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

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ESC/EAS GUIDELINES

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 Assocciation for Cardiovascular Prevention & Rehabilitation (EACPR)

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CURRENT OPINION

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

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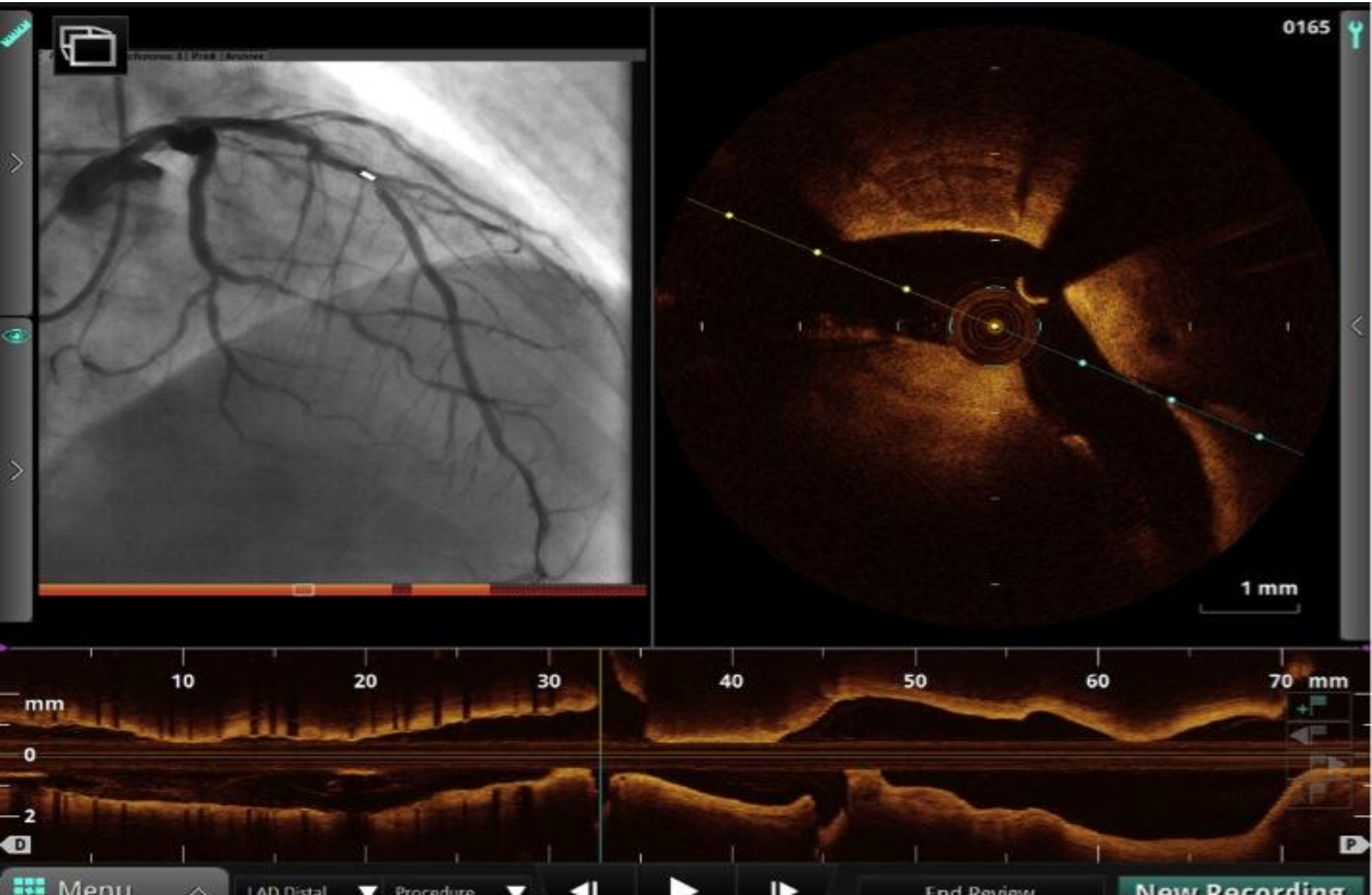
Patient Case

- **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 managment 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

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.

ESC/EAS Dyslipidemia Guidelines - Eur Heart J 2016

Dyslipidemia Guidelines

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

Total CV risk (SCORE) %	LDL-C levels				
	<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[a]/Level[b]	I/C	I/C	I/C	I/C	IIa/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[a]/Level[b]	I/C	I/C	IIa/A	IIa/A	IIa/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[a]/Level[b]	IIa/A	IIa/A	I/A	I/A	I/A
≥10 or very high-risk	Lifestyle intervention, consider drug[c]	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[a]/Level[b]	IIa/A	IIa/A	I/A	I/A	I/A

SCORE = Systematic Coronary Risk Estimation.

[a]Class of recommendation; [b]Level of evidence; [c]In patients with MI, statin therapy should be considered irrespective of total cholesterol levels

Patient Case – Lipid-targeted treatment

- **Diagnosis: Coronary artery disease = Very high cardiovascular risk**
- **What is the target for LDL-C managment ?**

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

Recommendations	Class [a]	Level [b]	Ref [c]
In patients at VERY HIGH CV risk[d], an LDL-C goal of <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.	I	B	61, 62, 65, 68, 69, 128
In patients at HIGH CV risk[d], an LDL-C goal of <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.	I	B	65, 129
In subjects at LOW or MODERATE risk[d] an LDL-C goal of <3.0 mmol/L (<115 mg/dL) should be considered.	IIa	C	-

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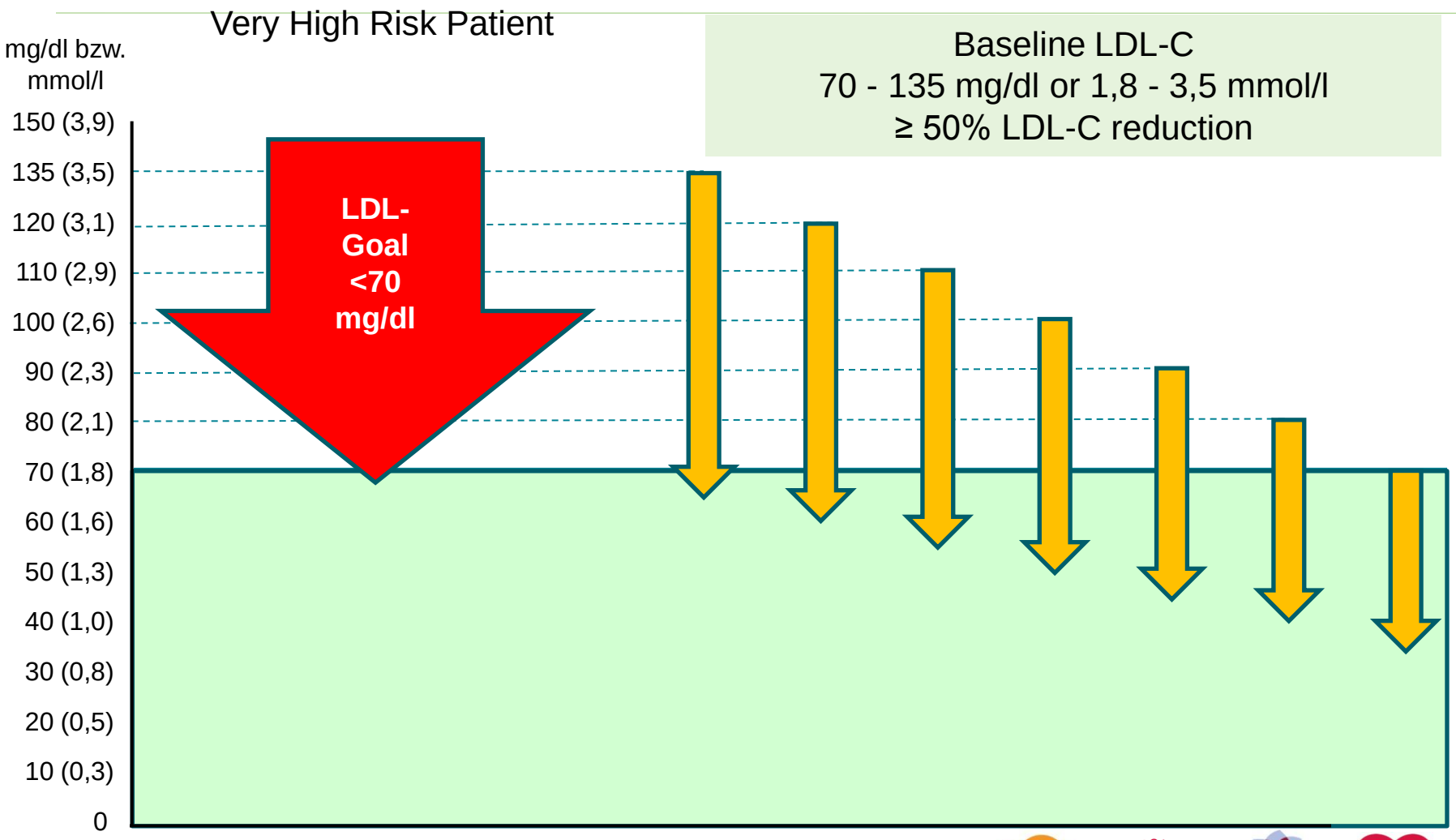
ESC/EAS Dyslipidemia Guidelines 2016:



