Genetic Approaches to Prevention and Treatment

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Dept. of Vascular Medicine
AMC - Amsterdam Netherlands
Paradigm Shift in Medicine

18th-19th Century - Anatomy

Diagnosis – recognition of diseased organs
Paradigm Shift in Medicine

20th Century - Physiology

- Treatment of disease: infectious disease, blood pressure, cancer, cholesterol
Next Paradigm Shift in Medicine

Analysis of a Mutant Strain of Human Fibroblasts with a Defect in the Internalization of Receptor-Bound Low Density Lipoprotein

Michael S. Brown and Joseph L. Goldstein
Division of Medical Genetics
Department of Internal Medicine
University of Texas Health Science Center at Dallas
Dallas, Texas 75235

The cholesterol-carrying protein in human plasma, binds to a specific cell surface receptor (Brown and Goldstein, 1974a; Goldstein et al., 1974a; Anderson Goldstein, and Brown, 1976). The receptor-bound lipoprotein is internalized and delivered to lysosomes wherein its protein and cholesterol ester components are hydrolyzed (Goldstein and Brown, 1974b; Brown, 1975; and Goldstein, 1976). The un

21st century - Biology

Prevention of disease:
Translational medicine, genetics, metabolomics, advanced maging, ICT
Translational Research
Zen & The Art of Lipid Metabolism
Exogenous Pathway

Liver

Intestine

Chylomicron

Chylomicron Remnant
Endogenous Pathway

Liver

VLDL

Remnant

VLDL

LDL
Reversed Cholesterol Transport
Transmission of Genetic Disease

Vertical Transmission

Horizontal Transmission
Causes of Dyslipidemia

Environmental/Secondary dyslipidemia

Genetic/Primary dyslipidemia
Secondary Dyslipidemia

<table>
<thead>
<tr>
<th>Cause</th>
<th>Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>TG ↑, HDL-C ↓</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>LDL-C ↑</td>
</tr>
<tr>
<td>Acromegaly</td>
<td>TG ↑</td>
</tr>
<tr>
<td>Anorexia nervosa</td>
<td></td>
</tr>
<tr>
<td>Lipodystrophy</td>
<td></td>
</tr>
<tr>
<td>Glycogen storage disorders</td>
<td></td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td></td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td></td>
</tr>
<tr>
<td>Obstructive liver disease</td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td></td>
</tr>
<tr>
<td>Immunoglobulin excess: paraprotein</td>
<td></td>
</tr>
<tr>
<td>Medications:</td>
<td></td>
</tr>
<tr>
<td>β-adrenoceptor antagonists (e.g.,</td>
<td></td>
</tr>
<tr>
<td>thiazide diuretics</td>
<td></td>
</tr>
<tr>
<td>glucocorticoids</td>
<td></td>
</tr>
<tr>
<td>ciclosporin</td>
<td></td>
</tr>
<tr>
<td>interferons</td>
<td></td>
</tr>
<tr>
<td>antiviral medications (HIV protease</td>
<td></td>
</tr>
<tr>
<td>inhibitors)</td>
<td></td>
</tr>
<tr>
<td>exogenous estrogens</td>
<td></td>
</tr>
<tr>
<td>retinoic acid derivatives</td>
<td></td>
</tr>
<tr>
<td>HDL-C = high-density lipoprotein-cholesterol; LDL-C = low-density lipoprotein-cholesterol; TG = triglyceride; ↑ indicates increased levels; ↓ indicates decreased levels.</td>
<td></td>
</tr>
</tbody>
</table>

Lab Test

1. Glucose/HbA1c
2. Kreatinine
3. Transamininases
4. TSH
5. Urine dip stick
Low Isolated HDL-cholesterol

It is a riddle wrapped in a mystery inside an enigma: but perhaps there is a key?
Low HDL-c and Cardiovascular Risk

