New Targets in Lipid Management

John J.P. Kastelein, MD PhD
Academic Medical Center / University of Amsterdam
The Netherlands
Novel Approaches to Modify Lipids and Lipoproteins

- Low Density Lipoprotein
- High Density Lipoprotein
- Triglyceride Rich Lipoproteins
- Inflammation
- Lipoprotein a
Statin Prescription in the UK

Prescribed Items (000s)

Net Ingredient Cost (£000s)

Statins – Prescribed

Statins – Cost (£000s)
Percentage of the UK-population with TC > 5 mmol/l
All-Cause Mortality in the UK in those < 75 Years

Mortality - DSR per 100,000 - All Causes

- Data
  - Other
  - Cancer
  - Other Circulatory
  - CHD

53% reduction

1995-1997: 397
1996-1997: 115
1998-1999: 89
2000-2001: 52
2006-2008: 296
2007-2008: 107
2009-2010: 114
2011-2012: 32
2013-2014: 42
New Approaches to LDL Reduction

What is in development?

• Cholesterol Absorption Inhibitors
• Squalene Synthase (SSI) inhibitors
• Apo B mRNA antisense drugs
• Microsomal Triglyceride Transfer Protein (MTP) inhibitors
• Thyroxin Receptor Agonists
• PCSK9 Inhibitors
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Mipomersen: Apo B-100 as a Target

- Apo B-100 is an important structural and functional component of lipoproteins
- Blocking Apo B-100 production blocks VLDL and LDL production
Overview of Mipomersen

- A 20-mer phosphorothioate antisense oligonucleotide that is complementary in sequence to a segment of the human Apo B mRNA

Antisense: A Novel Approach to Drug Discovery by Inhibition of Translation of a Specific Targeted Protein

RNase H Dependent Mechanism of Action

2nd Generation Antisense Drugs

- ~20X more potent
- 1X/week to 1X/quarter dosing
- Better tolerated
- Lower cost of therapy

Cell Membrane

Antisense Strand

Sense-Antisense Duplex

mRNA

RNase H

DNA

Nucleus Cytoplasm
Patients were randomized 2:1 to receive weekly subcutaneous injections of mipomersen 200 mg or placebo for 26 weeks.

- 225 patients screened; 124 patients enrolled
- Active treatment: 2:1 active:placebo
- Placebo
- Safety follow-up (for patients not entering OLE study)

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<tr>
<th>Screening</th>
<th>Treatment period</th>
<th>Safety follow-up</th>
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<td>≤4 weeks</td>
<td>26 weeks</td>
<td>24 weeks</td>
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Cromwell W, et al, [poster]. American Heart Association Scientific Sessions; Nov 14-18; Orlando, FL; 2009
Mipomersen Significantly Reduced LDL-C

Reduction in LDL-C over 28 weeks (full analysis set)

Mean (95% CI) % change from baseline in LDL-C

Weeks

0 5 10 15 20 25 30

Placebo  Mipomersan 200 mg

PET

5.2%

-28.0%
**Distribution of LDL-C % Change From Baseline**

PET, primary efficacy time point, 2 weeks after final dose.

Data on file.
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The Rationale

- Thyroid hormone receptors modulate lipid metabolism and energy expenditure through transcriptional effects.

- The liver is the target organ for thyroid hormone-mediated regulation of lipid metabolism.

- Association between thyroid status and atherosclerosis clearly demonstrated.

- The thyroid hormone receptor is a well known target.
Selective Thyroid Receptor Agonist Provides New Treatment Opportunities

Selective thyroid agonist

**Side effects**
- Heart
- Bone
- Skeletal muscle

**Metabolic effects**
- Cholesterol
- Triglycerides
- Lipoprotein(a)
- Reverse cholesterol transport
- Metabolic rate
Eprotirome is...

- a small molecule
- a thyroid receptor agonist
- acting in the liver
- as potent as T3
- for once daily oral administration
Eprotirome Monotherapy Efficiently Lowers LDL-C

**LDL cholesterol**

![Graph showing LDL cholesterol levels](chart.png)

**LDL-cholesterol**

Baseline to week 12

- Placebo
- 25 µg
- 50 µg
- 100 µg

% change

-6 -21 -26 -32

Time (weeks)

0 4 8 12 16

p <0.0001 Mean ± 95% CI
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Hepatic LDL-Rs Play a Key Role in Regulating Plasma LDL-C Levels

PCSK9 Regulates the Surface Expression of Hepatic LDL-Rs

Loss-of-Function Mutations in Human PCSK9 are Associated with Lower LDL-C Levels

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<th>PCSK9 Variant</th>
<th>Population</th>
<th>LDL-C</th>
<th>CHD Risk</th>
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<td>↓ 47%1</td>
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<td>CGPS</td>
<td>↓ 11%3</td>
<td>↓ 46%3</td>
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- Found in 1% to 4% of population1
- Associated with
  - Lower serum LDL-C1
  - Lower incidence of coronary heart disease1
- Inhibiting LDL-R / PCSK9 interaction may lower plasma LDL-C levels4

Anti-PCS K9 Monoclonal Antibodies (mABs) Block PCSK9/LDL-R Interaction and Lower LDL-C Levels

LDL-R and PCSK9 Expression Are Both Upregulated When Intercellular Cholesterol Levels Are Low

[SREBP] = sterol regulatory element-binding protein

Anti-PCSK9 mAbs May Further Lower LDL-C Levels Under These Conditions

LDL-C Mean % Change from Baseline in Subjects Treated with IV REGN727/SAR236553 or Placebo

Novel Approaches to Modify Lipids and Lipoproteins

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- Inflammation
- Lipoprotein a
New Approaches for Raising HDL

What is in development?

