Kaiser Permanente National Dyslipidemia Guideline
May 2015

Adoption of the 2013 AHA/ACC Guideline for the Treatment of Blood Cholesterol with KP Modifications (noted in red)

AHA/ACC Cholesterol Guideline


There were 5 KP modifications (in red listed below) for recommendations that address the following:

Primary Prevention in Individuals without Diabetes Mellitus and With LDL–C 70 to 189 mg/dL
  ● 4 modifications (see below)

Monitoring Statin Therapy
  ● 1 modification (see below)

The triglyceride treatment recommendations were carried over from the 2012 Kaiser Permanente Dyslipidemia Guideline as they were not addressed by the AHA/ACC Cholesterol Guidelines. In addition, the 2012 KP secondary prevention recommendations pertaining to Asymptomatic Non-Coronary Atherosclerosis and unrepaired Abdominal Aortic Aneurysm (AAA) were added and subsequently updated in 2015 (in red listed below).

Secondary Prevention
  ● 2 additions (see below)

To view the complete guidelines and supplemental reports from the AHA/ACC, click on the links provided below:

2013 AHA/ACC Cholesterol Guidelines:

2013 AHA/ACC Cholesterol Guidelines Supplemental Report:

2013 AHA/ACC Risk Assessment Guideline:
2013 AHA/ACC Risk Assessment Guidelines Supplemental Report:

http://cl.kp.org/pkc/national/cmi/programs/dyslipidemia/guideline/files/aha_acc_risk_assessmt_s
upplemental.pdf
Recommendations

Treatment Targets
• No recommendation for or against specific LDL–C or non-HDL–C targets for the primary or secondary prevention of ASCVD. (No recommendation-Grade N)

Secondary Prevention
• High-intensity statin therapy should be initiated or continued as first-line therapy in women and men ≤75 years of age who have clinical ASCVD\(^1\), unless contraindicated. (Strong recommendation-Grade A)

• In individuals with clinical ASCVD in whom high-intensity statin therapy would otherwise be used, when high-intensity statin therapy is contraindicated or when characteristics predisposing to statin-associated adverse effects are present, moderate-intensity statin should be used as the second option if tolerated. (Strong recommendation-Grade A)

• In individuals with clinical ASCVD >75 years of age, it is reasonable to evaluate the potential for ASCVD risk-reduction benefits and for adverse effects, drug-drug interactions and to consider patient preferences, when initiating a moderate- or high-intensity statin. It is reasonable to continue statin therapy in those who are tolerating it. (Expert opinion-Grade E)

• For patients with asymptomatic non-coronary atherosclerosis, including asymptomatic peripheral arterial disease (PAD), carotid stenosis and aortic atherosclerosis, a statin is an option to reduce the risk of developing symptomatic cardiovascular disease. (KP Weak Recommendation)

1 Clinical ASCVD (Atherosclerotic Cardiovascular Disease) is defined by the inclusion criteria for the secondary prevention statin RCTs (acute coronary syndromes, or a history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, TIA, or clinically significant peripheral arterial disease presumed to be of atherosclerotic origin, such as claudication or revascularization*).

*This clarification (in bold) was added to address internal inconsistencies in the AHA/ACC guidelines. Asymptomatic peripheral arterial disease is not considered to be "clinical ASCVD" but is considered a risk factor for clinical ASCVD, as the authors state, "...additional factors may be considered to inform treatment decision making. These factors include...coronary artery calcium (CAC) score >300 Agatston units or >75 percentile for age, sex, and ethnicity, ankle-brachial index <0.9..." (Page 18).

Click here to go directly to the rationale table supporting this recommendation

For patients with abdominal aortic aneurysm (AAA) in the absence of other significant cardiovascular risk factors or without elevated estimated 10-year ASCVD risk, there is insufficient evidence to make a recommendation for or against the use of statins to reduce the risk of cardiovascular disease progression. (KP No Recommendation For or Against)

Click here to go directly to the rationale table supporting this recommendation

Primary Prevention in Individuals ≥21 Years of Age with LDL–C ≥190 mg/dL
• Individuals with LDL–C ≥190 mg/dL or triglycerides ≥500 mg/dL should be evaluated for secondary causes of hyperlipidemia (Moderate Recommendation-Grade B)

Kaiser Permanente, Care Management Institute, Oakland, California, May 2015
• Adults ≥21 years of age with primary LDL–C ≥190 mg/dL should be treated with statin therapy (10-year ASCVD risk estimation is not required):
  o Use high-intensity statin therapy unless contraindicated.
  o For individuals unable to tolerate high-intensity statin therapy, use the maximum tolerated statin intensity. (Moderate recommendation-Grade B)

