

# Atherosclerotic Cardiovascular Disease (ASCVD) Primary Prevention Guideline

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**Last guideline approval:** October 2020

**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 October 2020

New	Previous
<p>Updated aspirin recommendations:</p> <ul style="list-style-type: none"><li>• Initiating low-dose aspirin therapy is no longer routinely recommended for primary prevention, given new evidence that the benefits do not generally outweigh the risks of bleeding.</li><li>• It is appropriate to discontinue aspirin therapy in many patients who are already taking it, with the exception of patients at high cardiovascular risk (10-year ASCVD risk <math>\geq</math> 10%), who may still benefit. Shared decision-making is encouraged.</li></ul>	<p>Previous aspirin recommendations:</p> <ul style="list-style-type: none"><li>• Aspirin is recommended for patients aged 50–59 if <math>\geq</math> 10% risk of ASCVD (myocardial infarction or stroke) over 10 years.</li><li>• Use shared decision-making for patients aged 60–69 if <math>\geq</math> 10% risk over 10 years.</li><li>• No recommendation on aspirin for patients under age 50 or over age 70 due to insufficient evidence.</li></ul>
<p>Coronary artery calcium (CAC) scores may be helpful for patients at intermediate ASCVD risk who are uncertain about taking a statin, and/or for patients whose calculated risk is higher or lower than expected.</p>	<p>Coronary artery calcium scoring is not routinely recommended because it does not add significantly to clinical decision-making in a way that improves outcomes.</p>

## 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, 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. Patients with incidental aortic atherosclerosis should follow usual care recommendations for ASCVD prevention (e.g., lifestyle changes, statins).

**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.

## Goals of Primary Prevention

Modify risk factors or prevent their development with the aim of delaying or preventing new-onset ASCVD. This guideline addresses the primary prevention of ASCVD in general. It does not attempt to address screening or treatment of specific potential manifestations of ASCVD.

# Lipid Screening and ASCVD Risk Calculation

Eligible population	Test	Frequency
Under age 40	Routine screening is not recommended unless patient has a major cardiovascular risk factor (e.g., diabetes, hypertension, family history, smoking).	
Age 40–75	Non-fasting lipid panel	Every 5 years at a minimum <sup>1</sup>
Over age 75	Routine screening is not recommended.	Upon patient request or based on other ASCVD risk factors

<sup>1</sup> Consider re-screening intervals based on ASCVD risk:

- Every **5 years** if ASCVD risk < 7.5% over 10 years
- Every **2 years** if ASCVD risk 7.5–14.9% over 10 years
- **Annually** if ASCVD risk ≥ 15% over 10 years and not on statin

## Lipid screening tests

### Lipid panel: for most patients

The results of a **lipid panel**—total cholesterol, HDL, LDL, and triglycerides—ordered through KP HealthConnect include the patient’s 10-year risk calculation for cardiovascular disease. It is recommended that the patient be non-fasting for the lipid panel, as this is much easier for the patient and does not require a return visit. Any patient who has a triglyceride level > 400 mg/dL (regardless of LDL level) will need to return for a fasting lipid panel.

### hs-CRP: consider for patients at 7.5–14.9% risk

For patients **at 7.5–14.9% ASCVD risk over 10 years**, consider testing with hs-CRP to help confirm elevated risk when deciding whether to recommend statin therapy.

Result	Interpretation
< 1 mg/L	Risk is lower than the ASCVD risk calculation.
1–3 mg/L	Risk is close to the ASCVD risk calculation.
3.1–9.9 mg/L	Risk is higher than the ASCVD risk calculation.
≥ 10 mg/L	These elevations are associated with a nonspecific inflammatory process. Cardiac risk CRP should be reevaluated after the inflammatory condition has resolved.

### Coronary artery calcium scoring: consider for patients at indeterminate risk or at intermediate risk and undecided about statins

Coronary artery calcium (CAC) scoring is not routinely recommended. However, CAC may be helpful for patients at intermediate ASCVD risk who are uncertain about taking a statin, and/or patients whose calculated risk is higher or lower than expected.