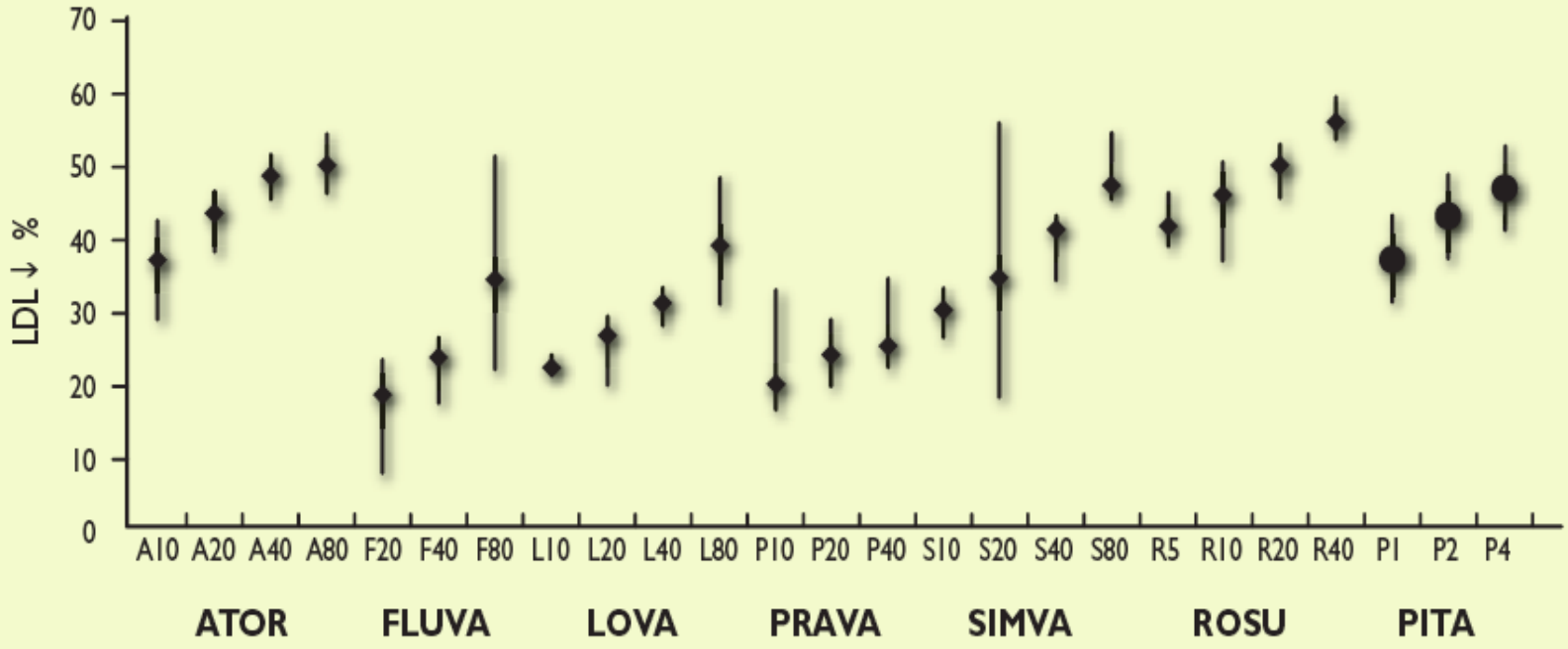
ESC/EAS Dyslipidemia Guidelines - Eur Heart J 2016

Dyslipidemia Guidelines

Recommendations for the pharmacological treatment of hypercholesterolaemia

Recommendations	Class	Level
Prescribe statin up to the highest recommended dose or highest tolerable dose to reach the goal.	I	A
In the case of statin intolerance, ezetimibe or bile acid sequestrants, or these combined, should be considered.	IIa	C
If the goal is not reached, statin combination with a cholesterol absorption inhibitor should be considered.	IIa	B
If the goal is not reached, statin combination with a bile acid sequestrant may be considered.	IIb	C
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.	IIb	C

Statin Therapy - A systematic reviewand meta-analysis of the therapeutic equivalence



Weng TC, *et al. J Clin Pharm Ther* . 2010;35:139-151
Mukhtar RY, *et Al. Int J Clin Pract* . 2055;59(2):239-252

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**

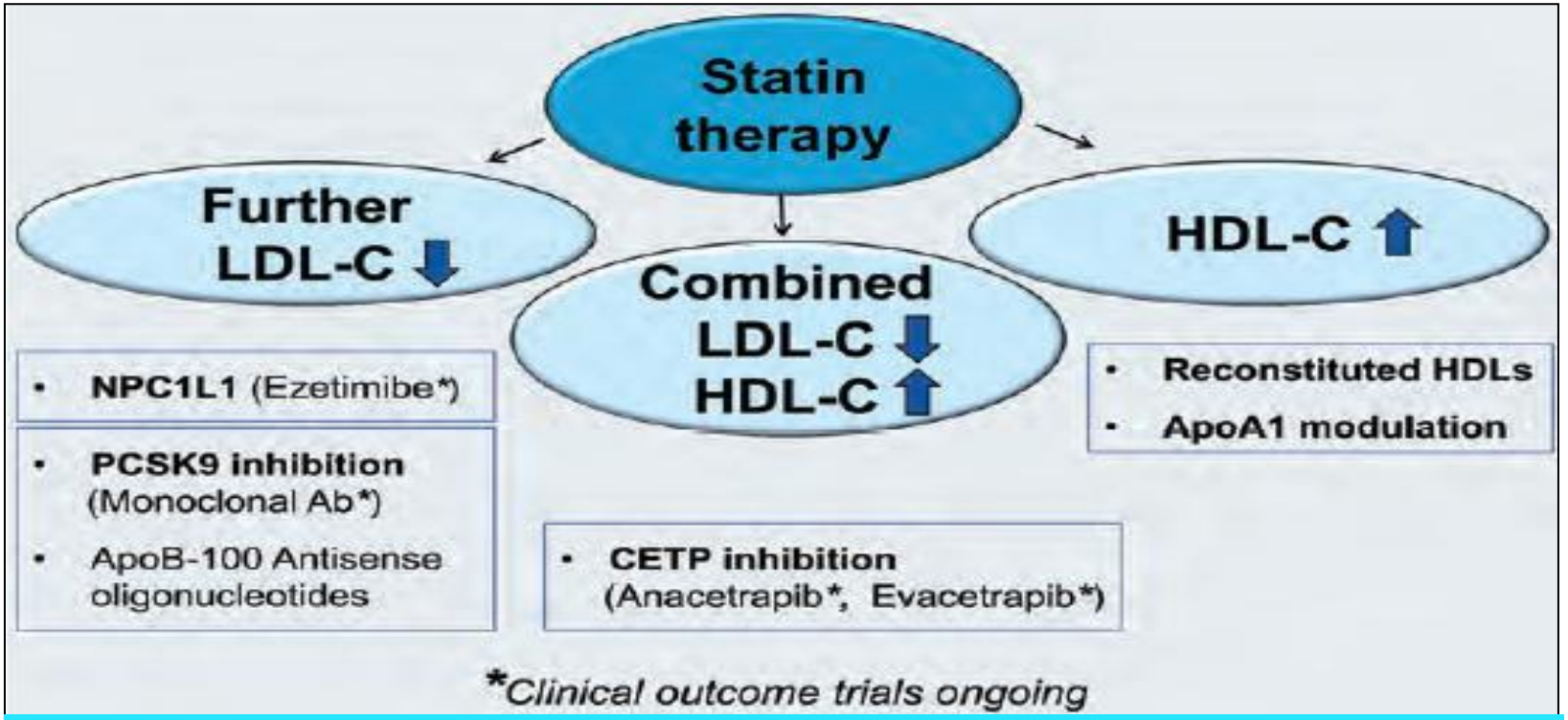
Lipid analysis and treatment targets in prevention of CVD

Recommendations	Class [a]	Level [b]	Ref [c]
LDL-C is recommended as the primary target for treatment.	I	A	64, 68
TC should be considered as a treatment target if other analyses are not available.	IIa	A	64, 123
Non-HDL-C should be considered as a secondary treatment target.	IIa	B	103
ApoB should be considered as a secondary treatment target, when available.	IIa	B	103, 124
HDL-C is not recommended as a target for treatment.	III	A	92, 93
The ratios apoB/apoA1 and non-HDL-C/HDL-C are not recommended as targets for treatment.	III	B	103

European Heart Journal (2013) **34**, 1254–1257
doi:10.1093/eurheartj/eht064

EDITORIAL

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

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

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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

