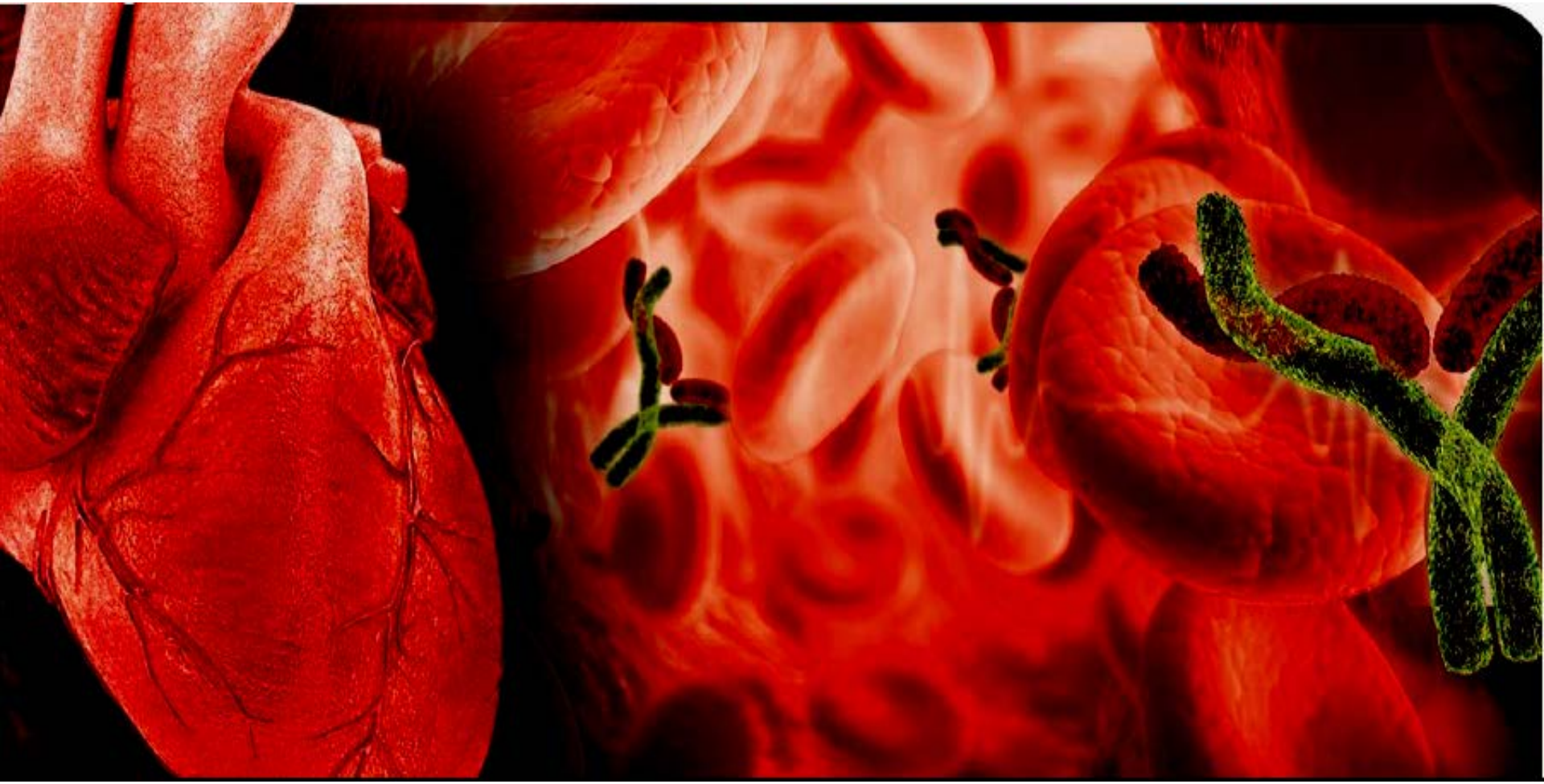
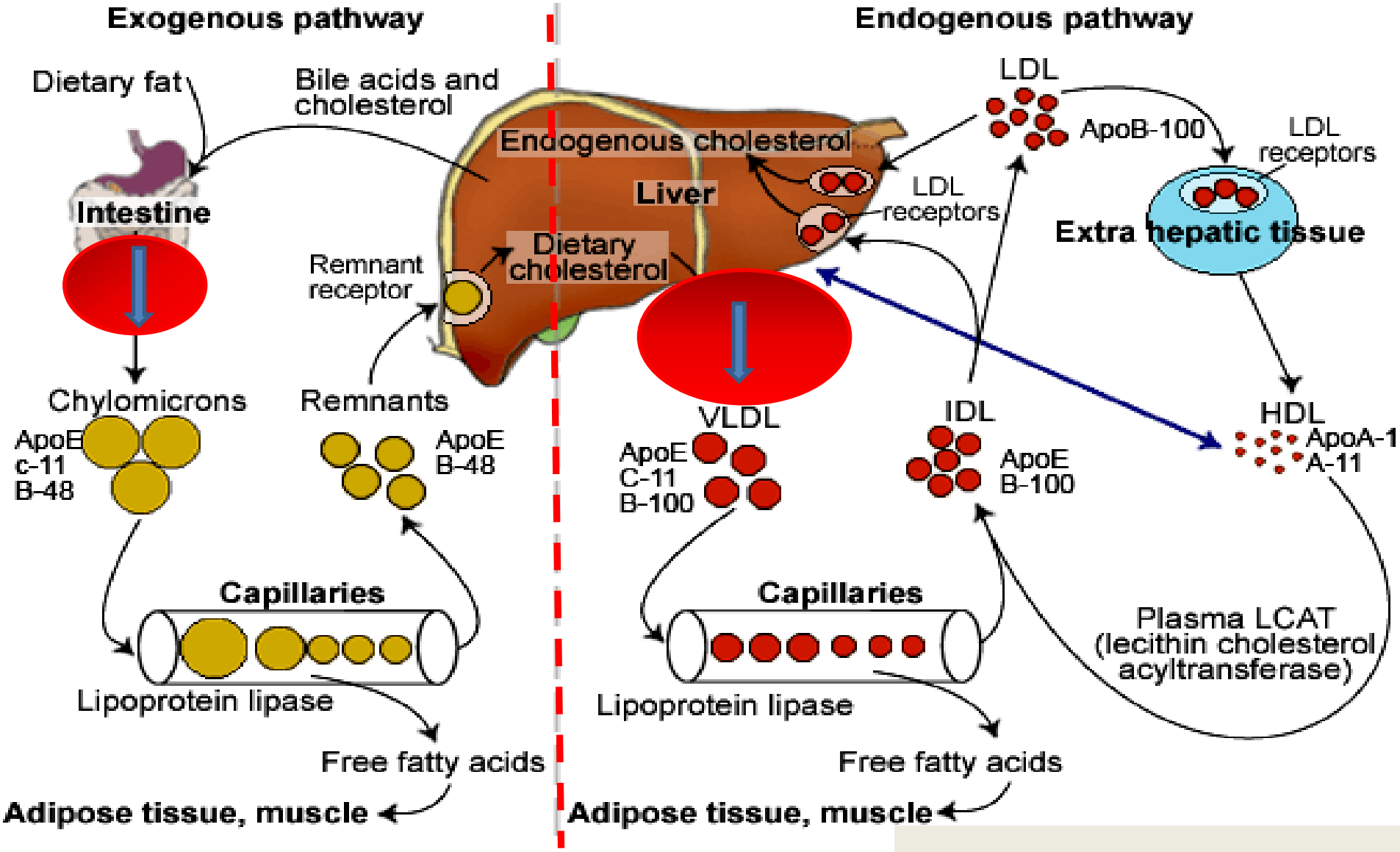
Από τις στατίνες στα νεώτερα υπολιπιδαιμικά φάρμακα

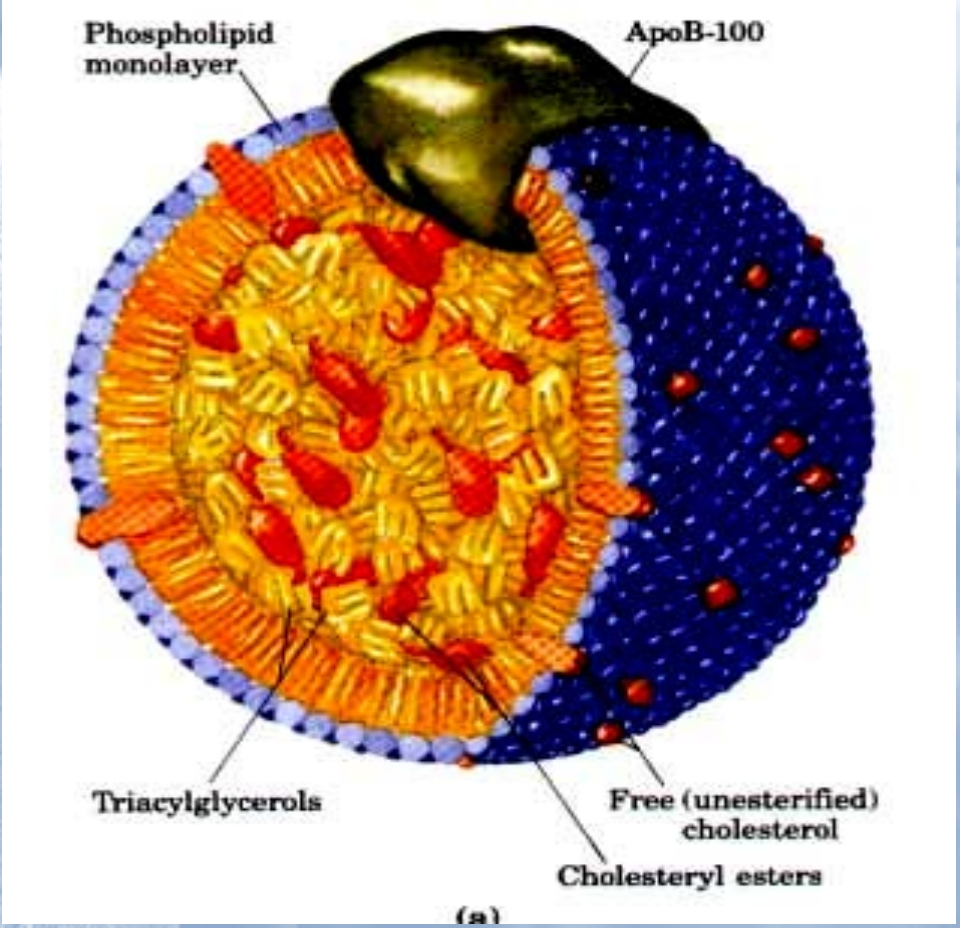


Β. 'Αθυρος, MD, FESC, FRSPH, FASA, FACS
2η Προπ. Παθολογική Κλινική, Ιπποκράτειο Νοσοκομείο,
Αριστοτέλειο Πανεπιστήμιο Θεσσαλονίκης

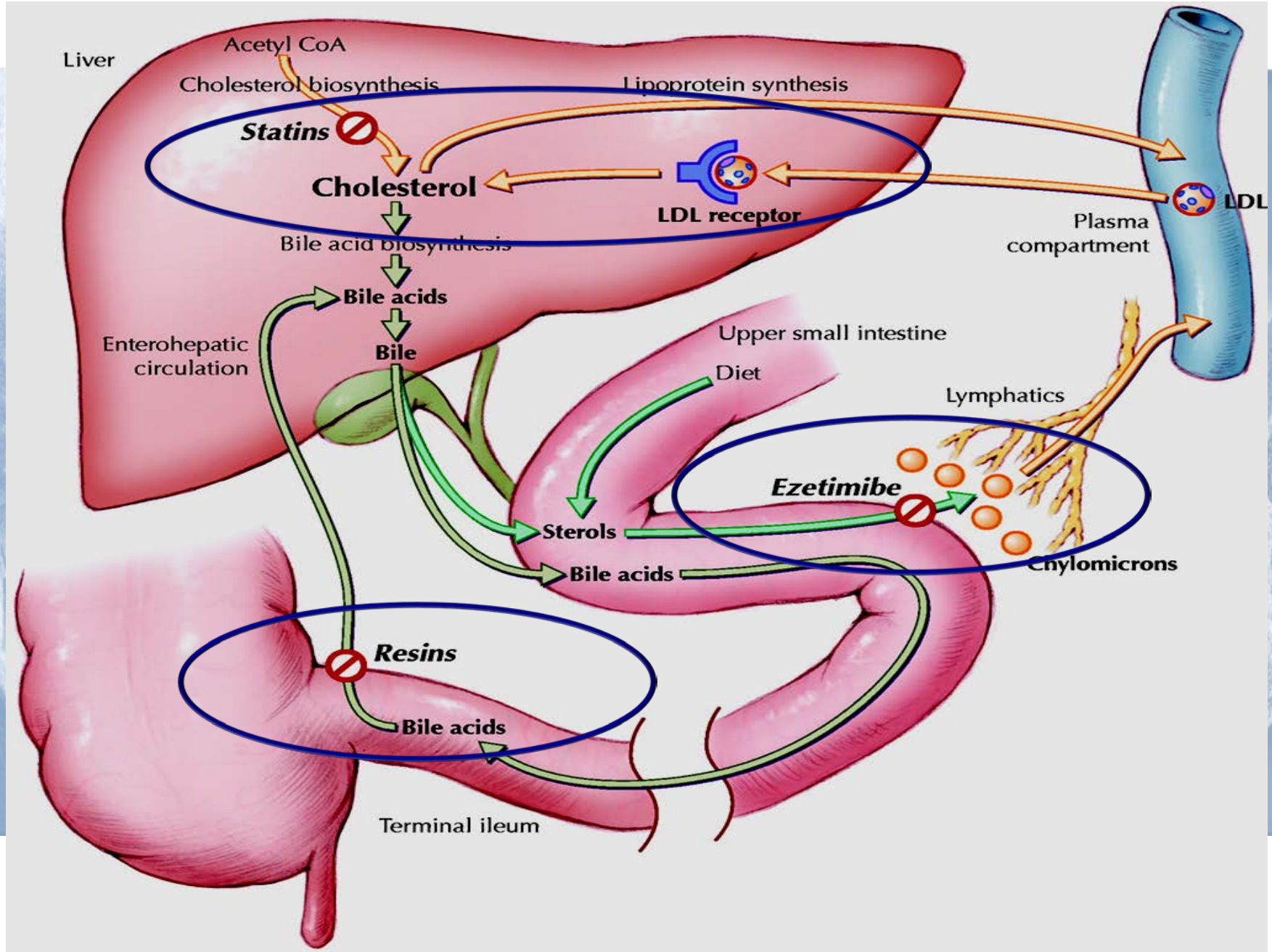
Μεταβολισμός των λιπιδίων



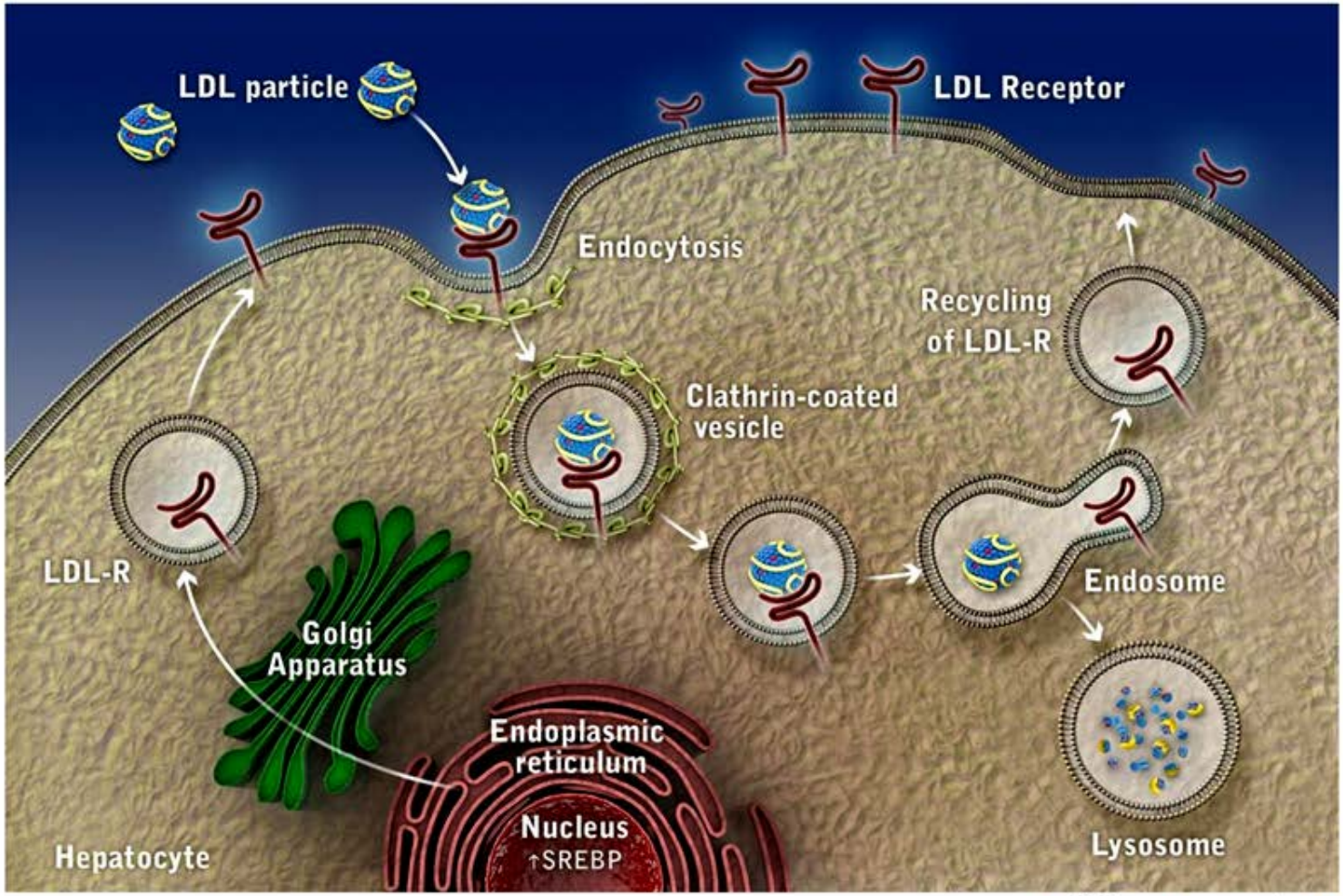
Λιποπρωτεΐνη LDL



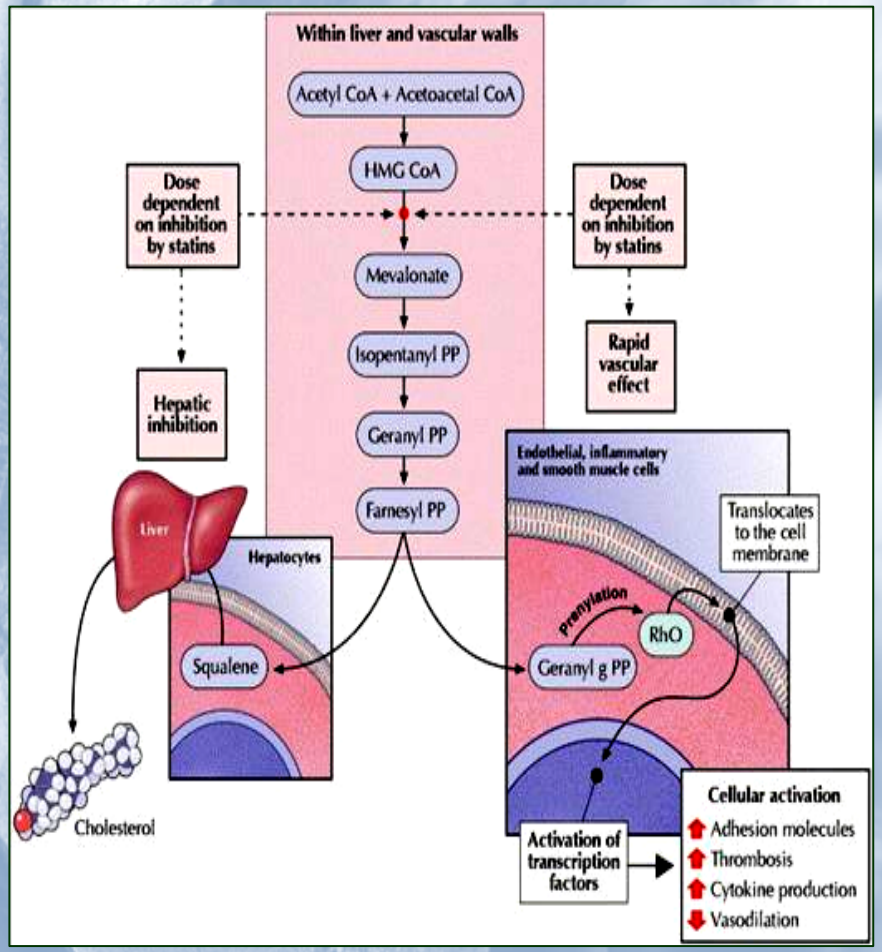
Μεταβολισμός της LDL χοληστερόλης

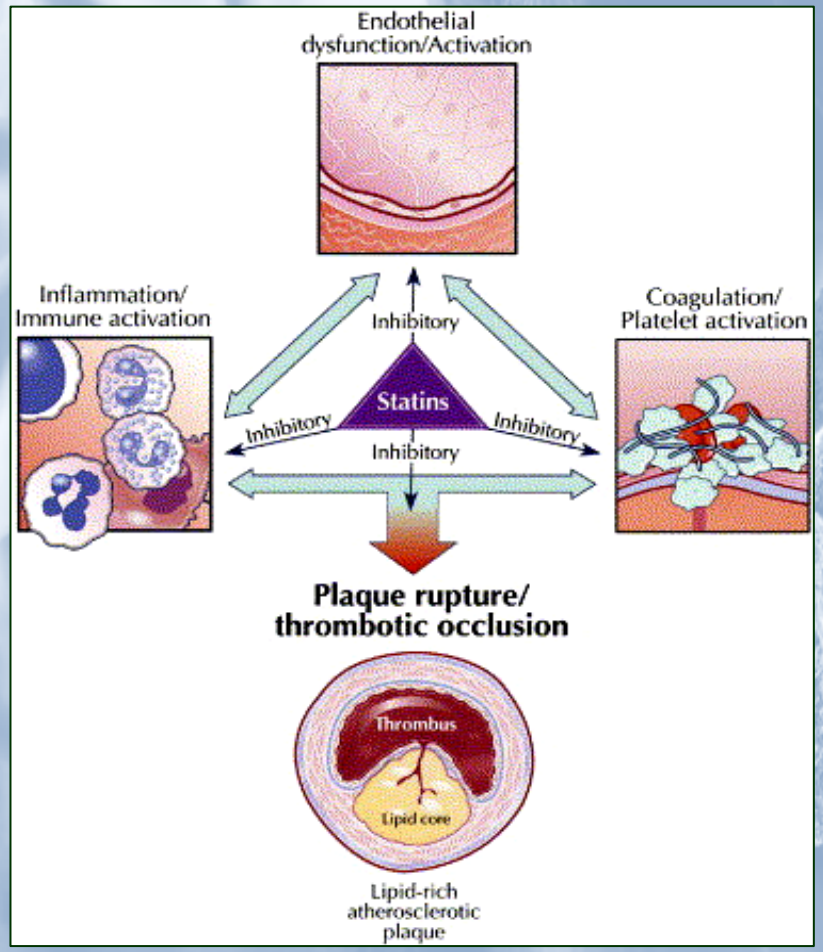


LDLR Function and Life Cycle

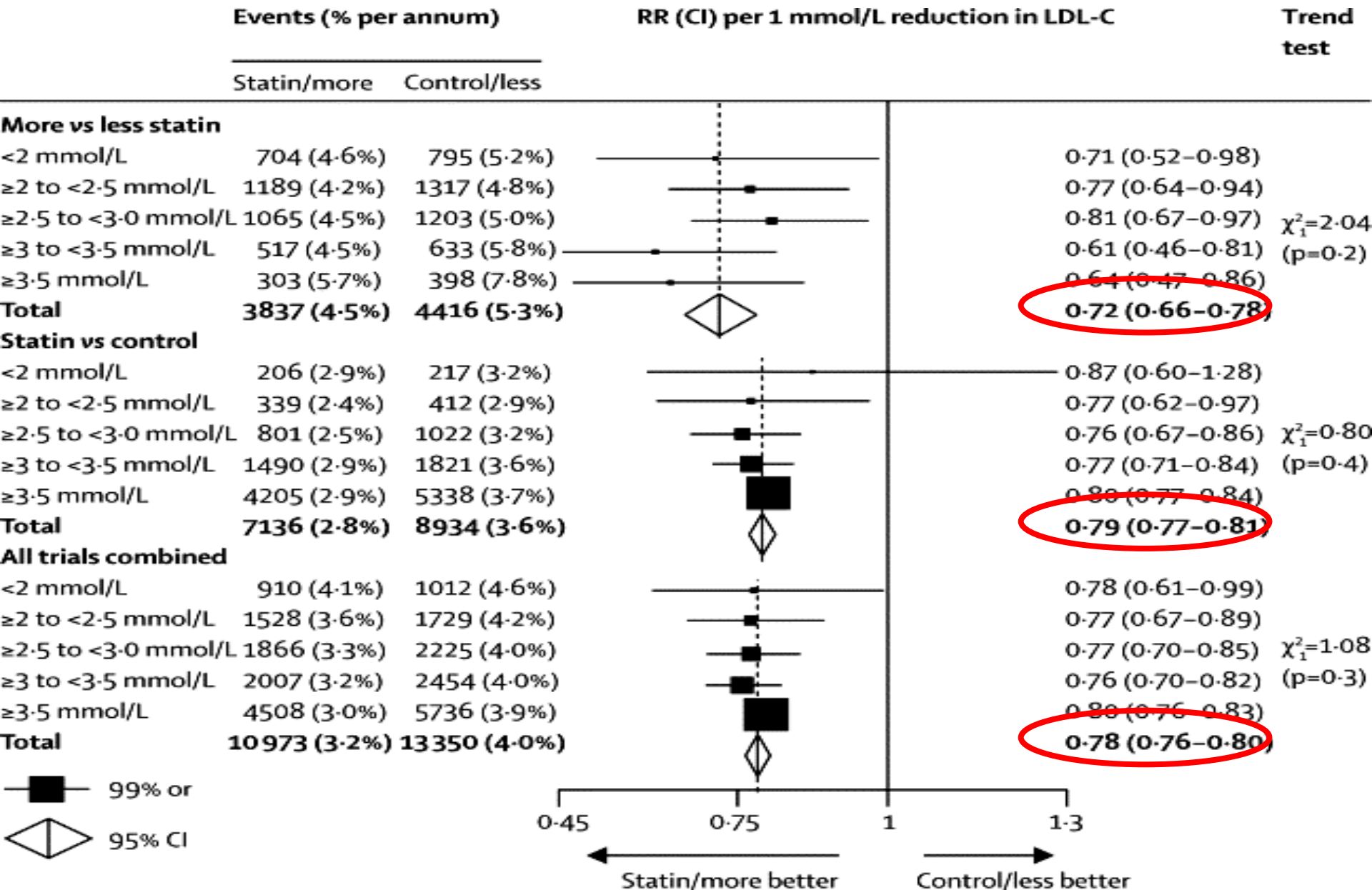


Μηχανισμός δράσης των στατινών





Μετα-ανάλυση 26 τυχαιοποιημένων κλινικών μελετών με 170,000 συμμετέχοντες (Cholesterol Treatment Trialists' (CTT) Collaboration)



Ανεπιθύμητες ενέργειες των στατινών

In the drug-level network meta-analysis of individual statins, 165,534 participants contributed information on 2,075 clinically meaningful elevations in hepatic transaminases (1% of all participants).