• For individuals ≥21 years of age with an untreated primary LDL–C ≥190 mg/dL, it is reasonable to intensify statin therapy to achieve at least a 50% LDL–C reduction. (Expert opinion-Grade E)

• For individuals ≥21 years of age with an untreated primary LDL–C ≥190 mg/dL, after the maximum intensity of statin therapy has been achieved, addition of a nonstatin drug may be considered to further lower LDL–C. Evaluate the potential for ASCVD risk reduction benefits, adverse effects, drug-drug interactions, and consider patient preferences. (Expert opinion-Grade E)

**Primary Prevention in Individuals with Diabetes Mellitus and LDL–C 70-189 mg/dL**

• Moderate-intensity statin therapy should be initiated or continued for adults 40 to 75 years of age with diabetes mellitus who have LDL 70-189 and who do not have ASCVD. (Strong recommendation-Grade A)

• High-intensity statin therapy is reasonable for adults 40 to 75 years of age with diabetes mellitus, who have LDL 70-189 and who do not have ASCVD, with a ≥7.5% estimated 10-year ASCVD risk unless contraindicated. (Expert opinion-Grade E)

• In adults with diabetes mellitus, who have LDL 70-189 and who do not have ASCVD, who are <40 or >75 years of age, it is reasonable to evaluate the potential for ASCVD benefits and for adverse effects, for drug-drug interactions, and to consider patient preferences when deciding to initiate, continue, or intensify statin therapy. (Expert opinion-Grade E)

**Primary Prevention in Individuals without Diabetes Mellitus and With LDL–C 70 to 189 mg/dL**

• Use of the The Pooled Cohort Equations [AHA/ACC CV Risk Calculator] or other risk calculator to estimate 10-year ASCVD risk for individuals with LDL–C 70 to 189 mg/dL without clinical ASCVD to guide initiation of statin therapy for the primary prevention of ASCVD is an option. (KP weak recommendation)
  o If using The Pooled Cohort Equations for populations other than Non-Hispanic Whites or African Americans, use the equations for Non-Hispanic Whites (Expert Opinion-Grade E).

> *Because no cardiovascular risk calculator has been studied prospectively and compared to another risk calculator, some clinicians may choose a different risk calculator to estimate cardiovascular risk. Clinicians selecting a different risk calculator may decide to apply different treatment thresholds than those proposed in the Pooled Cohort Equations [AHA/ACC CV Risk Calculator].*

[Click here to go directly to the rationale table supporting this modified recommendation]
• For adults 40 to 75 years of age with LDL–C 70 to 189 mg/dL, without clinical ASCVD or diabetes at elevated risk (e.g. 7.5-14.9% risk by the AHA/ACC Pooled Cohort Equations) treatment with moderate- to high-intensity statin therapy is an option, after a discussion which considers the potential for ASCVD risk reduction benefits and for adverse effects, for drug-drug interactions, and patient preferences for treatment (KP weak recommendation)

Click here to go directly to the rationale table supporting this modified recommendation

• For Adults 40 to 75 years of age with LDL–C 70 to 189 mg/dL, without clinical ASCVD or diabetes and a very elevated estimated 10-year ASCVD risk (e.g. ≥15% risk by the AHA/ACC Pooled Cohort Equations), treatment with moderate- to high-intensity statin therapy is recommended (KP strong recommendation).

Click here to go directly to the rationale table supporting this modified recommendation

• It is reasonable to offer treatment with a moderate intensity statin to adults 40 to 75 years of age, with LDL–C 70 to 189 mg/dL, without clinical ASCVD or diabetes and a slightly elevated estimated 10-year ASCVD risk (e.g. ≥5% to 7.4% risk by the AHA/ACC Pooled Cohort Equations). (Weak recommendation-Grade C)

• Use of additional factors (baseline LDL-C >=160 or other evidence of genetic hyperlipidemias, family history of premature ASCVD with onset <55 years in a first degree male relative, or <65 in a first degree female relative, or lifetime risk of ASCVD, testing for hsCRP, ABI, or CAC), is an option for individuals who are not otherwise identified in a statin benefit group, or those for whom a risk-based treatment decision is uncertain after quantitative risk assessment. Testing should only be ordered if the result will prompt a therapeutic decision and the clinician and patient have agreed to initiate statin therapy if the result is abnormal, and to forgo statin therapy if the result is normal. Testing should be discussed in shared decision-making, taking into consideration the significant differences in convenience, cost, invasiveness, and radiation exposure (weak recommendation).

