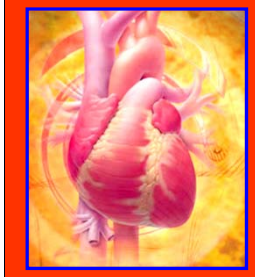
Ο ρόλος των στατινών στην μη αλκοολική λιπώδη νόσο του ήπατος



Β. ‘Αθυρος, MD, FESC, FRSPH, FASA, FACS

Β Προπ. Παθολογική Κλινική ΑΠΘ, Ιπποκράτειο Θεσσαλονίκης

ΜΑΛΝΗ

Κλινικο-παθολογικό σύνδρομο που περιλαμβάνει **ένα ευρύ φάσμα λιπώδους διηθήσεως του ήπατος (>5%)**

σε απουσία κατάχρησης αλκοόλ
(2 ποτά ή λιγότερες ημερησίως)

και άλλων αιτίων στεάτωσης
(χρόνιες ηπατίτιδες).

ΜΑΛΝΗ - Φάσμα εκδηλώσεων

Στεάτωση

Στεατοηπατίτιδα (NASH)

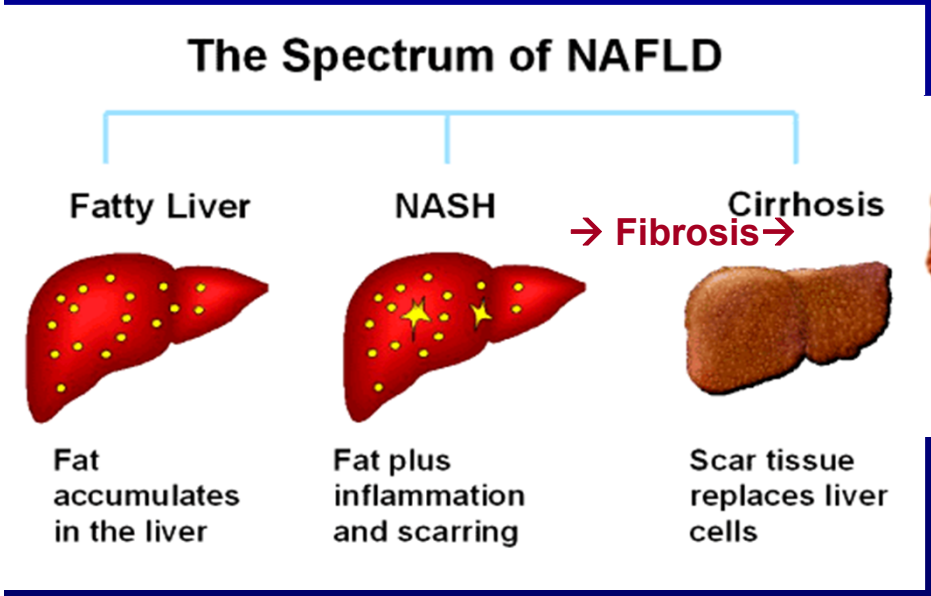
NASH με ίνωση

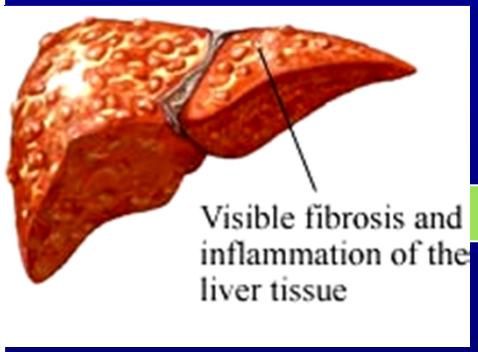
Κίρρωση

ΜΑΛΝΗ

Non-Alcoholic Liver Disease

model for the study of the secondary complications of obesity





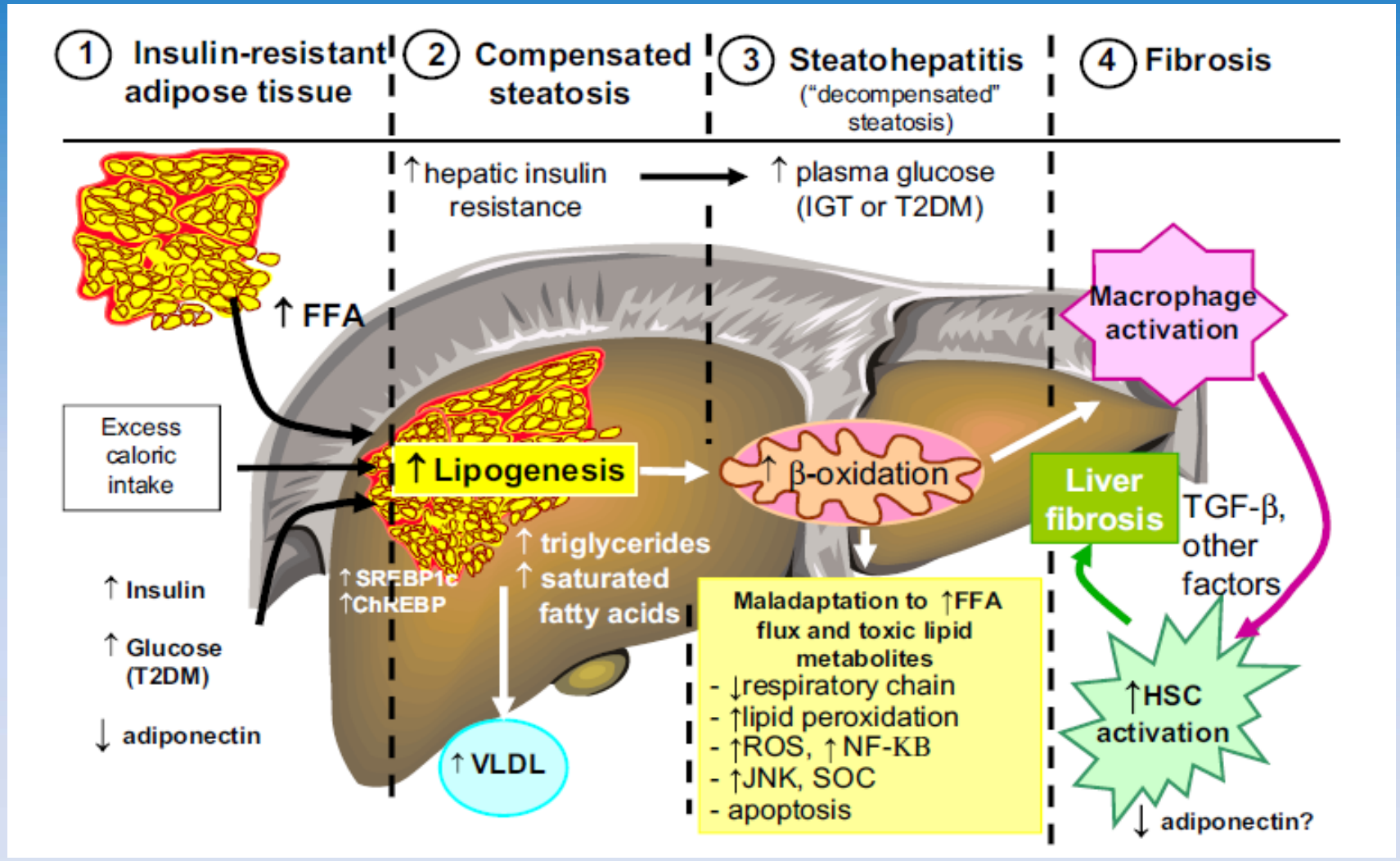
Increased risk of hepatocellular carcinoma

