Objectives
- Review 2013 ACC/AHA cholesterol Guidelines
- Analyze the rationale supporting the new guidelines and address areas of confusion
- Consolidate information into a practical approach to clinical management

2013 ACC/AHA Expert Panel
- All 16 members of the National Heart, Lung and Blood Institute Adult Treatment Panel (ATP) IV
- Document review included 23 expert reviewers

Why new guidelines?
- ATP III published in 2002
- Update in 2004
- Multiple new studies since

Clinical Questions
- 1. What is the evidence for LDL-C and non-HDL-C goals in secondary prevention?
- 2. What is the evidence for primary prevention?
- 3. Evaluation of the reduction in ASCVD events and safety of cholesterol lowering drugs in US

Why new guidelines?
- Evaluate higher quality RCT evidence for cholesterol-lowering drug therapy to reduce ASCVD risk
- Use CQs to create the evidence search from which guideline developed
- RCT and systematic reviews/meta-analyses of RCTs assessed as fair to good quality
Goals

- Develop recommendations based on RCT evidence
- Less expert opinion than in prior guidelines
- Lit search 1/95-December 2009
- RCTs with ASCVD outcomes of MI, CVA and CV death eligible 7/09 through 7/13

Systematic Review Process

- RCTs identified in evidence review showed consistent reduction in ASCVD events from statin therapy in primary and secondary prevention, with the exception of no reduction in those with NYHA II-IV or those on HD
- Compared either fixed doses of statins with placebo or untreated controls, or fixed doses of higher intensity statins with moderate intensity
- Not designed to evaluate the effect of titrated statin treatment to achieve prespecified LDL-C or non-HDL-C goals

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
  - May result in undertreatment with statin and overtreatment with nonstatin

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

New Prescription

<table>
<thead>
<tr>
<th>Patient Categories</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>With diagnosed cardiovascular disease and over 21 years old</td>
<td>75 or younger, or over 75</td>
</tr>
<tr>
<td>With an LDL cholesterol level of &lt;190 mg/dL</td>
<td>High-intensity statin</td>
</tr>
<tr>
<td>With age 75 or more or risk of heart attack in the next 10 years</td>
<td>Moderate-intensity statin</td>
</tr>
<tr>
<td>With age 40 to 74 years and diabetes between 40 and 75 years old</td>
<td>High-intensity statin</td>
</tr>
<tr>
<td>With age 40 to 74 years and a 7.5% or more risk of heart attack in the next 10 years</td>
<td>Moderate-intensity statin</td>
</tr>
</tbody>
</table>

*Risk determined by a new calculation that accounts for age, cholesterol, blood pressure, smoking status and other risk factors. See website for more information.
ASCVD Risk Reduction is Goal

<table>
<thead>
<tr>
<th>Then</th>
<th>New</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statin therapy to achieve LDL-C and non-HDL-C targets</td>
<td>Statin therapy for all individuals at increased risk for ASCVD who are likely to benefit from risk reduction</td>
</tr>
</tbody>
</table>

Who Should be on a Statin?

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

Secondary Prevention

- Evidence supports high-intensity statin therapy for this group to maximally lower LDL-C
- It does not support the use of an LDL-C target

ASCVD

- Acute Coronary Syndromes, history of MI or USA, Coronary or other revascularization, stroke, TIA, PAD

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 yr ASCVD Risk of first nonfatal MI, CHD death, nonfatal or fatal stroke

Primary Prevention Statin Therapy

- Thresholds for initiating statin therapy derived from 3 exclusively primary prevention RCTs
- Available RCT evidence indicates a clear net absolute benefit of mod to intensive statin therapy when estimated risk >7.5%
- 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
Pooled Cohort Equation

- Developed by Risk Assessment Work Group
- Designed to include estimate of 10 yr risk of stroke as well as cardiac outcomes
- Considers race and gender
- Includes age and smoking

Controversy

- Pooled cohort would qualify 1 in 3 American adults for statin
- No trial of statin therapy has ever used a global risk prediction score as an enrollment criterion
- High absolute risk doesn’t always predict statin benefit.
  - CORONA and AURORA trials enrolled pts with high vascular risk in settings of heart failure or renal failure and found no evidence of event reduction with statin therapy despite large reductions in LDL cholesterol

Does pooled cohort accurately assess risk?

