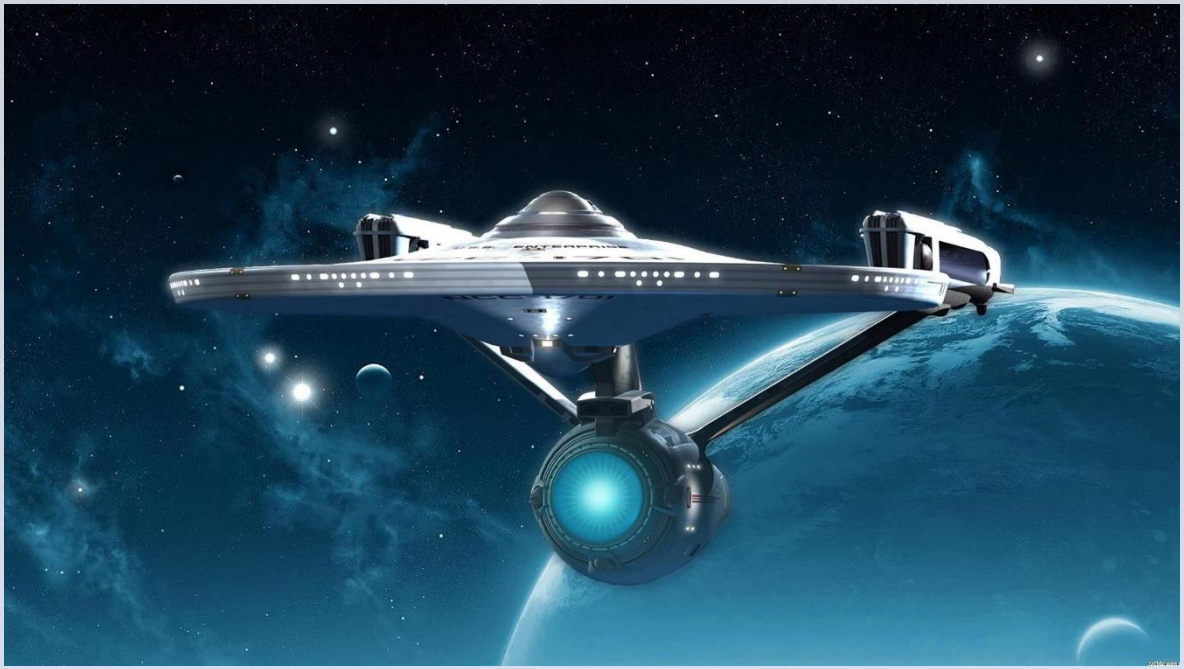
חזיתות חדשות בטיפול בכולסטרול - היישום העדכני לאור הגיידלנס החדשים



Elad Asher, M.D, M.H.A
Head CICU, Interventional Cardiologist,
Jesselson Integrated Heart Center,
Shaare Zedek Medical Center
Jerusalem, Israel

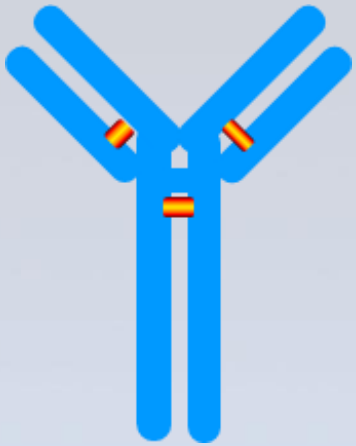
בחסות SANOFI

Outline

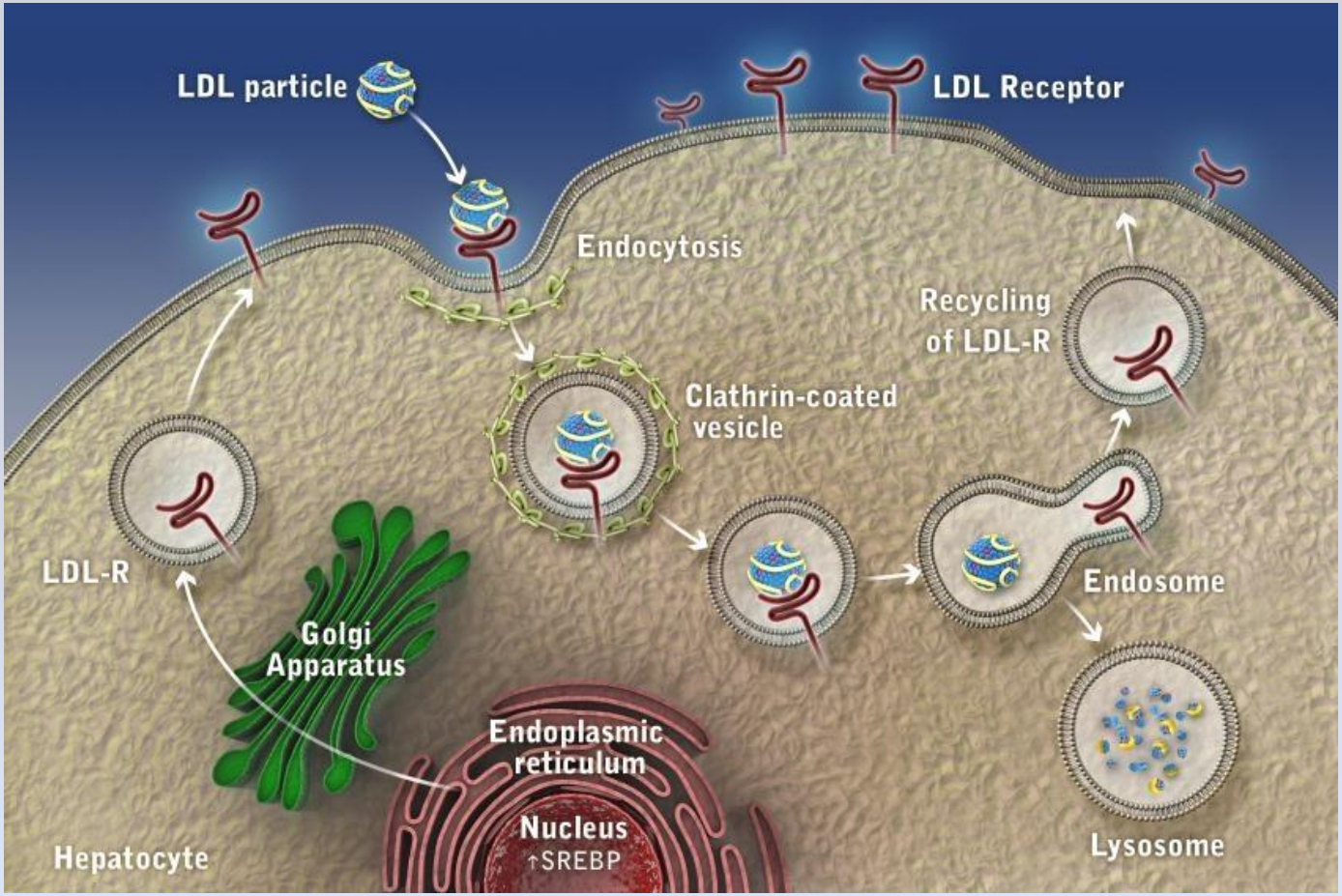
- Background
- Results of PCSK9i CVOT trials: Fourier & ODYSSEY outcomes
- Very low LDL-C levels – Safety
- PCSK9i indication and Availability

α-PCSK9

נוגדן
חד שבטי
אנושי לחלוטין
כנגד החלבון PCSK9



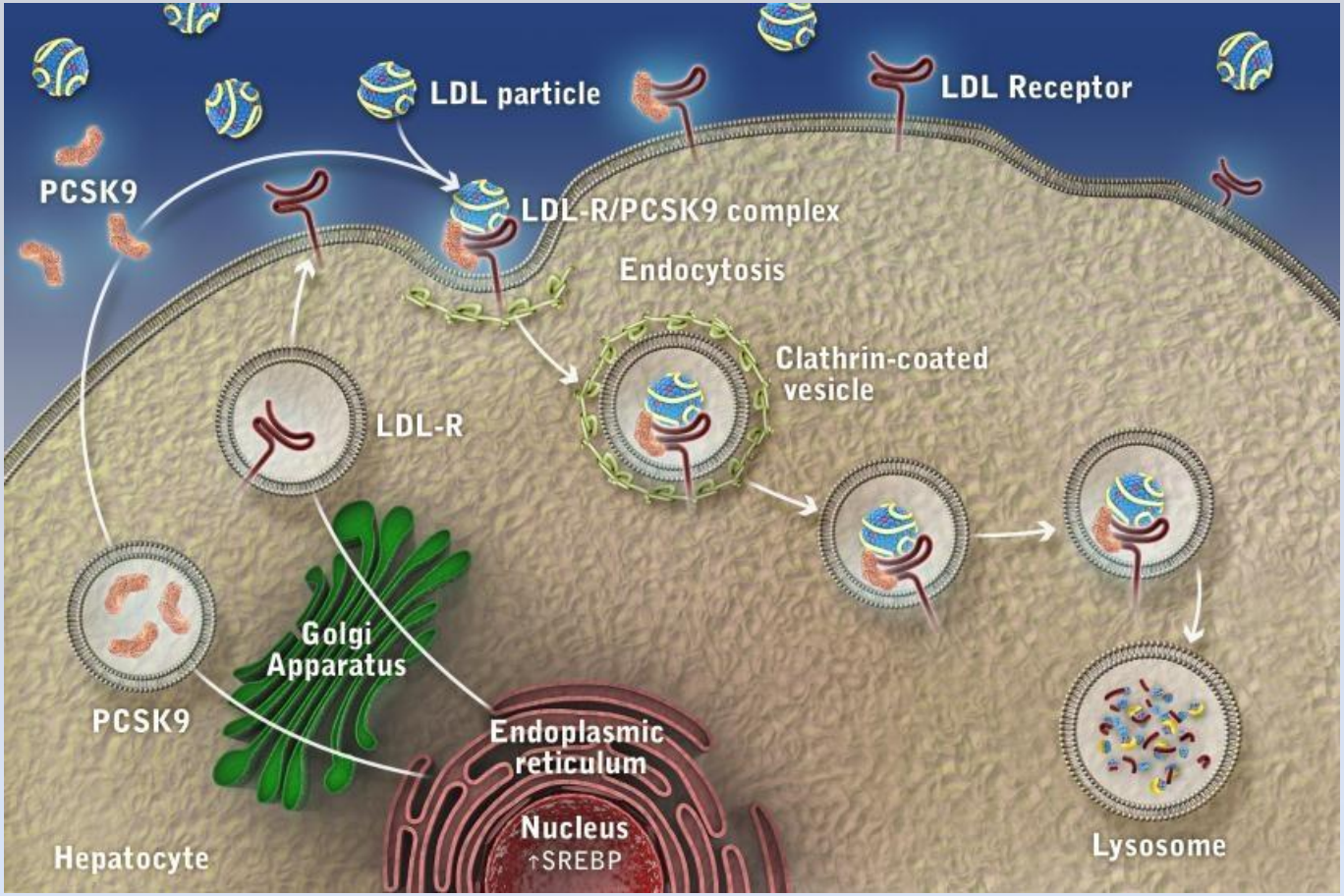
LDL receptor function and life cycle



SREBP-2, sterol regulatory element-binding protein-2

Semenkovich CF et al. In: Williams Textbook of Endocrinology, Melmed S et al. (Eds), 12th ed. Philadelphia, Elsevier Saunders 2011, pp. 1633–74

