Role of PCSK9 inhibitors in primary and secondary prevention

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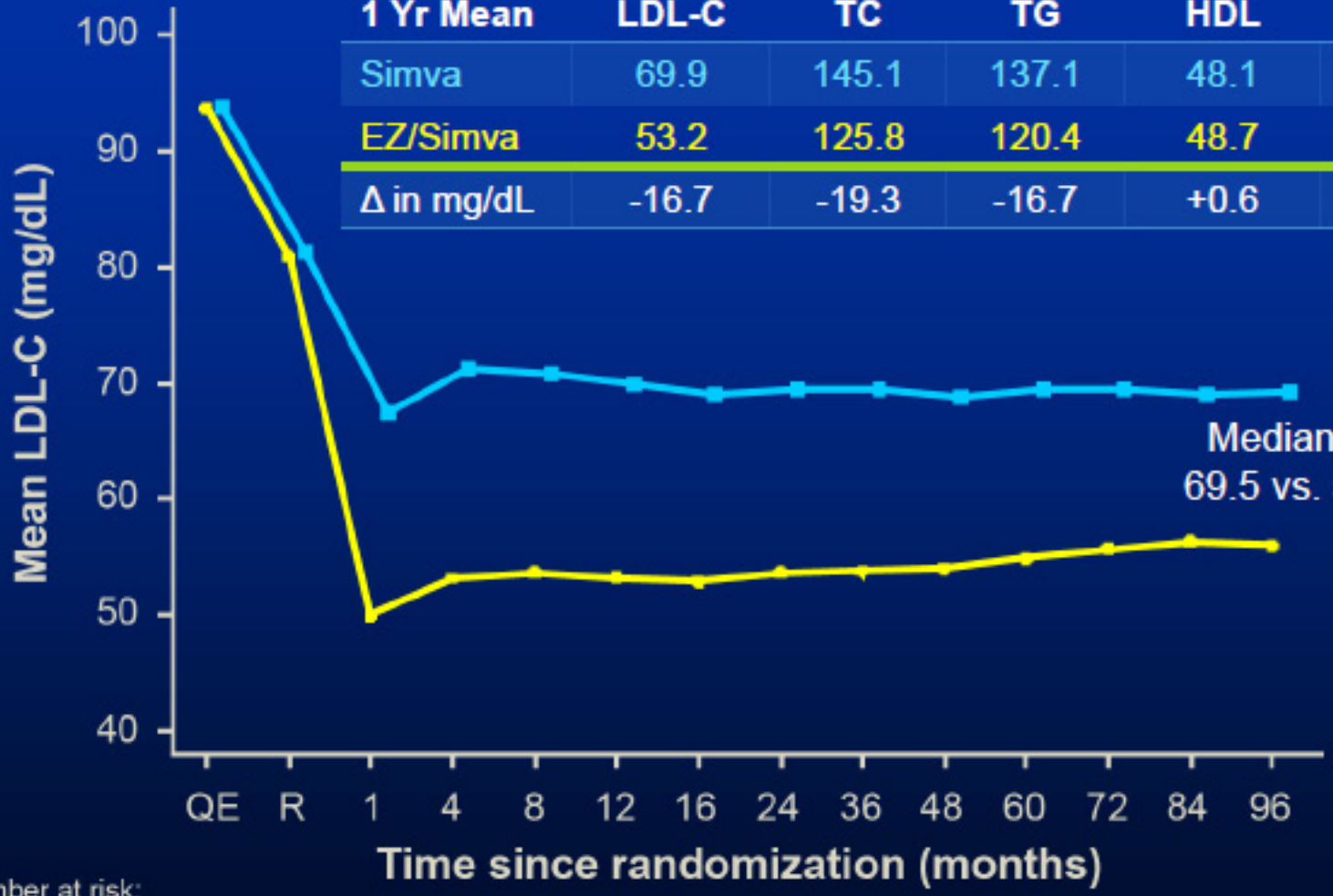
LDL-C and Lipid Changes in IMPROVE-IT

1 Yr Mean	LDL-C	TC	TG	HDL	hsCRP
Simva	69.9	145.1	137.1	48.1	3.8
EZ/Simva	53.2	125.8	120.4	48.7	3.3
Δ in mg/dL	-16.7	-19.3	-16.7	+0.6	-0.5

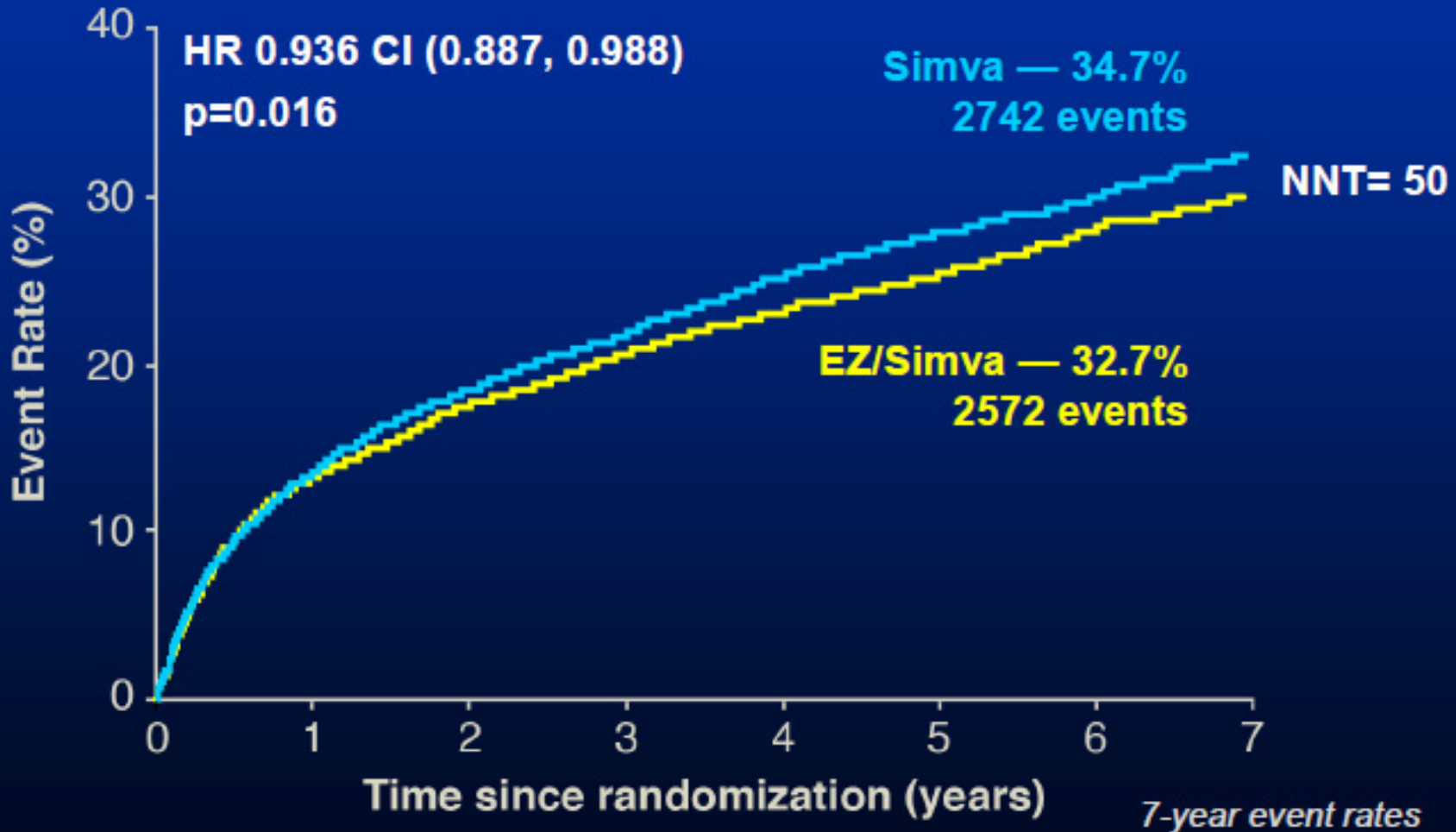


Number at risk:

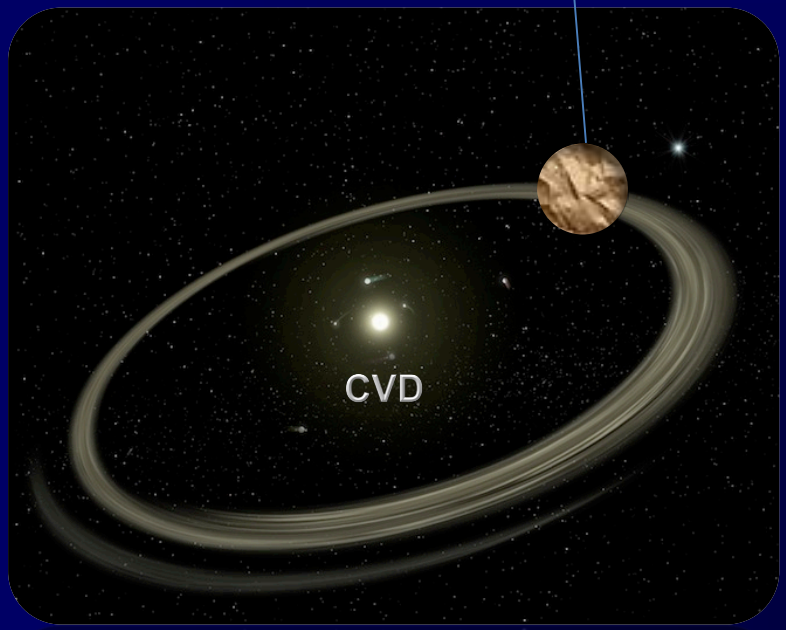
EZ/Simva	8990	8889	8230	7701	7264	6864	6583	6256	5734	5354	4508	3484	2608	1078
Simva	9009	8921	8306	7843	7289	6939	6607	6192	5684	5267	4395	3387	2569	1068

Primary Endpoint — ITT

Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke

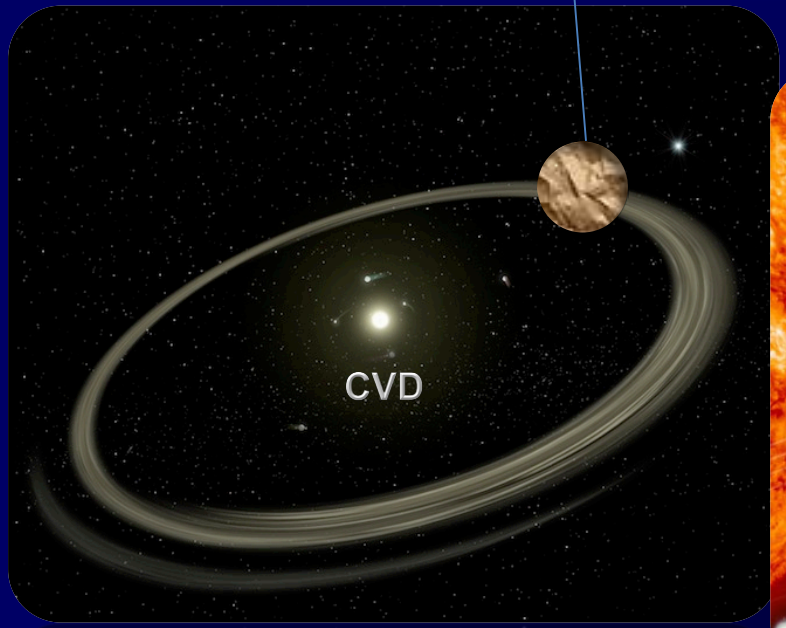


STATINE



- Prevenzione CVD
- Non target colesterolo
- Adeguato dosaggio statina in rapporto al rischio

