LDL come target lipidico post SCA: dalle statine agli iPCSK9

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ASL CITTÀ DI TORINO

Il Paziente Fragile in cardiologia

CARDIOLOGI E MEDICI DI MEDICINA GENERALE "IN RETE"

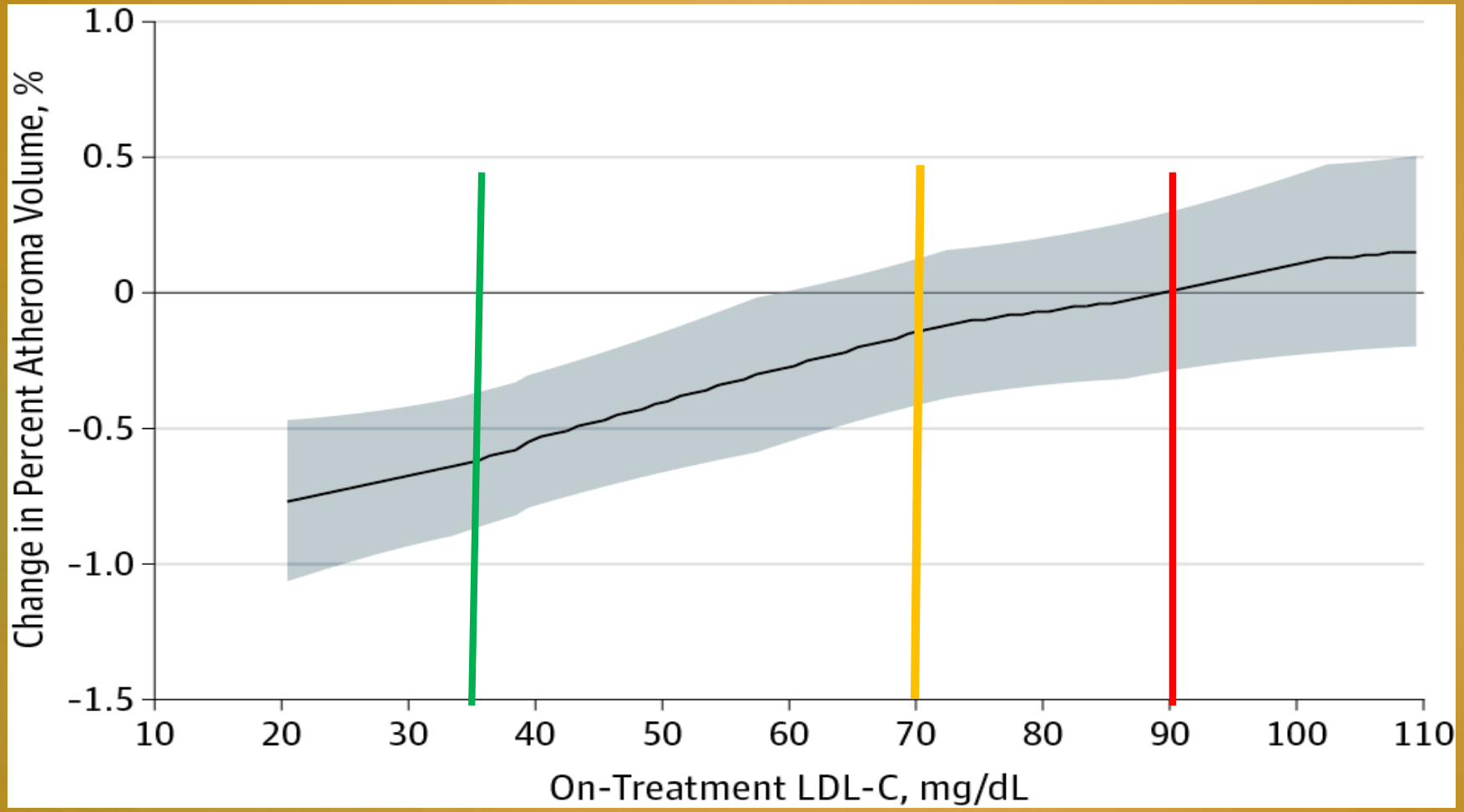
La costruzione di percorsi condivisi

SABATO 9 NOVEMBRE 2019

Aula Carlo Ravetti
Ospedale San Giovanni Bosco


PER SICUREZZA, DUBITO DI TUTTO.

Il colesterolo LDL è un fattore causale per lo sviluppo dell'arteriosclerosi



THE LOWER,

THE BETTER

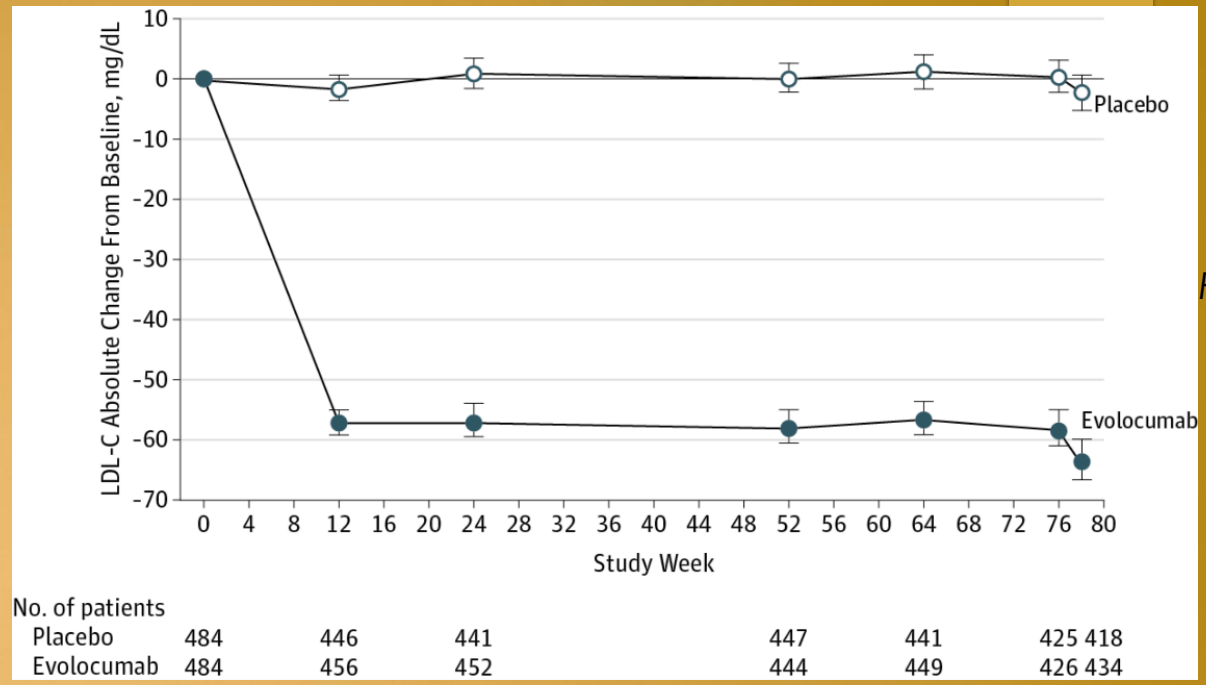
THE LOWEST

THE BETTER!!

Effect of Evelocumab on progression of coronary disease in statin-treated patients. The GLAGOV randomized clinical trial. JAMA. 2016;316(22):2373-2384

Effect of Evolocumab on Progression of Coronary Disease in Statin-Treated Patients. The GLAGOV Randomized Clinical Trial. JAMA. 2016;316(22):2373-2384. doi:10.1001/jama.2016.16951

