Success and Limitations of Current Hypolipidemic Drug Therapy

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Conflicts of Interest

Advisory Boards or Speaker’s Fees from Amgen, AstraZeneca, MSD, Sanofi, Pfizer
Success of Current Hypolipidemic Drug Therapy

- Statins
- Statin/Ezetimibe
- PCSK9 inhibitors

\[ \text{LDL-Lowering} \]
Statins have repeatedly shown a great benefit by lowering LDL-C.
5 Years’ Benefit of LDL-C Lowering by Statins at Various Risk

The higher the risk, the higher the benefit.
Statins, what else?
IMPROVE-IT

40 mg Simvastatin compared to 40 mg Simvastatin + 10mg Ezetimibe

• IMPROVE-IT – the largest and longest study on the efficacy and safety of a lipid lowering agent (18‘144 participants, follow up 7 years)

Cannon CP et al Ezetimibe added to statin therapy after acute coronary syndromes. NEJM publ on June 3, 2015
IMPROVE-IT
Primary Endpoint — ITT

Event Rate (%)

Time since randomization (years)

HR 0.936 CI (0.887, 0.988)
p=0.016

Simva — 34.7%
2742 events

RRR 6.4%
NNT= 50

EZ/Simva — 32.7%
2572 events

7-year event rates

Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke
IMPROVE-IT - Extrapolation of Benefit

Dechamps, Catapano, Packard, Understanding IMPROVE-IT. EHJ 2014
Plot of the IMPROVE-IT Trial Data and Statin Trials for Change in LDL Cholesterol versus Clinical Benefit

(Cannon CP et al. NEJM 2015, DOI: 10.1056/NEJMoa1410489)
Conclusions from IMPROVE-IT

Simvastatin 40mg + Ezetimibe vs Simvastatin 40mg

• IMPROVE-IT: First study to show an incremental benefit from the addition of a non-statin drug (Ezetimibe) to a statin therapy
  - Non-Statin lowering of LDL-C with Ezetimibe reduces cardiovascular events
  - Even lower is even better (mean LDL-C 1.4 vs. 1.8 mmol/l after 1 year)
  - Confirms the safety profile Ezetimibe

Confirms the LDL- theory, that lowering of LDL-C reduces cardiovascular events
Limitations of Current Hypolipidememic Drug Therapy

- Statins and risk for incident type 2 diabetes
- Statins and myopathy
- Niacin and Fibrates and reduction of CV risk
- Residual risk in statin therapy
Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials

9% increase in risk for diabetes

(Sattar N et al Lancet 2010 online Febr.17,2010)
Diabetes Risk in Statin therapy – Harm and Risk

