Atherosclerotic Cardiovascular Disease (ASCVD) Primary Prevention Guideline

Last guideline approval: January 2016

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 January 2016

<table>
<thead>
<tr>
<th>New</th>
<th>Previous</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL target for primary prevention &lt; 100 mg/dL</td>
<td>LDL target for primary prevention &lt; 130 mg/dL</td>
</tr>
<tr>
<td>Ezetimibe has been added as an option for high-risk patients who are not able to achieve an LDL &lt; 100 mg/dL on maximally tolerated statin doses or who have intolerance or contraindications to statins.</td>
<td>Ezetimibe was not an option for primary prevention.</td>
</tr>
</tbody>
</table>

High-risk is defined as:
- 5-year risk > 10% based on customized CVD risk calculator, or
- 10-year risk ≥ 7.5% based on ACC/AHA risk calculator, or
- Patients aged 40 and older with diabetes, or
- Any patient with LDL ≥ 190 mg/dL.

Preface

In November 2013, the American College of Cardiology (ACC) and the American Heart Association (AHA) published new clinical practice guidelines for assessment of cardiovascular risk, lifestyle modifications to reduce cardiovascular risk, and management of blood cholesterol, overweight, and obesity in adults.

Recommendations in the ACC/AHA guidelines have much in common with the recommendations in this guideline and in the ASCVD Secondary Prevention Guideline. But there are differences. Members of this guideline team discussed the ACC/AHA recommendations before finalizing their recommendations for the 2014 and 2016 updates of both ASCVD prevention guidelines.

Here are some of the key similarities and differences between the ACC/AHA and Kaiser Foundation Health Plan of Washington recommendations for both primary and secondary prevention.

Cardiovascular risk calculator

One of the most controversial points of the 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk was the adoption of a new risk calculator. The ACC/AHA calculator estimates 10-year risk of “hard ASCVD” (stroke, MI), and it recommends statins at 7.5% (0.75%/year). The ACC/AHA calculator leads to many healthy people with favorable lipid values and no apparent disease being recommended for statin therapy on the basis of age alone.

Here, we continue to use a customized version of the 2008 Framingham calculator (D’Agostino 2008), which estimates 5-year risk of “total ASCVD” (stroke, MI, CABG/PCI, PAD, HF), and we generally recommend statins at 10% (2%/year). We believe at this point that the estimates from our version of the calculator are more clinically meaningful than those from the 2013 ACC/AHA version, and we recommend continuing to use them. The customized calculator includes age, total cholesterol, HDL cholesterol, systolic blood pressure, antihypertensive medication used, current smoking, and diabetes status.

Intensity of statin therapy

The 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults stresses the importance of starting statins with at least moderate-intensity therapy (e.g., simvastatin 40 mg or atorvastatin 20 mg). Depending on the situation, it sometimes recommends high-intensity therapy (atorvastatin 40–80 mg). The recommendations are a bit difficult to remember, and we believe somewhat arbitrary. By contrast, our recommendation is simpler, and we believe more evidence-based: Generally treat primary-prevention patients with moderate-intensity therapy, and secondary-prevention patients with high-intensity therapy.
For primary-prevention patients, we continue to recommend starting with at least moderate-intensity therapy, as we have for years. In practice, this means generally starting primary-prevention patients on 40 mg of simvastatin, not 10 or 20 mg, unless there is a reason (e.g., age, drug interaction, hepatic/renal dysfunction) that they can’t handle the 40 mg.

For secondary-prevention patients, we recommend starting with high-intensity therapy, which is consistent with ACC/AHA. We believe the evidence has been mounting for this approach, and that it is evidence-based. In particular, we recommend starting with the highest dose—atorvastatin 80 mg—unless, again, there is reason to suspect that the patient will not be able to safely tolerate that dose (e.g., age, drug interactions, hepatic/renal dysfunction). The best evidence is behind the highest dose of atorvastatin, not 40 mg, even though both are considered “high-intensity” therapy.

**LDL targets**

One of the most significant changes in the ACC/AHA guideline was that it discarded the use of LDL targets. There is some logic to this, in that if you routinely start with moderate- to high-intensity statin therapy, you will achieve the LDL target in the majority of cases even without checking and adjusting. We continue to believe, however, that it is still important to recognize cases where even the higher doses of statins have not achieved the targets, and where patients might therefore benefit from a change to their medication. The best way to identify these cases is to continue checking the LDL annually, and to have a low threshold for increasing the dose when targets are not comfortably achieved. Be aware that ACC/AHA also recommends checking LDL annually, largely to ensure compliance with the medication.

**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 (TIA), ischemic stroke, and carotid artery stenosis > 50%.
- Peripheral artery disease, such as claudication.
- Aortic atherosclerotic disease, such as abdominal aortic aneurysm (AAA) 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.

**Goals of ASCVD 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.
### Table 1. Cholesterol screening for patients not already on statins

<table>
<thead>
<tr>
<th>Eligible population</th>
<th>Test</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic patients under 40 years old</td>
<td>Cholesterol screen</td>
<td>Annually</td>
</tr>
</tbody>
</table>

**Men**

<table>
<thead>
<tr>
<th>Age 35–79</th>
<th>Cholesterol screen</th>
<th>Every 5 years if low CVD risk ²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Every 2–4 years if moderate CVD risk ²</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Annually if high CVD risk ²</td>
</tr>
</tbody>
</table>

| Over age 79                          | Routine screening is not recommended. | Upon patient request or based on other ASCVD risk factors |

**Women**

<table>
<thead>
<tr>
<th>Age 45–79</th>
<th>Cholesterol screen</th>
<th>Every 5 years if low CVD risk ²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Every 2–4 years if moderate CVD risk ²</td>
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<tr>
<td></td>
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<td>Annually if high CVD risk ²</td>
</tr>
</tbody>
</table>

| Over age 79                          | Routine screening is not recommended. | Upon patient request or based on other ASCVD risk factors |

1 Patients with diabetes aged 40 years or older should already be taking a statin medication and therefore are not part of the screening population. Please see Medication Monitoring (p. 18) for recommendations on LDL testing for these patients.

