PCSK-9 inhibition:
Wat kan deze nieuwe therapie betekenen?

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NVVC, Papendal

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Outline

- **Best lipid target**
- Need for more LDL-c lowering
- ‘Study’ evidence
- Competition for LDL-c lowering

HDL-c as a therapeutic target

No association 'drug-induced' HDL-c increase and risk

- ILLUMINATE — *Torcetrapib:*
  - HDLc↑+72% : CV-death OR +1.25
- DALOUTCOMES — *Dalcetrapib:*
  - HDLc↑+35% : CV-events no change
- ACCELERATE : *Evacetrapib*
  - *HDLc + >70%* CV-events no change
- HPS2-THRIVE — *Nicotinic acid*:
  - HDLc↑+15-25% : CV-events no change

Barter, New Engl J Med 2007; Schwartz GG, New Engl J Med 2012
Eur Heart J 2013; Briel, BMJ 2009

TG as a therapeutic target

No effect of TG-lowering and risk

- ORIGIN : *Omega-3 fatty acid*
  - TG – 20% CVD risk unchanged
- FIELD : *Fenofibrate*
  - TG – 15% CVD risk unchanged
- ACCORD : *Fenofibrate*
  - TG – 15% CVD risk unchanged

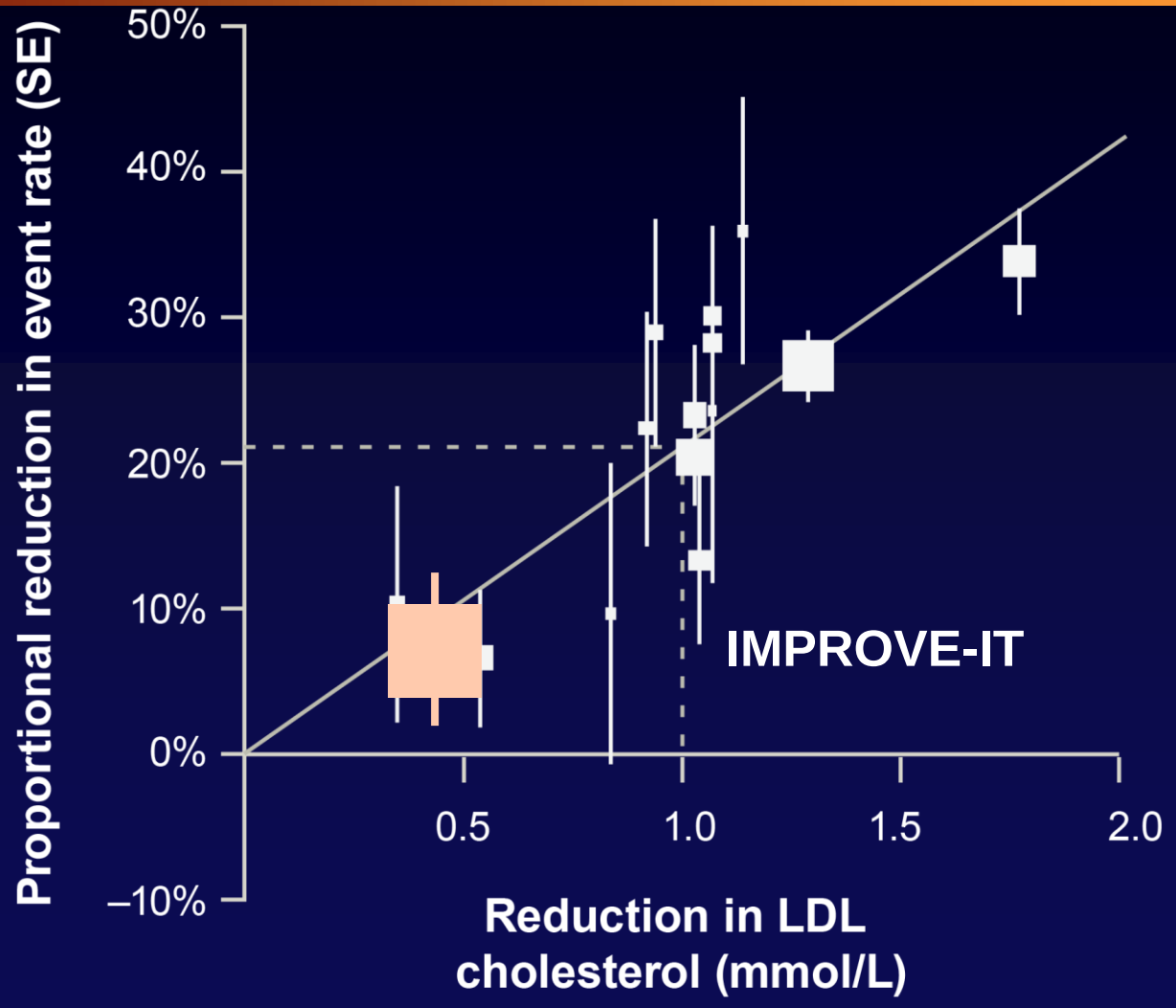
Although …

Subgroup analyses of fibrate studies

Trial (treatment)	Primary endpoint: All patients	Lipid subgroup criteria (mg/dL)	Primary endpoint: Subgroup
ACCORD Lipid (fenofibrate)	-8% (p=0.32)	TG ≥ 200 + HDL-C ≤ 34	-31% (p=0.05)
FIELD (fenofibrate)	-11% (p=0.16)	TG ≥ 200 + Low HDL-C	-27% (p=0.005)
BIP (bezafibrate)	-7.3% (p=0.24)	TG ≥ 200	-39.5% (p=0.02)
Helsinki Heart Study (gemfibrozil)	-34% (p=0.02)	TG> 200	-56% (p<0.005)

LDL-c lowering as a therapeutic target

Lower LDLc = lower risk



Lancet 2005; 366:1267-78; Lancet 2010;376:1670-81; Cannon, N Engl J Med 2015

Outline

- Best lipid target
- **Need for more LDL-c lowering**
- ‘Study’ evidence
- Competition for LDL-c lowering

Need for additional LDL-C lowering therapies

I. Most guidelines set LDL-C goals in (very) high risk patients

II. Special populations (Severe hypercholesterolemia/FH) do not achieve LDL-C goals

III. Growing number of patients with adverse effects on statins with limited alternatives

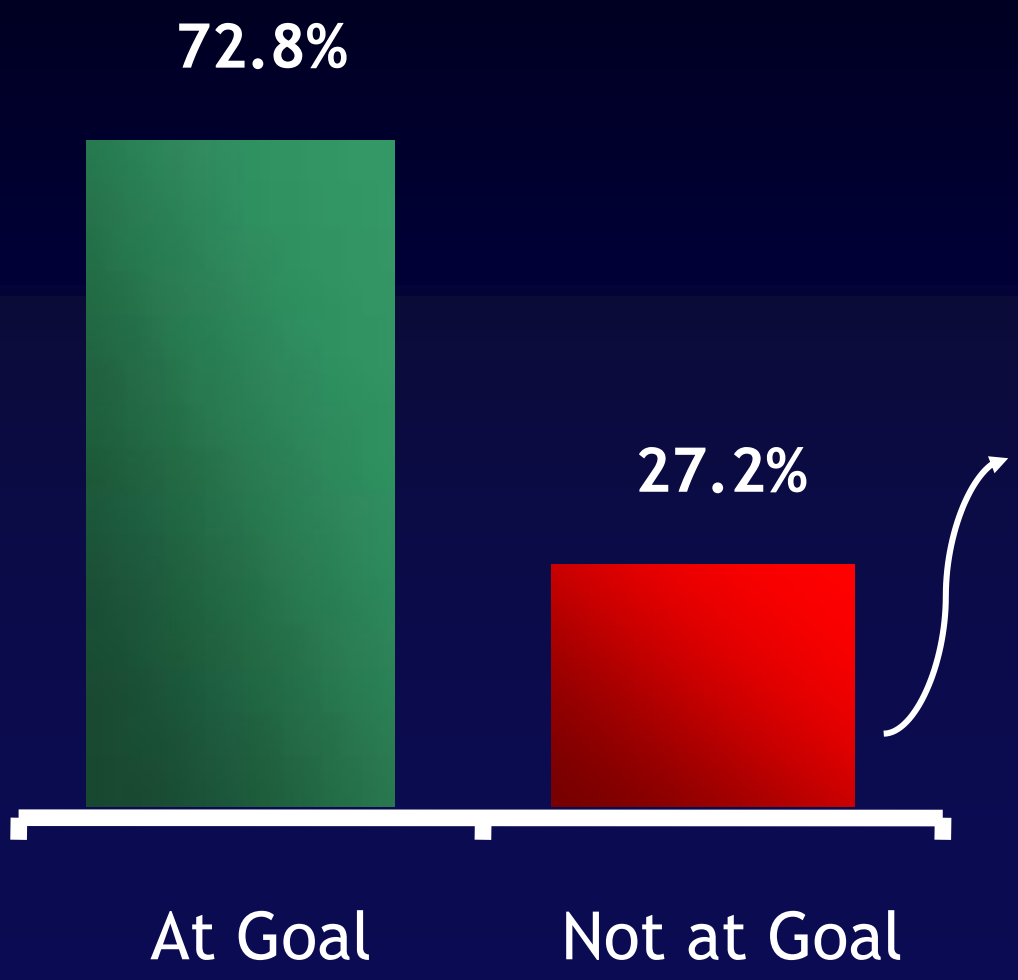
I. ESC guidelines: LDL-c target levels

ESC/EAS (2011) Guidelines for the management of dyslipidaemias

Clinical risk categories	Treatment
Those with CVD	LDL-C <1.8 mmol/L or 50% reduction in LDL-C
Diabetes mellitus (Type II) or Type I with target organ damage	LDL-C <1.8 mmol/L or 50% reduction in LDL-C
Familial dyslipidaemia (FH or FCH or chylomicronaemia)	LDL-C <2.5 mmol/L or maximal reduction in LDL-C with any possible drug combination plus LDL apheresis
If none of the above estimate 10 year risk of a first fatal atherosclerotic CV event (SCORE), with a SCORE >10% considered, very high risk, SCORE 5–10% considered high risk and SCORE 1–5% moderate risk Above risk can be modified if additional information is available on: ↑ TGs, social deprivation, central obesity, ↑ Lipoprotein(a), familial hypercholesterolaemia, subclinical atherosclerosis, CKD, family history of pre-mature CVD (× 1.7 – women, × 2 – men), very high HDL-C, family history of longevity	Very high risk LDL-C <1.8 mmol/L or 50% reduction in LDL-C, high risk LDL-C <2.5 mmol/L, moderate risk LDL-C <3.0 mmol/L

