**Where Inflammation Meets Lipids:**
Eliminating the Confusion about Cholesterol and Advanced Lipids

Lynn Cofer-Chase, MSN, RN, FNLA, FPCNA, FAHA
Clinical Lipid Specialist
Clinical Education Manager
Cleveland HeartLab Inc.

**Disclosure of Affiliations and Significant Relationships**

<table>
<thead>
<tr>
<th>Relationship</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consultant/Advisor</td>
<td>Amgen, Sanofi-Regeneron, American Egg Board</td>
</tr>
<tr>
<td>Employment</td>
<td>Cleveland HeartLab, Inc.</td>
</tr>
<tr>
<td>Board of Directors</td>
<td>President, Accreditation Council for Clinical Lipidology, Board Member, Foundation of the National Lipid Association</td>
</tr>
<tr>
<td>Speakers’ Bureau</td>
<td>American Egg Board</td>
</tr>
</tbody>
</table>

I will not discuss off label or investigational use in my presentation.

**Statement of the Problem**

- Heart Disease continues to be the #1 killer of American men and women
- The first symptom, too often, is sudden death
- Lipid, lipoprotein, and inflammatory biomarkers that identify people at risk are underutilized
American Heart Association (AHA)
(First Scientific Statement on Acute MI in Women – 2016)

• Cardiovascular Disease (CVD) is an equal opportunity killer
• Since 1984 the mortality burden has been significantly higher in women than in men
• 26% of women die within the year following their first myocardial infarction (MI) and 47% die within the 5 years that follow (Women ages 35-54 had increasing death rates 2000-2002)
• 64% of women who die suddenly of coronary heart disease (CHD) have no previous symptoms


Women Only Risk Factors
Women who have failed “natures stress test” by developing any of the following during pregnancy:

Preeclampsia
Gestational diabetes
Pregnancy-induced hypertension
are at a significantly higher risk of CVD events within the 5-10 years post pregnancy.

Be sure to include this on your history intake forms and aggressively look for (subclinical) disease in these women

L. Mosca et al. Circulation 2011. DOI:10.1161/CIR.0b013e31820faff8

High Incidence of Subclinical Disease

• 2016 study of 9,498 men and women enrolled in the Atherosclerosis Risk in Communities (ARIC)
  – No cardiovascular disease at baseline
  – Silent MI (SMI) defined by ECG-evidence of MI without clinically documented MI (CMI)
  – Median follow-up of 8.9 years
    317 (3.3%) developed SMI, 386 (4.1%) developed CMI
  – Both SMI & CMI were associated with ↑ CHD death & ↑ all cause mortality
• SMI represented >45% of incident MIs and was associated with poor prognosis

Zhang ZM et al. Circ 2016; DOI:10.1161/CIRCULATIONAHA.115.021177
86% of Heart Attacks Occur Where Blood Flow Has Been Good (i.e., No Warning Signs)

Lesions that cause a 50% stenosis or narrowing of the artery are not all the same!

Blocked Coronary Artery
Identifying Coronary Disease by Detecting Flow-Limiting Lesions

- Testing
  - Treadmill exercise
  - Radionuclide exercise
  - Radionuclide pharmacologic
  - Nuclear echocardiographic
- Angina
- Unstable angina
- Myocardial infarction
- CPR for sudden cardiac arrest

WAITING TO IDENTIFY FLOW-LIMITING LESIONS AS AN INDICATION FOR THERAPY IS NOT ACCEPTABLE!

If We are to AIM at PREVENTING EVENTS...

The paradigm of risk stratification must move from identification of obstructive atherosclerosis and beyond identifying risk factors.

We can proactively:
1. Look for signs of hidden (subclinical) disease
2. Identify where a patient falls on a risk spectrum
3. Intervene early in order to stop the disease process.

1. Pepine CJ et al. JACC 2015:66 (17);1918-1933.

2013 ACC/AHA Cardiovascular Risk Assessment Guidelines

- It is reasonable to assess traditional Atherosclerotic Cardiovascular Disease (ASCVD) risk factors every 4-6 years in adults 20-79 years of age who are free from ASCVD, and to estimate 10-year ASCVD risk every 4-6 years in adults 40-79 years of age without ASCVD.

