

Αντιμετώπιση Διαβητικής Δυσλιπιδαιμίας με συνδυασμούς υπολιπιδαιμικών φαρμάκων



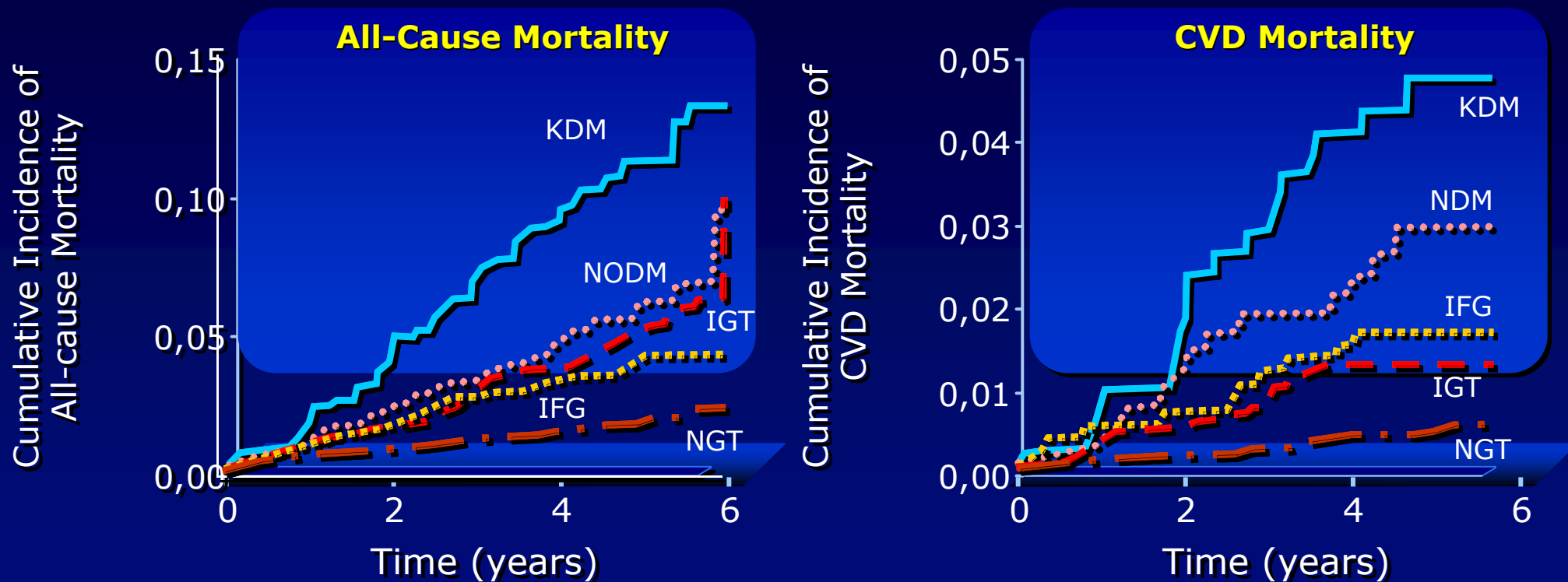
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**Ιατρεία Αθηροσκλήρωσης και
Μεταβολικού Συνδρόμου,
Β' Προπ. Παθολογική Κλινική ΑΠΘ,
Ιπποκράτειο Νοσοκομείο, Θεσσαλονίκη.**

ΔΕΒΕ 13 Νοεμβρίου 2009



Mortality According to Glucose Metabolism: Data from AusDiab



AusDiab = Australian Diabetes, Obesity, and Lifestyle Study; CVD = cardiovascular;
KDM = known diabetes mellitus; NODM = new onset diagnosed diabetes mellitus;
IFG = impaired fasting glucose; IGT = impaired glucose tolerance;
NGT = normal glucose tolerance

Putative Mechanism for Increased Atherosclerosis in Type 2 Diabetes



- Dyslipidemia
- Hypertension
- Hyperinsulinemia/insulin resistance
- Hemostatic abnormalities
- Hyperglycemia
- AGE proteins
- Oxidative stress

AGE = advanced glycation end products

Bierman EL. Arterioscler Thromb 1992;12:647-656.

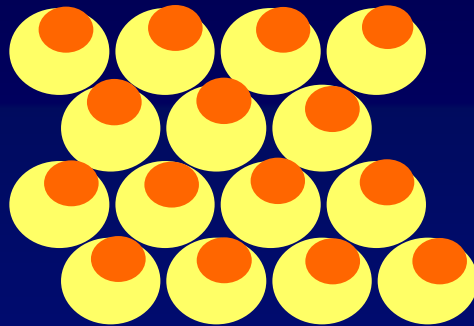


Misleading...

Small, Dense LDL-C Particles Are More Atherogenic

No diabetes

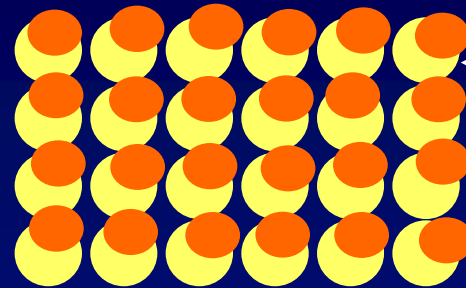
LDL particles



“Normal” LDL-C level

Diabetes

LDL particles



Small, dense
LDL with more
apoB

“Normal” LDL-C level, however:

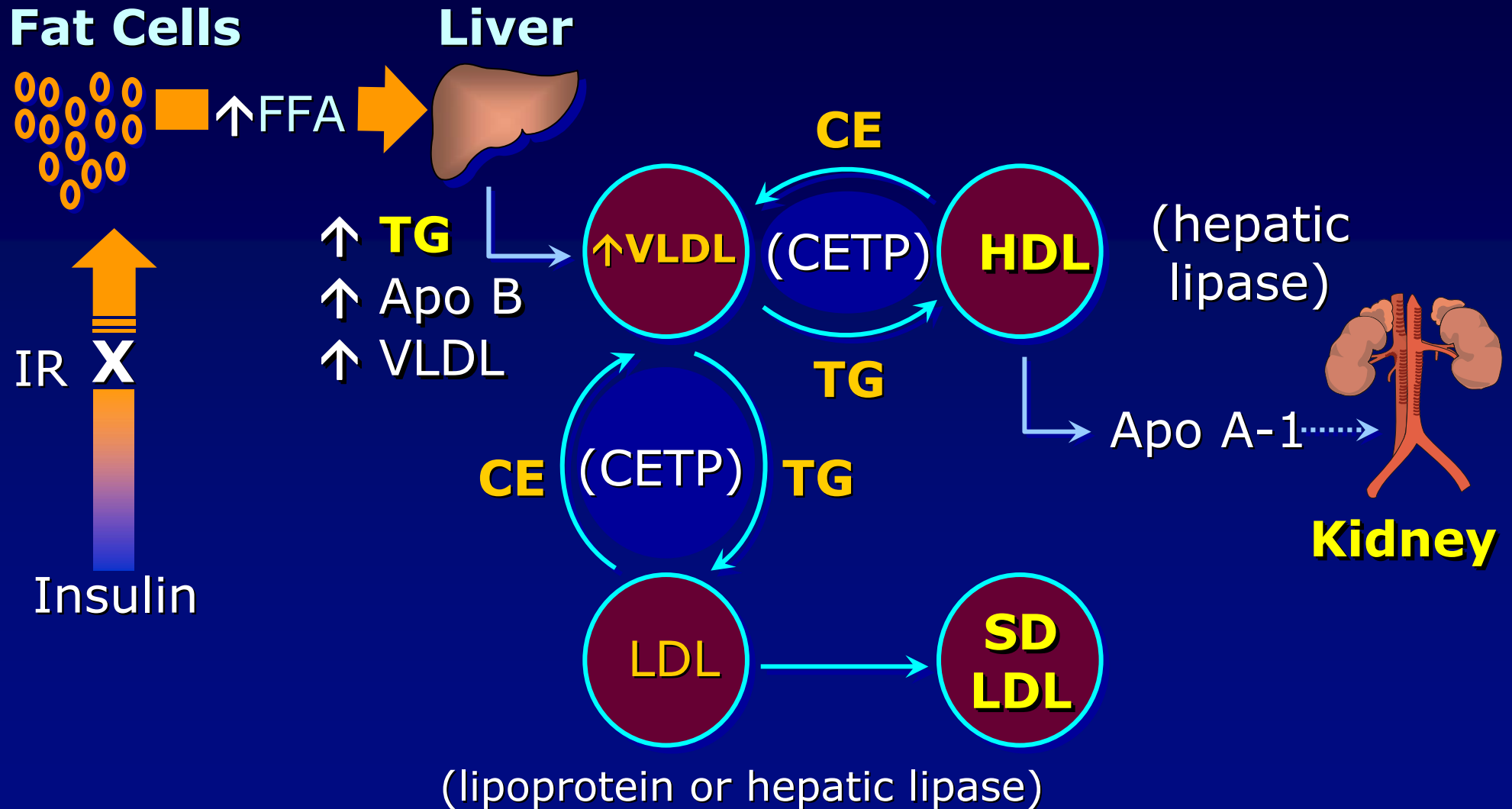
- ↑ Number of LDL particles
- ↑ Concentration of apoB

Lower

Higher

CHD risk

Mechanisms Relating Insulin Resistance and Dyslipidemia



In UKPDS: LDL-C Was the Strongest Predictor of CHD Risk in People with Diabetes

	% Increase in CHD risk
LDL-C ↑ of 1 mmol/L	57
HDL-C ↑ of 0.1 mmol/L	-15
Systolic blood pressure ↑ of 10 mmHg	15
HbA _{1c} level ↑ of 1%	11
Smoking was also a major contributor to CHD risk	

These data support the need for reducing LDL-C to lower CHD risk in people with diabetes mellitus.

Glucose control is also important in reducing the risk of microvascular complications.



NCEP ATP III: 2004 Updated LDL-C Goals, Treatment Cutpoints

Risk Category	LDL-C Goal	Initiate TLC	Consider Drug Therapy
Lower risk: 0–1 risk factor	<160 mg/dL	≥160 mg/dL	≥190 mg/dL
Moderate risk: ≥2 risk factors (10-year risk <10%)	<130 mg/dL	≥130 mg/dL	≥160 mg/dL
Moderately high risk: ≥2 risk factors (10-year risk 10%–20%)	<130 mg/dL optional: <100 mg/dL	≥130 mg/dL	≥130 mg/dL (100–129 mg/dL: consider drug options)
High risk: CHD or CHD risk equivalents* (10-year risk >20%)	<100 mg/dL optional: <70 mg/dL	≥100 mg/dL	≥100 mg/dL (<100 mg/dL: consider drug options)



Προτεραιότητες στην αντιμετώπιση της διαβητικής δυσλιπιδαιμίας

■ Ελάττωση LDL-Χ

- Πρώτη επιλογή: **Στατίνες**
- Δεύτερη επιλογή : Φαινοφιμπράτη

■ Αύξηση HDL-Χ

- ΑΤΖ
- Έλεγχος γλυκαιμίας
- **Νικοτινικό ή φιβράτες**

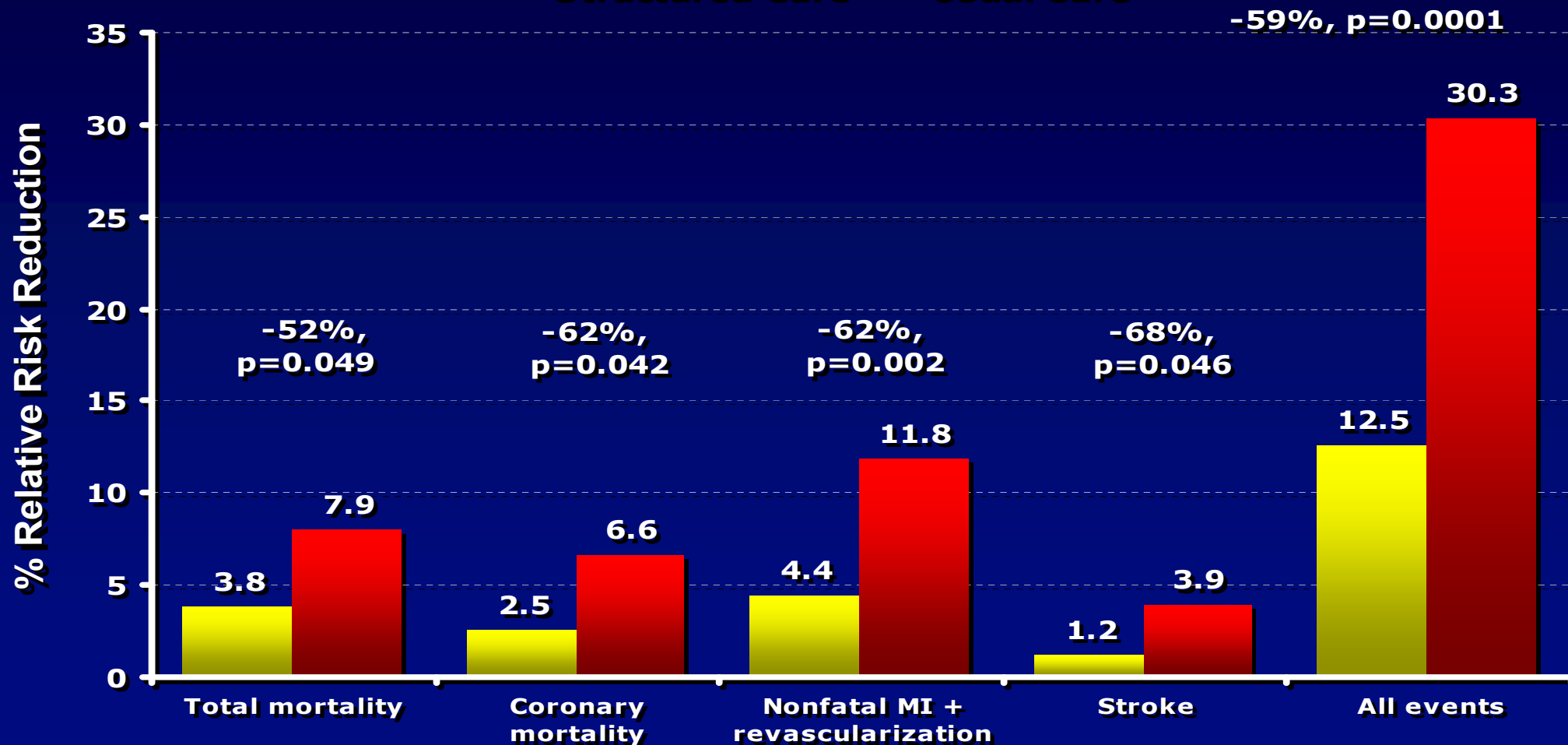
■ Ελάττωση ΤΡ

- Έλεγχος γλυκαιμίας πρώτη προτεραιότητα
- **Φιβράτες-ω3 λιπαρά οξέα**
- **Στατίνες σε υψηλές δόσεις**

