III SESSIONE

Non solo cuore e diabete

Non scordiamoci dei lipidi

Marcello Arca

Dipartimento di Medicina Traslazionale e di Precisione

Sapienza Università di Roma

SAPIENZA
UNIVERSITÀ DI ROMA

Dichiarazione conflitto di interessi

Il sottoscritto Marcello Arca dichiara che negli ultimi due anni ha ricevuto compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

ALFASIGMA, AKCEA/IONIS, AMRYT, AMGEN, DAICHII-SANKIO, NOVARTIS, PFIZER, REGENERON, SANOFI, SERVIER

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici)

Questione 1

E’ giusto affermare che le alterazioni del profilo lipidico rappresentano il principale fattore di rischio cardiovascolare nei pazienti diabetici?

1. VERO
2. FALSO

Risk Factors* in Patients with Type 2 Diabetes with Dependent Variable as Time to First Event: *UKPDS*

Coronary Artery Disease (n=280)

Position in Model	Variable	p Value
First	LDL Cholesterol	<0.0001
Second	HDL Cholesterol	0.0001
Third	Hemoglobin A_{1c}	0.0022
Fourth	Systolic Blood Pressure	0.0065
Fifth	Smoking	0.056

*Adjusted for age and sex.

Turner RC et al. *BMJ* 1998;316:823-828.

CHD Events in Type 2 Diabetes (1° Prevention Lipid-LoweringStudies)

Study	Control (n/n)	Intervention (n/n)	RR (95% CI)	ARR (95% CI)	NNT
AFCAPS/TexCAPS	6/71	4/84	0.56 (0.17–1.92)	0.04 (-0.04–0.12)	27.1
ALLHAT-LLT	Not reported	Not reported	0.89 (0.71–1.10)	Not reported	Not reported
HHS	8/76	2/59	0.32 (0.07–1.46)	0.07 (-0.01–0.15)	14.0
HPS	367/1976	276/2006	0.74 (0.64–0.85)	0.05 (0.03–0.07)	20.8
PROSPER*	28/205	32/191	1.23 (0.77–1.95)	-0.03 (-0.10–0.04)	-32.3
ASCOT-LLA	46/1274	38/1258	0.84 (0.55–1.29)	0.01 (-0.01–0.02)	169.5
Pooled†	—	—	0.78 (0.67–0.89)	0.03 (0.01–0.04)	34.5‡

* Shepherd J, Blauw GJ, Murphy MB. Personal communication.
† Meta-analysis; due to no heterogeneity between 1° prevention studies (P=0.18), fixed-effects model used.
‡ Number needed to treat for benefit is for 4.3 years.

Vijan S, Hayward RA. *Ann Intern Med*. 2004;140:650-658.

CHD Events in Type 2 Diabetes (2° Prevention Lipid-Lowering Studies)

Study	Control (n/n)	Intervention (n/n)	RR (95% CI)	ARR (95% CI)	NNT
4S	44/97	24/105	0.50 (0.33–0.76)	0.23 (0.10–0.35)	4.4
CARE	112/304	81/282	0.78 (0.62–0.99)	0.08 (0.01–0.16)	12.3
HPS	381/1009	325/972	0.89 (0.79–1.00)	0.04 (0.00–0.09)	23.1
LIPID	88/386	76/396	0.84 (0.64–1.11)	0.04 (-0.02–0.09)	27.7
LIPS	31/82	26/120	0.53 (0.29–0.97)	0.16 (0.03–0.29)	6.2
Post-CABG	14/53	9/63	0.53 (0.18–1.60)	0.12 (-0.03–0.27)	8.2
PROSPER*	31/115	38/112	1.26 (0.85–1.87)	-0.07 (-0.19–0.05)	NA
VA-HIT	116/318	88/309	0.76 (0.57–1.01)	0.08 (0.01–0.15)	12.5
Pooled†	—	—	0.76 (0.59–0.93)	0.07 (0.03–0.12)	13.8‡

*Shepherd J, Blauw GJ, Murphy MB. Personal communication.
†Meta-analysis: due to substantial between-study heterogeneity (*P*=0.026), random-effects model used.
‡Number needed to treat for benefit is for 4.9 years.

Vijan S, Hayward RA. *Ann Intern Med*. 2004;140:650-658.

Change in recommendations (2)

ESC European Society of Cardiology

2013	2019
Lipid targets	
In DM at high CV risk, an LDL-C target of <2.5 mmol/L (<100 mg/dL) In DM at very high CV risk, an LDL-C target of <1.8 mmol/L (<70 mg/dL) is recommended	In patients with T2DM at moderate CV risk, an LDL-C target of <2.6 mmol/L (<100 mg/dL) is recommended In patients with T2DM at high CV risk, an LDL-C target of <1.8 mmol/L (<70 mg/dL) and LDL-C reduction of at least 50% is recommended In patients with T2DM at very high CV risk, an LDL-C target of <1.4 mmol/L (<55 mg/dL) and LDL-C reduction of at least 50% is recommended

ESC Guidelines on Diabetes, pre-diabetes and cardiovascular diseases in collaboration with EASD (European Heart Journal 2019 - doi/10.1093/eurheartj/ehz486)

CV risk categories in patients with DM

ESC
European Society of Cardiology

Very high-risk	Patients with DM **and** established CVD **or** other target organ damage[a] **or** three or more major risk factors[b] **or** early onset T1DM of long duration (>20 years)
High-risk	Patients with DM duration ≥10 years without target organ damage plus any other additional risk factor
Moderate-risk	Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years, without other risk factors

[a]Proteinurea, renal impairment defined as eGFR < 30mL/min/1.73m², left ventricular hypertrophy, or retinopathy.
[b]Age, hypertension, dyslipidaemia, smoking, obesity

ESC Guidelines on Diabetes, pre-diabetes and cardiovascular diseases in collaboration with EASD (European Heart Journal 2019 - doi/10.1093/eurheartj/ehz486)

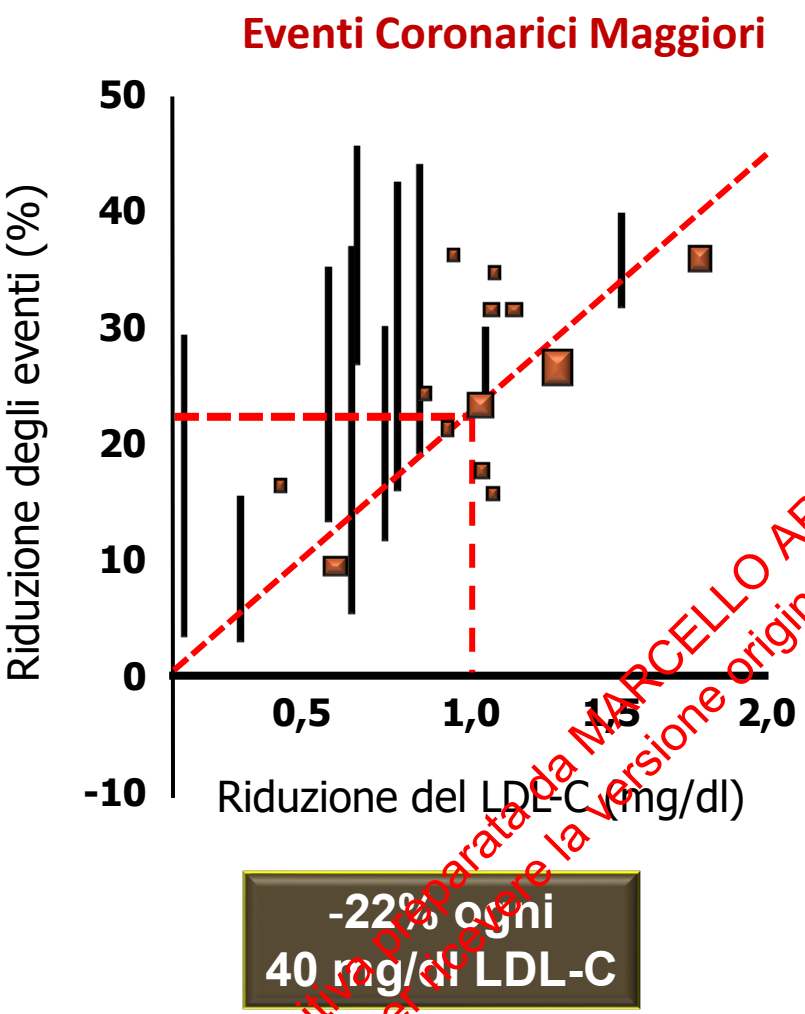
Questione 2

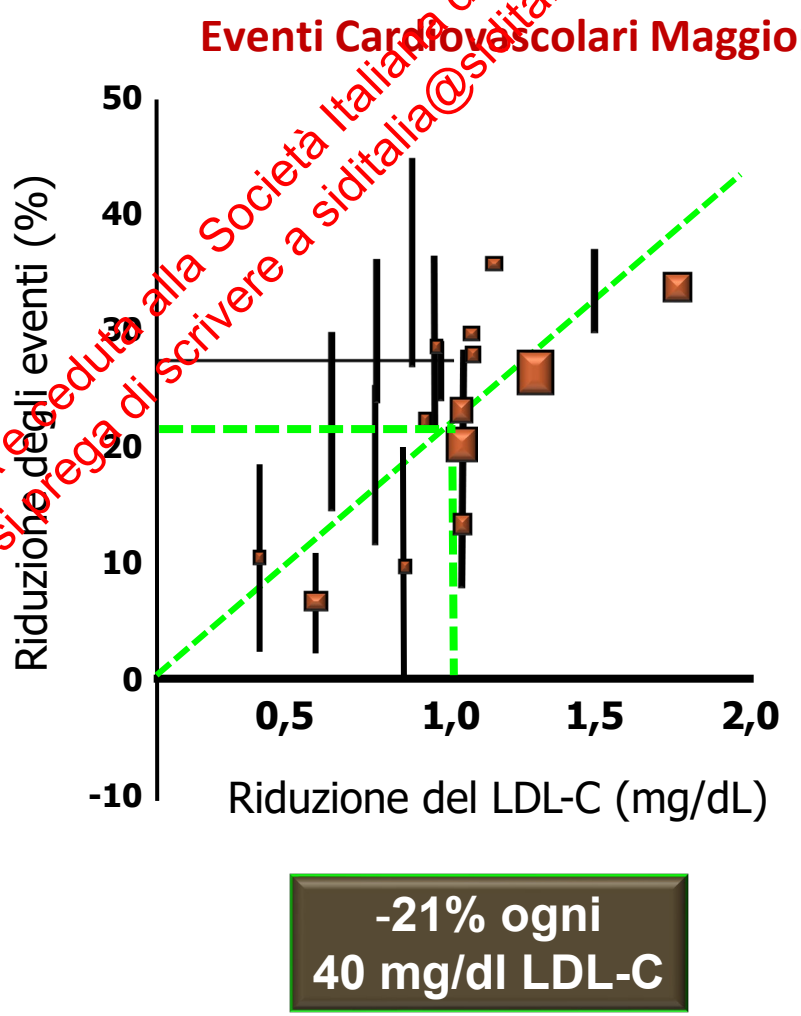
Quale è il beneficio in termini di protezione cardiovascolare che si può ottenere nei pazineti diabetici mediante l'impiego delle statine?

A. Dipende dal livello di rischio di ciascun paziente
B. In media del 30% per ogni anno
C. Di circa il 20% per ogni 40 mg/dl riduzione delle LDL-C
D. Di circa del 20% per ogni riduzione del 50% dei livelli di LDL-C

Riduzione dell'incidenza degli eventi coronarici e cardiovascolari maggiori e riduzione media del LDL-C

(Meta-analisi di 14 trials, n=18.686 PAZIENTI DIABETICI, 1994-2004)