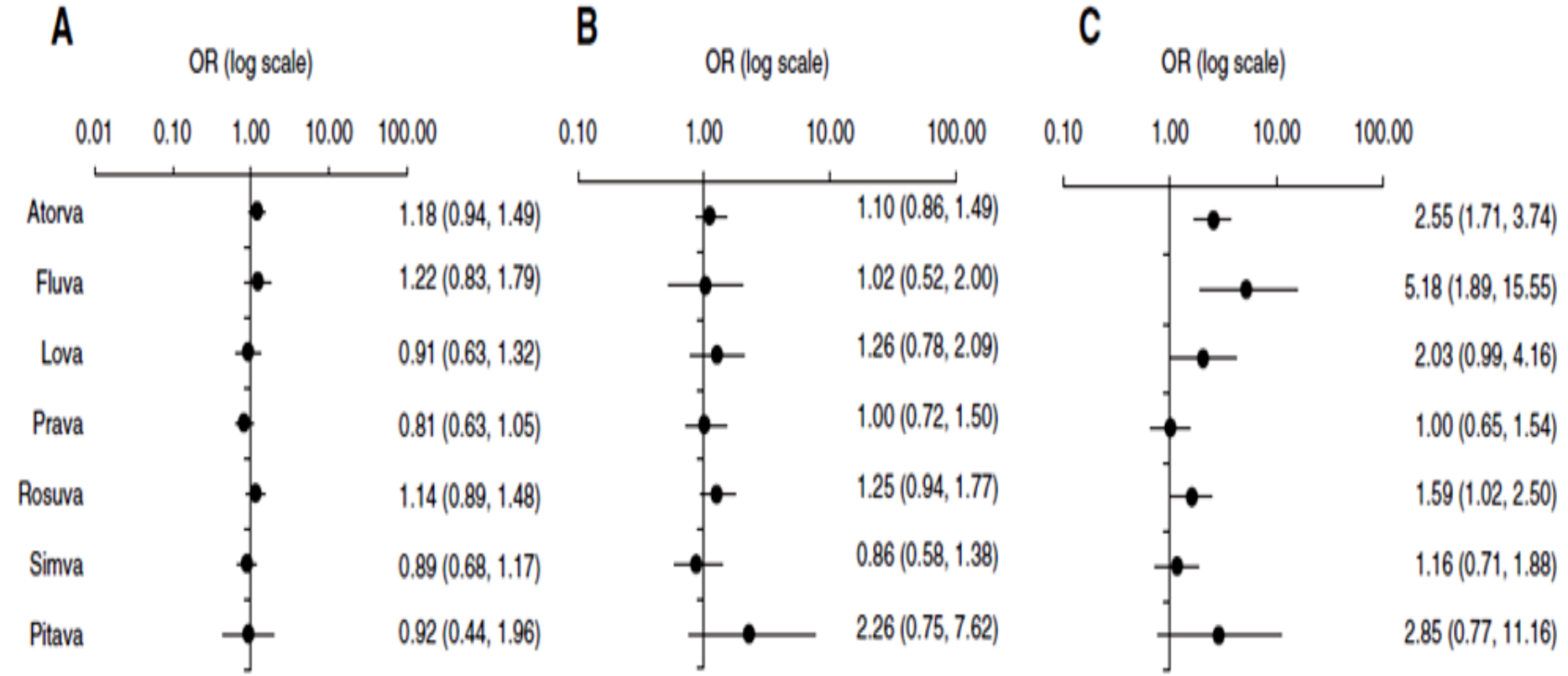
In the drug-level network meta-analysis of individual statins 127,571 participants provided information on 721 individuals with clinically meaningful CK elevations (0.6% of all participants).

According to the findings of the network meta-analysis including 84,391 participants with 1,986 clinically meaningful myalgia events (2% of all participants)

Rare-very rare: Cataract, fractures, recent memory loss, arthritis

Naci H, Brugts J, Ades T. **Comparative tolerability and harms of individual statins: a study-level network meta-analysis of 246 955 participants from 135 randomized, controlled trials.** Circulation Cardiovasc Qual Outcomes 2013;6:390-9.

Ανεπιθύμητες ενέργειες των στατινών



Naci H, Brugts J, Ades T. **Comparative tolerability and harms of individual statins: a study-level network meta-analysis of 246 955 participants from 135 randomized, controlled trials.** Circulation Cardiovasc Qual Outcomes 2013;6:390-9.

Ανεπιθύμητες ενέργειες των στατινών

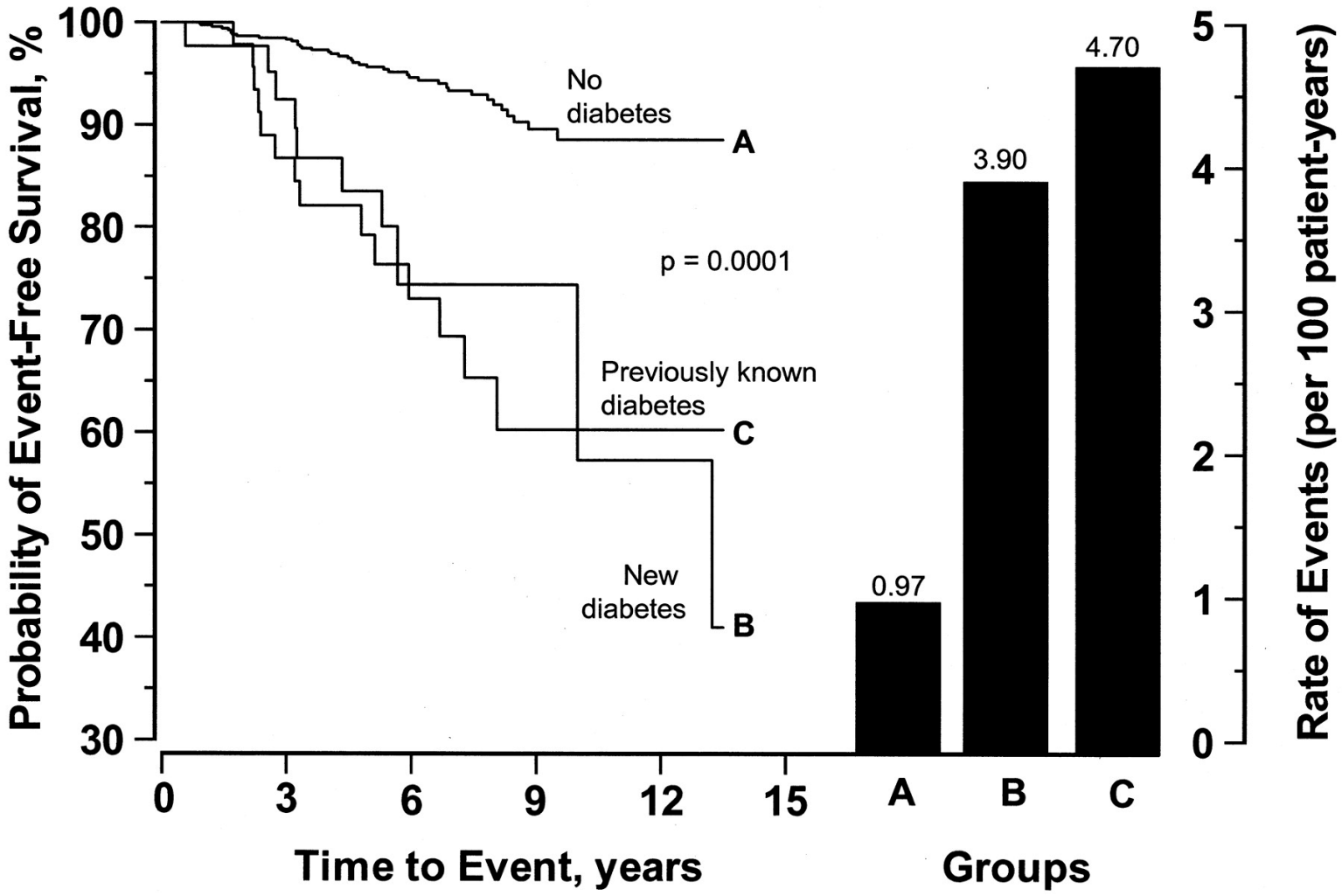
Meta-analysis of 13 statin trials with 91,140 participants, of whom 4,278 (2,226 assigned statins and 2,052 assigned control treatment) developed new onset diabetes (NOD) during a mean of 4 years.

Statin therapy was associated with a 9% increased risk for incident diabetes (odds ratio [OR] 1.09; 95% CI 1.02-1.17).

Meta-regression showed that risk of development of diabetes with statins was highest in trials with older participants, but neither baseline body-mass index (BMI) nor change in LDL-cholesterol concentrations accounted for residual variation in risk.

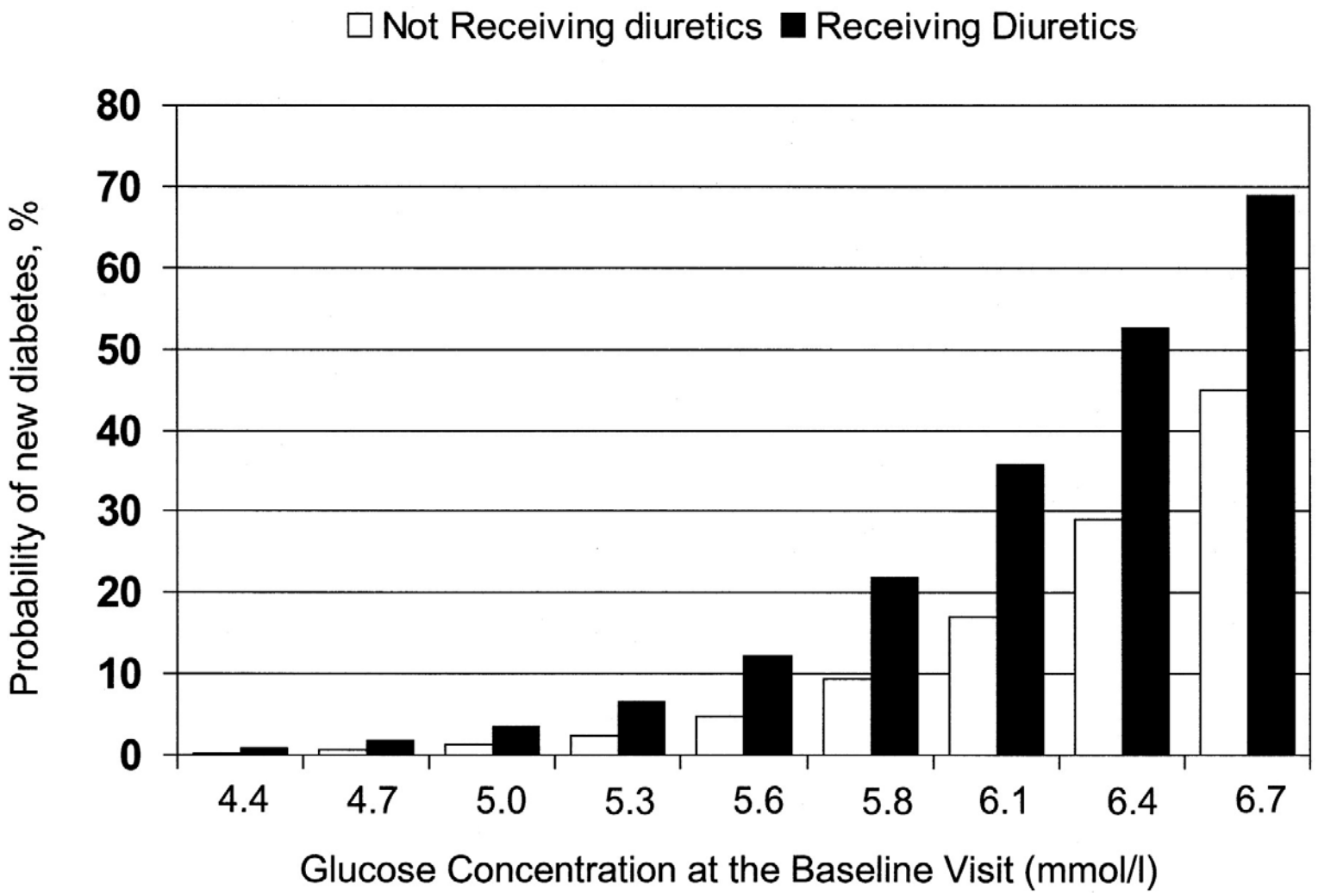
Sattar N, Preiss D, Murray HM, et al. **Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials.** Lancet 2010;375(9716):735-42

Figure 3. Cardiovascular events in treated hypertensive subjects without diabetes (group A), new-onset diabetes (group B), and previously known diabetes (group C).



Verdecchia P et al. Hypertension. 2004;43:963-969

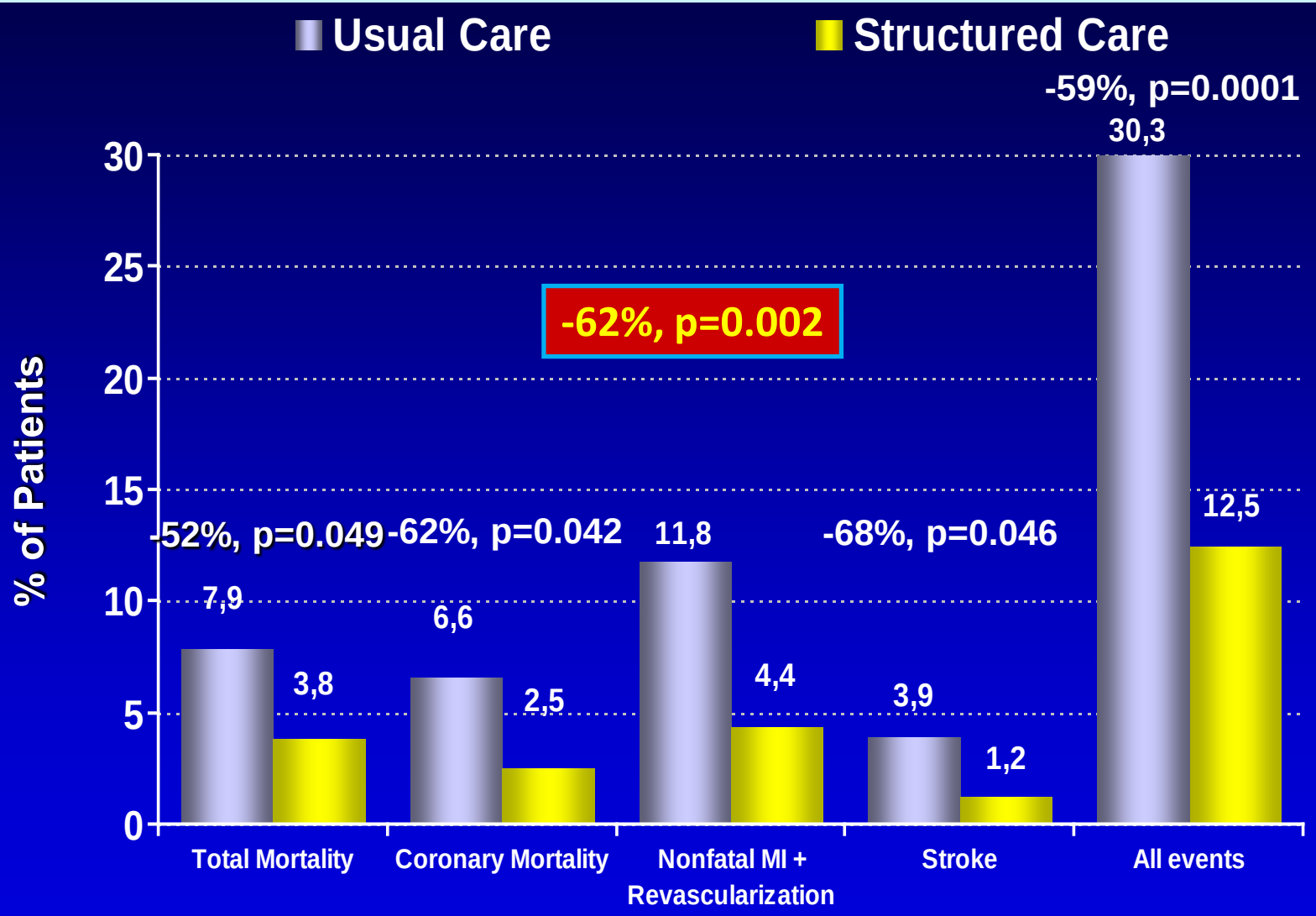
Figure 2. Probability of new diabetes in relation to baseline glucose concentration and treatment with a diuretic.



Verdecchia P et al. Hypertension. 2004;43:963-969

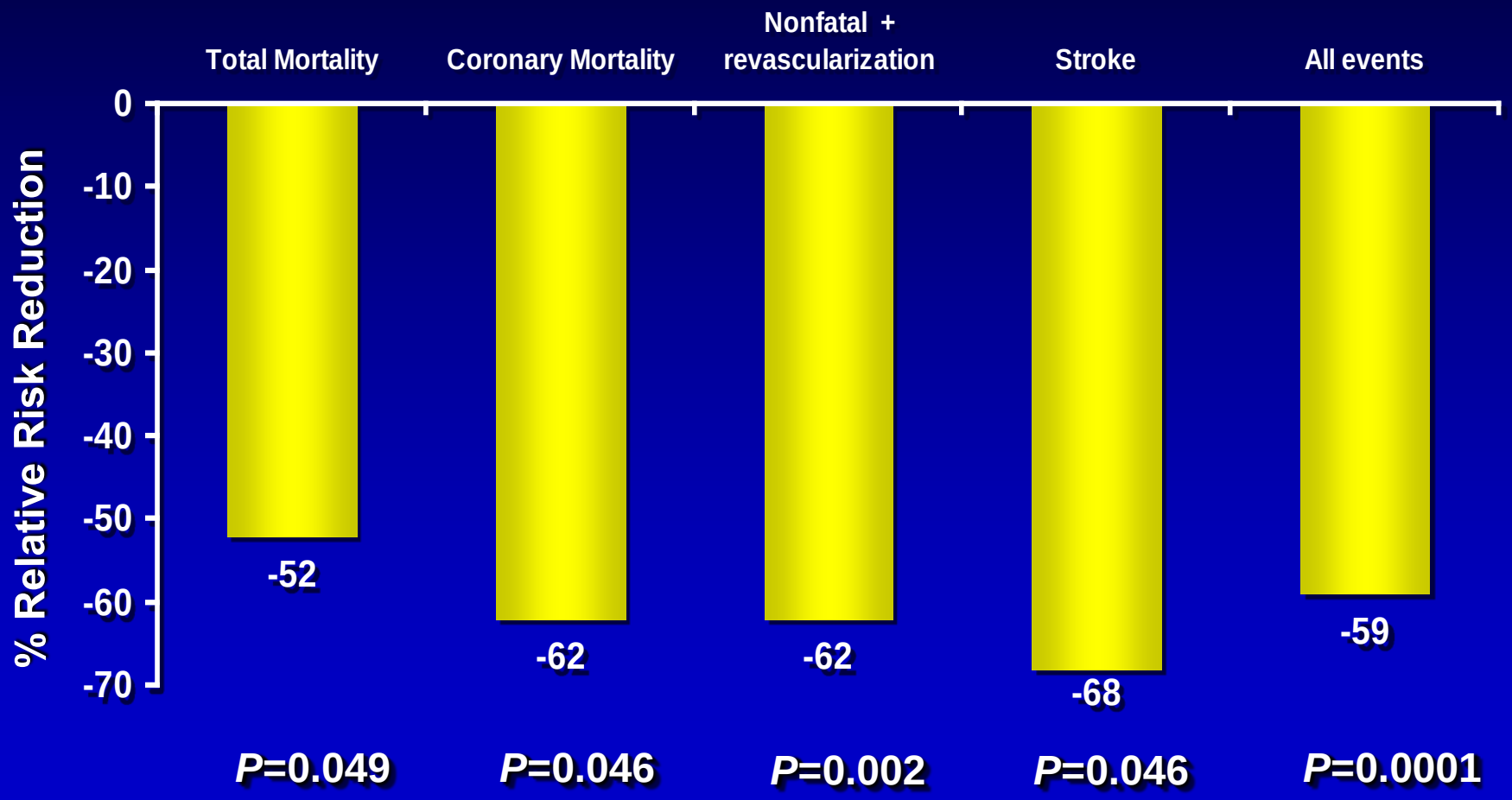
American Heart Association.

Patients with DM Primary Endpoints : 3-year Mortality and Morbidity rates



Athyros et al Jurnal of Cardiovascular Risk 2003 (in press).

Τελικά σημεία σε διαβητικούς ασθενείς : 3-ετής ΕΣΚ νοσηρότητας και θνητότητας



Athyros VG, et al. *Angiology* 2003;54:679-90.

Cai R, et al. Lower Intensified Target LDL-c Level of Statin Therapy Results in a Higher Risk of Incident Diabetes: A Meta-Analysis of 14 RCT 95,102 non-diabetic participants. PLoS One 2014 Aug 14;9:e104922.

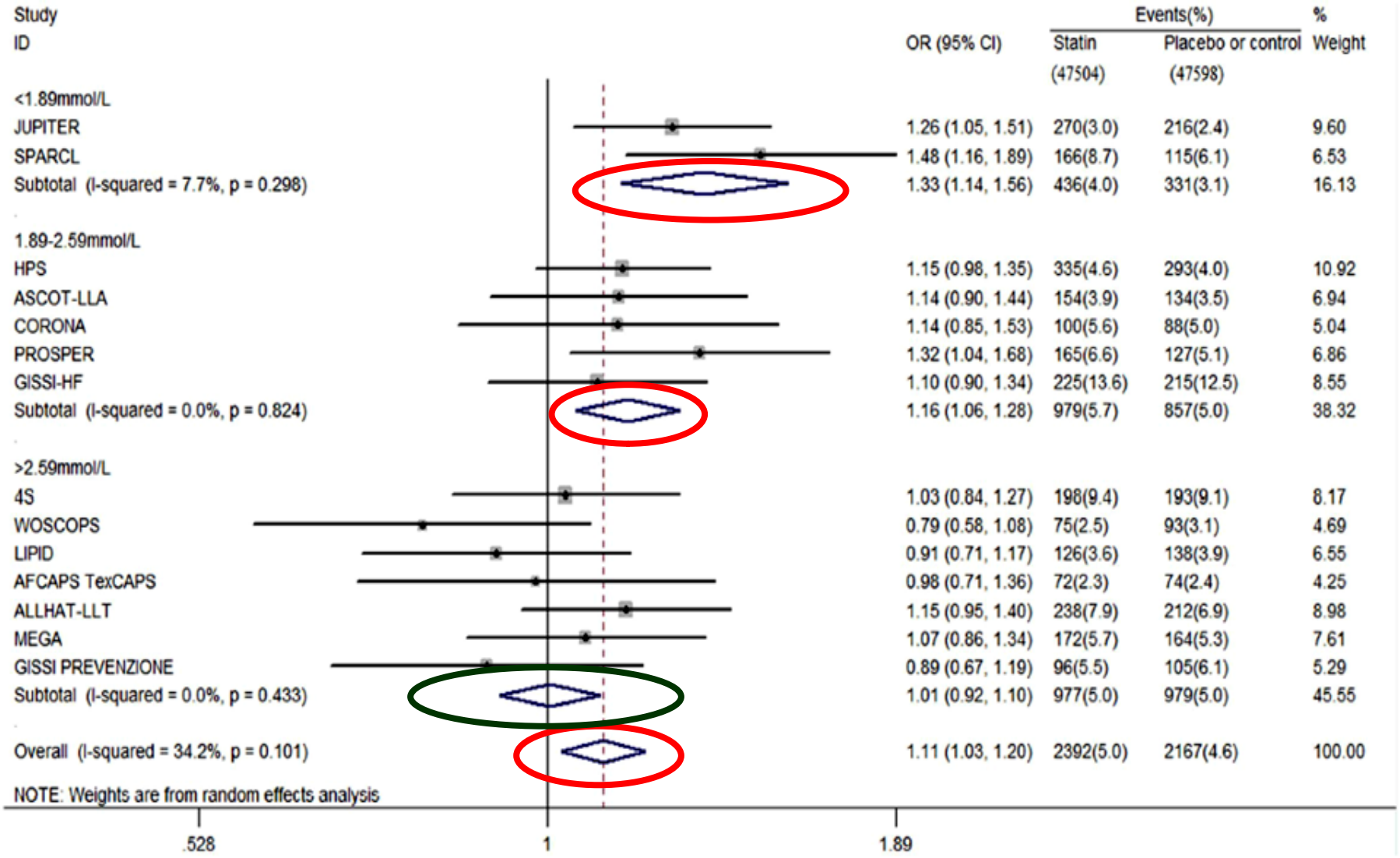


Figure 2. Association between different target LDL-c level and incident diabetes.

