How do we treat dyslipidemia according to new ESC/EAS Guidelines?

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Charite Universitätsmedizin Berlin, Germany
2016 ESC/EAS Guidelines for the Management of Dyslipidaemias

The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)

Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR)

Authors/Task Force Members: Alberico L. Catapano* (Chairperson) (Italy), Ian Graham* (Chairperson) (Ireland), Guy De Backer (Belgium), Olov Wiklund (Sweden), M. John Chapman (France), Heinz Drexel (Austria), Arno W. Hoes (The Netherlands), Catriona S. Jennings (UK), Ulf Landmesser (Germany), Terje R. Pedersen (Norway), Željko Reiner (Croatia), Gabriele Riccardi (Italy), Marja-Riitta Taskinen (Finland), Lale Tokgozoglu (Turkey), W. M. Monique Verschuren (The Netherlands), Charalambos Vlachopoulos (Greece), David A. Wood (UK), Jose Luis Zamorano (Spain)

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European Society of Cardiology/European Atherosclerosis Society Task Force consensus statement on proprotein convertase subtilisin/kexin type 9 inhibitors: practical guidance for use in patients at very high cardiovascular risk

Ulf Landmesser\textsuperscript{1*†}, M. John Chapman\textsuperscript{2†}, Michel Farnier\textsuperscript{3}, Baris Gencer\textsuperscript{4}, Stephan Gielen\textsuperscript{5}, G. Kees Hovingh\textsuperscript{6}, Thomas F. Lüscher\textsuperscript{7}, David Sinning\textsuperscript{1}, Lale Tokgözoğlu\textsuperscript{8}, Olov Wiklund\textsuperscript{9}, Jose Luis Zamorano\textsuperscript{10}, Fausto J. Pinto\textsuperscript{11}, and Alberico L. Catapano\textsuperscript{12} on behalf of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS)
Patient Case

• 58 yo male patient

• Stable angina pectoris, cardiac ischemia in MRI (anterior)

• Patient undergoes coronary angiogram: Significant LAD lesion – treated with DES
Coronary angiogram (and OCT imaging)
Patient Case

- 58 yo male patient

- **Stable angina pectoris, cardiac ischemia in MRI (anterior)**

- **Patient undergoes coronary angiogram:** Significant LAD lesion – treated with DES

- Lipid profile?
Patient Case – Lipid profile

- LDL-C: 102 mg/dl
- HDL-C: 35 mg/dl
- Triglycerides: 186 mg/dl
- Lp(a): 60 mg/dl

Which lipid parameter is the therapeutic target?
How would you treat this patient?

- A  Life style management only
- B  Moderate statin therapy
- C  Intense statin therapy
- D  Statin and ezetimibe therapy
- E  Statin and PCSK9 inhibition
Patient Case – Lipid-targeted treatment

• Diagnosis: Coronary artery disease = Very high cardiovascular risk
Cardiovascular risk categories

ESC/EAS Dyslipidemia Guidelines - Eur Heart J 2016

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
</table>
| Very high-risk| Subjects with any of the following:  
- Documented cardiovascular disease (CVD), clinical or unequivocal on imaging. Documented CVD includes previous myocardial infarction (MI), acute coronary syndrome (ACS), coronary revascularisation (percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG)) and other arterial revascularization procedures, stroke and transient ischaemic attack (TIA), and peripheral arterial disease (PAD). Unequivocally documented CVD on imaging is what has been shown to be strongly predisposed to clinical events, such as significant plaque on coronary angiography or carotid ultrasound.  
- DM with target organ damage such as proteinuria or with a major risk factor such as smoking, hypertension or dyslipidaemia.  
- Severe CKD (GFR <30 mL/min/1.73 m²).  
- A calculated SCORE ≥10% for 10-year risk of fatal CVD. |
| High-risk     | Subjects with:  
- Markedly elevated single risk factors, in particular cholesterol >8 mmol/L (>310 mg/dL) (e.g. in familial hypercholesterolaemia) or BP ≥180/110 mmHg.  
- Most other people with DM (some young people with type 1 diabetes may be at low or moderate risk).  
- Moderate CKD (GFR 30–59 mL/min/1.73 m²).  
- A calculated SCORE ≥5% and <10% for 10-year risk of fatal CVD. |
| Moderate-risk | SCORE is ≥1% and <5% for 10-year risk of fatal CVD.                                                                                              |
| Low-risk      | SCORE <1% for 10-year risk of fatal CVD.                                                                                                       |
### Dyslipidemia Guidelines