2 As estimated in lab results, using customized version of Framingham calculator.

### Screening tests

**Cholesterol screen: for most patients**

The results of a cholesterol screen—total cholesterol, HDL cholesterol, and total cholesterol/HDL ratio—ordered through Epic include the patient’s 5-year risk calculation for cardiovascular disease. It is not necessary to order LDL for screening, because for the vast majority of patients the LDL doesn’t affect the calculated risk level. A small number of patients will have very high LDLs (≥ 190 mg/dL), but these patients can be detected by looking at their non-HDL (total cholesterol minus HDL) cholesterol levels. If the non-HDL cholesterol is 220 mg/dL or above, the LDL is likely to be above 190 mg/dL; in that case, a fasting lipoprotein panel can be ordered as a follow-up.
hs-CRP: consider for patients at moderate risk

For patients at moderate risk, consider testing hs-CRP. This test provides information that is helpful in confirming elevated risk when making the decision whether or not to recommend statin therapy for these patients.

<table>
<thead>
<tr>
<th>Table 2. Interpreting hs-CRP test results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Result</td>
</tr>
<tr>
<td>&lt; 1 mg/L</td>
</tr>
<tr>
<td>1–3 mg/L</td>
</tr>
<tr>
<td>3.1–9.9 mg/L</td>
</tr>
<tr>
<td>≥ 10 mg/L</td>
</tr>
</tbody>
</table>

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

Coronary artery calcium scoring: not recommended

Coronary artery calcium scoring generally is not recommended because it has not been proven to add significantly to clinical decision making in a way that improves outcomes. If available, the score can be used to help decide whether someone in the moderate-risk category should receive statins. See Clinical Review Criteria for CT Angiography and CT Cardiography: Screening & Calcium Scores for more information.

CVD risk calculation

Kaiser Foundation Health Plan of Washington uses a customized version of the Framingham CVD risk calculator to help determine which patients might benefit from primary prevention interventions. The calculations—returned with cholesterol screen results or by using a SmartLink in Epic—approximate the patient’s absolute 5-year risk of ASCVD and congestive heart failure.

Note: CVD risk calculators and measures such as the total cholesterol/HDL ratio can provide only an estimate of risk. Interpretation of CVD risk calculations should always reflect informed clinical judgment.

The customized calculator is available:
- On the public website for use by clinicians, contracted providers, and members.
- Through the Epic SmartLink .fram, which pulls information from a patient’s record to calculate the risk.
- In the Health Profile interactive online tool for members.
- In the Clinical Lab’s cholesterol screen.

For more information about the customized CVD risk calculator and a list of questions asked, see Appendix 1 (p. 30).
Total cholesterol/HDL ratio
The total cholesterol/HDL ratio is one component of the Framingham CVD risk calculator and is reported to patients as part of the cholesterol screen results. The ratio has been used as a stand-alone measure to estimate risk levels and can be more predictive than LDL for ASCVD events in people without prior CAD.

For 50-year-old men, the average total cholesterol/HDL ratio is about 5, and for 50-year-old women, the average ratio is about 4. Ratios over 6 indicate an increased risk, similar to other known risk factors, such as smoking, hypertension, diabetes, and family history. A ratio of less than 3.5 is desirable and indicates low risk.

Lifestyle Modifications for All Patients

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

Healthy diet
All patients should strive to:
- Make smart choices from every food group to meet caloric needs.
- Get the most and best nutrition from the calories consumed.

There is strong evidence that adhering to a Mediterranean-style eating plan reduces the incidence of major cardiovascular events in people at high risk for CVD. 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 2 fish servings weekly may reduce CHD mortality.

Moderation of alcohol consumption
- Consider having patients complete the AUDIT-C alcohol use questionnaire.
- See the Unhealthy Drinking in Adults Guideline for additional information.

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 Adult Weight Management Guideline for additional information.
Blood pressure management

- For patients aged 79 or younger, the blood pressure goal is < 140/90 mm Hg.
- For patients aged 80 or older, the blood pressure goal is < 150/90 mm Hg. Consider using this goal for frail elderly patients under age 80 who are not tolerating pharmacologic treatment.
- If a patient’s blood pressure is higher than goal, see the Hypertension Guideline for management recommendations.

Dietary Supplements

Calcium and vitamin D

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

<table>
<thead>
<tr>
<th>Population</th>
<th>Statin therapy</th>
<th>Antiplatelet therapy</th>
<th>ACE inhibitor therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with diabetes</td>
<td>Recommended for age ≥ 40</td>
<td>Use shared decision making.</td>
<td>See recommendations in ACE inhibitor section.</td>
</tr>
<tr>
<td>Low CVD risk (&lt; 5% over 5 years)</td>
<td>Not recommended</td>
<td>Not recommended</td>
<td>ACE inhibitor therapy is <em>not routinely recommended</em> for patients without diabetes.</td>
</tr>
<tr>
<td>Moderate CVD risk (5–10% over 5 years)</td>
<td>Can be considered; use shared decision making, hs-CRP testing if needed.</td>
<td>Use shared decision making.</td>
<td></td>
</tr>
<tr>
<td>High CVD risk (&gt; 10% over 5 years)</td>
<td>Recommended</td>
<td>Recommended</td>
<td></td>
</tr>
<tr>
<td>LDL cholesterol ≥ 190 mg/dL</td>
<td>Should be considered; use shared decision making.</td>
<td>Use shared decision making.</td>
<td></td>
</tr>
</tbody>
</table>

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1. Testing a patient’s hs-CRP may provide minimal prognostic value when added to the CVD risk calculation. Test hs-CRP once to adjust the risk calculation (similar to how family history and other factors are used to adjust risk).

