Management of Hypercholesterolemia

Clinical Practice Guideline
MedStar Health

"These guidelines are provided to assist physicians and other clinicians in making decisions regarding the care of their patients. They are not a substitute for individual judgment brought to each clinical situation by the patient's primary care provider-in collaboration with the patient. As with all clinical reference resources, they reflect the best understanding of the science of medicine at the time of publication but should be used with the clear understanding that continued research may result in new knowledge and recommendations".

The following MedStar guideline is based on the Guideline published by American College of Cardiology/American Heart Association in 2018. Statins have been shown to reduce fatal and non-fatal ASCVD events (except in those w/ NYHA class II-IV heart failure or chronic dialysis patients) in studies of both primary prevention and secondary prevention. Many studies also demonstrate a reduction in all-cause mortality. The 2013 guideline abandoned a "treat to target" paradigm and embraced a method of using the maximum tolerated statin intensity in the groups known to benefit. Prior proposed approaches to statin treatment lack supporting randomized controlled trial (RCT) data. Both the 2013 and the present guideline use the pooled cohort equations to estimate 10-year ASCVD (first occurrence nonfatal and fatal MI and fatal stroke) risk in non-Hispanic white and black patients without clinical ASCVD and identify those most likely to benefit from statins for primary prevention. The current guidelines continue to recommend a heart healthy diet, regular exercise, avoidance of tobacco products, and maintenance of a healthy weight and stress that all these interventions were included as background therapy of RCTs of pharmacological cholesterol therapy. In addition, the guideline makes clearer that the decision to start a stain medication should only occur after a frank discussion with the patient and shared decision making.

The current guideline is more detailed than prior guidelines and contains numerous recommendations. While we will attempt to highlight them here, we suggest review of the full report for additional detail. Additionally, while the guideline contains recommendations for patients of all ages, we will restrict comments here to patients 18 and older.

Guideline Summary

As a summary, we reprint ten "Take-Home Messages" from the report: "Top 10 Take-Home Messages to Reduce Risk of Atherosclerotic Cardiovascular Disease Through Cholesterol Management."

1. In all individuals, emphasize a heart-healthy lifestyle across the life course. A healthy lifestyle reduces atherosclerotic cardiovascular disease (ASCVD) risk at all ages. In younger individuals, healthy lifestyle can reduce development of risk factors and is the foundation of ASCVD risk reduction. In young adults 20 to 39 years of age, an assessment of lifetime risk facilitates the clinician–patient risk discussion (see No. 6) and emphasizes intensive lifestyle efforts. In all age groups, lifestyle therapy is the primary intervention for metabolic syndrome.
2. In patients with clinical ASCVD, reduce low-density lipoprotein cholesterol (LDL-C) with high-intensity statin therapy or maximally tolerated statin therapy. The more LDL-C is reduced on statin therapy, the greater will be subsequent risk reduction. Use a maximally tolerated statin to lower LDL-C levels by ≥50%.

3. In very high-risk ASCVD, use a LDL-C threshold of 70 mg/dL (1.8 mmol/L) to consider addition of non-statins to statin therapy. Very high-risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions. In very high-risk ASCVD patients, it is reasonable to add ezetimibe to maximally tolerated statin therapy when the LDL-C level remains ≥70 mg/dL (≥1.8 mmol/L). In patients at very high risk whose LDL-C level remains ≥70 mg/dL (≥1.8 mmol/L) on maximally tolerated statin and ezetimibe therapy, adding a PCSK9 inhibitor is reasonable, although the long-term safety (>3 years) is uncertain.
4. In patients with severe primary hypercholesterolemia (LDL-C level ≥190 mg/dL [≥4.9 mmol/L]), without calculating 10-year ASCVD risk, begin high-intensity statin therapy without calculating 10- year ASCVD risk. If the LDL-C level remains ≥100 mg/dL (≥2.6 mmol/L), adding ezetimibe is reasonable. If the LDL-C level on statin plus ezetimibe remains ≥100 mg/dL (≥2.6 mmol/L) and the patient has multiple factors that increase subsequent risk of ASCVD events, a PCSK9 inhibitor may be considered, although the long-term safety (>3 years) is uncertain.
5. In patients 40 to 75 years of age with diabetes mellitus and LDL-C ≥70 mg/dL (≥1.8 mmol/L), start moderate-intensity statin therapy without calculating 10-year ASCVD risk. In patients with diabetes mellitus at higher risk, especially those with multiple risk factors or those 50 to 75 years of age, it is reasonable to use a high-intensity statin to reduce the LDL-C level by ≥50%.
6. In adults 40 to 75 years of age evaluated for primary ASCVD prevention, have a clinician–patient risk discussion before starting statin therapy. Risk discussion should include a review of major risk factors (e.g., cigarette smoking, elevated blood pressure, LDL-C, hemoglobin A1C [if indicated], and calculated 10-year risk of ASCVD); the presence of risk-enhancing factors (see No. 8); the potential benefits of lifestyle and statin therapies; the potential for adverse effects and drug–drug interactions; consideration of costs of statin therapy; and patient preferences and values in shared decision-making.
7. In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥70 mg/dL (≥1.8 mmol/L), at a 10-year ASCVD risk of ≥7.5%, start a moderate-intensity statin if a discussion of treatment options favors statin therapy. Risk-enhancing factors favor statin therapy (see No. 8). If risk status is uncertain, consider using coronary artery calcium (CAC) to improve specificity (see No. 9). If statins are indicated, reduce LDL-C levels by ≥30%, and if 10-year risk is ≥20%, reduce LDL-C levels by ≥50%.
8. In adults 40 to 75 years of age without diabetes mellitus and 10-year risk of 7.5% to 19.9% (intermediate risk), risk-enhancing factors favor initiation of statin therapy (see No. 7). Risk-enhancing factors include family history of premature ASCVD; persistently elevated LDL-C levels ≥160 mg/dL (≥4.1 mmol/L); metabolic syndrome; chronic kidney disease; history of preeclampsia or premature menopause (age <40 years); chronic inflammatory disorders (e.g., rheumatoid arthritis, psoriasis, or chronic HIV); high-risk ethnic groups (e.g., South Asian); persistent elevations of triglycerides ≥175 mg/dL (≥1.97 mmol/L); and, if measured in selected individuals, apolipoprotein B ≥130 mg/dL, high-sensitivity C-reactive protein ≥2.0 mg/L, ankle-brachial index <0.9 and lipoprotein (a) ≥50 mg/dL or 125 nmol/L, especially at higher values of lipoprotein (a). Risk-enhancing factors may favor statin therapy in patients at 10-year risk of 5-7.5% (borderline risk).
9. In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥70 mg/dL- 189 mg/dL (≥1.8-4.9 mmol/L), at a 10-year ASCVD risk of ≥7.5% to 19.9%, if a decision about statin therapy is uncertain, consider measuring CAC. If CAC is zero, treatment with statin therapy may be withheld or delayed, except in cigarette smokers, those with diabetes mellitus, and those with a strong family history of premature ASCVD. A CAC score of 1 to 99 favors statin therapy, especially in those ≥55 years of age. For any patient, if the CAC score is ≥100 Agatston units or ≥75th percentile, statin therapy is indicated unless otherwise deferred by the outcome of clinician–patient risk discussion.
10. Assess adherence and percentage response to LDL-C–lowering medications and lifestyle changes with repeat lipid measurement 4 to 12 weeks after statin initiation or dose adjustment, repeated