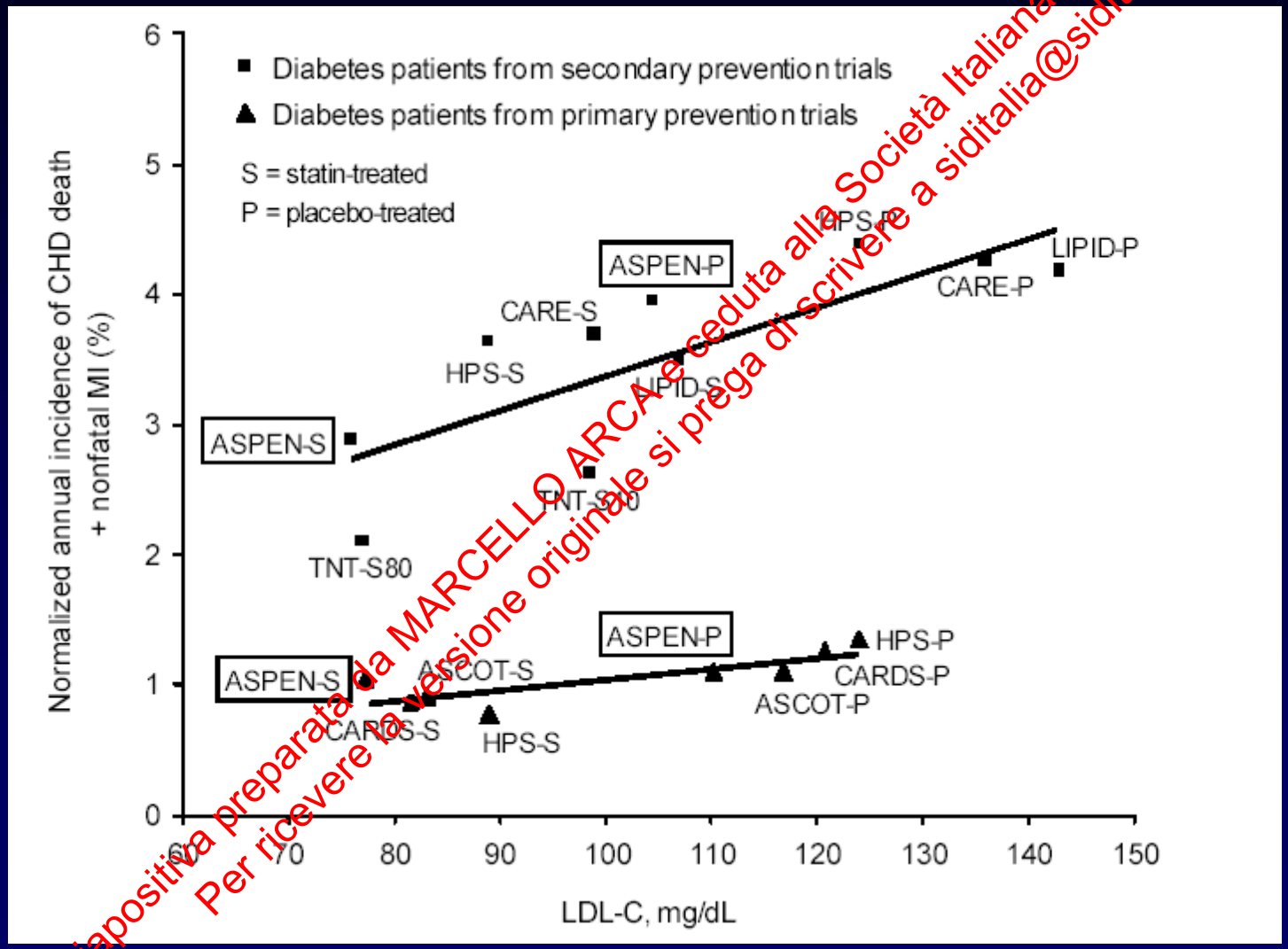




Cholesterol 1.0 mmol/l= 39 mg/dl

Lancet 2008; 371:117-125

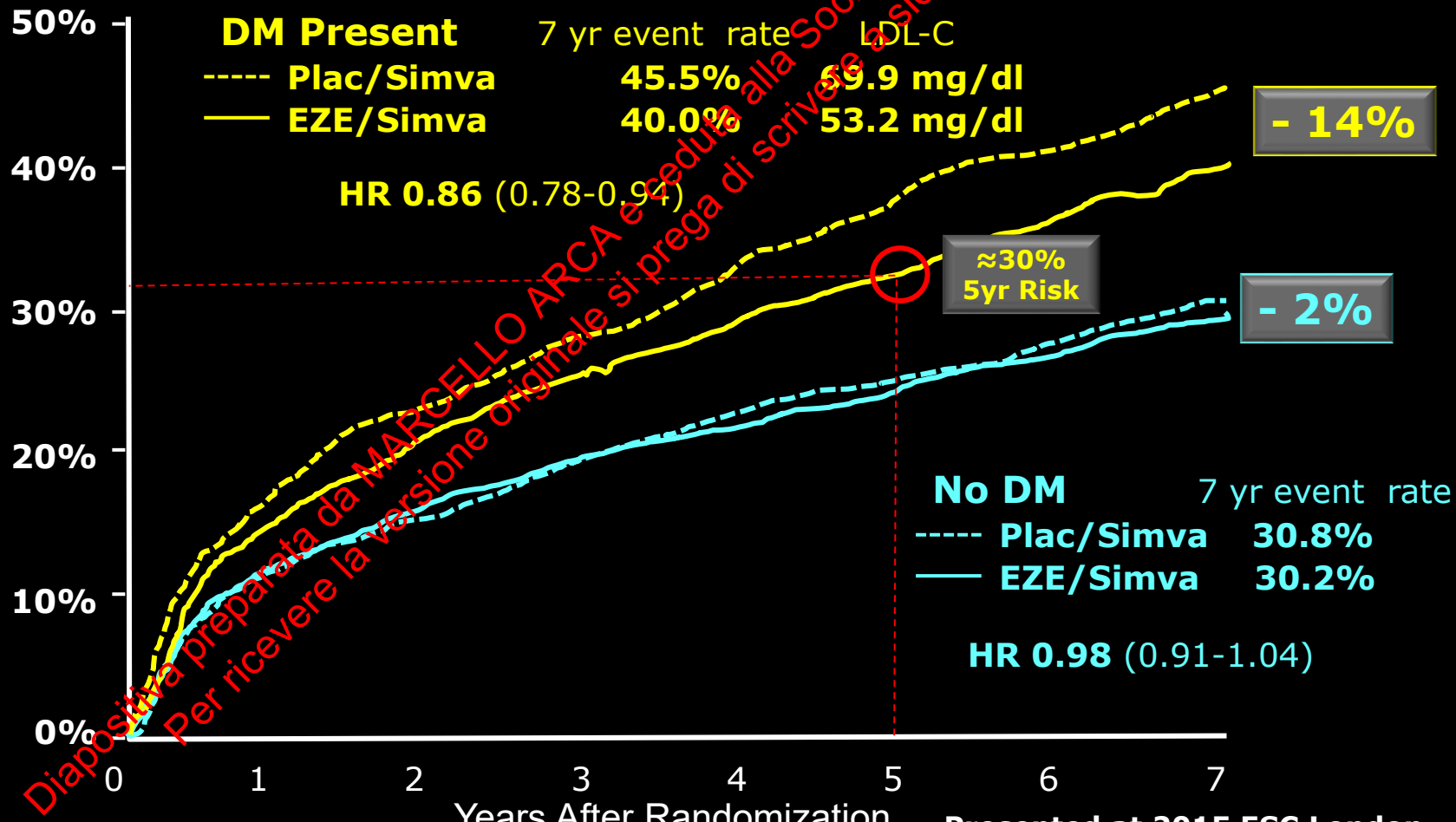
Relation between LDL-C levels and incidence of CHD in statin trials in T2DM patients



IMPROVE-IT: Primary Endpoint

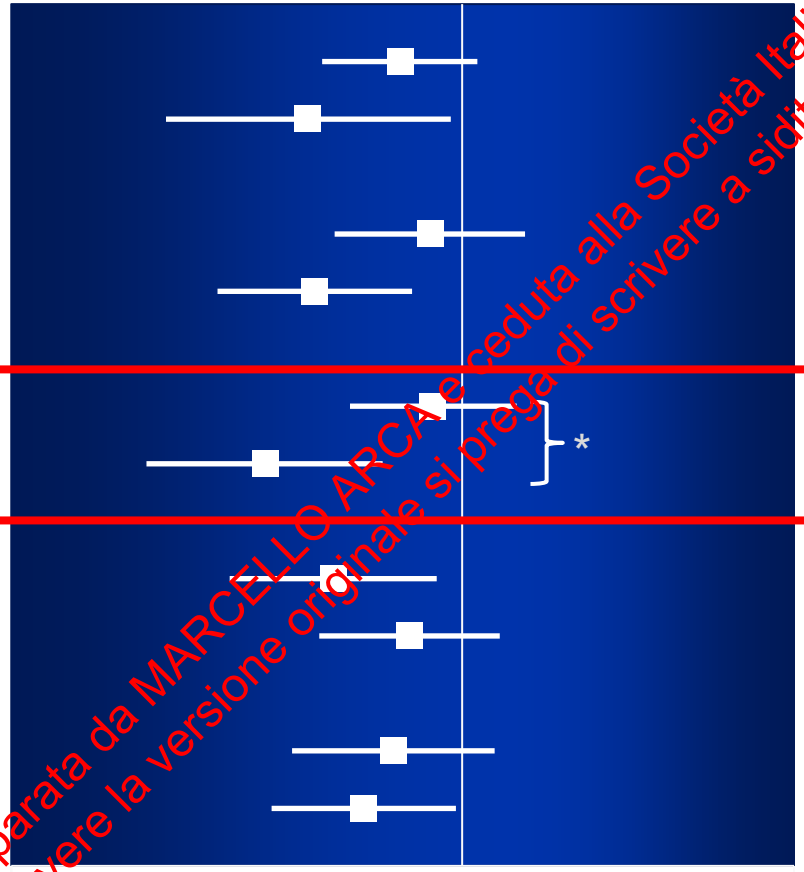
Diabetes YES vs Diabetes NO

Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary rivascularization (≥30 days), stroke



Presented at 2015 ESC London

IMPROVE-IT
Major Pre-specified Subgroups

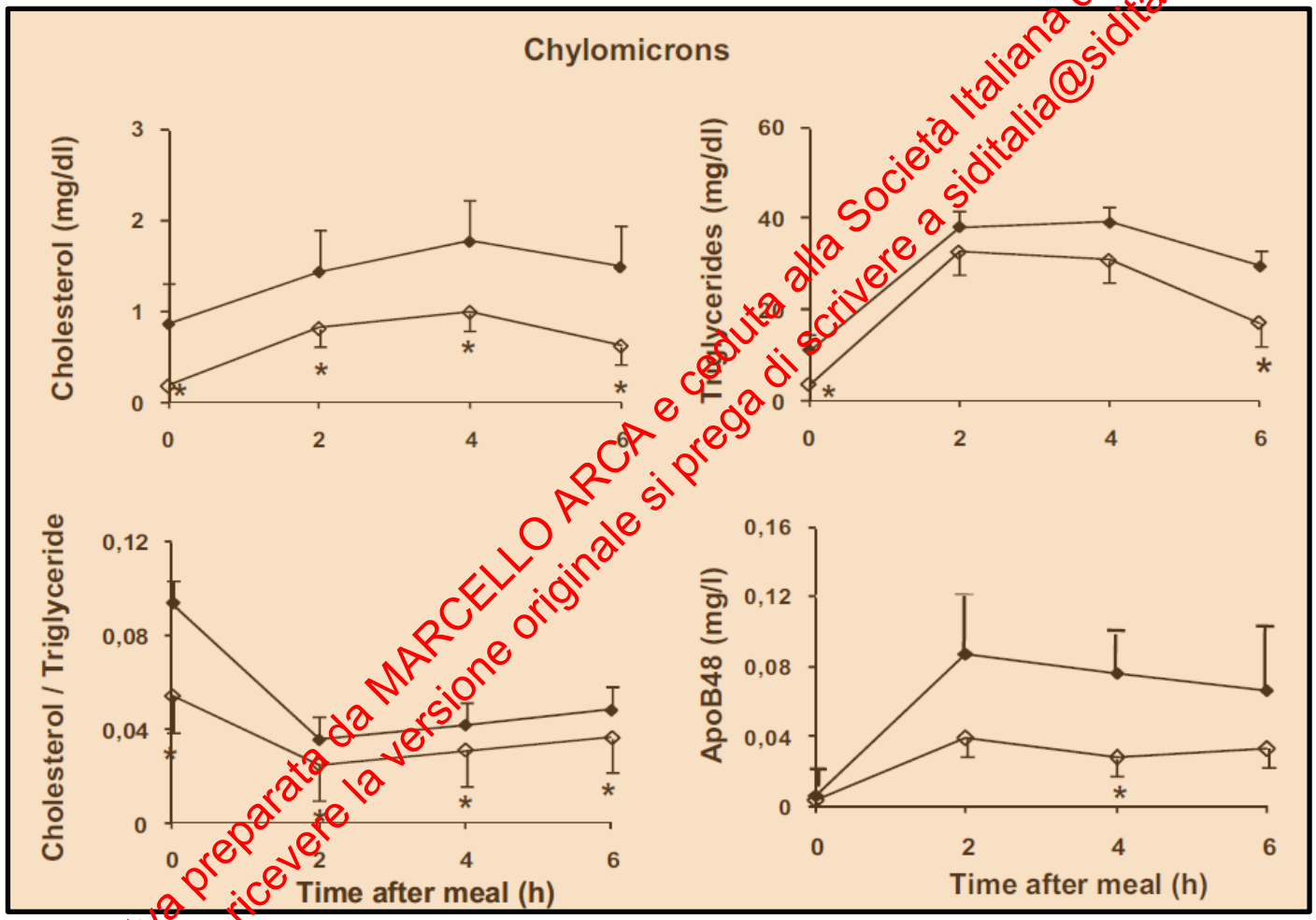


	Simva†	EZ/Simva†
Male	34.9	33.3
Female	34.0	31.0
Age < 65 years	30.8	29.9
Age ≥ 65 years	39.9	36.4
No diabetes	30.8	30.2
Diabetes	45.5	40.0
Prior LLT	43.4	40.7
No prior LLT	30.0	28.6
LDL-C > 95 mg/dl	31.2	29.6
LDL-C ≤ 95 mg/dl	38.4	36.0