Cai R, et al. Lower Intensified Target LDL-c Level of Statin Therapy Results in a Higher Risk of Incident Diabetes: A Meta-Analysis of 14 RCT 95,102 non-diabetic participants. PLoS One 2014 Aug 14;9:e104922.

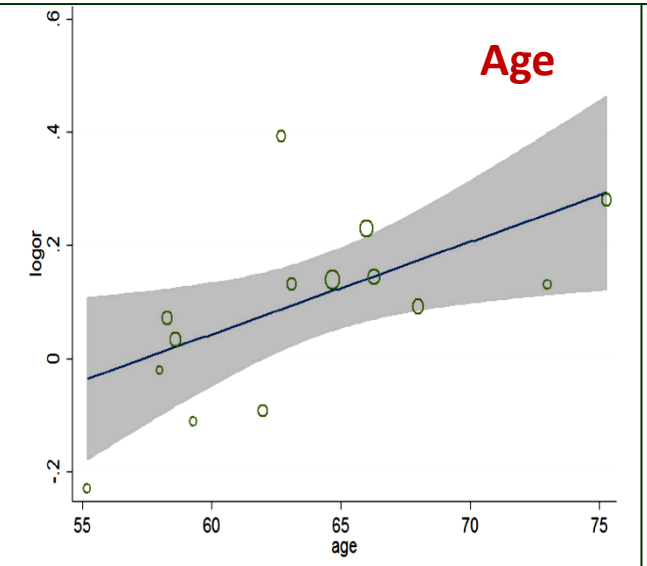


Figure 4. Meta-regression of baseline age for incident diabetes.

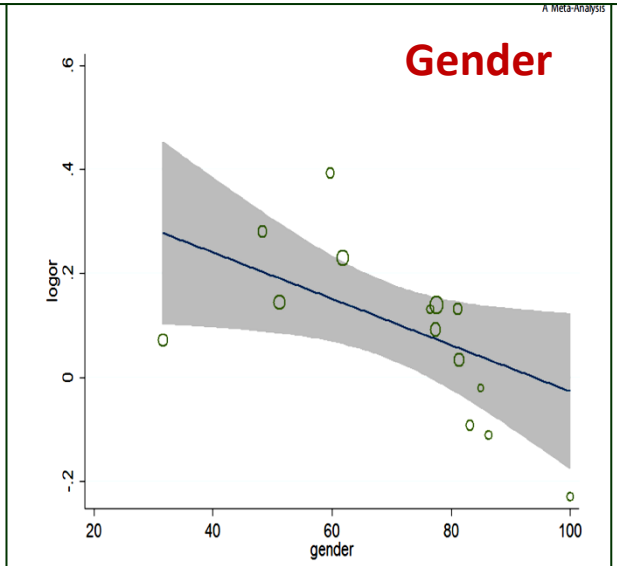


Figure 5. Meta-regression of gender for incident diabetes.

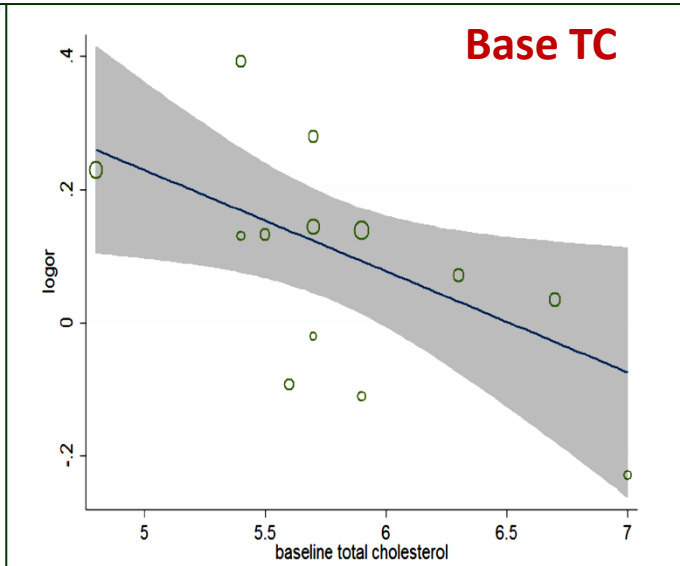


Figure 6. Meta-regression of baseline cholesterol for incident diabetes.

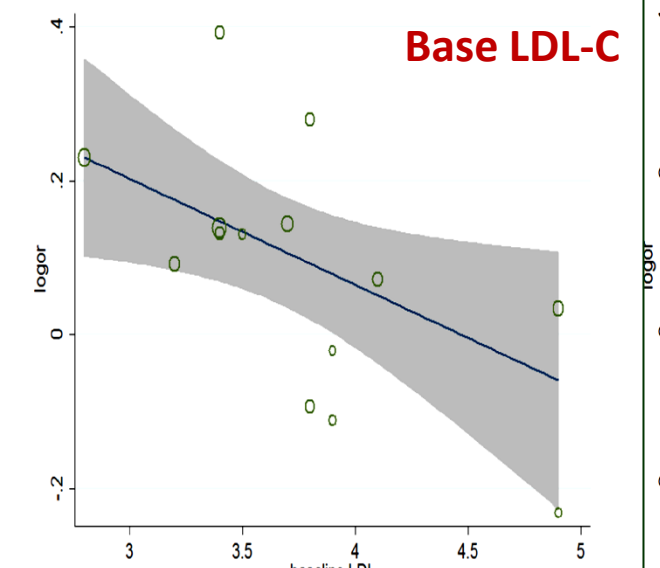
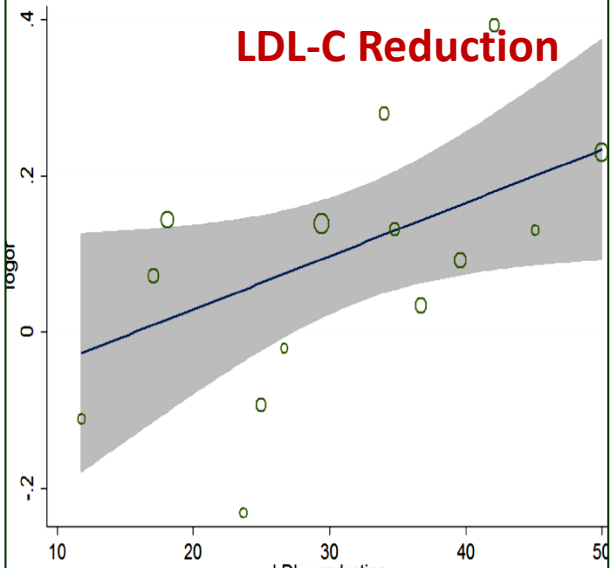


Figure 7. Meta-regression of baseline LDL for incident diabetes.



9. Meta-regression of LDL reduction for incident diabetes.

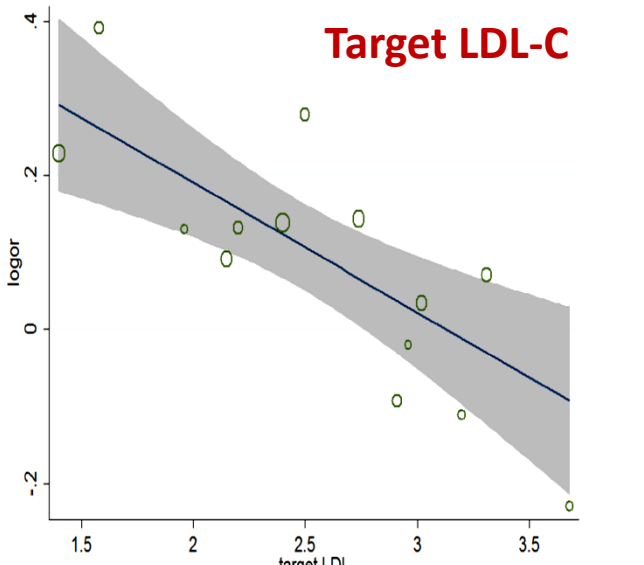


Figure 8. Meta-regression of target LDL for incident diabetes.

LDLR, SREBS, statin potency, increased NOD

The **prevalence of NOD is significantly lower in familial hypercholesterolemia (FH)** patients (n=14,296) compared with their unaffected relatives (n=24,684). For **receptor-negative and receptor-defective low density lipoprotein receptor (LDLr) mutations, the odds ratio was 0.35 (0.27-0.45) and 0.51 (0.42-0.62)** (p for trend <0.001)

In contrast, statins increase LDLr numbers through **activation of SREBPs 1a, 1c, and 2,6 which are also causally related to insulin resistance**. Thus, the more potent the statin, the greater the increase in SREBPs and LDLr as well as the plasma LDL cholesterol (LDL-C) reduction; however, the "cost" may be in terms of insulin resistance and a higher incidence of NOD.

Athyros VG, Katsiki N, Karagiannis A, Mikhailidis DP. Statin Potency, LDL Receptors and New Onset Diabetes. Curr Vasc Pharmacol 2014 Aug 19. [Epub ahead of print]

LDLR, SREBS, statin potency, increased NOD

Thus, the **stronger the statin, the greater the LDL-C reduction might result in increased NOD**.

Cardiovascular benefit from statin treatment overweighs the diabetes risk, NOD should be considered to weigh the pros and cons when LDL-c reaches a lower level, e.g., less than 1.8 mmol/L, **especially in primary prevention low-risk patients**.

Athyros VG, Katsiki N, Karagiannis A, Mikhailidis DP. Statin Potency, LDL Receptors and New Onset Diabetes. Curr Vasc Pharmacol 2014 Aug 19. [Epub ahead of print]

Μικρότερη συχνότητα μικροαγγειαπαθητικών επιπλοκών στους χρήστες στατινών που αναπτύσσουν διαβήτη

During 215,725 person-years of follow-up,
statin users, compared with non-statin users,
had **a lower cumulative incidence of**
diabetic retinopathy (HR 0.60, 95% CI 0.54-0.66; p<0.0001),
diabetic neuropathy (0.66, 0.57-0.75; p<0·0001),
and **gangrene** of the foot (0.88, 0.80-0.97; p=0·010),
but not diabetic nephropathy (0.97, 0.85-1.10; p=0·62).

Nielsen SF, Nordestgaard BG**. Statin use before diabetes diagnosis and risk of microvascular disease: a nationwide nested matched study.** The Lancet Diabetes & Endocrinology, Sep 2014

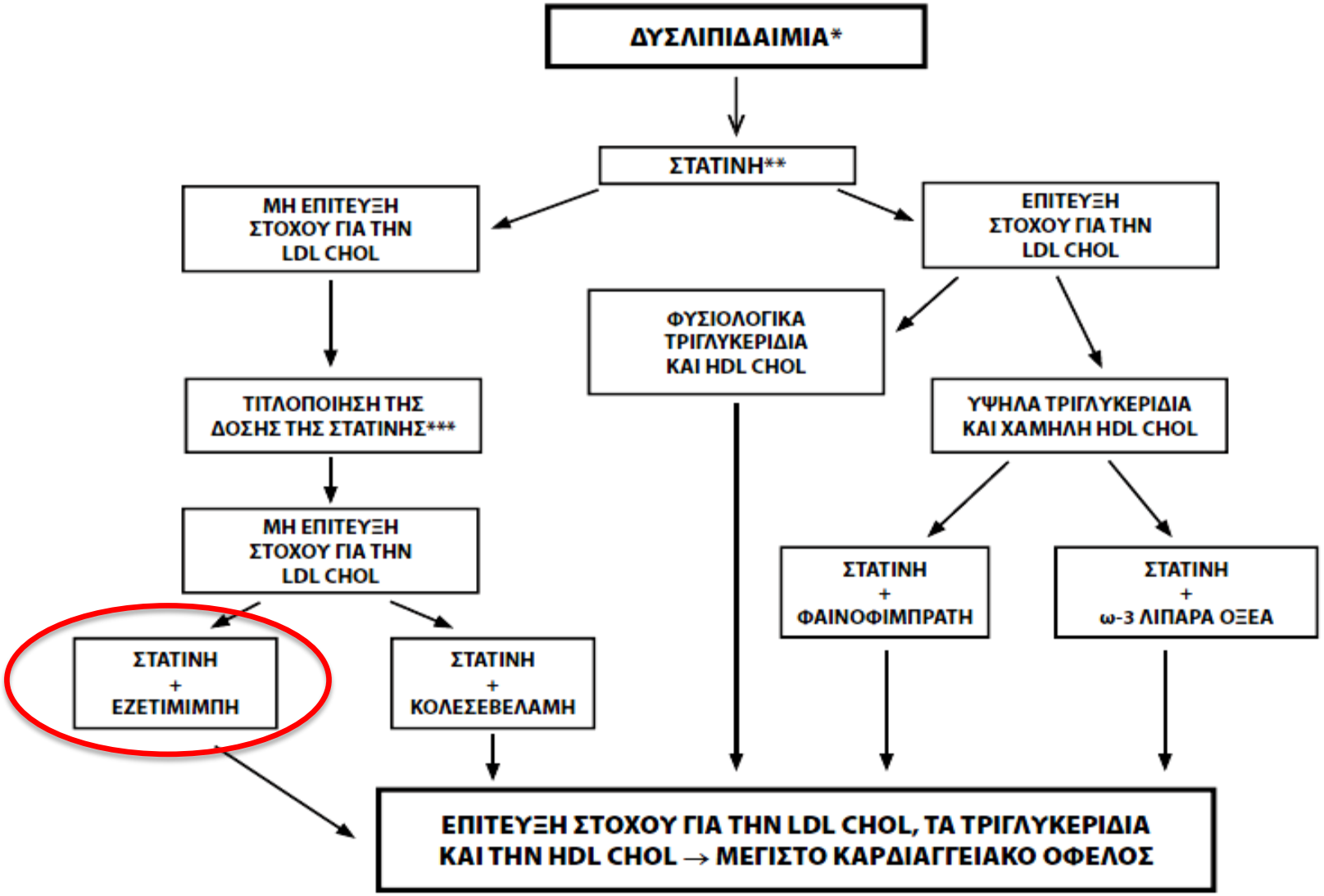
Μικρότερη συχνότητα μικροαγγειαπαθητικών επιπλοκών στους χρήστες στατινών που αναπτύσσουν διαβήτη

For every 1000 primary prevention patients randomized to statin,
5 patients developed NOD,
5 patients were saved from death,
10 from nonfatal myocardial infarction, and
6 from stroke.

Some people find this a good deal, but others are cautious because of the justified fear of diabetes.

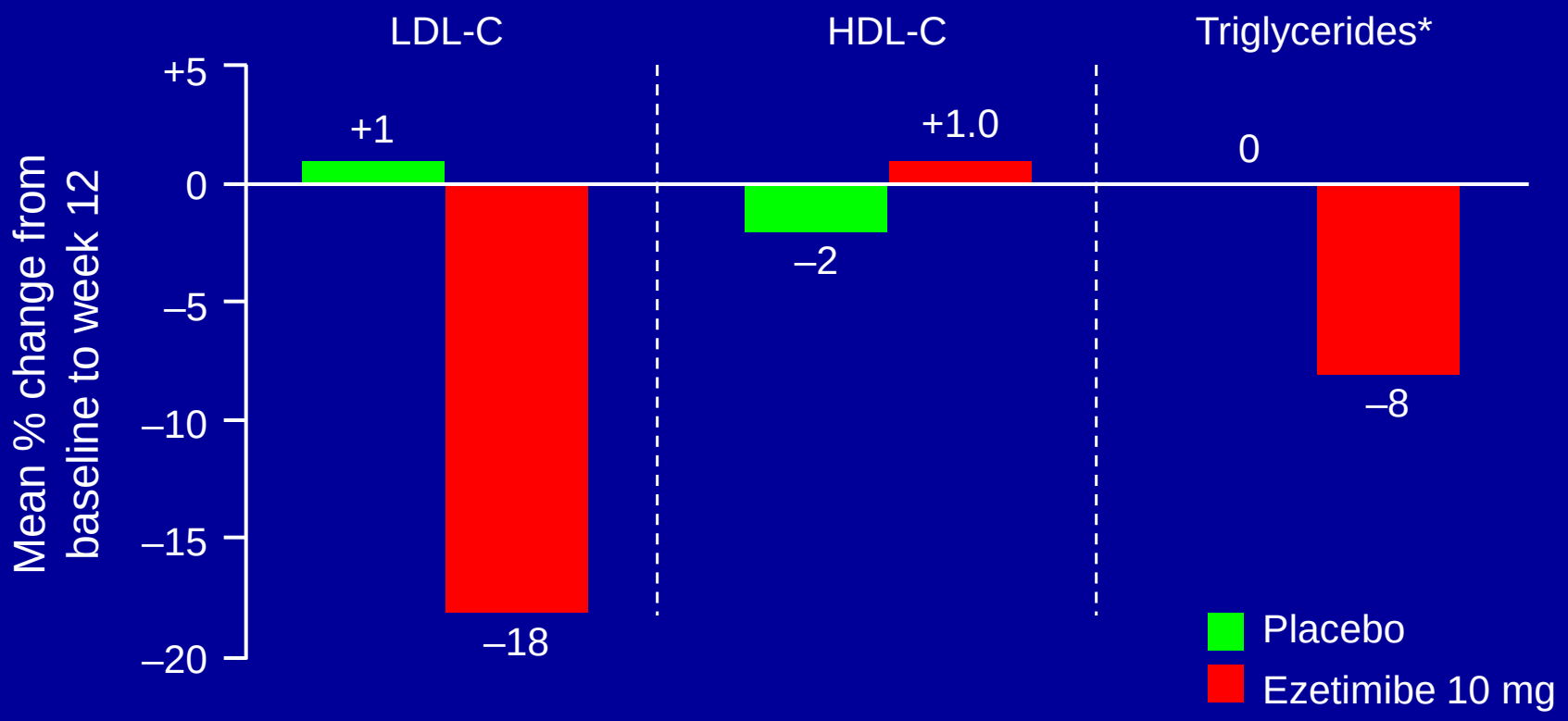
Nielsen SF, Nordestgaard BG**. Statin use before diabetes diagnosis and risk of microvascular disease: a nationwide nested matched study.** The Lancet Diabetes & Endocrinology, Sep 2014

Θεραπευτικός αλγόριθμος δυσλιπιδαιμιών (2014)



Η στατίνη αποτελεί το υπολιπιδαιμικό φάρμακο εκλογής

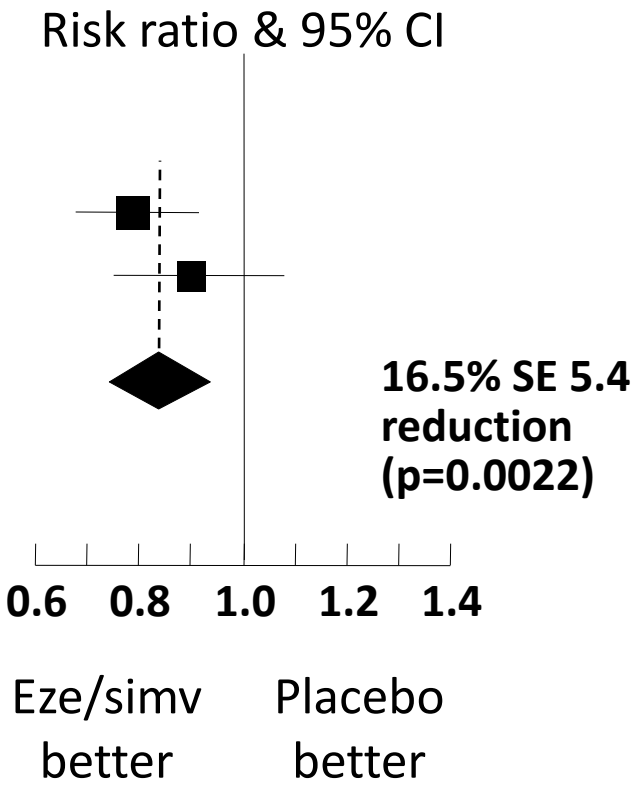
Ezetimibe: Efficacy at Reducing LDL



SHARP: Major Atherosclerotic Events by renal status at randomization

	Eze/simv (n=4650)	Placebo (n=4620)
Non-dialysis (n=6247)	296 (9.5%)	373 (11.9%)
Dialysis (n=3023)	230 (15.0%)	246 (16.5%)
Major atherosclerotic event	**526 (11.3%)**	**619 (13.4%)**

No significant heterogeneity between non-dialysis and dialysis patients (p=0.25)



SHARP
STUDY OF HEART AND RENAL PROTECTION

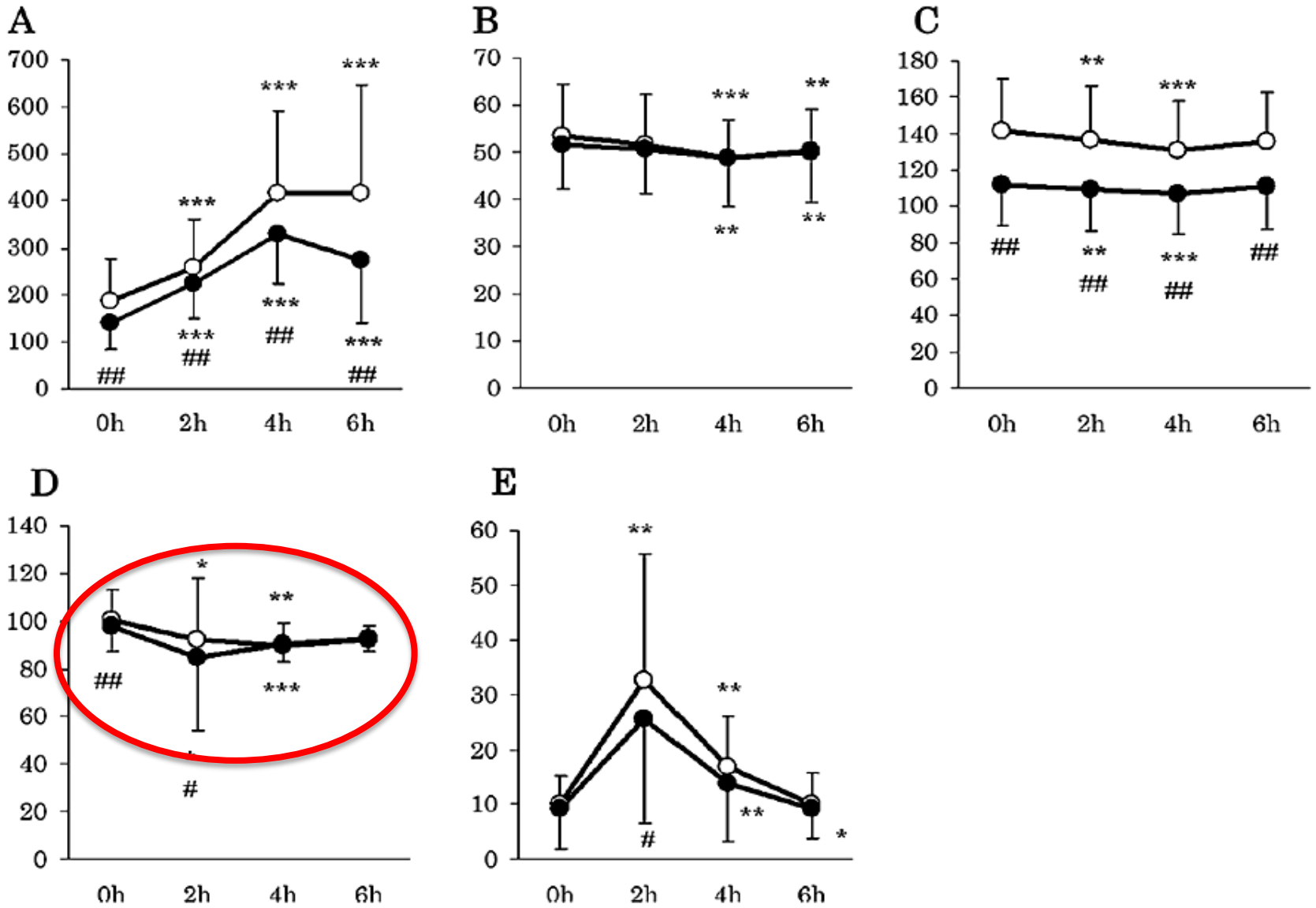
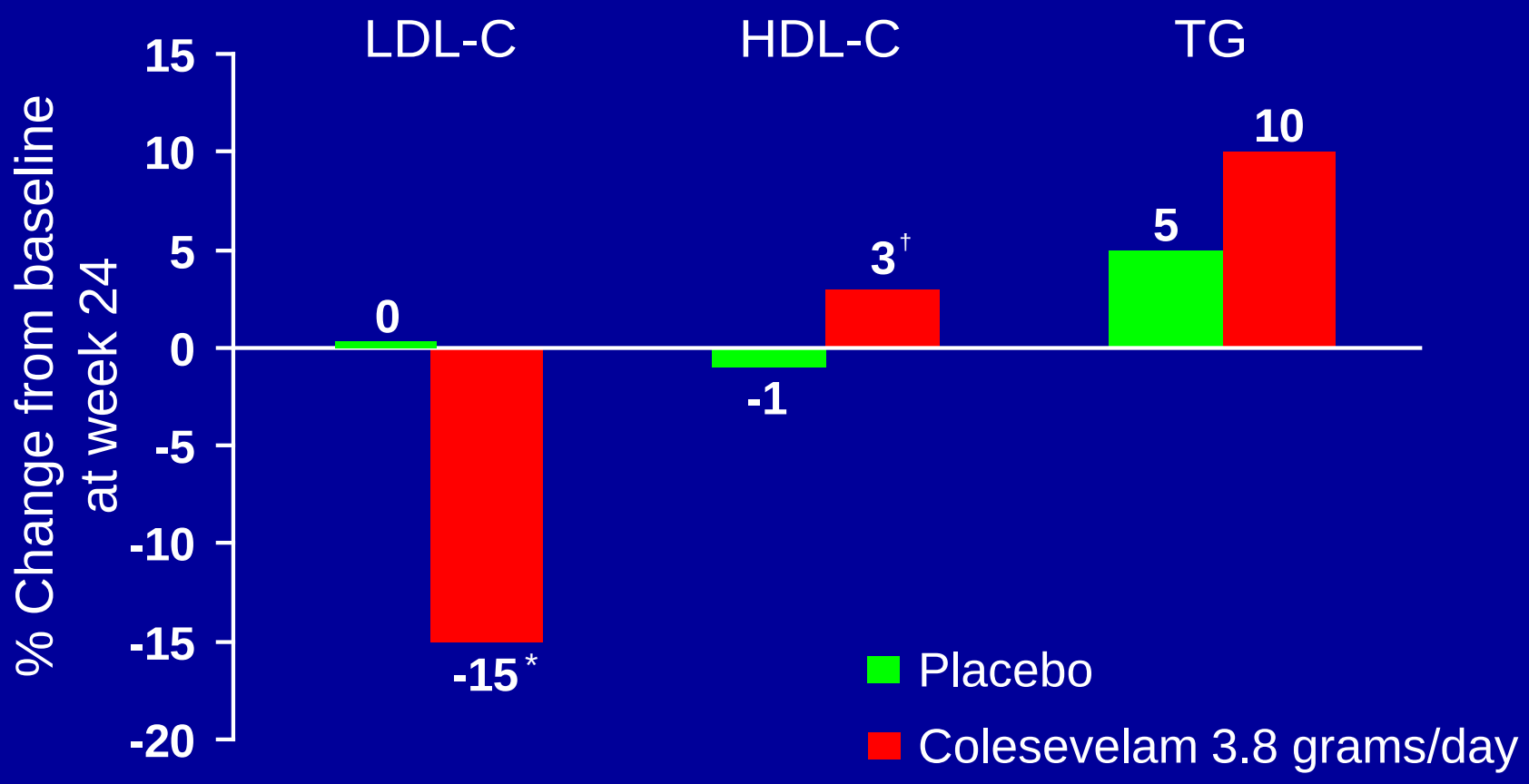


Fig. 1. Effects of the test meal before (open circles) and after (solid circles) ezetimibe treatment. The subjects ($n = 20$) received a high-fat and high-glucose meal (1001 kcal, protein 31.6 g, fat 61.4 g, carbohydrate 79.8 g, cholesterol 299 mg) before and after the treatment with ezetimibe. Blood samples were obtained while fasting and 2, 4, and 6 h after the test meal. (A) Triglycerides; (B) high-density lipoprotein cholesterol; (C) low-density lipoprotein cholesterol; (D) blood glucose; and (E) insulin. The Bonferroni *t*-test was used to compare before and after the test meal ($^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$). The paired *t*-test was employed to compare before and after treatment with ezetimibe ($\#p < 0.05$; $\#\#p < 0.01$; $\#\#\#p < 0.001$).

