Le dislipidemie nel paziente cardiometabolico: dai nutraceutici alle statine ed oltre le statine

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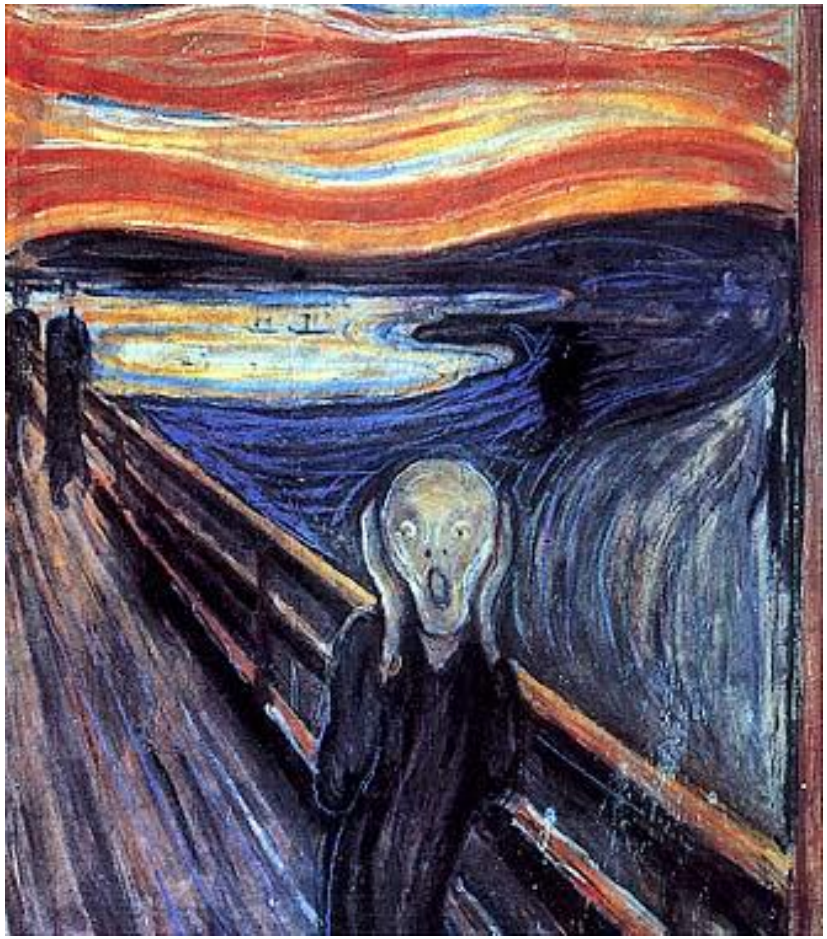
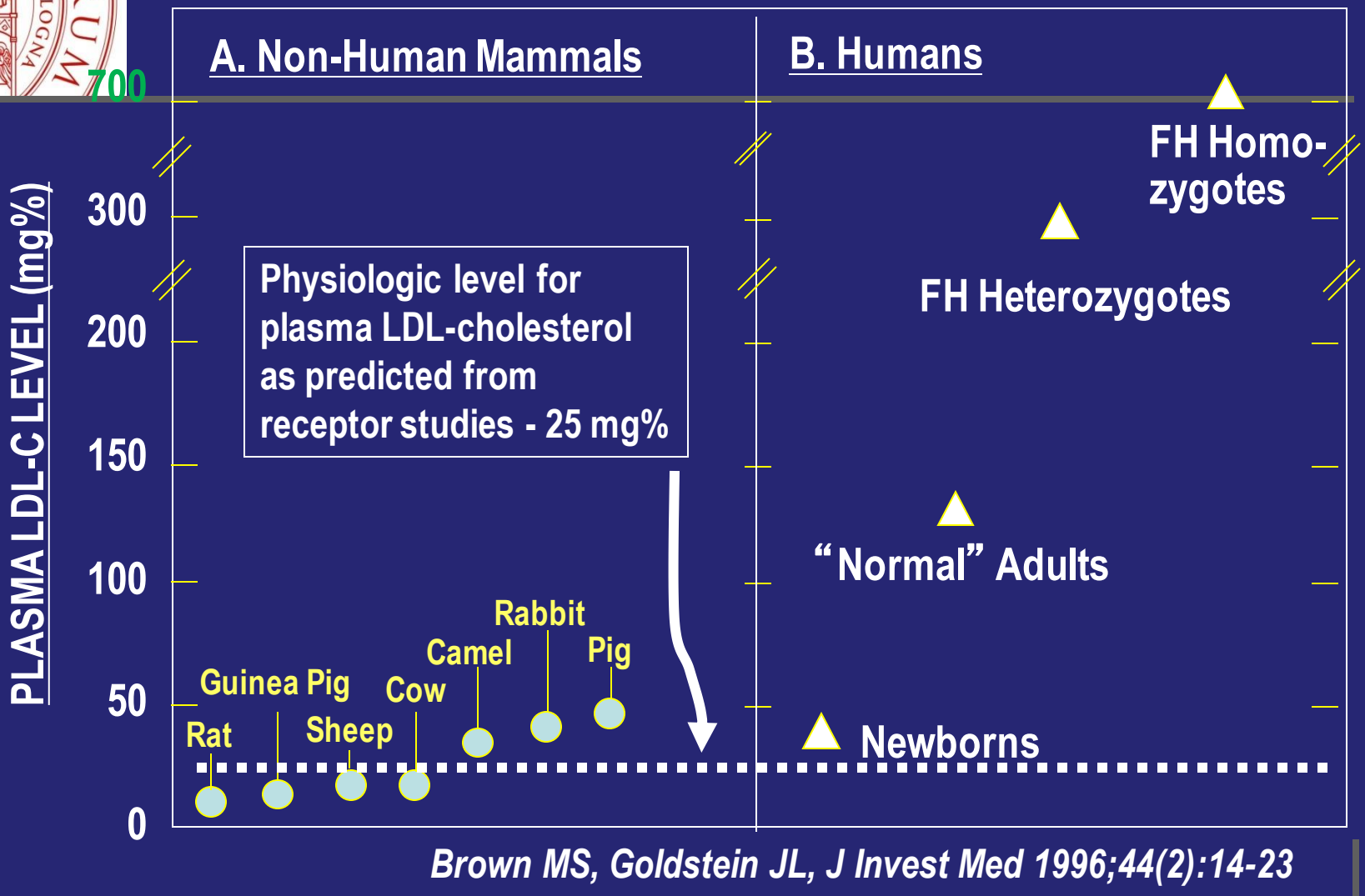
La mia reazione alla proposta di titolo…



LDL-C LEVELS IN HUMANS AND NON-HUMAN MAMMALS



Brown MS, Goldstein JL, J Invest Med 1996;44(2):14-23

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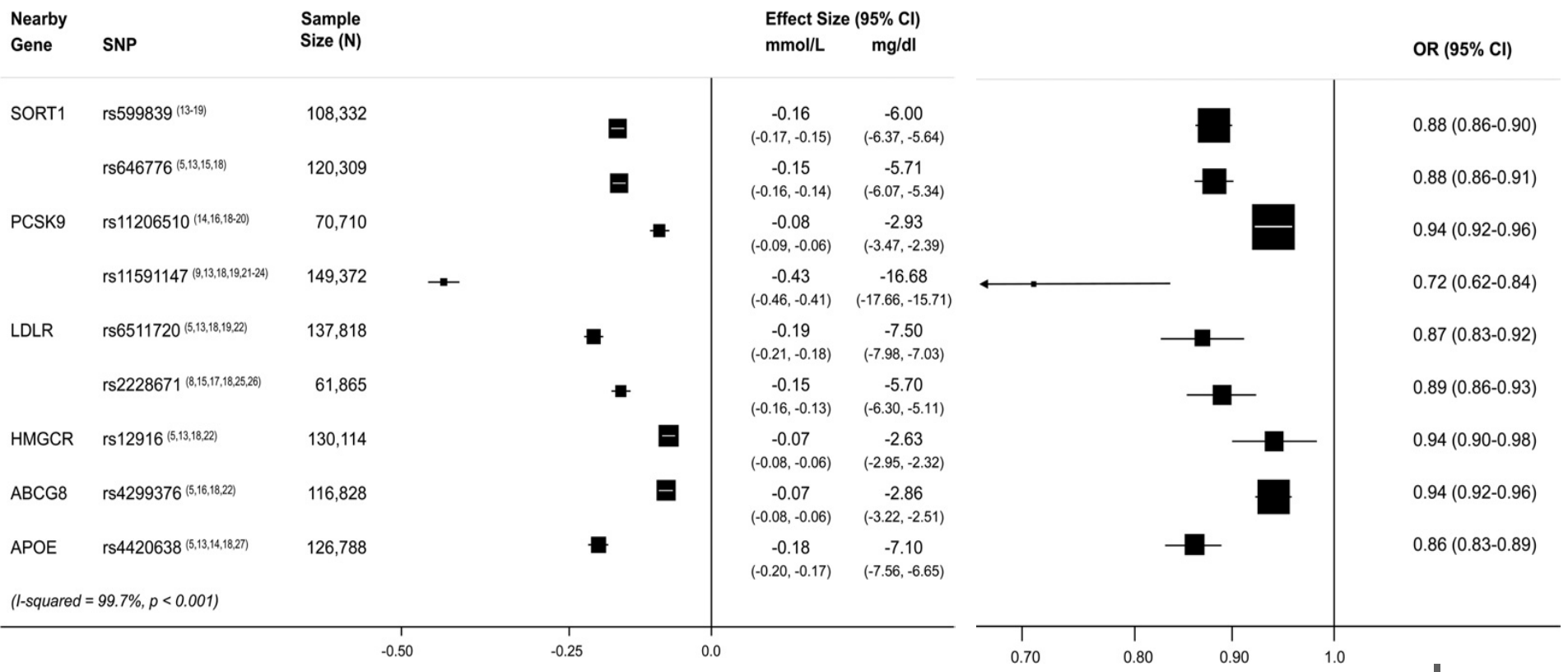
http://dx.doi.org/10.1016/j.jacc.2012.09.017