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

Primary endpoints : 3-year mortality and morbidity rates

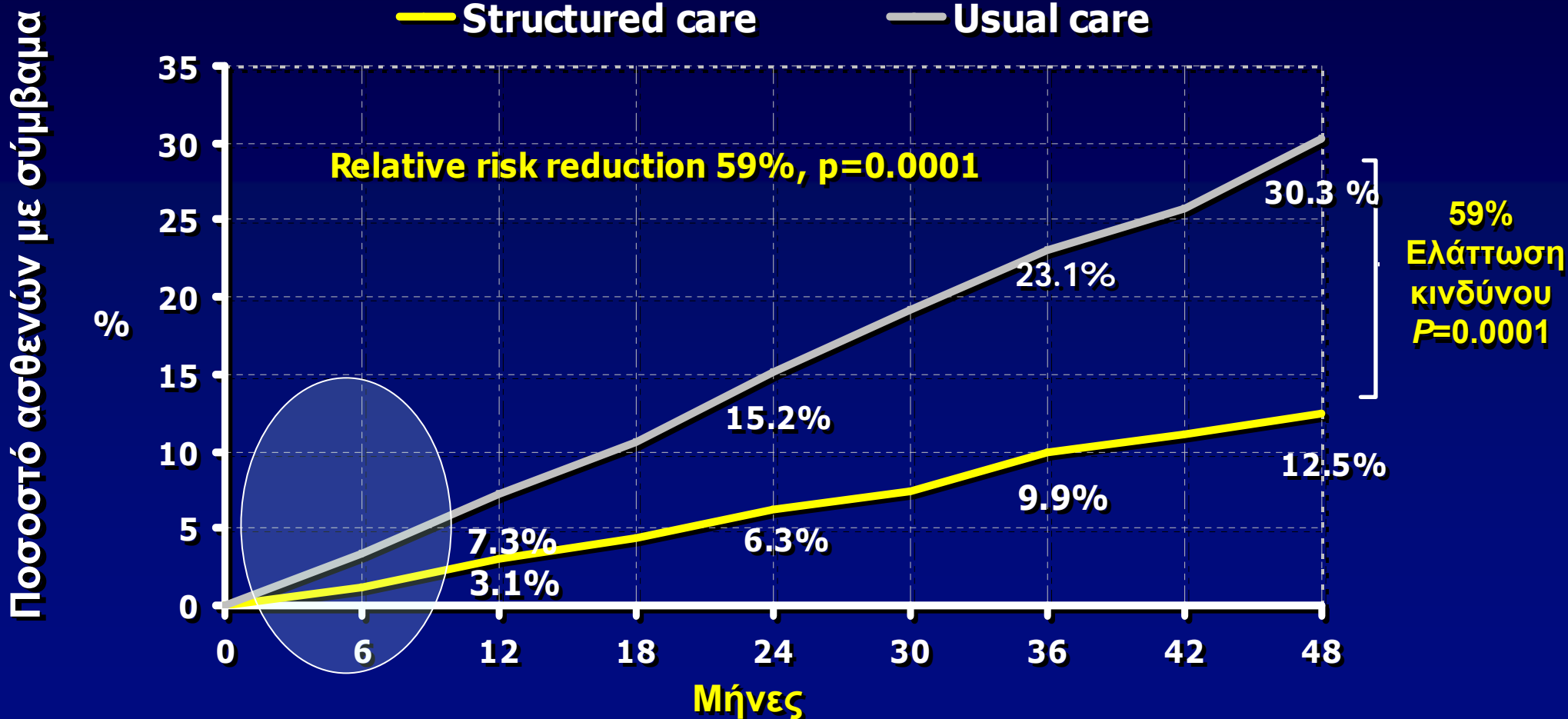
■ Structured Care ■ Usual Care



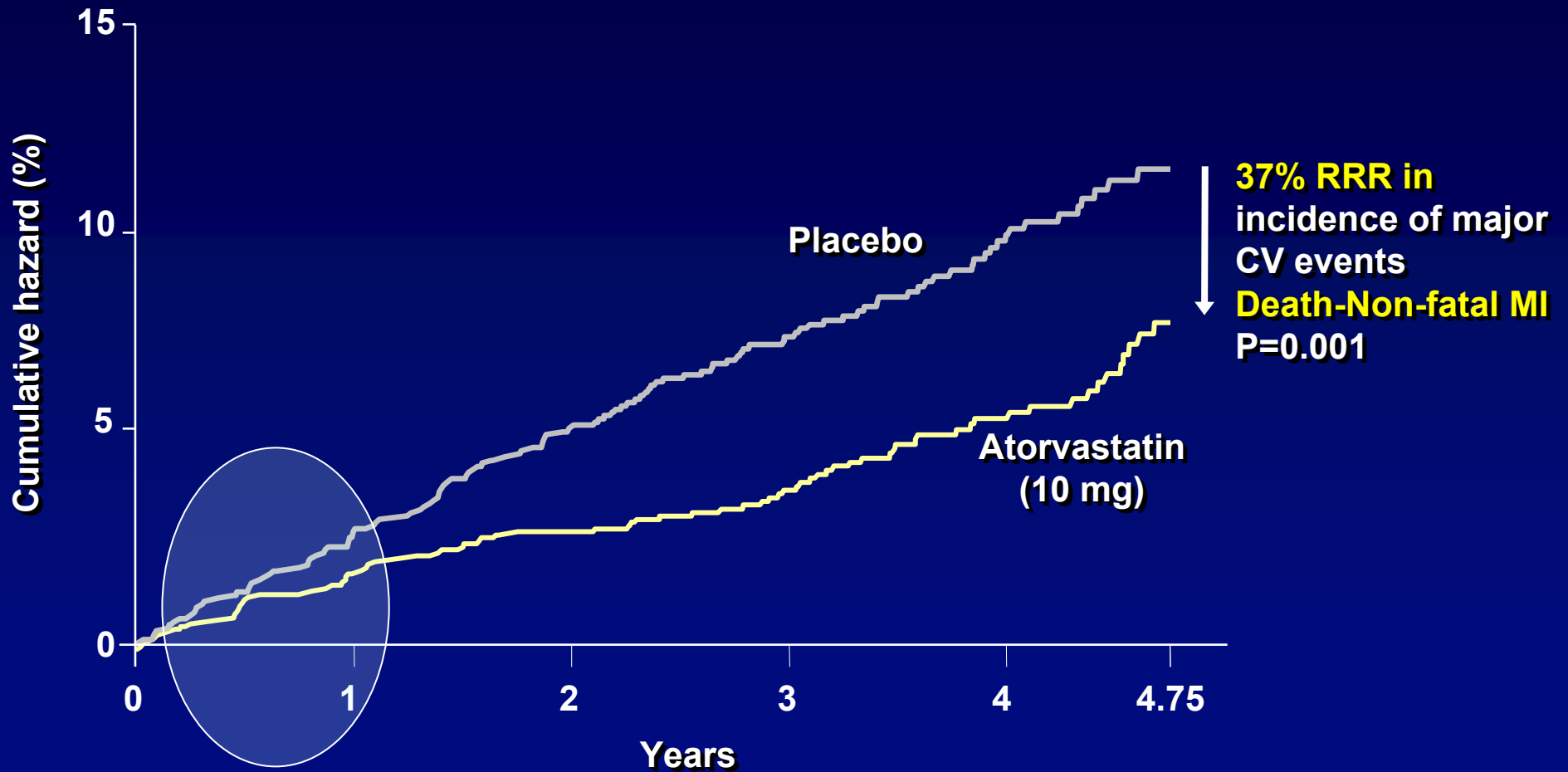
Ασθενείς με ΣΔ :

Καμπύλες συμβαμάτων για όλα τα συμβάματα

Όλα τα συμβάματα

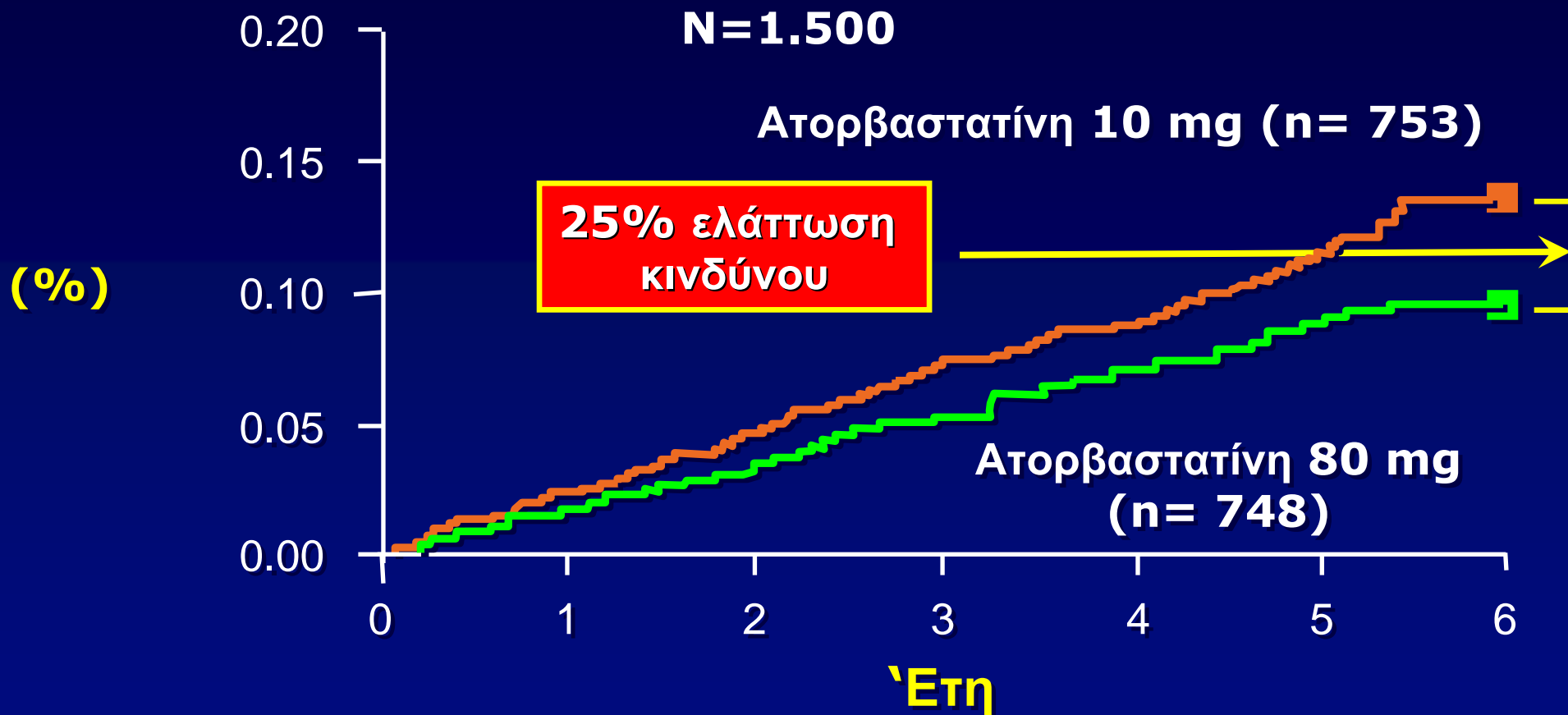


CARDS: Atorvastatin Reduced the Risk of Primary CV Events in Patients With Type 2 Diabetes





TNT diabetes analysis: Μείζονα Κ/Α συμβάματα

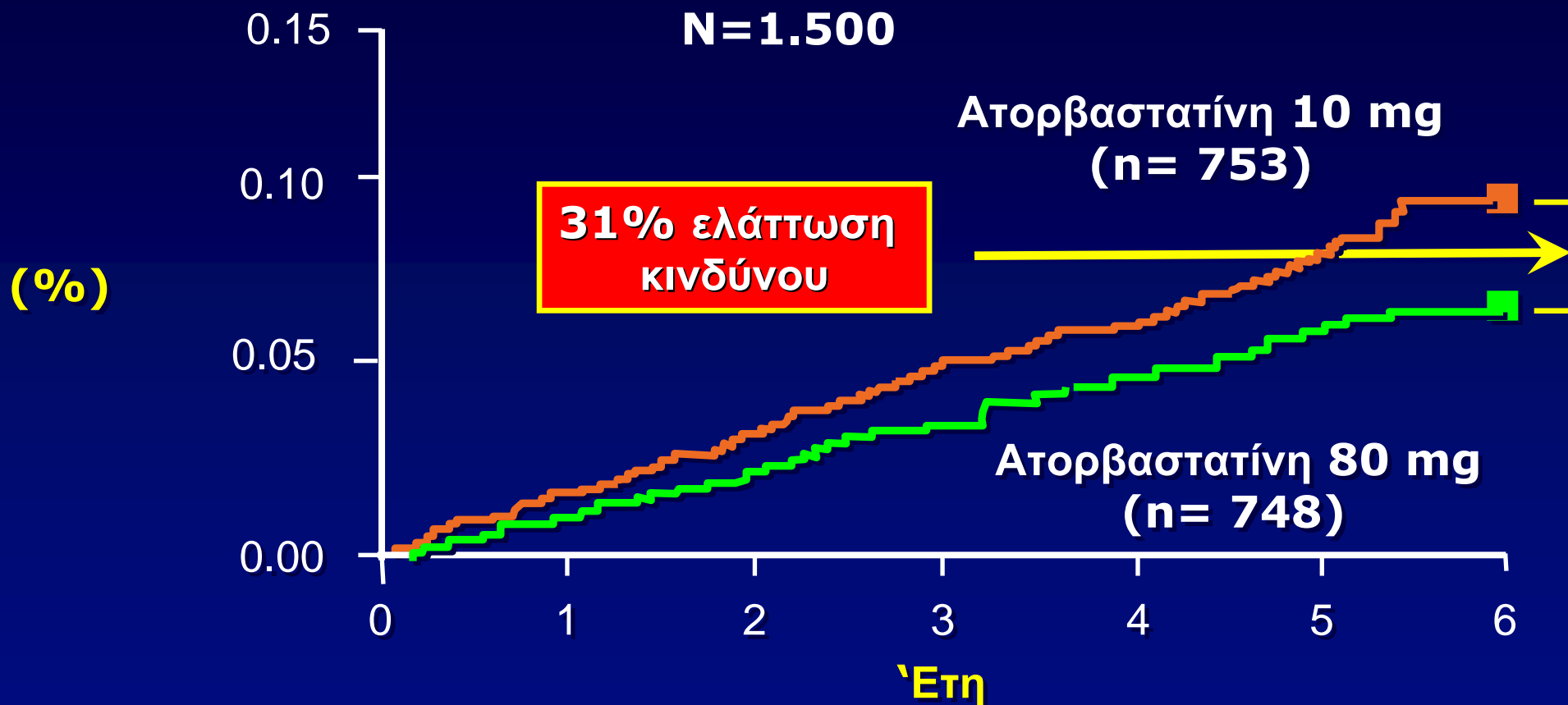


HR = 0.75, P = 0.026

Shepherd J, et al . Diabetes Care 2006;29:1220-1226.



