Atherosclerotic Cardiovascular Disease (ASCVD)
Secondary Prevention Guideline

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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 secondary prevention &lt; 70 mg/dL</td>
<td>LDL target for secondary prevention &lt; 100 mg/dL</td>
</tr>
<tr>
<td>Ezetimibe has been added as a first-line option for patients who are not able to achieve an LDL &lt; 70 mg/dL on maximally tolerated doses of formulary statins or who have intolerance or contraindications to statins.</td>
<td>Ezetimibe was a third-line option for statin-intolerant ASCVD patients.</td>
</tr>
</tbody>
</table>
| PCSK9 inhibitors (alirocumab) have been added as an option for patients with ASCVD who are not able to achieve an LDL < 100 mg/dL and meet one of the following:  
  - Are currently 90% adherent to maximally tolerated high-intensity statin therapy (i.e., atorvastatin 80 mg or rosuvastatin 40 mg) in combination with ezetimibe for at least 8 weeks  
  - Have a documented contraindication to statin and ezetimibe therapy  
  - Have a documented intolerance to statin therapy, as defined by the National Lipid Association (NLA) | PCSK9 inhibitors were not available. |
| PCSK9 inhibitors must be prescribed by, or in conjunction with, a cardiologist. |

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 Primary 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.

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 of Secondary Prevention of ASCVD

Reduce recurrent cardiovascular events and decrease coronary mortality.

Lifestyle Modifications for All Patients with ASCVD

Tobacco cessation

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

Healthy diet

All patients should strive to:

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

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

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

Limitation of alcohol consumption

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

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

Physical activity

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

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

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

Weight management

- Assess BMI at every visit. Encourage getting to or maintaining a healthy weight through an appropriate balance of caloric intake and physical activity.
- See the Adult Weight Management Guideline for additional information.
Blood pressure management
- For 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 BP is higher than goal, see the Hypertension Guideline for management recommendations.

Dietary Supplements

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

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

The majority of 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.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Initial dose</th>
<th>Maximum dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start with:</td>
<td>Atorvastatin</td>
<td>80 mg daily</td>
</tr>
<tr>
<td>If LDL goal is not met:</td>
<td>Add Ezetimibe</td>
<td>10 mg daily</td>
</tr>
<tr>
<td>and continue</td>
<td>Atorvastatin</td>
<td>80 mg daily</td>
</tr>
<tr>
<td>If LDL goal is still not met:</td>
<td>Continue Ezetimibe</td>
<td>10 mg daily</td>
</tr>
<tr>
<td>and switch statin to</td>
<td>Rosuvastatin ¹ [NF-PA]</td>
<td>40 mg daily</td>
</tr>
<tr>
<td>If LDL goal is still not met:</td>
<td>Refer to Cardiology for:</td>
<td></td>
</tr>
<tr>
<td>PCSK9 inhibitors (alirocumab) [NF]</td>
<td>75 mg subcutaneously every 2 weeks</td>
<td>150 mg subcutaneously every 2 weeks</td>
</tr>
<tr>
<td>Note: Cardiology consultation is required.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹ Rosuvastatin nonformulary criteria: Failure, contraindication, or intolerance of all equipotent doses of formulary alternatives (i.e., lovastatin, pravastatin, simvastatin, atorvastatin).
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.

<table>
<thead>
<tr>
<th>Line</th>
<th>Medication</th>
<th>Initial dose ¹</th>
<th>Maximum dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>Simvastatin</td>
<td>10–40 mg daily at bedtime</td>
<td>40 mg ² daily at bedtime</td>
</tr>
<tr>
<td></td>
<td>Atorvastatin</td>
<td>10–40 mg daily</td>
<td>80 mg daily</td>
</tr>
<tr>
<td>2nd</td>
<td>Pravastatin ³</td>
<td>20–40 mg daily at bedtime</td>
<td>80 mg daily at bedtime</td>
</tr>
<tr>
<td></td>
<td>(Alternative in cases of drug interactions or side effects)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 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 Lowering Triglycerides to Prevent Pancreatitis, p. 12.) 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. 6) 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. 6.
3. If the patient is still not able to achieve an LDL < 100 after adding ezetimibe to maximally tolerated high-intensive statins, refer to Cardiology. For patients meeting certain criteria, PCSK-9 inhibitors (alirocumab) 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 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 ACC statin intolerance tool.
4. Consider supplementation with co-enzyme Q10 to relieve statin-induced muscle symptoms. Evidence is conflicting, but some studies suggest a benefit.
5. If the patient is still intolerant, switch to one of the medications in Table 2, p. 9.

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.
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 one of the following: |                  |                  |
|                      | Niacin IR        | 100 mg twice daily | 1,000 mg 3 times daily |
|                      | Niacin SR (Slo-Niacin) | 250 mg twice daily | 1,000 mg twice daily |
|                      | Gemfibrozil      | 600 mg twice daily | 600 mg twice daily |
|                      | 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 for: |                  |                  |
|                      | PCSK9 inhibitors (alirocumab) (NF) | 75 mg subcutaneously every 2 weeks | 150 mg subcutaneously every 2 weeks |

Notes: Cardiology consultation is required, and at least one second-line medication must be tried before referral.

