XX Congresso AMD
Genova, 15 maggio 2015

Anticorpi monoclonali nell'ipercolesterolemia

Dott. Carlo Giorda
S. C. M. Metaboliche e Diabetologia, ASL Torino 5

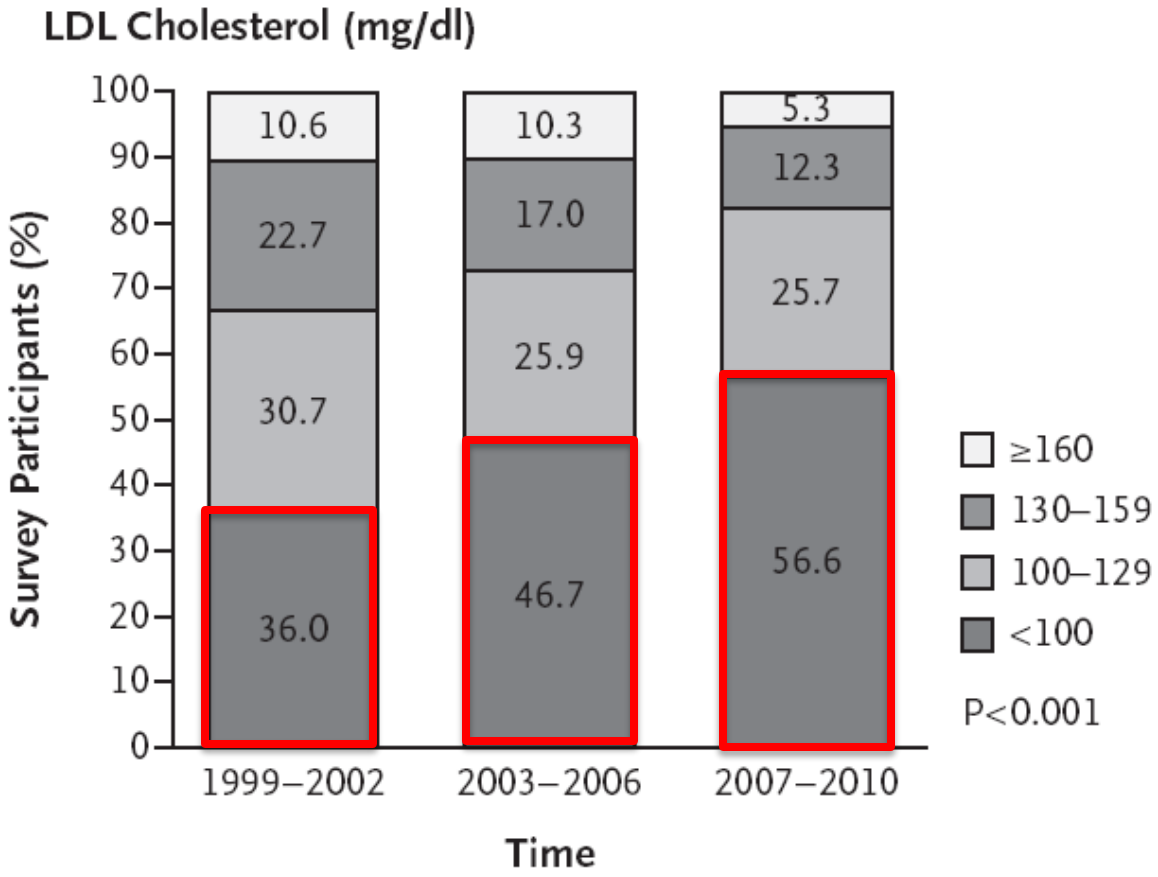
Guidelines to Manage Dyslipidemia

2013 ACC/AHA Guidelines[a,c]		2011 ESC/EAS Guidelines[b,c]	
Category	**Recommendation**	**Category**	**Recommendation**
Clinical ASCVD	• High-intensity statin • Combination therapy if 50% LDL-C lowering not reached	CVD	• LDL-C < 70 mg/dL or 50% reduction in LDL-C
Primary LDL-C ≥ 190 mg/dL	• High-intensity statin	Familial dyslipidemia (FH, FCH)	• LDL-C < 100 mg/dL or maximal LDL-C reduction with drug combination and LDL apheresis
Diabetes (type 1 or 2) without clinical ASCVD but LDL-C = 70-189 mg/dL	• Low risk: moderate-intensity statin • High risk: high-intensity statin	Diabetes mellitus or type 1 with target organ damage	• LDL-C < 70 mg/dL or 50% reduction in LDL-C
None of the above but estimated 10-y risk ≥ 7.5%	• Moderate- to high-intensity statin	None of the above but estimate 10-y risk (SCORE)	• Very high risk (SCORE > 10%) LDL-C • < 70 mg/dL or 50% reduction • High risk (SCORE 5% to 0%) LDL-C • < 100 mg/dL • Moderate risk (SCORE 1% to 5%) LDL-C < 120 mg/dL

a. Stone NJ, et al. *J Am Coll Cardiol*. 2014;63(25 Pt B):2889-2934[11]; b. European Association for Cardiovascular Prevention & Rehabilitation, et al. *Eur Heart J* 2011;32:1769-1818[12]; c. Ray KK, et al. *Eur Heart J*. 2014;35:960-968.[13]