Variazione percentuale dell'ateroma coronarico dopo 78 settimane di terapia



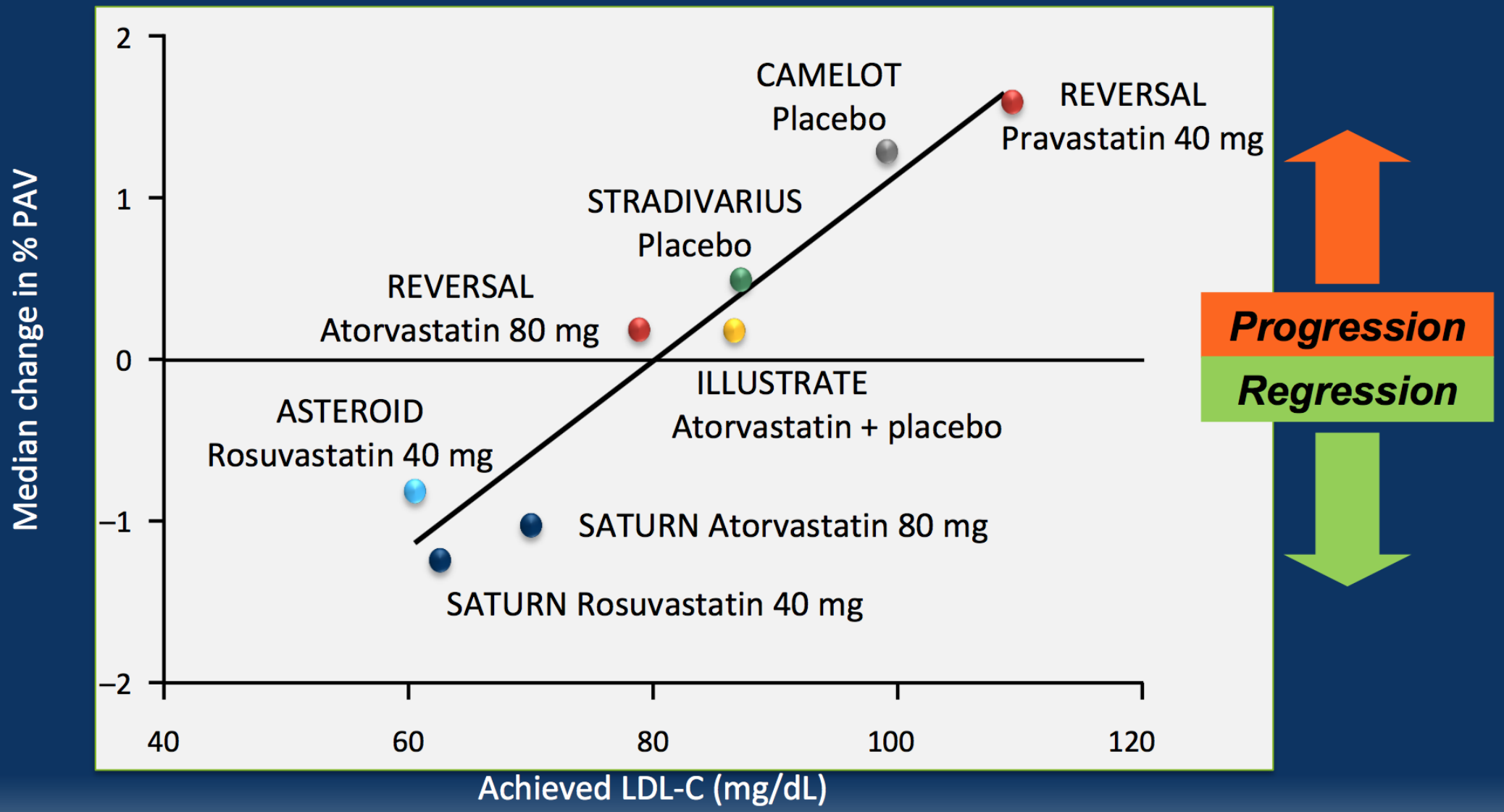
P < 0.001*

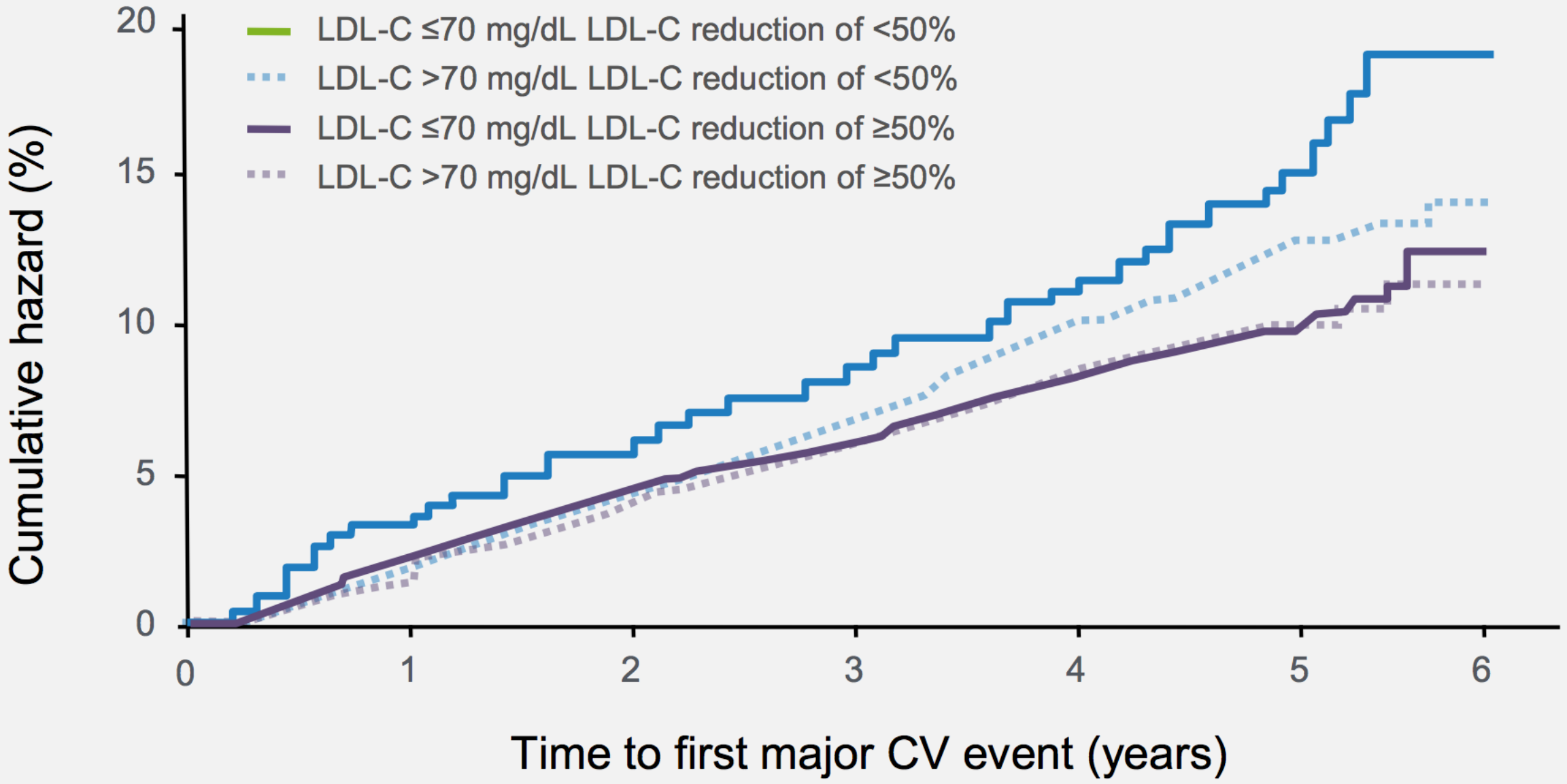
Group differences: -1.0% (-1.8 to -0.64); *P* < 0.001

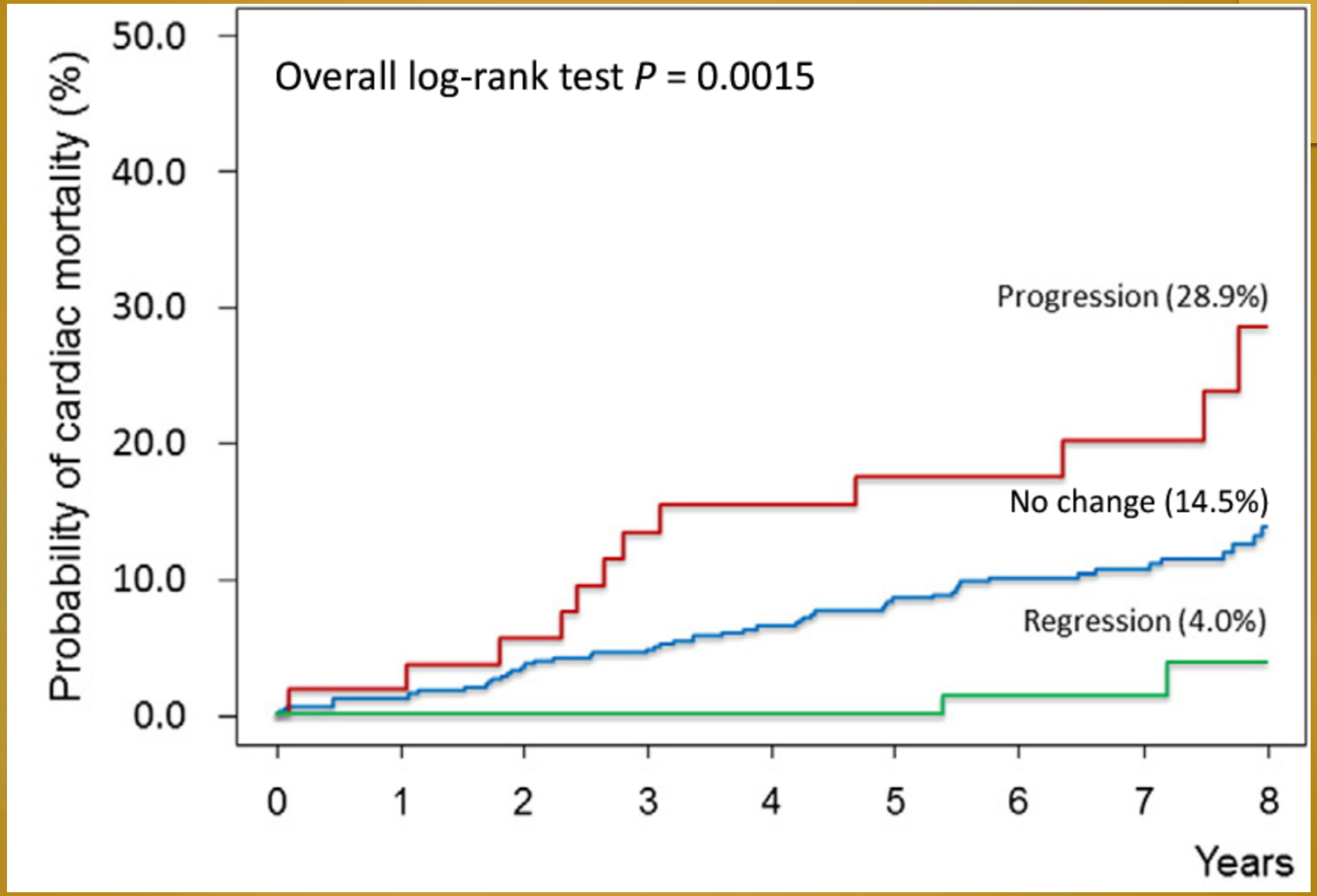
Nicholls SJ, et al. *JAMA*. [published online ahead of print November 15, 2016]. doi: 10.1001/jama.2016.16951.

JAMA Network™

LDL-C and atherosclerotic burden



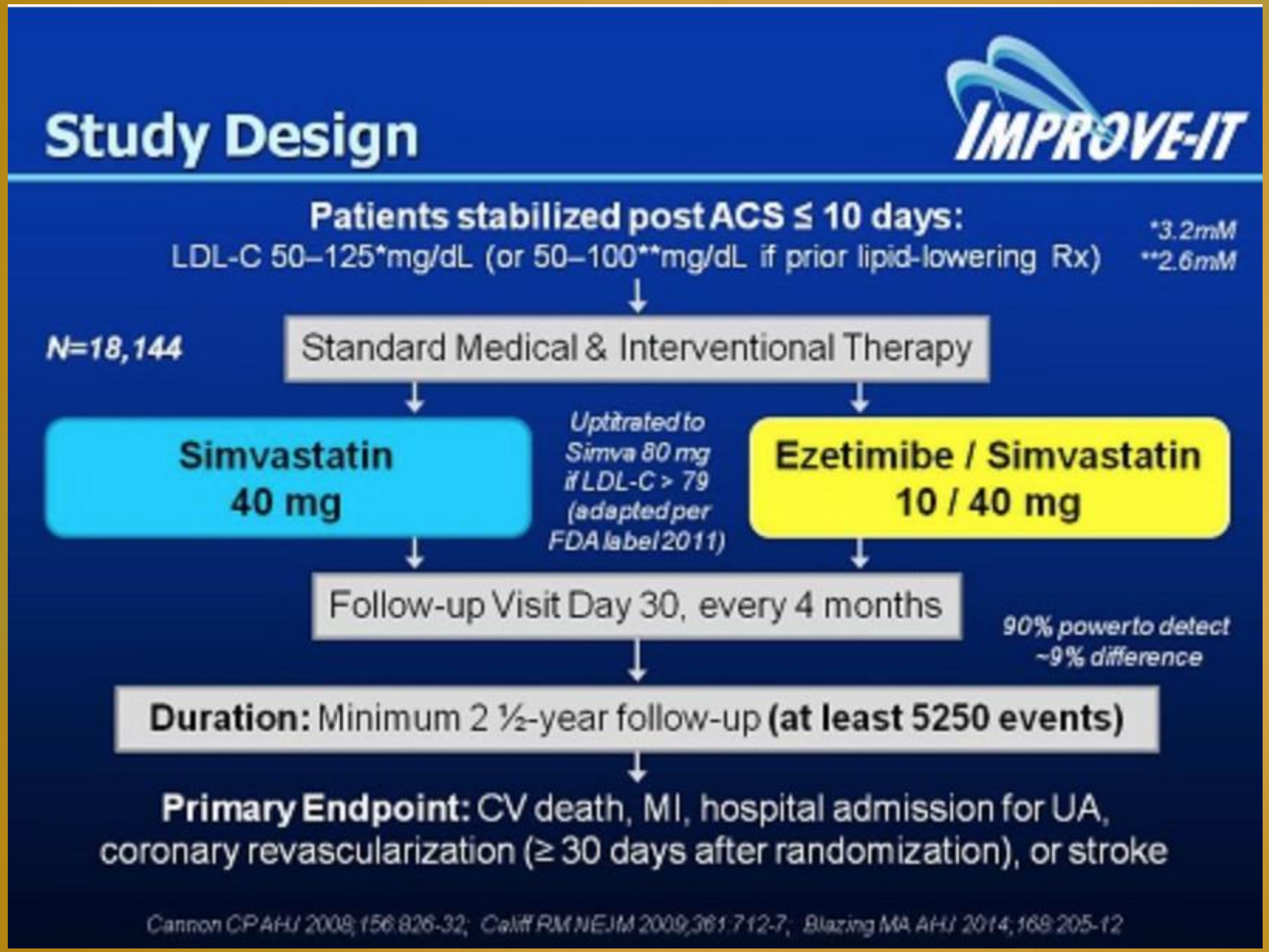

LDL-C ≤70 mg/dL LDL-C reduction of <50%
LDL-C >70 mg/dL LDL-C reduction of <50%
LDL-C ≤70 mg/dL LDL-C reduction of ≥50%
LDL-C >70 mg/dL LDL-C reduction of ≥50%
Cumulative hazard (%)
20
15
10
5
0
0
1
2
3
4
5
6
Time to first major CV event (years)


Overall log-rank test P = 0.0015
Probability of cardiac mortality (%)
50.0
40.0
30.0
20.0
10.0
0.0
0
1
2
3
4
5
6
7
8
Years
Progression (28.9%)
No change (14.5%)
Regression (4.0%)


FUORI
DI
TESTA

Caratteristica	*Atorvastatina*	*Fluvastatina*	*Lovastatina*	*Pravastatina*	*Rosuvastatina*	*Simvastatina*
Riduzione del colesterolo-LDL sierico ottenuta (%)	50	24	34	34	50	41
Riduzione del triacilglicerolo sierico ottenuta (%)	29	10	16	24	18	18
Aumento del colesterolo-HDL sierico ottenuto (%)	6	8	9	12	8	12
Emivita plasmatica (h)	14	1–2	2	1–2	19	1–2
Penetrazione nel sistema nervoso centrale	No	No	Sì	No	No	Sì
Escrezione renale della dose assorbita (%)	2	<6	10	20	10	13

Le statine sono farmaci che inibiscono la sintesi del colesterolo endogeno agendo sull'enzima idrossimetilglutaril-CoA reduttasi, che converte la molecola del 3-idrossi-3-metilglutaril-CoA in acido mevalonico, un precursore del colesterolo