Ray KK et al. Eur Heart J 2014

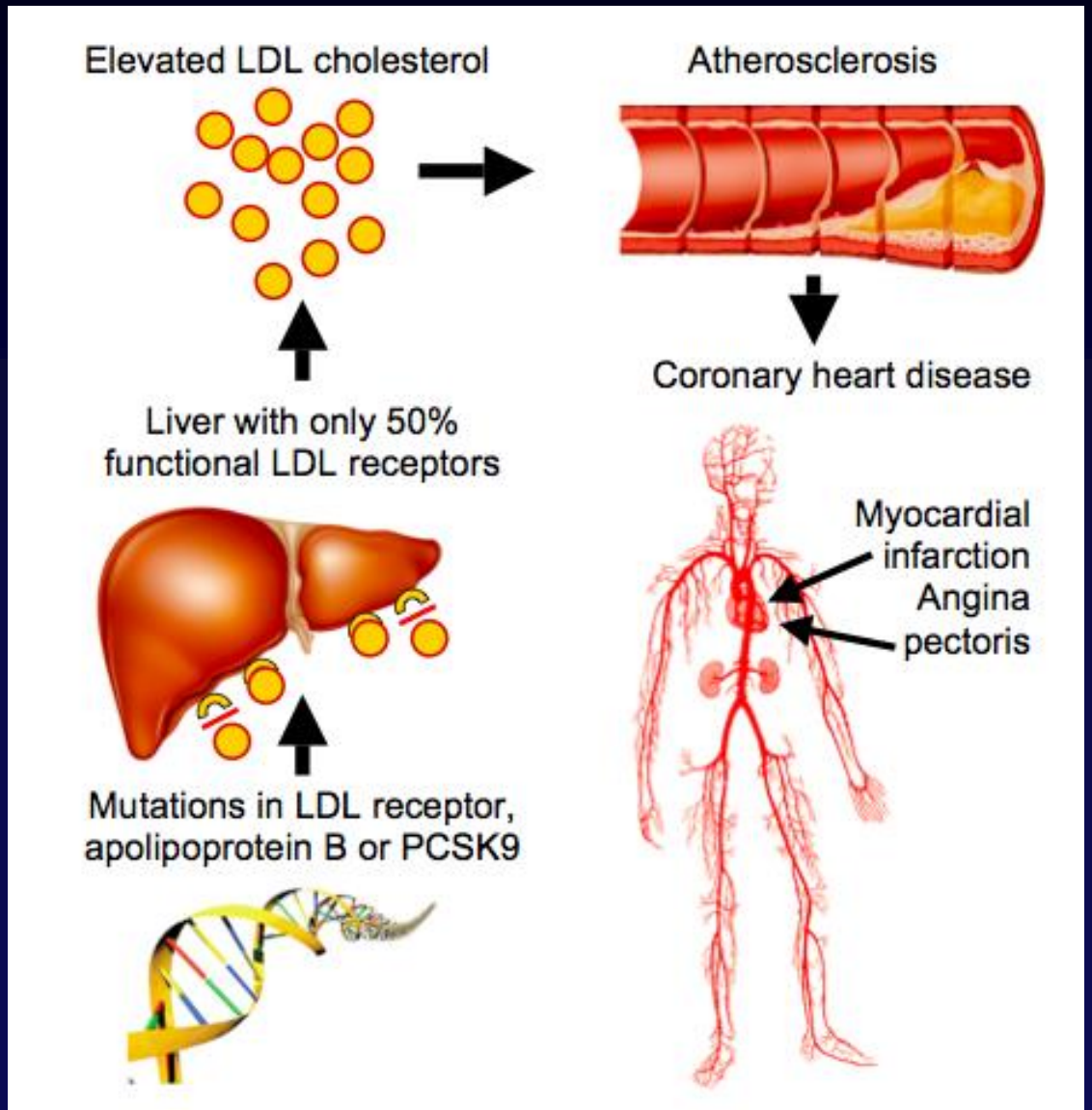
I. % LDL-C Goal Attainment *according to guidelines*



- 91% high CHD risk
- 65% required ≥ 10% additional LDL-C reduction
- 36% already taking high dose statin (≥ 40 mg)
- 27% perceived as being at goal
- 24% up-titrated at study visit
- 67% no change in treatment following study visit

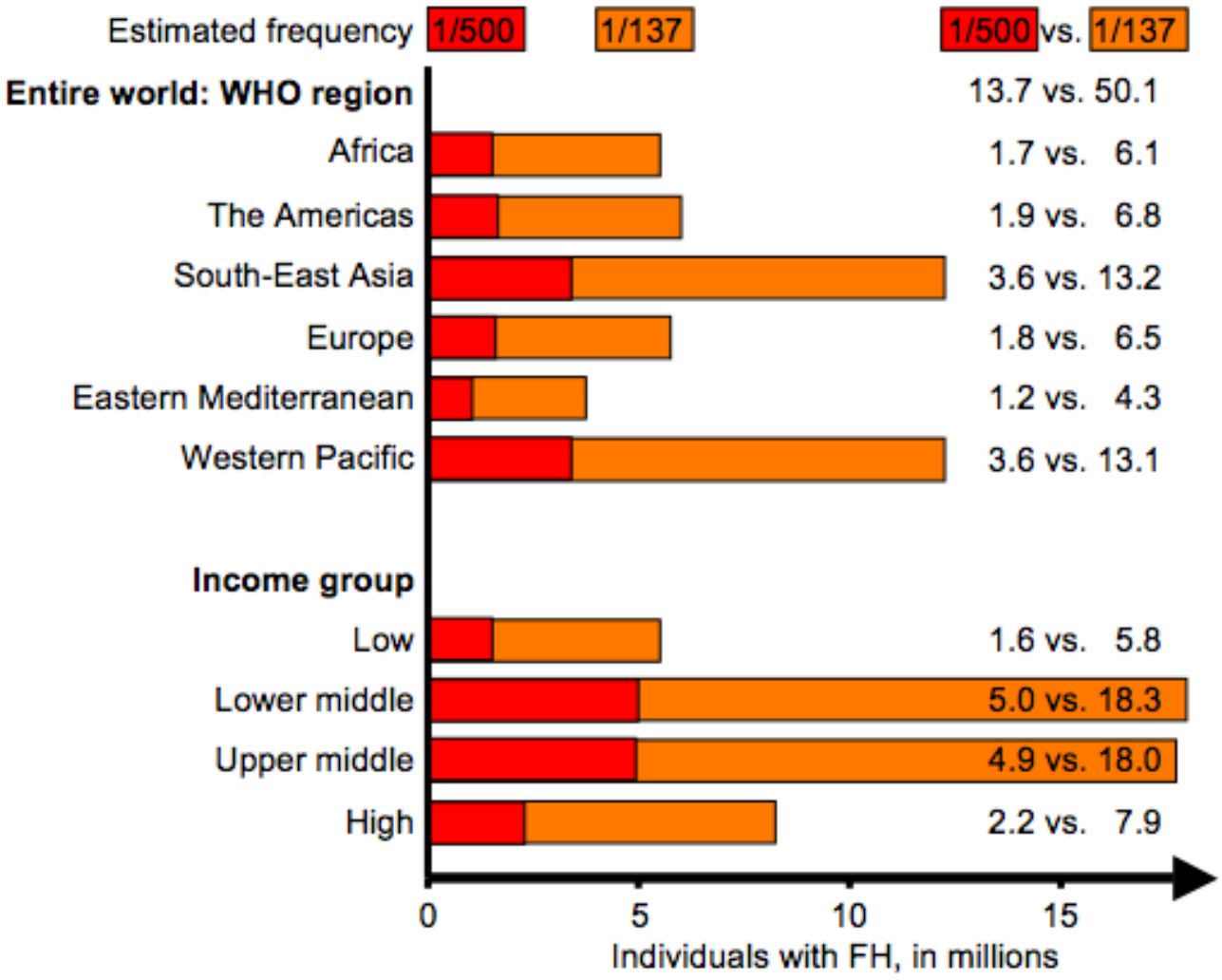
II. Special populations – Fam. Hypercholesterolemia

High [chol] and high CV-risk



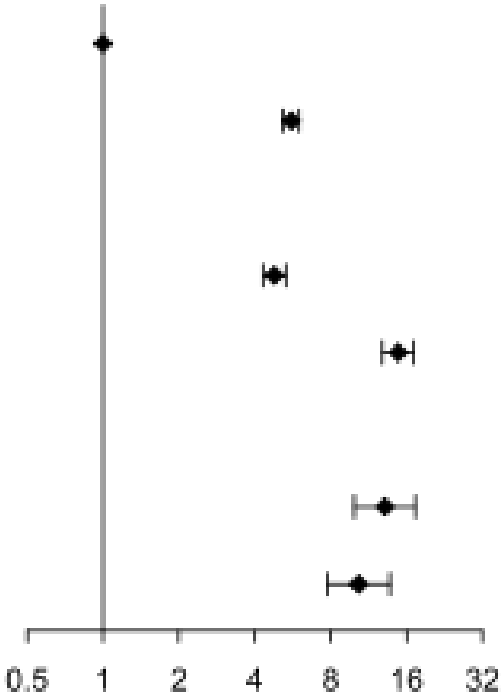
Nordestgaard, Eur Heart J 2014

II. FH: high(er) prevalence – 1 : 200



II. FH and Cardiovascular risk

	Statin	No. of participants	No. of CHDs	Odds ratio (95% CI)
Unlikely FH	Off	58,158	2,592	1 (Reference)
	On	6,061	1,884	5.6 (5.2-6.0)
Possible FH	Off	3,380	604	4.8 (4.3-5.3)
	On	915	406	14.8 (12.9-17.1)
Definite or probable FH	Off	260	84	13.2 (10.0-17.4)
	On	242	84	10.3 (7.8-13.8)



II. LDL-C goal attainment
in FH / Severe Hypercholesterolemia

N=107 (% change from diet)

PARAMETER	Diet R mean	RSV 40 mg	RSV + EZE	%change
LDL cholesterol mg/dL (SD)	291 (59)	141 (30)	100 (26)	-65%**
HDL cholesterol	45	50	50	+13%**
Hs-CRP	1.9	1.0	0.9	-54%**

