Università di Foggia

DIPARTIMENTO CARDIO-TORACO-VASCOLARE
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Cardiologia Italiana del Territorio

XXIX
CONGRESSO
NAZIONALE
ANCE

PROGRAMMA

10 - 13 OTTOBRE 2019

Centro Congressi
Hilton Sorrento Palace
Sorrento (NA)

Nuovi approcci ipocolesterolemizzanti: Gli anti PCSK9

Prof Natale Daniele Brunetti, MD, PhD, HD, FESC

Sorrento, 11 ottobre 2019

Statine: una lunga storia…

Akira Endo
1976

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Format: Abstract Send to

J Antibiot (Tokyo). 1976 Dec;29(12):1346-8.

ML-236A, ML-236B, and ML-236C, new inhibitors of cholesterogenesis produced by Penicillium citrinium.

Endo A, Kuroda M, Tsujita Y.

PMID: 1010803

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Inhibition of cholesterol synthes
vivo by ML-236A and ML-2 [Eur

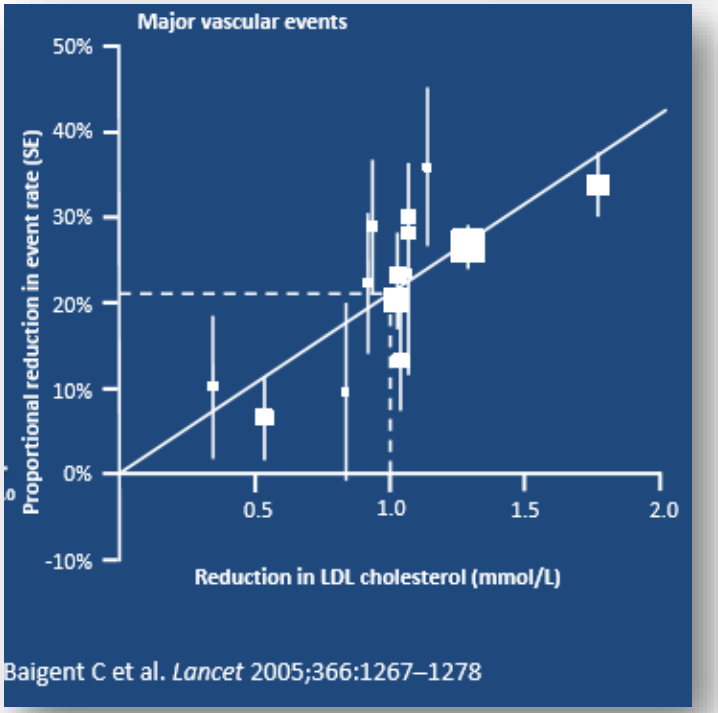
Meva-statina

Atherosclerosis Supplements 5 (2004) 125–130

Ipercolesterolemia e malattie CV: the lower, the better

Per riduzione di 1 mmol/L (39 mg/dl)
il rischio si riduce del 22%

Lancet 2010;376:1670–81



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

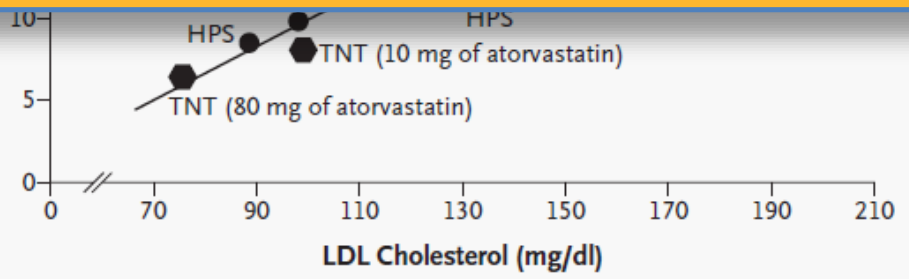


Figure 4. Event Rates Plotted against LDL Cholesterol Levels during Statin Therapy in Secondary-Prevention Studies.

HPS denotes Heart Protection Study,[1] CARE Cholesterol and Recurrent Events Trial,[10] LIPID Long-term Intervention with Pravastatin in Ischaemic Disease,[11] and 4S Scandinavian Simvastatin Survival Study. [12] Event rates

The lower, the better

N Engl J Med 2005;352:1425–1435

1.000 pz con statina dose media

18 IMA

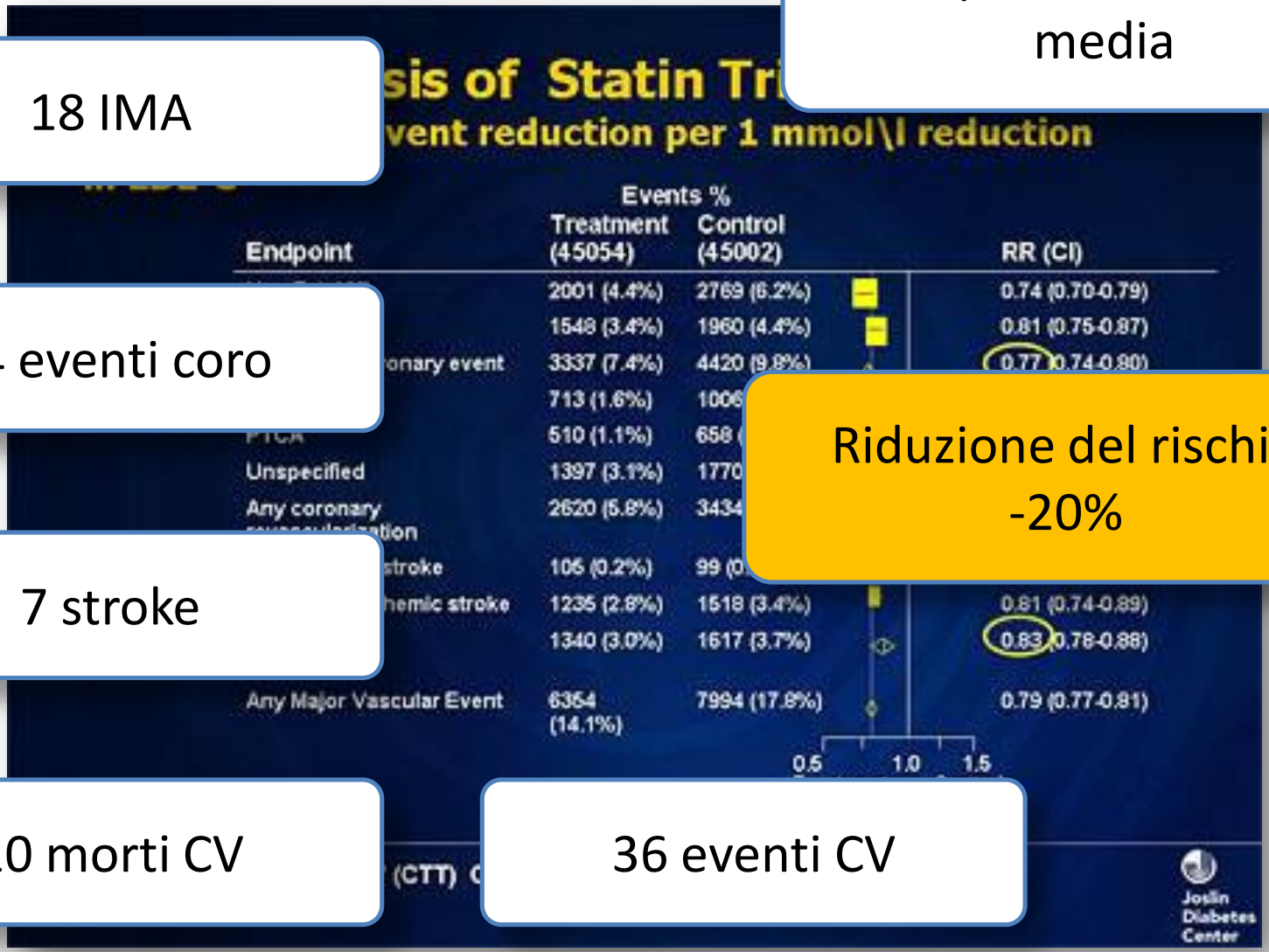
24 eventi coro

7 stroke

10 morti CV

36 eventi CV

Riduzione del rischio -20%



Statine e riduzione rischio cardiovascolare

Interpretation of the evidence for the efficacy and safety of statin therapy

Rory Collins, Christina Reith, Jonathan Emberson, Jane Armitag
David DeMets, Stephen Evans, Malcolm Law, Stephen MacMa
Anthony Rodgers, Peter Sandercock, Kenneth Schulz, Peter Seve

Summary

This Review is intended to help clinicians, patients, and the public make informed decisions about statin therapy for the prevention of heart attacks and strokes. It explains how the evidence that is available from randomised controlled trials yie In addition, it discusses how claims t limitations of other sources of

September 8, 2016
http://dx.doi.org/10.1016/
S0140-6736(16)31357-5

10.000 pz con atorva 40mg 5 anni

- 1.000 eventi CV maggiori

- 2 sterline /mese

- 5 miopatie
- 50-100 diabete
- 5-10 stroke emorragici

Linee guida americane vs europee: TNT study

- fine

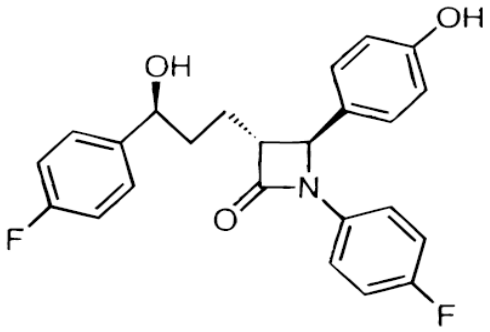
- mezzi

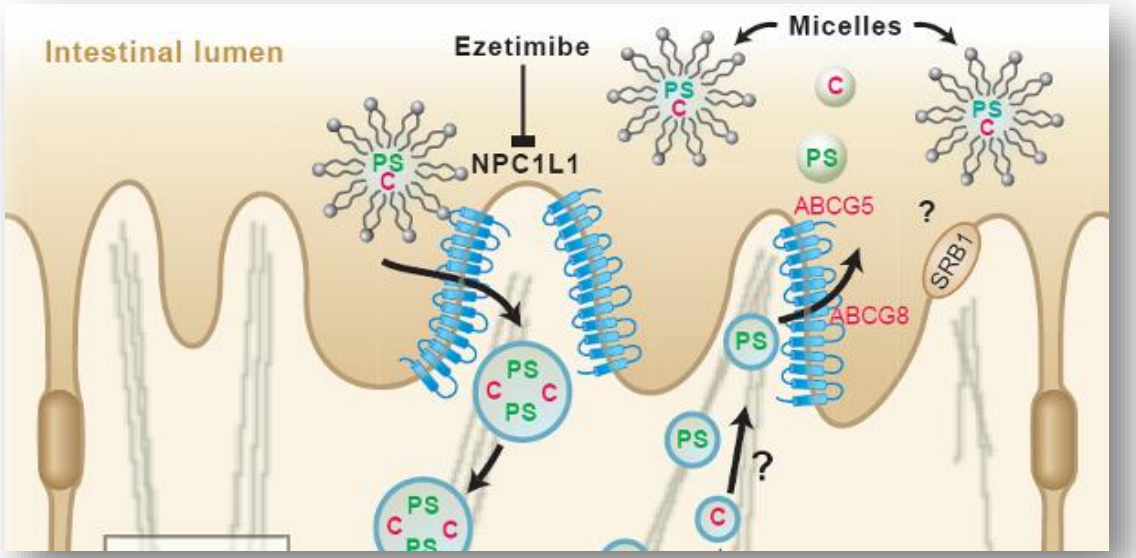
- 80 mg atorvastatina
- 70 mg LDL

Terapia ipocolesterolemizzante: ezetimibe

2015

PNAS



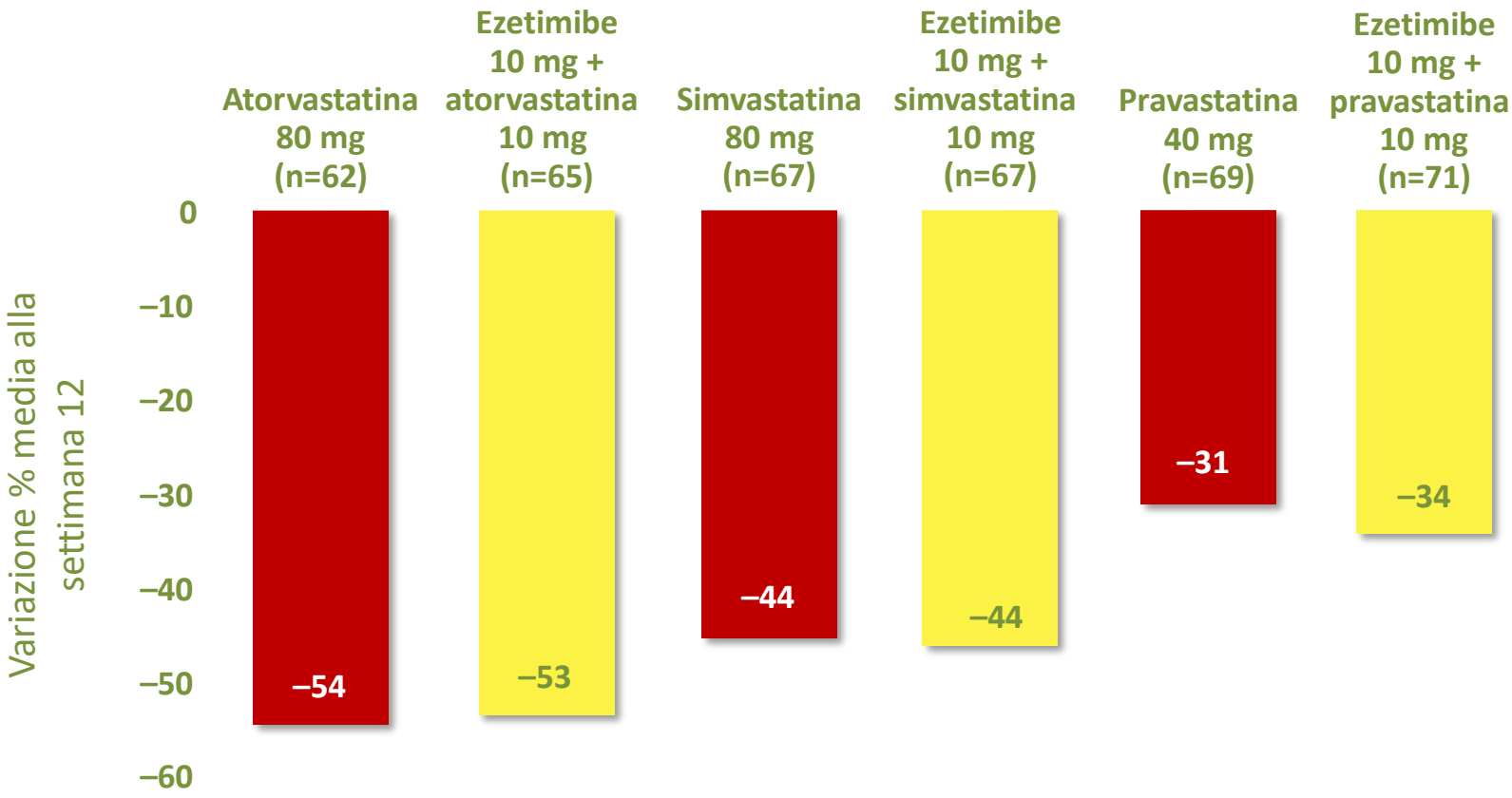


Science, 303, 1149, 2004

The target of ezetimibe is Niemann-Pick C1-Like 1 (NPC1L1)

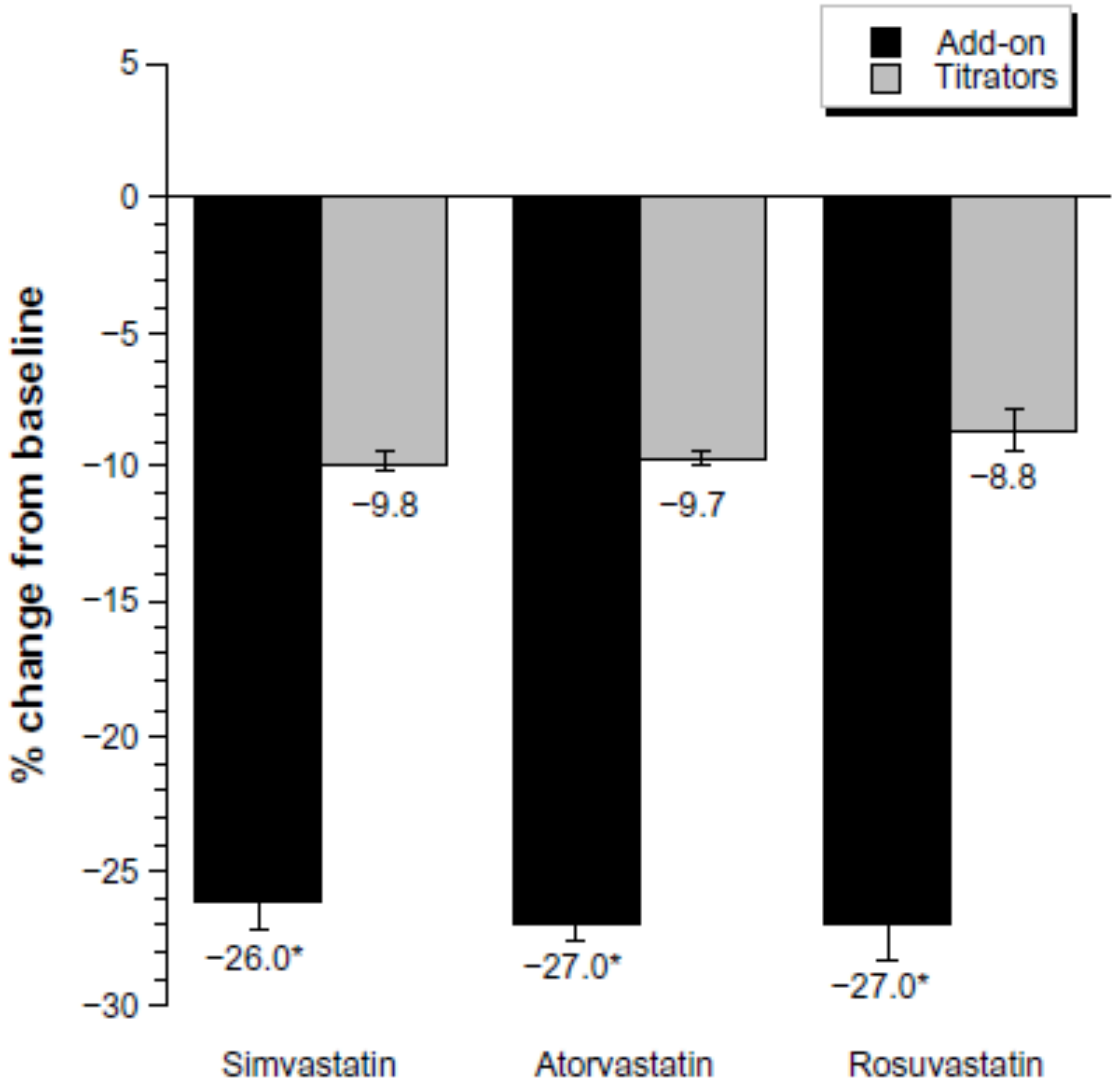
PNAS 102, 8132, 2005

Effetto ezetimibe: stesso risultato con meno statina



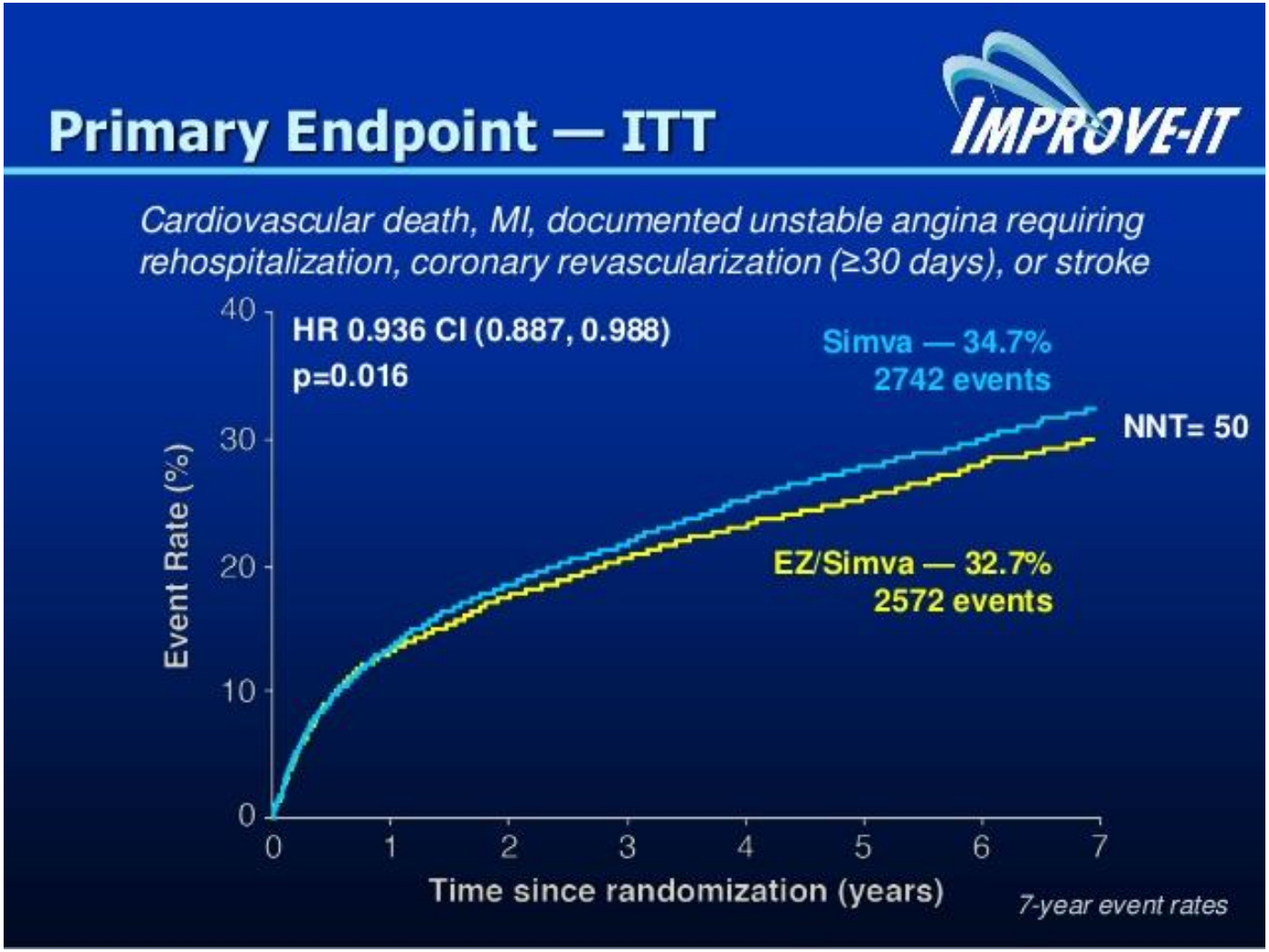
Ballantyne CM et al Circulation 2003;107:2409-2415
Davidson MH et al J Am Coll Cardiol 2002;40:2125-2134.

