2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults

Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation, American Pharmacists Association, American Society for Preventive Cardiology, Association of Black Cardiologists, Preventive Cardiovascular Nurses Association, and WomenHeart: The National Coalition for Women with Heart Disease

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Citation

This slide set is adapted from the 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults. E-Published on November 12, 2013, available at:


http://circ.ahajournals.org/lookup/doi/10.1161/01.cir.0000437738.63853.7a

The full-text guidelines are also available on the following Web sites: ACC (www.cardiosource.org) and AHA (my.americanheart.org)
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Key Points

• Encourage adherence to a heart-healthy lifestyle.
• Statin therapy is recommended for adults in groups demonstrated to benefit.
• Statins have an acceptable margin of safety when used in properly selected individuals and appropriately monitored.
• Engage in a clinician-patient discussion before initiating statin therapy, especially for primary prevention.
Key Points (cont.)

• Use the newly developed Pooled Cohort Equations for estimating 10-year ASCVD risk.
• Initiate the appropriate intensity of statin therapy to reduce ASCVD risk.
• Evidence is inadequate to support treatment to specific LDL-C or non-HDL-C treatment goals.
• Regularly monitor patients for adherence to lifestyle and appropriate intensity of statin therapy.
• Nonstatin drug therapy may be considered in selected individuals.
Conflict of Interest/Relationships With Industry

• Panel members disclosed conflict of interest information to the full panel in advance of the deliberations
• Members with conflicts recused themselves from voting on any aspect of the guideline where a conflict might exist
• All 16 members of the NHLBI ATP IV Panel transitioned to the ACC/AHA guideline Expert Panel
• Independent contractors performed the systematic review with the assistance of the Expert Panel and provided methodological guidance to the Expert Panel
NHLBI Charge to the Expert Panel

Evaluate higher quality randomized controlled trial (RCT) evidence for cholesterol-lowering drug therapy to reduce ASCVD risk

• Use Critical Questions (CQs) to create the evidence search from which the guideline is developed
  • Cholesterol Panel: 3 CQs
  • Risk Assessment Work Group: 2 CQs
  • Lifestyle Management Work Group: 3 CQs

• RCTs and systematic reviews/meta-analyses of RCTs independently assessed as fair-to-good quality

• Develop recommendations based on RCT evidence

• Less expert opinion than in prior guidelines
Systematic Review Process

• Expert Panel constructed CQs relevant to clinical practice
• Expert Panel identified (a priori) inclusion/exclusion (I/E) criteria for published clinical trial reports for each CQ
• Independent contractor developed a literature search strategy, based on I/E criteria, for published clinical trial reports for each CQ
• Independent contractor executed a systematic electronic search of the published literature from relevant bibliographic databases for each CQ
• The date for the overall literature search was from January 1, 1995 through December 1, 2009
• However, RCTs with the ASCVD outcomes of MI, stroke, and cardiovascular death published after that date were eligible for consideration until July 2013
### Classification of Recommendations and Levels of Evidence

#### SIZE OF TREATMENT EFFECT

<table>
<thead>
<tr>
<th>CLASS</th>
<th>Benefit</th>
<th>Risk</th>
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<tbody>
<tr>
<td>CLASS I</td>
<td>Benefit $$&gt;&gt;$$ Risk</td>
<td>Procedure/Treatment SHOULD be performed/administered</td>
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<tr>
<td>CLASS IIa</td>
<td>Benefit $$&gt;$$ Risk</td>
<td>Additional studies with focused objectives needed</td>
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<tr>
<td>CLASS IIb</td>
<td>Benefit $$\geq$$ Risk</td>
<td>Additional studies with broad objectives needed; additional registry data would be helpful</td>
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<tr>
<td>CLASS III</td>
<td>No Benefit</td>
<td>Procedure/Test</td>
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<table>
<thead>
<tr>
<th>LEVEL</th>
<th>Data derived from multiple randomized clinical trials or meta-analyses</th>
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<tr>
<td>A</td>
<td>Multiple populations evaluated*</td>
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<tr>
<td></td>
<td>Recommendation that procedure or treatment is useful/effective</td>
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<td></td>
<td>Sufficient evidence from multiple randomized trials or meta-analyses</td>
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<thead>
<tr>
<th>LEVEL</th>
<th>Data derived from a single randomized trial or nonrandomized studies</th>
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<tbody>
<tr>
<td>B</td>
<td>Limited populations evaluated*</td>
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<tr>
<td></td>
<td>Recommendation that procedure or treatment is useful/effective</td>
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<td>Evidence from single randomized trial or nonrandomized studies</td>
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<th>LEVEL</th>
<th>Very limited populations evaluated*</th>
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<tr>
<td>C</td>
<td>Only expert opinion, case studies, or standard of care</td>
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<tr>
<td></td>
<td>Recommendation that procedure or treatment is useful/effective</td>
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<tr>
<td></td>
<td>Only diverging expert opinion, case studies, or standard of care</td>
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### Estimate of Certainty (Precision) of Treatment Effect

