JPS, AE2BM 2016 :
Museum National d'Histoire Naturelle, Paris

Inhibition de PCSK9 : Mecanisme et Impacts sur la Plaque d'Atherome

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Is there a clinical need

for additional LDL-C lowering agents ?

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for additional LDL-C lowering agents ?

- ESC/EAS Guideline recommendations
- Role of LDL in Plaque pathophysiology
- Therapeutic impact of LDL-C lowering
- Current trans-European status of LDL-C goal attainment in very high risk patients

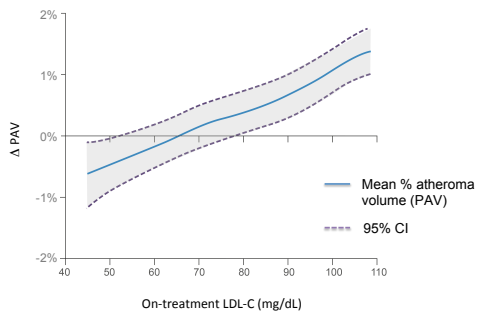
Recommendations for treatment targets for LDL-C

Recommendations	Class	Level
In patients at VERY HIGH CV risk (established CVD, type 2 diabetes, type 1 diabetes with target organ damage, moderate to severe CKD or a SCORE level ≥ 10%) the LDL-C goal is < 1.8 mmol/L (less than ~ 70 mg/dL) and/or ≥ 50% LDL-C reduction when target level cannot be reached.	I	A
In patients at HIGH CV risk (markedly elevated single risk factors, a SCORE level ≥ 5 to < 10%) an LDL-C goal < 2.5 mmol/L (less than ~ 100 mg/dL) should be considered.	IIa	A
In subjects at MODERATE risk (SCORE level > 1 to ≤ 5%) an LDL-C goal < 3.0 mmol/L (less than ~ 115 mg/dL) should be considered.	IIa	C

www.escardio.org/guidelines

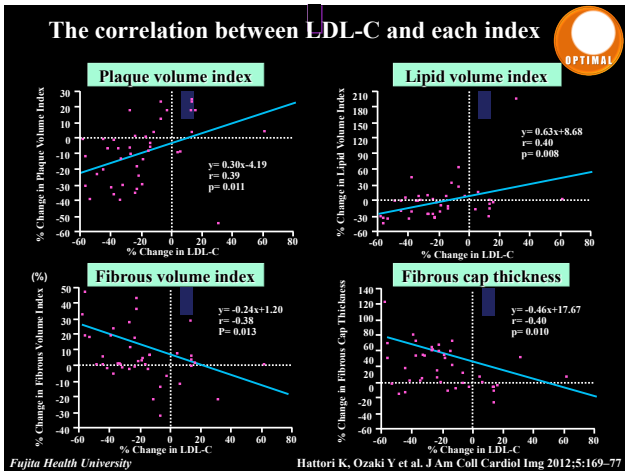
European Heart Journal (2011) 32, 1769–1818

Marked Statin-mediated LDL lowering stops atherosclerosis progression



Nicholls et al. JAMA 2007;297:499–508.

The correlation between LDL-C and each index



Fujita Health University

Hattori K, Ozaki Y et al. J Am Coll Cardiol Img 2012;5:169–77

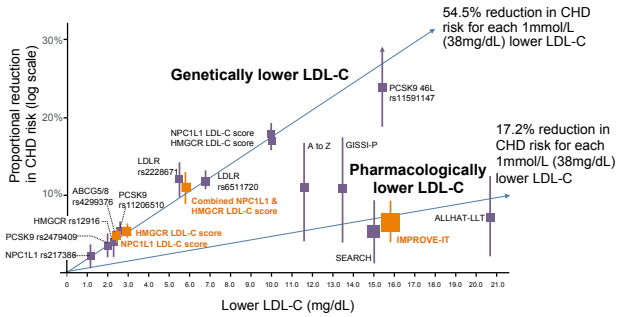
Very low LDL-C levels are associated with plaque structural features consistent with enhanced stability

	LDL-C <50mg/dL (87 plaques)	LDL-C 50–70mg/dL (81 plaques)	LDL-C 70–100mg/dL (117 plaques)	LDL-C >100mg/dL (130 plaques)	P
Plaque microstructures in lipid plaques (n=293)					
Fibrous cap thickness (μm)	139.9 ± 93.9	103.1 ± 66.4	92.5 ± 48.5	92.1 ± 47.8	0.001
Plaque rupture, n (%)	1/42 (2.3)	2/46 (4.3)	7/91 (7.6)	12/114 (10.5)	0.17
Thrombus, n (%)	0/42 (0.0)	1/46 (2.1)	2/91 (2.1)	3/114 (2.6)	0.18