Prescribing notes – Table 2

Ezetimibe (Zetia)
Formulary—prior authorization required. See Pharmacy criteria on the staff intranet.
• For use in patients with a history of ASCVD who are not able to achieve an LDL < 70 mg/dL on maximally tolerated doses of formulary statins or who have intolerance or contraindications to statins.

PCSK9 inhibitors (alirocumab)
Nonformulary—specialty tier. See Pharmacy criteria on the staff intranet.
• Patients will continue maximally tolerated statin therapy while receiving alirocumab 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 alirocumab.

Two groups of patients may be considered for PCSK9 inhibitors:

1. Patients with ASCVD who are not able to achieve an LDL < 100 mg/dL and meet one of the following:
   • Are currently 90% adherent to maximally tolerated high-intensity statin therapy (i.e., atorvastatin 80 mg or rosuvastatin 40 mg) in combination with ezetimibe for at least 8 weeks
   • Have a documented contraindication to statin and ezetimibe therapy
• Have a documented intolerance to statin therapy, as defined by the National Lipid Association (NLA)

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

2. Patients 18 years and older with heterozygous familial hypercholesterolemia (HeFH)—defined as diagnosis of HeFH based on genetic testing or a score of > 8 on the World Health Organization diagnostic criteria—who have failed to achieve an LDL < 130 mg/dL and meet one of the following:
  • Are currently 90% adherent to maximally tolerated high-intensity statin therapy (i.e., atorvastatin 80 mg or rosuvastatin 40 mg) in combination with ezetimibe for at least 8 weeks
  • Have a documented contraindication to statin and ezetimibe therapy
  • Have a documented intolerance to statin therapy, as defined by the National Lipid Association (NLA)

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

Niacin IR and SR
• Avoid use if ALT/AST > 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
• Use caution for patients with mild to moderate renal impairment (CKD 2–3).
• Do not use for patients with severe renal impairment (serum creatinine > 2 mg/dL or CKD 4–5).

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 for All Patients with ASCVD

Table 3. ACE inhibitor or ARB therapy for secondary 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>1st</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></td>
<td></td>
<td></td>
<td>20 mg daily (target dose is 10 mg daily)</td>
</tr>
<tr>
<td>2nd</td>
<td>Angiotensin receptor blocker</td>
<td>Losartan</td>
<td>25 mg/day in 1–2 doses</td>
</tr>
</tbody>
</table>

\(^1\) Use an ARB (losartan) for patients who cannot tolerate an ACE inhibitor because of cough, rash, or angioedema (rather than because of renal failure, hyperkalemia, or hypotension). In a patient who previously developed angioedema with an ACE inhibitor, an ARB is less likely to cause angioedema, but there is still a risk of cross-reactivity. In the CHARM-Alternative study, the ARB group had 2.6% ACE-ARB cross-reactivity versus 0% in the placebo group (Granger 2003).

Combination therapy is not recommended

ACE inhibitor and ARB combination therapy is not recommended. There is evidence that there is harm and no additional benefit in combining an ACE inhibitor and an ARB. Numbers needed to harm (NNH) are 33 for hypotensive symptoms, 1,000 for syncope, 250 for diarrhea, and 250 for renal impairment.

Antiplatelet Therapy for All Patients with ASCVD

Daily aspirin is recommended in all patients with ASCVD unless contraindicated due to hypersensitivity to aspirin 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

<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>

\(^1\) Clopidogrel is equally effective in patients with ASCVD who have a contraindication or intolerance to aspirin.

Antiplatelet therapies that are not recommended

**Combined clopidogrel and aspirin therapy**

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.

**NSAIDs alone**

NSAIDs are not appropriate substitutes for aspirin as antiplatelet agents.
Lowering Triglycerides to Prevent Pancreatitis

Triglycerides do not require investigation or treatment unless they are higher than 500 mg/dL. (Treatment/investigation at higher than 1,000 mg/dL would also be reasonable. Use shared-decision making.) If a patient has elevated triglycerides, consider the following workup:

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

Consult with Endocrinology if:

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

### Table 5. Medications for lowering triglyceride levels to prevent possible pancreatitis
See also the prescribing notes that follow Table 5.

<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>
</tbody>
</table>

If TG still not < 500 mg/dL: Add

- **Fenofibrate (preferred)**  
  - 54–160 mg daily  
  - 160 mg daily
- **or**
  - Niacin
    - Niacin IR or  
      - 100 mg twice daily  
      - 1,000 mg 3 times daily
    - Niacin SR (Slo-Niacin)  
      - 250 mg twice daily  
      - 1,000 mg twice daily

If TG still not < 500 mg/dL: Add

- Fish oil (if LDL is at goal)  
  - 2,000 mg DHA/EPA in divided doses daily  
  - 4,000 mg DHA/EPA in divided doses daily

**OR**

1st 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 who are elderly, have kidney disease (CKD 3–5), have untreated hypothyroidism, or are taking interacting drugs.

