MÁSTER EN HEPATOLOGÍA

UAM Universidad Autónoma de Madrid

Universidad de Alcalá

# TRATAMIENTO MEDICO DE LA EHMET

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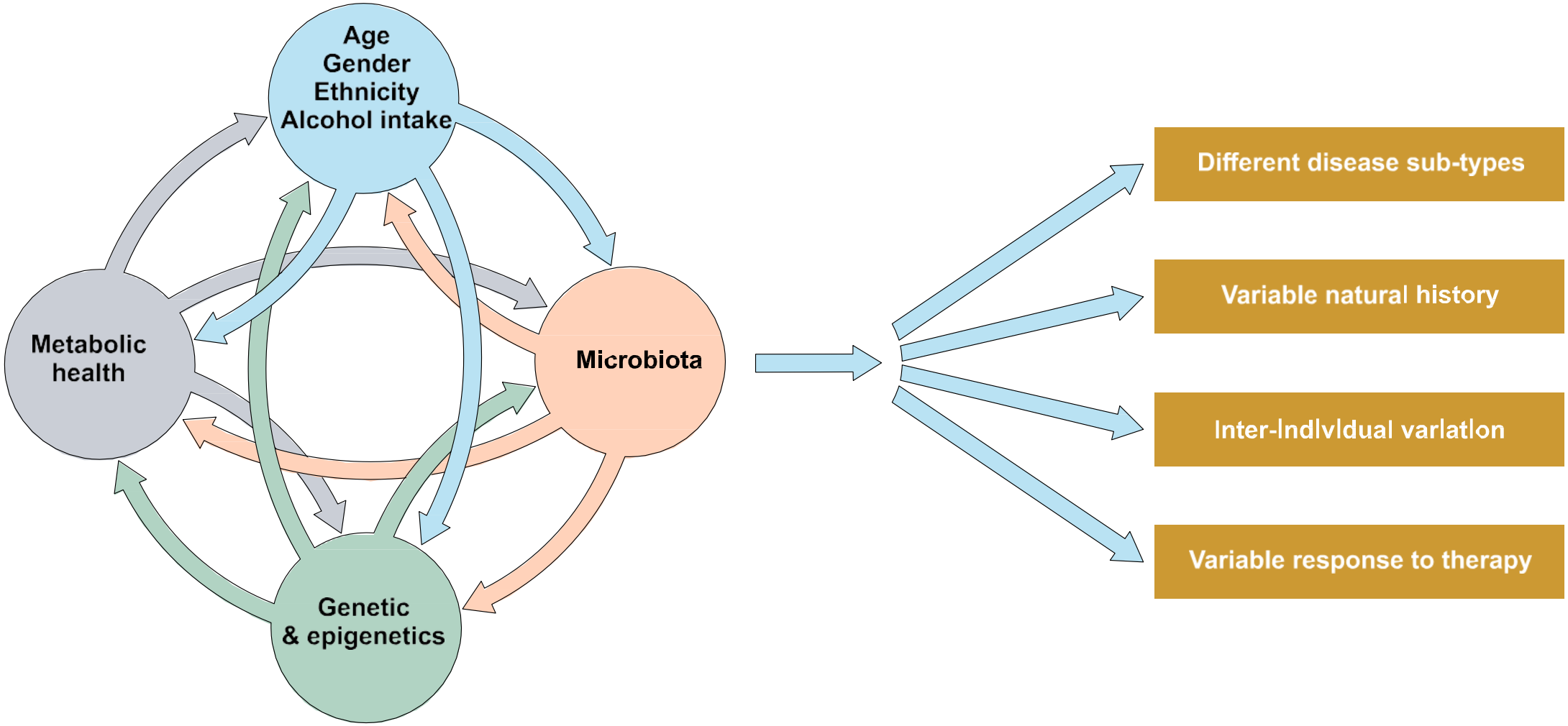
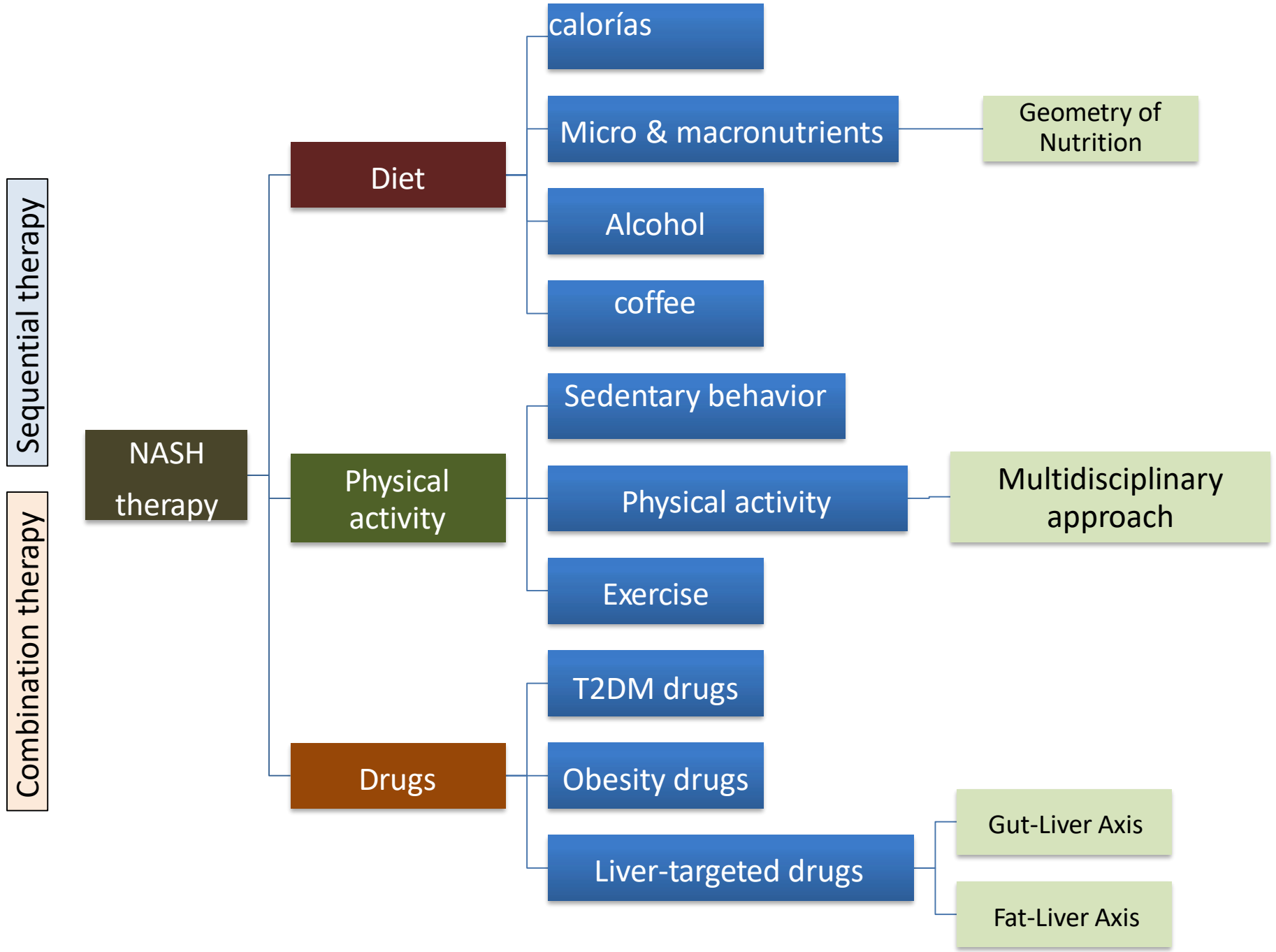
47005 - VALLADOLID

# EHMET: UNA ENFERMEDAD HETEROGENEA

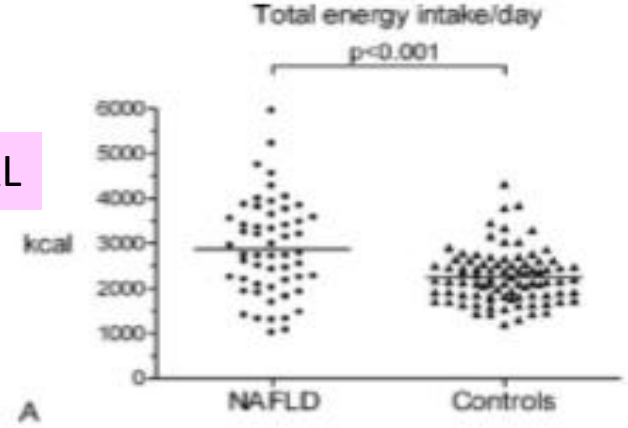



Zezos et al, World J Gastroenterol 2014; Ekstedt et al, Hepatology 2015; Wong et al, Gastroenterology 2015

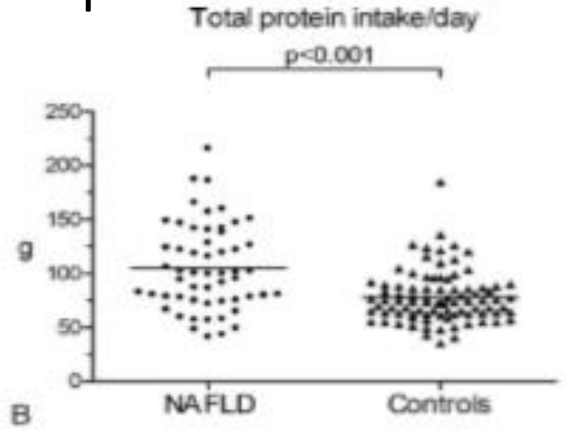

Sequential therapy
Combination therapy
NASH therapy
Diet
calorías
Micro & macronutrients
Geometry of Nutrition
Alcohol
coffee
Physical activity
Sedentary behavior
Physical activity
Multidisciplinary approach
Exercise
Drugs
T2DM drugs
Obesity drugs
Liver-targeted drugs
Gut-Liver Axis
Fat-Liver Axis

# Composición de la dieta de los pacientes con EHmet

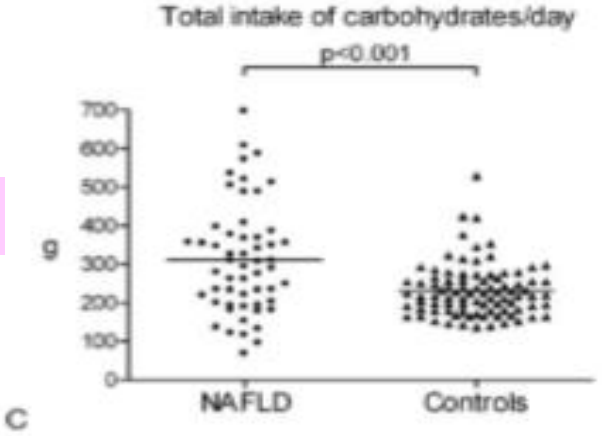
kCAL



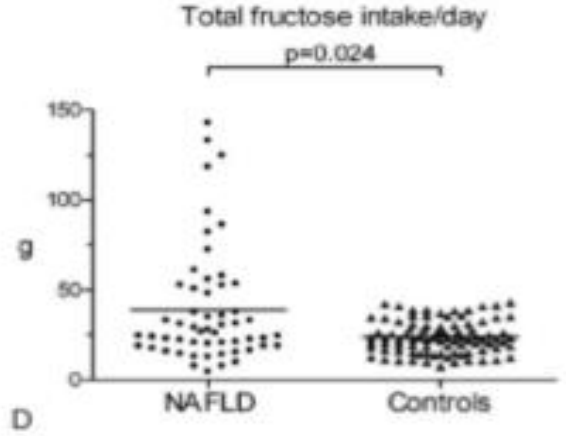

Proteinas



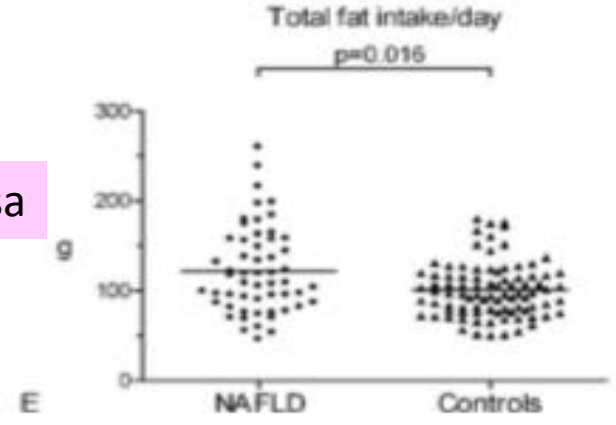

HC



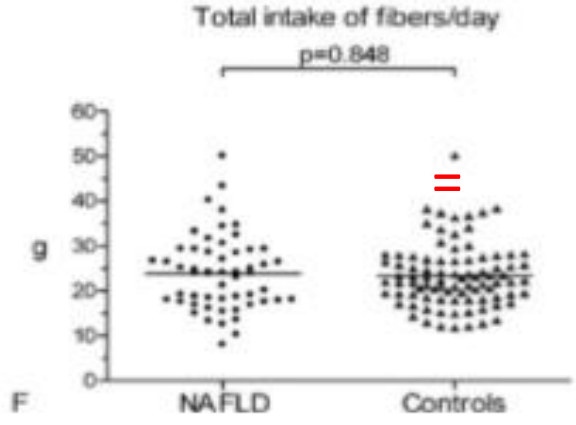

Fructosa



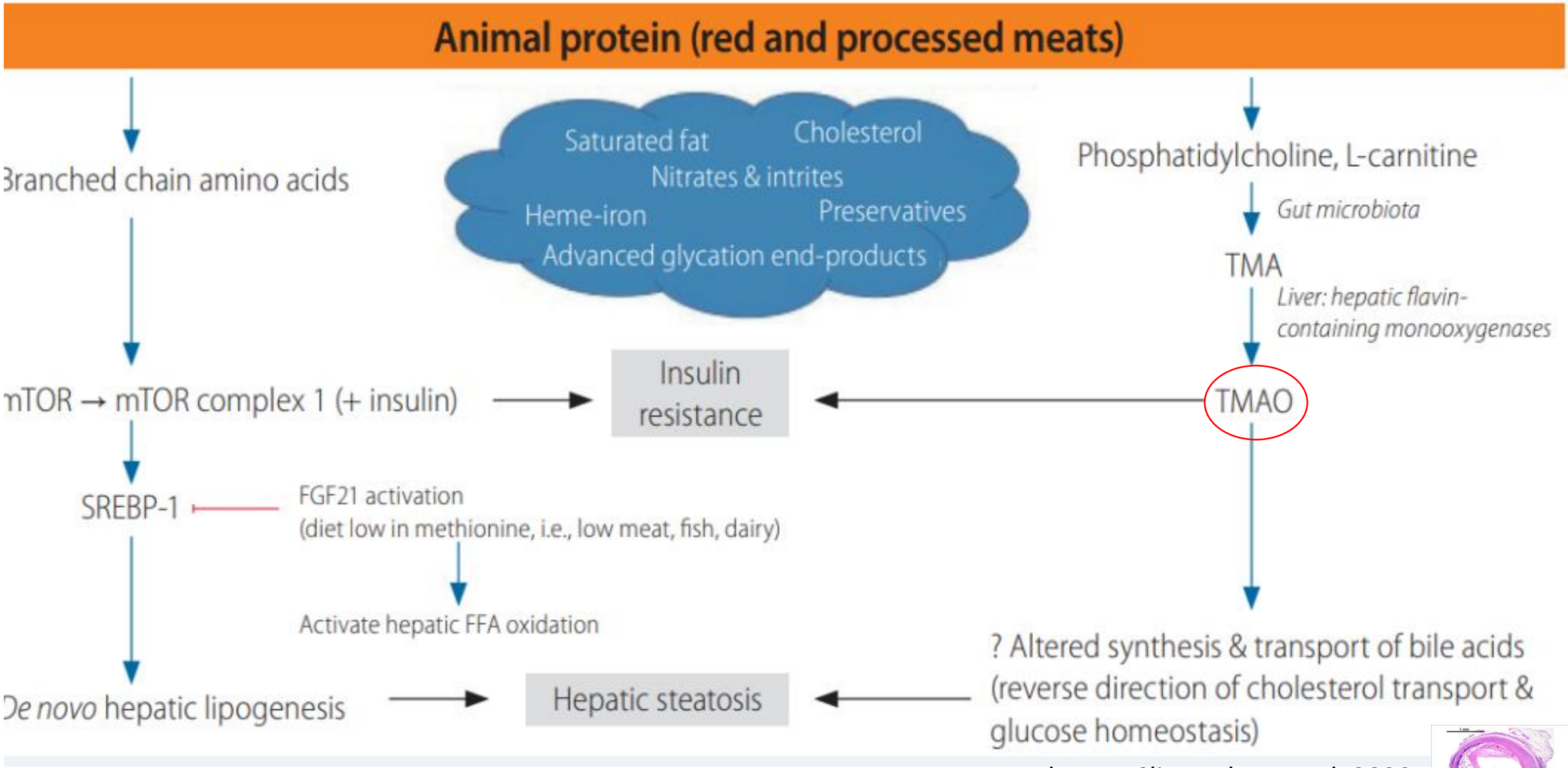

Grasa



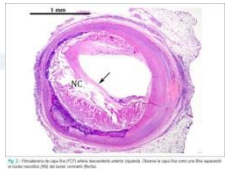

Fibra

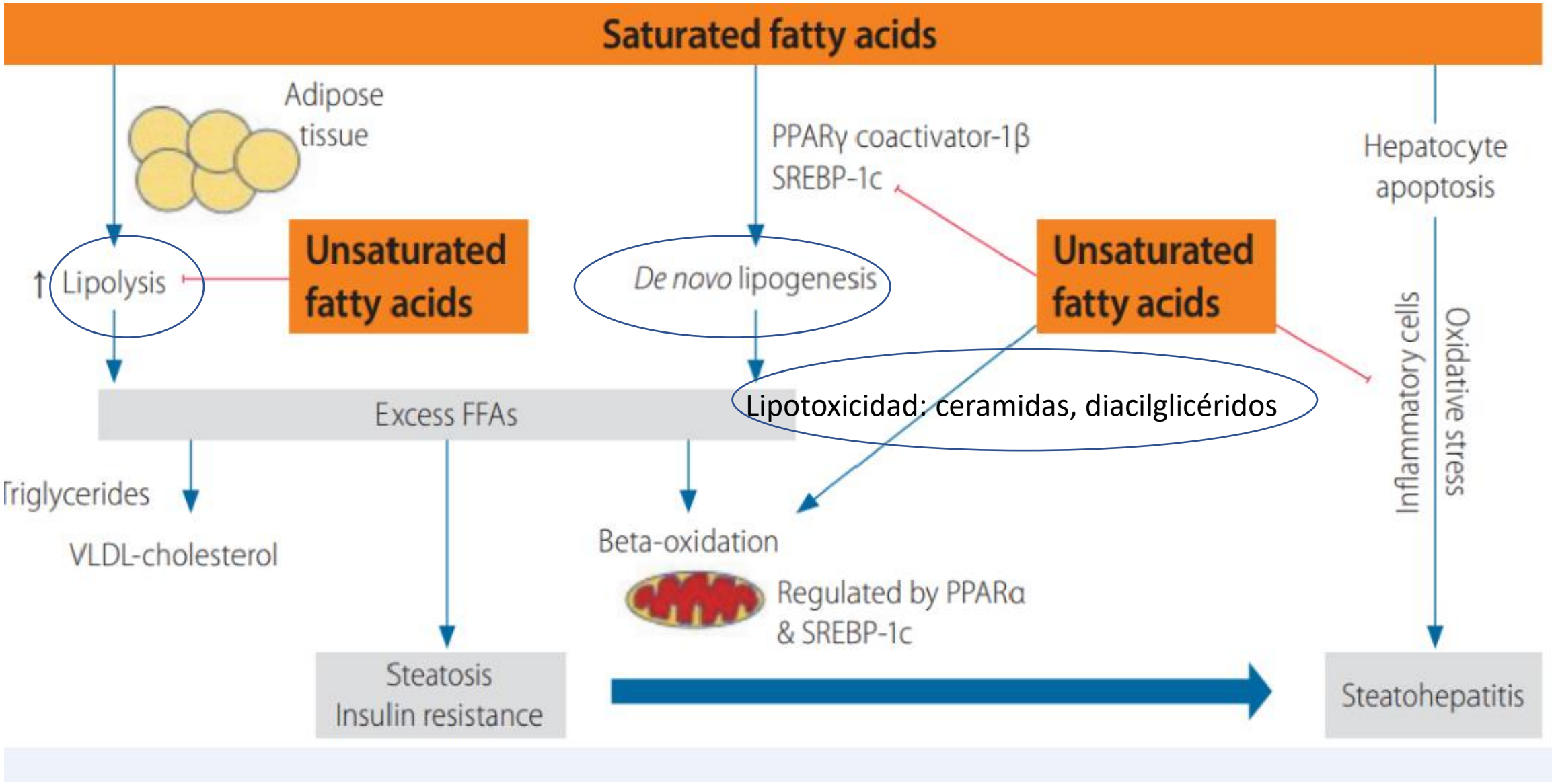



Wehmeyer et al. Medicine (2016) 95:23



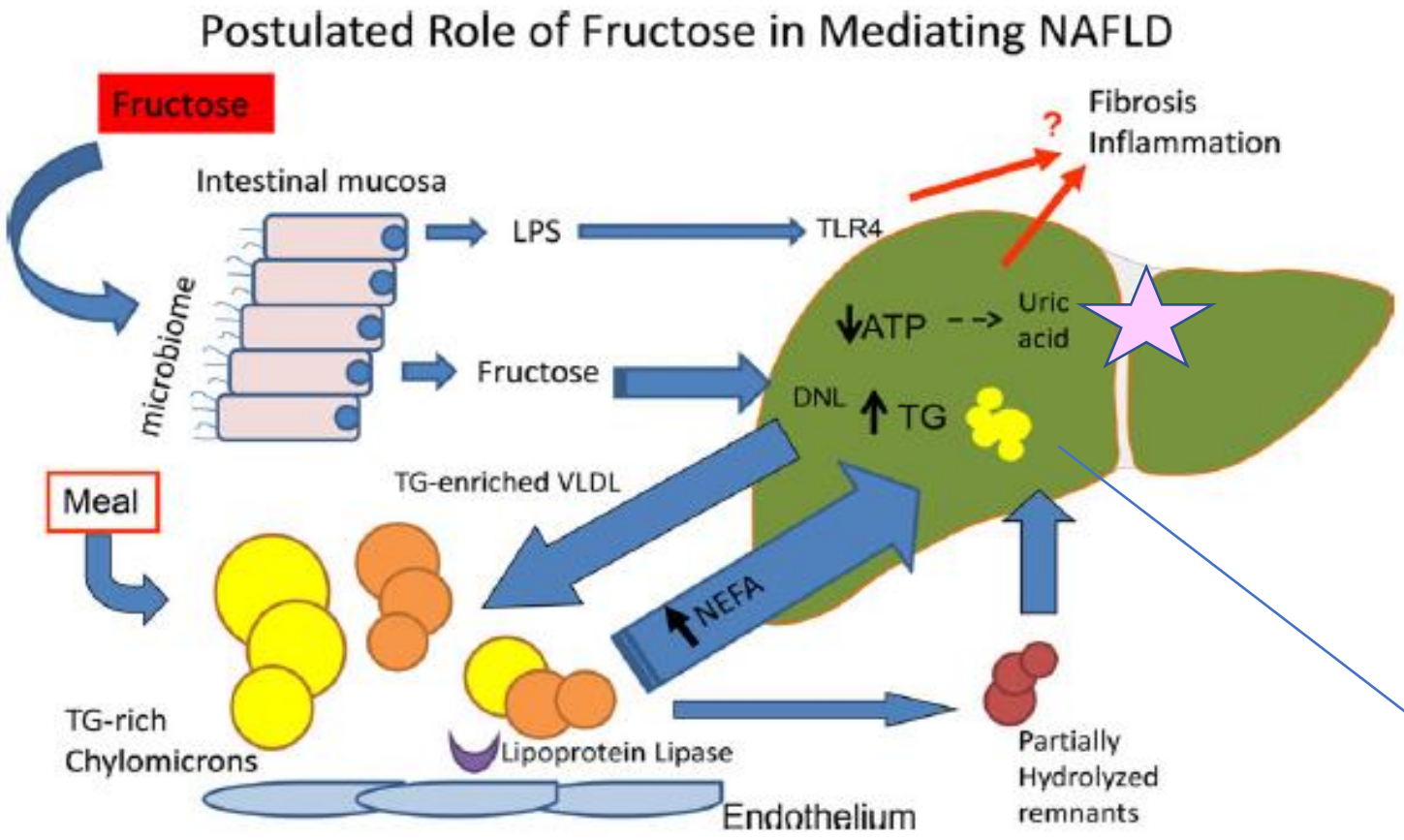

Hydes TJ,. Clin Mol Hepatol. 2020.

