ΜΗ ΑΛΚΟΟΛΙΚΗ ΣΤΕΑΤΟΗΠΑΤΙΤΙΔΑ

Χ. Τριάντος

Επίκουρος Καθηγητής Παθολογίας-Γαστρεντερολογίας

Ιατρικό Τμήμα, Πανεπιστήμιο Πατρών

Πίνακας 1. Αίτια λίπωσης ήπατος.

- Κατάχρηση αιθυλικής αλκοόλης
- Μη αλκοολική λιπώδης νόσος
- HCV-λοίμωξη
- Φλεγμονώδεις νόσοι του εντέρου
- Χειρουργική παράκαμψη του ειλεού
- Ολική παρεντερική διατροφή
- Μεγάλη/ταχεία απώλεια βάρους, καχεξία
- Σύνδρομο επανασίτισης
- Μεταβολικά
  - Γλυκογονιάσεις
  - Τυροσιναιμία
  - Διαταραχές του μεταβολισμού των λιπιδίων [Αβητα-(υποβητα)-λιποπρωτεϊναιμία, νόσος Andersen]
  - Νόσος Wilson
- Λιποδυστροφίες, νόσος Weber-Christian
- Λήψη φαρμάκων (αμιωδαρόνη, κορτικοστεροειδή, μεθοτρεξάτη, αντι-HIV, ταμοξιφαίνη κ.λπ.)

ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2010, 27(2):165–179
ARCHIVES OF HELLENIC MEDICINE 2010, 27(2):165–179

Σ.Π. Ντουράκης

NAFLD – NAFL - NASH

Sub-classification of NAFLD*	Most common concurrent diseases
NAFL • Pure steatosis • Steatosis and mild lobular inflammation	**AFLD†** **Drug-induced fatty liver disease†** **HCV-associated fatty liver disease (GT 3)†** **Others†** • Haemochromatosis • Autoimmune hepatitis • Coeliac disease • Wilson disease • A/hypo-betalipoproteinaemia lipoatrophy • Hypopituitarism, hypothyroidism • Starvation, parenteral nutrition • Inborn errors of metabolism – Wolman disease (lysosomal acid lipase deficiency)
NASH • Early NASH (no or mild fibrosis) • Fibrotic NASH (significant/advanced fibrosis) • NASH cirrhosis	
HCC‡	

*Also called primary NAFLD and associated with metabolic risk factors/components of MetS: 1. Waist circumference ≥94/≥80 cm for Europid men/women; 2. Arterial pressure ≥130/85 mmHg or treated for hypertension; 3. Fasting glucose ≥100 mg/dl (5.6 mmol/L) or treated for T2DM; 4. Serum triacylglycerols >150 mg/dl (>1.7 mmol/L); 5. HDL cholesterol <40/50 mg/dl for men/women (<1.0/<1.3 mmol/L); †Also called secondary NAFLD. Note that primary and secondary NAFLD may coexist in individual patients. Also NAFLD and AFLD may coexist in subjects with metabolic risk factors and drinking habits above safe limits; ‡Can occur in the absence of cirrhosis and histological evidence of NASH, but with metabolic risk factors suggestive of ''burned-out" NASH

EASL–EASD–EASO CPG NAFLD. J Hepatol 2016;64:1388–402

Κριτήρια διάγνωσης του μεταβολικού συνδρόμου

Five definitions of the metabolic syndrome

Parameters	NCEP ATP3 2005*	IDF 2009	EGIR 1999	WHO 1999	AACE 2003
Required			Insulin resistance or fasting hyperinsulinemia (ie, in top 25% of the laboratory-specific reference range)	Insulin resistance in top 25%[Δ]; fasting glucose ≥6.1 mmol/L (110 mg/dL); 2-hour glucose ≥7.8 mmol/L (140 mg/dL)	High risk of insulin resistance[◇] or BMI ≥25 kg/m^2 or waist ≥102 cm (men) or ≥88 cm (women)
Number of abnormalities	**≥3 of:**	**≥3 of:**	**And ≥2 of:**	**And ≥2 of:**	**And ≥2 of:**
Glucose	Fasting glucose ≥5.6 mmol/L (100 mg/dL) or drug treatment for elevated blood glucose	Fasting glucose ≥5.6 mmol/L (100 mg/dL) or diagnosed diabetes	Fasting glucose 6.1 to 6.9 mmol/L (110 to 125 mg/dL)		Fasting glucose ≥6.1 mmol/L (110 mg/dL); ≥2-hour glucose 7.8 mmol/L (140 mg/dL)
HDL cholesterol	<1.0 mmol/L (40 mg/dL) (men); <1.3 mmol/L (50 mg/dL) (women) or drug treatment for low HDL cholesterol[§]	<1.0 mmol/L (40 mg/dL) (men); <1.3 mmol/L (50 mg/dL) (women) or drug treatment for low HDL cholesterol	<1.0 mmol/L (40 mg/dL)	<0.9 mmol/L (35 mg/dL) (men); <1.0 mmol/L (40 mg/dL) (women)	<1.0 mmol/L (40 mg/dL) (men); <1.3 mmol/L (50 mg/dL) (women)
Triglycerides	≥1.7 mmol/L (150 mg/dL) or drug treatment for elevated triglycerides[§]	≥1.7 mmol/L (150 mg/dL) or drug treatment for high triglycerides	or ≥2.0 mmol/L (180 mg/dL) or drug treatment for dyslipidemia	or ≥1.7 mmol/L (150 mg/dL)	≥1.7 mmol/L (150 mg/dL)
Obesity	Waist ≥102 cm (men) or ≥88 cm (women)[¥]	Waist ≥94 cm (men) or ≥80 cm (women)	Waist ≥94 cm (men) or ≥80 cm (women)	Waist/hip ratio >0.9 (men) or >0.85 (women) or BMI ≥30 kg/m^2	
Hypertension	≥130/85 mmHg or drug treatment for hypertension	≥130/85 mmHg or drug treatment for hypertension	≥140/90 mmHg or drug treatment for hypertension	≥140/90 mmHg	≥130/85 mmHg

NCEP: National Cholesterol Education Program; IDF: International Diabetes Federation; EGIR: Group for the Study of Insulin Resistance; WHO: World Health Organization; AACE: American Association of Clinical Endocrinologists; HDL: high-density lipoprotein; CVD: cardiovascular disease; BMI: body mass index.

* Most commonly agreed upon criteria for metabolic syndrome. Note that abdominal obesity is **not** a prerequisite for diagnosis; the presence of any 3 of the 5 risk criteria constitutes a diagnosis of metabolic syndrome.

¶ For South Asian and Chinese patients, waist ≥90 cm (men) or ≥80 cm (women); for Japanese patients, waist ≥90 cm (men) or ≥80 cm (women).

Δ Insulin resistance measured using insulin clamp.

◇ High risk of being insulin resistant is indicated by the presence of at least 1 of the following: diagnosis of CVD, hypertension, polycystic ovary syndrome, non-alcoholic fatty liver disease or acanthosis nigricans; family history of type 2 diabetes, hypertension of CVD; history of gestational diabetes or glucose intolerance; nonwhite ethnicity; sedentary lifestyle; BMI 25 kg/m^2 or waist circumference 94 cm (men) or 80 cm (women); and age 40 years.

§ Treatment with 1 or more of fibrates or niacin.

¥ In Asian patients, waist ≥90 cm (men) or ≥80 cm (women).

Μη αλκοολική λιπώδης νόσος του ήπατος (ΜΑΛΝΗ)
(Non-alcoholic fatty liver disease (NAFLD))

NAFL

- Pure steatosis
- Steatosis and mild lobular inflammation

NASH

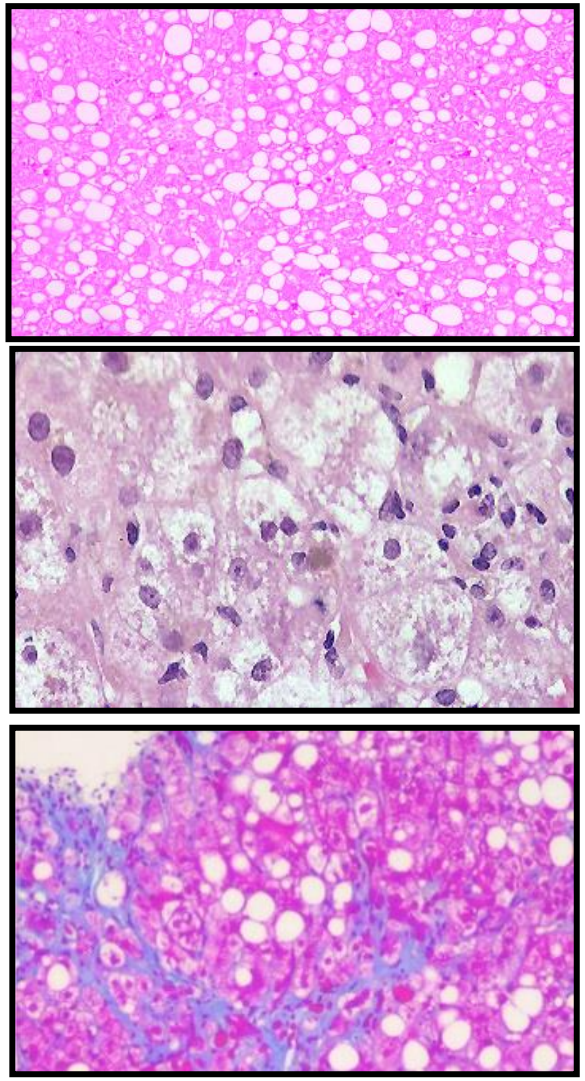
- Early NASH: no or mild (F0-F1) fibrosis
- Fibrotic NASH: significant (≥F2)

or advanced (≥F3,bridging) fibrosis

- NASH-Cirrhosis (F4)

Hepatocellular carcinoma

EASL 2016



Fat infiltration > 5%
± mild inflammation

Steatosis + necroinflammation (eg, ballooning, Mallory bodies, megamitochondria)

Increasing fibrosis, eventually leading to cirrhosis

Μη αλκοολική λιπώδης νόσος του ήπατος (ΜΑΛΝΗ) (Non-alcoholic fatty liver disease (NAFLD))

Οι ασθενείς με ΜΑΛΝΗ/μη αλκοολική στεατοηπατίτιδα (ΜΑΣΗ) (Non alcoholic steatohepatitis NASH)

- 70–100% παχυσαρκία
- 35–75% ΣΔ -2
- 20–80% δυσλιπιδαιμία

Πίνακας 5. Σχετιζόμενες με τη ΜΑΛΝΗ/ΜΣΗ καταστάσεις.

ΜΑΛΝΗ/ΜΣΗ: Μη αλκοολική νόσος του ήπατος/μη αλκοολική στεατοηπατίτιδα

ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2010, 27(2):165–179
ARCHIVES OF HELLENIC MEDICINE 2010, 27(2):165–179

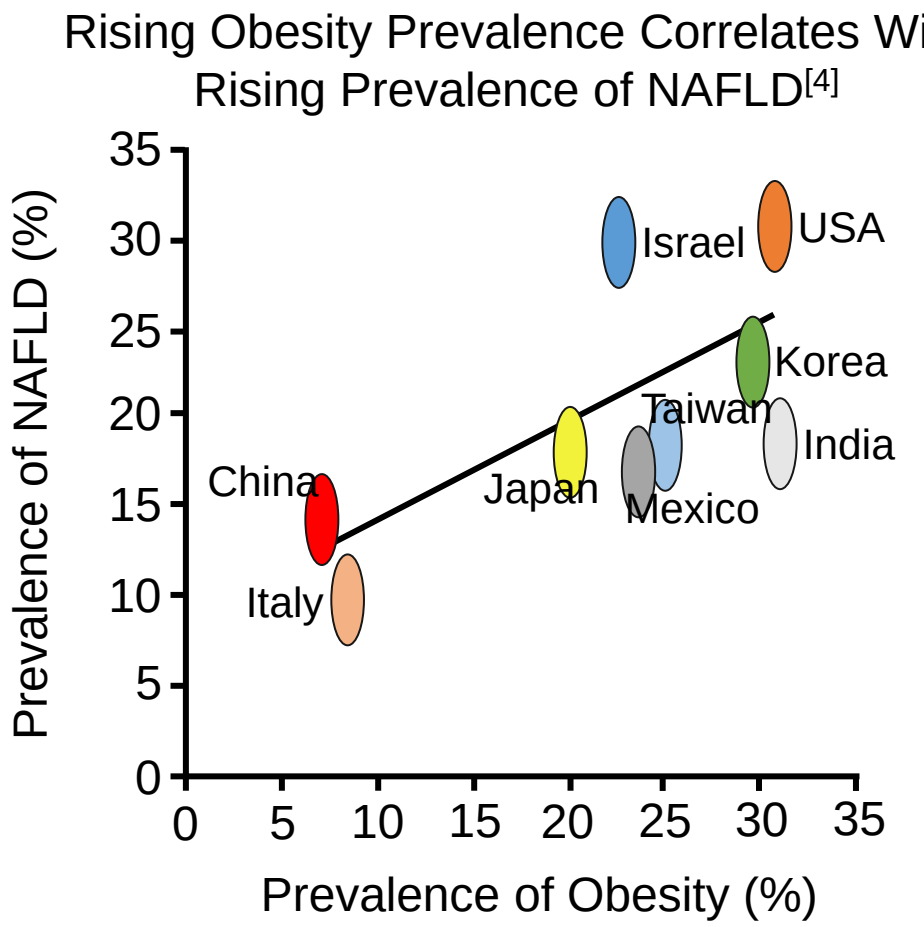
Σ.Π. Ντουράκης

Επιπολασμός ΜΑΛΝΗ – Γενικός πληθυσμός

ΗΠΑ (n = 328)[1]:
- ΜΑΛΝΗ (u/s 46%)
- ΜΑΣΗ 12.2% (29.9% από τους ΜΑΛΝΗ)

Dionysos study, ΜΑΛΝΗ [2]:
- BMI > 30, 94%
- BMI > 25, 67%
- Φυσιολογικό ΣΒ, 25%

Σε υγιείς ζώντες δότες ήπατος ΜΑΣΗ ιστολογικά[3]:
- Ευρώπη, 3% - 16%
- ΗΠΑ, 6% - 15%



1. Williams CD, et al. Gastro. 2011;140:124-31.
2. Bellentani S, et al. E J Gastro Hep. 2004; 1087-1093. 3. Anstee et al. Nat Rev Gastroenterol Hepatol. 2013;10:330-344. 4. Loomba R, et al. Nat Rev Gastroenterol Hepatol. 2013;10:686-690.

