Cholesterin senken-Gefäßrisiko senken-warum wir PCSK 9 brauchen

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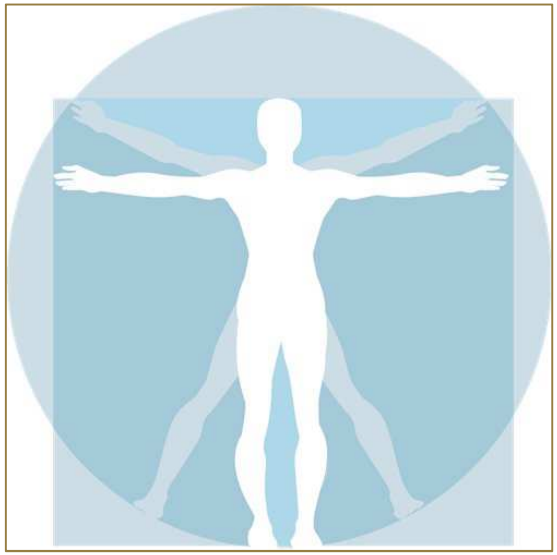


…..Grundsatzfragen zum Thema **Lipide**

Müssen wir hohe Lipide (indikationsgemäß) behandeln ?

A: Ja

B: Nein

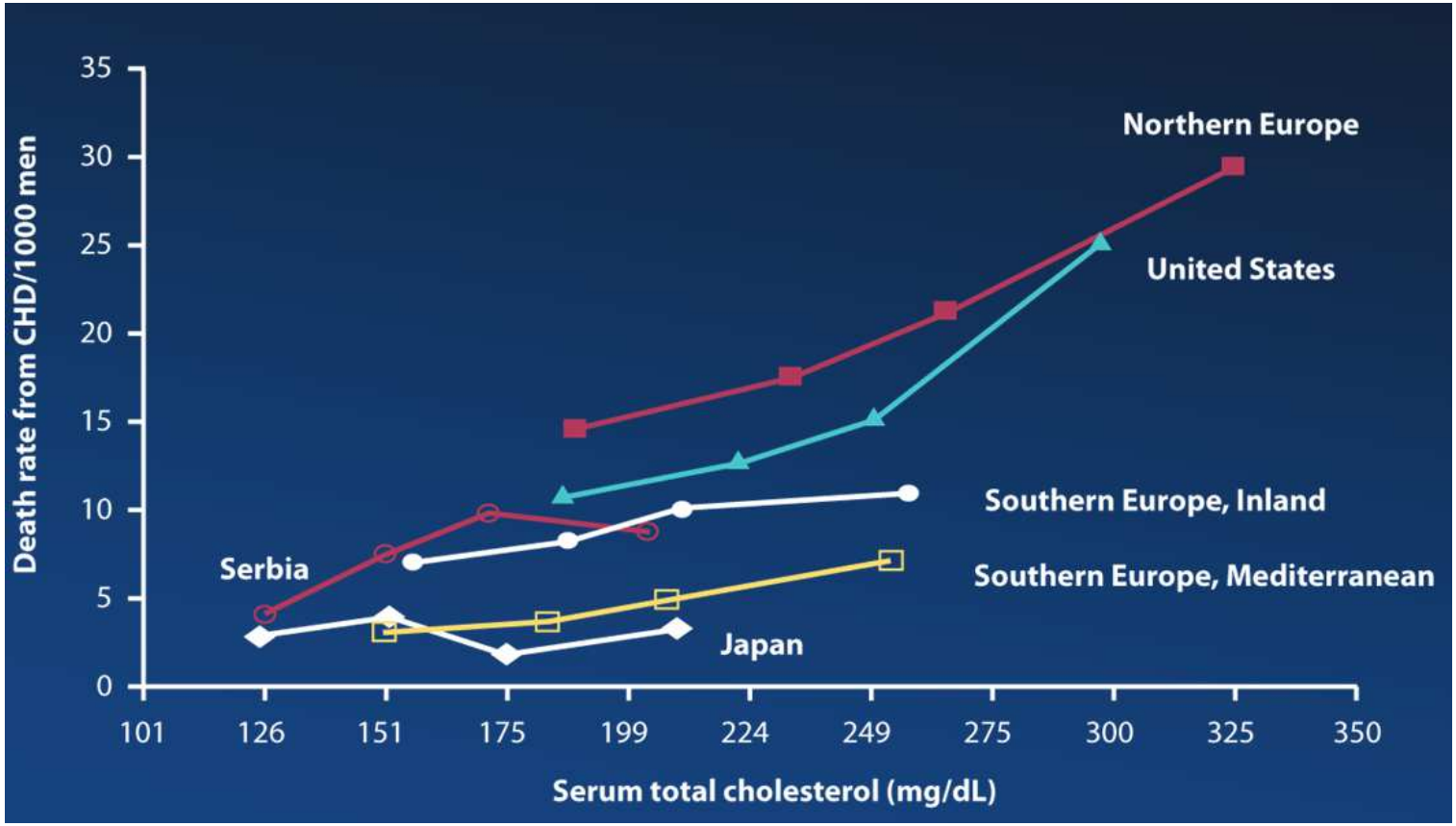
…..Grundsatzfragen zum Thema **Lipide**

Sollten wir LDL-Zielwerte gemäß des Lipidkonsensus anstreben ?

A: Ja

B: Nein

Hypercholesterinämie: Die Risiken sind regional unterschiedlich

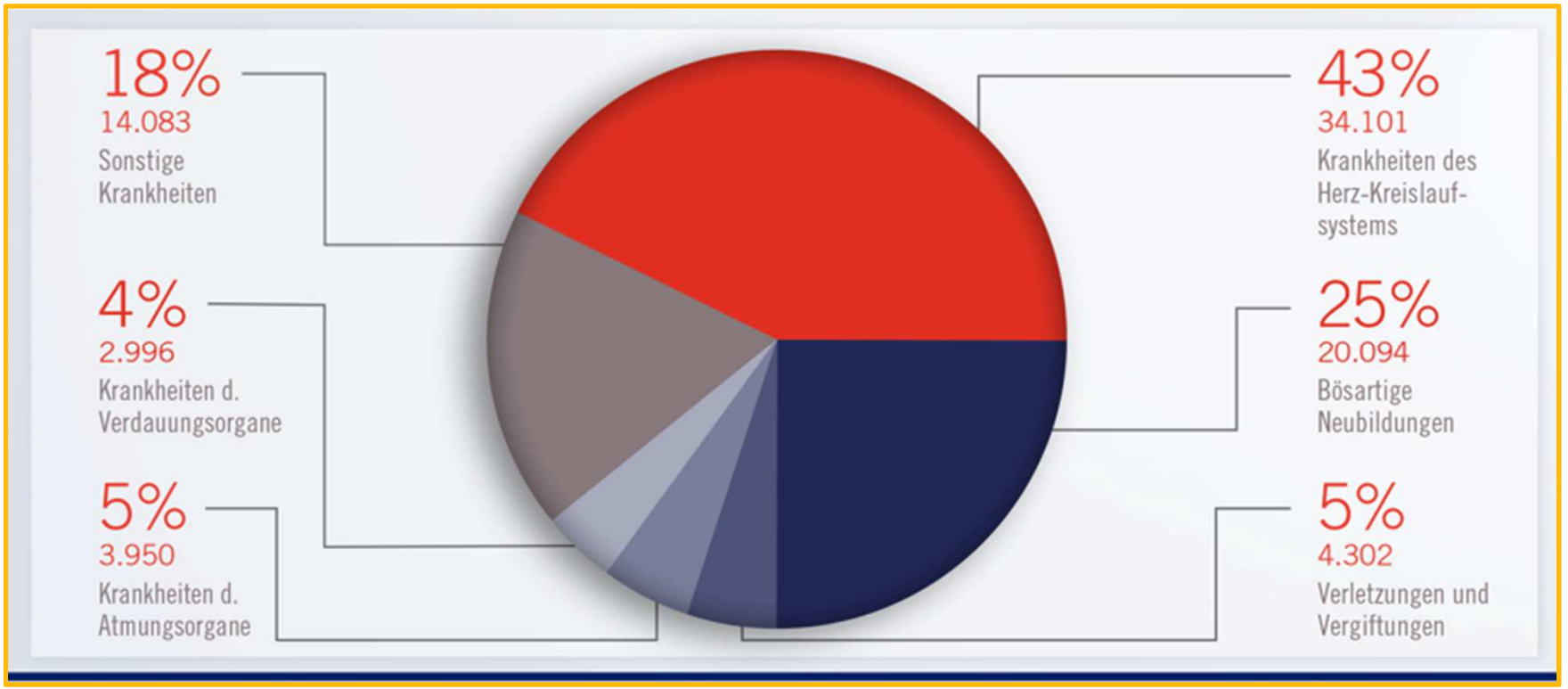


Neugeborene haben LDL-C von 20-30mg/dl

- Nach: Verschuren WM et al. . Serum Total Cholesterol and Long-term Coronary Heart Disease Mortality in Different Cultures*JAMA*.1995;274(2):131-136

Kardiovaskuläre Erkrankungen verursachen jedes Jahr mehr als 30.000 Todesfälle in Österreich[1]

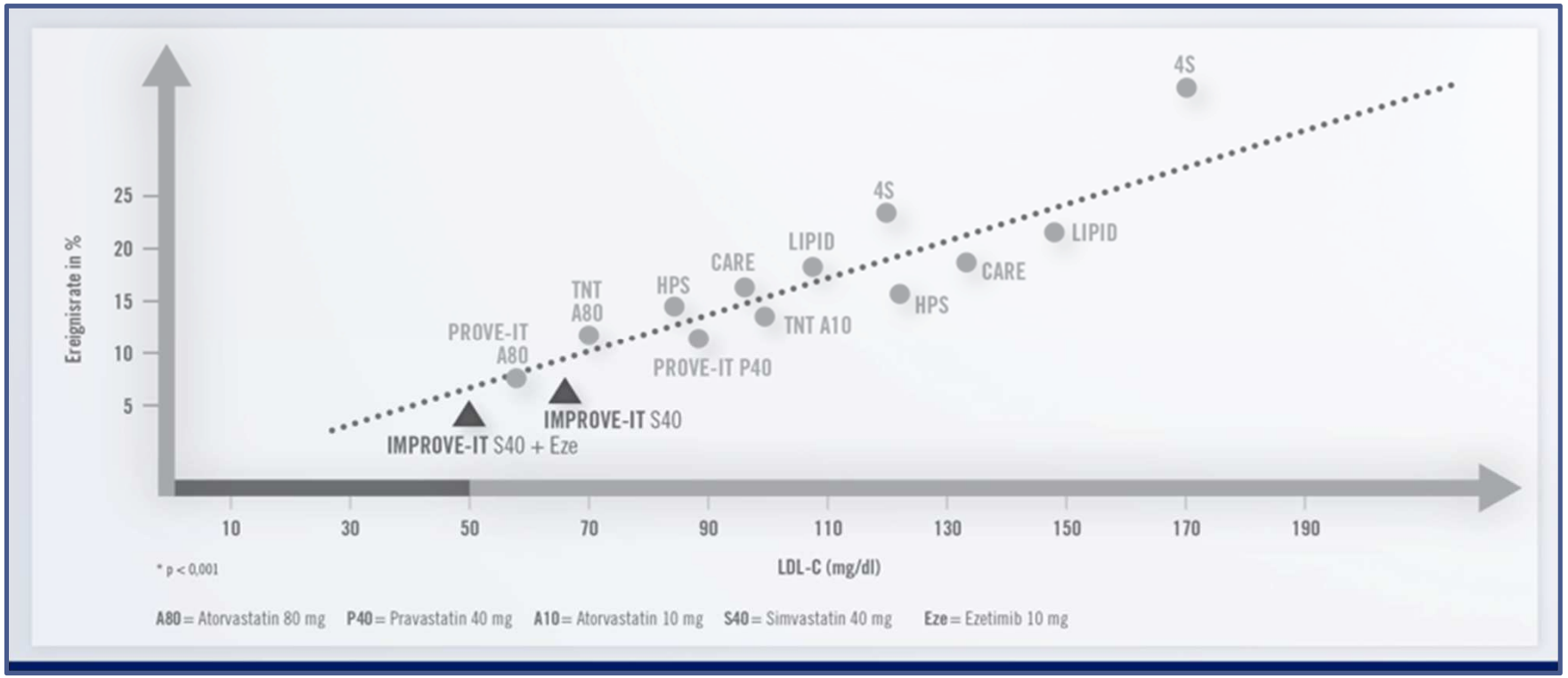
TODESURSACHEN 2013 (ABSOLUT UND IN %)



1. Statistik Austria, Todesursachenstatistik. Erstellt am 03.06.2014

Klare Korrelation zwischen Reduktion von LDL-C und kardiovaskulärem Risiko

Epidemiologie – Pathogenese



Adaptiert nach LaRosa et. al.

~39 mg/dl Reduktion von LDL-C = ~20% Risikoreduktion für kardiovaskuläre Ereignisse[1*]

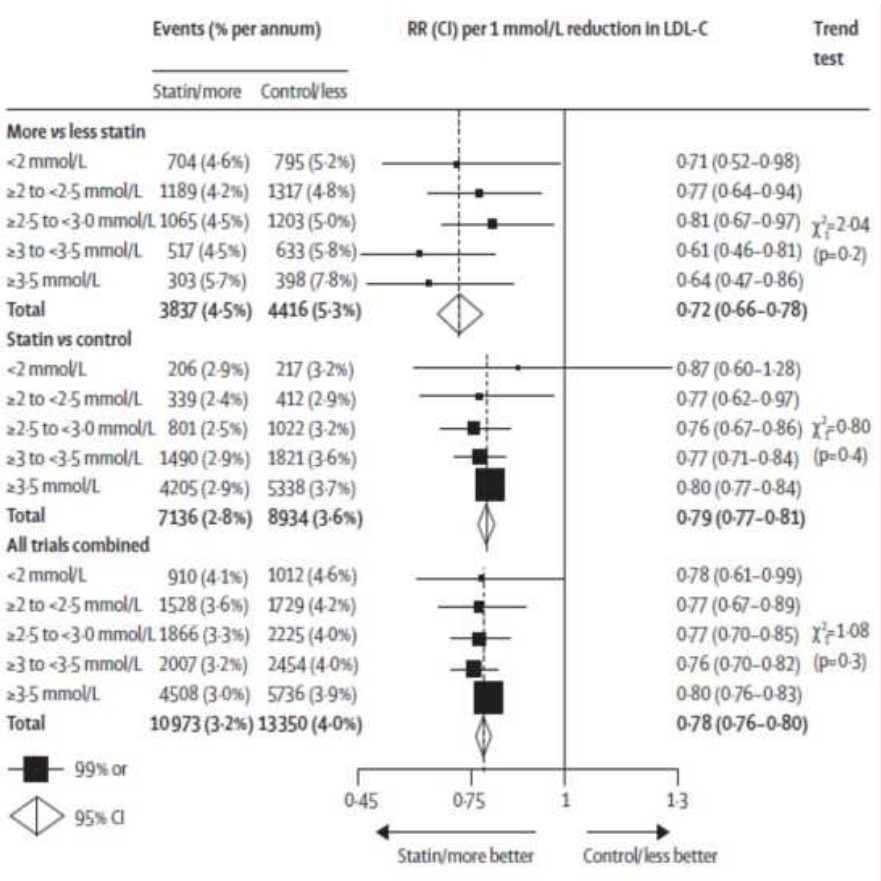
Klinische Bedeutung der LDL-C-Senkung durch Statine

Meta-Analyse von **26 RCT** mit n =**170.000 Patienten** und d =**4,8 Jahren** mittlerer Nachbeobachtungszeit

Je 1 mmol/l (16mg/dl LDL-C Senkung:)