Recommendations	Class	Level
Prescribe statin up to the highest recommended dose or highest tolerable dose to reach the goal.	I	A
In the case of statin intolerance, ezetimibe or bile acid sequestrants, or these combined, should be considered.	IIa	C
If the goal is not reached, statin combination with a cholesterol absorption inhibitor should be considered.	IIa	B
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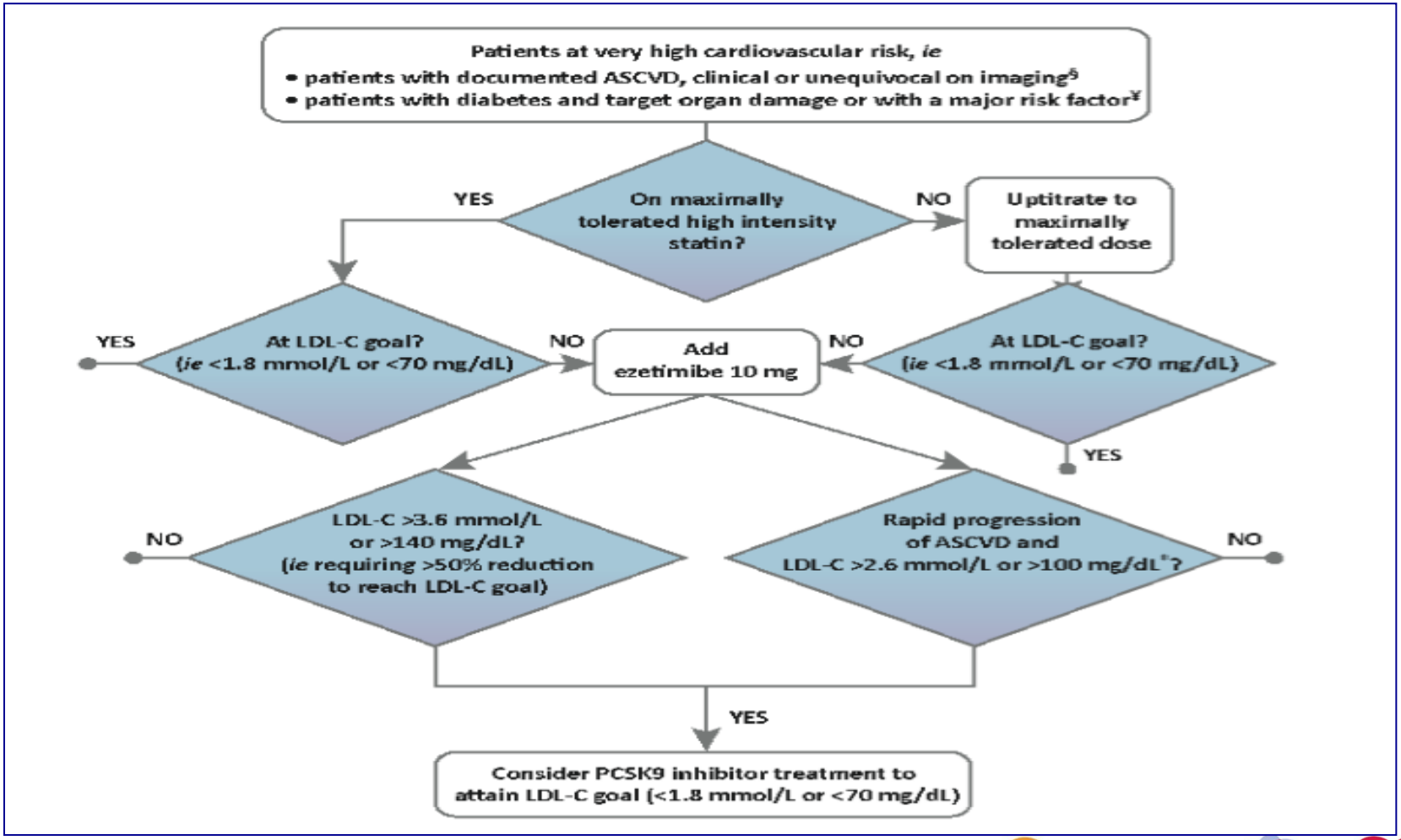
In patients at very high-risk, with persistent high LDL-C despite treatment with maximal tolerated statin dose, in combination with ezetimibe or in patients with statin intolerance, a PCSK9 inhibitor may be considered.	IIb	C

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



www.escardio.org/EAPC

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

Thank you

BERLIN INSTITUTE OF HEALTH
Charité & Max Delbrück Center

www.escardio.org/EAPC

EAPC European Association of Preventive Cardiology
ESC COUNCIL Cardiovascular Nursing and Allied Professions
Acute Cardiovascular Care Association ACCA
EUROPEAN SOCIETY OF CARDIOLOGY®

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)

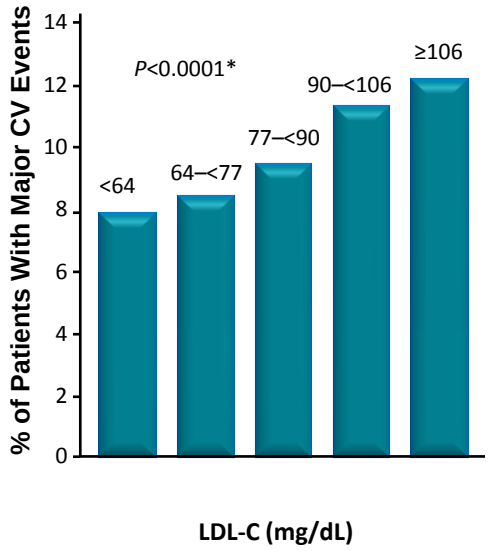
- **Lecture Fees from**
  - AMGEN
  - AstraZeneca
  - Pfizer
  - Sanofi

LDL-C: „The lower the better“ (!?)

The lower the LDL-C achieved, the lower the risk of CV events

TNT[1,a]

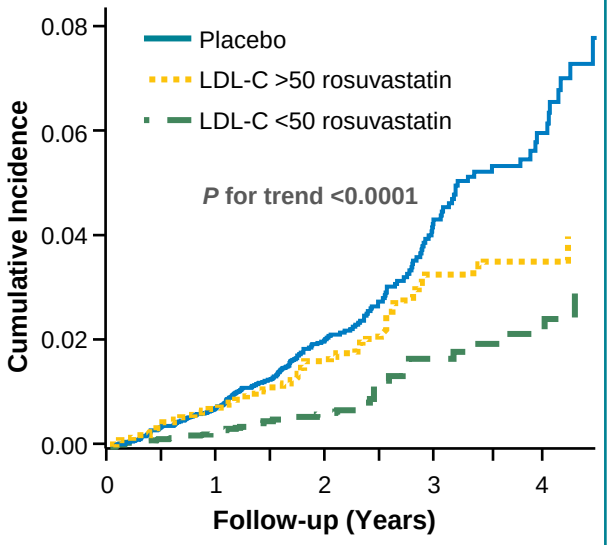
Rate of major CV events



*P value for trend across LDL-C

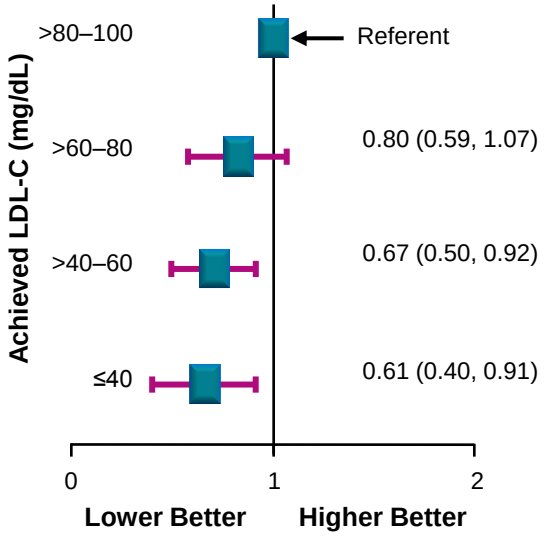
JUPITER[2,b]

Time to occurrence of major CV events



PROVE-IT[3,c]

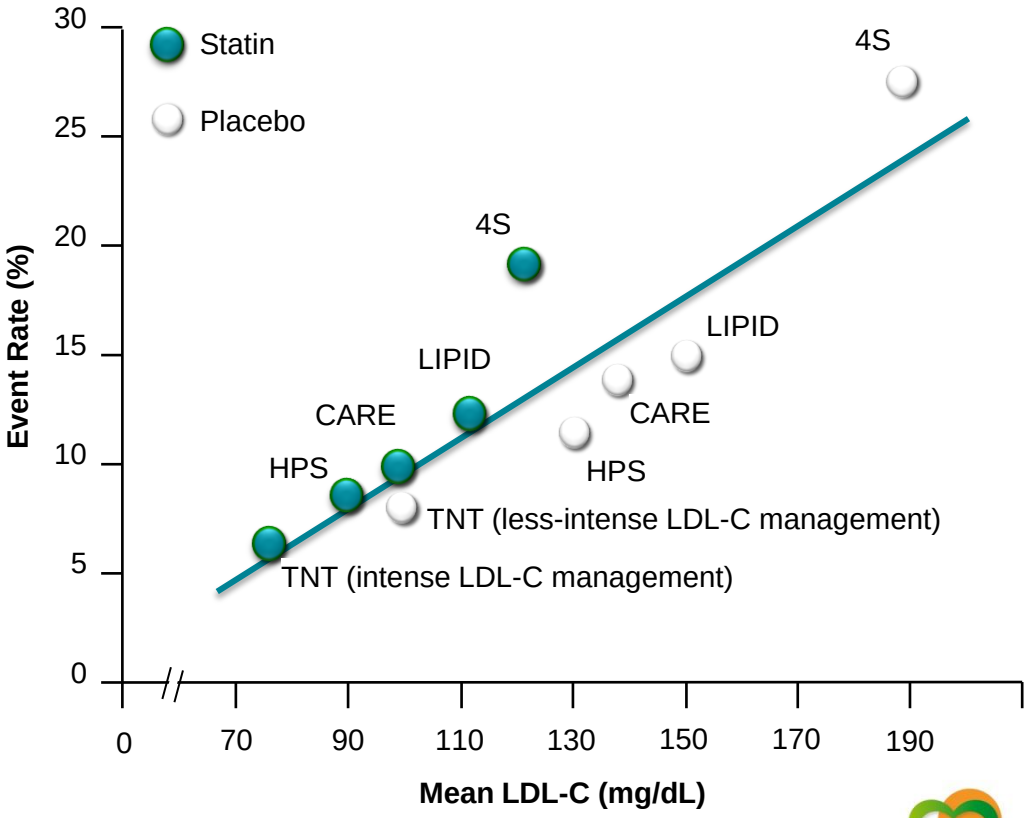
Hazard ratio of primary endpoint



1. LaRosa JC, et al. J Am Coll Cardiol 2007;100:747–52.
2. Hsia J, et al. J Am Coll Cardiol 2011;57:1666–75.
3. Wiviott SD, et al. J Am Coll Cardiol 2005;46:1411–6.