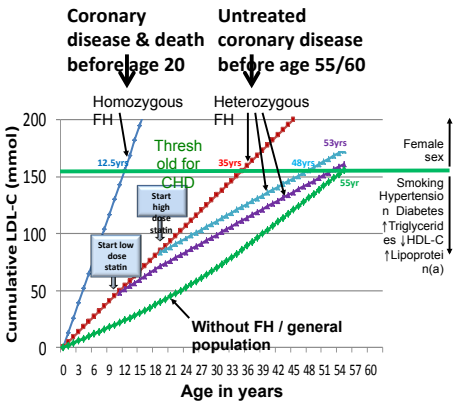
Plaque microstructure was more stable in statin-treated patients with lower LDL-C levels

Kataoka et al. Atherosclerosis 2015;242:490–495

Clinical benefit of lower LDL-C is determined by absolute exposure to lower LDL

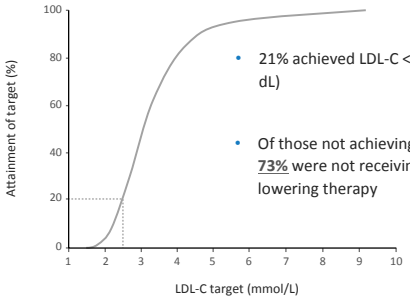


Ference et al. J Am Coll Cardiol 2015;65:1552–1561.



Nordestgaard et al, EHJ 2013; EAS Consensus Panel

High-risk patients with HeFH do not attain recommended LDL-C goals



- 21% achieved LDL-C <2.6mmol/L (100mg/dL)
- Of those not achieving LDL-C <2.6mmol/L, 73% were not receiving maximal lipid-lowering therapy

Pijlman et al. Atherosclerosis 2010;209:189–194.

JUPITER

LDL-C reduction 20 mg rosuvastatin

46.3% **> 50%**

42.8% **0-50%**

10.8% **NO reduction**

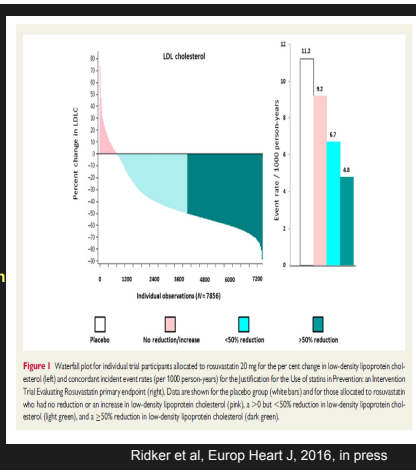
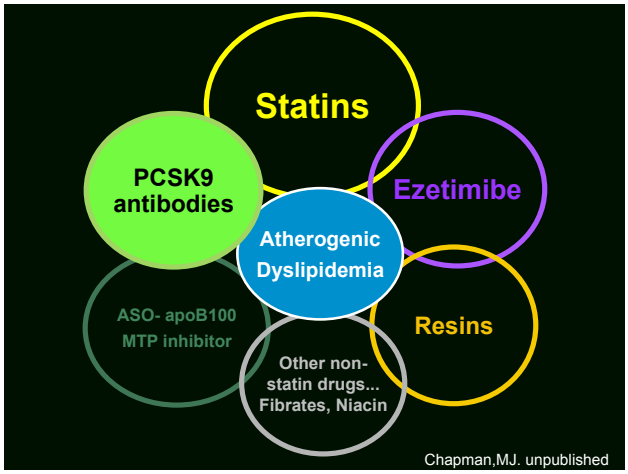


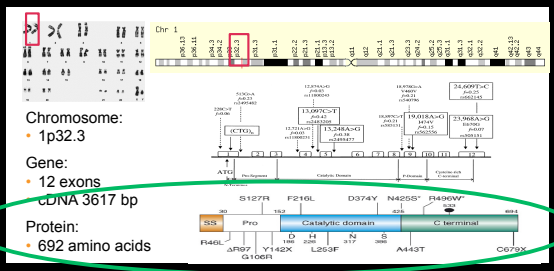
Figure 1 Waterfall plot for individual trial participants allocated to rosuvastatin 20 mg for the per cent change in low-density lipoprotein cholesterol (left) and concordant incident event rates (per 1000 person-years) for the justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin primary endpoint (right). Data are shown for the placebo group (white bars) and for those allocated to rosuvastatin who had no reduction or an increase in low-density lipoprotein cholesterol (pink), a >0 but <50% reduction in low-density lipoprotein cholesterol (light green), and a ≥50% reduction in low-density lipoprotein cholesterol (dark green).

Ridker et al, Europ Heart J, 2016, in press



Chapman,MJ. unpublished

What is PCSK9?



