LIPID MANAGEMENT TO REDUCE ASCVD RISK

Federal Bureau of Prisons

Clinical Guidance

July 2021

WHAT'S NEW IN THIS DOCUMENT

This 2021 BOP Clinical Guidance for *Lipid Management to Reduce ASCVD Risk* is an extensive update of the BOP *Clinical Practice Guidelines for Management of Lipid Disorders*, published in April 2009.

This update has been issued to reflect the recommendations in the *2018 American College of Cardiology (ACC)/American Heart Association (AHA) Guideline on the Management of Blood Cholesterol*, the 2016 U.S. Preventive Services Task Force (USPSTF) Final Recommendation Statement on *Statin Use for the Primary Prevention of Cardiovascular Disease in Adults: Preventive Medication*, and the 2021 American Diabetes Association Standards of Care (see the full citation listed under *References and Resources*).

Key changes to the ACC/AHA guidelines since 2009 include:

- In 2013, the ACC/AHA guidelines created the four statin benefit groups.
- In 2018, the ACC/AHA guidelines included the following additional guidance:
  - Additional recommendations for each benefit group
  - Recommendations for special populations
  - Considerations for when to add non-statins for patients not at their LDL-C goal
  - Additional risk factors to consider when determining a patient's ASCVD risk

Key updates related to the USPSTF guidelines include:

- Use of low- to moderate-dose statins in adults aged 40 to 75 years without a history of CVD who have 1 or more CVD risk factors (dyslipidemia, diabetes, hypertension, or smoking) and a calculated 10-year CVD event risk of 10% or greater.
- Selectively offer low- to moderate-dose statins to adults aged 40 to 75 years without a history of CVD who have 1 or more CVD risk factors and a calculated 10-year CVD event risk of 7.5% to 10%.
- Current evidence is insufficient to assess the balance of benefits and harms of initiating statin use in adults 76 years and older.
- The current USPSTF recommendation statement (2016) is under review and is being updated.

Key updates related to the ADA guidelines include:

- For **primary prevention for patients with diabetes** aged 40–75 years, use moderate-intensity statin therapy in addition to lifestyle therapy. For patients with diabetes aged 20–39 years with additional atherosclerotic cardiovascular disease risk factors, it may be reasonable to initiate statin therapy in addition to lifestyle therapy. In diabetic patients with higher cardiovascular risk, especially those aged 50–70 years or who have multiple atherosclerotic cardiovascular disease risk factors, it is reasonable to use high-intensity statin therapy.
- In adults with diabetes and 10-year atherosclerotic cardiovascular disease risk of 20% or higher, it may be reasonable to add ezetimibe to maximally tolerated statin therapy to reduce LDL cholesterol levels by 50% or more.
- For **secondary prevention for all ages with diabetes**, high-intensity statin therapy should be added to lifestyle therapy. For patients considered very high risk using specific criteria, if LDL cholesterol is ≥70 mg/dL on maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor).

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1. PURPOSE AND OVERVIEW

Cardiovascular disease remains the number one cause of death in the United States. Certain lipid abnormalities are associated with an increased risk of **atherosclerotic cardiovascular disease (ASCVD)** and the lowering of total and LDL cholesterol levels with HMG-CoA reductase inhibitors (a.k.a statins) has been shown to decrease adverse cardiovascular events and mortality. This Federal Bureau of Prisons (BOP) Clinical Guidance for *Lipid Management to Reduce ASCVD Risk* provides recommendations for the screening and medical management of blood cholesterol to reduce the risk of **ASCVD.**

A variety of guidelines have been published with recommendations for statin therapy to reduce ASCVD risk including the U.S. Preventive Services Task Force (USPSTF) Final Recommendation Statement on *Statin Use for the Primary Prevention of Cardiovascular Disease in Adults: Preventive Medication* (2016), the *American College of Cardiology (ACC)/American Heart Association (AHA) Task Force on Practice Guidelines***,** published online on November 12, 2018 and the American Diabetes Association Standards of Care 2021 (See the *References and Resources* section for the full citations). There are noticeable differences in the primary prevention recommendations from these organizations. Where they differ, the BOP recommends following the USPSTF recommendations for primary prevention in non-diabetics, the American Diabetes Association recommendations for diabetics, and the ACC/AHA guidelines for other scenarios as applicable. However, some of the recommendations in the latter guidelines are based on limited evidence or expert opinion and clinical judgment may be appropriate.

2. CARDIOVASCULAR RISK ASSESSMENT AND SCREENING FOR LIPID DISORDERS

Cardiovascular risk assessment and screening for lipid disorders are conducted as part of the BOP preventive health care services, as outlined in the BOP *Clinical Guidance for Preventive Health Care*. The frequency of ASCVD risk assessment and lipid screening is not clearly established by the available evidence and needs to be individualized. In general, it is reasonable to obtain lipid levels at **baseline** and approximately **every 5 years** thereafter for people 40 to 75 years old with no known ASCVD and for those with diabetes mellitus of any age.

➔ See *APPENDIX 1 for a complete list of evaluation considerations*.

SCREENING METHODS

Lipid measurements should be obtained using the **lipid panel** laboratory order located in the Bureau Electronic Medical Record (BEMR) and includes total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol and Chol/HDLC ratio. Non-HDL-C can be calculated by subtracting HDL from the total cholesterol value. The lipid profile should be completed in accordance with the following guidelines:

- Venipuncture should be performed after 5 minutes in the sitting position, using the tourniquet as briefly as possible to minimize the effect of plasma volume and posture on cholesterol levels.
- Recent surgery or trauma, acute infections, weight loss, a very high-fat meal, and pregnancy can all affect lipid metabolism and cholesterol levels.
- There is a lack of data to inform the decision for when to perform a lipid panel in the fasting state. Expert opinion, patient convenience, and clinical criteria are important considerations. ACC/AHA guidelines indicate that the non-fasting state is appropriate for most situations, including ASCVD risk assessment for primary prevention and for establishing baseline LDL-C levels prior to initiating

statin therapy. Patients should avoid consuming a high fat content meal before collection of a non-fasting sample.

- LDL cholesterol levels are calculated from total and HDL cholesterol and triglyceride levels. If triglyceride levels are > 400 mg/dL, the low-density lipoprotein cholesterol (LDL-C) cannot be accurately estimated from a routine lipoprotein analysis.
- Triglyceride levels are affected by the fasting vs. non-fasting state and if triglyceride levels are > 400 mg/dL, a fasting lipid panel is necessary.

ASCVD Risk Assessment of Inmates

Follow this step-by-step method to evaluate the risk of ASCVD among inmates:

STEP 1. **Obtain a baseline lipid panel for all patients 40 to 75 years old, and for patients with diabetes mellitus or a history of ASCVD.**

STEP 2. **Evaluate all patients for presence of clinical ASCVD.**

➔ *If clinical ASCVD is identified by the presence of any of the conditions in **TABLE 1** below, skip **STEP 3** and go directly to **STEP 4**. If clinical ASCVD is not identified, go to **STEP 3** to estimate the 10-year ASCVD risk.*

TABLE 1. CRITERIA FOR CLINICAL ASCVD

- Acute coronary syndrome
- History of myocardial infarction (MI)
- Stable or unstable angina
- Coronary or another arterial revascularization
- Stroke or transient ischemic attack (TIA)
- Peripheral artery disease (PAD) including aortic aneurysm (atherosclerotic origin)

STEP 3. **For those without clinical ASCVD and LDL < 190 mg/dL, calculate ASCVD risk using the ACC ASCVD risk calculator. This online calculator should be used for primary prevention patients (those without ASCVD) ONLY. Also assess patients for risk enhancers (*See TABLE 3*).**

➔ *The ACC ASCVD Risk Estimator Plus is available at: http://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/.*

STEP 4. **Assign patients to statin benefit groups for recommended therapy and treatment goals.**

Clinical evidence supports the use of statin in four major benefit groups in which ASCVD risk reduction outweighs risk of adverse events. The groups and suggested statin intensity are listed in *TABLE 2*, and each group is discussed further in *SECTION 3*.

TABLE 2. STATIN BENEFIT GROUPS AND SUGGESTED STATIN INTENSITY

STATIN BENEFIT GROUP	SUGGESTED STATIN INTENSITY	ADDITIONAL CONSIDERATIONS
Clinical ASCVD	High	Moderate or high intensity statin may be considered as part of a shared decision-making approach if age > 75. A maximally tolerated dose is recommended if patient is not a candidate for or cannot tolerate high-intensity statins.
Baseline LDL ≥ 190 mg/dL (severe hypercholesterolemia)	High	A maximally tolerated dose is recommended if patient is not a candidate or cannot tolerate high-intensity statins
Diabetes mellitus (DM) and age 40–75	Moderate	Consider statin therapy (shared decision-making) for patients 20-39 years old. Consider high intensity statin therapy for patients with multiple ASCVD risk factors or 50 to 70 years old Consider adding ezetimibe if 10-yr ASCVD risk ≥ 20%
10-yr ASCVD risk ≥ 10% and age 40–75	Low to Moderate	_____

RISK ENHANCERS

In addition to using the screening tools described above in this section, clinicians should also determine if the patient has any of the following risk enhancers. While risk enhancers do not dictate treatment, the clinician should consider risk enhancers when making treatment decisions about initiating or intensifying statin therapy, especially when statin treatment is not specifically indicated for primary prevention (e.g. in patients with a 10-year ASCVD risk between 5-10%) or with patients who are undecided about taking indicated statin therapy. In addition to risk enhancers, some experts also suggest using the Coronary Artery Calcium (CAC) score if the decision to start statin therapy is unclear. However, the role of the CAC score is not yet well defined by the available evidence and requires a secondary review by the Regional Medical Director prior to ordering.