LDL-C is a major contributor to CV risk

LDL-C levels and event rates[a] in secondary prevention statin studies



LaRosa JC, et al. N Engl J Med 2005;352:1425–35.

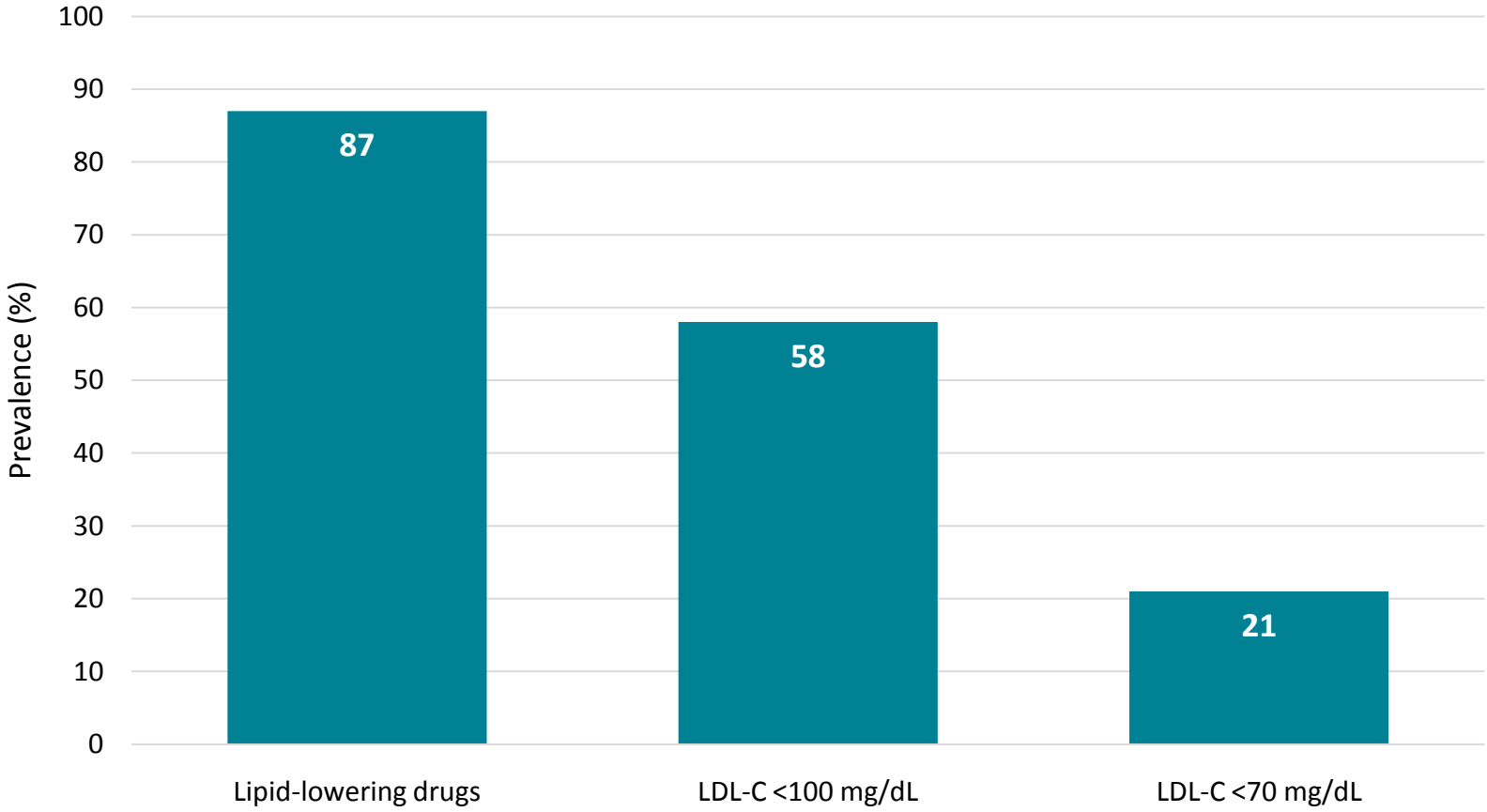
Statins and Ezetimibe frequently are insuffient in reaching the treatment goal

In which percentage is an LDL-C goal of <70 mg/dl (<1,8 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*



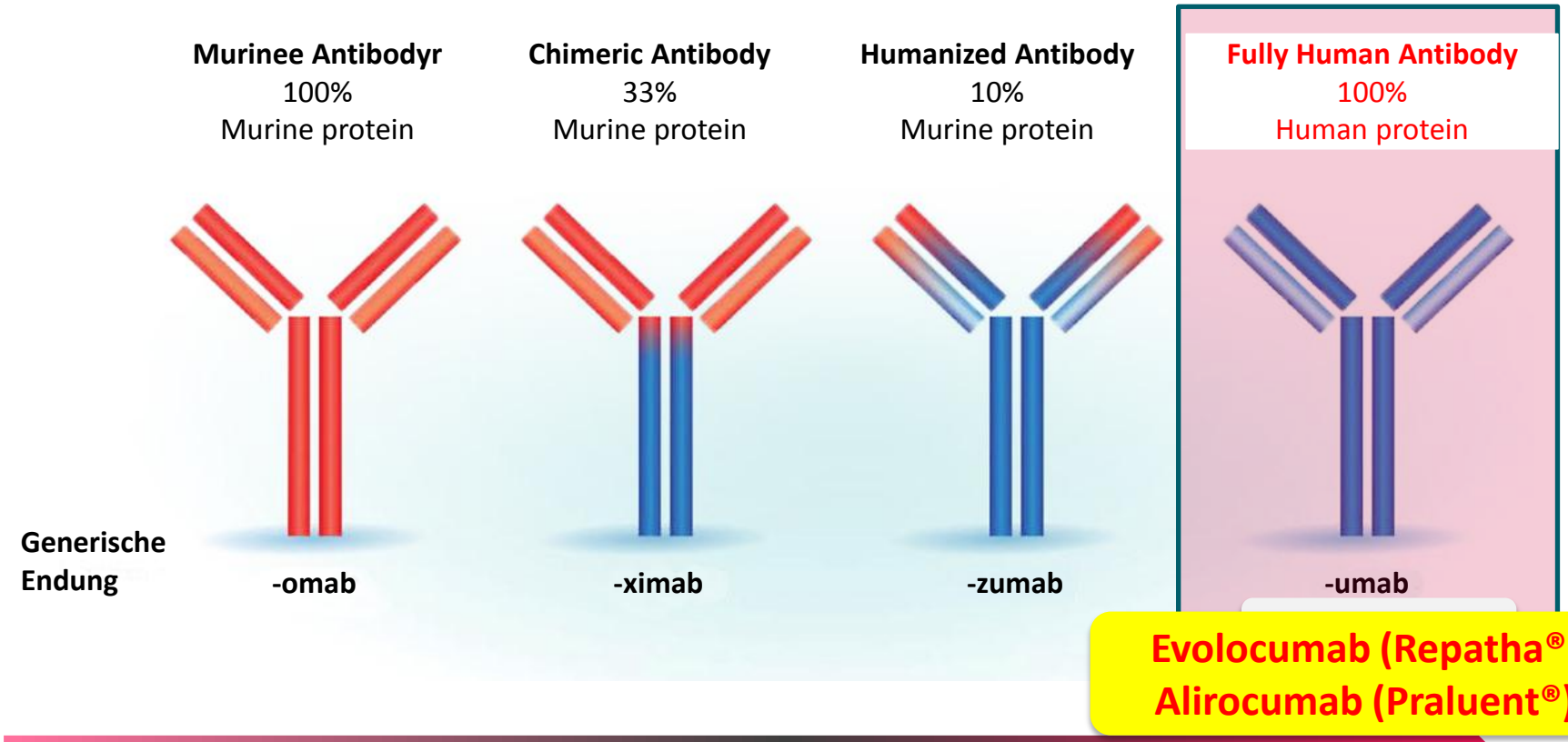
*25% women, mean age 64 years, one third <60 years old, 2012–2013.
CHD, coronary heart disease; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction.

