EAS

TERAPIA IPOLIPEMIZZANTE DI ASSOCIAZIONE ED INIBITORI PCSK9

Prof. Marcello Arca
Università di Roma La Sapienza

Programma Webinar EAS
Lipid Clinics

Terapia ipolipemizzante di associazione ed inibitori PCSK9

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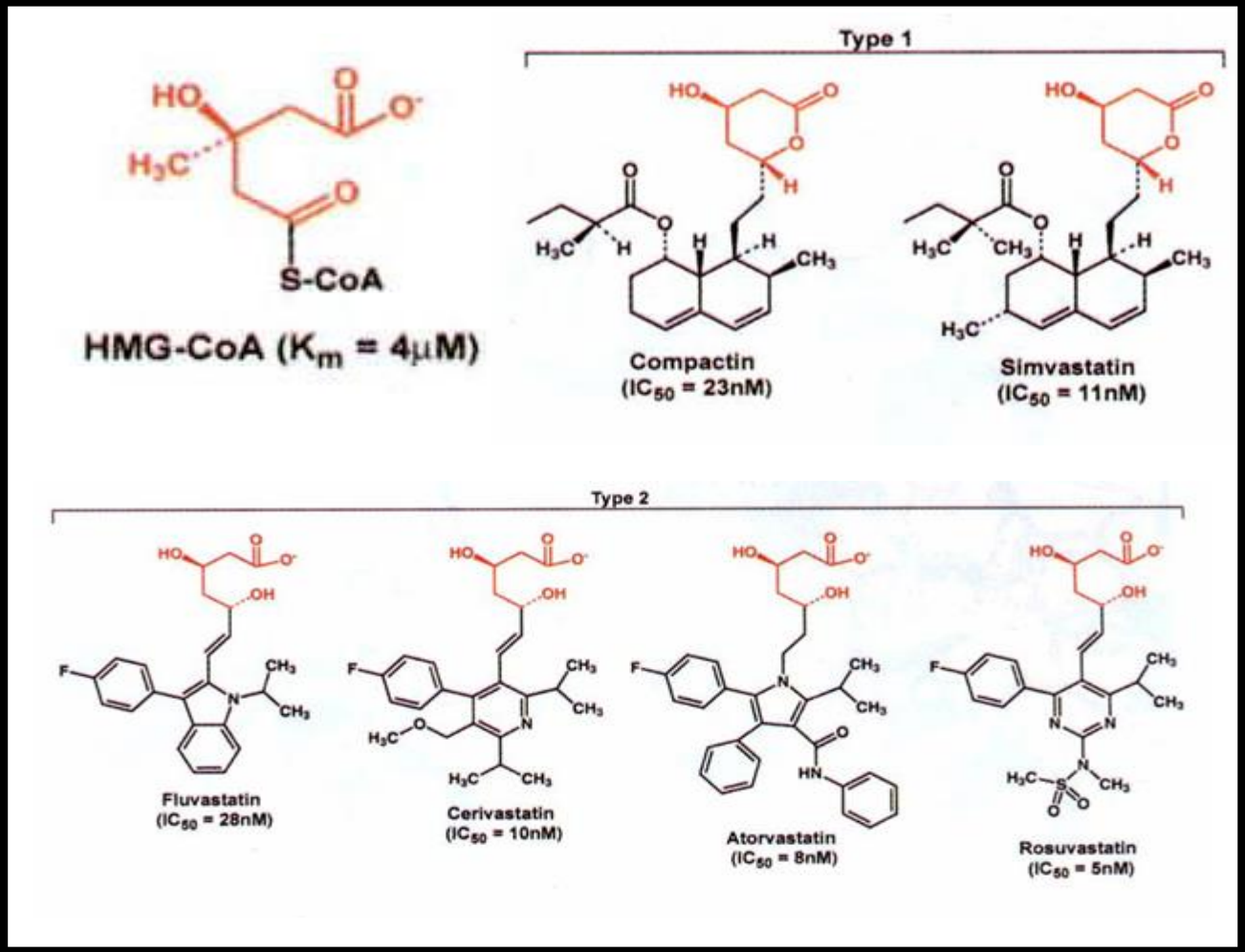
SAPIENZA
UNIVERSITÀ DI ROMA

DICHIARAZIONE CONFLITTO DI INTERESSI

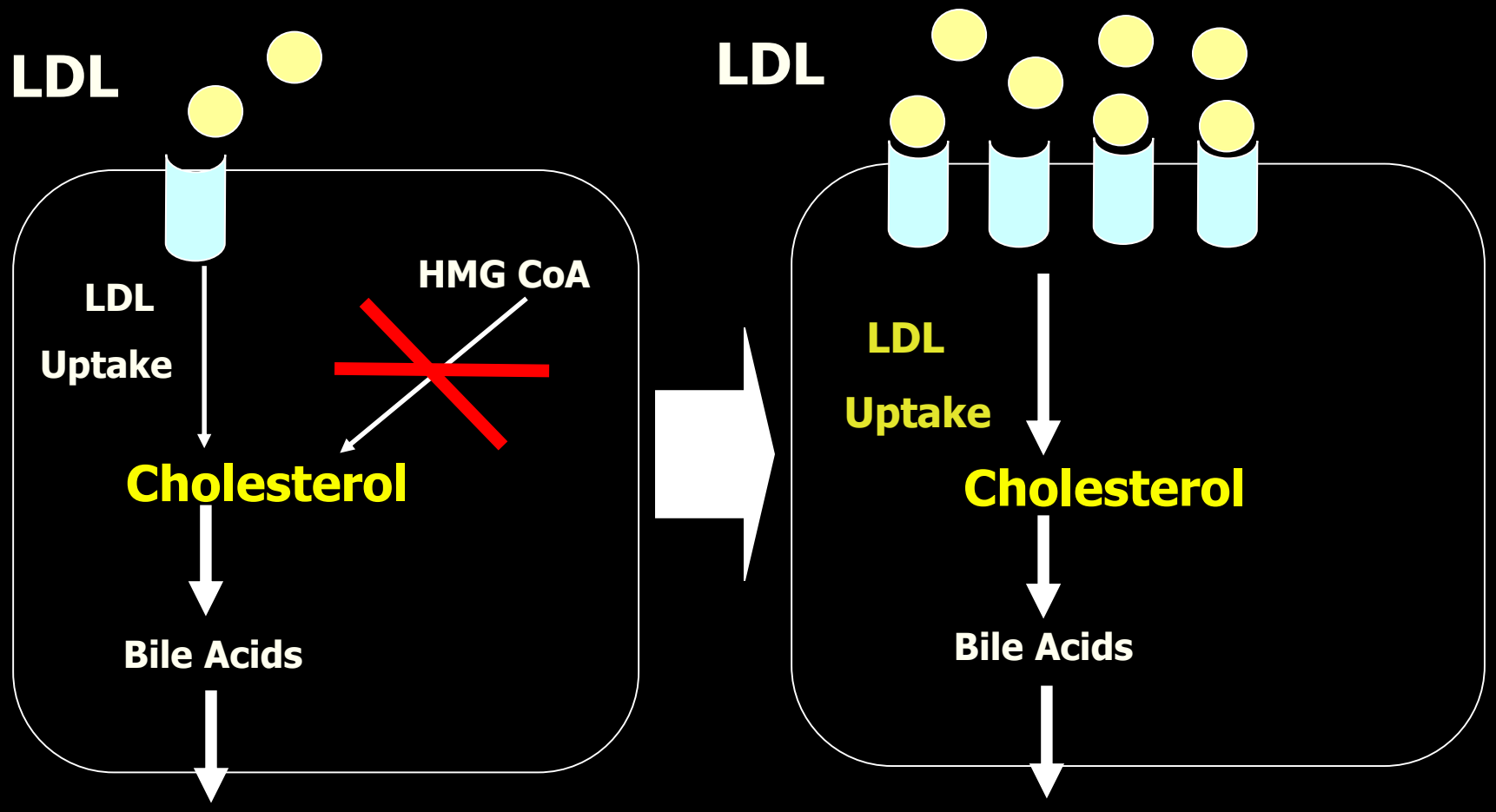
Il Prof. **Marcello Arca** dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

Akcea/Ionis, Alfasigma, Amryt, Amgen, Daichi–Sankio, Novartis, Pfizer, Regeneron, Sanofi, Viatris

Structural Formulas of HMG-CoA and of some type 1 and 2 Statins

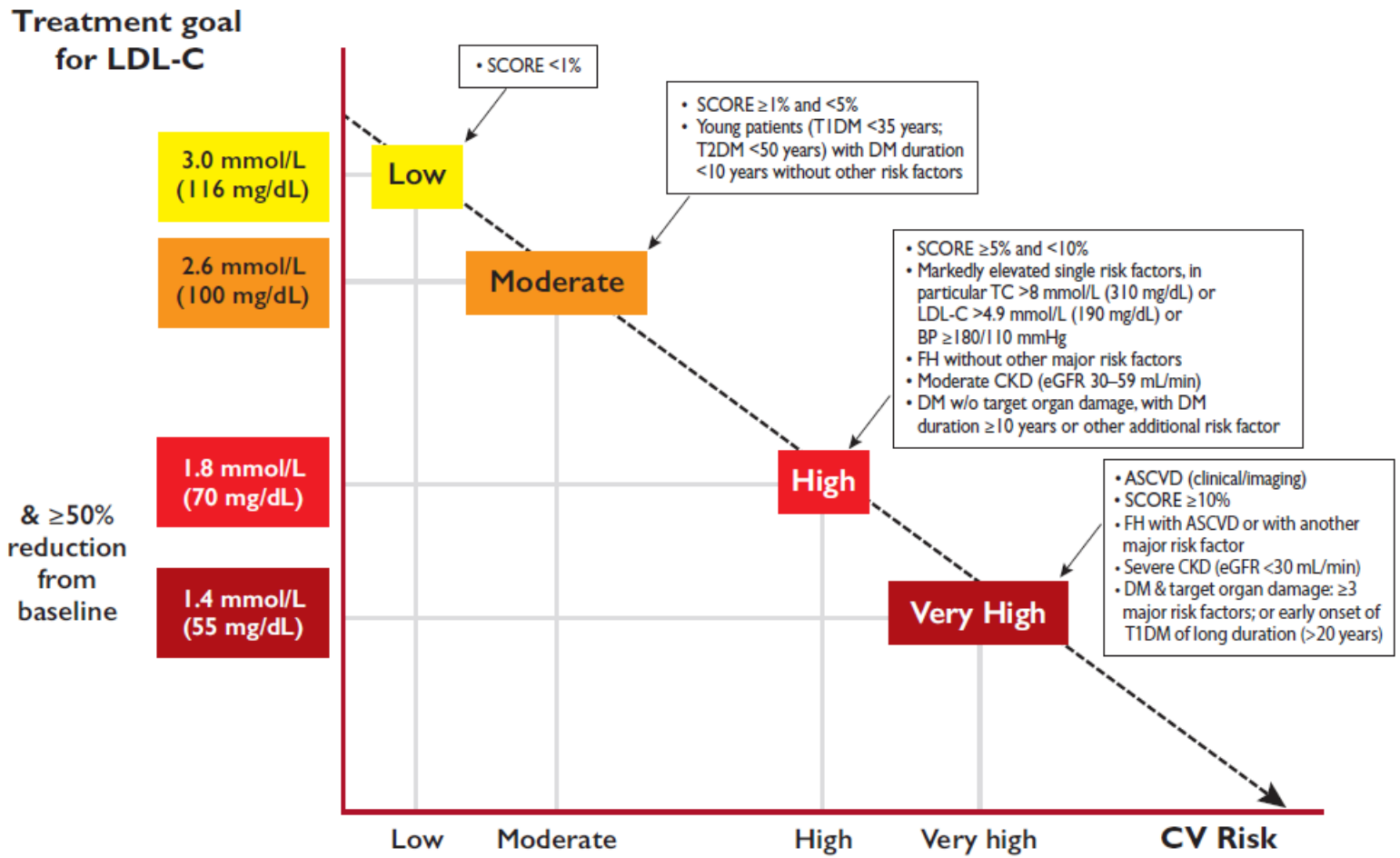


HMG CoA Reductase Inhibitors



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

2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce cardiovascular risk*



Meta-analysis of Comparative Efficacy of Increasing Dose of *Atorvastatin* Versus *Rosuvastatin* Versus *Simvastatin* on Lowering Levels of Atherogenic Lipids (from VOYAGER)

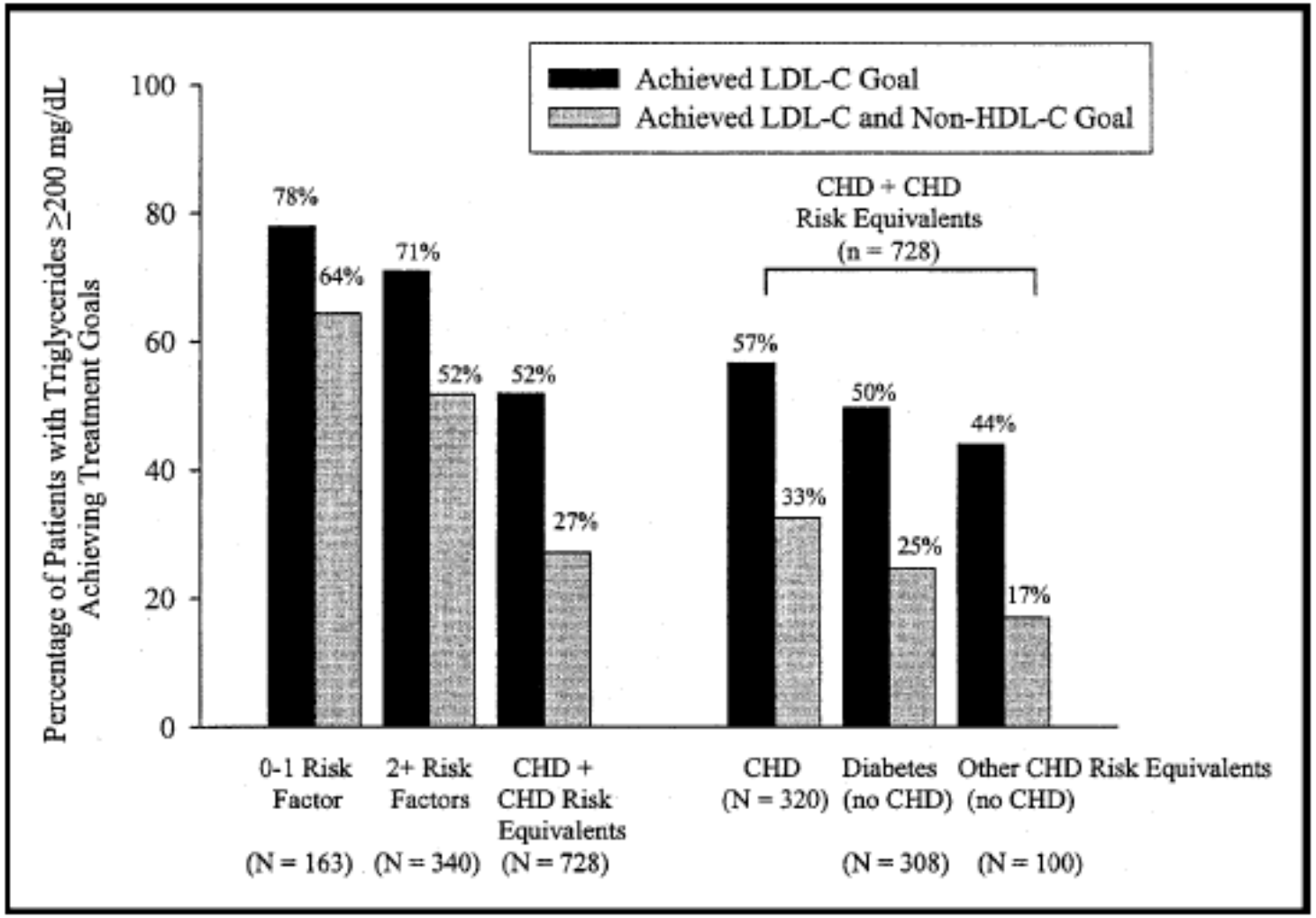
Percentage of patients achieving low-density lipoprotein cholesterol (LDL-C) goals with increasing statin doses

