Farmaci innovativi in ambito cardiovascolare: considerazioni di Farmacologia

Prof. Alberto Corsini

University of Milan, Italy

Outline of the presentation

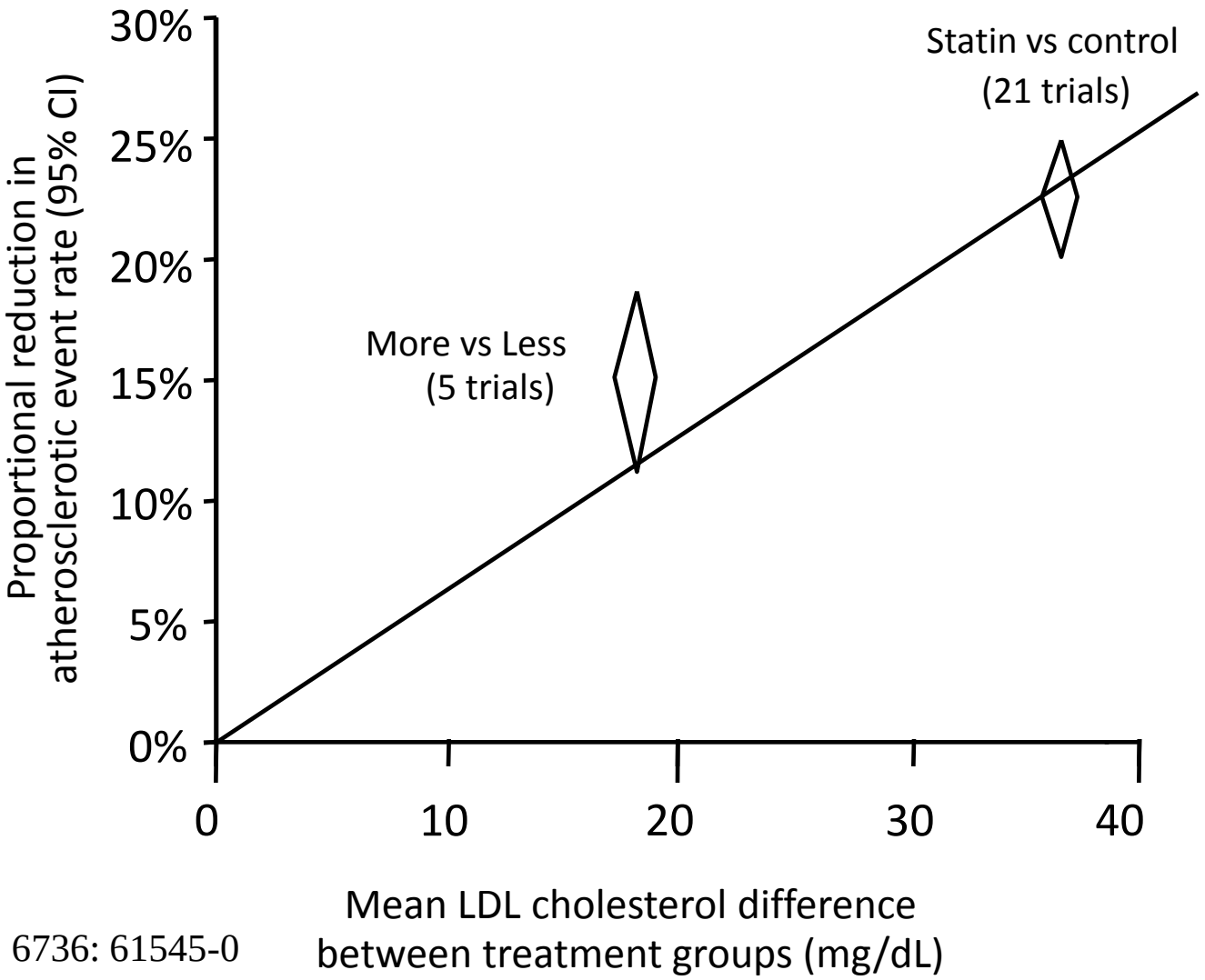
- **State of the art on statin therapy**
- **Explore unmet needs in CVD risk reduction**
- Pharmacological strategies:
  - the role of ezetimibe
  - biologics

Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials

Cholesterol Treatment Trialists' (CTT) Collaboration

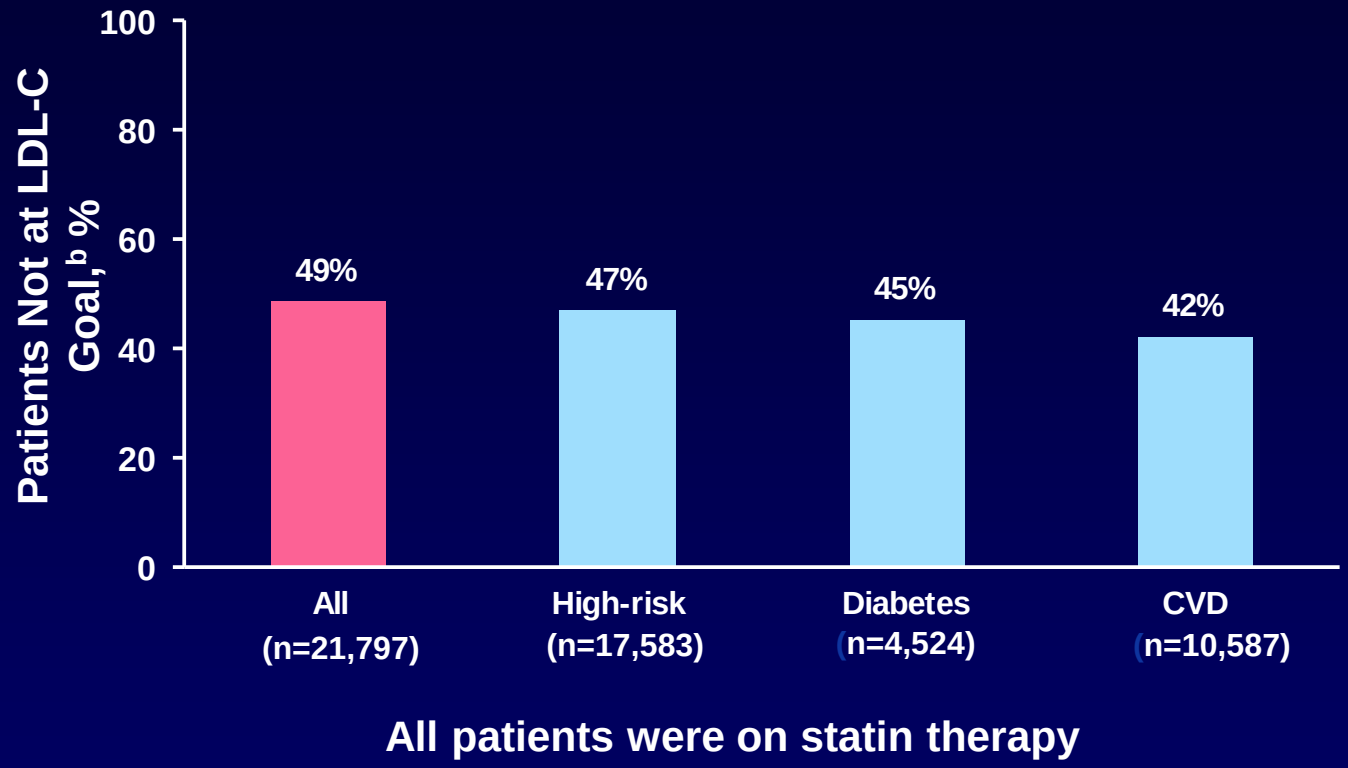
Lancet, November 9th, 2010; 6736(10) 61545-0

CTT: Effects on Major Atherosclerotic Events



Lancet, 2010; 6736: 61545-0

DYSIS (2008–2009): Almost Half of Statin-Treated Patients Were Not at LDL-C Goal[1,a]



High-risk = patients with preexisting CVD, diabetes, and/or ESC score ≥5%.

[a]Study population: 22,063 statin-treated outpatients enrolled from 2,954 sites across 11 European countries and Canada. All data were collected from clinical examination and medical charts from single outpatient visits between April 2008 and February 2009.

[b]LDL-C ≥3 mmol/L in patients with ESC score <5% and LDL-C ≥2.5 mmol/L in patients with ESC score ≥5%, diabetes, and/or CVD.

DYSIS = Dyslipidemia International Study; CVD = cardiovascular disease; ESC = European Society of Cardiology.

1. Gitt AK et al. *Eur J Prevent Cardiol*. 2011;19:221–230.

Factors affecting the response to statins

Extrinsic factors (extraneous influences)

poor compliance
background diet
dose and uptitration of drug
concomitant drug therapy

Intrinsic factors (genetically-determined)

LDL-receptor gene mutations
apo-B-100 gene mutations
rate of cholesterol biosynthesis
rate of cholesterol absorption
CYP/transporter polymorphism
apoE polymorphism

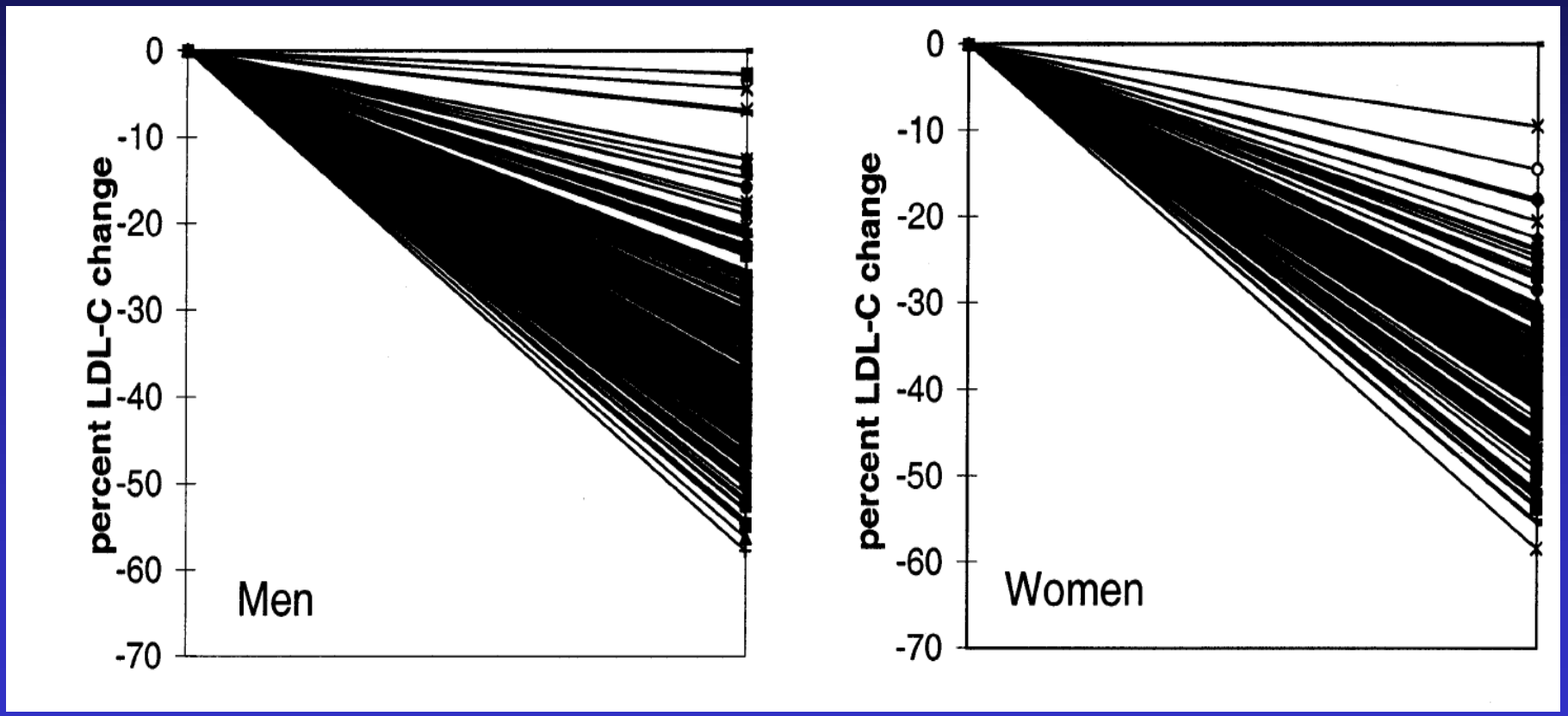
Discontinuation of statin therapy due to muscular side effects: A survey in real life

