Are recent cholesterol treatment guidelines still controversial?

Woo Je Lee, M.D., Ph.D.
Department of Internal Medicine
Asan Medical Center
University of Ulsan College of Medicine
Conflict of interest disclosure

None
Content Overview

- Dyslipidemia and Cardiovascular Disease
- 2013 ACC/AHA Guideline
- Controversies on 2013 ACC/AHA Guideline
- Summary & Conclusion
Major risk factors for cardiovascular disease

- Age
- Gender
- Genetic factors
- Race & ethnicity
- High cholesterol
- Smoking
- Diabetes
- Physical inactivity
- Obesity
- Hypertension
Major risk factors for cardiovascular disease

- High cholesterol
- Age
- Gender
- Genetic factors
- Race & ethnicity
- Smoking
- Diabetes
- Physical inactivity
- Obesity
- Hypertension
Management of dyslipidemia (NCEP ATP III)

- **Very high risk**: established CHD + major risk factor(s)
  - LDL-C < 70 mg/dl ("option")

- **High risk**: CHD or CHD equivalent, or 10-yr risk > 20%
  - LDL-C < 100 mg/dl

- **Secondary target**: non-HDL-C
Evolution of the lipid treatment guideline

<table>
<thead>
<tr>
<th>NCEP ATP I</th>
<th>NCEP ATP II</th>
<th>NCEP ATP III</th>
<th>ATP III Update</th>
<th>ESC/EAS 2011</th>
<th>ADA, IAS ACC/AHA 2013</th>
</tr>
</thead>
</table>

- **Exclusive focus on LDL-C**  
- **LDL-C goal ≤100 mg/dL for CHD**  
- **LDL-C goal <100 mg/dL for CHD equivalent**  
- **Non-HDL-C as secondary targets**  
- **Optional LDL-C goal <70 mg/dL for very high risk**  
- **Apo-B as secondary targets**

**More intensive LDL-C goal recommendation**

**Change of risk calculator**

- Framingham risk scores  
- SCORE (Systemic Coronary Risk Estimation)
2013 ACC/AHA guideline

- Update the clinical practice recommendations for the treatment of blood cholesterol levels to reduce atherosclerotic cardiovascular disease (ASCVD) risk

- Evidences
  - Randomized controlled trials (RCTs) with CV outcomes
  - Systemic reviews of RCTs
  - Meta-analyses of RCTs
Major changes compared to ATP III guideline

1. Four major statin benefit groups
2. Development of the Pooled Cohort Equations
3. High- or moderate-intensity statin therapy
4. No specific LDL-cholesterol target
5. No routine use of non-statin drugs combined with statin
## Target patient groups

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Individuals with clinical ASCVD*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 2</td>
<td>Individuals with primary elevations of LDL-C ≥190 mg/dL</td>
</tr>
<tr>
<td>Group 3</td>
<td>Individuals 40 to 75 years of age with diabetes with LDL-C 70-189 mg/dL</td>
</tr>
<tr>
<td>Group 4</td>
<td>Individuals without clinical ASCVD or diabetes who are 40 to 75 years of age with LDL-C 70-189 mg/dL and an estimated 10-year ASCVD risk of 7.5% or higher (*New Pooled Cohort risk equation)</td>
</tr>
</tbody>
</table>

* Clinical ASCVD is defined by the inclusion criteria for the secondary prevention statin RCTs (acute coronary syndromes, or a history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, TIA, or peripheral arterial disease presumed to be of atherosclerotic origin).
The new pooled cohort equations to estimate 10-year ASCVD risk

Pooled Cohort Risk Assessment Equations
Predicts 10-year risk for a first atherosclerotic cardiovascular disease (ASCVD) event

Risk Factors for ASCVD

- Gender: Male, Female
- Age: 55 years
- Race: White or other
- Systolic BP: 140 mmHg
- Receiving treatment for high blood pressure (if SBP > 120 mmHg): No, Yes
- Diabetes: No, Yes
- Smoker: No, Yes
- Total Cholesterol: 180 mg/dL
- HDL Cholesterol: 30 mg/dL

Reset, Calculate

http://clincalc.com/Cardiology/ASCVD/PooledCohort.aspx
# Specific dose of statins by the percent reduction in LDL-C level