(TABLE 3. RISK ENHANCERS begins on the next page)

TABLE 3. RISK ENHANCERS

DIABETES-SPECIFIC RISK ENHANCING FACTORS
► Long duration of diabetes mellitus ▪ ≥ 10 years for type 2 DM ▪ ≥ 20 years for type 1 DM ► Microvascular complications ▪ eGFR < 60 ml/min/1.73m^2 ▪ Albuminuria ≥ 30mcg albumin/mg creatinine ▪ Neuropathy ▪ Retinopathy
RISK-ENHANCING FACTORS IN NON-DIABETIC PATIENTS
► Family history of premature ASCVD (males <55 years; females <65 years) ► Metabolic syndrome ► Chronic kidney disease (CKD) ► Persistently elevated LDL-C ≥ 160-189 mg/dL or non-HDL-C 190–219 mg/dL ► History of preeclampsia ► History of premature menopause (<40 years) ► Chronic Inflammatory disorders ▪ Rheumatoid arthritis ▪ Psoriasis ▪ HIV/AIDS ► High-risk ethnic groups (South Asian ancestry)
LIPID/BIOMARKERS
► Persistently elevated triglycerides ≥ 175 mg/dL ► If measured ▪ Hs-CRP ≥ 2.0 mg/L ▪ Lp(a) levels ≥ 50 mg/dL or ≥ 125 nmol/l ▪ apoB ≥ 130 mg/dL especially at higher levels of Lp(a) ▪ ABI < 0.9

VERY HIGH-RISK ASCVD

Very high-risk ASCVD is defined as ≥ 2 major ASCVD events or a major ASCVD event and multiple (≥ 2) high-risk conditions, as listed in **TABLE 4** below.

TABLE 4. MAJOR ASCVD EVENTS AND HIGH-RISK CONDITIONS

MAJOR ASCVD EVENTS
► Acute coronary syndrome (ACS) within previous 12 months ► Previous MI or ischemic stroke ► History of stroke or TIA ► Symptomatic PAD

(table continues on next page)

HIGH-RISK CONDITIONS
► Age ≥ 65 years ► Prior revascularization (CABG or PCI) outside of ASCVD event ► DM ► Hypertension ► Current smoking ► CKD (eGFR 15-59 mL/min/1.73 m2) ► Persistently elevated LDL-C ≥ 100mg/dL despite maximally tolerated statin therapy and ezetimibe ► Familial hypercholesterolemia (FH) ► History of heart failure

3. TREATMENT BENEFIT GROUPS

Among the treatment benefit groups described in this section are patients with clinical ASCVD, patients with severe hypercholesterolemia, patients with diabetes mellitus, and primary prevention of ASCVD in patients with increased risk.

SECONDARY PREVENTION IN PATIENTS WITH CLINICAL ASCVD

All patients ≥ 18 years of age with clinical ASCVD should begin high-intensity statin therapy (unless contraindicated), as shown in ***FIGURE 1***.

➔ *See **SECTION 4** for evaluation of patients unable to tolerate statins.*

➔ *See **TABLE 5** in **SECTION 4**, which lists low-, medium-, and high-intensity statins.*

- The goal of treatment is a reduction of LDL-C by 50% or more from baseline.
- In patients at very-high risk of ASCVD (see *definition* above) and LDL-C ≥ 70 mg/dL after confirmed compliance with high-intensity or maximally tolerated statin, additional treatments should be considered.

PRIMARY PREVENTION FOR PATIENTS WITH SEVERE HYPERCHOLESTEROLEMIA

All patients 20–75 years of age with severe hypercholesterolemia (baseline LDL ≥ 190 mg/dL) should begin high-intensity statin therapy without calculating their 10-year ASCVD risk, as shown in ***FIGURE 1***.

➔*See **SECTION 4** for evaluation of patients unable to tolerate statins.*

- The goal of treatment is a reduction of LDL-C by 50% or more from baseline.
- In patients with LDL-C ≥ 100 mg/dL and/or < a 50% reduction from baseline after confirmed compliance with high-intensity or maximally tolerated statin, additional treatments should be considered.

PRIMARY PREVENTION OF ASCVD

Assessment for statin therapy requires measurement of lipid levels and calculation of the 10-year ASCVD risk using the **ASCVD RISK CALCULATOR**, as well as assessing for other risk-enhancing factors and age, as shown in ***FIGURE 1***.

➔ *See **TABLE 3** for a list of risk enhancers.*

There are considerable differences between the USPSTF and the ACC/AHA recommendations for primary prevention of ASCVD. The BOP recommends following the USPSTF recommendations but clinicians may use their clinical judgment and preferentially follow the ACC/AHA guidelines.

The guidelines referenced in this document do not address obesity as a risk factor for dyslipidemia and ASCVD, both of which are increased in obesity. The BOP recommends obtaining a lipid panel and conducting an ASCVD risk assessment in all patients, regardless of age, with a body mass index ≥ 30.

USPSTF recommendations include:

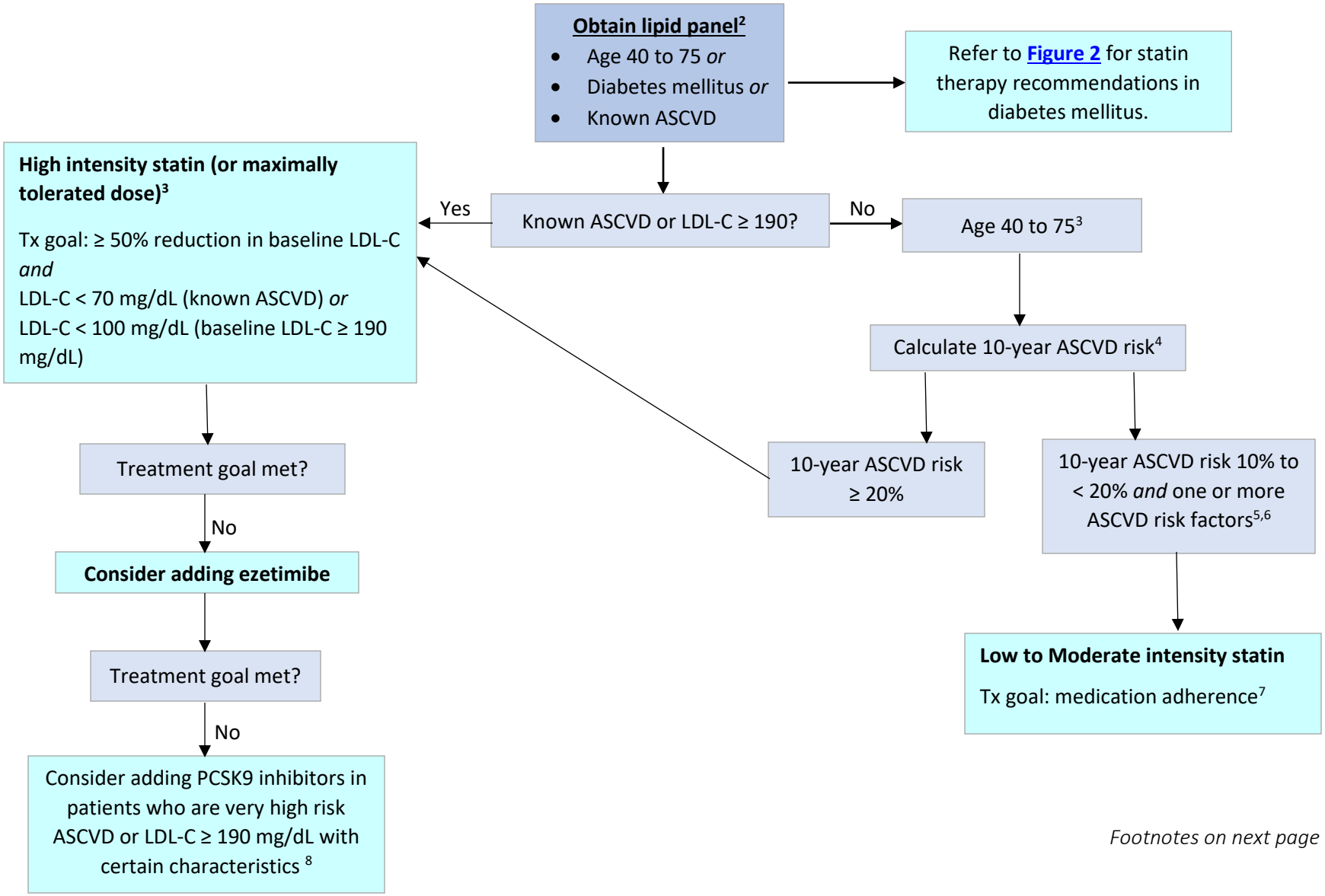
- A low to moderate dose statin for adults with no cardiovascular disease who meet all of the following criteria.
  - Age 40 to 75 (inclusive) and
  - One or more ASCVD risk factors (dyslipidemia, hypertension, or smoking) and
  - 10-year ASCVD risk ≥ 10%
- Treatment is considered optional (shared decision-making with the patient) when the ASCVD risk is 7.5 to 9.9%.
- There is insufficient evidence to make a recommendation for people 20-29 and ≥ 76 years of age.
- The USPSTF does not use LDL target treatment goals but recommends periodic monitoring of cholesterol levels to assess medication adherence.