Click here to go directly to the rationale table supporting this modified recommendation

Heart Failure and Hemodialysis
• The Expert Panel makes no recommendations regarding the initiation or discontinuation of statins in patients with NYHA class II–IV ischemic systolic heart failure or in patients on maintenance hemodialysis (No Recommendation-Grade N).

Safety
• To maximize the safety of statins, selection of the appropriate statin and dose in men and nonpregnant/nonnursing women should be based on patient characteristics, level of ASCVD** risk, and potential for adverse effects.

• Moderate-intensity statin therapy should be used in individuals in whom high-intensity statin therapy would otherwise be recommended when characteristics predisposing them to statin-associated adverse effects are present.
Characteristics predisposing individuals to statin adverse effects include, but are not limited to:
- Multiple or serious comorbidities, including impaired renal or hepatic function.
- History of previous statin intolerance or muscle disorders.
- Unexplained ALT elevations $>$3 times ULN.
- Patient characteristics or concomitant use of drugs affecting statin metabolism.
- $>75$ years of age.

Additional characteristics that may modify the decision to use higher statin intensities may include, but are not limited to:
- History of hemorrhagic stroke.
- Asian ancestry. (Strong Recommendation - Grade A)

**Based on the presence of clinical ASCVD, diabetes mellitus, LDL–C $>$190 mg/dL, or level of estimated 10-year ASCVD risk.

- CK should not be routinely measured in individuals receiving statin therapy (Strong Recommendation - Grade A)

- Baseline measurement of CK is reasonable for individuals believed to be at increased risk for adverse muscle events based on a personal or family history of statin intolerance or muscle disease, clinical presentation, or concomitant drug therapy that might increase the risk for myopathy (Expert opinion-Grade E)

- During statin therapy, it is reasonable to measure CK in individuals with muscle symptoms, including pain, tenderness, stiffness, cramping, weakness, or generalized fatigue (Expert opinion-Grade E)

- Baseline measurement of hepatic transaminase levels (ALT) should be performed before initiating statin therapy (Moderate Recommendation-Grade B)

- During statin therapy, it is reasonable to measure hepatic function if symptoms suggesting hepatotoxicity arise (e.g., unusual fatigue or weakness, loss of appetite, abdominal pain, dark colored urine or yellowing of the skin or sclera) (Expert opinion-Grade E)

- Decreasing the statin dose may be considered when 2 consecutive values of LDL–C levels are $<$40 mg/dL (Weak Recommendation-Grade C)

- It may be harmful to initiate simvastatin at 80 mg daily or increase the dose of simvastatin to 80 mg daily. (Moderate Recommendation-Grade B)

- Individuals receiving statin therapy should be evaluated for new-onset diabetes mellitus according to the current diabetes screening guidelines (93). Those who develop diabetes mellitus during statin therapy should be encouraged to adhere to a heart healthy dietary pattern, engage in physical activity, achieve and maintain a healthy body weight, cease tobacco use, and continue statin therapy to reduce their risk of ASCVD events (Moderate Recommendation-Grade B)
For individuals taking any dose of statins, it is reasonable to use caution in individuals >75 years of age, as well as in individuals that are taking concomitant medications that alter drug metabolism, taking multiple drugs, or taking drugs for conditions that require complex medication regimens (e.g., those who have undergone solid organ transplantation or are receiving treatment for HIV). A review of the manufacturer’s prescribing information may be useful before initiating any cholesterol-lowering drug. (Expert opinion-Grade E)

It is reasonable to evaluate and treat muscle symptoms, including pain, tenderness, stiffness, cramping, weakness, or fatigue, in statin-treated patients according to the following management algorithm:

- To avoid unnecessary discontinuation of statins, obtain a history of prior or current muscle symptoms to establish a baseline before initiating statin therapy.
- If unexplained severe muscle symptoms or fatigue develop during statin therapy, promptly discontinue the statin and address the possibility of rhabdomyolysis by evaluating CK, creatinine, and a urinalysis for myoglobinuria.
- If mild to moderate muscle symptoms develop during statin therapy:
  - Discontinue the statin until the symptoms can be evaluated.
  - Evaluate the patient for other conditions that might increase the risk for muscle symptoms (e.g., hypothyroidism, reduced renal or hepatic function, rheumatologic disorders such as polymyalgia rheumatica, steroid myopathy, vitamin D deficiency, or primary muscle diseases.)
  - If muscle symptoms resolve, and if no contraindication exists, give the patient the original or a lower dose of the same statin to establish a causal relationship between the muscle symptoms and statin therapy.
  - If a causal relationship exists, discontinue the original statin. Once muscle symptoms resolve, use a low dose of a different statin.
  - Once a low dose of a statin is tolerated, gradually increase the dose as tolerated.
  - If, after 2 months without statin treatment, muscle symptoms or elevated CK levels do not resolve completely, consider other causes of muscle symptoms listed above.
  - If persistent muscle symptoms are determined to arise from a condition unrelated to statin therapy, or if the predisposing condition has been treated, resume statin therapy at the original dose. (Expert opinion-Grade E)