An Independent Frequent Risk Factor

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Controls (n = 601)</th>
<th>Cases (n = 321)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cigarette smoking</td>
<td>29%</td>
<td>67%*</td>
</tr>
<tr>
<td>HDL-C &lt; 35 mg/dl</td>
<td>19%</td>
<td>63%*</td>
</tr>
<tr>
<td>Hypertension (BP &gt; 150/90)</td>
<td>21%</td>
<td>41%*</td>
</tr>
<tr>
<td>LDL-C ≥ 160 mg/dL</td>
<td>26%</td>
<td>26%</td>
</tr>
<tr>
<td>Diabetes melitus</td>
<td>1%</td>
<td>12%*</td>
</tr>
</tbody>
</table>

Kannel WB AJC 52, 1983 – Framingham Study

High Density Lipoprotein

Levels <35 mg/dl

Levels >65 mg/dl

Low levels
  • Genetic factors
  • Cigarette smoking, anabolic steroids, beta blockers, polyunsaturated fats
Established human HDL genes

- **APOAI**
- **LCAT**
- **ABCA1**

\{ \}
Severe HDL deficiency

- **HL**
- **CETP**

\{ \}
Hyperalphalipoproteinemia
Lecithin:Cholesterol Acyl Transferase Deficiency

Converts cholesterol to cholesteryl ester in HDL

Accumulation of free cholesterol in:

- Cornea $\rightarrow$ corneal opacities
- Red blood cells membranes $\rightarrow$ Anemia
- Renal glomeruli $\rightarrow$ Renal failure
- Blood vessels $\rightarrow$ Atherosclerosis
Tangier Disease – ABCA1 mutation

Autosomal Recessive

Enhanced catabolism of HDL

CE accumulation in macrophages

- Orange tonsils
- Corneal deposits
- Hepatomegaly/Splenomegaly
- Peripheral neuropathy
- Premature CVD
Familial Hypo-Alpha-Lipoproteinemia
Apo A1 Deficiency

Mutation in Apo A1 gene
Very low HDL-C levels (<10mg/dl)
- Premature CVD
- Positive Family History
- Corneal opacities
Hyper-Alpha-Lipoproteinemia

HDL-C $> 90^{th}$ percentile

CETP – Deficiency

Apo A1 overexpression

SR-BI - ↓function
Newly proposed HDL genes

Genome-wide association studies

New loci:

- **GALNT2** N-actetylgalactosaminytransferase 2
- **MVK** mevalonate kinase
- **MMAB** cob(I)alamin adenosyltransferase
Pseudo low HDL- C

Multiple Myeloma

M. Kahler

M. Waldenström
Isolated High Triglycerides

Lipoprotein type: Chylomicron
Density: <0.950 g/mL
Diameter: 80-1000 nm
Major lipids: dietary triacylglycerols
Apolipoproteins: B48, A1, A2, C, E

Protein: ~1%
Triglyceride: ~90%
Cholesterol: ~5%
Phospholipids: ~4%

Lipoprotein type: VLDL
Density: 0.950-1.006 g/mL
Diameter: 30-80 nm
Major lipids: endogenous triacylglycerols
Apolipoproteins: A1, A2, C, E

Protein: ~10%
Triglyceride: ~65%
Cholesterol: ~13%
Phospholipids: ~13%

Lipoprotein type: IDL
Density: 1.006-1.019 g/mL
Diameter: 25-30 nm
Major lipids: endogenous triacylglycerols and cholesterol
Apolipoproteins: B100, C, E

Protein: ~18%
Triglyceride: ~34%
Cholesterol: ~22%
Phospholipids: ~22%

Lipoprotein type: LDL
Density: 1.019-1.063 g/mL
Diameter: 20-22 nm
Major lipids: cholesterol and cholesteryl ester
Apolipoproteins: B100

Protein: ~20%
Triglyceride: ~10%
Cholesterol: ~45%
Phospholipids: ~23%

Lipoprotein type: HDL
Density: 1.063-1.090 g/mL
Diameter: 9-15 nm
Major lipids: cholesteryl ester and phospholipid
Apolipoproteins: A1, A2, C, E

Protein: ~50%
Triglyceride: ~20%
Cholesterol: ~18%
Phospholipids: ~30%
Chylomicronemia – Type 1

Clinical manifestations
- Eruptive or tuberous xanthomas,
- Lipemia retinalis
- Hepatosplenomegaly.
- Acute Pancreatitis → mortality 20%
Chylomicronemia – Type 1

Autosomal Recessive: LPL gene ( >220 mutations!)

