Lipids, Lipoproteins and Cardiovascular Risk: Getting the Most out of New and Old Biomarkers

William Cromwell, MD, FAHA, FNLA
Diplomate, American Board of Clinical Lipidology
Chief
Lipoprotein and Metabolic Disorders Institute
Adjunct Associate Professor
Wake Forest University School of Medicine

Disclosures

Speaker: Abbott, Kowa, LipoScience, Merck
Consultant: Genzyme, Health Diagnostic Laboratory, Isis LabCorp

Three Part Lecture Series

1. Lipids, Lipoproteins and Cardiovascular Risk: Getting the Most out of New and Old Biomarkers
   - Analytic Issues Involving Alternate Lipid and Lipoprotein Quantity Measures
   - Clinical Expectations of Cardiovascular Biomarkers
2. LDL-C, Non-HDL-C, Measures of LDL Particle Number (apoB and LDL-P): And the Winner is...
   - Influence of concordance versus discordance between lipid and lipoprotein measures on cardiovascular outcomes
   - Impact of confounding factors and methods of data analysis on outcome associations of lipid and lipoprotein biomarkers
3. Can We Optimize Individual Care Without Knowledge of Particle Number?
   - Expert opinion and guideline recommendations on use of lipid and lipoprotein measures to optimize of individual management
Analytic Issues Involving Alternate Lipid and Lipoprotein Quantity Measures

Lipids, Lipoproteins and Atherosclerosis: Historic Perspective

“...there is no single test that infallibly separates all those who have dyslipoproteinemia from those who do not....

the majority of laboratories still employ a combination of chemical measurements of plasma lipids for this purpose.”

Fredrickson et al., NEJM 1967; 276: 148

Distinction Between Lipids (Cholesterol) and Lipoproteins Noted in 1960s - But Then Forgotten
LDL-C and HDL-C Were the Only Clinically Accessible Biomarkers of LDL and HDL Levels For Decades

Friedewald Equation Introduced in 1972
Sealed the Deal

\[ \text{LDL-C} = \text{TC} - \text{HDL-C} - \left( \frac{\text{TG}}{5} \right) \]

As did the National Cholesterol Education Program

Does Cholesterol Accurately Quantify Lipoprotein Particles?
Cholesterol Carried Inside Lipoprotein Particles Is Highly Variable

Cholesterol Content Variability of LDL is Driven Partly by LDL Size Differences
Framingham Offspring Study (n=3,066)

Cholesterol Content Variability of LDL is Driven Also by LDL Concentration!
Framingham Offspring Study (n=3,066)
"... all abnormalities in plasma lipid concentrations, or dyslipidemia, can be translated into dyslipoproteinemia."

"... the shift of emphasis to lipoproteins offers distinct advantages in the recognition and management of such disorders."

Distinction Between Lipids (Cholesterol) and Lipoproteins Noted in 1960s - But Then Forgotten

Fredrickson et al., NEJM 1967; 276: 148

What’s Actually “Bad” and “Good” are Different Lipoprotein Particles

Other Lipoprotein Biomarkers Are Now Available:
Apolipoproteins

Other Lipoprotein Biomarkers Are Now Available: Particle Number by NMR

Analytic Relations of Lipid and Particle Number Measures
Quebec Cardiovascular Study (n=2,103)

Analytic Relations of Lipid and Particle Number Measures
Multi Ethnic Study of Atherosclerosis (MESA) (n=6,697)

Adapted from Sniderman AD, et al. Am J Cardiol 2003;91:1173-1177

Concordance / Discordance Associations with Alternate Measures of LDL Quantity

1. Discordance between LDL-C and LDL particle number (Apo B, NMR LDL-P)
   - Noted in up to 59% of all subjects [1-8]
   - 75% among T2DM and Met Syn subjects with LDL-C <100 mg/dL [2,3]

2. Less discordance between non-HDL-C and LDL particle number (Apo B, NMR LDL-P) [2,4,6,9]
   - Noted in more than 1/3 of all subjects and up to 40% of subjects with T2DM

