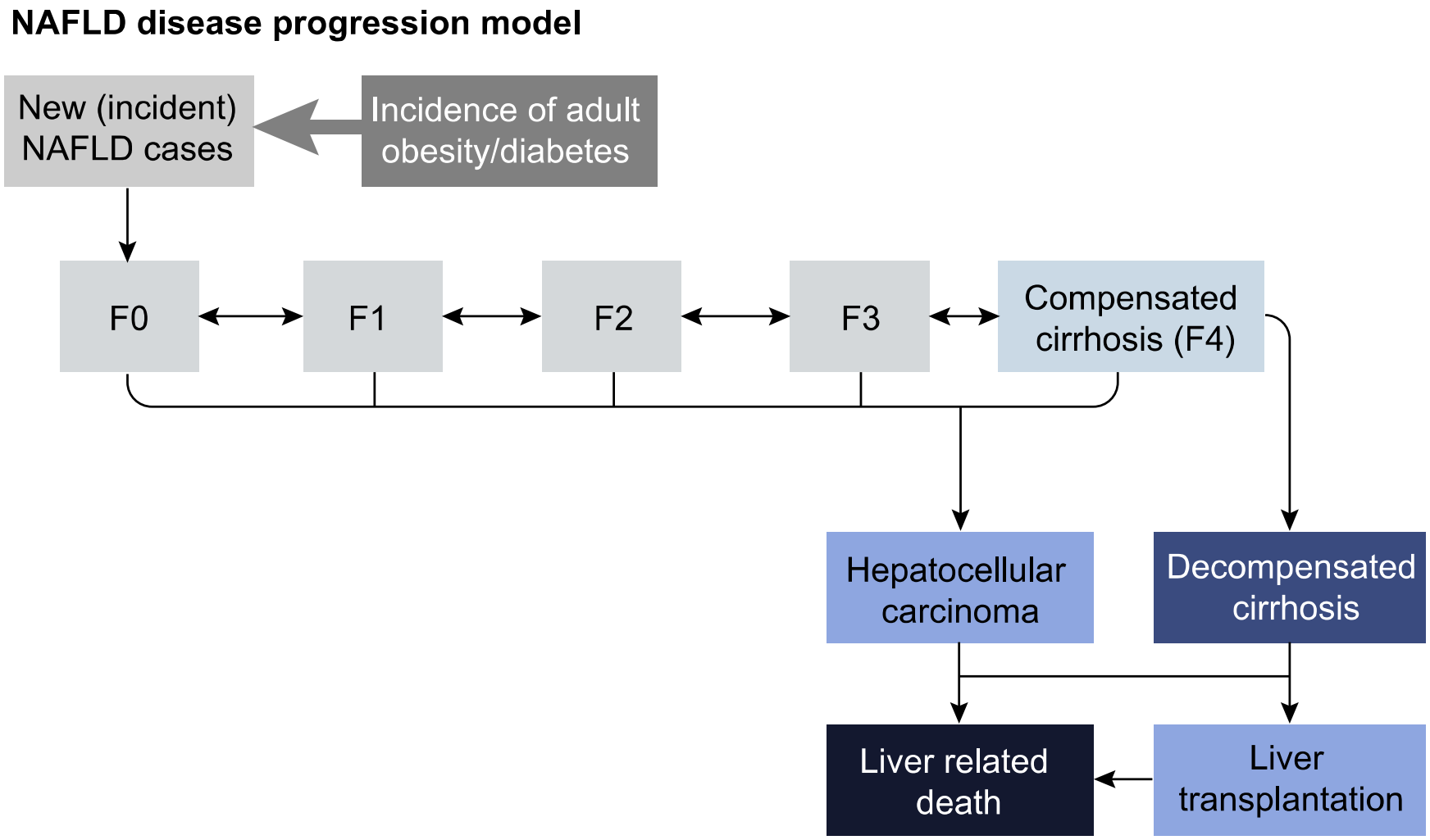
Tratamiento del Hígado Graso no Alcohólico