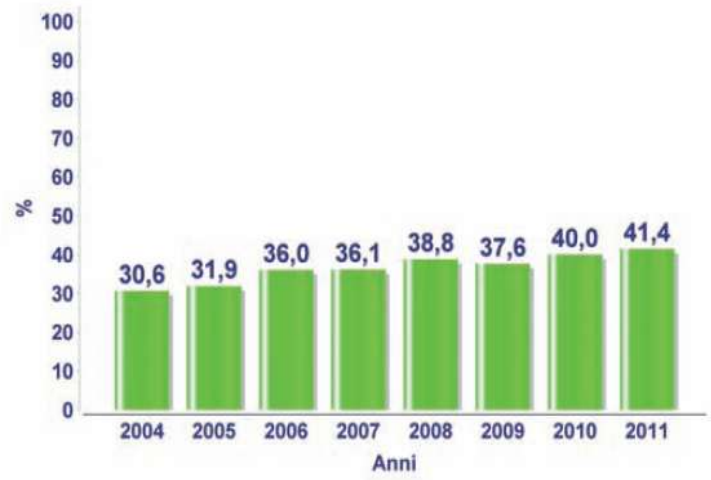
La realtà assistenziale

Achievement of Goals in U.S. Diabetes Care, 1999–2010

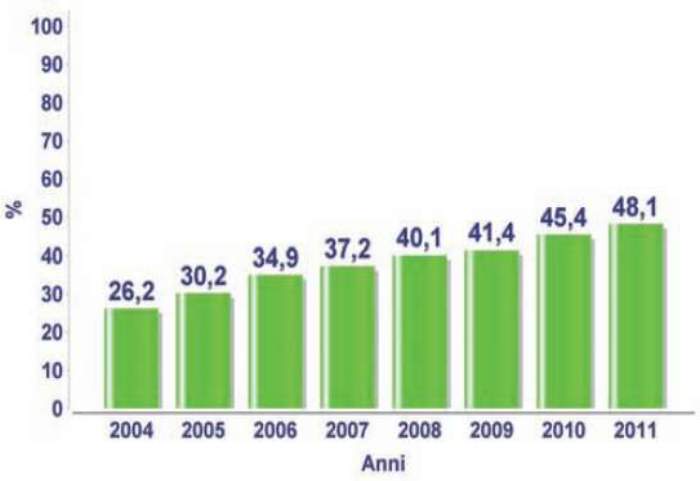


Ali MK et al. N Engl J Med 2013;368:1613-24

Soggetti con C-LDL <100 mg/dl DM1

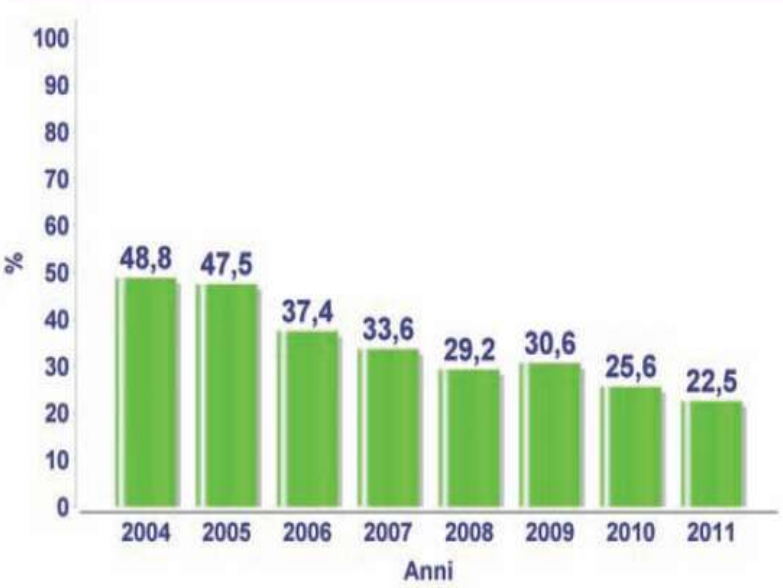


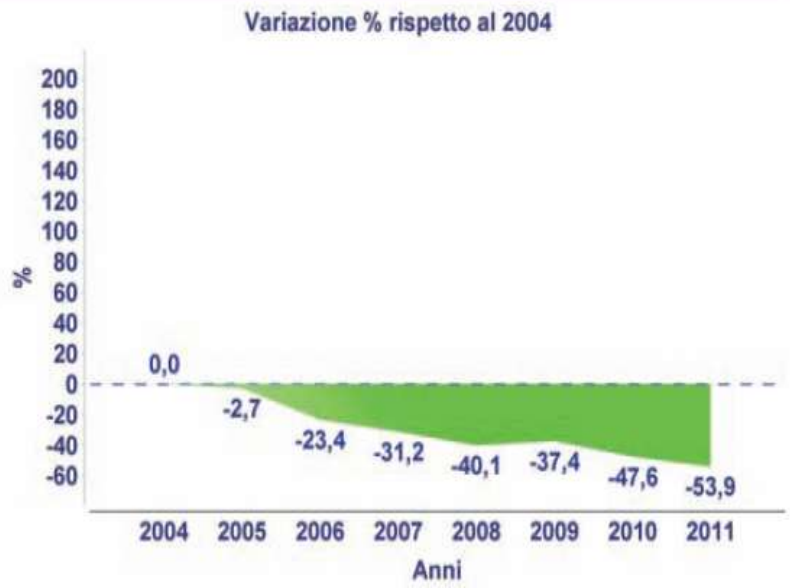
Soggetti con C-LDL <100 mg/dl DM2



Soggetti con valori di C-LDL ≥130 mg/dl nonostante il trattamento con statine

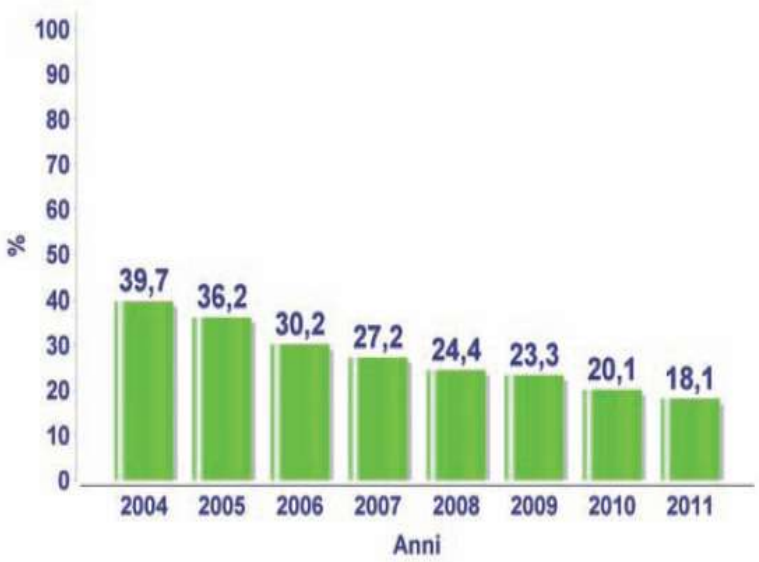
DM1





Soggetti con valori di C-LDL ≥130 mg/dl nonostante il trattamento con statine

DM2



Pregi e limiti delle terapie attuali

Terapie farmacologiche esistenti

- **Statine**
- **Fibrati**
- **Ezetimibe**
- **Resine a scambio ionico**
- **Acidi grassi Omega 3**

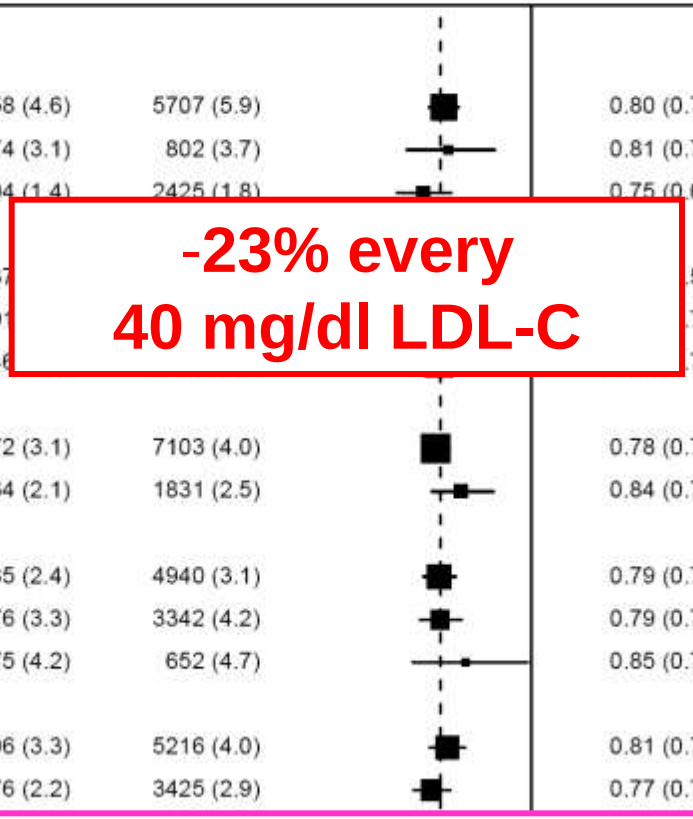
Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials

Cholesterol Treatment Trialists' (CTT) Collaboration*

Lancet 2010; 376: 1670–81

Webfigure 10: Effects on MAJOR VASCULAR EVENTS per mmol/L reduction in LDL cholesterol, by baseline prognostic factors in 21 statin vs control trials

Subgroup	Events (% p.a.) Statin/more	Events (% p.a.) Control/less	RR (CI) per 1 mmol/L reduction in LDL–C	Heterogeneity/ trend test
Previous vascular disease:				
CHD	4558 (4.6)	5707 (5.9)	0.80 (0.77 – 0.83)	
Non–CHD vascular	674 (3.1)	802 (3.7)	0.81 (0.71 – 0.92)	χ^2_2=3.15 (p=0.2)
None	1904 (1.4)	2425 (1.8)	0.75 (0.69 – 0.82)	
Diabetes:				
Type 1 diabetes	137		.58 – 1.01)	
Type 2 diabetes	1791		.74 – 0.86)	χ^2_2=0.21 (p=0.9)
No diabetes	5146		.76 – 0.82)	
Sex:				
Male	5572 (3.1)	7103 (4.0)	0.78 (0.75 – 0.81)	χ^2_1=3.93 (p=0.05)
Female	1564 (2.1)	1831 (2.5)	0.84 (0.77 – 0.91)	
Age (years):				
≤ 65	3885 (2.4)	4940 (3.1)	0.79 (0.75 – 0.83)	
>65, ≤ 75	2676 (3.3)	3342 (4.2)	0.79 (0.74 – 0.84)	χ^2_1=0.68 (p=0.4)
> 75	575 (4.2)	652 (4.7)	0.85 (0.73 – 0.99)	
Treated hypertension:				
Yes	4306 (3.3)	5216 (4.0)	0.81 (0.77 – 0.85)	χ^2_1=2.53 (p=0.1)
No	2576 (2.2)	3425 (2.9)	0.77 (0.73 – 0.81)	