#### Who should consider getting CAC score testing?

- Individuals at **intermediate ASCVD risk** (aged 40–75 years without diabetes and with LDL-C levels ≥ 70 mg/dL, at a 10-year ASCVD risk of ≥ 7.5% and < 20%), **if risk status or decision about statin therapy is uncertain** (for example, due to patient reluctance to start pharmacotherapy). For these patients, treatment with statin therapy may be withheld or delayed if CAC = 0, except in cigarette smokers and those with a strong family history of premature

ASCVD. A CAC score of 1–99 favors statin therapy, especially in those aged  $\geq 55$  years. For any patient, if the CAC score is  $\geq 100$  or  $\geq 75$ th percentile, statin therapy is indicated.

- Measurement of CAC may be considered in select adults with **borderline elevated ASCVD risk** (5–7.4% 10-year ASCVD risk) for further risk stratification, **in whom the presence of CAC may change decision-making** with regard to statin treatment and intensity of ASCVD risk factor modification.

If patients get CAC testing but remain untreated, repeating CAC measurement in 5–10 years may have some value in reassessing for CAC progression, but data are limited.

#### Who should **not** get CAC score testing?

- Routine CAC measurement is not recommended in patients **at low (< 5% 10-year risk) or high ( $\geq 20\%$  10-year risk) ASCVD risk**, as the results are generally unlikely to change management.
- Patients who are **averse to treatment and unlikely to initiate treatment** even if CAC is identified should not undergo CAC testing.

Patients should be advised to contact Member Services to determine their coverage benefit for CAC testing, as it may incur out of pocket costs. See [Clinical Review Criteria for CT Angiography and CT Cardiology: Screening & Calcium Scores](#) for more information.

**Note:** The U.S. Preventive Services Task Force (USPSTF 2018) examined whether the addition of coronary artery calcium to the traditional risk factors improves risk classification. The report concluded that—while CAC scoring statistically improves risk stratification—there was insufficient evidence to determine either the benefits and harms of using CAC score testing for risk assessment, or whether adding it to the tools currently used would reduce the incidence of CHD or mortality following statin therapy.

#### **Biomarker tests: not recommended**

Testing for the following biomarkers of inflammation and lipid-related markers is **not** recommended. Although they may be independently associated with cardiovascular disease risk, they have only a minimal prognostic value when added to conventional risk markers:

- Fibrinogen
- Lipoprotein(a)
- Phospholipase A<sub>2</sub>
- Apolipoprotein B and A-1 combined

## ASCVD risk calculation

KP Washington is now using the **Pooled Cohort Equation** to estimate a patient's risk of developing an ASCVD event (myocardial infarction or stroke) over the following 10 years. Use of this risk estimate will help determine which patients might benefit from primary prevention interventions. The calculations will be returned with the lipid panel results or by using a SmartLink in KP HealthConnect.

**Note: ASCVD risk calculators can only estimate risk. Interpretation of ASCVD risk calculations should always reflect informed clinical judgment.**

The ASCVD calculator is available:

- On the public website for use by clinicians, contracted providers, and members.
- Through the KP HealthConnect SmartLink **.ascvdrisk**, which pulls information from a patient's record to calculate the risk.
- In the Health Profile online tool for members.
- In the Clinical Lab's lipid panel results.

# 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.

There is strong evidence that adhering to a Mediterranean-style eating plan reduces the incidence of major cardiovascular events in people at risk for ASCVD. Adhering to a DASH eating plan can be an alternative. Both eating plans provide similar key elements: an emphasis on plant foods (fruits, 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 that consuming an average of two fish servings weekly may reduce CHD mortality.

## Moderation of alcohol consumption

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

Alcohol consumption is not considered to be a strategy for preventing ASCVD.

## Physical activity

The American Heart Association recommends the following physical activity goals:

- At least 30 minutes of moderate-intensity aerobic activity 5 or more days per week.
- Moderate- to high-intensity muscle-strengthening activity 2 or more days per week.

An example of moderate-intensity aerobic 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.

## Weight management

- 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

- The target the blood pressure for the general population is **< 140/90 mm Hg**.
- For patients who are at  $\geq 10\%$  10-year risk of ASCVD, have chronic kidney disease (CKD), or are age 75 or older, the blood pressure target is **< 130/80 mm Hg**.
- If a patient's blood pressure 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.
- Folic acid, vitamin B12, and vitamin E: There is evidence of no benefit and/or possible harm with the use of these supplements/vitamins in the primary prevention of ASCVD.
- 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.
- Vitamin C: There is evidence that vitamin C supplementation has no benefit in the primary prevention of ASCVD.
- Fish oil: There is some evidence that fish oil supplementation has no significant benefit in reducing cardiovascular events or mortality among individuals with no history of ASCVD.

