Proposta per un accesso controllato al mercato dei nuovi anticorpi monoclonali per la cura dell'ipercolesterolemia

Le strategie terapeutiche ad oggi disponibili

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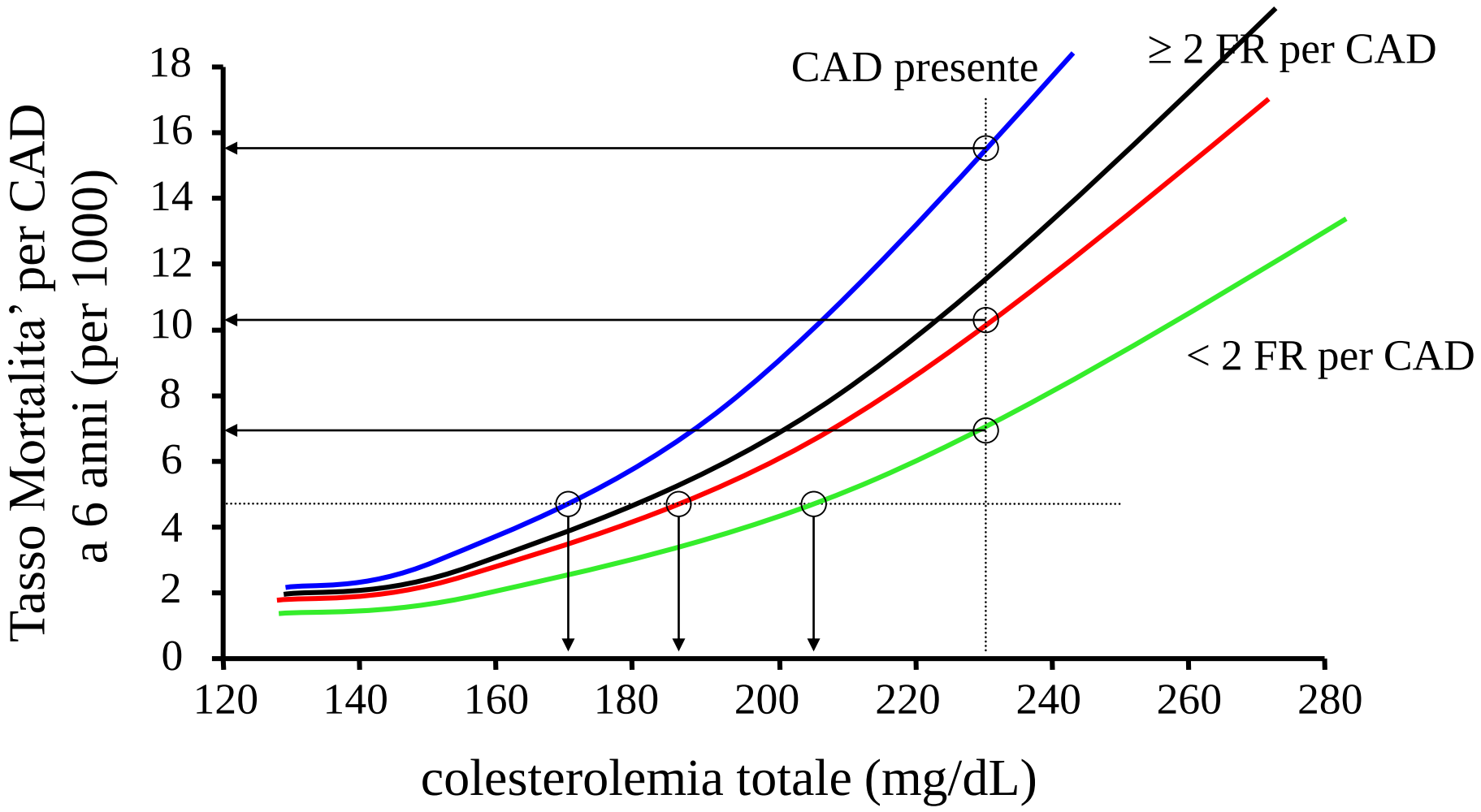
La scelta della strategia terapeutica deve garantire il raggiungimento del target di C-LDL

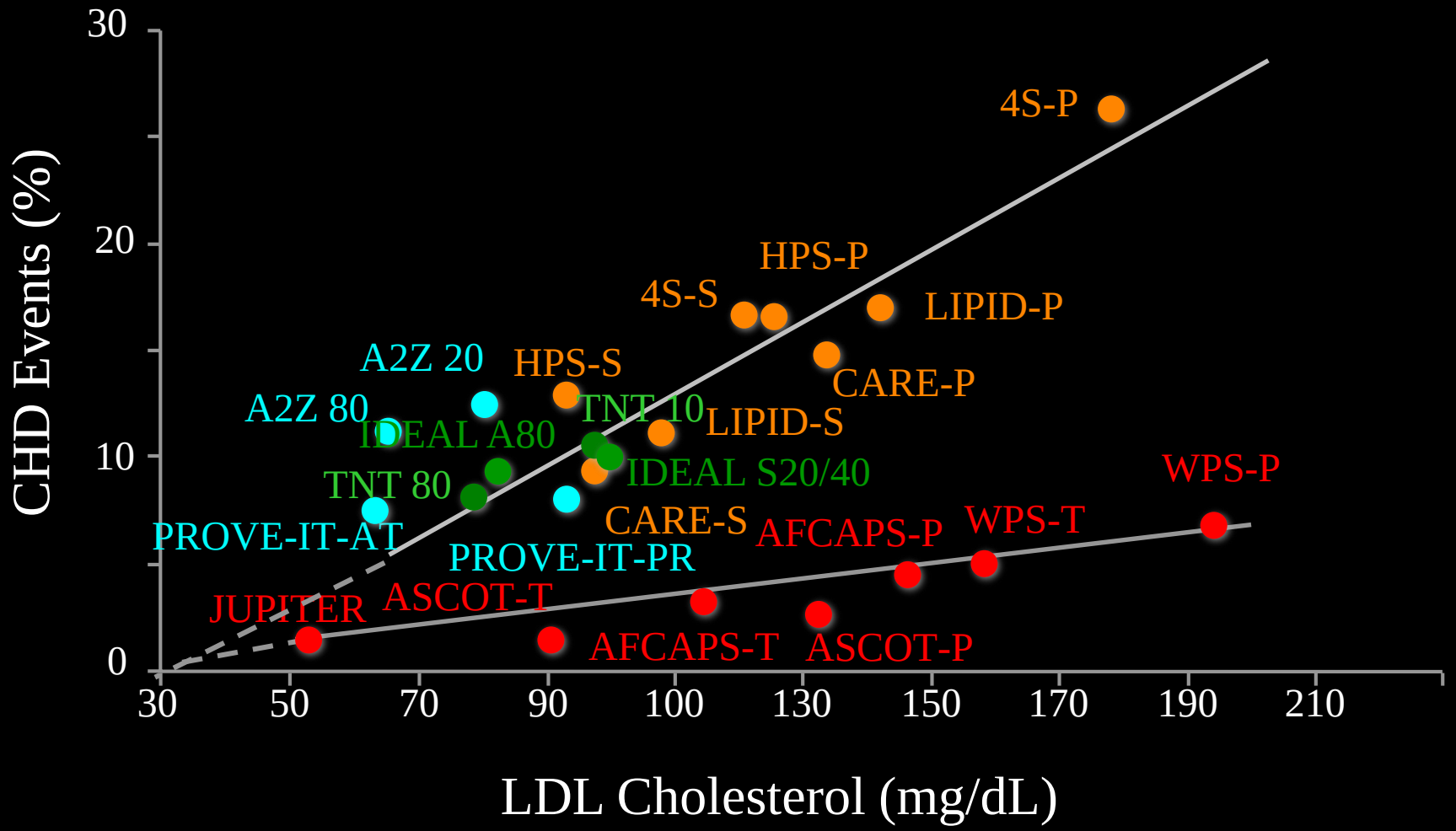
Il target di C-LDL da raggiungere dipende dal livello di rischio cardiovascolare globale

MRFIT: Livelli di Colesterolo e Rischio di Mortalità per Malattia Coronarica (CAD)



Arch. Intern Med. 1992 JAMA 1986.

	Basso rischio (5%)		Alto rischio (30%)	
Riduzione RR	-30%	-50%	-30%	-50%
trattati	100	100	100	100
eventi aspettati	5	5	30	30
eventi evitati	1,5	2,5	9	15
NNT	67	40	11	6,7



Update from O' Keefe, J Am Coll Cardiol 2004

European Heart Journal Advance Access published August 27, 2016

European Heart Journal
doi:10.1093/eurheartj/ehw272

2016 ESC/EAS Guidelines for the Management of Dyslipidaemias

Recommendations	Class [a]	Level [b]
In patients at VERY HIGH CV risk[d], an LDL-C goal of <1.8 mmol/L (70 mg/dL) or a reduction of at least 50% if the baseline LDL-C[e] is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL) is recommended.	I	B
In patients at HIGH CV risk[d], an LDL-C goal of <2.6 mmol/L (100 mg/dL), or a reduction of at least 50% if the baseline LDL-C[e] is between 2.6 and 5.2 mmol/L (100 and 200 mg/dL) is recommended.	I	B
In subjects at LOW or MODERATE risk[d] an LDL-C goal of <3.0 mmol/L (<115 mg/dL) should be considered.	IIa	C

Basso rischio

SCORE <1% di evento CVD fatale nei prossimi 10 anni in assenza di elementi che pongano i soggetti a rischio moderato

Rischio moderato

SCORE compreso tra 1 e 5%. La gran parte dei soggetti di media età appartiene a tale categoria