TNT diabetes analysis: Επίδραση της θεραπείας στο ΑΕΕ

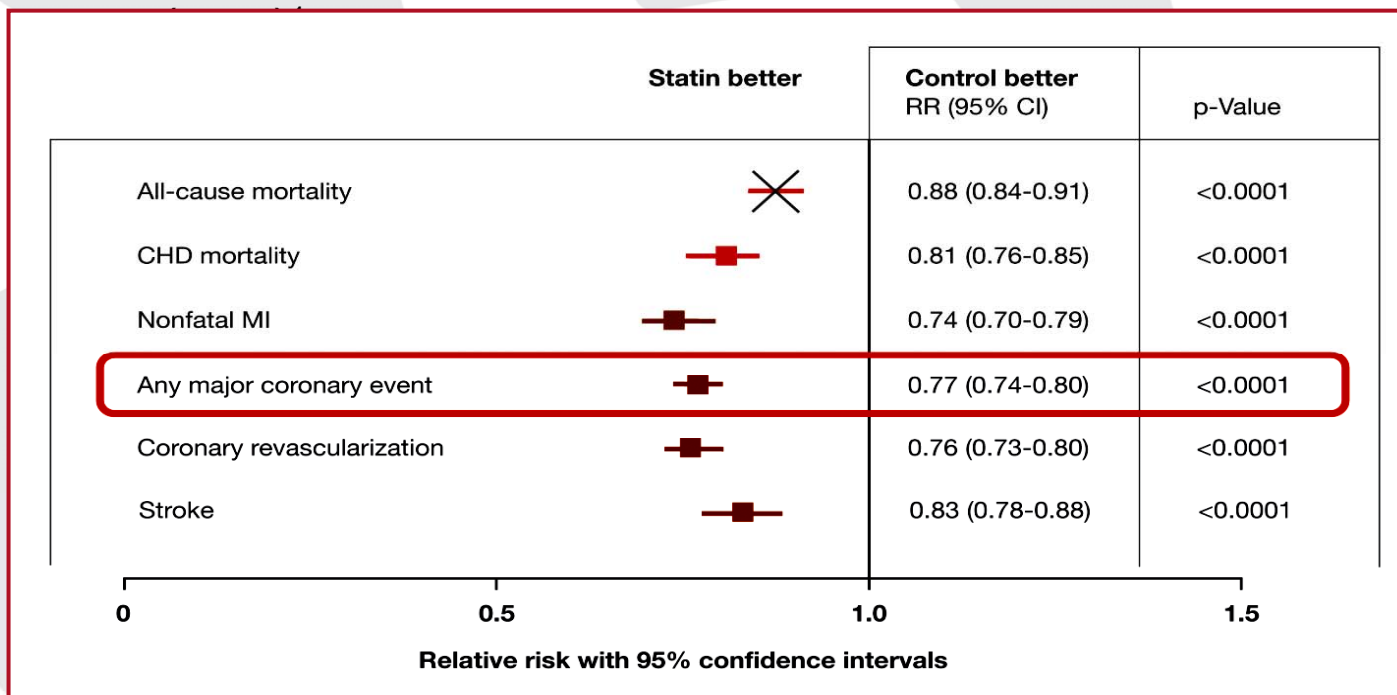


HR = 0.69, P = 0.037

Shepherd J, et al . Diabetes Care 2006;29:1220-1226.

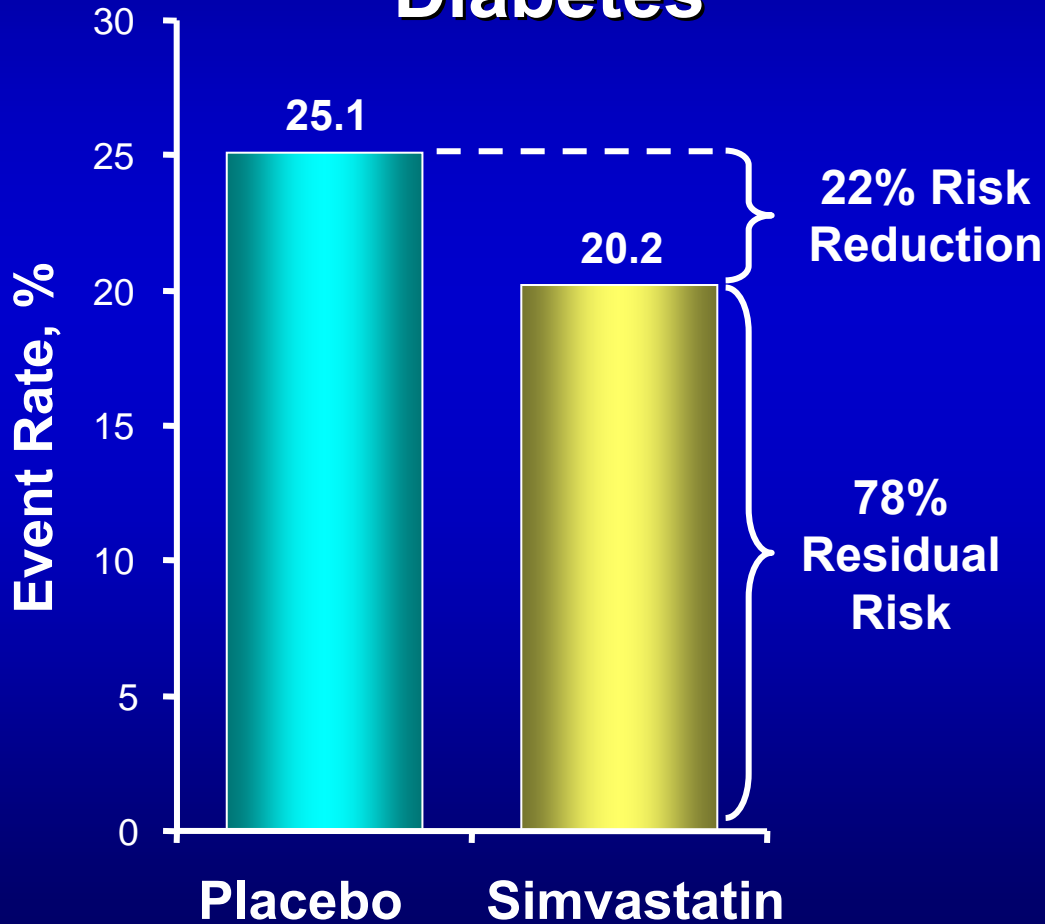
Παρά την επίτευξη των στόχων μείωσης της LDL-C, ο κίνδυνος εμφάνισης ΜΑΚΡΟαγγειακών επιπλοκών εξαιτίας του Υπολειπόμενου Καρδιαγγειακού Κινδύνου είναι αυξημένος

Η μείωση της LDL-χοληστερόλης κατά 1 mmol/L (περίπου 40 mg/dL) με στατίνες ελάττωσε την πιθανότητα εμφάνισης μείζωνων επεισοδίων ΣΤ κατά 23%, αλλά δεν μείωσε τον Υπολειπόμενο Καρδιαγγειακό Κίνδυ

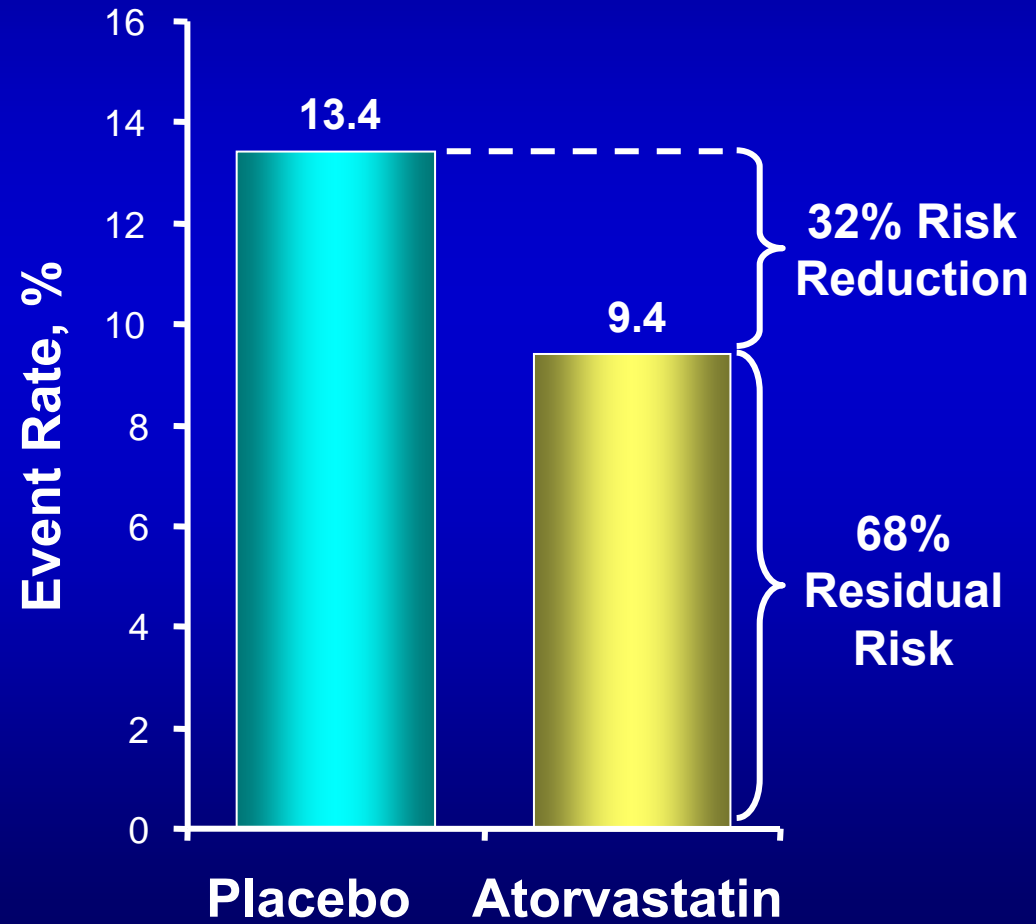


Residual CVD Risk With Statin Therapy: Standard Doses in Diabetes

HPS: Patients With Diabetes

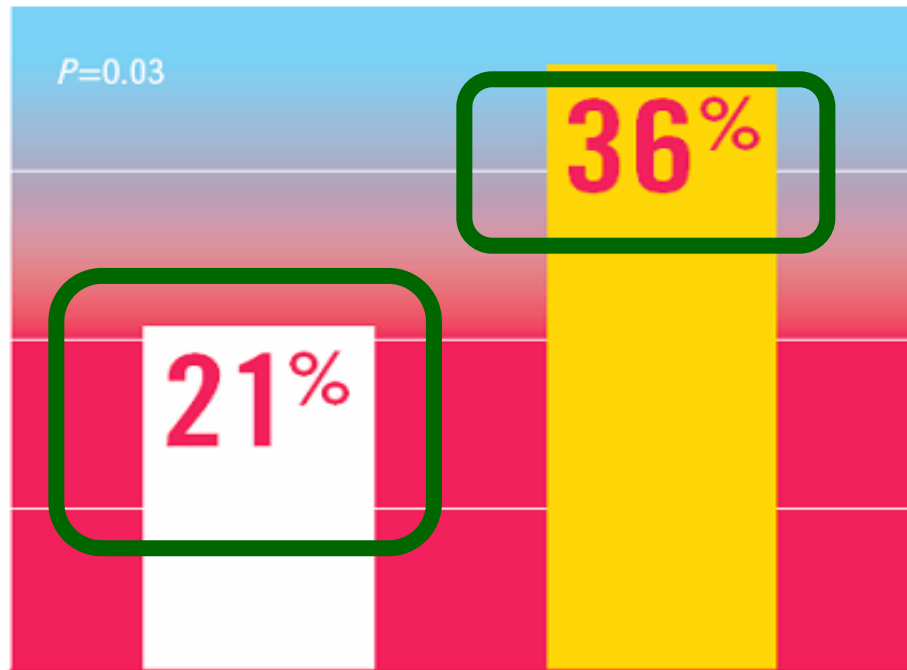


CARDS (diabetes)



Οι ασθενείς με παθολογικές τιμές και των 3 λιπιδαιμικών παραμέτρων έχουν υψηλότερο κίνδυνο εμφάνισης ΣΝ, σε σχέση με τα άτομα που έχουν μεμονωμένη αύξηση της LDL-C

Ποσοστά σοβαρών στεφανιαίων συμβαμάτων ασθενών με ΣΚΝ που ελάμβαναν εικονικό φάρμακο, στα 5 χρόνια



**Μεμονωμένη
αύξηση της LDL-C**

**3 λιπιδαιμικές
διαταραχές**

ΣΥΝΔΥΑΣΜΟΙ ΦΑΡΜΑΚΩΝ ΓΙΑ ΤΗ ΒΕΛΤΙΩΣΗ ΤΟΥ ΣΥΝΟΛΙΚΟΥ ΛΙΠΙΔΑΙΜΙΚΟΥ ΠΡΟΦΙΛ

ΣΤΑΤΙΝΗ + ω -3 ΛΙΠΑΡΑ ΟΞΕΑ

ΣΤΑΤΙΝΗ + ΦΙΜΠΡΑΤΗ

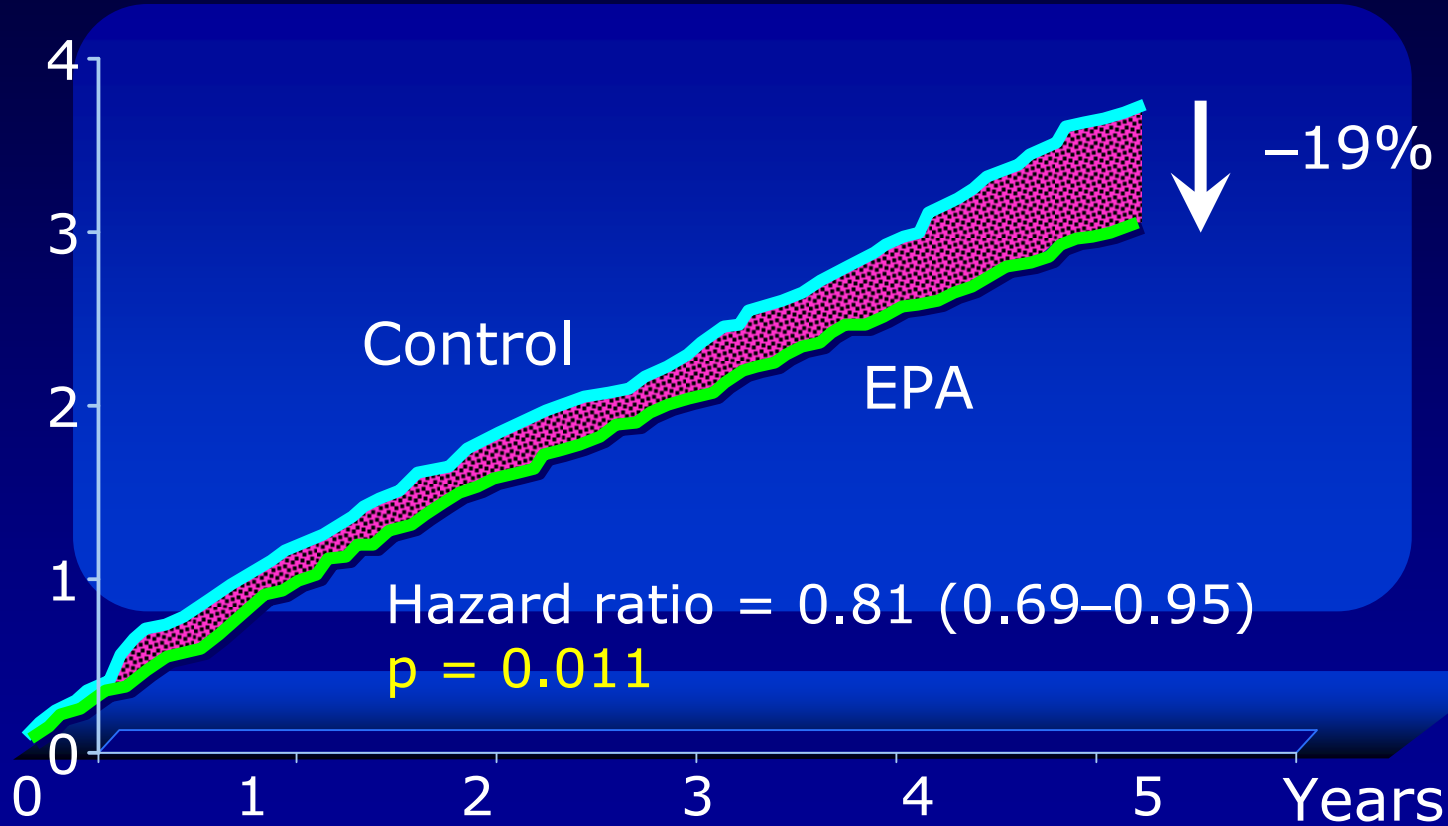
ΣΤΑΤΙΝΗ + ΝΙΑΣΙΝΗ

AHA Recommendations for Omega-3 FA Intake

Population	Recommendation
Patients without documented CHD	Eat a variety of (preferably oily) fish at least twice a week . Include oils and foods rich in α -linolenic acid (flaxseed, canola, and soybean oils; flaxseeds; and walnuts)
Patients with documented CHD	Consume ~1 g of EPA+DHA per day , preferably from oily fish. EPA+DHA supplements could be considered in consultation with the physician
Patients needing triglyceride lowering	2-4 grams of EPA+DHA per day provided as capsules under a physician's care

