Βέλτιστη αντιμετώπιση των ασθενών με δυσλιπιδαιμία

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ΓΝΜ“ΕΛΕΝΑ ΒΕΝΙΖΕΛΟΥ”
Disclosures

Research Grants, Honoraria, Advisory Boards

- ELPEN
- MENARINI
- NOVARTIS
- PHARMANEL
- ANGELINI
- MYLAN
- BAYER
- GALENICA
Number of Deaths Worldwide/year

- NCD: 36 millions
- CVD (2012): 18 millions
- CVD (2030): 23.6 millions

WHO 2014
Risk Factors for Cardiovascular Disease

**Modifiable**
- Smoking
- Dyslipidaemia
  - Raised Cholesterol
  - Raised LDL-C
  - Low HDL-C
  - Raised triglycerides
- Raised blood pressure
- Diabetes mellitus
- Obesity
- Dietary factors
- Lack of exercise

**Non-modifiable**
- Personal history of CVD
- Family history of CVD
- Age
- Gender

Attributable Risk Factors for a First Myocardial Infarction

INTERHEART Study

n=15,152 patients and 14,820 controls in 52 countries

Lifestyle factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>PAR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>36</td>
</tr>
<tr>
<td>Fruits/Veg</td>
<td>14</td>
</tr>
<tr>
<td>Exercise</td>
<td>12</td>
</tr>
<tr>
<td>Alcohol</td>
<td>7</td>
</tr>
<tr>
<td>Hypertension</td>
<td>18</td>
</tr>
<tr>
<td>Diabetes</td>
<td>10</td>
</tr>
<tr>
<td>Abdominal obesity</td>
<td>20</td>
</tr>
<tr>
<td>Psychosocial</td>
<td>33</td>
</tr>
<tr>
<td>Lipids</td>
<td>50</td>
</tr>
<tr>
<td>All 9 risk factors</td>
<td>90</td>
</tr>
</tbody>
</table>

MI=Myocardial infarction, PAR=Population attributable risk (adjusted for all risk factors)

In apparently healthy persons, CVD risk is most frequently the result of multiple, inter-acting risk factors.

This is the basis for total CV risk estimation and management.

Risk factor screening including the lipid profile should be considered in men >40 years old and in women >50 years of age or post-menopausal.

European Heart Journal 2016 -doi:10.1093/eurheartj/ehv272
A risk estimation system such as SCORE can assist in making logical management decisions, and may help to avoid both under- and over-treatment.

ESC SCORE
(10-year risk of CVD death)

- low <10%
- moderate 10% - 20%
- high >20%

European Heart Journal 2016 - doi:10.1093/eurheartj/ehv272
<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC is to be used for the estimation of total CV risk by means of the SCORE system.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>LDL-C is recommended to be used as the primary lipid analysis for screening, risk estimation, diagnosis and management</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>HDL-C is a strong independent risk factor and is recommended to be used in the Heart Score algorithm</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>TG adds information to risk and is indicated for risk estimation.</td>
<td>I</td>
<td>C</td>
</tr>
</tbody>
</table>

2016 ESC/EAS Guidelines on the management of dyslipidaemias
Dyslipidemia

The most common metabolic disorder

Isolated hypercholesterolemia

Isolated hypertriglyceridemia

Combined (Mixed) dyslipidemia:

- T-ch ≥ 5.0, LDL-ch ≥ 3.0 mmol/L
- TG ≥ 1.7 mmol/L + normal ch
  - a) LDL-ch ≥ 3.0 + TG ≥ 1.7 mmol/L
  - b) TG ≥ 1.7 + HDL-Ch < 1.3 mmol/L for females, < 1.0 mmol/L for males
The most important risk factor for CVD
The first target for lipid lowering treatment
<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C is recommended as the primary target for treatment.</td>
<td>I</td>
<td>A</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>
</tr>
<tr>
<td>Non-HDL-C should be considered as a secondary treatment target.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>ApoB should be considered as a secondary treatment target, when available.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>HDL-C is not recommended as a target for treatment.</td>
<td>III</td>
<td>A</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>
</tr>
</tbody>
</table>
Benefits of Decreased LDL-C
### Recommendations for treatment goals for LDL-C

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class a</th>
<th>Level b</th>
</tr>
</thead>
<tbody>
<tr>
<td>In patients at <strong>VERY HIGH CV risk</strong>d, an LDL-C goal of &lt;1.8 mmol/L (70 mg/dL) or a reduction of at least 50% if the baseline LDL-Ce is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL) is recommended</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>In patients at <strong>HIGH CV risk</strong>d, an LDL-C goal of &lt;2.6 mmol/L (100 mg/dL), or a reduction of at least 50% if the baseline LDL-Ce is between 2.6 and 5.2 mmol/L (100 and 200 mg/dL) is recommended</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>In subjects at <strong>LOW or MODERATE risk</strong>d, an LDL-C goal of &lt;3.0 mmol/L (&lt;115 mg/dL) should be considered</td>
<td>Ila</td>
<td>C</td>
</tr>
</tbody>
</table>