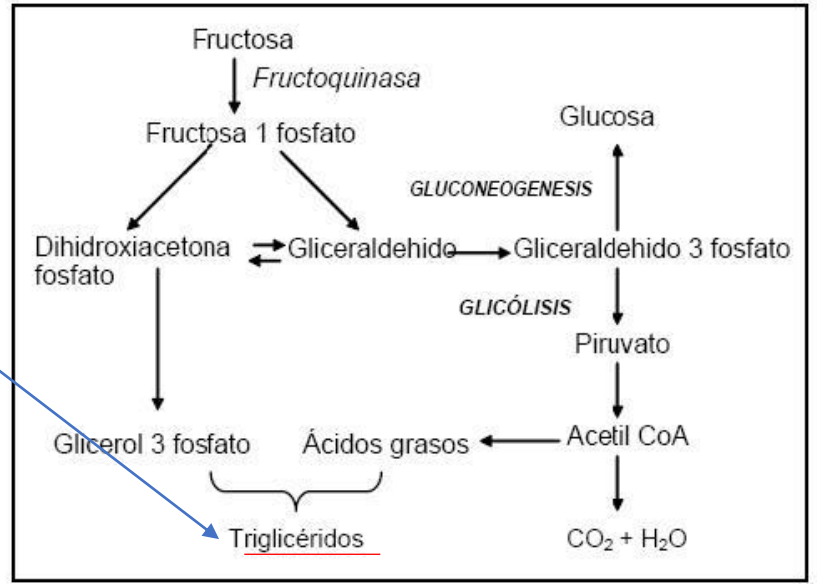




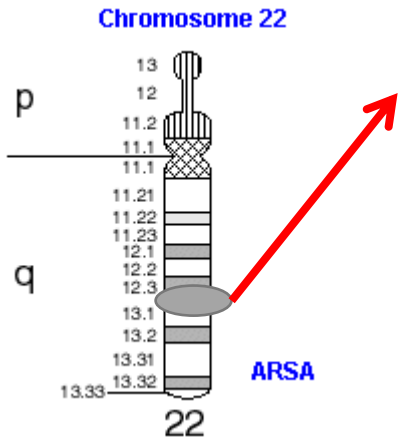

Hydes TJ,. Clin Mol Hepatol. 2020

# Fructosa


Postulated Role of Fructose in Mediating NAFLD
Fructose
Intestinal mucosa
LPS
TLR4
?
Fibrosis
Inflammation
microbiome
↓ATP --> Uric acid
Fructose
DNL ↑ TG
Meal
TG-enriched VLDL
↑NEFA
TG-rich
Chylomicrons
Lipoprotein Lipase
Partially
Hydrolyzed
remnants
Endothelium


Fructosa
Fructoquinasa
Fructosa 1 fosfato
Glucosa
GLUCONEOGENESIS
Dihidroxiacetona fosfato
Gliceraldehido
Gliceraldehido 3 fosfato
GLICÓLISIS
Piruvato
Glicerol 3 fosfato
Ácidos grasos
Acetil CoA
Triglicéridos
$CO_2 + H_2O$

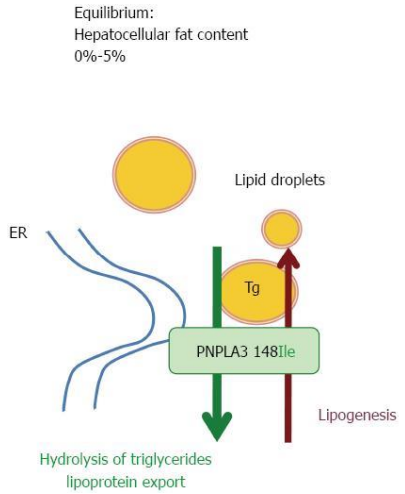
# Fructosa-genética Gen PNPLA3

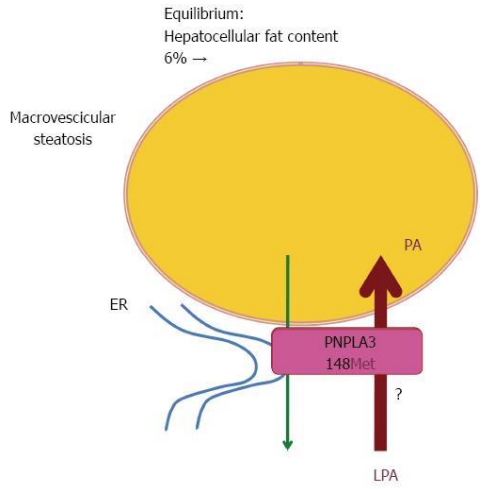



Síntesis de la **adiponutrina** con **actividad lipasa** específica de tejido adiposo y hepatocitos

La variante mutada (rs738409) pierde la actividad lipasa.
Cambio de 148Ile → 148Met

**PROMUEVE ACUMULACIÓN DE LÍPIDOS**

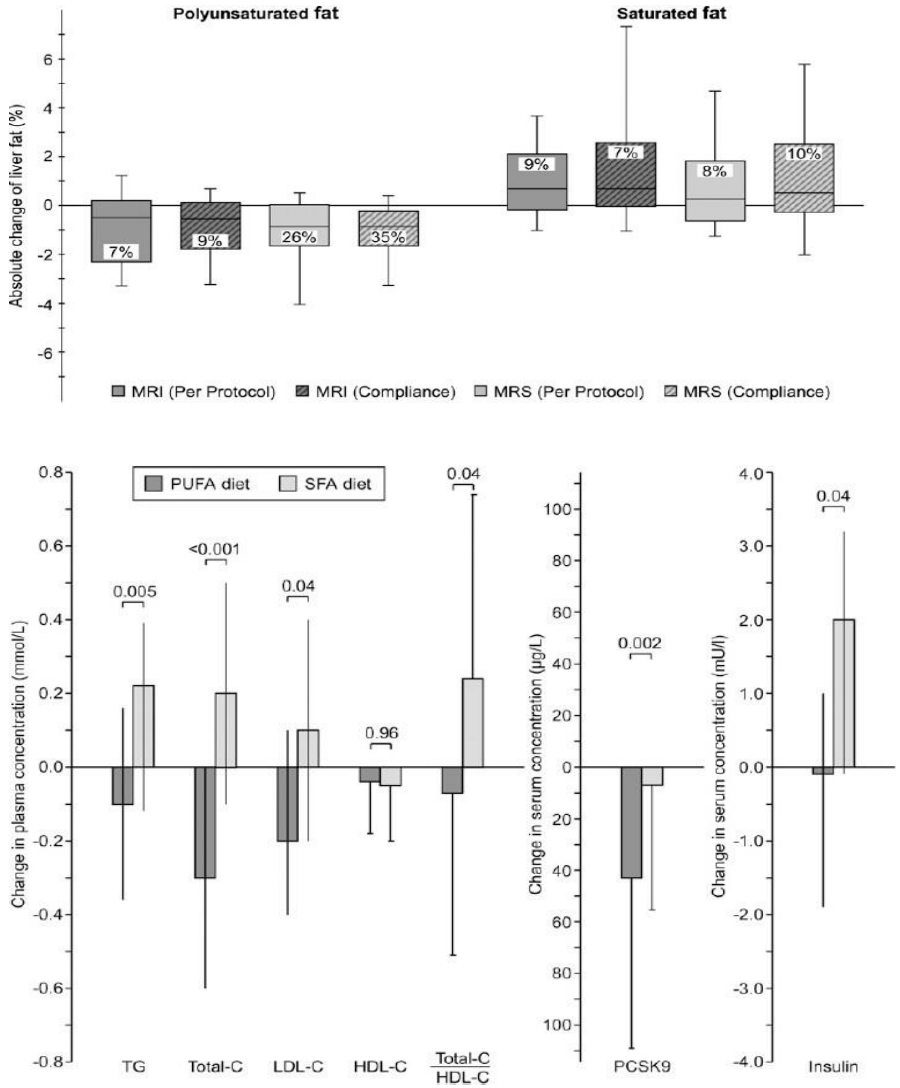



Estudios recientes evaluaron la predisposición genética de influencia de **fructosa en el hígado**. La variante I148M (rs738409 C / G) en el patatina-como dominio que contienen proteínas fosfolipasa

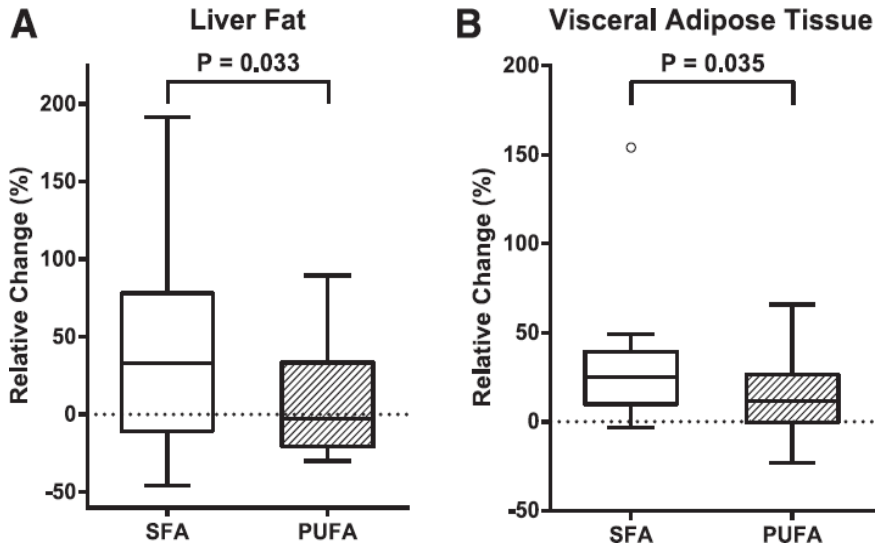

Cantidad
Calidad

## *Dieta isocalórica*




Bjermo et al, Am JClin Nutr 2012

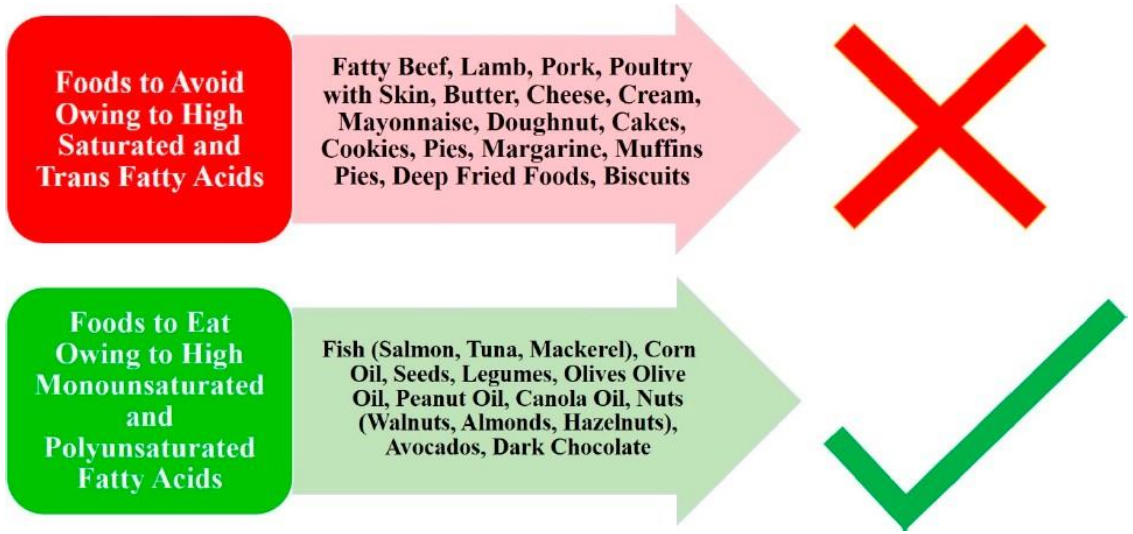
## *Dieta hipercalórica*




Rosqvist et al, Diabetes 2014

# ¿Hay algo más allá de la dieta que ayude?

| Author | Type of coffee | Sample size | Improvement in steatosis | Improvement in fibrosis |
|---|---|---|---|---|
| Zelber-Sagi 2015 [80] | All caffeinated coffee types | 347 | No | Yes (Fibrotest) |
| Bambha 2013 [82] | Caffeinated and decaffeinated | 782 | No | Yes |
| Anty 2012 [81] | Regular coffee, not espresso | 195 | NE | Yes |
| Birerdinc 2012 [84] | Caffeine intake | 41,658 | Yes | NE |
| Molloy 2012 [79] | Regular coffee | 306 | No | Yes |
| Catalano 2010 [83] | Only espresso coffee | 245 | Yes | NE |



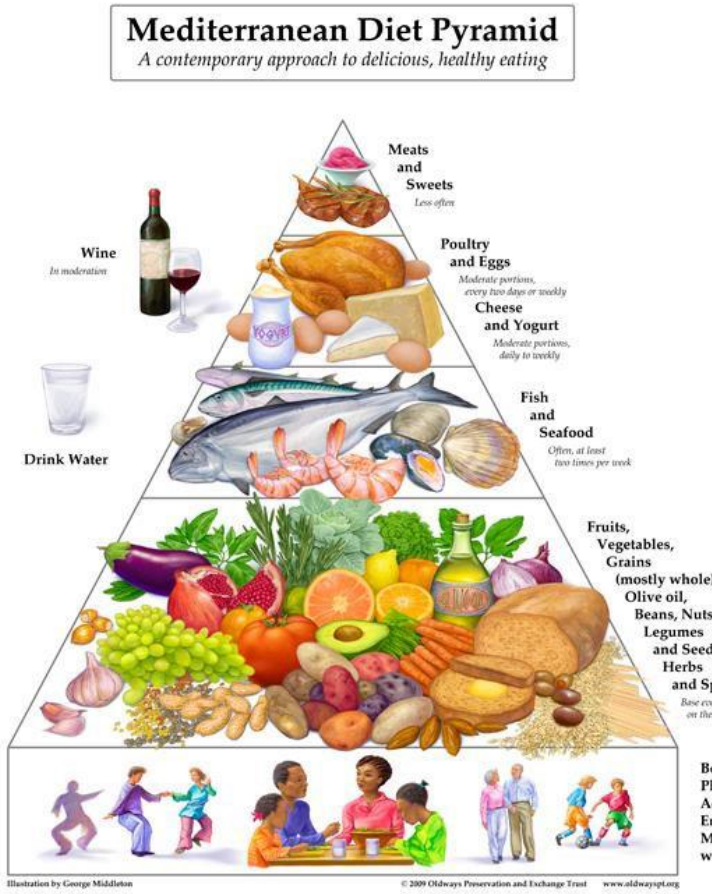

Perumpail et al, Diseases 2017

Maersk et al, Am JClin Nutr 2012

# The Mediterranean diet is superior to low fat diet in RCTs

**High in**

- Olive oil≥4 tbsp/day
- nuts handful/day
- Fish ≥3 /wk
- Legumes ≥3 /wk
- Fruits &Vegetables
- Fat - 40% /kcal, mostly MUFA and ω3 PUFA




**Low in**

- Soda drinks
- Sweets
- Red and processed meats
- Carbohydrate- 40% /kcal

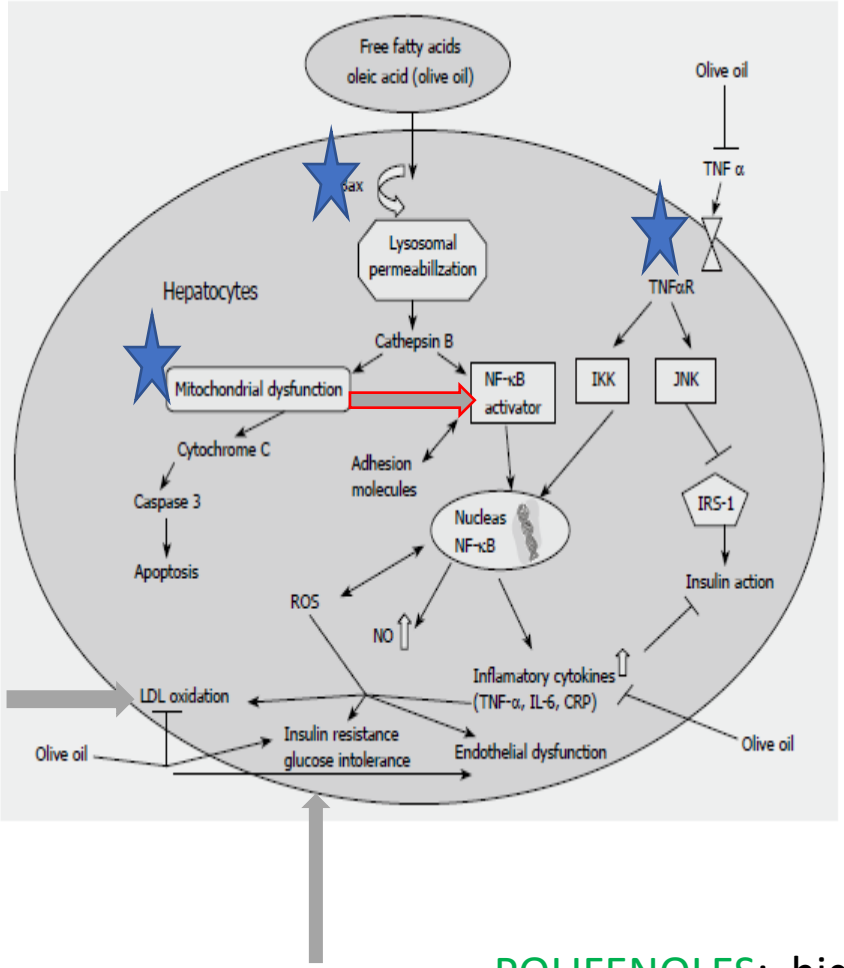
Salas-Salvadó J., Ann Intern Med 2014

Ryan MC., Journal of Hepatology 2013

Nordmann AJ., The American Journal of Medicine 2011

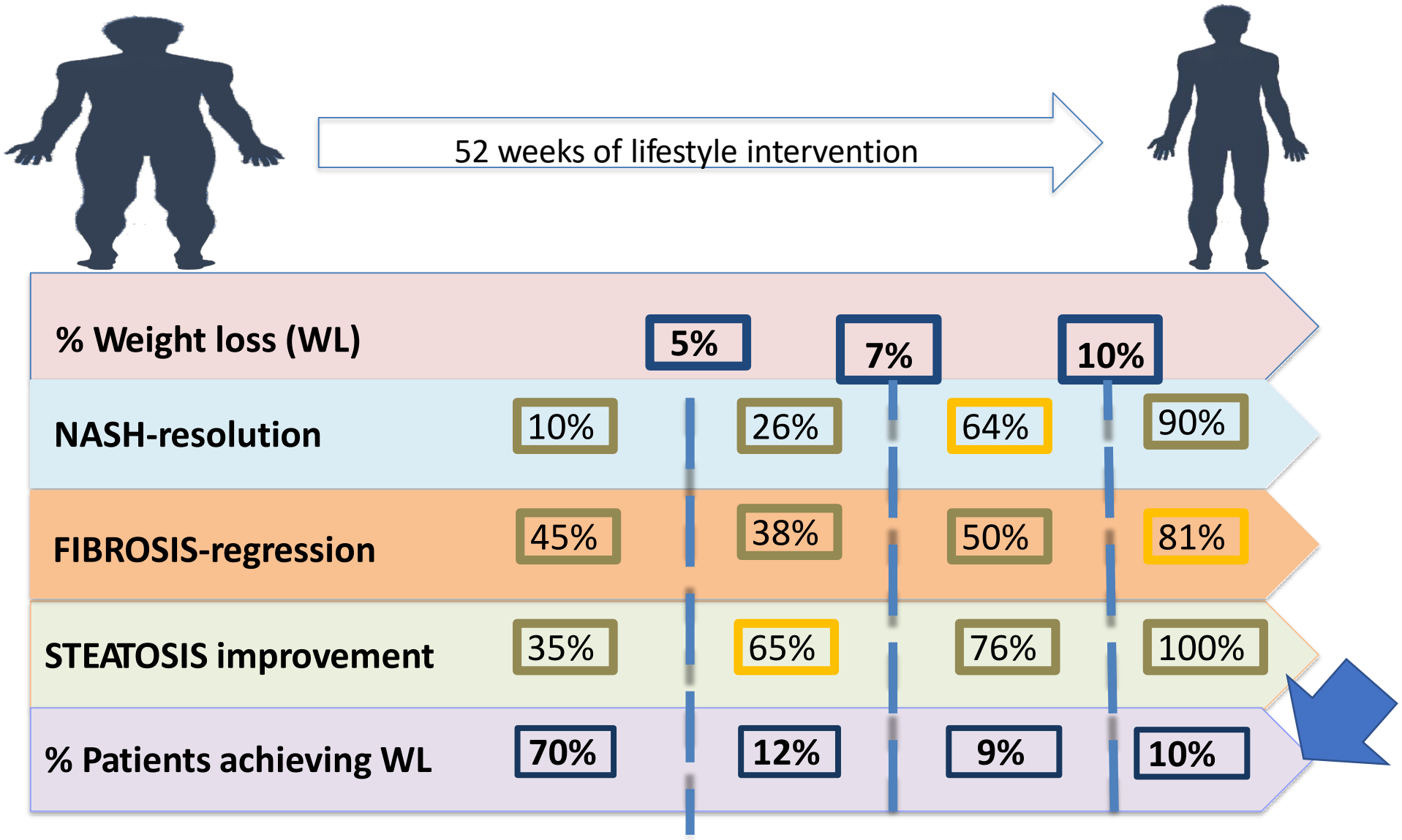
Estruch R., N Engl J Med 2013

# ACEITE OLIVA



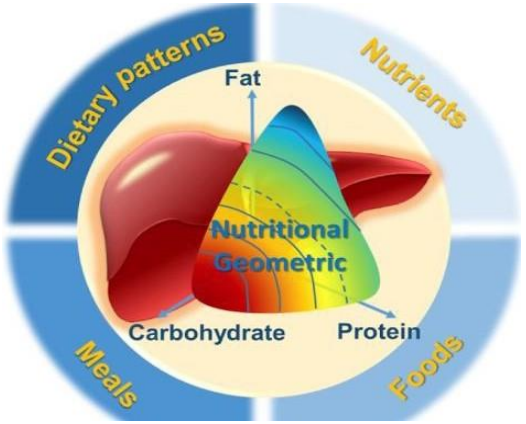

| Mechanism | Component involved |
|---|---|
| Anti-inflammatory and immunomodulatory effects | Oleic acid<br>Phenolic compounds |
| Anti-oxidants: | Oleic acid |
| Decrease lipid peroxidation<br>Decrease oxidative DNA damage | Phenolic compounds: hydroxytyrosol, oleuropein, caffeic acid, o-coumaric acid, vanillic acid, and 3,4-dihydroxyphenylethanol (3,4-DHPEA). |
| Modulation of transduction pathways: | Oleic acid |
| Decreases arachidonic acid | Phenolic compounds: protocatecuic acid |
| Inhibits lipooxygenase | Hydroxytyrosol |
| Inhibits HMG-CoA reductase | Squalene |
| Decreases RAS activation | Squalene |
| Regulation of gene expression in liver regeneration:<br>(Oleic acid inhibits δ6-desaturase which decreases PGE2 and inhibits liver regeneration) | Oleic acid<br>Minor compounds |
| Change in membrane fluidity and membrane peroxidation (estrogen modulator, regulates G protein) | Oleic acid<br>Lignans |

