A Systemic Approach to Lipid Management
Making Sense of the Fatty Debate
M Ranu Muttreja MD
Aria Jefferson Health
October 8, 2017

Historical Perspective
Lipid Hypothesis

• Early 1900’s Anitschkow fed rabbits purified cholesterol
  – First link between cholesterol and vascular damage

• 1940’s Gofman identified components of cholesterol

• 1948- Formation of the National Heart, Lung and Blood Institute (NHLBI)
  – Began to follow people aged 30-62 in Framingham, MA
    • Looked at smoking, high blood pressure, high blood cholesterol

• 1955 Ansel Keys suggested importance of large scale clinical trials with diet and health
  – 1958-Seven Countries Study
    • Linked high intake of dietary cholesterol to heart disease regardless of cultural background

• 1961-NHLBI reported high blood cholesterol as risk factor
Historical Perspective
Lipid Hypothesis

• 1950’s- Laurance Kinsel (UK) and Edward Ahrens (NY) showed replacing saturated fats with unsaturated fats reduced blood cholesterol
  – 1966 Paul Leren Oslo Study
  – 1969 Wadsworth Veterans Administration Hospital Study
  – 1968 Finnish Mental Hospitals Study

• 1973-Joe Goldstein first to genetically classify lipoproteins in blood
  – 1970’s-80’s – collaborated with Michael Brown and studied the genetic regulation of cholesterol metabolism
  – 1985 Nobel Prize in Physiology or Medicine

• 1973 Coronary Primary Prevention Trial (CPPT) by NHBI started
  – Published in early 1980’s Lowering blood cholesterol with cholesteryamine lead to reduction in heart attacks

Historical Perspective
Statin Development

• 1970’s  Akiro Endo purified mevastatin from fermentation broth of Penicilium citrinum
  – Animal and clinical trial showed good promise but high dose in dogs showed toxicity

• 1978 Alfred Aberts (Merck) purified lovastatin from fermentation broth of Aspergillus terrus
  – Merck researches synthesized simvastatin-side chain ester analog of lovastatin

• Warner Lambert researchers synthesized atorvastatin – substituted H pyrolle compound that was 3-4 times as potent as lovastatin in rat models
Historical Perspective
Statin Development

• 1987 - Lovastatin (Mevacor) approved by FDA
  – Peak annual sales initially of >$1 billion
• 1988 Simvastatin (Zocor) approved in Sweden
• 1991 Pravastin (Pravachol)
• 1994 Fluvastatin (Lescol)
• 1997 atorvastatin (Lipitor)
• 1998 cerivastatin (Baychol)
• 2003 rosuvastatin (Crestor)
• 2009 pitavastatin (Livalo)

Historical Perspective
Lipid Guidelines

• 1985-National Cholesterol Education Program (NCEP)

• 1988 Adult Treatment Panel (ATP)
  – Total cholesterol as primary screening test
  – LDL treatment goal of <130 mg/dl in patients with CHD or two or more risk factors
  – Nicotinic Acid and Bile Acid sequestrants as drugs of choice
  – Statin therapy third line agent
Historical Perspective
Lipid Guidelines

• 1993-ATP II
  – LDL < 160 mg/dl for patients at low CHD risk
  – LDL < 130 mg/dl for patients at moderate risk
  – LDL < 100 mg/dl for patients at high risk
  – Age was included as risk factor (men > 45, women > 55)
  – Statin therapy was treatment of choice

Historical Perspective
Lipid Guidelines

• 2001 ATP III
  – LDL treatment goal of < 100 mg/dl in patients with CHD or CHD risk equivalents
  – Added risk calculator - 10 year risk of CHD event from Framingham Risk Score
  • 10 year risk > 20% and no CHD or CHD risk equivalent
  – Measure LDL, HDL and triglyceride levels
  – Statin treatment of choice with combination therapy to reach goals

• 2004 ATP III update
  – LDL goal < 70 mg/dl for very high CHD risk
  – Need 30-40% reduction in high and mod high risk persons
Mean age-adjusted LDL-C trends 2001–2011 in the United States: Analysis of 105 million patient records from a single national diagnostic laboratory

US age-standardized death rates attributable to CVD, 2000 to 2010
Guideline Leadership Transition

- 2013 NHLBI/NCEP asked American Heart Association (AHA) and American College of Cardiology (ACC) to assume governance and management of lipid management guidelines.