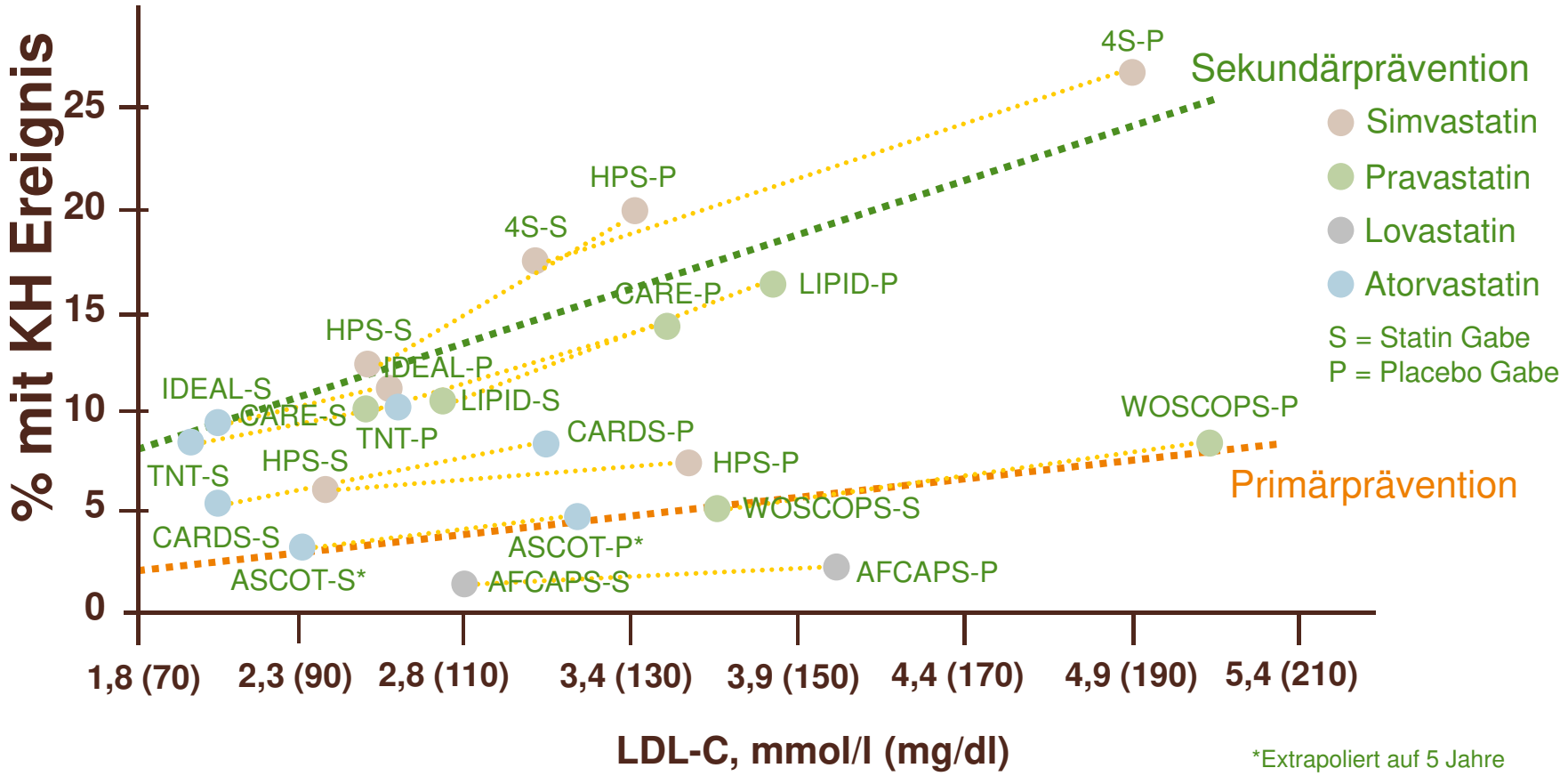
Koronarereignisse	- 22%
- Gesamt-Mortalität	- 10%
- KHK-Mortalität	- 20%
- andere Koronarmortalität	- 11%
- Schlaganfallmortalität	- 4% (n.s.)
- andere Gefässmortalität	- 2% (n.s.)
- Krebsmortaliät	- 3% (n.s.)
- Inzidenz von Krebs	+ 0 (n.s.)

Senkung von LDL-C um 70-100 mg/dl senkt KHK-Inzidenz um 40 - 50%



- The Cholesterol Treatment Trialists' (CTT) Collaborators: Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials.Lancet 376: 1670-1681, 2010

Primär versus Sekundär-Prävention



- Adapted from Kastelein JP: The future of best practice. *Atherosclerosis*. 1999;143(suppl 1):S17-S21

Familiäre Hypercholesterinämie

- Ca. 1: 300, NEU
- LDL-C über 20 aa > 200 mg/ dl
- LDL-C über 30 aa > 250 mg / dl
- Erbgang autosomal dominant
- Familienscreening !!

FH Registerdaten Graz

Team: Prof. Dr. H. Toplak

OA.Dr. K.Mellitzer, A. Beck , Dr. D. Leitner

Screeningbeginn: 10.10.2016

Insgesamt **65** Personen mit heFH , davon 40 Frauen und 25 Männer

Durschnittsalter: 48,9 Jahre

Primärprävention: (32 P) 45,8 Jahre

LDL-C : 158,4mg/dl

8 P **ohne Therapie LDL-C von 227,6mg/dl**

5 P Alternativen (Roter Reis, Omega-3-FS)

Sekundärprävention: (33P) 51,8 Jahre

KHK : 22, davon 8 mit St.p. MI

Rest: Carotisstenosen und PAVK

LDL-C : 104,8mg/dl

1 P keine Therapie (84 Jahre, LDL 414)

19 P auf PCSK 9-NACH Registereinschluss

K.Mellitzer,Nov.2017

Patient, 21 Jahre ; FH

Vater heFH, 48J.,kein Ereignis bisher, Atorvastatin 40mg

Chol 207, HDL 51 , LDL 104 , TG 159

Oma heFH, 71J., KHK,MI mit 64J.,Atorvastatin 80mg und PCSK9

Chol 171, HDL 69, LDL 83, TG 97

- Mutter ? Keine Daten

- NATIV: Chol 399, LDL 333,
- Crestor 10mg (mit 20mg NW) : Chol 326, LDL 269

➡ Patient, 21 Jahre ; FH

- Hat bereits eine 30%ige Carotisstenose, damit klar in der Sekundärprävention

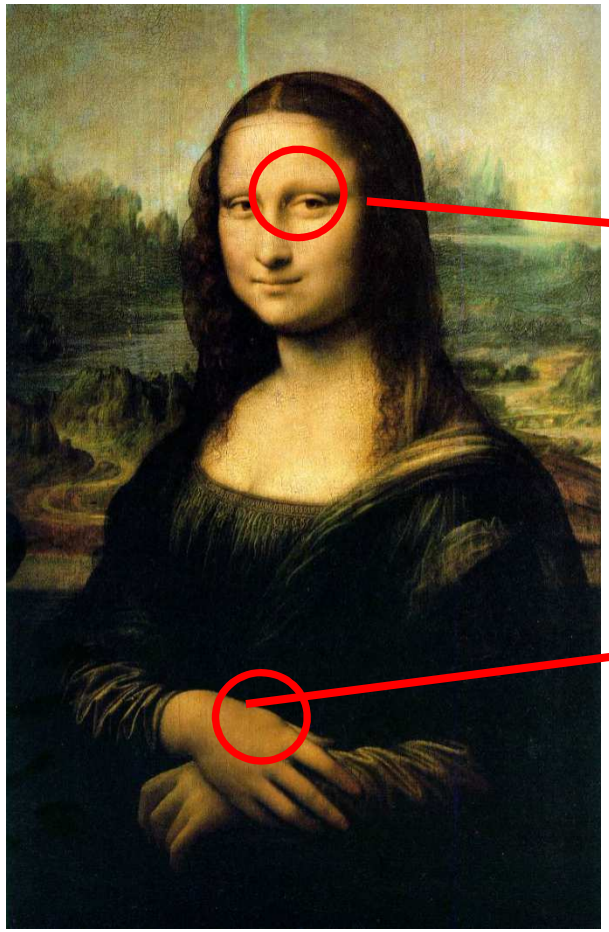
Therapie: Crestor 10mg + Repatha 140mg

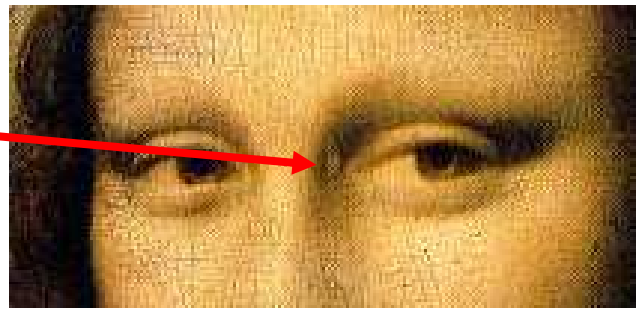
Chol 253 **HDL** 51 **LDL** 176 **TG** 126

Doppelmutation ??

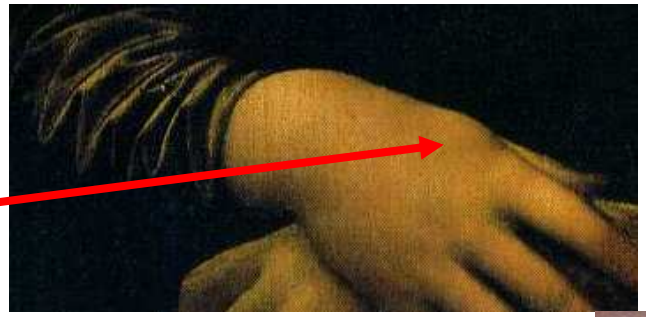
Genetik wird in der Steiermark nicht bezahlt !

Mona Lisa, zum Zeitpunkt der Entstehung des Bildes zw. 25-30 Jahre alt (1503 -1504), verstorben mit 37 Jahren,
bei **V.a. familiäre Hypercholesterinämie**



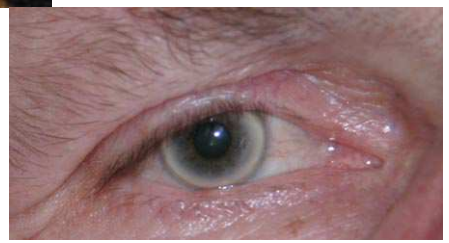


Xanthelasma



Xanthome

Arcus lipoides



- Bildquelle: Leonardo da Vinci: *La Gioconda* (Louvre, Paris)

Dutch Lipid Clinic Network-Kriterien

für die klinische Diagnose von heFH

Bewertung	Charakteristika
1 Punkt	Verwandter 1. Grades mit vorzeitiger CVD oder LDL-C >95. Perzentile *oder* Eigenanamnese der vorzeitigen CVD *oder* LDL-C zwischen 155 und 189 mg/dl
2 Punkte	Verwandter 1. Grades mit Sehnen-Xanthom oder Arcus lipoides corneae *oder* Verwandtes Kind ersten Grades (<18 Jahre) mit LDL-C >95. Perzentile *oder* Eigenanamnese von KHK
3 Punkte	LDL-C zwischen 190 und 249 mg/dl
4 Punkte	Vorhandensein eines Arcus lipoides corneae bei Patienten <45 Jahren
5 Punkte	LDL-C zwischen 250 und 329 mg/dl
6 Punkte	Vorhandensein eines Sehnen-Xanthoms
8 Punkte	LDL-C >330 mg/dl *oder* funktionelle Mutation eines LDLR-Gens
Risiko	3-5 Punkte: mögliche FH, 6-7 Punkte: wahrscheinliche FH, ≥8 Punkte: sichere FH

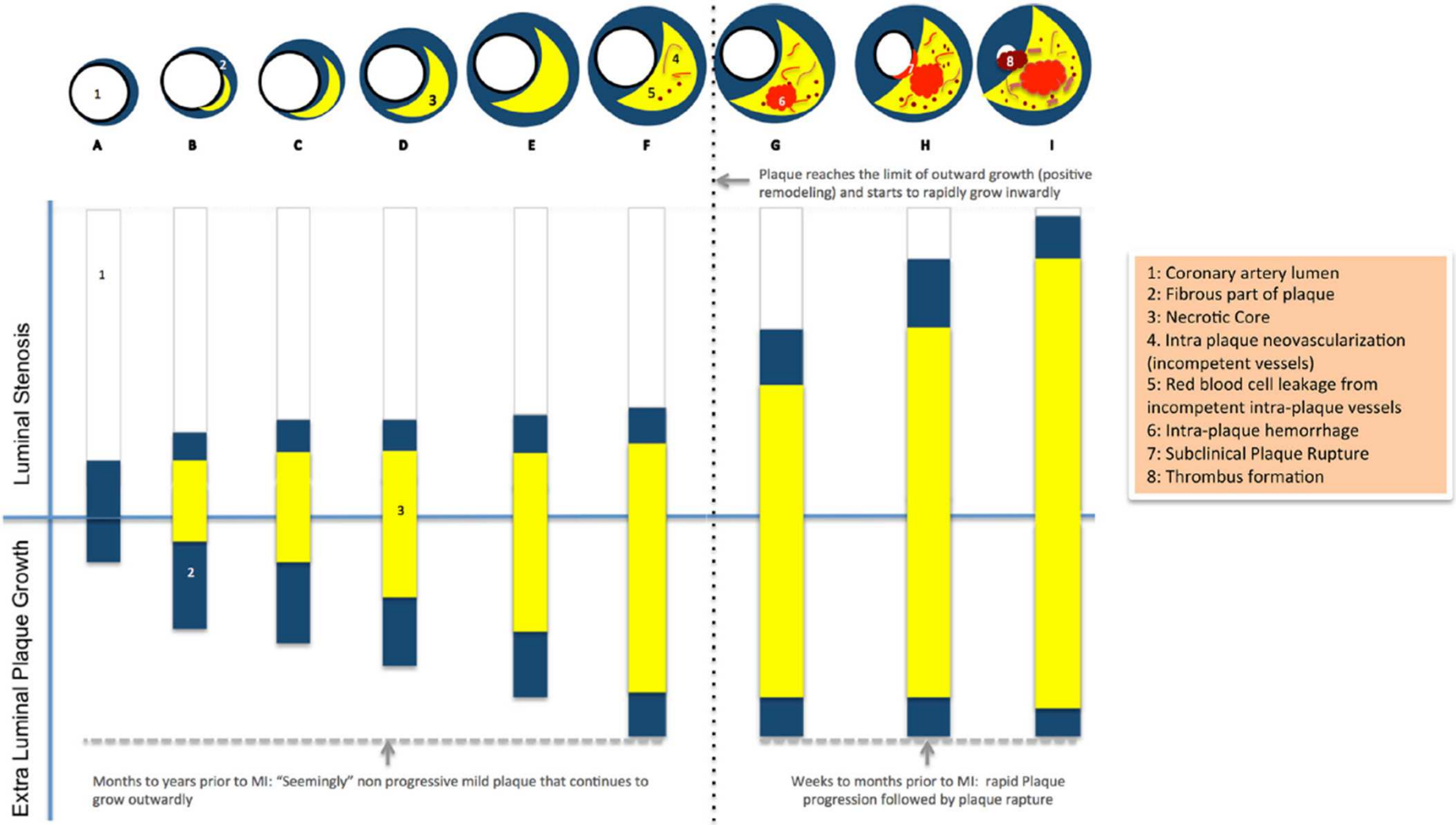
- Civeira et al. Guidelines for the diagnosis and management of heterozygous familial hypercholesterolemia. Atherosclerosis 2004;173:55-68.

Was macht ein Lipidsenker ?

Laborkosmetik oder mehr ?

