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

Endorsed by the National Lipid Association

Carl E. Orringer, MD, FNLA, FACC
Associate Professor of Medicine
University of Miami Miller School of Medicine
Disclosures

• None
ACC Expert Consensus Decision Pathways -1

• Provide clinical policy based on expert opinion in areas in which important clinical decisions are not adequately addressed by existing trials.

• Complement the guidelines and bridge the gaps in clinical guidance that remain.
• Provide algorithms that are actionable and can be implemented as tools or apps at point of care.
• Encourage clinicians to consider important factors as they reach a decision on a treatment plan together with patients.
• Facilitate shared decision-making.
1. Statin treatment should be based on ASCVD risk and potential for net benefit. Strong evidence for net benefit is present in the 4 statin benefit groups.

2. Statins are first-line therapy for ASCVD risk reduction.
   - Use recommended or maximally tolerated statin intensity
   - May consider non-statins in selected individuals; non-statins proven to reduce ASCVD events in RCTs are preferred

3. Lipid monitoring is necessary to assess adherence and response to lifestyle and drug therapy.

4. For primary prevention of ASCVD, clinician-patient discussion is necessary to appropriately guide the decision to initiate statin therapy.
ACC/AHA Statin Benefit Groups

H=High-intensity statin; M=Moderate-intensity statin

• Clinical ASCVD (H preferred; M if age >75 or if not candidate for H).
• Primary elevations of LDL-C ≥190 mg/dL (H preferred; M if not candidate for H).
• Age 40-75 years with diabetes, and LDL-C 70-189 mg/dL, no clinical ASCVD (M if 10-year risk <7.5%; H if ≥7.5%).
• Age 40-75 years, no clinical ASCVD or diabetes, LDL-C 70-189 mg/dL, and estimated 10-year ASCVD risk ≥7.5% using Pooled Cohort Risk Equations (M or H).
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, who are unable to tolerate a less than recommended intensity of a statin or who are completely statin intolerant, may consider the addition of non-statin cholesterol lowering therapy…”

• “In this situation, this guideline recommends that clinicians preferentially prescribe drugs in which ASCVD risk-reduction benefits outweigh the potential for adverse effects and drug-drug interactions and consider patient preferences.”
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Background

• 2013: ACC launches “LDL: Address the Risk”
  – Multi-stakeholder quality initiative to improve patient outcomes

• 9/2015: “LDL: Address the Risk Think Tank”
  – Invited expert clinicians, and representatives from health systems, health plans, pharmacy benefit managers, drug manufacturers, and EHR vendors
  – Identified need for expert consensus guidance regarding incorporation of non-statin therapies into treatment strategies for higher-risk patients
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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

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

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

2) In what situations should non-statin therapies be considered, i.e., 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 Process

- Writing Group convened 10/2015
- Operated by consensus
- Document and care algorithms drafted 1/2016
- Formal peer review process led by ACC
  - Expert reviewers and public comment period
  - 342 specific comments addressed in detail
- Endorsed by the NLA BOD 3/2016
- Reviewed and approved by ACC Board of Trustees 3/2016
- Published in JACC 4/1/2016
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Assumptions and Definitions -1

• Writing Group (WG) endorsed recommendations of evidence-based 2013 ACC/AHA guidelines

• Statins remain first-line agents for LDL-C reduction to reduce ASCVD risk

• Principle of “net ASCVD risk-reduction benefit”
  – Potential benefits of additional non-statin therapy should outweigh any potential for harm
Thresholds for consideration of net benefit

- Maximally-tolerated statin therapy
- Achievement of \( \geq 50\% \) 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 in treatment decisions ("LDL-C or non-HDL-C treatment thresholds")

WG emphasizes that these are not firm triggers for adding medication but factors that may be considered within the broader context of an individual patient’s clinical situation
• Other important factors to consider in shared decision-making
  – Available scientific evidence for safety and tolerability
  – Potential for drug-drug interactions
  – Efficacy of additional LDL-C lowering
  – Cost
  – Convenience and medication storage
  – Pill burden
  – Route of administration
  – Potential to jeopardize adherence to evidence-based therapies
  – Patient preferences
WG endorsed use of fasting lipid-panel and Friedewald calculation of LDL-C as per 2013 guidelines
  - As done in almost all RCTs
  - Widely available, lower cost
  - Acknowledged limitations in accuracy, esp. at lower LDL-C levels
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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