L'ezetimibe è un farmaco capace di inibire selettivamente l'assorbimento intestinale del colesterolo assunto con la dieta e di quello proveniente dalla bile, senza causare gli effetti collaterali tipici delle resine sequestranti gli acidi biliari. Riduzione LDL 10-20%

STATE-OF-THE-ART PAPER

Targeting the Proprotein Convertase Subtilisin/Kexin Type 9 for the Treatment of Dyslipidemia and Atherosclerosis

Daniel Urban, MD, Janine Pöss, MD, Michael Böhm, MD, Ulrich Laufs,
Homburg/Saar, Germany

PCSK9 è una proteina appartenente alla famiglia delle subtilisine, che agisce mediante legame all'LDLR, **accelerandone la degradazione lisosomiale e riducendone, quindi, la densità recettoriale sulla superficie degli epatociti → questo aumenta la quota di LDL circolanti riducendone la captazione epatica ; anche sull'orletto a spazzola intestinale è espresso e ha lo stesso effetto: riduce l'assorbimento di lipidi**

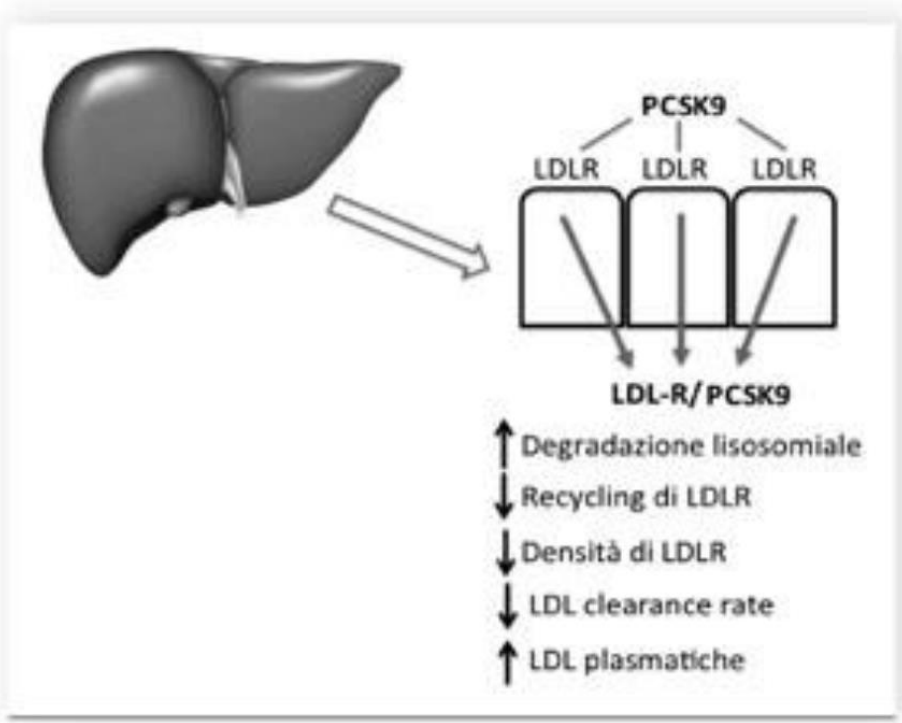
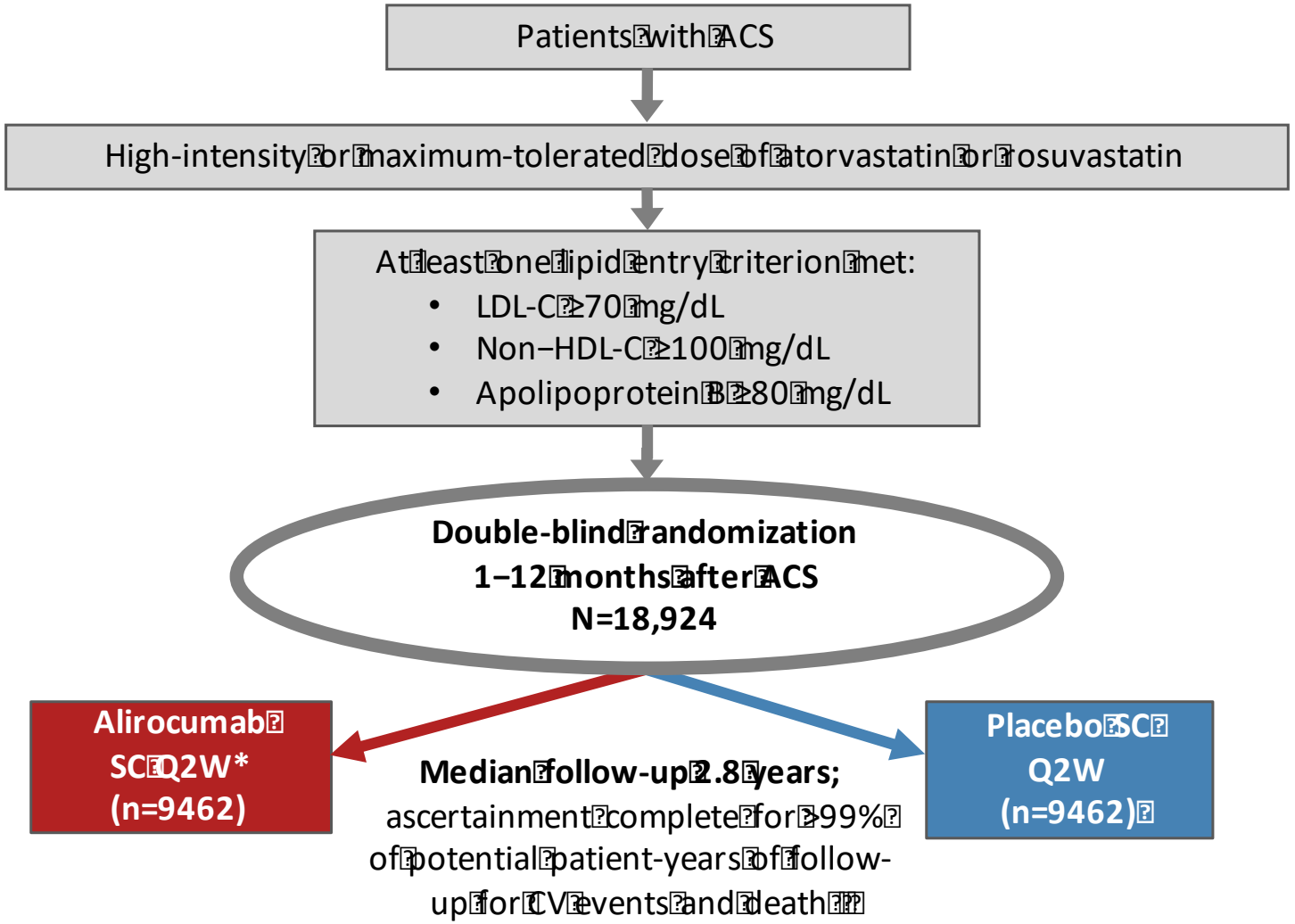


Figura 1. Meccanismo d'azione di PCSK9.
PCSK9 è una proteina appartenente alla famiglia delle subtilisine che, legandosi al recettore delle lipoproteine a bassa densità (LDLR), ne accelera la degradazione lisosomiale, riducendo quindi la densità recettoriale sulla superficie degli epatociti.

ALIROCUMAB ed EVOLOCUMAB

Design of the ODYSSEY OUTCOMES trial



*Blinded adjustment of alirocumab dose to target achieved LDL-C 25–50 mg/dL and avoid sustained levels <15 mg/dL

CV, cardiovascular; Q2W, every 2 weeks; SC, subcutaneous.

Baseline characteristics by history of PAD or CeVD

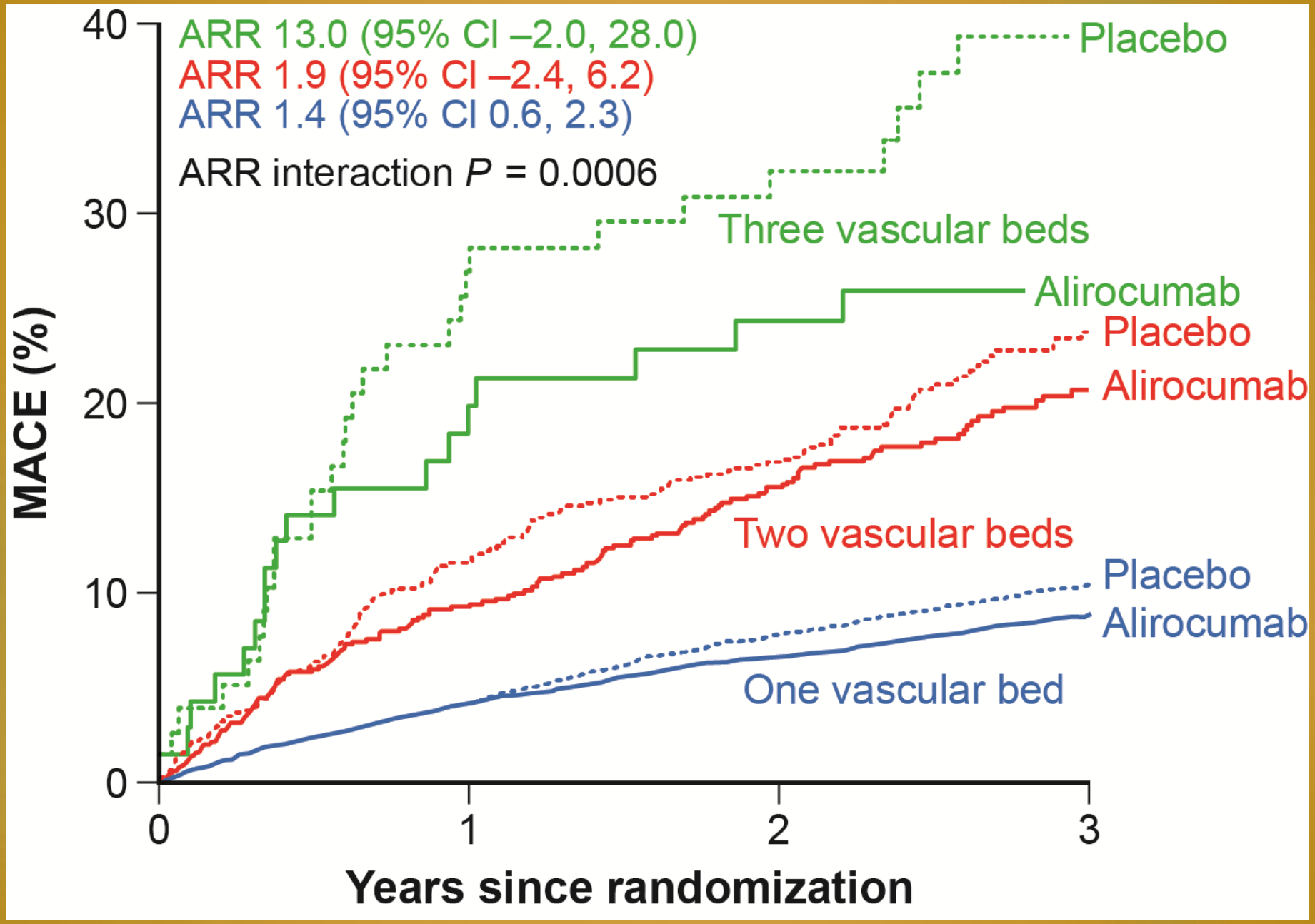
	Monovascular disease	Disease in two vascular beds		Disease in three vascular beds	P*
	Coronary without PAD or CeVD (n=17,370)	Coronary and PAD (n=610)	Coronary and CeVD (n=795)	Coronary, PAD, and CeVD (n=149)	
Age, years	58 (51,65)	62 (56,68)	62 (56,69)	66 (60,71)	<0.0001
Women	24.7	26.7	33.2	24.8	<0.0001
Index event					<0.0001
NSTEMI	47.9	56.3	55.4	63.1	
STEMI	35.1	31.1	28.6	22.8	
Unstable angina	17.1	11.7	16.0	14.1	
LLT at randomization					<0.0001
High-dose atorvastatin or rosuvastatin	89.2	86.1	85.4	81.2	
Other LLT	10.0	12.3	12.8	16.1	
No LLT	0.9	1.6	1.8	2.7	

Values are median (quartile 1, quartile 3) or %; LLT, lipid-lowering therapy. *Across disease subgroups.