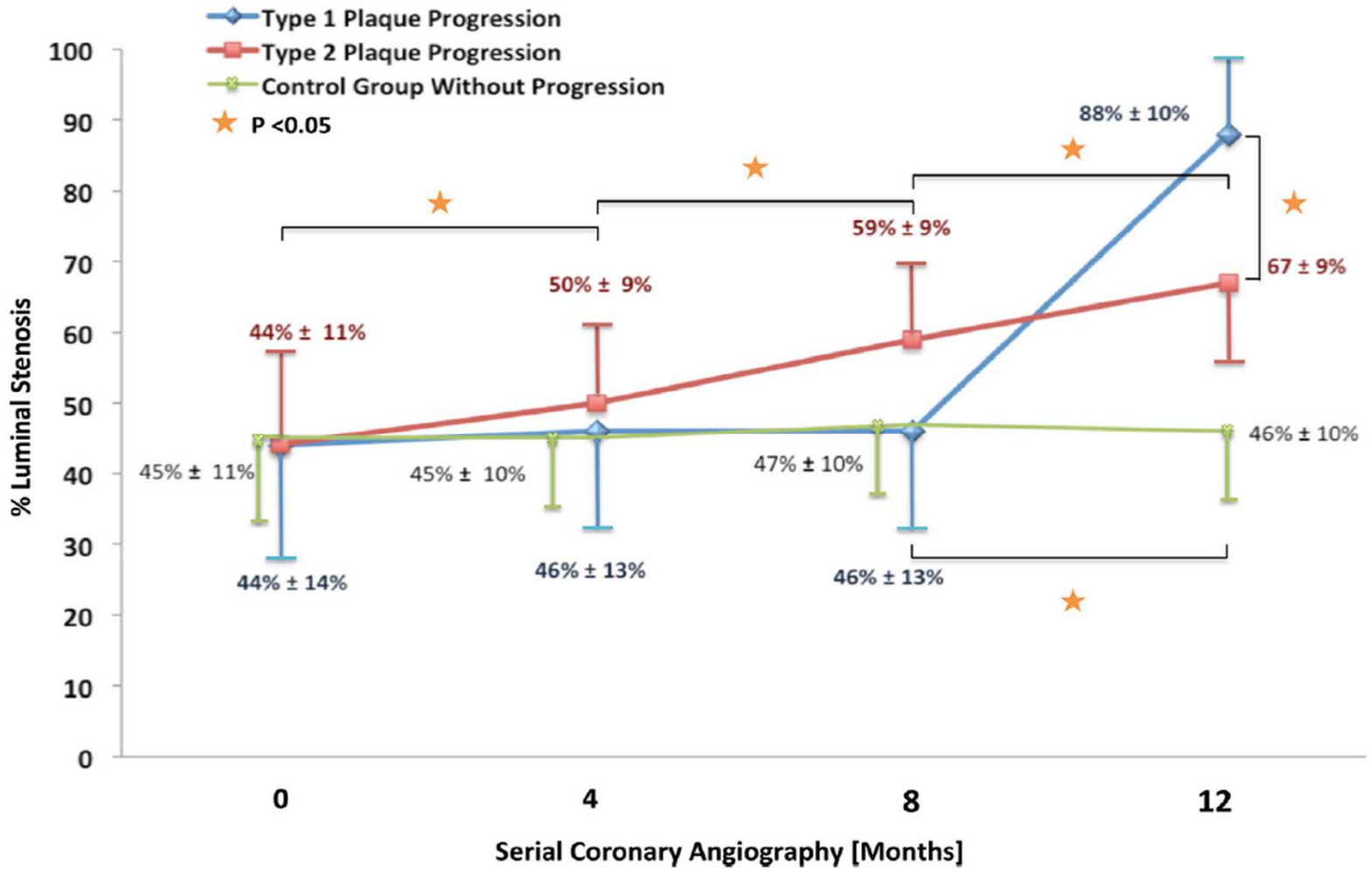
Bezeichnung		Wert		Normbereich
18.06.13	Leuko.	9,4	µ/l	4,6 - 10,2
	Ery.	5,2	Mio/µl	4,2 - 5,4
	HB	14,7	g/dl	12,0 - 16,0
	HKT	43,1	%	36,0 - 46,0
	MCV	83,4	fl	85,0 - 95,0
	MCH	28,4	pg	27,0 - 33,0
	MCHC	34,1	g/dl	32,0 - 35,0
	Thrombo.	351,0	x1000/µl	150,0 - 400,0
	GOT	21,0	U/l	10,0 - 35,0
	GPT	22,0	U/l	10,0 - 35,0
	25 OH Vit.D	47,9	nmol/l	75,0 - 116,0
	Eisen	46,0	µg/dl	33,
	Ferritin	30.3	ng/ml	2
	Creatinin	0,9	mg/dl	0,
	FT3	2,50	pg/ml	2,0
	FT4	13,10	ng/ml	9,3
	TSH basal	3,27	µlU/ml	0,2
	ACTH	23,30	ng/l	4,7
	Cortisol basal	87.9	ng/ml	2
	Androstendion	4,3	ng/ml	0,
	DHEAS	3,4	µg/ml	0,
	SHBG	6,8	nmol/l	18,
	Freier Androg.	22,7	Index	0,
	E2	47,3	pg/ml	5,
	Progesteron	0,7	ng/ml	0,
	17OHP basal	0,91	µg/l	0,1
	FSH	6,9	mIE/ml	3,
	LH	20,1	mlU/ml	1,
	Prolaktin	14,40	ng/ml	4,7
	Testosteron	0,44	ng/ml	0,0
	Dihydrotesto.	436.3	pg/dl	1
	Androstandiol	3,87	ng/ml	0,0 - 0,00

Atherosklerose und Plaque-Progression



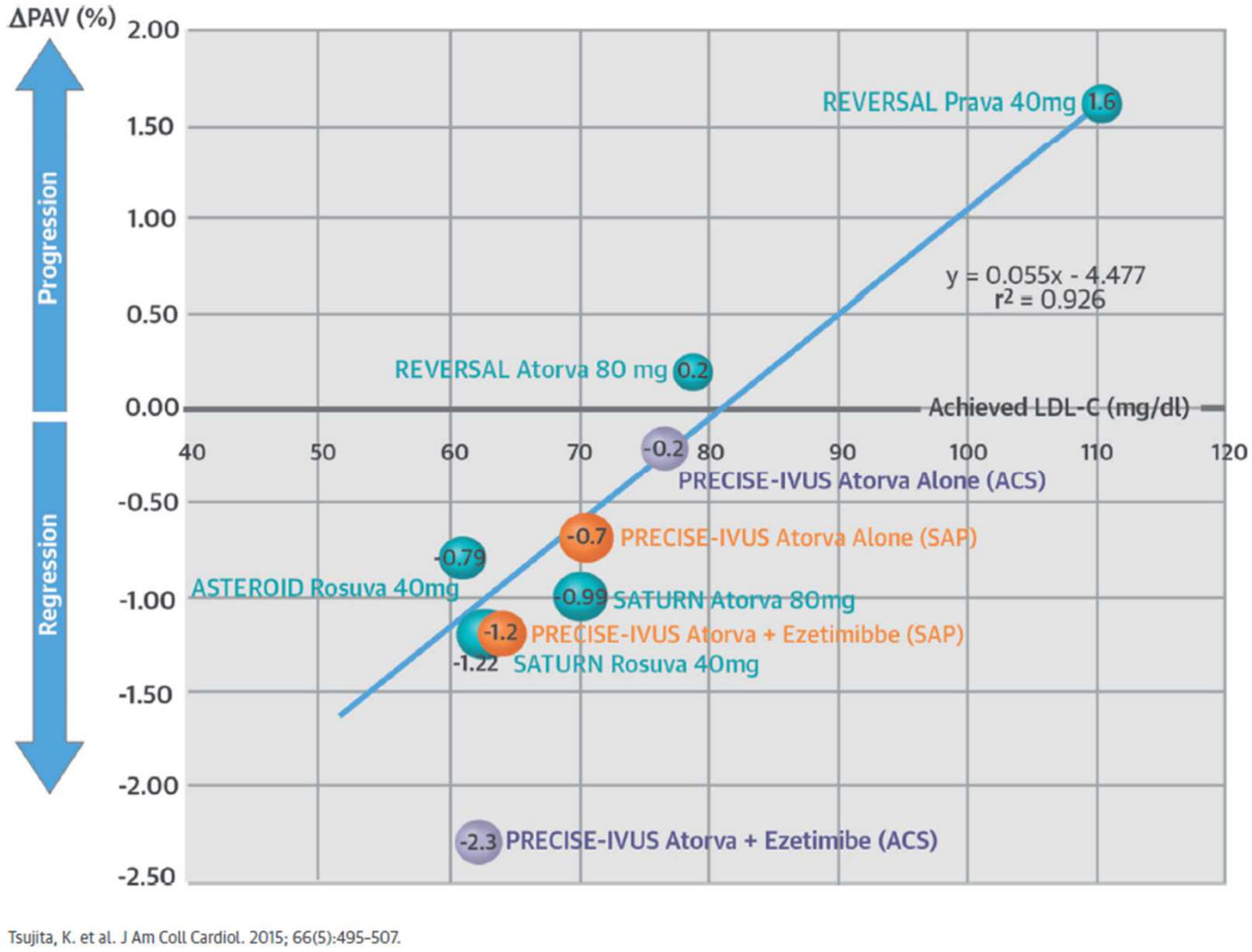
Ahmadi A. et al Do Plaques Rapidly Progress Prior to Myocardial Infarction? Circ. Res. 2015

Zwei Typen einer Plaque Progression



Ahmadi A. et al Do Plaques Rapidly Progress Prior to Myocardial Infarction? Circ. Res. AHA 2015

Effekt von Statinen auf die koronare Plaque-Regression (ACS und SAP Patienten)



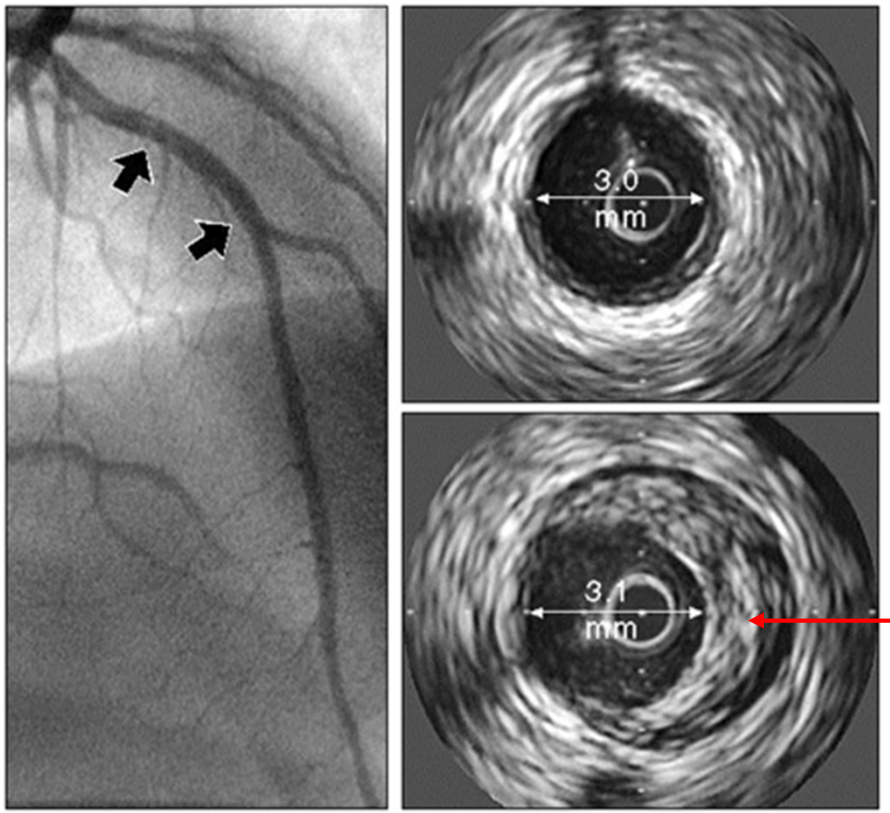
Tsujita, K. et al. J Am Coll Cardiol. 2015; 66(5):495-507.

K. Tsujita et al, Impact of Dual Lipid-Lowering Strategy With Ezetimibe and Atorvastatin on Coronary Plaque Regression in Patients With Percutaneous Coronary Intervention, JACC 2015

The IVUS technique can detect angiographically "silent " atheroma

Angiogram

No evidence of disease



Little evidence of disease

IVUS

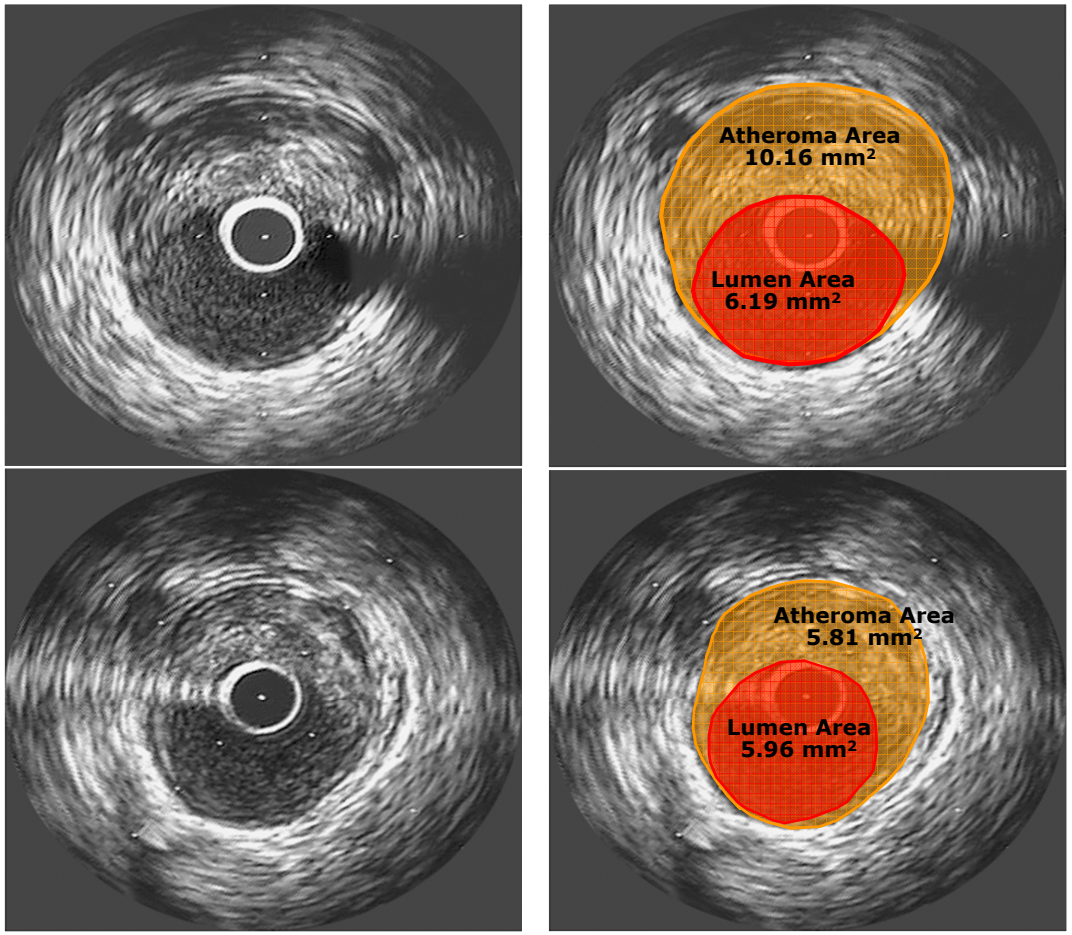
Atheroma

IVUS=intravascular ultrasound
Nissen S, Yock P. *Circulation 2001*; 103: 604–616

Example of regression of atherosclerosis with rosuvastatin in ASTEROID, measured by IVUS

Baseline IVUS

Follow-up IVUS 24 months rosuvastatin



Ref: Nissen S *et al.* JAMA 2006; **295**: e-publication ahead of print

Lipidkonsensus 2015/2016

Tabelle 1: Optionen zur Abschätzung des vaskulären Risikos

Risiko-Kategorie	RF*	SCORE§ (10-Jahre-Risiko)	Framingham# (10-Jahre-Risiko)	vaskuläre Morbidität
sehr hoch		≥ 10 %		• manifeste koronare Herzkrankheit (KHK) • ischämischer Schlaganfall oder transitorische ischämische Attacke (TIA) + Nachweis von Atherosklerose • periphere arterielle Verschlusskrankheit (PAVK) • Typ-2-Diabetes • Typ-1-Diabetes mit Endorganschädigung (z. B. Albuminurie) • moderate bis schwere Nephropathie • progrediente oder rezidivierende KHK trotz LDL-C < 100 mg/dl
hoch	> 2	≥ 5 %	> 20 %	• familiäre Hypercholesterinämie • Typ-1-Diabetes + Alter > 40 Jahre ohne Zielorganerkrankung • merklich erhöhte einzelne Risikofaktoren (z. B. familiäre Hypertension, schwere Hypertension)
mäßig	2	1–5 %	10–20 %	
gering	0–1	< 1 %	(meist < 10 %)	

RF = Risikofakoren/-marker; LDL-C = Low-Level-Lipoprotein-Cholesterin

LDL-C
< 70mg/dl

LDL-C
< 100mg/dl

…..Grundsatzfragen zum Thema **Lipide**

Brauchen wir neue Lipidsenker ?