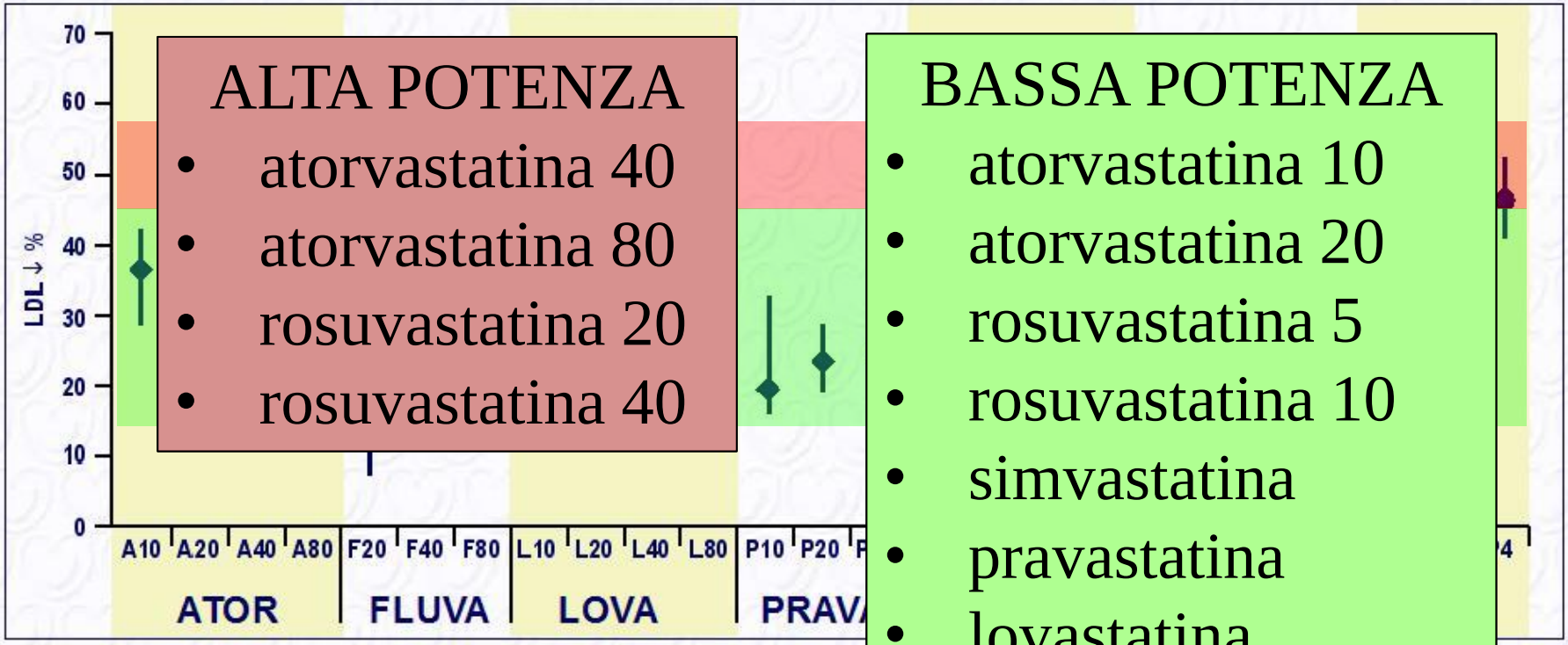
Alto rischio

- presenza di significativo fattore di rischio come dislipidemia familiare o ipertensione severa
- diabete mellito in assenza di altri fattori di rischio CV o di danno d' organo
- insufficienza renale cronica moderata (GFR stimata di 30-59 mL/min/1.73 m2
- SCORE compreso tra il 5% e il 10%

Rischio molto alto

- presenza di malattia CV documentata con test invasivi o non (coro, scintigrafia, ecostress, placca carotidea all' ecoDoppler TSA), **pregresso IMA, SCA, rivascolarizzazione coronarica (PCI o CABG)** o altre procedure di rivascolarizzazione arteriosa, stroke ischemico, malattia vascolare periferica
- diabete mellito in presenza di uno o più fattori di rischio CV e/o di danno d' organo (es. microalbuminuria)
- insufficienza renale cronica severa (GFR stimata < 30 mL/min/1.73 m2
- SCORE maggiore o pari al 10%

A systematic review and meta-analysis on the therapeutic equivalence of statins



ALTA POTENZA

- atorvastatina 40
- atorvastatina 80
- rosuvastatina 20
- rosuvastatina 40

BASSA POTENZA

- atorvastatina 10
- atorvastatina 20
- rosuvastatina 5
- rosuvastatina 10
- simvastatina
- pravastatina
- lovastatina
- fluvastatina

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

Percentage reduction of LDL-C required to achieve goals as a function of the starting value

STARTING LDL-C		% REDUCTION TO REACH LDL-C		
mmol/L	~ mg/dL	< 1.8 mmol/L (~ 70 mg/dL)	< 2.5 mmol/ (~ 100 mg/dL)	< 3 mmol/L (~ 115 mg/dL)
> 6.2	> 240	> 70	> 60	> 55
5.2–6.2	200–240	65–70	50–60	40–55
4.4–5.2	170–200	60–65	40–50	30–45
3.9–4.4	150–170	55–60	35–40	25–30
3.4–3.9	130–150	45–55	25–35	10–25
2.9–3.4	110–130	35–45	10–25	< 10
2.3–2.9	90–110	22–35	< 10	–
1.8–2.3	70–90	< 22	–	–

www.escardio.org/guidelines

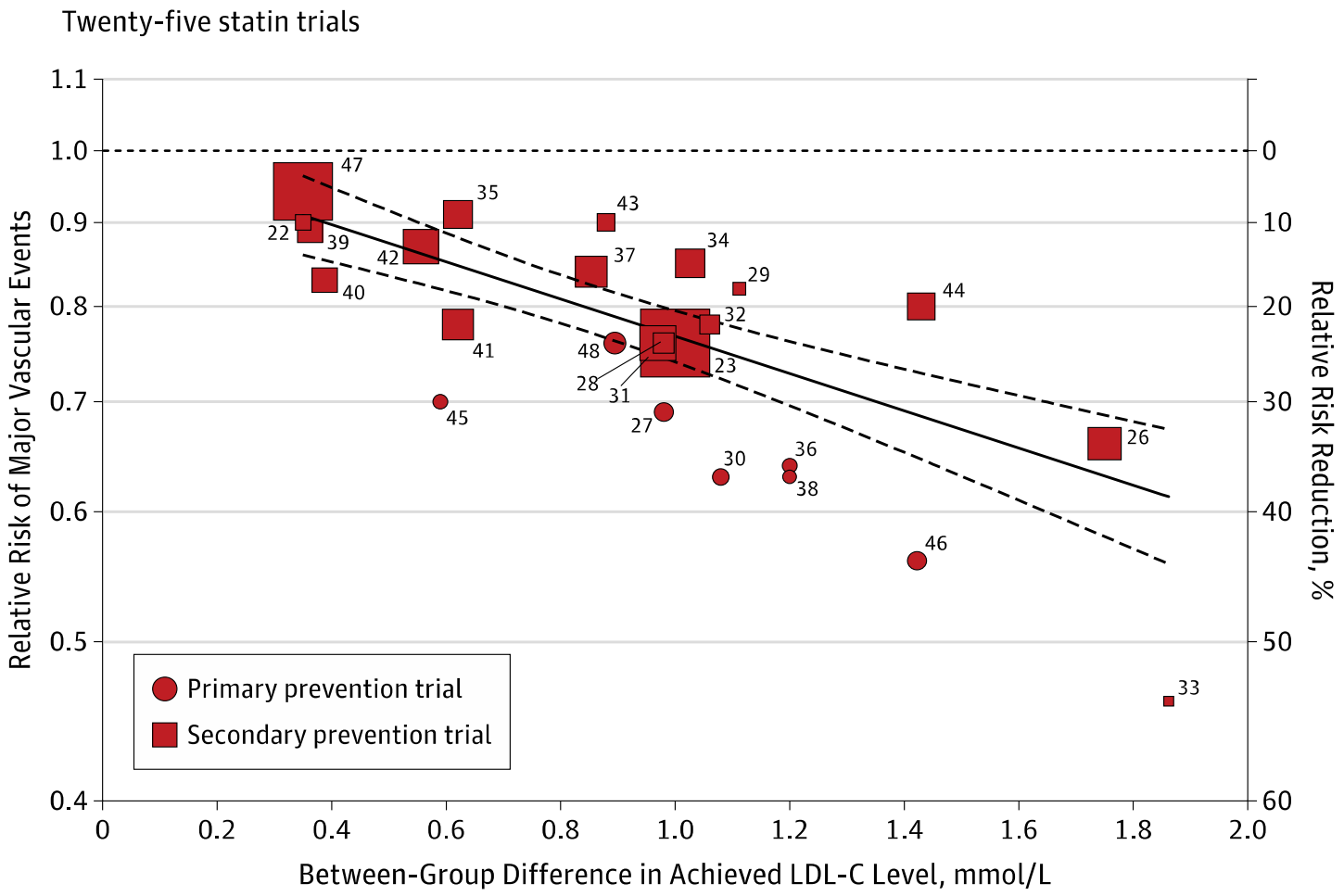
European Heart Journal 2011;32 (14):1769–1818
Atherosclerosis 2011 Jul;217(1):3-46

EUROPEAN SOCIETY OF CARDIOLOGY®

JAMA | Original Investigation

Association Between Lowering LDL-C and Cardiovascular Risk Reduction Among Different Therapeutic Interventions

