KAISER PERMANENTE®

Atherosclerotic Cardiovascular Disease (ASCVD) Primary Prevention Guideline

Last guideline approval: April 2023

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

Major Changes as of April 2023

- Shared decision-making is recommended when deciding whether to prescribe statins for the primary prevention of cardiovascular events for those over 75 years. Considerations should include functional ability, comorbidities, polypharmacy, frailty, cognitive status, life expectancy, quality of life, and patient preference.

- The blood pressure target for patients at high risk (age ≥ 75, with CKD, or with a ASCVD risk ≥ 10%) was changed from 130/80 to 130/90, to be in alignment with the KP National Blood Pressure Guideline.

- Clinicians should consider reducing rosuvastatin dose to 10 mg daily for patients with CKD 4–5 (eGFR < 30 mL/min).

Definitions

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

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

Table 1. Lipid screening for patients not already on statins		
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 [1]
Over age 75	Routine screening is not recommended.	Upon patient request or based on other ASCVD risk factors

[1] 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 test

Lipid panel: Use 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. Interpret LDL with caution in patients with triglycerides > 400 mg/dL; consider having patient return for fasting lipids and/or directly measuring LDL.

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. The Pooled Cohort Equation tends to overestimate risk of cardiovascular events. Interpretation of ASCVD risk calculations should always reflect informed clinical judgment and consideration of additional factors, such as family history and lifestyle.**

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.
- As a link at the end of lipid panel results.

Risk modifiers/additional factors to consider

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.

Table 2. Interpreting hs-CRP test results

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 ≥ 55 years. For any patient, if the CAC score is ≥ 100 or ≥ 75th 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 (≥ 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 Cardiography: 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.

Subclinical atherosclerosis

Subclinical atherosclerosis includes elevated coronary artery calcium, low ankle brachial index (ABI), or aortic atherosclerosis. Consider subclinical atherosclerosis as a risk modifier when the patient is undecided on whether to take a statin.

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_2
- Apolipoprotein B and A-1 combined

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 blood pressure for the general population is **< 140/90 mm Hg.**
- For patients who are at ≥ 10% 10-year risk of ASCVD, have chronic kidney disease (CKD), or are age 75 or older, the blood pressure target is **< 130/90 mm Hg.**
- If a patient's blood pressure is higher than goal, see the Blood Pressure Guideline for management recommendations.

Type 2 diabetes management

For patients with type 2 diabetes at high risk of ASCVD or with heart failure or chronic kidney disease, consider use of SGLT2 inhibitor after metformin to reduce cardiorenal events per the Type 2 Diabetes Guideline.

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 evidence that fish oil supplementation has no significant benefit in reducing cardiovascular events or mortality among individuals with no history of ASCVD.

Statin Therapy

Table 3. Overview of statin therapy recommendations for primary prevention of ASCVD	
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 ≥ 15% over 10 years	Initiate or continue moderate- to high-intensity statin.
People **with diabetes,** aged 40–75, with ASCVD risk ≥ 7.5% over 10 years	Initiate or continue moderate-intensity statin. Consider use of a high-intensity statin.
People **with diabetes**, aged 40–75, with LDL cholesterol 70–189 mg/dL	Initiate or continue moderate-intensity statin.
LDL cholesterol ≥ 190 mg/dL	Initiate or continue high-intensity statin.
Patients over age 75	Use shared decision-making. [1]

[1] Considerations should include functional ability, comorbidities, polypharmacy, frailty, cognitive status, life expectancy, quality of life, and patient preference.

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/age over 75, those taking interacting drugs, and those with hepatic/renal impairment or untreated hypothyroidism—should be initiated on reduced doses, as given in Table 5.

Table 4. STANDARD (moderate-intensity) statin dosing for primary prevention of ASCVD
Standard dosing applies to patients for whom there are no concerns about their ability to tolerate moderate-intensity statin therapy.

Line	Medication	Initial dose	Maximum dose
1st	Atorvastatin	20 mg daily	80 mg daily
	Rosuvastatin	5–10 mg daily	40 mg daily [1]
2nd	Simvastatin	40 mg daily at bedtime	40 mg daily at bedtime [2]

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

[2] 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.

Table 5. REDUCED (low-intensity) statin dosing for primary prevention of ASCVD
Reduced dosing applies only to patients with questionable ability to tolerate moderate-intensity statin therapy, including those who are over 75/frail, have hepatic/renal impairment or untreated hypothyroidism, or are taking interacting drugs.

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

[1] Clinicians should consider reducing rosuvastatin dose to 10 mg daily for patients with CKD 4-5/ eGFR < 30 mL/min. See the Rosuvastatin in CKD huddle card.
[2] 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 optimal interval has not been determined for routine LDL monitoring after goal has been reached. 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 11.) 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 ≥ 50%). On the other hand, if a patient has achieved a very low LDL level, **do not lower** the intensity of statin therapy. Evidence suggests that no LDL level is too low.

