

# Atherosclerotic Cardiovascular Disease (ASCVD) Secondary Prevention Guideline

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**Last guideline approval:** April 2018

**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 2018

New	Previous
Rosuvastatin is now a first-line option, along with atorvastatin, for secondary prevention.	Previously, rosuvastatin was non-formulary and was a second-line option for secondary prevention.
Annual LDL monitoring is no longer required.	Annual LDL monitoring was recommended for all patients on a statin.
Non-fasting lipid panel is now the preferred cholesterol test.	Fasting lipoprotein panel or direct LDL cholesterol were the preferred cholesterol tests.
Updated blood pressure targets: <ul style="list-style-type: none"><li>• &lt; 140/90 mm Hg for most people</li><li>• &lt; 130/80 mm Hg for patients with ASCVD, diabetes, systolic heart failure or CKD</li></ul>	Previous blood pressure targets: <ul style="list-style-type: none"><li>• &lt; 140/90 mm Hg for most people</li><li>• &lt; 150/90 mm Hg for patients aged 80 and over</li></ul>

## Definitions

**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%.
- 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 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 Use 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 alcohol use 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.

## 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 [Adult Weight Management Guideline](#) for additional information.

## Blood pressure management

- For the general population, the blood pressure goal is **< 140/90 mm Hg**.
- For patients with ASCVD, diabetes, systolic heart failure or chronic kidney disease, the blood pressure goal is **< 130/80 mm Hg**.
- If a patient's BP is higher than goal, see the [Hypertension 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.

# 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 1a on the following page.

**Only** patients with questionable ability to tolerate high-intensity statins—the frail/elderly, those taking interacting drugs, and those with hepatic/renal impairment or untreated hypothyroidism—should be initiated on reduced doses, as given in Table 1b on the following page.

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

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

\* Cardiology or Endocrinology consultation is required.

**Table 1b. 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/elderly, have hepatic/renal impairment or untreated hypothyroidism, or are taking interacting drugs.

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

<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.

<sup>2</sup> 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.

<sup>3</sup> 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.

# Cholesterol and lipid goals for patients on statin therapy

## LDL levels

**LDL goal: < 70 mg/dL**

## 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, 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. 11.) 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 1a, 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. Expert opinion is 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 statin, if necessary. This is especially important in the case of rosuvastatin, given that drug's increased cost share for most patients. Consider switching to rosuvastatin mainly when atorvastatin is clearly not working despite regular use, and when the patient is considerably above goal.
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 1a, p. 5.
3. If the patient is still not able to achieve an LDL < 100 after adding ezetimibe to maximally tolerated high-intensive statins, **refer to Cardiology**. For patients meeting certain criteria, PCSK-9 inhibitors (evolocumab) may be prescribed as an alternative to the ezetimibe.

## 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 a consult with Cardiology.
3. To determine if myalgia symptoms can be attributed to use of the statin, consider using [the ACC statin intolerance tool](#).
4. Consider supplementation with co-enzyme Q10 to relieve statin-induced muscle symptoms. Evidence is conflicting, but some studies suggest a benefit.
5. If the patient is still intolerant, switch to one of the medications in Table 2, p. 7.

## What is statin intolerance?

The National Lipid Association (Guyton 2014) defines statin treatment intolerance as: ...a clinical syndrome characterized by the inability to tolerate at least 2 statins: one statin at the lowest starting daily dose AND another statin at any daily dose, due to either objectionable symptoms (real or perceived) or abnormal lab determinations, which are temporally related to statin treatment and reversible upon statin discontinuation, but reproducible by re-challenge with other known determinants being excluded (such as hypothyroidism, interacting drugs, concurrent illnesses, significant changes in physical activity or exercise, and underlying muscle disease). Specifically, the lowest starting statin daily dose, is defined as rosuvastatin 5 mg, atorvastatin 10 mg, simvastatin 10 mg, lovastatin 20 mg, pravastatin 40 mg, fluvastatin 40 mg, and pitavastatin 2 mg.

## Therapy for statin-intolerant patients

See also the **prescribing notes** that follow Table 2.

	<b>Medication</b>	<b>Initial dose</b>	<b>Maximum dose</b>
Start with:	Ezetimibe	10 mg daily	10 mg daily
If LDL goal is not met:	<b>Continue</b> Ezetimibe	10 mg daily	10 mg daily
	<b>and add</b> Cholestyramine resin	4 g 1–2 times daily	24 g divided 1–6 times daily
If LDL goal is still not met:	<b>Refer to Cardiology or Endocrinology* for:</b>		
	PCSK9 inhibitors (evolocumab) [NF]	140 mg subcutaneously every 2 weeks	140 mg subcutaneously every 2 weeks
* Cardiology or Endocrinology consultation is required, and at least one second-line medication must be tried before referral.			