D. Rosenbaum [a,b,*], J. Dallongeville [c], P. Sabouret [d], E. Bruckert [a,b]

Muscular symptoms were reported in 10% of statin treated patients and led to discontinuation in 30% of the symptomatic patients

Nutrition, Metabolism & Cardiovascular Diseases 1-5, 2012 in press

Individual LDL-C % Response to Atorvastatin 10mg/day

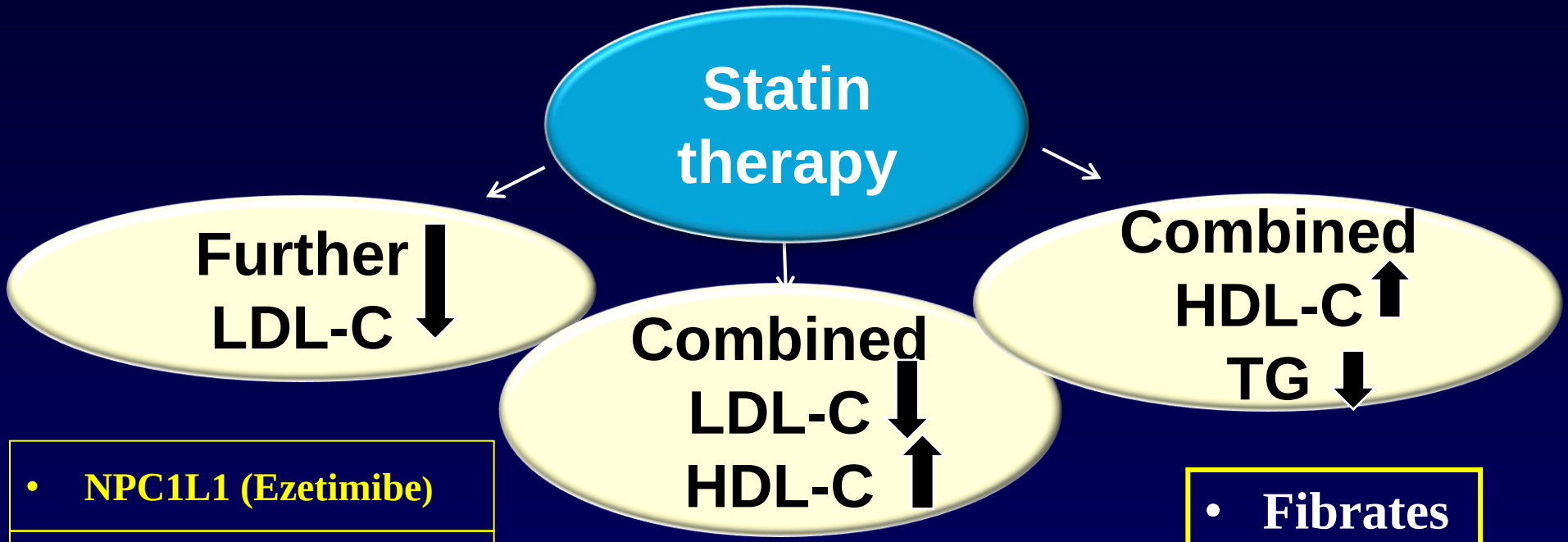


Pedro-Botet J et al. Atherosclerosis 158 (2001) 183-193

Outline of the presentation

- State of the art on statin therapy
- Explore unmet needs in CVD risk reduction
- Pharmacological strategies:
  - the role of ezetimibe
  - biologics

Future development of lipid-lowering drugs



- NPC1L1 (Ezetimibe)
- PCSK9 inhibition (Monoclonal Ab*)
- ApoB-100 Antisense oligonucleotides
- Lopitamide

- CETP inhibition (Anacetrapib*, Evacetrapib*)

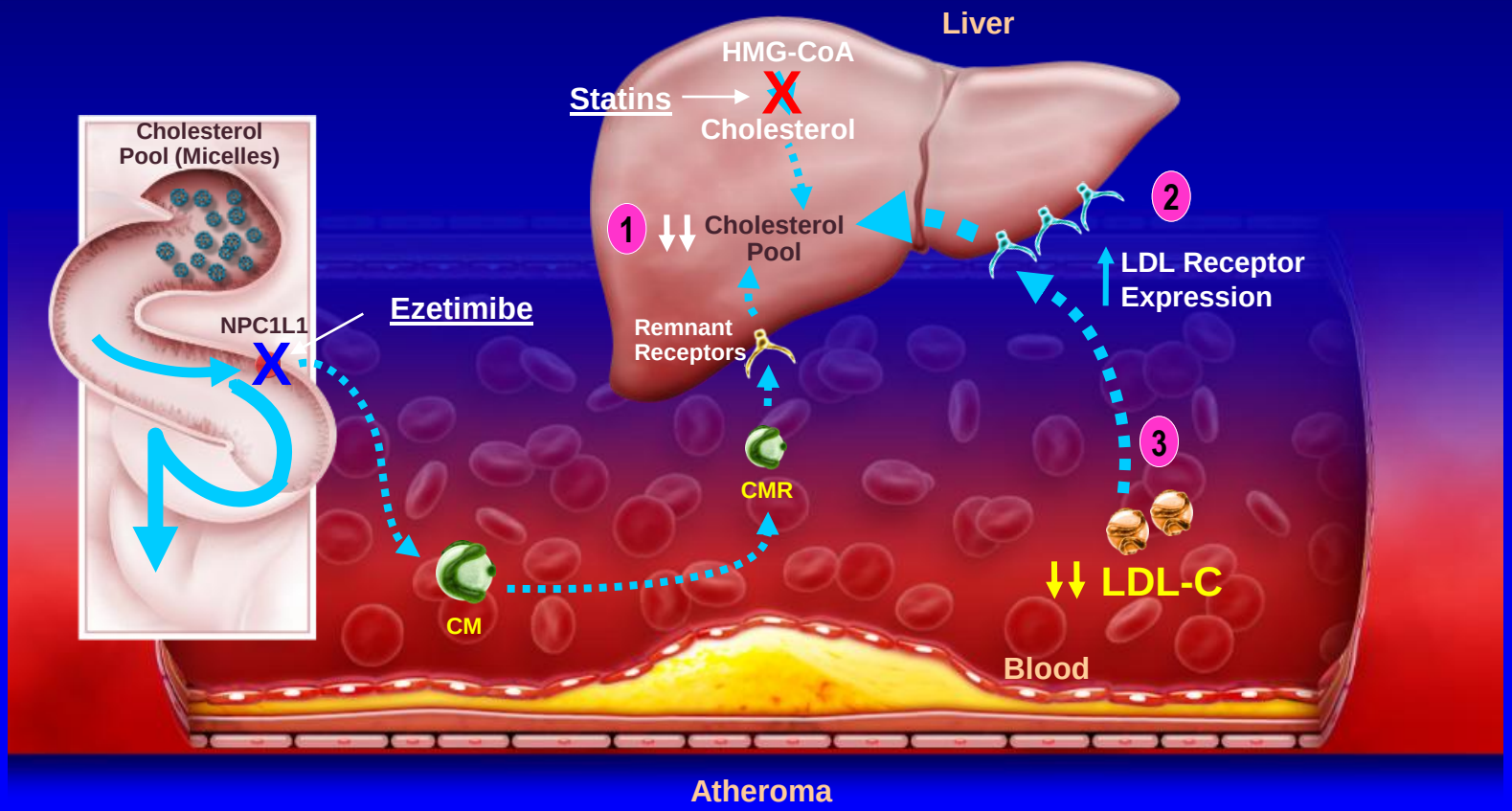
- Fibrates
- ApoCIII Antisense oligonucleotides
- Gene Therapy for LPL deficiency

Modified from Landmesser U Eur Heart J. 2013 ;34(17):1254-7

Ezetimibe and Statins Have Complementary Mechanisms of Action[1]

Together, ezetimibe in combination with a statin provides:

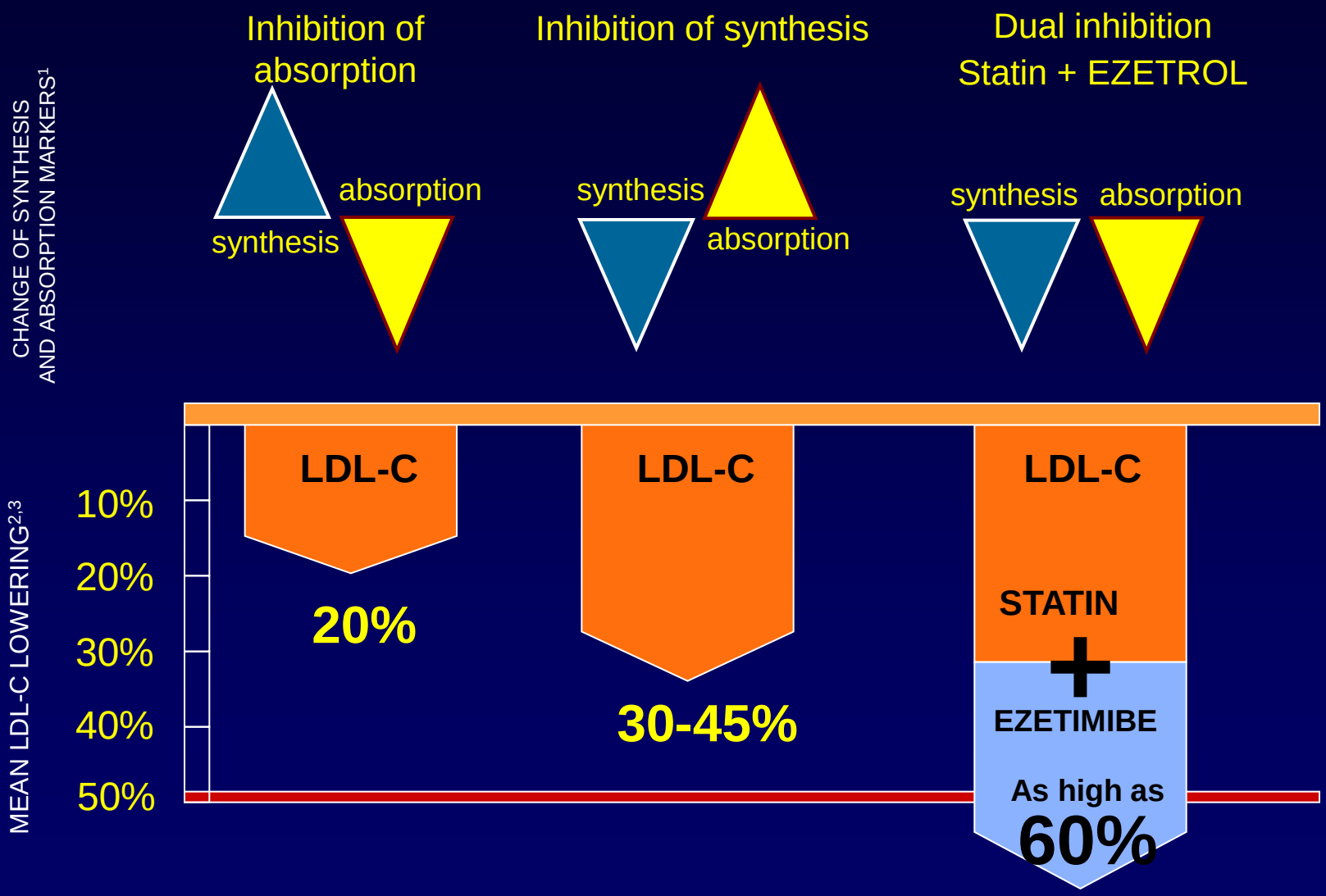
1. Reduction of hepatic cholesterol
2. Increased LDL receptor expression
3. Increased clearance of plasma LDL-C



