Novità in tema di dislipidemie nel paziente ad alto rischio cardiovascolare

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CORE

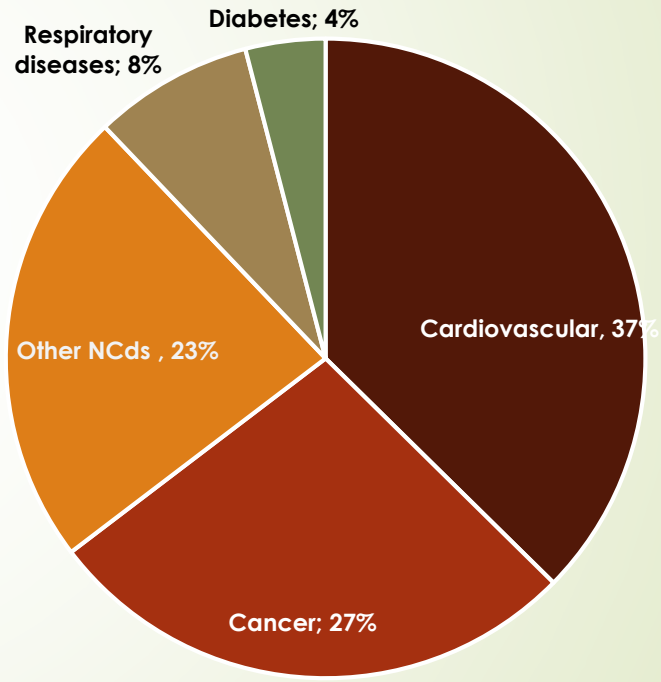
Cardiovascular Disease Leads as the Global Cause of Death

Cardiovascular Disease (CVD)

Leading cause of death in the world[1]

- Cardiovascular diseases claim more lives than all forms of cancer combined[1,2]
- **> 17.3 million** deaths per year globally[1]
- CVD causes > 4 million deaths each year across Europe accounting for 45% of all deaths. CHD and stroke account for 1.8 million and 1.0 million deaths, respectively[3]
- ~2,200 Americans die of CVD each day, an average of 1 death every 40 seconds[4]
- Accounts for **10%** of the global disease burden (DALYs)[1]
- In 2015, ischemic heart disease was the leading cause for years of lost life (YLL), accounting for 9.5% of YLL, globally[5]

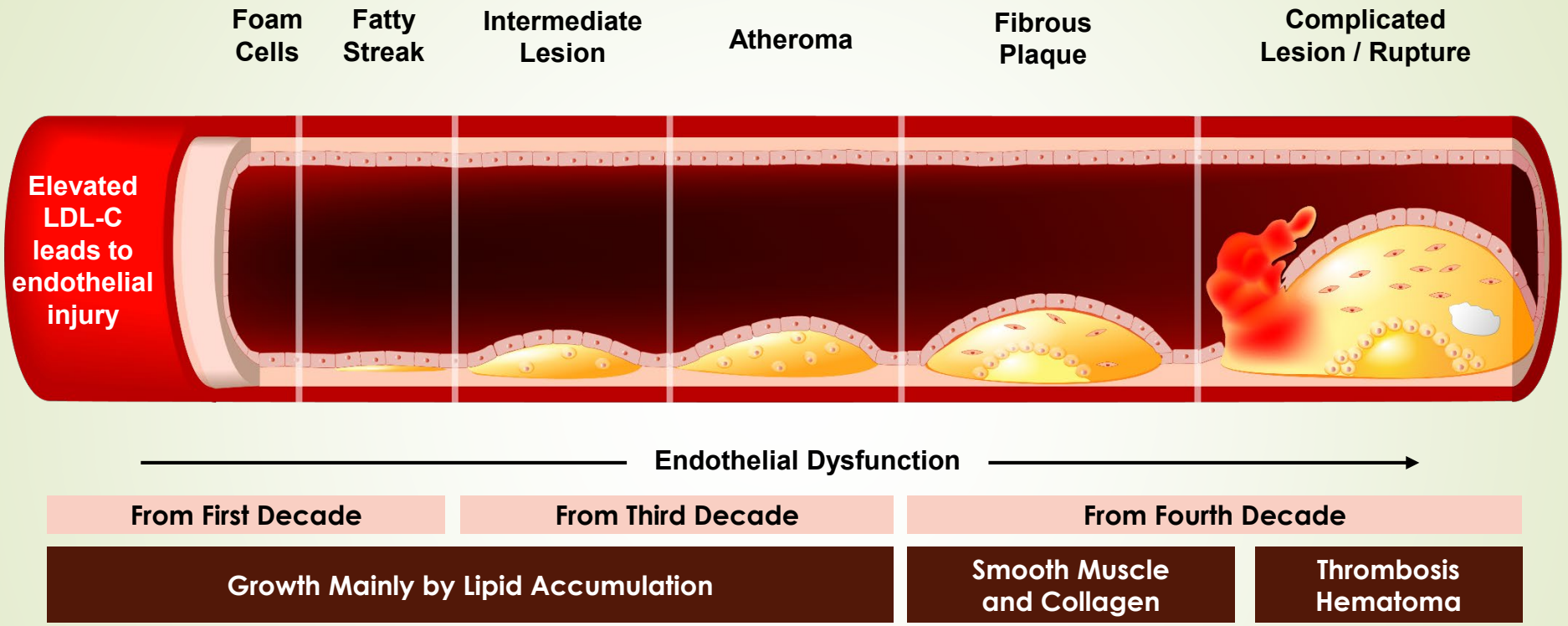
Leading Causes of Premature Death Globally[2*]



disease; DALY = Disability Adjusted Life Years;

ol. Geneva: World Health Organization in collaboration with
6. *World Health Statistics 2016: Monitoring health for the*
2016;37:3232-3245. 4. Mozaffarian D, et al, *Circulation.*
2016;133:e38-360. 5. WHO. Estimates for 2000–2015. http://www.who.int/healthinfo/global_burden_disease/estimates/en/index2.html. Accessed July 25, 2017.

Atherosclerosis Driven by High LDL-C Is the Underlying Cause of CVD That Begins Early in Life[1-3]

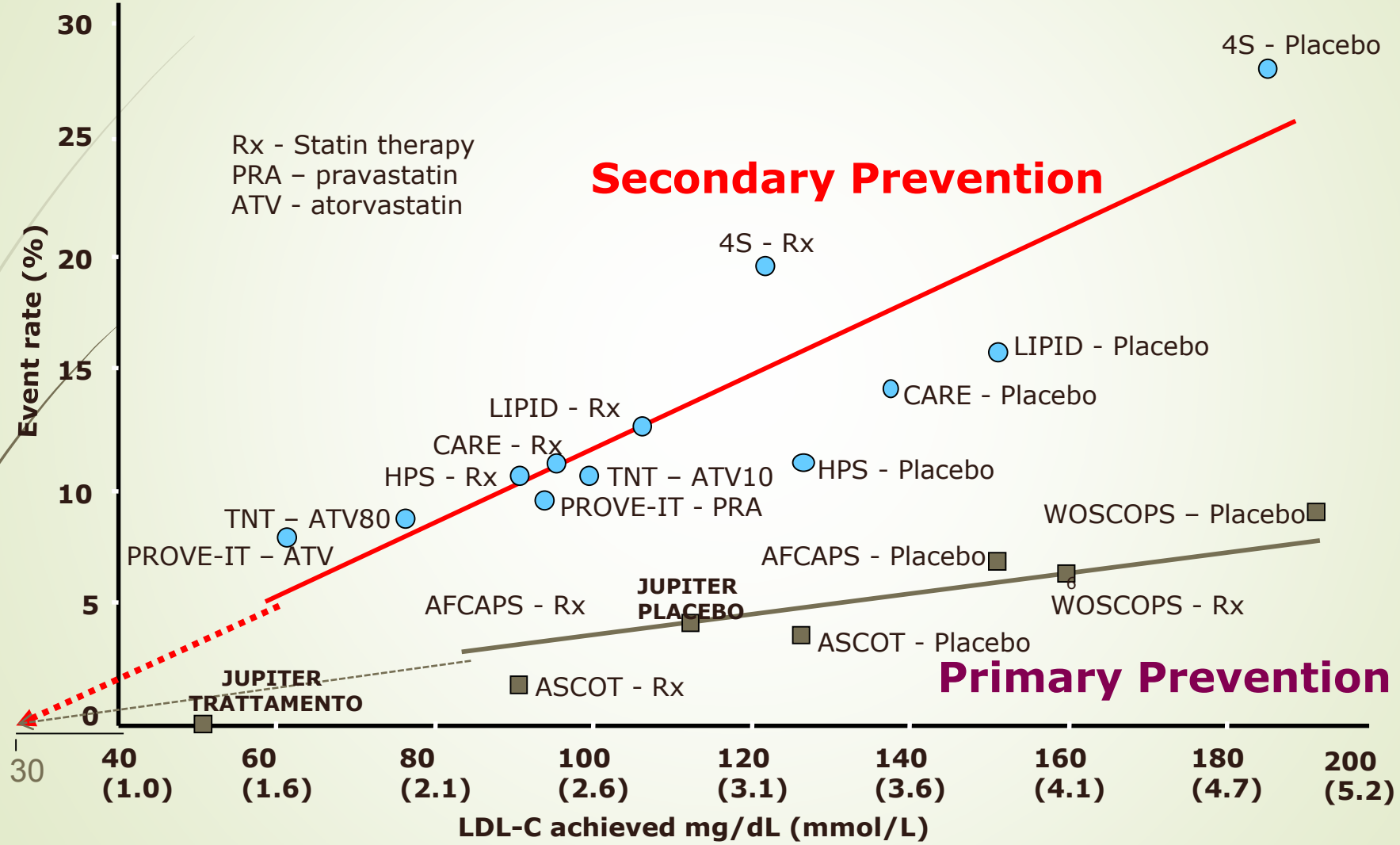


Unstable or ruptured plaques occlude blood flow and increase the risk of CV events; therefore, early and aggressive treatment of atherosclerosis may reduce the risk of CV events[2,4]

CV = cardiovascular; CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol.

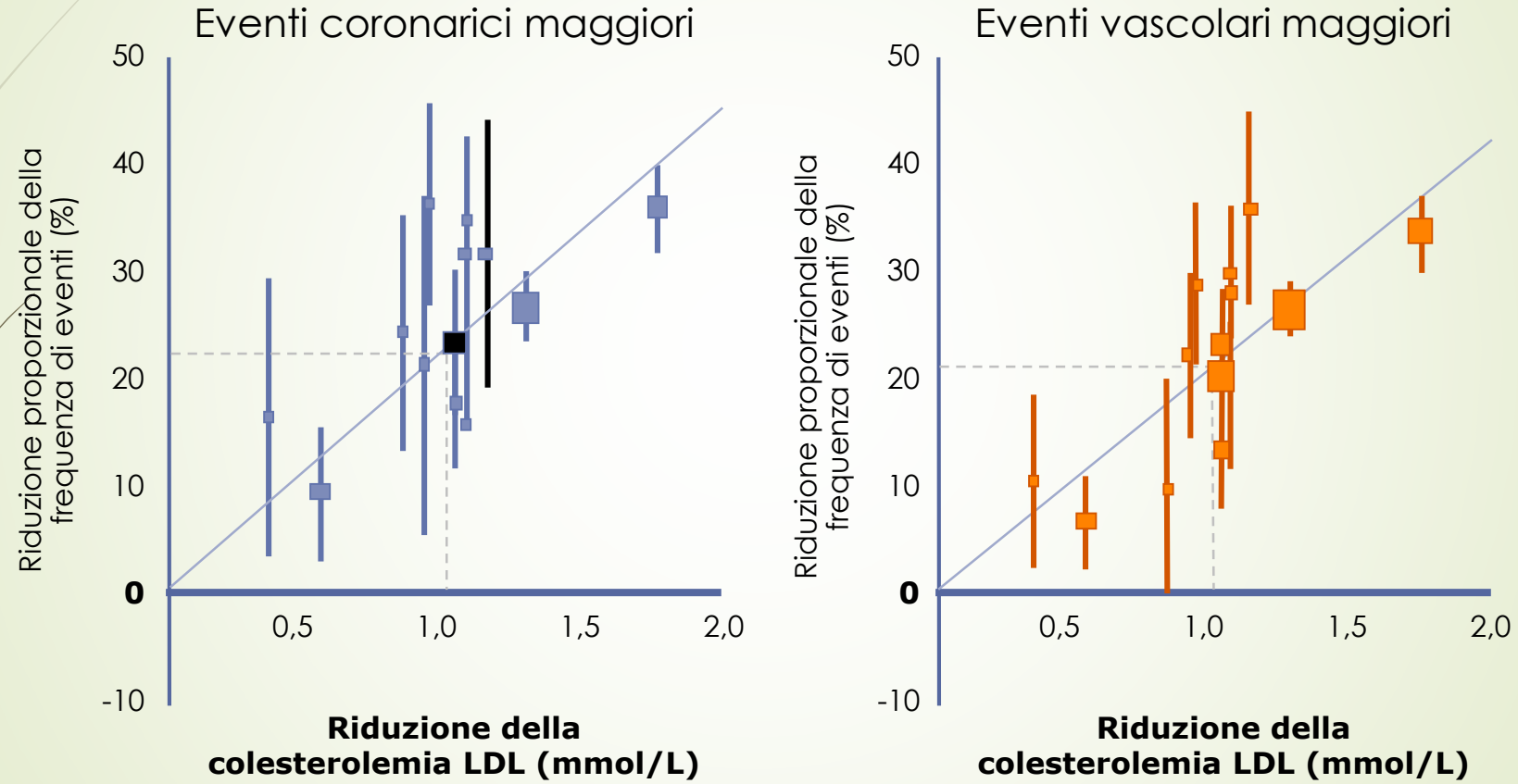
1. Pepine CJ. *Am J Cardiol*. 1998;82:23S-27S. 2. Ross R. *N Engl J Med*. 1999;340:115-126. 3. Stary HC, et al. *Circulation*. 1995;92:1355-1374. 4. Okazaki S et al. *Circulation*. 2004;110:1061-1068.

Every reduction in LDL-C is associated with a corresponding reduction in CVD events



Adapted from Rosensen RS. *Exp Opin Emerg Drugs* 2004; 9(2):269-279
LaRosa JC et al. *NEJM* 2005; 352:1425-1435
Ridker PM et al. *NEJM* 2008; 359: 2195-2207

Relazione tra riduzione del colesterolo LDL e degli eventi cardio-vascolari maggiori

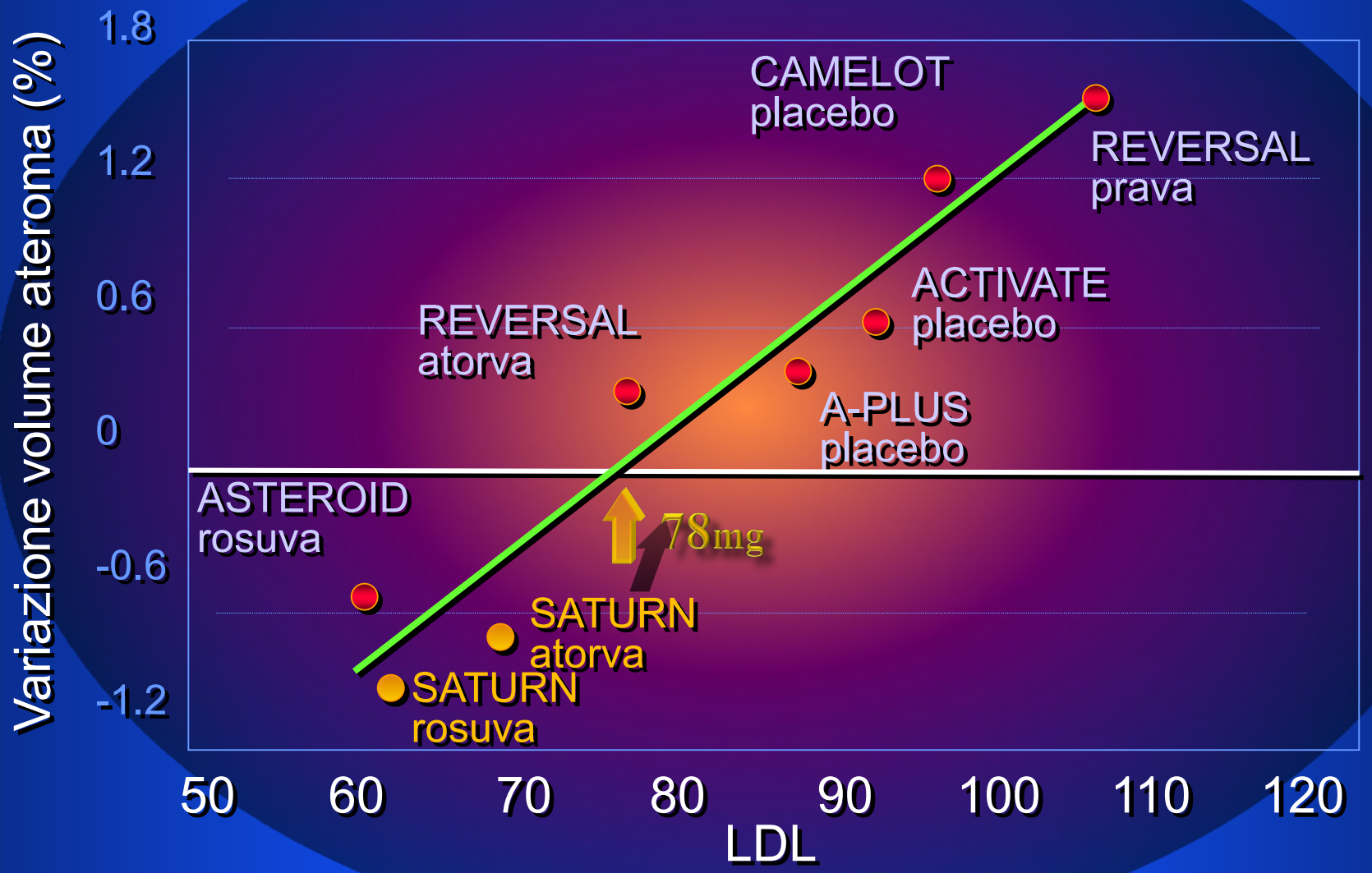


I quadrati rappresentano un singolo studio confrontato verso la riduzione media assoluta di colesterolemia LDL ad 1 anno, con le linee verticali sopra e sotto che corrispondono ad un ES della riduzione non pesata della frequenza di eventi. Per ogni esito, la linea di regressione (che è forzata per passare dall'origine) rappresenta la riduzione pesata della frequenza di eventi per mmol/L di riduzione di colesterolemia LDL.