#### Intervention strategies as a function of total cardiovascular risk and low density lipoprotein cholesterol level

<table>
<thead>
<tr>
<th>Total CV risk (SCORE) %</th>
<th>LDL-C levels</th>
</tr>
</thead>
</table>
|                         | <70 mg/dL  
<1.8 mmol/L | 70 to <100 mg/dL  
1.8 to <2.6 mmol/L | 100 to <155 mg/dL  
4.0 to <4.9 mmol/L | 155 to <190 mg/dL  
4.0 to <4.9 mmol/L | ≥190 mg/dL ≥4.9 mmol/L |  
| <1                      | No lipid intervention | No lipid intervention | No lipid intervention | No lipid intervention | Lifestyle intervention, consider drug if uncontrolled |  
| Class<sup>a</sup>/Level<sup>b</sup> | I/C | I/C | I/C | I/C | I<sub>a</sub>/A |  
| ≥1 to <5                | No lipid intervention | No lipid intervention | Lifestyle intervention, consider drug if uncontrolled | Lifestyle intervention, consider drug if uncontrolled | Lifestyle intervention, consider drug if uncontrolled |  
| Class<sup>a</sup>/Level<sup>b</sup> | I/C | I/C | I<sub>a</sub>/A | I<sub>a</sub>/A | I<sub>a</sub>/A |  
| ≥5 to <10, or high-risk | No lipid intervention | Lifestyle intervention, consider drug if uncontrolled | Lifestyle intervention and concomitant drug intervention | Lifestyle intervention and concomitant drug intervention | Lifestyle intervention and concomitant drug intervention |  
| Class<sup>a</sup>/Level<sup>b</sup> | I<sub>a</sub>/A | I<sub>a</sub>/A | I/A | I/A | I/A |  
| ≥10 or very high-risk   | Lifestyle intervention, consider drug<sup>c</sup> | Lifestyle intervention and concomitant drug intervention | Lifestyle intervention and concomitant drug intervention | Lifestyle intervention and concomitant drug intervention | Lifestyle intervention and concomitant drug intervention |  
| Class<sup>a</sup>/Level<sup>b</sup> | I<sub>a</sub>/A | I<sub>a</sub>/A | I/A | I/A | I/A |  

**SCORE** = Systematic Coronary Risk Estimation.  
<sup>a</sup>Class of recommendation;  
<sup>b</sup>Level of evidence;  
<sup>c</sup>In patients with MI, statin therapy should be considered irrespective of total cholesterol levels  

[www.escardio.org/EAPC](http://www.escardio.org/EAPC)
Patient Case – Lipid-targeted treatment

- **Diagnosis:** Coronary artery disease = Very high cardiovascular risk

- **What is the target for LDL-C management?**
What is the target for LDL-C?

- **A** LDL < 70 mg/dl
- **B** LDL-C reduction ≥ 50 % from baseline
- **C** LDL-C < 100 mg/dl
Recommendations for treatment goals for LDL-C

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>In patients at VERY HIGH CV risk(^d), an LDL-C goal of &lt;1.8 mmol/L (70 mg/dL) or a reduction of at least 50% if the baseline LDL-C(^e) is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL) is recommended.</td>
<td>I</td>
<td>B</td>
<td>61, 62, 65, 68, 69, 128</td>
</tr>
<tr>
<td>In patients at HIGH CV risk(^d), an LDL-C goal of &lt;2.6 mmol/L (100 mg/dL), or a reduction of at least 50% if the baseline LDL-C(^e) is between 2.6 and 5.2 mmol/L (100 and 200 mg/dL) is recommended.</td>
<td>I</td>
<td>B</td>
<td>65, 129</td>
</tr>
<tr>
<td>In subjects at LOW or MODERATE risk(^d) an LDL-C goal of &lt;3.0 mmol/L (&lt;115 mg/dL) should be considered.</td>
<td>IIa</td>
<td>C</td>
<td>-</td>
</tr>
</tbody>
</table>