NPC1L1 = Niemann-Pick C1-like 1; HMG-CoA = 3-hydroxy-3-methylglutaryl acetyl coenzyme A; CMR = chylomicron remnant.

1. Grigore L et al. *Vas Health Risk Manag*. 2008;4:267–278.

As high as 60% LDL-C lowering via dual inhibition



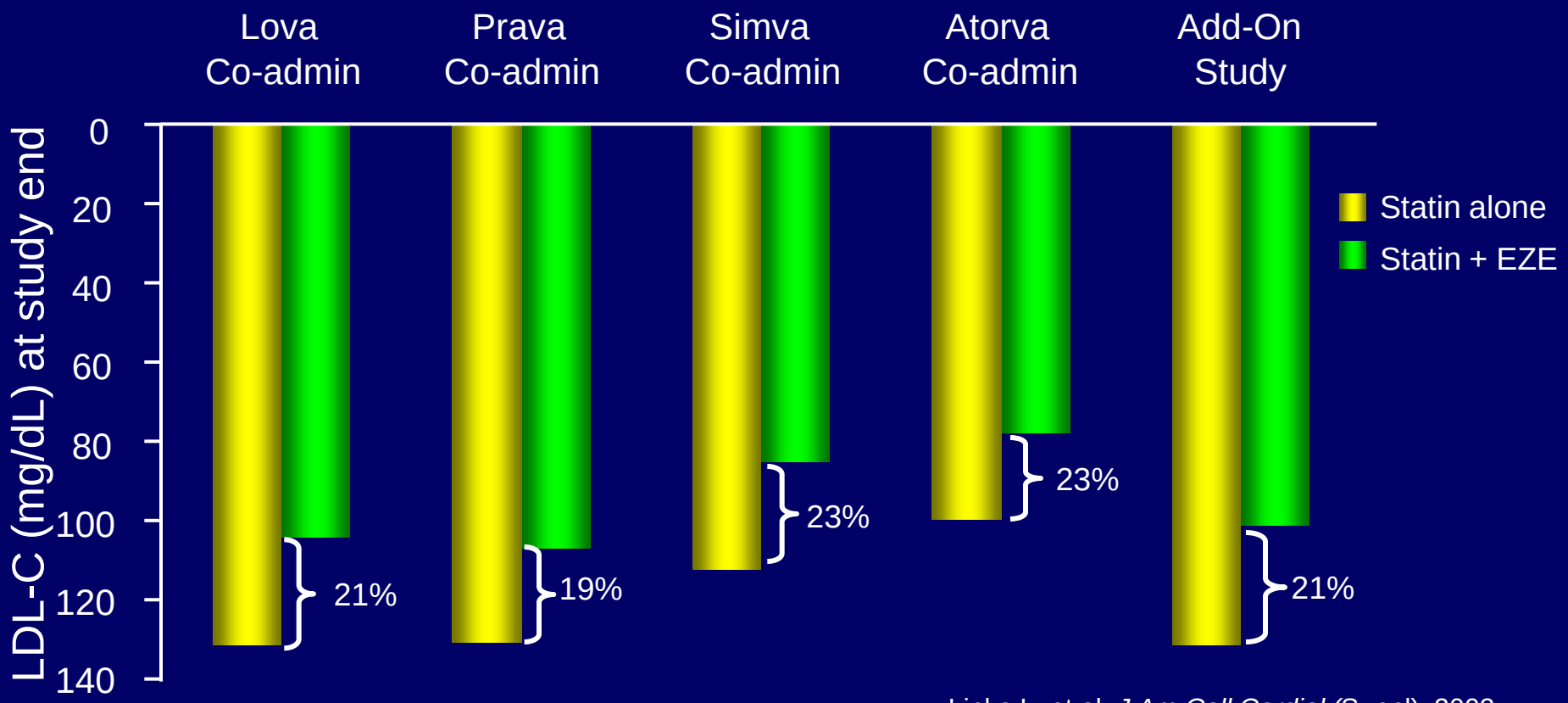
1. Assmann G, et al. *J Am Coll Cardiol* 2004;43(5, Suppl. 2):A445-A446; **2.** Goldberg AC, et al. *Mayo Clin Proc.* 2004 May;79(5):620-9.; **3.** Davidson M et al. J Am Coll Cardiol 2002; 40:2125–34.

Lipid-Lowering Efficacy of Ezetimibe and Ezetimibe/Simvastatin

- Adding ezetimibe to ongoing statin therapy
- Adding ezetimibe to ongoing statin therapy vs doubling the statin dose vs switching to rosuvastatin
- Heterozygous FH
- Statin intolerance

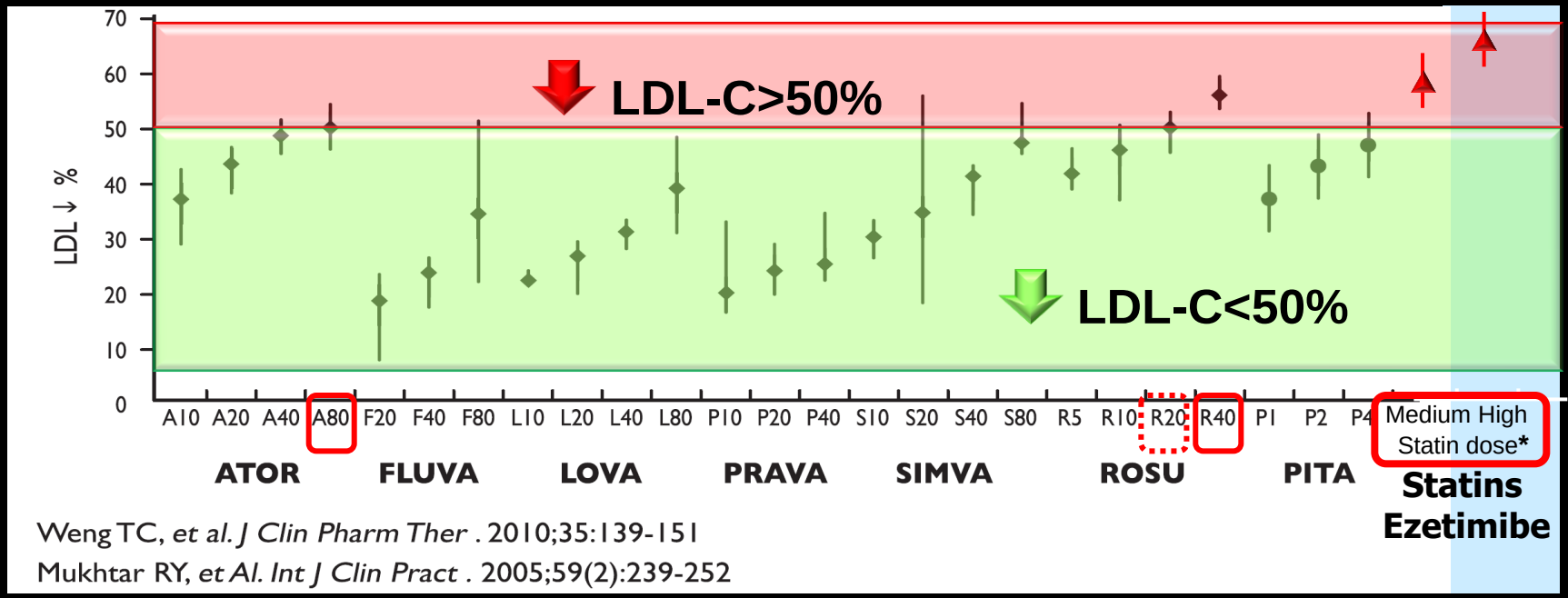
Consistency of Co-Administration Studies

Ezetimibe lowers LDL-C an added 19%-23% compared with statin alone



Lipka L, et al. *J Am Coll Cardiol* (Suppl). 2002.
Melani L, et al. *J Am Coll Cardiol* (Suppl). 2002.
Davidson M, et al. *J Am Coll Cardiol* (Suppl). 2002.
Ballantyne C, et al. *J Am Coll Cardiol* (Suppl). 2002.
Bays H, et al. *J Am Coll Cardiol* (Suppl). 2002.