ACC/AHA recommendations for primary prevention are more detailed and include further stratification of ASCVD risk into low, borderline, intermediate, and high risk categories. A moderate-intensity statin is recommended if a discussion of treatment options favors statin therapy in patients with borderline or intermediate risk, and a high-intensity or maximally tolerated statin dose is recommended for patients at high risk. Patient-clinician discussion should include:

- Potential benefits of treatment, risk of adverse effects, potential drug-drug interactions, lifestyle modification and evaluation for the presence of risk-enhancing factors.
- The goal of treatment to be a reduction in LDL-C levels by ≥ 30%. If 10-year risk is ≥ 20%, reduce LDL- C levels by ≥ 50%.

(Figure 1 begins on next page)

FIGURE 1. STATIN THERAPY TO REDUCE ASCVD RISK[1]



Footnotes on next page

1. There are notable differences in the recommendations for statin therapy published by the USPSTF, AHA/ACC, and ADA. This algorithm prioritizes the USPSTF recommendations for primary prevention of ASCVD when there is no known ASCVD, no diabetes, and LDL-C < 190 md/dL.

2. The guidelines referenced in this document do not address obesity as a risk factor for dyslipidemia and ASCVD, both of which are increased in obesity. The BOP recommends obtaining a lipid panel and conducting an ASCVD risk assessment in all patients, regardless of age, with a body mass index ≥ 30.

3. See *SECTION 4. SPECIAL POPULATIONS* for treatment of adult patients younger than 40 and the very elderly.

4. AHA/ACC recommends using 7.5% as the lower cutoff for starting statins.

5. USPSTF defines ASCVD risk factors as diabetes mellitus, dyslipidemia, hypertension, or smoking

6. AHA/ACC recommends consideration of risk-enhancing factors in making treatment decisions for patients with borderline or higher ASCVD risk (≥ 5%) who are undecided about statin therapy. See *TABLE 3* for a list of risk enhancer.

7. AHA/ACC recommends a treatment goal of 30%-49% LDL reduction in this group.

8. In patients with a baseline LDL-C ≥ 190, this recommendation applies to ages 30-75 years with FH and patients 40-75 years old with baseline LDL-C ≥ 220 mg/dL whose LDL-C remains ≥ 130 mg/dL on a maximally-tolerated statin and ezetimibe.

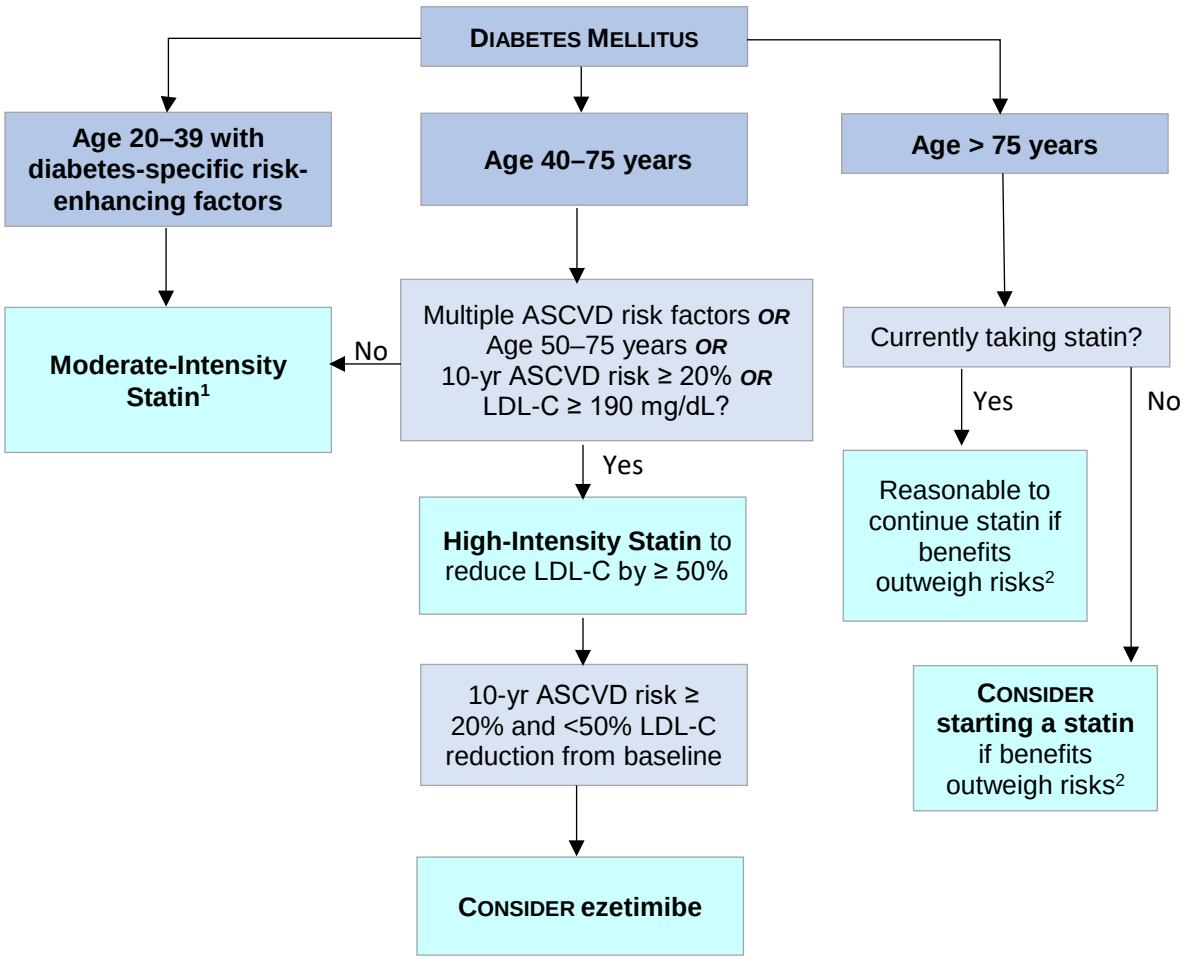
PRIMARY PREVENTION FOR PATIENTS WITH DIABETES MELLITUS (DM)

All patients aged 40–75 years, regardless of estimated 10-year ASCVD risk, with DM and LDL-C of 70–189 mg/dL should receive moderate-intensity statin, as shown in *FIGURE 2* below.

- The goal of treatment in most patients is a reduction of LDL-C by 30–49% from baseline.
- The ASCVD risk calculator and an evaluation of additional risk enhancers should be used to further identify those with high ASCVD risk who may require high-intensity statin therapy.

➔ *See TABLE 3 for a list of risk enhancers.*

FIGURE 2. STEPWISE APPROACH FOR PATIENTS WITH DM



[1] In 40 to 75 year old patients with diabetes, a moderate-intensity statin is recommended. However, in 20-39 year old patients with diabetes and additional diabetes-specific risk-enhancing factors, the evidence for using statin therapy is not as strong and a moderate intensity statin *may be reasonable*.

[2] See *SPECIAL POPULATIONS* for treatment of the very elderly.

4. SPECIAL POPULATIONS

ADULT PATIENTS YOUNGER THAN 40 YEARS OLD

The ASCVD risk calculator is only validated for patients 40 to 79 years old. However, in patients 20-39 years old without ASCVD or DM, and with baseline LDL-C < 190 mg/dL, the ASCVD risk calculator may be useful in assessing lifetime risk and educating patients on therapeutic lifestyle changes (see *SECTION 6*) that may help to lower their risk.

USPSTF indicates there is insufficient data to make a recommendation for statin therapy in this age group. ACC/AHA recommends statin therapy for patients in this category with any of the following conditions:

- Familial hypercholesterolemia – very high levels of LDL-C
- Consistently elevated LDL-C 160mg/dL or higher
- Family history of premature ASCVD

PRIMARY PREVENTION IN THE VERY ELDERLY (> 75 YEARS OF AGE)

The ASCVD risk calculator is only validated for patients 40 to 79 years old. However, for patients > 79 years old, a default age of 79 may be used to calculate 10-year ASCVD risk, which is usually > 10% in this population. These patients should be evaluated for the risks vs. benefits of initiating or continuing statin therapy.

- Although studies in this population group are limited, evidence has shown that while statin therapy reduces the incidence of non-fatal ASCVD events, therapy has not shown a reduction in mortality.
- USPSTF indicates there is insufficient data to make a recommendation for statin therapy in this age group.
- The 2018 ACC/AHA guidelines indicate that moderate-intensity statin therapy for primary prevention of ASCVD in patients > 75 years of age who have an LDL-C of 70–189 mg/dL may be reasonable. For patients with known ASCVD, initiating or continuing moderate- to high-intensity statin therapy is reasonable.
- The ADA guidelines recommend that in patients with diabetes and > 75 years of age already on statin therapy, it is reasonable to continue. In patients with diabetes and >75 years of age it may be reasonable to initiate statin therapy after discussion of benefits and risks.
- Polypharmacy may increase the risk of statin-associated effects.
- Consider discontinuing statins with functional decline, frailty, multi-morbidity, and reduced life expectancy.

