Management of Blood Cholesterol

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ECU HEALTH

CLINICAL PRACTICE GUIDELINE

2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

EXPERT CONSENSUS DECISION PATHWAY

2021 ACC Expert Consensus Decision Pathway on the Management of ASCVD Risk Reduction in Patients With Persistent Hypertriglyceridemia

A Report of the American College of Cardiology Solution Set Oversight Committee

Endorsed by the National Lipid Association

EXPERT CONSENSUS DECISION PATHWAY

2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk

A Report of the American College of Cardiology Solution Set Oversight Committee

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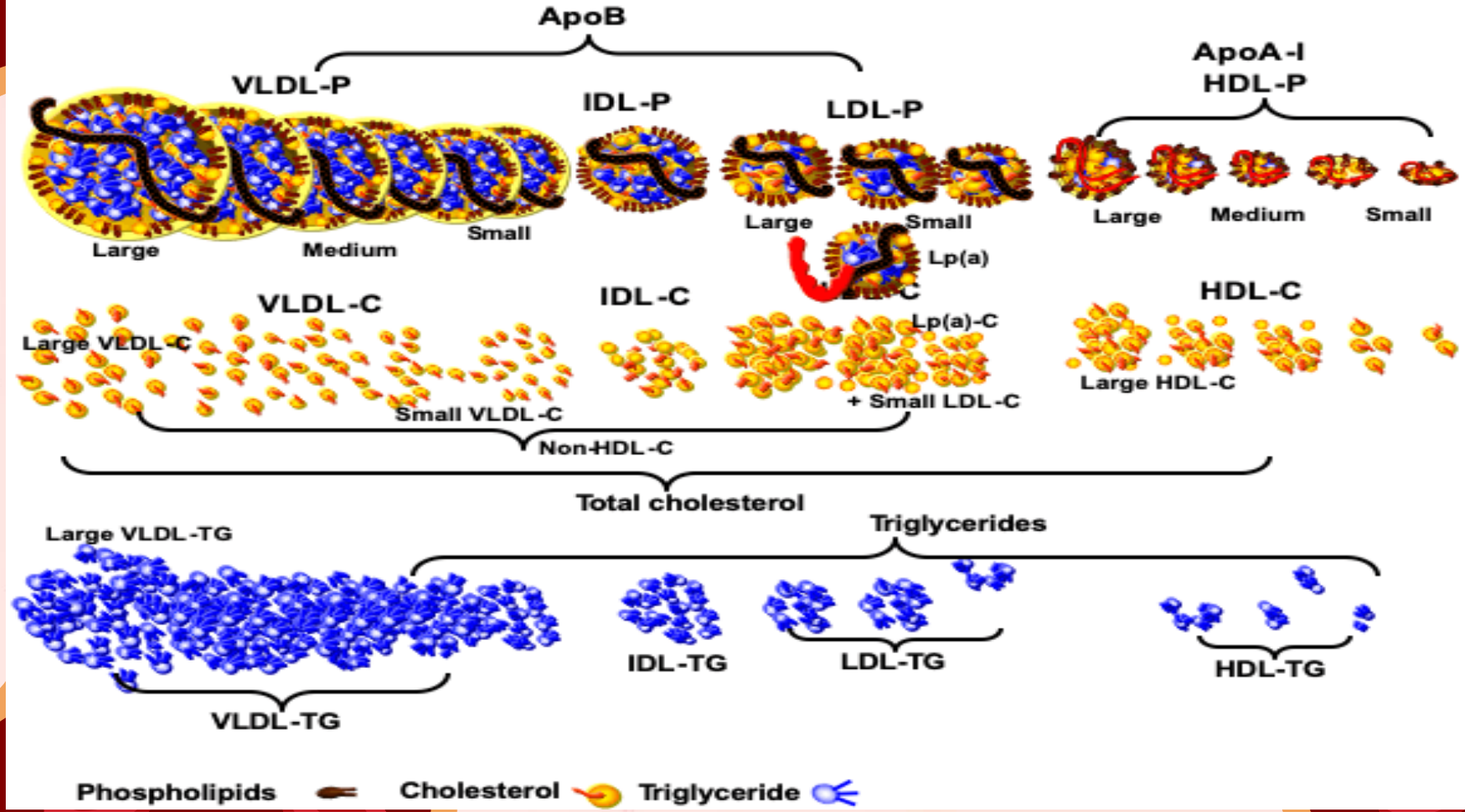
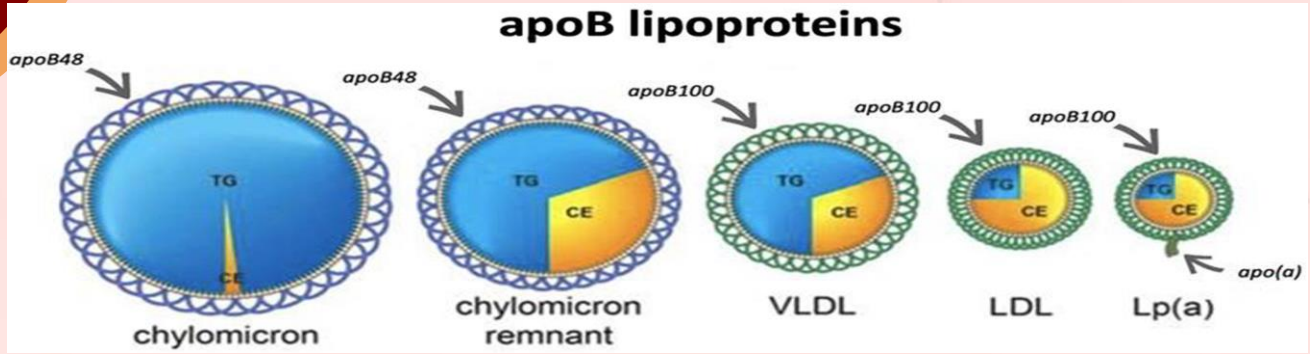

ApoB
VLDL-P
IDL-P
LDL-P
ApoA-I
HDL-P
Large
Medium
Small
Large
Small
Large
Medium
Small
Lp(a)
VLDL-C
IDL-C
HDL-C
Large VLDL-C
Small VLDL-C
Lp(a)-C
+ Small LDL-C
Large HDL-C
Non-HDL-C
Total cholesterol
Triglycerides
Large VLDL-TG
IDL-TG
LDL-TG
HDL-TG
VLDL-TG
Phospholipids
Cholesterol
Triglyceride



From the liver

TG C → TG C → C → C

apoB apoB apoB apoB

VLDL IDL large buoyant LDL small dense LDL

Atherogenic

Back to the liver

"Reverse cholesterol transport"

C apo A-I

HDL

Anti-atherogenic

Cholesterol levels for adults, ages 20 and over

AMOUNT (mg/dL)	TOTAL	LDL	HDL	TRIGLYCERIDES
Ideal	<200	<100	>60	<150
Borderline	200–239	130–159	Men: 40–59 Women 50–59	150–199
Too high or low	>240	High: 160–189 Very high: >190	Men: <40 Women <50	High: 200–499 Very high: >500

Source: Mayo Clinic and US National Library of Medicine

INSIDER

Measurements of LDL-C and Non-HDL-C

Recommendations for Measurements of LDL-C and Non-HDL-C		
COR	**LOE**	**Recommendations**
I	**B-NR**	**In adults who are 20 years of age or older and not on lipid-lowering therapy, measurement of either a fasting or a nonfasting plasma lipid profile is effective in estimating ASCVD risk and documenting baseline LDL-C.**
I	**B-NR**	**In adults who are 20 years of age or older and in whom an initial nonfasting lipid profile reveals a triglycerides level of 400 mg/dL (≥4.5 mmol/L) or higher, a repeat lipid profile in the fasting state should be performed for assessment of fasting triglyceride levels and baseline LDL-C.**

Friedewald formula

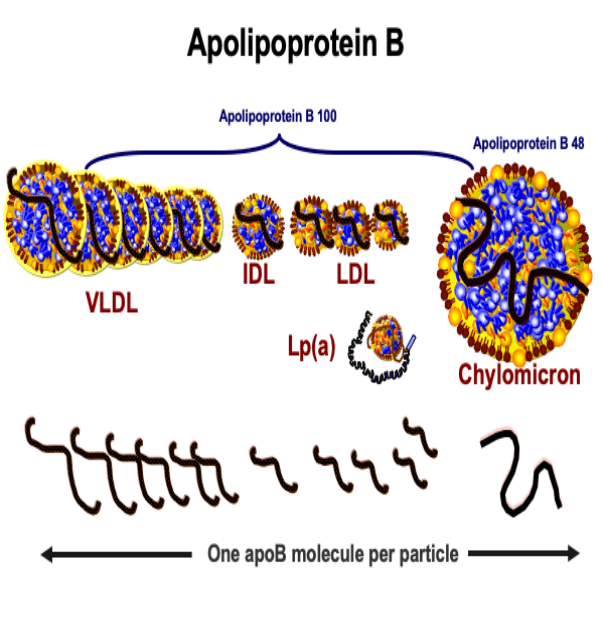
- Total cholesterol = HDL + LDL + VLDL
- VLDL = Tg(in mg/dl) / 5
  = Tg (in mmol/l) / 2.2
- Formula not valid if Triglycerides are > 400 mg/dl (4.5 mmol/l)

The unreliability of the Friedewald-calculated LDL-C levels appears to be greatest at lower levels of LDL-C, particularly <70 mg/dL (<1.8 mmol/L)

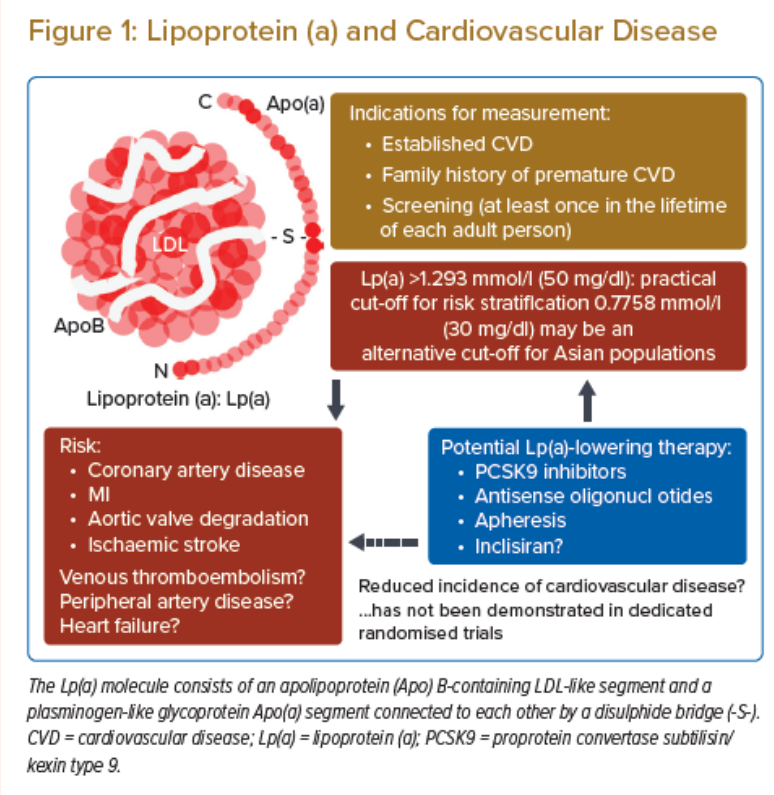
Measurements of LDL-C and Non-HDL-C

Recommendations for Measurements of LDL-C and Non-HDL-C		
COR	**LOE**	**Recommendations**
IIa	**C-LD**	**For patients with an LDL-C level less than 70 mg/dL (<1.8 mmol/L), measurement of direct LDL-C or modified LDL-C estimate is reasonable to improve accuracy over the Friedewald formula.**
IIa	**C-LD**	**In adults who are 20 years of age or older and without a personal history of ASCVD but with a family history of premature ASCVD or genetic hyperlipidemia, measurement of a fasting plasma lipid profile is reasonable as part of an initial evaluation to aid in the understanding and identification of familial lipid disorders.**

Measurements of Apolipoprotein B and Lipoprotein (a)



A relative indication for its measurement would be triglyceride >= 200 mg/dl. A level >130 mg/dl corresponds to an LDL-C level >= 160mg/dl



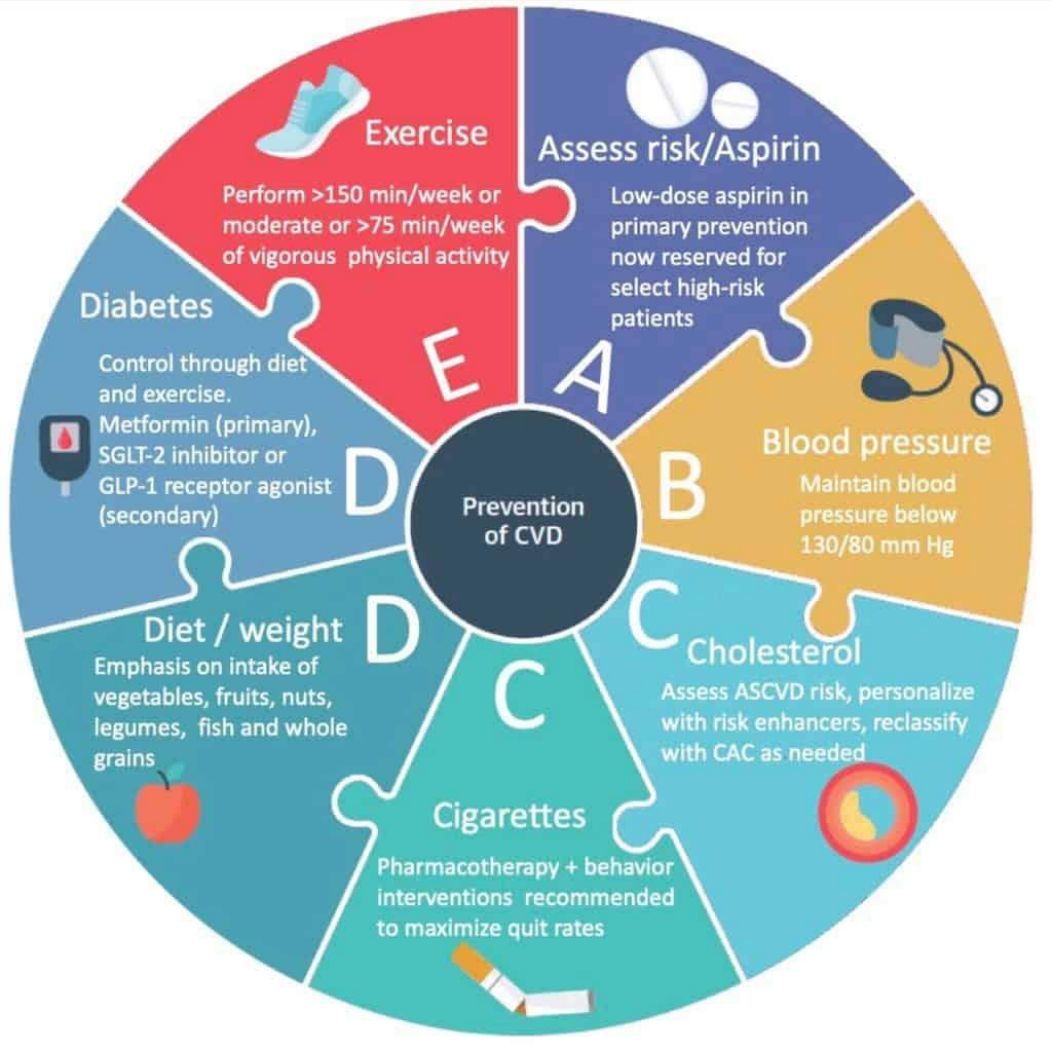
The Lp(a) molecule consists of an apolipoprotein (Apo) B-containing LDL-like segment and a plasminogen-like glycoprotein Apo(a) segment connected to each other by a disulphide bridge (-S-). CVD = cardiovascular disease; Lp(a) = lipoprotein (a); PCSK9 = proprotein convertase subtilisin/kexin type 9.

THERAPEUTIC MODALITIES

THERAPEUTIC MODALITIES

Lifestyle Therapies

Particularly indicated for the metabolic syndrome



THERAPEUTIC MODALITIES

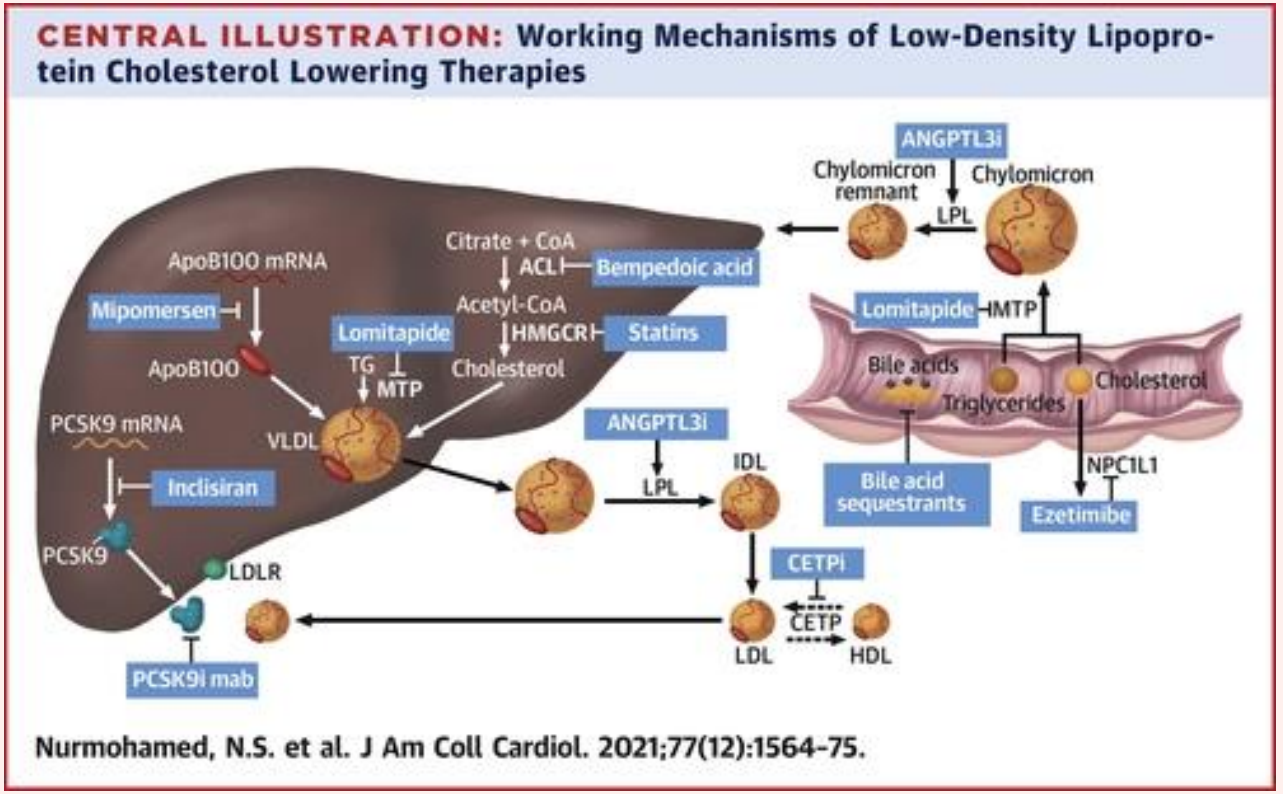
Statin Therapy

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 approximately 30-49%	Daily dose lowers LDL on average by <30%
Atorvastatin 40-80 mg Rosuvastatin 20-40 mg	Atorvastatin 10-20 mg Rosuvastatin 5-10 mg Simvastatin 20-40 mg Pravastatin 40-80 mg Lovastatin 40 mg Fluvastatin 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

4S trial:
8% vs. 12% mortality
19% vs. 28% MCE

THERAPEUTIC MODALITIES

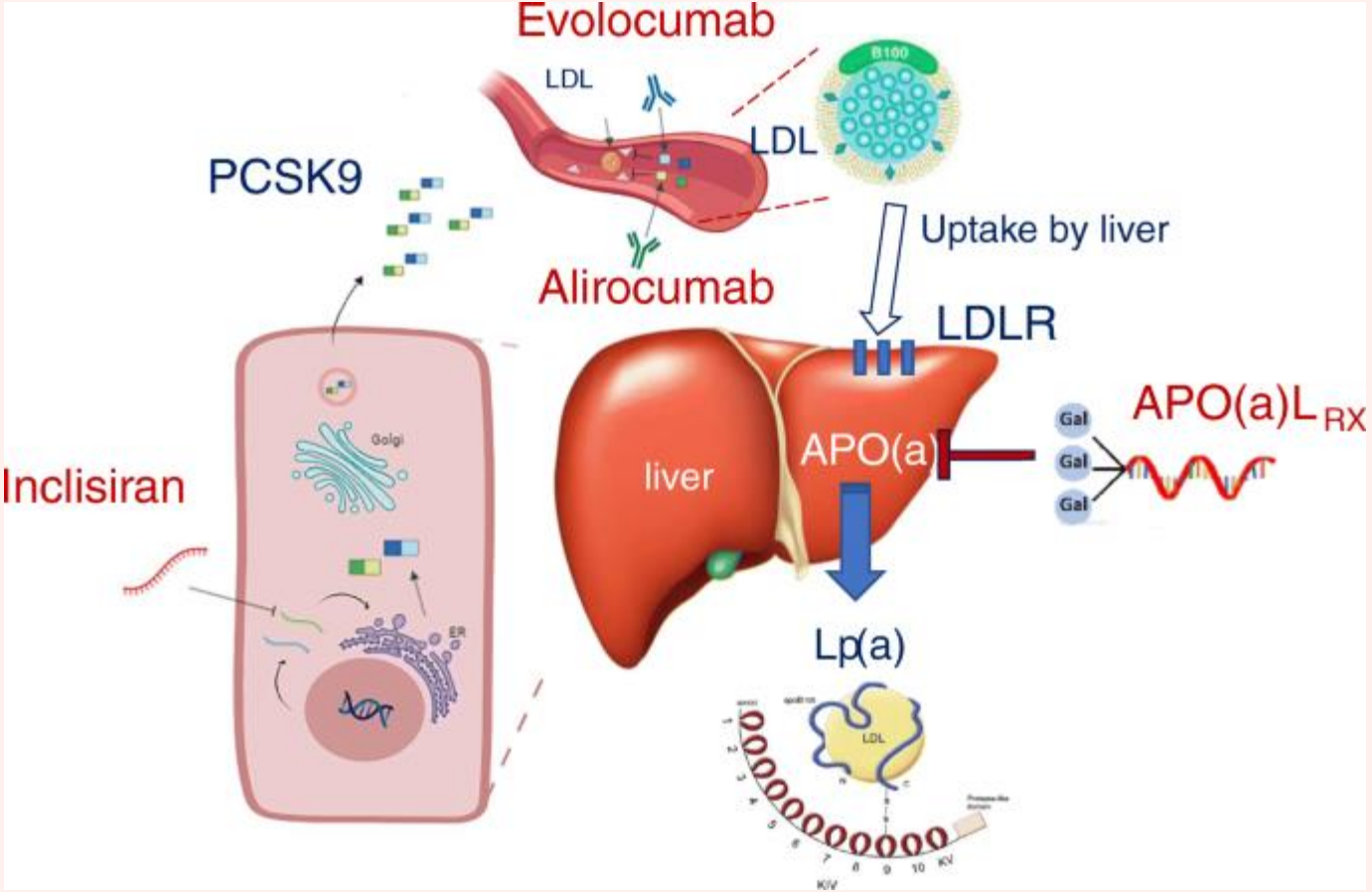
Non-Statin Therapy



Nurmohamed, N.S. et al. J Am Coll Cardiol. 2021;77(12):1564-75.