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www.escardio.org/EAPC
**ESC/EAS Dyslipidemia Guidelines 2016:**

Very High Risk Patient

Baseline LDL-C
70 - 135 mg/dl or 1,8 - 3,5 mmol/l
≥ 50% LDL-C reduction

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mg/dl bzw.
mmol/l

- 150 (3,9)
- 135 (3,5)
- 120 (3,1)
- 110 (2,9)
- 100 (2,6)
- 90 (2,3)
- 80 (2,1)
- 70 (1,8)
- 60 (1,6)
- 50 (1,3)
- 40 (1,0)
- 30 (0,8)
- 20 (0,5)
- 10 (0,3)
- 0

**LDL-Goal**
<70 mg/dl

ESC/EAS Dyslipidemia Guidelines - Eur Heart J 2016
## Recommendations for the pharmacological treatment of hypercholesterolaemia

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
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<tbody>
<tr>
<td>Prescribe statin up to the highest recommended dose or highest tolerable dose to reach the goal.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>In the case of statin intolerance, ezetimibe or bile acid sequestrants, or these combined, should be considered.</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>If the goal is not reached, statin combination with a cholesterol absorption inhibitor should be considered.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>If the goal is not reached, statin combination with a bile acid sequestrant may be considered.</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>In patients at very high-risk, with persistent high LDL-C despite treatment with maximal tolerated statin dose, in combination with ezetimibe or in patients with statin intolerance, a PCSK9 inhibitor may be considered.</td>
<td>IIb</td>
<td>C</td>
</tr>
</tbody>
</table>
Statin Therapy - A systematic review and meta-analysis of the therapeutic equivalence

Patient Case – Lipid profile

- LDL-C: 102 mg/dl
- HDL-C: 35 mg/dl
- Triglycerides: 186 mg/dl
- Lp(a): 60 mg/dl

Should HDL-C be a therapeutic target?

A Yes  B No
Lipid analysis and treatment targets in prevention of CVD

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C is recommended as the primary target for treatment.</td>
<td>I</td>
<td>A</td>
<td>64, 68</td>
</tr>
<tr>
<td>TC should be considered as a treatment target if other analyses are not available.</td>
<td>IIa</td>
<td>A</td>
<td>64, 123</td>
</tr>
<tr>
<td>Non-HDL-C should be considered as a secondary treatment target.</td>
<td>IIa</td>
<td>B</td>
<td>103</td>
</tr>
<tr>
<td>ApoB should be considered as a secondary treatment target, when available.</td>
<td>IIa</td>
<td>B</td>
<td>103, 124</td>
</tr>
<tr>
<td>HDL-C is not recommended as a target for treatment.</td>
<td>III</td>
<td>A</td>
<td>92, 93</td>
</tr>
<tr>
<td>The ratios apoB/apoA1 and non-HDL-C/HDL-C are not recommended as targets for treatment.</td>
<td>III</td>
<td>B</td>
<td>103</td>
</tr>
</tbody>
</table>
The difficult search for a ‘partner’ of statins in lipid-targeted prevention of vascular events: the re-emergence and fall of niacin

Strategies of ongoing clinical trials to examine which lipid-targeted therapy should be added to statin treatment in patients with high vascular risk

Landmesser U. Eur Heart J (2013) 34, 1254–1257
## Impact of Life style changes on TC and LDL-C levels

