Guidelines for Lipid Management in 2014

William Virgil Brown, MD, FNLA*
What is the purpose of clinical guidelines?

Improve the art of treating or preventing disease in the individual patient.

Clinical guidelines are not for public health applications or guiding treatment of large groupings of patients.

They are meant to help in dealing with a set of problems brought by a specific patient.
Guidelines should be provided by OPINION of EXPERTS:

1. That opinion should be derived from a fundamental understanding of the theory of the disease process. The theory should be scientifically developed and refined by repeated experimentation.

2. The theory guides hypothesis testing and interpretation of all observational and experimental results.

3. A logical outgrowth of the evolving theory will guide definitions of targets and goals into the future as well as the development of new modalities of treatment.
We have a well developed Theory: ApoB containing lipoproteins drive atherosclerotic lesions

- Cholesterol found in atherosclerotic lesions
- Dietary cholesterol produced lesions in animals
- Familial hypercholesterolemia and CVD
- Community based studies demonstrate relationship of plasma cholesterol with CVD
- Relevance of blood lipoproteins to CVD
- Increased dietary saturated fat and cholesterol associated with plasma cholesterol and CVD.
- Multiple interventions demonstrate that reduction in apoB containing lipoproteins reduces atherosclerosis.
Multiple Factors May Contribute to Coronary Heart Disease Risk

NONMODIFIABLE
Aging
Gender
Family History

MODIFIABLE
Atherogenic Diet
Elevated Blood Pressure
Diabetes
Hyperlipidemia
Obesity
Physical Inactivity
Smoking

Guidelines must be sellable.

The physician and the patient must believe:
• that you can define the problem
• you understand the issues
• issues are both qualitative and quantitative
• you can offer feasible effective and safe therapy
• you know the appropriate milestones of successful therapy.
## Guideline Terminology

**Objective:** Prevention of clinical events due to atherosclerosis.

**Target of treatment.**

**Goals of treatment.**

- What you treat.
- How aggressively you treat.
Choosing a Target for Treatment

Most Guidelines require the TARGET to have convincing scientific evidence of causation and to respond to feasible therapy:

1. Community based association with cardiovascular event rates related to atherosclerosis (CHD or CHD death)

2. Evidence that a change in the risk factor produces effective reduction in vascular events (RDB Clinical Trials)

3. Available treatment modalities that allow adjustment of the specific risk factor to a level that is effective

4. Method of measurement that is precise, accurate and generally available.
Lipid Related Risk Factor Targets

**Clinical lipid measures that have been documented as targets:**

- LDL- cholesterol
- Non-HDL cholesterol (Total C – HDL-C)

Confirmed by multiple RDB Clinical Trials.

**Good future candidates:**
- Apo B and LDL particle number
- Lp(a)
Choosing a Goal for Guidelines

Considerations:

1. The set of specific independent measures that add to the estimate of incidence of chosen endpoints (i.e. MI and CHD death).
2. How great is the risk?
   - Estimation of the rate of major events.
   - Examples:
     - The Framingham Risk Score
     - The Reynolds Score
     - Modified by – Diabetes, FamH, Lp(a), CVD events
3. The time frame of interest (10 years or lifetime).
4. Clinical trials that confirm safety
5. The societal comfort level with an event rate without treatment (5%, 10%, 20%).
ATP III Guidelines: LDL-C Goals and Cut Points for Therapy

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>LDL-C Goal* (mg/dL)</th>
<th>LDL-C to Consider Drug Therapy (mg/dL)</th>
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</thead>
<tbody>
<tr>
<td>Low Risk</td>
<td>&lt;160</td>
<td>≥190**</td>
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<tr>
<td>0-1 Risk Factor</td>
<td></td>
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</tr>
<tr>
<td>Moderate Risk</td>
<td>&lt;130</td>
<td>≥160</td>
</tr>
<tr>
<td>≥2 Risk Factors; 10-Year Risk &lt;10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderately High Risk</td>
<td>&lt;130</td>
<td>≥130</td>
</tr>
<tr>
<td>≥2 Risk Factors; 10-Year Risk 10%-20%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High Risk</td>
<td>&lt;100</td>
<td>≥130†</td>
</tr>
<tr>
<td>CHD or CHD Risk Equivalents; 10-Year Risk &gt;20%</td>
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*Lifestyle changes should be initiated when LDL-C level is at or above goal; **160-189 mg/dL LDL-C-lowering drug optional; †100-129 mg/dL LDL-C-lowering drug optional; Moderate terms incorporated per subsequent update. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. JAMA. 2001;285:2486-2497.
LDL-C Goals for High-Risk Patients Have Become More Intensive Over Time

- As part of therapeutic lifestyle changes, including diet, LDL-C treatment goals for high-risk patients have been lowered over time.

