Using Newer Biomarkers to Improve Cardiovascular Risk Assessment and Prevent Events 2013 Update

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Clinical Lipid Specialist
Manager of Clinical Education
Cleveland HeartLab Inc.

Questions for Audience Response

1. Experts from the following organization(s) have published targets for Apo B for cardiovascular risk reduction:
   a.) American Association of Clinical Endocrinology and the American Diabetes Association
   b.) American College of Cardiology and the National Lipid Association
   c.) None of the above
   c.) All of the above
Questions for Audience Response

2. Investigators from both the INTERHEART and Apolipoprotein-related Mortality Risk (AMORIS) trials conclude that increased levels of the following biomarker(s) powerfully identify subjects at risk for heart attack and stroke –
   a.) Lipoprotein-associated phospholipase A2
   b.) Apo B/ Apo A1 ratio
   c.) Myeloperoxidase
   d.) All of the above

Questions for Audience Response

3. Current guidelines by the National Heart Lung and Blood Institute and the American Academy of Pediatrics recommend universal screening via non-HDL-C or a lipid profile
   a.) At ages 2 and above
   b.) At ages 9-11 and 17-21
   c.) At ages 12-16 (during puberty)
   d.) Only in children at high risk (strong family history or presence of major risk factors)
Questions for Audience Response

4. Researchers have discovered that myeloperoxidase
   a.) Interferes with the activity of Apo A1 and renders HDL dysfunctional
   b.) Contributes to the atherosclerotic disease process by oxidizing Apo B
   c.) Neither a or b
   d.) Both a and b

Disclosure of Affiliations and Significant Relationships

<table>
<thead>
<tr>
<th>Relationship</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speaker's Bureau</td>
<td>Abbott Laboratories, Amarin, Merck &amp; Co.</td>
</tr>
<tr>
<td>Consulting</td>
<td>Merck &amp; Co., National Lipid Association</td>
</tr>
<tr>
<td>Employment</td>
<td>Cleveland HeartLab, Inc.</td>
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<tr>
<td>Board of Directors</td>
<td>Accreditation Council for Clinical Lipidology</td>
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<td></td>
<td>Foundation of the National Lipid Association</td>
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</table>
Prevalence of cardiovascular disease in adults ≥20 years of age by age and sex (NHANES 2007-2010)

Percentage breakdown of deaths due to cardiovascular disease (United States: 2009)

*Not a true underlying cause. With any mention of deaths, heart failure accounts for 35 percent of cardiovascular disease deaths. Total may not add to 100 because of rounding. Coronary heart disease includes ICD-10 I20-I25, stroke, I60-I69, heart failure, I50; high blood pressure, I10-I15; disease of arteries, I70-I79; other, I85-I89.
NEW GUIDELINES EMPHASIZE PRIMORDIAL PREVENTION OF CARDIOVASCULAR RISK

National Heart Lung and Blood Institute (NHLBI) Pediatric Cardiovascular Risk Reduction Guidelines

- Comprehensive guidelines for consideration of the whole child incorporating family history, nutrition, physical activity, tobacco, blood pressure, lipids, obesity, diabetes and metabolic syndrome
- Emphasis on Primordial Prevention (prevention of CV risk in the first place)
- First new lipid recommendations since 1992
- Followed Institute of Medicine’s procedures for Evidence Based Guidelines

www.nhlbi.nih.gov/guidelines/cvd_ped/summary.htm
Published November 2011
Current NHLBI Lipid Guidelines for Children & Adolescents *

- Family history to determine lipid screening for children misses 30-60% of children with dyslipidemias
- Non-HDL-C should be added as a screening tool to identify a dyslipidemic state in childhood
- The goal of LDL-lowering therapy in childhood & adolescence is LDL-C ≤130 mg/dL

*Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents


Non-HDL-C is a measure of cholesterol in atherogenic lipoprotein subclasses

Non-HDL Cholesterol

Chylomicrons

Triglycerides

Chylomicron Remnants

LDL Cholesterol

HDL Cholesterol

All Apo B containing lipoproteins
### US Health Professionals Study

<table>
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<th>Biomarker</th>
<th>CHD RR, 95% CI</th>
<th>P-Trend</th>
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- Quintile 5 vs. Quintile 1
- P-Trend is a test for a rise or fall in RR from Q1 to Q5