THERAPEUTIC MODALITIES

Non-Statin Therapy



THERAPEUTIC MODALITIES

Non-Statin Therapy

Table 1. Nonstatin Lipid-Lowering Medications

Medication	Mechanism of Action	LDL-C Reduction	Trials
Ezetimibe	Reduces absorption of cholesterol from small intestine	15%-25%	IMPROVE IT **Improve-it:** **32.% vs. 34.7%** **Sharp:** **11.3% vs. 13.4%**
Bempedoic acid	Inhibits adenosine triphosphate citrate lyase	15%-20% (alone), 25%-30% (with ezetimibe)	CLEAR Tranquility, CLEAR Outcomes (pending) ACC.23
PCSK9 inhibitors	Inhibits PCSK9 protein, resulting in availability of more LDL receptors and increased uptake of LDL-C into cells	45%-60%	FOURIER, GAUSS-2, GAUSS-3, ODYSSEY ALTERNATIVE **Odyssey:** **9.5% vs. 11.1%** **Fourier:** **9.8% vs. 11.3%**

TABLE 3 Strategies and Nonstatin Agents Considered for Management of LDL-Related ASCVD Risk

Strategy/Agent	Comments
Referral to another clinician	
Referral to lipid specialist	■ Consider referring any patient with ASCVD and/or baseline LDL-C ≥190 mg/dL, baseline LDL-C ≥190 mg/dL, or intolerance to at least 2 (preferably 3) statin therapies with 1 attempt at the lowest FDA-approved dose and a trial of an alternative statin therapy regimen (eg, every-other-day dosing) ■ Referral is recommended for patients with ASCVD and baseline LDL-C ≥190 mg/dL who did not achieve ↓ LDL-C ≥50% and LDL-C <70 mg/dL (or non-HDL-C <100 mg/dL) on maximally tolerated statin therapy in combination with nonstatin therapy ■ May also consider referring other patients unable to achieve adequate LDL-C reduction ■ **Considerations in referring:** Lipid specialists may be available for virtual visits for patients in some rural or remote locations
Referral to RD/RDN	■ Consider referring any patient with ASCVD and/or baseline LDL-C ≥190 mg/dL, or baseline LDL-C ≥190 mg/dL ■ Referral is recommended for patients with ASCVD and baseline LDL-C ≥190 mg/dL who did not achieve ↓ LDL-C ≥50% and LDL-C <70 mg/dL (or non-HDL-C <100 mg/dL) on maximally tolerated statin therapy in combination with nonstatin therapy ■ May also consider referring other patients unable to achieve adequate LDL-C reduction

Nonstatin agents that may be used to manage LDL-related ASCVD risk

Ezetimibe[34]

- **Mechanism of action:** Inhibits NPC1L1 protein; reduces cholesterol absorption in small intestine.
- **FDA-approved indication(s):** As adjunct to diet to: 1) ↓ TC, LDL-C, ApoB, non-HDL-C in patients with primary hyperlipidemia, either alone or in combination with statin therapy; 2) ↓ TC, LDL-C, ApoB, non-HDL-C in patients with mixed hyperlipidemia in combination with fenofibrate; 3) ↓ TC, LDL-C with HoFH, in combination with atorvastatin or simvastatin; and 4) ↓ sitosterol and campesterol in patients with homozygous sitosterolemia (phytosterolemia)
- **Dose:** 10 mg orally daily, with or without food. Take either ≥2 h before or ≥4 h after BAS, if used in combination
- **Mean % reduction in LDL-C (per PI):** Monotherapy—18%; combination therapy with statin therapy (incremental reduction)—25%
- **Contraindication:** History of hypersensitivity to this medication.
- **Warnings/precautions:**
  1. Not recommended in patients with moderate/severe hepatic impairment.
  2. Persistent elevations in hepatic transaminases may occur with concomitant statin therapy. Monitor hepatic transaminases before and during treatment based on monitoring recommendations for statin therapy.
  3. Cases of myopathy and rhabdomyolysis have been reported when ezetimibe was used alone or in combination with statin therapy.
- **Adverse effects:** Monotherapy—upper respiratory tract infection, diarrhea, arthralgia, sinusitis, pain in extremities. In combination with statin—nasopharyngitis, myalgia, upper respiratory tract infection, arthralgia, diarrhea
- **Use during pregnancy/lactation:** No safety data in humans; avoid use
- **Drug-drug interactions:** Cyclosporine, fibrates, BAS
- **CV outcomes trials:** IMPROVE-IT[8] (The addition of ezetimibe to moderate-intensity statin therapy in patients with recent ACS resulted in incremental lowering of LDL-C and reduced the primary composite endpoint of CV death, nonfatal MI, UA requiring rehospitalization, coronary revascularization [≥30 days after randomization], or nonfatal stroke. The median follow-up was 6 years); SHARP[35] (Simvastatin plus ezetimibe reduced LDL-C and reduced the primary endpoint of first major ASCVD event [nonfatal MI or CHD death, nonhemorrhagic stroke, or any arterial revascularization procedure] compared with placebo in patients with CKD over a median follow-up of 4.9 years)
- **Other prescribing considerations:** Generally well tolerated. Generic available

Improve-it:
32.% vs. 34.7%
Sharp:
11.3% vs. 13.4%

PCSK9 mAb (alirocumab,[36] evolocumab[37])

- **Mechanism of action:** Human mAb to PCSK9. Binds to PCSK9 and increases the number of LDL receptors available to clear circulating LDL-C
- **FDA-approved indication(s):**

Alirocumab and evolocumab: 1) ↓ LDL-C in adults with primary hyperlipidemia (including HeFH) as adjunct to diet, either alone or in combination with other lipid-lowering therapies

Alirocumab: 1) ↓ risk of MI, stroke, and unstable angina requiring hospitalization in adults with ASCVD; 2) ↓ LDL-C in adults with HoFH as adjunct to other LDL-C–lowering therapies

Evolocumab: 1) ↓ risk of MI, stroke, and coronary revascularization in adults with ASCVD; 2) ↓ LDL-C in pediatric patients (aged ≥10 years) with HeFH as adjunct to diet and other LDL-C–lowering therapies; 3) ↓ LDL-C in adults and pediatric patients (aged ≥10 years) with HoFH as adjunct to diet and other LDL-C–lowering therapies

- **Dose and route of administration:**

Alirocumab: Administer SC in the thigh, abdomen, or upper arm. In adults with ASCVD or primary hyperlipidemia: initiate 75 mg SC every 2 weeks. If more LDL-C reduction needed, may ↑ dose to 150 mg every 2 weeks. Alternative starting dose is 300 mg SC every 4 weeks. For the 300-mg dose, administer 2 (150-mg) injections consecutively at 2 different injection sites. In adults with HeFH undergoing LDL apheresis or adults with HoFH, administer 150 mg SC every 2 weeks

Evolocumab: Administer SC in the thigh, abdomen, or upper arm. In adults with ASCVD, adults with primary hypercholesterolemia, including with established clinical ASCVD or HeFH, or in pediatric patients (aged ≥10 years) with HeFH, administer 140 mg SC every 2 weeks or 420 mg SC once monthly in abdomen, thigh, or upper arm. In adults or pediatric patients (aged ≥10 years) with HoFH, administer 420 mg SC once monthly; if more LDL-C reduction is needed after 12 weeks, may ↑ dose to 420 mg every 2 weeks. In adults or pediatric patients (age ≥10 years) with HoFH on LDL apheresis, may initiate 420 mg SC every 2 weeks to correspond with apheresis schedule; evolocumab should be given after apheresis is complete. To administer 420-mg dose, either use the prefilled single-dose on-body infuser or give 3 (140-mg) injections consecutively within 30 min.

Strategy/Agent	Comments
	■ **Mean % LDL-C reduction (per PI):** ***Alirocumab:*** when added to maximally tolerated statin therapy, alirocumab 75 mg and 150 mg SC every 2 weeks ↓ LDL-C by an additional 45% and 58%, respectively, when added to maximally tolerated statin therapy. ***Evolocumab:*** 140 mg every 2 weeks and 420 mg SC every 4 weeks, ↓ LDL-C by an additional 64% and 58%, respectively.
	■ **Contraindication:** History of hypersensitivity to the medication. ■ **Warnings/precautions:** Hypersensitivity reactions occurred during clinical trials. If a serious hypersensitivity reaction occurs, discontinue therapy; treat according to standard of care; monitor until signs and symptoms resolve. ■ **Adverse effects:** ***Alirocumab:*** In patients with primary hyperlipidemia: nasopharyngitis, injection site reactions, influenza; in patients with ASCVD: noncardiac chest pain, nasopharyngitis, myalgia. No evidence of increase in cognitive adverse effects observed in ODYSSEY Outcomes or CANTAB.[9,38] ***Evolocumab:*** In patients with primary hyperlipidemia: nasopharyngitis, upper respiratory tract infection, influenza, back pain, and injection site reactions; in patients with ASCVD: diabetes, nasopharyngitis, upper respiratory tract infection. No evidence of an increase in cognitive adverse effects observed in FOURIER or EBBINGHAUS.[5,39] ■ **Use during pregnancy/lactation:** No safety data in humans; avoid use. ■ **Drug-drug interactions:** No clinically significant drug-drug interactions identified for alirocumab or evolocumab ■ **CV outcomes trials:**
Odyssey: 9.5% vs. 11.1%	***Alirocumab:*** ODYSSEY Outcomes[9] in 18,600 post-ACS (4-52 weeks) patients on evidence-based statin therapy; Demonstrated that addition of alirocumab reduced the primary endpoint of CHD death, MI, ischemic stroke, or hospitalization for UA.
Fourier: 9.8% vs. 11.3%	***Evolocumab:*** FOURIER[5] in 27,564 patients with prior MI, stroke, or PAD on atorvastatin ≥20 mg or equivalent; Demonstrated that addition of evolocumab reduced the primary endpoint of CV death, MI, stroke, revascularization, or hospitalization for unstable angina.
	■ **Other prescribing considerations:** Robust LDL-C reduction, cost, SC administration at home, may require prior authorization. ***Evolocumab:*** Advise latex-sensitive patients that the needle covers on the products contain latex.

Bempedoic acid[40]	■ **Mechanism of action:** ACL inhibitor; inhibits cholesterol synthesis in the liver; increases LDL receptor density. Bempedoic acid and its active metabolite require coenzyme A activation by ACSVL1, which is expressed primarily in the liver. ■ **FDA-approved indication(s):** ↓ LDL-C in adults with ASCVD or HeFH as adjunct to diet and maximally tolerated statin therapy. ■ **Dose:** 180 mg orally once daily, with or without food. ■ **Mean % reduction in LDL-C (per PI):** Combination therapy with statin therapy (placebo-corrected incremental reduction)—17%-18%. ■ **Contraindication:** none ■ **Warnings/precautions:** 1) May ↑ serum uric acid. Advise patients to contact their clinician if symptoms of hyperuricemia occur. Assess serum uric acid when clinically indicated. Monitor patients for signs and symptoms of hyperuricemia, and initiate treatment with urate-lowering drugs, as appropriate. Assess uric acid level before initiation and if signs and symptoms of hyperuricemia occur. 2) Discontinue immediately if the patient experiences rupture of a tendon. Consider discontinuing if the patient experiences joint pain, swelling, or inflammation. Advise patients to rest at the first sign of tendinitis or tendon rupture and to contact their health care provider if tendinitis or tendon rupture symptoms occur. Consider alternative therapy in patients with a history of tendon disorders or tendon rupture.[17] ■ **Adverse effects:** Upper respiratory tract infection, muscle spasms, hyperuricemia, back pain, abdominal pain or discomfort, bronchitis, pain in extremity, anemia, elevated liver enzymes. ■ **Use during pregnancy/lactation:** Discontinue when pregnancy is recognized unless the benefits of therapy outweigh the potential risks to the fetus. There are no available data on use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes.[17] ■ **Drug-drug interactions:** Avoid concomitant simvastatin >20 mg daily or pravastatin >40 mg daily. ■ **CV outcomes trials:** CV outcomes trials not completed. CLEAR Outcomes trial completion expected later in 2022. ■ **Other prescribing considerations:** cost; pill burden; requires prior authorization

Bempedoic acid and ezetimibe[41]	■ **Refer to section on ezetimibe for information specific to this agent.** ■ **Mechanism of action:** See the mechanisms of action for bempedoic acid and ezetimibe included in this table. ■ **FDA-approved indication(s):** ↓ LDL-C in adults with ASCVD or HeFH as adjunct to diet and maximally tolerated statin therapy. ■ **Dose:** 1 tablet (180 mg bempedoic acid/10 mg ezetimibe) orally, once daily, with or without food. Swallow whole. Take either ≥2 hours before or ≥4 hours after BAS, if used in combination. ■ **Mean % reduction in LDL-C (per PI):** Combination therapy with statin therapy (placebo-corrected incremental reduction)—38%. ■ **Contraindication:** History of hypersensitivity to ezetimibe. ■ **Warnings/precautions:** 1. May ↑ serum uric acid. Advise patients to contact their clinician if symptoms of hyperuricemia occur. Assess serum uric acid when clinically indicated. Monitor patients for signs and symptoms of hyperuricemia, and initiate treatment with urate-lowering drugs as appropriate. Assess uric acid level before initiation and if signs and symptoms of hyperuricemia occur. 2. Discontinue immediately if the patient experiences tendon rupture. Consider discontinuing if the patient experiences joint pain, swelling, or inflammation. Advise patients to rest at the first sign of tendinitis or tendon rupture and to contact their health care provider if tendinitis or tendon rupture symptoms occur. Consider alternative therapy in patients with a history of tendon disorders or tendon rupture.[17]

Strategy/Agent	Comments
	■ **Adverse effects:** Upper respiratory tract infection, muscle spasms, hyperuricemia, back pain, abdominal pain or discomfort, bronchitis, pain in extremities, anemia, elevated liver enzymes, diarrhea, arthralgia, sinusitis, fatigue, influenza. Consider alternative therapy if history of tendon disorder or rupture; discontinue immediately if tendon rupture occurs. ■ **Use during pregnancy/lactation:** Discontinue when pregnancy is recognized unless the benefits of therapy outweigh the potential risks to the fetus. There are no available data on use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes.[42] ■ **Drug-drug interactions:** Cyclosporine; fibrates. Avoid concomitant simvastatin >20 mg daily or pravastatin >40 mg daily. ■ **CV outcomes trials:** CV outcomes trials for bempedoic acid not completed. Completion of CLEAR Outcomes trial expected later in 2022. CV outcomes trial will not be required for fixed-dose combination of ezetimibe and bempedoic acid. ■ **Prescribing considerations:** ↓ LDL-C within the range of moderate-intensity statin therapy; cost; requires prior authorization

Inclisiran[43]	■ **Mechanism of action:** siRNA targeting PCSK9; inhibits PCSK9 production in liver, thereby prolonging activity of LDL receptors. ■ **FDA-approved indication(s):** ↓ LDL-C in adults with ASCVD or HeFH as adjunct to diet and maximally tolerated statin therapy. ■ **Dose:** Administer 284 mg SC on day 1, day 90, and then every 6 months by a clinician. ■ **Mean % reduction in LDL-C (per PI):** 48%-52% ■ **Contraindications (per PI):** None ■ **Warnings/precautions (per PI):** None ■ **Adverse effects:** Injection site reaction, arthralgia, urinary tract infection, diarrhea, bronchitis, pain in extremities, dyspnea ■ **Use during pregnancy/lactation:** No safety data in humans; avoid use. ■ **Drug-drug interactions (per PI):** None ■ **CV outcomes trials:** CV outcomes trials not yet completed. ORION-4 currently in progress with estimated completion in 2026. VICTORION-2P currently in progress with estimated completion in 2027. ■ **Other prescribing considerations:** robust LDL-C reduction, cost, requires SC administration by a clinician, requires prior authorization.

BAS[44,45]

- **Mechanism of action:** Nonabsorbed, lipid-lowering polymer that binds bile acids in the intestine and impedes their reabsorption. As the bile acid pool ↓, the hepatic enzyme cholesterol 7-α-hydroxylase is up-regulated, which ↑ conversion of cholesterol to bile acids. This causes ↑ demand for cholesterol in the liver cells, resulting in the dual effect of increasing transcription and activity of the cholesterol biosynthetic enzyme HMG-CoA reductase and ↑ numbers of hepatic LDL receptors. These compensatory effects result in ↑ clearance of LDL particles from the blood, in turn resulting in ↓ serum LDL-C levels. Serum TG levels may ↑ or remain unchanged.
- **FDA-approved indication(s):**

Colesevelam: As an adjunct to diet and exercise to 1) ↓ LDL-C in adults with primary hyperlipidemia; 2) ↑ glycemic control in adults with type 2 diabetes; 3) ↓ LDL-C in boys and post-menarchal girls (aged 10-17 years) with HeFH who are unable to reach LDL-C targets after an adequate trial of diet therapy and lifestyle modifications. ***Cholestyramine, colestipol:*** ↓ LDL-C with primary hyperlipidemia, as adjunct to diet

- **Dose and route of administration:**

Colesevelam: Tablets: 6 tablets orally once daily or 3 tablets orally twice daily; take tablets with a meal and liquid. Suspension: one 3.75-g packet orally daily, or one 1.875-g packet orally twice daily; mix powder with 8 ounces of water, fruit juice, or soft drink; take with meal.

3.75 g is equivalent to 6 tablets. 1.875 g is equivalent to 3 tablets;

Cholestyramine: 8-16 g/day orally, divided into 2 doses;

Colestipol: 2-16 g/day orally, given once or in divided doses

- **Mean % LDL reduction (per PI):**

Colesevelam: Monotherapy—15% (6 tablets daily); in combination with low- to moderate-intensity statin therapy—additional 10%-16% reduction in LDL-C (data from simvastatin 10 mg, atorvastatin 10 mg). ***Cholestyramine:*** Monotherapy—10.4% vs placebo.

Colestipol: not provided in PI. In dose-ranging RCT with monotherapy, doses of 5, 10, and 15 g resulted in 16.3%, 22.8%, and 27.2% reductions in LDL-C, respectively[46]

- **Contraindications (per PI):**

Colesevelam: TG >500 mg/dL; history of hypertriglyceridemia-induced pancreatitis; bowel obstruction.

Cholestyramine: History of serious hypersensitivity to this medication.

Colestipol: Complete biliary obstruction, history of serious hypersensitivity to this medication.

- **Warnings/precautions:** May ↑ TG and cause acute pancreatitis, monitor TG, discontinue if signs and symptoms of acute pancreatitis occur; may cause GI obstruction, avoid with gastroparesis, other GI motility disorders, and history of major GI tract surgery with risk for bowel obstruction; may cause vitamin K or fat-soluble vitamin deficiencies, oral vitamins should be given ≥4 hours before this medication; may decrease absorption of other medications, other medications should be given ≥4 hours before this medication. Some products contain phenylalanine, which may be harmful to patients with phenylketonuria.