- Calculated predicted 10 yr risk using new calculator and compared with observed event rates in three large scale primary prevention cohorts
- New ACC/AHA risk prediction algorithm overestimated observed risks by 75 - 150%, roughly doubling the observed risk

Defense of the Pooled Cohort Equation

- Considers the following when estimating risk
  - Gender
  - Age
  - Race
  - Total cholesterol
  - HDL
  - Systolic blood pressure
  - Medical conditions - hypertension, diabetes
  - Smoking status

- Other than age, major determinants of risk are smoking and hypertension
  - Eliminate tobacco and lower blood pressure instead of prescribing statin

- Includes race and gender
- 7.5% 10 yr risk threshold has demonstrated risk reduction in RCTs
- Most events occur after 70, giving those > 70 the greatest potential for absolute risk reduction
- RCTs used represented a healthier population
### Why not use inclusion criteria from RCT to decide who should get statin?
- Less accurately identifies those at increased ASCVD risk than does a strategy based on assessment of global ASCVD risk
- Selective use of RCT inclusion criteria excludes well-established risk factors such as smoking and advancing age (strongest risk factor)
- Poor discrimination of RCT inclusion criteria for identifying increased 10 yr risk shown by Risk Assessment Work Group
  - Overtreated low risk and undertreated high risk

### Pooled Cohort Benefits
- Avoids overtreatment of lower risk groups, such as young, non-Hispanic women who, despite elevation in LDL-C, are typically not at significantly increased ASCVD risk
- Ignoring increased ASCVD risk in African American women and men may result in undertreatment with significantly higher risk at same LDL-C level

### What is the Optimal Statin Dose?

<table>
<thead>
<tr>
<th>Statin Dose</th>
<th>High intensity</th>
<th>Moderate intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily dose</td>
<td>Daily dose lowers LDL-C 30-50%</td>
<td>Daily dose lowers LDL-C 30-50%</td>
</tr>
<tr>
<td>Atorvastatin 40-80 mg</td>
<td>Atorvastatin 10-20 mg</td>
<td>Atorvastatin 10-20 mg</td>
</tr>
<tr>
<td>Rosuvastatin 20-40 mg</td>
<td>Rosuvastatin 5-10 mg</td>
<td>Rosuvastatin 5-10 mg</td>
</tr>
<tr>
<td>Simvastatin 20-40 mg</td>
<td>Simvastatin 20-40 mg</td>
<td>Simvastatin 20-40 mg</td>
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<tr>
<td>Pravastatin 40 mg</td>
<td>Pravastatin 40 mg</td>
<td>Pravastatin 40 mg</td>
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<tr>
<td>Lovastatin 40 mg</td>
<td>Lovastatin 40 mg</td>
<td>Lovastatin 40 mg</td>
</tr>
<tr>
<td>Fluvastatin 40 BID</td>
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</tr>
</tbody>
</table>

### Statin Dosing
- Consider dose decrease when 2 consecutive LDL-C < 40 mg/dL
- May be harmful to start or increase simvastatin 80 mg
- Evaluate for new onset DM
- Use caution at any dose
  - > 75 yrs
  - Those on other drugs that alter metabolism

### Monitoring
- Lipid measurements at baseline, 1-3 m after statin initiation, and yearly thereafter
- Assess for expected decreased of LDL levels
  - 30-45% with moderate intensity statin
  - > 50% with high intensity statin
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
- 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

- 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

Management of Muscle Symptoms on Statin Therapy

- 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

Non-Statin Therapy
Guidance on Nonstatin therapies

- Reinforce adherence to lifestyle and statin therapy before adding non-statin drugs
- Consider addition of nonstatin drug only in high-risk patients with
  - Insufficient response to statin therapy
  - Intolerance to less than recommended intensity statin
  - Intolerance to any statin