1 : 1 000 000 → Eastern Quebec 1 : 5 000 (‘founder effect’)

Mass vs activity (60% of defective activity normal mass)
Chylomicronemia – Type 1

APOC2
GPIHBP1
LMF1
APOA5
New Therapies Type I

1. **Alipogene Tiparvovec** – *LPL deficient patients only*
   
   LPL gene + Adeno associate Virus (AAV1-LPLS447x)
   
   - serum TG by 40%!
   - After 6 Months back to baseline – despite gene expression

2. **Intestinal lipase inhibitor** - Orlistat

3. **Diacylglycerol acyltransferase inhibitor**: LCQ908;

4. **Intestinal-specific MTP1 inhibitor**: SLx-4090

5. **APOC3 inhibitor/Apo C3 MiRNA**
Standard Therapies Type I

1. **Diet < 10% -15% Fat intake / exercise / optimal weight**

2. **No alcohol**

3. **Fibrates/Niccotinic acid/Fish oils**

4. **Plasmapheresis (acute pancreatitis)**

5. **Women: no hormonal birth control / replacement**
IM admin of AAV1-LPL$^{S447X}$ in mice

- Dose-dependent complete resolution of plasma TG in LPL-/- mice
- Effective dose of $8 \times 10^{11}$- $8 \times 10^{12}$ gc/kg
- Long-term transgene expression & efficacy: >1 year

Ross et al., Human Gene Therapy 2004
LPL – Gene therapy

40 (low dose), 60 (mid dose) injections sites in leg (under epidural anaesthesia)
High Triglycerides + High cholesterol

**Lipoprotein type: Chylomicron**
- Protein: ~1%
- Triglyceride: ~90%
- Cholesterol: ~5%
- Phospholipids: ~4%
- Density: ~0.950 g/mL
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- Protein: ~50%
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Familial Combined Hyperlipidemia

- Elevated TC and TG with other family members also having one or both lipids elevated
- Affects 1% of population.
- Heterogeneous disorder
- Autosomal dominant with age dependent penetrance
- Increased risk of CAD
- Increased production of apo B and VLDL
Familial Combined Hyperlipidemia

Loci implicated in different families

- apoAI-CIII-AIV
- LPL
- USF1
- TXNIP gene
probability of being affected by FCH

TG 91-95%: 8P
TC 75-90%: 3P
ApoB 1600 mg/L 4.2P
Total: 15.2P
FCH prob. 0.95

Veerkamp et al., Circulation. 2004;109:2980-2985.)
Standard Therapies FCH

1. **Diet - reduced Fat intake / exercise / optimal weight**

2. **Limit alcohol intake**

3. **Statins (high intensity – high dose)**

4. **Fibrates/Nicotinic acid/Fish oils**

5. **Combination : Statin + Fibrate**
Familial Dysbetaalipoproteinemia Type III

Autosomal Recessive trait + extra factor (1:5000)

- Apo E mutation (E2/E2)
- TG + TC ↑↑ + VLDL-c/TG <0.3 + ↓LDL-apo B + normal HDL-C
- Rapid progressive atherosclerosis (PAD + CAD)

Extra factor:
1. Insulin resistance
2. Alcohol intake
3. Hypothyroidism
4. Steroids - Estrogen
Familial Dysbetalipoproteinemia Type III

Apo E

- TC 10% higher in subjects with E4
  - Risk of Alzheimer disease
- TC 10% lower in subjects with E2
- Type III in 1-2% of E2/E2
  - LDL binding < 1% of normal activity

Familial Dysbetalipoproteinemia
Clinical signs

- Striated xanthomas
- Cholesterol: 300-600 mg/dl
- TG: 400-800 mg/dl
- Increased IDL, “broad beta” band
- E2/E2
- rare variants E3 E4
Familial Dysbetalipoproteinemia Treatment

1. *Diet* - reduced Fat intake / exercise / optimal weight

2. *Limit alcohol intake*

3. *Statins* (high intensity – high dose)