## Statin Therapy

Population	Statin therapy
ASCVD risk 5–7.4% over 10 years	Use shared decision-making. Consider treatment with a moderate-intensity statin.
ASCVD risk 7.5–14.9% over 10 years	Use shared decision-making. Consider treatment with a moderate- to high-intensity statin.
ASCVD risk $\geq$ 15% over 10 years	Initiate or continue moderate- to high-intensity statin.
People <b>with diabetes</b> , aged 40–75, with ASCVD risk $\geq$ 7.5% over 10 years	Initiate or continue moderate-intensity statin. Consider use of a high-intensity statin.
People <b>with diabetes</b> , aged 40–75, with LDL cholesterol 70–189 mg/dL	Initiate or continue moderate-intensity statin.
LDL cholesterol $\geq$ 190 mg/dL	Initiate or continue high-intensity statin.

### Recommended statin dosing

Most patients who are taking statins for primary prevention of ASCVD should be initiated on moderate-intensity statins, defined as those lowering LDL cholesterol by an average of 30–49%. See Table 4.

**Only** patients with questionable ability to tolerate moderate-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 5.

Line	Medication	Initial dose	Maximum dose
1 <sup>st</sup>	Atorvastatin	20 mg daily	80 mg daily
	Rosuvastatin	5–10 mg daily	40 mg daily
2 <sup>nd</sup>	Simvastatin	40 mg daily at bedtime	40 mg <sup>1</sup> daily at bedtime
<sup>1</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.			

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

## LDL levels

**LDL goal < 100 mg/dL**

Generally, LDL is measured only as follow-up for patients on statin therapy to assess response and adjust dose if needed. The LDL goals listed above may not fit all patients. An alternative goal is a 30–40% reduction from the previous LDL measure.

## 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 (TGs) and health outcomes. Neither the threshold nor the 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 section on page 12.) Treatment/investigation at > 1,000 mg/dL would also be reasonable; use shared decision making.

## Follow-up for patients on statins

Statin therapy should be adjusted if patients are not meeting the LDL goals above. For patients on at least moderate-intensity therapy who are above the LDL goal, consider increasing to high-intensity statin therapy (defined as lowering LDL cholesterol by an average of  $\geq 50\%$ ). 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.

### If the statin is not working (patient is not achieving LDL goal)

1. First, assess adherence to therapy. Patients often are not taking their medication regularly. Approximately half of patients who start on statin drugs stop them on their own within 1 year.
2. If they are taking their medication regularly, consider increasing dose (if not already at maximum).
3. If the statin is still not working, use shared decision-making to decide whether to consider switching to another statin. Consider an E-Consult with Cardiology, where available.
4. Consider adding ezetimibe 10 mg for patients who are not able to achieve an LDL < 100 mg/dL on maximally tolerated doses of formulary statins **and** meet at least one of the following criteria:
  - o 10-year ASCVD risk  $\geq 7.5\%$  based on Pooled Cohort Equation, or
  - o Patient aged 40 or older with diabetes, or
  - o Any patient with LDL  $\geq 190$  mg/dL



### 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, where available.
3. To determine if myalgia symptoms can be attributed to use of the statin, consider using the [American College of Cardiology's statin intolerance tool](#).

### If the patient is *still* intolerant or has contraindications to statins

- For patients who are not able to achieve an LDL < 100 mg/dL **and** meet at least one of the following criteria, **stop the statin and consider prescribing ezetimibe**:
  - 10-year ASCVD risk  $\geq$  7.5% based on Pooled Cohort Equation, or
  - Patient aged 40 or older with diabetes, or
  - Any patient with LDL  $\geq$  190 mg/dL

#### 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.

### Shared decision-making for statin therapy

To help providers discuss the risks and benefits of taking statins for primary prevention of ASCVD, Kaiser Permanente has developed a shared decision-making (SDM) tool that calculates ASCVD risk using pre-populated data from KP HealthConnect. This tool is available in any KP HealthConnect encounter and can also be accessed at <https://clm.kp.org/pkc/national/cmi/programs/dyslipidemia/cadrisk/index.html>.