Chromosome:
- 1p32.3

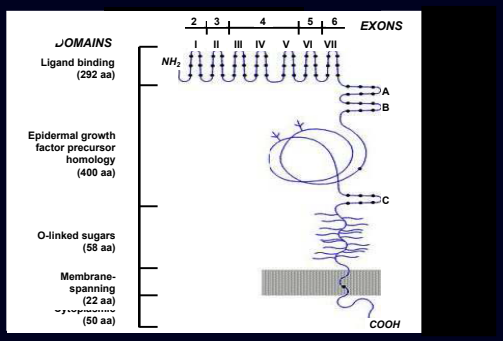
Gene:
- 12 exons
- cDNA 3617 bp

Protein:
- 692 amino acids

- NARC-1 : Neural apoptosis regulated convertase 1; neurogenesis
- Expressed in liver, kidney, intestine
- Undergoes autocatalytic cleavage in the ER to active conformation
- Appears to play the role of an intracellular protein chaperone

http://www.genecards.org/cgi-bin/carddisp.pl?gene=PCSK9/. [Accessed 19 July 2011]
Abifadel M, et al. Nature Genet 2003;34:154–6.
Abifadel M, et al. Hum Mutat 2009;30:520–9.
Horton JD, et al. Trends Biochem Sci 2007;32:71–7.
Chen SN, et al JACC 2005;45:1611–9.

Control of plasma LDL- cholesterol levels: Key role of the cellular LDL receptor



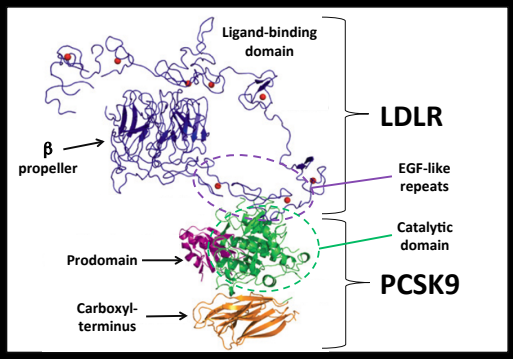
http://www.iemrams.spb.ru/english/molgen/fh-en/domain-e.htm. [Accessed 6 August 2015]

Control of hepatic LDL-Receptor activity

- **Intracellular levels of cholesterol**
(reflecting uptake of cholesterol contained in LDL, VLDL and chylomicron remnants, and HDL), endogenous cholesterol synthesis, cholesterol conversion to bile acids, and excretion of bile acids and biliary cholesterol)
via the SREBP pathway

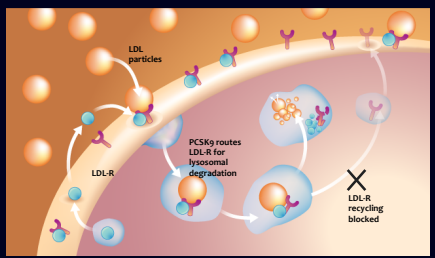
- **PCSK9**

PCSK9 and the LDL Receptor



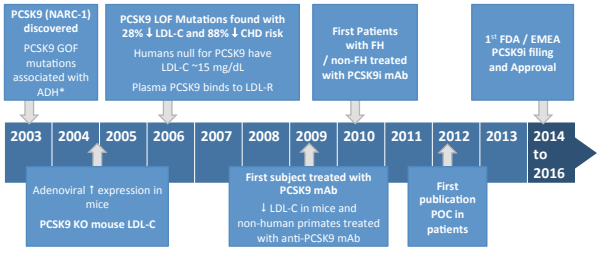
Horton JD, et al. *J Lipid Res*. 2009;50:S172-S177

Role of PCSK9 in regulation of the surface expression of LDL receptors



Chan JC, et al. Proc Natl Acad Sci USA 2009;106:9820–5.

PCSK9 Inhibitors: From Target Discovery to Phase III to the Clinic



* ADH: Autosomal Dominant Hypercholesterolemia; Seidah NG. Proc Natl Acad Sci US 2003;100(3):928-33, Abifadel M. Nat Genet 2003;34(2):154-6, Maxwell KN. Proc Natl Acad Sci US 2004;101(18):7100-5, Rashid S. Proc Natl Acad Sci US 2005;102(15):5374-79, Lagace TA et al. JCI 2006;116:2995-3005 Cohen JC. N Engl J Med 2006;354(12):1264-72, Zhao Z. Am J Hum Genet 2006;79(3):514-23, Hooper AJ. Atherosderosis 2007;193(2):445-8, Chan JC. Proc Natl Acad Sci US 2009;106(24):9820-5. Stein et at N Engl J Med 2012;366:1108-18; Stein modified from Swergold, Regeneron.