From: Ariel E. Feldstein and Marsha H. Kay, ACG website

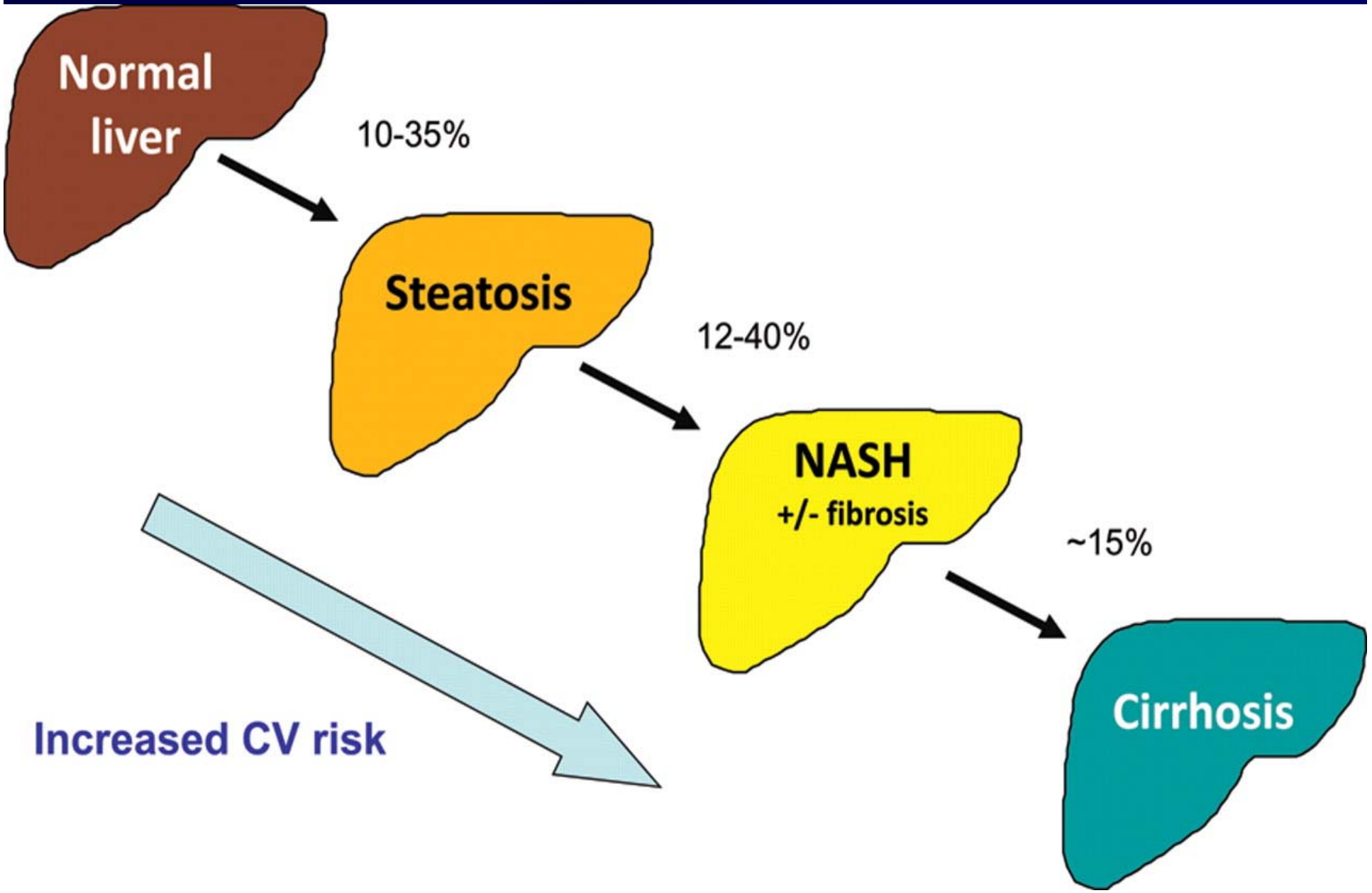
NAFLD affects **up to 35 % of adults and nearly 5 % of children.**

NASH → **5-7 % of adult Americans; up to 20 % of obese subjects.**

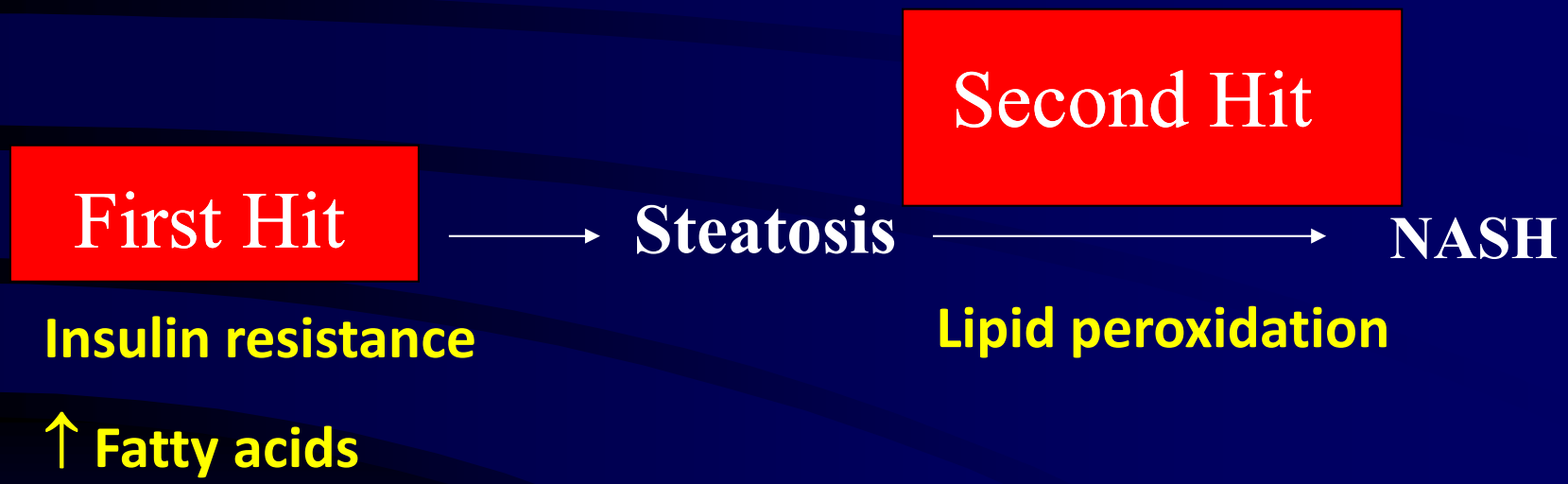
The majority of individuals with NAFLD have no symptoms and a normal examination


1 Insulin-resistant adipose tissue
2 Compensated steatosis
3 Steatohepatitis ("decompensated" steatosis)
4 Fibrosis
↑hepatic insulin resistance
↑ plasma glucose (IGT or T2DM)
↑ FFA
Excess caloric intake
↑ Lipogenesis
↑ β-oxidation
Macrophage activation
Liver fibrosis
TGF-β, other factors
↑ Insulin
↑ Glucose (T2DM)
↓ adiponectin
↑SREBP1c
↑ChREBP
↑ triglycerides
↑ saturated fatty acids
↑ VLDL
Maladaptation to ↑FFA flux and toxic lipid metabolites
- ↓respiratory chain
- ↑lipid peroxidation
- ↑ROS, ↑ NF-KB
- ↑JNK, SOC
- apoptosis
↑HSC activation
↓ adiponectin?

