

## Atherosclerotic Cardiovascular Disease (ASCVD) Secondary Prevention Guideline

Major Changes as of April 2023	
Definitions	
Target Population	
Goals	2
Lifestyle Modifications	3
Dietary Supplements	
Influenza Vaccination	
Statin Therapy	
Icosapent Ethyl for ASCVD Reduction	
ACE Inhibitor or ARB Therapy	
SGLT2 Inhibitors for Patients with Type 2 Diabetes	
Antiplatelet Therapy	
Lowering Triglycerides to Prevent Pancreatitis	
Beta-blocker Therapy for Post-MI Patients	
Medication Monitoring	
Note: Chronic Disease Management Support	
Evidence Summary	
References	
Guideline Development Process and Team	18

#### Last guideline approval: April 2023

**Guidelines** are systematically developed statements to assist patients and providers in choosing appropriate health care for specific clinical conditions. While guidelines are useful aids to assist providers in determining appropriate practices for many patients with specific clinical problems or prevention issues, guidelines are not meant to replace the clinical judgment of the individual provider or establish a standard of care. The recommendations contained in the guidelines may not be appropriate for use in all circumstances. The inclusion of a recommendation in a guideline does not imply coverage. A decision to adopt any particular recommendation must be made by the provider in light of the circumstances presented by the individual patient.

## Major Changes as of April 2023

- **PCSK9 inhibitors** may now be ordered directly by primary care providers; consultation with Cardiology or Endocrinology is no longer required.
- **SGLT2 inhibitors** are recommended for patients with type 2 diabetes and established ASCVD (in addition to or after metformin therapy) due to their ability to reduce the risk of major cardiovascular (CV) events.
- For patients at very high risk of ASCVD, an LDL target of well below 70 mg/dL may be considered. Very high risk of ASCVD is defined as a history of multiple major ASCVD events or one major ASCVD event in the presence of multiple high-risk conditions (see "Cholesterol and lipid goals for patients on statin therapy," page 6). An exact LDL target has not been defined in this population.
- In-hospital influenza vaccination after an acute MI is recommended based on evidence that it is associated with a lower risk of CV mortality and all-cause mortality in patients with CVD.
- The blood pressure target for patients at high risk (age ≥ 75, with CKD, or with ASCVD) was changed from 130/80 to 130/90, to be in alignment with the KP National Blood Pressure Guideline.
- Clinicians should consider reducing rosuvastatin dose to 10 mg daily for patients with CKD 4–5 (eGFR < 30 mL/min).</li>
- A Virtual Cardiac Rehab Program designed to reduce risk of future cardiac events and improve
  patient quality of life is available at KPWA. The program includes regular meetings with a
  program nurse to set goals, check on progress, and provide education.

### **Definitions**

**Clinical ASCVD, or atherosclerotic cardiovascular disease,** is caused by plaque buildup in arterial walls and refers to the following conditions:

- Coronary heart disease (CHD), such as myocardial infarction (MI), angina, and coronary artery stenosis > 50%.
- Cerebrovascular disease, such as transient ischemic attack, ischemic stroke, and carotid artery stenosis > 50%.
- Symptomatic peripheral artery disease, such as claudication.
- Aortic atherosclerotic disease, such as abdominal aortic aneurysm and descending thoracic aneurysm.

**Primary prevention** refers to the effort to prevent or delay the onset of clinical ASCVD.

**Secondary prevention** refers to the effort to treat known, clinically significant ASCVD, and to prevent or delay the onset of disease manifestations.

## **Target Population**

The target population for secondary prevention of ASCVD is patients who have been diagnosed with ASCVD.

This guideline addresses treatment of underlying ASCVD only, and does **not** address treatment of any associated conditions.

## Goals

Reduce recurrent cardiovascular events and decrease coronary mortality.

## Lifestyle Modifications

#### Tobacco cessation

- Ask patients about tobacco use at every office visit.
- Advise tobacco users to quit.
- Advise patients at every office visit to avoid exposure to environmental tobacco smoke at home, work, and in public places.
- See the Tobacco and Nicotine Cessation Guideline for additional information.

### Healthy diet

All patients should strive to:

- Make smart choices from every food group to meet caloric needs.
- Get the most and best nutrition from the calories consumed.

Note that adhering to a Mediterranean-style eating plan has been shown to lead to improved ASCVD outcomes. Adhering to a DASH eating plan can be an alternative. Both eating plans provide similar key elements: an emphasis on plant foods (fruit, vegetables, whole-grain breads or other forms of cereals, beans, nuts, and seeds), minimally processed foods, and seasonally fresh foods; inclusion of fish; and minimal intake of red meat. The SmartPhrases .avsmediterraneandiet, .avsdash, and .avsnutrition are available for after-visit summaries.

There is some evidence from observational studies that fish consumption of an average of 2 servings per week may reduce CHD mortality.

### Limitation of alcohol consumption

Because consumption of alcohol can exacerbate ASCVD (by increasing blood pressure and subsequently the workload of the heart), patients with existing ASCVD should not exceed 1 drink per day for women or 2 drinks per day for men.

- Consider having patients complete the AUDIT-C (part of the Annual Mental Health Questionnaire).
- See the Unhealthy Drinking in Adults Guideline for additional information.

