

Μετεκπαιδευτικά μαθήματα Β' Προπαιδευτικής Παθολογικής Κλινικής
Ιπποκράτειο Νοσοκομείο Θεσσαλονίκης
Νοέμβριος 2011

**ΑΝΤΙΜΕΤΩΠΙΣΗ ΑΣΘΕΝΟΥΣ
ΜΕ ΑΘΗΡΟΓΟΝΟ ΔΥΣΛΙΠΙΔΑΙΜΙΑ**

Άννα Ι. Κακαφήκα
Παθολόγος
Υπεύθυνη Ιατρείου Λιπιδίων
Βιοκλινική Θεσσαλονίκης



Παρουσίαση περιστατικού

- Άνδρας 46 ετών, με ΣΔ τύπου II γνωστό από 4ετίας, χωρίς ΚΑΝ
- Οικογενειακό ιστορικό θετικό για ΣΝ
- ΑΠ = 115/75 mmHg
- Δεν καπνίζει, μέτρια κατανάλωση αλκοόλ, κακή διατροφή (Π.Μ.=108 cm)
- Φαρμακευτική αγωγή: μετφορμίνη 1g/d

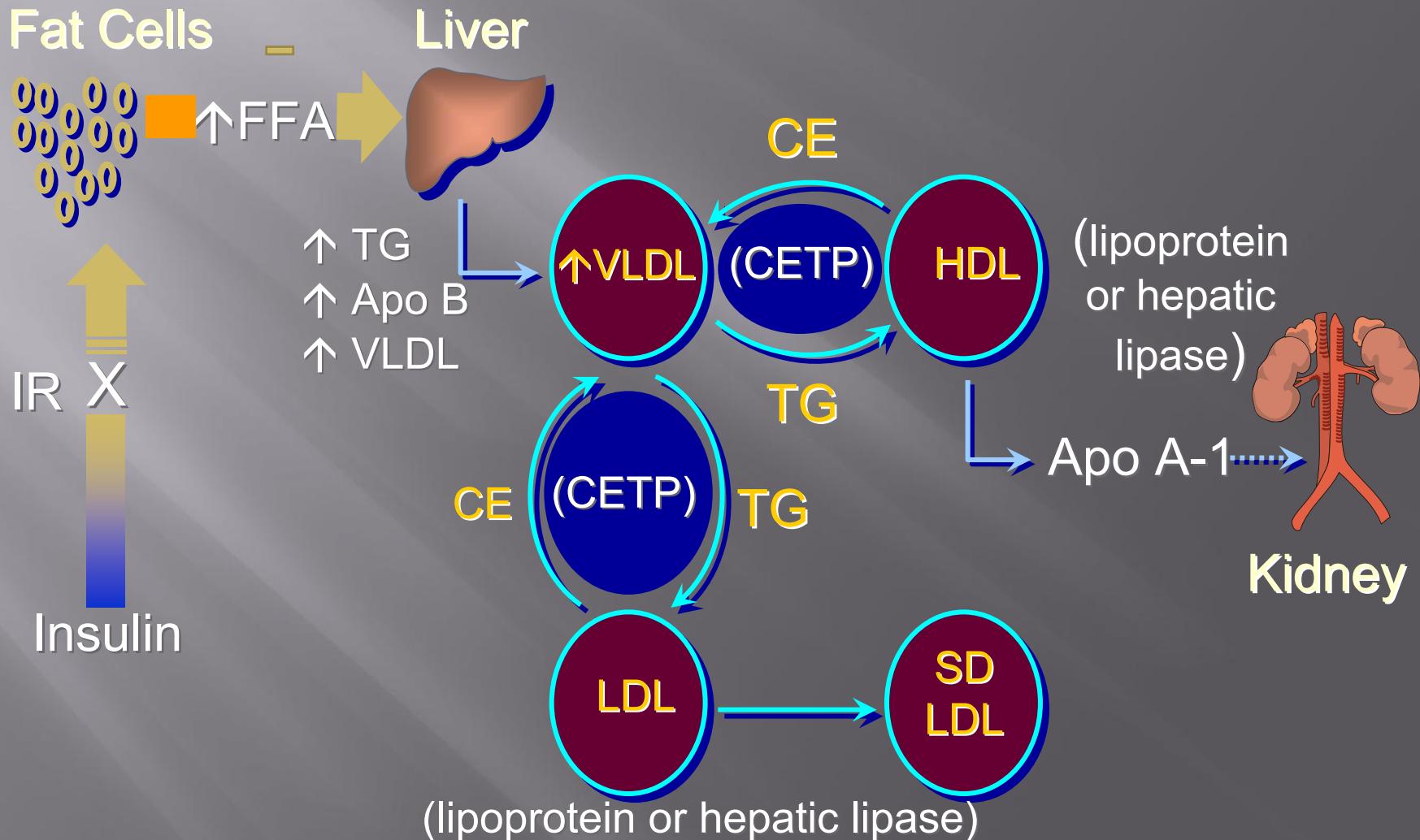
Πρώτη εξέταση

HbA1c	7,4%
Ολική χοληστερόλη	195 mg/dl
HDL-C	32 mg/dl
TRG	240 mg/dl
LDL-C	115 mg/dl

Παράμετροι αθηρογόνου δυσλιπιδαιμίας

- 1) Υψηλά επίπεδα TRG
- 2) Χαμηλά επίπεδα HDL-C
- 3) Υψηλά επίπεδα sd LDL
- 4) Μεταγευματική λιπαιμία

Παθοφυσιολογία αθηρογόνου δυσλιπιδαιμίας



2004 NCEP ATP III Update Establishes LDL-C Goals and Cut Points

Risk Category	LDL-C Goal
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High risk:

CHD or CHD risk equivalents
(10-y risk >20%)

<100 mg/dL

(optional goal: <70 mg/dL)

Moderately high risk:

2+ risk factors
(10-y risk 10% to 20%)

<130 mg/dL

(optional goal: <100 mg/dL)

Moderate risk:

2+ risk factors
(10-y risk <10%)

<130 mg/dL

Lower risk:

0-1 risk factor

<160 mg/dL

Θεραπευτική παρέμβαση 1: Τήρηση υγιεινοδιαιτητικών οδηγιών

- 1) Διακοπή καπνίσματος
- 2) Απόλεια βάρους
- 3) Αλλαγή διατροφικών συνηθειών (Αντικατάσταση κεκορεσμένων και trans λιπαρών οξέων με μονο- πολυ- ακόρεστα, κατανάλωση τροφών πλούσιων σε ίνες και πτωχών σε υδατάνθρακες: β-γλυκάνες (βρώμη, κριθάρι, μαγιά) , μέτρια κατανάλωση αλκοόλ (έως 2 ποτά/ημέρα)
- 4) Αερόβια άσκηση

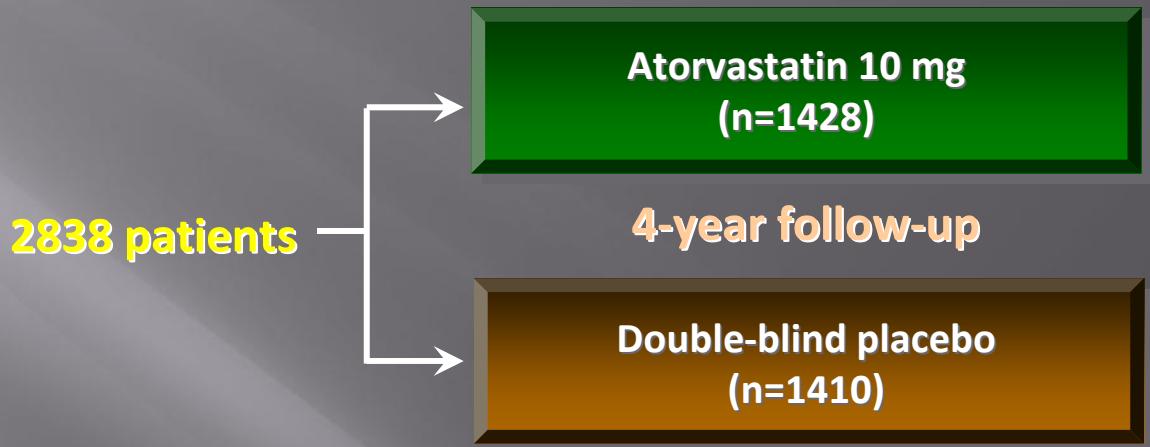
30 λεπτά αερόβιας άσκησης, 5 φορές την εβδομάδα