Baigent C et al. Lancet 2005; 366:1267-1278

LDL e progressione ateroma

(Nissen, JAMA 2005)



European Heart Journal (2017) **38**, 2459–2472
doi:10.1093/eurheartj/ehx144

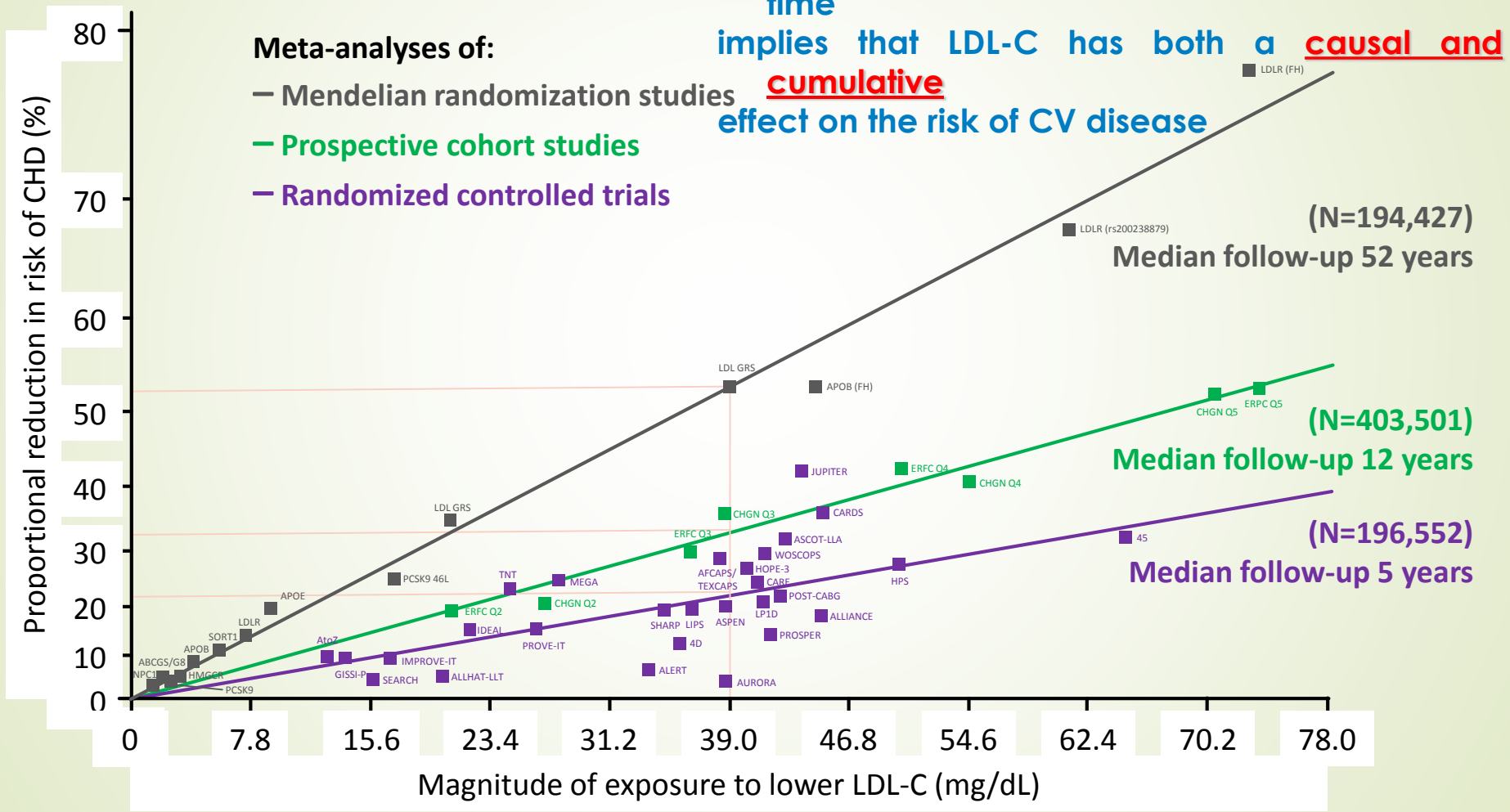
CURRENT OPINION

Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel

Brian A. Ference[1]*, Henry N. Ginsberg[2], Ian Graham[3], Kausik K. Ray[4], Chris J. Packard[5], Eric Bruckert[6], Robert A. Hegele[7], Ronald M. Krauss[8], Frederick J. Raal[9], Heribert Schunkert[10,11], Gerald F. Watts[12], Jan Borén[13], Sergio Fazio[14], Jay D. Horton[15,16], Luis Masana[17], Stephen J. Nicholls[18], Børge G. Nordestgaard[19,20,21], Bart van de Sluis[22], Marja-Riitta Taskinen[23], Lale Tokgözoğlu[24], Ulf Landmesser[25,26], Ulrich Laufs[27], Olov Wiklund[28,29], Jane K. Stock[30], M. John Chapman[31†], and Alberico L. Catapano[32†]

Log-linear association per unit change in LDL-C and the risk of CV disease

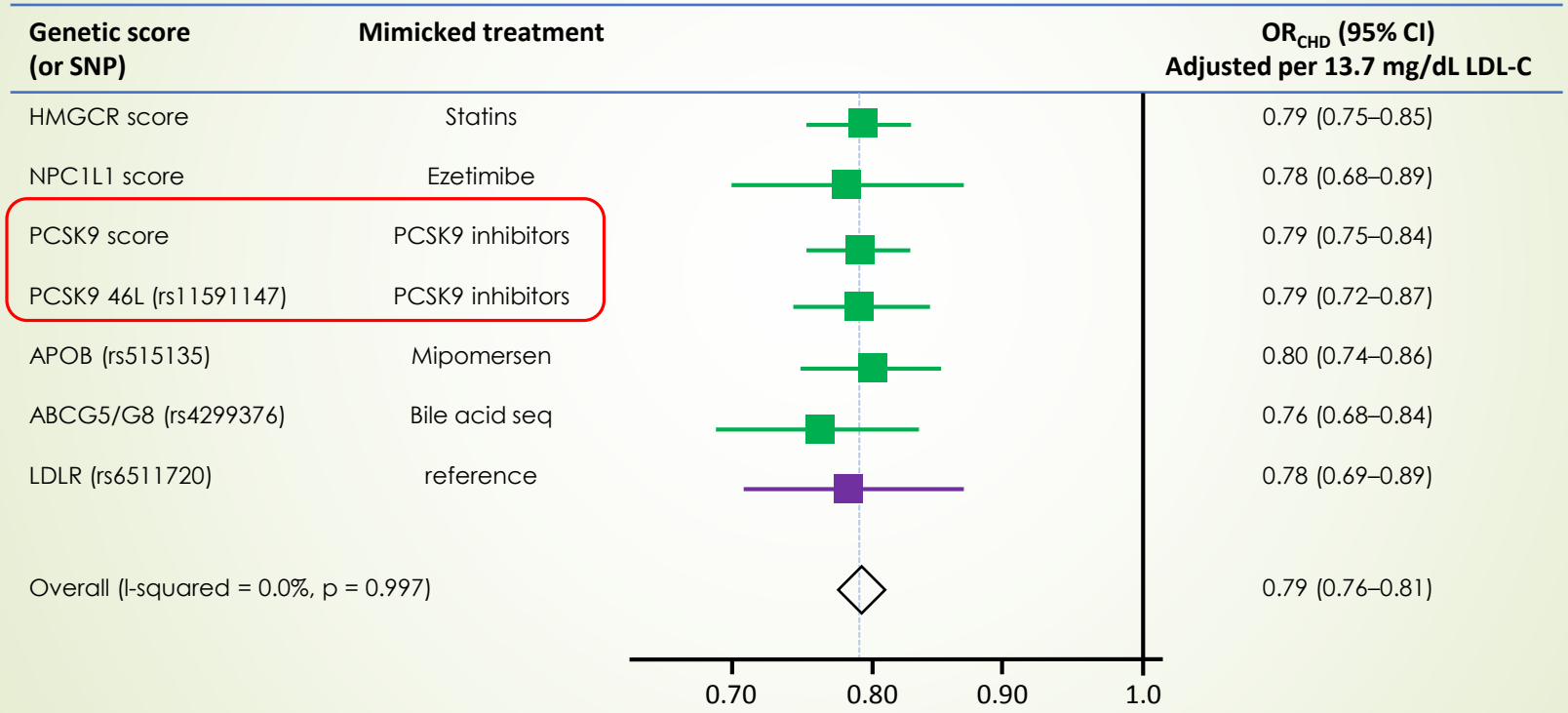
The increasingly steeper slope of the log-linear association with increasing length of follow-up time implies that LDL-C has both a causal and cumulative effect on the risk of CV disease



Ference BA, et al. Eur Heart J. 2017;38:2459-2472

Exposure to lower LDL-C by mechanism of LDL-C lowering: genetic data

Effect of genetic variants or genetic scores combining multiple variants in the genes that encode for targets of LDL-C-lowering therapies in comparison with the effect of lower LDL-C mediated by variants in the LDL receptor gene



The effect of LDL-C on the risk of cardiovascular events is approximately the same per unit change in LDL-C for any mechanism that lowers LDL-C via up-regulation of the LDL receptor

Ference BA, et al. Eur Heart J. 2017;38:2459-2472

ESC/EAS Guidelines: CV Risk Categories

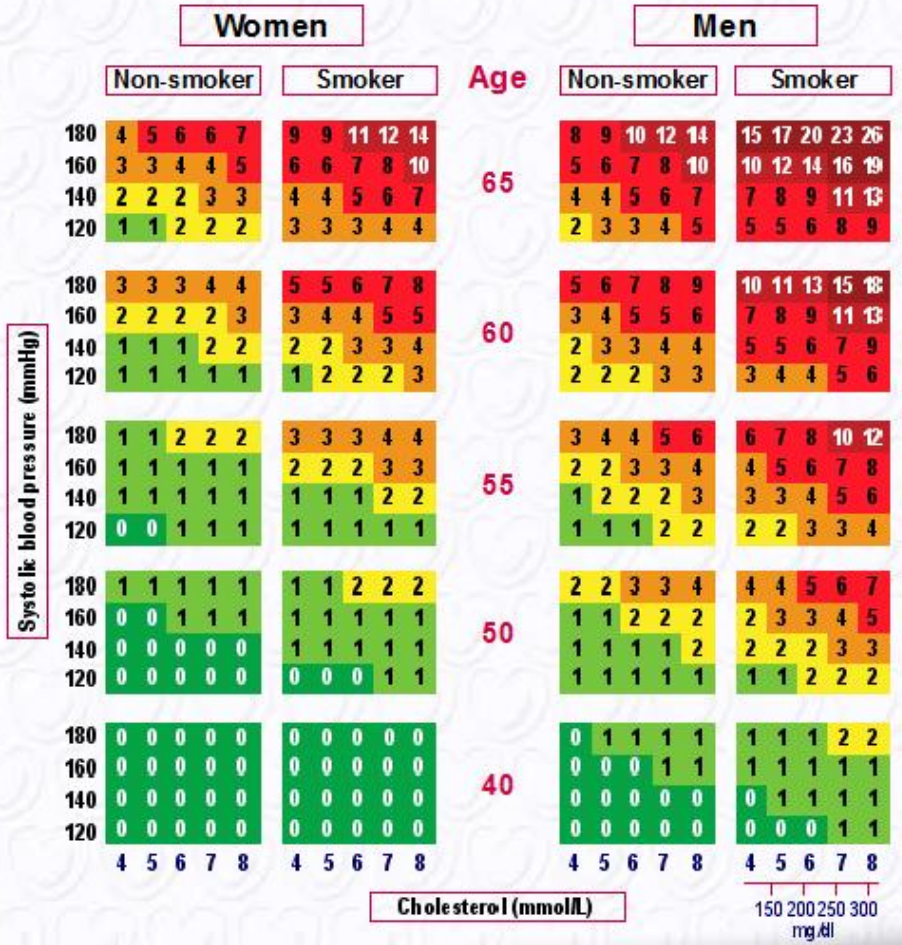
Very high risk	High risk	Moderate risk	Low risk
Subjects with any of the following: •Documented CVD, clinical or unequivocal on imaging •DM with target organ damage such as proteinuria or with a major risk factor (e.g., smoking or dyslipidemia or hypertension) •Severe CKD (GFR < 30 mL/min/ '3 m^2) •SCORE ≥ 10%	Subjects with: •Markedly elevated single risk factors, in particular cholesterol > 310 mg/dL (> 8 mmol/L; e.g., in FH) or BP ≥ 180/110 mmHg •Most other people with DM† •Moderate CKD (GFR 30–59 mL/min/1.73 $m^{2)}$ •SCORE 5 – < 10%	SCORE 1–< 5%	SCORE < 1%
Drug treatment frequently required	Lifestyle advice and candidate for drug treatment if LDL-C ≥ 70 mg/dL (1.8 mmol/L)	Offered lifestyle advice to maintain status with option to consider drug treatment if LDL-C above a certain threshold‡	

‡LDL-C ≥100 mg/dL (2.6 mmol/L) or ≥190 mg/dL (4.9 mmol/L) in moderate- or low-risk patients, respectively (see next slide for further details).

BP = blood pressure; CKD = chronic kidney disease; DM = diabetes mellitus; EAS = European Atherosclerosis Society; ESC = European Society of Cardiology; FH = familial hypercholesterolaemia; GFR = glomerular filtration rate; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; TIA = transient ischemic attack.

Catapano AL, et al. *Atherosclerosis.* 2016;253:281-344

SCORE chart: 10 year risk of fatal cardiovascular disease (CVD) in populations at low CVD risk



10-year risk of fatal CVD in populations at **Low CVD risk**

European Heart Journal 2011;32 (14):1769–1818
Atherosclerosis 2011 Jul;217(1):3-46

www.escardio.org/guidelines

EUROPEAN SOCIETY OF CARDIOLOGY®

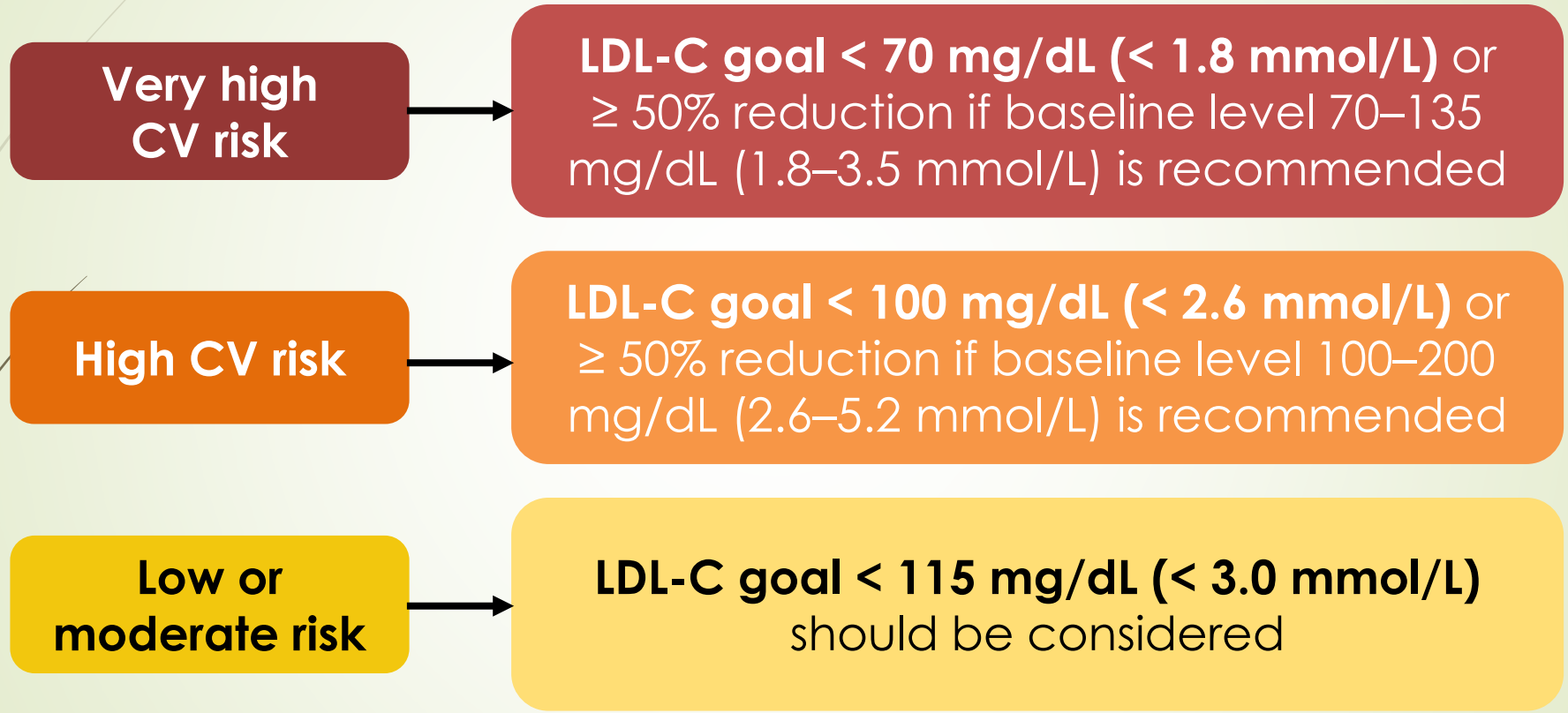
CATEGORIA DI RISCHIO	PUNTEGGIO (SCORE)	CARATTERISTICHE DEI SOGGETTI
Molto alta	≥10%	Soggetti con: • malattia CV documentata mediante test invasivi e non invasivi; • precedente infarto del miocardio; • sindrome coronarica acuta; • rivascolarizzazione coronarica; • stroke ischemico; • arteriopatia periferica; • diabete di tipo II, diabete di tipo I con markers di danno d'organo; • patologia renale cronica moderata-severa (FG <60 ml/min/1.73m^2).
Alta	≥5% e <10%	Soggetti con: • SCORE ≥5% e <10% • singoli fattori di rischio marcatamente elevati come dislipidemie familiari e ipertensione severa.
Moderata	≥1% e <5%	Soggetti con: • SCORE ≥1% e <5% Il rischio è ulteriormente influenzato da: • storia familiare di patologia coronarica precoce; • obesità addominale; • attività fisica; • Col-HDL, TG, CRP ad alta sensibilità, Lp(a), fibrinogeno, omocisteina, Apo B; • classe sociale.
Bassa	<1%	

CV = cardiovascolare
FG = filtrato glomerulare
Col-HDL = colesterolo a lipoproteine ad alta densità
TG = trigliceridi
CRP = proteina C reattiva
Lp = lipoproteina
Apo = apolipoproteina

Target c-LDL <70 mg/dl

la 1. Categorie di rischio cardiovascolare secondo il punteggio SCORE.