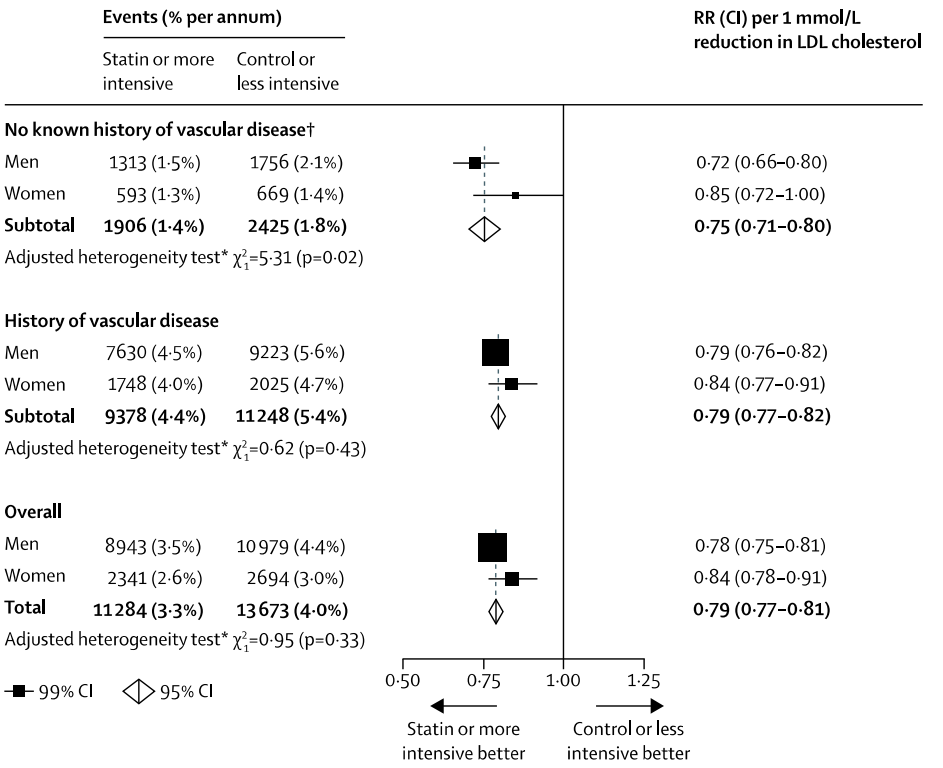
A Systematic Review and Meta-analysis



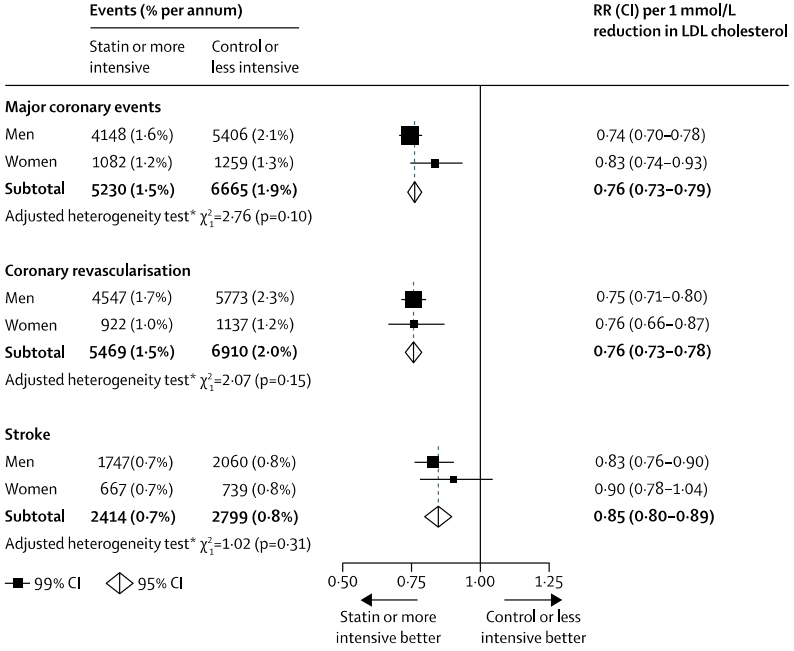
Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174 000 participants in 27 randomised trials

*Cholesterol Treatment Trialists' (CTT) Collaboration**

Effects on major vascular events per 1·0 mmol/L reduction in LDL cholesterol, subdivided by history of vascular disease and sex

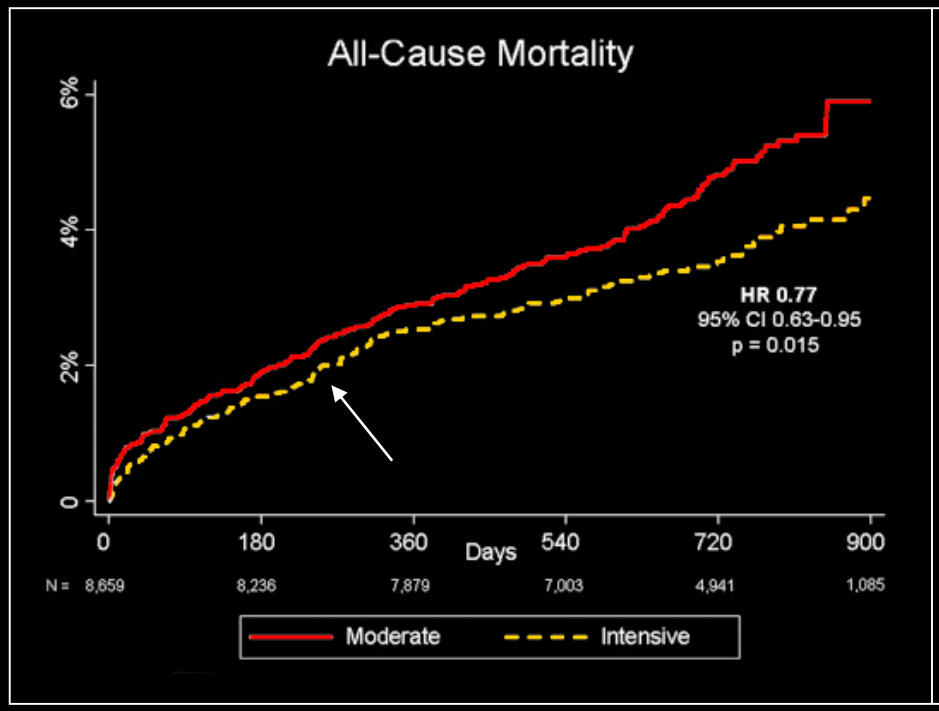


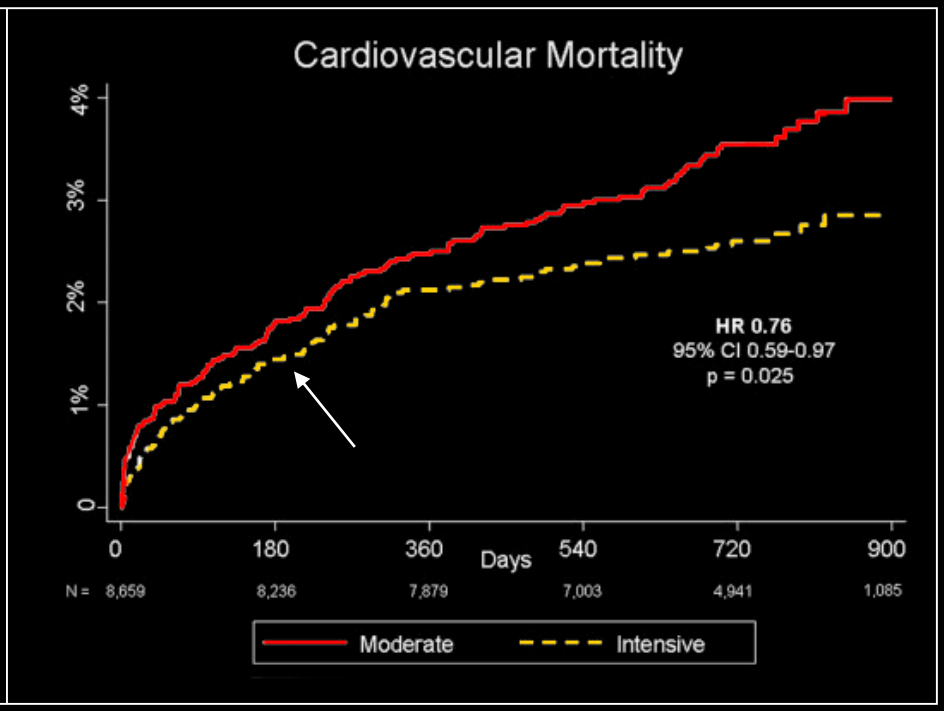
Effects on components of major vascular events per 1·0 mmol/L reduction in LDL cholesterol, subdivided by sex



Il trattamento intensivo con statine nella SCA riduce la mortalità totale e cardiovascolare

A pooled, patient-level analysis of 8658 ACS patients of the PROVE-IT and A-to-Z trials





Murphy et al , Am J Cardiol 2007

European Heart Journal Advance Access published August 29, 2015

European Heart Journal
doi:10.1093/eurheartj/ehv320

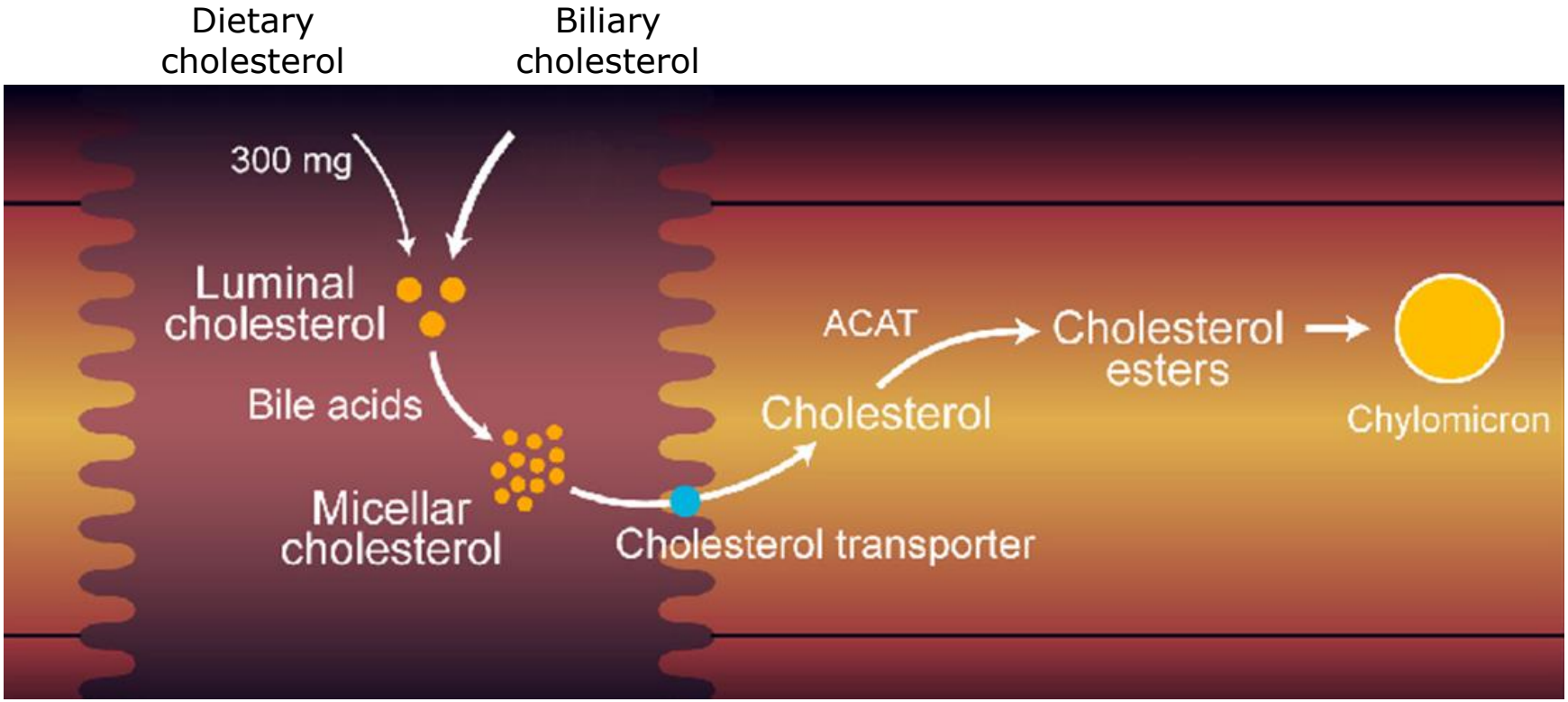
2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC)

Participation in a well-structured cardiac rehabilitation programme to modify lifestyle habits and increase adherence to treatment should be considered.	IIa	A
In patients with LDL cholesterol ≥70 mg/dL (≥1.8 mmol/L) despite a maximally tolerated statin dose, further reduction in LDL cholesterol with a non-statin agent[e] should be considered.	IIa	B
A systolic blood pressure goal of <140 mmHg should be considered.	IIa	B

[e]At the time of finalizing the guidelines, this recommendation applies only to ezetimibe.