A: Ja

B: Nein

Patient, m, 67 Jahre
KHK II, St.p.2 fach Stent , St.p. Carotis TEA li

- Klare Indikation zur Lipidsenkung, mit Ziel LDL-C < 70mg/dl
- Nativwerte: Chol 195 HDL 36, LDL 133 TG 127

  restl. Labor weitestgehend unauff., Leber- und Nierenfunktion normal

- **Problem :** Unter Atorvastatin 40mg CK bei knapp 17.000

CK nativ ca. 600, Abklärung incl. Muskelbiopsie ohne Ergebnis

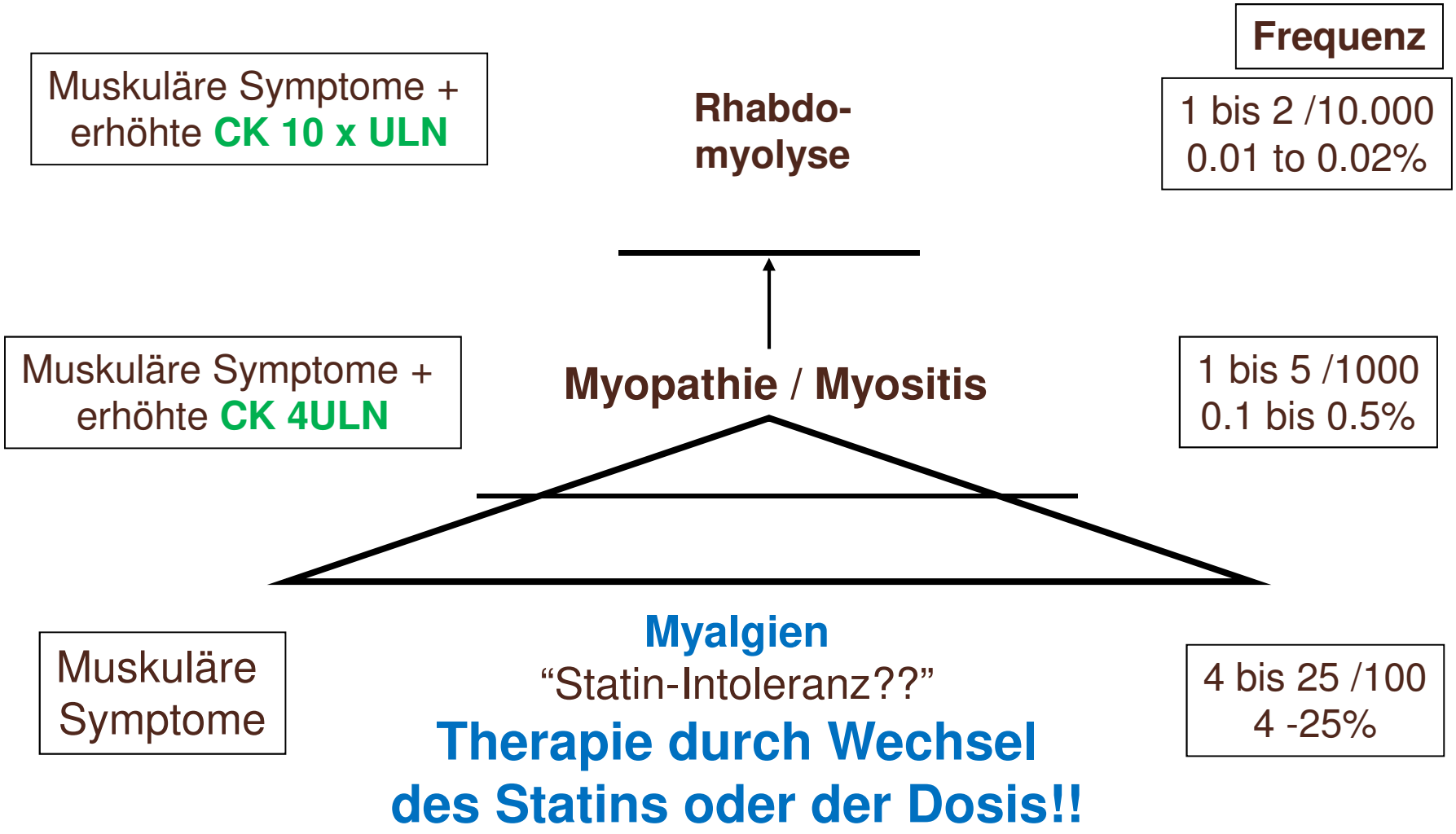
….mein erster Fall von Rhabdomyolyse unter Statin in dieser Größenordnung

….ich kam zum Schluss, kein Statin mehr zu probieren

Beginn PCSK 9 , nach 2xiger Gabe Kontrolle :

Chol 136 **HDL** 41 **LDL** 57 **TG** 191 (nach Weihnachten) , **CK 652**

Inzidenz von Myopathien durch Statine



Statin-Intoleranz
…Muskelsymptome bei Statin-Therapie

PRIMO Studie

n = 7900

Statin	% Patienten mit Muskelbeschwerden (n=832)
Pravastatin 40 mg	10,9
CYP 450 Atorvastatin 40–80 mg	14,9
CYP 450 Simvastatin 40–80 mg	18,2
Fluvastatin XL 80 mg	5,1
% Patienten mit Symptomatik	**10,5**

- Bruckert E et al. : Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients--the PRIMO study. Cardiovasc Drugs Ther. 2005:19(6):403-414.

Unerwünschte Wirkungen von Statinen

- Übelkeit, **Dyspepsie, Blähungen**, Diarrhö, Obstipation, Magen-Darm-Krämpfe,
- **Kopfschmerzen, Müdigkeit, Schlaflosigkeit, Hautausschlag**, Juckreiz, Augentrockenheit, Mundtrockenheit, Sehstörungen,
- reversible Transaminaseanstiege
- vermehrte Inzidenz von Typ 2 Diabetes
- am häufigsten sind ***Muskelschmerzen, Myopathien***
  Rhabdomyolysen (extrem selten)

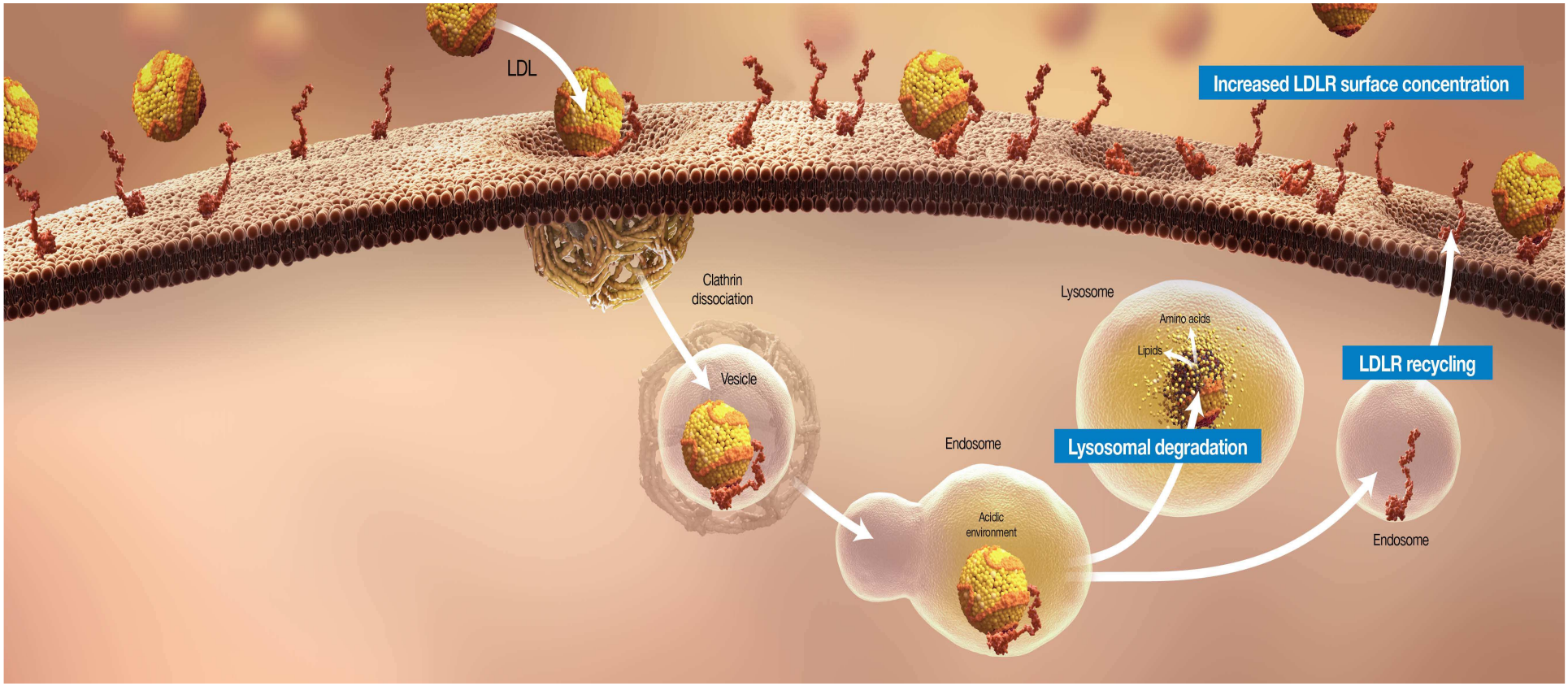
PCSK9 Inhibitoren

Humane monoklonale Antikörper

- **Evolocumab** - Amgen (REPATHA 140mg)
- **Alirocumab** - Sanofi-Aventis (PRALUENT 75/150mg)

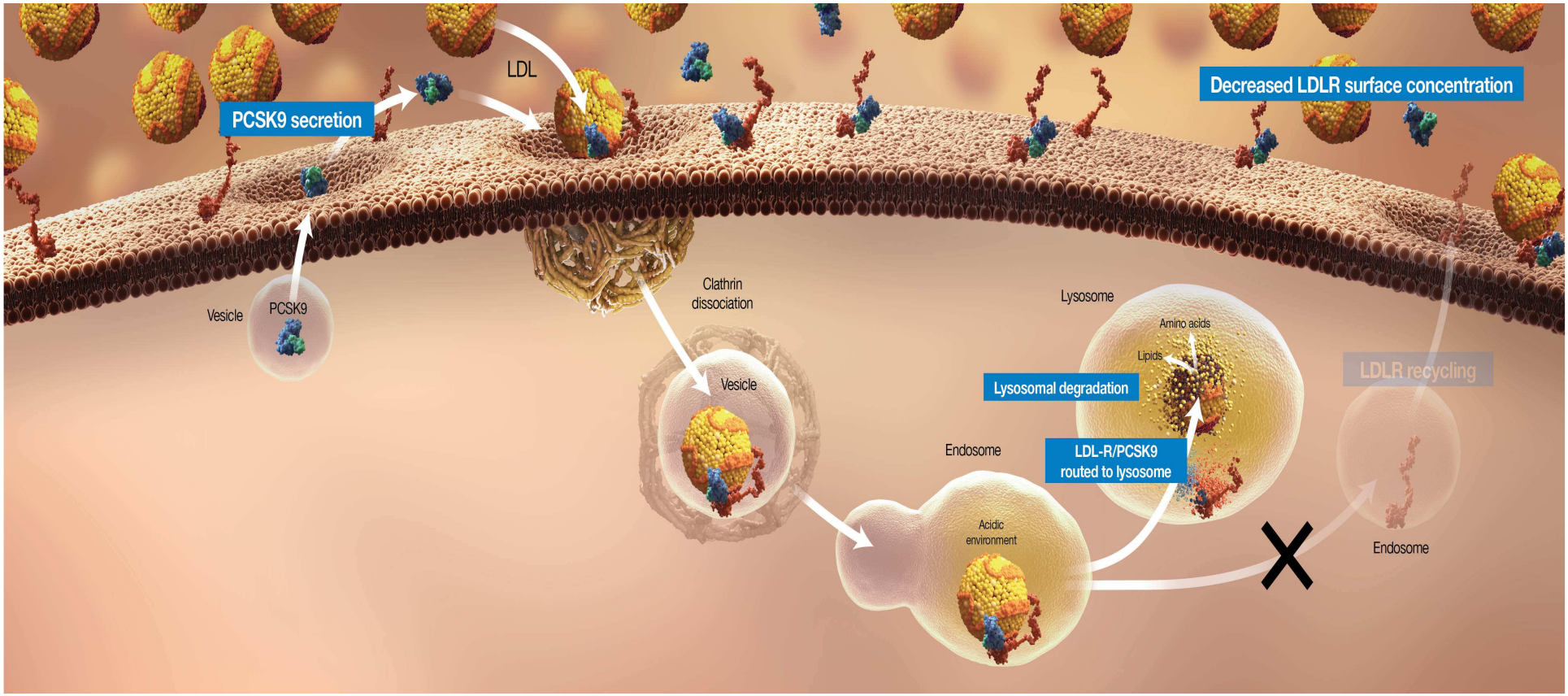
Jeweils alle 14 Tage s.c.

Recycling of LDLRs Enables Efficient Clearance of LDL-C Particles



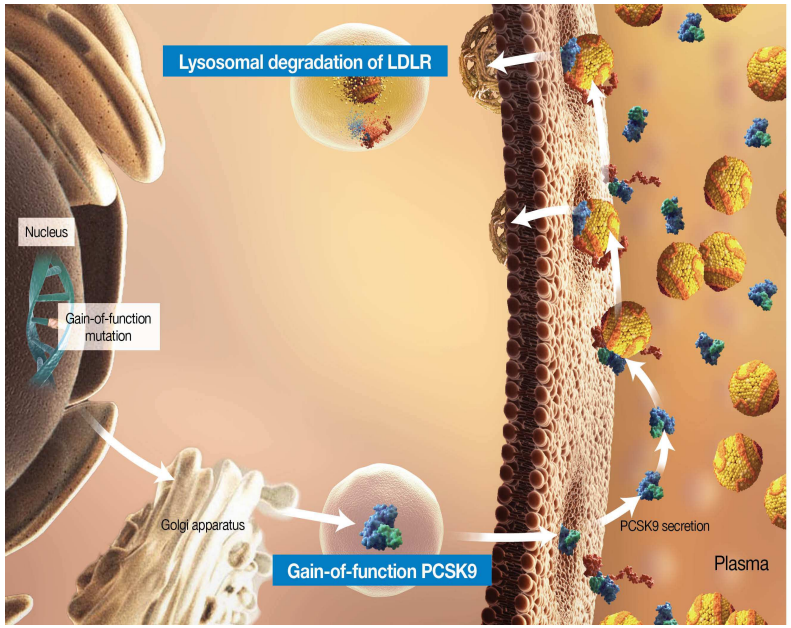
1. Brown MS, et al. *Proc Natl Acad Sci U S A*. 1979;76:3330-3337.
2. Steinberg D, et al. *Proc Natl Acad Sci U S A*. 2009;106:9546-9547.
3. Goldstein JL, et al. *Arterioscler Thromb Vasc Biol*. 2009;29:431-438.

PCSK9 Regulates the Surface Expression of LDLRs by Targeting for Lysosomal Degradation

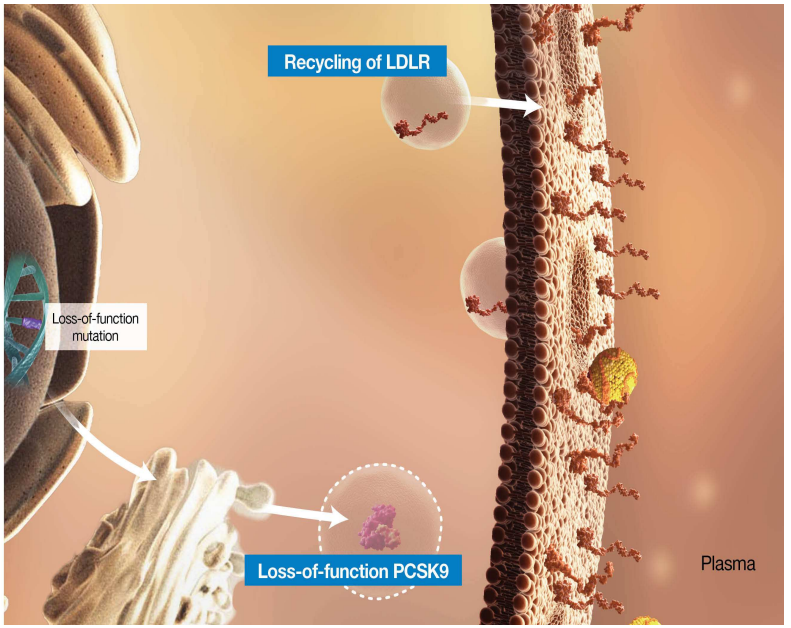


1. Qian YW, et al. *J Lipid Res*. 2007;48:1488-1498.
2. Horton JD, et al. *J Lipid Res*. 2009;50:S172-S177.
3. Zhang DW, et al. *J Biol Chem*. 2007;282:18602-18612.