4. *Fibrates/Nicotinic acid/Fish oils*

5. *Combination : Statin + Fibrate*
High (LDL)-Cholesterol

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Protein: ~20%
Triglyceride: ~10%
Cholesterol: ~45%
Phospholipids: ~23%
Familial Hypercholesterolemia

Clinical Characteristics

Genetics:
• autosomal dominant
• heterozygous: 1:250-500
• homozygous: 1: 250 00 - 1:10^6

Physical examination:
• xanthomas - extensor tendons
  - Achilles tendon
  - elbow/knee
• arcus cornealis
• xanthelasmas

Clinical characteristics:
• myocardial infarction
• angina
• sudden death

Laboratory:
• LDL-C ↑: > 95th perc.
• HDL-C ↔ or ↓
• triglycerides ↔
Familial Hypercholesterolemia
Genetics

**Autosomal Dominant:**
- LDL-receptor → > 1200 point mutations / insertions / deletions
- Apo B → 6 variants
- PCSK9 → gain of function mutations

**Autosomal recessive:**
- LDLRAP1/ARH → <10 mutations

**Putative genes**
- CYP 7A1
- SREBP-2
- SCAP
Coronary Artery Disease in 116 Kindred with Familial Type II Hyperlipoproteinemia
NEIL J. STONE, ROBERT I. LEVY, DONALD S. FREDRICKSON and JOEL VERTER

Circulation 1974; 49:476-488
doi: 10.1161/01.CIR.49.3.476
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/49/3/476.citation

Figure 3
CUMULATIVE PROBABILITY BY DECADE OF FATAL AND NONFATAL CAD

Type II
0
0.100
0.200
0.300
0.400
0.500
0.600
0.700
0.800
0.900
1.000
10
20
30
40
50
60
AGE (year)

♂ Relatives
Over 19
Normals
Smoking in heterozygous FH confers an extra relative risk of 4 or decreases longevity by 12 – 15 years!
Atherosclerosis
Risk Factors
New Treatments

- PCSK9 antibodies
- MTP inhibitor Lometapide
- Anti mRNA Mipomersin
A

**Figure A**

- **Plasma**
- **LDL**
- **PCSK9/LDL-R complex**
- **PCSK9**
- **Hepatocyte**

**Process Diagram:***

1. **Endocytosis**
   - LDL binds to LDL-R on the cell membrane.
   - LDL-R/LDL complex is internalized into an endosome.

2. **Lysosome**
   - Lysosomes fuse with endosomes, and LDL, LDL-R, and PCSK9 are degraded.

3. **Secretion**
   - PCSK9 is secreted from the cell.
   - PCSK9 self-processing occurs.

---

**European Heart Journal (2015) 36, 2415–2424**
PCSK9-directed therapies in development

<table>
<thead>
<tr>
<th>Company</th>
<th>Drug</th>
<th>Agent</th>
<th>Indication</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sanofi/Regeneron</td>
<td>Alirocumab</td>
<td>Human monoclonal antibody</td>
<td>Hypercholesterolaemia</td>
<td>3 (published)</td>
</tr>
<tr>
<td>Amgen</td>
<td>Evolocumab</td>
<td>Human monoclonal antibody</td>
<td>Hypercholesterolaemia</td>
<td>3 (published)</td>
</tr>
<tr>
<td>Pfizer/Rinata</td>
<td>Bococizumab</td>
<td>Monoclonal antibody</td>
<td>Hypercholesterolaemia</td>
<td>3 (ongoing)</td>
</tr>
<tr>
<td>Novartis</td>
<td>LGT-209</td>
<td>Monoclonal antibody</td>
<td>Hypercholesterolaemia</td>
<td>2</td>
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<tr>
<td>Genentech</td>
<td>MPSK3169A, RG7652</td>
<td>Monoclonal antibody</td>
<td>Hypercholesterolaemia</td>
<td>2</td>
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<tr>
<td>Alnylam Pharmaceuticals/The Medicines Company</td>
<td>ALN-PCS02</td>
<td>siRNA oligonucleotide</td>
<td>Hypercholesterolaemia</td>
<td>1</td>
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<tr>
<td>Idera Pharmaceuticals</td>
<td>TBD</td>
<td>Antisense oligonucleotide</td>
<td>Hypercholesterolaemia</td>
<td>Preclinical</td>
</tr>
</tbody>
</table>
Phase III Clinical trials