- Cholesterol Ester Transfer Protein (CETP) inhibitors
- ER-Niacin / Laropiprant combination
- ApoA1 based strategies
- LCAT replacement strategies
- ABCA1 agonists
HDL Drugs: What Now?

After a spectacular failure last year, researchers and heart patients are about to get some answers.

Whether the other CETP inhibitors have a future will become clearer this weekend at the annual meeting of the American College of Cardiology. It’s common knowledge among researchers that torcetrapib raised blood pressure in early tests. Scientists will reveal just how big the increase was—and, by implication, whether that was the drug’s fatal flaw. (Roche and Merck are both working on CETP inhibitors that do not appear to raise blood pressure.)

But what if the problem with torcetrapib was more fundamental, such as an adverse effect on HDL’s basic function? Presentations at ACC could shed light on that, too. In three separate trials, Nissen and other investigators scanned thousands of patients’ blood vessels before they began taking torcetrapib, and again months later. If HDL functioned well, the trials should show that arterial plaques shrank. No matter what the results, it will take years to bring a drug like this to market.

In the meantime, what’s a person who wants to boost HDL to do? The drug Niaspan—a version of the B-vitamin niacin—
Odds ratio for future CAD

**CETP Levels and CAD risk: The EPIC – Norfolk study**

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Boekholdt et al. Circulation 2004
Anacetrapib Dose Ranging Study

LDL-C and HDL-C Percent Change from Baseline

Weeks on Treatment

Placebo
Anacetrapib 10 mg
Anacetrapib 40 mg
Anacetrapib 150 mg
Anacetrapib 300 mg

Future

- 30,000 patients with occlusive arterial disease in North America, Europe and Asia
- Background LDL-lowering with atorvastatin
- Randomized to anacetrapib 100 mg vs. placebo
- Primary outcome: Coronary death, myocardial infarction or coronary revascularization

The Verdict is Still Out on CETP Inhibition as a Mechanism
New Approaches for Raising HDL

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Niacin-Induced Flushing Limits Niacin Utilization
Niacin Flushing Pathway: Two Separate Steps and Sites of Action

1. Epidermal Langerhans Cells
   - Niacin binds
   - PGD$_2$ is produced and released

2. Dermal Blood Vessels
   - PGD$_2$ binds to DP1
   - Vasodilation results

Illustrations are artistic renditions.
PGD$_2$=prostaglandin D$_2$; PLA$_2$=phospholipase A$_2$; DP1=prostaglandin D$_2$ receptor 1.
An Overview of the Niacin-Induced Flushing Pathway

Epidermal Langerhans Cells

Niacin → Niacin Receptor

Arachidonic Acid Pathway

Niacin Receptor → Phospholipids → Arachidonic Acid

PLA₂ → PGG₂ → PGH₂ → PGI₂ → PGF₂α → TXA₂ → PGD₂

Dermal Blood Vessel

Prostaglandin D₂ Receptor 1 (DP1) Pathway

PGD₂ → DP1 → Vasodilation and Flushing

PG=prostaglandin; PLA₂=phospholipase A₂; TXA₂=thromboxane A₂.
Dashed arrows are normal parts of the arachidonic acid pathway that may or may not occur in Langerhans cells.
Factorial Study: Lipid Efficacy

Primary end point

- LDL-C
- HDL-C
- TG

- ER niacin/laropiprant (n = 160)
- Simvastatin (all doses pooled; n = 565)
- ER niacin/laropiprant + simvastatin (all doses pooled; n = 520)
All patients receive either simvastatin 40mg or ezetimibe/simvastatin 10/40 mg

**ER niacin/laropiprant 2 g/40mg**

**Placebo**

### Patient Population
- Age 50-80
- History of MI or cerebrovascular atherosclerotic disease or PAD or diabetes mellitus with any of the above or with other evidence of symptomatic CHD

### Subjects
- 25,000
- UK (n=8500), Scandinavia (n=6000) and China (n=10500)

### Primary End Point
- Major vascular events (non-fatal MI or coronary death, non-fatal or fatal stroke or revascularisation)
New Approaches for Raising HDL

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ApoA1 Based Therapies

- ApoA1 Mimetics, such as APL-180 Novartis
- Full-length ApoA1, such as ApoA1 Cerenis Therapeutics
- Pre-Beta HDL, as generated by delipidation, HDL Therapeutics Inc.
- Reconstituted HDL, CSL Ltd.
- ApoA1 Milano, The Medicines Company
- Trimeric ApoA1, Borean Pharma and now Roche
- RVX-208, as developed by Resverlogix
Cerenis HDL (CER-001)
Homogeneous Drug Product

