Merits of Targeting LDL-C, Triglycerides, HDL-C, and Non-HDL-C, and Addressing Residual Risk
Introduction

• What risk factors contribute to a patient's total risk profile for cardiometabolic disease, including residual CAD risk?

• How does targeting HDL-C vs HDL-P affect risk?

• What are the merits of targeting (reducing) TG and how does the setting of high cholesterol contribute to risk associated with high TGs?

• What are the benefits of lowering LDL-C, non-HDL-C, Apo B, and LDL-P? How low should LDL-C lowering go?

Apo = apolipoprotein; CAD = coronary artery disease; HDL-C = high-density lipoprotein cholesterol; HDL-P = high-density lipoprotein particle; LDL-C = low-density lipoprotein cholesterol; LDL-P = low-density lipoprotein particle; TG = triglyceride.
Close Interrelationship of Metabolic Pathways

Apo A-1 Apo A-1


HDL maturation

Lipid exchange

Lipolysis

HDL interconversion

Delivery of HDL constituents PLTP, PL, Apos: C1, CII, CIII AV

Apo = apolipoprotein; CE = cholesteryl ester; HDL = high-density lipoprotein; HTG = hypertriglyceridemia LDL = low-density lipoprotein; PL = phospholipid; PLTP = phospholipid transfer protein; TG = triglyceride; VLDL = very-low-density lipoprotein.

Unstable Plaque

- Thin fibrous cap
- Few SMCs
- Activated macrophages “foam cells”
- Soft lipid-rich (necrotic) core
- Eroded endothelium
- Inflammatory cells (T-lymphocytes)
- CV Risks ↑

Stable Plaque

- Thick fibrous cap
- More SMCs
- Intact endothelium
- Minimal foam cells
- Delipidated lipid core
- Lack of inflammatory cells
- CV Risks ↓

• Unstable plaques have a thin fibrous cap and are at greater risk for rupture; the lipid-rich core represents the majority of plaque volume.¹

• In stable plaques, a thick fibrous cap represents >70% of plaque volume. It stabilizes the plaque and prevents it from undergoing rupture.¹

CV = cardiovascular; SMC = smooth muscle cell.

Classic Atherogenic Lipid Triad

HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TG = triglyceride.
LDL-C = low-density lipoprotein cholesterol.
• Elevated LDL-C is a major ASCVD risk factor\textsuperscript{1}
• LDL-C comprises \textasciitilde 75\% of circulating cholesterol carried by lipoprotein particles other than HDL-C\textsuperscript{2}
  • This percentage may be ↓ in patients with HTG
• 70\% of U.S. adults have suboptimal LDL-C levels (>100 mg/dL)\textsuperscript{1}

ASCVD = atherosclerotic cardiovascular disease; HDL-C = high-density lipoprotein Cholesterol; HTG = hypertriglyceridemia; LDL-C = low-density lipoprotein cholesterol.

Major Cardiovascular Event Outcomes According To Quintile of On-treatment LDL-C in TNT

Mean LDL-C (mg/dL):
- 101 (10-mg atorvastatin)
- 77 (80-mg atorvastatin)

49% of patients on atorvastatin 80 mg/day did not reach LDL-C <70mg/dL

Mean LDL-C (mg/dL):
- <64
- 64-76
- 77-89
- 90-105
- ≥106

P<0.0001 for trend

Mean LDL-C <55 mg/dL

Percent Major CV Events*

* = CHD death, myocardial infarction, resuscitated cardiac arrest, and stroke.

Trends for rates of CHD death (P<0.01), nonfatal MI (P<0.0001), fatal or nonfatal stroke (P<0.05)

<table>
<thead>
<tr>
<th>LDL-C Range</th>
<th>&lt;64</th>
<th>64-76</th>
<th>77-89</th>
<th>90-105</th>
<th>≥106</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean LDL-C, mg/dL</td>
<td>54</td>
<td>70</td>
<td>83</td>
<td>97</td>
<td>122</td>
</tr>
<tr>
<td>Quintile</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>No of Pts, Atorva (80mg/10mg)</td>
<td>1722/114</td>
<td>1403/529</td>
<td>968/1019</td>
<td>515/1515</td>
<td>266/1718</td>
</tr>
</tbody>
</table>

CHD = coronary heart disease; CV = cardiovascular; HDL = high-density lipoprotein; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; TNT=treating to new targets.
## AACE 2017 LDL-C Risk Categories and Treatment Goals

