Dyslipidemia and Combination Therapy: A Framework for Clinical Decision Making

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COMING TO CONSENSUS IN A NEW ERA: THE ROLE OF NON-STATIN THERAPIES

Introduction: Pamela B. Morris, MD, FACC
2013 Cholesterol Guidelines: Recommendations for Initiating Statin Therapy

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

Diabetes Type 1 or 2
Age 40-75 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

Moderate-intensity statin

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%
2013 Cholesterol Guidelines: Recommendations for Initiating Statin Therapy - 2

Primary prevention
(No diabetes, LDL-C 70-189 mg/dL, and not receiving statin therapy)

Estimate 10-y ASCVD Risk every 4-6 years
Pooled Cohort Equations

DM age <40 or >75 y

<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%-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. 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
3. Potential for adverse effects and drug-drug interactions
4. Healthy lifestyle
5. Management of other risk factors
6. Patient preferences

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)
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 clinicians 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.”
2016 Expert Consensus Decision Pathway

Background

• September 2015: 2\textsuperscript{nd} “LDL: Address the Risk Think Tank”
  – Expert clinicians, patient advocacy groups, health plans, pharmacy benefit managers, drug manufacturers, EHR vendors, and health systems
  – \textbf{Identified need for expert consensus guidance regarding incorporation of non-statin therapies into treatment strategies for higher-risk patients}
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
  – HPS2-THRIVE (niacin/laropiprant)
  – IMPROVE-IT (ezetimibe+simvastatin)

• Consider use of drugs FDA-approved after publication of 2013 guideline (alirocumab, evolocumab)
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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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?
Thresholds for consideration of net benefit

- Maximally-tolerated statin therapy
- **Percent** LDL-C reduction: Achievement of ≥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
Non-Statin Therapies Considered

- Ezetimibe
- Bile-acid sequestrants (BAS)
- PCSK9 inhibitors
  - Alirocumab, evolocumab
- Mipomersen
- Lomitapide
  \{ For selected pts with HoFH under care of a lipid specialist
- LDL apheresis

\}\n- Niacin NOT routinely recommended
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**
Decision Pathway Algorithms

**General**

- **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**
Summary: Patient Populations Addressed

- Ezetimibe first
- PCSK9i may then be added or replace ezetimibe
- LDL-C >190 mg/dl either agent first

- Ezetimibe OR PCSK9i may be considered first

- Ezetimibe may be considered
- PCSK9i not recommended in primary prevention patients with DM

- Ezetimibe may be considered
- PCSK9i are not recommended
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 re-challenge
  – N of 1 trials altering drug, dose, alternative dosing
Addressing Potential Statin Intolerance

The ACC Statin Intolerance App guides clinicians through the process of managing and treating patients who report muscle symptoms while on statin therapy. Clinicians can use the app to:

- Answer questions to evaluate possible intolerance to a patient's current statin prescription.
- Follow steps to manage and treat a patient who reports muscle symptoms on a statin.
- Compare statin characteristics and drug interactions to inform management of LDL-related risk.

“Named one of the best apps for 2015 by iMedicalApps.”

This app is available for free in the iTunes and Google Play app stores. Use the links below to download the app today.

Download the App From iTunes >>>
Download the App From Google Play >>>
Launch the Web Version >>>
Addressing Potential Statin Intolerance

Welcome to ACC’s Statin Intolerance Tool

This tool should be used by clinicians to assess, treat, and manage patients with possible statin intolerance.

Although muscle symptoms may occur, true statin intolerance is uncommon. Given the benefits of statins in ASCVD risk reduction, clinicians should partner with the patient to gain a thorough symptom history and determine if he or she is truly statin intolerant. Walk through the steps of treating and managing a patient who reports muscle symptoms, including cycles of statin discontinuation and rechallenge to identify a tolerated statin and dose.

1. Evaluate
   Evaluate possible intolerance to patient’s current statin prescription.

2. Follow-Up
   Follow steps to treat and manage possible statin-related muscle symptoms.

3. Drug Compare
   Compare statin characteristics and drug interactions to determine the best cholesterol-lowering therapy.