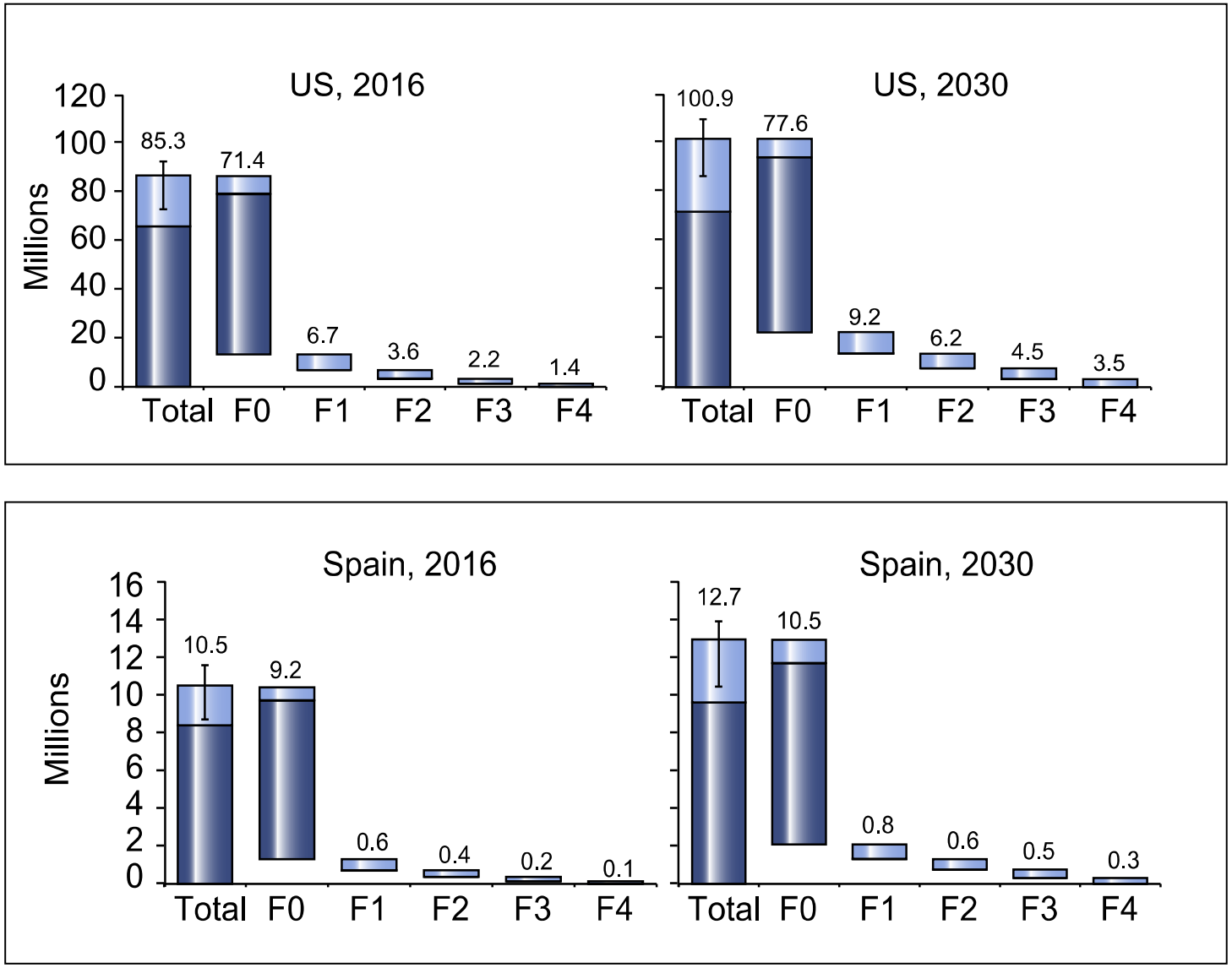
Fernando Cairo

Riesgo de Desarrollar NASH



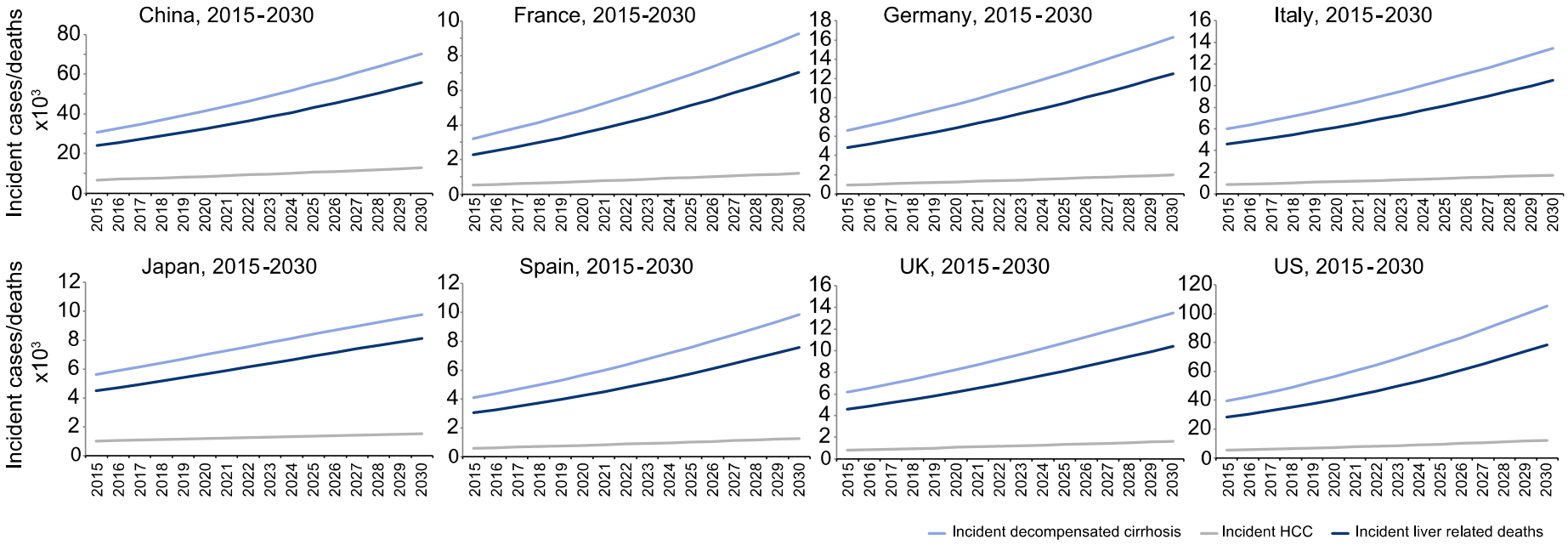
C Estes, et al. J hepatol 2018, vol 69:896-904

Riesgo de Progresion de NASH



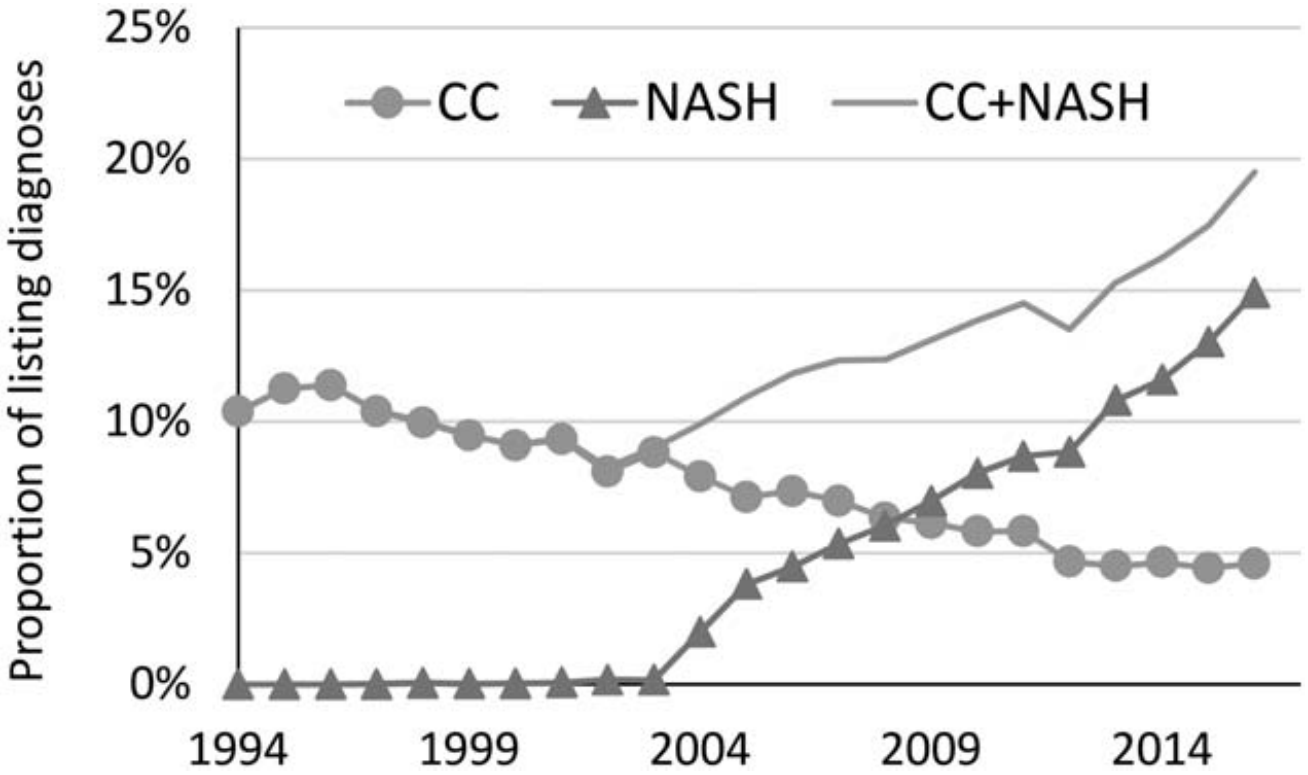
C Estes, et al. J hepatol 2018, vol 69:896-904