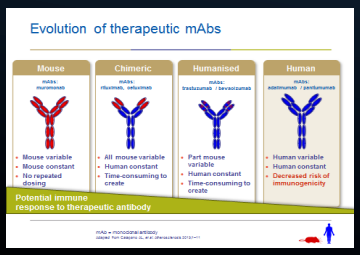
Monoclonal antibodies to PCSK9

Bind and eliminate plasma PCSK9 as an Ab-Ag complex

- Monoclonal antibodies
  - Evolocumab, (Amgen)
  - Alirocumab, (Regeneron/Sanofi)
  - Bococizumab (Pfizer)

Evolocumab and Alirocumab

- Fully human PCSK9 monoclonal antibodies
- Less likely to have immune side effects:
  - Neutropenia
  - Thrombocytopenia
  - Hemolytic anemia
  - Hypersensitivity reactions



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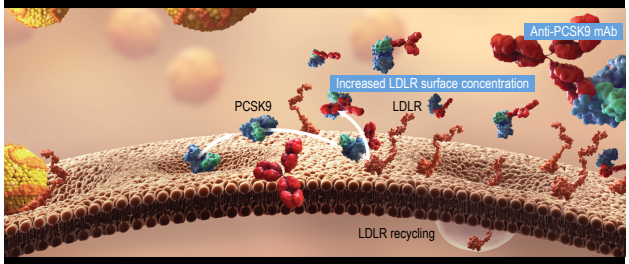
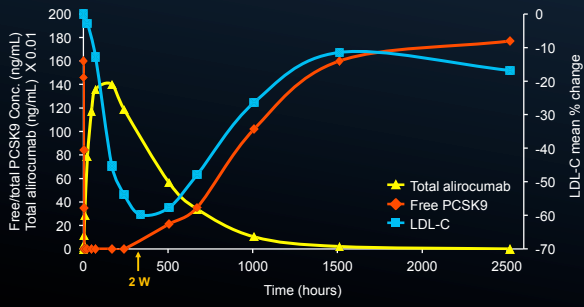
Impact of an anti-PCSK9 monoclonal antibody on LDL-R expression



Chan JC, et al. Proc Natl Acad Sci USA 2009;106:9820–5.

Alirocumab:
Dynamic Relationship Between mAb Levels, PCSK9 and LDL-C



Stein EA *et al. New Engl J Med* 2012;366:1108–18.

ODYSSEY Phase 3 Clinical Trial Program

14 global phase 3 trials including >23,500 patients across >2,000 study centers

HeFH population — Add-on to max-tolerated statin (± other LMT)

- ODYSSEY FH I (NCT01623115; EFC12492): LDL-C ≥ 70 mg/dL OR LDL-C ≥100 mg/dL; N=471; 18 months
- ODYSSEY FH II (NCT01709500; CL1112): LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL; N=250; 18 months
- ODYSSEY HIGH FH (NCT01617655; EFC12732): LDL-C ≥160 mg/dL; N=105; 18 months
- ODYSSEY OLE (NCT01954394; LTS 13463): Open-label study for FH from EFC 12492, CL 1112, EFC 12732 or LTS 11717; N≥1000; 30 months
- ODYSSEY LONG TERM (NCT01507831; LTS11717): LDL-C ≥70 mg/dL; N=2,100; 18 months

HC in high CV risk population — Add-on to max-tolerated statin (± other LMT)

- ODYSSEY COMBO I (NCT01644175; EFC11568): LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL; N=306; 12 months
- *ODYSSEY COMBO II (NCT01644188; EFC11569): LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL; N=660; 24 months
- ODYSSEY CHOICE I (NCT01926782; CL1308): LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL; N=700; 12 months
- ODYSSEY OUTCOMES (NCT01663402; EFC11570): LDL-C ≥70 mg/dL; N=18,000; 64 months

Additional populations

- ODYSSEY MONO (NCT01644474; EFC11716): Patients on no background LMTs; LDL-C ≥100 mg/dL; N=100; 6 months
- ODYSSEY ALTERNATIVE (NCT01709513; CL1119): Patients with defined statin intolerance; LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL; N=250; 6 months
- 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
- 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=350; 6 months
- 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=300; 6 months

FH=familial hypercholesterolemia; HC=hypercholesterolemia; LMT=lipid-modifying therapy; OLE=open-label extension.
*For the ODYSSEY COMBO II other LMT not allowed at entry.
ClinicalTrials.gov. ODYSSEY Phase 3 Trials. http://clinicaltrials.gov. Accessed February 12, 2014.