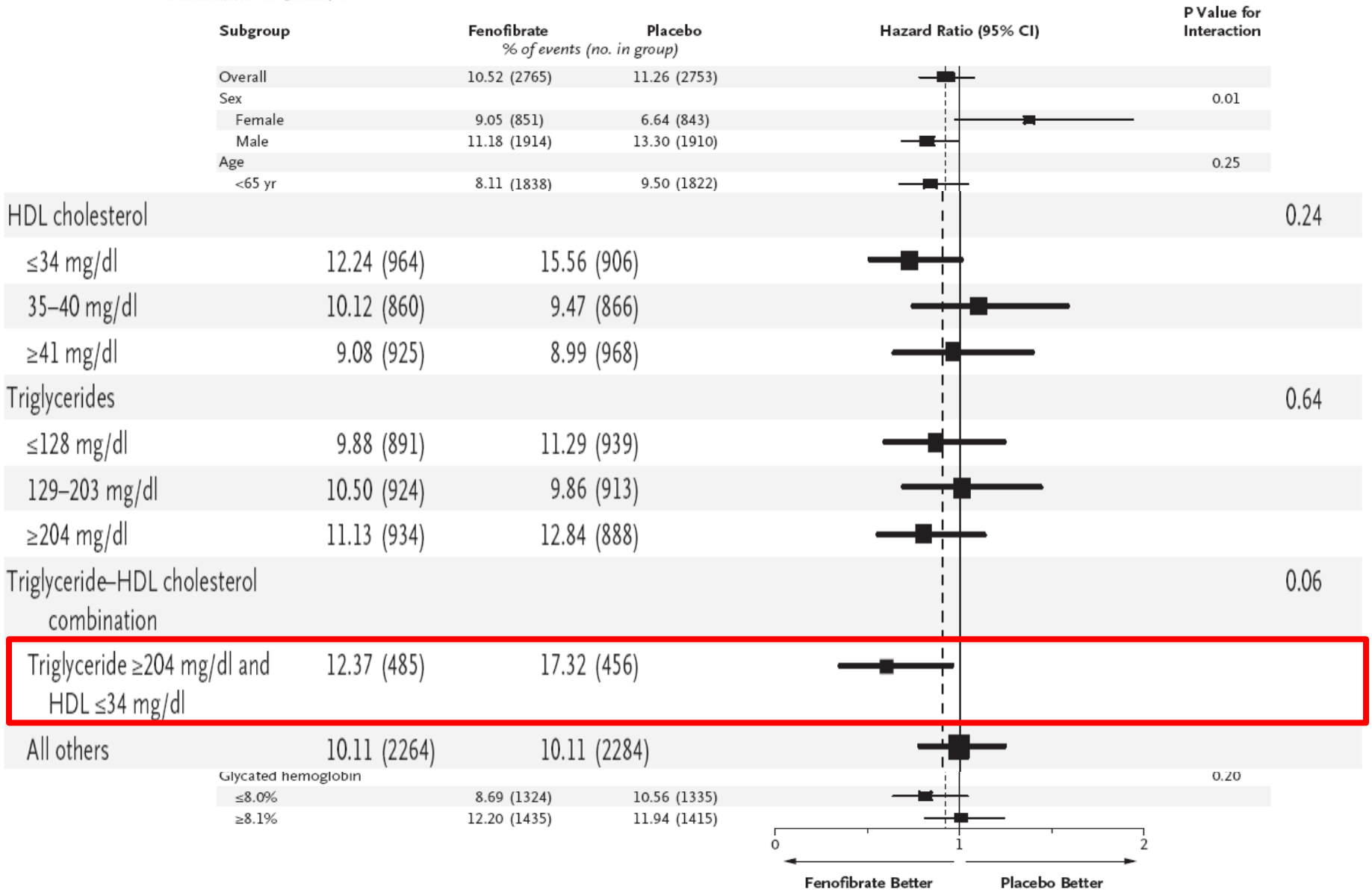
-23% every 40 mg/dl LDL-C

ORIGINAL ARTICLE

N Engl J Med 2010; 362:1563-74

Effects of Combination Lipid Therapy in Type 2 Diabetes Mellitus

The ACCORD Study Group*



Approximate Dose Equivalency of Statin LDL-C Efficacy

Statin Drug	Dosage, mg/d				
Rosuvastatin[a]	40	20	10*	5	
Atorvastatin[b,c]	80	40	20	10*	
Simvastatin[b,c]		(80)	40	20*	10
Pitavastatin[d]			4	2*	1
Lovastatin[b,c]			80	40*	20
Pravastatin[b,c]				80	40*
Fluvastatin[b,c]				80*	40
Approximate ↓LDL-C	51%-55%	46%-52%	39%-47%	35%-42%	28%-34%

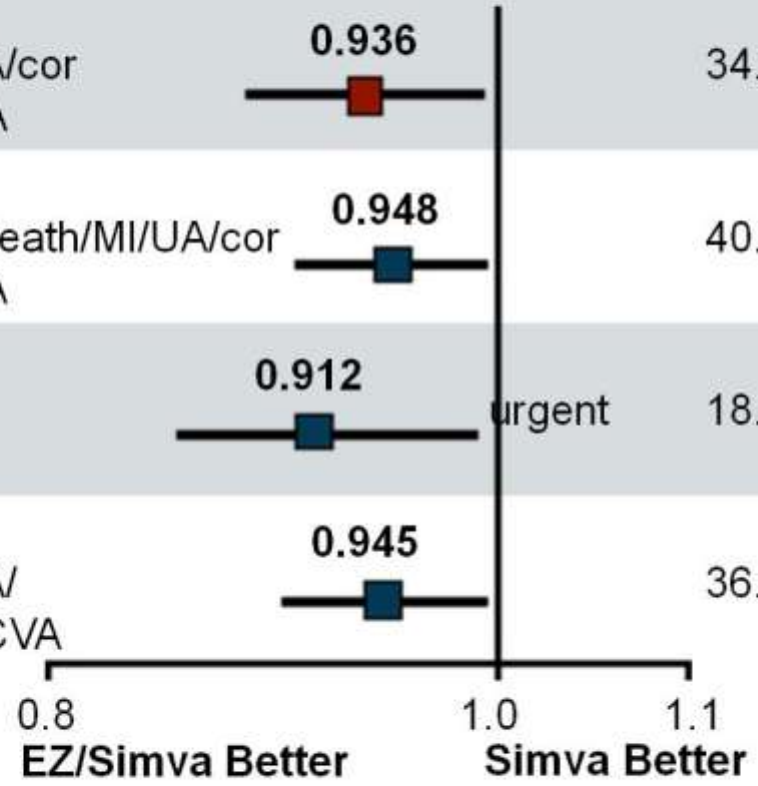
*Most commonly used dose in the United States.

a. Crestor® PI 2013[1]; b. Roberts WC. *Am J Cardiol*. 1997;80:106-107[2]; c. Stein E, et al. *J Cardiovasc Pharmacol Therapeut*. 1997;2:7-16[3]; d. Livalo® PI 2013.[4]

IMPROVE-IT

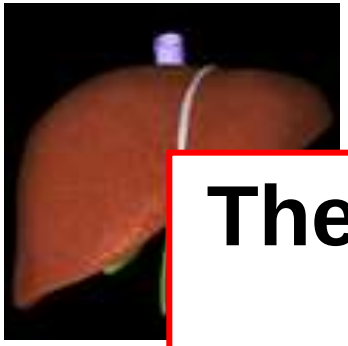
Efficacy …and proof of concept

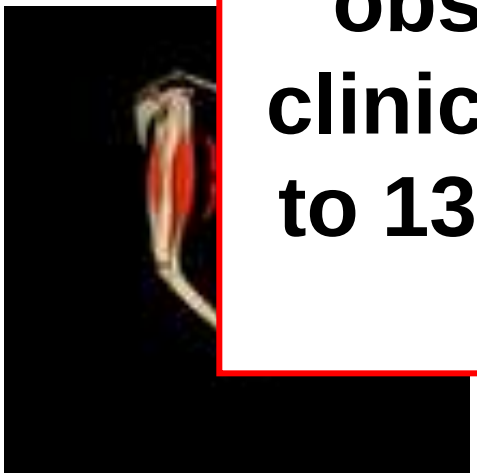
		Simva*	EZ/ Simva*	*P* Value
Primary • CVD/MI/UA/cor revasc/CVA	0.936	34.7	32.7	.016
Secondary #1 • All-cause death/MI/UA/cor revasc/CVA	0.948	40.3	38.7	.034
Secondary #2 • CHD/MI/ cor revasc	0.912	18.9	17.5	.016
Secondary #3 • CVD/MI/UA/ all revasc/CVA	0.945	36.2	34.5	.035



Coronary revascularization, ≥ 30 days after randomization; All revascularization, ≥ 30 days.
*7-year event rates (%)
Cannon CP, et al. AHA 2014. LBCT.02.[10]

Problemi con le Statine





The rate of statin discontinuation owing to adverse events, observed in clinical trials and clinical practice, ranges from 4% to 13%, and is mainly caused by myalgias.

0.08% Miopatia grave (CK>10 volte)
< 0.01% Rabdomiolisi, fatale nel 8%

***JACC* 2002; 40:567**

Persistence and determinants of statin therapy among middle-aged patients free of cardiovascular disease.

RESULTS

• Persistence with statin therapy **fell to 67%** in the first 6 months after treatment and continued to decline over the next 3 years **to 39**%.

• We observed **lower persistence** in patients who used the **greatest number of pharmacies** and **prescribing physicians**

Perreault S et al. Eur J Clin Pharmacol 2005; 61:667-74

Nutr Metab Cardiovasc Dis.2014 Oct;24(10):1057-1066.

«True» resistance to statins.

Reiner Z

The resistance to statins has been associated with :

polymorphisms in the 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA-R), P-glycoprotein (Pg-P/ABCB1), breast cancer resistance protein (BCRP/ABCG2), multidrug resistance-associated proteins (MRP1/ABCC1 and MRP2/ABCC2), organic anion transporting polypeptides (OATP), RHOA, Nieman-Pick C1-like1 protein (NPC1L1), farnesoid X receptor (FXR), cholesterol 7alpha-hydroxylase (CYP7A1), Apolipoprotein E (ApoE), proprotein convertase subtilisin/kexin type 9 (PCSK9), low density lipoprotein receptor (LDLR), lipoprotein (a) (LPA), cholesteryl ester transfer protein (CETP), and tumor necrosis factor α (TNF-α) genes.

Il rischio residuo

Residual CV Risk

- The relative CV risk reduction in patients with dyslipidemia following statin therapy is ~ 25% - 35%[a]
  - Management guidelines for dyslipidemia focus on reducing hypercholesterolemia through aggressive LDL-C treatment
- Use of high-dose statins does not eliminate risk in patients with established CV disease and hypercholesterolemia
  - PROVE-IT trial[a] → 20% CV event recurrence rate in patients with ACS, despite maximal-dose atorvastatin[b]

a. Hermans MP, et al. *Ther Adv Chronic Dis*. 2011;2:307-323[5]; b. Cannon CP, et al. *N Engl J Med*. 2004;350:1495-1504.[6]

Trattamento ipocolesterolemizzante in Italia sulla base del target di LDL-C, tra i soggetti ad alto o altissimo rischio CV di età compresa tra 40 e 79 anni (n=7,047 milioni di soggetti*)

- La grande maggioranza dei pazienti non a target è a rischio CV alto o molto alto

	LDL target SI	LDL target NO
Pazienti con diabete tipo 2:	**20.1%**	**79.9%**
Pazienti in prevenzione secondaria:	**14.7%**	**85.3%**

- Tra i pazienti ad alto o altissimo rischio, i farmaci a maggiore efficacia sono necessari per portare a target quasi 6 pazienti su 10

- Quasi 3 su 10, in particolare, necessitano farmaci in grado di ridurre LDL-C almeno del 50%