STATINE



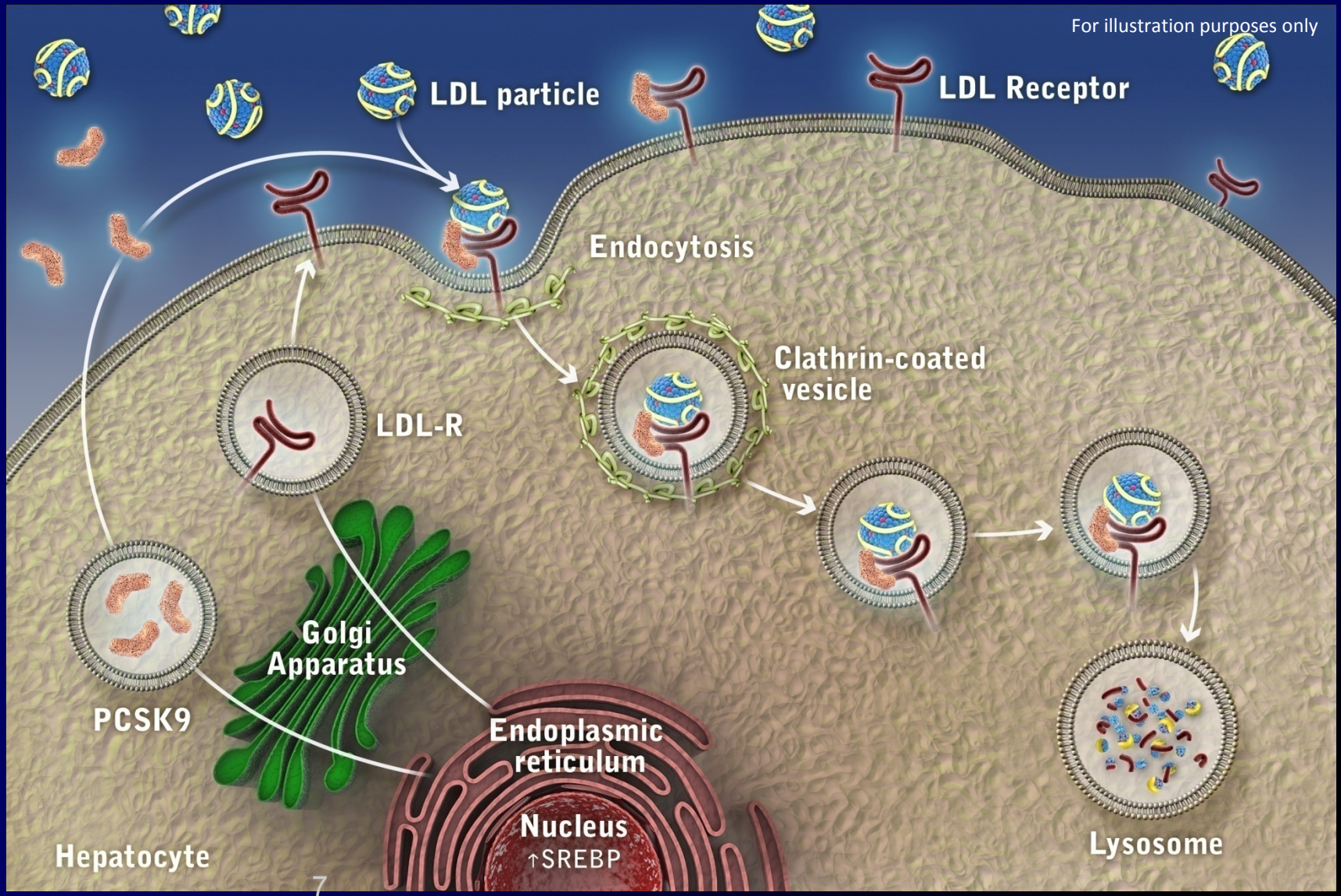
- Prevenzione CVD
- Non target colesterolo
- Adeguato dosaggio statina in rapporto al rischio

Farmaci ipolipemizzanti

statine,ezetimibe, lomitapide, ac.anti-PCSK9

- Target colesterolo
- Tutti i farmaci che riducono colesterolo

The Role of PCSK9 in the Regulation of LDL Receptor Expression



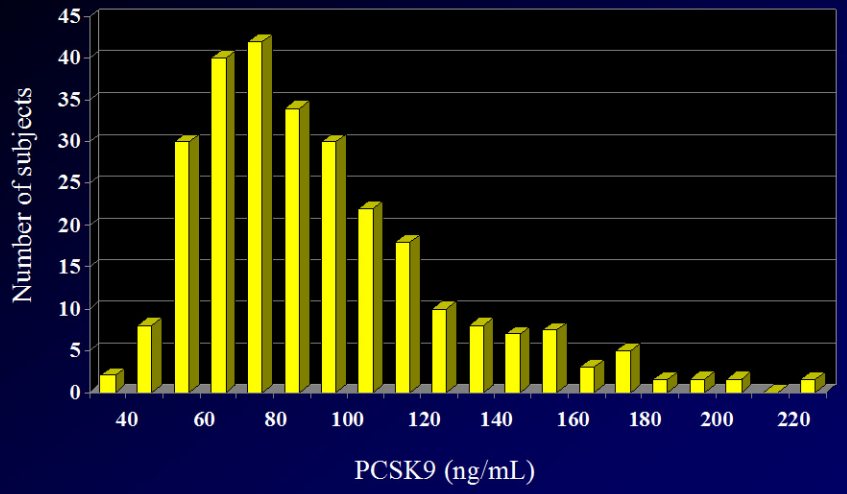
7

PCSK9 in human plasma

Plasma concentrations in control subjects range from 35 to 225 ng/mL (mean 89.5±31.9 ng/mL) and are positively correlated with LDL-C ($r = 0.543$, $P<0.01$)

Dubuc G et al J Lipid Res 2009

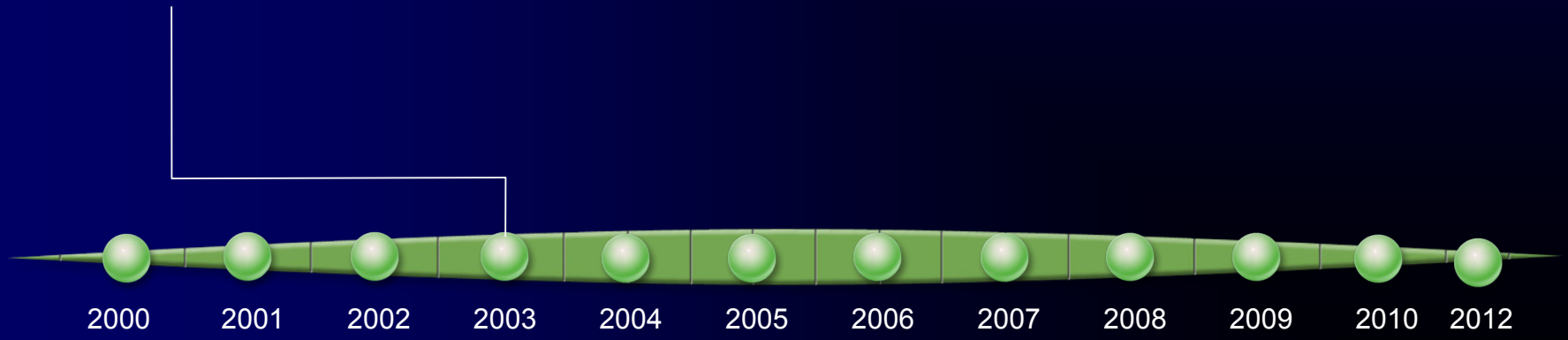
Chan D et al. Clin Chem 2009



Plasma levels of PCSK9 in 254 healthy subjects

PCSK9:
Rapid Progress From Discovery to Clinic

- PCSK9 (NARC-1) discovered
- PCSK9 GOF mutations associated with ADH



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

Stein modified from Swergold, Regeneron

HeFH: DIAGNOSTIC CRITERIA

Simon Broome criteria

Total-cholesterol (LDL-C) in mg/dl >260 (155) in patients with age <18 years and >290 (190) in patients >18 years	AND	Family history of elevated total-cholesterol >290 mg/dl in first or second degree relative or Family history of coronary disease at age <60 years in first degree relative or <50 years in second degree relative	Possible FH
		Tendon xanthomas in the patient or in first or second degree relative	Probable FH
		DNA mutation consistent with FH	Definite FH

MEDPED criteria (87% sensitivity and 98% specificity)

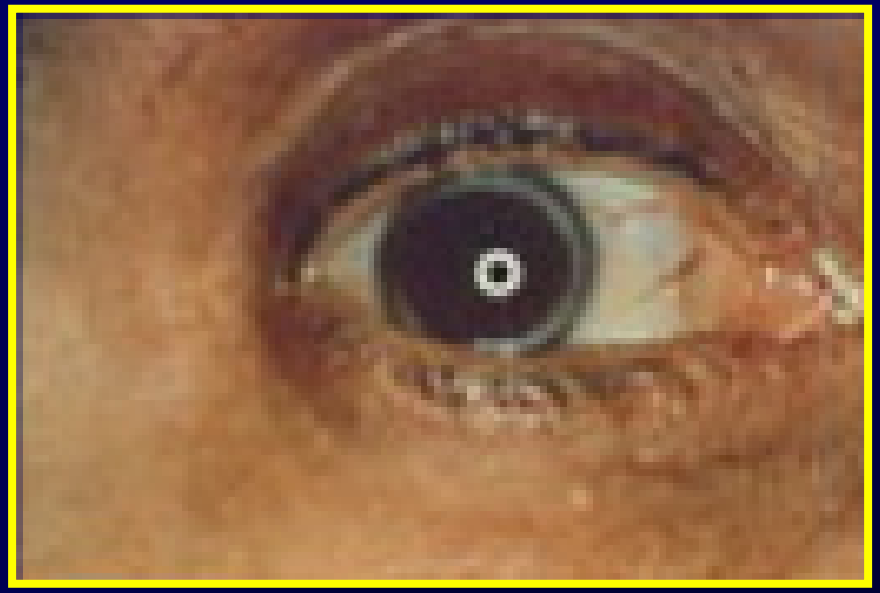
Age in years	Total-cholesterol (LDL-C) in mg/dl			
	General population	First degree relative	Second degree relative	Third degree relative
<18	270 (200)	220 (155)	230 (165)	240 (170)
18-29	290 (220)	240 (170)	250 (185)	260 (185)
30-39	340 (240)	270 (190)	280 (200)	290 (210)
≥40	360 (260)	290 (205)	300 (215)	310 (225)

Dutch Lipid Clinic criteria

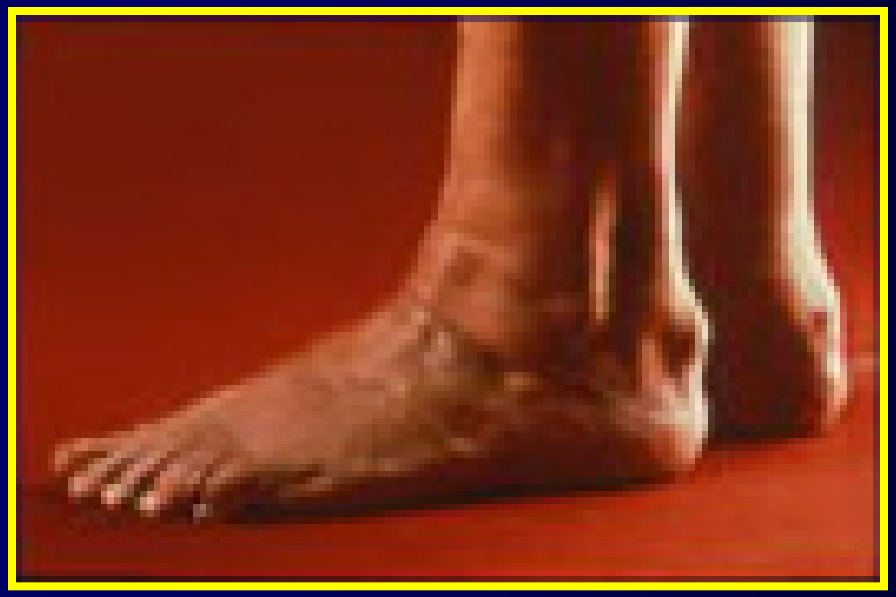
LDLR gene functional mutation or LDL-cholesterol >330 mg/dl	8 points	Possible FH 3-5 points
Presence of tendon xanthoma	6 points	
LDL-C between 250 and 329 mg/dl	5 points	Probable FH 6-7 points
Presence of arcus corneae at age <45 years	4 points	
LDL-C between 190 and 249 mg/dl	3 points	Definite FH ≥8 points
Personal history of CAD or First degree relative age <18 years with LDL-C >95th percentile or First degree relative with tendon xanthoma or arcus corneae	2 points	
LDL-C between 190 and 249 mg/dl or Personal history of premature cerebral or peripheral artery disease or First degree adult relative with premature CAD or LDL-C >95th percentile	1 points	