Strategy/Agent	Comments
	■ **Adverse effects:** Constipation, dyspepsia, and nausea. ■ **Use during pregnancy/lactation:** Considered safe to use ■ **Drug-drug interactions:** In general, BAS may decrease absorption of other medications; it is a good practice for all other medications to be given ≥4 hours before BAS. Concomitant use of BAS is known to decrease absorption of cyclosporin, oral contraceptives containing ethinyl estradiol and norethindrone, olmesartan, phenytoin, sulfonylureas, thyroid replacement therapy, warfarin; give these medications ≥4 hours before BAS. For patients on warfarin, monitor INR frequently during BAS initiation and then periodically. Cholestyramine may increase exposure to metformin; monitor glycemic control. ■ **CV outcomes trials:** In LRC-CPPT, 3,806 asymptomatic middle-aged men with primary hypercholesterolemia were randomized to cholestyramine resin vs placebo for an average of 7.4 years. The cholestyramine group experienced a 19% reduction in risk ($P < 0.05$) of the primary endpoint—definite CHD death and/or definite nonfatal MI. The effects of colesevelam and colestipol on cardiovascular morbidity and mortality have not been determined ■ **Considerations in prescribing:** Pill burden; inconvenience in preparation of oral suspension preparations; drug interactions, GI side effects; exacerbation of hypertriglyceridemia; orally administered, colesevelam lowers HbA_{1c} 0.5% in diabetes; CV outcomes data not available for all products

THERAPEUTIC MODALITIES

Non-Statin Therapy

Agents that may be used to treat HoFH under care of a lipid specialist	
Evinacumab[21]	■ **Mechanism of action:** Human monoclonal antibody that binds to and inhibits ANGPTL3. Promotes VLDL processing and clearance upstream of LDL formation ■ **FDA-approved indication(s):** ↓ LDL-C in adults and pediatric patients (aged ≥12 years) with HoFH as adjunct to other LDL-C–lowering therapies ■ **Dose and route of administration:** 15 mg/kg administered by healthcare professional as IV infusion once monthly (every 4 weeks). See PI for preparation and administration instructions. ■ **Mean % reduction in LDL-C (per PI):** Combination therapy with other lipid-lowering therapies (incremental reduction)—49%. ■ **Contraindication:** History of serious hypersensitivity to this medication. ■ **Warnings/precautions:** 1. Hypersensitivity reactions occurred during clinical trials. If a serious hypersensitivity reaction occurs, discontinue therapy; treat according to standard of care; monitor until signs and symptoms resolve. 2. May cause fetal toxicity; inform patients who may become pregnant of risk to fetus; obtain a pregnancy test before initiating therapy in patients who may become pregnant; advise patients who may become pregnant to use contraception during treatment and for ≥5 months following the last dose. Discontinue this medication if patient becomes pregnant. Clinicians should report pregnancies that occur while taking this medication (1-833-385-3392). ■ **Adverse effects:** nasopharyngitis, influenza-like illness, dizziness, rhinorrhea, nausea. ■ **Use during pregnancy/lactation:** Avoid use. ■ **Drug-drug interactions:** No clinically significant drug-drug interactions have been identified ■ **CV outcomes trials:** The effect of evinacumab on CV morbidity and mortality has not been determined ■ **Other prescribing considerations:** See prescribing information for complete preparation and administration instructions. Robust LDL-C reduction; cost, IV administration, requires prior authorization

Lomitapide[47]

- **Mechanism of action:** Directly binds and inhibits microsomal triglyceride transfer protein, which resides in the lumen of the endoplasmic reticulum, thereby preventing the assembly of apoB-containing lipoproteins in enterocytes and hepatocytes. This inhibits synthesis of chylomicrons and VLDL and leads to ↓ LDL-C
- **FDA-approved indications:** ↓ LDL-C, TC, apoB, and non-HDL-C in patients with HoFH, as adjunct to a low-fat diet and other lipid-lowering treatments (including LDL apheresis, where available)
- **Dose and route of administration:** Initiate 5 mg orally once daily. Titrate dose based on acceptable safety/tolerability: increase to 10 mg daily after at least 2 weeks and then, at a minimum of 4-week intervals, to 20 mg, 40 mg, up to the maximum recommended dose of 60 mg daily
- **Mean % LDL reduction (per PI):** Mean and median percent changes in LDL-C from baseline when added to baseline lipid-lowering therapy were −40% and −50%, respectively
- **Black box warnings:**
  1. May cause elevations in liver transaminases; measure ALT, AST, alkaline phosphatase, total bilirubin before initiating this medication; during treatment, adjust dose if ALT or AST ≥3 times the upper limit of normal; discontinue this medication for clinically significant liver toxicity.
  2. Increases hepatic fat (hepatic steatosis) with or without concomitant increases in transaminases. Hepatic steatosis associated with lomitapide may be a risk factor for progressive liver disease, including steatohepatitis and cirrhosis. Because of the risk of hepatotoxicity, lomitapide is only available through the REMS program
- **Contraindications:** 1) Pregnancy; 2) concomitant use with strong/moderate CYP3A4 inhibitors; 3) moderate/severe hepatic impairment or active liver disease including unexplained persistent abnormal liver function tests.
- **Warnings/precautions:** 1) May cause fetal toxicity; inform patients who may become pregnant of risk to fetus; obtain a pregnancy test before initiating therapy in patients who may become pregnant; advise patients who may become pregnant to use contraception during treatment and for ≥2 weeks following the last dose. Discontinue this medication if patient becomes pregnant. Clinicians should report pregnancies that occur while taking this medication (1-877-902-4099).

Strategy/Agent	Comments
	■ **Adverse effects:** Diarrhea, nausea, vomiting, dyspepsia, and abdominal pain. ■ **Use during pregnancy/lactation:** Avoid use. ■ **Drug-drug interactions:** 1. CYP3A4 inhibitors increase exposure to lomitapide. Strong/moderate CYP3A4 inhibitors are contraindicated with lomitapide. Avoid grapefruit juice. 2. Do not exceed 30 mg daily of lomitapide when used concomitantly with weak CYP3A4 inhibitors, including atorvastatin and oral contraceptives. 3. Increases plasma concentration of warfarin; monitor INR regularly, especially with lomitapide dose adjustment. 4. Increased systemic exposure to simvastatin and lovastatin exposure with lomitapide. Limit statin dose when coadministered due to myopathy risk. 5. Consider dose reduction of P-glycoprotein substrates because of possible increased absorption with lomitapide. 6. Separate lomitapide dosing with BAS by at least 4 hours. ■ **CV outcomes trials:** The effect of lomitapide on CV morbidity and mortality has not been determined ■ **Considerations in prescribing:** Cost, oral administration, requires strict adherence to low-fat diet and gradual dose escalation to reduce GI side effects, requires daily doses of specific vitamins (Vitamin E 400 IU, linoleic acid ≥200 mg, alpha-linolenic acid ≥210 mg, eicosapentaenoic acid ≥110 mg, docosahexaenoic acid ≥80 mg); requires monitoring of transaminase levels, long-term consequences of hepatic steatosis unknown, prescriber training, REMS program

LDL apheresis	■ **Mechanism of action:** Selectively removes apo B-containing lipoproteins, producing an acute reduction in LDL-C. ■ **FDA approved indication:** Patients with FH unresponsive to pharmacologic and dietary management who are either functional homozygotes with an LDL-C >500 mg/dL, functional heterozygotes with no known CV disease but an LDL-C >300 mg/dL, or functional heterozygotes with known cardiovascular disease and LDL-C >200 mg/dL ■ **Dose and route of administration:** Extracorporeal technique performed weekly or biweekly ■ **Mean % LDL-C reduction:** With weekly or biweekly treatment, average LDL-C can ↓ to ~50-60% of the original levels. LDL-C increases after each apheresis session but does not return to the original level ■ **Adverse effects:** Problems with venous access; transient hypotension, fatigue; bleeding; hypocalcemia; iron deficiency due to regular phlebotomy for diagnostic purposes; heparin allergy; and bradykinin syndrome (especially with ACEi) ■ **Drug-drug interactions:** ACEi should not be used with dextran sulfate method owing to risk of bradykinin syndrome ■ **CV outcomes trials:** Limited due to ethical considerations in RCTs of very high-risk patients with HoFH, but it is reasonable to assume reductions in CV disease events are proportional to the degree of LDL-C lowering ■ **Considerations in prescribing:** Cost, extracorporeal technique, inconvenient, locations not readily available in some regions, time-consuming, robust reduction in LDL-C

2018 Cholesterol Guideline

Patient Management Groups

- Secondary ASCVD Prevention
- Severe Hypercholesterolemia (LDL-C ≥190 mg/dL [≥4.9 mmol/L])
- Diabetes Mellitus in Adults
- Primary Prevention Adults 40 to 75 Years of Age With LDL-C Levels 70 to 189 mg/dL (1.7–4.8 mmol/L)

Clinical ASCVD:

ACS, history of MI, stable or unstable angina, coronary
or
other arterial revascularization, stroke, TIA
or
PAD including aortic aneurysm, all of atherosclerotic origin.

Secondary ASCVD Prevention

Recommendations for Statin Therapy Use in Patients With ASCVD		
COR	**LOE**	**Recommendations**
I	**A**	**In patients who are 75 years 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.**
I	**A**	**In patients with clinical ASCVD in whom high-intensity statin therapy is contraindicated or who experience statin-associated side effects, moderate-intensity statin therapy should be initiated or continued with the aim of achieving a 30% to 49% reduction in LDL-C levels.**

Table 4. Very High-Risk* of Future ASCVD Events

Major ASCVD Events
Recent ACS (within the past 12 mo)
History of MI (other than recent ACS event listed above)
History of ischemic stroke
Symptomatic peripheral arterial disease (history of claudication with ABI <0.85, or previous revascularization or amputation)

*** Very high risk include those with a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions**

Table 4. Very High-Risk* of Future ASCVD Events

High-Risk Conditions
Age ≥65 y
Heterozygous familial hypercholesterolemia
History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s)
Diabetes mellitus
Hypertension
CKD (eGFR 15-59 mL/min/1.73 m^2)
Current smoking
Persistently elevated LDL-C (LDL-C ≥100 mg/dL [≥2.6 mmol/L]) despite maximally tolerated statin therapy and ezetimibe
History of congestive HF

*** Very high risk include those with a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions**

Secondary ASCVD Prevention

Recommendations for Statin Therapy Use in Patients With ASCVD		
COR	**LOE**	**Recommendations**
IIa	**B-R**	**In patients with clinical ASCVD who are on maximally tolerated statin therapy and are judged to be at very high risk and have an LDL-C level of 70 mg/dL (≥1.8 mmol/L) or higher, it is reasonable to add ezetimibe therapy.**

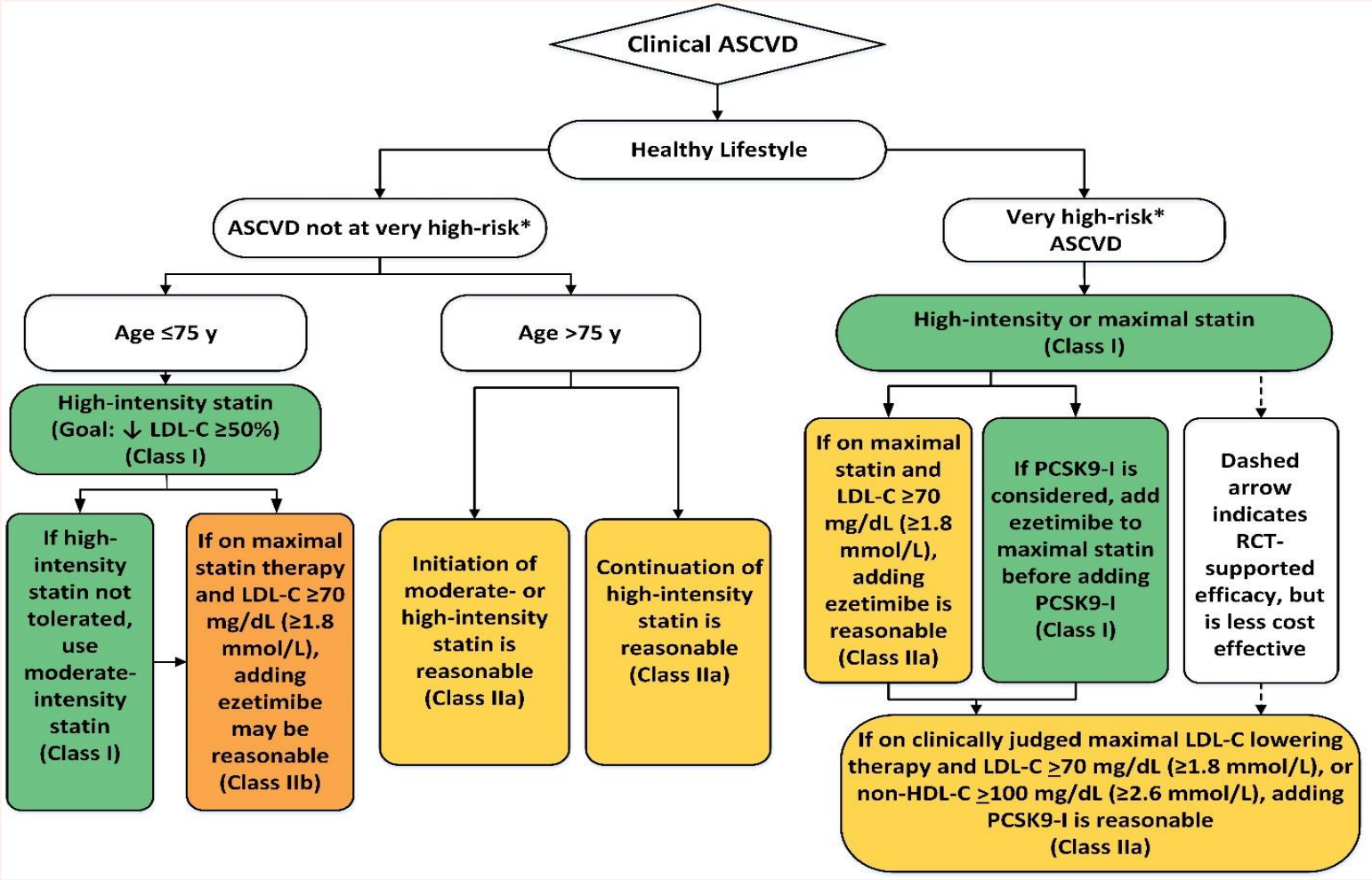
Secondary ASCVD Prevention

Recommendations for Statin Therapy Use in Patients With ASCVD		
COR	**LOE**	**Recommendations**
I	**B-NR**	**In patients with clinical ASCVD who are judged to be very high risk and *considered for PCSK9 inhibitor therapy,* maximally tolerated LDL-C lowering therapy should include maximally tolerated statin therapy and ezetimibe.**
IIa	**A^{SR}**	**In patients with clinical ASCVD who are judged to be very high risk and who are on maximally tolerated LDL-C lowering therapy with LDL-C 70 mg/dL (≥1.8 mmol/L) or higher or a non-HDL-C level of 100 mg/dL (≥2.6 mmol/L) or higher, it is reasonable to add a PCSK9 inhibitor following a clinician–patient discussion about the net benefit, safety, and cost.**
Value Statement: Low Value (LOE: B-NR)		**At mid-2018 list prices, PCSK9 inhibitors have a low cost value (>$150,000 per QALY) compared to good cost value (<$50,000 per QALY) (Section 7 provides a full discussion of the dynamic interaction of different prices and clinical benefit).**

Secondary ASCVD Prevention

Recommendations for Statin Therapy Use in Patients With ASCVD		
COR	**LOE**	**Recommendations**
IIa	**B-R**	**In patients older than 75 years of age with clinical ASCVD, it is reasonable to initiate moderate- or high-intensity statin therapy after evaluation of the potential for ASCVD risk reduction, adverse effects, and drug–drug interactions, as well as patient frailty and patient preferences.**
IIa	**C-LD**	**In patients older than 75 years of age who are tolerating high-intensity statin therapy, it is reasonable to continue high-intensity statin therapy after evaluation of the potential for ASCVD risk reduction, adverse effects, and drug-drug interactions, as well as patient frailty and patient preferences.**

Secondary Prevention



Severe Hypercholesterolemia (LDL-C ≥190 mg/dL [≥4.9 mmol/L])

Recommendations for Primary Severe Hypercholesterolemia (LDL-C ≥190 mg/dL [≥4.9 mmol/L])		
COR	**LOE**	**Recommendations**
I	**B-R**	**In patients 20 to 75 years of age with an LDL-C level of 190 mg/dL (≥4.9 mmol/L) or higher, maximally tolerated statin therapy is recommended.**
IIa	**B-R**	**In patients 20 to 75 years of age with an LDL-C level of 190 mg/dL (≥4.9 mmol/L) or higher 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 (≥2.6 mmol/L) or higher, ezetimibe therapy is reasonable.**

Severe Hypercholesterolemia (LDL-C ≥190 mg/dL [≥4.9 mmol/L])

Recommendations for Primary Severe Hypercholesterolemia (LDL-C ≥190 mg/dL [≥4.9 mmol/L])		
COR	**LOE**	**Recommendations**
IIb	**B-R**	**In patients 20 to 75 years of age with a baseline LDL-C level ≥190 mg/dL (≥4.9 mmol/L), who achieve less than a 50% reduction in LDL-C levels and have fasting triglycerides ≤300 mg/dL (≤3.4 mmol/L). while taking maximally tolerated statin and ezetimibe therapy, the addition of a bile acid sequestrant may be considered.**
IIb	**B-R**	**In patients 30 to 75 years of age with heterozygous FH and with an LDL-C level of 100 mg/dL (≥2.6 mmol/L) or higher while taking maximally tolerated statin and ezetimibe therapy, the addition of a PCSK9 inhibitor may be considered.**

Severe Hypercholesterolemia (LDL-C ≥190 mg/dL [≥4.9 mmol/L])

Recommendations for Primary Severe Hypercholesterolemia (LDL-C ≥190 mg/dL [≥4.9 mmol/L])		
COR	**LOE**	**Recommendations**
IIb	**C-LD**	**In patients 40 to 75 years of age with a baseline LDL-C level of 220 mg/dL (≥5.7 mmol/L) or higher and who achieve an on-treatment LDL-C level of 130 mg/dL (≥3.4 mmol/L) or higher while receiving maximally tolerated statin and ezetimibe therapy, the addition of a PCSK9 inhibitor may be considered.**
Value Statement: Uncertain Value (B-NR)		**Among patients with FH without evidence of clinical ASCVD taking maximally tolerated statin and ezetimibe therapy, PCSK9 inhibitors provide uncertain value at 2018 U.S. list prices.**

Diabetes Mellitus in Adults

Recommendations for Patients With Diabetes Mellitus		
COR	**LOE**	**Recommendations**
I	**A**	**In adults 40 to 75 years of age with diabetes mellitus, regardless of estimated 10-year ASCVD risk, moderate-intensity statin therapy is indicated.**
IIa	**B-NR**	**In adults 40 to 75 years of age with diabetes mellitus and an LDL-C level of 70 to 189 mg/dL (1.7 to 4.8 mmol/L), it is reasonable to assess the 10-year risk of a first ASCVD event by using the race and sex-specific PCE to help stratify ASCVD risk.**

Diabetes Mellitus in Adults

Recommendations for Patients With Diabetes Mellitus		
COR	**LOE**	**Recommendations**
IIa	**B-R**	**In adults with diabetes mellitus 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.**
IIa	**B-NR**	**In adults older than 75 years of age with diabetes mellitus and who are already on statin therapy, it is reasonable to continue statin therapy.**
IIb	**C-LD**	**In adults with diabetes mellitus and 10-year ASCVD risk of 20% or higher, it may be reasonable to add ezetimibe to maximally tolerated statin therapy to reduce LDL-C levels by 50% or more.**

Diabetes Mellitus in Adults

Recommendations for Patients With Diabetes Mellitus		
COR	**LOE**	**Recommendations**
IIb	**C-LD**	**In adults older than 75 years with diabetes mellitus, it may be reasonable to initiate statin therapy after a clinician–patient discussion of potential benefits and risks.**
IIb	**C-LD**	**In adults 20 to 39 years of age with diabetes mellitus that is either of long duration (≥10 years of type 2 diabetes mellitus, ≥20 years of type 1 diabetes mellitus), albuminuria (≥30 mcg of albumin/mg creatinine), estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m^2, retinopathy, neuropathy, or ankle-brachial index (ABI; <0.9), it may be reasonable to initiate statin therapy.**

Table 5. Diabetes-Specific Risk Enhancers That Are Independent of Other Risk Factors in Diabetes Mellitus

Risk Enhancers
• Long duration (≥10 years for type 2 diabetes mellitus (S.4.3-20) or ≥20 years for type 1 diabetes mellitus) • Albuminuria ≥30 mcg of albumin/mg creatinine • eGFR <60 mL/min/1.73 m^2 • Retinopathy • Neuropathy • ABI <0.9

Primary Prevention Adults 40 to 75 Years of Age With LDL-C Levels 70 to 189 mg/dL (1.7–4.8 mmol/L)

Primary Prevention Recommendations for Adults 40 to 75 Years of Age With LDL Levels 70 to 189 mg/dL (1.7–4.8 mmol/L)		
COR	**LOE**	**Recommendations**
I	B-NR	For the primary prevention of clinical ASCVD* in adults 40 to 75 years of age without diabetes mellitus and with an LDL-C level of 70 to 189 mg/dL (1.7 to 4.8 mmol/L), the 10-year ASCVD risk of a first "hard" ASCVD event (fatal and nonfatal MI or stroke) should be estimated by using the race- and sex-specific PCE, and adults should be categorized as being at low risk (<5%), borderline risk (5% to <7.5%), intermediate-risk (≥7.5% to <20%), and high-risk (≥20%).
I	B-NR	Clinicians and patients should engage in a risk discussion that considers risk factors, adherence to healthy lifestyle, the potential for ASCVD risk-reduction benefits, and the potential for adverse effects and drug–drug interactions, as well as patient preferences, for an individualized treatment decision.