* Estrapolazione dallo studio CHECK

Poli A. et al. Pharmacol Res. 2011 Oct;64(4):393-6

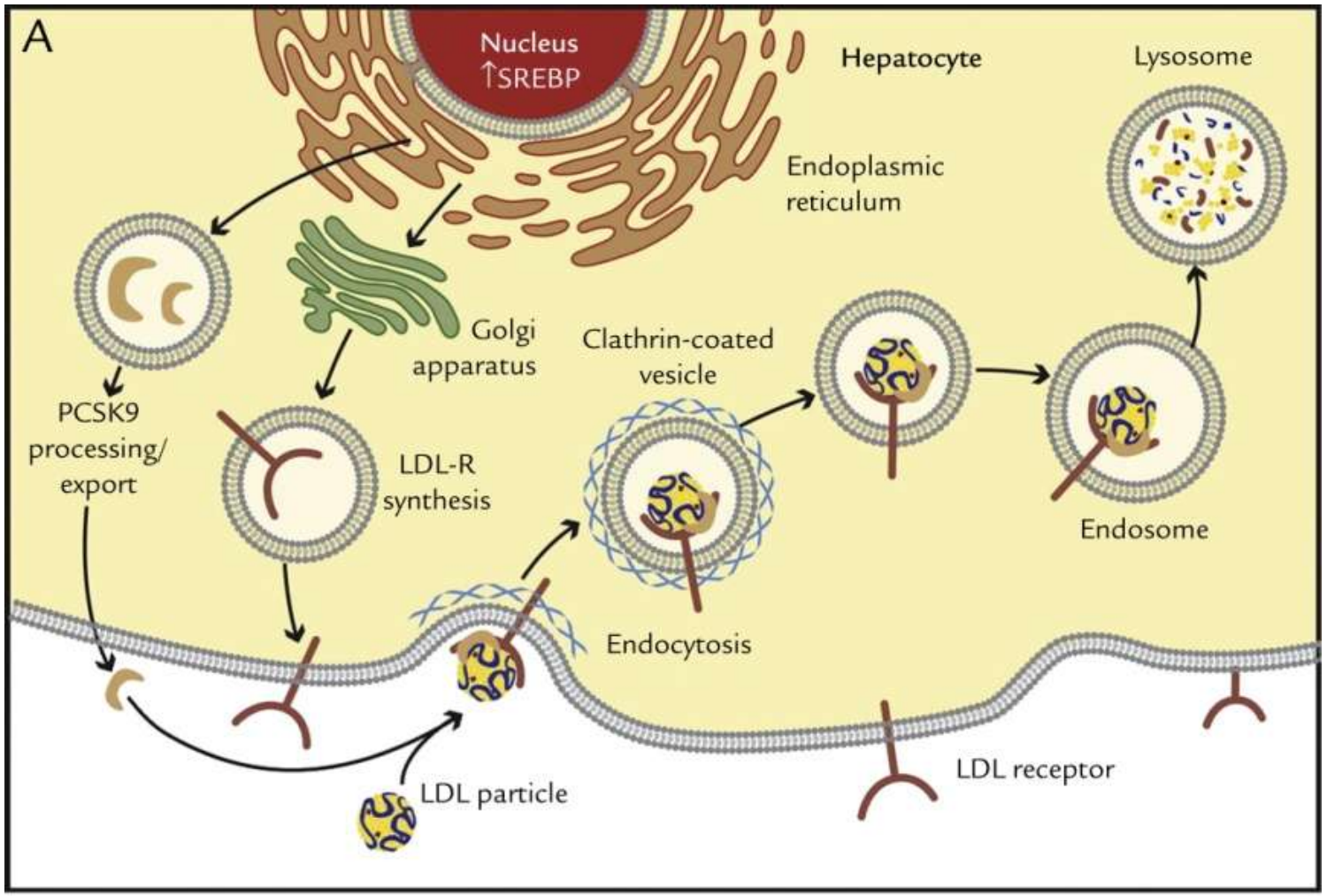
Le nuove frontiere della terapia

Terapie farmacologiche innovative

- **Oligonucletoidi antisenso** (Mipomersen, anti ApoB)
- **Inibitori di proteina MTP*** (Lomitapide)
- **Anticorpi contro PCSK9**
- **Oligonucleotidi antisenso** (Anti ApoCIII)
- **Inibitori di CETP**

*MTP = proteina microsomiale che trasferisce i trigliceridi

Interazione della proproteina convertasi subtilisina/kexin tipo 9 (PCSK9) con LDL-R



Capacità di PCSK9 di ridurre il riciclo del LDLR sulla superficie della cellula favorendone la sua degradazione.

MUTATION UPDATE

Human Mutation

OFFICIAL JOURNAL
HGVS
HUMAN GENOME VARIATION SOCIETY
www.hgvs.org

Mutations and Polymorphisms in the Proprotein Convertase Subtilisin Kexin 9 (*PCSK9*) Gene in Cholesterol Metabolism and Disease

Marianne Abifadel,[1,2,4,5]* Jean-Pierre Rabès,[1,3–6] Martine Devillers,[1,4,5] Arnold Munnich,[1,4,5] Danièle Erlich,[1,4,5] Claudine Junien,[1,4,5] Mathilde Varret,[1,4,5] and Catherine Boileau[1,3–6]

- **Varianti del gene** che codifica per la proteina PCSK9 siano **associate a variazioni dei livelli circolanti di LDL-C**.

- **Mutazioni geniche** che comportano un'aumentata attività di PCSK9 (gain of function) caratterizzano alcune forme di **ipercolesterolemia familiare autosomica dominante** con una normale espressione del LDL-R e LDL con normale affinità per il recettore, ma elevati livelli di LDL-C ed un aumentato rischio cardiovascolare

HUMAN MUTATION, Vol. 30, No. 4, 520–529, 2009

PCSK9 Mutations

Gain of function → **High LDL-C**
Premature heart disease

Loss of function → **Low LDL-C**
Prevention of heart disease

- Theoretical estimated prevalence of 1/500 for HeFH
- < 1% of cases are diagnosed in most countries

Nordestgaard BG, et al. *Eur Heart J*. 2013;34:3478-3490.[32]

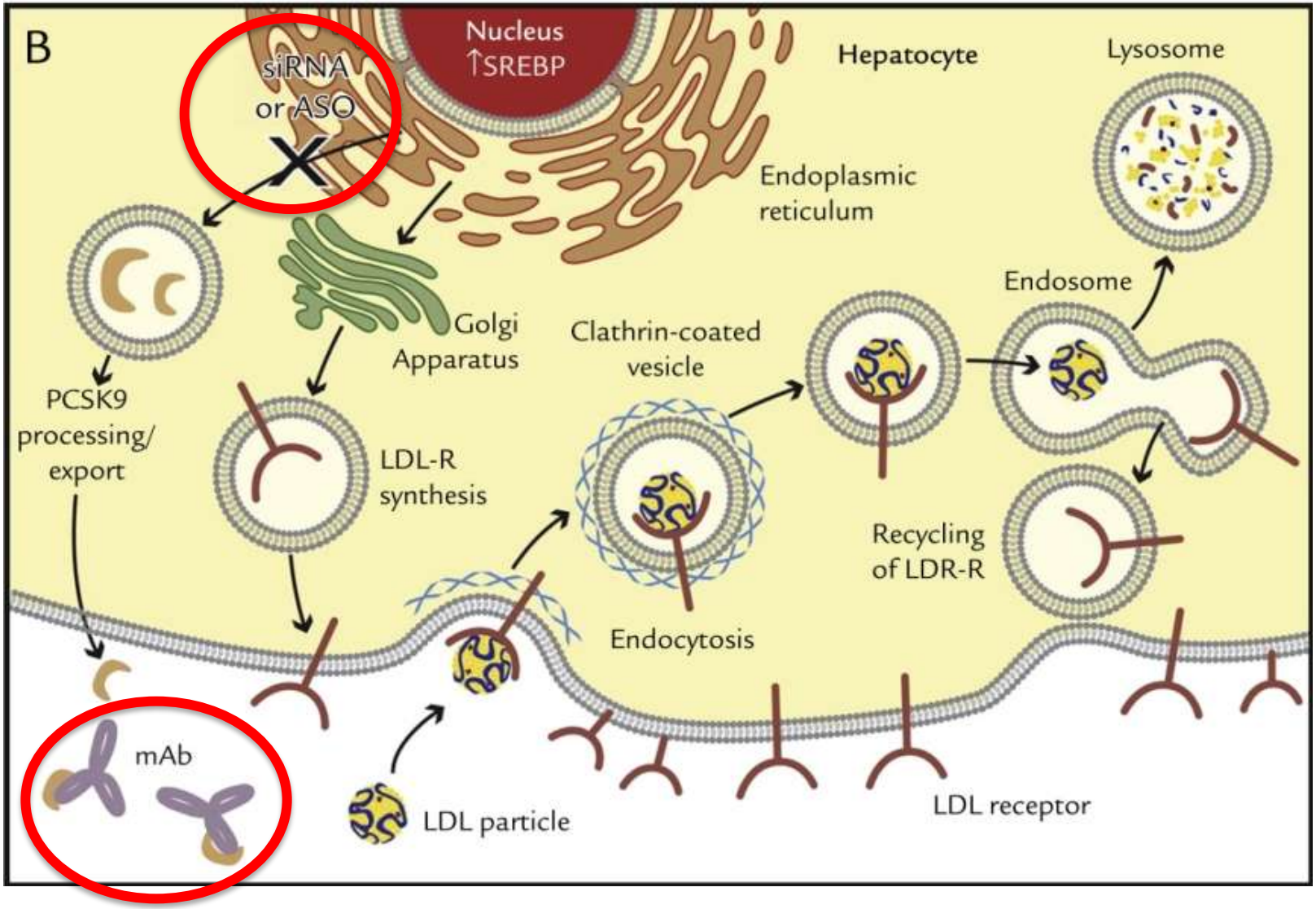
Anti-PCSK9 therapeutic agents

- **Inhibition of PCSK9 binding to LDLR**
  - Monoclonal antibodies (mAb)
  - Small peptide molecules
  - Adnectins

- **Inhibition of PCSK9 synthesis (gene silencing)**
  - Antisense oligonucleotides (ASO)
  - Small interfering RNA (siRNA)

