Statin intolerance and PCSK9 inhibitors

Ulf Landmesser
Chairman, Department of Cardiology
Charité – Universitätsmedizin Berlin (CBF)
1) LDL cholesterol in prevention of coronary disease

2) Statin intolerance – SAMS

3) Recent developments using PCSK9 inhibition
A Century of Cholesterol and Coronaries: From Plaques to Genes to Statins

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http://dx.doi.org/10.1016/j.cell.2015.01.036

Table 1. A Century of Cholesterol and Coronaries

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
</table>

**First Half—The Era of Cholesterol**

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1910</td>
<td>Human atherosclerotic plaques contain cholesterol</td>
</tr>
<tr>
<td>1913</td>
<td>High cholesterol diet causes atherosclerosis in rabbits</td>
</tr>
<tr>
<td>1919</td>
<td>Heart attacks recognized in humans</td>
</tr>
<tr>
<td>1933</td>
<td>Feedback inhibition of cholesterol synthesis demonstrated</td>
</tr>
<tr>
<td>1938</td>
<td>Familial hypercholesterolemia described</td>
</tr>
<tr>
<td>1950</td>
<td>Cholesterol biosynthetic pathway elucidated</td>
</tr>
<tr>
<td>1951</td>
<td>High-fat diets raise plasma cholesterol in humans</td>
</tr>
<tr>
<td>1953</td>
<td>Risk factor concept advanced</td>
</tr>
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</table>

**Second Half—The Era of LDL**

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1955</td>
<td>LDL identified as risk factor for CHD</td>
</tr>
<tr>
<td>1973</td>
<td>LDL receptor discovered</td>
</tr>
<tr>
<td>1976</td>
<td>HMG CoA reductase inhibitors (statins) discovered</td>
</tr>
<tr>
<td>1981</td>
<td>Statins increase LDL receptors in vivo</td>
</tr>
<tr>
<td>1987</td>
<td>First statin (Mevacor) approved for human use</td>
</tr>
<tr>
<td>1994</td>
<td>Statins decrease heart attacks and prolong life</td>
</tr>
<tr>
<td>1997</td>
<td>SREBP pathway elucidated</td>
</tr>
<tr>
<td>2006</td>
<td>PCSK9: Destroyer of LDL receptors</td>
</tr>
</tbody>
</table>
Atherosclerosis development: subendothelial LDL deposition - electron microscopy studies

Subendothelial LDL particles

Transmigration of monocytes

Lipid-lowering agents:
Patients with documented CAD should be treated with statins.

The treatment target is:
LDL-C < 1.8 mmol/L and/or < 50% reduction (if the target level cannot be reached)
Prevalence of raised BP*, elevated LDL-C** and diabetes in CAD: EUROASPIRE

* SBP/DBP ≥ 140/90 mmHg (≥ 140/80 mmHg for patients with diabetes); LDL ≥ 1.8 mmol/L;
***Fasting glucose ≥ 7 mmol/L for patients without history of diabetes
Statin intolerance and PCSK9 inhibitors

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Statin Associated Muscle Symptoms (SAMS)

Muscle symptoms

Statin therapy

Liver toxicity

Dysglycemia New onset diabetes

Proteinuria

Neurocognitive Symptoms ?
Definition of Muscle Symptoms

Myalgia:
muscle discomfort – no CK elevations

Myositis:
muscle discomfort (‘inflamm.’) + CK elev.

  mild: < 4-fold
  moderate: 4–10-fold
  severe: > 10-fold

Rhabdomyolysis:
Myonecrosis + CK elevation and
Myoglobinuria/serum creatine increase

Statin Associated Muscle Symptoms (SAMS)

Clinical update

Statin-associated muscle symptoms: impact on statin therapy—European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management

Management of a patient with SAMS

step II: Use a standardized approach

Consider if statin-attributed muscle symptoms favour statin continuation / reinitiation

