PCSK-9 antibodies: 

*LDLc lowering and Beyond?*

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Disclosures:

- Lecturing fees from
  - Amgen, Sanofi, Merck, Chiesi, Novartis, Cerenis
- No stocks
- No patents
Outline

- LDLc as ‘best’ lipid target
- ‘Study’ evidence for PCSK9-antibodies
- LDLc lowering and Inflammation
**Lipoprotein Pathways for MI**

### Epidemiology
- **LDL**: MI Risk increases with Plasma Level
- **HDL**: MI Risk decreases with Plasma Level
- **TG**: MI Risk increases with Plasma Level

### Genetics
- **LDL**: 
  - Common variants: Yes
  - Rare variants: No effect on MI
- **HDL**: Common variants: No effect on MI
- **TG**: Common variants: No effect on MI
  - Rare variants: Yes

### Therapy
- **LDL**: Statins, PCSK9 Abs, Ezetimibe
- **HDL**: Failed
- **TG**: ?

* Courtesy S Katherisan
No Evidence for a Lower LDL-C Limit in Reducing Major CV Events

### TNT¹
**Rate of major CV events**

<table>
<thead>
<tr>
<th>Achieved LDL-C, mg/dL</th>
<th>P for trend across LDL-C &lt; .0001</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥106</td>
<td></td>
</tr>
<tr>
<td>90–&lt;106</td>
<td></td>
</tr>
<tr>
<td>77–&lt;90</td>
<td></td>
</tr>
<tr>
<td>64–&lt;77</td>
<td></td>
</tr>
<tr>
<td>&lt;64</td>
<td></td>
</tr>
</tbody>
</table>

### JUPITER²
**Risk of primary endpoint**

<table>
<thead>
<tr>
<th>Achieved LDL-C, mg/dL</th>
<th>&lt;50 vs placebo</th>
<th>Not &lt;50 vs placebo</th>
<th>&lt;50 vs not &lt;50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0.35 (0.25–0.49)</td>
<td>0.76 (0.57–1.00)</td>
<td>0.39 (0.26–0.59)</td>
</tr>
</tbody>
</table>

### PROVE-IT³
**Risk of primary endpoint**

<table>
<thead>
<tr>
<th>Achieved LDL-C, mg/dL</th>
<th>Lower LDL-C Better</th>
<th>Higher LDL-C Better</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;80–100</td>
<td>0.80 (0.59, 1.07)</td>
<td>Referent</td>
</tr>
<tr>
<td>&gt;60–80</td>
<td>0.67 (0.50, 0.92)</td>
<td></td>
</tr>
<tr>
<td>&gt;40–60</td>
<td>0.61 (0.40, 0.91)</td>
<td></td>
</tr>
<tr>
<td>≤40</td>
<td>0.76 (0.57–1.00)</td>
<td></td>
</tr>
</tbody>
</table>

Going below 1.3 mmol/L Reduces CV Risk: IMPROVE-IT Study

Adjusted HR: 0.90 (95% CI 0.85-0.96)  
\( P = .002 \)

Need for additional LDL-C lowering therapies

I. Guidelines lower LDL-C goals in high risk patients

II. Special populations do not achieve LDL-C goals

III. More patients with adverse effects on statins
I. Proportion of Patients Achieving LDL-C Levels:
EURO-ASPIRE IV

Although guideline-recommended goals get lower and lower, few patients achieve LDL-C targets

Cross-sectional study including 24 European countries; 16,426 medical records were reviewed, and 7,998 patients aged <80 years with coronary disease who had coronary artery bypass graft, PCI, or ACS were interviewed

II. Familial hypercholesterolaemia patients reach LDL-C threshold levels for CHD at an early age

II. HeFH is under-diagnosed and undertreated

21% of HeHF patients achieved the LDL-C treatment goal of <2.5mmol/L

Based on prevalence 1 in 500
Based on prevalence 1 in 200

- In many countries <10% of patients are diagnosed

III. Statin-Associated Muscle symptoms (SAMS) are common in observational studies

PRIMO: 7,924 patients with hyperlipidaemia receiving high-dosage statin therapy

III. Risk of death for adherence >80% versus <80%

Meta-analysis of 44 studies, n= 1,978,919; 135,627 CVD events; 94,126 cases of all-cause mortality