Europe's largest meta-analysis on the prevalence of NAFLD, NASH and advanced fibrosis (F3–F4)

BACKGROUND & AIMS

- NAFLD and NASH prevalence is increasing and are a significant health burden
- The only clinical marker associated with overall mortality and liver-related morbidity in NAFLD and NASH is the presence of advanced fibrosis
- Up-to-date European prevalence data are lacking
  - Previous systematic review included data up to 2015
  - Cohorts with information on advanced fibrosis in the general population are scarce
- **AIM**: to estimate the European prevalence of NAFLD, NASH, and advanced fibrosis (stage F3–F4) considering recently published data

METHODS

A European systematic review of observational studies with data on NAFLD, NASH and advanced fibrosis prevalence according to PRISMA guidelines

↓

PubMed search of published studies (Cut-off: Oct 2019)

→ **Excluded studies**
- Those in individuals with alcohol abuse
- Those on patients with liver disease related to other aetiologies
- Those exclusively enrolling morbidly obese patients and those with diabetes

↓

NAFLD prevalence studies N=28
NASH prevalence studies N=12
Advanced fibrosis prevalence studies N=5

↓

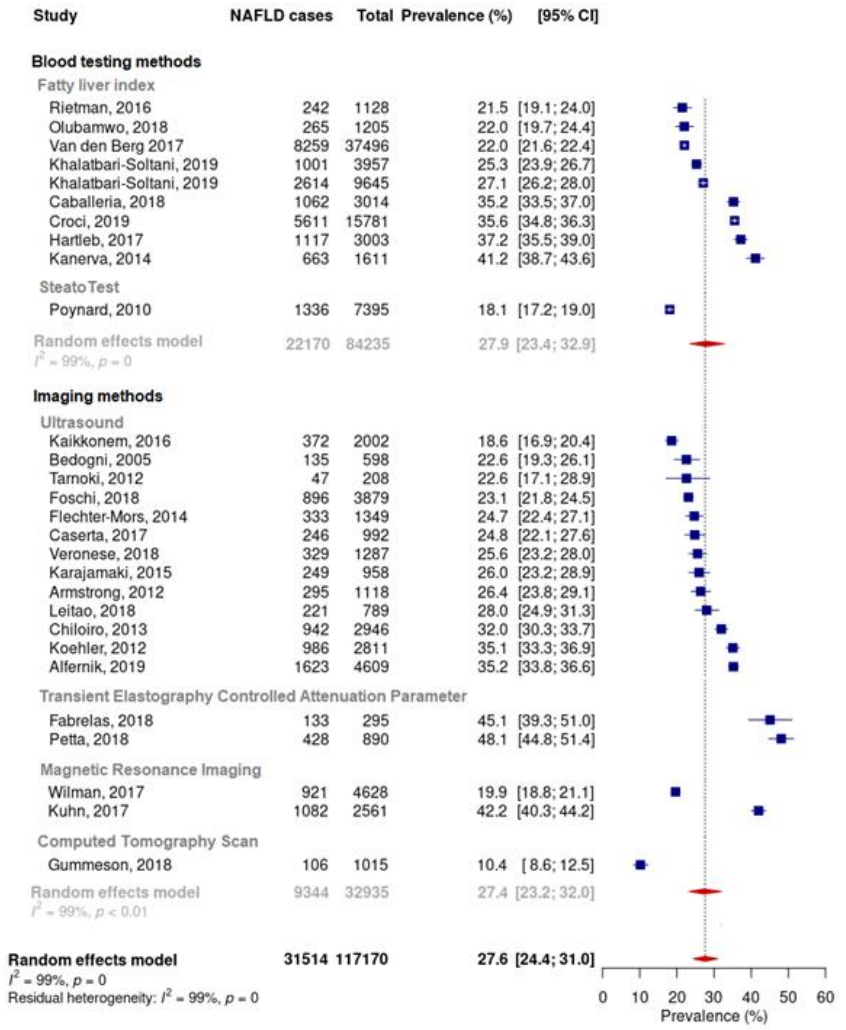
Random effects model meta-analysis was used to estimate prevalence (95% CI)

Petta S, et al. DILC 2020; THU053

Europe's largest meta-analysis on the prevalence of NAFLD, NASH and advanced fibrosis (F3–F4)

RESULTS

NAFLD prevalence in European studies



- From 588 studies identified, 42 studies from 15 European countries met inclusion criteria, comprising 125,674 unique adult individuals
  - **Overall NAFLD prevalence estimated in the random effects meta-analysis model was 27.6% (95% CI 24.4–31.0; 28 studies)**
  - **No difference in prevalence observed when NAFLD was assessed by imaging or blood test methods**
- **Among 4,696 biopsy-proven NAFLD patients**
  - **64.3% had NASH (95% CI 52.7–74.4; 12 studies)**
- **In 5 studies reporting information on advanced fibrosis in the general population, prevalence was 6.1% (95% CI 4.3–8.7)**

CONCLUSION

- Identification of advanced liver fibrosis remains an important priority due to its association with mortality and morbidity. Although easily assessed with current noninvasive tools, only 5 studies reported its prevalence in the general population
- These data add to the evidence base and may be particularly useful in European settings that currently lack data

Petta S, et al. DILC 2020; THU053

Screening

- 17–46% στους ενήλικες[1]
- 7% με φυσιολογικό ΣΒ individuals[2]

Recommendations	Grade of evidence	Grade of recommendation
Patients with **IR and/or metabolic risk factors** (i.e. obesity or MetS) should undergo procedures for the diagnosis of NAFLD	A	1
Screen individuals with steatosis for **secondary causes** of NAFLD, including a careful assessment of alcohol intake. Always consider the interaction between moderate amounts of **alcohol** and metabolic factors in fatty liver	A	1
Identify other **chronic liver diseases that may coexist** with NAFLD as these might result in more severe liver injury	B	1

1. Vernon G, et al. Aliment Pharmacol Ther 2011;34:274–85; 2. Younossi ZM, et al. Medicine 2012;91:319–27;
EASL–EASD–EASO CPG NAFLD. J Hepatol 2016;64:1388–402

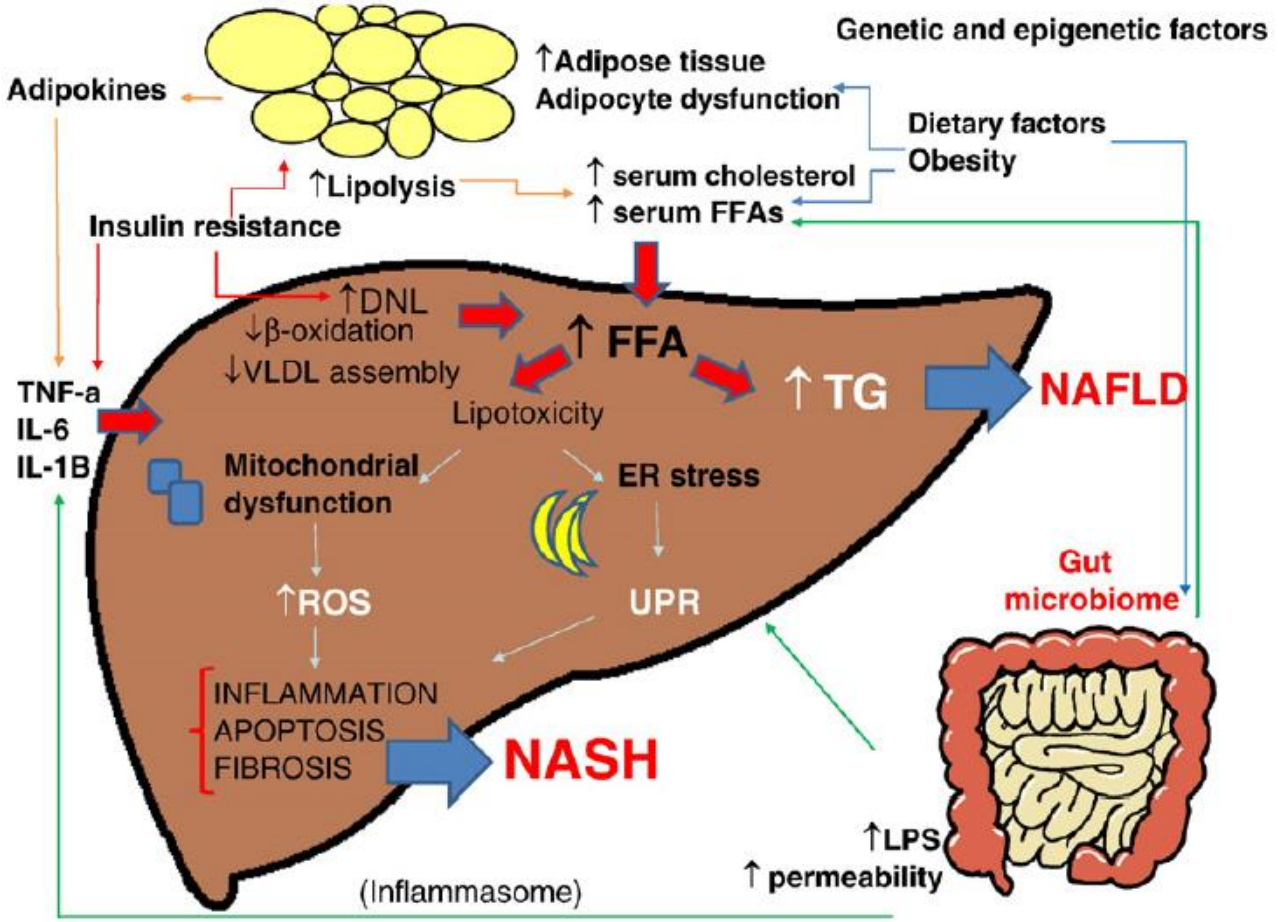
Screening

Recommendations	Grade of evidence	Grade of recommendation
All individuals with steatosis should be screened for features of MetS, independent of liver enzymes. **All individuals with persistently abnormal liver enzymes should be screened** for NAFLD	A	1
In subjects with obesity or MetS, screening for NAFLD should be part of routine work-up. **In high-risk individuals* case finding of advanced disease is advisable**	A	2

*Aged >50 years, T2DM, MetS

EASL–EASD–EASO CPG NAFLD. J Hepatol 2016;64:1388–402

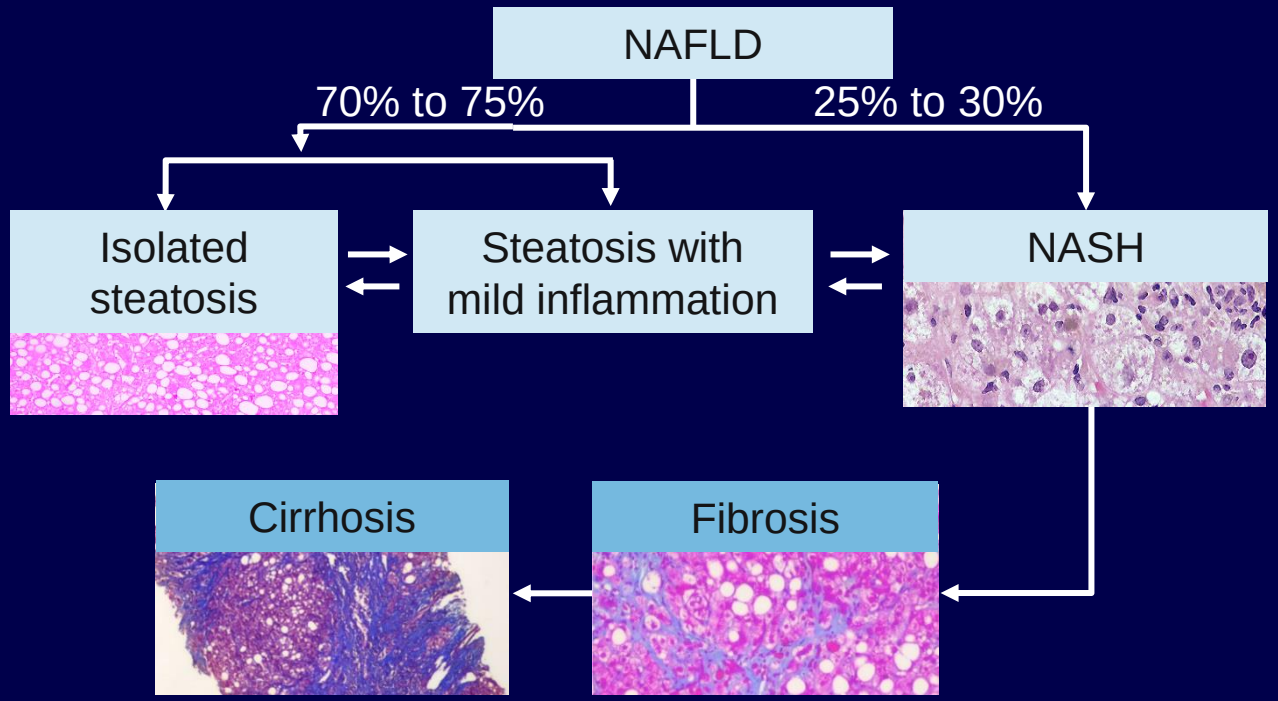
Multiple hit hypothesis for the development of NAFLD



Buzzetti E, Metabolism Clinical and Experimental 2016

ΜΑΛΝΗ – Φυσική ιστορία

Histological Subtypes[1,2]



Change in Fibrosis*[3,4]