<table>
<thead>
<tr>
<th>Risk category (^1,^2)</th>
<th>Risk factors/10-year risk (^1,^2)</th>
<th>Treatment goals (^1,^2) LDL-C (mg/dL)</th>
</tr>
</thead>
</table>
| Extreme risk            | • Progressive ASCVD, including unstable angina in patients after achieving an LDL-C <70 mg/dL  
• Established clinical CVD in patients with DM, CKD 3/4, or HeFH  
• History of premature ASCVD (<55 male, <65 female) | <55 |
| Very high risk          | • Established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease, 10-year risk >20%  
• Diabetes or CKD 3/4 with ≥1 risk factor(s)  
• HeFH | <70 |
| High risk               | • ≥2 risk factors and 10-year risk 10%-20%  
• Diabetes or CKD 3/4 with no other risk factors | <100 |
| Moderate risk           | • ≤2 risk factors and 10-year risk <10% | <100 |
| Low risk                | • 0 risk factors | <130 |

AACE = American Association of Clinical Endocrinologists; ACS = Acute coronary syndrome; ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; CVD = cardiovascular disease; HeFH = heterozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol.

NR = not recommended.

Lipid Levels and Risk of Major Cardiovascular Events in Statin-Treated Individuals

Mean LDL-C achieved quartiles and Major CV Events

Lowest ASCVD risk = LDL-C goal of <62 mg/dL (mean 49 mg/dL)

Major CV event rate, %, in statin-treated individuals

P<0.001 for trend and per 1 SD increase from lowest mean LDL-C

ASCVD = atherosclerotic cardiovascular disease; CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; SC = stratum corneum; SD = standard deviation.

JUPITER: Rosuvastatin-Allocated Participants Attaining LDL-C <50 mg/dL had a Lower Risk of CV Events

A cohort (N=17,802) of apparently healthy individuals with hsCRP ≥2 mg/dL and LDL-C <130 mg/dL randomized to rosuvastatin 20 mg/day or placebo. Primary endpoint = composite of MI, stroke, arterial revascularization, unstable angina, or CV death.

**Primary Endpoint**

<table>
<thead>
<tr>
<th>LDL-C</th>
<th>Placebo</th>
<th>P for trend &lt;0.0001</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50 mg/dL</td>
<td>0.44</td>
<td>0.25 to 0.49</td>
</tr>
<tr>
<td>not &lt;50 mg/dL</td>
<td>0.86</td>
<td>0.57-1.00</td>
</tr>
<tr>
<td>Placebo</td>
<td>1.18</td>
<td></td>
</tr>
</tbody>
</table>

**All-Cause Mortality**

<table>
<thead>
<tr>
<th>LDL-C</th>
<th>Placebo</th>
<th>P for trend =0.004</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50 mg/dL</td>
<td>0.39</td>
<td>0.29-0.70</td>
</tr>
<tr>
<td>not &lt;50 mg/dL</td>
<td>0.65</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>0.67</td>
<td></td>
</tr>
</tbody>
</table>

Cumulative incidence per 100 person-years

Medians: LDL-C, mg/dL: 40, 70, 110

CV = cardiovascular; HDL = high-density lipoprotein; hsCRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol.

Patients Who Achieved Very-Low vs Moderately Low LDL-C Levels Had Lower Risk for Major CV Events: Meta-Analysis of 8 Statin Trials

Hazard ratio for major CV events

Apo = apolipoprotein; CV = cardiovascular; HDL = high-density lipoprotein; LDL-C = low-density lipoprotein cholesterol.

Despite Benefits of Statin-induced LDL-C Lowering, Treated Individuals have Substantial Residual Risk for CAD Events

Residual Risk

4S = Scandinavian Simvastatin Survival Study; AFCAPS = Air Force Coronary Atherosclerosis Prevention Study; CAD = coronary artery disease; CARDS = Collaborative Atorvastatin Diabetes Study; CARE = Cholesterol And Recurrent Events; HPS = Heart Protection Study; LIPID = Long-term Intervention with Pravastatin in Ischaemic Disease; LDL-C = low-density lipoprotein cholesterol; PROSPER = PROspective Study of Pravastatin in the Elderly at Risk; WOSCOPS = West of Scotland Coronary Prevention Study.