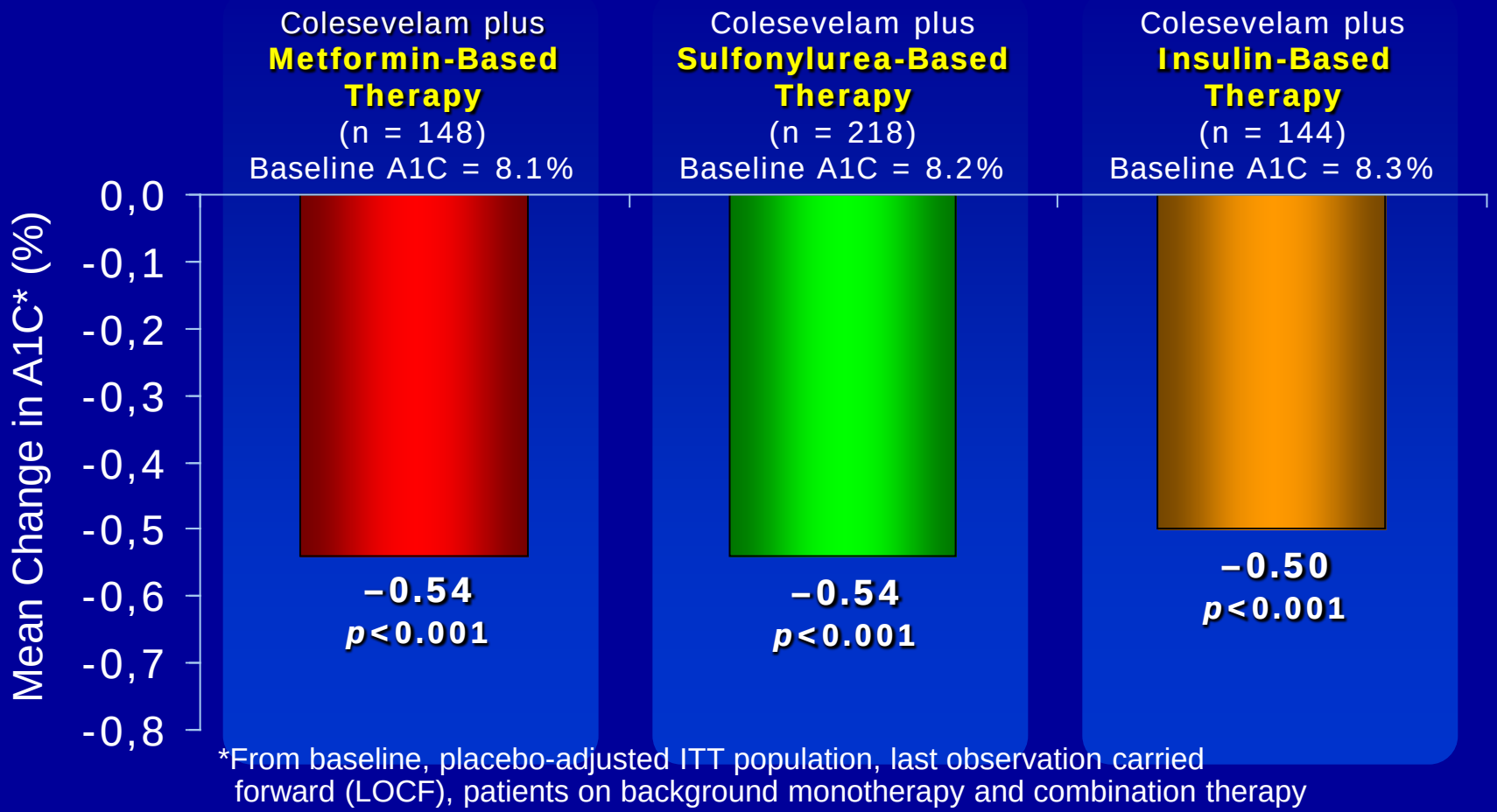
Bile Acid Sequestrant: Efficacy at Reducing LDL-C



*P<0.001 vs placebo
†P=0.04 vs placebo

Insull W et al. *Mayo Clin Proc* 2001;76:971-82

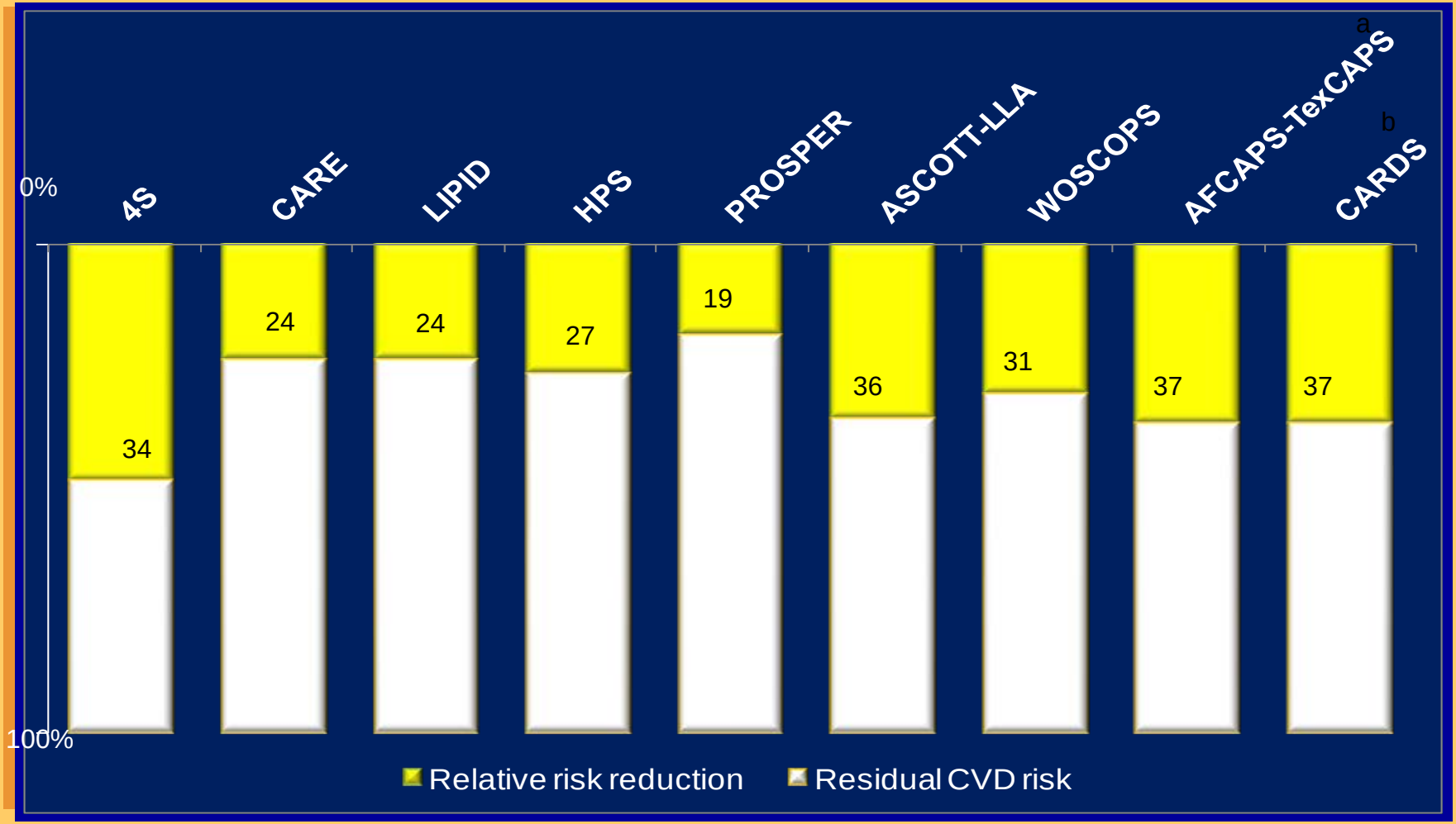
Colesevelam Consistently Lowers A1C by an Additional Mean 0.5%



*From baseline, placebo-adjusted ITT population, last observation carried forward (LOCF), patients on background monotherapy and combination therapy

Bays HE et al. *Arch Intern Med.* 2008;168:1975-1983 | Fonseca VA et al. *Diabetes Care.* 2008;31:1479-1484 | Goldberg RB et al. *Arch Intern Med.* 2008;168:1531-1540.

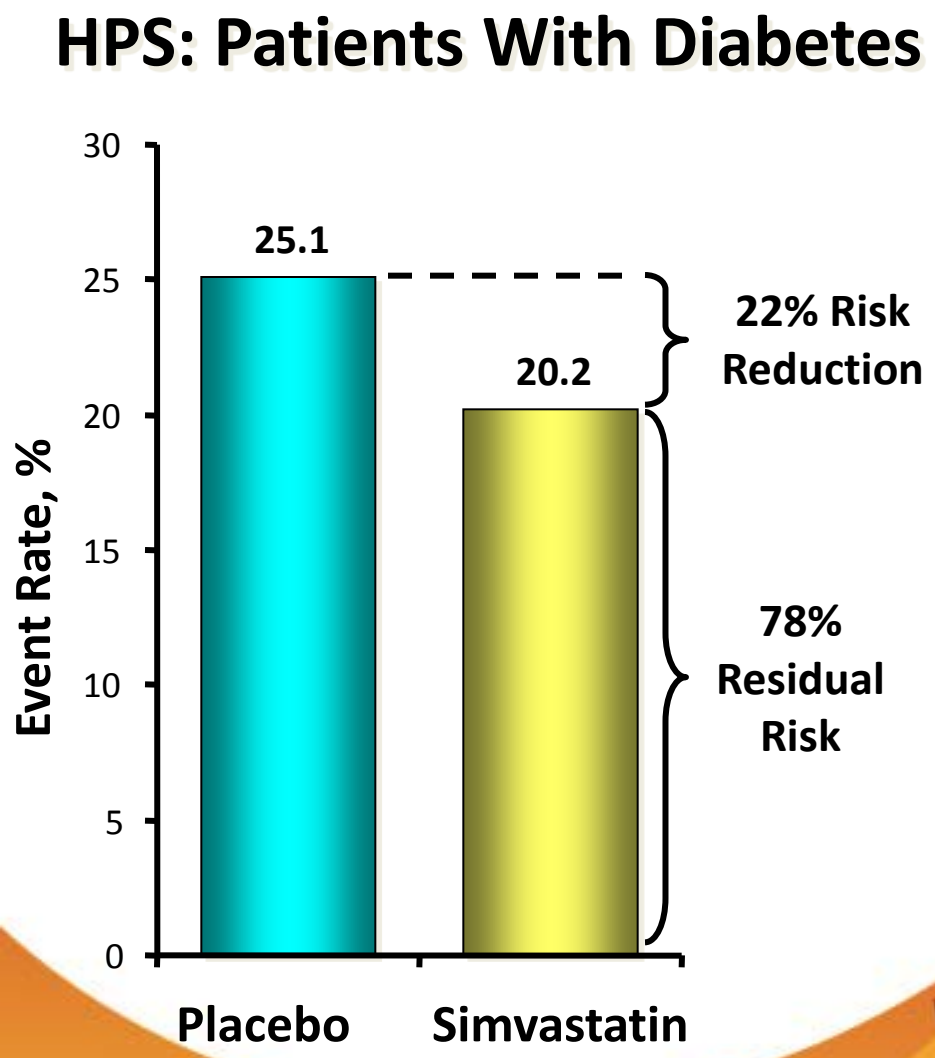
Καρδιαγγειακός κίνδυνος στα αποτελέσματα των κλινικών μελετών με στατίνες

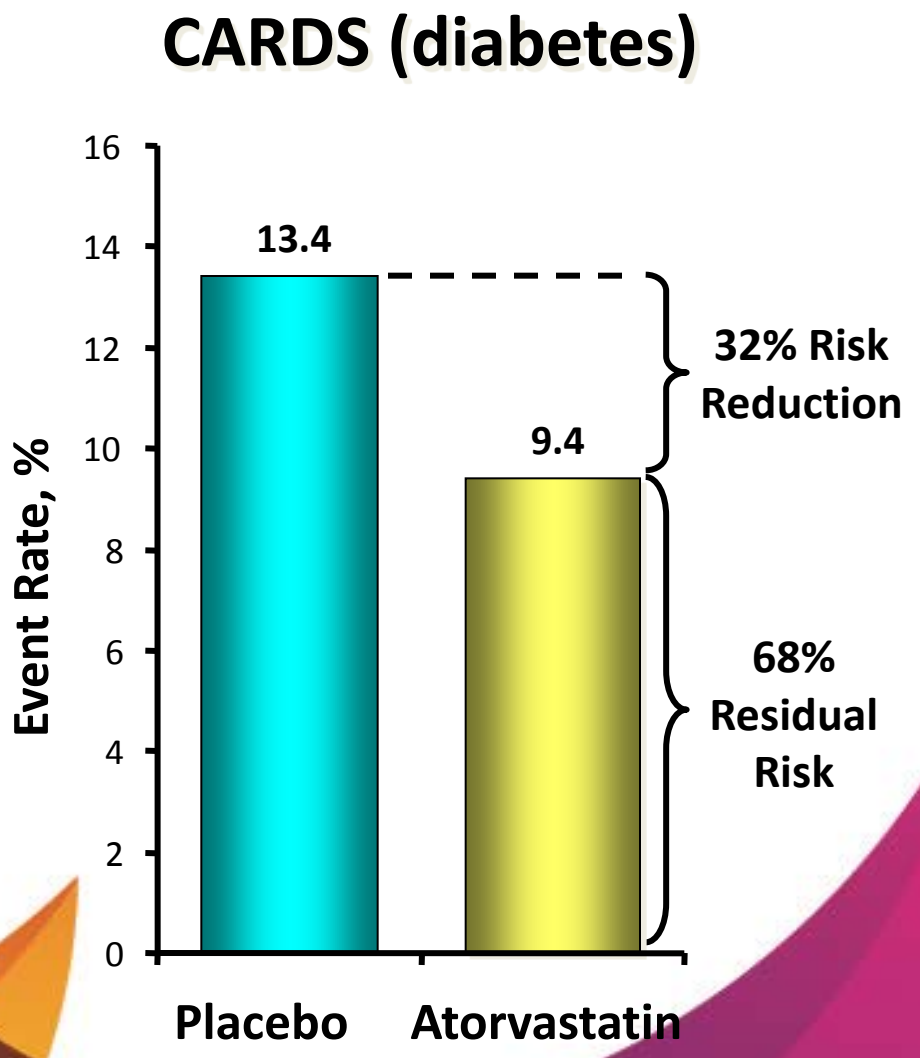


Endpoint : nonfatal MI or CHD death, major coronary events, major cardiovascular events

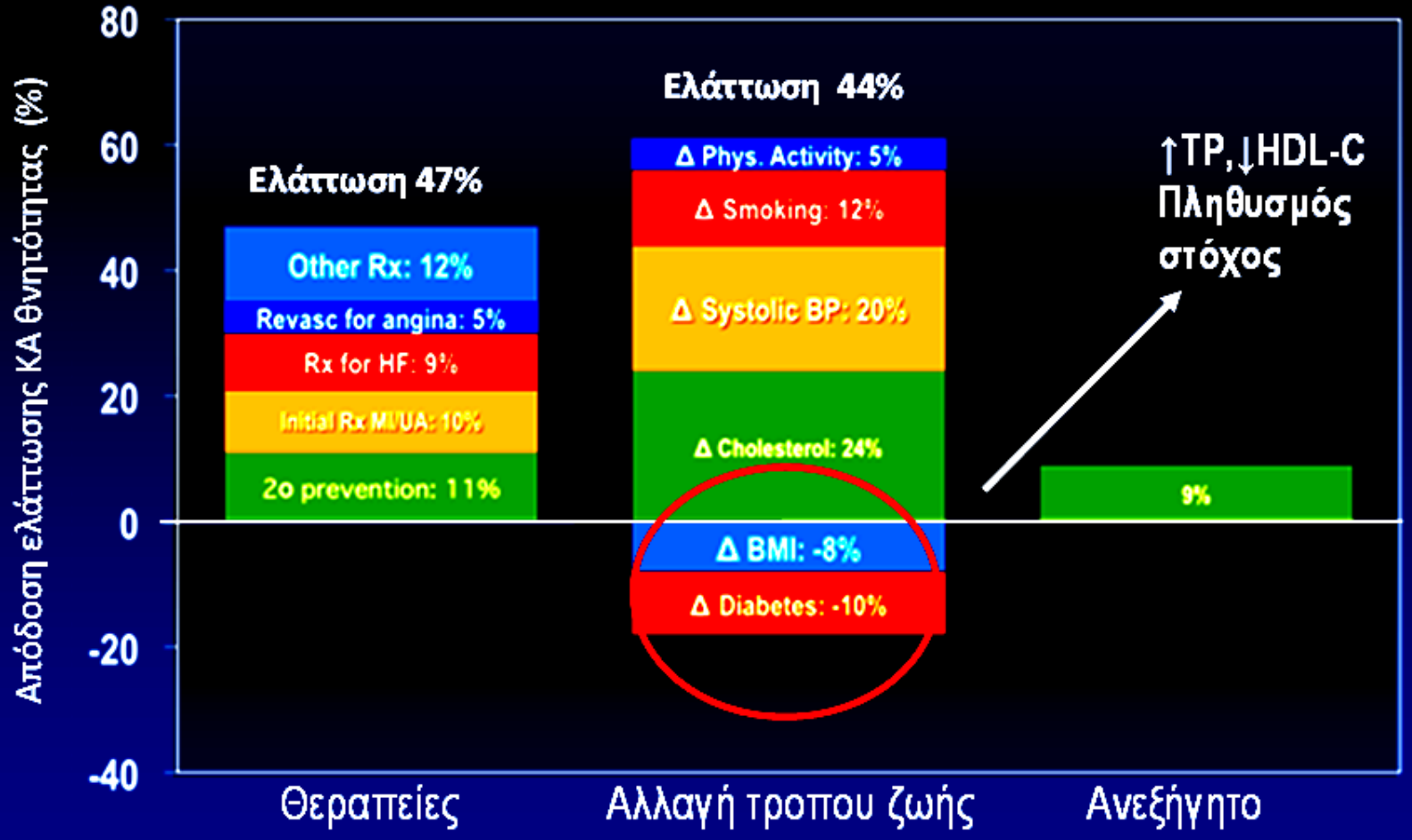
Adapted from Fruchart et al. Am J Cardiol 2008; 102(Suppl.): 1K-34K

Υπολειπόμενος καρδιαγγειακός κίνδυνος σε μελέτες με στατίνες σε διαβητικούς





Αιτίες ελάττωσης των Καρδιαγγειακών Θανάτων στις ΗΠΑ μεταξύ 1980 και 2000



Ford ES et al. N Engl J Med. 2007;356:2388-2398.

Ελληνική Επιθεώρηση Αθηροσκλήρωσης 5(3):151–163 Hellenic Journal of Atherosclerosis 5(3):151–163

Αναθεωρημένες κατευθυντήριες οδηγίες της Ελληνικής Εταιρείας Αθηροσκλήρωσης για τη διάγνωση και αντιμετώπιση των δυσλιπιδαιμιών-2014

Updated guidelines of the Hellenic Society of Atherosclerosis for the diagnosis and treatment of dyslipidemia-2014

Μ. Ελισάφ,[1] Χρ. Πίτσαβος,[2] Ευ. Λυμπερόπουλος,[3] Κ. Τζιόμαλος,[4] Β. Άθυρος[5]

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[2]Καθηγητής Καρδιολογίας, Ιατρική Σχολή, Πανεπιστήμιο Αθηνών, Αθήνα,
[3]Επίκουρος Καθηγητής Παθολογίας, Ιατρική Σχολή, Πανεπιστήμιο Ιωαννίνων, Ιωάννινα,
[4]Επίκουρος Καθηγητής Παθολογίας, Ιατρική Σχολή, Αριστοτέλειο Πανεπιστήμιο, Θεσσαλονίκης, Θεσσαλονίκη,
[5]Αναπληρωτής Καθηγητής Παθολογίας, Ιατρική Σχολή, Αριστοτέλειο Πανεπιστήμιο Θεσσαλονίκης, Θεσσαλονίκη

M. Elisaf,[1] Chr. Pitsavos,[2] Ev. Liberopoulos,[3] K. Tziomalos,[4] V. Athyros[5]

[1]Professor of Medicine, Medical School, University of Ioannina, Ioannina,
[2]Professor of Cardiology, Medical School, University of Athens, Athens,
[3]Assistant Professor of Medicine, Medical School, University of Ioannina, Ioannina,
[4]Assistant Professor of Medicine, Medical School, Aristotle University of Thessaloniki, Thessaloniki,
[5]Associate Professor of Medicine, Medical School Aristotle University of Thessaloniki, Thessaloniki, Greece

Hellenic Journal of Atherosclerosis 2014;5(3):151–163

2014 HAS Lipid Guidelines

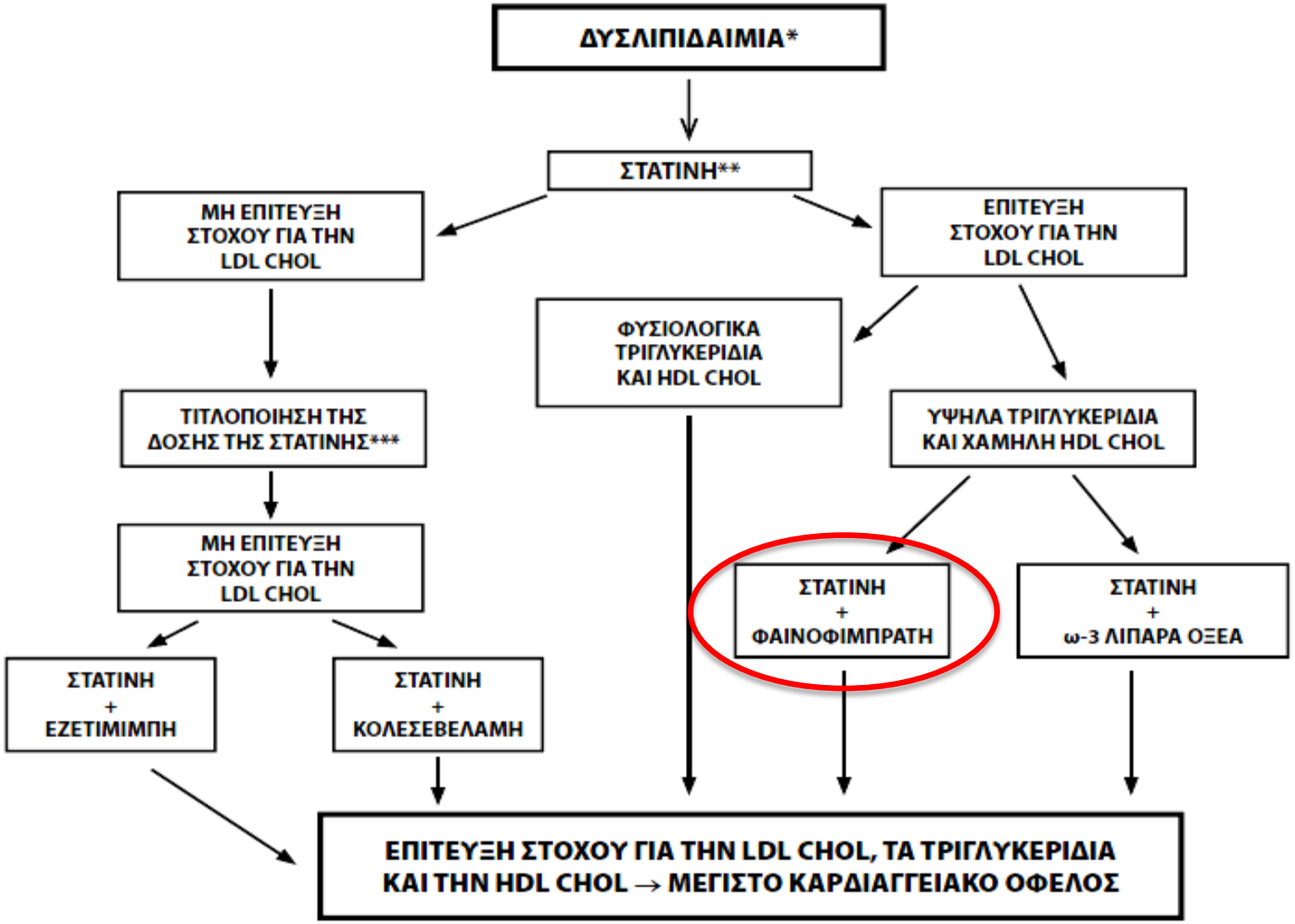
LDL-C remains the main target with specific goals