ΜΑΛΝΗ – Επιδημιολογία των ιστολογικών μορφών



ΜΑΛΝΗ - Παθογένεση

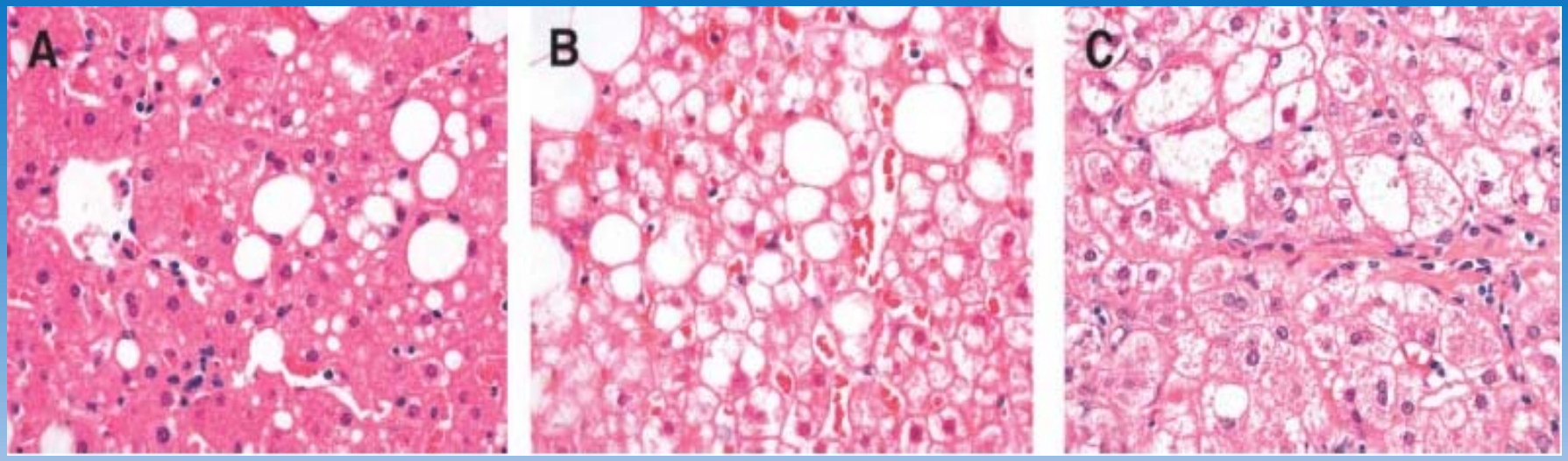


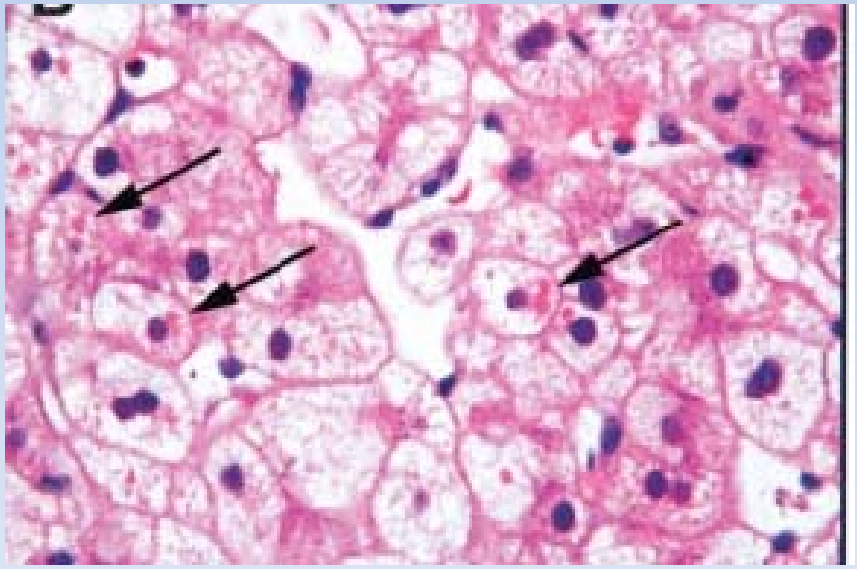
ΜΑΛΝΗ - Απεικόνιση

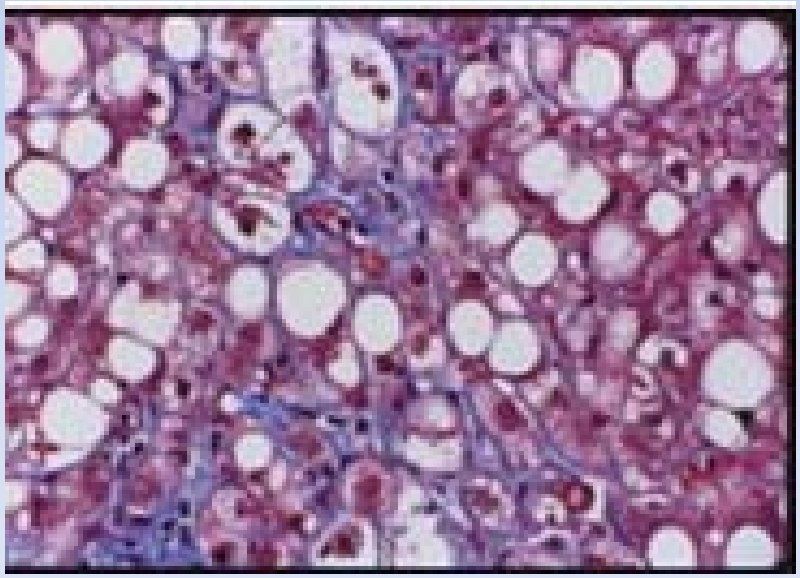
- **Υπέρηχος**
- **Αξονική τομογραφία**
- **Απεικόνιση μαγνητικού συντονισμού**

Fibroscan μια μη επεμβατική μέθοδος που είναι σε θέση να ανιχνεύσει με την NASH με ίνωση.

Saadeh et al. The Utility of Radiological Imaging in NAFLD. Gastroenterology 2002; 123: 745-750


A
B
C





NAFLD activity score (NAS)

Findings:

- Macrovesicular steatosis
- Lobular inflammation
- Hepatocyte balooning
- Perisinusoidal fibrosis

- Histologic scoring system
- Score 5 or greater is consistent with NASH
- Score 2 or less is consistent with simple fatty liver

Προδιαθεσικοί παράγοντες για την εξέλιξη της ΜΑΛΝΗ

1) **Obesity** – Pt undergoing Bariatric surgery (90% steatosis, 30% NASH, 10% advanced fibrosis / cirrhosis)

2) **Metabolic conditions**
   - Type 2 DM – 66% will have US evidence of NAFLD
   - Polycystic ovarian syndrome – 50%

3) **Age** (may reflect longer standing undiagnosed NAFLD)

4) **Gender**
   M>F (?protective effect of oestrogen)

5) **Ethnicity**
   - Hispanics > Other white > African Americans

6) **Genetics**
   - PNPLA3 gene (Others include NCAN, GCKR, LYPLAL1)

7) **Other** (HCV/HIV)

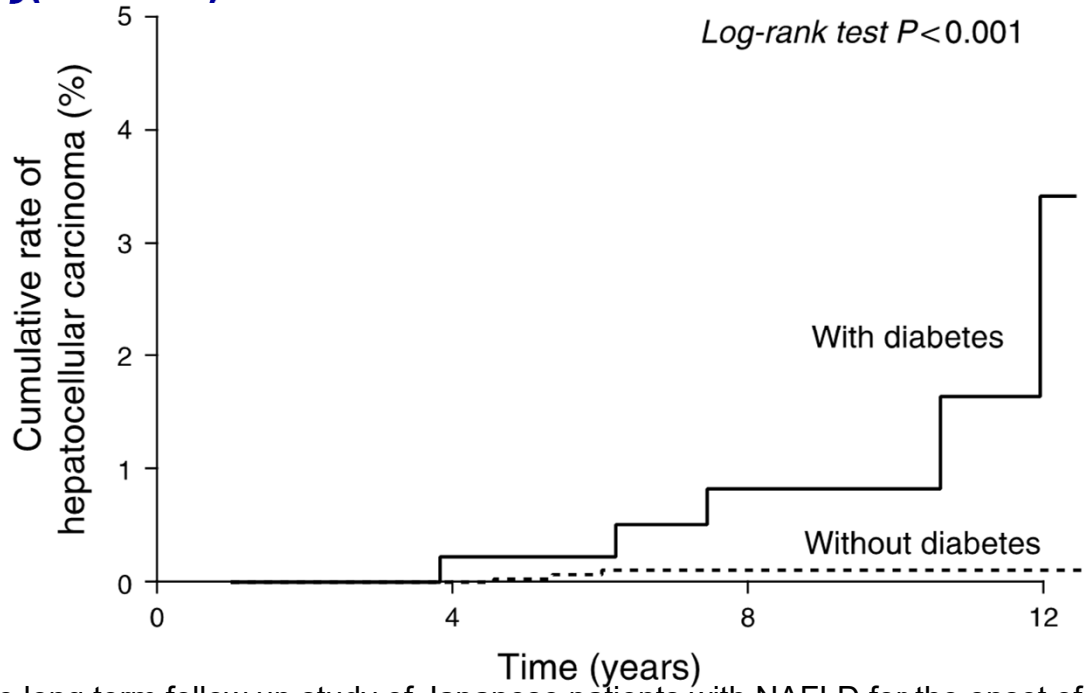
Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of NAFLD and NASH in adults. Alimentary Pharmacology and Therapeutics 2011;34:274-285

ΜΑΛΝΗ - Πρόγνωση

- **Η αυξημένη συνολική θνησιμότητα συγκριτικά με τους αντίστοιχους πληθυσμούς ελέγχου.**

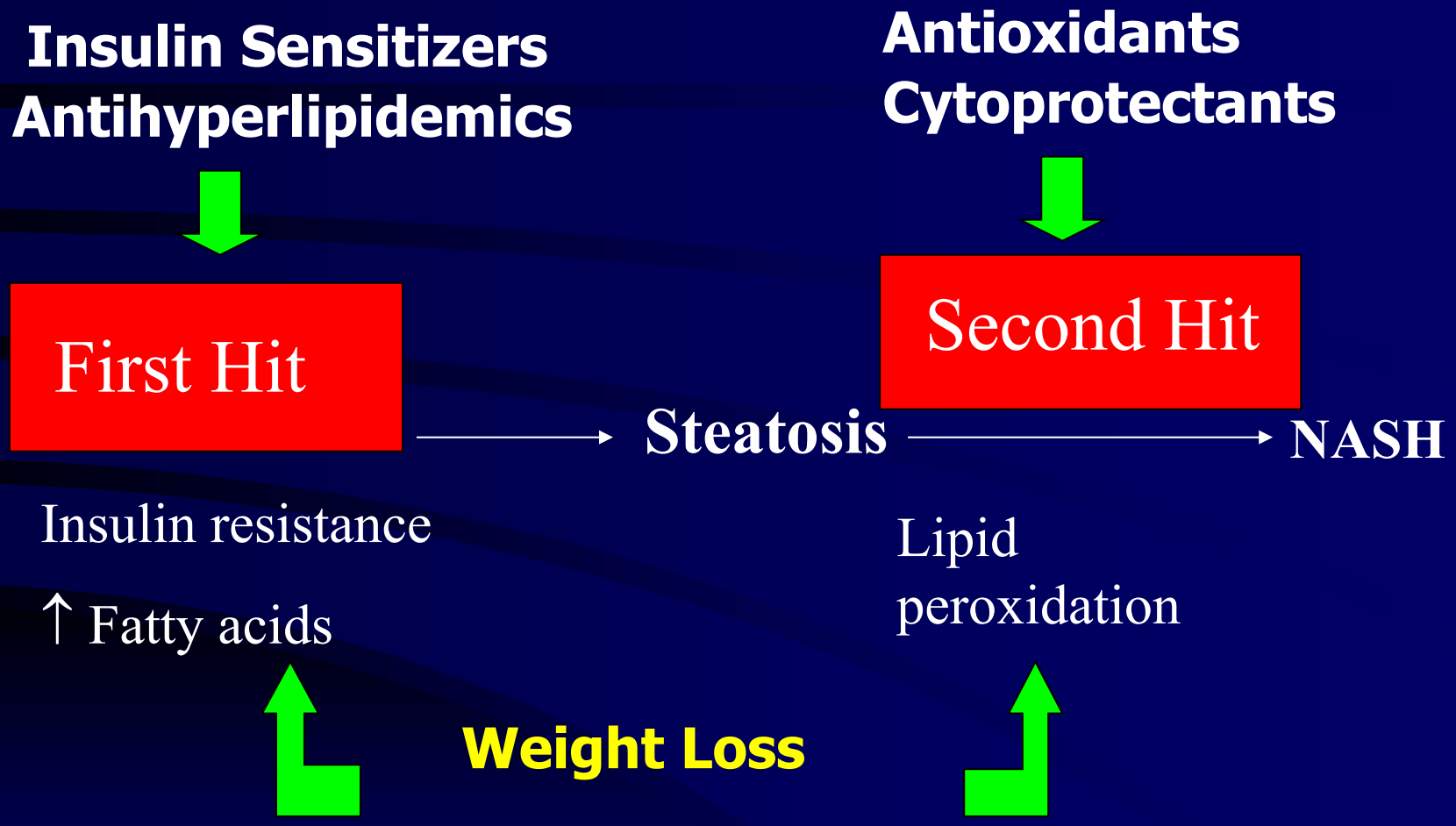
- **Συχνότερη αιτία θανάτου σε ασθενείς με NAFLD, NAFL και NASH είναι η καρδιαγγειακή νόσος, ιδίως επί υπάρξεως ηπατικής ίνωσης.**

