Two Different Prevention Approaches
Two Different Perspectives


Original Articles
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Objectives

• To provide an overview of the American College of Cardiology/American Heart Association and the National Lipid Association lipid management approaches for ASCVD prevention
• To identify the similarities and differences between the two approaches
• To provide the information needed to decide which approach to use and when
Similarities between the ACC/AHA Guideline and the NLA Recommendations

• ASCVD risk reduction is the goal of therapy
• Lipid screening for primary prevention is recommended at 5-year intervals
• Lifestyle therapy is advocated as first step in all treatment algorithms
• Moderate- or high-intensity statin therapy is the central focus of pharmacotherapy
• Patient-provider discussion of risk/benefit ratio precedes all decisions on drug treatment
• Regular lipid follow-up is warranted to assess adherence to therapy
The Differences

Evidence base
Central focus
Lipid goals
Non-statins
Risk calculator

ACC/AHA

NLA
Evidence Base

**ACC/AHA**
- Randomized controlled trials (RCT) with ASCVD outcomes
- Meta-analyses of RCT

**NLA**
- RCT with ASCVD outcomes
- Meta-analyses of RCT
- Selected post-hoc analyses of RCT
- Observational epidemiologic studies
- Genetic studies
- Metabolic studies
- Mechanistic studies
Randomized Controlled Trials (RCT)

**Strengths**

- Systematically test effect(s) of an intervention on pre-specified outcomes in defined populations
- Their use minimizes confounding
- Considered to be the highest level of evidence

**Limitations**

- Ability to generalize results to real-world patients may be limited due to exclusion criteria
- Many are designed primarily to gain regulatory registration for pharmaceutical agents
Observational Epidemiologic Studies

**Strengths**
- Worldwide in scope and may assess ASCVD risk across populations
- Cohort studies evaluate mortality and morbidity within populations

**Limitations**
- Residual confounding may occur even after matching, stratification, and multivariate adjustment because of measurement imprecision or unmeasured or unknown risk factors
Observational Epidemiologic Cohort Study of 2146 Patients with FH and no CHD at Baseline

Kaplan-Meier curve estimates of cumulative coronary heart disease-free survival among patients with Familial hypercholesterolemia according to statin treatment (P<0.001 for difference)

Genetic Linkage Studies

**Strengths**
- Good for identifying areas of increased risk across the genome
- Reduces the likelihood of confounding by focusing on single variables: genetic mutations

**Limitations**
- Inherently limited in identifying complex traits such as ASCVD, in which multiple genes are likely involved in causation
Data Demonstrating Genetic Variants Affecting ASCVD Risk

• Loss of function mutations in the gene encoding for PCSK9 (the serine protease responsible for lysosomal catabolism of the LDL receptor) are associated in Black subjects with 28% reduction in LDL-C and an 88% CHD relative risk reduction (p=0.008 for the reduction, 95% CI 0.02-0.81, p=0.03)

• Loss of function mutations in the gene encoding for NPC1L1 (the protein that facilitates proximal small intestinal absorption of cholesterol) are associated with a 12 mg/dL reduction in LDL-C and a 55% CHD relative risk reduction (p=0.04 for the reduction, 95% CI 0.25-0.87, p=0.008)

Evidence Base: Summary

• ACC/AHA
  – Examined RCT with ASCVD outcomes and meta-analyses of RCT. Only the highest level of evidence on statins in defined populations was employed to assess ASCVD outcomes.

• NLA
  – Included evidence from RCT, meta-analysis of RCT, selected post-hoc analyses of RCT, genetic, metabolic and mechanistic studies. This approach is consistent with the perspective of previous NCEP ATPs and international guidelines.
# Central Focus of Guideline

**ACC/AHA**
- Identification of statin benefit groups
- Initiation and maintenance of high- or moderate-intensity statin therapy
- No recommendation for or against lipid goals
- Recommendation against non-statin therapy because of less favorable net benefit

**NLA**
- Identification of an individual patient’s ASCVD risk based on clinical parameters and risk factors
- Initiation of ASCVD risk-based lipid-lowering therapy
- Maintenance of lipid goals to assess effective reduction of atherogenic lipoproteins and enhance adherence
- Use of high- or moderate-intensity statins, ± non-statins, if necessary, to achieve goals
ACC/AHA Statin Benefit Groups