- **Suggested phrases for writing recommendations**
  - Should be **recommended**
  - Is **indicated**
  - Is **useful/effective/beneficial**
  - Is **reasonably expected to be useful/effective/beneficial**
  - May/might be **considered useful/effective/beneficial**
  - Is **probably recommended or indicated**

- **Comparative effectiveness phrases**
  - Treatment A is **recommended**/indicated in preference to treatment B
  - Treatment A is **probably recommended**/indicated in preference to treatment B
  - Treatment A should be chosen over treatment B

### Levels of Evidence

- **Level I:** Evidence derived from multiple randomized clinical trials or meta-analyses
- **Level II:** Limited populations evaluated
- **Level III:** Very limited populations evaluated

### Comparative Effective

- **Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations:**
  - Age, sex, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use.

- **Comparative effectiveness recommendations (Class I and IIa; Level of Evidence A and B only):**
  - Studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Although randomized trials are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

*For comparative effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.
### NHLBI Grading the Strength of Recommendation

<table>
<thead>
<tr>
<th>Grade</th>
<th>Strength of Recommendation</th>
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<tbody>
<tr>
<td>A</td>
<td><strong>Strong recommendation:</strong> There is high certainty based on evidence that the net benefit is substantial.</td>
</tr>
<tr>
<td>B</td>
<td><strong>Moderate recommendation:</strong> 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><strong>Weak recommendation:</strong> There is at least moderate certainty based on evidence that there is a small net benefit.</td>
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<tr>
<td>D</td>
<td><strong>Recommendation against:</strong> There is at least moderate certainty based on evidence that it has no net benefit or that risks/harms outweigh benefits.</td>
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<tr>
<td>E</td>
<td><strong>Expert opinion</strong> (&quot;There is insufficient evidence or evidence is unclear or conflicting, but this is what the Panel recommends.&quot;)&lt;br&gt;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 in this area.</td>
</tr>
<tr>
<td>N</td>
<td><strong>No recommendation for or against</strong> (&quot;There is insufficient evidence or evidence is unclear or conflicting.&quot;) 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 in this area.</td>
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### NHLBI Quality Rating the Strength of Evidence

<table>
<thead>
<tr>
<th>Quality Rating</th>
<th>Type of Evidence</th>
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| **High**       | • Well-designed, well-executed RCTs that adequately represent populations to which the results are applied and directly assess effects on health outcomes.  
                 • Met-analyses of such studies.  
                 Highly certain about the estimate of effect. Further research is unlikely to change the Panel’s confidence in the estimate of effect. |
| **Moderate**   | • RCTs with minor limitations affecting confidence in, or applicability of, the results.  
                 • Well-designed, well-executed nonrandomized controlled studies § and well-designed, well-executed observational studies.  
                 • Meta-analyses of such studies.  
                 Moderately certain about the estimate of effect. Further research may have an impact on the Panel’s confidence in the estimate of effect and may change the estimate. |
| **Low**        | • RCTs with major limitations.  
                 • Nonrandomized controlled studies and observational studies with major limitations affecting confidence in, or applicability of, the results.  
                 • Uncontrolled clinical observations without an appropriate comparison group (e.g., case series, case reports).  
                 • Physiological studies in humans.  
                 • Meta-analyses of such studies.  
                 Low certainty about the estimate of effect. Further research is likely to have an impact on the Panel’s confidence in the estimate of effect and is likely to change the estimate. |
Guideline Scope

• Focus on treatment of blood cholesterol to reduce ASCVD risk in adults
• Emphasize adherence to a heart healthy lifestyle as foundation of ASCVD risk reduction
  • See Lifestyle Management Guideline
• Identify individuals most likely to benefit from cholesterol-lowering therapy
  • 4 statin benefit groups
• Identify safety issues
4 Statin Benefit Groups