For individuals presenting with a confusional state or memory impairment while on statin therapy, it may be reasonable to evaluate the patient for nonstatin causes, such as exposure to other drugs, as well as for systemic and neuropsychiatric causes, in addition to the possibility of adverse effects associated with statin drug therapy. (Expert opinion-Grade E)

**Safety of Niacin**

- Baseline hepatic transaminases, fasting blood glucose or hemoglobin A1c, and uric acid should be obtained before initiating niacin, and again during up-titration to a maintenance dose and periodically thereafter. (Moderate Recommendation-Grade B)

- Niacin should not be used if:
  - Hepatic transaminase elevations are higher than 2 to 3 times ULN. (Strong Recommendation-Grade A)
- Persistent severe cutaneous symptoms, persistent hyperglycemia, acute gout or unexplained abdominal pain or gastrointestinal symptoms occur. (Moderate Recommendation-Grade B)
- New-onset atrial fibrillation or weight loss occurs. (Weak Recommendation-Grade C)

- In individuals with adverse effects from niacin, the potential for ASCVD benefits and the potential for adverse effects should be reconsidered before reinitiating niacin therapy. (Expert opinion-Grade E)

- To reduce the frequency and severity of adverse cutaneous symptoms, it is reasonable to:
  - Start niacin at a low dose and titrate to a higher dose over a period of weeks as tolerated.
  - Take niacin with food or premedicating with aspirin 325 mg 30 minutes before niacin dosing to alleviate flushing symptoms.
  - If an extended-release preparation is used, increase the dose of extended-release niacin from 500 mg to a maximum of 2,000 mg/day over 4 to 8 weeks, with the dose of extended release niacin increasing not more than weekly.
  - If immediate-release niacin is chosen, start at a dose of 100 mg 3 times daily and up-titrate to 3 g/day, divided into 2 or 3 doses. (Expert opinion-Grade E)

**Safety of Bile Acid Sequestrants (BAS)**
- BAS should not be used in individuals with baseline fasting triglyceride levels ≥300 mg/dL or type III hyperlipoproteinemia, because severe triglyceride elevations might occur. (A fasting lipid panel should be obtained before BAS is initiated, 3 months after initiation, and every 6 to 12 months thereafter.) (Weak Recommendation-Grade C)
- It is reasonable to use BAS with caution if baseline triglyceride levels are 250 to 299 mg/dL, and evaluate a fasting lipid panel in 4 to 6 weeks after initiation. Discontinue the BAS if triglycerides exceed 400 mg/dL. (Expert opinion-Grade E)

**Safety of Cholesterol-Absorption Inhibitors**
- It is reasonable to obtain baseline hepatic transaminases before initiating ezetimibe. When ezetimibe is coadministered with a statin, monitor transaminase levels as clinically indicated, and discontinue ezetimibe if persistent ALT elevations >3 times ULN occur. (Weak Recommendation-Grade C)

**Safety of Fibrates**
- Gemfibrozil should not be initiated in patients on statin therapy because of an increased risk for muscle symptoms and rhabdomyolysis. (Moderate Recommendation-Grade B)
- Fenofibrate may be considered concomitantly with a low- or moderate-intensity statin only if the benefits from ASCVD risk reduction or triglyceride lowering when triglycerides are >500 mg/dL, are judged to outweigh the potential risk for adverse effects. (Expert opinion-Grade E)
- Renal status should be evaluated before fenofibrate initiation, within 3 months after initiation, and periodically thereafter. Assess renal safety with both a serum creatinine level and an eGFR based on creatinine.
If eGFR is between 30 and 59 mL/min per 1.73 m², the dose of fenofibrate should not exceed 54 mg/day.

Fenofibrate should not be used if moderate or severe renal impairment, defined as eGFR <30 mL/min per 1.73 m², is present.