every 3 to 12 months as needed. Define responses to lifestyle and statin therapy by percentage reductions in LDL-C levels compared with baseline. In ASCVD patients at very high-risk, triggers for adding non-statin drug therapy are defined by threshold LDL-C levels ≥70 mg/dL (≥1.8 mmol/L) on maximal statin therapy (see No. 3)."

Who to Screen?
Prior to the publication of the AHA/ACC 2018 guideline, the USPSTF recommended that adults without CAD and a >=10% CV risk by the pooled cohort equation be treated with a statin medication (B recommendation). To achieve this, they recommended screening all adults 40-75 years old (the range of the ACC/AHA guideline) for hyperlipidemia.

The AHA/ACC guideline does not present traditional evidence for screening (e.g., RCT of screened vs unscreened individuals) nor do they present an analytic framework connecting screening to improved morbidity or mortality. They recommend screening solely based on evidence of treatment trials.

The guideline recommends consideration of lifetime risk in patients 20-39 and treatment of those with a family history and LDL ≥160. The main argument provided is to allow risk reduction strategies to take place (e.g., diet and exercise). They further recommend screening non-pregnant adults 40-75 with risk re-evaluated every 4-6 yrs.

The guideline clearly states that a fasting lipid panel is NOT REQUIRED. Studies indicate that a less than 10 percent improvement in levels occur with fasting (Sidhu Arch Int Med 2012; Nov 12:1).

Risk Calculation
An integral first step in the guideline is calculation of the ASCVD pooled risk. There are several calculators available to calculate this risk. We recommend use of one of our MedConnect Calculators:

- Using MedConnect
  - Calculators Tab > Cardiology > ACC/AHA 2013 Cardiovascular Risk Assessment -- Allows copying and pasting into note
  - FHIR App > Black menu bar > Cardiac Risk
    Imports data from chart but no copying and pasting to note
  - ASCVD Risk Estimator > a component that can be added to the appropriate specialty clinic Workflow. Has a link to the ACC Guideline, Risk enhancing factors, and a "Risk Educator" section where inputs can be varied to help the patient understand the impact of interventions.
- Phone: ACC ASCVD Risk Estimator Plus
  - iOS App: https://itunes.apple.com/us/app/ascvd-risk-estimator/id808875968?mt=8
  - Android App: https://play.google.com/store/apps/details?id=org.acc.cvrisk&hl=en
- Web
  - http://tools.acc.org/ASCVD-Risk-Estimator/
- ACC lipid app
- LDLc Manager calculator for % risk reduction

Concerns have been raised as the Pooled Cohort Equations still lack validation in certain ethnic groups and does not include family history. Validation studies indicate that they generally overestimate risk (Cook NR, Ridker PM. Ann Intern Med. 2016;165:786–794.) but may underestimate risk in patients with chronic inflammatory conditions. Further studies may help clarify the calculator's broad utility. All calculators have benefits and drawbacks; clinician judgment may be used in choice of calculator, but the clinician should be well acquainted with

the calculator they are using. For practical purposes, the provider may decide to quantify risk using another calculator, for example:

- Framingham Coronary Heart Disease 10-year Risk which is validated in whites, African Americans, and Hispanic women, but may be less accurate in certain patients and *does not estimate stroke risk*
- Framingham General Cardiovascular Disease 10-year Risk which is based on data from primarily *white patients*
- Reynolds risk scores for men and for women

Guideline Summary based on Four Statin Benefit Groups

As with the 2013 guideline, in the 2018 guideline there are four groups of age ≥ 21 yo men and non-pregnant/non-nursing women for whom atherosclerotic cardiovascular disease benefit from statins clearly exceeds adverse event risk (w/o NYHA II-IV HF and/or on hemodialysis). The guidelines recommend which intensity statin should be initiated in these cases, with some caveats:

1) **Individuals with clinical ASCVD** (ACS, h/o MI, stable or unstable angina, coronary or arterial revascularization, CVA, TIA or PAD presumed atherosclerotic) □ High-Intensity statin preferred
2) **Individuals with LDL-C >= 190 mg/dL** □ □ High-Intensity statin preferred
3) **Individuals 40-75 years of age *with diabetes and* LDL-C 70-189 mg/dL**: Moderate intensity statin is recommended for these patients. If diabetes risk-enhancing factors are present (p 31 Table 5) such as long duration, albuminuria, low GFR, retinopathy, neuropathy, or a low ABI, a high-intensity statin is recommended. If >20% risk, then statin+ ezetimibe is recommended.
4) **Individuals 40-75 years of age *without* diabetes *or* clinical ASCVD *and* with LDL 70-189 mg/dL *and* an estimated 10-year ASCVD risk of 7.5% or higher** □ Moderate to High-Intensity Statin
5) **Age >= 75 yo**
    i. Fewer people > 75 were included in the reviewed RCTs but evidence supports continuing tolerated statins. The small amount of available data does not clearly support starting high-intensity statins for secondary prevention; a larger amount of data does support the use of moderate-intensity statins.
    ii. Few data in this group indicate a primary prevention benefit, so one must consider risk and benefits; Pooled Cohort Equations can be used in ages 76-79