**NOTE:** The SDM tool also provides recommendations on aspirin, which are based on 2018 ACC/AHA guidance. However, ***these aspirin recommendations should be interpreted with caution*** as we no longer recommend routine use of low-dose aspirin for primary prevention based on new evidence showing that the increased risk of major bleeding outweighs the small benefit in risk reduction. See the Antiplatelet Therapy section (page 11) for more information.

## Atherosclerotic Cardiovascular Disease (ASCVD) Prevention Tool

Enter Patient Data | Shared Decision

*Intended for use if there is not ASCVD and the LDL-cholesterol is <190 mg/dL.*

Age (years)

African American  Yes  No

Gender  Male  Female

Diabetes  Yes  No

On BP Medications  Yes  No

Smoker  Yes  No

Total Cholesterol  mg/dL

HDL Cholesterol  mg/dL

Systolic Blood Pressure  mm/Hg

LDL Cholesterol  mg/dL

**Estimated Risk**

**41.9%** Your Estimated 10-Year ASCVD Risk

**KP Guideline Recommendations**

**Start High-Intensity Statin**  
Start atorvastatin 40 mg.

**Consider Aspirin at 81 mg**  
Consider initiating aspirin in adults aged 60-69 years with a  $\geq 10\%$  10-year ASCVD risk.

**Smoking Cessation**  
Smoking Cessation should be encouraged to reduce the risk of ASCVD.

**Recalculate Risk**

ASCVD risks can also be displayed in a format that shows patients how much their risks would do down if they added interventions such as taking a statin or aspirin or quitting smoking:

## Atherosclerotic Cardiovascular Disease (ASCVD) Prevention Tool

Enter Patient Data | **Shared Decision**

*Intended for use if there is not ASCVD and the LDL-cholesterol is <190 mg/dL.*

**Shared Decision**

Explore how different actions could reduce your risk of heart attack or stroke

**Choose Intervention**

High-Intensity Statin  
 Moderate-Intensity Statin  
 Aspirin  
 Quit Smoking

**Impact of Intervention(s)**

**Selected Intervention(s)** **12.6%**  
Your Estimated 10-Year ASCVD Risk:

**No Intervention(s)** **41.9%**  
Your Estimated 10-Year ASCVD Risk:

**Order Statin:**  No  Yes  Undecided

**Order Aspirin:**  No  Yes  Undecided

13 will have a cardiovascular event

58 will not have a cardiovascular event

29 will have a cardiovascular event prevented with this treatment

### Risks of statin therapy

For patients who are concerned about the risks of statins, the following evidence summary on potential harms of statin therapy may be helpful.

- **Cognitive impairment:** Per the U.S. Food and Drug Administration (FDA), rare post-marketing reports of cognitive impairment (e.g., memory loss/impairment, forgetfulness, amnesia, confusion) have been reported with statin use, with time to onset ranging from 1 day to years after starting statin therapy (USFDA 2012). The incidence of cognitive-related adverse events reported to the FDA for statins (1.9 per 1 million prescriptions) was similar to those reported for losartan (1.6 per 1 million prescriptions) and clopidogrel (1.9 per 1 million prescriptions) (Richardson 2013). If cognitive

impairment occurs, discontinue the statin (median time to symptom resolution was 3 weeks upon statin discontinuation).