Incidencia de Cirrosis, HCC y Muertes relacionadas a NASH



C Estes, et al. J hepatol 2018, vol 69:896-904

Prevalencia de NASH en Lista para Trasplante Hepático



Golabi et al. Medicine (2018) 97:31

Ingresos a lista de espera para trasplante hepático

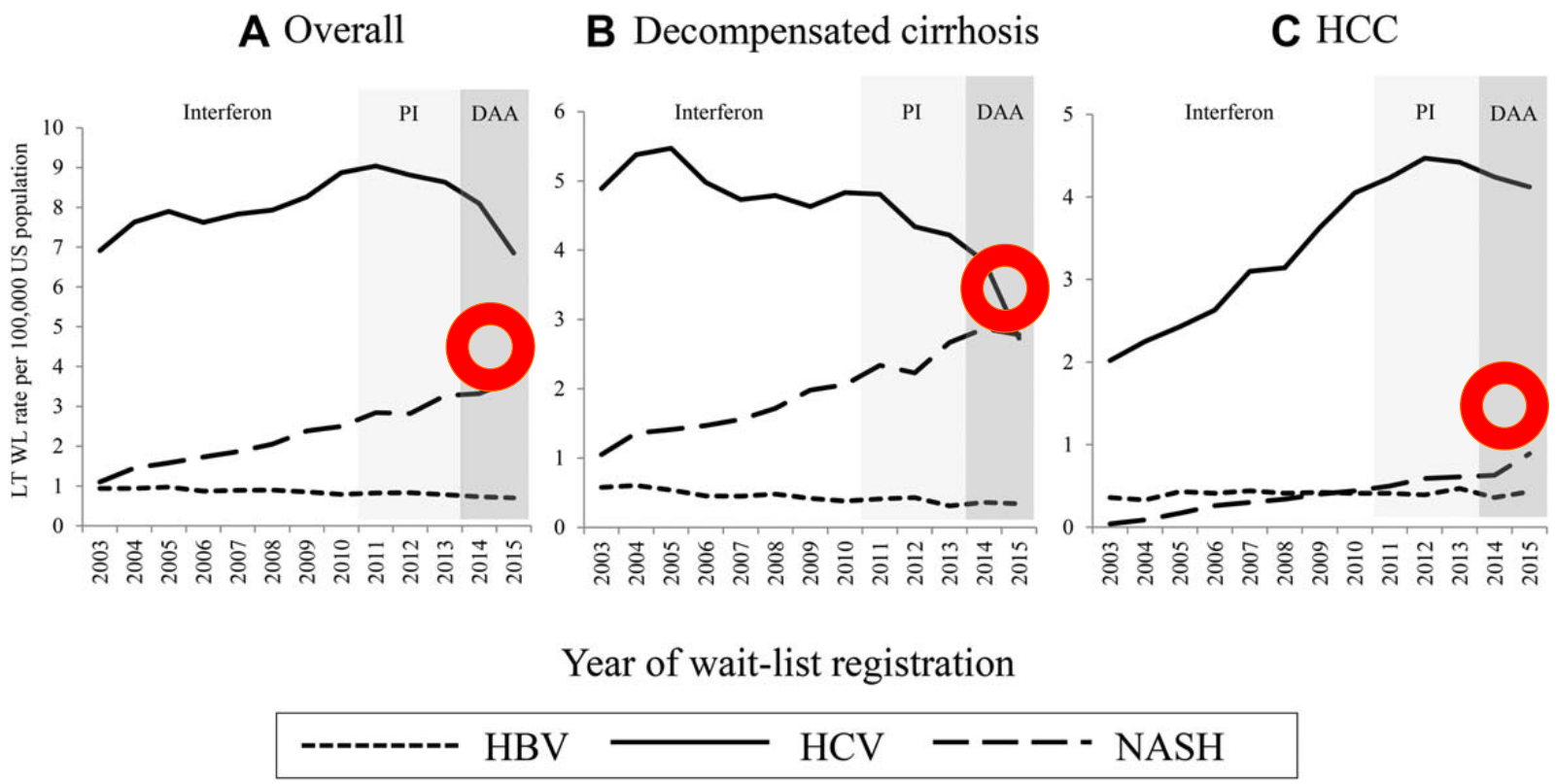
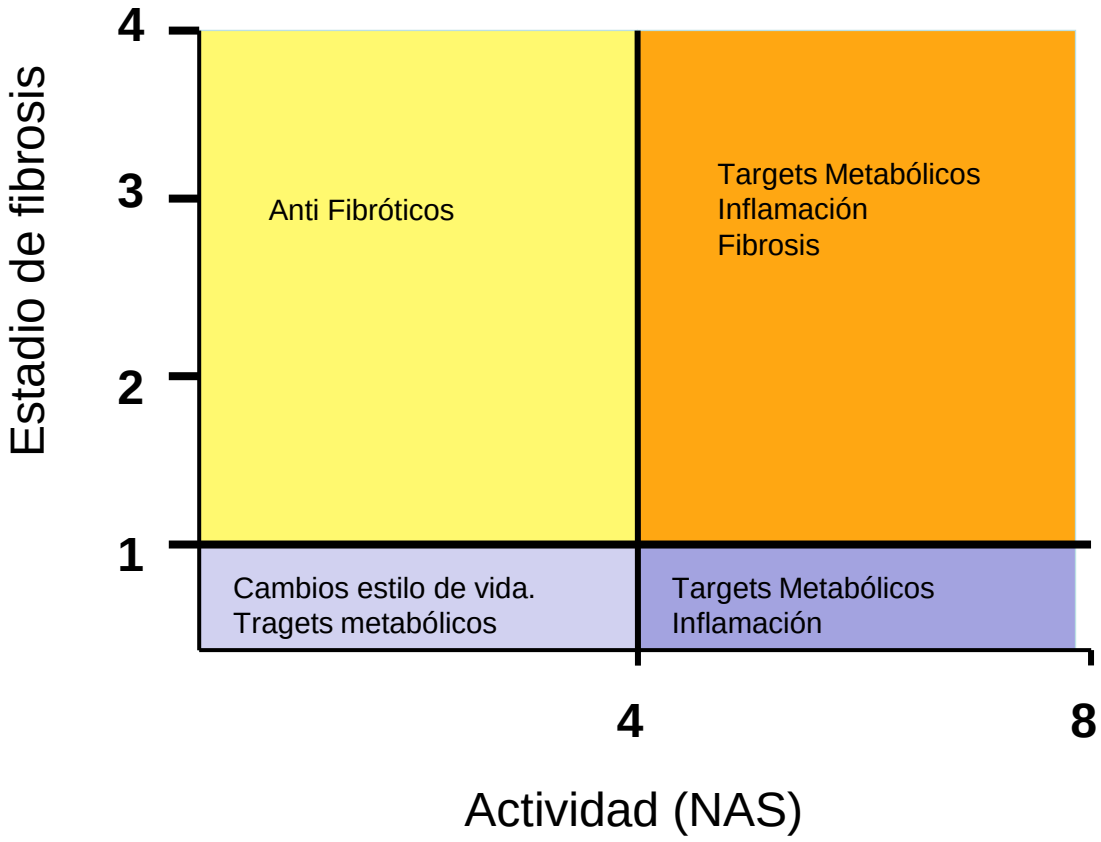


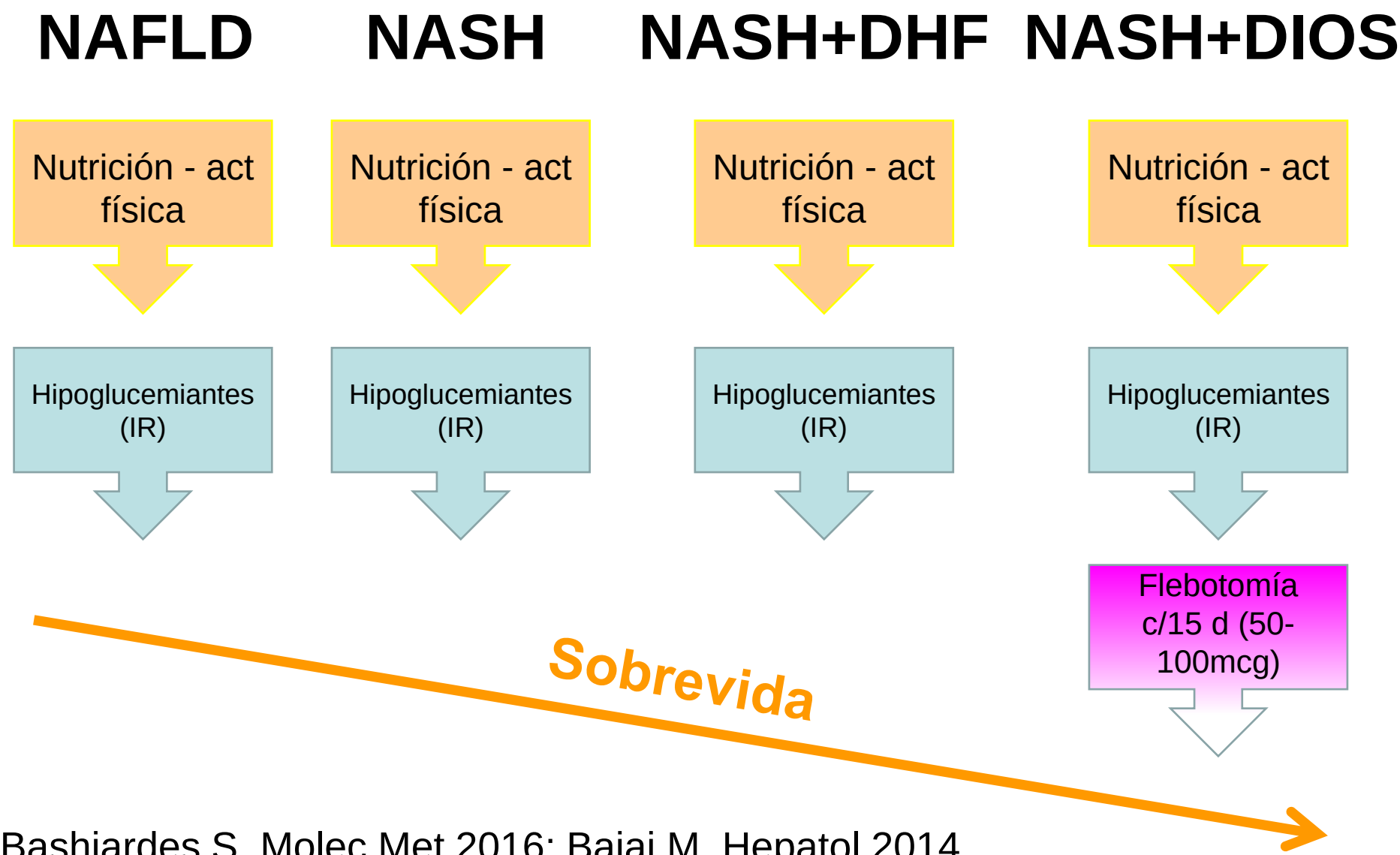
FIG. 2. ASIRs of LT WL per 100,000 U.S. population by etiology of liver disease and indication for WL. X-axis is the year of LT WL registration.