PCSK9-Inhibition

PCSK9-inhibition on top of standard lipid lowering reduces LDL-C levels for further

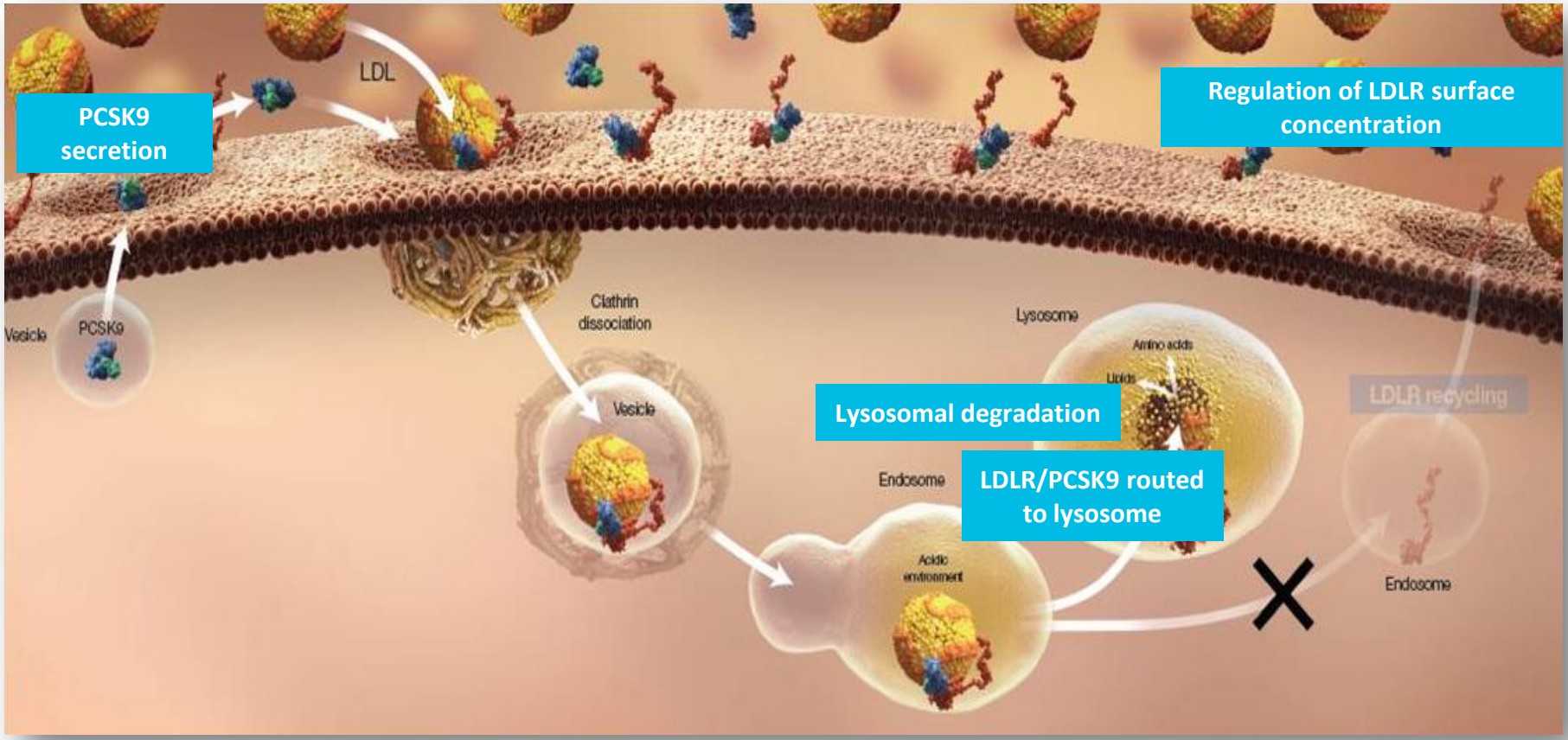
1) 20%
2) 40%
3) 60%
4) 80%

Different Types of Monoclonal Antibodies



- I. N. Foltz et al.: Evolution and emergence of therapeutic monoclonal
- antibodies: what cardiologists need to know. Circulation 127, 2222 (2013).

PCSK9: A Bad Guy



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Horton JD et al. J Lipid Res. 2009;50(suppl):S172–S177;
Zhang D-W et al. J Biol Chem. 2007;282:18,602–18,612

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PCSK9: Experiments of Nature

Gain of Function

Loss of Function

Abifadel M et al. Hum Gen. 2009;30:520-529.
Horton JD et al. J Lipid Res. 2009;50:S172-S177.
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EAPC European Association of Preventive Cardiology
ESC Council Cardiovascular Nursing and Allied Professions
Acute Cardiovascular Care Association ACCA
European Society of Cardiology

Alirocumab: ODYSSEY Phase 3 Programs

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

HeFH population

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

ODYSSEY FH I (NCT01623115; EFC12492)
LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
n=486; 18 months

ODYSSEY FH II (NCT01709500; CL1112)
LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
n=249; 18 months

ODYSSEY HIGH FH (NCT01617655; EFC12732)
LDL-C ≥160 mg/dL
n=107; 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=2341; 18 months

HC in high CV-risk population

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

ODYSSEY COMBO I (NCT01644175; EFC11568)
LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
n=316; 12 months

†**ODYSSEY COMBO II (NCT01644188; EFC11569)**
LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
n=720; 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 LLTs
LDL-C ≥100 mg/dL
n=103; 6 months

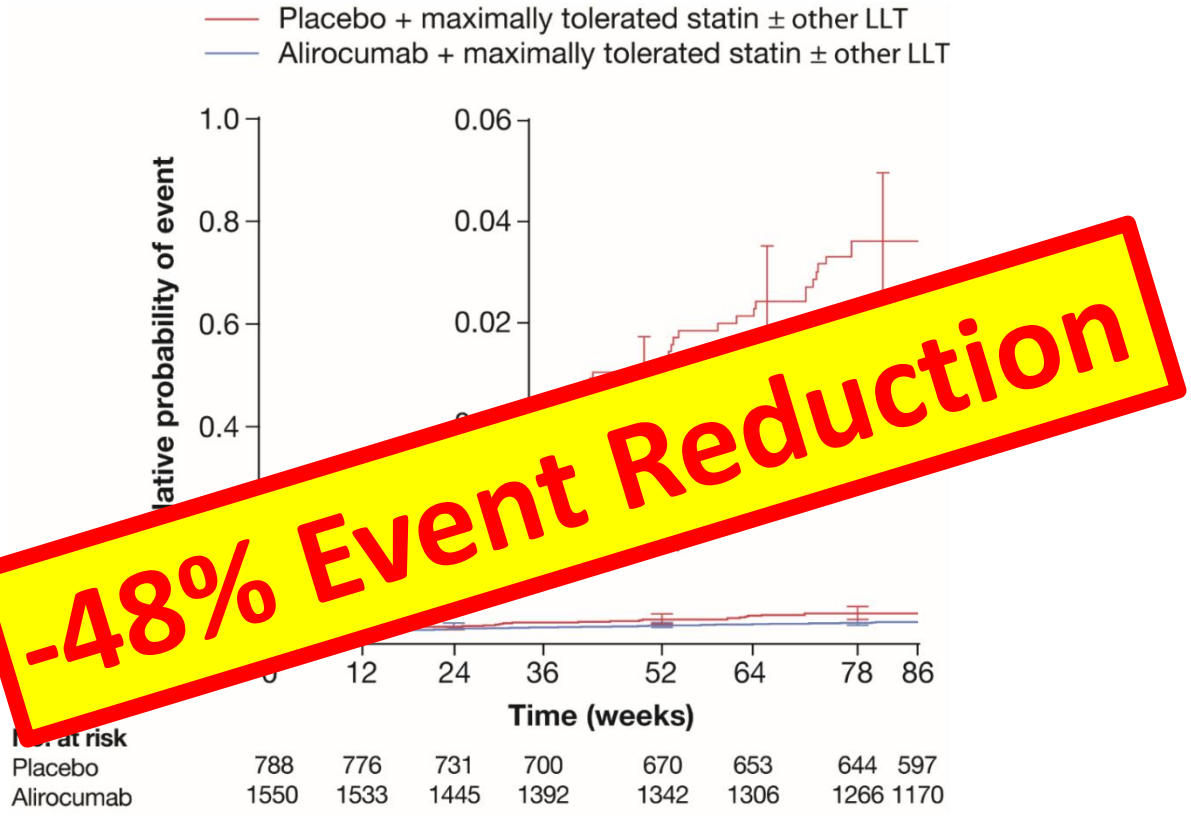
ODYSSEY ALTERNATIVE (NCT01709513; CL1119)
Patients with defined statin intolerance
LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
n=314; 6 months

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=355; 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=305; 6 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

					*
laplace	Combo-therapy	→	Phase 2 (N = 629) ✓	Phase 3 (N = 1896) ✓	Evo + Statin
mendel	Mono-therapy	→	Phase 2 (N = 406) ✓	Phase 3 (N = 614) ✓	Evo Mono
gauss	Statin-intolerant	→	Phase 2 (N = 157) ✓	Phase 3 (N = 307) / Phase 3 (N = 100)	Evo +/-Statin
rutherford	HeFH	→	Phase 2 (N = 167) ✓	Phase 3 (N = 329) ✓	Evo + Statin +/- Eze
tesla / taussig	HoFH/ Severe FH	→	Phase 2/3 (N = 58) ✓	Phase 2/3 (N = 310)	Evo + Statin +/- Eze
descartes	Long-term safety and efficacy	→		Phase 3 (N = 901) ✓	Evo +/- Statin +/- Eze
osler	Open-label Extension	→	Phase 2 (N = 1324) ✓	Phase 3 (N > 3800)	Evo + Statin +/- Eze
glagov	Athero	→		Phase 3 (N = 950)	Evo + Statin +/- Eze
fourier	Secondary Prevention	→		Phase 3 (N = 27,500)	Evo + Statin

