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

Presented by
Robert H. Eckel, M.D.
Professor of Medicine
Division of Endocrinology, Metabolism & Diabetes
Division of Cardiology
Professor of Physiology and Biophysics
Charles A. Boettcher II Chair in Atherosclerosis
Director, Lipid Clinic University of Colorado Hospital
University of Colorado Anschutz Medical Campus
Aurora, Colorado
Scope of the CVD Problem (2000-2009)
Learning Objectives

1. To update you on the ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults.

2. To discuss the controversial issues related to interpretation of the Guideline and how it influences the practice of preventive cardiology.
ACC/AHA Blood Cholesterol Guideline

Panel Members

Neil J. Stone, MD, MACP, FAHA, FACC, Chair
Jennifer G. Robinson, MD, MPH, FAHA, Vice Chair
Alice H. Lichtenstein, DSc, FAHA, Vice Chair

Anne C. Goldberg, MD, FACP, FAHA
Conrad B. Blum, MD, FAHA
Robert H. Eckel, MD, FAHA, FACC
Daniel Levy, MD*
David Gordon, MD*
C. Noel Bairey Merz, MD, FAHA, FACC

Donald M. Lloyd-Jones, MD, ScM, FACC, FAHA
J. Sanford Schwartz, MD
Patrick McBride, MD, MPH, FAHA
Sidney C. Smith, Jr, MD, FACC, FAHA
Karol Watson, MD, PhD, FACC, FAHA
Susan T. Shero, MS, RN*
Peter W.F. Wilson, MD, FAHA

*Ex-Officio Members.

Acknowledgements

Methodology Members
Karen M. Eddleman, BS
Nicole M. Jarrett

Ken LaBresh, MD
Lev Nevo, MD
Janusz Wnek, PhD

National Heart, Lung, and Blood Institute
Glen Bennett, M.P.H.
Denise Simons-Morton, MD, PhD

Helping Cardiovascular Professionals
Conflict of Interest/Relationships With Industry

1) All panel members disclosed conflict of interest information to the full panel in advance of the deliberations

2) Members with conflicts recused themselves from voting on any aspect of the guideline where a conflict might exist

3) All 16 members of the NHLBI ATP IV Panel transitioned to the ACC/AHA guideline Expert Panel

4) Independent contractors performed the systematic review with the assistance of the Expert Panel and provided methodological guidance to the Expert Panel
Conflict of Interest/Relationships With Industry

Advisory Boards or Consultant

Abbott
Foodminds
Merck
Pfizer
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 was 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
Systematic Review Process

- The Expert Panel constructed CQs relevant to clinical practice.
- The Expert Panel identified (a priori) inclusion/exclusion (I/E) criteria for each CQ.
- An independent contractor developed a literature search strategy, based on I/E criteria, for published clinical trial reports for each CQ.
- An 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.
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.

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

†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.
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‡

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*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.
Reduction in Major Vascular Events by Statins is Independent of Baseline LDL-C

CTT 2010: Meta-analysis of 26 RCTs (170,000 Participants)

<table>
<thead>
<tr>
<th>LDL-C</th>
<th>Events (% per annum)</th>
<th>RR (CI) per 1 mmol/L reduction in LDL-C</th>
<th>Trend test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Statin/more</td>
<td>Control/less</td>
<td></td>
</tr>
<tr>
<td>&lt;2 mmol/L</td>
<td>910 (4.1%)</td>
<td>1012 (4.6%)</td>
<td>0.78 (0.61–0.99)</td>
</tr>
<tr>
<td>≥2 to &lt;2.5 mmol/L</td>
<td>1528 (3.6%)</td>
<td>1729 (4.2%)</td>
<td>0.77 (0.67–0.89)</td>
</tr>
<tr>
<td>≥2.5 to &lt;3.0 mmol/L</td>
<td>1866 (3.3%)</td>
<td>2225 (4.0%)</td>
<td>0.77 (0.70–0.85)</td>
</tr>
<tr>
<td>≥3 to &lt;3.5 mmol/L</td>
<td>2007 (3.2%)</td>
<td>2454 (4.0%)</td>
<td>0.76 (0.70–0.82)</td>
</tr>
<tr>
<td>≥3.5 mmol/L</td>
<td>4508 (3.0%)</td>
<td>5736 (3.9%)</td>
<td>0.80 (0.76–0.83)</td>
</tr>
<tr>
<td>Total</td>
<td>10,973 (3.2%)</td>
<td>13,350 (4.0%)</td>
<td>0.78 (0.76–0.80)</td>
</tr>
</tbody>
</table>

