Considering the Evidence From Epidemiological and Genetic Studies in Addition to Randomized Controlled Trials in Recommendations for Dyslipidemia Management

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Many similarities, some differences, which include (but are not limited to):

1. The evidence base considered;
2. Inclusion by the NLA panel of atherogenic cholesterol (non-HDL-C and LDL-C) goals.

ACC/AHA - Evidence Considered

- Evaluation was limited to primary analyses from randomized controlled trials (RCTs) with atherosclerotic cardiovascular disease (ASCVD) outcomes and systematic reviews and meta-analyses of RCTs with ASCVD outcomes (published through July 2013).
- Followed the Institute of Medicine’s recommended procedure for establishing evidence-based treatment guidelines based on “Risk-Benefit” evaluation from RCT evidence.
  - Mainly applied to pharmaceutical interventions
  - Few RCTs with ASCVD outcomes were available for lifestyle interventions


NLA - Evidence Considered

- Results from RCTs published through July 2014 to evaluate the effects of lipid-altering interventions on clinical ASCVD events (mainly myocardial infarction, coronary death, and stroke) were examined.
  - Included subgroup assessments and pooled analyses (including of subgroups) from multiple trials, where available.
- Epidemiological, genetic, metabolic and mechanistic investigations were also considered.
  - Applied a combination of the “Risk-Benefit Paradigm” and the “Causal Exposure Paradigm”
    - Underlying framework based on the view that atherosclerosis develops over an extended period and that elevated levels of atherogenic lipoproteins (as indicated by atherogenic cholesterol levels) are “causal exposures”
Strengths and Weaknesses of Lines of Evidence

- **RCTs**
  - **Strengths:** gold standard for testing clinical interventions with least susceptibility to certain types of bias (e.g., selection bias)
  - **Weaknesses:**
    - Generally restricted to evaluation of drugs – reliable RCTs of lifestyle therapies are few
    - Narrow study samples generally – results may be of uncertain clinical relevance to patients with characteristics that differ from those who participated in RCTs
    - Typically aimed at regulatory registration – not necessarily designed to answer the most important clinical questions
- **Epidemiological (observational) studies**
  - **Strengths:** worldwide in scope and have provided reasonably consistent results regarding lipid-related associations with ASCVD event risk
  - **Weaknesses:** more subject to bias and confounding than RCTs
- **Genetic studies (a subset of epidemiological investigations)**
  - **Strength:** reduced likelihood of bias and confounding due to random distribution of genetic variants that affect lipoprotein lipids (Mendelian randomization) and reflect long-term exposure

ACC/AHA - Cholesterol Goals

- The Expert Panel made no recommendations for or against specific LDL-C or non-HDL-C targets for the primary or secondary prevention of ASCVD.
- The ACC/AHA Expert Panel did not find RCT evidence to support titrating cholesterol-lowering drug therapy to achieve LDL-C and non-HDL-C levels as recommended by the National Cholesterol Education Program Adult Treatment Panel III.
NLA - Cholesterol Goals

NLA Expert Panel Consensus Views:

• Treatment goals are useful to ensure that the aggressiveness of therapy to lower atherogenic cholesterol is matched to absolute risk for an event, and also to facilitate effective communication between patients and clinicians to maximize long-term adherence to treatment.

• Treatment goals were established for LDL-C and non-HDL-C, based on extrapolation of results from RCTs, observational and genetic studies:
  – Primary prevention
    • Non-HDL-C <130, LDL-C <100 mg/dL
  – Secondary and very high risk prevention
    • Non-HDL-C <100, LDL-C <70 mg/dL
    • ASCVD or DM plus ≥ 2 major ASCVD risk factors


NLA Cholesterol Goals - Continued

• Results from RCTs of various methods for lowering atherogenic cholesterol (e.g., pharmacotherapy, diet, ileal bypass surgery) indicate that lower on-treatment levels have been consistently associated with lower absolute risk for an ASCVD event.
  – Most RCTs of lipid-lowering drug therapies tested drug treatment against a placebo control, or a more intensive vs. less-intensive statin treatment regimen.
  – The strategy of treating patients to a specific LDL-C or non-HDL-C level has not been tested in any of the large outcomes trials assessing ASCVD morbidity and mortality.