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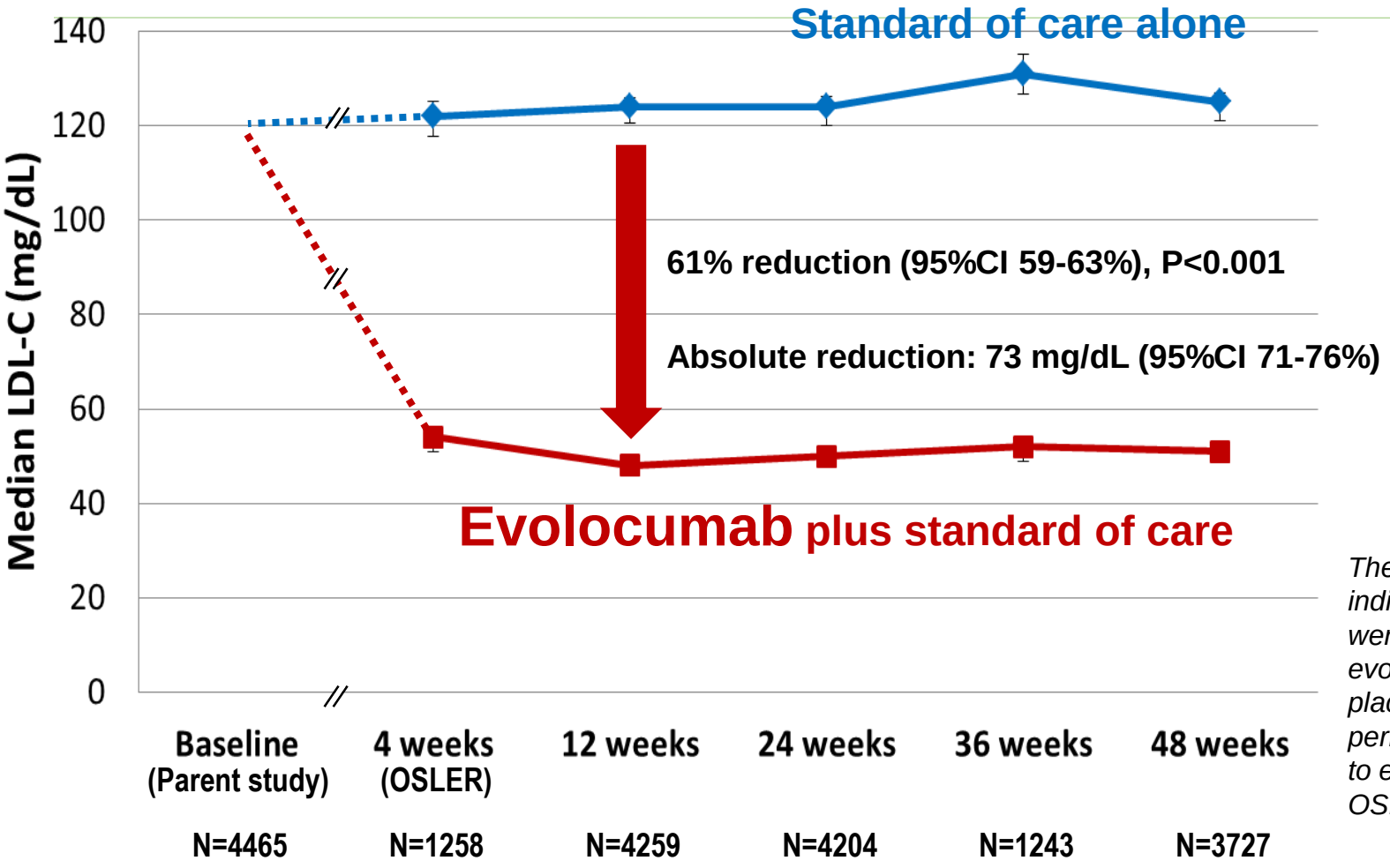
*** Aktiver Arm (Evolocumab); Vergleichsarm: Plazebo +/- Statin +/- Ezetemib**

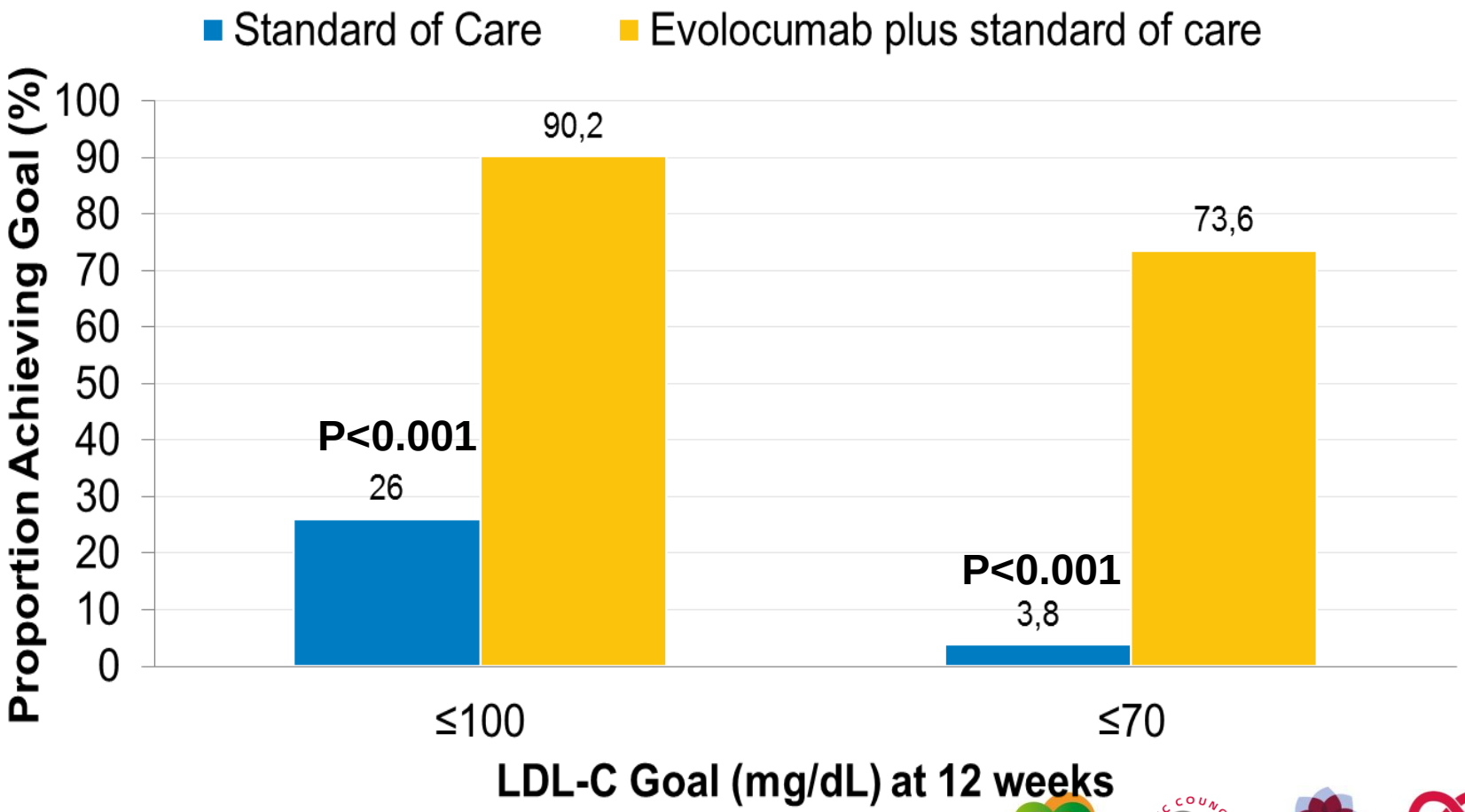
OSLER Studies: LDL Cholesterol Reduction