If, during follow-up, the eGFR decreases persistently to ≤30 mL/min per 1.73 m², fenofibrate should be discontinued. (Moderate Recommendation-Grade B)

**Safety of Omega-3 Fatty Acids**
- If EPA and/or DHA are used for the management of severe hypertriglyceridemia, defined as triglycerides ≥500 mg/dL, it is reasonable to evaluate the patient for gastrointestinal disturbances, skin changes, and bleeding. (Weak Recommendation-Grade C)

**Monitoring Statin Therapy**
- *Adherence to medication and lifestyle, and safety should be regularly assessed. Safety measurements should be measured as clinically indicated. (KP strong recommendation)*

**Optimizing Statin Therapy**
- The maximum tolerated intensity of statin should be used in individuals for whom a high- or moderate-intensity statin is recommended, but not tolerated. (Moderate Recommendation-Grade B)

**Insufficient Response to Statin Therapy**
- In individuals who have a less-than-anticipated therapeutic response or are intolerant of the recommended intensity of statin therapy, the following should be performed:
  - Reinforce medication adherence.
  - Reinforce adherence to intensive lifestyle changes.
  - Exclude secondary causes of hyperlipidemia. (Strong Recommendation-Grade A)

- It is reasonable to use the following as indicators of anticipated therapeutic response to the recommended intensity of statin therapy. Focus is on the intensity of the statin therapy. As an aid to monitoring:
  - High-intensity statin therapy† generally results in an average LDL–C reduction of ≥50% from the untreated baseline;
  - Moderate-intensity statin therapy generally results in an average LDL–C reduction of 30 to <50% from the untreated baseline;
  - LDL–C levels and percent reduction are to be used only to assess response to therapy and adherence. They are not to be used as performance standards. (Expert opinion-Grade E)

- In individuals at higher ASCVD risk receiving the maximum tolerated intensity of statin therapy who continue to have a less than-anticipated therapeutic response, addition of a nonstatin cholesterol-lowering drug(s) may be considered if the ASCVD risk-reduction benefits outweigh the potential for adverse effects. Higher-risk individuals include:
  - Individuals with clinical ASCVD<75 years of age.
  - Individuals with baseline LDL–C ≥190 mg/dL.
  - Individuals 40 to 75 years of age with diabetes mellitus.
Preference should be given to nonstatin cholesterol-lowering drugs shown to reduce ASCVD events in RCTs. (Expert opinion-Grade E)

- In individuals who are candidates for statin treatment but are completely statin intolerant, it is reasonable to use nonstatin cholesterol lowering drugs that have been shown to reduce ASCVD events in RCTs if the ASCVD risk-reduction benefits outweigh the potential for adverse effects. (Expert opinion-Grade E)

**Triglyceride Treatment**
- There is evidence that elevated TG is independently associated with increased risk of atherosclerosis. However, not all people with high TGs are at increased risk, and neither the threshold for initiation of therapy, nor the goal of therapy, is known. Although there is direct evidence that lowering LDL–C reduces the risk of CAD events, there are no clinical trials to demonstrate that reducing TG levels will reduce CAD events. There is expert opinion that a desirable TG level is < 150 mg/dL, but there are no studies to support the benefit of obtaining this level. Treatment decisions should be influenced by a person’s other lipid levels and nonlipid CAD risk factors. Although there is no direct evidence, there is consensus that TG > 500 mg/dL warrants treatment to prevent pancreatitis. **Specific recommendations for treating high TG level are presented in the Triglyceride Algorithm.**

**Risk Assessment**
- The contribution to risk assessment for a first ASCVD event using ApoB, CKD, albuminuria, or cardiorespiratory fitness is uncertain at present. (No Recommendation For or Against-Grade N)

- The Carotid Intima-Media Test (CIMT) is not recommended for routine measurement in clinical practice for risk assessment for a first ASCVD event. (Recommendation Against-Grade D)

- It is reasonable to assess traditional ASCVD risk factors every 4 to 6 years in adults 20 to 79 years of age who are free from ASCVD and to estimate 10-year ASCVD risk every 4 to 6 years in adults 40 to 79 years of age without ASCVD. (Moderate Recommendation-Grade B)

- Assessing 30-year or lifetime ASCVD risk based on traditional risk factors may be considered in adults 20 to 59 years of age without ASCVD and who are not at high short-term risk. (Weak Recommendation-Grade C)
## Appendix A: Strength of Recommendation