LDL-C: Low-density lipoprotein-cholesterol, FH: Familial hypercholesterolemia, DNA: Deoxyribonucleic acid, CAD: Coronary artery disease, LDLR: LDL receptor

Arco corneale



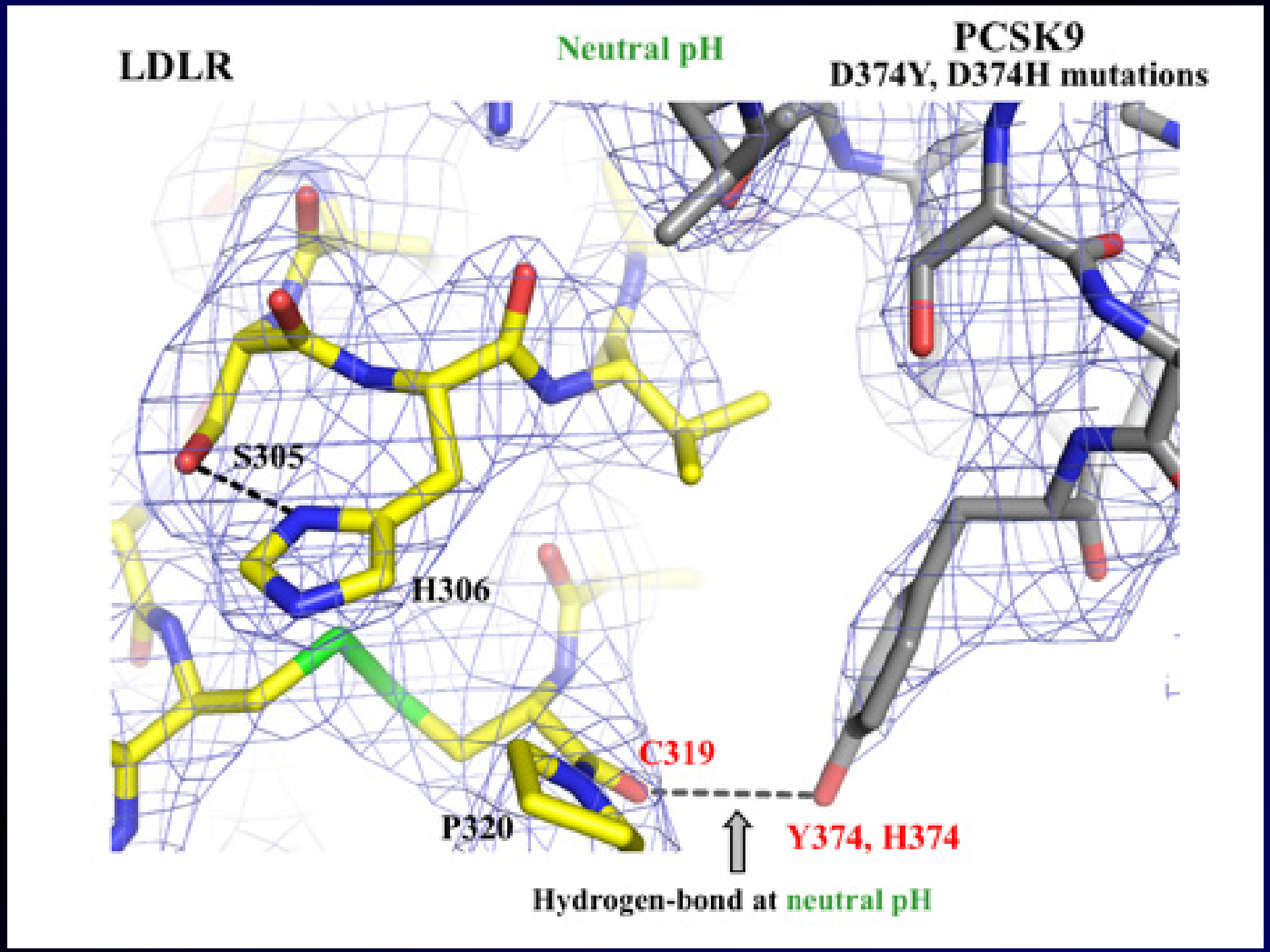
Xantomi tendinei

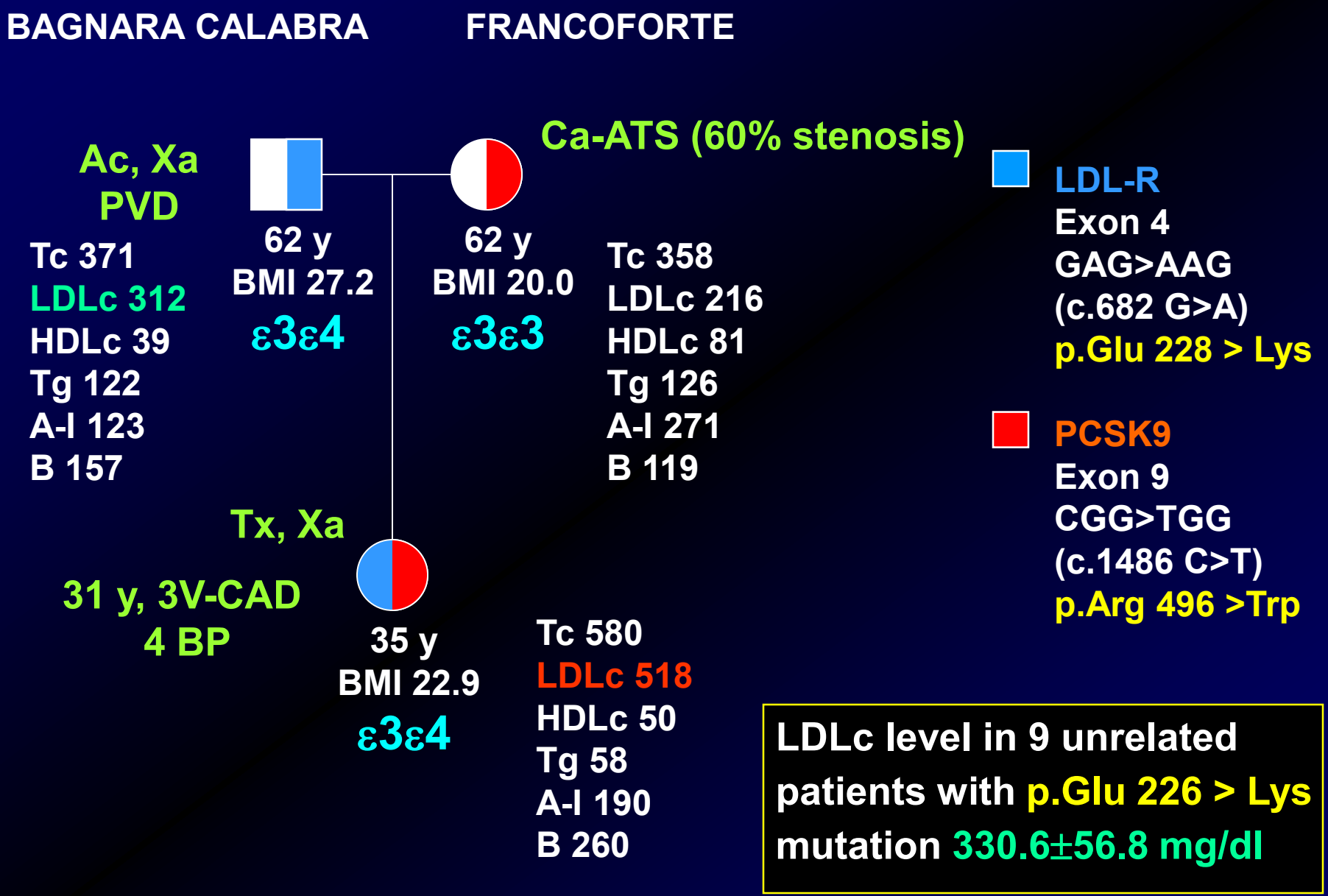


PCSK9

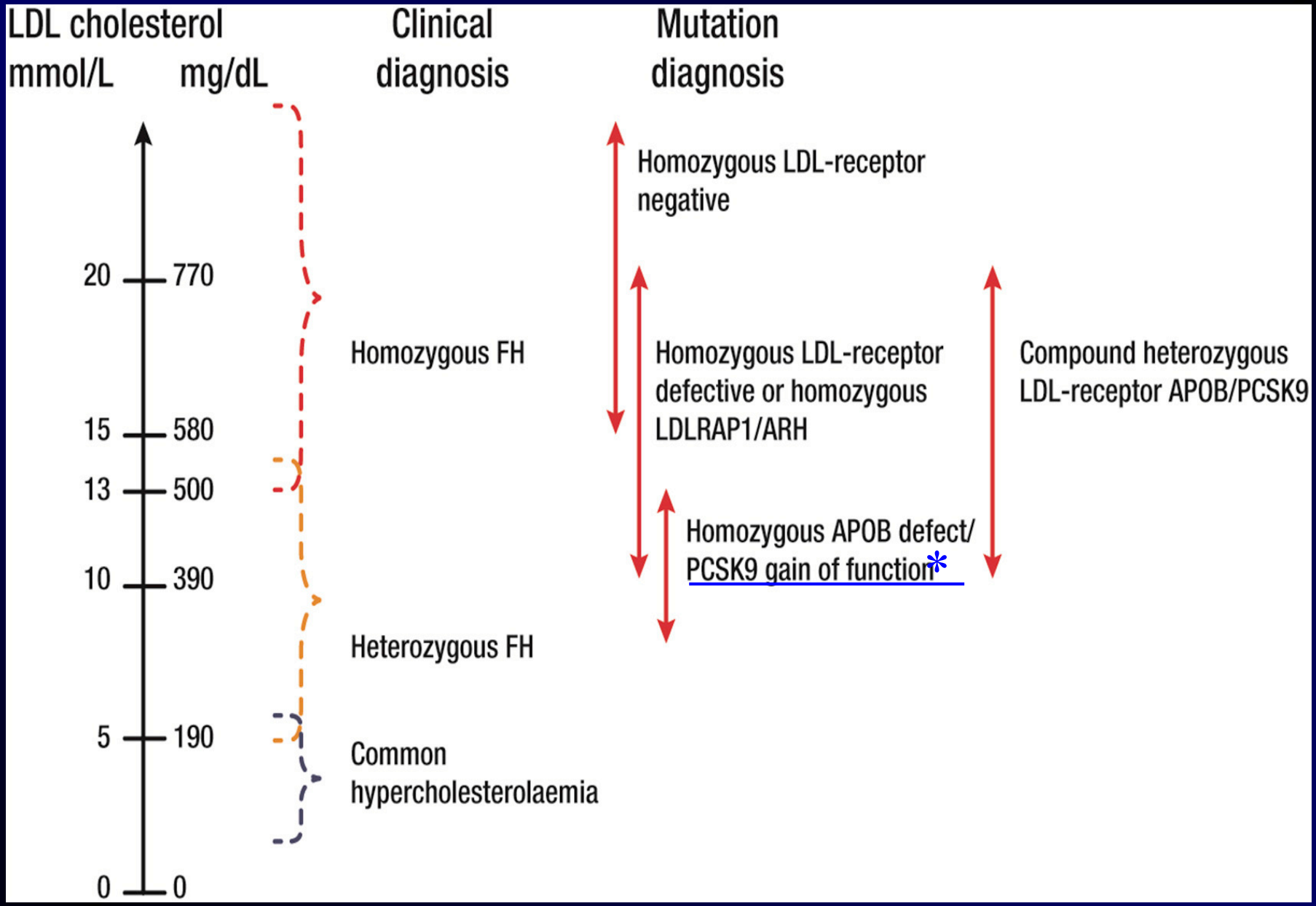
D374Y (English)