2. Familial hypercholesterolemia is a high possibility. If this is not the case, consider testing for secondary causes (e.g., diabetes, obesity, albuminuria).

3. Younger patients with low short-term but high lifetime risk of ASCVD may not need aspirin; this decision is independent of the decision on statin treatment.
Statin Therapy for Primary Prevention of ASCVD

Statin therapy is recommended for:
- Patients with a CVD risk calculation > 10%.
- Patients with diabetes who are aged 40 years or older.

For patients with a moderate 5-year CVD risk calculation (5–10%), statin therapy can be considered. For patients with LDL cholesterol ≥ 190 mg/dL, statin therapy should be considered. In both cases, use shared decision making (see page 12).

Recommended statin dosing

The majority of patients who are taking statins for primary prevention of ASCVD should be initiated on moderate-intensity statins, defined as those lowering LDL cholesterol on average 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.

<table>
<thead>
<tr>
<th>Table 4. STANDARD (moderate-intensity) statin dosing for primary prevention of ASCVD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Line</strong></td>
</tr>
<tr>
<td>1st</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

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>
<thead>
<tr>
<th>Table 5. REDUCED (low-intensity) statin dosing for primary prevention of ASCVD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Line</strong></td>
</tr>
<tr>
<td>1st</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>2nd</td>
</tr>
</tbody>
</table>

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**

<table>
<thead>
<tr>
<th>Patients at moderate or high CVD risk:</th>
<th>LDL goal &lt; 100 mg/dL</th>
</tr>
</thead>
</table>

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 CVD, 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 the Pharmacologic Options—Lowering Triglycerides to Prevent Pancreatitis section on page16.) 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. 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 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 or not to consider switching to another statin. Consider a virtual consult with Cardiology.
4. For patients who are at high risk and not able to achieve an LDL < 100 mg/dL on maximally tolerated doses of formulary statins, consider adding ezetimibe 10 mg. See Pharmacy criteria on the staff intranet.

High-risk is defined as:
- 5-year risk > 10% based on the customized risk calculator, or
- 10-year risk ≥ 7.5% based on ACC/AHA risk calculator, 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 or not to consider switching to another statin. Consider a virtual consult with Cardiology.
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 supplementation with co-enzyme Q10 to relieve statin-induced muscle symptoms. Evidence is conflicting, but some studies suggest a benefit.

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

- For patients who are **not** at high risk, **stop the statin** and do not prescribe further medications.
- For patients who are **are** at high risk and not able to achieve an LDL < 100 mg/dL, **stop the statin and consider prescribing ezetimibe**. See [Pharmacy criteria](#) on the staff intranet.

High-risk is defined as:
- 5-year risk > 10% based on the customized CVD risk calculator, or
- 10-year risk ≥ 7.5% based on ACC/AHA risk calculator, or
- Patient aged 40 or older with diabetes, or
- Any patient with LDL ≥ 190 mg/dL

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**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 rosvastatin 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

Making a decision to initiate long-term lipid lowering with medication requires knowledge of the patient’s absolute risk of CVD in the next 5 years.

Benefits of statin therapy

Statins decrease major vascular events by approximately 25%. The overall benefit is therefore dependent on the baseline risk. Numbers are expressed in number needed to treat (NNT) for 5 years.

<table>
<thead>
<tr>
<th>CV risk</th>
<th>Absolute risk reduction</th>
<th>NNT/5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>2%</td>
<td>0.5%</td>
<td>200</td>
</tr>
<tr>
<td>4%</td>
<td>1.0%</td>
<td>100</td>
</tr>
<tr>
<td>6%</td>
<td>1.5%</td>
<td>67</td>
</tr>
<tr>
<td>8%</td>
<td>2.0%</td>
<td>50</td>
</tr>
<tr>
<td>10%</td>
<td>2.5%</td>
<td>40</td>
</tr>
<tr>
<td>12%</td>
<td>3.0%</td>
<td>33</td>
</tr>
<tr>
<td>14%</td>
<td>3.5%</td>
<td>29</td>
</tr>
<tr>
<td>16%</td>
<td>4.0%</td>
<td>25</td>
</tr>
</tbody>
</table>

Keep in mind that the benefits of therapy likely do extend beyond 5 years, especially for relatively young patients. So the actual NNT is likely lower than this at each risk level. This needs to be weighed against the known risks of therapy (summarized below).

Risks of statin therapy

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 (FDA 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 recent 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, where patients who were intolerant of the statins were excluded from the study. A recent 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 old 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 (FDA 2011).
Antiplatelet Therapy for Primary Prevention of ASCVD

Use antiplatelet therapy as described in Table 6 for the following patients:

- Those with a high CVD risk calculation (> 10%).

For patients with a moderate CVD risk calculation (5–10%) or with LDL cholesterol ≥ 190 mg/dL, use shared decision making. For patients with a low CVD risk calculation (< 5%), antiplatelet therapy is not recommended.

(The recommendations in this guideline differ from those of the USPSTF [http://www.uspreventiveservicestaskforce.org/uspstf/uspsasmi.htm] in that this guideline team agreed to focus on level of risk as determined by the CVD risk calculator rather than by patient age/gender.)

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

<table>
<thead>
<tr>
<th>Line</th>
<th>Medication</th>
<th>Initial dose</th>
<th>Maximum dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>Aspirin</td>
<td>81 mg daily</td>
<td>81 mg daily</td>
</tr>
<tr>
<td>2nd</td>
<td>Clopidogrel †</td>
<td>75 mg daily</td>
<td>75 mg daily</td>
</tr>
</tbody>
</table>

Clopidogrel may be an option for patients who have aspirin intolerance and a high CVD risk calculation (> 10%).