ESC/EAS Guidelines: LDL-C Targets



Guidance on the best treatment strategy for different patient profiles is provided through several example cases. This is based on total CV risk, baseline LDL-C level and current LLT (see next slide for further details).

CV = cardiovascular; EAS = European Atherosclerosis Society; ESC = European Society of Cardiology; LDL-C = low-density lipoprotein cholesterol; LLT = lipid-lowering therapy.

Catapano AL, *et al. Eur Heart J*. 2016;37:2999-3058.

European Heart Journal Advance Access published August 27, 2016

European Heart Journal
doi:10.1093/eurheartj/ehw272

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)

Table 5 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 2.6 to <4.0 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	I/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	IIa/A	I/A	I/A
≥10 or very high-risk	Lifestyle intervention, consider drug	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

Linee guida ESC/EAS 2016

Le linee guida congiunte della Società Europea dell'Aterosclerosi e della Società Europea di Cardiologia sulla gestione clinica delle dislipidemie

- **il target fondamentale dell'intervento terapeutico ipolipemizzante e rappresentato dal C-LDL** (raccomandazione di classe I, livello di evidenza A);

- **nei pazienti con rischio cardiovascolare molto elevato, inclusi quelli con SCA, i valori di C-LDL devono essere ridotti e mantenuti al di sotto dei 70 mg/dl.**

- Nell'eventualità un tale obiettivo non risulti raggiungibile, si deve comunque ottenere almeno una riduzione del 50% del C-LDL (raccomandazione di classe I, livello di evidenza A).
- Dove nonostante un trattamento con la massima dose tollerata di statina, non sia possibile raggiungere il target lipidico raccomandato di 70 mg/dl **viene consigliato di aggiungere ezetimibe** alla terapia ipocolesterolemizzante

G Ital Cardiol 2016;17(6):456-461

AACE: ASCVD Risk Categories and LDL-C Treatment Goals

Risk category	Risk factors/10-year risk	Treatment goals		
		LDL-C (mg/dL)	Non-HDL-C (mg/dL)	Apo B (mg/dL)
Extreme risk	• Progressive ASCVD including unstable angina in patients after achieving an LDL-C < 70 mg/dL • Established clinical cardiovascular disease in patients with DM, CKD 3/4, or HeFH • History of premature ASCVD (< 55yr male, < 65yr female)	< 55	< 80	< 70
Very high risk	• Established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease, 10-year risk > 20% • Diabetes or CKD 3/4 with 1 or more risk factors(s) • HeFH	< 70	< 100	< 80
High risk	• ≥ 2 risk factors and 10-year risk 10-20% • Diabetes or CKD 3/4 with no other risk factors	< 100	< 130	< 90
Moderate risk	• ≤ 2 risk factors and 10-year risk < 10%	< 100	< 130	< 90
Low risk	• 0 risk factors	< 130	< 160	NR

*Major independent risk factors are high LDL-C, polycystic ovary syndrome, cigarette smoking, hypertension (blood pressure ≥ 140/90 mm Hg or on hypertensive medication), low HDL-C (< 40 mg/dL), family history of coronary artery disease (in male, first-degree relative younger than 55 years; in female, first-degree relative younger than 65 years), chronic renal disease (CKD) stage 3/4, evidence of coronary artery calcification and age (men ≥ 45; women ≥ 55 years). Subtract 1 risk factor if the person has high HDL-C. †Framingham risk scoring is applied to determine 10-year risk.

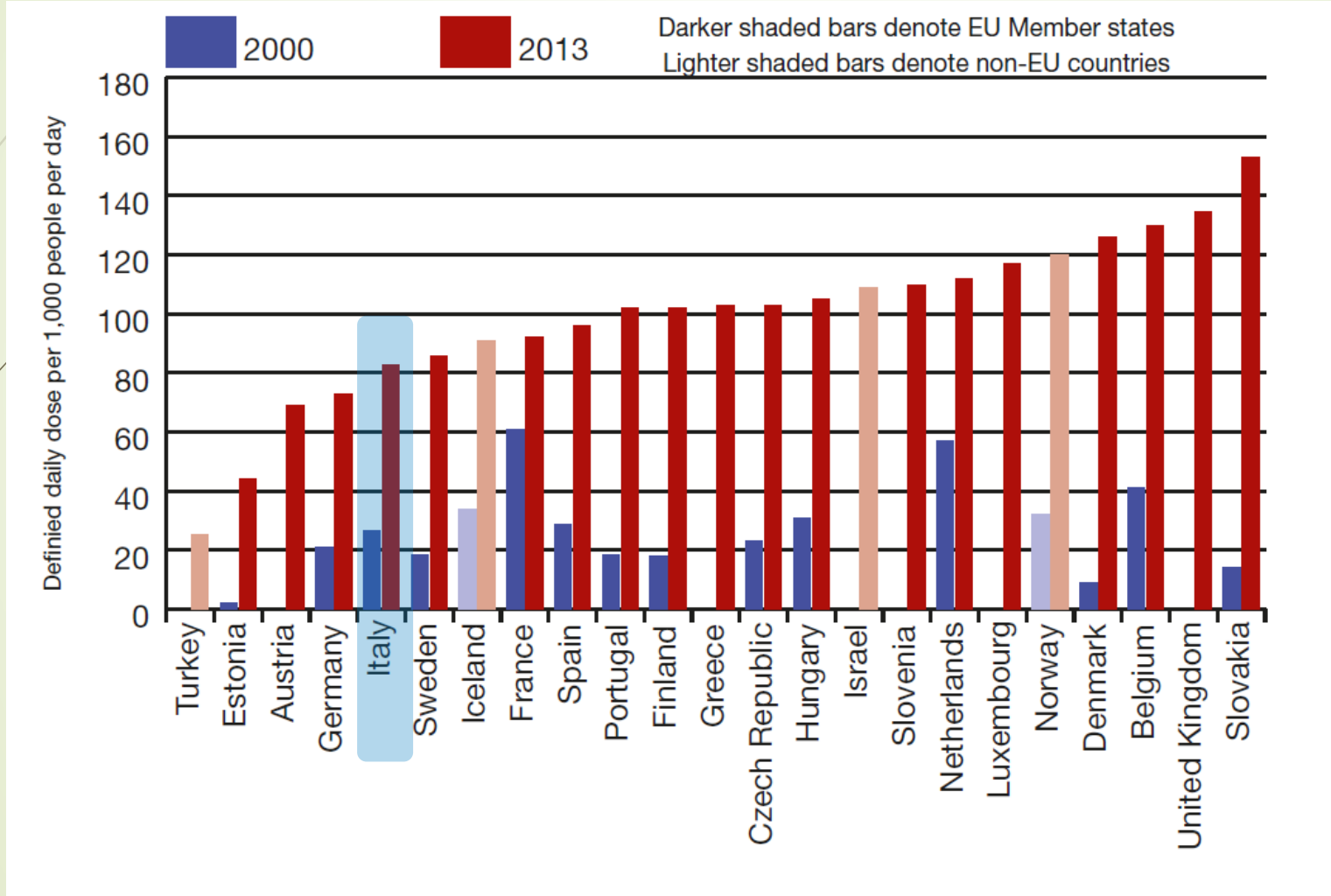
AACE = American Association of Clinical Endocrinologists; Apo B = apolipoprotein B; ACS = acute coronary syndrome; ASCVD = atherosclerotic cardiovascular disease; CAD = coronary artery disease; CHD = coronary heart disease; CKD = chronic kidney disease; DM = diabetes mellitus; HDL-C = high-density lipoprotein cholesterol; HeFH = heterozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; NR = not recommended.

Jellinger PS, et al. *Endocr Pract.* 2017;23:1-87.

Categoria di rischio	Fattori di rischio / RCV stimato a 10 anni	Obiettivi del trattamento		
		LDL-C (mg/dL)	Non-HDL-C (mg/dL)	Apo B (mg/dL)
Estremo	- MCV progressiva compresa l'angina instabile in pazienti che hanno raggiunto valori di LDL-C <70 mg/dL - MCV documentata in pazienti con DM, MRC 3/4 o IFE - anamnesi di MCV prematura (<55 negli uomini, < 65 nelle donne)	<55	<80	<70
Molto alto	- SCA documentata o recente ricovero per SCA, vasculopatia carotide ao periferica, RCV a 10 anni >20% - DM o MRC 3/4 con un fattore di rischio aggiuntivo - IFE	<70	<100	<80
Alto	- ≥ 2 fattori di rischio e RCV a 10 anni 10-20% - DM o IRC 3/4 senza altri fattori di rischio	<100	<130	<90
Moderato	- ≤ 2 fattori di rischio e RCV a 10 anni <10%	<100	<130	<90
Basso	- assenza di fattori di rischio	<130	<160	NR

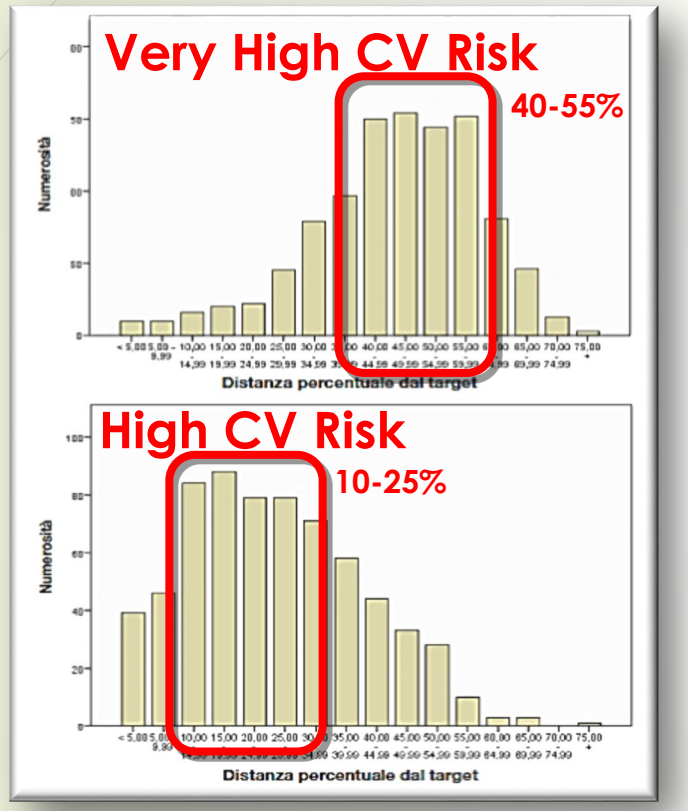
RCV = rischio cardiovascolare
MCV = malattia cardio-vascolare
DM = diabete mellito
MRC 3/4 = malattia renale cronica stadio 3 o 4
IFE = ipercolesterolemia familiare eterozigote
SCA = sindrome coronarica acuta
NR = non raccomandato

Lipid-modifying drug prescriptions, 2000 and 2013, Europe



European Cardiovascular Disease Statistics – 2017 Edition

Terapia Ipolipemizzante in Italia in base ai target di LDL-C, in soggetti a rischio CV alto o molto alto di età tra 40 e 79 anni (n=7,047 milioni di persone*)



5367 persone, età 40-79 anni

35% a rischio CV alto (15,1%)
o rischio CV molto alto (19,9%)

area dei soggetti "non a target"

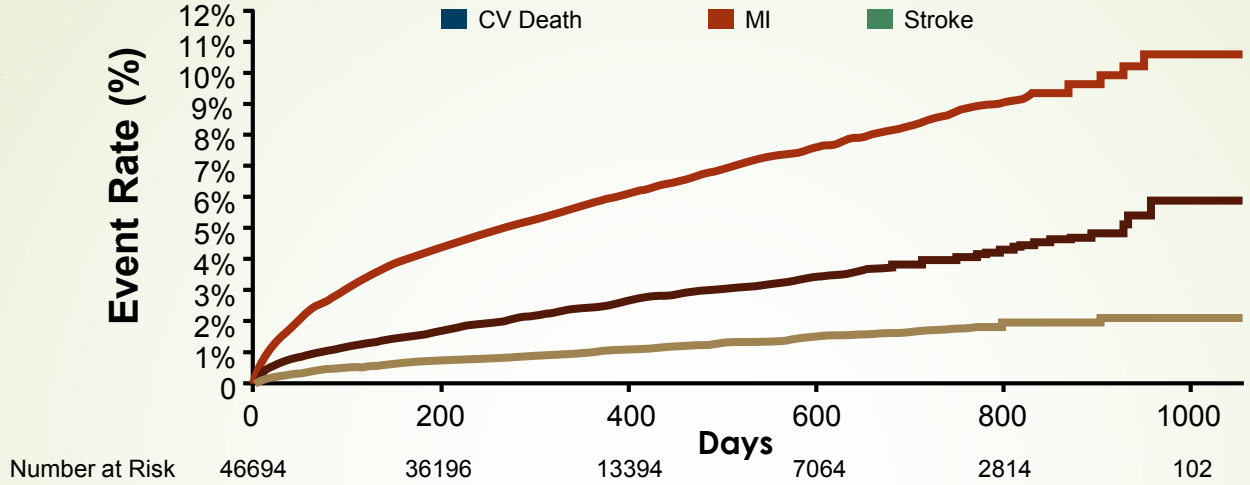
Sei su 10 pazienti a rischio CV alto o molto alto hanno necessità di statine ad elevata efficacia ad alte dosi (atorvastatina o rosuvastatina ±ezetimibe) per raggiungere il target di LDL-C

	LDL target SI	LDL target NO
Soggetti a rischio CV molto alto:	**2,6%**	**97,4%**
Soggetti a rischio CV alto:	**14,7%**	**85,3%**

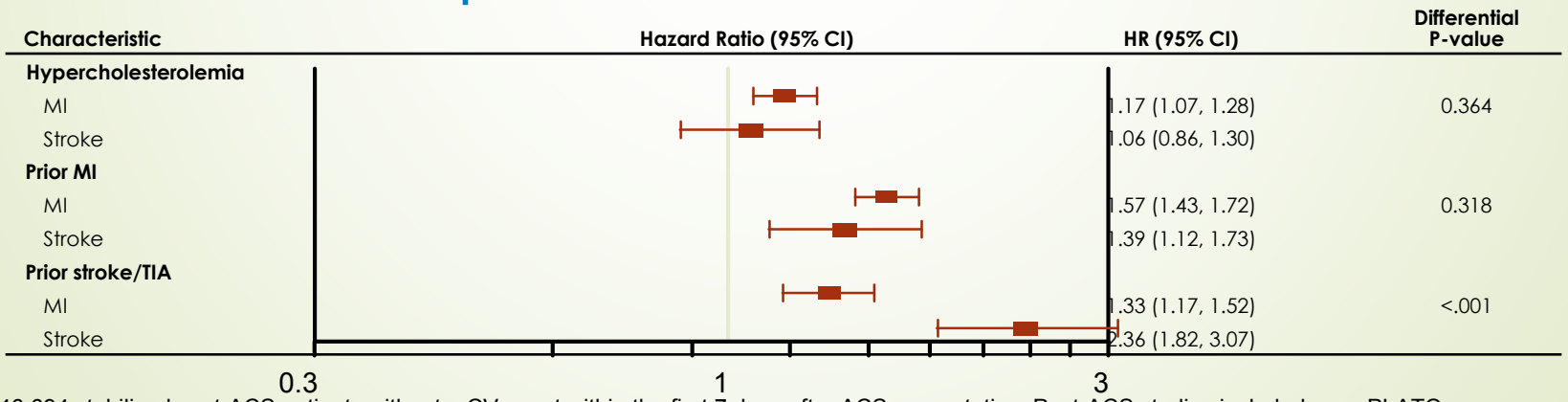
**Estrapolazione dallo studio CHECK*
Poli A et al GIA 2015;6:1-12 ; Poli A. et al. NMCD 2012 Apr;22(4):327-36;
Poli A. et al. Pharmacol Res. 2011 Oct;64(4):393-6

Event Rates Significantly Increase After the First Event

First Recurrent CV Event Over Time, by Event Type (Unadjusted)



Risk Profile Comparison of Stroke vs. MI as First Recurrent CV Event



Study population consisted of 46,694 stabilized post-ACS patients without a CV event within the first 7 days after ACS presentation. Post-ACS studies included were PLATO, APPRAISE-2, TRACER, and TRILOGY ACS with a median follow-up: 4.3 years.
Top figure shows the cumulative incidence curves for MI vs. stroke vs. CV death as the first recurrent event.
ACS = acute coronary syndrome; CV = cardiovascular; MI = myocardial infarction; TIA = transitory ischemic attack.
Hess CN, et al. Am Heart J. 2017;187:194-203.