Drug	LDL-C Goal <70 mg/dl			LDL-C Goal <100 mg/dl		
	Baseline LDL-C <130 mg/dl	Baseline LDL-C 130–160 mg/dl	Baseline LDL-C ≥160 mg/dl	Baseline LDL-C <130 mg/dl	Baseline LDL-C 130–160 mg/dl	Baseline LDL-C ≥160 mg/dl
Rosuvastatin (mg)						
5	NA	0%*	3.2%	NA	66.7%*	38.0%
10	47.2%	33.0%	11.4%	82.0%	75.9%	56.8%
20	81.1%	57.2%	20.5%	94.6%	90.1%	64.5%
40	83.5%	67.6%	31.7%	97.3%	95.4%	74.1%
Atorvastatin (mg)						
10	28.4%	8.8%	2.0%	71.4%	62.1%	28.7%
20	64.7%	26.4%	4.1%	91.2%	83.8%	45.0%
40	72.8%	45.2%	9.8%	97.4%	91.1%	56.6%
80	76.4%	52.4%	18.1%	94.2%	86.4%	71.4%
Simvastatin (mg)						
10	NA	0%*	0%	NA	50.0%*	8.8%
20	10.3%	7.0%	1.6%	51.0%	57.3%	24.0%
40	31.3%	19.9%	1.5%	87.5%	76.7%	34.2%
80	NA	NA	4.0%	NA	NA	38.5%

*32258 patients included in the meta-analysis

Am J Cardiol 2010;105:69 –76

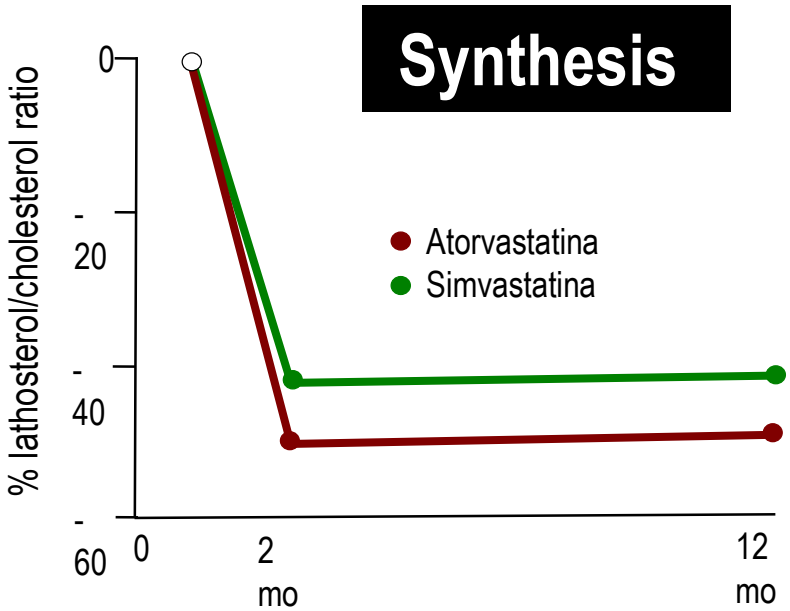
Percentage of patients with triglycerides 200 mg/dl (2.25mmol/L) achieving LDL-C treatment goals and combined LDL-C and non-HDL cholesterol treatment goals

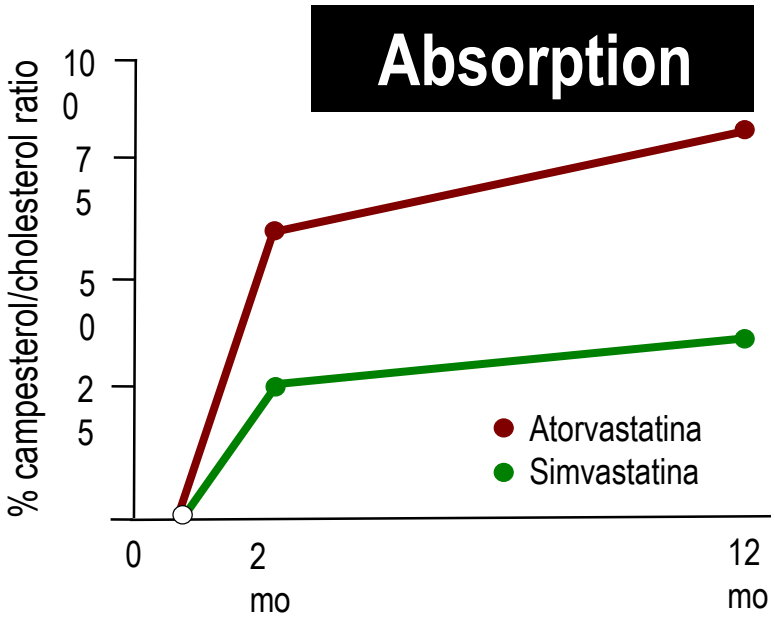


Am J Cardiol 2005;96:556 –563

Journal of Laboratory and Clinical Medicine
Volume 141, Issue 2, February 2003, Pages 131-137

Serum noncholesterol sterols during inhibition of cholesterol synthesis by statins ☆, ☆☆, ★, ★★

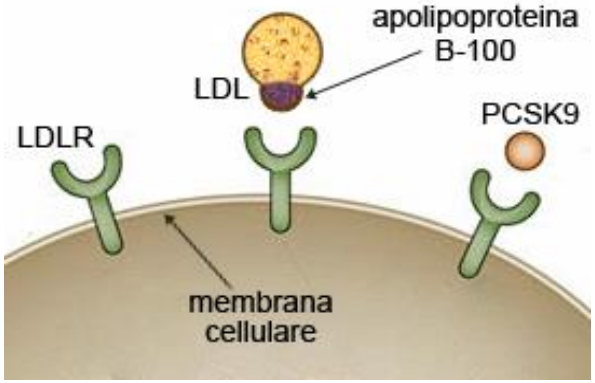




- Changes in serum cholestanol and plant sterols (indexes of cholesterol absorption) and cholesterol precursors (indexes of cholesterol synthesis) in response to cholesterol reduction by 1 year's treatment with atorvastatin (n = 102) and simvastatin (n = 105) in patients with coronary heart disease.
- Serum cholesterol levels and ratios of the precursor sterols to cholesterol after 1 year treatment were reduced in proportion to the pretreatment values (33%±1% by simvastatin and 36%±1% by atorvastatin; P <.01 for difference between groups)
- Plant sterol concentrations ratios with respect to cholesterol were increased by as much as 82% with atorvastatin and by as much as 39% with simvastatin.

Ipercolesterolemia Familiare (FH)

MALATTIA AUTOSOMICA CO-DOMINANTE



Mutazione di:

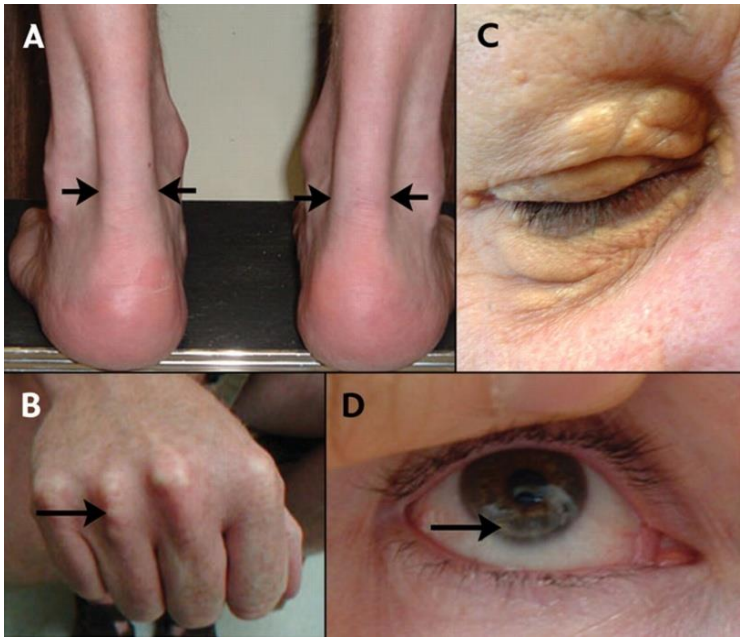
- LDL-R >90% casi
- Apo B ~ 5% casi
- PCSK9 ~ 1% casi

Caratteristiche cliniche <u>forma eterozigote</u> (1/500)

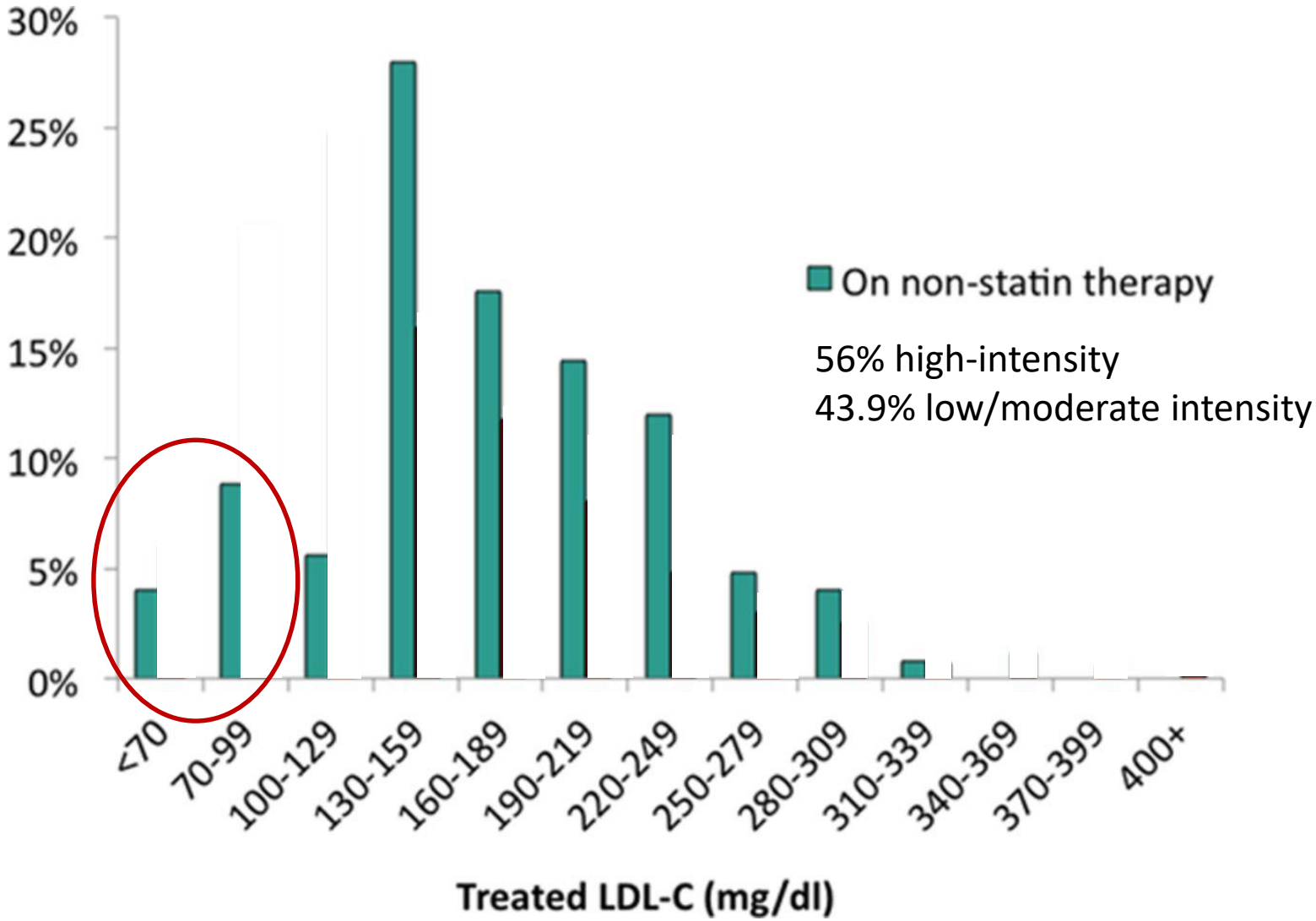
- Ipercolesterolemia: LDL-C 95 percentile (190 mg/dl)
- Xantomi tendinei: tendine d'Achille, tendini estensori delle dita, tendine rotuleo
- Arco corneale
- Cardiopatia ischemica (CHD) in età precoce

Caratteristiche cliniche forma omozigote (1/1000000)

- LDL-C marcatamente elevato (>300 mg/dl)
- Xantomatosi tendinea e cutanea (infanzia)
- Stenosi aortica e stenosi osti coronarici
- Angina, IMA, morte improvvisa (entro la III decade)



Distribution of treated LDL-C levels by treatment status among adults with heterozygous FH on LDL-lowering therapy (n=1084) The CASCADE FH Registry.