<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 $\geq 50%$</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 Rosuvastatin 20 (40) mg</td>
<td>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</td>
<td>Simvastatin 10 mg Pravastatin 10-20 mg Lovastatin 20 mg Fluvastatin 20-40 mg Pitavastatin 1 mg</td>
</tr>
</tbody>
</table>

*Source: Circulation. 2014;129:S1-45*
No evidences for target goals and non-statin drug use

- No more LDL-C / non-HDL goal
- No routine use of non-statin drugs combined with statin
Controversies on 2013 ACC/AHA guideline
Controversies on 2013 ACC/AHA guideline

- Too many statin eligible patients
- Pooled cohort equations
- Intensity of statins
- No lipid target goals
- Role of non-statin drugs
Controversies on 2013 ACC/AHA guideline

- Too many statin eligible patients
  - Pooled cohort equations
  - Intensity of statins
  - No lipid target goals
  - Role of non-statin drugs
## Too many statin eligible patients

<table>
<thead>
<tr>
<th></th>
<th>ATP-III guideline</th>
<th>ACC/AHA guideline</th>
<th>New Candidates for statin therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>American</strong></td>
<td>43.2 million (37.5%)</td>
<td>56.0 million (48.6%)</td>
<td><strong>14.4 million (12%)</strong></td>
</tr>
<tr>
<td>(115.4 million)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Korean</strong></td>
<td>3.5 million (18.6%)</td>
<td>6.7 million (35.1%)</td>
<td><strong>3.6 million (19%)</strong></td>
</tr>
<tr>
<td>(19 million)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Too many statin eligible patients in U.S.
Too many statin eligible patients in Korea
Controversies on 2013 ACC/AHA guideline

• Too many statin eligible patients

• Pooled cohort equations

• Intensity of statins

• No lipid target goals

• Role of non-statin drugs
Pitfalls of the new risk calculator

- Individuals in the fourth group can be identified by using the new Pooled Cohort Equations for ASCVD risk prediction, developed by the Risk Assessment Work Group

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>M or F</td>
</tr>
<tr>
<td>Age</td>
<td>Years</td>
</tr>
<tr>
<td>Race</td>
<td>African/Americans or whites/others</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>mg/dL</td>
</tr>
<tr>
<td>HDL-C</td>
<td>mg/dL</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>mm Hg</td>
</tr>
<tr>
<td>Treatment for High Blood Pressure</td>
<td>Y or N</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Y or N</td>
</tr>
<tr>
<td>Smoker</td>
<td>Y or N</td>
</tr>
</tbody>
</table>
Pitfalls of the new risk calculator

Observation event rates

Event rates predicted by new ACC/AHA risk prediction algorithm

Pitfalls of the new risk calculator

Observed 10-Year Risk (%) vs. Predicted 10-Year Risk (%)

- Predicted
- Observed

Am Heart J. 2015;170:598-605.e7
Controversies on 2013 ACC/AHA guideline

- Too many statin eligible patients
- Pooled cohort equations
- Intensity of statins
- No lipid target goals
- Role of non-statin drugs
High- or moderate-intensity statin therapy

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 → Clinical ASCVD

Yes → Clinical ASCVD

No → Yes

LDL–C ≥190 mg/dL

Yes → High-intensity statin (Moderate-intensity statin if not candidate for high-intensity statin)

No → Yes

Diabetes
Type 1 or 2
Age 40-75 y

Yes → Moderate-intensity statin

No → Yes

Estimated 10-y ASCVD risk ≥7.5%

High-intensity statin

(Permanent)
Specific dose of statins by the percent reduction in LDL-C level

<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 $\geq 50%$</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* |

*Circulation. 2014;129:S1-45*
Statin use in real world practice

In Europe & Canada


Statin dose potency

Non-high risk patients
High risk patients

Percentage of patients

1 2 3 4 5 6

Statin use in real world practice

Simva 80 mg
Atorva 40 mg
Rosuva 20 mg

Atorva 80 mg
Rosuva 40 mg
Statin use in Korea

Atorva ≥ 40 mg
Rosuva ≥ 20 mg
Controversies on 2013 ACC/AHA guideline

- Too many statin eligible patients
- Pooled cohort equations
- Intensity of statins
- No lipid target goals
- Role of non-statin drugs
No lipid target goals

WHAT???