Genetic Variants of PCSK9 Demonstrate Its Importance in Regulating LDL Levels



PCSK9 Gain of Function = Less LDLRs



PCSK9 Loss of Function = More LDLRs

PCSK9 Variant	Population	LDL-C	CHD Risk
R46L	ARIC, DHS	↓ 15%[1]	↓ 47%[1]
Y142X or C679X	ARIC, DHS	↓ 28%-40%[1,2]	↓ 88%[1]
R46L	CGPS	↓ 11%[3]	↓ 46%[3]

1. Cohen JC, et al. *N Engl J Med.* 2006;354:1264-1272.
2. Cohen J, et al. *Nat Genet.* 2005;37:161-165.3. Benn M, et al. *J Am Coll Cardiol.* 2010;55:2833-2842.
4. Zhao et al. *Am Journal of Hum Gen.* 2006;79:514-534.
5. Steinberg D, et al. *Proc Natl Acad Sci U S A.* 2009;106:9546-9547.

DESCARTES:

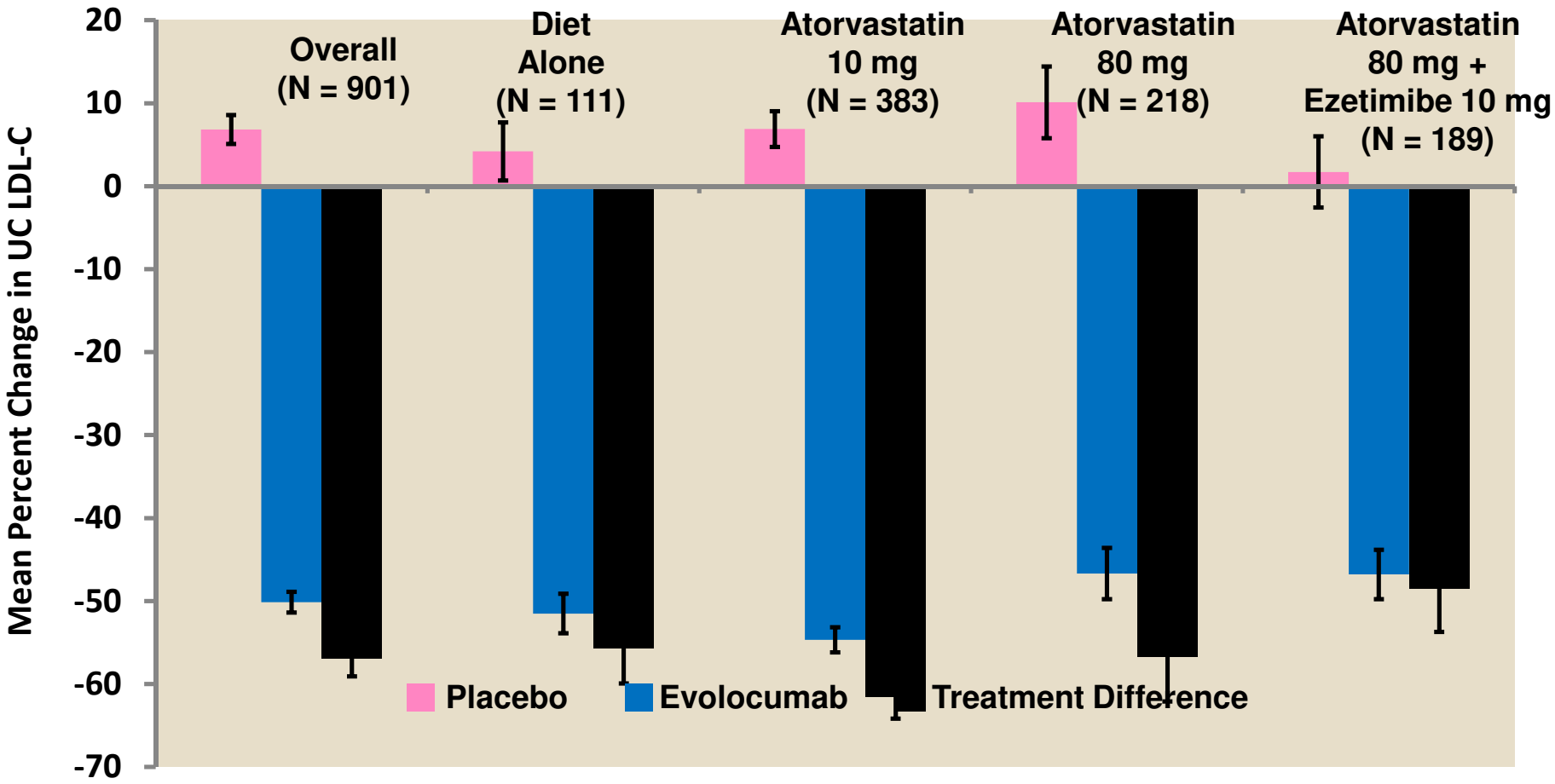
Long-term Tolerability and Efficacy of Evolocumab (AMG 145) in Hyperlipidemic Subjects: A 52 Week Phase 3 Double-blind, Randomized, Placebo-controlled Study

Dirk J. Blom, Tomas Hala, Michael Bolognese, Michael J Lillestol,
Phillip D Toth, Lesley Burgess, Richard Ceska, Eli Roth,
Michael J Koren, Christie M Ballantyne, Maria Laura Monsalvo,
Kate Tsirtsonis, Jae B Kim, Rob Scott, Scott M Wasserman, and Evan A Stein,
for the DESCARTES Investigators

Durable **E**ffect of PC**S**K9 antibody **C**omp**AR**ed wi**T**h plac**E**bo **S**tudy (NCT01516879)

29 Mar 2014, Featured Clinical Research Session 400, American College of Cardiology and N Engl J Med 2014;370:1809–19
Disclaimer: Evolocumab has not been approved for use by the EMA and/or any other regulatory authorities outside of the EU

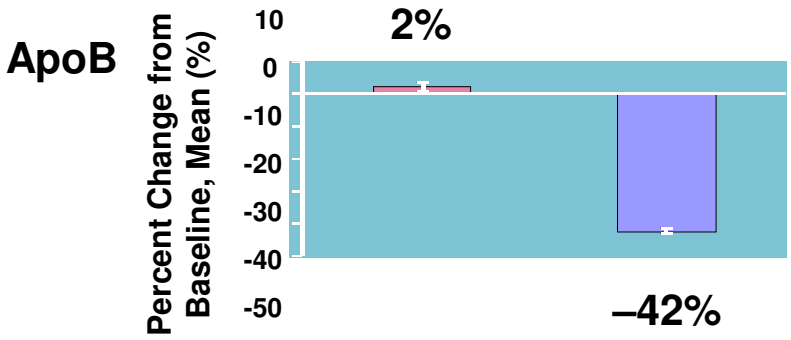
DESCARTES: % Change in UC LDL-C from Baseline at Week 52

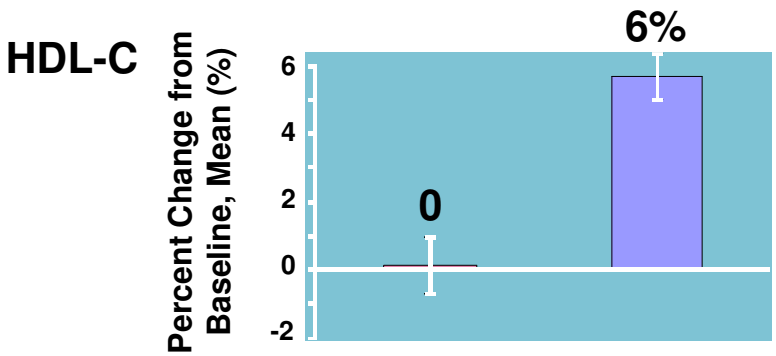


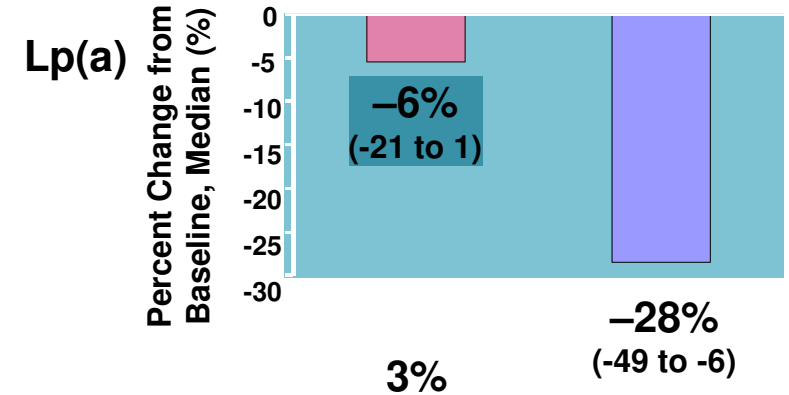
- 6.8% increase from baseline in LDL-C observed in placebo group (N = 302)
- 50.1% decrease from baseline in LDL-C observed in evolocumab group (N = 599)*
- 57% treatment difference

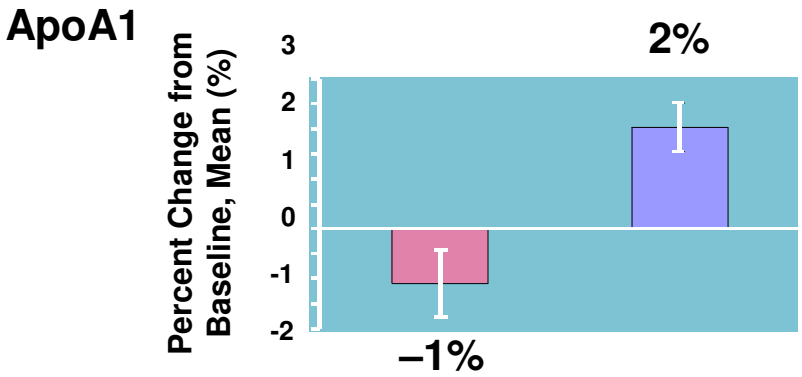
Error bars represent standard error for treatment difference. Treatment difference are least squares mean derived from a repeated measures model. *Average of all evolocumab patients. UC, ultracentrifugation

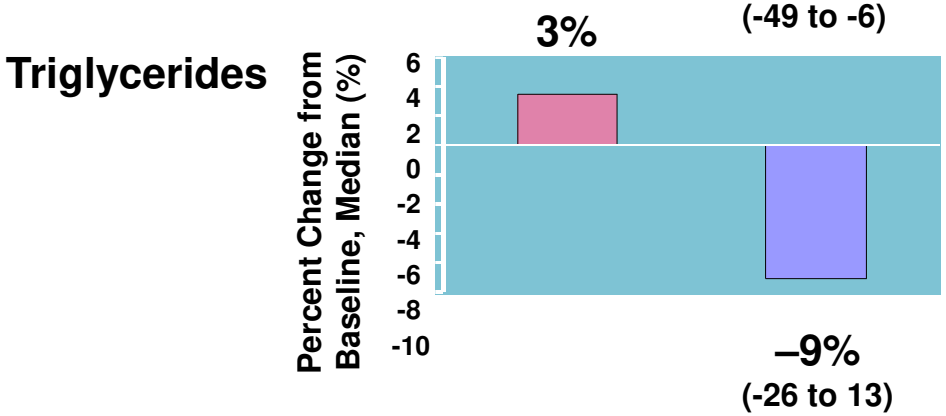
DESCARTES: Other Lipids at Week 52











Placebo QM

Evolocumab 420 mg QM

Error bars represent standard error
Data in parentheses represent Q1 to Q3

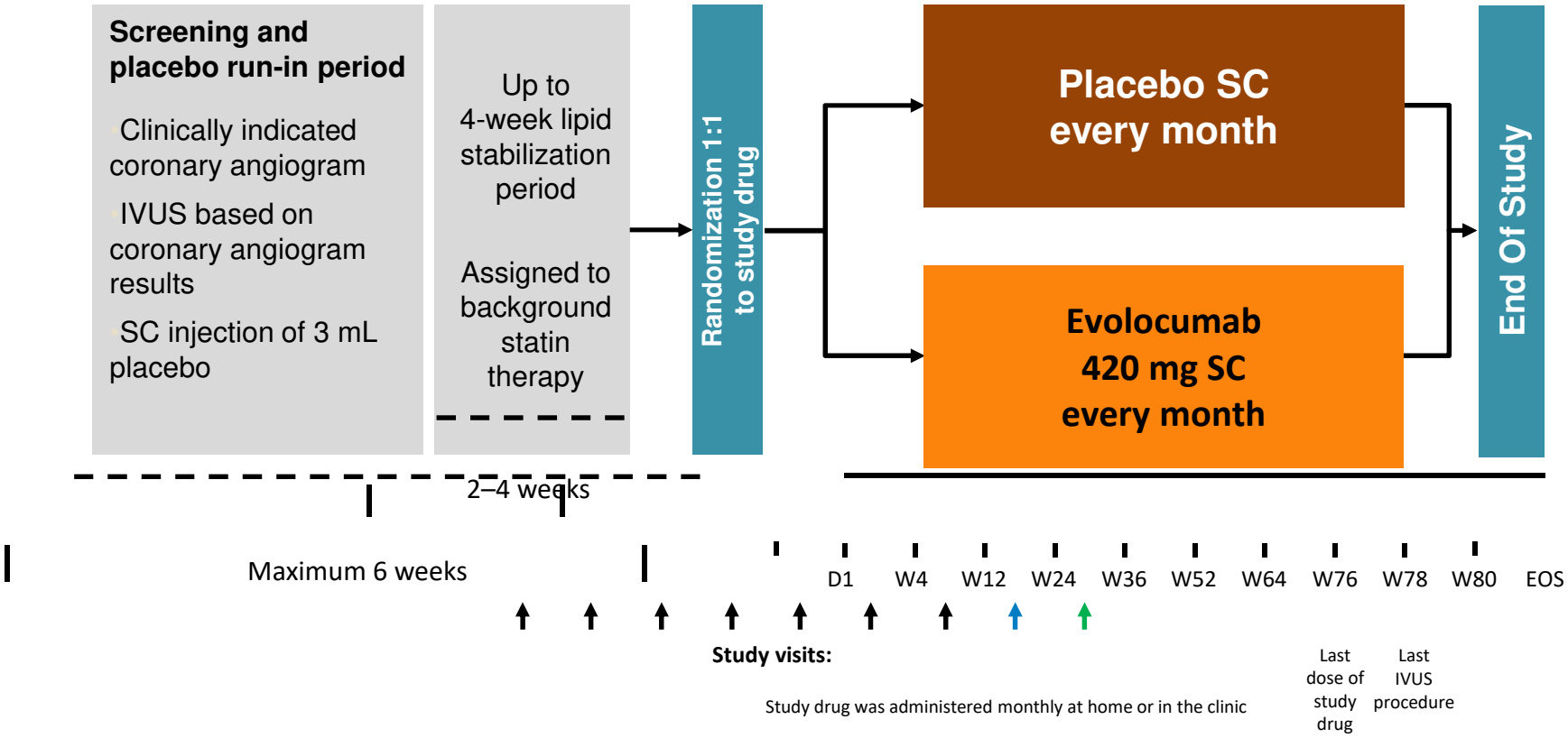
DESCARTES: Treatment Emergent Adverse Events II

n (%)	Placebo N = 302	Evolocumab N = 599
Most Common Treatment Emergent AEs		
Nasopharyngitis	29 (9.6)	63 (10.5)
Upper respiratory tract infection	19 (6.3)	56 (9.3)
Influenza	19 (6.3)	45 (7.5)
Back pain	17 (5.6)	37 (6.2)
Neurocognitive AEs*	2 (0.7)	1 (0.2)
Amnesia - Short-term memory loss	0 (0.0)	1 (0.2)
Dementia With Lewy Bodies	1 (0.3)	0 (0.0)
Encephalopathy	1 (0.3)	0 (0.0)