## Prescribing notes – Table 2

### Ezetimibe (Zetia)

**Formulary—prior authorization required.** See [Pharmacy criteria](#) on the staff intranet.

- 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 (evolocumab)

**Nonformulary—specialty tier.** See [Pharmacy criteria](#) on the staff intranet.

- Patients will continue maximally tolerated statin therapy while receiving evolocumab therapy.
- Authorization will be reviewed after 6 and 12 months of therapy to confirm continued clinical benefit, as demonstrated by LDL reduction since initiation of therapy with evolocumab.

Two groups of patients may be considered for PCSK9 inhibitors:

1. Patients with ASCVD who are not able to achieve an LDL < 100 mg/dL and meet 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)

For this group of patients, PCSK9 inhibitors may only be prescribed by, or in conjunction with, a cardiologist.

2. Patients 18 years and older with heterozygous familial hypercholesterolemia (HeFH)—defined as diagnosis of HeFH based on genetic testing or a score of > 8 on the [World Health Organization diagnostic criteria](#)—who have failed to achieve an LDL < 130 mg/dL and meet 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)

For this group of patients, PCSK9 inhibitors may only be prescribed by, or in conjunction with, a cardiologist or an endocrinologist with lipid management expertise.

### **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.

## ACE Inhibitor or ARB Therapy

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
<sup>1</sup> 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.

## Antiplatelet Therapy

Daily aspirin is recommended in most patients with ASCVD unless contraindicated due to hypersensitivity to aspirin, 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.

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
<sup>1</sup> Clopidogrel is equally effective in patients with ASCVD who have a contraindication or intolerance to aspirin.			

### 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 investigation or treatment unless they are higher than 500 mg/dL. (Treatment/investigation at higher than 1,000 mg/dL would also be reasonable. Use shared decision making.)

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.

<b>Table 5. Medications for lowering triglyceride levels to prevent possible pancreatitis</b> See also the <b>prescribing notes</b> that follow.			
<b>Line</b>	<b>Medication</b>	<b>Initial dose</b>	<b>Maximum dose</b>
1 <sup>st</sup>	Atorvastatin	80 mg daily	80 mg daily
If TG still not < 500 mg/dL:	<b>Add</b>		
	Fenofibrate ( <b>preferred</b> )	54–160 mg daily	160 mg daily
	<b>or</b>		
	Niacin		
	Niacin IR <b>or</b>	100 mg twice daily	1,000 mg 3 times daily
	Niacin SR (Slo-Niacin)	250 mg twice daily	1,000 mg twice daily
If TG still not < 500 mg/dL:	<b>Add</b>		
	Fish oil (if LDL at goal)	2,000 mg DHA/EPA in divided doses daily	4,000 mg DHA/EPA in divided doses daily
<b>OR</b>			
1 <sup>st</sup>	Gemfibrozil monotherapy	600 mg twice daily	600 mg twice daily

### Prescribing notes for Table 5

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

## Niacin

- Use niacin with care in patients on a statin. When niacin at doses of 1,000 mg daily or higher is combined with a statin, patients are at increased risk of myalgia and rhabdomyolysis.
- Avoid use if ALT/AST is greater than 2–3 times upper limit of normal or if persistent severe cutaneous symptoms, persistent hyperglycemia, acute gout, or gastrointestinal symptoms occur.
- Niacin IR is the preferred form of niacin. If niacin SR is to be used, Slo-Niacin is the brand. Trials with niacin SR made by other manufacturers showed an increased risk of **hepatotoxicity**, so caution is advised if other brands of niacin SR are used. For information on dosing escalation, see [Niacin IR or Niacin SR \(Slo-Niacin\) patient dosing instructions](#) on the staff intranet.

## Gemfibrozil

- Gemfibrozil is contraindicated with statin therapy.
- 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. In general, however, therapy continues indefinitely unless the patient becomes unable to tolerate the beta-blocker.

