Lipid lowering therapies - past, present and future

Professor Mogens Lytken Larsen
Aalborg University Hospital, Denmark
"I have some good news. While your cholesterol level has remained the same, the research findings have changed."
It began with the population studies!
Relationship between total serum cholesterol concentration and stroke risk by subtype from MRFIT. From Ansell in Curr Atheroscler Rep 2000.
Before statins

- Bile acid sequestering resins *
- Neomycin
- Beta-sitosterol
- Nicotinic acid *
- Clofibrate *
- Probucol
- D-thyroxine

* tested in clinical trials
LRC-CPPT: LOWERING LDL-C LOWERS RISK

LDL-C reduction of 12.6% with cholestyramine

- CHD death and/or Nonfatal MI
  - 19%*

- CHD Death
  - 24%

- Nonfatal MI
  - 19%

* P < .05 vs placebo

Coronary Drug Project - Niacin

- 3,908 men aged <65 yrs with history of MI.
- 27% decrease in nonfatal MI in niacin group.
- Follow-up 9 years after end of trial: 11% lower total mortality in niacin group.

JAMA 1975; 231:360; JACC 1986; 8:1245
POSCH study – ilial bypass

Cholesterol Level Reductions and CHD Risk

Program on the Surgical Control of Hyperlipidemia (ileal bypass - 38% LDL-c reduction)

LDL lowering today

• Statins (1987)
• Ezetimibe (2002)
• Combinations
  • Statin + resins
  • Statin + Nicotinic acid
  • Statin + ezetimibe
# 4S To IDEAL

11 Years Of Landmark Statin Trials

<table>
<thead>
<tr>
<th>Year</th>
<th>Trial</th>
<th>Overview</th>
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<tbody>
<tr>
<td>1994</td>
<td>4S</td>
<td>First 5 Trials Proved RRR in morbidity and mortality vs placebo</td>
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<tr>
<td>1995</td>
<td>WOSCOPS</td>
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<td>1996</td>
<td>CARE</td>
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<td>1998</td>
<td>AFCAPS/TexCAPS</td>
<td>LIPID</td>
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<tr>
<td>2001</td>
<td>MIRACL</td>
<td>Second Wave Of Trials</td>
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<tr>
<td>2002</td>
<td>HPS</td>
<td>• Focus on other high-risk groups</td>
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<tr>
<td></td>
<td>PROSPER</td>
<td>– ACS, elderly, DM, HTN</td>
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<tr>
<td></td>
<td>ALL-HAT LLT</td>
<td>• Comparisons beyond placebo</td>
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<tr>
<td></td>
<td></td>
<td>– vs usual care (ALLIANCE, ALL-HAT)</td>
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<tr>
<td></td>
<td></td>
<td>– active comparator (PROVE IT, A to Z)</td>
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<tr>
<td>2003</td>
<td>ASCOT-LLA</td>
<td></td>
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<tr>
<td>2004</td>
<td>PROVE IT</td>
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<td></td>
<td>ALLIANCE</td>
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<td></td>
<td>CARDS</td>
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<tr>
<td></td>
<td>A to Z</td>
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<tr>
<td>2005</td>
<td>TNT</td>
<td>Intensity Of Statin Treatment In Stable</td>
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<tr>
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<td>IDEAL</td>
<td>CHD Patients Receiving Contemporary Therapy</td>
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</table>

Intensity Of Statin Treatment In Stable CHD Patients Receiving Contemporary Therapy
Relationship Between LDL-C and CV Incidence

Event, %

0 5 10 15 20 25 30

Mean Treatment LDL-C at Follow-up, mg/dL (mmol/L)

0 40 60 80 100 120 140 160 180 200

(1.0) (1.6) (2.1) (2.6) (3.1) (3.6) (4.1) (4.7) (5.2)

Secondary Prevention

Primary Prevention

Statin
Placebo

4S

ASCOT
ASCOT

TNT
HPS

TNT
HPS

PROVE-IT
(IDéal Sim)

PROVE-IT
(IDéal Atv)

CARE

LIPID

LIPID

HPS

IDéal (Atv 10 mg)

IDéal (Atv)

PROVE-IT (Pra)

WOSCOPS
AIM-HIGH (N Eng J Med nov. 2011)

Figure 1. Kaplan–Meier Curve for the Primary End Point.
Ezetimibe: LDL-C Lowering Efficacy Regardless of Statin

*Lovastatin, pravastatin, cerivastatin, and fluvastatin
Adapted from Gagné C et al Am J Cardiol 2002;90:1084–1091.
Study Design

Patients stabilized post ACS ≤ 10 days:
LDL-C 50–125*mg/dL (or 50–100**mg/dL if prior lipid-lowering Rx)

*3.2mM
**2.6mM

N=18,144

Standard Medical & Interventionsal Therapy

Simvastatin
40 mg

Uptitrated to Simva 80 mg if LDL-C > 79 (adapted per FDA label 2011)

Ezetimibe / Simvastatin
10 / 40 mg

Follow-up Visit Day 30, every 4 months

90% power to detect ~9% difference

Duration: Minimum 2 ½-year follow-up (at least 5250 events)