- **Inhibition of PCSK9 autocatalytic processing**
  - Small molecule inhibitors

Il legame dell'anticorpo monoclonale a PCSK9 impedisce la degradazione del LDL-R



Efficacia su LDL

Efficacy of Alirocumab mAb 150 mg every 2 weeks

(data from phase 2 trials)

Patient population	LDL-C (%)	ApoB (%)	Lp(a) (%)	TG (%)
On stable atorvastatin therapy [1]	- 67.3	- 58.3	- 28.6	- 28.6
On atorvastatin 10 mg [2]	- 66.2	- 54.4	- 34.7	- 4.0
Heterozygous FH [3]	- 57.3	- 43.8	- 19.5	- 5.7

Data expressed as % change vs placebo (except ref. 2 : % change vs baseline)

1. Mc Kenney et al. J Am CollCardiol 2012; 59: 2344-53
2. Roth et al. N EnglJ Med 2012; 367: 1891-900
3. Stein et al. Lancet 2012; 380: 29-36

Efficacy of Evolocumab

(140 mg every 2 weeks and 420 mg every 4 weeks)

(data from phase 2 trials)

Dose	Trial	Patient population	LDL-C (%)	ApoB (%)	Lp(a) (%)	TG (%)
140 mg Q2W	LAPLACE-TIMI 57 [1]	On statin w/ or w/o ezetimibe	- 66.1	- 56.4	---	- 33.7
	MENDEL [3]	Monotherapy	- 47.2	- 44.2	- 29.3	- 12.0
420 mg Q4W	LAPLACE-TIMI 57 [1]	On statin w/ or w/o ezetimibe	- 50.3	- 42.0	---	- 19.4
	RUTHERFORD [2]	Heterozygous FH	- 56.4	- 46.2	- 31.5	- 19.9
	MENDEL [3]	Monotherapy	- 52.5	- 42.5	- 29.2	- 3.3
	GAUSS [4]	Statin intolerance	- 50.7	- 42.1	- 23.6	- 14.2

Data expressed as % change vs placebo (except ref. 4 : % change vs baseline)

1.Giugliano et al. Lancet 2012; 380: 2007-17

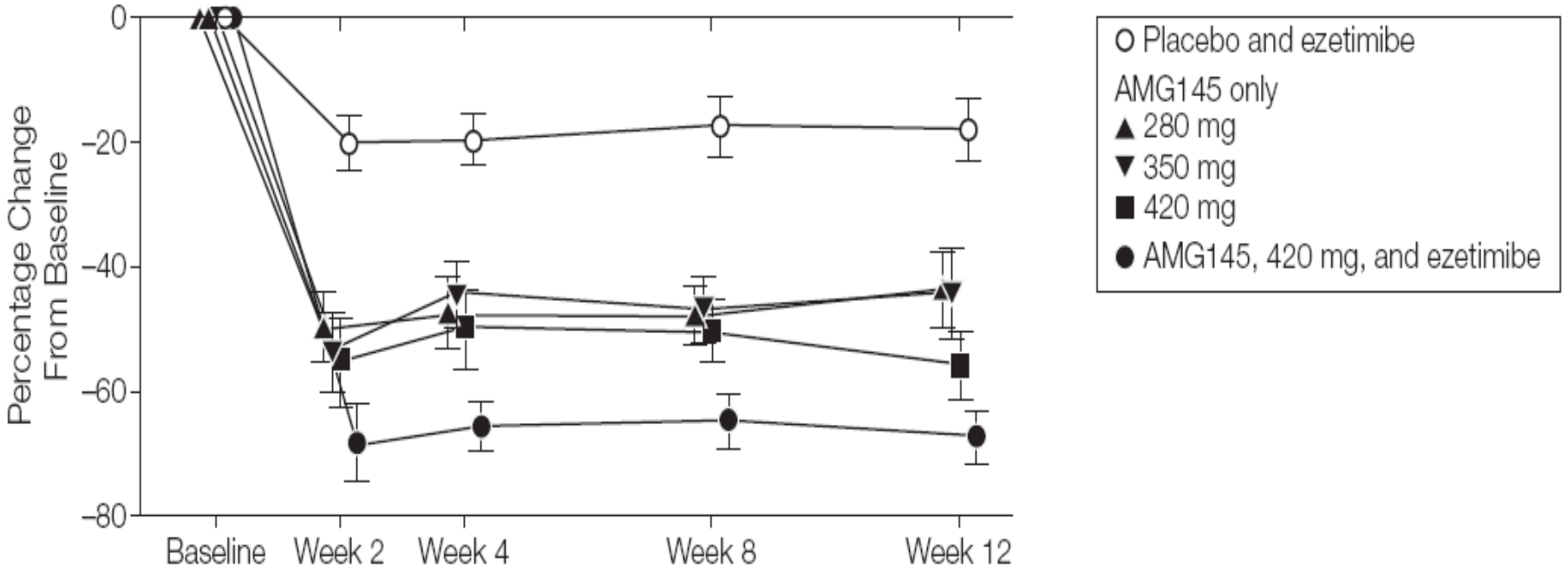
2.Raal et al. Circulation 2012; 126: 2408-17

3.Koren et al. Lancet 2012; 380: 1995-2006

4.Sullivan et al; JAMA 2012; Nov5

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

The GAUSS Randomized Trial

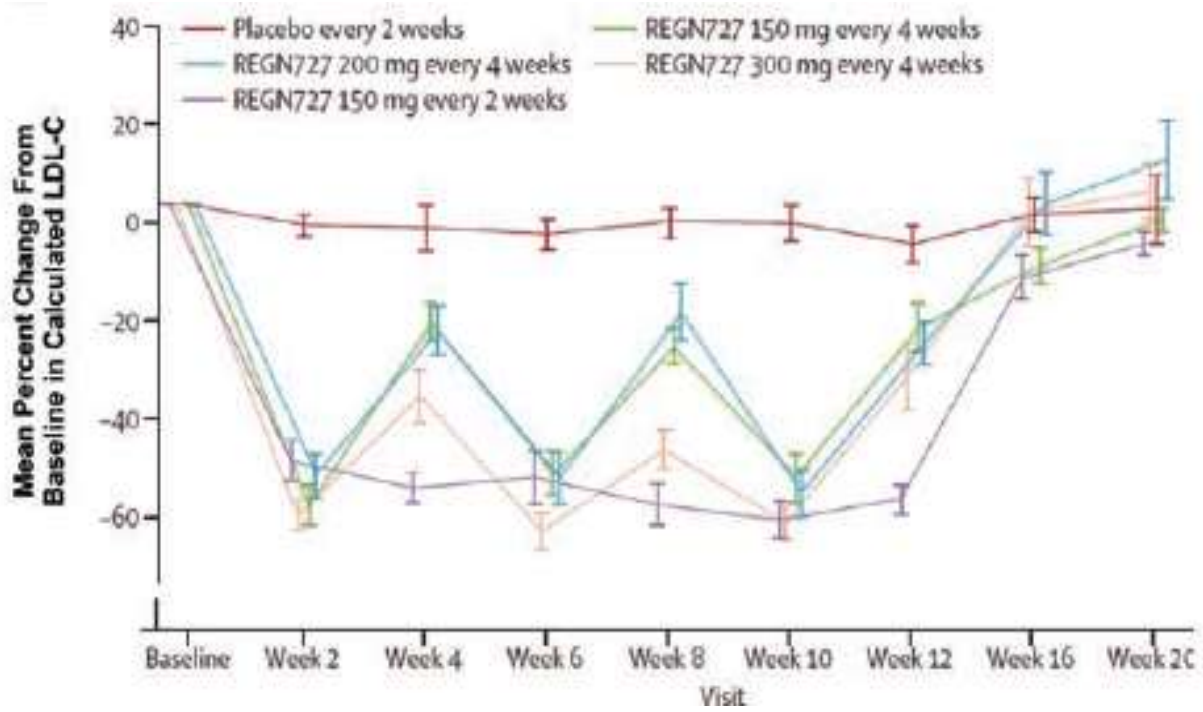


JAMA. 2012;308(23):2497-2506

Evolocumab

Effetto di mAb contro PCSK9 sui livelli plasmatici di LDL-C.

Riduzione del LDL-C osservato (-55-70%) in pazienti ipercolesterolemici non a target dopo trattamento con alte dosi di statine +/- ezetimibe