- **Αυξημένα ηπατική θνητότητα - όλο και πιο κοινή ένδειξη για μεταμόσχευση ήπατος(15-20%).**



Kawamura Y et al (2011). Large scale long term follow up study of Japanese patients with NAFLD for the onset of HCC. American Journal of Gastroenterology doi:10.1038/ajg.2011.327

ΜΑΛΝΗ - ΘΕΡΑΠΕΙΑ



NAFLD - Weight Loss/Exercise

Palmer et al. Gastroenterology 1990

--39 obese patients, no primary liver disease

--Retrospective analysis after weight loss

--Lower ALT seen in patients with >10% weight loss

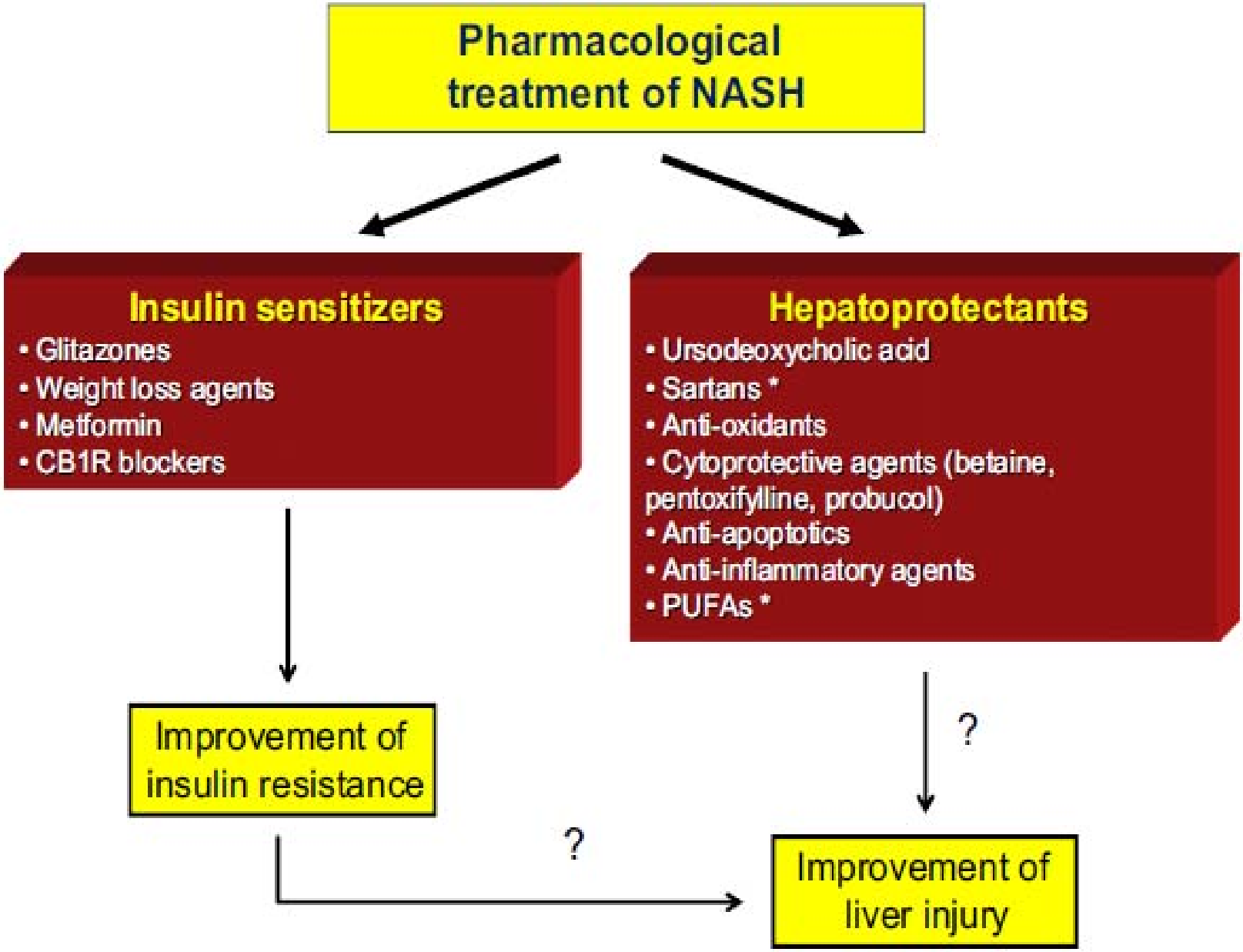
Anderson et al. Journal Hepatology 1991

--41 obese patients with biopsy-proven NAFLD

--Low calorie diet (~400 kcal/d) x 8 months then re-biopsied

--Most improved, but 24% with worse fibrosis/inflammation

--Histological worsening associated with rapid weight loss



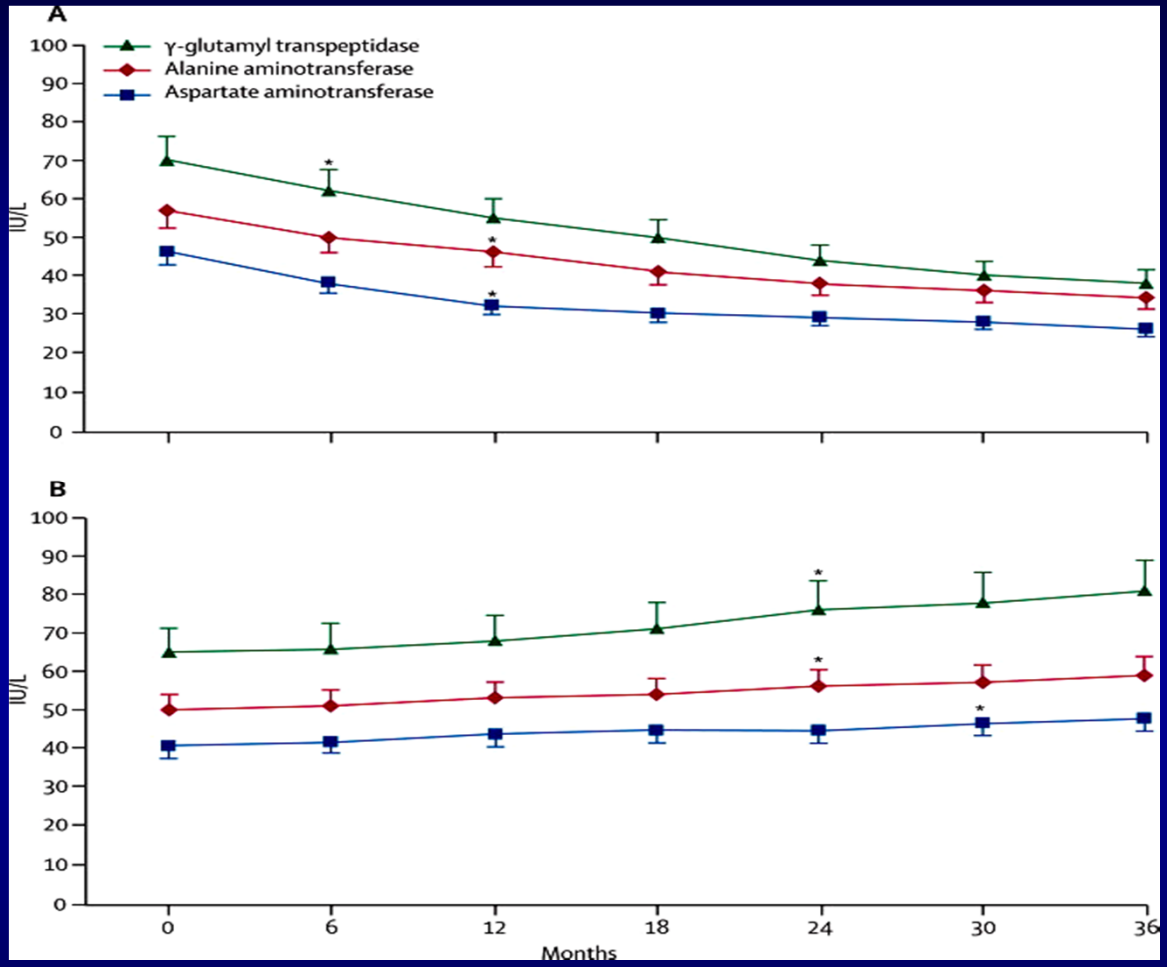
* also have insulin sensitizing properties.