2016 ESC/EAS Guidelines on the management of dyslipidaemias
<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescribe statin up to the highest recommended dose or highest tolerable dose to reach the goal.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>In the case of statin intolerance, <strong>ezetimibe</strong> or bile acid sequestrants, or these combined, should be considered</td>
<td>Iia</td>
<td>C</td>
</tr>
<tr>
<td>If the goal is not reached, statin combination with a cholesterol absorption inhibitor should be considered</td>
<td>Iia</td>
<td>B</td>
</tr>
<tr>
<td>If the goal is not reached, statin combination with a bile acid sequestrant may be considered</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>In patients at very high-risk, with persistent high LDL-C despite treatment with maximal tolerated statin dose, in combination with ezetimibe or in patients with statin intolerance, a <strong>PCSK9 inhibitor</strong> may be considered</td>
<td>IIb</td>
<td>C</td>
</tr>
</tbody>
</table>

2016 ESC/EAS Guidelines on the management of dyslipidaemias
Meta-analysis of outcomes from 174,000 participants in 27 randomized trials

- Overall, a 20% to 25% RRR of major vascular events with statin therapy or more intensive statin therapy

- This translated to an approximate 1% reduction in CHD deaths for every 2 mg/dL lowering in LDL-C

Rosuvastatin
LDL-C: % Change From Baseline
Rosuvastatin 10 to 40 mg vs Comparators

Change in LDL-C From Baseline (%)

0  -5  -10  -15  20  -25  -30  -35  -40  -45  -50  -55  -60

10 mg

20 mg

40 mg

Rosuvastatin

20 mg

40 mg

80 mg

atorvastatin

simvastatin

pravastatin

*** p<0.001 vs Rosuvastatin 10mg

^^^ p<0.002 vs Rosuvastatin 20mg

Rosuvastatin 10mg (-46%)

Rosuvastatin 20mg (-52%)

STELLAR Trial.(Am J Cardiol 2003;93:152-160)
STELLAR: Attainment of Optimal LDL-C < 100mg/dl

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rosuvastatin (n = 473)</th>
<th>Simvastatin (n = 648)</th>
<th>Atorvastatin (n = 634)</th>
<th>Pravastatin (n = 485)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mg</td>
<td>*P &lt; .002 vs atorvastatin 10 mg; simvastatin 10 mg, 20 mg, 40 mg; pravastatin 10 mg, 20 mg, 40 mg.</td>
<td>**P &lt; .002 vs atorvastatin 20 mg; simvastatin 20 mg, 40 mg, 80 mg; pravastatin 20 mg, 40 mg.</td>
<td>†P &lt; .002 vs atorvastatin 40 mg; simvastatin 40 mg, 80 mg; pravastatin 40 mg.</td>
<td></td>
</tr>
<tr>
<td>20 mg</td>
<td>53</td>
<td>18</td>
<td>44</td>
<td>1</td>
</tr>
<tr>
<td>40 mg</td>
<td>76</td>
<td>44</td>
<td>60</td>
<td>28</td>
</tr>
<tr>
<td>80 mg</td>
<td>80</td>
<td>76</td>
<td>70</td>
<td>53</td>
</tr>
</tbody>
</table>

A Randomized Trial of Rosuvastatin in the Prevention of Cardiovascular Events Among 17,802 Apparently Healthy Men and Women With Elevated Levels of C-Reactive Protein (hsCRP): The JUPITER Trial

To investigate whether rosvuvastatin 20 mg compared to placebo would decrease the rate of first major cardiovascular events among apparently healthy men and women with LDL < 130 mg/dL (3.36 mmol/L) who are nonetheless at increased vascular risk on the basis of an enhanced inflammatory response, as determined by hsCRP ≥ 2 mg/L
136,905 patients hospitalized with CAD, more than 75% had LDL levels below 130 mg/dl

Heart attack with normal LDL

Lipid levels in patients hospitalized with coronary artery disease: An analysis of 136,905 hospitalizations in Get With The Guidelines
What are the environmental and genetic influences on CRP?

Relative Risk of Future CV Events

- "low risk"
- "moderate risk"
- "high risk"


hsCRP (mg/L)
However, while intriguing and of potential public health importance, the observation in AFCAPS/TexCAPS that statin therapy might be effective among those with elevated hsCR but low cholesterol was made on a post hoc basis. Thus, a large-scale randomized trial of statin therapy was needed to directly test this hypotheses.