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

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 or Clinical Pharmacy, 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:
    - 10-year ASCVD risk ≥ 7.5% based on Pooled Cohort Equation, or
    - Patient aged 40 or older with diabetes, or
    - Any patient with LDL ≥ 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 or intermittent statin dosing. Consider referral to Clinical Pharmacy.
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.
4. Consider checking and repleting vitamin D, as some studies suggest that vitamin D deficiency may predispose patients to statin intolerance. See this FAQ.

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 ≥ 7.5% based on Pooled Cohort Equation, or
    - Patient aged 40 or older with diabetes, or
    - Any patient with LDL ≥ 190 mg/dL

What is statin intolerance?

In 2022 the National Lipid Association (Cheeley 2022) updated its definition of statin treatment intolerance as

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

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 10) for more information.

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

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 ≤ 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 ≥ 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).

Table 6. Patients with diabetes and elevated risk: ACE inhibitor or ARB therapy for primary prevention of ASCVD

Line	Medication	Initial dose	Maximum dose
1st	ACE inhibitor		
	Lisinopril **or** Ramipril	5–10 mg daily 2.5–5 mg daily	40 mg daily (target dose is 20 mg daily) 20 mg daily (target dose is 10 mg daily)
2nd	ARB [1]		
	Losartan	25–50 mg/day in 1–2 doses	100 mg/day in 1–2 doses

[1] 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. 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 nutritional supplement alternatives are also available in this treatment category.

Table 7. Medications for lowering triglyceride levels to prevent possible pancreatitis [1]
See also the **prescribing notes** that follow Table 7.

	Medication	Initial dose	Maximum dose
If elevated ASCVD risk, start with:	Atorvastatin	80 mg daily	80 mg daily
	or		
	Rosuvastatin	20 mg daily	40 mg daily
If TG not < 500 mg/dL:	**Add** Fenofibrate	54–160 mg daily	160 mg daily
	or		
	Generic omega-3 fatty acids (Lovaza)	2,000 mg DHA/EPA in divided doses daily	4,000 mg DHA/EPA in divided doses daily
If TG still not < 500 mg/dL:	**Add** Omega-3 fatty acids or fenofibrate per agent chosen in previous step		
	or		
	Gemfibrozil monotherapy	600 mg twice daily	600 mg twice daily
If TG 1,000 mg/dL or higher:	**Consider starting with** Fenofibrate	54–160 mg daily	160 mg daily

[1] In adults with severe hypertriglyceridemia, consider implementing a very low-fat diet, avoiding refined carbohydrates and alcohol, and consuming omega-3 fatty acids.

Prescribing notes for Table 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 over 75 years of age, have severe kidney disease (rosuvastatin max dose = 10 mg/day with eGFR < 30 mL/min), have untreated hypothyroidism, or are taking interacting drugs.

Fenofibrate

- In patients with CKD 3 (eGFR 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 **and** Creatinine	At baseline **and** 2 weeks after initiating therapy **and** With each dose increase **and** Annually
Patients on fenofibrate therapy	Creatinine **and**	At baseline **and** 3 months after initiating therapy **and** Every 6 months
	ALT/AST (Only for patients on combo therapy with a statin)	At baseline **and** 4–6 weeks after initiating therapy **and** Annually

Medication monitoring that is *not* recommended

ALT/AST

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

Creatine kinase (CK)

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

Note: Chronic Disease Management Support

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

Evidence Summary

The 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

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

Key questions addressed in the KPWA evidence review

1. In individuals aged 40–79 years without a pre-existing cardiovascular disease, what is the comparative accuracy of Kaiser Permanente ASCVD Risk Estimator (KPARE) and the Pooled Cohort Equation (PCE) in estimating the 10-year risk of ASCVD?

KPARE was developed and internally validated within Kaiser Permanente populations in three KP regions (and one province in Canada), which may limit the generalization of the findings observed in that KP study (Go 2018), which was only published in an abstract form.

- The results of the study showed that the KPARE improved ASCVD risk prediction over the ACC/AHA PCE by 23% in the KPNC validation cohort, 24% in KPSC, 33% in KPNW, and 25% in Ontario, Canada. Results were similar when stratified by race-gender subgroups.
- The literature search did not identify any published studies that externally validated KPARE for estimating ASCVD risk in other KP regions or non-KP populations.

  The only study on KPARE published in a peer-reviewed journal was the KP REACH (Kaiser Permanente Residual Risk by Ethnicity, Gender, and Age in a Statin-Treated CoHort) study (Wagner 2022). KP REACH was intended not to compare the performance of KPARE versus PCE but rather to assess the performance of KPARE and PCE combined in the risk assessment

of ASCVD over a wide range of TG levels in adults with ASCVD risk factors (primary prevention) or established ASCVD (secondary prevention) who had well-controlled LDL-C and were receiving statin therapy.