<table>
<thead>
<tr>
<th>Lifestyle interventions to reduce TC and LDL-C levels</th>
<th>Magnitude of the effect</th>
<th>Level of evidence</th>
</tr>
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<tbody>
<tr>
<td>Reduce dietary trans fat</td>
<td>+++</td>
<td>A</td>
</tr>
<tr>
<td>Reduce dietary saturated fat</td>
<td>+++</td>
<td>A</td>
</tr>
<tr>
<td>Increase dietary fibre</td>
<td>++</td>
<td>A</td>
</tr>
<tr>
<td>Use functional foods enriched with phytosterols</td>
<td>++</td>
<td>A</td>
</tr>
<tr>
<td>Use red yeast rice supplements</td>
<td>++</td>
<td>A</td>
</tr>
<tr>
<td>Reduce excessive body weight</td>
<td>++</td>
<td>A</td>
</tr>
<tr>
<td>Reduce dietary cholesterol</td>
<td>+</td>
<td>B</td>
</tr>
<tr>
<td>Increase habitual physical activity</td>
<td>+</td>
<td>B</td>
</tr>
<tr>
<td>Use soy protein products</td>
<td>+/-</td>
<td>B</td>
</tr>
</tbody>
</table>
Patient Case

- 58 yo male patient
- Patient was started on 80 mg Atorvastatin
- Comes back with an NSTE-ACS (Proximal LAD lesion) – Receives PCI/DES
- Lipid profile?
Patient Case – Lipid profile

- LDL-C 87 mg/dl
- HDL-C 39 mg/dl
- Triglycerides 167 mg/dl
- Lp(a) 45 mg/dl

Which lipid therapy should we consider?

A. No change
B. Add ezetimibe
C. Add PCSK9 inhibition
## Dyslipidemia Guidelines

### Recommendations for the pharmacological treatment of hypercholesterolaemia

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<td>IIb</td>
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ESC/EAS Consensus Statement on PCSK9 inhibitors: Practical Guidance for Use in Patients at Very High Cardiovascular Risk

Landmesser U, Chapman J et al. 
Eur Heart J 2016 (in press)
Thank you

www.escardio.org/EAPC
Aggressive Lowering of LDL-Cholesterol with PCSK9-Inhibitors – A New Principle of Action

Kurt HUBER, MD, FESC, FACC, FAHA
Director, 3rd Department of Internal Medicine, Cardiology and Intensive Care Medicine, Wilhelminenhospital
Vienna, Austria
Conflicts of Interest (K. Huber 2015/16)

- Lecture Fees from
  - AMGEN
  - AstraZeneca
  - Pfizer
  - Sanofi
LDL-C: „The lower the better“ (!?)
The lower the LDL-C achieved, the lower the risk of CV events

**TNT**¹,a
Rate of major CV events

**JUPITER**²,b
Time to occurrence of major CV events

**PROVE-IT**³,c
Hazard ratio of primary endpoint

---


www.escardio.org/EAPC
LDL-C is a major contributor to CV risk

LDL-C levels and event rates\textsuperscript{a} in secondary prevention statin studies


www.escardio.org/EAPC
Statins and Ezetimibe frequently are insufficient in reaching the treatment goal
In which percentage is an LDL-C goal of $<70 \text{ mg/dl} (<1,8 \text{ mmol/L})$ reached in the „real world“?

1) 20%
2) 40%
3) 60%
4) 80%
Only 1 in 5 MI patients achieve LDL-C target <70 mg/dL (< 1.8 mmol/L) despite high statin prescription rate and good adherence.

EUROASPIRE IV: 7998 patients <80 years old with established CHD*

*25% women, mean age 64 years, one third <60 years old, 2012–2013.
CHD, coronary heart disease; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction.

www.escardio.org/EAPC
PCSK9-Inhibition
PCSK9-inhibition on top of standard lipid lowering reduces LDL-C levels for further

1) 20%
2) 40%
3) 60%
4) 80%
Different Types of Monoclonal Antibodies

- **Murine Antibody**: 100% Murine protein
- **Chimeric Antibody**: 33% Murine protein
- **Humanized Antibody**: 10% Murine protein
- **Fully Human Antibody**: 100% Human protein

- **Immunogenenic Potential**: High
- **Generische Endung**: -omab, -ximab, -zumab, -umab

