Lipid disease – does standardization affect clinical practice?

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Does lipid standardization affect clinical practice?

- Current understanding of significance of serum lipids
- Clinical utility of lipid measurements
- Impact of standardization
- Impact on clinical practice
Lipid oxidation

Lipid deposition

Inflammation

Atherosclerosis
Cholesterol in Hunter-Gatherers, Higher Primates and Other Mammals

- Hazda
- Inuit
- Ikung
- Pygmy
- San
- Baboon
- Howler
- Night
- Horse
- Boar
- Peccary
- Black Rhino
- African Elephant

Total Cholesterol mmol/l

0 0.50 1.00 1.50 2.00 2.50 3.00 3.50

PROVE IT - TIMI 22

Achieved LDLc (mmol/L)

- 2.07-2.59
- 1.55-2.06
- 1.03-1.54
- <1.03

Wiviott et al. JACC 2005;46:1411-16
Atherosclerosis does not progress when LDL is $< 1.73$ mmol/l

LDLc - The greater the reduction the greater the benefit

Reduction in cholesterol (mmol/l)

% reduction in CHD events

R²=0.63, p<0.003

Brady A, Betteridge J. Br J Cardiol 2003
LDLc - The greater the reduction the greater the benefit

Brady A, Betteridge J. *Br J Cardiol* 2003
Reduce LDL-C and raise HDL-C

1% decrease in LDL-C gives 1% decrease in CHD risk

1% increase in HDL-C gives 2-3% decrease in CHD risk

Low HDL-C and Cardiovascular Risk

An Independent and Frequent Risk Factor


<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Controls (N=601)</th>
<th>Cases (N=321)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cigarette smoking</td>
<td>29%</td>
<td>67%*</td>
</tr>
<tr>
<td>HDL-C &lt;0.90 mmol/l</td>
<td>19%</td>
<td>63%*</td>
</tr>
<tr>
<td>Hypertension (BP &gt;150/90 mmHg)</td>
<td>21%</td>
<td>41%*</td>
</tr>
<tr>
<td>LDL-C ≥160 mg/dL</td>
<td>26%</td>
<td>26%*</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1%</td>
<td>12%*</td>
</tr>
</tbody>
</table>
Why Does HDL Protect?

- Endothelial repair
- Protection against oxidation
- Modulation of endothelial function
- Anti-inflammatory
- Anti-thrombotic
- Protection of the vessel wall
- Cholesterol acceptor
- Cholesterylester donor
- Reverse Cholesterol Transport (RCT)

HDL
Other serum lipids

- Non-HDLc
- Triglycerides
- Lp(a)
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This person’s QRISK score is 14.8.
Their QRiskAge is 62.
A person’s QRiskAge is the age at which a typical person of their sex and ethnicity has their QRISK score.
This QRISK score is calculated using estimated or corrected data. BMI was estimated to be 27.2.
A typical person of the same age, sex and ethnicity has a score of 17.2.

In a crowd of 100 people like you, 15 will get heart disease in the next 10 years.
Heart-healthy lifestyle habits are the foundation of ASCVD prevention
(See 2013 AHA/ACC Lifestyle Management Guideline)

Age ≥21 y and a candidate for statin therapy

Clinical ASCVD

Yes

High-intensity statin
(Moderate-intensity statin if not candidate for high-intensity statin)

No

Age >75 y OR if not candidate for high-intensity statin

Moderate-intensity statin

LDL-C ≥190 mg/dL

Diabetes

LDL-C 70-189 mg/dL

Age 40-75 y

High-intensity statin
(Moderate-intensity statin if not candidate for high-intensity statin)

Yes

Moderate-intensity statin

No

Estimated 10-y ASCVD risk ≥7.5%†

High-intensity statin

Diabetes

LDL-C <70 mg/dL

Primary prevention
(No diabetes, LDL-C 70 to 189 mg/dL, and not receiving statin therapy)

Estimate 10-y ASCVD risk every 4-6 y using Pooled Cohort Equations†

<5%

10-y ASCVD risk‡

In selected individuals, additional factors may be considered to inform treatment decision making§

Clinician-Patient Discussion
Prior to initiating statin therapy, discuss:
1. Potential for ASCVD risk-reduction benefits
2. Potential for adverse effects and drug-drug interactions¶
3. Heart-healthy lifestyle
4. Management of other risk factors
5. Patient preferences
6. If decision is unclear, consider primary LDL-C ≥160 mg/dL, family history of premature ASCVD, lifetime ASCVD risk, abnormal CAC score or ABI, or hs-CRP ≥2 mg/L$
Simon Broome Criteria

- **A diagnosis of definite familial hypercholesterolaemia requires:**
  - cholesterol >7.5 mmol/l in an adult (>6.7 mmol/l in children under 16) or LDL cholesterol >4.9 mmol/l in adults
  - plus tendon xanthomas in patient or first or second degree relative.

- **A diagnosis of possible FH requires:**
  - cholesterol >7.5 mmol/l in an adult (>6.7 mmol/l in children under 16) or LDL cholesterol >4.9 mmol/l in adults
  - plus family history of MI before 60 years in first degree relative or cholesterol >7.5 mmol/l in first or second degree relative.
Changes in use of serum lipids

- Continued use for risk estimation
- Decreasing use of absolute decision limits
- Increasing use of non-HDLc
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Total cholesterol – 3% positive bias, 4% analytical CV

- 9% false positives using a treatment threshold of 6.2 mmol/l
Impact of assay bias on distribution of cholesterol in middle aged men

Impact of assay bias on distribution of cholesterol in middle aged men

Supplementary Fig. 2. Effects of within-subject biological variation of serum-cholesterol, analytical bias and imprecision on cut-off, shown in the figure with two abscises, one lower for cholesterol in mmol/L and the other upper for the same in natural logarithms The cumulated frequency distribution of values with a CVwithin-subject = 6.0 % around the cut-off point 6.21 mmol/L for one sampling (pink) and for two samplings (green).
Distribution of Set-Points of Low Risk Individuals and Probability of Results Above Cut-Off - No Bias

"Cut-off" = 6.21 mmol/L

Frequency or Probability

Cholesterol, mmol/L

0.0 0.2 0.4 0.6 0.8 1.0

1.3 1.4 1.5 1.6 1.7 1.8 1.9 2.0 2.1

In(cholesterol)

Cut-off = 1.8262 = 6.21
CVAnalytical = 0 %
CVAnalytical = 2 %
CVAnalytical = 4 %
CVAnalytical = 6 %
CVAnalytical = 8 %
CVAnalytical = 10 %

Mean = 1.66 = 5
CVBetween = 13.90%
CVWithin = 6.00%
Bias % = 0.0

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Laboratory users and lipid standardization

- Specialists are aware of biological variability
- Other clinicians believe results
- Patients believe results

- We reinforce this by reporting exact values
Impact on patient management

- Management decisions vary for patients close to decision thresholds
  - Family screening
  - Initiation of treatment
  - Intensification of treatment
Can we do better?
Heterogeneity of LDL

antioxidant content
LDL receptor affinity

Particle diameter (nm)

27  26  25.5  24.2  21.8

I   II  III  IV

1.025 1.034 1.038 1.049 1.065

Particle density (g/ml)

triglyceride content
susceptibility to oxidation
HDL and inflammation

Anti-inflammatory HDL

Pro-inflammatory HDL
Apolipoprotein measurement

- ApoB and ApoA1
- Others
- May offer improved reproducibility and better clinical utility
- But measurement not widely available and guidelines are lipid based