Randomized Controlled Trials (RCT)

- Systematically test effect(s) of an intervention on pre-specified outcomes in defined populations.
- Minimizes confounding.
- Study populations are often not diverse.
- Exclusion criteria may hamper physician’s ability to apply results to real-world patients.
- Most are designed to gain regulatory registration for pharmaceutical agents.
- Lifestyle trials, studies of generic drugs or of those produced by smaller companies may be under-represented in RCT due to inadequate financial support.
Observational Epidemiologic Studies

- Worldwide in scope and may assess ASCVD risk across populations
- Cohort studies evaluate mortality and morbidity within populations
- Confounding may occur even after matching, stratification, and multivariate adjustment because of measurement error or unmeasured or unknown risk factors

Genetic Studies

- Genetic epidemiology reduces the likelihood of confounding by focusing on single variables: genetic mutations
- Identification of specific mutations may serve to generate hypotheses for other types of trials
- Often limited in patient selection and costly
Recent Lipid Guidelines

- 2013 AHA/ACC Guideline on the Treatment of Cholesterol
- National Lipid Association (NLA) Recommendations for Managing Dyslipidemia: Part 1, 2014; Part 2, 2015; annual updates
- European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) Guideline for Management of Dyslipaemias, 2011
- 2012 Update of the Canadian Cardiovascular Society (CCS) Guidelines for the Diagnosis and Treatment of Dyslipidemia

Guidelines Evidence Base

**ACC/AHA**
- Randomized controlled trials (RCT) of statin therapy
- Meta-analyses of RCT

**NLA, ESC, CCS**
- RCT of statins and non-statin drug therapy
- Meta-analyses of RCT
- Observational epidemiologic studies
- Genetic studies
- Metabolic studies
- Mechanistic studies
Central Focus of Guideline

**ACC/AHA**
- Identification of patient groups benefiting from statin therapy
- Initiation and maintenance of high or moderate intensity statin therapy
- Abandonment of lipid goals
- Avoidance of non-statin therapy because of “unfavorable risk/benefit ratio.”

**NLA, ESC, CCS**
- Identification of an individual patient’s ASCVD risk based on clinical parameters and risk factors
- Initiation of ASCVD risk-based lipid-lowering therapy
- Maintenance of lipid goals to assess effective reduction of atherogenic lipoproteins and enhance adherence
- Use of high or moderate dose statins, ± non-statins, if necessary, to achieve goals

**ACC/AHA Statin Benefit Groups**

H=High intensity statin; M=Moderate intensity statin

- Individuals with clinical ASCVD without New York Heart Association class II-IV heart failure or receiving hemodialysis (H preferred; M if age >75 or if not candidate for H).
- Individuals with primary elevations of LDL-C ≥190 mg/dl (H preferred; M if not candidate for H).
- Individuals age 40-75 years with diabetes, and LDL-C 70-189 mg/dl without clinical ASCVD (M if 10 yr risk <7.5%; H if ≥7.5%).
- Individuals without clinical ASCVD or diabetes, who are age 40-75 years with LDL-C 70-189 mg/dl, and have an estimated 10-year ASCVD risk of ≥ 7.5% using Pooled Cohort Equations (M or H).
High- and Moderate-Intensity Daily Statin Therapy

- High Intensity (Lowers LDL-C ≥ 50%)
  - Atorvastatin 40-80 mg
  - Rosuvastatin 20-40 mg

- Moderate Intensity (Lowers LDL-C 30-50%)
  - Atorvastatin 10 (20) mg
  - Rosuvastatin (5) 10 mg
  - Simvastatin 20-40 mg
  - Simvastatin 80 mg*
  - Pravastatin 40 (80) mg
  - Lovastatin 40 mg
  - Fluvastatin XL 80 mg
  - Fluvastatin 40 mg 2x/day

**Pitavastatin 2–4 mg**

**Bold = Tested in RCT and reviewed by Expert Panel**

**Blue = Not tested in RCT reviewed by Expert Panel**

ACC/AHA Guidelines
Perspective on Statin Therapy

- Statin intensity trials showed clear benefit for high intensity versus moderate intensity statins

- Because fixed doses, not dosage titrations, were employed, one should not assume that a dosage titration strategy is correct or that addition of non-statins to achieve low LDL-C is indicated
ACC/AHA Perspective on Non-Statin Lipid Drug Therapy