- Symptomatic & CK <4 X ULN
  - 2-4 weeks washout of statin
  - Symptoms persist: statin re-challenge
  - Symptoms improve: Second statin at usual or starting dose
    - Symptom-free: Continue statin
    - Symptoms re-occur
      - 1) Low dose third efficacious (potent) statin;
      - 2) Efficacious statin with alternate day or once/twice weekly dosing regimen

- CK ≥4 X ULN +/- rhabdomyolysis
  - 6 week washout of statin until normalisation of CK/creatinine and symptoms

Aim: achieve LDL-C goal* with maximally tolerated dose of statin

- Ezetimibe

PCSK9 Inhibition?
1) LDL cholesterol in prevention of coronary disease

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PCS9K und LDL: Development towards clinical application

• Entdeckung PCSK9 (NARC-1)
• PCSK9 GOF-Mutationen sind ursächlich für FH

• PCSK9-Überexpression in vitro (LDL-C ↑)

• Entdeckung PCSK9 knockout Maus (LDL-C ↓)

• PCSK9 bindet an den LDL-Rezeptor

• PCSK9 bindet an den LDL-Rezeptor in Affen

• Erste PCSK9-Antikörper-Tests in Affen

• Erster Mensch wird mit einem PCSK9-Antikörper behandelt

• Erste Patienten werden mit einem PCSK9-Antikörper behandelt

• Start der Phase III Studien

• PCSK9 LOF-Mutationen: 28% LDL-C-Reduktion + 88% Risikoreduktion kardiovaskulärer Ereignisse
• Individuen ohne PCSK9 haben einen LDL-C-Spiegel von ~15 mg/dl


• Seidah, N. G. et al., Circ. Res. 114, 1022-1036 (2014).
PCSK9 – mechanisms to lower LDL
Development of monoclonal antibodies

- Muriner Antikörper: 100% Maus-Proteine
- Chimärer Antikörper: ca. 33% Maus-Proteine
- Humanisierter Antikörper: ca. 10% Maus-Proteine
- Vollhumaner Antikörper: 100% menschliche Proteine

Immunogenes Potential:
- hoch
- niedrig

- omab
- ximab
- zumab
- umab

- I. N. Foltz et al., Circulation 127, 2222 (2013).
PCSK9 Inhibitors: clinical trial programs

Evolocumab (AMG 145) PROFICIO programme Phase III

Lipid lowering

- Monotherapy MENDEL 2\textsuperscript{1032} n = 600 12 weeks
- Statin intolerance GAUSS 2\textsuperscript{1033} n = 500 24 weeks
- At-target LDL-C DESCARTES\textsuperscript{104} n = 905 52 weeks
- High LDL-C LAPLACE 2\textsuperscript{105} n = 1,700 12 weeks
- FH RUTHERFORD-2\textsuperscript{106} n = 300 12 weeks
- Safety
- Imaging (IVUS)
- MACE

Alirocumab (SAR236553/REGN727) ODYSSEY programme Phase III

Lipid lowering

- Monotherapy ODYSSEY MONO\textsuperscript{0} n = 103 24 weeks
- Statin intolerance ODYSSEY ALTERNATIVE\textsuperscript{91} n = 314 24 weeks
- High LDL-C ODYSSEY OPTIONS I\textsuperscript{92} n = 347 24 weeks
- High LDL-C ODYSSEY COMBO I\textsuperscript{94} n = 306 52 weeks
- High LDL-C ODYSSEY COMBO II\textsuperscript{93} n = 660 115 weeks
- High LDL-C ODYSSEY CHOICE I\textsuperscript{95} n = 700 24 weeks
- FH ODYSSEY FH I\textsuperscript{97} n = 471 78 weeks
- FH ODYSSEY FH II\textsuperscript{98} n = 249 52 weeks
- FH ODYSSEY HIGH FH\textsuperscript{99} n = 106 78 weeks
- Safety
- MACE ODYSSEY OLE n = 1,200 Up to 120 weeks
- Safety ODYSSEY LONG TERM\textsuperscript{100} n = 2,100 88 weeks
- MACE ODYSSEY OUTCOMES\textsuperscript{101} n = 18,000 5–6 years
Anti-PCSK9 Antibody Effectively Lowers Cholesterol in Patients With Statin Intolerance