Effetto ezetimibe: meglio add on che titolazione



Vascular Health and Risk Management 2013:9 719–727

Studio IMPROVE-IT: risultati



N Engl J Med. 2015 Jun 18;372(25):2387-97

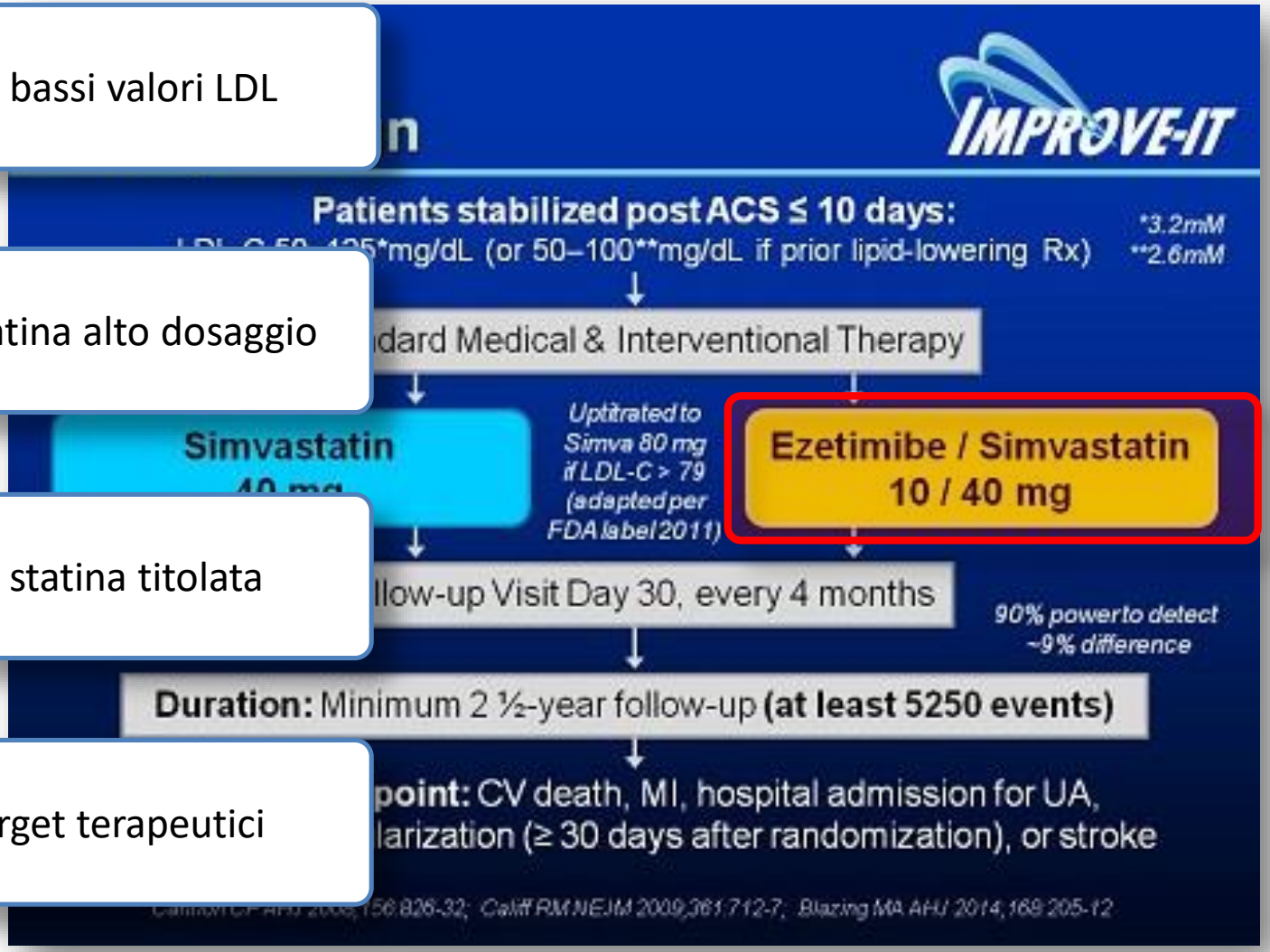
Studio IMPROVE-IT

Vs bassi valori LDL

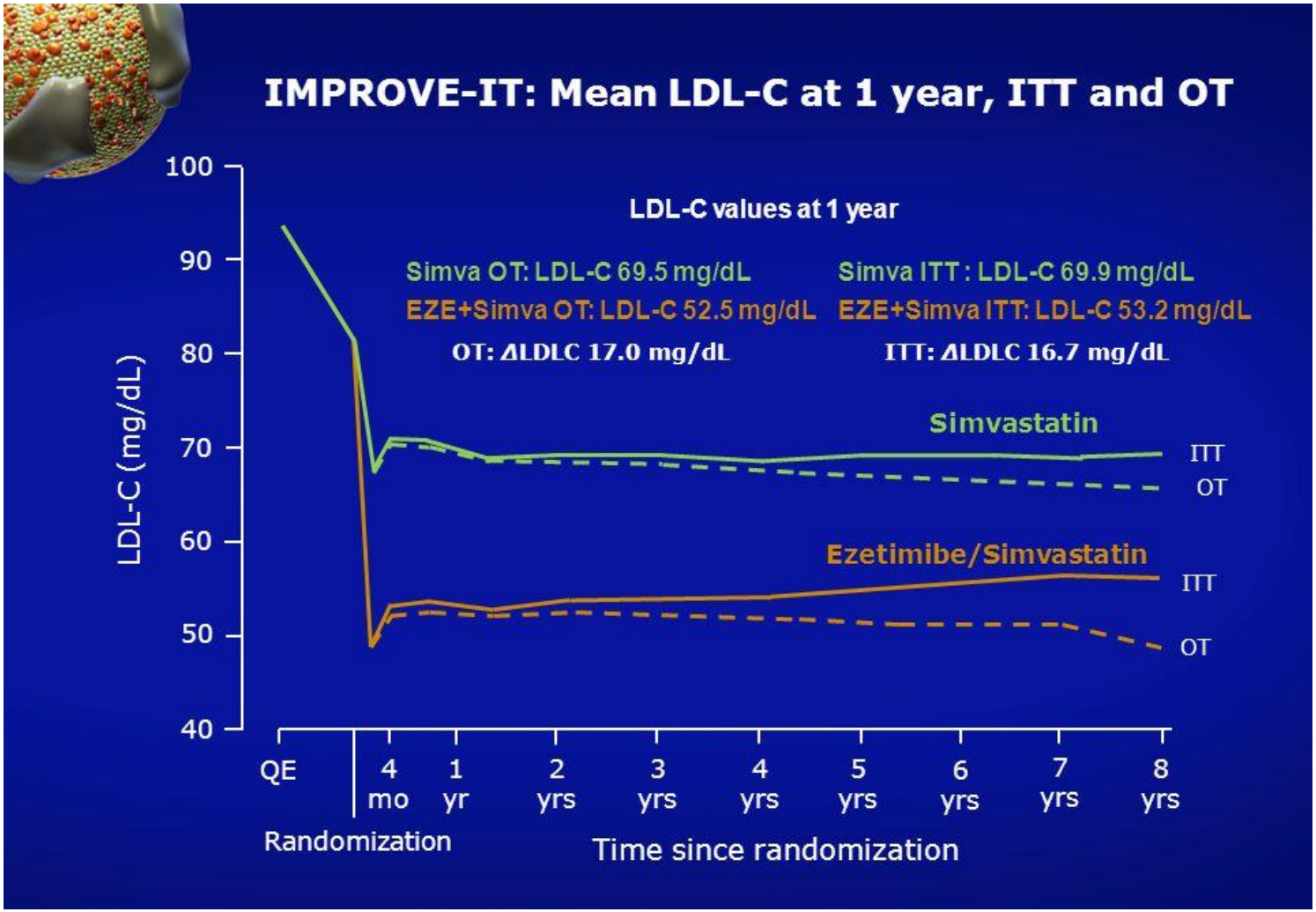
Vs statina alto dosaggio

Vs statina titolata

Target terapeutici



Livelli colesterolemia LDL nello studio IMPROVE-IT



N Engl J Med. 2015 Jun 18;372(25):2387-97

Ipercolesterolemie familiari associati a mutazioni

Mutations in *PCSK9* cause autosomal dominant hypercholesterolemia

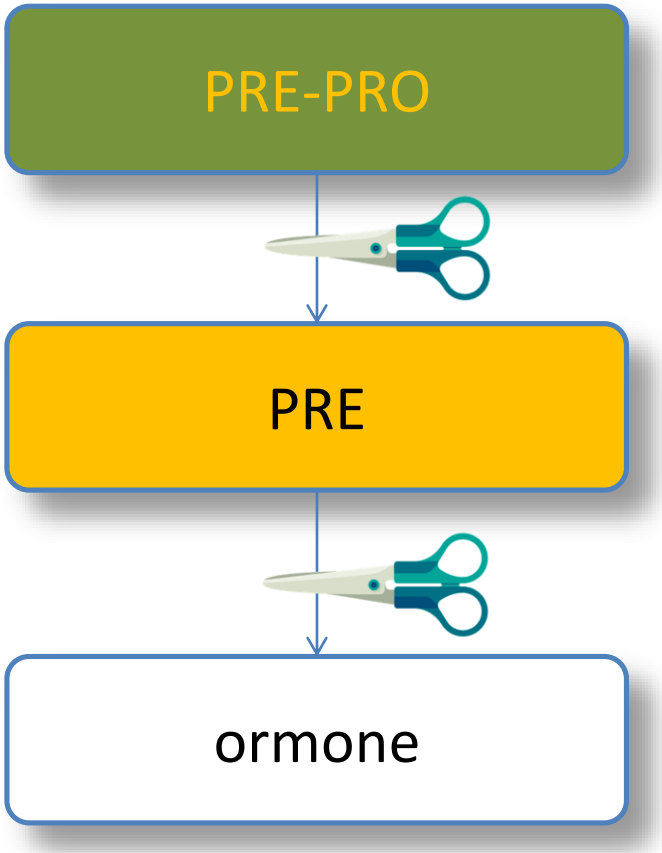
Marianne Abifadel[1,2], Mathilde Varret[1], Jean-Pierre Rabès[1,3], Delphine Allard[1], Khadija Ouguerram[4], Martine Devillers[1], Corinne Cruaud[5], Suzanne Benjannet[6], Louise Wickham[6], Danièle Erlich[1], Aurélie Derré[1], Ludovic Villéger[1], Michel Farnier[7], Isabel Beucler[8], Eric Bruckert[9], Jean Chambaz[10], Bernard Chanu[11], Jean-Michel Lecerf[12], Gerald Luc[12], Philippe Moulin[13], Jean Weissenbach[5], Annick Prat[6], Michel Krempf[4], Claudine Junien[1,3], Nabil G Seidah[6] & Catherine Boileau[1,3]

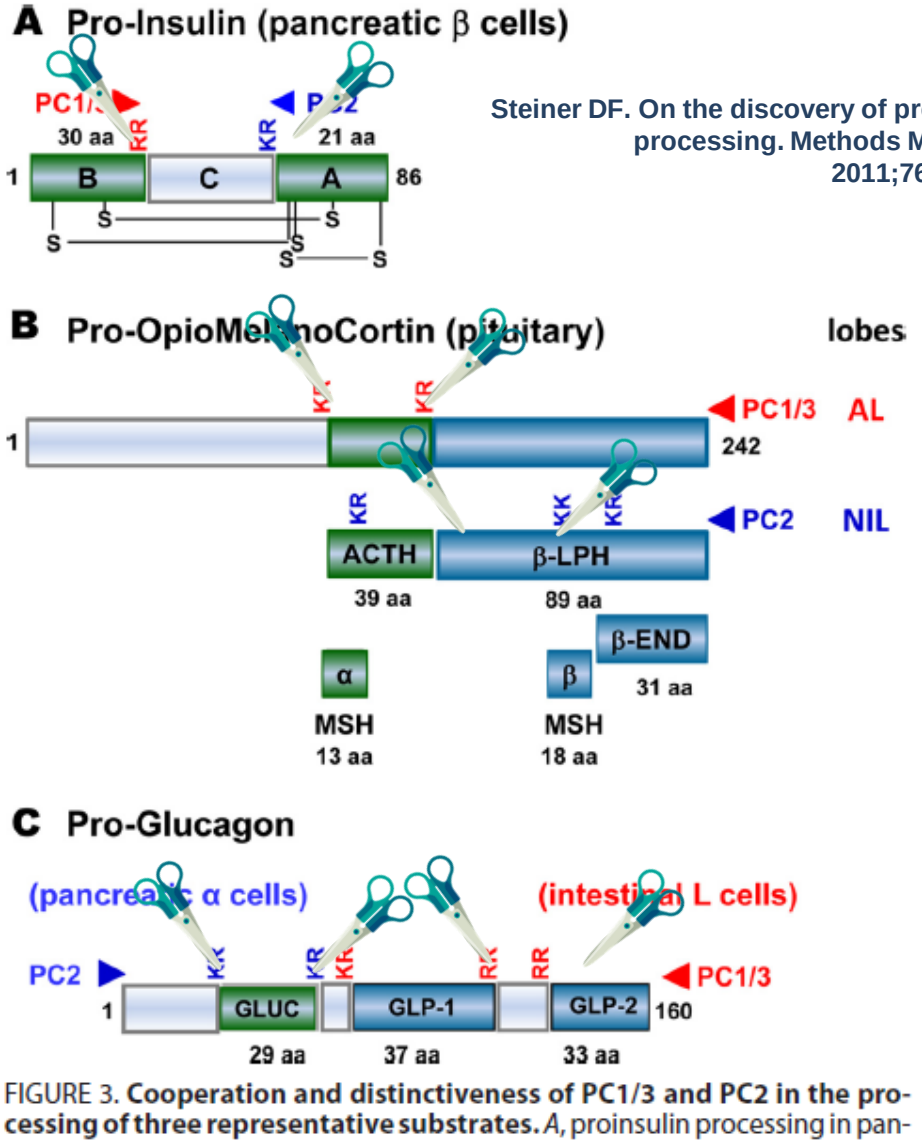
Autosomal dominant hypercholesterolemia (ADH; OMIM144400), a risk factor for coronary heart disease, is characterized by an increase in low-density lipoprotein cholesterol levels that is associated with mutations in the genes *LDLR* (encoding low-density lipoprotein receptor) or *APOB* (encoding apolipoprotein B). We mapped a third locus associated with ADH, *HCHOLA3* at 1p32, and now report two mutations in the gene *PCSK9* (encoding proprotein convertase subtilisin/kexin type 9) that cause ADH. *PCSK9* encodes NARC-1 (neural apoptosis regulated convertase), a newly identified human subtilase that is highly expressed in the liver and contributes to cholesterol homeostasis.

Gain of function PCSK9

Nat Genet. 2003;34:154–156

Pro-protein convertasi





Steiner DF. On the discovery of precursor processing. Methods Mol Biol. 2011;768:3–11.

FIGURE 3. **Cooperation and distinctiveness of PC1/3 and PC2 in the processing of three representative substrates.** *A*, proinsulin processing in pan-

J Biol Chem 288 (30), 21473-21481

Diffusione e differenziazione regionale del PCSK9

Cardiovascular Research (2016) 112, 429–442
doi:10.1093/cvr/cvw194

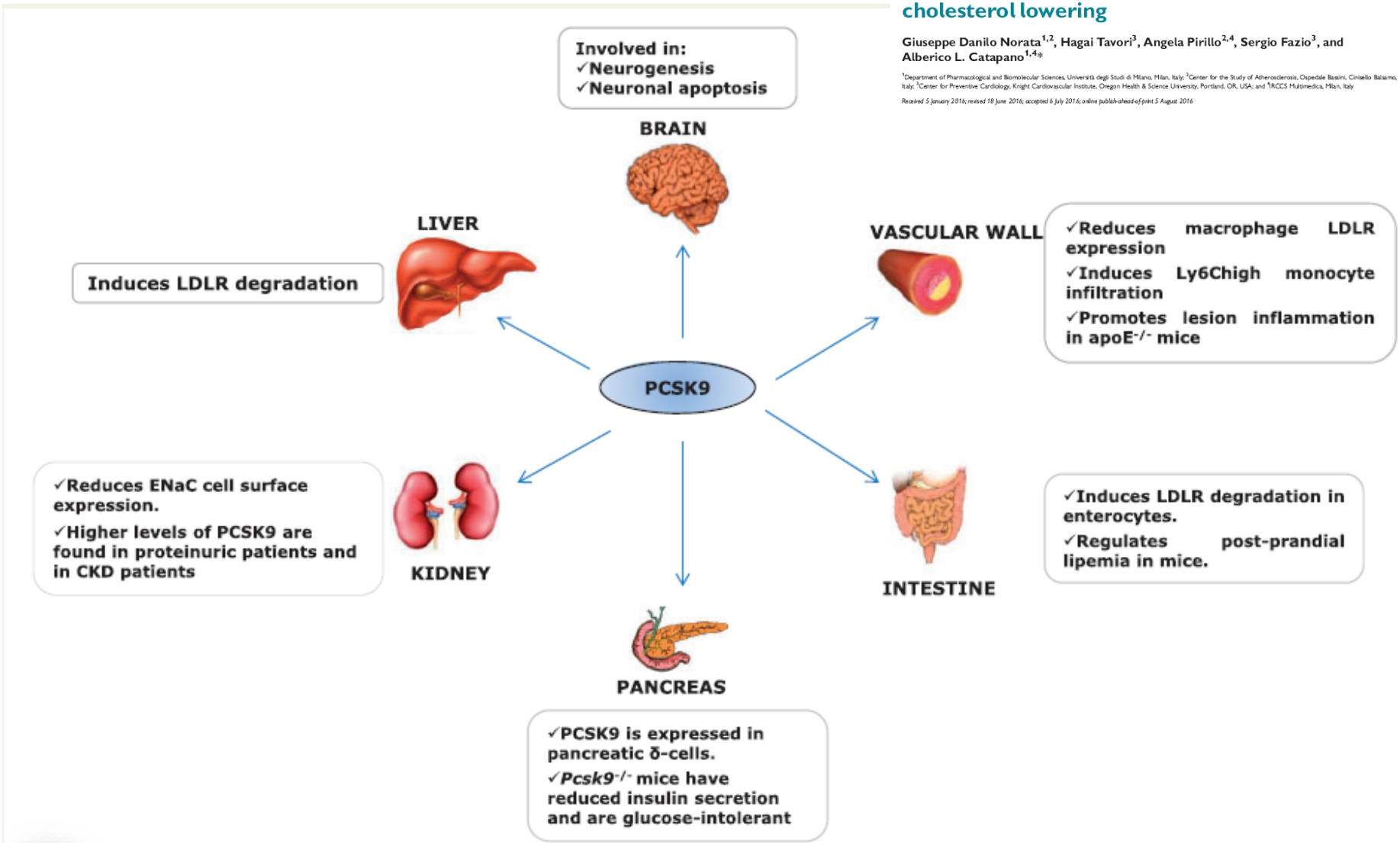
REVIEW

Biology of proprotein convertase subtilisin kexin 9: beyond low-density lipoprotein cholesterol lowering

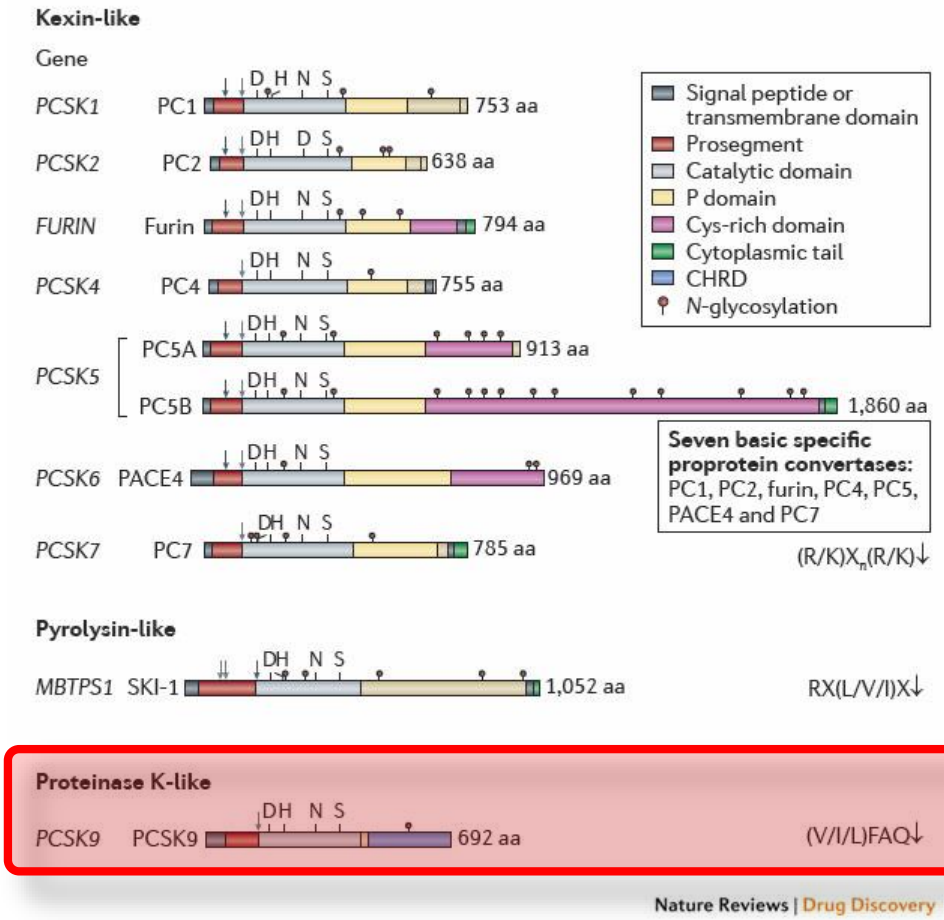
Giuseppe Danilo Norata[1,2], Hagai Tavori[3], Angela Pirillo[2,4], Sergio Fazio[3], and Alberico L. Catapano[1,4]*