National Lipid Association Taskforce on Non-HDL Cholesterol

- NCEP ATP III guidelines recognize non-HDL-C as the preferred method to measure residual risk after LDL-C lowering in patients with:
  - Elevated triglycerides
  - Metabolic syndrome
  - Diabetes

- 2008 ADA/ACC Foundation Consensus Conference on Lipoprotein Management in Patients with Cardiometabolic Risk states:
  - “Routine calculation and use of non-HDL-C constitute a better index than LDL-C for identifying high-risk patients.”

Non-HDL-Cholesterol and CVD Risk

- Non–HDL-C calculation\(^1\)
  - Non–HDL-C = TC – HDL-C

- Non–HDL-C goal\(^1\)
  - Normal VLDL-C defined as value when TG <150 mg/dL (≤30 mg/dL)
  - Non–HDL-C goal is 30 mg/dL above goal for LDL-C

- Significance of non-HDL-C
  - Encompasses all known and potential atherogenic lipid particles\(^1\)
  - Correlates closely with obesity and especially visceral adiposity\(^2\)
  - Has been shown to be a stronger predictor of cardiovascular risk than LDL-C\(^2-6\)

Conclusions of the National Lipid Association Taskforce on Non-HDL Cholesterol

- Non-HDL-C is an inclusive measure of all atherogenic lipoproteins
- Non-HDL-C outperforms all other traditional lipid measures in the prediction of cardiovascular disease
- Non-HDL-C can be readily available and accurately calculated on all routine lipid profiles, fasting or non-fasting, at no further expense to patient or third-party payer


Highlights of the New NHLBI Lipid Recommendations for Children & Adolescents*

- ALL children should have cholesterol screening once between ages 9 – 11 years and once between 17 – 21 years
- Non-fasting total cholesterol and HDL-C can be used for initial screening (to provide Non-HDL-C); if elevated, follow up with a fasting lipid profile (x2)

* Endorsed by the American Academy of Pediatrics

Familial Hypercholesterolemia (FH):
Background Information

• A group of inherited genetic defects resulting in severely ↑ cholesterol levels
• One of the most common inherited metabolic disorders (affects >600,000 Americans) and is more common than:
  – type 1 diabetes
  – cystic fibrosis
  – Down’s Syndrome

Background re: FH

• Heterozygous FH
  – cholesterol 350 - 500 mg/dL range
  – occurs in ~ 1 in every 300 -500 people
• Homozygous FH
  – cholesterol 650 - 1000 mg/dL
  – occurs in ~ 1 in every 1,000,000 people
• Risk for premature CHD increases- 20-fold in untreated FH patients
• FH is a treatable condition (only 20% are diagnosed and less than half are treated appropriately

History

• 1970’s
  – Focus on angiography and % stenosis

• 1995
  – Cardiovascular event risk determined to be related to
    vulnerable (soft) plaque more so than by the %
    stenosis

• 1999
  – Russel Ross MD reintroduces atherosclerosis as an
    inflammatory disease (originally described in 1976)

• 2008
  – JUPITER trial demonstrates the importance of
    inflammation as a player in cardiovascular events

86% of Heart Attacks Occur Where
Blood Flow Has Been Good
(i.e., No Warning Signs)

So...How does THIS happen?

Coronary Artery with Unstable Plaque

- Large Lipid Core
- Thin Fibrous Cap
Blocked Coronary Artery

Coronary Artery with Stable Plaque
Diabetes and CHD

- Diabetes introduced as a Coronary Heart Disease (CHD) risk equivalent in 1998

- Incidence of Diabetes increasing exponentially with no signs of a slow-down

Increased Rates of MI in Type 2 Diabetes
Seven Year Incidence of Fatal/Nonfatal MI


DM - diabetes mellitus
MI - myocardial infarction
CHD - coronary heart disease
“Yes, I do feel a bypass is in order. Bypass the refrigerator, bypass the cupboard, bypass the pizza parlor.”