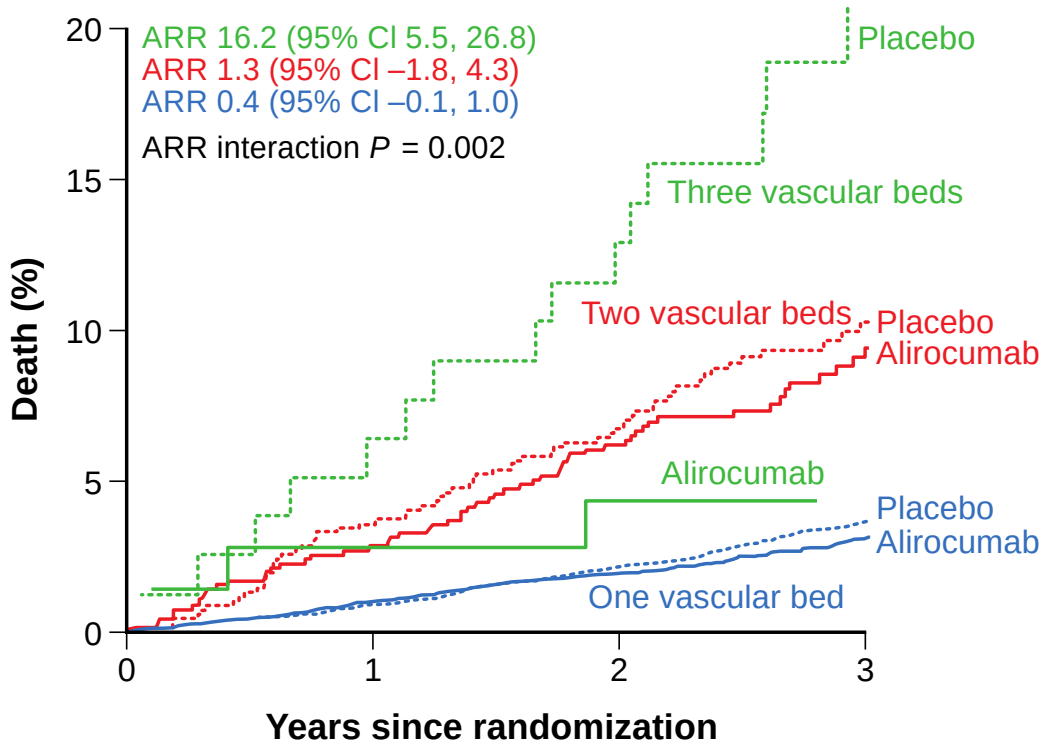
Baseline characteristics by history of PAD or CeVD

	Monovascular disease	Disease in two vascular beds		Disease in three vascular beds	*P**
	Coronary without PAD or CeVD (n=17,370)	Coronary and PAD (n=610)	Coronary and CeVD (n=795)	Coronary, PAD, and CeVD (n=149)	
LDL-C, mg/dL	86 (73, 103)	91 (76, 108)	90 (75, 109)	95 (80, 115)	<0.0001
LDL-C ≥100 mg/dL	29.1	35.7	36.5	40.9	<0.0001
HDL-C, mg/dL	42 (36, 50)	42 (36, 50)	43 (36, 51)	43 (37, 51)	NS
Non–HDL-C, mg/dL	114 (99, 136)	121 (105, 143)	120 (103, 144)	124 (108, 143)	<0.0001
Triglycerides, mg/dL	128 (94, 181)	134 (99, 187)	136 (98, 190)	135 (94, 182)	0.002
Apolipoprotein B, mg/dL	79 (69, 93)	83 (72, 96)	83 (71, 96)	82 (75, 95)	<0.0001
Lipoprotein(a), mg/dL	20.8 (6.6, 59.4)	25.5 (7.5, 68.1)	23.0 (7.1, 61.7)	29.4 (9.4, 74.5)	0.004
eGFR, mL/min per 1.73 m^2	78.5 (68.1, 90.4)	74.1 (61.6, 86.7)	72.9 (59.5, 85.8)	67.0 (52.2, 84.4)	<0.0001
eGFR <60 mL/min per 1.73 m^2	12.3	22.1	25.9	39.6	<0.0001

Values are median (quartile 1, quartile 3) or %. NS = p>0.05. eGFR, estimated glomerular filtration rate. *Across disease subgroups.


ARR 13.0 (95% CI –2.0, 28.0)
ARR 1.9 (95% CI –2.4, 6.2)
ARR 1.4 (95% CI 0.6, 2.3)
ARR interaction P = 0.0006
Placebo
Three vascular beds
Alirocumab
Placebo
Alirocumab
Two vascular beds
Placebo
Alirocumab
One vascular bed
MACE (%)
40
30
20
10
0
0
1
2
3
Years since randomization

Death: one, two or three vascular beds

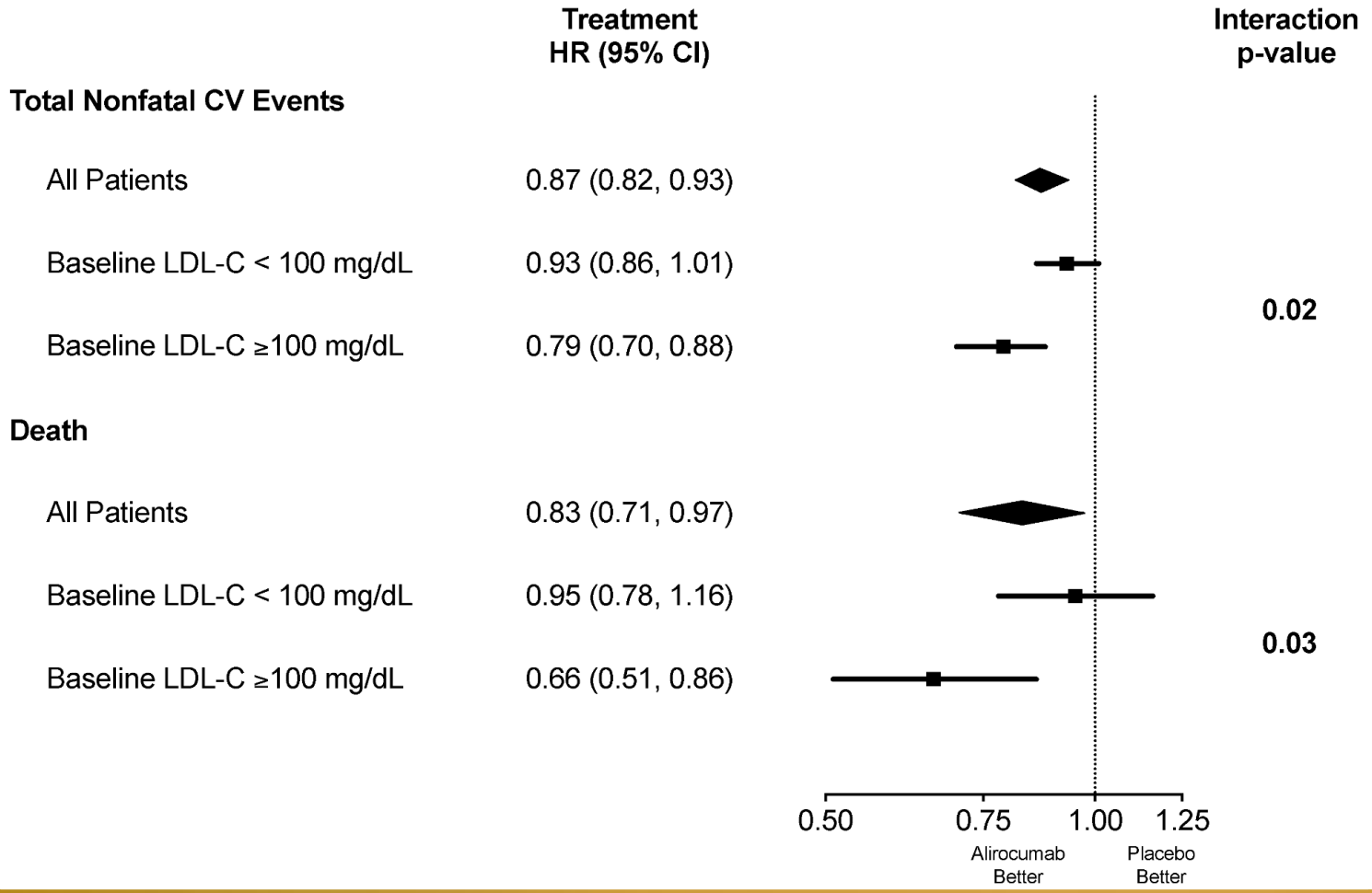


Safety endpoints

- Overall, no differences in incidence of adverse events or laboratory abnormalities between alirocumab and placebo, with the exception of local injection-site reactions, which occurred more often in the alirocumab group

- No major differences were observed between the vascular groups

Higher Baseline LDL-C Associated with Greater Alirocumab Benefit on Total Events



- 255 fewer total events with alirocumab among 5,629 patients with LDL-C ≥100 mg/dL at baseline
- 130 fewer total events with alirocumab among 13,295 patients with LDL-C <100 mg/dL at baseline

Criteri di prescrivibilità in prevenzione secondaria

- Ipercolesterolemia Non familiare LDL ≥ 100 mg/dl in presenza di trattamento on top con la massima dose di statine tollerate + Ezetimible
- Ipercolesterolemia Familiare Eterozigote LDL ≥ 100 mg
- Almeno 3 dosaggi di LDL non in range