Primary Endpoint: CV death, MI, hospital admission for UA, coronary revascularization (≥ 30 days after randomization), or stroke

Cannon CP AHJ 2008;156:826-32; Califf RM NEJM 2009;361:712-7; Blazing MA AHJ 2014;168:205-12
**LDL-C and Lipid Changes**

<table>
<thead>
<tr>
<th>1 Yr Mean</th>
<th>LDL-C</th>
<th>TC</th>
<th>TG</th>
<th>HDL</th>
<th>hsCRP</th>
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</thead>
<tbody>
<tr>
<td>Simva</td>
<td>69.9</td>
<td>145.1</td>
<td>137.1</td>
<td>48.1</td>
<td>3.8</td>
</tr>
<tr>
<td>EZ/Simva</td>
<td>53.2</td>
<td>125.8</td>
<td>120.4</td>
<td>48.7</td>
<td>3.3</td>
</tr>
<tr>
<td>Δ in mg/dL</td>
<td>-16.7</td>
<td>-19.3</td>
<td>-16.7</td>
<td>+0.6</td>
<td>-0.5</td>
</tr>
</tbody>
</table>

**Median Time avg**
69.5 vs. 53.7 mg/dL

1.8 vs. 1.4
CV Death, Non-fatal MI, or Non-fatal Stroke

HR 0.90 CI (0.84, 0.97)
p = 0.003
NNT = 56

Simva — 22.2%
1704 events

EZ/Simva — 20.4%
1544 events

7-year event rates
**Conclusions**

**IMPROVE-IT:** First trial demonstrating incremental clinical benefit when adding a non-statin agent (ezetimibe) to statin therapy:

- **YES:** *Non-statin* lowering LDL-C with ezetimibe reduces cardiovascular events
- **YES:** Even Lower is Even Better (achieved mean LDL-C 53 vs. 70 mg/dL at 1 year)
- **YES:** Confirms ezetimibe safety profile

- **Reaffirms the LDL hypothesis,** that reducing LDL-C prevents cardiovascular events
- **Results could be considered for future guidelines**
- Bempodoic acid
- CETP inhibitors
- PCSK9 inhibitors
Fig. 1 Major metabolic pathways affected by bempedoic acid (ETC-1002) in humans as supported by clinical trial data. Animal data suggested additional effects on triglyceride metabolism via ACL inhibition and other cardiometabolic pathways via AMP-activated protein kinase (AMPK) activation. ACL ATP citrate lyase, Acetyl-CoA acetyl coenzyme A, HMG-S HMG-CoA synthase, HMG-R HMG-CoA reductase.
Three CETP inhibitors failed - # 4 succesfull ???
PCSK9 Inhibition Using Monoclonal Antibodies

LDL Degradation and Recycling of LDL-R

PCSK9-Mediated Degradation of LDL-R

PCS K9 Inhibition in Patients With Hypercholesterolemia Receiving Statin Therapy

| Treatment          | 100 | 150 | 200 | 300 | 150 | 300 | 105 | 140 | 280 | 350 | 420 |
|--------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Arilocumab\(^a\)   |     |     |     |     | -64.2| -72.4|     |     |     |     |     |     |
| Bococizumab\(^b\)  | -43.3| -47.7|     |     | -53.4| -44.9|     |     |     |     |     |     |
| Evolocumab\(^c\)   |     |     |     |     | -60.2| -66.1| -41.8| -50.0| -50.3|     |     |     |

Change From Baseline in LDL-C vs Placebo at Week 12, %

P < .0001 for each comparison

NEJM March 17, 2017

**LDL Cholesterol**

- **Placebo**
  - 59% mean reduction (95% CI 58-60), P < 0.00001
  - Absolute reduction: 56 mg/dl (95% CI 55-57)

- **Evolocumab**
  - Median 30 mg/dl, IQR 19-46 mg/dl

**Key Secondary Endpoint**

- Hazard ratio 0.80 (95% CI, 0.73-0.88)
  - P < 0.00001
  - CV Death, MI, or Stroke

- Placebo: 7.9%
- Evolocumab: 9.9%
Small interferingRNA – a new PCSK9 approach
HIGHLY DURABLE RNAi THERAPEUTIC INHIBITOR OF PCSK9

A Change in PCSK9 Level in Single-Dose Cohorts

Cohort
- Placebo (N=6)
- Inclisiran, 25 mg (N=3)
- Inclisiran, 100 mg (N=3)
- Inclisiran, 300 mg (N=3)
- Inclisiran, 500 mg (N=3)
- Inclisiran, 800 mg (N=6)

Mean Change from Baseline (%) vs Days after Dose

NEJM 2017;376;41-51
CONCLUSION

• Statins and ezetimibe will reduce cardiovascular events

• The first PCSK9 inhibitor have been shown to reduce cardiovascular events - more to come?

• After three failures with CETP inhibitors one successful will be presented next week (??)

• What will the future bring?
Nostradamus

It’s all in the stars

Jules Verne

Let your imagination run free – science will make everything possible

Karl Popper

We cannot know what we do not yet know