Riduzione del colesterolo LDL con le statine disponibili a vari dosaggi



Weng TC, *et al. J Clin Pharm Ther* . 2010;35:139-151

Mukhtar RY, *et Al. Int J Clin Pract* . 2005;59(2):239-252

*High Efficacy Statins

Modified from ESC/EAS Guidelines for the Management of Dyslipidaemias: Addenda, European Heart Journal 2011

Programma di studi sugli esiti clinici in >21.000 pazienti ad alto rischio

	N	Study Population	Treatments	Primary Endpoint
ENHANCE (Ezetimibe + Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression)	~725	HeFH	Ezetimibe/ simvastatin 10/80 mg Simvastatin 80 mg	CA IMT
SEAS (Simvastatin + Ezetimibe in Aortic Stenosis)	~1873	Asymptomatic aortic stenosis with LDL-C <6 mmol/L	Ezetimibe/ simvastatin 10/40 mg vs Placebo	CV death, aortic surgery, CV outcomes
SHARP (Study of Heart and Renal Protection)	~9000	Chronic kidney disease	Ezetimibe/ simvastatin 10/20 mg vs Placebo	CV outcomes (MI, stroke, coronary revascularization)
IMPROVE-IT (Improved Reduction of Outcomes: VYTORIN™ Efficacy International Trial)	~10,000	ACS	Ezetimibe/ simvastatin 10/40 mg vs Simva 40 mg	CV endpoints (death, MI, ACS, revascularization)

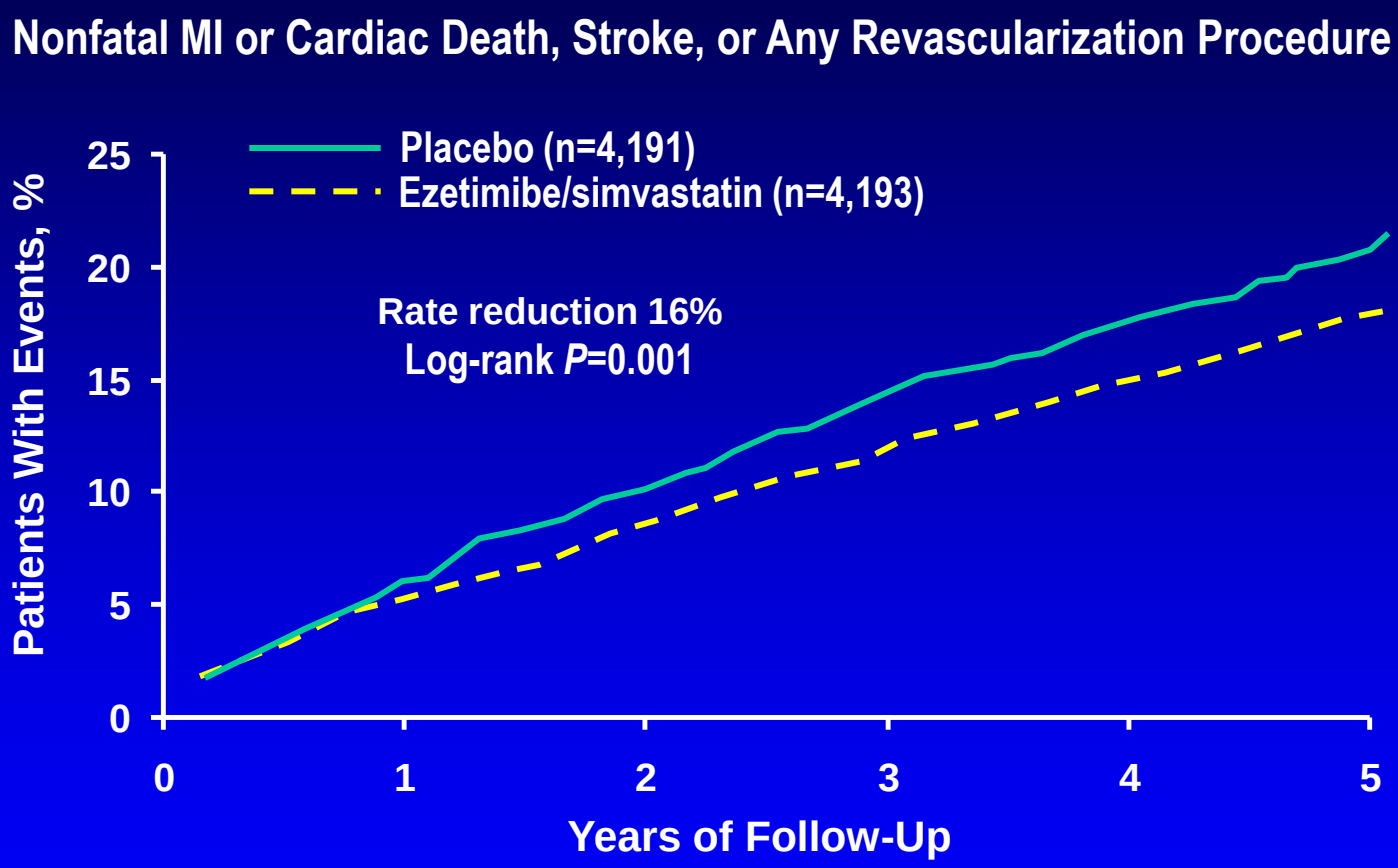
Adapted from Kastelein JJP, et al. *Am Heart J*. 2005;149:234–239; Baigent C, Landry M. *Kidney Int*. 2003;63(suppl 84):S207–S210; Oxford Clinical Trial Service Unit. The Study of Heart and Renal Protection (SHARP). Available at: http://www.ctsu.ox.ac.uk/ ~sharp/. Accessed June 2005; Rossebo A, et al, for the SEAS Steering Committee. Presented at: XIII International Symposium on Atherosclerosis; September 23–October 2, 2003; Kyoto, Japan. Poster 3P-0870; Schering-Plough. IMPROVE-IT: Examining outcomes in subjects with acute coronary syndrome: Vytorin (ezetimibe/simvastatin) vs simvastatin (Study P04103). Available at: http://www.clinicaltrials.gov/ct/show/NCT00202878. Accessed November 2006.

The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial

*Colin Baigent, Martin J Landray, Christina Reith, Jonathan Emberson, David C Wheeler, Charles Tomson, Christoph Wanner, Vera Krane, Alan Cass, Jonathan Craig, Bruce Neal, Lixin Jiang, Lai Seong Hooi, Adeera Levin, Lawrence Agodoa, Mike Gaziano, Bertram Kasiske, Robert Walker, Ziad A Massy, Bo Feldt-Rasmussen, Udom Krairittichai, Vuddidhej Ophascharoensuk, Bengt Fellström, Hallvard Holdaas, Vladimir Tesar, Andrzej Wiecek, Diederick Grobbee, Dick de Zeeuw, Carola Grönhagen-Riska, Tanaji Dasgupta, David Lewis, William Herrington, Marion Mafham, William Majoni, Karl Wallendszus, Richard Grimm, Terje Pedersen, Jonathan Tobert, Jane Armitage, Alex Baxter, Christopher Bray, Yiping Chen, Zhengming Chen, Michael Hill, Carol Knott, Sarah Parish, David Simpson, Peter Sleight, Alan Young, Rory Collins, on behalf of the SHARP Investigators**

Published Online
June 9, 2011

SHARP: Major Vascular Events in Patients Initially Assigned Ezetimibe/Simvastatin or Placebo

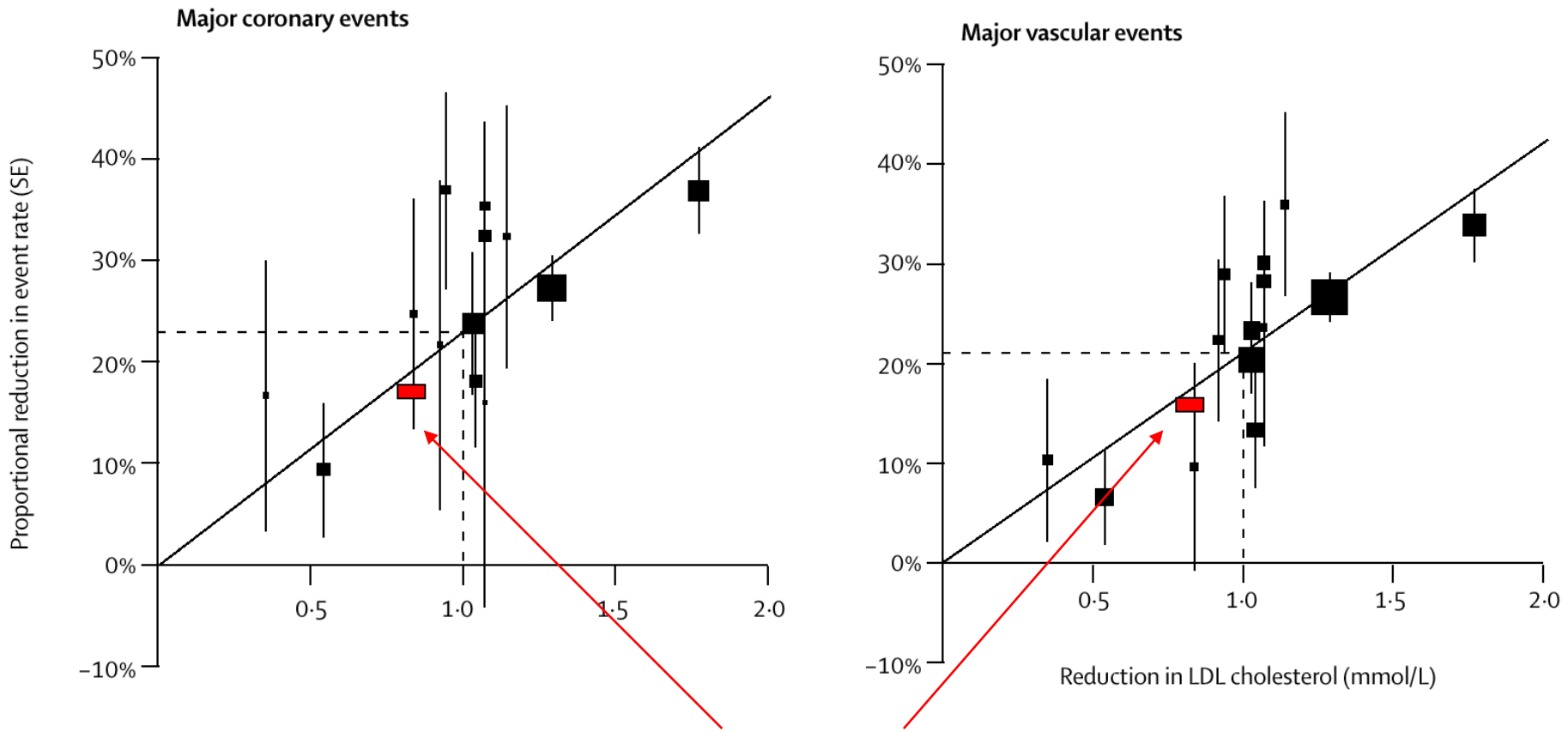


Major vascular events occurred in 639 patients (15.2%) treated with ezetimibe/simvastatin 10/20 mg vs 749 patients (17.9%) treated with placebo, corresponding to a 16% relative risk reduction

SHARP = Study of Heart and Renal Protection; MI = myocardial infarction.