• Non-statin drugs without demonstrated ASCVD risk reduction may favorably alter lipids but have an unfavorable risk/benefit ratio
  – Niacin in AIM-HIGH and HPS-2 THRIVE
  – Fibrates in ACCORD-Lipid, FIELD
  – Lack of ASCVD event end-point data on ezetimibe
  – CETP inhibitors torcetrapib and dalcetrapib
• The use of non-statin drugs should generally be avoided

AHA/ACC Guidelines
Removal of LDL goals

• No evidence to support treat to target paradigm
• No RCT have compared different LDL goals
• Potential problems with treat to target strategy
  – Undertreatment if LDL already at goal
  – Addition of non-statin drugs to achieve pre-specified goals may increase risk without decreasing ASCVD event rates
  – May unnecessarily increase provider visits and costs
**Controversies of 2013 ACC/AHA**
**Pooled Cohort CV risk calculators**

- Would increase statin candidates by 12 to 45 million
  - Pecina et al (NEJMC 2014) estimated 87.4% of men and 53.6% of women age 60-75 now eligible for statin therapy

- Validation attempts showed conflicting results
  - Ridker et al (Lancet 2013) — overestimation of risk by 75-150% when applied to Women’s Health Study and Physician’s Health Study
  - Munter et al (JAMA 2014) similar results in predicted vs actual 5 year risk in REGARDS study

**Controversies of 2013 ACC/AHA**
**Removal of LDL Goals**

- Concern over message to patients and providers
  - Are cholesterol levels no longer important
  - Role of LDL goals in patient motivation
  - Providers not follow up on patients lipid response
Controversies of 2013 ACC/AHA

Removal of LDL Goals

• Do we need a target to support adherence/lifestyle changes

• Does a lack of RCT evidence mean lack of benefit
  – Decades of clinical experience with treating to target

• Effect on current performance measures
  – Will quality assurance measures follow these guidelines

Controversies of 2013 ACC/AHA

• Management of other patient groups
  – Age <40 or >75 without clinical ASCVD
  – 10 year risk of 5-7.5%
  – LDL>160 or other primary hyperlipidemias

• Additional risk assessment markers
  – High sensitivity C reactive protein
  – Ankle-brachial index
  – Coronary artery scores
  – Family history of premature CHD
  – Elevated lifetime risk of ASCVD
NLA ASCVD Risk Category Criteria

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Criteria</th>
</tr>
</thead>
</table>
| Very High     | • ASCVD  
                • Diabetes mellitus (type 1 or 2)  
                • ≥2 other major ASCVD risk factors; or  
                • Evidence of end-organ damage |
| High          | • ≥3 major ASCVD risk factors  
                • Diabetes mellitus (type 1 or 2)  
                0-1 other major ASCVD risk factor, and  
                • no evidence of end-organ damage  
                • Chronic kidney disease Stage 3B or 4  
                • LDL-C ≥190 or non-HDL-C ≥220 mg/dL |
| Moderate      | • 2 major ASCVD risk factors  
                • For specific clinical features, high  
                quantitative risk score or specific  
                biomarker levels, consider reclassification  
                to high risk |
| Low           | • 0-1 major ASCVD risk factor  
                • For specific clinical features, consider  
                reclassification to moderate risk |
NLA ASCVD Risk Categories, Levels for Consideration of Drug Therapy and Treatment Goals

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Consider Drug Therapy</th>
<th>Treatment Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-HDL-C /LDL-C Goal (mg/dL)</td>
<td>Non-HDL-C/LDL-C Goal (mg/dL)</td>
</tr>
<tr>
<td>Very-high</td>
<td>≥100</td>
<td>&lt;100</td>
</tr>
<tr>
<td></td>
<td>≥70</td>
<td>&lt;70</td>
</tr>
<tr>
<td>High</td>
<td>≥130</td>
<td>&lt;130</td>
</tr>
<tr>
<td></td>
<td>≥100</td>
<td>&lt;100</td>
</tr>
<tr>
<td>Moderate</td>
<td>≥160</td>
<td>&lt;130</td>
</tr>
<tr>
<td></td>
<td>≥130</td>
<td>&lt;100</td>
</tr>
<tr>
<td>Low</td>
<td>≥190</td>
<td>&lt;130</td>
</tr>
<tr>
<td></td>
<td>≥160</td>
<td>&lt;100</td>
</tr>
</tbody>
</table>

For patients with ASCVD or diabetes mellitus, consider use of moderate or high intensity statins, irrespective of baseline atherogenic cholesterol levels.