*** 40% achieved LDLC < 100 mg/dL with combination**
60% of patients still not at goal

Stein EA, J Clin Lipidol 2007; 1:280-286

III. Special populations - Statin intolerance
Discontinuation due to Statin-Associated Side Effects

- **Observational studies:**
  - **Most frequent: statin-attributed muscle symptoms (SAMS)**
  - Gastro-intestinal discomfort
  - Fatigue
  - Peripheral neuropathy
  - Insomnia
  - Neurocognitive symptoms

Carter AA et al. *BMJ*. 2013;346:f2610;
Mancini GB et al. *Can J Cardiol*. 2013;29(12):1553-68;
Richardson K et al. *Ann Intern Med*. 2013 Nov 19;159(10):688-97

III. Impact Statin Associated Muscle Symptoms *SAMS*

- Statin- attributed symptoms
  - ~75% of pts discontinue statin within 2 years[1]
  - SAMS prevailing reason in ~ 60% of subjects [2]

- Consequences of low statin adherence:
  - Increased CV-risk / mortality

Proportion of days covered with statin therapy, %	Hazard ratio (95% CI), Primary-prevention	Hazard ratio (95% CI), Secondary-prevention
<10	1 (reference)	1 (reference)
10–19	1.35 (1.22–1.50)	1.28 (1.18–1.39)
50–59	0.77 (0.67–0.88)	0.69 (0.63–0.76)
>90	0.55 (0.49–0.61)	0.49 (0.46–0.53)

1. Chodick G .*Clin Ther*. 2008;30:2167-79 ; 2. Cohen J *J Clin Lipidol.* 2012 ;6:208-15 3. Shalev. Arch Int Med 2009

III. Prevalance of SAMS in Observational study

Risk of Muscle Symptoms with High Dose Statins (PRIMO)

Statin	Dosage	% patients with musle sympt	Odds Ratio† [95% CI]	P value‡
Pravastatin	40 mg/day	10.9%		
Atorvastatin	40–80 mg/day	14.9%	1.28 [1.02–1.60]	0.035
Simvastatin	40–80 mg/day	18.2%	1.78 [1.39–2.29]	<0.0001
Fluvastatin	80 mg/day	5.1%	0.33 [0.26–0.42]	<0.0001

*% values relative to the total number of patients with or without muscular symptoms.
†
Odds ratios were calculated using pravastatin as the reference.

Bruckert E et al. Cardiovascular Drugs and Therapy 2005 ;19: 403–414.

III. Successful statin re-challenge in vast majority

- **Blinded challenge[1]**
  - 361 patients intolerant to ≥ 2 statins
  - Randomized to ezetimibe, alirocumab, atorvastatin
  - Results:

atorva challenge:	22% muscle symptoms	75% free of AE's
ezetimibe challenge:	20% muscle symptoms	75% free of AE's
alirocumab challenge:	16% muscle symptoms	82% free of AE's

- **Statin rechallenge[2]**
  - From 107.835 records – 18.778 statin-attributed AE (40% muscle s.)
  - From 11.124 discontinued – 6.579 rechallenged
  - Results:
    92% successfully used 'a statin' for > 12 months after rechallenge

1. Zheng, Ann Int Med2013; 2. Moriarty, AHA 2014;

III. Management of patients with SAMS

'True' Incidence < 2% of statin users

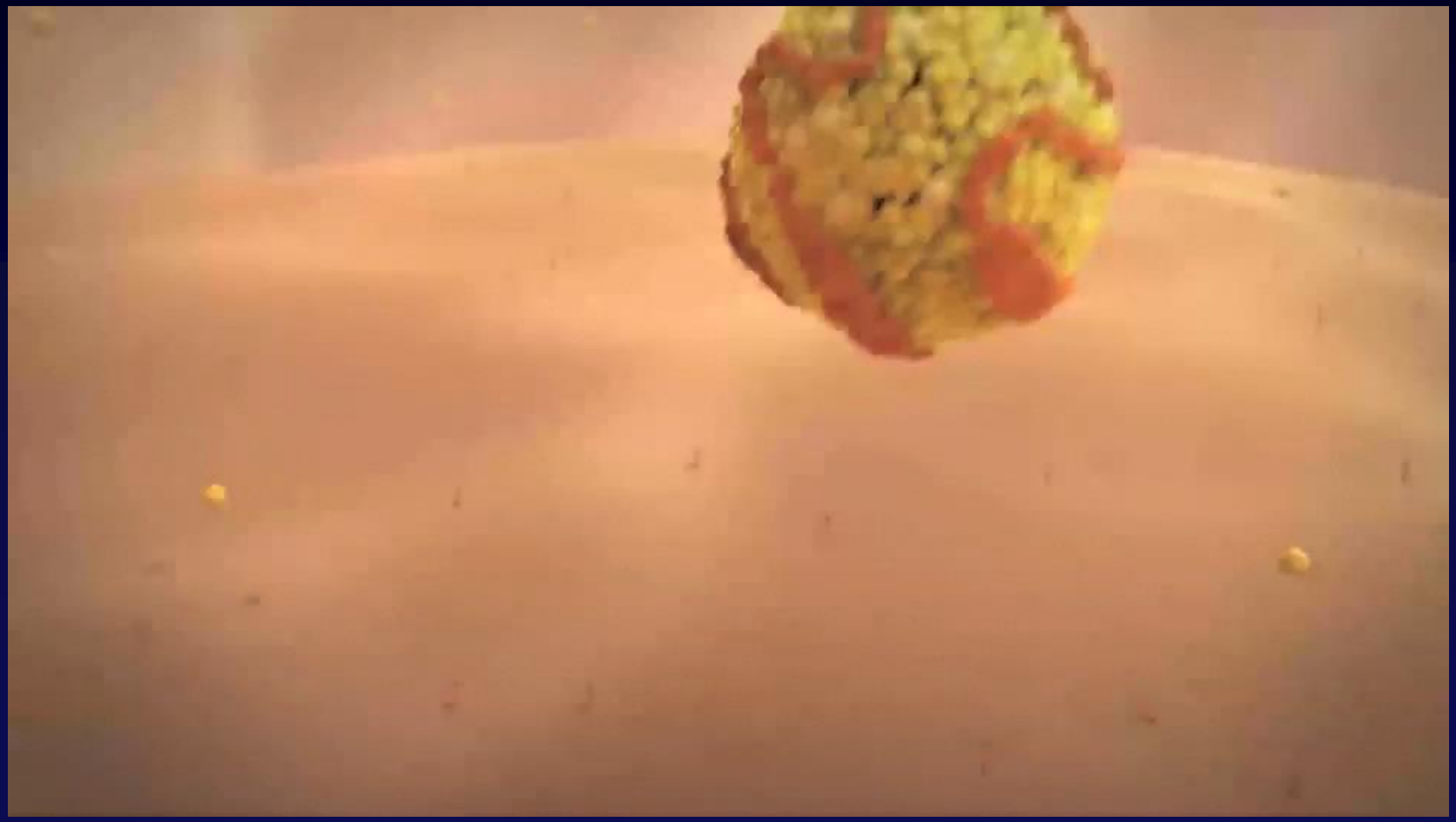
Stroes E, Eur H J 2015

Outline

- Best lipid target
- Need for more LDL-c lowering
- **‘Study’ evidence for PCSK9 antibodies**
- Competition for LDL-c lowering

PCSK-9 inhibiton

Mechanism of Action



Overview of the ODYSSEY Phase 3 Program

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

HeFH population

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

ODYSSEY FH [illegible] EFC12492)
LDL-C [illegible]
n= [illegible]

ODYSSEY FH I

ODYSSEY FH II

ODYSSEY [illegible] EFC12732)
LDL-C ≥160 mg/dL
n=107; 18 months

ODYSSEY HIGH FH

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 OLE

Familial Hypercho-lesterolemia

HC in high CV-risk population

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

ODYSSEY CO [illegible] EFC11568)
LDL-C [illegible]
n= [illegible]

ODYSSEY COMBO I

ODYSSEY COMBO II

High-risk 'progressive' CV-disease

ODYSSEY CHOICE I (NCT01926782; CL11[illegible])
LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
n=700; 12 months

ODYSSEY CHOICE I

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

ODYSSEY LONG TERM

ODYSSEY OUTCOMES (NCT01663402; EFC11570)
LDL-C ≥70 mg/dL
n=18,000; 64 months

ODYSSEY OUTCOMES

Additional populations

ODYSSEY MONO (NCT01644474; EFC11716)
Patients on no background LLTs
LDL-C ≥10[illegible]
n=10[illegible]

ODYSSEY MONO

ODYSSEY [illegible] 1119)
n [illegible]

ODYSSEY ALTERNATIVE

Statin intolerance

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 CHOICE II

ODYSSEY OPTIONS I (NCT01730040; CL1110)
Patients not at goal on moderate-dose atorvastatin
LDL-C ≥70 mg/dL OR LDL-C ≥100 m[illegible]
n=355; 6 months