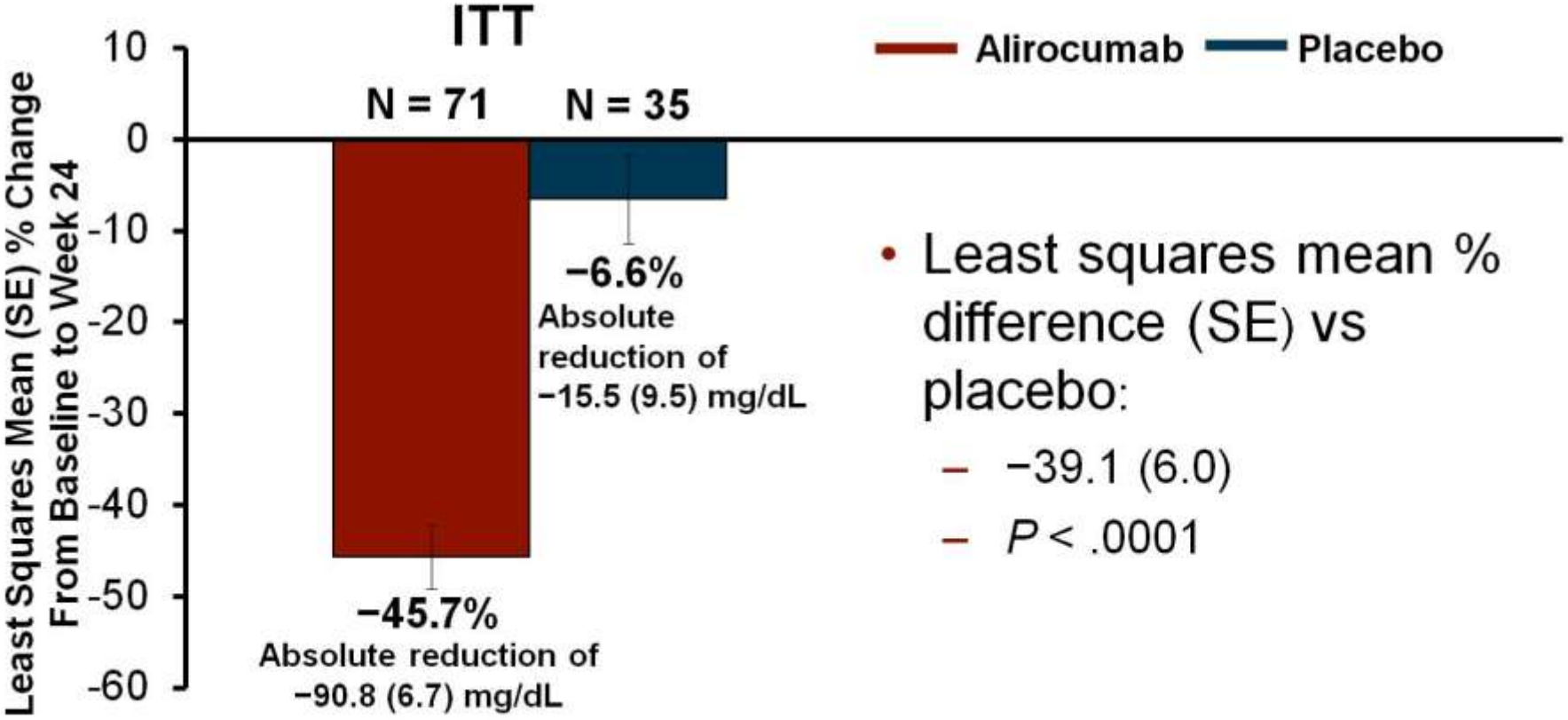


Alirocumab

Stein EA et al. Lancet 2012, 380(9836):29-36

ODYSSEY HIGH FH

- 78-week study in Heterozygous FH patients on maximally tolerated statin
- Alirocumab 150 mg Q2W SC vs placebo
- Primary end point: % change from baseline to week 24 in calculated LDL-C

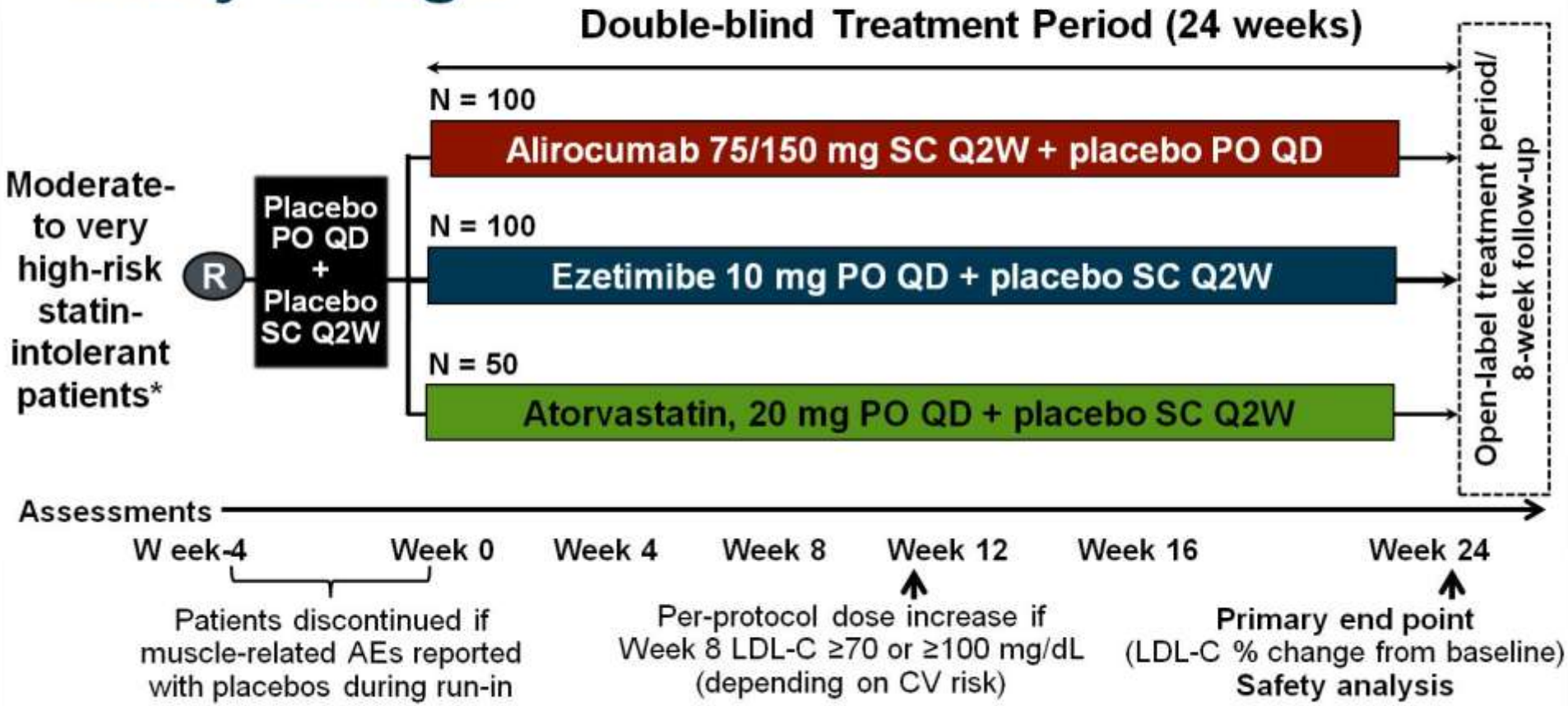


- Least squares mean % difference (SE) vs placebo:
  - −39.1 (6.0)
  - $P < .0001$

Ginsberg HN, et al. AHA 2014.CS.05.[16]

ODYSSEY ALTERNATIVE: PCSK9 in Statin-Intolerant Patients

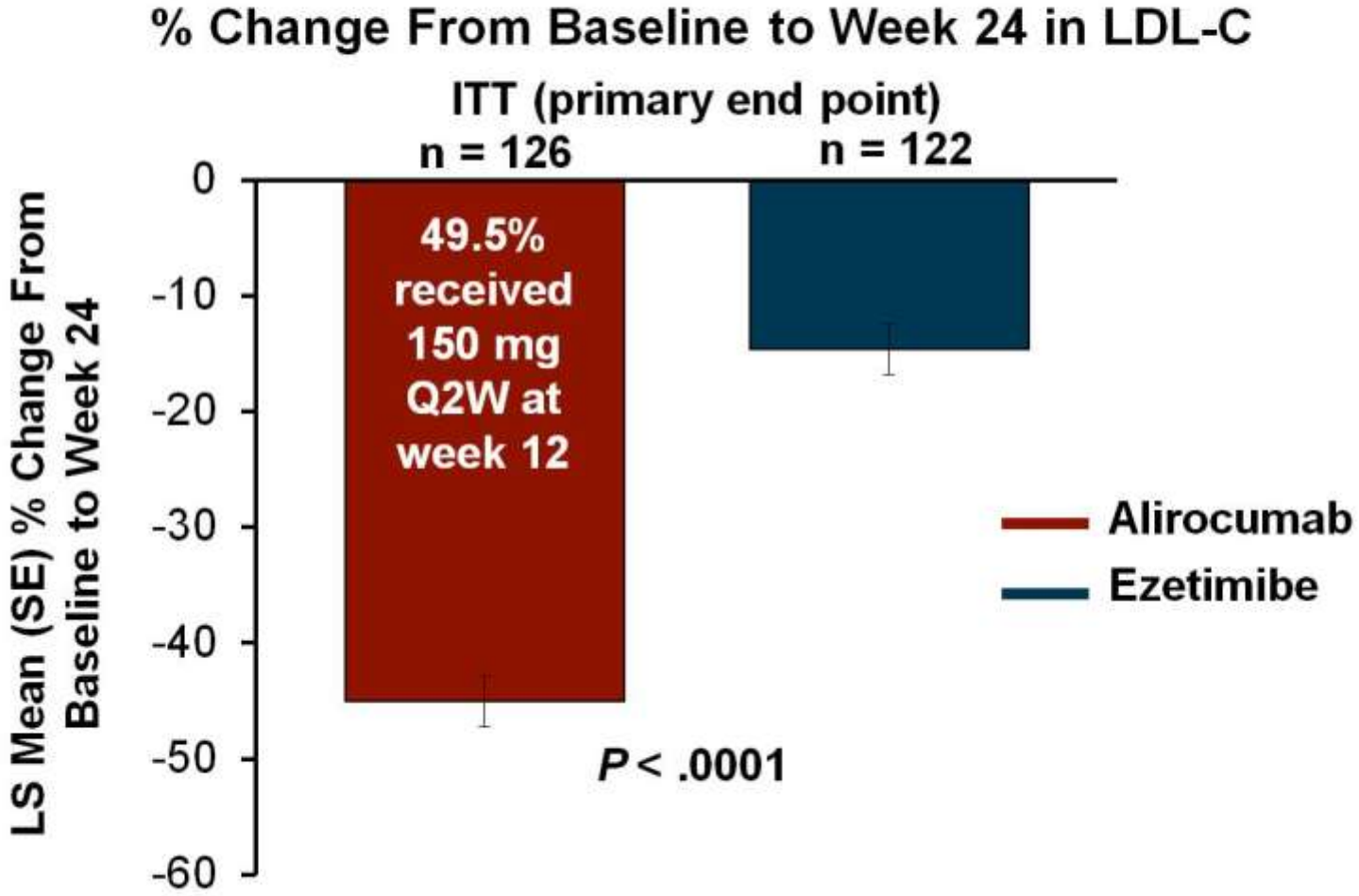
Study Design



*Unable to tolerate at least 2 different statins, including one at the lowest dose, due to muscle-related symptoms.