How about the idea of bypassing or not having a stroke or heart attack?

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, Apo B/ Apo A1 ratio, and Lp(a)</td>
<td>hsCRP, MPO, and Lp-PLA2</td>
</tr>
</tbody>
</table>
But is that sufficient?

Why use Lipid Biomarkers other than Calculated LDL-C?:
Residual Cardiovascular Risk in Major Statin Trials

<table>
<thead>
<tr>
<th></th>
<th>4S</th>
<th>LIPID</th>
<th>CARE</th>
<th>HPS</th>
<th>WOS</th>
<th>AFCAPS / TexCAPS</th>
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<tbody>
<tr>
<td>N</td>
<td>4444</td>
<td>9014</td>
<td>4159</td>
<td>20136</td>
<td>6595</td>
<td>6605</td>
</tr>
<tr>
<td>∆LDL</td>
<td>-36%</td>
<td>-25%</td>
<td>-28%</td>
<td>-29%</td>
<td>-26%</td>
<td>-27%</td>
</tr>
</tbody>
</table>

Secondary | High Risk | Primary

Why Not Use the Best Prevention Tests?

- **Experts who recommend Apo B**

- **Experts who recommend Apo B/ Apo A1 ratio**

- **Cleveland Clinic** (ranked #1 heart program in the US for 18 consecutive years) heart disease prevention experts check myeloperoxidase

Heart disease is typically thought of as a “lipid disease”....

But we know that ~50% of people who have heart attacks or strokes have normal cholesterol levels

“I have some bad news. While your cholesterol level has remained the same, the research findings have changed.”

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

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

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>Cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C</td>
<td>130 mg/dL</td>
<td></td>
</tr>
<tr>
<td>TG</td>
<td>90 mg/dL</td>
<td></td>
</tr>
<tr>
<td>HDL-C</td>
<td>50 mg/dL</td>
<td></td>
</tr>
<tr>
<td>Non–HDL-C</td>
<td>146 mg/dL</td>
<td></td>
</tr>
<tr>
<td>ApoB</td>
<td>95 mg/dL</td>
<td></td>
</tr>
</tbody>
</table>

Large, buoyant LDL (pattern A)

- Same LDL-C

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

Small, dense LDL (pattern B)

- ApoB 118 mg/dL
- Non-HDL-C 140 mg/dL
- ApoB 118 mg/dL
Advanced Cholesterol Assessment

- ApoB (or LDL-P)
- ApoA1
- ApoB/ApoA1 Ratio
- Lp(a)
### US Health Professionals Study

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- P-Trend is a test for a rise or fall in RR from Q1 to Q5

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.
Lipoprotein Management in Patients With Cardiometabolic Risk
Consensus statement from ADA and ACC

<table>
<thead>
<tr>
<th>Goal Values (mg/dL)</th>
<th>LDL-C</th>
<th>Non-HDL-C</th>
<th>Apo B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highest Risk:</td>
<td>&lt;70</td>
<td>&lt;100</td>
<td>&lt;80</td>
</tr>
<tr>
<td>• CVD or</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• DM with ≥1 major risk factor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High Risk:</td>
<td>&lt;100</td>
<td>&lt;130</td>
<td>&lt;90</td>
</tr>
<tr>
<td>• No CVD, no DM with ≥2 major risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• DM with no major risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Other major risk factors (beyond dyslipidemia) include cigarette smoking, hypertension, and family history of premature coronary artery disease.

ADA = American Diabetes Association  (reaffirmed 2011)
ACC = American College of Cardiology

Treatment Lipid Targets
2009 Canadian Guidelines

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Initiate Rx if:</th>
<th>LDL-C Target</th>
<th>Apo B Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Risk</td>
<td>CAD</td>
<td>&lt; 77 or ≥ 50% ↓ LDL C</td>
<td>&lt; 80</td>
</tr>
<tr>
<td></td>
<td>Most pts with DM FRS &gt; 20%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate FRS 10-20%</td>
<td>LDL-C &gt;135 TC/HDL &gt; 5.0 Hs-CRP &gt;2.0 m/L</td>
<td>&lt; 77 or ≥ 50% ↓ LDL C</td>
<td>&lt; 80</td>
</tr>
<tr>
<td></td>
<td>Men &gt;50</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Women &gt;60</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>FH and HsCRP modulates risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low Risk FRS &lt;10%</td>
<td>LDL-C ≥ 193</td>
<td>≥ 50% ↓ LDL C</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Genest, J. Can J Cardiol 2009;24:567-579

