Considerations and Controversies in the Management of Dyslipidemia for ASCVD Risk Reduction

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Management of dyslipidemia for cardiovascular risk reduction
What we know...

- LDL-C is causally related to ASCVD
- Lowering LDL-C with statin therapy, diet, or ileal bypass reduces risk of ASCVD events
What we know...

- Reduction in ASCVD events is *proportionally similar* in pts at all levels of risk.
- Greatest *absolute* number of events avoided in pts at greatest risk.
- Reduction in ASCVD events is related to the extent of LDL-C reduction.

*Effects of Lowering LDL-C with Statin Therapy in Patients at Variable Risk of Vascular Disease: Meta-analysis of Individual Data from 27 Randomized Trials.*

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What we know...

- JUPITER trial participants receiving rosuvastatin 20 mg
  - Marked inter-individual variability in response to therapy
  - Reduction in ASCVD events greatest in those with greatest % reduction in LDL-C
What we have recently learned...

- Statins reduce ASCVD risk regardless of baseline LDL-C in primary prevention.
- When added to moderate-intensity statin therapy in high-risk post-ACS patients, ezetimibe provides incremental reduction in ASCVD risk.
Primary Prevention: Intermediate Risk

HOPE-3

- 2-by-2 factorial trial
- 12,705 participants from 21 countries
- Intermediate risk patients who did not have CVD
- Randomly assigned rosuvastatin 10 mg per day or placebo
- Median follow-up 5.6 years
- No entry criteria based on lipid level
- Mean baseline LDL-C 127.8 mg/dl
- Mean on-treatment LDL-C 93.2 mg/dl
- Mean LDL-C reduction 34.6 mg/dl
- No routine monitoring
- No dose titration

Primary Prevention: Intermediate Risk

HOPE-3

- Rosuvastatin 10 mg/d reduced:
  - LDL-C by 34.6 mg/dL
  - CVD by 25%
  - Greater than 18% predicted by CTTC

CV Death, MI, Stroke, Cardiac Arrest, Revascularization, Heart Failure

Primary Prevention: Intermediate Risk

HOPE-3

- Consistent benefits regardless of:
  - LDL-C
  - Systolic blood pressure
  - Risk
  - C-reactive protein
  - Ethnicity

HOPE-3 Results: MVE Reduction vs LDL-C (mg/dL) Lowering in RCTs

• Addition of ezetimibe to simvastatin 40 mg resulted in additional 16.9 mg/dl reduction in LDL-C
IMPROVE-IT: ASCVD risk reduction post-ACS
Ezetimibe + simvastatin vs. simvastatin monotherapy

- Addition of ezetimibe to simvastatin 40 mg resulted in statistically significant reduction in ASCVD events
- HR 0.936 CI (0.887-0.988)
IMPROVE-IT: ASCVD risk reduction post-ACS
Ezetimibe + simvastatin vs. simvastatin monotherapy

- **CTTC**
  - Every 1 mmol/L (38.7 mg/dl) reduction in LDL-C results in approximate 20% reduction in ASCVD

- **IMPROVE-IT**
  - 0.44 mmol/l reduction in LDL-C
  - 7% reduction in CV events
Management of dyslipidemia for cardiovascular risk reduction

Where questions, controversy, and confusion remain...
Controversies and Confusions

• Risk assessment tools: Which one(s) in which patients?
• Lipoprotein targets of therapy: What target and according to whom?
  – LDL-C, non-HDL-C, apo B, LDL-P
• Statin dosing: Fixed dose/intensity or dose titration?
• Lipoprotein goals of therapy: To use or not to use...that is the question.
• Monitoring of response to therapy: The most misunderstood concept.
• Assessing response to therapy: When is enough...enough?
• Safety and efficacy of very low levels of atherogenic lipoproteins: How do we know if therapy has gone too far?
• PCSK9 inhibitors: Waiting for the evidence...
Guidelines for the Management of LDL-related ASCVD Risk

- Multiple guidelines published by numerous professional societies committed to ASCVD prevention
Guidelines: What is the same...

• Intensity of therapy is guided by level of ASCVD risk.

• Statin therapy is first line therapy in all at-risk patients, regardless of how “at-risk” is defined.

• Response to therapy should be monitored.

• Inadequate response to therapy should be addressed.