†*7-year event rates*

**p-interaction = 0.023, otherwise > 0.05*

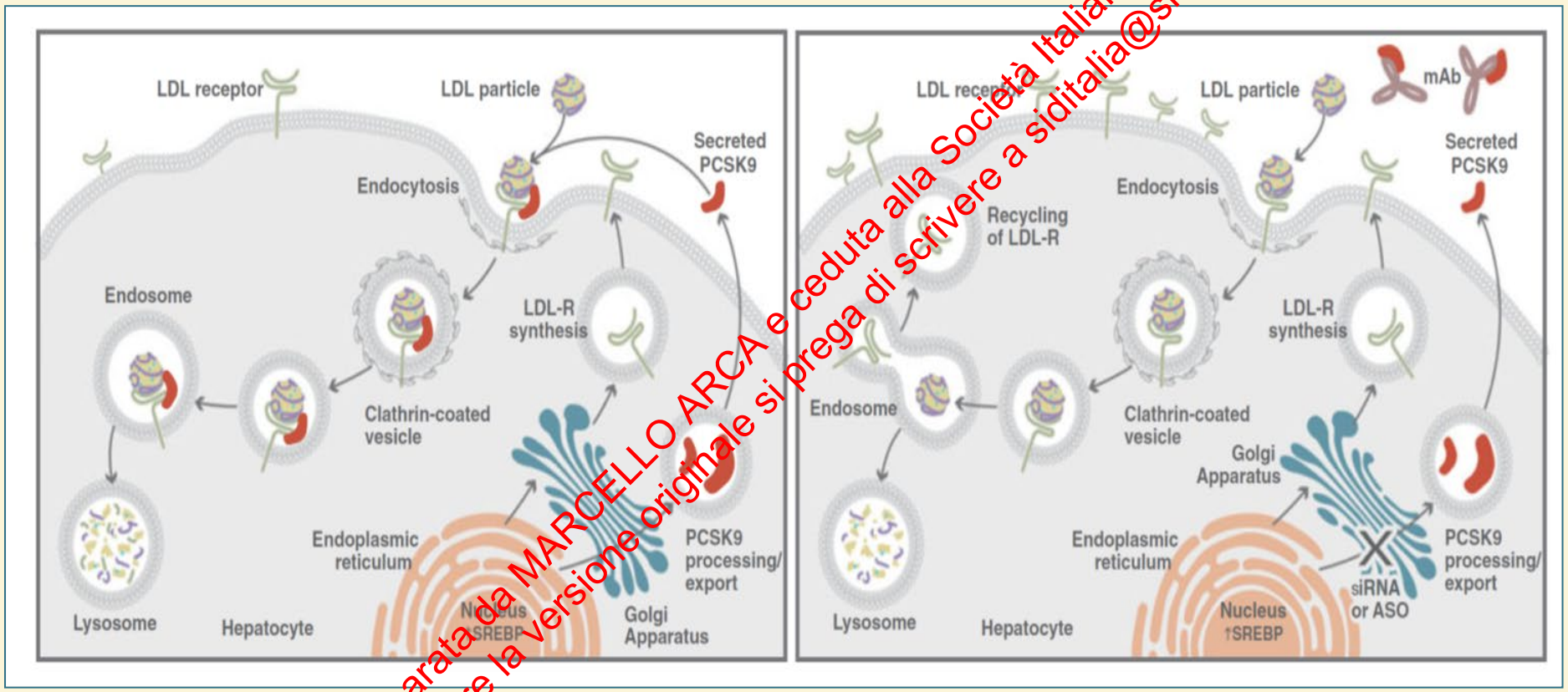
Ezetimibe beneficially influences fasting and postprandial triglyceride-rich lipoproteins in type 2 diabetes



ezetimibe and placebo treatment.

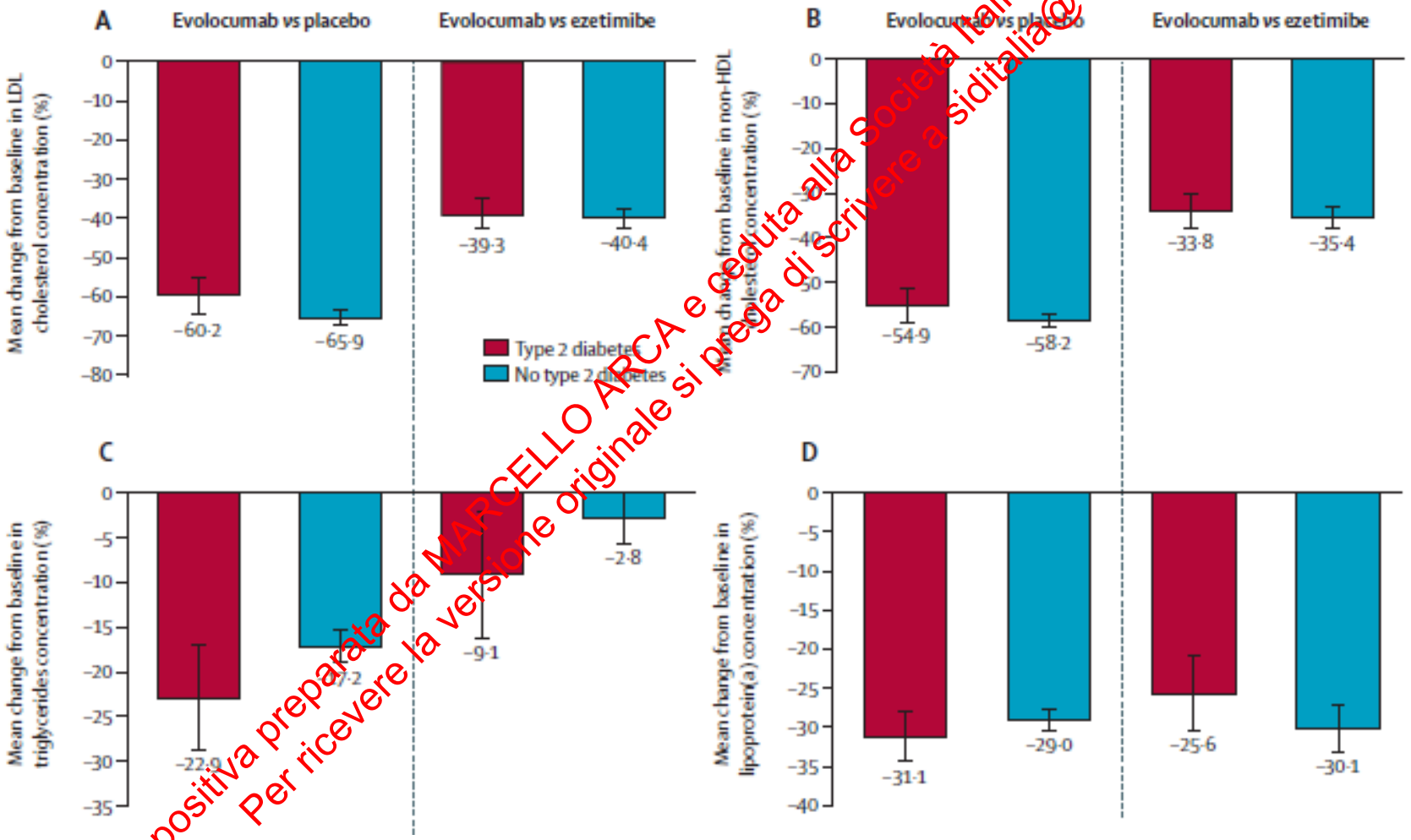
Atherosclerosis 217 (2011) 142–148

Meccanismo di azione degli Ab monoclonali anti-PCSK9



Stein EA et al. Curr Atheroscler Rep, 2013

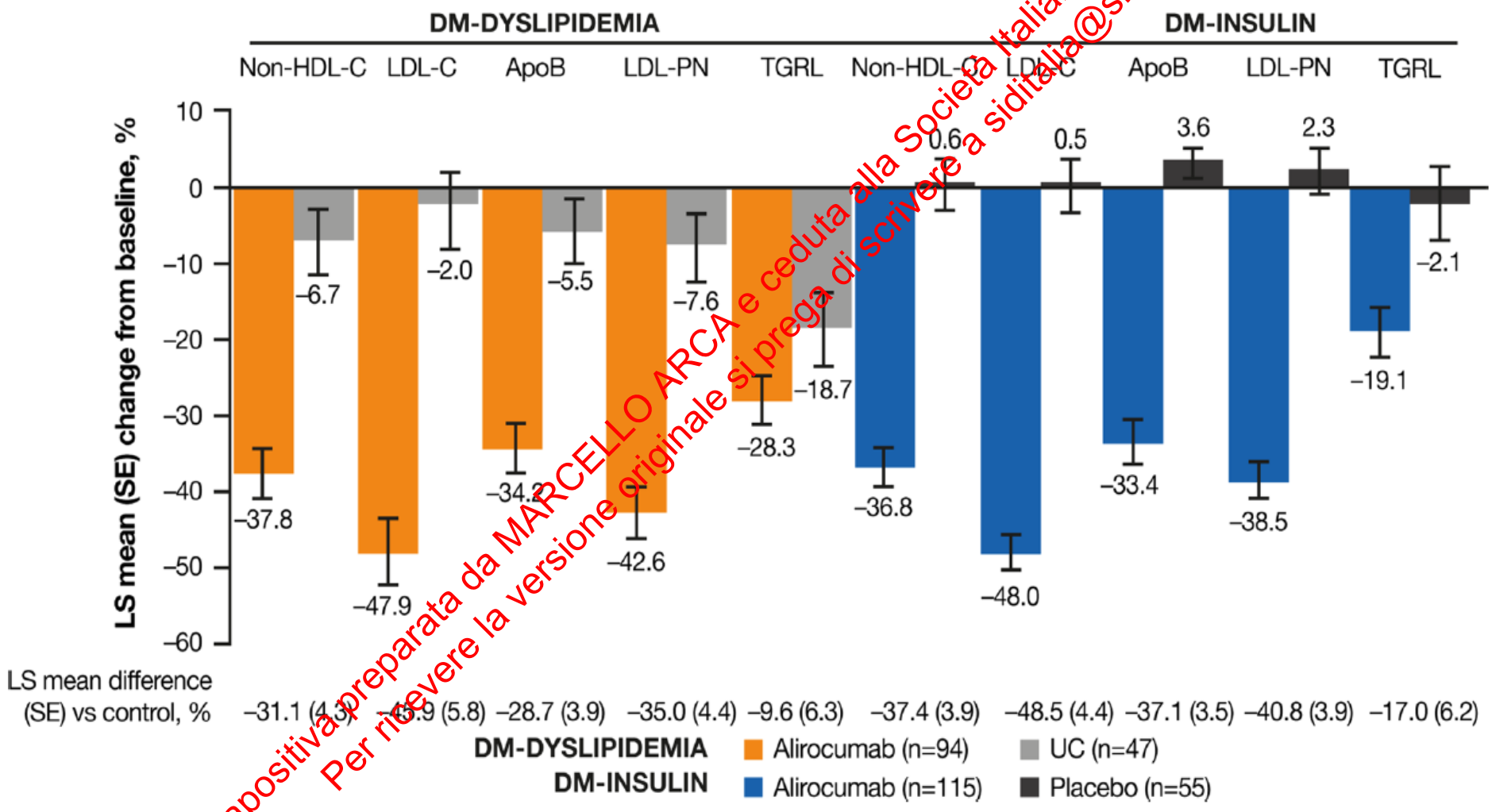
Lipid-lowering efficacy of the PCSK9 inhibitor evolocumab in patients with type 2 diabetes: a meta-analysis of individual patient data



Lancet Diabetes Endocrinol, published online February 8, 2016

ORIGINAL INVESTIGATION Open Access

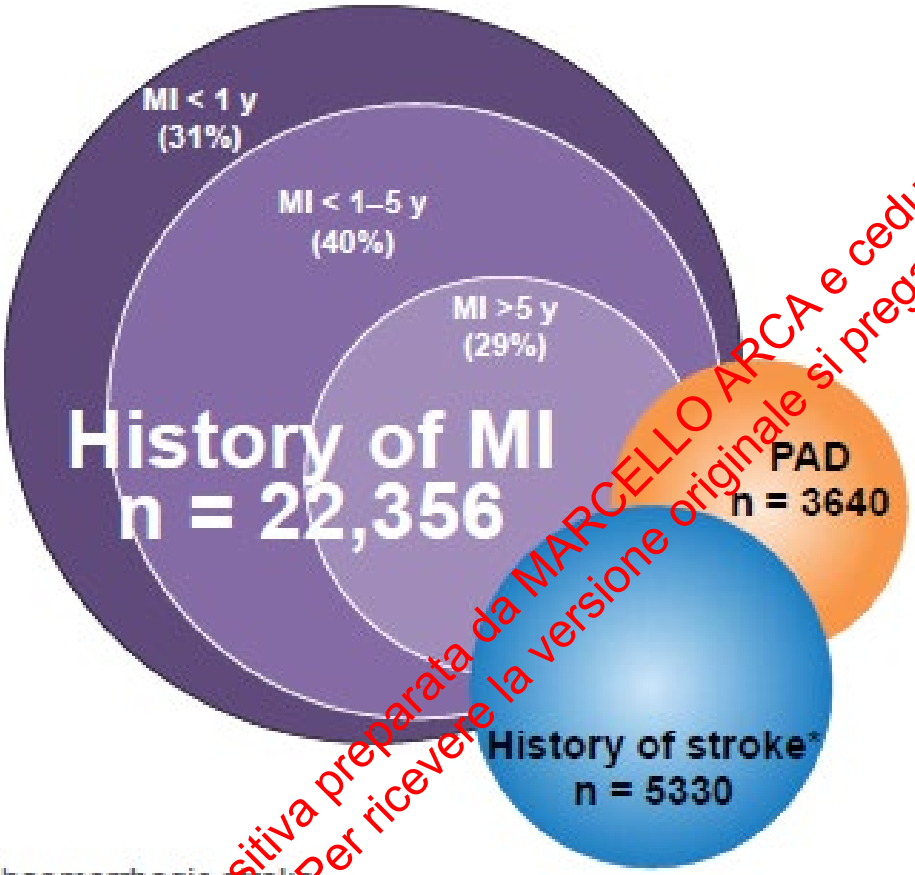
Alirocumab therapy in individuals with type 2 diabetes mellitus and atherosclerotic cardiovascular disease: analysis of the ODYSSEY DM-DYSLIPIDEMIA and DM-INSULIN studies