## Physical activity

As recommended by the American Heart Association, encourage patients with coronary and other vascular diseases who are physically capable of exercising to participate in **moderate-intensity aerobic activity** for 30–60 minutes a day for at least 5 days and preferably 7 days a week. An example of moderate-intensity physical activity is walking at a pace that makes a patient feel slightly out of breath but still able to maintain a conversation.

For patients who have been inactive for a while, recommend that they start slowly and work up to at least 30 minutes per day at a pace that is comfortable. If they are unable to be active for 30 minutes at one time, suggest accumulating activity over the course of the day in 10- to 15-minute sessions.

In addition, encourage patients to do resistance training 2 days per week.

Consider referral to the **Virtual Cardiac Rehab Program** (REF CARDIOLOGY INTERNAL, select patient's home clinic, then select Virtual Cardiac Rehab), which is a secondary prevention program designed to reduce risk of future cardiac events and improve patient quality of life. The program nurse meets regularly with patients to set goals, check on progress, and provide education and motivation. Use SmartPhrase .cardrehabref, which provides information about the program for patients. See the Cardiology Quick Care Guide for more information about inclusion/exclusion criteria.

### Weight management

- Assess BMI at every visit. Encourage getting to or maintaining a healthy weight through an
  appropriate balance of caloric intake and physical activity.
- See the Weight Management Guideline for additional information.

### Blood pressure management

- For the general population, the blood pressure goal is < 140/90 mm Hg.
- For patients who have ASCVD or chronic kidney disease (CKD) or are age 75 or older, the blood pressure goal is < 130/90 mm Hg.</li>
- If a patient's BP is higher than goal, see the Blood Pressure Guideline for management recommendations.

## **Dietary Supplements**

#### Calcium and vitamin D

- If a patient is taking a calcium supplement for the prevention of osteoporosis, recommend that it be taken in combination with vitamin D and that its dose not exceed 1,200 mg per day.
- There is some evidence that calcium supplementation may be associated with increased risk of cardiovascular events, particularly myocardial infarction. The co-administration of vitamin D with the calcium supplement may weaken the observed adverse effects of calcium supplementation.
- The literature indicates that intake of calcium from whole foods is not associated with an increased ASCVD risk.

### Dietary supplements that are *not* recommended

- Multivitamins: There is evidence that daily intake of a multivitamin does not reduce major cardiovascular events, MI, stroke, or ASCVD mortality.
- Beta-carotene: There is good evidence that supplemental doses of beta-carotene do not improve cardiovascular outcome and that they may be associated with increased cardiovascular deaths and overall mortality.

## Influenza Vaccination

Patients with cardiovascular disease should get an annual influenza vaccination.

Patients who receive an in-hospital influenza vaccination after an acute MI during flu season have a lower risk of cardiovascular mortality and all-cause mortality than patients who do not receive the influenza vaccine.

## **Statin Therapy**

Attention to adherence is important for patients to be successful in treatment. Approximately half of the patients who start on statin drugs stop them on their own within 1 year. Use clinical judgment before escalating doses or changing or adding medications.

Combination therapy (with a statin plus ezetimibe) is recommended in cases where LDL goal is unmet with statin therapy alone.

### Recommended statin dosing

Most patients with ASCVD should be initiated on high-intensity statins, defined as those lowering LDL cholesterol on average by at least 50%. See Table 1.

**Only** patients with questionable ability to tolerate high-intensity statins—the frail/age >75 years, those taking interacting drugs, and those with hepatic/renal impairment or untreated hypothyroidism—should be initiated on reduced doses, as given in Table 2 on the following page.

Table 1. STANDARD dosing: Statins for lowering cholesterol for secondary prevention of ASCVD
Standard dosing applies to patients for whom there are <b>no</b> concerns about their ability to tolerate high-
intensity statin therapy.

	Medication	Initial dose	Maximum dose
Start with:	Atorvastatin <b>or</b>	40 mg daily	80 mg daily
	Rosuvastatin	20 mg daily	40 mg daily
If LDL goal is not met:	Continue Atorvastatin or	40 mg daily	80 mg daily
	Rosuvastatin <sup>1</sup>	20 mg daily	40 mg daily
	and add		
	Ezetimibe	10 mg daily	10 mg daily
If LDL goal is still not			
met:	PCSK9 inhibitors (evolocumab) [NF-PA]	140 mg subcutaneously every 2 weeks	140 mg subcutaneously every 2 weeks

Clinicians should consider reducing rosuvastatin dose to 10 mg daily for patients with CKD 4–5 and eGFR < 30 mL/min. See the Rosuvastatin in CKD huddle card.</p>

**Table 2. REDUCED dosing: Statins for lowering cholesterol for secondary prevention of ASCVD** Reduced dosing applies to patients with questionable ability to tolerate high-intensity statin therapy, including those who are frail/age over 75, have hepatic/renal impairment or untreated hypothyroidism, or are taking interacting drugs.