*Free from evidence (diagnosed) obstructive CAD

Goff, D.G et al. Circulation on line. ISSN: 1524-4539 Nov 12, 2013
Individualized Risk Assessment Tools:

- Lp(a)
- Advanced lipids/lipoproteins (Apo B or LDL-P)
- Inflammation Tests (hsCRP, MACR, Lp-PLA₂, MPO)
- Coronary Artery Calcium (CAC)
- Carotid Intima Media Thickness (CIMT)

Importance of Family History

- ACC/AHA Risk Assessment Guideline states family history is an "independent contributor" to risk appraisal and "unequivocally" supports inclusion of family history for improved risk estimation.¹
- No reference in the ACC/AHA document recommends evaluating Lp(a), an inherited lipoprotein disorder which substantially increases CV risk and is endorsed by numerous other organizations.²

¹ Goff DC et al. Circulation 2013; DOI: 10.1161/01.cir.0000437741.48606.98
² Cofer-Chase, L. Journal Nurse Pract 2014; 10(5):293-301

Structure of Lp(a)

Lp(a) is an LDL-like particle with an apolipoprotein (a) attached. Apo (a): binds vascular matrix and cells, inhibits fibrinolysis, promotes smooth muscle cell activity. Lp(a) structure named after Danish pastry "kringle" with repeated (18-40) K4 loops (resembles plasminogen which has 1-5 kringle domains).

Why Assess Lipoprotein “little a” Lp(a)

- Lp(a) has positive predictive power that is additive to other measures of lipoprotein risk factors and Framingham risk factors
- Lp(a) is associated with ↑ CHD risk in a continuous matter without a threshold
- Lp(a)’s association with CHD risk is independent of LDL-C, non-HDL-C, and other CV risk factors


Lp(a) Measurement Methodologies and Cutoffs Vary

- Lp(a) total particle mass: ELISA, GGE
  - Desirable <30 mg/dL*
- Lp(a) protein mass: ELISA
  - Desirable <5 mg/dL
- Lp(a) cholesterol content: VAP
  - Desirable <10 mg/dL (no longer available)

*Use of a very high density of isoform insensitive antibodies and detection reagent ensure Lp(a) bound antibodies are detected providing a more accurate measurement. This method is recommended by the International Atherosclerosis Society (2010) and the National Lipid Association (2015).

National Lipid Association Statements re: Lp(a)

- Any patient with early disease not explained by the composite of other risk factors should be assessed
- Since family history is often inaccurate and the impact of other risk factors variable, one could argue that anyone presenting with vascular disease should have this
- Aggressive lowering of low-density lipoprotein (LDL-C) cholesterol is beneficial in those with elevated Lp(a) and LDL-C
- Lp(a) ≥50 mg/dL performed using an isoform-insensitive assay constitutes an additional risk factor

Implementing New Guidelines: Changing Paradigms for the Prevention of Cardiovascular Events

- 2013 ACC/AHA treatment recommendations led to confusion (because of the elimination of targets) for those who focus on wellness or treat patients with recurrent events.

- Implementation of a “hybrid” of recently published guidelines that includes information from randomized controlled trials plus recent guidelines from various expert groups based on other types of research is warranted.

1. Cofer-Chase, L. *Journal Nurse Pract* 2014; 10(5):293-301
2. Raymond, C et al. *Cleveland Clinic Med* 2014;81:11-19

“Interventional Prevention”

Prevention specialists now look “beyond traditional risk factors to include evaluating not only the presence of disease (e.g., structurally via CAC etc.) but are also attempting to determine “the presence of active metabolic derangements” by evaluating both lipoprotein and inflammatory biomarkers."}

1. Baum, SJ *JAMA* 2013;310:2201-2202
2. Cofer-Chase, L *Journal Nurse Pract* 2014; 10(5):293-301

Biomarkers that can help define cardiovascular risk

<table>
<thead>
<tr>
<th>Long-Term (Traditional) Risk</th>
<th>Mid-Term Risk</th>
<th>Near-Term Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard Lipid Panel</td>
<td>Advanced Cholesterol Assessment</td>
<td>Inflammation Tests</td>
</tr>
<tr>
<td>Total Chol, HDL, LDL, Trigs and Non-HDL-C</td>
<td>Apolipoprotein B, Apolipoprotein A1, and Apo B/Apo A1 ratio, Lp(a)</td>
<td>hsCRP, MACR, MPO, and Lp-PLA2</td>
</tr>
</tbody>
</table>

© Cleveland HeartLab, Inc. 2011 (adapted 2013 LCC)
Secondary Causes of Altered Lipids

- Uncontrolled diabetes
  - ↑ Non-HDL, ↑ Apo B, ↑ LDL, ↑ TG, ↓ HDL
- Hypothyroidism
  - ↑ Non-HDL, ↑ Apo B, ↑ LDL, ↑ TG
- Nephrotic Syndrome
  - ↑ Non-HDL, ↑ Apo B, ↑ LDL, ↑ TG ; ↑ Lp(a)
- Chronic renal failure
  - With hemodialysis - ↑ TG, ↓ HDL
  - S/P transplant - ↑ TG, ↑ TC
- Obstructive liver disease
  - ↑ TC