Cardiovasc Diabetol (2019) 18:149

PCSK9i Outcome Trials: Are They Similar?

fourier



*non-haemorrhagic stroke

Sabatine MS, et al. N Engl J Med 2017;376:1713

ODYSSEY OUTCOMES

Recent ACS
(4-52 weeks)

Schwartz GG et al. N Engl J Med 2018 [Epub ahead of print]

PCSK9i Outcome Trials: Baseline Patients Characteristics

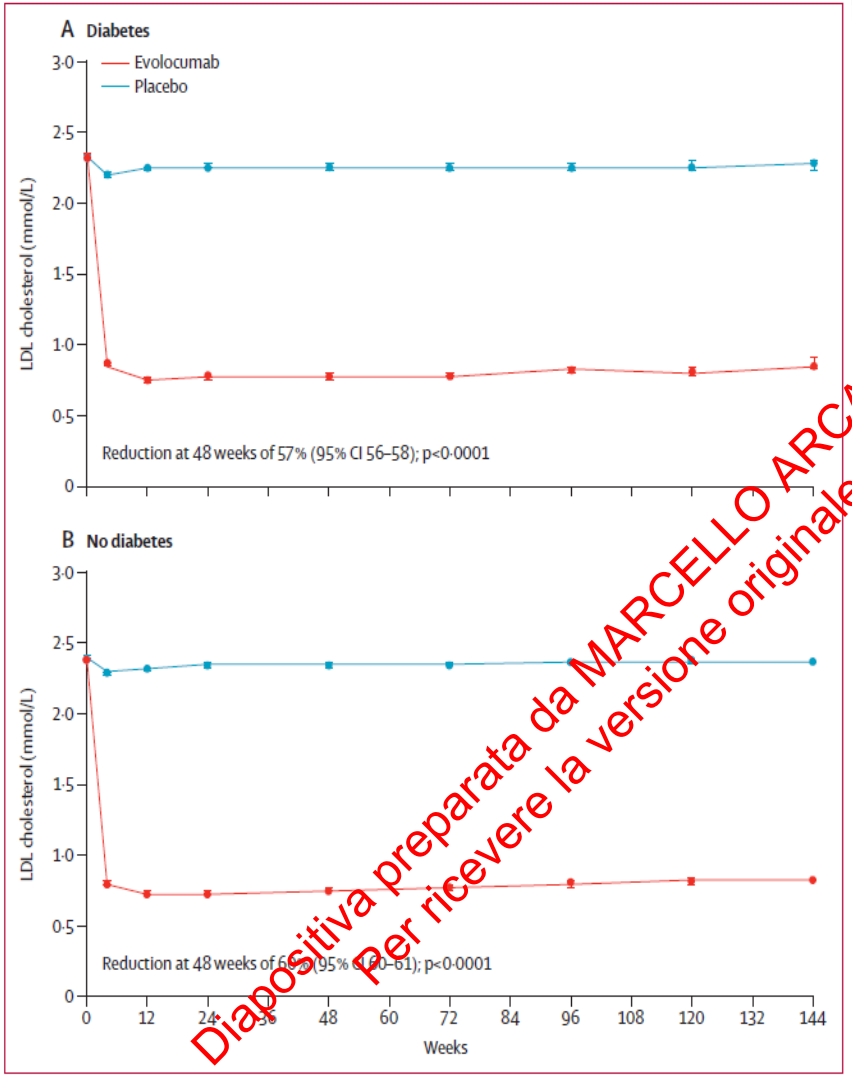
	fourier	ODYSSEY OUTCOMES
Number of Pts	27,564	18,924
Mean age	63	59
Females	25	25
Diabetes mellitus	36	29
Hypertension	80	64
Current smokers	28	24
Prior MI	81	19
PAD	13	4
Any revascularization	67	72

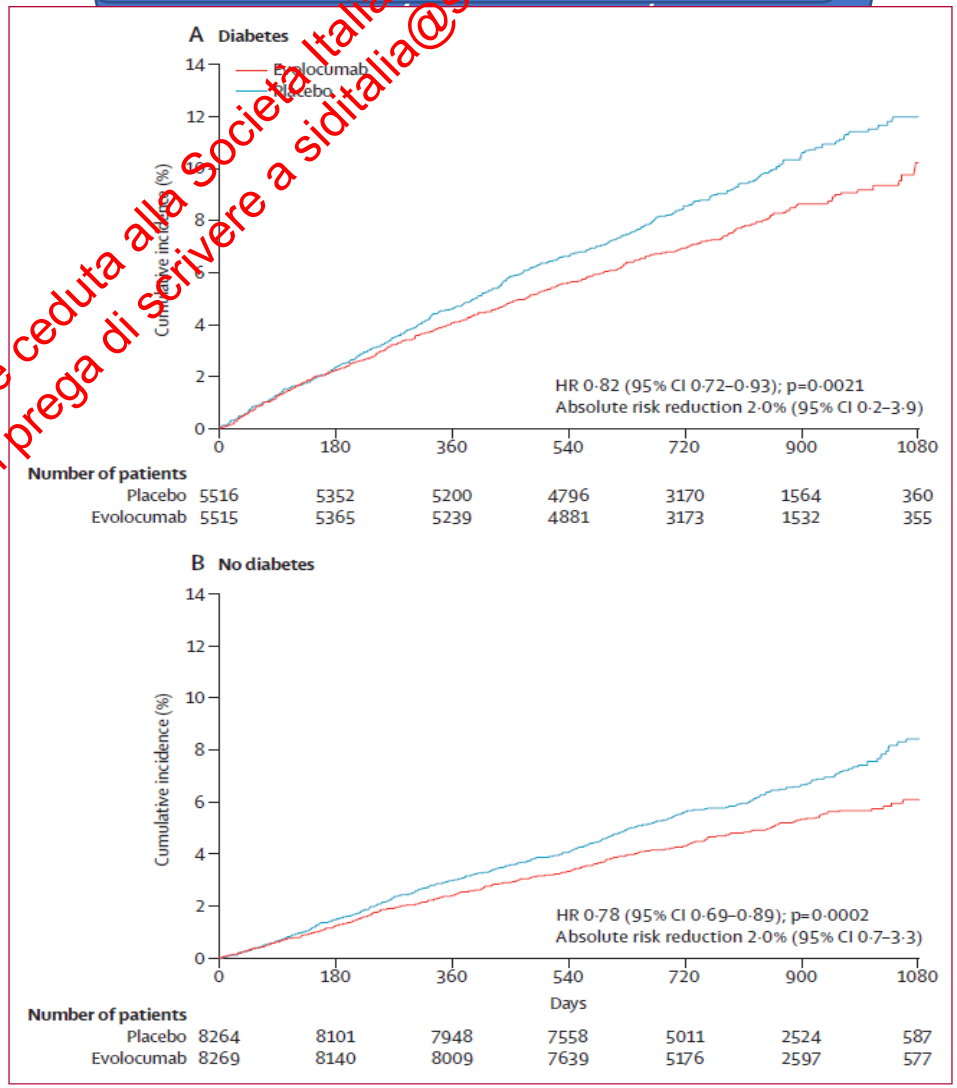
Sabatine MS, et al. N Engl J Med 2017;376:1713
Schwartz GG et al. N Engl J Med 2018 [Epub ahead of print]

Cardiovascular safety and efficacy of the PCSK9 inhibitor evolocumab in patients with and without diabetes and the effect of evolocumab on glycaemia and risk of new-onset diabetes: a prespecified analysis of the FOURIER randomised controlled trial

Lancet Diabetes Endocrinol 2017; 5: 941–50

Key secondary efficacy endpoint (composite of cardiovascular death, MI, or stroke)



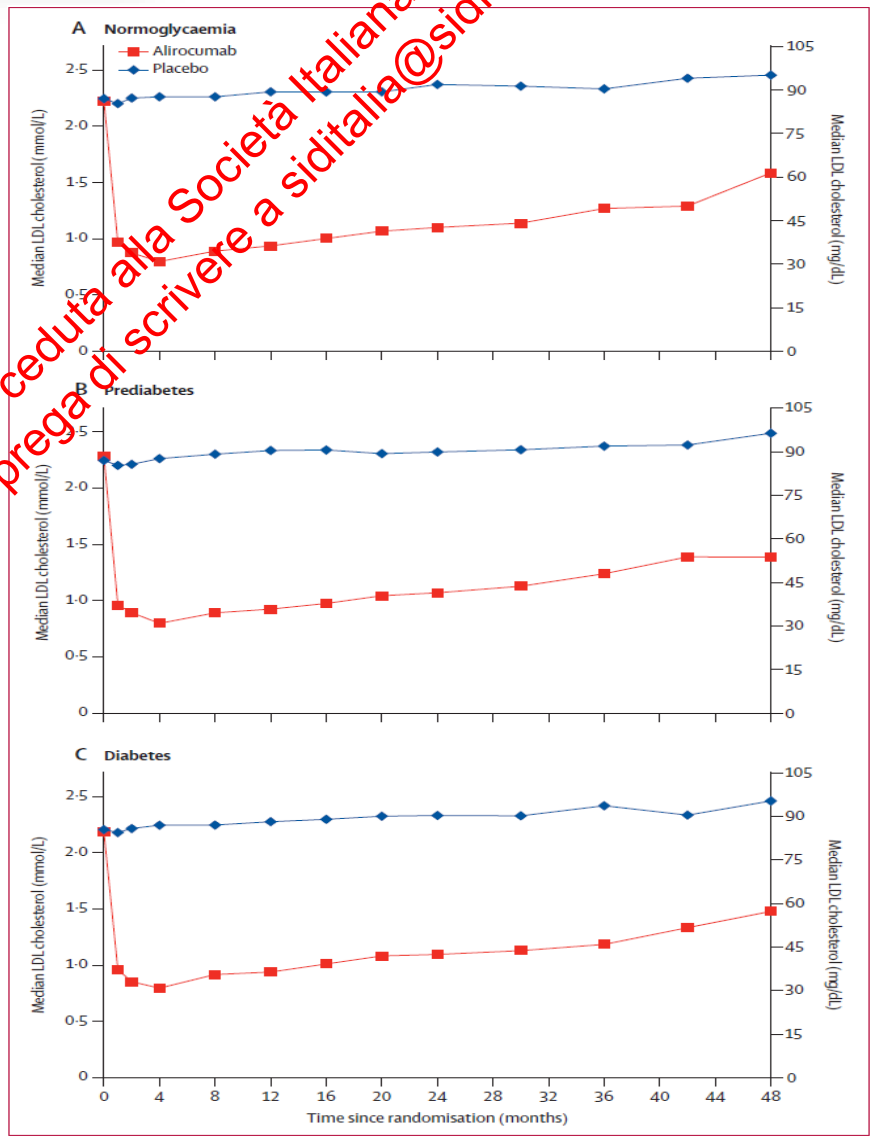


Effects of alirocumab on cardiovascular and metabolic outcomes after acute coronary syndrome in patients with or without diabetes: a prespecified analysis of the ODYSSEY OUTCOMES randomised controlled trial

