Can the desired cholesterol levels change with the use of new lipid-lowering medication?

Γενοβέφα Κολοβού
Disclosures

• Attended conferences, advisory boards and gave talks sponsored by MSD, Vianex, Amgen, Sanofi, Lilly, Inovis

• Chairperson: Expert Panel on:
  2. Longevity syndrome
Can the desired cholesterol levels change with the use of new lipid-lowering medication?

A Century of Cholesterol
Clinical study
New agents
Low LDL
Conclusions
A Century of Cholesterol and Coronaries

First Half - The Era of Cholesterol
1910  Human Atherosclerotic Plaques Contain Cholesterol
1913  High Cholesterol Diet Causes Atherosclerosis in Rabbits
1919  Heart Attacks Recognized in Humans
1933  Feedback Inhibition of Cholesterol Synthesis Demonstrated
1938  FH Described
1950  Cholesterol Biosynthetic Pathway Elucidated
1951  High Fat Diets Raise Plasma Cholesterol in Humans
1953  Risk Factor Concept Advanced

Second Half - The Era of LDL
1955  LDL Identified as Risk Factor for CHD
1973  LDLR Discovered
1976  HMGCR Inhibitors Discovered
1981  Statins Increase LDLRs in vivo
1987  First Statin (Mevacor) Approved for Human Use
1994  Statins Decrease Heart Attacks and Prolong Life
1997  SREBP Pathway Elucidated
2006  PCSK9: Destroyer of LDLRs

Goldstein JL Brown MS. A century of cholesterol and coronaries: from plaques to genes to statins. Cell. 2015
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- 1994, 4S established the benefit of statins in CV pts mean LDL in the active group was 120 mg/dl

- More trials followed supporting the benefits of statins and of reducing LDL from 120s to 100 mg/dl

- 2004, PROVEIT-TIMI 22 risk reduction in ACS pts Atorva 80mg mean LDL ~62mg/dl

- 2004, ATP III optional goal of LDL<70 mg/dl

- 2008, JUPITER, lower incidence of CVDs at 2 years in healthy men and women with baseline LDL<130mg/dl median LDL of 55 mg/dl

- 2008, IMPROVE-IT
18,000 pts with LDL<125mg/dl or 100mg/dl after LL-therapy after acute CVD event

Randomized to receive simva 40mg ± ezetimibe 10mg

Study intended to determine 2 things:
1. Whether ezetimibe could further lower LDL when combined with a statin
2. Whether risk could be reduced further by driving the LDL <70 mg/dl and down to the mid-50s.
LDL: 70mg/dl in the simva
LDL: 53mg/dl in simva + ezetimibe

At 7 years

\[\downarrow 6\%\] primary end point in active group, NNT 50

\[\downarrow 10\%\] nonfatal MI + nonfatal stroke in active group

*Primary end point: CV death, MI, UA requiring hospitalization, coronary revascularization, or stroke*
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Most of pts with severe hypercholesterolemia are not achieving the recommended by guidelines LDL-C targets. Thus, the new agents are required to further LDL-C decrease acting in different metabolic pathway than HMGCRi, bile acids sequestrants and others.
PCSK9
Loss of function vs without mutation

↓ 28% LDL
↓ 88% in CHD risk
LDL particle PCSK9
LDL and LDLR
Degradation
LDLR Recycling
LDL-degradation
Lysosome
Hepatic cell

Kolovou G. Severe Hypercholesterolemia Phenotype. Nova Science Publishers, 2018
Table 2: Effects of PCSK9 inhibitors evolocumab and alirocumab in HeFH