TG = triglycerides
HDL = high density lipoprotein
LDL = low density lipoprotein
Lp(a) = lipoprotein “little a”
TC = total cholesterol

LDL-C is NOT the Best Lipid Predictor for Cardiovascular Events

- Important to pay attention to the lipoproteins that carry cholesterol due to possible discordance between LDL-C and Apo B (LDL-P)¹
- July 2013 International Atherosclerosis Society¹ recommendations favor non-HDL-C as the major lipid target
  - Optimal levels world wide for primary prevention
    - LDL-C <100 mg/dL and non-HDL-C <130 mg/dL
  - Optimal levels for patients with ASCVD
    - LDL-C <70 mg/dL and non-HDL-C <100 mg/dL

International Atherosclerosis Society 2013 and the National Lipid Association 2015 Cholesterol Recommendations

<table>
<thead>
<tr>
<th></th>
<th>LDL-C</th>
<th>Non-HDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Prevention</td>
<td>&lt;100 mg/dL</td>
<td>&lt;130 mg/dL</td>
</tr>
<tr>
<td>Secondary Prevention</td>
<td>&lt;70 mg/dL</td>
<td>&lt;100 mg/dL</td>
</tr>
</tbody>
</table>

¹ Cofer-Chase L. Journal Nurse Pract 2014; 10(5):293-301

Why Test Beyond Standard Lipids in Adults?

• The Friedewald calculation of LDL-C is an indirect method of measurement\(^1\)
• LDL-C is not the best predictor of cardiac events\(^2,3\)
• Newer methodologies for measuring various lipoproteins are included in recommendations by the American College of Cardiology (ACC), American Diabetic Association (ADA), American Association of Clinical Endocrinologists (AACE), Canada, Europe, and the International Atherosclerosis Society (IAS)

Lipids/Lipoproteins ????

• What’s the difference?
  – Cholesterol is a lipid or fat-like substance that does not mix with water-based blood
  – The vehicles or particles that carry cholesterol in the blood are called lipoproteins

However…when assessing cardiovascular disease risk…

“It's really not about cholesterol. It's about the lipoproteins that carry cholesterol”

William Cromwell MD, FAHA, FNLA 2012

A high number of vehicles, not the number of people, portend increased risk…
Lipoprotein Subclasses

Diameter (nm)

Density (g/mL)

5 10 20 40 60 80 100

1.20 1.10 1.06 1.02 1.006 0.95

HDL2
HDL3
LDL
IDL
VLDL
Chylomicron Remnants
Chylomicrons

There is one Apo B on each atherogenic lipoprotein particle

Atherosclerosis Overview

- Atherosclerosis involves a cascade of events (mainly top to bottom of this list, but with some feedback in reverse)
  - High Apo B plus focal endothelial trauma (endothelial dysfunction)
  - ↑ infiltration of Apo B into the subendothelium (SE)
  - ↑ retention of Apo B into SE
  - ↑ modification of Apo B in SE
  - ↑ inflammation
  - Plaque rupture
  - Thrombosis (clot)
  - ↓↓↓ blood blow
  - Ischemic event

Cardiovascular Risk Increases With Increased Plasma Apo B Lipoproteins

Rationale for therapeutic lowering of Apo B lipoproteins: decrease the probability of inflammatory response to retention
Advantages of Measuring Apo B

- Apo B specifically identifies the particles that attach to and directly deliver cholesterol ester into the arterial intima and generate atherosclerosis.
- Apo B has four advantages over LDL-C
  - Superior to LDL-C for identification of CV risk
  - Includes **ALL** of the potentially atherogenic lipoproteins
  - Each atherogenic lipoprotein carries only one Apo B
  - Serum Apo B does NOT REQUIRE FASTING

Gleeson R, Davidson D. Lipidology a Primer 2010, p 49

2015 National Lipid Association
“Apo B is a root cause of atherosclerosis”

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Non-HDL-C</th>
<th>LDL-C</th>
<th>Apo B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>&lt;130</td>
<td>&lt;100</td>
<td>&lt;90</td>
</tr>
<tr>
<td>Moderate</td>
<td>&lt;130</td>
<td>&lt;100</td>
<td>&lt;90</td>
</tr>
<tr>
<td>High</td>
<td>&lt;130</td>
<td>&lt;100</td>
<td>&lt;90</td>
</tr>
<tr>
<td>Very high</td>
<td>&lt;100</td>
<td>&lt;70</td>
<td>&lt;80</td>
</tr>
</tbody>
</table>

Apo apo lipoprotein: LDL-C, low-density lipoprotein cholesterol; Non-HDL-C, non-high-density lipoprotein cholesterol; Apo B is a secondary, optional target of treatment.