<table>
<thead>
<tr>
<th>Grade</th>
<th>Strength of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Strong Recommendation</td>
</tr>
<tr>
<td></td>
<td>There is high certainty based on evidence that the net benefit is substantial.</td>
</tr>
<tr>
<td>B</td>
<td>Moderate Recommendation</td>
</tr>
<tr>
<td></td>
<td>There is moderate certainty based on evidence that the net benefit is moderate to substantial or there is high certainty that the net benefit is moderate.</td>
</tr>
<tr>
<td>C</td>
<td>Weak Recommendation</td>
</tr>
<tr>
<td></td>
<td>There is at least moderate certainty based on evidence that there is a small net benefit.</td>
</tr>
<tr>
<td>D</td>
<td>Recommendation against</td>
</tr>
<tr>
<td></td>
<td>There is at least moderate certainty based on evidence that it has no net benefit or that risks/harms outweigh benefits.</td>
</tr>
<tr>
<td>E</td>
<td>Expert Opinion (&quot;There is insufficient evidence or evidence is unclear or conflicting, but this is what the committee recommends.&quot;)</td>
</tr>
<tr>
<td></td>
<td>Net benefit is unclear. Balance of benefits and harms cannot be determined because of no evidence, insufficient evidence, unclear evidence, or conflicting evidence, but the committee thought it was important to provide clinical guidance and make a recommendation. Further research is recommended in this area.</td>
</tr>
<tr>
<td>N</td>
<td>No Recommendation for or against (&quot;There is insufficient evidence or evidence is unclear or conflicting.&quot;)</td>
</tr>
<tr>
<td></td>
<td>Net benefit is unclear. Balance of benefits and harms cannot be determined because of no evidence, insufficient evidence, unclear evidence, or conflicting evidence, and the committee thought no recommendation should be made. Further research is recommended in this area.</td>
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</tbody>
</table>
NHLBI Grading the Strength of Recommendation

<table>
<thead>
<tr>
<th>Category</th>
<th>Recommendation Strength</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Strong</td>
<td>High certainty based on evidence that net benefit† is substantial.</td>
</tr>
<tr>
<td>B</td>
<td>Moderate</td>
<td>Moderate certainty based on evidence that net benefit is moderate to substantial, or high certainty that net benefit is moderate.</td>
</tr>
<tr>
<td>C</td>
<td>Weak</td>
<td>At least moderate certainty based on evidence of small net benefit.</td>
</tr>
<tr>
<td>E</td>
<td>Expert Opinion</td>
<td>Net benefit is unclear. Balance of benefits and harms cannot be determined because of no evidence, insufficient evidence, unclear evidence, or conflicting evidence, but the Panel thought it was important to provide clinical guidance and make a recommendation. Further research is recommended.</td>
</tr>
<tr>
<td>N</td>
<td>No Recommendation For or Against</td>
<td>Net benefit is unclear. Balance of benefits and harms cannot be determined because of no evidence, insufficient evidence, unclear evidence or conflicting evidence, and the Panel thought no recommendation should be made. Further research is recommended.</td>
</tr>
<tr>
<td>D</td>
<td>Against</td>
<td>At least moderate certainty based on evidence of no net benefit or that risks/harms outweigh benefits.</td>
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</table>

† For comparative effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparators should involve direct comparisons of the treatments or strategies being evaluated.
## Topic: Statins for CVD RR in patients with asymptomatic non-coronary atherosclerosis

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>For patients with asymptomatic non-coronary atherosclerosis, including asymptomatic peripheral arterial disease (PAD), carotid stenosis and aortic atherosclerosis, a statin is an option to reduce the risk of developing symptomatic cardiovascular disease. <em>(weak recommendation)</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Basis of Recommendation</td>
<td>There is insufficient direct evidence to determine the balance of benefits versus harms of statins in this population. However, there is an indirect chain of evidence linking statins to clinical benefit. Epidemiologic studies demonstrate an association between asymptomatic atherosclerosis and risk of CVD. There is good evidence that statins benefit patients with a range of baseline CVD risks, including those at a lower risk for CVD. Therefore, those with asymptomatic atherosclerosis are expected to also benefit from statins. Cost and potential for harms are low, and the underlying values &amp; preferences put more weight on the potential benefits than the potential harms. Ease of implementation was an important consideration.</td>
</tr>
<tr>
<td>Balance of desirable and undesirable effects</td>
<td>Direct evidence on mortality and cardiovascular outcomes is lacking. There is no evidence in patients with asymptomatic PAD, and evidence in patients with asymptomatic carotid stenosis and aortic atherosclerosis primarily focuses on the intermediate outcome of disease progression. However, indirect evidence in people at very low risk for CVD (&lt;5%) shows that statins decrease the risk of total coronary events, total stroke, and revascularization with no increased risk of serious adverse events. Known serious adverse events (myopathy, rhabdomyolitis) are very rare. Uncertainty: High as the impact on mortality and cardiovascular outcomes in target populations is unknown.</td>
</tr>
<tr>
<td>Quality of Evidence</td>
<td>Asymptomatic PAD: No evidence exists Asymptomatic carotid stenosis: moderate quality (imprecision) Asymptomatic aortic atherosclerosis: low quality (risk of bias, indirectness (intermediate outcomes))</td>
</tr>
<tr>
<td>Values and Preferences</td>
<td>The GDT places a high value on the potential reduction in CV events, and a low value on the small risk of SAEs. Uncertainty regarding values and preferences is estimated to be high as values and preferences are derived by polling the GDT. Variability of values and preferences is estimated to be low.</td>
</tr>
<tr>
<td>Resource implications</td>
<td>From an operations perspective, it is much easier to operationalize a recommendation for statins in all patients with atherosclerotic cardiovascular disease, including asymptomatic non-coronary atherosclerosis, than to make one recommendation for those with</td>
</tr>
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</table>
symptomatic cardiovascular disease and no recommendation in those with asymptomatic non-coronary atherosclerosis.

