Data Supported Evidence for Differences in the ACC/AHA Guidelines and NLA Recommendations for Dyslipidemia Management

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Selected Differences in the ACC/AHA Guidelines and NLA Expert Panel Recommendations

Many similarities, some differences, which include:

1. Evidence considered
2. Inclusion by the NLA panel of atherogenic cholesterol (non-HDL-C and LDL-C) goals
3. Recommended pharmacological therapies
   - Greater support for use of combination drug therapies (to reach goal levels of atherogenic cholesterol) as a therapeutic option in the NLA recommendations, particularly for high and very high risk patients
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).
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, as well as subgroup assessments and pooled analyses from multiple trials, where available.
- Epidemiological, genetic, metabolic and mechanistic investigations were also considered.

ACC/AHA - Cholesterol Goals

- **Recommendation:** The Expert Panel made no recommendations for or against specific LDL-C or non-HDL-C targets (goals) 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 [goal] levels as recommended by the National Cholesterol Education Program Adult Treatment Panel III.
  - The ACC/AHA Expert Panel noted that they did find RCT evidence that use of therapy (e.g., niacin) to additionally lower non-HDL-C after the LDL-C target was achieved did not further reduce ASCVD outcomes.

NLA - Cholesterol Goals

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 recommended
  – Primary prevention: non-HDL-C <130, LDL-C <100 mg/dL
  – Secondary 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 are 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.

• The evidence from RCTs generally aligns with results from observational 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

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

MRFIT SIX-YEAR FOLLOW-UP

N = 356,222

CHD Mortality Per 1000 (Age Adjusted)

Serum Cholesterol (mg/dL)

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

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

On-Treatment LDL-C and CHD Events

\[ y = 0.046x - 1.53 \]
\[ R^2 = 0.95 \]

Primary Prevention

% with CHD Events, Projected to 5 Years

Mean or Median LDL-C, mg/dL

Data abstracted from original publications
Relationship Between LDL-C Levels and CHD Events in Secondary Prevention

![Graph showing the relationship between LDL-C levels and CHD events.](#)

Very Low LDL-C and Non-HDL-C in Statin Trials and Major CVD Event Risk

Boekholdt et al. JACC 2014;64:485-494
Risk of Major Cardiovascular Events by LDL-C and Non-HDL-C Categories

<table>
<thead>
<tr>
<th>Target Level</th>
<th>LDL-C</th>
<th>Non-HDL-C</th>
<th>No. of Major Cardiovascular Events</th>
<th>Total No. of Participants</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥100 mg/dL</td>
<td>≥130 mg/dL</td>
<td>1877</td>
<td>10419</td>
<td>1.21 (1.13-1.29)</td>
<td></td>
</tr>
<tr>
<td>≥100 mg/dL</td>
<td>&lt;130 mg/dL</td>
<td>467</td>
<td>2873</td>
<td>1.02 (0.92-1.12)</td>
<td></td>
</tr>
<tr>
<td>&lt;100 mg/dL</td>
<td>≥130 mg/dL</td>
<td>283</td>
<td>1435</td>
<td>1.32 (1.17-1.50)</td>
<td></td>
</tr>
<tr>
<td>&lt;100 mg/dL</td>
<td>&lt;130 mg/dL</td>
<td>2760</td>
<td>23426</td>
<td>1.00 [Reference]</td>
<td></td>
</tr>
</tbody>
</table>

**ACC/AHA-Statin Therapy**

- **Recommendation:** The appropriate intensity of statin therapy should be used to reduce ASCVD risk in those most likely to benefit:
  a) secondary prevention in individuals with clinical ASCVD,
  b) primary prevention in individuals with primary elevations of LDL-C ≥190 mg/dL,
  c) primary prevention in individuals with diabetes 40 to 75 years of age who have LDL-C 70 to 189 mg/dL, and
  d) primary prevention in individuals without diabetes and with estimated 10-year ASCVD risk ≥7.5%, 40 to 75 years of age who have LDL-C 70 to 189 mg/dL.

- Nonstatin therapies, as compared with statin therapy, do not provide acceptable ASCVD risk-reduction benefits relative to their potential for adverse effects in the routine prevention of ASCVD.