Regression: 18%-22%

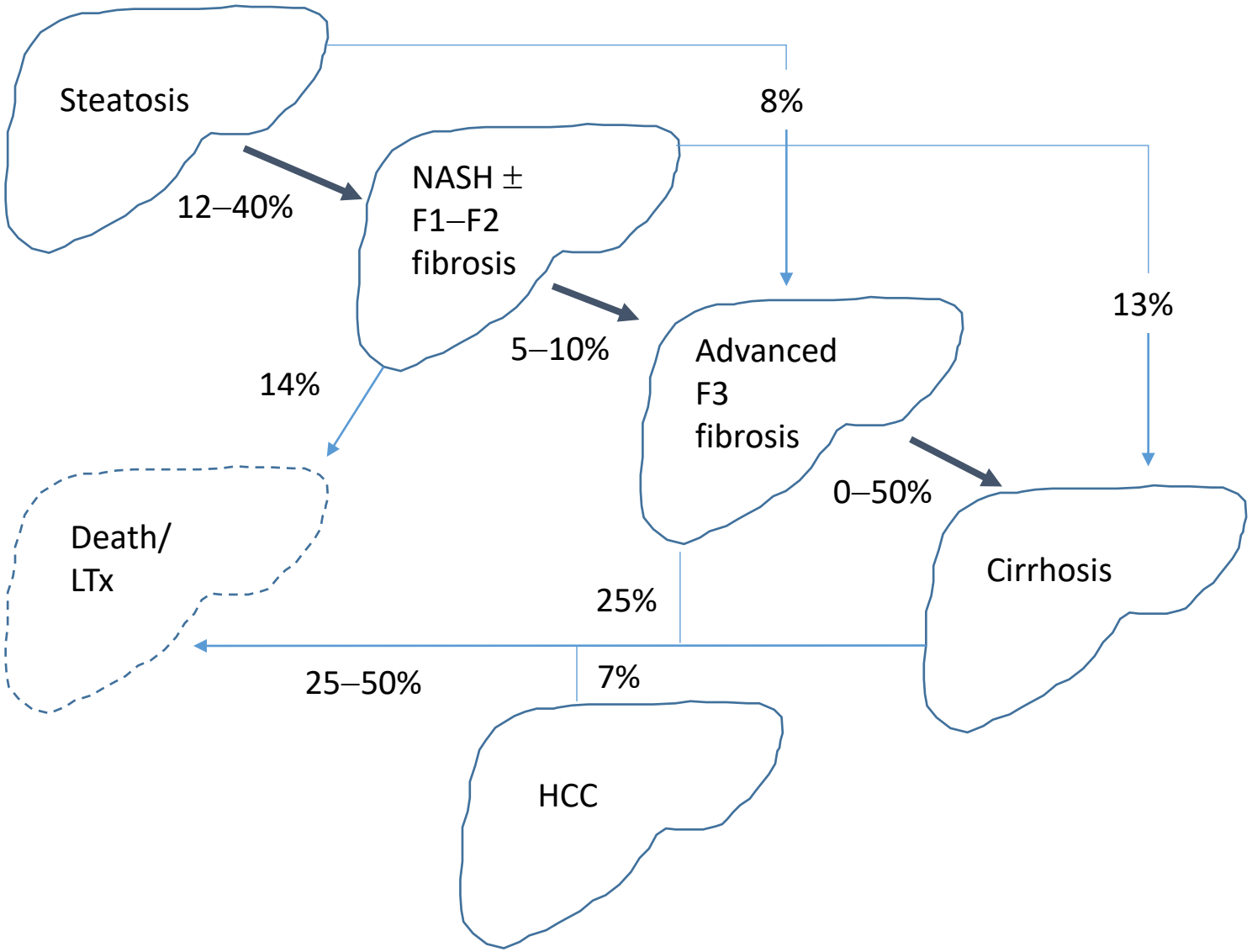
Stable: 40%-43%

Progression: 34-42%

*N = 108 NAFL/NASH, 6.6 yrs follow-up

1. Ludwig J, et al. Mayo Clin Proc. 1980;55(7):434-438.
2. Kleiner DE, et al. Hepatology. 2005;41(6):1313-1321.
3. McPherson S, et al. J Hepatol. 2015;62:1148-1155.
4. Singh S, et al. Clin Gastroenterol Hepatol. 2015 Apr;13(4):643-54

ΜΑΛΝΗ – Φυσική ιστορία



de Alwis NMW, Day CP. J Hepatol 2008;48:S104–12

ΜΑΛΝΗ και ΗΚΚ

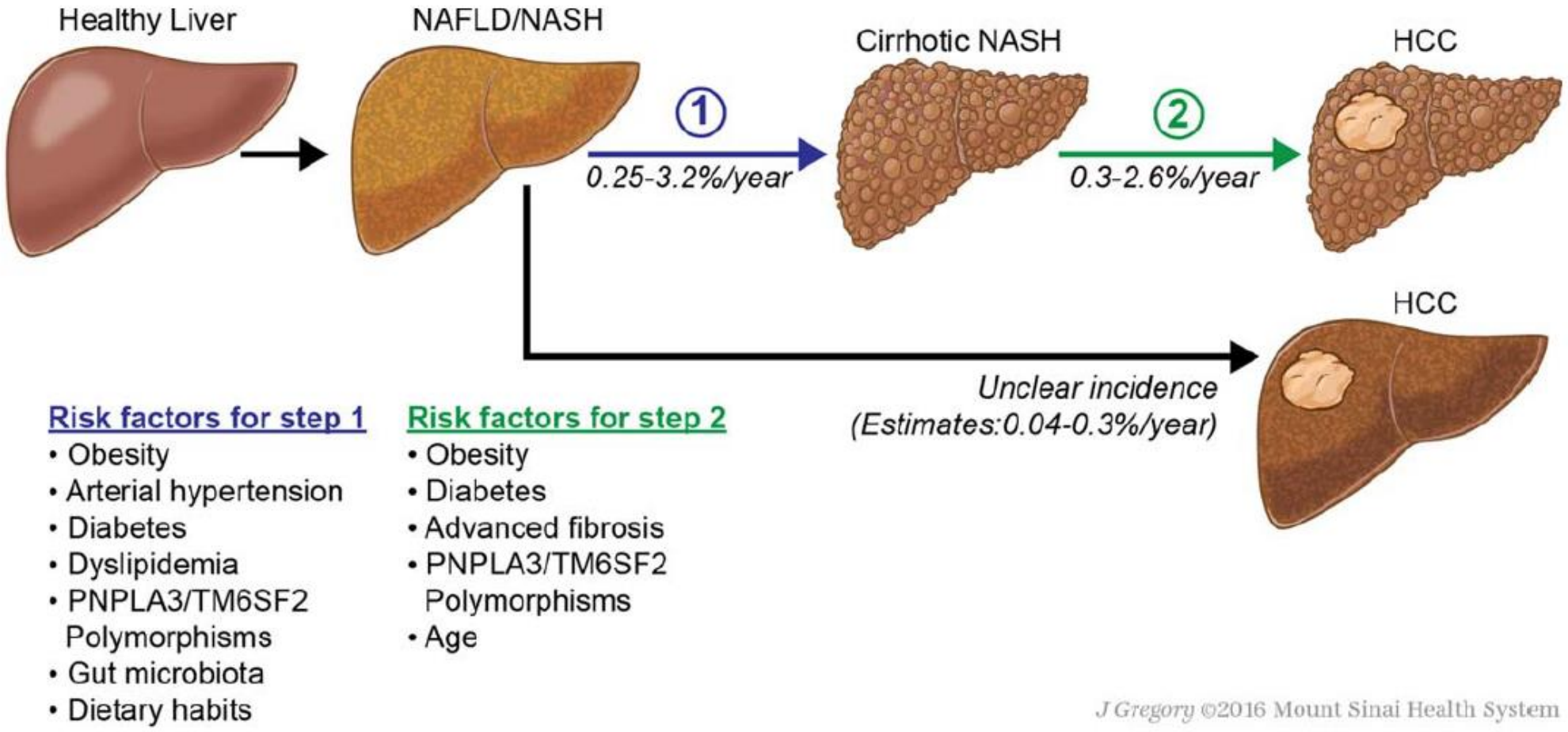


FIG 1 Natural history of NASH/NAFLD-related HCC. Illustration by Jill K. Gregory, CMI. Mount Sinai Health System.

Θνητότητα σε ασθενείς με ΜΑΛΝΗ

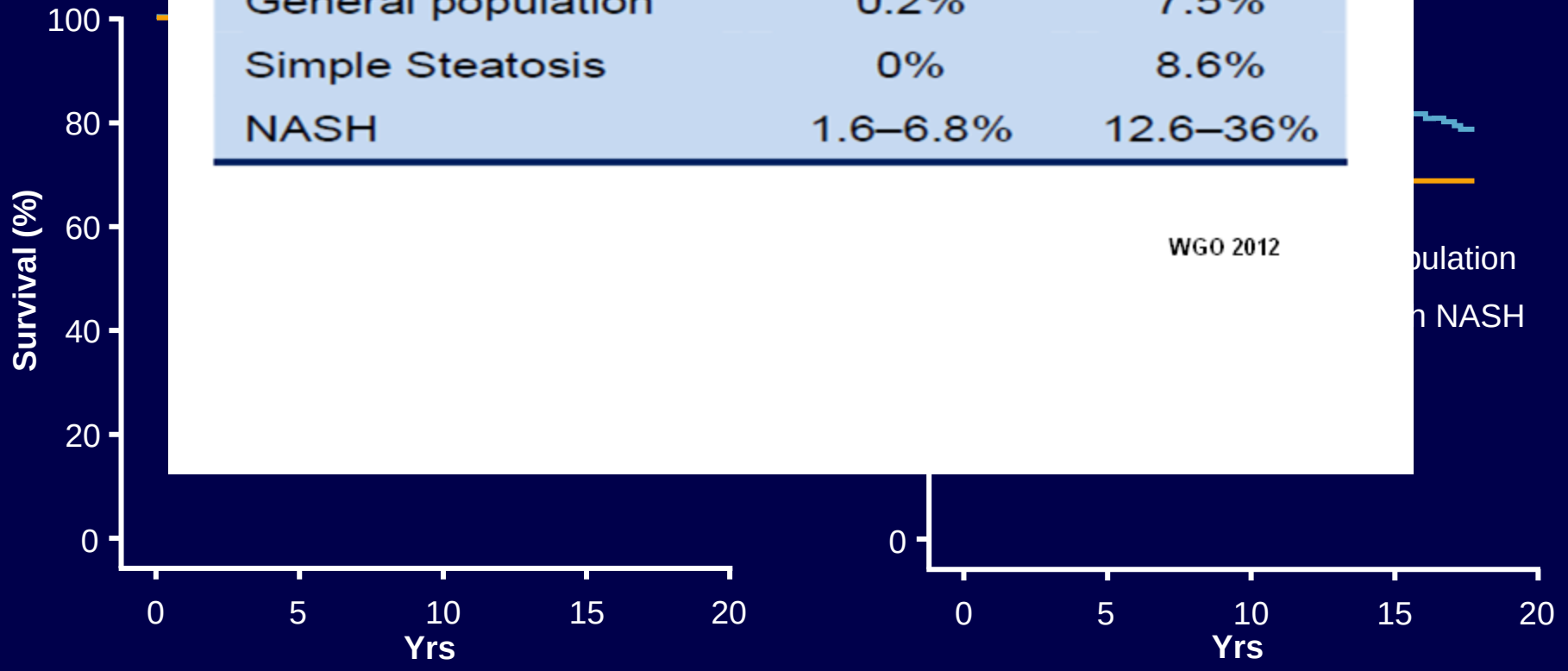
- Pa… same cou…

N…

Table 1 Mortality in NAFLD/NASH

	Liver	Cardiac
General population	0.2%	7.5%
Simple Steatosis	0%	8.6%
NASH	1.6–6.8%	12.6–36%

WGO 2012



Ekstedt M, et al. Hepatology. 2006;44:865-873.

Προγνωστικοί παράγοντες ΜΑΣΗ σε ασθενείς με ΜΑΛΝΗ

- Ηλικία [1]
- Φύλο[2]
- Φυλή[3,4]
- ΥΠΤ, κεντρική παχυσαρκία, (↑ TG, ↓ HDL), αντίσταση στην ινσουλίνη/ΣΔ[5]
- AST/ALT ratio > 1,[8] χαμηλά PLTs[9]
- Υψηλές τιμές ALT[10]

1. McPherson S, et al. Am J Gastroenterol. 2016;[Epub ahead of print]. 2. Yang JD, et al. Hepatology. 2014;59:1406-1414.
3. Pan JJ, et al. World J Hepatol. 2014;6:274-283. 4. Williams CD, et al. Gastroenterology. 2011;140:124-31. 5. Younossi ZM, et al. Hepatology. 2016;64:73–84.
6. Ratziu V, et al. Gastroenterology. 2000;118:1117-1123. 7. Angulo P, et al. Hepatology. 1999;30:1356-1362.
8. Neuschwander-Tetri BA, et al. Hepatology. 2010;52:913-924. 9. McPherson S, et al. Gut. 2010;59:1265-1269 10. Ekstedt M, et al. Hepatology. 2006;44:865-873.

NAFLD - NASH

- ✓ Οι περισσότεροι ασθενείς με NAFLD είναι ασυμπτωματικοί.
- ✓ Κάποιοι με NASH κόπωση, αδιαθεσία και βάρος ΔΕ
- ✓ Μπορεί ηπατομεγαλία
- ✓ Μπορεί αύξηση AST και ALT
- ✓ 2-5 φορές ΑΦ με AST/ALT ratio <1. Τα επίπεδα δεν είναι προγνωστικός παράγοντας φλεγμονής ή ίνωσης και οι φυσιολογικές τιμές δεν αποκλείουν σημαντική ιστολογική βλάβη
- ✓ ALP μπορεί 2-3 φορές ΑΦ. Αλβουμίνη, χολερυθρίνη, PT, KI
- ✓ Μπορεί αυξημένη φερριτίνη ή κορεσμό τρανσφερίνης. Φερριτίνη > 1.5 φορές ΑΦ σχετίζεται με υψηλότερο nonalcoholic fatty liver disease activity score και προχωρημένη ίνωση.
- ✓ Ενδέχεται θετικά ANA, ASMA
- ✓ Απεικονιστικά ευρήματα

Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis

June 2012

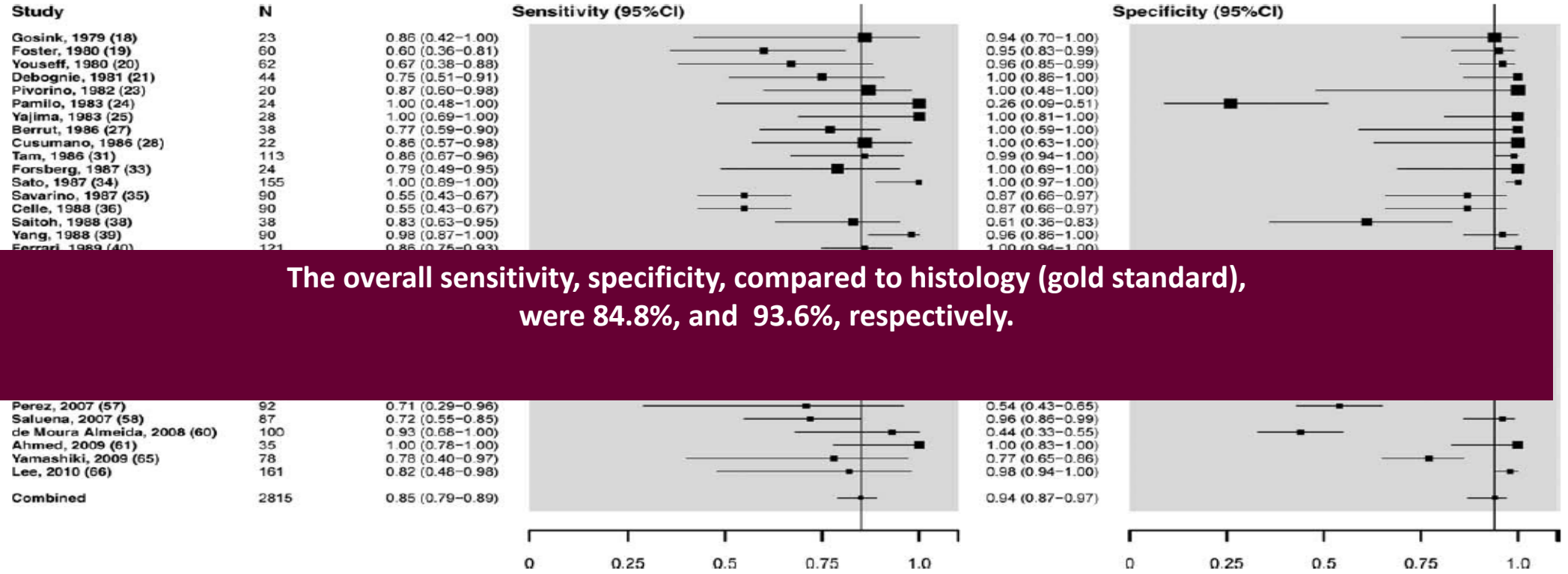
Διάγνωση ΜΑΛΝΗ

Table 12 Diagnostic tests for fatty liver

Test	Sensitivity	Specificity	Remarks
Histology, liver biopsy	The gold standard	Cannot reliably distinguish between ASH and NASH	Significant variability between pathologists' reading of the same sample; a highly experienced hepatopathologist is best
Liver enzymes	Low	Low	AST/ALT usually < 1.0; values may be normal
Imaging			
Ultrasound	Limited	Limited	Insensitive unless steatosis > 33%; operator-dependent
MRI, MRS, CT scan ± contrast enhancement	Results are variable and not well verified		Test are costly, less available, cannot distinguish steatosis and fibrosis or NASH/ASH or stage disease, and are insensitive if there is < 33% steatosis; see reference list and extended reference list

ALT, alanine aminotransferase; ASH, alcoholic steatohepatitis; AST, aspartate aminotransferase; CT, computed tomography; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NASH, nonalcoholic steatohepatitis.