• Nevertheless, the evidence from RCTs generally aligns with results from observational and genetic studies.
  – Consistent with a log-linear relationship between the levels of atherogenic cholesterol and absolute ASCVD event risk;
  – Support “lower is better” hypothesis for atherogenic cholesterol;
  – Subsequent RCT evidence has further supported this hypothesis
    • Statin + ezetimibe and statin + PCSK9 inhibition

Log-Linear Relationship Between Serum Cholesterol and Coronary Heart Disease (CHD) Mortality

![Graph showing log-linear relationship between serum cholesterol and CHD mortality.]


Relationship Between % Reduction in Total Cholesterol and % Reduction in CHD Incidence

![Graph showing the relationship between % reduction in total cholesterol and % reduction in CHD incidence.]


Reduction in Atherogenic Cholesterol with a PCSK9 Inhibitor Produced a Further Decrease in Cardiovascular Events

Hazard ratio, 0.47 (95% CI, 0.28–0.78)
P = 0.003

LDL-C = 120 mg/dL with standard therapy vs. 48 mg/dL with evolocumab

On-Treatment LDL-C and CHD Events

Data abstracted from original publications

Relationship Between LDL-C Levels and CHD Events in Secondary Prevention

Change in Relative Risk of CHD Events According to Non-HDL-C Reduction

Statin Trials: Better Outcomes for Lower Atherogenic Cholesterol
Risk of Major Cardiovascular Events by LDL-C and Non-HDL-C Categories

When only one is elevated (discordance) during statin treatment, risk follows non-HDL-C rather than LDL-C


Studies of Genetic Variants that Alter Lipoprotein Lipids Have Changed the Landscape in Recent Years

Results from studies of genetic variants have suggested the following:

1. Support the view that “lower is better” for atherogenic cholesterol;
2. Suggest that it is not only how low, but how long atherogenic cholesterol levels are low, that is important;
3. Are consistent with a causal role for VLDL-C (or a variable strongly correlated with VLDL-C) in ASCVD risk;
4. Raise questions about the potential for raising HDL-C per se as a strategy to reduce ASCVD risk.
Study Design – Loss of Function Alleles

Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Reference Group</th>
<th>NPQ1L LDL-C Score Above Median</th>
<th>HMGR LDL-C Score Above Median</th>
<th>Both LDL-C Scores Above Median</th>
<th>p Value</th>
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<tbody>
<tr>
<td>Sample size</td>
<td>27,744</td>
<td>28,611</td>
<td>25,577</td>
<td>26,444</td>
<td>2.3 × 10⁻⁶⁷</td>
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<tr>
<td>LDL-C, mg/dl</td>
<td>132.5 ± 31.8</td>
<td>130.1 ± 33.1</td>
<td>126.6 ± 27.7</td>
<td>126.7 ± 23.3</td>
<td>NS</td>
</tr>
<tr>
<td>Age, yrs</td>
<td>59.4 ± 6.3</td>
<td>59.1 ± 6.7</td>
<td>58.9 ± 6.1</td>
<td>59.6 ± 3.9</td>
<td>NS</td>
</tr>
<tr>
<td>Males</td>
<td>43.6</td>
<td>44.1</td>
<td>43.3</td>
<td>43.9</td>
<td>NS</td>
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<tr>
<td>Weight, lbs</td>
<td>165.5 ± 35.8</td>
<td>165.2 ± 36.5</td>
<td>165.9 ± 36.2</td>
<td>167.4 ± 35.4</td>
<td>NS</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.2 ± 5.4</td>
<td>27.9 ± 5.7</td>
<td>27.1 ± 5.1</td>
<td>27.7 ± 4.9</td>
<td>NS</td>
</tr>
<tr>
<td>HDL-C, mg/dl</td>
<td>51.8 ± 14.7</td>
<td>51.0 ± 14.8</td>
<td>51.7 ± 14.2</td>
<td>51.2 ± 15.1</td>
<td>NS</td>
</tr>
<tr>
<td>TG, mg/dl</td>
<td>135.3 (78-158)</td>
<td>134.4 (77-161)</td>
<td>134.9 (81-164)</td>
<td>135.3 (79-156)</td>
<td>NS</td>
</tr>
<tr>
<td>Lipid treatment</td>
<td>4.0</td>
<td>4.7</td>
<td>5.1</td>
<td>4.6</td>
<td>NS</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>125.8 ± 16.4</td>
<td>125.1 ± 16.1</td>
<td>126.0 ± 17.5</td>
<td>125.7 ± 16.8</td>
<td>NS</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>73.9 ± 11.2</td>
<td>74.2 ± 10.8</td>
<td>74.3 ± 11.5</td>
<td>73.7 ± 11.0</td>
<td>NS</td>
</tr>
<tr>
<td>BP treatment</td>
<td>36.1</td>
<td>37.8</td>
<td>36.5</td>
<td>36.9</td>
<td>NS</td>
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<tr>
<td>Current smoker</td>
<td>12.8</td>
<td>12.5</td>
<td>13.3</td>
<td>12.7</td>
<td>NS</td>
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<tr>
<td>Former smoker</td>
<td>32.1</td>
<td>30.9</td>
<td>31.4</td>
<td>32.6</td>
<td>NS</td>
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<td>Diabetes</td>
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<td>6.6</td>
<td>6.0</td>
<td>5.9</td>
<td>NS</td>
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</tbody>
</table>