Guidance on nonstatin therapy

- AIM-HIGH showed no additional ASVCD benefit when non statin added to further treat non-HDL cholesterol when LDL was at goal.
- Niacin reduced levels of ApoB, Lp(a), and triglycerides in addition to raising HDL-C, but DID NOT further reduce ASCVD events in those with LDL 40-80 mg/dL

Guidance on nonstatin therapy

- "As of yet, there are no data to show that adding a nonstatin drug to high-intensity statin therapy will provide incremental ASCVD risk reduction benefits with an acceptable margin of safety"

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

Fibrates

- Do not use gemfibrozil with statin
- Fenofibrate with low or mod intensity statin only if ASCVD risk reduction benefits or TG lowering when TG>500
- Evaluate renal status before fenofibrate initiation, within 3 months and every 6 months thereafter
  - Don’t use if GFR < 30
  - If GFR 30-59, don’t exceed 54 mg/d

Niacin

- Baseline hepatic transaminases, fasting blood glucose or Hgb A1c, and uric acid levels checked prior to initiation
- Don’t start if LFT 2-3 times ULN
- Persistent hyperglycemia, acute gout, or significant GI or cutaneous symptoms
Omega-3 Fatty Acids

- If EPA/DHA used for severe hypertriglyceridemia, reasonable to look for GI disturbance and bleeding

Special Populations

Heart Failure and Hemodialysis

- No recommendation was made regarding the initiation or continuation of statin therapy in 2 groups
  - NYHA Class II-IV heart failure
  - Maintenance hemodialysis

Heart Failure and Hemodialysis

- 4 RCT reviewed which addressed statin treatment in these groups
  - Included those with and without heart disease
  - Statin therapy did not reduce ASCVD events in 2 of the trials
  - Insufficient information
    - Risk-benefit analysis, drug-drug interaction, adverse effects
    - Clinical decision

HIV Positive and Solid Organ Transplant

- Excluded from RCTs
- Drug-drug interactions
- Clinical decision

Practical Approach
New Perspective on LDL-C and 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

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

New Drugs

- Praluent (alirocumab) and Repatha (evolocumab)
- PCSK9 Inhibitors. Injected antibodies that block enzyme that regulates LDL levels
- Lowers LDL 50-70%, statins 25-50%. No outcome data yet
- >$14,000/yr
- Lomitapide (juxtapid) MTP inhibitor, reduces LDL production
- Heterozygous Familial Hypercholesterolemia (FH).

Summary

- 1. ASCVD should receive high intensity statin, if not tolerated try moderate intensity
- 2. LDL>190 should receive high intensity statin, if not tolerated try moderate intensity
- 3. DM with 10 yr risk >7.5% high intensity, < 7.5% moderate intensity
- 4. 40-75 with >7.5% 10 yr risk should receive mod to high intensity statin

No Longer Acceptable

- Treat to target
- Lower is best
- Instead
  - Treat to level of ASCVD risk

Perspective

- Importance of physician-patient review of risk and decision making
- ASCVD risk calculator heavily influenced by age.
- 65 yo man and 71 yo woman with optimal risk factors have a >7.5% 10 yr risk.
- Physician judgment, statin safety and consideration of patient preferences can inform decision
- Prescription of a statin is not automatic, but part of comprehensive approach to risk reduction
Three Principles

- Do not focus on LDL-C or non-HDL-C cholesterol 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

Unanswered Questions for Future Guidelines

- Whether markers such as ApoB, Lp(a) or LDL particles are useful for guiding treatment decisions
- Best approaches to using noninvasive imaging for refining risk estimates to guide treatment decisions
- Subgroups of heart failure and hemodialysis patients that may benefit from statins
- Efficacy and safety of statins in pt groups excluded from RCTs (HIV + or solid organ transplant)

Conclusions

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