Ο ρόλος του υπερηχογραφήματος στη διάγνωση ΜΑΛΝΗ. Μετα-ανάλυση



The overall sensitivity, specificity, compared to histology (gold standard), were 84.8%, and 93.6%, respectively.

Fig. 1. Overall sensitivity and specificity of ultrasound to detect moderate-1severe histologically defined fatty liver from the absence of steatosis.

HEPATOLOGY, Vol. 54, No. 3, 2011

Μη επεμβατική διάγνωση της ίνωσης σε ασθενείς με ΜΑΛΝΗ

Clinical or Laboratory Tests		Imaging
Simple	**Complex**	**Elastography**
▪ AST/platelet ratio index ▪ FIB-4 index ▪ NAFLD fibrosis score ▪ BARD score	▪ NASH *FibroSure* ▪ ELF ▪ HepaScore	▪ VCTE *FibroScan* ▪ MR elastography ▪ ARFI

Εκτίμηση προχωρημένης ίνωσης (F3/4) σε ασθενείς με ΜΑΛΝΗ

NAFLD Fibrosis Score:

FIB-4 score:

Parameter
Age, yrs
AST
ALT
Platelet count, cells x 10^9
BMI
Albumin, g/L
Impaired fasting glucose/diabetes?

NAFLD Cutoff Value[1]	Stage
< -1.455	F0-F2
-1.455 to 0.676	Indeterminate
> 0.676	F3-F4

FIB-4 Cutoff Value[2]	Stage
< 1.45	F0-F2
1.45 to 3.25	Indeterminate
> 3.25	F3-F4

1. Angulo P, et al. Hepatology. 2007;45:846-854.
2. Sterling RK, et al. Hepatology. 2006;43:1317-1325.

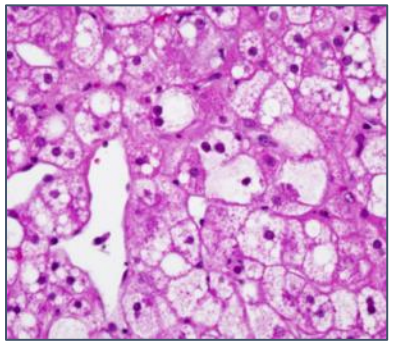
βιοψία ήπατος

- Απαραίτητη για τη διάγνωση NASH
- NAFLD >5 % ηπατοκύτταρα με στεάτωση - mild (5 – 33 %) - moderate (34 - 66 %) - severe (>66 %)

Neuschwander-Tetri BA, Hepatology 2003

Brunt EM, World J Gastroenterol 2010

- NAFL
  - Steatosis alone plus **ONE** of lobular or portal inflammation **OR** ballooning
- NASH
  - Steatosis **AND**
  - Lobular or portal inflammation **AND**
  - Ballooning
- NAS scoring - σοβαρότητα νόσου*



Recommendations	Grade of evidence	Grade of recommendation
NASH has to be diagnosed by a liver biopsy showing **steatosis, hepatocyte ballooning and lobular inflammation**	A	1

*Should not be used for initial diagnosis

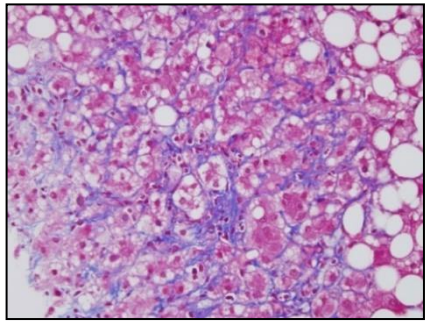
EASL–EASD–EASO CPG NAFLD. J Hepatol 2016;64:1388–402

Histological Scoring System for Nonalcoholic Fatty Liver Disease (NAFLD)

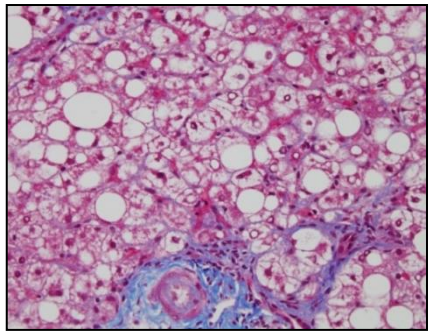
Components of NAFLD Activity Score (NAS) and Fibrosis Staging

NAS Components (see scoring interpretation)			
Item	**Score**	**Extent**	**Definition and Comment**
Steatosis	0	<5%	Refers to amount of surface area involved by steatosis as evaluated on low to medium power examination; minimal steatosis (<5%) receives a score of 0 to avoid giving excess weight to biopsies with very little fatty change
	1	5-33%	
	2	>33-66%	
	3	>66%	
Lobular Inflammation	0	No foci	Acidophil bodies are not included in this assessment, nor is portal inflammation
	1	<2 foci/200x	
	2	2-4 foci/200x	
	3	>4 foci/200x	
Hepatocyte Ballooning	0	None	
	1	Few balloon cells	The term "few" means rare but definite ballooned hepatocytes as well as cases that are diagnostically borderline
	2	Many cells/prominent ballooning	Most cases with prominent ballooning also had Mallory's hyalin, but Mallory's hyaline is not scored separately for the NAS
Fibrosis Stage (Evaluated separately from NAS)			
Fibrosis	0	None	
	1	Perisinusoidal or periportal	
	1A	Mild, zone 3, perisinusoidal	"delicate" fibrosis
	1B	Moderate, zone 3, perisinusoidal	"dense" fibrosis
	1C	Portal/periportal	This category is included to accommodate cases with portal and/or peri portal fibrosis without accompanying pericellular/perisinusoidal fibrosis
	2	Perisinusoidal and portal/periportal	
	3	Bridging fibrosis	
	4	Cirrhosis	

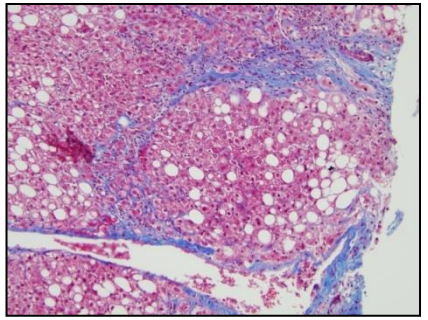
Total NAS score represents the sum of scores for steatosis, lobular inflammation, and ballooning, and ranges from 0-8. Diagnosis of NASH (or, alternatively, fatty liver not diagnostic of NASH) should be made first, then NAS is used to grade activity. In the reference study, NAS scores of 0-2 occurred in cases largely considered not diagnostic of NASH, scores of 3-4 were evenly divided among those considered not diagnostic, borderline, or positive for NASH. Scores of 5-8 occurred in cases that were largely considered diagnostic of NASH.



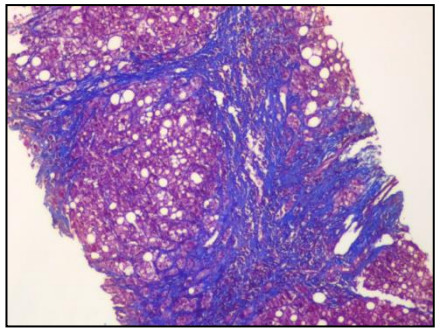
F1: Perisinusoidal



F2: Perisinusoidal + Portal



F3: Bridging Fibrosis



F4: Cirrhosis

Kleiner, Hepatology 2005

Στεάτωση

Recommendations	Grade of evidence	Grade of recommendation
US is the preferred first-line diagnostic procedure for imaging of NAFLD, **as it provides additional diagnostic information**	A	1
Whenever imaging tools are not available or feasible **serum biomarkers and scores** are an acceptable alternative for the diagnosis of steatosis	B	2
A **quantitative estimation** of liver fat **can only be obtained by ^{1}H-MRS**. This technique is of value in clinical trials and experimental studies, but is expensive and not recommended in the clinical setting	A	1

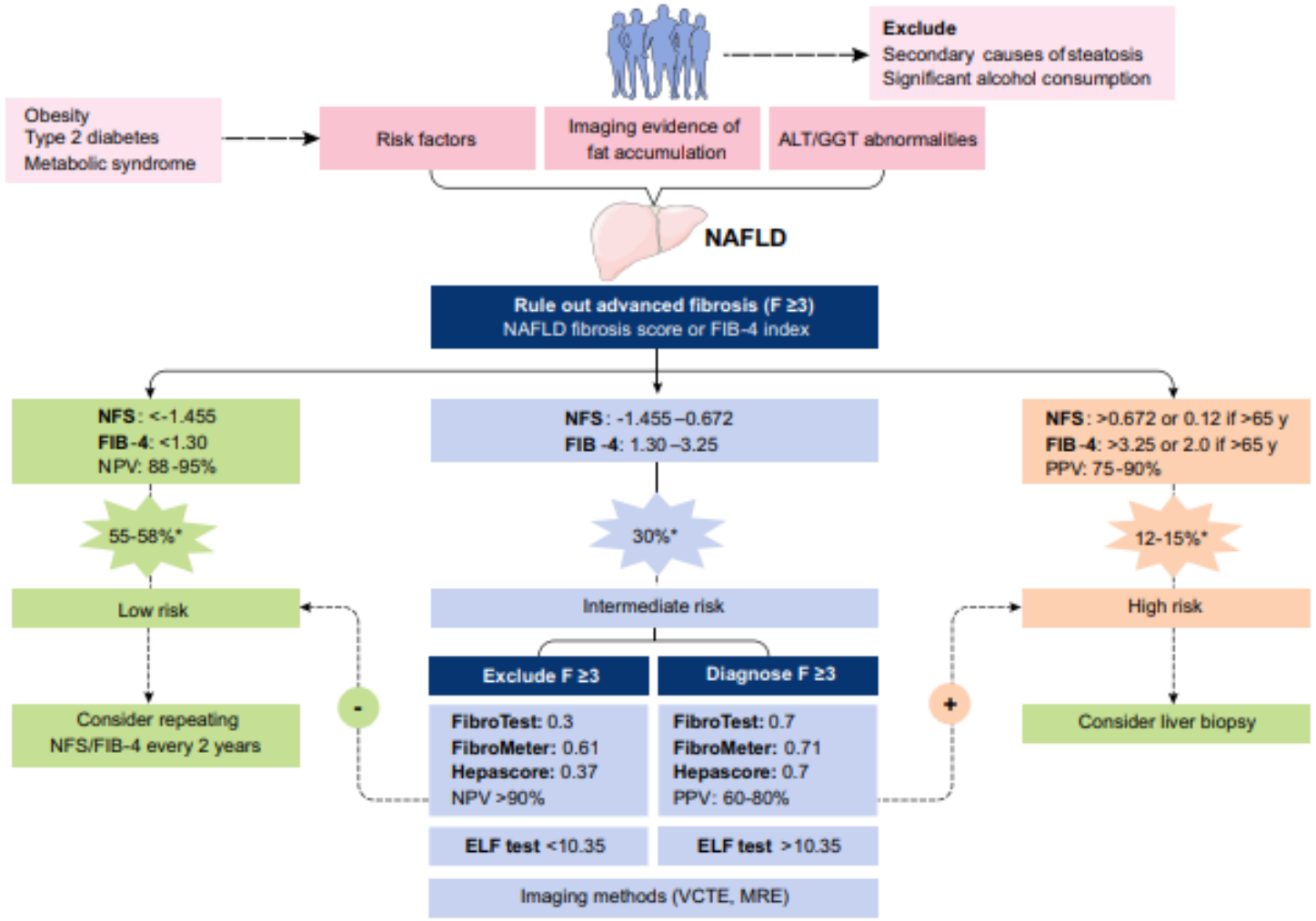
EASL–EASD–EASO CPG NAFLD. J Hepatol 2016;64:1388–402

Ίνωση

Recommendations	Grade of evidence	Grade of recommendation
Biomarkers, fibrosis scores, and transient elastography, are acceptable **non-invasive procedures to identify <u>those at low risk of advanced fibrosis/cirrhosis</u>**	A	2
Biomarkers/scores PLUS **transient elastography** might confer **additional diagnostic accuracy** and reduce need for liver biopsy	B	2
Monitoring of fibrosis progression may rely on biomarkers/scores and transient elastography, although this strategy requires validation	C	2
The **identification of advanced fibrosis or cirrhosis** by serum biomarkers/scores and/or elastography is less accurate and **<u>needs to</u>** be confirmed by liver biopsy, according to the clinical context	B	2
In selected patients at high risk of liver disease progression, monitoring should include a repeat biopsy after ≥5-year follow-up	C	2

EASL–EASD–EASO CPG NAFLD. J Hepatol 2016;64:1388–402

Πιθανός αλγόριθμος



*Estimated prevalence for low-, intermediate- and high-risk groups
Vilar-Gomez E, Chalasani N. J Hepatol 2018;68:305–15

Θεραπεία ΜΑΣΗ

- ✓ Πρόληψη νοσηρότητας και θνητότητας που σχετίζεται με το καρδιαγγειακό σύστημα
- ✓ Πρόληψη νοσηρότητας και θνητότητας που σχετίζεται με το ήπαρ

Θεραπεία

Weight loss[1-3]

- Lifestyle (diet, physical activity)
- Weight loss medications
- Bariatric surgery

In patients with advanced liver disease, choose or dose drugs appropriately.