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NLA - Cholesterol-Lowering Drug Therapies

• **Expert Panel Consensus View:** Unless contraindicated, first-line drug therapy for treatment of elevated atherogenic cholesterol levels is a moderate or high intensity statin. Some patients have contraindications for, or intolerance to, statin therapy. For such patients, non-statin drug therapy may be considered. Non-statin drug classes for lipid management include cholesterol absorption inhibitors, bile acid sequestrants, fibric acids, long-chain omega-3 fatty acid concentrates, and nicotinic acid.
  
  – Therapy with a statin plus a second (or third) agent may be considered for patients who have not reached their treatment goals for atherogenic cholesterol levels, particularly in patients with high or very high risk.
  – The maximum tolerated statin dosage should generally be used before add-on therapy is considered.
  – Evidence from RCTs does not support the routine use of a second agent when atherogenic cholesterol levels are below goal thresholds while on statin therapy.

Rationale for Non-Statin Drug Therapies

- Statins are not unique in their cholesterol-lowering effects, except in potency.
- Results from studies of non-statin approaches to cholesterol lowering suggest that the degree of risk reduction with statin therapy for a given reduction in atherogenic cholesterol is similar to that observed with other cholesterol-lowering interventions.

Rationale for Non-Statin Drug Therapies - Continued

• Much of the available data for the effects of add-on therapy was in studies of administration to patients with relatively low levels of atherogenic cholesterol during statin treatment.

• Limited RCT evidence is available to guide therapy in the patient taking the highest tolerated dosage of a statin whose levels of atherogenic cholesterol remain above goal.
  – Until RCT data are available to better define the potential benefits and risks of add-on therapies in patients whose levels of atherogenic cholesterol remain elevated while taking the highest tolerated dosage of statin, the NLA Expert Panel recommends that consideration be given to use of combination therapy with agents that further lower non-HDL-C and LDL-C to achieve goal levels.

Baseline (On Statin) Mean or Median Atherogenic Cholesterol Levels in Studies of Add-On Therapy

<table>
<thead>
<tr>
<th>Trial</th>
<th>LDL-C (mg/dL)</th>
<th>Non-HDL-C (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPS2-THRIVE</td>
<td>64</td>
<td>89</td>
</tr>
<tr>
<td>AIM-HIGH</td>
<td>74</td>
<td>111</td>
</tr>
<tr>
<td>ACCORD*</td>
<td>101</td>
<td>137</td>
</tr>
</tbody>
</table>

*Median triglyceride concentration 162 mg/dL, top tertile ≥204 mg/dL

CHD Event Risk in Dyslipidemia Subgroups from Trials of Fibrates

### A Subgroups with Dyslipidemia

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds Ratio (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>ACCORD</td>
<td>0.65 (0.54–0.78)</td>
</tr>
<tr>
<td>FIELD</td>
<td></td>
</tr>
<tr>
<td>BIP</td>
<td></td>
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<tr>
<td>HHS</td>
<td></td>
</tr>
<tr>
<td>VA–HIT</td>
<td></td>
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</tbody>
</table>

### B Complementary Subgroups

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds Ratio (95% CI)</th>
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<tr>
<td>ACCORD</td>
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<tr>
<td>FIELD</td>
<td></td>
</tr>
<tr>
<td>BIP</td>
<td></td>
</tr>
<tr>
<td>HHS</td>
<td>0.94 (0.84–1.05)</td>
</tr>
<tr>
<td>VA–HIT</td>
<td></td>
</tr>
</tbody>
</table>

Dyslipidemia subgroups: ACCORD, TG ≥204 mg/dL, HDL-C ≤34 mg/dL; FIELD, TG ≥204 mg/dL, HDL-C <40 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.

Japan EPA Lipid Intervention: Subgroup with TG ≥150 mg/dL, HDL-C <40 mg/dL

Conclusions

• Commonalities and differences exist between the cholesterol management guidelines recently issued by the ACC/AHA and the recommendations of the NLA Expert Panel.
  – Differences largely reflect a greater willingness of the NLA Expert Panel to consider evidence beyond primary results from RCTs, and to apply expert opinion in areas where RCT evidence is incomplete, such as in the use of combination therapy for patients with elevated levels of atherogenic cholesterol despite maximally tolerated statin therapy.
  – Commonalities include the centrality of lifestyle therapies, use of statins as first-line pharmacotherapy, and a patient-centered approach in which patients and clinicians fully discuss the objectives and potential risks associated with the recommended therapies.