Line	Medication	Initial dose 1	Maximum dose
1 <sup>st</sup>	Atorvastatin	10–40 mg daily	80 mg daily
	Rosuvastatin	2.5–5 mg daily	40 mg <sup>2</sup> daily
2 <sup>nd</sup>	Simvastatin	10–40 mg daily at bedtime	40 mg <sup>3</sup> daily at bedtime
3 <sup>rd</sup>	Pravastatin <sup>4</sup> (Alternative in cases of drug interactions or side effects)	20–40 mg daily at bedtime	80 mg daily at bedtime

<sup>&</sup>lt;sup>1</sup> Start statin at the highest dose you believe the patient will be able to tolerate. It is then very important to move the patient up from there to as close to standard high-intensity therapy as possible.

## Cholesterol and lipid goals for patients on statin therapy

#### LDL levels

## LDL goal: < 70 mg/dL

There is some evidence showing an association between even lower LDL levels (well below 70 mg/dL) and lower risk for recurrent cardiovascular events. Therefore, it may be beneficial for patients at very high risk to aim for an LDL well below 70. LDL targets should be considered on a case-by-case basis and at the discretion of the treating provider using a multifactorial approach. While the ideal LDL target is not defined for the very high-risk population, there is also no evidence that any LDL is too low. **Very high risk of ASCVD** is defined as a history of multiple major ASCVD events or one major ASCVD event in the presence of multiple high-risk conditions, including:

- Age ≥ 65 years
- Heterozygous familiar hypercholesterolemia
- History of revascularization
- Diabetes mellitus
- Hypertension
- CKD (eGFR 15–59 ml/min/1.73 m<sup>2</sup>
- Current smoking
- Persistent LDL-C ≥ 100 mg/dL despite maximally tolerated statin and ezetimibe
- History of heart failure

#### **HDL** levels

#### All patients on statins: no specific HDL target for therapy

A low HDL level is an independent risk factor for ASCVD, but there is no evidence to date that increasing HDL levels reduces cardiovascular risk. Encourage patients to increase HDL levels through lifestyle measures

Clinicians should consider reducing rosuvastatin dose to 10 mg daily for patients with CKD 4–5 and eGFR < 30 mL/min. See the Rosuvastatin in CKD huddle card.</p>

For patients already on simvastatin 80 mg daily, it is acceptable to maintain the dose if they have been taking the drug for 12 months or longer, are not taking interacting medications, are at LDL goal, and are without myopathy.

Pravastatin has about half the potency of simvastatin; however, it is less likely to interact with other medications, particularly medications that are strong CYP3A4 inhibitors.

(e.g., increased physical activity, weight loss if overweight, and tobacco cessation). Medications generally are not recommended.

#### Triglycerides and pancreatitis

#### All patients on statins: triglyceride target < 500 mg/dL

Evidence has shown, at most, a weak association between elevated triglycerides (TG) and health outcomes. Neither the threshold nor target of therapy is known. Although there is no direct evidence, there is consensus that TG levels of 500 mg/dL or greater warrant treatment to prevent pancreatitis. (See Lowering Triglycerides to Prevent Pancreatitis, p. 10.) Treatment/investigation at higher than 1,000 mg/dL would also be reasonable; use shared decision-making.

### Follow-up for patients on statins

Patients should generally be at a high-intensity level of therapy (Table 1, p. 5) if possible. If they are at the high-intensity level (lowering LDL cholesterol on average by at least 50%) and still above the LDL goal, it is reasonable to consider increasing the statin dose or adding ezetimibe. On the other hand, if a patient has achieved a very low LDL level, **do not lower** the intensity of statin therapy. Evidence suggests that no LDL level is too low.

Use clinical judgment before escalating doses or changing or adding medications.

#### For patients not at goal, but able to tolerate statins

- 1. First, assess adherence to therapy. If the patient is taking statin regularly, consider increasing dose or changing to high-intensity statin. If already on high-intensity dose atorvastatin and relatively close to goal (within 10–15%), consider changing to rosuvastatin.
- 2. If the patient is still not able to achieve an LDL < 70 while adherent to maximally tolerated high-intensity statin therapy, add ezetimibe. See Table 1, p. 5.
- 3. In adults with very high risk of ASCVD, if the patient is still not able to achieve an LDL < 70 after adding ezetimibe to maximally tolerated high-intensive statins, consider PCSK9 inhibitor.

#### If the patient appears intolerant to statins

- 1. First, consider decreasing the dose.
- 2. If the patient is still intolerant, use shared decision-making to decide whether to consider switching to another statin. Consider an E-Consult with Cardiology or Clinical Pharmacy.
- 3. To determine if myalgia symptoms can be attributed to use of the statin, consider using the American College of Cardiology statin intolerance tool.
- 4. If the patient is still intolerant, switch to one of the medications in Table 3, p. 8.

#### What is statin intolerance?

In 2022, The National Lipid Association updated its definition of statin treatment intolerance as:

... one or more adverse effects associated with statin therapy, which resolves or improves with dose reduction or discontinuation, and can be classified as complete inability to tolerate any dose of a statin, or partial intolerance, with inability to tolerate the dose necessary to achieve the patient-specific therapeutic objective. To classify a patient as having statin intolerance, a minimum of two statins should have been attempted, including at least one at the lowest approved daily dosage.

### Therapy for statin-intolerant patients

See also the prescribing notes that follow Table 3.