The decision on daily antiplatelet therapy should be based on individualized risk, which includes assessment of both the risk of a first cardiovascular event and the risk of major bleeds.

Factors that increase GI bleeding risk (Bhatt 2008):

- Patient has one of the following risk factors: history of ulcer disease, history of GI bleeding, current dual antiplatelet therapy (clopidogrel plus daily NSAID/aspirin), or current concomitant anticoagulant therapy (warfarin, enoxaparin, etc.).
- Patient has more than one of the following risk factors: aged 60 years or older, concomitant systemic corticosteroid use, or dyspepsia or GERD symptoms.

Antiplatelet therapy that is not recommended

NSAIDs alone are not appropriate substitutes for aspirin as antiplatelet agents.
Patients with Diabetes Only: ACE Inhibitor or ARB Therapy for Primary Prevention of ASCVD

Use an ACE inhibitor as described in Table 7 for only the following patients with diabetes:
- Those aged 40–54 with a high CVD risk calculation (> 10%).
- Those aged 55 and older at any risk calculation level.

Consider using an ACE inhibitor for only the following patients with diabetes, using shared decision making:
- Those aged 40–54 with a moderate CVD risk calculation (5–10%).
- Those younger than 40 years of age, regardless of CVD risk calculation.

**Table 7. Diabetes patients only: ACE inhibitor or ARB therapy for primary prevention of ASCVD**

<table>
<thead>
<tr>
<th>Line</th>
<th>Medication</th>
<th>Initial dose</th>
<th>Maximum dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt;</td>
<td>ACE inhibitor</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lisinopril or Ramipril</td>
<td>5–10 mg daily</td>
<td>40 mg daily (target dose is 20 mg daily)</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt;</td>
<td>ARB&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Losartan</td>
<td>25–50 mg/day in 1–2 doses</td>
<td>100 mg/day in 1–2 doses</td>
</tr>
</tbody>
</table>

<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 investigation or treatment unless they are higher than 500 mg/dL. (Treatment/investigation at higher than 1,000 mg/dL would also be reasonable. Use shared-decision making.) If a patient has elevated triglycerides, consider the following workup:

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

Consult with Endocrinology if:

- 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.

Table 8. Medications for lowering triglyceride levels to prevent possible pancreatitis

See also the prescribing notes that follow Table 8.

<table>
<thead>
<tr>
<th>Line</th>
<th>Medication</th>
<th>Initial dose</th>
<th>Maximum dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>Atorvastatin</td>
<td>80 mg daily</td>
<td>80 mg daily</td>
</tr>
<tr>
<td></td>
<td>Add</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>If TG still not &lt; 500 mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fenofibrate (preferred)</td>
<td>54–160 mg daily</td>
<td>160 mg daily</td>
</tr>
<tr>
<td></td>
<td>or</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Niacin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Niacin IR</td>
<td>100 mg twice daily</td>
<td>1,000 mg 3 times daily</td>
</tr>
<tr>
<td></td>
<td>Niacin SR (Slo-Niacin)</td>
<td>250 mg twice daily</td>
<td>1,000 mg twice daily</td>
</tr>
<tr>
<td></td>
<td>If TG still not &lt; 500 mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td>Fish oil (if LDL is at goal)</td>
<td>2,000 mg DHA/EPA in divided doses daily</td>
<td>4,000 mg DHA/EPA in divided doses daily</td>
</tr>
<tr>
<td>1st</td>
<td>Gemfibrozil monotherapy</td>
<td>600 mg twice daily</td>
<td>600 mg twice daily</td>
</tr>
</tbody>
</table>

Prescribing notes for Table 8

**Atorvastatin**

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

**Fenofibrate**

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

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

Gemfibrozil

- Gemfibrozil is contraindicated with statin therapy.
- Use caution for patients with mild to moderate renal impairment (CKD 2–3).
- Do not use for patients with severe renal impairment (serum creatinine greater than 2 mg/dL or CKD 4–5).
Medication Monitoring

Table 9. Medication monitoring

<table>
<thead>
<tr>
<th>Eligible population</th>
<th>Test(s)</th>
<th>Frequency of lab testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients on statin</td>
<td>Fasting lipoprotein panel or Direct LDL cholesterol</td>
<td>At minimum 4–6 weeks after initiating therapy and Annually</td>
</tr>
<tr>
<td>Patients on ACE inhibitor or ARB</td>
<td>Potassium and Creatinine</td>
<td>At baseline and 2 weeks after initiating therapy and With each dose increase and Annually</td>
</tr>
<tr>
<td>Patients on fenofibrate therapy</td>
<td>Creatinine</td>
<td>At baseline and 3 months after initiating therapy and Every 6 months</td>
</tr>
<tr>
<td>Patients on niacin</td>
<td>ALT/AST and Fasting blood glucose or HbA1c and Uric acid</td>
<td>At baseline and 2–4 weeks after increasing dose and Every 6 months</td>
</tr>
</tbody>
</table>

1 LDL values can come from either a fasting lipoprotein panel or a direct LDL test. The lipoprotein panel indirectly calculates LDL cholesterol by using the Friedewald equation (LDL = TC - HDL - TG/5). In general, either test can be used, but be aware that the Friedewald equation tends to underestimate LDL when LDL is low (~70) or triglycerides are high (> 150–200). In these cases, the true LDL value can be 10–20 points higher. So, in such cases, consider using a direct LDL test or ensuring that the patient is well below target.