Residual CVD Risk with Intensive Statin Therapy
Less, But Still Unacceptably High

Patients experiencing major CVD events, %

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>LDL-C* (mg/dL)</th>
<th>Between-group delta</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROVE IT-TIMI 22</td>
<td>4162</td>
<td>95</td>
<td>-33</td>
</tr>
<tr>
<td>IDEAL</td>
<td>8888</td>
<td>104</td>
<td>-23</td>
</tr>
<tr>
<td>TNT</td>
<td>10,001</td>
<td>101</td>
<td>-24</td>
</tr>
</tbody>
</table>

*Mean or median LDL-C after treatment

CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; TNT = treating to new targets.

Statistically significant, but clinically inadequate CVD reduction

Why Focusing on LDL-C Is Not Enough

- Residual ASCVD risk persists even in intensively treated individuals\(^1\)
- Elevated fasting/postprandial HTG and lipoproteins other than LDL-C are involved in atherogenesis\(^1\)
  - VLDL, IDL, and small, dense LDL-P
- Plaque instability also contributes to ASCVD\(^2\)
  - Reducing lipid content and inflammatory cells within plaque contributes to plaque stability

ASCVD = atherosclerotic cardiovascular disease; HTG = hypertriglyceridemia; IDL = intermediate-density lipoprotein; LDL-C = low-density lipoprotein cholesterol; LDL-P = low-density lipoprotein particle; VLDL = very-low-density lipoprotein.

Triglycerides
Plasma TG Independently Predicts CVD Death and Total Mortality, Meta-Analysis of >1 Million Patients

- 33 studies evaluate CVD mortality (17,018 CVD deaths among 726,030 patients), and 38 studies evaluate all-cause mortality (58,419 all-cause deaths among 330,566 patients).
- Median duration of follow-up was 12.0 years; patients with diabetes, CVD, or cancer were excluded.

<table>
<thead>
<tr>
<th>TG quartile/mg/dL</th>
<th>CVD Mortality</th>
<th>All-Cause Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
<td>P-value</td>
</tr>
<tr>
<td>I. &lt;90</td>
<td>0.83</td>
<td>0.001</td>
</tr>
<tr>
<td>II. 90-149 (referent)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>III. 150-199</td>
<td>1.15</td>
<td>0.015</td>
</tr>
<tr>
<td>IV. ≥200</td>
<td>1.25</td>
<td>0.013</td>
</tr>
</tbody>
</table>

CVD = cardiovascular disease; RR = relative risk; TG = triglyceride.

Algorithm for Pharmacologic Management of Dyslipidemia in Individuals with Cardiometabolic Risk and Diabetes

• Treatment Objectives for Elevated TGs\textsuperscript{1,3}

<table>
<thead>
<tr>
<th>Triglyceride Level</th>
<th>Rationale (Primary Goal) for Therapy\textsuperscript{2}</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Very High” TGs ≥500 mg/dL</td>
<td>Prevention of Pancreatitis*</td>
</tr>
<tr>
<td>“High” or “Moderate Hypertriglyceridemia” 200-499 mg/dL</td>
<td>Prevention of CVD*</td>
</tr>
</tbody>
</table>

* To date, no large clinical outcome trials have been completed to provide support

CVD = cardiovascular disease; TG = triglyceride.

Proposed Relationship Between Primary and Secondary Causes of Hypertriglyceridemia and Their Relationship to Pancreatitis

Genetic
Familial HTG → Marked Hypertriglyceridemia → Chylomicrons → Abdominal Pain, Pancreatitis

Secondary HTG

HTG = hypertriglyceridemia.

HDL-C and HDL-P
High-Density Lipoprotein Cholesterol

- Elevated non-HDL-C and low HDL-C levels constitute major ASCVD risk factors
  - Research shows a strong predictive link between higher HDL-C levels and longevity
  - Low HDL-C can act synergistically with other lipid risk factors to increase ASCVD risk
  - The atherogenicity of low HDL-C can depend on both genetic and environmental factors
- Low HDL-C is associated with:
  - Metabolic syndrome
  - HTG
  - T2D
  - Overweight or obesity
  - Physical inactivity
  - Cigarette smoking
  - Very high carbohydrate intake
  - Certain drugs (beta-adrenergic blockers, anabolic steroids, progestational agents)
  - Genetic factors

ASCVD = atherosclerotic cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; HTG = hypertriglyceridemia; T2D = type 2 diabetes.

Risk of Major CV Events By Absolute Change in HDL-C and Apo A-I Among Individuals on Statins

Increased Apo A-1, Not HDL-C, Associated With Reduced CV Risk

Apo = apolipoprotein; CI = confidence interval; CV = cardiovascular; HDL-C = high-density lipoprotein cholesterol; HR = heart rate; LDL-C = low-density lipoprotein cholesterol; SC = stratum corneum; SD = standard deviation.