Primary Prevention Adults 40 to 75 Years of Age With LDL-C Levels 70 to 189 mg/dL (1.7–4.8 mmol/L)

Primary Prevention Recommendations for Adults 40 to 75 Years of Age With LDL Levels 70 to 189 mg/dL (1.7–4.8 mmol/L)		
COR	**LOE**	**Recommendations**
I	**A**	**In adults at intermediate-risk, statin therapy reduces risk of ASCVD, and in the context of a risk discussion, if a decision is made for statin therapy, a moderate-intensity statin should be recommended.**
I	**A**	**In intermediate-risk patients, LDL-C levels should be reduced by 30% or more, and for optimal ASCVD risk reduction, especially in high-risk patients, levels should be reduced by 50% or more.**

Table 6. Risk-Enhancing Factors for Clinician–Patient Risk Discussion

Risk-Enhancing Factors
• **Family history of premature ASCVD** (males, age <55 y; females, age <65 y) • **Primary hypercholesterolemia** (LDL-C, 160–189 mg/dL [4.1–4.8 mmol/L); non–HDL-C 190–219 mg/dL [4.9–5.6 mmol/L])* • **Metabolic syndrome** (increased waist circumference, elevated triglycerides [>175 mg/dL], elevated blood pressure, elevated glucose, and low HDL-C [<40 mg/dL in men; <50 in women mg/dL] are factors; tally of 3 makes the diagnosis) • **Chronic kidney disease** (eGFR 15–59 mL/min/1.73 m^2 with or without albuminuria; not treated with dialysis or kidney transplantation) • **Chronic inflammatory conditions** such as psoriasis, RA, or HIV/AIDS • **History of premature menopause (before age 40 y) and history of pregnancy-associated conditions that increase later ASCVD risk such as preeclampsia** • **High-risk race/ethnicities** (e.g., South Asian ancestry)

Table 6 continued

Risk-Enhancing Factors

• **Lipid/biomarkers**: Associated with increased ASCVD risk
  ○ Persistently* elevated, primary hypertriglyceridemia (≥175 mg/dL);
  ○ If measured:
  ▪ **Elevated high-sensitivity C-reactive protein** (≥2.0 mg/L)
  ▪ **Elevated Lp(a):** A relative indication for its measurement is family history of premature ASCVD. An Lp(a) ≥50 mg/dL or ≥125 nmol/L constitutes a risk-enhancing factor especially at higher levels of Lp(a).
  ▪ **Elevated apoB** ≥130 mg/dL: A relative indication for its measurement would be triglyceride ≥200 mg/dL. A level ≥130 mg/dL corresponds to an LDL-C >160 mg/dL and constitutes a risk-enhancing factor
  ▪ **ABI** <0.9

Primary Prevention Adults 40 to 75 Years of Age With LDL-C Levels 70 to 189 mg/dL (1.7–4.8 mmol/L)

Primary Prevention Recommendations for Adults 40 to 75 Years of Age With LDL Levels 70 to 189 mg/dL (1.7–4.8 mmol/L)		
COR	**LOE**	**Recommendations**
IIa	**B-R**	**In intermediate-risk adults, risk-enhancing factors favor initiation or intensification of statin therapy.**
IIa	**B-NR**	**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.**

Primary Prevention Adults 40 to 75 Years of Age With LDL-C Levels 70 to 189 mg/dL (1.7–4.8 mmol/L)

Primary Prevention Recommendations for Adults 40 to 75 Years of Age With LDL Levels 70 to 189 mg/dL (1.7–4.8 mmol/L)		
COR	**LOE**	**Recommendations**
IIa	**B-NR**	**In intermediate-risk adults or selected borderline-risk adults in whom a CAC score is measured for the purpose of making a treatment decision, AND** **•If the coronary calcium score is zero, it is reasonable to withhold statin therapy and reassess in 5 to 10 years, as long as higher risk conditions are absent (diabetes mellitus, family history of premature CHD, cigarette smoking);** **•If CAC score is 1 to 99, it is reasonable to initiate statin therapy for patients ≥55 years of age;** **•If CAC score is 100 or higher or in the 75th percentile or higher, it is reasonable to initiate statin therapy.**

Primary Prevention Adults 40 to 75 Years of Age With LDL-C Levels 70 to 189 mg/dL (1.7–4.8 mmol/L)

Primary Prevention Recommendations for Adults 40 to 75 Years of Age With LDL Levels 70 to 189 mg/dL (1.7–4.8 mmol/L)		
COR	**LOE**	**Recommendations**
IIb	**B-R**	**In intermediate-risk adults who would benefit from more aggressive LDL-C lowering and in whom high-intensity statins are advisable but not acceptable or tolerated, it may be reasonable to add a nonstatin drug (ezetimibe or bile acid sequestrant) to a moderate-intensity statin.**
IIb	**B-R**	**In patients at borderline risk, in risk discussion, the presence of risk-enhancing factors may justify initiation of moderate-intensity statin therapy.**

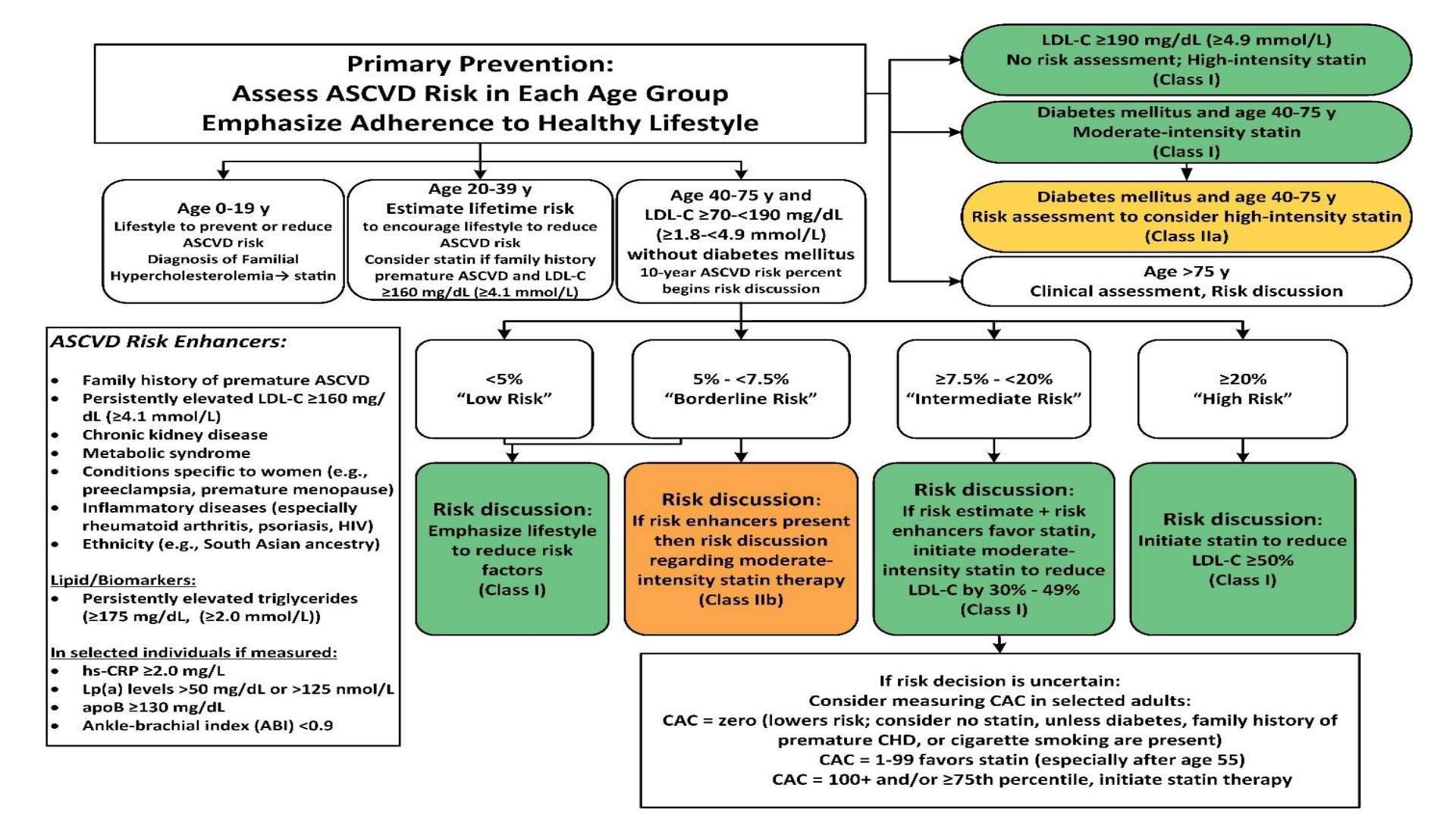

Primary Prevention:
Assess ASCVD Risk in Each Age Group
Emphasize Adherence to Healthy Lifestyle
LDL-C ≥190 mg/dL (≥4.9 mmol/L)
No risk assessment; High-intensity statin
(Class I)
Diabetes mellitus and age 40-75 y
Moderate-intensity statin
(Class I)
Diabetes mellitus and age 40-75 y
Risk assessment to 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

Table 7. Checklist for Clinician–Patient Shared Decision-Making for Initiating Therapy

Checklist Item	Recommendation

ASCVD risk assessment	• Assign to statin treatment group; use ASCVD Risk Estimator Plus.*
	  ○ In lower-risk primary-prevention adults 40-75 y of age with LDL-C ≥70 mg/dL (≥1.8 mmol/L).
	  ○ Not needed in secondary prevention, in those with LDL-C ≥190 mg/dL (≥4.9 mmol/L), or in those 40-75 y of age with diabetes mellitus.
	• Assess other patient characteristics that influence risk. See Risk-Enhancing Factors (Section 4.4.1.3. and Table 6)
	• Assess CAC (Section 4.4.1.4.) if risk decision is uncertain and additional information is needed to clarify ASCVD risk.
	  ○ Use decision tools to explain risk (e.g., ASCVD Risk Estimator Plus,* Mayo Clinic Statin Choice Decision Aid).

Lifestyle modifications	• Review lifestyle habits (e.g., diet, physical activity, weight or body mass index, and tobacco use). • Endorse a healthy lifestyle and provide relevant advice, materials, or referrals. (e.g., CardioSmart, AHA Life's Simple 7, NLA Patient Tear Sheets, PCNA Clinicians' Lifestyle Modification Toolbox, cardiac rehabilitation, dietitian, smoking cessation program).

Table 7 continued

Checklist Item	Recommendation
Potential net clinical benefit of pharmacotherapy	• Recommend statins as first-line therapy. • Consider the combination of statin and nonstatin therapy in selected patients. • Discuss potential risk reduction from lipid-lowering therapy. • Discuss the potential for adverse effects or drug–drug interactions.

Table 7 continued

Checklist Item	Recommendation
Cost considerations	• Discuss potential out-of-pocket cost of therapy to the patient (e.g., insurance plan coverage, tier level, copayment).
Shared decision-making	• Encourage the patient to verbalize what was heard (e.g., patient's personal ASCVD risk, available options, and risks/benefits). • Invite the patient to ask questions, express values and preferences, and state ability to adhere to lifestyle changes and medications. • Refer patients to trustworthy materials to aid in their understanding of issues regarding risk decisions. • Collaborate with the patient to determine therapy and follow-up plan.

Table 8. Selected Examples of Candidates for CAC Measurement Who Might Benefit From Knowing Their CAC Score Is Zero

CAC Measurement Candidates Who Might Benefit from Knowing Their CAC Score Is Zero
• Patients reluctant to initiate statin therapy who wish to understand their risk and potential for benefit more precisely • Patients concerned about need to reinstitute statin therapy after discontinuation for statin-associated symptoms • Older patients (men, 55-80 y of age; women, 60-80 y of age) with low burden of risk factors who question whether they would benefit from statin therapy • Middle-aged adults (40-55 y of age) with PCE-calculated 10-year risk of ASCVD 5% to <7.5% with factors that increase their ASCVD risk, although they are in a borderline risk group

Monitoring in Response to LDL-C–Lowering Therapy

Recommendation for Monitoring		
COR	**LOE**	**Recommendation**
I	**A**	**Adherence to changes in lifestyle and effects of LDL-C–lowering medication should be assessed by measurement of fasting lipids and appropriate safety indicators 4 to 12 weeks after statin initiation or dose adjustment and every 3 to 12 months thereafter based on need to assess adherence or safety.**

Primary Prevention in Other Age Groups (Older Adults)

Recommendations for Older Adults		
COR	**LOE**	**Recommendations**
IIb	**B-R**	**In adults 75 years of age or older with an LDL-C level of 70 to 189 mg/dL (1.7 to 4.8 mmol/L), initiating a moderate-intensity statin may be reasonable.**
IIb	**B-R**	**In adults 75 years of age or older, it may be reasonable to stop statin therapy when functional decline (physical or cognitive), multimorbidity, frailty, or reduced life-expectancy limits the potential benefits of statin therapy.**
IIb	**B-R**	**In adults 76 to 80 years of age with an LDL-C level of 70 to 189 mg/dL (1.7 to 4.8 mmol/L), it may be reasonable to measure CAC to reclassify those with a CAC score of zero to avoid statin therapy.**

Primary Prevention in Other Age Groups (Children and Adolescents)

Recommendations for Children and Adolescents		
COR	**LOE**	**Recommendations**
I	**A**	**In children and adolescents with lipid disorders related to obesity, it is recommended to intensify lifestyle therapy, including moderate caloric restriction and regular aerobic physical activity.**
I	**B-NR**	**In children and adolescents with lipid abnormalities, lifestyle counseling is beneficial for lowering LDL-C.**

Primary Prevention in Other Age Groups (Children and Adolescents)

Recommendations for Children and Adolescents		
COR	**LOE**	**Recommendations**
IIa	**B-R**	**In children and adolescents 10 years of age or older with an LDL-C level persistently 190 mg/dL (≥4.9 mmol/L) or higher or 160 mg/dL (4.1 mmol/L) or higher with a clinical presentation consistent with FH (see Section 4.2.) and who do not respond adequately with 3 to 6 months of lifestyle therapy, it is reasonable to initiate statin therapy.**
IIa	**B-NR**	**In children and adolescents with a family history of either early CVD* or significant hypercholesterolemia,† it is reasonable to measure a fasting or nonfasting lipoprotein profile as early as age 2 years to detect FH or rare forms of hypercholesterolemia.**

Primary Prevention in Other Age Groups (Children and Adolescents)

Recommendations for Children and Adolescents		
COR	**LOE**	**Recommendations**
IIa	**B-NR**	**In children and adolescents found to have moderate or severe hypercholesterolemia, it is reasonable to carry out reverse-cascade screening of family members, which includes cholesterol testing for first-, second-, and when possible, third-degree biological relatives, for detection of familial forms of hypercholesterolemia.**
IIa	**C-LD**	**In children and adolescents with obesity or other metabolic risk factors, it is reasonable to measure a fasting lipid profile to detect lipid disorders as components of the metabolic syndrome.**

Primary Prevention in Other Age Groups (Children and Adolescents)

Recommendations for Children and Adolescents		
COR	**LOE**	**Recommendations**
IIb	**B-NR**	**In children and adolescents without cardiovascular risk factors or family history of early CVD, it may be reasonable to measure a fasting lipid profile or nonfasting non HDL-C once between the ages of 9 and 11 years, and again between the ages of 17 and 21 years, to detect moderate to severe lipid abnormalities.**

Table 9. Normal and Abnormal Lipid Values in Childhood*†

	Acceptable, mg/dL	Borderline, mg/dL	Abnormal, mg/dL
TC	<170 (<4.3 mmol)	170-199 (4.3-5.1 mmol)	≥200 (≥5.1 mmol)
Triglycerides (0-9 y)	<75 (<0.8 mmol)	75-99 (0.8-1.1 mmol)	≥100 (≥1.1 mmol)
Triglycerides (10-19 y)	<90 (<1.0 mmol)	90-129 (1.0-1.5 mmol)	≥130 (≥1.4 mmol)
HDL-C	>45 (>1.2 mmol)	40-45 (1.0-1.2 mmol)	<40 (<1.0 mmol)
LDL-C	<110 (<2.8 mmol)	110-129 (2.8-3.3 mmol)	≥130 (≥3.4 mmol)
Non-HDL-C	<120 (<3.1 mmol)	120-144 (3.1-3.7 mmol)	≥145 (≥3.7 mmol)

Other Populations at Risk (Ethnicity)

Recommendation for Other Populations at Risk		
COR	**LOE**	**Recommendation**
IIa	**B-NR**	**For clinical decision-making in adults of different race/ethnicities, it is reasonable for clinicians to review race/ethnic features that can influence ASCVD risk so as to adjust choice of statin or intensity of treatment.**

Table 10. Racial/Ethnic Issues in Evaluation, Risk Decisions, and Treatment of ASCVD Risk

	Racial/Ethnic Groupings			
	Asian Americans*	**Hispanic/Latino Americans†**	**Blacks**	**Comments**
Evaluation				
ASCVD issues informed by race/ethnicity	**ASCVD risk in people of South Asian and East Asian origin varies by country of origin; individuals from South Asia (see below) have increased ASCVD risk.**	Race/ethnicity and country of origin, together with socioeconomic status and acculturation level, may explain risk factor burden more precisely (e.g., ASCVD risk is higher among individuals from Puerto Rico than those from Mexico).	ASCVD risk assessment in black women shows increased ASCVD risk compared with their otherwise similar white counterparts.	There is heterogeneity in risk according to racial/ethnic group and within racial/ethnic groups. Native American/Alaskan populations have high rates of risk factors for ASCVD compared to non-Hispanic whites.
Lipid issues informed by race/ethnicity	**Asian Americans have lower levels of HDL-C than whites.** **There is higher prevalence of LDL-C among Asian Indians, Filipinos, Japanese, and Vietnamese than among whites. An increased prevalence of high TG was seen in all Asian American subgroups.**	Hispanic/Latino women have higher prevalence of low HDL-C compared with Hispanic/Latino men.	Blacks have higher levels of HDL-C and lower levels of triglycerides than non-Hispanic whites or Mexican Americans.	All ethnic groups appear to be at greater risk for dyslipidemia, but important to identify those with more sedentary behavior and less favorable diet.
Metabolic issues informed by race/ethnicity	**Increased MetS is seen with lower waist circumference than in whites.** **DM develops at a lower lean body mass and at earlier ages. Majority of risk in South Asians is explained by known risk factors, especially those related to insulin resistance.**	DM is disproportionately present compared with whites and blacks. There is increased prevalence of MetS and DM in Mexican Americans compared with whites and Puerto Ricans.	There is increased DM and hypertension.	There is increased prevalence of DM. Features of MetS vary by race/ethnicity. Waist circumference, not weight, should be used to determine abdominal adiposity when possible.

Table 10 continued

	Racial/Ethnic Groupings			
	Asian Americans*	**Hispanic/Latino Americans†**	**Blacks**	**Comments**
Treatment				
Lifestyle counseling (use principles of Mediterranean and DASH diets)	**Use lifestyle counseling to recommend a heart-healthy diet consistent with racial/ethnic preferences to avoid weight gain and address BP and lipids.**	Use lifestyle counseling to recommend a heart-healthy diet consistent with racial/ethnic preferences to avoid weight gain and address BP and lipids.	Use lifestyle counseling to recommend a heart-healthy diet consistent with racial/ethnic preferences to avoid weight gain and address BP and lipids.	Asian and Hispanic/Latino groups need to be disaggregated because of regional differences in lifestyle preferences. Challenge is to avoid increased sodium, sugar, and calories as groups acculturate.
Intensity of statin therapy and response to LDL-C lowering	**Japanese patients may be sensitive to statin dosing. In an open-label, randomized primary-prevention trial, Japanese participants had a reduction in CVD events with low-intensity doses of pravastatin as compared with placebo. In a secondary-prevention trial, Japanese participants with CAD benefitted from a moderate-intensity dose of pitavastatin.**	No sensitivity to statin dosage is seen, as compared with non-Hispanic white or black individuals.	No sensitivity to statin dosage is seen, as compared with non-Hispanic white individuals.	Using a lower statin intensity in Japanese patients may give results similar to those seen with higher intensities in non-Japanese patients.
Safety	**Higher rosuvastatin plasma levels are seen in Japanese, Chinese, Malay, and Asian Indians as compared with whites. FDA recommends a lower starting dose (5 mg of rosuvastatin in Asians versus 10 mg in whites). Caution is urged as dose is uptitrated.**	There are no specific safety issues with statins related to Hispanic/Latino ethnicity.	Baseline serum CK values are higher in blacks than in whites. The 95th percentile race/ethnicity- specific and sex-specific serum CK normal levels are available for assessing changes in serum CK.	Clinicians should take Asian race into account when prescribing dose of rosuvastatin (See package insert). In adults of East Asian descent, other statins should be used preferentially over simvastatin.

Table 10 continued

	Racial/Ethnic Groupings			
	Asian Americans*	**Hispanic/Latino Americans†**	**Blacks**	**Comments**
Risk Decisions				
PCE	**No separate PCE is available; use PCE for whites. PCE may underestimate ASCVD risk in South Asians. PCE may overestimate risk in East Asians.**	No separate PCE is available; use PCE for non-Hispanic whites. If African-American ancestry is also present, then use PCE for blacks.	Use PCE for blacks.	Country-specific race/ethnicity, along with socioeconomic status, may affect estimation of risk by PCE.
CAC score	**In terms of CAC burden, South Asian men were similar to non-Hispanic white men, but higher CAC when than blacks, Latinos, and Chinese Americans. South Asian women had similar CAC scores to whites and other racial/ethnic women, although CAC burden higher in older age.**	CAC predicts similarly in whites and in those who identify as Hispanic/Latino.	In MESA, CAC score was highest in white and Hispanic men, with blacks having significantly lower prevalence and severity of CAC.	Risk factor differences in MESA between ethnicities did not fully explain variability in CAC. However, CAC predicted ASCVD events over and above traditional risk factors in all ethnicities.

