2017 Focused Update of the 2016 ACC Expert Consensus Decision Pathway on the Role of Non-statin Therapies for LDL-C Lowering in the Management of ASCVD Risk

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Lipoprotein goals of therapy...

2013 ACC/AHA Blood Cholesterol Guideline

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

- Adults age >21 y and a candidate for statin therapy
  - Clinical ASCVD
    - LDL-C ≥190 mg/dL
      - High-intensity statin
        - Age ≤75 y
          - High-intensity statin (Moderate-intensity statin if not candidate for high-intensity statin)
        - Age >75 y or if not candidate for high-intensity statin
          - Moderate-intensity statin
      - LDL-C ≥190 mg/dL
      - Diabetes Type 1 or 2
        - Age 40-75 y
          - Estimated 10-y ASCVD risk ≥7.5%
            - High-intensity statin

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%

<table>
<thead>
<tr>
<th>High-intensity statin therapy</th>
<th>Moderate-intensity statin therapy</th>
<th>Low-intensity statin therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin 40*-80* mg</td>
<td>Rosuvastatin 20*-40** mg</td>
<td>Simvastatin 10** mg</td>
</tr>
<tr>
<td>Atorvastatin 10* (20**) mg</td>
<td>Rosuvastatin (5**) 10* mg</td>
<td>Pravastatin 10*-20* mg</td>
</tr>
<tr>
<td>Simvastatin 20*-40* mg</td>
<td>Simvastatin 20* (80**) mg</td>
<td>Lovastatin 20* mg</td>
</tr>
<tr>
<td>Pravastatin 40* (80**) mg</td>
<td>Lovastatin 40* mg</td>
<td>Fluvastatin 20*-40** mg</td>
</tr>
<tr>
<td>Fluvastatin XL 80** mg</td>
<td>Fluvastatin 40 mg BID*</td>
<td>Pitavastatin 1** mg</td>
</tr>
<tr>
<td>Pitavastatin 2-4** mg</td>
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</table>

J Am Coll Cardiol. 2014;63:2889-2934
2013 ACC/AHA Cholesterol Guidelines
Recommendations on Use of Non-Statins

- Clinicians treating high risk patients who have a
  - Less than anticipated response to statins
  - Unable to tolerate a less than recommended intensity of a statin
  - Completely statin intolerant

- When to add non-statin therapy?
- As we await updated guidelines, expert consensus is needed on the use of non-statin agents.
2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk

A Report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents

Endorsed by the National Lipid Association

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2016 Expert Consensus Decision Pathway: Rationale

• Provide more specific guidance on the adequacy of statin therapy and whether or when to use non-statin therapies if response to statins is deemed inadequate or less than anticipated

• Extend beyond 2013 evidence base to incorporate recent trial data and address current gaps in care for LDL-C lowering to reduce ASCVD risk

• Consider use of drugs FDA-approved after publication of 2013 guideline (alirocumab, evolocumab)
2016 Expert Consensus Decision Pathway: Questions Addressed

1. In what patient populations should non-statin therapies be considered?

2. In what situations should non-statin therapies be considered?
   - When is the amount of LDL-C lowering less than anticipated, less than desired, or inadequate, and which treatment options should be considered in patients who are truly statin intolerant?

3. If non-statin therapies are to be added, which agents or therapies should be considered and in what order?
2016 Expert Consensus Decision Pathway: Assessing Response to Therapy

• Thresholds for consideration of net benefit
  – Maximally-tolerated statin therapy
  – **Percent** LDL-C reduction: Achieve ≥50% LDL-C reduction on high-intensity statin, or ≥30% to <50% reduction for moderate-intensity statin
  – May consider **absolute** LDL-C levels (or non-HDL-C in patients with DM) as factors
    • **WG emphasizes that these are not firm triggers** (not “goals”) for adding medication but factors that may be considered within the broader context of an individual patient’s clinical situation
2016 Expert Consensus Decision Pathway: Patient Populations Addressed