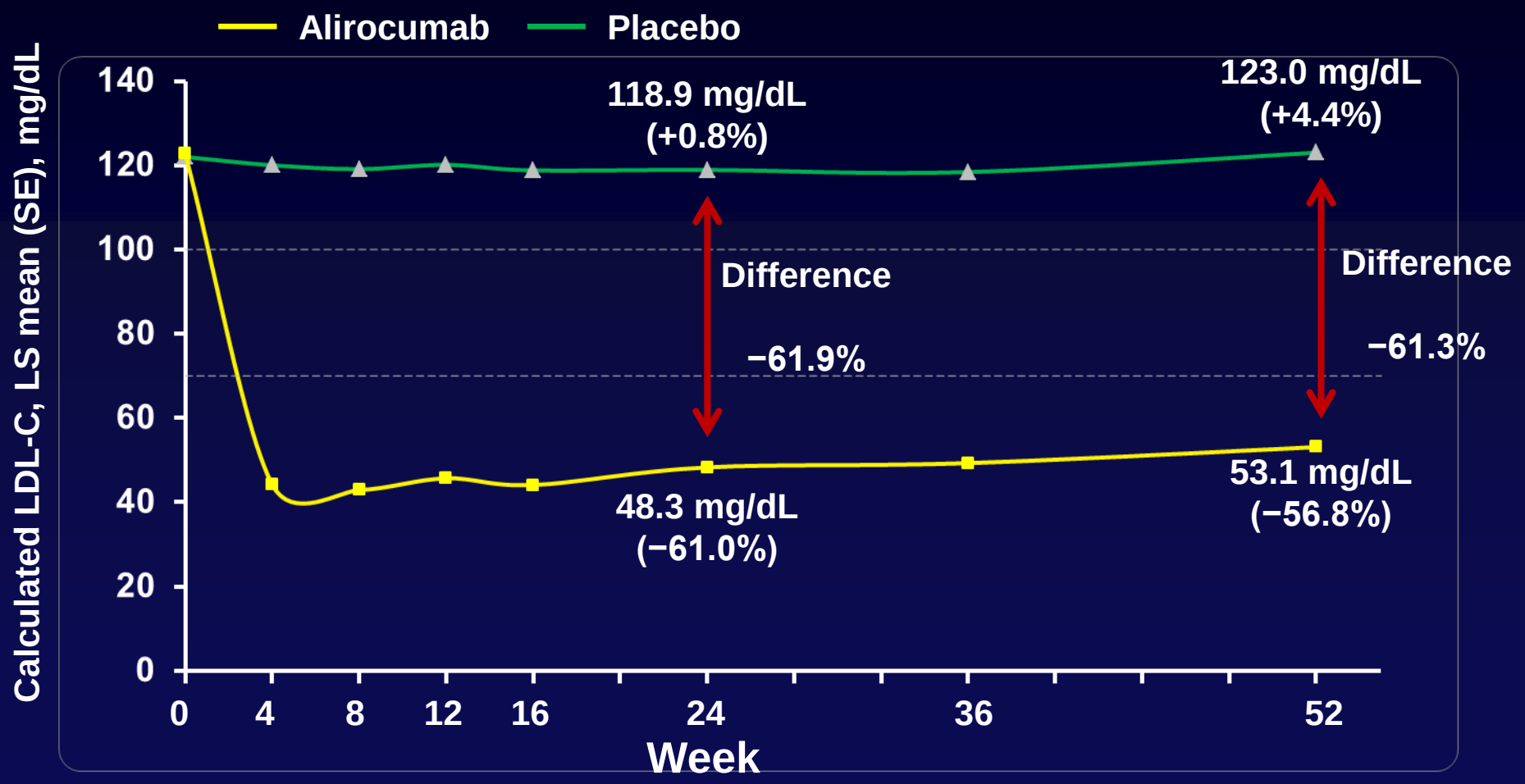
ODYSSEY OPTIONS I

ODYSSEY OPTIONS II (NCT01730053; CL1118)
Patients not at goal on moderate-dose rosuvastatin
LDL-C ≥70 mg/dL OR LDL-C ≥100 m[illegible]
n=305; 6 months

ODYSSEY OPTIONS II

*For ODYSSEY COMBO II other LLT not allowed at entry

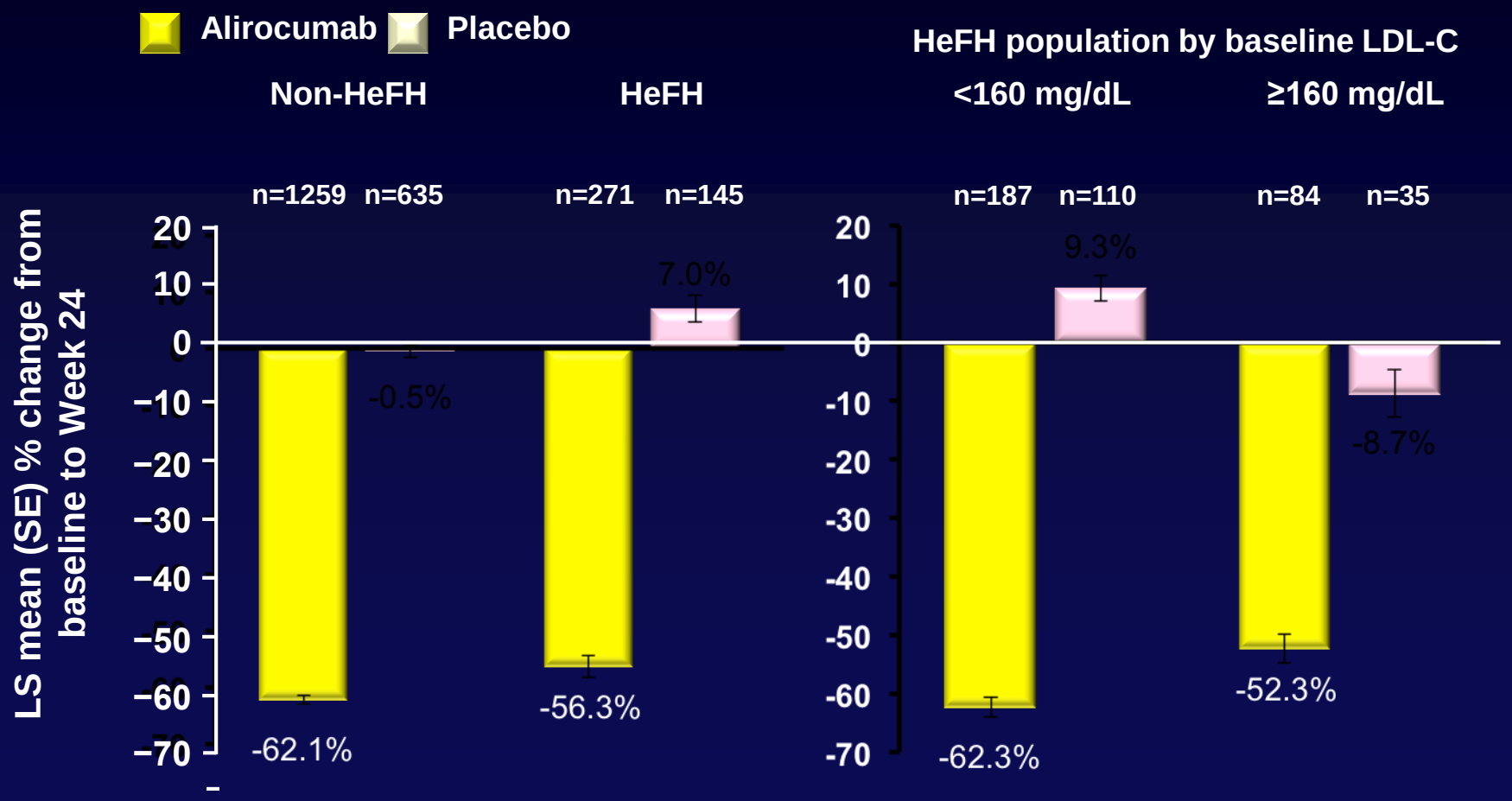
Alirocumab in hyperlipidemic CV-patients



Robinson J, Am Coll Cardiol 2014

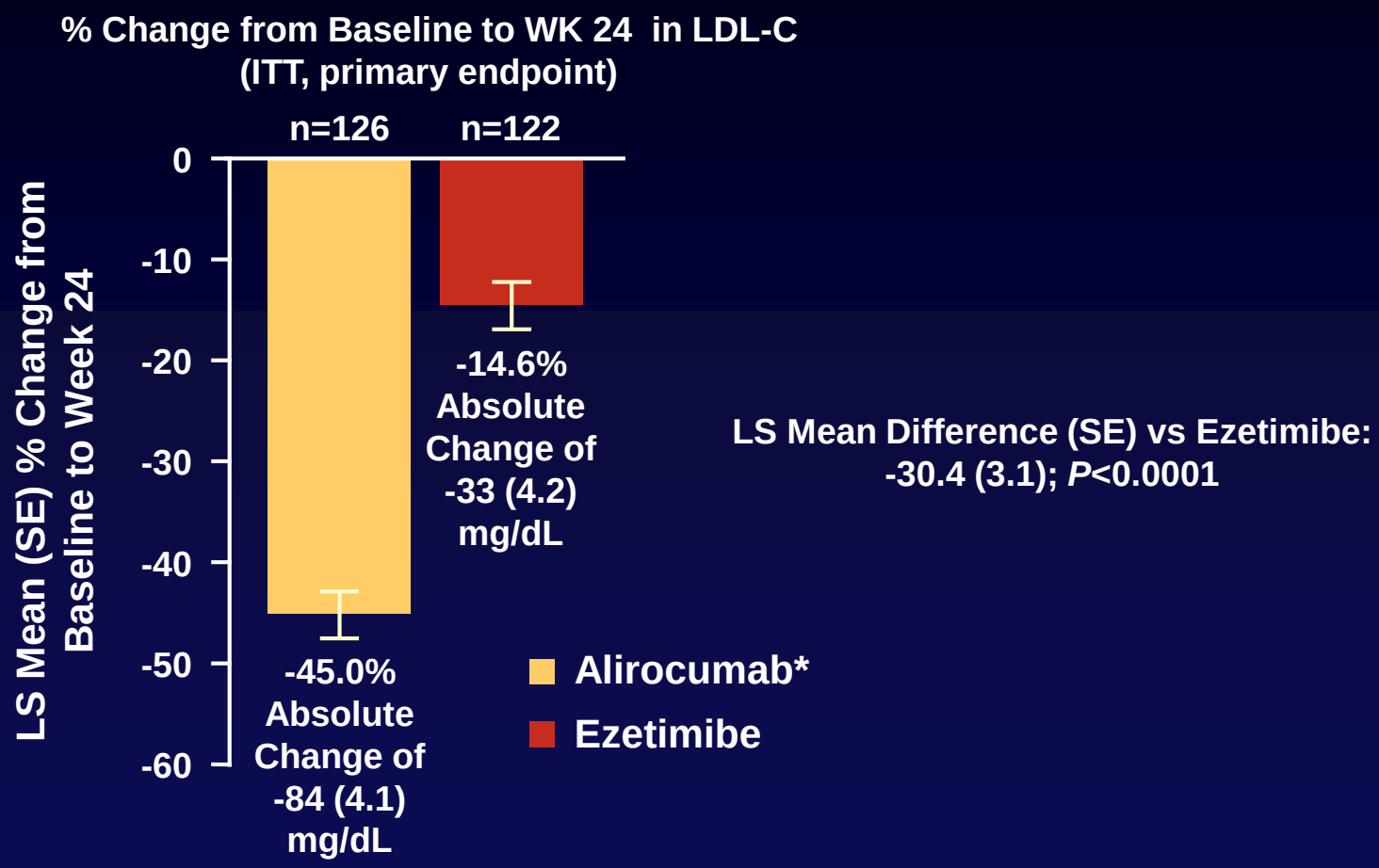
Alirocumab in Familial hypercholesterolemia

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



Robinson J, Am Coll Cardiol 2014

Alirocumab in statin-intolerance



†49.5% of 109 patients who received at least one injection after Week 12 had dose increase. *Not FDA approved.

