

Atherosclerotic Cardiovascular Disease (ASCVD) Secondary 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
SGLT2 inhibitors are recommended for patients with type 2 diabetes and established ASCVD (in addition to or after metformin therapy) due to their ability to reduce the risk of major cardiovascular events.	SGLT2 inhibitors were not included in the guideline.

Definitions

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

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

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

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

Target Population

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

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

Goals

Reduce recurrent cardiovascular events and decrease coronary mortality.

Lifestyle Modifications

Tobacco cessation

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

Healthy diet

All patients should strive to:

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

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

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

Limitation of alcohol consumption

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

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

Physical activity

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

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

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

Weight management

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

Blood pressure management

- For the general population, the blood pressure goal is **< 140/90 mm Hg**.
- For patients who have ASCVD or chronic kidney disease (CKD) or are age 75 or older, the blood pressure goal is **< 130/80 mm Hg**.
- If a patient's BP is higher than goal, see the Blood Pressure Guideline for management recommendations.

Dietary Supplements

Calcium and vitamin D

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

Dietary supplements that are *not* recommended

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

Influenza Vaccination

Patients with cardiovascular disease should get an annual influenza vaccination.

Statin Therapy

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

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

Recommended statin dosing

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

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

Table 1a. STANDARD dosing: Statins for lowering cholesterol for secondary prevention of ASCVD			
Standard dosing applies to patients for whom there are no concerns about their ability to tolerate high-intensity statin therapy.			
	Medication	Initial dose	Maximum dose
Start with:	Atorvastatin	40 mg daily	80 mg daily
	or Rosuvastatin	20 mg daily	40 mg daily
If LDL goal is not met:	Continue Atorvastatin	40 mg daily	80 mg daily
	or Rosuvastatin	20 mg daily	40 mg daily
	and add Ezetimibe	10 mg daily	10 mg daily
If LDL goal is still not met:	Refer to Cardiology or Endocrinology * for: PCSK9 inhibitors (evolocumab) [NF]	140 mg subcutaneously every 2 weeks	140 mg subcutaneously every 2 weeks
		* Cardiology or Endocrinology consultation is required.	

Table 1b. REDUCED dosing: Statins for lowering cholesterol for secondary prevention of ASCVD

Reduced dosing applies to patients with questionable ability to tolerate high-intensity statin therapy, including those who are frail/elderly, have hepatic/renal impairment or untreated hypothyroidism, or are taking interacting drugs.

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

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

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.

³ Pravastatin has about half the potency of simvastatin; however, it is less likely to interact with other medications, particularly medications that are strong CYP3A4 inhibitors.

Cholesterol and lipid goals for patients on statin therapy

LDL levels

LDL goal: < 70 mg/dL

HDL levels

All patients on statins: no specific HDL target for therapy

A low HDL level is an independent risk factor for ASCVD, but there is no evidence to date that increasing HDL levels reduces cardiovascular risk. Encourage patients to increase HDL levels through lifestyle measures (e.g., increased physical activity, weight loss if overweight, and tobacco cessation). Medications generally are not recommended.

Triglycerides and pancreatitis

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

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

Follow-up for patients on statins

Patients should generally be at a high-intensity level of therapy (Table 1a, p. 5) if possible. If they are at the high-intensity level (lowering LDL cholesterol on average by at least 50%) and still above the LDL goal, it is reasonable to consider increasing the statin dose or adding ezetimibe. On the other hand, if a patient has

achieved a very low LDL level, **do not lower** the intensity of statin therapy. Expert opinion is that no LDL level is too low.

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

For patients not at goal, but able to tolerate statins

1. First, assess adherence to therapy. If the patient is taking statin regularly, consider increasing dose or changing statin, if necessary. This is especially important in the case of rosuvastatin, given that drug's increased cost share for most patients. Consider switching to rosuvastatin mainly when atorvastatin is clearly not working despite regular use, and when the patient is considerably above goal.
2. If the patient is still not able to achieve an LDL < 70 while adherent to maximally tolerated high-intensity statin therapy, add ezetimibe. See Table 1a, p. 5.
3. If the patient is still not able to achieve an LDL < **100** after adding ezetimibe to maximally tolerated high-intensity statins, **refer to Cardiology**. For patients meeting certain criteria, PCSK9 inhibitors (evolocumab) may be prescribed as an alternative to the ezetimibe.

If the patient *appears* intolerant to statins

1. First, consider decreasing the dose.
2. If the patient is still intolerant, use shared decision-making to decide whether to consider switching to another statin. Consider a consult with Cardiology.
3. To determine if myalgia symptoms can be attributed to use of the statin, consider using [the American College of Cardiology statin intolerance tool](#).
4. If the patient is still intolerant, switch to one of the medications in Table 2, p. 7.

What is statin intolerance?