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

<b>Table 7. Medication monitoring</b>		
<b>Eligible population</b>	<b>Recommended tests</b>	<b>Recommended frequency</b>
Patients on statin	Non-fasting lipoprotein panel	4–6 weeks after initiating therapy
Patients on niacin	ALT/AST <b>and</b> Fasting blood glucose or HbA1c <b>and</b> Uric acid	At baseline <b>and</b> 2–4 weeks after increasing dose <b>and</b> Every 6 months
Patients on bile acid sequestrant	Non-fasting lipoprotein panel	At baseline <b>and</b> 3 months after initiating therapy <b>and</b> Every 6 months
Patients on ACE inhibitor or ARB	Potassium <b>and</b> Creatinine	At baseline <b>and</b> 2 weeks after initiating therapy <b>and</b> With each increase in dose <b>and</b> 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.

# 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.

## Key questions addressed in the KPWA guideline

1. How accurate is assessing the lipid profile using blood samples collected in the nonfasting state compared to the fasting state in monitoring response to statin therapy?
2. In adults on lipid-lowering therapy, does the use of treatment targets reduce CV events? Should we keep following the treat-to-target approach, and to what targets according to the individual patient risk of CV events?
3. What is the safety and effectiveness of PCSK9 inhibitors in preventing or reducing CV events in patients at high CV risk who have not reached their LDL-C targets with other lipid-lowering drugs?
4. What is the optimal blood pressure target for the general population and for those at high cardiovascular risk? What are the comparative benefits and harms of intensive treatment of blood pressure to an SBP target of < 120 mm Hg versus standard SBP target of < 140 mm Hg?
5. What is the safety and tolerability of the long-term use of high-intensity statins (e.g., atorvastatin 80 mg)?

## External guidelines meeting KPWA criteria for adaptation/adoption

2017	ACC/AHA (and 9 other Professional Societies) Guideline: Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults
2017	Focused Update of the 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statins Therapies for LDL: Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease
2017	American Association of Clinical Endocrinologists and American College of Endocrinology Guidelines for management of dyslipidemia and prevention of cardiovascular disease (Jellinger 2017)
2017	Update on the use of PCSK9 inhibitors in adults: Recommendations from an Expert Panel of the National Lipid Association (Orringer 2017)
2017	Hypertension Canada's 2017 Guidelines for Diagnosis, Risk Assessment, Prevention, and Treatment of Hypertension in Adults (Leung 2017)
2016	Kaiser Permanente National Integrated Cardiovascular Health Guidelines: Aspirin therapy
2016	ACC Expert Consensus Decision Pathway on the Role of Non-Statins Therapies for LDL: Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular disease. A Report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents Cardiovascular Disease Risk (Lloyd-Jones 2016)
2016	Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult (Anderson 2016) w
2016	European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts): Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR) (Piepoli 2016)
2016	ESC/EAS Guidelines for the Management of Dyslipidaemias: The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR) (Catapano 2016)

- 2016 European Atherosclerosis Society and European Federation of Clinical Chemistry and Laboratory Medicine Joint Consensus Statement. Fasting Is Not Routinely Required for Determination of a Lipid Profile: Clinical and Laboratory Implications Including Flagging at Desirable Concentration Cutpoints (Nordestgaard 2016)
- 2014 Management of dyslipidemia for cardiovascular disease risk reduction: synopsis of the 2014 U.S. Department of Veterans Affairs and U.S. Department of Defense clinical practice guideline (Downs 2015)
- 2014 National Institute for Health Care Excellence (NICE). Cardiovascular disease: risk assessment and reduction, including lipid modification. Clinical guideline [CG181]. Last updated September 2016.
- 2013 ACC/AHA Guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults (Goff 2014, Stone 2014)

### Key question 1

**How accurate is assessing the lipid profile using blood samples collected in the nonfasting state compared to the fasting state in monitoring response to statin therapy?**