<table>
<thead>
<tr>
<th>Year</th>
<th>Goal:</th>
<th>Notes</th>
</tr>
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<tbody>
<tr>
<td>1988 ATP I</td>
<td>&lt;130 mg/dL(^1)</td>
<td></td>
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<tr>
<td>1993 ATP II</td>
<td>&lt;100 mg/dL(^2)</td>
<td></td>
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<tr>
<td>2001 ATP III</td>
<td>&lt;100 mg/dL(^3)</td>
<td></td>
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<tr>
<td>2004 ATP III Update</td>
<td>&lt;100 mg/dL(^4)</td>
<td><strong>Very-high-risk pts(^a)</strong> Optional goal: &lt;70 mg/dL(^4)</td>
</tr>
<tr>
<td>2006 2(^o) AHA/ACC</td>
<td>&lt;100 mg/dL(^5)</td>
<td><strong>High-risk pts</strong> Reasonable goal: &lt;70 mg/dL(^5)</td>
</tr>
<tr>
<td>2010 ADA</td>
<td>&lt;100 mg/dL(^6)</td>
<td><strong>Overt CVD</strong> &lt;70 mg/dL(^6)</td>
</tr>
</tbody>
</table>

**Definition of high-risk or highest-risk patient:**

- ATP I: definite CHD or 2 other CHD risk factors\(^1\)
- ATP II: prior CHD or other atherosclerotic disease\(^2\)
- ATP III and the 2004 update: CHD or CHD risk equivalents\(^3,4\)
- 2\(^o\) AHA/ACC 2006: established coronary and other atherosclerotic disease\(^5\)
- ADA 2010: overt CVD\(^6\)

\(^a\)Factors that place a patient at very high risk are multiple components of the metabolic syndrome, established CVD plus any of the following: multiple major risk factors (especially diabetes), severe and poorly controlled risk factors (eg, cigarette smoking), multiple components of the metabolic syndrome (especially TG \(\geq 200 \text{ mg/dL} + \text{ non–HDL-C} \geq 130 \text{ mg/dL with HDL-C} < 40 \text{ mg/dL}), and recent acute coronary syndromes.\(^4\)

Related and Treatable Factors

- Diabetes (elevated FPG)
- Higher Triglycerides
- Lower HDL-C
- Blood pressure
- Obesity

“The Metabolic Syndrome”
Target: Non-HDL-C

Incorporates:

- the problems of elevated VLDL and the distortions of particle size and number.
- part of the impact of low HDL-C
- non fasting blood samples
- no added costs (total cholesterol – HDL-C)
- simple
Cardiovascular Death in USA
(Over 85% arteriosclerosis)

Deaths from Cardiovascular Disease
United States: 1900–2006

Percentage Breakdown of Deaths from Cardiovascular Diseases
United States: 2006 (Preliminary)

Source: NCHS.
Note: Cardiovascular disease does not include congenital heart disease.

*Not a true underlying cause. Heart failure, any mention mortality was 282,754 in 2006.
Source: NCHS.
Note: May not add to 100% due to rounding.
Mortality from ASCVD In USA (over 10 years)

- All CVD: 31% decrease
- CAD: 38% decrease
- Stroke: 36% decrease
Trends in cardiovascular procedures, United States: 1979–2010

CATHS

CABG

PCI

Procedures in Thousands

Note: Inpatient procedures only. Source: National Hospital Discharge Survey, NCHS, and NHLBI.
The Evidence Changes

- New interventional trials demonstrate extension of benefit at lower target levels.
  - *HPS, TNT, Prove IT*
- Secular drifts in population characteristics
  - *Obesity, diabetes*
- New markers of risk are discovered
  » *CRP, Lp(a), PLA2*
- New susceptible groups are recognized
  - Women, South Asians, Aboriginals and S. Pacific Islanders
ESC/EAS Guidelines for the Management of Dyslipidemias

2011

European Heart Journal & Journal of Atherosclerosis

1. Redefined risk strategies with useful tools for practice
2. Maintained LDL-C as primary target but added others
3. Set lipoprotein goals of treatment related to risk status of patients
Major Risk Factors:
- 45yrs M,
- >55 yrs W,
- high blood pressure,
- DM,
- smoking,
- family hX of CHD,
- HDL−C <40 mg/dL.
### IAS Panel Members

<table>
<thead>
<tr>
<th>Members</th>
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<tbody>
<tr>
<td>Scott M. Grundy (Chair)</td>
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<tr>
<td>Hidenori Arai</td>
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<tr>
<td>Philip Barter</td>
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<tr>
<td>Thomas P. Bersot</td>
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<td>D. John Betteridge</td>
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<td>Rafael Carmena</td>
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<td>Ada Cuevas</td>
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<td>Michael H. Davidson</td>
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<td>Jacques Genest</td>
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<td>Y. Antero Kesäniemi</td>
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<td>Shaukat Sadikot</td>
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<td>Raul D. Santos</td>
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<td>Andrey Susekov</td>
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<tr>
<td>Rody Sy</td>
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<tr>
<td>Lale Tokgozoglu</td>
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<tr>
<td>Gerald F. Watts</td>
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<td>Dong Zhao</td>
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Purposes of Position Paper

- To amplify existing national guidelines
- Not to replace national guidelines
- To offer an international framework for future guideline development
- To provide a simplified approach to dyslipidemia management
- To emphasize lifestyle approaches to prevention of cardiovascular diseases
International Position Paper