Cardiometabolic Risk

Effect of Long-Term Exposure to Lower Low-Density Lipoprotein Cholesterol Beginning Early in Life on the Risk of Coronary Heart Disease

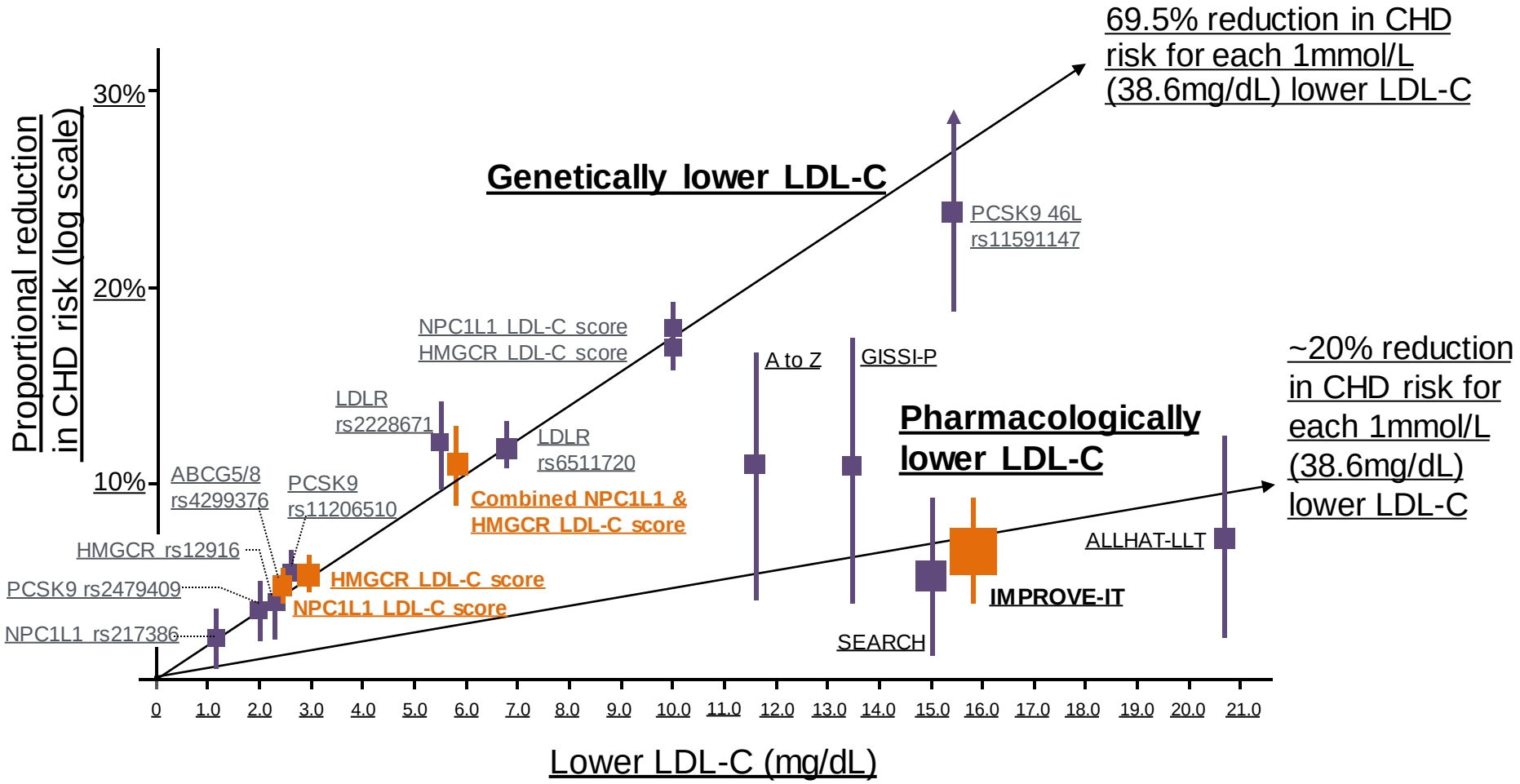
A Mendelian Randomization Analysis



LDL-C level

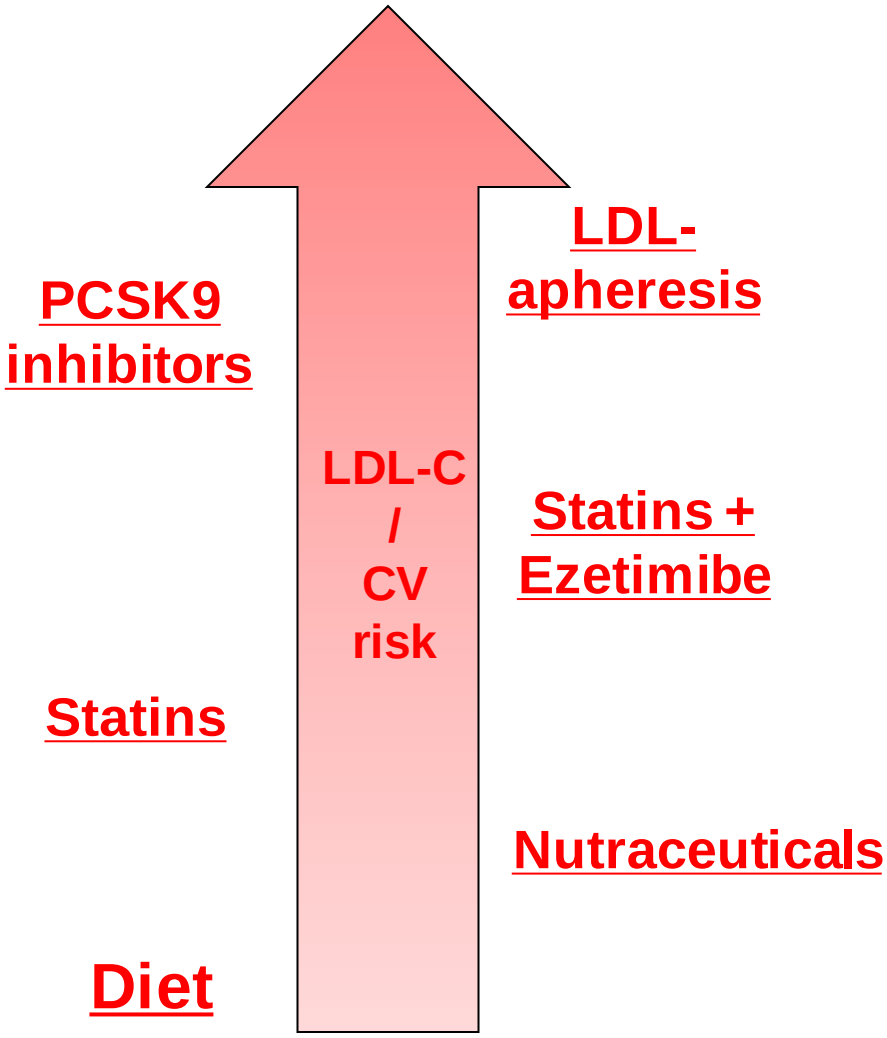
CHD event risk

Clinical benefit of lower LDL is determined by absolute exposure to lower LDL



Ference et al. J Am Coll Cardiol 2015;65:1552–1561.