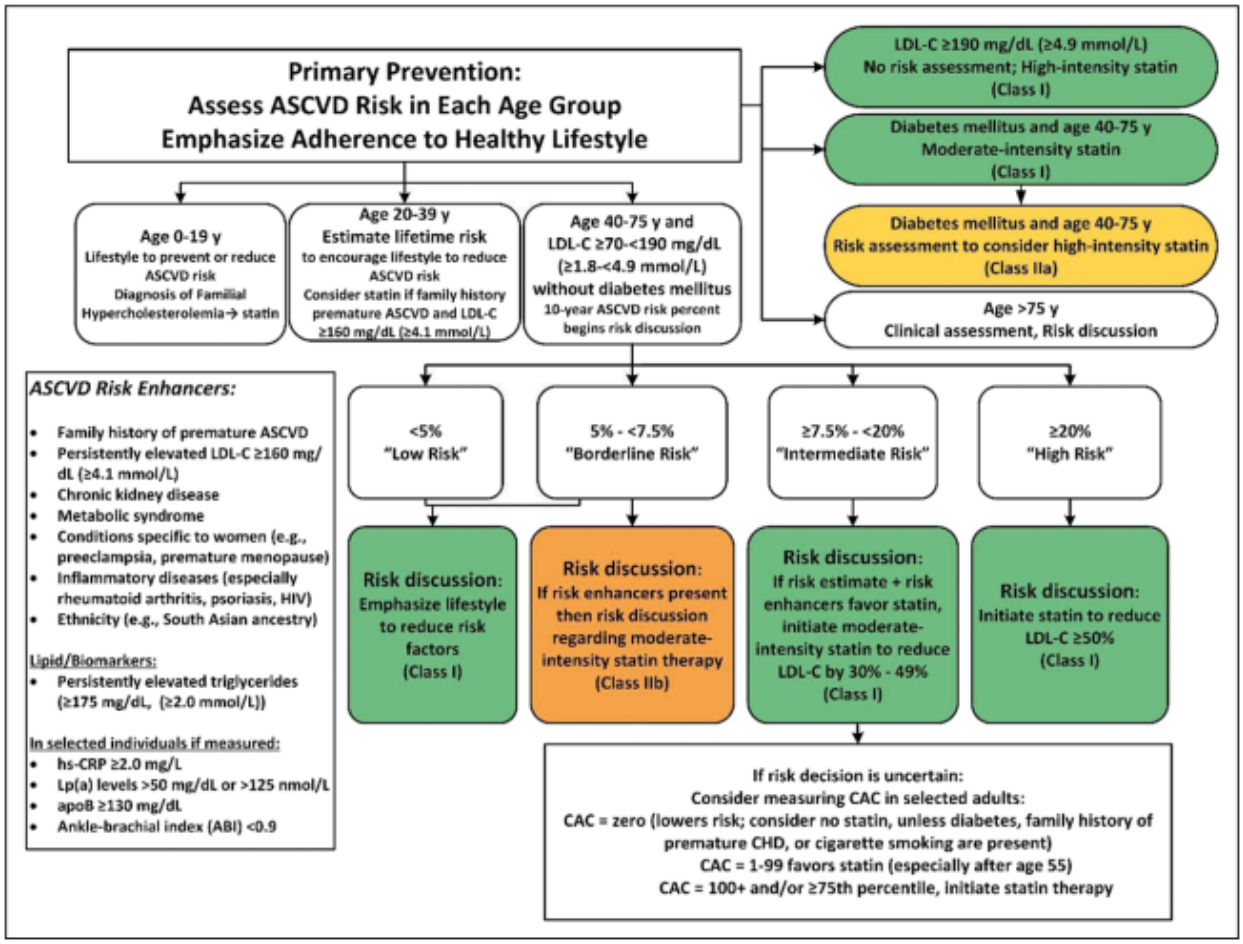
Shared Decision-Making

While present in the 2013 guideline, the 2018 version makes much more explicit that a shared decision-making decision needs to occur before starting a statin medication. They imply that patients should not be started on medication if the outcome of the discussion is not favorable. Detailed advice on conducting this risk discussion is provided via a checklist (Table 7, p 41) and reprinted below

	○ In lower-risk primary-prevention adults 40-75 y of age with LDL-C ≥70 mg/ (≥1.8 mmol/L). ○ Not needed in secondary prevention, in those with LDL-C ≥190 mg/dL (≥4 mmol/L), or in those 40-75 y of age with diabetes mellitus. • Assess other patient characteristics that influence risk. See Risk-Enhancing Fac (Section 4.4.1.3. and Table 6) • Assess CAC (Section 4.4.1.4.) if risk decision is uncertain and additional inform is needed to clarify ASCVD risk. ○ Use decision tools to explain risk (e.g., ASCVD Risk Estimator Plus,* Mayo Statin Choice Decision Aid).
ɔdifications	• Review lifestyle habits (e.g., diet, physical activity, weight or body mass index, 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 Clinicia Lifestyle Modification Toolbox, cardiac rehabilitation, dietitian, smoking cessat program).
ɛt clinical ıerapy	• 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.
erations	• Discuss potential out-of-pocket cost of therapy to the patient (e.g., insurance coverage, tier level, copayment).
sion-	• Encourage the patient to verbalize what was heard (e.g., patient's personal AS risk, available options, and risks/benefits). • Invite the patient to ask questions, express values and preferences, and state 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.

Care Algorithm for Primary Prevention

Based on age, co-morbid diseases, and risk, the algorithm guides you through a decision on whether to start a statin medication.