2011 National Lipid Association Expert Panel Recommendations

• Measuring Apo B is “reasonable for many patients” at intermediate risk (5-20% 10 year CHD event risk) for initial assessment and on-treatment decisions

• Measuring Apo B should be considered for selected patients
  – Those with CHD or CHD risk equivalent at LDL-C and non-HDL-C goals
  – Patients on treatment with a family history of premature CHD or those with recurrent events


2011 National Lipid Association Expert Panel Recommendations

• The available results from clinical trials show that the effects of lowering Apo B values to <80 mg/dL are consistent with the potential for further risk reduction

• Selecting Apo B targets based on population percentiles based on the Framingham Offspring Study, Apo B values of 80 and 55 mg/dL would be equivalent to LDL-C levels of 100 mg/dL and 70 mg/dL respectively.

Atherosclerosis is caused by the Apo B lipoproteins . . .
not by LDL-C

- Our treatments should lower Apo B to the same population percentiles as LDL-C and non-HDL-C
- Statins lower LDL-C an average of 42%
- Statins lower Apo B an average of 33%
- Treating only to LDL-C goals often leaves Apo B substantially above goal
- To be maximally effective, we need to get Apo B to goal which often requires higher doses, higher potency statins, or combination therapies

Gleeson R, Davidson M. Lipidology A Primer 2012, p. 73

Steps to Optimal Lipid Management
After calculating the patient’s CV risk category and their LDL-C and non-HDL-C goal per NCEP ATP III Update 2004, then other lipid targets can be calculated to the same LDL-C’s population percentile.

<table>
<thead>
<tr>
<th>Percentile</th>
<th>LDL-C</th>
<th>Non-HDL-C</th>
<th>LDL-P</th>
<th>Apo B</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>70</td>
<td>83</td>
<td>720</td>
<td>54</td>
</tr>
<tr>
<td>10</td>
<td>88</td>
<td>104</td>
<td>940</td>
<td>69</td>
</tr>
<tr>
<td>20</td>
<td>100</td>
<td>119</td>
<td>1100</td>
<td>78</td>
</tr>
<tr>
<td>50</td>
<td>130</td>
<td>153</td>
<td>1440</td>
<td>97</td>
</tr>
<tr>
<td>80</td>
<td>160</td>
<td>187</td>
<td>1820</td>
<td>118</td>
</tr>
</tbody>
</table>

Distribution of Lipids in Framingham Offspring
Adapted from Contois JH Clin Chem 2009;407-419

Gleeson R, Davidson M. Lipidology A Primer 2012, p. 49.
American Association of Clinical Endocrinology (AACE) Lipid and Atherosclerosis Guidelines 2012

• Support Apo B (or LDL-P) as uniquely powerful assessment of total atherogenic particle burden
• Classify elevations in Apo B (or LDL-P) as an additional risk factor
• Recommend
  – Apo B <90 (patients at risk of CAD, inc those with DM)
  – Apo B <80 (patients with CAD or DM +≥ added RFs)
  – “Lower Apo B targets may be considered in certain clinical situations characterized by persistent CAD”

Fihn SD et al. Endocrine Prac 2012;18 (Suppl 1).

What’s this about Apo A1?

• 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 (“as many as 4” per E. Schaeffer MD)
• Low levels of Apo A1 → increased CV risk
  - High risk Apo A1 <120 mg/dL for men
  - or <140 mg/dL for women

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 look at the Apo B/Apo A1 ratio as part of cardiovascular risk assessment?
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


INTERHEART STUDY

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

INTERHEART STUDY

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


Figure 2: Risk of acute myocardial infarction associated with exposure to multiple risk factors
Smk=smoking, DM=diabetes mellitus, HTN= hypertension, Obes=abdominal obesity, PS=psychosocial, RF=risk factors. Note the doubling scale on the y axis. The odds ratios are based on current vs never smoking, top vs lowest tertile for abdominal obesity, and top vs lowest quintile for ApoB/ApoA1. If these three are substituted by current and former smoking, top two tertiles for abdominal obesity and top four quintiles for ApoB/ApoA1, then the odds ratio for the combined risk factor is 1.29-20 (99% CI 90-24-184-99).