This is consistent with those of the 2008 American Diabetes Association/American College of Cardiology Foundation


Atherogenic Dyslipidemia: Discordance Between LDL-C and LDL-P / ApoB / non-HDL-C

<table>
<thead>
<tr>
<th>TC</th>
<th>198 mg/dL</th>
<th>210 mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C</td>
<td>130 mg/dL</td>
<td>130 mg/dL</td>
</tr>
<tr>
<td>HDL-C</td>
<td>40 mg/dL</td>
<td>30 mg/dL</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>148 mg/dL</td>
<td>180 mg/dL</td>
</tr>
<tr>
<td>ApoB</td>
<td>95 mg/dL</td>
<td>118 mg/dL</td>
</tr>
</tbody>
</table>

Large, buoyant LDL (pattern A)

Cholesterol

- Same LDL-C
- Different non-HDL-C, ApoB, and LDL-P

Small, dense LDL (pattern B)
Apo B – Preferred Target of Statin Rx

Evidence based study published Sept 2016 concludes:
“More complete examination of the evidence reveals that Apo B is a more accurate marker of cardiovascular risk than non-HDL-C and that the practice of lipidology would be improved by inclusion of Apo B along with lipoprotein lipids in routine clinical care.”

“Evidence is consistent that the benefit from statin therapy is more closely related to the decrease in Apo B than to the decreases in LDL-C or non-HDL-C. This evidence supports the use of Apo B as the preferred target of statin therapy.”


Population Percentile Targets for Apo B are <80 + <60 mg/dL

Table 4: NLA goals for LDL-C, non-HDL-C, apoB, and equivalent population goal for apoB

<table>
<thead>
<tr>
<th>Markers</th>
<th>Low Risk</th>
<th>Low Risk</th>
<th>High Risk</th>
<th>High Risk</th>
<th>Low Risk PP</th>
<th>High Risk PP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mg/dL</td>
<td>PP</td>
<td>mg/dL</td>
<td>PP</td>
<td>mg/dL</td>
<td>mg/dL</td>
</tr>
<tr>
<td>LDL-C</td>
<td>100</td>
<td>33rd</td>
<td>70</td>
<td>8th</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>130</td>
<td>42nd</td>
<td>100</td>
<td>15th</td>
<td></td>
<td></td>
</tr>
<tr>
<td>apoB</td>
<td>90</td>
<td>51st</td>
<td>80</td>
<td>35th</td>
<td>80 mg/dL</td>
<td>60 mg/dL</td>
</tr>
</tbody>
</table>

PP: percentile population.


How does Apo A1 relate to HDL?

- Apo A1 is the major apolipoprotein of HDL
- Apo A1 provides a good estimate of HDL concentration
- Each HDL particle may carry several Apo A1 molecules
- Apo A1 <120 mg/dL for men and <140 mg/dL for women is considered low and increases CV risk

Eur Heart J 2013;34:1759-1768
Apo A1 Function

- Apo A1 promotes cholesterol efflux from the artery wall to the liver for excretion\(^1\)
- Cholesterol efflux is associated with higher levels of Apo A1 (a rough measure of HDL-P) independent of HDL-C\(^2\)
- Newer research demonstrates a strong predictive value benefit of looking at both Apo B and Apo A1 simultaneously\(^3\)


Why should I look at the Apo B/Apo A1 ratio as part of my cardiovascular risk assessment process?

- INTERHEART STUDY
  - The higher the Apo B/Apo A1 ratio, the higher the risk of heart attack

- AMORIS and INTERSTROKE STUDIES
  - The higher the Apo B/Apo A1 ratio, the higher the risk of stroke

Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): a case-controlled study

- Global standardized case-control study (n = 15,152 cases and n= 14,820 controls)
- 262 centers in 52 countries
- Subjects on all continents (Asia, Europe, the Middle East, Africa, Australia, North America, and South America)
- Subjects from all ethnic groups
- Men and women
- Young and old (<45, 46-55, 56-65, 55-70, >70 years)
- Nine easily measured risk factors

Odds of myocardial infarction according to number of cigarettes smoked/day. Note the doubling of scale on the y axis.


Odds of myocardial infarction according to Apo B/Apo A1 ratio. Note the doubling scale on the y axis.

INTERHEART STUDY

**INTERHEART Results**

- **Smoking** (odds ratio 2.87 for current vs. never, PAR 35.7% for current and former vs. never)
- Elevated Apo B/Apo A1 ratio (odds ratio 3.25 for top vs. lowest quintile, PAR 49.2% for top four quintiles vs. lowest quintile)
- Apo B/Apo A1 ratio showed a graded relation with myocardial infarction (MI) risk, with no evidence of a threshold for the top vs. the lowest decile of Apo B/Apo A1.