Circulation. 2019;139: e1046–e1081. DOI: 10.1161/CIR.0000000000000624

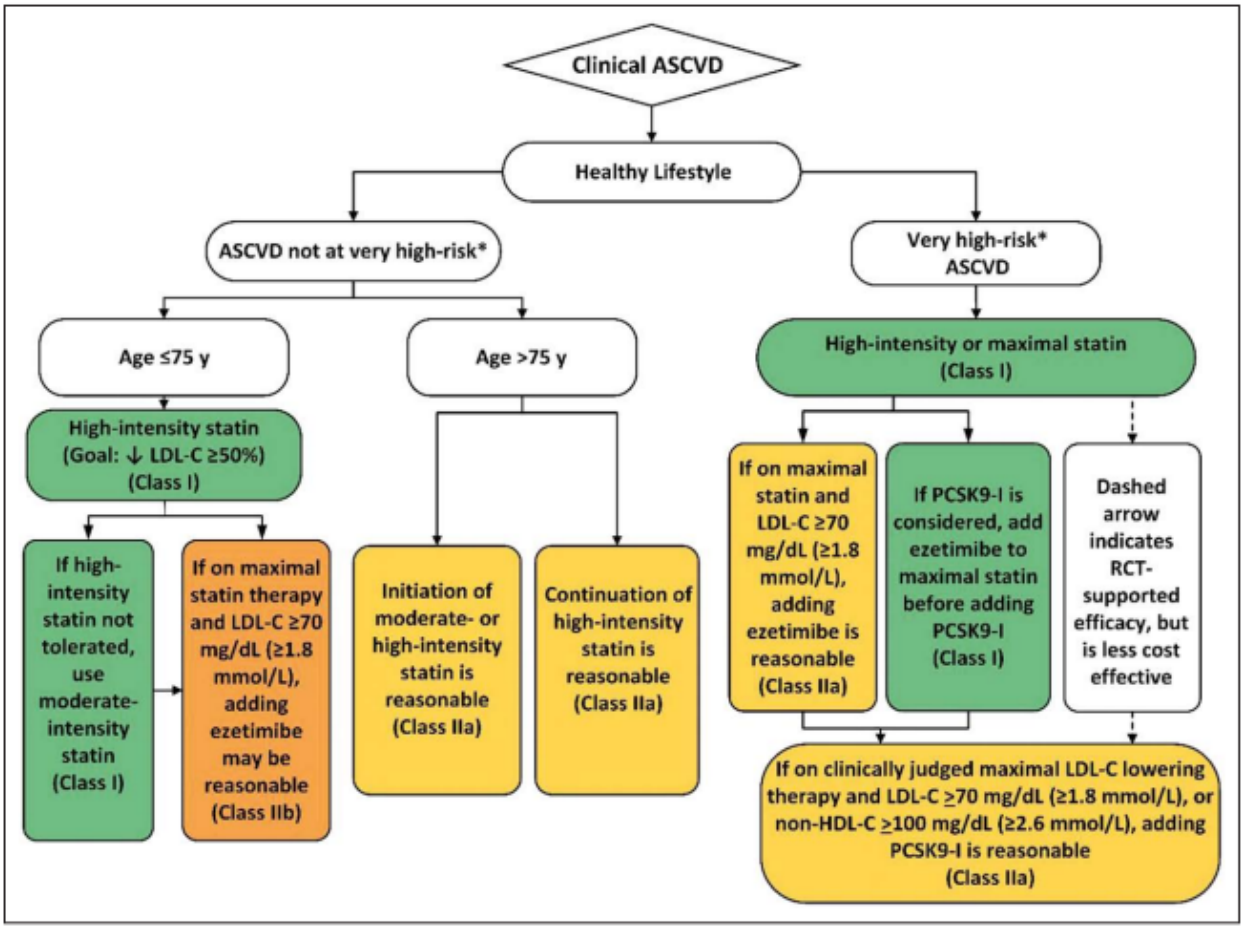
Ongoing lifestyle modification is recommended for all patients. All patients should have a risk discussion as noted above before starting a statin.

For those with risk between 5 and 20%, the guideline now lists ASCVD Risk Enhancers that may favor a decision toward statin use. These include LDL-C ≥160 mg/dL, persistently elevated triglyceride > 175, family h/o premature ASCVD (first degree male relative with onset < 55 yo or female < 65 yo), CKD, metabolic syndrome, inflammatory diseases, hs-CRP ≥2 mg/dL, ethnicity, ABI < 0.9 (see Figure 2 from guideline above for full list).

If a risk decision is "uncertain," the guideline now gives the option to measure coronary artery calcium (CAC). If the score is 0, consideration may be given to avoiding statin use except in smokers, diabetics, and those with a positive family history. A score of 1-99 favors statin therapy, and if ≥100 the guideline recommends statin therapy.

Care Algorithm for Secondary Prevention/Clinical ASCVD

Statin medications are recommended for most patients with ASCVD. A risk calculation is generally not needed.



Circulation. 2019;139: e1046–e1081. DOI: 10.1161/CIR.0000000000000624

The algorithm is divided into two branches based on whether the patient has "very high-risk ASCVD" or not, meaning the risk for future ASCVD events. The guideline suggests a "history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions" as defining very high risk. See below for Table 4, criteria for very high risk).

For patients ≤75 yrs. or at very high risk, if a suggested goal of <70 LDL is not reached on maximal statin levels, it is suggested to add ezetimibe.

To consider a PCSK9 inhibitor, the patient should be very high risk, already on maximal statin therapy and ezetimibe, and not have reached LDL <70.

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 (S4.1-39))
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) (S4.1-15, S4.1-17)
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 includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions.

ABI indicates ankle-brachial index; ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HF, heart failure; LDL, low-density lipoprotein cholesterol; and MI, myocardial infarction.

Statin Choice

Choose medication and dose to achieve the desired LDL-C reduction. From Table 3, page 17:

High Intensity	**Moderate Intensity**	**Low Intensity**
Lowers LDL-C ≥50%	*Lowers LDL-C 30-49%*	*Lowers LDL-C ≤30%*
Atorvastatin (40 mg‡) 80 mg Rosuvastatin 20 mg (40 mg)	Atorvastatin 10 mg (20 mg) Rosuvastatin (5 mg) 10 mg Simvastatin 20-40 mg**	Simvastatin 10 mg*
	Pravastatin 40mg (80 mg) Lovastatin 40 mg (80 mg) Fluvastatin XL 80 mg Fluvastatin 40 mg BID Pitavastatin 1-4 mg	Pravastatin 10-20 mg Lovastatin 20 mg Fluvastatin 20-40 mg

**-FDA does not recommend use of simvastatin 80 mg due to increased risk of myopathy

Modification of Statin Choice

1) Since the following patient characteristics predispose to adverse statin effects, a moderate-intensity statin should be used:

A) Multiple or serious co-morbidities, including impaired renal/ hepatic function
B) H/o previous statin intolerance or muscle disorder
C) Unexplained elevation of ALT > 3 x upper limit of normal
D) Patient characteristics or concomitant use of medicines affecting statin metabolism

2) A lower intensity than recommended statin may be considered for other compelling indications including a history of hemorrhagic stroke or Asian ancestry