Moriarty PM, et al. ODYSSEY ALTERNATIVE. American Heart Association 2014 Scientific Sessions; November 17, 2014; Chicago, IL. Abstract.

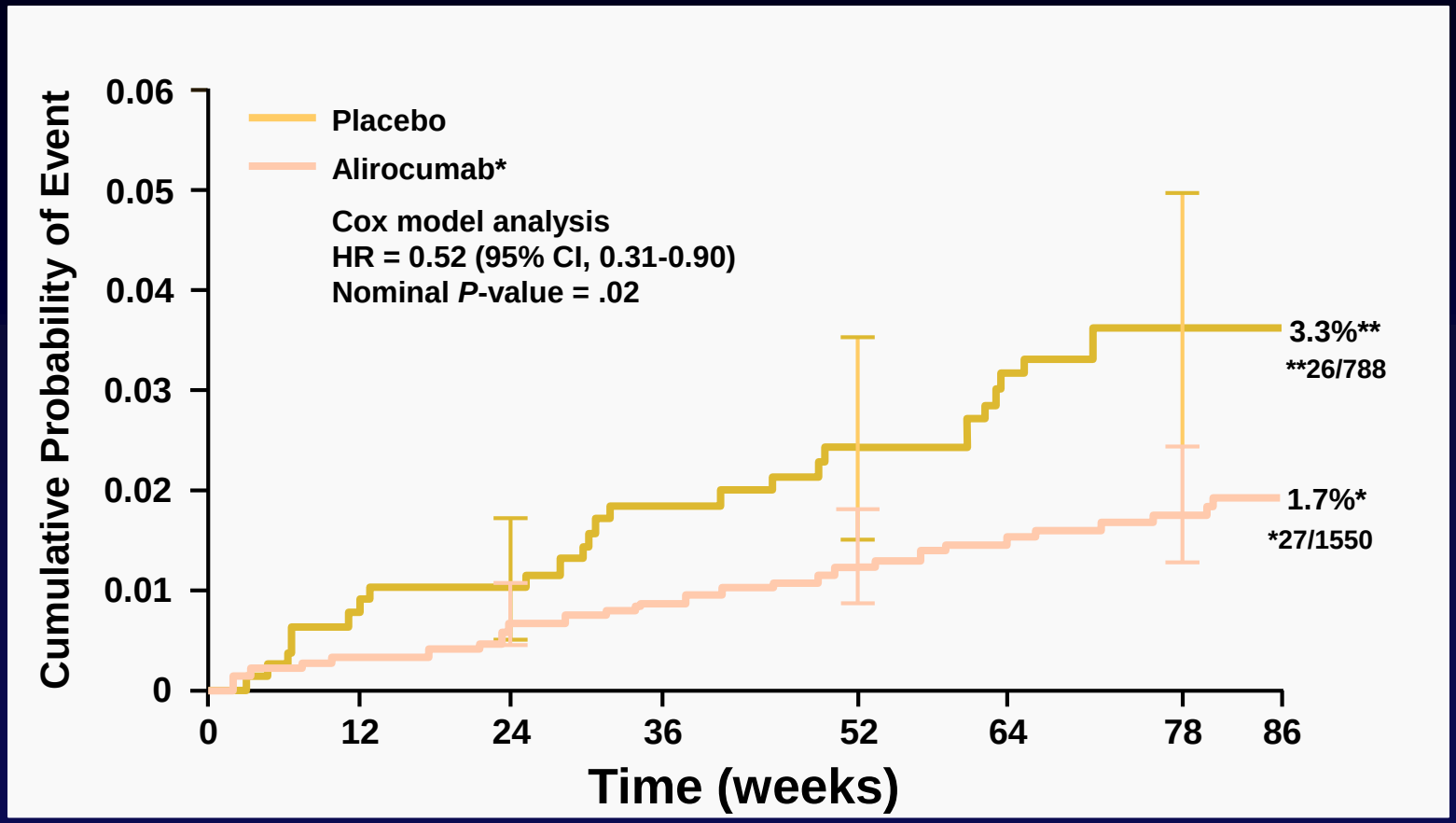
Alirocumab and safety

Subanalysis in patients with LDLc < 25mg/dl

% of patients All pts on background of maximally tolerated statin ± other LLT	**ALI (n=1550)**	**ALI with 2 consecutive LDL-C <25 mg/dL (n=562, 37%)**	**PBO (n=788)**
Nasopharyngitis	12.6	**10.0**	12.7
URTI	7.0	**5.7**	8.0
Injection-site reaction	5.7	**3.6**	3.4
Influenza	5.4	**4.1**	5.5
Diarrhea	5.3	**3.9**	5.1
Urinary tract infection	5.2	**5.5**	6.2
Bronchitis	5.2	**5.2**	4.7
Myalgia	4.9	**3.0**	3.0
Headache	4.8	**1.8**	5.6
Back pain	4.7	**5.0**	6.0
Arthralgia	4.5	**3.2**	6.0
Muscle spasms	3.7	**2.8**	3.2
Fatigue	3.0	**3.0**	3.8
Pain in extremity	3.0	**2.1**	4.4
Hypertension	3.5	**2.0**	3.4

Robinson J, N Engl J Med 2015

Alirocumab and Incidence of Cardiovascular Events¶

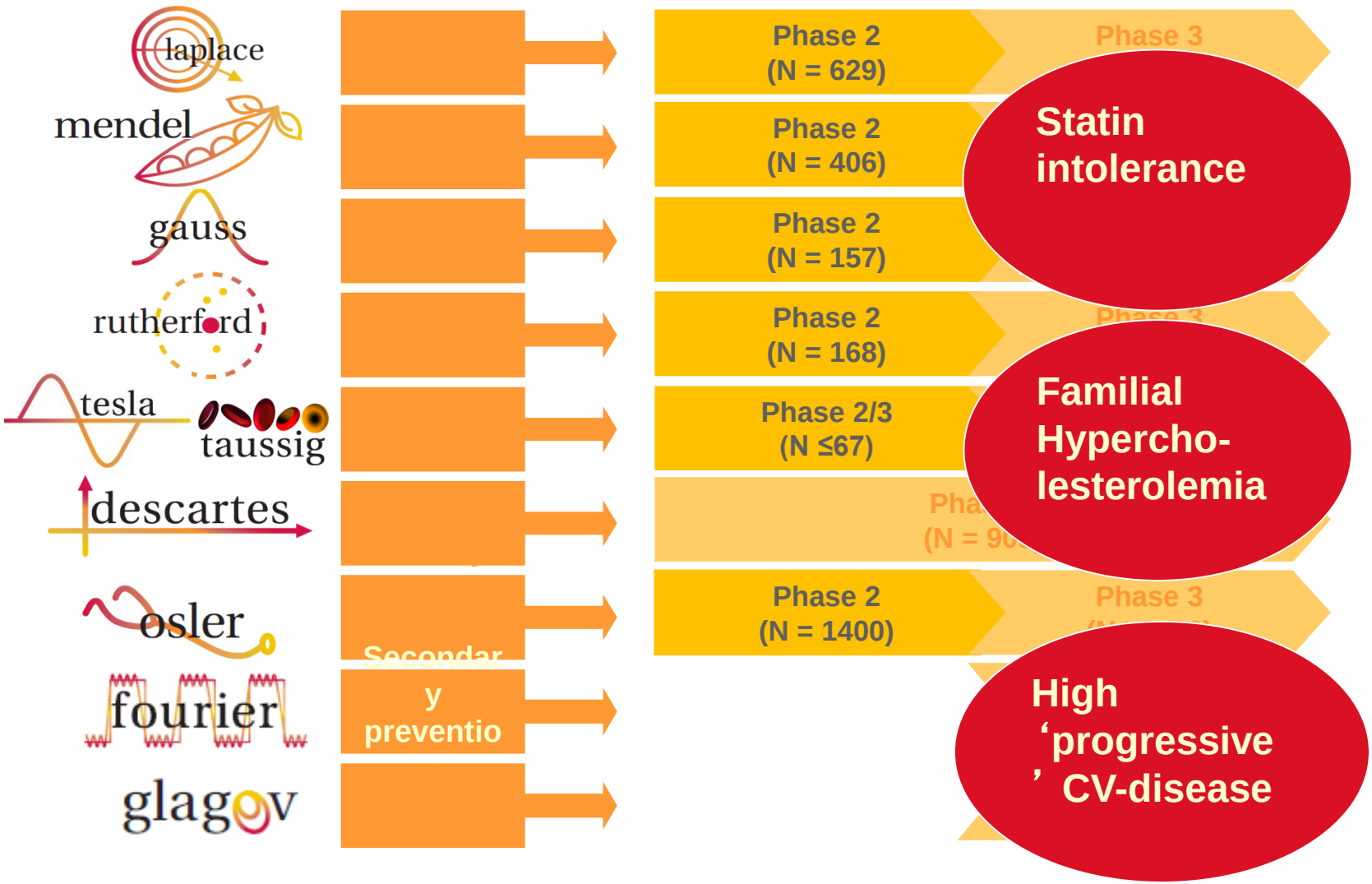


¶post-hoc analysis not specified in the study protocol - included cardiovascular event categories which comprise the endpoint in ODYSSEY Outcomes (Study to Evaluate the Effect of Alirocumab on the Occurrence of Cardiovascular Events in Patients Who Have Experienced an Acute Coronary Syndrome).