Lancet Diabetes Endocrinol 2019; 7: 618–28

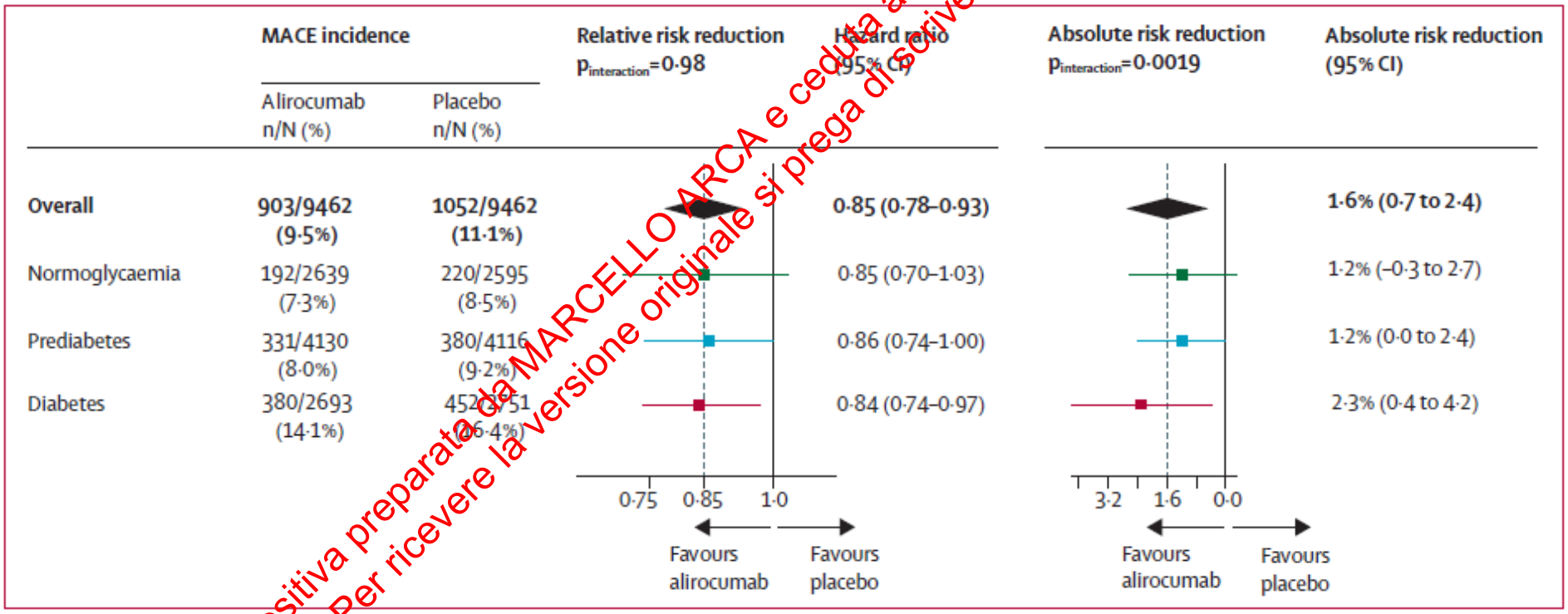
	Normoglycaemia (n=5234)	Prediabetes (n=8246)	Diabetes (n=5444)
Age, years	56 (50–63)	59 (52–65)	59 (53–66)
Sex			
Women	1078 (20·6%)	1948 (23·6%)	1736 (31·9%)
Men	4156 (79·4%)	6298 (76·4%)	3708 (68·1%)
BMI, kg/m²	27 (25–30)	28 (25–31)	29 (26–33)
Blood pressure, mm Hg			
Systolic	125 (115–135)	126 (117–137)	130 (120–140)
Diastolic	78 (70–83)	79 (70–83)	79 (70–84)
Index acute coronary syndrome event			
Non-ST-segment elevation myocardial infarction	2478 (47·4%)	3921 (47·6%)	2776 (51·1%)
ST-segment elevation myocardial infarction	1922 (36·8%)	2971 (36·1%)	1643 (30·3%)
Unstable angina	826 (15·8%)	1344 (16·3%)	1012 (18·6%)
Laboratory values at randomisation			
LDL cholesterol, mmol/L	2·23 (1·92–2·69)	2·28 (1·92–2·69)	2·20 (1·84–2·69)
Non-HDL cholesterol, mmol/L	2·90 (2·51–3·47)	2·97 (2·59–3·52)	3·09 (2·61–3·62)
HDL cholesterol, mmol/L	1·14 (0·98–1·35)	1·11 (0·96–1·32)	1·06 (0·91–1·24)
Triglycerides, mmol/L	1·32 (0·98–1·85)	1·44 (1·05–2·00)	1·66 (1·20–2·32)
HbA_{1c}, %	5·4 (5·3–5·5)	5·9 (5·7–6·0)	7·0 (6·5–8·2)
Fasting serum glucose, mmol/L	5·2 (4·9–5·5)	5·6 (5·2–6·2)	7·4 (6·2–9·4)
High-intensity statin treatment*	4624 (88·3%)	7403 (89·8%)	4784 (87·9%)
Ezetimibe	171 (3·3%)	234 (2·8%)	149 (2·7%)
Fibrates	49 (0·9%)	95 (1·2%)	174 (3·2%)
Duration of follow-up, years	2·9 (2·3–3·5)	2·8 (2·3–3·4)	2·7 (2·3–3·4)
Eligible for ≥3 years of follow-up†	2405 (45·9%)	3550 (43·1%)	2287 (42·0%)

Data are n (%) or median (IQR). LDL cholesterol was calculated via the Friedewald formula. To convert the values for cholesterol to mg/dL, divide by 0·0259. To convert the values for triglycerides to mg/dL, divide by 0·0113. To convert the values for glucose to mg/dL, divide by 0·0555. *Atorvastatin 80 mg or rosuvastatin 40 mg. †Subset of participants that either were or could have been followed up for 3 years or longer because they were randomly assigned on or before Nov 11, 2014 (≥3 years before the common study end date).



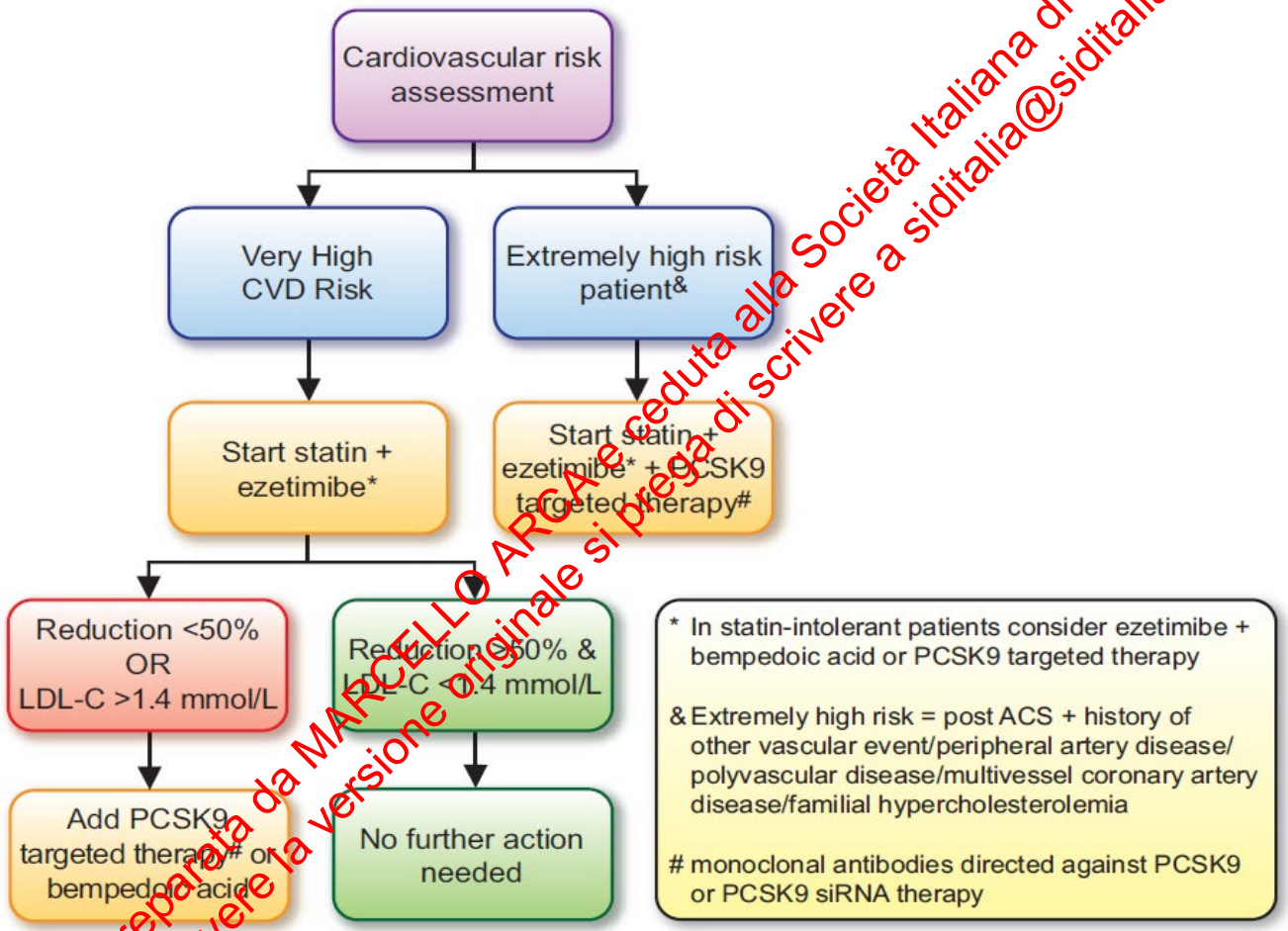
Effects of alirocumab on cardiovascular and metabolic outcomes after acute coronary syndrome in patients with or without diabetes: a prespecified analysis of the ODYSSEY OUTCOMES randomised controlled trial

Relative and absolute risk reduction with alirocumab, by baseline glycaemic status



Lancet Diabetes Endocrinol 2019; 7: 618–28

Combination lipid-lowering therapy as first line strategy in very high-risk patients



European Heart Journal (2021) 00, 1–4

Questione 3

E’ giusto affermare che nei pazienti diabetico occorre considerare solo le alterazioni nei livelli della colesterolemia LDL ?

1. VERO
2. FALSO

Patients With Diabetes Have Particularly High Residual CVD Risk After Statin Treatment

	Event Rate (No Diabetes)		Event Rate (Diabetes)	
	On Statin	On Placebo	On Statin	On Placebo
HPS[1]* (CHD patients)	19.8%	25.7%	**33.4%**	37.8%
CARE[2]†	19.4%	24.6%	**28.7%**	36.8%
LIPID[3]‡	11.7%	15.2%	**19.2%**	22.8%
PROSPER[4]§	13.1%	16.0%	**23.1%**	18.4%
ASCOT-LLA[5]‡	4.9%	8.7%	**9.6%**	11.4%
TNT[6]|	7.8%	9.7%	**13.8%**	17.9%

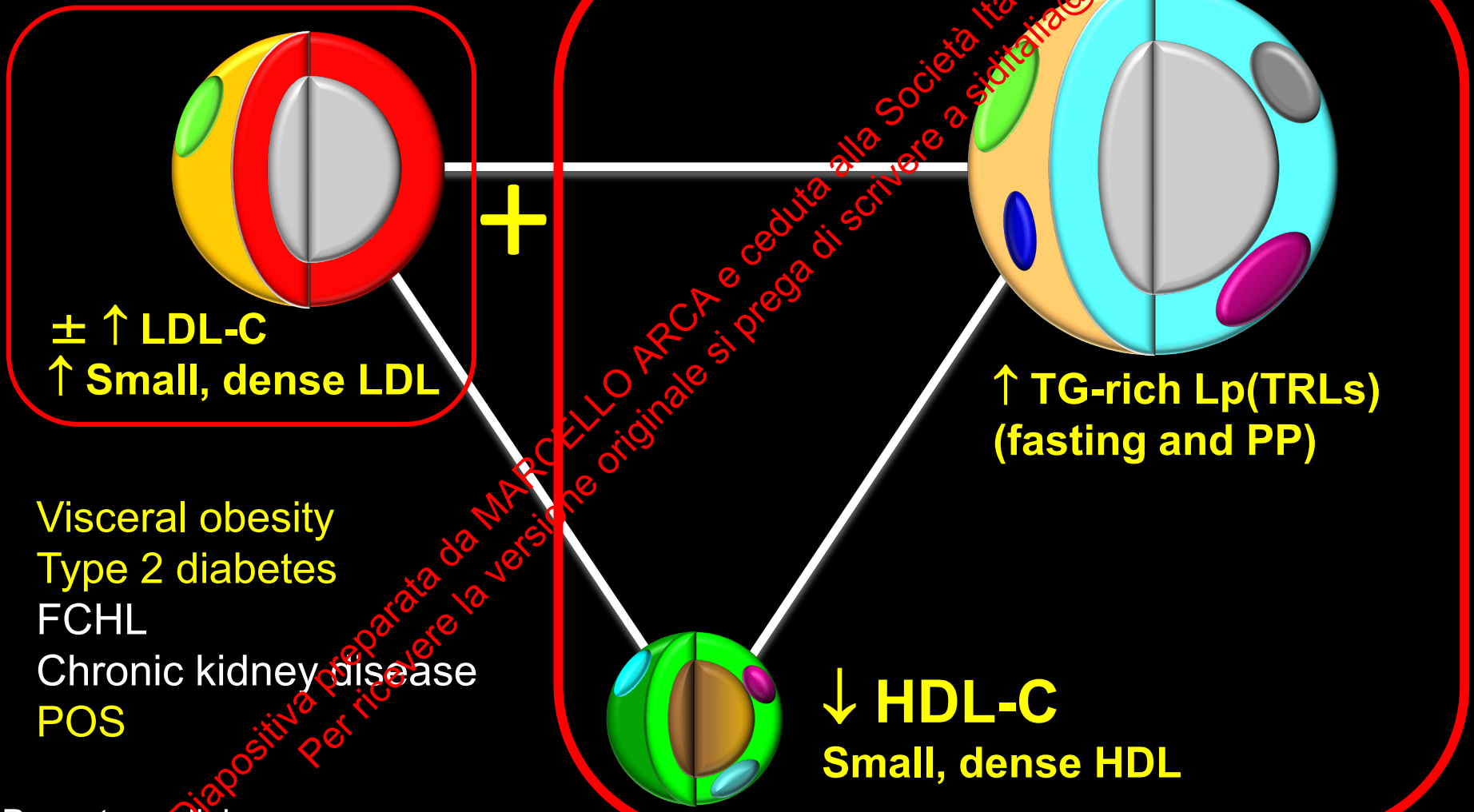
*CHD death, nonfatal MI, stroke, revascularizations
†CHD death, nonfatal MI, CABG, PTCA
‡CHD death and nonfatal MI
§CHD death, nonfatal MI, stroke
|CHD death, nonfatal MI, resuscitated cardiac arrest, stroke (80 mg versus 10mg atorvastatin)

[1]HPS Collaborative Group. *Lancet*. 2003;361:2005-2016.
[2]Sacks FM, et al. *N Engl J Med.* 1996;335:1001-1009.
[3]LIPID Study Group. *N Engl J Med.* 1998;339:1349-1357.
[4]Shepherd J, et al. *Lancet.* 2002;360:1623-1630.
[5]Sever PS, et al. *Lancet.* 2003;361:1149-1158.
[6]Shepherd J, et al. *Diabetes Care.* 2006;29:1220-1226.