LLT: a «classical» approach

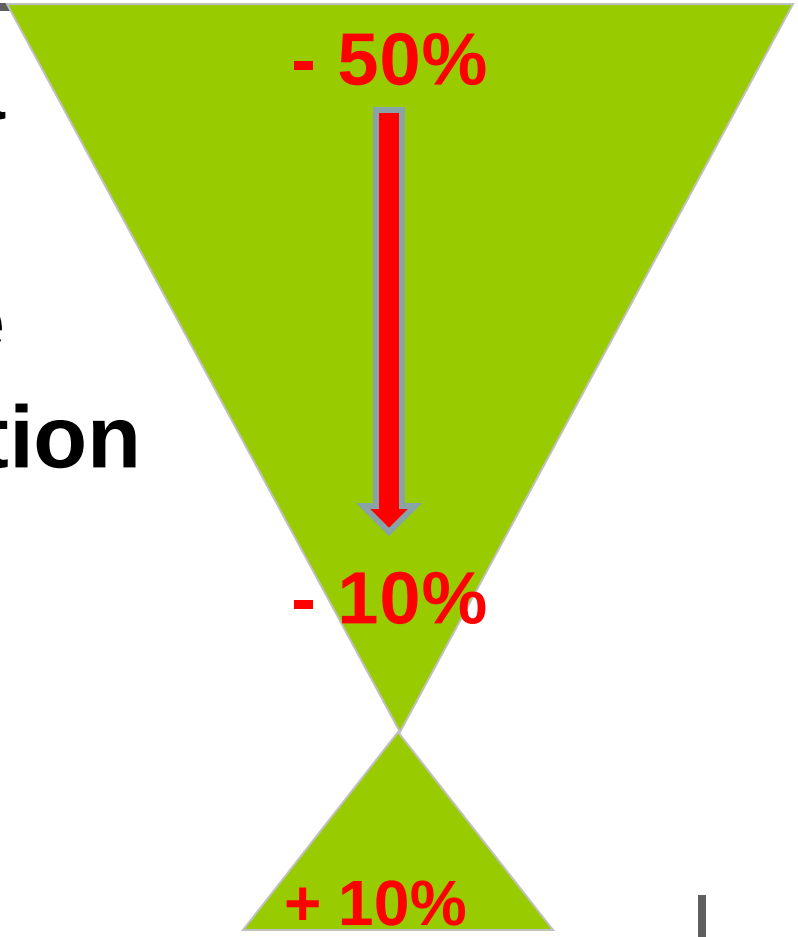


Relative efficacy of life-style change in improving different CV risk factors

Med Low-Chal Diet

- **Triglyceridemia**
- **Glycemia**
- **Blood Pressure**
- **Microinflammation**
- **LDL-C**
- **Lp(a)**

- **HDL-C**



European Heart Journal
doi:10.1093/eurheartj/ehw272

2016 ESC/EAS Guidelines for the Management of Dyslipidaemias

- **Miglioramento stile di vita**
- **Miglioramento stile di vita + Nutraceutici**
- **Miglioramento stile di vita + Farmaci**
- **Miglioramento stile di vita + Farmaci + Nutraceutici**

Atherosclerosis 2016;253:281-344

European Heart Journal
doi:10.1093/eurheartj/ehw272

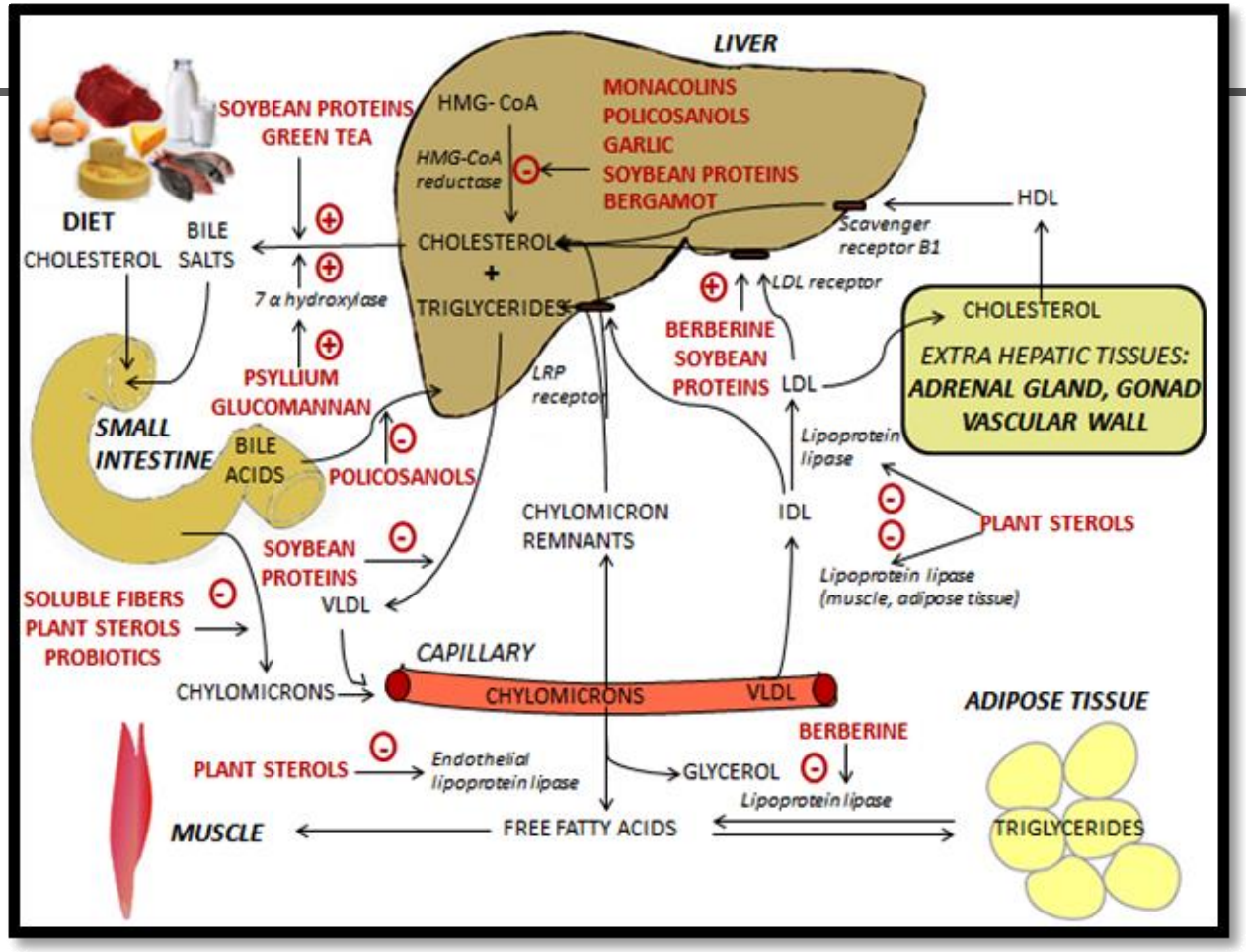
2016 ESC/EAS Guidelines for the Management of Dyslipidaemias

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

DIET + NUTRACEUTICALS

Atherosclerosis 2016;253:281-344

Lipid-lowering nutraceuticals: sites of action



Cicero AFG, Colletti A. In: Combined therapy in dyslipidemia. Springer-Verlag. 2015

Lipid lowering nutraceuticals in clinical practice: an evidence based consensus

Avvallato da: SINut, FADOI, AME, NFI, SITOX, SINSEB, ANDID, OSDI, SIMF, SINE, Lipid and Blood Pressure Meta-analysis Collaboration (LBPMC)

- **<u>Classe A, Evidenza I (singoli componenti):</u> Riso rosso fermentato, Fitosteroli, Fibre solubili, Berberina, Omega-3 (EPA/DHA), Semi di lino, Frutta secca**
- **<u>Classe A, Evidenza I (associazioni):</u> Riso rosso fermentato+Berberina, Riso rosso fermentato+Omega 3, Riso rosso fermentato + Fitosteroli**