• Combination therapy may be considered in high-risk patients.
Monitoring...
Monitoring therapy

- 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias

**Table 36  Summary of recommendations for monitoring lipids and enzymes in patients on lipid-lowering therapy**

<table>
<thead>
<tr>
<th>Testing lipids</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>How often should lipids be tested?</strong></td>
</tr>
<tr>
<td>• Before starting lipid-lowering drug treatment, at least two measurements should be made, with an interval of 1–12 weeks, with the exception of conditions where concomitant drug treatment is suggested such as ACS and very high-risk patients.</td>
</tr>
<tr>
<td><strong>How often should a patient’s lipids be tested after starting lipid-lowering treatment?</strong></td>
</tr>
<tr>
<td>• 8 (±4) weeks after starting treatment.</td>
</tr>
<tr>
<td>• 8 (±4) weeks after adjustment of treatment until within the target range.</td>
</tr>
<tr>
<td><strong>How often should lipids be tested once a patient has reached the target or optimal lipid level?</strong></td>
</tr>
<tr>
<td>• Annually (unless there is adherence problems or other specific reasons for more frequent reviews).</td>
</tr>
</tbody>
</table>
Monitoring response to statin therapy... so misunderstood

- “A high level of RCT evidence supports the use of an initial fasting lipid panel (total cholesterol, triglycerides, HDL-C, and calculated LDL-C), followed by a second lipid panel **4 to 12 weeks after initiation of statin therapy**, to determine a patient’s adherence. Thereafter, assessments should be performed **every 3 to 12 months** as clinically indicated.”
Monitoring therapy

- National Lipid Association Recommendations for Patient-centered Management of Dyslipidemia: Part 1

7. The measurement and monitoring of atherogenic cholesterol levels remain an important part of a comprehensive ASCVD prevention strategy.

Results from RCTs of a variety of atherogenic cholesterol-lowering therapies as well as results from observational studies have generally found that lower on-treatment atherogenic cholesterol levels are associated with lower ASCVD risk. This suggests that treatment goals and periodic monitoring of atherogenic cholesterol are useful for allowing a clinician to match the aggressiveness of lipid-lowering therapy to a patient’s absolute risk for an ASCVD event and for assessing the adequacy of a patient’s response and adherence to therapy. Treatment goals and monitoring of atherogenic cholesterol are particularly valuable tools in patient–clinician communication.
Targets of therapy...
Lipoprotein targets of therapy

- 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias
  - Primary: LDL-C
  - Secondary: non-HDL-C or apoB
  - Not recommended: HDL-C, ratios

Table 9: Recommendations for lipid analyses as treatment targets in the prevention of cardiovascular disease

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C is recommended as the primary target for treatment.</td>
<td>I</td>
<td>A</td>
<td>64, 68</td>
</tr>
<tr>
<td>TC should be considered as a treatment target if other analyses are not available.</td>
<td>IIa</td>
<td>A</td>
<td>64, 123</td>
</tr>
<tr>
<td>Non-HDL-C should be considered as a secondary treatment target.</td>
<td>IIa</td>
<td>B</td>
<td>103</td>
</tr>
<tr>
<td>ApoB should be considered as a secondary treatment target, when available.</td>
<td>IIa</td>
<td>B</td>
<td>103, 124</td>
</tr>
<tr>
<td>HDL-C is not recommended as a target for treatment.</td>
<td>III</td>
<td>A</td>
<td>92, 93</td>
</tr>
<tr>
<td>The ratios apoB/ apoA1 and non-HDL-C/ HDL-C are not recommended as targets for treatment.</td>
<td>III</td>
<td>B</td>
<td>103</td>
</tr>
</tbody>
</table>
Lipoprotein targets of therapy

• 2014 International Atherosclerosis Society Global Recommendations for the Management of Dyslipidemia

• Primary: LDL-C
• Non-HDL-C is an alternate target and has growing advantages.
  – Includes atherogenic cholesterol-rich VLDL remnants
  – Does not require fasting for accurate measurement.
  – In future guidelines non-HDL-C will replace LDL-C as the better target of treatment.

• Total apo B is an optional target, but is not recommended as a primary target treatment.
  – Issues of cost, lack of standardization, and lack of consensus on its use stand in the way of making apo B the primary treatment target.

• A low HDL-C is a target of intervention, but predominately through lifestyle therapies.

An International Atherosclerosis Society Position Paper: Global Recommendations for the Management of Dyslipidemia

Lipoprotein targets of therapy

- Primary: non-HDL-C

- Although LDL-C has traditionally been the primary target of therapy...the NLA Expert Panel’s consensus view is that non-HDL-C is a better primary target for modification than LDL-C.
Lipoprotein targets of therapy

- 2013 ACC/AHA Blood Cholesterol Guideline

- “RCT evidence to support the use of specific LDL-C or non–HDL-C targets was not identified. The focus is on the intensity of the statin therapy....”