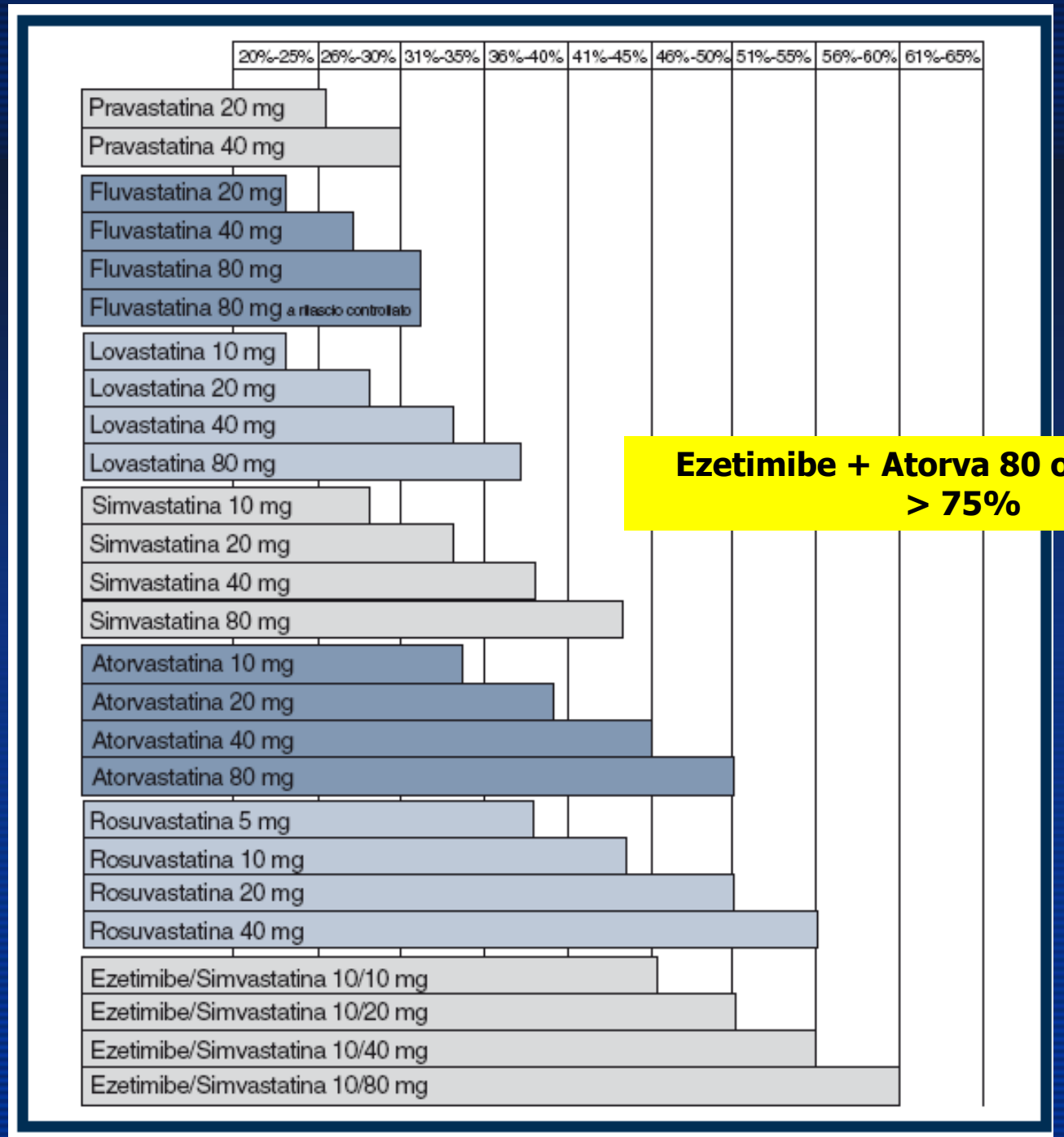
Come scegliere il farmaco adeguato: il concetto della “Distanza dal Target”

DdT :

$$\frac{\text{(LDLc basale – LDLc target)}}{\text{LDLc basale}} \times 100$$

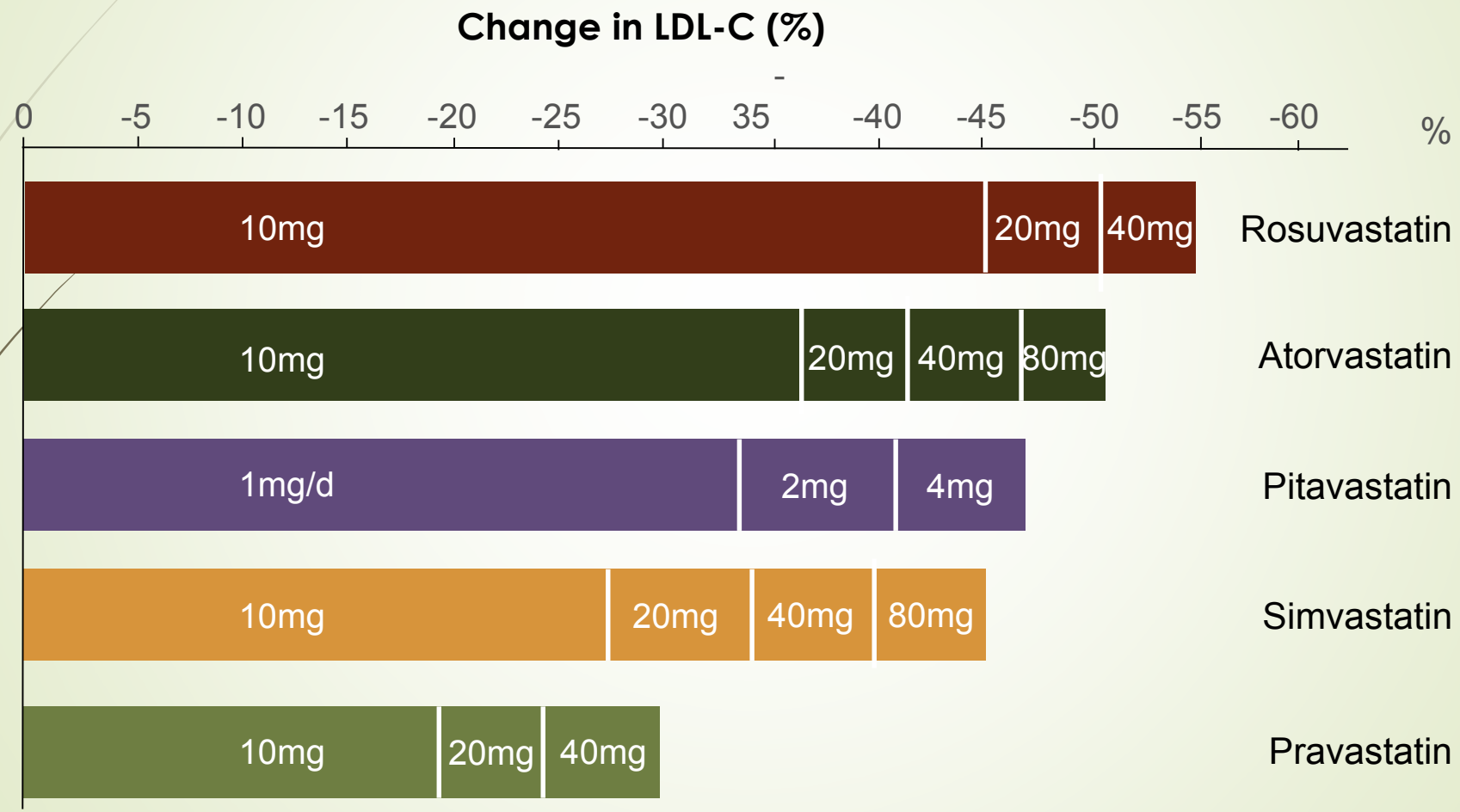
Esempio: LDLc basale 169, LDLc target 100

DdT% = [(169-100) / 169] x 100 = 41%



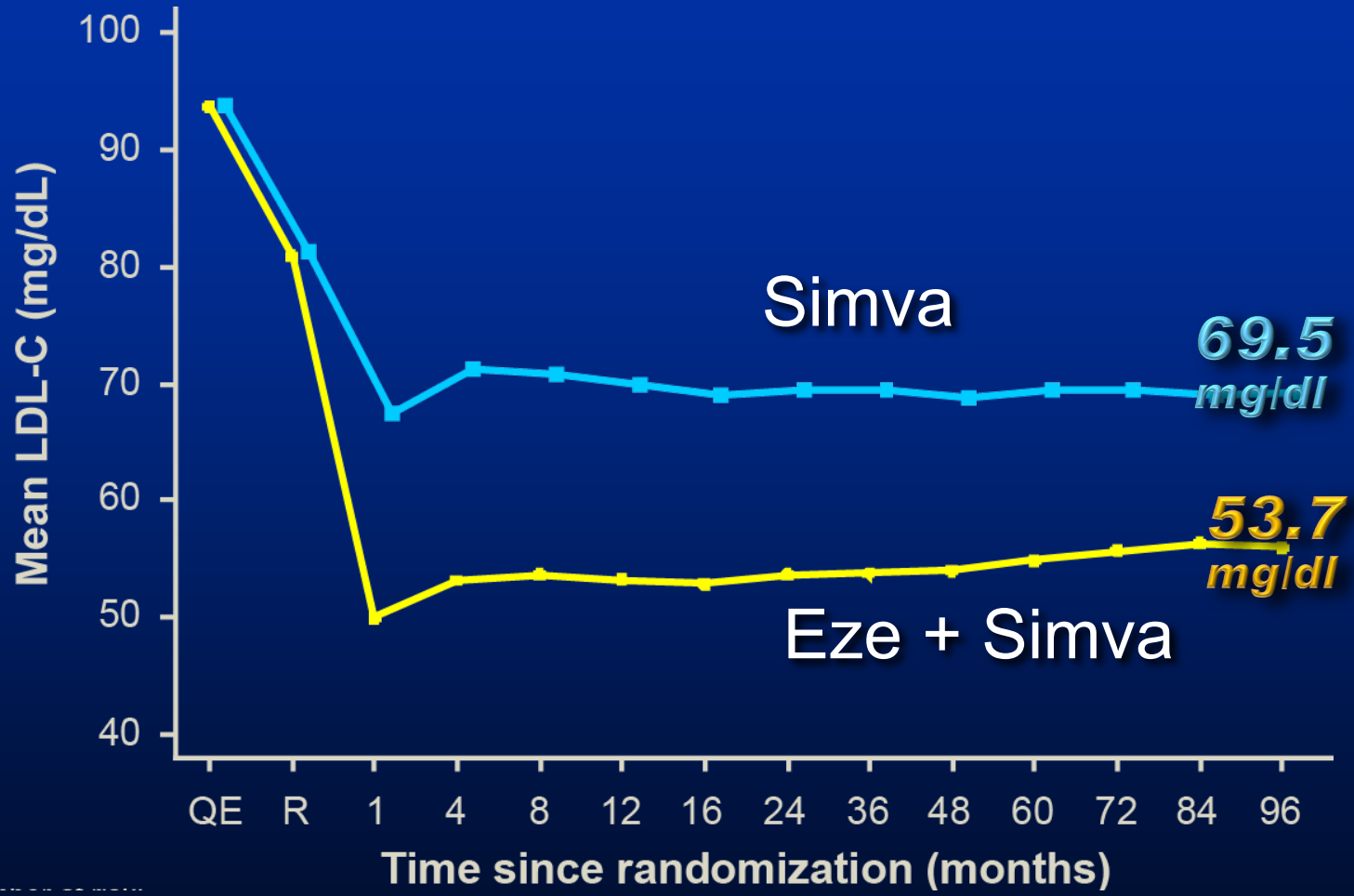
Ezetimibe + Atorva 80 o Rosuva 40
> 75%

Doubling statin dose achieves ~6% additional LDL-C reduction

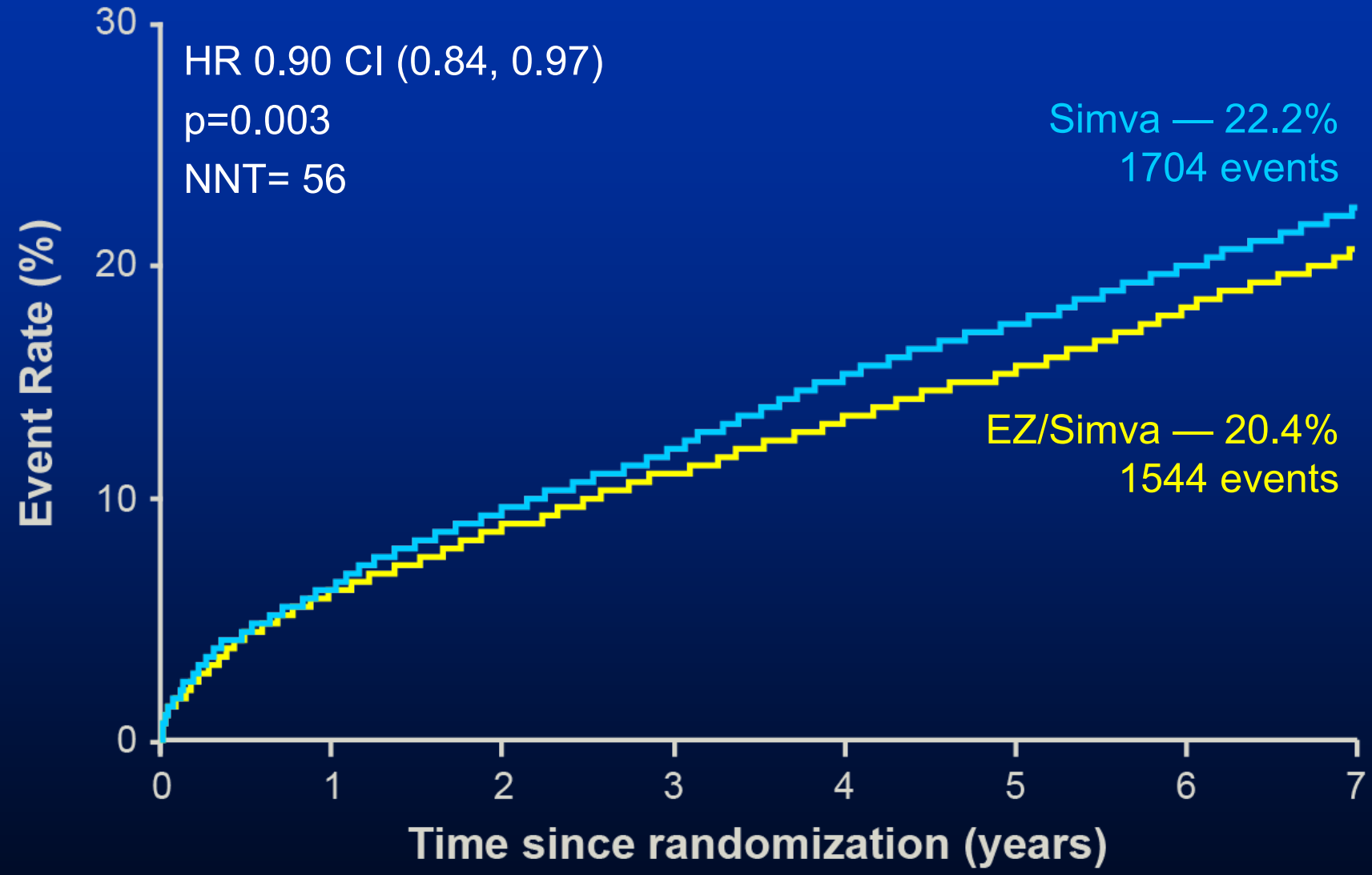


www.fda.gov/drugs/drugsafety/ucm256581.htm#relative. Accessed 10 Jan 2016.