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

The evidence reviewed for the 2016 update was limited to answering the following questions:
1. Is there any new direct evidence to determine that the lower the LDL cholesterol level, the better the outcomes?
2. What is the optimal effective and safe LDL target for the primary prevention of ASCVD in men and women?
3. Is there evidence on the efficacy and safety of ezetimibe when used alone or in combination with a statin for lowering LDL and improving outcomes in patients without a known ASCVD?
4. Is there an association between statin therapy and plasma CoQ10 concentrations?
5. Does CoQ10 supplementation decrease statin-associated muscle symptoms (SAMS)?

In addition, the guideline team adopted and/or adapted evidence-based recommendations from high-quality national and international external guidelines, if available and appropriate.

The following external guidelines were published after the evidence review for the 2014 edition of this guideline, and were reviewed for the 2016 update:
- 2014 Kaiser Permanente National Cardiovascular Risk and Dyslipidemia Management Guideline (Kaiser Permanente 2014)
- 2013 ACC/AHA Guidelines on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults (Stone 2014)

The following position statements of the Canadian Cardiovascular Society (CCS) and joint European societies were also considered for the 2016 update:
- Are the ACC/AHA guidelines on the treatment of blood cholesterol a game changer? A perspective from the Canadian Cardiovascular Society Dyslipidemia Panel (Anderson 2014)
- New AHA and ACC guidelines on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk: Statement of the D•A•CH Society for Prevention of Cardiovascular Diseases, the Austrian Atherosclerosis Society and the Working Group on Lipids and Atherosclerosis (AGLA) of the Swiss Society for Cardiology (Klose 2014)
CVD risk estimation

we use a customized version of the 2008 Framingham calculator (D'Agostino 2008), which estimates 5-year risk of “total ASCVD” (stroke, MI, CABG/PCI, PAD, HF), and we generally recommend statins at 10% (2%/year).

One of the most controversial points of the 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk is the adoption of a new risk calculator. The ACC/AHA calculator estimates 10-year risk of “hard ASCVD” (stroke, MI), and it recommends statins at 7.5% (0.75%/year). The ACC/AHA calculator leads to many healthy people with favorable lipid values and no apparent disease being recommended for statin therapy on the basis of age alone.

We believe at this point that the estimates from the 2008 version of the calculator are more clinically meaningful than those from the 2013 ACC/AHA version, and we recommend continuing to use them. The customized calculator includes age, total cholesterol, HDL cholesterol, systolic blood pressure, antihypertensive medication used, current smoking, and diabetes status.

Screening

Lipid screening

There is no direct evidence to determine the optimal age for screening men and women for lipid disorders, the appropriate interval for screening, or the appropriate age to stop screening. In 2008, the U.S. Preventive Services Task Force (USPSTF) strongly recommended screening all men 35 years of age or older, and screening women 45 years or older if they are at increased risk for CHD. The USPSTF also recommended screening men aged 20–35 years and women aged 20–45 years if they are at increased risk for CHD. The USPSTF made no recommendation for or against routine screening of men aged 20–35 years or of women aged 20 years or older who are not at increased risk for CHD. The USPSTF indicated that screening may be appropriate in older people who were never screened but that repeated screening is less important in older people, as lipid levels are less likely to increase after age 65. However, because older adults have an increased baseline risk for CHD, they would gain greater absolute benefit from the treatment of dyslipidemia compared with younger adults.

Serum triglycerides

There is insufficient evidence to recommend for or against triglyceride measurement as part of routine screening for lipid disorders. Large observational studies and a meta-analysis that pooled data from 29 studies (Sarwar 2007) indicate that hypertriglyceridemia is independently associated with CHD. However, there is insufficient evidence to determine that this association is causal, that including triglyceride values would add incremental value to the traditional variables used to estimate CHD or CVD risk, or that lowering isolated serum triglyceride levels would reduce future CHD events.

ASCVD emerging risk markers

<table>
<thead>
<tr>
<th>Biomarker tests that are not recommended</th>
<th>NNS ¹ over 10 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen ²</td>
<td>490</td>
</tr>
<tr>
<td>Lipoprotein(a) ³</td>
<td>801</td>
</tr>
<tr>
<td>Phospholipase A₂ ³</td>
<td>973</td>
</tr>
<tr>
<td>Apolipoprotein B and A-1 combined ³</td>
<td>4,541</td>
</tr>
</tbody>
</table>

¹ Number needed to screen or use marker to assess individuals at medium CVD risk to prevent an additional cardiovascular event.
² Analysis performed by Emerging Risk Factors Collaboration (Kaptoge 2012).
³ Analysis performed by Emerging Risk Factors Collaboration (Di Angelantonio 2012).

There are multiple published studies and meta-analyses on novel biomarkers used as risk predictors of CVD. Among these are CRP, fibrinogen, homocysteine, lipoproteins, LP-PLA2, and many others. The studies are relatively large, prospective, and have long-term event follow-up. However, the majority were
nested case-cohort studies, and CRP levels as well as other markers' levels were measured only once at baseline. In addition, the blood samples were stored for up to 10 years before analysis. Moreover, there were several possible uncontrolled risk factors and confounders unadjusted for in the analysis. Many of the studies did not report on the results of cerebrovascular and coronary events separately. The authors mainly presented the results in hazard ratios comparing the lowest with the highest tertile, quartile, or quintile values. The results may indicate a statistical association but do not show that the marker or test adds to the risk prediction. The association observed, however, is purely statistical and depends on the variables included in the analysis. An independent risk factor does not imply causality, and vice versa.