**Fenofibrate**

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

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

Gemfibrozil

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

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

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

<table>
<thead>
<tr>
<th>Eligible population</th>
<th>Line</th>
<th>Medication</th>
<th>Initial dose</th>
<th>Maximum or target dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-MI patients with preserved LV function (EF ≥ 50%)</td>
<td>1st</td>
<td>Metoprolol</td>
<td>25 mg twice daily</td>
<td>100 mg twice daily is maximum dose.</td>
</tr>
<tr>
<td>Post-MI patients with LV systolic dysfunction (EF &lt; 50%) with or without heart failure</td>
<td>1st</td>
<td>Carvedilol</td>
<td>3.125 mg twice daily</td>
<td>25 mg twice daily is target dose for patients ≤ 187 lb. 50 mg twice daily is target dose for patients &gt; 187 lb.</td>
</tr>
<tr>
<td></td>
<td>2nd</td>
<td>Metoprolol LA</td>
<td>12.5–25 mg daily</td>
<td>200 mg daily is maximum dose.</td>
</tr>
</tbody>
</table>
Medication Monitoring

<table>
<thead>
<tr>
<th>Eligible population</th>
<th>Recommended test(s)</th>
<th>Recommended frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients on statin</td>
<td>Fasting lipoprotein panel (^1) or Direct LDL cholesterol</td>
<td>At minimum 4–6 weeks after initiating therapy and Annually</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>
<tr>
<td>Patients on bile acid sequestrant</td>
<td>Fasting lipoprotein panel (^1)</td>
<td>At baseline and 3 months after initiating therapy and Every 6 months</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 increase in dose and Annually</td>
</tr>
</tbody>
</table>

\(^1\) The lipoprotein panel indirectly calculates LDL cholesterol by using the Friedewald equation (LDL = TC - HDL - TG/5). Be aware, however, 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 consider ensuring that the patient is well below the 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 Secondary 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 secondary 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 with 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)

Pharmacologic therapy

Aspirin therapy

There is strong evidence from large trials and meta-analyses that antiplatelet therapy significantly reduces the risk of serious vascular events among high-risk patients. The results of several meta-analyses (Berger 2008, ATT Collaboration 2009, Bartolucci 2011, and Raju 2011) showed that compared with placebo, aspirin therapy was associated with a significant reduction in a composite of serious vascular events, any major coronary event, and stroke. However, it was associated with a significantly higher rate of major bleeds. Based on the results of Berger’s meta-analysis, treating 1,000 patients with aspirin for an average of 33 months would prevent 33 cardiovascular events, 12 nonfatal MIs, 25 nonfatal strokes, and 14 deaths, and cause 9 major bleeds.
Aspirin dose
A subgroup analysis revealed no significant difference in any of the clinical outcomes between aspirin doses of 50–100 mg daily and 300 mg daily. However, the odds ratio for major bleed was higher with the 300 mg dose than the 50–100 mg dose (OR=3.02, 95% CI, 1.51–6.03 versus OR=2.09, 95% CI, 1.33–3.28).

Aspirin resistance
There is evidence from multiple cohort studies and meta-analyses (Snoep 2007, Krasopoulouos 2008) that aspirin resistance/nonresponsiveness is common (ranging among studies from 5 to 65%, with an average of 28%). This was higher in women and in patients with a history of renal impairment. The studies show that aspirin resistance is associated with worse outcomes. Aspirin-resistant patients are at three to four times higher risk of developing a cardiovascular event compared with those who are aspirin-sensitive. However, there is insufficient evidence to date on the standard assay for assessing aspirin resistance, or on whether or how the resistance could be modified.

Krasopoulouos and colleagues’ meta-analysis showed that adding clopidogrel to aspirin did not provide any benefit for patients identified as aspirin-resistant.

Clopidogrel plus aspirin versus aspirin monotherapy
There is good evidence from RCTs and meta-analyses that in patients at high risk or with acute coronary syndrome, the addition of clopidogrel to aspirin therapy may be associated with lower incidence of death and cardiovascular events, but also with a higher incidence of major and minor bleeding episodes (Yusuf 2001, Keller 2007, Helton 2007). It was calculated that treating 1,000 patients with combination therapy for 9 months is expected to prevent 13 cardiovascular events and cause 6 major bleeds.

The CHARISMA trial showed that the combination of clopidogrel plus aspirin was not significantly more effective than aspirin alone in reducing the rate of myocardial infarction, stroke, or death from cardiovascular causes among patients with stable cardiovascular disease or multiple cardiovascular risk factors. It was, however, associated with an increased risk of moderate to severe bleeding (Bhatt 2006).

Aspirin and anticoagulants
The results of studies investigating the combined use of aspirin and anticoagulants with a target international normalized ratio (INR) of 2.0–2.5 showed benefit of the combined therapy in reducing the composite outcome of death, myocardial infarction, and stroke. The combined therapy, however, was also associated with a higher risk of minor and major bleeds.

A recent meta-analysis of 10 randomized control trials with WARIS-II (Warfarin Aspirin Reinfarction Study) dominating showed that the addition of warfarin to aspirin in the treatment of acute coronary syndrome is associated with a significant reduction in the rates of MI (NNT=53) and ischemic strokes (NNT=203), but not in the mortality rates (Rothberg 2005). The addition of warfarin to aspirin was also associated with an increased risk of a major bleed (NNH=113).

Statin therapy
Statin monotherapy—secondary prevention of ASCVD
There is good direct evidence from large statin trials and meta-analyses of RCTs that statin therapy lowers LDL cholesterol levels and reduces the risk of cardiovascular events, regardless of the baseline prognostic criteria. In the Heart Protection Study (HPS Collaborative Group 2002), patients with low LDL levels—even lower than 100 mg/dL—achieved the same level of risk reduction as those with high levels.