LDL-C and Lipid Changes

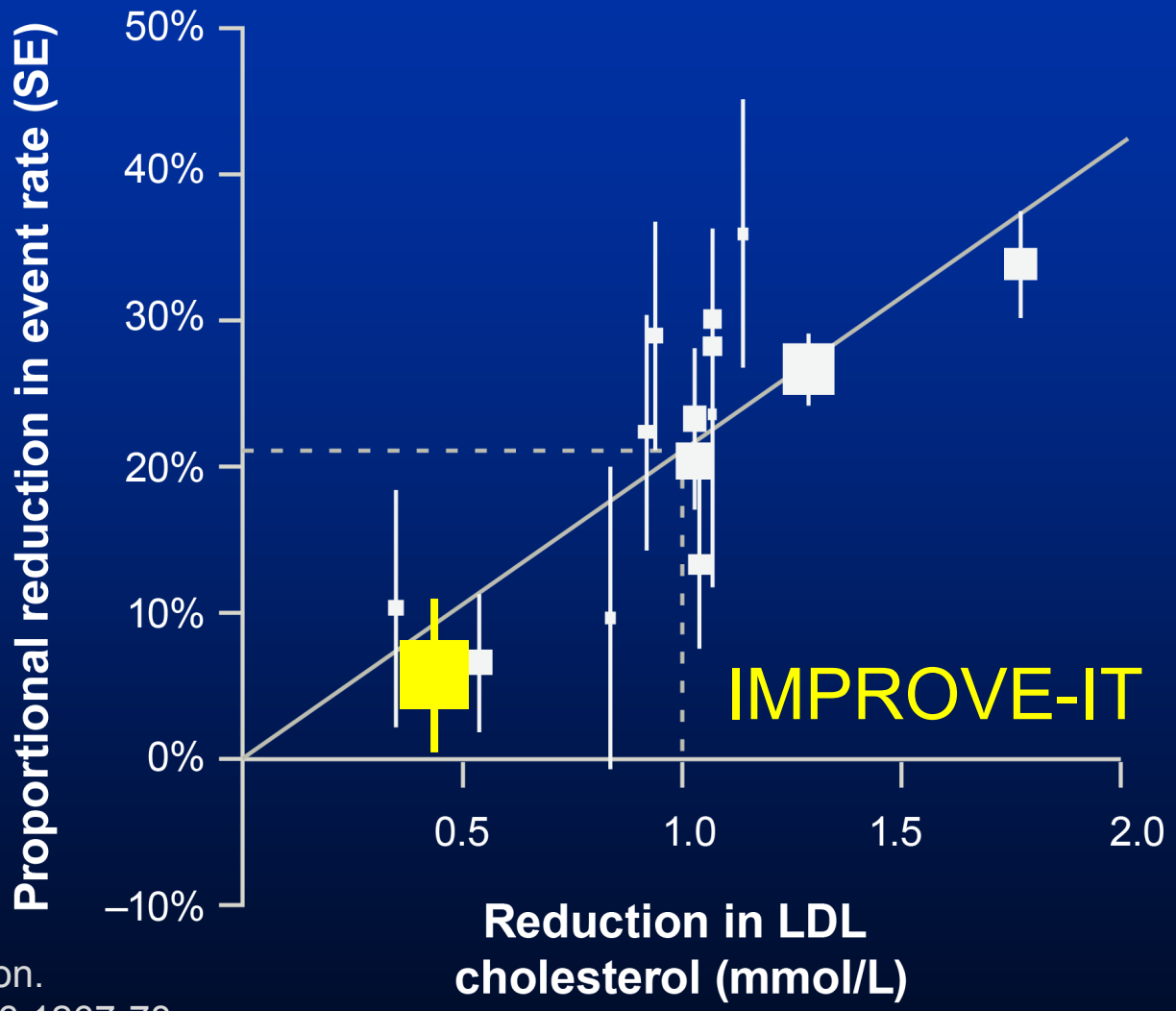


CV Death, Non-fatal MI, or Non-fatal Stroke



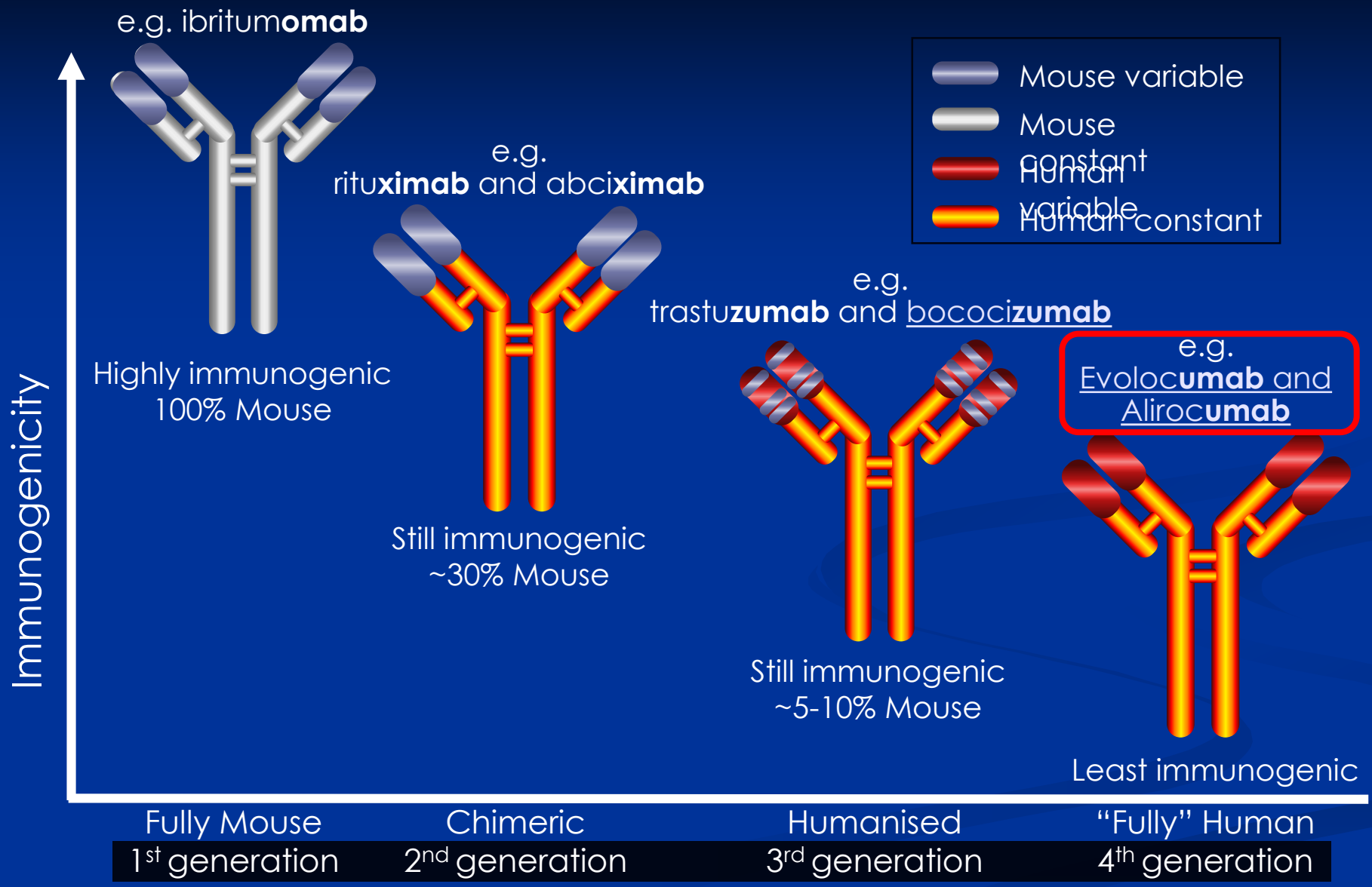
7-year event rates

IMPROVE-IT vs. CTT: Ezetimibe vs. Statin Benefit



CTT Collaboration.
Lancet 2005; 366:1267-78;
Lancet 2010;376:1670-81.

Monoclonal Antibody Evolution

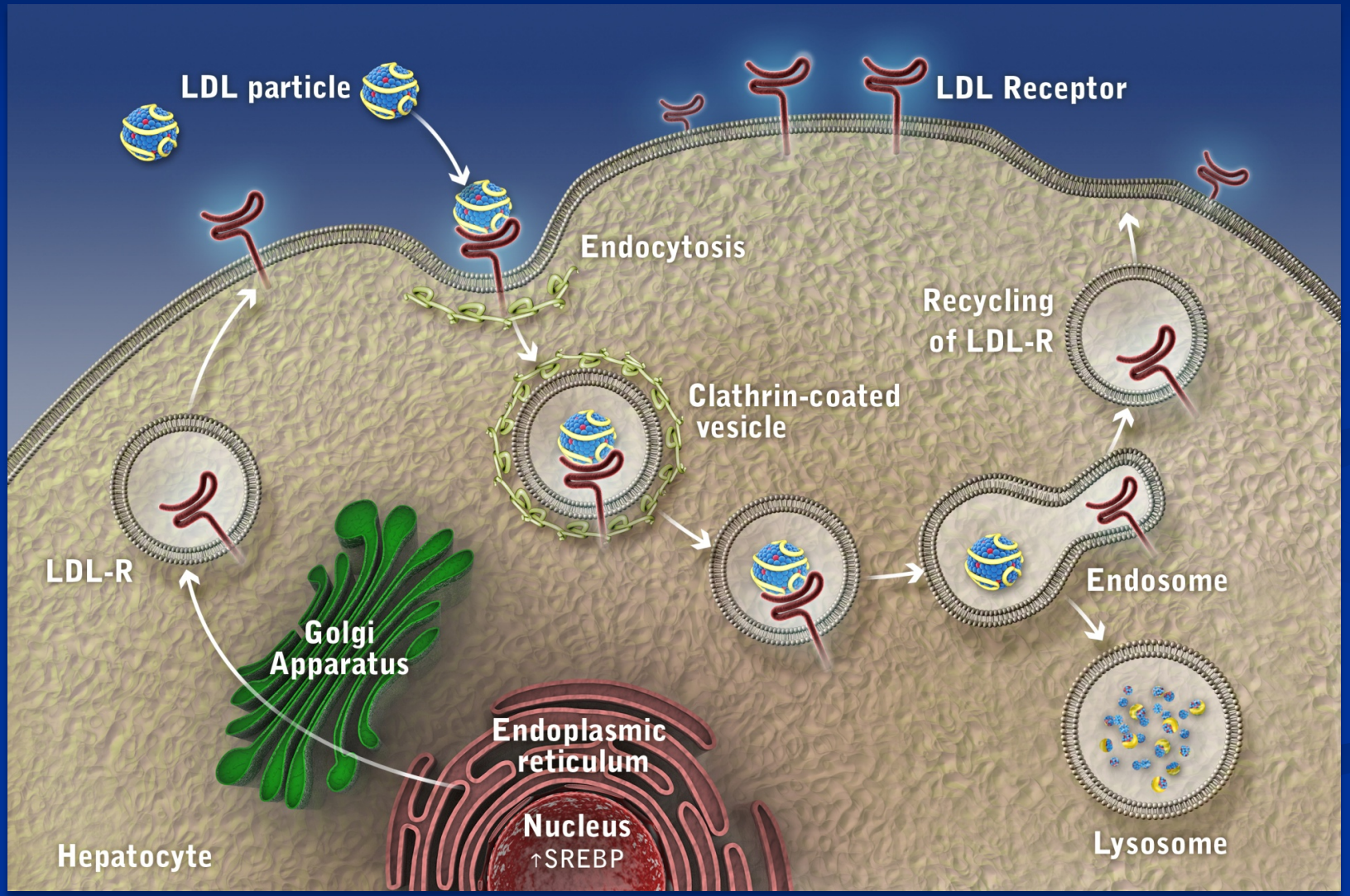


1. *Foltz I et al. Circulation 2013 Jun 4;127(22):2222-30;*
2. *Nelson AL et al. Nature Reviews Drug Discovery 2010 Oct;9(10):767-74*

- Il recettore lega le LDL
- Il complesso recettore-LDL viene internalizzato
- I lisosomi degradano le LDL
- Il recettore ritorna sulla superficie dell'epatocita

Funzione e Ciclo Biologico del Recettore LDL

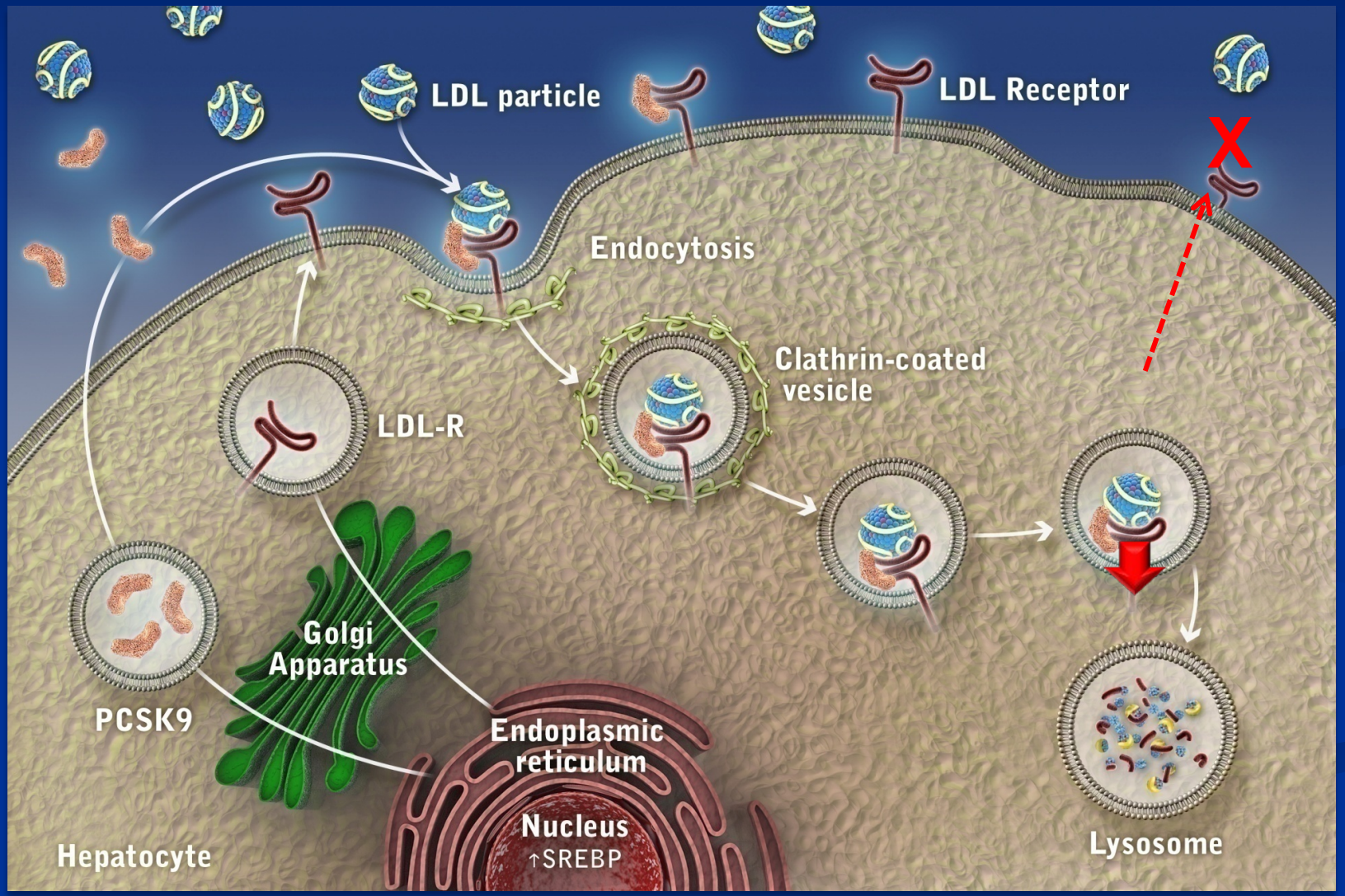
For illustration purposes only



- La presenza di PCKS9 permette la degradazione del recettore nel lisosoma
- Ne consegue un minor numero di recettori disponibili sulla membrana cellulare
- Si riduce la clearance delle LDL con conseguente ipercolesterolemia

Il Ruolo di PCSK9 nella Regolazione dell'Espressione del Recettore per le LDL

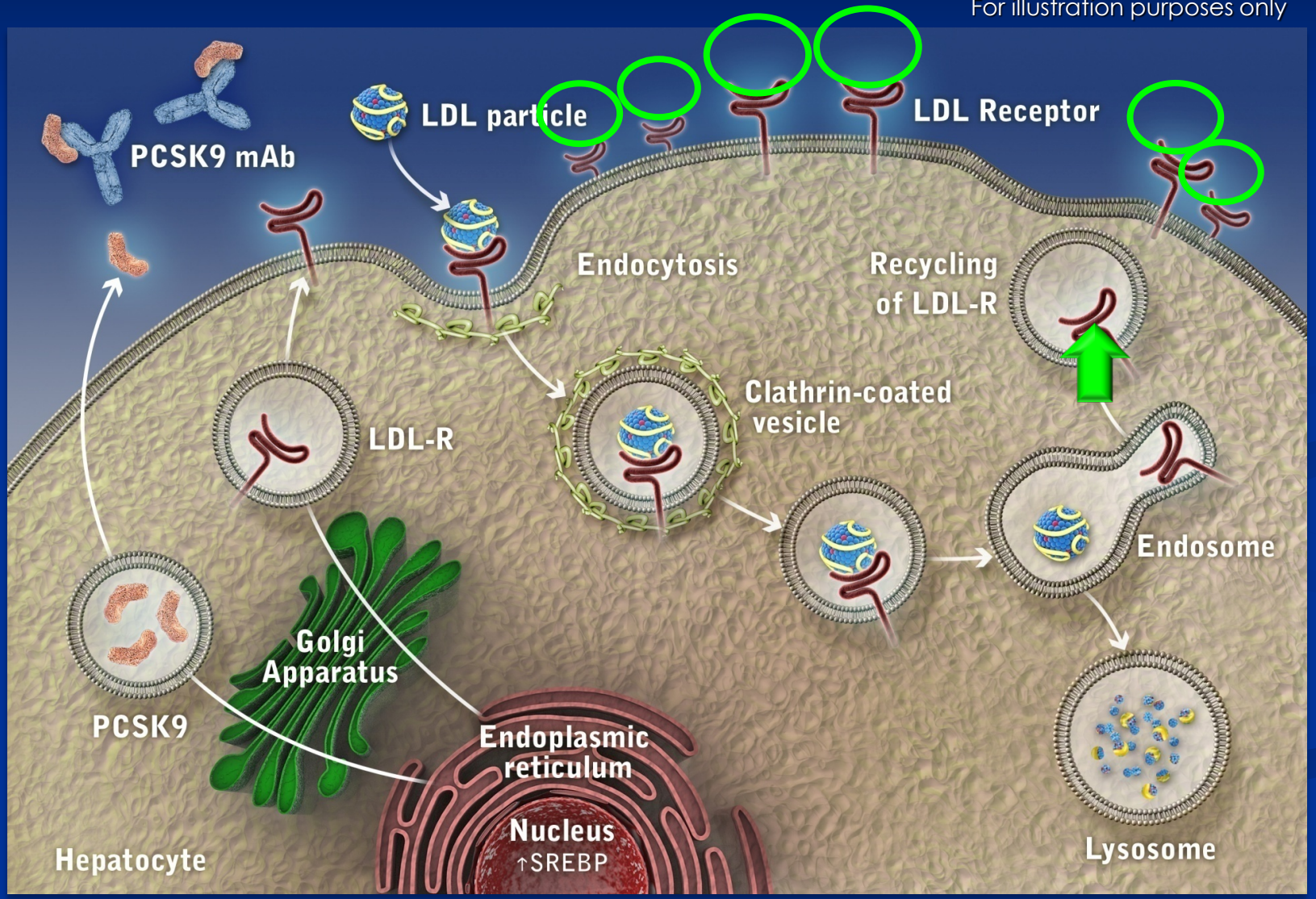
For illustration purposes only



- La inibizione del PCKS9 previene la degradazione lisosomiale del recettore
- Il numero di recettori sulla membrana aumenta
- La clearance delle LDL viene mantenuta