**Conclusion**

“Collectively these 9 risk factors accounted for 90% of PAR for MIs in men and 94% in women”

**Apolipoprotein-related Mortality Risk (AMORIS) Study**

- Large prospective study (n= 98,722 men & 76,831 women)
- Objective: To determine if stroke risk is related to the balance between Apo B and Apo A1 particles
- Subjects aged 20 to >80 years
- Acutely ill and hospitalized subjects were excluded
- Average follow-up 10.3 ± 3.9 years
- Subjects with the highest Apo A1 and lowest Apo B were used as the reference cell
AMORIS Results

- Strong, direct relationship between increasing values of the Apo B/Apo A1 ratio and risk of fatal stroke
- Low Apo A1 was single strongest contributing factor to an ↑ Apo B/Apo A1
- Proportions of deaths in AMORIS corresponded closely to national and international statistics from other developed countries
  - Strokes (6.2%)
  - MI and other coronary events (24.4%)
  - Aortic Aneurysm (1.7%)
  - Cancer (31.7%)
  - Other causes of non-ischaemic deaths (34%)
AMORIS Conclusions

- “We believe that the Apo B/Apo A1 ratio is a more robust and more informative and relevant risk marker than the lipids and lipoproteins.”
- Results from AMORIS and INTERHEART indicate that the Apo B/Apo A1 ratio is a simple and powerful summary index to identify subjects at risk for ischaemic vascular diseases
  - Easy to use, no fasting required
  - Testing methods internationally standardized
  - Reporting scale is universal
  - Easier for patients and physicians to estimate risk based on only one index
  - The risk ratio is a valuable tool to monitor the effects of lipid lowering therapy

Walldius G et al. J Int Med 2006; 259-266

Global and Regional Effects of Potentially Modifiable Risk Factors Associated with Acute Stroke in 32 Countries (INTERSTROKE): a case-control study

- Standardized international case-control study (n = 13,447 cases (10,388 with ischaemic stroke and 3059 intracerebral haemorrhage) and n = 13,472 controls)
- Subjects on 6 continents (Asia, Europe, the Middle East, Africa, Australia, and America) in 32 countries
- Average age 62.2 (11.8% ≤45 years)
- Men and women
- Cases – acute 1st stroke (within 5 days of symptoms onset and 72 h of hospital admission)
- Ten easily measured risk factors


INTERSTROKE Results

- Cardiac causes (odds ratio 3.17)
- History of hypertension or BP ≥140/90 mm Hg (odds ratio 2.98 for stroke, PAR 47.9%)
- Elevated Apo B/Apo A1 ratio (odds ratio 1.84 for top vs. lowest tertile, PAR 26.8% for top 2 tertiles vs. lowest tertile)
- Current smoking (odds ratio 1.67)
- Diabetes (odds ratio 1.16)

Conclusion

“Collectively these 10 risk factors accounted for 90.7% of PAR for all stroke worldwide (91.5 for ischemic stroke, 87.1% for intracerebral hemorrhage) among ethnic groups, in men and women, and in all ages.”

**National Academy of Clinical Biochemistry 2009 Recommendations**

"The Apo B/Apo A1 ratio can be used to determine lipoprotein related risk for cardiovascular disease."

**2012 European Guidelines on Cardiovascular Disease Prevention in Clinical Practice**

"It is beyond doubt that the Apo B/Apo A1 ratio is one of the strongest risk markers."

---

**What About LDL-P?**

**2015 National Lipid Association 2015 Expert Recommendations**

- Practitioners "may consider lowering low-density lipoprotein particle number (LDL-P) as an alternative to Apo B".
- Apo B and LDL-P have been reported to perform similarly regarding risk prediction.
- LDL-P can be useful clinically.
- Most studies used a proprietary* nuclear magnetic resonance (NMR) method, but others are available.
- No current standardization program for LDL-P as there is for Apo B, therefore no goals stated.

* Lipoprofile®

---

**Lipoprotein Subclasses**

- Diameter (nm)
- Density (g/mL)
- HDL-C
- LDL-C
- Triglycerides
- Chylomicrons
- VLDL
- Chylomicron Remnants

There is one Apo B on each atherogenic lipoprotein particle.
NMR LipoProfile®

An advanced cardiovascular diagnostic test that uses nuclear magnetic resonance (NMR) spectroscopy to provide rapid, simultaneous and direct measurement of LDL particle number and size of LDL particles, and also direct measurement of HDL and VLDL subclasses.