Θεραπευτική παρέμβαση 2 : Έναρξη στατίνης

Collaborative Atorvastatin Diabetes Study (CARDS)

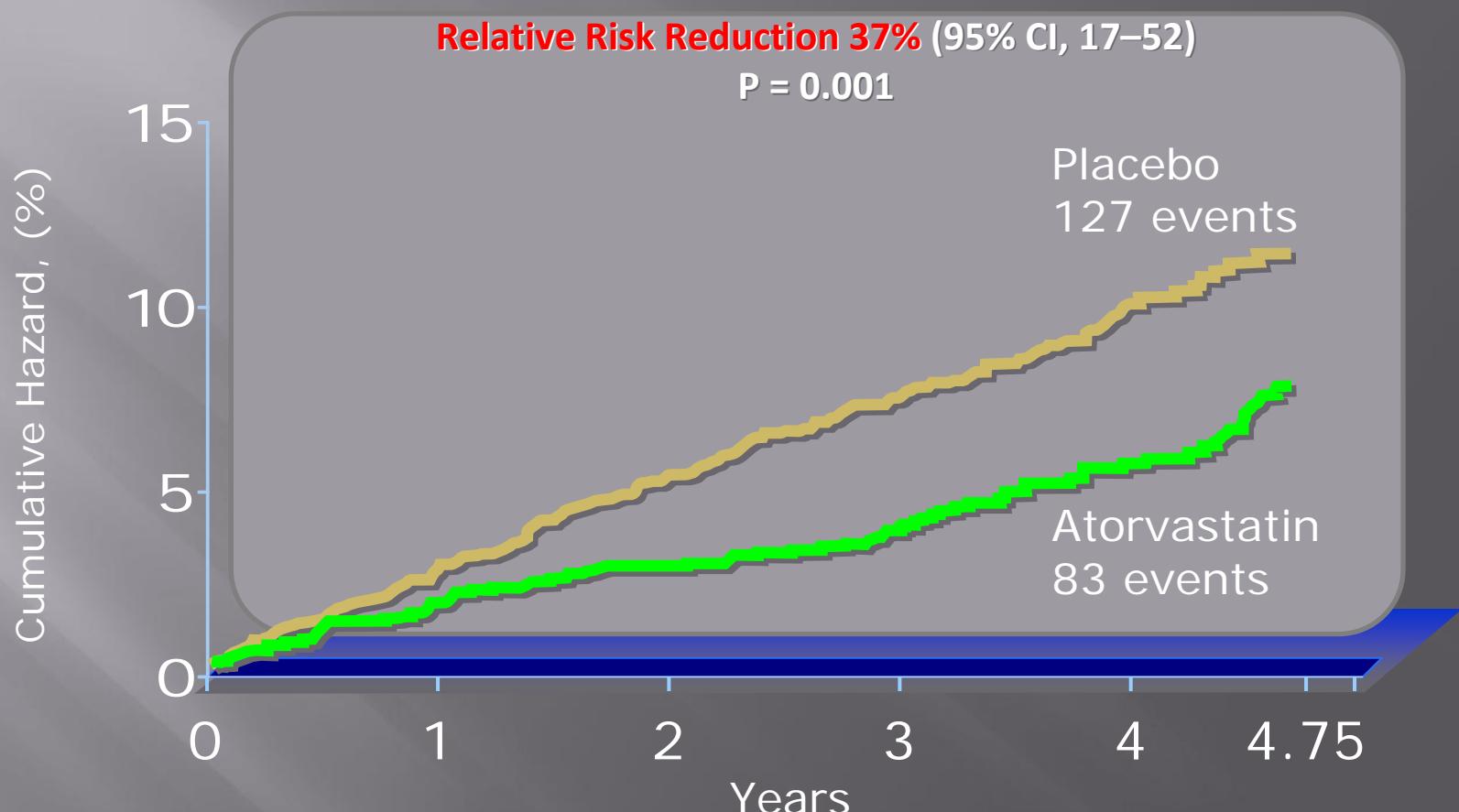
Patient Population

- Type 2 diabetes mellitus
- Men and women 40-75 years of age
- Primary CHD and stroke prevention
- LDL-C \leq 160 mg/dL
- TG \leq 600 mg/dL
- \geq 1 additional RF
 - HTN (or on HTN treatment)
 - Retinopathy
 - Albuminuria
 - Current smoking



- **Primary endpoint:** time to first major CV event (CHD death, nonfatal MI, unstable angina, resuscitated cardiac arrest, coronary revascularization, stroke)
- **Secondary endpoints:** total mortality, any CV endpoint, lipids, and lipoproteins

CARDS: Effect of Atorvastatin on the Primary Endpoint: Major CV Events Including Stroke



Placebo 1410

Atorvastatin 1428

1351

1392

1306

1361

1022

1074

651

694

305

328

Στατίνες και ΣΔ

Efficacy of cholesterol-lowering therapy in 18 686 people with diabetes in 14 randomised trials of statins: a meta-analysis

Cholesterol Treatment Trialists' (CTT) Collaborators    

Summary

Background

Although statin therapy reduces the risk of occlusive vascular events in people with diabetes mellitus, there is uncertainty about the effects on particular outcomes and whether such effects depend on the type of diabetes, lipid profile, or other factors. We undertook a prospective meta-analysis to help resolve these uncertainties.

Methods

We analysed data from 18 686 individuals with diabetes (1466 with type 1 and 17 220 with type 2) in the context of a further 71 370 without diabetes in 14 randomised trials of statin therapy. Weighted estimates were obtained of effects on clinical outcomes per 1·0 mmol/L reduction in LDL cholesterol.

Findings

During a mean follow-up of 4·3 years, there were 3247 major vascular events in people with diabetes. There was a 9% proportional reduction in all-cause mortality per mmol/L reduction in LDL cholesterol in participants with diabetes (rate ratio [RR] 0·91, 99% CI 0·82–1·01; $p=0·02$), which was similar to the 13% reduction in those without diabetes (0·87, 0·82–0·92; $p<0·0001$). This finding reflected a significant reduction in vascular mortality (0·87, 0·76–1·00; $p=0·008$) and no effect on non-vascular mortality (0·97, 0·82–1·16; $p=0·7$) in participants with diabetes. There was a significant 21% proportional reduction in major vascular events per mmol/L reduction in LDL cholesterol in people with diabetes (0·79, 0·72–0·86; $p<0·0001$), which was similar to the effect observed in those without diabetes (0·79, 0·76–0·82; $p<0·0001$). In diabetic participants there were reductions in myocardial infarction or coronary death (0·78, 0·69–0·87; $p<0·0001$), coronary revascularisation (0·75, 0·64–0·88; $p<0·0001$), and stroke (0·79, 0·67–0·93; $p=0·0002$). Among people with diabetes the proportional effects of statin therapy were similar irrespective of whether there was a prior history of vascular disease and irrespective of other baseline characteristics. After 5 years, 42 (95% CI 30–55) fewer people with diabetes had major vascular events per 1000 allocated statin therapy.