H=High-intensity statin; M=Moderate-intensity statin

- **Clinical ASCVD** (H preferred; M if age >75 or if not candidate for H).
- **Primary elevations of LDL-C ≥190 mg/dL** (H preferred; M if not candidate for H).
- **Age 40-75 years with diabetes, and LDL-C 70-189 mg/dL, no clinical ASCVD** (M if 10-year risk <7.5%; H if ≥7.5%).
- **Age 40-75 years, no clinical ASCVD or diabetes, LDL-C 70-189 mg/dL, and estimated 10-year ASCVD risk ≥7.5% using Pooled Cohort Equations** (M or H).
ACC/AHA Perspective on Statin Therapy

- Statin intensity trials showed clear benefit for high-intensity versus moderate-intensity statins.
- Because fixed doses, not dosage titrations, were employed, one should not assume that a dosage titration strategy is correct or that addition of non-statins to achieve low LDL-C is indicated.
ACC/AHA Perspective on Non-Statin Lipid Drug Therapy

• Non-statin therapies, as compared to statin therapy, do not provide acceptable ASCVD risk reduction benefits relative to their potential for adverse effects in the routine prevention of ASCVD.
  – Niacin in AIM-HIGH and HPS-2 THRIVE
  – Fibrates in ACCORD-Lipid and FIELD
2013 ACC/AHA Guideline
Additional Markers of Increased ASCVD Risk

• Consider for additional assessment of ASCVD risk in patients who do not fall into one of the 4 statin benefit groups (5-7.4% 10-year risk)
  – LDL-C ≥160 mg/dL
  – Family history premature ASCVD
  – CAC score ≥300 Agatston units or 75th %-ile
  – Hs-CRP ≥2 mg/L
  – Ankle-brachial index <0.9
  – High lifetime risk @ age 20-59
Overview of the NLA Recommendations

1. A stepwise approach to risk assessment should be employed to identify the most appropriate risk management strategy
2. Lifestyle therapy is the first step in all ASCVD preventive recommendations, regardless of baseline risk
3. Judicious use of evidence-based drug therapy, particularly moderate and high dose statins, is associated with optimal ASCVD risk reduction
4. When excessive circulating atherogenic cholesterol (non-HDL-C [primary target] and LDL-C) persists after appropriate lifestyle and statin therapy, the use of non-statin therapy should be considered
5. Long-term follow-up fostered by provider-patient communication is essential for optimal ASCVD prevention
Meta-Analysis: Changes in Non-HDL-C Predict CHD Risk Reduction

What is the Advantage of Non-HDL-C over LDL-C in Assessing ASCVD Risk?

• Non-HDL-C is more predictive of ASCVD risk than LDL-C in observational studies. The same is true for on-treatment levels in clinical trials of statin therapy.

• When non-HDL-C and LDL-C are discordant, risk follows non-HDL-C.

• Non-HDL-C testing is universally available, requires no additional cost, and accurate values may be obtained in the non-fasting state.

NLA Recommendations: Stepwise Approach to Risk Assessment

1. Identify highest ASCVD risk category that applies to the patient
2. Employ atherogenic cholesterol (non-HDL-C and LDL-C) goals
3. If very-high risk, begin with moderate- or high-intensity statin with non-HDL-C and LDL-C goals <100 and <70 mg/dL respectively
4. In remaining patients count number of major risk factors and treat to goals for non-HDL-C <130 and LDL-C <100 mg/dL respectively
Major ASCVD Risk Factors

- Age (♂ ≥45 years or ♀ ≥55 years)
- CHD in 1° relative <55 years ♂ or 65 years ♀
- Current cigarette smoking
- BP ≥140/90 mm Hg
- HDL-C <40 mg/dL ♂ or <50 mg/dL ♀
### Criteria for ASCVD Risk Assessment, Treatment Goals, Levels at which to Consider Drug Therapy