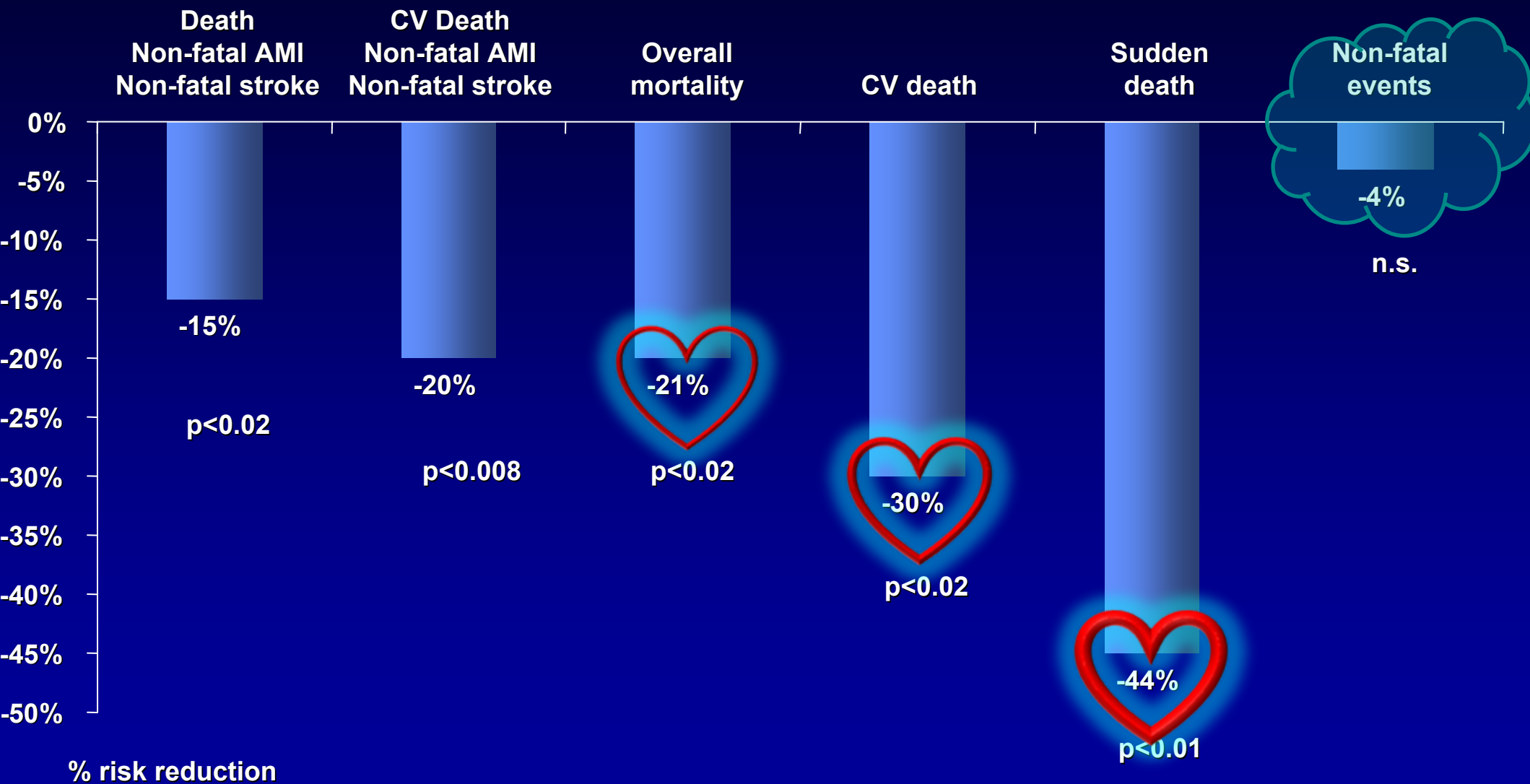
Japan EPA Lipid Intervention Study (JELIS)

Cumulative Incidence of
Major Coronary Events
(%)



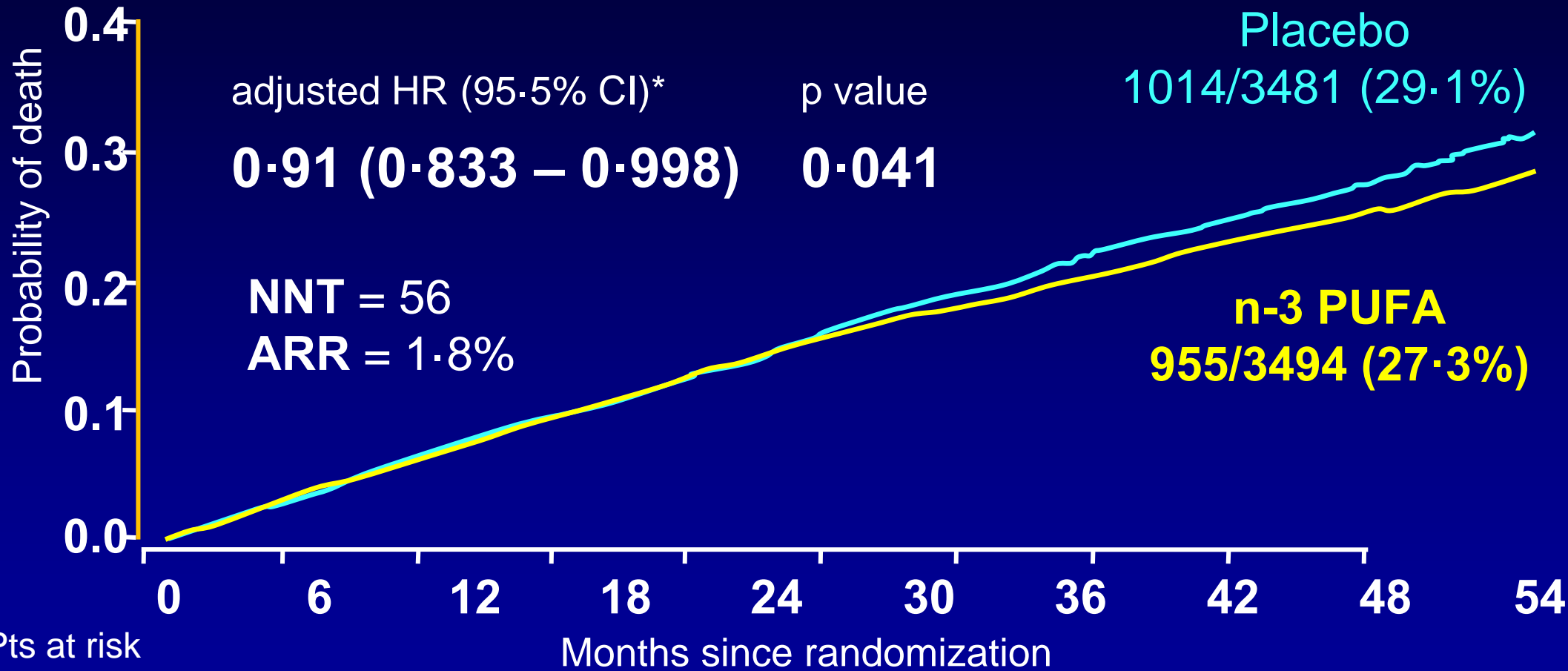
18,645 Japanese (70% women, mean age 61 years) randomized to statin alone or statin + EPA (1.8 g/d) and followed for 5 years

GISSI-Prevenzione: Effect of n-3 PUFA treatment in GISSI-Prevenzione (11,323 post-MI pts)



(GISSI-Prevenzione Investigators, Lancet 1999; 354:447)

GISSI-HF n-3 PUFA: All-cause Death



*Cox proportional hazards model adjusted for HF hospitalization in the previous year, prior pacemaker, and aortic stenosis