Στατίνες και ΣΔ

Age >40 years with either type 1 or type 2 diabetes

Age 18-39 years with either type 1 or type 2 diabetes and with at least one of the following:

- Substantial retinopathy (preproliferative or proliferative, or maculopathy)
- Nephropathy, including persistent microalbuminuria
- Poor glycemic control (HbA_{1c} level >9%)
- Hypertension requiring antihypertensive therapy
- Total cholesterol ≥6.0 mmol/l
- Features of the metabolic syndrome, such as fasting triglycerides >1.7 mmol/l and/or HDL cholesterol <1.0 mmol/l in men or <1.2 mmol/l in women
- Family history of premature (men aged <55 years; women aged <65 years) cardiovascular disease in a first-degree relative

From the Joint British Societies' Guidelines on prevention of CVD in clinical practice.⁴³ Abbreviation: DM, diabetes mellitus; HbA_{1c} , glycated hemoglobin A_{1C}.

Επανεκτίμηση του ασθενούς

χορήγηση 2 g μετφορμίνης και 20 mg ροσουβαστατίνης

	Πρώτη επίσκεψη	Δεύτερη επίσκεψη (μετά από 2 μήνες)
HbA1c	7,4%	6,9%
Ολική χοληστερόλη	195 mg/dl	144 mg/dl
HDL-C	32 mg/dl	37 mg/dl
TRG	240 mg/dl	190 mg/dl
LDL-C	115 mg/dl	69 mg/dl

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 vs 10-mg atorvastatin)

MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

¹HPS Collaborative Group. *Lancet*. 2003;361:2005-2016.

²Sacks FM, et al. *N Engl J Med*. 1996;335:1001-1009.

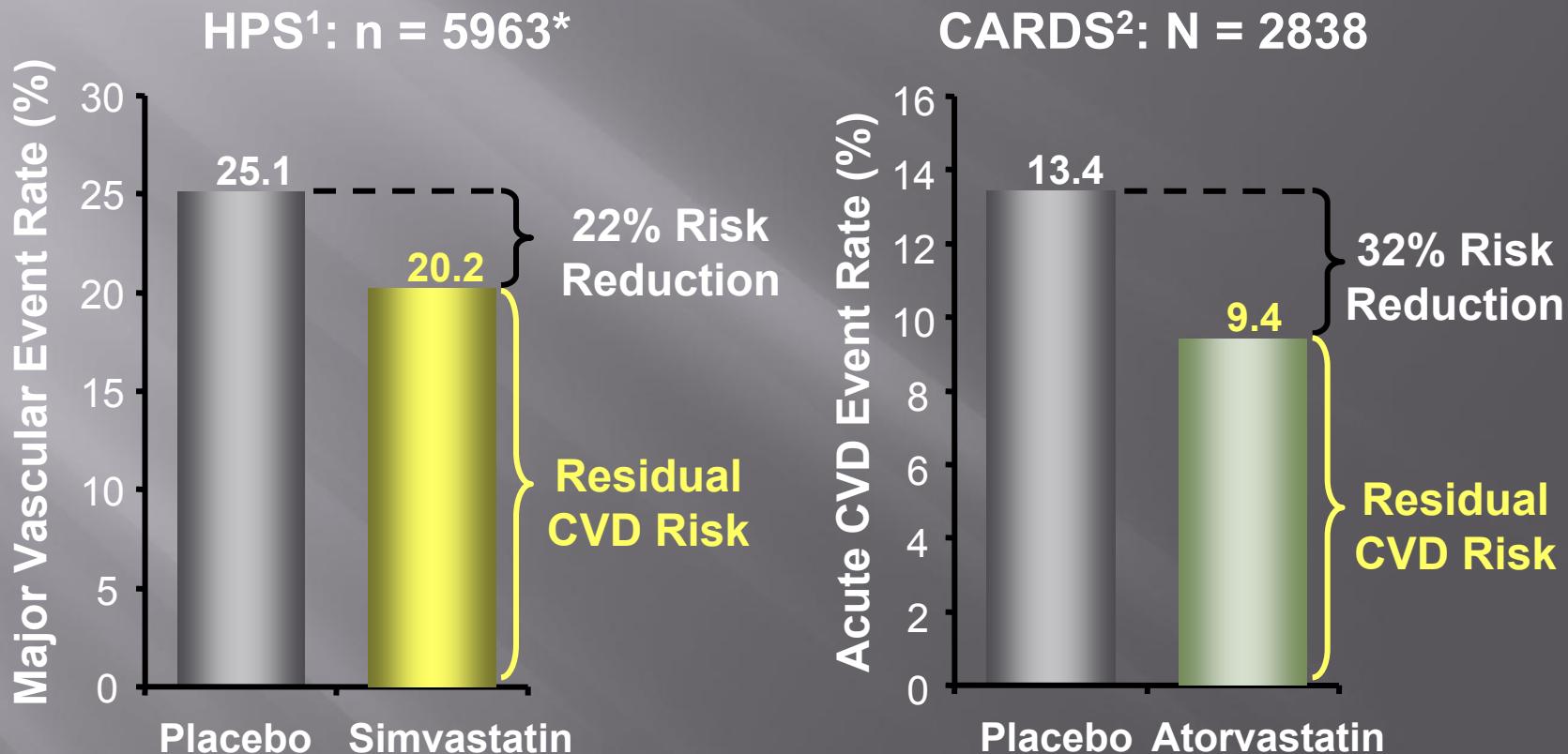
³LIPID Study Group. *N Engl J Med*. 1998;339:1349-1357.

⁴Shepherd J, et al. *Lancet*. 2002;360:1623-1630.

⁵Sever PS, et al. *Lancet*. 2003;361:1149-1158.

⁶Shepherd J, et al. *Diabetes Care*. 2006;29:1220-1226.

Residual CVD Risk in Patients With Diabetes Treated With Statins



*Patients with diabetes. (HPS also enrolled 14,573 high-risk patients without diagnosed diabetes.)

Collins R, et al. *Lancet*. 2003;361:2005-2016
Colhoun HM, et al. *Lancet*. 2004;364:685-696

ATP III Guidelines At-A-Glance

Quick Desk Reference

Treatment of elevated triglycerides (≥ 150 mg/dL)

- Primary aim of therapy is to reach LDL goal
- Intensify weight management
- Increase physical activity
- If triglycerides are ≥ 200 mg/dL after LDL goal is reached, set secondary goal for non-HDL cholesterol (total - HDL) 30 mg/dL higher than LDL goal.

If triglycerides 200-499 mg/dL after LDL goal is reached, consider adding drug if needed to reach non-HDL goal:

- intensify therapy with LDL-lowering drug, or
- add nicotinic acid or fibrate to further lower VLDL.

Treatment of low HDL cholesterol (<40 mg/dL)

- First reach LDL goal, then:
- Intensify weight management and increase physical activity
- If triglycerides 200-499 mg/dL, achieve non-HDL goal
- If triglycerides <200 mg/dL (isolated low HDL) in CHD or CHD equivalent consider nicotinic acid or fibrate.