Asp374>Tyr

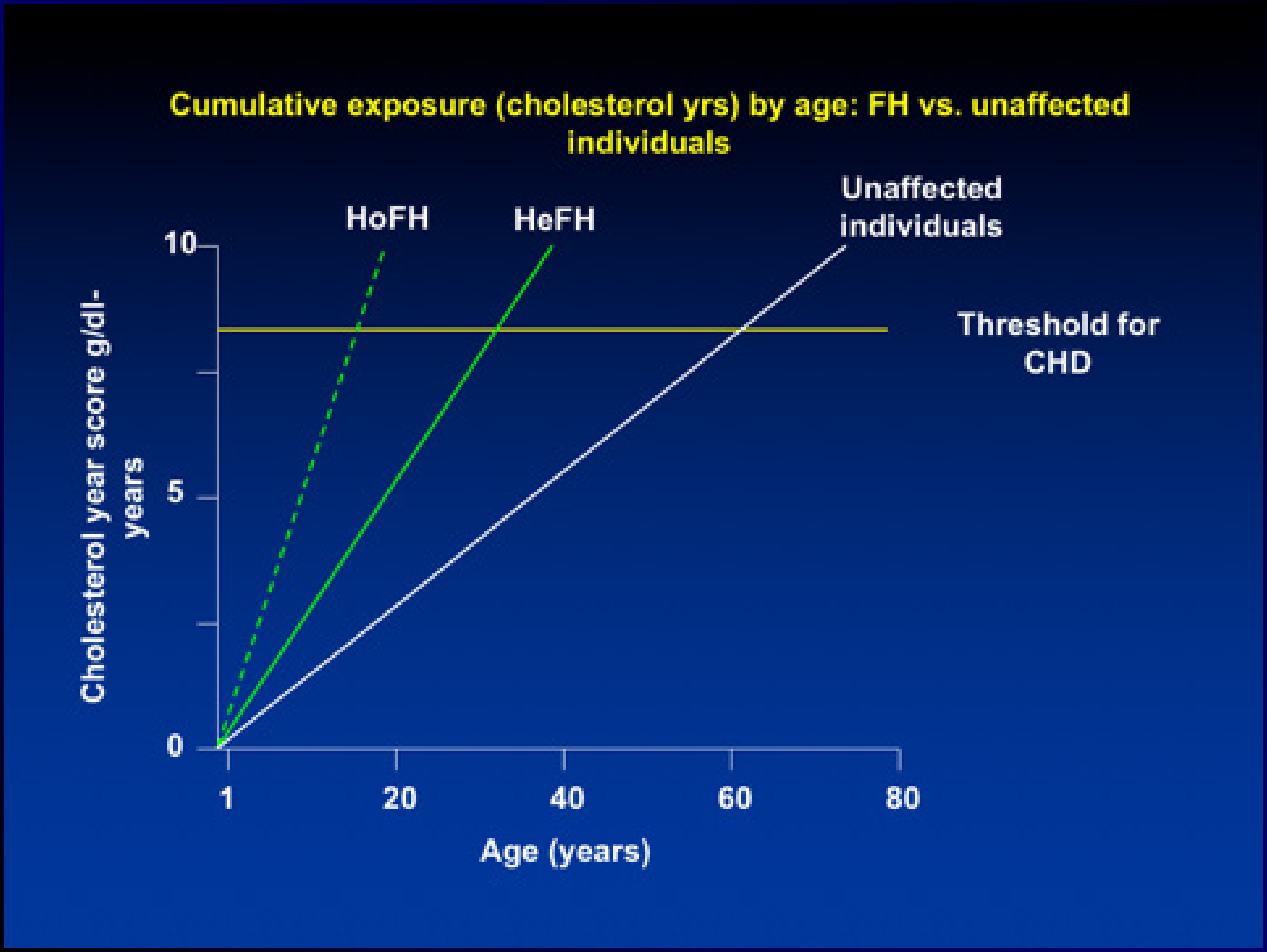




Pisciotta L et al. Atherosclerosis 2006



EAS Consensus Panel statement on homozygous FH Stock J. *Atherosclerosis* 2015; 242: 323-6


Cumulative exposure (cholesterol yrs) by age: FH vs. unaffected individuals
HoFH
HeFH
Unaffected individuals
Threshold for CHD
Cholesterol year score g/dl-years
10
5
0
1
20
40
60
80
Age (years)

PCSK9 protein

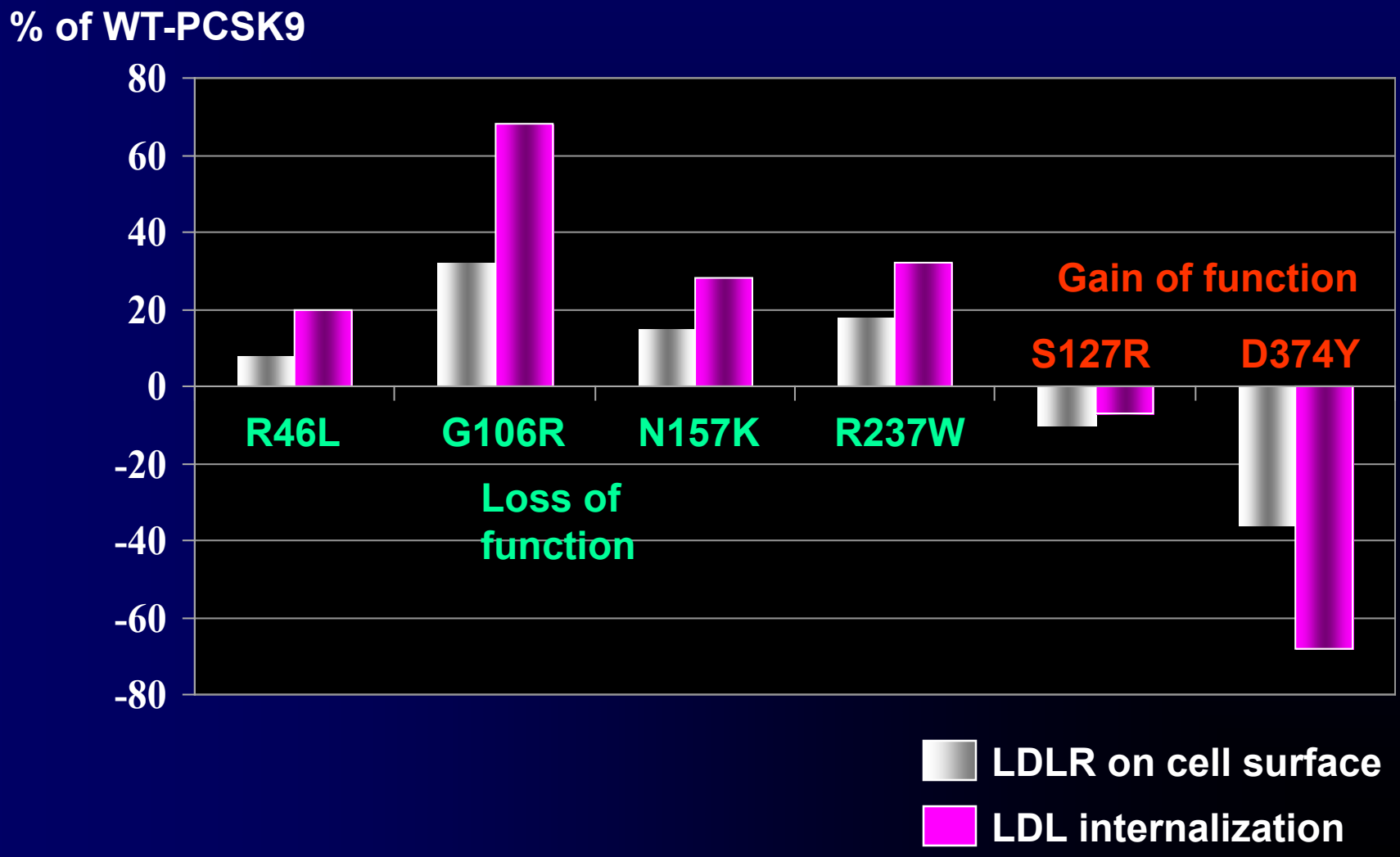
Gain of function mutations

A220T
E32K R357H
E54A D186Y D374Y S465L
R104C R215H D374H R469W A514T
S127R F216L H417Q E482G H553R
V4I D129G R218S N425S R496W V624M

L9/L10 R46L N157K A239D W428X Q554E
E57K Q219E L253F A443T P616L
c.202 del G, A68FsX82 G236S N354I G452D S668R
T77I V114A R237W S386A S462P C679X
R93C Y142X H391N A522T
del R97 G106R

Loss of function mutations

Amount of cell surface LDLR and internalization of LDL in HepG2 cells transfected with mutant PCSK9 plasmids



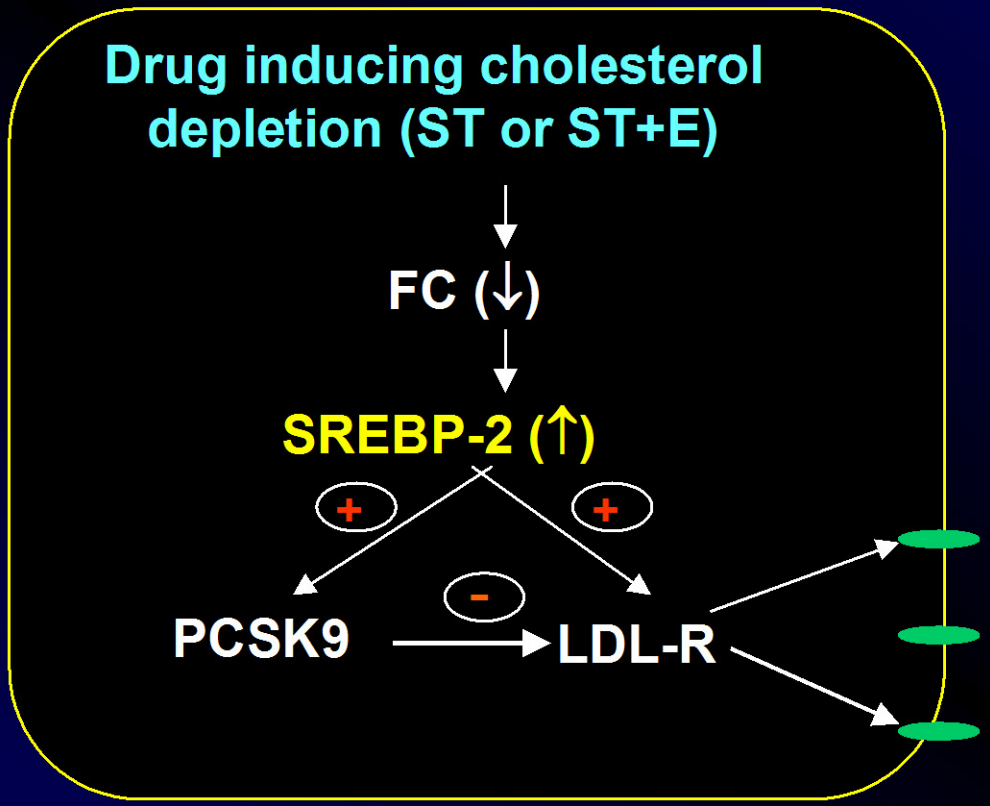
Cameron J et al Hum Mol Genet 2006;15:1551

	LDL-C
Y142X + R97 del CHE	14-34 mg/dl
C679X HO	15.4 mg/dl
Y142X HE (n. 10)	48.2±22.2 mg/dl
C679X HE (n. 49)	64.0±16.0 mg/dl
R97 del HE (n. 2)	58.0±26.8 mg/dl
c.202 del G (A68fs82) HE (n. 4)	64.0±16.0 mg/dl