1. MSD. Worldwide product circular. WPC–MK0653A-T-102012.

Relation between proportional reduction in incidence of major coronary and vascular events and absolute LDL cholesterol reduction at 1 year



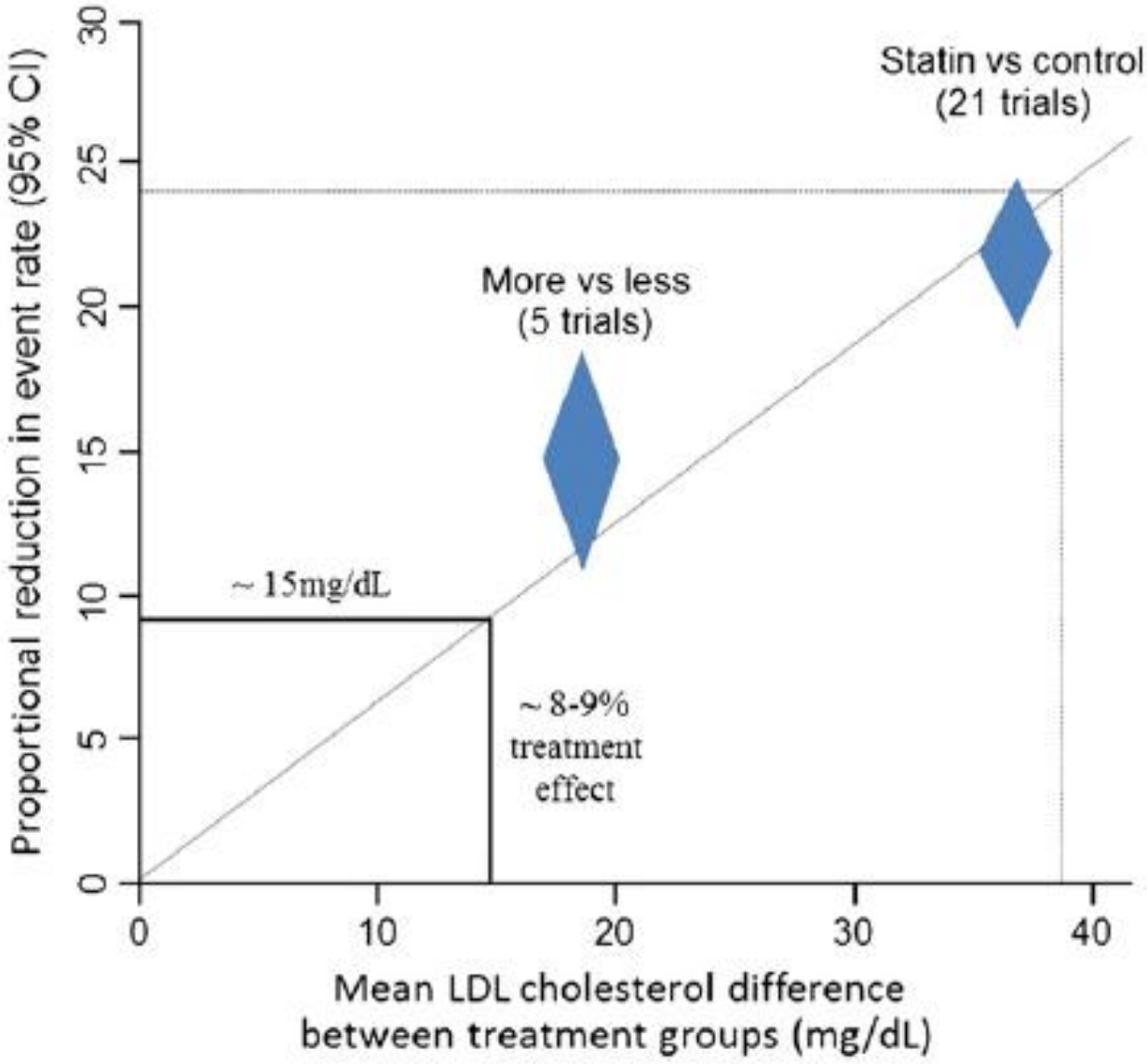
SHARP

Cholesterol Treatment Trialists' (CTT) Collaborators *Lancet* 2005;366:1

IMProved Reduction of Outcomes: Vytorin Efficacy International Trial

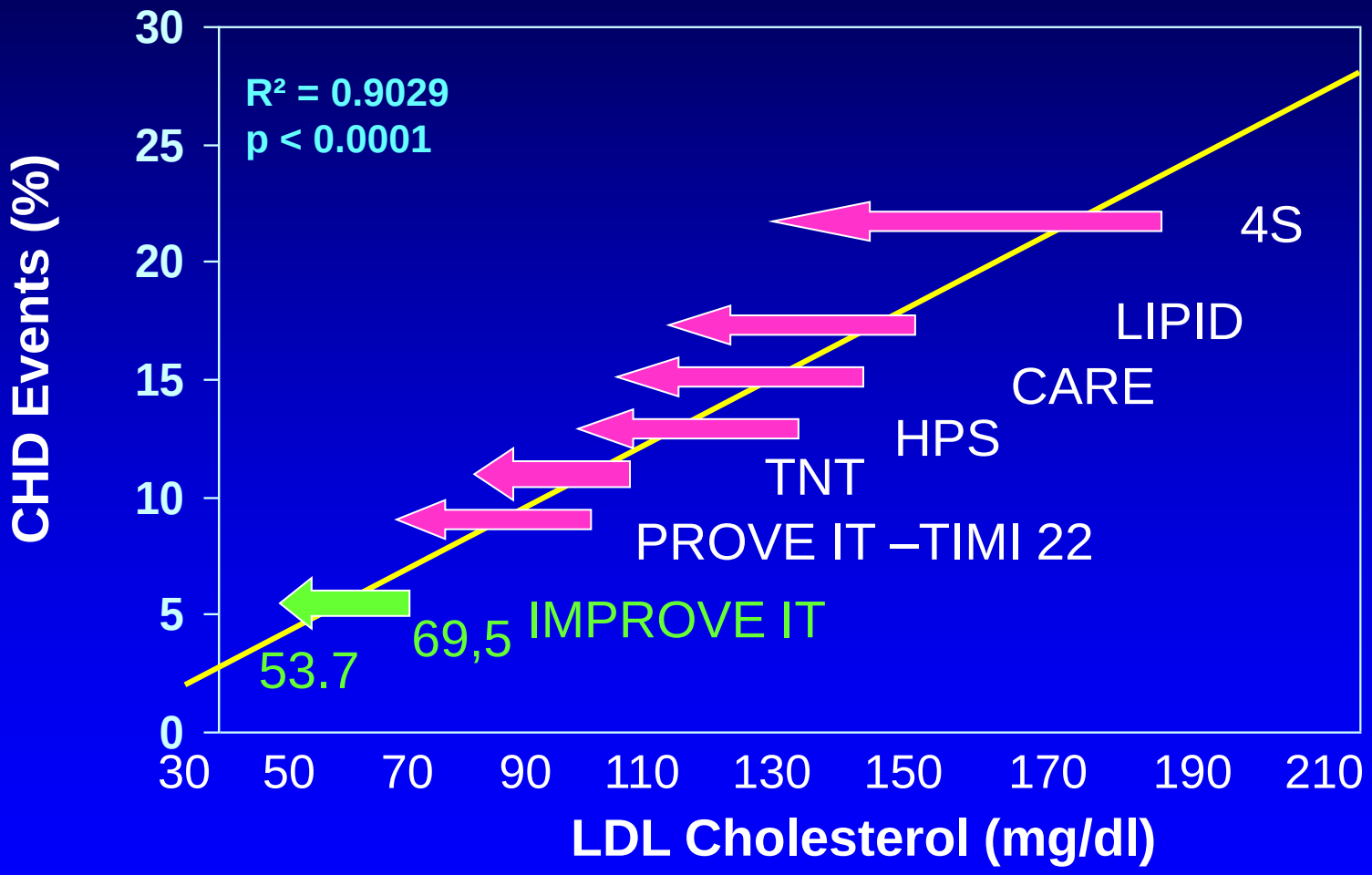
A Multicenter, Double-Blind, Randomized Study to Establish the Clinical Benefit and Safety of Vytorin (Ezetimibe/Simvastatin Tablet) vs Simvastatin Monotherapy in High-Risk Subjects Presenting With Acute Coronary Syndrome

Projected positioning of IMPROVE-IT in comparison with the relationship of LDL-C difference and proportional event reduction for intensive versus less intensive statin therapy trials



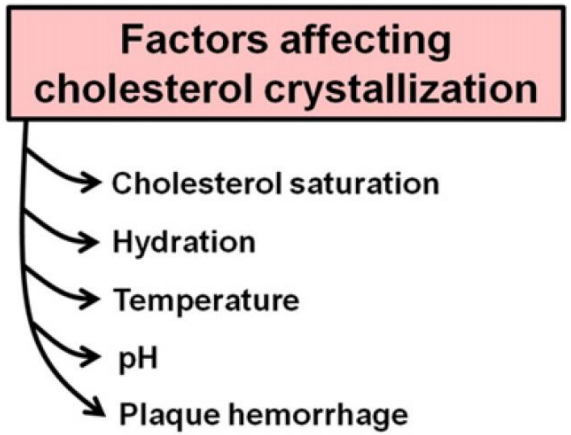
Am Heart J 2014; 168:205-212

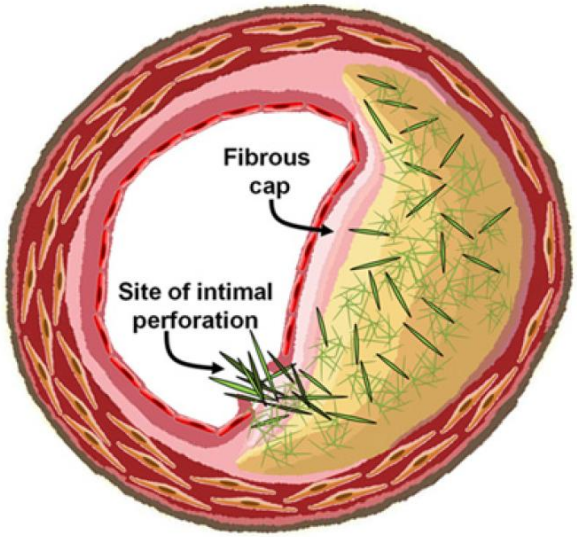
The LDL-C Decade: “Lower is Better”

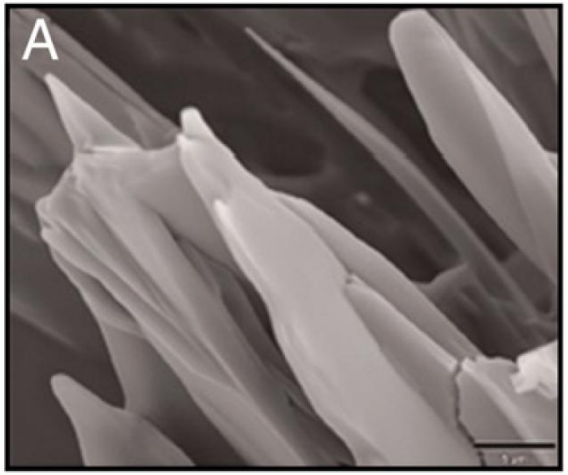


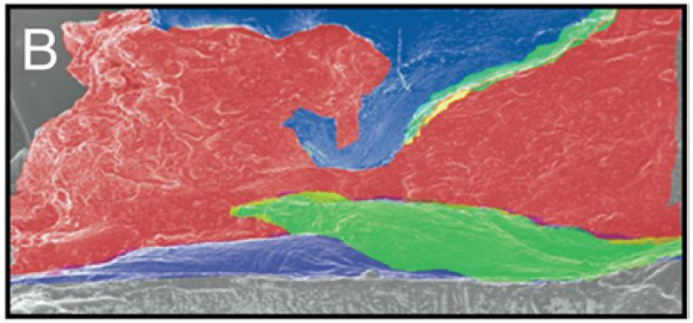
Adapted and Updated from O’Keefe, J. et al., J Am Coll Cardiol 2004;43:2142-6.