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

Therapy for statin-intolerant patients

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

Table 2. Medications for lowering cholesterol in statin-intolerant patients for secondary prevention of ASCVD			
	Medication	Initial dose	Maximum dose
Start with:	Ezetimibe	10 mg daily	10 mg daily
If LDL goal is not met:	Continue Ezetimibe	10 mg daily	10 mg daily
	and add Cholestyramine resin	4 g 1–2 times daily	24 g divided 1–6 times daily
If LDL goal is still not met:	Refer to Cardiology or Endocrinology* for:		
	PCSK9 inhibitors (evolocumab) (NF)	75 mg subcutaneously every 2 weeks	150 mg subcutaneously every 2 weeks
* Cardiology or Endocrinology consultation is required, and at least one second-line medication must be tried before referral.			

Prescribing notes – Table 2

Ezetimibe (Zetia)

Formulary

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

PCSK9 inhibitors (evolocumab)

Nonformulary—specialty tier. See Pharmacy criteria on the staff intranet.

- Patients will continue maximally tolerated statin therapy while receiving evolocumab therapy.
- Authorization will be reviewed after 6 and 12 months of therapy to confirm continued clinical benefit, as demonstrated by LDL reduction since initiation of therapy with evolocumab.
- Clinical criteria for patients with ASCVD not able to achieve an LDL < 70mg/dL and meeting one of the following:
 - Are currently 90% adherent to maximally tolerated high-intensity statin therapy (i.e., atorvastatin 80 mg or rosuvastatin 40 mg) in combination with ezetimibe for at least 8 weeks
 - Have a documented contraindication to statin and ezetimibe therapy
 - Have a documented intolerance to statin therapy, as defined by the National Lipid Association (NLA)

Cholestyramine

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

ACE Inhibitor or ARB Therapy

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

Table 3. ACE inhibitor or ARB therapy for secondary prevention of ASCVD			
Line	Medication	Initial dose	Maximum dose
1 st	ACE inhibitor		
	Lisinopril or	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 nd	Angiotensin receptor blocker ¹		
	Losartan	25 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

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

SGLT2 Inhibitors for Patients with Type 2 Diabetes

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

SGLT2 inhibitors are not currently recommended for patients with ASCVD without diabetes, but this remains an area of investigation, including clinical trials pending publication at the time of this guideline review.

Antiplatelet Therapy

Daily aspirin is recommended in most patients with ASCVD unless contraindicated due to hypersensitivity to aspirin, medication interactions, or the presence of severe peptic ulcer disease or gastritis.

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

Table 4. Antiplatelet therapy for secondary prevention of ASCVD			
Line	Medication	Initial dose	Maximum dose
1 st	Aspirin	81 mg daily	81 mg daily
2 nd	Clopidogrel ¹	75 mg daily	75 mg daily
¹ Clopidogrel is equally effective in patients with ASCVD who have a contraindication or intolerance to aspirin.			

Combination therapy is *not* recommended

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

Lowering Triglycerides to Prevent Pancreatitis

Triglycerides do not require 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:

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

Icosapent ethyl

Icosapent ethyl has been approved by the FDA for the treatment of patients with hypertriglyceridemia (not shown to reduce pancreatitis), and to reduce cardiovascular events in patients with ASCVD and triglycerides remaining > 150 mm/dL on maximum tolerated statin. Due to the weakness of the evidence and concerns about study design, our recommendation is neither for nor against this medication. The generic omega-3 fatty acids (Lovaza) and over-the-counter alternatives are also available to treat hypertriglyceridemia.

Table 5. Medications for lowering triglyceride levels to prevent possible pancreatitis See also the prescribing notes that follow Table 5.			
	Medication	Initial dose	Maximum dose
Start with:	Atorvastatin	80 mg daily	80 mg daily
If TG not < 500 mg/dL:	Add Fenofibrate (preferred) or Generic omega-3 fatty acids (Lovaza)	54–160 mg daily 2,000 mg DHA/EPA in divided doses daily	160 mg 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

Prescribing notes for Table 5

Atorvastatin

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

Fenofibrate

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

Omega-3 fatty acids

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

Gemfibrozil

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

Beta-blocker Therapy for Post-MI Patients

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

Note that it is a HEDIS® measure to continue beta-blocker therapy for at least 6 months. In general, however, therapy continues indefinitely unless the patient becomes unable to tolerate the beta-blocker.

Table 6. Beta-blocker therapy for post-MI patients				
Eligible population	Line	Medication	Initial dose	Maximum or target dose
Post-MI patients with preserved LV function (EF ≥ 50%)	1 st	Metoprolol	25 mg twice daily	100 mg twice daily is maximum dose.
Post-MI patients with LV systolic dysfunction (EF < 50%) with or without heart failure	1 st	Carvedilol	3.125 mg twice daily	25 mg twice daily is target dose for patients ≤ 187 lb. 50 mg twice daily is target dose for patients > 187 lb.
	2 nd	Metoprolol LA	12.5–25 mg daily	200 mg daily is maximum dose.