Pharmanutrition & Functional foods 2017

European Heart Journal
doi:10.1093/eurheartj/ehw272

2016 ESC/EAS Guidelines for the Management of Dyslipidaemias

STATINS +/- EZETIMIBE

Recommendations	Class [a]	Level [b]
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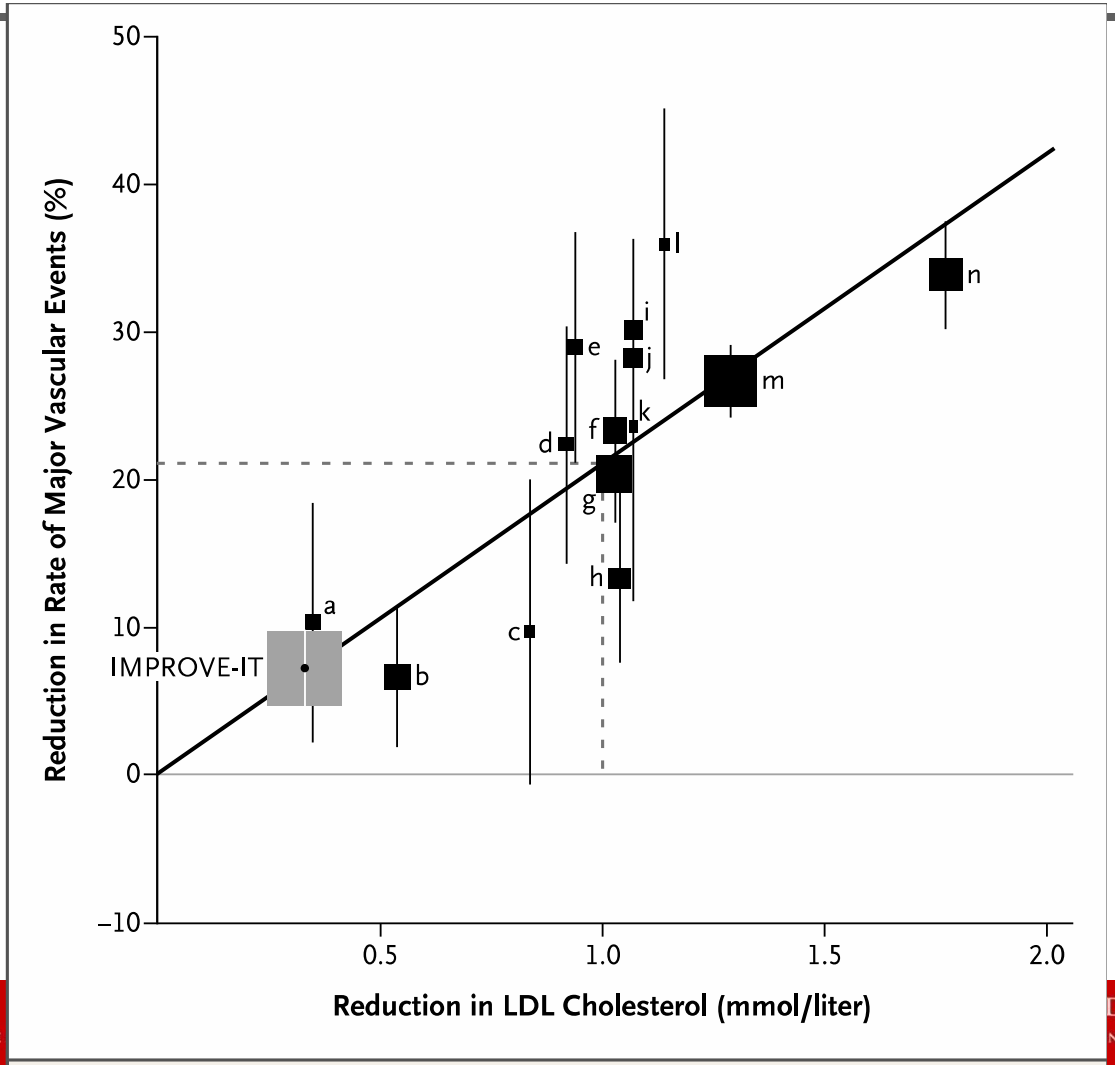
In subjects at LOW or MODERATE risk[d] an LDL-C goal of <3.0 mmol/L (<115 mg/dL) should be considered.	IIa	C

Atherosclerosis 2016;253:281-344

Metaregressione dei dati relativi a riduzione di LDL-C e riduzione del rischio CV nei grandi studi di intervento con statine

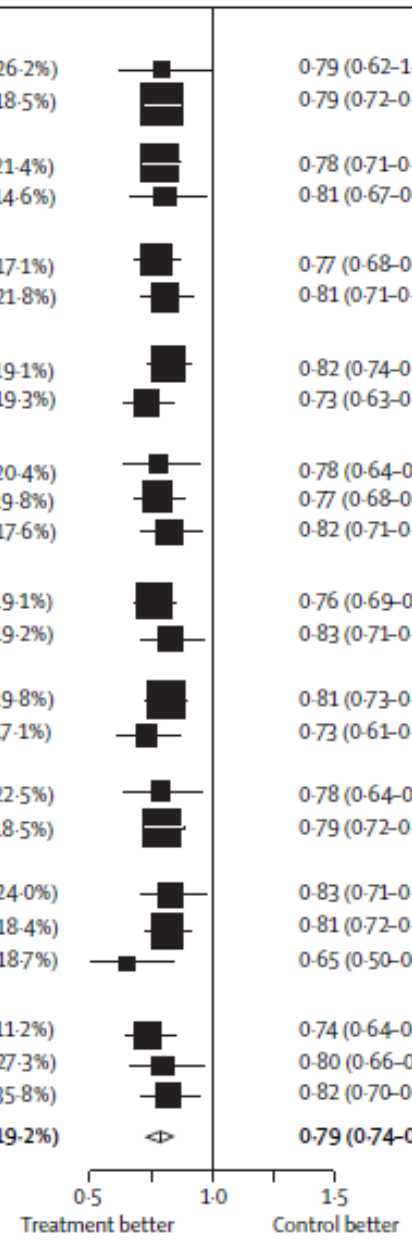


Cannon CP et al. NEJM 2015; 372(25): 2387-97.

Lancet 2008; 371: 117–25

Efficacy of cholesterol-lowering therapy in 18686 people with diabetes in 14 RCTs of statins: a meta-analysis

Groups	Events (%) Treatment	Control	RR (CI)
Type of diabetes:			
Type 1 diabetes	147 (20·5%)	196 (26·2%)	0·79 (0·62–1·01)
Type 2 diabetes	1318 (15·2%)	1586 (18·5%)	0·79 (0·72–0·87)
Sex:			
Men	1082 (17·2%)	1332 (21·4%)	0·78 (0·71–0·86)
Women	383 (12·4%)	450 (14·6%)	0·81 (0·67–0·97)
Age (years):			
≤65	701 (13·1%)	898 (17·1%)	0·77 (0·68–0·87)
>65	764 (18·9%)	884 (21·8%)	0·81 (0·71–0·92)
Currently treated hypertension:			
Yes	1030 (16·3%)	1196 (19·1%)	0·82 (0·74–0·91)
No	435 (14·2%)	586 (19·3%)	0·73 (0·63–0·85)
Body-mass index:			
<25·0	276 (15·7%)	362 (20·4%)	0·78 (0·64–0·95)
≥25·0–<30·0	639 (15·9%)	774 (19·8%)	0·77 (0·68–0·88)
≥30·0	532 (15·1%)	628 (17·6%)	0·82 (0·71–0·95)
Systolic blood pressure (mm Hg):			
<160	993 (15·0%)	1276 (19·1%)	0·76 (0·69–0·85)
≥160	472 (17·1%)	505 (19·2%)	0·83 (0·71–0·96)
Diastolic blood pressure (mm Hg):			
≤90	1176 (16·5%)	1417 (19·8%)	0·81 (0·73–0·89)
>90	288 (12·9%)	364 (17·1%)	0·73 (0·61–0·87)
Smoking status:			
Current smokers	266 (17·5%)	347 (22·5%)	0·78 (0·64–0·96)
Non-smokers	1199 (15·2%)	1435 (18·5%)	0·79 (0·72–0·87)
Estimated GFR (mL/min/1·73m²):			
<60	415 (20·6%)	477 (24·0%)	0·83 (0·71–0·97)
≥60–<90	816 (15·5%)	961 (18·4%)	0·81 (0·72–0·91)
≥90	194 (12·5%)	286 (18·7%)	0·65 (0·50–0·84)
Predicted risk of major vascular event (per year):			
<4·5%	474 (8·4%)	631 (11·2%)	0·74 (0·64–0·85)
≥4·5–<8·0%	472 (23·2%)	540 (27·3%)	0·80 (0·66–0·96)
≥8·0%	519 (30·5%)	611 (35·8%)	0·82 (0·70–0·95)
All diabetes	**1465 (15·6%)**	**1782 (19·2%)**	**0·79 (0·74–0·84)**