Table 3. Medications for lowering cholesterol in statin-intolerant patients for secondary prevention of ASCVD			
	Medication	Initial dose	Maximum dose
Start with:	Ezetimibe	10 mg daily	10 mg daily
If LDL goal is not met:	Continue Ezetimibe and add	10 mg daily	10 mg daily
	PCSK9 inhibitors (evolocumab) (NF-PA)	140 mg subcutaneously every 2 weeks	140 mg subcutaneously every 2 weeks
Alternative therapy	Cholestyramine resin 4 g 1–2 times daily 24 g divided 1–6 times daily		

#### Prescribing notes - Table 3

#### Ezetimibe (Zetia)

#### **Formulary**

For use in patients with a history of ASCVD who are not able to achieve an LDL < 70 mg/dL on maximally tolerated doses of formulary statins or who have intolerance or contraindications to statins.

#### PCSK9 inhibitors

#### Nonformulary—PA required with criteria below for clinical ASCVD

- Patients will continue maximally tolerated statin therapy while receiving evolocumab therapy.
- Authorization will be reviewed after 6 months of therapy to confirm continued clinical benefit, as demonstrated by LDL reduction since initiation of therapy with evolocumab.
- Clinical criteria for patients with ASCVD not able to achieve an LDL < 70 mg/dL and meeting one of the following:
  - Are currently 90% adherent to maximally tolerated high-intensity statin therapy (i.e., atorvastatin 80 mg or rosuvastatin 40 mg) in combination with ezetimibe for at least 8 weeks
  - Have a documented contraindication to statin and ezetimibe therapy
  - Have a documented intolerance to statin therapy, as defined by the National Lipid Association (NLA)

#### Cholestyramine

- Because bile acid sequestrants (e.g., cholestyramine, colestipol) can increase serum triglycerides, they should be used cautiously. Patients with TG 250–299 mg/dL should be monitored while on bile acid sequestrants, which should be discontinued if TG reaches > 400 mg/dL. Bile acid sequestrants should be avoided for patients with TG ≥ 300 mg/dL.
- Cholestyramine has many drug interactions due to its ability to reduce absorption of other medications. Other drugs should be administered at least 1 hour before or 4–6 hours after cholestyramine.

## Icosapent Ethyl for ASCVD Reduction

Icosapent ethyl has been approved by the FDA to reduce cardiovascular events in patients with ASCVD and triglycerides remaining > 150 mm/dL on maximum tolerated statin. Due to the weakness of the evidence and concerns about study design, our recommendation is neither for nor against this medication.

## ACE Inhibitor or ARB Therapy

Consider ACE inhibitor or ARB therapy for patients with clinical ASCVD.

Line	Medication	Initial dose	Maximum dose
1 <sup>st</sup>	ACE inhibitor		
	Lisinopril <b>or</b>	5–10 mg daily	40 mg daily (target dose is 20 mg daily)
	Ramipril	2.5–5 mg daily	20 mg daily (target dose is 10 mg daily)
2 <sup>nd</sup>	Angiotensin receptor blocker <sup>1</sup>		
	Losartan	25 mg/day in 1–2 doses	100 mg/day in 1–2 doses

Use an ARB (losartan) for patients who cannot tolerate an ACE inhibitor because of cough, rash, or angioedema (rather than because of renal failure, hyperkalemia, or hypotension). In a patient who previously developed angioedema with an ACE inhibitor, an ARB is less likely to cause angioedema, but there is still a risk of cross-reactivity. In the CHARM-Alternative study, the ARB group had 2.6% ACE-ARB cross-reactivity versus 0% in the placebo group (Granger 2003).

### Combination therapy is *not* recommended

There is evidence that there is harm and no additional benefit in **combining an ACE inhibitor and an ARB.** Numbers needed to harm (NNH) are 33 for hypotensive symptoms, 1,000 for syncope, 250 for diarrhea, and 250 for renal impairment.

## SGLT2 Inhibitors for Patients with Type 2 Diabetes

Sodium-glucose cotransporter 2 (SGLT2) inhibitors (e.g., empagliflozin) are recommended for patients with type 2 diabetes and established ASCVD, chronic kidney disease, or heart failure, in addition to or after metformin therapy due to their ability to reduce the risk of major cardiovascular events. Metformin should remain the first-line oral hypoglycemic, but SGLT2 inhibitors should be added as well regardless of current glycemic control if the patient has established cardiovascular disease. See the <a href="KPWA Type 2 Diabetes Guideline">KPWA Type 2 Diabetes Guideline</a> for information on dosing and potential adverse events (e.g., diabetic ketoacidosis, genital mycotic infections) as well as other indications for their use. SGLT2 inhibitors are not recommended in type 1 diabetes.

SGLT2 inhibitors have also demonstrated cardiorenal benefits in patients with chronic kidney disease or heart failure and no diabetes. See KP National Chronic Kidney Disease Guideline: Treatment with SGLT2 Inhibitors and KP National Heart Failure Guideline.

## **Antiplatelet Therapy**

Antiplatelet therapy is recommended in most patients with ASCVD unless contraindicated due to medication interactions or the presence of severe peptic ulcer disease or gastritis.

Note that patients who need to take an NSAID should continue taking it during antiplatelet therapy.