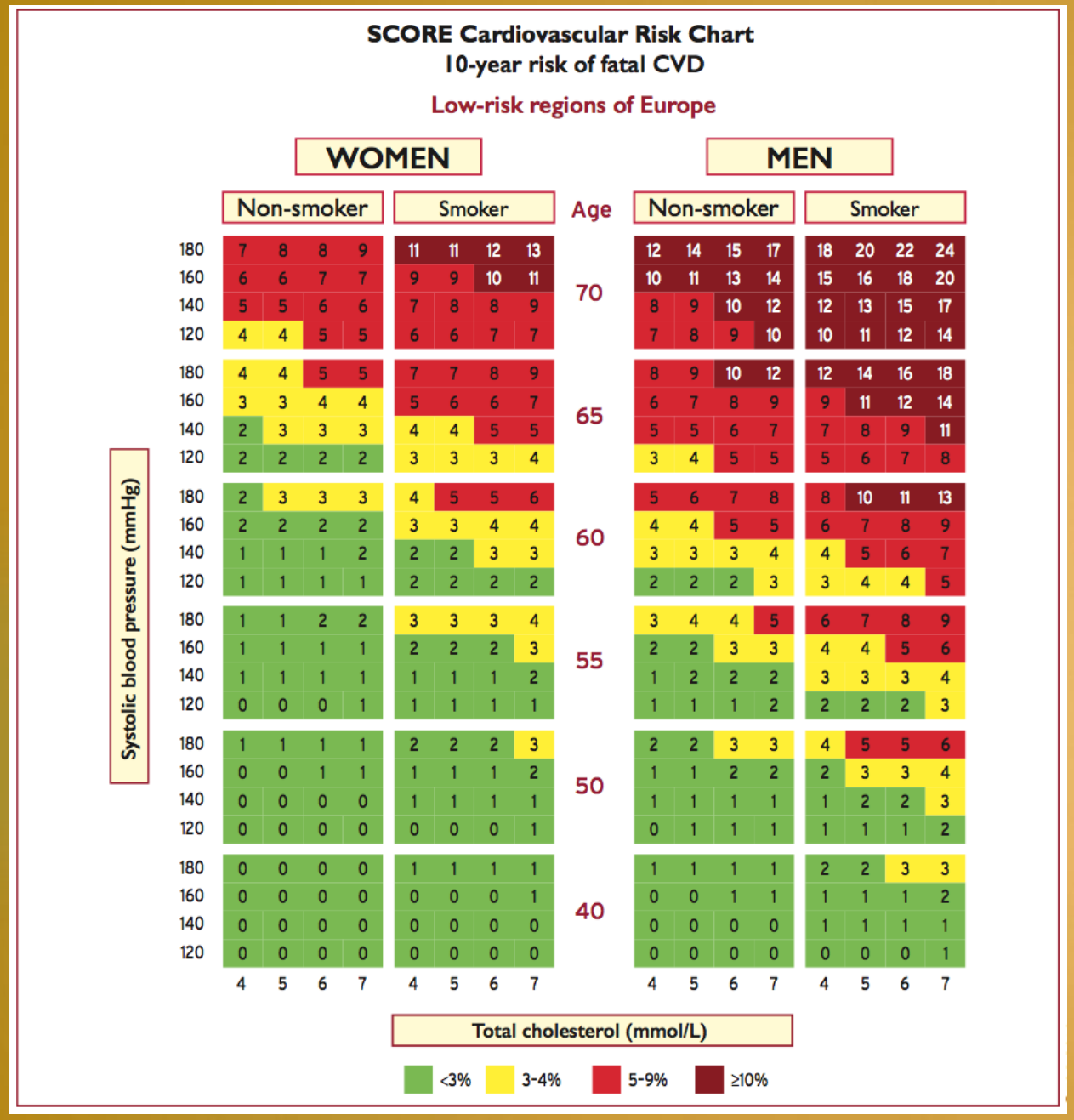
ESC European Society of Cardiology

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

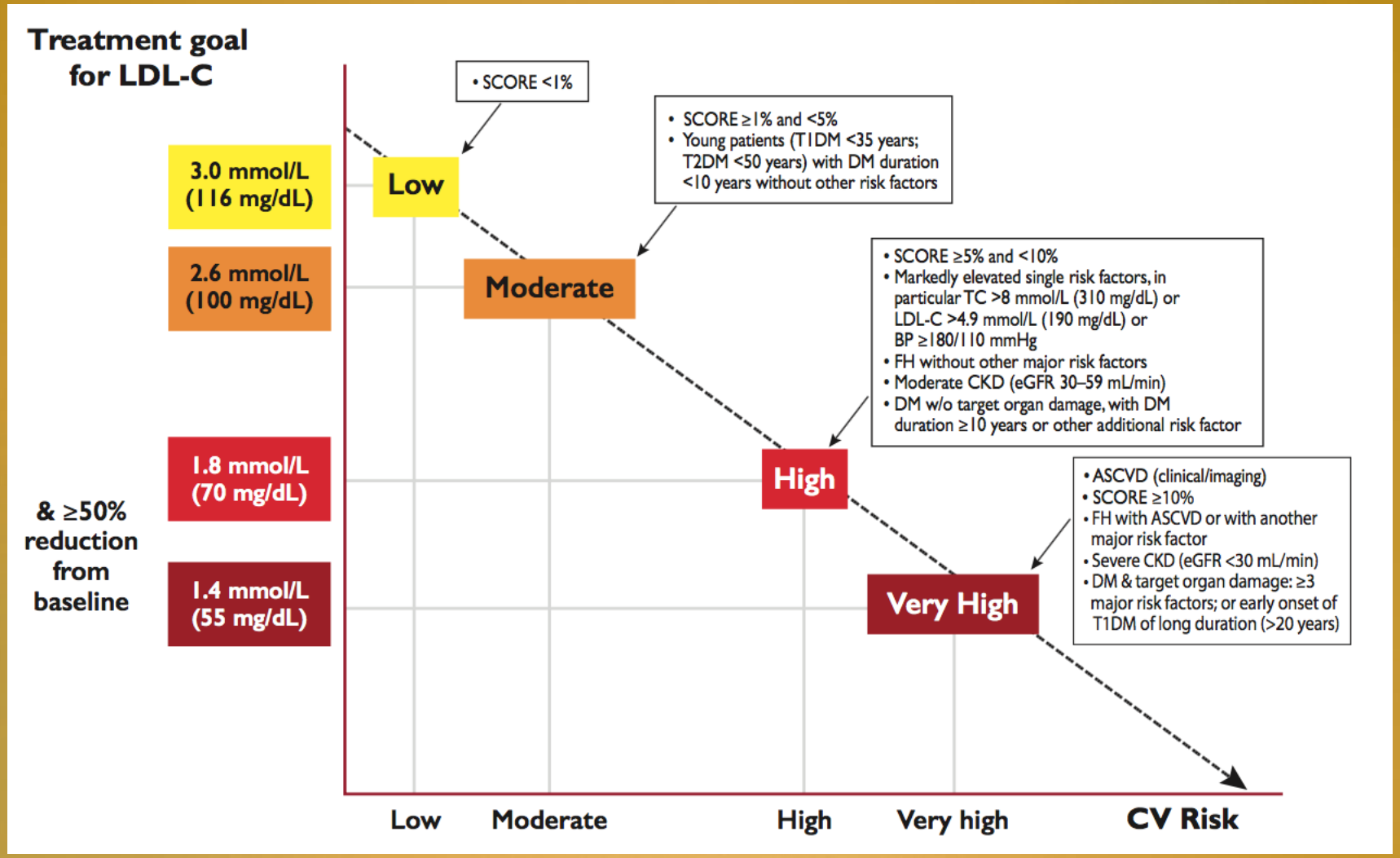
ESC/EAS GUIDELINES

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)



Very-high-risk	People with any of the following: Documented ASCVD, either clinical or unequivocal on imaging. Documented ASCVD includes previous ACS (MI or unstable angina), stable angina, coronary revascularization (PCI, CABG, and other arterial revascularization procedures), stroke and TIA, and peripheral arterial disease. Unequivocally documented ASCVD on imaging includes those findings that are known to be predictive of clinical events, such as significant plaque on coronary angiography or CT scan (multivessel coronary disease with two major epicardial arteries having >50% stenosis), or on carotid ultrasound. DM with target organ damage,[a] or at least three major risk factors, or early onset of T1DM of long duration (>20 years). Severe CKD (eGFR <30 mL/min/1.73 m^2). A calculated SCORE ≥10% for 10-year risk of fatal CVD. FH with ASCVD or with another major risk factor.
High-risk	People with: Markedly elevated single risk factors, in particular TC >8 mmol/L (>310 mg/dL), LDL-C >4.9 mmol/L (>190 mg/dL), or BP ≥180/110 mmHg. Patients with FH without other major risk factors. Patients with DM without target organ damage,[a] with DM duration ≥10 years or another additional risk factor. Moderate CKD (eGFR 30–59 mL/min/1.73 m^2). A calculated SCORE ≥5% and <10% for 10-year risk of fatal CVD.
Moderate-risk	Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years, without other risk factors. Calculated SCORE ≥1 % and <5% for 10-year risk of fatal CVD.
Low-risk	Calculated SCORE <1% for 10-year risk of fatal CVD.



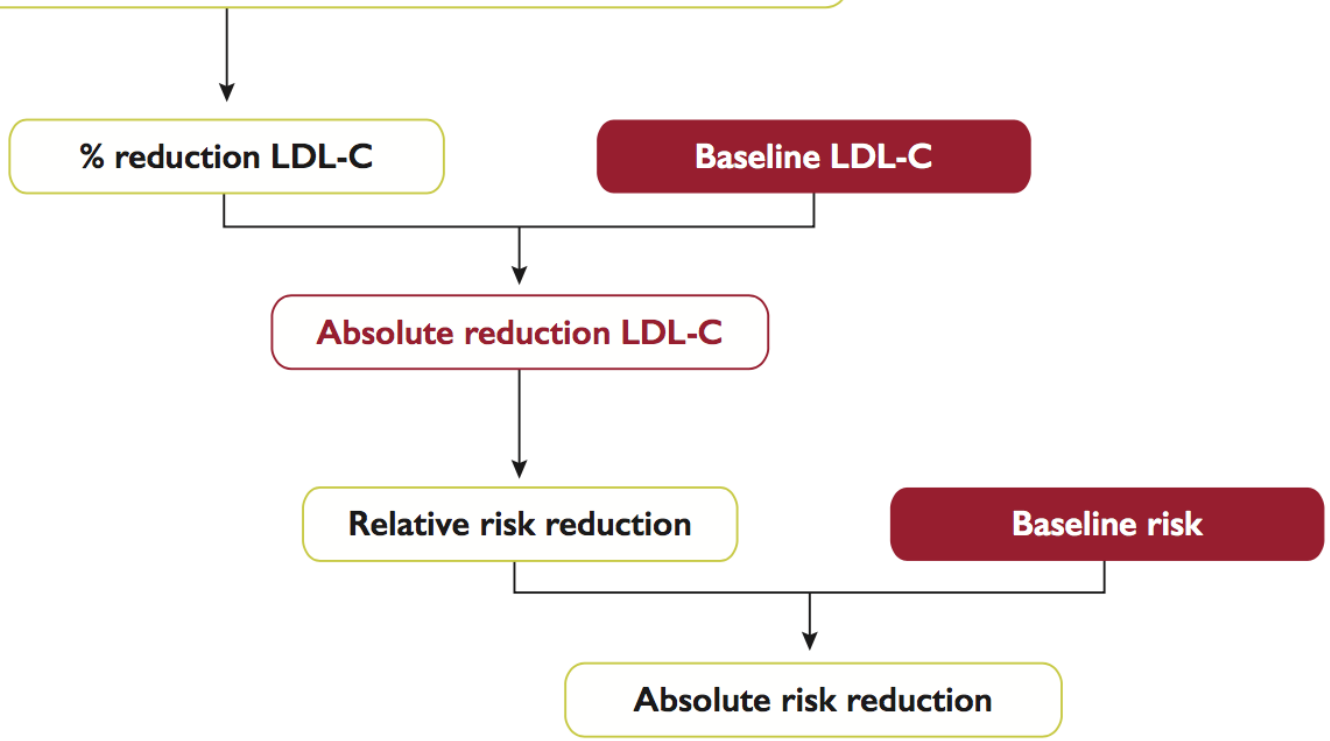
- **New/revised concepts**

More intensive reduction of LDL-C across CV risk categories

- For secondary prevention in very-high-risk patients, an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) are recommended.
  - 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 therapy, an LDL-C goal of <1.0 mmol/L (<40 mg/dL) may be considered.

Intensity of lipid lowering treatment

Treatment	Average LDL-C reduction
Moderate intensity statin	≈ 30%
High intensity statin	≈ 50%
High intensity statin plus ezetimibe	≈ 65%
PCSK9 inhibitor	≈ 60%
PCSK9 inhibitor plus high intensity statin	≈ 75%
PCSK9 inhibitor plus high intensity statin plus ezetimibe	≈ 85%



Testing lipids

How often should lipids be tested?

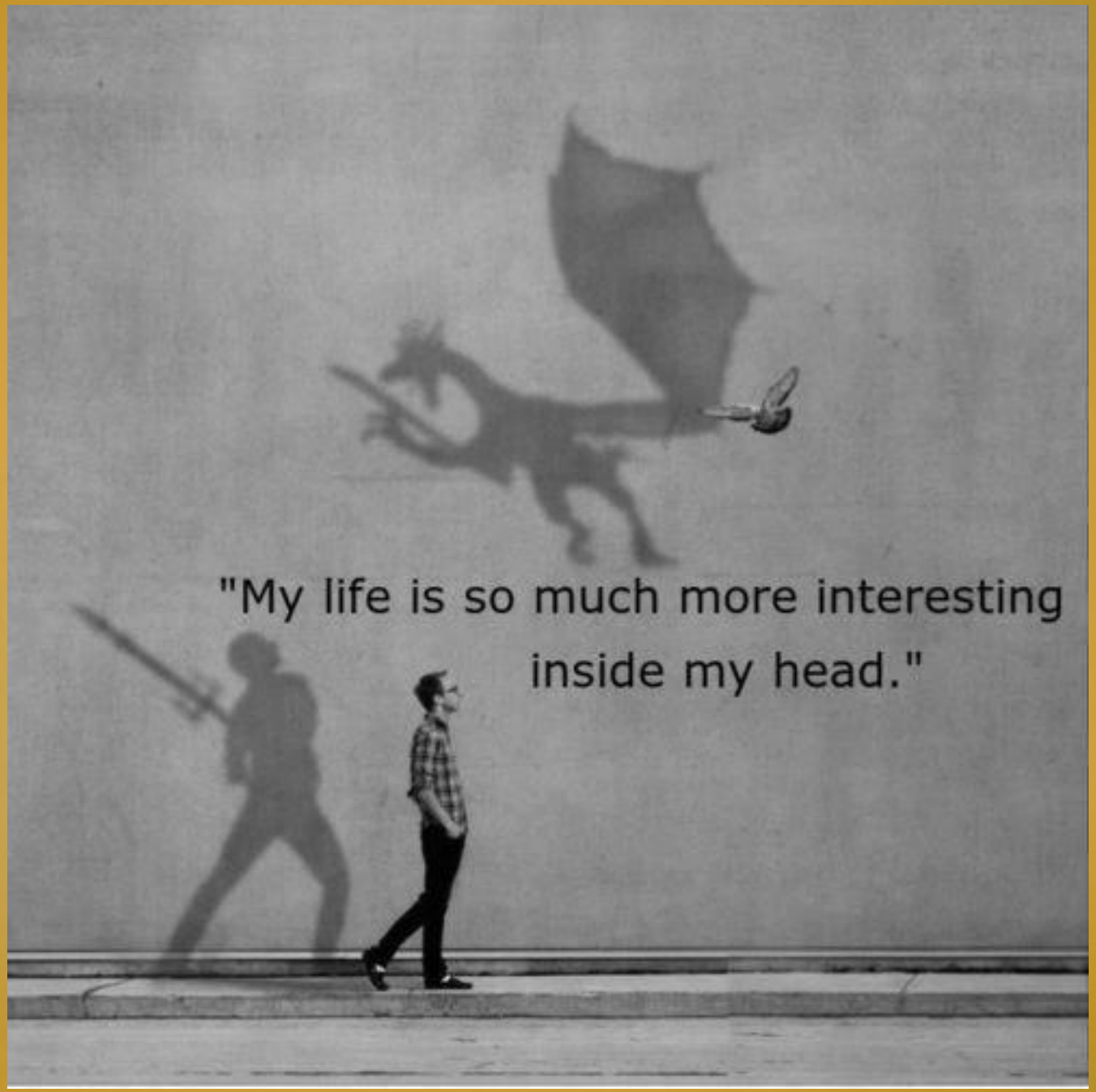
- Before starting lipid-lowering drug treatment, at least two measurements should be made, with an interval of 1–12 weeks, with the exception of conditions where prompt drug treatment is suggested, such as ACS and very high-risk patients.