The GAUSS-2 Randomized, Placebo-Controlled Phase 3 Clinical Trial of Evolocumab

Erik Stroes, MD, PhD,* David Colquhoun, MD,† David Sullivan, MD,‡ Fernando Civeira, MD,§ Robert S. Rosenson, MD,‖ Gerald F. Watts, DSc, PhD, DM,¶ Eric Bruckert, MD,# Leslie Cho, MD,** Ricardo Dent, MD,†† Beat Knusel, PhD,‡‡ Allen Xue, PhD,‡‡ Rob Scott, MD,‡‡ Scott M. Wasserman, MD,‖‖ Michael Rocco, MD,‖‖ for the GAUSS-2 Investigators

Amsterdam, the Netherlands; Auchenflower, Camperdown, and Perth, Australia; Zargoza, Spain; New York, New York; Paris, France; Cleveland, Ohio; and Thousand Oaks, California
Intolerance to ≥3 statins or 2 statins (one of which was atorvastatin ≤10 mg/day) or with a history of marked creatine kinase elevation accompanied by muscle symptoms while on a statin.
Tolerability of Evolocumab vs Ezetimibe in Patients With Muscle-Related Statin Intolerance: The GAUSS-3 Randomized Clinical Trial

JAMA. Published online April 03, 2016. doi:10.1001/jama.2016.3608
**Efficacy and Tolerability of Evolocumab vs Ezetimibe in Patients With Muscle-Related Statin Intolerance: The GAUSS-3 Randomized Clinical Trial**

*JAMA. Published online April 03, 2016. doi:10.1001/jama.2016.3608*
From: Efficacy and Tolerability of Evolocumab vs Ezetimibe in Patients With Muscle-Related Statin Intolerance: The GAUSS-3 Randomized Clinical Trial

JAMA. Published online April 03, 2016. doi:10.1001/jama.2016.3608

**Time to First Occurrence of a Muscle-Related Adverse Effect Resulting in Discontinuation of Study Drug**

**A** Phase A period 1

Hazard ratio, 1.34 (95% CI, 1.05-1.71)
Log-rank P = .02

**B** Phase A period 2

Hazard ratio, 1.96 (95% CI, 1.44-2.66)
Log-rank P < .001

**Time to First Occurrence of a Muscle-Related Adverse Effect Resulting in Discontinuation of Study Drug During Period 1 and Period 2 of Phase A, GAUSS-3 Trial**

Atorvastatin dose, 20 mg daily; placebo indicates matching placebo.

GAUSS-3 indicates Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects 3.
Mean Percent Change in Low-Density Lipoprotein Cholesterol Level During Randomized Treatment With Ezetimibe or Evolocumab, GAUSS-3 Trial

Ezetimibe dose, 10 mg daily; evolocumab dose, 140 mg 3 times monthly (420 mg total dosage). GAUSS-3 indicates Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects 3. Error bars indicate 95% CIs.
Original Articles

Efficacy and safety of alirocumab, a monoclonal antibody to PCSK9, in statin-intolerant patients: Design and rationale of ODYSSEY ALTERNATIVE, a randomized phase 3 trial

Patrick M. Moriarty, MD*, Terry A. Jacobson, MD, Eric Bruckert, MD, Paul D. Thompson, MD, John R. Guyton, MD, Marie T. Baccara-Dinet, MD, Daniel Gipe, MD
ODYSSEY ALTERNATIVE

* Unfähigkeit 2 verschiedene Statine aufgrund muskulärer Beschwerden zu tolerieren, eines davon bereits in der geringsten Dosierung.
Figure 4  Kaplan–Meier estimates for time to first skeletal muscle–related AE (predefined as myalgia, muscle spasms, muscular weakness, musculoskeletal stiffness, or muscle fatigue). AE, adverse event; ALI, alirocumab; ATV, atorvastatin; CI, confidence interval; EZE, ezetimibe; HR, hazard ratio.
ODYSSEY ALTERNATIVE

Graph showing LDL-C levels over weeks with comparison of Alirocumab and Ezetimibe treatments.