- 99% or
- 95% CI

Statin/more better

Control/less better
Cholesterol Treatment Trialist’s 2010 Meta-analysis
(26 Trials, 170,000 Participants)

<table>
<thead>
<tr>
<th>Events (% per annum)</th>
<th>RR (CI) per 1 mmol/L reduction in LDL-C</th>
<th>Heterogeneity/trend test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statin/more Control/less</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Previous vascular disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHD</td>
<td>8395 (4.5%) 10123 (5.6%)</td>
<td>0.79 (0.76–0.82)</td>
</tr>
<tr>
<td>Non-CHD vascular</td>
<td>674 (3.1%) 802 (3.7%)</td>
<td>0.81 (0.71–0.92)</td>
</tr>
<tr>
<td>None</td>
<td>1904 (1.4%) 2425 (1.8%)</td>
<td>0.75 (0.69–0.82)</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1 diabetes</td>
<td>145 (4.5%) 192 (6.0%)</td>
<td>0.77 (0.58–1.01)</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>2494 (4.2%) 2920 (5.1%)</td>
<td>0.80 (0.74–0.86)</td>
</tr>
<tr>
<td>No diabetes</td>
<td>8272 (3.2%) 10163 (4.0%)</td>
<td>0.78 (0.75–0.81)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>8712 (3.5%) 10725 (4.4%)</td>
<td>0.77 (0.74–0.80)</td>
</tr>
<tr>
<td>Female</td>
<td>2261 (2.5%) 2625 (2.9%)</td>
<td>0.83 (0.76–0.90)</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤65</td>
<td>6056 (2.9%) 7455 (3.6%)</td>
<td>0.78 (0.75–0.82)</td>
</tr>
<tr>
<td>&gt;65 to ≤75</td>
<td>4032 (3.7%) 4908 (4.6%)</td>
<td>0.78 (0.74–0.83)</td>
</tr>
<tr>
<td>&gt;75</td>
<td>885 (4.8%) 987 (5.4%)</td>
<td>0.84 (0.73–0.97)</td>
</tr>
<tr>
<td><strong>Treated hypertension</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>6176 (3.7%) 7350 (4.5%)</td>
<td>0.80 (0.76–0.84)</td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>10973 (3.2%) 13350 (4.0%)</td>
<td>0.78 (0.76–0.80)</td>
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</table>

Cholesterol Treatment Trialsists. Lancet 2010; 376:1670-1681
Vignettes: Putting a face on patients in whom ASCVD risk reduction works

- 63 yo man with STEMI, discharged on a high-intensity statin
- 26 yo woman with an LDL–C of 220 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
Case 1

A 48 year old white woman with diabetes and microalbuminuria has a lipid panel:

TC 197; TG 300; HDL-C 42; LDL-C 95

Her BMI is 34; weight up 4 lbs.
Systolic BP 134. A1c 8.4%. Non-smoker

In addition to adherence to an optimal lifestyle what is the next step to reduce her risk for heart attack and stroke?
Case 1

A. Moderate intensity statin; no follow up lipids needed.

B. No need to use the risk estimator; she has diabetes.

C. Moderate intensity statin, regular lipid follow ups to determine adherence and response to therapy.

D. US guidelines don’t allow a non-statin to be added.

E. Time spent on adherence not useful; missing 25% of doses per month not likely to affect potential for benefit.
Case 1

Answer is C.

She’s in a statin “benefit” group.