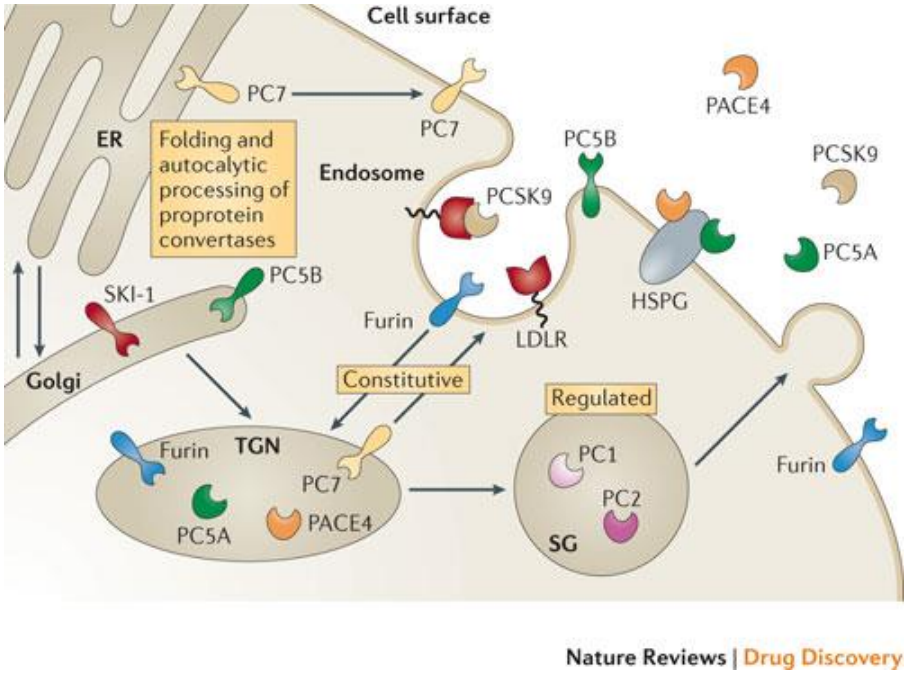
[1]Department of Pharmacological and Biomolecular Sciences, Università degli Studi di Milano, Milan, Italy; [2]Center for the Study of Atherosclerosis, Ospedale Bassini, Cinisello Balsamo, Italy; [3]Center for Preventive Cardiology, Knight Cardiovascular Institute, Oregon Health & Science University, Portland, OR, USA; and [4]IRCCS Multimedica, Milan, Italy

Received 5 January 2016; revised 18 June 2016; accepted 6 July 2016; online publish-ahead-of-print 5 August 2016



Famiglia delle pro-protein convertasi





Nat Rev Drug Discov. 2012;11:367–383

Ipercolesterolemie familiari: terzo meccanismo

Am. J. Hum. Genet. 64:1378–1387, 1999

A Third Major Locus for Autosomal Dominant Hypercholesterolemia Maps to 1p34.1-p32

Mathilde Varret,[1,*] Jean-Pierre Rabès,[1,3,*] Bruno Saint-Jore,[1] Ana Cenarro,[6] Jean-Christophe Marinoni,[1] Fernando Civeira,[6] Martine Devillers,[1] Michel Krempf,[4] Monique Coulon,[1] Rochelle Thiart,[7] Maritha J. Kotze,[7] Helena Schmidt,[8] Jean-Claude [illegible], Gert M. Kostner,[8] Stephano Bertolini,[9] Miguel Pocovi,[6] Alberto Rosa,[10] Michel Farnier,[5] Maria Martinez,[2] Claudine Junien,[1,3] and Catherine Boileau[1,3]

[1]Hôpital Necker-Enfants Malades, Institut National de la Santé et de la Recherche Médicale, Unit 383, Université René Descartes and [2]Hôpital Saint-Louis, Institut National de la Santé et de la Recherche Médicale, Unit 358, Paris, [3]Laboratoire Central de Biochimie, d'Hormonologie et de Génétique Moléculaire, Centre Hospitalo-Universitaire Ambroise Paré, Boulogne, [4]Service d'endocrinologie, Centre Hospitalo-Universitaire Hôtel Dieu, Nantes, and [5]Point Médical, Dijon, France; [6]Departamento de Bioquímica y Biología Molecular y Celular, Facultad de Ciencias, Universidad de Zaragoza, Zaragoza, Spain; [7]Medical Research Council Cape Heart Group, Division of Human Genetics, Faculty of Medicine, University of Stellenbosch, Tygerberg, South Africa; [8]Institute of Medical Biochemestry, University of Graz, Graz, Austria; [9]Atherosclerosis Preven[illegible] Química Biológica (Centro de Investi[illegible] Técnicas), Facultad de Ciencias Quím[illegible]

Gain of function

Ipercolesterolemie familiari

- Recettori LDL
- ApoB
- PCSK9

ipocolesterolemie in Texas

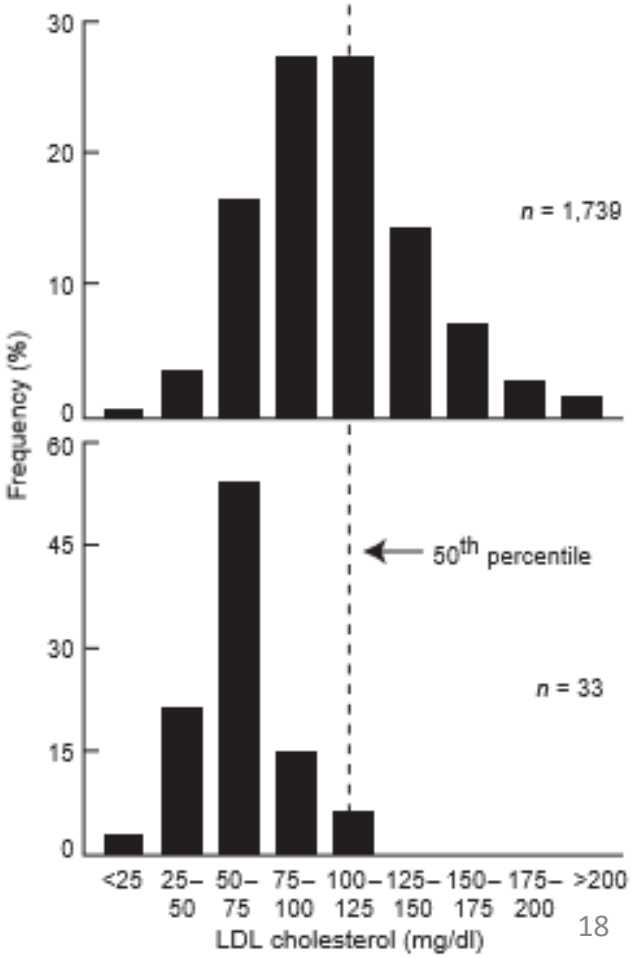
LETTERS

nature genetics

Low LDL cholesterol in individuals of African descent resulting from frequent nonsense mutations in *PCSK9*

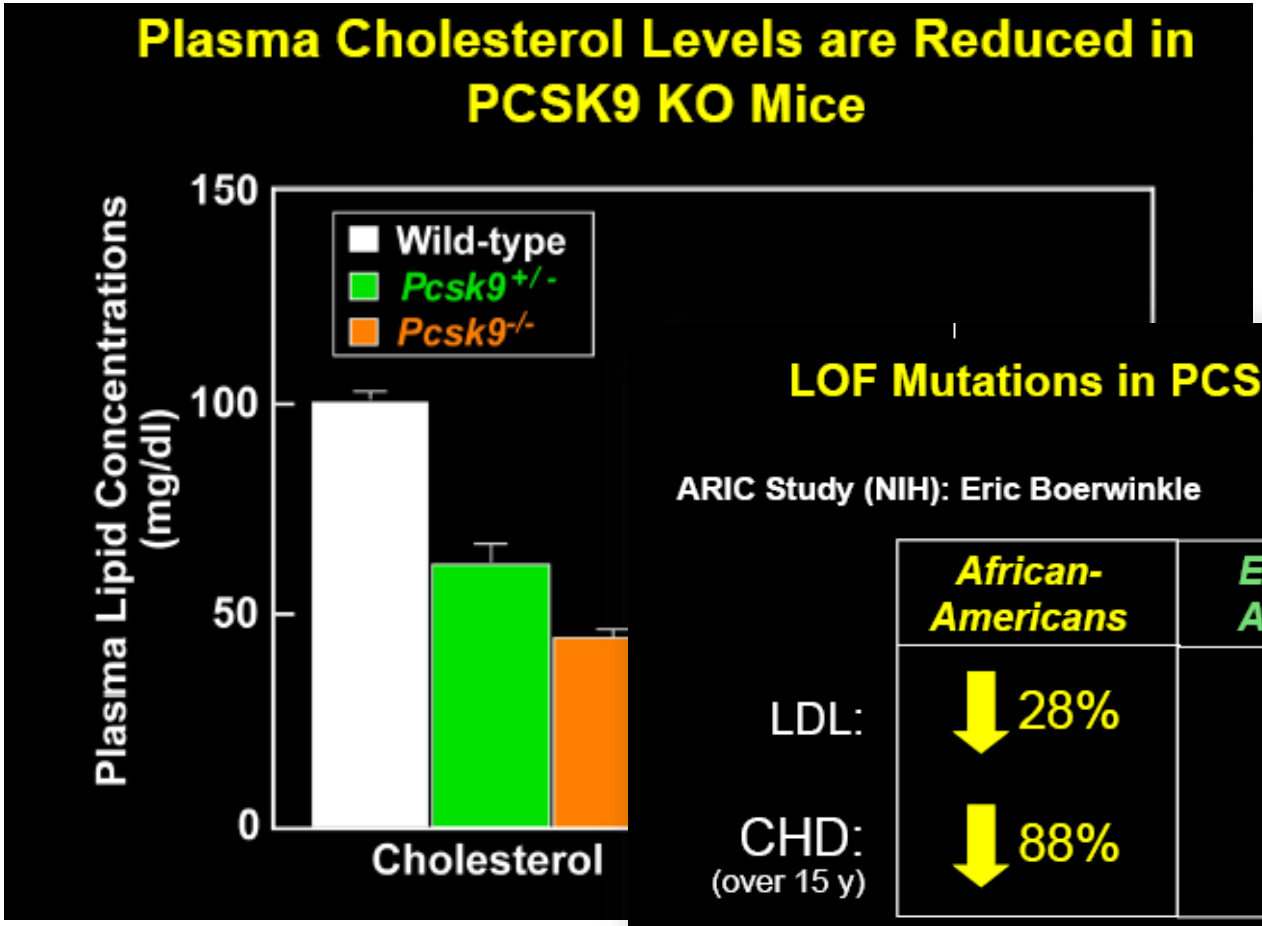
Jonathan Cohen[1–3], Alexander Pertsemlidis[2,3], Ingrid K Kotowski[4], Randall Graham[1], Christine Kim Garcia[1] & Helen H Hobbs[1–4]

The low-density lipoprotein receptor (LDLR) prevents hypercholesterolemia and atherosclerosis by removing low-density lipoprotein (LDL) from circulation. Mutations in the genes encoding either LDLR[1] or its ligand (APOB)[2] cause severe hypercholesterolemia. Missense mutations in *PCSK9*, encoding a serine protease in the secretory pathway[3], also cause hypercholesterolemia[4]. These mutations are probably gain-of-function mutations, as overexpression of *PCSK9* in the liver of mice produces hypercholesterolemia[5–7] by reducing LDLR number. To test whether loss-of-function mutations in *PCSK9* have the opposite effect, we sequenced the coding region of *PCSK9* in 128 subjects (50% African American) with low plasma levels of LDL and found two nonsense mutations (Y142X and C679X). These mutations were common in Afric Americans (combined frequency, 2%) but rare in European Americans (<0.1%) and were associated with a 40% reduction in plasma levels of LDL cholesterol. These data indicate that common sequence variations have large effects on plasma cholesterol levels in selected populations.



Loss of function

Riduzione del colesterolo associata a riduzione eventi CV



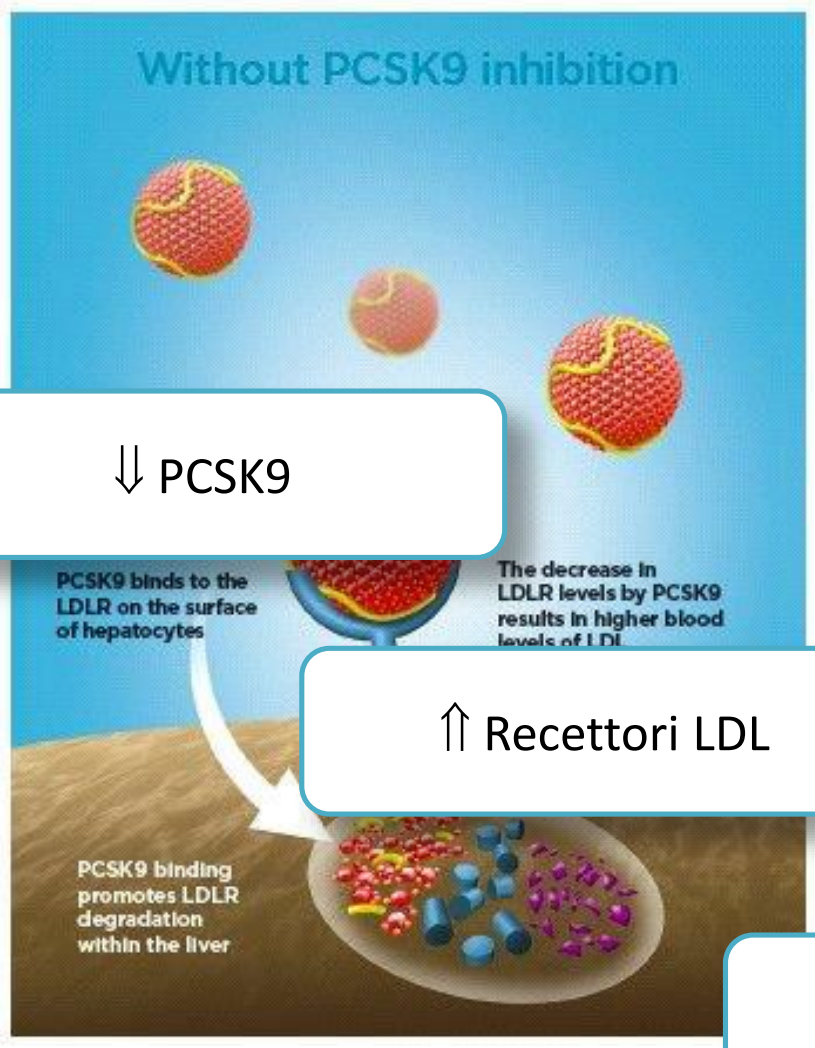
LOF Mutations in PCSK9 Lower CHD

ARIC Study (NIH): Eric Boerwinkle

	African-Americans	European-Americans
LDL:	↓ 28%	↓ 15%
CHD: (over 15 y)	↓ 88%	↓ 46%

Lancet, 2007 (McPherson)
NEJM, 2008 (Katherisan)

PCSK9i: meccanismo d'azione

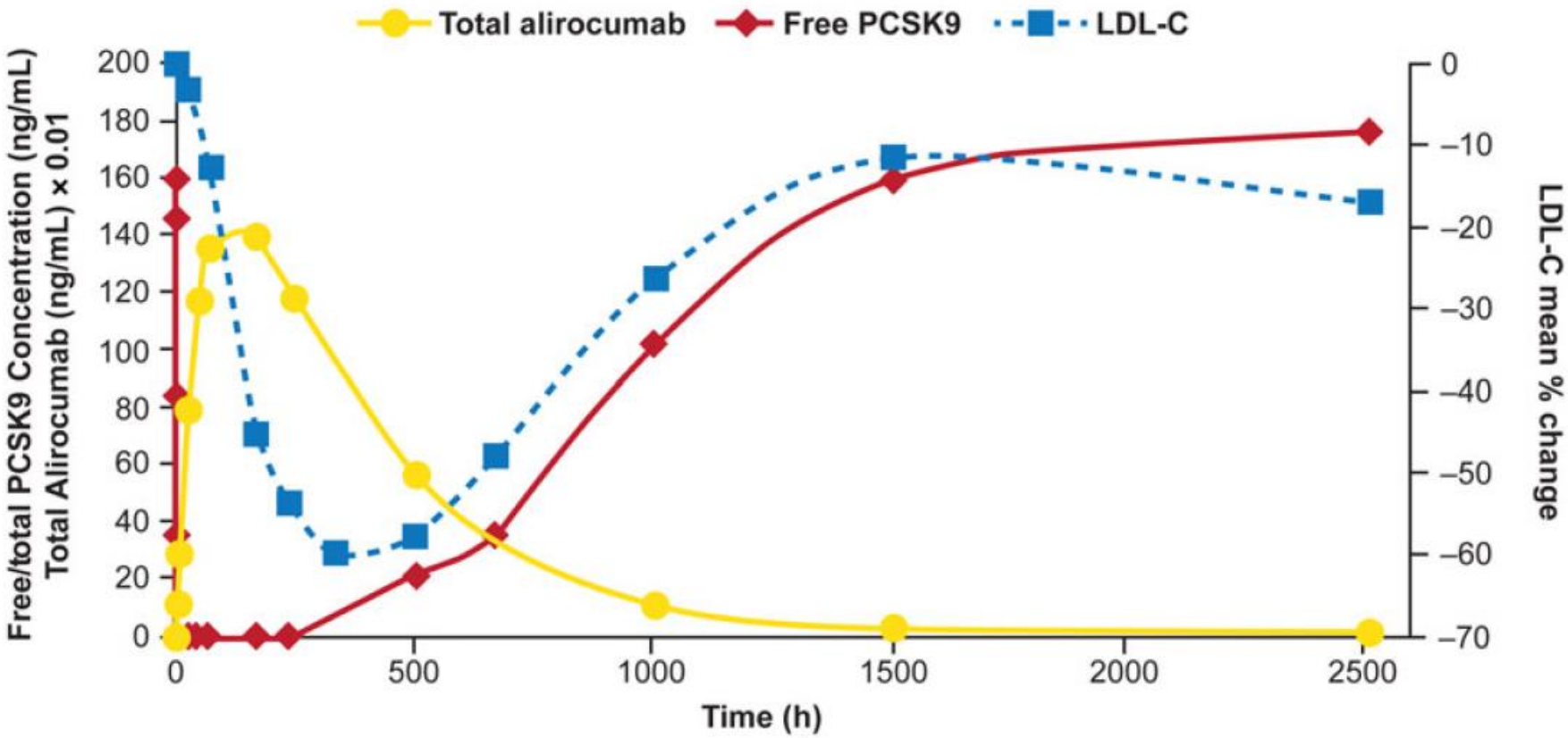


⇓ PCSK9

⇑ Recettori LDL

⇓ LDL

Farmacocinetica PCSK9i



Future Cardiol 2014;10:183–99.