Reset All Data
Addressing Potential Statin Intolerance

Demographics:
Possible predispositions to muscle symptoms
- Sex
- Age
- Race/Ethnicity

Current Statin and Drug Interactions
- Current Statin
- Dose
- Frequency
- Time of Day
- When did the patient start the statin?
  - Month
  - Year
- Has the patient had muscle pain while taking a previous statin?
  - Yes
  - No

Use worksheet to determine interacting medications (e.g., fenofibrate, strong CYP3A4 inhibitors)
- Evaluate
- Skip
Addressing Potential Statin Intolerance

Select any patient risk factors.

**Patient Characteristics**
- Low BMI
- Frailty
- Excessive grapefruit juice consumption (>1.2 liters per day)
- High alcohol consumption

**Drug abuse (cocaine, amphetamine, heroin)**
**Heavy exercise/physical exertion**
**Dehydration or decrease in daily fluid intake**
**Personal or immediate family history of statin intolerance**

**Medical History**
- Unexplained ALT elevations >3 times ULN
- Renal Insufficiency
- Hepatic dysfunction
- Multiple or serious comorbidities

[Done Selecting] [Clear All]
Possible alternate causes of muscle symptoms.

Select all that apply:

**Medical History**
- Multiple or serious comorbidities
- Previous muscle disorder history
- Heavy exercise/Physical exertion
- Trauma
- Seizures
- Electrolytic abnormalities
- Vitamin D deficiency
- Hypothyroidism
- Multi-organ disease
- Post-op state, especially surgery with high metabolic demands

**Medical Conditions**

- Elevated ESR (erythrocyte sedimentation rate)
- Systemic Lupus
- Tendonitis or joint disorder
- Myopathy
- Polymyalgia rheumatica
- Polymyositis
- Rhabdomyolysis
- Steroid myopathy
- Arthritis
- Fibromyalgia
- Diabetic myopathy
- Adrenal insufficiency/Cushing Syndrome
- Addison's disease
- Anemia
- Hyperparathyroidism
- Peripheral arterial disease
- Viral illness

**Additional Disorders**
- Diabetes
- Systemic lupus
- Tendonitis or joint disorder

**Done Selecting**  **Clear All**
Likelihood of Statin-Related Muscle Symptoms with Current Prescription

Statin: Aторвастатин (Lipitor®)
Dose: 10 (20) mg
Frequency: Once daily

<table>
<thead>
<tr>
<th>Value</th>
<th>Result</th>
<th>Statin-Related Muscle Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom timing allows for statin intolerance</td>
<td>Yes</td>
<td>Possible</td>
</tr>
<tr>
<td>Symptom Type</td>
<td>Tingling, Twitching, Shooting Pain, Nocturnal Cramps, Joint Pain</td>
<td>Unlikely</td>
</tr>
<tr>
<td>Symptom Location</td>
<td>Unilateral</td>
<td>Unlikely</td>
</tr>
<tr>
<td>Sex</td>
<td>Female predisposes to statin adverse effects. May need lower dose or alternate statin.</td>
<td>Unlikely</td>
</tr>
<tr>
<td>Age</td>
<td>40-74</td>
<td>Unlikely</td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td>Asian ancestry predisposes to statin adverse effects. May need to lower dose or alternate statin.</td>
<td>Unlikely</td>
</tr>
<tr>
<td>CK Elevated &gt; 5x UCL?</td>
<td>No</td>
<td>Possible</td>
</tr>
<tr>
<td>Risk Factors for Statin Symptoms</td>
<td>None identified / 0</td>
<td>Possible / Unlikely</td>
</tr>
<tr>
<td>Non-Statin Causes</td>
<td>None identified / 0</td>
<td>Possible / Unlikely</td>
</tr>
</tbody>
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Next Steps
1. Consider suspending statins until symptoms resolve.
2. Conduct any labs needed to establish risk factors or secondary causes.
3. Check for rhabdomyolysis by evaluating CK level and creatinine, and performing urinalysis for myoglobinuria. Fever, discolored urine, and/or marked weakness in the patient signal the need for emergency attention.