PEOPLE LIVING WITH HIV/AIDS (PLWH)

As the life-span of this group increases, the occurrence of CVD also increases. Additionally, because of inflammation and reduced immune function associated with the virus, HIV/AIDS is an independent risk factor for an ASCVD event. Consequently, the ASCVD morbidity/mortality rate for PLWH is 1.5 to 2 times higher than those without HIV/AIDS.

- Periodic screening for lipid abnormalities is reasonable, however there is no evidence-based standard for how frequently to monitor. DHHS guidelines recommend annual lipid screening while the Infectious Disease Society of America guidelines recommend screening every 5 years with

increased screening if abnormal. Clinicians may use their clinical judgment when determining how frequently to screen for lipid abnormalities in these patients.

- Statin therapy for PLWH does not vary from that of the general population. Treatment goals are based on the treatment benefit group for which they are assigned, based on the individual's risk factors and risk-enhancers.
- Certain medications for HIV may cause dyslipidemia. Refer to the *BOP Clinical Guidance on the Management of HIV Infection* for additional information. Consult a BOP regional HIV consultant or infectious disease specialist prior to making any changes to HIV medication regimen.
- There are clinically significant drug interactions between some statins and medications for HIV:
  - Rosuvastatin is the preferred medication for patients taking protease inhibitors (PIs) or cobicistat. If adverse events occur, pravastatin is the preferred alternative.
  - **DO NOT** use simvastatin or lovastatin in patients taking PIs or cobicistat.
  - Atorvastatin doses may need to be adjusted in patients taking PIs or cobicistat.

  ➔ *For further information related to drug interactions, see the DHHS guidelines:* https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/367/overview

PATIENTS WITH VIRAL HEPATITIS

- Statins can be used in patients with chronic viral hepatitis. Dosage adjustments are not required unless aminotransferase values are > 3 times the upper limit of normal. If aminotransferases are elevated, statins should be started at a low dose.
- Pravastatin and rosuvastatin are less hepatically metabolized and are preferred agents in these patients. Monitor patients for myopathies while on hepatitis C virus (HCV) treatment and concurrent statin therapy. If myopathies occur, a statin dose reduction may be necessary.
- There are clinically significant drug interactions between some statins and HCV treatment regimens. The following combinations are not recommended:
  - Rosuvastatin with ledipasvir/sofosbuvir (Harvoni®)
  - Rosuvastatin or pitavastatin with sofosbuvir/velpatasvir/ voxilaprevir (Vosevi®)
  - Atorvastatin, simvastatin, or lovastatin with glecaprevir/pibrentasvir (Mavyret™)
- Dosage adjustment may be needed for some statins during treatment of HCV with certain direct acting antiviral medications.
- Patients with chronic viral hepatitis should be evaluated for treatment of the hepatitis.

PREGNANT WOMEN

- Evidence-based guidelines do not address the role of lipid screening during pregnancy. It is reasonable to follow general screening guidelines for non-pregnant patients.
- Pregnant women with dyslipidemia should be educated on proper diet, exercise, and other lifestyle changes. Exercise routine and intensity should be determined in consultation with the treating obstetrician.
- For pregnant women, bile acid sequestrants and omega-3 fatty acids are FDA Risk Category B. In patients with significantly elevated triglycerides (TG), fenofibrate and gemfibrozil may be considered (FDA Risk Category C).
- Statins are FDA Risk Category X and should not be used in pregnant patients.

CHRONIC KIDNEY DISEASE (CKD) PATIENTS

The ACC/AHA Task Force considers CKD to be a risk-enhancing factor for ASCVD.

CKD NOT TREATED WITH DIALYSIS OR KIDNEY TRANSPLANTATION

- Individuals who are 40–75 years of age with LDL-C 70–189 mg/dL and an estimated 10-year ASCVD risk ≥ 7.5% should be initiated on moderate-intensity statin therapy.

PATIENTS ON DIALYSIS

- Because data is limited or shows conflicting results or no benefit, the role of statin therapy for ASCVD risk reduction in dialysis patients is not clearly defined. Recommendations for statin use in this group are primarily based on expert opinion or extrapolation from other populations.
- Individuals who require dialysis, and are currently on statin therapy, may continue their statin therapy.
- Otherwise, statin therapy should **not** be initiated in individuals whose advanced CKD requires dialysis.

5. MANAGEMENT OF HYPERTRIGLYCERIDEMIA (HTG)

Triglyceride (TG) levels are considered moderately elevated at 175 to < 500 mg/dL and severely elevated if ≥ 500 mg/dL. In adults who are ≥ 20 years of age with a TG level of 400 mg/dL or higher, LDL-C calculations are inaccurate and a repeat lipid profile in the fasting state should be performed. Although there is an association between elevated triglyceride levels and coronary events, a causal relationship has not been established and treatment with non-statin medications has not consistently resulted in improved ASCVD outcomes. Persistently elevated fasting TG ≥ 175 mg/dL is considered a **RISK-ENHANCING FACTOR**, and assessment should be included as part of the ASCVD risk evaluation. Because HTG is often caused by other conditions, primary treatment involves lifestyle modifications and addressing secondary causes of HTG.

Patient education should be provided to all patients with TG ≥ 175mg/dL

- Eliminate dietary trans-fatty acids
- Increase fiber
- Reduce simple carbohydrates
- Weight loss of 5–10% (if overweight or obese)

Evaluate secondary causes of HTG

- Hypothyroidism
- Medications
- Renal disease
- Diabetes

RECOMMENDATIONS FOR PHARMACOLOGIC TREATMENT OF HTG

There are two goals of pharmacologic treatment of HTG: 1) reduce the risk of pancreatitis when TG levels are > 885 mg/dL (or ≥ 500 mg/dL in patients with a prior episode of pancreatitis), and 2) reduce ASCVD risk when TG levels are elevated.

Management for reduction of ASCVD risk: Consensus guidelines recommend **NOT** starting therapy unless the patient has other indications for ASCVD risk reduction. Lifestyle modifications and interventions for secondary causes of HTG are recommended **prior to** starting non-statin triglyceride-lowering medications.

- In patients with an indication for statin therapy, optimizing and / or intensifying the statin dose is recommended prior to adding other triglyceride-lowering medications. High intensity statin therapy alone may reduce TGs by 30–40%.
- If TG levels remain ≥ 150 to 175 mg/dL despite optimal/intensified statin therapy, consider non-statin triglyceride lowering medication - a fibrate or icosapent ethyl (Vascepa®).
  - When given with a statin, fenofibrate has less risk of inducing myalgia than gemfibrozil and is the preferred fibrate treatment option in the BOP.
  - Both niacin and omega-3 fatty acid (other than icosapent ethyl) failed to show ASCVD risk reduction in several large randomized controlled trials. For this reason, their use is not typically approved in the BOP.
- Icosapent ethyl omega-3 (Vascepa®), a highly refined omega-3 fatty acid, is approved as an add-on therapy to maximally-tolerated statin for patients with:
  - TG levels ≥ 150 mg/dL *and*
  - Established ASCVD *or*
  - Diabetes and two or more additional risk factors for cardiovascular disease

Severely elevated TG and/or risk for pancreatitis: Treatment targeting TG reduction should be initiated for these patients in order to reduce the risk of pancreatitis.

- For these patients, a fibrate is recommended and may lower triglyceride levels as much as 70%. If triglyceride levels remain ≥ 500 mg/dL, more intensive dietary modifications are recommended along with adding an omega-3 fatty acid (e.g. icosapent ethyl/Vascepa®, a highly refined omega-3 fatty acid).
- These patients commonly have an indication for a statin to reduce ASCVD risk, in addition to TG-targeted treatment. When given with a statin, fenofibrate has less risk of inducing myalgias than gemfibrozil and is the preferred treatment option in the BOP.

6. THERAPEUTIC LIFESTYLE CHANGES

A key component of both primary and secondary ASCVD prevention is a heart-healthy lifestyle, including eating a heart-healthy diet, maintaining a healthy body weight, regular aerobic exercise, and avoidance of tobacco products. Patients should be provided education on healthy lifestyle choices at each visit.

DIETARY GUIDANCE

The AHA/ACC recommendation for lowering LDL-C emphasizes a diet high in vegetables, fruit, and whole grains. Further recommendations include low-fat dairy products, poultry, fish, legumes, non-tropical vegetable oils, and nuts, as well as limited intake of sweets, sugar-sweetened beverages, and red meats.

Inmates should be counseled to eat reduced-calorie, low-sodium, and low-fat foods offered as part of the **Heart Healthy and No-Flesh** dietary menu through Food Services and to select healthy options in commissary. The treating clinician should review the inmate's current eating habits and make dietary recommendations accordingly.

The BOP Heart Healthy and No-Flesh food offerings consist of many of these healthier food items and can assist with meeting dietary recommendations associated with lowering cholesterol including:

- Reducing intake of saturated fat to < 7% of calories with target of 0% to 6% of energy from saturated fatty acids.
- Minimal intake of trans fatty acids
- Reducing cholesterol intake to <200 mg/day
- At least 5-10 g/day and preferably more (up to 25 g/day) of viscous fiber

WEIGHT MANAGEMENT

The degree of unhealthy weight can be assessed by determining the patient's BMI, which defines **healthy weight**, **overweight**, and **obesity** based on height and weight.