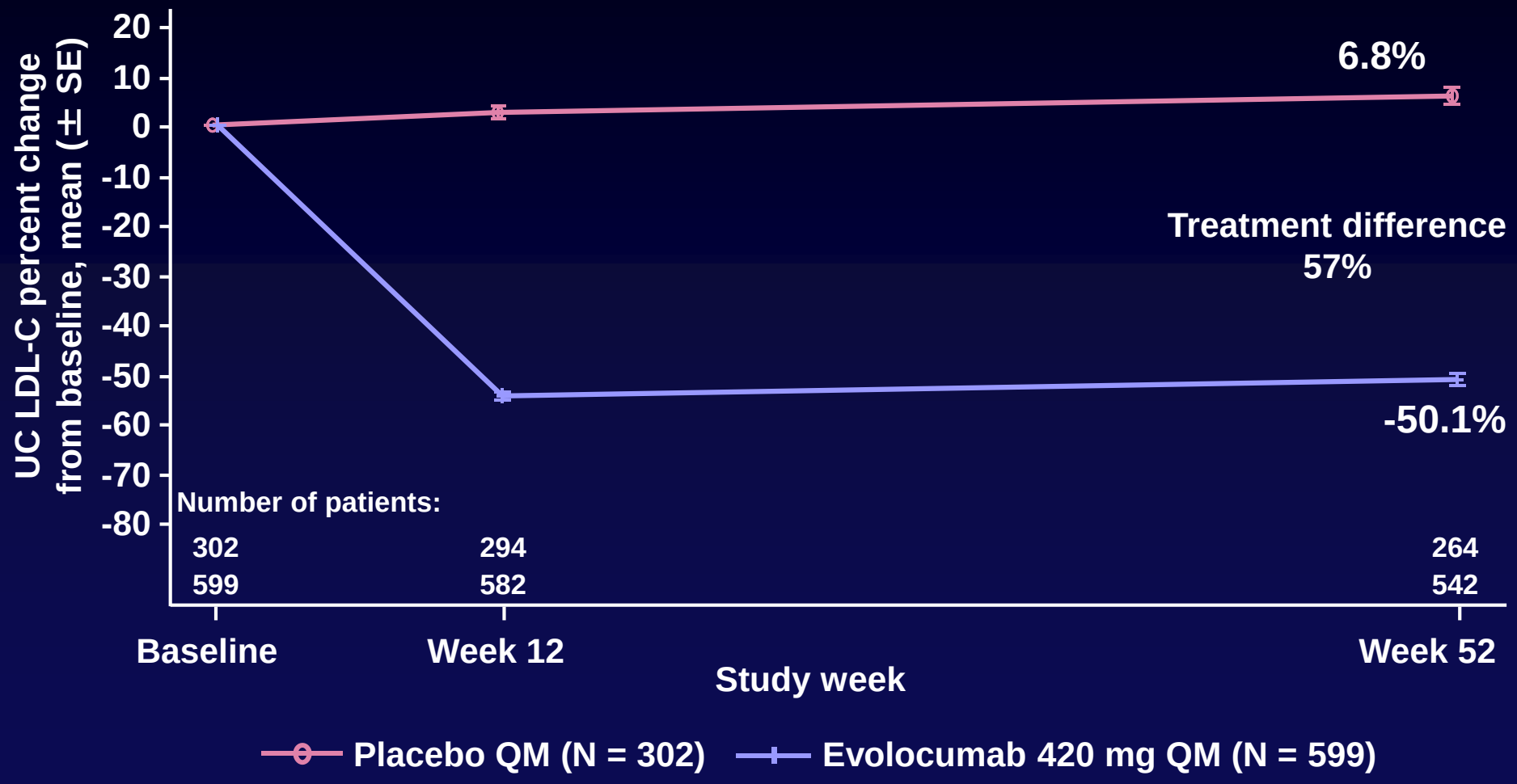
Robinson JG et al. N Engl J Med 2015;372:1489-1499

PROFICIO

Program to **R**educe LDL-C and Cardiovascular **O**utcomes **F**ollowing **I**nhibition of P**C**SK9 **I**n Different P**o**pulations

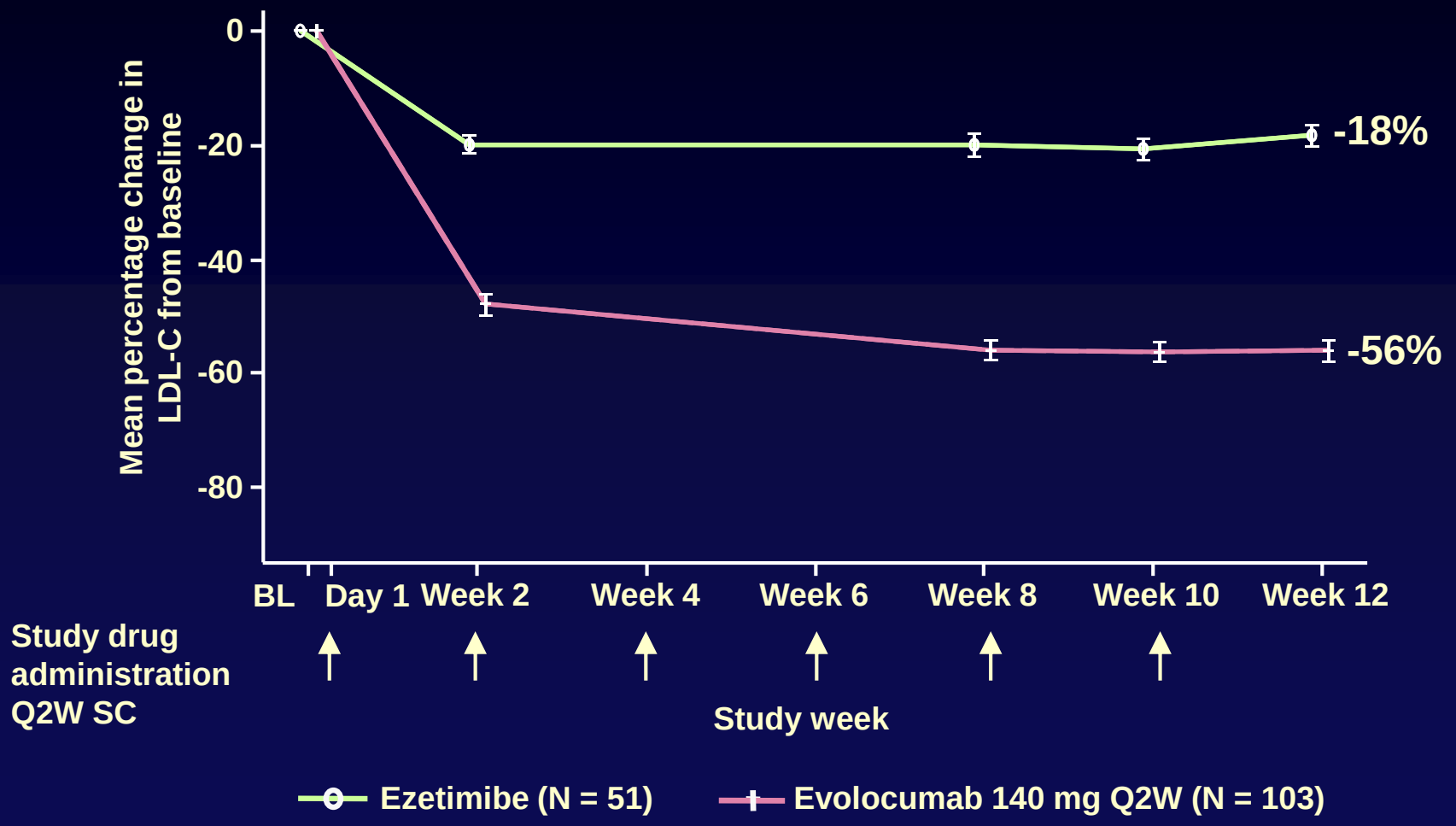


Evolocumab in hyperlipidemic CV-patients
DESCARTES



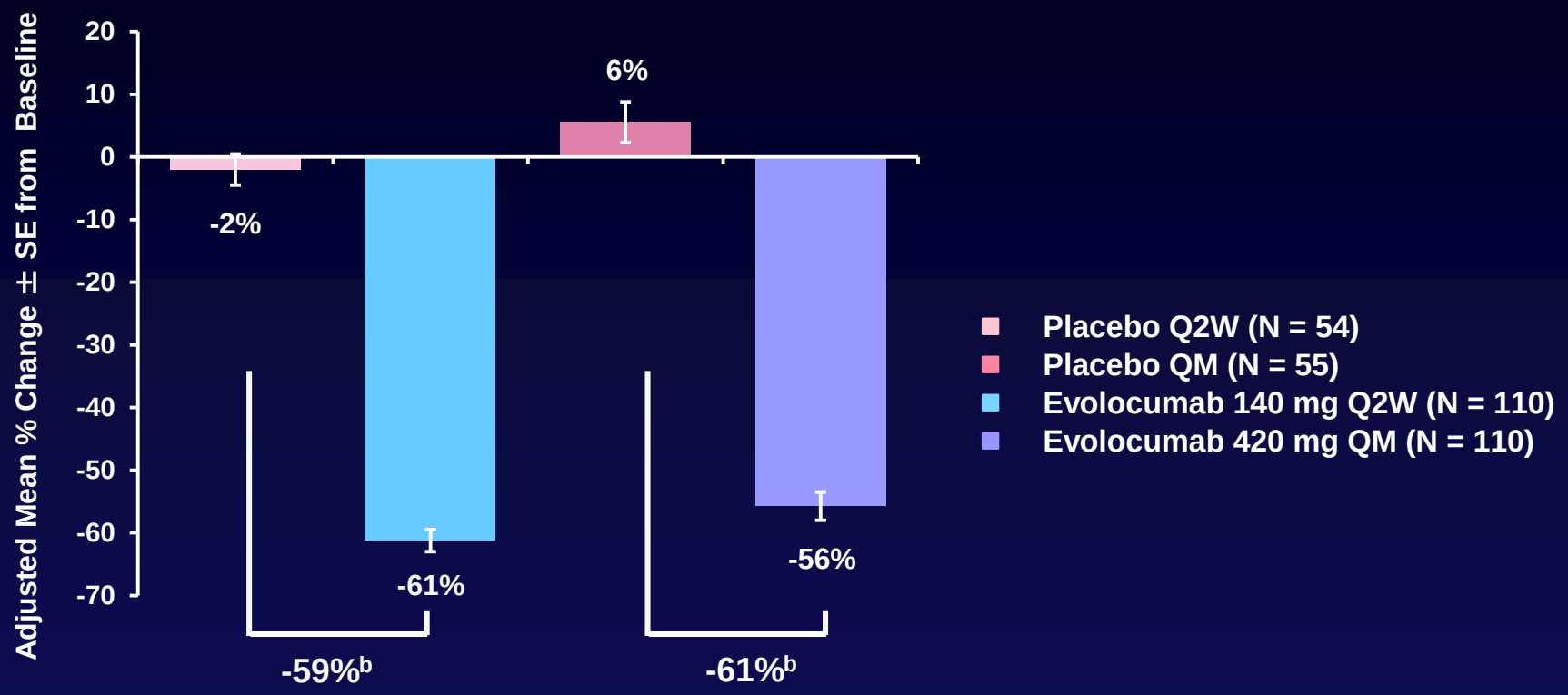
Blom et al. N Engl J Med 2014;370:1809–19

Evolocumab in Statin-intolerance
GAUSS-2



Stroes et al. J Am Coll Cardiol 2014;63:2541–8.