LDL receptor function and life cycle



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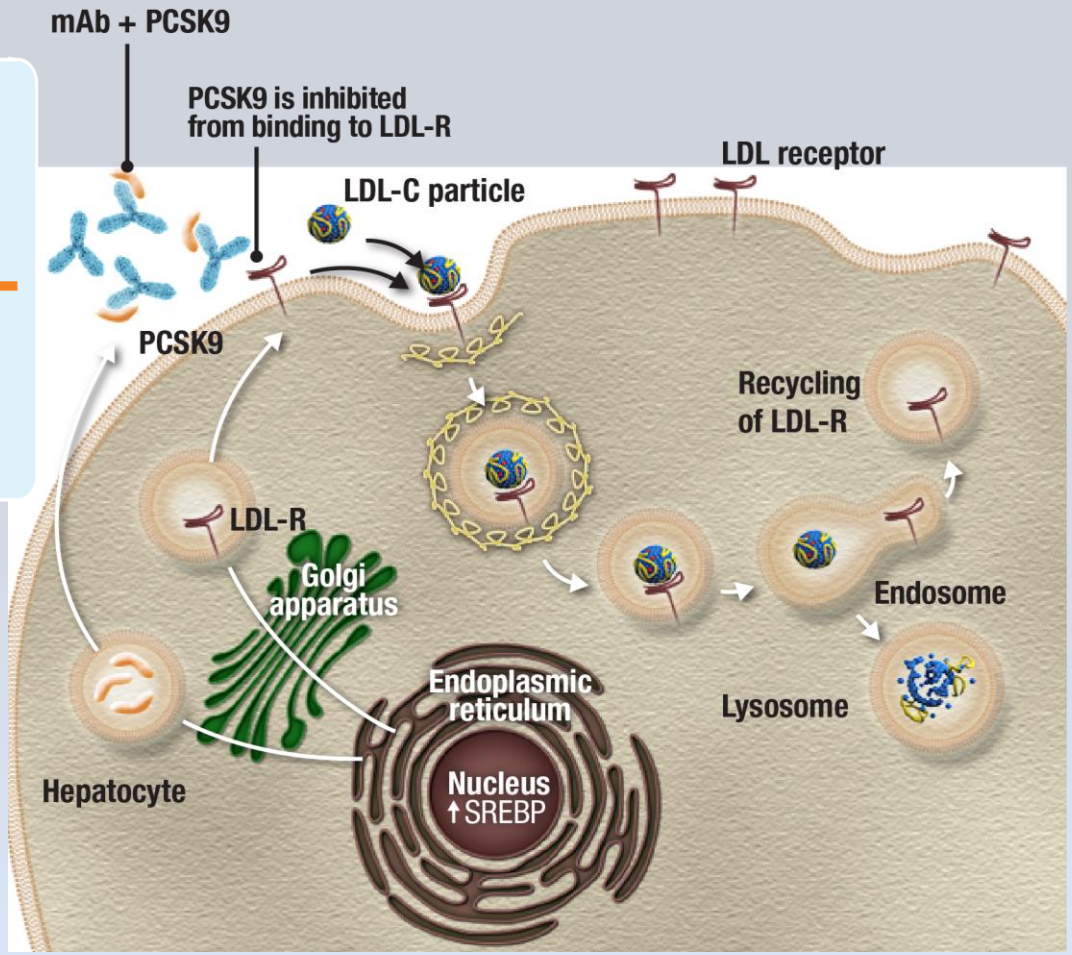
PCSK9 inhibition

PCSK9 → LDLR → LDL-C

PCSK9 → LDLR → LDL-C

פראלואנט הינה נוגדן חד שבטי אנושי לחלוטין כנגד החלבון PCSK9



Overview of ODYSSEY Phase III Program

22 global trials, including more than 29,000 patients across more than 3,000 study centers

HeFH population	HC in high CV risk population	Additional populations/studies
Add-on to max tolerated statin (± other LMT)	Add-on to max tolerated statin (±other LMT)	
	ODYSSEY OUTCOMES (EFC11570) N=18,600 **Event-driven, 2 year minimum follow-up** **Enrollment Completed Nov 2015 [Ongoing]** ✓	
ODYSSEY OLE (LTS13463) N=1000 18 months **[Ongoing]**	**ODYSSEY COMBO I** (EFC11568) N=316 12 months ✓	**ODYSSEY MONO** (EFC11716) N=103 6 months ✓
ODYSSEY FH I (EFC12492) N=486 18 months ✓	**ODYSSEY COMBO II** (EFC11569) N=720 24 months ✓	**ODYSSEY ALTERNATIVE** (CL1119) N=314 6 months (+OLE) ✓
ODYSSEY FH II (CL1112) N=249 18 months ✓	**ODYSSEY EAST** (EFC13389) N=600 6 months **[Ongoing]**	**ODYSSEY OPTIONS I** (CL1110) N=355 6 months ✓
ODYSSEY HIGH FH (EFC12732) N=107 18 months ✓	**ODYSSEY KT** (EFC14074) N=199 6 months ✓	**ODYSSEY OPTIONS II** (CL1118) N=305 6 months ✓
ODYSSEY LONG TERM (LTS11717) N=2,341 18 months ✓		**ODYSSEY CHOICE I** (CL1308) 300 mg Q4w dosing , 12 months ✓
ODYSSEY JAPAN (EFC 13672) N=216 12 months ✓		**ODYSSEY CHOICE II** (EFC13786) N=233 150 mg Q4W dosing, 6 months (+OLE) ✓
ODYSSEY APPRISE (LPS14245) N=1300 3 – 30 months **[Ongoing]**		**ODYSSEY NIPPON** (EFC14305) N=159 3 months (+OLE) ✓
ODYSSEY ESCAPE (R727-CL-1216) N=63 4 months ✓	**ODYSSEY DM – Insulin** (LTS14354) N=500 6 months ✓	
	ODYSSEY DM – Dyslipidemia (LTS14355) 6 months ✓	

Core Registrational Studies

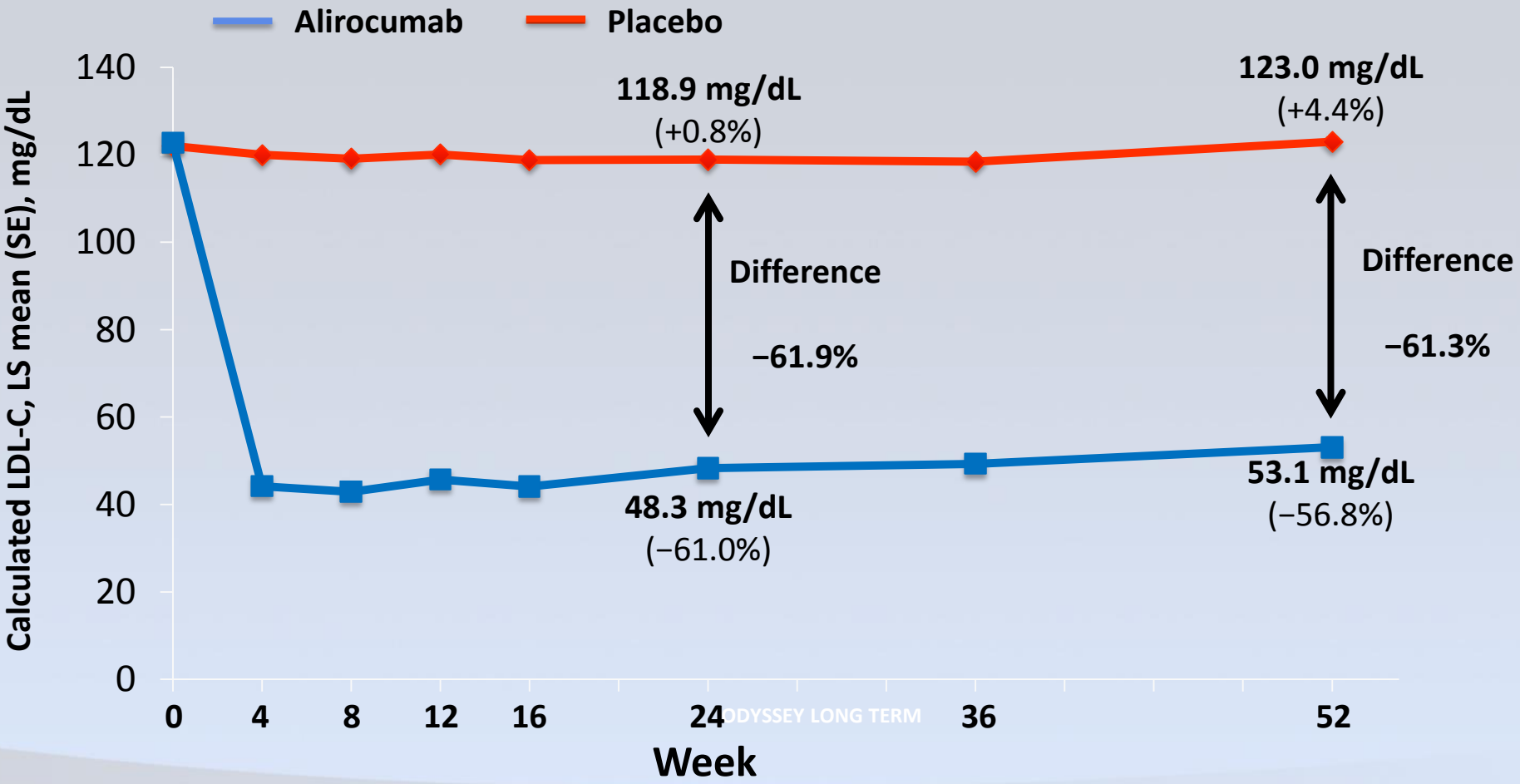
✓ Primary endpoint met; data presented or published

Jesselson Integrated Heart Center
Shaare Zedek Medical Center, Jerusalem

מרכז הלב המשולב ע"ש ג'סלזון
מרכז רפואי שערי צדק, ירושלים

PCSK9 inhibition ➡lowers LDL-C consistently over time

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



Intent-to-treat (ITT) analysis

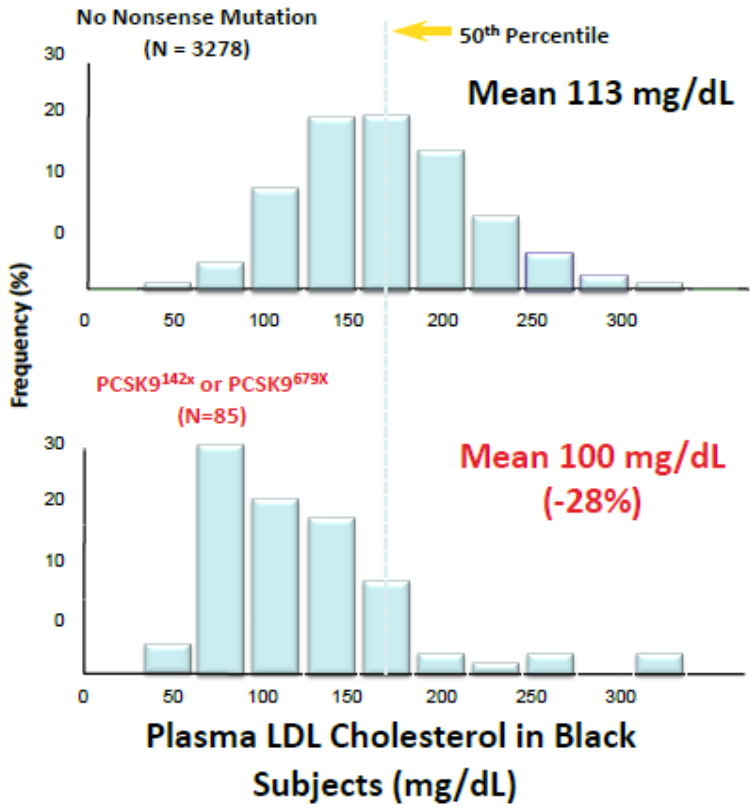
N Engl J Med 2015;372:1489-99

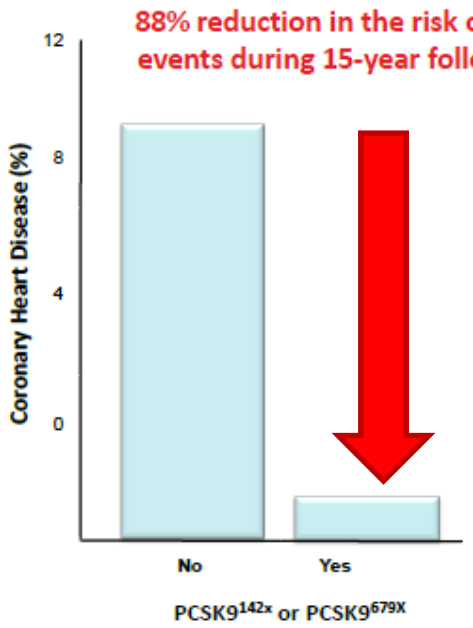
PCSK9 inhibition ➡lowers LDL-C.