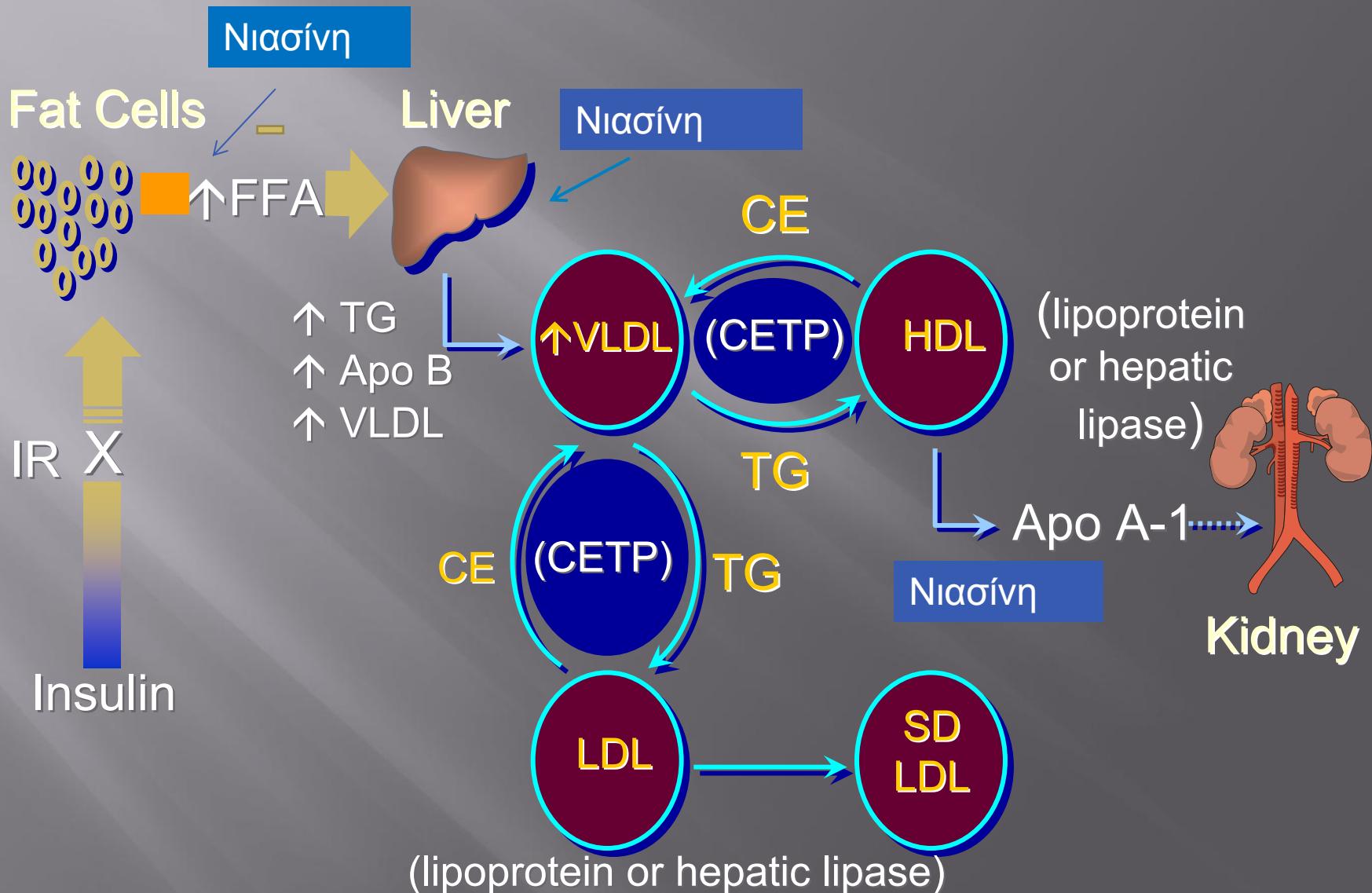
Θεραπευτική παρέμβαση 3: Προσθήκη νικοτινικού οξέος

- ↓ LDL-C (15 – 25%)
- ↑ HDL-C (20 – 35%)
- ↓ TG (20 – 40%)

Περιορισμοί

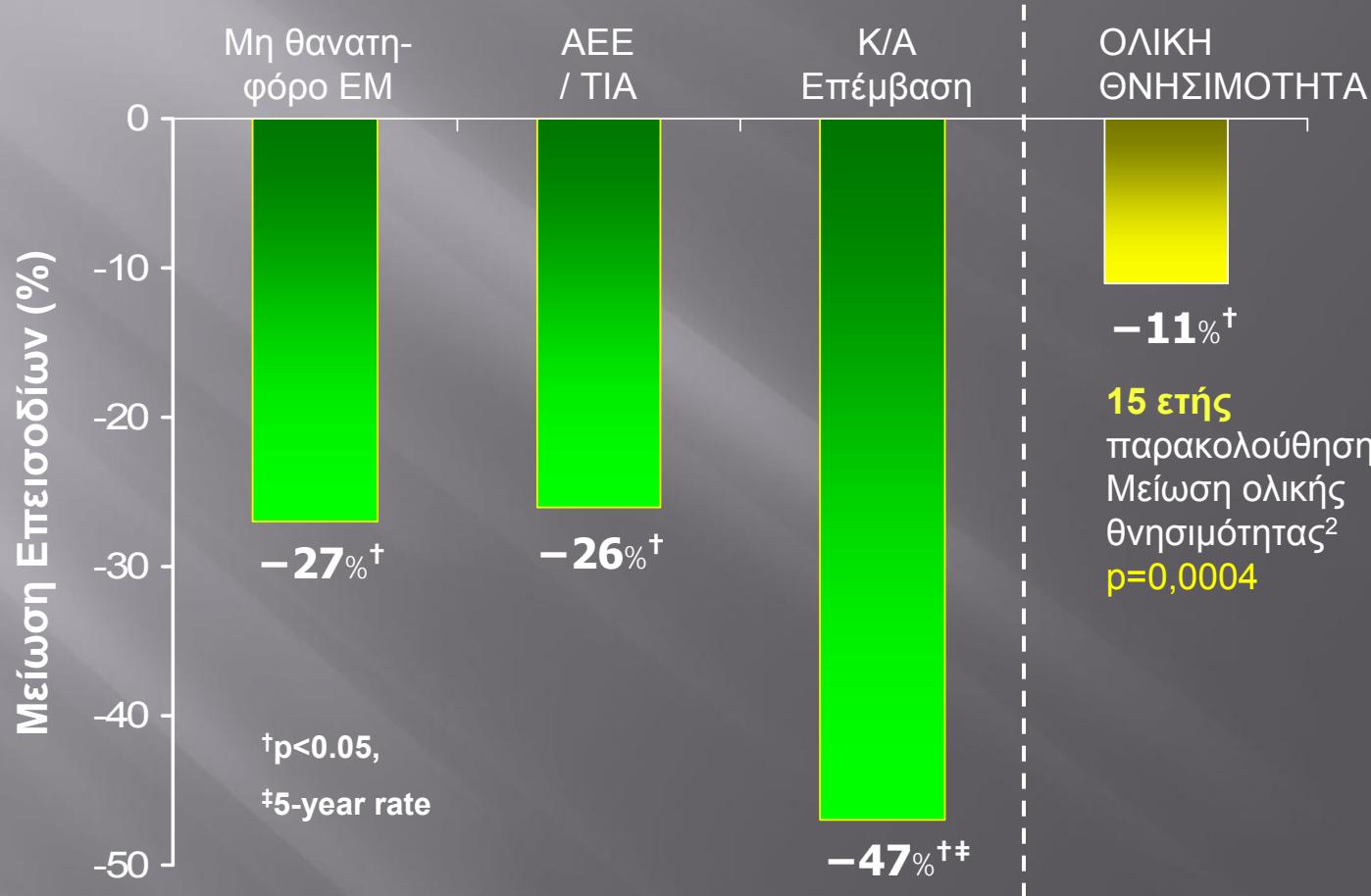
- Έξαψη
- Παροδική αύξηση των επιπέδων γλυκόζης