Impatto dell'Anticorpo contro PCSK9 sull'Espressione del Recettore delle LDL

For illustration purposes only



Lo studio FOURIER

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 4, 2017 VOL. 376 NO. 18

Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease

Marc S. Sabatine, M.D., M.P.H., Robert P. Giugliano, M.D., Anthony C. Keech, M.D., Narimon Honarpour, M.D., Ph.D., Stephen D. Wiviott, M.D., Sabina A. Murphy, M.P.H., Julia F. Kuder, M.A., Huei Wang, Ph.D., Thomas Liu, Ph.D., Scott M. Wasserman, M.D., Peter S. Sever, Ph.D., F.R.C.P., and Terje R. Pedersen, M.D., for the FOURIER Steering Committee and Investigators*

Further cardiovascular **OU**tcomes **R**esearch with PCSK9 **I**nhibition in subjects with **E**levated **R**isk

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

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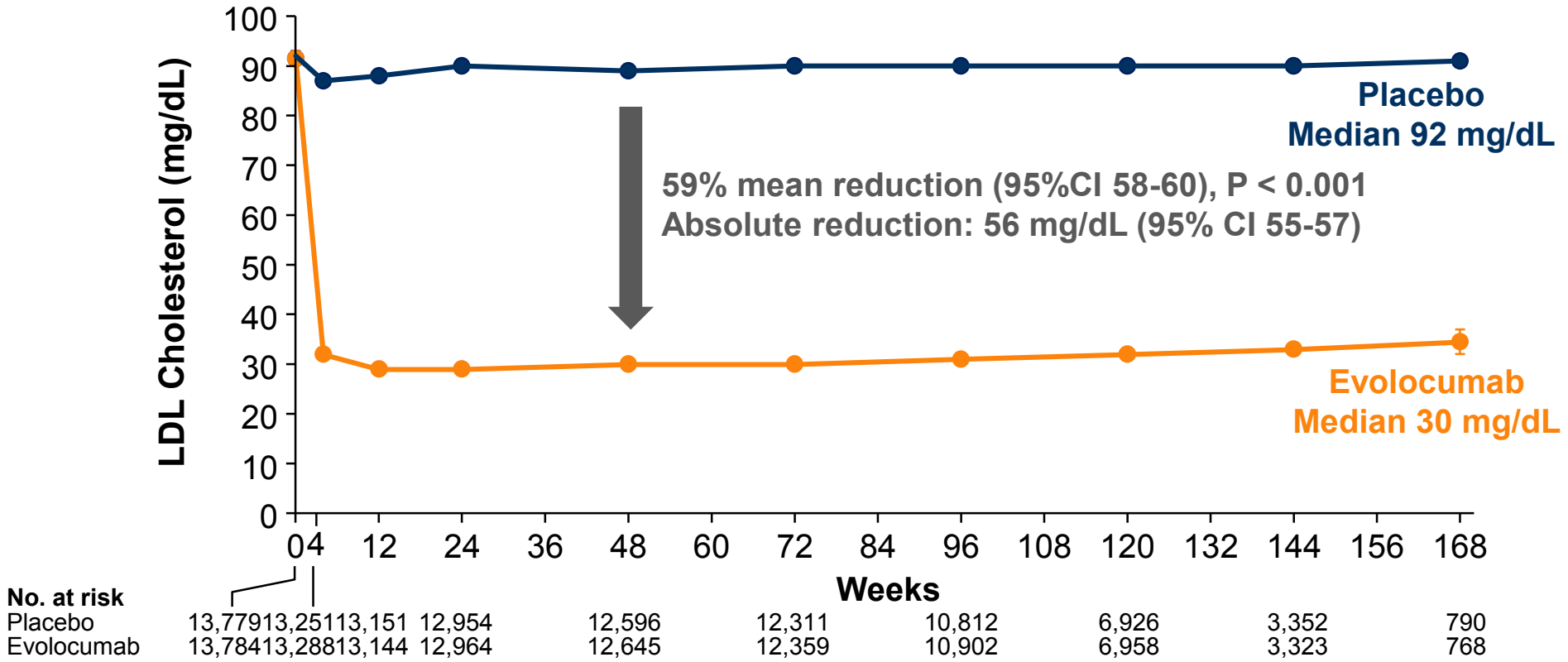
Median LDL-C Levels Over Time: All Patients



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. *N Engl J Med.* 2017;376:1713-1722.

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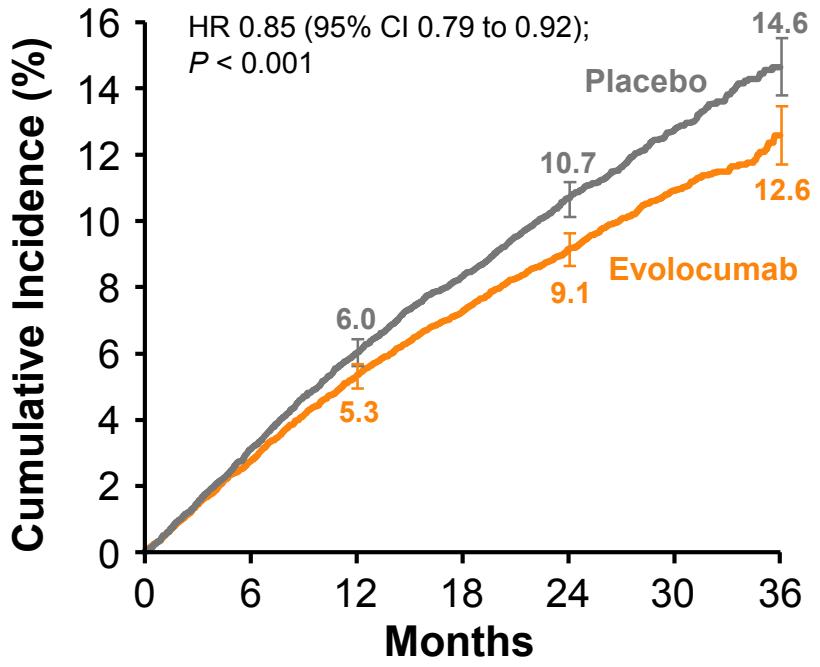
Cardiovascular

Evolocumab Outcomes Trial: Primary and Key Secondary Endpoints Were Met With Statistical Significance

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

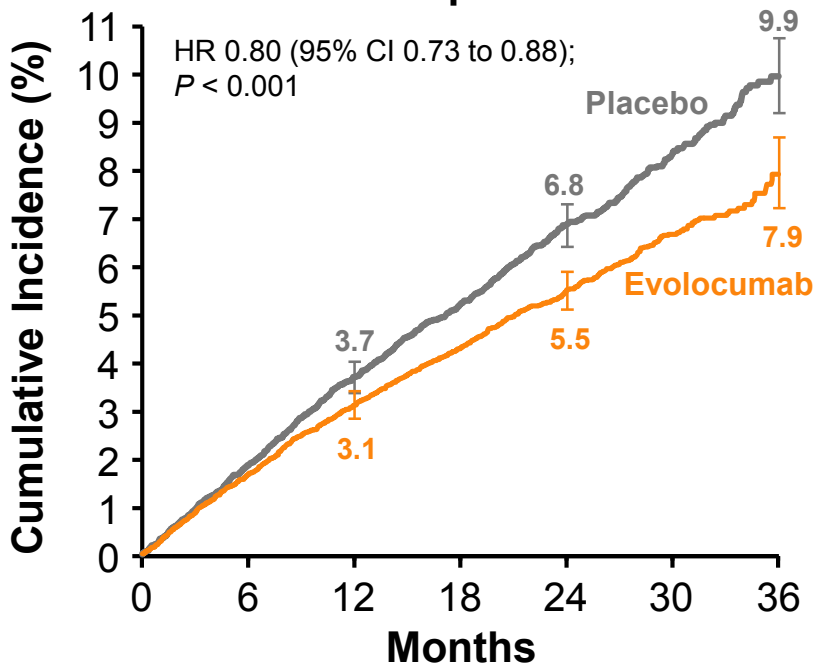
Primary Endpoint



No. at Risk							
Placebo	13780	13278	12825	11871	7610	3690	686
Evolocumab	13784	13351	12939	12070	7771	3746	689

Composite of CV Death, MI, or Stroke

Key Secondary Composite Endpoint



No. at Risk							
Placebo	13780	13449	13142	12288	7944	3893	731
Evolocumab	13784	13501	13241	12456	8094	3935	724

CI = confidence interval; CV = cardiovascular; HR = hazard ratio; MI = myocardial infarction; UA = unstable angina.

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

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Primary, Key Secondary, and Other Endpoints

Outcome	Evolocumab (n = 13,784) n (%)	Placebo (n = 13,780) n (%)	HR (95% CI)	P-value ‡
Primary endpoint*	1,344 (9.8)	1,563 (11.3)	0.85 (0.79-0.92)	<0.001
Key secondary endpoint†	816 (5.9)	1,013 (7.4)	0.80 (0.73-0.88)	<0.001
Other endpoints				
CV death	251 (1.8)	240 (1.7)	1.05 (0.88-1.25)	0.62
Death from any cause	444 (3.2)	426 (3.1)	1.04 (0.91-1.19)	0.54
MI	468 (3.4)	639 (4.6)	0.73 (0.65-0.82)	<0.001
Hospitalization for UA	236 (1.7)	239 (1.7)	0.99 (0.82-1.18)	0.89
Stroke	207 (1.5)	262 (1.9)	0.79 (0.66-0.95)	0.01
Coronary revascularization	759 (5.5)	965 (7.0)	0.78 (0.71-0.86)	<0.001
CV Death or Hospitalization for Worsening Heart Failure	402 (2.9)	408 (3.0)	0.98 (0.86-1.13)	0.82
Ischemic stroke or TIA	229 (1.7)	295 (2.1)	0.77 (0.65-0.92)	0.003
CTTC composite endpoint**	1,271 (9.2)	1,512 (11.0)	0.83 (0.77-0.90)	<0.001

The primary endpoint was driven by reductions in MI, stroke, and coronary revascularization

*Time to CV death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization, whichever occurs first †CV death, myocardial infarction, or stroke, whichever occurs first ‡Given the hierarchical nature of the statistical testing, the P values for the primary and key secondary endpoint should be considered statistically significant, whereas all other P values should be considered nominal.
**CTTC stands for Cholesterol Treatment Trialists Collaboration and the composite endpoint consists of coronary heart death, nonfatal MI, stroke, or coronary revascularization
MI = Myocardial infarction; UA = Unstable angina; TIA = Transient ischemic attack
Sabatine MS, et al. N Engl J Med. 2017;376:1713-1722

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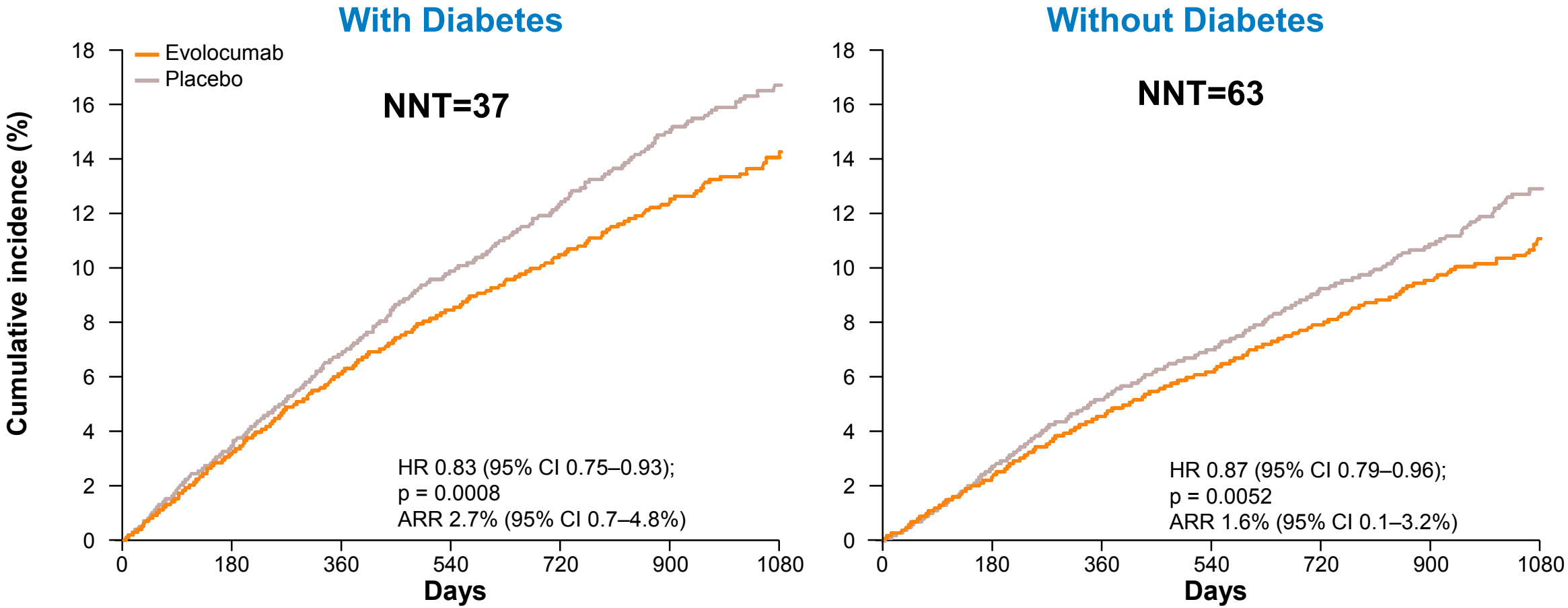
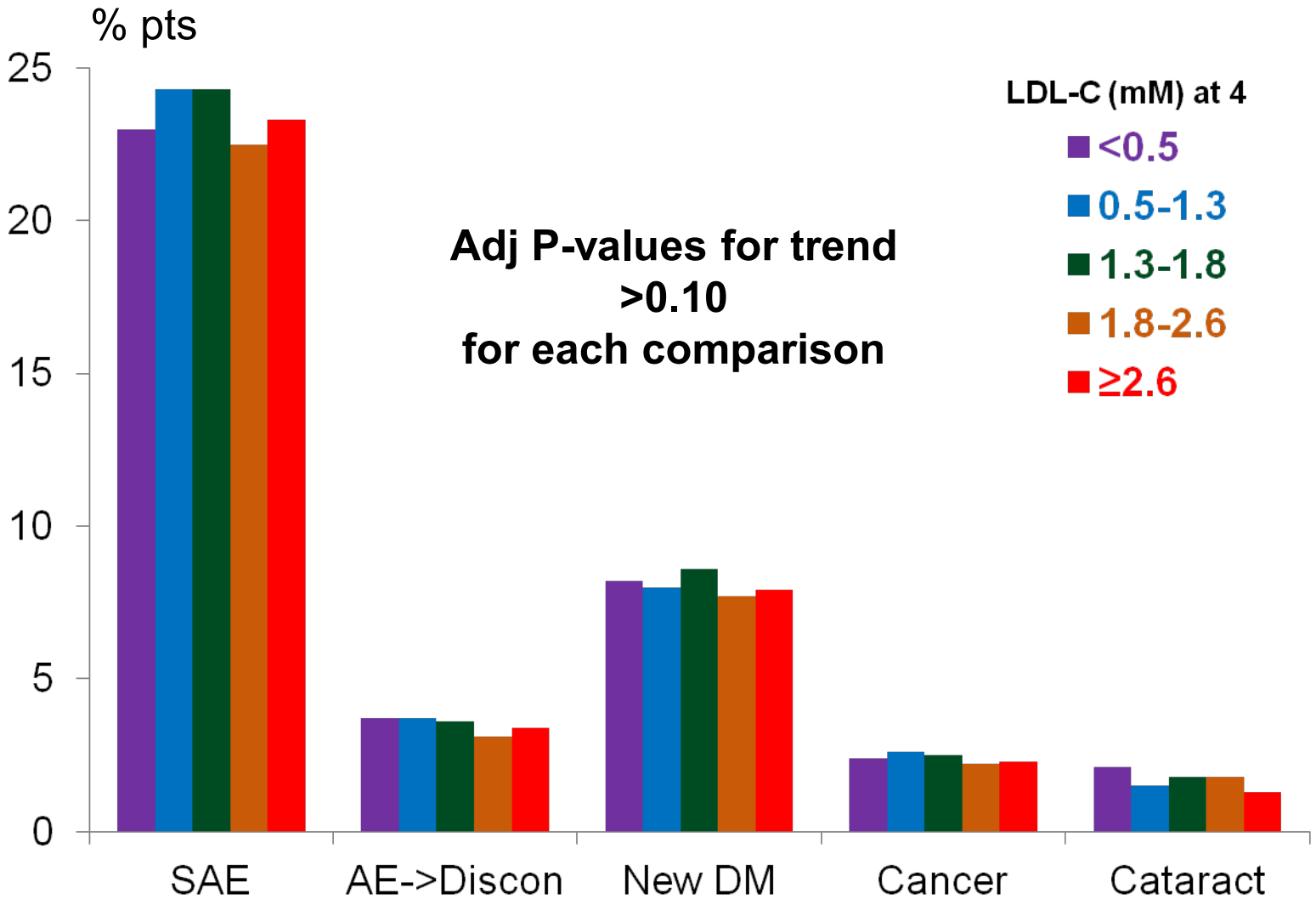
Primary Endpoint by Baseline Diabetic Status



Patients with diabetes treated with evolocumab showed a greater ARR because of their heightened baseline risk than those without diabetes (2.7% vs 1.6%); driven by a larger ARR in coronary revascularization (2.7% vs 1.8%)