- Sub-populations of these groups
- Special populations
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Non-Statin Therapies Considered

- Ezetimibe
- Bile-acid sequestrants (BAS)
  - Alirocumab, evolocumab
- PCSK9 inhibitors
- Mipomersen
- Lomitapide
- LDL apheresis
- Niacin NOT routinely recommended

For selected pts with FH under care of a lipid specialist
Clinical Approaches to Achieving Adequate Response to Lifestyle/Statin

• Adherence to statin and to heart healthy diet, regular exercise habits, avoidance of tobacco products, and maintenance of a healthy weight
  – 2013 ACC/AHA Lifestyle Guidelines and 2014 NLA Recommendations
  – May consider referral to RDN

• May consider phytosterols and soluble fiber

• Evaluate for statin intolerance

• Control other RFs
Addressing Potential Statin Intolerance

• ACC Statin Intolerance App
  – http://www.acc.org/StatinIntoleranceApp
• NLA 2014 Statin Intolerance Panel
• Careful history of myalgia patterns
• Consideration of secondary causes
• Wash-out and rechallenge
  – Consider changing drug, dose, alternative dosing
1. Patient with Stable Clinical ASCVD without Comorbidities

- Treat with maximal tolerated statin
- Achieve at least $\geq 50\%$ LDL-C reduction
- If this reduction is not achieved, initiate patient clinician discussion and consider non-statins: LDL-C treatment threshold $\geq 100 \text{ mg/dL}$
- Try ezetimibe first; consider BAS if TG $< 300 \text{ mg/dL}$
- PCSK9 inhibitor next
- If treatment objective achieved, follow lipids
- If not, reassess medication adherence and lifestyle
2. Clinical ASCVD with Co-morbidities:
DM, Recent acute ASCVD event, ASCVD event on statin, Baseline LDL-C ≥190 mg/dL, Uncontrolled risk factors, Elevated Lp(a), CKD

- Treat with maximal tolerated statin
- Achieve at least ≥50% LDL-C reduction
- If this reduction is not achieved, initiate patient clinician discussion and consider non statins if LDL-C ≥70 mg/dL, or non-HDL-C ≥ 100 if diabetic
- Ezeimibe first
- PCSK9 inhibitor next
- If treatment objective achieved, follow lipids
- If not, reassess medication adherence and lifestyle
- Mipomersen, lomitapide and/or LDL apheresis in appropriate patients
3. Patient without Clinical ASCVD and Baseline LDL-C ≥ 190 mg/dL

- Treat with maximal tolerated statin
- Strong recommendation for referral to lipid specialist
- Achieve at least ≥50% LDL-C reduction
- If this reduction is not achieved, initiate patient clinician discussion and consider non-statins if LDL-C ≥ 100 mg/dL
- Try ezetimibe first; consider BAS if TG < 300 mg/dL
- PCSK9 inhibitor next
- If treatment objective achieved, follow lipids
- If not, reassess medication adherence and lifestyle
- Consider mipomersen, lomitapide and/or LDL apheresis in appropriate patients
4. Patients 40-75 yo without Clinical ASCVD and with DM (10 yr. ASCVD risk <7.5%)

- Treat with moderate- or high-intensity statin
- Achieve expected % LDL-C or non-HDL-C reduction → follow serial lipids
- If expected % reduction not achieved, or if LDL-C ≥ 100 mg/dL or non-HDL-C ≥ 130 mg/dL, if at moderate intensity, consider increase to high-intensity statin and monitor adherence
- Additional therapy not recommended
5. Patients 40-75 y.o. without Clinical ASCVD and with DM (10 yr. ASCVD risk $\geq 7.5\%$)

- Start with moderate- or high-intensity statin
- Increase to high-intensity statin if need to achieve expected LDL-C or non-HDL-C % reduction
- May consider non-statins for LDL-C $\geq 100$ mg/dL or non-HDL-C $\geq 130$ mg/dL
  - Ezetimibe or BAS (if TG <300 mg/dL)
  - PCSK9 inhibitors not currently indicated
- Monitor adherence
6. Patients 40-75 yo without Clinical ASCVD and with 10-year ASCVD Risk ≥7.5%