Emil M. deGoma et al. Circ Cardiovasc Genet. 2016;9:240-249

The association therapy in dyslipidaemia

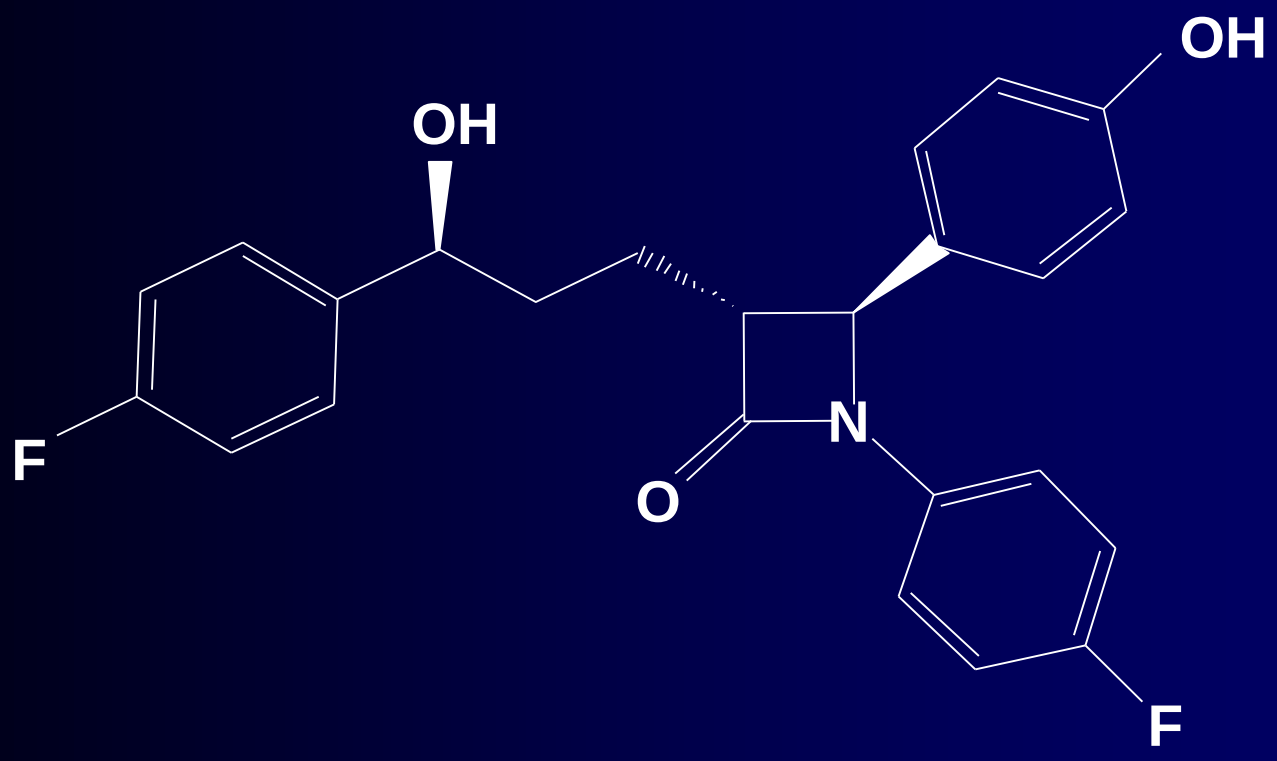
How to improve LDL-C reduction

- **Ezetimibe**
- **Colesevelam**
- **iPCSK9**
- **Lomitapide**

How to improve highTG/low HDL

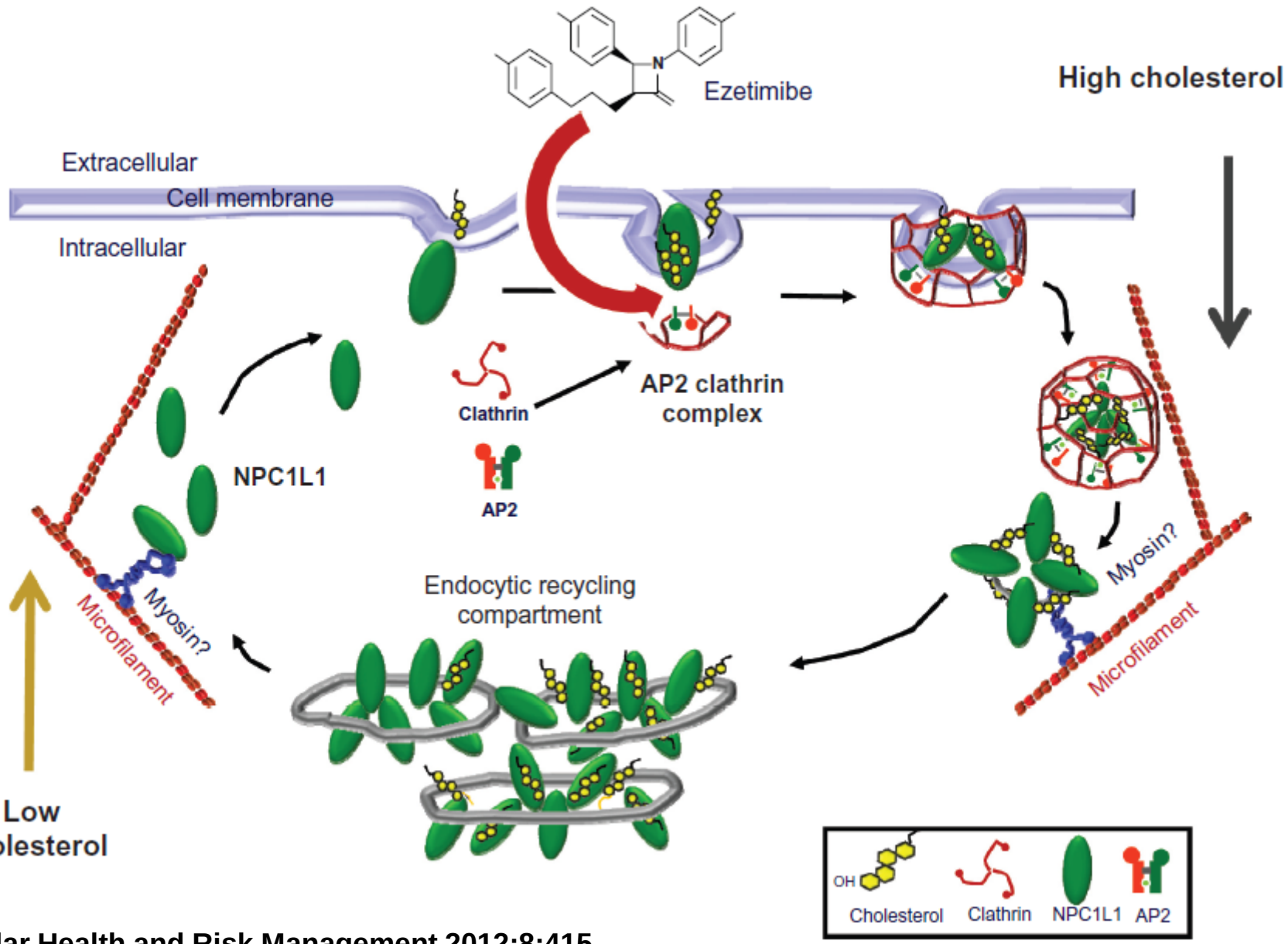
- **Fibrates**
- **Omega-3**

Structure of Ezetimibe



Ezetimibe is a potent and specific inhibitor of dietary and biliary cholesterol absorption

Mechanism of action of ezetimibe



Vascular Health and Risk Management 2012:8:415

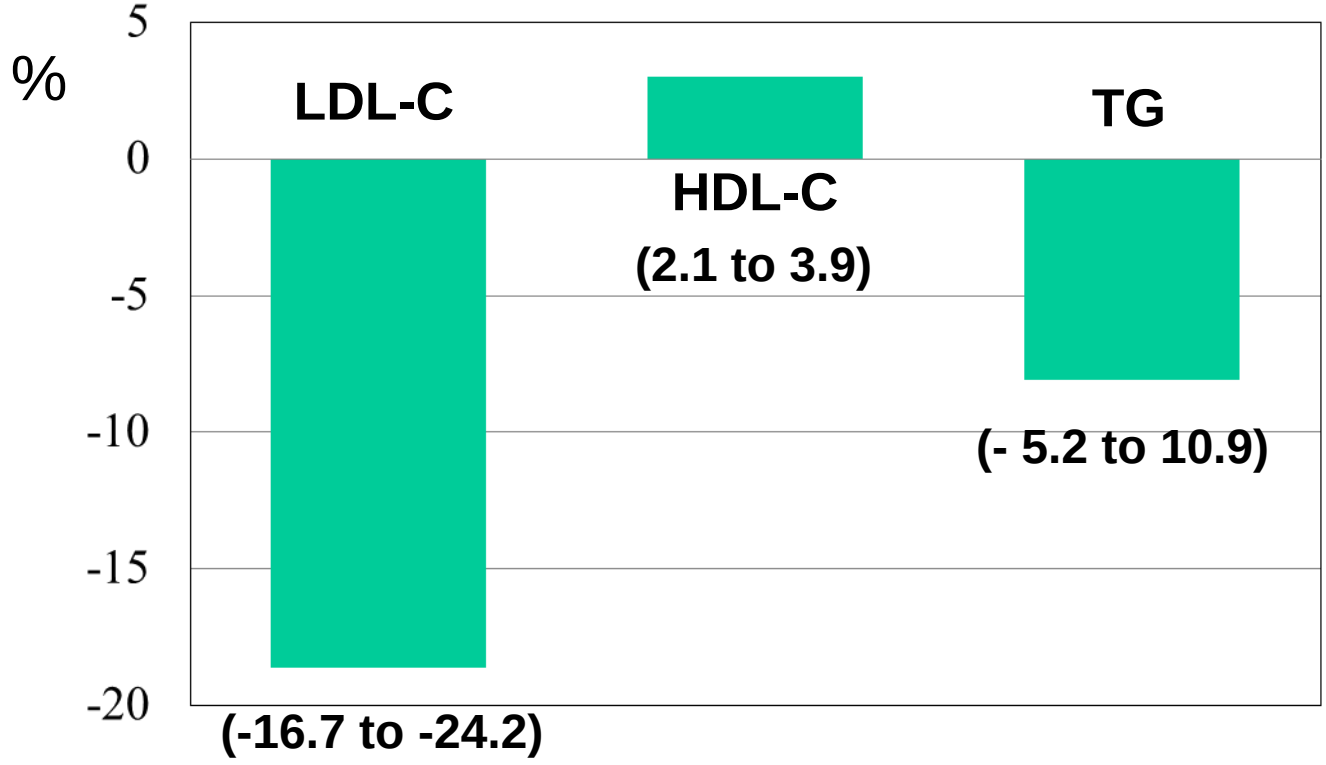
Effect of Ezetimibe on the In Vivo Kinetics of ApoB-48 and ApoB-100 in Men With Primary Hypercholesterolaemia

	VLDL ApoB-100				IDL ApoB-100				LDL ApoB-100			
	ApoB-100, mg/dL	PS, mg	FCR, pools/d	PR, $mg \cdot kg^{-1} \cdot d^{-1}$	ApoB-100, mg/dL	PS, mg	FCR, pools/d	PR, $mg \cdot kg^{-1} \cdot d^{-1}$	ApoB-100, mg/dL	PS, mg	FCR, pools/d	PR, $mg \cdot kg^{-1} \cdot d^{-1}$
Baseline												
Mean (range)	10.4 (7.4–15.6)	387.7 (253.8–618.5)	7.7 (4.8–12.8)	33.9 (22.7–42.9)	1.1 (0.4–1.9)	41.4 (13.8–69.1)	7.2 (4.2–12.0)	3.3 (1.2–5.9)	99.9 (83.3–127.6)	3661 (2792–4872)	0.25 (0.11–0.48)	11.1 (5.3–18.5)
Ezetimibe												
Mean (range)	9.6 (6.6–14.3)	350.2 (225.7–462.0)	10.1 (7.1–18.4)	41.0 (30.7–54.8)	1.0 (0.2–1.9)	37.4 (8.2–75.3)	8.7 (6.8–11.3)	4.0 (0.7–7.5)	76.9 (65.4–87.8)	2812 (2368–3478)	0.31 (0.16–0.48)	10.9 (5.9–16.3)
%Δ	−7.7	−9.7	+31.2	+20.9	−9.1	−9.7	+20.8	+21.2	−23.0	−23.2	+24.0	−1.8
P	0.2	0.2	0.02	0.04	0.7	0.4	0.04	0.1	0.004	0.004	0.04	0.5

FCR indicates fractional catabolic rate; PS, pool size; PR, production rates.

Arterioscler Thromb Vasc Biol 2006;26:1101-1106

Ezetimibe monotherapy for cholesterol lowering in 2,722 people: systematic review and meta-analysis of randomized controlled trials

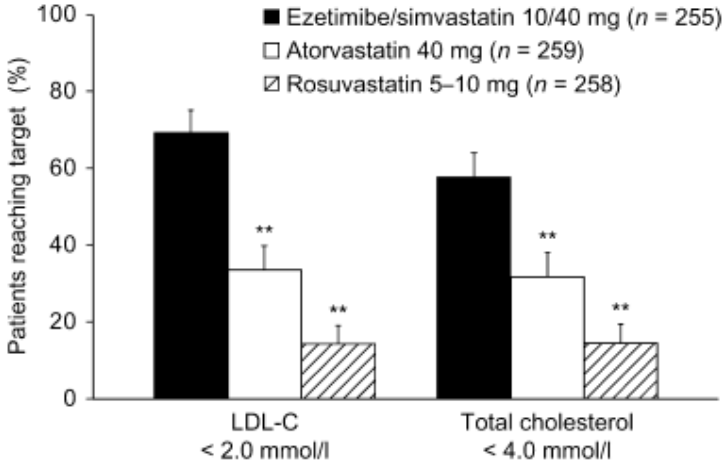


J Intern Med 2009; 265: 568–580

Table 2 Summary of secondary and exploratory efficacy outcome measures (Full Analysis Set, n = 772)

	Ezetimibe/simvastatin 10/40 mg (n = 255)	Atorvastatin 40 mg (n = 259)	Rosuvastatin 5–10 mg (n = 258)
Percentage change from baseline			
LDL-C	−26.2 (−29.1 to −23.2)	−11.1 (−14.0 to −8.2)**	−3.0 (−5.9 to −0.1)**
Total cholesterol	−16.3 (−18.2 to −14.5)	−8.3 (−10.2 to −6.5)**	−2.5 (−4.4 to −0.7)**
Triglycerides	−9.5 (−12.5 to −6.7)	−8.1 (−11.8 to −2.9)	−4.3 (−7.0 to 0.0)
HDL-C	−1.4 (−2.9 to 0.0)	−2.3 (−3.7 to −0.9)	−0.1 (−1.5 to +1.3)
Non-HDL-C	−22.2 (−24.7 to −19.6)	−10.5 (−13.0 to −8.0)**	−3.1 (−5.6 to −0.6)**
Total cholesterol:HDL-C ratio	−14.4 (−16.4 to −12.4)	−5.5 (−7.5 to −3.4)**	−2.0 (−4.0 to 0.0) **
ApoA1	−1.6 (−3.1 to −0.2)	−4.5 (−5.9 to −3.1)*	+0.6 (−0.8 to +2.1)*
ApoB	−17.5 (−19.7 to −15.4)	−9.0 (−11.1 to −6.9)**	−3.2 (−5.3 to −1.1)**
ApoB:ApoA1 ratio	−15.4 (−17.8 to −12.9)	−3.8 (−6.2 to −1.4)**	−3.1 (−5.5 to −0.7)**

*$p < 0.05$, **$p < 0.001$ vs. ezetimibe/simvastatin 10/40 mg.
Data are least-squares mean (95% CI) percentage change from baseline, except for triglycerides which are median per cent change (ANOVA with treatment and strata as factors).
ANOVA, analysis of variance; Apo, apolipoprotein; CI, confidence interval; HDL-C, high-density-lipoprotein cholesterol; LDL-C, low-density-lipoprotein cholesterol.