Treatment targets (LDL-C) according to European Guidelines 2011

Ασθενείς (με βάση τον καρδιαγγειακό τους κίνδυνο)	LDL-C Στόχος
SCORE ≥ 10% (ή εγκατεστημένη ΚΑ νόσο, Διαβήτη τύπου II, Διαβήτη τύπου I με βλάβη σε όργανο στόχο, μέτρια προς σοβαρή χρόνια νεφροπάθεια, πολύ υψηλού κινδύνου)	<70 mg/dL ή/και ≥50% μείωση της LDL-C
5 ≤ SCORE <10% (ή σημαντικά αυξημένα επίπεδα μεμονωμένων παραγόντων κινδύνου, υψηλού κινδύνου)	**<100 mg/dL**
1 ≤ SCORE <5% Μέτριου κινδύνου	**<115 mg/dL**

European Heart Journal (2011) **32**, 1769–1818

Θεραπευτικός αλγόριθμος δυσλιπιδαιμιών (2014)



Η στατίνη αποτελεί το υπολιπιδαιμικό φάρμακο εκλογής

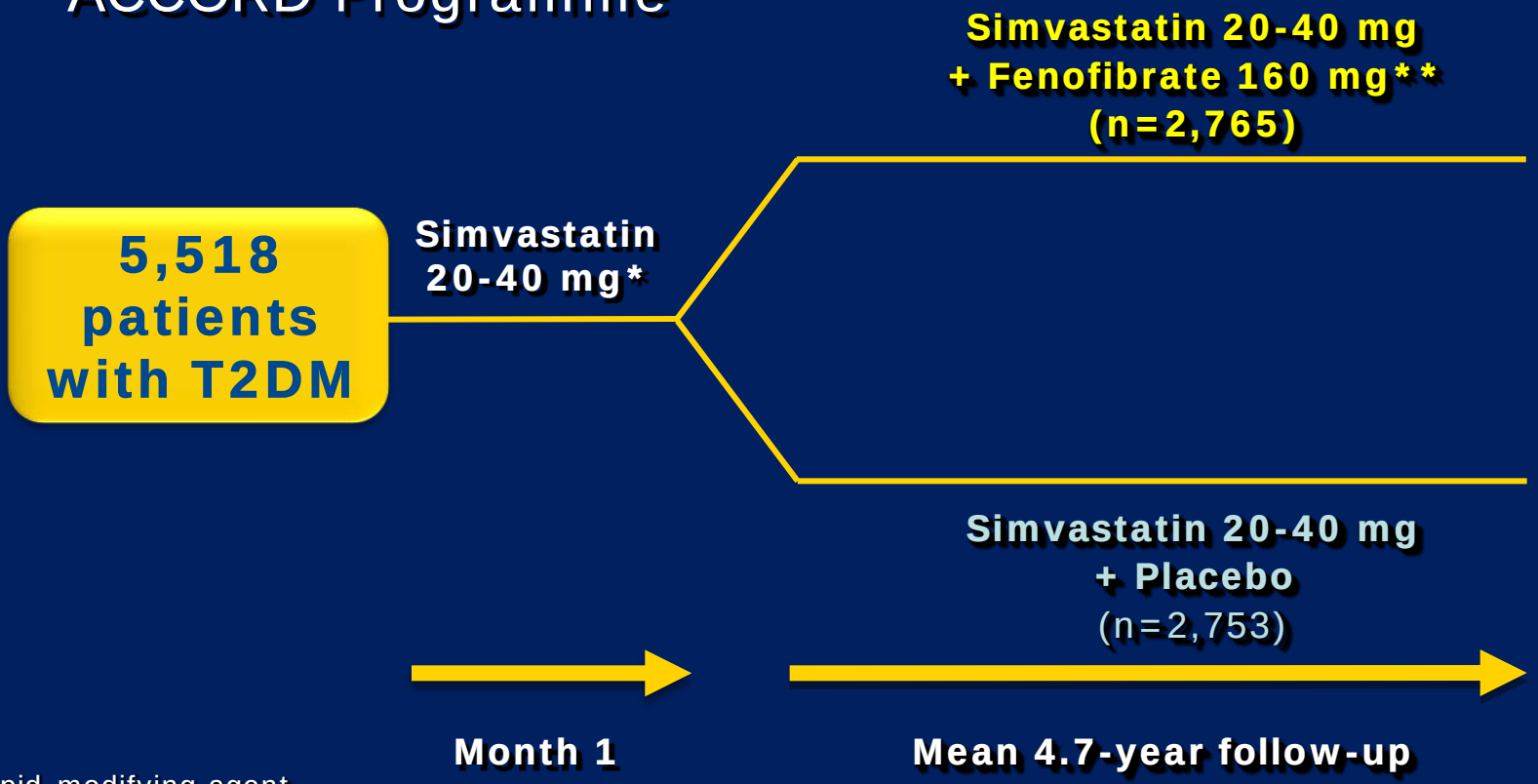
ACCORD Lipid

The Action to Control Cardiovascular Risk in Diabetes Lipid Trial

ACCORD Lipid was sponsored by the NIH. The fenofibrate used for study was provided by Abbott Laboratories.

The first study to evaluate adding an LMA to a statin in patients with T2DM at goal for LDL-C

- The only placebo-controlled, double-blind arm of the ACCORD Programme

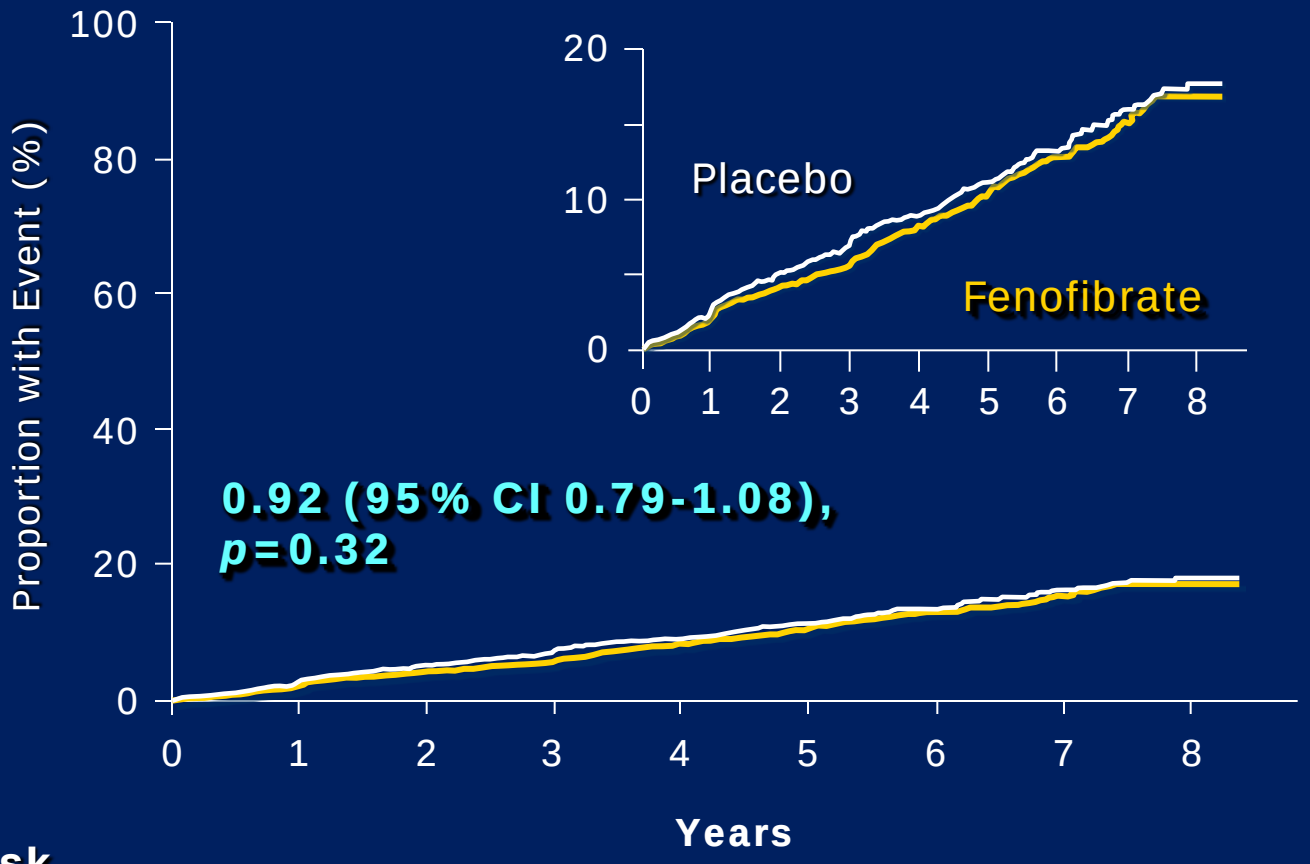


LMA: lipid-modifying agent
*According to patients' LDL-C levels and CVD history
**Bioequivalent to 200 mg micronised and 145 mg nanocrystal. Patients whose eGFR was 30-50 mL/min/1.73 m^2 received a lower dose of fenofibrate, corresponding to 1/3 of the normal daily dose

Ginsberg HN et al. Am J Cardiol 2007;99(12A):56i-67i.
ACCORD Study Group. N Engl J Med. 2010. Epub.

ACCORD Lipid

Primary endpoint
Major CV events (overall population)



No. At Risk

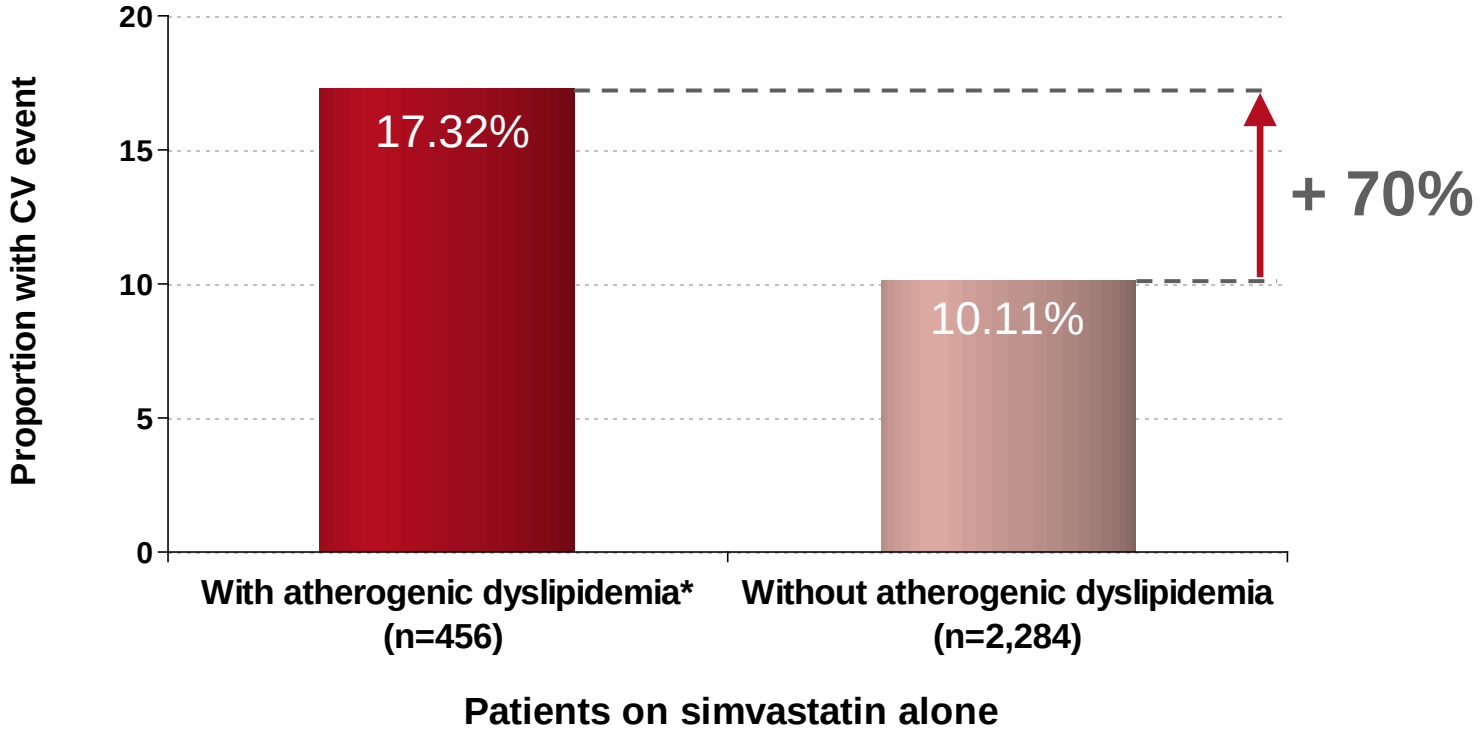
Fenofibrate	2765	2644	2565	2485	1981	1160	412	249	137
Placebo	2753	2634	2528	2442	1979	1161	395	245	131

Major CV events defined as CV death, nonfatal MI and nonfatal stroke

ACCORD Study Group. N Engl J Med March 14, 2010. Epub.

1. ACCORD Lipid results reinforce the residual risk hypothesis

- Despite achieving a mean LDL-C of 80 mg/dL, patients in the atherogenic dyslipidemia* subgroup had a 70% higher rate of major CV events compared to those without atherogenic dyslipidemia



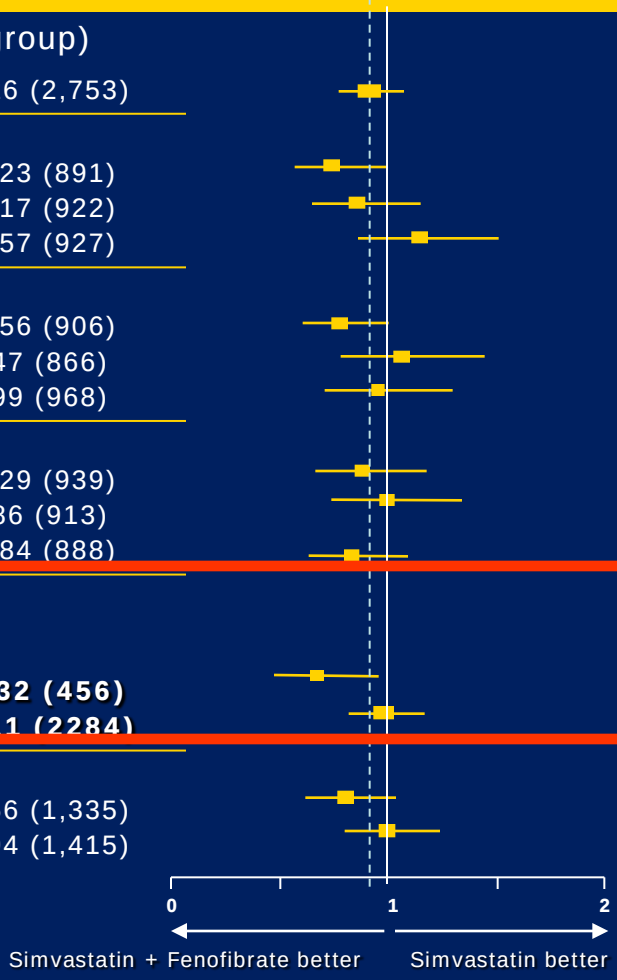
*TG ≥204 mg/dL and HDL-C ≤34 mg/dL

ACCORD Study Group. N Engl J Med March 14, 2010. Epub.

ACCORD Lipid

Primary endpoint in pre-specified subgroups

Subgroup	Simvastatin + Fenofibrate	Simvastatin	Hazard ratio (95% CI)	*P* value for interaction
	% of events (no. in group)			
Overall	10.52 (2,765)	11.26 (2,753)		
LDL cholesterol				
≤84 mg/dl	9.38 (938)	12.23 (891)		
85-111 mg/dl	9.85 (934)	11.17 (922)		
≥112 mg/dl	12.43 (877)	10.57 (927)		0.12
HDL cholesterol				
≤34 mg/dl	12.24 (964)	15.56 (906)		
35-40 mg/dl	10.12 (860)	9.47 (866)		
≥41 mg/dl	9.08 (925)	8.99 (968)		0.24
Triglycerides				
≤128 mg/dl	9.88 (891)	11.29 (939)		
129-203 mg/dl	10.50 (924)	9.86 (913)		
≥204 mg/dl	11.13 (934)	12.84 (888)		0.64
Triglyceride-HDL cholesterol combination				
Triglyceride ≥204 mg/dl and HDL ≤34 mg/dl	**12.37 (485)**	**17.32 (456)**		
All others	**10.11 (2264)**	**10.11 (2284)**		**0.06**
Glycated hemoglobin				
≤8.0%	8.69 (1,324)	10.56 (1,335)		
≥8.1%	12.20 (1,435)	11.94 (1,415)		0.20

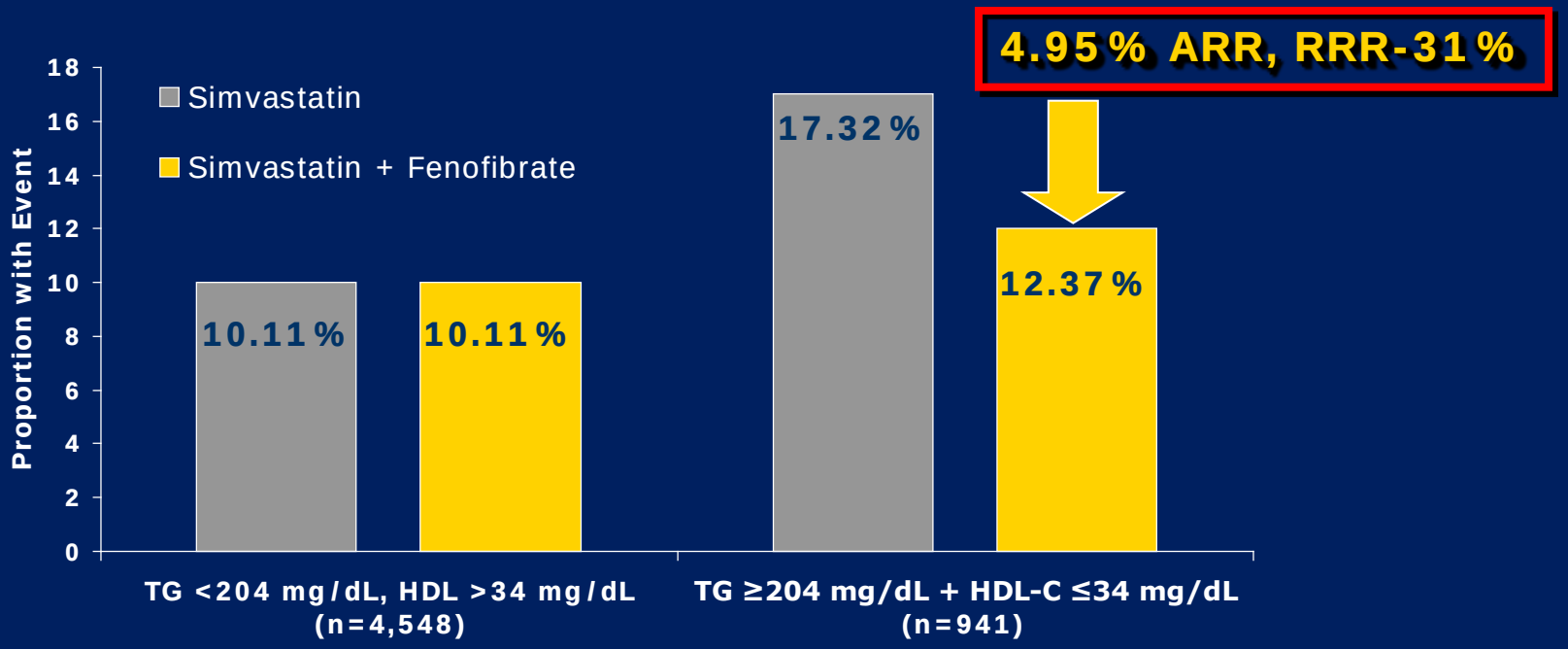


ACCORD Study Group. N Engl J Med March 14, 2010. Epub.

ACCORD Lipid

Fenofibrate reduces the residual risk associated with elevated TG and low HDL-C

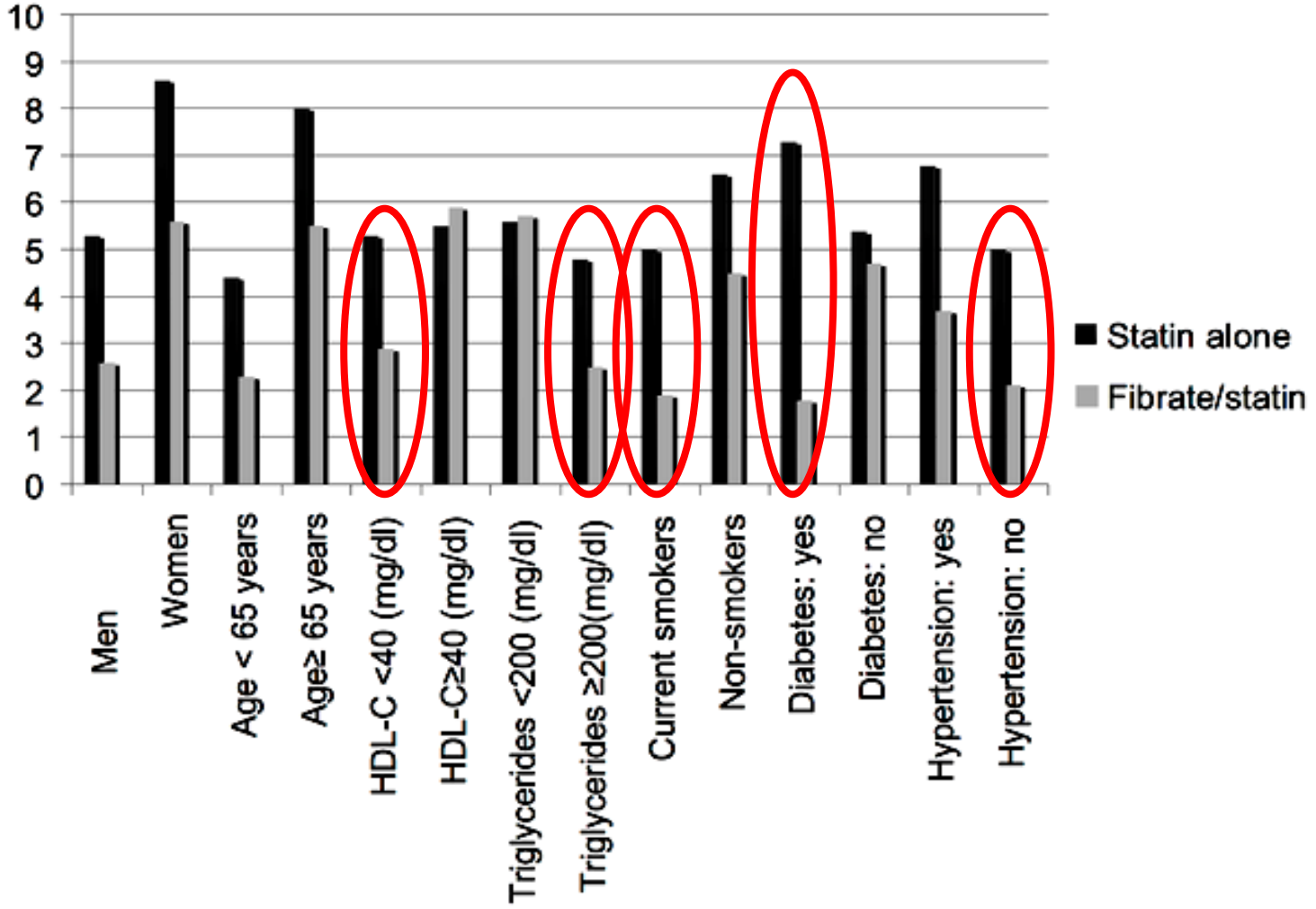
- Patients in the dyslipidaemia subgroup had a 70% higher relative risk of major CV events* compared to those with TG <204 mg/dL and HDL >34 mg/dL, despite achieving a mean LDL-C of 80 mg/dL



ARR: absolute risk reduction
*Major CV events defined as CV death, nonfatal MI and nonfatal stroke

ACCORD Study Group. N Engl J Med March 14, 2010. Epub.