Will it lower event rates??

PCSK9 inhibition -Will it lower event rates? Genetic evidence

LoF PCSK9 mutations are associated with low LDL-C and low prevalence of CHD events





ARIC=Atherosclerosis Risk in the Community
Adapted from Cohen JC. N Engl J Med 2006; 354: 1264–72.

JAMA | Original Investigation

Effect of Evolocumab on Progression of Coronary Disease in Statin-Treated Patients

The GLAGOV Randomized Clinical Trial

Objective

- To test the hypothesis that LDL-C lowering with a monthly subcutaneous injection of evolocumab 420 mg for 78 weeks will result in a significantly greater change from baseline in percentage atheroma volume (PAV) compared with placebo in subjects taking background statin therapy

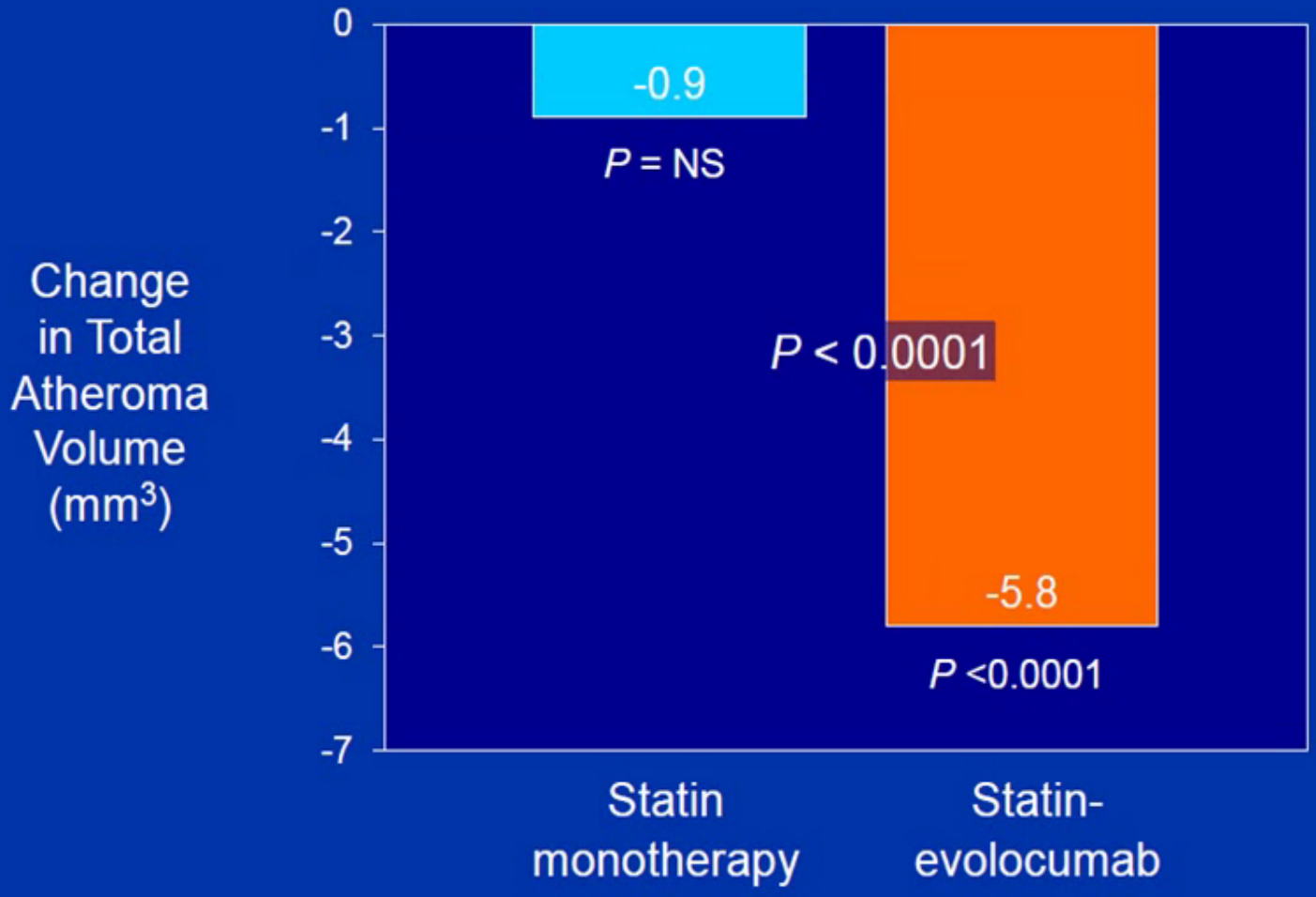
Design

- A 76-week, randomized, double-blind, placebo-controlled, multicenter, phase 3 study.
- 968 Participants with angiographic coronary disease were randomized to receive monthly evolocumab (420mg) (n = 484) or placebo (n = 484) via subcutaneous injection for 76 weeks, in addition to statins

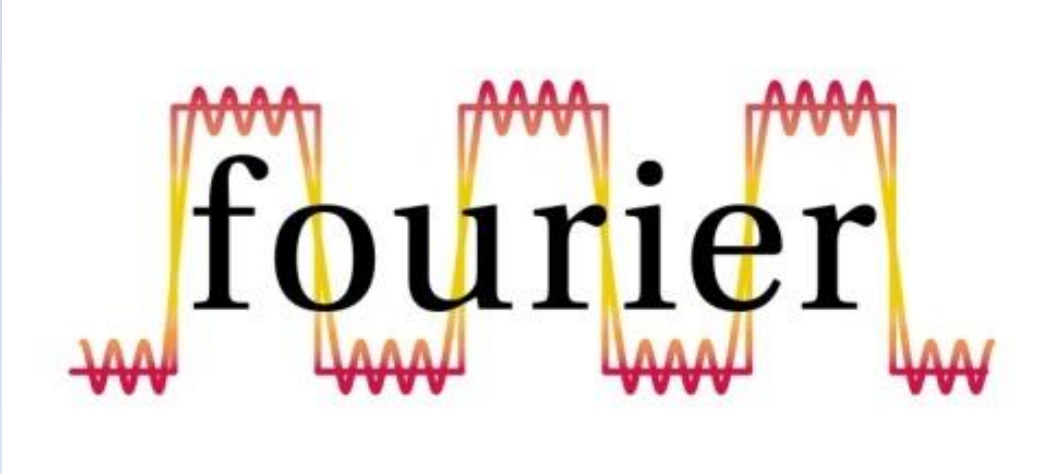
Nicholls SJ, et al. JAMA. [published online ahead of print November 15, 2016]. doi: 10.1001/jama.2016.16951.
Puri R, et al. Am Heart J. 2016;176:85-92.

GLAGOV Presentation – AHA 2016

Secondary Endpoint: Total Atheroma Volume



PCSK9 inhibition -Will it lower event rates?
CV OUTCOMES trials



Main differences in study design between FOURIER and ODYSSEY OUTCOMES

	FOURIER[1]	ODYSSEY OUTCOMES[2]
Population	N=27,564	N=18,312
	Established ASCVD ~3 yrs prior to randomization= (Stable CVD) **LDL-C ≥70 mg/dL or non-HDL-C ≥100 mg/dL**	**Recent ACS ≤ 1 year (median time : 2.6 months prior to randomization) LDL-C ≥70 mg/dL or non-HDL-C ≥100 mg/dL or ApoB ≥80 mg/dL**
Background therapy	**High (69%) or moderate (30%) intensity statin therapy**	**89.5% on high-intensity statin**
Median Follow-up (Median, Max)	**2.2 years Max 3 years**	**2.8 years** **44% pts with follow-up ≥3 years** **Max 5 years**

1. Sabatine MS *et al.* N Engl J Med. 2017 Mar 17. doi: 10.1056/NEJMoa1615664 2. Roth EM, Diller P. Future Cardiol 2014;10:183–99

FOURIER Trial Design

27,564 high-risk, stable patients with established CV disease
(prior MI, prior stroke, or symptomatic PAD)

Median time from most recent event
~3 yrs

Background therapy : On an **effective statin dose***
High intensity (69%) statin therapy (± 5% ezetimibe)

LDL-C ≥70 mg/dL or
non-HDL-C ≥100 mg/dL

Median baseline LDL-C:
92 mg/dl

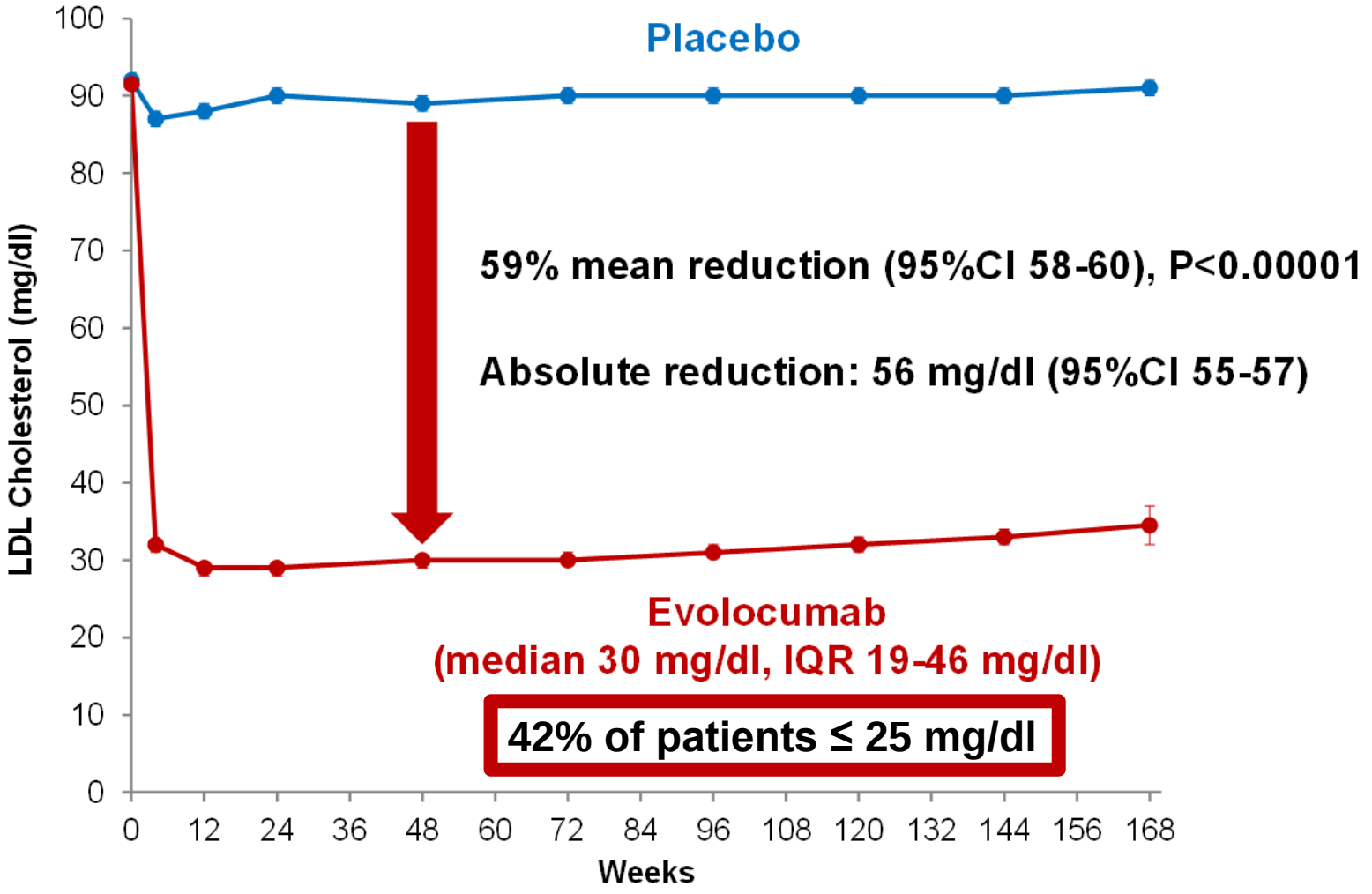
Evolocumab
(N=13,784)
140 mg Q2W or 420 mg QM