IMPROVE-IT

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 18, 2015 VOL. 372 NO. 25

Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes

Christopher P. Cannon, M.D., Michael A. Blazing, M.D., Robert P. Giugliano, M.D., Amy McCagg, B.S., Jennifer A. White, M.S., Pierre Theroux, M.D., Harald Darius, M.D., Basil S. Lewis, M.D., Ton Oude Ophuis, M.D., Ph.D., J. Wouter Jukema, M.D., Ph.D., Gaetano M. De Ferrari, M.D., Witold Ruzyllo, M.D., Paul De Lucca, Ph.D., KyungAh Im, Ph.D., Erin A. Bohula, M.D., D.Phil., Craig Reist, Ph.D., Stephen D. Wiviott, M.D., Andrew M. Tershakovec, M.D., M.P.H., Thomas A. Musliner, M.D., Eugene Braunwald, M.D., and Robert M. Califf, M.D., for the IMPROVE-IT Investigators*

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

Study Design

IMPROVE-IT

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

*3.2mM
**2.6mM

N=18,144

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

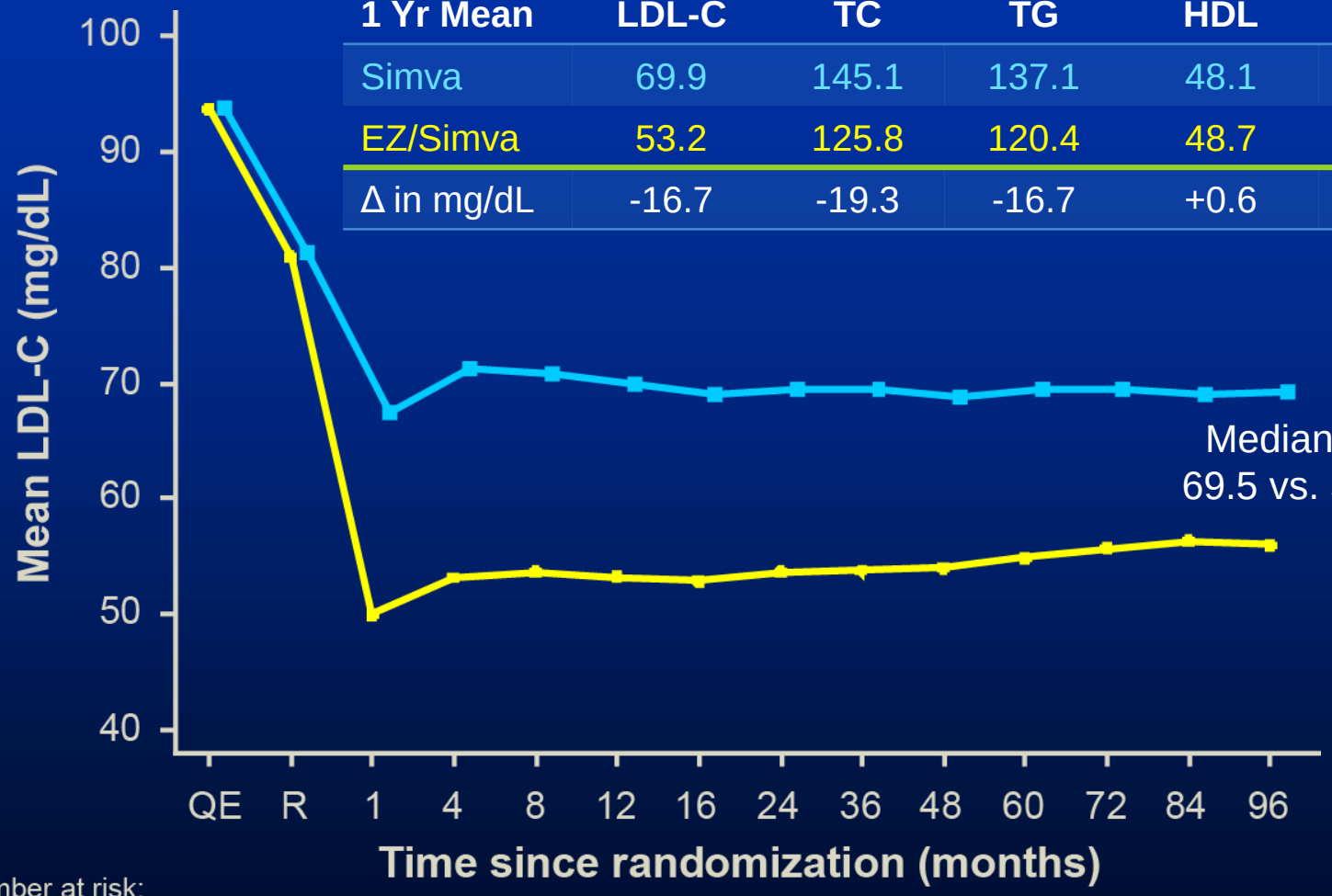
Duration: Minimum 2 ½-year follow-up **(at least 5250 events)**

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

Cannon CP AHJ 2008;156:826-32; Califf RM NEJM 2009;361:712-7; Blazing MA AHJ 2014;168:205-12

LDL-C and Lipid Changes

1 Yr Mean	LDL-C	TC	TG	HDL	hsCRP
Simva	69.9	145.1	137.1	48.1	3.8
EZ/Simva	53.2	125.8	120.4	48.7	3.3
Δ in mg/dL	-16.7	-19.3	-16.7	+0.6	-0.5



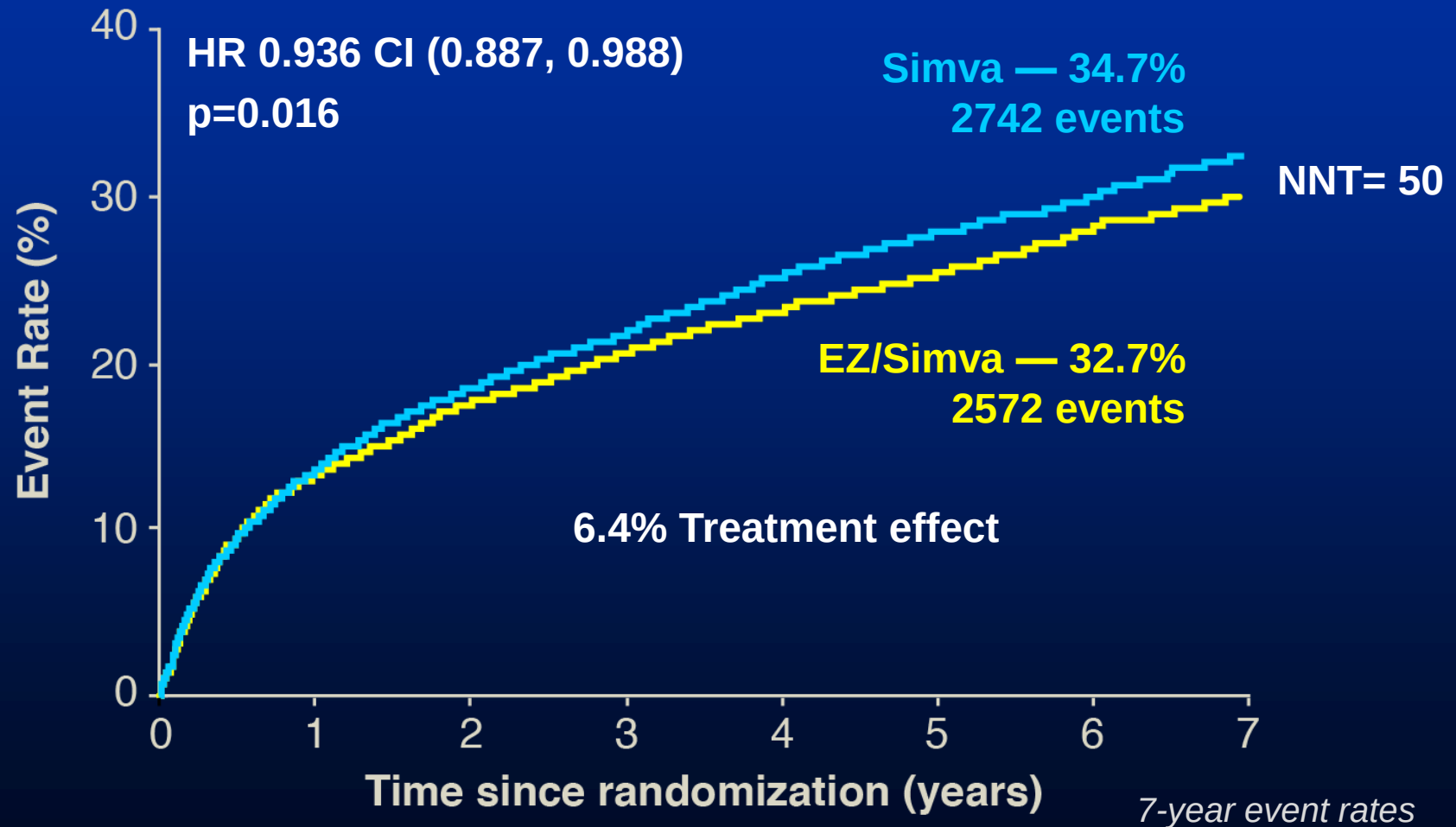
Median Time avg
69.5 vs. 53.7 mg/dL

Number at risk:

	QE	R	1	4	8	12	16	24	36	48	60	72	84	96
EZ/Simva	8990	8889	8230	7701	7264	6864	6583	6256	5734	5354	4508	3484	2608	1078
Simva	9009	8921	8306	7843	7289	6939	6607	6192	5684	5267	4395	3387	2569	1068

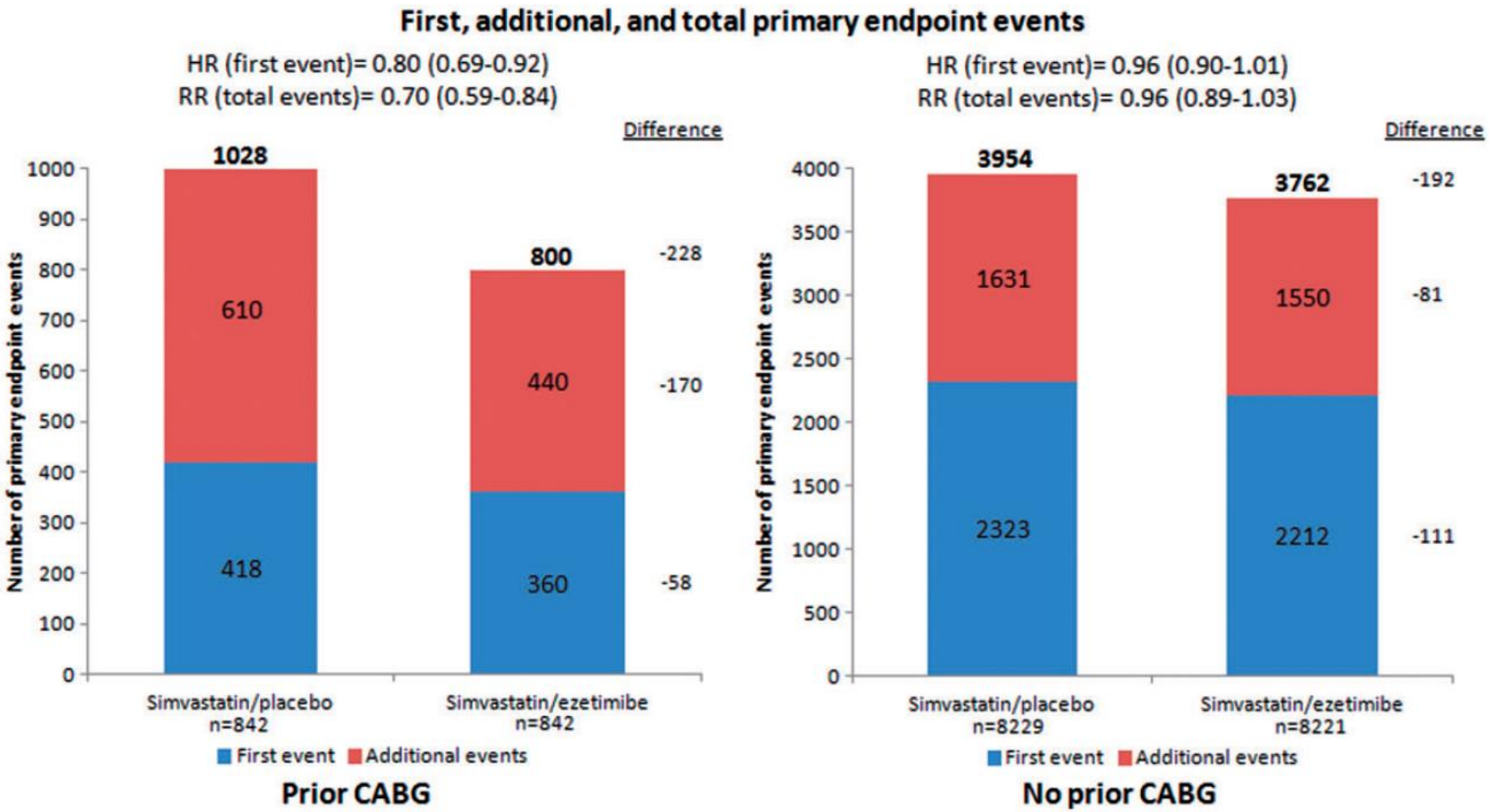
Primary Endpoint — ITT

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



7-year event rates

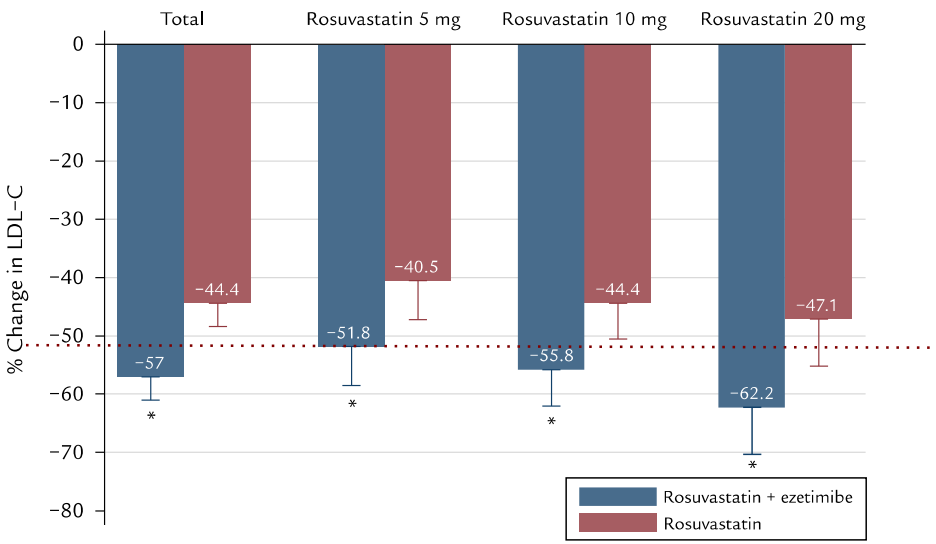
First, additional, and total primary endpoint events during follow-up by randomization group and by prior CABG status. IMPROVE-IT study



European Heart Journal 2016 0, 1–9

Clinical Therapeutics/Volume 40, Number 2, 2018

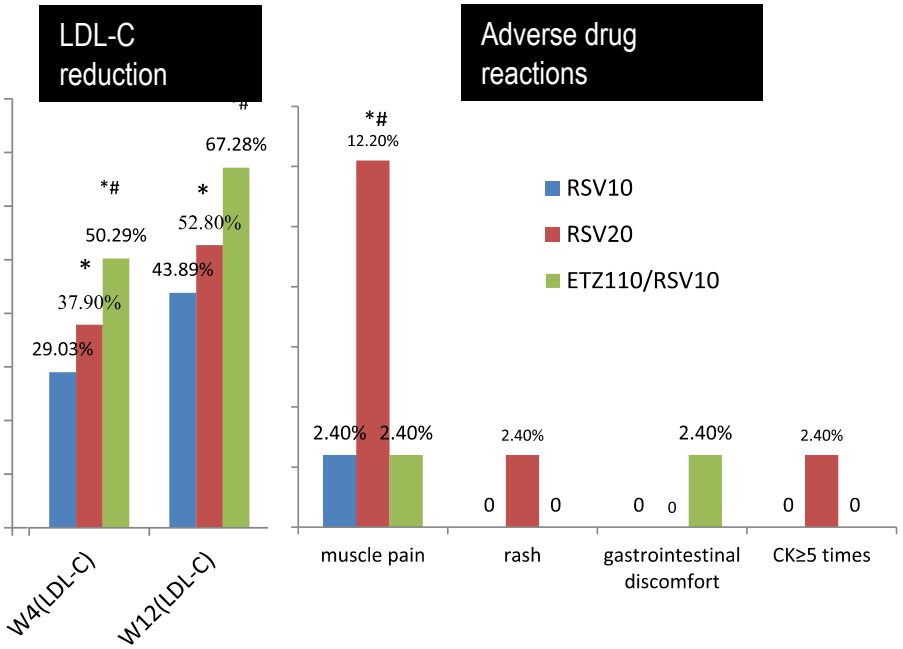
A Phase III, Multicenter, Randomized, Double-blind, Active Comparator Clinical Trial to Compare the Efficacy and Safety of Combination Therapy With Ezetimibe and Rosuvastatin Versus Rosuvastatin Monotherapy in Patients With Hypercholesterolemia: I-ROSETTE Trial



- 396 patients randomly assigned to receive ezetimibe 10 mg/rosuva 20 mg, ezetimibe 10 mg/rosuva 10 mg, ezetimibe 10 mg/rosuva 5 mg, rosuva 20 mg, rosuva 10 mg, or rosuva 5 mg in a 1:1:1:1:1:1 ratio.
- Primary end point was the difference in the mean percent change from baseline in LDL-C level after 8 weeks of treatment between the ezetimibe/ rosuvastatin and rosuvastatin treatment groups

International Journal of Cardiology 235 (2017) 49–55

A randomized, controlled comparison of different intensive lipid-lowering therapies in Chinese patients with non-ST-elevation acute coronary syndrome (NSTE-ACS): Ezetimibe and rosuvastatin versus high-dose rosuvastatin☆



125 post ACS patients randomly assigned to a rosuvastatin (10 mg/d, n = 42, 20 mg/d, n = 41) or combination therapy (ezetimibe 10 mg/d and rosuvastatin 10 mg/d, n = 42) with a 12-week follow-up.