Meta-Analysis of 5 Studies which analyzed intensive vs moderate Statin Therapy

<table>
<thead>
<tr>
<th>Incident Diabetes</th>
<th>Intensive Dose</th>
<th>Moderate Dose</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROVE IT-TIMI 22, 2004</td>
<td>101/1707 (5.9)</td>
<td>99/1688 (5.9)</td>
<td>1.01 (0.76-1.34)</td>
</tr>
<tr>
<td>A to Z, 2004</td>
<td>65/1768 (3.7)</td>
<td>47/1736 (2.7)</td>
<td>1.37 (0.94-2.01)</td>
</tr>
<tr>
<td>TNT, 2005</td>
<td>418/3798 (11.0)</td>
<td>358/3797 (9.4)</td>
<td>1.19 (1.02-1.38)</td>
</tr>
<tr>
<td>IDEAL, 2005</td>
<td>240/3737 (6.4)</td>
<td>209/3724 (5.6)</td>
<td>1.15 (0.95-1.40)</td>
</tr>
<tr>
<td>SEARCH, 2010</td>
<td>625/5398 (11.6)</td>
<td>587/5399 (10.9)</td>
<td>1.07 (0.95-1.21)</td>
</tr>
<tr>
<td><strong>Pooled odds ratio</strong></td>
<td><strong>1449/16408 (8.8)</strong></td>
<td><strong>1300/16344 (8.0)</strong></td>
<td><strong>1.12 (1.04-1.22)</strong></td>
</tr>
<tr>
<td><strong>Heterogeneity:</strong></td>
<td>$\hat{p}^2 = 0%$; $P = .60$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>Incident CVD</th>
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<tr>
<td>PROVE IT-TIMI 22, 2004</td>
<td>315/1707 (18.4)</td>
<td>355/1688 (21.0)</td>
<td>0.85 (0.72-1.01)</td>
</tr>
<tr>
<td>A to Z, 2004</td>
<td>212/1768 (12.0)</td>
<td>234/1736 (13.5)</td>
<td>0.87 (0.72-1.07)</td>
</tr>
<tr>
<td>TNT, 2005</td>
<td>647/3798 (17.0)</td>
<td>830/3797 (21.9)</td>
<td>0.73 (0.65-0.82)</td>
</tr>
<tr>
<td>IDEAL, 2005</td>
<td>776/3737 (20.8)</td>
<td>917/3724 (24.6)</td>
<td>0.80 (0.72-0.89)</td>
</tr>
<tr>
<td>SEARCH, 2010</td>
<td>1184/5398 (21.9)</td>
<td>1214/5399 (22.5)</td>
<td>0.97 (0.88-1.06)</td>
</tr>
<tr>
<td><strong>Pooled odds ratio</strong></td>
<td><strong>3134/16408 (19.1)</strong></td>
<td><strong>3550/16344 (21.7)</strong></td>
<td><strong>0.84 (0.75-0.94)</strong></td>
</tr>
<tr>
<td><strong>Heterogeneity:</strong></td>
<td>$\hat{p}^2 = 74%$; $P = .004$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data marker size indicates relative weight of the studies; OR, odds ratio; and CI, confidence interval.

High Statin doses: 1 patient with incident diabetes vs prevention of 3 CV events

Preiss D JAMA 2011; 305: 2556
Statins and Diabetes

• Risk of incident type 2 diabetes increases with increasing statin dose
• Especially patients with impaired glucose tolerance or MetS affected
• Increased risk for diabetes may partially be explained by the inhibition of HMGCoAR
• Mutations, which decrease production of LDL-receptors, are associated with the lowest risk for diabetes
• Statins increase production of LDL-receptors
Statins and Diabetes

- Statins reduce macrovascular events
- Microvascular events?
Statin Therapy and cumulative Incidence of microvascular Events und Gangrene
(Nielsen SF and Nordestgaard BG, Lancet Diabetes Endocrinol 2014;2: 894–900)

215,725 Personenjahre Follow-up
Possibilities for Reduction of Diabetes Risk with Statins

• Combination of low dose with Ezetimibe
  Ezetimibe appears to be neutral or even protective with respect to diabetes
• LDL-decrease with PCSK9-Inhibitors

The cardiovascular risk reduction balances by far the potential for diabetes development in patients with high risk
Most Frequent Adverse Effect of Statin Therapy: Muscle Problems

Muscle problems are associated with

- Statin drug interactions
- Patient characteristics
- Statin pharmacokinetics
Limitations in Hypolipidemic Drug Therapy

Niacin from Success to Failure
Niacin - Effects on various Lipoproteins

Niaspan®-daily dosage

Change from baseline (%)

0  500  1000  1500  2000  2500  3000

HDL-C
LDL-C
Lp(a)
TG
## Nicotinic Acid and Atherosclerosis: A Positive Effect on Clinical Outcomes