<table>
<thead>
<tr>
<th>No. Pts.</th>
<th>Baseline</th>
<th>Week 12</th>
<th>Week 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alirocumab</td>
<td>123</td>
<td>109</td>
<td>90</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>118</td>
<td>95</td>
<td>78</td>
</tr>
</tbody>
</table>
Efficacy and Safety of Alirocumab in Reducing Lipids and Cardiovascular Events

Jennifer G. Robinson, M.D., M.P.H., Michel Farnier, M.D., Ph.D., Michel Krempf, M.D., Jean Bergeron, M.D., Gérald Luc, M.D., Maurizio Averna, M.D., Erik S. Stroes, M.D., Ph.D., Gisle Langslet, M.D., Frederick J. Raal, M.D., Ph.D., Mahfouz El Shahawy, M.D., Michael J. Koren, M.D., Norman E. Lepor, M.D., Christelle Lorenzato, M.Sc., Robert Pordy, M.D., Umesh Chaudhari, M.D., and John J.P. Kastelein, M.D., Ph.D., for the ODYSSEY LONG TERM Investigators*
Kaplan-Meier Estimates for Time to First Adjudicated Major CV Event

Safety Analysis (at least 52 weeks for all patients continuing treatment, including 607 patients who completed W78 visit)

Cox model analysis:
HR=0.46 (95% CI: 0.26 to 0.82)
Nominal p-value = <0.01

Intent-to-treat (ITT) analysis
Efficacy and Safety of Evolocumab in Reducing Lipids and Cardiovascular Events
Treatment effect was apparent in all subgroups
Relative risk reduction of major adverse cardiovascular events (MACE) by lipid-lowering strategy

Baris Gencer, and François Mach Eur Heart J 2015;36:1146-1148
Network meta-analysis in primary hypercholesterolemia

Lipids

The impact of proprotein convertase subtilisin-kexin 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*

Our meta-analysis included 17 RCTs with 13 083 patients that were randomized to PCSK9 inhibitors (n = 8250), placebo (n = 3957),
Network meta-analysis in primary hypercholesterolemia

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PCSK9</th>
<th>Placebo</th>
<th>Odds Ratio</th>
<th>1.3.1 Follow-up &lt;6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>LAPLACE</td>
<td>1</td>
<td>158</td>
<td>0</td>
<td>155</td>
</tr>
<tr>
<td>LAPLACE-2</td>
<td>0</td>
<td>1117</td>
<td>1</td>
<td>558</td>
</tr>
<tr>
<td>Mckenney</td>
<td>0</td>
<td>59</td>
<td>0</td>
<td>31</td>
</tr>
<tr>
<td>MENDEL</td>
<td>0</td>
<td>90</td>
<td>0</td>
<td>90</td>
</tr>
<tr>
<td>MENDEL-2</td>
<td>0</td>
<td>306</td>
<td>0</td>
<td>154</td>
</tr>
<tr>
<td>RUTHERFORD</td>
<td>0</td>
<td>56</td>
<td>0</td>
<td>56</td>
</tr>
<tr>
<td>RUTHERFORD 2</td>
<td>0</td>
<td>220</td>
<td>0</td>
<td>109</td>
</tr>
<tr>
<td>Stein</td>
<td>0</td>
<td>31</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>YUKAWA</td>
<td>0</td>
<td>105</td>
<td>0</td>
<td>102</td>
</tr>
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</table>

Subtotal (95% CI): 2142/1270 = 8.2%

Heterogeneity: Tau² = 1.47; Chi² = 1.55, df = 1 (P = 0.21); I² = 36%
Test for overall effect: Z = 0.25 (P = 0.80)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PCSK9</th>
<th>Placebo</th>
<th>Odds Ratio</th>
<th>1.3.2 Follow-up ≥6 months</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>DESCRATRES</td>
<td>2</td>
<td>599</td>
<td>0</td>
<td>302</td>
</tr>
<tr>
<td>ODYSSEY COMBO I</td>
<td>2</td>
<td>207</td>
<td>3</td>
<td>107</td>
</tr>
<tr>
<td>ODYSSEY LONG TERM</td>
<td>8</td>
<td>1550</td>
<td>10</td>
<td>788</td>
</tr>
<tr>
<td>OSLER 2</td>
<td>4</td>
<td>2976</td>
<td>6</td>
<td>1489</td>
</tr>
</tbody>
</table>