- Primary prevention
  - Randomized controlled trials
  - Epidemiology
  - Genetics
  - Other lines of evidence
- Secondary prevention
  - Mainly randomized controlled trials
## Criteria for Clinical Diagnosis of the Metabolic Syndrome

<table>
<thead>
<tr>
<th>Measures</th>
<th>Categorical Cut Points</th>
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<tbody>
<tr>
<td>Elevated Waist Circumference</td>
<td>Population- and country-specific definitions</td>
</tr>
<tr>
<td>Elevated triglycerides</td>
<td>( \geq 150 \text{ mg/dL} ) (1.7 mmol/L)</td>
</tr>
<tr>
<td>Reduced HDL-C</td>
<td>(&lt; 40 \text{ mg/dL} ) (1.0 mmol/L) in males</td>
</tr>
<tr>
<td></td>
<td>(&lt; 50 \text{ mg/dL} ) (1.3 mmol/L) in females</td>
</tr>
<tr>
<td>Elevated blood pressure</td>
<td>Systolic ( \geq 130 ) and/or diastolic ( \geq 85 ) mm Hg</td>
</tr>
<tr>
<td>Elevated fasting glucose</td>
<td>( \geq 100 \text{ mg/dL} )</td>
</tr>
</tbody>
</table>
Innovations-2

- Assigning priority to long-term risk categories over short-term risk
- Adjustment of risk estimation according to baseline risk of different nations or regions
- Primary emphasis on lifestyle intervention; secondary emphasis on drug therapy
2013 ACCF/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults

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

Circulation November 2013
Critical Questions regarding cholesterol management.

• The panel was asked to answer three critical questions (CQ).
• 1. Whom do you treat?
• 2. With what treatment?
• 3. How intensively do you treat?
Data Considered in Evidentiary Review

- Randomized clinical trials published between 1995 and 2009 or until the panel deliberations began.
- Publications were defined by a protocol of desirable traits and selected by staff of a contracting service.
- Publications that did not meet the standards were not considered.
Critical Questions Regarding Cholesterol Management: ACCF/AHA Answers

• Whom do you treat?
  – Answer:

  1. With established atherosclerosis or diabetes mellitus if:
     age 40 to 75 years and LDL-C > 70mg/dL (1.8 mmol/L)
  2. LDL-C of 70 to 189 mg/dL (1.8 to 5.0 mmol/L) with estimated 10 year risk of > 7.5%.
  3. If age > 21 yrs and LDL-C > 190 mg/dL
  4. Consider treating triglycerides > 500 mg/dL
Critical Questions Regarding Cholesterol Management: ACCF/AHA Answers

With what treatment?

Moderate or high dose statins.
3. How intensively do you treat?

Answer:
Achieve a 50% reduction
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 ≥21 years of age and a candidate for statin therapy

Yes → Clinical ASCVD and age ≥75 y

No →

LDL-C ≥190 mg/dL

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

No →

Diabetes type 1 or 2 and age 40-75 y

Yes → Moderate-intensity statin

No →

Estimate 10-y ASCVD Risk

≥7.5% estimated 10-y ASCVD risk and age 40-75 y

Yes → Moderate-to-high intensity statin

No →

ASCVD prevention benefit of statin therapy may be less clear in other groups. Consider potential ASCVD risk reduction benefits and for adverse effects, drug-drug interactions, and patient preferences for treatment.
Question # 1

What is the evidence for setting specific LDL-C and non-HDL-C goals of treatment for the secondary prevention of ACVD?

Answer:
The evidence is insufficient to justify this. Do not recommend.
Question # 2

What is the evidence for setting specific LDL-C and non-HDL-C goals of treatment for the primary prevention of ACVD?

Answer:
The evidence is insufficient. Do not recommend.
What is in the new guidelines?

• **Future Updates to the Blood Cholesterol Guideline** — This is a comprehensive guideline for the evidence based treatment of blood cholesterol to reduce ASCVD risk. Future updates will build on this foundation to provide expert guidance on the management of complex lipid disorders and incorporate refinements in risk stratification based on critical review of emerging data.
Case study:
Mr. Jones, age 55 years, has an LDC- of 175 mg/dL one month after an angioplasty. You prescribed rosuvastatin 20 mg/d. He returns after 8 weeks. Reports taking every dose prescribed. His LDL-C has fallen to 132 mg/dL (25%).

His question: How am I doing?
Would you say:
1. You are doing great since you are taking your statin.
2. Not down by 50% so lets increase your statin.
3. You need more reduction than an additional 6% so I am going to add a second drug.
4. I want your LDL-C under 70 mg/dL and we are going to double the rosuvastatin and add ezetimibe.
Is there a Future of lipoprotein management?

How do we make a case for:

- Inhibiting bile acid absorption?
  - colesvelam, cholestyramine, colestipol
- Inhibiting cholesterol absorption?
  - ezetimibe
- Targeting PCSK-9?
  - Monoclonal antibodies or small molecules
- Inhibiting LDL Synthesis?
  - Antisense oligonucleotides (ASO)
Thank you for your attention.