THE LANCET

Safety and efficacy of long-term statin treatment for cardiovascular events in patients with coronary heart disease and abnormal liver tests in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) Study: a post-hoc analysis

Athyros V.G, et al. Lancet 2010, December 10; DOI:10.1016/S0140-6736(10)61272-X.

Effect of statin treatment on liver function tests

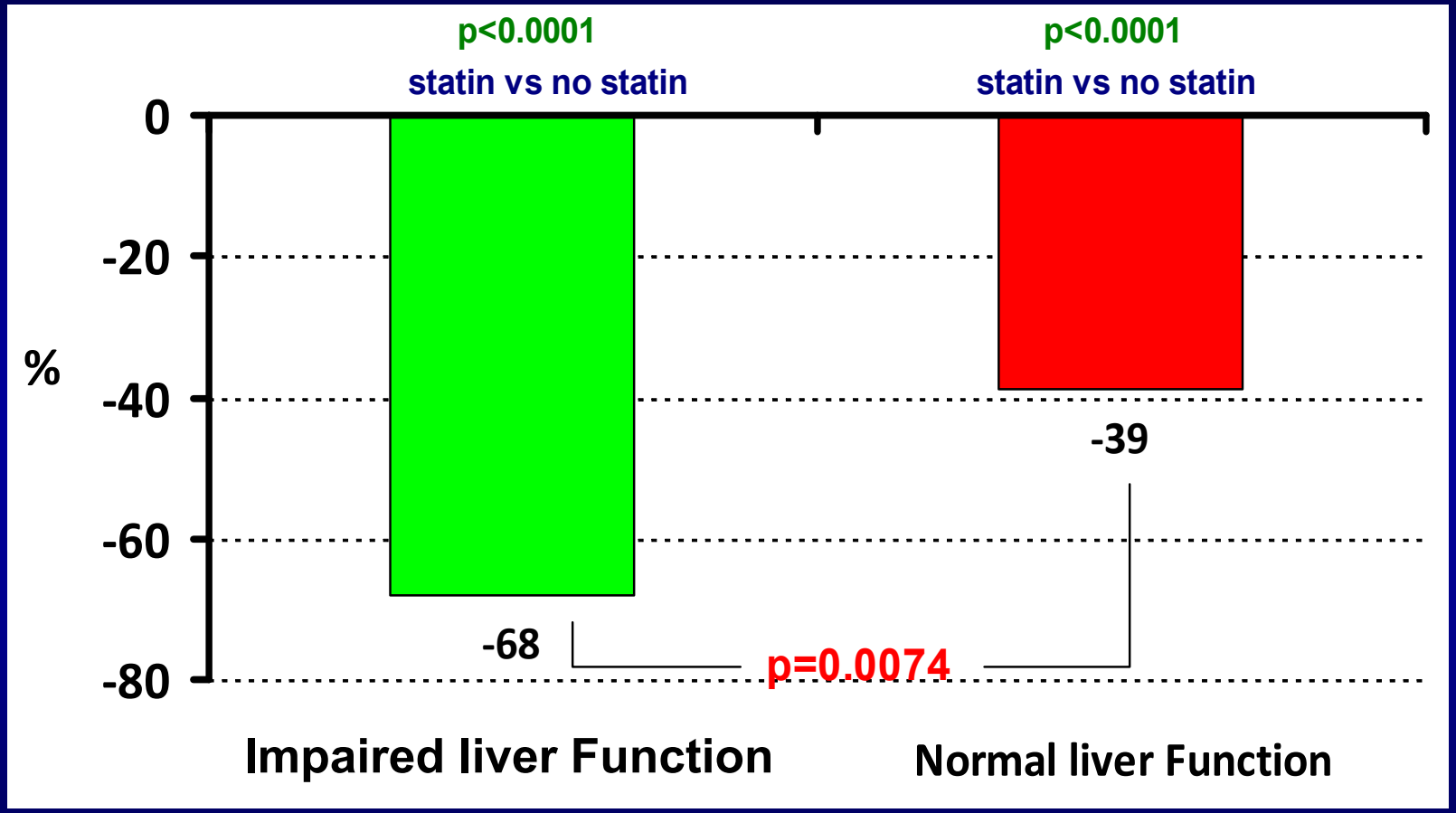


3-ετής παρακολούθηση των ηπατικών ενζύμων σε ασθενείς με αυξημένες τιμές (A) Ασθενείς υπό αγωγή με στατίνη (n=227). (B) Ασθενείς χωρίς στατίνη (n=210). ALT=alanine aminotransferase. AST=aspartate aminotransferase. GGT=γ-glutamyl transferase. Για περισσότερες πληροφορίες, ανατρέξτε στα slide 4, 22,23.

Για τις ενδείξεις και άλλες συνταγογραφικές πληροφορίες της ατορβαστατίνης, ανατρέξτε στο slide 33

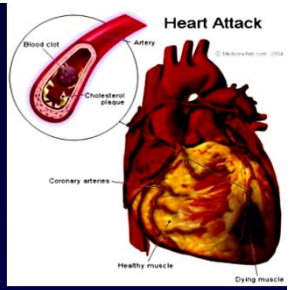
Προσαρμογή από Athyros V, et al. Lancet 2010 ;376(9756):1916-22.

Cardiovascular Relative Risk Reduction within and between the Treatment Groups



Καρδιαγγειακά συμβάματα παρατηρήθηκαν σε 22 (10%) από τους 227 ασθενείς με διαταραγμένες ηπατικές εργαστηριακές εξετάσεις που λάμβαναν στατίνη (3·2 συμβάματα ανά 100 ανθρωπο-έτη) και σε 63 (30%) από τους 210 ασθενείς με διαταραγμένες ηπατικές εργαστηριακές εξετάσεις που δεν λάμβαναν στατίνη (10·0 συμβάματα ανά100 ανθρωπο-έτη; 68% μείωση σχετικού κινδύνου, p<0·0001). Για περισσότερες πληροφορίες, ανατρέξτε στα slide 4, 22,23.

Προσαρμογή από Athyros V, et al. Lancet 2010 ;376(9756):1916-22.



ATTEMPT

Assessing The Treatment Effect in Metabolic syndrome without Perceptible diabeTes (ATTEMPT).

A prospective-randomized study in middle aged men and women.

Safety and impact on CVD events of long-term multifactorial treatment in patients with MetS and Abnormal liver function tests.

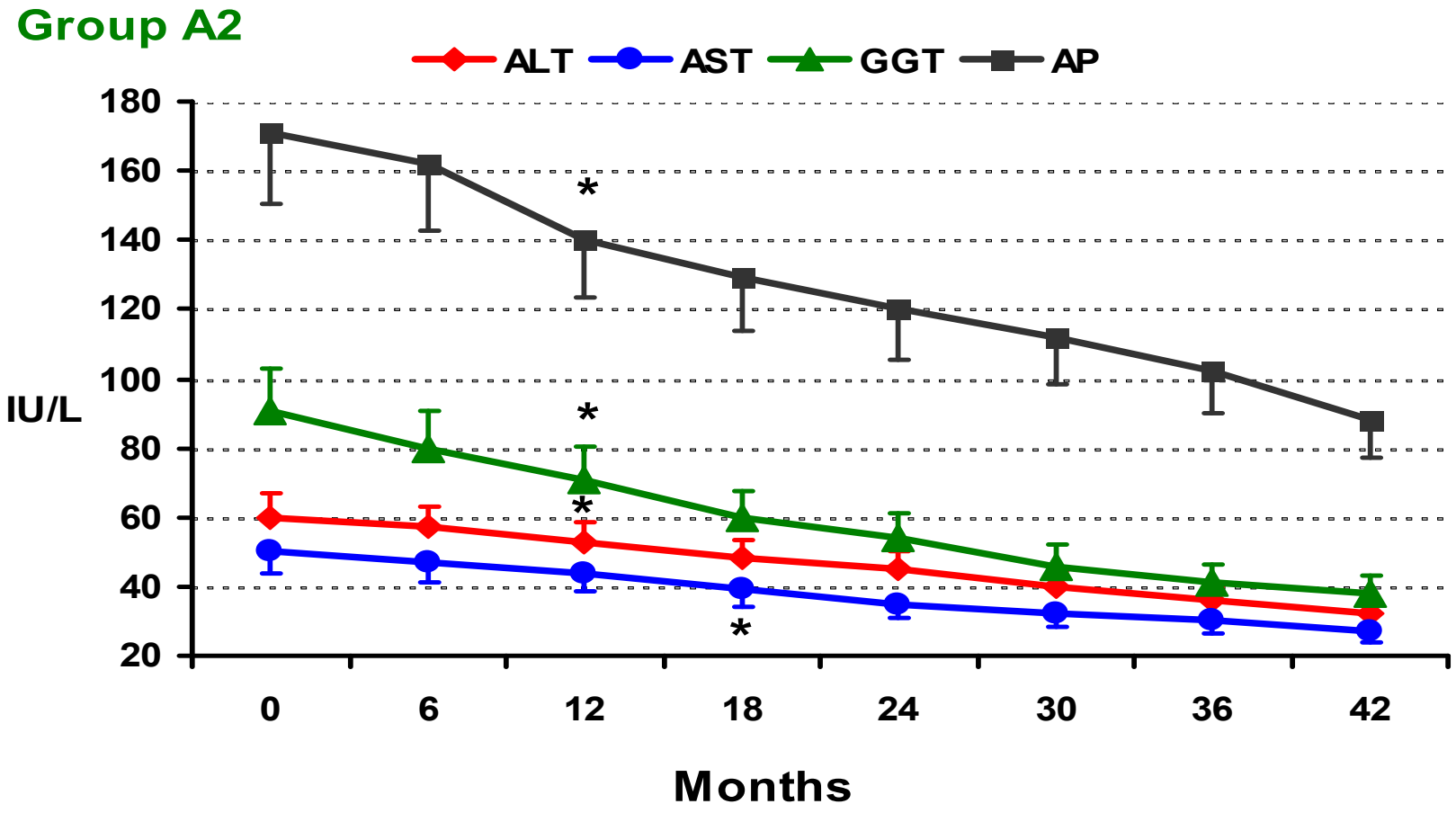
Athyros VG, Giouleme O, Ganotakis ES, Elisaf M, Tziomalos K, Vassiliadis T, Liberopoulos EN, Theocharidou E, Karagiannis A, Mikhailidis DP.; for the Assessing The Treatment Effect in Metabolic Syndrome Without Perceptible diabeTes (ATTEMPT) Collaborative Group*

Arch Med Sci 2011 Oct;7(5):796-805.