<b>Summary of recommendations of different guidelines/consensus statements on fasting for lipid testing</b>		
<b>Guideline/Consensus statement</b>	<b>ASCVD risk assessment</b>	<b>Monitoring lipid-lowering therapy</b>
2016 American College of Cardiology (Lloyd-Jones 2016)	—	Fasting sample initially before initiating statin therapy and for follow-up monitoring.
2016 European Society of Cardiology and European Atherosclerosis Society (Catapano 2016)	Non-fasting. (However, may underestimate risk in diabetic patients.)	Unclear recommendation.
2016 European Atherosclerosis Society and European Federation of Clinical Chemistry and Laboratory Medicine (Nordestgaard 2016)	Fasting lipids are not routinely required.	Fasting is not required if patients are on stable drug therapy.
2016 Canadian Cardiovascular Society (Anderson 2016)	Recommends nonfasting testing for risk assessment to reduce CVD events.  Suggests fasting samples for individuals with a history of triglyceride levels > 4.5 mmol/L.	—
2014 NICE and Joint British Societies (2014)	Fasting sample is not needed.	Consider an annual nonfasting non-HDL-C.
2013 American College of Cardiology/ American Heart Association (Goff 2014, Stone 2014)	Fasting sample preferred (not mandated).	Fasting lipids to assess percent reduction in LDL-C and adequate response to statin therapy.
2014 U.S. Department of Veterans Affairs and U.S. Department of Defense (Downs 2015)	Nonfasting lipid profile provides acceptably accurate measures for risk calculation.  Fasting lipid measures are indicated if triglyceride levels > 4.52 mmol/L (> 400 mg/dL), and to measure or monitor triglyceride levels.	—

The published studies on the comparative accuracy and benefits of assessing the lipid profile from blood samples collected in the nonfasting versus fasting state were based on secondary analyses of data from population-based studies. Fasting and nonfasting lipids were not collected from the same individuals, nor at a fixed time after the last meal, which was not standardized among the individuals.

Overall there is insufficient evidence to support the use of nonfasting lipid panel to monitor lipid therapy. Major guidelines differ in their recommendations, but it appears that more guidelines recommend fasting lipid profile for monitoring LDL-C in patients taking lipid-lowering medications. It is also recommended to use fasting lipid samples for monitoring response to lipid-lowering treatment in patients with high triglyceride levels.

### **Key question 2**

**In adults on lipid-lowering therapy, does the use of treatment targets reduce CV events? Should we keep following the treat-to-target approach, and to what targets according to the individual patient risk of CV events?**

- To date, there is insufficient evidence to determine an optimal LDL-C target or a threshold beyond which there is no further reduction in CV events or increased harm.
- The following guidelines and pathways recommend a treat-to-target approach in the management of dyslipidemia to diminish CVD risk: 2016 American College of Cardiology (Lloyd-Jones 2016), 2016 Canadian Cardiovascular Society (Anderson 2016), and 2016 ESC/EAS (Catapano 2016).
- There is insufficient evidence to determine the safety profile of achieving very low (< 30 mg/dL) LDL-C. An analysis of IMPROVE-IT trial results (Giugliano 2017) shows no significant differences in long-term safety outcomes with intensive lipid-lowering therapy. On the other hand, a post hoc analysis of the JUPITER trial (Everett 2014) suggests that achieving LDL-C levels < 30 mg/dL with high-intensity statin therapy may be generally well tolerated, but may also be associated with a small but statistically significant increase in the rates of diabetes, hematuria, hepatobiliary disorders, and insomnia when compared to LDL-C levels > 30 mg/dL with rosuvastatin. The FOURIER trial results (Sabatine 2017) that compared the effect of lipid lowering with evolocumab versus a placebo showed no differences between the two groups in the overall rates of adverse events, serious adverse events, or events leading to the discontinuation of the study regimen. There were, however, a statistically significant higher rate of injection site reactions and a statistically insignificant higher rate of adjudicated cases of new-onset diabetes in the evolocumab group.

### **Key question 3**

**What is the safety and effectiveness of PCSK9 inhibitors in preventing or reducing CV events in patients at high CV risk who have not reached their LDL-C targets with other lipid-lowering drugs?**

- There is evidence that PCSK9 inhibitors may significantly lower LDL-C levels compared to placebo.
- Medium-term follow-up studies suggest that PCSK9 inhibitors may reduce incidence of CV events compared to placebo, but with little or no difference in reducing overall mortality.
- There is insufficient evidence to determine the relative efficacy and safety of PCSK9 inhibitors to active lipid-lowering drugs.
- The FOURIER trial (Sabatine 2017), the first study on PCSK9 inhibitors that had cardiovascular outcomes, shows that the use of evolocumab in selected high-risk individuals reduced the LDL-C to a median of 30 mg/dL and decreased the composite CV outcomes, with an NNT of 67 in an average of 2.2 years. However, this was not associated with a reduction in CV or all-cause mortality, which on the contrary was insignificantly higher in the evolocumab group. This might be due to chance, as the study was not powered to detect a difference in mortality, but the early termination of the study does not allow examination of the long-term risks or benefits of evolocumab.
- To date, there is no evidence to determine that the addition of PCSK9 inhibitors to the highest tolerable dose of statin with or without ezetimibe is more beneficial than the use of the maximally tolerated dose of statin with or without ezetimibe. Evolocumab was tested against a placebo and not against a statin-plus-ezetimibe combination therapy, which would be the appropriate comparator. In addition, FOURIER study participants were not receiving the maximal tolerated statin therapy at randomization.
- There is insufficient evidence to determine the long-term harms of reducing the LDL-C level to  $\leq 30$  mg/dL (discussed earlier).
- There is some evidence suggesting that PCSK9 inhibitors may be associated with a significant increase in any adverse events, including neurocognitive events and cataract, compared to placebo.