Effect of Lower LDL-C Mediated by Polymorphisms for NPC1L1, HMGCR, or Both

2.5% ↓ Odds for CHD per 1% ↓ LDL-C


LDL-C CHD Risk – How Low for How Long?

Each 1% Genetic ↓ LDL-C Associated with ~2.5% to 3.0% ↓ CHD Risk

Percent Reduction in LDL-C

Percent Reduction in CHD

Statins - 5 y

APOB

SORT1

LDLR

PCSK9

Y142X

C679X

Cholesterol Levels as a Function of Lipoprotein Cholesterol-altering Genetic Alleles

Risk Estimates for Ischemic Heart Disease According to Lipoprotein Cholesterol Level
Summary: Copenhagen Studies

• Top quintile vs. bottom quintile
  • LDL-C: 80% increase in CHD risk
  • Remnant-C (VLDL-C): 130% increase in CHD risk

• Genetic variants associated with elevated LDL-C and remnant-C (VLDL-C) – but not HDL-C – are associated with increased CVD risk.
  • Effect for LDL-C-raising alleles: each 1 mmol/L (38.7 mg/dL) increase in LDL-C is associated with 47% increased risk
  • Effect for remnant-C (VLDL-C)-raising alleles: each 1 mmol/L (38.7 mg/dL) increase in VLDL-C is associated with 182% increased risk
  • Thus, a given increase in VLDL-C in mg/dL is associated with a larger increase in risk than a given increase in LDL-C
  • Supports the importance of non-HDL-C treatment goals

Of 15 Variants that Alter HDL-C, 6 Are Associated with MI Risk: All of These Alter at Least One Other Lipid Fraction (LDL-C or VLDL-C)