- **Diabetes risk:** The FDA added warnings to all statins (except pravastatin) that statin use can increase HbA1c and fasting serum glucose levels. The absolute excess risk of new-onset diabetes is very low, approximately 0.1% per year (number needed to harm [NNH] 255 over 4 years; Sattar 2010). The FDA (2012) also analyzed this data, and stated that the cardiovascular benefits of statins in clinically appropriate patients outweigh this risk. Therefore, statin treatment alone does not constitute an indication to screen for diabetes, but screening should still be considered if other risk factors for diabetes exist.
- **Myalgias/musculoskeletal injuries/decreased benefits of exercise:** In a meta-analysis of 55 placebo-controlled RCTs (N=43,531), there was no significant increase in myalgia with statins compared with control (Naci 2013), whereas observational studies have reported myalgia incidence varying from 1 to 25% (Sathasivam 2012, Parker 2013). Keep in mind, however, that many of the RCTs had a “run-in” period of 30 days, when patients who were intolerant of the statins were excluded from the study. A retrospective, propensity-matched cohort study (N=13,934) reported a 0.6% per-year risk of dislocation/strain/sprain with statin use (NNH 38 over 4.7 years; Mansi 2013). Other small RCTs have reported conflicting results of whether statin use decreases muscle strength or exercise capacity (Parker 2013, Mikus 2013).
- **Rhabdomyolysis:** Very rare. A large (N=473,343) observational cohort study reported that for commercially available statins, rates of hospitalized rhabdomyolysis events were approximately 0.3–1.6 per 10,000 person-years of statin use (NNH 6,250–33,334 per year) (Cziraky 2013).
- **Acute kidney injury (AKI):** Rare. A large (N=2,067,639) retrospective observational analysis reported that in non-CKD patients on low-dose statins, hospitalizations for acute kidney injury at 6 months ranged from 1.0 to 3.5 per 1,000 patients in those younger than 65 years and 3.1 to 4.0 per 1,000 patients in those aged 65 years and older (Dormuth 2013). Non-CKD patients on high-potency statins versus low-potency statins were 34% more likely to be hospitalized for acute kidney injury, but incidence remained rare, with NNH 1,700 over 120 days.
- **Hepatotoxicity:** Per the FDA, statins have a very low risk of serious liver injury (reported at a rate of  $\leq 2$  per 1 million person-years), and routine liver function monitoring is not recommended, as ALT monitoring does not appear to detect or prevent serious liver injury (USFDA 2011).

## Antiplatelet Therapy

Use of low-dose aspirin for ASCVD primary prevention is no longer routinely recommended and should be decided on an individual basis. This is because its small benefit in preventing adverse cardiovascular events such as myocardial infarction and stroke is generally offset by the risk of major bleeding. Based on current data, it would also be appropriate to discontinue low-dose aspirin in many patients who are already taking it. However, patients at high risk of ASCVD (10-year risk  $\geq 10\%$ ), may still benefit from low-dose aspirin, so shared decision-making is encouraged.

# Patients with Diabetes: ACE Inhibitor or ARB Therapy

ACE inhibitor or ARB therapy should be prescribed for patients with diabetes who have the following risk factors:

- Hypertension (BP > 140/90 mm Hg) (type 1 or 2), **or**
- Elevated microalbumin to creatinine ratio (type 2 only), **or**
- Are aged 55 or older and have additional cardiovascular risk factors (type 2 only).

<b>Table 6. Patients with diabetes and elevated risk: ACE inhibitor or ARB therapy for primary prevention of ASCVD</b>			
<b>Line</b>	<b>Medication</b>	<b>Initial dose</b>	<b>Maximum dose</b>
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>	ARB <sup>1</sup>		
	Losartan	25–50 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

ACE inhibitor and ARB 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.

## Lowering Triglycerides to Prevent Pancreatitis

Triglycerides do not require pharmacologic 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:

- 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 over-the-counter alternatives are also available in this treatment category.

<b>Table 7. Medications for lowering triglyceride levels to prevent possible pancreatitis</b> See also the <b>prescribing notes</b> that follow Table 7.			
	<b>Medication</b>	<b>Initial dose</b>	<b>Maximum dose</b>
<b>Start with:</b>	Atorvastatin	80 mg daily	80 mg daily
	<b>or</b> Rosuvastatin	20 mg daily	40 mg daily
If TG not < 500 mg/dL:	<b>Add</b> Fenofibrate	54–160 mg daily	160 mg daily
	<b>or</b> 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:	<b>Add</b> Omega-3 fatty acids or fenofibrate per agent chosen in previous step		
	<b>or</b> Gemfibrozil monotherapy	600 mg twice daily	600 mg twice daily

### Prescribing notes for Table 7

#### *Atorvastatin and rosuvastatin*

Use maximum dose of atorvastatin and rosuvastatin with caution in patients at risk for statin intolerance or adverse effects, such as those who are elderly, have kidney disease (rosuvastatin max dose = 10 mg/day with CrCl < 30 mL/min), have untreated hypothyroidism, or are taking interacting drugs.