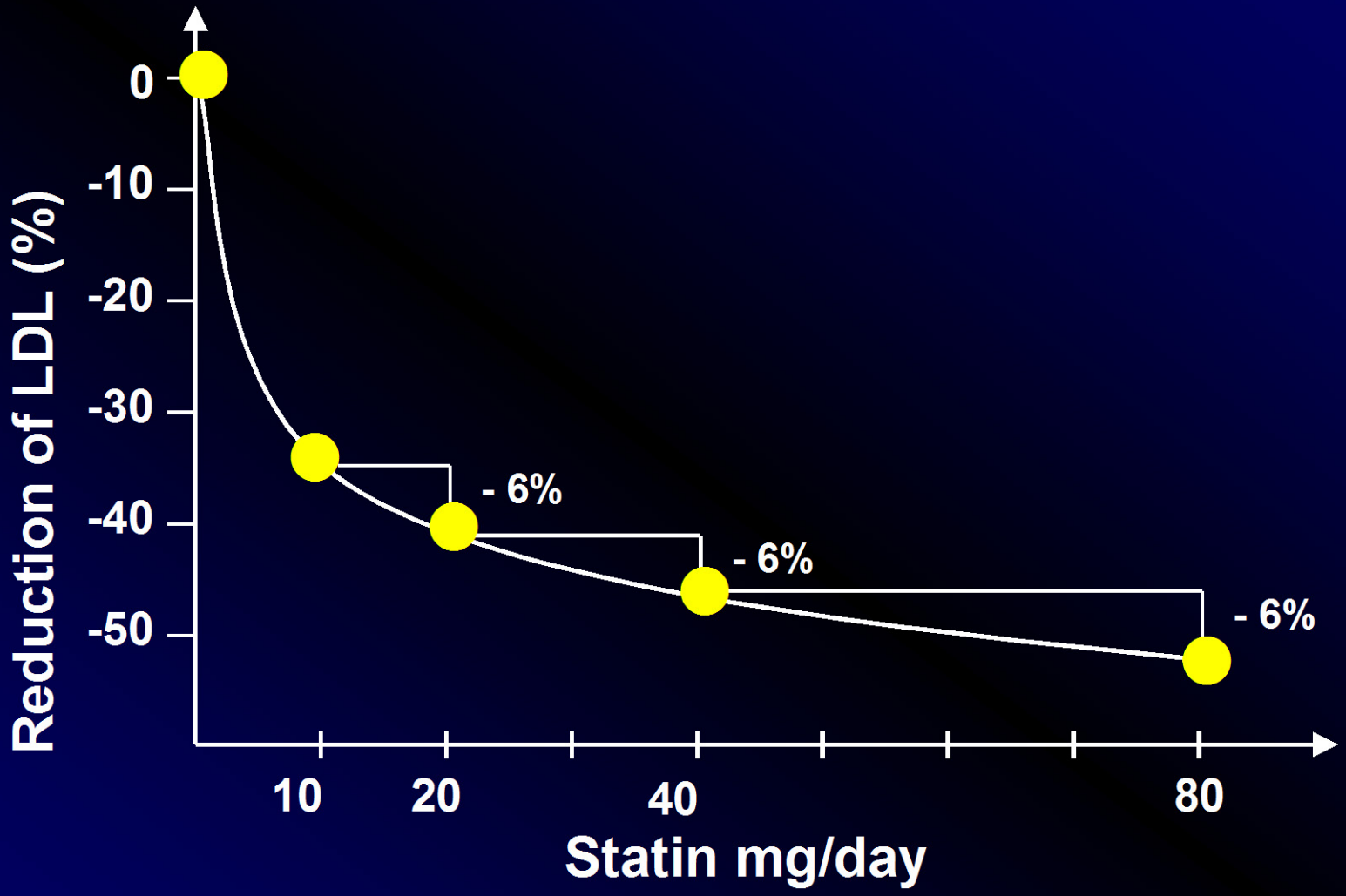
88% reduction of CAD risk

Cohen et al. Nat Genet 2005; Tarugi et al. ATVB 2007

EPATOCYTE


Drug inducing cholesterol depletion (ST or ST+E)
FC (↓)
SREBP-2 (↑)
+
+
-
PCSK9
LDL-R

Statins: “Rule of six”



Grundy SM et al. Circulation 2004; 110: 227-39

PCSK9 loss of function mutations increase the LDL-C lowering effect of Statins in patients with LDLR gene mutations

	LDLR mut	LDLR mut PCSK9 mut
	C210G	C210G + R46L
LDL-C on SIMV 40	-34.5%	-54.0%
	N804K	N804K + N157K
LDL-C on ATORV 10	-32.0%	-51.4%
	P664L	P664L + R46L
LDL-C on ATORV 40	-45.0%	-67.2%

Berge K et al. Arterioscler Thromb Vasc Biol 2006; 26: 1094-100

An additional Leucine in the signal peptide of PCSK9 impairs the protein processing in ER causing a partial LOF and icreases the response to Statins in HE-FH patients

	L9/L9 (n. 42)	L9/L10 (n. 40) + L10/L10 (n. 2)	P
Baseline LDL-C (mmol/L)	7.58 ± 1.28	7.71 ± 1.30	NS
Absolute changes (mmol/L)	-2.44 (2.29-3.05)	-3.14 (2.53-3.77)	<0.001
Percent changes	-34.3 ± 5.6	-42.5 ± 6.2	<0.001

FH patients were matched for gender, age, type of LDLR gene mutation, and for type, dose and duration of statin treatment

Pisciotta L et al. Nutr Metab Cardiovasc Dis 2012; 22: 831-5

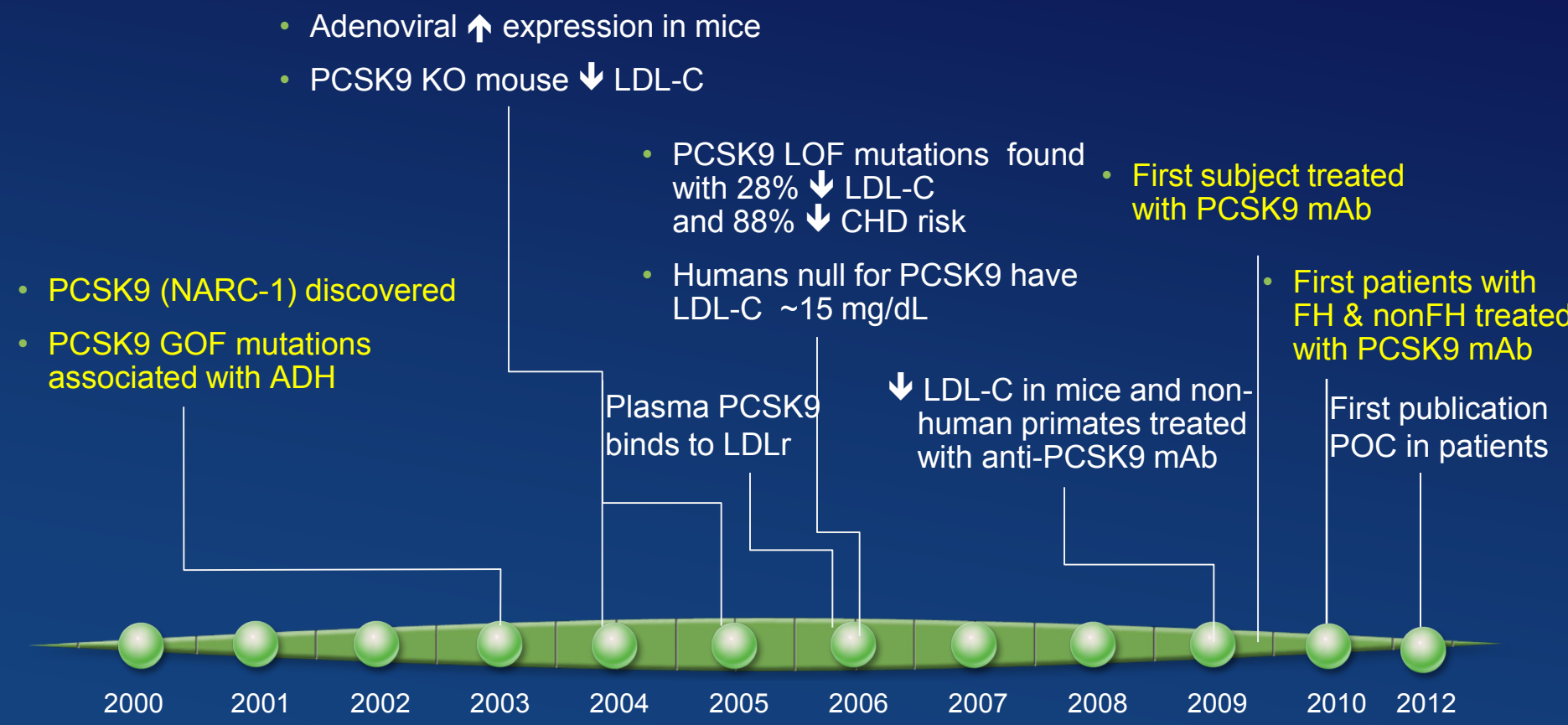
Comprehensive Whole-Genome and Candidate Gene Analysis for response to Statin therapy in the Treating to New Targets (TNT) Cohort

(Thompson J et al. Circ Cardiovasc Genet 2009; 2: 173-81)

Number of SNPs investigated 291,988 in 11490 CHD subjects treated with ATORV 80

Among SNPs tested only SNPs in APOE (rs 7412 ε2/ε3 and rs 429358 ε3/ε4) and a SNP in PCSK9 (rs 11591147 R46L) were found to influence statin response significantly

PCSK9:
Rapid Progress From Discovery to Clinic

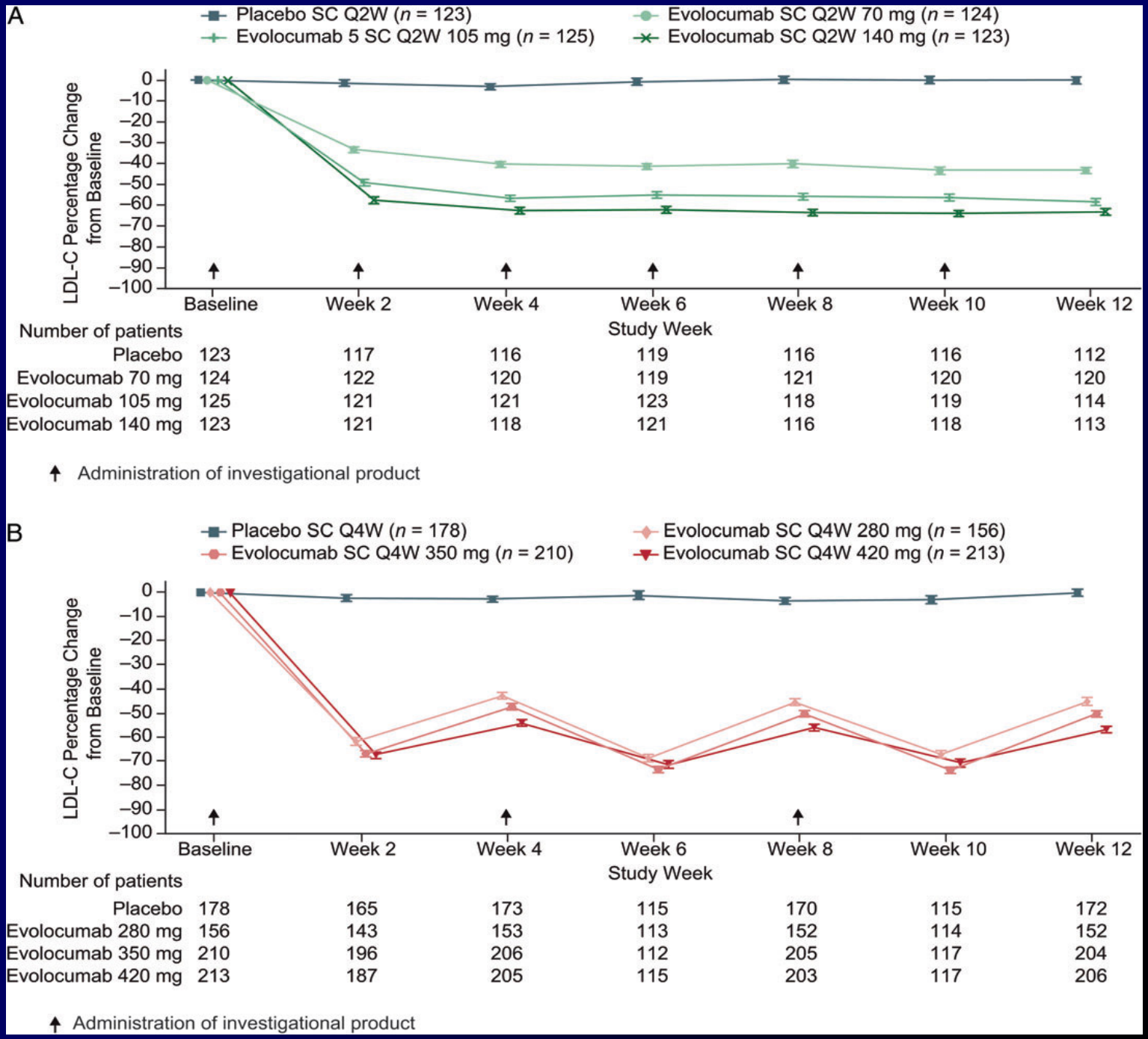


Seidah NG. *Proc Natl Acad Sci USA* 2003;100(3):928-33, Abifadel M. *Nat Genet* 2003;34(2):154-6, Maxwell KN. *Proc Natl Acad Sci USA* 2004;101(18):7100-5, Rashid S. Proc Natl Acad Sci USA 2005;102(15):5374-79, Lagace TA et al. JCI 2006;116:2995-3005 Cohen JC. *N Engl J Med* 2006;354(12):1264-72, Zhao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