POLIFENOLES: hidroxitirosol mitigando el estrés del retículo endoplásico (RE) en el tejido adiposo y hepático.
Suprime la expresión hepática de los genes involucrados en la lipogénesis




Romero-Gómez M, Zelber-Sagi S, Trenell M. J Hepatol 2017

# Geometric Framework for Nutrition in liver diseases

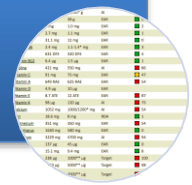



- Fructose
- Glucose
- AGE

**CARBO-HYDRATES**

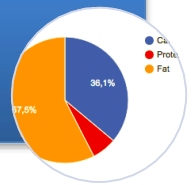
- Hypercaloric
- Isocaloric
- Hypocaloric

**CALORIES**



- Micronutrients:
  - Vitamins
  - Choline
  - Coffee
  - Selenium
  - Carotenoids

**Nutrients**




- MUFA
- SFA
- PUFA

**FAT**

HCUV (Valladolid)

HUVR (Sevilla)

# NASH resolution and fibrosis regression in INAMET trial

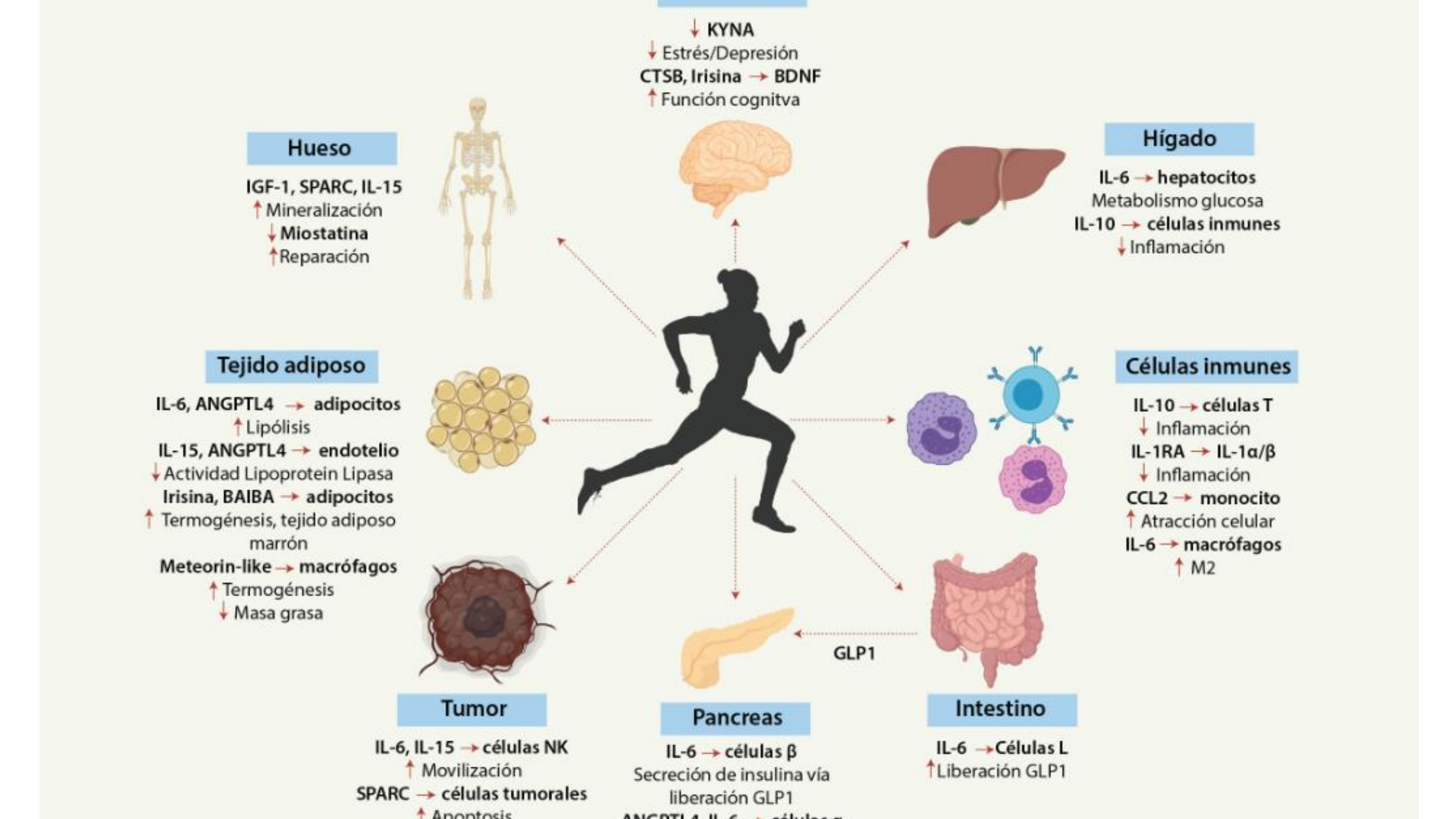
| | NASH resolution | | |
|---|---|---|---|
| **Nutritional intervention** | No | Yes | |
| **LFD** | 20 (76%) | 7 (24%) | |
| **MD** | 14 (43%) | 18 (57%) | P<0.05 |

| | Fibrosis TE (kPa) | | |
|---|---|---|---|
| **Nutritional intervention** | Progression (%) | Stable (%) | Improvement (%) |
| **LFD** | 19 | 19 | 62 |
| **MD** | 22 | 20 | 58 |

| | Fibrosis (Hepamet fibrosis score) | | |
|---|---|---|---|
| **Nutritional intervention** | Progression | Stable (%) | Improvement (%) |
| **LFD** | 15 | 73 | 12 |
| **MD** | 10 | 80 | 10 |

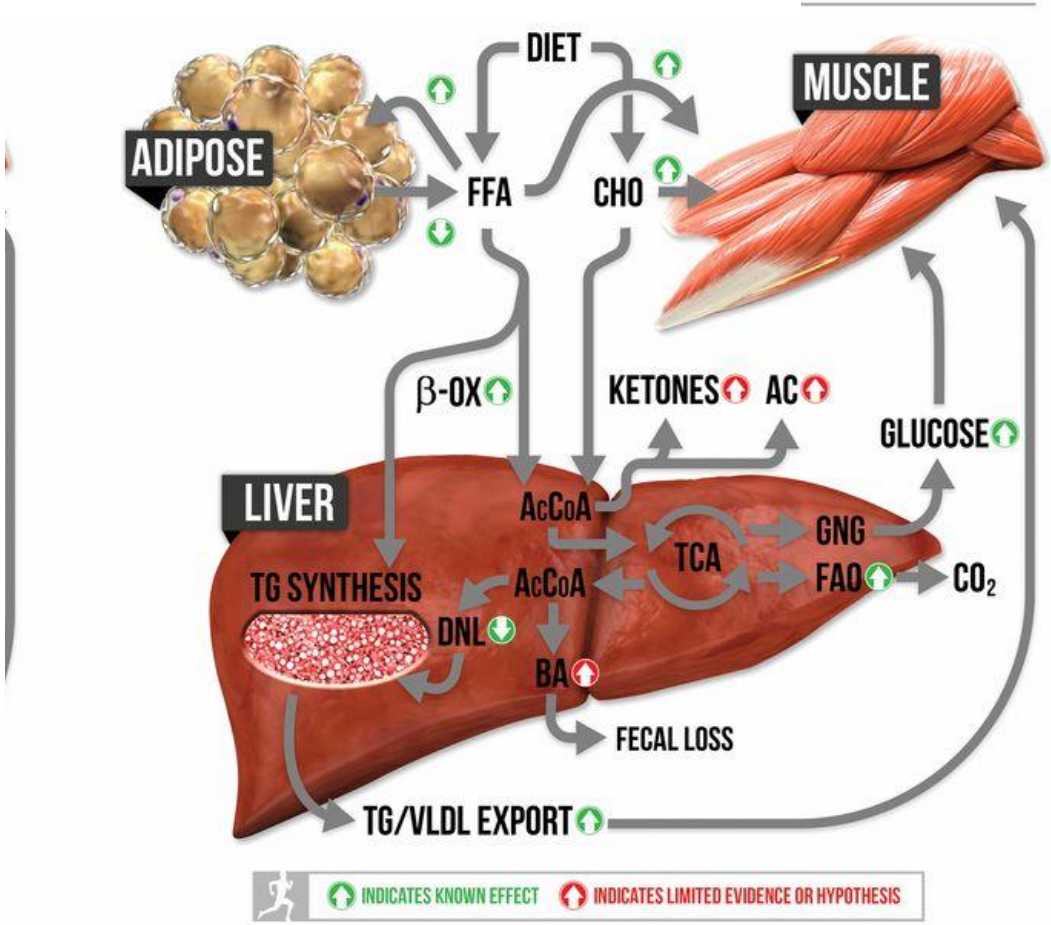
PERDIDA DE PESO 2,5%

# EJERCICIO FISICO


↓ KYNA
↓ Estrés/Depresión
CTSB, Irisina → BDNF
↑ Función cognitva
Hueso
IGF-1, SPARC, IL-15
↑ Mineralización
↓ Miostatina
↑ Reparación
Hígado
IL-6 → hepatocitos
Metabolismo glucosa
IL-10 → células inmunes
↓ Inflamación
Tejido adiposo
IL-6, ANGPTL4 → adipocitos
↑ Lipólisis
IL-15, ANGPTL4 → endotelio
↓ Actividad Lipoprotein Lipasa
Irisina, BAIBA → adipocitos
↑ Termogénesis, tejido adiposo marrón
Meteorin-like → macrófagos
↑ Termogénesis
↓ Masa grasa
Células inmunes
IL-10 → células T
↓ Inflamación
IL-1RA → IL-1α/β
↓ Inflamación
CCL2 → monocito
↑ Atracción celular
IL-6 → macrófagos
↑ M2
GLP1
Tumor
IL-6, IL-15 → células NK
↑ Movilización
SPARC → células tumorales
↑ Apoptosis
Pancreas
IL-6 → células β
Secreción de insulina vía liberación GLP1
Intestino
IL-6 → Células L
↑ Liberación GLP1

# EFECTOS DEL EJERCICIO A NIVEL HEPATICO

-Promover la regulación a la baja de los genes y las proteínas en la vía del LDN
-Mejorar respiración mitocondrial
-Aumentar la capacidad gluconeogénica
-Degradación de los lípidos intrahepáticos
-Exportar de sustratos fuera del hígado mediante la cetogénesis, las acilcarnitinas, el colesterol y los ácidos biliares.



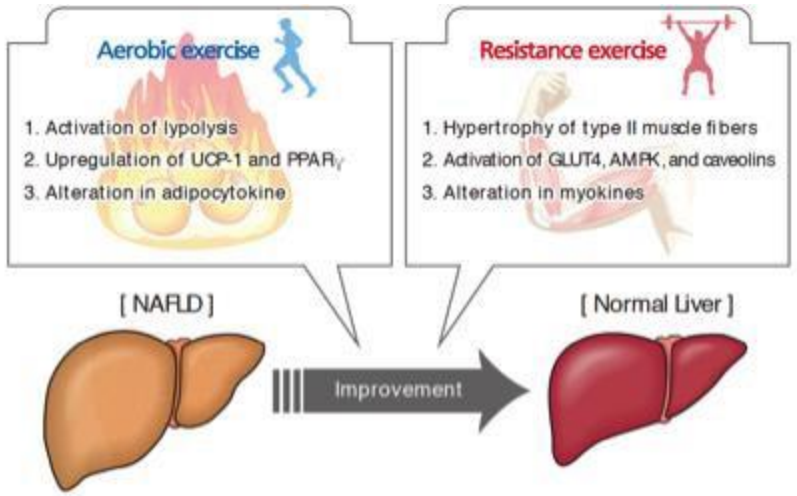

John P. Thyfault, and R. Scott Rector Diabetes 2020;69:517-524

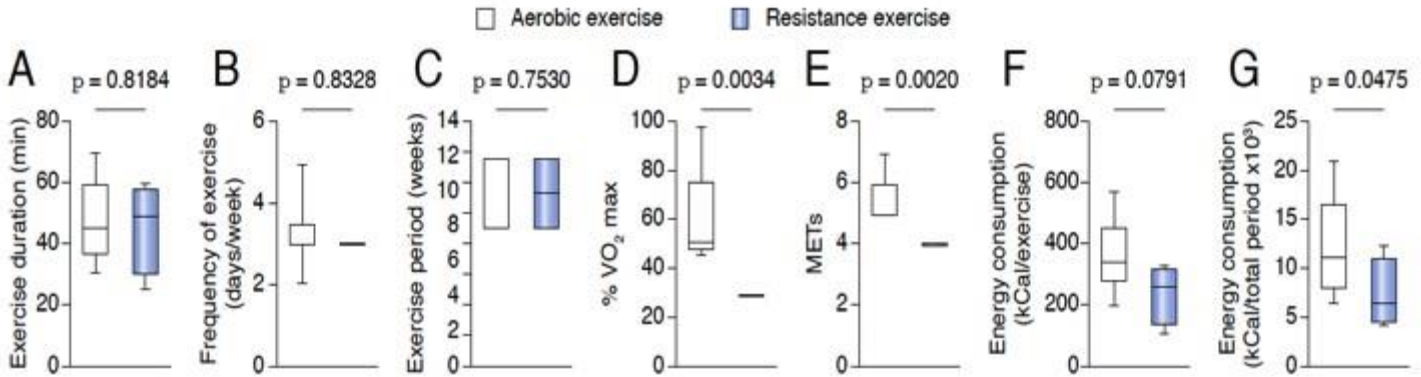


American Diabetes Association.

# Aerobic vs. resistance exercise in NAFLD: A systematic review

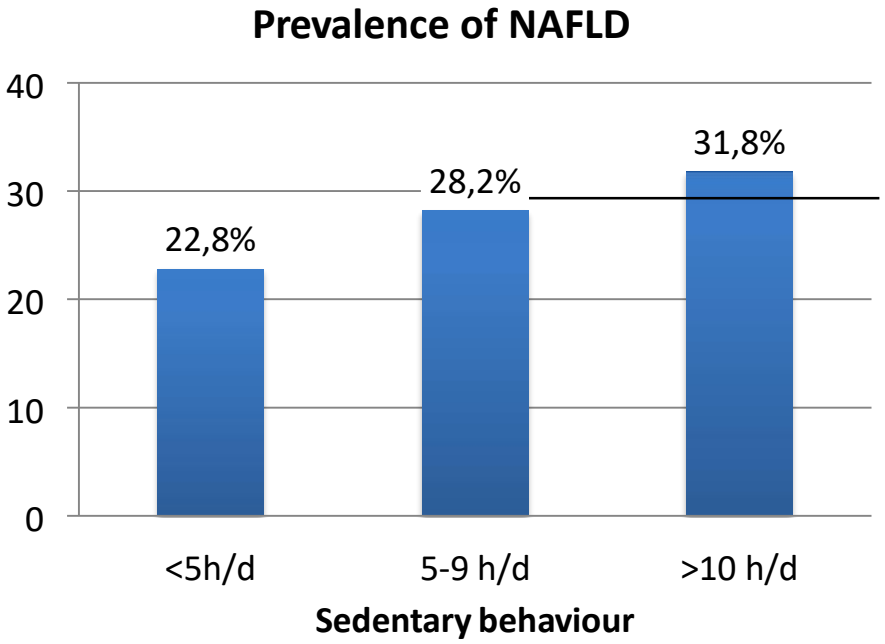
| | Aerobic exercise | Resistance exercise | p value |
|---|---|---|---|
| Number of protocols (number of articles) | 13 (9) | 4 (4) | |
| Number of enrolled subjects | 314 | 68 | |
| Age (years old) | 44.2 (15.2-61) | 52.0 (45.9-55.5) | 0.1064 |
| Sex (Male; %) | 63.45 | 100 | 0.6018 |
| BMI | 31 (27-36) | 32 (29-25) | 0.4190 |
| Body weight (kg) | 85 (69-107) | 94 (72-98) | 0.4953 |
| Dietary counseling (Yes) | 46.2% (6/13) | 25.0% (1/4) | 0.4522 |
| Changes in BMI | -1 (-4 to 1) | -0.5 (-1 to 0) | 0.4106 |
| Changes in ALT level | -12 (-56 to 4) | -15 (-19 to 0) | 0.5325 |
| Changes in Intrahepatic lipids (%) | -2 (-3 to 0) | -7.5 (-13 to -2) | 0.3150 |




Hashida R et al. J Hepatol 2017

# Sedentary behaviour & physical activity in NAFLD



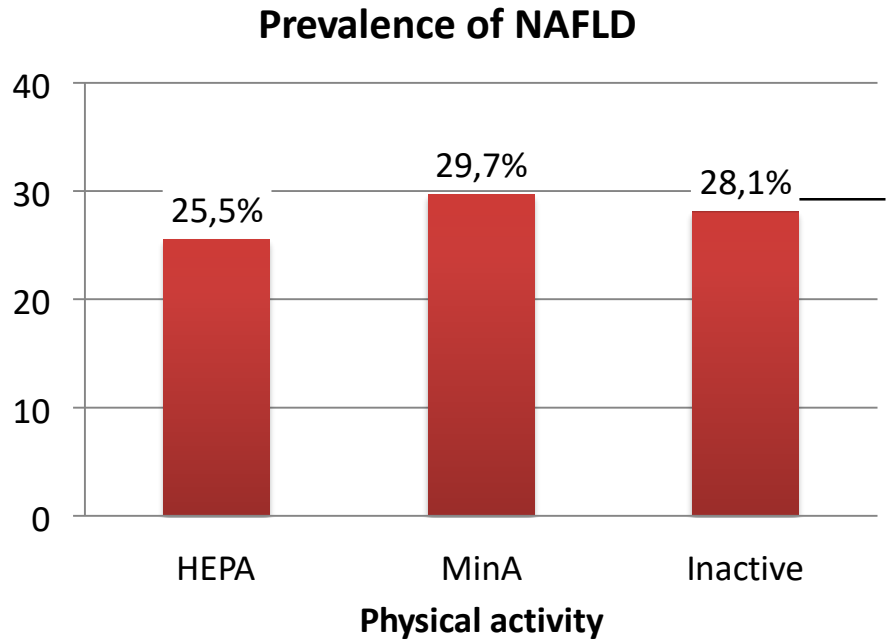
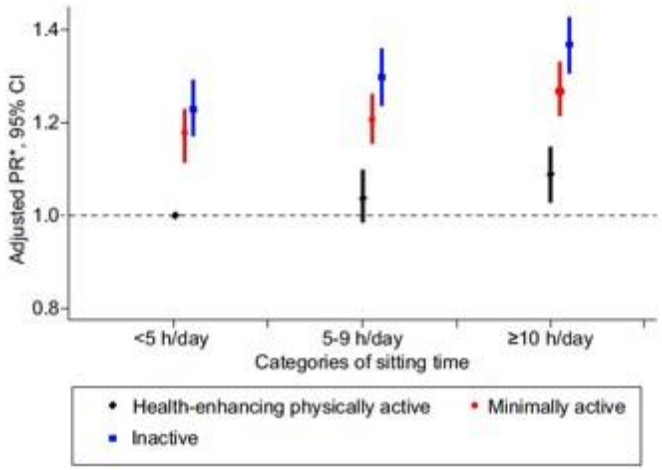




Table 2. Prevalence ratios[a] (95% CI) of non-alcoholic fatty liver disease (NAFLD) by sitting time and physi

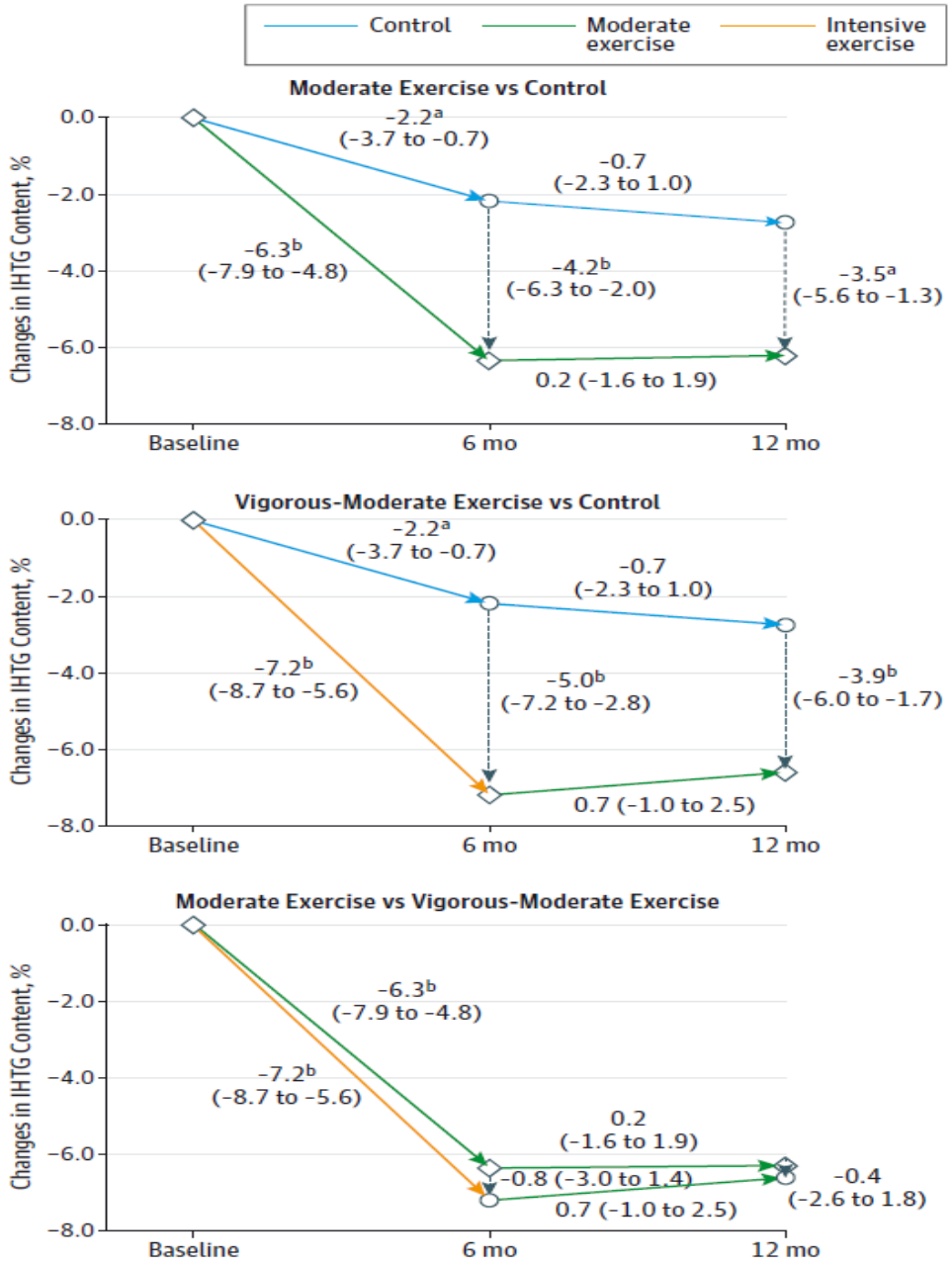
| | Number | Cases | Age-sex-adjusted PR[a] (95% CI) |
|---|---|---|---|
| Sitting time | | | |
| <5 h/day | 33,892 | 7724 | 1.00 (reference) |
| 5-9 h/day | 53,618 | 15,133 | 1.05 (1.02-1.07) |
| ≥10 h/day | 51,546 | 16,400 | 1.12 (1.09-1.14) |
| *p* value for trend | | | <0.001 |
| Physical activity level | | | |
| Inactive | 62,313 | 17,473 | 1.00 (reference) |
| Minimally active | 52,536 | 15,619 | 0.94 (0.92-0.95) |
| HEPA | 24,207 | 6165 | 0.81 (0.79-0.83) |
| *p* value for trend | | | <0.001 |