Placebo
(N=13,780)
Q2W or QM

Follow-up
median 26 months, Max 3 years

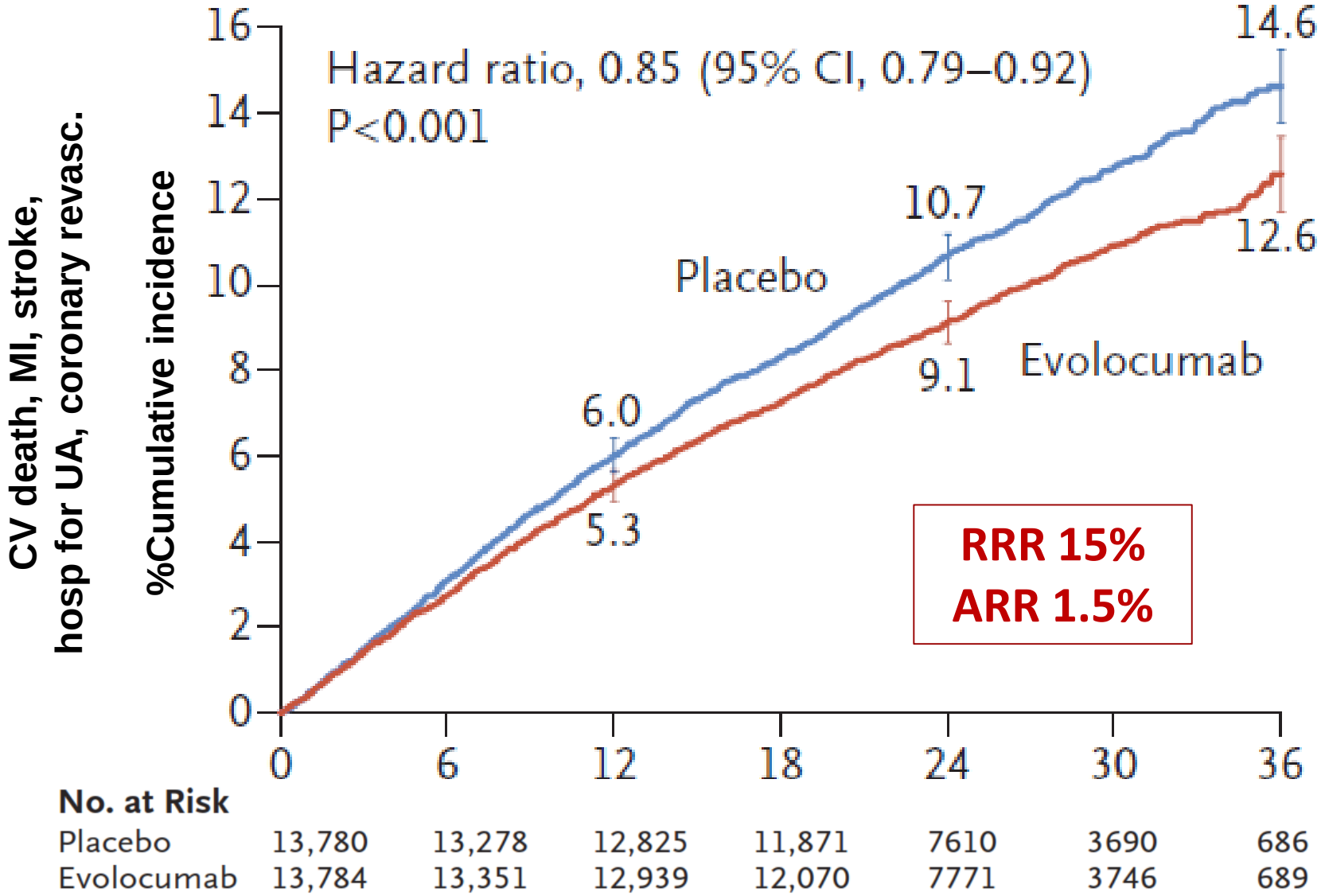
*on atorvastatin 20-80 mg or rosuvastatin 5-40mg, simvastatin 40-80mg, pitavastatin 4mg

LDL-C Reduction



Sabatine MS *et al.* N Engl J Med. 2017 Mar 17. doi: 10.1056/NEJMoa1615664.

Cumulative event rates for the Primary Efficacy end point



RRR, Rela

Moa1615664.

Types of CV Outcomes

Endpoint		Evolocumab (N=13,784)	Placebo (N=13,780)	HR (95% CI)
		3-yr Kaplan-Meier rate		
CV Death, MI, stroke, UA, or revasc	***15% RRR***	**12.6**	**14.6**	**0.85 (0.79-0.92)**
Cardiovascular death	⟺	**2.5**	**2.4**	**1.05 (0.88-1.25)**
MI	**27% RRR**	**4.4**	**6.3**	**0.73 (0.65-0.82)**
Stroke	**21% RRR**	**2.2**	**2.6**	**0.79 (0.66-0.95)**
Hosp for unstable angina	⟺	**2.2**	**2.3**	**0.99 (0.82-1.18)**
Coronary revasc	**22% RRR**	**7.0**	**9.2**	**0.78 (0.71-0.86)**
Urgent		3.7	5.4	0.73 (0.64-0.83)
Elective		3.9	4.6	0.83 (0.73-0.95)

Sabatine MS, *et al*. N Engl J Med. 2017;376(18):1713-1722.

Study Design

ODYSSEY OUTCOMES

18,924 Post-ACS patients (1 to 12 months)

Median time from most recent event ~2.6 months

~ 90% On High-intensity statin therapy*
Atorvastatin 40 to 80 mg daily or
Rosuvastatin 20 to 40 mg daily or
Maximum tolerated dose of one of these agents for ≥2 weeks

LDL-C ≥70 mg/dL or
Non-HDL-C ≥100 mg/dL or
Apolipoprotein B ≥80 mg/dL

Median baseline LDL-C: 87 mg/dl

Alirocumab SC Q2W (N=9462)

Placebo SC Q2W (N=9462)

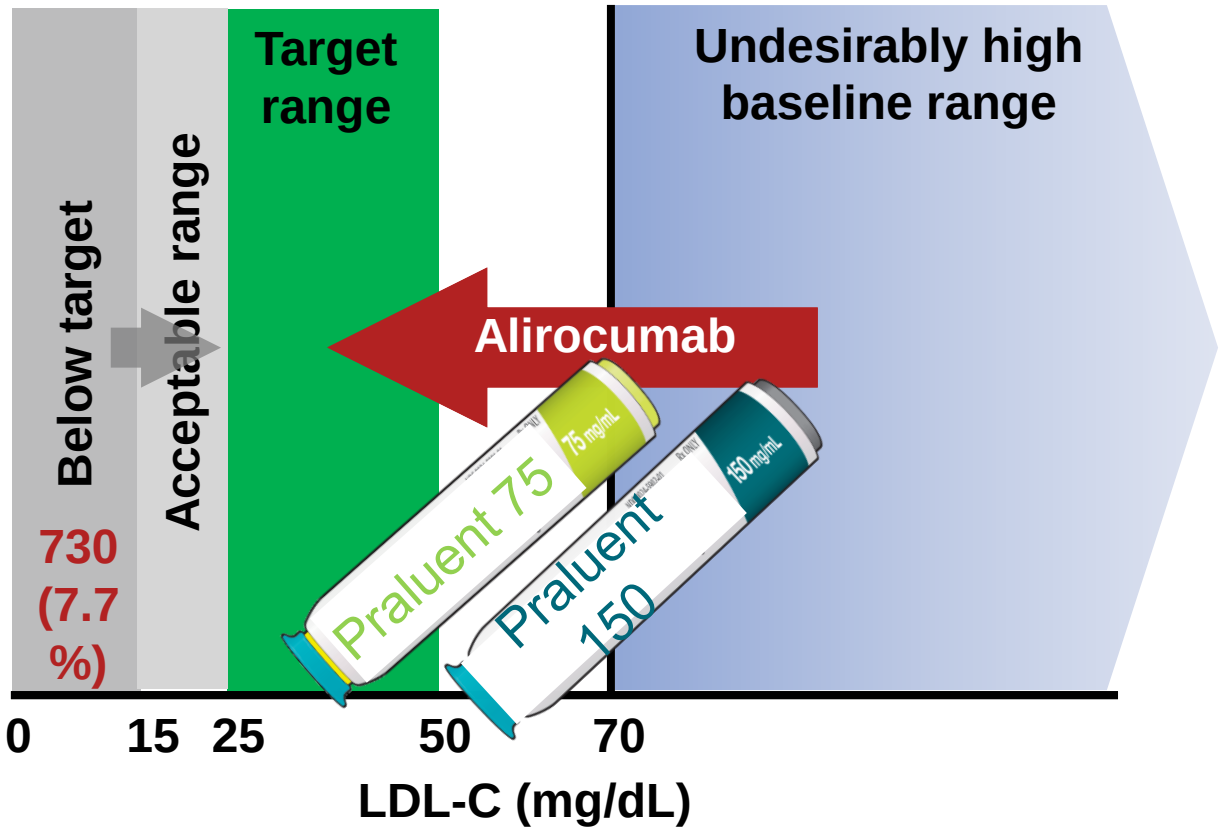
Follow-up*: median 2.8 years, Max 5 years
8242 (44%) patients with potential follow-up ≥3 years

Schwartz GG, et al. Am Heart J 2014;168:682-689.e1.