Stein modified from Swergold, Regeneron

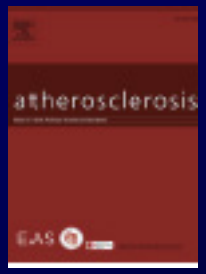
STRATEGIES FOR PCSK9 INHIBITION

- Antisense oligonucleotides (stopped in phase 1)
- Small interfering RNA (siRNA): specific degradation of mRNA
- EGFA mimetic peptide that inhibits PCSK9 binding to LDLR (SX-PCSK9)
- Adnectin (recombinant protein derived from fibronectin) which bloks interaction between PCSK9 and LDLR-EGFA
- Monoclonal antibody SAR236553/REGN727 (Alirocumab)
- Monoclonal antibody AMG 145 (Evolocumab)
- Humanized mAb RN316 which interacts with LDLR-EGFA (longer serum half life and increased duration of LDL-C lowering in mice and monkeys)


A
Placebo SC Q2W (n = 123)
Evolocumab SC Q2W 70 mg (n = 124)
Evolocumab 5 SC Q2W 105 mg (n = 125)
Evolocumab SC Q2W 140 mg (n = 123)
LDL-C Percentage Change from Baseline
0
−10
−20
−30
−40
−50
−60
−70
−80
−90
−100
Baseline
Week 2
Week 4
Week 6
Week 8
Week 10
Week 12
Study Week
Number of patients
Placebo 123 117 116 119 116 116 112
Evolocumab 70 mg 124 122 120 119 121 120 120
Evolocumab 105 mg 125 121 121 123 118 119 114
Evolocumab 140 mg 123 121 118 121 116 118 113
Administration of investigational product
B
Placebo SC Q4W (n = 178)
Evolocumab SC Q4W 280 mg (n = 156)
Evolocumab SC Q4W 350 mg (n = 210)
Evolocumab SC Q4W 420 mg (n = 213)
LDL-C Percentage Change from Baseline
0
−10
−20
−30
−40
−50
−60
−70
−80
−90
−100
Baseline
Week 2
Week 4
Week 6
Week 8
Week 10
Week 12
Study Week
Number of patients
Placebo 178 165 173 115 170 115 172
Evolocumab 280 mg 156 143 153 113 152 114 152
Evolocumab 350 mg 210 196 206 112 205 117 204
Evolocumab 420 mg 213 187 205 115 203 117 206
Administration of investigational product

Quale ruolo degli inibitori di PCSK9 in prevenzione primaria e secondaria?

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 Association for Cardiovascular Prevention & Rehabilitation (EACPR)



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 ures, stroke and k (TIA), and peripheral nequivocally aging is what has been disposed to clinical plaque on coronary ltrasound. mage such as jor risk factor such or dyslipidaemia. nL/min/1.73 m²). % for 10-year risk of

risk factors, in mmol/L (>310 mg/dL) esterolaemia) or

DM (some young tes may be at low or

–59 mL/min/1.73 m²). % and <10% for 10-year

r 10-year risk of fatal

Low-risk SCORE <1% for 10-year risk of fatal CVD.

Recommendations for treatment goals for low-density lipoprotein-cholesterol

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	-

Cause di mancato raggiungimento del TARGET di LDL-C con statina in monoterapia

- Utilizzo inappropriato di Statine a bassa potenza (LOV, FLUV, PRAV) o di Statine a potenza intermedia (SIMV) anche a dosi massimali
- Utilizzo di Statine a più elevata potenza ma a dosi non massimali (ATORV 10-20 mg, ROSUV 5-10 mg)
- Pressione sul MMG da parte delle ASL con l'obiettivo di un risparmio economico
- Scarsa aderenza alla terapia farmacologica ed alle prescrizioni dietetiche
- Cause secondarie di ipercolesterolemia non correttamente diagnosticate (ipotiroidismo, colestasi, e farmaci concomitanti che inducono ipercolesterolemia e/o accelerano il metabolismo delle statine (steroidi, paroxetina, ciclosporina…)

Cause di mancato raggiungimento del TARGET di LDL-C con statina in monoterapia

- terapia farmacologica discontinua per intolleranza reale o presunta

European Heart Journal
doi:10.1093/eurheartj/ehv043

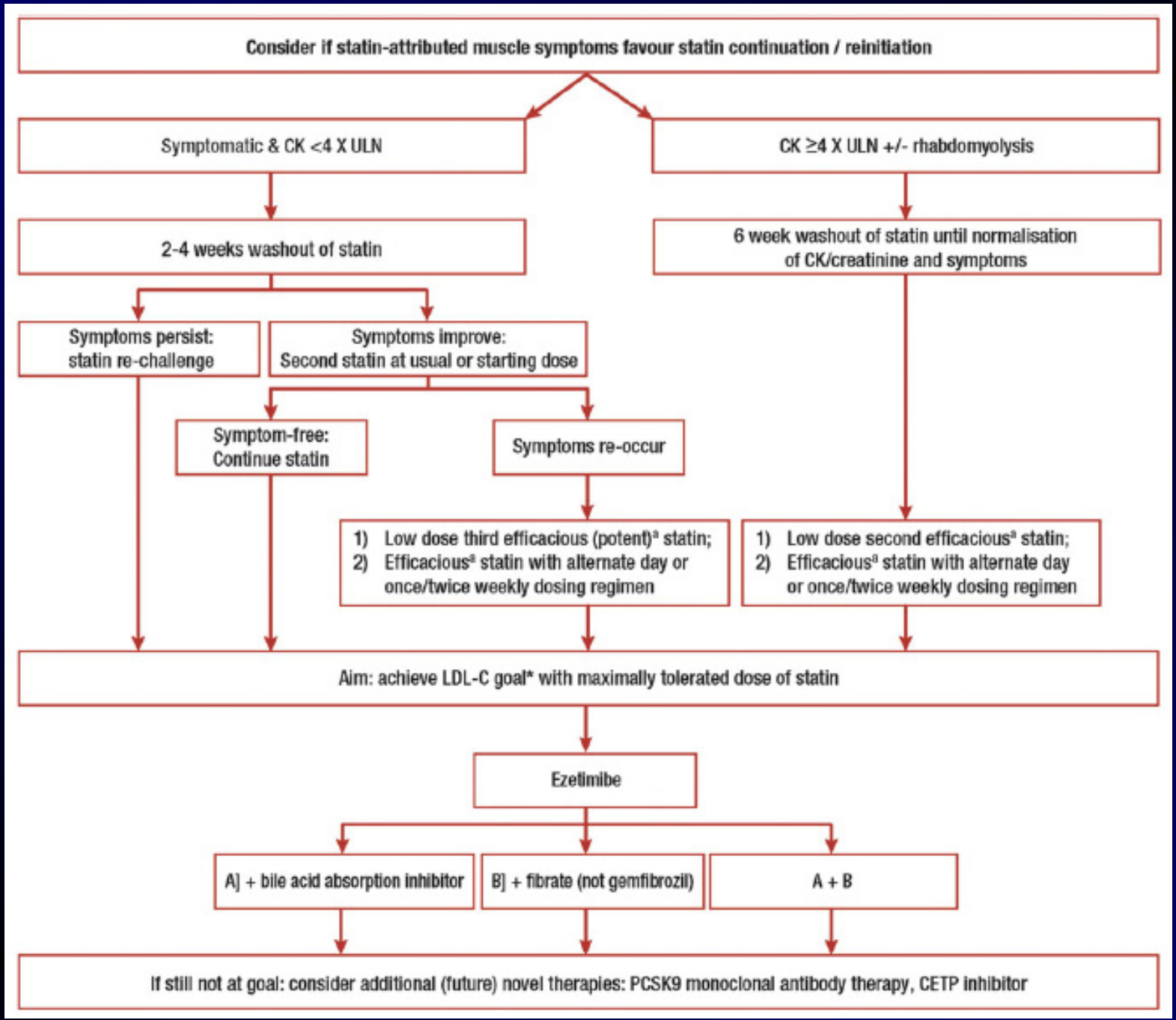
Clinical update

Statin-associated muscle symptoms: impact on statin therapy—European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management

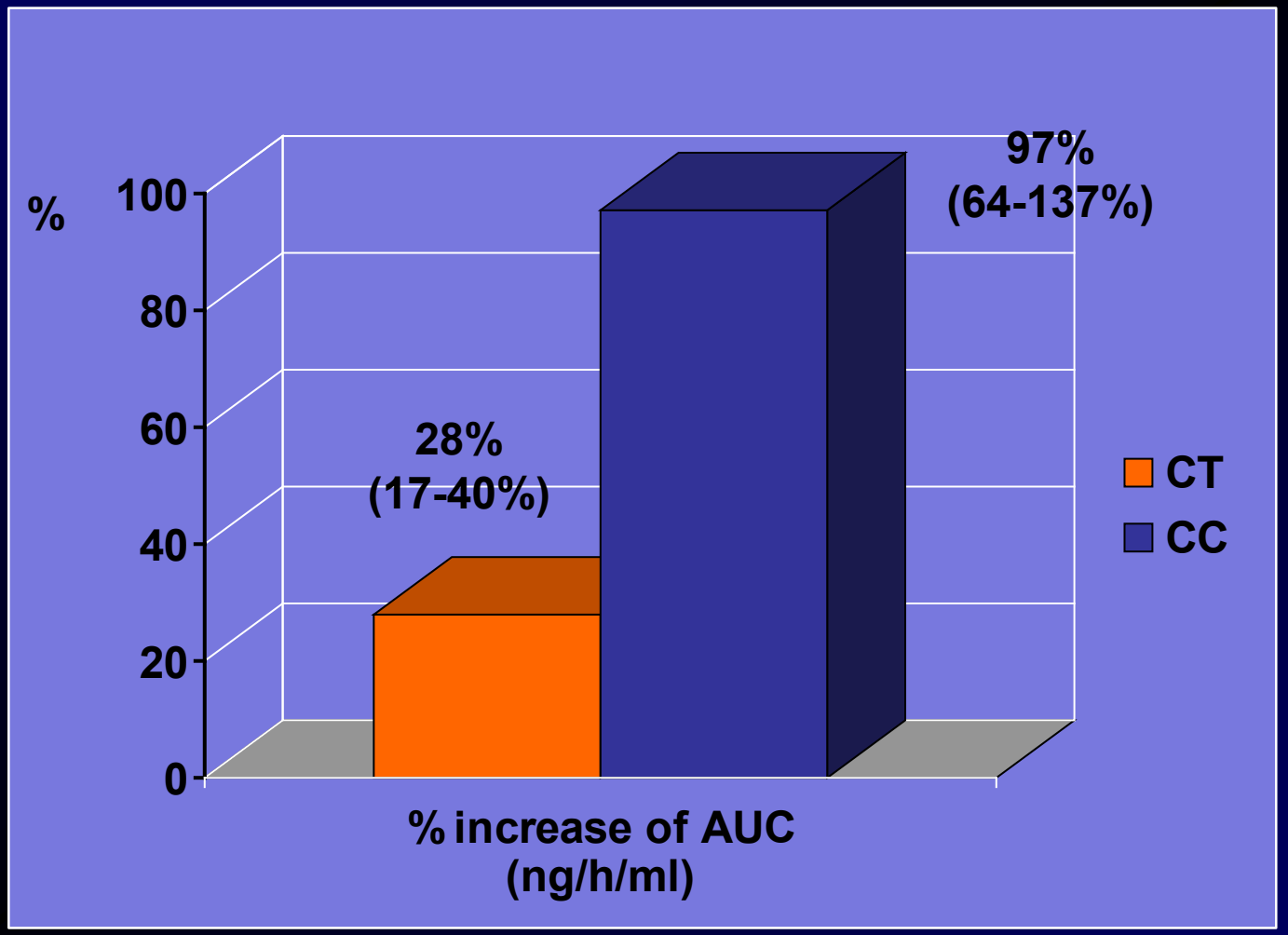
Table I **Definitions of statin-associated muscle symptoms proposed by the EAS Consensus Panel**