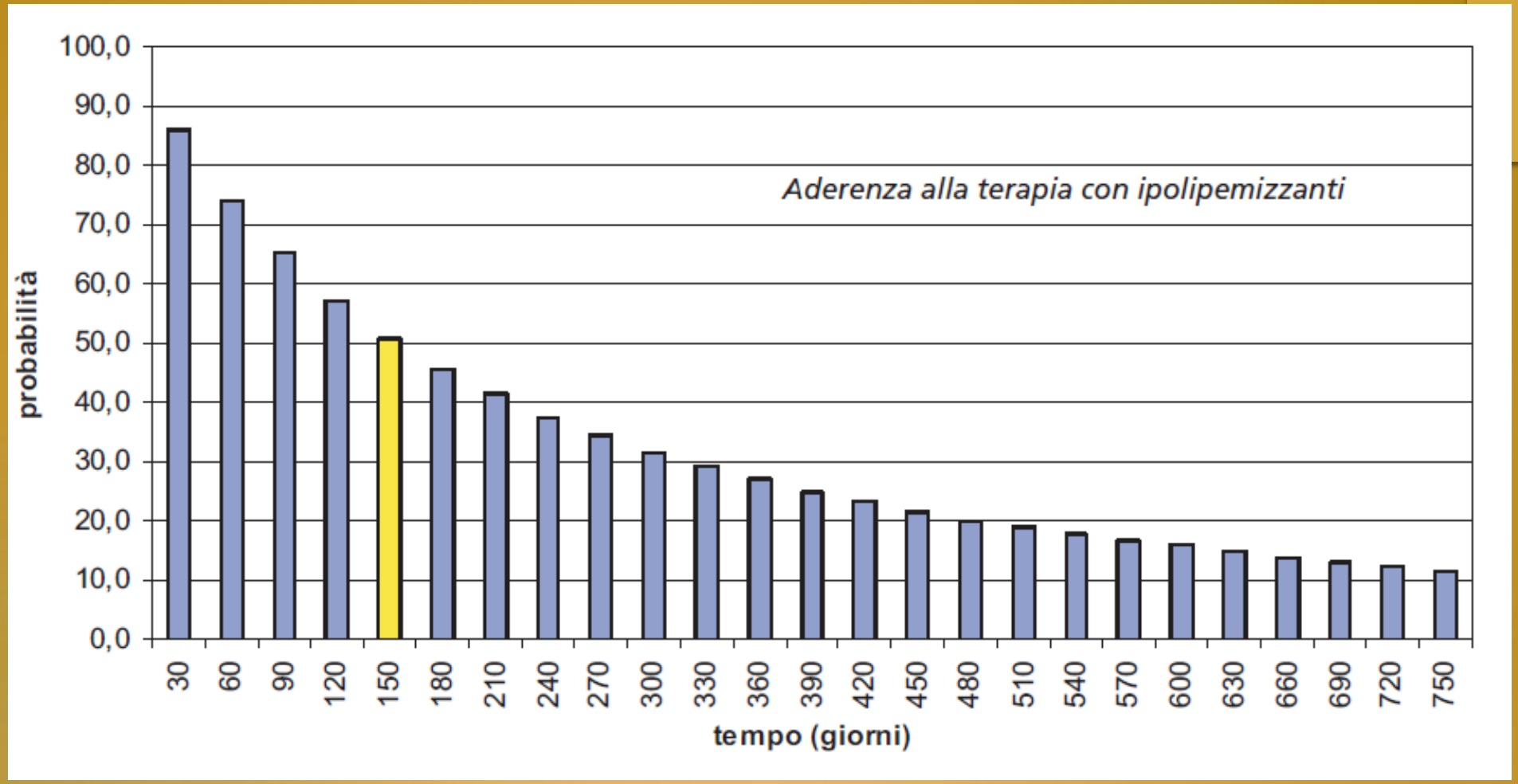
How often should a patient's lipids be tested after starting lipid-lowering treatment?

- After starting treatment: 8 (±4) weeks.
- After adjustment of treatment: 8 (±4) weeks until the goal is achieved.

How often should lipids be tested once a patient has achieved the target or optimal lipid level?

- Annually (unless there are adherence problems or other specific reasons for more frequent reviews).


"My life is so much more interesting
inside my head."



Prevenzione primaria: 50% di sospensione della terapia a 120 giorni
Prevenzione secondaria: 50 % di sospensione della terapia a 210 giorni

Aderenza e persistenza alla terapia con ipolipemizzanti in relazione agli esiti clinici in una popolazione in prevenzione cardiovascolare nella Regione Friuli Venezia Giulia. G Ital Cardiol 2010; 11 (2 Suppl 2): 85S-91S

ClinicoEconomics and Outcomes Research
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ORIGINAL RESEARCH

Adherence to statin treatment following a myocardial infarction: an Italian population-based survey

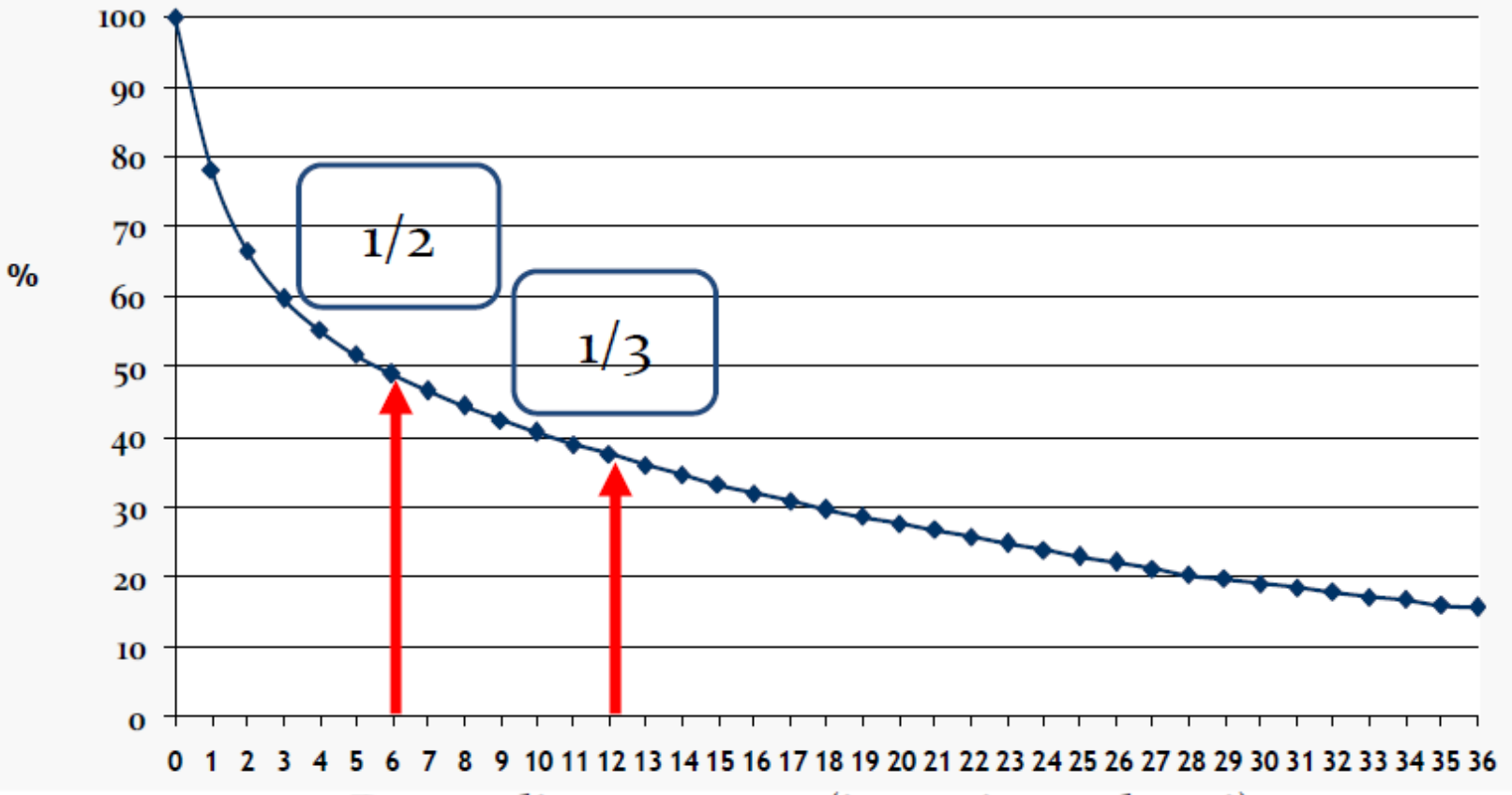
Studio su 3.369 pazienti ricoverati per IMA in 10 ospedali Italiani

- 28,5% non erano stati trattati adeguatamente con statine durante il ricovero
- 36,2% non avevano ricevuto una prescrizione di statine alla dimissione
- 57.6% non era trattato con statine a due anni dalla dimissione

ClinicoEconomics and Outcomes Research
1 June 2015

Probabilità cumulata di continuazione del trattamento con statine

(Dati Umbria 1997-2000)

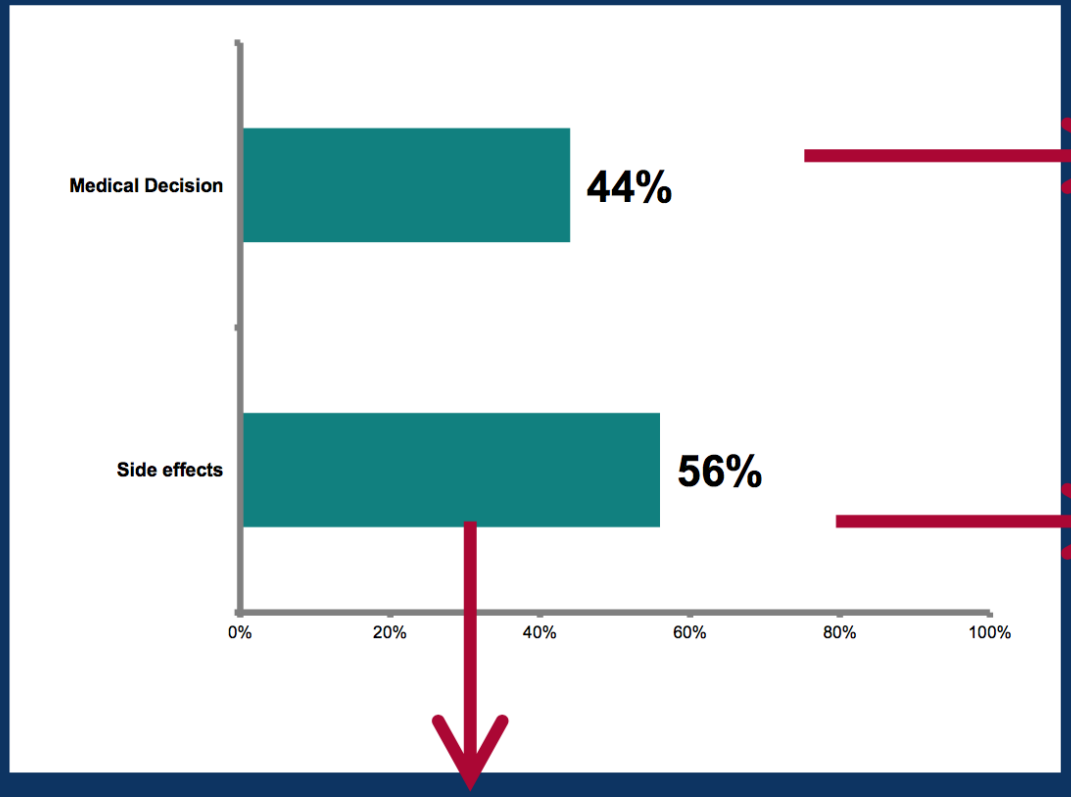


Da Cas et al, Eur J Clin Pharm 2003

Le cause di non-aderenza alla terapia della ipercolesterolemia sono complesse e possono dipendere