SANOFI REGENERON

Treat-to-target approach

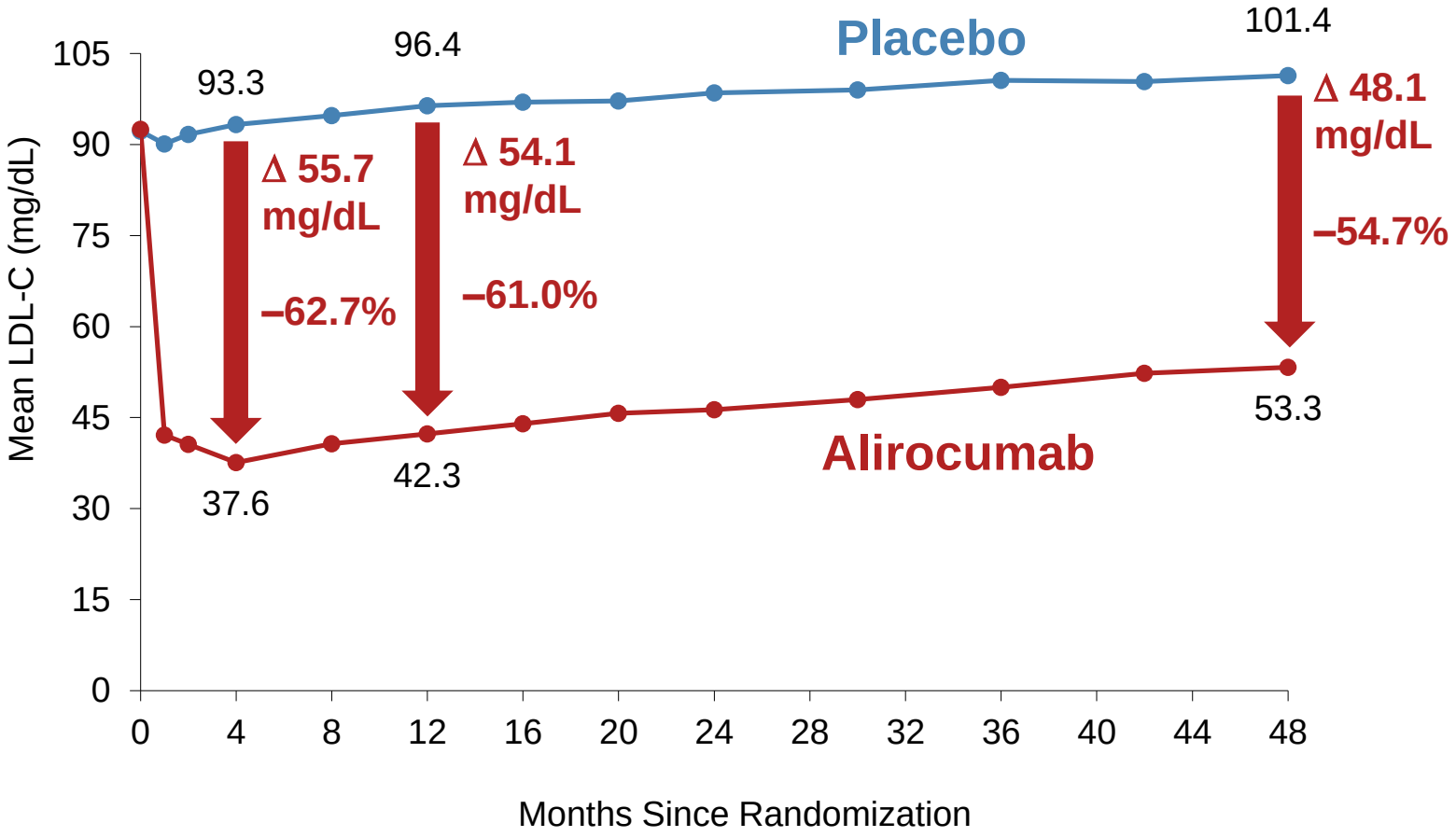
maximize the number of patients in the target range and minimize the number below target



Schwartz GG, et al. Am Heart J 2014;168:682-689.e1.

SANOFI REGENERON

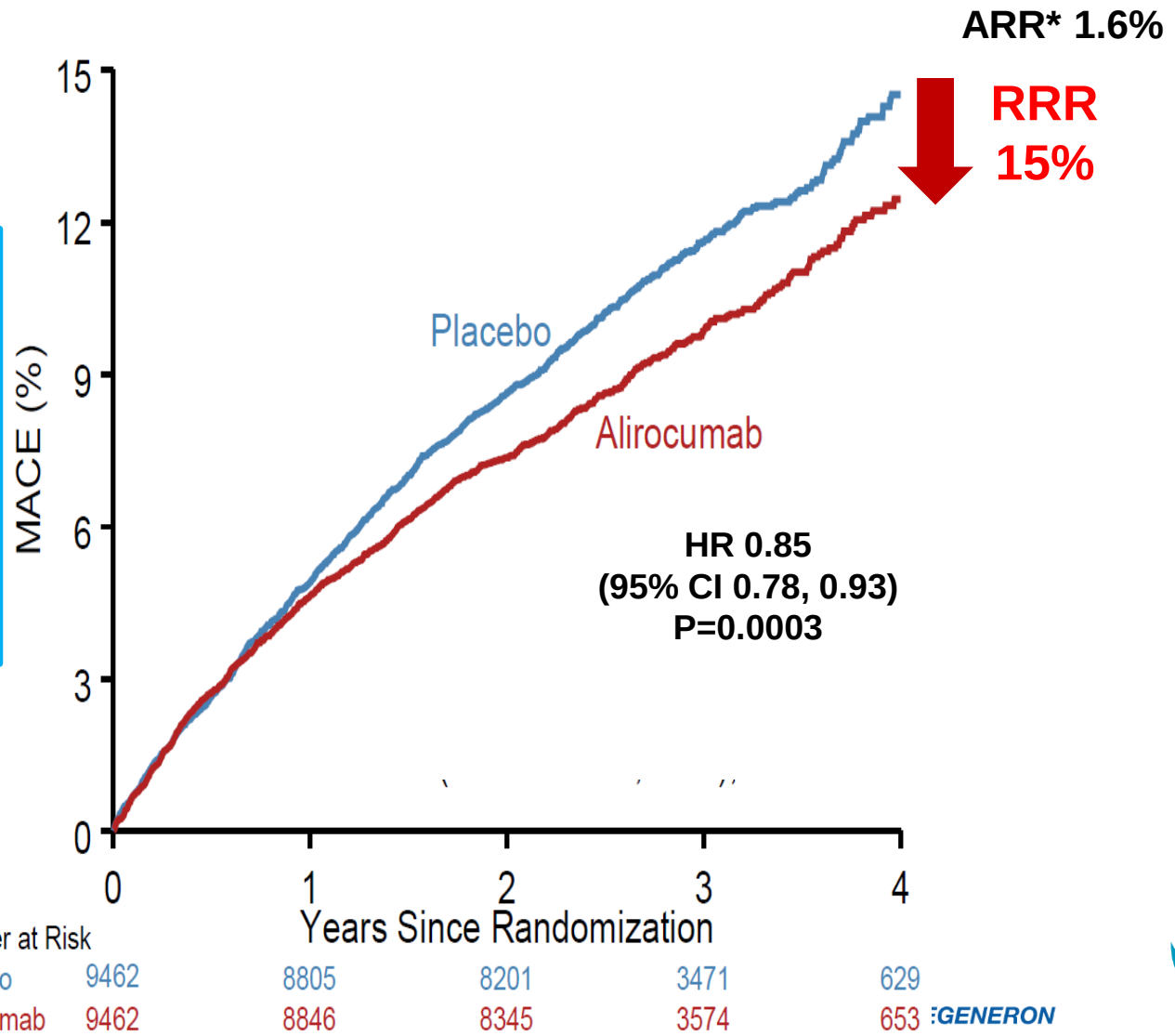
LDL-C: On-Treatment Analysis



Excludes LDL-C values after premature treatment discontinuation or blinded switch to placebo
Approximately 75% of months of active treatment were at the 75 mg dose

Primary Efficacy Endpoint: MACE

MACE:
- CHD death
- Non-fatal MI
- Ischemic stroke
- unstable angina requiring hospitalization



*Based on cumulative incidence

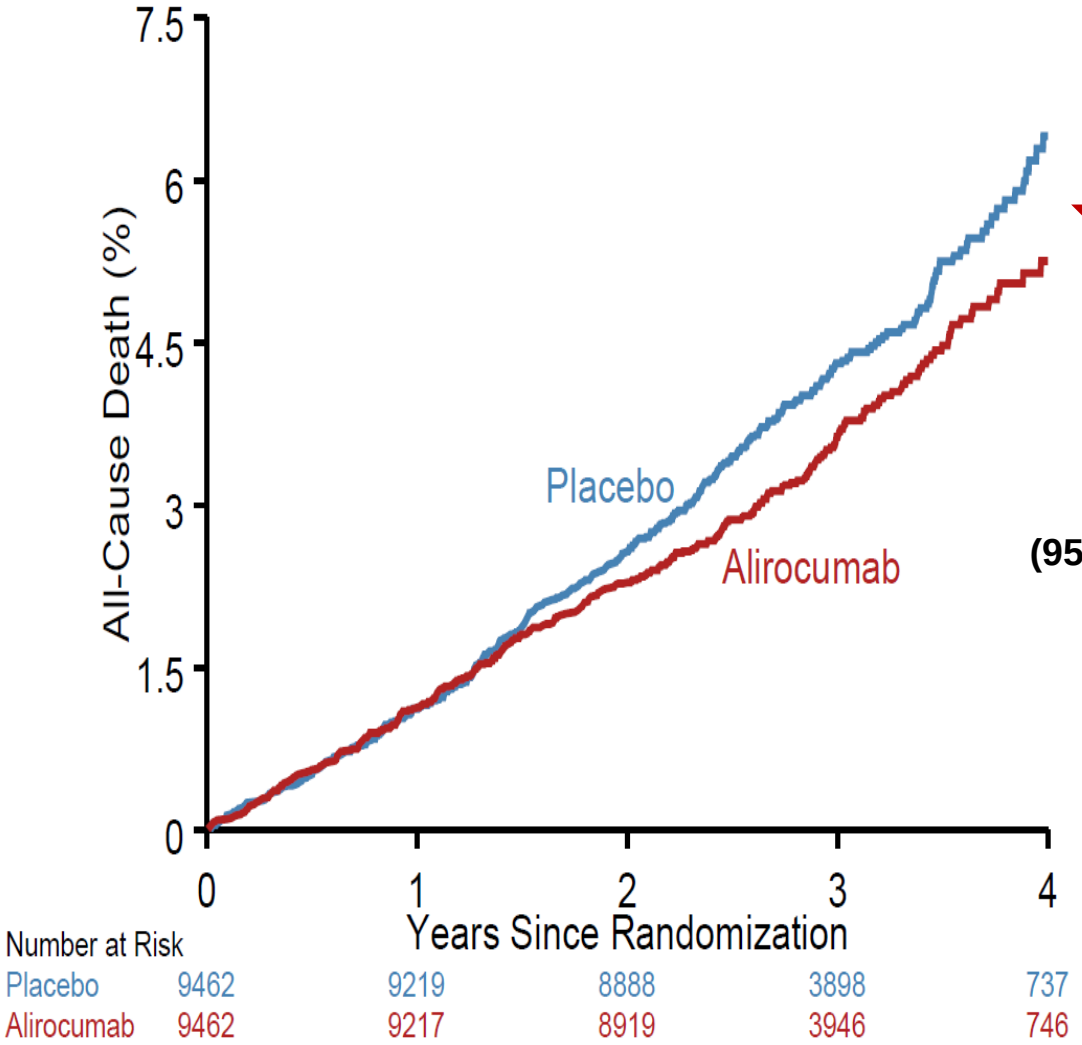
Primary Efficacy and Components

ODYSSEY OUTCOMES

Endpoint, n (%)	Alirocumab (N=9462)	Placebo (N=9462)	HR (95% CI)	Log-rank P-value
MACE	**903 (9.5)**	**1052 (11.1)**	**0.85 (0.78, 0.93) ↓ 15%**	**0.0003**
CHD death	**205 (2.2)**	**222 (2.3)**	0.92 (0.76, 1.11) **8%**	0.38
Non-fatal MI	**626 (6.6)**	**722 (7.6)**	0.86 (0.77, 0.96) ↓ **14%**	0.006
Ischemic stroke	**111 (1.2)**	**152 (1.6)**	0.73 (0.57, 0.93) ↓ **27%**	0.01
Unstable angina	**37 (0.4)**	**60 (0.6)**	0.61 (0.41, 0.92) ↓ **39%**	0.02