<table>
<thead>
<tr>
<th>Gene(s) of interest within or near associated interval</th>
<th>Major allele, minor allele frequency</th>
<th>Modelled allele</th>
<th>Effect of modelled allele on plasma HDL cholesterol (mmol/L)</th>
<th>Effect of modelled allele on plasma triglycerides (mmol/L)</th>
<th>Effect of modelled allele on plasma LDL cholesterol (mmol/L)</th>
<th>Sample size (MI cases/MI-free controls)</th>
<th>For modelled allele, observed change in MI risk (%; 95% CI)</th>
<th>For modelled allele, p-value for association with MI</th>
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</thead>
<tbody>
<tr>
<td>PLI</td>
<td>G, T (0.10)</td>
<td>T</td>
<td>-0.14</td>
<td>-1.06</td>
<td>19.12 (6.50; 14.72)</td>
<td>17.16 (7.57; 12.60)</td>
<td>4x10^-1</td>
<td>6x10^-1</td>
</tr>
<tr>
<td>TNX1</td>
<td>A, G (0.15)</td>
<td>G</td>
<td>-0.24</td>
<td>-1.06</td>
<td>19.12 (6.50; 14.72)</td>
<td>17.16 (7.57; 12.60)</td>
<td>4x10^-1</td>
<td>6x10^-1</td>
</tr>
<tr>
<td>APOA1-APOC3-APOA4-APOA5</td>
<td>A, G (0.07)</td>
<td>A</td>
<td>-0.27</td>
<td>-0.05</td>
<td>18.12 (6.50; 14.72)</td>
<td>17.16 (7.57; 12.60)</td>
<td>4x10^-1</td>
<td>6x10^-1</td>
</tr>
<tr>
<td>GALNT2</td>
<td>A, C (0.10)</td>
<td>A</td>
<td>-0.27</td>
<td>-1.06</td>
<td>19.12 (6.50; 14.72)</td>
<td>17.16 (7.57; 12.60)</td>
<td>4x10^-1</td>
<td>6x10^-1</td>
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<tr>
<td>ANGPTL4</td>
<td>C, T (0.10)</td>
<td>C</td>
<td>-0.27</td>
<td>-1.06</td>
<td>19.12 (6.50; 14.72)</td>
<td>17.16 (7.57; 12.60)</td>
<td>4x10^-1</td>
<td>6x10^-1</td>
</tr>
<tr>
<td>CEPT1</td>
<td>C, A (0.10)</td>
<td>A</td>
<td>-0.30</td>
<td>-0.05</td>
<td>16.50 (6.50; 14.72)</td>
<td>17.16 (7.57; 12.60)</td>
<td>4x10^-1</td>
<td>6x10^-1</td>
</tr>
<tr>
<td>LPSG</td>
<td>A, G (0.05)</td>
<td>G</td>
<td>0.54</td>
<td>0.05</td>
<td>17.16 (7.57; 12.60)</td>
<td>17.16 (7.57; 12.60)</td>
<td>4x10^-1</td>
<td>6x10^-1</td>
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<tr>
<td>MUXPL</td>
<td>C, T (0.11)</td>
<td>T</td>
<td>0.05</td>
<td>0.05</td>
<td>19.12 (6.50; 14.72)</td>
<td>17.16 (7.57; 12.60)</td>
<td>4x10^-1</td>
<td>6x10^-1</td>
</tr>
<tr>
<td>ARB12</td>
<td>G, A (0.14)</td>
<td>G</td>
<td>0.03</td>
<td>-0.05</td>
<td>19.12 (6.50; 14.72)</td>
<td>17.16 (7.57; 12.60)</td>
<td>4x10^-1</td>
<td>6x10^-1</td>
</tr>
<tr>
<td>MAN1A-M4X</td>
<td>G, C (0.05)</td>
<td>G</td>
<td>0.03</td>
<td>-0.05</td>
<td>19.12 (6.50; 14.72)</td>
<td>17.16 (7.57; 12.60)</td>
<td>4x10^-1</td>
<td>6x10^-1</td>
</tr>
<tr>
<td>FCIT1</td>
<td>T, C (0.12)</td>
<td>T</td>
<td>0.03</td>
<td>-0.05</td>
<td>15.16 (6.50; 14.72)</td>
<td>17.16 (7.57; 12.60)</td>
<td>4x10^-1</td>
<td>6x10^-1</td>
</tr>
<tr>
<td>LOXL1-SNPs</td>
<td>T, C (0.12)</td>
<td>T</td>
<td>0.03</td>
<td>-0.05</td>
<td>19.12 (6.50; 14.72)</td>
<td>17.16 (7.57; 12.60)</td>
<td>4x10^-1</td>
<td>6x10^-1</td>
</tr>
<tr>
<td>LPC</td>
<td>C, T (0.22)</td>
<td>T</td>
<td>0.05</td>
<td>0.07</td>
<td>17.16 (6.50; 14.72)</td>
<td>17.16 (7.57; 12.60)</td>
<td>4x10^-1</td>
<td>6x10^-1</td>
</tr>
<tr>
<td>PPARA</td>
<td>C, T (0.11)</td>
<td>T</td>
<td>0.01</td>
<td>-0.05</td>
<td>17.16 (6.50; 14.72)</td>
<td>17.16 (7.57; 12.60)</td>
<td>4x10^-1</td>
<td>6x10^-1</td>
</tr>
</tbody>
</table>