Cholesterol Absorption in the Intestine



ACAT=acyl-coenzyme A:cholesterol acyltransferase; NPC1L1=Niemann-Pick C1 Like 1

Adapted from Champe PC, Harvey RA. In Biochemistry. 2nd ed. Philadelphia: Lippincott Raven, 1994; Ginsberg HN, Goldberg IJ. In Harrison's Principles of Internal Medicine. 14th ed. New York: McGraw-Hill, 1998:2138–2149; Shepherd J Eur Heart J Suppl 2001;3(suppl E):E2–E5; Hopfer U. In Textbook of Biochemistry with Clinical Correlations. 5th ed. New York: Wiley-Liss, 2002:1082–1150; Davis JP et al Genomics 2000;65:137–145

ORIGINAL ARTICLE

Inactivating Mutations in *NPC1L1* and Protection from Coronary Heart Disease

The Myocardial Infarction Genetics Consortium Investigators

Table 3. Association between the Presence of Inactivating Mutations in *NPC1L1* and the Risk of Coronary Heart Disease (CHD).

Inactivating Mutation	Mutation Carriers		Total Participants		Carrier Frequency	
	With CHD	Without CHD	With CHD	Without CHD	Participants with CHD	Participants without CHD
	number				*percent*	
All mutations*	11	71	29,954	83,140	0.04	0.09
p.L71RfsX50	0	2	709	4,378	0	0.05
p.Q167X	0	1	966	987	0	0.10
p.A296VfsX57	0	3	1,794	1,745	0	0.17
p.R406X	6	49	26,507	75,654	0.02	0.06
p.Y483X	0	1	844	1,107	0	0.09
c.1681+1G→A†	0	3	709	4,378	0	0.07
p.W592X	1	0	1,157	4,561	0.09	0
p.R601X	1	0	474	2,362	0.21	0
p.Q604X	0	3	652	2,639	0	0.11
p.R738X	0	2	382	401	0	0.50
p.E803X	1	0	1,157	4,561	0.09	0
c.2637+2T→G†	1	1	1,525	4,897	0.07	0.02
p.C967X	0	1	474	2,362	0	0.04
p.A1201V†	0	2	235	2,016	0	0.10
p.R1325X	1	3	1,866	8,939	0.05	0.03

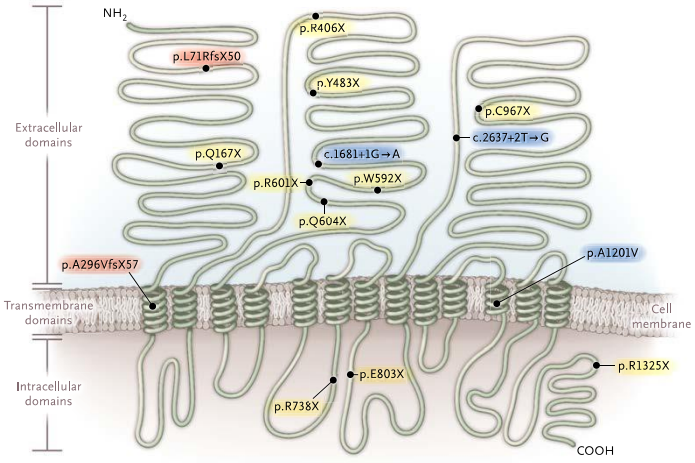
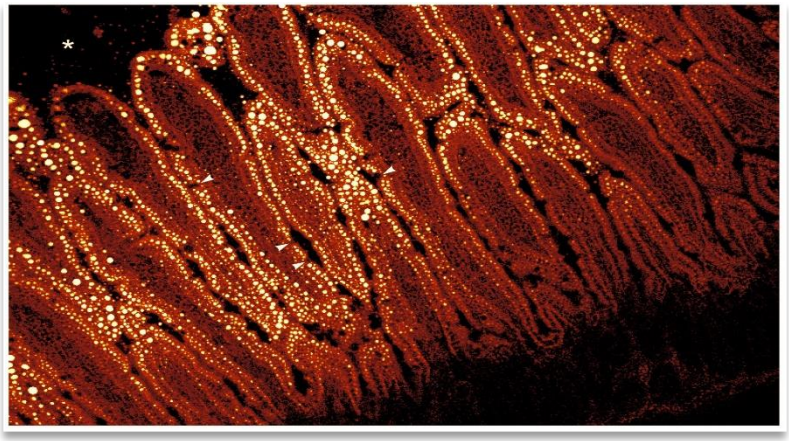


Table 2. Association between the Presence of Inactivating Mutations in *NPC1L1* and Plasma Lipid Levels.*

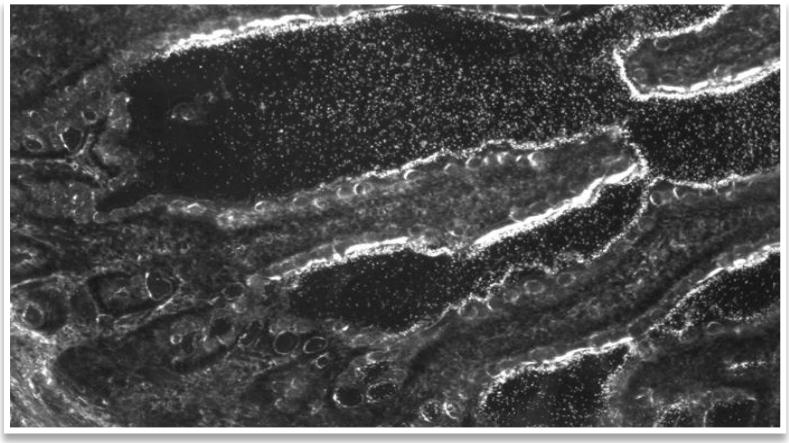
Variable	Mean Difference between Carriers and Noncarriers*	P Value
Cholesterol (mg/dl)		
Total	–13	0.03
Low-density lipoprotein	–12	0.04
High-density lipoprotein	2	0.29
Triglycerides (% change)	–12	0.11†

Ezetimibe: Localization at Site of Cholesterol Absorption

Absorption of cholesterol in intestine (hamster)



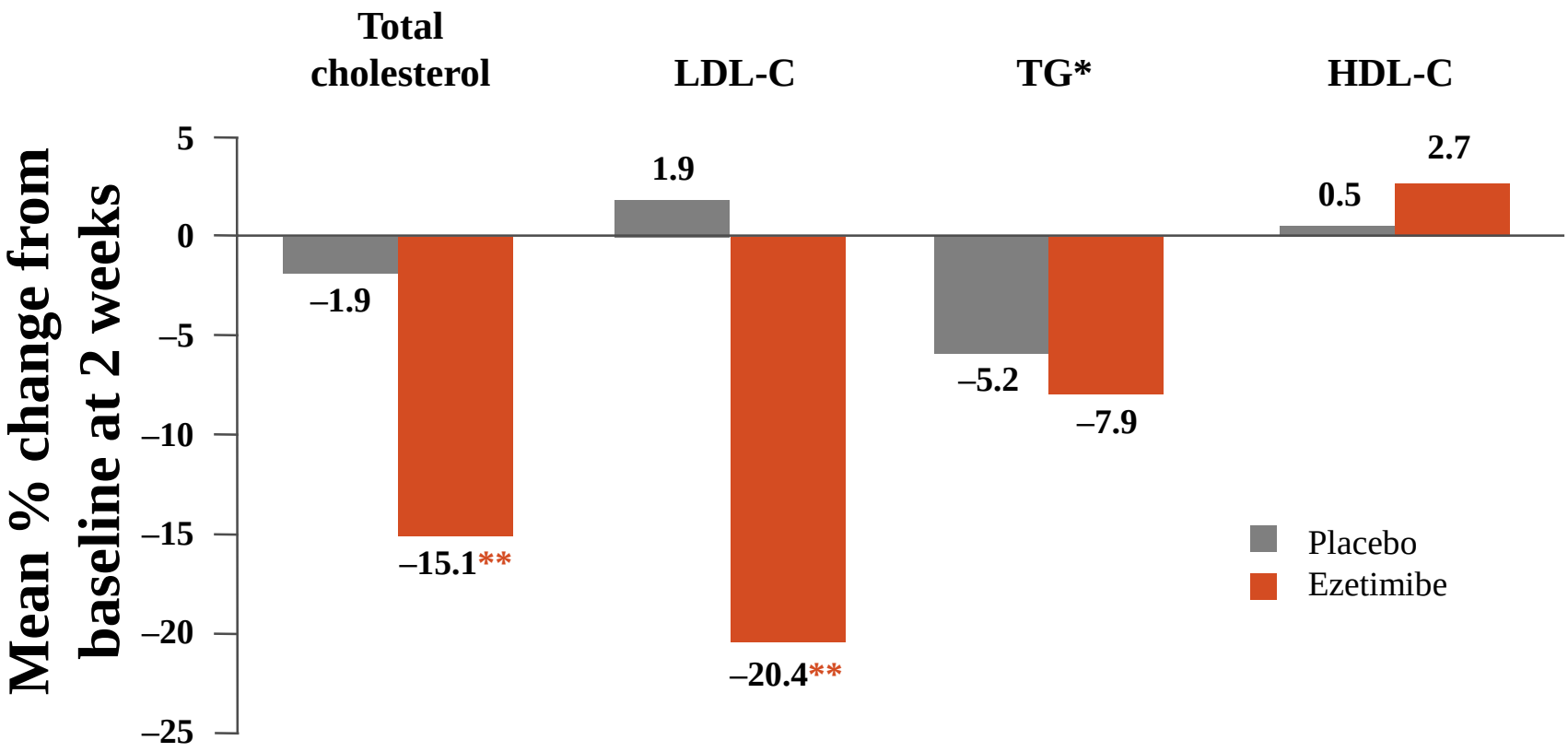
Ezetimibe localization at intestinal brush border (rat)



- Localizes at brush border of small intestine and prevents uptake of cholesterol into enterocytes
- Decreases delivery of intestinal cholesterol to liver resulting in
  - ✧ Up-regulation of LDL-C–receptor synthesis
  - ✧ Increased cholesterol clearance from the blood