- **dal paziente**
- **dal medico**
- **dal Sistema sanitario**

Reported causes of Switch form Intensive Statin Therapy after ACS



1. "Dosage too high"
2. "Afraid of major adverse reactions"

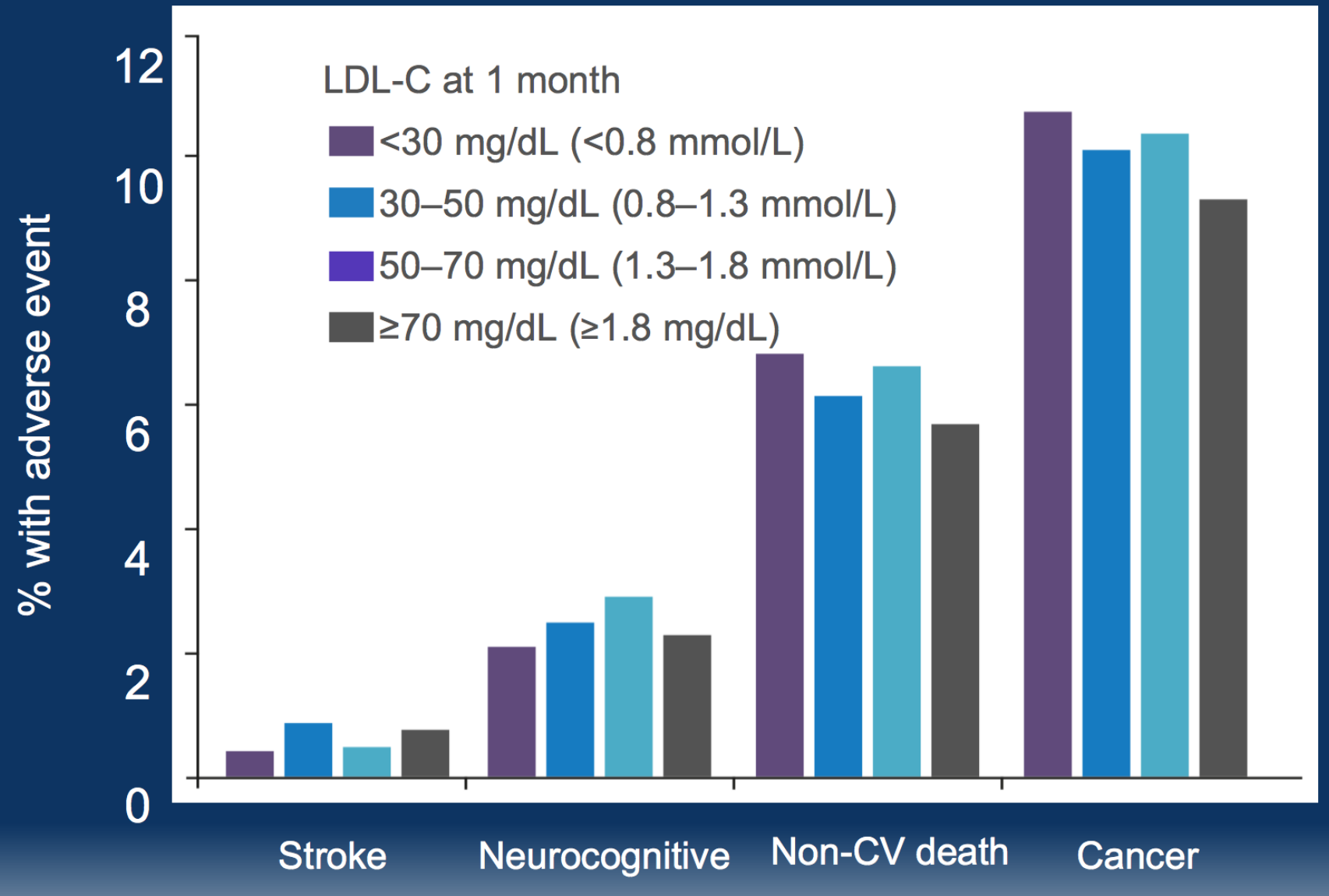
Reported Side Effects

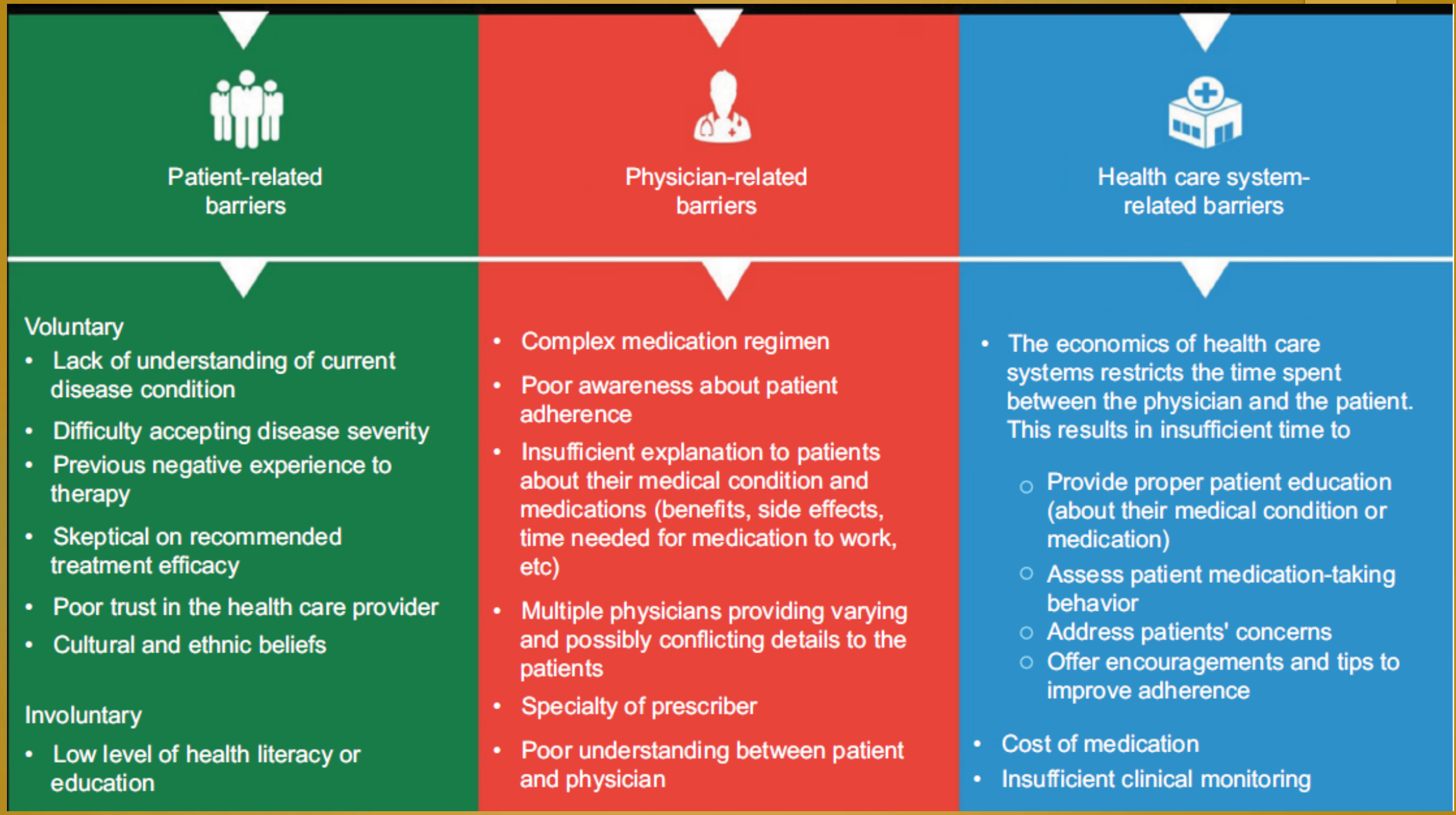
- Dyspepsia
- Fatigue
- Headache
- Myalgias
- Asymptomatic increase in liver enzymes
- Asymptomatic increase in total CK

eGFR < 60 ml/min: HR 1.4 (95% CI, 2.9-1.2)

Colivicchi F, et al. Int J Cardiol (2011), 152: 56-60

Adverse events are not increased at lower achieved LDL-C

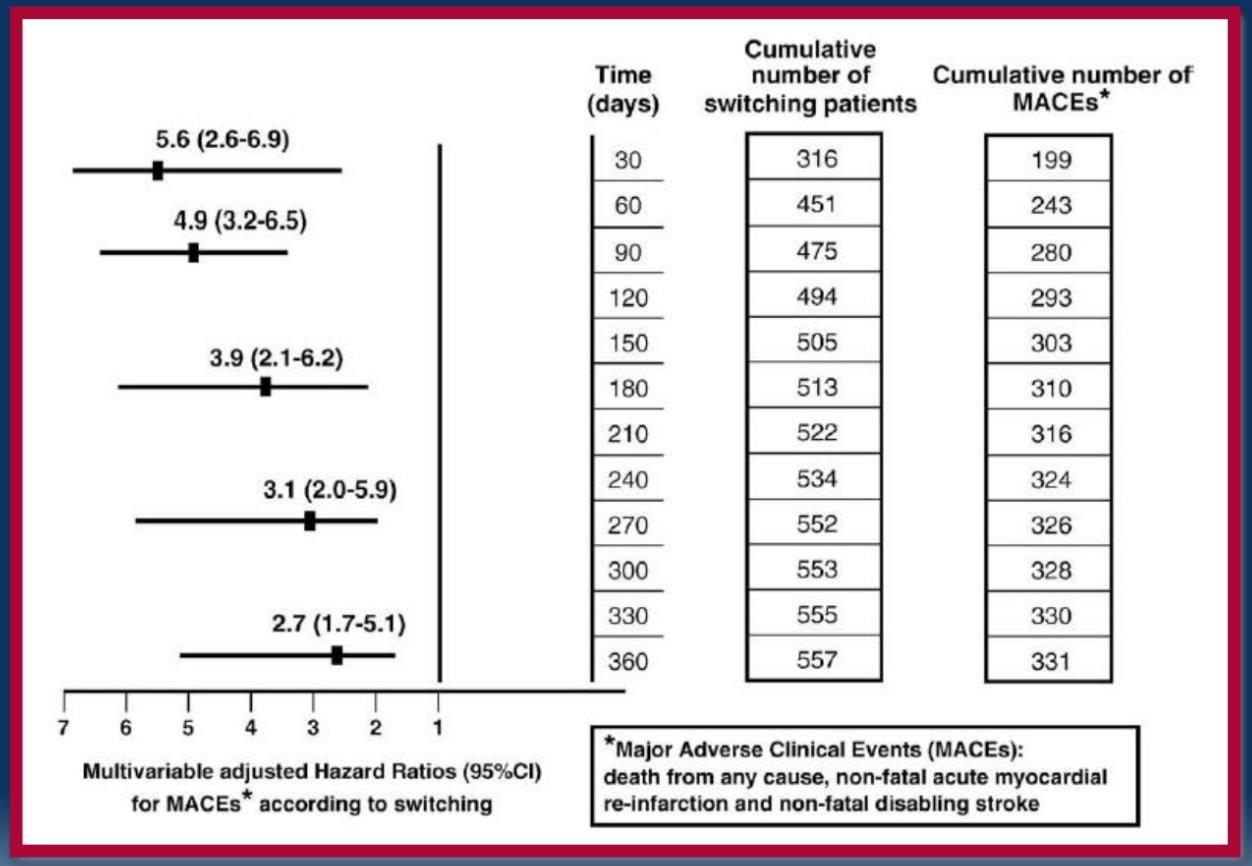




Lansberg P et al. Nonadherence to statins: individualized intervention strategies outside the pill box. Vascular Health and Risk Management 2018:14 91–102.