Moriarty PM, et al. AHA 2014. LBCT.02.[17]

Alirocumab Significantly Reduced LDL-C in Statin-Intolerant Patients



Moriarty PM, et al. AHA 2014. LBCT.02.[17]

Sicurezza

AMG 145: Phase 1a/b Safety

Adverse Events, n (%)	Phase 1a		Phase 1b	
	AMG 145 N = 42	Placebo N = 14	AMG 145 N = 43	Placebo N = 14
Deaths on study	0 (0)	0 (0)	0 (0)	0 (0)
Serious AEs	0 (0)	0 (0)	0 (0)	0 (0)
Discontinuations due to AEs	0 (0)	0 (0)	0 (0)	0 (0)
Treatment-related AEs*	18 (43)	10 (71)	10 (23)	2 (14)
Overall incidence of treatment-emergent AEs	29 (69)	10 (71)	28 (65)	9 (64)
Treatment-emergent AEs reported in ≥ 3 subjects				
Increased CK	9 (21)	2 (14)		
Pharyngitis	7 (17)	1 (7)		
Cough	4 (10)	3 (21)		
Upper respiratory tract infection	3 (7)	2 (14)		
Myositis	3 (7)	0 (0)		
Nasal congestion	2 (5)	2 (14)		
Diarrhea	2 (5)	1 (7)		
Oropharyngeal pain	1 (2)	2 (14)		
Nasopharyngitis			3 (7)	1 (7)
Injection site hematoma			2 (5)	2 (14)
Viral upper respiratory tract infection			2 (5)	1 (7)

Adapted from Dias CS et al. J Am Coll Cardiol 2012; 60:1888-98

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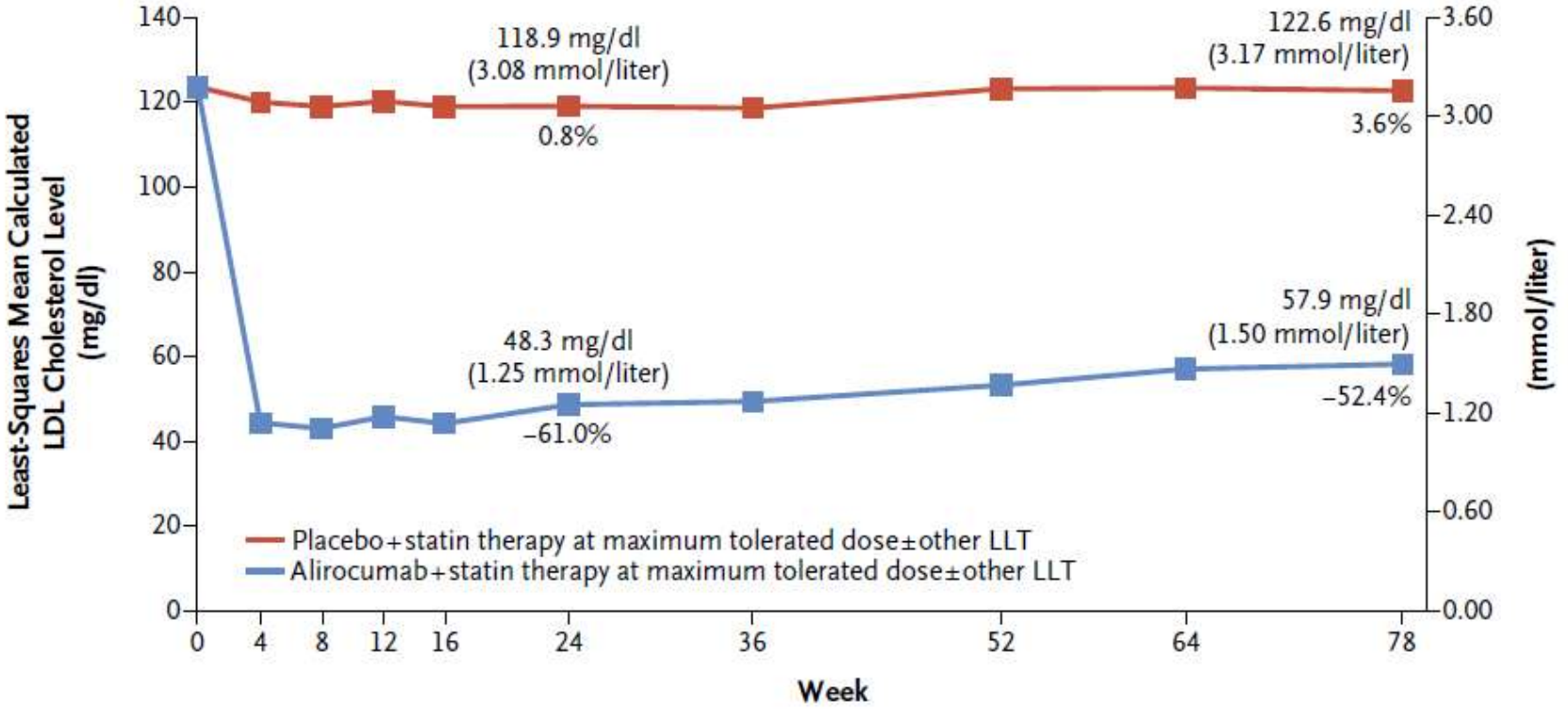
Efficacy and Safety of Alirocumab in Reducing Lipids and Cardiovascular Events

Jennifer G. Robinson, M.D., M.P.H., Michel Farnier, M.D., Ph.D., Michel Krempf, M.D., Jean Bergeron, M.D., Gérald Luc, M.D., Maurizio Averna, M.D., Erik S. Stroes, M.D., Ph.D., Gisle Langslet, M.D., Frederick J. Raal, M.D., Ph.D., Mahfouz El Shahawy, M.D., Michael J. Koren, M.D., Norman E. Lepor, M.D., Christelle Lorenzato, M.Sc., Robert Pordy, M.D., Umesh Chaudhari, M.D., and John J.P. Kastelein, M.D., Ph.D., for the ODYSSEY LONG TERM Investigators*



No. of Patients with Data Available										
Placebo	780	754	747	746	716	708	694	676	659	652
Alirocumab	1530	1473	1458	1436	1412	1386	1359	1349	1324	1269

Figure 2. Calculated LDL Cholesterol Levels over Time (Intention-to-Treat Analysis).