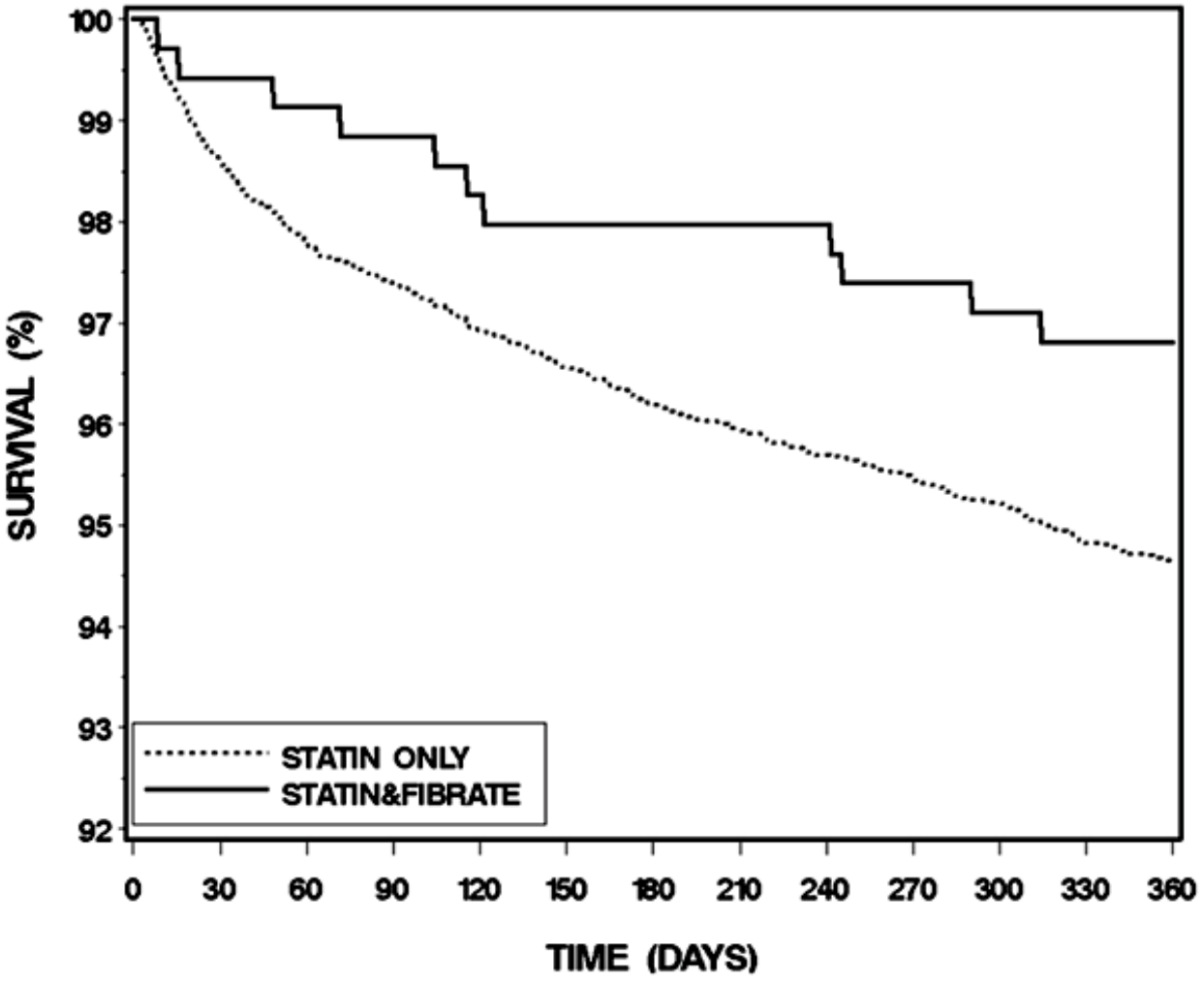
Rate (%) of 30-day Major Adverse Coronary Events (MACE) among the study patients according to the age, gender, level of HDL cholesterol, triglycerides, smoking status, presence of diabetes and hypertension.



Tenenbaum A, Medvedofsky D, Fisman EZ, Bubyr L, et al. (2012) Cardiovascular Events in Patients Received Combined Fibrate/Statin Treatment versus Statin Monotherapy: Acute Coronary Syndrome Israeli Surveys Data. PLoS ONE 7(4): e35298. doi:10.1371/journal.pone.0035298
http://www.plosone.org/article/info:doi/10.1371/journal.pone.0035298

PLoS one

Kaplan-Meier curve of mortality rate during one year follow-up for 7,243 patients from years 2000-2008 (combined fibrate/statin therapy vs. statin monotherapy, p log-rank = 0.066).



Tenenbaum A, Medvedofsky D, Fisman EZ, Bubyr L, et al. (2012) Cardiovascular Events in Patients Received Combined Fibrate/Statin Treatment versus Statin Monotherapy: Acute Coronary Syndrome Israeli Surveys Data. PLoS ONE 7(4): e35298. doi:10.1371/journal.pone.0035298
http://www.plosone.org/article/info:doi/10.1371/journal.pone.0035298

Νέα φάρμακα για τη θεραπεία της οικογενούς υπερχοληστερολαιμίας

Lomitapide inhibits the microsomal triglyceride transfer protein (MTP) which is necessary for very low-density lipoprotein (VLDL) assembly and secretion in the liver. Approved by FDA and EMA for HoFH with or without LDL apheresis.

Mipomersen is a 'second-generation' antisense oligonucleotide that targets the messenger RNA for apolipoprotein B. Approved by FDA but not by EMA for HoFH with or without LDL apheresis.

Both drugs might be related to lipid accumulation in the liver (NAFLD)

PCSK9

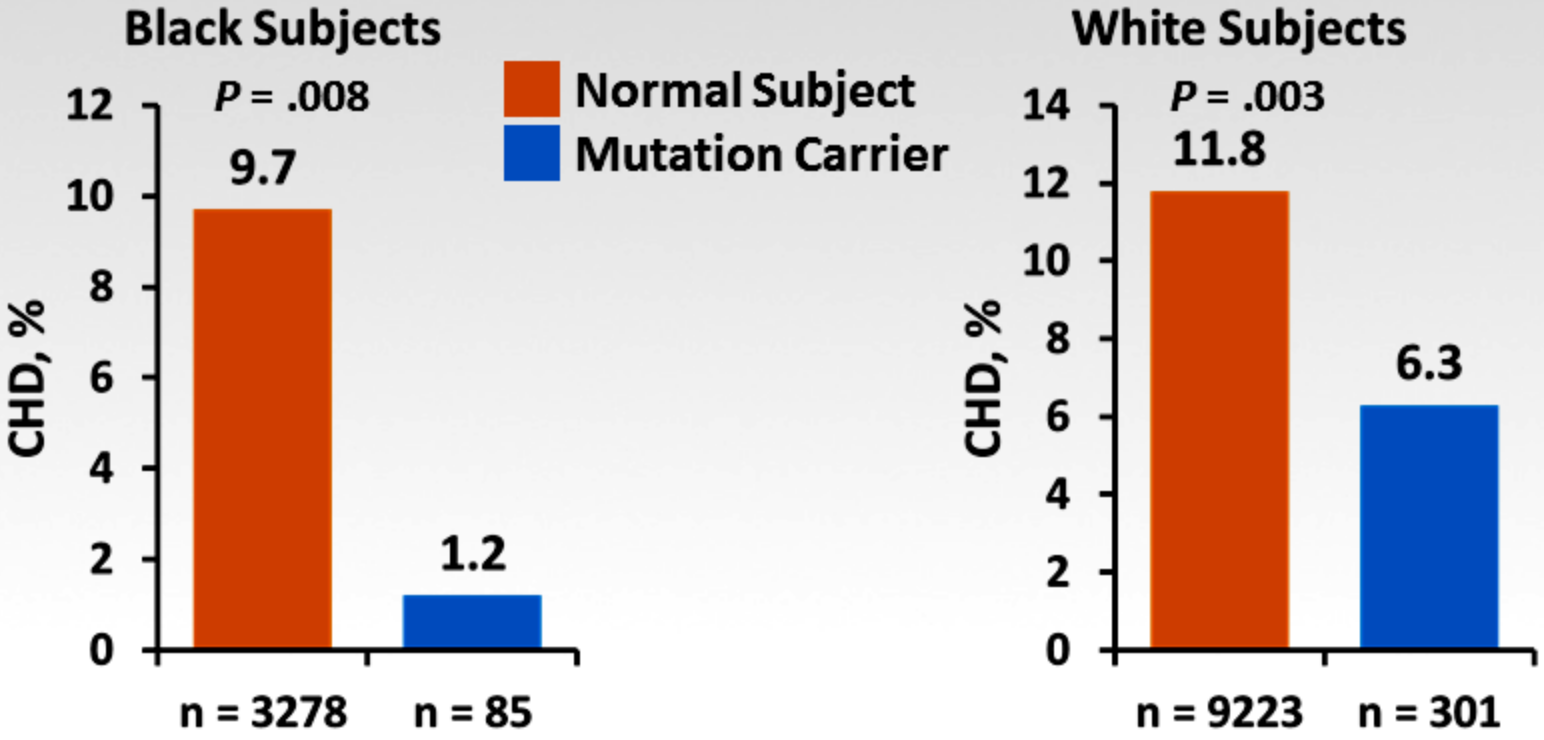
The effect of decreased PCSK-9 activity on LDL-C and CVD event rates was demonstrated in the 15-year follow-up of the **ARIC Atherosclerosis Risk in Communities study (n=12,887).**

Participants with PCSK-9 nonsense mutations had **substantially lower LDL-C levels and atherosclerotic CVD event rates** (up to 88% lower) compared with those with optimal PCSK-9 function.

Monoclonal antibodies against PCSK-9 prolong LDLR activity resulting in lower circulating LDL-C levels

Cohen JC, Boerwinkle E, Mosley TH Jr, Hobbs HH. **Sequence variations in PCSK9, low LDL, and protection against coronary heart disease**. N. Engl. J. Med. 2006; 354, 1264-1272.

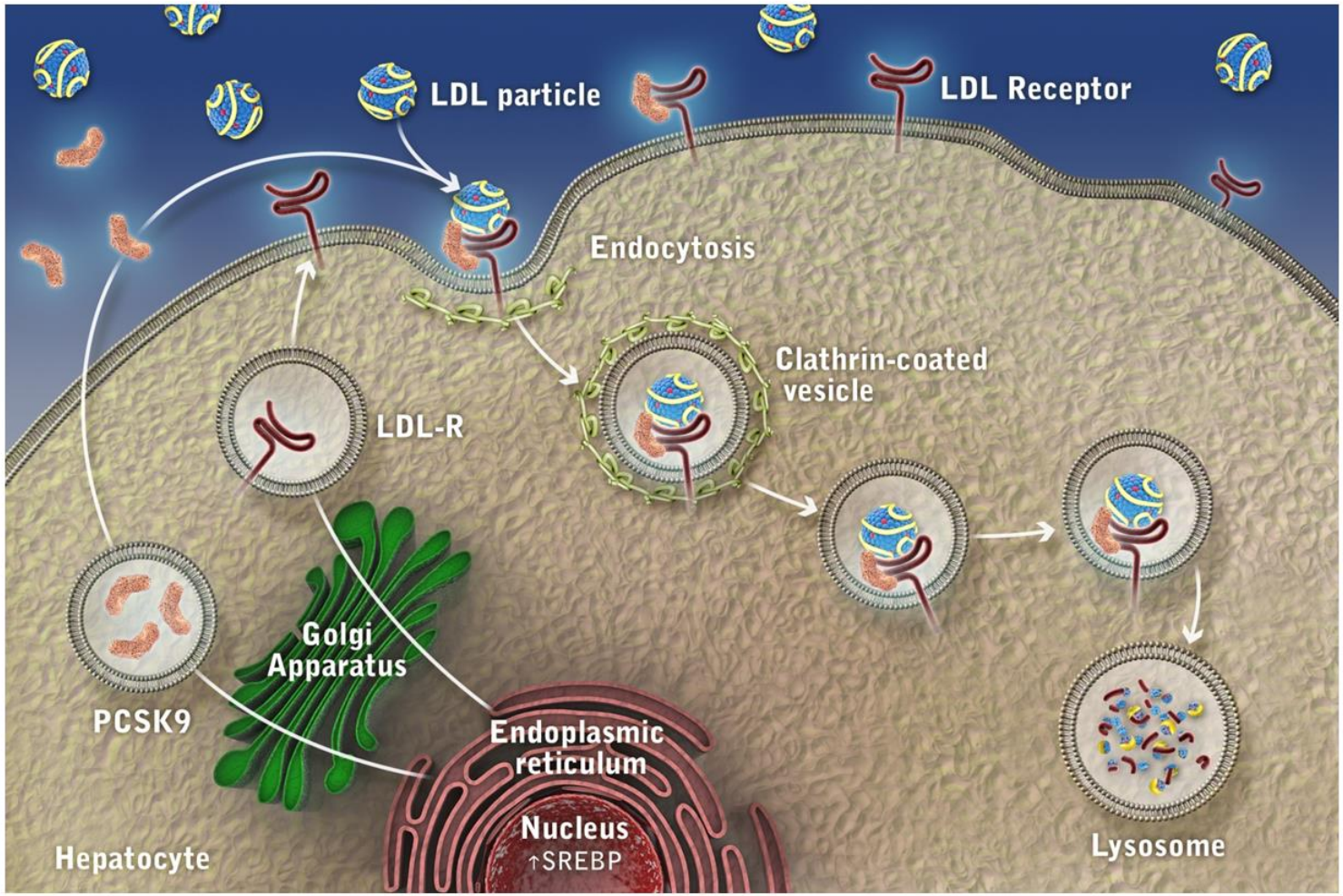
PCSK9 Loss-of-Function Mutations Resulted in Low LDL-C Levels and Reduced CHD Rates[a]



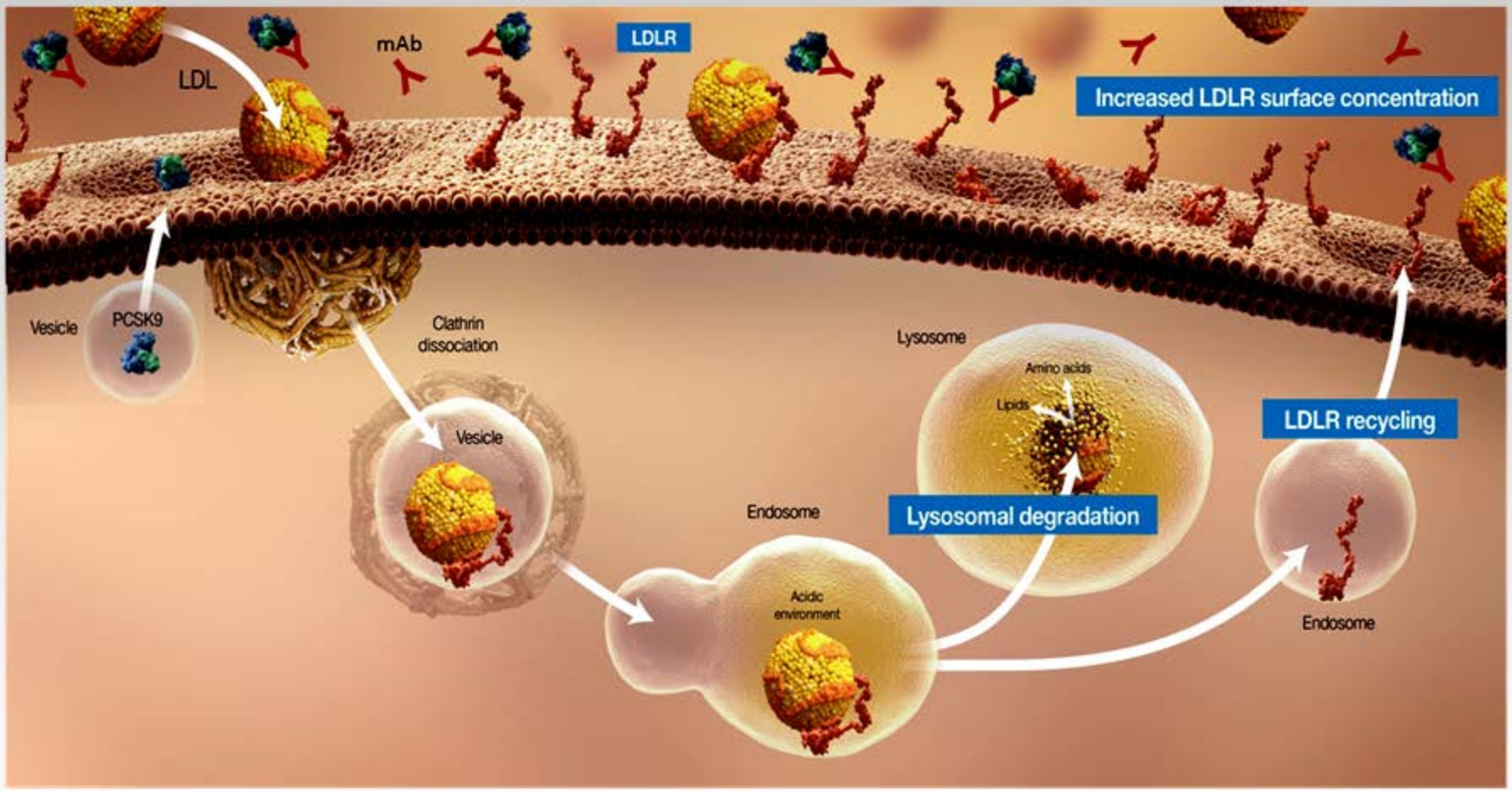
- Wild-type PCSK9 degrades LDL receptors[b-c]
- Loss-of-function mutations increase hepatic *LDLR* expression, reducing LDL-C levels by 15%-40%[a,c]
- CHD was reduced 47%-88% in *PCSK9* loss-of-function mutation carriers compared with normal individuals[a]

a. Cohen JC, et al. *N Engl J Med*. 2006;354:1264-1272.
b. Peterson AS, et al. *J Lipid Res*. 2008;49:1595-1599.
c. Cohen J, et al. *Nat Genet*. 2005;37:161-165.

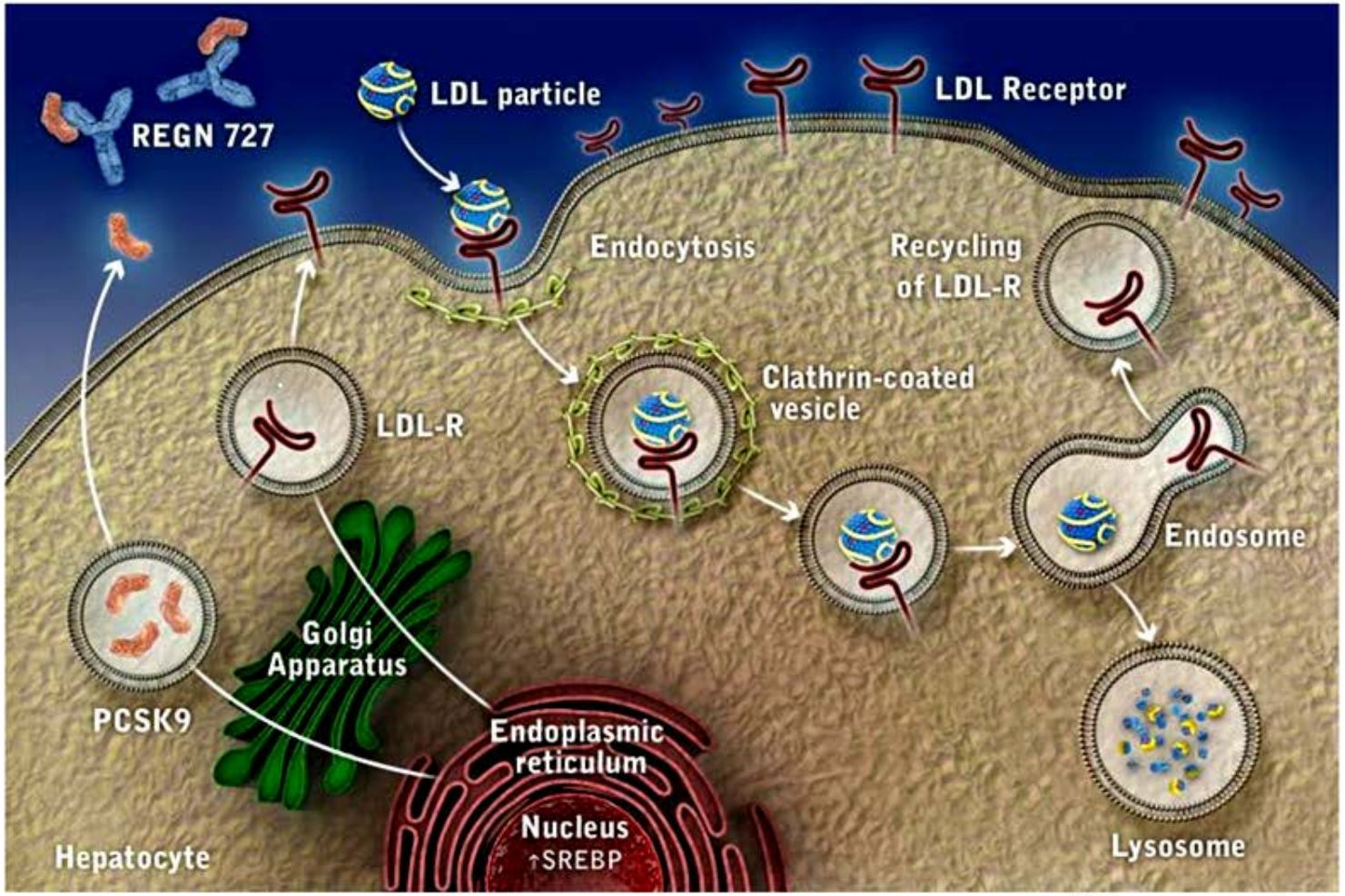
The Role of PCSK9 in the Regulation of LDLR Expression



Impact of PCSK9 Monoclonal Antibodies on LDL Receptor Surface Concentrations



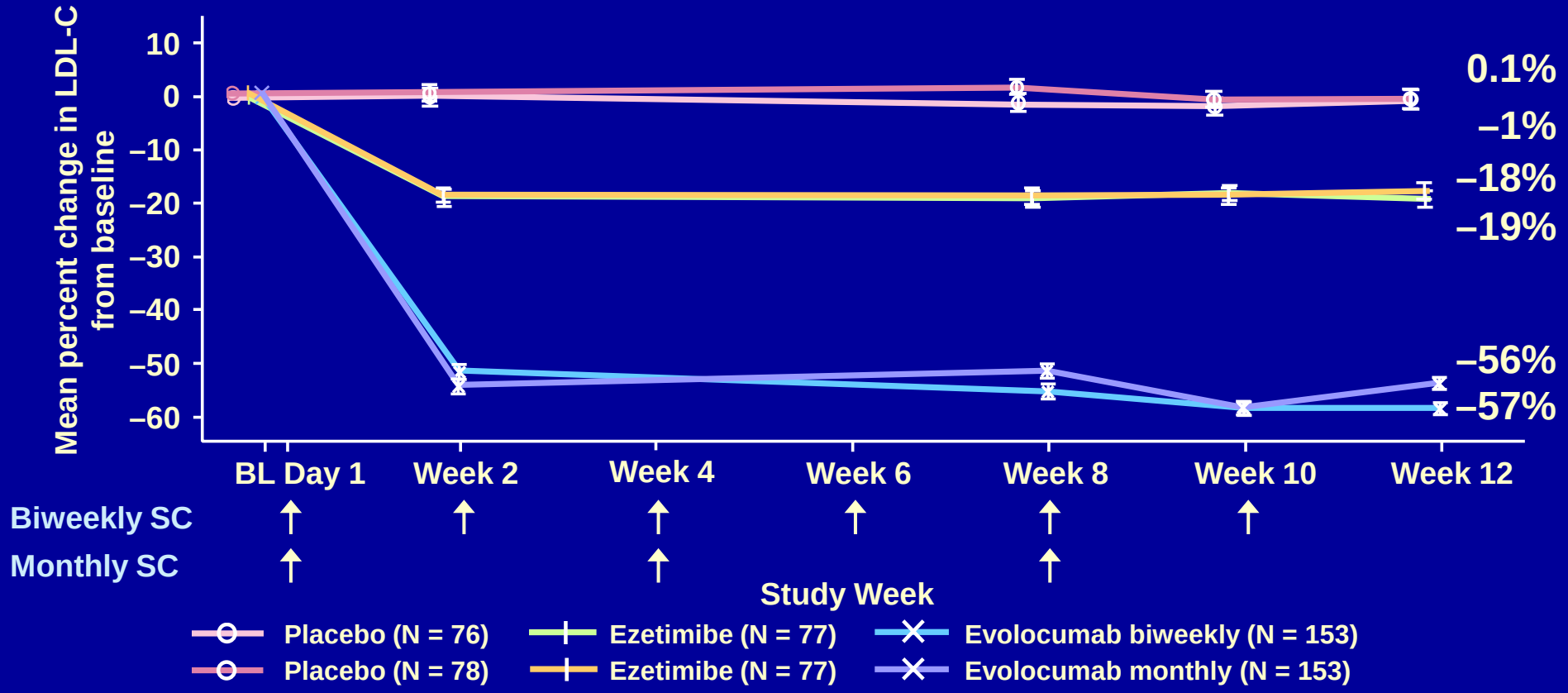
Impact of a PCSK9 mAb on LDLR Expression



placebo and oral ezetimibe in patients with hypercholesterolemia in a phase III trial.