Click Follow Up tab to see next steps for continuing statin therapy. Click Drug Compare tab for help in selecting a different statin.
Case Presentations
Case Presentation #1
Case Presentation #1: Management of Statin-associated muscle symptoms in ASCVD

• 62 yo male with type 2 diabetes, NSTEMI and PCI to LAD approximately 6 weeks ago presents for monitoring of response to high-intensity statin therapy.
  – His baseline fasting lipid panel demonstrated:
    • TC 248 mg/dL (6.41 mmol/L)
    • HDL-C 45 mg/dL (1.16 mmol/L)
    • LDL-C 168 mg/dL (4.34 mmol/L)
    • TG 175 mg/dL (1.98 mmol/L)
Case Presentation #1: Management of Statin-associated muscle symptoms in ASCVD

- He was discharged on atorvastatin 80 mg but developed intolerable myalgias within 2 weeks.
  - Symptoms described as intolerable symmetric myalgias of upper arms and legs.
  - CK is normal.
  - The dose was reduced to atorvastatin 40 mg daily and symptoms resolved.

- He is tolerating therapy well and has been carefully adherent to medications and lifestyle recommendations.
  - He has lost 15 pounds and walks briskly about 155 minutes per week.
Case Presentation #1:
Management of Statin-associated muscle symptoms in ASCVD

• At follow-up on atorvastatin 40 mg his current results are:
  – TC 190 mg/dL (4.91 mmol/L)
  – HDL-C 40 mg/dL (1.03 mmol/L)
  – LDL-C 120 mg/dL (3.10 mmol/L)
  – TG 148 mg/dL (1.67 mmol/L)
  – LDL-C reduction = 29%
Audience Response System

Which of the following would you pursue as the next step in management?

A. Continue current regimen
B. Re-challenge with atorvastatin 80 mg daily
C. Switch to rosuvastatin 40 mg daily
D. Add ezetimibe 10 mg daily
Discussion

• Has this patient achieved anticipated reduction in atherogenic lipoproteins?

• Is the degree of lowering of atherogenic lipoproteins acceptable?

• Would you consider additional modifications to the patient’s regimen?

• What factors would you consider in the decision to further modify the patient’s medical regimen?
Clinical ASCVD with comorbidities
(DM, recent acute ASCVD event, ASCVD event while on statin, baseline LDL-C $\geq 190$ mg/dl, uncontrolled major RFs, elevated $Lp(a)$, CKD)

Evaluation and management of statin-associated muscle symptoms
Case Presentation #2
Case Presentation #2:
Role of non-statin therapies in primary prevention

- 66 yo female presents with baseline lipid panel:
  - TC 246 mg/dL (6.36 mmol/L)
  - HDL-C 47 mg/dL (1.22 mmol/L)
  - LDL-C 168 mg/dL (4.34 mmol/L)
  - TG 155 mg/dL (1.75 mmol/L)
  - Blood pressure 142/92 mmHg

- 10-year ASCVD risk of 8.8% as calculated by the Pooled Cohort Equations.
Case Presentation #2:
Role of non-statin therapies in primary prevention

• Lifestyle recommendations are discussed in detail and she is prescribed pravastatin 80 mg daily.

• She returns in 12 weeks and reports excellent adherence to lifestyle modification and medication.
  – TC 202 mg/dL (5.22 mmol/L)
  – HDL-C 56 mg/dL (1.45 mmol/L)
  – LDL-C 128 mg/dL (3.31 mmol/L)
  – TG 90 mg/dL (1.02 mmol/L)
  – LDL-C reduction 24%
Audience Response System

Which of the following would you pursue next?
A. Assess statin adherence
B. Switch to atorvastatin 80 mg daily
C. Add ezetimibe 10 mg daily
D. Continue current regimen
Discussion

• Has this patient achieved anticipated reduction in atherogenic lipoproteins?

• Is the degree of lowering of atherogenic lipoproteins acceptable?

• Would you consider additional modifications to the patient’s regimen?

• What factors would you consider in the decision to further modify the patients medical regimen?
Primary prevention in patients with high ASCVD risk
ACC Latin America Conference 2016

MEXICO CITY
OCTOBER 7 - 8, 2016

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