**Patient Populations Addressed: 4 Statin Benefit Groups**

- **Adults ≥21 years of age with clinical ASCVD, on statin for secondary prevention**
- **Adults ≥21 years of age with LDL-C ≥190 mg/dL (not due to secondary modifiable causes), on statin for primary prevention**
- **Adults aged 40-75 years without ASCVD but with diabetes and LDL-C 70-189 mg/dL, on statin for primary prevention**
- **Adults aged 40-75 years without clinical ASCVD or diabetes, with LDL-C 70-189 mg/dL and an estimated 10-year risk for ASCVD of ≥7.5%, on statin for primary prevention**
Patient group addressed

Threshold for considering additional action

Clinical actions to consider to achieve desired response

Factors to consider in clinician-patient discussion re: use of non-statin therapies

Non-statin therapies to consider in order

Continued monitoring for adherence and response
2017 Focused Update

• Since the publication of 2016 ECDP, additional evidence and perspectives emerged from RCTs and other sources
  – Longer-term efficacy and safety of PCSK9 inhibitors in secondary prevention of ASCVD and final results of CVOTs in patients with clinical ASCVD and a smaller number of high-risk primary prevention patients
    • FOURIER
    • SPIRE-1 and -2
  – Further evidence on types of patients most likely to benefit from the use of ezetimibe in addition to statin therapy after ACS.
2017 Focused Update

• ECDP writing committee judged that it would be desirable to provide a focused update to help guide clinicians more clearly on decision making regarding the use of ezetimibe and PCSK9 inhibitors in patients with
  – Clinical ASCVD with or without comorbidities

• New data did not warrant changes to algorithms regarding the use of ezetimibe or PCSK9 inhibitors in primary prevention patients with LDL-C <190 mg/dL with or without diabetes mellitus or patients without ASCVD and LDL-C ≥190 mg/dL not due to secondary causes.
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2017 Focused Update

Includes consideration of FOURIER, SPIRE-1 and -2, and recent post-hoc analysis of IMPROVE-IT
## 2017 Focused Update

<table>
<thead>
<tr>
<th>Figures 2A, 2B, and 4</th>
<th>2016 ECDP</th>
<th>2017 ECDP Focused Update</th>
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<tbody>
<tr>
<td><strong>ECDP Algorithms</strong></td>
<td>Thresholds for consideration of net ASCVD risk reduction benefit were percent reduction in LDL-C and may consider absolute LDL-C level in patients with clinical ASCVD, baseline LDL-C ≥190 mg/dL, and primary prevention. In patients with diabetes with or without clinical ASCVD, it was stated that the clinician may consider absolute LDL-C and/or non-HDL-C levels.</td>
<td>Thresholds for consideration of net ASCVD risk reduction are percent reduction in LDL-C and may consider absolute LDL-C or non-HDL-C levels for patients in each of the 4 statin benefit groups.</td>
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**Comment/Rationale:** The FOURIER trial of evolocumab included patients with clinical ASCVD with or without diabetes on statin dose equivalent of at least atorvastatin 20 mg who had either LDL-C ≥70 mg/dL or non-HDL-C ≥100 mg/dL (2). The ongoing ODYSSEY Outcomes trial of alirocumab includes patients with non-HDL-C ≥100 mg/dL (4). The SPIRE-2 trial of bococizumab included high-risk primary prevention patients (18.9%) and patients with familial hypercholesterolemia (7.0%) with LDL-C ≥100 mg/dL or non-HDL-C ≥130 mg/dL (5). In alignment with these inclusion criteria, the 2017 Focused Update includes both LDL-C and non-HDL-C thresholds for evaluation of net ASCVD risk reduction benefit when considering the addition of non-statin therapies for patients in each of the 4 statin benefit groups.

Includes both LDL-C and non-HDL-C thresholds for consideration of net ASCVD risk reduction in each of the 4 statin benefit groups
Thresholds in patients with clinical ASCVD with and without comorbidities are LDL-C <70 mg/dL or non-HDL-C <100 mg/dL.
Considerations that may favor the initial choice of ezetimibe include: patients who require <25% additional lowering of LDL-C, patients with recent ACS <3 months, cost considerations with recent availability of generic ezetimibe and future cost savings, ease of use as oral agent with low pill burden, patient preferences, heart failure, hypertension, age >75 years, diabetes, stroke, CABG, PAD, eGFR <60 mL/min/1.73 m², and smoking.