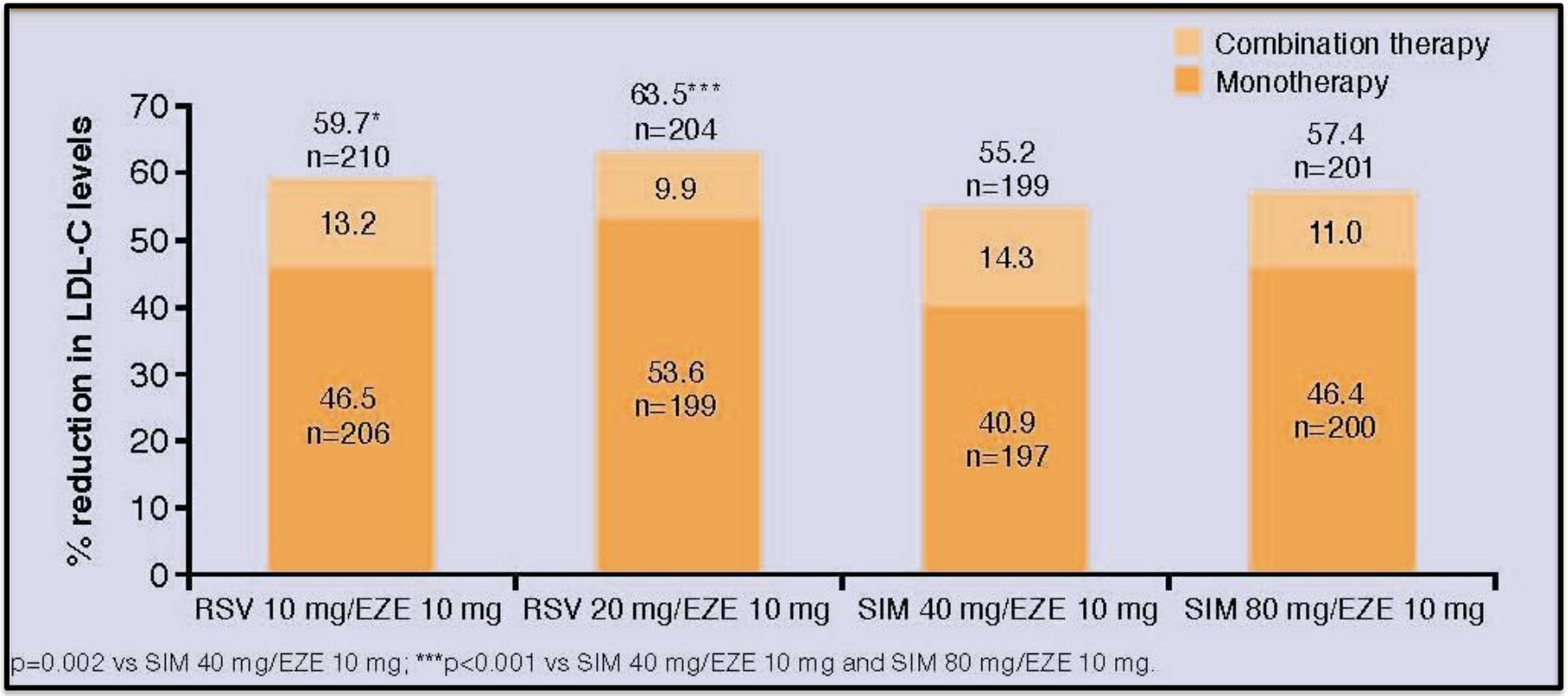
Brown WV Am J Cardiol 2001;87(suppl):23B–27B;
Sparrow CP et al J Lipid Res 1999;10:1747–1757

Effects of Ezetimibe on Plasma Lipids



HDL-C=high-density lipoprotein cholesterol
*Median values; **$p<0.001$
Sudhop T et al. Circulation 2002;106:1943–1948

LDL-C Reduction with Statin Monotherapy and Statin Plus Ezetimibe: GRAVITY



Ballantyne, 2013

Study Design

18,144 patients stabilized post ACS ≤ 10 days:
LDL-C 50–125 mg/dL (or 50–100 mg/dL if prior lipid-lowering Rx)

Standard Medical & Interventional Therapy

Simvastatin 40 mg

Uptitrated to Simva 80 mg if LDL-C > 79 (adapted per FDA label 2011)

Ezetimibe/Simvastatin 10/40 mg

Follow-up Visit Day 30, every 4 months

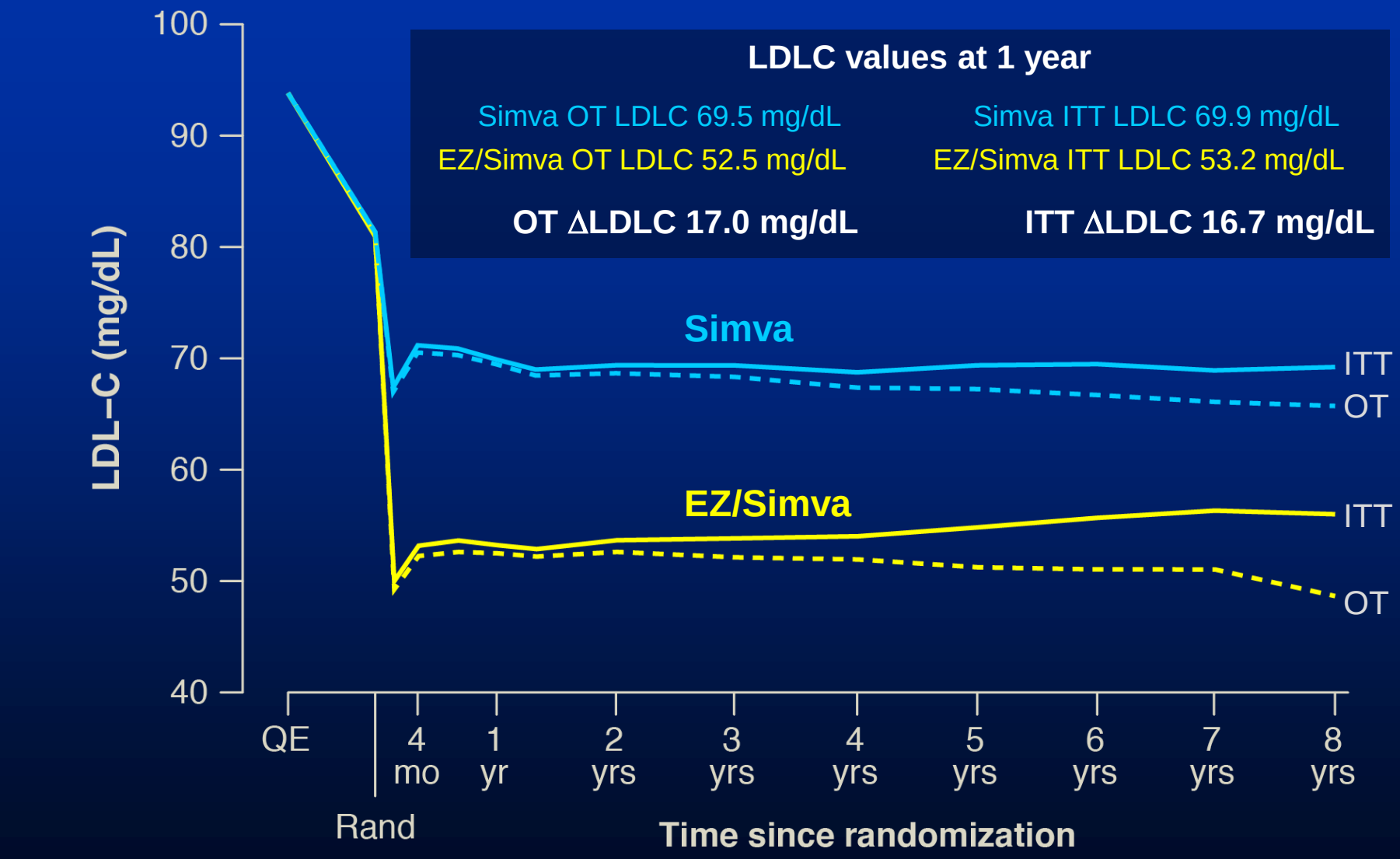
90% power to detect ~9% difference

Duration: Minimum 2 ½-year follow-up **(at least 5250 events)**

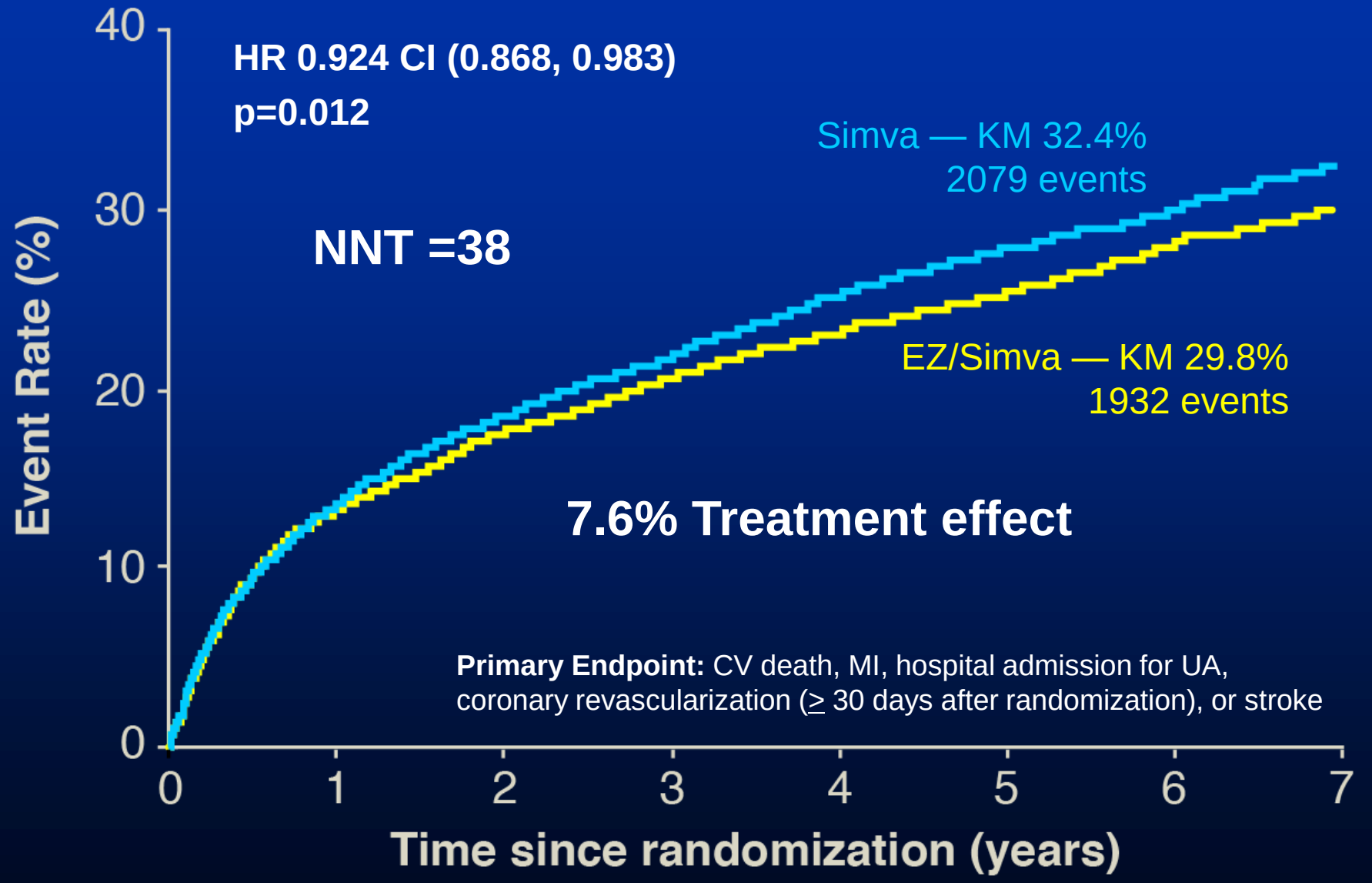
Primary Endpoint: CV death, MI, hospital admission for UA, coronary revascularization (≥ 30 days after randomization), or stroke