INTERHEART Results

- Diabetes (odds ratio 2.37 vs. non-diabetes)
- 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

Risk of Dying From Any Type of Stroke

Apo B/Apo A1 and Overall CV Risk
(Stroke, MI, other ischaemic coronary events & Aortic Aneurysm)


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 (8.2%)
  - 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


<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC is recommended to be used for the estimation of total CV risk by means of the</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>SCORE system.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL-C is recommended to be used as the primary lipid analysis for screening and</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>risk estimation.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TG adds information on risk and is indicated for risk estimation.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>HDL-C is a strong risk factor and is recommended to be used for risk estimation.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Non-HDL-C should be considered as an alternative risk marker, especially in</td>
<td>IIA</td>
<td>C</td>
</tr>
<tr>
<td>combined hyperlipidaemias, diabetes, the MetS or CKD.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lp(a) should be recommended in selected cases at high risk and in subjects with</td>
<td>IIA</td>
<td>C</td>
</tr>
<tr>
<td>a family history of premature CVD.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apo B should be considered as an alternative risk marker, especially in</td>
<td>IIA</td>
<td>C</td>
</tr>
<tr>
<td>combined hyperlipidaemias, diabetes, the MetS or CKD.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The ratio of apo B/apo A1 combines the risk information of apo B and apo A1 and</td>
<td>IIB</td>
<td>C</td>
</tr>
<tr>
<td>may be recommended as an alternative analysis for risk screening.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The ratio non-HDL-C/HDL-C may be recommended as an alternative analysis for</td>
<td>IIB</td>
<td>C</td>
</tr>
<tr>
<td>risk screening.</td>
<td></td>
<td></td>
</tr>
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*Class of recommendation.
*Level of evidence.
Apo = apolipoprotein; CKD = chronic kidney disease; CVD = cardiovascular disease; HDL-C = high-density lipoprotein-cholesterol; LDL-C = low-density lipoprotein-cholesterol; Lp = lipoprotein; MetS = metabolic syndrome; TC = total cholesterol; TG = triglycerides.

Joint EAS/ESC Guidelines for the Management of Dyslipidemia
Class I is indicated
Class Ila consider; evidence favors
Class Iib may consider, less well established evidence

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.”

American Association of Clinical Endocrinology (AACE) Lipid and Atherosclerosis Guidelines 2012

• When triglycerides are >150mg/dL or HDL-C is <40 mg/dL, the Apo B/Apo A1 ratio may be particularly useful in assessing residual risk in patients at risk for CAD (even when LDL-C levels are controlled). This includes patients with established CAD, type 2 DM, or insulin resistance syndrome who are at risk for CAD

Fihn SD et al. Endocrine Prac 2012;18 (Suppl 1).
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


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)

Lp(a)

- Is complex and not well understood
- Represents a link between the atherogenicity of LDL-C and the thrombogenicity of plasminogen
- When Lp(a) and LDL-C are both elevated, numerous studies reveal elevated Lp(a) increases CV risk
- When HDL-C is low and Lp(a) is elevated, CV risk increases significantly


Lp(a) Measurement 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
Current 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 an Lp(a) evaluated
- Aggressive lowering of low-density lipoprotein (LDL-C) cholesterol is beneficial in those with elevated Lp(a) and LDL-C


Atherosclerosis is a Chronic Inflammatory Disease

- First described as an inflammatory disease by Russell Ross MD in 1976
- Atherosclerosis and acute coronary syndromes are recognized as manifestations of vascular inflammation
- A number of inflammatory biomarkers predict increased risk for cardiovascular events
  - High sensitivity C-reactive protein (hsCRP)
  - Myeloperoxidase (MPO)
  - Lipoprotein-associated phospholipase A₂ (Lp-PLA₂)