- 60-70%

Original Investigation

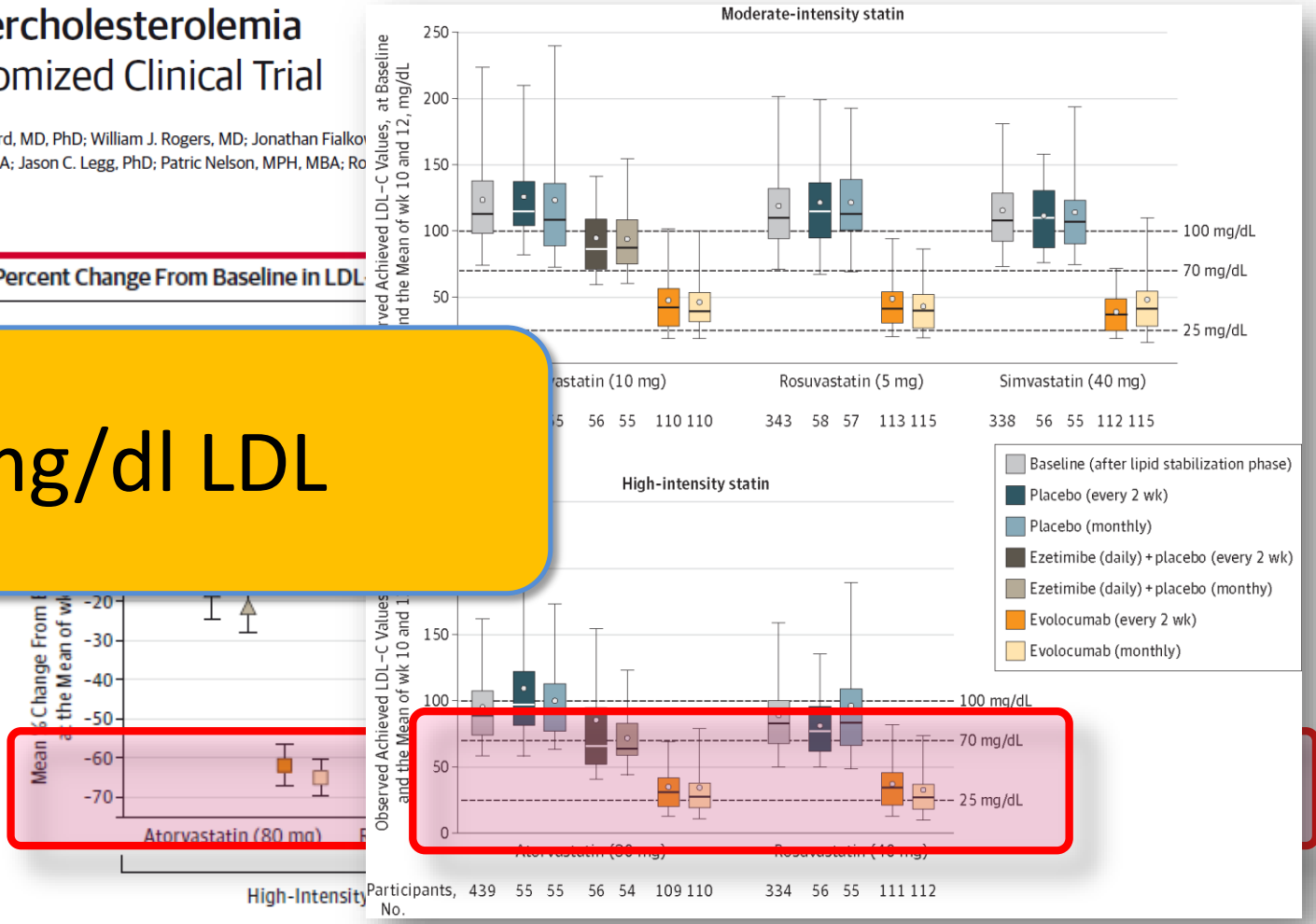
Effect of Evolocumab or Ezetimibe Added to Moderate- or High-Intensity Statin Therapy on LDL-C Lowering in Patients With Hypercholesterolemia

The LAPLACE-2 Randomized Clinical Trial

Jennifer G. Robinson, MD, MPH; Bettina S. Nedergaard, MD, PhD; William J. Rogers, MD; Jonathan Fialkow; David Ramstad, MD, MPH; Ransi Somaratne, MD, MBA; Jason C. Legg, PhD; Patric Nelson, MPH, MBA; Ro; Robert Weiss, MD; for the LAPLACE-2 Investigators

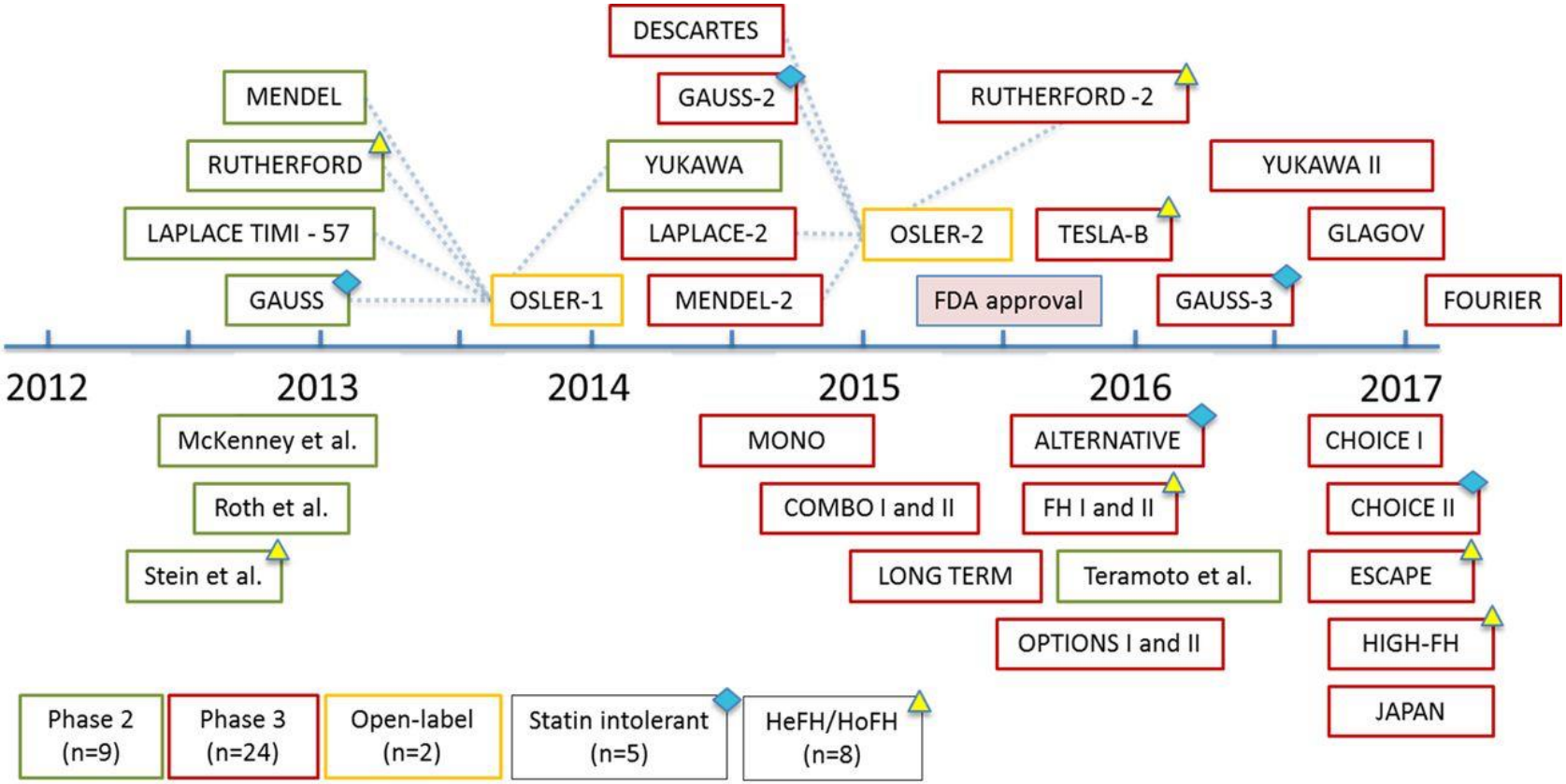
Figure 3. Mean Percent Change From Baseline in LDL-

30 mg/dl LDL



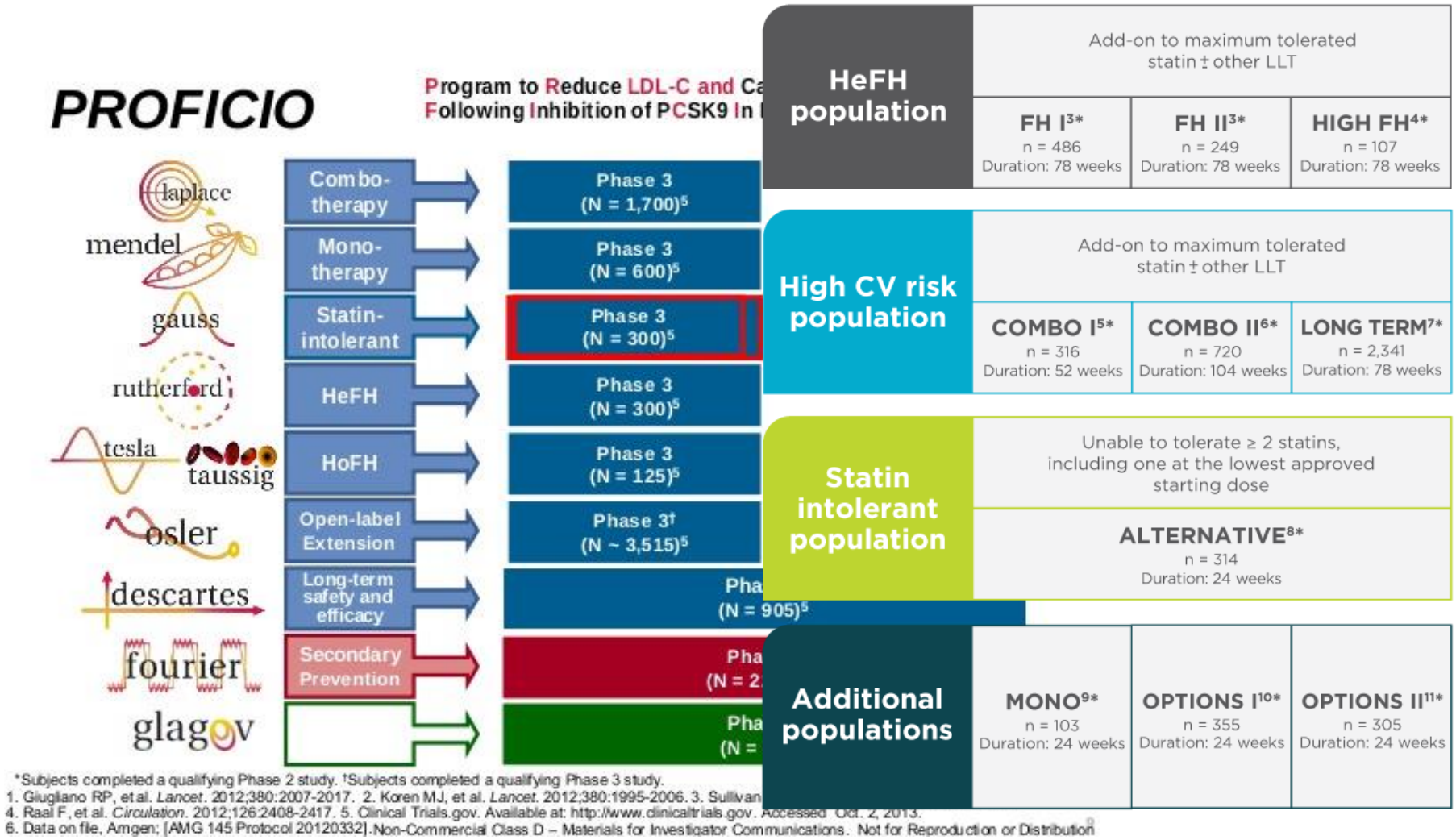
JAMA. 2014;311:1870-1882

PCSK9i: una storia di 10 anni



Journal of the American Heart Association. 2017;6:e006910

PCSK9i: una storia di 10 anni



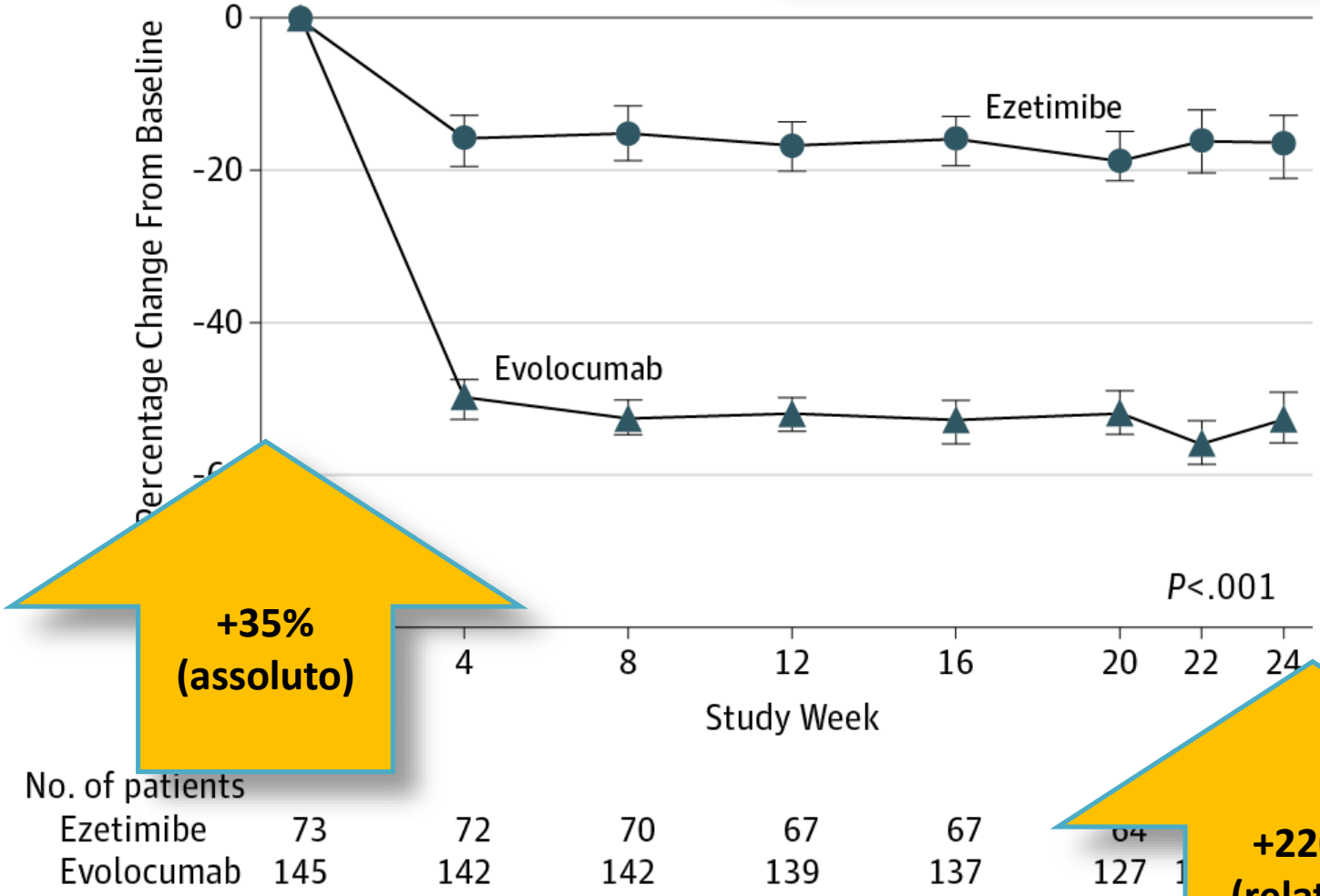
*Subjects completed a qualifying Phase 2 study. †Subjects completed a qualifying Phase 3 study.

1. Giugliano RP, et al. *Lancet*. 2012;380:2007-2017. 2. Koren MJ, et al. *Lancet*. 2012;380:1995-2006. 3. Sullivan
4. Raal F, et al. *Circulation*. 2012;126:2408-2417. 5. Clinical Trials.gov. Available at: http://www.clinicaltrials.gov. Accessed Oct. 2, 2013.
6. Data on file, Amgen; [AMG 145 Protocol 20120332].Non-Commercial Class D – Materials for Investigator Communications. Not for Reproduction or Distribution

Key points

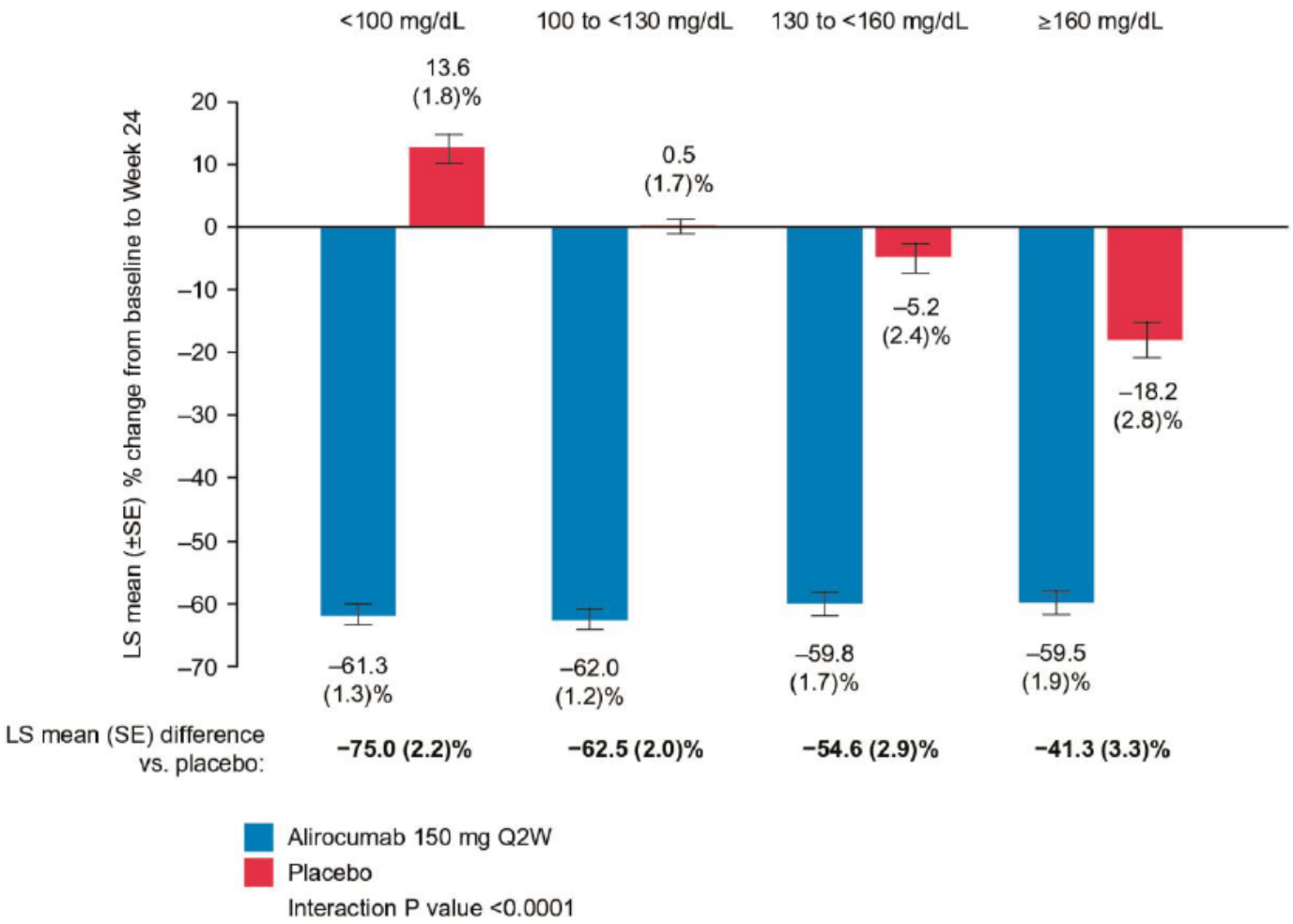
Riduzione colesterolemia vs ezetimibe

- efficaci in più di ezetimibe



JAMA. 2016;315(15):1580-1590

- risultato indipendente da valori LDL



N Engl J Med 2012;367:1891-900.

Risultati clinici: in aggiunta in soggetti trattati con atorva ma non a target

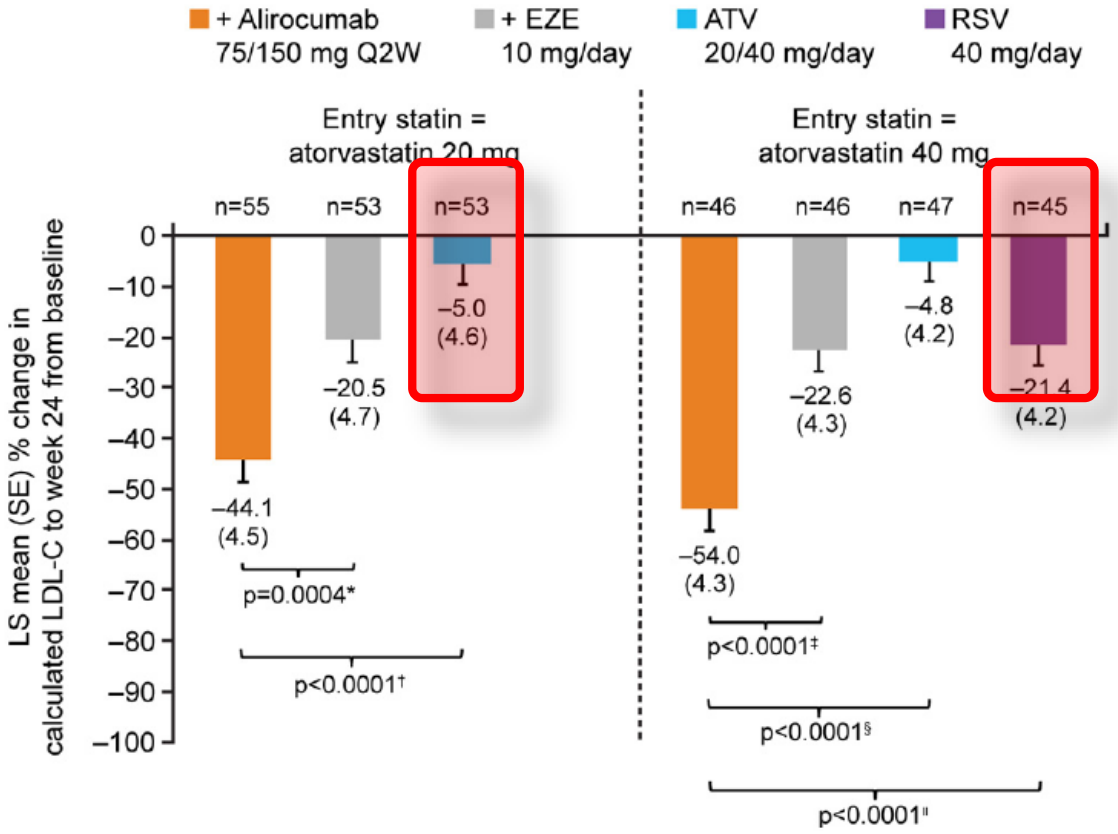
Alirocumab as Add-On to Atorvastatin Versus Other Lipid Treatment Strategies: ODYSSEY OPTIONS I Randomized Trial

Harold Bays, Daniel Gaudet, Robert Weiss, Juan Lima Ruiz, Gerald F. Watts, Ioanna Gouni-Berthold, Jennifer Robinson, Jian Zhao, Corinne Hanotin, and Stephen Donahue