<table>
<thead>
<tr>
<th>High-intensity statin therapy</th>
<th>Moderate-intensity statin therapy</th>
<th>Low-intensity statin therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily dose lowers LDL-C on average, by approximately ≥50%</td>
<td>Daily dose lowers LDL-C on average, by approximately 30 to &lt;50%</td>
<td>Daily dose lowers LDL-C on average by approximately &lt;30%</td>
</tr>
<tr>
<td>Atorvastatin 40*-80* mg</td>
<td>Atorvastatin 10* (20**) mg</td>
<td>Simvastatin 10** mg</td>
</tr>
<tr>
<td>Rosuvastatin 20*-40** mg</td>
<td>Rosuvastatin (5**) 10* mg</td>
<td>Pravastatin 10*-20* mg</td>
</tr>
<tr>
<td></td>
<td>Simvastatin 20*-40* mg</td>
<td>Lovastatin 20* mg</td>
</tr>
<tr>
<td></td>
<td>Pravastatin 40* (80**) mg</td>
<td>Fluvastatin 20**-40** mg</td>
</tr>
<tr>
<td></td>
<td>Lovastatin 40* mg</td>
<td>Pitavastatin 1** mg</td>
</tr>
<tr>
<td></td>
<td>Fluvastatin XL 80** mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fluvastatin 40 mg BID*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pitavastatin 2-4** mg</td>
<td></td>
</tr>
</tbody>
</table>
Lipoprotein goals of therapy...
Lipoprotein goals of therapy

- 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias
  - Primary: LDL-C
  - Secondary: non-HDL-C or apoB
  - Not recommended: HDL-C, ratios
Lipoprotein goals of therapy...

• 2014 International Atherosclerosis Society Global Recommendations for the Management of Dyslipidemia

An International Atherosclerosis Society Position Paper:
Global Recommendations for the Management of Dyslipidemia

• The IAS does not specifically prescribe “treatment goals” for atherogenic lipoproteins.

• Identifies optimal levels and makes the general statement that the intensity of lipid-lowering therapy should be adjusted to long-term risk.

• Guidelines leave to clinical judgment and national recommendations on intensities of therapies.
Lipoprotein goals of therapy...

- 2013 ACC/AHA Blood Cholesterol Guideline

- The Expert Panel was unable to find any RCTs that evaluated titration of all individuals in a treatment group to specific LDL-C targets <100 mg/dL or <70 mg/dL, nor were any RCTs comparing 2 LDL-C treatment targets identified.

- No statin RCTs reporting on-treatment non-HDL-C levels were identified.
Lipoprotein goals of therapy...

2013 ACC/AHA Blood Cholesterol Guideline

Heart healthy lifestyle habits are the foundation of ASCVD prevention
(See 2013 AHA/ACC Lifestyle Management Guideline)

Adults age >21 y and a candidate for statin therapy

Clinical ASCVD

Age ≤75 y
High-intensity statin
(Moderate-intensity statin if not candidate for high-intensity statin)

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

LDL-C ≥190 mg/dL

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

High-intensity statin

Diabetes
Type 1 or 2
Age 40-75 y

Estimated 10-y ASCVD risk ≥7.5%
High-intensity statin

Definitions of High- and Moderate-Intensity Statin Therapy
(See Table 5)

High
Daily dose lowers LDL-C by approx. ≥50%
Moderate
Daily dose lowers LDL-C by approx. 30% to <50%

High-intensity statin therapy

Moderate-intensity statin therapy

Low-intensity statin therapy

Daily dose lowers LDL-C on average, by approximately ≥50%
Daily dose lowers LDL-C on average, by approximately 30 to <50%
Daily dose lowers LDL-C on average by approximately <30%

Atorvastatin 40-60 mg
Rosuvastatin 20*-40** mg

Atorvastatin 10* (20** mg
Rosuvastatin (5*** 10 mg
Simvastatin 20**-40** mg
Pravastatin 40* (80** mg
Lovastatin 40* mg
Fluvastatin XL 80** mg
Fluvastatin 40 mg BID*
Pitavastatin 2-4** mg

J Am Coll Cardiol. 2014;63:2889-2934
Lipoprotein goals of therapy...

- National Lipid Association Recommendations for Patient-centered Management of Dyslipidemia
- “...treatment goals are useful as means to ensure that the aggressiveness of therapy to lower atherogenic cholesterol is matched to absolute risk for an event.
- Moreover, treatment goals facilitate effective communication between patients and clinicians, providing an easily interpretable means through which the clinician can communicate progress toward meeting treatment objectives...”