Treatment emergent adverse events are adverse events occurring between the first dose of Study Drug and End of Study

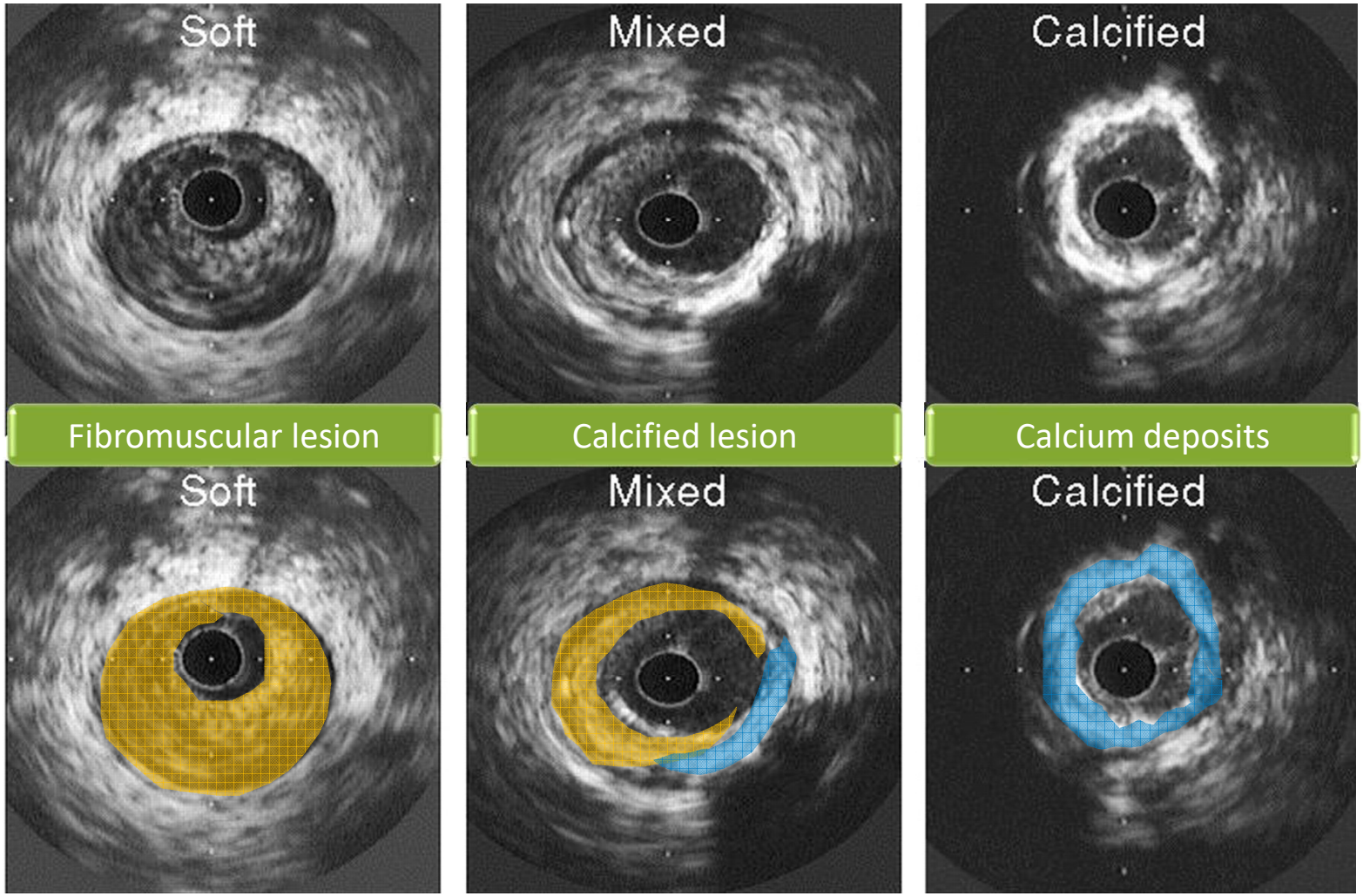
* Searched HLGT terms: Deliria (incl confusion); cognitive and attention disorders and disturbances; dementia and amnestic conditions; disturbances in thinking and perception; mental impairment disorders

GLAGOV: Study Design



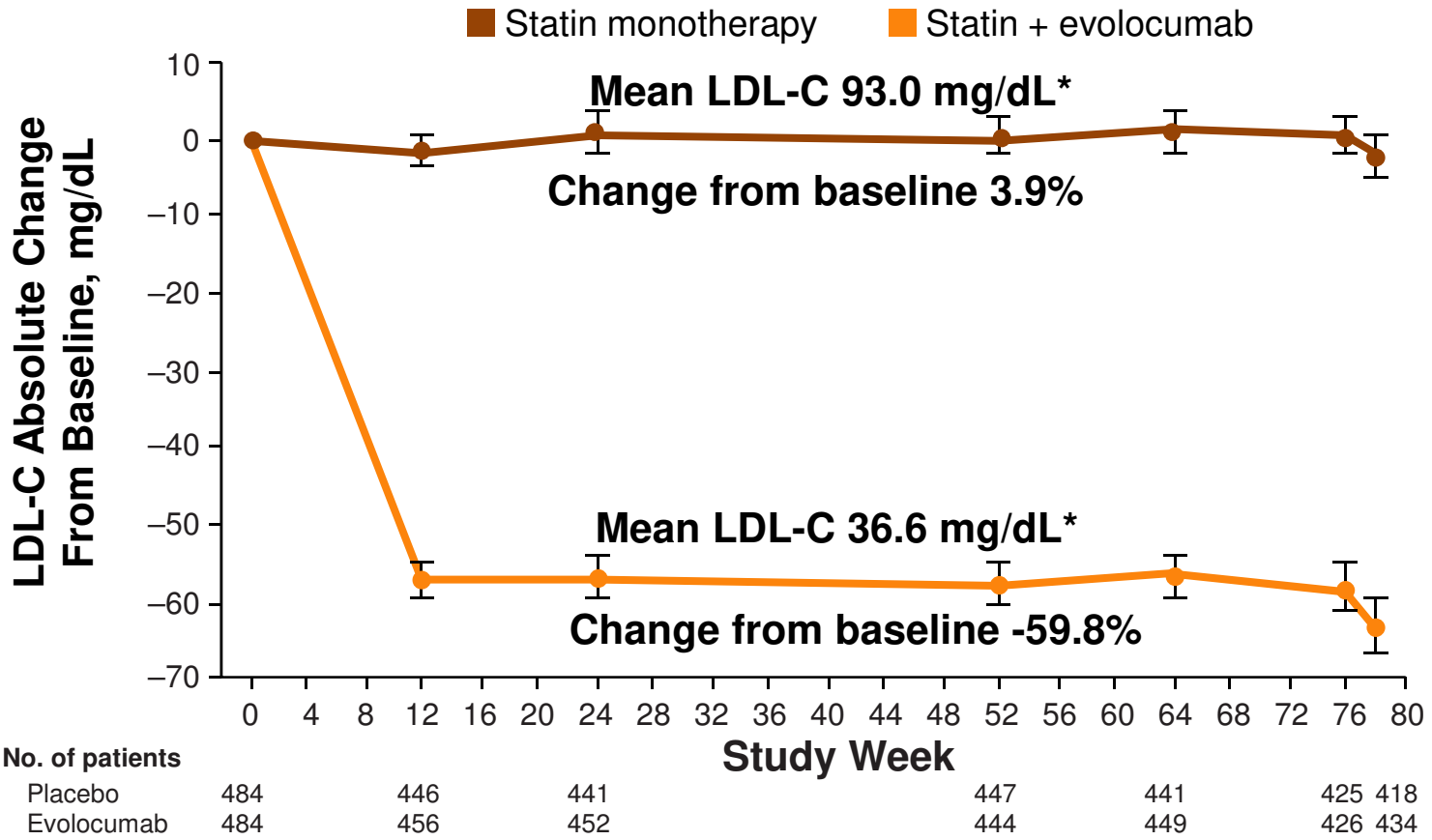
*Nominal change refers to the actual number, as opposed to percent change
D = day; IVUS = intravascular ultrasound; SC = subcutaneously; W = week.
Puri R, et al. *Am Heart J*. 2016;176:83-92.

IVUS Images of Plaque Morphology



Nissen SE, Yock P. *Circulation*. 2001;103:604–616.

Mean Absolute Change in LDL-C

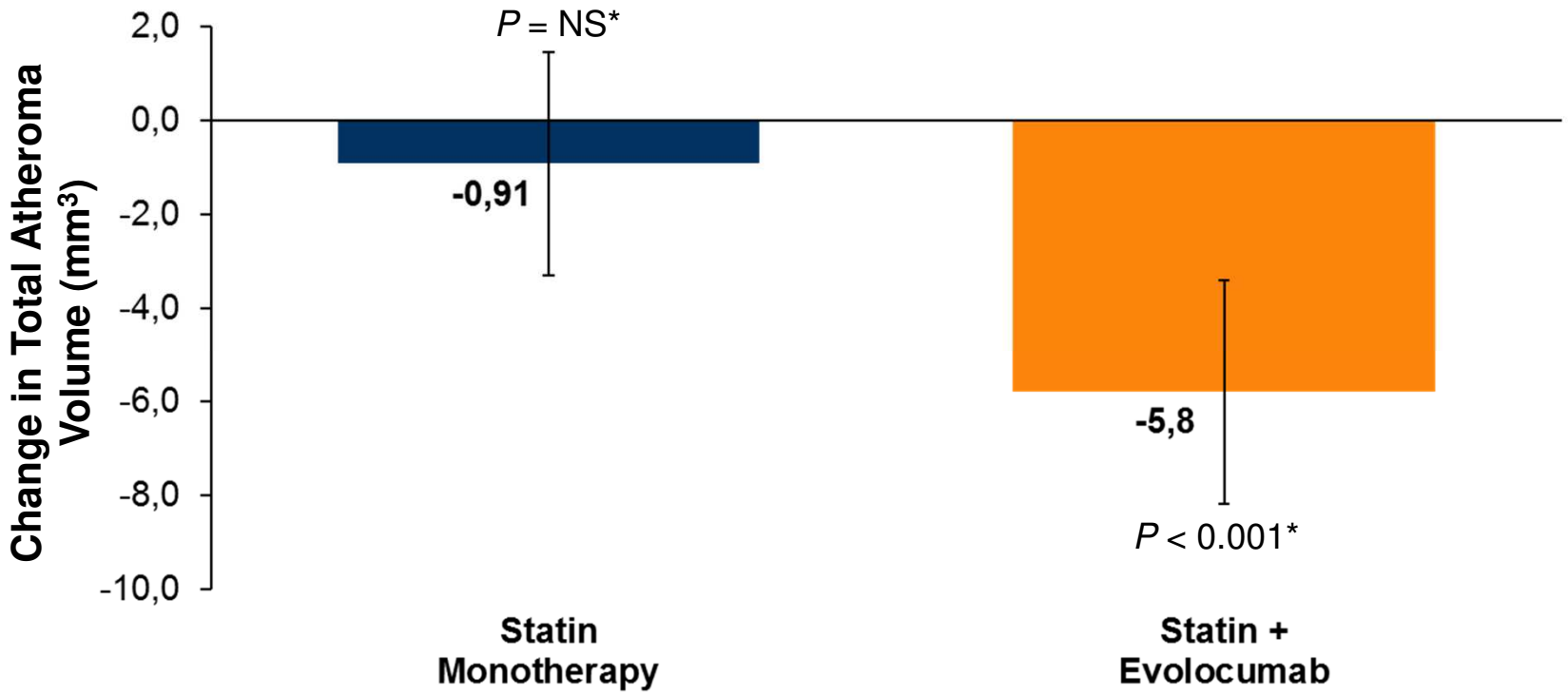


Absolute change for evolocumab-statin group: -56.3 mg/dL (-59.4 to -53.1); *P* < 0.001

Data shown are Mean (95% CI) *Time-weighted LDL-C; LDL-C = low-density lipoprotein cholesterol

Nicholls SJ, et al. *JAMA*. [published online ahead of print November 15, 2016]. doi: 10.1001/jama.2016.16951.
Nissen SE, et al. *American Heart Association Scientific Sessions,* Nov 12 - 16, 2016, New Orleans, Louisiana. Oral Presentation.

Secondary Endpoint: Nominal Change in TAV From Baseline to Week 78

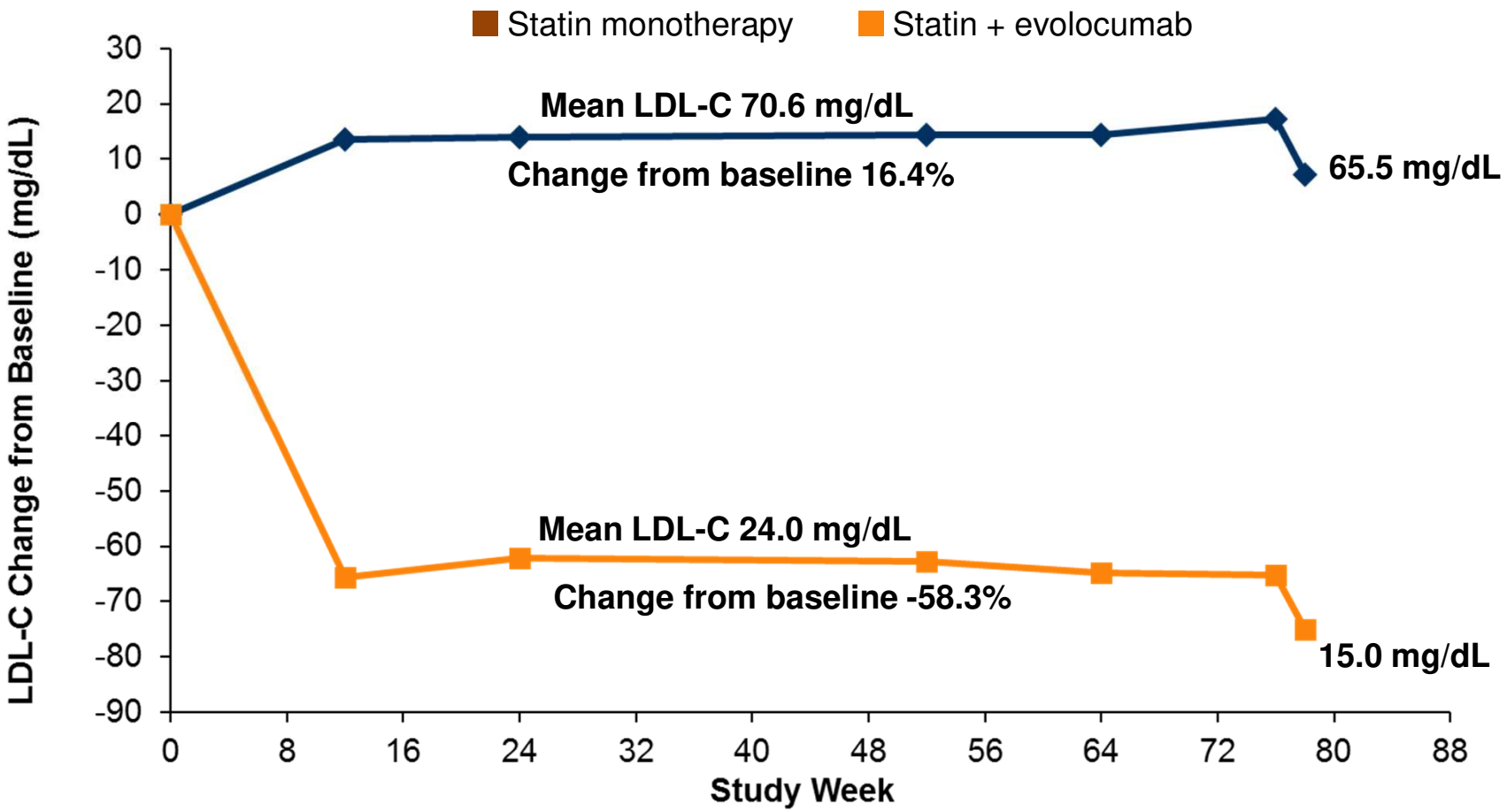


Difference between groups: -4.9mm³ (-7.3 to -2.5); *P* < 0.001

Data shown are least-squares mean (95% CI). TAV = Total Atheroma Volume
*Comparison versus baseline
Nicholls SJ, et al. *JAMA*. [published online ahead of print November 15, 2016]. doi: 10.1001/jama.2016.16951.