Treat T2D and CV risk factors[4,5]

- Hyperglycemia (GLP-1 RA and/or SGLT-2i)
- Hypertension
- Dyslipidemia*

*NAFLD does not increase statin risk of drug-induced liver injury.[8]

Liver-directed treatment

- Vitamin E (except in diabetes)[6]
- Pioglitazone[6,7]

1. Promrat. Hepatology. 2010;51:121. 2. Vilar-Gomez. Gastroenterology. 2015;149:367. 3. Lassailly. Gastroenterology. 2015;149:379. 4. Musso. Hepatology. 2010;52:79. 5. Ratziu. J Hepatol. 2010;53:372. 6. Sanyal. NEJM. 2010;362:1675. 7. Cusi. Ann Intern Med. 2016;165:305. 8. Bril. J Clin Endocrinol Metab. 2017;102:2950.

Slide credit: clinicaloptions.com

Ολοκληρωμένη αντιμετώπιση παχυσαρκίας, ΣΔ και NAFLD

- **Ηπατολόγος, ενδοκρινολόγος, διατροφολόγος, ψυχολόγος**

- **Μείωση καρδιαγγειακού κινδύνου**
  - Αντιμετώπιση δυσλιπιδαιμίαςκαι υπέρτασης. Διακοπή καπνίσματος, αντιαιμοπεταλιακή αγωγή

- **΄Ελεγχος και θεραπεία συννοσηροτήτων**
  - sleep apnea κλπ

- Αλλαγές στον τρόπο ζωής, εάν απαιτείται φαρμακευτική θεραπεία παχυσαρκίας και βαριατρική χειρουργική
- Κατά περίπτωση αντιδιαβητικά ανάλογα με τον καρδιαγγειακό κίνδυνο και τη μείωση ΣΒ
- Σε προχωρημένη ηπατοπάθεια προσοχή στην επιλογή και δοσολογία αντιδιαβητικών και του ΣΒ

Φαρμακευτική αγωγή - ΜΑΣΗ

Targeting Insulin Resistance

Compound	Mechanism of Action	Trial	Primary Endpoint(s)	AASLD Recommendation as NASH Treatment
Metformin	Multiple	Multiple studies	Various	Not recommended
Pioglitazone	PPARγ agonist	PIVENS Multiple studies	Improvement in NAS ≥ 2 without fibrosis worsening	May be used in patients with biopsy-proven NASH
Liraglutide	GLP-1 receptor agonist	LEAN*	Resolution of NASH without fibrosis worsening	Premature to consider GLP-1 receptor agonists

Targeting Oxidative Stress

Compound	Mechanism of Action	Trial Name	Primary Endpoint(s)	AASLD Recommendation as NASH Treatment
Vitamin E	Antioxidant	PIVENS TONIC	Improvement in NAS ≥ 2 without fibrosis worsening	May be used in **nondiabetic** adults with biopsy-proven NASH

*Phase IIb.

Chalasani. Hepatology. 2018;67:328.

Θεραπεία ΜΑΣΗ

Vitamin E (800 IU/day)

- Πιθανώς αύξηση θνητότητας σε > 800 IU/day[1]
- Αύξηση κινδύνου αιμορραγικού ΑΕΕ [2]
- Αυξημένος κίνδυνος καρκίνου προστάτη (HR vs placebo: 1.17; 99% CI: 1.004-1.36; *P* = .008)[3]

Pioglitazone

- Οίδημα, αύξηση ΣΒ (~ 2-3 kg σε 2-4 yrs)[4]
- Κίνδυνος οστεοπόρωσης σε γυναίκες [5]
- Καρκίνος ουροδόχου κύστης ?
  - Αύξηση [6].
  - Μη συσχέτιση [7,8]

Ιστολογικά επιβεβαιωμένη ΜΑΣΗ μετά προσεκτική εκτίμηση όφελους/κινδύνου

1. Miller. Ann Intern Med. 2005;142:37. 2. Schurks. BMJ. 2010;341:c5702. 3. Klein. JAMA. 2011;306:1549.
4. Bril. Diabetes Care. 2017;40:419. 5. Yau. Curr Diab Rep. 2013;13:329. 6. Tuccori. BMJ. 2016;352:i1541.
7. Lewis. JAMA. 2015;314:265. 8. Davidson. Diabetes Complications. 2016;30:981.

T2D - NAFLD/NASH

Ενήλικες με ΣΔ και προϋπάρχουσα *atherosclerotic cardiovascular disease* (ASVCD) ή *heart failure (*HF) ή *chronic kidney disease* (CKD)[1]:

- GLP-1 RA με αποδεδειγμένο όφελος (cardiovascular) CV
- SGLT2 με αποδεδειγμένο όφελος HF (heart failure) και CKD (chronic kidney disease)

- Κάποιοι GLP-1 RAs και SGLT2 μπορεί όφελος σε NAFLD

Ενήλικες με ΣΔ που απαιτείται απώλεια ΣΒ[1]:

- GLP-1 RA με αποτελεσματικότητα στην απώλεια ΣΒ
- SGLT2 inhibitors

- Κάποιοι GLP-1 RAs και SGLT2 μπορεί όφελος σε NAFLD

American Diabetes Association. Diabetes Care 2019;42(suppl 1):S90.

Απώλεια ΣΒ και NAFLD

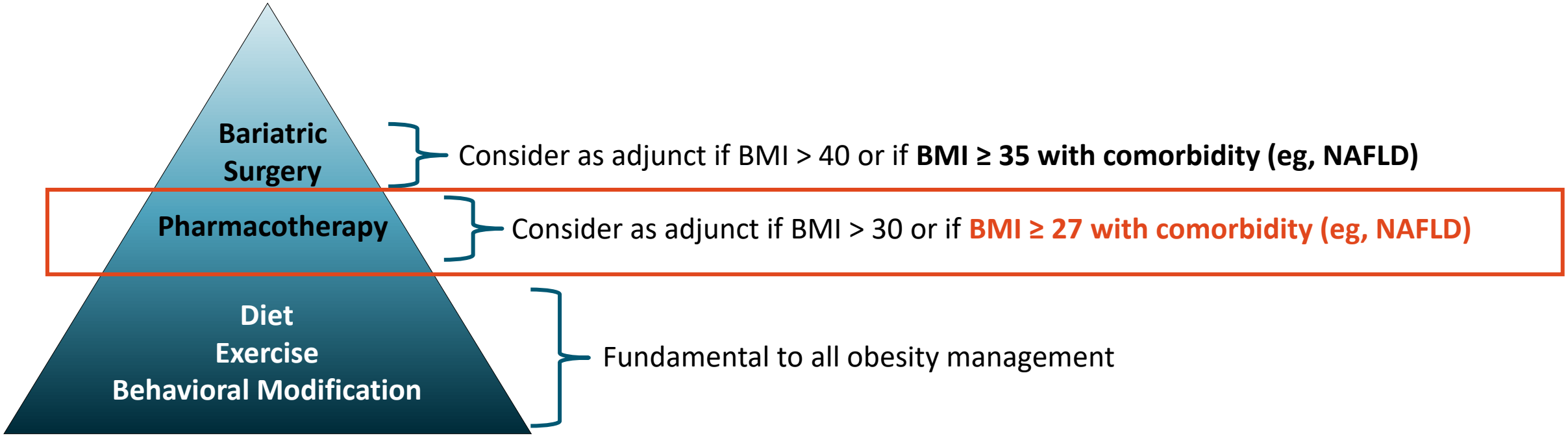
Weight Loss	Outcome Among Patients Achieving Weight Loss	Patients Sustaining Weight Loss at 1 Yr[1]
≥ 10%[1]	Fibrosis regression (45% of patients)[1]	< 10%
≥ 7%[1]	NASH resolution (64% to 90% of patients)*	18%
≥ 5%[1-3]	Ballooning/inflammation improvement (41% to 100% of patients)*	30%
≥ 3%[1-4]	Steatosis improvement (35% to 100% of patients*)	Not reported

*Depending on degree of weight loss.

1. Vilar-Gomez. Gastroenterology. 2015;149:367. 2. Promrat. Hepatology. 2010;51:121.

3. Harrison. Hepatology. 2009;49:80. 4. Wong. J Hepatol. 2013;59:536.

Απώλεια ΣΒ



" . . . we suggest the use of approved weight loss medication (over no pharmacologic therapy)"

Apovian. J Clin Endocrinol Metab. 2015;100:342.

Απώλεια ΣΒ και ΜΑΛΝΗ

- Αλλαγή τρόπου ζωής, δίαιτα, άσκηση
- +
  - ΦΑ **(BMI > 27)**
  - **Χειρουργική αντιμετώπιση**

Αλλαγή τρόπου ζωής, δίαιτα, άσκηση	Φαρμακευτική αγωγή	Βαριατρική χειρουργική
~ 5% - 8% απώλεια ΣΒ[1]	~ 8% - 10% απώλεια ΣΒ [1]	~ 10% - 30% απώλεια ΣΒ [2]

1. Garvey. Endocr Pract. 2016;(suppl 3):1. 2. Maciejewski. JAMA Surg. 2016;151:1046.

Φαρμακευτική αγωγή και απώλεια ΣΒ

Drug	Daily Dose for Weight Loss	MoA	Mean Weight Loss, % Total Body Weight	Improves NAFLD?
Orlistat[1,2]	360 mg PO	Lipase inhibitor	8.78 (8.30 in NASH[2])	In small studies but not RCT[3]
Lorcaserin[1]	20 mg PO	5-HT2c serotonin receptor agonist	7.9	Not studied
Phentermine/ topiramate[1]	7.5/46 mg or 15/92 mg PO	Multiple	9.6-12.4	Not studied
Naltrexone/ bupropion[1]	32/360 mg PO titrated to max	Multiple	8.1	Not studied
Liraglutide[1]	3 mg SC titrated to max	GLP-1 agonist	9.2 (5.5 in NASH*[4])	LEAN study*[4]

*Studied in NASH at 1.8-mg dose approved for diabetes, not 3-mg dose approved for weight loss.

Mean efficacy criterion: significant difference in mean proportion achieving weight loss ≥ 5% drug vs placebo
Categorical efficacy criterion: weight loss ≥ 5% in ≥ 35% of participants, with a significant and ≥ 2-fold difference in proportion achieving this in drug vs placebo groups

1. Garvey. Endocr Pract. 2016;(suppl 3):1. 2. Harrison. Hepatology. 2009;49:80
3. Wang. Biomed Rep. 2018;9:90. 4. Armstrong. Lancet. 2015;387:679.

ΜΑΛΝΗ και Βαριατρική Χειρουργική

Study or Subgroup	Before Bariatric Sx Mean	SD	Total	After Bariatric Sx Mean	SD	Total	Weight	Mean difference IV, Random, 95% CI	Year
Liu 2007	4.87	1.89	39	1.97	0.58	39	8.9%	2.90 [2.28, 3.52]	2007
Mathurin 2009	1.97	1.33	362	1.07	1.26	267	9.4%	0.90 [0.70, 1.10]	2009
Tai 2012	3.33	1	21	0.857	0.5	21	9.1%	2.47 [1.99, 2.95]	2012
Caiazzo 2014	1.87	1.46	1201	0.92	1.13	578	9.4%	0.95 [0.83, 1.07]	2014
Raj 2015	2.6	1.3	30	0.57	0.97	30	9.0%	2.03 [1.45, 2.61]	2015
Lassailly 2015	5	0.7	81	1	0.67	81	9.4%	4.00 [3.79, 4.21]	2015
Schneck 2016	5.11	0.33	9	0.67	1	9	8.8%	4.44 [3.75, 5.13]	2016
Froylich 2016	3.6	1.8	25	1.18	1.49	25	8.4%	2.42 [1.50, 3.34]	2016
Aldoheyan 2017	4	0.5	27	2	0.5	27	9.3%	2.00 [1.73, 2.27]	2017
Manco 2017	4.15	0.67	20	1.6	0.99	20	9.1%	2.55 [2.03, 3.07]	2017
Schewenger 2018	2.07	1.53	42	0.33	0.78	42	9.1%	1.74 [1.22, 2.26]	2018
Total (95% CI)			**1857**			**1139**	**100.0%**	**2.39 [1.58, 3.20]**	

Heterogeneity: $Tau^2 = 1.81$; $Chi^2 = 759.94$, df = 10 ($P < .00001$); $I^2 = 99\%$

Test for overall effect: Z = 5.79 ($P < .00001$)

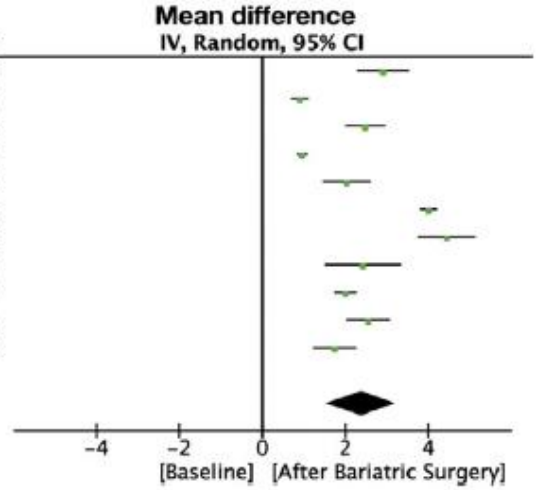


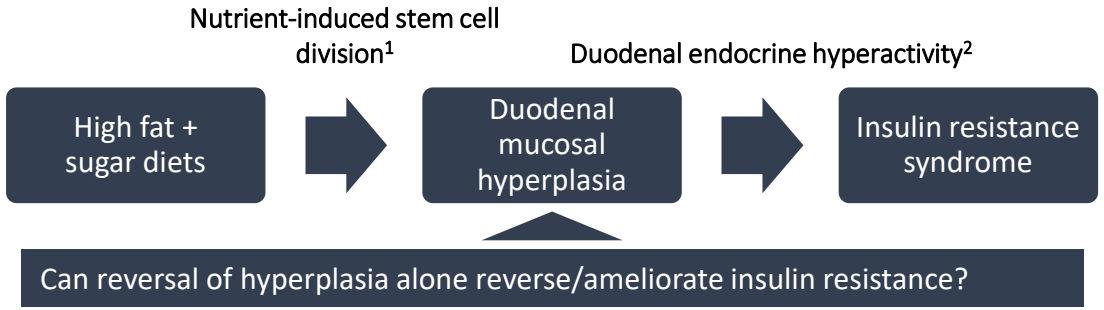
Figure 3. Random effects meta-analysis forest plot of NAS before and after surgery. IV, inverse variance; Sx, surgery.