Flemming, et al. Hepatol 2016

Manejo Racional del Tratamiento del NASH

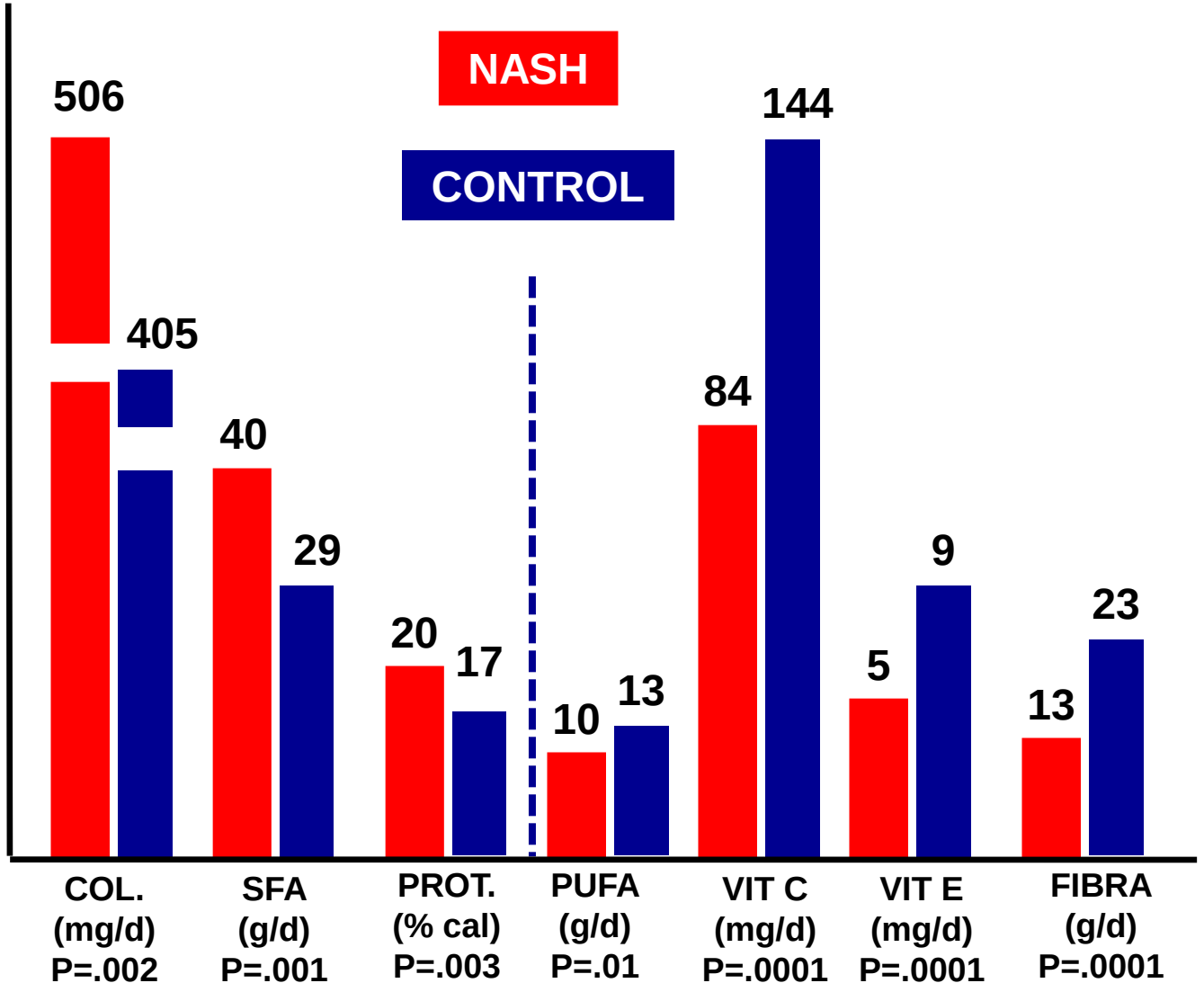


Tratamiento General



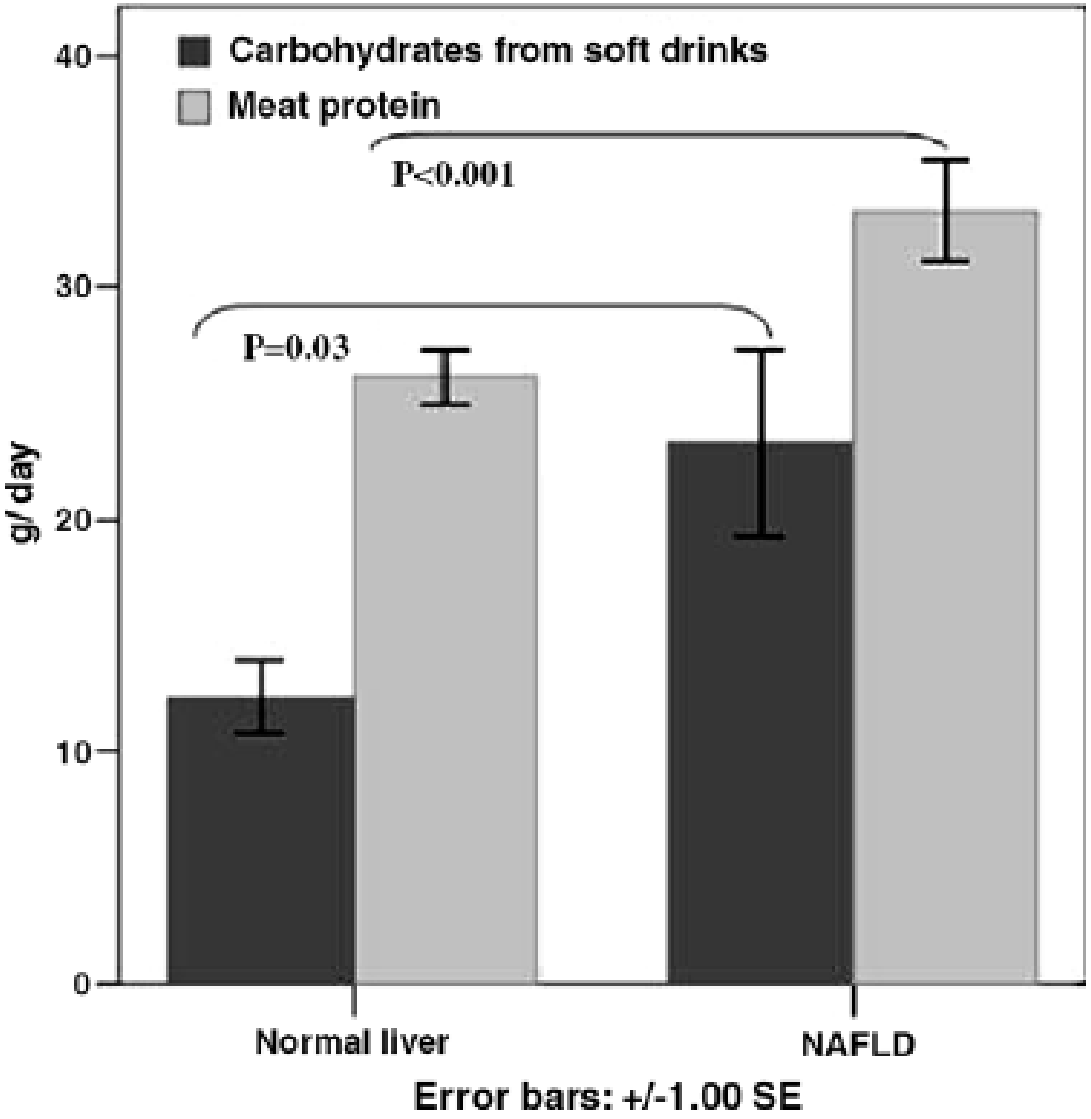
Bashiardes S, Molec Met 2016; Bajaj M, Hepatol 2014.