Atherogenic Dyslipidaemia

At optimal LDL-C impact on CVD Residual Risk

#1 target CVD Risk



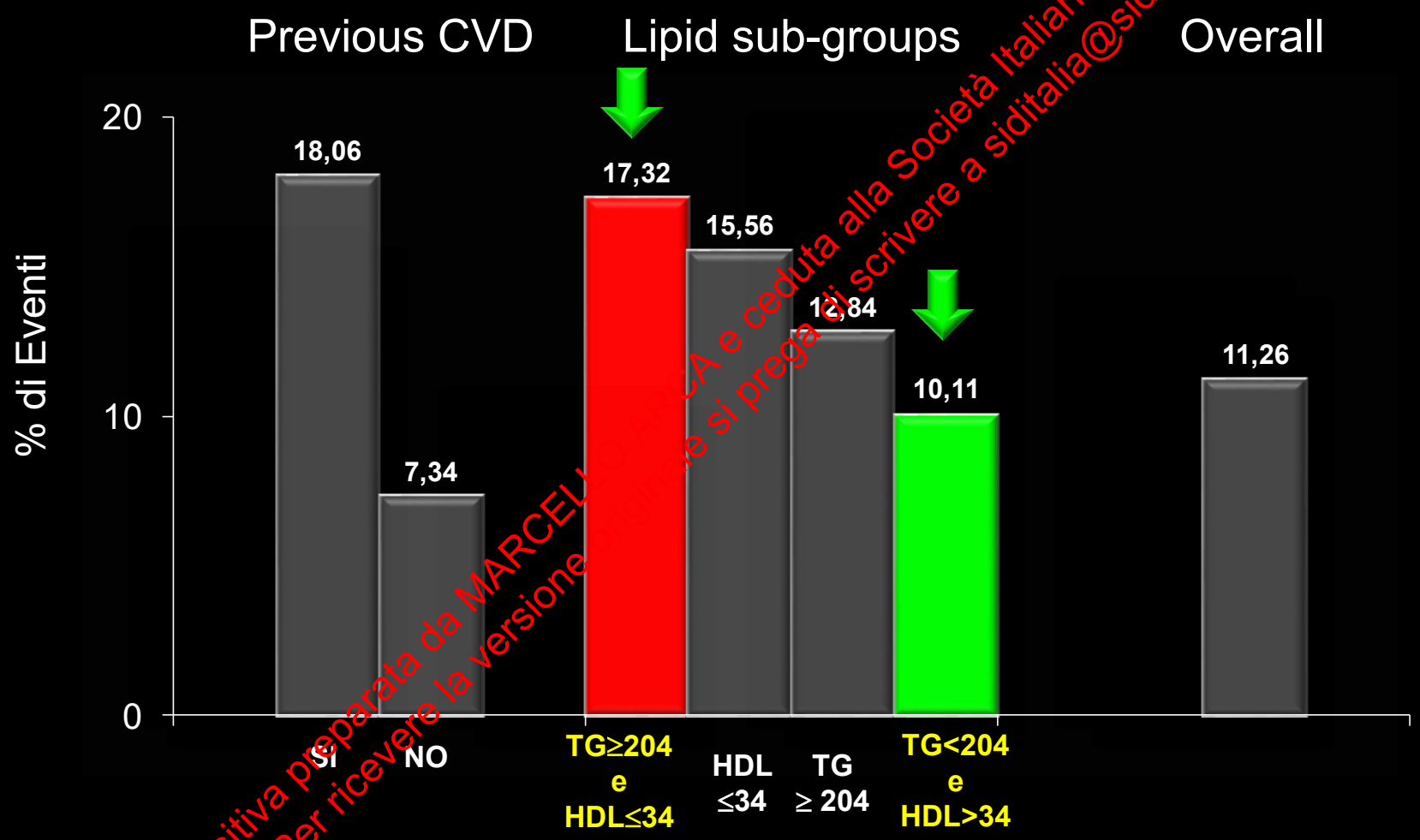
Visceral obesity
Type 2 diabetes
FCHL
Chronic kidney disease
POS

PP=postprandial

Austin et al. Circulation 1990

ACCORD-Lipid Study

Diabetes and Residual Risk on Statin* (placebo group)



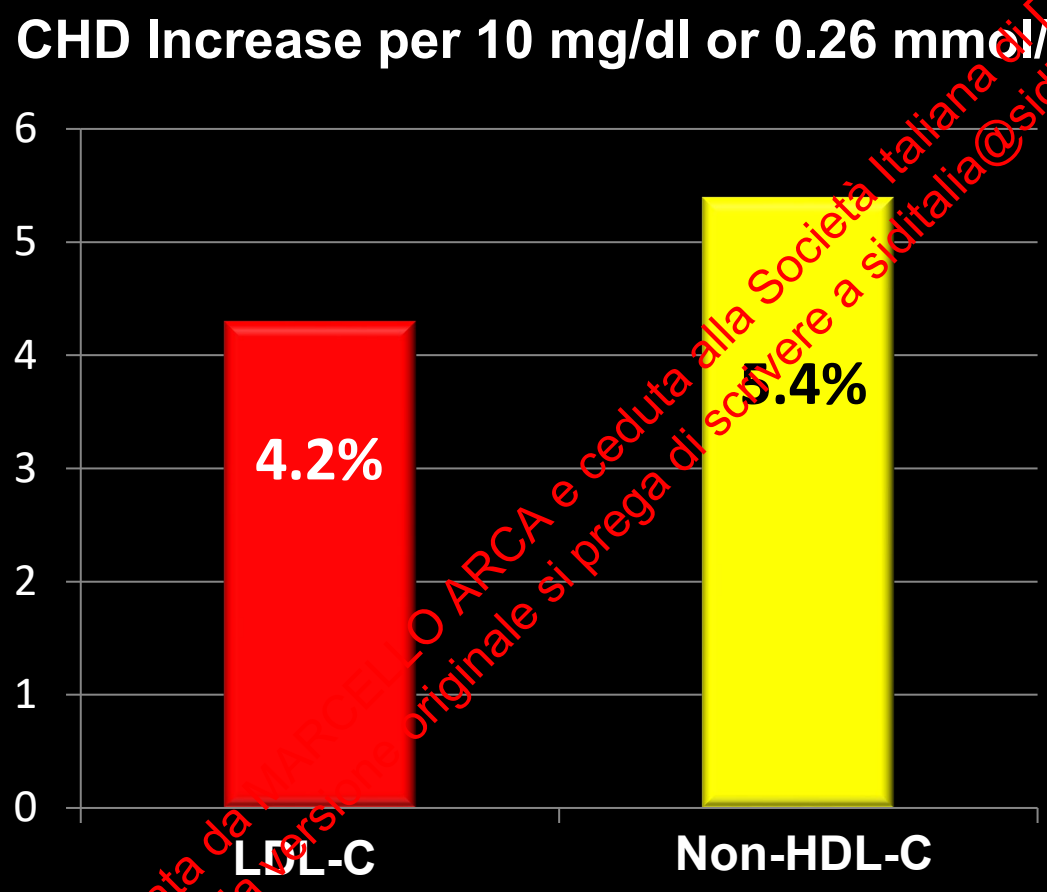
TG =2,3, HDL-c=0,84 in mmol/L

% events = non-fatal MI, non-fatal stroke, CV death (follow-up : 4.7 years)

*** LDL-c ≈ 2.0 mmol/L (80 mg/dL) on simvastatin**

ACCORD Study Group. NEJM 2010; 362: 1563-74

Non HDL-C
A better marker of CVD risk than LDL-C

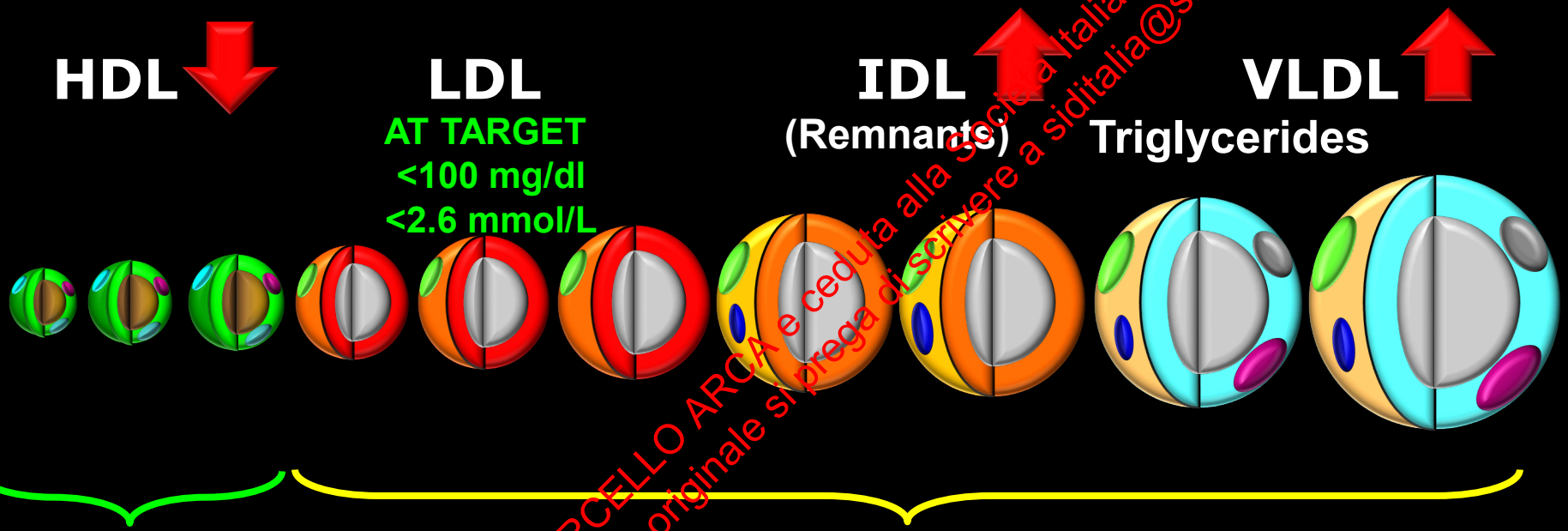


CHD risk per 10 mg/dl of Non-HDL-C relative to LDL-C: ↑ 26%

U.S. population from National Health and Nutrition Examination Survey 2005 to 2006 accounting for complex sample design.

Sniderman A et al. Journal of Clinical Lipidology (2010) 4, 152–155

Non-HDL Cholesterol



Anti Atherogenic Lipoproteins

Non HDL-C ≥130 mg/dl or 3.4 mmol/L NOT AT TARGET

Atherogenic Lipoproteins

Lipid Targets and Pharmacological Approaches

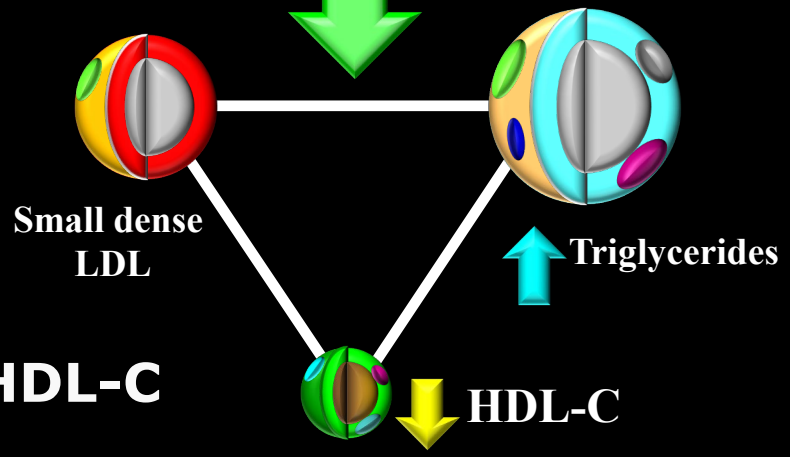
Statin High intensity
Statin + Ezetimibe
Statin + *PCSK9 Inhibitors*

Target LDL-C

At target LDL-C: NO

STATIN → **Combination statin + 2° lipid-lowering drug**

At target LDL-C: YES, but…..