Multi-National Randomized Double Blind Placebo Controlled Trial of Rosuvastatin in the Prevention of Cardiovascular Events Among Individuals With Low LDL and Elevated hsCRP

JUPITER Trial Design

Rosuvastatin 20 mg (N=8901)

Placebo (N=8901)

MI
Stroke
Unstable Angina
CVD Death
CABG/PTCA

No Prior CVD or DM
Men >50, Women >60
LDL <130 mg/dL
hsCRP >2 mg/L

4-week run-in

Argentina, Belgium, Brazil, Bulgaria, Canada, Chile, Colombia, Costa Rica, Denmark, El Salvador, Estonia, Germany, Israel, Mexico, Netherlands, Norway, Panama, Poland, Romania, Russia, South Africa, Switzerland, United Kingdom, Uruguay, United States, Venezuela

<table>
<thead>
<tr>
<th></th>
<th>Rosuvastatin (N = 8901)</th>
<th>Placebo (n = 8901)</th>
</tr>
</thead>
<tbody>
<tr>
<td>hsCRP, mg/L</td>
<td>4.2 (2.8 - 7.1)</td>
<td>4.3 (2.8 - 7.2)</td>
</tr>
<tr>
<td>LDL, mg/dL</td>
<td>108 (94 - 119)</td>
<td>108 (94 - 119)</td>
</tr>
<tr>
<td>HDL, mg/dL</td>
<td>49 (40 – 60)</td>
<td>49 (40 – 60)</td>
</tr>
<tr>
<td>Triglycerides, mg/L</td>
<td>118 (85 - 169)</td>
<td>118 (86 - 169)</td>
</tr>
<tr>
<td>Total Cholesterol, mg/dL</td>
<td>186 (168 - 200)</td>
<td>185 (169 - 199)</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>94 (87 – 102)</td>
<td>94 (88 – 102)</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>5.7 (5.4 – 5.9)</td>
<td>5.7 (5.5 – 5.9)</td>
</tr>
</tbody>
</table>

All values are median (interquartile range). [ Mean LDL = 104 mg/dL ]
Comparison of the JUPITER trial population to previous statin trials of primary prevention

<table>
<thead>
<tr>
<th></th>
<th>JUPITER</th>
<th>WOSCOPS</th>
<th>AFCAPS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sample size (n)</strong></td>
<td>17,802</td>
<td>6,595</td>
<td>6,605</td>
</tr>
<tr>
<td><strong>Women (n)</strong></td>
<td>6,801</td>
<td>0</td>
<td>997</td>
</tr>
<tr>
<td><strong>Minority (n)</strong></td>
<td>5,118</td>
<td>0</td>
<td>350</td>
</tr>
<tr>
<td><strong>Duration (yrs)</strong></td>
<td>1.9 (max 5)</td>
<td>4.9</td>
<td>5.2</td>
</tr>
<tr>
<td><strong>Diabetes (%)</strong></td>
<td>0</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td><strong>Baseline LDL-C (mg/dL)</strong></td>
<td>108</td>
<td>192</td>
<td>150</td>
</tr>
<tr>
<td><strong>Baseline HDL-C (mg/dL)</strong></td>
<td>49</td>
<td>44</td>
<td>36-40</td>
</tr>
<tr>
<td><strong>Baseline TG (mg/dL)</strong></td>
<td>118</td>
<td>164</td>
<td>158</td>
</tr>
<tr>
<td><strong>Baseline hsCRP (mg/L)</strong></td>
<td>&gt; 2</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>Rosuvastatin 20 mg</td>
<td>Pravastatin 40 mg</td>
<td>Lovastatin 10-40 mg</td>
</tr>
</tbody>
</table>

JUPITER Trial Study Group, Am J Cardiol 2007
JUPITER
Effects of rosuvastatin 20 mg on LDL, HDL, TG, and hsCRP

- LDL decrease 50 percent at 12 months
- HDL increase 4 percent at 12 months
- hsCRP decrease 37 percent at 12 months
- TG decrease 17 percent at 12 months
JUPITER
Primary Trial Endpoint: MI, Stroke, UA/Revascularization, CV Death

HR 0.56, 95% CI 0.46-0.69
P < 0.00001

Number Needed to Treat (NNT<sub>5</sub>) = 25

- 44%

Rosuvastatin 142 / 8901
Placebo 251 / 8901

Cumulative Incidence

Number at Risk
- Rosuvastatin: 8,901, 8,631, 8,412, 6,508, 3,893, 1,958, 1,353, 983, 544, 157
- Placebo: 8,901, 8,621, 8,353, 6,508, 3,872, 1,963, 1,333, 955, 534, 174

Follow-up (years)
JUPITER
Fatal or Nonfatal Myocardial Infarction

HR 0.45, 95%CI 0.30-0.70
P < 0.0002
JUPITER
Fatal or Nonfatal Stroke

HR 0.52, 95%CI 0.34-0.79
P = 0.002

Follow-up Years
0.000 0.005 0.010 0.015 0.020 0.025 0.030
Cumulative Incidence

0 1 2 3 4

Placebo
Rosuvastatin
- 48 %
JUPITER
Primary Endpoint – Subgroup Analysis

- Men: 11,001, P for Interaction 0.80
- Women: 6,801
- Age ≤ 65: 8,541, P for Interaction 0.32
- Age > 65: 9,261
- Smoker: 2,820, P for Interaction 0.63
- Non-Smoker: 14,975
- Caucasian: 12,683, P for Interaction 0.57
- Non-Caucasian: 5,117
- USA/Canada: 6,041, P for Interaction 0.51
- Rest of World: 11,761
- hsCRP > 2 mg/L Only: 6,375