- FH patients (Heterozygous + Homozygous)
- Statin Intolerant patients
- Not at LDL-C Goal
- Monotherapy
PCSK-9 LDL-C Reduction
PCSK-9 → LDL-C Reduction with Different doses over 12 Weeks
Lipids

The impact of proprotein convertase subtilisinkexin type 9 serine protease inhibitors on lipid levels and outcomes in patients with primary hypercholesterolaemia: a network meta-analysis

Michael J. Lipinski1, Umberto Benedetto2, Ricardo O. Escarcega1, Giuseppe Biondi-Zoccai3, Thibault Lhermusier1, Nevin C. Baker1, Rebecca Torguson1, H. Bryan Brewer Jr1, and Ron Waksman1

1. Novartis Cardiac Research Network, Medical Heart and Vascular Institute, Medical Washington Hospital Center, 199 Irving Street, NW, Suite 15-1, Washington, DC 20010, USA
2. University of Bristol, School of Clinical Sciences, Bristol Royal Infirmary, Bristol, UK
3. Department of Medicina Sistemi e Bioteche, University of Rome, La Sapienza, Rome, Italy

Remitted 19 June 2015; revised 29 September 2016; accepted 2 October 2015.
meta-analysis of 17 RCTs – PCSK9ab
13 083 patients

✓ LDL of 122 mg/dL → 51 mg/dL (abs. reduction of 71 mg/dL!)
✓ All-cause mortality → significant reduction
✓ CV Death → trend towards reduction
✓ CV events → trend towards reduction

➢ Neuro cognitive adverse events → significant increase
All Cause Mortality

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PCSK9 Events</th>
<th>Placebo Events</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.3.1 Follow-up &lt;6 months</td>
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<tr>
<td>LAPLACE</td>
<td>1</td>
<td>0</td>
<td>2.96 [0.12, 73.27]</td>
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<tr>
<td>LAPLACE-2</td>
<td>0</td>
<td>1</td>
<td>0.17 [0.01, 4.09]</td>
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<tr>
<td>McKENNY</td>
<td>0</td>
<td>0</td>
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<tr>
<td>MENDEL</td>
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<td>0</td>
<td>Not estimable</td>
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<tr>
<td>MENDEL-2</td>
<td>0</td>
<td>0</td>
<td>Not estimable</td>
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<tr>
<td>RUTHERFORD</td>
<td>0</td>
<td>0</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>RUTHERFORD 2</td>
<td>0</td>
<td>0</td>
<td>Not estimable</td>
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<tr>
<td>Stein</td>
<td>0</td>
<td>0</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>YUKAWA</td>
<td>0</td>
<td>0</td>
<td>Not estimable</td>
<td></td>
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<tr>
<td>Subtotal (95% CI)</td>
<td>2142</td>
<td>1279</td>
<td>0.76 [0.04, 11.79]</td>
<td></td>
</tr>
</tbody>
</table>

| Total (95% CI)    | 7474         | 3956 100.0%   | 0.43 [0.22, 0.82]              |
| Total events      | 17           | 20             |                                |
Major Cardiovascular Events