La sostituzione dell'atorvastatina 80 mg con una terapia ipolipemizzante meno efficace si associa ad un significativo peggioramento della prognosi clinica

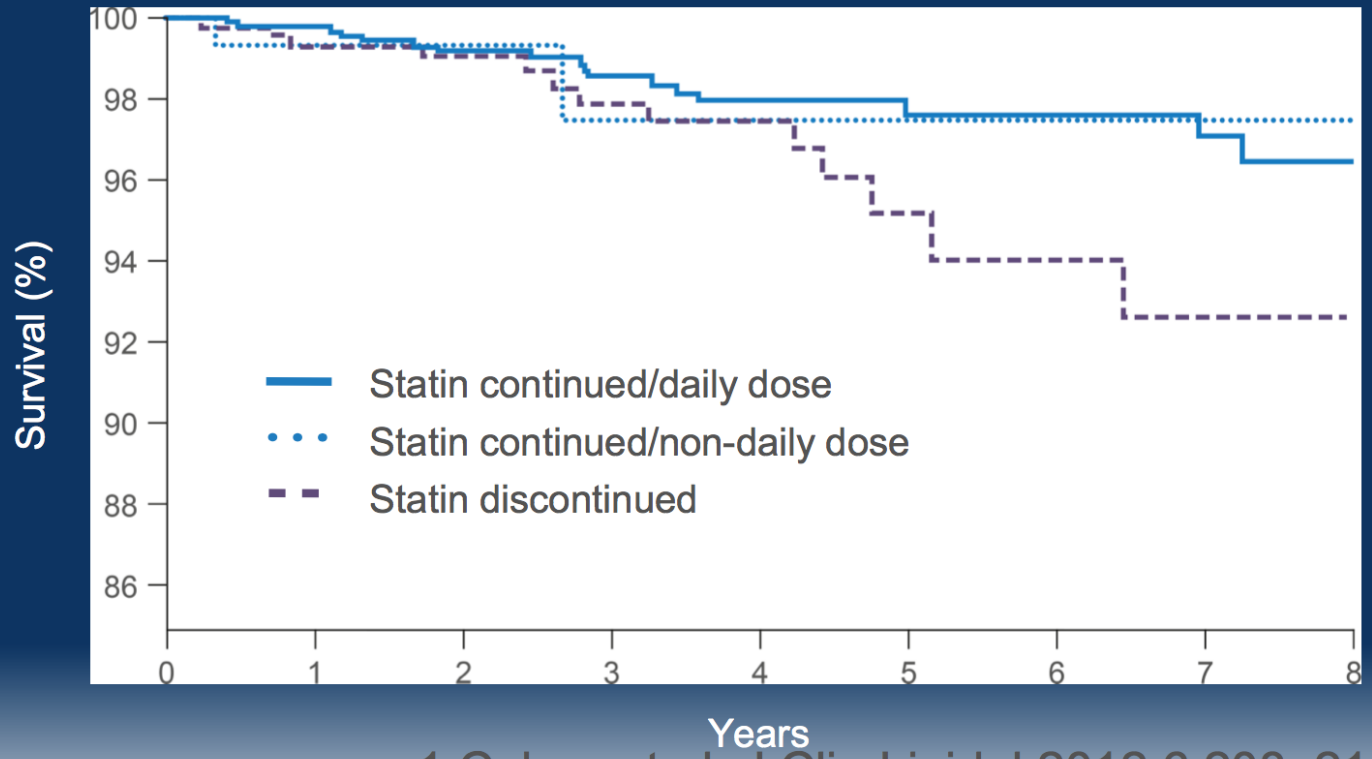
Incremento di circa 3 volte della probabilità di eventi cardiovascolari sfavorevoli. In caso di interruzione precoce (entro 30 giorni dalla dimissione) la probabilità di eventi sfavorevoli aumenta fino ad oltre 5 volte.



Colivicchi F, et al. Int J Cardiol (2011); 152: 56-60

Statin discontinuation leads to reduced survival

- Side effects are the most common reason patients discontinue statins[1]
- Survival is reduced in patients who discontinue, even compared to those on non-daily statin doses[2]



1.Cohen et al. J Clin Lipidol 2012;6:208–215.
2.Mampuya et al. Am Heart J 2013;166:597–603.

Monitoring liver and muscle enzymes

How often should liver enzymes (ALT) be routinely measured in patients on lipid-lowering drugs?

- Before treatment.
- Once, 8–12 weeks after starting a drug treatment or after dose increase.
- Routine control of ALT thereafter is not recommended during statin treatment, unless symptoms suggesting liver disease evolve. During treatment with fibrates, control of ALT is still recommended.

What if liver enzymes become elevated in a person taking lipid-lowering drugs?

If ALT <3× ULN:

- Continue therapy.
- Recheck liver enzymes in 4–6 weeks.

If ALT rises to ≥3× ULN

- Stop lipid-lowering therapy or reduce dose and recheck liver enzymes within 4–6 weeks.
- Cautious reintroduction of therapy may be considered after ALT has returned to normal.
- If ALT remains elevated check for the other reasons.

How often should CK be measured in patients taking lipid-lowering drugs?

Pre-treatment

- Before starting therapy.
- If baseline CK is >4× ULN, do not start drug therapy; recheck.

Monitoring:

- Routine monitoring of CK is not necessary.
- Check CK if patient develops myalgia.

Be alert regarding myopathy and CK elevation in patients at risk, such as: elderly patients, those on concomitant interfering therapy, multiple medications, liver or renal disease, or athletes.

What if CK becomes elevated in a person taking lipid-lowering drugs?

Re-evaluate indication for statin treatment.

If ≥4× ULN:

- If CK >10× ULN: stop treatment, check renal function, and monitor CK every 2 weeks.
- If CK <10× ULN: if no symptoms, continue lipid-lowering therapy while monitoring CK between 2 and 6 weeks.
- If CK <10× ULN: if symptoms present, stop statin and monitor normalization of CK, before rechallenge with a lower statin dose.
- Consider the possibility of transient CK elevation for other reasons such as exertion.
- Consider myopathy if CK remains elevated.
- Consider combination therapy or an alternative drug.

If <4× ULN:

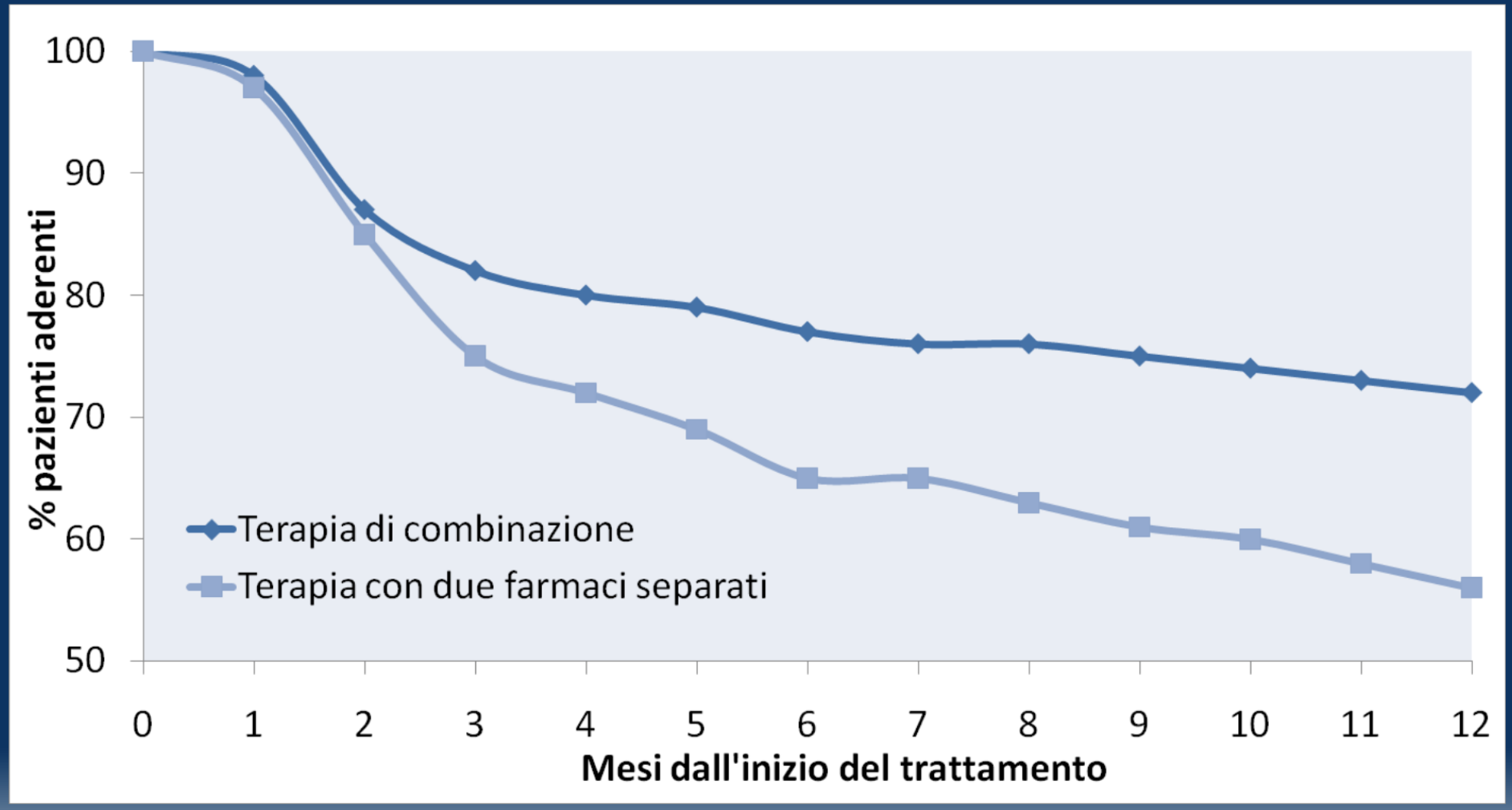
- If no muscle symptoms, continue statin (patient should be alerted to report symptoms; check CK).
- If muscle symptoms, monitor symptoms and CK regularly.
- If symptoms persist, stop statin and re-evaluate symptoms after 6 weeks; re-evaluate indication for statin treatment.
- Consider rechallenge with the same or another statin.
- Consider low-dose statin, alternate day or once/twice weekly dosing regimen, or combination therapy.

For details on CK elevation and treatment of muscular symptoms during statin treatment see algorithm in *Supplementary Figure 4*.

In which patients should HbA1c or blood glucose be checked?

- Regular checks of HbA1c or glucose should be considered in patients at high-risk of developing diabetes, and on high-dose statin treatment.
- Groups to be considered for glucose control are the elderly and patients with metabolic syndrome, obesity, or other signs of insulin resistance.

Uno schema posologico più semplice migliora la continuità della terapia



La necessità di coinvolgere il Paziente

Un approccio interamente incentrato sul medico comporta una elevata probabilità di non-aderenza

Un approccio incentrato sul paziente facilità l'identificazione e la gestione delle condizioni di rischio

Schema posologico più semplice possibile
Rassicurare in caso di dubbi immotivati

Una migliore comunicazione migliora l'aderenza, la soddisfazione e la prognosi clinica

Conclusioni

1. L'associazione tra i livelli di colesterolo e gli eventi cardiovascolari/mortalità CV è indiscutibile
2. Gli studi recenti hanno dimostrato come l'ottenimento di valori di LDL i più bassi possibile continuino a ridurre gli eventi
3. I pazienti vanno stratificati in maniera attenta e va considerata in pazienti very high risk una dose d'attacco "aggressiva" ed un follow-up stretto del paziente
4. E' fondamentale far squadra tra medici ospedalieri/specialisti sul territorio/MMG attorno al paziente nel coinvolgerlo permettendogli di capire l'importanza dei trattamenti che sta assumendo ed ottimizzare la compliance terapeutica.
5. Terapie di associazione o monoiniezioni mensili sono armi utili al fine di ottimizzare la compliance

Grazie per l’attenzione