¿Como nos alimentamos?



Musso G; Hepatology 2003

¿Como nos alimentamos?



Zelber-Sagi; J Hepatol 2007

Tratamiento no-Farmacológico

- **Pérdida de peso:**
  El objetivo inicial es ↓ el 10% del basal (1.6 Kg por semana)
- **Dieta hipograsa:**
  Pobre en ácidos grasos saturados y rica en fibra
- **Ejercicio aeróbico:**
  Un mínimo de 3 veces por semana. Cualquier tipo de actividad fisica (aeróbica) cambia la concentración hepática de grasa luego de un mes.

Normalización del hepatograma y mejoría de la esteatosis.

¿Cuánto peso hay que perder para mejorar la EHGNA?

Pérdida de peso

≥ 10% [3] → **(100%) Reducción NAS**

(90%) Resolución NASH

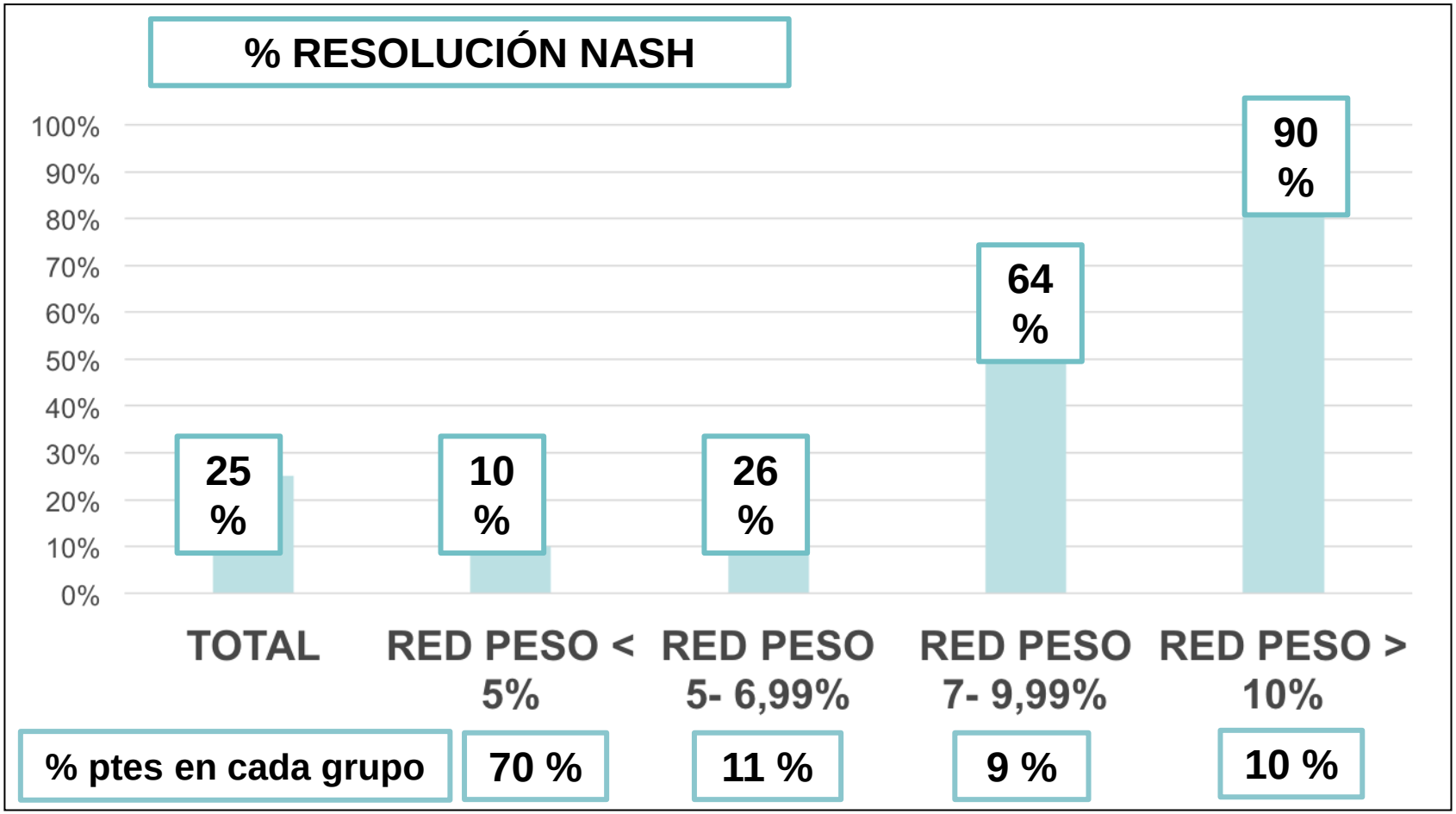
(45%)↓Estadio de Fibrosis

7 % a 10% [2] → **Reducción NAFLD Activity Score (NAS)**

5 % [1] → **Reducción de contenido de grasa hepática**
Reducción rigidez hepática

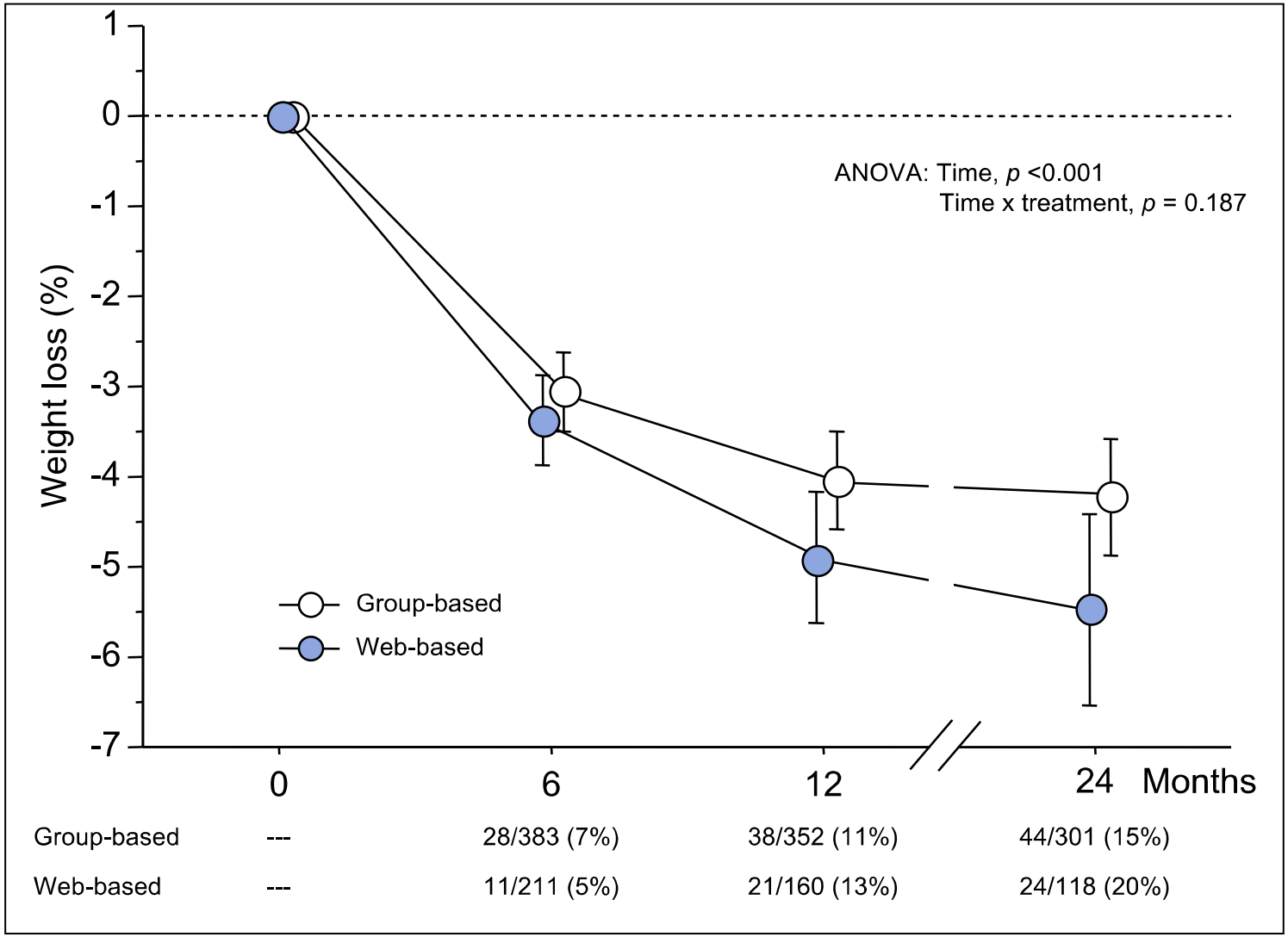
1. Patel NS, et al. Clin Gastroenterol Hepatol. 2017;15:463-464. 2. Promrat K, et al. Hepatology. 2010;51:121-129. 3. Vilar-Gomez E, et al. Gastronterology 2015;149:367-378.