- Consider high-risk markers
- After patient-clinician discussion, start moderate- or high-intensity statin
- Assess for % LDL-C reduction achieved
- If % reduction inadequate, increase to high-intensity
- If achieve expected % LDL-C reduction, follow
- May consider non-statins for LDL-C ≥100 mg/dL
  - Ezetimibe or BAS (if TG <300 mg/dL) in higher risk patients
  - PCSK9 inhibitors not indicated
7. Patients 40-75 yo without Clinical ASCVD and with 10-year ASCVD Risk $\geq 7.5\%$

- High risk markers
  - Pooled Cohort Equation 10-year risk $\geq 20\%$
  - LDL-C $\geq 160$ mg/dL
  - Uncontrolled major ASCVD risk factors
  - Family history of premature ASCVD
  - Elevated Lp(a)
  - Accelerated subclinical ASCVD
  - Elevated hs-CRP
  - CKD
  - HIV or other inflammatory disorders
• Pts with symptomatic HF
  – Generally excluded from statin RCTs
  – Major competing risks of death
  – Meta-analysis of CORONA and GISSI-HF reveals statin benefit for MI reduction in pts with ischemic etiology of HF

• Recommendations
  – In pts with NYHA class II-III HF, care should follow algorithm for ASCVD with comorbidities
  – Consider expected longevity
8. Treatment for Patients with NYHA Class 2-3 Heart Failure

• Treat with maximally tolerated statin
• If achieve % LDL-C reduction ≥ 50% continue to monitor adherence
• For those with LDL-C ≥ 70 mg/dL or diabetics with non-HDL-C ≥ 100 mg/dL:
  – Ezetimibe first
  – If inadequate response, PCSK9 inhibitor
• Monitor adherence
9. Treatment of Hemodialysis Patients

- Pts on maintenance hemodialysis
  - Generally excluded from statin RCTs
  - No benefit in SHARP and AURORA trials
  - Major competing risks of death

- Recommendations
  - Individualize care
  - May consider addition of non-statins after moderate or high intensity statin
  - PCSK9 inhibitors not indicated
10. Treatment of Dyslipidemia in Women in Childbearing Age

• Pts considering pregnancy
  – Statins should be used for premenopausal women generally only if ASCVD, FH or high risk, and on contraception
  – Discontinue lipid-lowering drugs immediately if pregnant; >1 and preferably 3 months prior to attempting conception
  – Lifestyle and monitor LDL-C during pregnancy
  – Consider referral to lipid specialist for FH
  – May consider BAS (monitor for vitamin K deficiency)
  – May resume statin/ezetimibe after completion of breast-feeding
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Take-Home Points

• Follow evidence-based guidelines for use of lipid-lowering therapies to reduce ASCVD risk
• Engage in shared decision-making to consider potential benefits and harms of non-statin therapies
• Consider specific non-statin therapies only in higher-risk pts who have inadequate response to statin or statin intolerance
• Individualize care for other patient groups
## Expert Consensus Panel RWI

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<th>Expert Witness</th>
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<tr>
<td><strong>Donald M. Lloyd-Jones (Chair)</strong></td>
<td>Northwestern University</td>
<td>None</td>
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<td><strong>Pamela Bowe Morris (Vice Chair)</strong></td>
<td>Medical University of South Carolina</td>
<td>Amgen, AstraZeneca, Sanofi Regeneron</td>
<td>None</td>
<td>Amgen</td>
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<tr>
<td><strong>Christie M. Ballantyne</strong></td>
<td>Baylor College of Medicine and Methodist Debakey Heart &amp; Vascular Center</td>
<td>Abbott Diagnostic, AstraZeneca, Eli Lilly, Esperion, Genzyme, Matinas BioPharma, Merck, Novartis, Pfizer, Regeneron, Roche Diagnostic, Sanofi-Synthethelabo</td>
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<td><strong>Kim K. Birtcher</strong></td>
<td>University of Houston</td>
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<tr>
<td><strong>David D. Daly Jr</strong></td>
<td>Medical University of South Carolina</td>
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<td><strong>Sondra M. DePalma</strong></td>
<td>Penn State Health Milton S. Hershey Medical Center</td>
<td>None</td>
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<tr>
<td><strong>Margo B. Minissian</strong></td>
<td>Cedars-Sinai Heart Institute</td>
<td>Sanofi-Aventis, Regeneron</td>
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<tr>
<td><strong>Carl E. Orringer</strong></td>
<td>University of Miami</td>
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<td><strong>Sidney C. Smith Jr</strong></td>
<td>University of North Carolina</td>
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