Evolocumab in Familial Hypercholesterolemia
RUTHERFORD-2



[a] Determined by the Friedewald formula with reflexive testing via preparative ultracentrifugation when calculated LDL-C was < 40 mg/dL or triglyceride levels were > 400 mg/dL

[b] P < 0.001; placebo-adjusted treatment difference analyzed using repeated measures model which included treatment group, stratification factors (from IVRS), scheduled visit and the interaction of treatment with scheduled visit as covariates

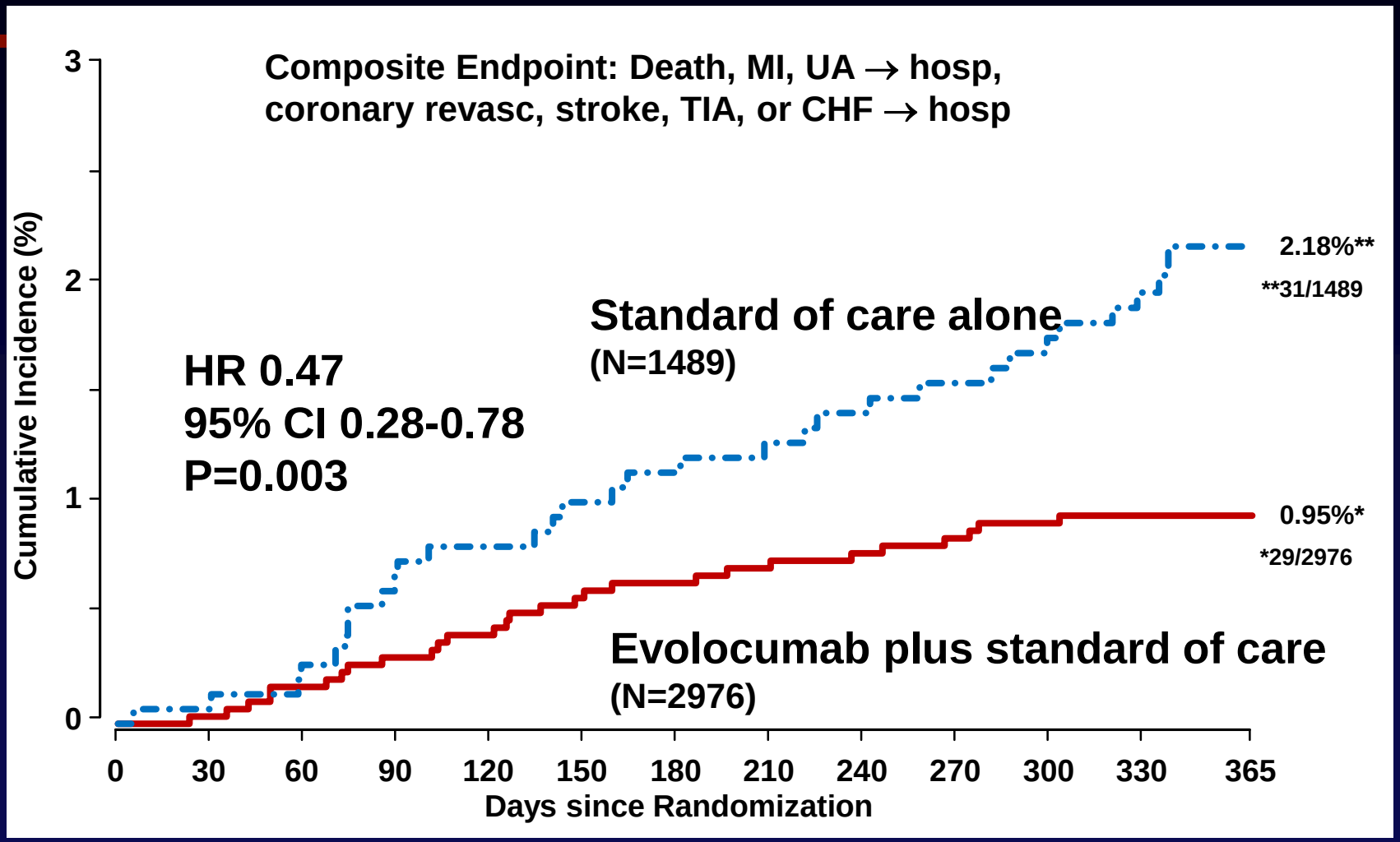
LDL-C, low-density lipoprotein cholesterol; Q2W, biweekly; QM, monthly; SE, standard error

Evolocumab and safety
OSLER

	Evolocumab subjects stratified by minimum achieved LDL-C				All EvoMab (n=2976)	SOC Alone (n=1489)
	<25 mg/dL (n=773)	25 to <40 mg/dL (n=759)	<40 mg/dL (n=1532)	≥40 mg/dL (n=1426)		
Adverse Events (%)						
Any	70.0	68.1	69.1	70.1	69.2	64.8
Serious	7.6	6.9	7.2	7.8	7.5	7.5
Muscle-related	4.9	7.1	6.0	6.9	6.4	6.0
Neurocognitive	0.5	1.2	0.8	1.0	**0.9**	**0.3**
Lab results (%)						
ALT/AST >3×ULN	0.9	0.8	0.8	1.3	1.0	1.2
CK >5×ULN	0.4	0.9	0.7	0.5	0.6	1.2

Sabatine MS et al. N Engl J Med 2015;372:1500-1509

Evolocumab and Cardiovascular Events¶
OSLER



¶CVD clinical outcomes (prespecified, exploratory): adjudicated by TIMI Study Group CEC, blinded to treatment Included death, myocardial infarction, unstable angina requiring hospitalization, revascularization, stroke or transient ischemic attack and Heart failure requiring hospitalization

Sabatine MS et al. N Engl J Med 2015;372:1500-1509

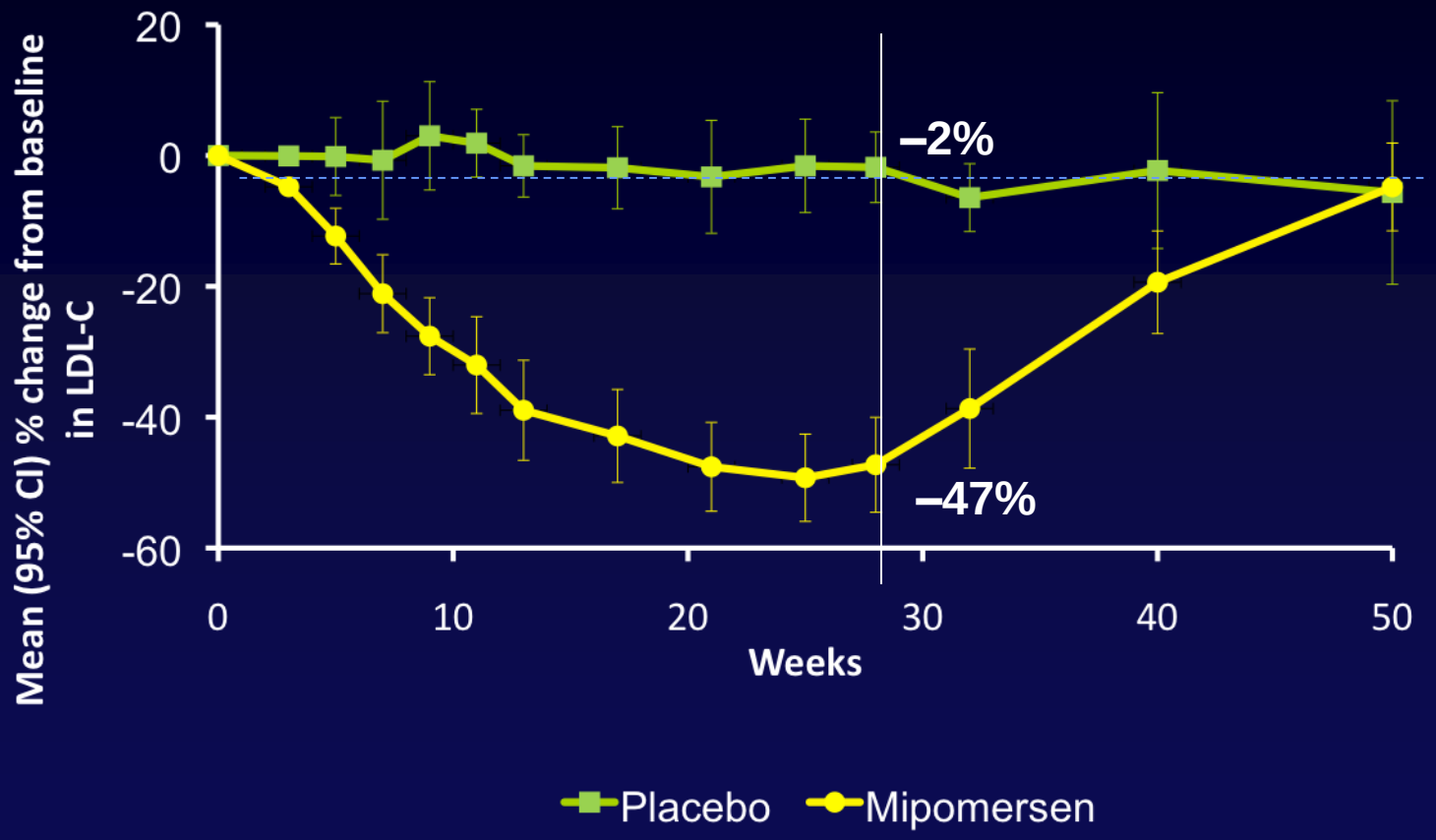
Outline

- Best lipid target
- Need for more LDL-c lowering
- ‘Study’ evidence
- **Competition for LDL-c lowering**

The competitive landscape for LDLc lowering

- **Apo B mRNA antisense**
- Microsomal Triglyceride Transfer Protein inhibitors
- Cholesteryl-ester transfer protein inhibitors