In a meta-analysis of seven RCTs (N=23,395), Josan and colleagues (2008) examined the efficacy and safety of intensive statin therapy in the secondary prevention of CHD. They included seven RCTs that compared different intensities of statin monotherapy regimens in 23,395 adult patients with coronary artery disease (CAD). The meta-analysis results showed a weighted mean difference of 0.72 mmol/L (27.86 mg/dL) in LDL levels between patients receiving the more intensive versus less
intensive statin therapy. Almost 50% of the patients receiving the more intensive therapy achieved an LDL level of < 77.4 mg/dL.

**Target LDL cholesterol level**

The 2013 ACC/AHA guideline (Stone 2014) has no recommendation for or against specific LDL or non-LDL targets for either primary or secondary prevention of ASCVD. Instead of the treatment-to-target approach, the ACC/AHA guideline suggests that, after patients have been stratified based on their risk, they should receive the most effective therapy. High-dose, high-potency statin (40–80 mg atorvastatin or 40 mg rosuvastatin) is recommended for patients at high risk of a cardiovascular event. If the patient doesn't achieve a ≥ 50% reduction of LDL, the guideline recommends considering combination therapy.

The 2014 Kaiser Permanente national guidelines adopted the 2013 ACC/AHA guideline with some modification.

In contrast, the National Lipid Association (Jacobson 2015) recommends continuing the use of lipid targets, non-HDL and LDL goal-setting, and regular lipid monitoring to assess adherence to lipid-lowering therapy. The NLA guideline recommends this stepwise approach to risk assessment and treatment goals:

1. Identify the highest-risk category that applies to the patient.
2. For patients who are at very high risk, begin with moderate- or high-intensity statin, with a non-HDL goal of < 100 mg/dL and an LDL goal of < 70 mg/dL.
3. For the remaining patients, count major risk factors and treat to the following goals: non-HDL < 130 mg/dL and LDL < 100 mg/dL.

If non-HDL and LDL goals are not met with statin therapy, the statin dose may be increased or the patient may be switched to a more efficacious agent.

The guideline panels of the European Societies (ESC/EAS) of Cardiology (Klose 2014) and the Canadian Cardiac Society (Anderson 2014) have both published statements recommending the use of individualized prevention strategies based on LDL levels.

There are no published outcomes studies to date that treated LDL to target. Results of the IMPROVE-IT trial (Cannon 2015) showed that clinical outcomes were better with lower LDL levels in high-risk patients, and that there was an incremental benefit for lowering the LDL below the 70 mg/dL target generally recommended for high-risk patients.

**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.

**Use of ezetimibe in combination with statin**

IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial, Cannon 2015) is a randomized controlled trial that evaluated the effect of ezetimibe combined with simvastatin versus simvastatin alone among over 18,000 high-risk patients (from 1,147 sites in 39 countries) who were hospitalized for an acute coronary syndrome (ACS). The trial had other strict inclusion criteria: LDL level between 50 and 125 mg/dL, and not receiving statins more potent than simvastatin 40 mg. The participants’ mean age was 64 years, their mean baseline LDL was 93.8 mg/dL, and 76% were men. The participants were randomly assigned to receive either a once-daily dose of 40 mg simvastatin plus 10 mg ezetimibe or 40 mg simvastatin monotherapy plus placebo. They were followed up for a minimum of 2.5 years or until 5,252 clinical events were reported. Seventy-five percent of the participants completed the final visit, and 42% prematurely discontinued the study drugs regardless of the treatment assignment, during a median follow-up duration of 6 years. The primary outcome was a composite of deaths from CVD, major coronary events, or nonfatal strokes. The trial also had safety endpoints and three secondary outcomes based on different combinations of the individual endpoints.

The results of the trial showed a modest, statistically significant difference in the composite endpoint of cardiovascular events among the group randomized to receive 40 mg simvastatin plus ezetimibe.
versus those in the simvastatin monotherapy group. Patients in the combination therapy group achieved a mean LDL level of 53.2 mg/dL, which is much lower than the commonly used 70 mg/dL target for high-risk patients. The Kaplan Meier event rate for the primary composite endpoint at 7 years was 32.7% in the combination therapy group and 34.7% in the simvastatin monotherapy group, with an absolute risk reduction of 2.0% and an NNT of 50. This reduction was driven mainly by the statistically significant reduction in the incidence of nonfatal myocardial infarction and ischemic stroke in the group receiving statin plus ezetimibe therapy. The number of strokes and MIs was reduced after 7–10 years of treatment, but mortality was unaffected; there were no significant differences between the two study groups in death from any cause, from CVD, or from CAD. Subgroup analysis showed similar outcomes across all subgroups, but diabetics had larger benefits.