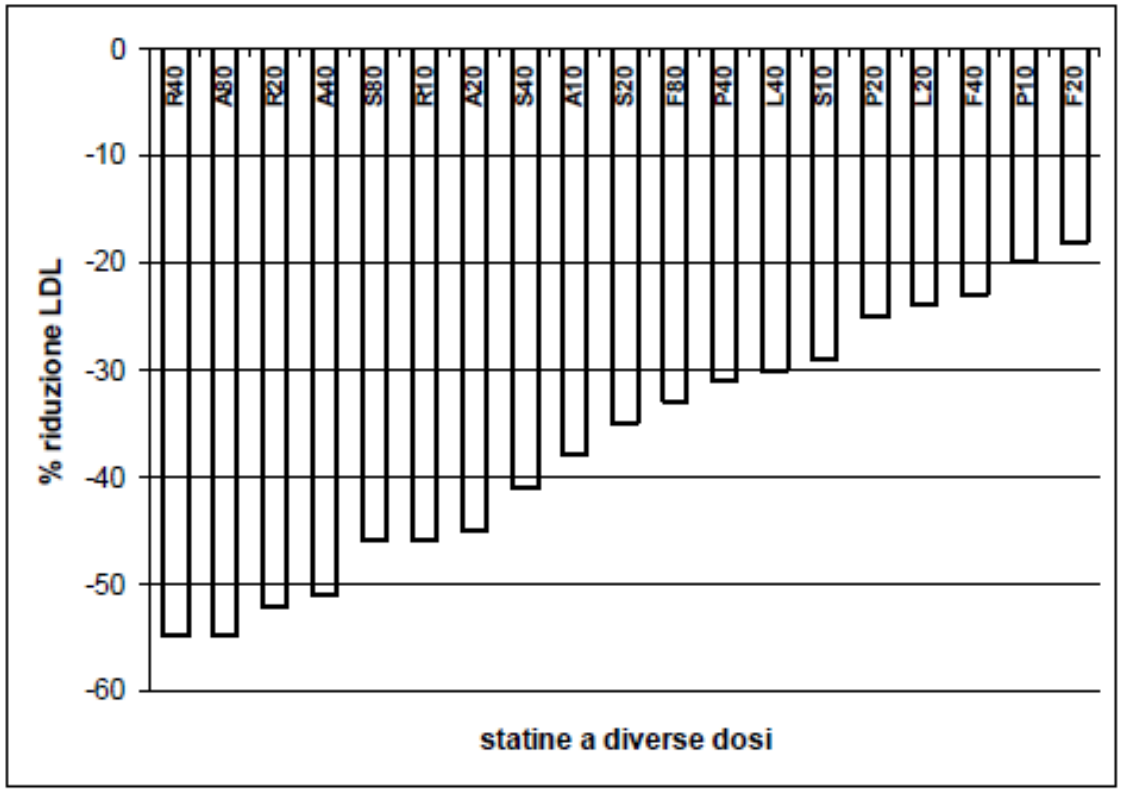


Global test for heterogeneity within subtotals: χ^2_{13}=13·9: p=0·4

RR (99% CI)

RR (95% CI)

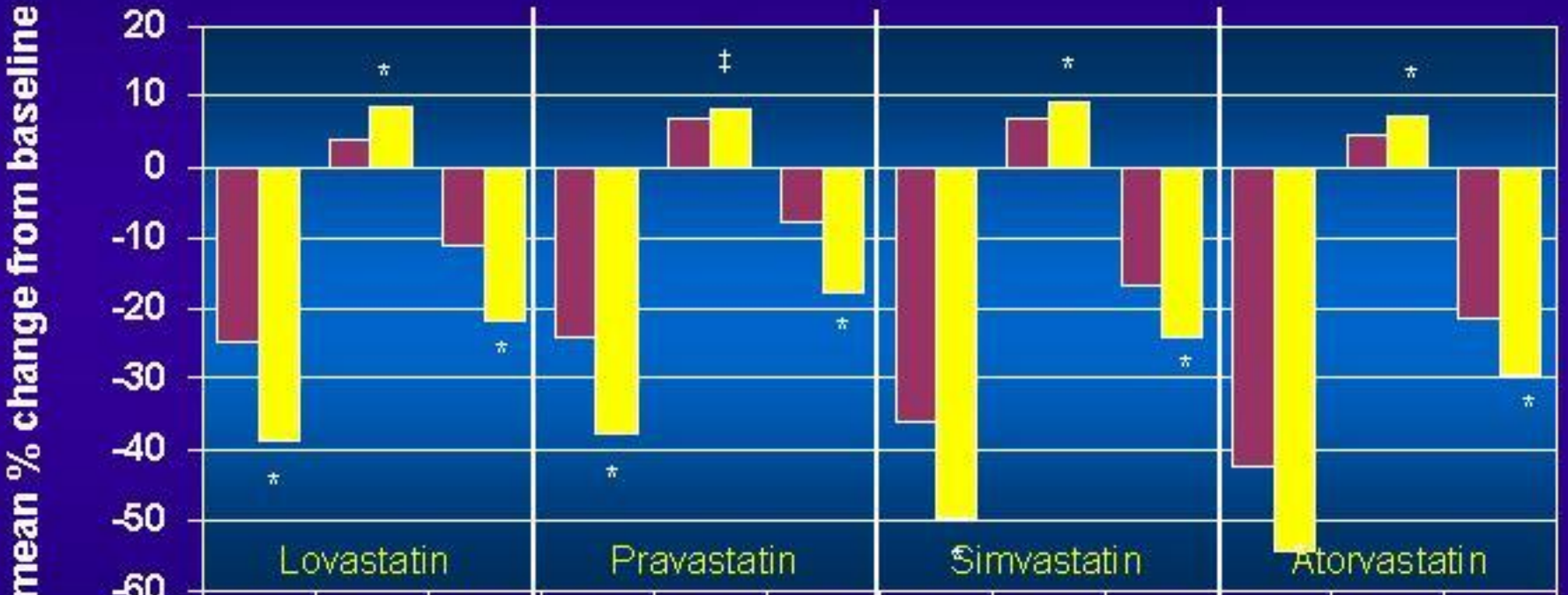
Difficoltà burocratiche? La nota 13



- **Statina a massima dose tollerata +/- ezetimibe per raggiungere il target (ezetimibe da solo se statina mal tollerata)**

GU 9/4/2013, Serie generale N. 83, Pag. 23-36

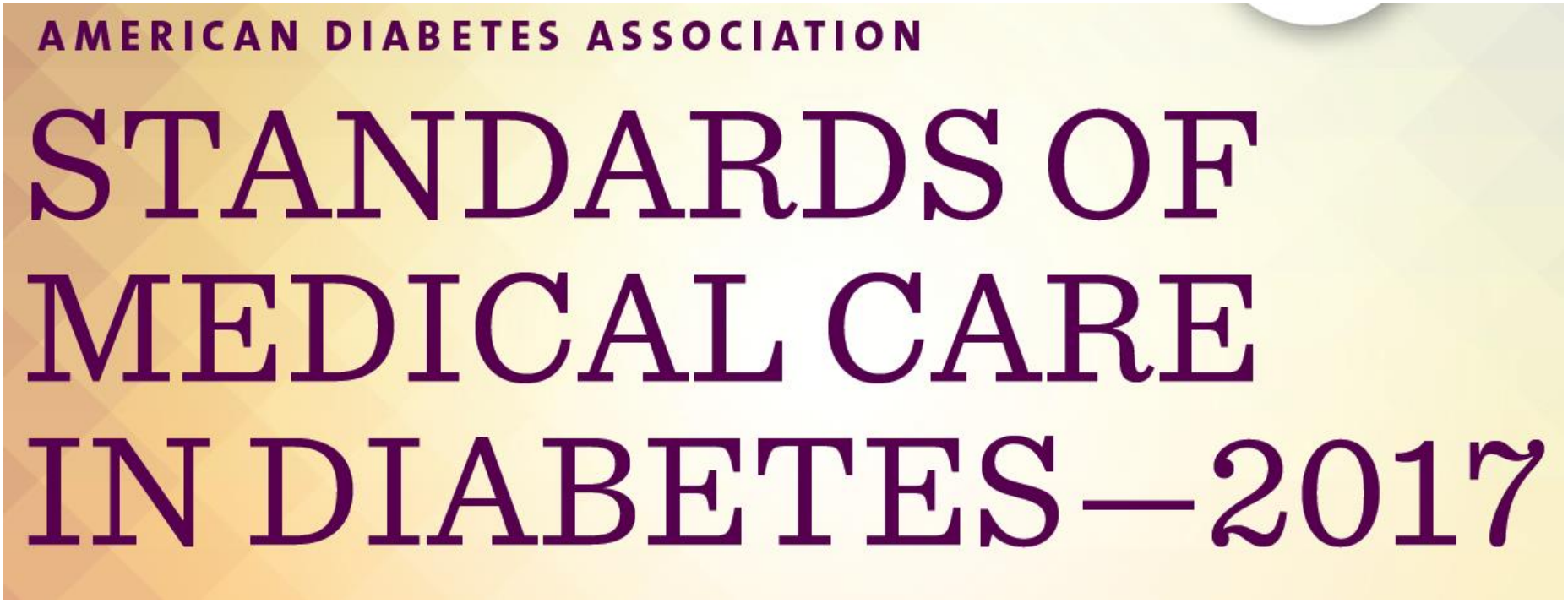
Results: Added Efficacy Across the Lipid Profile Regardless of Statin Used