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

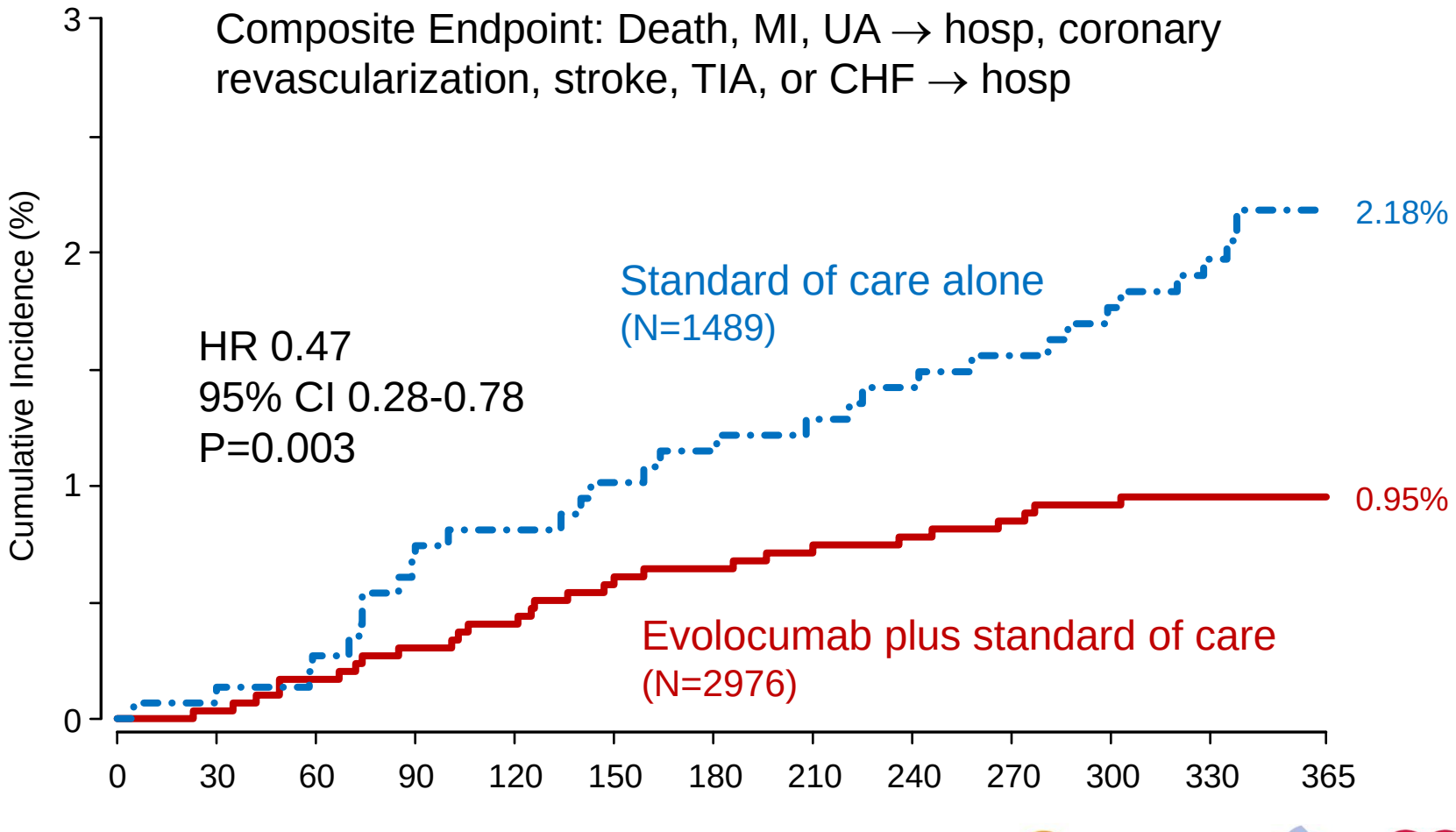
Sabatine et al. N Engl J Med. 2015 Apr 16;372(16):1500-9 (Suppl.):1-21

LDL Cholesterol Goals Reached



Sabatine et al. N Engl J Med. 2015 Apr 16;372(16):1500-9 (Suppl.):1-21

Cardiovascular Outcomes



Sabatine et al. N Engl J Med. 2015 Apr 16;372(16):1500-9 (Suppl.):1-21

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 ezetimbe
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

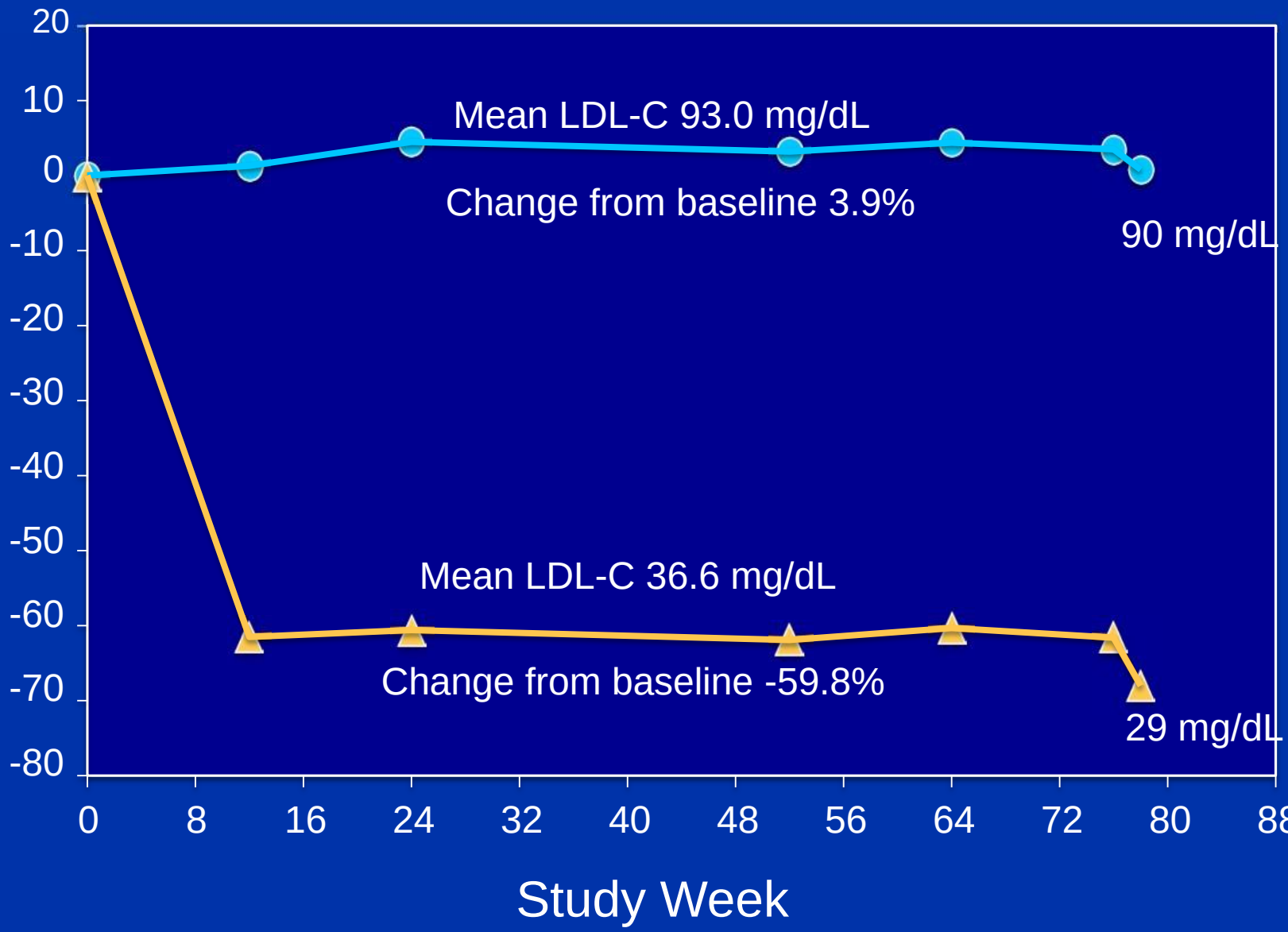
Stable, optimized statin dose for 4 weeks with LDL-C >80 mg/dL or 60-80 mg with additional high risk features

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

Statin monotherapy	**18 months treatment**	Statin plus monthly SC evolocumab 420 mg
61 patients did not complete		61 patients did not complete
423 statin completers		423 evolocumab completers

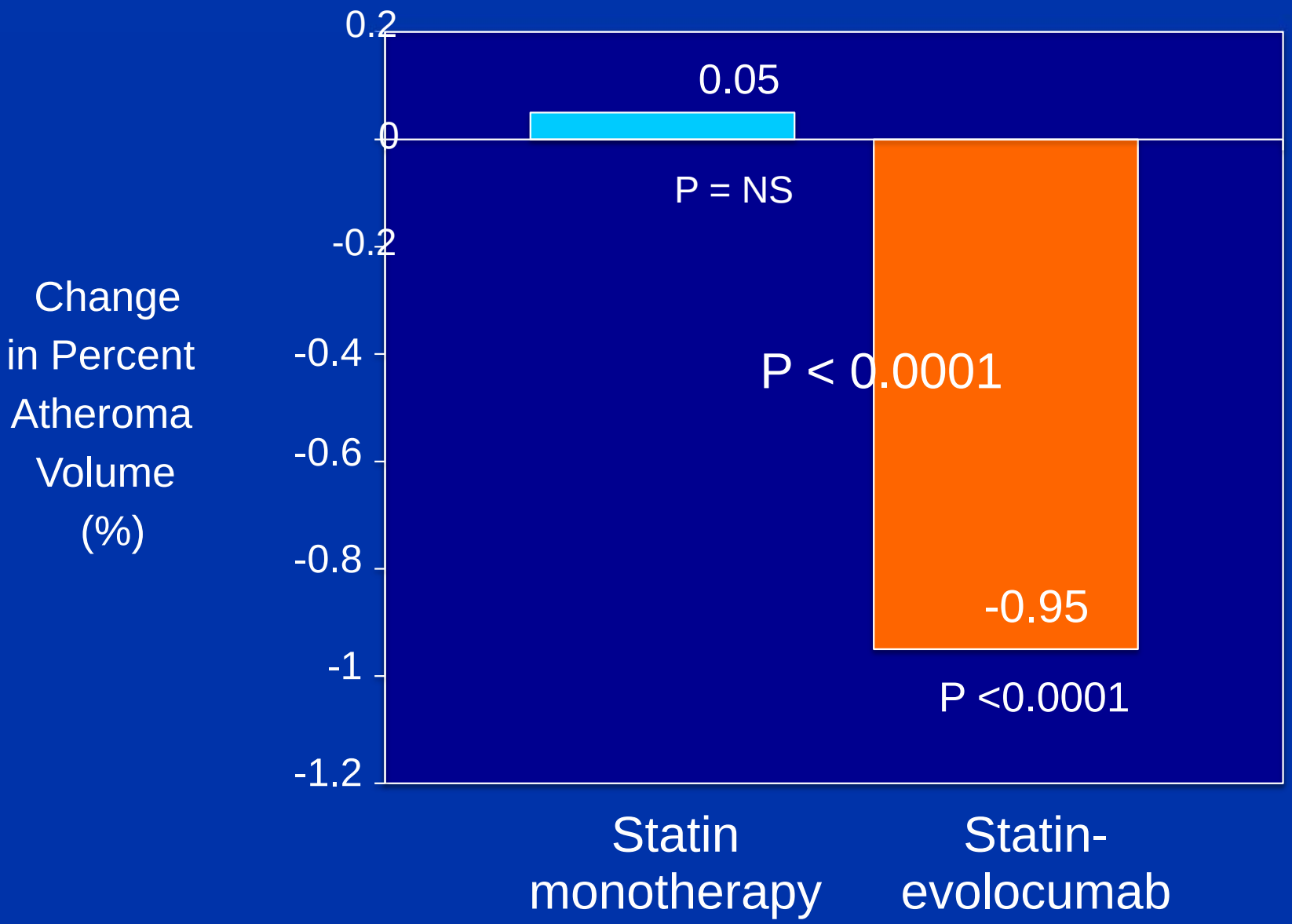
Follow-up IVUS of originally imaged "target" vessel (n=846)