In conclusion:
- IMPROVE-IT results show that the outcomes were better with lower LDL levels, and that there was an incremental benefit from lowering the LDL below the 70 mg/dL target generally recommended for high-risk patients. Many commentators have attributed these improved outcomes to the LDL lowering regardless of the drug therapy used. However, the study did not include an arm where patients were treated with an intensive dose of statin (e.g., atorvastatin 80 mg or rosuvastatin 40 mg) or with the addition of a non-statin lipid-lowering agent other than ezetimibe. This makes it difficult to conclude with certainty that the observed benefits were due to the lower LDL levels alone, and not possibly to additional clinical benefits of ezetimibe (i.e., potential pleiotropic effects of ezetimibe beyond cholesterol lowering).
- The trial included very high-risk post-ACS patients and its results may not be generalized to patients at lower risk, or to the primary prevention of ASCVD.
- IMPROVE-IT did not address whether the use of ezetimibe in combination with a moderate-dose statin has similar or superior outcomes to high-intensity statins (e.g., atorvastatin 80 mg or rosuvastatin 40 mg), which are currently recommend for post-ACS patients. Medical practice has significantly changed since the trial was designed, which may make its results less relevant with the current recommendations for using high-intensity statins post-MI and in high-risk patients.
- IMPROVE-IT did not address the safety and efficacy of using ezetimibe in combination with intensive statin therapy.

**Extended-release niacin/statin combination**

The AIM-HIGH trial (Boden 2011) examined whether extended-release niacin (niacin ER, Niaspan) added to simvastatin to raise HDL cholesterol levels is superior to simvastatin alone in reducing cardiovascular risk. After an open-label niacin run-in phase, 3,414 patients with established CVD and a low HDL level were randomized to receive niacin or a matching placebo, in addition to simvastatin 40–80 mg/day plus ezetimibe 10 mg/day if needed. All patients had an elevated triglyceride level of 150–400 mg/dL (median 162–164 mg/dL), and LDL < 180 mg/dL (median 74 mg/dL) if not taking a statin at entry. Screened patients were required to discontinue lipid-modifying drugs, except for statin and ezetimibe, at least 4 weeks before enrollment. The primary end point of the trial was the first event of the composite of death from coronary heart disease (CHD), nonfatal myocardial infarction (MI), ischemic stroke, hospitalization for an acute coronary syndrome (ACS), or symptom-driven coronary or cerebral revascularization. (The last outcomes were modified/added to the protocol due to the lower-than-expected rate of primary end point.) The trial was event-driven and designed to show a 25% reduction in cardiovascular events. It was statistically powered based on the expectation to observe 800 events during a mean follow-up of 4.6 years. However, due to lack of efficacy it was halted early after a mean follow-up of 3 years. The primary end point occurred in 16.4% of patients in the niacin group and in 16.2% of those in the placebo group (hazard ratio 1.02 [95% CI, 0.87–1.21, p=0.79]). At 2 years, however, the HDL level increased by 25% in the niacin group and 9.8% in the placebo group (p < 0.001). The study drug was discontinued in 25.4% of patients in the niacin group and 20.1% in the placebo group (p < 0.001).

The HPS2-THRIVE trial (2013) was a large trial that evaluated the effects of extended-release (ER) niacin with laropiprant (ERN/LRPT) given in addition to simvastatin 40 mg daily (with or without ezetimibe) in 25,673 patients at high risk of vascular events and enrolled from China and five European countries. The primary composite end point was time to first major vascular event (MVE: a composite of nonfatal MI, coronary death, stroke, or arterial revascularization). The study participants were followed up for a mean of 3.6 years (median 3.9 years) during which 25.4% of patients in the ERN/LRPT group had stopped their study medication compared with 16.6% of those in the placebo.
group (p < 0.0001). The article published in May 2013 did not report on the primary outcome, but on the muscle and liver outcomes as well as reasons for stopping the study treatment. The primary outcome results as presented in the 2013 ACC conference show no significant reduction in MVE with the ERN/LRPT compared with placebo (risk ratio=0.96; 95% CI, 0.90–1.03; p=0.3). The risk of myopathy was low but was 4 times higher in the ERN/LRPT group and 10 times higher among the Chinese.

The results of this trial should be interpreted with caution as the study participants had a well-controlled LDL at baseline, and 42% were Chinese who had some variations in their baseline characteristics compared with the European participants, and who (according to some investigators) have lower tolerance to statins and niacin compared with Caucasians.

**PCSK9 inhibitors**

FDA approval of alirocumab was based on five pivotal phase-3 placebo-controlled randomized controlled trials from the ODYSSEY clinical trial program, while FDA approval of evolocumab was based on six pivotal phase-3 placebo- or ezetimibe-controlled randomized controlled trials. Alirocumab significantly decreased LDL cholesterol versus placebo at week 24 in adults with heterozygous familial hypercholesterolemia (HeFH) or ASCVD by 39–62%. Evolocumab significantly decreased LDL cholesterol versus placebo at week 12 in adults with HeFH or ASCVD by 55–76% and by 31% in patients with homozygous familial hypercholesterolemia (HoFH) (FDA alirocumab and evolocumab summary reviews, 2015).

Safety data are limited, although potential adverse effects such as neurocognitive disorders and liver transaminase elevations and the long-term safety of very low LDL levels are still being investigated.

Although meta-analysis data of smaller trials indicate that PCSK9 inhibitors may decrease all-cause mortality and myocardial infarction, these need be confirmed by results from ongoing, large-scale outcomes trials (Navarese 2015). The 27,500-person FOURIER trial (evolocumab) results are expected in late 2016, while the 18,000-person ODYSSEY OUTCOMES trial (alirocumab) results are expected in early 2018.

Additionally, a recent cost-effectiveness review found that, based on current pricing, PCSK9 inhibitors were not cost-effective, with an estimated cost per quality-adjusted life year of $296,850 (Institute for Clinical and Economic Review 2015).