	Lovastatin			Pravastatin			Simvastatin			Atorvastatin		
	LDL	HDL	TG	LDL	HDL	TG	LDL	HDL	TG	LDL	HDL	TG
+ Pbo	-24,7	4,0	-11,2	-24,3	6,7	-7,6	-36,1	6,9	-16,6	-42,4	4,3	-21,5
+ EZE	-39	8,6	-21,7	-37,7	8,1	-17,6	-49,9	9,3	-24,1	-54,5	7,3	-29,5

*p<0.01 for EZE + statin vs statin alone; ‡p=0.22 for EZE + statin vs statin alone

Cominciamo con qualcosa di molto diabetologico…



Lo stile «pragmatico» americano

Age	Risk factors	Recommended statin intensity*
<40 years	None	None
	ASCVD risk factor(s)**	Moderate or high
	ASCVD	High
40–75 years	None	Moderate
	ASCVD risk factors	High
	ASCVD	High
	ACS and LDL cholesterol >50 mg/dL (1.3 mmol/L) in patients who cannot tolerate high-dose statins	Moderate plus ezetimibe
>75 years	None	Moderate
	ASCVD risk factors	Moderate or high
	ASCVD	High
	ACS and LDL cholesterol >50 mg/dL (1.3 mmol/L) in patients who cannot tolerate high-dose statins	Moderate plus ezetimibe

2017: Gli americani riabbracciano il rigore

CONSENSUS STATEMENT BY THE AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY ON THE COMPREHENSIVE TYPE 2 DIABETES MANAGEMENT ALGORITHM

2017 EXECUTIVE SUMMARY

Endocrine Practice 2017; doi: 10.4158/EP161682.CS

STATIN THERAPY

If TG > 500 mg/dL, fibrates, Rx-grade omega-3 fatty acids, niacin

If statin-intolerant

Try alternate statin, lower statin dose or frequency, or add nonstatin LDL-C- lowering therapies

Repeat lipid panel; assess adequacy, tolerance of therapy

Intensify therapies to attain goals according to risk levels

RISK LEVELS	HIGH	VERY HIGH	EXTREME
	DESIRABLE LEVELS	DESIRABLE LEVELS	DESIRABLE LEVELS
LDL-C (mg/dL)	<100	<70	<55
Non-HDL-C (mg/dL)	<130	<100	<80
TG (mg/dL)	<150	<150	<150
Apo B (mg/dL)	<90	<80	<70

RISK LEVELS:

- **HIGH:** DM but no other major risk and/or age <40
- **VERY HIGH:** DM + major ASCVD risk(s) (HTN, Fam Hx, low HDL-C, smoking, CKD3,4)*
- **EXTREME:** DM plus established clinical CVD

IF NOT AT DESIRABLE LEVELS: Intensify lifestyle therapy (weight loss, physical activity, dietary changes) and glycemic control; consider additional therapy

TO LOWER LDL-C: Intensify statin, add ezetimibe, PCSK9i, colesevelam, or niacin

TO LOWER Non-HDL-C, TG: Intensify statin and/or add Rx-grade OM3 fatty acid, fibrate, and/or niacin

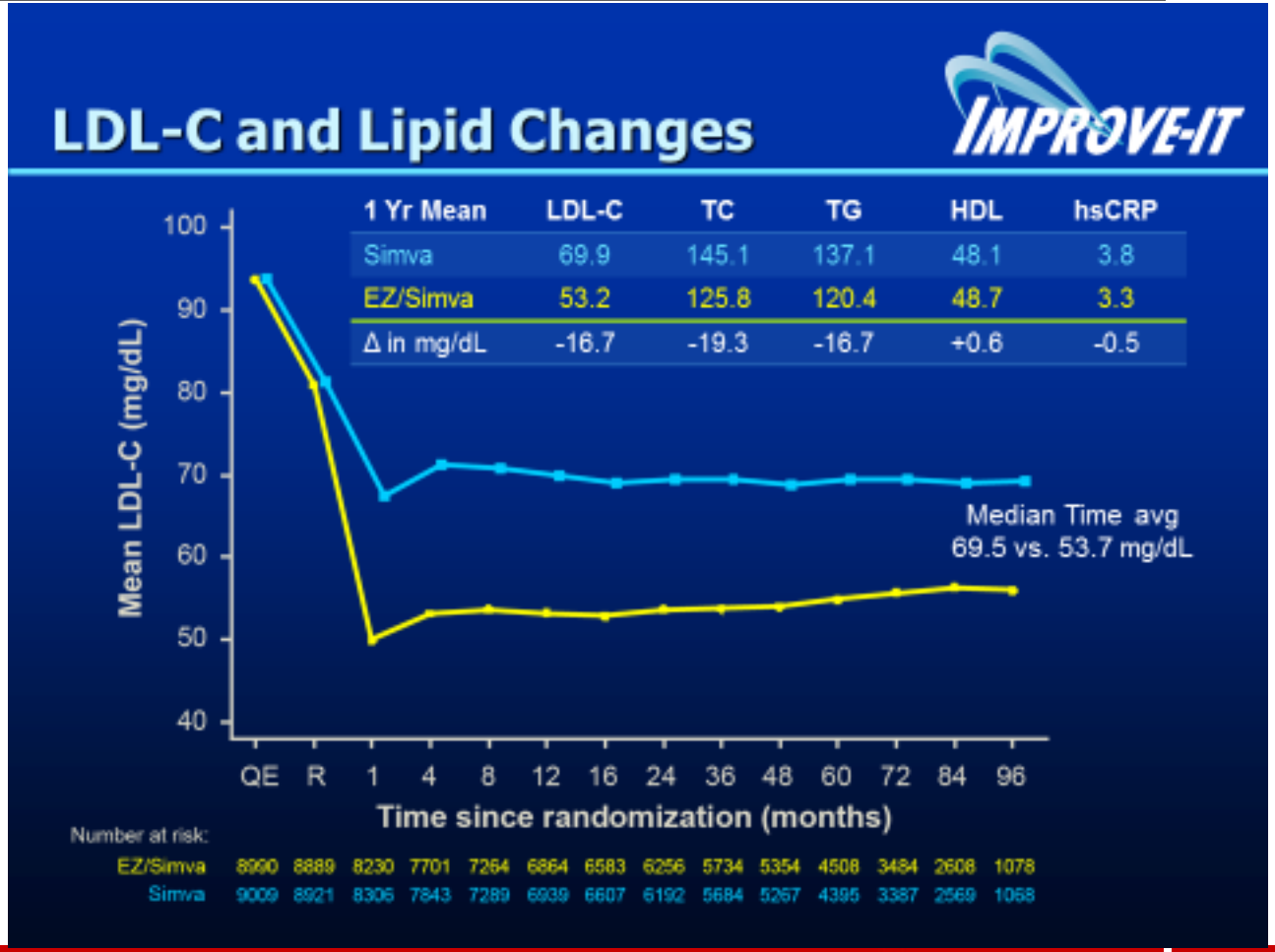
TO LOWER Apo B, LDL-P: Intensify statin and/or add ezetimibe, PCSK9i, colesevelam, and/or niacin

TO LOWER LDL-C in FH:** Statin + PCSK9i

Assess adequacy & tolerance of therapy with focused laboratory evaluations and patient follow-up

Da dove arriva il «50/55 mg/dL»?

Studio IMPROVE-IT: 18,000 soggetti di cui 27% diabetici seguiti per 7 anni



N Engl J Med 2015;372;2387-97.