- Clinical ASCVD*
- LDL-C ≥190 mg/dL, Age ≥21 years
- Primary prevention – Diabetes: Age 40-75 years, LDL-C 70-189 mg/dL
- Primary prevention - No Diabetes†: ≥7.5%‡ 10-year ASCVD risk, Age 40-75 years, LDL-C 70-189 mg/dL

*Atherosclerotic cardiovascular disease
†Requires risk discussion between clinician and patient before statin initiation
‡Statin therapy may be considered if risk decision is uncertain after use of ASCVD risk calculator
Vignettes

What is the optimal intensity of statin therapy for a:

- 63 yo man with STEMI?
- 26 yo woman with elevated LDL-C of 260 mg/dL, noted in teens + family history CHD?
- 44 yo woman with diabetes, well-controlled hypertension and micro-albuminuria
56 yo African-American woman with multiple ASCVD risk factors.

- What is her risk of stroke as well as heart attack?
- What risk calculator uses African-American status as an input?
- Does her risk factor burden indicate ASCVD risk that would benefit from statin therapy?
- What are her personal characteristics that would inform the decision regarding safe statin use?
- What is her informed preference?
38 yo Caucasian man with strong family history of premature coronary artery disease and LDL-C despite diet in the 160-180 mg/dL range. Otherwise normal risk profile.

- What is his lifetime risk of ASCVD?
- Does he have factors that the guidelines recommend can be considered if a risk decision is not certain?
- Does his risk factor burden indicate ASCVD risk that would benefit from statin therapy?
- What are his personal characteristics that would inform the decision regarding safe statin use?
- What is his informed preference?
New Perspective on LDL-C & Non–HDL-C

• Lack of RCT evidence to support titration of drug therapy to specific LDL-C and/or non–HDL-C goals
• Strong evidence that appropriate intensity of statin therapy should be used to reduce ASCVD risk in those most likely to benefit
• Quantitative comparison of statin benefits with statin risk
• Nonstatin therapies – did not provide ASCVD risk reduction benefits or safety profiles comparable to statin therapy
Why Not Continue to Treat to Target?

Major difficulties:

• Current RCT data do not indicate what the target should be
• Unknown magnitude of additional ASCVD risk reduction with one target compared to another
• Unknown rate of additional adverse effects from multidrug therapy used to achieve a specific goal
• Therefore, unknown net benefit from treat-to-target approach
Summary of Statin Initiation Recommendations to Reduce ASCVD Risk (Revised Figure)

Heart-healthy lifestyle habits are the foundation of ASCVD prevention
(See 2013 AHA/ACC Lifestyle Management Guideline)

- **Age ≥21 y and a candidate for statin therapy**
  - Yes: Clinical ASCVD
  - No: LDL-C ≥190 mg/dL

**Definitions of High- and Moderate-Intensity Statin Therapy**
(See Table 5)
- **High** Daily dose lowers LDL-C by approx. ≥50%
- **Moderate** Daily dose lowers LDL-C by approx. 30% to <50%

- **LDL-C ≥190 mg/dL**
  - Yes: High-intensity statin (Moderate-intensity statin if not candidate for high-intensity statin)
  - No: Diabetes

**Diabetes**
LDL-C 70-189 mg/dL
Age 40-75 y
- Yes: Estimated 10-y ASCVD risk ≥7.5%†
  - High-intensity statin
- No: Moderate-intensity statin

*High-intensity statin (Moderate-intensity statin if not candidate for high-intensity statin)

†Estimated 10-y ASCVD risk ≥7.5%

Flowchart:
- Age ≤75 y
  - Yes: High-intensity statin
  - No: Moderate-intensity statin
- Age >75 y OR if not candidate for high-intensity statin
  - Moderate-intensity statin

Regularly monitor adherence to lifestyle and drug therapy with lipid and safety assessments
(See Fig 5)
Summary of Statin Initiation Recommendations to Reduce ASCVD Risk (Revised Figure)

DM age <40 or >75 y or LDL-C <70 mg/dL

Primary prevention
(No diabetes, LDL-C 70 to 189 mg/dL, and not receiving statin therapy)
Estimate 10-y ASCVD risk every 4-6 y using Pooled Cohort Equations†

<5% 10-y ASCVD risk‡

Age <40 or >75 y and LDL-C <190 mg/dL‡

≥7.5% 10-y ASCVD risk (Moderate- or high-intensity statin)

5% to <7.5% 10-y ASCVD risk (Moderate-intensity statin)

In selected individuals, additional factors may be considered to inform treatment decision making§