**Beta-blocker therapy**

There is evidence from an earlier trial that beta-blocker therapy post-MI significantly reduces mortality, with an NNT of 38 in 2 years (Beta-Blocker Heart Attack Trial Research Group 1982).

**ACE inhibitor therapy**

There is strong evidence that the use of angiotensin-converting enzyme (ACE) inhibitors decreases ASCVD events in patients with known coronary artery disease.

The HOPE trial (Yusuf 2000) found an NNT of 27 over 5 years; the EUROPA trial (Fox 2003) found an NNT of 53 over 4 years.

The PEACE trial did not show any significant difference in the primary outcomes between the trandolapril and placebo groups (Braunwald 2004). The trial results might not be generalizable to all secondary prevention patients because participating patients had lower cardiovascular risk and well-controlled lipids, and the ASCVD event rates were relatively low.

A meta-analysis combining the results of these three studies (Dagenais 2006), as well as two other meta-analyses (Danchin 2006, Saha 2007) that included other, smaller trials, showed that the use of ACE inhibitors for the secondary prevention of ASCVD significantly decreased overall mortality, cardiovascular mortality, MI, and stroke among patients with preserved left ventricular function. Hospitalization rates for heart failure were also found to be reduced with the ACE-inhibitor therapy. Saha calculated an NNT of 100 patients for about 4.5 years to prevent 1 death, 1 nonfatal MI, or 1 invasive coronary revascularization.
Class effect of ACE inhibitors
There is insufficient direct evidence from large, head-to-head RCTs using ACE inhibitors in comparable doses, and with comparable targets and outcomes, to conclusively determine whether or not there is a class effect for ACE inhibitors. Earlier studies that compared 1 ACE inhibitor with another head to head among patients with congestive heart failure yielded conflicting results.

Indirect comparisons and analyses were performed by several investigators to prove or dispute the assumption of an ACE inhibitor class effect. These indirect comparisons suggest that such a class effect does not exist.
- Pilote’s 2004 analysis indicates that ramipril is associated with better survival benefits versus other ACE inhibitors in the first year after an MI in patients aged 65 and older.
- Pilote’s 2008 analysis suggests that ramipril is associated with a significantly lower mortality rate than enalapril or captopril when prescribed to patients with CHF.
- Hansen’s analysis (2008) suggests that treatment of acute MI patients with ACE inhibitors should focus on the dose rather than on ACE inhibitor used.
- Snyman’s meta-analysis (2009) shows that perindopril was associated with better outcomes than all other commonly used ACE inhibitors.

Angiotensin receptor blocker (ARB) therapy
There is insufficient evidence to recommend for or against angiotensin receptor blocker (ARB) therapy. There is no published data on the use of ARBs in nondiabetic patients or in those with preserved left ventricular function and intolerance to ACE inhibitors.

There are no placebo-controlled trials for the use of ARBs for secondary prevention in ASCVD patients. Nevertheless, ARBs should be considered routinely in the management of such patients if they are intolerant/allergic to ACE inhibitors, as ARB has been compared directly with ramipril therapy in this population and is noninferior.

The ONTARGET noninferiority trial (ONTARGET Investigators 2008) randomized 25,620 high-risk patients with cardiovascular disease or diabetes. The trial results showed that telmisartan was not inferior to ramipril in reducing the incidence of major cardiovascular events and mortality among the study population. Compared with ramipril, telmisartan monotherapy was associated with significantly lower rates of cough and angioedema, but also with significantly higher rates of hypotensive symptoms. The results also showed that combining the two drugs in the full doses was not superior to either of the two drugs given alone, but was associated with higher rates of hypotension, syncope, and renal impairment. These results, however, may be generalized only to patients who have conditions and characteristics similar to those of the patients included in the trial.

A meta-analysis of 19 studies that evaluated the effects of ARBs on MI risk among patients at risk of cardiovascular events showed that treatment with ARBs versus ACE inhibitors was not associated with an increased risk of MI (McDonald 2005).

There is evidence that ARBs are beneficial, though not superior to ACE inhibitors for patients with left ventricular dysfunction after MI.

ACE inhibitor/ARB combination therapy
There is evidence of harm and no additional benefit in combining ACE inhibitors and ARBs. The ONTARGET trial (2008) showed that combined therapy did not have any added benefit but resulted in increased risk of adverse outcomes. Numbers needed to harm (NNH) were 33 for hypotensive symptoms, 1,000 for syncope, 250 for diarrhea, and 250 for renal impairment.

Calcium channel blocker therapy
The results of two meta-analyses (Costanzo 2009 and Bangalore 2009) indicate that:
- Long-acting calcium channel blockers (CCBs) are not associated with an increased risk of all-cause mortality, cardiovascular mortality, or nonfatal MI among patients with CAD or other CVD.
- Long-acting CCBs may be associated with a higher risk of heart failure when compared with other active agents (ACE inhibitors, diuretics/beta-blockers, or ARBs), but with a lower risk when compared with placebo, mainly due to blood pressure reduction.
- Long-acting CCBs are associated with a statistically significant lower risk of fatal and nonfatal stroke among patients with CAD or other ASCVD. These differences, however, may not be clinically significant (ARR=0.006, NNT=16,666).
- Long-acting CCBs are associated with a statistically significant lower risk of angina pectoris in patients with CAD compared with placebo or other blood pressure–lowering agents (AR=0.008, NNT=12,500).