Cannon AHJ 2008; Califf NEJM 2009; Blazing AHJ 2014

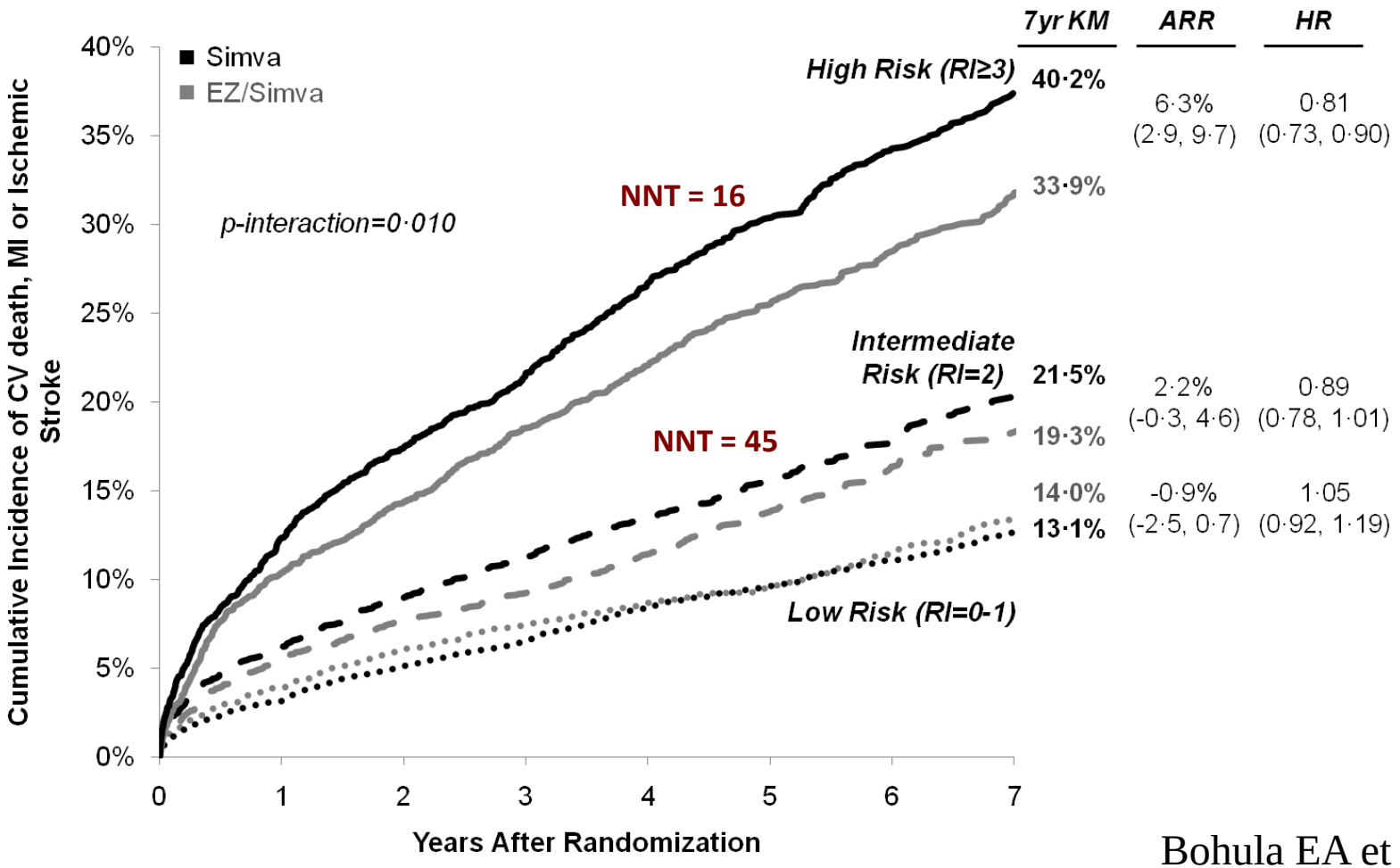
Mean LDL-C at 1 Year OT & ITT



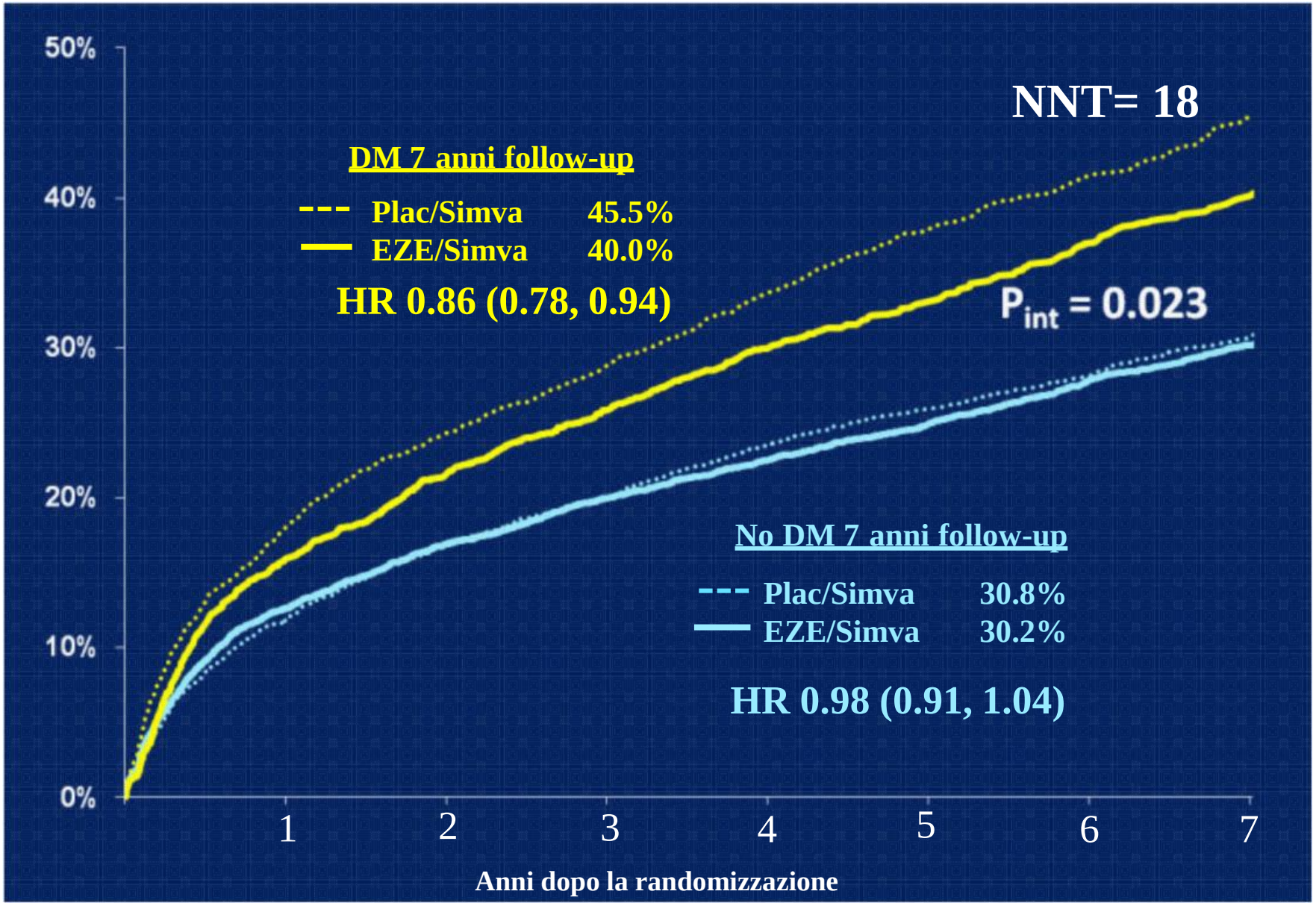
Primary Endpoint On-Treatment



Effects of ezetimibe by TRAP 2P risk score in IMPROVE-IT

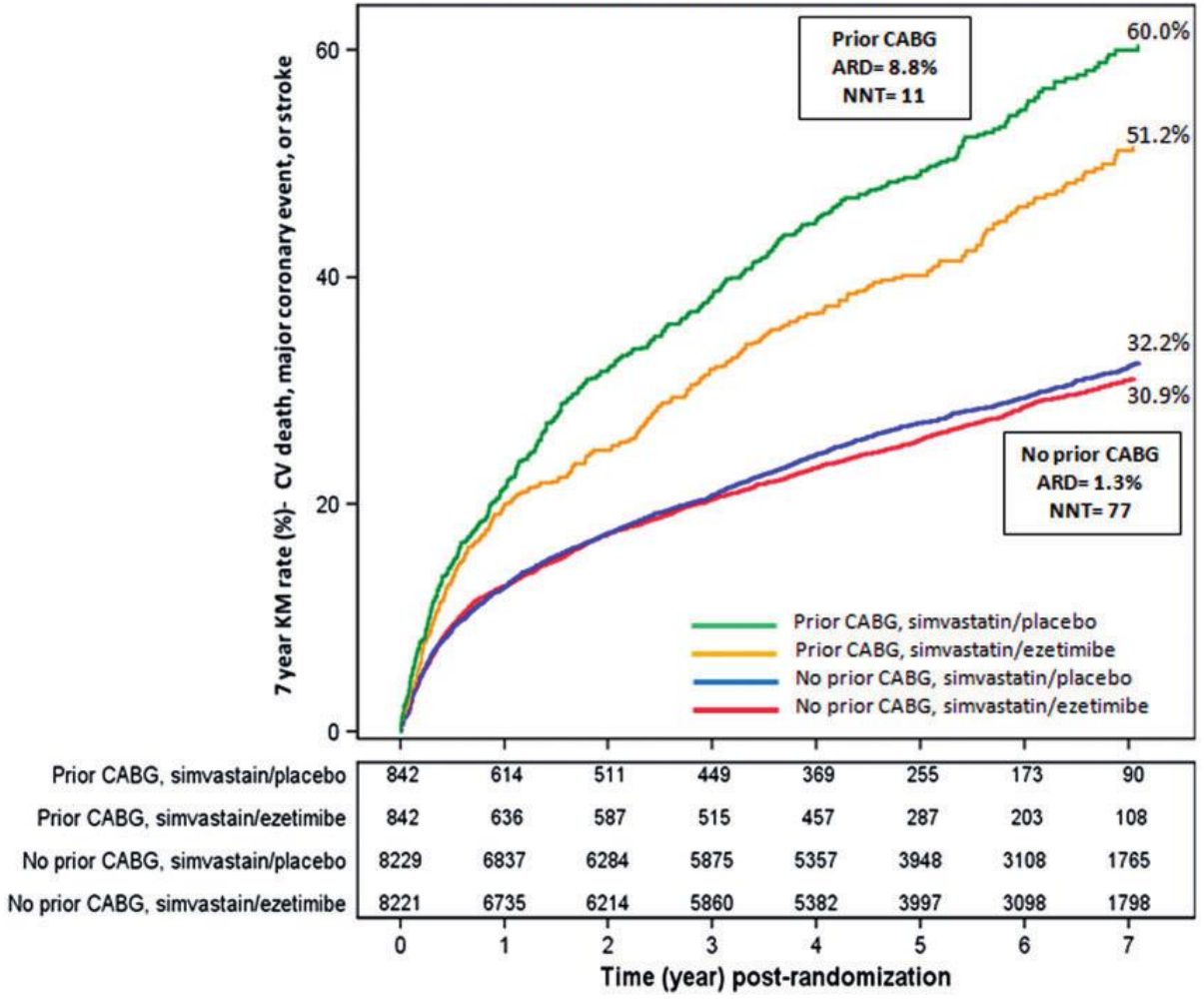


Bohula EA et al.

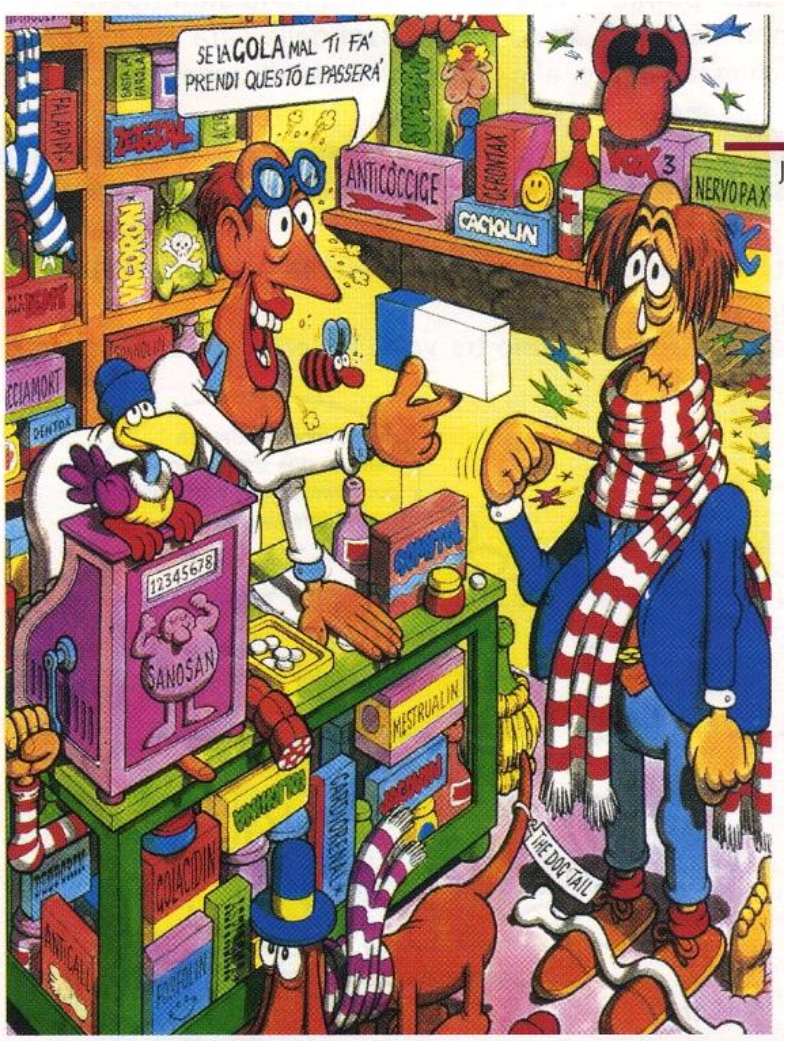

50%
40%
30%
20%
10%
0%
NNT= 18
DM 7 anni follow-up
Plac/Simva 45.5%
EZE/Simva 40.0%
HR 0.86 (0.78, 0.94)
P int = 0.023
No DM 7 anni follow-up
Plac/Simva 30.8%
EZE/Simva 30.2%
HR 0.98 (0.91, 1.04)
1
2
3
4
5
6
7
Anni dopo la randomizzazione

European Heart Journal (2016) **37**, 3576–3584