Table 5. Antiplatelet therapy for secondary prevention of ASCVD			
Line	Medication	Initial dose	Maximum dose
1 <sup>st</sup>	Aspirin	81 mg daily	81 mg daily
2 <sup>nd</sup>	Clopidogrel <sup>1</sup>	75 mg daily	75 mg daily

### Combination therapy is not recommended

There is evidence that the harms of **combined therapy (clopidogrel plus aspirin)** generally outweigh the benefits except in patients with acute coronary syndrome (ACS) or PCI with stent.

## Lowering Triglycerides to Prevent Pancreatitis

Triglycerides do not require pharmacologic treatment unless they are higher than 500 mg/dL.

If a patient has elevated triglycerides, consider the following workup:

- HbA1c, TSH, protein/creatinine ratio, and pregnancy test (if applicable).
- Review other items that can cause triglyceride elevations:
  - Obesity (review diet).
  - Alcohol intake.
  - Medications—estrogen replacement, oral contraceptives, tamoxifen, HIV antiretroviral regimens, beta-blockers (excluding carvedilol), retinoids, and immunosuppressive agents such as glucocorticoids and cyclosporine.

#### Consult with Endocrinology if:

- The cause of elevated triglycerides cannot be identified.
- You are not able to get triglyceride level lower than 500 mg/dL with treatment.
- You have any other questions about elevated triglycerides.

## Icosapent ethyl

Icosapent ethyl has been approved by the FDA for the treatment of patients with hypertriglyceridemia (not shown to reduce pancreatitis). The generic omega-3 fatty acids (Lovaza) and nutritional supplement alternatives are also available to treat hypertriglyceridemia.

	Medication	Initial dose	Maximum dose
Start with:	Atorvastatin	80 mg daily	80 mg daily
If TG not < 500 mg/dL:	Add Fenofibrate (preferred)	54–160 mg daily	160 mg daily
	or		
	Generic omega-3 fatty acids (Lovaza)	2,000 mg DHA/EPA in divided doses daily	4,000 mg DHA/EPA in divided doses daily
If TG still not < 500 mg/dL:	Add     Omega-3 fatty acids or fenofibrate per agent chosen in previous ste		
	or		
	Gemfibrozil monotherapy	600 mg twice daily	600 mg twice daily
If TG 1,000 mg/dL or higher:	Consider starting with Fenofibrate	54–160 mg daily	160 mg daily

<sup>&</sup>lt;sup>1</sup> In adults with severe hypertriglyceridemia, consider implementing a very low-fat diet, avoiding refined carbohydrates and alcohol, and consuming omega-3 fatty acids.

### **Prescribing notes for Table 6**

#### Atorvastatin

Weigh risks and benefits of using maximum dose (80 mg). Use maximum dose with caution in patients at risk of statin intolerance, such as those who are elderly, have kidney disease (CKD 3–5), have untreated hypothyroidism, or are taking interacting drugs.

#### Fenofibrate

- For patients with CKD 3 (eGFR 30–59 mL/min), do not exceed fenofibrate 54 mg per day.
- Do not use for patients with CKD 4–5.

#### Omega-3 fatty acids

- Use is associated with increased risk of significant bleeding and risk of atrial fibrillation/flutter requiring hospitalization.
- Use cautiously in patients with fish allergy.

#### Gemfibrozil

- Gemfibrozil is contraindicated with statin therapy due to an increased risk for muscle symptoms and rhabdomyolysis. Use caution for patients with mild to moderate renal impairment (CKD 2–3).
- Do not use for patients with severe renal impairment (serum creatinine greater than 2 mg/dL or CKD 4–5).

## Beta-blocker Therapy for Post-MI Patients

Initiate beta-blocker therapy for post-MI patients—in addition to ACE inhibitor or ARB therapy—unless contraindicated (e.g., in patients with severe bronchospasm, severe bradyarrhythmias, or a second-degree or higher heart block).

Note that it is a HEDIS® measure to continue beta-blocker therapy for at least 6 months. However, clinical evidence supports 3 years of use (Bockstall 2017).

Table 7. Beta-blocker therapy for post-MI patients				
Eligible population	Line	Medication	Initial dose	Maximum or target dose
Post-MI patients with preserved LV function (EF ≥ 50%)	1 <sup>st</sup>	Metoprolol	25 mg twice daily	100 mg twice daily is maximum dose.
Post-MI patients with LV systolic dysfunction (EF < 50%) with or without heart failure	1 <sup>st</sup>	Carvedilol	3.125 mg twice daily	25 mg twice daily is target dose for patients ≤ 187 lb.  50 mg twice daily is target dose for patients > 187 lb.
	2 <sup>nd</sup>	Metoprolol LA	12.5–25 mg daily	200 mg daily is maximum dose.

## **Medication Monitoring**

Table 8. Medication monitoring			
Eligible population	Recommended tests	Recommended frequency	
Patients on statin, ezetimibe, PCSK9	Non-fasting lipoprotein panel	At baseline and 4–6 weeks after initiating therapy	
Patients on bile acid sequestrant	Non-fasting lipoprotein panel	At baseline and 3 months after initiating therapy and Every 6–12 months (TG)	
Patients on ACE inhibitor or ARB	Potassium and Creatinine	At baseline and 2 weeks after initiating therapy and With each increase in dose and Annually	

### Medication monitoring that is *not* recommended

#### **ALT/AST**

For patients on statin monotherapy, routine baseline and periodic ALT or AST monitoring are not recommended. Liver function tests are recommended only if clinically indicated to work up symptoms of liver disease. Asymptomatic transaminase elevations with statin use are common but usually mild, transient, and reversible. They do not indicate liver dysfunction. Progression to liver toxicity is exceedingly rare and is likely due to idiosyncratic or immunoallergic reactions. The presence of chronic liver disease other than cirrhosis is not a contraindication for statin use. However, consultation with Gastroenterology first is recommended.