The impact of ezetimibe and high-dose of statin treatment on LDL levels in patients with heterozygous familial hypercholesterolaemia

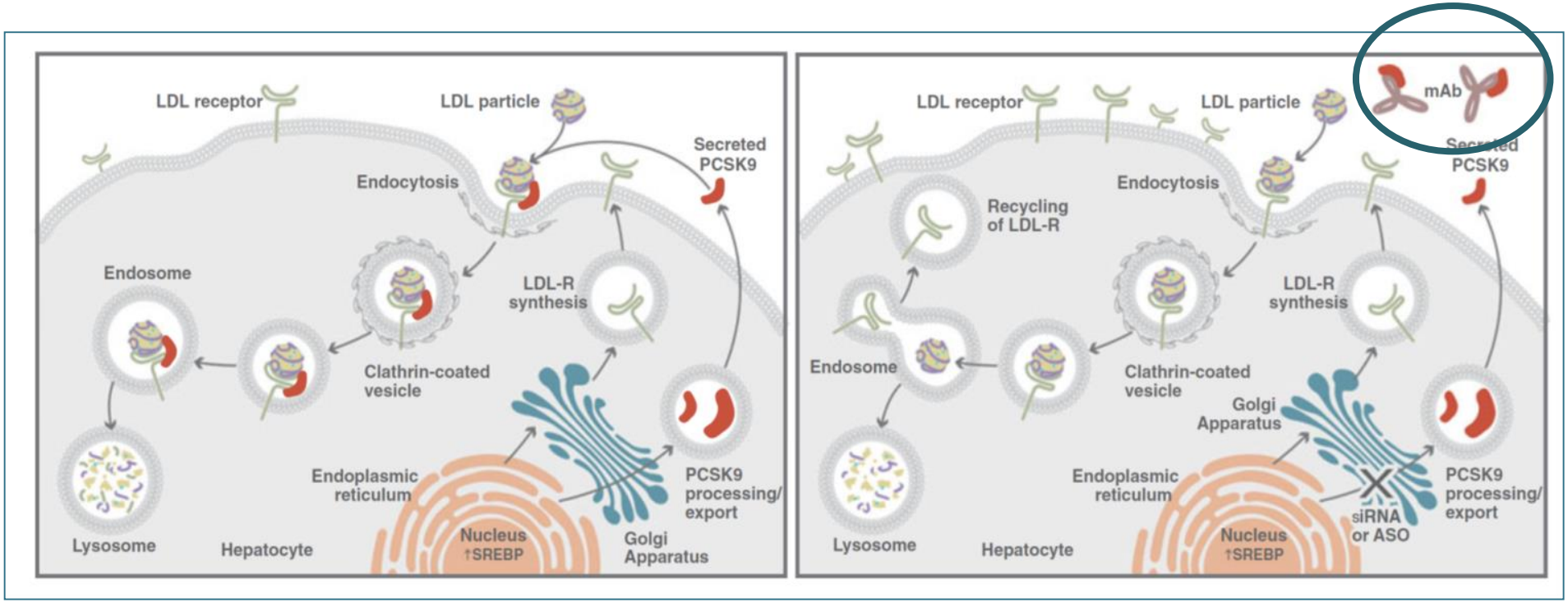
Table 1
Effects of treatment on serum lipids during the follow-up period.

	Baseline	Statins	Statins+ezetimibe (3 months)	Statins+ezetimibe (12 months)
Total cholesterol (mg/dl)	354.3±83.9	238.4±51.0	193.5±40.8†*	192.5±34.7†*
Triglycerides (mg/dl)	125.0±59.5	96.6±43.2	84.0±35.8†*	84.2±32.0†*
HDL (mg/dl)	48.8±10.8	55.7±13.7 †	53.5±11.6†	55.0±12.9†
LDL (mg/dl)	278.0±81.9	163.5±44.4 †	122.5±34.9†*	121.6±36.0†*
APO-A (mg/dl)	152.2±29.7	147.4±28.3	144.4±30.7	145.7±36.6
APO-B (mg/dl)	204.2±66.0	117.8±26.0 †	99.4±23.7†*	99.2±26.5†*
LPA (mg/dl)	42.7±39.6	36.2±40.7	33.8±39.6	35.0±43.6
CRP (mg/ml)	–	0.89±1.04	0.89±1.42	1.14±1.36
Fibrinogen (mg/ml)	316.5±64.5	294.5±66.7	304.8±83.7	323.5±76.7
SGOT (IU/L)	22.9±12.0	23.3±9.0	26.8±11.4	24.5±8.5
SGPT (IU/L)	20.6±13.6	25.2±13.7	27.8±13.8†	28.1±12.4†
CPK (IU/L)	91.0±39.4	110.6±51.7	121.5±68.1†	115.7±53.9†
LDL-Target achieved(%)	–	20%	55.7%	60%

HDL: High density lipoprotein; LDL: low density lipoprotein; Apo-A: Apolipoprotein A; Apo-B: Apolipoprotein B; LPA: Lipoprotein a; CRP: C-reactive protein; SGOT: Glutamate oxaloacetate transaminase; SGPT: Glutamate pyruvate transaminase; CPK: Creatine phosphokinase; †$p<0.05$ vs baseline; *$p<0.05$ vs statins.

Int J Cardiol. 2009;134:280-1

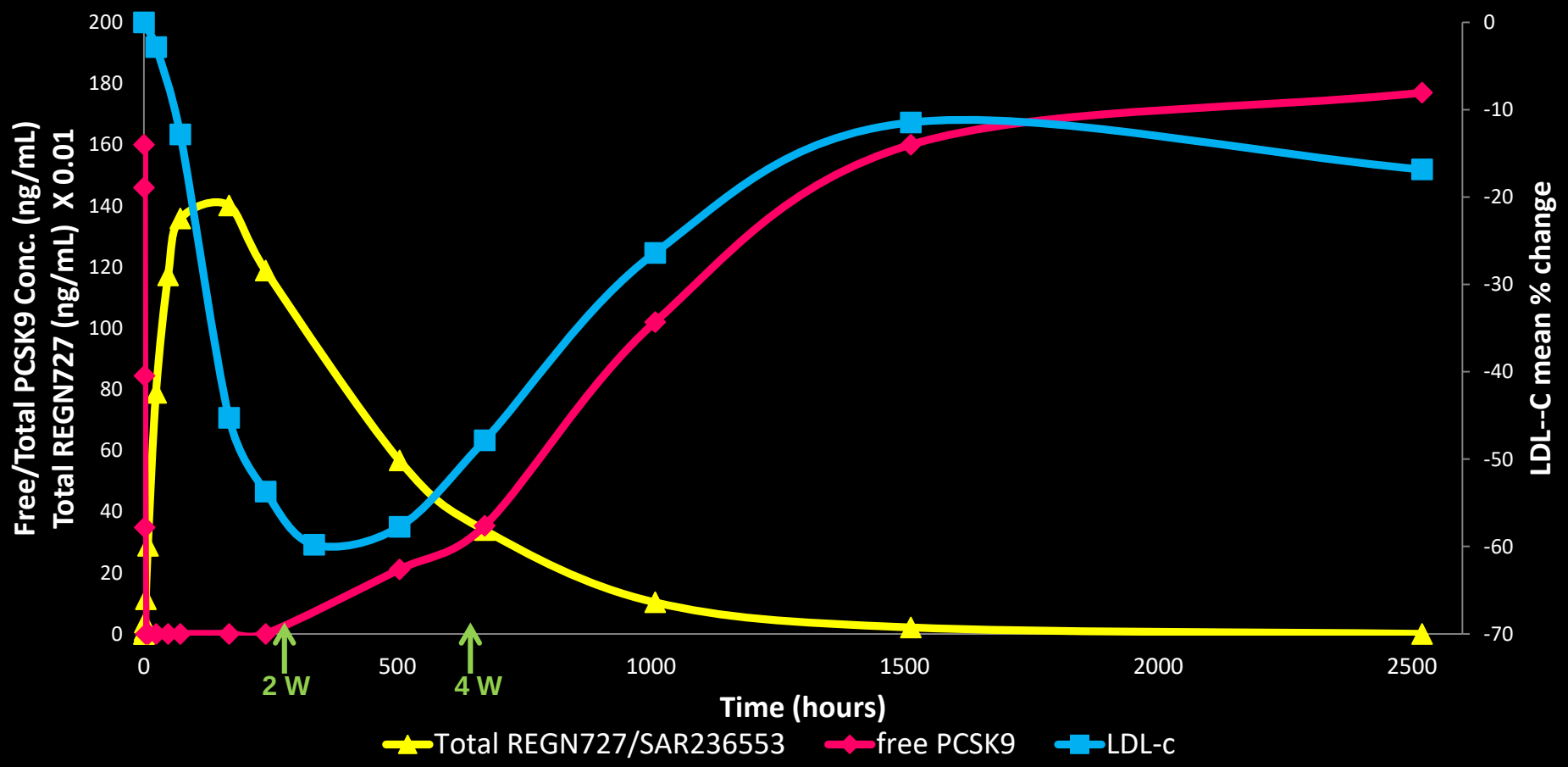
Meccanismo di azione antiPCSK9



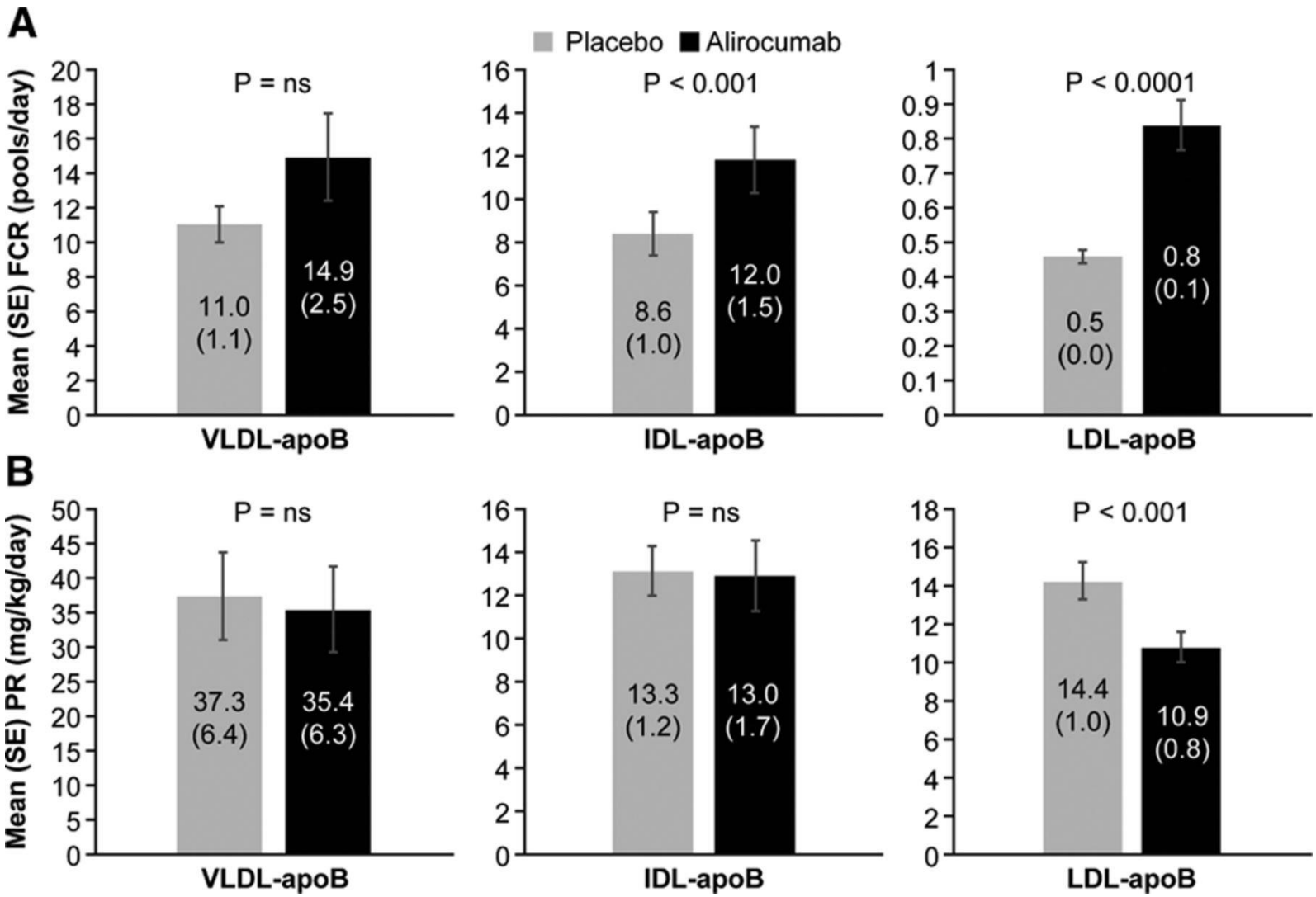
Riduzione attesa LDL-C in corso di trattamento con iPCSK9 50-60%

Stein EA et al. Curr Atheroscler Rep, 2013

Alirocumab: relationship between mAb levels, PCSK9 and LDL-C



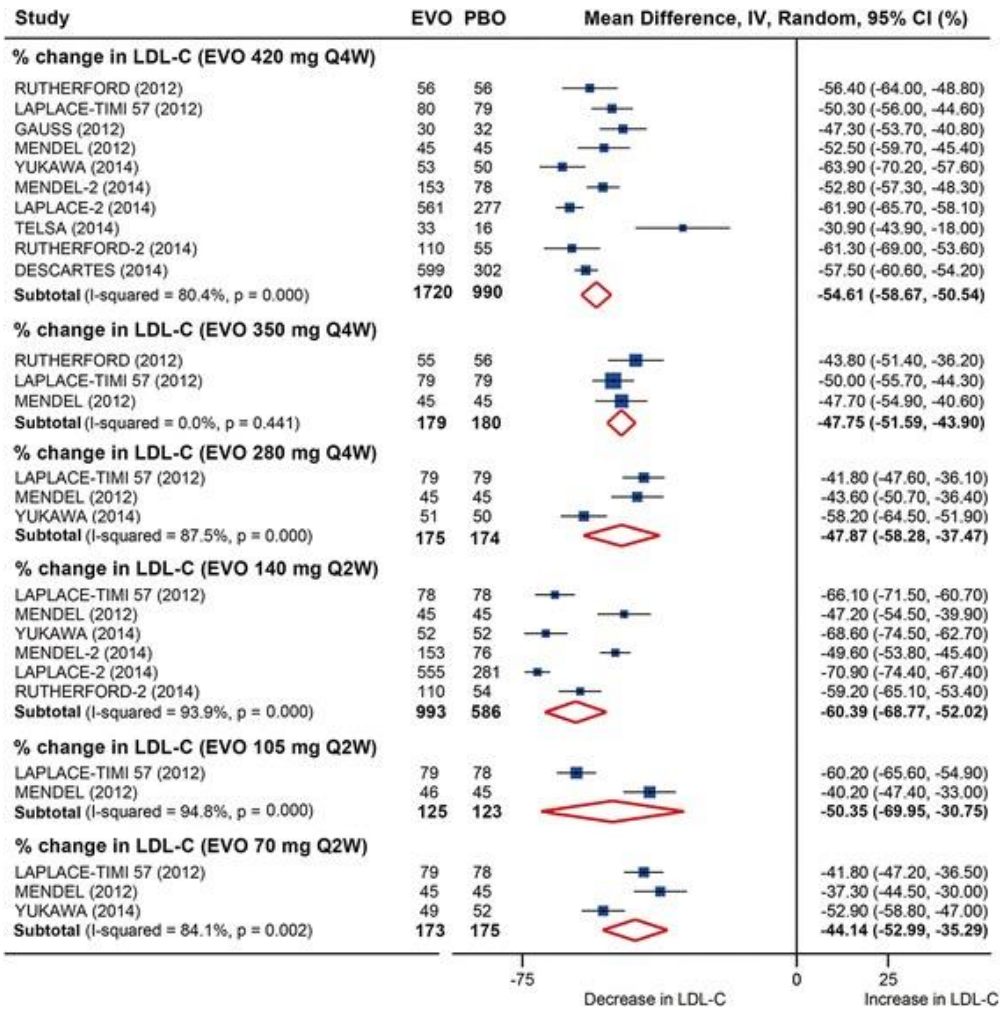
Effects of alirocumab on VLDL-, IDL-, and LDL–apoB fractional clearance rates (A) and production rates (B).