Clinician-Patient Discussion
Prior to initiating statin therapy, discuss:
1. Potential for ASCVD risk-reduction benefits ||
2. Potential for adverse effects and drug–drug interactions¶
3. Heart-healthy lifestyle
4. Management of other risk factors
5. Patient preferences
6. If decision is unclear, consider primary LDL-C ≥160 mg/dL, family history of premature ASCVD, lifetime ASCVD risk, abnormal CAC score or ABI, or hs-CRP ≥2 mg/L§

Emphasize adherence to lifestyle
Manage other risk factors
Monitor adherence

No to statin

Yes to statin

Encourage adherence to lifestyle
Initiate statin at appropriate intensity
Manage other risk factors
Monitor adherence† (See Fig 5)
Intensity of Statin Therapy

Table 5. High- Moderate- and Low-Intensity Statin Therapy (Used in the RCTs reviewed by the Expert Panel)*

<table>
<thead>
<tr>
<th>High-Intensity Statin Therapy</th>
<th>Moderate-Intensity Statin Therapy</th>
<th>Low-Intensity Statin Therapy</th>
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<tbody>
<tr>
<td>Daily dose lowers LDL–C on average, by approximately ≥50%</td>
<td>Daily dose lowers LDL–C on average, by approximately 30% to &lt;50%</td>
<td>Daily dose lowers LDL–C on average, by &lt;30%</td>
</tr>
<tr>
<td>Atorvastatin (40†)–80 mg</td>
<td>Atorvastatin 10 (20) mg</td>
<td>Simvastatin 10 mg</td>
</tr>
<tr>
<td>Rosuvastatin 20 (40) mg</td>
<td>Rosuvastatin (5) 10 mg</td>
<td>Pravastatin 10–20 mg</td>
</tr>
<tr>
<td></td>
<td>Simvastatin 20–40 mg‡</td>
<td>Lovastatin 20 mg</td>
</tr>
<tr>
<td></td>
<td>Pravastatin 40 (80) mg</td>
<td>Fluvastatin 20–40 mg</td>
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<tr>
<td></td>
<td>Lovastatin 40 mg</td>
<td>Pitavastatin 1 mg</td>
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<td>Fluvastatin XL 80 mg</td>
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<tr>
<td></td>
<td>Fluvastatin 40 mg bid</td>
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<td></td>
<td>Pitavastatin 2–4 mg</td>
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*Individual responses to statin therapy varied in the RCTs and should be expected to vary in clinical practice. There might be a biologic basis for a less-than-average response.
†Evidence from 1 RCT only: down-titration if unable to tolerate atorvastatin 80 mg in IDEAL (Pedersen et al).
‡Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg is not recommended by the FDA due to the increased risk of myopathy, including rhabdomyolysis.
Clinical ASCVD: Initiating Statin Therapy

Clinical ASCVD
Not currently on statin therapy
Initial evaluation prior to statin initiation
- Fasting lipid panel*
- ALT
- CK (if indicated)
- Consider evaluation for other secondary causes (Table 6) or conditions that may influence statin safety (Table 8, Rec 1).

Evaluate and Treat Laboratory Abnormalities
1. Triglycerides ≥500 mg/dL
2. LDL-C ≥190 mg/dL
   - Secondary causes (Table 6)
   - If primary, screen family for FH
3. Unexplained ALT ≥3 times ULN

*Fasting lipid panel preferred. In a nonfasting individual, a nonfasting non-HDL-C ≥220 mg/dL may indicate genetic hypercholesterolemia that requires further evaluation or a secondary etiology. If nonfasting triglycerides are ≥500 mg/dL, a fasting lipid panel is required.
†It is reasonable to evaluate the potential for ASCVD benefits and for adverse effects, and to consider patient preferences, in initiating or continuing a moderate- or high-intensity statin, in individuals with ASCVD >75 years of age.