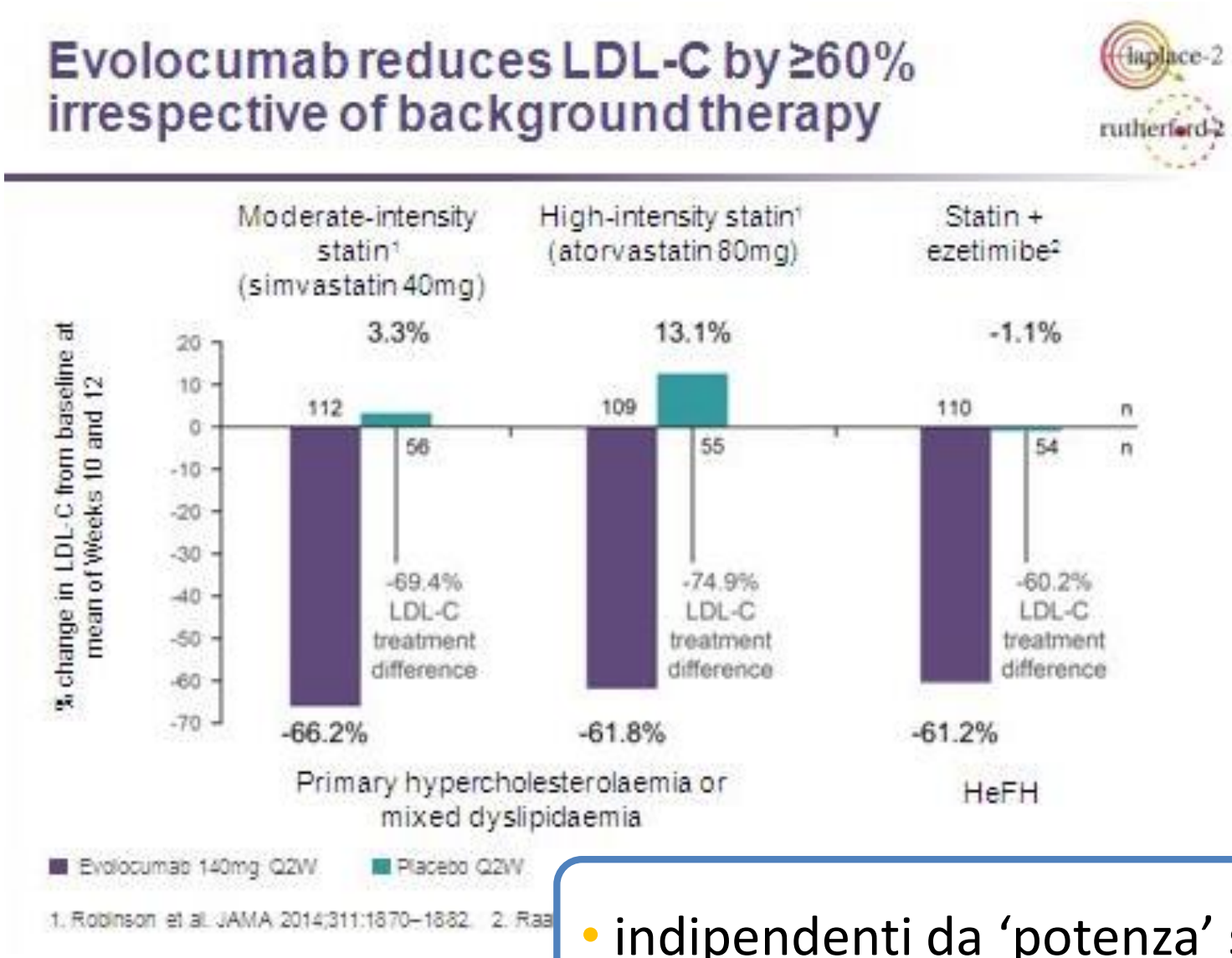
- meglio che titolare
- meglio che switch

+800% efficacia

-40% aggiuntivo



J Clin Endocrinol Metab 100: 3140–3148, 2015

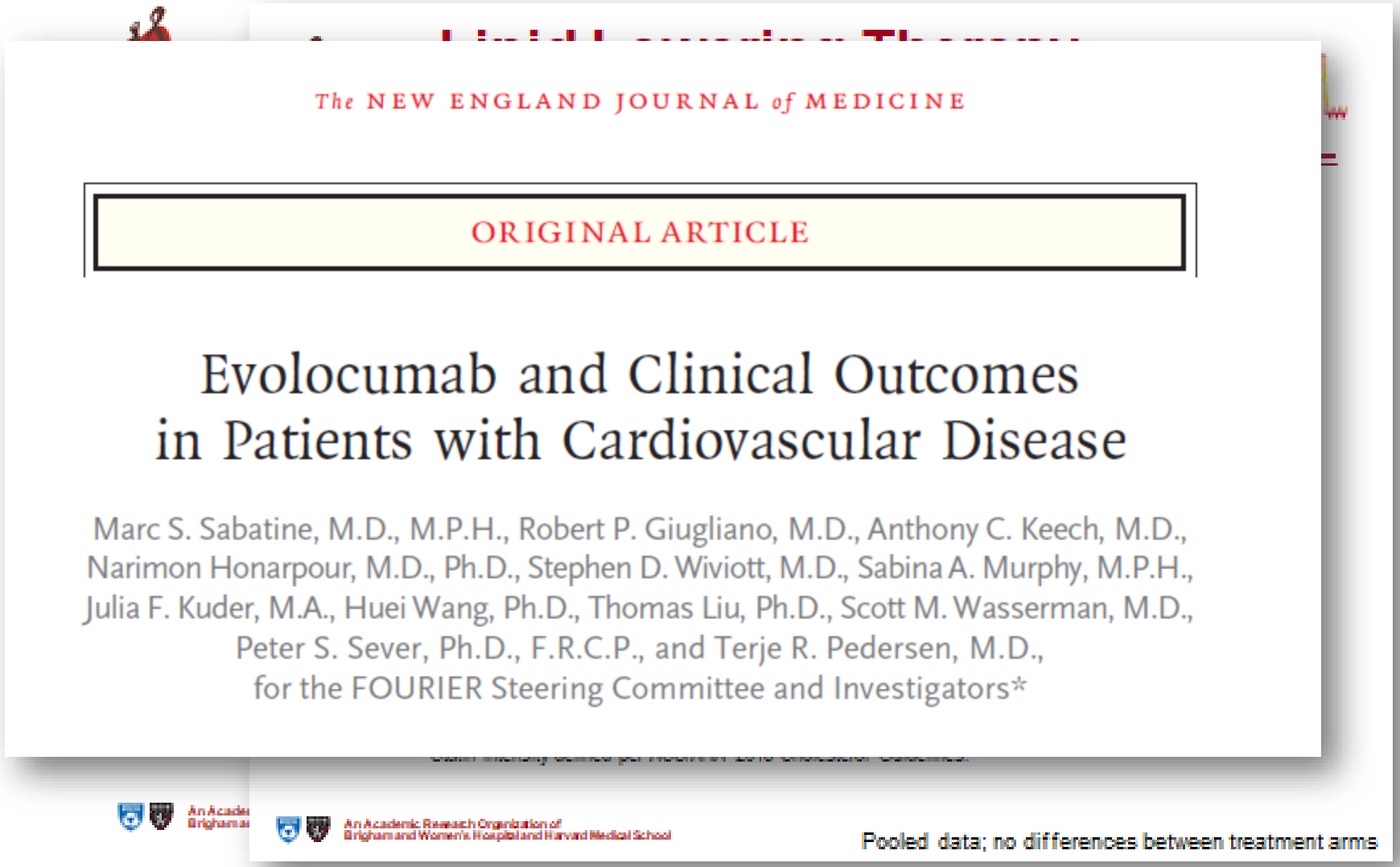


- indipendenti da ‘potenza’ statine

No data…

Studi su endpoints clinici

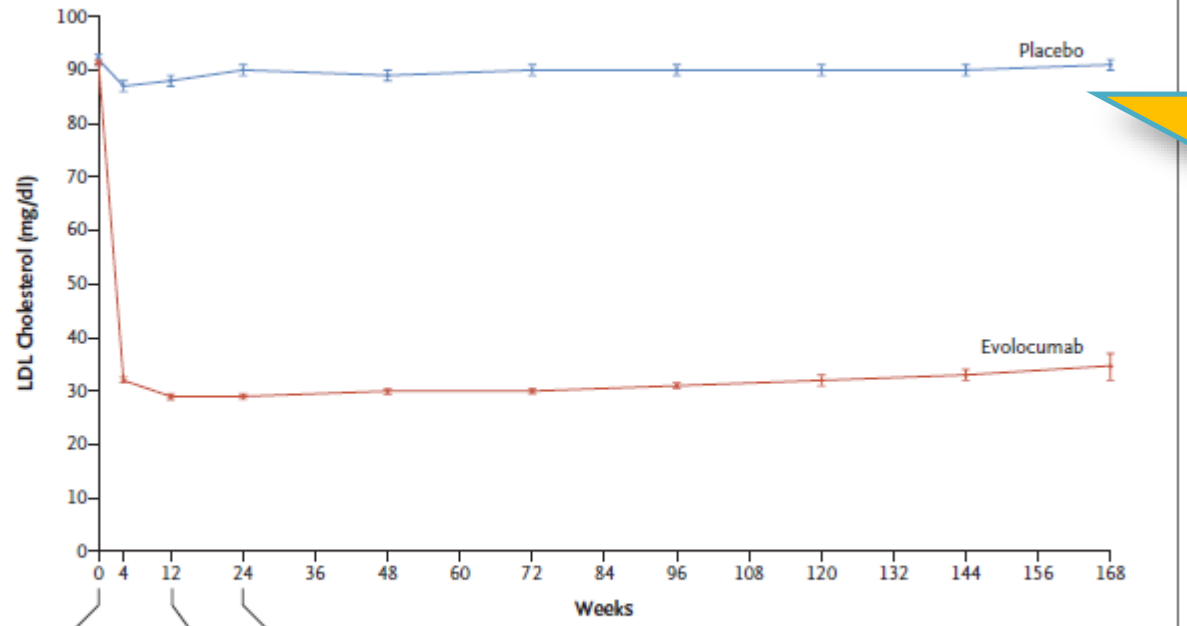
FOURIER study



N Engl J Med. 2017 May 4;376(18):1713-1722

Fourier: results

EVOLOCUMAB IN PATIENTS WITH CARDIOVASCULAR DISEASE



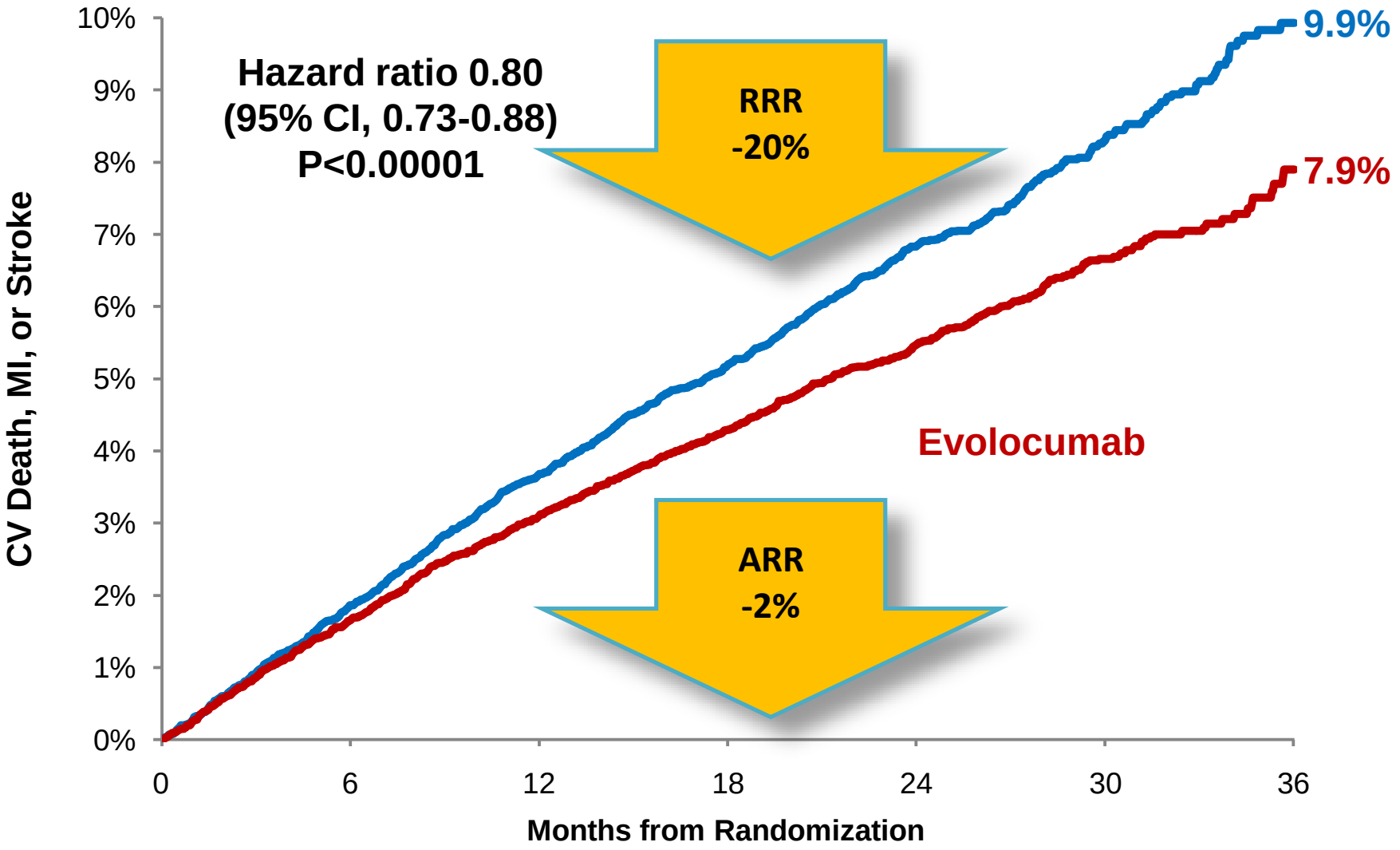
-60 mg/dl

No. at Risk										
Placebo	13,779	13,251	13,151	12,954	12,596	12,311	10,812	6926	3352	790
Evolocumab	13,784	13,288	13,144	12,964	12,645	12,359	10,902	6958	3323	768
Absolute difference (mg/dl)					56	55	54	52	53	50
Percentage difference					59	58	57	55	56	54
P value					0.001	<0.001	<0.001	<0.001	<0.001	<0.001

-66%

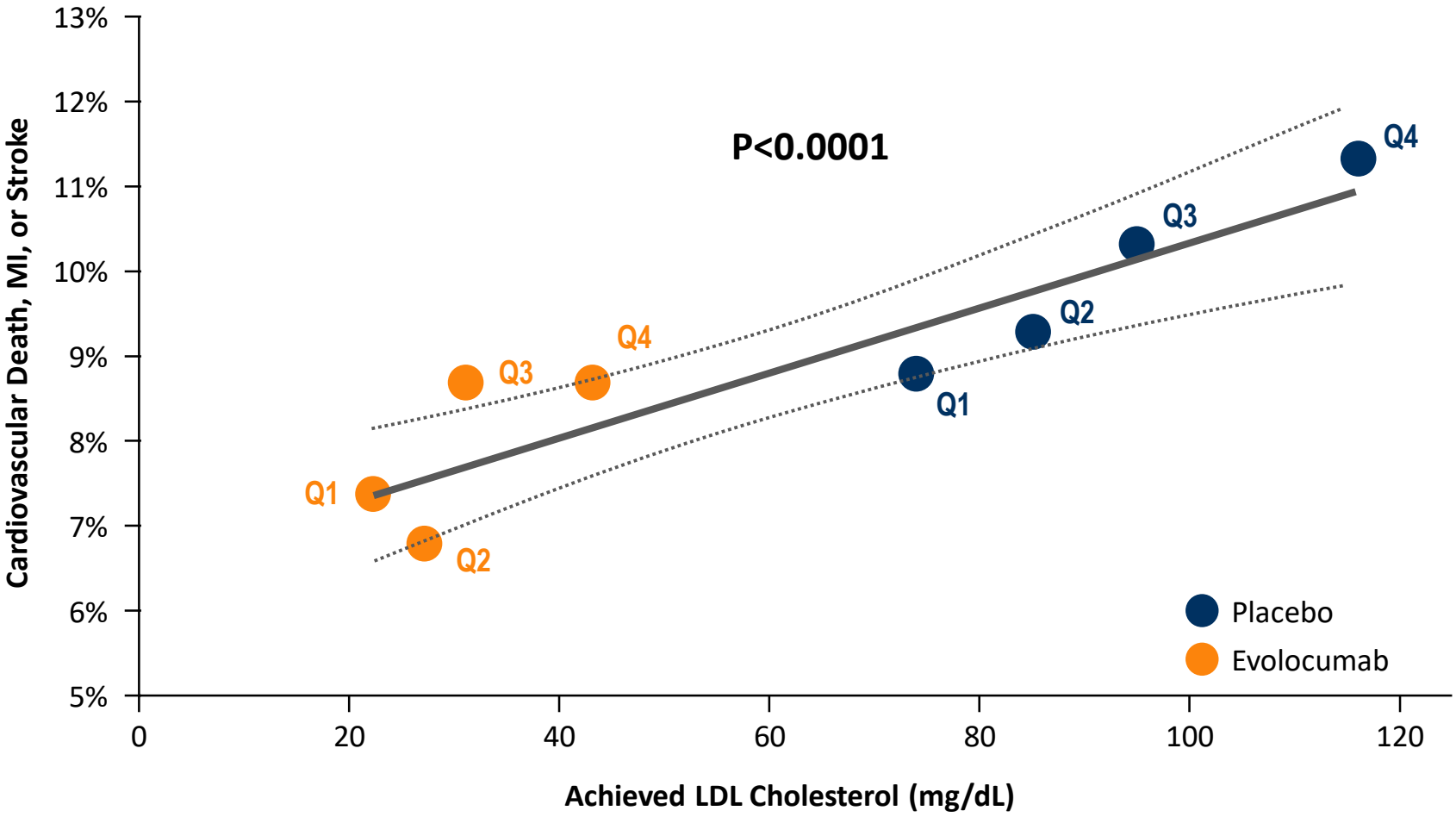
doi.org/10.1016/S0140-6736(17)32292-4

Key Secondary Endpoint



Fourier: results per quartiles

Patients divided by quartile of baseline LDL-C and by treatment arm



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

ODYSSEY OUTCOME: Inclusion criteria

- Age >40 years

The ODYSSEY OUTCOMES Trial: Topline Results

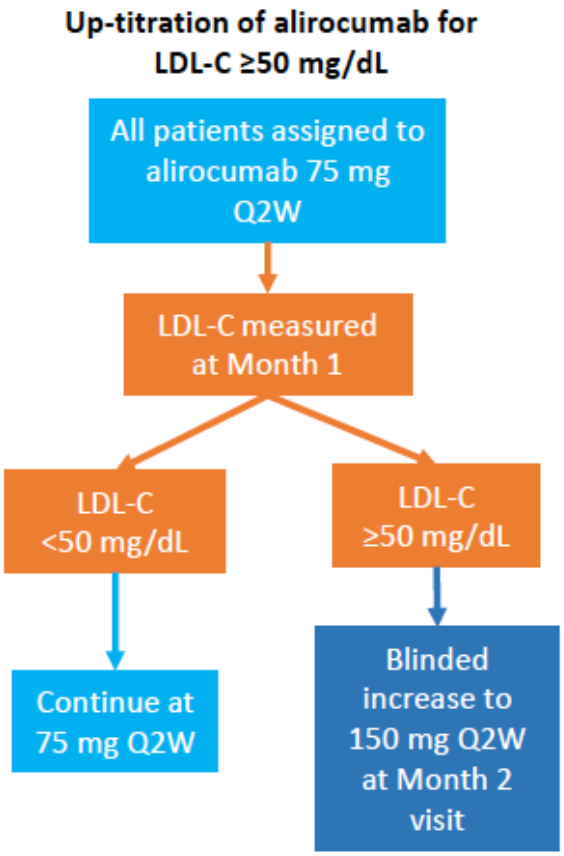
Alirocumab in Patients After Acute Coronary Syndrome

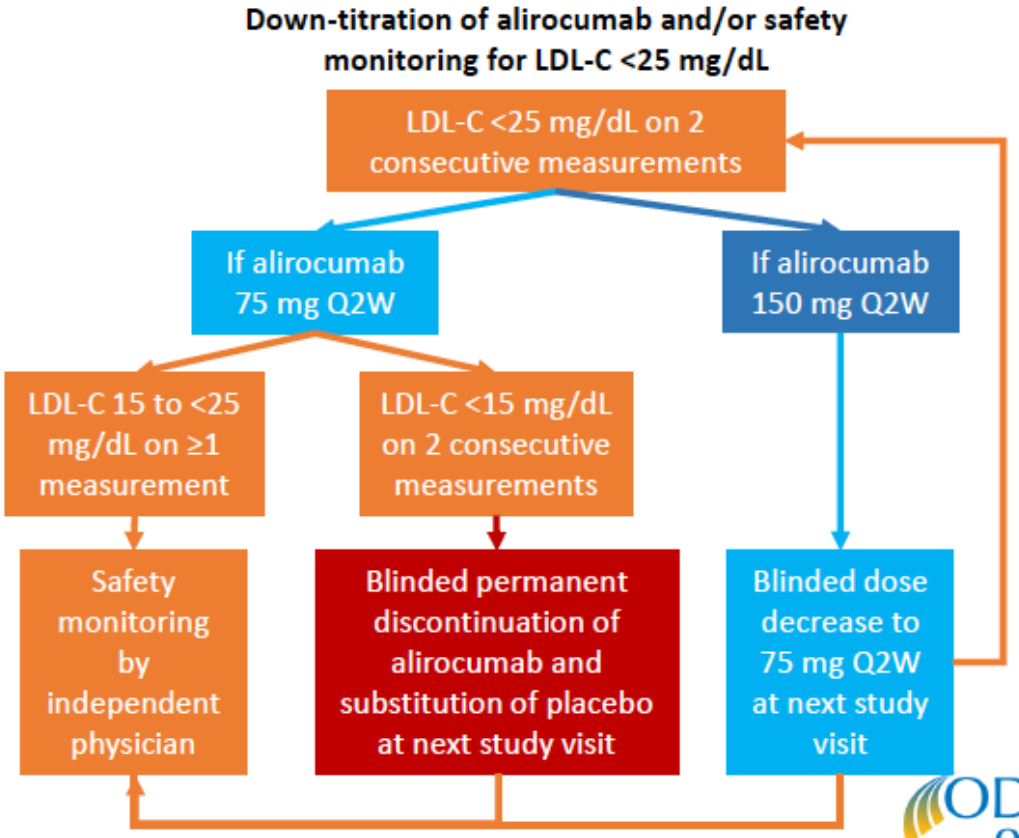
Gregory G. Schwartz, Michael Szarek, Deepak L. Bhatt, Vera Bittner, Rafael Diaz, Jay Edelberg,
Shaun G. Goodman, Corinne Hanotin, Robert Harrington, J. Wouter Jukema,
Guillaume Lecorps, Angèle Moryusef, Robert Pordy, Matthew Roe, Harvey D. White, Andreas Zeiher,
Ph. Gabriel Steg
On behalf of the ODYSSEY OUTCOMES Investigators and Committees

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

*Patients not on statins were authorized to participate if tolerability issues were present and documented
Schwartz GG, et al. Am Heart J 2014;168:682-689.e1.