ApoB antisense reduces LDL-c
in patients with statin intolerance



Akdim, Stroes, Eur H J 2012

Safety and tolerability issues
for apoB antisense

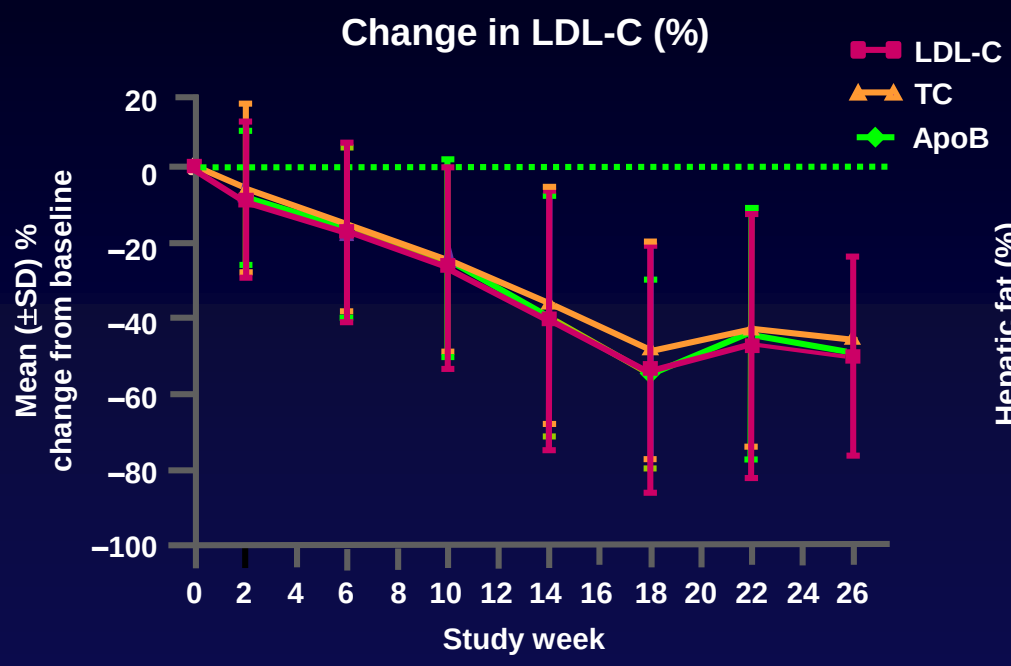
- Injection site reactions *(target-independent)*
- Hepatic steatosis *(target-dependent)*
- Heterogeneity of response *(target-dependent)*

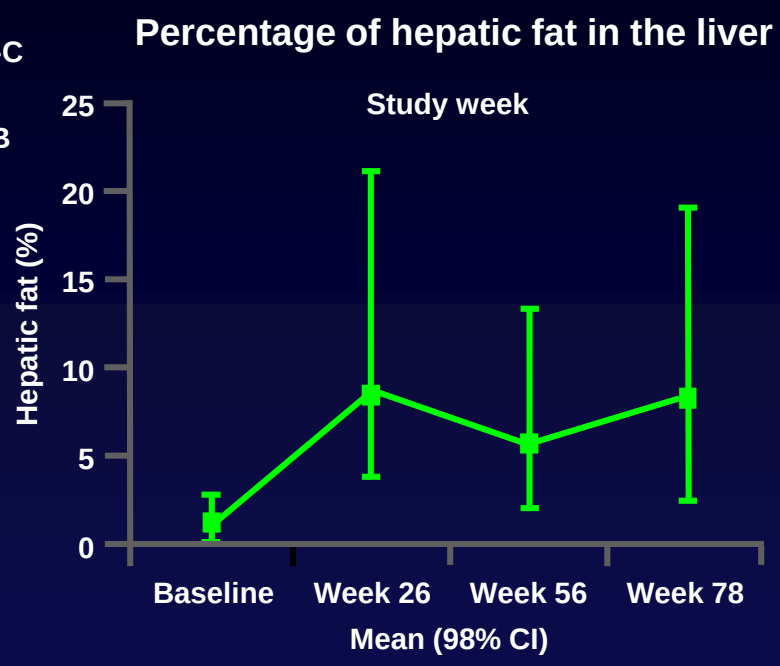
the competitive landscape of LDLc lowering

- Apo B mRNA antisense drugs
- **Microsomal Triglyceride Transfer Protein inhibitors**
- Cholesteryl-ester transfer protein inhibitors

Efficacy and safety of lomitapide in HoFH

open-label phase 3 study (n=29)





- Dose escalation biweekly: 5–60 mg
- LDL-C ↓ 50%, ApoB ↓ 49%, TC ↓ 45% (23/29 completer population)

Cuchel M et al. Lancet 2013; 381: 40–6.

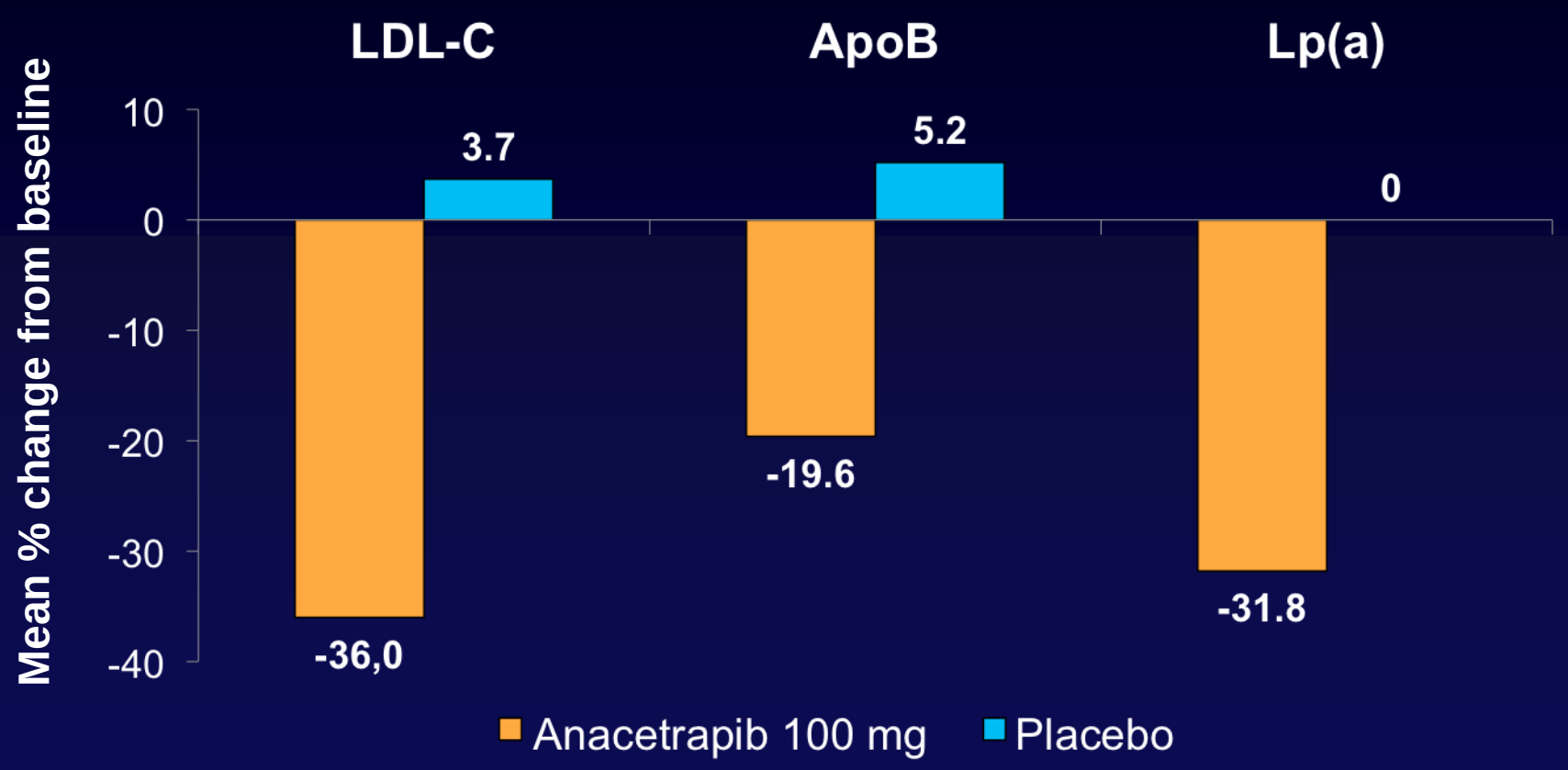
Safety and tolerability issues
for MTP-inhibition using Lomitapide

- **Gastrointestinal complaints**
  - Reported by 27 (93%) of 29 patients
  - Decreased by maintaining strict fat-restriction
- **Transaminase elevations**
  - 10 (34%) of 29 patients had elevation in ALT/ AST ≥3x ULN
- **Hepatic fat**
  - 18 (78%) of patients exhibited increase in hepatic fat > 5%
    3 (13%) of patients exhibited increase in hepatic fat >20%

The competitive landscape of LDLc lowering

- Apo B mRNA antisense drugs
- Microsomal Triglyceride Transfer Protein inhibitors
- **Cholesteryl-ester transfer protein inhibitors**

CETP inhibition by Anacetrapib lowers LDL-c
in patients with Heterozygous FH



Kastelein JJ et al. Lancet 2015

Summary for CETP inhibitor therapy

- Efficacy:
  - 30 – 50% lowering of LDL-c
  - 60-120% increase of HDL-c

- Safety:
  - No significant side effects ‘to date’
  -

- Ongoing endpoint studies:

REVEAL	Anacetrapib	30.000 patients	2017
ACCELERATE	Evacetrapib	11.000 patients	discontinued

Conclusion: PCSK9 antibodies
Happy few or all high risk ?

- **ONLY after maximal tolerated dose of effective statin ± ezetimibe *and***
  - **Very high risk: LDL-C > 'goal' in patients with 'progressive' CVD**
  - **Fam hyperchol: LDL-C >> 'goal' in patients with FH**
  - **Stat. intolerant: LDL-C > 'goal' after repetitive statin de/rechallenges**
  - **Homo.FH: Prior to mipomersen or lomitapide**
    (tolerability, serious side effects and cost)

- **Choice of dose and regimen**
  - **Alirocumab 75mg Q2W ~50% and 150mg Q2W for 60% LDL-C ↓**
  - **Evolocumab 140 mg Q2W and 420mg QM for 60% LDL-C ↓**