Da dove arriva il «50/55 mg/dL»?

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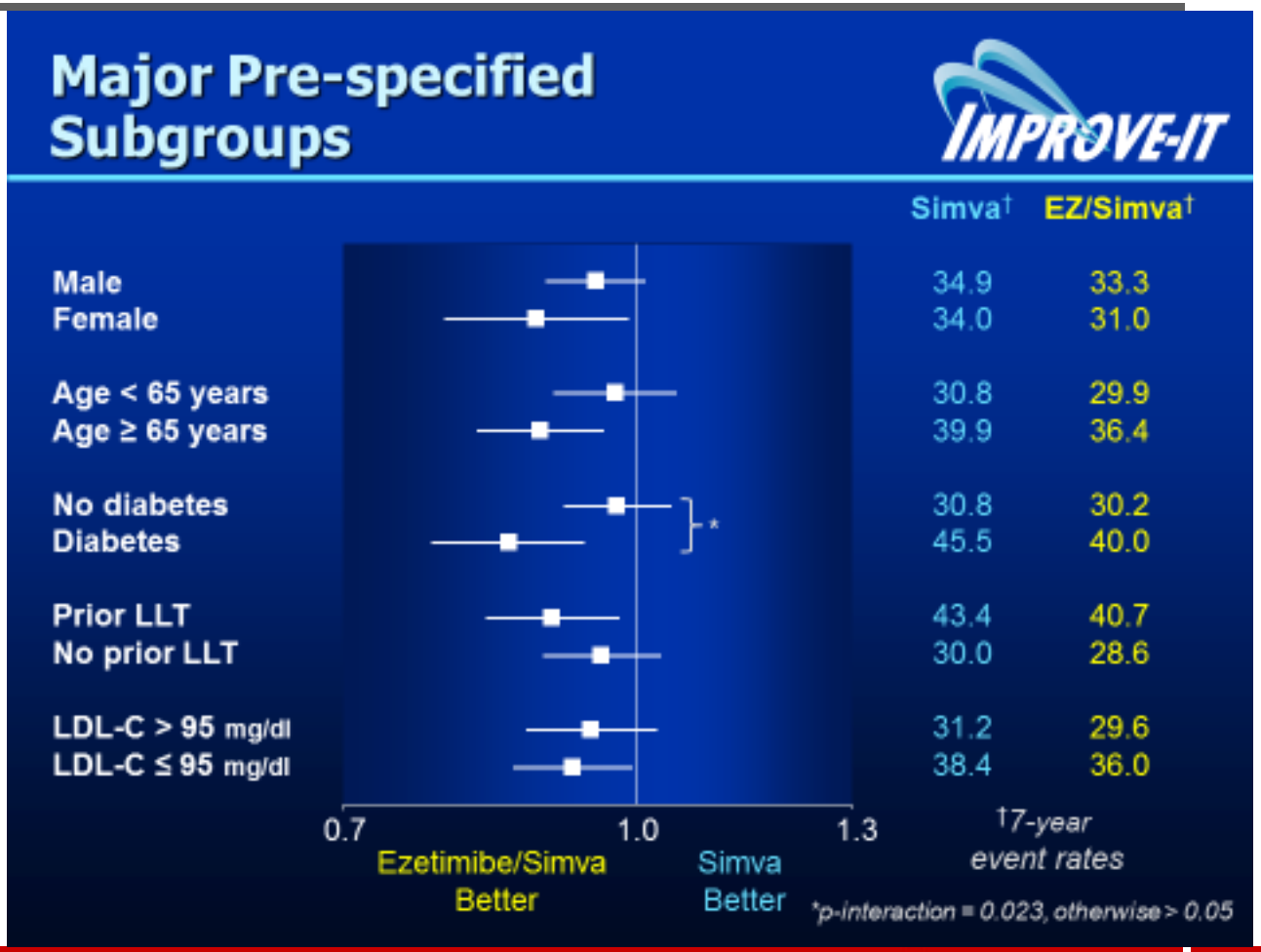
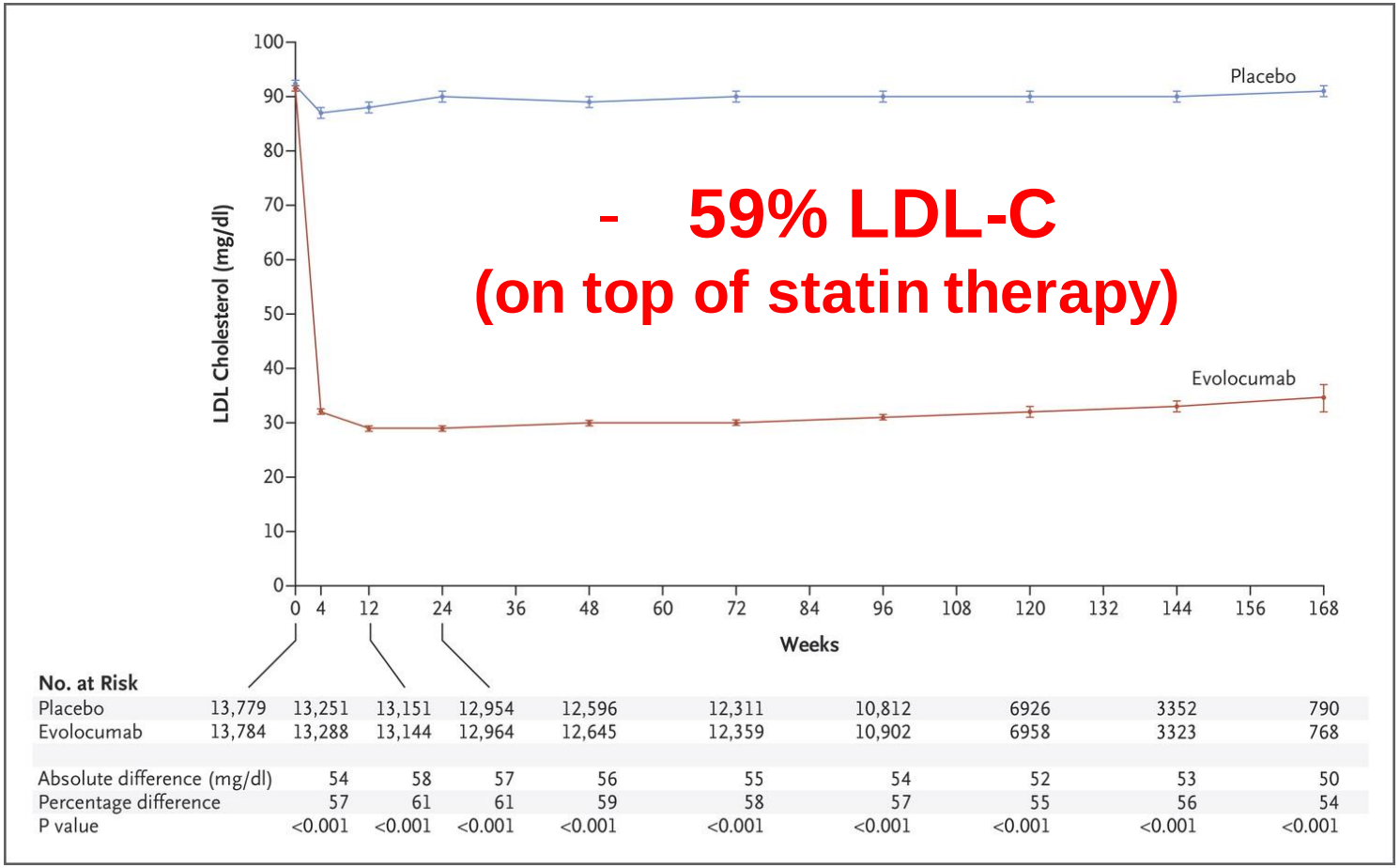


N Engl J Med 2015;372;2387-97.

Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease: The FOURIER trial



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)		54	58	57	56	55	54	52	53	50
Percentage difference		57	61	61	59	58	57	55	56	54
P value		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

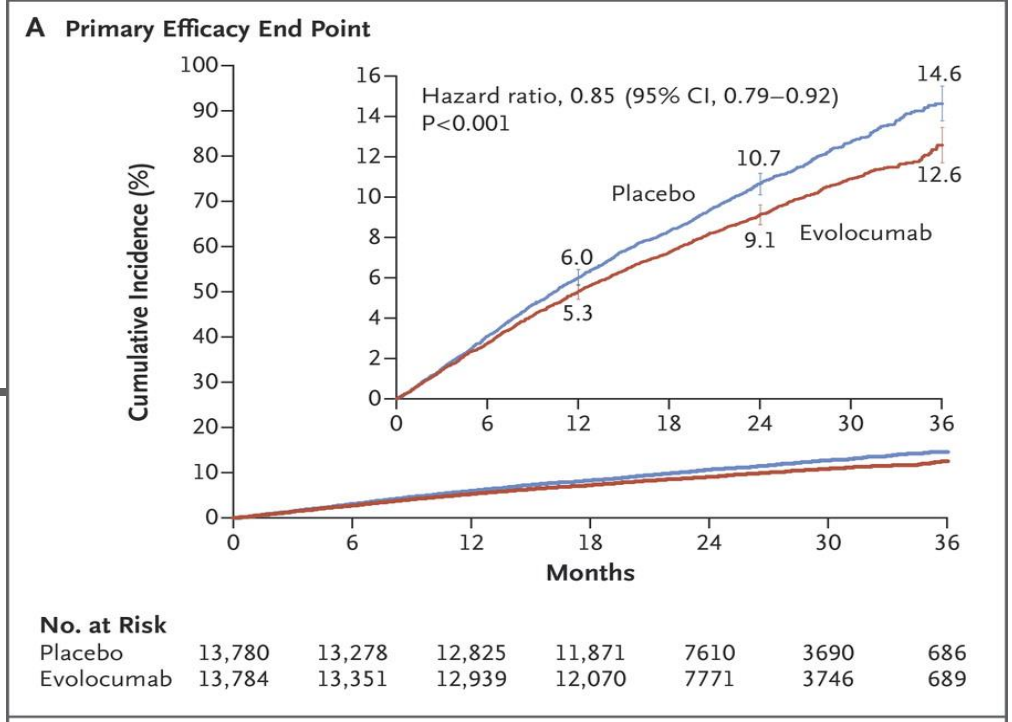
NEJM 2017

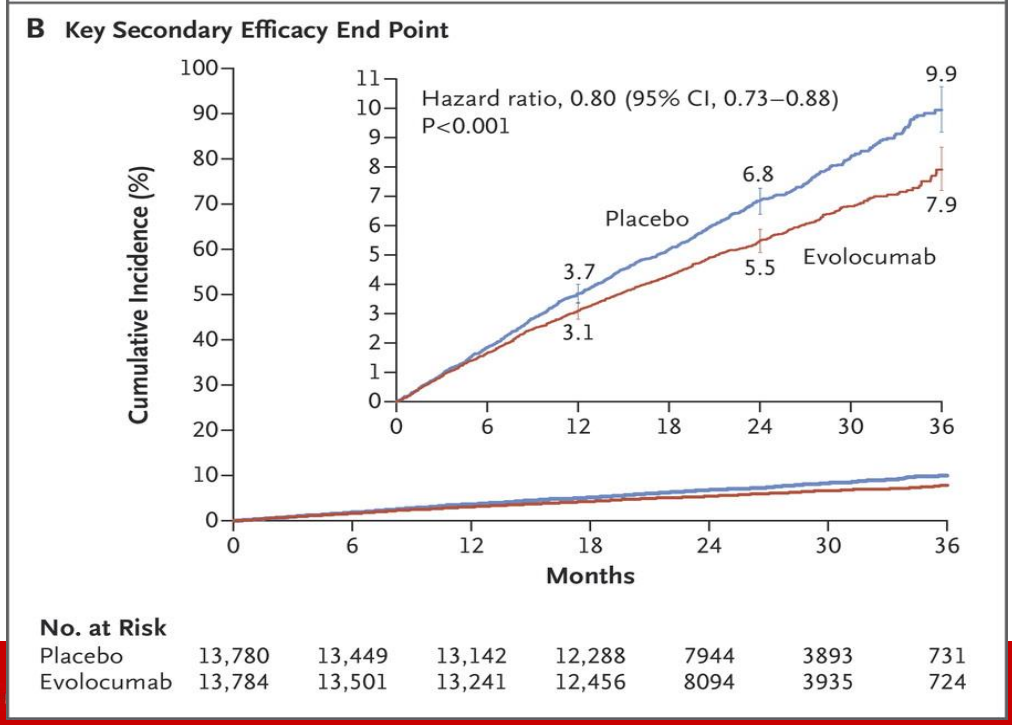
The FOURIER trial

<u>Primary efficacy end point</u>: the composite of CV death, MI, stroke, hospitalization for UA or coronary revascularization = -15%

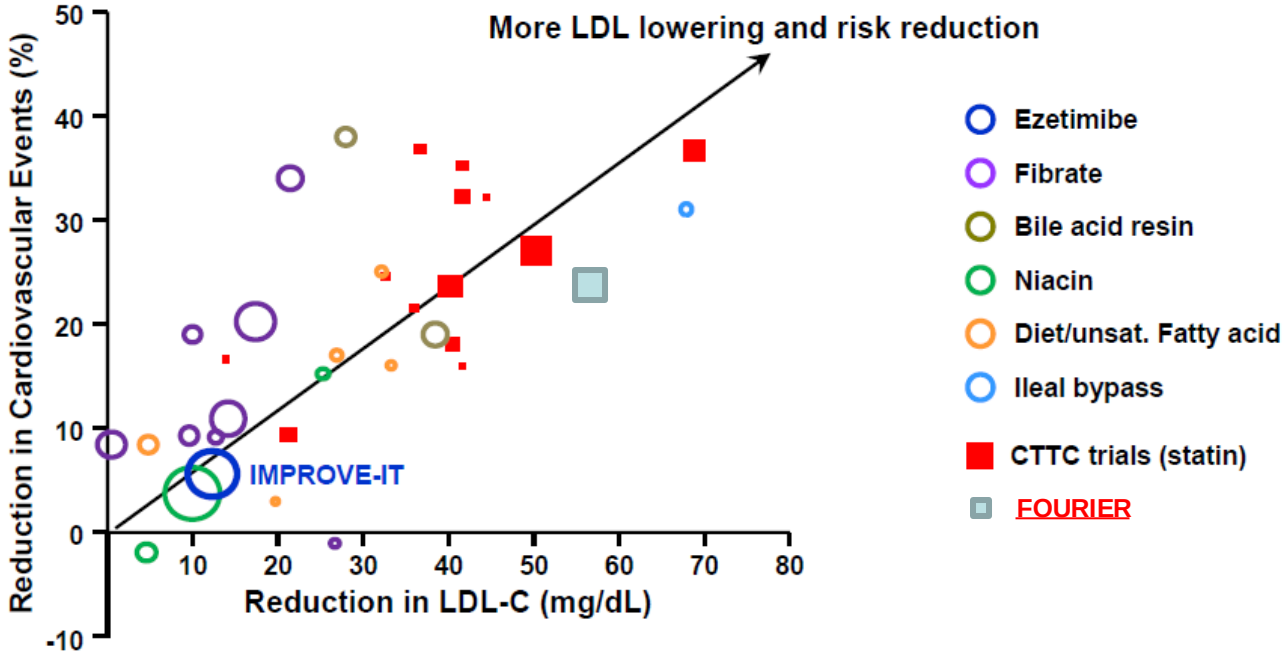
<u>Key secondary efficacy end point</u>: the composite of CV death, MI, or stroke = -20%

NEJM 2017





Relative Risk Reduction in Cardiovascular Events vs. Absolute Reduction in LDL-C



Data from studies of non-statin lipid-lowering medications suggest that reduction of coronary event risk due to reduction of LDL-C is independent of method

CM-20

Perché è così difficile ottimizzare i ns. pazienti ?

- Terrore/Disinformazione mediatica
- Scarsa tollerabilità delle massime dosi utilizzabili di statina
- Scarsa compliance
- Mancata volontà di aggiungere compresse
- Costi
- Non facile accesso a terapie innovative
- Timori/Inerzia del prescrittore

Outcomes «secondari» su cui agisce la terapia ipocolesterolemizzante

- LDL piccole e dense/ApoB (Statine, Ezetimibe, PUFA, Fenofibrato)
- HDL-C (poco: Statine, Ezetimibe, Fenofibrato)
- TG (PUFA, Fenofibrato)
- hsCRP (Statine, Ezetimibe)
- FMD/PWV (Statine)
- NAFLD (Ezetimibe, Fenofibrato)

Conclusioni operative

- **Misurare**
- **Trattare**
- **Monitorare (dopo i primi 2 mesi, 1 volta all'anno)**
- **Targettizzare**

-> < incidenza di eventi

-> < costi diretti ed indiretti