Ryu S et al. J Hepatol 2015

# ¿Importa la intensidad o la frecuencia del ejercicio?

INDIVIDUALIZAR
ADAPTAR
VALORACION INICIAL




Zhang et al, JAMA Intern Med 2016

# ¿CUANDO DEBEMOS RECURRIR AL TRATAMIENTO FARMACOLÓGICO?

# nvasive prediction of histological NASH resolution

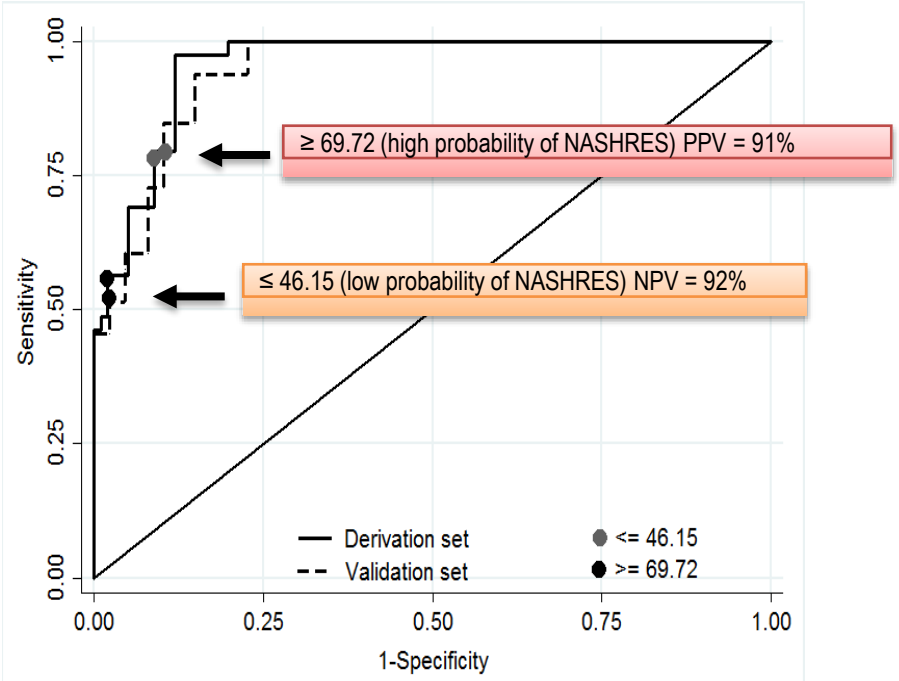
**Development and validation of a noninvasive model "NASH resolution model" -- NASHRES**

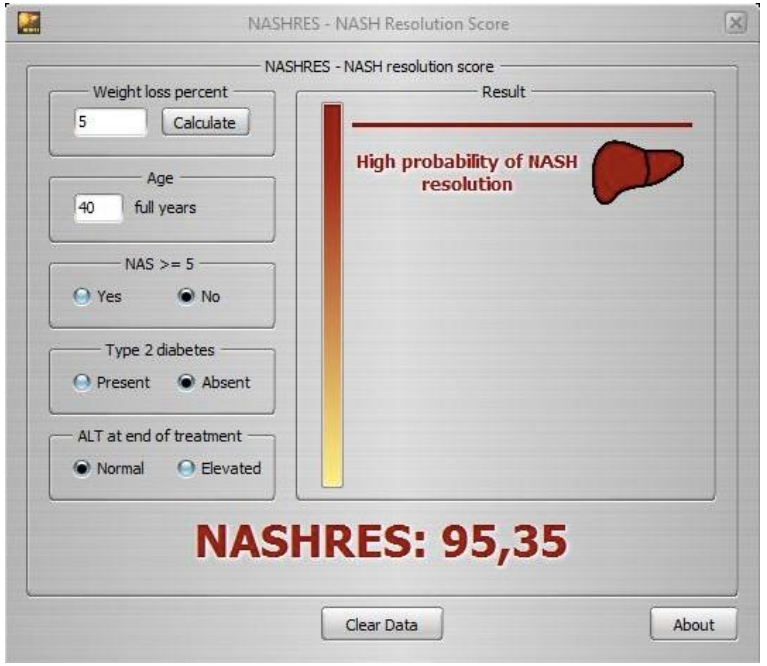
261 patients treated with lifestyle intervention and paired liver biopsies (140 in derivation set / 121 in temporary validation set)

***NASHRES formula for calculating NASH resolution probability**: EXP (0.047 + 0.972 x **weight loss** + 2.194 x normal levels of **ALT** (EOT) – 3.076 x **type 2 diabetes** – 2.376 x **NAS ≥ 5** – 0.102 x **age**) / (1 + EXP (0.047 + 0.972 x weight loss + 2.194 x normal levels of ALT (EOT) – 3.076 x type 2 diabetes – 2.376 x NAS ≥ 5 – 0.102 x age)) x 100.*

NASH
F >=2

**AUC in derivation (0.96) and validation (0.95) sets**



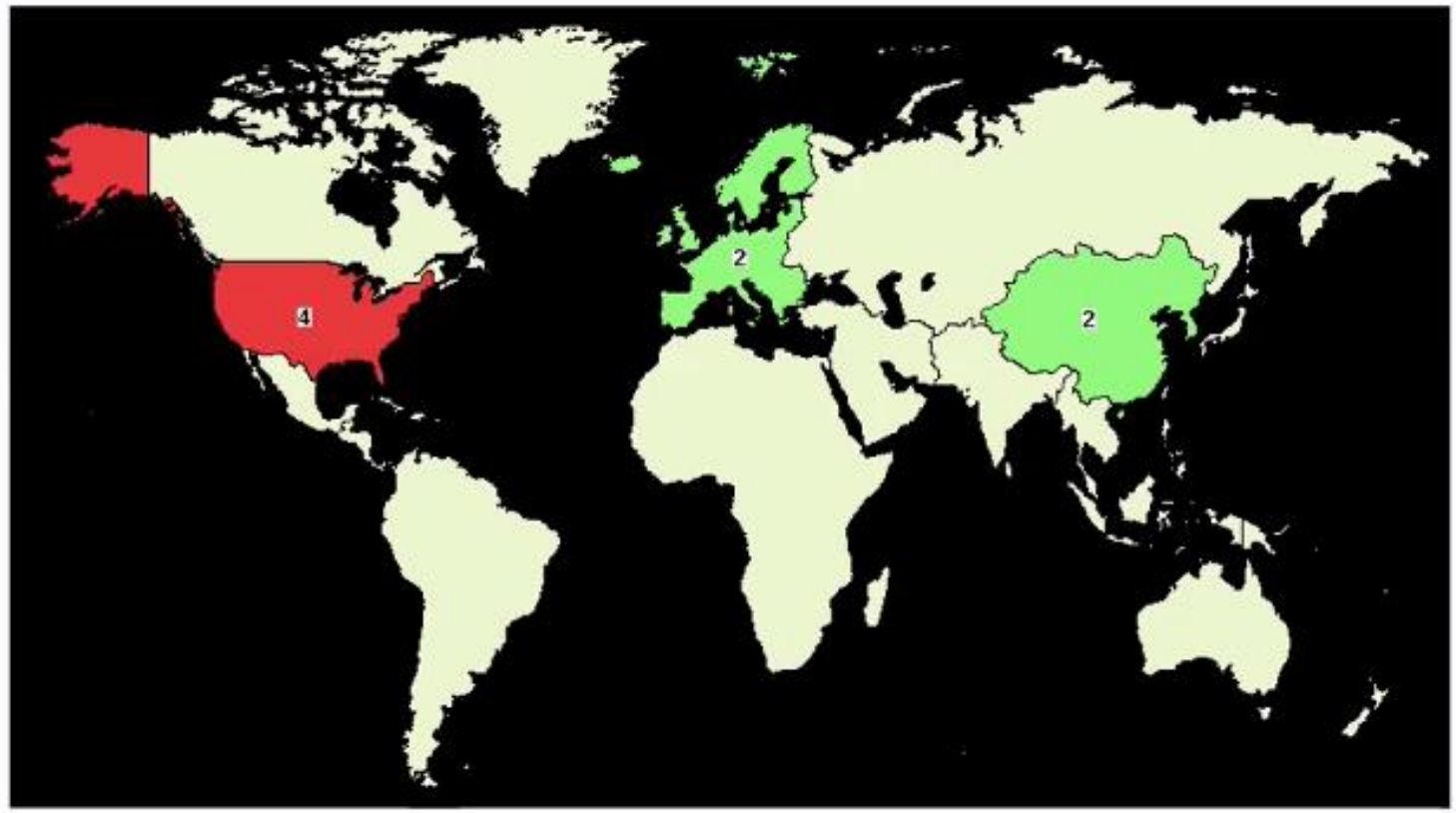




***A cutoff ≥ 69.72 accurately predict NASH resolution (0.96) and reversal of fibrosis (0.86)***

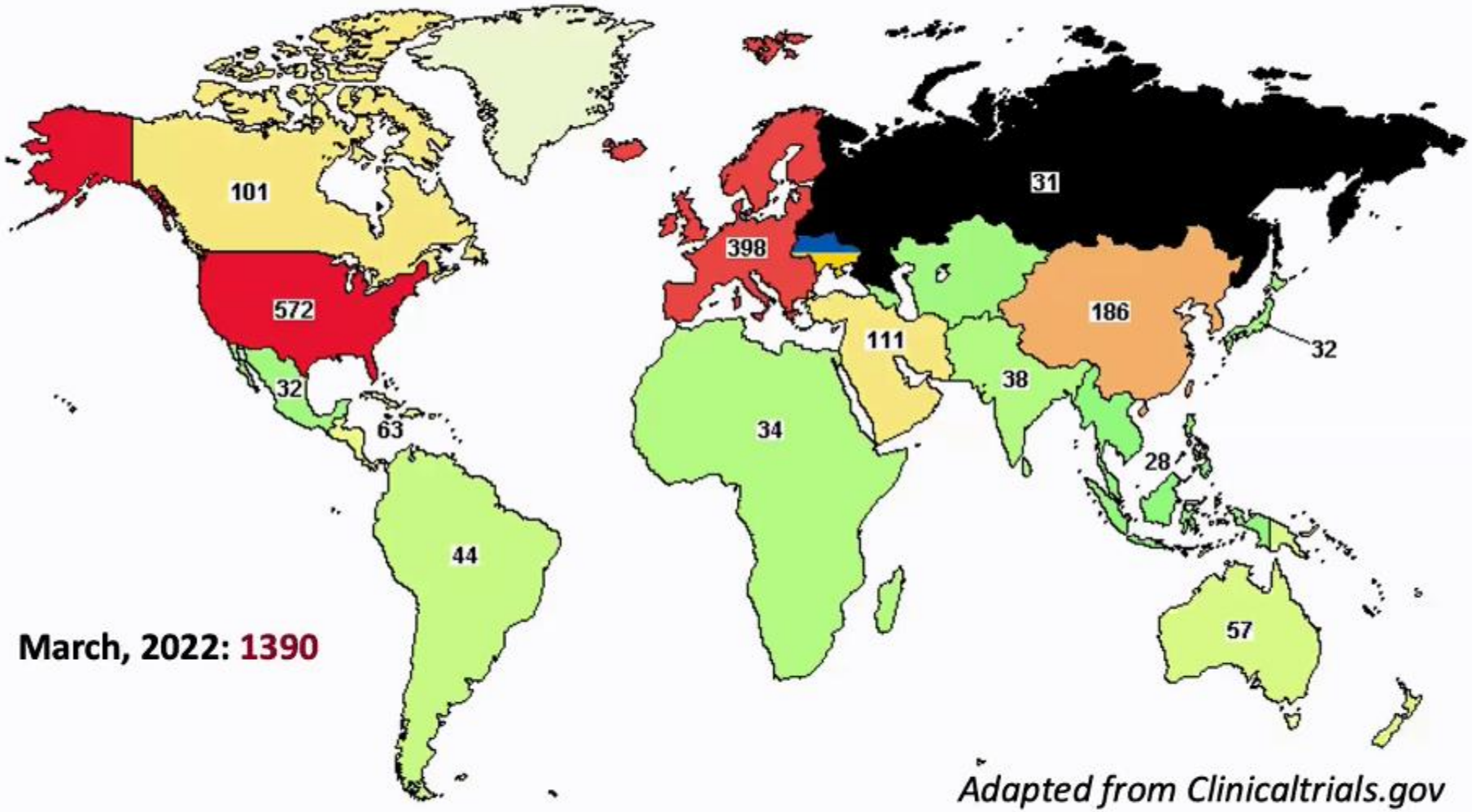
Vilar-Gomez, Romero-Gomez, Hepatology 2016 + EASL 2016

# Active clinical trials in NASH

**2013: 8**



# Active clinical trials in NASH




**March, 2022: 1390**

*Adapted from Clinicaltrials.gov*

Colors indicate the number of studies with locations in that region

Least — Most

Labels give the exact number of studies

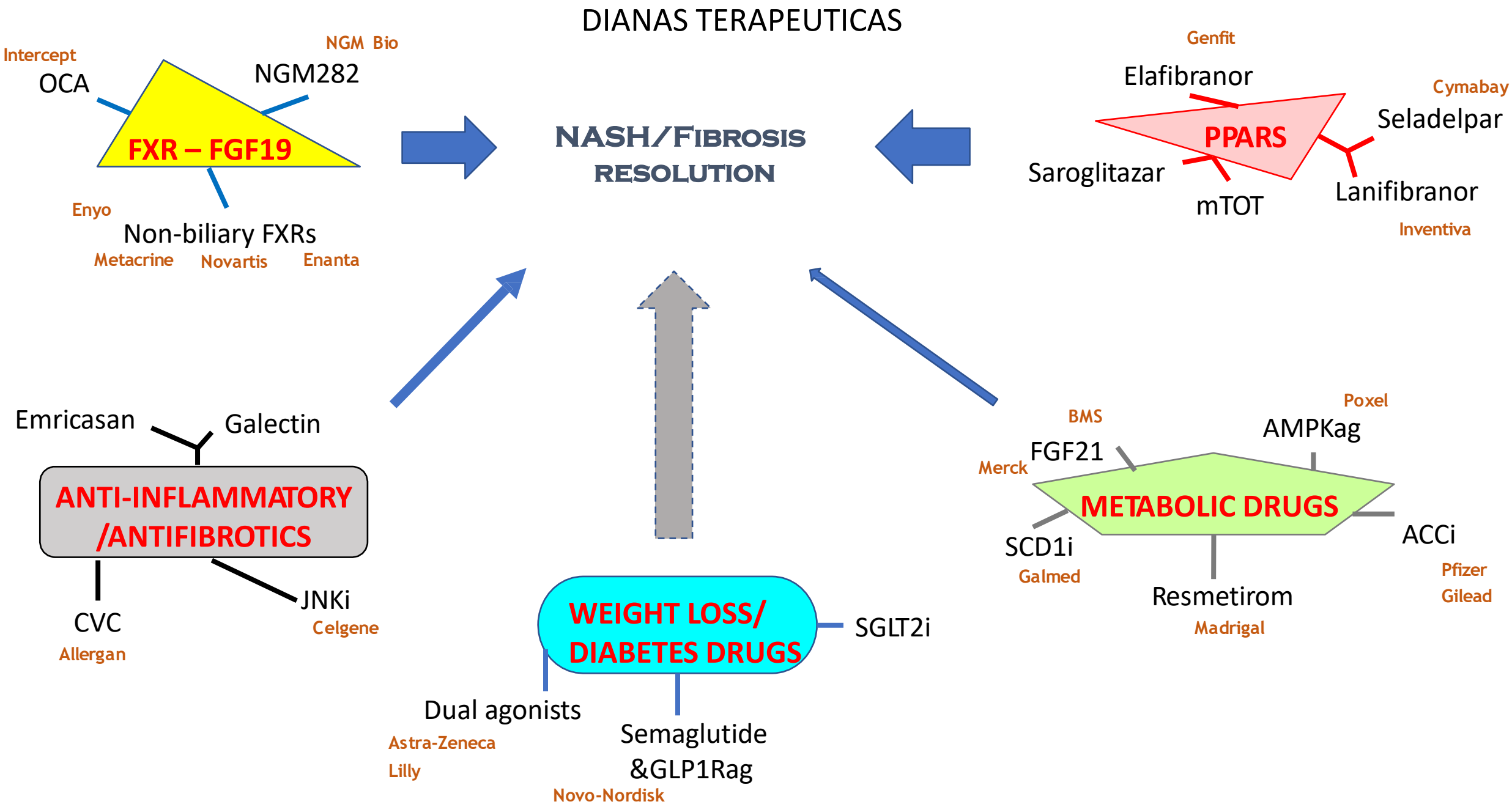

# PROBLEMAS ENSAYOS CLINICOS

DIANAS TERAPEUTICAS

SUBGRUPOS EHMET

PLACEBO

END POINT


DIANAS TERAPEUTICAS
Intercept
OCA
NGM Bio
NGM282
FXR – FGF19
Enyo
Non-biliary FXRs
Metacrine
Novartis
Enanta
NASH/FIBROSIS RESOLUTION
Genfit
Elafibranor
Cymabay
Seladelpar
PPARS
Saroglitazar
mTOT
Lanifibranor
Inventiva
Emricasan
Galectin
ANTI-INFLAMMATORY /ANTIFIBROTICS
CVC
Allergan
JNKi
Celgene
WEIGHT LOSS/ DIABETES DRUGS
SGLT2i
Dual agonists
Astra-Zeneca
Lilly
Semaglutide &GLP1Rag
Novo-Nordisk
BMS
FGF21
Merck
Poxel
AMPKag
METABOLIC DRUGS
SCD1i
Galmed
ACCi
Pfizer
Gilead
Resmetirom
Madrigal

Serum metabolomes of 535 patients with biopsy-proven NAFLD

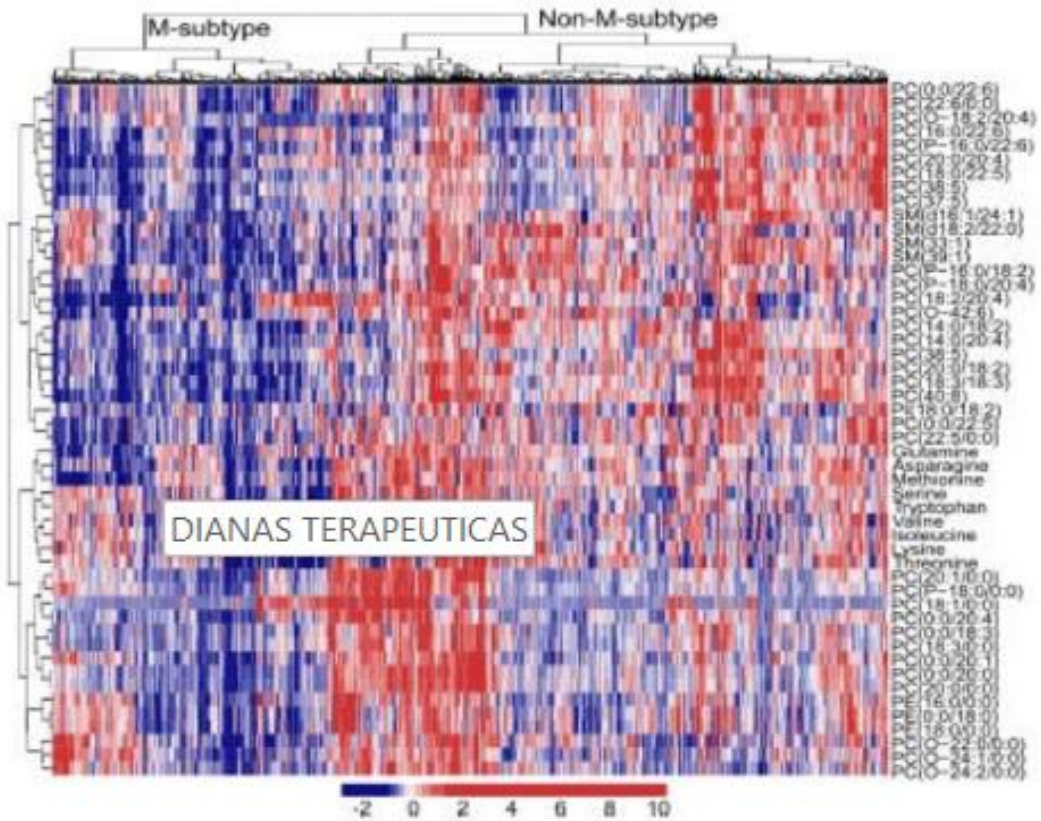
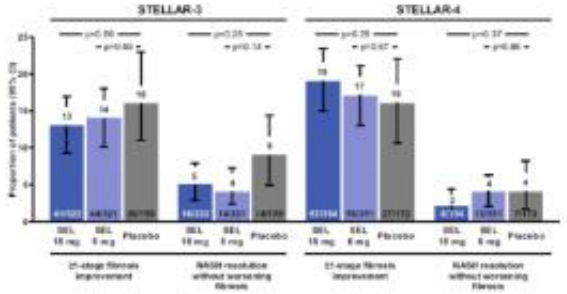



**Figure 4. Identification of a subset of NAFLD patients showing a *Mat1a*-KO serum metabolomic profile**

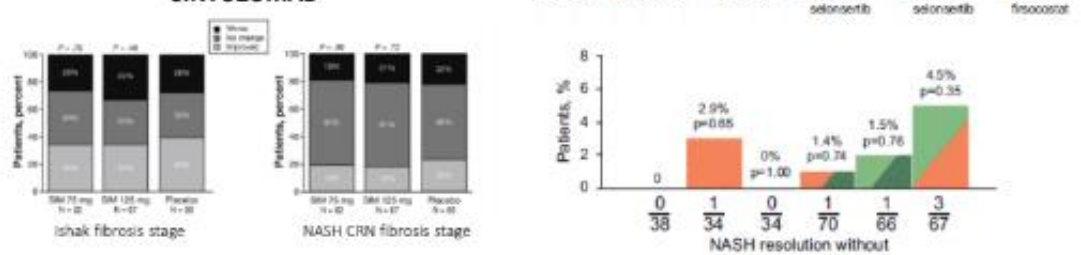
Alonso C et al. Gastroenterology 2017


## SELONSERTIB

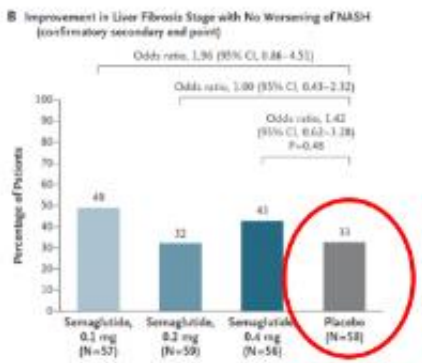



## CILOFEXOR / FIRSOCOSTAT

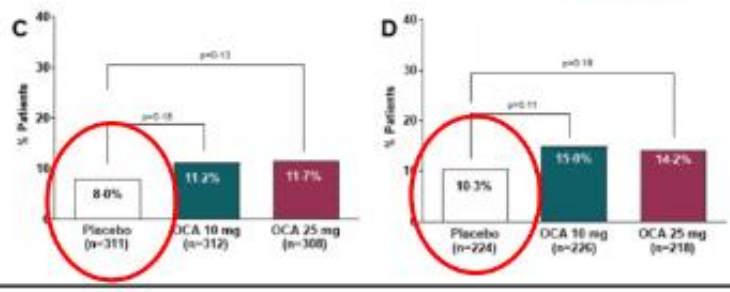
## SINTUZUMAB



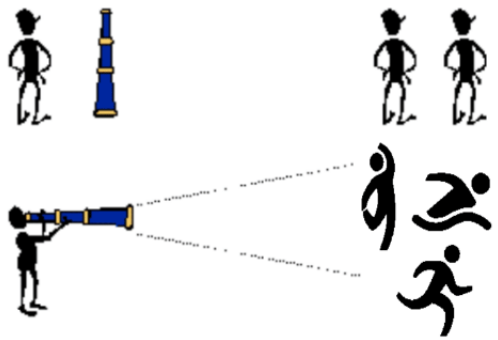

## SEMAGLUTIDE




## OBETICHOLIC ACID




Hawthorne effect



# Association between significant improvements in PDFF, serum biomarkers and NASH histology

| Intervention/MoA | PDFF | ALT | GGT | ELF | Pro-C3 | NASH res | Fibrosis |
|---|---|---|---|---|---|---|---|
| Weight loss/N/A | + | + | + | | | + | + |
| Pio/PPARγ | +MRS, not predictive | + | + | | | +* | + |
| OCA/FXR (FLINT/REG) | -, >30% OR 5 reduce NAS | + | + | | | -/+* | + |
| Resmiterom/THRβ | + | + | + | + | + | + | +/-** |
| Aldafermin/FGF19 | + | + | + | | + | +† | +† |
| Aramchol | | + | + | | | + | - |
| Semaglutide | + | + | + | + | | + | - |
| Lanifibranor/**PanPPAR** | | + | | | + | + | + |
| Seladelpar/PPAR-delta | - | + | | | | - | - |
| EFX | + | + | | + | + | +† | +† |
| Tropifexor | + | + | | | | - | -** |