If patients with clinical ASCVD and comorbidities require >25% additional lowering of LDL-C, a PCSK9 inhibitor may be preferred as the initial non-statin agent. The clinician-patient discussion should consider the extent of available scientific evidence for net ASCVD risk reduction benefit, cost, administration by subcutaneous injection, every 14-day or monthly dosing schedule, and storage requirements (refrigeration).
2017 Focused Update

The 2017 Focused Update also includes the following factors that may be considered for the identification of higher-risk patients with clinical ASCVD: age ≥65 years, prior MI or non-hemorrhagic stroke, current daily cigarette smoking, symptomatic PAD with prior MI or stroke, history of non-MI related coronary revascularization, residual coronary artery disease with ≥40% stenosis in ≥2 large vessels, HDL-C <40 mg/dL for men and <50 mg/dL for women, hs-CRP >2 mg/L, or metabolic syndrome (7).
2017 Focused Update: ASCVD without Comorbidities

FIGURE 2A Patients ≥21 Years of Age with Stable Clinical ASCVD without Comorbidities, on Statin for Secondary Prevention

Patients with stable clinical ASCVD without comorbidities,* on statin for secondary prevention

Patient has ≥50% LDL-C reduction (may consider LDL-C <70 mg/dL or non-HDL-C <100 mg/dL) on maximally tolerated statin therapy†

YES

1. Address statin adherence.
2. Intensify lifestyle (may consider phytosterols).
3. Increase to high-intensity statin if not already taking.
4. Evaluate for statin intolerance if unable to tolerate moderate-intensity statin.† Consider referral to lipid specialist if statin intolerant.
5. Control other risk factors.

NO

Patient has ≥50% LDL-C reduction (may consider LDL-C <70 mg/dL or non-HDL-C <100 mg/dL) on maximally tolerated statin therapy†

CLINICIAN-PATIENT DISCUSSION FACTORS TO CONSIDER
1. Potential for additional ASCVD risk reduction from addition of non-statin therapy to lower LDL-C (see Table 5)
2. Potential for adverse events or drug-drug interactions from addition of non-statin therapy (see Table 4)
3. Patient preferences (see Table 5)

YES

 Decision for no additional medication

NO

Optional non-statin medications to consider

Consider ezetimibe first§

YES

Consider adding or replacing with PCSK9 inhibitor second¶

Patient has ≥50% LDL-C reduction (may consider LDL-C <70 mg/dL or non-HDL-C <100 mg/dL) on maximally tolerated statin/other medications†

YES

Continue to monitor adherence to medications and lifestyle, and LDL-C response to therapy.

http://dx.doi.org/10.1016/j.jacc.2017.07.745
2017 Focused Update: ASCVD without Comorbidities
2017 Focused Update: ASCVD and Baseline LDL-C $\geq$ 190 mg/dL
2017 Focused Update

- New data *did not* warrant changes to algorithms regarding the use of ezetimibe or PCSK9 inhibitors in
  - primary prevention patients with LDL-C <190 mg/dL with or without diabetes mellitus
  - or
  - patients without ASCVD and LDL-C ≥190 mg/dL not due to secondary causes.
2017 Focused Update: Summary

• Includes consideration of FOURIER, SPIRE-1 and -2, and recent post-hoc analysis of IMPROVE-IT

• Includes both LDL-C and non-HDL-C thresholds for consideration of net ASCVD risk reduction in each of the 4 statin benefit groups

• Thresholds in patients with clinical ASCVD with and without comorbidities are LDL-C <70 mg/dL or non-HDL-C <100 mg/dL.
2017 Focused Update: Summary

- Includes factors to consider when selecting initial non-statin therapies in patients (ezetimibe vs. PCSK9 inhibitor)

- For patients with clinical ASCVD and comorbidities, ECDP identifies additional comorbidities based on FOURIER inclusion criteria
2017 Focused Update: Summary

• Consistent with 2013 ACC/AHA cholesterol guideline, ECDP notes that “Clinicians should preferentially prescribe drugs that have been shown in RCTs to provide ASCVD risk-reduction benefits that outweigh the potential for adverse effects and drug–drug interactions, and consider patient preferences.
Thank you!

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