ΣΥΝΔΥΑΣΜΟΙ ΦΑΡΜΑΚΩΝ ΓΙΑ ΤΗ ΒΕΛΤΙΩΣΗ ΤΟΥ ΣΥΝΟΛΙΚΟΥ ΛΙΠΙΔΑΙΜΙΚΟΥ ΠΡΟΦΙΛ

ΣΤΑΤΙΝΗ + ω -3 ΛΙΠΑΡΑ ΟΞΕΑ

ΣΤΑΤΙΝΗ + ΦΙΜΠΡΑΤΗ

ΣΤΑΤΙΝΗ + ΝΙΑΣΙΝΗ

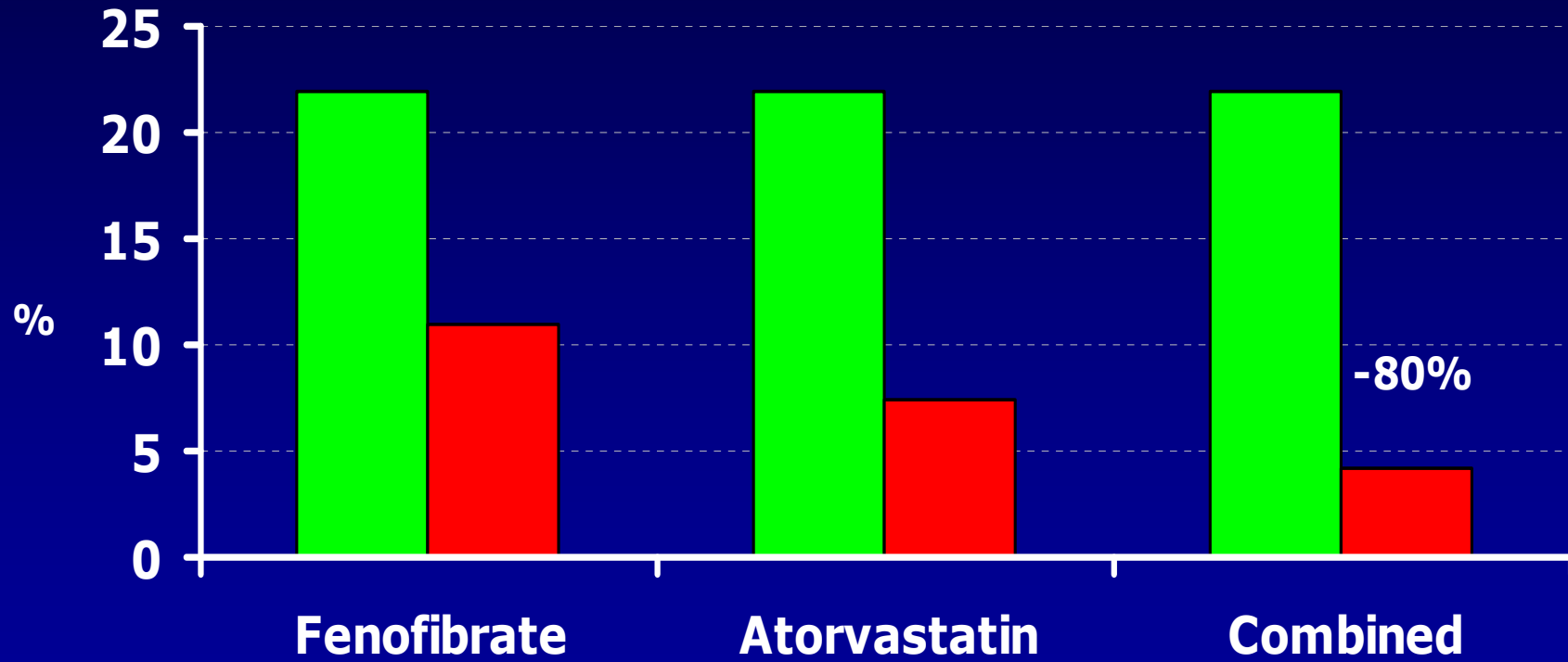


Diabetes Care

**Atorvastatin and Micronized
Fenofibrate Alone and in Combination
in Type 2 Diabetes With Combined
Hyperlipidemia**

Statin Fibrate Combination on 10-year CVD risk in T2DM

■ Baseline 10-year CVD risk ■ Intervention



$p < 0.0001$ vs baseline for all



ELSEVIER

METABOLISM

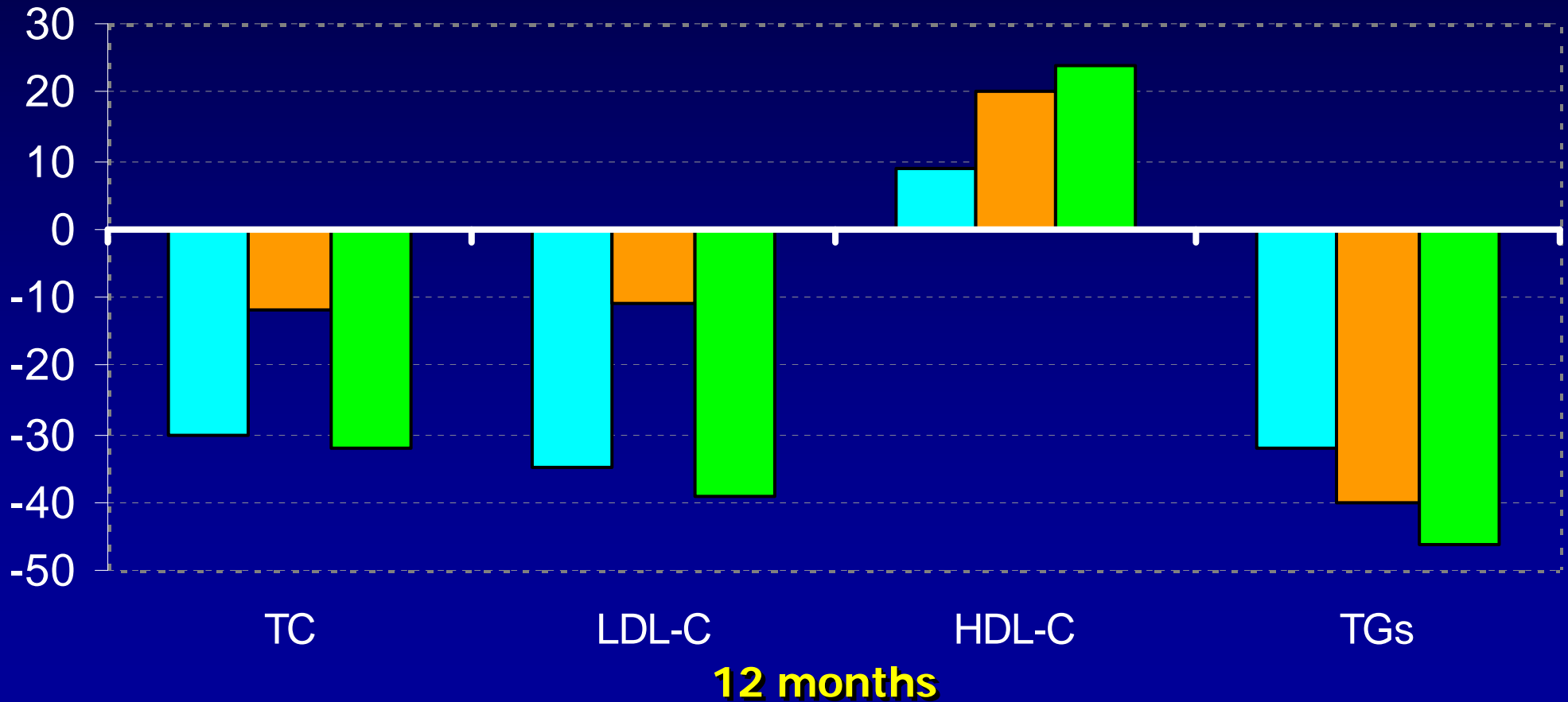
Clinical and Experimental

Targeting vascular risk in patients with metabolic syndrome but without diabetes



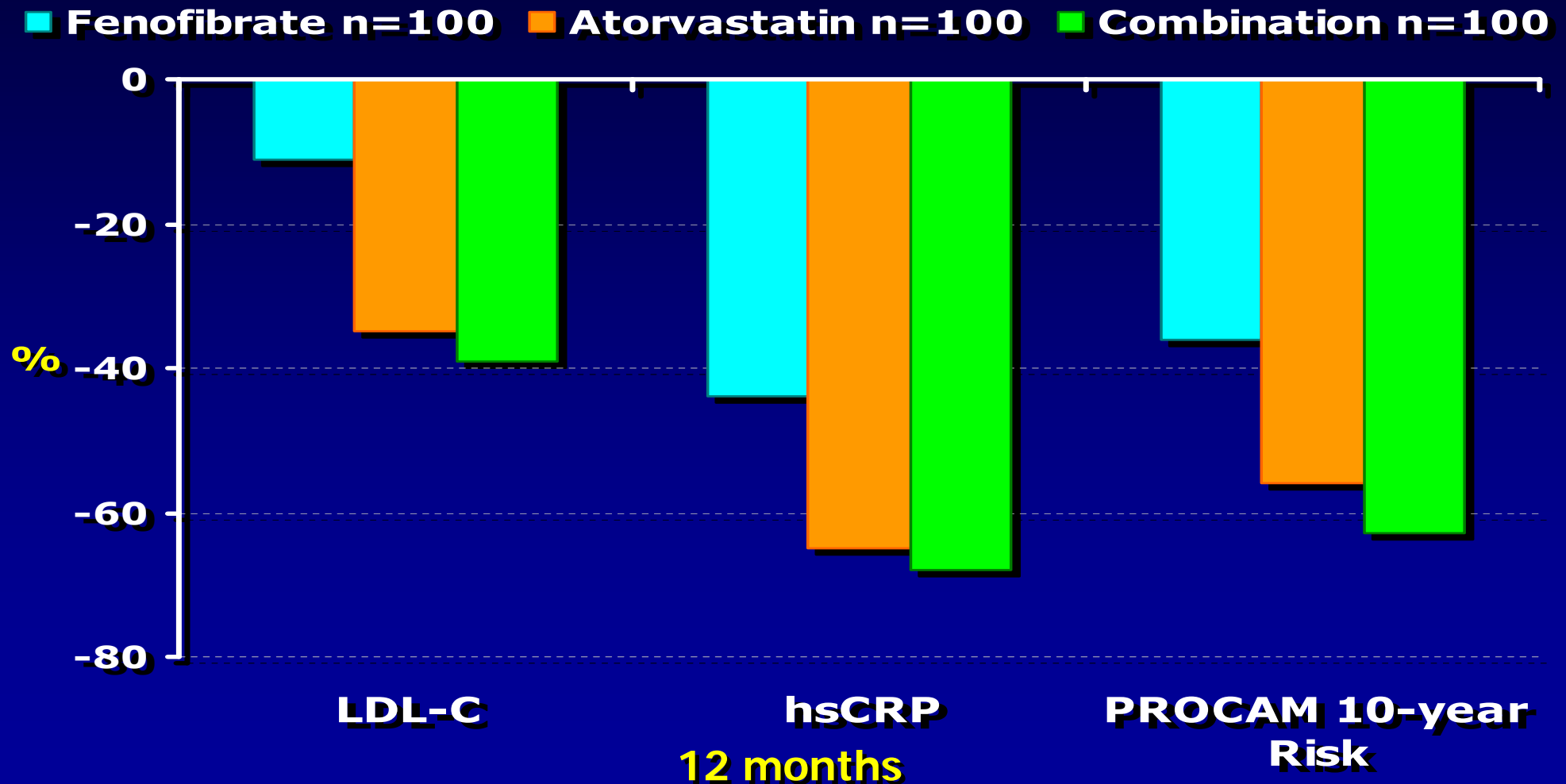
Targeting Cardiovascular Risk in Patients with Metabolic Syndrome

■ Atorvastatin ■ Fenofibrate ■ Combination



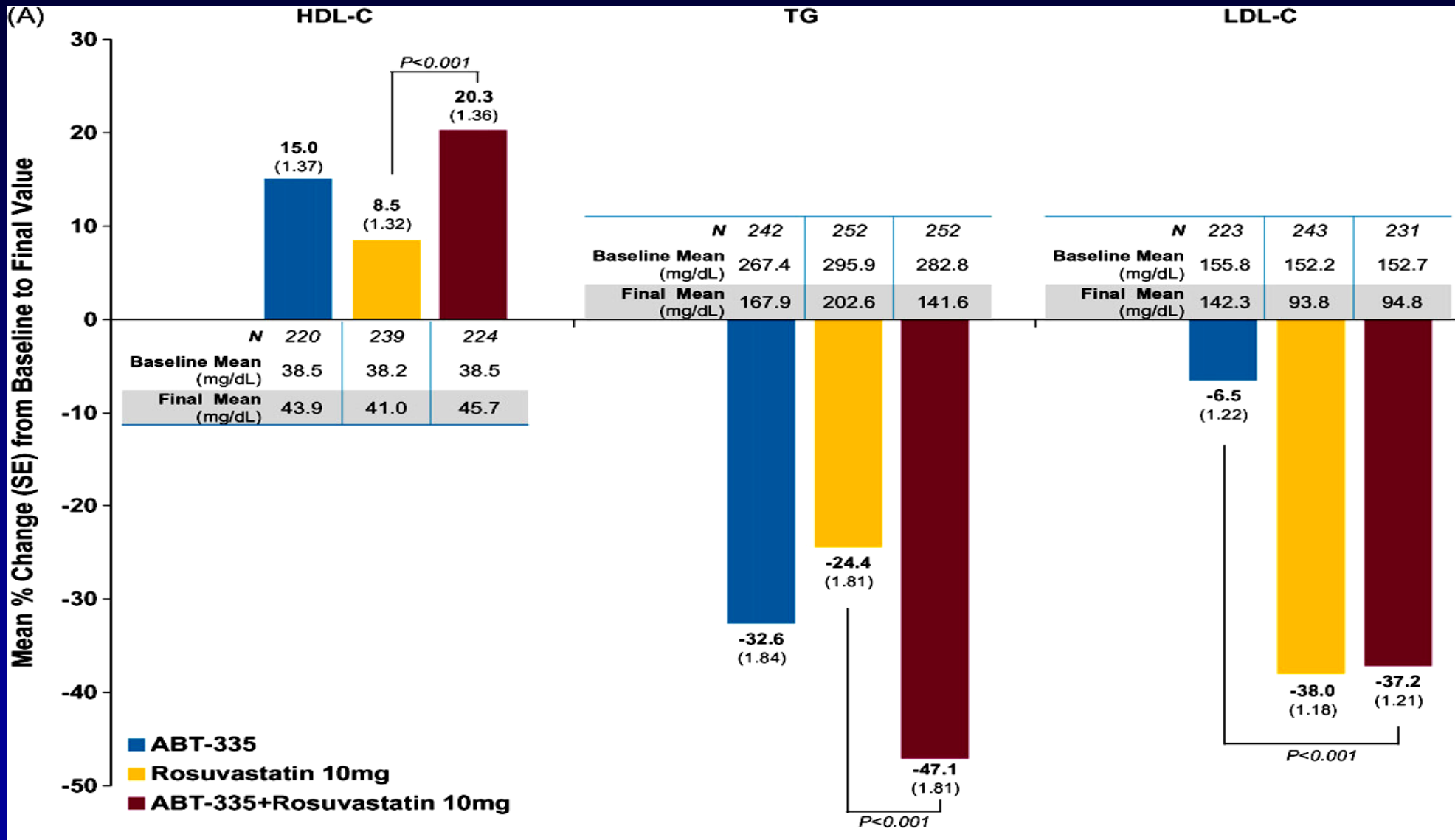


Targeting Cardiovascular Risk in Patients with Metabolic Syndrome without Diabetes



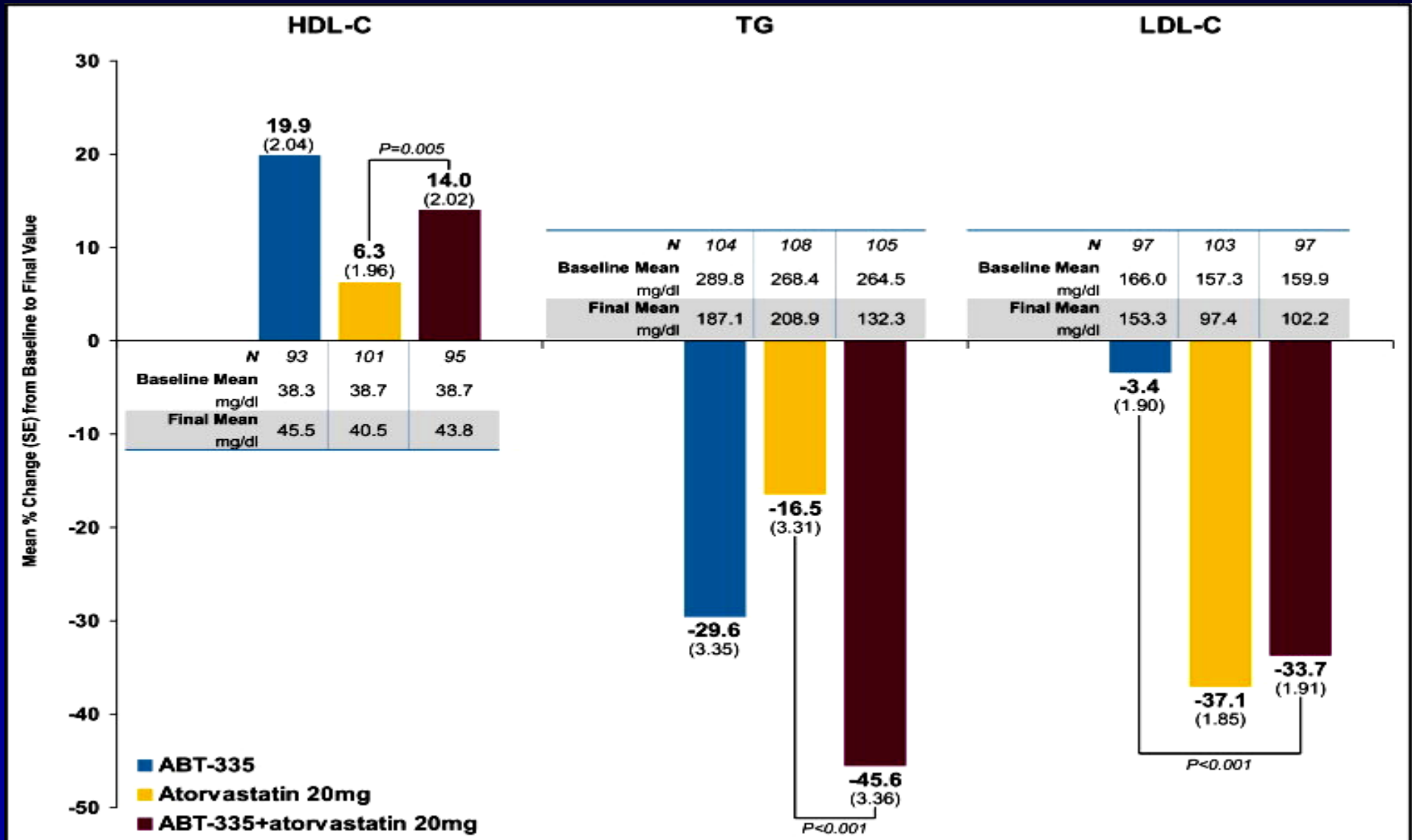
Efficacy and safety of combination with rosuvastatin dyslipidaemia