- **Evolocumab (Repatha®)**
- **Alirocumab (Praluent®)**

**References**:

www.escardio.org/EAPC
PCSK9: A Bad Guy

Qian Y-W et al. J Lipid Res. 2007;48:1488–1498;

www.escardio.org/EAPC
PCS-K9: Experiments of Nature

Gain of Function

- Lysosomal degradation of LDLR

Loss of Function

- Recycling of LDLR

Elevated LDL-C | Early Atherosclerosis
---|---
Loss of function Mutation | Low LDL-C | Atheroprotection


www.escardio.org/EAPC
Alirocumab: ODYSSEY Phase 3 Programs

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

<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>ODYSSEY FH I (NCT01623115; EFC12492)</strong></td>
<td>LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL n=486; 18 months</td>
<td><strong>ODYSSEY MONO (NCT01644474; EFC11716)</strong> Patients on no background LLTs LDL-C ≥100 mg/dL n=103; 6 months</td>
</tr>
<tr>
<td><strong>ODYSSEY FH II (NCT01709500; CL1112)</strong></td>
<td>LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL n=249; 18 months</td>
<td><strong>ODYSSEY ALTERNATIVE (NCT01709513; CL1119)</strong> Patients with defined statin intolerance LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL n=314; 6 months</td>
</tr>
<tr>
<td><strong>ODYSSEY HIGH FH (NCT01617655; EFC12732)</strong></td>
<td>LDL-C ≥160 mg/dL n=107; 18 months</td>
<td><strong>ODYSSEY CHOICE I (NCT01926782; CL1308)</strong> LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL n=700; 12 months</td>
</tr>
<tr>
<td><strong>ODYSSEY OLE (NCT01954394; LTS 13463)</strong> Open-label study for FH from EFC 12492, CL 1112, EFC 12732 or LTS 11717 n≥1000; 30 months</td>
<td><strong>ODYSSEY COMBO I (NCT01644175; EFC11568)</strong> LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL n=316; 12 months</td>
<td><strong>ODYSSEY CHOICE II (NCT02023879; EFC13786)</strong> Patients not treated with a statin LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL n=200; 6 months</td>
</tr>
<tr>
<td><strong>ODYSSEY COMBO II (NCT01644188; EFC11569)</strong> LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL n=720; 24 months</td>
<td><strong>ODYSSEY COMBO II (NCT01644188; EFC11569)</strong> LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL n=720; 24 months</td>
<td><strong>ODYSSEY OPTIONS I (NCT01730040; CL1110)</strong> Patients not at goal on moderate-dose atorvastatin LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL n=355; 6 months</td>
</tr>
<tr>
<td><strong>ODYSSEY OPTIONS II (NCT01730053; CL1118)</strong> 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 OPTIONS II (NCT01730053; CL1118)</strong> 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></td>
</tr>
</tbody>
</table>

Add-on to max tolerated statin (± other LLT)

**ODYSSEY LONG TERM (NCT01507831; LTS11717)** LDL-C ≥70 mg/dL n=2341; 18 months

**ODYSSEY OUTCOMES (NCT01663402; EFC11570)** LDL-C ≥70 mg/dL n=18 000; 64 months
Post-Hoc Analyse ODYSSEY LONG TERM: Reduktion CV Ereignisse mit Alirocumab

-48% Event Reduction
PROFICIO evaluates LDL-C-reduction, regression of atherosclerosis and reduction of CV risk with **Evolocumab**