**Biomarkers of inflammation (CRP and fibrinogen)**

The Emerging Risk Factors Collaboration (Kaptoge 2012) analyzed individual records of 52 prospective cohort studies with 246,669 participants without a history of CVD to investigate the value of adding CRP or fibrinogen levels to conventional risk factors for the prediction of cardiovascular risk. The analysis showed that adding information of an inflammation biomarker to the standard risk factors used to predict 10-year risk of first cardiovascular event leads to a very small but statistically significant increase in the C-statistics (0.0039 for CRP and 0.0027 for fibrinogen). Based on the results of the analysis, the authors estimated that targeted CRP assessment of individuals at an intermediate risk could help prevent one additional cardiovascular event over a period of 10 years for every 440 individuals screened, as a result of 23 additional people starting statin therapy.

**Lipid-related markers**

The Emerging Risk Factors Collaboration (Di Angelantonio 2012) used individual records for 165,544 participants without baseline CVD from 37 prospective cohorts to determine whether adding information on apolipoprotein, A-1, B, lipoprotein(a), or lipoprotein associated phospholipase A2 to total cholesterol and HDL-C would improve CVD risk prediction. The results of the analysis showed a minimal improvement in the C-index (change ranged from 0.0006 to 0.001 for the different markers with a <1% net classification improvement with the addition of each of these markers to the conventional risk factors). The authors estimated that in order to prevent one extra CVD outcome over 10 years, 4,500 people need to be additionally screened with a combination of apo B and apo A-1, or about 1,000 people need to be screened with lipoprotein associated phospholipase A2 mass, or about 800 people need to be screened with lipoprotein(a).

**Pharmacologic prophylaxis**

**Aspirin/antiplatelet chemoprophylaxis**

There is good evidence from multiple primary prevention of ASCVD studies and meta-analyses that aspirin is associated with a significant reduction in MI among men and ischemic stroke among women, and that it is also associated with a significant increase in bleeding in men and women.

Three recent meta-analyses (Raju 2011, Bartolucci 2011, and Seshasai 2012) pooled the results of nine trials enrolling just over 100,000 participants (the six original primary prevention trials—British Doctors Study, Physicians’ Health Study, Hypertension Optimal Treatment trial, Thrombosis Prevention Trial, Primary Prevention Project, and Women’s Health Study—and the Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes trial, Prevention of Progression of Asymptomatic Diabetic Arterial Disease trial, and Aspirin for Asymptomatic Atherosclerosis study) to examine the effect of aspirin in the primary prevention of CVD. All three meta-analyses had generally valid methodology and analysis. Seshasai and colleagues calculated NNT and NNH, and the results of their analysis showed that after a mean follow-up 6.0 ± 2.1 years aspirin reduced total CVD events by 10% (OR 0.90; 95% CI, 0.85–0.96), with a number needed to treat=120; this was driven primarily with the reduction in nonfatal MI (NNT=162). There was an increased risk of total bleeds and nontrivial bleeds. The odds ratio for nontrivial bleeds was 1.31 (95% CI, 1.14–1.50) with a NNH of 73.

**Aspirin use for the primary prevention of cardiovascular events in patients with diabetes**

Several published meta-analyses have focused on primary prevention of cardiovascular events with aspirin in diabetic patients. The findings of these meta-analyses are consistent despite slightly different
designs and sizes. The overall results show that aspirin use is associated with nonsignificant reduction in major cardiovascular events (MACE) and a nonsignificant increase in the risk of major bleeds.

The most recent of these meta-analyses (Butalia 2011) included 7 trials (N=11,618 patients) that reported on the use of aspirin on the primary prevention of MACE in patients with diabetes. The pooled results showed insignificant benefit of aspirin in reducing MACE, MI, stroke, cardiovascular deaths, or all-cause mortality, and an insignificant increase in bleeding and major bleeds. The authors concluded that the results indicate that for every 10,000 patients treated with aspirin, approximately 109 MACE may be prevented at the expense of 19 major bleeding events with no overall mortality benefit (duration of ASA therapy ranged between studies from 3.6 to 10.1 years).

**Statin therapy**

There is good evidence from multiple RCTs and meta-analyses of RCTs that statin treatment reduces the risk of major cardiovascular events and cardiovascular mortality even among individuals at low risk.

The recent report from the Cholesterol Treatment Trialists’ (CTT) Collaborators’ (Mihaylova 2012) meta-analysis showed that statins reduced the risk of major vascular events by 21% per 1 mmol/L (38.67 mg/dL) of LDL cholesterol reduction. (RR 0.79; 95% CI, 0.77–0.81), i.e., it might prevent 11 major cardiovascular events per 1,000 treated patients over 5 years. The analysis showed that the 5 years statin of therapy was associated with a small increased risk of myopathy (excess incidence of 0.5/1,000), and more rarely of rhabdomyolysis (excess incidence of 0.1/1,000). Statin therapy may also be associated with an increased risk of hemorrhagic stroke (excess risk 0.5/1,000 people treated over 5 years; which could be higher in Asian populations) and of diabetes (excess incidence 0.1% per year).

A more recent Cochrane review and meta-analysis (Taylor 2013) calculated a NNT with statin of 96 (95% CI, 64–244) for all-cause mortality, and 56 (95% CI, 46–75) for fatal and nonfatal CHD events over 5 years.

**Target LDL cholesterol level**

There is no direct evidence on the optimal target lipid level for primary prevention. The guideline team adopted the 2015 National Lipid Association (NLA) (Jacobson 2015) recommendation to use an LDL treatment target of < 100 for primary prevention of ASCVD in patients at low, moderate or high risk.

**Use of ezetimibe alone or in combination with a statin for lowering LDL and improving outcomes**

The new evidence on the use of ezetimibe comes from the IMPROVE–IT trial (Canon 2015), which was a secondary prevention of ASCVD trial. IMPROVE-IT provides new evidence that lowering LDL levels below 70 mg/dL in post–acute coronary syndrome patients leads to better outcomes. The 2013 ACC/AHA guidelines (Stone 2014) state that the addition of a nonstatin agent may be considered in certain clinical situations and that preference should be given to drugs shown to reduce ASCVD events in RCTs.