Effects of cholesterol crystals on plaque integrity in coronary arteries of patients who died of ACS



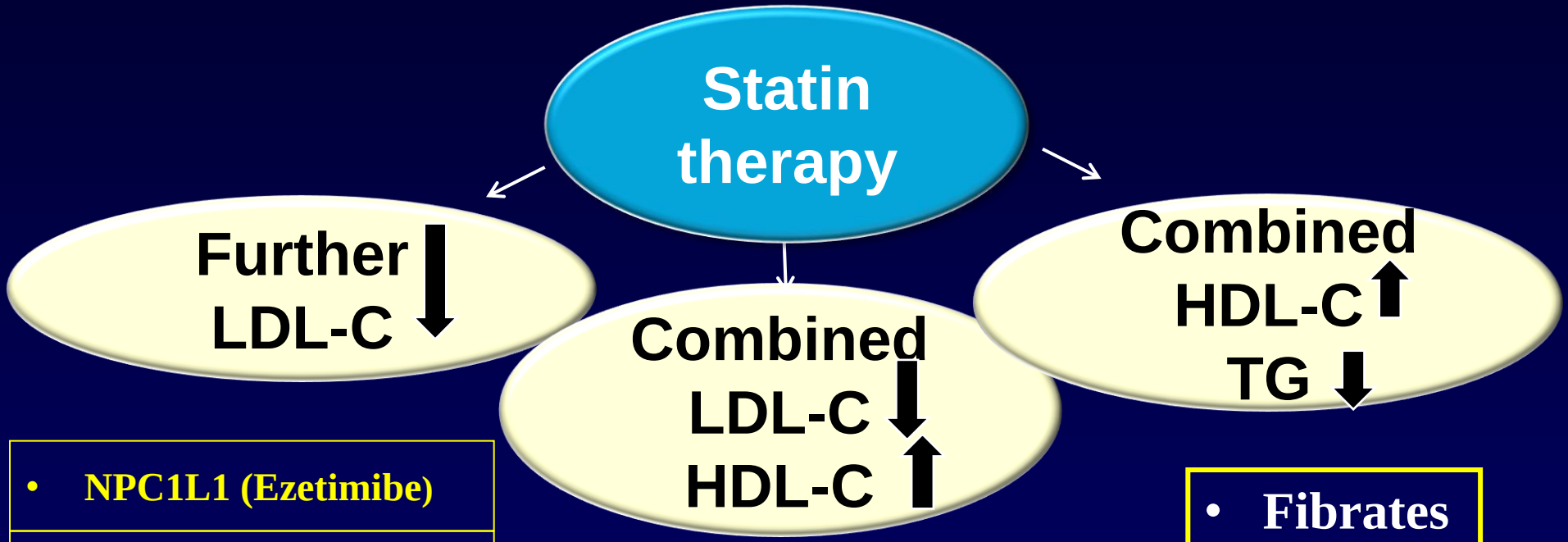






Crea F and Liuzzo G J Am Coll Cardiol 2013;61:1–11

Future development of lipid-lowering drugs



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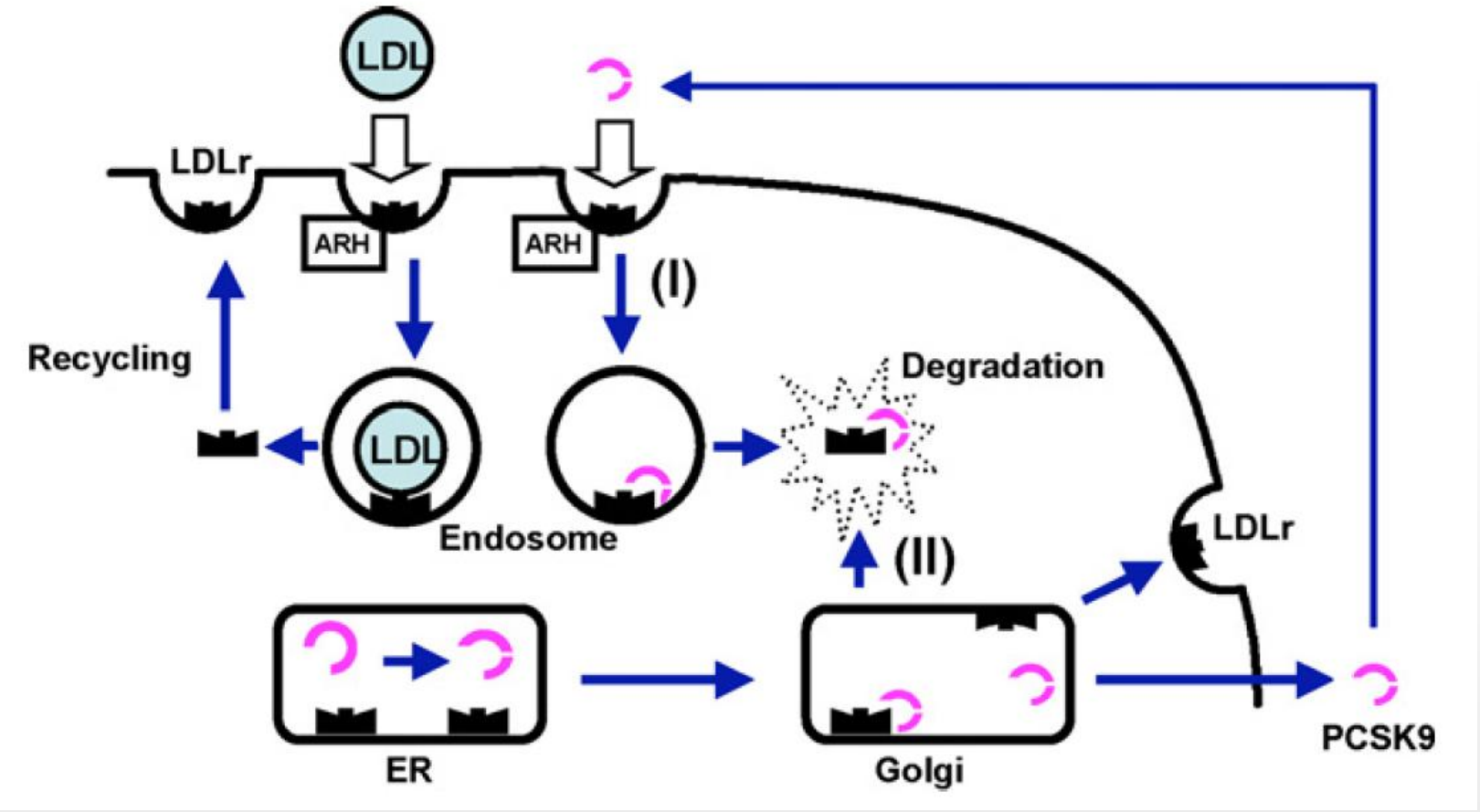
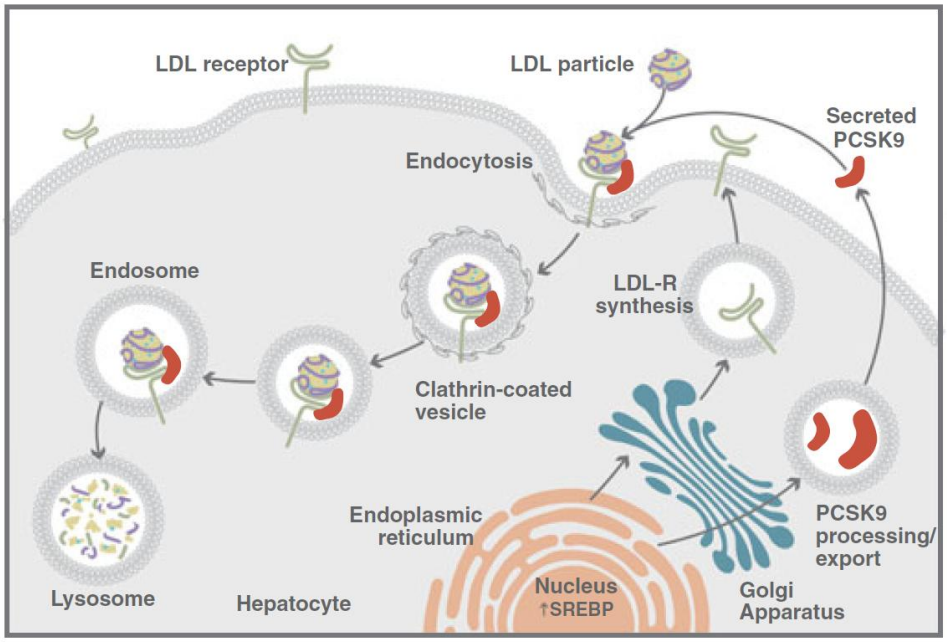
Modified from Landmesser U Eur Heart J. 2013 ;34(17):1254-7

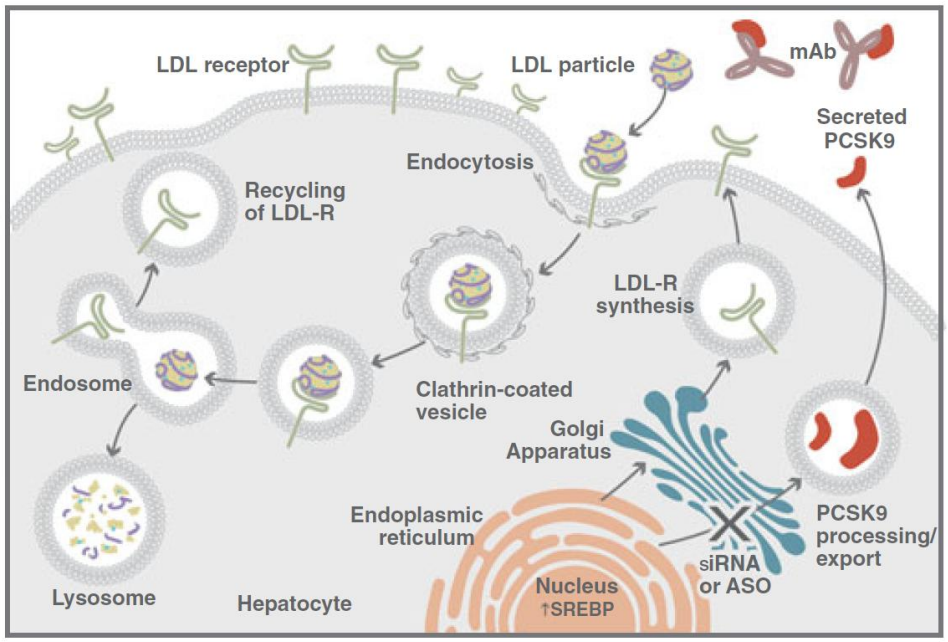
Regolazione dell'espressione di LDLR per opera di PCSK9