MENDEL-2: Evolocumab

Primary Endpoint Biweekly and Monthly Doses

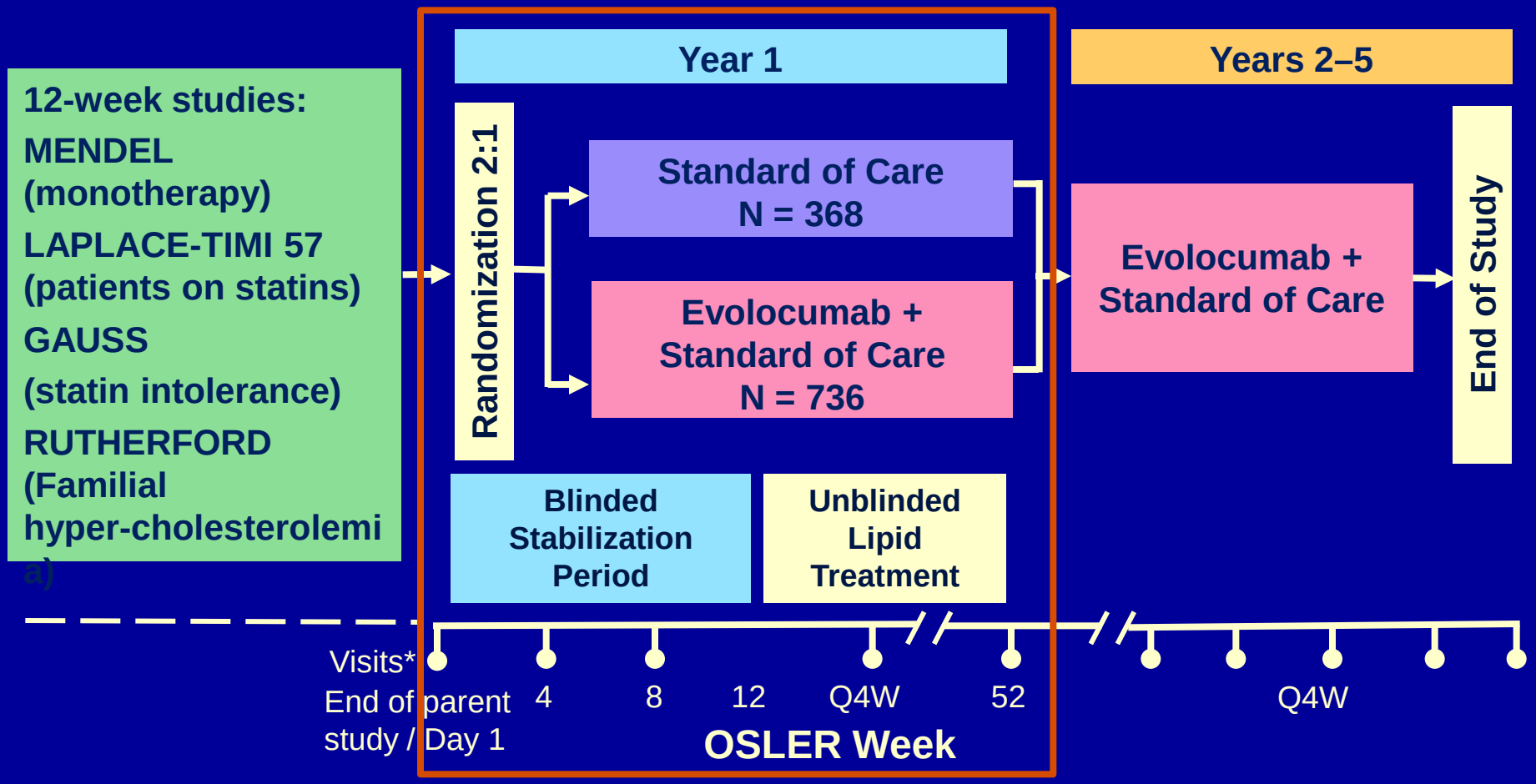


- Evolocumab resulted in significant LDL-C reductions compared with ezetimibe*
  - Biweekly: –39% and –39%, respectively†
  - Monthly: –40% and –38%, respectively†
- Biweekly and monthly dosing regimens were clinically equivalent

Vertical lines represent the standard error around the mean. Plot is based on observed data with no imputation for missing values. p values are multiplicity adjusted. *Average at Weeks 10 and 12 and Week 12; †p<0.001 for both.
BL, baseline

1 year hypercholesterolemic patients

OSLER Study Design

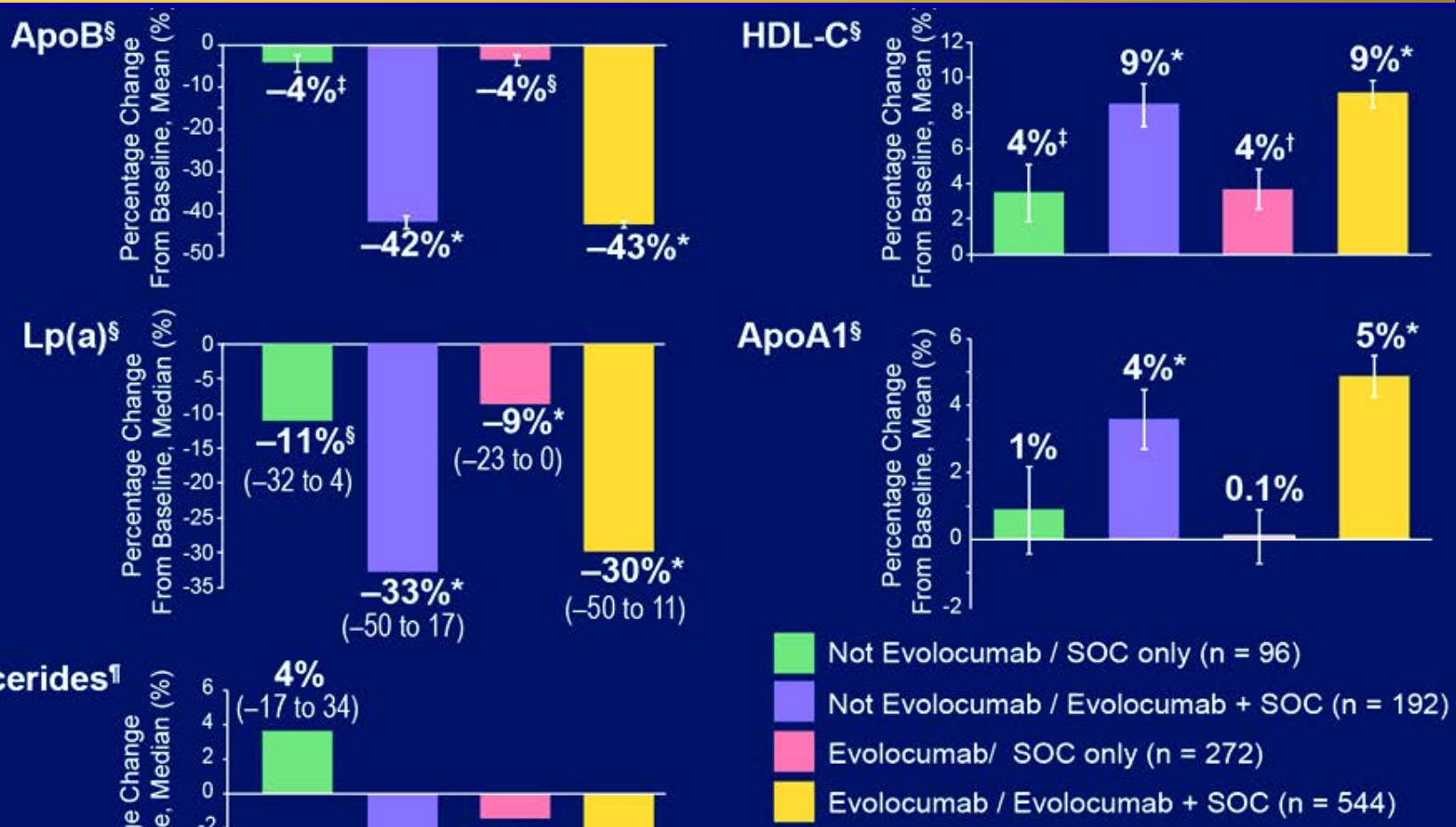


Primary Objectives:

- **Effects on LDL-C over 1 year**
- **Safety and Tolerability**

Q4W, every 4 weeks. * Patients in the evolocumab + SOC group had in-person visits every 4 weeks. Patients in the SOC group had in-person visits at week 4, then every 3 months, with telephone visits every 4 weeks.

OSLER: Effect of Evolocumab on Other Lipid Parameters at 1 Year

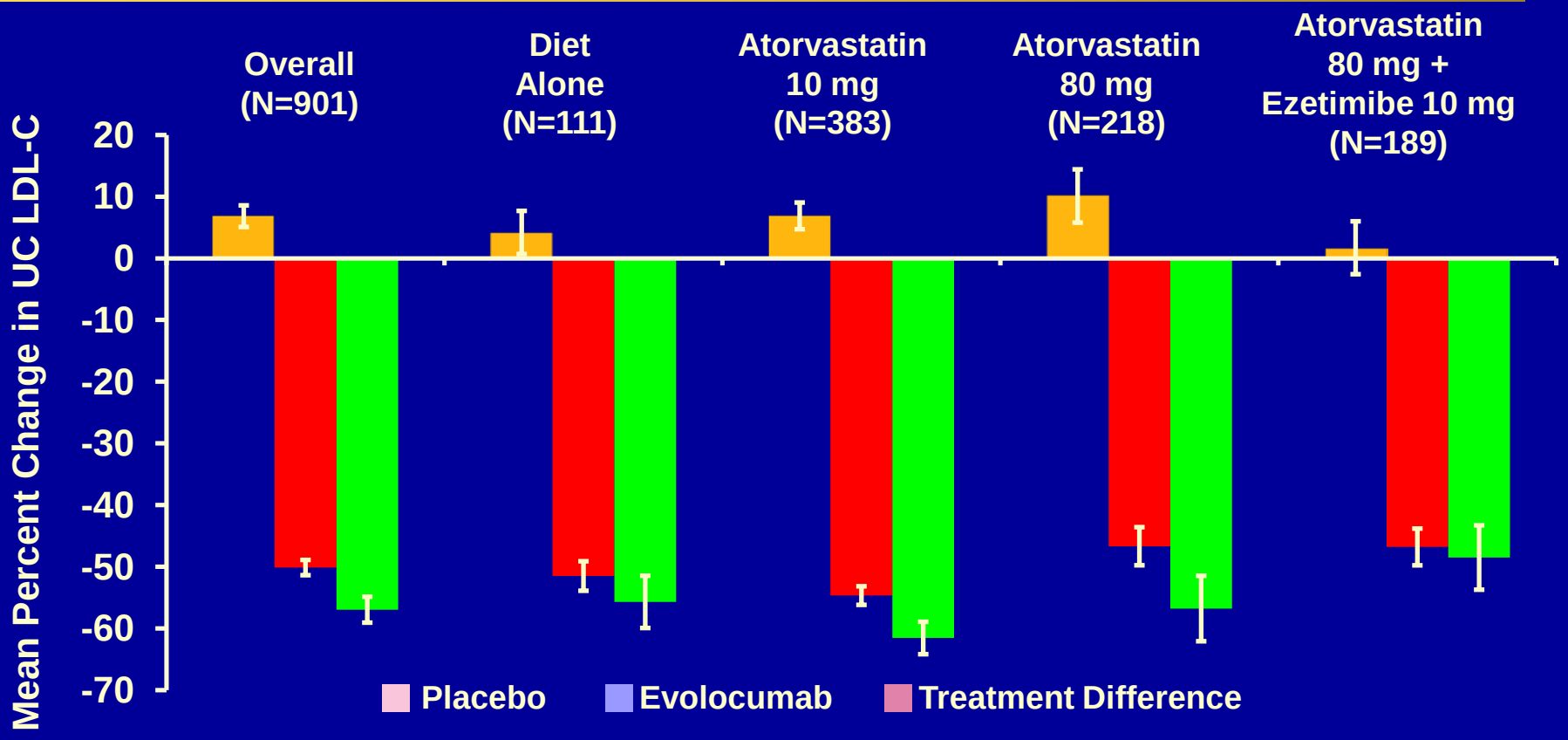


Error bars represent standard error.
Data in parentheses represent interquartile ranges.

Week 52 vs baseline:
* $P < 0.0001$; † $P < 0.001$; § $P < 0.01$; ‡ $P < 0.05$
Evolocumab vs placebo:
§ $P < 0.0001$; ¶ $P < 0.001$

evolocumab added to diet alone, to low-dose atorvastatin, or to high-dose atorvastatin with or without ezetimibe significantly reduced LDL-C in patients with a range of CVD risks

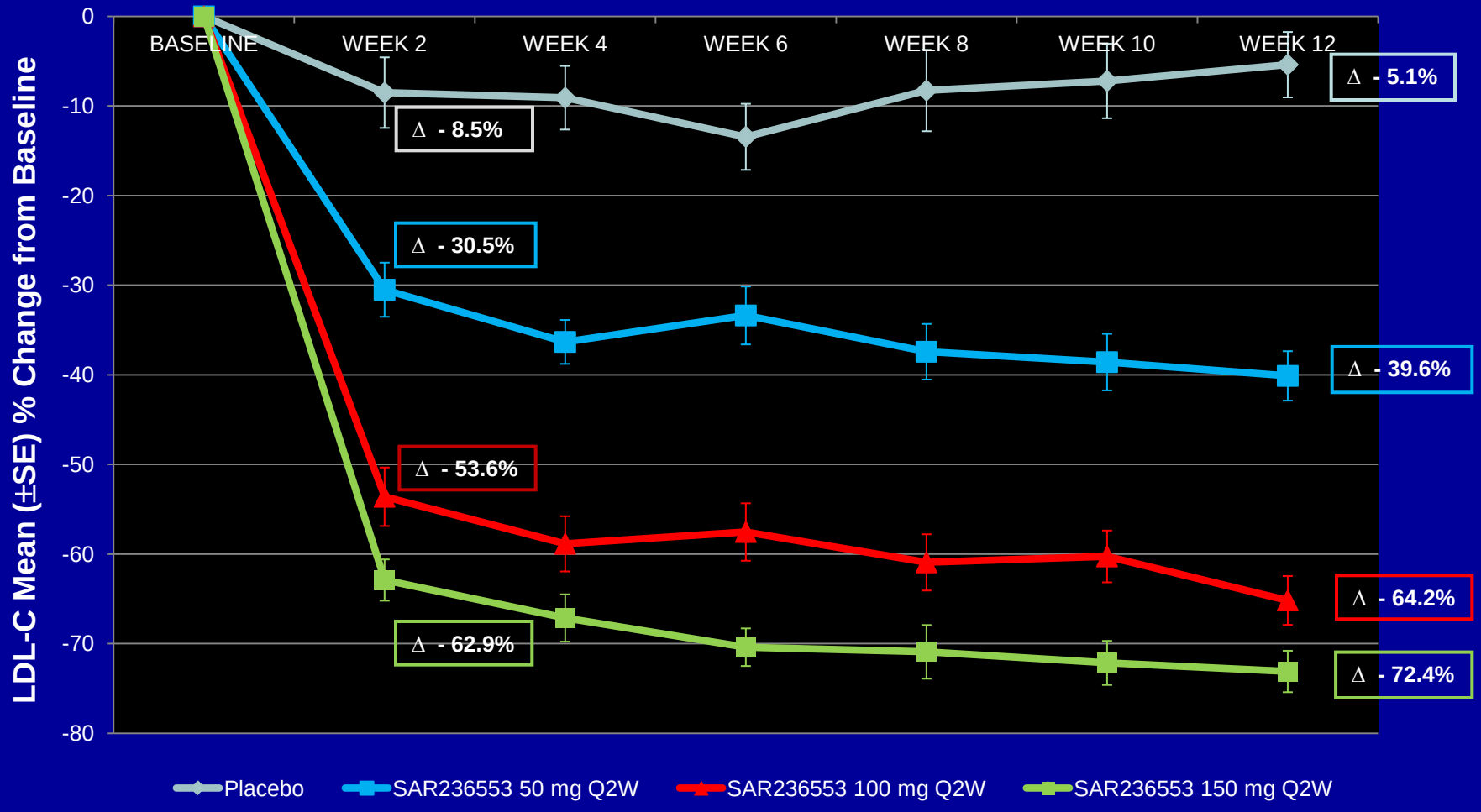
DESCARTES:% Change in UC LDL-C from Baseline at Week 52



- 6.8% increase from baseline in LDL-C observed in placebo group (n=302)
- 50.1% decrease from baseline in LDL-C observed in evolocumab group (n=599)*
- 57% treatment difference

Error bars represent standard error for treatment difference. Treatment difference are least squares mean derived from a repeated measures model. *Average of all evolocumab patients. UC, ultracentrifugation

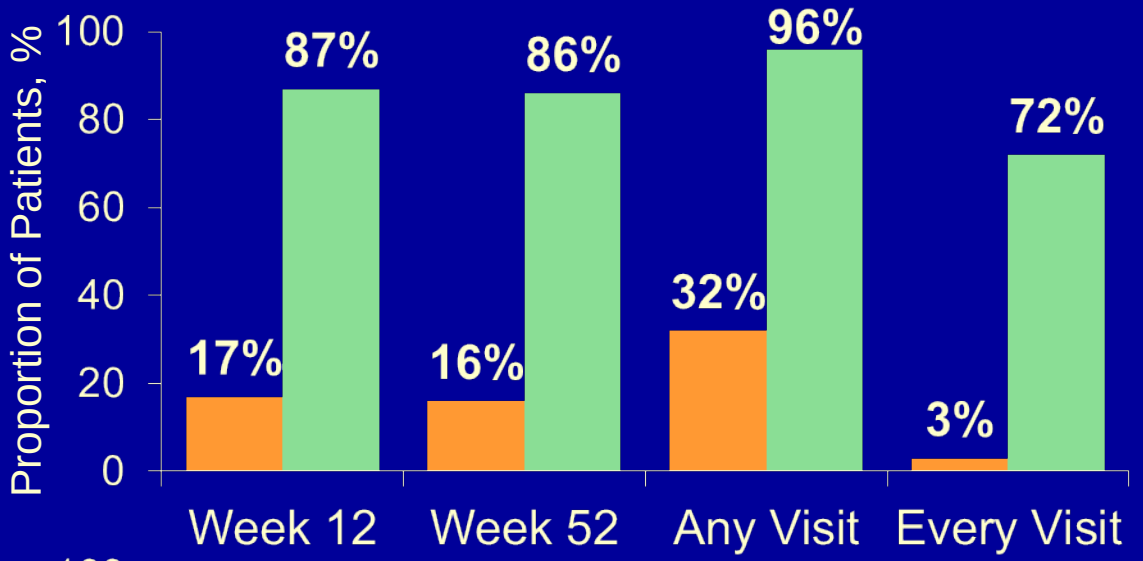
Change with Alirocumab in Calculated LDL-C at 2 Weekly Intervals from Baseline to Week 12



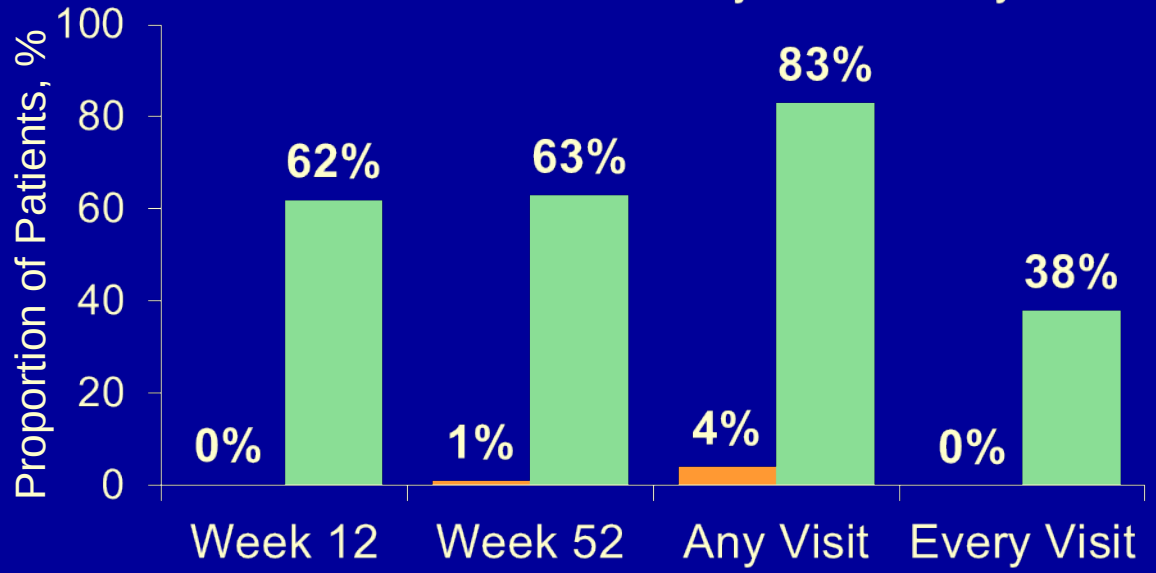
Mean percentage change in calculated LDL-C from baseline to weeks 2, 4, 6, 8, 10, and 12 in the modified intent-to-treat (mITT) population, by treatment group. Week 12 estimation using LOCF method.

OSLER: LDL-C Goal Achievement

< 100 mg/dL



< 70 mg/dL

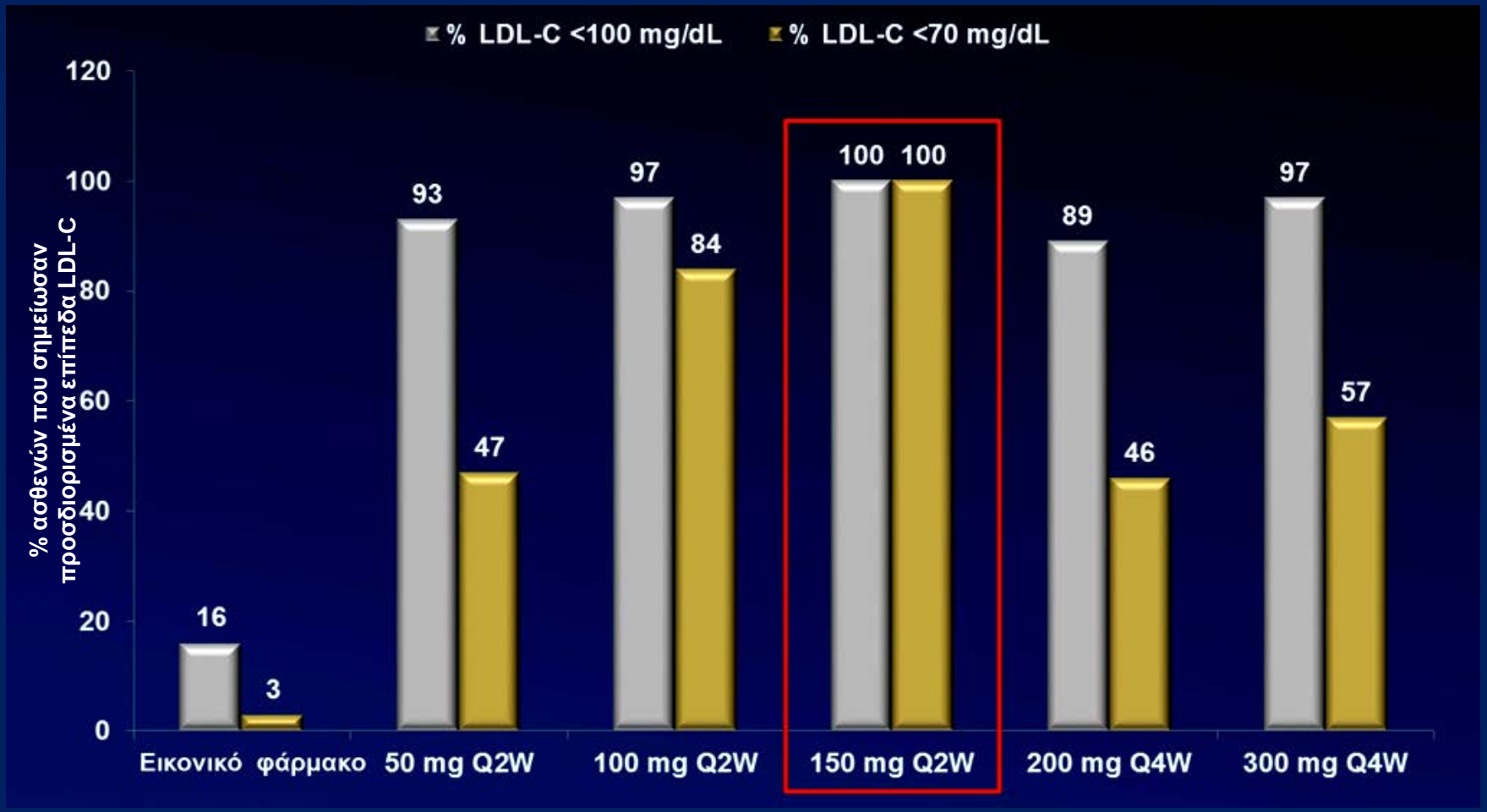


SOC

Evolocumab + SOC

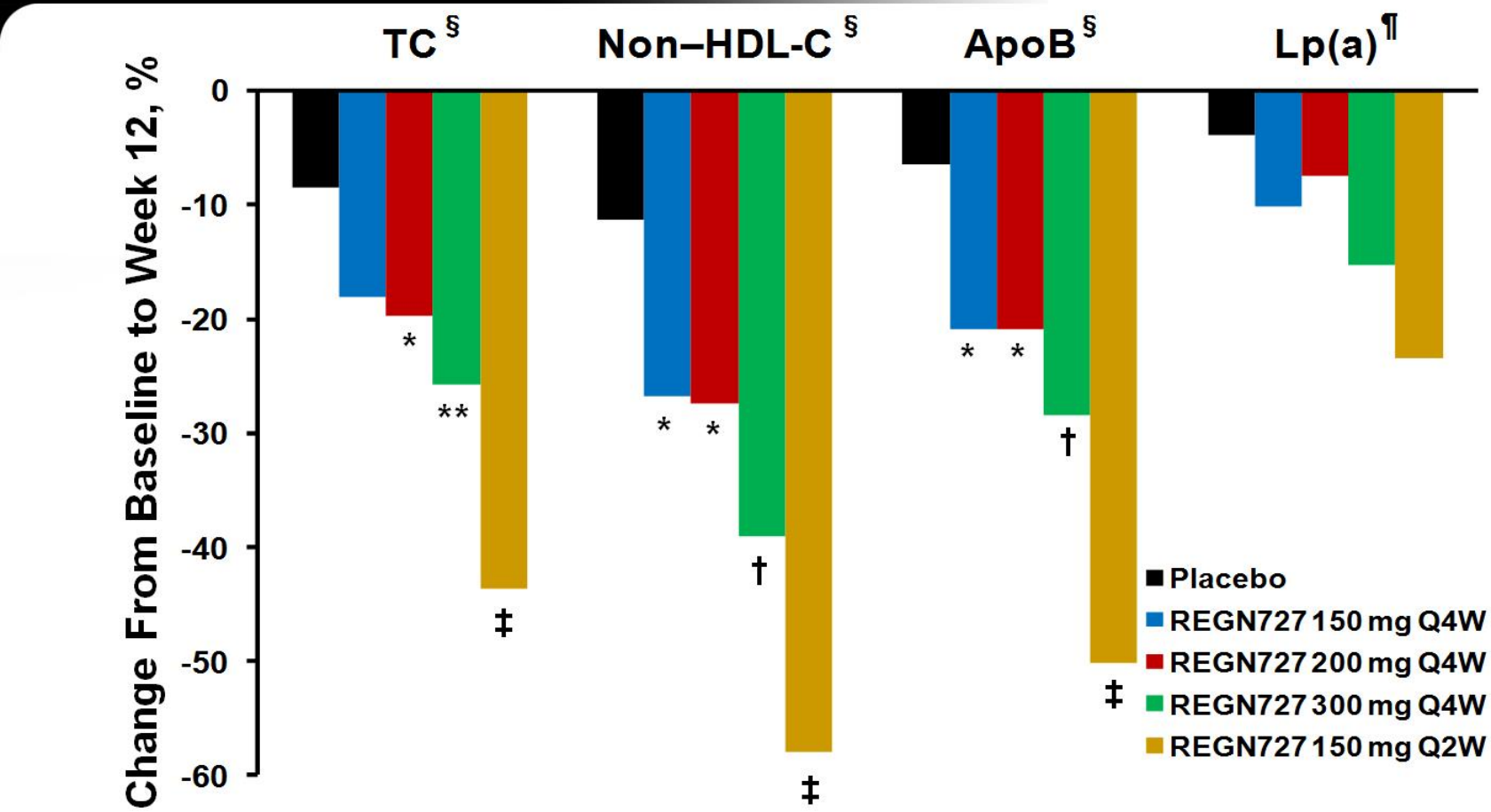
LDL-C values by ultracentrifugation. SOC, standard of care