#### *Fenofibrate*

- In patients with CKD 3 (CrCl 30–59 mL/min), do not exceed fenofibrate 54 mg per day.
- Do not use in 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 in patients with mild to moderate renal impairment (CKD 2–3).
- Do not use in patients with severe renal impairment (serum creatinine greater than 2 mg/dL or CKD 4–5).

# Medication Monitoring

Table 8. Medication monitoring		
Eligible population	Tests	Frequency of lab testing
Patients on statin	Non-fasting lipoprotein panel	4–6 weeks after initiating therapy
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 dose increase <b>and</b> Annually
Patients on fenofibrate therapy	Creatinine	<i>At baseline</i> <b>and</b> 3 months after initiating therapy <b>and</b> Every 6 months
	<b>and</b> ALT/AST (Only for patients on combo therapy with a statin)	<i>At baseline</i> <b>and</b> 4–6 weeks after initiating therapy <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 Primary 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

2020 American Diabetes Association. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes—2020. *Diabetes Care*. 2020;43(Suppl 1):S111-S134. doi:10.2337/dc20-S010

2020 National KP Clinical Practice Guidelines: Cholesterol and Cardiovascular Risk.

2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2019;74(10):1376-1414. doi:10.1016/j.jacc.2019.03.009

2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J*. 2020;41(1):111-188. doi:10.1093/eurheartj/ehz455

2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J*. 2020;41(2):255-323. doi:10.1093/eurheartj/ehz486

2018 U.S. Preventive Services Task Force. Risk Assessment for Cardiovascular Disease With Nontraditional Risk Factors: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2018;320(3):272-280. doi:10.1001/jama.2018.8359

## Key questions addressed in the KPWA guideline

### Key question 1

#### Coronary artery calcium (CAC) score

- a) Is there an association between CAC and major cardiovascular events in asymptomatic individuals with no history of ASCVD?
- b) Is the CAC score an independent predictor of ASCVD events in asymptomatic individuals?
- c) Does CAC scoring add an incremental predictive value to the traditional risk factors/calculators currently used for risk stratification of adult asymptomatic patients with no known history of ASCVD?
- d) Does CAC scoring have clinical utility in asymptomatic individuals at intermediate risk of ASCVD? In other words, does the measurement of CAC in addition to the traditional risk factors guide the long-term use of statin therapy and improve the clinical outcome in asymptomatic adults at intermediate CV risk?
  - There is moderate-quality evidence from large longitudinal long-term population studies, mainly the landmark MESA (Budoff 2018), indicating that CAC may be strongly associated in a graded fashion with 10-year risk of incident ASCVD (including stroke) in asymptomatic White, Black, Hispanic and Chinese American men and women aged 45–84 with no known history of CHD. MESA showed that 10-year event rates in participants with CAC = 0 were almost exclusively below 5%, while these rates were consistently above 7.5% in participants with CAC ≥ 100.
  - Moderate-quality evidence from large longitudinal long-term population studies shows that CAC may be independently associated with ASCVD risk in asymptomatic individuals with no known history of ASCVD (Hoffmann 2016, Lehman 2018, Mitchell 2018, Shaw 2015).

- Large longitudinal long-term population studies (Hoffmann 2016, Yeboah 2016) show that CAC scoring provides additional predictive information on ASCVD events and mortality, beyond the traditional risk factors, in men and women of different age groups, races, ethnic backgrounds, and risk levels, and in the presence or absence of comorbid conditions such as diabetes mellitus.
- The inclusion of CAC in the MESA risk score (McClelland 2015) was found to significantly improve the risk prediction of CAD (C-statistics 0.80 vs. 0.75,  $p < 0.0001$ ).
- There is insufficient published evidence from published RCTs to determine that treatment guided by CAC scoring levels in addition to the traditional risk factors improves the clinical management and/or clinical outcomes in asymptomatic adults at intermediate CV risk.

It should be noted that all data were obtained from observational population-based studies, which have inherent limitations, including relying on data recorded in registries and databases; baseline CAC measurement and assessment were done using earlier technology; and major developments were seen over time in lifestyle, statin use, antihypertensive drugs, antiplatelet and other therapies as well as in the technology and equipment used to measure and assess the CAC.