ATTEMPT Liver *post hoc* Analysis

Effect of atorvastatin treatment on liver function tests in patients with MetS & NAFLD

Time course of AP, GTT, ALT, AST change in the statin treated patients with NAFLD

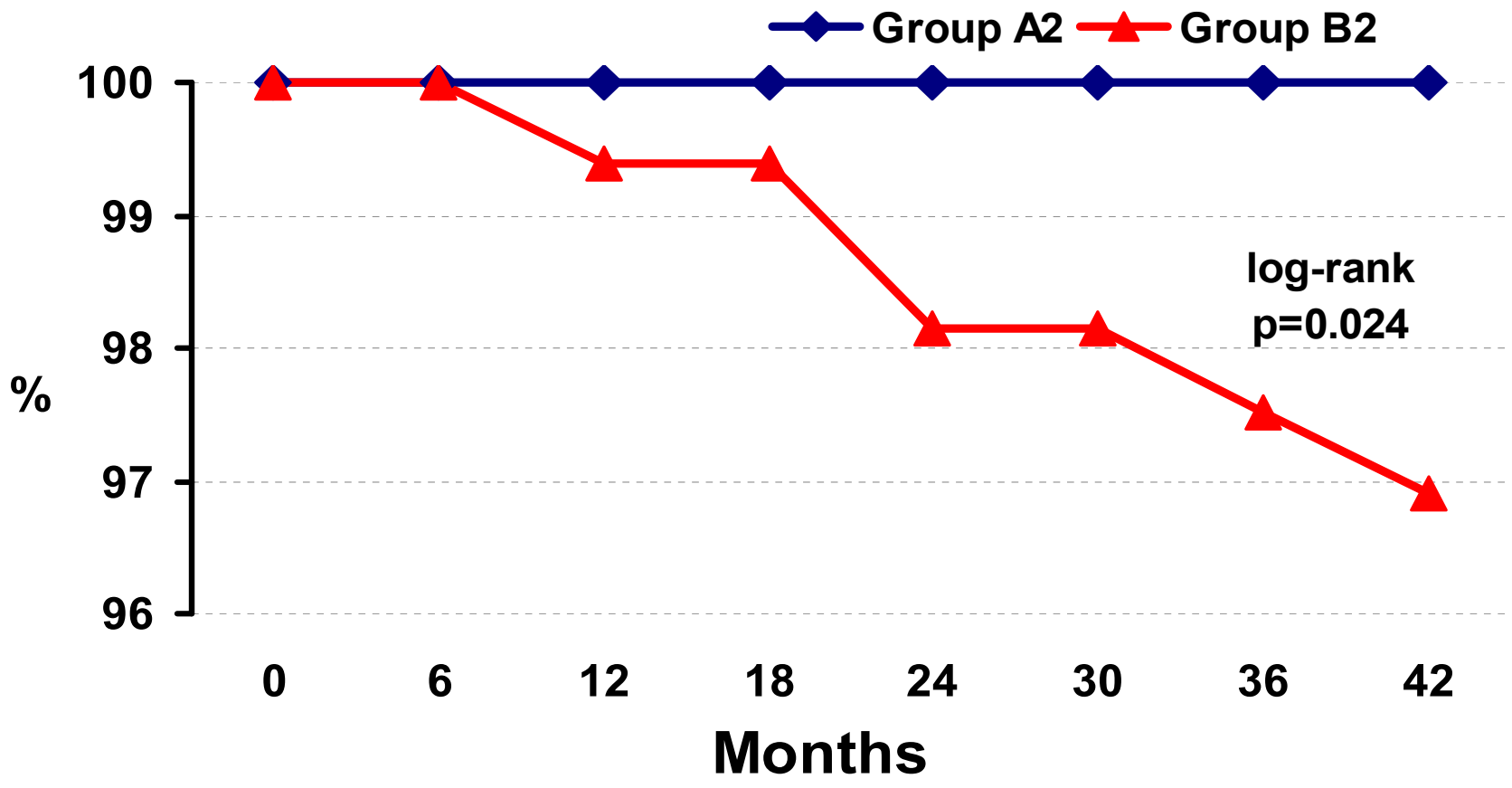


Athyros V, et al. Alimentary Pharmacology and Therapeutics 2011 (in Press).

ATTEMPT Liver *post hoc* Analysis

Effect of atorvastatin treatment on Event free survival of A2 and B2

Time course of AP, GTT, ALT, AST change in the statin treated patients with NAFLD



Athyros V, et al. Alimentary Pharmacology and Therapeutics 2011 (in Press).

IDEAL: Study design

Patient population

- Enrolled at 190 sites
- History of MI (no restriction on time since MI)
- Men and women aged ≤80 years
- Eligible for statin therapy
- 9,689 screened
- Serum ALT levels <2 × the upper limit of normal (ULN)

8,888 Patients Randomised

Open-label period with blinded endpoint evaluations

Atorvastatin 80 mg/day

Simvastatin 20 mg/day (titrated to 40 mg/day at week 24)*

4.8 Year Follow-up

* Simvastatin dose was increased to 40 mg/day at week 24 in patients whose plasma TC remained >5.0 mmol/L or whose LDL-C remained >3.0 mmol/L

Προσαρμογή από Pedersen TR et al. Am J Cardiol 2004 ; 94: 720-724

Για τις ενδείξεις και άλλες συνταγογραφικές πληροφορίες της ατορβαστατίνης, ανατρέξτε στο slide 33

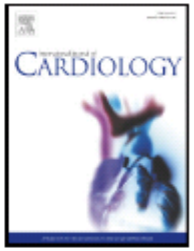
IDEAL Study: Post-hoc analysis in CVD patients with altered liver biochemistry

International Journal of Cardiology xxx (2013) xxx–xxx

Contents lists available at SciVerse ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard



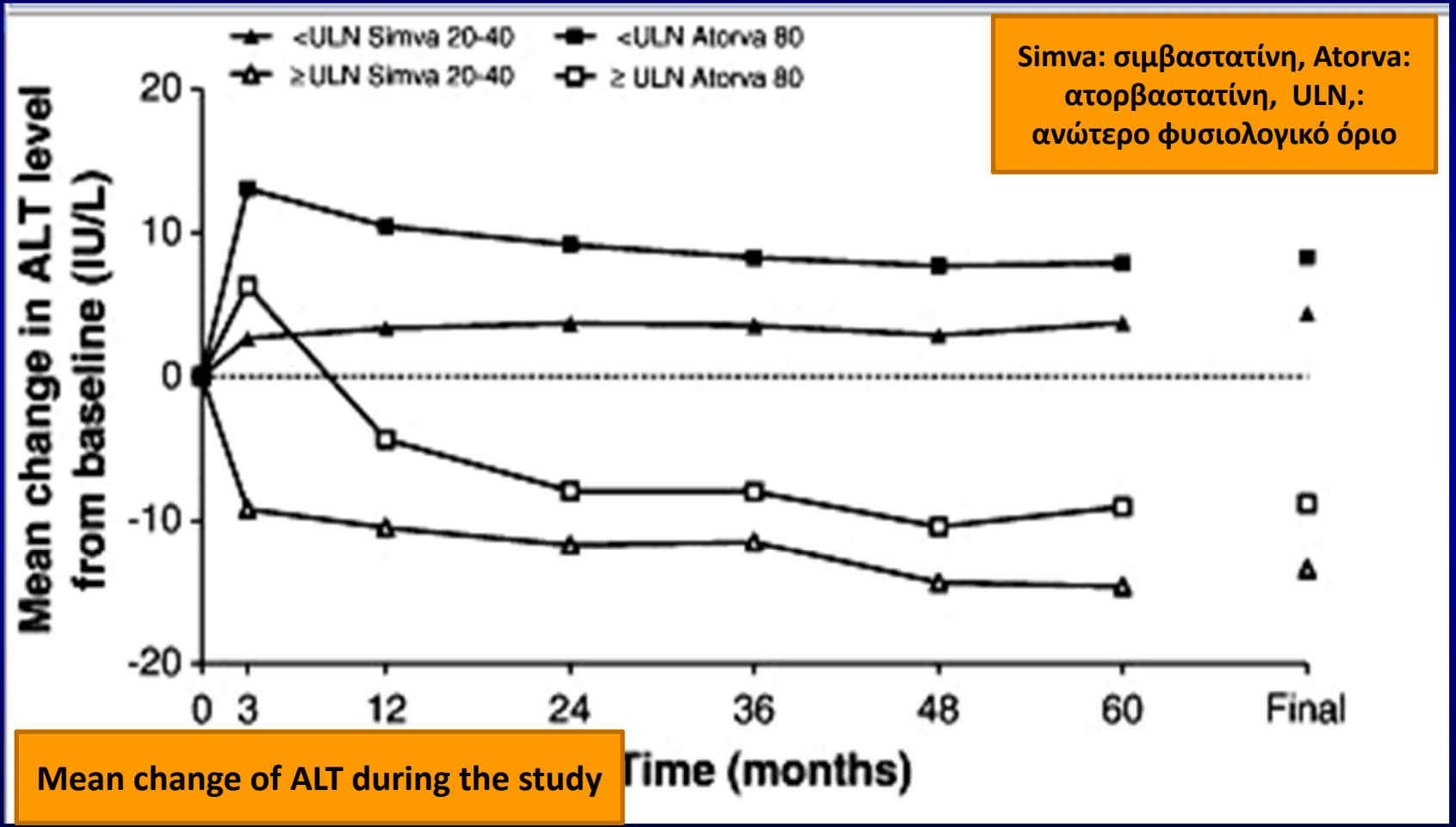
Effect of intensive lipid lowering with atorvastatin on cardiovascular outcomes in coronary heart disease patients with mild-to-moderate baseline elevations in alanine aminotransferase levels