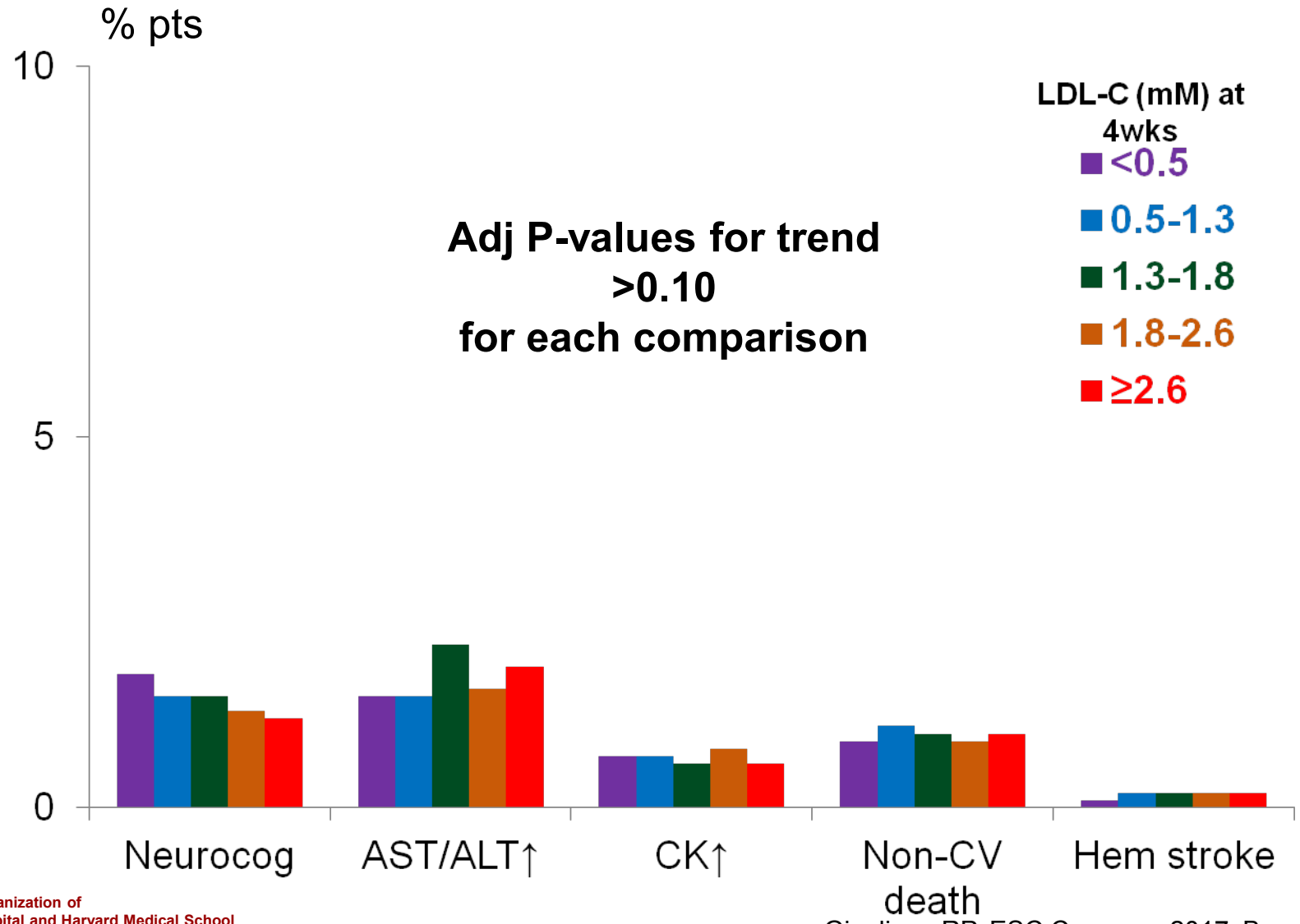
Data are the cumulative event rates for the primary efficacy endpoint (composite of cardiovascular death, myocardial infarction, stroke, hospital admission for unstable angina or coronary revascularization). p-values were calculated with log-rank tests. Hazard ratios (HRs) and 95% CI are from a Cox model. 3-year Kaplan-Meier rates. Absolute risk reduction (ARR) over 3 years. Sabatine MS, et al. *Lancet Diab Endocrinol.* [published online ahead of print September 15, 2017]. doi: 10.1016/S2213-8587(17)30313-3.

Safety Events - 1



Giugliano RP, ESC Congress 2017, Barcelona

Safety Events - 2



Giugliano RP, ESC Congress 2017, Barcelona

The ODYSSEY OUTCOMES Trial: Topline Results

Alirocumab in Patients After Acute Coronary Syndrome

Gregory G. Schwartz, Michael Szarek, Deepak L. Bhatt, Vera Bittner, Rafael Diaz, Jay Edelberg, Shaun G. Goodman, Corinne Hanotin, Robert Harrington, J. Wouter Jukema, Guillaume Lecorps, Angèle Moryusef, Robert Pordy, Matthew Roe, Harvey D. White, Andreas Zeiher,

Ph. Gabriel Steg

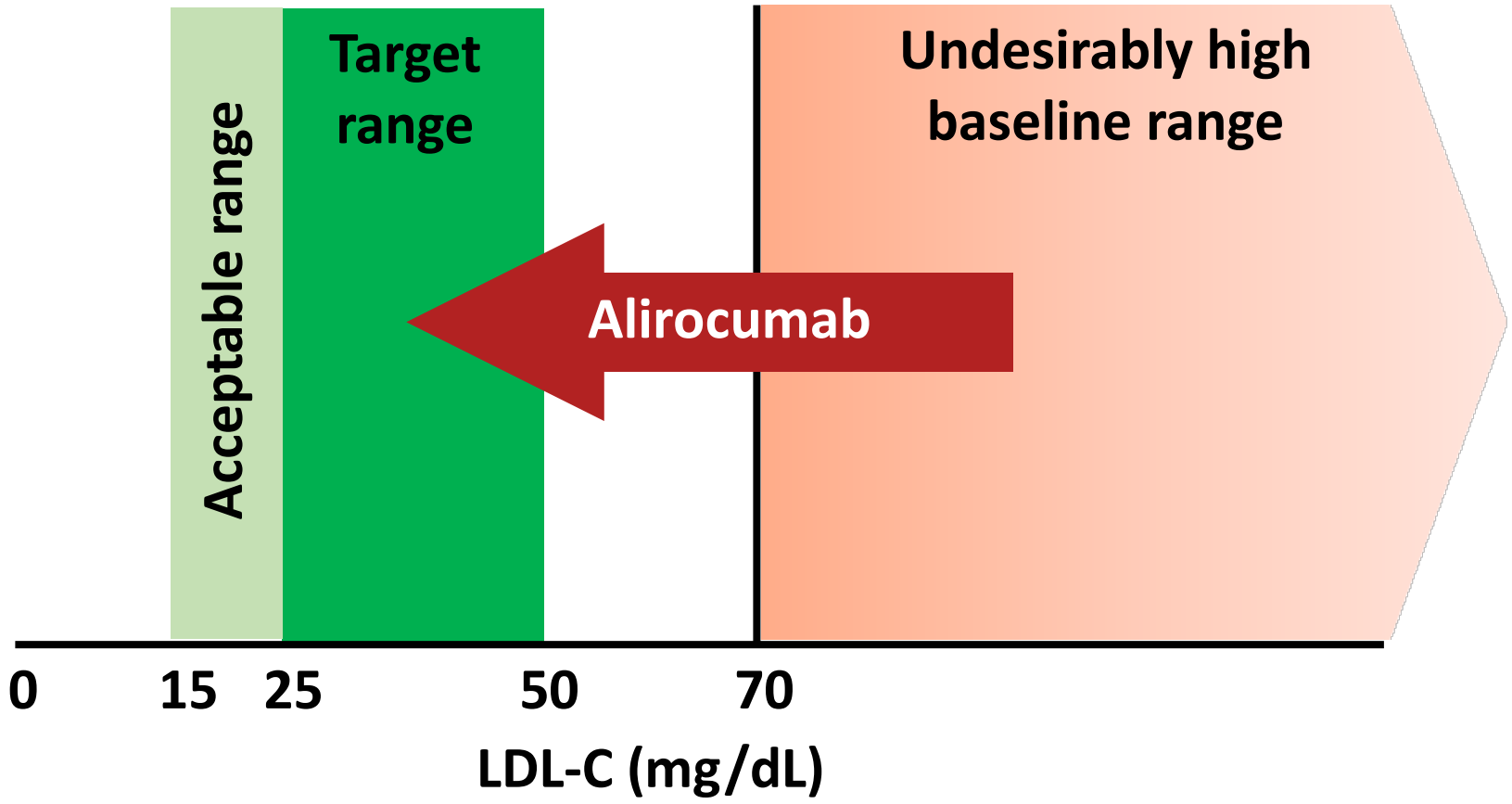
On behalf of the ODYSSEY OUTCOMES Investigators and Committees

American College of Cardiology – 67th Scientific Sessions March 10, 2018

ODYSSEY OUTCOMES

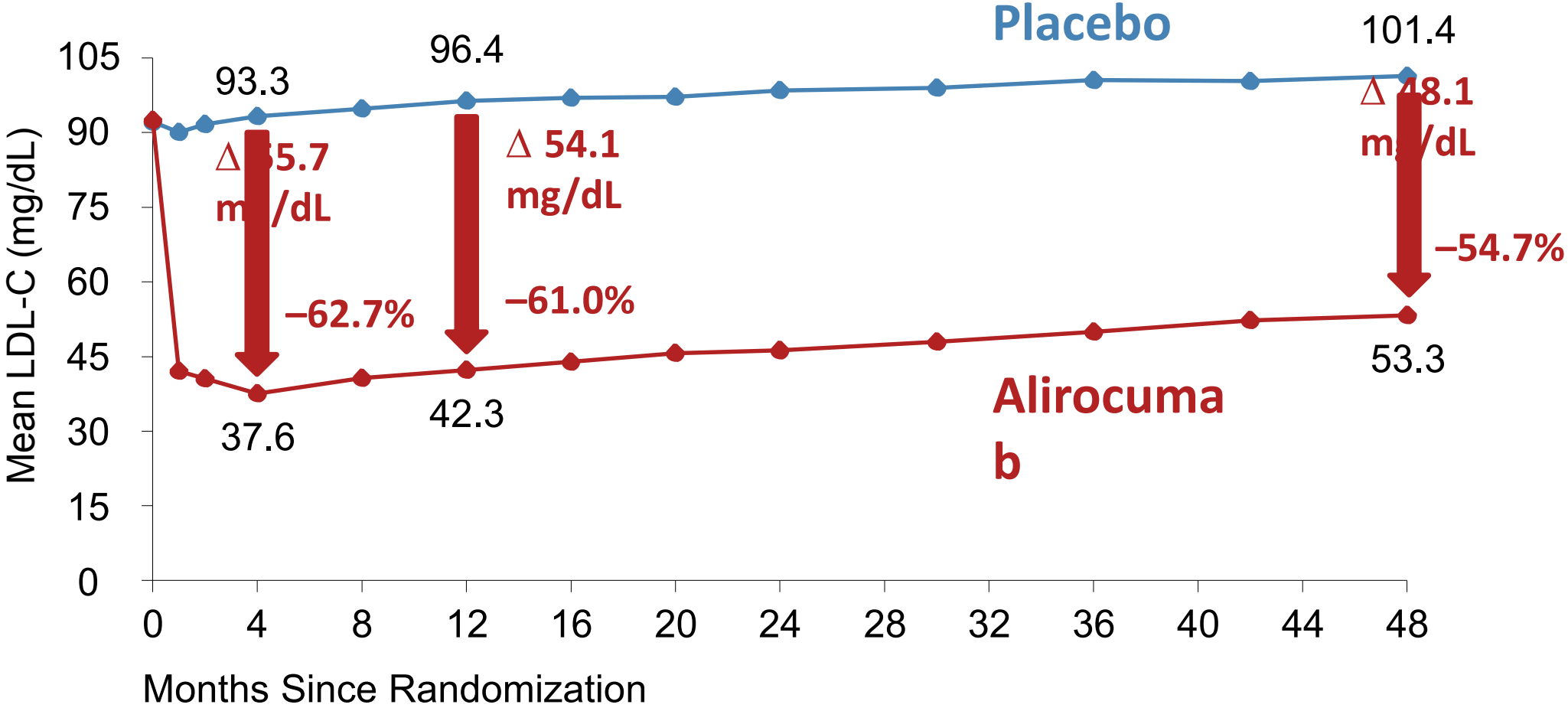
ClinicalTrials.gov: NCT01663402

A Target Range for LDL-C



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

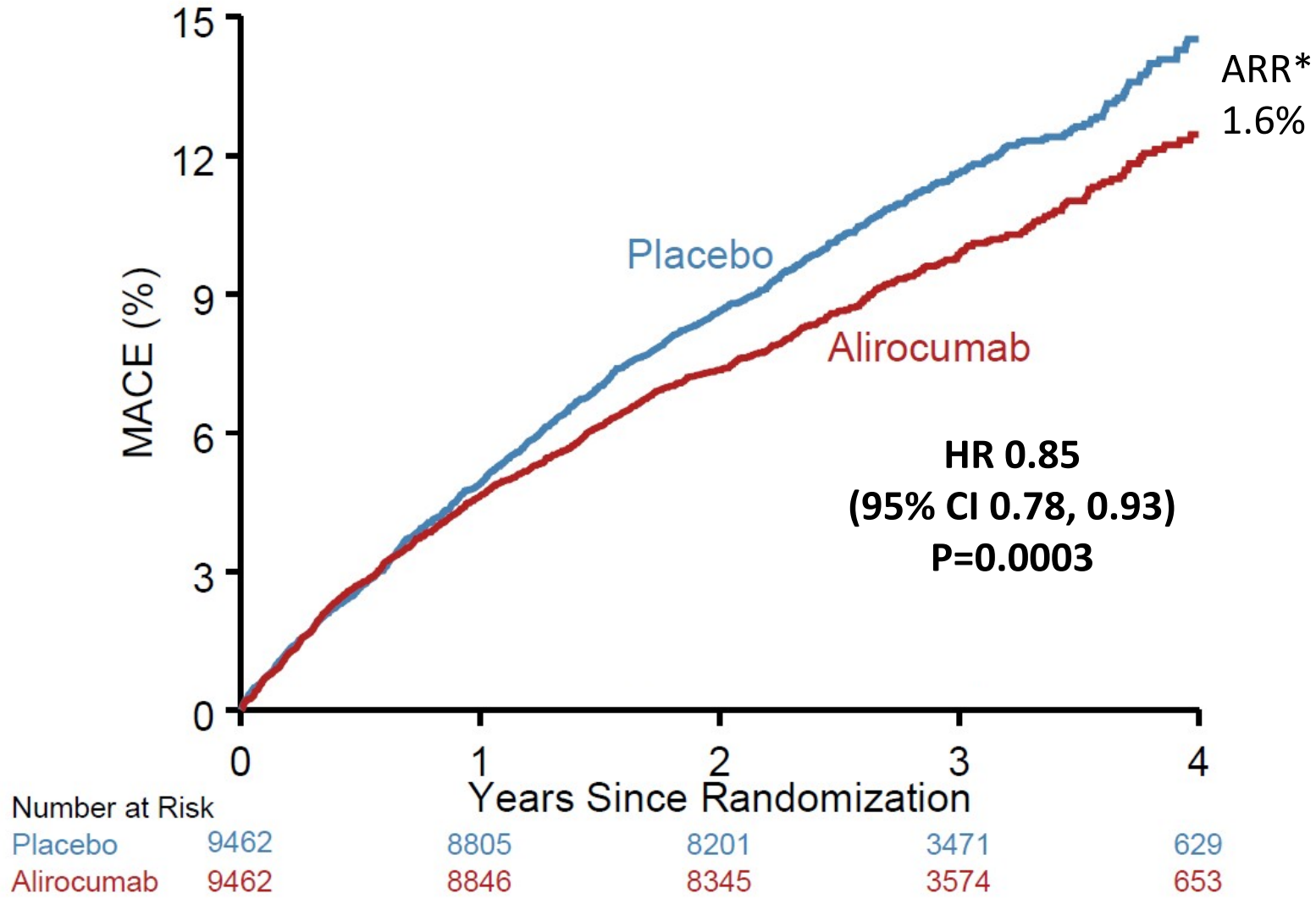
LDL-C: On-Treatment Analysis



Excludes LDL-C values after premature treatment discontinuation or blinded switch to placebo

Approximately 75% of months of active treatment were at the 75 mg dose

Primary Efficacy Endpoint: MACE

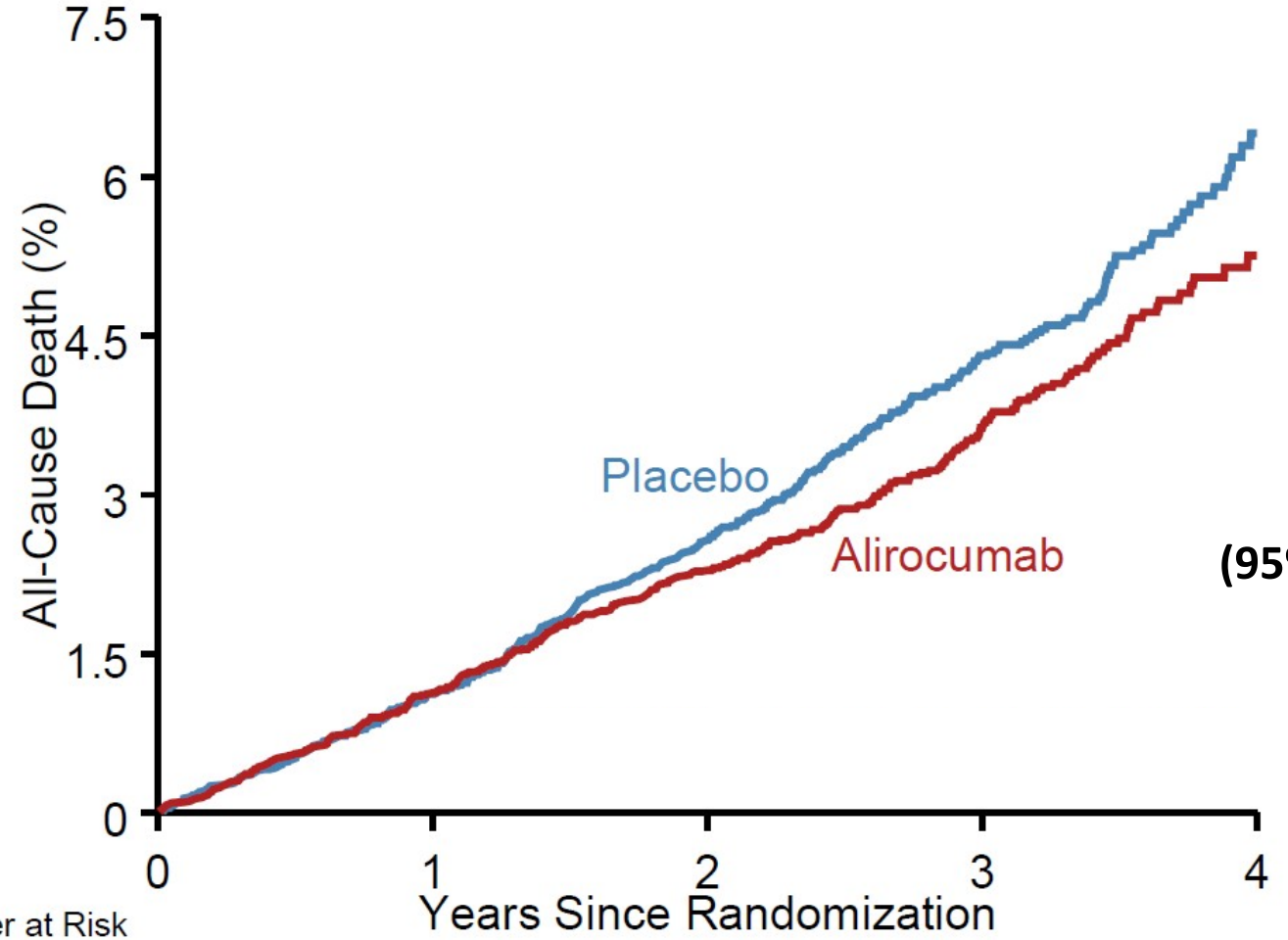


MACE: CHD death, non-fatal MI, ischemic stroke, or unstable angina requiring hospitalization