Yung Lee, Clinical Gastroenterology and Hepatology 2019

Endoscopic duodenal mucosal resurfacing improves hepatic fat fraction, glycaemic and lipid profiles in type 2 diabetes

High fat/sugar diet leads to duodenal hyperplasia in rodent models. In the foregut of subjects with type 2 diabetes (T2D), abnormal entero-endocrine cell population and co-expression of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) has been described.

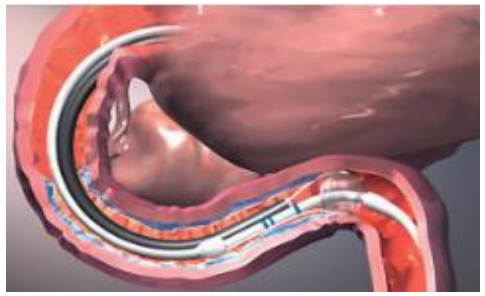
Putative role of duodenal mucosal hyperplasia in metabolic disease

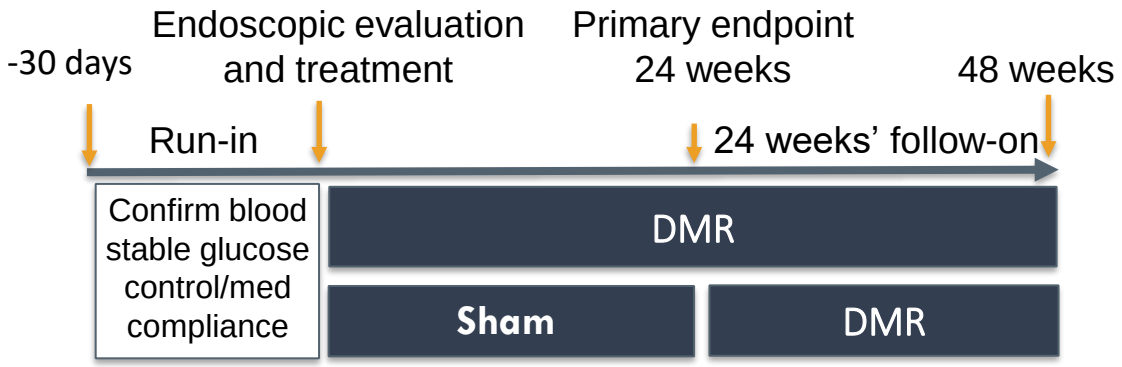


Aim: Evaluate effect of DMR on glycaemia, hepatic fat, and mechanistic endpoints

DMR: REVITA single catheter

Schematic of DMR





- Revita-2 (NCT02879383): multicentre study with early open-label cohort (training purposes, n=24) and randomized double-blind cohort (n=108)
  - 17/20 (85%) open-label subjects with MRI-PDFF data had excess baseline liver fat (>5%)
- Inclusion criteria: HbA1c 7.5–10%; 24≤BMI≤40; ≥1 oral medications
- DMR procedure: single catheter

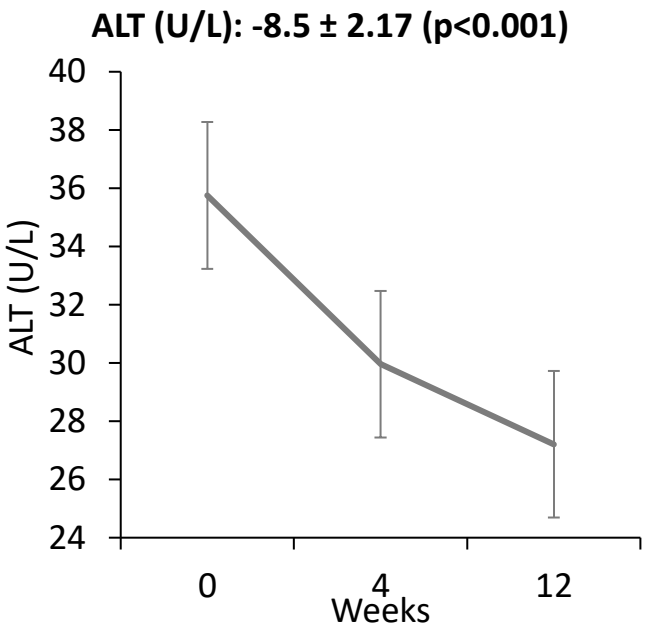
1. O'Brien LE, et al. Cell 2011;147:603–14; 2. Gniuli D, et al. Diabetologia 2010;53:2233–40.
Aithal G, et al. ILC 2019; PS-112

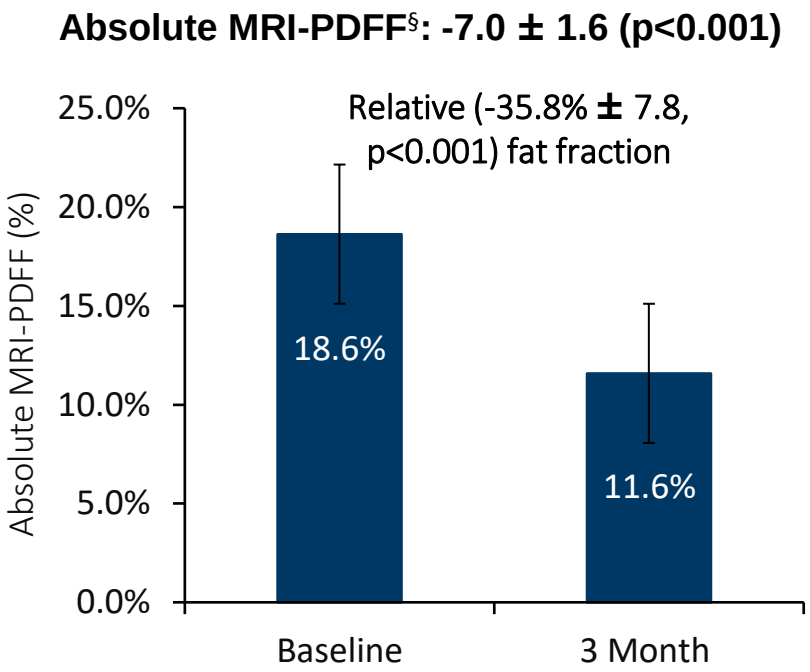
Endoscopic duodenal mucosal resurfacing improves hepatic fat fraction, glycaemic and lipid profiles in type 2 diabetes

Baseline and 12-week metabolic and glycaemic values*

Indices	Baseline	12 weeks	P-value
HbA1c (%)	8.4 ± 0.2	7.4 ± 0.2	0.001
Fasting plasma insulin† (uIU/ml)	13.6 ± 1.8	9.8 ± 1.1	<0.05
Fasting C-peptide (ng/ml)	3.2 ± 0.3	2.7 ± 0.2	0.01
Fasting TGs (mg/dl)	209.0 ± 32.0	150.0 ± 20.0	<0.01
Fasting HDL (mg/dl)	45.7 ± 2.8	49.2 ± 3.2	<0.05
Ferritin‡ (ng/ml)	90.8 ± 16.6	69.4 ± 15.5	<0.01
ALT (U/L)	35.8 ± 4.1	27.2 ± 2.4	<0.01
HOMA-IR†	6.0 ± 0.7	4.1 ± 0.6	0.01
Body weight (kg)	89.7 ± 1.9	86.6 ± 2.0	<0.01

Revita-2 open-label cohort: change over 12 weeks in ALT and liver MRI-PDFF*





DMR was successfully implemented in T2D subjects with a favourable safety/ tolerability profile (median procedure time = 45 minutes), and is a promising potential treatment for T2D and NAFLD/NASH. Randomized cohort data will follow later this year

*Values are all mean (± SEM); n=24 unless indicated; †n=22; ‡n=23; §Subset of 17 subjects with excess baseline liver fat by MRI-PDFF.

Aithal G, et al. ILC 2019; PS-112

Pegbelfermin (BMS-986036) σε ασθενείς με ΜΑΣΗ

- **Pegbelfermin (BMS-986036), a PEGylated fibroblast growth factor 21 analogue**
- **Randomised, double-blind, placebo-controlled, phase 2a trial**
- **N=75, (25, 10 mg/d - 24, 20 mg/w - 26 placebo),**
- **Σημαντική μείωση absolute hepatic fat fraction με 10 mg daily (−6·8% *vs* −1·3%; p=0·0004) και 20 mg weekly (−5·2% *vs* −1·3%; p=0·008) vs placebo.**

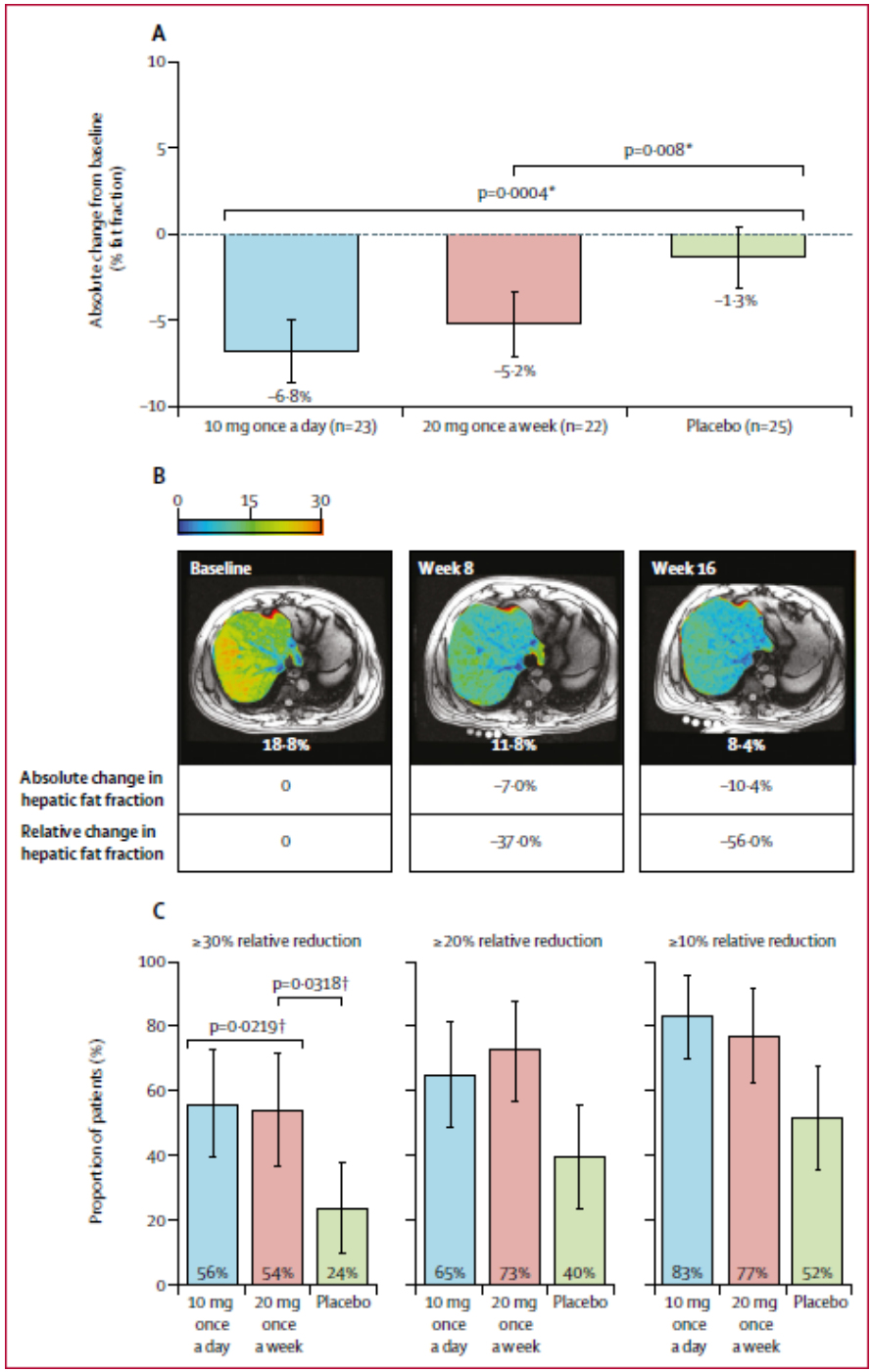
- **΄Ηπιας βαρύτητας ΑΕ,**

✓ **διάρροια σε 8/49 (16%) pegbelfermin vs 2/26 (8%)**

✓ **ναυτία 7 (14%) pegbelfermin vs 2 (8%)**

- **Όχι θάνατοι, διακοπές λόγω ΑΕ, ΣΑΕ**

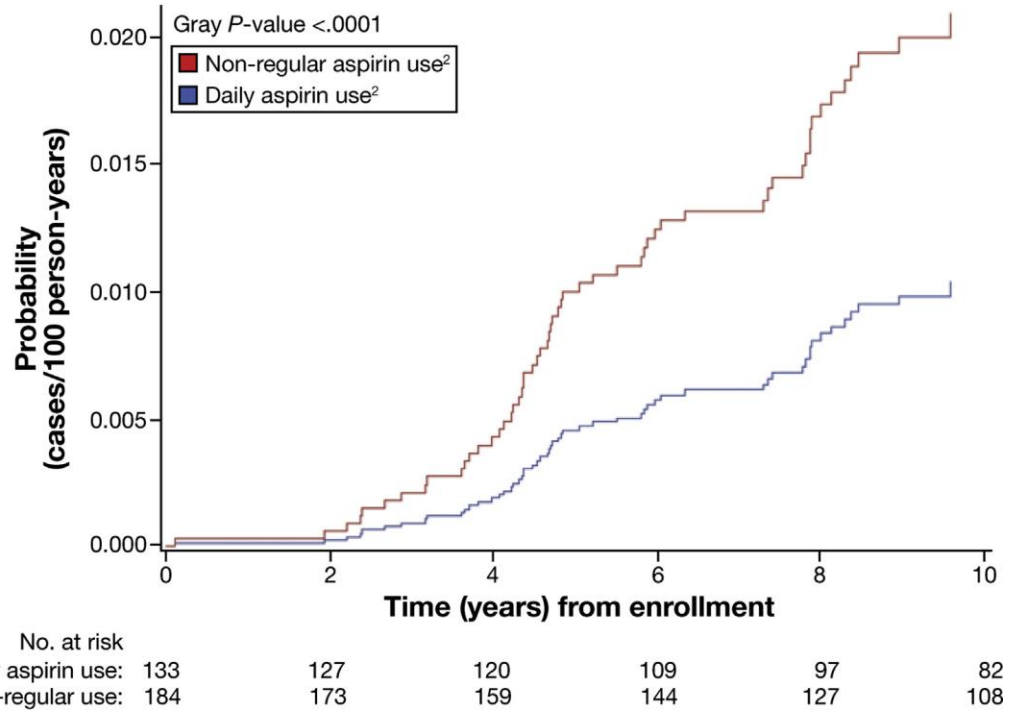
Sanyal A, Lancet. 2019



Καθημερινή χρήση ασπιρίνης σχετίζεται με μειωμένο κίνδυνο προόδου της ίνωσης σε ασθενείς με ΜΑΛΝΗ

- N = 361 με βιοψία, 2006-2015, έλεγχος κάθε 3–12 μ
- 151 ασπιρίνη καθημερινά

- Συγκριτικά με μη τακτική λήψη ασπιρίνης μικρότερα ποσοστά ΜΑΣΗ (adjusted odds ratio, 0.68; 95% CI, 0.37–0.89) και ίνωσης (adjusted odds ratio, 0.54; 95% CI, 0.31–0.82).
- baseline F0–F2 (n [317), 86 προχωρημένη ίνωση σε 3692 py).
- Καθημερινή χρήση ασπιρίνης μικρότερη πιθανότητα ανάπτυξης προχωρημένης ίνωσης [aHR], 0.63; 95% CI, 0.43–0.85).
- Συσχέτιση με τη διάρκεια (adjusted P trend[.026), μεγαλύτερο όφελος με 4 ή περισσότερα έτη χρήσης ασπιρίνης (aHR, 0.50; 95% CI, 0.35–0.73).
- Χρήση **NSAIDs** δεν σχετίστηκε με τον κίνδυνο ανάπτυξης προχωρημένης ίνωσης (aHR, 0.93; 95% CI, 0.81–1.05).