NLA Perspective on Statin Therapy

- Statin therapy is the most potent and evidence-based approach to lowering atherogenic lipoproteins (non-HDL-C and LDL-C)
- Statin intensity trials showed clear benefit for high-intensity versus moderate-intensity statins
- Broad-based evidence supports “lower is better” concept, and provides an opportunity for clinicians to address residual risk above that addressed by appropriately-dosed statin therapy
Is there an LDL threshold to treat?
NNT analysis

<table>
<thead>
<tr>
<th>10 Year CVD Risk</th>
<th>Pretreatment LDL Cholesterol(change on treatment)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>77(-7%)</td>
</tr>
<tr>
<td>5</td>
<td>412</td>
</tr>
<tr>
<td>7.5</td>
<td>274</td>
</tr>
<tr>
<td>10</td>
<td>206</td>
</tr>
<tr>
<td>20</td>
<td>103</td>
</tr>
</tbody>
</table>

-40 mg/dl decrease LDL-C=22% in CVD
-Atorvostatin 20-80 mg to a goal LDL-C 70 mg/dl
-European Qrisk model to assign 10 year CVD risk

Soran, H et al Eur Heart J 2015

Efficacy of Intensive Lowering of LDL-C in Subjects with Low Baseline LDL-C

- Meta-analysis of RCT’s of >1000 participants and ≥2 years treatment duration of more versus less intense statin trials involving 169,138 subjects
- The major vascular event reduction, among those with baseline LDL-C <77mg/dL per further 39 mg/dL reduction was 29% (99% CI 2-48, p=0.007)
Very Low LDL-C and Non-HDL-C in Statin Trials and Major CVD Event Risk

How low is too low?

- Meta analysis statin trials showed no adverse events
  - Individual patient data on 40,000+ patients followed at least 4 years
  - Most patients in 50-70 LDL range
- PCSK9 inhibitor trials show no adverse events in LDL<40
  - Studies only 1-1.5 years
- Await long term outcome studies with PCSK9 inhibitors
HDL story

• Epidemiology
  – HDL-C has an inverse relationship with ASCVD

• Science
  – HDL particle includes many proteins and lipids
  – Favorable effects by modulation of
    • Inflammation
    • Oxidation
    • Endothelial function
    • Insulin secretory capacity
    • Removal of free cholesterol from peripheral cells

HDL story

• Low HDL-C levels not consistently associated with premature ASCVD
  – Apoa-1 Milano variant has very low ASCVD risk

• High HDL-C levels are not consistently associated with atheroprotection
  – Genomic evidence shows that a mutation in the scavenger receptor (pulls cholesterol out of HDL-C) increased HDL-C but also increases ASCVD risk

• Several randomized studies that raise HDL-C levels have failed to reduce to risk of ASCVD
  – Niaspan
    • AIM HIGH 2011
    • HPS2-THRIVE 2013
  – CTEP inhibitor
    • Torcetrapib
    • Daltetrapid
    • evacetrapid
Residual Risk

• Despite treatment of LDL-C to goal, still is a high residual risk in all studies

• Non HDL
  – incorporates LDL and other atherogenic proteins including triglycerides
  – Discordance (>30 difference btwn non HDL and LDL-C) has increased risk compared with concordance (<30)
  – Negative studies looking at modifying HDL and triglycerides had study population averaged lipid profiles showed concordance between non-HDL and LDL-C
    • Look at subgroups of discordant non-HDL and LDL-C was a outcome benefit

• Lp(a)
  – genetically determined
  – Premature CAD, family history of premature CAD, FH, recurrent events on high intensity statin
  – >50 mg/dl considered a positive marker for more intensity treatment
  – No studies to date showing lowering Lp(a) decreased CVD

NLA Perspective on Non-Statin Lipid Drug Therapy

• If non-HDL-C and LDL-C goals are not achieved with maximal tolerated statin therapy, the addition of non-statin therapy should be considered to lower atherogenic cholesterol levels and to achieve goals
  – Doctors can be instructed not to use niacin in patients on aggressive statin regimens
  – Ezetimibe is safe and lowers atherogenic cholesterol, its use may be considered in selected patients with elevated non-HDL-C and/or LDL-C
  – Resins may be considered in selected patients
  – Meta-analyses of fibrate therapy in subgroups with atherogenic dyslipidemia suggest ASCVD risk reduction
Lipid Modification Treatment
Past-Present-Future