Age ≤75 y without contraindications, conditions or drug–drug interactions influencing statin safety, or a history of statin intolerance
- Initiate high-intensity statin therapy
  - Counsel on healthy-lifestyle habits

Age >75 y† OR with conditions or drug–drug interactions influencing statin safety, or a history of statin intolerance
- Initiate moderate-intensity statin therapy
  - Counsel on healthy-lifestyle habits

Monitor statin therapy (Figure 5)
Primary Prevention Global Risk Assessment

• To estimate 10-year ASCVD* risk
  • New Pooled Cohort Risk Equations
  • White and black men and women
• More accurately identifies higher risk individuals for statin therapy
  • Focuses statin therapy on those most likely to benefit
  • You may wish to avoid initiating statin therapy in high-risk groups found not to benefit (higher grades of heart failure and hemodialysis)

*10-year ASVD: Risk of first nonfatal myocardial infarction, coronary heart disease death, nonfatal or fatal stroke
Primary Prevention Statin Therapy

• Thresholds for initiating statin therapy derived from 3 exclusively primary prevention RCTs

• Before initiating statin therapy, clinicians and patients engage in a discussion of the potential for ASCVD risk reduction benefits, potential for adverse effects, drug-drug interactions, and patient preferences
Individuals Not in a Statin Benefit Group

• In those for whom a risk decision is uncertain, these factors may inform clinical decision making:
  • Family history of premature ASCVD
  • Elevated lifetime risk of ASCVD
  • LDL-C ≥160 mg/dL
  • hs-CRP ≥2.0 mg/L
  • CAC score ≥300 Agaston units
  • ABI <0.9

• Statin use still requires discussion between clinician and patient
Statin Therapy: Monitoring Response-Adherence

*Fasting lipid panel preferred. In a nonfasting individual, a nonfasting non–HDL-C ≥220 mg/dL may indicate genetic hypercholesterolemia that requires further evaluation or a secondary etiology. If nonfasting triglycerides are ≥500 mg/dL, a fasting lipid panel is required.

†In those already on a statin, in whom baseline LDL-C is unknown, an LDL-C <100 mg/dL was observed in most individuals receiving high-intensity statin therapy in RCTs.
Monitoring Response-Adherence (cont.)

Anticipated therapeutic response?

- No
  - Reinforce improved adherence
    - Increase statin intensity‡
    - OR Consider addition of nonstatin drug therapy
  - Follow-up 4-12 wk & thereafter as indicated

Intolerance to recommended dose of statin therapy?

- Yes
  - Management of statin intolerance (Table 8, Rec 8)
- No
  - Reinforce medication adherence
    - Reinforce adherence to intensive lifestyle changes
    - Exclude secondary causes of hypercholesterolemia (Table 6)
  - Follow-up 4-12 wk

‡See guideline text
Safety

• RCTs & meta-analyses of RCTs used to identify important safety considerations
• Allow estimation of net benefit from statin therapy
  • ASCVD risk reduction versus adverse effects
• Expert guidance on management of statin-associated adverse effects, including muscle symptoms
• Advise use of additional information including pharmacists, manufacturers prescribing information, & drug information centers for complex cases
Management of Muscle Symptoms on Statin Therapy

• It is reasonable to evaluate and treat muscle symptoms including pain, cramping, weakness, or fatigue in statin-treated patients according to the 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
Management of Muscle Symptoms on Statin Therapy (cont.)

If unexplained severe muscle symptoms or fatigue develop during statin therapy:

• Promptly discontinue the statin
• Address possibility of rhabdomyolysis with:
  • CK
  • Creatinine
  • Urinalysis for myoglobinuria
Management of Muscle Symptoms on Statin Therapy (cont.)

If mild-to-moderate muscle symptoms develop during statin therapy:

• Discontinue the statin until the symptoms are evaluated
• Evaluate the patient for other conditions* that might increase the risk for muscle symptoms
• If after 2 months without statin Rx, muscle symptoms or elevated CK levels do not resolve completely, consider other causes of muscle symptoms

*Hypothyroidism, reduced renal or hepatic function, rheumatologic disorders such as polymyalgia rheumatica, steroid myopathy, vitamin D deficiency or primary muscle diseases
Statin-Treated Individuals
Nonstatin Therapy Considerations

• Use the maximum tolerated intensity of statin
• Consider addition of a nonstatin cholesterol-lowering drug(s)
  • If a less-than-anticipated therapeutic response persists
• Only if ASCVD risk-reduction benefits outweigh the potential for adverse effects in higher-risk persons:
  • *Clinical* ASCVD <75 years of age
  • Baseline LDL-C ≥190 mg/dL
  • Diabetes mellitus 40 to 75 years of age
• Nonstatin cholesterol-lowering drugs shown to reduce ASCVD events in RCTs are preferred
Lessons From the Vignettes

None of these need ASCVD risk calculation:

• **Case 1:** ASCVD ≤75 years of age
  • Evidence supports high-intensity statin therapy for optimal risk reduction in those who tolerate it
  • Moderate intensity may be initiated or continued if >75 yo
  • Also, if high-intensity Rx not safe or not tolerated