All Participants: 17,802
JUPITER
Secondary Endpoint – All Cause Mortality

HR 0.80, 95% CI 0.67-0.97
P = 0.02

Placebo 247 / 8901
- 20 %

Rosuvastatin 198 / 8901

Cumulative Incidence

Number at Risk
Rosuvastatin 8,901 8,847 8,787 6,999 4,312 2,268 1,602 1,192 683 227
Placebo 8,901 8,852 8,775 6,987 4,319 2,295 1,614 1,196 684 246

Follow-up (years)
<table>
<thead>
<tr>
<th>Event</th>
<th>Rosuvastatin</th>
<th>Placebo</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any SAE</strong></td>
<td>1,352 (15.2)</td>
<td>1,337 (15.5)</td>
<td>0.60</td>
</tr>
<tr>
<td>Muscle weakness</td>
<td>1,421 (16.0)</td>
<td>1,375 (15.4)</td>
<td>0.34</td>
</tr>
<tr>
<td>Myopathy</td>
<td>10 (0.1)</td>
<td>9 (0.1)</td>
<td>0.82</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>1 (0.01)*</td>
<td>0 (0.0)</td>
<td>--</td>
</tr>
<tr>
<td>Incident Cancer</td>
<td>298 (3.4)</td>
<td>314 (3.5)</td>
<td>0.51</td>
</tr>
<tr>
<td>Cancer Deaths</td>
<td>35 (0.4)</td>
<td>58 (0.7)</td>
<td>0.02</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>6 (0.07)</td>
<td>9 (0.10)</td>
<td>0.44</td>
</tr>
<tr>
<td>GFR (ml/min/1.73m² at 12 mth)</td>
<td>66.8 (59.1-76.5)</td>
<td>66.6 (58.8-76.2)</td>
<td>0.02</td>
</tr>
<tr>
<td>ALT &gt; 3xULN</td>
<td>23 (0.26)</td>
<td>17 (0.19)</td>
<td>0.34</td>
</tr>
<tr>
<td>Fasting glucose (24 mth)</td>
<td>98 (91-107)</td>
<td>98 (90-106)</td>
<td>0.12</td>
</tr>
<tr>
<td>HbA1c (% at 24 mth)</td>
<td>5.9 (5.7-6.1)</td>
<td>5.8 (5.6-6.1)</td>
<td>0.01</td>
</tr>
<tr>
<td>Glucosuria (12 mth)</td>
<td>36 (0.46)</td>
<td>32 (0.41)</td>
<td>0.64</td>
</tr>
<tr>
<td>Incident Diabetes**</td>
<td>245 (2.8)</td>
<td>196 (2.2)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*Occurred after trial completion, trauma induced.

**Physician reported

All values are median (interquartile range) or N (%)
Statins may decrease CVS events by a number of mechanisms (important early after MI)

- Plaque stabilization
- Reversal of endothelial dysfunction
- Inhibition of monocyte recruitment
- ↓Ed thrombogenicity
- Reduction in inflammation

Early use of statins after an ACS

Secondary prevention trials:
- Primarily evaluated the role of statin therapy initiated 3 to 6 months or longer after acute MI

- led to the investigation of earlier initiation of statin therapy during ACS (MI or unstable angina)

Am J Cardiol 2012;109:1239 –1246
Rosuvastatin in Acute Coronary Syndromes

Comparison of Lipid-Modifying Efficacy of Rosuvastatin 20 or 40mg Versus Atorvastatin 80mg in Patients With ACS (LUNAR Study)

Prospective, multicenter, randomized, open-label, 3-arm, parallel-group trial.

ACS patients with in 48 hrs of ischemia
- STEMI pts with intervention with in 12 hrs of symptoms (TLT or PCI)
- NSTEMI/UA with conservative management
- LDL-C >70 mg/dl, fasting TG < 500 mg/dl with in 72 hrs of symptom onset

Am J Cardiol 2012;109:1239 –1246
Rosuvastatin in Acute Coronary Syndromes

Baseline values and percent changes (average of measurements at weeks 6 and 12) in lipids and related parameters