### Key question 2

**Does the benefit of using aspirin for the prevention of CVD events in adult patients with diabetes outweigh its harms?**

- Based on recent guidelines and meta-analyses (including Barbarawi 2019, Christiansen 2019, and Zheng 2019) and randomized controlled trials, aspirin may be used for CVD prevention in patients who are at high risk for CV events. Diabetic patients with 10-year CVD risk  $\geq 10\%$  will benefit the most from aspirin therapy. For diabetic patients who are at intermediate or low risk for CVD, aspirin therapy showed a slight benefit, but at a higher risk of bleeding (Seidu 2019, Khan 2019). According to the published guidelines, low-dose aspirin should not be given on a routine basis to prevent ASCVD among adults once they reach age 70, and it should not be considered for any adult with increased bleeding risk.
- The ASCEND trial (ASCEND Study Collaborative Group 2018), which examined the efficacy and safety of enteric coated aspirin in diabetic patients without known CVD, showed that the number of patients needed to treat to avoid a major CVD event (NNT) was 91 in an average of 7 years, while the corresponding number of major bleeding incidents (NNH) was 111; i.e., the observed reduction in CVD events may be offset by the risk of major bleeding.
- It is thus suggested that aspirin should not be used on a routine basis in the primary prevention of cardiovascular events, especially in individuals with diabetes. and that individual assessment of diabetic patients for CV risk should be considered before initiation of aspirin therapy.
- Shared decision-making is needed and should consider the patient's age, bleeding history and risk, cardiovascular risk factors, quality of life, preferences, and willingness to undergo long-term aspirin therapy.
- In cases where aspirin is to be used for primary prevention, it is recommended to be given at the lowest dose possible (75–100 mg). The ESC guideline recommends uncoated aspirin with co-administration of a proton-pump inhibitor for patients at high risk for bleeding.

### Key question 3

**Are the harms and benefits of aspirin use similar among patients with type 1 and type 2 diabetes?**

- There is no standardized method for measuring aspirin responsiveness/resistance.
- Rates of aspirin resistance may vary widely based on the method used to assess platelet function and have been reported to range from 5% to 40%.
- There is weak evidence indicating no significant difference between type 1 and type 2 diabetes in their responsiveness to aspirin therapy.
- There is insufficient evidence to determine whether there are any differences between type 1 and type 2 diabetes patients as regards the safety and efficacy of aspirin in the primary prevention of ASCVD or the harms associated with the use of aspirin.
- All national guideline recommendations on the use of aspirin therapy for reducing the risk of ASCVD in diabetics do not differentiate between patients with type 1 and type 2 diabetes.



- The published studies evaluating the efficacy and safety of aspirin use for the primary prevention of ASCVD in diabetics included patients with diabetes without distinction between types. No sub-analyses were performed to determine whether there were any differences between type 1 and type 2 diabetes patients in the observed benefits and harms associated with the use of aspirin.

#### Key question 4

**Is there published evidence to support annual or more frequent lipid monitoring of patients receiving statin with or without other lipid-lowering therapies (ezetimibe and PCSK9-I)?**

- The literature search did not identify any published studies that would provide evidence on the optimal frequency of monitoring patients receiving any lipid-lowering therapy.

#### Key question 5

**Does the use of SGLT2 drugs reduce cardiovascular risk and/or events in patients without a history of type 2 diabetes?**

