ApoB Versus Non-HDL Cholesterol – And the Winner Is...
Allan Sniderman
McGill University

Braunwald 10th Edition Chapter 45
J Genest PA Libby

• “The clinical usefulness of apolipoprotein levels has stirred debate... The Emerging Risk Factors Collaboration studies have shown that measurement of non-HDL-C is equivalent to measurement of apoB in determination of cardiovascular risk... Such observations prompted a joint statement from the American Heart Association on the lack of incremental values of apolipoprotein measurement or lipoprotein particle size in predicting cardiovascular risk”

Emerging Risk Factor Collaboration

• Major lipids, apolipoproteins, and risk of vascular Lipid Related Markers and Cardiovascular Prediction
  
  • Lipid-related markers and cardiovascular disease prediction
Major lipids apolipoproteins and the risk of vascular disease.
The Emerging Risk Factors Collaboration Group

The other side:

Meta-analysis of 13 epidemiology studies: overall vascular relative risk ratios (95% confidence intervals) per standard deviation increase

<table>
<thead>
<tr>
<th>Marker</th>
<th>RRR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C</td>
<td>1.25* (1.18 to 1.33)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>1.34 (1.24 to 1.44)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ApoB</td>
<td>1.43 (1.35 to 1.51)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Marker</td>
<td>1st marker % over 2nd (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>Non-HDL-C vs. LDL-C</td>
<td>5.0% (0.9% to 9.1%)</td>
<td>0.017</td>
</tr>
<tr>
<td>ApoB vs. Non-HDL-C</td>
<td>5.7%* (2.4% to 9.1%)</td>
<td>0.001</td>
</tr>
<tr>
<td>ApoB vs. LDL-C</td>
<td>12.0%* (8.5% to 15.4%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
**Calculated Gains of non-HDL C & apoB over LDL C**

<table>
<thead>
<tr>
<th>ALM</th>
<th>Saves</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-HDL C</td>
<td>300,000</td>
</tr>
<tr>
<td>apoB</td>
<td>500,000</td>
</tr>
</tbody>
</table>

Sniderman A et al Circ Cardiovasc Qual Outcomes 2011;4:337-45

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**How Guidelines Have Voted**

For ERFC

- ACC/AHA
- EAS/ESC*
- CCS*
- NLA*
- JBS3

* Accepted apoB but preferred non-HDL-C

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**What did ERFC actually find?**

The actual finding of ERFC was that:

TC=LDL-C=non-HDL-C=apoB

If you believe that, you should recommend measuring TC, not non-HDL-C.
Conventional Observational Studies, which do not support ERFC

<table>
<thead>
<tr>
<th>ApoB&gt;LDL-C</th>
<th>ApoB&gt;LDL-C Non-HDL-C</th>
<th>Non-HDL-C=ApoB but &gt;LDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quebec CV Study</td>
<td>INTERHEART</td>
<td>AMORIS</td>
</tr>
<tr>
<td>Framingham Heart</td>
<td>Carlo Monferrato</td>
<td>EPIC-NORFOLK</td>
</tr>
<tr>
<td>Finland</td>
<td>Chinese Heart Study</td>
<td>ARIC</td>
</tr>
<tr>
<td>Apolipoproteins &amp; IHD</td>
<td>Health Professionals F/U</td>
<td></td>
</tr>
<tr>
<td>4S Placebo</td>
<td>ISIS</td>
<td>COPENHAGEN City Heart</td>
</tr>
<tr>
<td>THROMBO</td>
<td>The Tromso Study</td>
<td></td>
</tr>
<tr>
<td>Northwick Park Heart</td>
<td>Framingham Heart Study</td>
<td></td>
</tr>
<tr>
<td>Quebec CV</td>
<td>Schmidt/Bergström</td>
<td></td>
</tr>
<tr>
<td>MONICA/KORA</td>
<td>Steffen MESA</td>
<td></td>
</tr>
<tr>
<td>Stettler Type I DM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Womens Heart Study</td>
<td></td>
<td></td>
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<tr>
<td>Gigante et al</td>
<td></td>
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</tbody>
</table>

Weaknesses of ERFC

1. Many studies that were included were of poor quality in design, execution and interpretation. Many were never published and their quality can not be assessed.

2. Many studies used inadequate methods to measure apoB.

Associations of apoB & LDL-C with TC in ERFC studies that did publish apoB results.
My conclusions:

- If the Guidelines reviewers and other authorities had actually read the ERFC JAMA papers in detail, they should have endorsed TC, not non-HDL-C.
- I strongly suspect they did not read ERFC in detail because the conclusions from ERFC fit their preexisting beliefs.
6 Discordance Analyses: 
Results are Concordant

- Quebec Cardiovascular Study: ApoB > LDL-C
- Framingham: ApoB > LDL-C ApoB > Non-HDL-C
- INTERHEART: ApoB > Non-HDL-C
- Women’s Health Study: ApoB, LDL P, non-HDL-C > LDL-C.
- Framingham: LDL P > LDL-C
- MESA: LDL P > LDL-C

Risk more closely related to particle number than LDL-C or non-HDL-C
• “The clinical usefulness of apolipoprotein levels has stirred debate...The Emerging Risk Factors Collaboration studies have shown that measurement of non-HDL-C is equivalent to measurement of apoB in determination of cardiovascular risk... Such observations prompted a joint statement from the American Heart Association on the lack of incremental values of apolipoprotein measurement or lipoprotein particle size in predicting cardiovascular risk”

Chapter 45 Lipoprotein Disorders Braunwald 10th Edition: J Genest, P Libby

• “An obese, hypertensive middle-aged man with a cholesterol level of 245 mg/dl, a triglyceride level of 274 mg/dl, an HDL-C level of 31 mg/dl and a calculated LDL-C of 162 mg/dL probably has metabolic syndrome and this should trigger the clinician to seek other components of this cluster including hypertension and hyperglycemia.”