Initial Evaluation for those not currently on statin

1. **Clinical ASCVD**: Lipid panel, ALT
    a. CK should not routinely be measured during statin therapy
    b. Baseline measurement of CK may be reasonable if there is concern for risk based on personal or family history of statin intolerance or muscle disease, clinical presentation, or concomitant drug treatment that may increase myopathy risk
    c. During statin treatment, it is reasonable to measure CK in individuals with muscle symptoms (pain, tenderness, stiffness, cramping, weakness, generalized fatigue)
    d. Routine monitoring of transaminases during statin therapy is no longer recommended. It is reasonable, however, to re-measure ALT in the setting of unusual fatigue, weakness, appetite loss, abdominal pain, dark urine, jaundice/icterus. For elevations in ALT > 3 times upper limit of normal, further investigation and either reducing statin dose, change to a different statin or stopping the medication are warranted.
2. **No Clinical ASCVD:** as above and screen for diabetes with HgbA1c or fasting glucose if diabetes status unknown
3. **Evaluate for secondary causes as appropriate, particularly if Triglycerides are ≥ 500 mg/dL or LDL-C ≥190 mg/dL.**

Common Secondary Causes of Hyperlipidemia Seen in Clinical Practice

Secondary Cause	Elevated LDL-C	Elevated Triglyceride
Diet	Saturated or trans-fat, weight gain, anorexia	Weight gain, very low-fat diets, high intake of refined carbohydrates, excessive alcohol intake
Drugs	Diuretics, cyclosporine, glucocorticoids, amiodarone	Oral estrogens, glucocorticoids, bile acid sequestrants, protease inhibitors, retinoic acid, anabolic steroids, sirolimus, raloxifene, tamoxifen, most beta blockers (carvedilol – most favorable)
Diseases	Biliary obstructions, nephrotic syndrome	Nephrotic syndrome, chronic renal failure, lipodystrophies
Disorders, altered metabolism	Hypothyroidism, obesity, pregnancy	Diabetes (poorly controlled), hypothyroidism, obesity, pregnancy

Monitoring Therapy

1) Lipid lowering agents should be taken indefinitely or as long as treating hypercholesterolemia remains consistent with the patient's health and treatment goals. Lipid levels return to baseline once medication is stopped. Guidance is included in the guideline for patients over 75years old.
2) Lipid panel 4-12 weeks after starting statin to determine adherence and then every 3-12 months as clinically indicated
    a. High-intensity statin therapy generally results in ≥50% decrease from untreated baseline (if baseline is unknown, LDL-C < 100 has generally been observed)
    b. Moderate-intensity statin therapy generally results in 30-49% reduction
    c. Percent reduction may be used to indicate adherence (but can also indicate biologic variability); attention should be paid to adherence and lifestyle therapy, evaluation, and treatment for secondary causes; clinical judgment should be used to decide if any therapy should be increased
3) Ongoing monitoring of LFTs is NOT recommended by the FDA given that there is a low risk of clinically significant increase in LFTs.
4) A decrease in statin dose may be considered when 2 consecutive LDL-C values are < 40 mg/dL
5) It may be harmful to initiate or increase a simvastatin dose to 80 mg/dL due to the risk of rhabdomyolysis; lovastatin should be avoided in the setting of several medicines and dose limitations exist for other medicines; make sure to check labeling
6) Current diabetes screening guidelines should be maintained for those on statins
7) A review of manufacturer's prescribing information may be useful prior to initiation of any cholesterol lowering drug
8) To evaluate and treat muscle symptoms:
    a. Obtain a history of baseline symptoms prior to starting therapy
    b. For unexplained severe symptoms, discontinue statin and evaluate CK, Cr, UA
    c. For mild-moderate symptoms
        i. Discontinue statin until symptoms can be evaluated
        ii. Evaluate for conditions that might increase risk (hypothyroidism, reduced renal or hepatic function, rheumatologic disorder like polymyalgia rheumatica, steroid myopathy, vitamin D deficiency, primary muscle disease)

1. If symptoms resolve and there is no contraindication, give the same statin at an original or lower dose and observe for symptoms
    a. If causal relationship exists, discontinue original statin and when symptoms resolve, use a low dose of different statin. Pravastatin and Fluvastatin are the statins with the least intrinsic muscle toxicity.
    b. Once that dose is tolerated, it can be gradually increased
2. If symptoms do not resolve after 2 months without statin, or CK does not return to normal, consider other causes
3. If the statin is determined to not be the cause, or if the predisposing condition has been treated, the original statin at the original dose can be resumed

9) For presentation with a confusional state or memory impairment, it may be reasonable to evaluate for non-statin causes (e.g., exposure to other drugs, systemic, or neuropsychiatric causes) in addition to possible statin adverse effects
10) Statins used in combination with other cholesterol-lowering drug therapies may require more intensive monitoring
11) Even lower-intensity statin therapy can reduce ASCVD events, so maximum intensity that does not cause adverse events should be used
12) Adverse events involving statins should be reported to the FDA MedWatch program

Non-statin Therapy

Non-statin therapy can be considered in high-risk patients (including those with clinical ASCVD less than 75 years old those with LDL-C > 190 or diabetes) who have a less-than-anticipated response to statins or are unable to tolerate the recommended statin intensity; clinicians should preferentially prescribe drugs w/ RCT proof of ASCVD risk reduction that exceeds risk of adverse effects.

a. **Cholesterol-Absorption Inhibitor (Ezetimibe)**
    a. Most common "add-on" medication in those not meeting goal with statin only.
    b. Lowers LDL-C levels by 13-20%
    c. Reasonable to obtain transaminases at baseline; when co-administered with statin, monitor LFTs as clinically indicated and stop if ALT > 3x ULN

b. **Bile Acid Sequestrants**
    d. Not absorbed and not associated with systemic side effects
    e. Lowers LDL-C levels by 15-30%
    f. Do not use if baseline fasting trig > 300 mg/dL or type III hyperlipoproteinemia; fasting lipids should be obtained at baseline, at 3 months and then Q6-12 months
    g. May be used with caution if baseline trig is 250-299 with fasting lipids at 6 weeks. discontinue if triglycerides exceed 400 mg/dL

c. **PCSK9 Inhibitors**
    h. Evolocumab (Repatha, Repatha SureClick) and Alirocumab (Praluent)
    i. Reduce LDL_C by as much as 60% in patients on statins; Evolocumab has been shown to reduce cardiovascular events but not mortality.