From the perspective of the healthcare delivery system, there is a relatively low cost of therapy and implementation.

Uncertainty: High as net benefits are unknown
**Topic: Statins for CVD RR in patients with Abdominal Aortic Aneurysm (AAA)**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>For patients with abdominal aortic aneurysm (AAA) in the absence of other significant cardiovascular risk factors or without elevated estimated 10-year ASCVD risk, there is insufficient evidence to make a recommendation for or against the use of statins to reduce the risk of cardiovascular disease progression. (KP No Recommendation For or Against)</th>
</tr>
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<tbody>
<tr>
<td>Basis of Recommendation</td>
<td>There is insufficient direct evidence to determine the balance of benefits versus harms of statins in this population.</td>
</tr>
<tr>
<td>Balance of desirable and undesirable effects</td>
<td>Direct evidence on mortality and cardiovascular outcomes is lacking. Known serious adverse events (myopathy, rhabdomyolysis) are very rare. Uncertainty: High as the impact on mortality and cardiovascular outcomes in target populations is unknown.</td>
</tr>
<tr>
<td>Quality of Evidence</td>
<td>Very week (small observational studies without cardiovascular outcomes)</td>
</tr>
<tr>
<td>Values and Preferences</td>
<td>The GDT places a high value on the potential reduction in CV events, and a low value on the small risk of SAEs. Uncertainty regarding values and preferences is estimated to be high as values and preferences are derived by polling the GDT. Variability of values and preferences is estimated to be low.</td>
</tr>
<tr>
<td>Resource implications</td>
<td>Low</td>
</tr>
</tbody>
</table>

Uncertainty: High as net benefits are unknown
<table>
<thead>
<tr>
<th><strong>Topic:</strong> Risk Calculator for estimating 10-year ASCVD Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommendation</strong></td>
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<td><strong>Values and Preferences</strong></td>
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<tr>
<td><strong>Resource implications</strong></td>
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</table>
### Topic: Statin therapy for patients with 10-year ASCVD risk ≥ 7.5%

#### Recommendation

For adults 40 to 75 years of age with LDL–C 70 to 189 mg/dL, without clinical ASCVD or diabetes at elevated risk (e.g. 7.5-14.9% risk by the AHA/ACC Pooled Cohort Equations) treatment with moderate- to high-intensity statin therapy is an option, after a discussion which considers the potential for ASCVD risk reduction benefits and for adverse effects, for drug-drug interactions, and patient preferences for treatment (KP weak recommendation).

#### Basis of Recommendation

Desirable effects probably outweigh undesirable effects for people at 7.5-14.9% risk of ASCVD. However, the balance of desirable and undesirable effects of using cardiovascular risk calculators to select people for lipid-lowering therapy has not been prospectively tested, and the quality of evidence is low. Therefore, statins should be initiated after a discussion with patients taking into consideration patient preferences, and a weak recommendation is warranted.

#### Balance of desirable and undesirable effects

Statins in people without ASCVD or diabetes prevent cardiac events consistently (on a relative risk basis) across the entire spectrum of ASCVD risk. Absolute risk reduction is higher at higher baseline risk. Although a small risk of adverse events would also exist with the use of statins (eg, incident diabetes, significant myopathy), the benefits would probably outweigh the risk, at 7.5-14.9% risk (eg. by the AHA/ACC Pooled Cohort Equations).

#### Quality of Evidence

Low quality (Indirect evidence); AHA/ACC: Stone et al., 2013

#### Values and Preferences

This recommendation places a high value on preventing ASCVD events and a lower value on the small risk of harms. Values and preferences were derived by polling the GDT. Uncertainty around and variability of values and preferences are estimated to be high.