*Based on cumulative incidence

ODYSSEY OUTCOMES

All-Cause Death



ARR†
0.6%

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

*Nominal P-value

†Based on cumulative

Conclusions

Compared with placebo in patients with recent ACS, alirocumab 75 or 150 mg subcutaneous Q2W targeting LDL-C levels 25–50 mg/dL, and allowing levels as low as 15 mg/dL:

1. Reduced MACE, MI, and ischemic stroke
2. Was associated with a lower rate of all-cause death
3. Was safe and well-tolerated over the duration of the trial

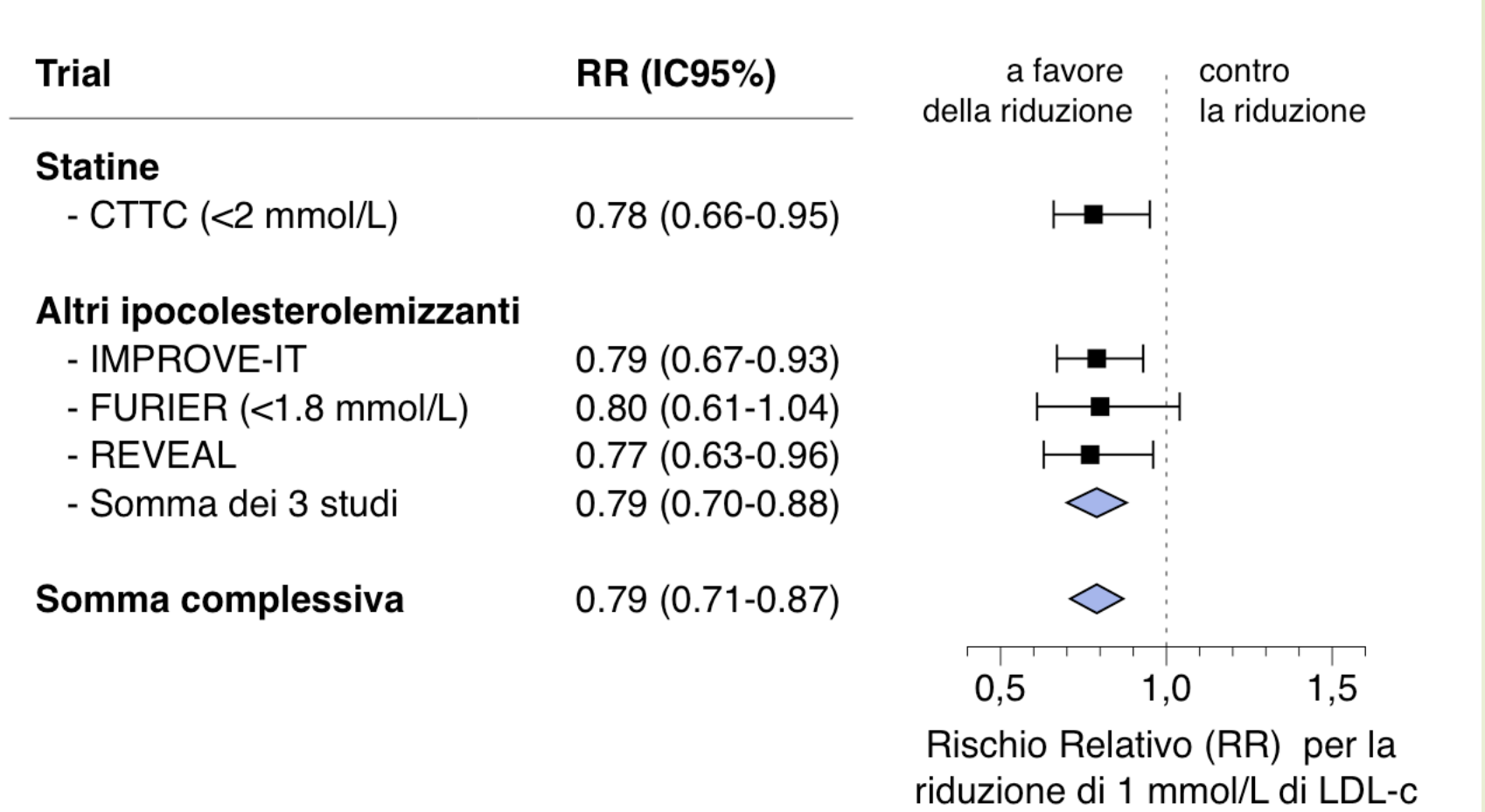
Clinical Perspective

- In this nearly 19,000-patient placebo-controlled trial, including many patients treated for ≥3 years, there was no safety signal with alirocumab other than injection site reactions

- Among patients with ACS and baseline LDL-C ≥100 mg/dL, alirocumab reduced MACE by 24% (ARR 3.4%) and all-cause death by 29% (ARR 1.7%) compared with placebo

 These are the patients who may benefit most from treatment

ARR, absolute risk reduction



August 1, 2018

Efficacy and Safety of Further Lowering of Low-Density Lipoprotein Cholesterol in Patients Starting With Very Low LevelsA Meta-analysis

Marc S. Sabatine, MD, MPH[1,2]; Stephen D. Wiviott, MD[1]; KyungAh Im, PhD[1]; et al
Sabina A. Murphy, MPH[1]; Robert P. Giugliano, MD, SM[1]
Author Affiliations

JAMA Cardiol. Published online August 1, 2018. doi:10.1001/jamacardio.2018.2258

LDL molto basse e rischio di eventi cardiaci

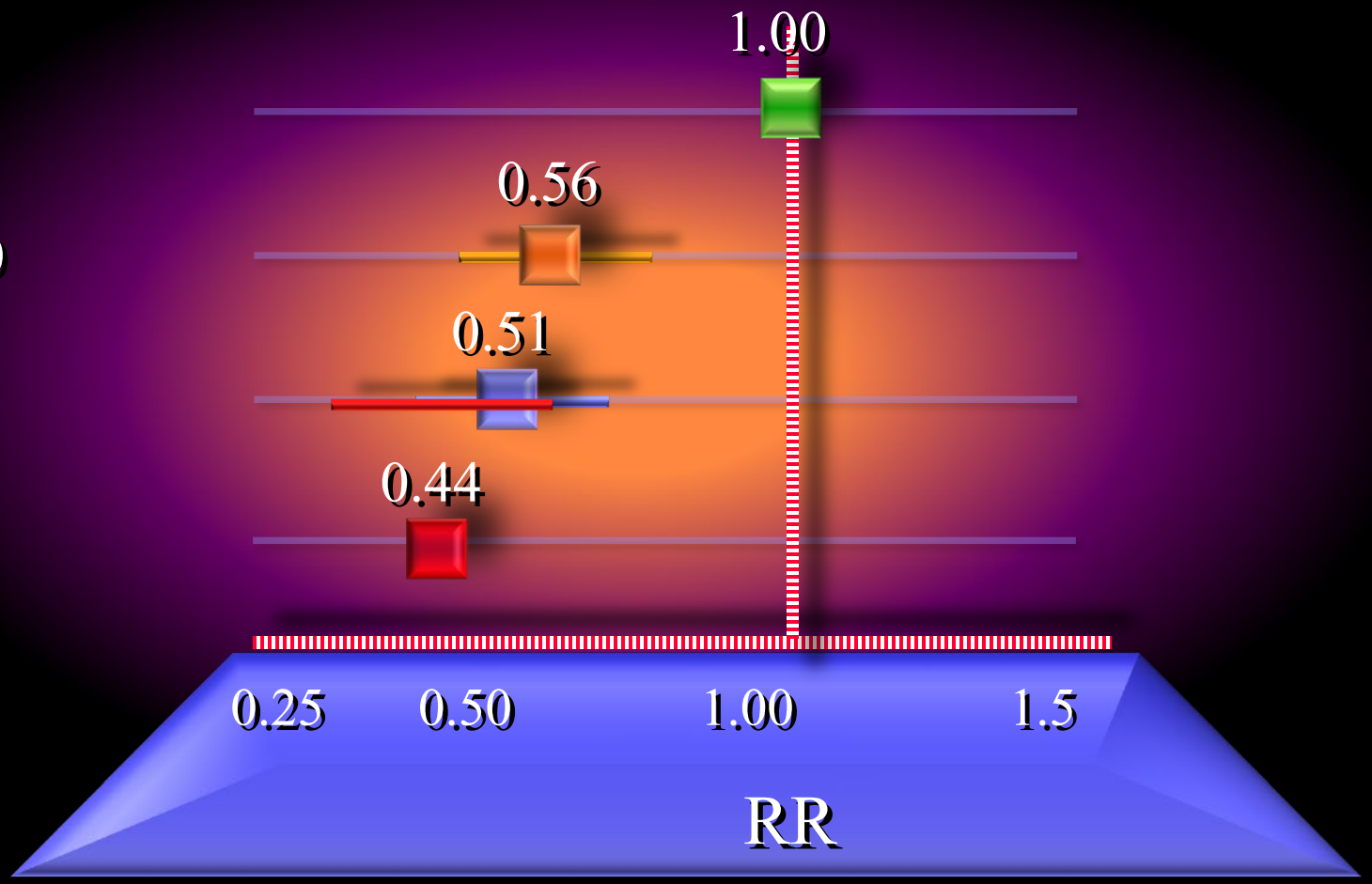
(Boekholdt, JACC 2014)

LDL > 175

LDL 75-100

LDL 50-75

LDL < 50



Il profilo del paziente eleggibile alla terapia con PCSK9-i

Indicazioni autorizzate e rimborsate SSN (decisione CTS):

- in **PREVENZIONE PRIMARIA** in pazienti di età ≥18 e ≤80 aa con ipercolesterolemia familiare eterozigote e livelli di **LDL-C ≥130 mg/dL** nonostante terapia da almeno 6 mesi con statina ad alta potenza alla massima dose tollerata + ezetimibe oppure con dimostrata intolleranza alle statine
- in **PREVENZIONE SECONDARIA** in pazienti di età ≥18 e ≤80 aa con ipercolesterolemia familiare eterozigote o ipercolesterolemia non familiare o dislipidemia mista e livelli di **LDL-C ≥100 mg/dL** nonostante terapia da almeno 6 mesi con statina ad alta potenza alla massima dose tollerata + ezetimibe oppure con dimostrata intolleranza alle statine.

Agenzia Italiana del Farmaco
AIFA

Patients' Reported Causes of Statin Therapy Discontinuation

INTOLLERANZA ALLE STATINE

FENOMENO DI DIFFICILE DEFINIZIONE E IDENTIFICAZIONE NELLA POPOLAZIONE, CARATTERIZZATO DALLA PERCEZIONE DI SINTOMI PREVALENTEMENTE MIALGICI CHE DI FATTO IMPEDISCONO L'ASSUNZIONE DELLA STATINA O IL RAGGIUNGIMENTO DELLA DOSE OTTIMALE PER IL CONTROLLO ADEGUATO DELLA COLESTEROLEMIA

- No documented major adverse reaction

Colivicchi F, et al. *Stroke* 2007; 38:2652-2657

The GAUSS-3 Trial

Goal Achievement after Utilizing an anti-PCSK9 antibody in Statin Intolerant Subjects-3

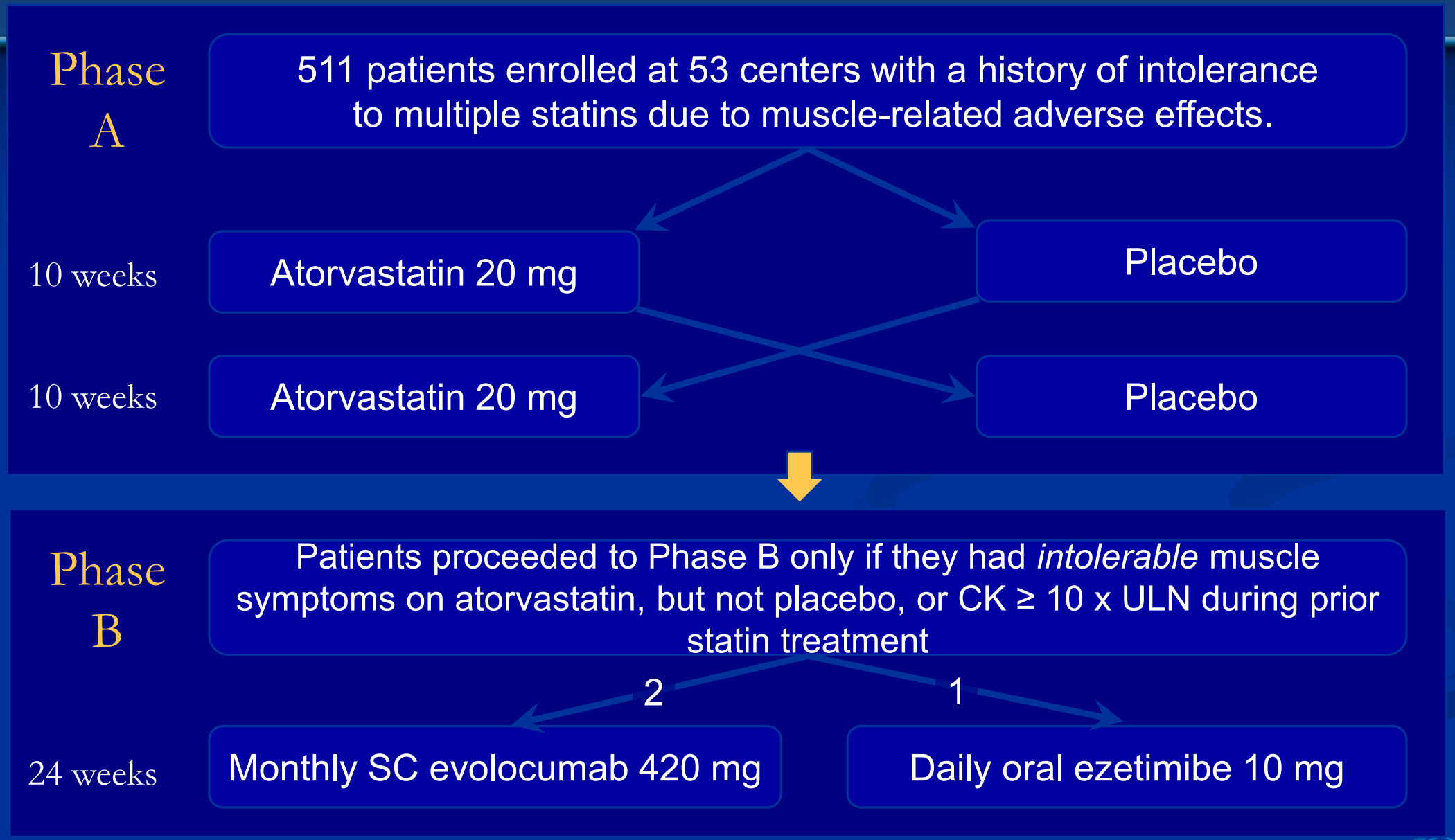
Steven E. Nissen MD MACC*
Erik Stroes MD PhD

***Disclosure**

Study Sponsor: Amgen
Consulting: Many pharmaceutical companies
Clinical Trials: Amgen, AstraZeneca, Cerenis, Eli Lilly, Novartis, Novo Nordisk, The Medicines Company, Orexigen, Takeda, and Pfizer.

ODYSSEY

Study Design: Two Double-Blind Phases



ODYSSEY

Phase A: Study Drug Discontinuation Events

Intolerable Muscle Symptoms	N = 491
On atorvastatin, but not placebo	209 (42.6%)*
On placebo, but not atorvastatin	130 (26.5%)
On both placebo and atorvastatin	48 (9.8%)
No symptoms on either treatment	85 (17.3%)
Did not complete Phase A	*20/511*

Bypassed Phase A due to CK elevation ≥ 10 x ULN	19 (3.9%)*

**218 of these 228 eligible patients proceeded to Phase B*

CONCLUSIONI (1)

- I pazienti vanno valutati e trattati secondo il loro rischio cv
- I pazienti a rischio molto alto vanno trattati «aggressivamente» per raggiungere il target consigliato
- Il raggiungimento del target non è un punto di arrivo, ma il risultato va mantenuto nel tempo

CONCLUSIONI (2)

- Le terapie oggi a disposizione ci permettono di raggiungere obiettivi fino a pochi anni fa impensabili
- Seppur nelle limitazioni imposte dagli enti regolatori, è indispensabile conoscere queste formidabili armi terapeutiche da utilizzare nei pazienti elegibili