PROFICIO : Evolocumab

PROFICIO >35,000 patients

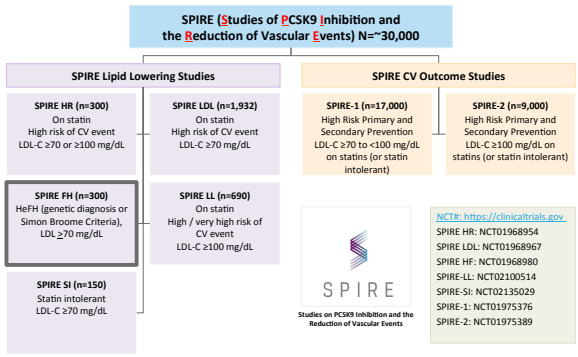
laplace	Combination therapy	Phase 2 (n=631) ✓	Phase 3 (n=2067) ✓
mendel	Monotherapy	Phase 2 (n=411) ✓	Phase 3 (n=615)
gauss	Statin intolerant	Phase 2 (n=160) ✓	Phase 3 (n=30) ✓ / Phase 3 (n=511)*
ruthenford	HeFH	Phase 2 (n=168) ✓	Phase 3 (n=331)
tesla / taussig	HoFH/ Severe FH	Phase 2/3 (n=58) ✓	Phase 2/3 (n=300)
descartes	Long-term safety and efficacy		Phase 3 (n=905) ✓
osler	Open-label extension	Phase 2 (n=1104)	Phase 3 (n=3671)*
glagov	Atherosclerosis		Phase 3 (n=970)
fourier	Secondary Prevention		Phase 3 (n=27,564)
ebbinghaus	Neurocognition		Phase 3 (n=1971)*

✓ Completed trials

HeFH, heterozygous hypercholesterolaemia; HoFH, homozygous hypercholesterolaemia. Clintrials.gov. * Amgen data on file.

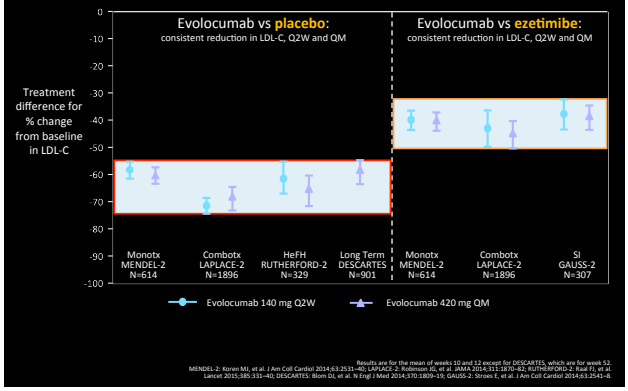
SPIRE Phase 3 Bococizumab Clinical Development Programme

Unmet Needs in the Management of CVD in High Risk Patients



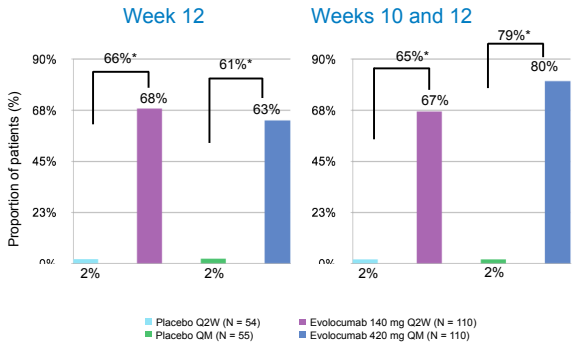
Evolocumab Q2W or QM:

consistent LDL-C reductions across different studies



Results are for the mean of weeks 10 and 12 except for DESCARTES, which are for week 52.
MENDEL-2: Koren MJ, et al. J Am Coll Cardiol 2014;63:2531–40; LAPLACE-2: Robinson JG, et al. JAMA 2014;311:1870–82; RUTHERFORD-2: Raal FJ, et al. Lancet 2015;385:331–40; DESCARTES: Blom DJ, et al. N Engl J Med 2014;370:1809–19; GAUSS-2: Stroes E, et al. J Am Coll Cardiol 2014;63:2541–8.

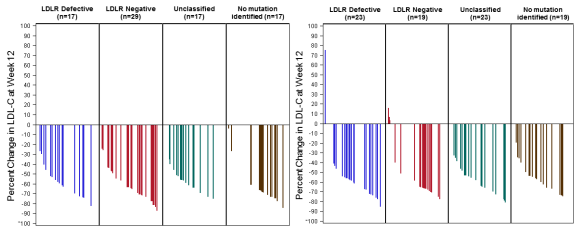
RUTHERFORD-2:
LDL-C Goal Achievement < 1.8 mmol/L



*P< 0.0001 evolocumab treatment difference vs placebo.
Raal FJ, et al. Lancet 2014; doi.org/10.1016/S0140-6736(14)61399–4 and supplementary material.