Percent Change in LDL-C During Treatment



AHA 2016

Primary Endpoint: Percent Atheroma Volume



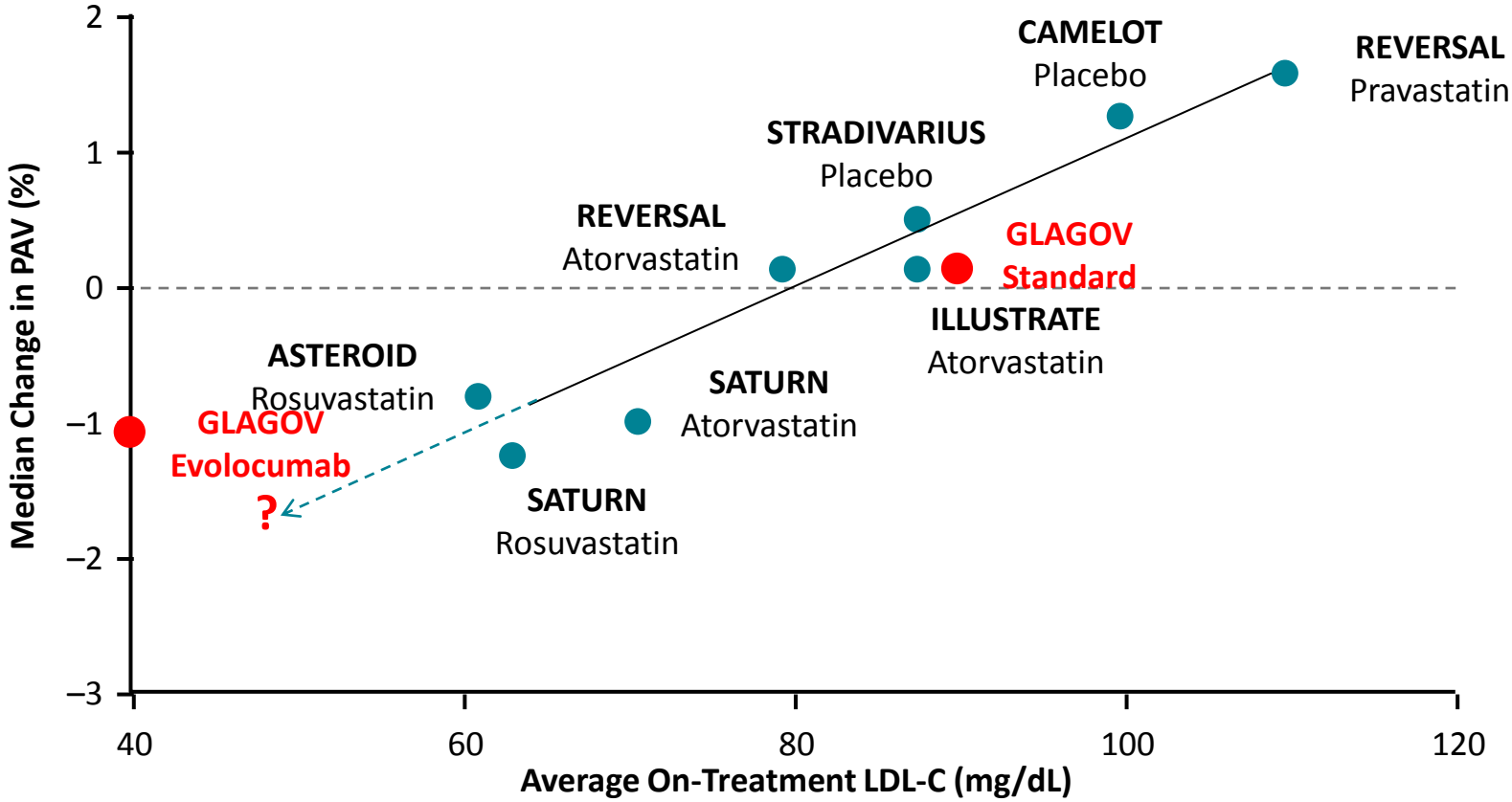
AHA 2016

Adverse Clinical Events and Safety Findings

Event	Placebo (N=484)	Evolocumab (N=484)
Death	0.8%	0.6%
Nonfatal MI	2.9%	2.1%
Nonfatal Stroke	0.6%	0.4%
Hosp. for Unstable Angina	0.8%	0.6%
Coronary Revascularization	13.6%	10.3%
First Major Cardiovascular Event	15.3%	12.2%
Injection site reactions	0%	0.4%
Anti-evolocumab binding antibody	NA	0.2%
Neutralizing antibodies	NA	0%
Neurocognitive events	1.2%	1.4%
New onset diabetes	3.7%	3.6%
Myalgia	5.8%	7.0%

AHA 2016

Achieved LDL-C and Atheroma Regression

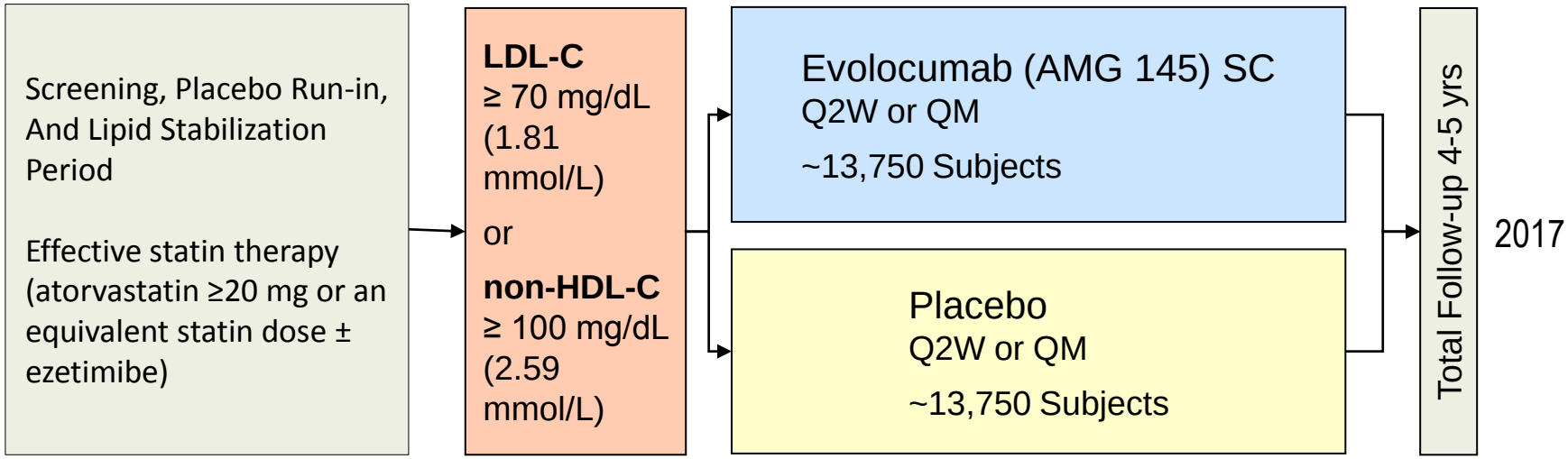


Median changes in percentage atheroma volume (PAV) vs average on-treatment LDL-C in serial coronary IVUS trials. Dotted blue line shows a projected outcome of the degree of plaque regression in those patients receiving evolocumab in GLAGOV.

Puri R, et al. ***Am Heart J.*** **doi: 10.1016/j.ahj.2016.01.019.**

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



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

NCT01764633

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

www.escardio.org/EAPC

EAPC European Association of Preventive Cardiology
ESC Council Cardiovascular Nursing and Allied Professions
Acute Cardiovascular Care Association ACCA
EUROPEAN SOCIETY OF CARDIOLOGY®

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

Clinial 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 ezetimbe, and possibly also patients who want to avoid lipid apheresis

K Huber

THANK YOU !