HDL-P Predicts Benefit (Reduction of Coronary Events) Better Than HDL-C in Adjusted Analyses

**Hazard ratio**

<table>
<thead>
<tr>
<th></th>
<th>VA-HIT¹</th>
<th>HPS²</th>
<th>MESA³</th>
<th>JUPITER⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HDL-C</strong></td>
<td>0.95</td>
<td>0.91</td>
<td>0.80</td>
<td>0.96</td>
</tr>
<tr>
<td>(0.83–1.08)</td>
<td>P=0.42</td>
<td>(0.86–0.96)</td>
<td>P&lt;0.0003</td>
<td>(0.72–1.29)</td>
</tr>
<tr>
<td><strong>HDL-P</strong></td>
<td>0.71</td>
<td>0.89</td>
<td>0.74</td>
<td>0.78</td>
</tr>
<tr>
<td>(0.61 to 0.81)</td>
<td>P&lt;0.0001</td>
<td>(0.63–0.87)</td>
<td>P=0.002</td>
<td>(0.61–0.99)</td>
</tr>
</tbody>
</table>

**HDL-C** = high-density lipoprotein cholesterol; **HDL-P** = high-density lipoprotein particle; **HPS** = Heart Protection Study; **LDL-C** = low-density lipoprotein cholesterol; **JUPITER** = Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; **MESA** = Multi-Ethnic Study of Atherosclerosis; **VA-HIT** = Veterans Affairs High-Density Lipoprotein Intervention Trial.

HDL Complexity: Anti-Atherogenic Actions

- Cellular cholesterol efflux and reverse cholesterol transport
- Anti-thrombotic \( \uparrow \) prostacyclin
- Endothelial function & repair
- Anti-apoptotic
- \( \uparrow \) NOS \( \rightarrow \) Vasodilatory
- Anti-infectious
- Beta-cell integrity, glucose homeostasis
- Anti-oxidative, protect LDL-C From oxidation
- Anti-inflammatory properties
- Hematopoiesis

HDL-C Apo A-I / II

Apo = apolipoprotein; HDL-C = high-density lipoprotein cholesterol; LDL-C = high-density lipoprotein cholesterol; NOS = not otherwise specified.

Non-HDL Cholesterol and Apo B
AACE 2017 Non-HDL-C Risk Categories and Treatment Goals

<table>
<thead>
<tr>
<th>Risk category&lt;sup&gt;1,2&lt;/sup&gt;</th>
<th>Risk factors/10-year risk&lt;sup&gt;1,2&lt;/sup&gt;</th>
<th>Treatment goals&lt;sup&gt;1,2&lt;/sup&gt; Non-HDL-C (mg/dL)</th>
</tr>
</thead>
</table>
| Extreme risk                | • Progressive ASCVD, including unstable angina in patients after achieving an LDL-C <70 mg/dL  
• Established clinical CVD in patients with DM, CKD 3/4, or HeFH  
• History of premature ASCVD (<55 male, <65 female) | <80 |
| Very high risk              | • Established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease, 10-year risk >20%  
• Diabetes or CKD 3/4 with ≥1 risk factor(s)  
• HeFH | <100 |
| High risk                   | • ≥2 risk factors and 10-year risk 10%-20%  
• Diabetes or CKD 3/4 with no other risk factors | <130 |
| Moderate risk               | • ≤2 risk factors and 10-year risk <10% | <130 |
| Low risk                    | • 0 risk factors | <160 |

NR=not recommended.

AACE = American Association of Clinical Endocrinologists; ACS = acute coronary syndrome; ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; CVD = cardiovascular disease; DM = diabetes mellitus; HDL-C = high-density lipoprotein; HeFH = heterozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol.

Possible Explanations for Superiority of Non–HDL-C Over LDL-C for Predicting ASCVD Event Risk

- Like LDL-C, some TG-rich lipoprotein remnants enter the arterial wall and contribute to atherosclerosis initiation and progression.
- Non–HDL-C correlates more closely than LDL-C with apo B and, thus, more closely correlates with the total burden of atherogenic particles.
- Elevated levels of TG and VLDL-C reflect hepatic production of particles with greater atherogenic potential (such as those with poor interactivity with hepatic receptors); this results in a longer residency in circulation.

ASCVD = atherosclerotic cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TG = triglyceride; VLDL-C = very-low-density lipoprotein cholesterol.