Efficacy of LDL-C lowering by Evolocumab in heterozygous FH patients : RUTHERFORD-2

Evolocumab 140 mg Q2W **Evolocumab 420 mg QM**

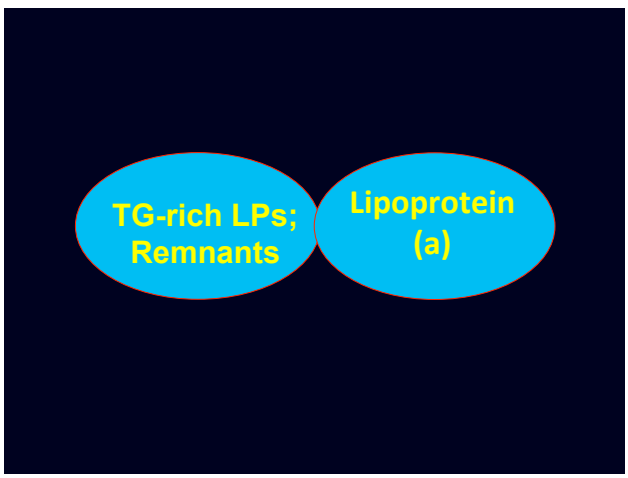


Raal FJ, et al. Lancet 2014; doi.org/10.1016/S0140-6736(14)61399-4 and supplementary material.

In addition to LDL…..

Do other atherogenic lipoproteins contribute to atherosclerotic vascular disease and cardiovascular events ?

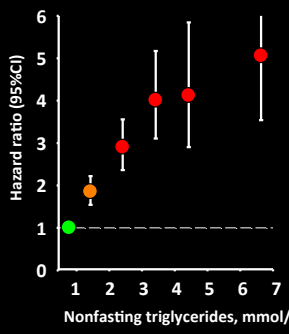
Do PCSK9 inhibitors impact such lipoproteins ?



Copenhagen City Heart Study and Copenhagen General Population Study

Myocardial infarction

N = 96,394 (Events = 3,287)



Nordestgaard & Varbo, Lancet 2014; 384: 626-635

European Heart Journal Advance Access published April 26, 2016

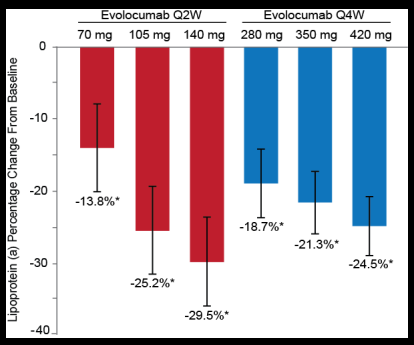
European Heart Journal
doi:10.1093/eurheartj/ehw152

CURRENT OPINION

Fasting is not routinely required for determination of a lipid profile: clinical and laboratory implications including flagging at desirable concentration cut-points—a joint consensus statement from the European Atherosclerosis Society and European Federation of Clinical Chemistry and Laboratory Medicine

Børge G. Nordestgaard[1*], Anne Langsted[1], Samia Mora[2], Genovefa Kolovou[3], Hannsjörg Baum[4], Eric Bruckert[5], Gerald F. Watts[6], Grazyna Sypniewska[7], Olov Wiklund[8], Jan Borén[8], M. John Chapman[9], Christa Cobbaert[10], Olivier S. Descamps[11], Arnold von Eckardstein[12], Pia R. Kamstrup[1], Kari Pulkki[13], Florian Kronenberg[14], Alan T. Remaley[15], Nader Rifai[16], Emilio Ros[17,18], and Michel Langlois[19,20], for the European Atherosclerosis Society (EAS) and the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) joint consensus initiative

Reduction in Lipoprotein(a) With Evolocumab: Pooled Analysis of > 1,300 Patients in 4 Phase II Trials



Error bars represent standard error. * P < 0.001

Raal et al JACC 2014;():. doi:10.1016/j.jacc.2014.01.006 Online First

No meaningful between-group imbalances in TEAEs

Select TEAEs ≥2% incidence in any group in the pooled group and ODYSSEY LONG TERM (1)

Primary system organ class, % (n) Preferred term, % (n)	Pooled control (n=1894)	Pooled alirocumab (n=3340)	Pooled alirocumab ≥2 LDL-C <25 mg/dL (n=796)	Pooled alirocumab ≥2 LDL-C <15 mg/dL (n=288)	LONG TERM alirocumab ≥2 LDL-C <25 mg/dL (n=562)
Infections and infestations	36.3 (687)	38.5 (1286)	34.0 (271)	35.4 (102)	39.0 (219)
Nasopharyngitis	9.3 (176)	9.8 (326)	8.3 (66)	10.1 (29)	10.0 (56)
Upper respiratory tract infection	6.7 (126)	6.1 (203)	4.5 (36)	5.2 (15)	5.7 (32)
Urinary tract infection	4.1 (77)	4.1 (137)	4.6 (37)	4.9 (14)	5.5 (31)
Influenza	3.9 (73)	5.2 (173)	3.6 (29)	4.2 (12)	4.1 (23)
Bronchitis	3.3 (63)	3.8 (126)	4.4 (35)	3.1 (9)	5.2 (29)
Sinusitis	2.7 (51)	2.6 (87)	2.6 (21)	3.1 (9)	3.0 (17)
Lower respiratory tract infection	1.4 (26)	1.6 (53)	2.0 (16)	2.1 (6)	2.8 (16)
Gastroenteritis	2.3 (43)	1.9 (62)	0.6 (5)	1.0 (3)	0.7 (4)
Musculoskeletal and connective tissue disorders	25.2 (478)	24.2 (808)	21.1 (168)	20.1 (58)	22.6 (127)
Back pain	4.3 (82)	4.0 (133)	4.3 (34)	4.2 (12)	5.0 (28)
Arthralgia	5.0 (95)	4.0 (134)	3.1 (25)	2.1 (6)	3.2 (18)
Myalgia	4.8 (91)	4.9 (162)	3.1 (25)	3.8 (11)	3.0 (17)
Muscle spasms	2.4 (45)	2.8 (94)	2.5 (20)	3.5 (10)	2.8 (16)
Pain in extremity	3.4 (64)	2.4 (81)	2.1 (17)	1.4 (4)	2.1 (12)
Osteoarthritis	2.2 (42)	2.1 (69)	1.8 (14)	1.0 (3)	2.1 (12)
Musculoskeletal pain	1.4 (27)	1.9 (65)	1.0 (8)	1.0 (3)	1.4 (8)