NO GOAL?
For LDL-C; ”Lower is better”

% Patients with CHD Event

LDL cholesterol

Primary prevention trials
Secondary prevention trials
HPS

NEJM. 2005;352:1425–1435
# LDL-C target goals in recent guidelines

<table>
<thead>
<tr>
<th></th>
<th>Very high risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>NLA (2016)</td>
<td>&lt; 70 mg/dL</td>
<td>&lt; 100 mg/dL</td>
</tr>
<tr>
<td>ESC/EAS (2016)</td>
<td>&lt; 70 mg/dL</td>
<td>&lt; 100 mg/dL</td>
</tr>
<tr>
<td>AACE (2016)</td>
<td>&lt; 70 mg/dL</td>
<td>&lt; 100 mg/dL</td>
</tr>
<tr>
<td>IAS (2014)</td>
<td></td>
<td>&lt; 70 mg/dL (optimal level for 1° prevention)</td>
</tr>
</tbody>
</table>

Eur Heart J. 2016 [Epub ahead of print]  
Endocr Pract. 2016;22:84-113  
J Clin Lipidol. 2014;8:29-60*
Controversies on 2013 ACC/AHA guideline

- Too many statin eligible patients
- Pooled cohort equations
- Intensity of statins
- No lipid target goals
- Role of non-statin drugs
Residual CVD risk despite optimal LDL-C reduction

Risk Attributable to LDL-C

Residual Risk of CVD ~ 70%

Role of other lipid and non-lipid factors

Clinical event rate

LDL-C (mg/dL)

TNT = Treating to New Targets study, PROVE IT = Pravastatin or Atorvastatin Evaluation and Infection Therapy study, CARDS = Collaborative Atorvastatin Diabetes Study, Post CABG = Post Coronary Artery Bypass Graft Study

J Am Coll Card. 2005;46:1225-8
No evidences for non-statin drug use

- FIELD
- ILLUMINATE
- ACCORD-LIPID
- AIM-HIGH
- HPS2-THRIVE

Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes

Christopher P. Cannon, M.D., Michael A. Blazing, M.D., Robert P. Giugliano, M.D., Amy McCagg, B.S., Jennifer A. White, M.S., Pierre Theroux, M.D., Harald Darius, M.D., Basil S. Lewis, M.D., Ton Oude Ophuis, M.D., Ph.D., J. Wouter Jukema, M.D., Ph.D., Gaetano M. De Ferrari, M.D., Witold Ruzyllo, M.D., Paul De Lucca, Ph.D., KyungAh Im, Ph.D., Erin A. Bohula, M.D., D.Phil., Craig Reist, Ph.D., Stephen D. Wiviott, M.D., Andrew M. Tershakovec, M.D., M.P.H., Thomas A. Musliner, M.D., Eugene Braunwald, M.D., and Robert M. Califf, M.D., for the IMPROVE-IT Investigators*
Primary efficacy endpoint

Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke

Hazard ratio, 0.936 (95% CI, 0.89–0.99)
P=0.016

Simvastatin monotherapy vs. Simvastatin–ezetimibe
(Possible) **Evidences** for non-statin drug use

- IMPROVE-IT
- PCSK-9 inhibitors
  (OSLER & ODYSSEY LONG TERM)
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
The role of non-statin therapies

Adulthood ≥21 years of age with clinical ASCVD, on statin for secondary prevention

Adulthood ≥21 years of age with baseline LDL-C ≥190 mg/dL (not due to secondary modifiable causes), on statin for primary prevention

Adults aged 40-75 years without clinical ASCVD but with diabetes and baseline LDL-C 70-189 mg/dL, on statin for primary prevention

Adults aged 40-75 years without clinical ASCVD or diabetes, with baseline LDL-C 70-189 mg/dL and an estimated 10-year risk for ASCVD of ≥7.5%, on statin for primary prevention