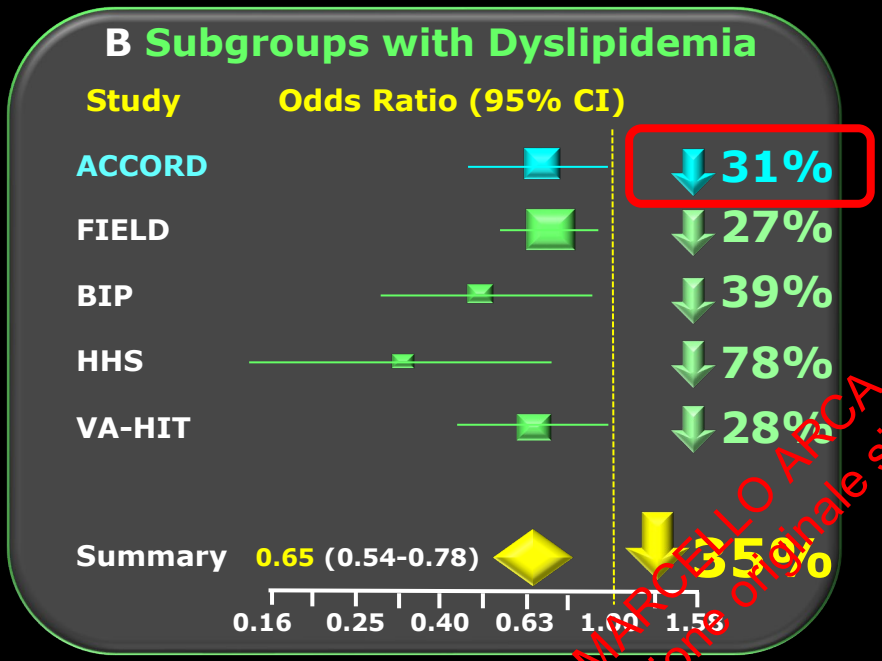


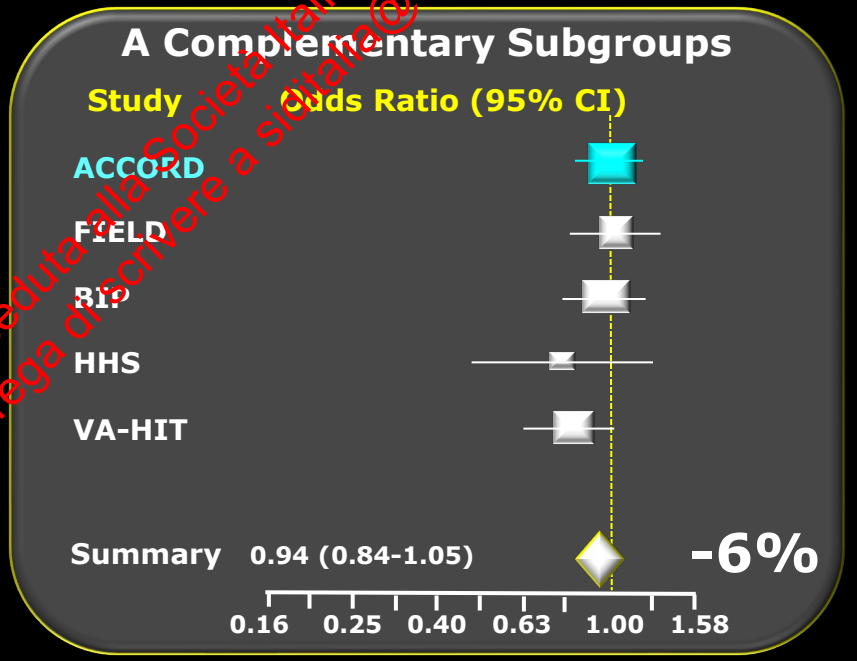
Statin + Fenofibrate
Statin + Niacin
Statin + Omega 3 fatty acids

Target (HDL-C and TG) **Non HDL-C**

Effect of fibrates in subgroups without (A) and with (B) dyslipidemia

A total of 2428 fibrate-treated subjects (302 events) and 2298 placebo-treated subjects (408 events) with dyslipidemia were included in the analysis





LIPID CRITERIA FOR DYSLIPIDEMIA

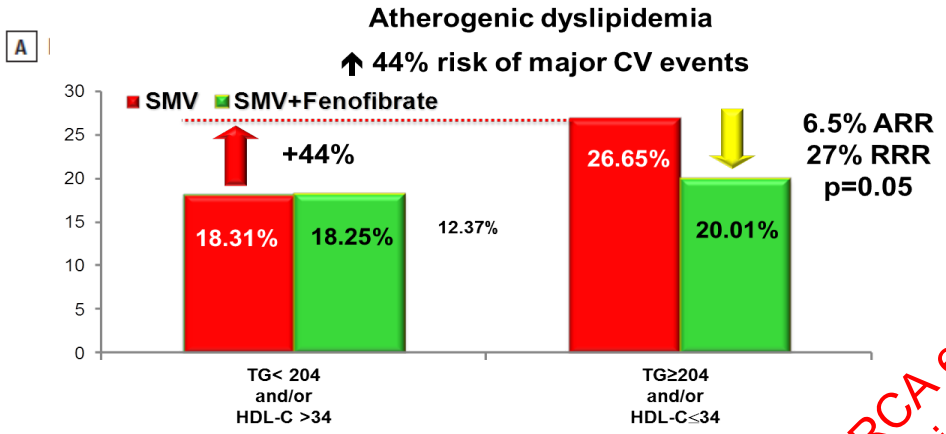
Trial	Triglycerides cut-off (mg/dL)	HDL cholesterol cut-off (mg/dL)
FIELD	≥204 (2.2 mmol/L)	<40 in men (1.0) ; <50 in women (1.3)
BIP	≥200	<35
Helsinki Heart Study	>204	<42
VA-HIT	>180	<40

Bruckert E et al J Cardiovasc PharmacolT 57:267, 2011
Lee M et al Atherosclerosis (2011), doi:10.1016/j.atherosclerosis
Sacks FM et al. N Engl J Med 2010

JAMA Cardiology | Original Investigation

Association of Fenofibrate Therapy With Long-term Cardiovascular Risk in Statin-Treated Patients With Type 2 Diabetes

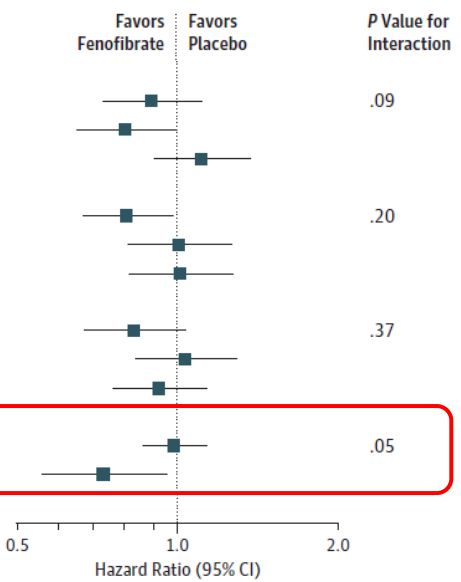
ACCORDION – 9.7 yrs Follow-up



…..despite these overall neutral results, we continued to find evidence that fenofibrate therapy effectively reduced CVD in study participants with dyslipidemia, TG>204mg/dL and HDL_C >34mg/dl (HR, 0.73; 95%CI, 0.56-0.95)…..

Figure 3. Hazard Ratios for the Primary Outcome in Prespecified Subgroups

Characteristic	Statin + Fenofibrate Events/No. (%)	Statin + Placebo Events/No. (%)	Hazard Ratio (95% CI)	P Value for Interaction
LDL-C				
<85	169/925 (18.27)	175/885 (19.77)	0.90 (0.73-1.11)	.09
85+111	155/928 (16.70)	182/916 (19.87)	0.80 (0.65-1.00)	
≥112	182/871 (20.90)	179/919 (19.48)	1.11 (0.91-1.37)	
HDL				
<35	197/956 (20.61)	224/903 (24.81)	0.81 (0.67-0.98)	.20
35-40	159/852 (18.66)	157/858 (18.30)	1.01 (0.81-1.26)	
>41	150/916 (16.38)	155/959 (16.16)	1.02 (0.81-1.27)	
Triglycerides				
<129	146/879 (16.61)	186/930 (20.00)	0.83 (0.67-1.03)	.37
129-203	171/918 (18.63)	160/908 (17.62)	1.04 (0.84-1.29)	
≥204	189/927 (20.39)	190/882 (21.54)	0.93 (0.76-1.13)	
Dyslipidemia				
No	407/2242 (18.15)	415/2266 (18.31)	0.99 (0.86-1.13)	.05
Triglycerides >204 and HDL-C <34	99/482 (20.54)	121/454 (26.65)	0.73 (0.56-0.95)	



Elam MB et al. JAMA Cardiol. doi:10.1001/jamacardio.2016.4828, Published online December 28, 2016.

Plasma lipoproteins in FHBL2 carriers and non-carriers controls identified within families and in the whole cohort.

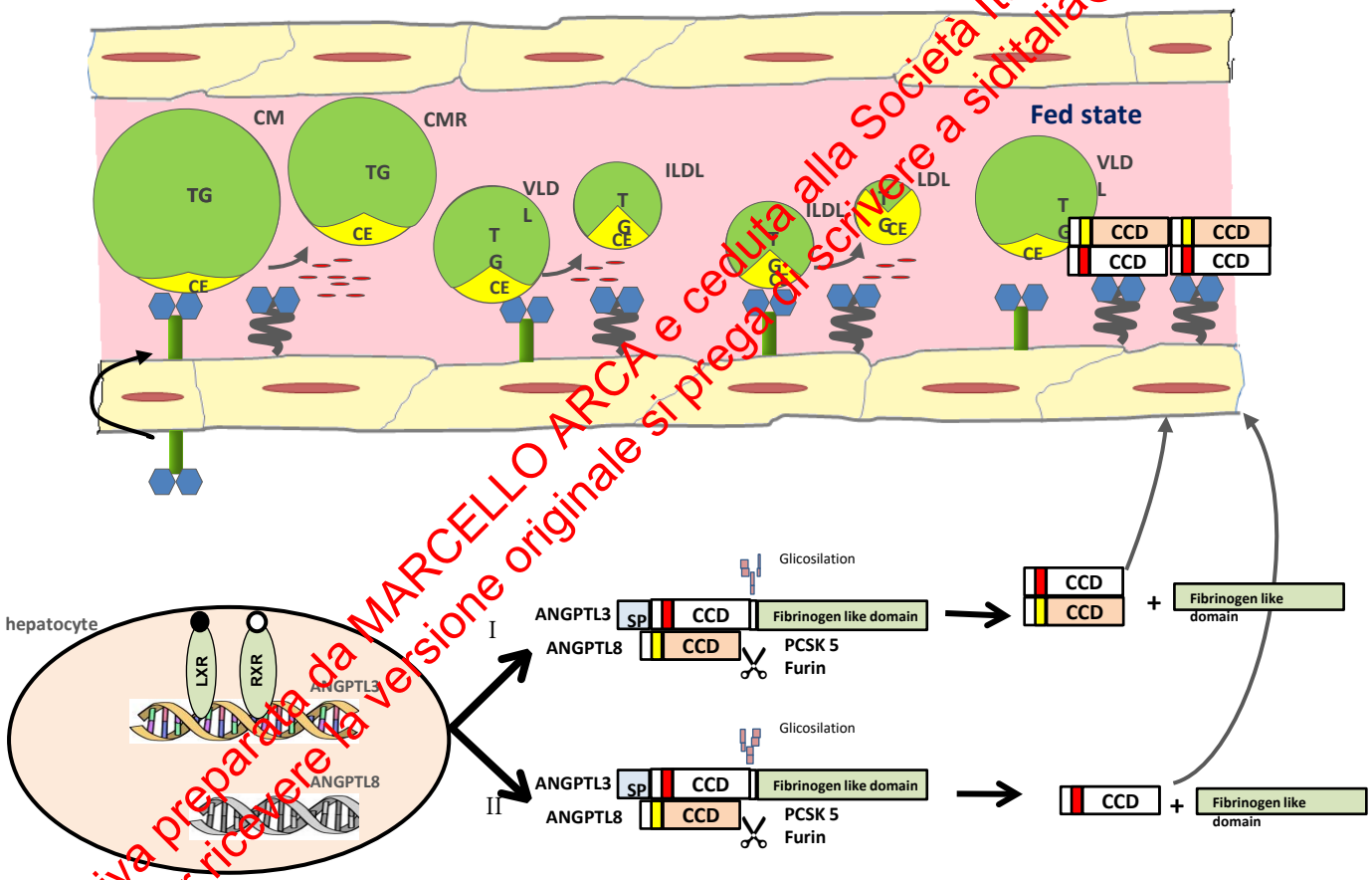
Variables	Family study (n=225)			All subjects (n=517)		
	FHBL2 (n=98)		Non carriers (n=127)	FHBL2 (n=115)		Non carriers (n=402)
	Homozygous / Compound	Heterozygous		Homozygous / Compound	Heterozygous	
TC (mmol/L)						4.9 ± 0.9 (3.1 – 9.5) (n=402)
HDL-C (mmol/L)						1.6 ± 0.4 (0.8 – 2.8) (n=402)
TG (mmol/L)						1.1 ± 0.7 (0.3 – 4.3) (n=402)
LDL-C (mmol/L)						2.8 ± 0.9 (1.0 – 7.3) (n=402)
	(n=19)	(n=79)	(n=127)	(n=22)	(n=93)	
ApoB (g/L)	0.5 ± 0.1***### (0.3 – 0.7) (n=19)	0.8 ± 0.2 (0.4 – 1.3) (n=79)	0.9 ± 0.2 (0.5 – 1.6) n=126	0.5 ± 0.1***### (0.3 – 0.7) n=20	0.8 ± 0.2§§ (0.3 – 1.3) n=92	0.9 ± 0.2 (0.5 – 1.8) n=398
ApoAI (g/L)	0.7 ± 0.2***### (0.4 – 1.1) n=18	1.5 ± 0.3 (0.7 – 2.2) n=79	1.6 ± 0.3 (1.0 – 2.4) n=114	0.7 ± 0.2***### (0.4 – 1.1) n=18	1.5 ± 0.4§ (0.7– 2.2) n=92	1.6 ± 0.3 (0.9 – 2.4) n=302
Lp(a) (µmol/L)	0.2 (0.1– 2.1) n=13	0.5 (0.2 – 0.9) n=70	0.6 (0.2– 1.9) n=85	0.2 (0.2 – 1.2) n=13	0.5 (0.2 –0.9) n=78	1.0 (0.1 – 2.1) n=193