The benefit of adding ezetimibe to statin therapy in patients with prior coronary artery bypass graft surgery and acute coronary syndrome in the IMPROVE-IT trial



Difficile non è prescrivere un farmaco; è fare in modo che il paziente lo assuma. Compliance e aderenza sono gli «assi» per la gestione dei soggetti ad alto rischio.



Strategie di ottimizzazione

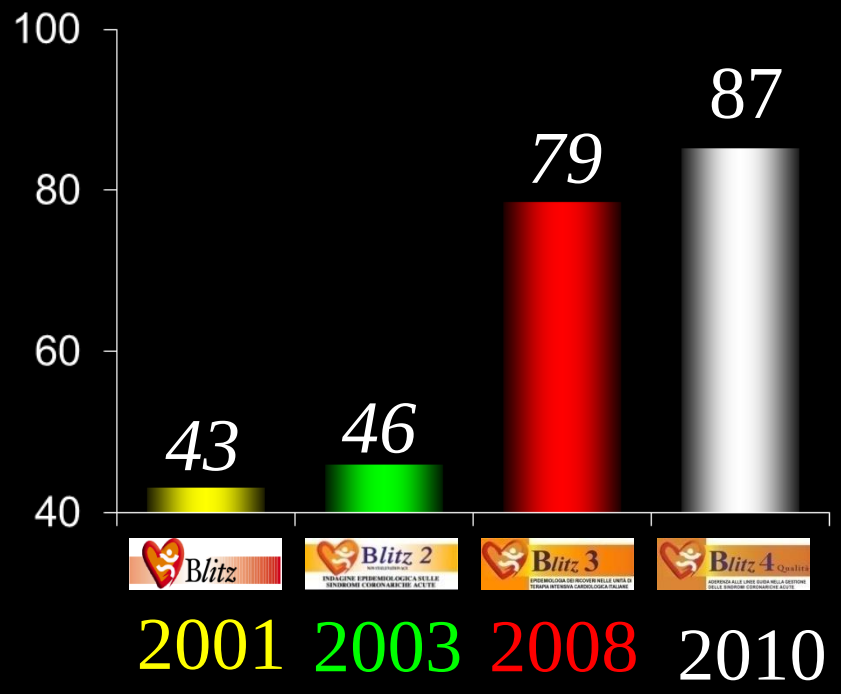
- Il paziente è aderente

- Il paziente è a target

- Il paziente lamenta effetti collaterali

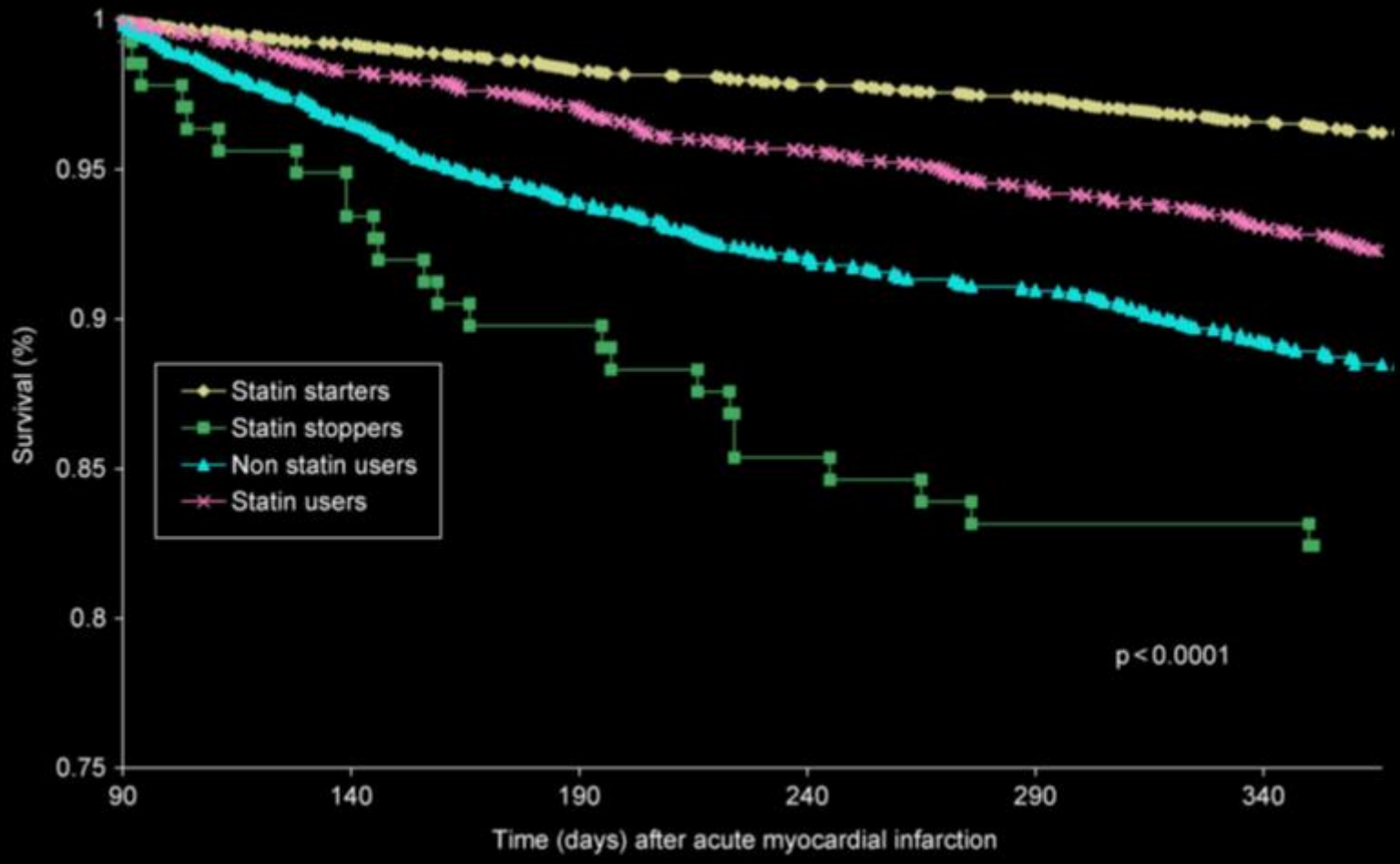
Il paziente non è aderente

% di utilizzo di statine nella SCA
in Italia: dati dagli studi BLITZ



Follow-up 6 mesi

Effect of statin treatment patterns on 1-year all-cause mortality among 9939 survivors of a first AMI