Matti J. Tikkanen [a,*,1], Rana Fayyad [b,1], Ole Faergeman [c,1], Anders G. Olsson [d,1], Chuan-Chuan Wun [b,1], Rachel Laskey [b,1], John J. Kastelein [e,1], Ingar Holme [f,1], Terje R. Pedersen [g,1] On behalf of the IDEAL Investigators

[a] Department of Medicine, Division of Cardiology, Helsinki University Central Hospital, and Folkhälsan Research Center, Helsinki, Finland
[b] Pfizer Inc., New York, NY, USA
[c] Department of Cardiology B, Århus University Hospital, Århus, Denmark
[d] Department of Internal Medicine, Faculty of Health Sciences, University Hospital, Linköping, and Stockholm Heart Center, Stockholm, Sweden
[e] Department of Vascular Medicine, Academic Medical Center, Amsterdam, The Netherlands
[f] Center of Preventive Medicine, Oslo University Hospital, Ullevål, Oslo, Norway
[g] University of Oslo and Center of Preventive Medicine, Oslo University Hospital, Ullevål, Oslo, Norway

Primary endpoint: reduction in recurrent CVD events

Change in ALT levels according to statin treatment

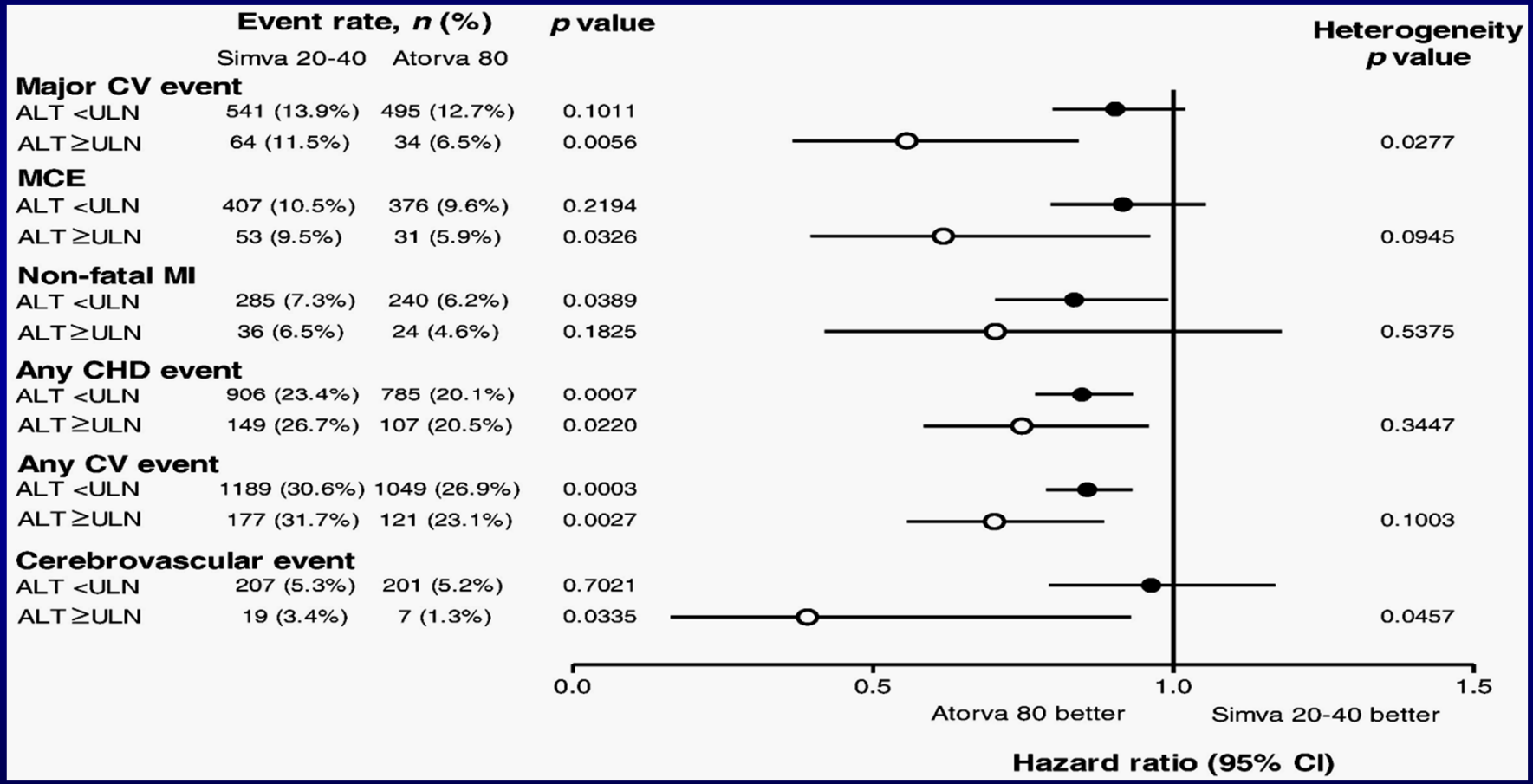


Simva: σιμβαστατίνη, Atorva: ατορβαστατίνη, ULN,: ανώτερο φυσιολογικό όριο

Mean change of ALT during the study

TikkanenMJ, et al. Int J Cardiol (2013), http://dx.doi.org/10.1016/j.ijcard.2013.06.024l

Effect of therapy on CVD events in patients with increased or normal ALT levels



TikkanenMJ, et al. Int J Cardiol (2013), http://dx.doi.org/10.1016/j.ijcard.2013.06.024l

Effect of rosuvastatin (10 mg) on non-alcoholic steatohepatitis in patients with metabolic syndrome and hypercholesterolaemia. A preliminary report.

Konstantinos Kargiotis, Niki Katsiki, Vasilios G. Athyros, Olga Giouleme, Kalliopi Patsiaoura, Evangelia Katsiki, Dimitri P. Mikhailidis, Asterios Karagiannis.

Current Vascular Pharmacology 2014 May;12(3):505-11

World Journal of Gastroenterology

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Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.3748/wjg.v21.i25.7860

World J Gastroenterol 2015 July 7; 21(25): 7860-786
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