NLA Recommendations: Non-HDL-C as a Target of Lipid-Altering Therapy

- Non-HDL-C treatment goal for participants at low, moderate and high ASCVD risk is <130 mg/dL.
- Non-HDL-C treatment goal and is <100 mg/dL for participants with ASCVD and very high risk.
- Non-HDL-C comprises cholesterol carried by all potentially atherogenic particles:
  - LDL
  - IDL
  - VLDL and VLDL remnants
  - chylomicron remnants
  - lipoprotein (a)

ASCVD = atherosclerotic cardiovascular disease;
HDL-C = high-density lipoprotein cholesterol;
IDL = intermediate-density lipoprotein;
LDL-C = low-density lipoprotein cholesterol;
VLDL = very-low-density lipoprotein.

Targets of Therapy: Apo B

• Provides an assessment of total atherogenic particle burden that is equivalent or superior to LDL-C, non-HDL-C, or other cholesterol ratios in predicting ASCVD risk
• More closely associated with insulin resistance syndrome than LDL-C or non-HDL-C, and more closely associated with central adiposity, thrombosis, and inflammation than non-HDL-C
• Potential contributor to lipoprotein-related residual risk; may remain elevated in some individuals at LDL-C and/or non-HDL-C goal
• Apo B and/or an Apo B/Apo A1 ratio is useful to assess residual risk in at-risk individuals: TG ≥150, HDL-C <40, prior ASCVD event, T2D, and/or insulin resistance syndrome
• Can be accurately measured in the non-fasting state

Apo = apolipoprotein; ASCVD = atherosclerotic cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TG = triglycerides; T2D = type 2 diabetes.

CVD Events Prevented in High-Risk U.S. Adult Population, According to Atherogenic Marker (LDL-C, Non-HDL-C, and Apo B)

Meta-analysis of CV risk markers in 15 independent published analyses (N=233,455)
CVD events over 10 years prevented by a high-risk treatment regimen

Over a 10-year period, a non-HDL-C strategy would prevent 300,000 more events than an LDL-C strategy; an Apo B strategy would prevent 500,000 more events than a non-HDL-C strategy.

Apo = apolipoprotein; CVD = cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.
## AACE 2017 Apo B Risk Categories and Treatment Goals

<table>
<thead>
<tr>
<th>Risk category&lt;sup&gt;1,2&lt;/sup&gt;</th>
<th>Risk factors/10-year risk&lt;sup&gt;1,2&lt;/sup&gt;</th>
<th>Treatment goals&lt;sup&gt;1,2&lt;/sup&gt; Apo B (mg/dL)</th>
</tr>
</thead>
</table>
| Extreme risk               | • Progressive ASCVD, including unstable angina in patients after achieving an LDL-C <70 mg/dL  
                                  • Established clinical CVD in patients with DM, CKD 3/4, or HeFH  
                                  • History of premature ASCVD (<55 male, <65 female) | <70 |
| Very high risk             | • Established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease, 10-year risk >20%  
                                  • Diabetes or CKD 3/4 with ≥1 risk factor(s)  
                                  • HeFH | <80 |
| High risk                  | • ≥2 risk factors and 10-year risk 10%-20%  
                                  • Diabetes or CKD 3/4 with no other risk factors | <90 |
| Moderate risk              | • ≤2 risk factors and 10-year risk <10% | <90 |
| Low risk                   | • 0 risk factors | NR |

NR = not recommended.
AACE = American Association of Clinical Endocrinologists; ACS = acute coronary syndrome; ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; CVD = cardiovascular disease; DM = diabetes mellitus; HDL-C = high-density lipoprotein; HeFH = heterozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol.

Summary

• Multiple ‘lipid’ risk factors contribute to a patient's total CV risk profile, including residual risk.

• LDL-C remains the primary target for reducing CV risk, but it should not be the sole focus of lipid management.

• There is merit in reducing TG, but by how much TG should be lowered remains to be determined.

• Low HDL-C is an important but complex risk factor; raising HDL-P cholesterol content appears to have no benefit; increasing the number of functional HDL-P may have benefit.

• Lowering LDL-C (and non-HDL-C, Apo B, and LDL-P) have the greatest proven benefit, but by how much needs to be determined.

Apo = apolipoprotein; CV = cardiovascular; HDL-C = high-density lipoprotein cholesterol; HDL-P = high-density lipoprotein particle; LDL-C = high-density lipoprotein cholesterol; LDL-P = low-density lipoprotein particle.