#### Creatine kinase (CK)

Routine CKs are not helpful and often are misleading. Check creatine kinase only if patient has symptoms of myopathy, an extremely rare side effect.

## Note: Chronic Disease Management Support

Patients identified as meeting regional registry criteria will be eligible for **Chronic Disease Management support** by a clinical pharmacist; the pharmacist will contact the provider to authorize referral into the program. For more information about collaborative drug therapy agreements (CDTAs) and covered medication classes, see Chronic Disease Management Support: Clinical Pharmacy on the KPWA Clinical Library.

## **Evidence Summary**

The Secondary Prevention of ASCVD Guideline was developed using an evidence-based process, including systematic literature search, critical appraisal, and evidence synthesis.

As part of our improvement process, the Kaiser Permanente Washington guideline team is working towards updating our clinical guidelines every 2–3 years. To achieve this goal, we are adapting evidence-based recommendations from high-quality external guidelines, if available and appropriate. The external guidelines must meet several quality standards to be considered for adaptation. They must: be developed by a multidisciplinary team with no or minimal conflicts of interest; be evidence-based; address a population that is reasonably similar to the KPWA population; and be transparent about the frequency of updates and the date the current version was completed.

In addition to identifying the recently published guidelines that meet the above standards, a literature search was conducted to identify studies relevant to the key questions that are not addressed by the external guidelines.

### External guidelines meeting KPWA criteria for adaptation/adoption

- 2022 United States Preventive Services Taskforce (USPSTF) recommendations for statin therapy eligibility for the primary prevention of cardiovascular disease.
- 2022 AHA Statement on the Comprehensive Management of CV Risk Factors for Adults with T2 DM
- 2022 KP National Clinical Practice Guideline: Cholesterol and Cardiovascular Risk
- 2021 KP National Coronary Artery Disease Guideline
- 2021 ACC Expert Consensus Decision Pathway on the Management of ASCVD Risk Reduction in Patients with Persistent Hypertriglyceridemia: A Report of the American College of Cardiology Solution Set Oversight Committee
- 2021 Department of Veterans Affairs (VA) and U.S. Department of Defense (DoD) guidelines for management of dyslipidemia and cardiovascular disease risk reduction: Putting evidence in context
- 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice:
- 2021 European Society of Cardiology (ESC) guidelines on statin use
- 2021 NICE Cardiovascular disease: risk assessment and reduction, including lipid modification
- 2020 Quantifying atherogenic lipoproteins for lipid-lowering strategies: consensus-based recommendations from EAS and EFLM

## Key questions addressed in the KPWA evidence review

1. In patients at high risk for ASCVD (e.g., past MI/CABG, symptomatic PAD, angina), what is the safety and clinical impact of reducing the target LDL-C goal to < 55 mg/dL from < 70 mg/dL?

The literature search on the safety and effectiveness of intensive lowering of LDL-C published in the last 5 years identifies several systematic reviews with meta-analyses (Khan 2022, Hsu 2020, Toyota 2019, Navaerese 2018, Sabatine 2018, and others). The two more recent analyses (Khan 2022 and Toyota 2019) that included studies evaluating more intensive LDL-C lowering with ezetimibe or PSCK9 in addition to the statins were selected for critical appraisal.

- The overall results of the meta-analyses pooling the results of published RCTs evaluating intensive LDL-C lowering with intensive statin therapy, ezetimibe, and/or PCSK9 inhibitors suggest that intensive therapies to achieve lower average LDL-C levels below 70 mg/dL (using any of the three therapies and/or combination therapy) was associated with reduced mortality and cardiovascular endpoints compared with treatments achieving higher average LDL-C values (≥ 70 mg/dL).
- The Khan 2022 meta-analysis found that patients with higher baseline LDL-C values achieved higher absolute LDL-C reductions and that the mortality was lower in patients with baseline LDL-C values ≥ 100 mg/dL. However, reduction in individual cardiovascular endpoints was independent of baseline LDL-C. The benefits observed were not associated with an increased risk of incident cancer, DM, or hemorrhagic stroke.

- The Toyota 2019 meta-analysis suggested that the overall odds reduction for major adverse cardiovascular events (MACE) and odds reduction for MACE per 20 mg/dL LDL-C reduction were different across the three types of more-intensive LDL-C therapies (the odds reduction for MACE per 20 mg/dL LDL-C reduction was smaller with PCSK9 inhibitors versus the more-intensive statin therapy and ezetimibe).
- Observational studies conducted among Asian participants showed no additional benefit of further lowering LDL-C kevel beyond 70 mg/dL. However, these studies were performed before the introduction of non-statin therapies to lower LDL-C levels.
- All published studies and meta-analyses had their limitations. The pivotal studies included in these
  meta-analyses mainly included white secondary prevention populations, which may limit
  generalization of their results.
- The published evidence on reducing the LDL-C to very low levels with PCSK9 inhibitors was limited to about a 5-year follow-up.
- To date, the optimal target LDL-C levels have yet to be determined in clinical trials.

