Leqvio)	**↓ LDL 48-52%,** ↓ TG 10-12%, ↑ HDL ~6%, **↓ Lp(a) ~15-30%** No CV outcomes data available (2026)	COST – brand name only Subcutaneous injection 3 months after initial dose, then every 6 months; **must be administered by healthcare professional** Alternative for PCSK9-I mAb intolerance or poor adherence; **do not use w / PCSK9-I mAb**	$$$$$
Bile Acid Sequestrants Bind bile acids, ↓ biliary cholesterol absorption	Cholestyramine (Prevalite, Questran) Colestipol (Colestid) Colesevelam (Welchol)	↓ LDL 10-27% (dose dependent), ↑ HDL 3-5% **↓ CV event risk** (LRC-CPPT trial) Modest A1c ↓ in pts w/DM	**Can ↑ TG – do not start if TG ≥ 300 or if high risk of pancreatitis** Constipation/obstruction, avoid if gastroparesis Dosed multiple times daily with meals Must take all other meds 2 hrs before or 4 hrs after (↓ absorption of other meds)	$
Fibrates ↓ hepatic secretion of VLDL and ↑ lipolysis and clearance of TGs	Fenofibrate (Fenoglide) Gemfibrozil (Lopid)	↓ LDL 5-20%, **↓ TG 30-50%,** ↑ HDL ~15% Fenofibrate dosed once daily **May ↓ risk of DM retinopathy** (FIELD trial)	Do not ↓ ASCVD risk; **1st line option for severe hypertriglyceridemia** **Fenofibrate preferred** (gemfibrozil no longer recommended for use) Caution when adding to statins or ezetimibe (↑ risk of myopathies) Product dosing is variable – depends on manufacturer & formulation	$
Omega-3 Fatty Acids ↓ hepatic production of TG-rich VLDL	Omega-3 acid ethyl esters (Lovaza) Icosapent ethyl (Vascepa)	**↓ TG 15-61%** Icosapent ethyl 2 grams BID ↓ CV event & CV death risk in pts w/ CVD or DM w/ TG > 150, and on statin (REDUCE-IT)	**1st line option for severe hypertriglyceridemia;** not enough DHA/EPA in OTC products ↑ bleed risk, ↑ Afib risk **Fishy burps** – store capsules in the freezer to avoid	$$
Nicotinic Acid ↓ hepatic production of VLDL and LDL	Niacin (Niaspan, Slo-Niacin)	↓ LDL 5-20%, ↓ TG 10-50% (formulation dependent), ↑ HDL 15-35%	*Should generally be avoided due to poor tolerability and side effects when used w/ or w/o statin therapy – hepatotoxicity, myopathy, flushing, hyperuricemia, ↑ insulin resistance*	¢-$

Coronary Artery Calcium (CAC) Score

Only useful in primary prevention for men ≥ 40 y and women ≥ 45 y Cost: $50-250

- Aids the decision to start statin when clinically uncertain or pt hesitancy
- **Not useful in pts w/ hx of statin use or on a statin** – statin stabilizes coronary calcium, so CAC will often be positive

CAC scoring & action:

- **CAC 0:** reasonable to defer statin in intermediate- or lower-risk adults
- **CAC 1-99:** moderate intensity statin recommended; LDL goal < **100** mg/dL
- **CAC 100-999:** high-intensity statin indicated,* add additional agents as needed to achieve LDL goal < **70** mg/dL
- **CAC ≥ 1000:** high-intensity statin indicated,* add additional agents as needed to achieve LDL goal < **55** mg/dL

*Guideline recommends lipid lowering therapy to achieve goal of ≥ 50% LDL lowering; high-intensity statins are first line

Apolipoprotein B (ApoB) Testing

Directly measures atherogenic particle number – better predictor of ASCVD risk than LDL

- **Useful to improve risk assessment and guide therapy once LDL and non-HDL goals are met**
  - If apoB above respective goal, consider lower LDL target

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