<table>
<thead>
<tr>
<th>Variable</th>
<th>RSV20 (n = 246)</th>
<th>RSV40 (n = 251)</th>
<th>ATV80 (n = 257)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-density lipoprotein cholesterol (mg/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean baseline</td>
<td>138.4</td>
<td>138.8</td>
<td>133.2</td>
</tr>
<tr>
<td>Percent change, mean ± SD</td>
<td>−42.0 ± 18.5</td>
<td>−46.8* ± 18.2</td>
<td>−42.7 ± 17.7</td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol (mg/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean baseline</td>
<td>39.5</td>
<td>38.8</td>
<td>39.9</td>
</tr>
<tr>
<td>Percent change, mean ± SD</td>
<td>9.7† ± 16.4</td>
<td>11.9† ± 19.7</td>
<td>5.6 ± 19.1</td>
</tr>
<tr>
<td>Non-high-density lipoprotein cholesterol (mg/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean baseline</td>
<td>161.2</td>
<td>162.8</td>
<td>156.0</td>
</tr>
<tr>
<td>Percent change, mean ± SD</td>
<td>−37.9 ± 73.3</td>
<td>−42.6 ± 17.6</td>
<td>−39.8 ± 17.4</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean baseline</td>
<td>200.7</td>
<td>201.7</td>
<td>195.9</td>
</tr>
<tr>
<td>Percent change, mean ± SD</td>
<td>−28.6* ± 15.4</td>
<td>−32.2 ± 15.7</td>
<td>−30.9 ± 15.1</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects</td>
<td>254</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean baseline</td>
<td>180.8</td>
<td>182.7</td>
<td>157.5</td>
</tr>
<tr>
<td>Percent change, mean ± SD</td>
<td>−9.5† ± 40.4</td>
<td>−14.6 ± 48.3</td>
<td>−18.0 ± 38.7</td>
</tr>
</tbody>
</table>

* p < 0.05; † p < 0.01; ‡ p < 0.001 versus atorvastatin 80 mg/day.
Mean percent change from baseline by weeks 2, 6, and 12 in low-density lipoprotein cholesterol (LDL-C)
Rosuvastatin in Acute Coronary Syndromes

Mean percent change from baseline by weeks 2, 6, and 12 in (high-density lipoprotein cholesterol (HDL-C))
5011 elderly patients (age >60) with ischemic cardiomyopathy
- NYHA class II to IV HF
- median follow-up of 32.8 months

Randomly assigned to Rosuvastatin 10 mg or placebo

Primary composite outcome:
CVS death, nonfatal MI, or nonfatal stroke

Secondary outcomes:
Death from any cause, any coronary event, death CVS causes, number of hospitalizations.
CORONA Trial:
Controlled Rosuvastatin in Multinational Trial in HF

Rate of Heart Failure Hospitalizations

Cardiovascular Death

Meta-analysis of Statin Use in HF

Meta-analysis of 13 HF trials estimated *survival benefit of statin use in patients with HF* of ischemic and non ischemic etiologies

Statin use in HF associated with 26% RRR in mortality
(HR 0.74; 95% CI, 0.68 to 0.8)

8 trials - statin use associated with an improved survival among patients who had HF

Effect is noted independent of etiology for HF
(For ischemic etiology HR 0.73; 95% CI 0.65 to 0.82)
(For nonischemic etiology HR 0.73; 95% CI 0.61 to 0.87)

*J Am Coll Cardiol* 2008;51:423
(A) Adjusted mortality among patients with ischemic HF (n = 62,273) using statins, compared with those not using statins.

(B) Mortality among patients with HF of non ischemic HF (n = 31,551) using statins compared with those not using statins.
Mixed dyslipidemia
Atherogenic dyslipidaemia

- Small, dense LDL: ↑
- TG: ↑
- HDL-c: ↓

Most Common Lipid Profile in Patients with Coronary Artery Disease (60%)

Metabolic Syndrome
FCHL
Type 2 Diabetes
Polycystic ovarian syndrome

Diabetes Care 2003;26 (Suppl. 1):S83-86
Individuals in top vs bottom third of usual log-triglyceride values, adjusted for at least age, sex, smoking status, lipid concentrations, and blood pressure (most)

CHD Risk Ratio* (95% CI)

1.72 (1.56-1.90)

A

N=262,525

Decreased Risk

Increased Risk

Groups

Duration of follow-up
- ≥10 years: 5902
- <10 years: 4256

Sex
- Male: 7728
- Female: 1994

Fasting status
- Fasting: 7484
- Nonfasting: 2674

Adjusted for HDL
- Yes: 4469
- No: 5689

Overall CHD Risk Ratioā

1.72 (1.56-1.90)

A

N=262,525

Decreased Risk

Increased Risk

The analysis arising from major intervention studies demonstrates

Atherogenic Dyslipidemia

↑ TG
↓ HDL-C

↑ Acute Coronary Syndrome
↑ Chronic Ischemic Cardiovascular Diseases

Even in populations with recommended LDLC levels according to the guidelines

CALIPSO Findings:

Results Based on NCEP ATP III Update

% of Patients Not at Goal

- High-risk target: 2.5 mmol/L
- High-risk target: 1.8 mmol/L

- All patients
- High-risk patients

27% 36% 57% 81%

Residual CVD Risk in Patients Treated With Intensive Statin Therapy

Patients Experiencing Major CVD Events, %

- PROVE IT-TIMI 22
- IDEAL
- TNT

Statistically significant, but clinically inadequate CVD reduction

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients Treated</th>
<th>LDL-C, mg/dL</th>
<th>% Experiencing Major CVD Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROVE IT-TIMI 22</td>
<td>4162</td>
<td>95</td>
<td>26.3</td>
</tr>
<tr>
<td>IDEAL</td>
<td>8888</td>
<td>104</td>
<td>13.7</td>
</tr>
<tr>
<td>TNT</td>
<td>10,001</td>
<td>101</td>
<td>10.9</td>
</tr>
</tbody>
</table>

*Mean or median LDL-C after treatment

Residual vascular risk in patients treated by statins

Παρά την ρύθμιση της ΑΠ του ΣΔ και η επίτευξη του στόχου για την μείωση της LDL-C, οι ασθενείς παραμένουν εκτεθειμένοι εξαιτίας του υπολειπόμενου Καρδιαγγειακού κινδύνου ο οποίος οδηγεί σε:

- Μακρο-αγγειακές επιπλοκές
  - Εμφραγμα του μυοκαρδίου
  - Αγγειακό Εγκεφαλικό επεισόδιο

- Μικρο-αγγειακές επιπλοκές
  - Αμφιβληστροειδοπάθεια
  - Νεφροπάθεια
  - Νευροπάθεια

Lancet Published Online January 9, 2015
HDL-C & TG remain predictive of CVD events even when LDL-C < 70mg/dl: TNT & PROVE-IT


Miller et al. 2008
Παρά την εντατική θεραπευτική αντιμετώπιση με αντιδιαβητικά δίσκια, αντιυπερτασική αγωγή, αντιλιπιδαιμικά φάρμακα + διαίτα και πρόγραμμα αλλαγής τρόπου ζωής, ύστερα από παρακολούθηση για 13,3 έτη παρατηρούνται ακόμη:

- Στο 51%: εξέλιξη της αμφιβληστροειδοπάθεια
- Στο 25%: εμφάνιση νεφροπάθειας
- Στο 55%: εξέλιξη περιφερικής νευροπάθειας
Οι στατίνες έχουν μικρή επίδρασή στις ΜΙΚΡΟαγγειακές επιπλοκές

- Έχουν θετική επίδραση στη νεφροπάθεια όμως
- Δεν επιφέρουν σημαντική βελτίωση σε άλλες μικροαγγειακές επιπλοκές (αμφιβληστροειδοπάθεια, νευροπάθεια)

Επίσης δεν έχουν ανάλογη επίδραση στα επίπεδα της HDL-C και των TG σε σχέση με την αντίστοιχη στα επίπεδα της LDL-C

Σε ένα ποσοστό ασθενών δεν επιτυγχάνουν τον στόχο ως προς τα επίπεδα της LDL-C

Treatment of CVD: Residual Risk

- Statins
  - Residual Risk
    - Focused on: HDL-C, TGs

% CV events

0 100

40% 60%
Συνδυασμένη υπολιπιδαιμική αγωγή

STATIN and FIBRATE
Mixed dyslipidemia
Atherogenic dyslipidaemia

Small, dense LDL

TG

HDL-c

FIBRATES

Diabetes Care 2003;26 (Suppl. 1):S83-86
Οι φιμπράτες στοχεύουν στη λιπιδαιμική τριάδα

Επιδράσεις στην αθηρογόνο δυσλιπιδαιμία
Μείωση των τριγλυκεριδίων: 30-60%
Αύξηση της HDL-c: 5-15%

Επιδράσεις σε άλλες παραμέτρους σχετικές με τα λιπίδια
Μείωση της απολιποπρωτεΐνης CIII: 17-35%
Μείωση της LDL-c: 17-22%,6 (σε μονοθεραπεία) και ως 31% (σε συνδυασμό με μια στατίνη)

5 – Ducobu et al. Cardiovasc Pharmacol 2003;41:60-7
Fibrate: Primary and Secondary Prevention

*Post hoc analysis of subgroup with TG >200 mg/dL and HDL-C <42 mg/dL
**Post hoc analysis of subgroup with TG ≥200 mg/dL and HDL-C <35 mg/dL
***Difference between placebo and Rx for primary endpoint was statistically significant (p < 0.05)

Frick MH et al. *NEJM* 1987;317:1237-1245
Rubins HB et al. *NEJM* 1999;341:410-418
Drug treatments of hypertriglyceridaemia

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug treatment should be considered in high-risk patients with TG&gt;2.3 mmol/L (200 mg/dL).</td>
<td>Ila</td>
<td>B</td>
</tr>
<tr>
<td>Statin treatment may be considered as the first drug of choice for reducing CVD risk in high-risk individual with hypertriglyceridaemia.</td>
<td>Iib</td>
<td>B</td>
</tr>
<tr>
<td>In high-risk patients with TG&gt;2.3 mmol/L (200 mg/dL) despite statin treatment fenofibrate may be considered in combination with statins.</td>
<td>Iib</td>
<td>C</td>
</tr>
</tbody>
</table>