Lambert G. et *al*, Atherosclerosis 203 (2009) 1–7

Interaction of PCSK9 and the LDL receptor



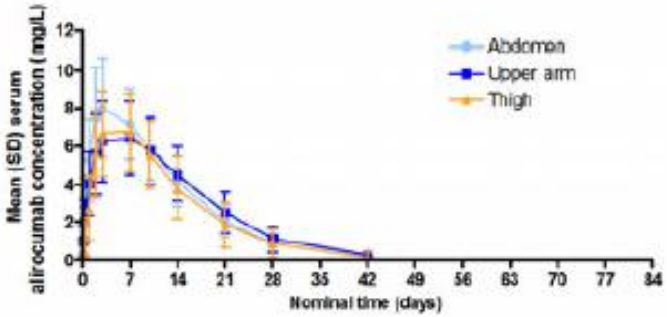


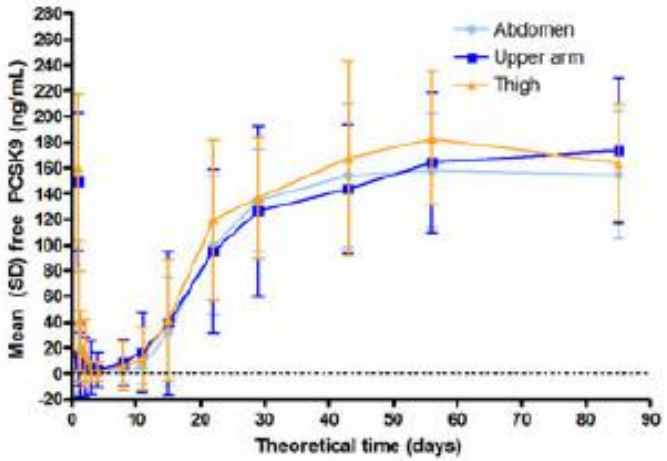
Stein EA and Swergold GD Curr Atheroscler Rep (2013) 15:310

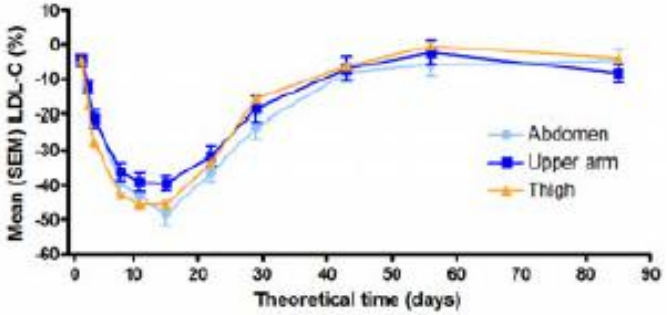
Clinical Pharmacology of PCSK9 inhibitors

Agent	Evolocumab (AMG 145)	Alirocumab (REGN727/ SAR236553)	Bococizumab (RN 316)	LGT-209	RG7652 (MPSK3169A)
Mechanism of action	PCSK9 inhibitor	PCSK9 inhibitor	PCSK9 inhibitor	PCSK9 inhibitor	PCSK9 inhibitor
Type of inhibitor	Humanized monoclonal antibody	Humanized monoclonal antibody	Humanized monoclonal antibody	Humanized monoclonal antibody	Humanized monoclonal antibody
Manufacturer	Amgen	Sanofi/ Regeneron	Pfizer/Rinat	Novartis/ KaloBios	Roche/ Genentech
Study Phase	3	2 / 3	2 / 3	1 / 2	1 / 2
Administration	sc	sc	sc	sc	sc
Studies	GAUSS,[21] RUTHERFORD,[22] MENDEL,[23] LAPLACE-TIMI 57,[24] OSLER,[25] PROFICIO, DESCARTES (NCT01516879), FOURIER (NCT01764633),[26] TAUSSIG (NCT01624142), GLAGOV (NCT01813422), TESLA (NCT01588496)	3 phase I studies,[27] 2 phase II studies,[28,29] ODYSSEY Outcomes program (NCT01663402)	NCT01592240, SPIRE-LDL (NCT01968967), SPIRE-HR (NCT01968954), SPIRE-1 (NCT01975376), SPIRE-2 (NCT01975389)	NCT01979601 & NCT01859455	NCT01609140 http://eurheartj.oxfordjournals.org/content/34/suppl_1/P4183 ?
Liver metabolism	No	No	No	No	No
Half-life	2.5-11.5 d	3.2 d	7-13 d	?	?
Dose	**140 mg q 2 weeks or 420 mg q 1 month**	**75/150 mg q 2 weeks**	**150 mg q 2 weeks**	**50/300 mg q ?**	**? mg q 4 weeks**
Indications	↑risk for CVD; statin intolerant or resistant	↑risk for CVD; statin intolerant or resistant	↑risk for CVD; statin intolerant or resistant	↑risk for CVD; statin intolerant or resistant	↑risk for CVD; statin intolerant or resistant

Manolis AS t al
HOSPITAL CHRONICLES
2014, 9(1): 3–10







Alirocumab concentration (A), free PCSK9 levels (B), and % change in LDL-C froe baseline (C) after subcutaneous administration of alirocumab 75 mg

Cardiovasc Ther. 2014 Sep 24

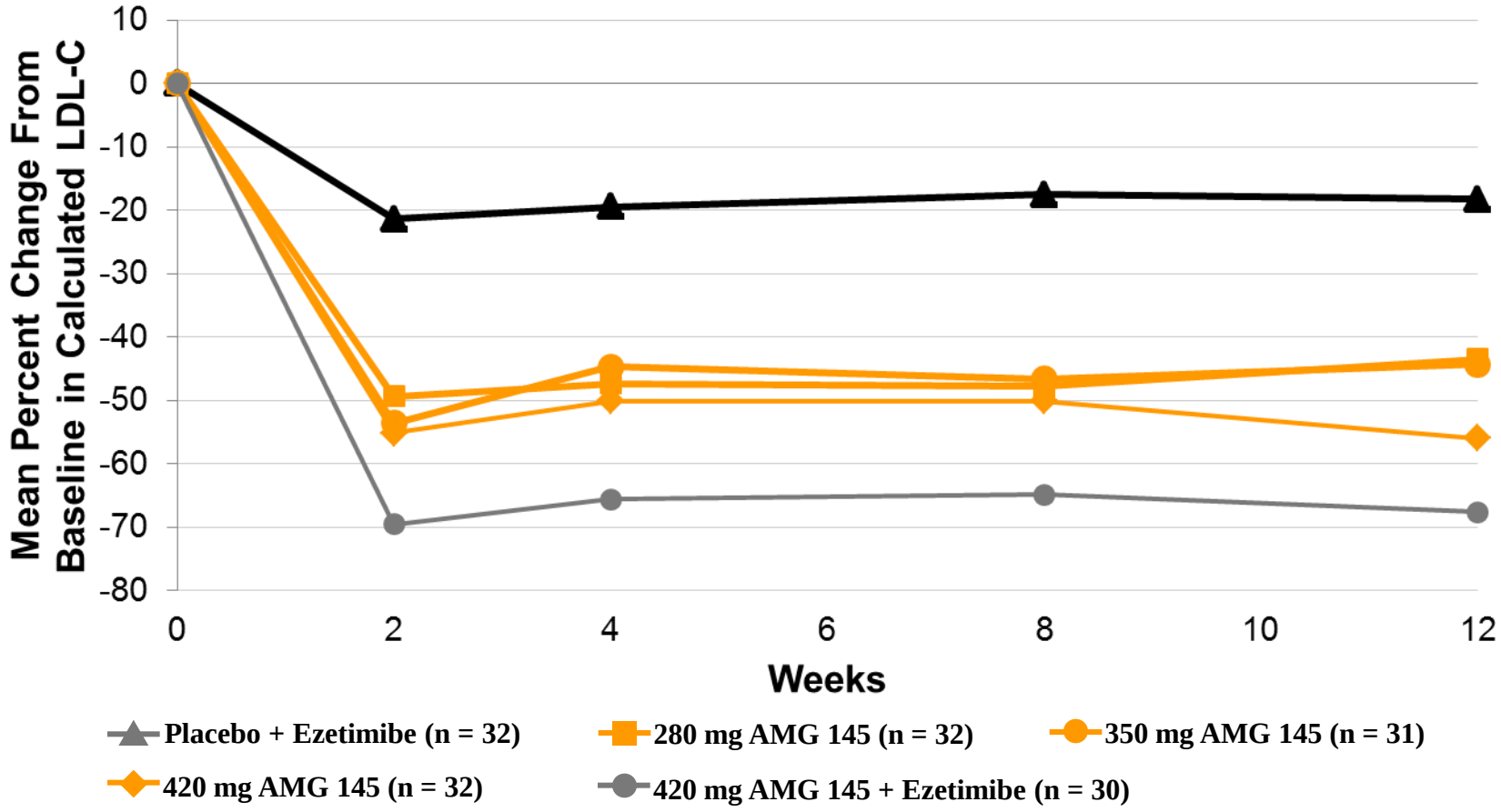
Effect of a Monoclonal Antibody to PCSK9 on Low-Density Lipoprotein Cholesterol Levels in Statin-Intolerant Patients

The GAUSS Randomized Trial

David Sullivan, MD
Anders G. Olsson, MD, PhD
Rob Scott, MD
Jae B. Kim, MD
Allen Xue, PhD
Val Gebski, MStat
Scott M. Wasserman, MD
Evan A. Stein, MD, PhD