### Randomized Controlled Clinical Trials of Nicotinic Acid and Effect on HDL-C and Clinical Outcomes

<table>
<thead>
<tr>
<th>Imaging studies</th>
<th>Special agent(s)</th>
<th>Patients receiving treatment, n/N (%)</th>
<th>Increase in HDL-C levels, %</th>
<th>Follow-up duration, years</th>
<th>Outcomes[^a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDP</td>
<td>Niacin</td>
<td>1119/8341 (13.4)</td>
<td>NR</td>
<td>6</td>
<td>Decreased (27%) nonfatal MI</td>
</tr>
<tr>
<td>CDP follow-up</td>
<td>Niacin</td>
<td>1119/8341 (13.4)</td>
<td>NR</td>
<td>15</td>
<td>Decreased (11%) death</td>
</tr>
<tr>
<td>Stockholm</td>
<td>Niacin + clofibrate</td>
<td>279/555 (50.3)</td>
<td>NR</td>
<td>5</td>
<td>Decreased (26%) death; decreased (36%) CAD death</td>
</tr>
<tr>
<td>HATS</td>
<td>Niacin + simvastatin</td>
<td>38/160 (23.8)</td>
<td>26</td>
<td>3.2</td>
<td>Decreased (90%) death, MI, stroke, or revascularization</td>
</tr>
<tr>
<td>AFREGS</td>
<td>Niacin + gemfibrozil + cholestyramine</td>
<td>71/143 (49.7)</td>
<td>36</td>
<td>2.5</td>
<td>Decreased (13%) composite clinical outcome of angina, MI, TIA, stroke, death, and cardiovascular procedures; decreased focal coronary stenosis (secondary outcome)</td>
</tr>
</tbody>
</table>

[^a]: Death indicates all-cause mortality.

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CDP = Coronary Drug Project; Stockholm = Stockholm Ischemic Heart Disease Secondary Prevention Study; HATS = HDL Atherosclerosis Treatment Study; AFREGS = Armed Forces Regression Study; NR = not reported; MI = myocardial infarction; CAD = coronary artery disease; TIA = transient ischemic attack.

Adapted from Singh IM et al. *JAMA*. 2007;298:786–798.
# Nicotinic Acid and Atherosclerosis: A Positive Effect in Imaging Studies

Randomized Controlled Clinical Trials of Nicotinic Acid and Effect on HDL-C and Atherosclerosis

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<th>Outcomes $^a$</th>
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</thead>
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<tr>
<td>CLAS I</td>
<td>Niacin + colestipol</td>
<td>94/188 (50.0)</td>
<td>37</td>
<td>2</td>
<td>Decreased coronary atherosclerosis</td>
</tr>
<tr>
<td>CLAS II</td>
<td>Niacin + colestipol</td>
<td>75/138 (54.3)</td>
<td>37</td>
<td>4</td>
<td>Decreased coronary atherosclerosis</td>
</tr>
<tr>
<td>FATS</td>
<td>Niacin + colestipol</td>
<td>48/146 (32.9)</td>
<td>43</td>
<td>2.5</td>
<td>Decreased coronary atherosclerosis; Decreased death, MI, or revascularization (secondary outcome)</td>
</tr>
<tr>
<td>CLAS Fem</td>
<td>Niacin + colestipol</td>
<td>80/162 (49.4)</td>
<td>38</td>
<td>2</td>
<td>Decreased femoral atherosclerosis</td>
</tr>
<tr>
<td>CLAS IMT</td>
<td>Niacin + colestipol</td>
<td>39/78 (50.0)</td>
<td>38</td>
<td>4</td>
<td>Decreased carotid IMT; regression also observed at years 1 and 2</td>
</tr>
<tr>
<td>SCRIP</td>
<td>Niacin + colestipol + gemfibrozil + lovastatin + aggressive lifestyle modification</td>
<td>145/300 (48.3)</td>
<td>12</td>
<td>4</td>
<td>Decreased coronary atherosclerosis; Decreased frequency of new coronary lesion formation</td>
</tr>
<tr>
<td>ARBITER 2</td>
<td>Niacin + statin</td>
<td>87/167 (52.1)</td>
<td>21</td>
<td>1</td>
<td>Decreased carotid IMT ($P&gt;0.05$)</td>
</tr>
<tr>
<td>ARBITER 3</td>
<td>Niacin + statin</td>
<td>69/130 (53.1)</td>
<td>23</td>
<td>2</td>
<td>Decreased carotid IMT</td>
</tr>
</tbody>
</table>

$^a$Outcomes:
- Death indicates all-cause mortality.