2016 ESC/EAS Guidelines on the management of dyslipidaemias
Type 2 diabetes is increasingly prevalent

At least 68% of people >65 years with diabetes die of heart disease

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) Trial

9,795 patients

Fenofibrate 200 mg/day
(n = 4,895)

Placebo
(n = 4,900)

Average follow-up: 5 years and 500 CHD events

<table>
<thead>
<tr>
<th>Type 2 diabetes</th>
<th>No prior cardiovascular disease</th>
<th>78%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 50–75 years</td>
<td>With prior cardiovascular disease</td>
<td>22%</td>
</tr>
</tbody>
</table>

- 5-year, double-blind, placebo-controlled study
- All patients received usual care, including the option to add other lipid-lowering therapies

Primary endpoint CHD events (nonfatal MI, CHD death)

HR = 0.89
95% CI = 0.75–1.05
p = 0.16

Number of patients still followed-up at the given year

<table>
<thead>
<tr>
<th>Year</th>
<th>Placebo</th>
<th>Fenofibrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4,900</td>
<td>4,895</td>
</tr>
<tr>
<td>1</td>
<td>4,835</td>
<td>4,837</td>
</tr>
<tr>
<td>2</td>
<td>4,741</td>
<td>4,745</td>
</tr>
<tr>
<td>3</td>
<td>4,646</td>
<td>4,664</td>
</tr>
<tr>
<td>4</td>
<td>4,547</td>
<td>4,555</td>
</tr>
<tr>
<td>5</td>
<td>2,541</td>
<td>2,553</td>
</tr>
<tr>
<td>6</td>
<td>837</td>
<td>850</td>
</tr>
</tbody>
</table>

FIELD Subgroup Analysis: Primary Prevention Pts

CHD events
n=7,664

Total CVD
n=7,664

Risk reduction (%)

Fenofibrate
Pts With No Prior CVD

-25
p=0.014

-19
p=0.014

FIELD: Effects on Microvascular and Peripheral Vascular Disease

**Effects independent of the degree of glycaemic control (HbA1c)**

- Retinopathy needing laser therapy: $P < 0.001$ (30%)
- Albumin Excretion Rate: $P = 0.002$ (15%)
- Non-Traumatic Amputation: $P = 0.01$ (38%)
The first study to evaluate adding an LMA to a statin in patients with T2DM at goal for LDL-C

The only placebo-controlled, double-blind arm of the ACCORD Programme

- Simvastatin 20-40 mg + Fenofibrate 160 mg** (n=2,765)
- Simvastatin 20-40 mg + Placebo (n=2,753)

5,518 patients with T2DM

Month 1

Mean 4.7-year follow-up

LMA: lipid-modifying agent
*According to patients’ LDL-C levels and CVD history
**Bioequivalent to 200 mg micronised and 145 mg nanocrystal. Patients whose eGFR was 30-50 mL/min/1.73 m² received a lower dose of fenofibrate, corresponding to 1/3 of the normal daily dose

Patients with atherogenic dyslipidaemia (HDL-C < 34 and TG > 204 mg/dL) had a 70% higher relative risk of major CV events compared to those without atherogenic dyslipidaemia, despite achieving a mean LDL-C of 80 mg/dL.
Fenofibrate was associated with a reduction in major CV events* in the subgroup of dyslipidaemic patients (TG ≥204 mg/dL and HDL-C ≤34 mg/dL)

*Major CV events defined as CV death, nonfatal MI and nonfatal stroke


* 20 of these patients need to be treated for 5 years to prevent one event (NNT =20)

ARR: absolute risk reduction
Significant reduction of albuminuria was achieved with combination therapy

Incidence of albuminuria (number of subjects [%])\(^1\)

<table>
<thead>
<tr>
<th></th>
<th>Simvastatin + Fenofibrate (n=2,765)</th>
<th>Simvastatin (n=2,753)</th>
<th>(p) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microalbuminuria (≥30 to &lt;300 mg/g)</td>
<td>1,050 (38.2%)</td>
<td>1,137 (41.6%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Macroalbuminuria (≥300 mg/g)</td>
<td>289 (10.5%)</td>
<td>337 (12.3%)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Expressed as mg/g creatinine

- These results are consistent with previous findings in DAIS and the FIELD study
- Pre-specified microvascular results are due to be reported at a later date

Fenofibrate significantly reduced the rate of progression of diabetic retinopathy* by 40%

ARR = 3.7%
NNT = 27

OR 0.60
95% CI 0.42-0.87

* 3 step or more progression on the ETDRS scale or development of diabetic retinopathy necessitating laser photocoagulation or vitrectomy
Ασφάλεια του συνδυασμού στατίνης + φαινοφιμπράτης

FDA: Περιστατικά ραβδομυόλυσης στη συγχορήγηση με στατίνες ανά 1.000.000 συνταγές

“Στη μελέτη FIELD (n=9.795) δεν παρατηρήθηκε κανένα περιστατικό ραβδομυόλυσης από τη συγχορήγηση στατίνης+φαινοφιμπράτη στα 5 χρόνια παρακολούθησης”

AmJCardiol 2005;95:120-122
Efficacy of drug combinations for the management of mixed dyslipidaemias

A combination of statins with fenofibrate can also be considered, but the combination with gemfibrozil should be avoided.