<table>
<thead>
<tr>
<th>Number of studies</th>
<th>Number of participants</th>
<th>Number of deaths</th>
<th>Proportion (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Adherence to statins</td>
<td>11</td>
<td>291,864</td>
<td>29,605</td>
</tr>
<tr>
<td>(1) Adherence to RR agents</td>
<td>11</td>
<td>205,598</td>
<td>12,288</td>
</tr>
<tr>
<td>ACE inhibitors/ARB</td>
<td>4</td>
<td>62,196</td>
<td>886</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>7</td>
<td>67,991</td>
<td>5,441</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>1</td>
<td>9,168</td>
<td>2,696</td>
</tr>
<tr>
<td>Multiple agents</td>
<td>3</td>
<td>81,342</td>
<td>2,978</td>
</tr>
<tr>
<td>(3) Adherence to aspirin</td>
<td>3</td>
<td>12,980</td>
<td>1,573</td>
</tr>
<tr>
<td>(4) Adherence to any CVD medication</td>
<td>23</td>
<td>533,381</td>
<td>94,126</td>
</tr>
</tbody>
</table>

9% of all CVD events in Europe could be attributed to poor adherence to vascular medications alone.

Approaching patients with SAMS

- European Atherosclerosis Society (EAS) Consensus Panel recommendations

Exclude other causes of muscle symptoms and interactions

2–4 weeks statin washout

Statin rechallenge

Continue statin

No symptoms

Succes of Rechallenging the patient

- Most patients rechallenged can tolerate statins long-term
  - Retrospective cohort study in 107,835 patients

- 18,778 (17.4%) patients had statin-related events
  - Statins were discontinued at least temporarily by 11,124 of these patients

- On re-challenge
  - 92.2% were still on a statin >12 months later
  - 47.6% were on the same statin to which they had the statin-related adverse event

Establish highest tolerable statin dose:
very low dose, different statin, more potent statin, alternate day dosing

Rechallenge to identify maximally tolerated statin dose and beyond …

Exclude other causes of muscle symptoms and interactions

2–4 weeks statin washout

Statin rechallenge

No symptoms

Establish highest tolerable statin dose:
very low dose, different statin, more potent statin, alternate day dosing

Symptoms recur

Continue statin

Not at LDL-C target

Add ezetimibe

LDL-C, low-density lipoprotein cholesterol; PCSK9, protein convertase subtilisin/kexin type 9.
Outline

- LDLc as ‘best’ lipid target
- ‘Study’ evidence for PCSK9 antibodies
- LDLc lowering and Inflammation
Plasma LDL-C is controlled by hepatic LDL-receptor

PCSK9 reduces LDLR recycling, increasing plasma LDL-C

Lower lifetime LDL by PCSK9- Loss of Function provides CV-benefit

54.5% reduction in CHD risk for each 1mmol/L (38mg/dL) lower LDL-C

18.2% reduction in CHD risk for each 1mmol/L (38mg/dL) lower LDL-C

Genetically lower LDL-C

Pharmacologically lower LDL-C

Clinical impact of PCSK9-ab in patients
PCSK9 and LDLc following evolocumab

Overview of the ODYSSEY Phase 3 Program *(Alirocumab)*

Fourteen global Phase 3 trials including >23,500 patients across >2000 study centers