Why not an LDL-C or non HDL-C?
The evidence points to proper intensity of therapy

Why not high intensity statin therapy?
The 10 year risk is 3.1%. Had she been a smoker, her risk would be 9.3%. Then tobacco cessation + intensive statin therapy if tolerated would be appropriate

Non-statins can be used in any of the high risk groups if statin therapy gives a less than anticipated response.
Case 2

79 yo man had AMI & received a stent to his LAD. Home on atorvastatin 40 mg daily & usual 2° prevention Rx TC 150; TG 150; HDL-C 45; LDL-C 75; Non HDL-C 105

Which of these is a true statement?

A. Getting under 70 mg/dL will provide an outcomes difference for him

B. Statin dose should be atorvastatin 80 mg or rosuvastatin 40 mg/d

C. Guidelines recommend lipids monitored periodically to assess adherence to statin/lifestyle; also for safety issues

D. No need to have lipids checked. It's a set it and go on strategy
Case 2

Answer is C. Since he is over 75, use of 40 mg atorvastatin would be reasonable, even though there are data to support high dose statin after age 75.

The issue of competing co-morbidities, multiple medications, and greater potential for side-effects with a high-intensity statin affect the decision here. What is crucial is to monitor lipids periodically and discuss safety issues.

After checking lipids 4-12 weeks after the statin is started, they should be checked at 3-12 months regularly with the interval dependent on how likely the patient is to have problems with adherence or safety issues.
What’s Similar to ATP-III?

– Emphasis on lifestyle measures as crucial
– Focus on treatment of LDL-C
– Greatest intensity of treatment for patients at highest risk
– Preference for statins over other medications that lower LDL-C
  • Although this is more emphasized in the new ACC/AHA Guideline
New Perspective on LDL–C & Non-HDL–C Goals

• 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

• LDL-C <40 mg/dL is too low - reduce statin dose
Why Not Continue to Treat to Target?

Major difficulties:

1. Current RCT data do not indicate what the target should be
2. Unknown magnitude of additional ASCVD risk reduction with one target compared to another
3. Unknown rate of additional adverse effects from multidrug therapy used to achieve a specific goal
4. Therefore, unknown net benefit from treat-to-target approach
Important to Note

• ‘No Evidence’ could be
  – There is no evidence, or
  – The existing evidence is inconclusive
• We treat people not populations.
• Goal-setting is not precluded;
  – It’s just not evidence-based.
4 Statin Benefit Groups

ASCVD Statin Benefit Groups
Heart healthy lifestyle habits are the foundation of ASCVD prevention. In individuals not receiving cholesterol-lowering drug therapy, recalculate estimated 10-y ASCVD risk every 4-6 y in individuals aged 40-75 y without clinical ASCVD or diabetes and with LDL–C 70–189 mg/dL.

- **Adults age ≥21 y and a candidate for statin therapy**
  - Yes: Clinical ASCVD
    - Yes: Age ≤75 y
      - High-intensity statin (Moderate-intensity statin if not candidate for high-intensity statin)
    - No: Age >75 y OR if not candidate for high-intensity statin
      - Moderate-intensity statin

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

- **Diabetes Type 1 or 2**
  - Age 40-75 y
    - Yes: Estimated 10-y ASCVD risk ≥7.5%
      - High-intensity statin
    - No: Moderate-intensity statin

*Percent reduction in LDL–C can be used as an indication of response and adherence to therapy, but is not in itself a treatment goal.
2013 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines

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

EXPERT WORK GROUP MEMBERS
Robert H. Eckel, MD, FAHA, Co-Chair
John M. Jakicic, PhD, Co-Chair
Jamy D. Ard, MD
Van S. Hubbard, MD, PhD*
Janet M. de Jesus, MS, RD*
I-Min Lee, MD, ScD
Alice H. Lichtenstein, DSc, FAHA
Catherine M. Loria, PhD, FAHA*
Barbara E. Millen, DrPH, RD, FADA
Nancy Houston Miller, RN, BSN, FAHA
Cathy A. Nonas, MS, RD
Frank M. Sacks, MD, FAHA
Sidney C. Smith, Jr, MD, FACC, FAHA
Laura P. Svetkey, MD, MHS
Thomas W. Wadden, PhD
Susan Z. Yanovski, MD*
Maintain an Overall Healthy Diet!
Nutrition Lifestyle Recommendations

- Dietary patterns emphasis-based:
  - DASH and Mediterranean eating plans
- Fruits, vegetables, and whole grains
- 30 – 35% fat intake of monounsaturated fats (low saturated fats, no trans fats)
- Low sodium (<2400 mg/day)
- Cut out processed or pre-prepared food
- Healthy eating for a lifetime
Dietary Pattern Recommendations for LDL-C Lowering

Advise adults who would benefit from LDL-C lowering to:

• Choose a heart-healthy dietary pattern.
• Reduce % of calories from saturated fat.
  – 5% to 6% of calories.
• Reduce % of calories from trans fat.