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Figure 1Summary Graphic: Patient Populations Addressed and Factors and Interventions to Consider

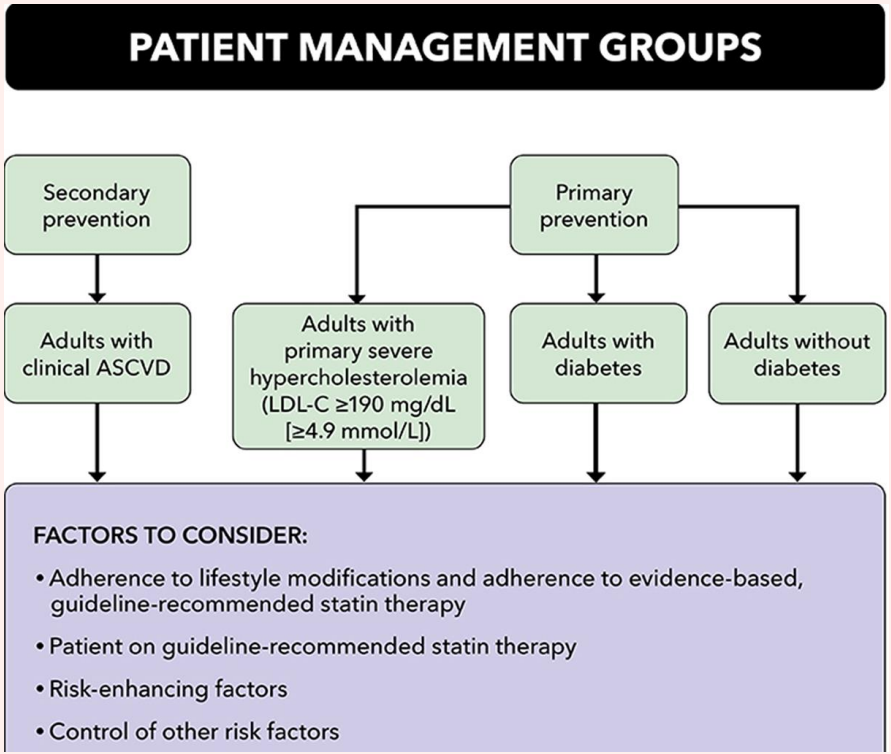

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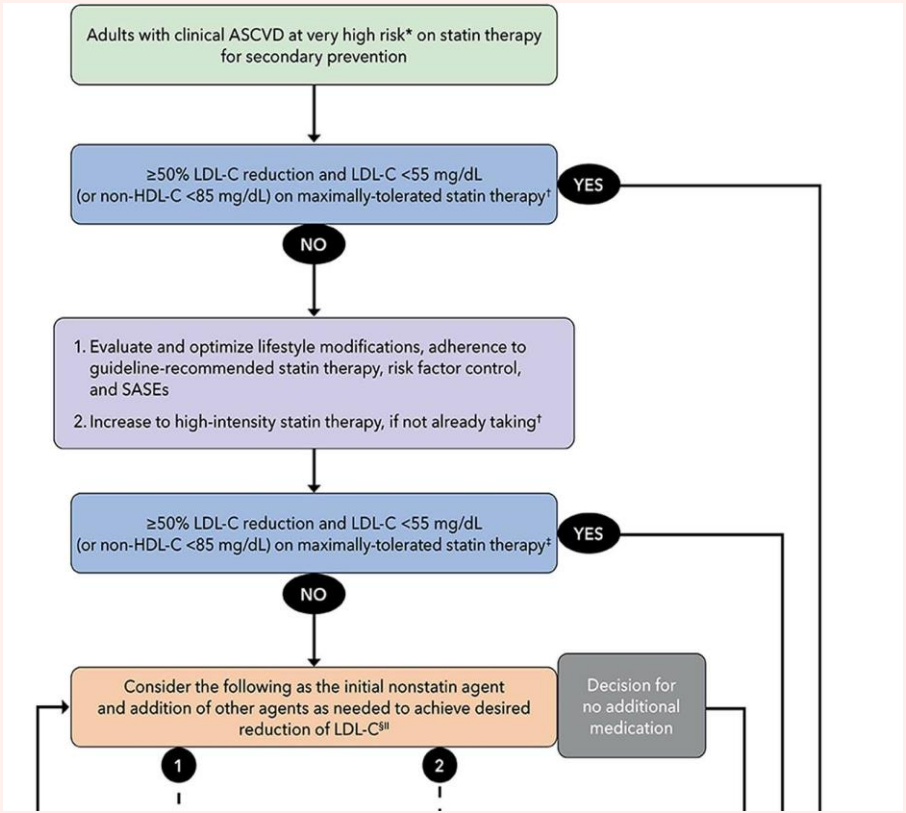
Figure 2A Adults With Clinical ASCVD at Very High Risk on Statin Therapy for Secondary Prevention



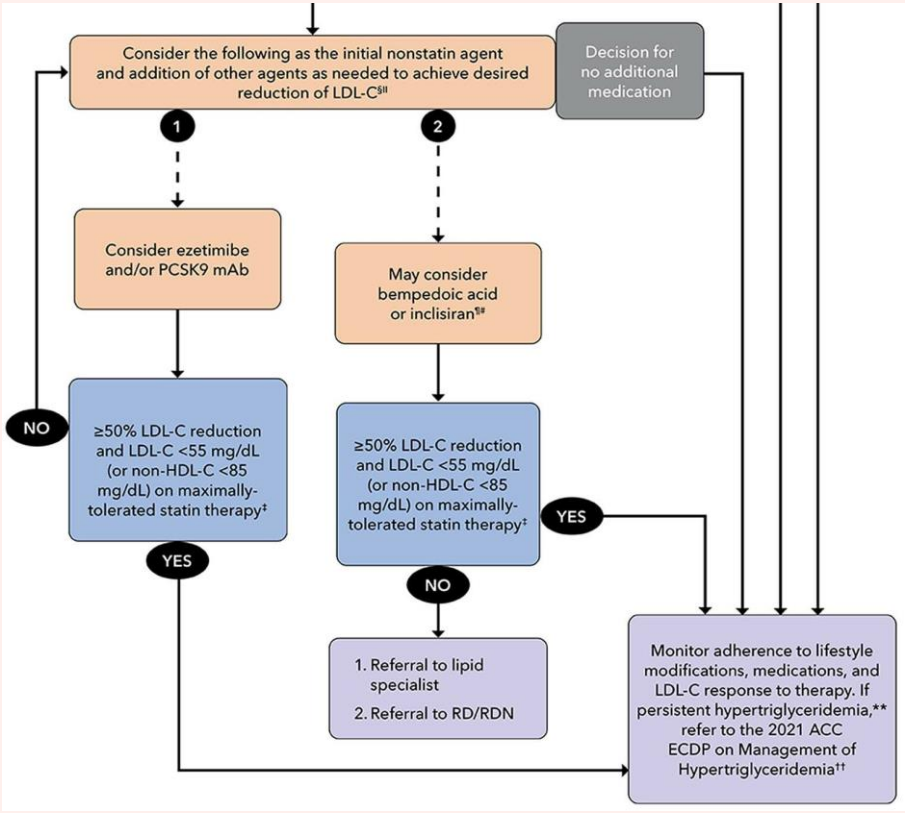


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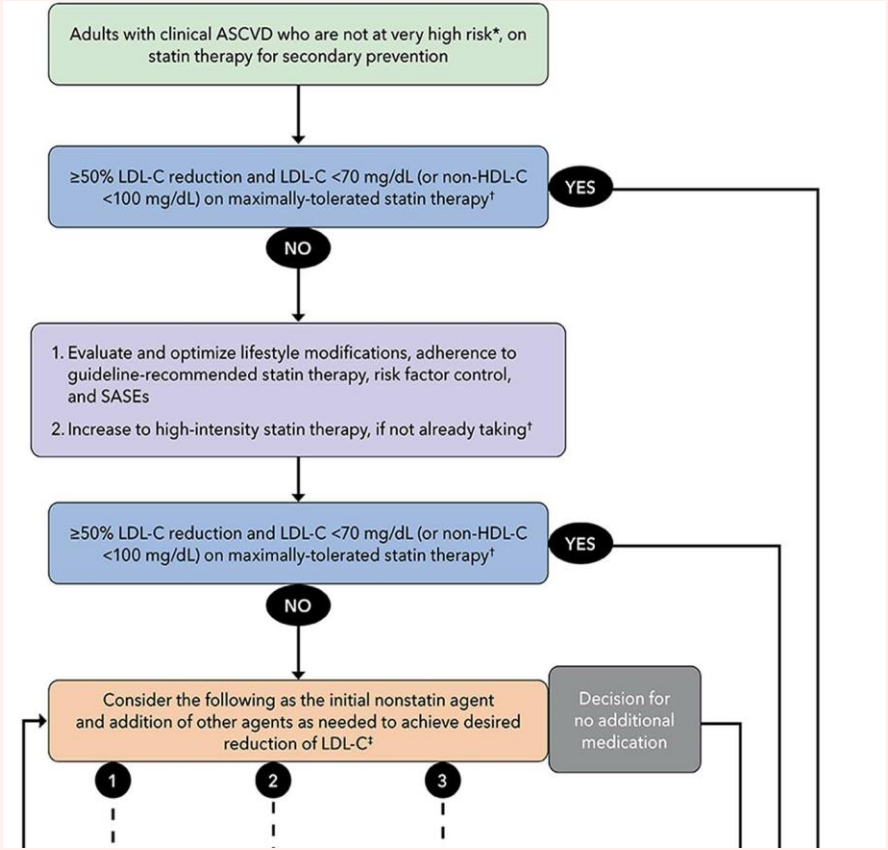
Figure 2B Adults With Clinical ASCVD, Not at Very High Risk, on Statin Therapy for Secondary Prevention



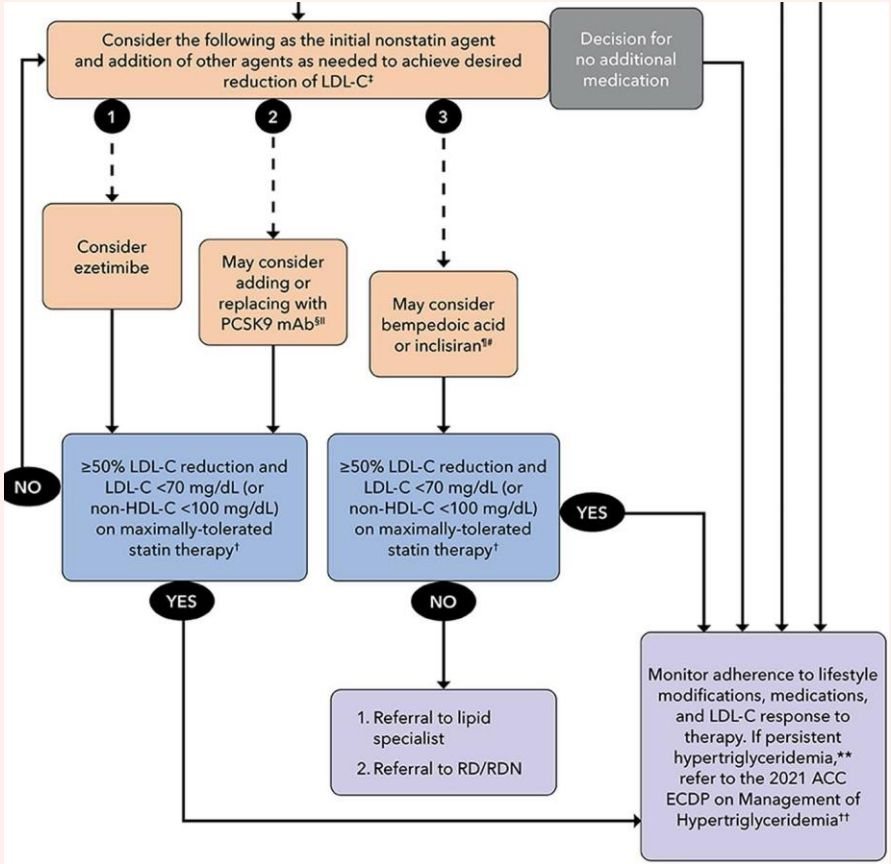


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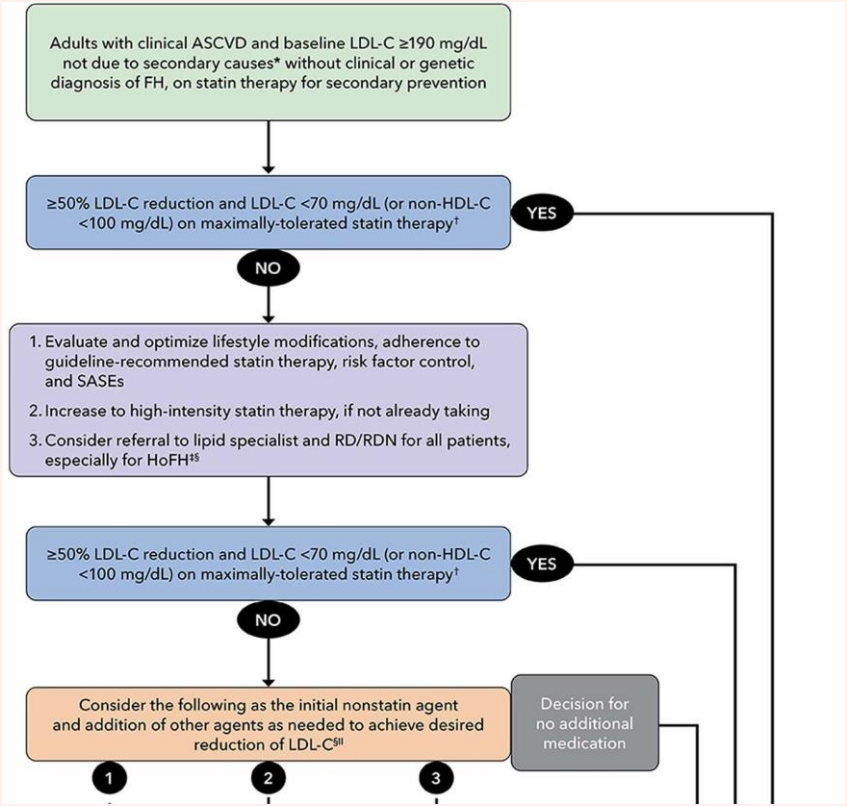
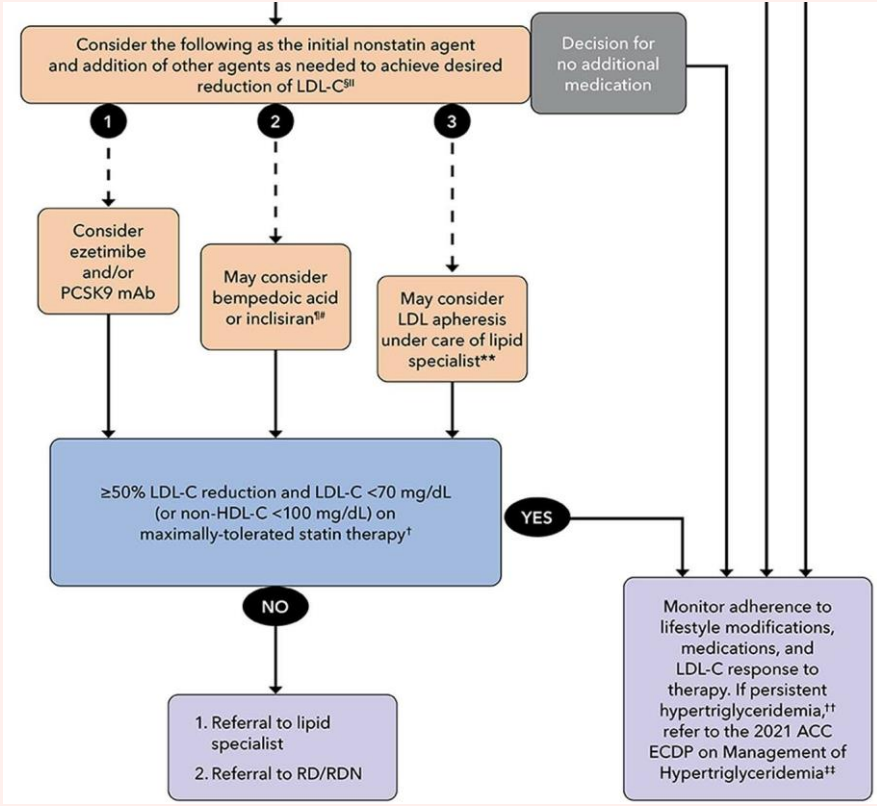
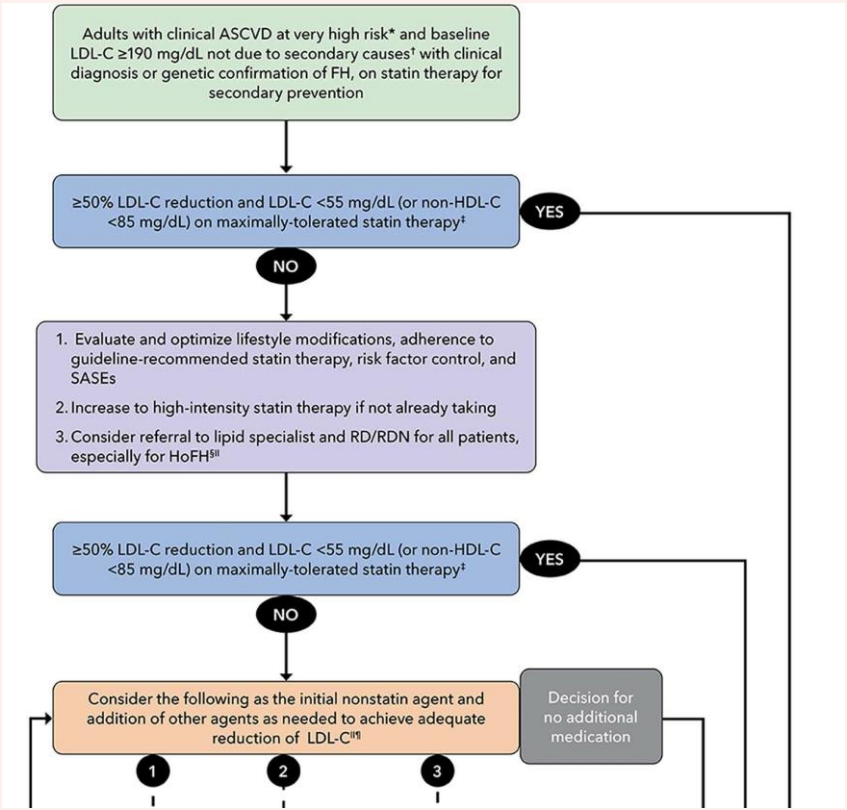
Figure 2C Adults With Clinical ASCVD and Baseline LDL-C ≥190 mg/dL Not Due to Secondary Causes Without Clinical or Genetic Diagnosis of Familial Hypercholesterolemia, on Statin Therapy for Secondary Prevention





2022 ECDP

Figure 2D Adults With Clinical ASCVD at Very High Risk and Baseline LDL-C ≥190 mg/dL Not Due to Secondary Causes and With Clinical Diagnosis or Genetic Confirmation of Familial Hypercholesterolemia, on Statin for Secondary Prevention



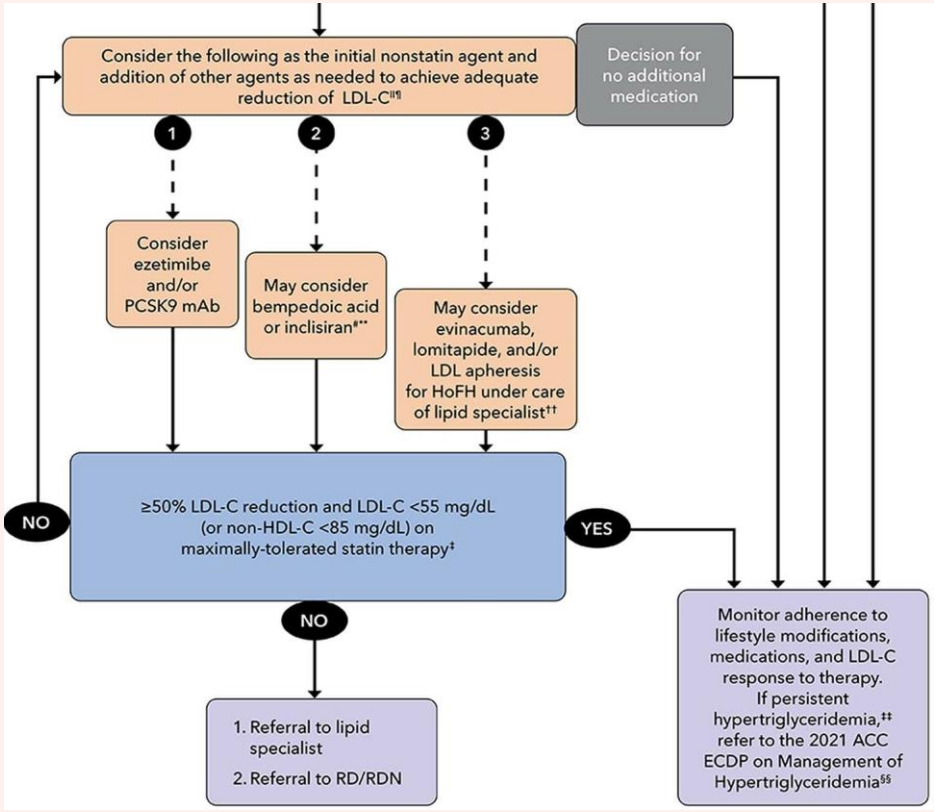


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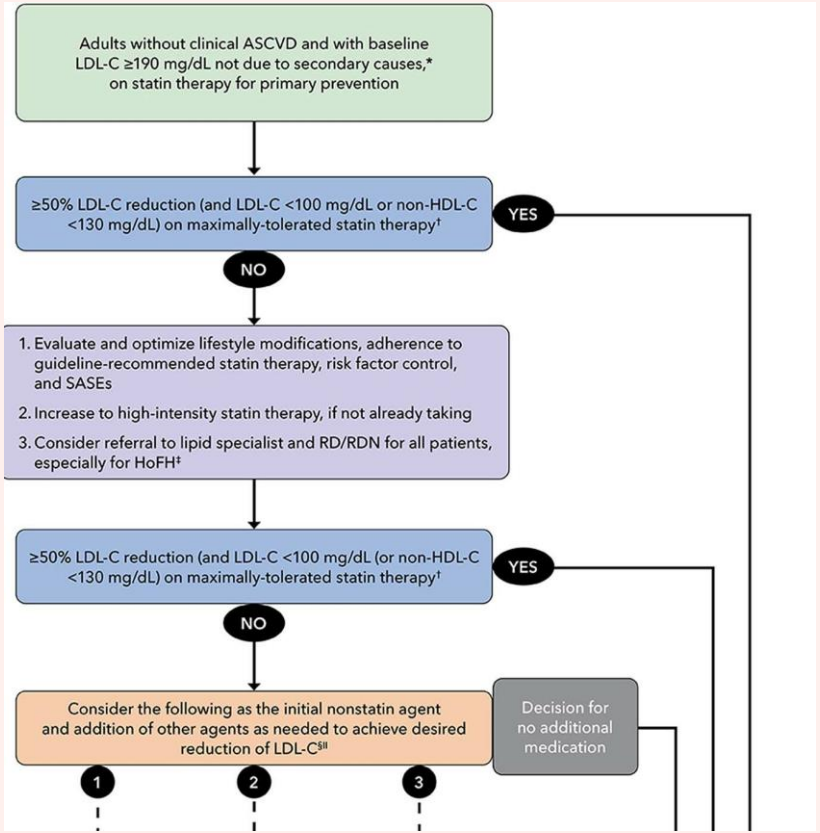
Figure 3 Adults Without Clinical ASCVD and With Baseline LDL-C ≥190 mg/dL Not Due to Secondary Causes on Statin Therapy for Primary Prevention