j. The current guideline recommends that patients be on high-intensity or maximal tolerated dose of a statin and ezetimibe before considering.
k. Indications
    i. **Homozygous familial hypercholesterolemia:** Adjunct to diet and other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) for the treatment of patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C. (evolocumab only)
    ii. **Hyperlipidemia, primary:** Adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (CVD), who require additional lowering of low-density lipoprotein cholesterol (LDL-C). (evolocumab and alirocumab)
l. Administered subcutaneously: monthly evolocumab (Repatha) or every 2 weeks alirocumab
m. (Praluent). Evolocumab does have an alternate q 2week regimen for primary hyperlipidemia)
n. Repatha (140 mg) $303 per dose; Praluent (75 mg – 150 mg) $270 per dose; Repatha –utilizing monthly dosing regimen $188/420mg

d. **Fibrates**
    a. Primarily used for hypertriglyceridemia
    b. Gemfibrozil should not be initiated in patients on statin therapy due to increased risk of muscle symptoms and rhabdomyolysis
    c. Fenofibrate –concurrent use with statin therapy is no longer recommended. FDA has deemed that benefits of combined therapy do not outweigh risks.

e. **Omega-3 Fatty Acids**
    a. Primarily used for hypertriglyceridemia
    b. If EPA and/or DHA are used for trig > 500 mg/dL, evaluate in setting of GI disturbance, skin changes, bleeding

f. **Niacin**
    a. Rarely used as there are more effective and safer medications available
    b. Obtain transaminases, fasting glucose or A1c and uric acid before initiation, during up- titration to maintenance dose, then every 6 months
    c. Niacin should not be used if LFTs are > 2-3 x ULN; there are persistent severe cutaneous symptoms, persistent hyperglycemia, acute gout, unexplained abdominal pain, or GI symptoms, or if new onset atrial fibrillation or weight loss occurs
    d. If an adverse effect occurs, risk: benefit ratio must be considered before restarting
    e. To reduce cutaneous symptoms:
        i. Start low dose and titrate over weeks as tolerated
        ii. Take w/ food or premedicate w/ 325 mg ASA 30 min prior to dose
        iii. If using extended-release preparation: increase from 500 mg to 2000 mg/day over 4-8 weeks, <= weekly
        iv. If using immediate-release preparation: increase from 100 mg TID and up-titrate to 3g/daily, in 2-3 divided doses

g**. Icosapent ethyl**

The REDUCE-IT (Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial showed that **use of IPE 2 g twice daily was superior to placebo** in

reducing the risk of ischemic events, including cardiovascular death, in high patients, and CV death among patients with high TGs and either known CVD or those at high risk for developing it, and who were already on statin therapy with relatively well-controlled LDL levels. Icosapent ethyl is a highly purified eicosapentaenoic acid ethyl ester-marine derived omega-3 fatty acid that works by reducing the hepatic production of triglyceride-rich very low-density lipoproteins. Patients in the icosapent ethyl group were more likely to be hospitalized for atrial fibrillation or flutter; this is not a contraindication for its use but is a consideration and should be part of clinician-patient shared decision making.

2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease
A separate Guideline on the Primary Prevention of Cardiovascular Disease was also issued by the AHA/ACC in 2019. The guideline emphasizes the following:

- Maintenance of a healthy weight
- Consuming a diet consisting of vegetables, fruits, nuts, whole grains, lean vegetable or animal protein and fish and avoiding trans fats, red meat (especially processed red meats), refined carbohydrates and sweetened beverages.
- Engaging in at least 150 per week of moderate-intensity physical activity or 75 minutes per week of vigorous intensity physical activity
- Smoking cessation

Patient education:

https://www.uptodate.com/contents/high-cholesterol-and-lipid-treatment-options-beyond-the-basics?search=high-cholesterol-treatment-options-beyond-the-basics&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1
http://www.uptodate.com/contents/diet-and-health-the-basics?source=see_link

https://healthyforgood.heart.org/eat-smart

http://health.gov/dietaryguidelines/2015/guidelines/

References

1. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, Goldberg R, Heidenreich PA, Hlatky MA, Jones DW, Lloyd-Jones D, Lopez-Pajares N, Ndumele CE, Orringer CE, Peralta CA, Saseen JJ, Smith Jr SC, Sperling L, Virani SS, Yeboah J, 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol, Journal of the American College of Cardiology (2018), doi: https://doi.org/10.1016/j.jacc.2018.11.003.

2. Stone NJ, Robinson J, Lichtenstein AH, Bairey Merz CN, Lloyd-Jone DM, Blum CB, McBride P, Eckel RH, Schwartz JS, Goldberg AC, Shero ST, Gordon D, Smith Jr SC, Levy D, Watson K, Wilson PWF, 2013 ACC/AHA. Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Risk in Adults, Journal of the American College of Cardiology (2013), doi: 10.1016/j.jacc.2013.11.02.

3. Eckel RH, Jakicic JM, Ard JD, Hubbard VS, de Jesus JM, Lee IM, Lichtenstein AH, Loria CM, Millen BE, Houston Miller N, Nonas CA, Sacks FM, Smith SC Jr, Svetkey LP, Wadden TW, Yanovski SZ. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013; 00: 000-000.

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4. Final Recommendation Statement: Statin Use for the Primary Prevention of Cardiovascular Disease in Adults: Preventive Medication. U.S. Preventive Services Task Force. November 2016.
5. https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/statin-use-in-adults-preventive-medication1

6. Arnett, Donna et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease. Circulation 2019; 140: 596-e646.

7. FDA Drug Safety Communication: Important safety label changes to cholesterol-lowering statin drugs, 2-28-2012.

8. PL Detail-Document, Common Cardiovascular Risk Calculators. Pharmacist's

   Letter/Prescriber's Letter. January 2014. PL Detail-Document, Common Cardiovascular