Strength of evidence: IA

Physical Activity Recommendations

• Goal is 30 - 40 minutes / day, 150 minutes per week
• Minimum 3 days per week
• F – I – T  (frequency / intensity / time)
• Variety including strength, flexibility, and endurance
• Prescription – Just Do It!
Physical Activity Guidelines: Lipids and BP

• Advise adults to engage in aerobic physical activity
  – 3 to 4 sessions a week
  – lasting on average 40 min per session
  – involving moderate-to-vigorous intensity physical activity.

Strength of evidence – IIA

4 Statin Benefit Groups (con’t)

†Before writing the prescription for statin therapy, clinicians and patients should engage in a discussion that focuses on issues related to ASCVD risk reduction and statin appropriateness, which include safety and patient preferences (see Figure 4). For those in whom a risk assessment is uncertain, factors such as family history of premature ASCVD, lifetime risk of ASCVD, LDL–C ≥160 mg/dL, hs-CRP ≥2.0, CAC score ≥300 Agatston units, and ABI ≤0.90 may be considered to inform the treatment decision.


§ Primary LDL–C ≥160 mg/dL or other evidence of genetic hyperlipidemias, family history of premature ASCVD with onset <55 years of age in a first degree male relative or <65 years of age in a first degree female relative, high-sensitivity C-reactive protein ≥2 mg/L, CAC score ≥300 Agatston units or ≥75 percentile for age, sex, and ethnicity, ankle-brachial index <0.9, or elevated lifetime risk of ASCVD.
# 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>
</tr>
</thead>
<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>
</tr>
<tr>
<td></td>
<td>Lovastatin 40 mg</td>
<td>Pitavastatin 1 mg</td>
</tr>
<tr>
<td></td>
<td>Fluvastatin XL 80 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fluvastatin 40 mg bid</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pitavastatin 2–4 mg</td>
<td></td>
</tr>
</tbody>
</table>

*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 >3X ULN

**Aged ≤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

**Aged >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)**

*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.
Primary Prevention

Initiating Statin Therapy

No Clinical ASCVD
Not currently on cholesterol-lowering drugs
Initial evaluation prior to statin initiation
- Fasting lipid panel*
- ALT
- Hemoglobin A1c (if diabetes status unknown)
- 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 >3X ULN

Assign to statin benefit group (Figure 2)
Counsel on healthy lifestyle habits

Diabetes and age 40-75 y†
OR
LDL–C ≥190 mg/dL

No diabetes, age 40-75 y, and
LDL–C 70-189 mg/dL

*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.
Primary Prevention

Initiating Statin Therapy (con’t)

1) Potential ASCVD risk reduction benefits (e.g., absolute risk reduction from moderate- or high-intensity statin therapy can be approximated by using the estimated 10-year ASCVD risk and the relative risk reduction of ~30% for moderate-intensity statin or ~45% for high-intensity statin therapy. 2) Potential adverse effects. The excess risk of diabetes is the main consideration in ~0.1 excess case per 100 individuals treated with a moderate-intensity statin for 1 year and ~0.3 excess cases per 100 individuals treated with a high-intensity statin treated patients for 1 year. Note: a case of diabetes is not considered equivalent to a fatal or nonfatal MI or stroke. Both statin-treated and placebo-treated participants experienced the same rate of muscle symptoms. The actual rate of statin-related muscle symptoms in the clinical population is unclear. Muscle symptoms attributed to statin should be evaluated in Table 8, Safety Rec 8.


‡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 of age in a first degree male relative or <65 years of age in a first degree female relative, sensitivity-C-reactive protein ≥2 mg/L, ≥300 Agatston units or ≥75 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.