2. Libby P. Am J Cardiol 2001;88:3J-6J.
Inflammation Tests: Beyond Traditional Risk Assessment

As inflammatory test results increase (Lp-PLA₂, hsCRP, and MPO), so does the risk of heart attack, stroke, and sudden death¹⁻⁴

Looking at just one inflammatory marker may not be enough. Optimal risk prediction may involve a panel of risk markers that look at systemic inflammation and evidence of inflamed, unstable plaque prone to rupture.⁵


Cleveland HeartLab –
CVD Inflammation Profile

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These Inflammation Tests Together Give a More Complete Picture for Individual Risk Assessment

- hsCRP
  - High sensitivity C-Reactive Protein
- Lp-PLA$_2$
  - Lipoprotein-associated phospholipase-A$_2$
- MPO
  - Myeloperoxidase

High-sensitivity C-reactive Protein (hsCRP)

- An acute-phase protein released into the blood by the liver during inflammation
- Compared to standard CRP testing, hsCRP testing can more accurately detect lower concentrations of CRP making it more useful in predicting a healthy person’s risk for cardiovascular disease
- hsCRP is a well documented clinical marker of general and cardiac-related inflammation
Use of hsCRP for Predicting Cardiovascular Events
(Helpful in those at Intermediate Risk)

How to Interpret hsCRP results

- Desirable levels are <1.0 mg/L and reflect low CV risk (slight increases occur with age however)
- Levels between 1 and 3 mg/L are indicative of moderate risk (e.g., levels >2.4 mg/L have been associated with a doubling of risk for coronary events compared with levels <1 mg/L)
- Levels >3 mg/L suggest an elevated vascular risk
- Individuals with levels >3 mg/L have 4-6x ↑ risk of diabetes vs. those with lower levels

How to Interpret hsCRP results

- Elevated hsCRP levels should be confirmed with an additional measurement at least 1 month later
- For levels >10 mg/L, the test should be repeated in 2-3 weeks as levels above 10 mg/L can reflect acute infection
  - Viral infections (10-40 mg/L)
  - Active inflammation and bacterial infections (40-200 mg/L)
  - Severe bacterial infections/burns (>200 mg/L)

Ridker PM Circ 2003;108:e81-e85.

hsCRP is a stronger predictor of cardiovascular events in women than LDL-C

Women’s Health Study

- 28,345 women (8 yrs.; 15,745 were not on HRT)
- hsCRP and LDL-C measured at baseline
- hsCRP adds prognostic information to Framingham risk scores

Incidence of Recurrent MI or CHD Death by Achieved Levels of LDL-C and CRP

PROVE IT–TIMI 22

N = 4162

JUPITER: (17,802 pts. with LDL<130mg% & hs-CRP>2.0 mg/L) Primary Trial Endpoint: MI, Stroke, UA/Revascularization, CV Death

HR 0.56, 95% CI 0.46–0.69
P < 0.00001

Placebo 251 / 8901
- 44 %

Rosuvastatin 142 / 8901

LDL-C 108mg%
hsCRP 2mg/L
HDL-C 49mg% Tg 118mg mg%

Cumulative Incidence

Follow-up (years)

Number at Risk
Rosuvastatin 8,801 8,031 8,412 6,548 3,893 1,353 583 544 57
Lipoprotein-associated phospholipase-\(A_2\) (Lp-PLA\(_2\); The PLAC\(^\text{®}\) Test)

- Lp-PLA\(_2\) is an enzyme bound primarily to LDL that is an indicator of macrophage activity and inflammation within the arterial wall.
- Lp-PLA\(_2\) accumulates within atherosclerotic plaque and vulnerable lesions.
- The PLAC\(^\text{®}\) Test is a blood test cleared by the FDA to help assess risk for both coronary heart disease and ischemic stroke.

Clinical implications of Lp-PLA\(_2\)

- Elevated Lp-PLA\(_2\) levels can predict the development of coronary artery disease in apparently healthy individuals as well as the risk of future adverse cardiac and cerebrovascular events.
- Measurement of Lp-PLA\(_2\) can help identify patients at increased risk for heart attack, stroke, or death.
What does Lp-PLA$_2$ measure?