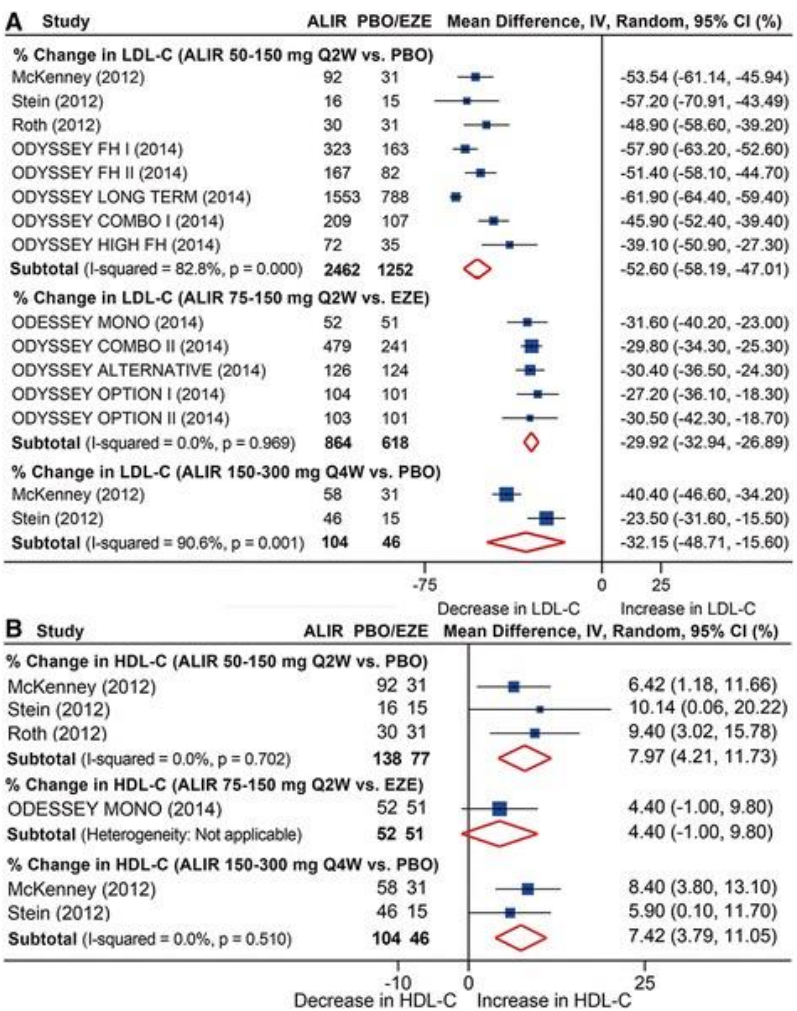
Gissette Reyes-Soffer et al. Circulation. 2017;135:352-362

Safety and efficacy of anti-PCSK9 antibodies: a meta-analysis of 25 randomized, controlled trials

Evolocumab



Alirocumab

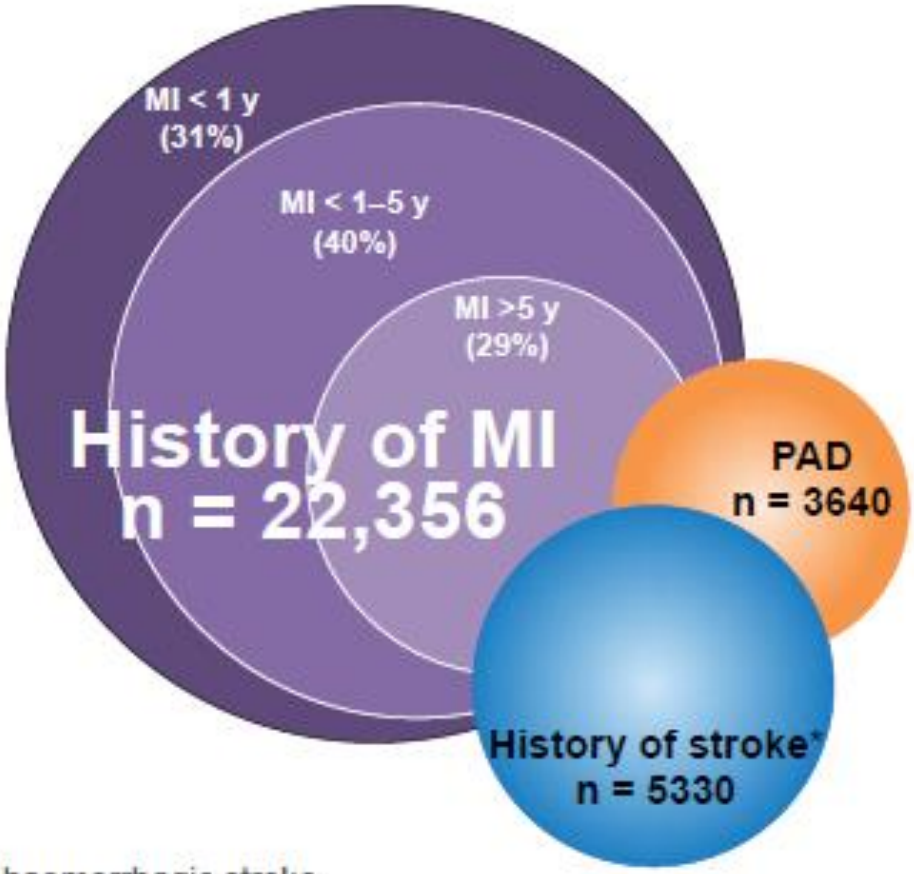


Riduzione LDL-C del 50-60%

Zhang et al. BMC Medicine 2015; 13:123

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: Lipid-lowering Therapies and Lipid Levels @ Baseline

	fourier	ODYSSEY OUTCOMES
Lipid-lowering therapies		
High-intensity statin (%)	69.2	89.5
Moderate-intensity statin (%)	30.4	7.8
Ezetimibe (%)	5.1	2.9
No statin (%)	0.2	2.5
Median LDL-C (mg/dL)	91.5	86.5
Total cholesterol (mg/dL)	167.0	160.0
HDL cholesterol (mg/dL)	44.0	42.5
Triglycerides (mg/dL)	133.0	129.2

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

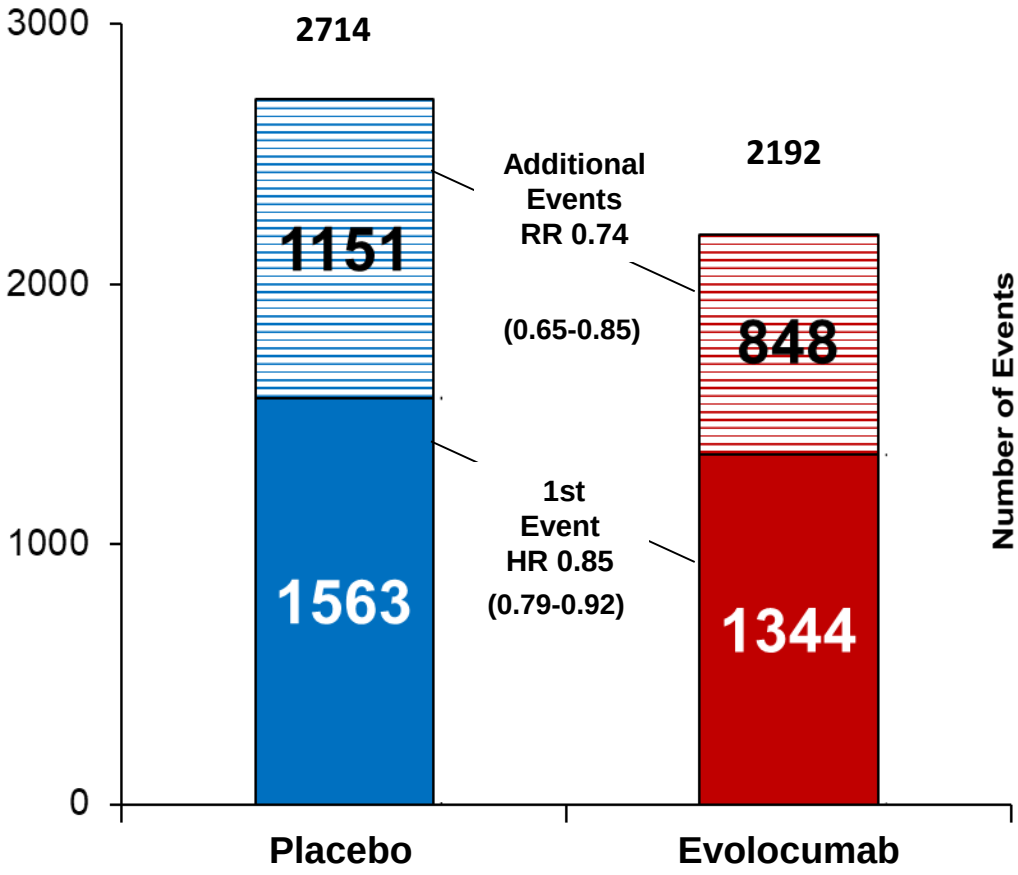
PCSK9i Outcome Trials: Main Results at a Glance

Outcomes relative reduction	fourier	ODYSSEY OUTCOMES
Primary endpoint	15%	15%
MI	27%	14%
Stroke	21%	27%
Unstable angina	1%	39%
CV death	+5% increase (NS)	12% (NS)
All cause death	+4% increase (NS)	15% (p=0.026*)

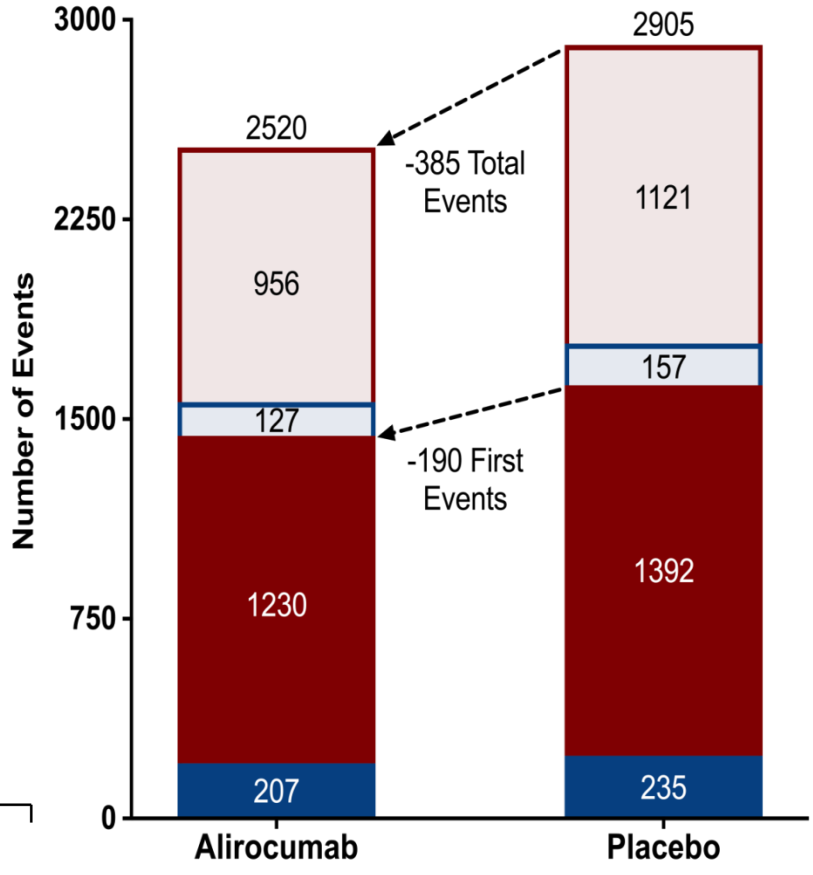
* Nominal p value

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

PCSK9i Reduced Total Events



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



Szarek M, et al. J Am Coll Cardol 2018, *in press*

The association therapy in dyslipidaemia

How to improve LDL-C reduction

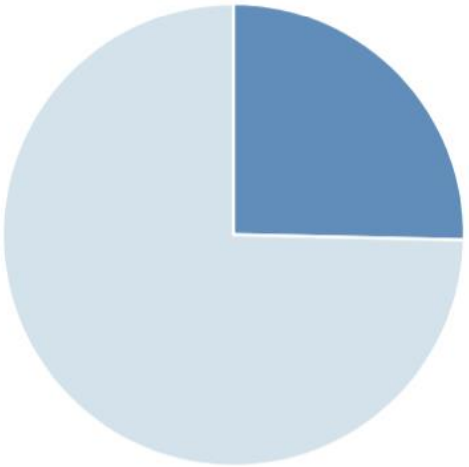
- **Ezetimibe**
- **Colesevelam**
- **iPCSK9**
- **Lomitapide**

How to improve highTG/low HDL

- **Fibrates**
- **Omega-3**

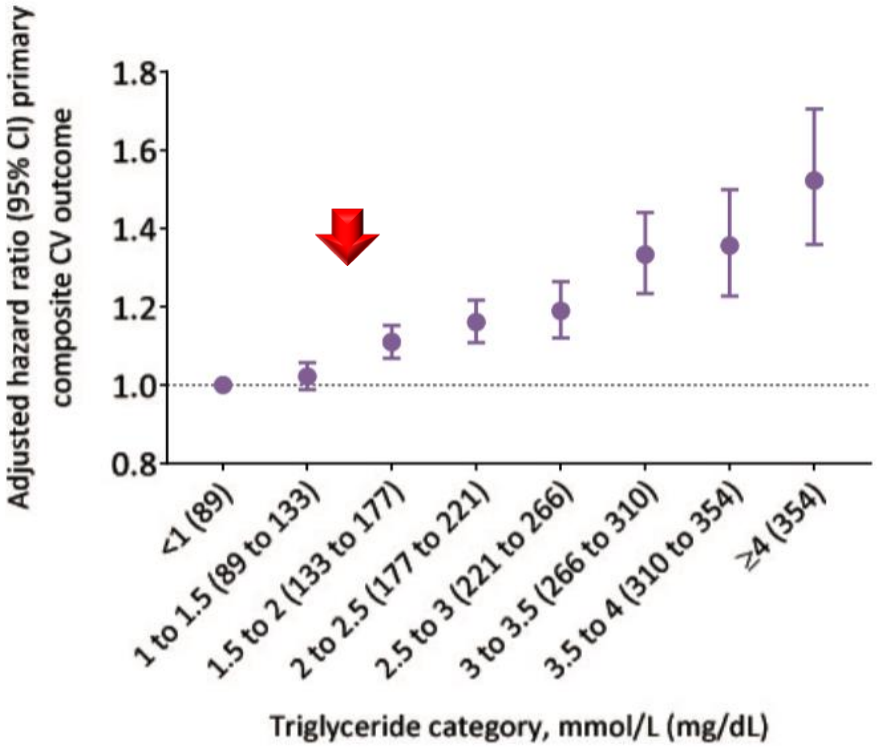
Proportion of patients with **atherosclerotic cardiovascular disease** in the Ontario, Canada, population with hypertriglyceridaemia and controlled LDLc