Mechanism of action of lipid lowering drugs
LDL Receptors (LDLRs) Play a Central Role in the Regulation of Plasma LDL-C

LDL = low density lipoprotein; LDLR = low density lipoprotein receptor

LDLRs Are Recycled After Delivery of LDL to Endosomes for Degradation

LDL = low density lipoprotein; LDLR = low density lipoprotein receptor
Future Trends

Biopharmaceuticals

- Sequence variants in the gene encoding for PCSK9 resulting in loss of function mutations
  - 28% reduction in LDL-C
  - 88% reduction in CHD risk
  - provide support for the value of long term low LDL-C in promoting CHD risk reduction

Repatha™ Binding to PCSK9 Prevents Degradation of the LDLR

Repatha® (evolocumab) Primary Hyperlipidemia in Patients with Clinical ASCVD – Study 2 (52 Week Trial)

| Study Design | Multicenter, double-blind, randomized placebo-controlled, 52-week trial
|             | After stabilization on background therapy, patients were randomly assigned to the addition of placebo or Repatha® 420 mg SC once monthly*

| Primary Endpoint | Mean % change from baseline in LDL-C at week 52
| Post lipid stabilization baseline characteristics for patients with ASCVD on atorvastatin 80 mg daily | Mean age = 59
|                                                         | Mean baseline LDL-C = 105 mg/dL
|                                                         | Gender = 40% women, 60% men

Effect of Repatha® on Lipid Parameters in Patients with ASCVD on Atorvastatin 80 mg with or without Ezetimibe 10 mg Daily (Mean % Change from Baseline to week 52 in Study 2)

- Placebo
- Repatha® 420 mg once monthly

Mean Difference: 
-54%

p < 0.0001

n = 135 patients with ASCVD who received protocol-determined background lipid-lowering therapy of atorvastatin 80 mg daily with or without ezetimibe 10 mg daily. Estimates based on multiple imputation model that accounts for treatment adherence. Error bars indicate 95% confidence intervals.

Repatha® (evolocumab) Prescribing Information. Amgen.
Common Themes between ACC/AHA and NLA

- Recommend concomitant healthy lifestyle habits
  - No smoking, weight control, physical activity, healthy eating
- Secondary prevention
- Consider familial hypercholesterolemia high risk
- Primary prevention in Type 2 Diabetes
- Recommend appropriate statin dosing as initial drug choice
- Require baseline assessment of ASCVD risk for at least 10 years

Common Themes Between ACC/AHA and NLA

- Risk calculators aid in, but do not take the place of clinical judgment
- Whether or not lipid goals are set, regular lipid follow-up is warranted to assess adherence
- Patient engagement in preventive care decision making aids in long-term adherence
Differences

• Method of risk assessment for primary prevention
  – US Framingham vs pooled cohort equation
  – 10 year vs lifetime risk
• Use of LDL and or non-HDL
  – ACC/AHA LDL
  – NLA both
• Recommendation of appropriateness on non statin drugs
  – ACC- no real guidance as relied on RCT as of 2013
  – NLA, EAS, CCS- give recommendations using recent data
    • IMPROVE IT (2015)-studied ezetimide in addition to moderate dose statin
• Identifying high risk populations
  – Chronic Kidney Disease-NLA, CCS
  – Biomarkers (Lpa)- NLA and ESC/EAS

Central Focus of Guidelines:
Summary

• ACC/AHA
  – define statin benefit groups
  – risk/benefit discussion
  – use moderate or high-intensity statin therapy with lifestyle change as background therapy
  – generally avoid non-statin drug therapy
  – no lipid goals
• NLA
  – Identify ASCVD risk level
  – risk/benefit discussion
  – emphasize healthy lifestyle and use moderate or high-intensity statin therapy, and if necessary, adjunctive non-statin therapy, to lower atherogenic cholesterol
  – maintain lipid goals (non-HDL-C is favored lipoprotein target)
Lipid treatment October 2017

• Remember that these are just guidelines
  – ACC/AHA has no recommendation for people not in the 4 statin benefit group
  – ACC/AHA Guidelines released in 2013 using RCT data only
• Apply an evidence-based approach
  – New trials involving ezetimide, PCSK9 inhibitors and novel agents on the horizon
  – Understand the different types of trial and data
• Consider your patient population and Individualize treatment strategies
• Discuss risks and benefits with patients and include patient preferences in decision