Subtotal (95% CI): 5332/2686 = 91.8%

Heterogeneity: Tau² = 0.00; Chi² = 1.54, df = 3 (P = 0.67); I² = 0%
Test for overall effect: Z = 2.60 (P = 0.009)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PCSK9</th>
<th>Placebo</th>
<th>Odds Ratio</th>
<th>1.3.2 Follow-up ≥6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

Total (95% CI): 7474/3956 = 100.0%

Heterogeneity: Tau² = 0.00; Chi² = 3.31, df = 5 (P = 0.65); I² = 0%
Test for overall effect: Z = 2.58 (P = 0.010)
Test for subgroup differences: Chi² = 0.13, df = 1 (P = 0.72), I² = 0%
Network meta-analysis in primary hypercholesterolemia

We only included neurocognitive adverse event data from studies that specifically defined an outcome as an adverse neurocognitive event.
PCSK9 inhibition clinical outcome trials

- **EVOLOCUMAB FOURIER:**
  - Patients aged 40-85 with history of clinically evident CVD; high risk for recurrent event; DL-C ≥ 70 mg/dL (or non-HDL-C ≥ mg/dL) (N=27,500)

- **ALIROCUMAB ODYSSEY OUTCOMES:**
  - Patients aged ≥ 40 hospitalized for ACS recently (<52 weeks); LDL-C ≥ 70 mg/dL (N=18,000)

CV Outcome trials of PCSK9 inhibitors

- **BOCOCIZUMAB SPIRE-1:**
  - High RISK Primary and Secondary Prevention; LDL-C ≥ 70 to <100 mg/dL (N=17,000)

- **BOCOCIZUMAB SPIRE-2:**
  - High RISK Primary and Secondary Prevention; LDL-C ≥ 100 mg/dL on statins (or statin intolerant) (N=17,000)

Statin intolerance and PCSK9 inhibitors

1) LDL cholesterol in prevention of coronary disease

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3) Recent developments using PCSK9 inhibition
Thank you
PCSK9 Inhibitors: clinical trial programs

- Bococizumab
  - (RN316/PF-04950615)
  - SPIRE programme
  - Phase III

**Lipid lowering**
- SPIRE-HF
  - $n=600$
  - 18 months
- SPIRE-HR
  - $n=300$
  - 12 months
- SPIRE-LDL
  - $n=1,600$
  - 18 months

**MACE**
- SPIRE-1
  - MACE in patients with LDL-C 70–99 mg/dl
  - $n=12,000$
- SPIRE-2
  - MACE in patients with LDL-C ≥100 mg/dl
  - $n=6,300$

Nature Cardiology 2014
Neue ESC NSTE-ACS-Guidelines

2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC)

Authors/Task Force Members: Marco Roffi* (Chairperson) (Switzerland), Carlo Patrono* (Co-Chairperson) (Italy), Jean-Philippe Collet† (France), Christian Mueller† (Switzerland), Marco Valgimigli† (The Netherlands), Felicita Andreotti (Italy), Jeroen J. Bax (The Netherlands), Michael A. Borger (Germany), Carlos Brotons (Spain), Derek P. Chew (Australia), Baris Gencer (Switzerland), Gerd Hasenfuss (Germany), Keld Kjeldsen (Denmark), Patrizio Lancellotti (Belgium), Ulf Landmesser (Germany), Julinda Mehilli (Germany), Debabrata Mukherjee (USA), Robert F. Storey (UK), and Stephan Windecker (Switzerland)

ESC Committee for Practice Guidelines, Review Coordinators, Reviewers, ESC staff, EHJ

www.escardio.org

Eur Heart J. 2016 Jan 14;37(3):267-315