#### Key question 4

**What is the optimal blood pressure target for the general population and for those at high cardiovascular risk? What are the comparative benefits and harms of intensive treatment of blood pressure to an SBP target of < 120 mm Hg versus standard SBP target of < 140 mm Hg?**

- SPRINT results (Wright 2015) provide evidence that intensive blood pressure control targeting an SBP  $\leq$  120 mm Hg versus < 140 mm Hg among community-dwelling adults aged 50 or older at high risk of CVD with SBP 130–180 mm Hg, significantly lowers the rates of fatal and nonfatal major CV events and death from any cause, but at the expense of higher rates of a number of serious adverse events that may increase ED visits, including hypotension, syncope, electrolyte abnormalities, and acute kidney injury or acute renal failure.
- SPRINT results may not be generalized to patients with diabetes mellitus, history of stroke, symptomatic heart failure, LVEF < 35%, polycystic kidney disease, medical conditions that limit survival to < 3 years, or dementia; nor may they be generalized to individuals living in nursing homes and other population groups excluded from the study.
- SPRINT used programmed automated oscillometric blood pressure meters, which may give BP values 5–10 mm Hg lower than those measured in the office by conventional methods.
- Subanalyses for elderly patients showed similar results and had similar limitations as SPRINT. The elderly patients were analyzed as one group with no categorization or subanalyses according to age. The authors performed an exploratory secondary analysis to examine modification of the treatment effect by frailty status, which was a specified outcome in the trial protocol. The results of the analysis stratified by baseline frailty status showed higher event rates with increasing frailty in both treatment groups. However, within each frailty stratum, absolute event rates were lower for the intensive treatment group. According to the authors and some investigators, frail older SPRINT participants do not represent the entire population of frail older adults.
- Two recent meta-analyses (Ettehad 2016, Xie 2016) provide supporting evidence on the cardiovascular benefits of more intensive blood pressure lowering in individuals, including high-risk patients with SBP < 140 mm Hg.
- During follow-up of patients with no CV disease at baseline who were at intermediate risk, the HOPE-3 trial (Yusuf 2016) showed a decrease in SBP/DBP that was 6.0/3.0 mm Hg greater in the active treatment group versus the placebo group. However, this did not result in a statistically significant difference in the incidence of the first co-primary outcome, second primary outcome, secondary outcome, or components of each in patients receiving BP lowering alone, but it did lead to significantly better clinical outcomes in the group that received both the BP- and lipid-lowering drugs. A pre-specified subgroup analysis showed that participants in the upper third of SBP (> 143.5 mm Hg [mean 154.1 $\pm$ 8.9 mm Hg]) receiving active treatment had significantly lower rates of the first and second primary outcomes compared to those in the placebo group.

#### Key question 5

**What is the safety and tolerability of the long-term use of high-intensity statins (e.g., atorvastatin 80 mg)?**

- Li and colleagues' 2016 meta-analysis on the safety profile of atorvastatin 80 mg/day suggests that it is less well tolerated than atorvastatin with lower intensity or placebo when used for more than 52 weeks, and is associated with a higher risk of transaminase elevation when used for more than 16 weeks, especially among patients with CAD.
- There is more recent evidence supporting the association of statins in general with the risk of diabetes mellitus. The association appears to be stronger with atorvastatin 80 mg and rosuvastatin compared to lower-intensity atorvastatin and other statins used.

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# 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 2018

## Team

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

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## Disclosure of conflict of interest

Kaiser Permanente requires that team members participating on a guideline team disclose and resolve all potential conflicts of interest that arise from financial relationships between a guideline team member or guideline team member's spouse or partner and any commercial interests or proprietary entity that provides or produces health care–related products and/or services relevant to the content of the guideline.

Team members listed above have disclosed that their participation on the Secondary Prevention of ASCVD Guideline team includes no promotion of any commercial products or services, and that they have no relationships with commercial entities to report.