SANOFI REGENERON

All-Cause Death



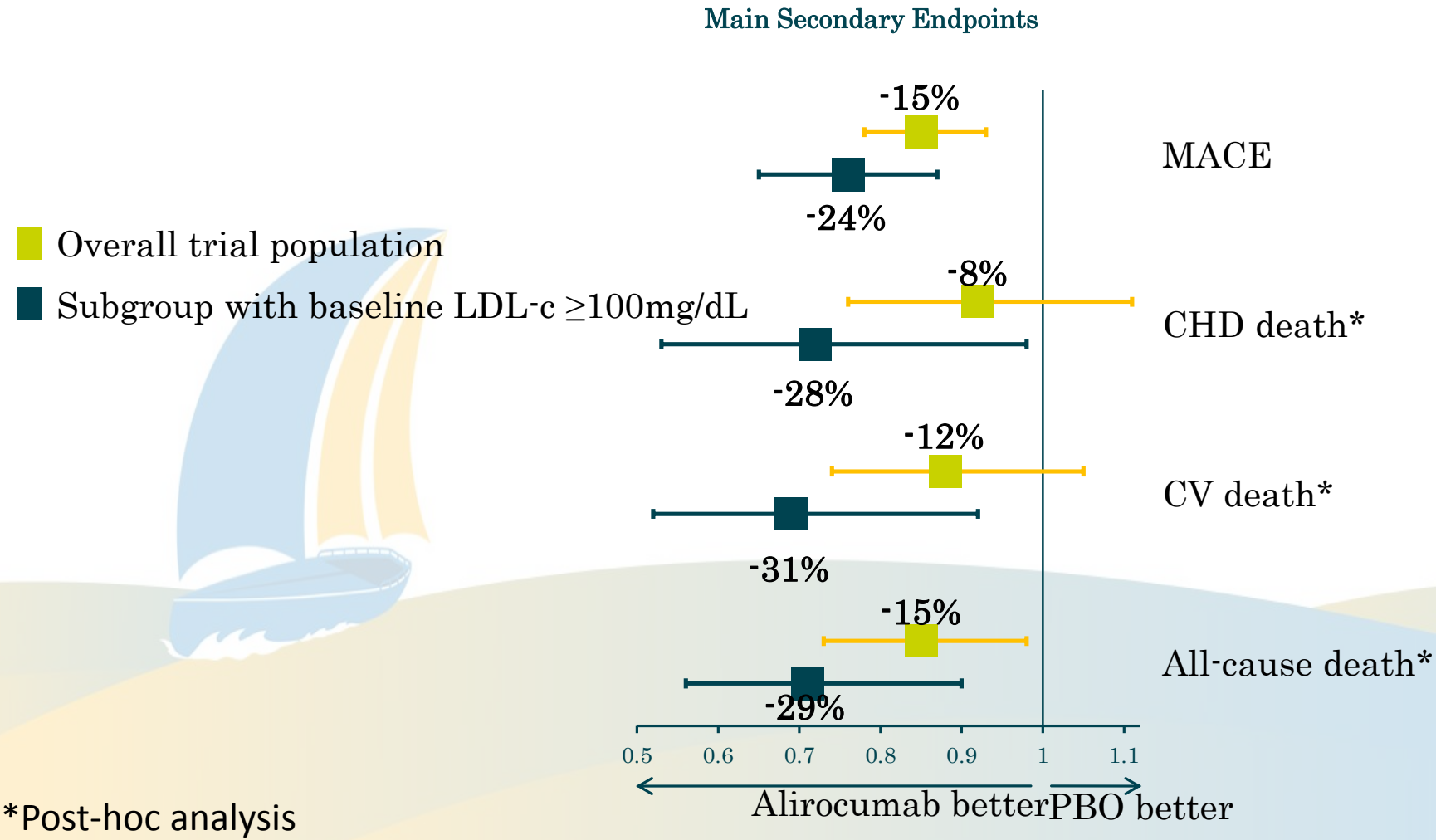
ARR † 0.6%

RRR 15%

HR 0.85
(95% CI 0.73, 0.98)
P=0.026*

*Nominal P-value
†Based on cumulative incidence

Overall efficacy vs subgroup with Baseline LDL-c ≥100 mg/dL (Median Baseline LDL-C 118 mg/dL)



*Post-hoc analysis

ODYSSEY OUTCOMES

Safety

Treatment-emergent adverse events	Alirocumab	Placebo
Any	75.8%	77.1%
Serious	23.3%	24.9%

Laboratory value	Alirocumab	Placebo
ALT >3 × ULN, n/N (%)	2.3%	2.4%
Creatine kinase >10 × ULN, n/N (%)	0.5%	0.5%

Event	Alirocumab	Placebo	
Diabetes worsening or diabetic complications w/DM at baseline)	18.8%	21.2%	
New onset diabetes (pts w/o DM at baseline)	9.6%	10.1%	
General allergic reaction	7.9%	7.8%	
Hepatic disorder	5.3%	5.7%	
Local injection site reaction*	3.8%	2.1%	**Significantly higher vs PBO**
Neurocognitive disorder	1.5%	1.8%	
Cataracts	1.3%	1.4%	
Hemorrhagic stroke	<0.1%	0.2%	

*HR vs. placebo 1.82 (95% CI 1.54, 2.17)

http://www.acc.org/~/media/Clinical/PDF-Files/Approved-PDFs/2018/03/05/ACC18_Slides/March10_Sat/9amET-ODYSSEY-Outcomes-acc-2018.pdf

Safety

ODYSSEY OUTCOMES

Follow up -4 years

Event	Alirocumab (N=9451)	Placebo (N=9443)
Diabetes worsening or diabetic complications: *pts w/DM at baseline*, n/N (%)	506/2688 (18.8)	583/2747 (21.2)
New onset diabetes; *pts w/o DM at baseline*, n/N (%)	648/6763 (9.6)	676/6696 (10.1)
General allergic reaction, n (%)	748 (7.9)	736 (7.8)
Hepatic disorder, n (%)	500 (5.3)	534 (5.7)
Local injection site reaction, n (%)*	360 (3.8)	203 (2.1)
Neurocognitive disorder, n (%)	143 (1.5)	167 (1.8)
Cataracts, n (%)	120 (1.3)	134 (1.4)
Hemorrhagic stroke, n (%)	9 (<0.1)	16 (0.2)

*HR vs. placebo 1.82 (95% CI 1.54, 2.17)

SANOFI REGENERON

ESC
European Society of Cardiology

European Heart Journal (2019) **00**, 1–78
doi:10.1093/eurheartj/ehz455

ESC/EAS GUIDELINES

2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce cardiovascular risk*

The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)

Secondary prevention/Very high Risk

Recommendations for treatment goals for low-density lipoprotein cholesterol (1)

EAS ESC European Society of Cardiology

Recommendations	Class	Level
In secondary prevention patients at very-high risk, an LDL-C reduction of at least 50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) are recommended.	I	A
In primary prevention, for individuals at very-high risk but without FH, an LDL-C reduction of at least 50% from baseline[d] and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) are recommended.	I	C
In primary prevention, for individuals with FH at very-high risk, an LDL-C reduction of at least 50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) should be considered.	IIa	C

The term 'baseline' refers to the LDL-C level in a person not taking any LDL-C lowering medication. In people who are taking LDL-C-lowering medication(s), the projected baseline (untreated) LDL-C levels should be estimated, based on the average LDL-C-lowering efficacy of the given medication or combination of medications.

www.escardio.org/guidelines

2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

Second episode (2 years)/High risk

Recommendations for treatment goals for low-density lipoprotein cholesterol (2)

EAS ESC European Society of Cardiology

Recommendations	Class	Level
For patients with ASCVD who experience a second vascular event within 2 years (not necessarily of the same type as the first event) while taking maximally tolerated statin therapy, an LDL-C goal of <1.0 mmol/L (<40 mg/dL) may be considered.	IIb	B
In patients at high risk, an LDL-C reduction of at least 50% from baseline[d] and an LDL-C goal of <1.8 mmol/L (<70 mg/dL) are recommended.	I	A

The term 'baseline' refers to the LDL-C level in a person not taking any LDL-C lowering medication. In people who are taking LDL-C-lowering medication(s), the projected baseline (untreated) LDL-C levels should be estimated, based on the average LDL-C-lowering efficacy of the given medication or combination of medications.

www.escardio.org/guidelines

2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

Moderate/Low Risk

Recommendations for treatment goals for low-density lipoprotein cholesterol (3)

EAS ESC European Society of Cardiology

Recommendations	Class	Level
In individuals at moderate risk[c], an LDL-C goal of <2.6 mmol/L (<100 mg/dL) should be considered.	IIa	A
In individuals at low risk[c] an LDL-C goal <3.0 mmol/L (<116 mg/dL) may be considered.	IIb	A

[c] For definitions see Table 1.

www.escardio.org/guidelines

2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

Older/DM

Treatment of dyslipidaemias in older people
Treatment with statins is recommended for primary prevention, according to the level of risk, in older people aged ≤75.
Treatment of dyslipidaemias in older people
Initiation of statin treatment for primary prevention in older people aged >75 may be considered, if at high risk or above.
Treatment of dyslipidaemias in DM
In patients with T2DM at very-high risk, an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.4 mmol/L (<55mg/dL) is recommended.
In patients with T2DM at high risk, an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.8 mmol/L (<70 mg/dL) is recommended.
Statins are recommended in patients with T1DM who are at high or very-high risk.

- **New/revised concepts**

More intensive reduction of LDL-C across CV risk categories

- For secondary prevention in very-high-risk patients, an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) are recommended.
  - For patients with ASCVD who experience a second vascular event within 2 years (not necessarily of the same type as the first event) while taking maximally tolerated statin therapy, an LDL-C goal of <1.0 mmol/L (<40 mg/dL) may be considered.
- In primary prevention, for individuals at very-high risk but without FH, an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) are recommended. For individuals at very-high risk (that is, with another risk factor but without ASCVD), in primary prevention the same goals for LDL-C lowering should be considered.
- For patients at high risk, an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.8 mmol/L (<70 mg/dL) are recommended.
- For individuals at moderate risk, an LDL-C goal of <2.6 mmol/L (<100 mg/dL) should be considered.
- For individuals at low risk, an LDL-C goal of <3.0 mmol/L (<116 mg/dL) may be considered.