If he is 45, normotensive and not diabetic, his 10-year risk is 5.6% and therefore he does not qualify for statin preventive therapy based on risk alone.

We will come back to this patient in a little bit ...

First, we will learn to make a lipoprotein diagnosis ...
What is wrong with this patient?

- TC: 217 mg/dl
- Non-HDL C: 165 mg/dl (75th)
- LDL-C: 144 mg/dl (80th)
- HDL C: 52 mg/dl
- TG: 106 mg/dl

Is this patient at high risk of CVD?

- TC: 217 mg/dl
- Non-HDL C: 165 mg/dl (75th)
- LDL-C: 144 mg/dl (80th)
- HDL C: 52 mg/dl
- TG: 106 mg/dl
- apoB: 90 mg/dl (51st)

Framingham Heart Study: Kaplan-Meier survival for different Non-HDL-C and ApoB combinations.
He is not this.

High non-HDL/C/LDL-C HyperapoB: High Risk Phenotype

He is this.

High Non-LDL-C/LDL-C NormoapoB: Low Risk Phenotype

Is this patient at high or low risk of CVD?

- TC 195 mg/dl
- LDL-C 116 mg/dl 52%
- Non-HDL-C 148 mg/dl 58%
- HDL C 42 mg/dl
- TG 150 mg/dl
Is this patient at Low Risk or High Risk of CVD?

- TC 195 mg/dl
- LDL-C 116 mg/dl
- Non-HDL-C 148 mg/dl
- HDL C 42 mg/dl
- TG 187 mg/dl
- apoB 109 mg/dl

Framingham Heart Study: Kaplan-Meier survival for different LDL and apoB combinations in Men

HyperTG NormoapoB

He is not this.
He is this.

What is wrong with this patient?

- TC: 345 mg/dl
- Non-HDL C: 271 mg/dl
- HDL C: 36 mg/dl
- TG: 539 mg/dl

Let me add apoB

- TC: 345 mg/dl
- Non-HDL C: 271 mg/dl
- HDL C: 36 mg/dl
- TG: 539 mg/dl
- apoB: 104 mg/dl
**Frequency of Type III Hyperlipoproteinemia**

- LRC Prevalence Study- 0.4% of men >20 and 0.2 in women not on hormones.
- Hopkins et al- 0.68% in a general population of 1700
- Many cases have triglycerides 150-300 mg/dl
- Prevalence amongst CAD is 2.7%.
- Prevalence by apoB app 10.6% of 3272 consecutive patients in lipid clinic
- By contrast, prevalence of FH is perhaps 0.2%.

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**350/3722 (9.4%) consecutive patients in German Lipid Clinic have Type III**

<table>
<thead>
<tr>
<th>ApoE Genotype</th>
<th>Number patients</th>
<th>Type III</th>
<th>% apoE2-2 genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-2</td>
<td>108</td>
<td>55</td>
<td>50.9</td>
</tr>
<tr>
<td>2-3</td>
<td>338</td>
<td>53</td>
<td>15.7</td>
</tr>
<tr>
<td>2-4</td>
<td>105</td>
<td>20</td>
<td>19</td>
</tr>
<tr>
<td>3-3</td>
<td>1701</td>
<td>141</td>
<td>8.3</td>
</tr>
<tr>
<td>3-4</td>
<td>901</td>
<td>72</td>
<td>8.0</td>
</tr>
<tr>
<td>4-4</td>
<td>110</td>
<td>6</td>
<td>5.5</td>
</tr>
<tr>
<td>ApoE abn</td>
<td>7</td>
<td>3</td>
<td>5</td>
</tr>
</tbody>
</table>

What is wrong with this patient and is he at increased risk of CVD?

- TC: 317 mg/dl
- Non-HDL C: 293 mg/dl
- HDL C: 42 mg/dl
- TG: 1360 mg/dl

And the answer is yes!

↑ Chylo+ ↑ VLDL+ ↑ LDL

- TC: 317 mg/dl
- Non-HDL C: 293 mg/dl
- HDL C: 42 mg/dl
- TG: 1360 mg/dl
- apoB: 120 mg/dl

↑ Chylomicrons, VLDL, LDL
• “An obese, hypertensive middle-aged man with a cholesterol level of 245 mg/dl, a triglyceride level of 274 mg/dl, an HDL-C level of 31 mg/dl and a calculated LDL-C of 162 mg/dL probably has metabolic syndrome and this should trigger the clinician to seek other components of this cluster including hypertension and hyperglycemia.”

If he is 45, normotensive and not diabetic, his 10-year risk is 5.6% and therefore he does not qualify for statin preventive therapy based on risk alone.

Back to Braunwald

Back to Braunwald:

• If apoB is 85, dx is remnant lipoprotein disorder
• If apoB is 105, dx is elevated HyperTG NormoapoB.
• If apoB is 125, dx is HyperTG HyperapoB.

• 1 and 3 are high risk apoB dyslipoproteinemias, 2 is not. The treatments and treatment targets however are not the same. Not only do Genest and Libby miss the fact that the dx is unknown from the data they believe are complete, but the LDL-C they calculate, may be right or may be totally wrong.
Apolipoprotein B improves risk assessment of future CHD in the Framingham Heart Study beyond LDL-C and non-HDL-C

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