Validated, scaleable GMP process for producing proprietary charged lipoprotein complexes
CER-001 Mobilizes Cholesterol in Rabbits: Comparison with ETC-216

CER-001 is at least 10 to 20 time more potent to mobilize cholesterol than ETC-216

CHI SQUARE Study Design

- 4 Treatment Groups
  - Placebo
  - Low dose CER-001
  - Mid dose CER-001
  - High dose CER-001

- 6 doses per subject

- 125 subjects enrolled per group
  - Estimated 75 - 80% completion rate
    ==> ~98 subjects w/ follow-up IVUS per group
N = 126 Placebo

N = 126 Low dose

N = 126 Mid dose

N = 126 High dose

50 Sites
Canada, US, France, Netherlands

Core IVUS Lab
Montreal Heart

Up to 1000 Subjects
Screened w/ Baseline IVUS following Acute ACS Event

504 Subjects Randomized

CHI-SQUARE Study Design

Screen Period
2 weeks

Screening

IVUS Visit

Therapy Period
5 weeks

Observation Period
2 to 5 weeks

Long Term Follow-up
6 months

Infusion Visits

Interim Visit

Follow-Up IVUS Visit

Follow-Up Visit
Delipidation
IVUS clinical trial using selective delipidated HDL

Step 1
Collected~1 litre of plasma

Step 2
Plasma enriched through process

Step 3
Re-infused preβ enriched plasma

- Used patients own HDL
- Cholesterol removed from αHDL to yield preβ-HDL
- Preβ enriched plasma is re-infused into patient

**IVUS Clinical Trial Using Selective Delipidated HDL**

- **Treatment arm (N=14)**
- **Control arm (N=14)**

**Day 0**

- 1:1 randomization

**Day 1 - Day 8**

- Treatment or control plasma infusion

- IVUS

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Results of the IVUS Clinical Trial Using Selective Delipidated HDL

Conclusion

In the next five years, we will prove or disprove that additional LDL lowering with other agents than statins is effective

and

we will show or not show that the HDL hypothesis is true

and

that lowering of triglycerides in patients on statins and inhibiting inflammation leads to a reduction of CVD events
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<table>
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VRN Website - Frontpage

Ons netwerk
Een bron van nieuw onderzoek
✓ Toegang tot een groot pharmaceutisch netwerk
✓ Ook voor startende onderzoekscentra
✓ De zekerheid die VRN u biedt
✓ Geaccrediteerde GCP en BROK cursussen

VRN Diensten

Dienstverlening voor het hele netwerk.
LEES VERDER

Trial Bureau

Onze eigen Trial Bureau staat voor u klaar.
CONTACT

Cursussen

GCP en BROK, natuurlijk via VRN.
LEES VERDER
VRN Website - Congresses

Komende congressen

Cardio Vascular Conference
is een gemeenschappelijk initiatief van verschillende verenigingen op het gebied van de cardiovasculaire geneeskunde. Als clinici of wetenschapper actief op het gebied van de cardiovasculaire geneeskunde mag u dit niet missen!

American College of Cardiology
ACC.12 in Chicago will highlight the ACC's focus on lifelong learning and practice improvement, and with a new learning pathway structure we can better address the needs of you, our learners.

International Symposium on Atherosclerosis (ISA)
ISA.2012 will focus on recent clinical and scientific advances in key and emerging areas of atherosclerosis. The key aim is to provide a comprehensive, state-of-the-art overview of the current understanding of the origins.
VRN Website - Publications

Efficacy and Safety of Statin Therapy in Children With Familial Hypercholesterolemia

A Randomized, Double-Blind, Placebo-Controlled Trial With Simvastatin

Saskia de Jongh, MD; Leiv Ose, MD; Temás Szamosi, MD, PhD; Claude Gagné, MD; M. Lambert, MD; Russell Scott, MD; P. Perron, MD; Dries Dubbelaere, MD; M. Selborio, MD; Mary B. Tushy, RN; Michael Stepanavage, MS; Athl Saper, PhD; Barry Gunbiner, MD; Michele Mercuri, MD, PhD; A.S. Paul van Trotsenburg, MD; Henk D. Bakker, MD, PhD; John J.P. Kastelein, MD, PhD; for the Simvastatin in Children Study Group

Background A multicenter, randomized, double-blind, placebo-controlled study was conducted to evaluate LDL cholesterol-lowering efficacy, overall safety, and tolerability and the influence on growth and pubertal development of simvastatin in a large cohort of boys and girls with heterozygous familial hypercholesterolemia (HeFH).

Methods and Results A total of 123 HeFH children (98 boys and 75 girls) were included in this study. After a 4-week diet/placebo run-in period, children with HeFH were randomized to either simvastatin or placebo in a ratio of 3:2. Simvastatin was started at 10 mg/d and titrated at 4-week intervals to 20 and then 40 mg/d. During a 24-week extension period, the patients continued to receive simvastatin (60 mg) or placebo according to their