3. Discordance is highly prevalent among 22,000 subjects at ATP goal values [6]
   - In 14,425 subjects with TG <200 mg/dL, 66% and 58% met LDL-C and non-HDL-C goals (100 mg/dL and < 130 mg/dL), respectively; however, only 30% of these same individuals met the Apo B goal
   - Among 7,611 subjects with TG levels greater than 200 mg/dL, only 17% met the Apo B goal, whereas 66% and 51% of subjects met the LDL-C and non-HDL-C goals, respectively

Concordance / Discordance Associations with Alternate Measures of LDL Quantity

4. Discordance is highly prevalent among T2DM subjects at ATP goal values [2]
   - Among 1,484 subjects with LDL-C 70-100 mg/dL (5th-20th percentile), 75% manifested discordantly high LDL particle number (>20th percentile).
   - Among 871 subjects with LDL-C < 70 mg/dL (<5th percentile), 40% showing similar magnitude of LDL particle discordance (> 20th percentile).

5. Statin therapy results in greater LDL-C & non-HDL-C reductions versus LDL particle number (Apo B or NMR LDL-P) [10]

6. Thus, many patients show discordant elevations in LDL particle number despite having low or very low LDL-C or non-HDL-C values.
Evaluating Cardiovascular Biomarkers

<table>
<thead>
<tr>
<th>Intended Application</th>
<th>Type of Biomarker</th>
<th>Clinical Use</th>
<th>Impact on Clinical Decision Making</th>
<th>Evidence Needed to Support Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk Assessment</td>
<td>New Biomarker</td>
<td>Evaluate patient for cardiovascular risk, allocate to different risk category</td>
<td>Allocate patient to different risk category which may result in more aggressive or less aggressive therapy</td>
<td>Significant improvement in risk stratification with the addition of new biomarker, or substitution of new measure of existing biomarker, in risk models (net reclassification)</td>
</tr>
<tr>
<td></td>
<td>(Inflammatory measures, particle size)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>New Measure of Established Biomarker</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk Management</td>
<td>New Biomarker</td>
<td>Modify therapy (agents, dosage, or combinations), as indicated to achieve new therapeutic target</td>
<td>Modify therapy (agents, dosage, or combinations), as indicated to achieve new therapeutic target</td>
<td>New measure consistently outperforms the existing measure in the setting of discordance</td>
</tr>
<tr>
<td></td>
<td>(inflammatory measures, particle size)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>New Measure of Established Biomarker</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Criteria and principles for accepting a new test as a better reference standard:

1) Value of the new reference test is best examined in cases of disagreement (discordance) between the current and new tests.


Criteria and principles for accepting a new test as a better reference standard:

2) Resolving disagreements between old and new test requires a fair “umpire” test.

3) Fair umpire tests include clinical events or disease progression.
Evaluating Lipid and Lipoprotein Measures

1. What are the associations of various biomarkers with cardiovascular outcomes?
   A. Simple univariate biomarker associations are often incomplete and potentially misleading.
   B. Is there a consistent, strong and independent association between the biomarker and clinical outcomes after adjustment for confounding factors?
2. Does the biomarker add substantial new information and/or uniquely change risk assessment?
3. Does the biomarker meet expectations for use in risk management?
4. Can the clinician feasibly measure the biomarker?
   A. Are there accurate and reproducible analytical methods readily available to the clinician?
   B. Is the cost reasonable for the information obtained?

Summary

1. History, not biomarker performance, made “bad” LDL and “good” HDL cholesterol the clinical standard of care.
2. The cholesterol content of lipoprotein particles can differ more than two fold between patients, as well as in the same patient over time.
3. Differences in cholesterol content of lipoprotein particles results in discordance between cholesterol and particle number measures of LDL and HDL quantity.
4. Outstanding questions to be discussed in upcoming lectures:
   What is the clinical significance of discordance between lipid and lipoprotein measures?
   How do confounding factors and methods of data analysis affect our understanding of lipid and lipoprotein biomarkers?
   How can we use lipid and lipoprotein biomarkers to optimize individual management?