Exploratory Subgroup: LDL-C Change from Baseline in Patients with LDL-C < 70 mg/dL at Baseline

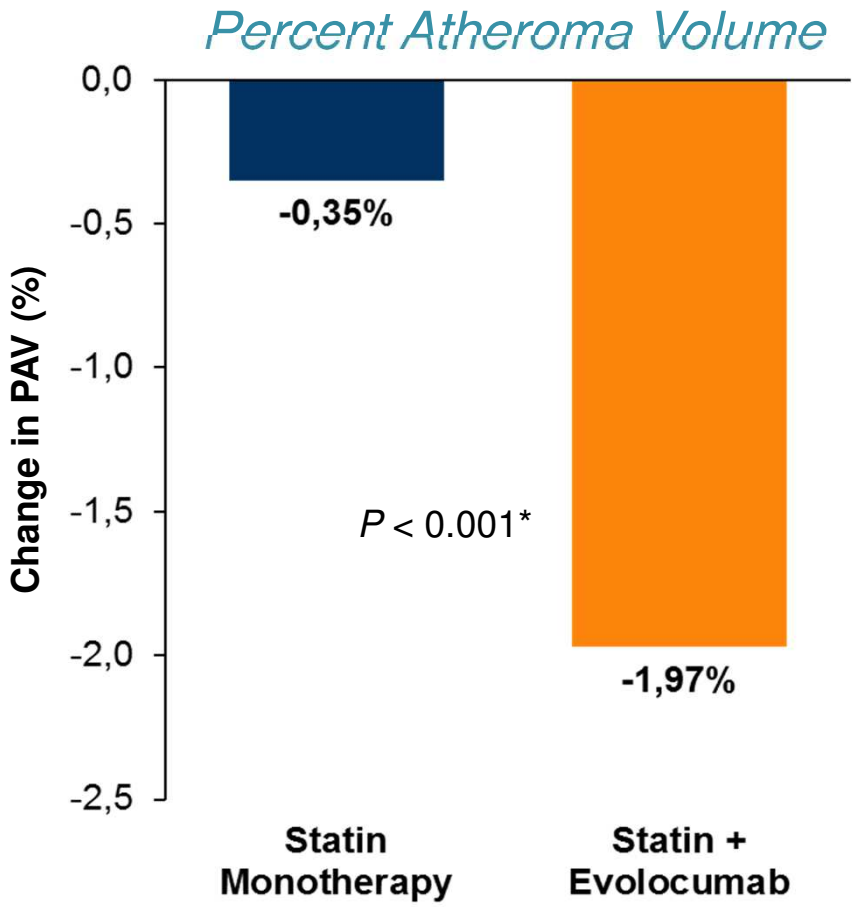
Patients with LDL-C < 70 mg/dL at Baseline (n = 144)

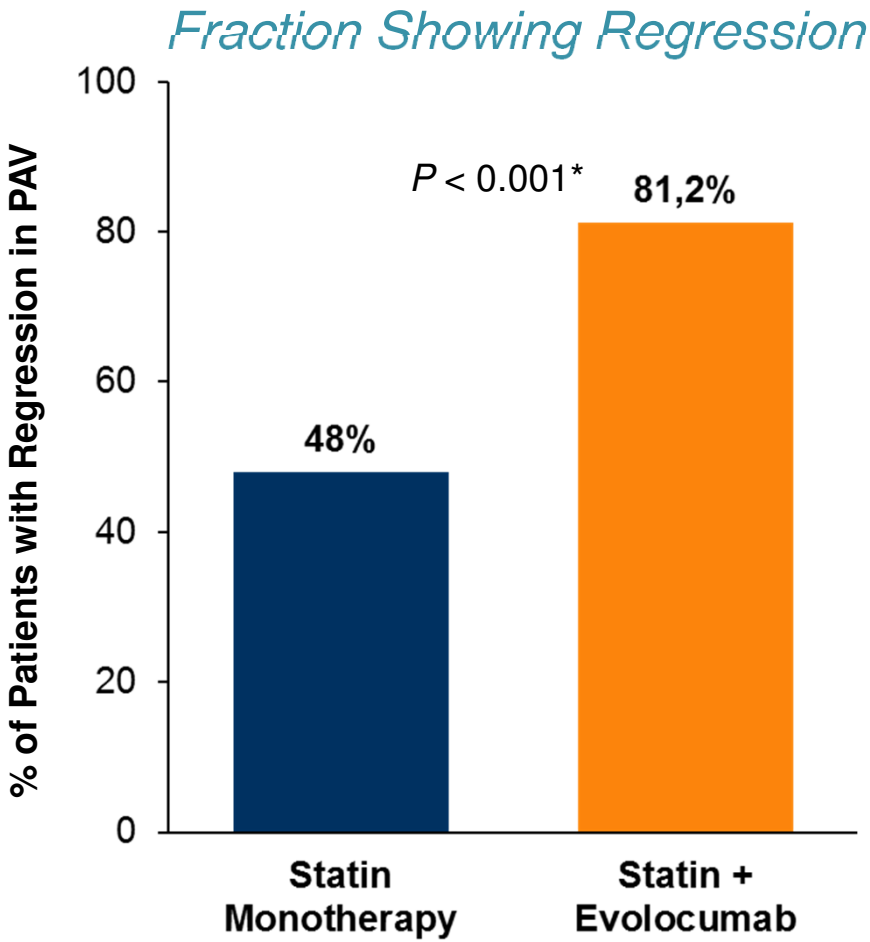


Nissen SE, et al. *American Heart Association Scientific Sessions,* Nov 12 - 16, 2016, New Orleans, Louisiana. Oral Presentation

Exploratory Subgroup: Change in PAV & Regression in Patients with LDL-C < 70 mg/dL at Baseline

Patients with LDL-C < 70 mg/dL at Baseline (n = 144)





*Between-treatment group comparison
PAV = percentage atheroma volume
Nicholls SJ, et al. *JAMA*. [published online ahead of print November 15, 2016]. doi: 10.1001/jama.2016.16951.

FOURIER: Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk

27,564 patients aged 40–85 years

Clinically evident CV disease
- History of myocardial infarction
- Nonhemorrhagic stroke
- Symptomatic peripheral artery disease

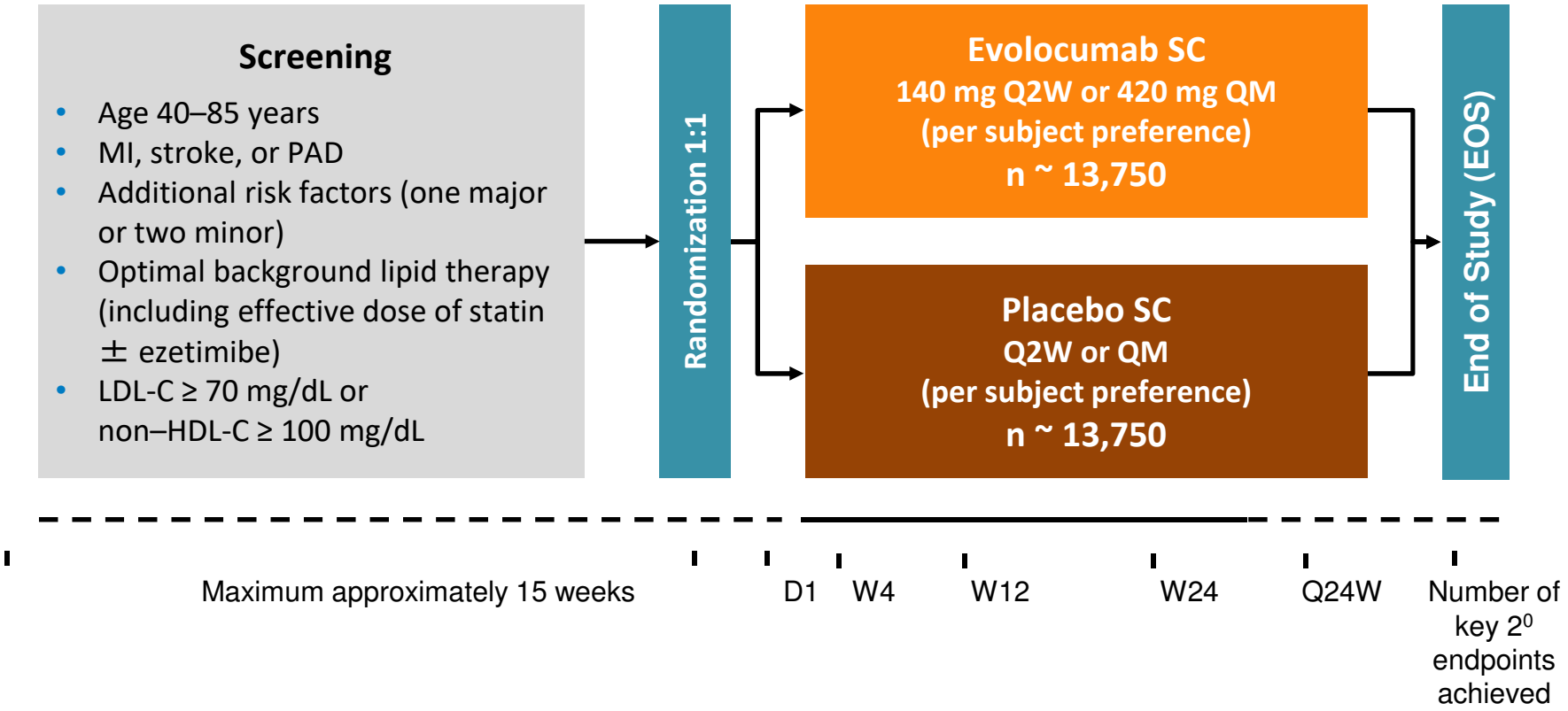
Plus additional risk factors

Fasting LDL-C ≥ 70 mg/dL or non–HDL-C ≥ 100 mg/dL after > 2 weeks of optimized stable lipid-lowering therapy*

*Ideally a high-intensity statin, but must be at least atorvastatin 20 mg daily or equivalent
CV, cardiovascular; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9.
Sabatine MS, et al. *Am Heart J*. 2016;173:94-101.
Sabatine MS, et al . *NEJM*. [published online ahead of print March 17, 2017]. doi: 10.1056/NEJMoa1615664

Evolocumab Outcomes Trial

Study Design Overview



D = day; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; PAD = peripheral artery disease; Q2W = every 2 weeks; Q24W = every 24 weeks; QM = every month; SC = subcutaneous; W = week.

Sabatine MS, et al. *Am Heart J*. 2016;173:94-101.

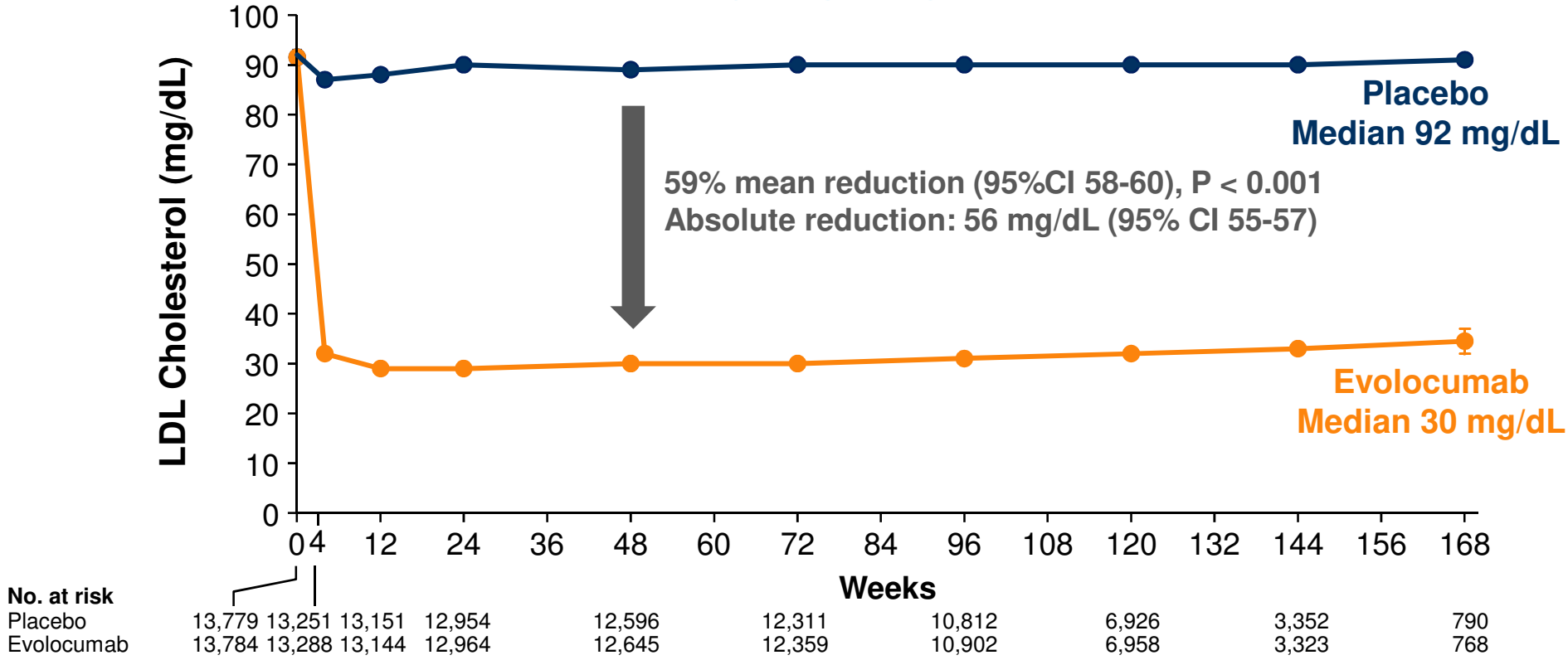
Study Endpoints

Endpoint	Description
Primary*	• Composite of CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization
Key secondary†	• Composite of CV death, MI, or stroke
Other Secondary	• All-cause death; CV death; MI; stroke; coronary revascularization; CV death or hospitalization for heart failure; ischemic stroke or transient ischemic attack

- Sample size based on key secondary endpoint and powered to detect a 15% risk reduction at 90% power
  - Assuming 2% per year event rate in placebo arm, 27,500 patients followed up for a median of ~43 months should have provided 1,630 key secondary endpoints
- Efficacy analysis was hierarchical:
  - If primary endpoint was significantly reduced, then key secondary endpoint was to be tested, followed in order by CV death, all-cause mortality, then additional secondary endpoints

*Time to CV death, MI, stroke, hospitalization for UA, or coronary revascularization, whichever occurs first
†Time to CV death, MI, or stroke, whichever occurs first
CV = cardiovascular; MI = myocardial infarction
Sabatine MS, et al. *Am Heart J*. 2016;173:94-101.
Sabatine MS, et al . *NEJM*. [published online ahead of print March 17, 2017]. doi: 10.1056/NEJMoa1615664

Median LDL-C Levels Over Time: All Patients



LDL-C was significantly reduced in the evolocumab group (median: 30 mg/dL) including 42% who achieved levels ≤ 25 mg/dL vs < 0.1% in the placebo group

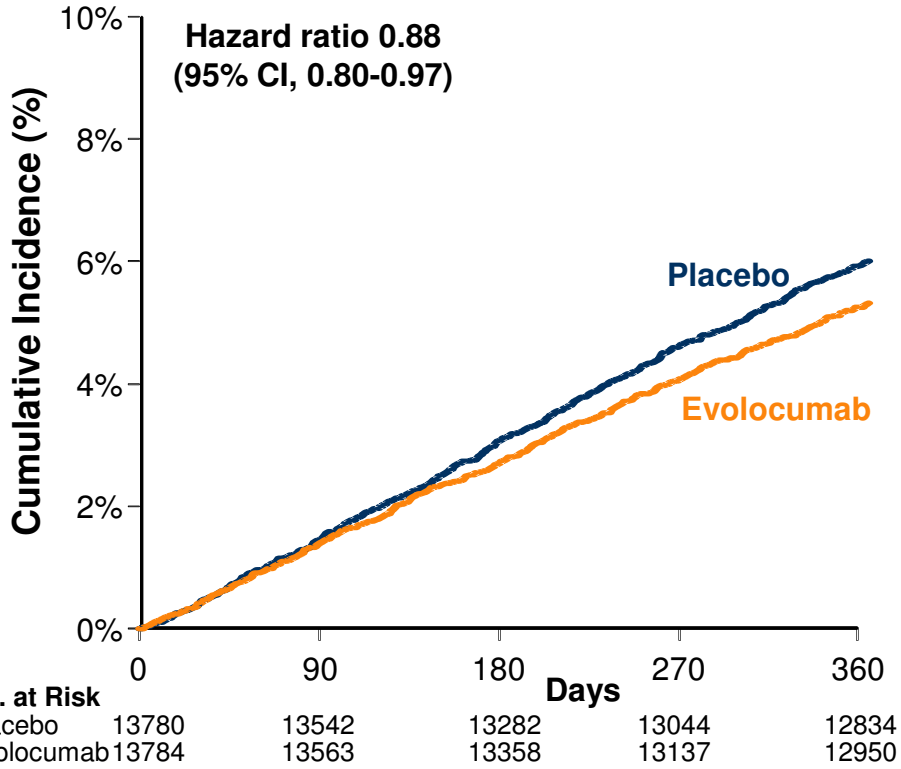
Data shown are median values with 95% confidence intervals in the two arms; ITT.