These results should be interpreted with caution due to the variations between studies in definition of existing conditions and outcomes, as well as the lack of data on heart failure (hospitalized versus nonhospitalized), degree of blood pressure control, dose of medications used, additional therapies, compliance, and other factors.

Diet

**Mediterranean diet**

There is good evidence that diets low in fat or higher in monounsaturated fats improve blood lipids. There is additional evidence from large studies (de Lorgeril 1999, Singh 2002) that the Mediterranean diet leads to improved ASCVD outcomes. While these studies have flaws, the large event difference in those randomized to diet versus control groups suggests it is likely a true benefit.

The published literature provides fair evidence that adhering to a Mediterranean diet has a cardioprotective effect. This diet was evaluated in a large number of observational studies and a limited number of RCTs. The majority of the published trials were conducted in Mediterranean countries, with some differences in the components of the Mediterranean diet, co-interventions, patient age, gender, and other characteristics.

Nordmann and colleagues (2011) performed a meta-analysis of 6 randomized trials (total N=3,650 participants) that compared the effects of the Mediterranean diet with those of low-fat diets on cardiovascular risk factors. Only one of the included trials was strictly a secondary prevention trial, another included both primary and secondary prevention patients, and the rest were primary prevention trials. All outcomes were intermediate, as only one very small trial had clinical outcomes. The pooled results of the studies showed that the Mediterranean diet was significantly more effective than low-fat diets in reducing weight and several cardiovascular risk factors: hypertension, dyslipidemia, and diabetes.

In another meta-analysis (Sofi 2008, updated 2010) of prospective cohort studies investigating the health benefits of adhering to a Mediterranean diet, the pooled results of 18 studies involving more than 2 million participants demonstrated that adherence to the Mediterranean diet was associated with significant reduction in the risk of mortality and the incidence of cardiovascular events, cancers, and chronic degenerative diseases. The analysis showed that a slight increase of 2 points in the adherence score was associated with an 8% decrease in all-cause mortality and a 10% reduction in cardiovascular events and related deaths.

**Fish consumption**

Zheng and colleagues (2011) performed a meta-analysis of 17 cohort studies with 315,812 participants with an average follow-up of 15.9 years (range 6–30 years). Seven studies were conducted in the United States, 8 in Europe, and 2 in Asia. Eight cohorts used a self-administered questionnaire, and 9 used an interview. The authors of the meta-analysis categorized the fish consumption into 4 groups based on fish intake frequency: 1. High (> 5 servings/week), 2. Moderate (2–4 servings/week), 3. Low (1 serving/week), and 4. Very low (comparison group: < 1 serving/week or 1–3 servings/month). The results indicate that low (1 serving/week) or moderate fish consumption (2–4 servings/week) has a significantly beneficial effect on the prevention of CHD mortality.

**Vitamins and supplements**

**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.

**Fish oil**

A study by the GISSI-Prevenzione Investigators (1999) showed a modest but significant benefit with the daily intake of n-3 polyunsaturated fatty acid (omega-3 fatty acid), which produced an absolute reduction in cardiovascular events of 1.3% over 3.5 years, with a relative risk reduction of 10%. The results of two meta-analyses (Bucher 2002, Yzebe 2004) showed that the incidence of overall mortality and fatal MI in patients with a history of CHD was significantly lowered among the group who received n-3 polyunsaturated fatty acids in their diet or as a supplement compared with those who received a placebo or a control diet.

The Japan EPA Lipid Interventional Study (JELIS) (Yokoyama 2007) showed significantly lower major-event rates among patients with a history of coronary events who received EPA in addition to their statin therapy versus those receiving statins alone. The lower risk observed was mainly due to the reduction in the rates of nonfatal events, mainly unstable angina. The EPA therapy was not associated with a significant benefit on coronary or sudden cardiac death. The event rates, however, were too small, and the trial was not powered to detect differences in subgroups. EPA plus statin therapy was compared with low doses of statin therapy, which does not allow investigation of whether a higher statin dose would lead to similar outcomes.

A more recent meta-analysis of 20 primary and secondary prevention RCTs (Rizos 2012) that evaluated the effect of omega-3 supplementation on major cardiovascular events and mortality showed no significant benefit on major CV events or mortality.

Kwak and colleagues’ meta-analysis (2012) also investigated the efficacy of omega-3 supplements on the secondary prevention of CVD. The meta-analysis pooled the results of 14 secondary prevention double-blind placebo-controlled RCTs (20,485 patients with a history of CVD). This analysis, as well as Rizos and colleagues’ meta-analysis, included the three more recent trials (Alpha Omega, OMEGA, and SU.FOL.OM3), all of which had negative outcomes. The larger GISSI and JELIS trials were not included in Kwak and colleagues’ analysis as they were open-label studies. The meta-analysis had valid methodology and design. It included only double-blind RCTs, and their mean Jadad score was 4.4 (out of 5). The trials however, were relatively small in size (59–500 participants) and had short duration of follow-up (1–2 years in 10 trials, and 2.3–4.7 years in 4 trials). The daily dose of EPA or DHA ranged from 0.4 to 4.8 g/day. The pooled results showed that omega-3 fatty acid supplementation had no significant secondary prevention effect in reducing the risk of overall CV events. There was a small reduction in cardiovascular death that disappeared after the exclusion of the trial with significant difference in baseline history of MI. No significant benefits were observed with subgroup analyses based on history of CVD, country or geographic location, duration of treatment, dose of EPA or DHA, concomitant medication use, methodological quality of trials, type of placebo, or use of fish oil supplementations only as treatment.