fenofibric acid in patients with mixed



Efficacy and safety of combination with atorvastatin mixed dyslipidaemia

fenofibric acid in patients with



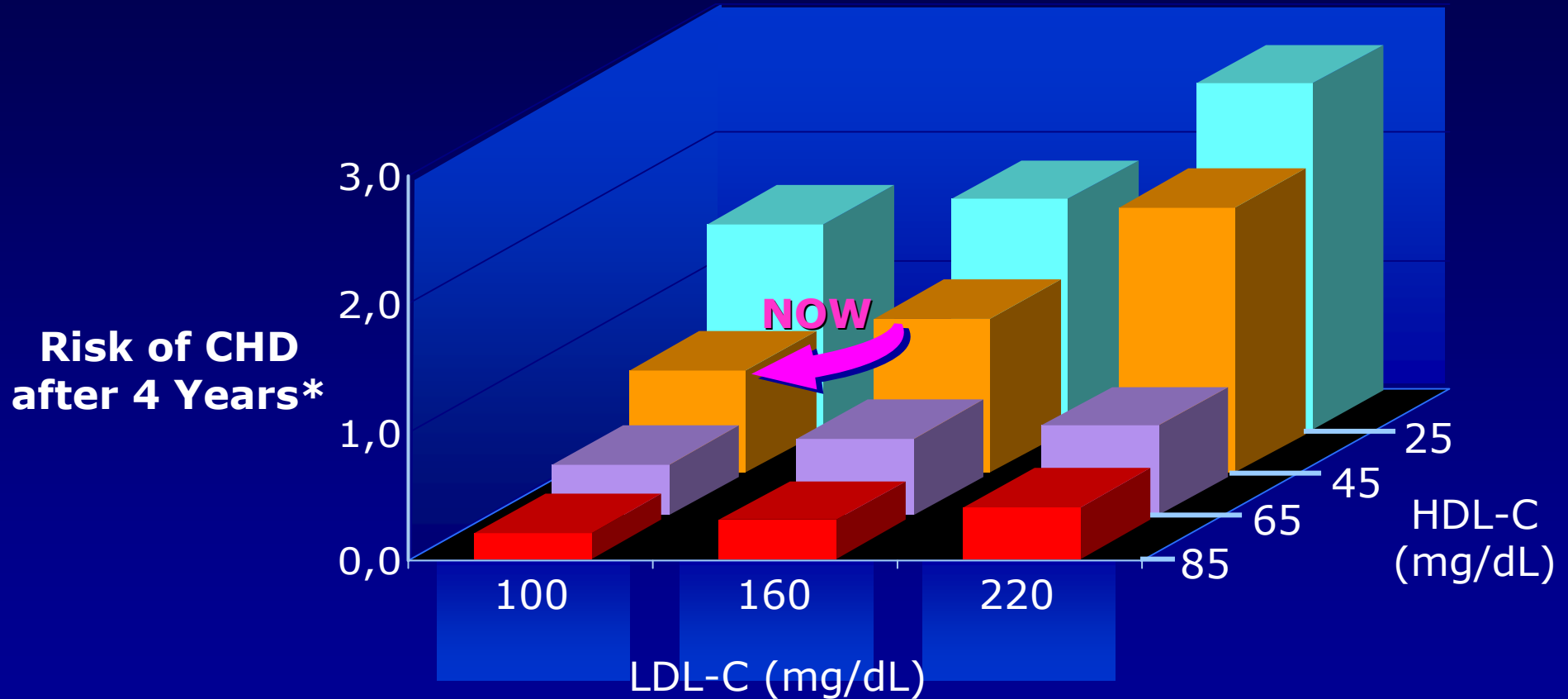
ΣΥΝΔΥΑΣΜΟΙ ΦΑΡΜΑΚΩΝ ΓΙΑ ΤΗ ΒΕΛΤΙΩΣΗ ΤΟΥ ΣΥΝΟΛΙΚΟΥ ΛΙΠΙΔΑΙΜΙΚΟΥ ΠΡΟΦΙΛ

ΣΤΑΤΙΝΗ + ω -3 ΛΙΠΑΡΑ ΟΞΕΑ

ΣΤΑΤΙΝΗ + ΦΙΜΠΡΑΤΗ

ΣΤΑΤΙΝΗ + ΝΙΑΣΙΝΗ

Framingham Study

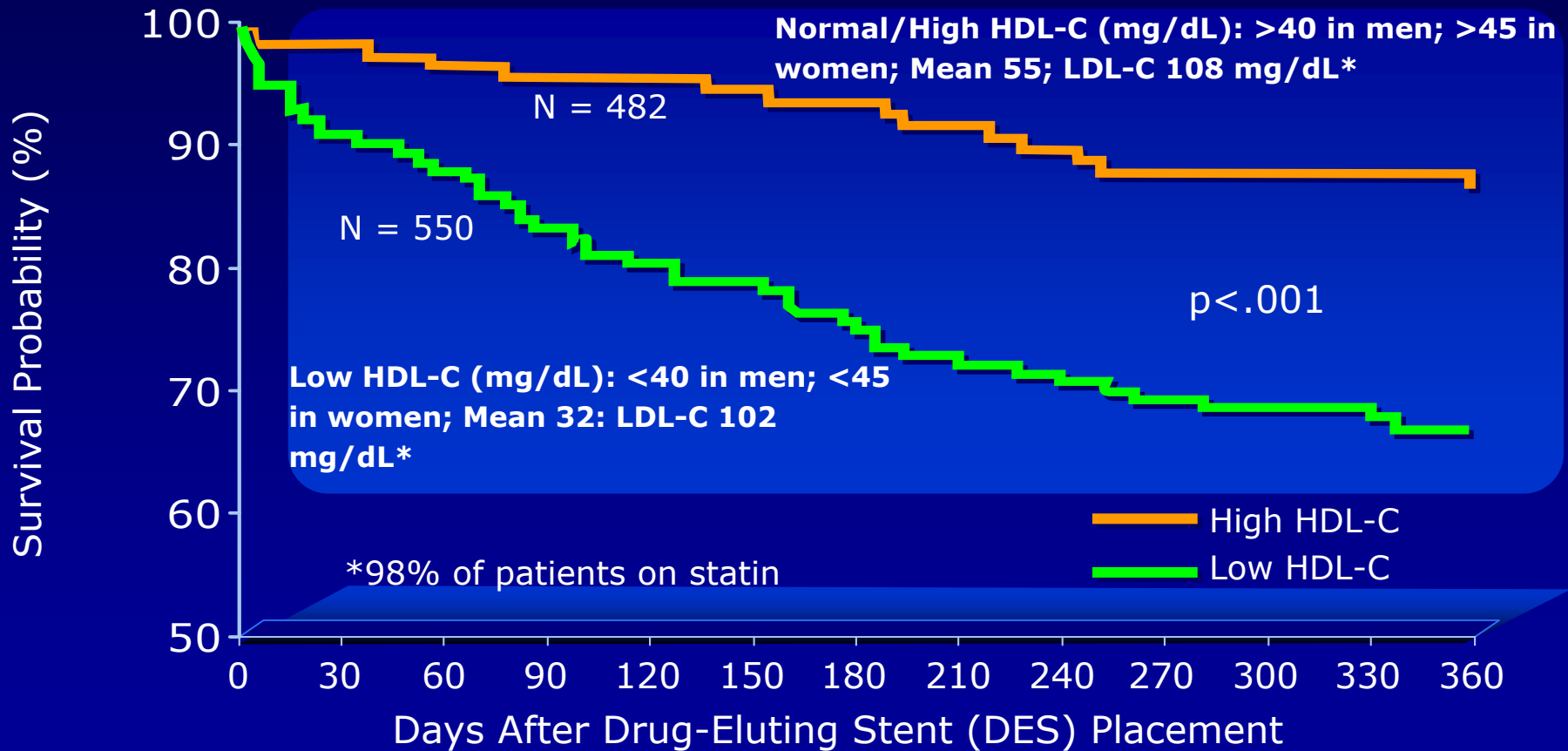


*Risk of coronary heart disease (CHD) over 4 years of follow-up for men ages 50 to 70

Adapted from Castelli WP. Can J Cardiol 1988;4 Suppl A:5A-10A.

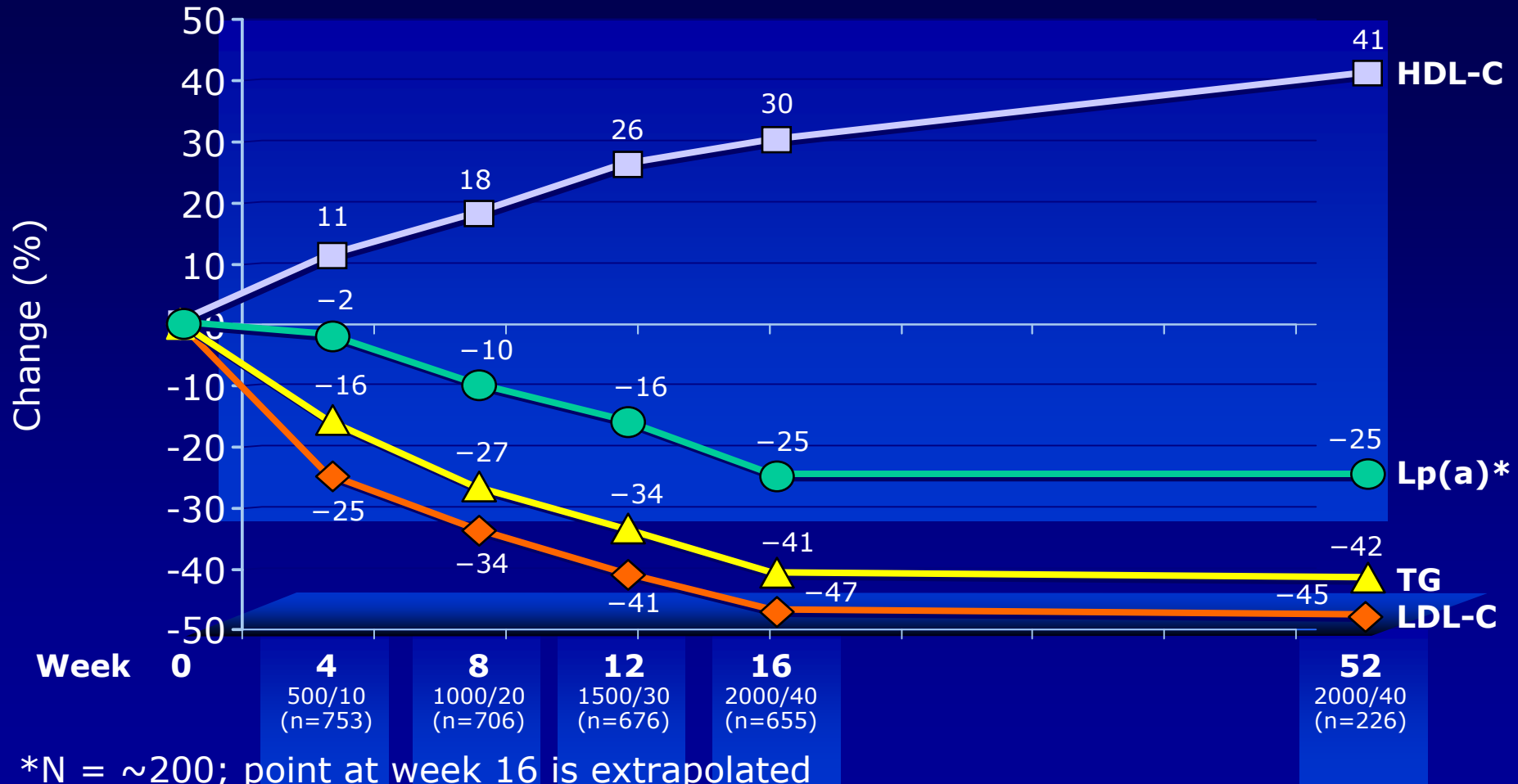
1-Year Event-Free Survival Post-DES: Low vs. High HDL at Baseline

TLR/MACE Survival Curves



TLR=target lesion revascularization; MACE=major adverse cardiac event

Extended-Release Niacin and Lovastatin: Long-Term Study

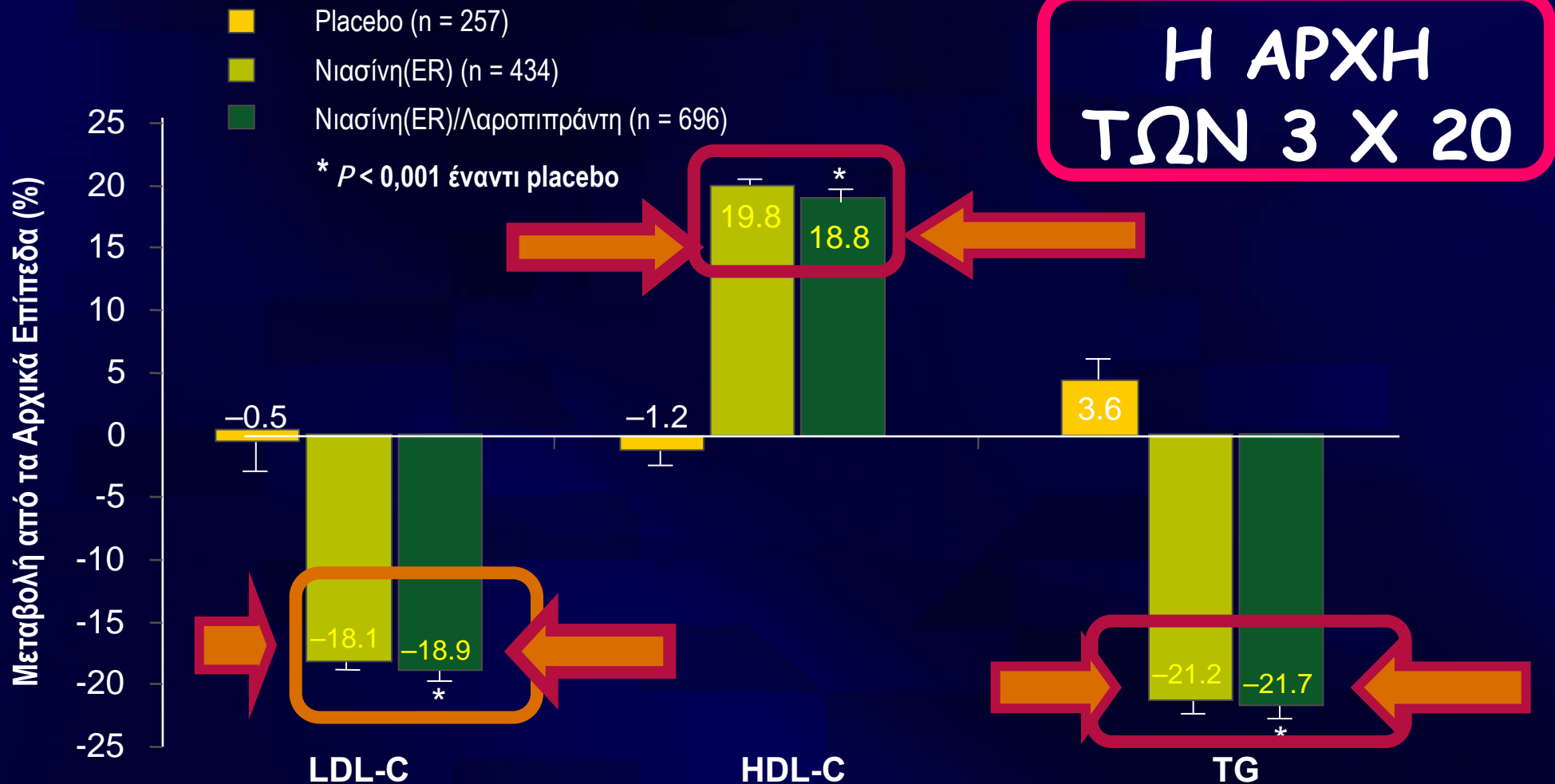


HDL-C=high-density lipoprotein cholesterol; Lp(a)=lipoprotein (a); TG=triglyceride; LDL-C=low-density lipoprotein cholesterol

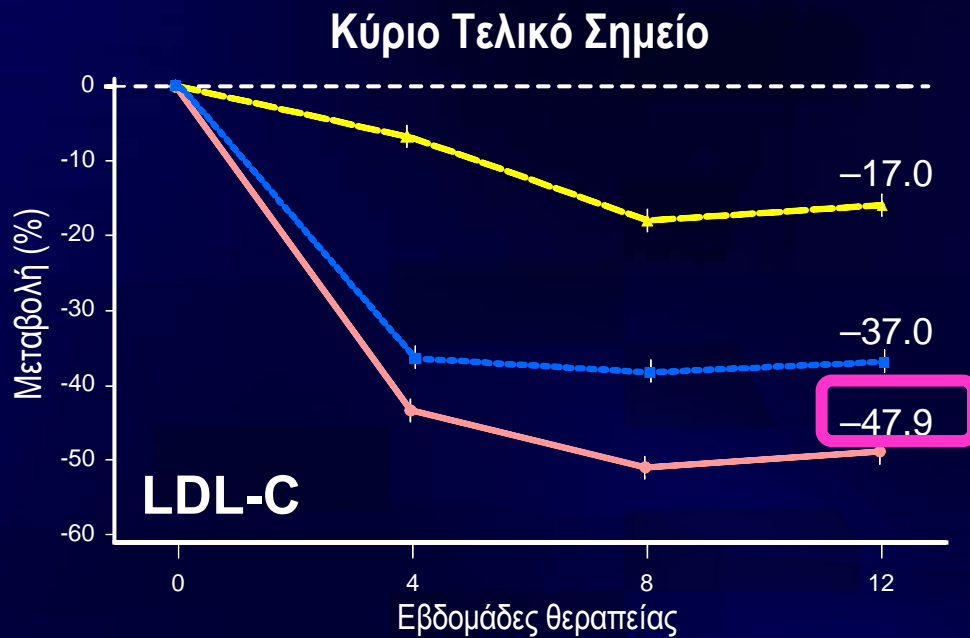
Kashyap ML et al. *Am J Cardiol* 2002;89:672-678.