Sabatine MS, et al . *NEJM*. [published online ahead of print March 17, 2017]. doi: 10.1056/NEJMoa1615664

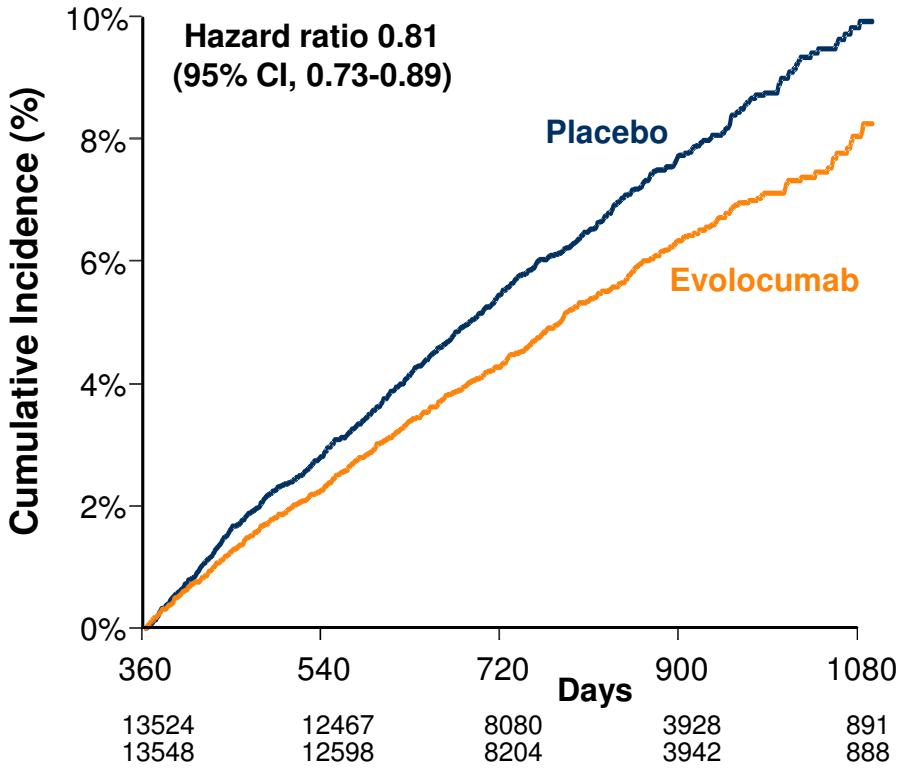
Landmark Analysis of Primary Endpoint

Primary Endpoint: Composite of CV Death, MI, Stroke, Hospitalization for UA, or Coronary Revascularization

Year 1: RRR 12%



> Year 1: RRR 19%



No. at Risk					
Placebo	13780	13542	13282	13044	12834
Evolocumab	13784	13563	13358	13137	12950

13524	12467	8080	3928	891
13548	12598	8204	3942	888

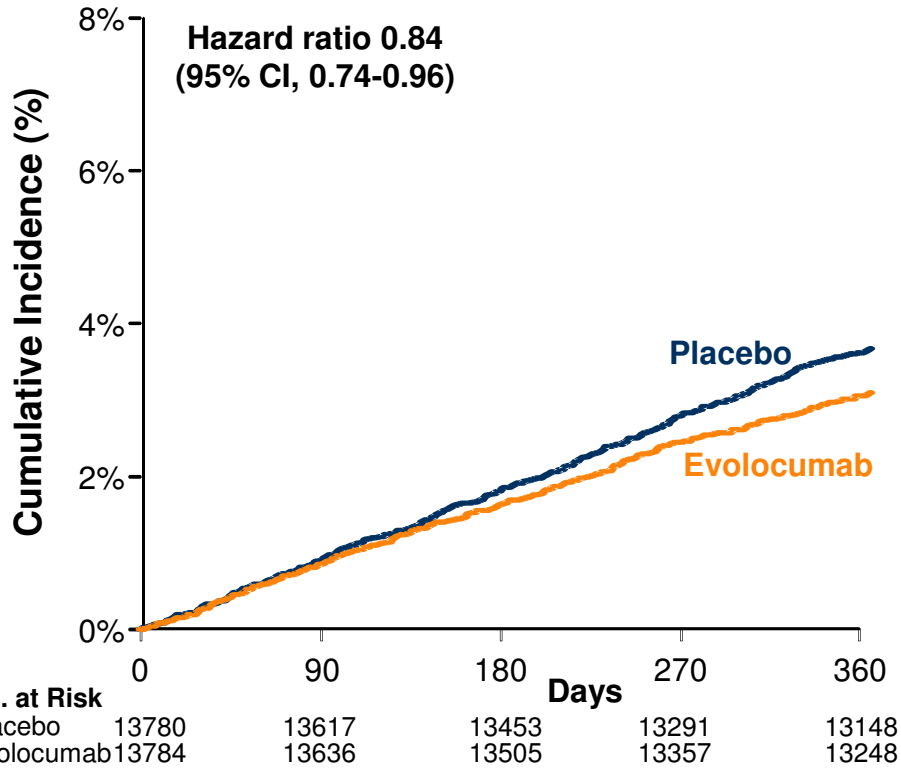
Longer duration of treatment and follow up suggests larger risk reduction

Patients treated with Evolocumab to reduce high LDL-C.
Disclaimer: Application to adapt label text will be submitted to the European Medicines Agency in Q2 2017.
Landmark analyses were performed in which patients who were alive and in follow-up at the start of the period of interest formed the group at risk.
Sabatine MS, et al . *NEJM*. [published online ahead of print March 17, 2017].
doi: 10.1056/NEJMoa1615664 (Supplementary Figure S4)

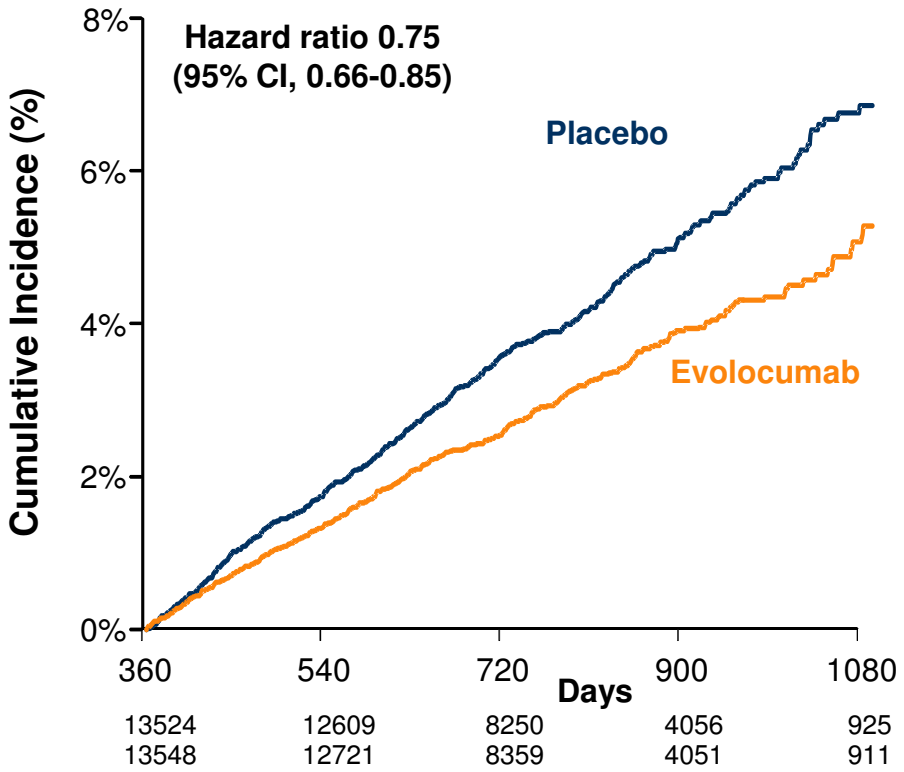
Landmark Analysis of Key Secondary Endpoint

Secondary Endpoint:Composite of CV Death, MI, or Stroke

Year 1: RRR 16%



> Year 1: RRR 25%



Longer duration of treatment and follow up suggests larger risk reduction

Patients treated with Evolocumab to reduce high LDL-C.
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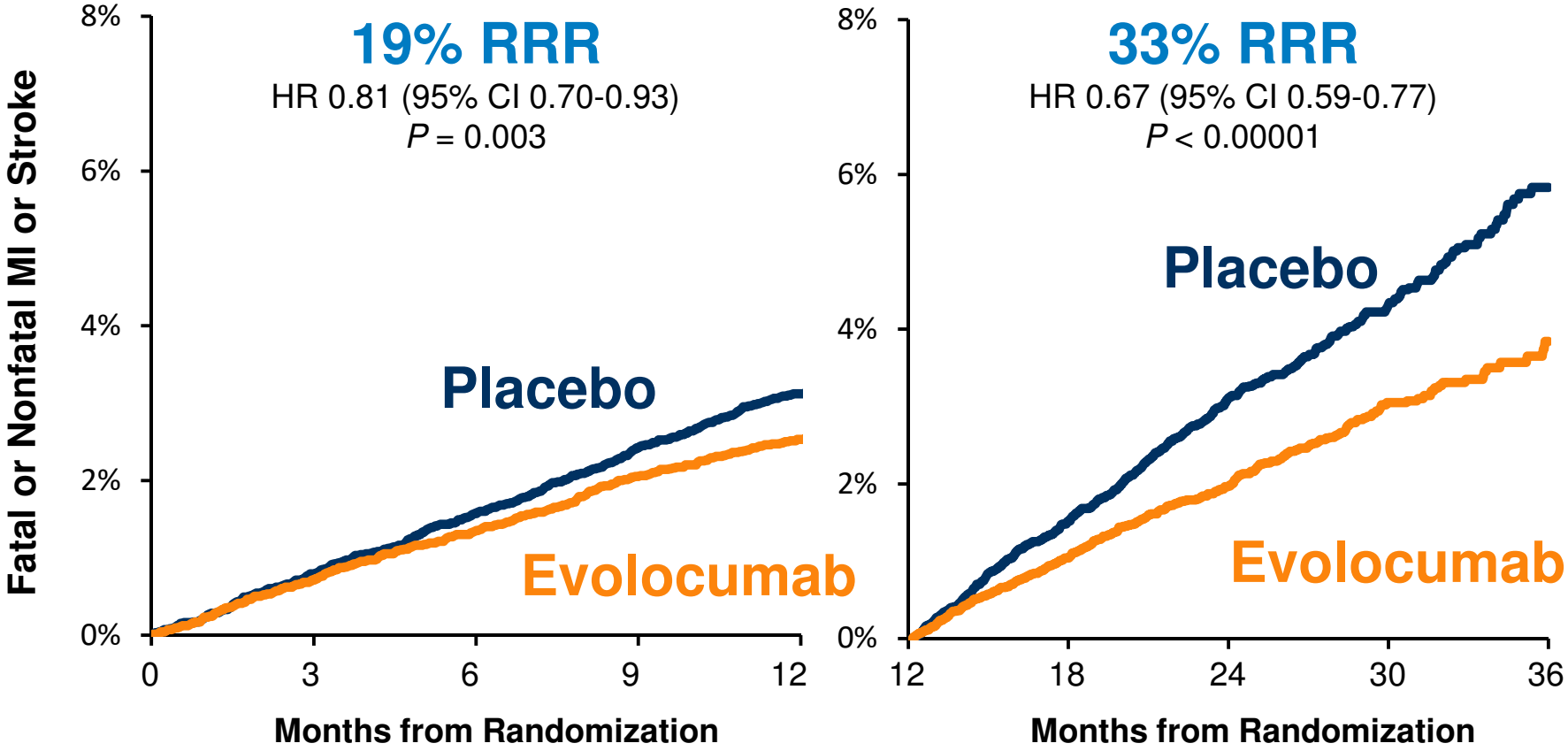
Sabatine MS, et al . *NEJM.* [published online ahead of print March 17, 2017].
doi: 10.1056/NEJMoa1615664 (Supplementary Figure S4)

Fatal or Nonfatal MI or Stroke



Patients treated with Evolocumab to reduce high LDL-C.

Disclaimer: Application to adapt label text will be submitted to the European Medicines Agency in Q2 2017.

Sabatine MS, et al. *American College of Cardiology – 66th Annual Scientific Session Late-Breaking Clinical Trial*. Washington, D.C. March 17, 2017.

Adverse Events of Interest and Laboratory Measures in the Safety Population*

Adverse Events, n (%)	Evolocumab (N = 13,769)	Placebo (N = 13,756)
Injection-site reaction**	296 (2.1)	219 (1.6)
Allergic reactions	420 (3.1)	393 (2.9)
Muscle-related event	682 (5.0)	656 (4.8)
Rhabdomyolysis	8 (0.1)	11 (0.1)
Cataract	228 (1.7)	242 (1.8)
Adjudicated case of new-onset diabetes†	677 (8.1)	644 (7.7)
Neurocognitive event	217 (1.6)	202 (1.5)
Laboratory results - n/total n (%)		
Aminotransferase >3x ULN	240/13,543 (1.8)	242/13,523 (1.8)
Creatinine kinase >5x ULN	95/13,543 (0.7)	99/13,523 (0.7)

*Safety evaluations included all randomized patients who received at least one dose of study treatment and for whom post-dose data are available. **The between-group difference was nominally significant (P<0.001). †HR 1.05 (95% CI 0.94-1.17); denominators of 8337 (evolocumab) and 8339 (placebo) because patients with prevalent diabetes at the start of the trial were excluded.

- **Incidence of neurocognitive events, cataracts, and new-onset diabetes were similar between the two arms**
- **Post-baseline anti-evolocumab antibodies were detected in**

ULN = Upper Limit of Normal

Sabatine MS, et al . *NEJM.* [published online ahead of print March 17, 2017]. doi: 10.1056/NEJMoa1615664

Patientin, 61J. schlank, sehr gut diätcompliant,
St.p.Nikotin, ex 2010
Hypercholesterinämie (mit pos. Fam.anamnese)
PAVK IIb, St.p.fem-popl.Bypass li, St.p.EVR AFC re
KHK, 60% Abgangsstenose LAD,
3 kurzstreckige RCA Stenosen ca. 30-40%

Lipidwerte unter **Ezetrol 10mg**:

Chol 253

HDL 116

TG 67

LDL 122

Unter Simva-, Atorva-und Rosuvastatin
massive Myalgien, Arthralgien ???

Patientin, 61J. schlank, sehr gut diätcompliant,
St.p.Nikotin, ex 2010
Hypercholesterinämie (mit pos. Fam.anamnese)
PAVK IIb, St.p.fem-popl.Bypass li, St.p.EVR AFC re
KHK, 60% Abgangsstenose LAD,
3 kurzstreckige RCA Stenosen ca. 30-40%

(Primär in Fourier)

Lipidwerte unter Ezetrol 10mg und Repatha 140mg nach Ende der Studie

Chol 209 **HDL** 161 **LDL** 37 **TG** 53

Zitat Patientin „ Ich spritze mir das wie Wasser“

DANKE !