• **Case 2:** LDL-C ≥190 mg/dL; 2 causes ruled out
  • Evidence supports high-intensity statin therapy
  • LDL-C levels may still remain very high, even after the intensity of statin therapy has been achieved; addition of a nonstatin drug may be considered to further lower LDL-C
Lessons From the Vignettes

None of these need ASCVD risk calculation:

• **Case 1**: ASCVD ≤75 years of age
  • High-intensity statin therapy
    • For optimal risk reduction in those who tolerate it
  • Moderate-intensity statin therapy
    • If >75 yo may be initiated or continued
    • Also use if high-intensity Rx not safe or not tolerated
Lessons From the Vignettes

None of these need ASCVD risk calculation:

• **Case 2:** LDL-C ≥190 mg/dL with secondary causes ruled out:
  
  • High-intensity statin therapy for optimal risk reduction in those who can tolerate it
  
  • If LDL-C levels remain very high after the intensity of statin therapy has been achieved, addition of a nonstatin drug may be considered to lower LDL-C further
Lessons From the Vignettes

ASCVD risk calculation useful here:

- **Case 3**: Diabetes, 40-75 yo, LDL-C 70-189 mg/dL
  - Evidence supports moderate-intensity statin Rx to be initiated or continued
  - High-intensity statin Rx reasonable if estimated 10-year ASCVD risk calculated to be >7.5%
Lessons From the Vignettes

ASCVD risk calculation useful here:

- **Case 4**: Primary prevention 40-75 yo; LDL-C 70-189 mg/dL; not low risk for ASCVD
  - Use Pooled Cohort Equations (risk calculator) to est.10-y ASCVD risk for African American & white individuals
  - Clinician-patient discussion before statin Rx initiated
  - Moderate- or high-intensity statin when ≥7.5% 10-y ASCVD risk
  - Moderate-intensity statin therapy reasonable when ≥5% 10-y ASCVD risk or when other characteristics that increase ASCVD risk are present
Lessons From the Vignettes: Primary Prevention

• **Case 5:** LDL-C <190 mg/dL
  • Not otherwise identified in a statin benefit group
  OR
  • After quantitative risk assessment, a risk-based treatment decision is uncertain

• Additional factors that increase risk may be considered. In our case, can use LDL $\geq 160$ mg/dL and family history of premature ASCVD as factors to inform the decision about statin Rx.
Lessons From the Vignettes

• Case 5 (cont.)
  • In these individuals, statin therapy for primary prevention may be considered after evaluating the potential for ASCVD risk reduction benefits, adverse effects, drug-drug interactions, and discussion of patient preferences.
  • Example of where guidelines inform clinical judgment, but do not replace it.
Three Principles

• Do not focus on LDL-C or non–HDL-C levels as treatment goals
  • Although continue to obtain a lipid panel to monitor adherence
• Use medications proven to reduce ASCVD risk
• Risk decisions in primary prevention require a clinician-patient discussion to evaluate the benefits and harms for the individual patient
  • Optimal lifestyle emphasized
  • Clinician-patient discussion needed for appropriate shared decision-making
Future Updates to the Blood Cholesterol Guideline

• This is a comprehensive guideline for the evidence-based treatment of blood cholesterol to reduce ASCVD risk
• These guidelines represent a change from previous guidelines that aligns recommendations closely to the evidence
• For primary prevention, they are “patient-centered”
• Guidelines will change in the future as high-quality data will improve future cholesterol treatment guidelines
Specific Recommendations

The following slides are the full sentence ACC/AHA recommendations. See guideline text for further explanation.
The panel makes no recommendations for or against specific LDL-C or non–HDL-C targets for the primary or secondary prevention of ASCVD.
Secondary Prevention: Statin Treatment

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.

In individuals with *clinical ASCVD*[^1] in whom high-intensity statin therapy would otherwise be used, when high-intensity statin therapy is contraindicated[^2] or when characteristics predisposing to statin-associated adverse effects are present, moderate-intensity statin should be used as the second option if tolerated (Table 8 for Safety of Statins, Rec 1).

*[^1]*Clinical ASCVD includes acute coronary syndromes, history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, TIA, or peripheral arterial disease presumed to be of atherosclerotic origin.