Approximately 1 in 4 patients with ASCVD in the general population may have hypertriglyceridemia and controlled LDLc*



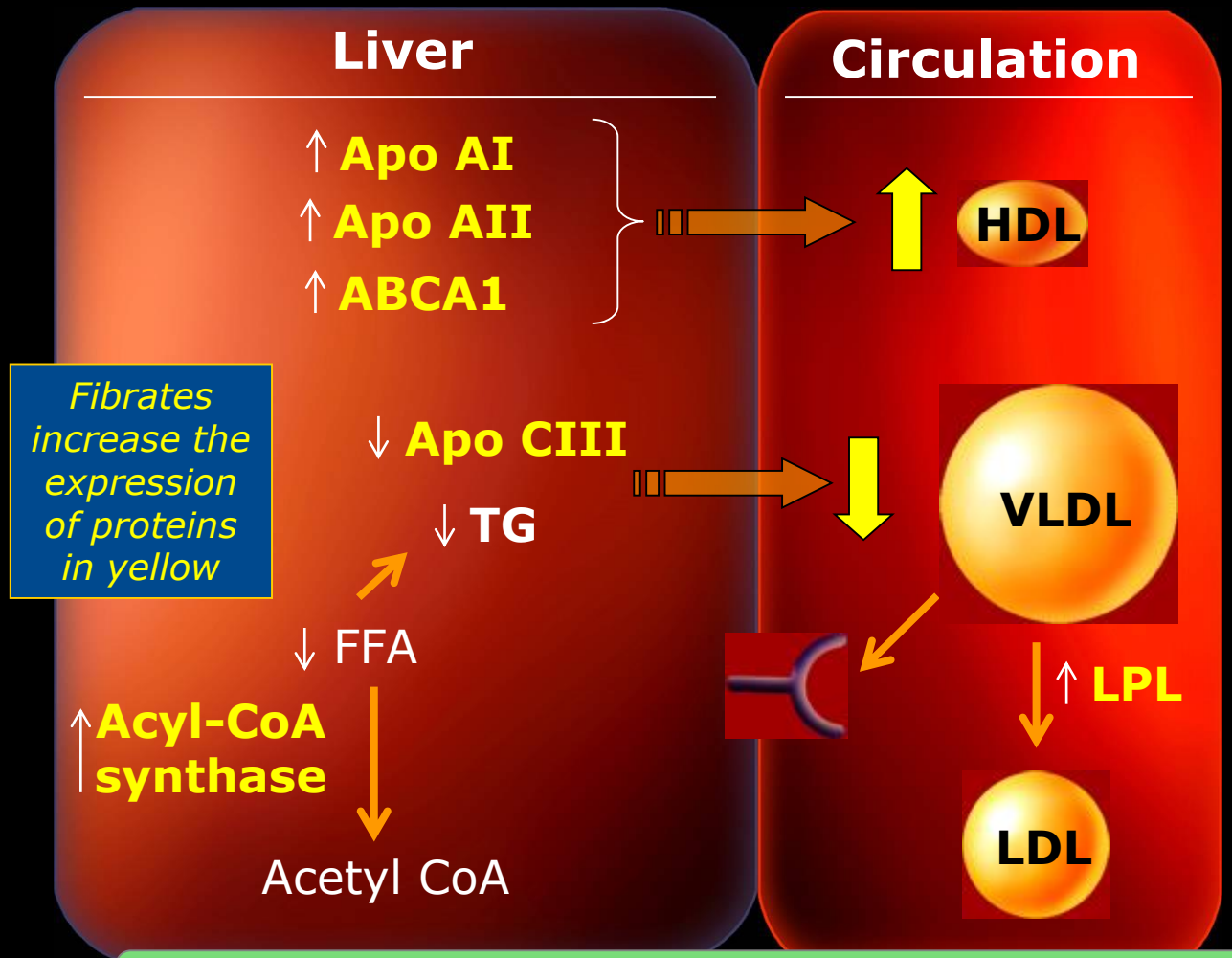
*defined as triglyceride 1.52-5.63 mmol/L (135-499 mg/dL) and LDLc 1.06-2.59 mmol/L (41-100 mg/dL)

Risk of ASCVD events associated with triglyceride level among 196,717 patients with prevalent ASCVD in the population



Lawler PR et al. Eur Heart J. 2020 Jan 1;41(1):86-94.

Fibrates: mechanisms of action on lipids



RESULTS

Increased HDL production

Decreased VLDL production

Increased VLDL clearance

Decreased LDL particles and increased particle size

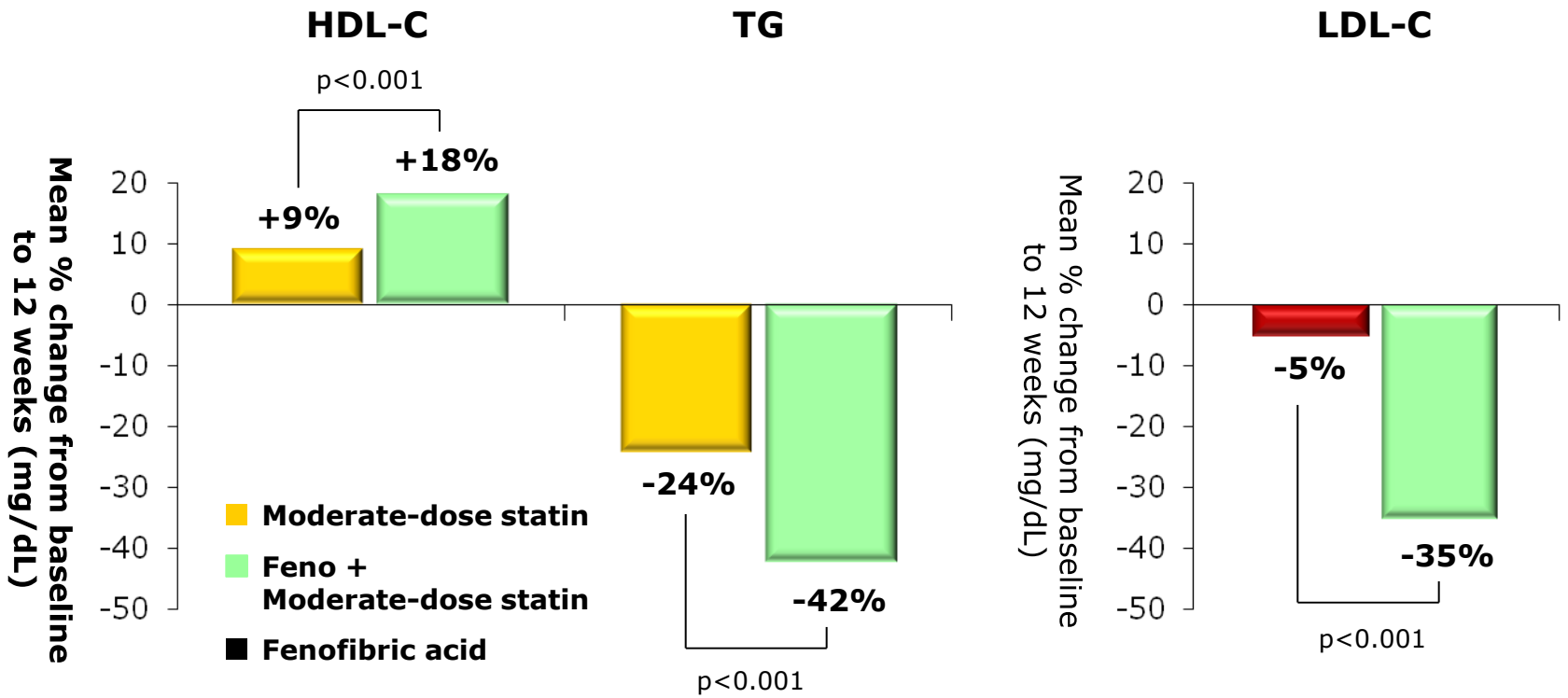
↓ 25-55%Triglycerides ↑ 5-20% HDL-C ↓ LDL-C Variabile

Duval C, et al. Trends Mol Med. 2002;8:422-430.
Lee CH, et al. Endocrinology. 2003;144:2201-2207.

Adding Fenofibric Acid* to a moderate-dose statin improved the three key lipids vs. monotherapy

Randomisation 2,715 patients with mixed dyslipidaemia : LDL-C ≥130 mg/dL, TG ≥150 mg/dL and HDL-C <40 mg/dL for men and <50 mg/dL for women

Feno + low-dose statin*: pooled results through 12 weeks



***Moderate-dose statins included in study: simvastatin 40 mg, atorvastatin 40 mg and rosuvastatin 20 mg**

***Bioequivalent to 145 mg of fenofibrate**

Jones PH et al. *J Clin Lipidol*. 2010;3(2):125-37.

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

A Primary outcome

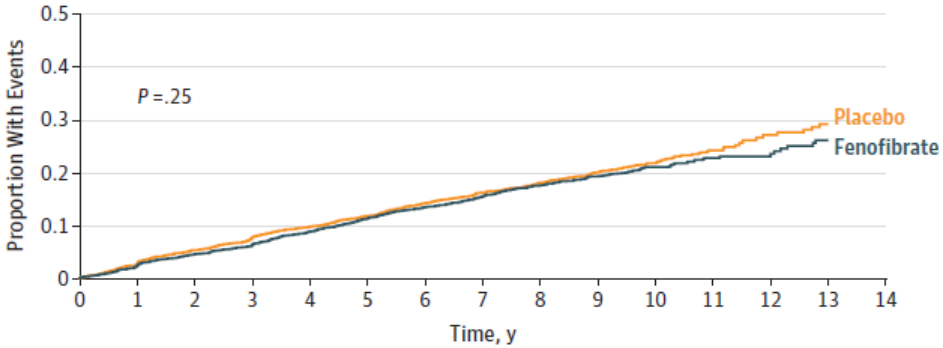
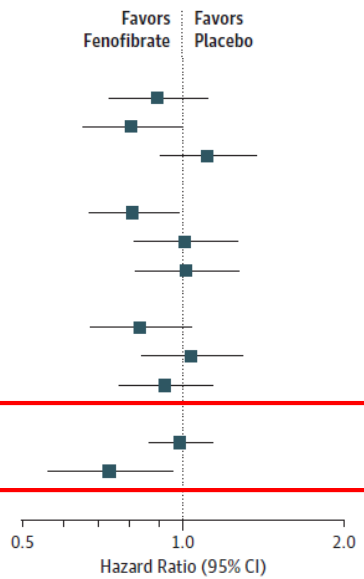


Figure 3. Hazard Ratios for the Primary Outcome in Prespecified Subgroups

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)	



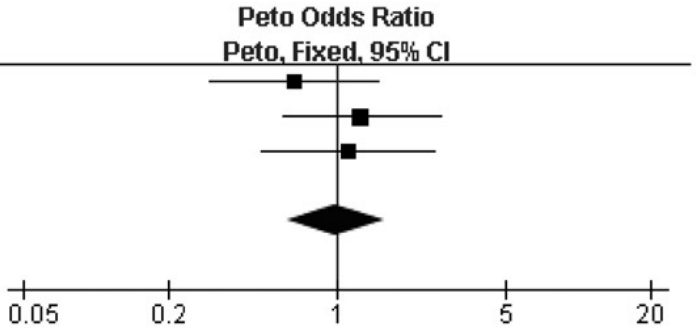
Elam MB et al. JAMA Cardiol. doi:10.1001/jamacardio.2016.4828, Published online December 28, 2016.

Meta-Analysis of Safety of the Coadministration of Statin With *Fenofibrate* in Patients With Combined Hyperlipidaemia

B

Study or Subgroup	coadministration Events	Total	statin Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Davidson MH 2009	12	73	17	74	32.2%	0.66 [0.30, 1.49]
Farnier M 2007	16	183	13	184	36.8%	1.26 [0.59, 2.68]
Farnier M 2010	13	123	12	125	31.0%	1.11 [0.49, 2.54]
Total (95% CI)		**379**		**383**	**100.0%**	**0.99 [0.62, 1.56]**
Total events	41		42			

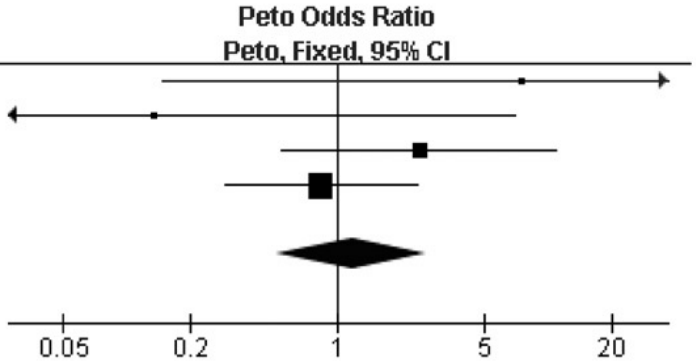
Heterogeneity: $Chi^2 = 1.40$, df = 2 (P = 0.50); $I^2 = 0\%$
Test for overall effect: Z = 0.06 (P = 0.95)



C

Study or Subgroup	coadministration Events	Total	statin Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Davidson MH 2009	1	73	0	74	4.4%	7.49 [0.15, 377.56]
Farnier M 2007	0	183	1	184	4.4%	0.14 [0.00, 6.86]
Farnier M 2010	5	123	2	125	30.0%	2.45 [0.55, 10.97]
SAFARI Trial 2005	10	411	6	207	61.2%	0.83 [0.29, 2.38]
Total (95% CI)		**790**		**590**	**100.0%**	**1.17 [0.51, 2.66]**
Total events	16		9			

Heterogeneity: $Chi^2 = 3.35$, df = 3 (P = 0.34); $I^2 = 11\%$
Test for overall effect: Z = 0.37 (P = 0.71)