Simon TG, Clin Gastroenterol Hepatol. 2019

Η χρήση ασπιρίνη σχετίζεται με μικρότερη πιθανότητα ανάπτυξης προχωρημένης ίνωσης (Gray P value < .001)

FDA: Liver Histologic Improvement Endpoints Likely to Predict Clinical Benefit

NASH Resolution

- Resolution of steatohepatitis on overall histopathologic reading

and

- No worsening of liver fibrosis

Fibrosis Improvement

- Improvement ≥ 1 fibrosis stage

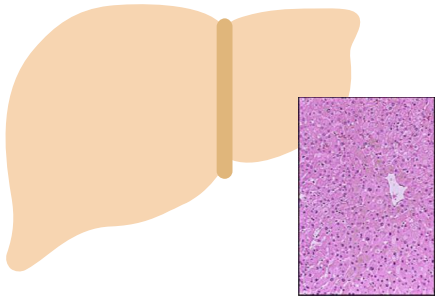
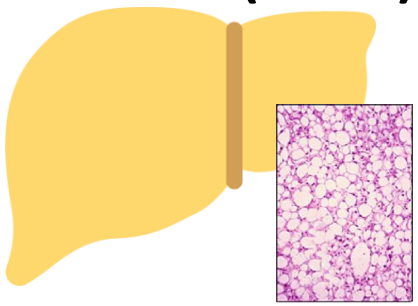
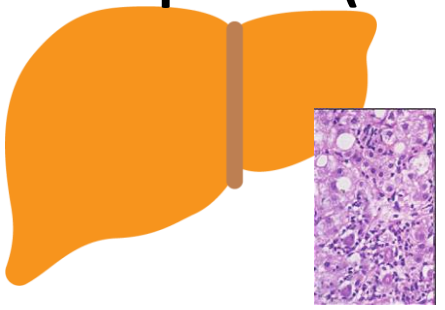
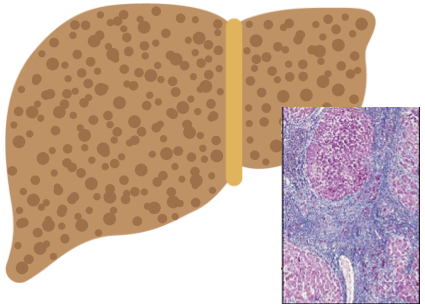
and

- No worsening of steatohepatitis

1. FDA. Draft Guidance. Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment Guidance for Industry. December 2018.

Examples of NASH Treatments in Phase II or III Investigations

NAFLD

Normal Liver	Steatosis (NAFL)	Steatohepatitis (NASH)	Cirrhosis
			

Insulin resistance and/or lipid metabolism → **Lipotoxicity and oxidative stress** → **Inflammation and immune activation** → **Cell death (apoptosis and necrosis)** → **Fibrogenesis and collagen turnover**

PPARγ:	Pioglitazone
GLP-1:	Liraglutide, semaglutide
SGLT:	Empagliflozin, licogliflozin, canagliflozin
DPP-4	Sitagliptin
ACC:	GS-0976, PF-05221304
SCD1:	Aramchol
ASBT:	Volixibat

PPARα/∂:	Elafibranor
PPARα/γ:	Saroglitazar
Pan-PPAR:	Lanifibranor
FGF19:	NGM282
FGF21:	Pegbelferim
FXR:	OCA, cilofexor, tropifexor, nidufexor
MPC:	MSDC-0602K
TGR-5:	INT-767/777
THR-β:	MGL-3196, VK2809

CCR2/5:	Cenicriviroc (inflammatory target but affects fibrosis)
AOC3:	BI-1467335
P2X7R:	SGM-1019
TLR-4:	JKB-121/122

ASK1:	Selonsertib (cell death target but affects fibrosis)
Caspase:	Emricasan

Galectin:	GR-MD-02
LOXL2:	Simtuzumab

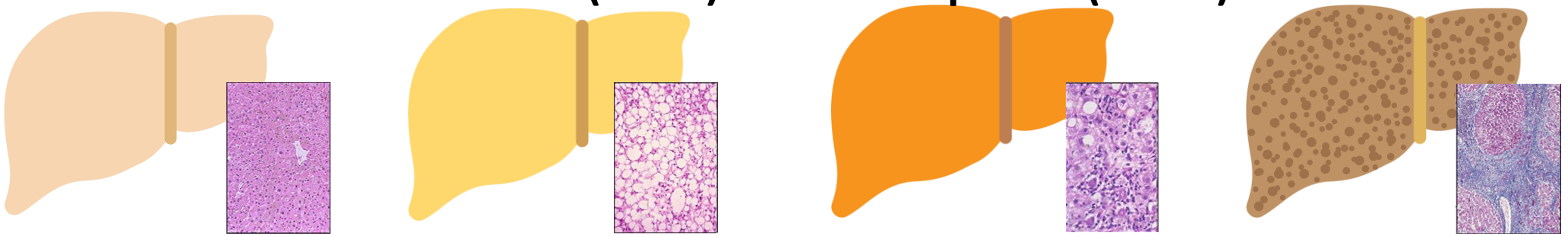
Some agents have multiple targets

Slide credit: clinicaloptions.com

Examples of NASH Treatments in Phase II or III Investigations

NAFLD

Normal Liver	Steatosis (NAFL)	Steatohepatitis (NASH)	Cirrhosis



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Not proceeding forward

Some agents have multiple targets

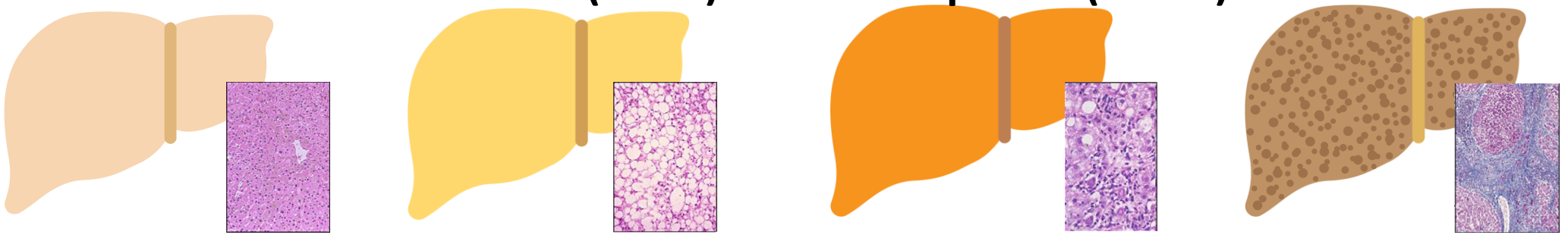
Effects of Belapectin, an Inhibitor of Galectin-3, in Patients With Nonalcoholic Steatohepatitis With Cirrhosis and Portal Hypertension, Chalasani N, Gastroenterology 2020 (not associated with significant reduction in HVPG or fibrosis compared with placebo) Gastroenterology 2020

Slide credit: clinicaloptions.com

Θεραπεία ΜΑΣΗ

NAFLD

Normal Liver | Steatosis (NAFL) | Steatohepatitis (NASH) | Cirrhosis



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Caspase:	Emricasan

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LOXL2:	Simtuzumab

Phase III

Some agents have multiple targets

Slide credit: clinicaloptions.com

Θεραπεία ΜΑΣΗ – Μελέτες φάσης III

Agent	MoA	Trial	N	Primary Endpoint(s)	Time Point
Cenicriviroc	CCR2/5 antagonist	AURORA[1]	2000	≥ 1 stage fibrosis improvement with no NASH worsening	12 mos
Elafibranor	PPARα/σ agonist	RESOLVE-IT[2]	2000	Resolution of NASH with no fibrosis worsening	72 wks
Obeticholic acid	FXR agonist	REGENERATE[3]	931	≥ 1 stage fibrosis improvement with no NASH worsening; resolution of NASH with no fibrosis worsening	18 mos
		REVERSE[4]	900	≥ 1 stage fibrosis improvement with no NASH worsening	18 mos
Resmetirom	THR-β agonist	MAESTRO-NASH[5]	2000	Resolution of NASH	52 wks
Aramchol	SCD1 inhibitor	ARMOR[6]	2000	≥ 1 stage fibrosis improvement with no NASH worsening; resolution of NASH with no fibrosis worsening	52 wks

Phase III/IV studies use adaptive design

- Histologic endpoints for Subpart H conditional approval
- Clinical endpoints for full approval

1. NCT03028740. 2. NCT02704403. 3. Younossi. Lancet. 2019;394:2184. 4. NCT03439254. 5. NCT03900429. 6. NCT04104321.

Slide credit: clinicaloptions.com

Μελέτες φάσης 3

- **OCALIVA (OCA), Laboratory : INTERCEPT**
- **Type of drug :** *FXR Agonist*
- **Clinical trials advancement :** *Ongoing Phase 3*
- *The drug got the Breakthrough Therapy Status granted by the FDA*
- **Estimated Time to market in months :** *42*
- **ELAFIBRANOR (GFT505), Laboratory : GENFIT**
- **Type of drug :** *dual PPAR alpha delta agonist*
- **Clinical trials advancement :** *Ongoing Phase 3*
- *The drug got the Fast Track Status granted by the FDA*
- **Estimated Time to market in months :** *42*

- **CENICRIVIROC (CENICRIVIROC), Laboratory : ALLERGAN**
- **Type of drug :** *CCR2CCR5 Antagonist*
- **Clinical trials advancement :** *Recruiting Phase 3*
- *The drug got the Fast Track Status granted by the FDA and is eligible for Subpart H on intermediate results of Phase 3*
- **Estimated Time to market in months :** *33*
- **RESMETIROM (MGL_3196), Laboratory : MADRIGAL**
- **Type of drug :** *THR-β Agonist*
- **Clinical trials advancement :** *Recruiting Phase 3*
- *and is eligible for Subpart H on intermediate results of Phase 3*
- **Estimated Time to market in months :** *35*

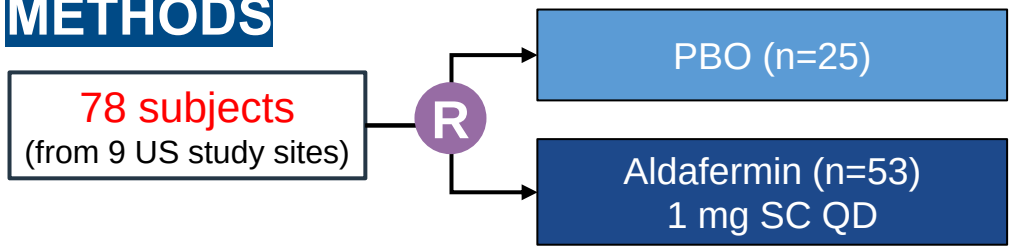
- **BELAPECTIN (GR_MD_02), Laboratory : GALECTIN**
- **Type of drug :** *Galectin Inhibitor*
- **Clinical trials advancement :** *Initiating Phase 3*
- *The drug got the Fast Track Status granted by the FDA*
- **Estimated Time to market in months :** *72*
- **ARAMCHOL (ARAMCHOL), Laboratory : GALMED**
- **Type of drug :** *FABACs*
- **Clinical trials advancement :** *Initiating Phase 3*
- *The drug got the Fast Track Status granted by the FDA*
- **Estimated Time to market in months :** *55*
- **IMM124E (IMM124E), Laboratory : IMMURON**
- **Type of drug :** *anti-LPS antibodies and adjuvants*
- **Clinical trials advancement :** *Initiating Phase 3*
- *The drug got the Breakthrough Therapy Status granted by the FDA*
- **Estimated Time to market in months :** *56*

Positive topline results from a 24-week, randomized, double-blind, placebo-controlled, multicenter, phase 2 study of aldafermin in patients with NASH

BACKGROUND & AIMS

- Aldafermin (NGM282) is an engineered FGF19 analogue
  - Significantly inhibited bile acid synthesis, reduced hepatic fibrosis, inflammation and steatosis in previous 12-week NASH trials
- **AIM**: to report the primary and key results from the 24-week study with **paired liver biopsy**

METHODS



- Subjects underwent MRI-PDFF and liver biopsy at baseline and Week 24
- Inclusion criteria: biopsy-proven NASH*
- Primary endpoint: change in LFC from baseline to Week 24
- Histological endpoints:
  - Improvement in liver fibrosis by ≥1 stage with no worsening of NASH
  - Resolution of NASH with no worsening of fibrosis†

RESULTS

- At Week 24, treatment with aldafermin resulted in statistically significant reductions in LFC

	PBO (n=25)	Aldafermin (n=52‡)	p value
Δ Absolute MRI-PDF, %	-2.7 (1.3)	-7.7 (0.8)	0.002
% Subjects with ↓ 5% absolute	24	68	<0.001
Δ Relative MRI-PDFF, %	-13.1	-38.8	0.008
% Subjects with ↓ 30% relative	29	66	0.004

Shown are LS mean (SE) or % subjects

*NAS ≥4, stage 2–3 fibrosis, absolute LFC ≥8%; †NASH CRN criteria;
‡One patient did not have any post-baseline measurements and was excluded from efficacy analysis as pre-specified in the statistical analysis plan
Harrison SA, et al. DILC 2020; LBO01

Positive topline results from a 24-week, randomized, double-blind, placebo-controlled, multicenter, phase 2 study of aldafermin in patients with NASH

RESULTS (CONT.)