- The amount of inflammation under the cap – inside the artery wall

Elevated Lp-PLA$_2$ levels are independently associated with high ischemic stroke risk

The ARIC study

- $N = 12,762$ men and women
- Follow-up $\sim 6$-8 yrs.
Myeloperoxidase (MPO)

- Myeloperoxidase is an enzyme synthesized and stored within polymorphonuclear (PMNs) leukocytes and monocytes
- MPO generates potent anti-microbial oxidants
  - that invade PMN leukocytes and monocytes to kill bacteria and other pathogens
  - that can also damage surrounding vasculature
  - that are enriched within human atherosclerotic plaque


Myeloperoxidase (MPO)

- MPO contributes to endothelial dysfunction
  - Diminishes nitric oxide bioavailability
- MPO contributes to cholesterol accumulation
  - Oxidatively modifies LDL making it atherogenic and HDL making it dysfunctional
- MPO is a specific marker of vulnerable plaque, erosions, fissures in the arterial wall
  - Contributes to plaque instability by activating protease cascades that ultimately degrade the collagen cap
  - Increasing levels of MPO signify increasing risk for cardiac events
100+ published studies support the use of MPO for improved risk stratification

MPO levels increase with the severity of Coronary Artery Disease

Case-controlled study

- 874 patients with angiographically proven CAD

In ACS patients, elevated MPO levels can predict the incidence of death or MI at 72 hours, 30-days, and 6-months

**The CAPTURE Trial**

- 1,090 patients with ACS
- Follow-up 6 mo.

Elevated MPO levels predict cardiovascular mortality at 13 yrs in patients with angiographic evidence of CAD

Log-rank test: p=0.007

HR: 2.38 (95% CI: 1.47-2.99) for top vs bottom MPO tertile

MPO and CRP have combined utility in predicting cardiovascular mortality in patients with angiographic evidence of CAD

Canada
- 885 coronary angiography patients
- Follow-up > 13 years

Patients with either a high MPO or high CRP elevated had 5.3-fold higher mortality risk

Patients with high levels of both MPO and CRP had a 4.3-fold risk vs. patients with only one elevated marker

In apparently healthy individuals, mean MPO levels were greater according to increasing CAC categories

Summary

• All of the following biomarkers can be used to improve cardiovascular risk assessment & PREVENT CARDIOVASCULAR EVENTS
  – Standard lipid profile and non-HDL-C
  – Additional lipoprotein tests to help detect abnormalities (discordance) not seen with standard lipids [e.g., Apo B, Apo A1, Apo B/Apo A1 ratio, and Lp(a)]
  – Inflammation tests (hsCRP, LpPLA₂ and MPO) to uncover hidden near term risk
Questions for Audience Response

1. Experts from the following organization(s) have published targets for Apo B for cardiovascular risk reduction:
   a.) American Association of Clinical Endocrinology and the American Diabetes Association
   b.) American College of Cardiology and the National Lipid Association
   c.) None of the above
   c.) All of the above

Questions for Audience Response

2. Investigators from both the INTERHEART and Apolipoprotein-related Mortality Risk (AMORIS) trials conclude that increased levels of the following biomarker(s) powerfully identify subjects at risk for heart attack and stroke –
   a.) Lipoprotein-associated phospholipase A2
   b.) Apo B/ Apo A1 ratio
   c.) Myeloperoxidase
   d.) All of the above
Questions for Audience Response

3. Current guidelines by the National Heart Lung and Blood Institute and the American Academy of Pediatrics recommend universal screening via non-HDL-C or a lipid profile
   a.) At ages 2 and above
   b.) At ages 9-11 and 17-21
   c.) At ages 12-16 (during puberty)
   d.) Only in children at high risk (strong family history or presence of major risk factors)

Questions for Audience Response

4. Researchers have discovered that myeloperoxidase
   a.) Interferes with the activity of Apo A1 and renders HDL dysfunctional
   b.) Contributes to the atherosclerotic disease process by oxidizing Apo B
   c.) Neither a or b
   d.) Both a and b
Please feel free to contact me at any time

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