Symptoms	Biomarker	Comment
Muscle symptoms	Normal CK	Often called 'myalgia'. May be related to statin therapy. Causality is uncertain in view of the lack of evidence of an excess of muscle symptoms in blinded randomized trials comparing statin with placebo.
Muscle symptoms	CK >ULN <4× ULN CK >4 <10× ULN	Minor elevations of CK in the context of muscle symptoms are commonly due to increased exercise or physical activity, but also may be statin-related; this may indicate an increased risk for more severe, underlying muscle problems.[19]
Muscle symptoms	CK >10× ULN	Often called myositis or 'myopathy' by regulatory agencies and other groups (even in the absence of a muscle biopsy or clinically demonstrated muscle weakness). Blinded trials of statin vs. placebo show an excess with usual statin doses of about 1 per 10 000 per year.[4] Pain is typically generalized and proximal and there may be muscle tenderness and weakness. May be associated with underlying muscle disease.
Muscle symptoms	CK >40× ULN	Also referred to as rhabdomyolysis when associated with renal impairment and/or myoglobinuria.
None	CK >ULN <4× ULN	Raised CK found incidentally, may be related to statin therapy. Consider checking thyroid function or may be exercise-related.
None	CK >4× ULN	Small excess of asymptomatic rises in CK have been observed in randomized blinded trials in which CK has been measured regularly. Needs repeating but if persistent, then clinical significance is unclear.

CK, creatine kinase; ULN, upper limit of the normal range.


Consider if statin-attributed muscle symptoms favour statin continuation / reinitiation
Symptomatic & CK <4 X ULN
CK ≥4 X ULN +/- rhabdomyolysis
2-4 weeks washout of statin
6 week washout of statin until normalisation of CK/creatinine and symptoms
Symptoms persist: statin re-challenge
Symptoms improve: Second statin at usual or starting dose
Symptom-free: Continue statin
Symptoms re-occur
1) Low dose third efficacious (potent)[a] statin;
2) Efficacious[a] statin with alternate day or once/twice weekly dosing regimen
1) Low dose second efficacious[a] statin;
2) Efficacious[a] statin with alternate day or once/twice weekly dosing regimen
Aim: achieve LDL-C goal* with maximally tolerated dose of statin
Ezetimibe
A] + bile acid absorption inhibitor
B] + fibrate (not gemfibrozil)
A + B
If still not at goal: consider additional (future) novel therapies: PCSK9 monoclonal antibody therapy, CETP inhibitor

Increase in the area under the plasma concentration - time curve (AUC) of statins according to genotypes in the SLCO1B1 gene: summary results of studies with different statins



*The TT wildtype is considered as the reference genotype

EDITORIAL

PCSK9 Inhibitors for Statin Intolerance?

David D. Waters, MD; Priscilla Y. Hsue, MD; Sripal Bangalore, MD, MHA

Statin intolerance is a common problem most clinicians encounter when treating patients taking these drugs. Balancing the symptoms of muscle aches in a patient in need of cholesterol-lowering medication with the clinical trial–proven benefits of statins for reducing cardiovascular events in a broad spectrum of patients can be a difficult clinical challenge.

Muscle-related adverse effects from statins are highly mutable. Considerable evidence suggests that nonpharmacologic mechanisms account for most muscle-related statin intolerance. The prevalence of statin-associated muscle symptoms ranges from 7% to 29% in registries and observational studies.[1] The incidence of muscle symptoms is similar among statin-treated and placebo-treated patients across 26 long-term trials involving 170 000 patients.[2] In a large retrospective cohort study, 6579 of 11 124 patients who discontinued a statin due to adverse effects were rechallenged, with 92% success in restoring therapy, although not necessarily with the same statin or dose.[3] In an international survey, the incidence of intolerable statin-related adverse effects ranged from 2% in Japan, Spain, Italy, and Sweden to 10% to 12% in Canada, the United Kingdom, and the United States.[4] These substantial differences are likely to be modulated by cultural factors and patient perception.

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Nevertheless, statins are capable of causing severe muscle damage, very rarely leading to rhabdomyolysis, with this adverse effect most common with simvastatin. In 2011, the US Food and Drug Administration recommended that the 80-mg dose of simvastatin should only be used in patients who had been taking this medication for a year without adverse effects.[5] Although the underlying mechanism of statin-induced myopathy remains unclear, risk factors include older age, impaired renal or hepatic function, surgery, human immunodeficiency virus infection, genetic susceptibility, and high levels of physical activity.[6] Statins may rarely cause an autoimmune myopathy that persists after the drug is discontinued, with muscle weakness, myocyte necrosis, autoantibodies against the HMG-CoA reductase enzyme, and a need for immunosuppressive therapy.[7]

Guidelines provide common-sense recommendations for the management of statin intolerance.[1,6,8] In some patients the appearance of muscle aches turns the risk-benefit ratio unfavorable, so that stopping the statin and turning to diet and exercise is reasonable. Restarting a different statin at a lower dose after symptoms abate is a widely recommended strategy. Almost all patients will eventually find a tolerable statin and dose, even if it is just a low dose taken once or twice per week. In general, any statin is better than no statin when indicated, and most low-density lipoprotein cholesterol (LDL-C) lowering is obtained with the first 5 to 10 mg of statin.[9]

Nonstatin therapies are available to lower LDL-C levels. Ezetimibe is not approved to prevent cardiovascular events, and data from the only outcomes trial with this drug indicate that the number needed to treat per year to prevent a cardiovascular event is 350.[10] Bile acid sequestrants are poorly tolerated at high doses because of gastrointestinal adverse effects, but these agents lower LDL-C levels synergistically with statins and can play a useful role at low doses. The newest class of drugs, protein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, has been shown to markedly lower LDL-C levels. Two of these monoclonal antibodies, evolocumab and alirocumab, were approved by the Food and Drug Administration in 2015 for use in addition to maximally tolerated statin therapy in adults with familial hypercholesterolemia or atherosclerotic cardiovascular disease who require additional lowering of LDL-C levels.

In this issue of *JAMA*, Nissen and colleagues[11] report the results of the GAUSS-3 trial, which used a rigorous protocol to investigate the use of the PCSK9 inhibitor evolocumab among patients with statin intolerance related to muscle-related adverse effects. The results are illuminating, but many unanswered questions remain.

In phase A of the trial, 491 patients with well-documented muscle-related adverse effects to 2 or more statins were randomized to receive either atorvastatin (20 mg daily) or placebo for 10 weeks, followed by a 2-week washout, followed by crossover to the alternate treatment for 10 weeks. Intolerable muscle-related symptoms developed in 209 patients (42.6%) while taking atorvastatin but not placebo, 130 (26.5%) while taking placebo but not atorvastatin, 48 (17.3%) while taking both treatments, and 85 (17.3%) while taking neither treatment. In phase B, 218 patients who had exhibited muscle-related adverse effects while taking atorvastatin but not while taking placebo, or who had experienced a 10-fold increase in creatine kinase level after statin administration, were randomized to receive ezetimibe (10 mg daily) (n = 73 patients) or evolocumab (420 mg monthly) (n = 145 patients). At 24 weeks, LDL-C levels were reduced by 16.7% (from 221.9 mg/dL at baseline to 181.5 mg/dL at 24 weeks) in the ezetimibe group and by 52.8% (from 218.8 mg/dL at baseline to 104.1 mg/dL at 24 weeks) in the evolocumab group ($P < .001$). This result is not surprising; indeed, similar results have been reported with evolocumab or alirocumab in statin-intolerant patients in 3 previous trials, although in this trial Nissen et al followed a precise protocol that identified patients who were truly statin intolerant.[12-14]

Should statin-intolerant patients be treated with PCSK9 inhibitors such as evolocumab? There are several arguments against such an approach. First, PCSK9 inhibitors are not approved for this indication. Although preliminary results are encouraging[15] and large, long-term outcome trials are

JAMA. 2016;315(15):1571-1572.

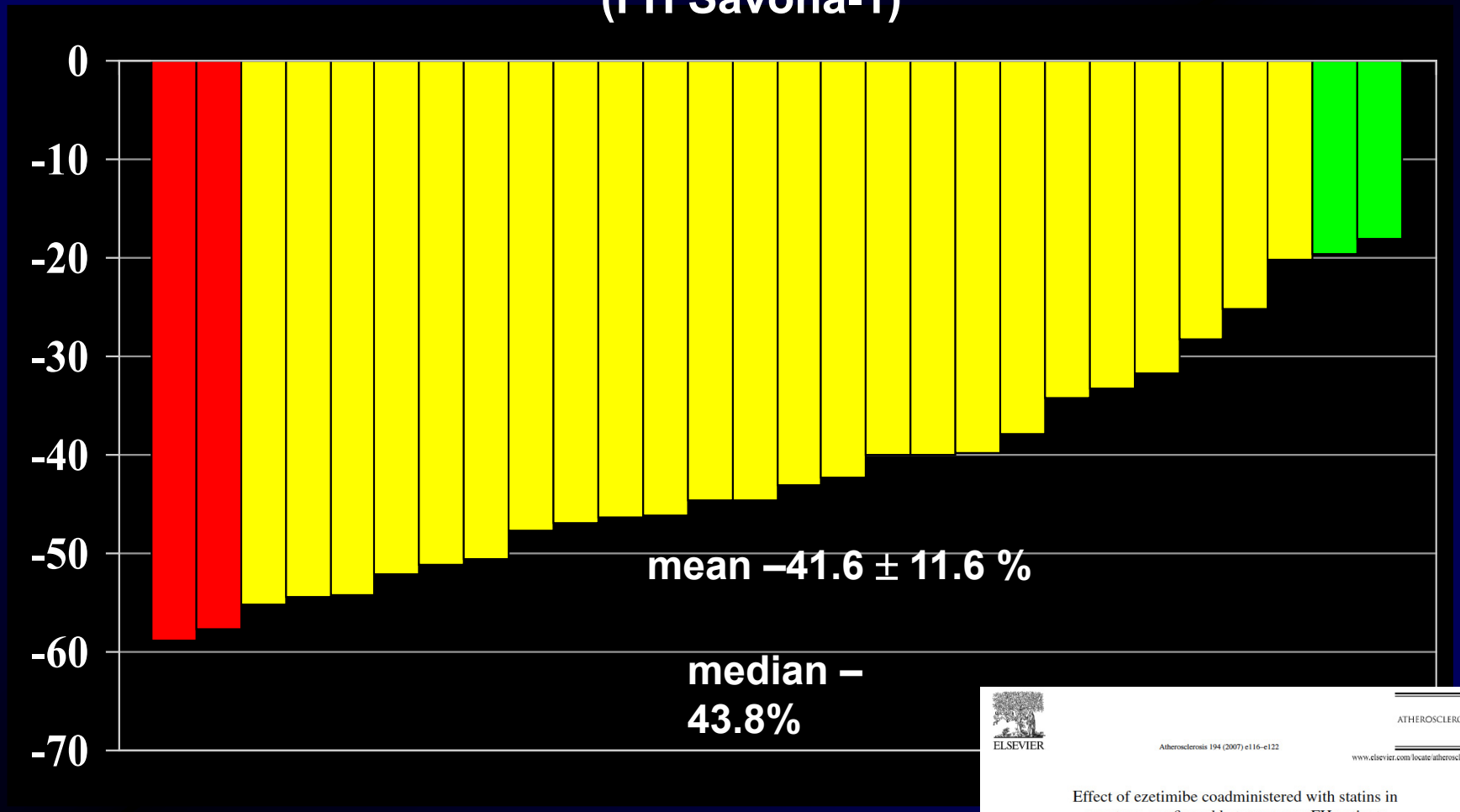
Cause di mancato raggiungimento del TARGET di LDL-C con statina in monoterapia