The NLA expert panel consensus states that until data are available from RCTs to better define the potential benefits and risks of add-on therapies in patients whose levels of atherogenic cholesterol remains elevated while taking the highest tolerated dosage of statin, consideration may be given to use combination therapy with agents that further lower non-HDL and LDL to achieve goal levels of atherogenic cholesterol. The recommendation extends to nonstatin drugs, alone or in combination, to achieve the goals in patients who have a contraindication or are intolerant to statin therapy.

**Monitoring statin therapy**

There is no direct evidence to determine the benefits and harms of routine monitoring of LFTs in patients receiving statin therapy, or the optimal management of elevated liver enzymes with statin therapy.
Coenzyme Q10 (CoQ10) supplementation for patients receiving statin therapy

The NLA (Jacobson 2015) and the European Atherosclerosis Society (Stroes 2015) both note that some clinicians have advocated using coenzyme Q10 ubiquinone for the prevention or alleviation of statin myopathy symptoms. While the limited published studies and their pooled results in meta-analysis (Banach 2015, *Pharmacol Res*) do show a significant association between statin therapy and decreased serum levels of CoQ10, the evidence on the effect of CoQ10 supplementation on reducing statin-related muscle symptoms is conflicting. Some studies suggest a benefit in improvement of muscle symptoms with CoQ10 supplementation, other trials and a meta-analysis that pooled the results of five published RCTs (Banach 2015, *Mayo Clin Proc*) do not demonstrate such a benefit.

Overall, the evidence on the effects of CoQ10 supplementation is unclear, equivocal, and insufficient to support its use for statin myopathy.

Lifestyle modifications

Diet

There is new good supporting evidence from the PREDIMED trial (Estruch 2013) that adhering to the Mediterranean diet reduced the risk of cardiovascular disease among high-risk adults. The trial randomized 7,447 men and women at high risk of CVD to one of 3 groups: Two groups received advice on Mediterranean diet (Med-Diet) and were provided with either extra virgin olive oil or mixed nuts, and the third group received advice to reduce dietary fat. The primary outcome was a composite of major cardiovascular events, and the secondary outcomes were the components of the primary outcome. Participants were followed up for a median of 4.8 years before the trial was terminated due to the benefits observed with the Med-Diet. During follow-up, participants in the 2 Mediterranean diet groups significantly increased their consumption of extra virgin olive oil and nuts, and increased their weekly servings of fish and legumes. On the other hand, participants in the low-fat diet group did not significantly lower their fat intake. Participants in the latter group started out with a diet that averaged 39% fat, and during the study period they decreased fat intake to just 37%. Thus the study was in fact comparing Mediterranean diet with usual modern diet.

The results of the study show that participants randomized to the 2 Mediterranean diet groups combined had a 30% lower incidence of the composite cardiovascular events versus the controls (NNT+105). This was more evident for stroke, most probably due to the reduction in blood pressure (reported reduction in blood pressure at 3 months after randomization).

The Mediterranean diet does not have a single dietary pattern but has emphasis on fruits and vegetables, legumes, grains (mostly whole), beans, nuts, seeds, olive oil, fish and seafood, limiting red meat, and eating fish and poultry at least twice a week.

Omega-3 fatty acid supplements

There is some evidence that fish oil supplementation has no significant benefit in reducing cardiovascular events or mortality among individuals with or without a history of CVD. A recent meta-analysis (Rizos 2012) that pooled the results of 20 primary and secondary prevention trials showed no significant benefit on major cardiovascular events or mortality with omega-3 supplementation.
Efficacy of omega-3 polyunsaturated fatty acid supplements

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>N studies</th>
<th>Weighted event rate %</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>17</td>
<td>9.8%</td>
<td>0.96 (0.91–1.02)</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>13</td>
<td>5.8%</td>
<td>0.91 (0.85–0.98)</td>
</tr>
<tr>
<td>Sudden death</td>
<td>7</td>
<td>2.3%</td>
<td>0.87 (0.75–1.01)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>13</td>
<td>2.9%</td>
<td>0.89 (0.76–1.04)</td>
</tr>
<tr>
<td>Stroke</td>
<td>9</td>
<td>2.9%</td>
<td>1.05 (0.93–1.18)</td>
</tr>
</tbody>
</table>

1. Excluding DART 1&2 trials where omega-3 PUFA was provided through diet.
2. The authors indicate that this was not significant after correction for multiple comparisons.

Fish consumption
A meta-analysis of 17 cohort studies with a total of 315,812 participants (Zheng 2011) and an average follow-up of 15.9 years (range 6–30 years) showed that fish consumption of at least 1 and no more than 4 servings a week was associated with significantly lower CHD mortality. The results should be interpreted with caution due to the nature of observational studies, method of assessment, variations in patient characteristics, and amounts of fish consumed, source, and method of cooking, as well as other potential confounders.

Vitamin E
There is evidence from the Physicians’ Health Study II (PHS II, Sesso 2008)—a double-blind RCT that evaluated the effect of vitamins C (500 mg daily) and E (400 IU every other day) supplementation on the risk of major cardiovascular events among 14,641 healthy male physicians aged 50 years and older—that vitamin E supplementation did not reduce the risk of major cardiovascular events when compared with placebo. However, vitamin E supplementation was associated with a slightly higher incidence of hemorrhagic stroke in middle-aged and older men as compared with placebo.

There is also good evidence from several RCTs and meta-analyses that vitamin E supplementation does not lower cardiac event rates in patients with coronary artery disease (GISSI-Prevenzione Investigators Heart Protection Study [HPS] and others).