<table>
<thead>
<tr>
<th>HeFH population</th>
<th>HC in high CV-risk population</th>
<th>Additional populations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Add-on to max tolerated statin</strong> (± other LLT)</td>
<td><strong>Add-on to max tolerated statin</strong> (± other LLT)</td>
<td><strong>ODYSSEY MONO</strong> (NCT01644474; EFC11716)</td>
</tr>
<tr>
<td>ODYSSEY FH I (NCT01623115; EFC12492) LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL n=486; 18 months</td>
<td>ODYSSEY COMBO I (NCT01644175; EFC11568) LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL n=316; 12 months</td>
<td>Patients on no background LLTs LDL-C ≥100 mg/dL n=103; 6 months</td>
</tr>
<tr>
<td>ODYSSEY FH II (NCT01709500; CL1112) LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL n=249; 18 months</td>
<td>*ODYSSEY COMBO II (NCT01644188; EFC11569) LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL n=720; 24 months</td>
<td>Patients with defined statin intolerance LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL n=314; 6 months</td>
</tr>
<tr>
<td>ODYSSEY HIGH FH (NCT01617655; EFC12732) LDL-C ≥160 mg/dL n=107; 18 months</td>
<td>ODYSSEY CHOICE I (NCT01926782; CL1308) LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL n=700; 12 months</td>
<td><strong>ODYSSEY ALTERNATIVE</strong> (NCT01709513; CL1119)</td>
</tr>
<tr>
<td>ODYSSEY OLE (NCT01954394; LTS 13463) Open-label study for FH from EFC 12492, CL 1112, EFC 12732 or LTS 11717 n ≥1000; 30 months</td>
<td>ODYSSEY CHOICE II (NCT02023879; EFC13786) Patients not treated with a statin LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL n=200; 6 months</td>
<td><strong>ODYSSEY OLE</strong> (NCT01954394; LTS 13463)</td>
</tr>
<tr>
<td>ODYSSEY LONG TERM (NCT01507831; LTS11717) LDL-C ≥70 mg/dL n=2341; 18 months</td>
<td>ODYSSEY OPTIONS I (NCT01730040; CL1110) Patients not at goal on moderate-dose atorvastatin LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL n=255; 6 months</td>
<td><strong>ODYSSEY OUTCOMES</strong> (NCT01663402; EFC11570) LDL-C ≥70 mg/dL n=18,000; 64 months</td>
</tr>
<tr>
<td>ODYSSEY OUTCOMES (NCT01663402; EFC11570) LDL-C ≥70 mg/dL n=18,000; 64 months</td>
<td>ODYSSEY OPTIONS II (NCT01730053; CL1118) Patients not at goal on moderate-dose rosuvastatin LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL n=305; 6 months</td>
<td><strong>ODYSSEY COMBO II</strong> (NCT01644188) other LLT not allowed at entry</td>
</tr>
</tbody>
</table>

*For ODYSSEY COMBO II other LLT not allowed at entry*
Alirocumab in hyperlipidemic CV-patients

Achieved LDL-C Over Time
All patients on background of maximally tolerated statin ± other lipid-lowering therapy

- Alirocumab
- Placebo

Alirocumab in Familial hypercholesterolemia

All patients on background of maximally tolerated statin ± other lipid-lowering therapy

<table>
<thead>
<tr>
<th></th>
<th>Alirocumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-HeFH</td>
<td>n=1259</td>
<td>n=635</td>
</tr>
<tr>
<td>HeFH</td>
<td>n=271</td>
<td>n=145</td>
</tr>
</tbody>
</table>

LS mean (SE) % change from baseline to Week 24

-0.5%
-62.1%
-56.3%
7.0%

ODYSSEY ALTERNATIVE:
Alirocumab effective in statin intolerance

Ezetimibe

Alirocumab

LDL-C, mean (SE), mg/dL

Δ 59 mg/dL
(1.52 mmol/L)

Δ 65 mg/dL

49.5% received 150 mg Q2W at W12


LDL-C, low-density lipoprotein; SE, standard error.
Study design: Data pooled from 14 trials in the alirocumab clinical program to examine treatment-emergent adverse event (TEAE) rates in patients who achieved two consecutive calculated LDL-C values of <25 or <15 mg/dL on alirocumab.

PROFICIO Program to Reduce LDL-C and Cardiovascular Outcomes Following Inhibition of PCSK9 In Different Populations

- Combo-therapy
- Monotherapy
- Statin-intolerant
- HeFH
- HoFH
- Long-term safety and efficacy
- Open-label extension
- Secondary prevention
- Athero

Phase 2
(N = 629)

Phase 3
(N = 1700)

Phase 2
(N = 406)

Phase 3
(N = 600)

Phase 2
(N = 157)

Phase 3
(N = 300)

Phase 3
(N = 500)

Phase 2
(N = 168)

Phase 3
(N = 300)

Phase 2/3
(N ≤67)

Phase 2/3
(N = 125)

Phase 3
(N = 905)

Phase 2
(N = 1400)

Phase 3
(N ≥3500)

Phase 3
(N = 27,500)

Phase 3
(N = 950)
Evolocumab in hyperlipidemic CV-patients

**DESCARTES**

UC LDL-C percent change from baseline, mean (± SE)