ARBITER = Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol; CLAS = Cholesterol-Lowering Atherosclerosis Study; CLAS Fem = femoral atherosclerosis group of CLAS; CLAS IMT = carotid ultrasound group of CLAS; FATS = Familial Atherosclerosis Treatment Study; IMT = intima-media thickness; MI = myocardial infarction; SCRIP = Stanford Coronary Risk Intervention Project.
AIM-HIGH (Niaspan®) Kaplan-Meier Curve for the Primary Endpoint

No. at Risk

<table>
<thead>
<tr>
<th>Condition</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo plus statin</td>
<td>1696</td>
<td>1581</td>
<td>1381</td>
<td>910</td>
<td>436</td>
</tr>
<tr>
<td>Niacin plus statin</td>
<td>1718</td>
<td>1606</td>
<td>1366</td>
<td>903</td>
<td>428</td>
</tr>
</tbody>
</table>

P = 0.79 by log-rank test
HPS2-Thrive (Niaspan® & Laropiprant®)
First Major Vascular Effect during Follow-up (prim. endpoint negative)
Limited Success with Fibrate Therapy

• FIELD (patients with type 2 diabetes): primary endpoint negative, inadequate study population
  – patients who qualified for statin therapy.
  – Important number of patients treated with statins in the placebo group
• ACCORD (patients with type 2 diabetes): primary endpoint negative, inadequate study population as in FIELD.
• However predefined subgroup of patients with atherogenic dyslipidemia (70% higher risk) showed more than 30% risk reduction
• Reduction in microvascular endpoints
**Limitation of LDL Lowering with Statins**

Substantial residual CV risk for many patients under statin therapy LDL lowering is not enough

<table>
<thead>
<tr>
<th>Trial (N)</th>
<th>Statin treatment</th>
<th>Risk reduction vs placebo</th>
<th>Remaining risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>WOSCOPS** (6595)</td>
<td>Pravastatin 40 mg</td>
<td>31%</td>
<td>69%</td>
</tr>
<tr>
<td>AFCAPS/TexCAPS** (6605)</td>
<td>Lovastatin 20/40mg</td>
<td>40%</td>
<td>60%</td>
</tr>
<tr>
<td>ASCOT-LLA** (10,305)</td>
<td>Atorvastatin 10 mg</td>
<td>38%</td>
<td>62%</td>
</tr>
<tr>
<td>4S** (4444)</td>
<td>Simvastatin 20 mg</td>
<td>26%</td>
<td>74%</td>
</tr>
<tr>
<td>CARE*** (4159)</td>
<td>Pravastatin 40 mg</td>
<td>24%</td>
<td>76%</td>
</tr>
<tr>
<td>LIPID*** (9014)</td>
<td>Pravastatin 40 mg</td>
<td>24%</td>
<td>76%</td>
</tr>
<tr>
<td>HPS*** (20,536)</td>
<td>Simvastatin 40 mg</td>
<td>27%</td>
<td>73%</td>
</tr>
<tr>
<td>PROSPER*** (5804)</td>
<td>Pravastatin 40 mg</td>
<td>24%</td>
<td>76%</td>
</tr>
<tr>
<td>JUPITER (17802)</td>
<td>Rosuvastatin 20 mg</td>
<td>44%</td>
<td>56%</td>
</tr>
</tbody>
</table>
Conclusions I

• Success of Hypolipidemic Drug Therapy
  – LDL-cholesterol lowering is associated with a proportional effect on vascular event reduction
  – Statins – therapy of choice (significant reduction of CV morbidity)
  – Extent of LDL-C lowering essential, not kind
Conclusions II

• **Limitations of Hypolipidemic Drug Therapy**
  – Statins and incident diabetes, statins and myopathy
  – Niacin – no more on market (adverse effects)
  – Fibrates only in atherogenic dyslipidemia
  – Residual risk after LDL-lowering
  ➞ Control of other CV risk factors? HDL-C?
Thank you very much for your attention!