	Homozygotes	Heterozygotes
LDL-C	- 67%	- 9%
TG	- 71%	- 21%
HDL-C	- 39%	- 17%
ApoB	- 48%	- 7%

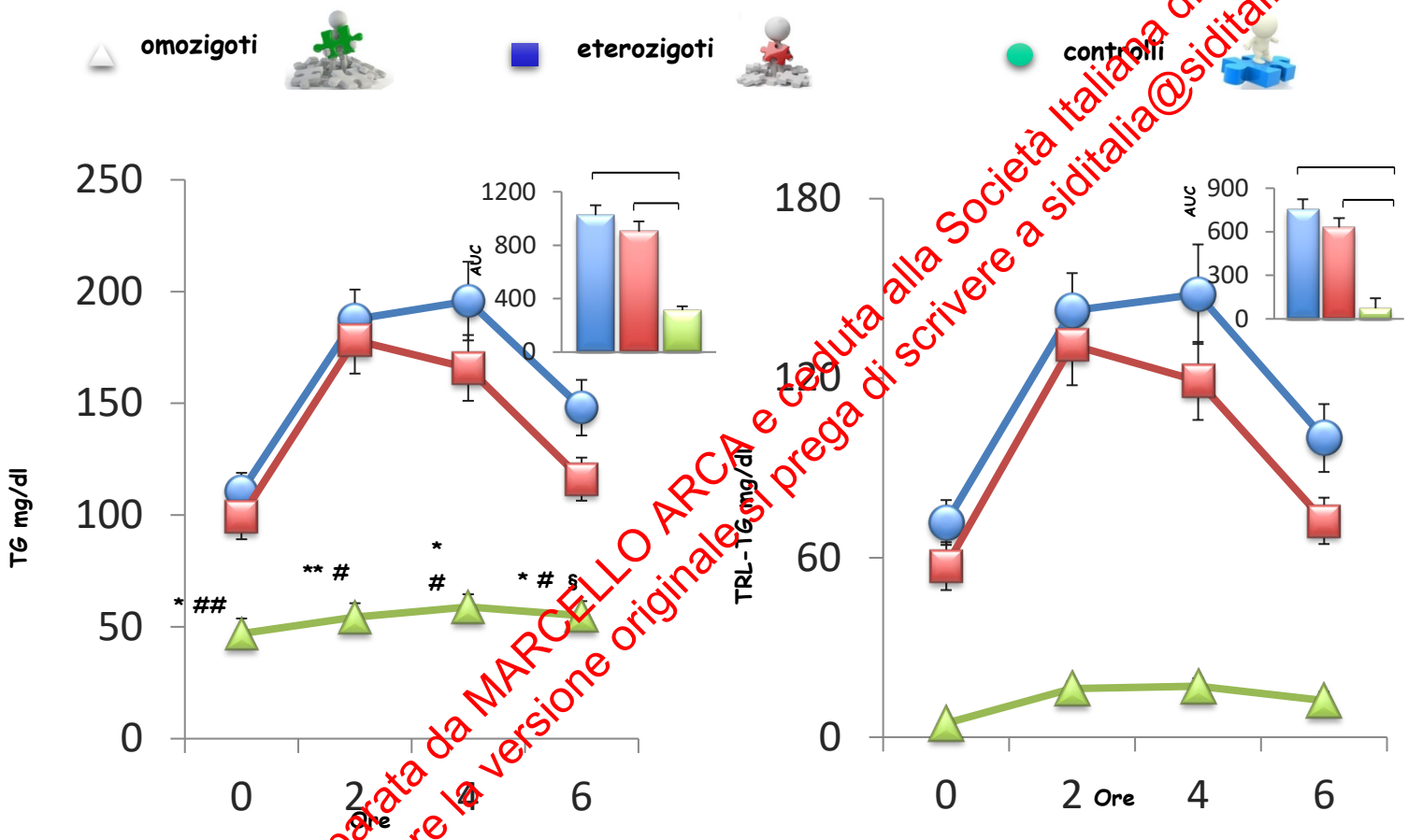
•p<0.05 **p≤0.01 ***p<0.001 for comparison between non-carriers vs homozygotes carriers.
§ p<0.05 §§p<0.01§§§p<0.001 for comparison between non-carriers vs heterozygotes carriers.
# p<0.05 ##p≤0.01###p<0.001 for comparison between homozygotes vs heterozygotes carriers.

Minicocci et al. JLR 2013

ANGPTL3/ANGPTL8:
proposed mechanism of action on lipoproteins



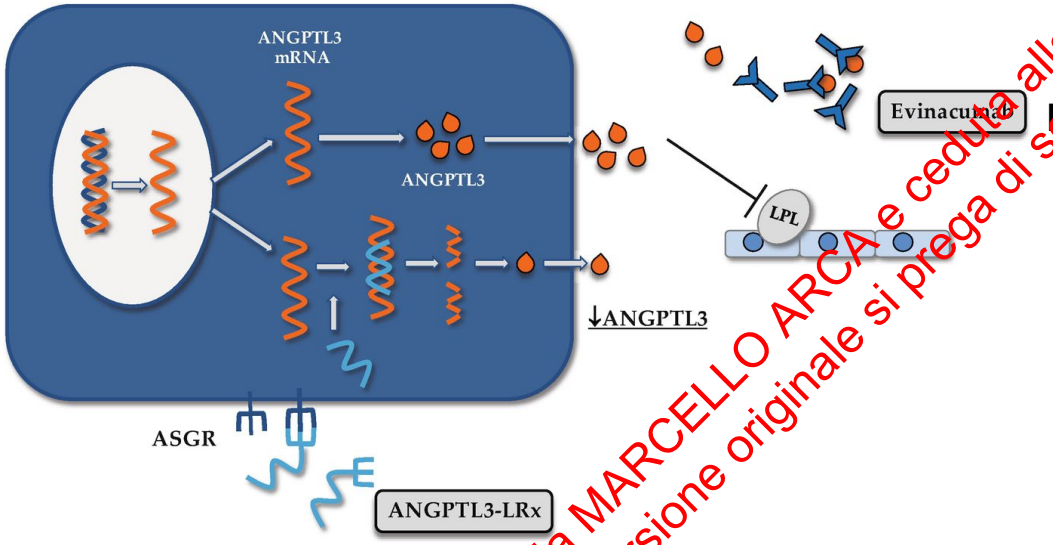
The complete absence of Angptl3 is associated with a marked reduction of post-prandial lipemia



**P<0.001 e *P<0.01 omozigoti vs controlli;
##P<0.05 e #P<0.01 omozigoti vs eterozigoti; §P<0.05 eterozigoti *vs.* controlli.

Minicocci I, et al ,J Lipid Res. 2016 Jun;57(6):1097-107

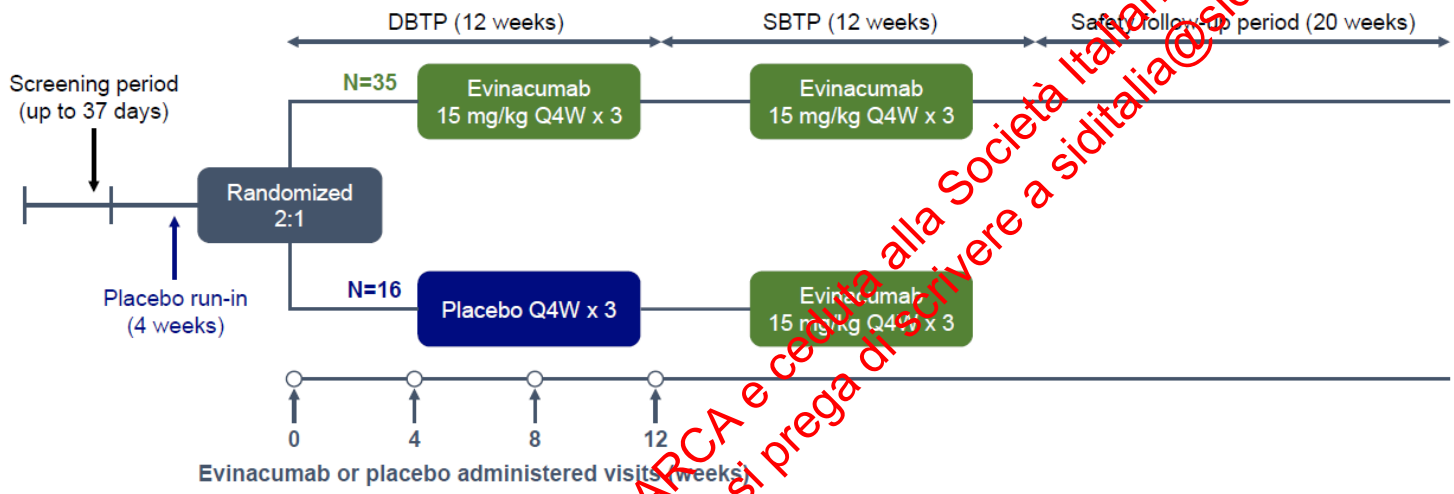
Evinacumab: mAb anti ANGPTL3



Evinacumab è un anticorpo monoclonale umanizzato con alta affinità verso ANGPTL3 diverse specie (topo, ratto, scimmia, e umano).

N Engl J Med 2020, 377:211–221

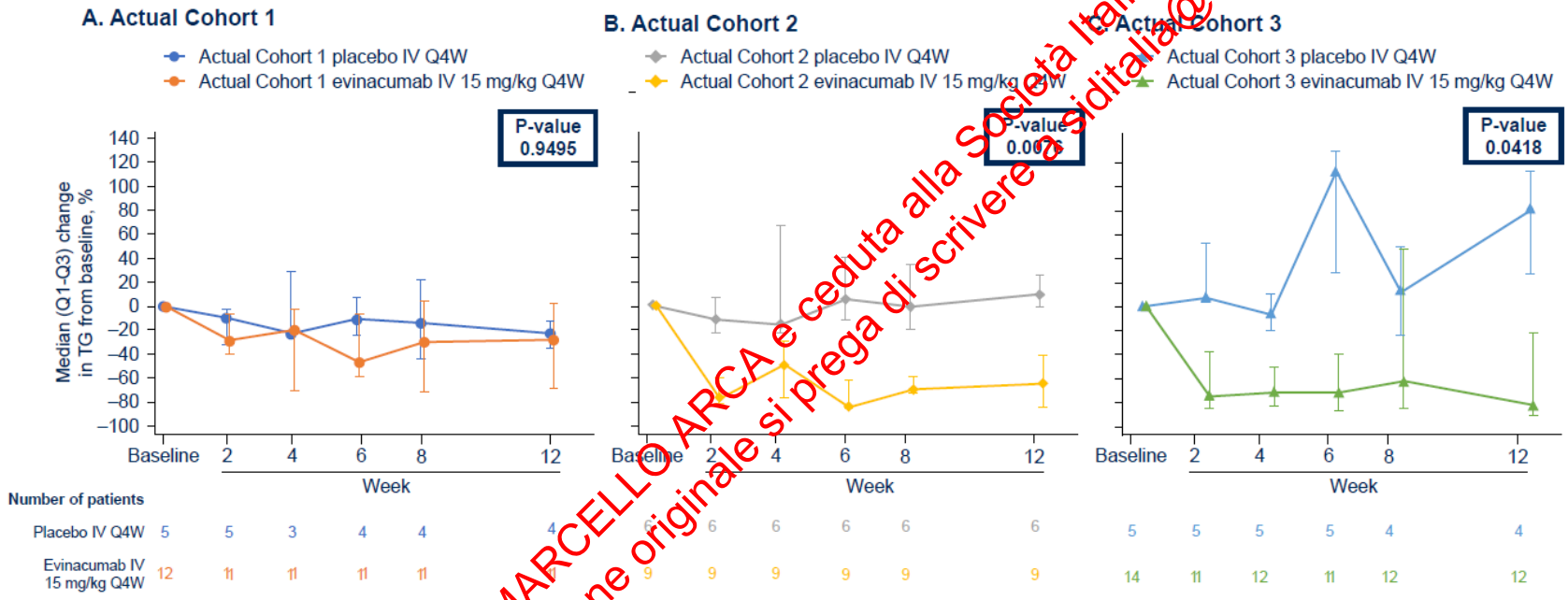
Methods



- The primary endpoint was to determine the intra-patient change in serum TGs from baseline following 12 weeks of intravenous evinacumab treatment (combination of DBTP and SBTP) in Cohort 3 patients*

*Patients with MCS and without LPL pathway mutations
DBTP, double-blind treatment period; Q4W, every 4 weeks; SBTP, single-blind treatment period; TG, triglyceride.

Results



IV, intravenous; Q4W, every 4 weeks; TG, triglyceride.