Θεραπεία αθηρωγόνου δυσλιπιδαιμίας



Coronary Drug Project: Κλινικά Αποτελέσματα

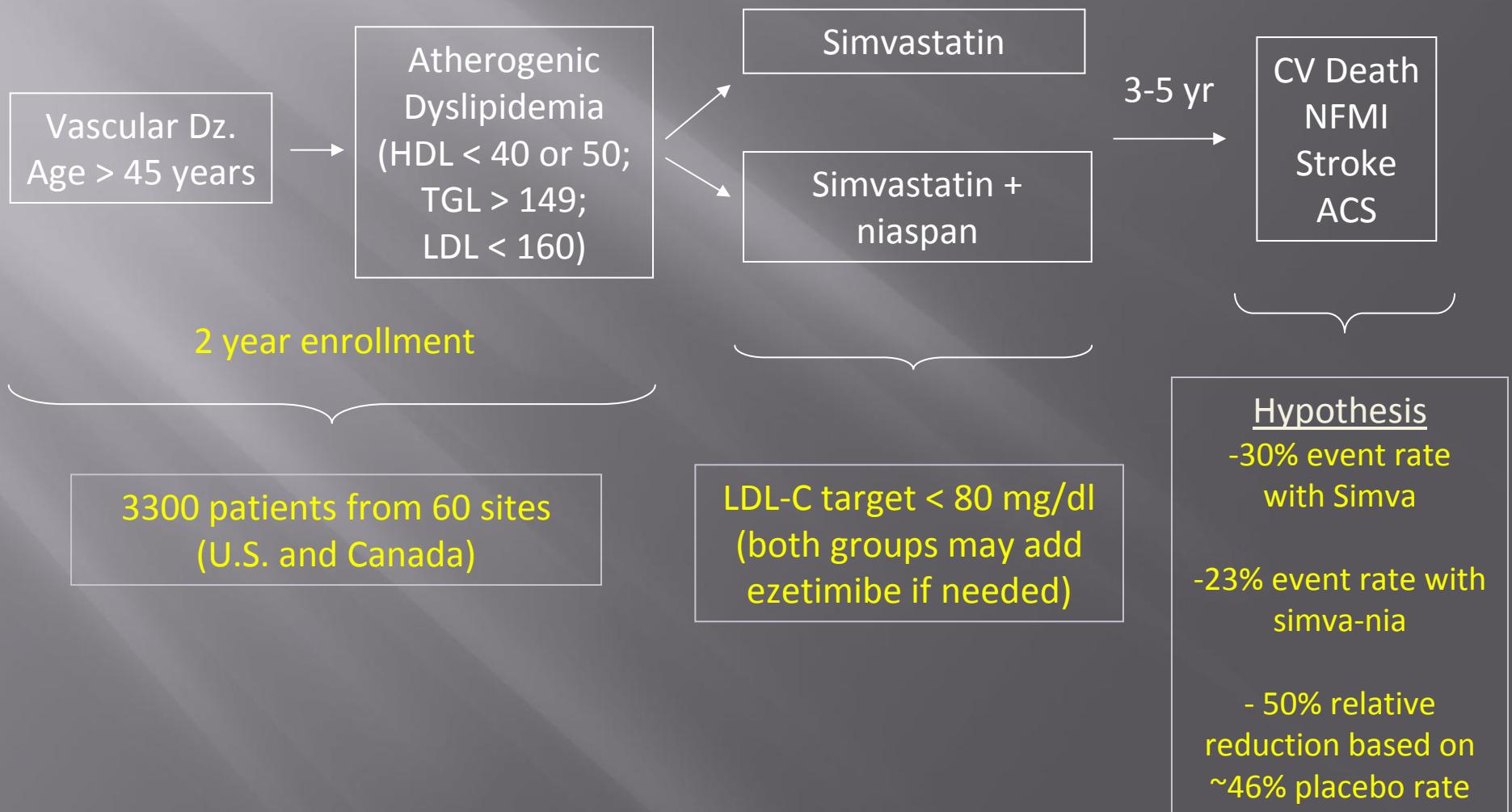
Νιασίνη έναντι placebo - Διάρκεια 5 έτη (επέκταση στα 15), 5.011 ασθενείς



¹Coronary Drug Project Research Group. *JAMA*. 1975;231:360–381

²Canner et al. *J.Am.Coll. Cardiol.* 1986;8:1245-1255

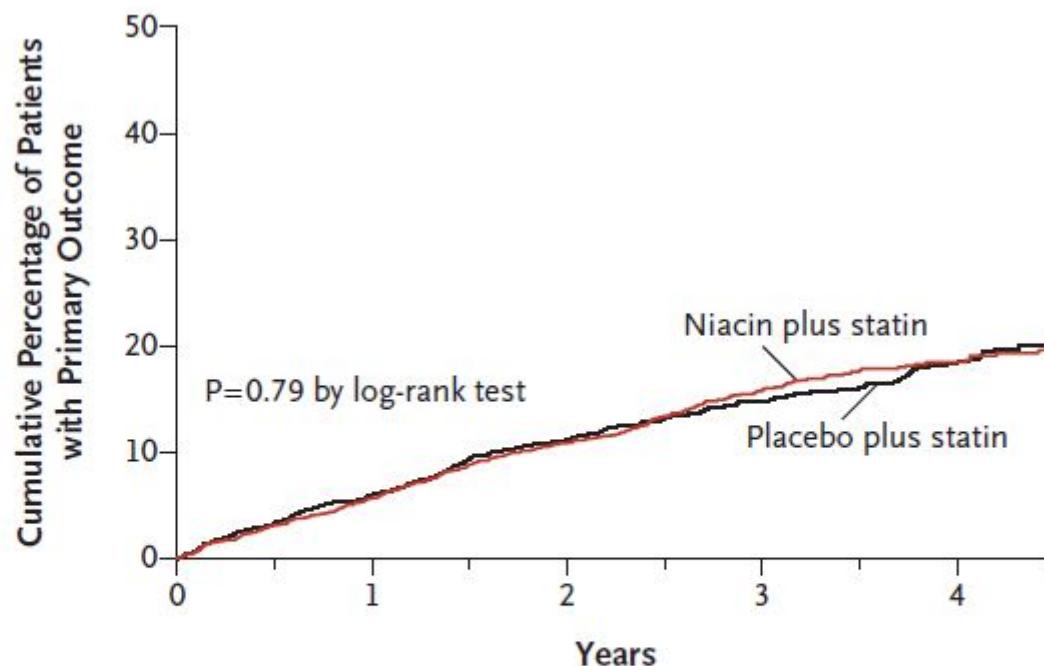
AIM-HIGH Study Overview



ORIGINAL ARTICLE

Niacin in Patients with Low HDL Cholesterol Levels Receiving Intensive Statin Therapy

The AIM-HIGH Investigators*

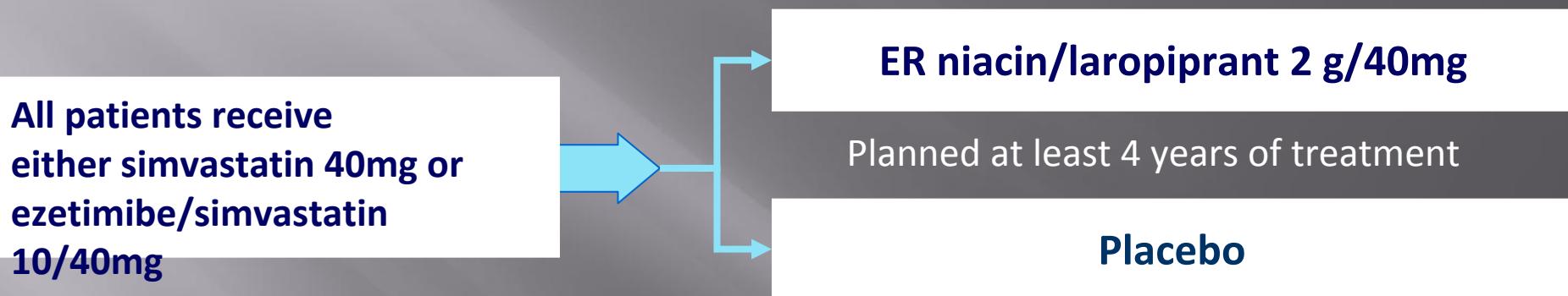
**No. at Risk**

Placebo plus statin	1696	1581	1381	910	436
Niacin plus statin	1718	1606	1366	903	428

Figure 1. Kaplan-Meier Curve for the Primary End Point.