NMR LipoProfile® Reportables

To transition to NMR goals, simply add a zero.
- If LDL-C goal <100, LDL-P goal <1000
- If LDL-C goal <70, LDL-P goal <700
Population Equivalent Cutpoints for Alternate LDL-C Measures (LDL-C, Measured Apo B and NMR LDL-P)

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Population</th>
<th>&lt; 5th</th>
<th>20th</th>
<th>50th</th>
<th>80th</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C (mg/dL)</td>
<td>Framingham</td>
<td>&lt; 70</td>
<td>100</td>
<td>130</td>
<td>160</td>
</tr>
<tr>
<td>Measured Apo B</td>
<td>Framingham</td>
<td>&lt; 60</td>
<td>80</td>
<td>100</td>
<td>120</td>
</tr>
<tr>
<td>NMR LDL-P (nmol/L)</td>
<td>Framingham</td>
<td>&lt; 850</td>
<td>1100</td>
<td>1400</td>
<td>1800</td>
</tr>
<tr>
<td></td>
<td>MESA</td>
<td>&lt; 700</td>
<td>1000</td>
<td>1300</td>
<td>1600</td>
</tr>
</tbody>
</table>


What do the experts say...
• National Lipid Association recommendations:

<table>
<thead>
<tr>
<th>Initial Clinical Assessment</th>
<th>Apo B</th>
<th>LDL-C</th>
<th>Lipids</th>
<th>HDL or LDL</th>
<th>Triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk (&lt;75 40-year CHD risk)</td>
<td>Recommended</td>
<td>Not recommended</td>
<td>Not recommended</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Intermediately high CHD risk</td>
<td>Recommended for many patients</td>
<td>Recommended for many patients</td>
<td>Consider for selected patients</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
<tr>
<td>High CHD risk</td>
<td>Consider for selected patients</td>
<td>Consider for selected patients</td>
<td>Consider for selected patients</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Family History</td>
<td>Recommended for very patients</td>
<td>Recommended for very patients</td>
<td>Recommended for very patients</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Recurrent Events</td>
<td>Recommended for many patients</td>
<td>Recommended for many patients</td>
<td>Recommended for many patients</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>


What do the experts say...
• National Lipid Association recommendations:

<table>
<thead>
<tr>
<th>On-Treatment Management Decision</th>
<th>Apo B</th>
<th>LDL-C</th>
<th>Lipids</th>
<th>HDL or LDL</th>
<th>Triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk (&lt;75 40-year CVD risk)</td>
<td>Recommended</td>
<td>Not recommended</td>
<td>Not recommended</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Intermediately high CVD risk</td>
<td>Recommended for many patients</td>
<td>Recommended for many patients</td>
<td>Consider for selected patients</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
<tr>
<td>High CVD risk</td>
<td>Consider for selected patients</td>
<td>Consider for selected patients</td>
<td>Consider for selected patients</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Family History</td>
<td>Consider for many patients</td>
<td>Consider for many patients</td>
<td>Consider for many patients</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Recurrent Events</td>
<td>Recommended for many patients</td>
<td>Recommended for many patients</td>
<td>Consider for selected patients</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>

Recent Changes in Dietary Guidelines Regarding Cholesterol

• 1961 AHA Guidelines: “Reduce intake of total fat, saturated fat, and cholesterol”
• 1968: AHA Committee on Nutrition sets 300 mg/day cholesterol limit for hypercholesterolemic patients
  – Debate went between 0 and 600 mg/day
  – Rationale for 100 mg/day?
• Many of us remember 2001 National Cholesterol Education Program recommendations to limit dietary cholesterol to <200 mg/day in patients at high risk

Dietary Cholesterol & Heart Disease Recommendations from the 1960’s to our current “evidence based” decade


There was a trend for serum cholesterol levels to increase with increases in dietary cholesterol with mechanisms coming into play at higher intake levels
• The extent to which each of these phenomena takes place is relatively modest and appears to vary from individual to individual

“In summary, the earlier purported adverse relationship between dietary cholesterol and heart disease risk was likely largely over-exaggerated.”

2013 American College of Cardiology / American Heart Association Guideline on Lifestyle Management to Reduce Cardiovascular Risk

- Rigorous systematic scientific reviews
- Significantly more limited in scope
- Focused on selected questions based on "the highest quality evidence available" including:
  - Randomized controlled trials
  - Meta-analyses
  - Observational studies evaluated for quality
- Recommendations were NOT formulated when sufficient evidence was not available


Dietary Cholesterol:
"There is insufficient evidence to determine whether lowering dietary cholesterol reduces LDL-C."

Strength of Evidence: Insufficient


Dietary Guidelines for Americans 2015-2020
8th Edition

"More research is needed regarding the dose-response relationship between dietary cholesterol and blood cholesterol levels."

Adequate evidence is not available for a quantitative limit for dietary cholesterol and no limit is now mentioned in these new guidelines.