<table>
<thead>
<tr>
<th>Clinical trial</th>
<th>Subjects (background LLT)</th>
<th>Intervention (dose, frequency)</th>
<th>LDL-C (% change from baseline)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EVOLOCUMAB</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RUTHERFORD45</td>
<td>HeFH, LDL-C 100 mg/dL (statin ± ezetimibe)</td>
<td>420 mg Q4W</td>
<td>56.4%</td>
</tr>
<tr>
<td>12 weeks</td>
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<tr>
<td>RUTHERFORD-246</td>
<td>HeFH, LDL-C 100 mg/dL (statin ± ezetimibe)</td>
<td>140 mg Q2W</td>
<td>59.2%</td>
</tr>
<tr>
<td>12 weeks</td>
<td></td>
<td>420 mg Q4W</td>
<td>61.3%</td>
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<tr>
<td><strong>ALIROCUMAB</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>ODYSSEY FH I and FH II39</td>
<td>HeFH, LDL-C 100 mg/dL (for primary prevention) or LDL-C 70 mg/dL (for secondary prevention) (max tolerated statin ± other LLT)</td>
<td>75 mg Q2W (increased at 150 mg Q2W if LDL-C 70 mg/dL at week 8)</td>
<td>FH I: 57.9%</td>
</tr>
<tr>
<td>78 weeks</td>
<td></td>
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<tr>
<td>ODYSSEY HIGH FH41</td>
<td>HeFH, LDL-C 160 (stable LLT)</td>
<td>150 mg Q2W</td>
<td>39%</td>
</tr>
<tr>
<td>78 weeks</td>
<td></td>
<td></td>
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<tr>
<td>ODYSSEY ESCAPE42</td>
<td>HeFH undergoing lipoprotein apheresis (lipoprotein apheresis + stable LLT + diet + exercise)</td>
<td>150 mg Q2W</td>
<td>42.5%</td>
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<tr>
<td>18 weeks</td>
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<tr>
<td>ODYSSEY LONG TERM43</td>
<td>HeFH or established CHD or CHD equivalent, LDL-C 70 mg/dL (max tolerated statin ± other LLT)</td>
<td>150 mg Q2w</td>
<td>61.9%</td>
</tr>
<tr>
<td>78 weeks</td>
<td></td>
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<tr>
<td>ODYSSEY OLE</td>
<td>HeFH who have completed one of the 4 parent studies (max tolerated statin ± other LLT)</td>
<td>ONGOING</td>
<td></td>
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<tr>
<td>176 weeks</td>
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</tbody>
</table>

FOURIER trial

27,564 pts with CVD and LDL-C >70 mg/dL on statin ± evolocumab sc 140mg/2 wks or 420mg/monthly

Evolocumab ↓LDL-C by 59%, (92-30 mg/dL)

↓ primary CV endpoint by 15%
↓ secondary endpoint (MI, or stroke) by 20%

Landmark Analysis

Evolocumab vs Placebo

16% RRR
HR 0.84 (95% CI 0.74-0.96)
P = 0.008

25% RRR
HR 0.75 (95% CI 0.66-0.85)
P < 0.00001

CV Death, MI, Stroke

Months from Randomization

ACC 2018, Odyssey

HR 0.85 (95% CI 0.78, 0.93); P=0.0003

<table>
<thead>
<tr>
<th>Number at Risk</th>
<th>Placebo</th>
<th>Alirocumab</th>
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<tbody>
<tr>
<td></td>
<td>9462</td>
<td>9462</td>
</tr>
<tr>
<td>0 Years</td>
<td>8805</td>
<td>8846</td>
</tr>
<tr>
<td>1 Year</td>
<td>8201</td>
<td>8345</td>
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<tr>
<td>2 Years</td>
<td>3471</td>
<td>3574</td>
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<tr>
<td>3 Years</td>
<td>629</td>
<td>653</td>
</tr>
</tbody>
</table>

ARR* 1.6%
PCSK9 inhibitors

↓LDL ~ 60% ➔ ↓CV events starting at 3 months
(sooner than observed in statin trials)

Benefits regardless sex, age, statin use, baseline LDL, or known CVD
Inclisiran

Inclisiran (formerly ALN-PCSsc) is an injectable small interfering RNA (siRNA) that causes the sequence-specific degradation of the PCSK9 mRNA transcript and similar, to already circulating PCSK9i

Bempedoic Acid

Bempedoic acid (ETC-1002) orally administered once daily that inhibits the hepatic adenosine triphosphate (ATP) citrate lyase (ACL, enzyme involved in intracellular cholesterol biosynthesis).
Angiopoietin-Like Protein 3 (ANGPTL3) Inhibitors

Hepatic glycoprotein, inhibits LPL and EL.

FDA approved evinacumab as an orphan drug for HoFH

Gemcabene

The gemcabene (PD72953) oral agent, inhibits hepatic TGs, cholesterol production and apo C-III synthesis. There are evidences that gemcabene LDL-C lowering effects is by about 28% and may be performed independently of the LDLRs.
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A

SREBP SCAP
COPII Golgi apparatus
Insig
Endoplasmic reticulum

B

SREBP SCAP
Insig
Endoplasmic reticulum
Cholesterol

COP II
Golgi apparatus

No transport

Cholesterol

Nucleus

Endoplasmic reticulum

No transport
Adults, C is transported via LDL (~115±35 mg/dL) and HDL (~ 53±15 mg/dL)

Fetus and newborn

1. via HDL (32 -49 mg/dL) and LDL (22-44 mg/dL)