- Ipercolesterolemie monogeniche resistenti alla terapia

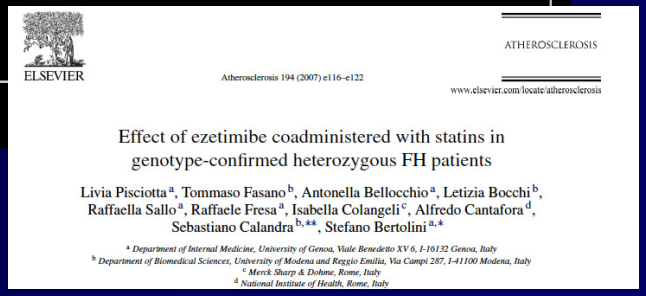
- Presenza nel paziente di varianti genetiche che riducono l'effetto ipocolesterolemizzante delle statine, o aumentano il rischio di miopatia

Individual of LDL-C response to Atorvastatin 40 mg/day in 28 FH patients with severe LDLR gene mutation

c.1415-1418 ACAT dupl in Exon 10 → Stop 515 (FH Savona-1)



Pisciotta L et al. Atherosclerosis 2007; 194: e116-22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Effect of ezetimibe coadministered with statins in genotype-confirmed heterozygous FH patients

Livia Pisciotta[a], Tommaso Fasano[b], Antonella Bellocchio[a], Letizia Bocchi[b], Raffaella Sallo[a], Raffaele Fresa[a], Isabella Colangeli[c], Alfredo Cantafora[d], Sebastiano Calandra[b,**], Stefano Bertolini[a,*]

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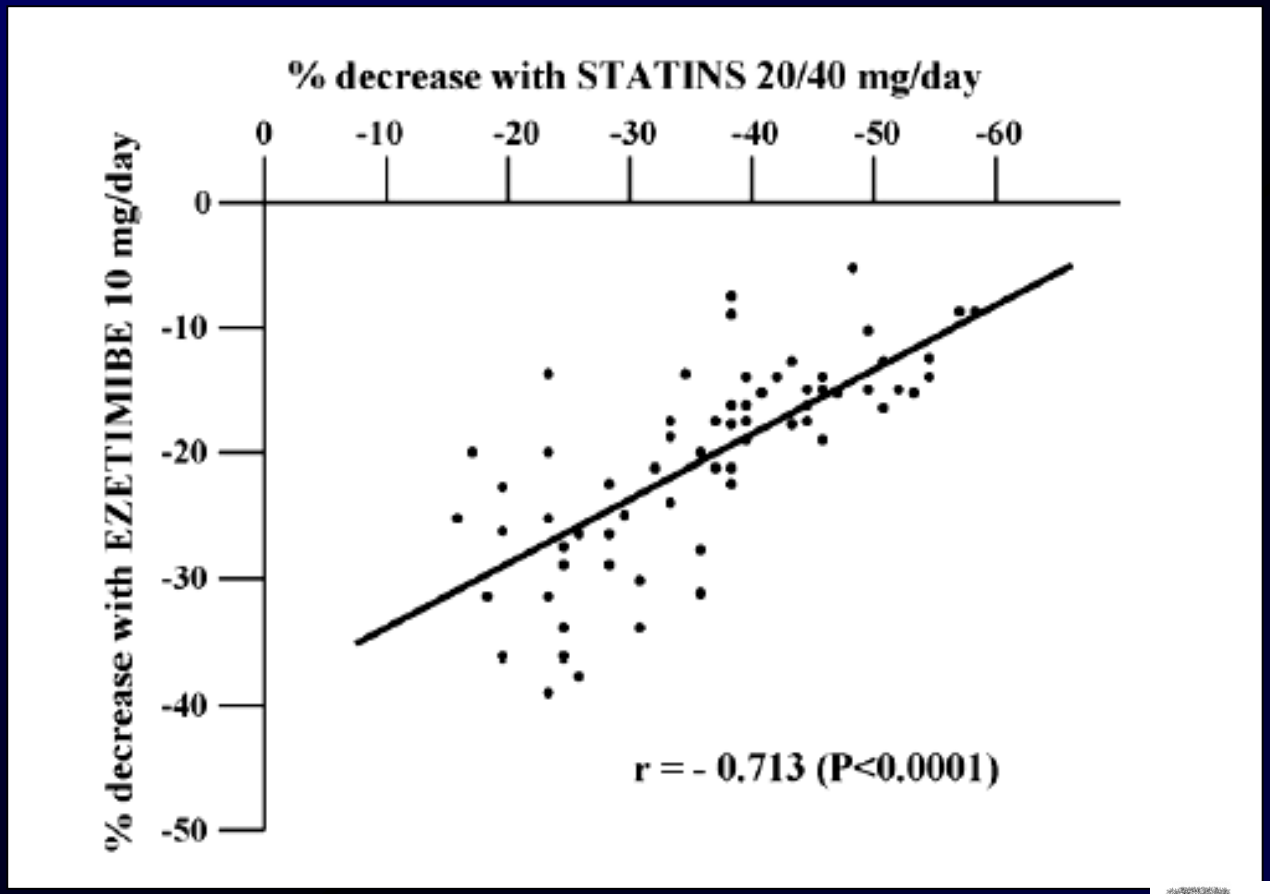
Correlation between % decrease of LDL-C induced by STATINS and by EZETIMIBE in 65 heterozygous FH



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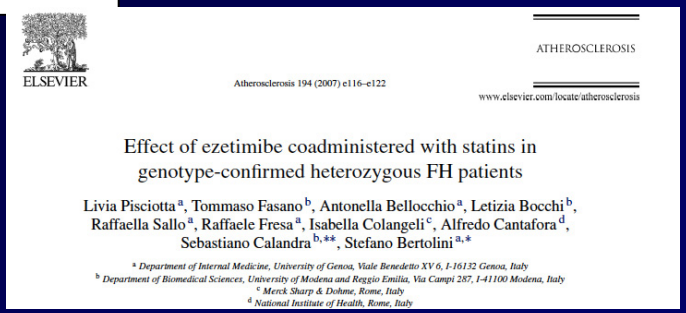

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Low-Density Lipoprotein Cholesterol–Lowering Effects of AMG 145, a Monoclonal Antibody to Proprotein Convertase Subtilisin/Kexin Type 9 Serine Protease in Patients With Heterozygous Familial Hypercholesterolemia

The Reduction of LDL-C With PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder (RUTHERFORD) Randomized Trial

Frederick Raal, MB, BCh, MMed, PhD; Rob Scott, MD; Ransi Somaratne, MD; Ian Bridges, MSc; Gang Li, PhD; Scott M. Wasserman, MD; Evan A. Stein, MD, PhD

Background—Despite statin treatment, many patients with heterozygous familial hypercholesterolemia do not reach desired low-density lipoprotein cholesterol (LDL-C) targets. AMG 145, a fully human monoclonal antibody against proprotein convertase subtilisin/kexin type 9 (PCSK9) serine protease, demonstrated significant reductions in LDL-C in phase 1 studies. This phase 2, multicenter, double-blind, randomized, placebo-controlled, dose-ranging study evaluated the efficacy and safety of AMG 145 in heterozygous familial hypercholesterolemia patients.

Methods and Results—Patients with heterozygous familial hypercholesterolemia diagnosed by Simon Broome criteria with LDL-C ≥2.6 mmol/L (100 mg/dL) despite statin therapy with or without ezetimibe were randomized 1:1:1 to AMG 145 350 mg, AMG 145 420 mg, or placebo-administered subcutaneously every 4 weeks. The primary end point was percentage change from baseline in LDL-C at week 12. Of 168 patients randomized, 167 received investigational product and were included in the full analysis set (mean [SD] age, 50 [13] years; 47% female; 89% white; mean [SD] baseline LDL-C, 4.0 [1.1] mmol/L (156 [42] mg/dL)). At week 12, LDL-C reduction measured by preparative ultracentrifugation (least squares mean [standard error (SE)]) was 43 (3)% and 55 (3)% with AMG 145 350 mg and 420 mg, respectively, compared with 1 (3)% increase with placebo (P<0.001 for both dose groups). Serious adverse events (not considered treatment-related) occurred in 2 patients on AMG 145.

Conclusions—AMG 145 administered every 4 weeks yielded rapid and substantial reductions in LDL-C in heterozygous familial hypercholesterolemia patients despite intensive statin use, with or without ezetimibe, with minimal adverse events and good tolerability.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01375751. **(*Circulation*. 2012;126: 2408-2417.)**

Key Words: familial hypercholesterolemia ■ low-density lipoprotein cholesterol ■ proprotein convertase subtilisin/kexin type 9 ■ randomized controlled trial

Heterozygous familial hypercholesterolemia (HeFH), one of the most common genetic disorders in humans, affecting ~12 million people worldwide, is associated with significant premature cardiovascular morbidity and mortality.[1] The accepted prevalence is 1 in 500 in most populations, with increased frequency where a gene founder effect is present, such as in French Canadians and Afrikaner South Africans.[1] HeFH is characterized by elevated low-density lipoprotein cholesterol (LDL-C), usually >5.2 mmol/L (200 mg/dL), and, if untreated, early cardiovascular disease with typical onset before age 50 in men and 60 in women.[2] In >98% of patients, the defect is attributable to loss-of-function mutations in the LDL receptor alleles, of which >1600 unique mutations have been identified.[3] Less common causes include defects in apolipoprotein B (ApoB), the protein that binds to the LDL receptor, and more recently

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ODYSSEY FH I and FH II: 78 week results with alirocumab treatment in 735 patients with heterozygous familial hypercholesterolaemia

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Aims	To assess long-term (78 weeks) alirocumab treatment in patients with heterozygous familial hypercholesterolaemia (HeFH) and inadequate LDL-C control on maximally tolerated lipid-lowering therapy (LLT).
Methods and results	In two randomized, double-blind studies (ODYSSEY FH I, n = 486; FH II, n = 249), patients were randomized 2 : 1 to alirocumab 75 mg or placebo every 2 weeks (Q2W). Alirocumab dose was increased at Week 12 to 150 mg Q2W if Week 8 LDL-C was ≥1.8 mmol/L (70 mg/dL). Primary endpoint (both studies) was percentage change in calculated LDL-C from baseline to Week 24. Mean LDL-C levels decreased from 3.7 mmol/L (144.7 mg/dL) at baseline to 1.8 mmol/L (71.3 mg/dL; −57.9% vs. placebo) at Week 24 in patients randomized to alirocumab in FH I and from 3.5 mmol/L (134.6 mg/dL) to 1.8 mmol/L (67.7 mg/dL; −51.4% vs. placebo) in FH II (P< 0.0001). These reductions were maintained through Week 78. LDL-C <1.8 mmol/L (regardless of cardiovascular risk) was achieved at Week 24 by 59.8 and 68.2% of alirocumab-treated patients in FH I and FH II, respectively. Adverse events resulted in discontinuation in 3.4% of alirocumab-treated patients in FH I (vs. 6.1% placebo) and 3.6% (vs. 1.2%) in FH II. Rate of injection site reactions in alirocumab-treated patients was 12.4% in FH I and 11.4% in FH II (vs. 11.0 and 7.4% with placebo).
Conclusion	In patients with HeFH and inadequate LDL-C control at baseline despite maximally tolerated statin ± other LLT, alirocumab treatment resulted in significant LDL-C lowering and greater achievement of LDL-C target levels and was well tolerated.
Clinical trial registration	Clinicaltrials.gov (identifiers: NCT01623115; NCT01709500).
Keywords	Alirocumab • PCSK9 • Heterozygous familial hypercholesterolaemia • Cardiovascular risk • LDL-C

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