Rationale for “Portfolio Diet” Choices

<table>
<thead>
<tr>
<th>Dietary Choices</th>
<th>Mechanism</th>
<th>Lowering of LDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viscous Fibers</td>
<td>Increase bile acid losses</td>
<td>6.7% for 10 gm of ppylum</td>
</tr>
<tr>
<td>Soy Proteins</td>
<td>Reduce hepatic cholesterol synthesis, increase LDL receptor messenger RNA</td>
<td>12.5% for 45 gm of soy proteins</td>
</tr>
<tr>
<td>Plant Sterols</td>
<td>Reduce cholesterol absorption</td>
<td>13 % for 1-2 gm of plant sterols</td>
</tr>
<tr>
<td>Almonds (MUFA and plant sterol rich oil)</td>
<td>Shown to lower LDL-C</td>
<td>1 % for 10 gm of almonds</td>
</tr>
</tbody>
</table>

Jenkins et al. JAMA 2003;290(4):502-10

Results of Portfolio Diet: Lipids and C-Reactive Protein (CRP)

LDL Lowering Medications

- Statins are the most effective, most commonly used, & are class of first choice to lower atherogenic lipids
- Cholesterol Absorption Inhibitor
- Resins or bile acid sequestrants (BAS)
- Niacin (Nicotinic Acid)
- 2 new agents approved only for homozygous familial hypercholesterolemia (HoFH) (extremely high LDL-C)
  - Anti-sense (subcutaneous injection)
  - Microsomal transfer protein inhibitor
- PSCK9 inhibitors
ACC/AHA Cholesterol Guideline Recommends 4 Statin Treatment Groups

- Individuals with diagnosed *clinical* atherosclerotic cardiovascular disease (ASCVD)
- Individuals ≥21 years of age with very high baseline LDL-C ≥190 mg/dL
- Adults aged 40-75 years with diabetes + LDL-C levels of 70-189 mg/dL without ASCVD
- Adults aged 40-75 without CVD or diabetes, with LDL-C 70-189 mg/dL and estimated 10-yr ASCVD risk ≥7.5% based on Pooled Cohort Equation calculator

---

AHA/ACC Cholesterol Guideline
Statin Dosing Recommendations – Based on the % Reduction of LDL-C

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Dose needed to ↓LDL-C about 30 -&lt;50%</th>
<th>Dose needed to ↓LDL-C about ≥50%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>Lipitor®</td>
<td>10 or 20 mg</td>
<td>40 or 80 mg</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>Lescol®</td>
<td>40mg BID</td>
<td>NA</td>
</tr>
<tr>
<td>Fluvastatin XL</td>
<td>Lescol® XL</td>
<td>80 mg</td>
<td>NA</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>Mevacor®</td>
<td>40 mg</td>
<td>NA</td>
</tr>
<tr>
<td>Pitavastatin*</td>
<td>Livalo®</td>
<td>2 or 4 mg</td>
<td>NA</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>Pravachol®</td>
<td>40 or 80 mg</td>
<td>NA</td>
</tr>
<tr>
<td>Rosuvastatin*</td>
<td>Crestor®</td>
<td>5 or 10 mg</td>
<td>20 or 40 mg</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>Zocor®</td>
<td>20 or 40 mg</td>
<td>NA</td>
</tr>
</tbody>
</table>

*BID = twice daily; LDL-C = Low-density lipoprotein cholesterol; NA = not applicable
*= not available as generic

2016 ACC Consensus on the Role of Non-Statins

- Clinical trials of agents that markedly ↑ HDL-C (niacin + CETP inhibitors) have failed to show ↓ all cause mortality, CHD mortality, MI, and stroke in statin treated patients
- Non-statin drug classes are generally safe and there is RCT evidence for ASCVD ↓ with monotherapy associated with niacin, gemfibrozil, & cholestyramine


Role of Niacin as an Add-on to Statin Therapy According to the ACC

- “On the basis of currently available evidence on non-efficacy and potential harms, the Committee judged that there are no clear indications for the routine use of niacin preparations as additional non-statin therapies”


NLA and ACC Expert Opinions (Recommendations - Not guidelines)

- Outcome data re: ASCVD event reduction are lacking for addition of BAS to statins
- Each 40 mg ↓ in LDL-C leads to approximately 20% relative risk ↓ in ASCVD
- Both NLA (2015) and ACC (2016) experts recommend consideration of ezetimibe first and BAS second (unless contraindicated or PCSK9 more likely to get to goal)

NLA Recommends the Following Statin Combination Therapies for LDL Lowering in the Indicated Order

1. Ezetimibe 10 mg qd
2. Colesevelam 625 mg 3 tabs 2x/day or 3.75 g powder qd in single or divided doses
3. Extended release niacin titrated to maximum 2000 mg/d