Vitamin C
There is good evidence that vitamin C supplementation has no benefit in the primary or secondary prevention of ASCVD (HPS study and PHS II).

Beta-carotene
There is good evidence that supplemental doses of beta-carotene do not improve cardiovascular outcome (HPS study), and that it may be associated with increased cardiovascular deaths and overall mortality (Vivekananthan 2003).

Folic acid and B vitamins
There is evidence from two large, well-conducted, randomized double-blind trials that combination therapy of folic acid, vitamin B6, and vitamin B12 was associated with a significant reduction in plasma homocysteine concentration. The combination did not reduce the risk of major cardiovascular events in patients with vascular disease (Lonn 2005) or after an acute myocardial infarction (Bønaa 2006). There was an observed trend toward more harm associated with the combination therapy.

Ebbing and colleagues (2009) pooled data from 2 double-blind vitamin intervention RCTs conducted in Norway (N=6,837) to determine the effects of treatment with B vitamins on cancer and all-cause mortality. The objective of the 2 trials (NORVIT and WENBIT) was to assess whether homocysteine-lowering treatment with folic acid and B12 could improve cardiovascular morbidity and mortality in patients with...
ischemic heart disease. Patients were followed up for a median of 39 months during treatment and for an additional 38 months after the trial ended (91.6% of the study population participated in the post-trial follow-up). The meta-analysis had some limitations, among which are the lack of data on patients’ characteristics and cancer risk. It was also assumed that all patients assigned to folic acid treatment also received vitamin B12. The overall results show that treatment with folic acid plus vitamin B12 was associated with increased cancer incidence, cancer mortality, and all-cause mortality. The association with vitamin B6 with cancer incidence and mortality was not significant.

**Multivitamins**

There is evidence from the PHS II (Sesso 2012) that taking a daily multivitamin does not reduce major cardiovascular events. The trial randomized 14,641 male physicians aged 50 years and older to receive a daily multivitamin or placebo to determine whether long-term multivitamin supplementation would decrease the risk of major cardiovascular events. During a median follow-up of 11.2 years, there were 1,732 confirmed major cardiovascular events and 19% of the participants died. The adjusted hazard ratio for multivitamin use was 1.02 (95% CI, 0.92–1.13) in those without baseline cardiovascular disease. The trial had valid methodology and analysis, but it included only a highly educated group of predominantly white, healthy, nonsmoking, male physicians, which may limit generalization of the results.

**Physical activity**

The Health Professionals Follow-up Study (Chiave 2006) that followed a cohort of more than 50,000 male health professionals aged 40–45 years, and free of diseases at baseline, for 16 years showed that the healthy lifestyle score was significantly inversely associated with the risk of CHD. It is to be noted, however, that the study included only male physicians, and follow-up data were obtained from a self-administered questionnaire, all of which may be potential sources of bias.
References


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 January 2016.

Team
The ASCVD Primary Prevention Guideline development team included representatives from the following specialties: cardiology, clinical laboratory, family medicine, nursing, 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.
Appendix 1: Customized CVD Risk Calculator

There are many different versions of the Framingham calculator that clinicians and patients will likely encounter in an internet search. Differences between the Kaiser Foundation Health Plan of Washington version and others are listed below, and include issues to consider when using risk calculations to inform intervention decisions:

**Risk time frame**
The customized version calculates risk for 5 years out instead of the usual 10. This is because most of the evidence in trials is for 5 years.

**ASCVD definition**
The customized version is based on the 2008 Framingham calculator (D’Agostino 2008), which calculates the risk of not only “hard ASCVD” (stroke, MI) but also of peripheral artery disease and heart failure. The 2002 ATP III version is common in internet search results—that calculator, by contrast, is essentially calculating the risk of “hard CVD” (MI). So partly because of this, the risk per year is significantly higher with the customized calculator for any given patient than it will be with the ATP III calculator. The new calculator released in 2013 as part of the ACC/AHA guidelines calculates the risk of “hard ASCVD” alone (stroke, MI), so it produces yet different numbers and can lead to healthy people with favorable lipid values and no apparent disease being recommended for statin therapy.

The guideline team continues to recommend using the customized version of the 2008 calculator because its risk estimates are more clinically meaningful.

**Family history**
The customized calculator adds 5 percentage points for family history of heart disease. Be aware that this is a rough estimate. For younger patients (< 50 years) and for patients with less clear-cut family history, the full 5-percentage-point value is likely to be an overestimate of added risk.

**Diabetes**
Some risk calculators ask about diabetes, and some do not. The customized calculator does ask for this information, as does the 2013 calculator from ACC/AHA. Newer or well-controlled diabetes has a minimal effect on a patient’s cardiovascular risk (compared with long-standing and/or poorly controlled diabetes). So for such patients, clinicians will likely want to adjust the risk calculation downward to account for the new or well-controlled diabetes.

The following versions of the customized are all the same:
- On the public website for use by clinicians, contracted providers, and members.
- Through the Epic SmartLinks .framinghamscore and .fram, which pull information from a patient’s record to calculate the risk.
- In the Health Profile interactive online tool for members.
- In the Clinical Lab’s cholesterol screen.

The customized CVD risk calculator asks the following questions:
- What is your age?
- What is your gender?
- Do you have heart disease or cardiovascular disease? This includes being diagnosed with angina, a heart attack, a stroke, a mini-stroke (TIA), or peripheral artery disease (PAD).
- Did your father or a brother have heart disease before the age of 55?
- Did your mother or sister have heart disease before the age of 60?
- What were the results of your most recent cholesterol test?
  - Total cholesterol
  - HDL cholesterol
- What is your blood pressure?
- Do you take medicine for high blood pressure?
- Do you have diabetes?
- Do you smoke? Answer "yes" if you've had a cigarette in the last month.