Επίτευξη προκαθορισμένων επιπέδων της LDL-C κατά την εβδομάδα 12 (πληθυσμός mITT)



McKenney JM *et al. J Am Coll Cardiol* 2012;59:2344–53

Changes in TC, non-HDL-C, ApoB, and Lp(a) From Baseline to Week 12 by Treatment Group (mITT Population)

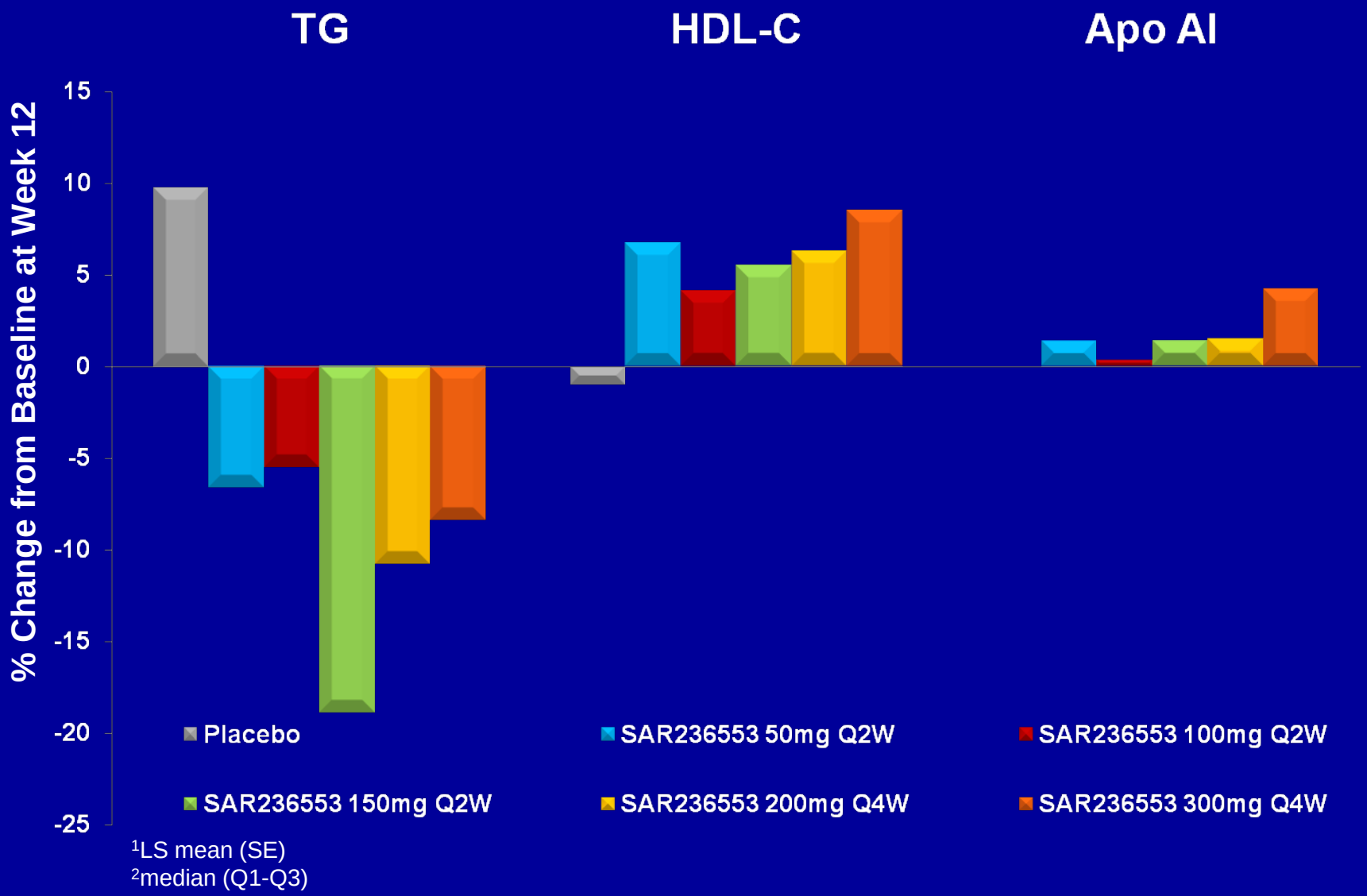


§ LS mean (SE); ¶median (Q1-Q3).

*P < .05; **P < .01; †P < .001; ‡P < .0001.

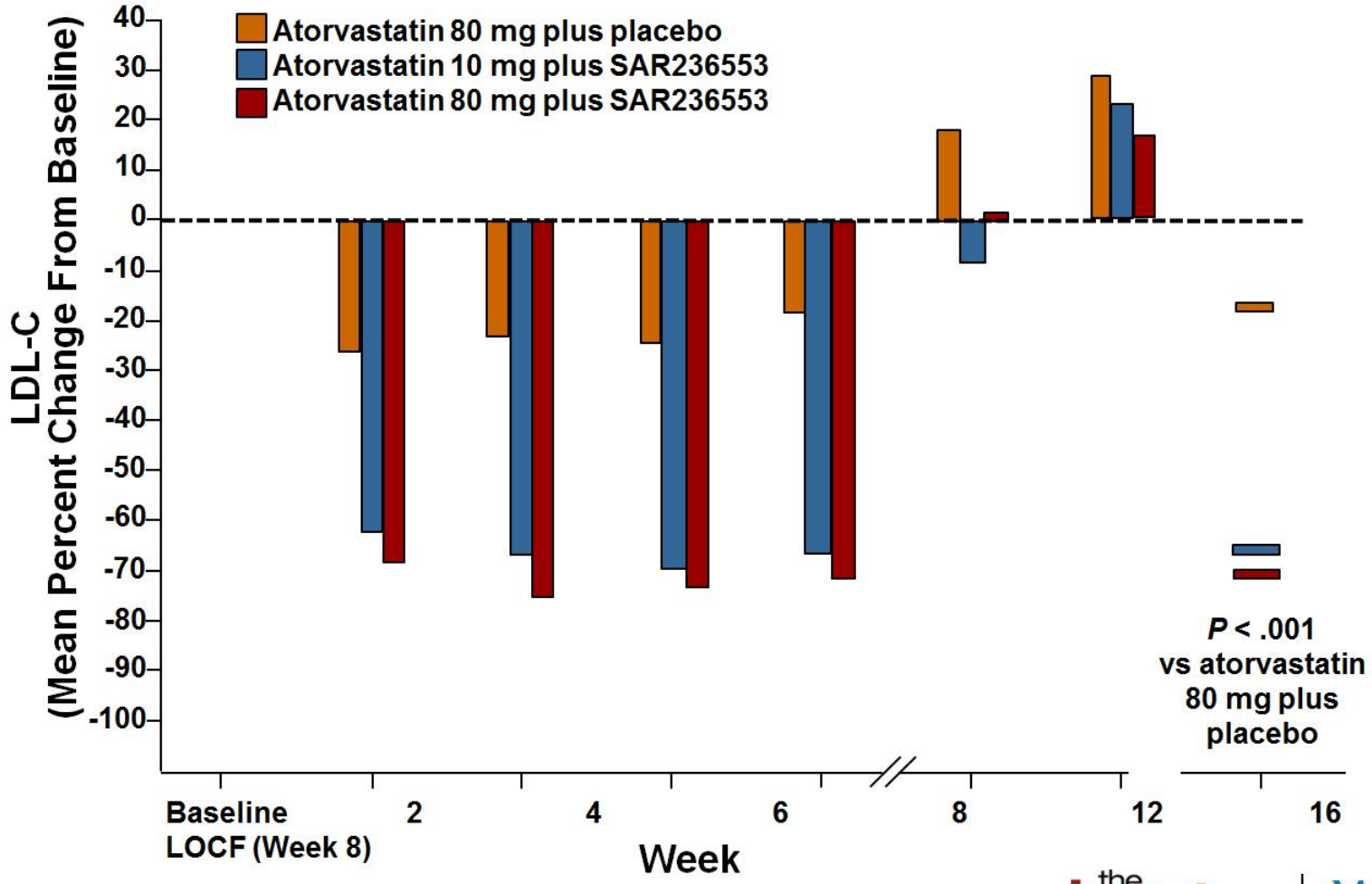
Stein EA, et al. *Lancet*. 2012;380:29-36.[17]

Changes in TG, HDL-C, and Apo AI from Baseline to Week 12 by Treatment Group (mITT Population)



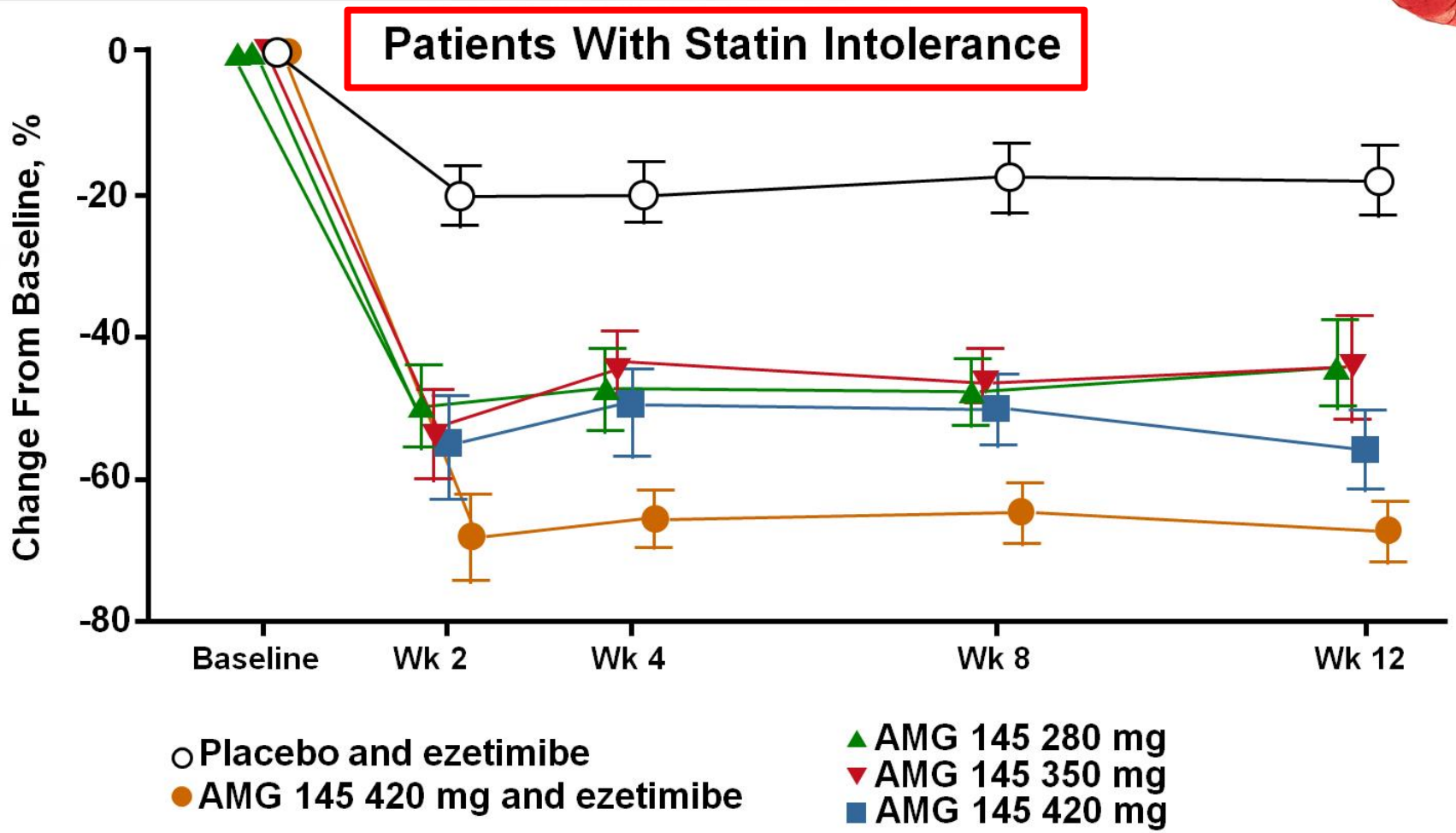
[1]LS mean (SE)
[2]median (Q1-Q3)

Alirocumab on Top of Atorvastatin in Primary Hypercholesterolemia: Phase 2



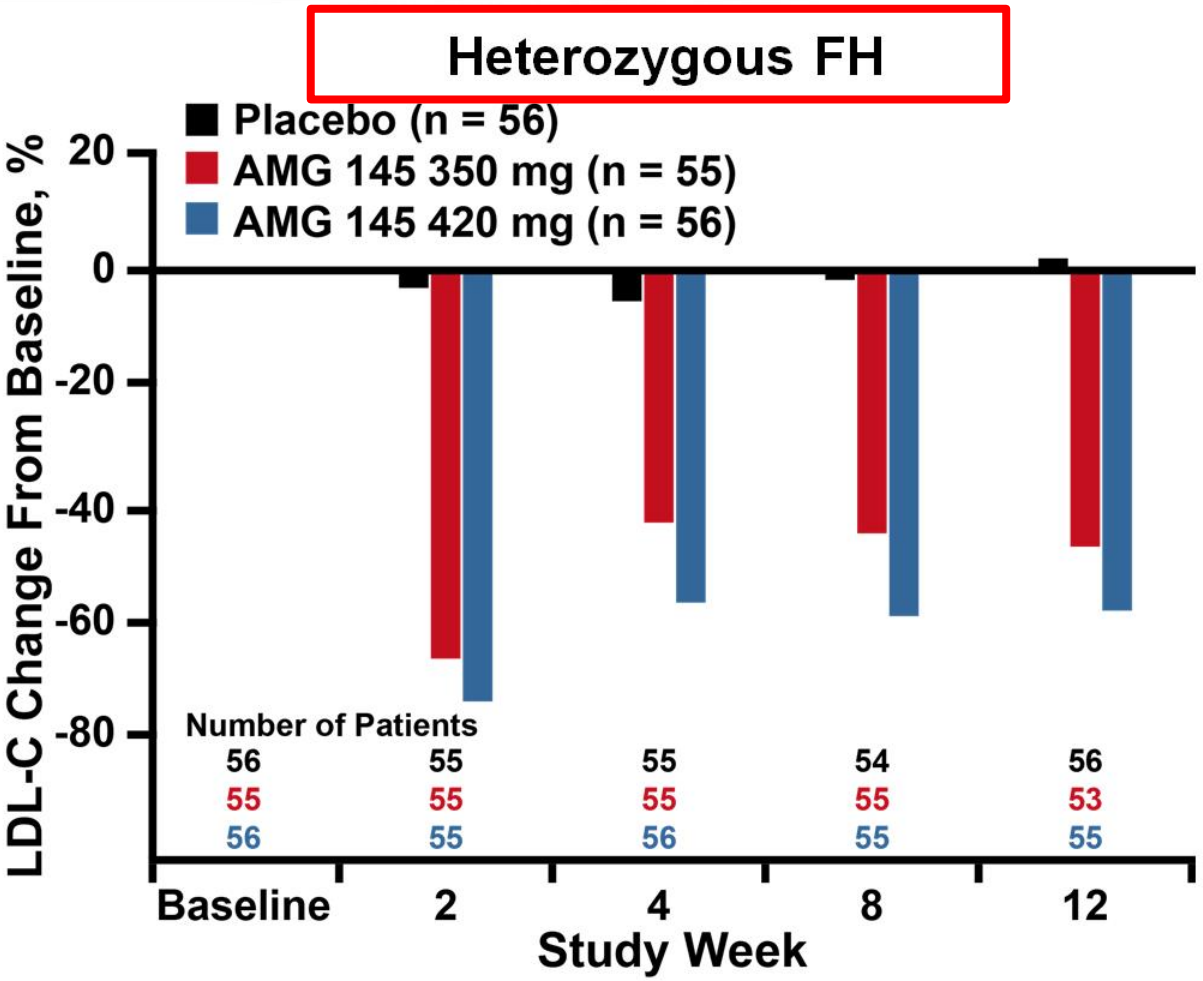
Roth EM, et al. *N Engl J Med*. 2012;367:1891-1900.[21]

GAUSS: Effect of AMG 145 on Percentage Change in LDL-C From Baseline



Sullivan D, et al. *JAMA*. 2012;308:2497-2506.[26]

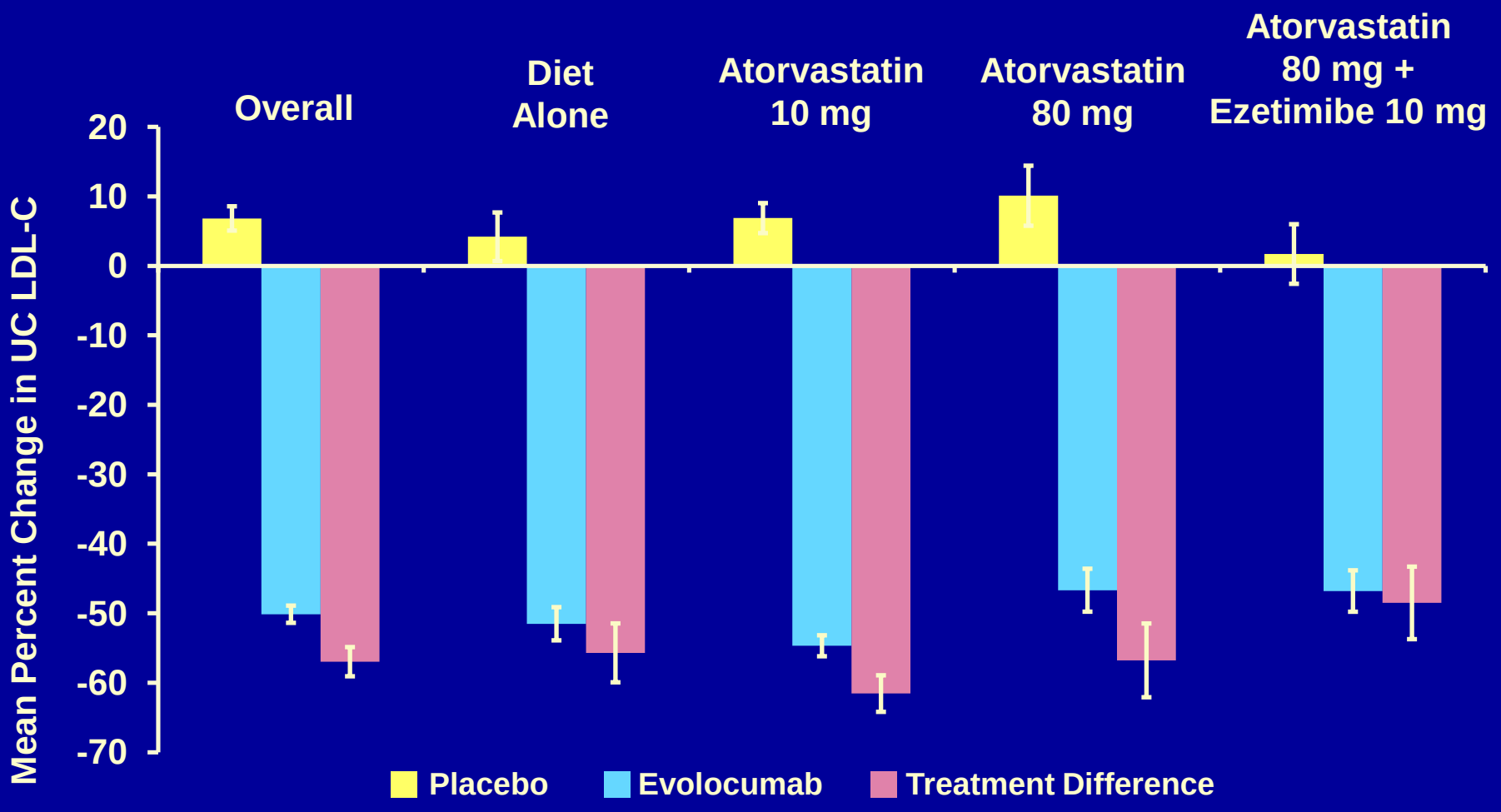
RUTHERFORD: Effect of AMG 145 on Percentage Change in LDL-C From Baseline



Raal F, et al. *Circulation*. 2012;126:2408-2417.[27]

DESCARTES: % Change in UC LDL-C from Baseline at Week 52

wide range of cardiovascular risk



Error bars represent standard error for treatment difference
Treatment difference are least squares mean derived from a repeated measures model

DESCARTES: Treatment Emergent Adverse Events

n (%)	Placebo N=302	Evolocumab N=599
Any Treatment Emergent Adverse Event	224 (74.2)	448 (74.8)
Serious	13 (4.3)	33 (5.5)
Death	0 (0.0)	2 (0.3)
Adjudicated events	2 (0.7)	6 (1.0)
Leading to discontinuation of study drug	3 (1.0)	13 (2.2)

Treatment emergent adverse events are adverse events occurring between the first dose of Study Drug and End of Study

Summary of Treatment-Emergent Adverse Events (TEAEs) (Safety Population)

		Q2W dosing			Q4W dosing	
	Placebo (N=31)	50mg (N=30)	100mg (N=31)	150mg (N=31)	200mg (N=30)	300mg (N=30)
Overview of all TEAEs – no.						
Any TEAE	14	18	20	19	20	14
Any treatment-emergent SAE	1	0	1	0	1	1
Any TEAE leading to permanent treatment d/c	0	0	1	1	3	1
AEs of special interest — no.						
ALT or AST >3 x ULN	0	0	0	0	0	0
Muscle (including pain, weakness)	1	1	2	1	1	2
CK >10 x ULN	1	0	0	0	0	0

Injection-site reactions occurred in the SAR236553 groups only and were generally mild and non-progressive.

Περίληψη και συμπεράσματα 1

Τα αντισώματα anti-PCSK9 μπορούν να προκαλέσουν

1. Σημαντική δοσοεξαρτώμενη μείωση της LDL-C, έως και 72%

2. Βελτιωμένη ικανότητα να επιτύχει τους στόχους της LDL-C

3. Συνεπείς και ισχυρές μειώσεις για όλες τις λιποπρωτεΐνες Apo B

4. Σημαντική μείωση σε Lp (a), συνεπές με προηγούμενες μελέτες

Περίληψη και συμπεράσματα 2

Τα αντισώματα anti-PCSK9 θα μπορούσε να χορηγηθεί με ασφάλεια σε ασθενείς με

Δυσανεξία στις στατίνες .

Οικογενή ετερόζυγο υπερχοληστερολαιμία.

Υψηλή Lp(a).

Κάθε αύξηση της LDL-C, που δεν μπορεί να ελεγχθεί αποτελεσματικά από τις στατίνες και τους συνδυασμούς των στατινών με άλλα υποχοληστερολαιμικά φάρμακα.

Περίληψη και συμπεράσματα 3

Οι στατίνες παραμένουν ο ακρογωνιαίος λίθος της υπολιπιδαιμικής θεραπείας

Χρειάζεται εκτίμηση του κόστους/οφέλους πριν αρχίσουμε στατίνες

Στη μικτή υπερλιπιδαιμία προσθέτουμε φιμπράτες

Στο προσεχές μέλλον που θα έχουμε τα αντισώματα έναντι PCSK9, εάν αποδειχθούν ασφαλή και έχουν προσιτή τιμή θα αντιμετωπίζονται πολύ αποτελεσματικά όλες οι δυσλιπιδαιμίες, περιλαμβανομένης της HeFH και της αυξημένης Lp(a)