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PCSK9 Events</th>
<th>Total Events</th>
<th>Placebo Events</th>
<th>Total Events</th>
<th>Odds Ratio (M-H, Random, 95% CI)</th>
<th>Odds Ratio (M-H, Random, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAPLACE</td>
<td>4</td>
<td>158</td>
<td>1</td>
<td>155</td>
<td>4.00 [0.44, 36.20]</td>
<td>1.25 [0.24, 6.46]</td>
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<tr>
<td>LAPLACE-2</td>
<td>5</td>
<td>1117</td>
<td>2</td>
<td>558</td>
<td>Not estimable</td>
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<td>MENDEL</td>
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<td>90</td>
<td>0</td>
<td>90</td>
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<tr>
<td>MENDEL-2</td>
<td>0</td>
<td>306</td>
<td>0</td>
<td>154</td>
<td>Not estimable</td>
<td>Not estimable</td>
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<tr>
<td>RUTHERFORD</td>
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<td>56</td>
<td>0</td>
<td>56</td>
<td>Not estimable</td>
<td>Not estimable</td>
</tr>
<tr>
<td>RUTHERFORD 2</td>
<td>3</td>
<td>220</td>
<td>0</td>
<td>109</td>
<td>3.52 [0.18, 68.83]</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Stein</td>
<td>0</td>
<td>31</td>
<td>0</td>
<td>15</td>
<td>Not estimable</td>
<td>Not estimable</td>
</tr>
<tr>
<td>YUKAWA</td>
<td>0</td>
<td>105</td>
<td>2</td>
<td>102</td>
<td>0.19 [0.01, 4.02]</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>12</td>
<td>2083</td>
<td>5</td>
<td>1239</td>
<td>1.52 [0.50, 4.65]</td>
<td>Not estimable</td>
</tr>
</tbody>
</table>

Total events: 80
Placebo: 3925 (100.0%)
Odds ratio: 0.67 [0.38, 1.04]

European Heart Journal Advance Access published November 17, 2015
Neurocognitive Adverse Events

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PCSK9 Events</th>
<th>Placebo Events</th>
<th>Weight</th>
<th>Odds Ratio (M-H, Random, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAPLACE-2</td>
<td>1</td>
<td>0</td>
<td>5.3%</td>
<td>1.50 [0.06, 36.90]</td>
</tr>
<tr>
<td>MENDEL-2</td>
<td>0</td>
<td>0</td>
<td>Not estimable</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>PSK9</th>
<th>Placebo</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (95% CI)</td>
<td>6376</td>
<td>3205</td>
<td>2.34 [1.11, 4.93]</td>
</tr>
<tr>
<td>Total events</td>
<td>46</td>
<td>9</td>
<td></td>
</tr>
</tbody>
</table>
## Trials PCSK9\textsubscript{ab}

<table>
<thead>
<tr>
<th>Drug</th>
<th>Lipid lowering</th>
<th>Safety</th>
<th>IVUS</th>
<th>MACE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alirocumab</strong></td>
<td>8 studies</td>
<td>2 studies</td>
<td>---</td>
<td>Odyssey Outcome 18 000 pts $\rightarrow$ 2018</td>
</tr>
<tr>
<td></td>
<td>3 006 pts</td>
<td>3 300 pts</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Evolocumab</strong></td>
<td>5 studies</td>
<td>2 studies</td>
<td>Glagov</td>
<td>Fourier 22 500 pts $\rightarrow$ 2018</td>
</tr>
<tr>
<td></td>
<td>4 004 pts</td>
<td>3 515 pts</td>
<td>900 pts $\rightarrow$ 2015</td>
<td></td>
</tr>
<tr>
<td><strong>Bocucizumab</strong></td>
<td>3 studies</td>
<td>2 studies</td>
<td>---</td>
<td>SPIRE I +II 18 300 pts $\rightarrow$ 2017</td>
</tr>
<tr>
<td></td>
<td>2 500 pts</td>
<td>3 515 pts</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Impact of Treatment

Starting Early

Lifetime CHD Incidence (%)
- PCSK9 Y142X or C679X
- General Population

Established CHD
- Atorvastatin 80 mg
- Starting Late

Impact of Treatment

FH Patients older than 55 years according compared with a sample from the general population (Rotterdam study)
Why a National Screening Program?

- Serious consequences at a young age
- Absent signs and symptoms
- Good therapeutic options
- Cost effective
- Responsibility
30 000 FH Patients Diagnosed

2003 - 2013
30 000 FH patients diagnosed
Costs ± Euro 1000 /patient
Take Home Messages

1. Lipid metabolism basics
2. HDL
   • Hypo Alpha
   • Hyper Alpha
3. Chylomicron
   • LPL Deficiency
4. VLDL – VLDL remnants
   • Familial Combined Hypercholesterolemia
   • Familial Dysbeta-lipoproteinemia
5. LDL
   • Familial Hypercholesterolemia
   • FH Cascade screening program
Questions?

Lansberg@gmail.com