Changes in recommendations (2)

EAS ESC European Society of Cardiology

2016	2019
Pharmacological LDL-C lowering	**Pharmacological LDL-C lowering**
If the LDL goal is not reached, statin combination with a cholesterol absorption inhibitor should be considered.	If the goals are not achieved with the maximum tolerated dose of statin, combination with ezetimibe is recommended.

www.escardio.org/guidelines

2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

Changes in recommendations (3)

EAS ESC European Society of Cardiology

2016	2019
Pharmacological LDL-C lowering	**Pharmacological LDL-C lowering**
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.	For secondary prevention, patients at very-high risk not achieving their goal on a maximum tolerated dose of statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended.
	For very-high-risk FH patients (that is, with ASCVD or with another major risk factor) who do not achieve their goals on a maximum tolerated dose of statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended.

www.escardio.org/guidelines

2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)


Thank you very much!
easher@szmc.org.il
052-5046080

New recommendations (1)

EAS ESC European Society of Cardiology

Cardiovascular imaging for assessment of ASCVD risk

Assessment of arterial (carotid and/or femoral) plaque burden on arterial ultrasonography should be considered as a risk modifier in individuals at low or moderate risk.

Cardiovascular imaging for assessment of ASCVD risk

CAC score assessment with CT may be considered as a risk modifier in the CV risk assessment of asymptomatic individuals at low or moderate risk.

Lipid analyses for CVD risk estimation

Lp(a) measurement should be considered at least once in each adult person's lifetime to identify those with very high inherited Lp(a) levels >180 mg/dL (>430 nmol/L) who may have a lifetime risk of ASCVD equivalent to the risk associated with heterozygous familial hypercholesterolaemia.

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2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

New recommendations (2)

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Drug treatments of patients with hypertriglyceridaemia
In high-risk (or above) patients with TG between 1.5 and 5.6 mmol/L (135 - 499 mg/dL) despite statin treatment, n-3 PUFAs (icosapent ethyl 2 x 2g/day) should be considered in combination with statins.

Treatment of patients with heterozygous FH
In primary prevention, for individuals with FH at very-high risk, an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) should be considered.

Treatment of dyslipidaemias in older people
Treatment with statins is recommended for primary prevention, according to the level of risk, in older people aged ≤75.

Treatment of dyslipidaemias in older people
Initiation of statin treatment for primary prevention in older people aged >75 may be considered, if at high risk or above.

www.escardio.org/guidelines

2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

New recommendations (3)

EAS ESC European Society of Cardiology

Treatment of dyslipidaemias in DM

In patients with T2DM at very-high risk, an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.4 mmol/L (<55mg/dL) is recommended.

In patients with T2DM at high risk, an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.8 mmol/L (<70 mg/dL) is recommended.

Statins are recommended in patients with T1DM who are at high or very-high risk.

Treatment of dyslipidaemias in DM

Intensification of statin therapy should be considered before the introduction of combination therapy.

If the goal is not reached, statin combination with ezetimibe should be considered.

Treatment of dyslipidaemias in DM

Statin therapy is not recommended in pre-menopausal patients with DM who are considering pregnancy or not using adequate contraception.

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2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

Changes in recommendations (3)

EAS ESC European Society of Cardiology

2016	2019
Pharmacological LDL-C lowering	**Pharmacological LDL-C lowering**
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.	For secondary prevention, patients at very-high risk not achieving their goal on a maximum tolerated dose of statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended.
	For very-high-risk FH patients (that is, with ASCVD or with another major risk factor) who do not achieve their goals on a maximum tolerated dose of statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended.

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2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

Changes in recommendations (4)

EAS ESC European Society of Cardiology

2016	2019
Drug treatments of hypertriglyceridaemia	**Drug treatments of hypertriglyceridaemia**
Statin treatment may be considered as the first drug of choice for reducing CVD risk in high-risk individuals with hypertriglyceridaemia.	Statin treatment is recommended as the first drug of choice for reducing CVD risk in high-risk individuals with hypertriglyceridaemia [TG >2.3 mmol/L (200 mg/dL)].

www.escardio.org/guidelines

2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

Changes in recommendations (5)

EAS ESC European Society of Cardiology

2016	2019
Treatment of patients with heterozygous FH	**Treatment of patients with heterozygous FH**
Treatment should be considered to aim at reaching an LDL-C <2.6 mmol/L (<100 mg/dL) or in the presence of CVD <1.8 mmol/L (<70 mg/dL). If targets cannot be reached, maximal reduction of LDL-C should be considered using appropriate drug combinations.	For FH patients with ASCVD who are at very-high risk, treatment to achieve at least a 50% reduction from baseline and an LDL-C <1.4 mmol/L (<55 mg/dL) is recommended. If goals cannot be achieved, a drug combination is recommended.

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2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

Changes in recommendations (6)

EAS ESC European Society of Cardiology

2016	2019
Treatment of patients with heterozygous FH	**Treatment of patients with heterozygous FH**
Treatment with a PCSK9 antibody should be considered in FH patients with CVD or with other factors putting them at very-high risk for CHD, such as other CV risk factors, family history, high Lp(a), or statin intolerance.	Treatment with a PCSK9 inhibitor is recommended in very-high-risk FH patients if the treatment goal is not achieved on maximal tolerated statin plus ezetimibe.

www.escardio.org/guidelines

2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

Changes in recommendations (7)

EAS ESC European Society of Cardiology

2016	2019
Treatment of dyslipidaemias in older adults	**Treatment of dyslipidaemias in older adults**
Since older people often have comorbidities and have altered pharmacokinetics, lipid-lowering medication should be started at a lower dose and then titrated with caution to achieve target lipid levels that are the same as in younger people.	It is recommended that the statin is started at a low dose if there is significant renal impairment and/or the potential for drug interactions, and then titrated upwards to achieve LDL-C treatment goals.

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2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

Changes in recommendations (8)

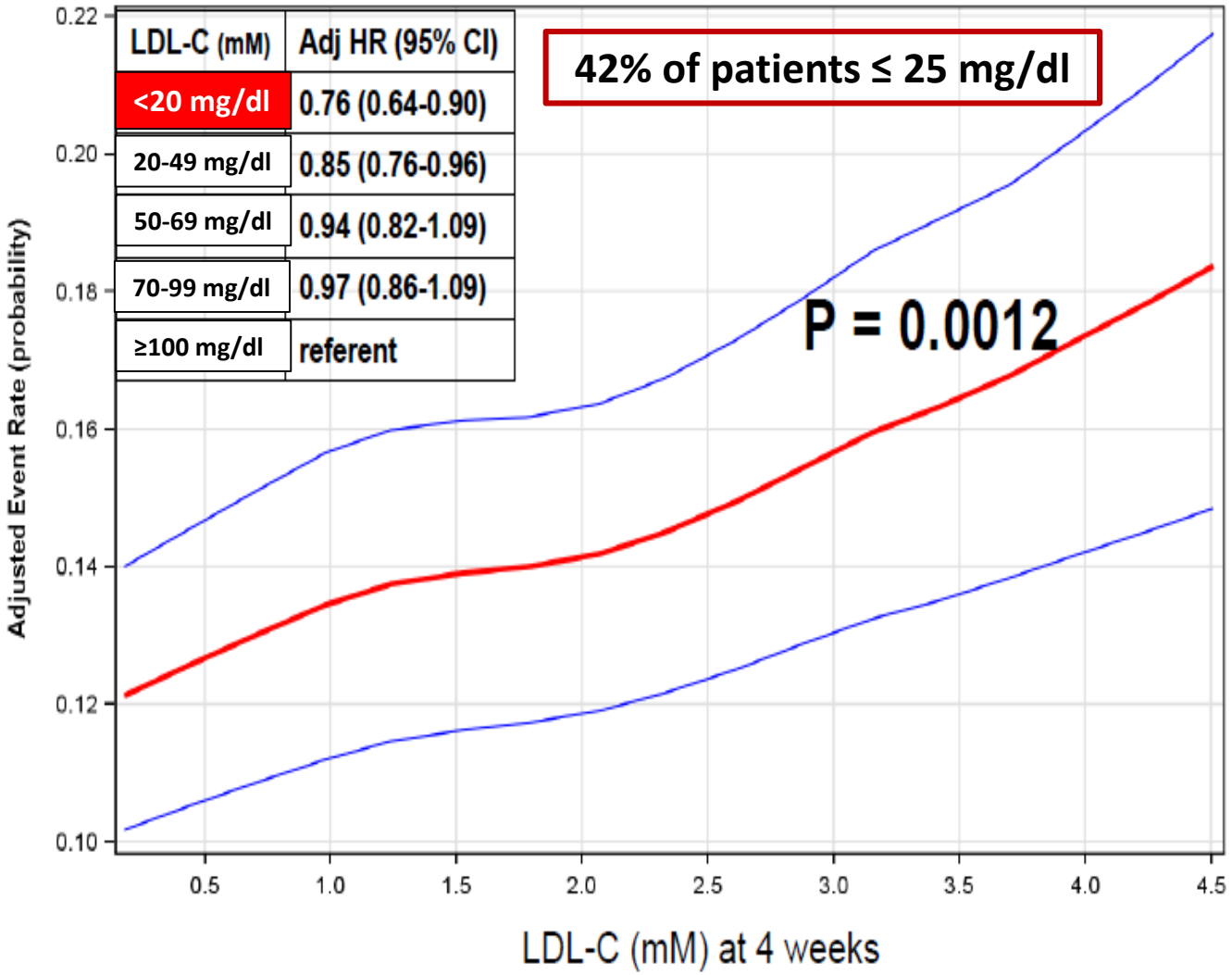
EAS ESC European Society of Cardiology

2016	2019
Lipid-lowering therapy in patients with ACS	**Lipid-lowering therapy in patients with ACS**
If the LDL-C target is not reached with the highest tolerated statin dose and/or ezetimibe, PCSK9 inhibitors may be considered on top of lipid-lowering therapy; or alone or in combination with ezetimibe in statin-intolerant patients or in whom a statin is contraindicated.	If the LDL-C goal is not achieved after 4 - 6 weeks despite maximal tolerated statin therapy and ezetimibe, addition of a PCSK9 inhibitor is recommended.

