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

“Lipid Targets & Treatments 2014”

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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.
Complications of Diabetes: 1990-2010

Gregg EW et al, NEJM 370:1514, 2014
# History of NHLBI CVD Clinical Guidelines

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>JNC 5: 1992</td>
<td>ATP II: 1993</td>
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</tbody>
</table>
### ACC/AHA Blood Cholesterol Guideline

#### Panel Members

**Chair**

Neil J. Stone, MD, MACP, FAHA, FACC

**Vice Chair**

Jennifer G. Robinson, MD, MPH, FAHA

Alice H. Lichtenstein, DSc, FAHA

- 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**
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
Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk Guideline

Blood Cholesterol Panel
Systematic review of RCTs and meta-analyses of RCTs

Risk Assessment Work Group Guideline
Systematic review of epidemiologic studies and meta-analyses of epidemiologic studies

Lifestyle Management Work Group Guideline
Systematic review of RCTs and observational studies
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.
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.
# Reduction in Major Vascular Events by Statins is Independent of Baseline LDL-C

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

**LDL-C** | **Events (% per annum)** | **RR (CI) per 1 mmol/L reduction in LDL-C** | **Trend test**
---|---|---|---
<2 mmol/L | Statin/more: 910 (4.1%) | 0.78 (0.61–0.99) | 0.77 (0.67–0.89) |
≥2 to <2.5 mmol/L | Control/less: 1012 (4.6%) | 0.77 (0.70–0.85) | χ²=1.08 | p=0.3
≥2.5 to <3.0 mmol/L | Statin/more: 1528 (3.6%) | 0.76 (0.70–0.82) | p=0.3 |
| Control/less: 1729 (4.2%) | 0.76 (0.70–0.82) |
≥3 to <3.5 mmol/L | Statin/more: 1866 (3.3%) | 0.76 (0.70–0.82) | p=0.3 |
| Control/less: 2225 (4.0%) | 0.76 (0.70–0.82) |
≥3.5 mmol/L | Statin/more: 2007 (3.2%) | 0.80 (0.76–0.83) | p=0.3 |
| Control/less: 2454 (4.0%) | 0.80 (0.76–0.83) |
**Total** | Statin/more: 10,973 (3.2%) | 0.78 (0.76–0.80) | 0.78 (0.76–0.80) |
| Control/less: 13,350 (4.0%) | 0.78 (0.76–0.80) |

99% or

95% CI

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Statin/more better

Control/less better

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**Helping Cardiovascular Professionals**


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**American Heart Association**
Cholesterol Treatment Trialist’s 2010 Meta-analysis (26 Trials, 170,000 Participants)

Cholesterol Treatment Trialists. Lancet 2010; 376:1670-1681
Statin Therapy in Patients with Diabetes 2008
(n=18,686 with diabetes, 3247 major CVD events in patients with diabetes)