Table 3. Adverse Events of Interest and Laboratory Values: Safety Analysis.*

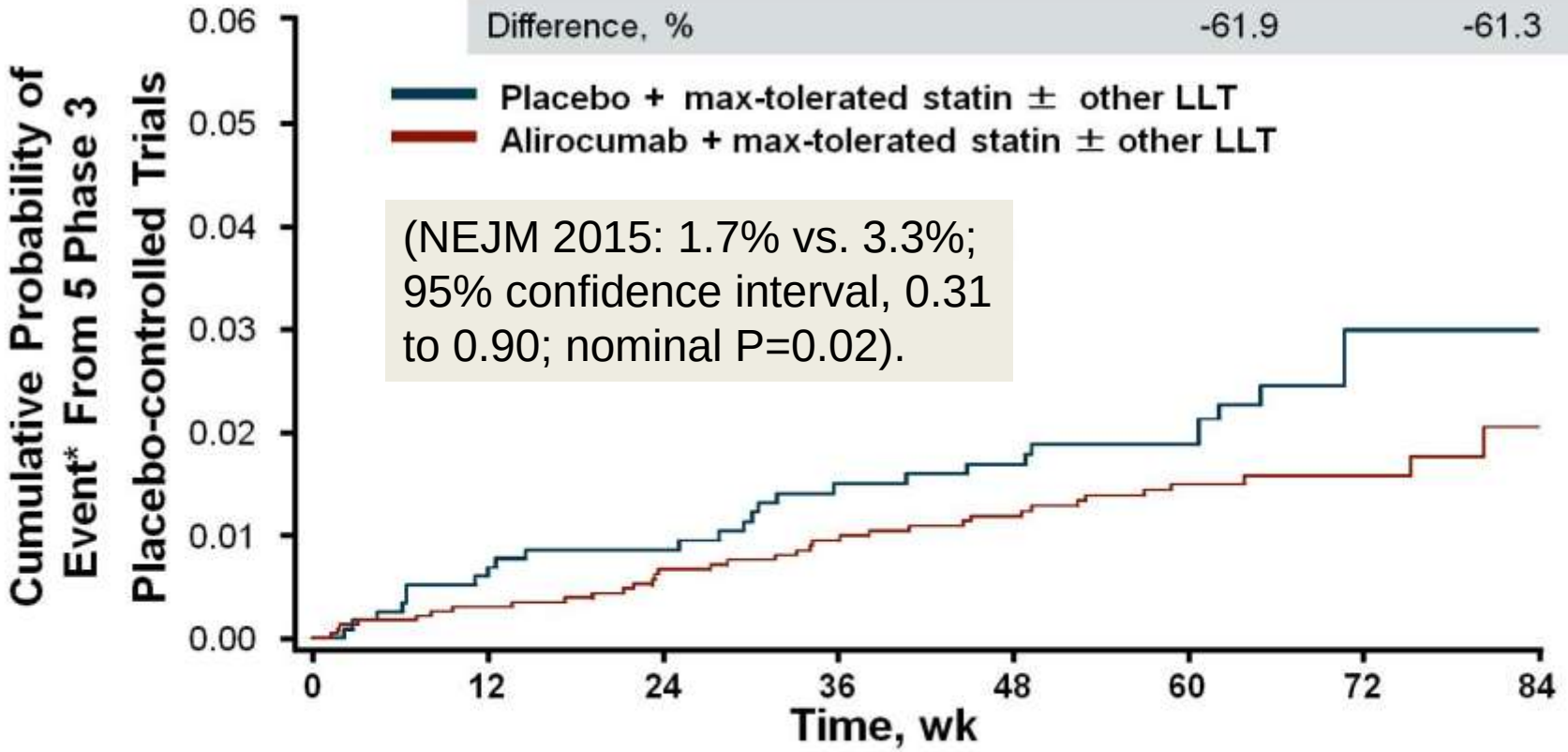
Event	Alirocumab (N=1550)	Placebo (N=788)	P Value†
Summary of adverse events — no. of patients (%)			
Any adverse event	1255 (81.0)	650 (82.5)	0.40
Serious adverse event	290 (18.7)	154 (19.5)	0.66
Adverse event leading to study-drug discontinuation	111 (7.2)	46 (5.8)	0.26
Adverse event leading to death	8 (0.5)	10 (1.3)	0.08
Cardiovascular adverse events of interest — no. of patients (%)			
Death from coronary heart disease, including death from unknown cause	4 (0.3)	7 (0.9)	0.26
Nonfatal myocardial infarction	14 (0.9)	18 (2.3)	0.01
Fatal or nonfatal ischemic stroke	9 (0.6)	2 (0.3)	0.35
Unstable angina requiring hospitalization	0	1 (0.1)	0.34
Congestive heart failure requiring hospitalization	9 (0.6)	3 (0.4)	0.76
Ischemia-driven coronary revascularization procedure	48 (3.1)	24 (3.0)	1
Positively adjudicated cardiovascular events, including all cardiovascular adverse events listed above	72 (4.6)	40 (5.1)	0.68
Adjudicated major adverse cardiovascular events in post hoc analysis‡	27 (1.7)	26 (3.3)	0.02
Other adverse events of interest			
General allergic reaction — no. of patients (%)	156 (10.1)	75 (9.5)	0.71
Local injection-site reaction — no. of patients (%)	91 (5.9)	33 (4.2)	0.10
Myalgia — no. of patients (%)	84 (5.4)	23 (2.9)	0.006
Neurologic event — no. of patients (%)§	65 (4.2)	35 (4.4)	0.83
Neurocognitive disorder — no. of patients (%)¶	18 (1.2)	4 (0.5)	0.17
Amnesia	5 (0.3)	0	0.17
Memory impairment	4 (0.3)	1 (0.1)	0.67
Confusional state	4 (0.3)	1 (0.1)	0.67
Ophthalmologic event — no. of patients (%)‖	45 (2.9)	15 (1.9)	0.65
Hemolytic anemia — no. of patients	0	0	NC
Diabetes in patients with no history of diabetes — no. of patients/total no. (%)**	18/994 (1.8)	10/509 (2.0)	0.84
Worsening of diabetes in patients with history of diabetes — no. of patients/total no. (%)**	72/556 (12.9)	38/279 (13.6)	0.83

ODYSSEY Long-Term

Time to First Adjudicated Major CV Event

Achieved LDL-C over time

	Baseline	24 weeks	52 weeks
Placebo, mg/dL	122.7	118.9 (+0.8%)	123.0 (+4.4%)
Alirocumab, mg/dL	121.9	48.3 (-61.0%)	53.1 (-56.8%)
Difference, %		-61.9	-61.3



(NEJM 2015: 1.7% vs. 3.3%; 95% confidence interval, 0.31 to 0.90; nominal P=0.02).

*Primary end point: CHD death, nonfatal MI, fatal and nonfatal ischemic stroke, unstable angina requiring hospitalization.

Robinson JG, et al. AHA 2014. CS.05.[15]

Altre inibizioni della PCSK-9

Effect of an RNA interference drug on the synthesis of proprotein convertase subtilisin/kexin type 9 (PCSK9) and the concentration of serum LDL cholesterol in healthy volunteers: a randomised, single-blind, placebo-controlled, phase 1 trial.

RESULTS

- 70% reduction in circulating PCSK9 plasma protein ($p<0.0001$)
- mean 40% reduction in LDL cholesterol from baseline relative to placebo ($p<0.0001$).

Fitzgerald K et al. Lancet 2014;383(9911):60-8

CONCLUSIONI SU Ab anti PCSK-9

- ✓ **Nuova classe di farmaci : si rivela di efficacia sorprendente nel ridurre LDL**

- ✓ **I dati ad oggi disponibili evidenziano una sicurezza d'uso confortante, superiore agli altri ipolipemizzanti**

- ✓ **Iniziano a comparire dati di efficacia anche su outcome CV**

- ✓ **Costi?**

Grazie per l’attenzione

Incidence of Muscle AEs on Statin Therapy

- Pravastatin
  - 40 mg once daily; patients with muscular symptoms = 10.9%
- Atorvastatin
  - 40 mg to 80 mg once daily; patients with muscular symptoms = 14.9%
- Simvastatin
  - 40 mg to 80 mg once daily; patients with muscular symptoms = 18.2%
- Fluvastatin
  - 80 mg once daily; patients with muscular symptoms = 5.1%
- Commonly reported muscular AEs
  - Myalgia = muscle ache or weakness without elevation in CK.
  - Myositis = muscle symptoms with elevation in CK.
  - Rhabdomyolysis = muscle symptoms with significant elevation in CK (typically > 10 × ULN) and elevation in creatinine.

Bruckert E, et al. *Cardiovasc Drugs Ther.* 2005;19:403-414.[19]

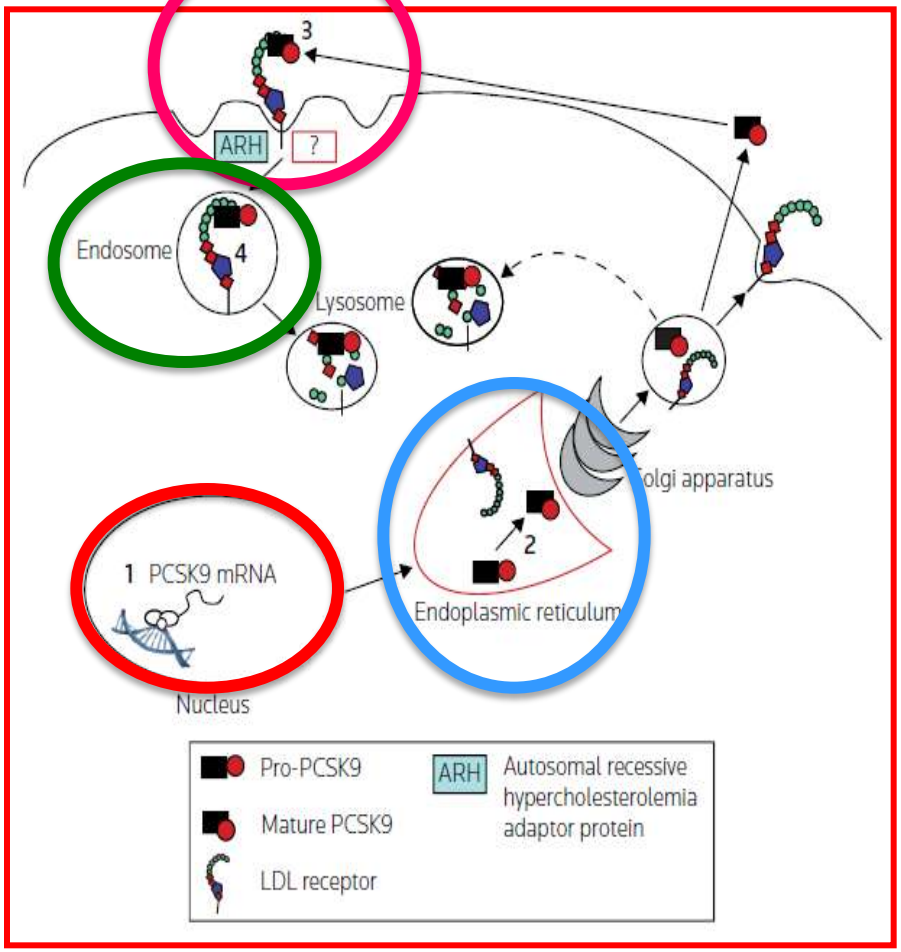
LDL-C Lowering
Cognitive Impairment

- Systematic review and meta-analysis evaluating effect of statins on short-term cognition and long-term incidence of dementia

	Time frame	Outcome
Short-term cognition	< 1 year after statin initiation	• No significant difference in mean change from baseline to follow-up between statin and placebo • Mean change:1.65; 95% CI, -0.03 to 3.32
Long-term cognition	> 1 year after statin initiation	• Pooled results show a 29% reduction in incident dementia in statin-treated patients • HR 0.71; 95% CI, 0.61 to 0.82

Swiger KJ, et al. *Mayo Clin Proc*. 2013;88:1213-1221.[20]

Major targeting points of the known PCSK9 pathway



1. Reducing the expression of PCSK9 mRNA

2. Reducing the expression of PCSK9 protein (inhibition of autocatalytic processing)

3. Inhibiting PCSK9 binding to the LDL-R

4. Inhibiting PCSK9-mediated LDL-R degradation

Hedrick JA, Curr Opin Investig Drugs 2009; 10: 938-46