<table>
<thead>
<tr>
<th>Study week</th>
<th>Baseline</th>
<th>Week 12</th>
<th>Week 52</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo QM (N = 302)</td>
<td>-50.1%</td>
<td>6.8%</td>
<td>57%</td>
</tr>
<tr>
<td>Evolocumab 420 mg QM (N = 599)</td>
<td>-50.1%</td>
<td>6.8%</td>
<td>57%</td>
</tr>
</tbody>
</table>

Number of patients:
- Baseline: 302, 599
- Week 12: 294, 582
- Week 52: 264, 542

GAUSS 3: Evolocumab in statin intolerance

Two double-blind phases

**Phase A**
- 10 weeks
  - Atorvastatin 20 mg
  - Placebo

**Phase B**
- 24 weeks
  - Monthly SC evolocumab 420 mg
  - Daily oral ezetimibe 10 mg

Participants entered Phase B only if they had muscle symptoms on atorvastatin, but not placebo, or CK ≥ 10 x ULN during statin treatment.

511 patients with a history of intolerance to multiple statins due to muscle-related adverse effects

### Phase A:
**Study Drug Discontinuation Events**

<table>
<thead>
<tr>
<th>Intolerable Muscle Symptoms</th>
<th>N = 491</th>
</tr>
</thead>
<tbody>
<tr>
<td>On atorvastatin, but not placebo</td>
<td>209 (42.6%)*</td>
</tr>
<tr>
<td>On placebo, but not atorvastatin</td>
<td>130 (26.5%)</td>
</tr>
<tr>
<td>On both placebo and atorvastatin</td>
<td>48 (9.8%)</td>
</tr>
<tr>
<td>No symptoms on either treatment</td>
<td>85 (17.3%)</td>
</tr>
<tr>
<td>Did not complete Phase A</td>
<td>20/511</td>
</tr>
<tr>
<td>Bypassed Phase A due to CK elevation ≥ 10 x ULN</td>
<td>19 (3.9%)*</td>
</tr>
</tbody>
</table>

Phase B: LDL-C lowering efficacy

Mean reduction 16.7% (LDL-C = 181 mg/dL)

Mean reduction 53.0% (LDL-C = 104 mg/dL)

Evolocumab and safety

**OSLER**

<table>
<thead>
<tr>
<th>Evolocumab subjects stratified by minimum achieved LDL-C</th>
<th>All EvoMab (n=2976)</th>
<th>SOC Alone (n=1489)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25 mg/dL (n=773)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25 to &lt;40 mg/dL (n=759)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40 mg/dL (n=1532)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥40 mg/dL (n=1426)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse Events (%)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>70.0</td>
<td>69.2</td>
</tr>
<tr>
<td>Serious</td>
<td>7.6</td>
<td>7.5</td>
</tr>
<tr>
<td>Muscle-related</td>
<td>4.9</td>
<td>6.0</td>
</tr>
<tr>
<td>Neurocognitive</td>
<td>0.5</td>
<td>0.9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lab results (%)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT/AST &gt;3×ULN</td>
<td>0.9</td>
<td>1.0</td>
</tr>
<tr>
<td>CK &gt;5×ULN</td>
<td>0.4</td>
<td>0.6</td>
</tr>
</tbody>
</table>