www.escardio.org/guidelines

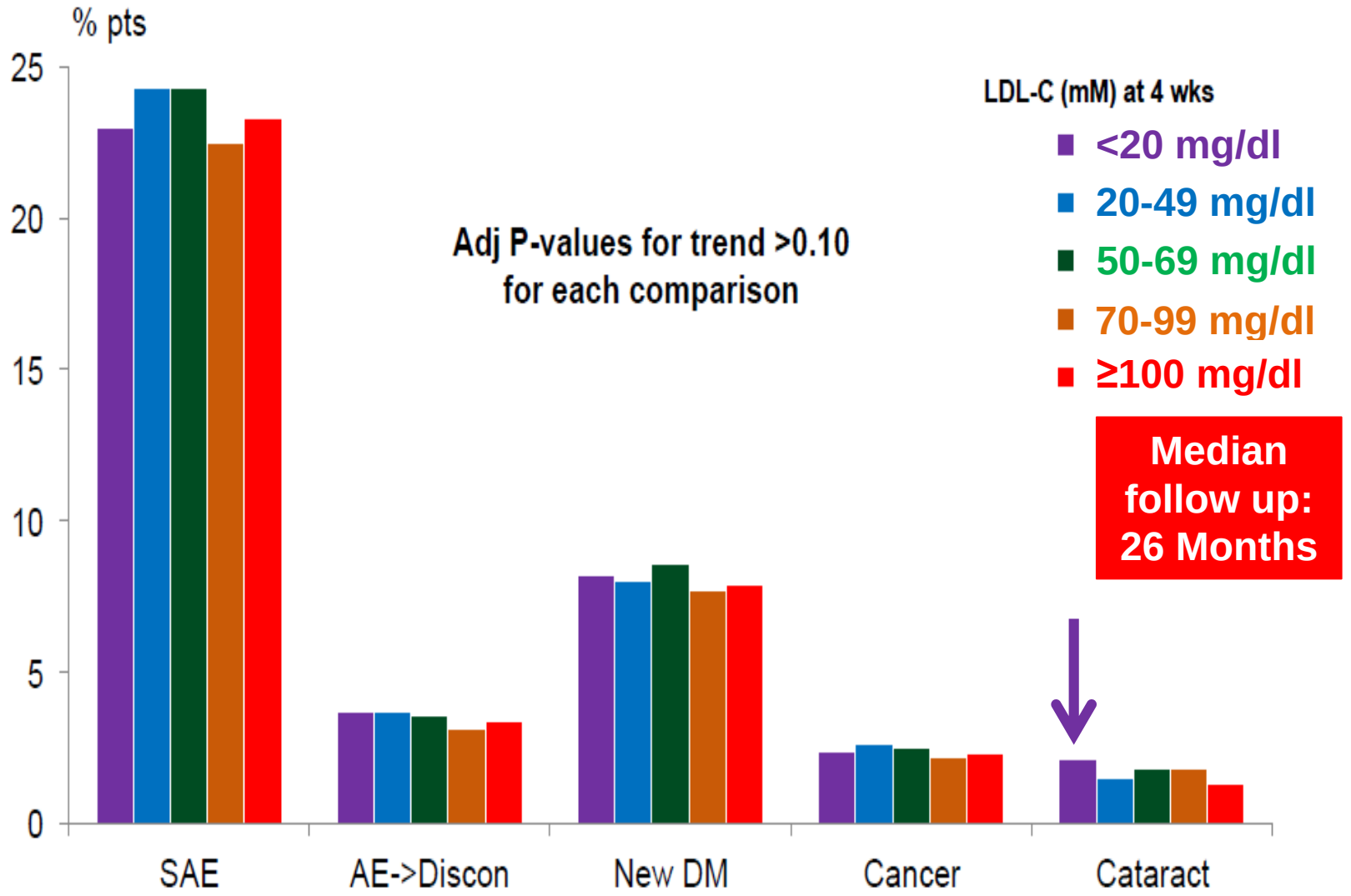
2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

Clinical efficacy of achieving very low LDL-C levels



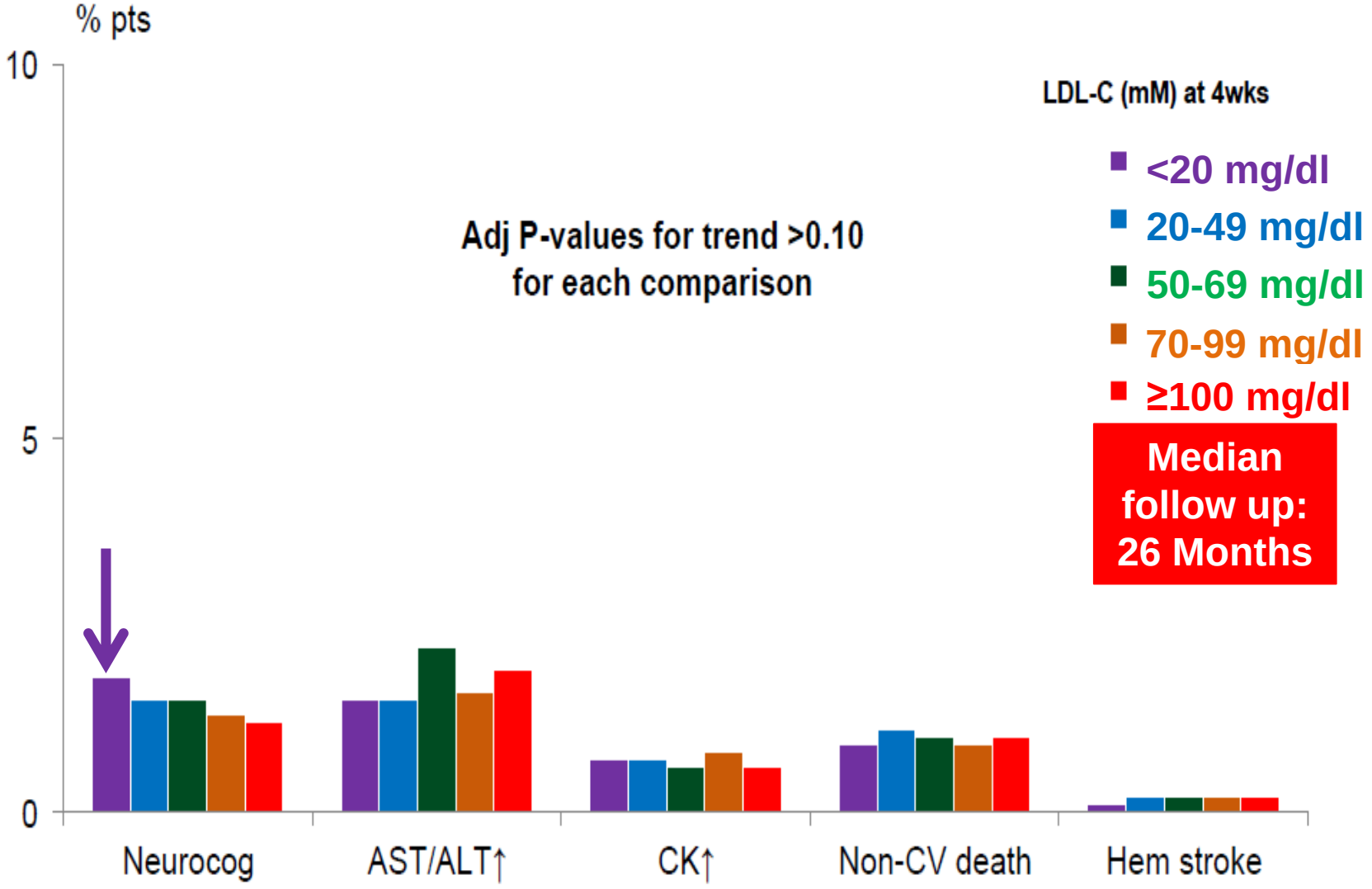
Published online August 28, 2017 http://dx.doi.org/10.1016/S0140-6736(17)32290-0

Safety Events - 1



Published online August 28, 2017 http://dx.doi.org/10.1016/S0140-6736(17)32290-0

Safety Events - 2



Published online August 28, 2017 http://dx.doi.org/10.1016/S0140-6736(17)32290-0

EBBINGHAUS - safety trial : Effect on cognitive function

1974 patients

Median follow up
19.8 months

MAJOR EXCLUSIONS
1. Not enrolled in FOURIER
2. >12 wk FOURIER visit
3. H/O dementia, cognitive impairment or other conditions interfering with participation

Endpoints:
1. **Cambridge Neuropsychological Test Automated Battery (CANTAB)**
2. **Patient survey of everyday cognition at study end**
3. **Investigator report of cognitive Aes**

*Cognitive tests performed at baseline; at 6, 12, 24 months; and end of study

Giugliano RP *et al*. Late breaking clinical trial; presented at the ACC 66th Annual Scientific Session on March 18, 2017. http://www.crtonline.org/presentation-detail/ebbinghaus-cognitive-study-of-patients-enrolled-in. Last access April 2017.

Conclusions

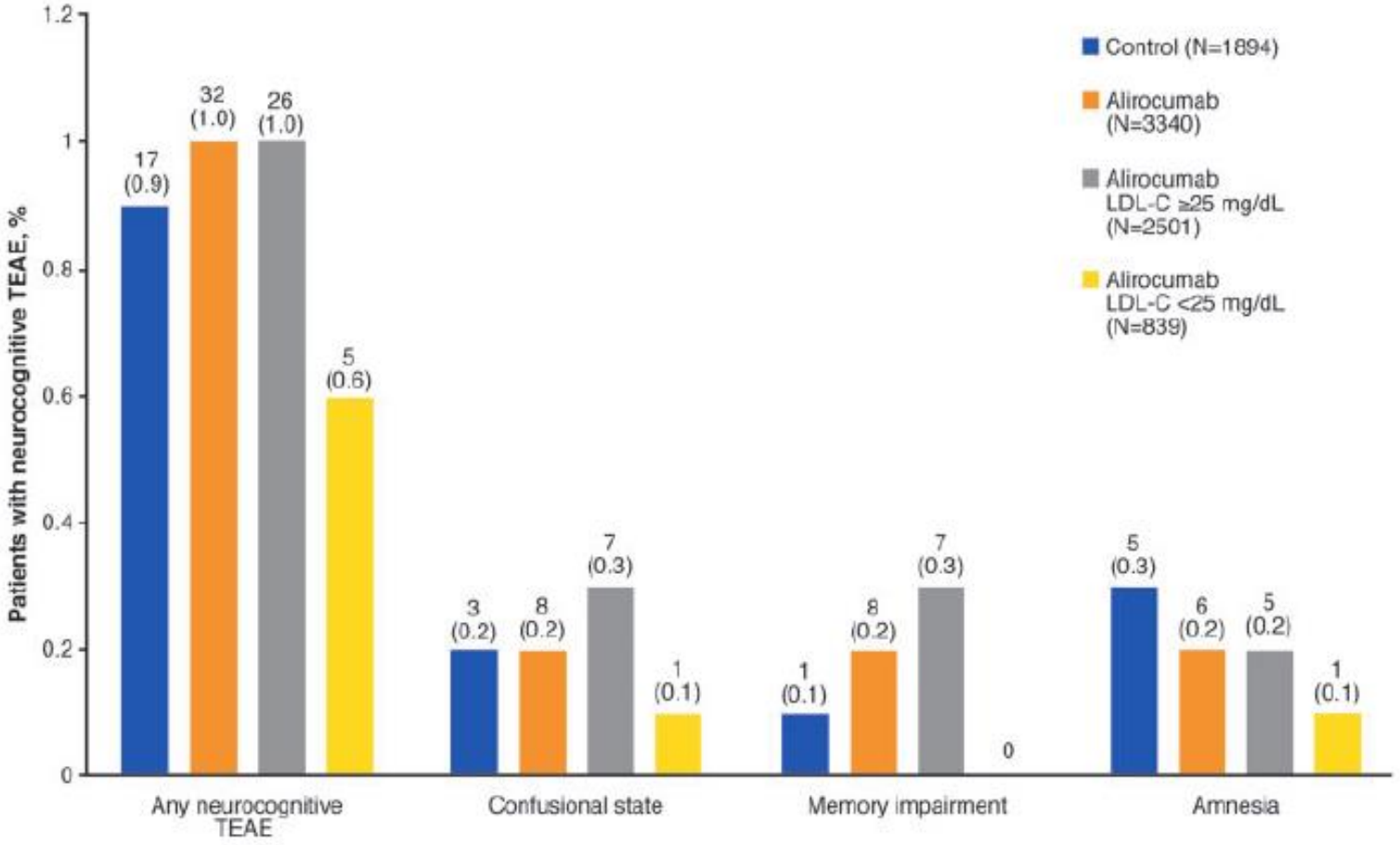
In patients with known cardiovascular disease on background statin followed for 20 months

1. **No differences btw evolocumab vs placebo**
   A. A battery of cognitive tests
   B. Patient-reported everyday cognition
   C. Adverse cognitive events reported by MD

2. **No evidence of differences in cognitive tests by achieved nadir LDL-C, even <25 mg/dL**

No evidence of neurocognitive adverse events associated with Alirocumab treatment

- 3340 patients from 14 randomized Phase 2 and 3 controlled trials: a meta-analysis of individual patient data



Follow up ~2 years

European Heart Journal (2017) 00, 1–9 doi:10.1093/eurheartj/ehx661