†[^2]Contraindications, warnings, and precautions are defined for each statin according to the manufacturer’s prescribing information.
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.
Primary Prevention: ≥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 (Table 6).‡

‡Individuals with secondary causes of hyperlipidemia were excluded from RCTs reviewed. Triglycerides ≥500 mg/dL were an exclusion criteria for almost all RCTs. Therefore, ruling out secondary causes is necessary to avoid inappropriate statin therapy.
Primary Prevention: ≥21 Years of Age With LDL-C ≥190 mg/dL (cont.)

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): §

- Use high-intensity statin therapy unless contraindicated.
- For individuals unable to tolerate high-intensity statin therapy, use the maximum tolerated statin intensity

§ No RCTs included only individuals with LDL-C ≥190 mg/dL. However, many trials did include individuals with LDL-C ≥190 mg/dL and all of these trials consistently demonstrated a reduction in ASCVD events. In addition, the CTT meta-analyses of statin trials have shown that each 39 mg/dL reduction in LDL-C reduced CVD events by 22%.
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.

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.
Primary Prevention: 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.

High-intensity statin therapy is reasonable for adults 40 to 75 years of age with diabetes with a ≥7.5% estimated 10-year ASCVD risk unless contraindicated.

∥Estimated 10-year or “hard” ASCVD risk includes first occurrence of nonfatal MI, CHD death, and nonfatal and fatal stroke as used by the Risk Assessment Work Group in developing the Pooled Cohort Equations.
In adults with diabetes, who are <40 or >75 years of age or with LDL-C <70mg/dL, 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.
Primary Prevention: Without Diabetes Mellitus and With LDL-C 70 to 189 mg/dL

The Pooled Cohort Equations should be used 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.

Adults 40 to 75 years of age with LDL-C 70 to 189 mg/dL, without clinical ASCVD* or diabetes and an estimated 10-year ASCVD∥ risk ≥7.5% should be treated with moderate- to high-intensity statin therapy.
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 with an estimated 10-year ASCVD risk of 5% to <7.5%.

Before initiation of statin therapy for the primary prevention of ASCVD in adults with LDL-C 70-189 mg/dL without clinical ASCVD* or diabetes it is reasonable for clinicians and patients to engage in a discussion which considers the potential for ASCVD risk reduction benefits and for adverse effects, for drug-drug interactions, and patient preferences for treatment.
Primary Prevention: Without Diabetes Mellitus and With LDL-C 70 to 189 mg/dL

In adults with LDL-C <190 mg/dL who are not otherwise identified in a statin benefit group, or for whom after quantitative risk assessment a risk-based treatment decision is uncertain, additional factors¶ may be considered to inform treatment decision making. In these individuals, statin therapy for primary prevention may be considered after evaluation of the potential for ASCVD risk reduction benefits, adverse effects, drug-drug interactions, and discussion of patient preferences.

¶ These factors may include primary LDL-C ≥160 mg/dL or other evidence of genetic hyperlipidemias, family history of premature ASCVD with onset <55 years in a first-degree male relative or <65 years in a first-degree female relative, hs-CRP ≥2 mg/L, CAC score ≥ 300 Agatston units or ≥75th percentile for age, sex, and ethnicity (for additional information, see http://www.mesa-nhlbi.org/CACReference.aspx), ABI <0.9, or lifetime risk of ASCVD. Additional factors that may aid in individual risk assessment may be identified in the future.
Statin Treatment: 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.
Statin 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

(recommendation cont. below)
Statin Safety (cont.)

(recommendation cont.)

- History of previous statin intolerance or muscle disorders
- Unexplained ALT elevations ≥3 times ULN
- Patient characteristics or concomitant use of drugs affecting statin metabolism
- Age >75 years

Additional characteristics that could modify the decision to use higher statin intensities might include, but are not limited to:

- History of hemorrhagic stroke
- Asian ancestry
Statin Safety (cont.)

I IIA IIB III 

CK should not be routinely measured in individuals receiving statin therapy.

I IIA IIB III 

Baseline measurement of CK is reasonable for individuals believed to be at increased risk for adverse muscle events because of a personal or family history of statin intolerance or muscle disease, clinical presentation, or concomitant drug therapy that might increase the risk of myopathy.
Statin Safety (cont.)

During statin therapy, it is reasonable to measure CK in individuals with muscle symptoms, including pain, tenderness, stiffness, cramping, weakness, or generalized fatigue.

Baseline measurement of hepatic transaminase levels (ALT) should be performed before initiation of statin therapy.
Statin Safety (cont.)

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).

Decreasing the statin dose may be considered when 2 consecutive values of LDL-C levels are <40 mg/dL.