- At Week 24, more subjects on aldafermin showed improvements in fibrosis and NASH
- ALT, AST and fibrogenesis biomarkers declined rapidly and significantly from baseline with aldafermin

	PBO (n=25)	Aldafermin (n=52)	p value
% Subjects achieving ≥1 stage improvement in fibrosis with no worsening of NASH	18	38	–
% Subjects achieving NASH resolution with no worsening of fibrosis	9	24	–
% Subjects achieving ≥1 stage improvement in fibrosis **AND** resolution of NASH with no worsening of fibrosis	0	22	0.015
Δ Absolute ALT, U/L	-15.9 (3.5)	-36.6 (2.4)	–
Δ Absolute AST, U/L	-8.5 (3.6)	-19.0 (2.4)	–
Δ Pro-C3, ng/mL	-0.9 (1.1)	-5.5 (0.7)	–

Shown are LS mean (SE) or % subjects

- Aldafermin was well tolerated, with any SAEs unrelated to study drug

CONCLUSION

- In patients with NASH, aldafermin therapy resulted in a statistically significant reduction in LFC and robust improvement in fibrosis and NASH histology compared with PBO. Aldafermin 1 mg maintained a durable response for 24 weeks, with a favourable tolerability and safety profile

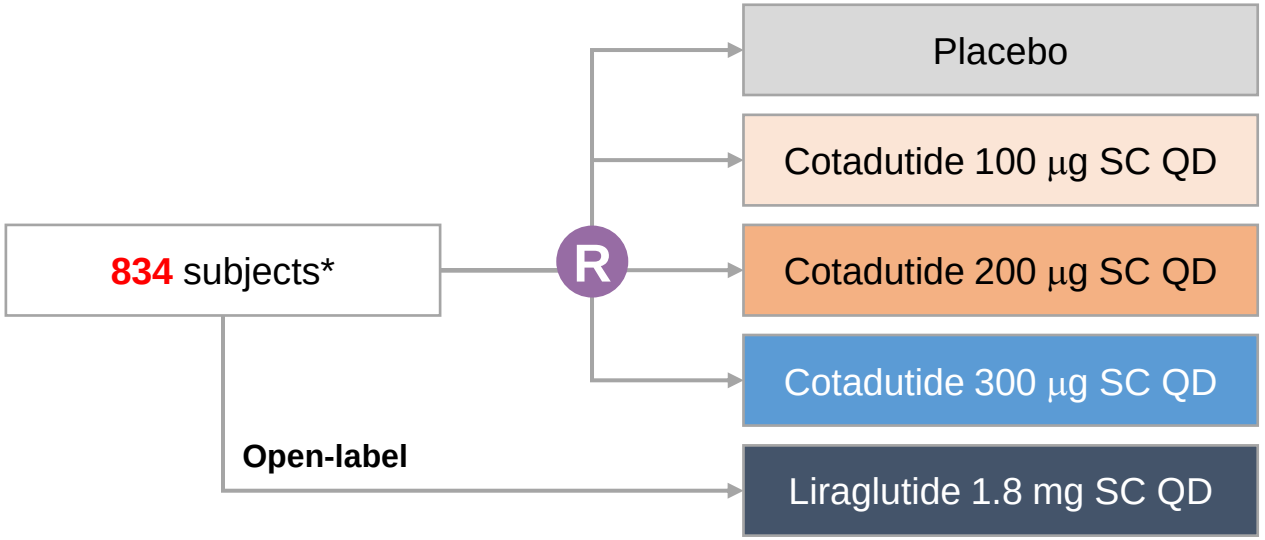
Harrison SA, et al. DILC 2020; LBO01

Effects of cotadutide on biomarkers of NASH in overweight or obese subjects with T2DM: a 54-week analysis of a randomized phase 2b study

BACKGROUND & AIMS

- Cotadutide is a dual-receptor agonist with GLP-1 and glucagon activity
  - Significantly decreased hepatic fat in obese or overweight T2DM subjects in an exploratory analysis of a phase 2a study
- **AIM**: to evaluate the effects of cotadutide at Week 54 on hepatic parameters and metabolic profiles of obese or overweight subjects with T2DM

METHODS



- Changes from BL to Week 54 analyzed:
  - Change in body weight (secondary endpoint)
  - Change in ALT, AST, and GGT (post hoc†)
  - Change in NFS and FLI (post hoc‡)
  - Changes in pro-C3 levels (post hoc)

*NCT03235050; †Per protocol population; ‡As-treated population

Nahra R, et al. DILC 2020; AS076

Effects of cotadutide on biomarkers of NASH in overweight or obese subjects with T2DM: a 54-week analysis of a randomized phase 2b study

RESULTS

- Significant reductions in body weight were observed with cotadutide 300 μg vs liraglutide (p=0.009)*
- 0.4% fall in pro-C3 for cotadutide 300 μg vs an 8% rise for liraglutide and a 13% rise for placebo
- Numerical reductions in ALT, AST, and GGT levels were observed with all cotadutide doses
  - Greatest ALT reductions were in 4th quartile: changes† vs placebo were –12.3 (p=0.259), -27.1 (p=0.002), and -31.3 (p<0.001)

		COT 100 μg (n=76)	COT 200 μg (n=202)	COT 300 μg (n=189)	Liraglutide (n=104)	Placebo (n=93)
ALT	BL, U/L‡	33.5 (21.6)	32.1 (18.1)	33.2 (18.7)	32.8 (18.2)	30.7 (19.2)
	Δ At Week 54, %†	-7.5 (-16.4, 1.3)	-12.0 (-17.4, -6.6)	-14.1 (-19.8, -8.6)	-3.2 (-10.8, 4.3)	0.9 (-7.1, 9.0)
	p-value vs placebo / liraglutide	0.165 / 0.467	0.009 / 0.063	0.003 / 0.023	0.461 / –	–
AST	BL, U/L‡	24.8 (12.3)	24.1 (13.3)	25.1 (17.4)	24.6 (11.9)	23.7 (11.5)
	Δ At Week 54, %†	-1.8 (19.8, 6.3)	-6.2 (-11.2, 1.3)	-9.1 (-14.3, -4.0)	0.4 (-6.5, 7.2)	5.7 (-1.7, 13.0)
	p-value vs placebo / liraglutide	0.182 / 0.695	0.009 / 0.129	0.001 / 0.030	0.302 / –	–
GGT	BL, U/L‡	40.3 (40.9)	42.5 (32.1)	45.1 (48.8)	48.1 (49.5)	41.5 (30.1)
	Δ At Week 54, %†	-10.5 (-26.8, 5.7)	-1.5 (-11.5, 8.4)	-12.2 (-22.5, -1.9)	-10.5 (-24.4, 3.3)	12.5 (-2.3, 27.2)
	p-value vs placebo / liraglutide	0.040 / 1.000	0.123 / 0.300	0.007 / 0.853	0.026 / –	–

- Clinically significant reductions were observed at Week 54 in NFS (p≤0.001) for all cotadutide doses and in FLI (p=0.010) for cotadutide 300 μg vs placebo

CONCLUSION

- Reductions in body weight and ALT with cotadutide 300 μg and improvements in *fatty liver index (*FLI) and NFS support prospective clinical trials with cotadutide for a NASH indication

*Significant reductions were observed for all doses vs placebo (p<0.001); †LS mean for % change from BL (95% CI); ‡Mean (SD)

Nahra R, et al. DILC 2020; AS076

Expert Opinion

JOURNAL OF HEPATOLOGY

A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement

Mohammed Eslam[1,*,†], Philip N. Newsome[2,*,†], Shiv K. Sarin[3], Quentin M. Anstee[4], Giovanni Targher[5], Manuel Romero-Gomez[6], Shira Zelber-Sagi[7], Vincent Wai-Sun Wong[8], Jean-François Dufour[9], Jörn M. Schattenberg[10], Takumi Kawaguchi[11], Marco Arrese[12], Luca Valenti[13], Gamal Shiha[14], Claudio Tiribelli[15], Hannele Yki-Järvinen[16], Jian-Gao Fan[17], Henning Grønbæk[18], Yusuf Yilmaz[19], Helena Cortez-Pinto[20], Claudia P. Oliveira[21], Pierre Bedossa[22], Leon A. Adams[23], Ming-Hua Zheng[24], Yasser Fouad[25], Wah-Kheong Chan[26], Nahum Mendez-Sanchez[27], Sang Hoon Ahn[28], Laurent Castera[29], Elisabetta Bugianesi[30], Vlad Ratziu[31,*,‡], Jacob George[1,*,‡]

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Journal Pre-proof

MAFLD: A consensus-driven proposed nomenclature for metabolic associated fatty liver disease

Mohammed Eslam, Arun J. Sanyal, Jacob George, on behalf of an international consensus panel

PII: S0016-5085(20)30171-2
DOI: https://doi.org/10.1053/j.gastro.2019.11.312
Reference: YGAST 63198

To appear in: *Gastroenterology*
Accepted Date: 5 November 2019

The outdated NAFLD/NASH acronyms, the criteria for diagnosis and a lack of adequate consideration of heterogeneity in risk profiles and treatment responsiveness represent barriers that hamper progress towards effective treatments. The consensus group has suggested an acronym (MAFLD) that we believe more accurately reflects current knowledge of fatty liver diseases associated with metabolic dysfunction that should replace NAFLD/NASH. In addition, we have identified gaps in current knowledge and highlight new strategies and tools to overcome the challenges

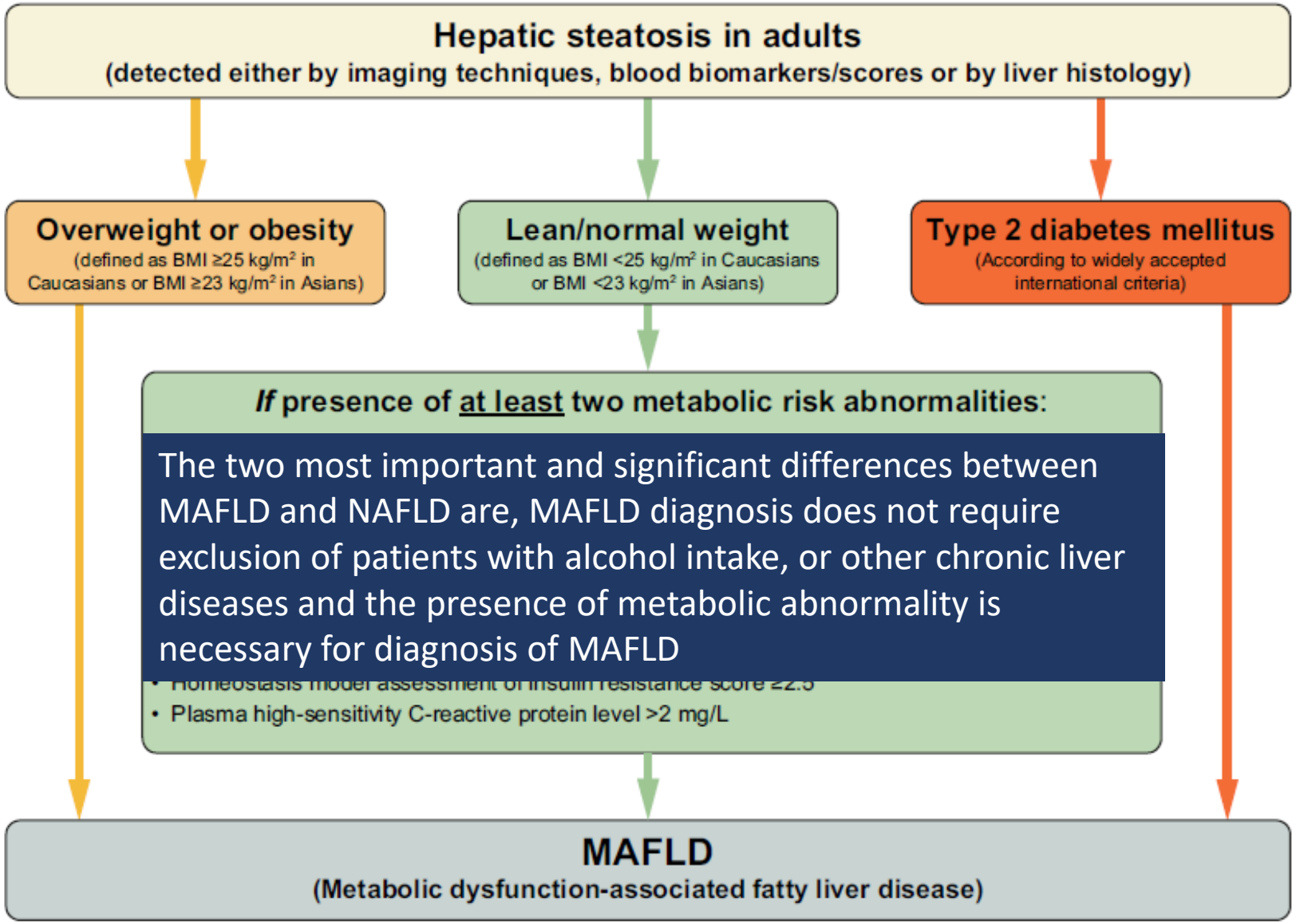

Fig. 1. Flowchart for the proposed "positive" diagnostic criteria for MAFLD.

From NAFLD to MAFLD: Implications of a premature change in terminology

Zobair M Younossi[1,2], Mary E. Rinella[3], Arun Sanyal[4], Stephen A. Harrison[5], Elizabeth Brunt[6], Zachary Goodman[1,2], David E. Cohen[7], Rohit Loomba[8]

Summary

Although we are in agreement that metabolic fatty liver disease (MAFLD) may more accurately and positively reflect the relevant risk factors better than the age-old term non-alcoholic fatty liver disease, (NAFLD), the term still leaves a great deal of ambiguity. A name change will be appropriate when informed by a new understanding of the molecular basis of the disease entity, insights that fundamentally change risk stratification or other important aspect of the disease. We may be on the cusp of this, but we are not here yet.

Hepatology. 2020