# 2. In adult patients who have a cardiovascular disease or who were recently admitted with a myocardial infarction, what is the safety and effectiveness of influenza vaccine in reducing future cardiovascular events?

The literature search identified the IAMI trial (Frobert 2021), which investigated the efficacy of administering influenza vaccination early after admission with myocardial infarction or high-risk CAD on reducing cardiovascular events. It also revealed a systematic review with a meta-analysis of RCTs and observational studies that evaluated the effects of the influenza vaccine on mortality and cardiovascular outcomes in patients with cardiovascular disease.

The IAMI trial was conducted at 30 centers across 8 countries from October 2016 through February 2020. The trial included adults aged  $\geq$  18 years with ST-segment or non–ST-segment elevation MI, completing a coronary angiography or PCI. Changes were made to the study inclusion criteria during the course of the trial to include patients with stable coronary artery disease if they were aged  $\geq$  75 years and had at least one additional risk.

The participants were enrolled during the influenza season and randomly assigned to receive an influenza vaccine or a placebo (sterile 0.9% normal saline solution). Trivalent vaccine was used in the first study season and quadrivalent vaccine was used in the following seasons. Patients were followed -up for 12 months, and the primary endpoint was a composite of all-cause death, MI, and stent thrombosis at the end of the follow-up period. The trial was halted early because of the COVID-19 pandemic. Its overall results show that patients who received an in-hospital influenza vaccination versus a placebo after an MI or PCI had a lower risk of the composite of all-cause death, myocardial infarction, or stent thrombosis, and a lower risk of all-cause death and cardiovascular death at 12 months.

## 3. In patients with advanced CKD, is rosuvastatin use associated with higher risk of kidney harm compared to other statin use?

- The published studies identified by the literature search assessed the safety of rosuvastatin in general and not specifically for patients with advanced CKD.
- There is moderate- to high-quality evidence from the PLANET I (de Zeeuw 2015) trial and several observational studies indicating that rosuvastatin given in high doses is associated with an increased risk of kidney injury.
  - The PLANET I RCT showed that acute kidney injury and doubling of serum creatinine concentration were more common among patients taking rosuvastatin 40 mg than among those taking rosuvastatin 10 mg or atorvastatin 80 mg. The study was powered to detect within-group but not within-statins differences.
  - More recently, Shin and colleagues' 2022 observational study that analyzed data from 40 health care electronic medical records in the US from 2011 to 2019 found that 2.9% of rosuvastatin patients experienced hematuria and 1.0% had proteinuria over 3.1 years of median follow-up. Rosuvastatin was associated with a 17% higher risk of proteinuria than

atorvastatin, along with an 8% higher risk of hematuria and 15% risk of kidney failure, which required kidney dialysis or transplantation.

- Low-level evidence suggests that the use of rosuvastatin was associated with a dose-dependent increase in proteinuria and microhematuria.
  - Subgroup analysis of Shin and colleague's 2022 study suggests that the risk of nephrotoxicity was greater with the increased doses of rosuvastatin.
  - An earlier review (Scott 2004) of the use of rosuvastatin in the management of dyslipidemia showed that the incidence of proteinuria or microscopic hematuria with rosuvastatin 10 or 20 mg/day was < 1% versus < 1.5% with rosuvastatin 40 mg/day.</li>
- RCTs using different statin intensities in CKD patients not requiring dialysis with a longer duration of study are needed to provide more evidence.

# 4. In patients with normal or low LDL-C levels and/or hypertriglyceridemia, does the use of the new NIH equation provide more accurate calculation and less misclassification of the LDL-C level compared to the standard Friedewald or Martin Hopkins equations?

The National Institutes of Health (NIH) equation (also known as Sampson equation, or Equation 2) was developed by Sampson and colleagues in 2020 using  $\beta$ -Quantification LDL-C values as the gold standard and multiple least-squares regressions.

- The proposed equation for LDL-C estimation is TC/0.948 -HDL-C/0.971 (TG/8.56 +[TG x non-HDL-c]/2140 -TG2/16100) -9.44.
- According to the results of the NIH equation derivation study, the equation provides a more accurate calculation of LDL than the Friedewald and Martin-Hopkins equations in patients with low LDL concentration and/or hypertriglyceridemia.
- The equation has no intellectual property restrictions and will not increase the cost of testing. It is more complicated than other equations, but the result can be automatically calculated by most laboratory information systems without any additional software changes (Sampson 2020).
- The NIH equation is not endorsed by any national US guideline, to date.
- The equation was validated at TG levels ≥ 400 mg/dL but has not been validated for LDL-C
   < 40 mg/dL, which may be achieved with the novel lipid-lowering therapies.</li>
- There is a lack of prospective studies that directly compared the three equations using the gold standard β-quantification method that directly measures the LDL-C.
- In patients with LDL-C < 100 mg/dL, the NIH equation was found to be the least likely to overestimate risk and thus the least to likely to cause overtreatment. The Martin equation, on the other hand, is more likely to overestimate risk and in turn overestimate treatment.
- The NIH equation may underestimate LDL-C at low levels, leading to undertreatment of high-risk patients.
- The NIH equation was externally validated in Canada, Spain, Turkey, and other countries—but not in the US—in routine clinical practice in various settings, including disease and therapeutic situations.
- Further studies are needed to validate and assess its performance in routine clinical practice.