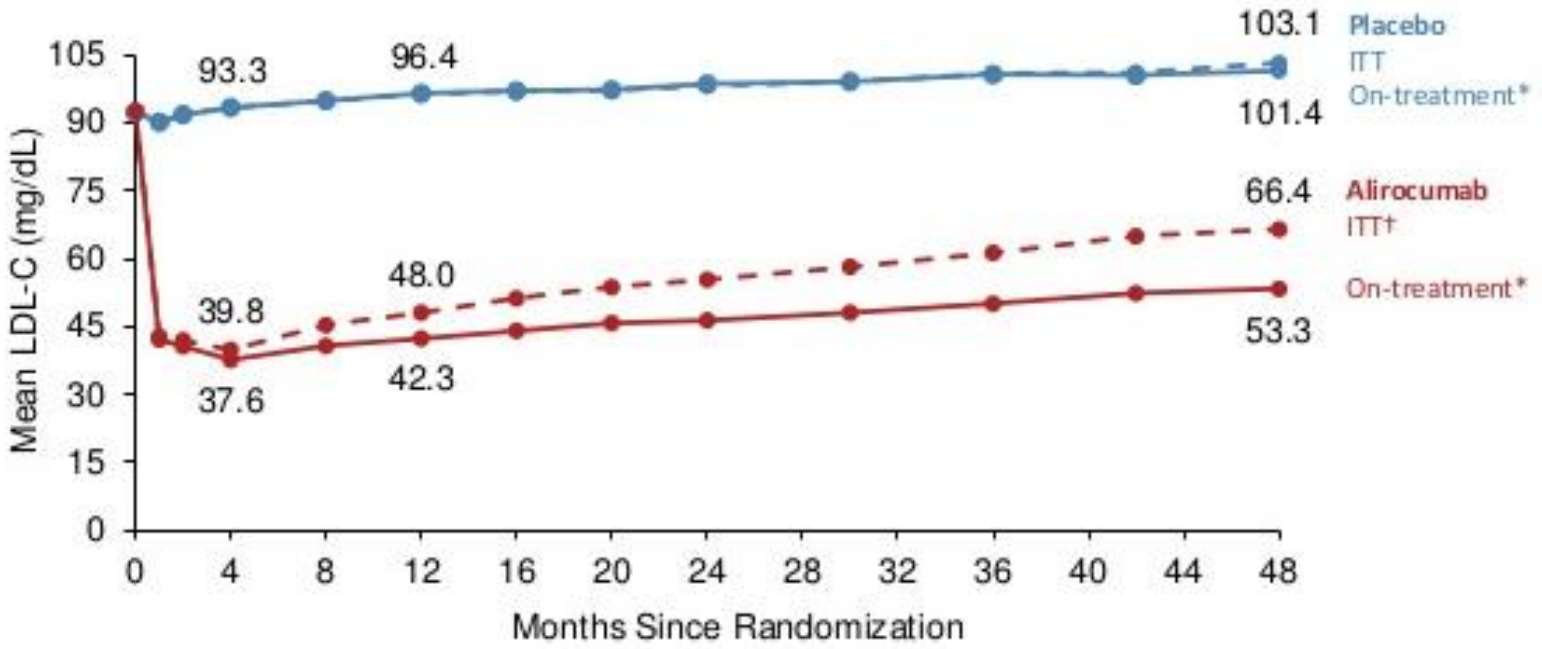
Blinded dose titration





ODYSSEY OUTCOMES

Odyssey outcome: livelli colesterolemia

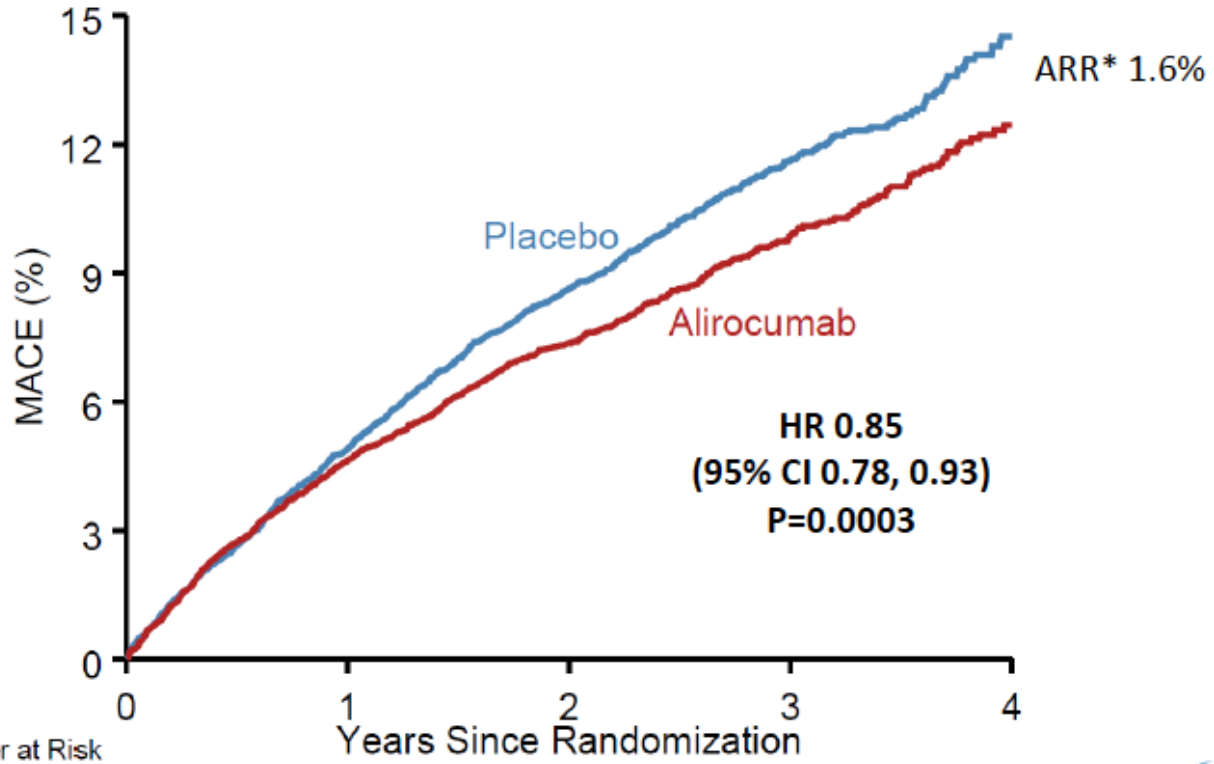


*Excludes LDL-C values after premature treatment discontinuation or blinded switch to placebo
†All LDL-C values, including those after premature treatment discontinuation, blinded down titration, or blinded switch to placebo

ODYSSEY OUTCOMES 28

Odyssey outcome: endpoint primario

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



Based on cumulative
cidence

RRR
-22%

ODYSSEY OUTCOMES

ODYSSEY OUTCOME: risultati

RRR -15%

Overall cohort						
Endpoint, n (%)	Alirocumab (N=9462)	Placebo (N=9462)	ARR	NNT	HR (95% CI)	Log-rank P-value
MACE	903 (9.5)	1052 (11.1)	1.6%	64	0.85 (0.78, 0.93)	0.0003
All-cause death	334 (3.5)	392 (4.1)	0.6%	163	0.85 (0.73, 0.98)	0.026*
Patients with baseline LDL-C ≥100 mg/dL						
Endpoint, n (%)	Alirocumab (N=2814)	Placebo (N=2815)	ARR	NNT	HR (95% CI)	
MACE	324 (11.5)	420 (14.9)	3.4%	29	0.76 (0.65–0.87)	
All-cause death	114 (4.1)	161 (5.7)	1.7%	60	0.71 (0.56–0.90)	

RRR -29%

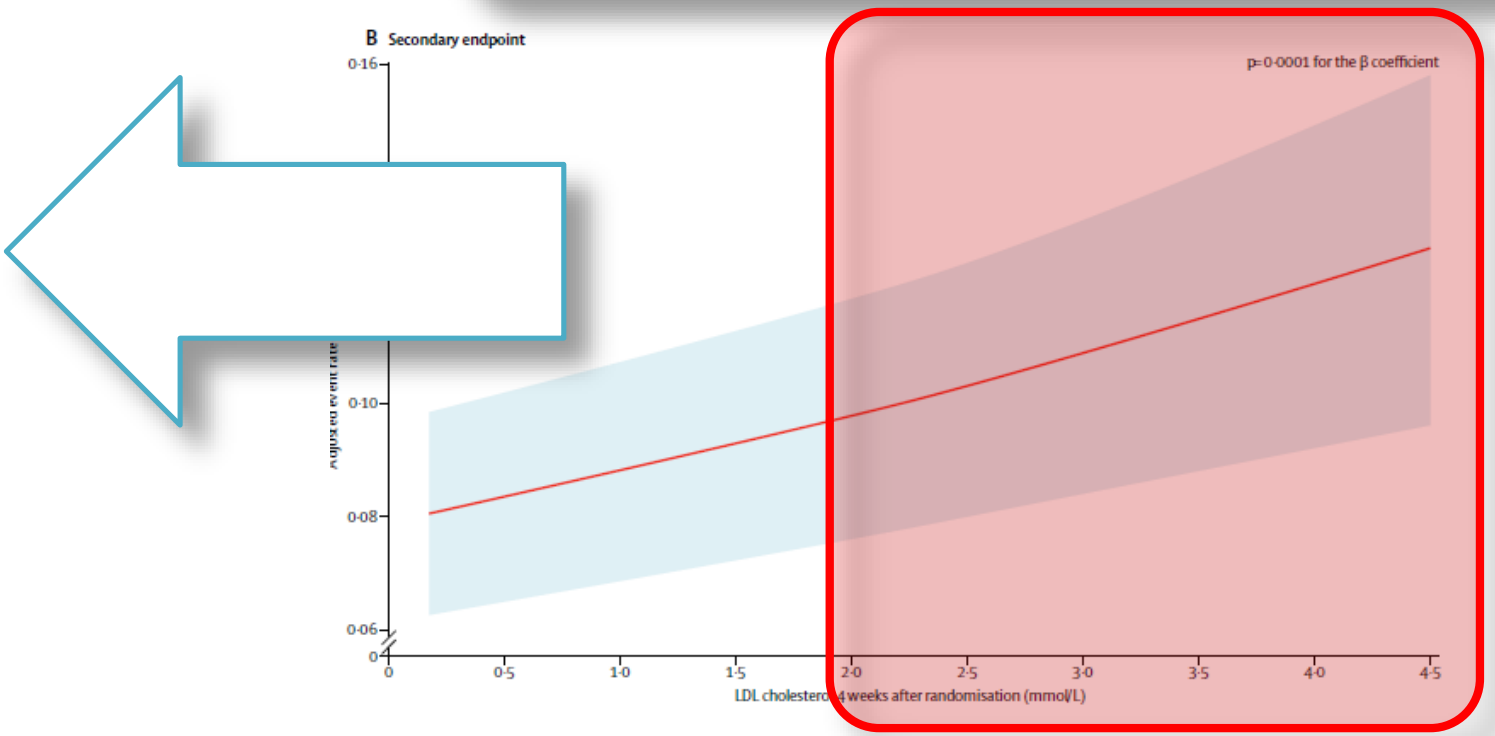
Key points

Retta, non curva…

Clinical efficacy and safety of ac
LDL-cholesterol concentrations
evolocumab: a prespecified sec
FOURIER trial

Robert P Giugliano, Terje R Pedersen, Jeong-Gun Park, Gaetano M De Ferrari, Z
Jose Lopez-Miranda, François Schiele, François Mach, Brian R Ott, Estella Kan
Anthony C Keech, Peter S Sever, Marc S Sabatine, on behalf of the FOURIER In

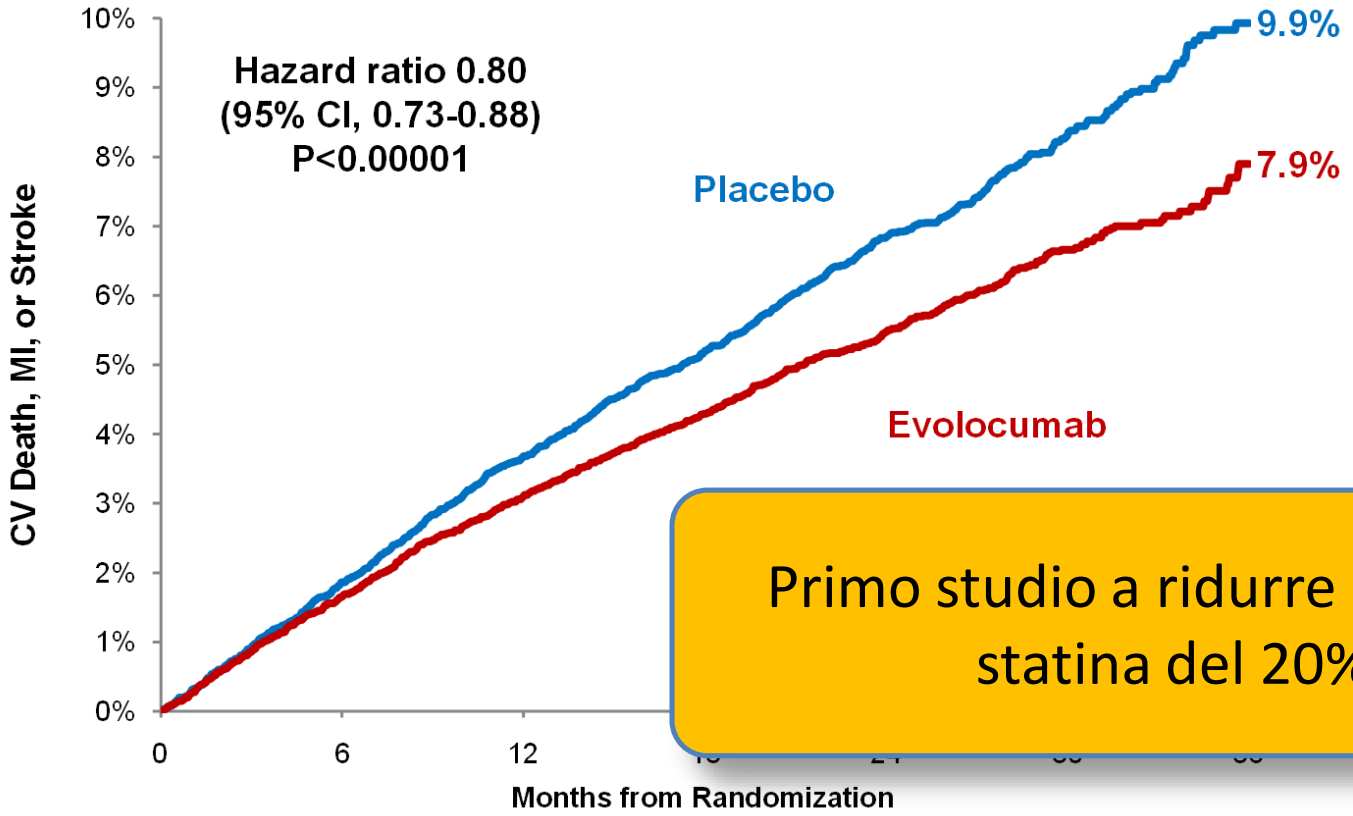
Primo studio a dimostrare riduzione lineare eventi anche sotto i vecchi target 70 (-50)mg/dl



doi.org/10.1016/S0140-6736(17)32292-4

20% RRR

Key Secondary Endpoint



An Academic Research Organization of
Brigham and Women's Hospital and Harvard Medical School

Primo studio a ridurre eventi vs statina del 20%

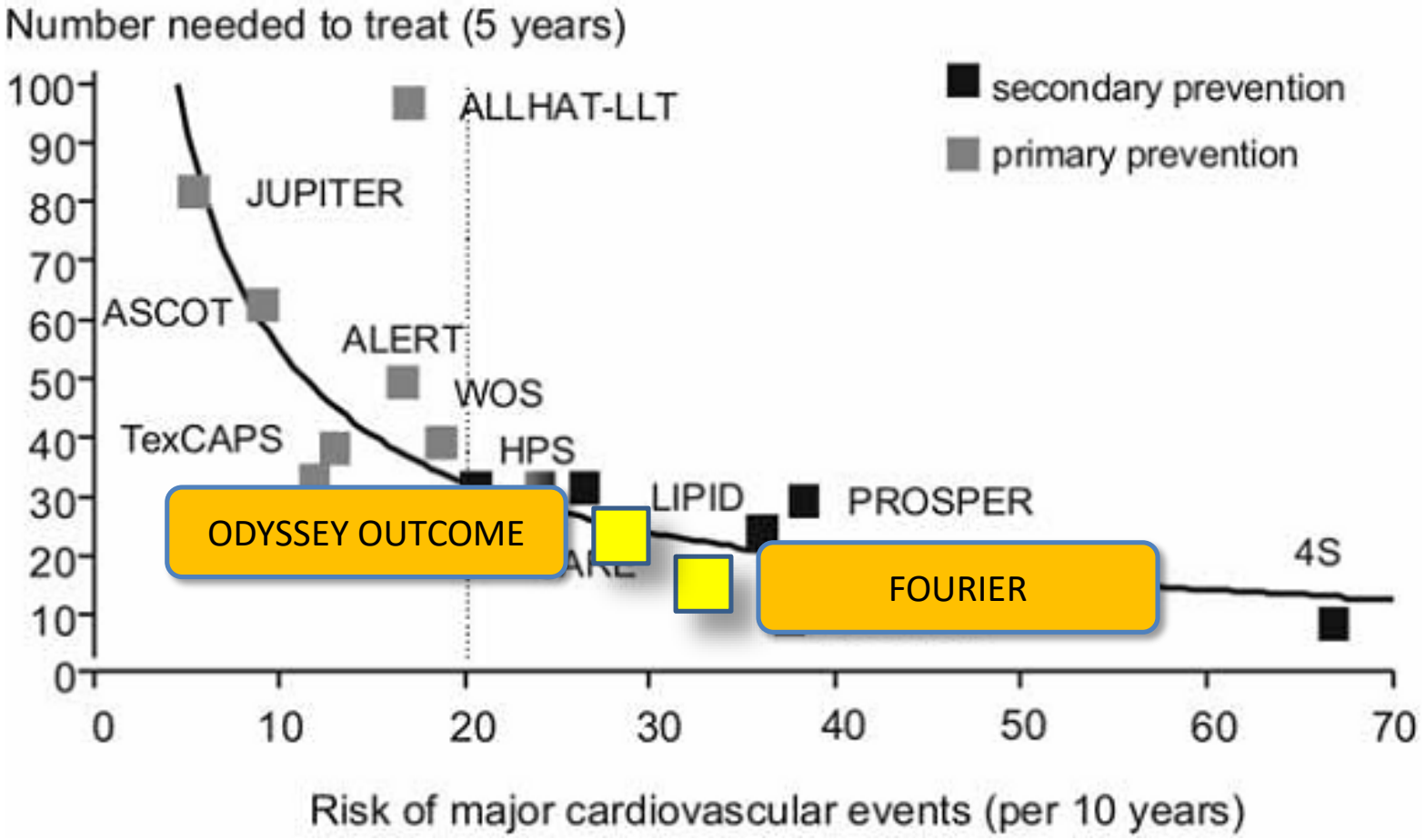
PCSK9i: risultati vs statine

15-30% RRR

Overall cohort						
Endpoint, n (%)	Alirocumab (N=9462)	Placebo (N=9462)	ARR	NNT	HR (95% CI)	Log-rank P-value
MACE	903 (9.5)	1052 (11.1)	1.6%	64	0.85 (0.78, 0.93)	0.0003
All-cause death	334 (3.5)	392 (4.1)	0.6%	163	0.85 (0.73, 0.98)	0.026*
Patients with baseline LDL-C ≥100 mg/dL						
Endpoint, n (%)	Alirocumab (N=2814)	Placebo (N=2815)	ARR	NNT	HR (95% CI)	
MACE	324 (11.5)	420 (14.9)	3.4%	29	0.76 (0.65–0.87)	
All-cause death	114 (4.1)	161 (5.7)	1.7%	60	0.71 (0.56–0.90)	

Primo studio a ridurre mortalità vs statina

Number needed to treat nei principali studi sulle statine



Int J Clin Pharmacol Ther 49: 293- 296.

Grande confusione…

Il 'padre' delle linee guida americane, del FIRE & FORGET

He also noted that this was a relatively short-term trial, "so this event reduction was seen relatively quickly, which I think is important. We also saw benefit with incremental LDL reduction, all the way down into the 20s and 30s. And frankly, that blows up the ACC/AHA prevention guidelines."

"In 2013, the guidelines were based on dosing of therapeutics and not based so much on level of LDL. But there's a lot of new science, including this trial, that's been published since then. And there are deliberations going on right now about updates," reported Chazal.

"If these drugs were inexpensive, I think they would be used by almost everybody. But because they are expensive, most clinicians are going to be selective. We're going to take the higher-risk patients and treat them," said Nissen.

More discussion on the medication's high cost continued at an afternoon press conference. "This is very expensive, and we can't say everybody will take it now. Instead, we need to be very cautious, and we have to be sure that we identify the right people for treatment," said Fuster.

The risk reduction at 2 years translated to a number needed to treat (NNT) of 74 to prevent a CV death, MI, or stroke. At 3 years, the NNT was about 50, reported Sabatine.