<table>
<thead>
<tr>
<th>Major vascular event and prior diabetes</th>
<th>Events (%)</th>
<th>RR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment</td>
<td>Control</td>
</tr>
<tr>
<td>Major coronary event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>776 (8.3%)</td>
<td>979 (10.5%)</td>
</tr>
<tr>
<td>No diabetes</td>
<td>2561 (7.2%)</td>
<td>3441 (9.6%)</td>
</tr>
<tr>
<td>Any major coronary event</td>
<td>3337 (7.4%)</td>
<td>4420 (9.8%)</td>
</tr>
<tr>
<td>Test for heterogeneity within subgroup: $\chi^2 = 0.1$; p = 0.8</td>
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<td></td>
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<tr>
<td>Coronary revascularisation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>491 (5.2%)</td>
<td>627 (6.7%)</td>
</tr>
<tr>
<td>No diabetes</td>
<td>2129 (6.0%)</td>
<td>2807 (7.9%)</td>
</tr>
<tr>
<td>Any coronary revascularisation</td>
<td>2620 (5.8%)</td>
<td>3434 (7.6%)</td>
</tr>
<tr>
<td>Test for heterogeneity within subgroup: $\chi^2 = 0.1$; p = 0.8</td>
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<td></td>
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<tr>
<td>Stroke</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>407 (4.4%)</td>
<td>501 (5.4%)</td>
</tr>
<tr>
<td>No diabetes</td>
<td>933 (2.7%)</td>
<td>1116 (3.2%)</td>
</tr>
<tr>
<td>Any stroke</td>
<td>1340 (3.0%)</td>
<td>1617 (3.7%)</td>
</tr>
<tr>
<td>Test for heterogeneity within subgroup: $\chi^2 = 0.8$; p = 0.4</td>
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<td></td>
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<tr>
<td>Major vascular event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>1465 (15.6%)</td>
<td>1782 (19.2%)</td>
</tr>
<tr>
<td>No diabetes</td>
<td>4889 (13.7%)</td>
<td>6212 (17.4%)</td>
</tr>
<tr>
<td>Any major vascular event</td>
<td>6354 (14.1%)</td>
<td>7994 (17.8%)</td>
</tr>
<tr>
<td>Test for heterogeneity within subgroup: $\chi^2 = 0.0$; p = 0.9</td>
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### ACC/AHA Cholesterol Guideline: Evidence for Statins in Diabetes

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Statin Dose</th>
<th>Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary</td>
<td>High</td>
<td>TNT PROVE-IT, MIRACL, IDEAL</td>
</tr>
<tr>
<td>Primary</td>
<td>Moderate</td>
<td>4S, WOSCOPS, CARE, Post-CABG, LIPID ASFCAPS/TexCAPS, GISSI-P, LIPS, HPS, PROSPER, ALLHAT-LLT, ASCOT-LLA, ALERT, CARDS</td>
</tr>
</tbody>
</table>
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
Important to Note

• ‘No Evidence’ could be
  – There is no evidence, or
  – The existing evidence is inconclusive

• We treat people not populations.

• Goal-setting and the use of other lipid modifying Rx is not precluded;
  – It’s just not evidence-based.
Maintain an Overall Healthy Diet!
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 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
- Resistance training can be added

Strength of evidence: IIA

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>
</tbody>
</table>
| Atorvastatin (40†)–80 mg  
Rosuvastatin 20 (40) mg | Atorvastatin 10 (20) mg  
Rosuvastatin (5) 10 mg  
Simvastatin 20–40 mg‡  
Pravastatin 40 (80) mg  
Lovastatin 40 mg  
Fluvastatin XL 80 mg  
Fluvastatin 40 mg bid  
Pitavastatin 2–4 mg | Simvastatin 10 mg  
Pravastatin 10–20 mg  
Lovastatin 20 mg  
Fluvastatin 20–40 mg  
Pitavastatin 1 mg |

*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.
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 ASCVD: Risk of first nonfatal myocardial infarction, coronary heart disease death, nonfatal or fatal stroke
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 >75%tile or ABI<0.9

- Discussion of potential for ASCVD risk reduction benefit, potential for adverse effects, drug-drug interactions, and patient preferences
Major Controversies

- Risk estimator validation
- Threshold of ≥ 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 estimator validation
Risk Estimator: The Controversy?

• Risk Estimator 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 Estimator

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

http://my.americanheart.org/professional/StatementsGuidelines/Prevention-Guidelines_UCM_457698_SubHomePage.jsp
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
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.

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

Pencina MJ et al, NEJM 370:1422, 2014
Major Controversies

• Risk estimator validation
• Threshold of $\geq 7.5\%$ 10-year CVD event risk for statins in primary prevention
Moderate Intensity Statin Treatment

NNT to prevent 1 ASCVD event over 10 years


NNT=82

10-year ASCVD risk

0.0% 2.5% 5.0% 7.5% 10.0% 15.0% 20.0% 25.0%
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 needs to be 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 estimator 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
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 estimator 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
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Important to Note

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• We treat people not populations.

• Goal-setting and the use of other lipid modifying Rx is not precluded;
  – It’s just not evidence-based.
“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!