Note: ACC non-statin recommendations recommends combining ezetimibe and BAS in some pathways

Cholesterol Absorption Inhibitor

- Ezetimibe (Zetia®) is the only FDA approved available agent in its class
- Safe and well tolerated
- Primary role is in addition to statin-based therapy or in statin-resistant patients
- Evidence exist for ezetimibe from IMPROVE-IT with a 6% relative/2% absolute risk ↓ in composite ASCVD endpoint over 7 yrs when added to moderate intensity statin
- When added to statins, ezetimibe may ↓ LDL-C an additional 20-25% on average

Ways to Achieve LDL-C/Non-HDL-C/Apo B Treatment Goals

<table>
<thead>
<tr>
<th>% Reduction in LDL-C</th>
<th>5-7%</th>
<th>5-7%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statin – starting dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statin – starting dose + Ezetimibe 10 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statin – starting dose + Sterols/Stanol + Viscous Fiber</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Slide courtesy of Kevin Maki PhD
Bile Acid Sequestrants

- Tablet and powder formulations:
  - Powders must be mixed with water before use
- GI complaints are the most common side effects (constipation, abdominal discomfort, intestinal gas, indigestion, heartburn)
  - Constipation less with colesvelam (Welcho®)
- Can bind other drugs and decrease absorption:
  - With colestipol and cholestyramine interacting drugs should be given 1 h before or 4 h after
  - Interaction risk is less problematic with colesevelam

Colesevelam HCl + Ezetimibe

- Double-blind trial
- 86 patients with randomized to:
  - Colesevelam 3.8 g/day with ezetimibe 10 mg/day, or
  - Placebo plus ezetimibe 10 mg/day
- Mean % change in LDL-C measured after 6 weeks


* P < 0.0001 for differences

PCSK9 Inhibitors: Role in Therapy

- Alirocumab and Evolocumab currently FDA approved as:
  - Adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-C
- Use in statin intolerance is debated and evolving
- Despite robust pre-approval clinical data, complete data evaluating CV Event Reduction will be available in the future
**PCSK9 Inhibitors**

- Human monoclonal antibodies that are subcutaneous injections every 2 weeks
- Patient education regarding administration is essential
- Typically available through specialty pharmacies with prior authorization processes
- Inability to take statins must be well documented
- Cost is a significant barrier

---

**Clinical Pearls**

- Prevention specialists look beyond traditional risk factors at lipoprotein and inflammatory biomarkers to evaluate the possible presence of an active atherogenic disease process.
- The cholesterol connection to heart disease story does not appear to be about cholesterol per se, but about the lipoproteins that transport cholesterol.
- The ACCF, ADA, Canadian Guidelines, AACE and NLA have all recommended Apo B goals for CV risk reduction.

---

**Clinical Pearls**

- The new ACC/AHA Cholesterol Guideline means that we start differently when implementing statin therapy to lower cholesterol.
- Using lower doses of statins, unproven in clinical trials, is only recommended when doses that have been proven effective are unable to be tolerated by the patient.
- The new ACC/AHA guidelines shift the focus from numbers to patient assessment.
- NLA & ACC experts agree that non-statins (ezetimibe, BAS, and niacin) may be added to lower LDL-C.
Clinical Pearls

- Hearth healthy eating recommendations no longer specifically limit cholesterol intake
- Dietary adjuncts are additive to LDL-C lowering
- Adding 8-10 g/day viscous fibers or 2 g/day sterols or stanols leads to approximately the equivalent of two doublings of the dose of statin medication
- In addition to heart healthy eating and medical nutrition therapy for dyslipidemias, various types of lipid altering agents (e.g. statins, a cholesterol absorption inhibitor, bile acid sequestrants, extended release niacin, and PCSK9 inhibitors) are available to treat lipid disorders and reduce cardiovascular risk

Summary

“Incorporating more precise biomarkers (e.g., lipoproteins such as Apo B (LDL-P) and Lp(a) and inflammatory markers such as hs-CRP, Lp-PLA2, and MPO) can help practitioners identify which patients may have the presence of subclinical atherosclerosis and need further diagnostic tests, which patients appear to be adequately treated on their current regimen, and which patients may exhibit signs of an active atherosclerotic disease state with evidence of vulnerable plaque.”

Cofer-Chase, L. Journal Nurse Pract 2014; 10(5):293-301

Please feel free to contact me

Lynn Cofer-Chase, MSN, RN, FNLA, FPCNA, FAHA
Clinical Education Manager/ Clinical Lipid Specialist
Cleveland HeartLab, Inc.
6701 Carnegie Avenue  Suite 500
Cleveland, OH 44103
Ph: (216) 548-9301 | Fax: (630) 752-9349
Email: lcchase@clevelandheartlab.com