Dr Steven Nissen

Documenti USA

JOURNAL OF THE AM
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AMERICAN COLLEGE

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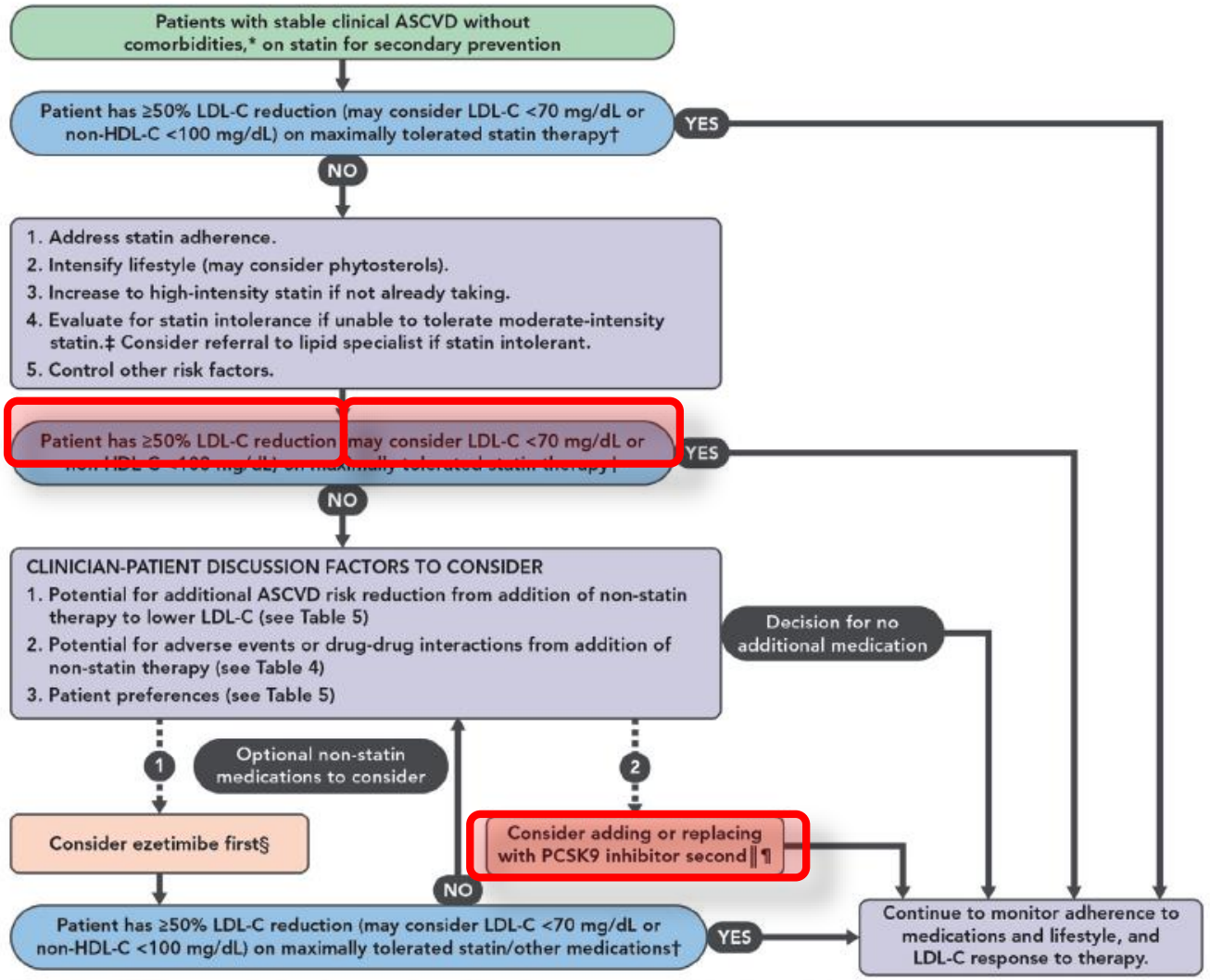
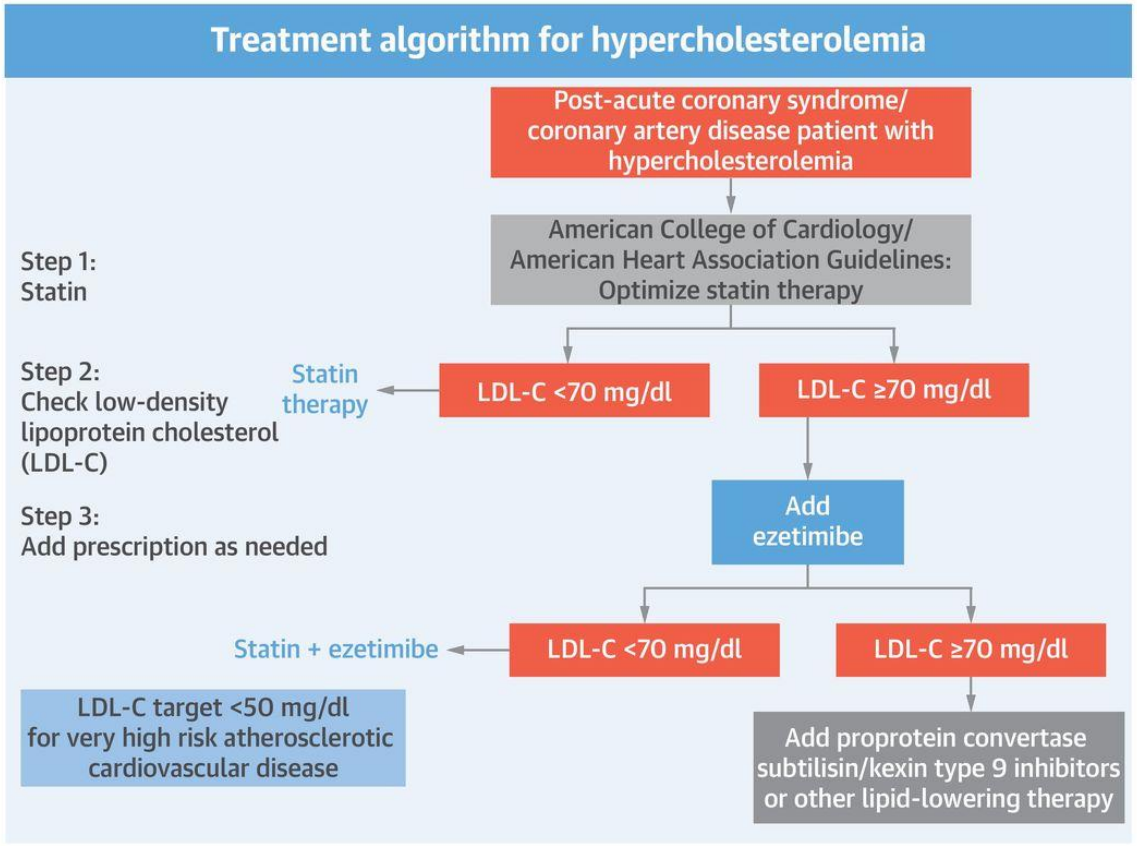
Endorsed by the N

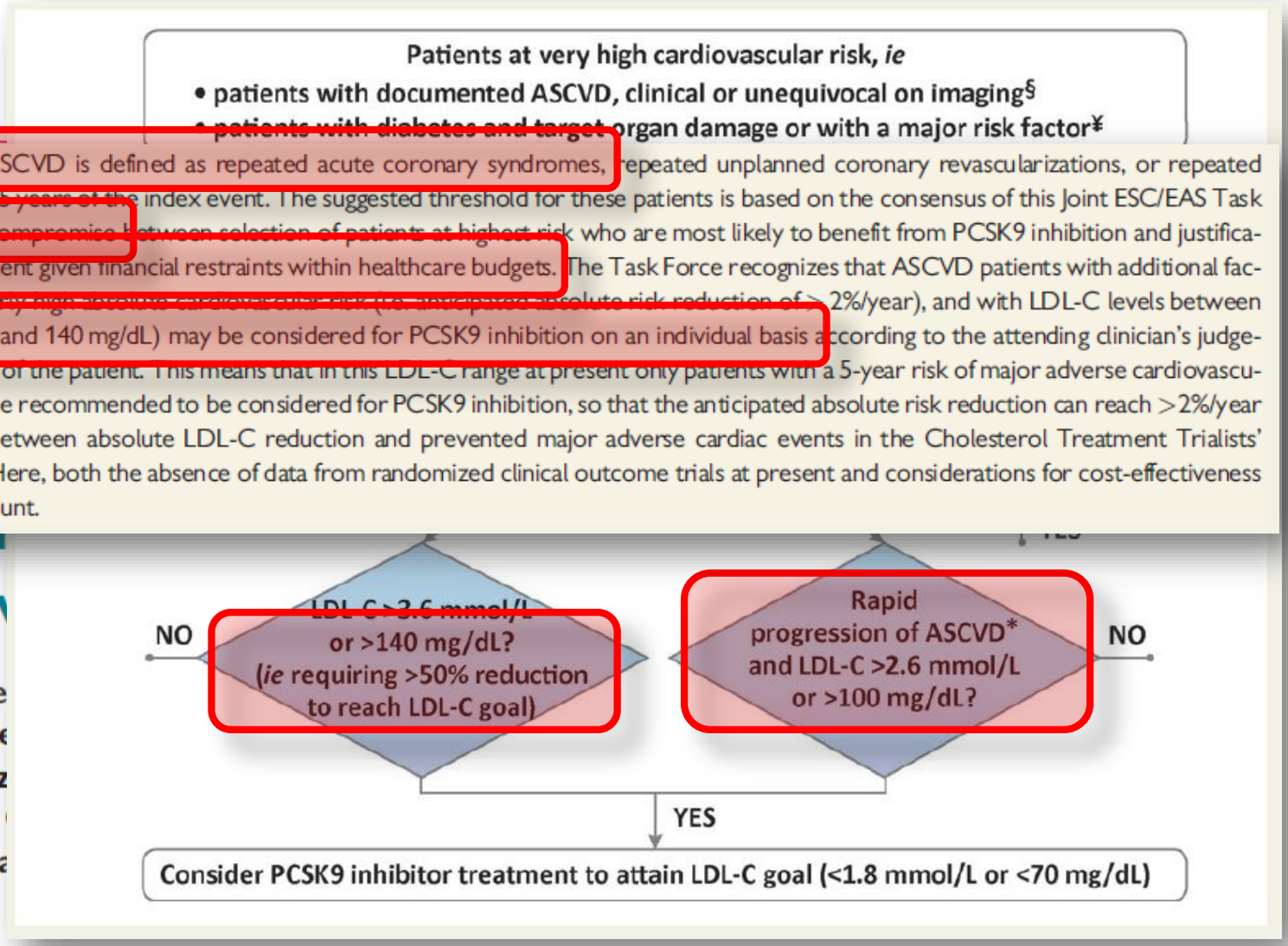
FIGURE 2A Patients ≥21 Years of Age with Stable Clinical ASCVD without Comorbidities, on Statin for Secondary Prevention



CENTRAL ILLUSTRATION: Clinical Algorithm for Managing Low-Density Lipoprotein Cholesterol



Rosenson, R.S. et al. J Am Coll Cardiol. 2018;72(3):314-29.


Patients at very high cardiovascular risk, *ie*
• patients with documented ASCVD, clinical or unequivocal on imaging§
• patients with diabetes and target organ damage or with a major risk factor¥
*Rapid progression of ASCVD is defined as repeated acute coronary syndromes, repeated unplanned coronary revascularizations, or repeated ischaemic strokes within 5 years of the index event. The suggested threshold for these patients is based on the consensus of this Joint ESC/EAS Task Force and represents a compromise between selection of patients at highest risk who are most likely to benefit from PCSK9 inhibition and justification of the cost of treatment given financial restraints within healthcare budgets. The Task Force recognizes that ASCVD patients with additional factors indicating a particularly high absolute cardiovascular risk (i.e. anticipated absolute risk reduction of >2%/year), and with LDL-C levels between 2.6 and 3.4 mmol/L (100 and 140 mg/dL) may be considered for PCSK9 inhibition on an individual basis according to the attending clinician's judgement of the absolute risk of the patient. This means that in this LDL-C range at present only patients with a 5-year risk of major adverse cardiovascular events >20% would be recommended to be considered for PCSK9 inhibition, so that the anticipated absolute risk reduction can reach >2%/year (based on the relation between absolute LDL-C reduction and prevented major adverse cardiac events in the Cholesterol Treatment Trialists' Collaboration analysis). Here, both the absence of data from randomized clinical outcome trials at present and considerations for cost-effectiveness had to be taken into account.
NO
LDL-C >3.6 mmol/L or >140 mg/dL? (*ie* requiring >50% reduction to reach LDL-C goal)
Rapid progression of ASCVD* and LDL-C >2.6 mmol/L or >100 mg/dL?
NO
YES
Consider PCSK9 inhibitor treatment to attain LDL-C goal (<1.8 mmol/L or <70 mg/dL)

Timing prescrittivo

IMA

Statina alta intensità (16 w)

Ezetimibe (2 m)

PCSK9i

Almeno 100 LDL

6 mesi

9-12 mesi

Am J Cardiol 2006;97:155–159

Lipid levels in patients hospitalized with coronary artery dis in Get Wi

Amit Sachdeva, MD,
Sidney C. Smith, Jr,
GWTG Steering Com
Chapel Hill and Du

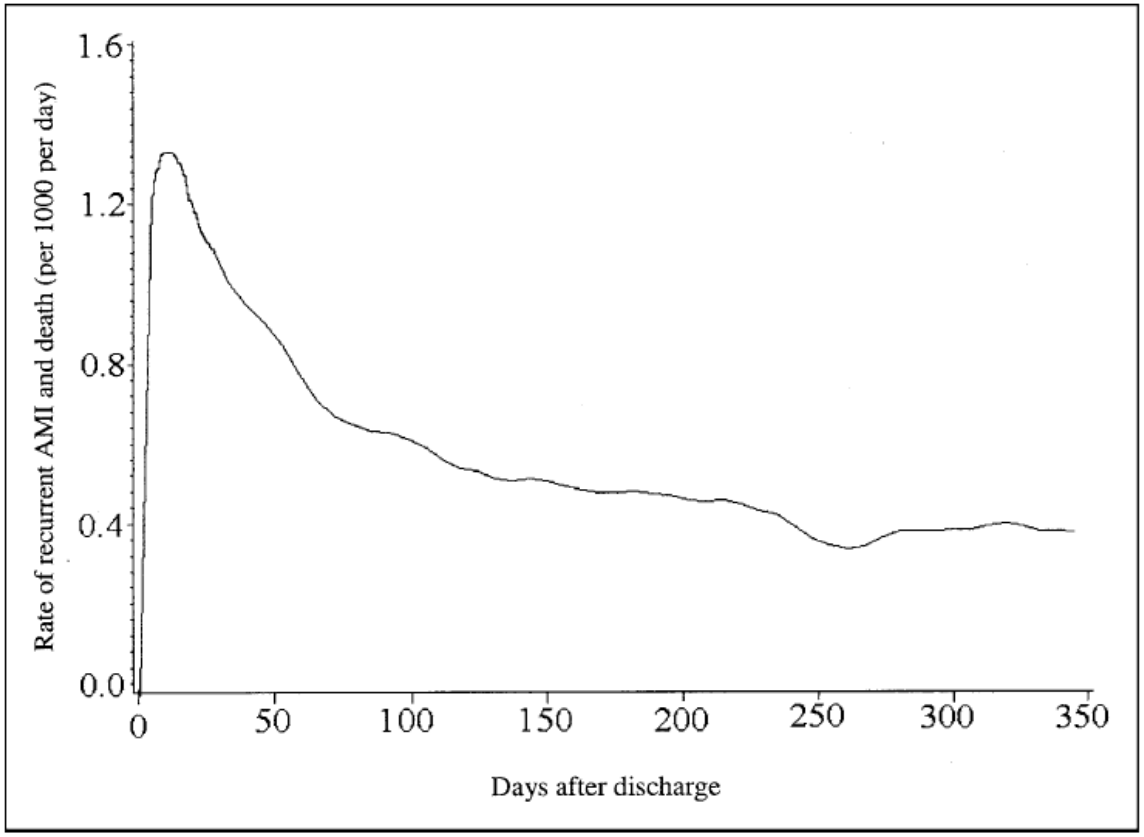


Figure 2. Rate of recurrent AMI or death during 1 year after hospital discharge (Quebec, Canada, 1996 to 2000).

0%

Am Heart J 2009;157:111-7.e2

Nuove linee guida ESC

ESC
European Society of Cardiology

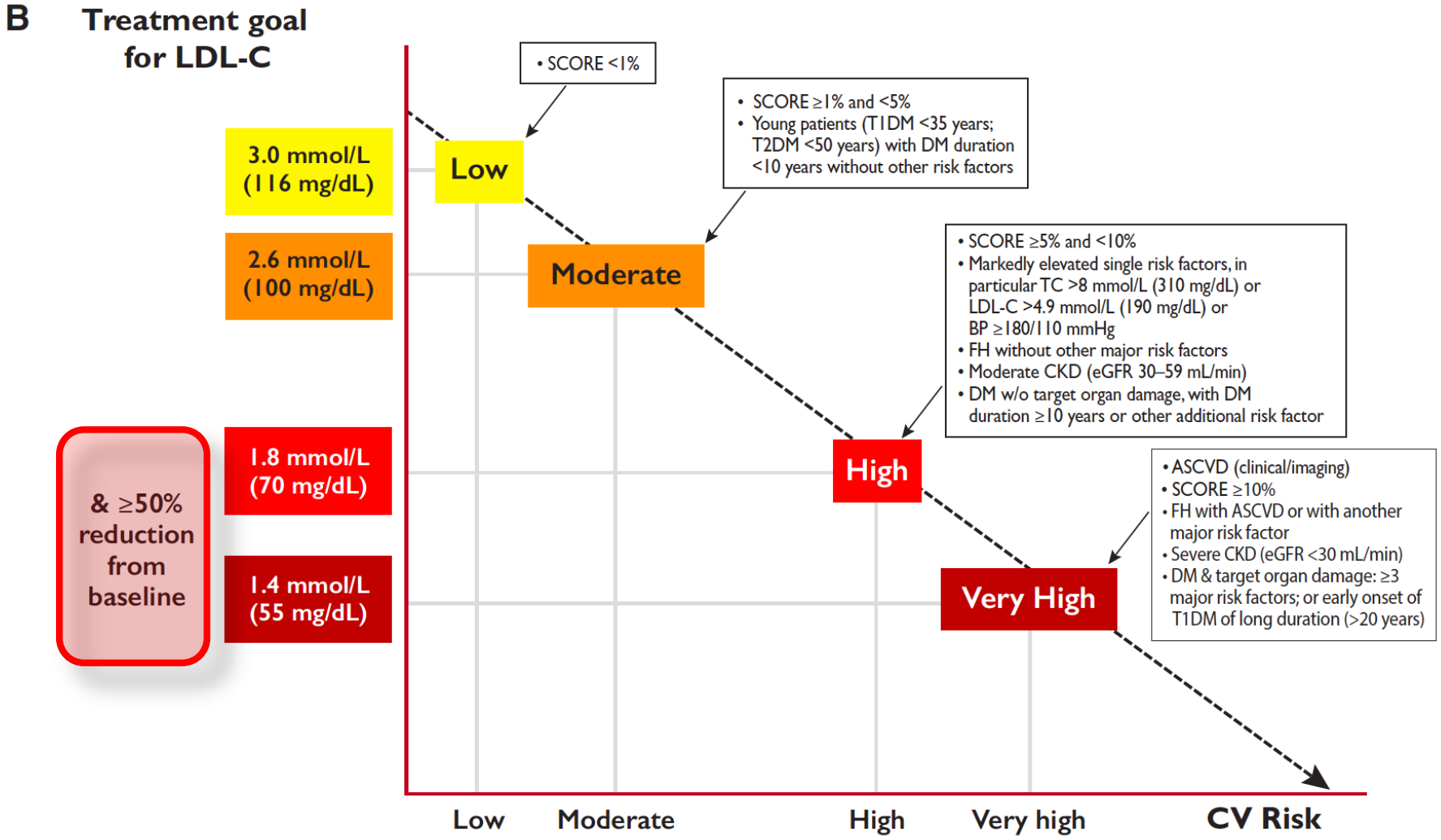
European Heart Journal (2019) **00**, 1–78
doi:10.1093/eurheartj/ehz455

ESC/EAS GUIDELINES

2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce cardiovascular risk*

The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)

Nuovi target



Nuovo timing

Recommendations for lipid-lowering therapy in very-high-risk patients with acute coronary syndromes

Recommendations	Class[a]	Level[b]
In all ACS patients without any contraindication or definite history of intolerance, it is recommended that high-dose statin therapy is initiated or continued as early as possible, regardless of initial LDL-C values.[438,440,442]	I	A
Lipid levels should be re-evaluated 4–6 weeks after ACS to determine whether a reduction of ≥50% from baseline and goal levels of LDL-C <1.4 mmol/L (<55 mg/dL) have been achieved. Safety issues need to be assessed at this time and statin treatment doses adapted accordingly.	IIa	C
If the LDL-C goal is not achieved after 4–6 weeks with the maximally tolerated statin dose, combination with ezetimibe is recommended.[33]	I	B
If the LDL-C goal is not achieved after 4–6 weeks despite maximal tolerated statin therapy and ezetimibe, the addition of a PCSK9 inhibitor is recommended.[119,120]	I	B
In patients with confirmed statin intolerance or in patients in whom a statin is contraindicated, ezetimibe should be considered.	IIa	C

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Journal of the American College of Cardiology
August 2019
DOI: 10.1016/j.jacc.2019.08.010

PDF Article

ORIGINAL INVESTIGATIONS

Just Accepted

Evolocumab for Early Reduction of LDL-Cholesterol Levels in Patients with Acute Coronary Syndromes (EVOPACS)