HPS2-THRIVE (Heart Protection Study 2 – Treating HDL to Reduce Vascular Events)

Does ER niacin/laropiprant 2g/40mg daily prevent vascular events in high-risk patients who are receiving intensive LDL-C lowering treatment?



Patient Population	Subjects	Primary End Point
<ul style="list-style-type: none">• Age 50-80• History of MI or cerebrovascular atherosclerotic disease or PAD or Diabetes mellitus with any of the above or with other evidence of symptomatic CHD	<ul style="list-style-type: none">• 20,000• UK (n=7500), Scandinavia (n=5000) and China (n=7500)	<ul style="list-style-type: none">• Major vascular events during the scheduled treatment period (non-fatal MI or coronary death, non-fatal or fatal stroke, or revascularization)

- Study start: January 2007
- Expected completion: January 2013

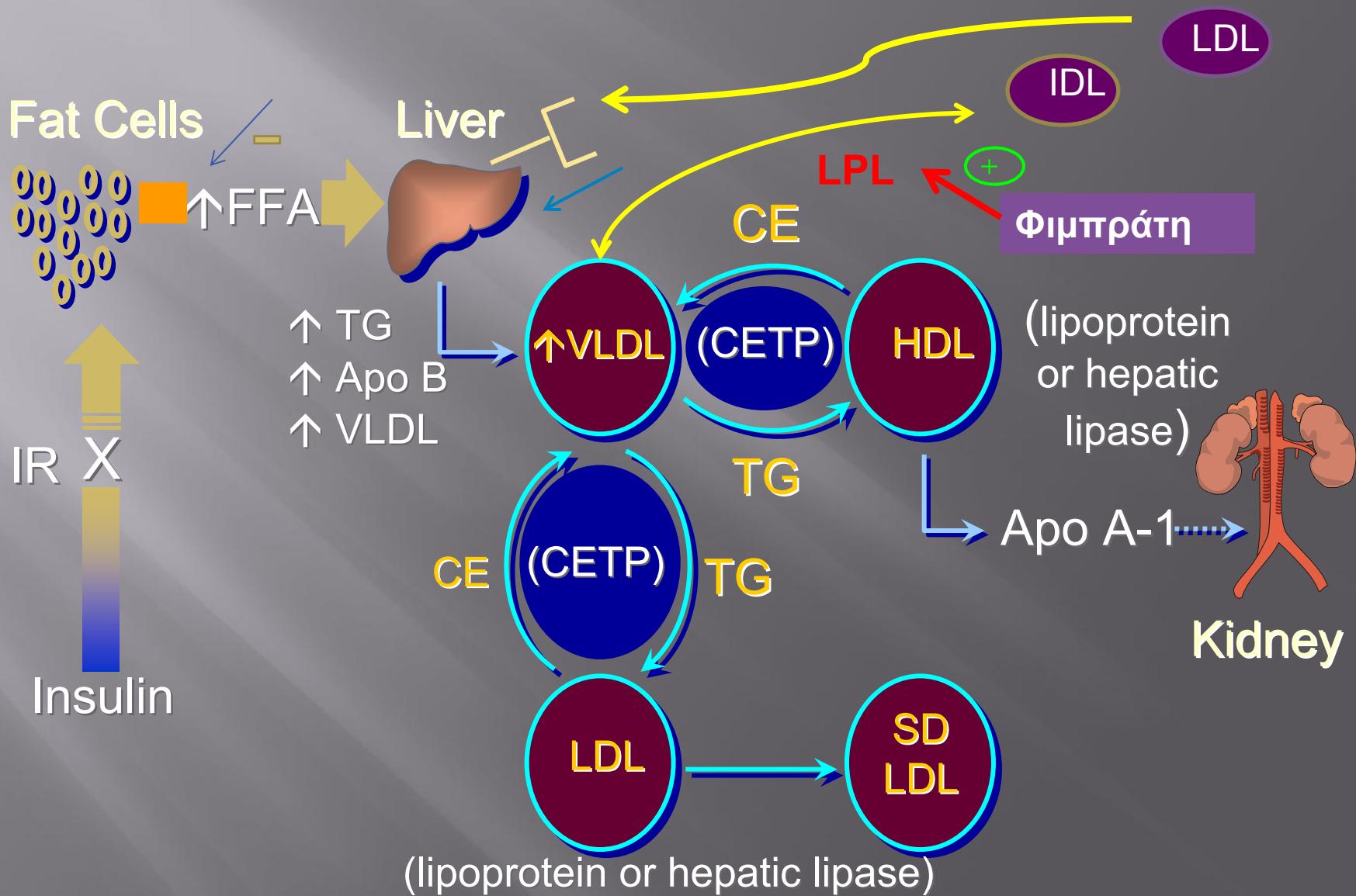
Θεραπευτική παρέμβαση 4: Προσθήκη φιμπράτης

- ↓ LDL-C (5 – 20%)
- ↑ HDL-C (10 – 35%)
- ↓ TG (20 – 50%)

Περιορισμοί

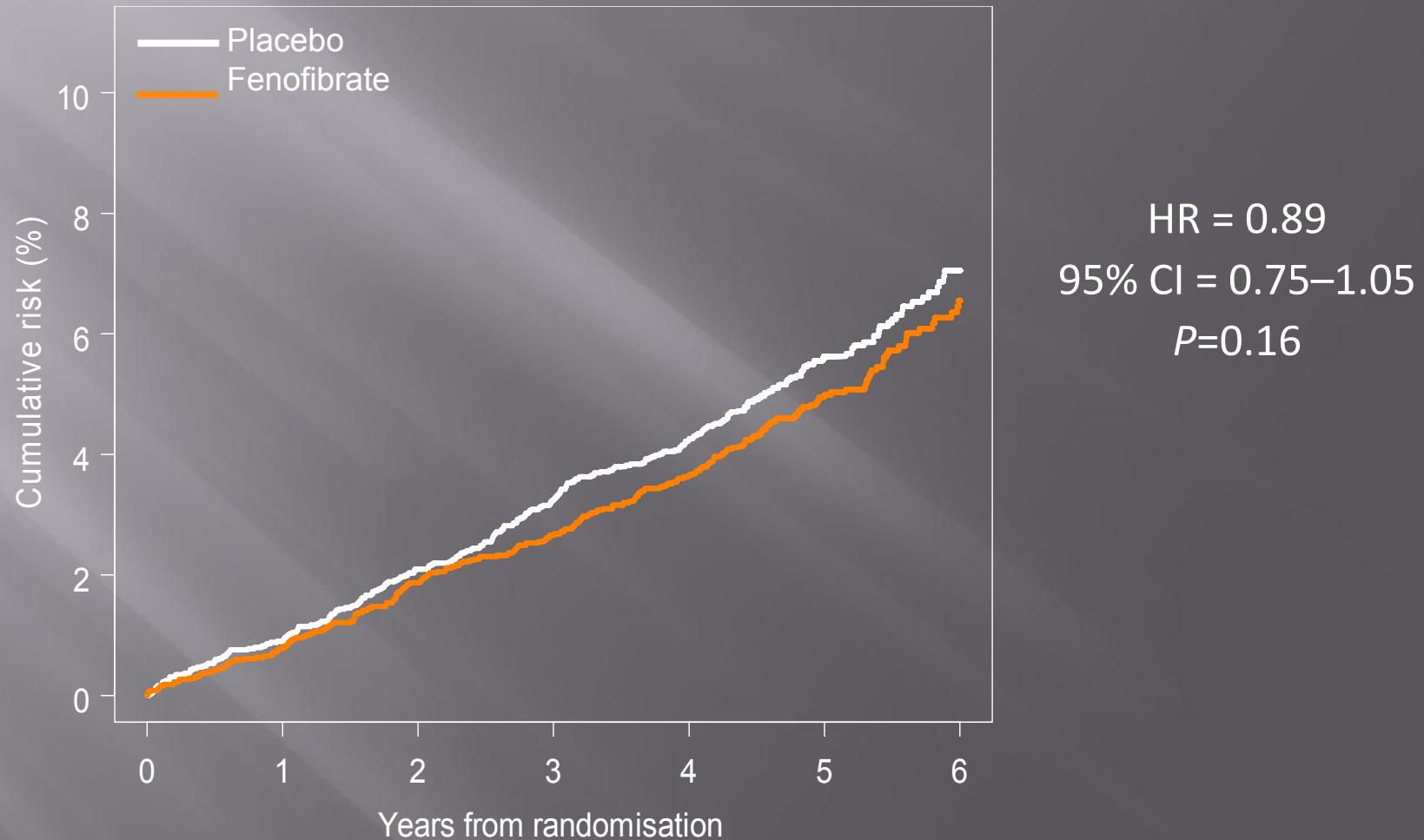
- στενή παρακολούθηση ηπατικής βιολογίας, CPK, e-GFR