Resolución del NASH. Dieta y Ejercicio



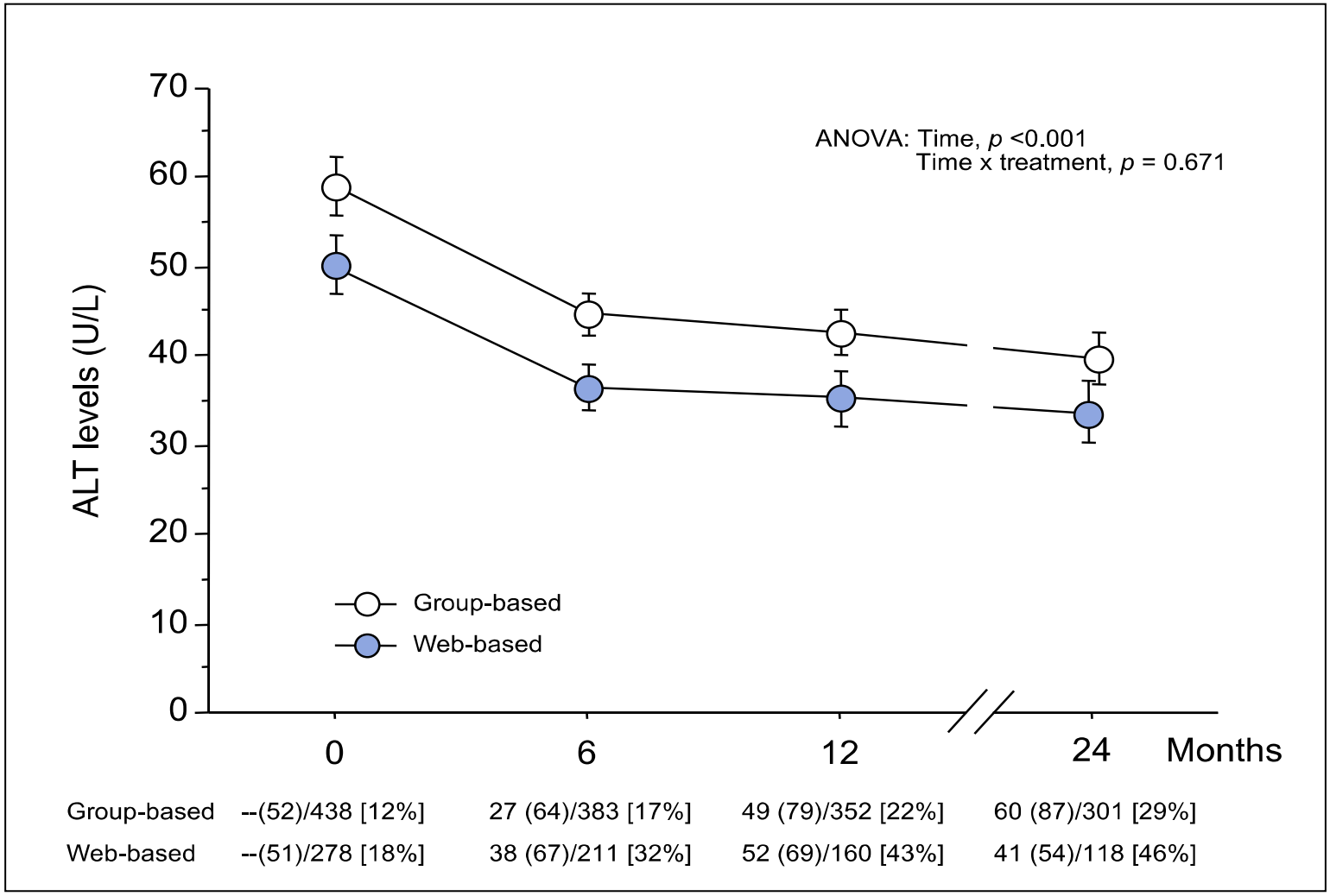
Vilar-Gomez E, et al. Gastronterology 2015;149:367-378

El Rol de los Grupos para Lograr Objetivos



A Mazzotti, et al. J Hepatol 2018

El Rol de los Grupos para Lograr Objetivos



A Mazzotti, et al. J Hepatol 2018 (in press)

El Rol de los Grupos para Lograr Objetivos

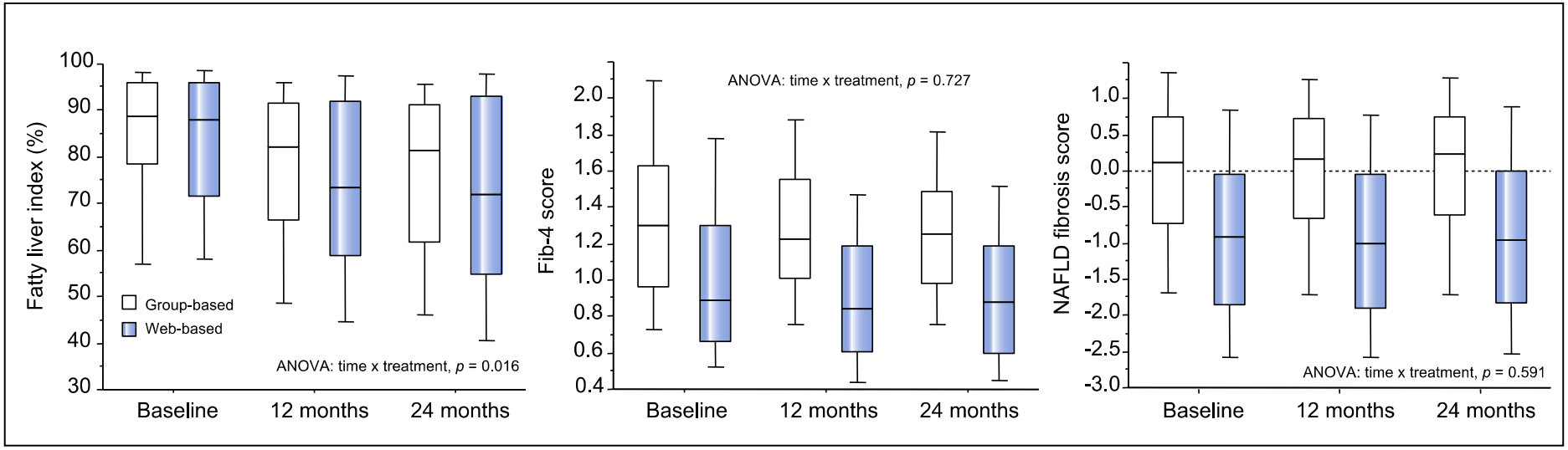
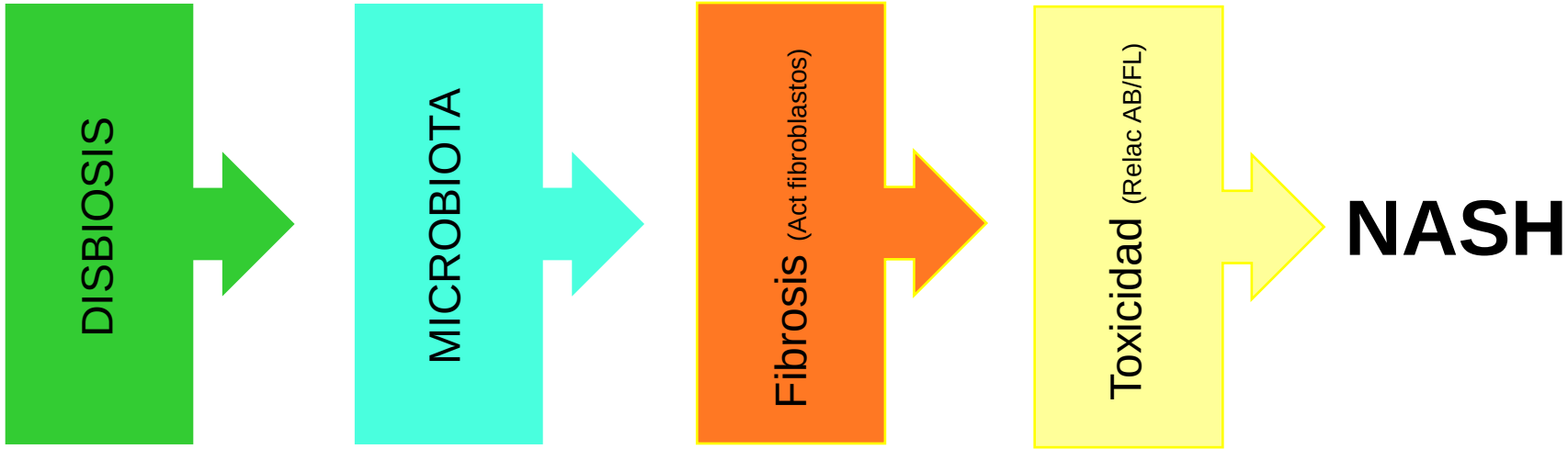