- The literature search identified a large number of randomized controlled trials and meta-analyses of RCTs evaluating the safety and efficacy of SGLT2 inhibitors for reducing HbA1c levels in patients with diabetes mellitus.
- However, the search did not reveal any published trials to date that examined the use of this class of medications in individuals without diabetes but with established ASCVD or risk factors for the disease. While recent trials have shown a benefit in patients with heart failure, guidance and management have not yet been established for SGLT2 inhibitors, and they should not be used routinely at this point.
- There is strong evidence from three major cardiovascular outcomes trials with valid methodology—EMPA-REG OUTCOME with empagliflozin (Zinman 2015), the CANVAS program with canagliflozin (Neal 2017), and DECLARE-TIMI 58 with dapagliflozin (Wiviott 2018)—as well as from the CREDENCE renal outcome trial (Perkovic 2019) and meta-analyses pooling their results (Zelniker 2019, Zou 2019, Arnott 2020) that SGLT2 inhibitors could have an overall cardioprotective benefit, particularly for heart failure, in patients with DM.
- The moderate benefit observed with SGLT2 inhibitors on atherosclerotic major adverse cardiovascular events was only significant in patients with established ASCVD, but not among those with risk factors and no ASCVD at baseline.
- There was a significant reduction in hospitalization for heart failure and progression of renal disease with the use of SGLT2 versus placebo regardless of existing ASCVD or a history of heart failure.
- Overall, the analyses of the individual studies and their pooled results suggest that patients with established CVD may gain greater benefits from SGLT2 inhibitor therapy than those at lower risk.
- SGLT2 is associated with increased rates of diabetic ketoacidosis.
- CANVAS found that canagliflozin was associated with significant increases in the risks of amputations or fractures compared with controls, but no such findings have been reported in trials with other SGLT2 inhibitors.
- The major published trials reviewed were at low risk of bias, but there were some differences between the treatment groups with regard to the concomitant medication used and HbA1c control.
- All participants in the EMPA-REG OUTCOME trial had an established CVD at enrollment, compared to two thirds in the CANVAS program, and 40% of those enrolled in the DECLARE-TIMI 58 study. The latter more closely resemble those seen in routine clinical practice.

#### Key question 6

**What is the incremental benefit of using the triglyceride-lowering drug (icosapent ethyl) on cardiovascular outcomes beyond the optimal reduction of low-density lipoprotein cholesterol?**

A recently published trial (Reduction of Cardiovascular Events with EPA-Intervention Trial [REDUCE-IT] [Bhatt 2019]) showed that in patients with established atherosclerotic heart disease, or diabetes and an additional risk factor, on statin therapy and with residual hypertriglyceridemia (fasting triglyceride level 135–499 mg/dL), icosapent ethyl was associated with an absolute 4.8% reduction in cardiovascular events (cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina), NNT = 21 (95% CI, 15–23) in 4.9 years (with a 0.9% absolute reduction in cardiovascular death, NNT = 111 in 4 years).

The results of the trial conflict with other RCTs that examined the effect of omega-3 fatty acids on CV outcomes and showed negative results. The JELIS trial (reviewed for the previous update of the guideline, showed a 19% relative risk reduction in cardiovascular events when 1.8 g daily of eicosapentaenoic acid (EPA) was added to low-intensity statin therapy. JELIS was limited by an open-label design, lack of placebo control, and geographic limitation to patients in Japan. The REDUCE-IT trial, on the other hand, used a higher dose of purified EPA formulation in selected patients and was controlled and double-blinded. However, the mechanism of action responsible for the observed benefit of icosapent ethyl is not known and is currently being investigated.

The REDUCE-IT trial was a multicenter, double-blinded, large RCT with sufficient power and ITT analysis. However, it had limitations, including but not limited to the following:

- The placebo used contained mineral oil which, as reported by some investigators, may reduce the absorption of statins leading to the increase in LDL-C and C-reactive protein levels, which may potentially magnify the effect of icosapent ethyl.
- The trial was initiated in 2011 when there were insufficient data to recommend ezetimibe and PCSK9 was not available.
- The protocol was amended twice during the study (changing the lower limit of TG level and amending the secondary end point).
- The trial was sponsored by Amarin Pharma, which was involved in the development of the protocol, collection, management and analysis, and interpretation of the data.
- In addition to the unknown mechanism for the benefit observed with icosapent ethyl, the REDUCE-IT trial leaves other questions unanswered, including:
  - Would the benefit of icosapent ethyl be significant in primary prevention individuals, who constituted only 30% of the study population?
  - Would the benefit of icosapent ethyl persist in patients receiving ezetimibe and PCSK9 drugs on top of baseline statin therapy?

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# Guideline Development Process and Team

## Development process

The guideline team developed the ASCVD Primary Prevention 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 October 2020.

## Team

The ASCVD Primary Prevention Guideline team included representatives from the following specialties: cardiology, clinical laboratory, endocrinology, family medicine, internal medicine, and 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 ASCVD Primary Prevention Guideline team includes no promotion of any commercial products or services, and that they have no relationships with commercial entities to report.