J. Robinson et al., *N Engl J Med* 2015 March 15; Epub ahead of print

No meaningful between-group imbalances in TEAEs

Select TEAEs ≥2% incidence in any group in the pooled group and ODYSSEY LONG TERM (2)

Primary system organ class, % (n) Preferred term, % (n)	Pooled control (n=1894)	Pooled alirocumab (n=3340)	Pooled alirocumab ≥2 LDL-C <25 mg/dL (n=796)	Pooled alirocumab ≥2 LDL-C <15 mg/dL (n=288)	LONG TERM alirocumab ≥2 LDL-C <25 mg/dL (n=562)
Gastrointestinal disorders	16.8 (318)	17.0 (567)	12.7 (101)	10.1 (29)	13.7 (77)
Diarrhea	3.9 (74)	4.3 (142)	3.0 (24)	1.4 (4)	3.9 (22)
Nausea	2.5 (47)	2.2 (74)	0.9 (7)	1.0 (3)	0.9 (5)
General disorders and administration-site conditions	14.9 (282)	15.1 (504)	10.2 (81)	6.9 (20)	11.0 (62)
Injection-site reaction	3.9 (73)	5.7 (191)	3.0 (24)	3.5 (10)	3.6 (20)
Fatigue	2.5 (48)	2.8 (93)	2.6 (21)	2.4 (7)	3.0 (17)
Non-cardiac chest pain	1.8 (35)	1.6 (54)	1.8 (14)	0.3 (1)	2.0 (11)
Nervous system disorders	14.9 (283)	14.9 (497)	10.3 (82)	9.0 (26)	11.2 (63)
Dizziness	3.6 (69)	3.0 (100)	1.8 (14)	1.4 (4)	1.4 (8)
Headache	4.6 (87)	4.6 (153)	1.8 (14)	1.4 (4)	1.8 (10)
Hemorrhagic stroke	0.1 (1)	0.1 (2)	0	0	0
Metabolism and nutrition disorders	6.3 (120)	6.9 (232)	7.0 (56)	7.3 (21)	8.0 (45)
Type 2 diabetes mellitus	0.7 (14)	1.1 (36)	1.8 (14)	1.4 (4)	2.5 (14)
Diabetes mellitus	1.3 (24)	1.2 (39)	1.5 (12)	2.4 (7)	1.4 (8)
Eye disorders	3.7 (71)	4.6 (152)	5.3 (42)	6.9 (20)	6.4 (36)
Cataract	0.9 (17)	0.8 (26)	1.5 (12)	2.4 (7)	1.8 (10)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	2.5 (48)	2.5 (85)	2.8 (22)	2.4 (7)	3.0 (17)

J. Robinson et al., *N Engl J Med* 2015 March 15; Epub ahead of print

Alirocumab : TEAEs in Patients With 2 Consecutive LDL-C <25 mg/dL

% (n) of patients All pts on background of maximally tolerated statin ± other lipid-lowering therapy	Alirocumab (n=1550)	Alirocumab with 2 consecutive LDL-C <25 mg/dL (n=562)	Placebo (n=788)
General allergic reaction events*	**9.0%** (140)	**6.0%** (34)	**9.0%** (71)
Treatment-emergent local injection site reactions	**5.8%** (90)	**3.7%** (21)	**4.3%** (34)
Neurological events‡	**4.2%** (65)	**1.8%** (10)	**3.9%** (31)
All cardiovascular events†	**4.0%** (62)	**3.2%** (18)	**4.4%** (35)
Ophthalmological events‡	**2.5%** (38)	**1.8%** (10)	**1.9%** (15)
Neurocognitive disorders‡	**1.2%** (18)	**0.5%** (3)	**0.5%** (4)
Haemolytic anaemia	0	0	0