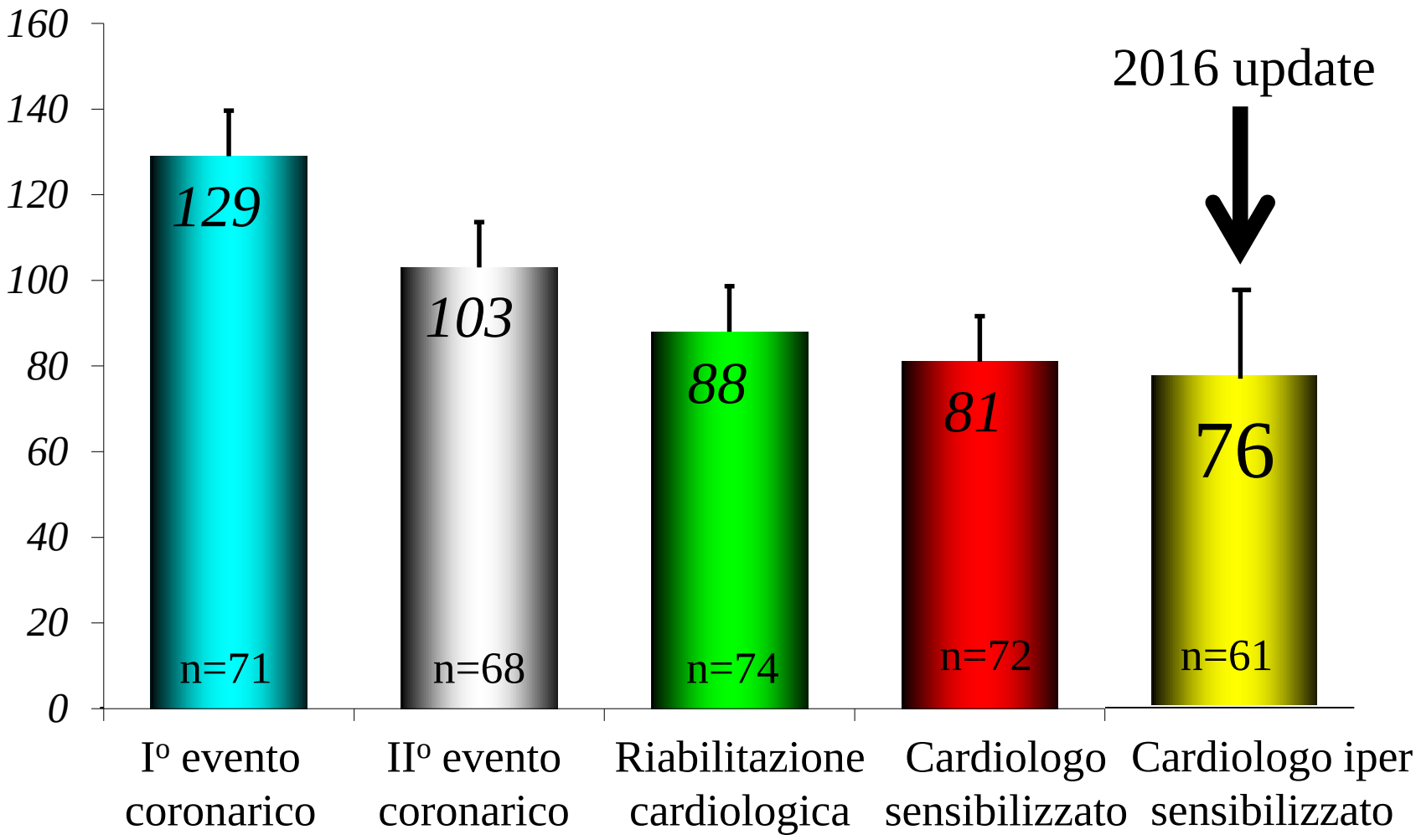


European Heart Journal 2008, 29, 2083–2091

Il paziente non è a target

- Aumentiamo la posologia della statina (max consentito: atorvastatina 80 mg/die; rosuvastatina 40 mg/die; simvastatina 40 mg/die)
- Aggiungiamo ezetimibe 10 mg;
- Non altra terapia EBM (considero fibrati, berberina)

C-LDL in differenti popolazioni con CHD



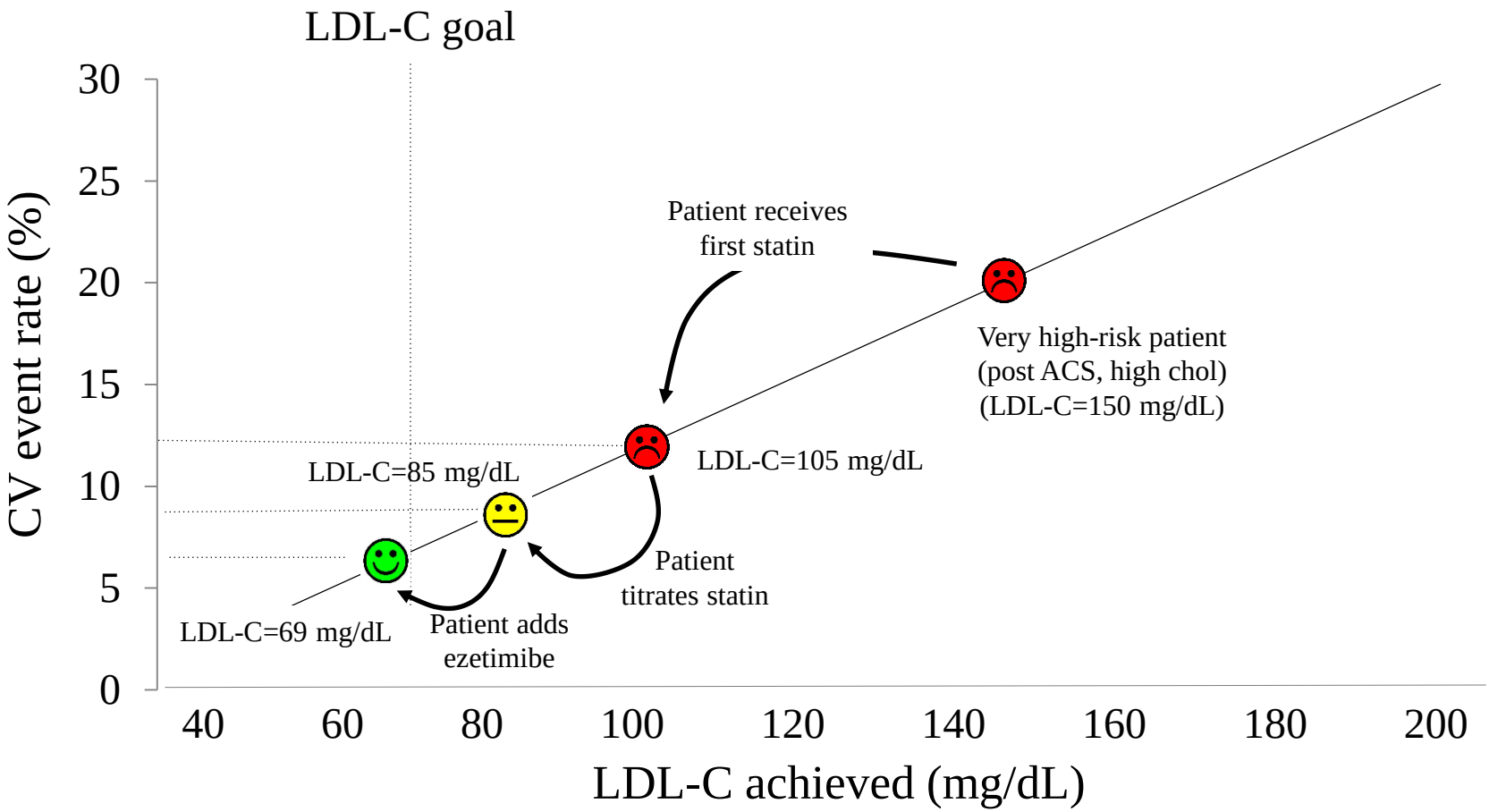
C. Bilato, dati personali

Il paziente è intollerante

incapace di proseguire la terapia con statine per effetti collaterali (mialgie, miopatie) o incremento di transaminasi e/o CPK

- fino al 15% dei pazienti trattati
- non consenso unanime: segnalazione di mialgia soggettiva e influenzata da comorbidità (età, sesso femminile, ipotiroidismo, asiatici, alcol, farmaci, succo di pompelmo)
- diagnosi difficile identificare reale "statin intolerance"
- rarissima la rabdomiolisi (1 su 23 milioni per atorva);
- strategia "drug holiday and rechallenging" (stessa statina a dosi più basse o altra statina);
- ezetimibe (meno altri farmaci, es. fibrati o resine);
- assunzione intermittente di statina (a più lunga durata d' azione);
- Nutraceutici, Vitamina D? Coenzima Q?

but…


LDL-C goal
CV event rate (%)
30
25
20
15
10
5
0
40
60
80
100
120
140
160
180
200
LDL-C achieved (mg/dL)
Patient receives first statin
Very high-risk patient (post ACS, high chol) (LDL-C=150 mg/dL)
LDL-C=105 mg/dL
LDL-C=85 mg/dL
Patient titrates statin
LDL-C=69 mg/dL
Patient adds ezetimibe

We still do have unmeet clinical needs