- **Obesity** is defined as a BMI of ≥ 30, and **overweight** as a BMI of 25–29. Some patients with a large muscle mass may be inaccurately classified as overweight when this method is used.
- Losing weight can be difficult for many patients. Health care providers should provide practical advice to patients and regularly reinforce attainable changes in daily dietary habits. Several provider resources and patient information handouts are available through the BOP Chief Dietitian's webpage regarding making healthy choices and achieving a healthy weight.

➔ *The AHA/ACC/TOS (The Obesity Society) Guideline for the Management of Overweight and Obesity in Adults is available at: http://circ.ahajournals.org/content/129/25_suppl_2/S102*

PHYSICAL ACTIVITY

Aerobic exercise and increased physical activity can, over time, result in significant weight loss and improved cardiovascular capacity.

- Health care providers should encourage inmates to participate in regular aerobic recreational activities (unless contraindicated) and to increase physical activity as part of their daily routines.
- To reduce LDL-C and non-HDL-C, the ACC/AHA recommends moderate to vigorous aerobic physical activity 3–4 sessions per week, lasting an average of 40 minutes per session.
- For patients who are deconditioned or who have risk factors for ASCVD, a pre-participation evaluation is recommended prior to the patient starting an exercise program.

7. MEDICATION MANAGEMENT

In most patients, drug therapy should be initiated with an **HMG-COA REDUCTASE INHIBITOR**, commonly referred to as a statin. Drug selection should be individualized based on the patient's risk factors, medical history, potential drug interactions, and other clinical considerations.

➔ *More information on medications for lipid disorders is in APPENDIX 2, Specific Drug Treatment Options for Lipid Disorders, and APPENDIX 3, Comparison of Medications for Hyperlipidemia.*

- The 2018 ACC/AHA Guidelines recommend treatment with the appropriate high-intensity or moderate-intensity statins therapy based on the treatment benefit group. TABLE 5 lists low-, medium-, and high-intensity statin regimens.
  ➔ *See SECTION 3, Treatment Benefit Groups.*

TABLE 5. STATIN INTENSITY

LOW-INTENSITY STATINS (< 30% expected LDL-C reduction)	MODERATE-INTENSITY STATINS (30–49% expected LDL-C reduction)	HIGH-INTENSITY STATINS (≥ 50% expected LDL-C reduction)
Pravastatin 10–20 mg	Atorvastatin 10–20 mg	Atorvastatin 40–80 mg
Fluvastatin 20–40 mg	Pravastatin 40–80 mg	Rosuvastatin 20–40 mg
Lovastatin 20 mg	Rosuvastatin 5–10 mg	
Pitavastatin 1 mg	Fluvastatin 40mg BID	
Simvastatin 10 mg	Fluvastatin XL 80 mg	
	Lovastatin 40 mg	
	Pitavastatin 2–4 mg	
	Simvastatin 20–40 mg	
Items in red are non-formulary in the BOP.		

MONITORING WHILE ON TREATMENT

The FDA revised its guidance to recommend **LIVER FUNCTION TESTING** prior to initiation of statin therapy and then repeated **ONLY IF** there are clinical indications. Routine monitoring is not necessary.

The percentage reduction of LDL-C is used in follow-up monitoring of patients to estimate the efficacy of statin therapy.

- As a rough guide, a lowering of LDL-C levels of 1% gives an approximate 1% reduction in the risk of ASCVD—somewhat more at higher baseline LDL-C levels, and somewhat less at lower baseline levels.
- Response to therapy should be measured with a repeat lipid panel 4–12 weeks after statin initiation or dose adjustment, repeated every 3–12 months as needed.
- For primary prevention, the USPSTF guidelines did not find clinical evidence supporting the titration of medications to a specified target LDL-C or non-HDL-C levels. A given dose of statins produces a similar percentage reduction in LDL-C levels across a broad range of baseline LDL-C levels.
- The ACC/AHA guidelines recommend treating to a goal of LDL-C ≤ 70 mg/dL for patients at very-high risk of ASCVD and a goal of LDL-C ≤ 100 mg/dL for patients with severe hypercholesterolemia (baseline LDL ≥ 190 mg/dL).

STATIN-ASSOCIATED SIDE EFFECTS

Approximately 10–25% of patients prescribed statins cannot tolerate the recommended intensity (e.g. moderate or high intensity) of a particular statin therapy—or sometimes any statin—because of adverse events. For patients unable to tolerate the recommended intensity of statin therapy, lowering the statin dose to the highest tolerable (i.e. maximally tolerated) dose is recommended. In the event of discontinuation due to reported side effects, if not severe, a rechallenge with the same or equivalent-dosed statin is recommended. **DISCONTINUATION OF STATINS MAY BE ASSOCIATED WITH INCREASED RISK OF ASCVD EVENTS.**

➔ *See information on significant side effects of statins in APPENDIX 2.*

- Hepatoxicity, defined as aminotransferase elevation greater than 3 times the upper limit of normal, is rare. Baseline LFTs should be checked prior to initiation and then only if the patient reports new onset myalgia or weakness.
  - If hepatotoxicity is suspected, options include using a different statin (pravastatin recommended), dose reduction, or alternative-day dosing.

STATIN-ASSOCIATED MUSCLE SYMPTOMS

One of the most common side effects of statin therapy is muscle symptoms, which may occur without an increase in creatinine kinase (CK). Symptoms often occur within two weeks of statin initiation or increased dose and resolve within 1–2 weeks after stopping the statin.

The incidence of muscle symptoms may be increased due to a patient's heightened awareness of side effects, and then attributing pain from a comorbidity to the statins. For this reason, it is important to thoroughly evaluate patient complaints of muscle symptoms, in order to determine the cause of the symptoms. (*See **FIGURE 3***.)

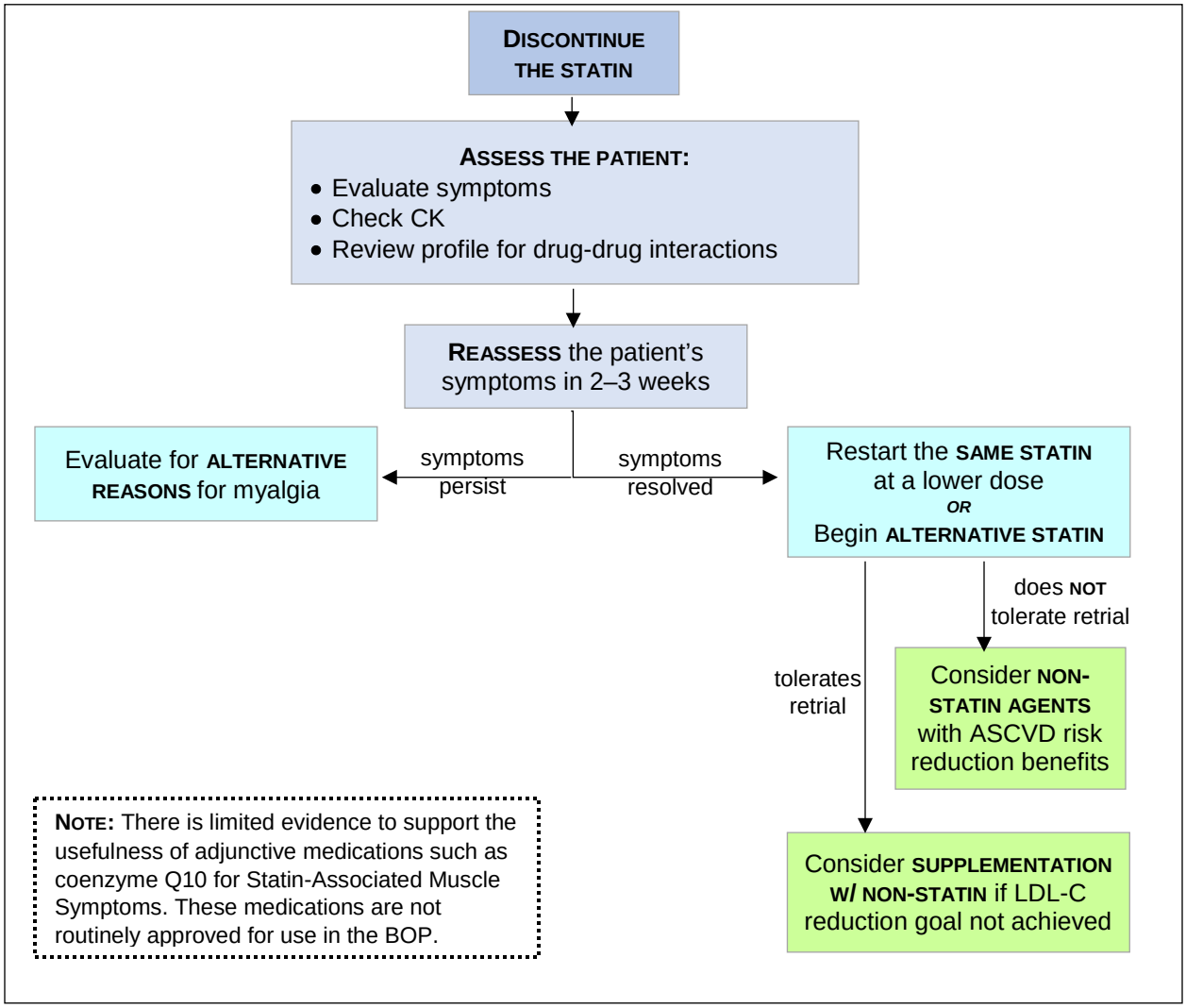
COMMON MUSCLE SYMPTOMS ASSOCIATED WITH STATIN USE INCLUDE THE FOLLOWING:

- Myalgia – typically bilateral and include large muscle groups
- Cramps – typically unilateral and occur in smaller muscle groups
- Muscle weakness

THESE CHARACTERISTICS MAY PREDISPOSE PATIENTS TO MUSCLE SYMPTOMS:

- Physical disability
- Lower BMI or reduced muscle mass
- Hypothyroidism
- Vitamin D deficiency
- ALT elevations > 3x ULN
- Use of other drugs affecting statin metabolism
- Age > 75 years old
- Hemorrhagic stroke history
- Asian ancestry

FIGURE 3. ASSESSMENT AND MANAGEMENT OF STATIN-ASSOCIATED MUSCLE SYMPTOMS



NON-STATIN THERAPIES FOR LDL-C

EZETIMIBE

Ezetimibe is the most commonly used non-statin agent. It inhibits the absorption of dietary and biliary cholesterol and, when added to statins, may lower LDL-C by 13–20%. Adverse reactions are minimal and may include fatigue, diarrhea, arthralgia, and respiratory tract infection. Follow monitoring recommendations for the statin being prescribed with it.

BILE ACID SEQUESTRANTS

Bile acid sequestrants include cholestyramine, colestipol, and colesevelam. While bile acid sequestrants are not systemically absorbed, gastrointestinal side effects are a frequent complaint.

> **NOTE:** These medications can cause severe hypertriglyceridemia and should not be used in patients with fasting triglycerides > 300mg/dL.

PROPROTEIN CONVERTASE SUBTILISIN/KEXIN TYPE 9 (PCSK9) INHIBITORS

PCSK9 inhibitors are a class of injectable human monoclonal antibody (IgG1 isotype) medications that bind to PCSK9, which binds to the low-density lipoprotein receptors on hepatocyte surfaces to promote LDLR degradation within the liver. LDLR is the primary receptor that clears circulating LDL. PCSK9 inhibitors may lower LDL-C up to 70% when added to statins. The two currently available medications include alirocumab and evolocumab.

> **NOTE:** The 2018 ACC/AHA guidelines classifies PCSK9 inhibitors as having "low-cost value" for patients with known ASCVD and uncertain cost vlue for patients with LCL-C ≥ 190 mg/dL.

NIACIN AND FENOFIBRATES

These medications have modest effects on LDL-C, but are not classified as LDL-lowering medications and should **not regularly** be used for LDL-C lowering. They may be considered for use in patients with hypertriglyceridemia.

8. PERIODIC EVALUATIONS

Periodic medical evaluations should be conducted as clinically indicated and in accordance with BOP policy for inmates enrolled in a chronic care clinic.

➔ *See APPENDIX 1, EVALUATION OF INMATES, for more details on the relevant sections listed below.*

MEDICAL HISTORY

The periodic patient interview should focus on the following:

- Review of progress in modifying ASCVD risk factors.
- Assessment of adherence to dietary therapy.
- Assessment of adherence to drug therapy and the presence of drug side effects.

PHYSICAL EXAMINATIONS

Performed as clinically warranted, physical examinations should target the following:

- Measurement of vital signs, including blood pressure.
- Measurement of weight and waist circumference.
- Examination of the heart, lungs, pulses, and extremities, with auscultation over the carotid and femoral arteries for bruits.

DIAGNOSTIC AND LABORATORY EVALUATIONS

The management of inmates with high blood cholesterol requires a multidisciplinary effort of the entire health services staff. Pharmacists and nurses can assist clinicians by providing inmates with information on diet modifications and medication use, and by monitoring for adherence to treatment and for occurrence of adverse drug reactions. Pharmacists, through a Collaborative Practice Agreement with the Clinical Director, can order and review laboratory work and provide medication management for lipid disorders.

- The LDL-C (as part of a lipid panel) should be measured 4–12 weeks after beginning or adjusting medication. Once LDL-C goals are met, it is reasonable to obtain a lipid panel annually or more frequently as clinically indicated (e.g. for inmates with poorly controlled hyperlipidemia, particularly when associated with underlying ASCVD and PAD).
- Drug side effects should be monitored by patient history and with laboratory evaluations, as clinically indicated.

9. INMATE EDUCATION

All inmates with elevated blood cholesterol and/or increased risk for ASCVD should receive education from a health care provider at the time of diagnosis and periodically during clinician evaluations and interactions with medical staff.

- Inmates should be counseled on the risks of elevated cholesterol, the importance of modifying ASCVD risk factors, specific treatment recommendations, and drug side effects.
- Inmates with ASCVD or severe or poorly controlled lipid disorders require more intensive individual or group educational efforts.

➔ *Patient education resources are available through BEMR, including handouts for high cholesterol, coronary artery disease, and nutrition.*

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OTHER RESOURCES FOR HEALTHCARE PROVIDERS

American College of Cardiology

- Website: ***https://www.acc.org/***
- "Guideline Hub" on Blood Cholesterol: *https://www.acc.org/guidelines/hubs/blood- cholesterol*

American Heart Association

- Website: ***https://www.heart.org/***
- Cholesterol Management Guide for Healthcare Practitioners: *https://www.heart.org/-/media/files/health-topics/cholesterol/chlstrmngmntgd_181110.pdf*
  (27-page, easy-to-follow summary of the ACA/ACC 2018 Cholesterol Guideline)

Centers for Disease Control and Prevention

- Website on Healthy Weight: *http://www.cdc.gov/healthyweight/index.html*

DEFINITIONS

Acute coronary syndrome (ACS) is a general term for clinical presentations of myocardial ischemia such as unstable angina and both Q-wave and non-Q-wave myocardial infarction (MI).

Atherosclerotic Cardiovascular Disease (ASCVD) is defined as acute coronary syndromes (ACSs), a history of myocardial infarction (MI), stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease presumed to be of atherosclerotic origin.

Body mass index (BMI) is a measure of a person's weight in relation to his or her height. The BMI equals the weight in pounds divided by the square of the height in inches, multiplied by 703; alternatively, the weight in kilograms divided by the square of the height in meters. BMI is highly correlated with total body fat and is used to assess for conditions of overweight and obesity.

➔ *BMI is available under "inmate detail" in BEMR or can be calculated here: http://www.nhlbi.nih.gov/health/educational/lose_wt/BMI/bmicalc.htm*

Cholesterol is a fat-like substance that is present in cell membranes and is a precursor to steroid hormones and bile acids.

Clinician is a physician, a mid-level provider, or an appropriately credentialed pharmacist.

Coronary atherosclerosis is the deposition of cholesterol and fibrin complexes within the lumen of a coronary artery that narrows the lumen, thereby limiting blood flow.

Coronary heart disease (CHD) (also known as coronary artery disease or ischemic heart disease) is atherosclerosis of one or more coronary arteries. Conditions associated with CHD may include angina pectoris, myocardial infarction, or congestive heart failure requiring coronary artery surgery or coronary angioplasty.

High density lipoproteins (HDL) are lipoproteins that contain 20–30% of total serum cholesterol and are inversely correlated with CHD risk.

Lipoproteins are lipid-containing proteins in the blood that transport cholesterol throughout the body.

Lipoprotein analysis is the measurement of levels of total cholesterol, total triglyceride, and LDL and HDL cholesterol.

Low density lipoproteins (LDL) are lipoproteins that contain 60–70% of the total serum cholesterol. *LDL cholesterol = Total cholesterol – HDL cholesterol – (Triglycerides/5)*. (This calculation is invalid if triglycerides are > 400 mg/dL.) LDL is often called "bad cholesterol" because it leads to a cholesterol build-up in the arteries.

Metabolic syndrome is a constellation of factors associated with insulin resistance and obesity that increase the risk of coronary events at every LDL-C level. Metabolic syndrome is diagnosed when three or more of the following risk determinants are present:

- Fasting glucose between 100–110 mg/dL
- Blood pressure ≥ 130/≥ 85 mm Hg
- Triglycerides ≥ 150 mg/dL
- HDL < 40 mg/dL for men and < 50 mg/dL for women
- Abdominal obesity (waist circumference > 40 inches for men and > 35 inches for women)

Peripheral arterial disease (PAD) is the presence of atherosclerotic disease in any of the blood vessels outside the heart—as evidenced by abdominal aortic aneurysms, clinical signs or symptoms of ischemia

to the extremities or to the brain (transient ischemic attacks or stroke), and documented by significant atherosclerosis on sonogram, angiogram, or other diagnostic studies.