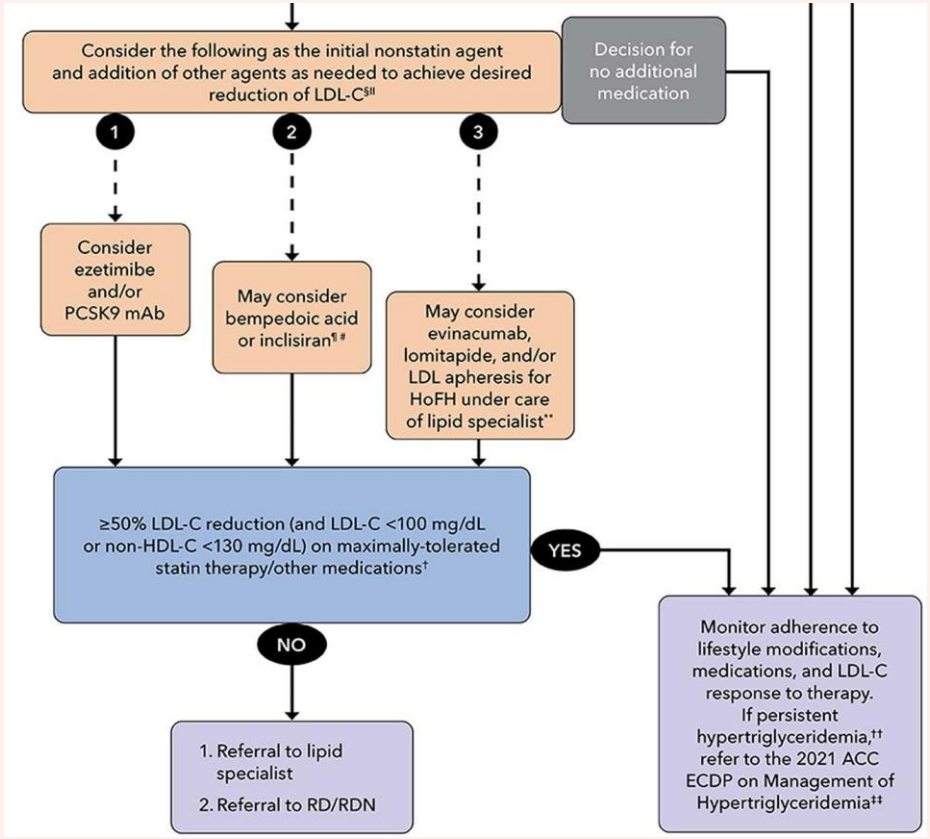


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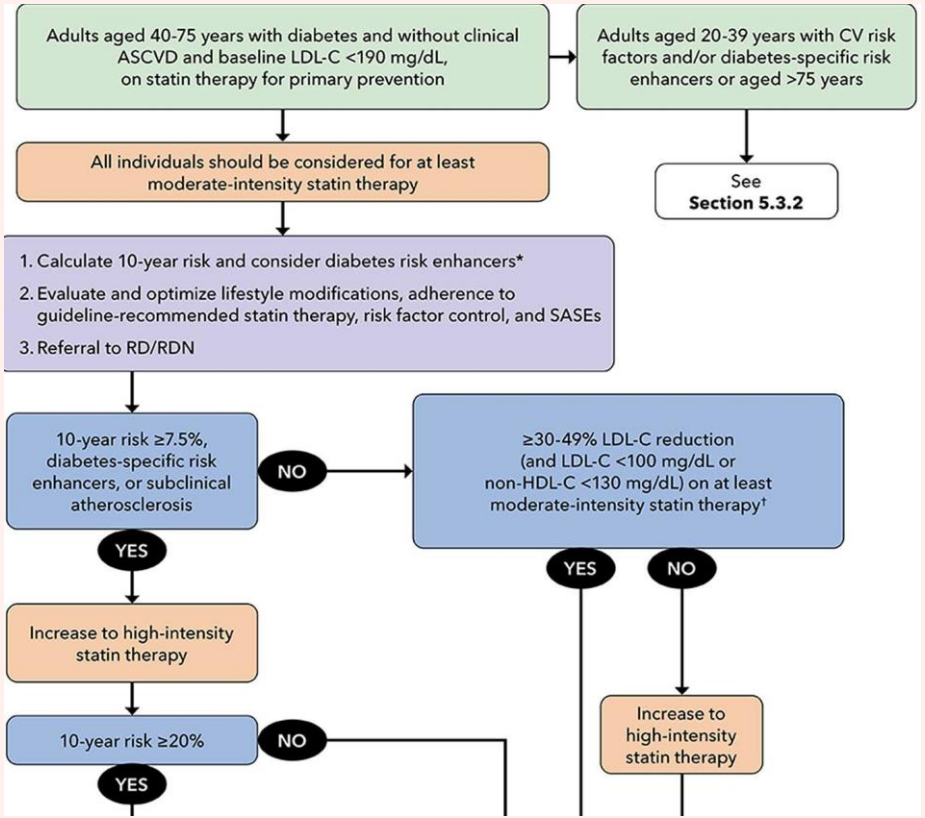
Figure 4 Adults With Diabetes and Without ASCVD and Baseline LDL-C <190 mg/dL on Statin Therapy for Primary Prevention



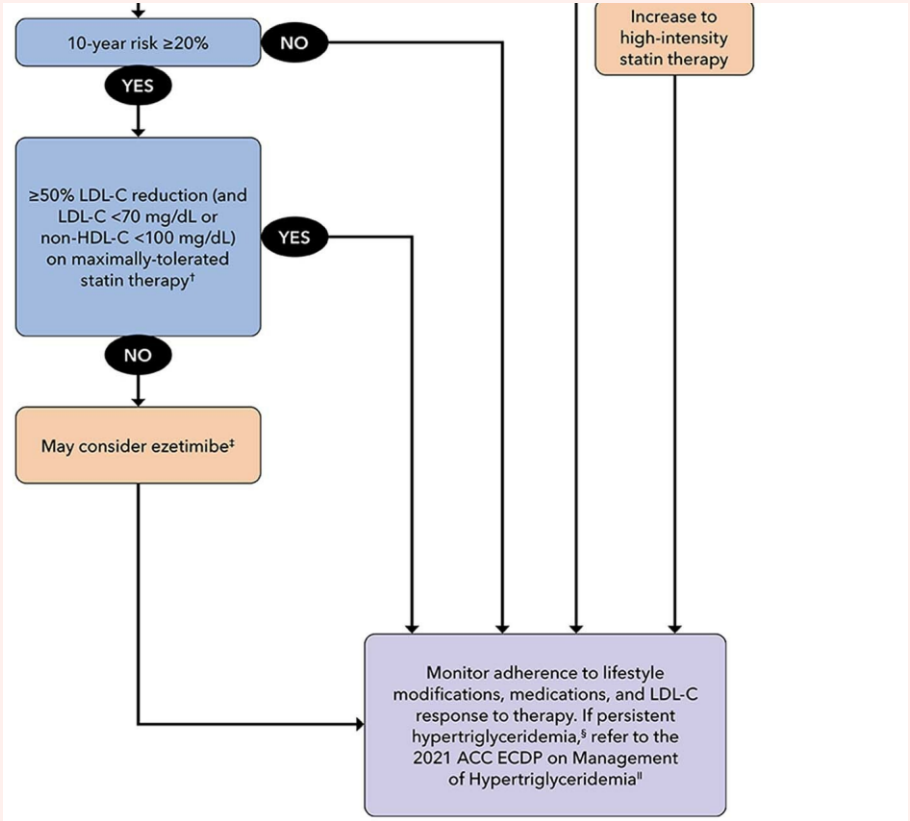


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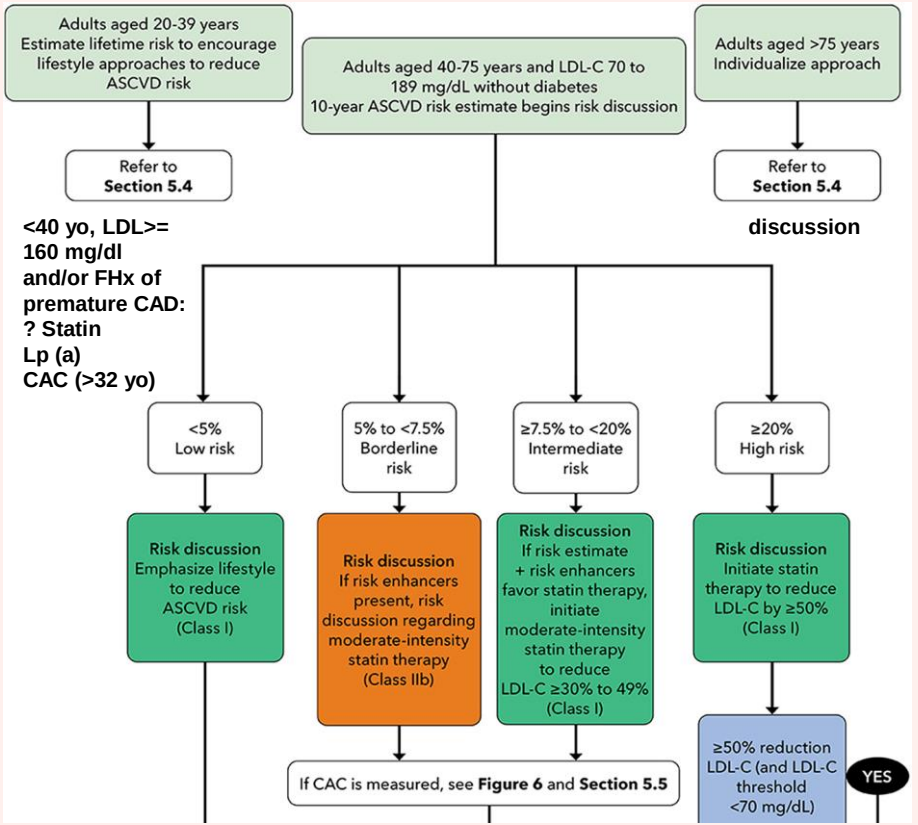
Figure 5 Adults Without Clinical ASCVD or Diabetes (LDL 70-189 mg/dL)



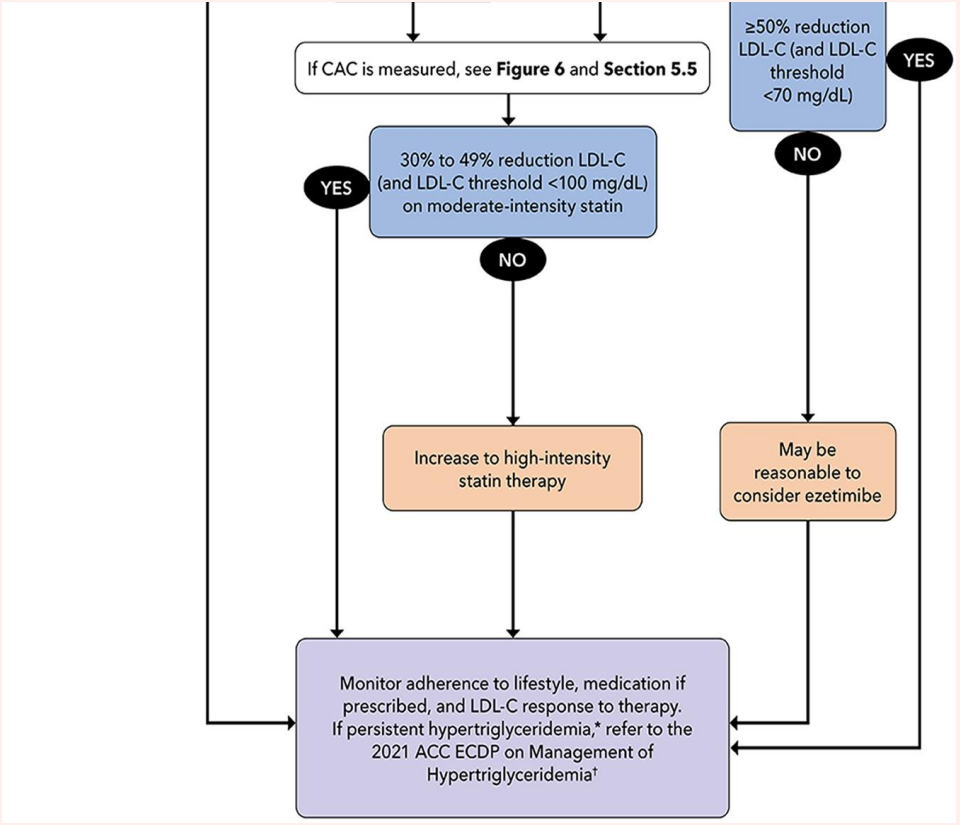


Figure 6 Incorporation of Subclinical Atherosclerosis Imaging Into Risk Assessment and Treatment for Adults Without Clinical ASCVD or Diabetes or LDL-C ≥190 mg/dL

- **PESA study (Progression of Early Subclinical Atherosclerosis)**

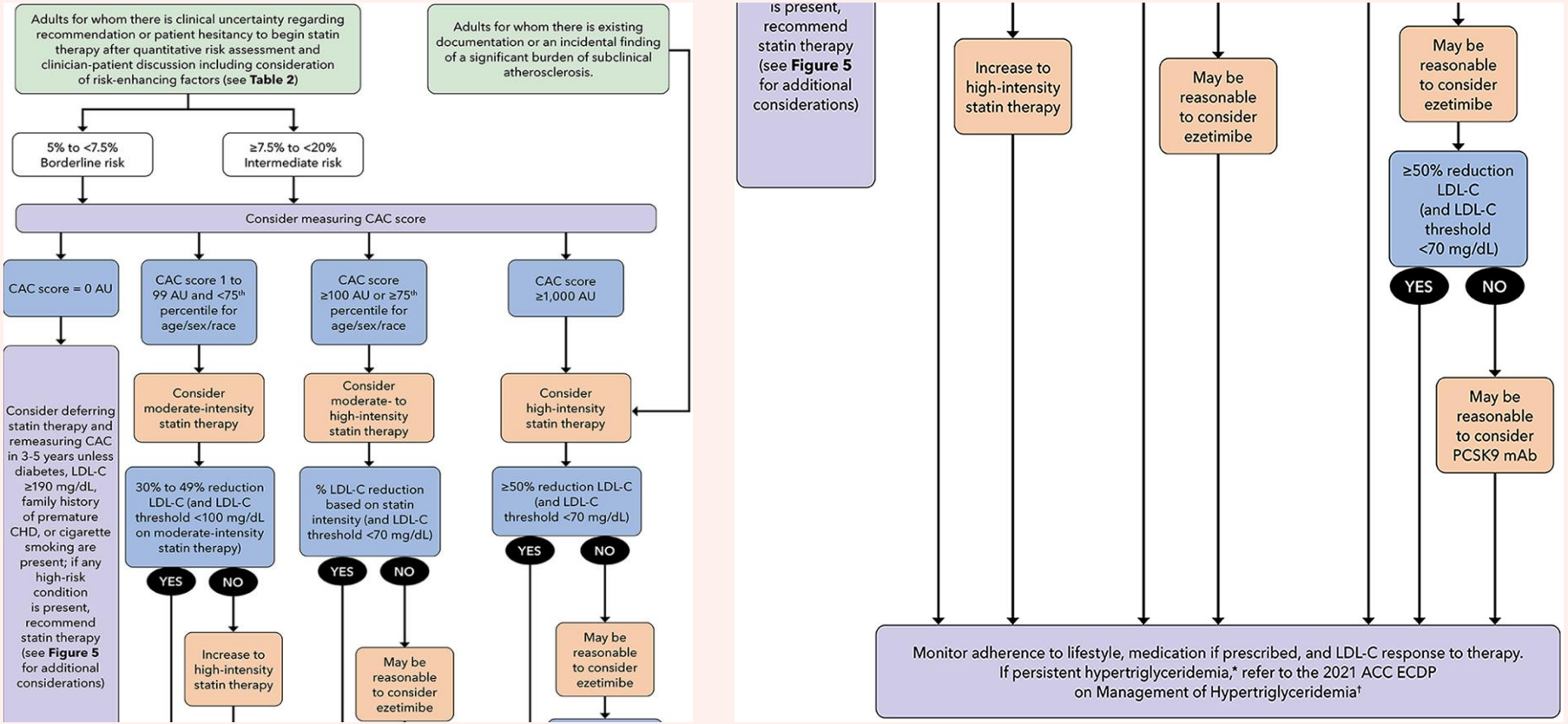
- Prospectively enrolled 4184 asymptomatic subjects employed by the bank Sant'Ander of Madrid, aged between 40 and 54 (average age 45 years, 63% males) to study the extent of atherosclerosis in **various vascular districts** (**carotid arteries, aorta, iliac-femoral axis, and coronary arteries**) by **vascular ultrasound and coronary CT**.

- **Subclinical atherosclerosis:**
  Presence of at least one plaque or a CAC ≥1
  Classified as focal (one site concerned), intermediate (2–3 sites concerned) or generalized (4–6 sites concerned).
  Plaque definition: a focal protrusion inside the vessel lumen with a thickness >0.5 mm or >50% of the surrounding average-intimal thickness or in general a diffuse intimal-media thickening >1.5 mm.

- *Borja Ibanez, et al. J Am Coll Cardiol. 2021 Jul 13;78(2):156-179*

2022 ECDP

Figure 6 Incorporation of Subclinical Atherosclerosis Imaging Into Risk Assessment and Treatment for Adults Without Clinical ASCVD or Diabetes or LDL-C ≥190 mg/dL



Issues Specific to Women

Recommendations for Issues Specific to Women		
COR	**LOE**	**Recommendations**
I	B-NR	Clinicians should consider conditions specific to women, such as premature menopause (age <40 years) and history of pregnancy-associated disorders (hypertension, preeclampsia, gestational diabetes mellitus, small-for-gestational-age infants, preterm deliveries), when discussing lifestyle intervention and the potential for benefit of statin therapy.
I	C-LD	Women of childbearing age who are treated with statin therapy and are sexually active should be counseled to use a reliable form of contraception.
I	C-LD	Women of childbearing age with hypercholesterolemia who plan to become pregnant should stop the statin 1 to 2 months before pregnancy is attempted, or if they become pregnant while on a statin, should have the statin stopped as soon as the pregnancy is discovered. (DC during conception, pregnancy and lactation except for very high risk patient, HoFH and clinical ASCVD)

Consider LDL apheresis for pregnant patients with HoFH, severe HeFH with LDL >= 300mg/dl, FH and ASCVD with LDL>= 190mg/dl

Adults With Chronic Kidney Disease

Recommendations for Adults With CKD		
COR	**LOE**	**Recommendations**
IIa	**B-R**	**In adults 40 to 75 years of age with LDL-C 70 to 189 mg/dL (1.7 to 4.8 mmol/L) who are at 10-year ASCVD risk of 7.5% or higher, CKD not treated with dialysis or kidney transplantation is a risk-enhancing factor and initiation of a moderate-intensity statin or moderate-intensity statins combined with ezetimibe can be useful.**
IIb	**C-LD**	**In adults with advanced kidney disease that requires dialysis treatment who are currently on LDL-lowering therapy with a statin, it may be reasonable to continue the statin.**
III: No Benefit	**B-R**	**In adults with advanced kidney disease who require dialysis treatment, initiation of a statin is not recommended.**

Renal transplant?
No recommendation for PCSK9 mAb

Adults With Chronic Inflammatory Disorders and HIV

Recommendations for Adults With Chronic Inflammatory Disorders and HIV		
COR	**LOE**	**Recommendations**
IIa	**B-NR**	**In adults 40 to 75 years of age with LDL-C 70 to 189 mg/dL (1.7 to 4.8 mmol/L) who have a 10-year ASCVD risk of 7.5% or higher, chronic inflammatory disorders and HIV are risk-enhancing factors and in risk discussion favor moderate-intensity statin therapy or high-intensity statin therapy.**
IIa	**B-NR**	**In patients with chronic inflammatory disorders or HIV, a fasting lipid profile and assessment of ASCVD risk factors can be useful as a) a guide to benefit of statin therapy and b) for monitoring or adjusting lipid-lowering drug therapy before and 4 to 12 weeks after starting inflammatory disease–modifying therapy or antiretroviral therapy.**
IIa	**B-NR**	**In adults with RA who undergo ASCVD risk assessment with measurement of a lipid profile, it can be useful to recheck lipid values and other major ASCVD risk factors 2 to 4 months after the patient's inflammatory disease has been controlled.**

Adults With Symptomatic Heart Failure

Symptomatic heart failure due to ischemic etiology:

- **Statin is reasonable**
- **Addition of Ezetimibe may be reasonable**
- **No recommendation for PCSK9 mAb**

Hypertriglyceridemia

Definition of Persistent Hypertriglyceridemia

Fasting triglycerides ≥150 mg/dL following a minimum of 4 to 12 weeks of lifestyle intervention, a stable dose of maximally tolerated statin therapy when indicated, as well as evaluation and management of secondary causes of hypertriglyceridemia.