Drug treatments of low high-density lipoprotein-cholesterol

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins and fibrates raise HDL-C with similar magnitude and these drugs may be considered</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>The efficacy of fibrates to increase HDL-C may be attenuated in people with type 2 diabetes.</td>
<td>IIb</td>
<td>B</td>
</tr>
</tbody>
</table>

2016ESC/EAS Guidelines on the management of dyslipidaemias
Μεικτή δυσλιπιδαιμία

Σταθερός συνδυασμός

FENOFIBRATE / SIMVASTATIN

Vascular Health and Risk Management 2017:13 29–41
4,444 patients with angina pectoris or previous MI randomized to simvastatin (20-40 mg) or placebo for 5.4 years

Statins provide significant benefit in those with average LDL-C levels

MI=Myocardial infarction, RRR=Relative risk reduction

20,536 patients with CAD, other occlusive arterial disease, or DM randomized to simvastatin (40 mg) or placebo for 5.5 years

- 13% RR \( P=0.0003 \)

- 24% RR \( p<0.0001 \)

- 25% RR \( p<0.0001 \)

HPS: Coronary Mortality

The Lancet, Vol 344, November 19, 1994
Adherence to statins after two years, by condition


JAMA 2002;288:462-467
The PURE (Prospective Urban Rural Epidemiology) study showed that among participants with a history of CHD or stroke 5 years after their event:

- **Antiplatelet drugs**: 25%
- **Statins**: 15%
- **ACEI or ARBs**: 20%
- **Beta-blockers**: 17%

Lancet 2011; 378: 1231-43
Μεικτή δυσλιπιδαιμία

Σταθερός συνδυασμός
FENOFIBRATE / SIMVASTATIN

Αποτελεσματικός
Ασφαλής
Χαμηλό κόστος

την προσήλωση
στη θεραπεία

ΚΚ νοσηρότητα
θνησιμότητα

Vascular Health and Risk Management 2017:13 29–41
• Οι διαταραχές των λιπιδίων αποτελούν βασικό θεραπευτικό στόχο τόσο στη πρωτογενή, όσο και στη δευτερογενή πρόληψη.

• Οι στατίνες, και ιδιαίτερα η rosvastatin, είναι θεραπεία εκλογής για τη ρύθμιση της ολικής και της LDL–Χ.

• Η χορήγησή της μειώνει σημαντικά τη νοσηρότητα και τη θνησιμότητα από καρδιαγγειακά νοσήματα.

• Είναι αποτελεσματική σε ασθενείς με ΟΣΣ, καθώς και σε ασθενείς με καρδιακή ανεπάρκεια.
Η μεικτή υπερλιπιδαιμία είναι συνυφασμένη με αυξημένο καρδιαγγειακό κίνδυνο και αφορά κυρίως ασθενείς με ΣΔ ΙΙ, μεταβολικό σύνδρομο και στεφανιαία νόσο.

Ο συνδυασμός στατίνης με φιμπράτη ρυθμίζει αποτελεσματικότερα τα επίπεδα των λιπιδίων και είναι ασφαλής χωρίς σοβαρές ανεπιθύμητες ενέργειες.

Ο σταθερός συνδυασμός FENOFIBRATE / SIMVASTATIN βελτιώνει την συμμόρφωση στη θεραπεία στοιχείο σημαντικό για την καρδιαγγειακή προστασία.

Ο σταθερός συνδυασμός είναι μια δελεαστική θεραπευτική πρόταση στη καθημερινή κλινική πράξη, τόσο στη πρωτογενή όσο και τη δευτερογενή πρόληψη.
Patients in the dyslipidaemia subgroup had a 70% higher relative risk of major CV events* compared to those with TG <204 mg/dL and HDL >34 mg/dL, despite achieving a mean LDL-C of 80 mg/dL.

ARR: absolute risk reduction

*Major CV events defined as CV death, nonfatal MI and nonfatal stroke

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Fenofibrate%</th>
<th>Placebo%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with (HDL-C &lt; 34 and TG &gt; 204 mg/dL)</td>
<td>* 12.4</td>
<td>17.3</td>
</tr>
<tr>
<td>All other patients</td>
<td>10.1</td>
<td>10.1</td>
</tr>
</tbody>
</table>

Fenofibrate was associated with a reduction in major CV events* 31% in the subgroup of dyslipidaemic patients (TG ≥204 mg/dL and HDL-C ≤34 mg/dL).