Very high risk ASCVD is defined as ≥ 2 major ASCVD events **or** major ASCVD event plus a high-risk condition, as listed in ***TABLE 4*****.**

APPENDIX 1. EVALUATION OF INMATES

MEDICAL HISTORY

All patients should be evaluated for increased ASCVD risk at baseline and then routinely thereafter. Assessment should include review and documentation of the following:

- **AGE, SEX, AND RACE**
- **CLINICAL ASCVD CONDITIONS AND RISK ENHANCERS**
  - See ***TABLE 1*** for criteria for clinical ASCVD.
  - See ***TABLE 3*** for risk enhancers.
- **FAMILY HISTORY:** Family history of premature cardiovascular disease (< age 55 in men, < age 65 in women), hypertension, diabetes mellitus, renal disease, or dyslipidemia.
- **MEDICATION HISTORY AND HABITS:** Assessment of current medications that may raise LDL-C or lower HDL-C, including progestins, anabolic steroids, corticosteroids, thiazide diuretics, retinoids (e.g., isotretinoin), and HIV protease inhibitors or other antiretroviral therapies.
- **DIETARY/LIFESTYLE HABITS**
- **SOCIAL HISTORY**
  - Attention to relevant portions of the social history, including history of alcohol intake and illicit drug usage (including anabolic steroid use).
  - Attention to factors that may affect the inmate's ability to understand or participate in treatment recommendations such as educational level, language and cultural barriers, or physical and mental disabilities.

REVIEW OF SYSTEMS

- **CARDIOVASCULAR SYSTEM**: Review for symptoms of cardiovascular disease and peripheral arterial disease (PAD), as well as secondary causes of elevated LDL-C, including hypothyroidism, diabetes, nephrotic syndrome, obstructive liver disease, and HIV infection treated with protease inhibitors.
- *See also **TABLE 1** for clinical ASCVD criteria and **TABLE 3** for ASCVD risk enhancers.*
- **GENITOURINARY SYSTEM:** Review for presence or absence of symptoms of renal disease (e.g., hematuria, prior calculi, nocturia, abnormal urinalysis, edema) and history of previous evaluations such as intravenous pyelogram studies or ultrasonography.
- **ENDOCRINE SYSTEM**: Review for presence or absence of symptoms of pheochromocytoma (sporadic attacks of hypertension and symptoms of headache, tachycardia, and sweating), hyperthyroidism, hypothyroidism, hyperparathyroidism, or Cushing's syndrome.

PHYSICAL EXAMINATION

The physical examination should include a focused evaluation for evidence of ASCVD and PAD, hypertension and associated target organ damage, and secondary causes of lipid disorders. **The examination should include:**

- **VITAL SIGNS, INCLUDING HEIGHT AND WEIGHT**

- **CALCULATION OF BODY MASS INDEX (BMI):** BMI is available under "inmate detail" in BEMR or can be calculated here: *http://www.nhlbi.nih.gov/health/educational/lose_wt/BMI/bmicalc.htm*
  Normal: BMI = 18.5–24.9
  Overweight: BMI = 25–29.9
  Obesity: BMI = 30–34.9 (class I obese)
  BMI = 35–39.9 (class II obese)
  BMI ≥ 40 (class III obese)
- **FUNDUSCOPIC EXAM**: Check for evidence of retinopathy (A-V nicking, hemorrhages, or exudates with or without papilledema).
- **EXAMINATION OF THE NECK**: Check for carotid bruits, distended veins, and thyroid palpation
- **CARDIAC EXAMINATION**: Check rate and rhythm, precordial heave, clicks, murmurs, and gallops; assessment for cardiomegaly.
- **PULMONARY EXAM**: Check for evidence of rales or wheezing.
- **EXAMINATION OF THE ABDOMEN**: Check for bruits, enlarged kidneys, masses, or abnormal aortic pulsation.
- **EXAMINATION OF THE EXTREMITIES**: Check for diminished or absent peripheral arterial pulsations, femoral bruits, or edema.
- **SCREENING NEUROLOGICAL EXAM**
- **SKIN EXAM:** Check for café-au-lait spots, xanthomas, and stigmata of Cushing's syndrome.

DIAGNOSTIC EVALUATIONS

- Screening and risk assessment for lipid disorders are conducted as part of the BOP preventive health care services, as outlined in the BOP Clinical Guidance for Preventive Health Care.
- Each inmate's risk factor(s) for lipid disorders should be assessed at the Baseline Prevention Visit and no less than every 5 years thereafter.

APPENDIX 2. SPECIFIC DRUG TREATMENT OPTIONS FOR LIPID DISORDERS

Medication/ Dose Range	Significant Side Effects	Dosing Considerations	Common Drug Interactions
HMG CoA REDUCTASE INHIBITORS (STATINS) [3,4]			
ATORVASTATIN Lipitor® 10–80 mg/day	• Headache • Nausea • Sleep disturbances • Myostitis and rhabdomyolysis (increased risk when given with gemfibrozil)	**RENAL IMPAIRMENT:** No dosage adjustment necessary. **HEPATIC IMPAIRMENT:** Contraindicated in severe liver disease or unexplained transaminase elevations.	• Interacts with drugs metabolized by CYP3A4 enzyme system,[5] but less than lovastatin and simvastatin. • If cobicistat, then max dose of atorvastatin is 20 mg/day.
PRAVASTATIN Pravachol® 10–80 mg/day		**RENAL IMPAIRMENT:** Do not exceed 10mg/day in severe impairment. **HEPATIC IMPAIRMENT:** Contraindicated in severe liver disease or unexplained transaminase elevations.	• Not metabolized by cytochrome P450 system, so less likely to have drug interactions. • Cyclosporine can increase pravastatin levels. • Can be used with protease inhibitors using low dose (consult with HIV pharmacist).
ROSUVASTATIN Crestor® 5–40 mg/day		**RENAL IMPAIRMENT:** CrCl < 30mL/minute/1.73m^2: Initial: 5mg/day (max 10mg/day) **HEPATIC IMPAIRMENT:** Contraindicated in severe liver disease or unexplained transaminase elevations.	• Not metabolized by cytochrome P450 system, so less likely to have drug interactions • May increase INR with warfarin. • If darunavir/cobicistat, then max dose of rosuvastatin = 20mg/day. • If atazanavir/cobicistat, then max dose of rosuvastatin = 10mg/day.
FLUVASTATIN[1] Lescol® Immediate Release: 20–80 mg/day Extended Release: 80 mg/day		• Divide dose to twice per day if dose > 40mg/day. **RENAL IMPAIRMENT:** Use with caution in severe renal impairment. Do not exceed 40mg/day. **HEPATIC IMPAIRMENT:** Contraindicated in severe liver disease or unexplained transaminase elevations.	• Metabolized by CYP2C9, *not* CYP3A4, and may be less likely to be involved in drug interactions. • Can increase warfarin, phenytoin, and NSAID levels. • Rifampin can lower fluvastatin levels. • Can be used with protease inhibitors.
LOVASTATIN[1] Mevacor® Immediate Release: 10–80 mg/day Extended Release: 20–60 mg/day		• Divide dose twice per day with meals if dose > 20mg/day. **RENAL IMPAIRMENT:** CrCl < 30mL/minute; do not exceed 20mg/day. **HEPATIC IMPAIRMENT:** No adjustment necessary (has not been studied).	• Interacts with drugs metabolized by CYP3A4 enzyme system.[5] • Warfarin, digoxin.

[1] *Medications in RED are non-formulary in BOP for hyperlipidemia (some are approved for other indications).*
[2] *The SIDE EFFECTS listed for the drugs in this table is not all-inclusive; the provider should refer to drug reference for a full list.*

Medication/ Dose Range	Significant Side Effects	Dosing Considerations	Common Drug Interactions
SIMVASTATIN[1] Zocor® 5–40 mg/day	Same as for other statins, as listed above.	• Patients should not be prescribed doses > 40mg daily unless they have been taking that dose for > 12 months without evidence of myopathy. **RENAL IMPAIRMENT:** No adjustment necessary for mild to moderate impairment. For severe impairment, do not exceed 5mg/day, with close monitoring. **HEPATIC IMPAIRMENT:** Contraindicated in severe liver disease or unexplained transaminase elevations.	• Interacts with drugs metabolized by CYP3A4 enzyme system.[5]
NOTES ON STATINS: [3] Use only one statin at a time, titrating to target dose before switching. [4] Consult drug information resource for further drug interaction evaluation. [5] Watch for drug interactions that inhibit this enzyme including: diltiazem, erythromycin, clarithromycin, ketoconazole, verapamil, nefazodone, fluvoxamine, cyclosporine, and protease inhibitors.			
BILE ACID SEQUESTRANTS			
CHOLESTYRAMINE[1] LoCholest® Questran® Prevalite® 4–24 gm/day	• GI effects: nausea, bloating, cramping, and constipation • Impaired absorption of folic acid and fat-soluble vitamins (A-D-E-K). • Contraindicated in patients with history of bowel obstruction or TGs > 500 mg/dL.	• Take within 30 minutes of a meal. • A double dose with dinner produces the same lipid-lower effect as twice-daily dosing. • Dose 1-6 times daily. • Take before meals. Do not consume dry powder. **RENAL IMPAIRMENT:** No dosage adjustments provided, use with caution. **HEPATIC IMPAIRMENT:** No dosage adjustment necessary	• May impair absorption of many drugs; consult drug information resource; separate by 1 hour before and 4 hours after the bile acid sequestrant.
COLESTIPOL[1] Colestid® Granules: 5–30 gm/day Tablets: 2–16 gm/day		• Take within 30 minutes of a meal. • A double dose with dinner produces the same lipid-lowering effect as twice-daily dosing. **RENAL IMPAIRMENT:** No dosage adjustment necessary **HEPATIC IMPAIRMENT:** No dosage adjustment necessary	
COLESEVELAM[1] Welchol® 3.75 gm/day		• Take with meals once daily or in two divided doses. **RENAL IMPAIRMENT:** No dosage adjustment necessary. **HEPATIC IMPAIRMENT:** No dosage adjustment necessary.	
*[1] Medications in **RED** are non-formulary in BOP for hyperlipidemia (some are approved for other indications).* *[2] The **SIDE EFFECTS** listed for the drugs in this table is not all-inclusive; the provider should refer to drug reference for a full list.*			