   Risk Calculators. Pharmacist's Letter/Prescriber's Letter. January 2014

9. Alirocumab (Praluent) to Lower LDL-Cholesterol. The Medical Letter August 17, 2015

10. Evolucumab (Repatha)—A Second PCSK9 Inhibitor to Lower LDL-Cholesterol. The Medical Letter. October 12, 2015.

11. Lipid Lowering Drugs. The Medical Letter October 24, 2016.

12. Reduction of Cardiovascular Risk with Evolucumab (Repatha). The Medical Letter April 24, 2017.

13. Reduction in Total Ischemic Events in the Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial-REDUCE-IT, Deepak L. Bhatt, MD, MPH, Gabriel Steg, MD, Michael Miller, MD et al

Initial Approval Date and Reviews:	Most Recent Revision and Approval Date: April 2022	Next Scheduled Review Date:
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Medications for Cholesterol Reduction

HMG- CoA Reductase Inhibitors (Statins)			
Average LDL-C reduction: Low Intensity <30%, Moderate Intensity 30% to <50%, High Intensity ≥50%			
Drug		**Dose**	**Comments /Safety**
Atorvastatin (Lipitor) ($116-$321)	Moderate Intensity	10 -20 mg daily	(see guideline pages 9-11 for additional recommendations) Baseline measurement of CK is reasonable for individuals believed to be at increased risk for adverse muscle events. During statin therapy, it is reasonable to measure CK in individuals with muscle symptoms, including pain, tenderness, stiffness, cramping, weakness, or generalized fatigue. Baseline measurement of hepatic transaminase levels (AST and ALT) should be performed before initiating statin therapy. During statin therapy, it is reasonable to measure hepatic function if symptoms suggesting hepatotoxicity arise. Individuals receiving statin therapy should be evaluated for new-onset diabetes mellitus. Continue statin therapy if diabetes develops. If unexplained severe muscle symptoms or fatigue develop during statin therapy, promptly discontinue the statin, and address the possibility of rhabdomyolysis by evaluating CK, creatinine, and a urinalysis for myoglobinuria.
	High Intensity	40 - 80 mg daily	
Fluvastatin ($150-$300)	Low Intensity	20-40 mg nightly	
	Moderate Intensity	40 mg twice daily	
Fluvastatin XL (Lescol XL) ($262-$277)	Moderate Intensity	80 mg daily	
Lovastatin ($68-$292) Lovastatin extended release (Altoprev) ($1300 – brand only)	Low Intensity	20 mg nightly *IR form to be taken with*	
	Moderate Intensity	40-80 mg nightly *IR form to be taken with evening meal*	
Pitavastatin (Livalo) ($384 – brand only) (Zypitamag) ($279 – brand only)	Low Intensity	1 mg daily	
	Moderate Intensity	2-4 mg daily	
Pravastatin ($30-$144)	Low Intensity	10-20 mg daily	
	Moderate Intensity	40-80 mg daily	
Rosuvastatin (Crestor) ($43-$269)	Moderate Intensity	5-10 mg daily, do not crush or chew	
	High Intensity	20-40 mg daily, do not crush or chew	
Simvastatin (Zocor) ($84-$147)	Low Intensity	10 mg nightly	
	Moderate Intensity	20-40 mg nightly	

Cost per 30 days of generic medication unless otherwise specified

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Significant Statin Drug Interactions	
Atorvastatin	Use with caution in patients in patients taking strong CYP3A4inhibitors. Consider alternate agents. Examples of common medications to avoid with atorvastatin: • Cyclosporine • Gemfibrozil • Tipranavir plus ritonavir • Telaprevir • Itraconazole Use with caution and use with the lowest atorvastatin dose necessary: • Lopinavir + ritonavir • Amiodarone Do not exceed 20 mg daily atorvastatin with the following agents: • Darunavir + ritonavir • Fosamprenavir • Fosamprenavir + ritonavir • Saquinavir + ritonavir Administer 1 hour before or at least 4 hours after cholestyramine or colestipol Use statins with caution with niacin ≥1000 mg/day Experts suggest avoiding grapefruit with atorvastatin due to inhibition of the CYP3A4 enzyme
Fluvastatin	Do not exceed Fluvastatin 20 mg twice daily (Fluvastatin may be least likely to interact): Cyclosporine Administer 1 hour before or at least 4 hours after cholestyramine or colestipol Avoid with Fluvastatin: Gemfibrozil, Fenofibrate Use statins with caution with niacin ≥1000 mg/day

Lovastatin	Use with caution in patients in patients taking strong CYP3A4 inhibitors. Consider alternate agents. Contraindicated with lovastatin: • Itraconazole • Ketoconazole • Posaconazole • Erythromycin • Clarithromycin • Telithromycin • HIV protease inhibitors • Boceprevir • Telaprevir • Nefazodone Avoid with lovastatin: • Cyclosporine • Gemfibrozil Do not exceed 20 mg lovastatin daily with: • Danazol • Diltiazem • Verapamil • Clarithromycin Administer 1 hour before or at least 4 hours after cholestyramine or colestipol. Use statins with caution with niacin ≥1000 mg/day. Limit extended-release niacin to 2000 mg and lovastatin dose to 40mg daily when used in combination.

Pitavastatin	Contraindicated with Pitavastatin: Cyclosporine Limit dose to 1 mg daily with: Erythromycin Limit dose to 2 mg daily with: Rifampin
Pravastatin	Administer 1 hour before or at least 4 hours after cholestyramine or colestipol Avoid use with pravastatin: Gemfibrozil Do not exceed pravastatin 20 mg daily: Cyclosporine Do not exceed pravastatin 40 mg daily: • Clarithromycin • Azithromycin Use statins with caution with niacin ≥1000 mg/day
Rosuvastatin	Do not exceed rosuvastatin 5 mg: • Cyclosporine Do not exceed rosuvastatin 10 mg daily: • Atazanavir ± ritonavir • Lopinavir + ritonavir Avoid use with rosuvastatin: • Gemfibrozil Administer 1 hr. before or at least 4 hours after cholestyramine or colestipol Use statins with caution with niacin ≥1000 mg/day
Simvastatin	Contraindicated with simvastatin: • HIV protease inhibitors • Boceprevir • Telaprevir • Itraconazole • Ketoconazole • Posaconazole • Danazol • Clarithromycin • Erythromycin Do not exceed simvastatin 20 mg: • Amiodarone • Amlodipine Administer 1 hour before or at least 4 hours after cholestyramine or colestipol Use statins with caution with niacin ≥1000 mg/day. Limit extended-release niacin to 2000 mg and simvastatin dose to 40mg daily when used in combination Experts suggest avoiding grapefruit with simvastatin.