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Criteria</th>
<th>Treatment Goal</th>
<th>Consider Drug Therapy</th>
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<tbody>
<tr>
<td></td>
<td><strong>Non-HDL-C mg/dL LDL-C mg/dL</strong></td>
<td></td>
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<tr>
<td>Low</td>
<td>0-1 major ASCVD risk factors</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Consider other risk indicators, if known</td>
<td>&lt;130</td>
<td>≥190</td>
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<tr>
<td></td>
<td></td>
<td>&lt;100</td>
<td>≥160</td>
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<tr>
<td>Moderate</td>
<td>2 major ASCVD risk factors</td>
<td>&lt;130</td>
<td>≥160</td>
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<tr>
<td></td>
<td>Consider quantitative risk scoring</td>
<td>&lt;100</td>
<td>≥130</td>
</tr>
<tr>
<td></td>
<td>Consider other risk indicators</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>≥3 major ASCVD risk factors</td>
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<td></td>
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<tr>
<td></td>
<td>Diabetes mellitus* (Type 1 or 2)</td>
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<tr>
<td></td>
<td>0-1 other major ASCVD risk factors, and</td>
<td></td>
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<tr>
<td></td>
<td>No evidence of end organ damage</td>
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<tr>
<td></td>
<td>Chronic kidney disease stage 3B or 4</td>
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<td></td>
<td>LDL-C ≥190 mg/dL (severe hypercholesterolemia)</td>
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<tr>
<td></td>
<td>Quantitative risk score reaching the high-risk threshold</td>
<td></td>
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<tr>
<td>Very High</td>
<td>ASCVD*</td>
<td></td>
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<tr>
<td></td>
<td>Diabetes mellitus* (Type 1 or 2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥2 other major ASCVD risk factors or</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Evidence of end organ damage</td>
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</table>

For patients with ASCVD or diabetes mellitus, consideration should be given to use of moderate- or high-intensity statin therapy, irrespective of baseline atherogenic cholesterol levels.

Further Risk Assessment in Patients with Two Major Risk Factors

- **Key Clinical Criteria**
  - Multi-pack/day cigarette smoking; strong family history of premature CHD; non-HDL-C ≥190 mg/dL or LDL-C ≥160 mg/dL

- **High Risk Quantitative Risk Scoring**
  - 10-year FRS ≥10%; ACC/AHA 10-year risk ≥15%; lifetime risk ≥45%

- **High Risk Biomarkers**
  - CAC score ≥300 Agatston units or ≥75th %-ile; hs-CRP ≥2.0 mg/L; Lp(a) ≥50 mg/dL (protein; isoform insensitive assay); or urine albumin/creatinine ratio ≥30 mg/g
NLA Perspective on Statin Therapy

- Statin therapy is the most potent and evidence-based approach to lowering atherogenic lipoproteins (non-HDL-C and LDL-C) and reduces ASCVD events
- Statin intensity trials showed clear benefit for high-intensity versus moderate-intensity statins
- Broad-based evidence supports “lower is better” concept, and provides an opportunity for clinicians to address residual risk above that addressed by appropriately-dosed statin therapy
NLA Perspective on Non-Statin Lipid Drug Therapy

- If non-HDL-C and LDL-C goals are not achieved with statin therapy, the addition of evidence-based non-statin therapy should be considered to lower atherogenic cholesterol levels and to achieve goals
  - Ezetimibe is a safe, evidence-based non-statin therapy that may be considered in post MI patients and selected other patients with elevated non-HDL-C and/or LDL-C
  - Resins or niacin may be considered in selected patients
  - Meta-analyses of fibrate therapy in subgroups with atherogenic dyslipidemia suggest ASCVD risk reduction
Key Question

• Does LDL-C Lowering using approaches aside from maximum statin monotherapy reduce ASCVD risk?
Efficacy of Intensive Lowering of LDL-C in Subjects with Low Baseline LDL-C

- Meta-analysis of RCT of >1000 participants and ≥2 years treatment duration of more versus less intense statin trials involving 169,138 subjects
- The major vascular event reduction, among in those with baseline LDL-C <77 mg/dL per further 39 mg/dL reduction was 29% (99% CI 2-48, p=0.007); in those with baseline LDL-C <70 mg/dL, similar reduction in LDL-C continued to demonstrate MVE reduction (RR 0.63, 99% CI 0.41-0.95, p=0.004).

Variability of Achieved LDL-C With High-Intensity Statin Therapy

Meta analysis of 8 statin RCT involving 38,253 subjects of whom 5,387 had 6,286 major CV events and had baseline and 1 year lipids and lipidproteins.