*By gestalt diagnosis, ** By Histoindex only, †**small numbers**

- PIOGLITAZONA, VIT E
- AGONISTAS R FX
- AGONISTAS GLP1-R
- AGONISTA PPAR
- AGONSIOTAS THR -BETA

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Pioglitazone, Vitamin E, or Placebo for Nonalcoholic Steatohepatitis

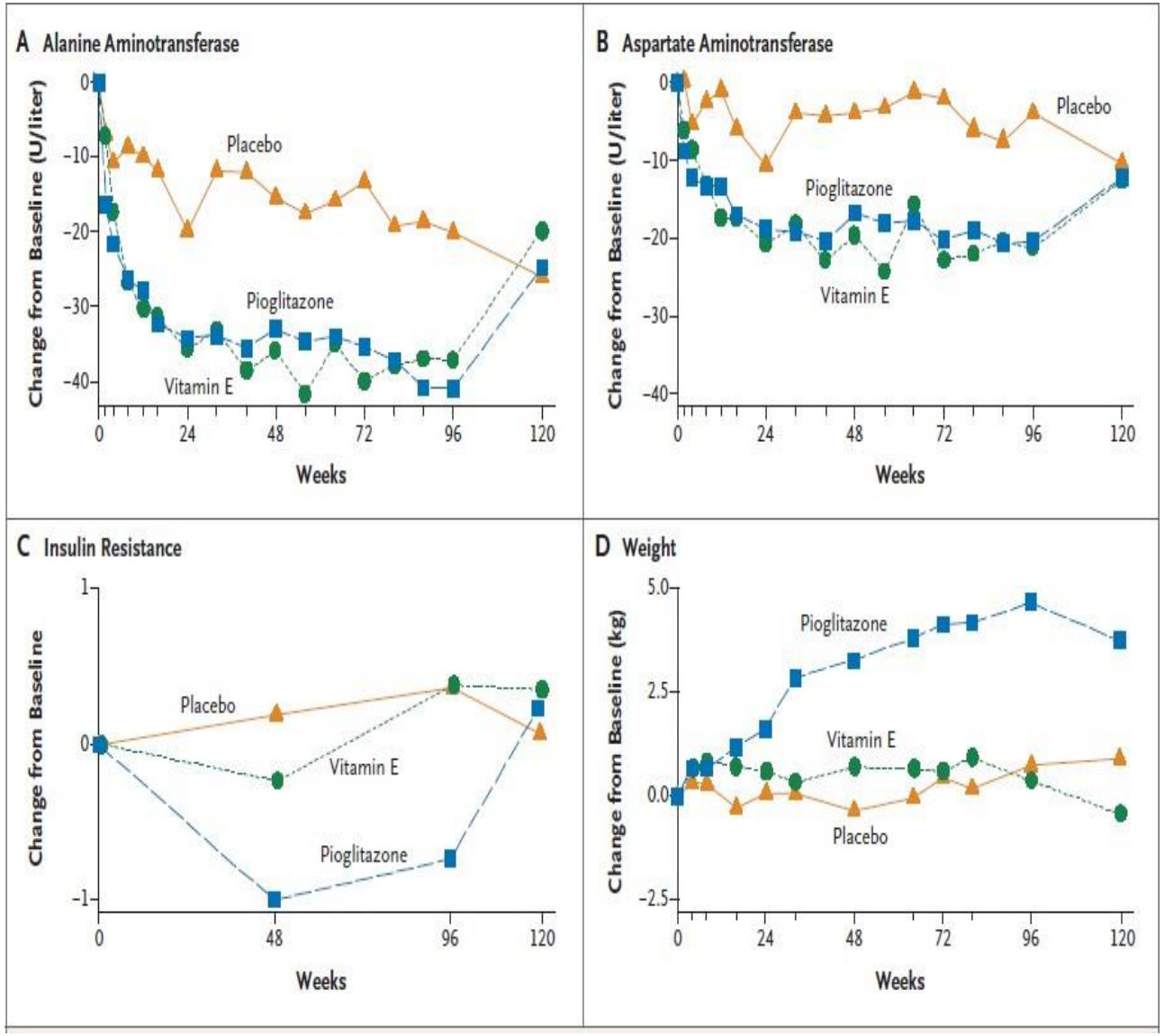
Arun J. Sanyal, M.D., Naga Chalasani, M.B., B.S., Kris V. Kowdley, M.D., Arthur McCullough, M.D., Anna Mae Diehl, M.D., Nathan M. Bass, M.D., Ph.D., Brent A. Neuschwander-Tetri, M.D., Joel E. Lavine, M.D., Ph.D., James Tonascia, Ph.D., Aynur Unalp, M.D., Ph.D., Mark Van Natta, M.H.S., Jeanne Clark, M.D., M.P.H., Elizabeth M. Brunt, M.D., David E. Kleiner, M.D., Ph.D., Jay H. Hoofnagle, M.D., and Patricia R. Robuck, Ph.D., M.P.H., for the NASH CRN*

**Table 2. Primary Outcome and Changes in Histologic Features of the Liver after 96 Weeks of Treatment.**

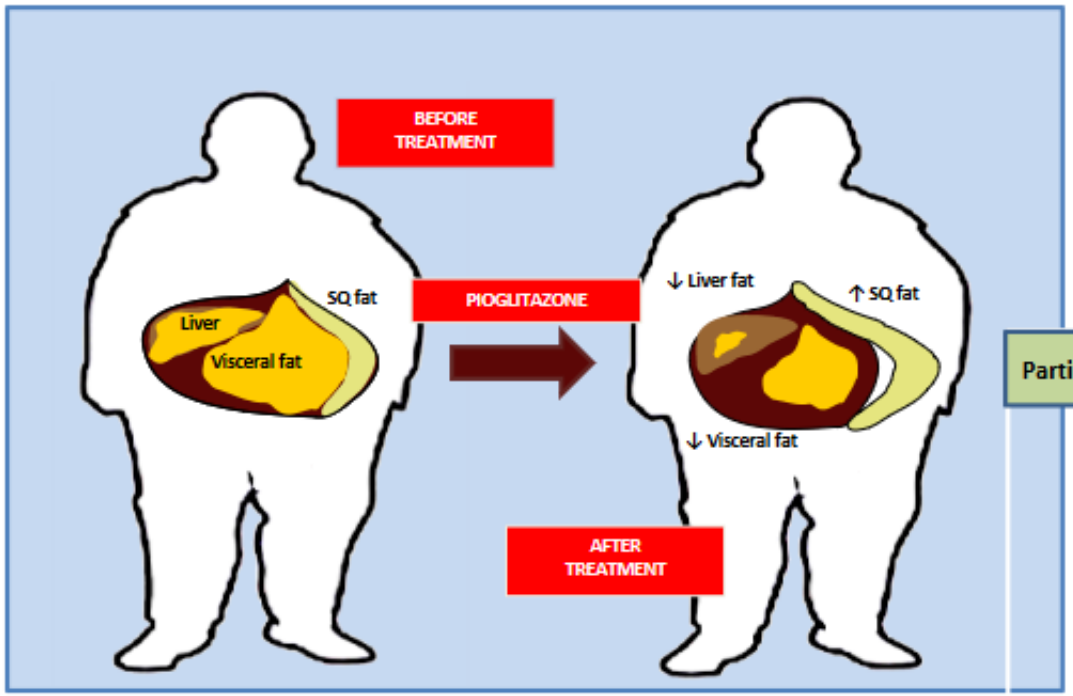
| Variable | Placebo | Vitamin E | Pioglitazone | P Value* | |
|---|---|---|---|---|---|
| | | | | Vitamin E vs. Placebo | Pioglitazone vs. Placebo |
| **Primary outcome†** | | | | | |
| No. of subjects randomly assigned | 83 | 84 | 80 | | |
| Subjects with improvement (%) | 19 | 43 | 34 | 0.001 | 0.04 |
| **Changes from baseline in histologic features** | | | | | |
| No. of subjects with biopsy specimens at baseline and 96 wk | 72 | 80 | 70 | | |
| Steatosis | | | | | |
| Subjects with improvement (%) | 31 | 54 | 69 | 0.005 | <0.001 |
| Mean change in score | −0.1 | −0.7 | −0.8 | <0.001 | <0.001 |
| Lobular inflammation | | | | | |
| Subjects with improvement (%) | 35 | 54 | 60 | 0.02 | 0.004 |
| Mean change in score | −0.2 | −0.6 | −0.7 | 0.008 | <0.001 |
| Hepatocellular ballooning | | | | | |
| Subjects with improvement (%) | 29 | 50 | 44 | 0.01 | 0.08 |
| Mean change in score | −0.2 | −0.5 | −0.4 | 0.03 | 0.01 |
| Total NAFLD activity score (mean change) | −0.5 | −1.9 | −1.9 | <0.001 | <0.001 |
| Fibrosis‡ | | | | | |
| Subjects with improvement (%) | 31 | 41 | 44 | 0.24 | 0.12 |
| Mean change in score | −0.1 | −0.3 | −0.4 | 0.19 | 0.10 |
| Resolution of definite nonalcoholic steatohepatitis (% of subjects) | 21 | 36 | 47 | 0.05 | 0.001 |

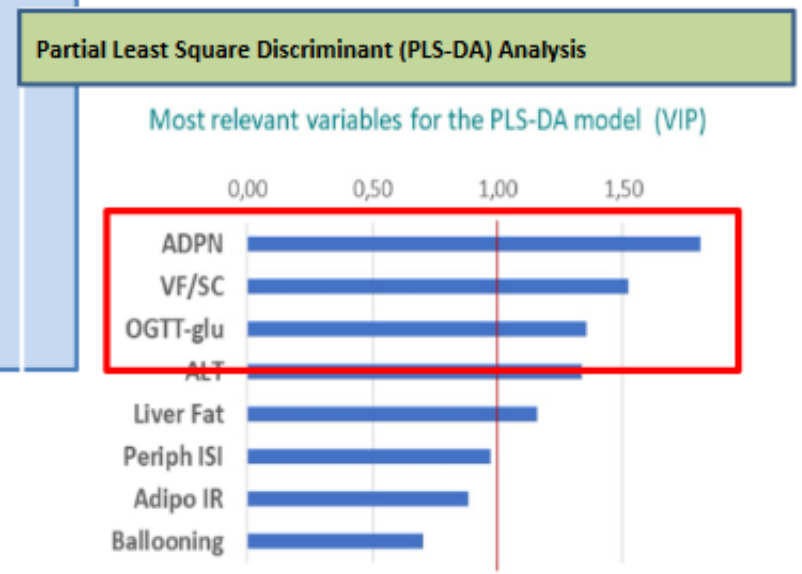
Sanyal et al, NEJM 2010

## PIVENS Trial: Phase 3 (Vitamina E - Pioglitazona)



# Pioglitazone Increases Adiponectin (improves adipose tissue function) and Reduces Visceral and Hepatic Fat in Subjects with NASH




Gastaldelli/Cusi et al,
June 2021 (doi: 10.1111/liv.15005)

# ACIDO OBETICOLICO

**Lipid and glucose Metabolism**

[redacted]

↓ VLDL production

[redacted]

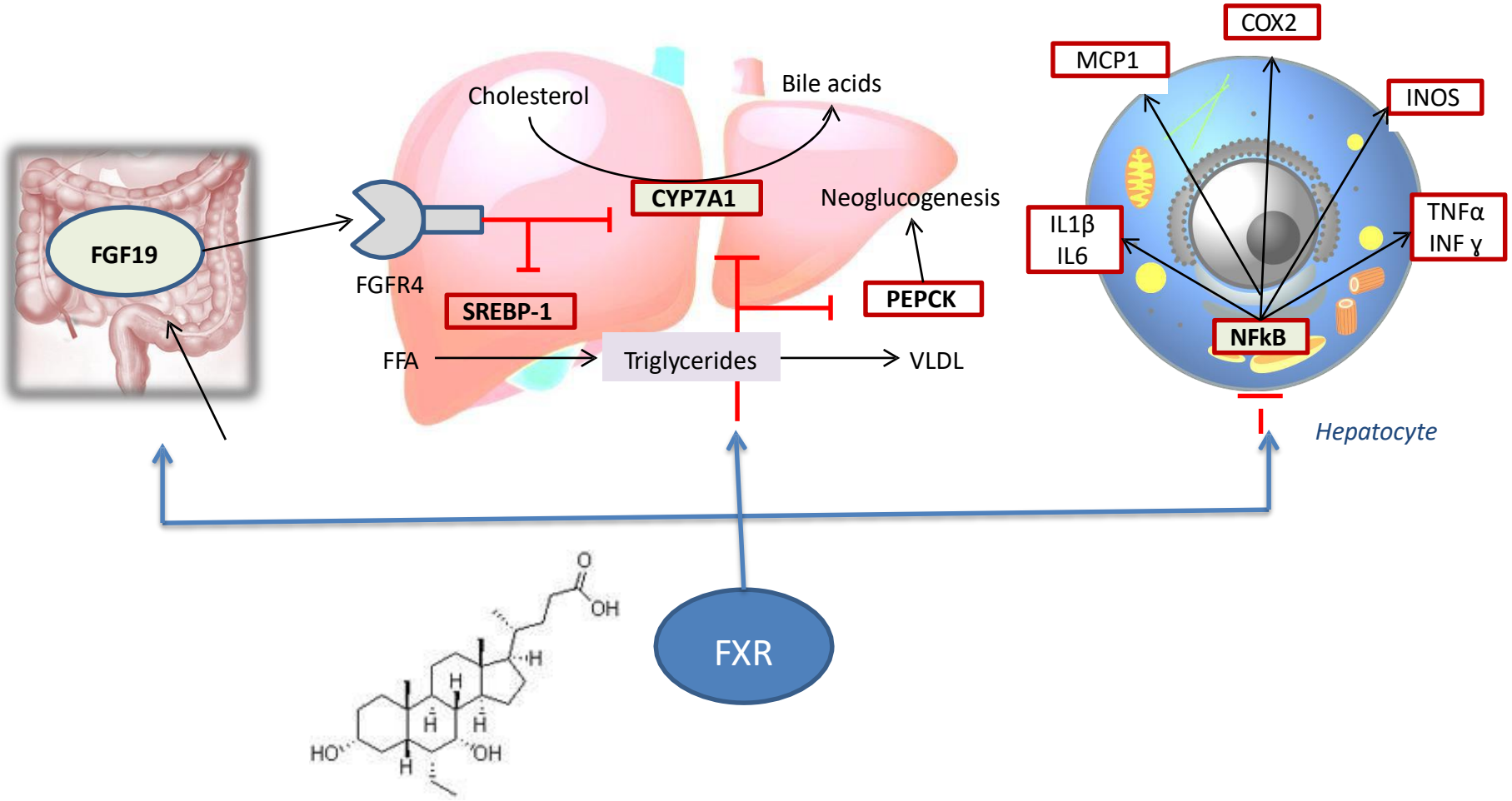
↓ Neoglucogenesis in the liver

**Inflammation**

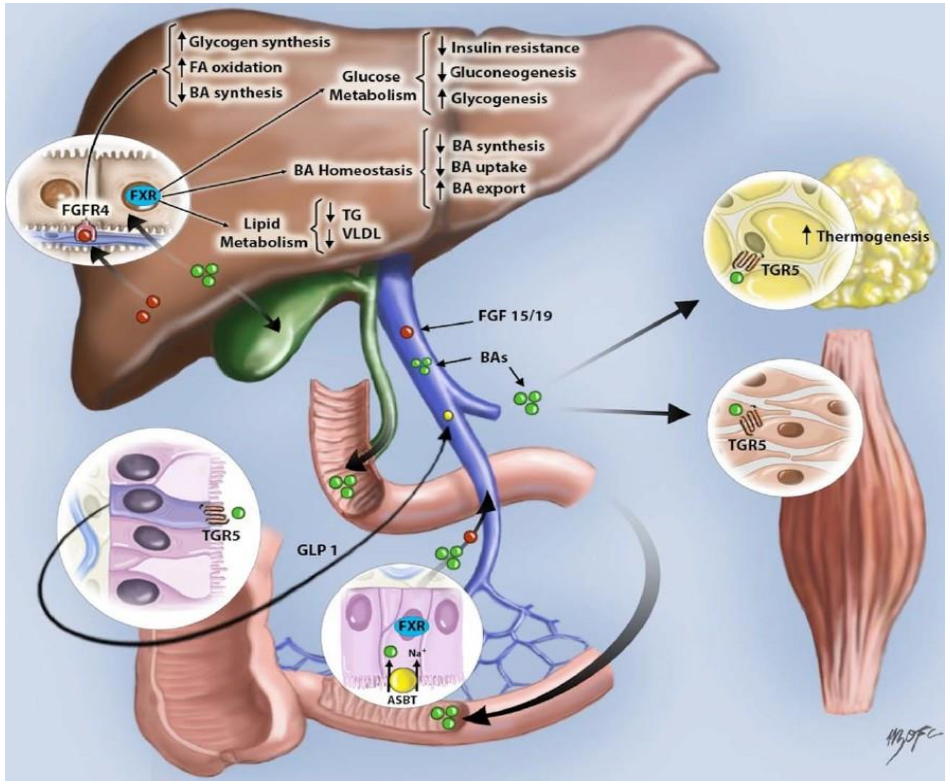
[redacted]

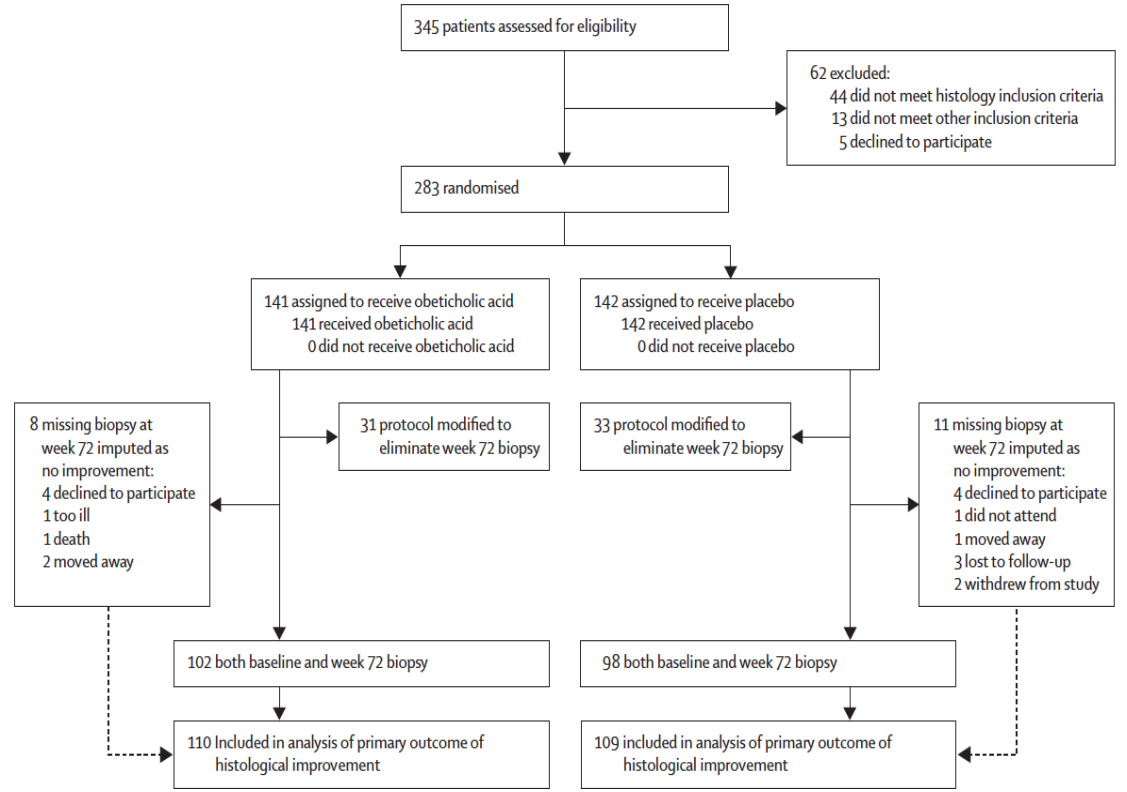
↓ TNFα, INF ɣ, IL1, IL17

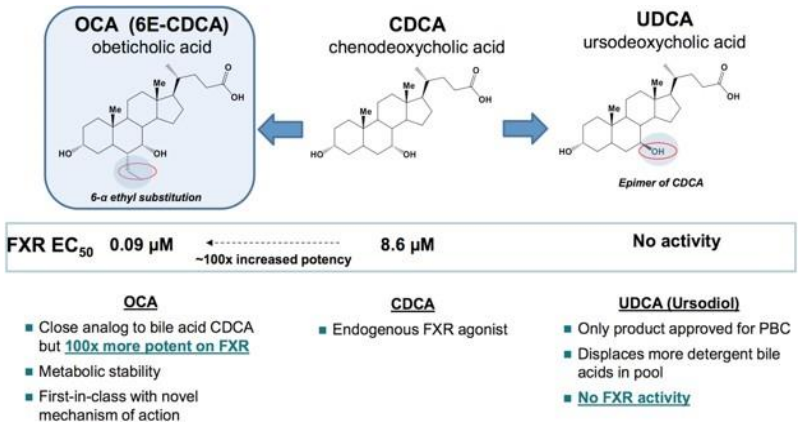
[redacted]