Fig. 3. Box plot representation of the time course of surrogate markers of steatosis and fibrosis in individuals enrolled in the group-based (white boxes) and web-based (grey boxes) lifestyle intervention programs. For all surrogate markers, ANOVA reveals significant differences between treatment categories (p <0.001).

A Mazzotti, et al. J Hepatol 2018 (in press)

Tratamiento Específico del NASH

Esquemas terapéuticos



Metronidazol
Rifaximina
Minociclina
Neomicina

Probióticos
(lactobacilus)
Prebióticos
(Rifaximina)

Acido
Obeticólico

Vit E
UDCA
nor UDCA
Metformina
Ac Obeticólico
Bezafibrato

Bashiardes S, Molec Met 2016; Bajaj M, Hepatol 2014.

Disbiosis

❶ Higado graso vinculado a sobrecrecimiento bacteriano

- pacientes sometidos a bypass (mejoría en pac tratados con metronidazol)

❷ Chicos obesos con o sin NASH

- poblaciones bacterianas diferentes (dieta deficiente en colina)

❸ Produccion de alcohol bacteriano

- población de bacterias productoras de alcoholes en obesos con NASH vs obesos sin NASH

Spencer MD. Gastroenterol 140(3). Zhu L. Hepatology 2014

Efectos de la Microbiota en NASH

● Regulación de la barrera intestinal

Permite el pasaje de moléculas antigénicas (LPS, endotoxinas)

● Estimulación de respuesta inflamatoria local

Activación de sistema reticuloendotelial, producción de citoquinas pro inflamatorias. Estimulación de fibroblastos

● Productos químicos instesinales

Baja concentracion de acidos biliares conjugados, acidos grasos de cadena mediana, etanol.

Luther J, Cell and Molec Gastro And Hepatol 2015. Zhu L. Hepatology 2014

Dysmetabolic Iron Overload Syndrome (DIOS)

NASH mas Sobrecarga de Hierro

- Mayor riesgo de desarrollar cirrosis
- Mayor riesgo de desarrollar HCC
- Mayor riesgo de IR, DBTNIR, Eventos Cardiovasc (aumento de mortalidad)
- El diagnóstico diferencia es el la hiperferretinemia dismetabólica (DHF)

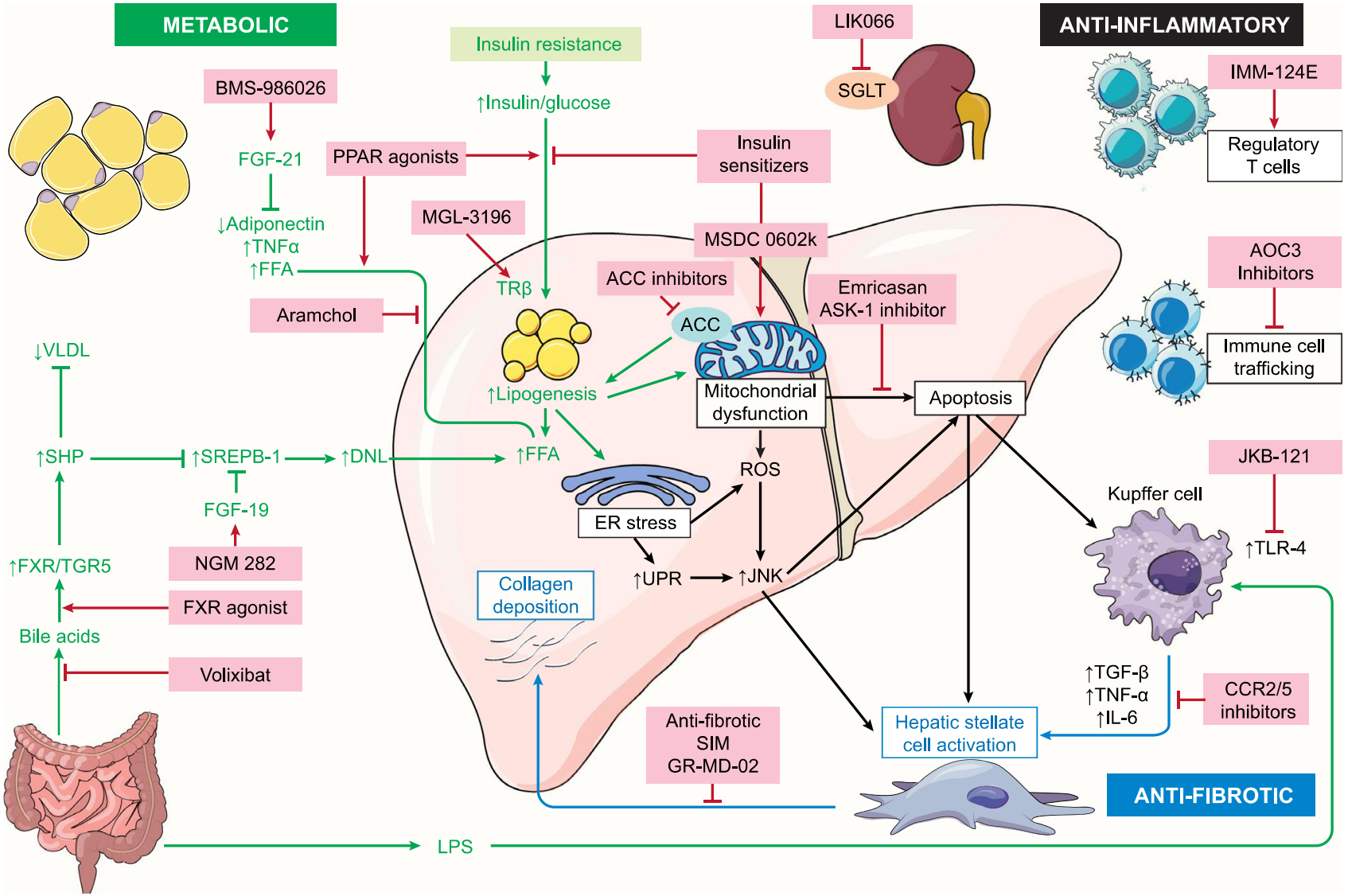
Bashiardes S, Molec Met 2016; Bajaj M, Hepatol 2014.