(Appendix 2, Specific Drug Treatment Options for Lipid Disorders, page 2 of 4)

Medication/ Dose Range	Significant Side Effects	Dosing Considerations	Common Drug Interactions
NIACIN			
NIACIN EXTENDED-RELEASE TABLETS[1] Niaspan® 500–2000 mg/day	• Flushing • Headache • Hyperpigmentation • Dry skin • GI symptoms: nausea, vomiting, diarrhea, peptic ulcer aggravation • Myositis	• Take at bedtime (after a low-fat snack). • Adjust dose every 4 weeks, as needed. • Take aspirin or ibuprofen ½ hour before administration to decrease flushing. • Take with meals. • Avoid drinking hot drinks at time of dosing. **RENAL IMPAIRMENT:** No dosage adjustments provided, use with caution. **HEPATIC IMPAIRMENT:** Contraindicated in severe liver disease or unexplained transaminase elevations.	• May increase the risk of rhabdomyolysis with rosuvastatin.
FIBRIC ACIDS			
GEMFIBROZIL Lopid® 1200 mg/day	• Myositis • Myopathy • Thrombocytopenia • Rhabdomyolysis • Hepatotoxicity • Pancreatitis • Cholelithiasis • Hypersensitivity • Cholestatic jaundice	• Initial dose 600 mg twice-daily, 30 minutes before morning and evening meals. • Discontinue after 3 months of maximum dose if inadequate response. **RENAL IMPAIRMENT:** Do not use in patients with SCr > 2mg/dL. Contraindicated in severe renal impairment. **HEPATIC IMPAIRMENT:** No dosage adjustments provided; use is contraindicated.	• Statins generally contraindicated due to increased risk of rhabdomyolysis and myopathy, which may occur acutely a few weeks to several months after combined therapy. (Periodic monitoring of CK is not helpful when monitoring risk.) • Anticoagulants may increase risk of bleeding (frequent monitoring needed). • Many other significant interactions noted; consult drug information for interaction evaluation.
FENOFIBRATE[1] Tricor® Antara® Lofibra® Triglide® Dose range depends on brand.	• Skin rash • GI complaints • Myalgia	• Take once-daily with main meal. • Discontinue after 2 months of maximum dose if inadequate response. **RENAL IMPAIRMENT:** • Dosing dependent upon brand, refer to drug reference. • For all brands, use is contraindicated if: CrCl < 30 mL/minute/1.73m^2. **HEPATIC IMPAIRMENT:** Use is contraindicated	• Monitor closely if given with statins for symptoms of myopathy, which may occur acutely a few weeks to several months after combined therapy. (Periodic monitoring of CK is not helpful when monitoring risk). • Anticoagulants may increase risk of bleeding (frequent monitoring is needed). • Cyclosporine increases risk of nephrotoxicity. Benefits must outweigh risks; use lowest possible dose.

[1] *Medications in **RED** are non-formulary in BOP for hyperlipidemia (some are approved for other indications).*
[2] *The **SIDE EFFECTS** listed for the drugs in this table is not all-inclusive; the provider should refer to drug reference for a full list.*

(Appendix 2, Specific Drug Treatment Options for Lipid Disorders, page 3 of 4)

Medication/ Dose Range	Significant Side Effects	Dosing Considerations	Common Drug Interactions
CHOLESTEROL ABSORPTION INHIBITOR			
EZETIMIBE[1] Zetia® 10 mg/day	• Myalgia	**RENAL IMPAIRMENT:** No dosage adjustment recommended. **HEPATIC IMPAIRMENT:** Use is not recommended in severe impairment (Child-Pugh score 7–15).	• Cyclosporine may significantly increase ezetimibe levels (~12-fold). Monitor carefully. • Fibric acids increase ezetimibe bioavailability and may lead to cholelithiasis. Use with caution. • Cholestyramine decreases ezetimibe AUC >50%. Administer at least 2 hours before or 4 hours after bile acid sequestrant.
PCSK9 (PROPROTEIN CONVERTASE SUBTILISIN/KEXIN TYPE 9) INHIBITORS			
ALIROCUMAB[1] Praluent® 75mg Q 2 weeks or 300 mg Q 4 weeks **EVOLOCUMAB**[1] Repatha® 140 mg Q 2 weeks or 420mg Q month	• These medications appear to be relatively safe. However, due to the limited use of these medications, long-term safety and efficacy is not yet known. The provider should refer to a medical reference before prescribing. • Injection site reactions	**RENAL IMPAIRMENT:** No dosage adjustments recommended (has not been studied). **HEPATIC IMPAIRMENT:** No dosage adjustments recommended (has not been studied).	• No significant drug interactions reported with commonly used medications.
OMEGA-3 FATTY ACIDS			
OMEGA-3S[1] Lovaza® Once-daily dose of 4 grams or divided into twice-daily doses of 2 grams, depending on brand	• Diarrhea • Nausea	**RENAL IMPAIRMENT:** No dosage adjustments recommended (has not been studied) **HEPATIC IMPAIRMENT:** No dosage adjustments recommended (has not been studied)	• May enhance antiplatelet effects of antiplatelet agents. • May enhance the anticoagulation effects of anticoagulants.
ICOSAPENT ETHYL Vascepa® 2 grams twice daily	• Long-term safety and efficacy is not yet known. The provider should refer to a medical reference before prescribing.	**RENAL IMPAIRMENT:** No dosage adjustments recommended (has not been studied) **HEPATIC IMPAIRMENT:** No dosage adjustments recommended (has not been studied)	• May enhance antiplatelet effects of antiplatelet agents. • May enhance the anticoagulation effects of anticoagulants.

[1] *Medications in **RED** are non-formulary in BOP for hyperlipidemia (some are approved for other indications).*
[2] *The **SIDE EFFECTS** listed for the drugs in this table is not all-inclusive; the provider should refer to drug reference for a full list.*

(Appendix 2, Specific Drug Treatment Options for Lipid Disorders, page 4 of 4)

APPENDIX 3. COMPARISON OF MEDICATIONS FOR HYPERLIPIDEMIA

Drug	Levels of Therapy		Effect on Lipids (% change from baseline)		
			LDL	TG	HDL
HMG CoA REDUCTASE INHIBITORS (STATINS)					
ATORVASTATIN	Moderate-Intensity	10 mg	↓34–39	↓13–19	↑4–6
		20 mg	↓41–46	↓20–26	↑5–9
	High-Intensity	40 mg	↓48–51	↓29–32	↑5–6
		80 mg	↓54–60	↓25–37	↑5
PRAVASTATIN	Low-Intensity	10 mg	↓19–22	↓3–15	↑7–10
		20 mg	↓24–32	↓11–15	↑2–3
	Moderate-Intensity	40 mg	↓33–34	↓10–24	↑6–12
		80 mg	↓37	↓19	↑3
ROSUVASTATIN	Moderate-Intensity	5 mg	↓43	↓21–35	↑3–13
		10 mg	↓50	↓10–37	↑8–14
	High-Intensity	20 mg	↓53	↓23–37	↑8–22
		40 mg	↓62	↓28–43	↑10–17
FLUVASTATIN	Low-Intensity	20 mg	↓17–22	↓5	↑1
		40 mg	↓23–27	↓10–20	↑4–8
	Moderate-Intensity	40 mg bid	↓33–36	↓15–25	↑4–8
Lovastatin	Low-Intensity	20 mg	↓25–29	↓12–13	↑6–8
	Moderate-Intensity	40 mg	↓31–34	↓2–10	↑5
		80 mg	↓41–48	↓13–15	↑4–8
SIMVASTATIN	Low-Intensity	10 mg	↓28–30	↓12–15	↑7–12
	Moderate-Intensity	20 mg	↓35–38	↓15–17	↑5–8
		40 mg	↓40–41	↓15–18	↑9–10
NON-STATINS					
BILE ACID SEQUESTRANTS	n/a		↓15–30	No change or increase	0 to slight increase
NIACIN	n/a		↓10–25	↓25–30	↑15–35
GEMFIBROZIL	n/a		↓10–15	↓35–50	↑5–20
FENOFIBRATE (miconized)	n/a		↓6–20	↓41–53	↑5–20
EZETIMIBE	n/a		↓17	↓7–8	↑1
PCSK9 INHIBITORS	n/a		↓38–72	↓2–23	↑4–9
OMEGA 3 FATTY ACIDS	n/a		↑ 4–49	↓23–45	↑5–9
OMEGA 3 FATTY ACIDS (ICOSAPENT EHTYL)	n/a		No sig effect	↓23–45	↑5–9
Medications in RED are non-formulary in BOP for hyperlipidemia (some are approved for other indications).					
Adapted from: Rosenson RS. Statins: actions, side effects, and administration. UpToDate. Waltham, MA: UpToDate, Inc. Last updated November 19, 2018					