Θεραπεία αθηρωγόνου δυσλιπιδαιμίας



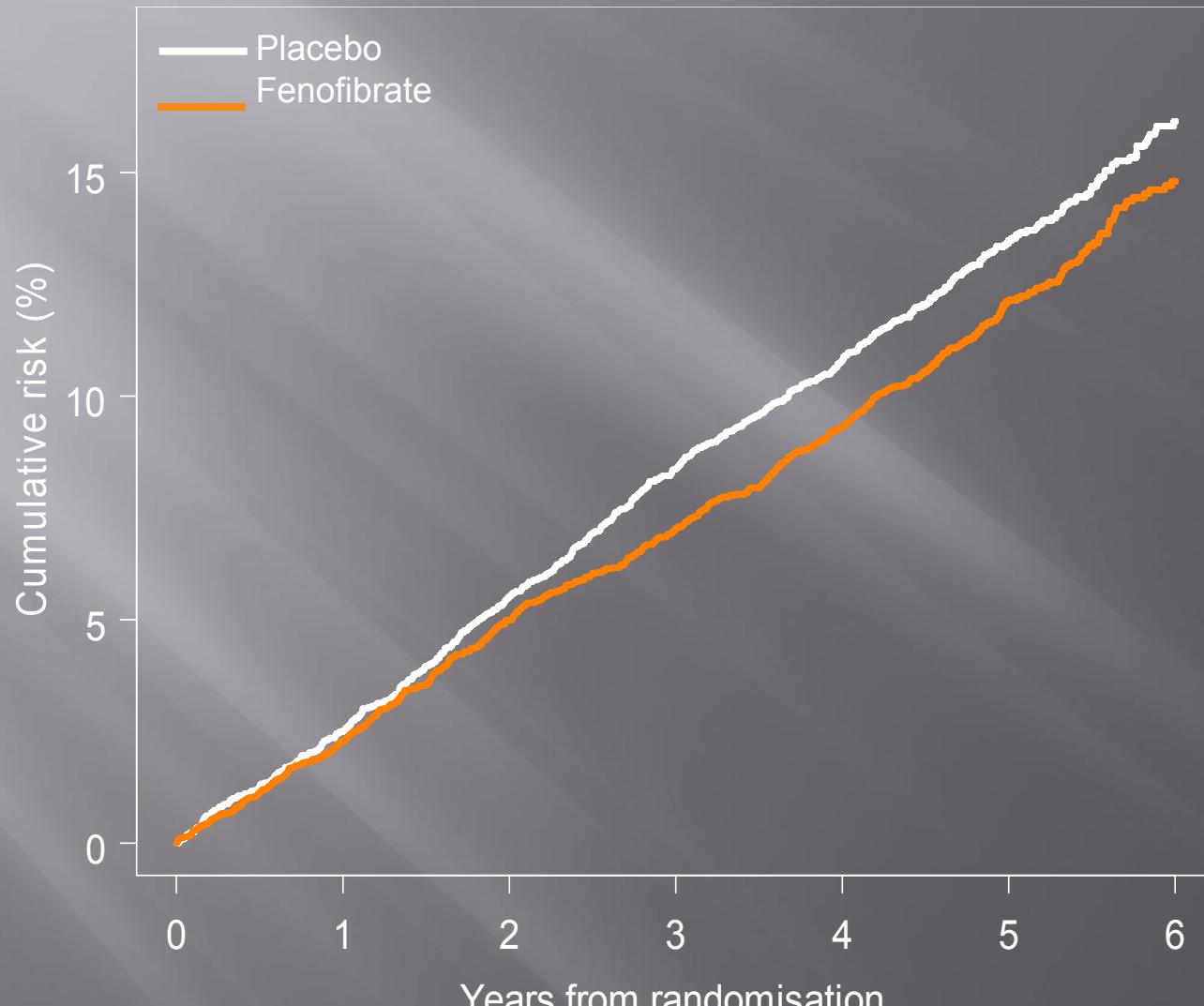
Results: primary outcome

CHD events (CHD death + nonfatal MI)



Placebo	4900	4835	4741	4646	4547	2541	837
Fenofibrate	4895	4837	4745	4664	4555	2553	850