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

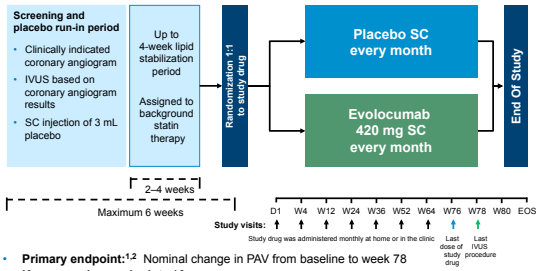
* 1 alirocumab-treated patient diagnosed with Miller Fisher Syndrome at week 27 after typical prodromal gastroenteritis, he had a complete recovery following treatment discontinuation; at week 24 the patient had low LDL-C, reaching 1.5 mg/dL.

† Confirmed by adjudication. Adjudicated CV events include all CV AEs positively adjudicated. The adjudication categories are the following: CHD death, non-fatal MI, fatal and non-fatal ischemic stroke, unstable angina requiring hospitalization, congestive heart failure requiring hospitalization, ischemia driven coronary revascularization procedure [PCI, CABG].

‡Company MedDRA Queries (CMQ).

Ongoing clinical trials…..

GLAGOV: Study Design

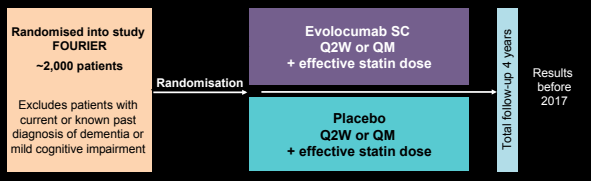


- **Primary endpoint:**[1,2] Nominal change in PAV from baseline to week 78
- **Key secondary endpoints:**[1,2]
  - Nominal change in TAV from baseline to week 78
  - Percentage of patients demonstrating regression (any reduction from baseline) in either PAV or TAV from baseline to week 78

1. Puri R, et al. *Am Heart J.* doi: 10.1016/j.ahj.2016.01.019. 2. ClinicalTrials.gov. NCT01813422. https://clinicaltrials.gov/ct2/show/NCT01813422. Accessed March 15,2016.

EBBINGHAUS: Evaluating PCSK9 Binding antiBody Influence oN coGnitive HeAlth in high cardiovascUlar risk Subjects (FOURIER substudy)

ebbinghaus



Ongoing trial to show effect of evolocumab on cognitive health (evaluated by Spatial Working Memory strategy index of executive function)

EBBINGHAUS. https://clinicaltrials.gov/ct2/show/NCT02207634?term=ebbinghaus+and+evolocumab&rank=1. Accessed 10 Jan 2016.

PCSK9 mAb Outcomes Trials

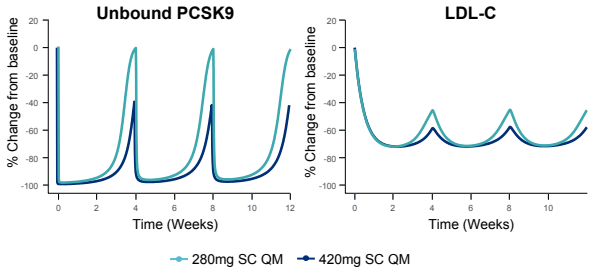
Study	FOURIER	ODYSSEY OUTCOMES	SPIRE-1	SPIRE-2
Who?	Patients aged 40-85 with history of clinically evident CVD at high risk for recurrent event	Patients aged ≥40 hospitalized for ACS recently (<52 weeks)	Background lipid lowering treatment and at high risk of a CV event	
N	**27,500**	**18,000**	**17,000**	**9000**
Primary endpt	Time to CV death, MI, hospitalization for UA, stroke, or coronary revasc, whichever occurs first	Time to CHD death, any non-fatal MI, fatal and non-fatal ischemic stroke, hospitalization for UA	Confirmed major cardiovascular event [CV death, non- fatal MI, non-fatal stroke, and hospitalization for UA needing urgent revascularization]	
LDL-C	≥70 mg/dL (or non-HDL-C ≥100 mg/dL)	≥70 mg/dL	≥70 and <100 mg/dL (or non-HDL-C ≥100 mg/dL and <130 mg/dL)	≥100 mg/dL (or non HDL C ≥130 mg/dL)

Questions

Which dose, which periodicity of injection, and what LDL-C level bring optimal clinical benefit ?

Which patients at very high CV risk urgently require substantial additional LDL-C reduction to attain an LDL-C goal of <70 mg/dL ?

Sustained PCSK9 inhibition gives stable LDL-C reduction



280mg SC QM 420mg SC QM

http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM452354.pdf. Accessed 25 Feb 2016.