# ACIDO OBETICOLICO



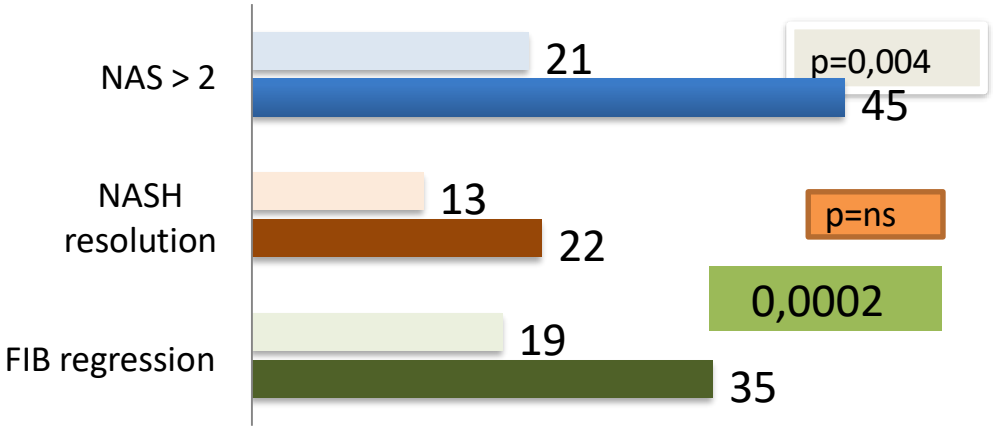



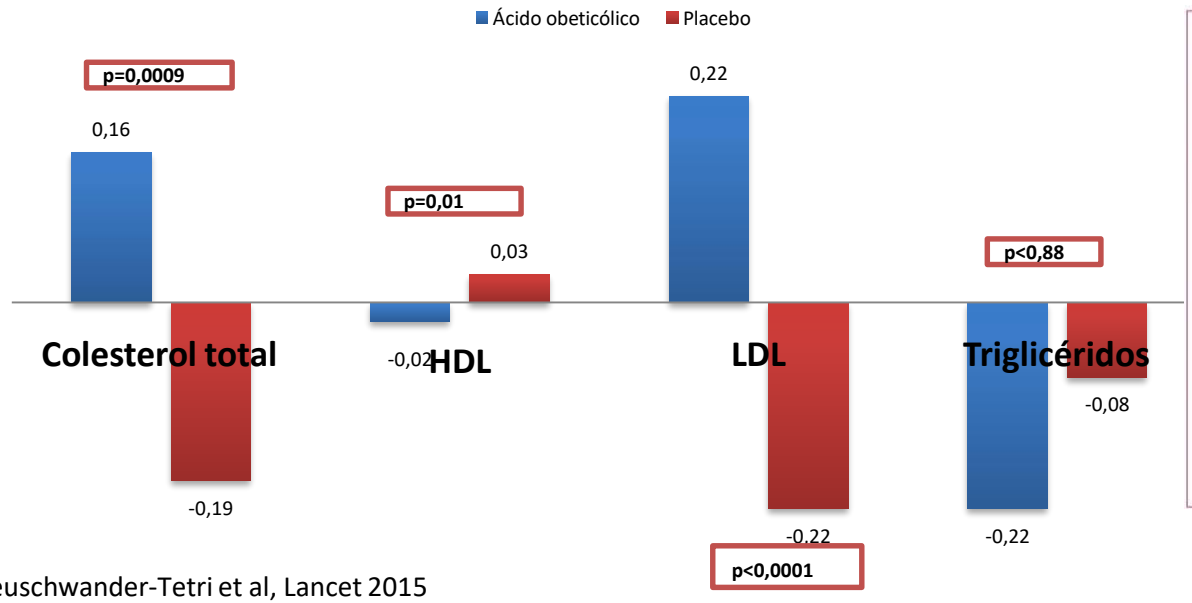

Neuschwander--Tetri et al, Lancet 2015

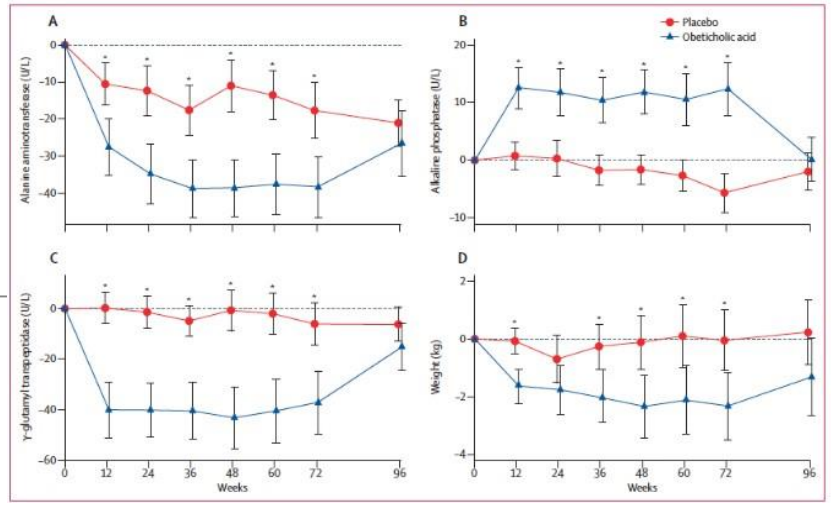
# ACIDO OBETICOLICO

**N**=283
n=141 Obeticholic acid (25 mg/d)
n=142 placebo 72 w.



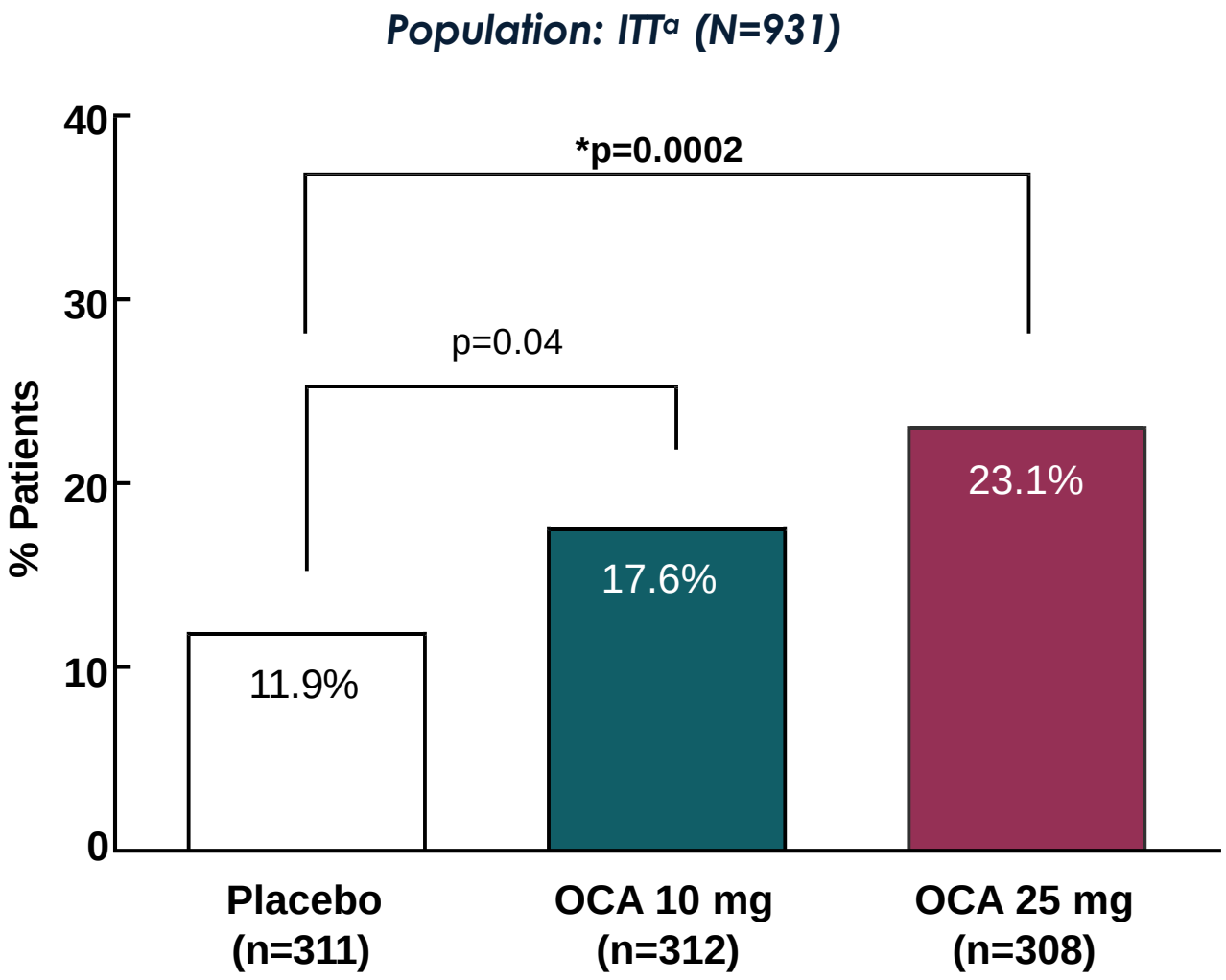

**N=219 NASH (110 OCA vs. 109 PLC)**

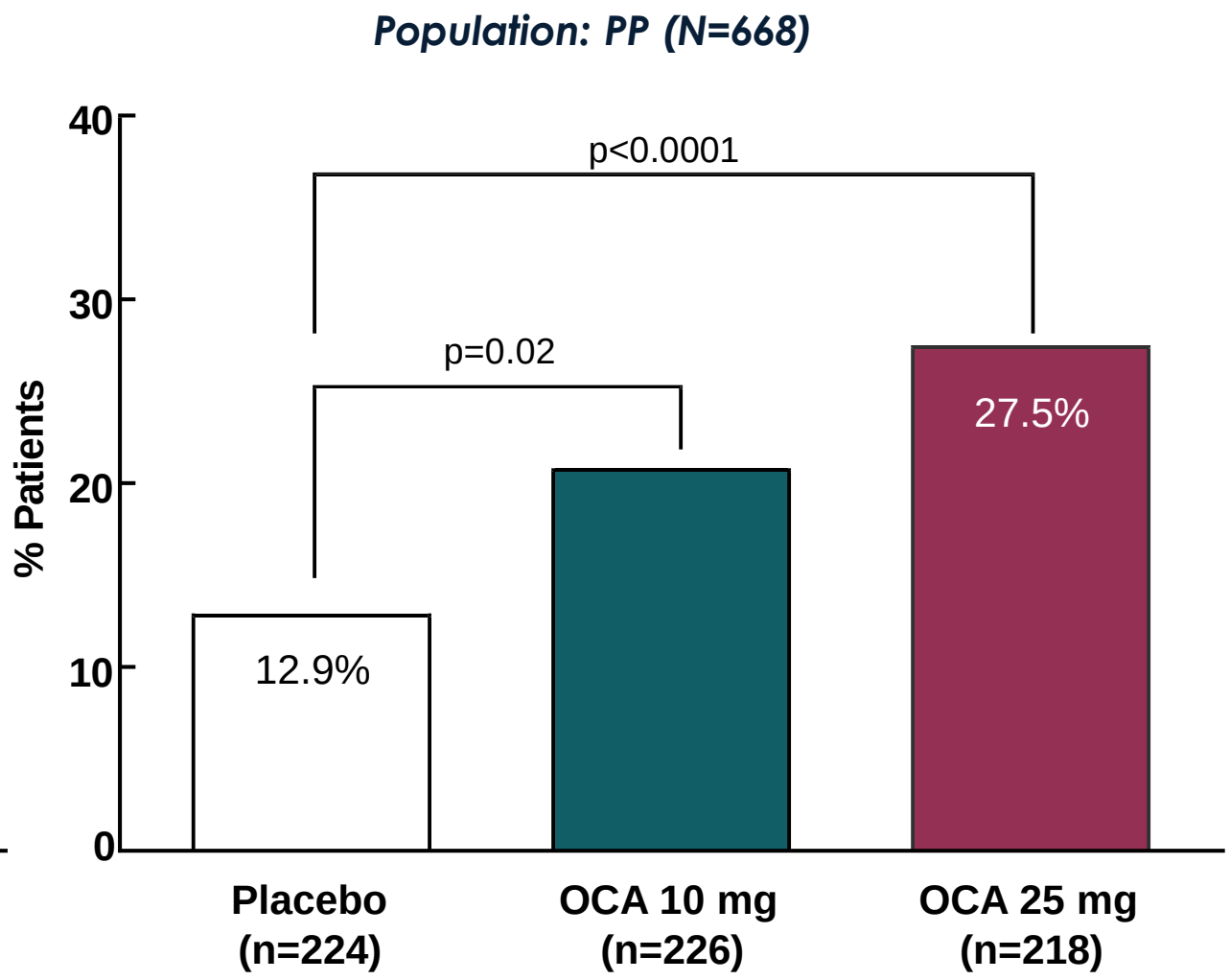



Neuschwander-Tetri et al, Lancet 2015

Primary endpoint definition: improvement in fibrosis by ≥1 stage (NASH CRN) with no worsening of lobular inflammation, hepatocellular ballooning or steatosis.




Study success was defined as achievement of one of the two primary endpoints evaluated in the Month 18 Interim Analysis.
*Statistically significant in accordance with the statistical analysis plan agreed with the FDA. All other p values are nominal.

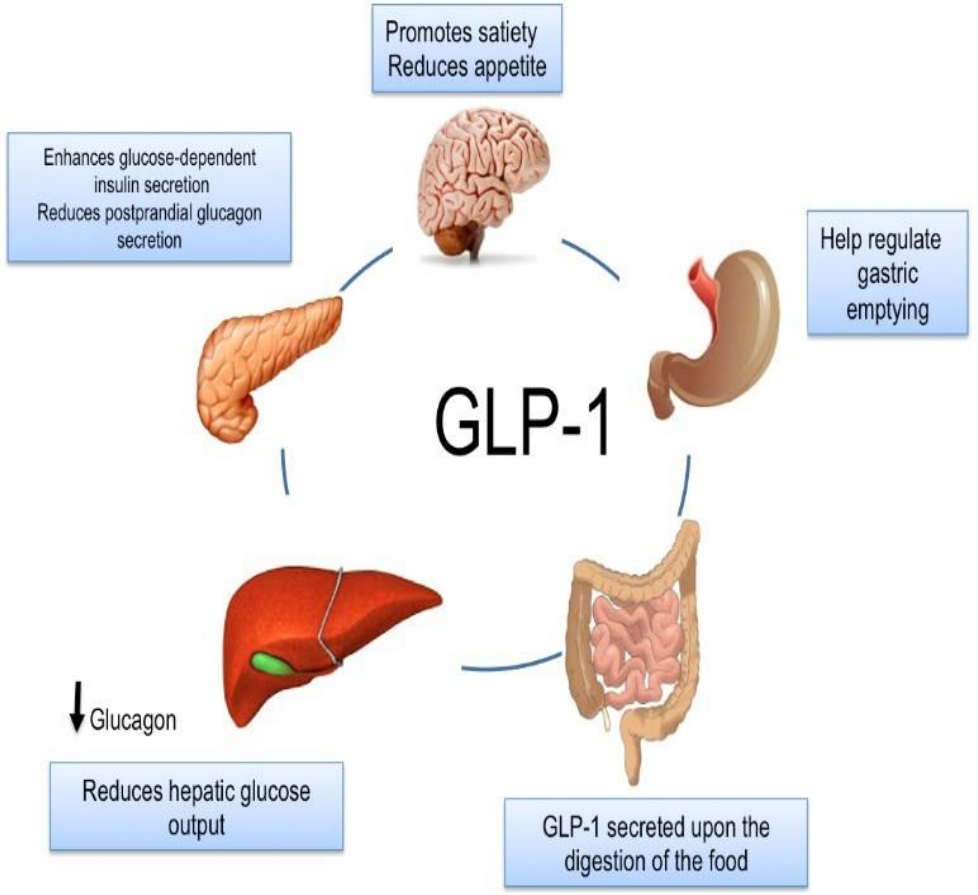
*Presented at EASL, April 10-14, 2019; Vienna, Austria*

# LEAN Study: Phase 2 (Liraglutide)

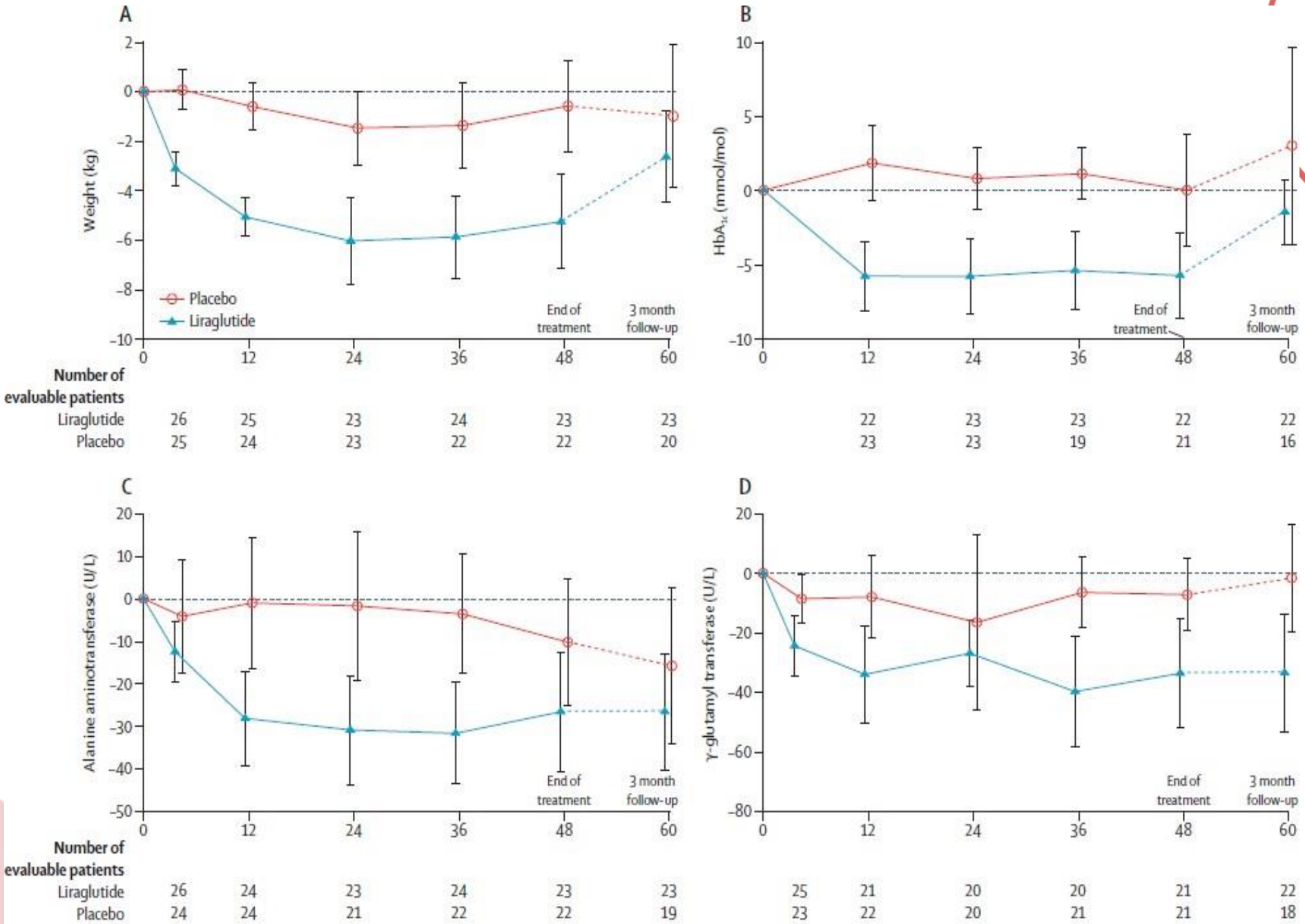
## Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study

*Matthew James Armstrong, Piers Gaunt, Guruprasad P Aithal, Darren Barton, Diana Hull, Richard Parker, Jonathan M Hazlehurst, Kathy Guo, LEAN trial team*, George Abouda, Mark A Aldersley, Deborah Stocken, Stephen C Gough, Jeremy W Tomlinson, Rachel M Brown, Stefan G Hübscher, Philip N Newsome*

| | Liraglutide | Placebo | Relative risks or mean changes (95% CI) from baseline to 48 weeks (liraglutide vs placebo) | p value* |
|---|---|---|---|---|
| **Primary outcome** | | | | |
| Number of patients with paired liver biopsies | 23 | 22 | .. | .. |
| Patients with resolution of non-alcoholic steatohepatitis | 9 (39%) | 2 (9%) | 4·3 (1·0 to 17·7) | 0·019 |
| **Changes from baseline in histopathological parameters** | | | | |
| Total NAFLD activity score | | | | |
| Change in score | −1·3 (1·6) | −0·8 (1·2) | −0·5 (−1·3 to 0·3) | 0·24 |
| Patients with improvement | 17 (74%) | 14 (64%) | 1·2 (0·8 to 1·7) | 0·46 |
| Hepatocyte ballooning score | | | | |
| Mean change | −0·5 (0·7) | −0·2 (0·6) | −0·3 (−0·7 to 0·1) | 0·15 |
| Patients with improvement | 14 (61%) | 7 (32%) | 1·9 (1·0 to 3·8) | 0·05 |
| Steatosis | | | | |
| Change in score | −0·7 (0·8) | −0·4 (0·8) | −0·2 (−0·6 to 0·2) | 0·32 |
| Patients with improvement | 19 (83%) | 10 (45%) | 1·8 (1·1 to 3·0) | 0·009 |
| Lobular inflammation | | | | |
| Change in score | −0·2 (0·6) | −0·2 (0·5) | −0·01 (−0·3 to 0·3) | 0·97 |
| Patients with improvement | 11 (48%) | 12 (55%) | 0·9 (0·5 to 1·6) | 0·65 |
| Kleiner fibrosis stage | | | | |
| Change in score | −0·2 (0·8) | 0·2 (1·0) | −0·4 (−0·8 to 0·1) | 0·11 |
| Patients with improvement | 6 (26%) | 3 (14%) | 1·9 (0·5 to 6·7) | 0·46† |
| Patients with worsening | 2 (9%) | 8 (36%) | 0·2 (0·1 to 1·0) | 0·04† |




**Armstrong et al, Lancet 2016**


A
Weight (kg)
2
0
−2
−4
−6
−8
−10
Placebo
Liraglutide
End of treatment
3 month follow-up
0
12
24
36
48
60
Number of evaluable patients
Liraglutide 26 25 23 24 23 23
Placebo 25 24 23 22 22 20
B
HbA1c (mmol/mol)
10
5
0
−5
−10
End of treatment
3 month follow-up
0
12
24
36
48
60
22 23 23 22 22
23 23 19 21 16
C
Alanine aminotransferase (U/L)
20
10
0
−10
−20
−30
−40
−50
End of treatment
3 month follow-up
0
12
24
36
48
60
Number of evaluable patients
Liraglutide 26 24 23 24 23 23
Placebo 24 24 21 22 22 19
D
γ-glutamyl transferase (U/L)
20
0
−20
−40
−60
−80
End of treatment
3 month follow-up
0
12
24
36
48
60
25 21 20 20 21 22
23 22 20 21 21 18

# GLP-1RAs in NAFLD

**Table 1.** Summary of studies on the effect of GLP-1RA on hepatic steatosis by imaging or liver histology in patients with NAFLD

Primary outcome: relative reduction in liver fat on imaging[a]

| Author | GLP1-RA | n | Study design | Weight change[b] | Reduction in liver fat content |
|---|---|---|---|---|---|
| Vanderheiden et al, 2016 | Liraglutide | 71 | RCT | ↓ 2.2% | ↓ 31% |
| Feng et al, 2017 | Liraglutide | 87 | Open label | ↓ 6.4% | ↓ 19% |
| Petit et al, 2017 | Liraglutide | 68 | Open label | ↓ 4.4% | ↓ 19% |
| Frossing et al, 2018 | Liraglutide | 72 | RCT | ↓ 5.7% | ↓ 32% |
| Kuchay et al, 2020 | Dulaglutide | 52 | Op | ↓ 2.6% | ↓ 20% |

[Sin título]

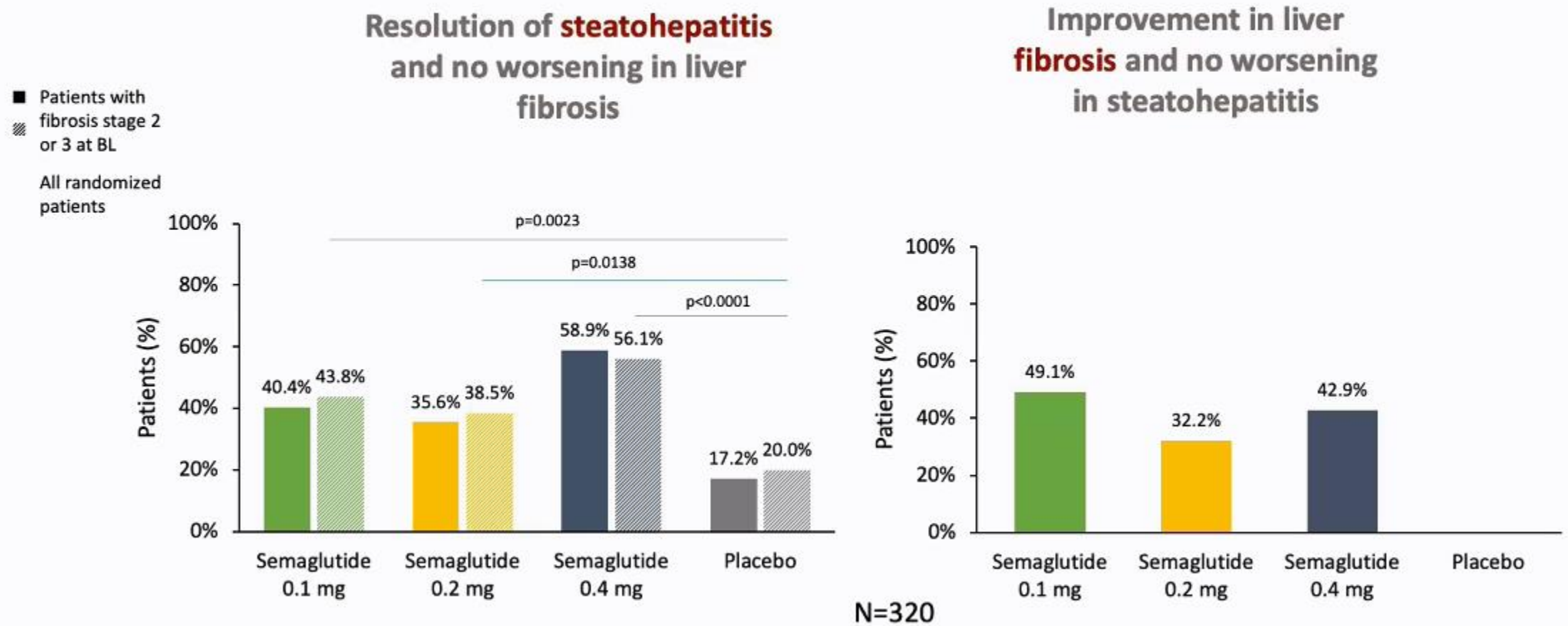
Primary outcome: percentage of patients with resolution of NASH (by liver histology)[c]

| Author | GLP1-RA | n | Study design | Weight change[b] | NASH resolution |
|---|---|---|---|---|---|
| Armstrong et al, 2016 | Liraglutide | 52 | RCT | ↓ 4.8% | 30% |
| Newsome et al, 2020 | Semaglutide | 320 | RCT | ↓ 4%-12% | 19%-42% |

Studies with a minimal treatment period of ≥24 weeks and ≥50 patients. Arrows indicate statistically significant changes vs comparator.
Abbreviations: GLP-1RA, glucagon-like peptide-1 receptor agonist; NAFLD, nonalcoholic fatty liver disease; RCT, randomized controlled trial.
[a] Placebo or comparator subtracted change in hepatic steatosis.
[b] Placebo or comparator subtracted weight loss.
[c] Placebo-subtracted change in number of patients with resolution of NASH.