Effects on Lipid/Lipoprotein Levels of Increasing Number of Apo A5 Alleles

<table>
<thead>
<tr>
<th></th>
<th>Mean difference per allele (95% CI)</th>
<th>p value for association</th>
<th>F (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglyceride</td>
<td>0.25 mmol/L [0.20 to 0.30]</td>
<td>4.4 x 10^-24</td>
<td>75% (56 to 82)</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>-0.03 mmol/L [-0.039 to 0.068]</td>
<td>3.0 x 10^-1</td>
<td>71% (59 to 88)</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>-0.01 mmol/L [-0.074 to 0.054]</td>
<td>0.76</td>
<td>81% (74 to 87)</td>
</tr>
<tr>
<td>Apolipoprotein A1</td>
<td>-0.023 g/L [-0.005 to 0.041]</td>
<td>0.01</td>
<td>42% (0 to 72)</td>
</tr>
<tr>
<td>Apolipoprotein B</td>
<td>0.037 g/L [0.018 to 0.054]</td>
<td>9.0 x 10^-4</td>
<td>37% (0 to 70)</td>
</tr>
</tbody>
</table>

Each Apo A5 loss-of-function allele is associated with an ↑ of 22.1 mg/dL in TG. This translates to ~4.4 mg/dL for ↑ VLDL-C (and an increase of 15-20% in CHD risk).
CHD Event Risk in Dyslipidemia Subgroups from Trials of Fibrates

Dyslipidemia subgroups: ACCORD, TG ≥204 mg/dL, HDL-C ≤34 mg/dL; FIELD, TG ≥204 mg/dL, HDL-C <80 mg/dL in men and <50 mg/dL in women; BIP, TG ≥200 mg/dL, HDL-C <35 mg/dL; HHS, TG ≥204 mg/dL, HDL-C <42 mg/dL; VA-HIT, TG >180 mg/dL, HDL-C <40 mg/dL.


Updated Meta-analysis of Fibrates and CVD Events in Subjects with High TG and Low HDL-C

Hypothesis – lower HDL-C reflects greater severity of postprandial HTG.

Conclusions

• The ACC/AHA Guidelines used the IOM Risk-Benefit paradigm to construct recommendations for lipid management based mainly on primary analyses from RCTs with ASCVD outcomes.
• The NLA Expert Panel Recommendations were based on a combination of the Risk-Benefit and Causal Exposure paradigms.
  – Considered results from RCTs of lipid-altering interventions with ASCVD outcomes, including subgroup analyses;
  – Also considered results from epidemiological studies, with particular emphasis on investigations of lipoprotein lipid-altering variants and their relationships with ASCVD outcomes.

Conclusions (continued)

• RCT results and results from genetic studies have been generally supportive of the following conclusions regarding ASCVD risk:
  – Lower is better for atherogenic cholesterol;
  – Length of exposure to lower or higher levels of atherogenic cholesterol influences risk;
  – A given mg/dL difference in VLDL-C is associated with an even larger difference in risk for CHD than the same difference in LDL-C;
    • This supports a causal role for VLDL-C, or some variable closely associated with VLDL-C, in ASCVD risk and the usefulness of non-HDL-C as a target of therapy;
  – Genetic studies raise questions about the likely efficacy of raising HDL-C per se as a strategy to lower ASCVD risk.