Non-statins		
Clinicians treating high-risk patients who have a less-than-anticipated response to statins, who are unable to tolerate recommended intensity of a statin, or who are completely statin intolerant may consider the addition of a non-statin cholesterol-lowering therapy.		
Drug	**Dose**	**Other**
Selective Cholesterol Absorption Inhibitor		When ezetimibe is co-administered with a statin, monitor transaminase levels as clinically indicated, and discontinue ezetimibe if persistent ALT elevations >3 times ULN occur. Absorption decreased by bile acid sequestrants; administer ezetimibe at least 2hrs before or 4hrs after
Ezetimibe (Zetia) ($78-396)	10 mg every day	
Bile Acid Sequestrants		BAS should not be used in individuals with baseline fasting triglyceride levels ≥300 mg/dL or type III hyperlipoproteinemia Use BAS with caution if baseline triglyceride levels are 250 to 299 mg/dL and evaluate a fasting lipid panel in 4 to 6 weeks after initiation. Discontinue the BAS if triglycerides exceed 400 mg/dL. The bile acid sequestrant should be taken 1 hour after or 4 hours before other medications due to binding interactions Granules must be administered as solution; not to be taken in dry form
Cholestyramine granules • Cholestyramine $2/4g powder or $5/4g packet • Questran $2/4g powder or $7/4g packet • Cholestyramine Light packets $4/4g or $4/4g powder (brand only) • Prevalite packets $3/4g powder or $5/4g packet	Initial: 4g 1-2 times daily with food Usual: 4g 2-4 times a day with food. Max 24g/day	
Colestipol (Colestid) • Colestipol granules $3-$14 • Colestipol tablets $76-$605	Tabs: Initial: 2 g 1-2 times daily Usual: 2-16 g/day, may be split into divided doses Granules: Initial: 5g 1-2 times daily Usual: 5-30g/day, may be split into divided doses	

Colesevelam (Welchol) $198-$713	3.75 g (6 tabs) once daily or 1.875g (3 tabs) twice daily with meals	
Fibrates		Gemfibrozil should not be initiated in patients on statin therapy because of an increased risk for muscle symptoms and rhabdomyolysis Fenofibrate dose may need to be adjusted based on patient's renal function
Fenofibrate (TriCor, Lofibra) Generic micronized $208 Generic for TriCor $172 Generic for Lofibra $86	Generic (micronized): 130mg daily Lofibra tab: 160mg daily TriCor: 145mg daily	
Gemfibrozil (Lopid) $140	600 mg twice a day 30 minutes before meals	
Antilipemic Agents		Niacin should not be used if: • Hepatic transaminase elevations are higher than 2 to 3 times ULN. • Persistent severe cutaneous symptoms, persistent hyperglycemia, acute gout or unexplained abdominal pain or gastrointestinal symptoms occur. New-onset atrial fibrillation or weight loss may occur Use only if triglyceride goals are not met with other therapies
Niacin (Most niacin products are available over the counter) Immediate release *Niacor* ($5-$14) Extended-release *Niaspan* ($2-$5)	Generally, not recommended unless intolerable to other therapies or goals cannot be achieved with other therapies. Immediate release: Initial: 250mg with evening meal Usual: 2-6 g in 3 divided doses Extended release: Initial: 500 mg every evening Usual: 1-2 g every evening	

Omega-3-acid ethyl esters *(Lovaza) $322*	4g/day as single dose or 2 divided doses	If used for the management of severe hypertriglyceridemia, defined as triglycerides ≥500 mg/dL, it is reasonable to evaluate the patient for gastrointestinal disturbances, skin changes, and bleeding. Do not crush, break, or chew
Icosapent Ethyl 2g twice daily 30 days of 2g BID is $377 Highly purified eicosapentaenoic acid ethyl ester-marine derived omega-3 fatty acid (*Vascepa*)	2 g twice daily	Patients in the icosapent ethyl group were more likely to be hospitalized for atrial fibrillation or flutter; this is not a contraindication for its use but is a consideration and should be part of clinician-patient shared decision making.
Combination Products Ezetimibe/Simvastatin *(Vytorin) $336*	Initial: 10/20 mg daily Usual: 10/20 mg – 10/40 mg daily	See individual agents

PCSK9 Inhibitors		
Evolocumab (brand name only) Repatha: $303/140mg Repatha SureClick: $303/140mg Repatha Pushtronex: $188/420mg	**Hyperlipidemia, primary:** SubQ: 140 mg every 2 weeks or 420 mg once monthly **Homozygous familial hypercholesterolemia:** SubQ: 420 mg once monthly; after 12 weeks may increase to 420mg every 2 weeks if needed	Most common side effect: >10%: Respiratory: Nasopharyngitis (6% to 11%) Influenza 8-9% Hypersensitivity reactions have been reported. Once monthly dose given as SubQ infusion over 9 minutes or as three 140mg injections within a 30- minute period
Alirocumab (Praluent – brand name only) $270/m	**Hyperlipidemia SubQ** Initial 75mg once every 2 weeks or 300mg every 4 weeks Maximum:150 mg every 2 weeks Homozygous familial hypercholesterolemia: SubQ: 150mg every 2 weeks	Most common side effect: injection site reaction (7%), Influenza (6%), Diarrhea 5%. Liver enzyme disorder 3% Hypersensitivity reactions have been reported. If giving 300mg dose, administer two 150mg injections in two different injection sites
Antilipemic Small Interfering Ribonucleic Acid (siRNA) Agent		
Inclisiran (Leqvio – brand name only) $3900/284mg	Single 284mg injection followed by a second injection at 3 months and then every 6 months	Most common side effects: injection site reaction (8%), arthralgia (5%), and bronchitis (4%)

Antilipemic Agents		
Bempedoic Acid (Nexletol – brand name only) $461	180mg once daily	May cause hyperuricemia, gout, and tendon rupture
Lomitapide (Juxtapid – brand name only) $2053	Initial: 5mg daily Max: 60 mg daily	Boxed Warning: hepatotoxicity; available through REMS program only Administer at least 2 hours after evening meal to decrease risk of GI adverse effects Do not crush or chew Most common side effects: chest pain (24%), fatigue (17%), GI effects such as
Combination Products Bempedoic Acid/Ezetimibe (Nexlizet- brand name only) $462	180/10 mg daily	See individual agents