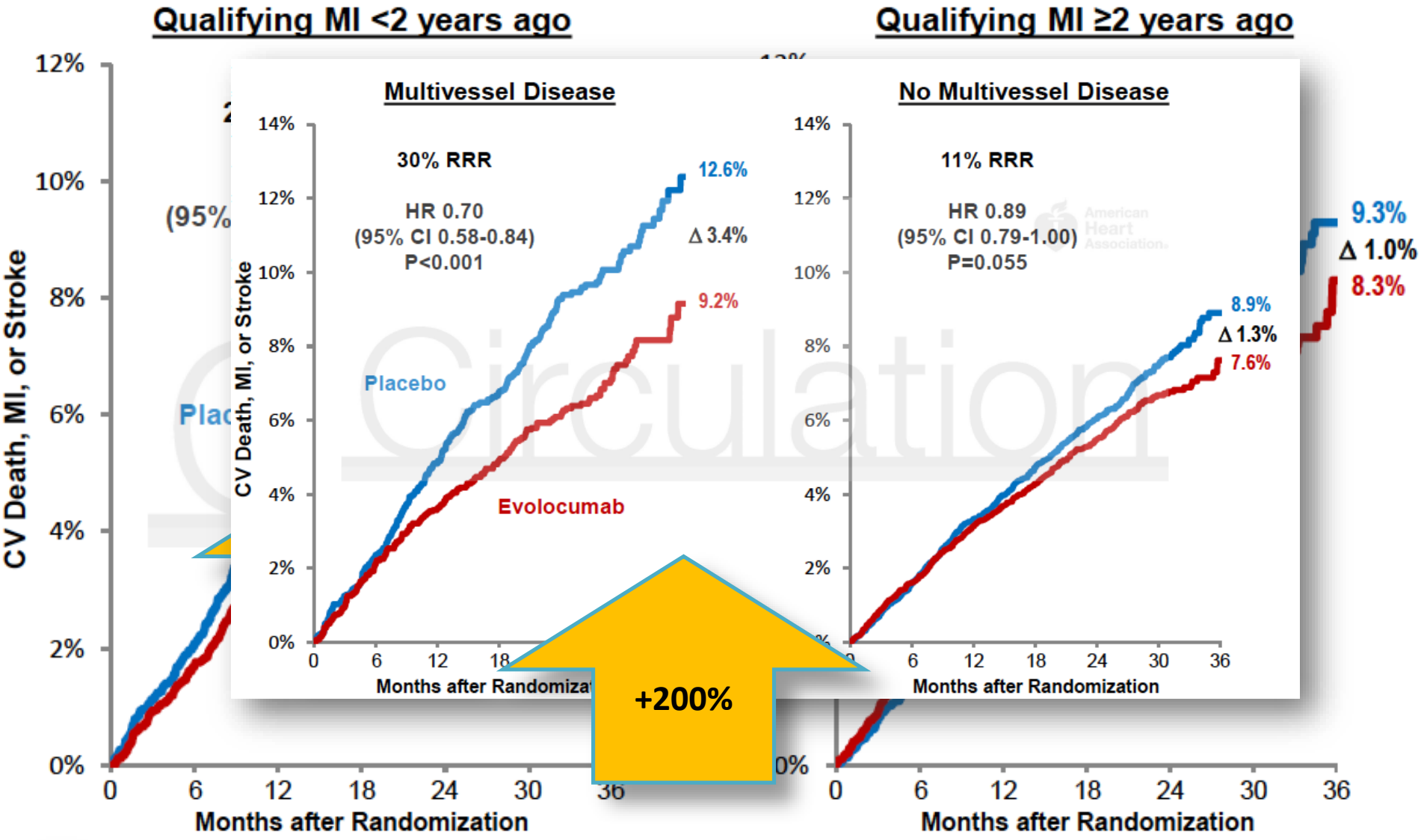
Konstantinos C. Koskinas, Stephan Windecker, Giovanni Pedrazzini, Christian Mueller, Stéphane Cook, Christian M. Matter, Olivier Muller, Jonas Häner, Baris Gencer, Carmela Crljenica, Poorya Amini, Olga Deckarm, Juan F. Iglesias, Lorenz Räber, Dik Heg and François Mach

Very very high risk patients

Recommendations for treatment goals for low-density lipoprotein cholesterol

Recommendations	Class[a]	Level[b]
In secondary prevention for patients at very-high risk,[c] an LDL-C reduction of ≥50% from baseline[d] and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) are recommended.[33–35,119,120]	I	A
In primary prevention for individuals at very-high risk but without FH,[c] an LDL-C reduction of ≥50% from baseline[d] and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) are recommended.[34–36]	I	C
In primary prevention for individuals with FH at very-high risk, an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) should be considered.	IIa	C
For patients with ASCVD who experience a second vascular event within 2 years (not necessarily of the same type as the first event) while taking maximally tolerated statin-based therapy, an LDL-C goal of <1.0 mmol/L (<40 mg/dL) may be considered.[119,120]	IIb	B
In patients at high risk,[c] an LDL-C reduction of ≥50% from baseline[d] and an LDL-C goal of <1.8 mmol/L (<70 mg/dL) are recommended.[34,35]	I	A
In individuals at moderate risk,[c] an LDL-C goal of <2.6 mmol/L (<100 mg/dL) should be considered.[34]	IIa	A
In individuals at low risk,[c] an LDL-C goal <3.0 mmol/L (<116 mg/dL) may be considered.[36]	IIb	A

Sottoanalisi Fourier: come identificare i pazienti con maggior beneficio



Terapia ipocolesterolemizzante: soggetti a target

- 17.000 pz
- Registro SWEDHEART

LDL <70 mg/dl
30%

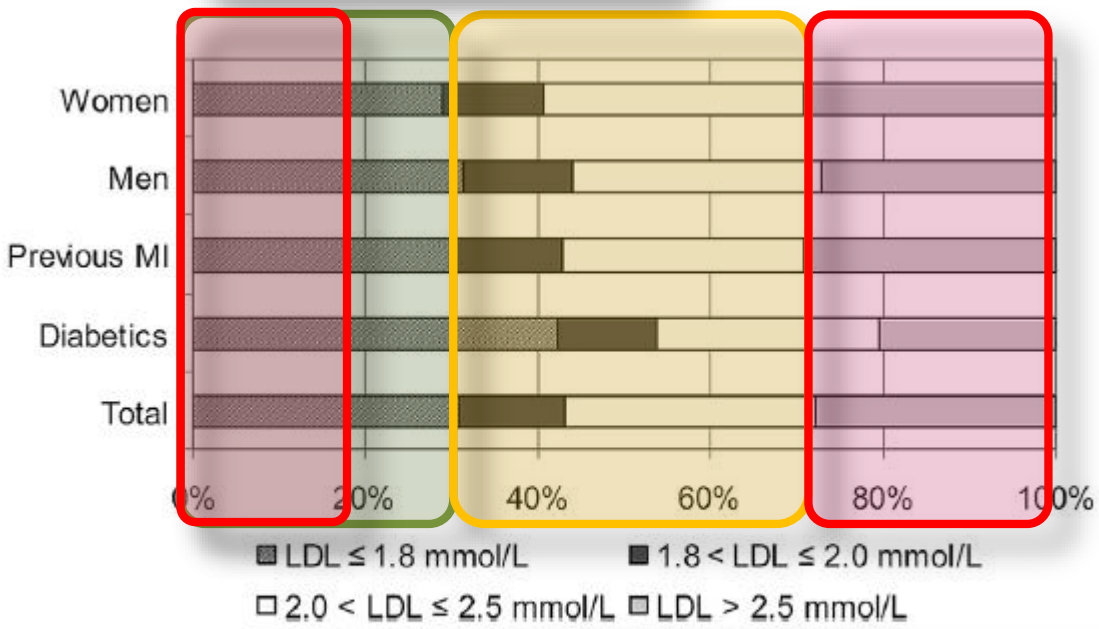


Figure 3. Frequency of LDL-C
MI, myocardial infarction.

LDL >120 mg/dl
30%

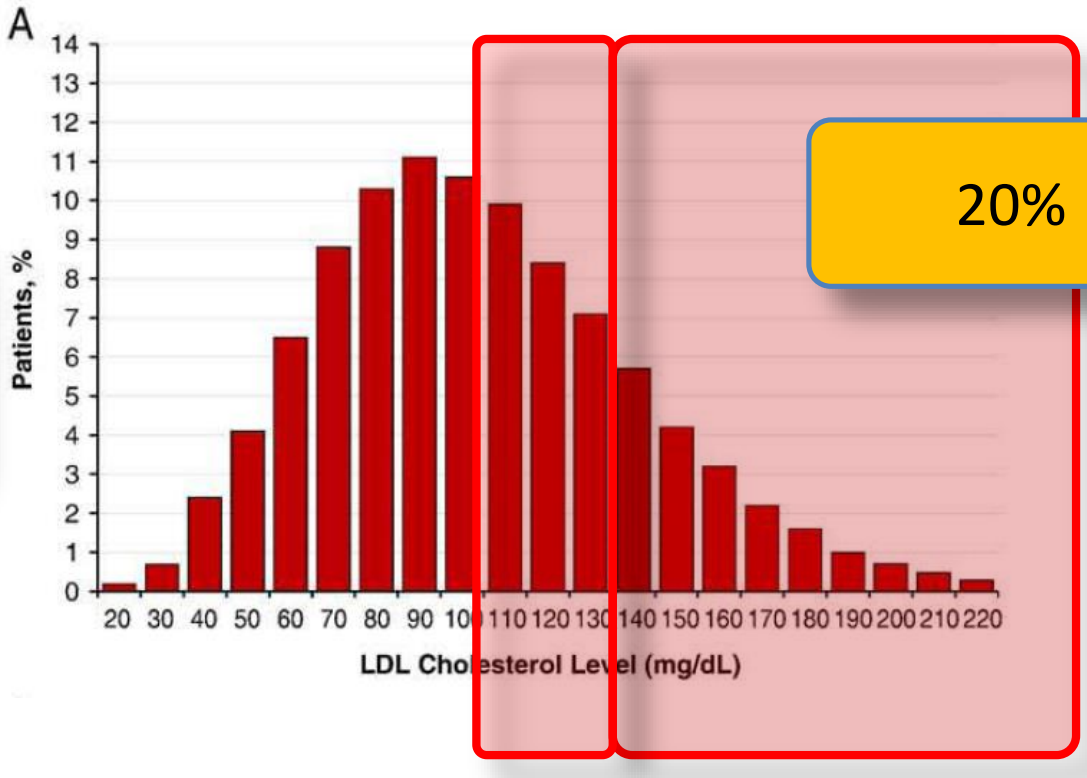
LDL 70- 120mg/dl
40%

Am J Cardiol 2014;113:17e22

Lipid levels in patients hospitalized with coronary artery disease: An analysis of 136,905 hospitalizations in Get With The Guidelines

Amit Sachdeva, MD,[a] Christopher P. Cannon, MD,[b] Prakash C. Deedwania, MD,[c] Kenneth A. LaBresh, MD,[d] Sidney C. Smith, Jr, MD,[e] David Dai, MS,[f] Adrian Hernandez, MD,[f] and Gregg C. Fonarow, MD [a] on behalf of the GWTG Steering Committee and Hospitals *Los Angeles and San Francisco, CA; Boston and Waltham, MA; and Chapel Hill and Durham, NC*

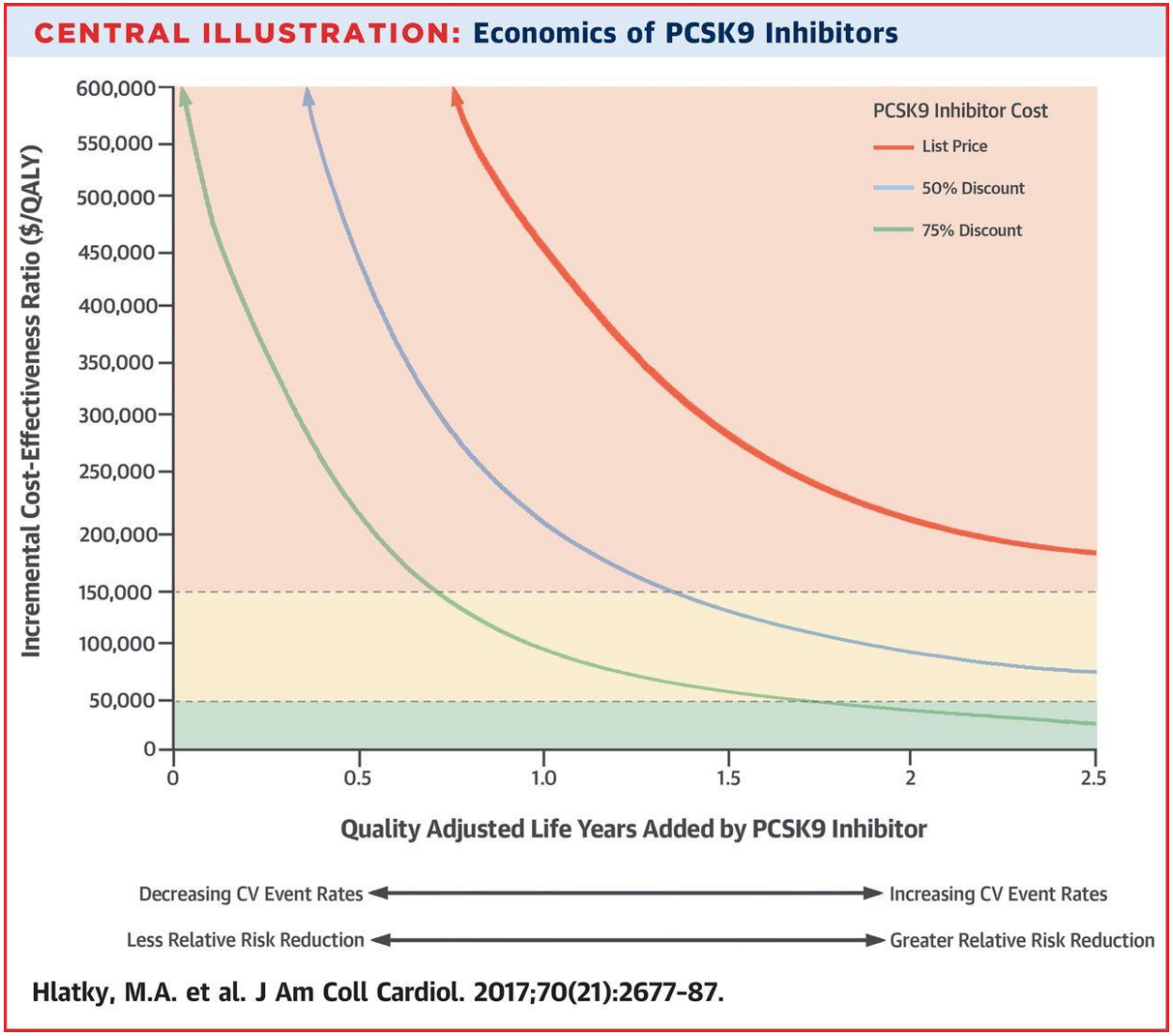
+25%
=45%



20%

Open Heart. 2019 Jul 29;6(2):e001018

Analisi dei costi



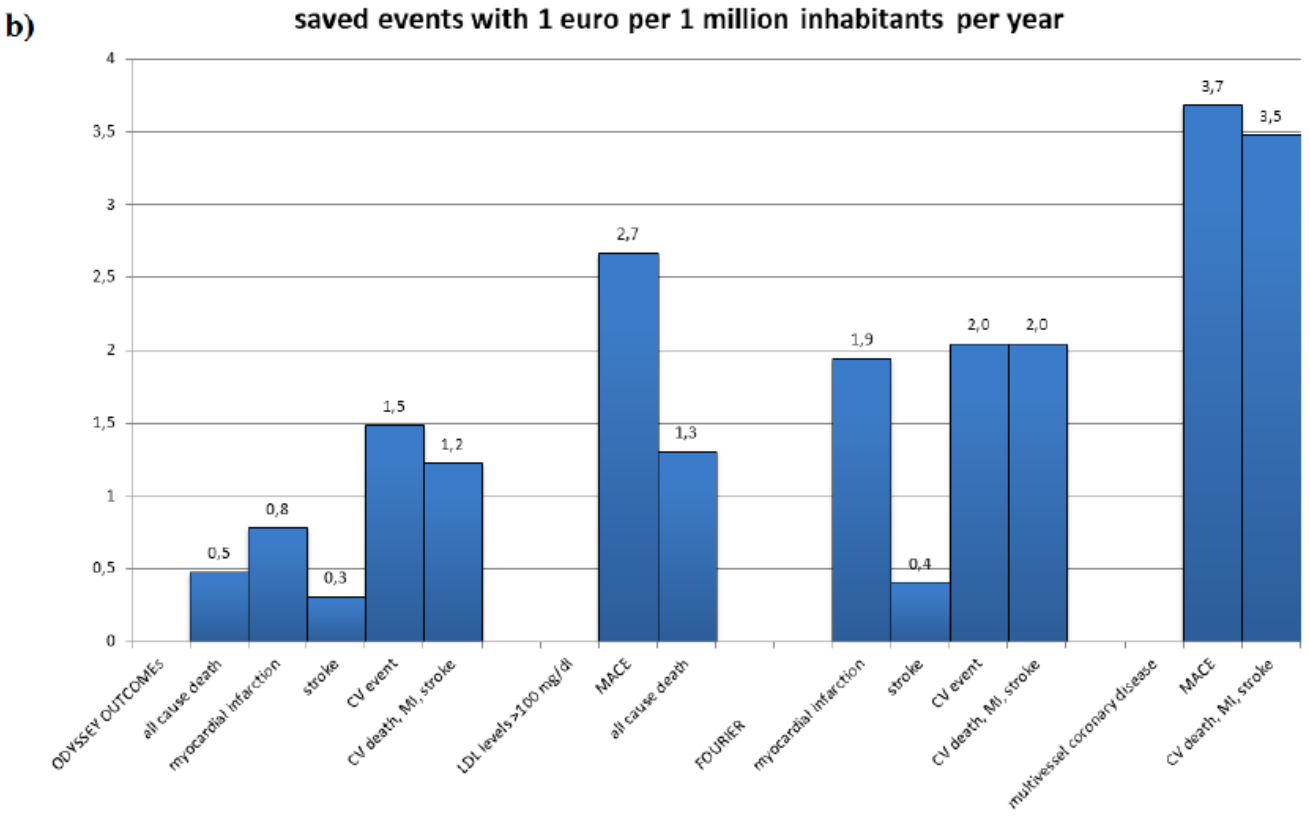
Analisi dei costi: budget impact analysis

Open access Health care delivery, economics and global health care

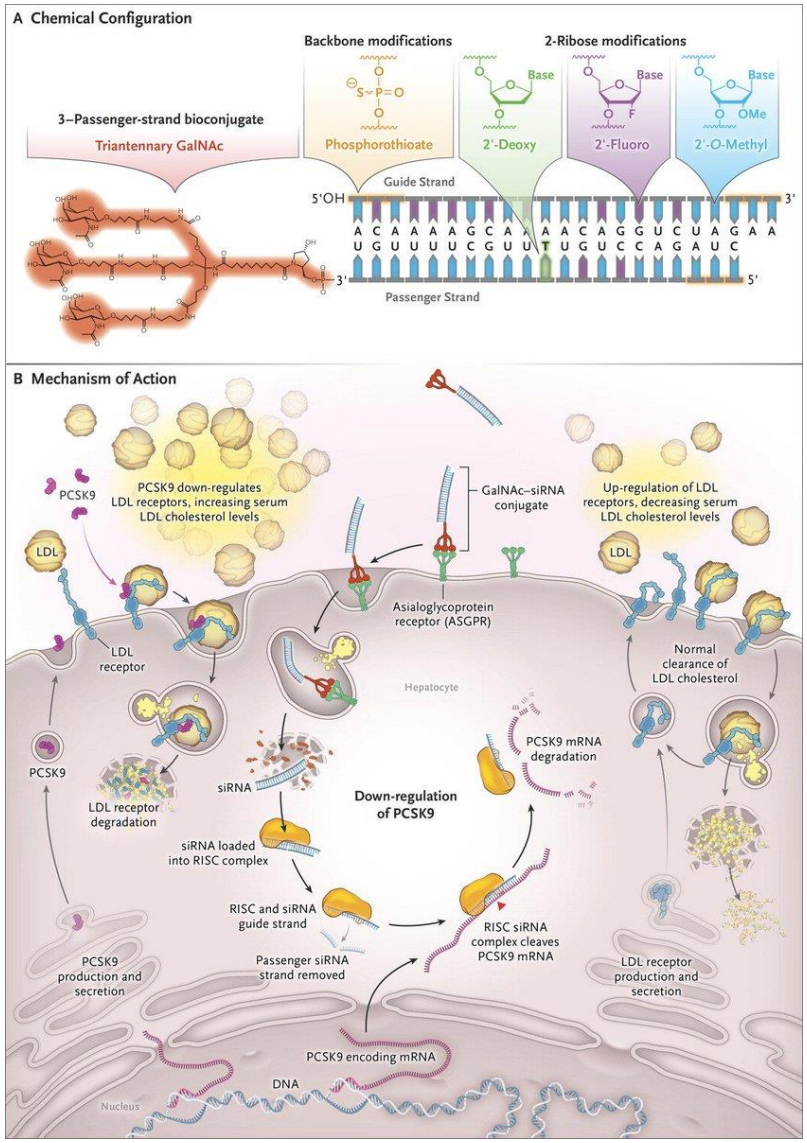
openheart

Budget impact analysis of PCSK9 inhibitors costs from a community payers' perspective in Apulia, Italy

Natale Daniele Brunetti,[1] Luisa De Gennaro,[2] Lucia Tricarico,[1] Pasquale Caldarola[2]



Inclisiran


A Chemical Configuration
Backbone modifications
2-Ribose modifications
3–Passenger-strand bioconjugate
Triantennary GalNAc
Phosphorothioate
2'-Deoxy
2'-Fluoro
2'-O-Methyl
Guide Strand
5'OH
3'
Passenger Strand
B Mechanism of Action
PCSK9
PCSK9 down-regulates LDL receptors, increasing serum LDL cholesterol levels
GalNAc–siRNA conjugate
Up-regulation of LDL receptors, decreasing serum LDL cholesterol levels
LDL
Asialoglycoprotein receptor (ASGPR)
LDL receptor
Hepatocyte
Normal clearance of LDL cholesterol
PCSK9 mRNA degradation
siRNA
Down-regulation of PCSK9
LDL receptor degradation
siRNA loaded into RISC complex
RISC and siRNA guide strand
RISC siRNA complex cleaves PCSK9 mRNA
Passenger siRNA strand removed
PCSK9 production and secretion
LDL receptor production and secretion
PCSK9 encoding mRNA
DNA
Nucleus

ORION-11: Background and rationale

Phase I-II inclisiran studies identified 2x/year dos

-60%

Dose-fir
durable,

- 300mg
- Tested
- PD mo
- Extens

1. Ray et al. N En

ORION-11: Exploratory endpoint

Adverse cardiovascular events

Cardiovascular TEAEs Safety population[1,2]	Placebo N = 804		Inclisiran N = 811	
Pre-specified exploratory CV endpoint[3]	83	(10.3%)	63	(7.8%)
Cardiovascular death	10	(1.2%)	9	(1.1%)
Fatal or non-fatal MI and stroke[4]	30	(3.7%)	12	(1.5%)
Fatal or non-fatal MI	22	(2.7%)	10	(1.2%)
Fatal or non-fatal stroke	8	(1.0%)	2	(0.2%)

Controllo colesterolo post SCA

Inibizione PCSK9

Valori estremamente bassi LDL

Nuovi target linee guida

Unmet needs