#### References

Bockstall K, Bangalore S. <u>How Long Should We Continue Beta-Blockers After MI?</u> *American College of Cardiology.* 2017 Jan 23.

Cheeley MK, Saseen JJ, Agarwala A, et al. NLA scientific statement on statin intolerance: a new definition and key considerations for ASCVD risk reduction in the statin intolerant patient. *J Clin Lipidol*. 2022;16(4):361-375. doi:10.1016/j.jacl.2022.05.068

de Zeeuw D, Anzalone DA, Cain VA, et al. Renal effects of atorvastatin and rosuvastatin in patients with diabetes who have progressive renal disease (PLANET I): a randomised clinical trial. *Lancet Diabetes Endocrinol.* 2015 Mar;3(3):181-90. doi: 10.1016/S2213-8587(14)70246-3.

Fröbert O, Götberg M, Erlinge D, et al. Influenza Vaccination After Myocardial Infarction: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial. *Circulation*. 2021 Nov 2;144(18):1476-1484. doi: 10.1161/CIRCULATIONAHA.121.057042.

Hsu HY, Lin CJ, Lee YS, et al. Efficacy of more intensive lipid-lowering therapy on cardiovascular diseases: a systematic review and meta-analysis. *BMC Cardiovasc Disord*. 2020 Jul 13;20(1):334. doi: 10.1186/s12872-020-01567-1.

Khan SU, Khan MU, Virani SS, et al. Efficacy and safety for the achievement of guideline-recommended lower low-density lipoprotein cholesterol levels: a systematic review and meta-analysis. *Eur J Prev Cardiol.* 2022 Feb 9;28(18):2001-2009. doi: 10.1093/eurjpc/zwaa093.

Navarese EP, Robinson JG, Kowalewski M, et al. Association Between Baseline LDL-C Level and Total and Cardiovascular Mortality After LDL-C Lowering: A Systematic Review and Meta-analysis. *JAMA*. 2018;319(15):1566–1579. doi:10.1001/jama.2018.2525

Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med 2017;376:1713–22.

Sampson M, Ling C, Sun Q, et al. A New Equation for Calculation of Low-Density Lipoprotein Cholesterol in Patients with Normolipidemia and/or Hypertriglyceridemia. JAMA Cardiol. 2020 May 1;5(5):540-548. doi: 10.1001/jamacardio.2020.0013.

Scott LJ, Curran MP, Figgitt DP. Rosuvastatin: a review of its use in the management of dyslipidemia. *Am J Cardiovasc Drugs*. 2004;4(2):117-38. doi: 10.2165/00129784-200404020-00005.

Shin JI, Fine DM, Sang Y, et al. Association of Rosuvastatin Use with Risk of Hematuria and Proteinuria. *J Am Soc Nephrol*. 2022 Jul 19;33(9):1767–77. doi: 10.1681/ASN.2022020135.

Toyota T, Morimoto T, Yamashita Y, et al. . More- Versus Less-Intensive Lipid-Lowering Therapy. Circ Cardiovasc Qual Outcomes. 2019 Aug;12(8):e005460. doi: 10.1161/CIRCOUTCOMES.118.005460.

## Guideline Development Process and Team

### Development process

The guideline team developed the Secondary Prevention of ASCVD Guideline using an evidence-based process, including systematic literature search, critical appraisal, and evidence synthesis. For details, see Evidence Summary and References.

This edition of the guideline was approved for publication by the Guideline Oversight Group in April 2023.

#### **Team**

The Secondary Prevention of ASCVD Guideline development team included representatives from the following specialties: cardiology, clinical laboratory, endocrinology, family medicine, internal medicine, and pharmacy.

Clinical expert: Rachael Wyman, MD, Medical Program Director, Virtual Cardiac Rehabilitation Clinician leads: Katie Paul, MD, MPH, Associate Medical Director, Clinical Knowledge Development & Education, and Tina Shah, MD, Quality Medical Director, Cardiovascular

Guideline coordinator: Avra Cohen, MN, RN, Clinical Improvement & Prevention

Fatimatou Bah, MD, Resident

Alice Chang, MD, Associate Medical Director Nephrology, North Scott Ekin, MD, Urgent Care Quality Medical Program Director

Melissa Hull, PharmD, CLS, Clinical Pharmacy Programs Coordinator

Megan Kavanagh, Patient Engagement Team, Clinical Improvement & Prevention

Annie Links, MD, Interim Medical Director Patient Safety

John Polnak, PharmD, Clinical Pharmacist

Emily Prazak, MD, Primary Care

Elizabeth Reilly, MD, Endocrinology

Nadia Salama, MD, MPH, PhD, Epidemiologist, Clinical Improvement & Prevention

David Schmidt, MD, Neurology

Elizabeth Slve. RN. Quality Improvement Consultant

Ann Stedronsky, Clinical Publications, Clinical Improvement & Prevention

Monika Wells, MD, District Medical Director Seattle

Min Xu, MD, PhD, Medical Director Laboratory