2. HDL particles are synthesized in plasma

3. Fetus liver is still immature  VLDL are synthesized in lesser degree

4. LDLR developed in 25 week of gestation leading to further decrease of LDL
Biologic Basis For Lowering LDL-C

- Newborn: Expected LDL-C of about 30 mg/dL within the first year of life
- After the consumption of breast milk or saturated fat, that LDL-C level doubles to about 60 mg/dL
- This LDL-C level should be maintained throughout life

Loss-of-function mutations in \textit{PCSK9}

Two women (ages 32 and 21, fertile) have been found who have inactivating mutations in both \textit{PCSK9} alleles, and both are in apparent good health, with LDL-C of 14 mg/dl and 15 mg/dl, respectively
Loss-of-function mutations in *NPC1L1*

Subjects who absorb reduced amounts of cholesterol from the intestine as a result of loss-of-function mutations in *NPC1L1*, the intestinal cholesterol transporter.
Hunter Gatherer Humans, LDL: 50-75 mg/dl
Neonates (even today), LDL: 30-70 mg/dl
LL agents

HMGCRi
PCSK9i
MTPi
Jupiter, Post-hoc analysis

4.154 subjects ↓ LDL <50 mg/dL with rosuvastatin
vs
subjects (3.640) ↓ LDL ≥50 mg/dL

↓ CVD

65% and 44%

Hsia J, MacFadyen JG, Monyak J Ridker PM. Cardiovascular event reduction and adverse events among subjects attaining low-density lipoprotein cholesterol <50 mg/dl with rosuvastatin. The JUPITER trial (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin). J Am Coll Cardiol. 2011;57:1666-75.
Meta-analysis 8 studies
(Jupiter, IMPROVE-IT and TNT)

38,153 subjects treated with statins

↓CVD in ↓ LDL <50 mg/dL vs >50 mg/dL

Δεν Υπάρχουν Ενδείξεις Ύπαρξης Κατώτατου Ορίου LDL-C για τη Μείωση των Μειζόνων Καρδιαγγειακών Επεισοδίων

Τα μείζονα καρδιαγγειακά επεισόδια για τη δοκιμή ορίστηκαν ως θάνατος λόγω ΣΝ, μη θανατηφόρο μη σχετιζόμενο με επέμβαση ΕΜ, ανάνηψη από καρδιακή ανακοπή και θανατηφόρο ή μη θανατηφόρο AEE.

† Το κύριο τελικό σημείο της μελέτης ΙΟΠΙΤ ήταν το σύνθετο τελικό σημείο του θανάτου, του EM, του AEE, της PCI/CABG της αστάθειας στηθάγχης που απαιτεί εισαγωγή στο νοσοκομείο. 

LDL goals?
Table 6
Atherosclerotic Cardiovascular Disease Risk Categories and LDL-C Treatment Goals

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Risk factors⁹/10-year riskᵇ</th>
<th>Treatment goals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>LDL-C (mg/dL)</td>
</tr>
</tbody>
</table>
| Extreme risk  | – Progressive ASCVD including unstable angina in patients after achieving an LDL-C <70 mg/dL  
– Established clinical cardiovascular disease in patients with DM, CKD 3/4, or HeFH  
– History of premature ASCVD (<55 male, <65 female) | <55           | <80            | <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 or more risk factor(s)  
– HeFH | <70           | <100           | <80           |
| High risk     | – ≥2 risk factors and 10-year risk 10-20%  
– Diabetes or CKD 3/4 with no other risk factors | <100          | <130           | <90           |
| Moderate risk | ≤2 risk factors and 10-year risk <10% | <100          | <130           | <90           |
| Low risk      | 0 risk factors              | <130          | <160           | NR            |
A  Spatial Working Memory Strategy Index of Executive Function

<table>
<thead>
<tr>
<th></th>
<th>Evolocumab group</th>
<th>Placebo group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>17.8</td>
<td>17.8</td>
</tr>
<tr>
<td>After Baseline</td>
<td>17.5</td>
<td>17.6</td>
</tr>
<tr>
<td>Change</td>
<td>-0.21</td>
<td>-0.29</td>
</tr>
</tbody>
</table>

B  Spatial Working Memory Between Errors

<table>
<thead>
<tr>
<th></th>
<th>Evolocumab group</th>
<th>Placebo group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>20.9</td>
<td>21.0</td>
</tr>
<tr>
<td>After Baseline</td>
<td>20.3</td>
<td>20.1</td>
</tr>
<tr>
<td>Change</td>
<td>-0.52</td>
<td>-0.93</td>
</tr>
</tbody>
</table>
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American Guidelines recommend that a reduction in statin dose may be considered in a patient who has LDL-C levels <40 mg/dl in 2 successive measurements.