§ 1) Potential ASCVD risk reduction benefits (e.g., absolute risk reduction from moderate- or high-intensity statin therapy can be approximated by using the estimated 10-year ASCVD risk and the relative risk reduction of ~30% for moderate-intensity statin or ~45% for high-intensity statin therapy. 2) Potential adverse effects. The excess risk of diabetes is the main consideration in ~0.1 excess case per 100 individuals treated with a moderate-intensity statin for 1 year and ~0.3 excess cases per 100 individuals treated with a high-intensity statin treated patients for 1 year. Note: a case of diabetes is not considered equivalent to a fatal or nonfatal MI or stroke. Both statin-treated and placebo-treated participants experienced the same rate of muscle symptoms. The actual rate of statin-related muscle symptoms in the clinical population is unclear. Muscle symptoms attributed to statin should be evaluated in Table 8, Safety Rec 8.
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 not clearly in 1 of 4 statin benefit groups, additional factors may inform treatment decision-making:
  - Family history of premature ASCVD
  - Elevated lifetime risk of ASCVD
  - LDL–C ≥160 mg/dL
  - hs-CRP ≥2.0 mg/L
  - Subclinical atherosclerosis
    - CAC score ≥300 or ABI<0.9

- Discussion of potential for ASCVD risk reduction benefit, potential for adverse effects, drug-drug interactions, and patient preferences
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
Assess medication and lifestyle adherence
Fasting lipid panel

Anticipated therapeutic response?

Indicators of anticipated therapeutic response and adherence to selected statin intensity:
- High-intensity statin therapy† reduces LDL-C approx. ≥50% from the untreated baseline.
- Moderate-intensity statin therapy reduces LDL-C approx. 30% to <50% from the untreated baseline.

Reinforce continued adherence
Follow-up 3–12 mo

Yes

Anticipated therapeutic response?

Yes

Management of statin intolerance (Table 8, Rec 8)

No

Less-than-anticipated therapeutic response

Intolerance to recommended dose of statin therapy?

Yes

No

American Heart Association
Helping Cardiovascular Professionals
Statin Therapy: Monitoring Response and Adherence

Assess medication and lifestyle adherence
Fasting lipid panel*

Anticipated therapeutic response?

Indicators of anticipated therapeutic response and adherence to selected statin intensity:
- High-intensity statin therapy† reduces LDL–C approx. ≥50% from the untreated baseline.
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Reinforce continued adherence
Follow-up 3-12 mo

Less-than-anticipated therapeutic response

Intolerance to recommended dose of statin therapy?

Yes
Management of statin intolerance (Table 8, Rec 8)

No

Anticipated therapeutic response?

Yes

No

Helping Cardiovascular Professionals

American Heart Association®
Reinforce continued adherence
Follow-up 3-12 mo

Anticipated therapeutic response?

Reinforce improved adherence
Increase statin intensity‡
OR
Consider addition of nonstatin drug therapy

Follow-up 4-12 wk & thereafter as indicated

Less-than-anticipated therapeutic response

Intolerance to recommended dose of statin therapy

Reinforce medication adherence
Reinforce adherence to intensive lifestyle changes
Exclude secondary causes of hypercholesterolemia (Table 6)

Follow-up 4-12 wk

Management of statin intolerance (Table 8, Rec 8)
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 (con’t)

If unexplained severe muscle symptoms or fatigue develop during statin therapy:
• Promptly discontinue the statin
• Address possibility of rhabdomyolysis with:
  ▪ CK
  ▪ Creatinine
  ▪ Urine for myoglobinuria
Management of Muscle Symptoms on Statin Therapy (con’t)

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
Asymptomatic CK in high risk patients only

CK measured: < 5 x normal

Mildly Symptomatic

Symptoms worse: repeat CK & Stop or Reduce Statin Dose

Moderate to Severely Symptomatic

Stop Statin: CK measured, hydrate if creatinine ↑

Symptoms gone: CK ↓ & creat↓

Red yeast rice, 600-1800 bid

Ezetimibe and/or BAS

Fluvastatin or pravastatin, 20 mg per night or every other night

Fluvastatin XL 80 mg per night

Rosuvastatin 5 mg daily, every other day, or weekly

Patient Types

Diagnostic Strategies

Therapeutic Options

Eckel RH, JCEM 95:2015, 2010
# Statin Benefits Compared to Adverse Effects

## 2013 Cochrane Review *(18 RCTs, 19 trial arms n=56,394)*

14 trials recruited patients with specific conditions (raised lipids, DM, HTN, microalb)