Before initiation of triglyceride risk-based nonstatin therapies, a fasting lipid panel should be obtained. It is recommended that clinical decision-making be based on the results of at least 2 measurements of fasting lipids, preferably at least 2 weeks apart.

Hypertriglyceridemia

Fasting lipid testing is favored under the following circumstances:

a) To establish the diagnosis of the metabolic syndrome, as one of the diagnostic criteria is fasting triglycerides ≥150 mg/dl;
b) To identify lipid disorders in those without clinical ASCVD, but with a family history of premature ASCVD or genetic lipid disorders;
c) To assess adherence to lifestyle and medical therapy in those patients being treated with lipid-lowering medication for ASCVD risk reduction; and
d) To identify those with triglycerides ≥500 mg/dl, individuals at risk for hypertriglyceridemia-induced pancreatitis, and to monitor their response to therapy.

Hypertriglyceridemia

Lipid Effects of Drug Classes in Dyslipidemia and HTG

Mixed Dyslipidemia	TG	LDL-C	HDL-C
		Range, %	
• Statins	-10 to -37	-26 to -63	+5 to +16
• Omega-3 fatty acids	-19 to -44	-6 to +25	-5 to +7
• Fenofibrate, fenofibric acid, and gemfibrozil	-24 to -36	-5 to -31	+10 to +16

Isolated HTG	TG	LDL-C	HDL-C
		Range, %	
• Statins	-21 to -52	-27 to -45	+3 to +22
• Omega-3 fatty acids	-26 to -52	+17 to +49	+9 to +14
• Fenofibrate, fenofibric acid, and gemfibrozil	-46 to -62	+3 to +47	+18 to +23

Maki KC, et al. *J Clin Lipidol*. 2012;6:413-426.

Hypertriglyceridemia

Prescription Omega-3-fatty acid products (data from package inserts)

Generic Name	Omega-3-ethyl esters	Icosapent ethyl	Omega-3-carboxylic acid
Brand Name	Lovaza or Omacor	Vascepa	Epanova
EPA/capsule	0.465g	1.0g	See below
DHA/capsule	0.375g	---	See below
Daily Dose	4 capsules/day	4 capsules/day	2-4 capsules/day

1-gram capsules of Epanova contain at least 850mg of fish oil derived fatty acids including multiple omega-3-fatty acids with EPA and DHA being the most abundant

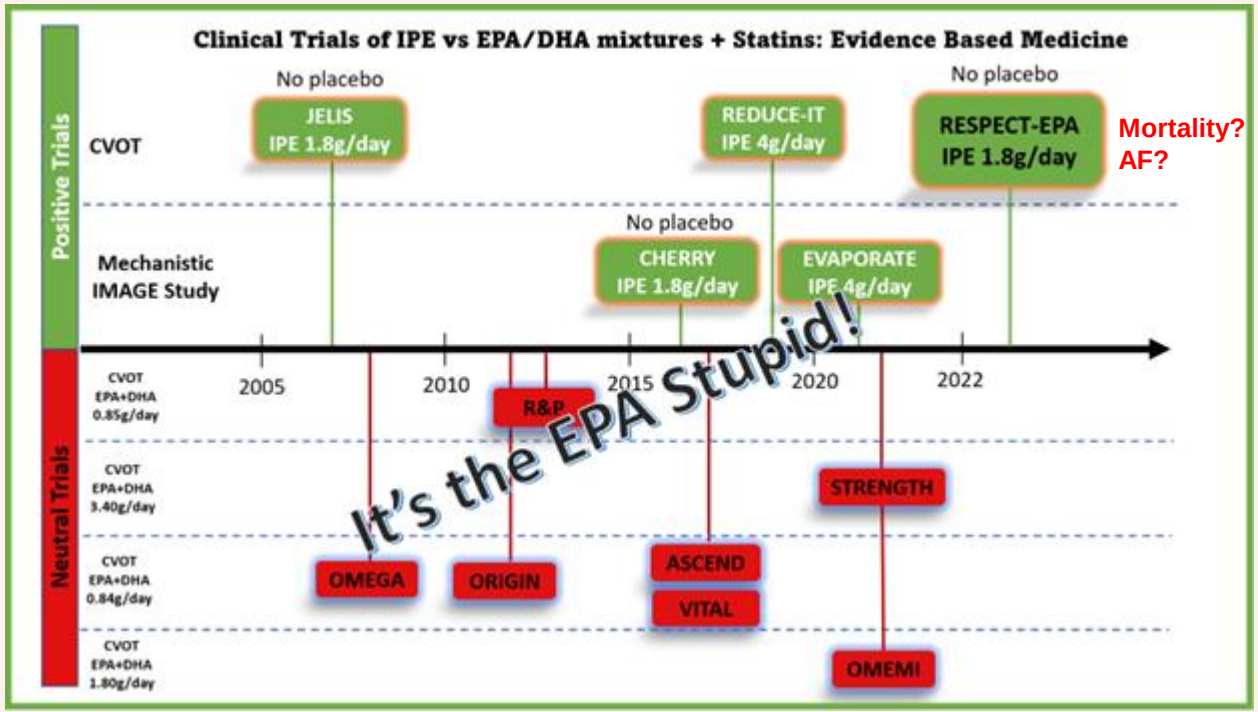
Hypertriglyceridemia

TABLE 2 Comparison of Nonprescription Fish Oil Preparations and Prescription Omega-3 Fatty Acid Medications

	Nonprescription Fish Oil Preparation	Prescription Omega-3 Products
FDA classification	Dietary supplement	Prescription drug
FDA-approved indication to treat elevated triglycerides	—	✓
Efficacy verified	—	✓
Consistent content	Varies	✓
Consistent purity	May contain saturated fat, oxidized fatty acids, contaminants, and/or additional calories	✓
Tolerability	Burping, fishy taste, dyspepsia	Generally well tolerated

FDA = Food and Drug Administration.

Hypertriglyceridemia

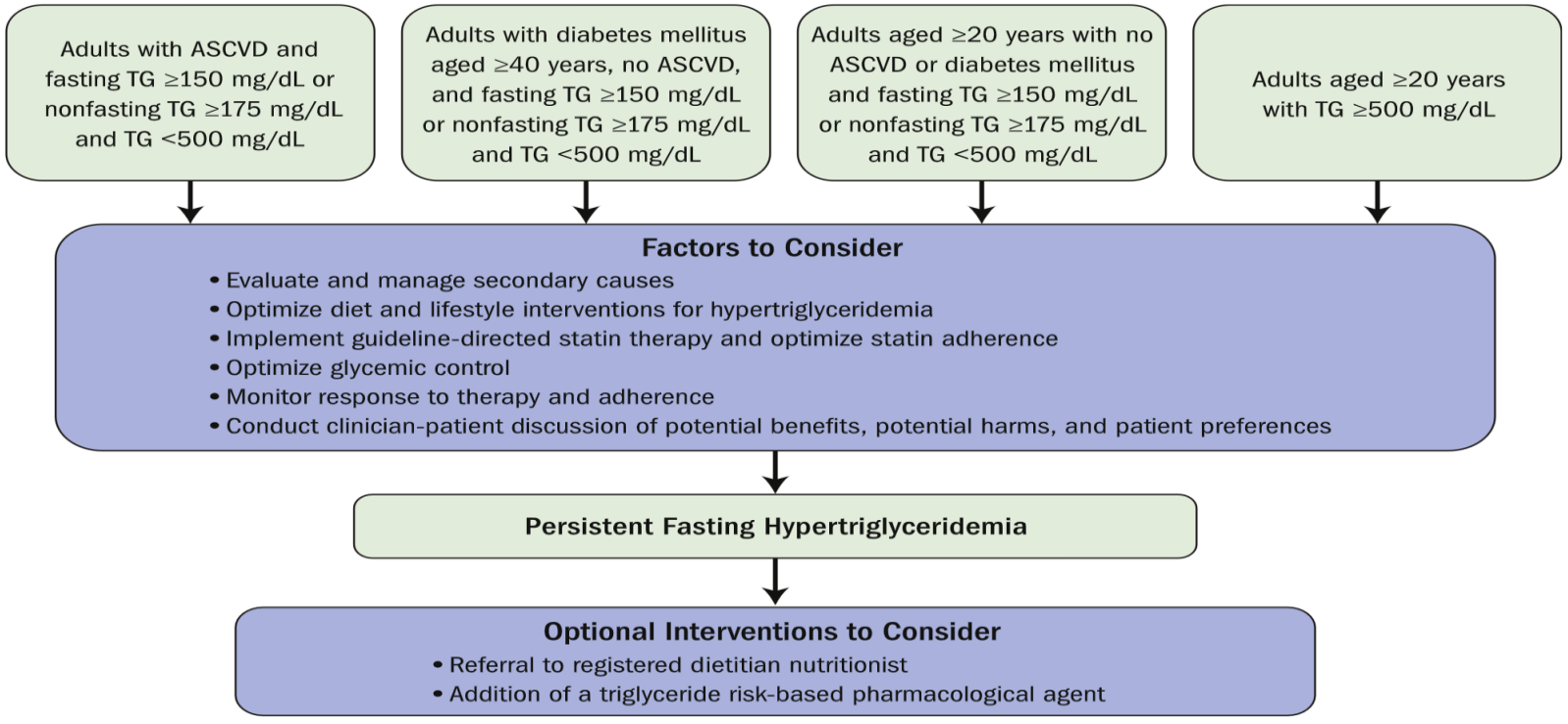


Hypertriglyceridemia

STRENGTH		REDUCE-IT
EPA + DHA carboxylic acids	Omega-3 preparation	Icosapent ethyl
Corn oil	Placebo used	Mineral oil
49.9%	High-intensity statin	30%
55.9%	% with ASCVD	70.7%
70.1%	% with diabetes	58.5%
239 mg/dL	Baseline triglycerides	216 mg/dL
3.2 years	Median follow-up	4.9 years
HR (95% CI)	**RESULTS**	HR (95% CI)
0.99 (0.90-1.09)	Overall	0.75 (0.68-0.83)
1.16 (0.95-1.41)	Primary prevention	0.88 (0.70-1.10)
0.94 (0.84-1.05)	Secondary prevention	0.73 (0.65-0.81)
0.6 0.7 0.8 0.9 1 1.1 1.2 1.3 1.4 1.5		0.6 0.7 0.8 0.9 1 1.1 1.2 1.3 1.4 1.5
EPA+DHA Better / Placebo Better		EPA Better / Placebo Better

Hypertriglyceridemia

FIGURE 1 Patient Population and Factors to Consider



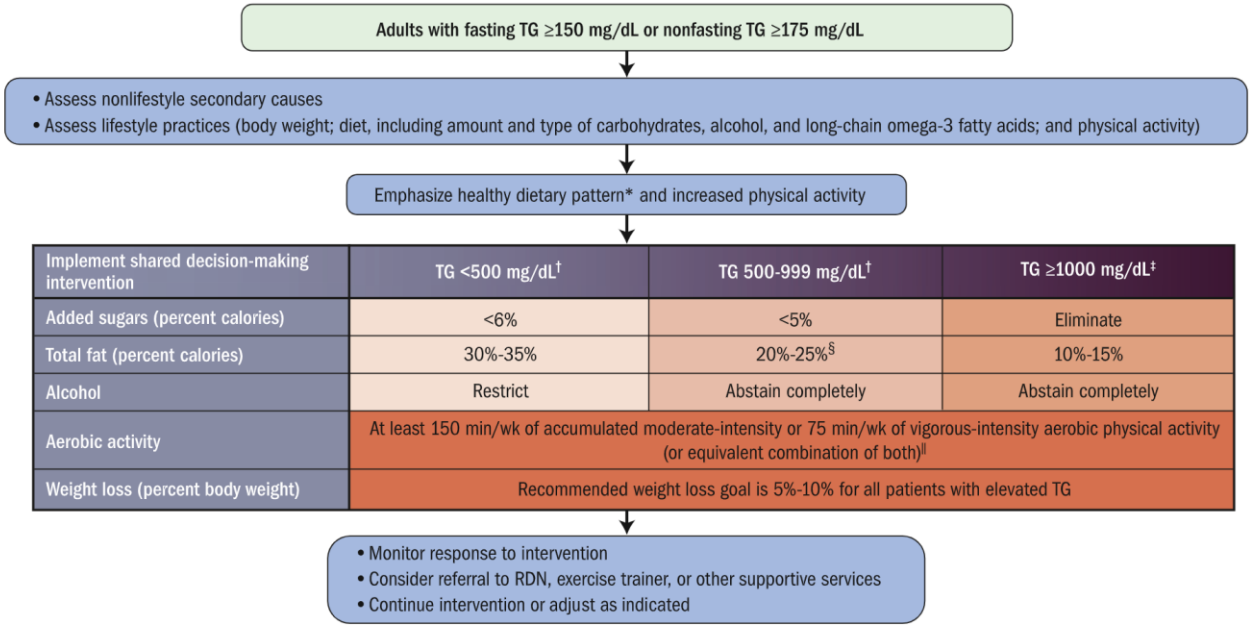
ASCVD = atherosclerotic cardiovascular disease; TG = triglycerides

Hypertriglyceridemia

	RECOMMENDED RANGES (% OF CALORIES)	LOWER CARB HIGHER PROTEIN (% OF CALORIES)	LOWER CARB & FAT HIGHER PROTEIN (% OF CALORIES)
CARBS	45-65%	45%	45%
PROTEIN	10-35%	25%	30%
FAT	20-35%	30%	25%

Hypertriglyceridemia

FIGURE 2 **Recommendations for Lifestyle Interventions in Patients With Increasing Levels of Weight Loss and Effects on Triglycerides**



RDN = registered dietician nutritionist; TG = triglycerides.

*Recommendations for a healthy dietary pattern emphasize: vegetables; fruits; legumes; nuts; whole grains; and fish/seafood (other healthy proteins such as low-fat dairy, low-fat poultry); liquid plant-based oils; and replacing saturated fatty acids with monounsaturated fatty acids and polyunsaturated fatty acids. Recommendations also emphasize limiting: red and processed meats; refined carbohydrates; added sugars (sweets and sugar-sweetened beverages); sodium and dietary cholesterol; and avoiding trans fats.

†RDN referral advised.

‡RDN referral necessary.

§Clinicians may opt to reduce total fat as percent of calories in some of these patients to 10%-15% (examples include those with a history of pancreatitis or those at the higher end of this range).

‖Although clinicians should aim for their patients to meet the guideline-recommended goals for physical activity, any amount of physical activity is likely beneficial in sedentary individuals and should therefore be encouraged to reduce cardiometabolic risk.

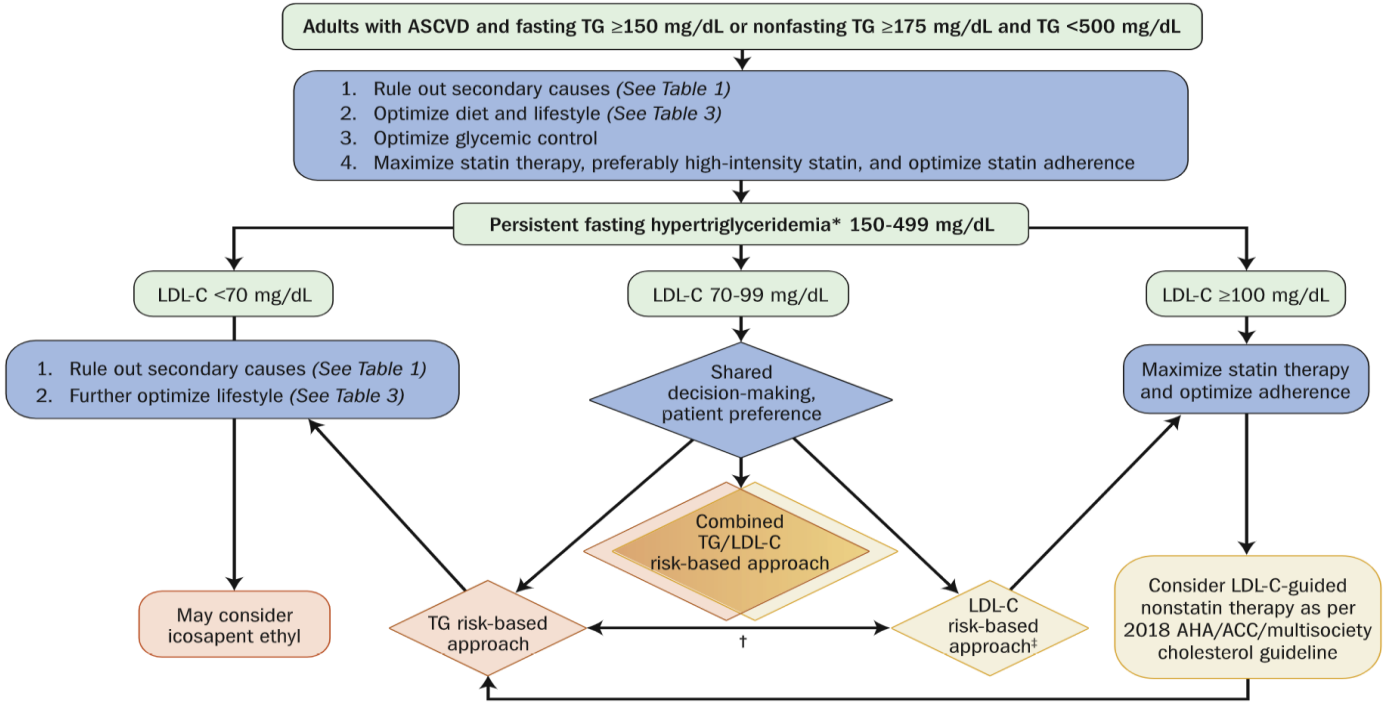
Hypertriglyceridemia

TABLE 3 **Lifestyle Modifications and Estimated Triglyceride-Lowering Response in Patients With Hypertriglyceridemia**

Lifestyle Intervention	Reduction in Triglycerides (%)	Qualifier
Weight loss (54-56)	Up to 70%	Although most patients will likely experience reductions in triglyceride levels of 10%-20% with weight loss, evidence suggests that in some patients, a reduction in triglyceride levels of up to 70% may be achieved
Dietary modifications (including alcohol—restrict or abstain completely) (57)	>70%	Response may vary depending on the baseline triglyceride level and how strictly dietary recommendations are followed
Physical activity and exercise (58-62)	Up to 30%	Response may vary depending on the type, duration, and intensity of activity

Hypertriglyceridemia

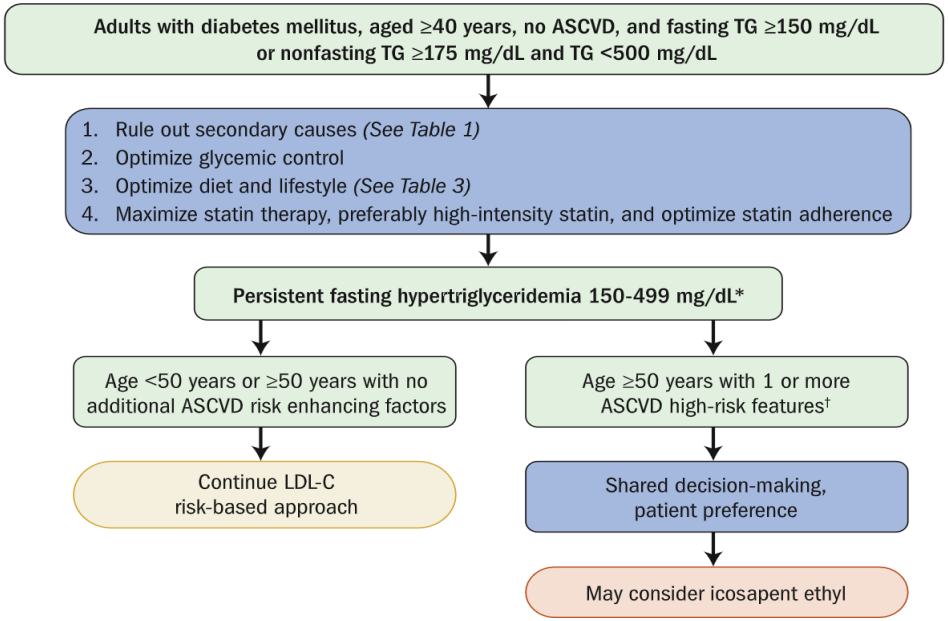
FIGURE 3 Adults With ASCVD and Fasting Triglycerides ≥150 mg/dL or Nonfasting Triglycerides ≥175 mg/dL and Triglycerides <500 mg/dL



ACC = American College of Cardiology; AHA = American Heart Association; ASCVD = atherosclerotic cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; TG = triglycerides.
*Please refer to Section 4.7 for detailed definition.
†Clinicians could use a TG risk-based approach once LDL-C levels are optimized and vice versa.
‡Patients at very high risk are most likely to benefit from the addition of LDL-C risk-based nonstatin therapies.