Chandani, Cusi and Kadiyala. JCEM October 2021
(https://doi.org/10.1210/clinem/dgab578)

# Efficacy and Safety of Semaglutide SC QD vs PBO in patients with NASH

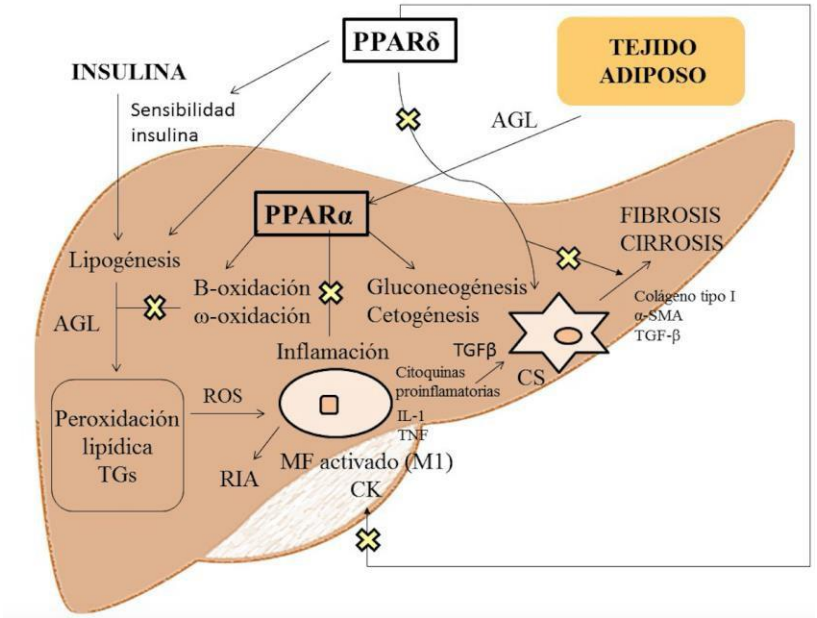



Newsome PN, et al. *NEJM* 2021 ;384(12):1113-1124.

# Dual PPARa/d Agonists

PPAR$\alpha$ ← **ELAFIBRANOR** → PPAR$\delta$

- Fatty acid oxidation
- TG lowering
- HDL raising
- Antiinflammatory




- Lipoprotein metabolism
- Glucose homeostasis
- Energy metabolism
- Antiinflammatory

Improvement of **glucose homeostasis** & **insulin sensitivity**

Favorable effects on **plasma lipids**

**GFT-505**

Improvement of markers of **liver dysfunction**

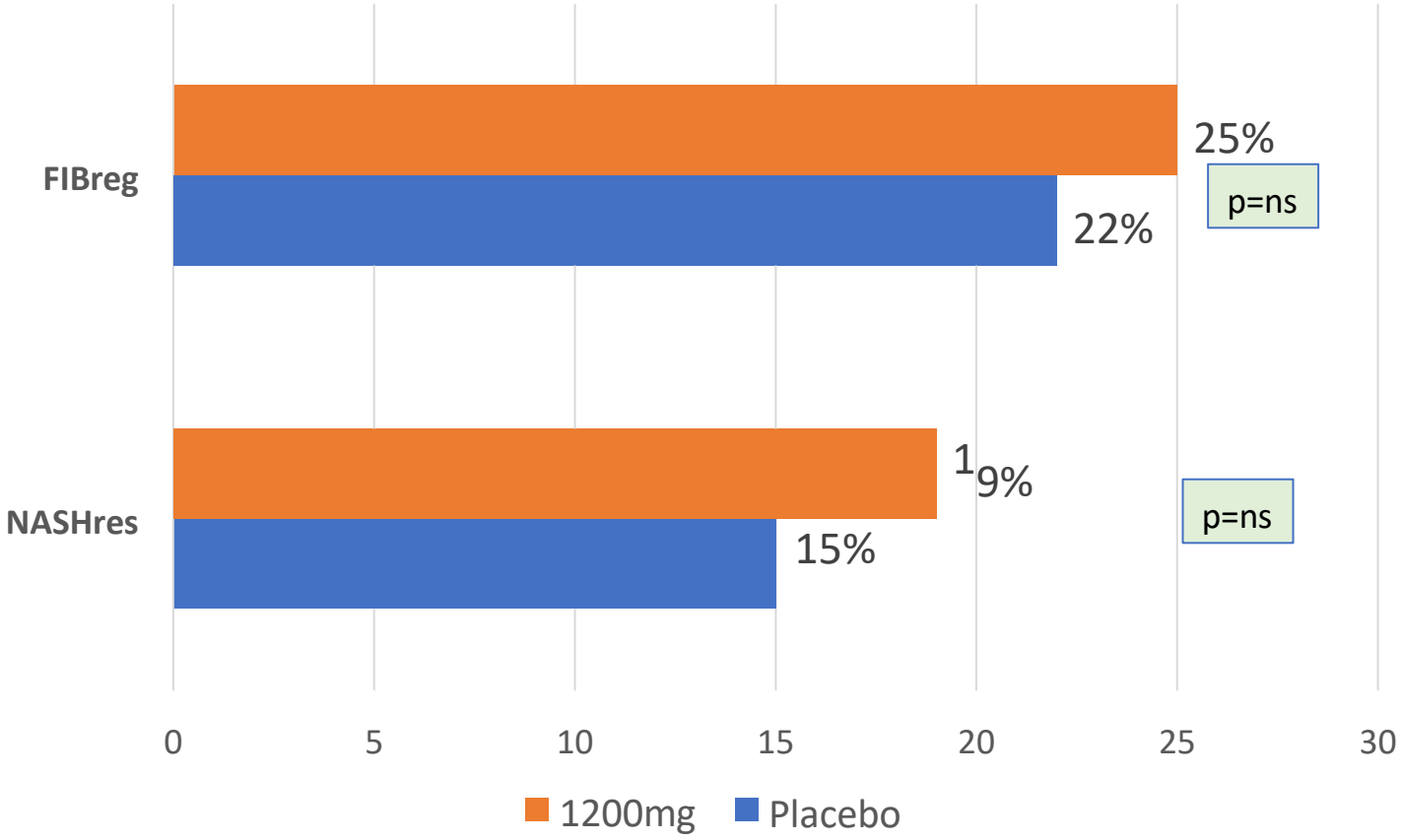
**Absence of safety concern**, Absence of PPAR deleterious effect

**Anti-inflammatory** properties

# Dual PPAR Agonists

## ELAFIBRANOR

N=1070 F2-F3 NASH patients
Placebo (n=535)
Elafibranor 120 mg (n=535)




Did not decrease of insulin, fasting glucose and glycated haemoglobin (HB1AC), triglycerides in comparison with placebo.

Press release Genfit 11 May 2020

247 PACIENTES
6 MESES
NO CIRROTICOS
Fase 2b
800 mg vs 1200 mg vs placebo

RESEARCH SUMMARY

# A Randomized, Controlled Trial of the Pan-PPAR Agonist Lanifibranor in NASH

Francque SM et al. DOI: 10.1056/NEJMoa2036205

CLINICAL PROBLEM

Management options for nonalcoholic steatohepatitis (NASH) are limited. Peroxisome proliferator–activated receptors (PPARs) are key for regulating metabolism, inflammation, and fibrogenesis. In preclinical studies, the pan-PPAR agonist lanifibranor showed promise against markers of disease activity in NASH, but its efficacy remains unknown.

CLINICAL TRIAL

**Design:** A phase 2b, double-blind, randomized, placebo-controlled trial evaluated the efficacy and safety of lanifibranor in patients with noncirrhotic NASH with severe disease activity.

**Intervention:** 247 adults with biopsy-confirmed, noncirrhotic, highly active NASH were randomly assigned to receive oral lanifibranor (800 mg or 1200 mg) or placebo once daily for 24 weeks. At baseline, all participants had a score of 3 or higher on the SAF-A (the activity part of the Steatosis, Activity, Fibrosis [SAF] scoring system that incorporates ballooning and inflammation; SAF-A scores range from 0 to 4, with higher scores indicating more-severe disease activity). The primary end point was a decrease of at least 2 points in the SAF-A score and no worsening of fibrosis by week 24.

RESULTS

**Efficacy:** The 1200-mg dose of lanifibranor — but not the 800-mg dose — was superior to placebo with respect to the primary end point.

**Safety:** The percentage of patients with severe adverse events during the treatment period was identical in the three trial groups. Gastrointestinal adverse events, peripheral edema, anemia, and weight gain were more common with lanifibranor.

LIMITATIONS AND REMAINING QUESTIONS

- Most patients in the study were White; whether the findings apply to other races or ethnic groups is unknown.
- A phase 3 trial with longer follow-up and more extensive efficacy and safety assessments is needed.

**Links: Full Article | NEJM Quick Take | Editorial**


**Decrease of ≥2 Points in SAF-A Score and No Worsening of Fibrosis**

| | Lanifibranor | Placebo | Risk Ratio (95%CI) | P Value |
|---|---|---|---|---|
| Lanifibranor, 800 mg | 48% | 33% | 1.41 (1.00–2.00) | P=0.07 |
| Lanifibranor, 1200 mg | 55% | 33% | 1.69 (1.22–2.34) | P=0.007 |

**Adverse Events**

| | Lanifibranor 1200 mg | Lanifibranor 800 mg | Placebo |
|---|---|---|---|
| | number (percent) | | |
| Severe adverse events | 3 (4) | 3 (4) | 3 (4) |
| Most frequent adverse events | | | |
| Diarrhea | 10 (13) | 8 (10) | 1 (1) |
| Nausea | 7 (9) | 8 (10) | 3 (4) |
| Weight gain | 7 (9) | 8 (10) | 0 |
| Peripheral edema | 7 (9) | 5 (6) | 2 (3) |

**CONCLUSIONS**

The pan-PPAR agonist lanifibranor, at a dose of 1200 mg daily, improved histologic outcomes in patients with noncirrhotic, highly active NASH.

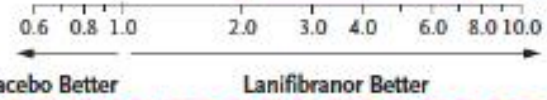
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 21, 2021 VOL. 385 NO. 17

# A Randomized, Controlled Trial of the Pan-PPAR Agonist Lanifibranor in NASH

S.M. Francque, P. Bedossa, V. Ratziu, Q.M. Anstee, E. Bugianesi, A.J. Sanyal, R. Loomba, S.A. Harrison, R. Balabanska, L. Mateva, N. Lanthier, N. Alkhouri, C. Moreno, J.M. Schattenberg, D. Stefanova-Petrova, L. Vonghia, R. Rouzier, M. Guillaume, A. Hodge, M. Romero-Gómez, P. Huot-Marchand, M. Baudin, M.-P. Richard, J.-L. Abitbol, P. Broqua, J.-L. Junien, and M.F. Abdelmalek, for the NATIVE Study Group*

| End Point | Placebo | Lanifibranor | Risk Ratio (95% CI) | P Value |
|---|---|---|---|---|
| | *percent of patients with response* | | | |
| Primary end point: reduction of ≥2 points in SAF-A score and no worsening of fibrosis | | | | |
| Lanifibranor, 800 mg | 33 | 48 | 1.45 (1.00–2.10) | 0.07 |
| Lanifibranor, 1200 mg | 33 | 55 | 1.69 (1.22–2.34) | 0.007 |
| Secondary end point: resolution of NASH without worsening of fibrosis | | | | |
| Lanifibranor, 800 mg | 22 | 39 | 1.70 (1.07–2.71) | |
| Lanifibranor, 1200 mg | 22 | 49 | 2.20 (1.49–3.26) | |
| Secondary end point: improvement in fibrosis stage of ≥1 without worsening of NASH | | | | |
| Lanifibranor, 800 mg | 29 | 34 | 1.15 (0.72–1.85) | |
| Lanifibranor, 1200 mg | 29 | 48 | 1.68 (1.15–2.46) | |
| Composite secondary end point: resolution of NASH and improvement in fibrosis stage of ≥1 | | | | |
| Lanifibranor, 800 mg | 9 | 25 | 2.57 (1.20–5.51) | |
| Lanifibranor, 1200 mg | 9 | 35 | 3.95 (2.03–7.66) | |

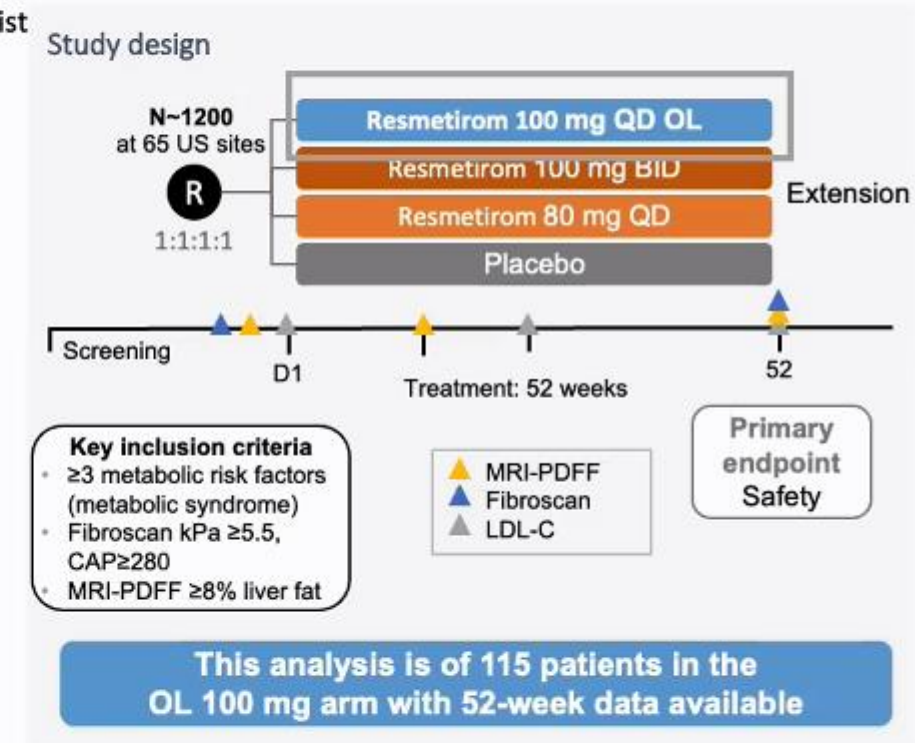


# MAESTRO-NAFLD-1: Reduction in fibrosis and steatohepatitis imaging and biomarkers in Phase 3, 52-week resmetirom NASH trial

- Resmetirom is a liver-directed, orally active, selective THR-β agonist

| Clinical trial | Preclinical | Phase 1 | Phase 2 | Phase 3 | Description |
|---|---|---|---|---|---|
| Phase 2 MGL-3196-05 | Completed | | | | • **MRI-PDFF, liver biopsy: endpoints achieved**<br>• 36 wks with 36-wk OLE |
| Phase 3 MAESTRO-NASH | | | Recruiting | | • **Treatment of NASH F2-F3**<br>• Serial liver biopsy<br>• 52-wk Phase 3; 54-month outcomes |
| Phase 3 MAESTRO-NAFLD-1 | | | Ongoing | | • **Treatment of NASH**<br>• **Safety, lipids and NASH biomarker and imaging study**<br>• 52-wk<br>• Enrolment of DB arms completed<br>• **OL 100 mg arm; includes NASH cirrhotics** |

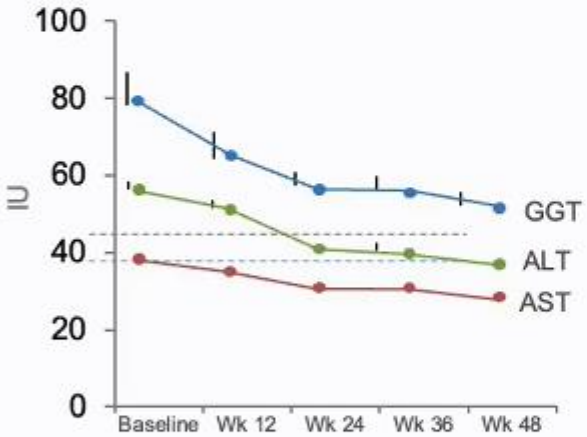
Primary and key secondary endpoints of MAESTRO-NAFLD-1 include: safety, relative percent reduction of MRI-PDFF (week 16), LDL cholesterol (LDL-C) (week 24), Apolipoprotein B and triglycerides, PRO-C3 (week 52), and safety.



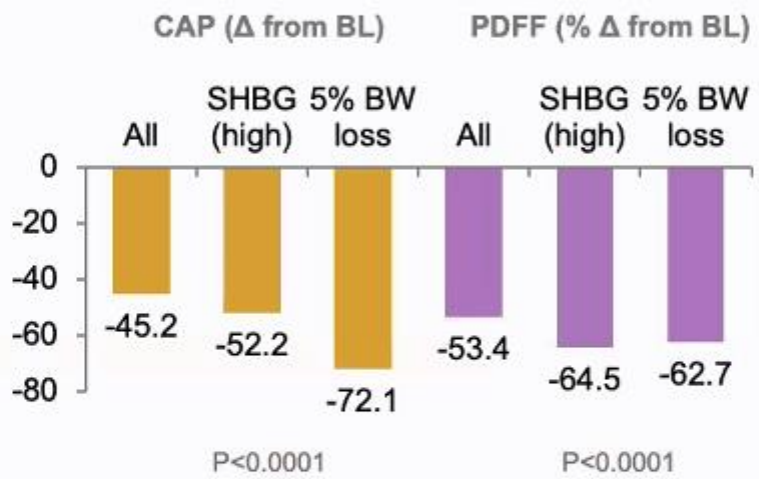

Harrison S, et al. EASL 2021. #GS-2563

# MAESTRO-NAFLD-1: Reduction in biomarkers in Phase 3, 52-week resmetirom NASH trial

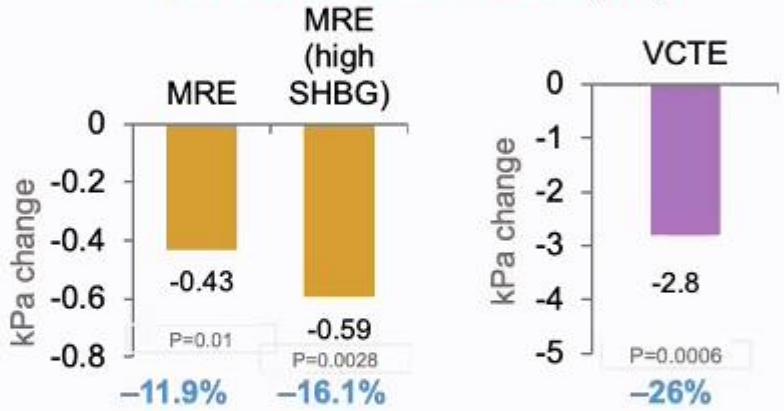
| Week 48 | Δ from BL | % Δ from BL | P-value |
|---|---|---|---|
| ALT | −20.36 | −33.04 | <0.0001 |
| AST | −10.19 | −21.50 | 0.0003 |
| GGT | −28.52 | −19.83 | 0.015 |




**Week 52 CAP and MRI-PDFF**




**Wee 52 MRE and FibroScan (kPa)**




SHBG (high), majority of patients at target resmetirom liver exposure based on % change in SHBG

%Δ

- Approximately 50% of patients had a 15% reduction in MRE (kPa) and/or 25% reduction in FibroScan (VCTE) kPa

Harrison S, et al. EASL 2021. #GS-2563

# FUTURO DEL TRATAMIENTO

Combination therapy

- Selonsertib + Cilofexor + Firsocostat
- Tropifexor + Cenicriviroc
- Semaglutide + Firsocostat + Cilofexor
- Pioglitazone + Empagliflozin
- Tropifexor + Licogliflozin

FXRa

SGLT2inh

GLP1-RA

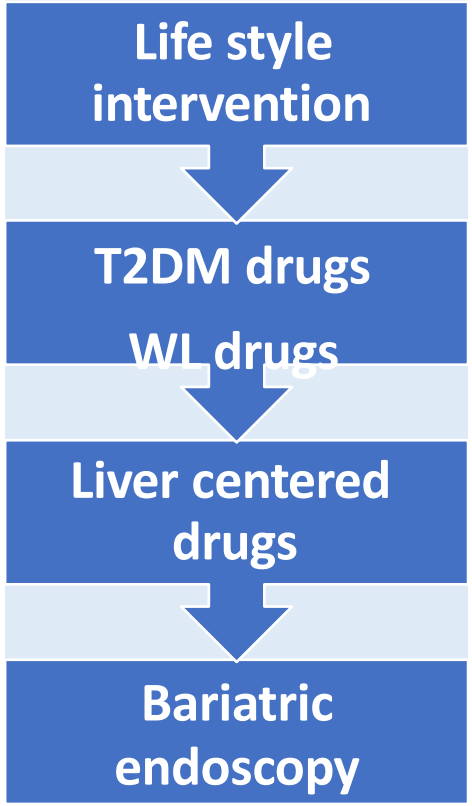
PPARa

ACCihb

ASK-1inh

CCR2 / CCR5 inh

Sequential therapy




http://www.clinicaltrials.gov/

## Enfermedad hepática

- **Mayor prevalencia HGNA/EHNA**
- **Peor progresión/pronóstico**
- **Oportunidad de:**
  - Prevenir EHNA
  - Identificar EHNA de forma precoz