<table>
<thead>
<tr>
<th>Benefit</th>
<th>Percentage Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>14% ↓</td>
</tr>
<tr>
<td>CHD (fatal and non fatal) events</td>
<td>27% ↓</td>
</tr>
<tr>
<td>Stroke (fatal and non fatal)</td>
<td>22% ↓</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>33% ↓</td>
</tr>
<tr>
<td>Revascularization</td>
<td>38% ↓</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>18% ↑</td>
</tr>
</tbody>
</table>

(2.8% on statin vs. 2.4% controls)

No significant increase in short-term risk of:

- Muscle adverse events
- Liver adverse events
- Cancer, memory loss
- Hemorrhagic stroke

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
• For primary prevention, they are “patient-centered”
• Guidelines will change in the future as high-quality data will improve future cholesterol treatment guidelines
Major Controversies

- Risk calculator validation
- Threshold of $\geq 7.5\%$ 10-year CVD event risk for statins in primary prevention
- Bias within committee and comparisons to other guidelines dismissed
- No LDL-C or non-HDL-C goals
Major Controversies

• Risk calculator validation
Risk Calculator: The Controversy?

- Risk Calculator from NHANES
- Very diverse U.S. population
- 12 years of follow-up
- When low risk populations are studied using this it can overestimate
- It is to be used as a guide, not a substitute for clinical decision making
Risk Assessment (i.e. risk calculation) has proven in RCTs to effectively identify those who benefit most from treatment.
Risk Calculator

• Includes:
  – Race
  – Gender
  – Age
  – Total cholesterol
  – HDL
  – Blood pressure / Use of BP medicines
  – Diabetes status
  – Smoking status

http://my.americanheart.org/professional/StatementsGuidelines/Prevention-Guidelines_UCM_457698_SubHomePage.jsp
ACC/AHA Risk Calculator

10-Year ASCVD Risk

- Gender: Male
- Age: 50
- HDL-Cholesterol: 80 mg/dL
- Total Cholesterol: 200 mg/dL
- Diabetes: Yes
- Systolic Blood Pressure: 110
- Smoker: No
- Treatment for Hypertension: Yes

Risk Factors:
- **Gender:** Male
- **Age:** 50
- **HDL-Cholesterol:** 80 mg/dL
- **Total Cholesterol:** 200 mg/dL
- **Diabetes:** Yes
- **Systolic Blood Pressure:** 110
- **Smoker:** No
- **Treatment for Hypertension:** Yes

*Intended for use if there is not ASCVD and the LDL cholesterol is <190 mg/dL.

**Optimal risk factors include:** Total cholesterol of <190 mg/dL, HDL cholesterol of ≥60 mg/dL, Systolic BP of <120 mm Hg, not taking medications for hypertension, not a diabetic, not a smoker.
Emphasis on Healthy Lifestyle

• For those 20-59 risk estimator provides lifetime risk estimate
  • Better in women?
• This is intended to drive discussions of greater adherence to heart-healthy lifestyle
• Part of risk discussion
2013 ACC/AHA GUIDELINE: Is the Risk Estimator Useful?

Claim: Pooled Cohort Equations overestimate ASCVD risk by 75-150% 

Claim based on analyses of Women’s Health Study, Physician’s Health Study, Women’s Health Initiative Observational Study, but:

— These studies lacked active surveillance for ASCVD events (can lead to ~30% undercounting of events**)

— High prevalence of statin use in contemporary cohorts may cause participants to ‘underperform’ in ASCVD event generation

— Risk factor levels were self-reported in these studies

— The participants in these studies (esp. PHS) were not broadly representative of the US population
Primary Prevention Statin Therapy