Medication Monitoring

Table 7. Medication monitoring		
Eligible population	Recommended tests	Recommended frequency
Patients on statin	Non-fasting lipoprotein panel	4–6 weeks after initiating therapy
Patients on bile acid sequestrant	Non-fasting lipoprotein panel	At baseline and 3 months after initiating therapy and Every 6 months
Patients on ACE inhibitor or ARB	Potassium and Creatinine	At baseline and 2 weeks after initiating therapy and With each increase in dose and Annually

Medication monitoring that is *not* recommended

ALT/AST

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

Creatine kinase (CK)

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

Evidence Summary

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

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

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

External guidelines meeting KPWA criteria for adaptation/adoption

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 question 1

Is aortic atherosclerosis considered a CHD equivalent?

- The overall published literature suggests that there may be an association between thoracic aortic calcification (TAC) and the risk of CHD and stroke.
- The vast majority of the studies were retrospective analyses, which may show an association but cannot determine whether it is a causal association.
- Published studies show that aortic atheromatous plaques are more frequently found in elders, smokers, and patients with hypertension, diabetes mellitus, or hypercholesterolemia.
- Katsanos and colleagues' 2014 systematic review and meta-analysis of studies investigating the association between complex atheromatous plaques in the descending aorta and the risk of stroke concluded that aortic plaques are considered a marker of generalized atherosclerosis, and that their presence could be considered a sufficient but not a necessary condition to prove that a patient has a systemic atherosclerotic disease.
- Analysis of data from MESA (Budoff 2011) suggests that TAC may be a significant predictor of future coronary events only in women, independent of CAC, and provides additional prognostic information for CHD risk in women beyond that obtained from assessment of coronary calcification.
- Kianoush and colleagues (2017), also using data from MESA, found that that multisite thoracic extra-coronary calcification (ECC) is independently associated with ischemic stroke, total stroke, and TIA, but with minimal insignificant incremental predictive value beyond traditional risk factors and CAC.
- An earlier analysis of data from the Framingham Study (Wittelman 1990) showed that

- The predictive value of aortic calcified plaques generally diminished with age. The risk of sudden coronary death in men with calcified plaques in the thoracic aorta ranged from a sevenfold increase at age 35 to no excess risk at age 70.
- The prevalence of thoracic aorta calcified plaques approximately doubled with each decade of age, with a slightly higher increase among men. These were associated with a twofold increase in risk of cardiovascular death in men and women < 65 years of age, even after adjusting for other risk factors.
- TAC was also associated with an increase in the risk of CAD and stroke among middle-aged women.
- The authors concluded that these results indicate that atherosclerosis is a generalized process, and that a finding of aortic calcified plaques in a relatively young subject on a routine chest X-ray should be regarded as a sign for potential development of clinically manifest atherosclerotic disease in the cardiac, cerebral and peripheral arterial circulation.
- TAC density was found to be inversely associated with incident CHD and CVD after adjustment for CVD risk factors and CAC volume and density (Thomas 2017, Craiem 2020).
- TAC volume may not be significantly associated with outcomes after full adjustment for CVD risk factors and CAC volume and density (Thomas 2017).
- The addition of TAC volume and density (each measured separately) to the risk prediction model may improve the risk prediction over CAC (Craiem 2020).
- Thoracic or abdominal aortic aneurysm calcifications are significantly associated with higher overall CV events and CV mortality (Chowdhury 2018).
- Research suggest that complex plaques in the thoracic aorta (≥ 4 mm in thickness or vulnerable plaques) increase the risk of vascular events (Wehrum 2017, Amarenco 1994).
- Simple (versus complex) aortic plaques are not independently associated with either cardiac or cerebrovascular events (Meissner 2004).
- Meissner and colleagues (2004) concluded that aortic atherosclerosis may not be an independent risk factor for vascular events in the general population.
- Li and colleagues (2016) showed that abdominal aortic plaques were independently associated with the presence of CAD and with the severity of the disease according to the number of stenotic coronary arteries.

Key question 2

What medications are recommended for treating incidentally diagnosed aortic atherosclerosis in adults to prevent or slow the progression of atherosclerosis and the risk of CVD events?

To date, there is no evidence from valid RCTs that examined the clinical outcomes of any specific therapy or treatment of patients with aortic atherosclerosis.

It is suggested that patients with atherosclerosis of the aorta be treated with lifestyle changes and medications that lower their risk of serious complications, including lipid-lowering drugs, blood pressure-lowering measures, and drugs such as ACE inhibitors, ARBs, and beta-blockers, as well as anticoagulants for the prevention of stroke in patients with atrial fibrillation, or in those with a history of stroke or TIA.

Key question 3

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 inhibitors)?

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 4

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.
- The search, however, 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.
- 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, Arnett 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 atherosclerotic cardiovascular disease, 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 5

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

This edition of the guideline was approved for publication by the Guideline Oversight Group in October 2020.

Team

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

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Disclosure of conflict of interest

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

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