Lipid / Flushing Study:

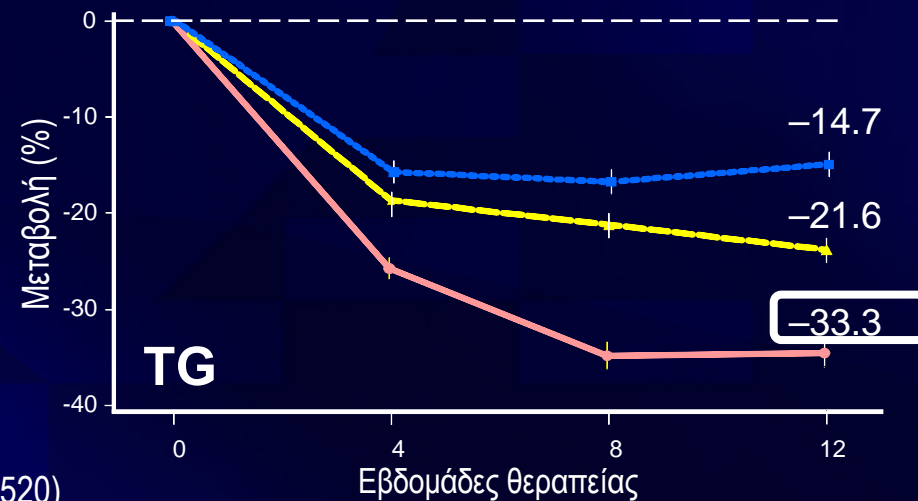
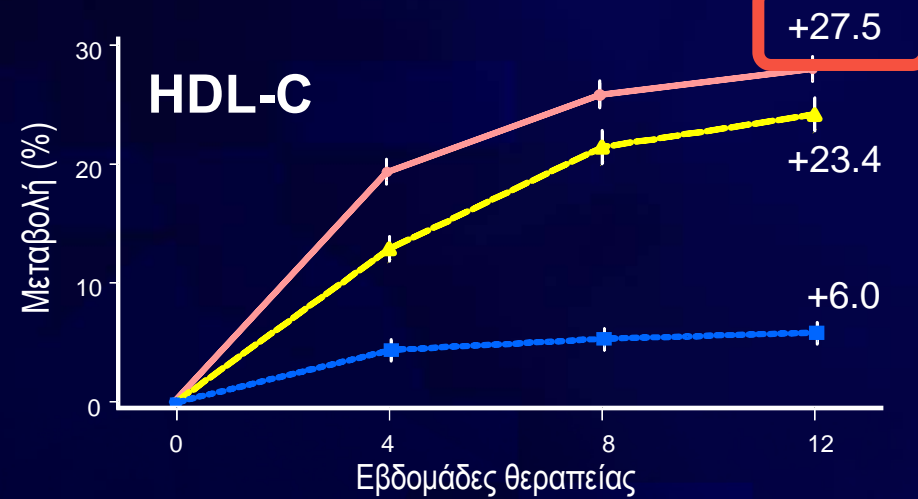
Υπολιπιδαιμική Αποτελεσματικότητα (εβδ. 12–24)



Factorial Study: Υπολιπιδαιμική Αποτελεσματικότητα

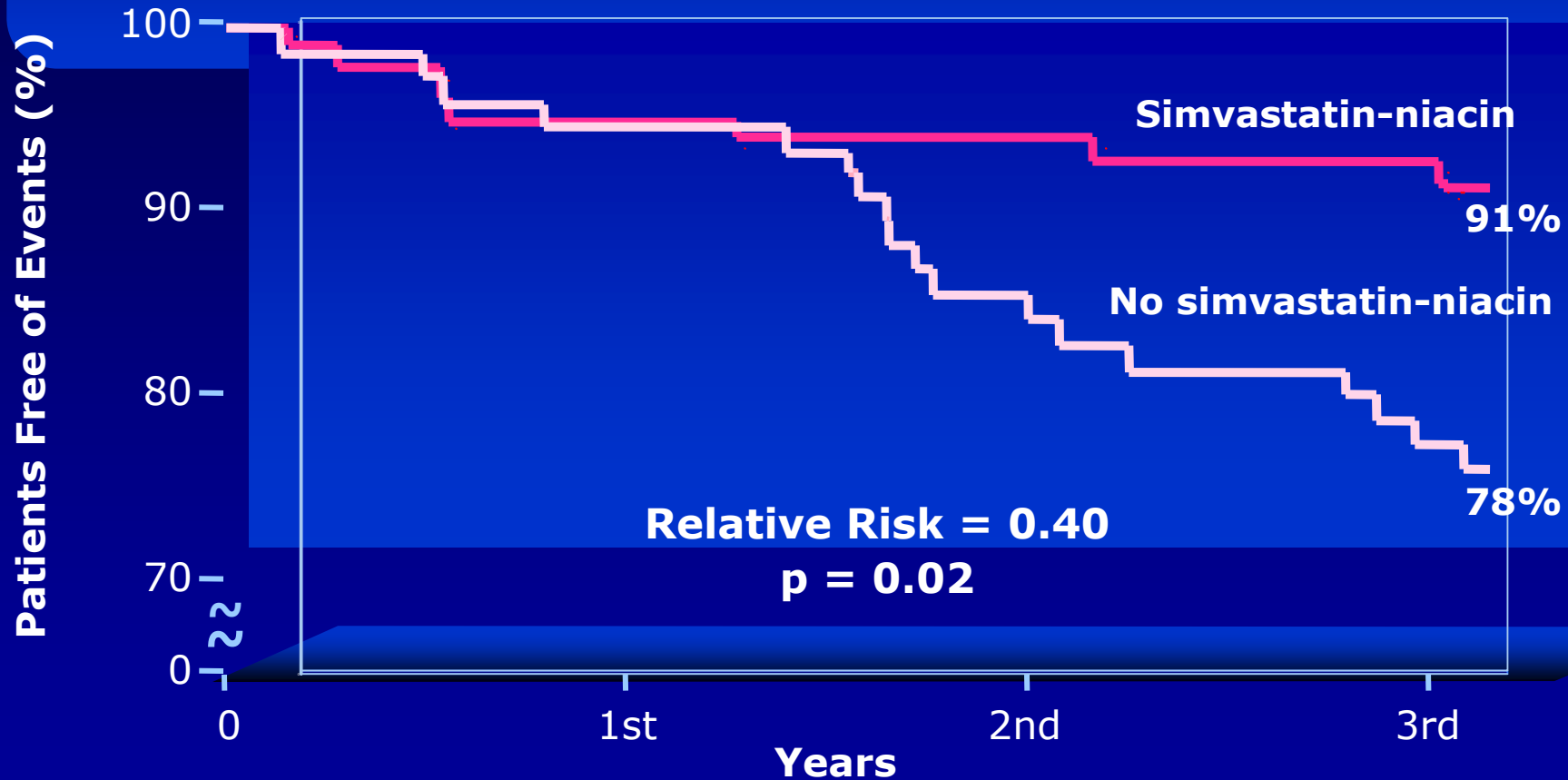


- ▲ Νιασίνη(ER)/Λαροπιπράντη (n = 160)
- Σιμβαστατίνη (όλες οι δόσεις, n = 565)
- Νιασίνη(ER)/Λαροπιπράντη + Σιμβαστατίνη (όλες οι δόσεις, n = 520)



HATS: Primary Clinical Endpoint

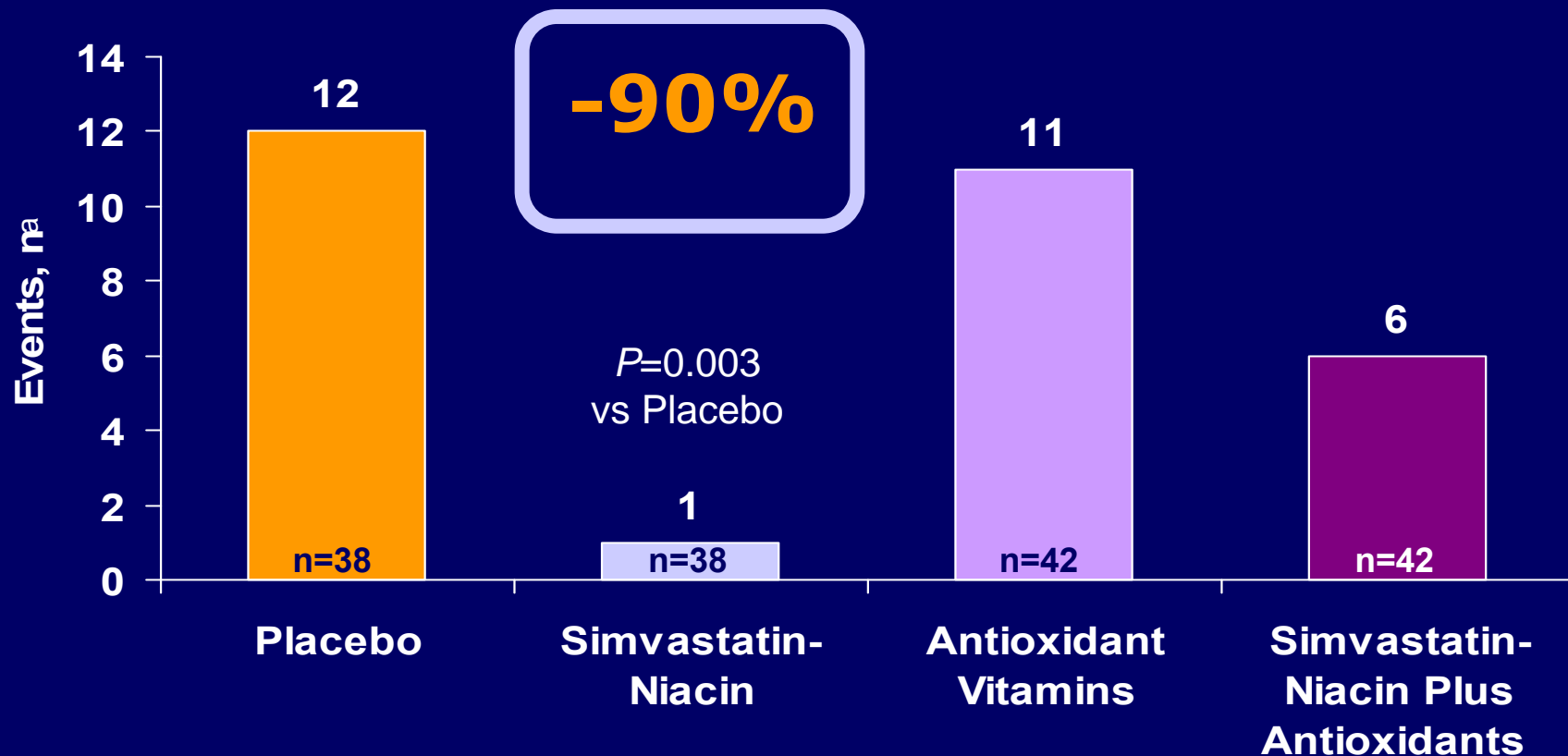
CAD Death, Non-fatal MI, CVA or Revascularization



HATS=HDL-atherosclerosis treatment study; CAD=coronary artery disease; MI=myocardial infarction; CVA=cerebrovascular accident

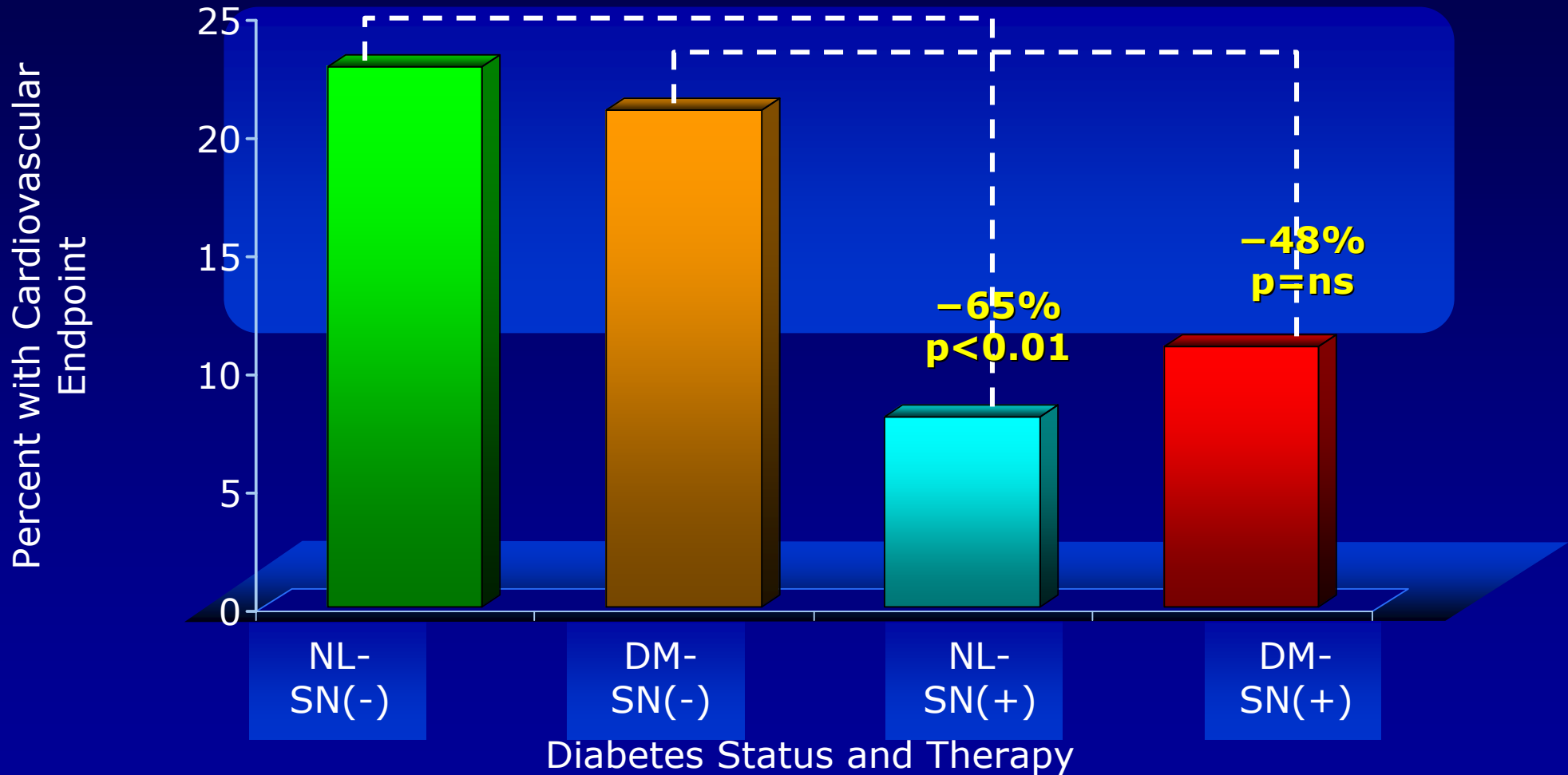
Brown BG et al. *N Engl J Med* 2001;345:1583-1592.