Hypertriglyceridemia

FIGURE 4 Adults Aged ≥40 Years With Diabetes Mellitus, no ASCVD, and Fasting Triglycerides ≥150 mg/dL or Nonfasting Triglycerides ≥175 mg/dL and Triglycerides <500 mg/dL



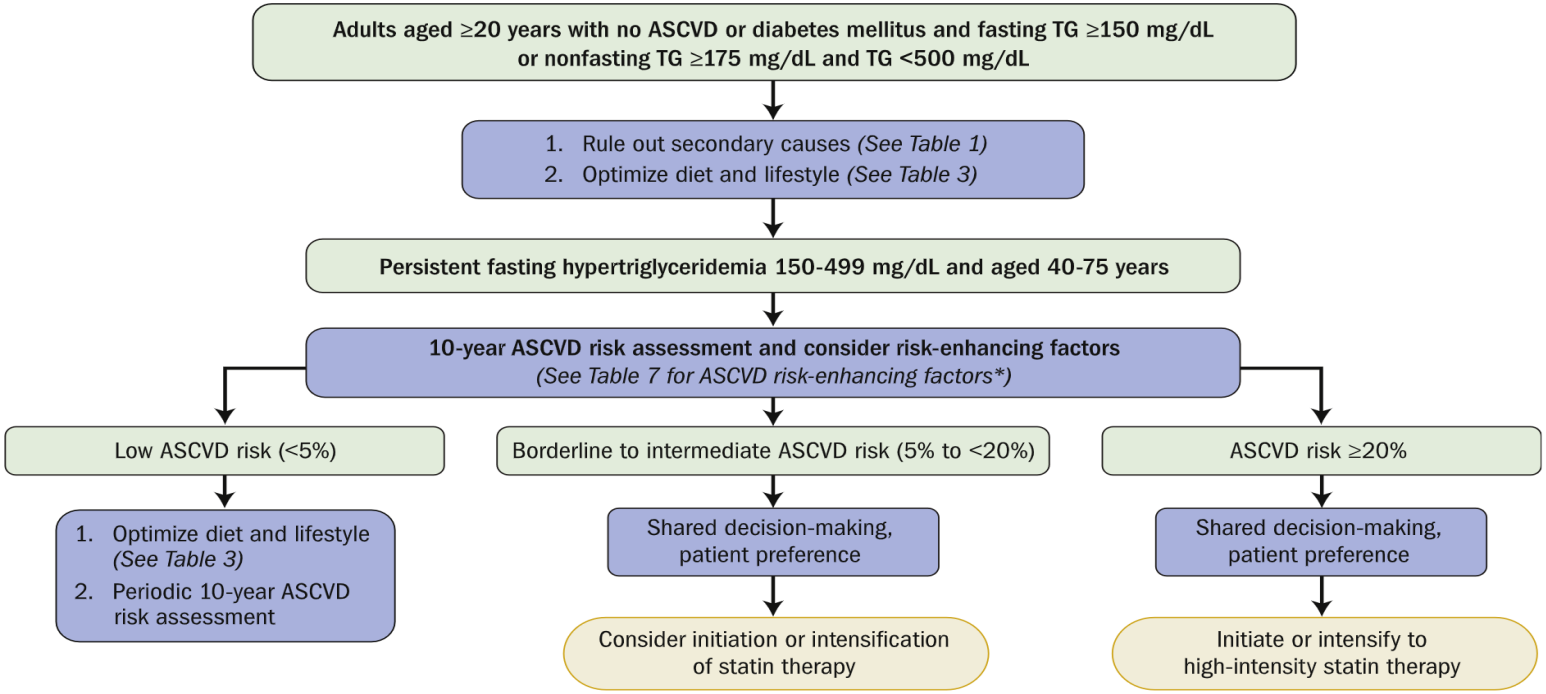
ASCVD = atherosclerotic cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; TG = triglycerides.

*Please refer to Section 4, Definition 1 for detailed definition of persistent hypertriglyceridemia.

†As per REDUCE-IT inclusion criteria, high-risk features include: Men ≥55 years or women ≥65 years; cigarette smoking or stopped smoking within 3 months; hypertension (blood pressure ≥140 mm Hg systolic or ≥90 mm Hg diastolic) or on antihypertensive medication; high density lipoprotein cholesterol ≤40 mg/dL for men or ≤50 mg/dL for women; high sensitivity C reactive protein >3.0 mg/L (if measured); renal dysfunction: creatinine clearance >30 and <60mL/min; retinopathy; albuminuria (≥30 mcg of albumin/mg creatinine); ankle-brachial index <0.90 without symptoms of intermittent claudication (if measured).

Hypertriglyceridemia

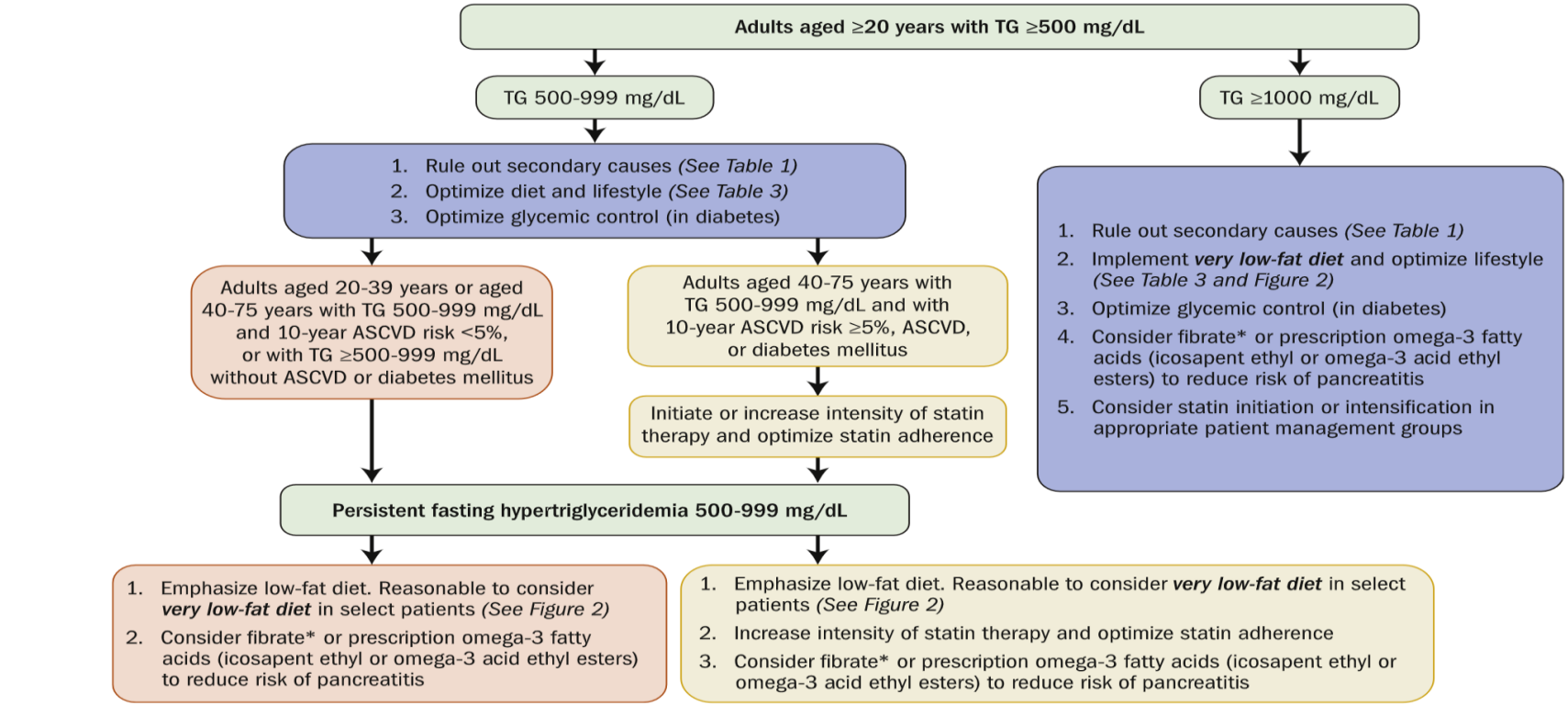
FIGURE 5 Adults Aged ≥20 Years With No ASCVD or Diabetes Mellitus and Fasting Triglycerides ≥150 mg/dL or Nonfasting Triglycerides ≥175 mg/dL and Triglycerides <500 mg/dL



ASCVD = atherosclerotic cardiovascular disease; TG = triglycerides
*Use persistent hypertriglyceridemia as a risk enhancing factor

Hypertriglyceridemia

FIGURE 6 Adults Aged ≥20 Years With Severe Hypertriglyceridemia, Triglycerides ≥500 mg/dL, and Especially With Triglycerides ≥1,000 mg/dL

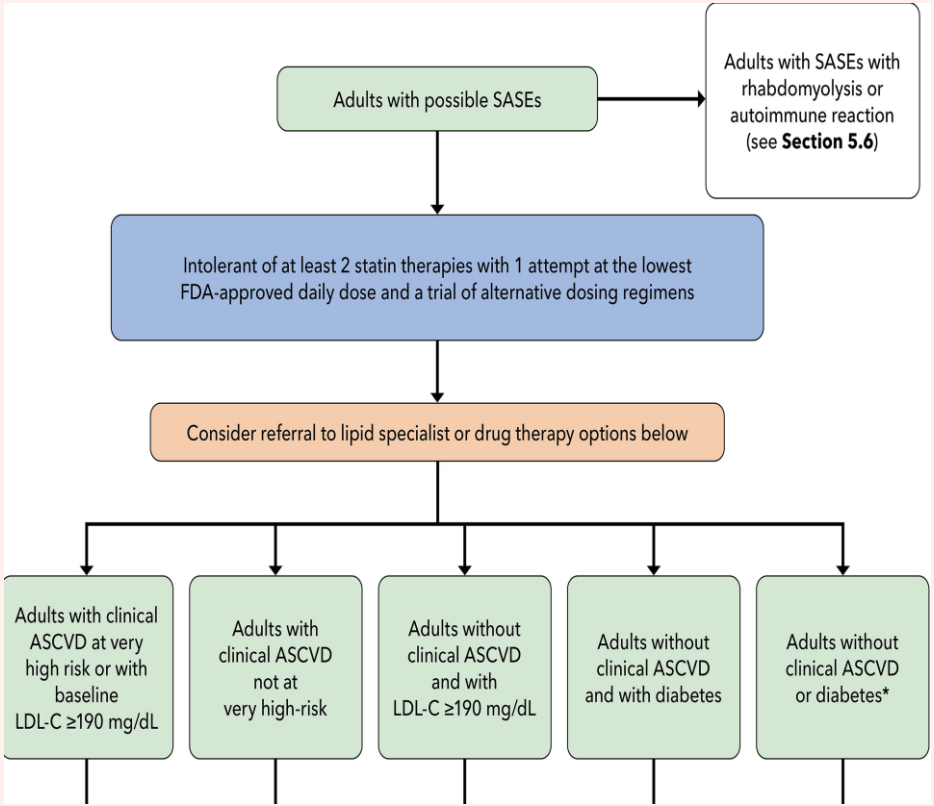


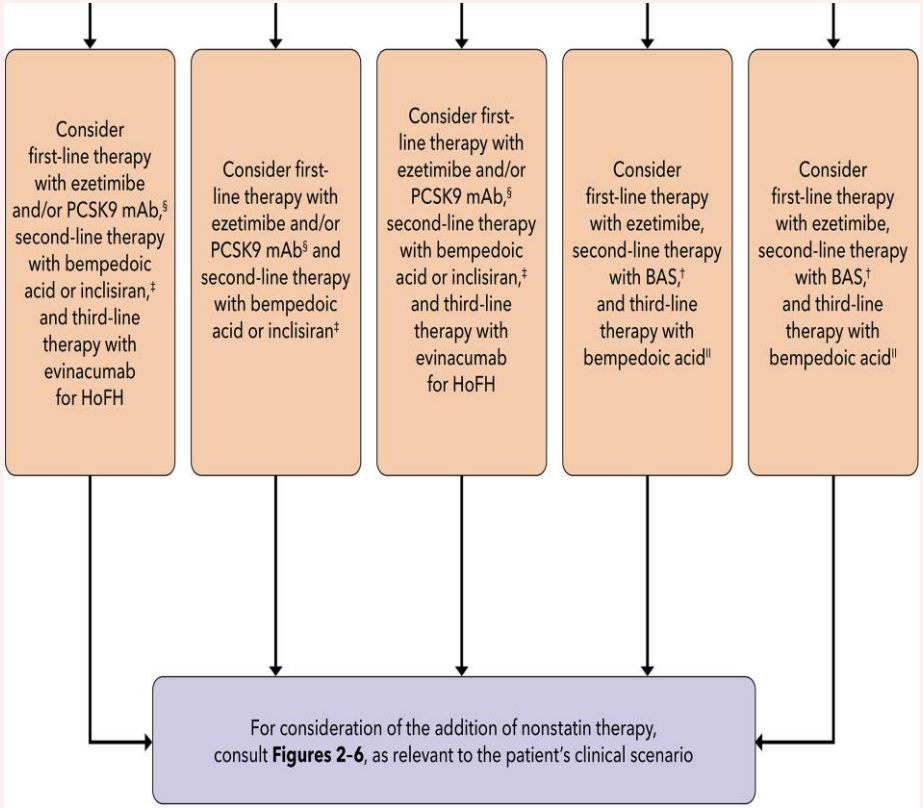
ASCVD = atherosclerotic cardiovascular disease; TG = triglycerides.

*Fenofibrate is the preferred fibric acid derivative due to better safety profile and fewer drug interactions compared to gemfibrozil.

Statin Safety and Statin-Associated Side Effects

Figure 7 Adults With Possible Statin-Associated Side Effects





Statin Safety and Statin-Associated Side Effects

Recommendations for Statin Safety and Statin-Associated Side Effects		
COR	**LOE**	**Recommendations**
I	**B-R**	**In patients at increased ASCVD risk with chronic, stable liver disease (including non-alcoholic fatty liver disease) when appropriately indicated, it is reasonable to use statins after obtaining baseline measurements and determining a schedule of monitoring and safety checks.**
IIa	**B-R**	**In patients at increased ASCVD risk with severe statin-associated muscle symptoms or recurrent statin-associated muscle symptoms despite appropriate statin rechallenge, it is reasonable to use RCT proven nonstatin therapy that is likely to provide net clinical benefit.**

Statin Safety and Statin-Associated Side Effects

Recommendations for Statin Safety and Statin-Associated Side Effects		
COR	**LOE**	**Recommendations**
III: No Benefit	**B-R**	**Coenzyme Q10 is not recommended for routine use in patients treated with statins or for the treatment of SAMS.**
III: No Benefit	**C-LD**	**In patients treated with statins, routine measurements of creatine kinase and transaminase levels are not useful.**

Table 11. Statin-Associated Side Effects

Statin-Associated Side Effects	Frequency	Predisposing Factors	Quality of Evidence
Statin-associated muscle symptoms (SAMS)			
Myalgias (CK Normal)	Infrequent (1% to 5%) in RCTs; frequent (5% to 10%) in observational studies and clinical setting	Age, female sex, low body mass index, high-risk medications (CYP3A4 inhibitors, OATP1B1 inhibitors), comorbidities (HIV, renal, liver, thyroid, preexisting myopathy), Asian ancestry, excess alcohol, high levels of physical activity, and trauma	RCTs cohorts/observational
Myositis/myopathy (CK > ULN) with concerning symptoms or objective weakness	Rare		RCTs cohorts/observational
Rhabdomyolysis (CK >10 × ULN + renal injury)	Rare		RCTs cohorts/observational
Statin-associated autoimmune myopathy (HMGCR antibodies, incomplete resolution)	Rare		Case reports
New-onset diabetes mellitus	Depends on population; more frequent if diabetes mellitus risk factors are present, such as body mass index ≥30, fasting blood sugar ≥100 mg/dL; metabolic syndrome, or A1c ≥6%.	Diabetes mellitus risk factors/metabolic syndrome High-intensity statin therapy	RCTs/meta-analyses

Table 11. Statin-Associated Side Effects

Statin-Associated Side Effects	Frequency	Predisposing Factors	Quality of Evidence
Liver			
Transaminase elevation 3 × ULN	Infrequent		RCTs/ cohorts/observational Case reports
Hepatic failure	Rare		
Central nervous system			
Memory/cognition	Rare/unclear		Case reports; no increase in memory/cognition problems in 3 large-scale RCTs
Cancer	No definite association		RCTs/meta-analyses

Table 11. Statin-Associated Side Effects

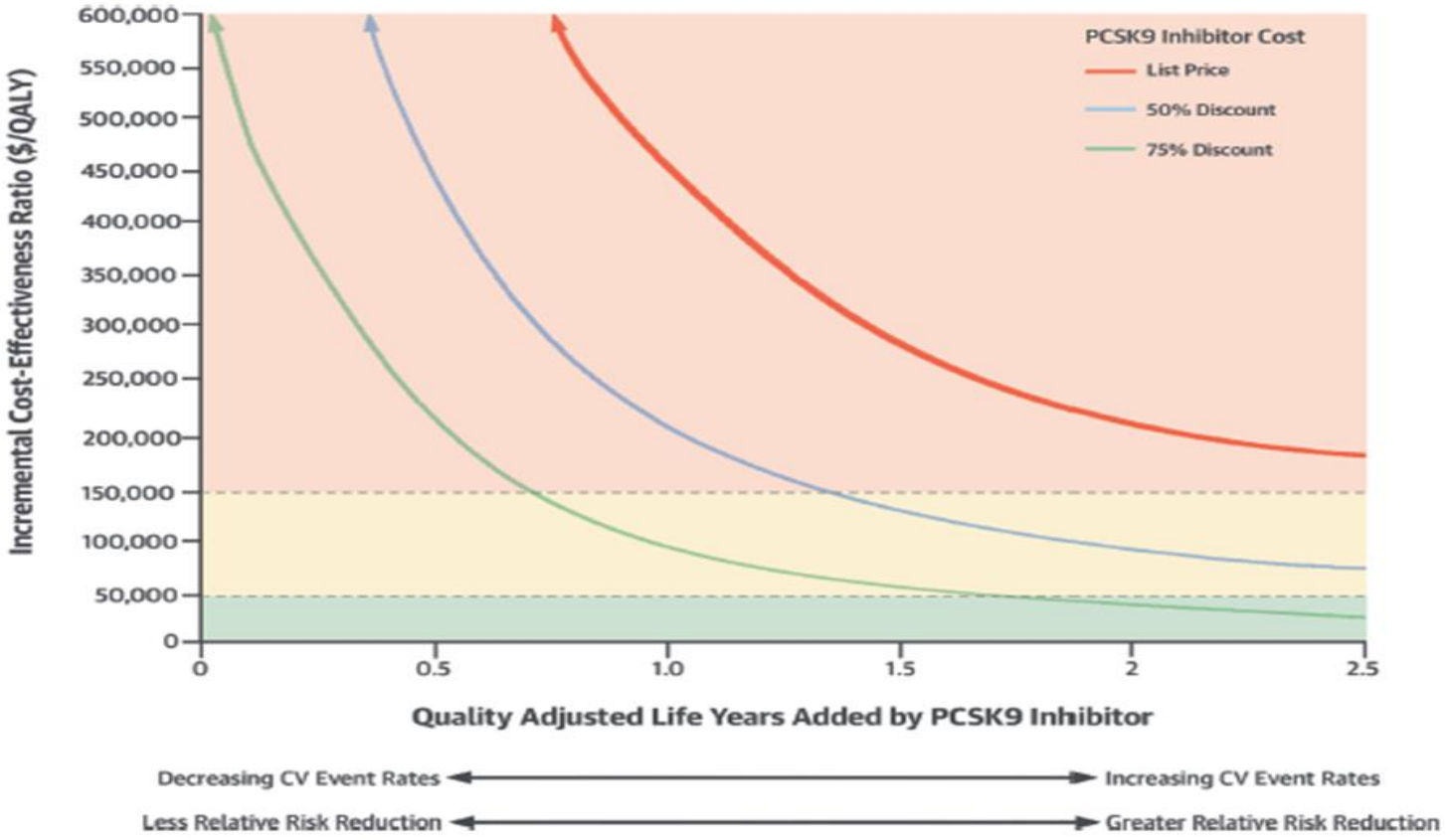
Statin-Associated Side Effects	Frequency	Predisposing Factors	Quality of Evidence
Other			
Renal function	Unclear/unfounded		
Cataracts	Unclear		
Tendon rupture	Unclear/unfounded		
Hemorrhagic stroke	Unclear		
Interstitial lung disease	Unclear/unfounded		
Low testosterone	Unclear/unfounded		

Cost and Value Considerations

Table 12. Proposed Integration of Level of Value Into Clinical Guideline Recommendations*

Level of Value
Level of Value
High value: Better outcomes at lower cost or ICER <$50,000 per QALY gained **Intermediate value:** $50,000 to <$150,000 per QALY gained **Low value:** ≥$150,000 per QALY gained **Uncertain value:** Value examined, but data are insufficient to draw a conclusion because of absence of studies, low-quality studies, conflicting studies, or prior studies that are no longer relevant **Not assessed:** Value not assessed by the writing committee
Proposed abbreviations for each value recommendation: Level of value: H to indicate high value; I, intermediate value; L, low value; U, uncertain value; and NA, value not assessed.

Figure 3. Cost-Effectiveness Analysis for PCSK9 Inhibitors

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