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Phase 2 (N)</th>
<th>Phase 3 (N)</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combo-therapy</td>
<td></td>
<td></td>
<td>Evo + Statin</td>
</tr>
<tr>
<td>Phase 2 (N = 629)</td>
<td>Phase 3 (N = 1896)</td>
<td></td>
<td>Evo + Statin</td>
</tr>
<tr>
<td>Mono-therapy</td>
<td>Phase 3 (N = 614)</td>
<td></td>
<td>Evo Mono</td>
</tr>
<tr>
<td>Statin-intolerant</td>
<td>Phase 3 (N = 329)</td>
<td></td>
<td>Evo +/- Statin</td>
</tr>
<tr>
<td>Phase 2 (N = 157)</td>
<td>Phase 3 (N = 100)</td>
<td></td>
<td>Evo +/- Statin</td>
</tr>
<tr>
<td>HeFH</td>
<td>Phase 3 (N = 329)</td>
<td></td>
<td>Evo + Statin +/- Eze</td>
</tr>
<tr>
<td>Phase 2 (N = 167)</td>
<td>Phase 2/3 (N = 310)</td>
<td></td>
<td>Evo + Statin +/- Eze</td>
</tr>
<tr>
<td>HoFH/Severe FH</td>
<td>Phase 3 (N = 901)</td>
<td></td>
<td>Evo +/- Statin +/- Eze</td>
</tr>
<tr>
<td>Long-term safety and efficacy</td>
<td>Phase 3 (N = 950)</td>
<td></td>
<td>Evo + Statin +/- Eze</td>
</tr>
<tr>
<td>Open-label Extension</td>
<td>Phase 3 (N = 27,500)</td>
<td></td>
<td>Evo + Statin</td>
</tr>
<tr>
<td>Phase 2 (N = 1324)</td>
<td>Phase 3 (N &gt; 3800)</td>
<td></td>
<td>Evo + Statin +/- Eze</td>
</tr>
<tr>
<td>Athero</td>
<td>Phase 3 (N = 950)</td>
<td></td>
<td>Evo + Statin +/- Eze</td>
</tr>
<tr>
<td>Secondary Prevention</td>
<td>Phase 3 (N = 27,500)</td>
<td></td>
<td>Evo + Statin</td>
</tr>
</tbody>
</table>

* Aktiver Arm (Evolocumab); Vergleichsarm: Plazebo +/- Statin +/- Ezetimib
OSLER Studies: LDL Cholesterol Reduction

- **N=4465**
- **N=1258**
- **N=4259**
- **N=4204**
- **N=1243**
- **N=3727**

**Evolocumab** plus standard of care

- **61% reduction (95%CI 59-63%), P<0.001**
- **Absolute reduction: 73 mg/dL (95%CI 71-76%)**

The dashed line indicate that patients were receiving either evolocumab or placebo during the period from baseline to enrollment into OSLER.


www.escardio.org/EAPC
LDL Cholesterol Goals Reached

- Standard of Care
- Evolocumab plus standard of care

Proportion Achieving Goal (%)

≤100
- 26
- P<0.001

≤70
- 3.8
- P<0.001

LDL-C Goal (mg/dL) at 12 weeks


www.escardio.org/EAPC
Cardiovascular Outcomes

Composite Endpoint: Death, MI, UA → hosp, coronary revascularization, stroke, TIA, or CHF → hosp

HR 0.47
95% CI 0.28-0.78
P=0.003

Evolocumab plus standard of care (N=2976)

Standard of care alone (N=1489)


www.escardio.org/EAPC
Two typical cases of inefficient action of lipid lowering agents
Case 1

66 yr old male
VF complicating his first anterior wall MI 11/2013
Risk factors: smoking, LDL-C 170 mg/dl
ASA, prasugrel, atorvastatin 80 mg, betalocker, ACEI
Pat. stopped smoking, intolerant to statins, + ezetimibe

Re-MI (anterior wall) 5/2014, LDL-C 135 mg/dl
ASA, ticagrelor, ezetimibe, betablocker, ACEI

Re-MI (Posterior wall) 2/2015, LDL-C 146 mg/dl
Switched to evolocumab on top of ezetimibe
No further event since 18 months
LDL-C is < 60 mg/dl since
Case 2

64 yr old female
NSTEMI 6/2008
Risk factors: LDL-C 210 mg/dl (FH)
ASA, clopidogrel, simvastatin 20 mg, betalocker intolerant to high-dose statins, + fenofibrate

STEMI (anterior wall) 5/2010, LDL-C 186 mg/dl
ASA, prasugrel, betablocker and lipid apheresis was started (twice per week)
LDL-C was 70-100 mg/dl over years, no further MACE

NSTEMI 3/2016, LDL-C 102 mg/dl
Alurocumab was started in combination with ezetimibe and lipid apheresis was stopped
No further event since 8 months
LDL-C is <70 mg/dl since
968 patients at 197 global centers with symptomatic CAD and other high risk features. Coronary angiography showing 20-50% stenosis in a target vessel measured by intravascular ultrasound.