From TNT, SPARCL, IDEAL and JUPITER demonstrating variability of LDL-C lowering. >40% did not achieve LDL-C <70 mg/dL on atorvastatin 80 or rosvuavastatin 20 mg daily.
LDL-C and Non-HDL-C Achieved in Statin Trials and Hazard Ratios for Major CVD Events

<table>
<thead>
<tr>
<th>Range of LDL-C (mg/dL)</th>
<th>Hazard Ratio for Major CVD Events</th>
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<tbody>
<tr>
<td>&lt;50, &lt;75</td>
<td>0.57</td>
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<tr>
<td>50-74, 75-99</td>
<td>0.51</td>
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<tr>
<td>75-99, 100-124</td>
<td>0.56</td>
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<tr>
<td>100-124, 125-149</td>
<td>0.58</td>
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<tr>
<td>125-149, 150-174</td>
<td>0.64</td>
</tr>
<tr>
<td>150-174, 175-199</td>
<td>0.71</td>
</tr>
<tr>
<td>&gt;=175, &gt;=200</td>
<td>1.00</td>
</tr>
</tbody>
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LDL-C, Non-HDL-C mg/dL

*p<0.05

IMPROVE-IT

• First large RCT evaluating efficacy of combination simvastatin/ezetimibe therapy vs. simvastatin monotherapy on ASCVD outcomes

• Clinical questions assessed:
  – Does additional LDL-C lowering with ezetimibe for patients with on statin therapy with LDL-C <70 mg/dL reduce with the incidence of ASCVD events?
  – Is ezetimibe therapy safe in this setting?
**IMPROVE-IT Study Design**

Patients stabilized post ACS ≤ 10 days:
LDL-C 50 – 125 mg/dL (or 50-100 mg/dL if prior lipid-lowering Rx)

- Standard Medical & Interventional Therapy

- N= 18, 144

- Simvastatin 40 mg

- Uptitrated to Simva 80 mg if LDL-C > 79 (adapted per FDA label 2011)

- Ezetimibe / Simvastatin 10 / 40 mg

- Follow-up Visit Day 30, every 4 months

- **Duration:** Minimum 2 ½-year follow-up (at least 5250 events)

- Primary Endpoint: CV death, MI, hospital admission for UA, coronary revascularization (≥ 30 days after randomization), or stroke
LDL-C and Lipid Changes

<table>
<thead>
<tr>
<th></th>
<th>LDL-C</th>
<th>TC</th>
<th>TG</th>
<th>HDL</th>
<th>hsCRP</th>
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</thead>
<tbody>
<tr>
<td>Simva</td>
<td>69.9</td>
<td>145.1</td>
<td>137.1</td>
<td>48.1</td>
<td>3.8</td>
</tr>
<tr>
<td>EZ/Simva</td>
<td>53.2</td>
<td>125.8</td>
<td>120.4</td>
<td>48.7</td>
<td>3.3</td>
</tr>
<tr>
<td>Δ in mg/dL</td>
<td>-16.9</td>
<td>-19.3</td>
<td>-16.7</td>
<td>+0.6</td>
<td>-0.5</td>
</tr>
</tbody>
</table>

Median Time avg 69.5 vs. 53.7 mg/dL
Primary Endpoint—ITT

Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke

HR 0.936 CI (0.887, 0.988)
p=0.016

Simva — 34.7%
2742 events

NNT=50

EZ/Simva — 32.7%
2572 events

p=0.016

7-year event rates
IMPROVE-IT vs. CTT: Ezetimibe vs. Statin Benefit

Proportional reduction in event rate (SE)

Reduction in LDL cholesterol (mmol/L)

CTT Collaboration.
Lancet 2005; 366:1267-78;
Lancet 2010;376;1670-81.
Central Focus of Guidelines: Summary

• ACC/AHA: define statin benefit groups; risk/benefit discussion; use moderate- or high-intensity statin therapy with lifestyle change as background therapy; generally avoid non-statin drug therapy; no lipid goals
• NLA: identify ASCVD risk level; risk/benefit discussion; emphasize healthy lifestyle and use moderate- or high-intensity statin therapy, and under appropriate circumstances, adjunctive non-statin therapy, to lower atherogenic cholesterol; maintain lipid goals (non-HDL-C is favored lipoprotein lipid target)
Risk Calculators

**ACC/AHA**

- Use Pooled Cohort Risk calculator in non-Hispanic Whites and non-Hispanic African Americans age 40-79 without ASCVD and not on statin therapy; may be considered in other populations
- Assessment of lifetime risk may be considered in those aged 20-59 with no ASCVD and not at high short-term risk

**NLA**

- Count number of major risk factors and use other risk indicators for clinical decision-making
- Consider the use of either the 10-year FRS, ACC/AHA Pooled Cohort Risk calculator, or 30-year risk in those with 2 major ASCVD risk factors; re-classify to higher risk those with ≥10% 10-year FRS, ≥15% ACC/AHA risk, or ≥45% long-term risk
ASCVD Risk Estimator