## Diabetes

- **Identifica subgrupo DM2**
  - Fisiopatología predominante RI
  - Mayor riesgo de complicaciones
- **Selección tratamiento**
  - Estilo de vida
  - Farmacológico

**American Diabetes Association: Standards of Medical Care in Diabetes – 2022**

**4.10** "Patients with type 2 diabetes or prediabetes and elevated liver enzymes (ALT) or fatty liver on ultrasound should be evaluated for presence of nonalcoholic steatohepatitis and liver fibrosis". **C**

Endocrine Practice 28 (2022) 528–562

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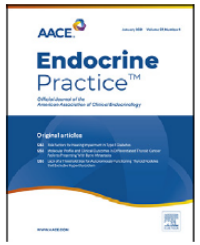


Clinical Practice Guidelines

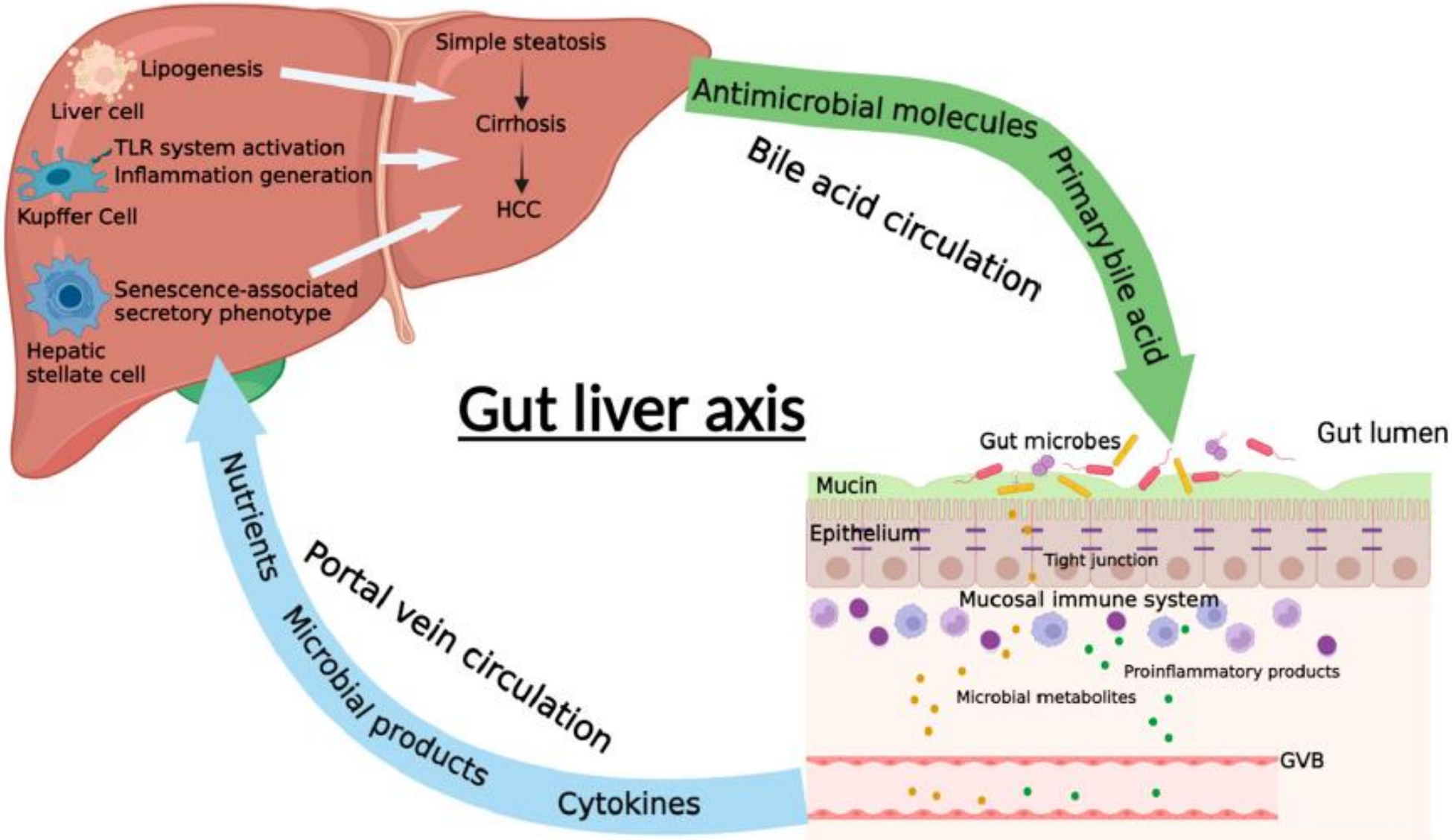
# American Association of Clinical Endocrinology Clinical Practice Guideline for the Diagnosis and Management of Nonalcoholic Fatty Liver Disease in Primary Care and Endocrinology Clinical Settings

## Co-Sponsored by the American Association for the Study of Liver Diseases (AASLD)

Medications to Treat Diabetes and Their Efficacy for the Treatment of Nonalcoholic Fatty Liver Disease

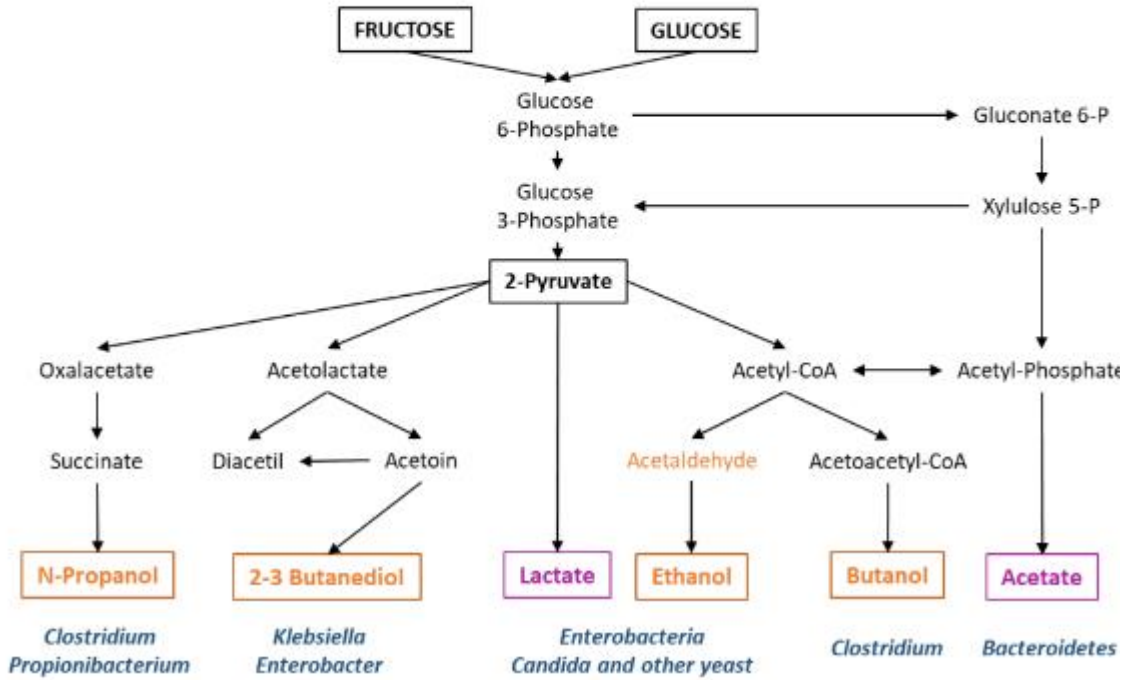
| Medication | Liver fat | Disease activity (steatohepatitis/NAS) |
|---|---|---|
| Metformin | Unchanged | Neutral |
| Pioglitazone | Decreased | Improved[a] |
| Insulin | Decreased | Effect unknown |
| GLP-1 RAs (semaglutide and liraglutide) | Decreased | Improved[a] |
| SGLT2 inhibitors (dapagliflozin, empagliflozin, and canagliflozin) | Decreased | Effect unknown |
| DPP-IV inhibitors (sitagliptin and vildagliptin) | Unchanged (in RCTs) | Effect unknown |

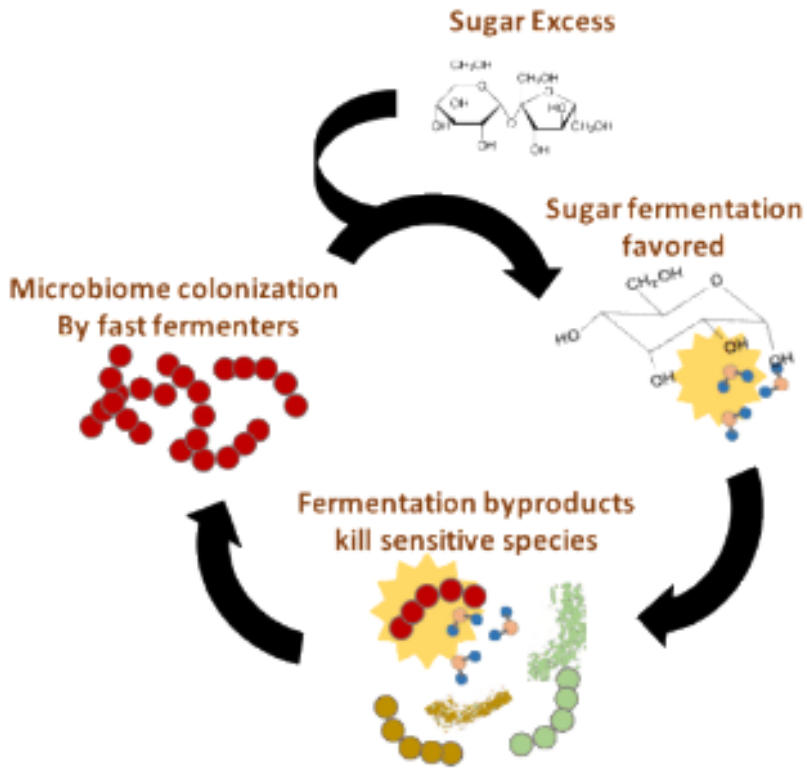
Abbreviations: DPP-IV = dipeptidyl peptidase IV; GLP-1 RAs = glucagon-like peptide11 receptor agonists; NAS = nonalcoholic fatty liver disease a

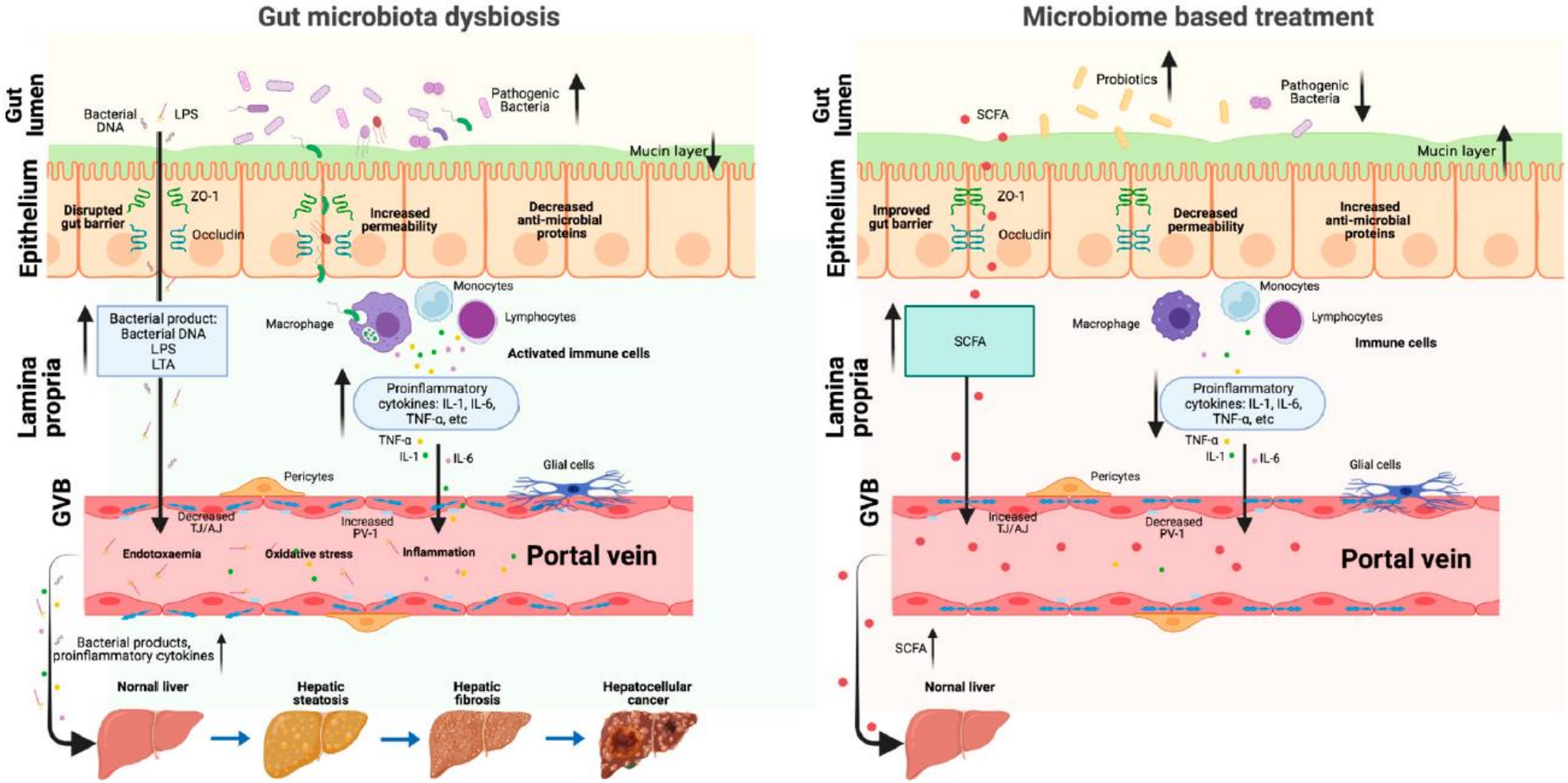



Song. Biomedicines. 2022

# Microbiota and NAFLD

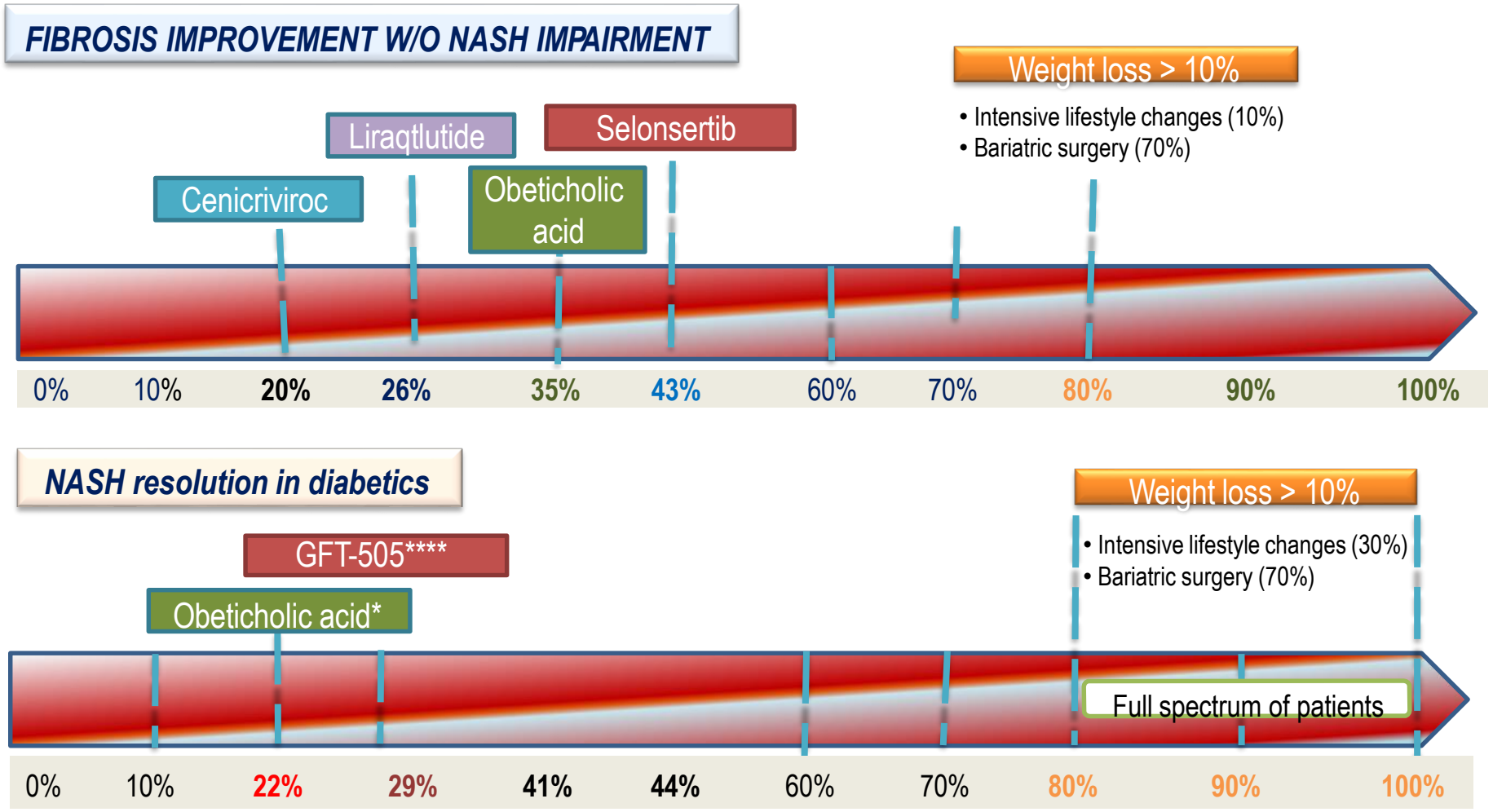





Song Q,. Biomedicines. 2022

# Physicians need effective pharmacotherapies that will reduce and maintain NASH and fibrosis remission



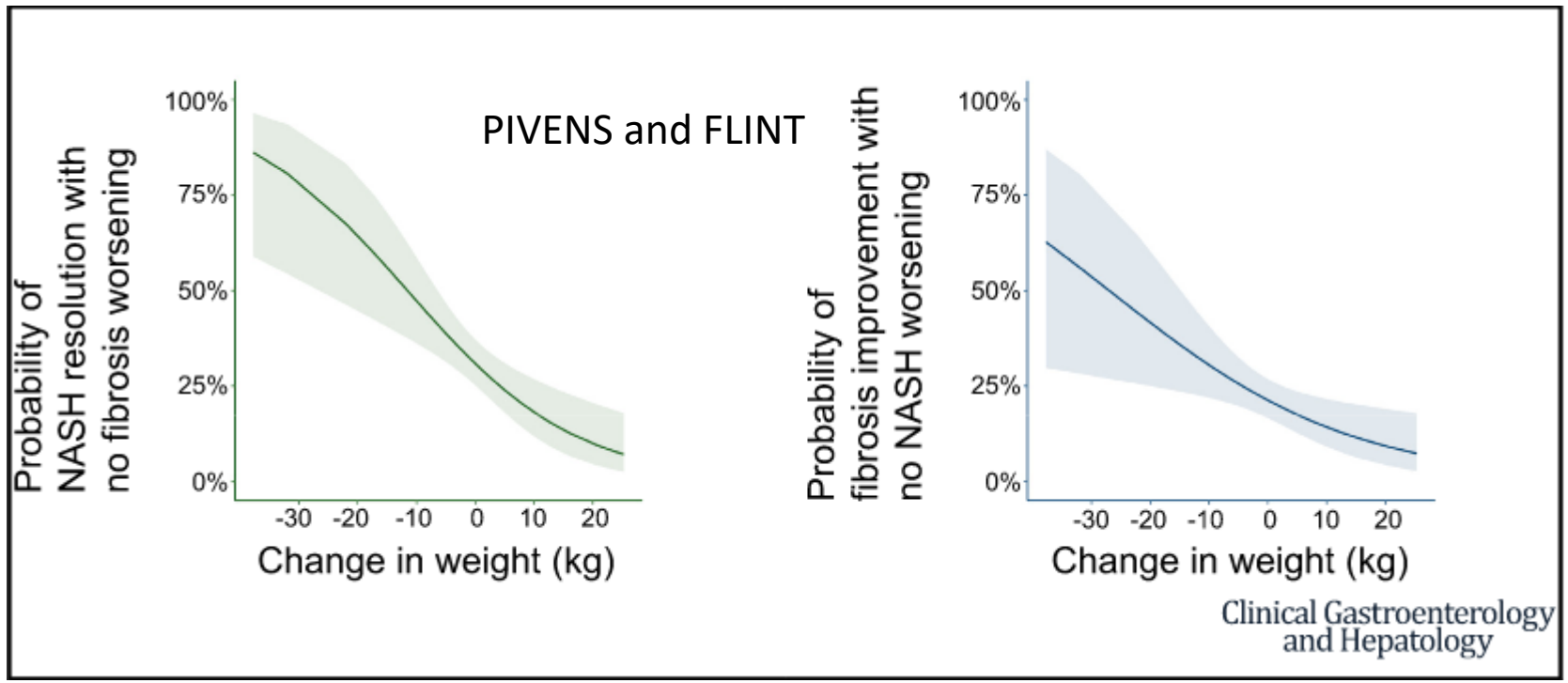

* Patients with T"DM included

** Increased risk of bladder cancer and MI. Unknown benefits in diabetic and cirrhotic pts.

*** May increase all-cause mortality

**** Patients with NAS >4

Sanyal AJ. N Engl J Med. 2010;362:1675-85; *Neuschwander-Tetri BA.* Lancet. 2015;385:956-965. Vilar-Gomez E. Gastroenterology. 2015;149:367-378. Lassailly G. Gastroenterology. 2015;149:379-388.




- 1 Kg de peso supone una 5% de probabilidad de mejorar la fibrosis y 7% resolución del NASH

Koutoukidis et al, 2022

Endocrine Practice 28 (2022) 528–562

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Co-Sponsored by the American Association for the Study of Liver Diseases (AASLD)

# Weight Management in NAFLD

## Fibrosis Risk Stratification

| |  **Low Risk** FIB-4: <1.3 LSM <8 kPa ELF <7.7 |  **Indeterminate Risk** FIB-4: 1.3 - 2.67 LSM 8 - 12 kPa ELF 7.7 - 9.8 |  **High Risk** FIB-4: >2.67 LSM >12 kPa ELF >9.8 |
|---|---|---|---|
| General lifestyle changes | Decrease sedentary time and increase daily movement. Stress reduction through exercise and other methods. | | |
| Dietary recommendations | Creating an energy deficit is the priority with reduction of saturated fat, starch, & added sugars. Persons with cirrhosis need an individualized nutritional assessment and treatment plan. | | |
| Exercise | To improve cardiometabolic health, support weight loss and mitigate sarcopenia. Aerobic exercise for 30-60 min (3-5 days/week) + resistance training 20-30 min (2-3 times/week). | | |
| Alcohol intake | Minimize | Minimize | Avoid if F3 or cirrhosis (F4)[1] |
| Weight loss goal to treat NAFLD (if overweight or obesity)[2] | Greater weight loss associated with greater liver and cardiometabolic benefit. | | |
| Weight loss tools | Behavioral modification counseling. In person or remote programs. | Greater intensity of weight loss to reverse steatohepatitis and fibrosis. | Specialized obesity management, with a structured program, anti-obesity medications, bariatric surgery. |
| Medical therapy to treat obesity | Phentermine, phentermine/topiramate ER, naltrexone/bupropion, orlistat, liragluitde 3 mg/d, semaglutide 2.4 mg/wk | GLP-1 RA preferred for NASH.[3,4] | GLP-1 RA preferred for NASH.[3,4] |
| Bariatric surgery | Consider to treat obesity and comorbidities. | Strong consideration to treat steatohepatitis and fibrosis. | Stronger consideration to treat steatohepatitis and fibrosis. Avoid in decompensated cirrhosis. |

cias

¡gracias!