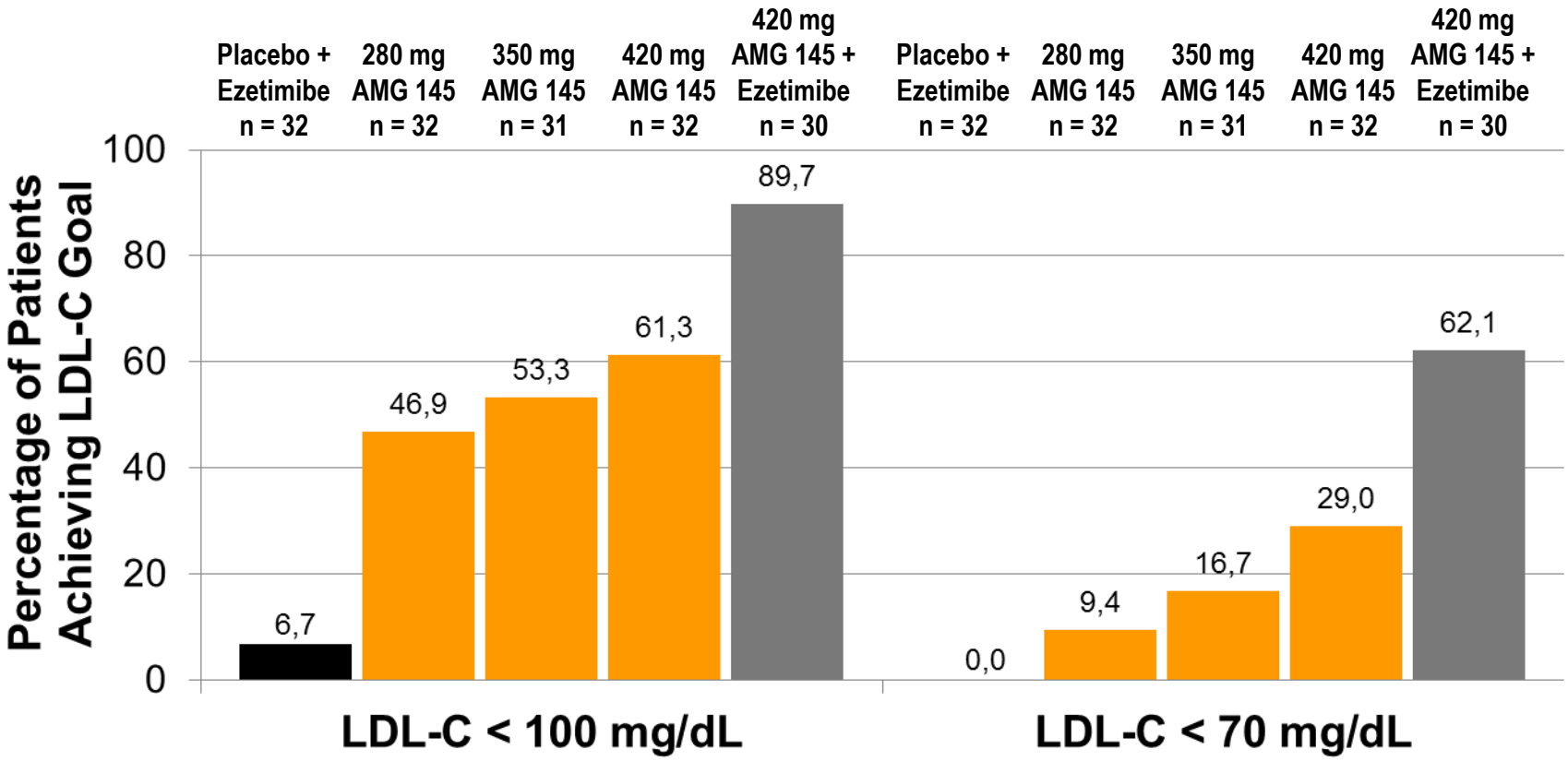
JAMA. 2012;308(23):2497-2506

Effects of AMG 145 and ezetimibe on LDL-C



JAMA. 2012;308(23):2497-2506

LDL-C Goal Attainment at Week 12



JAMA. 2012;308(23):2497-2506

Adverse Events and Laboratory Results

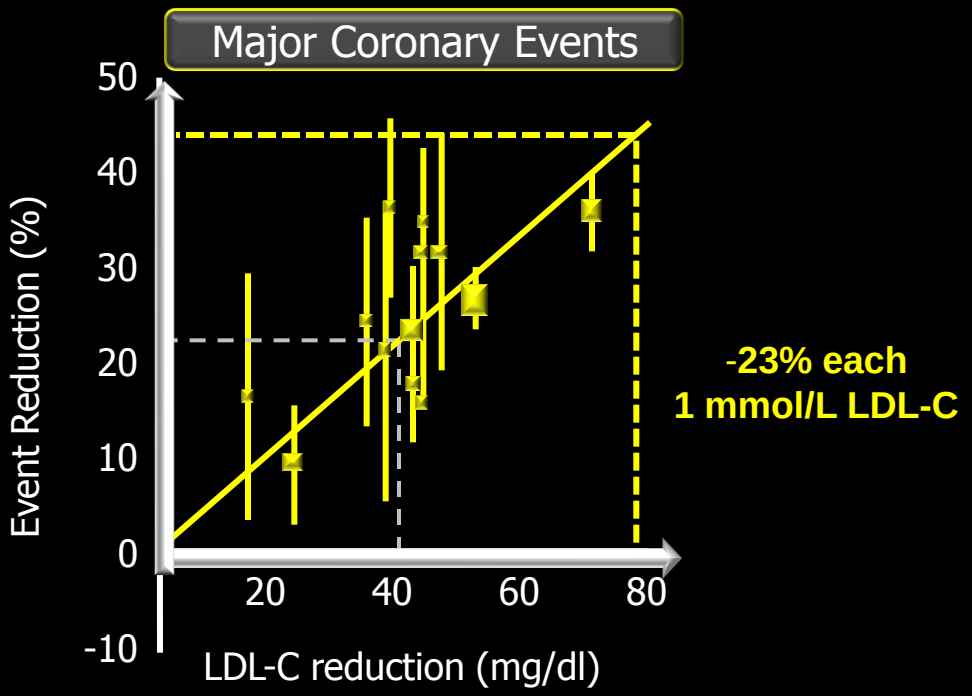
	No. of Patients (%)						
	AMG145 SC Every 4 wk				AMG145 or Placebo Every 4 wk and Ezetimibe, 10 mg, Once Daily		All Patients (N = 157)
	280 mg (n = 32)	350 mg (n = 31)	420 mg (n = 32)	All AMG145 Only (n = 95)	AMG145 SC, 420 mg (n = 30)	Placebo SC (n = 32)	
Treatment-emergent AEs							
Any	22 (68.8)	15 (48.4)	18 (56.3)	55 (57.9)	20 (66.7)	19 (59.4)	94 (59.9)
Serious[a]	2 (6.3)	1 (3.2)	1 (3.1)	4 (4.2)	0	0	4 (2.5)
Leading to discontinuation of investigational product	0	1 (3.2)	1 (3.1)	2 (2.1)	1 (3.3)	2 (6.3)	5 (3.2)
Treatment-related[b]	8 (25.0)	3 (9.7)	6 (18.8)	17 (17.9)	5 (16.7)	7 (21.9)	29 (18.5)
Serious treatment-relateda,[b]	0	0	0	0	0	0	0
Deaths	0	0	0	0	0	0	0
Muscle-related AEs							
Myalgia	5 (15.6)	1 (3.2)	1 (3.1)	7 (7.4)	6 (20.0)	1 (3.1)	14 (8.9)
Muscle fatigue	2 (6.3)	0	0	2 (2.1)	0	1 (3.1)	3 (1.9)
Muscle spasms	1 (3.1)	2 (6.5)	0	3 (3.2)	0	3 (9.4)	6 (3.8)

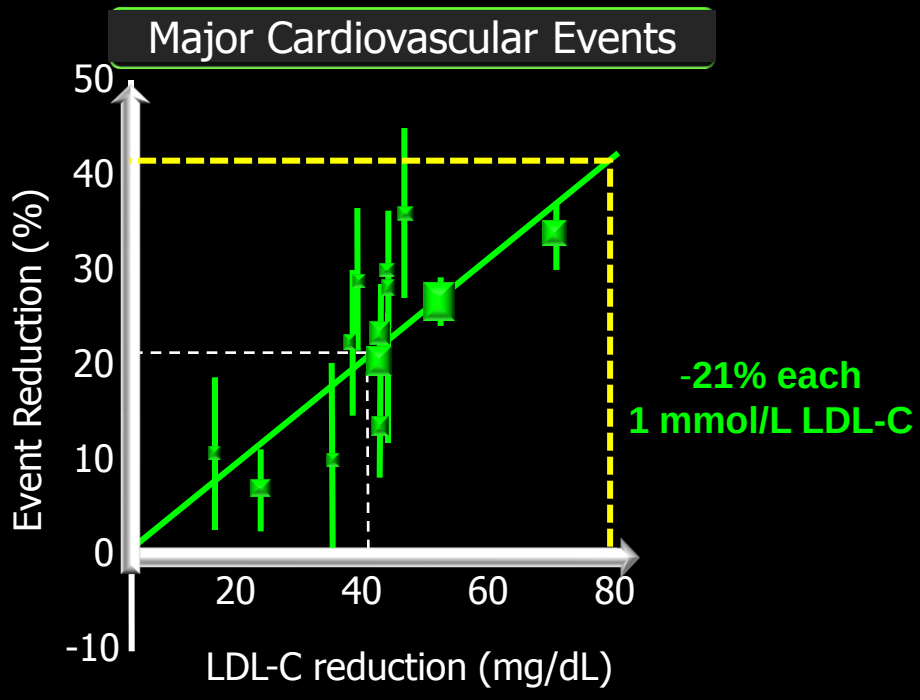
JAMA. 2012;308(23):2497-2506

Major **coronary** e and **cardiovascular events** and LDL-C reduction in statin trials

(Meta-analysis of 14 trials, n=90.056, published from 1994 to 2004)

Lancet 2005; 366:1267-1278

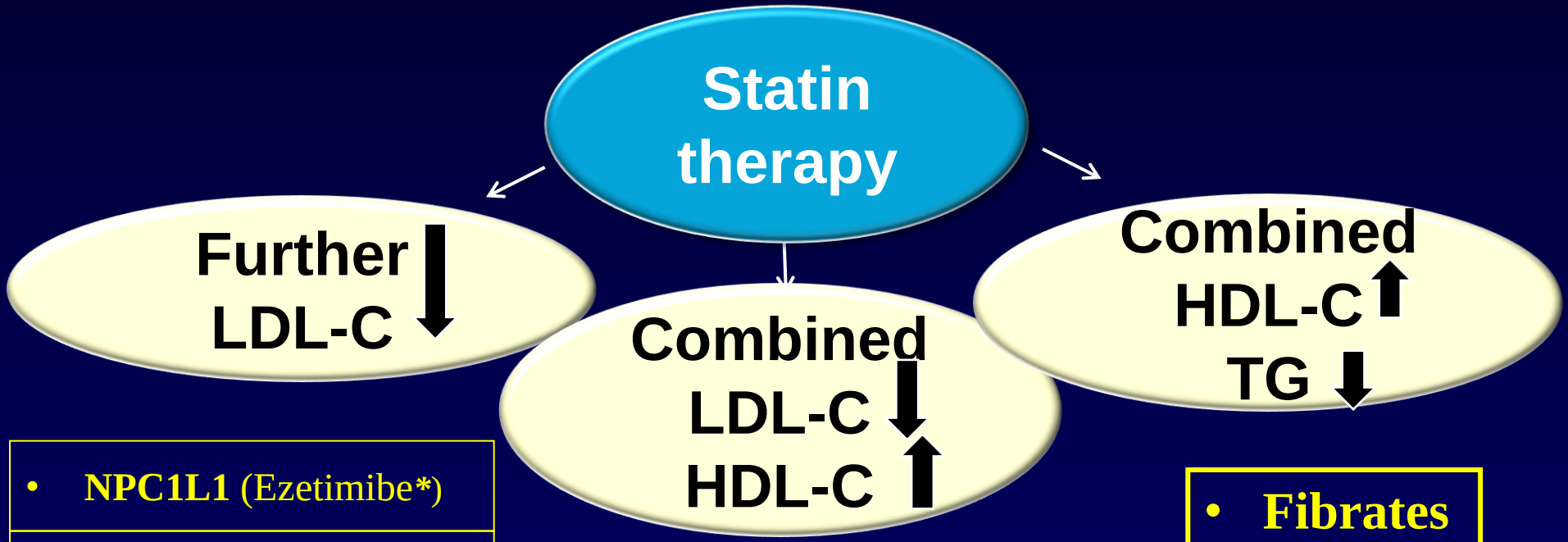




Statin+ PCSK9 inhibitors:

1) Further LDL-C reduction by 80-100 mg/dl (2.0 -2.5 mmol/l)
2) Potential FURTHER CHD/CVD EVENT REDUCTION UP TO 40-50%

Future development of lipid-lowering drugs



- **NPC1L1** (Ezetimibe*)

- **PCSK9 inhibition (Monoclonal Ab*)**
- **ApoB-100 Antisense oligonucleotides**
- **Lopitamide**

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- **ApoCIII Antisense oligonucleotides**
- **Gene Therapy for LPL deficiency**

Modified from Landmesser U Eur Heart J. 2013 ;34(17):1254-7