The difference in outcomes in the more recent trials (Alpha Omega, OMEGA, and SU.FOL.OM3) versus the GISSI trial could be attributed to the better treatment with statins, antithrombotics, and antihypertensives the patients in the more recent trials were receiving (e.g., statin was used among 29% of the participants in the GISSI trial, versus 85% in Alpha Omega, 94% in OMEGA, and 87% on SU.FOL.OM3). Another explanation could be the insufficient power of the studies to detect significant differences, especially with the more aggressive management of risk factors.

**Vitamin E**

There is good evidence from several randomized controlled trials and meta-analyses that vitamin E supplementation does not lower cardiac event rates in patients with coronary artery disease (GISSI-Prevenzione Investigators 1999, Heart Protection Study Collaborative Group 2002, and others).
Vitamin C
There is good evidence from the Heart Protection Study (HPS Collaborative Group 2002) and the Physicians’ Health Study II (Sesso 2012) that vitamin C supplementation has no benefit in the primary or secondary prevention of ASCVD.

Beta-carotene
There is good evidence that supplemental doses of beta-carotene do not improve cardiovascular outcome (HPS Collaborative Group 2002), 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 acute myocardial infarction (Bønnaa 2006). There was an observed trend toward more harm associated with the combination therapy.

Ebbing and colleagues (2009) pooled data from two 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 two 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 was ended (91.6% of the study population participated in the post-trial follow-up). The meta-analysis had some limitations, among which were 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 of vitamin B6 with cancer incidence and mortality was not significant.

Calcium
No randomized clinical trial has specifically tested the effect of calcium supplementation (with or without vitamin D) on CVD as its primary or secondary end point. Secondary analyses of trials (conducted mainly to examine the effect of calcium supplementation on reducing risk of fractures) and meta-analyses pooling their findings had conflicting results. While some showed a neutral effect of calcium (with or without vitamin D) supplements on CVD events, others showed an increased risk with calcium supplementation. The additive effect of vitamin D seemed to lower that risk; however, one meta-analysis showed an increased cardiovascular risk despite the co-administration of calcium with vitamin D (Avenall 2012; Bolland 2010, 2011; Lewis 2011; Li 2012; Prentice 2013; Samelson 2012; Wang TK 2010; Wang L 2012; and Xiao 2013).

The results of these secondary analyses presented in the trials and meta-analyses should be interpreted with caution. In many cases, the numbers were too small to provide statistically significant differences. In addition, CVD events were not prespecified end points in the majority of studies and, thus, were not systematically verified. The trials included populations with varying characteristics, did not adjust for all potential confounders, and used different definitions of outcomes and different analyses.

Overall the results of some of the trials, observational studies, and meta-analyses may suggest that:
- Calcium supplementation may be associated with increased risk of cardiovascular disease, mainly MI.
- The association of calcium with cardiovascular risk may be J-shaped (trend toward increased harm with higher doses > 1,200 or > 1,500 mg/day).
- Subgroup analyses by gender suggest that the cardiovascular harms associated with calcium supplementation were more significant among men.
- Dietary calcium may have a protective effect on cardiovascular risk.
- The co-administration of calcium with vitamin D may weaken the observed adverse effect of calcium.
- There is a trend toward reduced risk of stroke with calcium intake, which was explained by investigators to result from the blood pressure--lowering effect of dietary calcium.
• 2010 IOM report indicates that calcium intake promotes skeletal growth and maintenance, with insufficient evidence for other benefits. The report noted that the evidence for any benefits of calcium intake beyond bone health remains insufficient and that an intake of > 2,000 mg/day for both men and women > 51 years of age may increase the risk of harm.

Physical activity
A meta-analysis (Taylor 2004) of 48 RCTs on the effect of exercise on patients with CHD showed that patients who underwent any supervised or unsupervised structured exercise had a lower cardiac and overall mortality when compared with those who received the usual care with no exercise training or advice (NNT=62 and 45, respectively, in a median 15 months). There were also significant reductions in total cholesterol, triglyceride levels, and systolic blood pressure, but there were no significant differences in HDL or LDL cholesterol levels, diastolic blood pressure, or health-related quality of life.

Depression
There is evidence from randomized trials (Frasure-Smith 1993 and 1995) and a meta-analysis of 20 studies (Barth 2004) that clinical depression and depressive symptoms have an unfavorable impact on mortality among patients with coronary heart disease.

A trial of 2,481 post-MI patients who were given comprehensive integrated depression treatment—behavioral therapy and antidepressant medications—failed to show a significant benefit in all-cause mortality, cardiovascular mortality, nonfatal MI, hospitalization, or revascularization (Berkman 2003). This integrated depression treatment, however, improved the depression and low perceived social support among these patients.

References


Bolland MJ, Grey A, Avenell A, Gamble GD, Reid IR. Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of the Women's Health Initiative limited access dataset and meta-analysis. BMJ. 2011;342:d2040.


Guideline Development Process and Team

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

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

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