2. In patients at elevated cardiovascular risk who are treated with statins, 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?

The results of the published studies and meta-analyses evaluating the effects of n-3 PUFA supplements in addition to standard statin therapy on reducing cardiovascular events are conflicting and/or inconsistent. While earlier randomized clinical trials have demonstrated significant reduction in cardiovascular events with n-3 PUFA supplements in secondary prevention patients, the more recent trials did not show such benefits, with the exception of the REDUCE-IT trial (Bhatt 2019).

- The REDUCE-IT trial found a significant reduction in ischemic events in patients treated with 4 g icosapent ethyl daily. The trial used a large dose of icosapent ethyl, which is a different formulation from that typically used in other n-3 PUFA trials (icosapent ethyl contains eicosapentaenoic acid [EPA] as opposed to the typical mixed EPA/docosahexaenoic acid [DHA] formulations used in other trials).

    - REDUCE-IT trial had several disadvantages that may limit generalization of its results. In addition, as many investigators suggest, the beneficial effects seen in the REDUCE-IT trial are probably not attributable to reduction in triglycerides, as the magnitude of the CVD risk reduction observed in the trial is unlikely to be explained by the IPE-induced reductions in TG, non-HDL-C, and LDL-C levels.
    - Investigators believe that the benefits with IPE appear to be linked to the pleiotropic actions * associated with eicosapentaenoic acid levels (Mason 2021). * Pleiotropic actions: anti-inflammatory, anti-oxidation, anti-arrhythmic, anti-thrombotic, anti-platelet, and cell membrane stability/signaling effects; improvement of endothelial function; reduction of cholesterol crystal domains; and plaque stabilization and/or regression.
    - Some investigators considered the success of icosapent ethyl's purified EPA to be false-positive due to negative biomarker changes (including increase in CRP levels) associated with the mineral oil used as a control (Lou 2021).
    - Patients in the icosapent ethyl group had a statistically significant higher incidence of atrial fibrillation compared to those in the control group, which is safety concern.
    - Bleeding emergent adverse events of any type were also significantly higher among patient in the icosapent ethyl group versus the control group, which is also a concern, especially as the secondary prevention patients may be using antiplatelet and/or anticoagulant therapies.

- The STRENGTH trial (Nicholls 2020), which used high doses of both eicosapentaenoic acid and docosahexaenoic acid, was halted early for the lack of benefit and the increased incidence of atrial fibrillation associated with the active treatment.
- The OMEMI trial (Kalstad 2021), which randomized patients aged 70 to 82 years with a recent AMI to receive 1.8 g/day of EPA/DHA or control (corn oil) for 2 years, failed to show that PUFA was superior to placebo at preventing adverse cardiovascular outcomes.
- The REDUCE-IT USA (Bhatt 2020) subgroup analysis showed higher risk reductions compared to the overall trial across a variety of individual and composite end points, including all-cause mortality. It also showed significantly higher treatment-emergent atrial fibrillation/flutter and bleeding caused by the drug of any type in the icosapent ethyl group compared to the placebo group.
- Following the publication of STRENGTH and OMEMI, there was uncertainty regarding the clinical utility of omega-3 FA for the prevention of cardiovascular disease (Kapoor 2021).

3. In individuals over age 75 years with no history of cardiovascular disease (CVD), is statin treatment more effective than standard care for the prevention and/or reduction of future cardiovascular events?

There are variations between the major guidelines on the use of statin therapy for the primary prevention of ASCVD in patients aged > 75 years . The guidelines recommending statins for patients aged > 75 years mainly based their recommendations on indirect evidence and extrapolation of efficacy and safety data from studies involving younger adults and/or subgroup analyses of larger RCTs, including JUPITER (Ridker 2008), HOPE-3 (Yusuf 2016) , ALLHAT-LLT (ALLHAT Officers 2002), as well as on observational studies.

- There is insufficient published direct evidence to date to determine the safety and efficacy of prescribing statins for the primary prevention of cardiovascular events in patients aged ≥ 75 years.
- Due to the lack of direct evidence, researchers recommend that the clinical decision to prescribe statins for the primary prevention of ASCVD for those over 75 years be made on a case-by-case basis, considering their functional ability, comorbidities, polypharmacy, frailty, cognitive status, mental health, life expectancy, and quality of life. Patient preferences also have to be considered and there must be shared decision-making that considers potential benefits and harms.
- Two ongoing large trials (Statin Therapy for Reducing Events in the Elderly [STAREE, NCT02099123] and PRagmatic EValuation of evENTs And Benefits of Lipid-lowering in oldEr Adults [PREVENTABLE, NCT04262206]) may provide more evidence on the effectiveness of statin therapy in prolonging survival and reducing cardiovascular events and disability in older adults without cardiovascular disease.

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

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

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

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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 April 2023.

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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