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Criteria for ASCVD risk assessment, treatment goals for atherogenic cholesterol, and levels at which to consider drug therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risk category</strong></td>
<td><strong>Criteria</strong></td>
</tr>
<tr>
<td>Low</td>
<td>0–1 major ASCVD risk factors</td>
</tr>
<tr>
<td></td>
<td>Consider other risk indicators, if known</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>2 major ASCVD risk factors</td>
</tr>
<tr>
<td></td>
<td>Consider quantitative risk scoring</td>
</tr>
<tr>
<td></td>
<td>Consider other risk indicators*</td>
</tr>
<tr>
<td>High</td>
<td>≥3 major ASCVD risk factors</td>
</tr>
<tr>
<td></td>
<td>Diabetes mellitus (type 1 or 2)</td>
</tr>
<tr>
<td></td>
<td>o 0–1 other major ASCVD risk factors and</td>
</tr>
<tr>
<td></td>
<td>o No evidence of end organ damage</td>
</tr>
<tr>
<td></td>
<td>o Chronic kidney disease stage 3B or 4</td>
</tr>
<tr>
<td></td>
<td>o LDL-C ≥190 mg/dL (severe hypercholesterolemia)</td>
</tr>
<tr>
<td></td>
<td>o Quantitative risk score reaching the high-risk threshold</td>
</tr>
<tr>
<td>Very High</td>
<td>ASCVD</td>
</tr>
<tr>
<td></td>
<td>Diabetes mellitus (type 1 or 2)</td>
</tr>
<tr>
<td></td>
<td>o ≥2 other major ASCVD risk factors or</td>
</tr>
<tr>
<td></td>
<td>o Evidence of end-organ damage</td>
</tr>
</tbody>
</table>
Assessing response to therapy...
Assessing response to therapy...

- 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias
  - Primary: LDL-C
  - Secondary: non-HDL-C, apoB
  - Not recommended: HDL-C, ratios

Has patient achieved expected absolute LDL-C goal levels?

Table 11: Recommendations for treatment goals for low-density lipoprotein-cholesterol

- In patients at VERY HIGH CV risk:
  - Recommendations: I, B
  - Class: 65, 129

European Heart Journal doi:10.1093/eurheartj/ehw272
Assessing response to therapy...

- 2014 International Atherosclerosis Society Global Recommendations for the Management of Dyslipidemia

  - The IAS does not specifically prescribe “treatment goals” for atherogenic lipoproteins.
  - Identifies optimal levels and makes the general statement that the intensity of lipid-lowering therapy should be adjusted to long-term risk.
  - Guidelines leave to clinical judgment and national recommendations on intensities of therapies.

  Clinical judgment and national recommendations may be used to determine adequacy of reduction in atherogenic lipoproteins.
Assessing response to therapy...

- National Lipid Association Recommendations for Patient-centered Management of Dyslipidemia

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>LDL-C &lt; 100 mg/dL</td>
</tr>
<tr>
<td>Intermediate Low</td>
<td>LDL-C 100-129 mg/dL</td>
</tr>
<tr>
<td>Intermediate</td>
<td>LDL-C 130-159 mg/dL</td>
</tr>
<tr>
<td>Intermediate High</td>
<td>LDL-C 160-189 mg/dL</td>
</tr>
<tr>
<td>High</td>
<td>LDL-C ≥ 190 mg/dL or 5.2 mmol/L</td>
</tr>
</tbody>
</table>

Table 3: Criteria for ASCVD risk assessment, treatment goals for atherogenic cholesterol, and levels at which to consider drug therapy

<table>
<thead>
<tr>
<th>Treatment goal</th>
<th>Consider drug therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-HDL-C</td>
<td>LDL-C mg/dL</td>
</tr>
<tr>
<td>&lt; 190</td>
<td>&lt; 160</td>
</tr>
<tr>
<td>190-159</td>
<td>160-130</td>
</tr>
<tr>
<td>160-109</td>
<td>130-100</td>
</tr>
<tr>
<td>≥ 110</td>
<td>≥ 70</td>
</tr>
</tbody>
</table>

Has patient achieved expected absolute non-HDL-C and/or LDL-C goals levels?
Lipoprotein goals of therapy...

2013 ACC/AHA Blood Cholesterol Guideline

Has patient achieved expected % LDL-C reduction?
2013 ACC/AHA Cholesterol Guidelines
Recommendations on Use of Non-Statins

• Clinicians treating high risk patients who have a
  - Less than anticipated response to statins
  - Unable to tolerate a less than recommended intensity of a statin
  - Completely statin intolerant

• When to add non-statin therapy?
EXPERT CONSENSUS DECISION PATHWAY

2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk

A Report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents

Endorsed by the National Lipid Association

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2016 Expert Consensus Decision Pathway
Assessing response to therapy...