CVD events from ODYSSEY LONG TERM and OSLER Trials

HR 0.52 (95% CI 0.31-0.91)  
3.3  

HR 0.47 (95% CI 0.28-0.78)  
2.2

CVD Event rate (%)  
Placebo  
Alirocumab  
SOC  
Evolocumab

## PCSK9 Inhibitor in ongoing CVD Outcomes Trials

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Evolocumab</th>
<th>Alirocumab</th>
<th>Bococizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial</td>
<td>FOURIER</td>
<td>ODYSSEY Outcomes</td>
<td>SPIRE I</td>
</tr>
<tr>
<td>SPIRE II</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sample size</td>
<td>27,500</td>
<td>18,000</td>
<td>17,000</td>
</tr>
<tr>
<td></td>
<td>9,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>MI, stroke or PAD</td>
<td>4-52 wks post-ACS</td>
<td>High risk of CV event</td>
</tr>
<tr>
<td>Statin</td>
<td>Atorva ≥20 mg or equiv</td>
<td>Evid-based med Rx</td>
<td>Lipid-lowering Rx</td>
</tr>
<tr>
<td>LDL-C</td>
<td>≥70 (≥1.8)</td>
<td>≥70 (≥1.8)</td>
<td>70-99 (1.8-2.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>≥100 (≥2.6)</td>
</tr>
<tr>
<td>PCSK9i Dosing</td>
<td>Q2W or Q4W</td>
<td>Q2W</td>
<td>Q2W</td>
</tr>
<tr>
<td>Endpoint</td>
<td>1°: CV death, MI, stroke, revasc or hosp for UA, Key 2°: CV death, MI, or stroke</td>
<td>CHD death, MI, ischemic stroke, or hosp for UA</td>
<td>CV death, MI, stroke, or urgent revasc</td>
</tr>
<tr>
<td>Recruitment Status</td>
<td>Completed June 2015</td>
<td>Projected for Dec 2015</td>
<td>?</td>
</tr>
<tr>
<td>Completion</td>
<td>Q2 /2017 ?</td>
<td>Q4 /2017 ?</td>
<td>2018 ?</td>
</tr>
</tbody>
</table>

www.clinicaltrials.gov
Outline

- LDLc as ‘best’ lipid target
- ‘Study’ evidence for PCSK9 antibodies
- LDLc lowering and Inflammation
CRP is a marker, not a mediator of CVD

Circulating usual concentrations of CRP
- Adjusted for age, sex, and ethnicity
- Further adjusted†

| Risk ratio* (95% CI) for CHD per 1 SD higher ln CRP (mg/L) |
|-----------------|-----------------|
| 1.49 (1.40 to 1.59) |
| 1.33 (1.23 to 1.43) |
Role of immune cell influx in atherogenesis

Bone marrow and spleen as novel ‘atherogenic’ players

Swirski & Nahrendorf, Science 2013;339:161-6
Leucocyte behaviour in advanced atherogenesis
Rapid Monocyte influx in Athero-lesions in patients

Monocyte influx determines inflammatory status of the arterial wall

F van der Valk, Stroes E. J Am Coll Cardiol 2014
Splenic/BM activity predict CVD-risk in patients

Spleen and BM activity increased in ACS patients

Spleen and BM activity
Correlate with CVD risk

Emami, JACC CV imaging 2015
Relevance in hypercholesterolemia?

Circulating monocytes activated in patients with FH

Flow Cytometry: Chemokine receptors

- **CCR2**
  - Control vs. FH-high LDL
  - Classical, Intermediary, Non-Classical

- **CX3CR1**
  - Control vs. FH-high LDL
  - Classical, Intermediary, Non-Classical

Lipid uptake

- **CD36**
  - Control vs. FH-high LDL
  - Classical, Intermediary, Non-Classical

- **SR-A1**
  - Control vs. FH-high LDL
  - Classical, Intermediary, Non-Classical

Bernelot, Stroes, EAS 2016
Lipid accumulation in circulating monocytes in FH

Increased lipid content in monocytes

Reversibility upon PCSK9-ab

Reversibility ?
- statins?
- PCSK9-ab ?
Increased monocyte activation
Reversibility by PCSK9-ab LDLc lowering

Flow cytometry

Gene expression

Lipid efflux

Bernelot, Stroes, EAS 2016
Increased monocyte migration in FH
Reversibility by PCSK9-ab LDLc lowering

MCP-chemotaxis assay for monocytes

Monocyte migration distance and PCSK9-ab

Bernelot S, Stroes E, EAS 2016
Summary:

**PCSK9-ab: LDL-c lowering and beyond**

- There is a need for additional LDL-c lowering therapies
  - getting to target in high-CV risk subjects
  - Familial hypercholesterolemia
  - Statin intolerance

- PCSK9-antibodies effectively lower LDLc
  - Potent and prolonged
  - No significant safety signals / side effects
  - Beneficial CV-signal in post-hoc analyses

- LDL-c lowering attenuates cellular inflammatory ‘drive’
  - Decreased monocyte migration and activation by both statin and PCSK9-ab mediated LDLc lowering
Take Home

- LDL-c lowering ‘best’ target in CV prevention & therapy

- If statin-ezetimibe insufficient, PCSK9-antibodies offer potent LDLc lowering in patients facing residual LDLc-burden

- ‘Valued’ care necessitates balanced use of PCSK9-ab in selected patients combining ‘residual LDLc burden’ and ‘increased CV-risk’

- There is more than CRP involved in atherogenic inflammation