FACTORS TO CONSIDER
- Adherence and lifestyle
- Statin intolerance
- Control of other risk factors
- Clinician-patient discussion regarding potential benefits, potential harms, and patient preferences regarding addition of non-statin medications
- Percentage LDL-C reduction (may consider absolute LDL-C level achieved)
- Monitoring of response to therapy, adherence, and lifestyle

OPTIONAL INTERVENTIONS TO CONSIDER
- Referral to lipid specialist and registered dietitian nutritionist
- Ezetimibe
- Bile acid sequestrants
- PCSK9 inhibitors
- Mipomersen, lomitapide, LDL apheresis may be considered by lipid specialist for patients with familial hypercholesterolemia
Summary

• Choice of statin eligible patients using Pooled Cohort Equations

• Which is better? fixed dose vs. treat to target approach

• Non-statin therapies are non-effective?
Conclusion

Are recent cholesterol treatment guidelines still controversial?

YES!
Thank you!
Different risk assessment tools in different guidelines

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>Risk Assessment Tool</th>
<th>Population Cohorts</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACC/AHA</td>
<td>Pooled cohort equations (PCE)</td>
<td>USA (non-Hispanic Whites &amp; African-Americans)</td>
</tr>
<tr>
<td>CCS</td>
<td>Framingham risk score (FRS) for total CVD</td>
<td>USA</td>
</tr>
<tr>
<td>NICE</td>
<td>QRISK2</td>
<td>European</td>
</tr>
<tr>
<td>ESC/EAS</td>
<td>Systemic coronary risk evaluation (SCORE)</td>
<td>European</td>
</tr>
<tr>
<td>NLA</td>
<td>Consider 10yr-FRS, 30yr- FRS, or PCE</td>
<td>USA</td>
</tr>
</tbody>
</table>
# Efficacy of statins in Asians

Clinical trials of statin therapy in Asian patients: lipid-lowering efficacy

<table>
<thead>
<tr>
<th>Trial</th>
<th>No.</th>
<th>Locale</th>
<th>Statin (Dose, mg)</th>
<th>Mean % LDL</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Randomized</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASIA⁶</td>
<td>157</td>
<td>Multiple*</td>
<td>Atorvastatin (10–20)</td>
<td>48%</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Simvastatin (10–20)</td>
<td>41%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Simvastatin (10)</td>
<td>33%</td>
<td></td>
</tr>
<tr>
<td>Chan et al²⁸</td>
<td>76</td>
<td>China</td>
<td>Atorvastatin (5–20)</td>
<td>36%–50%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>J-CLAS²⁹</td>
<td>121</td>
<td>Japan</td>
<td>Rosuvastatin (1–40)</td>
<td>36%–66%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Saito et al³⁰</td>
<td>112</td>
<td>Japan</td>
<td>Atorvastatin (10)</td>
<td>42%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Wang et al³¹</td>
<td>54</td>
<td>Taiwan</td>
<td>Rosuvastatin (1–4)</td>
<td>30–42%</td>
<td>0.001</td>
</tr>
<tr>
<td>Yamamoto et al³²</td>
<td>60</td>
<td>Japan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Open label</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GOALLS⁹,³³</td>
<td>198</td>
<td>Multiple†</td>
<td>Simvastatin (20, 40, 80)</td>
<td>41%</td>
<td></td>
</tr>
<tr>
<td>Itoh et al³⁴</td>
<td>201</td>
<td>Japan</td>
<td>Simvastatin (5)</td>
<td>28%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mabuchi et al³⁵</td>
<td>37</td>
<td>Japan</td>
<td>Rosuvastatin (10–40)</td>
<td>49%–57%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>STATT³⁶</td>
<td>133</td>
<td>Multiple†</td>
<td>Simvastatin (20, 40, 80)</td>
<td>45%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Teramoto et al³⁷</td>
<td>212</td>
<td>Japan</td>
<td>Fluvastatin (20, 30, 40)</td>
<td>29%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tomlinson et al³⁸</td>
<td>31</td>
<td>Hong Kong</td>
<td>Fluvastatin (20, 40)</td>
<td>26%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Yoshida et al³⁹</td>
<td>22</td>
<td>Japan</td>
<td>Simvastatin (20)</td>
<td>40%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>