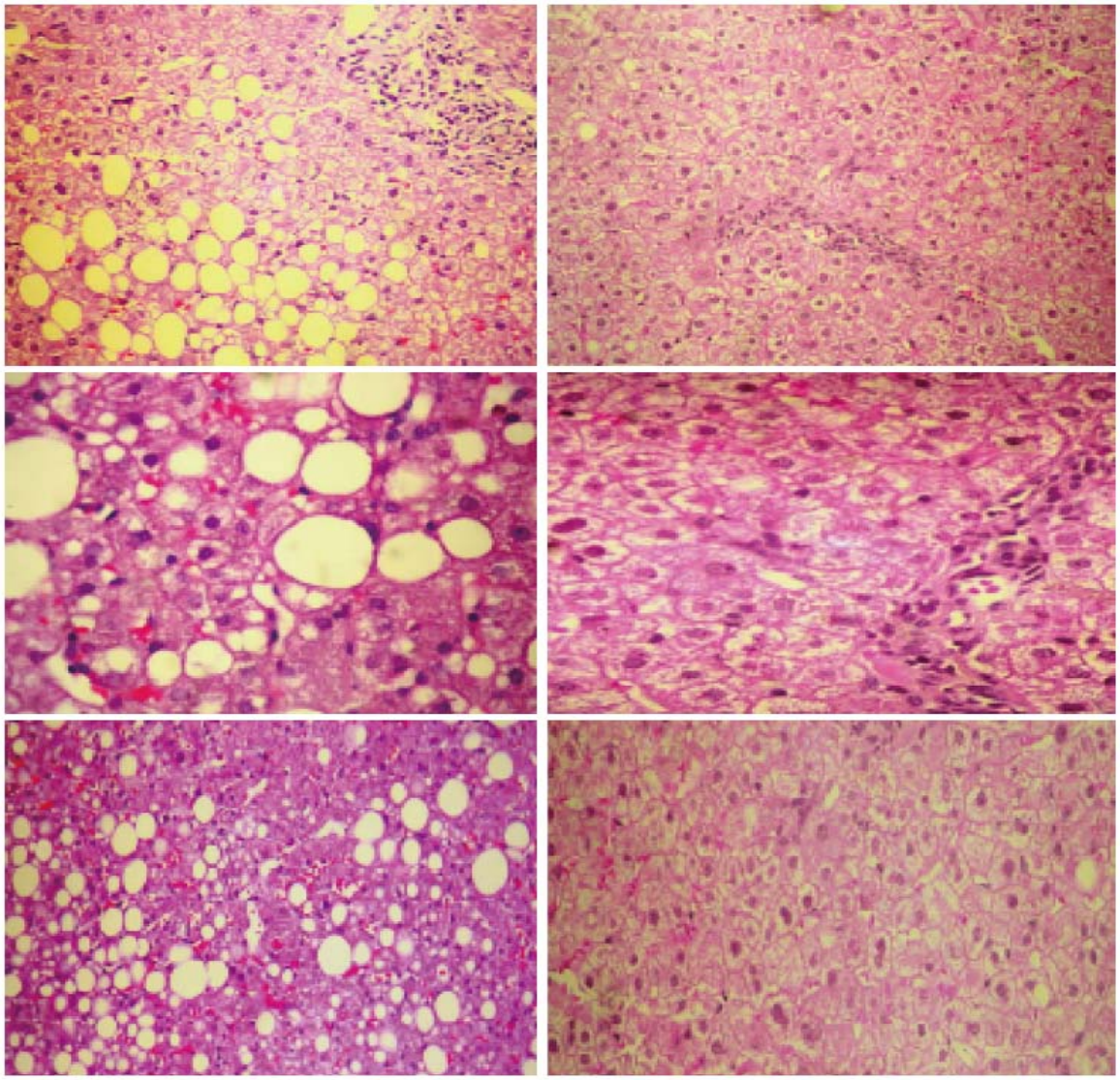
ORIGINAL ARTICL

Prospective Study

Resolution of non-alcoholic steatohepatitis by rosuvastatin monotherapy in patients with metabolic syndrome

Konstantinos Kargiotis, Vasilios G Athyros, Olga Giouleme, Niki Katsiki, Evangelia Katsiki, Panagiotis Anagnos
Chrysoula Boutari, Michael Doumas, Asterios Karagiannis, Dimitri P Mikhailidis

Resolution of non-alcoholic steatohepatitis by rosuvastatin monotherapy in patients with metabolic syndrome



World J Gastroenterol. 2015 Jul 7;21(25):7860-8.

Table 1 Changes in measured parameters during the study

Parameter	Baseline	1st mo	3rd mo	6th mo	9th mo	12th mo	*P* value (ANOVA)
Age (yr)	40.5 ± 5.6	-	-	-	-	-	-
Gender (male)	16	-	-	-	-	-	-
Cigarette smoking	13	13	13	12	12	11	NS
BMI (kg/m^2)	31.5 ± 1.1	31.3 ± 1.0	31.4 ± 1.0	31.6 ± 1.1	31.6 ± 1.2	31.5 ± 1.2	NS
Waist circumference (cm)	110.5 ± 6.2	110.4 ± 6.0	109.9 ± 6.1	110.6 ± 6.3	110.7 ± 6.2	110.4 ± 6.2	NS
Total cholesterol (mg/dL)	251 ± 22	226 ± 17	192 ± 16	185 ± 12	181 ± 8	179 ± 9	< 0.001
Triglycerides (mg/dL)	187 ± 19	161 ± 20	143 ± 26	123 ± 11	121 ± 22	117 ± 18	< 0.001
HDL-cholesterol (mg/dL)	38 ± 5	40 ± 5	42 ± 7	42 ± 4	43 ± 3	44 ± 5	< 0.001
LDL-cholesterol (mg/dL)	180 ± 23	152 ± 15	121 ± 17	118 ± 14	114 ± 9	110 ± 11	< 0.001
Serum creatinine (mg/dL)	0.93 ± 0.2	0.92 ± 0.2	0.94 ± 0.2	0.92 ± 0.2	0.91 ± 0.2	0.90 ± 0.2	NS
hsCRP (mg/L)	4.2 ± 1.3	-	-	2.7 ± 0.8	-	1.6 ± 0.5	< 0.001
BUN (mg/dL)	34 ± 8	34 ± 8	35 ± 8	34 ± 7	33 ± 6	31 ± 6	NS
SUA (mg/dL)	5.5 ± 1.1	5.4 ± 1.0	5.2 ± 0.9	5.0 ± 0.7	4.9 ± 0.8	4.8 ± 0.9	0.016
Plasma glucose (mg/dL)	102 ± 8	101 ± 8	96 ± 6	93 ± 7	89 ± 5	87 ± 5	< 0.001
HbA1c (%)	5.3 ± 0.4	-	5.1 ± 0.4	5.0 ± 0.5	4.9 ± 0.3	4.8 ± 0.3	< 0.001
Metabolic Syndrome, *n*	20	20	18	9	0	0	< 0.001

Data are presented as mean ± SD. BMI: Body mass index; HDL: High density lipoprotein; LDL: Low density lipoprotein; NS: Not significant; BUN: Blood urea nitrogen; SUA: Serum uric acid; HbA1c: Glycosylated haemoglobin.

Resolution of non-alcoholic steatohepatitis by rosuvastatin monotherapy in patients with metabolic syndrome

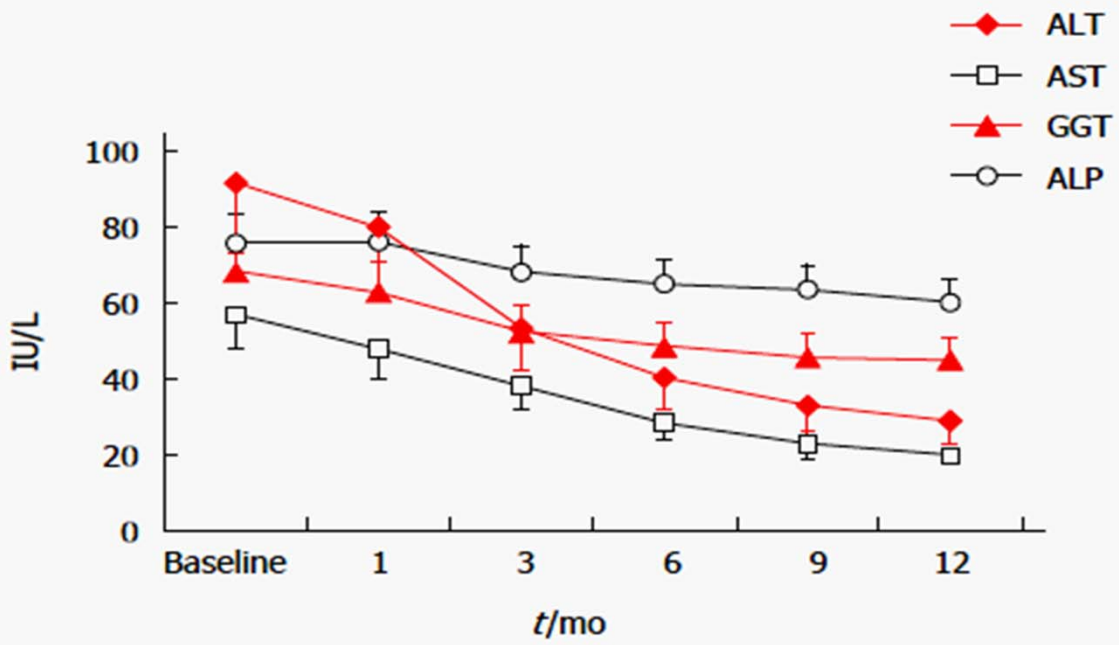


Figure 2 Liver enzyme changes in 20 patients with non-alcoholic steatohepatitis during the 12 mo of rosuvastatin (10 mg/d) monotherapy. The reduction in serum alanine transaminase (ALT), aspartate transaminase (AST) and γ-glutamyl transpeptidase (GGT) levels became statistical significant by the 3rd month of treatment (ANOVA for the 12 mo period $P < 0.001$) and for alkaline phosphatase (ALP) by the 6th mo of treatment (ANOVA for the 12 mo period $P = 0.01$).

World J Gastroenterol. 2015 Jul 7;21(25):7860-8.

ΜΑΛΝΗ - Συμπεράσματα

- Η ΜΑΛΝΗ επηρεάζει μέχρι και το 35% του πληθυσμού των ΗΠΑ
- Στεάτωση έχει σχετικά καλή πρόγνωση, αλλά η NASH έχει σημαντικό κίνδυνο νοσηρότητας/θνητότητας
- Η αντίσταση στην ινσουλίνη και οι κυτταρικές αλλοιώσεις είναι τα βασικά παθογενετικά αίτια
- Η συνεχής σταδιακή απώλεια βάρους και η άσκηση είναι σημαντικό στοιχείο της θεραπείες
- Ευαισθητοποιητές ινσουλίνης, κυτταροπροστατευτικά και αντιοξειδωτικά μπορεί να παίξουν
- Οι στατίνες μπορεί να αποτελούν μια πολλά υποσχόμενη λύση