It may be harmful to initiate simvastatin at 80 mg daily or increase the dose of simvastatin to 80 mg daily.
Statin Safety (cont.)

Individuals receiving statin therapy should be evaluated for new-onset diabetes according to the current diabetes screening guidelines. Those who develop diabetes 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.*

*Statins use is associated with a very modest excess risk of new onset diabetes in RCTs and meta-analyses of RCTs (i.e., ~0.1 excess cases per 100 individuals treated 1 year with moderate-intensity statin therapy and ~0.3 excess cases per 100 individuals treated for 1 year with high-intensity statin therapy. The increased risk of new onset diabetes appears to be confined to those with risk factors for diabetes. These individuals are also at higher risk of ASCVD due to these risk factors. Therefore, if a statin-treated individual develops diabetes as detected by current diabetes screening guidelines, they should be counseled 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 the risk of ASCVD events.
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 initiation of any cholesterol-lowering drug.
Statin Safety (cont.)

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 initiation of 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 performing a urinalysis for myoglobinuria.

• If mild to moderate muscle symptoms develop during statin therapy:
  • Discontinue the statin until the symptoms can be evaluated. (recommendation cont. below)
Statin Safety (cont.)

(recommendation cont.)

- 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.
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.
Nonstatin Safety: Niacin

Baseline hepatic transaminases, fasting blood glucose or hemoglobin A1c, and uric acid should be obtained before initiation of niacin, and again during up-titration to a maintenance dose and every 6 months thereafter.

Niacin should not be used if:

- Hepatic transaminase elevations are higher than 2 to 3 times ULN.
- Persistent severe cutaneous symptoms, persistent hyperglycemia, acute gout or unexplained abdominal pain or gastrointestinal symptoms occur.
- New-onset atrial fibrillation or weight loss occurs.
In individuals with adverse effects from niacin, the potential for ASCVD benefits and the potential for adverse effects should be reconsidered before reinitiation of niacin therapy.
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 premedicate 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.
Nonstatin Safety: BAS

I  IIa  IIb  III

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.)

Harm

I  IIa  IIb  III

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.
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.
Nonstatin Safety: Fibrates

Gemfibrozil should not be initiated in patients on statin therapy because of an increased risk for muscle symptoms and rhabdomyolysis.

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 $\geq 500$ mg/dL, are judged to outweigh the potential risk for adverse effects.
Renal status should be evaluated before fenofibrate initiation, within 3 months after initiation, and every 6 months thereafter. Assess renal safety with both a serum creatinine level and an eGFR based on creatinine.
Nonstatin Safety: Fibrates (cont.)

- Fenofibrate should not be used if moderate or severe renal impairment, defined as eGFR <30 mL/min per 1.73 m², is present.
- If eGFR is between 30 and 59 mL/min per 1.73 m², the dose of fenofibrate should not exceed 54 mg/day*.
- If, during follow-up, the eGFR decreases persistently to ≤30 mL/min per 1.73 m², fenofibrate should be discontinued.

*Consult the manufacturer's prescribing information as there are several forms of fenofibrate available.
Nonstatin Safety: 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.
Adherence to medication and lifestyle, therapeutic response to statin therapy, and safety should be regularly assessed. This should also include a fasting lipid panel performed within 4 to 12 weeks after initiation or dose adjustment, and every 3 to 12 months thereafter. Other safety measurements should be measured as clinically indicated.
The maximum tolerated intensity of statin should be used in individuals for whom a high- or moderate-intensity statin is recommended, but not tolerated.*

* Several RCTs found that low and low-moderate intensity statin therapy reduced ASCVD events. In addition, the CTT meta-analyses of statin trials have shown that each 39 mg/dL reduction in LDL-C reduced CVD events by 22%. Therefore, the Panel considered that submaximal statin therapy should be used to reduce ASCVD risk in those unable to tolerate moderate- or high-intensity 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.
Insufficient Response to Statin Therapy (cont.)

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; (recommendation cont. below)

†In those already on a statin, in whom baseline LDL-C is unknown, an LDL-C <100 mg/dL was observed in most individuals receiving high intensity statin therapy.
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.
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.

(recommendation cont. below)
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

Preference should be given to nonstatin cholesterol-lowering drugs shown to reduce ASCVD events in RCTs.

‡ Clinical ASCVD includes acute coronary syndromes, or a history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, TIA, or peripheral arterial disease presumed to be of the atherosclerotic origin.
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.