Stable, optimized statin dose for 4 weeks with LDL-C >80 mg/dL or 60-80 mg with additional high risk features.

Intravascular ultrasound via motorized pullback at 0.5 mm/sec through >40 mm segment.

- Statin monotherapy
  - 61 patients did not complete
  - 423 statin completers
  - Follow-up IVUS of originally imaged “target” vessel (n=846)

- Statin plus monthly SC evolocumab 420 mg
  - 61 patients did not complete
  - 423 evolocumab completers

Percent Change in LDL-C During Treatment

- Mean LDL-C 93.0 mg/dL
  - Change from baseline 3.9%
- Mean LDL-C 36.6 mg/dL
  - Change from baseline -59.8%

Study Week

AHA 2016
Primary Endpoint: Percent Atheroma Volume

Change in Percent Atheroma Volume (%)

Statin monotherapy

Statin-evolocumab

0.05

P = NS

P < 0.0001

-0.95

P < 0.0001

AHA 2016
## Adverse Clinical Events and Safety Findings

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (N=484)</th>
<th>Evolocumab (N=484)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0.8%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>2.9%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Nonfatal Stroke</td>
<td>0.6%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Hosp. for Unstable Angina</td>
<td>0.8%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Coronary Revascularization</td>
<td>13.6%</td>
<td>10.3%</td>
</tr>
<tr>
<td>First Major Cardiovascular Event</td>
<td>15.3%</td>
<td>12.2%</td>
</tr>
<tr>
<td>Injection site reactions</td>
<td>0%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Anti-evolocumab binding antibody</td>
<td>NA</td>
<td>0.2%</td>
</tr>
<tr>
<td>Neutralizing antibodies</td>
<td>NA</td>
<td>0%</td>
</tr>
<tr>
<td>Neurocognitive events</td>
<td>1.2%</td>
<td>1.4%</td>
</tr>
<tr>
<td>New onset diabetes</td>
<td>3.7%</td>
<td>3.6%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>5.8%</td>
<td>7.0%</td>
</tr>
</tbody>
</table>
Median changes in percentage atheroma volume (PAV) vs average on-treatment LDL-C in serial coronary IVUS trials. Dotted blue line shows a projected outcome of the degree of plaque regression in those patients receiving evolocumab in GLAGOV.


www.escardio.org/EAPC
FOURIER (20110118) Trial Ongoing

27,500 patients with cardiovascular disease (prior MI, stroke or PAD)
Age 40 to 85 years
≥1 other high-risk feature

Screening, Placebo Run-in, And Lipid Stabilization Period
Effective statin therapy (atorvastatin ≥20 mg or an equivalent statin dose ± ezetimibe)

LDL-C
≥ 70 mg/dL (1.81 mmol/L)
or
non-HDL-C
≥ 100 mg/dL (2.59 mmol/L)

Evolocumab (AMG 145) SC
Q2W or QM
~13,750 Subjects

Placebo
Q2W or QM
~13,750 Subjects

Total Follow-up 4-5 yrs
2017

Primary Endpoint: CV death, MI, hosp for UA, stroke, coronary revascularization

www.clinicaltrialsregister.eu EudraCT Number: 2012-001398-97
https://clinicaltrials.gov/ct2/show/NCT01764633?term=NCT01764633&rank=1
www.escardio.org/EAPC
Summary

PCSK9-inhibitors on top of standard lipid lowering therapy are able to reduce LDL-C levels by >50% and thereby help to reach the treatment goal in a high percentage.

Massive LDL-C reduction might also reduce coronary plaque size and volume.

Clinical outcome data (ODYSSEY OUTCOME, FOURIER) obtained from huge prospective randomized trials are awaited in order to learn about clinical efficacy and safety.

Potential indications for the use of PCSK-9 inhibitors include very high-risk patients with statin intolerance, insufficient action of statins and ezetimibe, and possibly also patients who want to avoid lipid apheresis.
THANK YOU!