Total CVD events



HR = 0.89

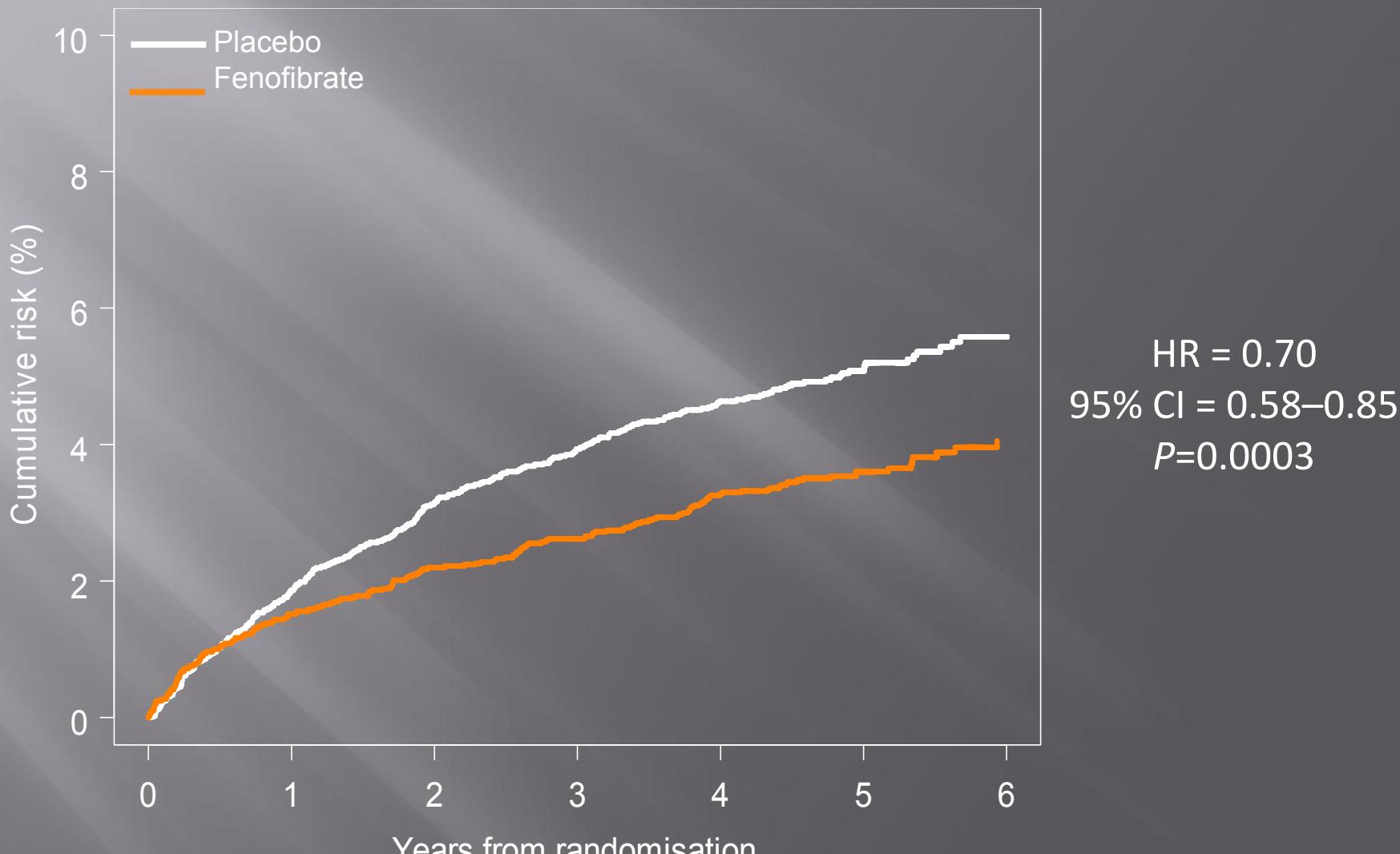
95% CI = 0.80–0.99

P=0.035

NNT ≈ 70

Placebo	4900	4762	4586	4419	4257	2340	750
Fenofibrate	4895	4771	4604	4469	4307	2370	775

Results: retinal laser therapy



Placebo	4900	4775	4664	4573	4472	2518	835
Fenofibrate	4895	4792	4701	4618	4502	2529	841

ACCORD Lipid Protocol

- ▣ All participants on open-labeled simvastatin, 20 to 40 mg/day
 - Simvastatin dose complied with lipid guidelines
- ▣ Patients randomized to double-blind placebo or fenofibrate, 54 to 160mg/day
 - Dosing based upon eGFR level
- ▣ Only blinded ACCORD trial
- ▣ Observed Follow-up: 4 to 8 years (mean 4.7 years)

ACCORD- Primary Outcome

	Fenofibrate (N=2765)		Placebo (N=2753)		HR (95% CI)	P Value
	N of Events	Rate (%/yr)	N of Events	Rate (%/yr)		
<u>Primary Outcome:</u> Major Fatal or Nonfatal Cardiovascular Event	291	2.24	310	2.41	0.92 (0.79 - 1.08)	0.32

Triglyceride-rich lipoproteins and high-density lipoprotein cholesterol in patients at high risk of cardiovascular disease: evidence and guidance for management

M. John Chapman^{1*}, Henry N. Ginsberg^{2*}, Pierre Amarenco³, Felicita Andreotti⁴, Jan Borén⁵, Alberico L. Catapano⁶, Olivier S. Descamps⁷, Edward Fisher⁸, Petri T. Kovanen⁹, Jan Albert Kuivenhoven¹⁰, Philippe Lesnik¹, Luis Masana¹¹, Børge G. Nordestgaard¹², Kausik K. Ray¹³, Zeljko Reiner¹⁴, Marja-Riitta Taskinen¹⁵, Lale Tokgözoglu¹⁶, Anne Tybjærg-Hansen¹⁷, and Gerald F. Watts¹⁸, for the European Atherosclerosis Society Consensus Panel

¹European Atherosclerosis Society, INSERM UMR-S939, Pitie-Salpetriere University Hospital, Paris 75651, France; ²Irving Institute for Clinical and Translational Research Columbia University, PH 10-305 630 West 168th Street, New York, NY 10032, USA; ³Bichat University Hospital, Paris, France; ⁴Catholic University Medical School, Rome, Italy; ⁵University of Gothenburg, Sweden; ⁶University of Milan, Italy; ⁷Hôpital de Jolimont, Haine-Saint-Paul, Belgium; ⁸New York University, New York, USA; ⁹Wihuri Research Institute, Helsinki, Finland; ¹⁰University of Amsterdam, The Netherlands; ¹¹Universitat Rovira i Virgili, Reus, Spain; ¹²Herlev Hospital, Copenhagen University Hospital, University of Copenhagen, Denmark; ¹³St. George's University of London, London, UK; ¹⁴University Hospital Center Zagreb, Croatia; ¹⁵Biomedicum, Helsinki, Finland; ¹⁶Hacettepe University, Ankara, Turkey; ¹⁷Rigshospitalet, University of Copenhagen, Denmark; and ¹⁸University of Western Australia, Perth, Australia

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Table 4 Subgroup analyses of cardiovascular outcome studies with fibrates

Trial	Treatment (mg/day)	Patient characteristics	All patients	Elevated triglycerides and low HDL-C subgroup			
			Primary endpoint	Relative risk reduction	Primary endpoint	Lipid criteria mmol/L	Relative risk reduction
Fibrate monotherapy vs. placebo							
WHO trial ²⁰² (n = 5331)	Clofibrate 1600	Upper-third of cholesterol values, without CHD	Non-fatal MI + CHD death	20% (P < 0.05)	–	–	–
CDP ²⁰³ (n = 3892)	Clofibrate 1800 (n = 1103)	CHD	Nonfatal MI + CHD death	9% (P = 0.12)	–	–	–
HHS ^{204,209} (n = 4081)	Gemfibrozil 1200	Non-HDL-C ≥ 200 mg/dL without CHD	Fatal + non-fatal MI + cardiac death	34% (P < 0.02)	As for all patients	TG > 2.3 + HDL-C < 1.08	65% (P = 0.01)
VA-HIT ^{205,210} (n = 2531)	Gemfibrozil 1200	CHD + low HDL-C (< 40 mg/dL)	Non-fatal MI + CHD death	22% (P = 0.006)	As for all patients	TG > 2.03 + HDL-C ≤ 1.03	28% (P < 0.05)
BIP ²⁰⁶ (n = 3090)	Bezafibrate 400	Previous MI or angina	Fatal + non-fatal MI + sudden death	9.4% (P = 0.26)	As for all patients	TG ≥ 2.26 + HDL-C < 0.91	42% (P = 0.02)
FIELD ^{106,207} (n = 9795)	Fenofibrate 200	Type 2 diabetes (22% with CVD)	Non-fatal MI + CHD death	11% (P = 0.16)	Total CV events	TG ≥ 2.30 + low HDL-C ^a	27% (P = 0.005)
Statin-fibrate vs. statin monotherapy							
ACCORD Lipid ¹⁰⁷ (n = 5518)	Fenofibrate 160 + simvastatin	Type 2 diabetes (37% with CVD)	CVD death, nonfatal MI + non-fatal stroke	8% (P = 0.32)	As for all patients	TG ≥ 2.30 + HDL-C ≤ 0.88	31%; P-value not reported

Επανεκτίμηση ασθενούς

	Πρώτη επίσκεψη	Δεύτερη επίσκεψη (μετά από 2 μήνες)	Τρίτη επίσκεψη (μετά από 2 μήνες)
HbA1c	7,4%	6,9%	6,8%
Ολική χοληστερόλη	195 mg/dl	144 mg/dl	132 mg/dl
HDL-C	32 mg/dl	38 mg/dl	41 mg/dl
TRG	240 mg/dl	190 mg/dl	145 mg/dl
LDL-C	115 mg/dl	69 mg/dl	62 mg/dl

Συμπεράσματα

- ✓ Οι ασθενείς με ΣΔ, ως ισοδύναμο ΣΝ, χρειάζονται
άμεση και επιθετική υπολιπιδαιμική παρέμβαση

- ✓ Η τήρηση συγκεκριμένων υγιεινοδιαιτητικών οδηγιών
αποτελεί απαραίτητη προϋπόθεση για την επίτευξη
των θεραπευτικών στόχων

- ✓ Ο συνδυασμός στατίνης με νικοτινικό οξύ ή με
φιμπράτη αποτελεί μία δόκιμη θεραπευτική
παρέμβαση σε ασθενείς με ΣΔ και αθηρογόνο
δυσλιπιδαιμία