#### Resource implications

Low
<table>
<thead>
<tr>
<th><strong>Topic: Statin therapy for patients with 10-year ASCVD risk ≥ 15%</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommendation</strong></td>
</tr>
<tr>
<td><strong>Basis of Recommendation</strong></td>
</tr>
<tr>
<td><strong>Balance of desirable and undesirable effects</strong></td>
</tr>
<tr>
<td><strong>Quality of Evidence</strong></td>
</tr>
<tr>
<td><strong>Values and Preferences</strong></td>
</tr>
<tr>
<td><strong>Resource implications</strong></td>
</tr>
</tbody>
</table>
## Topic: Additional factors for primary prevention to determine statin risk group

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Use of additional factors (baseline LDL-C &gt;=160 or other evidence of genetic hyperlipidemias, family history of premature ASCVD with onset &lt;55 years in a first degree male relative, or &lt;65 in a first degree female relative, or lifetime risk of ASCVD, testing for hsCRP, ABI, or CAC), is an option for individuals who are not otherwise identified in a statin benefit group, or those for whom a risk-based treatment decision is uncertain after quantitative risk assessment. Testing should only be ordered if the result will prompt a therapeutic decision and the clinician and patient have agreed to initiate statin therapy if the result is abnormal, and to forgo statin therapy if the result is normal. Testing should be discussed in shared decision-making, taking into consideration the significant differences in convenience, cost, invasiveness, and radiation exposure (weak recommendation).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basis of Recommendation</td>
<td>If treatment decisions cannot be reached using other criteria, additional factors may help guide decisions. However, since the balance of desirable and undesirable effects cannot be determined, and values &amp; preferences likely vary regarding both statin therapy and the risks of additional testing, only a weak recommendation is warranted.</td>
</tr>
<tr>
<td>Balance of desirable and undesirable effects</td>
<td>The incremental utility of using additional factors over quantitative risk assessment is unclear. If testing is done to guide treatment decisions, the benefit may outweigh the risks of radiation exposure, cost, invasiveness and inconvenience of testing.</td>
</tr>
<tr>
<td>Quality of Evidence</td>
<td>Low quality; AHA/ACC: Stone et al., 2013</td>
</tr>
<tr>
<td>Values and Preferences</td>
<td>This recommendation places a high value on preventing ASCVD events and a lower value on the small risk of harms (from both statin therapy and additional testing). Values and preferences were derived by polling the GDT. Uncertainty around and variability of values and preferences are estimated to be high, regarding statin therapy among patients in whom a risk-based treatment decision is unclear. Uncertainty and variability are also estimated to be high around invasive tests and radiation exposure.</td>
</tr>
<tr>
<td>Resource implications</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Topic: Assessment of medication adherence</strong></td>
<td></td>
</tr>
<tr>
<td>---------------------------------------------</td>
<td></td>
</tr>
<tr>
<td><strong>Recommendation</strong></td>
<td>Adherence to medication and lifestyle, and safety should be regularly assessed. Safety measurements should be measured as clinically indicated. (KP strong recommendation)</td>
</tr>
<tr>
<td><strong>Basis of Recommendation</strong></td>
<td>Although there is no direct evidence of benefit, no significant harms are expected from assessing adherence or evaluating for potential harms, when clinically indicated. The potential benefits, resource implications, and values and preferences support a strong recommendation.</td>
</tr>
<tr>
<td><strong>Balance of desirable and undesirable effects</strong></td>
<td>There is no direct evidence that regular assessment of adherence to medication and lifestyle results in reduction of CVD events. However, interventions cannot be expected to have any significant impact if they are not adhered to. Regular monitoring of LDL-C, could be used to assess adherence, however, other adherence measures are equally plausible, given the lack of specific goals for LDL-C. Similarly, there is no direct evidence of benefit for evaluation for potential adverse effects, especially when clinically indicated. But no specific harms are anticipated from either intervention, and the potential benefit is large and thus likely to outweigh any harms.</td>
</tr>
<tr>
<td><strong>Quality of Evidence</strong></td>
<td>Very low quality (indirect evidence)</td>
</tr>
<tr>
<td><strong>Values and Preferences</strong></td>
<td>This recommendation places a high value on preventing ASCVD events and avoiding serious adverse effects from statins. Values and preferences were derived by polling the GDT. Uncertainty around and variability of values and preferences are estimated to be low.</td>
</tr>
<tr>
<td><strong>Resource implications</strong></td>
<td>Low</td>
</tr>
</tbody>
</table>