HATS - Niacin and Statin Outcome Trial



^aComposite of coronary death, nonfatal MI, revascularization, hospitalization for confirmed ischemia
HATS=HDL Atherosclerosis Treatment Study
Brown BG et al. *N Engl J Med.* 2001;345:1583–1592.

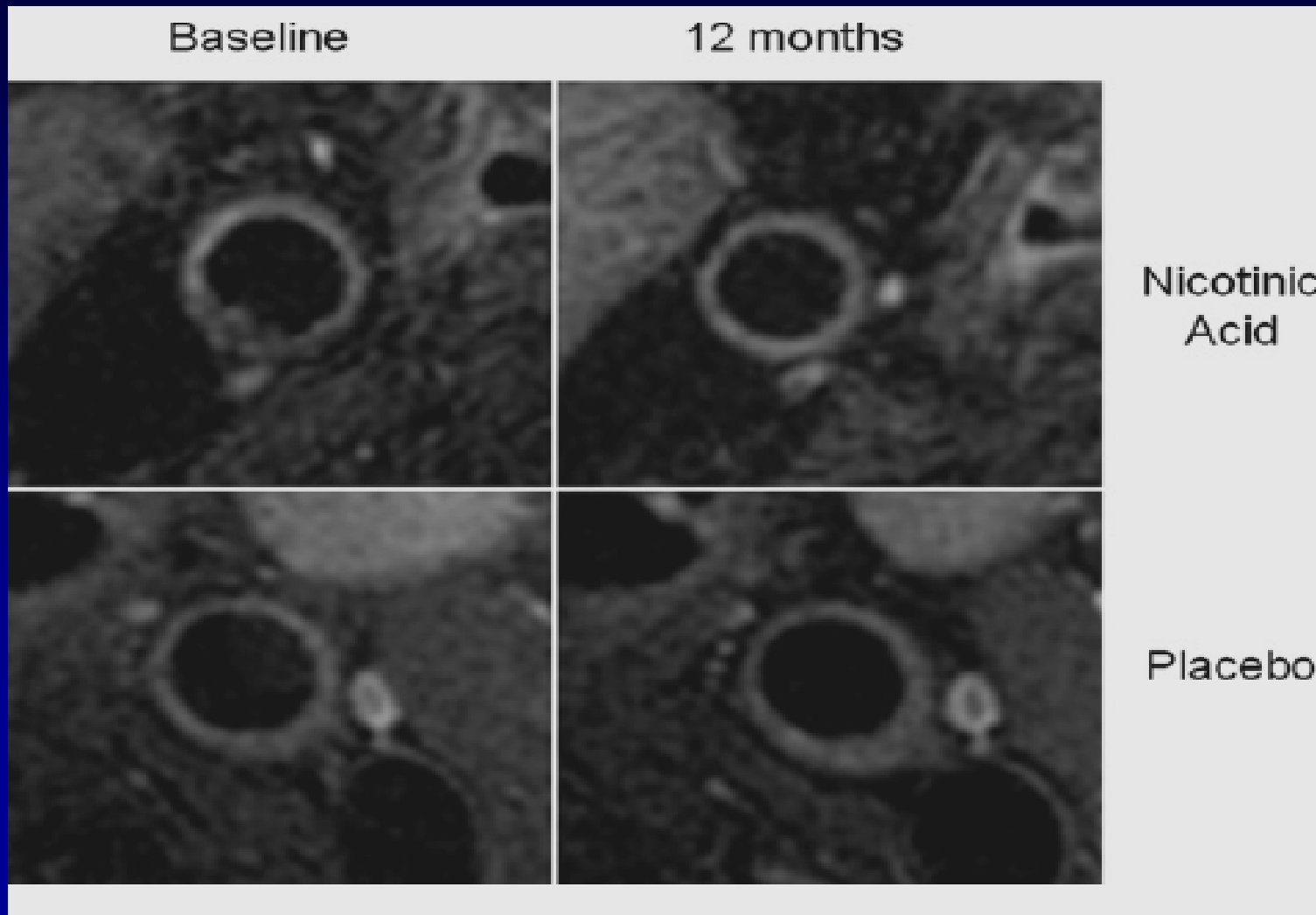
HATS: Cardiovascular Events in Diabetes



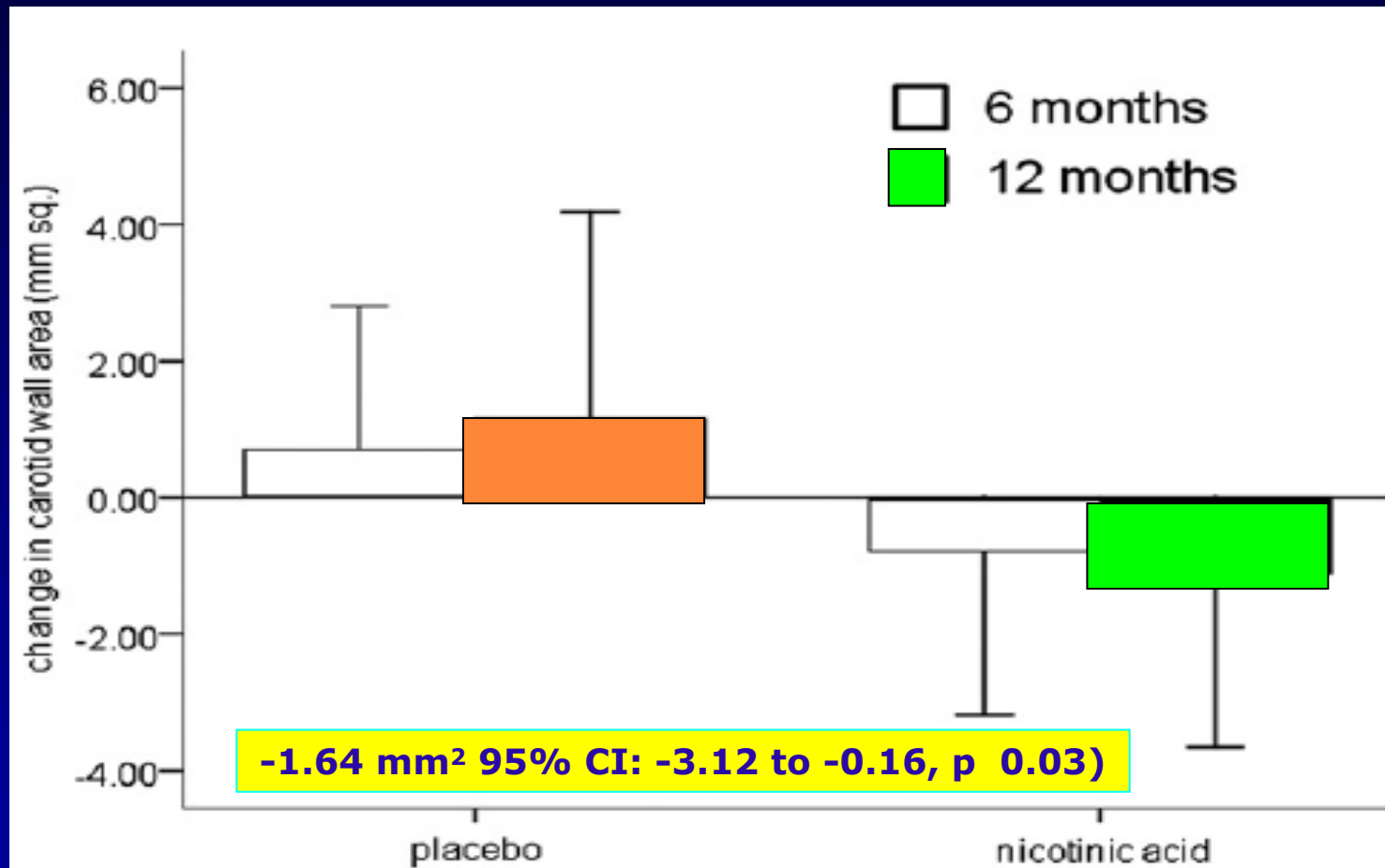
HATS=HDL-atherosclerosis treatment study; NL=normoglycemic; SN=simvastatin-niacin; DM=diabetes mellitus

Zhao XQ et al. Am J Cardiol 2004;93:307-312.

Effects of High-Dose Modified-Release Nicotinic Acid on Atherosclerosis and Vascular Function

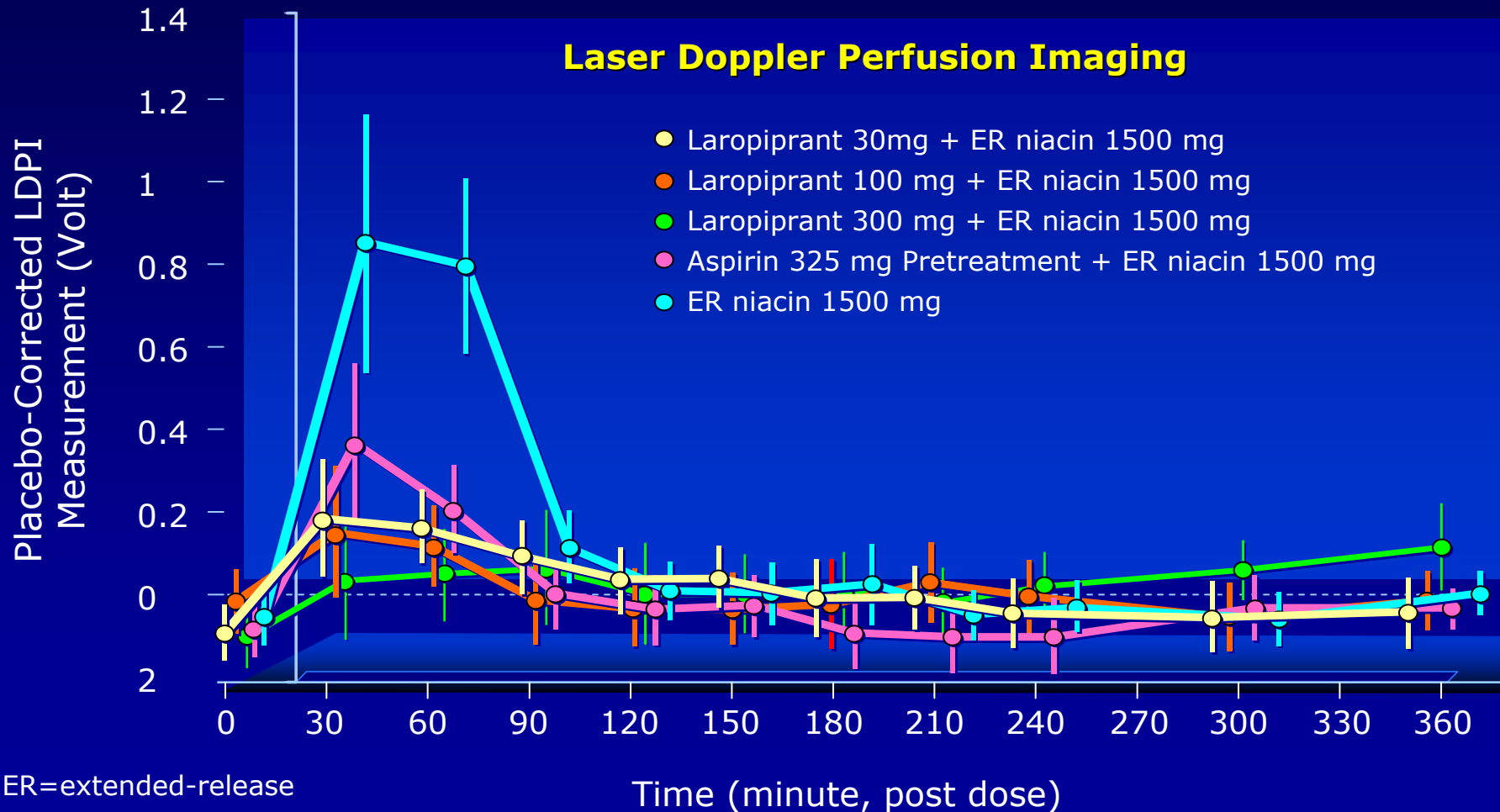


Effects of High-Dose Modified-Release Nicotinic Acid on Atherosclerosis and Vascular Function



Laropiprant (MK-0524)

Suppresses Niacin-Induced Increases in Skin Blood Flow





Περίληψη και Συμπεράσματα

- Σε διαβητικούς ασθενείς η **δυσλιπιδαιμία** είναι συνήθως **μικτή**. Αυτό απαιτεί **συνδυασμούς στατίνης με Ω-3 λιπαρά οξέα ή φιβράτες** (προσοχή ανεπιθύμητες ενέργειες) **ή νιασίνη**.
- Οι ενδείξεις λένε ότι η μελέτες που διενεργούνται θα δείξουν **μεγαλύτερη ελάττωση θνητότητας και νοσηρότητας με συνδυασμούς παρά με μονοθεραπεία με στατίνες** (υπολειπόμενος καρδιαγγειακός κίνδυνος)