• Thresholds for initiating statin therapy derived from 3 exclusively primary prevention RCTs
  – Placebo group 10 yr event rates:
    JUPITER – 7.6%;  MEGA 5.1%;  AFCAPS-TEXCAPS 6.9%

**Guideline Panel’s recommendation:**

• As a matter of caution, to avoid over-treating, the Panel identified those with risk ≥7.5% as a group in which statins provide benefit.
Reasons for Geographic and Racial Difference in Stroke
Observed and Predicted ASCVD Events in REGARDS Subjects

Application of New Cholesterol Guidelines to a Population-Based Sample

Michael J. Pencina, Ph.D., Ann Marie Navar-Boggan, M.D., Ph.D., Ralph B. D'Agostino, Sr., Ph.D., Ken Williams, M.S., Benjamin Neely, M.S., Allan D. Sniderman, M.D., and Eric D. Peterson, M.D., M.P.H.

ABSTRACT

BACKGROUND
The 2013 guidelines of the American College of Cardiology and the American Heart Association (ACC–AHA) for the treatment of cholesterol expand the indications for statin therapy for the prevention of cardiovascular disease.

METHODS
Using data from the National Health and Nutrition Examination Surveys of 2005 to
Percent of US Adults Who Would be Statin Eligible for Primary Prevention

Risk Assessment

- Recommended every 5 years
- For 40–79 year olds
- Gives 10 year and lifetime risk
- Includes heart attack, all heart disease, and stroke risk
- Can be integrated into an electronic medical record
Major Controversies

- Risk calculator validation
- Threshold of ≥7.5% 10-year CVD event risk for statins in primary prevention
Moderate Intensity Statin Treatment

Assumes a 35% relative risk reduction in ASCVD from moderate intensity statin therapy.

**NNT** to prevent 1 ASCVD event varies by baseline estimated 10-year ASCVD risk.

**NNH** based on 1 excess case of incident diabetes per 100 individuals; 0.012 for myopathy or rhabdomyolysis; 0.01 for hemorrhagic stroke.
**Moderate Intensity Statin Treatment**


NNT to prevent 1 ASCVD event over 10 years:
- 2.5%  
- 5.0%  
- 7.5%  
- 10.0%  
- 15.0%  
- 20.0%  
- 25.0%

10-year ASCVD risk:
- 0.0%  
- 5.0%  
- 10.0%  
- 15.0%  
- 20.0%  
- 25.0%

NNT=82
Adjudication for the 7.5% 10-Year Risk

• The benefit of statins actually extended down to a global risk of 5%; thus, this more than adjusts for any overestimation when 7.5% is used.

• A number of other factors were identified that could be used when there is concern of overtreatment in borderline and/or elderly patients:
  – CAC score, ABI, hsCRP, family history of premature ASCVD, elevated lifetime risk and/or LDL-C ≥160

• A risk discussion was repeatedly emphasized.
  – The intersection between not just the evidence, but also clinical judgment based on individual patient factors and informed patient choice.
Major Controversies

- Risk calculator validation
- Threshold of ≥7.5% 10-year CVD event risk for statins in primary prevention
- Bias within committee and comparisons to other guidelines dismissed
Bias and Comparisons Response

• Free-standing and unique committee
• Different societies working separately
• COIs upfront
  – Recusals when voting
• All but one potent statin generic
• Independent process
  – Other guidelines not considered
Major Controversies

- Risk calculator validation
- Threshold of $\geq 7.5\%$ 10-year CVD event risk for statins in primary prevention
- Bias within committee and comparisons to other guidelines dismissed
- No LDL-C or non-HDL-C goals
No LDL-C or non-HDL-C goals

- Not evidence-based
- Not precluded
- Performance measures
  - Secondary prevention
    - Optimal lifestyle and maximum tolerated statin prescribed
    - Follow-up lipids - adherence and responsiveness
  - Primary prevention
    - Risk estimation
    - Heart-healthy lifestyle
    - Risk/benefit of statins discussion
    - Informed patient preference
“Emerging from these documents and others is a sense that guidelines should inform but not dictate, guide but not enforce, and support but not restrict”

Harlan Krumholz, MD, SM
Yale University School of Medicine
Thank you!
Thank You!