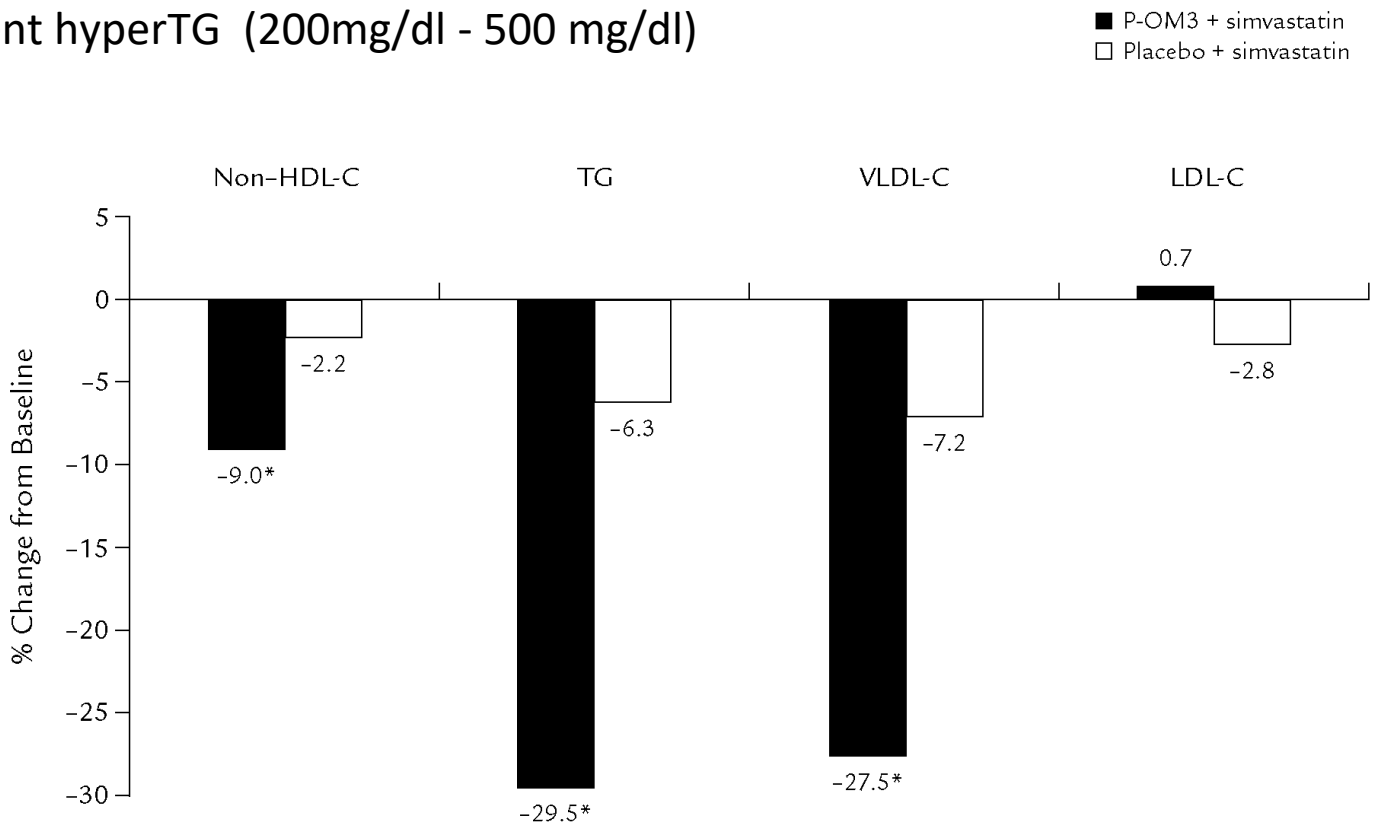


Summary of results of meta-analysis on *(B)* adverse events related to study drug, and *(C)* serious adverse events.

Am J Cardiol 2012;110:1296–1301

Efficacy and Tolerability of Adding Prescription Omega-3 Fatty Acids 4 g/d to Simvastatin 40 mg/d in Hypertriglyceridemic Patients*: An 8-Week, Randomized, Double-Blind, Placebo-Controlled Study (COMBOS STUDY)

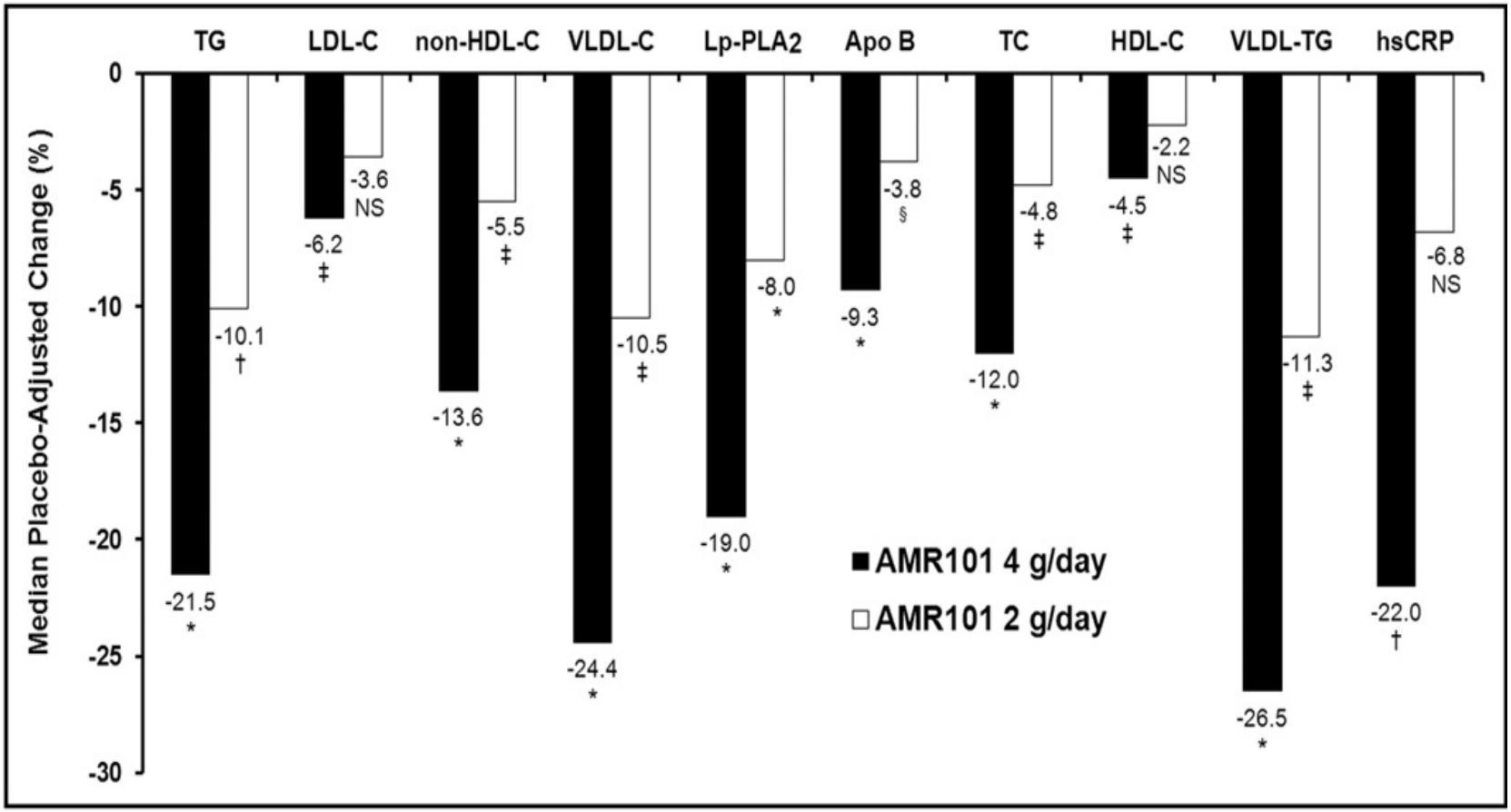
* Persistent hyperTG (200mg/dl - 500 mg/dl)



1-g capsule of P-OM3 contains ethyl esters of omega-3, EPA 465 mg and DHA 375 mg

Clinical Therapeutics 2007; 29: 1354

Efficacy and Safety of Eicosapentaenoic Acid Ethyl Ester Therapy in Statin-Treated Patients With Persistent High Triglycerides (ANCHOR Study)



73% diabetes mellitus; median baseline TG level was 259.0 mg/dl

Am J Cardiol 2012;110:984–992

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia

Deepak L. Bhatt, M.D., M.P.H., P. Gabriel Steg, M.D., Michael Miller, M.D., Eliot A. Brinton, M.D., Terry A. Jacobson, M.D., Steven B. Ketchum, Ph.D., Ralph T. Doyle, Jr., B.A., Rebecca A. Juliano, Ph.D., Lixia Jiao, Ph.D., Craig Granowitz, M.D., Ph.D., Jean-Claude Tardif, M.D., and Christie M. Ballantyne, M.D., for the REDUCE-IT Investigators*

Article available at https://www.nejm.org
Slides available for download at https://professional.heart.org
or at https://www.ACC.org

Reduction of CV Events with Icosapent Ethyl-Intervention Trial

- Men and women ≥45 years of age
- Established CHD or at high risk for CHD (diabetes + ≥1 risk factor)
- Atherogenic dyslipidemia
  - All patients required to be on stable statin therapy for at least 4 weeks
  - LDL-C >40 mg/dL and ≤100 mg/dL prior to randomization into the study
  - TG ≥200 to <500 mg/dL

reduce-it

N≈8000

VASCEPA + Stable Statin Therapy

Placebo + Stable Statin Therapy

Primary endpoint: Prevention of 1st major CV event

Study duration ≈ 5–7 years

Estimated completion: 2017–2018

- Randomized, double-blind, parallel-group design
- International trial; first patient enrolled: November 2011
- Other outcome measures: Incidence of additional CV events, lipid and lipoprotein levels, etc.
- Pre-defined subgroup analyses such as patients with diabetes
- Interim analysis planned for 967th event: Sept–Oct 2016; study expected to continue as planned

Primary Endpoint

Time from randomization to the first occurrence of composite of CV death, nonfatal MI, nonfatal stroke, coronary revascularization, unstable angina

4 g/die of 96% pure ethyl ester of EPA

Bhatt DL, Ballantyne CM et al. Clinical Cardiology. 2017;**40:**138–148.

Key Baseline Characteristics

reduce-it

	Icosapent Ethyl (N=4089)	Placebo (N=4090)
Age (years), Median (Q1-Q3)	64.0 (57.0 - 69.0)	64.0 (57.0 - 69.0)
Female, n (%)	1162 (28.4%)	1195 (29.2%)
Non-White, n (%)	398 (9.7%)	401 (9.8%)
Westernized Region, n (%)	2906 (71.1%)	2905 (71.0%)
CV Risk Category, n (%)		
Secondary Prevention Cohort	2892 (70.7%)	2893 (70.7%)
Primary Prevention Cohort	1197 (29.3%)	1197 (29.3%)
Ezetimibe Use, n (%)	262 (6.4%)	262 (6.4%)
Statin Intensity, n (%)		
Low	254 (6.2%)	267 (6.5%)
Moderate	2533 (61.9%)	2575 (63.0%)
High	1290 (31.5%)	1226 (30.0%)
Type 2 Diabetes, n (%)	2367 (57.9%)	2363 (57.8%)
Triglycerides (mg/dL), Median (Q1-Q3)	216.5 (176.5 - 272.0)	216.0 (175.5 - 274.0)
HDL-C (mg/dL), Median (Q1-Q3)	40.0 (34.5 - 46.0)	40.0 (35.0 - 46.0)
LDL-C (mg/dL), Median (Q1-Q3)	74.0 (61.5 - 88.0)	76.0 (63.0 - 89.0)
Triglycerides Category		
<150 mg/dL	412 (10.1%)	429 (10.5%)
150 to <200 mg/dL	1193 (29.2%)	1191 (29.1%)
≥200 mg/dL	2481 (60.7%)	2469 (60.4%)

TG 216 mg/dl

LDL-C 74 mg/dl

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2018.

Effects on Biomarkers from Baseline to Year 1

reduce-it

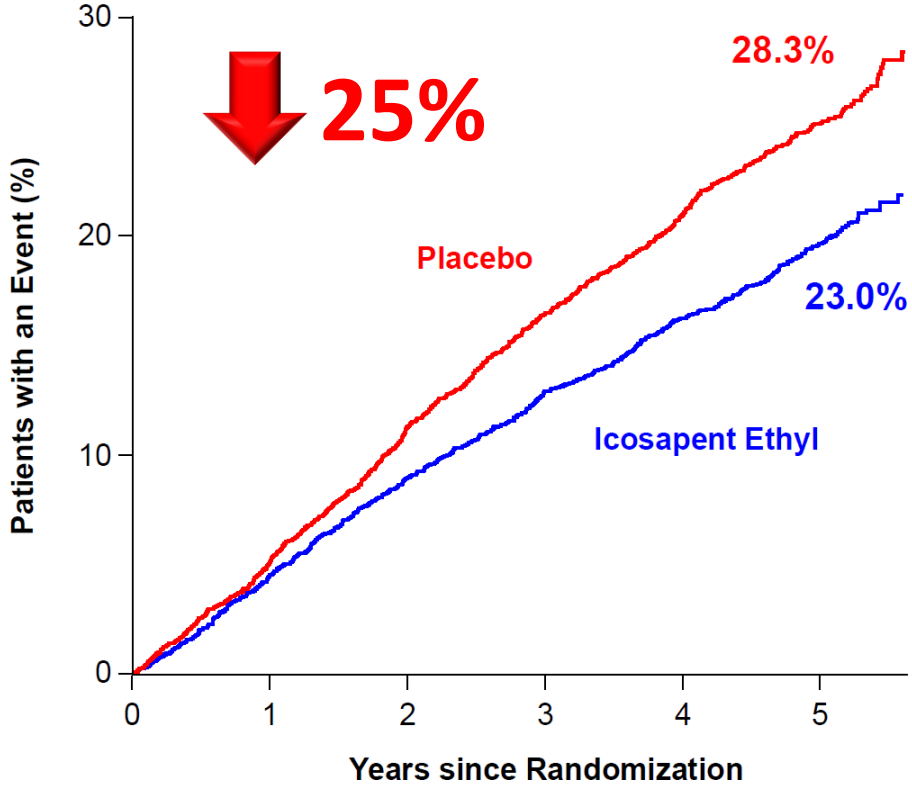
Biomarker*	Icosapent Ethyl (N=4089) Median		Placebo (N=4090) Median		Median Between Group Difference at Year 1		
	Baseline	Year 1	Baseline	Year 1	Absolute Change from Baseline	% Change from Baseline	% Change P-value
Triglycerides (mg/dL)	216.5	175.0	216.0	221.0	-44.5	-19.7	<0.0001
Non-HDL-C (mg/dL)	118.0	113.0	118.5	130.0	-15.5	-13.1	<0.0001
LDL-C (mg/dL)	74.0	77.0	76.0	84.0	-5.0	-6.6	<0.0001
HDL-C (mg/dL)	40.0	39.0	40.0	42.0	-2.5	-6.3	<0.0001
Apo B (mg/dL)	82.0	80.0	83.0	89.0	-8.0	-9.7	<0.0001
hsCRP (mg/L)	2.2	1.8	2.1	2.8	-0.9	-39.9	<0.0001
Log hsCRP (mg/L)	0.8	0.6	0.8	1.0	-0.4	-22.5	<0.0001
EPA (µg/mL)	26.1	144.0	26.1	23.3	+114.9	+358.8	<0.0001

*Apo B and hsCRP were measured at Year 2.

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2018.

Primary End Point:

CV Death, MI, Stroke, Coronary Revasc, Unstable Angina



Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2018. Bhatt DL. AHA 2018, Chicago.

Key notes

- A proportion of patients ranging between 30% to 70% may not adequately respond to statin monotherapy
- Dyslipidaemias where more frequently statin monotherapy therapy could fail are HeFH (residual LDL-C) and mixed hyperlipidaemia (residual highTG/low HDL-C)
- The association of statins with ezetimibe is good option to improve LDL-C reduction (additional 20% LDL-C) in HeFH as well as in high risk patients
- The association of statins with fibrates or omega-3 are good options to correct highTG residual dyslipidemia

nature medicine

EDITORIAL

Rationalizing combination therapies

NATURE MEDICINE VOLUME 23 | NUMBER 10 | OCTOBER 2017

- same pharmacokinetics
- synergistic effects: the efficacy should be higher compared to the sum of the single drugs
- less adverse events and better tolerated
- Simplified treatment regimen: better adherence and potential for improved outcomes
- Economic benefits (fewer copayments, health care costs reduced, fewer office visits)