10-Year ASCVD Risk

- 7.7% calculated risk
- 3.6% risk with optimal risk factors

Lifetime ASCVD Risk

- 50% calculated risk
- 5% risk with optimal risk factors

Gender

- Male
- Female

HDL - Cholesterol (mg/dL)

- 40

Age

- 55

Total Cholesterol (mg/dL)

- 200

Systolic Blood Pressure

- 126

Diabetes

- Yes
- No

Smoker

- Yes
- No

Race

- White
- African American
- Other

http://www.tools.cardiosource.org/ascvd-risk-estimator

Note: These estimates may underestimate the 10-year and lifetime risk for persons from some race/ethnic groups, especially American Indians, some Asian Americans (e.g., of south Asian ancestry), and some Hispanics (e.g., Puerto Ricans), and may overestimate the risk for others, including some Asian Americans (e.g., of east Asian ancestry) and some Hispanics (e.g., Mexican Americans).

Because the primary use of these risk estimates is to facilitate the very important discussion regarding risk reduction through lifestyle change, the imprecision introduced is small enough to justify proceeding with...
Key Disclaimer of the ACC/AHA Pooled Cohort Risk Calculator

• It does not definitively recommend statin therapy for individuals with 10-year risk ≥7.5%
• It advises that for such individuals before initiating statin therapy “it is reasonable for clinicians and patients to engage in a discussion which considers the potential for ASCVD risk reduction benefits and for adverse effects, for drug-drug interactions and patient preferences for treatment.”
Pooled Risk Cohort Equations
Criticisms and Responses

<table>
<thead>
<tr>
<th>Criticisms</th>
<th>Responses</th>
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<tbody>
<tr>
<td>• Lack of long-term prospective validation</td>
<td>• Validation better than previous risk equations; REGARDS population</td>
</tr>
<tr>
<td>• Possible overestimation of risk in some observational epidemiologic studies</td>
<td>• Over-representation of healthy individuals in certain observational epidemiologic studies does not invalidate application to general population</td>
</tr>
<tr>
<td>• Application to Rotterdam Study population suggested that &gt;96% of men age ≥65 are statin candidates</td>
<td>• Older patients are at higher risk and are good targets for statin therapy for prevention</td>
</tr>
</tbody>
</table>
NLA Perspective on Risk Calculators

• Count number of major risk factors and use other risk indicators for clinical decision-making

• Although any of 3 risk calculators are suggested for consideration (10-year Framingham risk, ACC/AHA Pooled Cohort Risk Calculator, lifetime Framingham risk), risk calculators measure diverse endpoints and have limited application in various ethnic and age groups

• The interpretation of a particular risk level using any risk calculator in a given patient must be done using careful clinical judgment
Risk Calculator

- ACC/AHA supports use of Pooled Risk Cohort calculator as initial step in non-Hispanic white and African American non-diabetics, age 40-79, with no ASCVD and with LDL-C 70-189 mg/dL to assess statin benefit; consider using long-term risk assessment in 20-59 year-old individuals not in high-risk groups
- NLA recommends risk factor counting and assessment of other ASCVD risk indicators first, with optional use of any of 3 risk calculators in patients with 2 major risk factors to aid in clinical decision-making
Management of Hypertriglyceridemia and the Metabolic Syndrome

ACC/AHA
- Not specifically addressed except for those with TG $\geq 500$ mg/dL, for whom reference is made to the 2011 AHA Scientific Statement on TG

NLA
- Lifestyle therapy is major focus, with TG-lowering drug therapy reserved for non-responders or those with TG $\geq 500$ mg/dL
- Focus on TG reduction if TG $\geq 500$ mg/dL
- For TG 200-499 mg/dL, targets of therapy are non-HDL-C and LDL-C
- Metabolic syndrome identified as a multiplex risk factor for T2DM and ASCVD
Lipid Guidelines in 2015
Common Ground

• Identify and treat patients in accordance with presumed ASCVD risk
• Exclude and address secondary causes
• Lifestyle intervention is always an important component of the initial management of dyslipidemia
• Engage patient in risk/benefit discussion if drug therapy is considered
• Employ evidence-based drug therapy for optimal ASCVD risk reduction
• Long term lipid follow-up is the key to assessing patient adherence to therapeutic recommendations