- **Thresholds for consideration of net benefit**
  - Maximally-tolerated statin therapy
  - **Percent** LDL-C reduction: Achieve ≥50% LDL-C reduction on high-intensity statin, or >30% to <50% reduction for moderate-intensity statin
  - May consider **absolute** LDL-C levels (or non-HDL-C in patients with DM) as factors
    - WG emphasizes that these are not firm triggers (not “goals”) for adding medication but factors that may be considered within the broader context of an individual patient’s clinical situation
2016 Expert Consensus Decision Pathway
Summary: Patient Populations Addressed

PATIENT POPULATIONS ADDRESSED: 4 STATIN BENEFIT GROUPS

- Adults ≥21 years of age with clinical ASCVD, on statin for secondary prevention
  - Ezetimibe first
  - PCSK9i may then be added or replace ezetimibe
  - LDL-C ≥190 mg/dl either agent first

- Adults ≥21 years of age with LDL-C ≥190 mg/dL (not due to secondary modifiable causes), on statin for primary prevention
  - Ezetimibe OR PCSK9i may be considered first

- Adults aged 40-75 years without ASCVD but with diabetes and LDL-C 70-189 mg/dL, on statin for primary prevention
  - Ezetimibe may be considered
  - PCSK9i not recommended in primary prevention patients with DM

- Adults aged 40-75 years without clinical ASCVD or diabetes, with LDL-C 70-189 mg/dL and an estimated 10-year risk for ASCVD of ≥7.5%, on statin for primary prevention
  - Ezetimibe may be considered
  - PCSK9i are not recommended
Safety and efficacy of lower levels of LDL-C...
Very low levels of LDL-C...

LDL-C Levels and Event Rates

Very low levels of LDL-C...

Post Hoc Adjudicated CV TEAEs*
Safety Analysis (at least 52 weeks for all patients in on-going study)

Kaplan-Meier Estimates for Time to First Adjudicated Major CV Event
Safety analysis (at least 52 weeks for all patients continuing treatment, including 607 patients who completed week-78 visit)

Mean Treatment Duration: 65 Weeks

Efficacy and Safety of Evolocumab in Reducing Lipids and CV Events: Cumulative Incidence of CV Events

Cox model analysis:
HR=0.46 (95% CI, 0.26-0.82)
Nominal P<.01

Placebo + maximum-tolerated statin ± other LLT
Allrocumab + maximum-tolerated statin ± other LLT

No. at Risk: 788 776 731 703 682 667 321 127
No. at Risk: 1550 1534 1446 1393 1352 1335 642 252

Placebo 788 776 731 703 682 667 321 127
Allrocumab 1550 1534 1446 1393 1352 1335 642 252

Efficacy and Safety of Evolocumab in Reducing Lipids and CV Events: Cumulative Incidence of CV Events

No. at Risk:
Standard 1486 1486 1481 1473 1467 1454 1447 1361 407
Evolocumab 2976 2970 2962 2949 2938 2930 2920 2910 2901 2885 2871 2778 843

Sabetine MS, et al. NEJM 2015;372:1500-9
*Primary endpoint for the ODYSSEY OUTCOMES trial: CHD death, non-fatal MI, fatal and non-fatal ischaemic stroke, unstable angina requiring hospitalization.
Robinson JG, et al. ESC hotline session; Barcelona, August 31, 2014.
Conclusions
What we know...

• LDL-C is causally related to ASCVD.

• Statin medications are first-line therapy for LDL-C lowering and ASCVD risk reduction.

• Lowering LDL-C with statin therapy, ezetimibe, and possibly PCSK9 inhibitors is associated with ASCVD risk reduction.

• It is important to monitor response to therapy.
What we know...

• There is considerable inter-individual variability in response to lipid-lowering therapy.

• High-risk patients with inadequate response to maximally-tolerated statin may be candidates for combination therapy.

• Lifestyle therapy is the foundation of all approaches to the management of dyslipidemia for ASDVD risk reduction.
What we await...

- How low should we go?
- What is the benefit/risk of very low levels of atherogenic lipoproteins?
- Is lowering of atherogenic lipoproteins with PCSK9 inhibitors associated with reduction in ASCVD events?
- What is the role of the only remaining CTEP inhibitor (anacetrapib/REVEAL) in clinical studies in ASCVD risk reduction?
- Will we ever understand and/or modify HDL-C to reduce ASCVD risk?