Fármacos recomendados en NALFD

	AGA/AALSLD (2012)	JSG/JSH (2014)	EASL/EASD/EAO (2016)	AASLD guidance (2017)
Vitamin E	First-line therapy for biopsy-proven NASH without diabetes and cirrhosis (800 mg/day)	Recommended	Not firmly recommended, but could be used	May be considered in biopsy-proven NASH without diabetes and cirrhosis (800 mg/day) Discuss benefit and risk with patients
UDCA	Not recommended	Not recommended	Not mentioned in detail	Not recommended
Pioglitazone	Can be used in patients with biopsy-proven NASH	Recommended in NASH with insulin resistance	Not firmly recommended, but could be used	Can be used in patients with biopsy-proven NASH Discuss benefit and risk with patients
Metformin	Not recommended as a specific treatment for NASH	Not recommended as a specific treatment for NASH	Insufficient evidence	Not recommended as a specific treatment for NASH
Liraglutide	Not mentioned	Not mentioned	Not mentioned	Premature as a specific treatment for NASH
ω3 fatty acid	May be considered in NAFLD with hypertriglyceridemia	Not mentioned	Reduced lipid in plasma and liver, but no evidence related to NASH	Not recommended as a specific treatment for NASH May be considered in NAFLD with hypertriglyceridemia
Statin	Can be used to treat dyslipidemia	Recommended for hypercholesterolemia	Can be used to reduce LDL-C and prevent cardiovascular risk	Can be used to treat dyslipidemia Should be avoided in decompensated cirrhosis
Pentoxifylline	Not mentioned	Recommended, but commercially unavailable in Japan	Not mentioned	Not mentioned
OCA	Not mentioned	Not mentioned	Not mentioned	Off-label use not recommended (approved for PBC in USA)

Thuluvath P. Hepatol Int 2019

Mecanismos de Acción de los Fármacos en NASH



Konerman M, et al. J Hepatol 2018 vol 68:362-375

FLINT-J Trial
(Obeticolico)
INT-767
LMB763
GS9674
MGL-3196

EMMINENCE
(MSDC 0602K)
Pemafibrato
(K-877)
EVIDENCES II
(Saroglitazar)
GOLDEN 505
(Elafibranor)
NATIVE
(IVA337)

LEAN Study
(Liraglutide)
SUSTAIN-6
(Semaglutide)
SGLT2
(Canaglifozin)

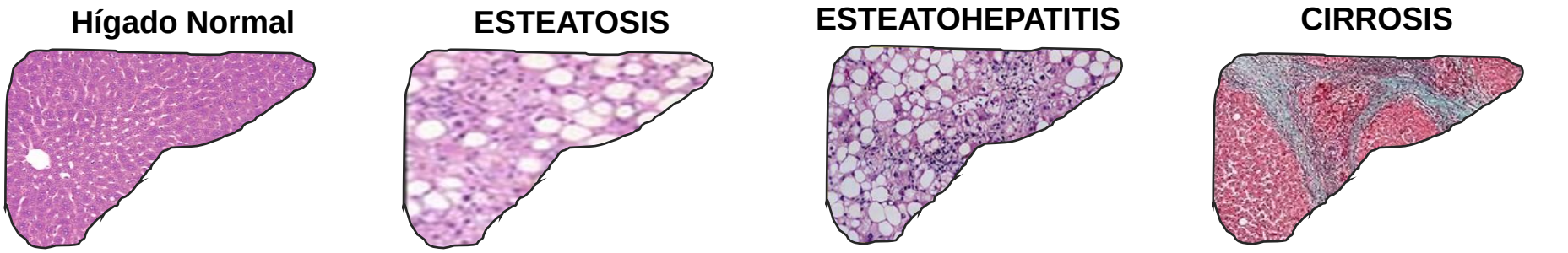
MOZART
(Ezetimibe)
Pemafibrato Study
Aramchol Study
GS-0976

Mechanism of action	Company (Product name)	Condition and stage	Primary endpoint(s)	N	Duration (wk)
FXR agonist non-bile acid					
	Novartis (LJN452)	NASH, stage 0–3, elevated ALT, OR PDFF >10%, obesity, DM2	Adverse event profile, safety, improvement in ALT	250	12
	Novartis (LMB763)	NASH, stage 0–3, elevated ALT, OR PDFF >10%, obesity, DM2	Adverse event profile, safety, improvement in ALT	100	12
FXR agonist non-bile acid + ACC inhibitor					
	Gilead (GS-9674)	MRE >2.5 kPa, PDFF >10%	Safety and tolerability	140	24
	Gilead (GS-976 + GS-9674)	MRE ≥NASH 2.88 kPa, PDFF ≥10%, OR MRE >4.67 kPa, not compensated, OR NASH, stage 2–3	Safety and tolerability	110	12
PPAR-α/γ agonist					
	Zydus (saroglitazar)	NAFLD stage 0–3, ALT >1.5 ULN	Percent change in ALT	104	16
PPAR-α/δ/γ agonist					
	Inventiva Pharma (IVA337)	NASH, SAF fibrosis score <4	Improvement in SAF without worsening fibrosis	225	24
GLP-1 analogue					
	Novo Nordisk (liraglutide)	NASH, fibrosis 1–4, compensated	Resolution of NASH without worsening of fibrosis	52	48
	Novo Nordisk (semaglutide)	NASH, stage 2–3 fibrosis	Resolution of NASH without worsening of fibrosis	372	72
ACCi					
	Gilead (GS-0976)	NAFLD OR NASH without cirrhosis	Safety and tolerability	127	12
	Pfizer (PF-05221304)	MRE ≥2.5 kPa, PDFF ≥8% NASH, stage 1–3	Change in hepatic fat	360	16
FGF-19 agonist					
	NGM BIO (NGM282)	NASH, stage 1–3	Change in hepatic fat	140	12
Recombinant FGF-21					
	BMS (BMS986036)	NASH, stage 1–3	Change in hepatic fat	74	16
TLR-4 antagonist					
	TAIWAN J (JKB-121)	NASH, stage 1–3	Improvement in ALT and change in hepatic fat	66	24
Thyroid hormone receptor-B agonist					
	Madrigal (MGL-3196)	NASH, stage 1–3	Change in hepatic fat	125	36
ASBT inhibitor					
	Shire (volixibat)	NASH, stage 0–3	Improvement in NAS without fibrosis worsening	266	48
mTOT modulating insulin sensitizer					
	Cirius (MSDC 0602k)	NASH, stage 1–3	Improvement in NAS without fibrosis worsening	380	48
Sodium glucose cotransporter 1 and 2 inhibitor					
	Novartis (LIK066)	NASH, stage 1–3	Percent change in ALT	110	12
AOC3 inhibitor					
	Boehringer Ingelheim (BI 1467335)	NASH stage 1–3, OR MRE ≥3.64 kPa, PDFF ≥5%	Target enzyme activity relative to baseline in percent, 24 h post dose	150	Up to 16
Induction of regulatory T cells					
	IMMURON (hyperimmune bovine colostrum)	NASH, stage 0–3	Change in hepatic fat	130	24

FXR ligando PPAR-agonista Anti-DBT Hipolipemiantes

Fase II Trials

Targets terapéuticos- fase II



Insulino – Resistencia Metabolismo Lipídico	Lipotoxicidad Stress Oxidativo	Inflamación Activación Inmunológica	Apoptosis Necrosis celular	Fibrogénesis Turn Over Colágeno

METABOLISMO

Pioglitazona
Liraglutide
Semaglutide
GS-0976
PF-05221304
Aramchol
LIK066
BMS-986036
MGL-3196

Elafibranor
Amlexanox
Saroglitazar
MSDC-0602K
OCA
Tropifexor
LMB-763
Volixibat
NGM282
Amlexanox

INFLAMACIÓN y MUERTE CELULAR

Pentoxifilina
Selonsertib

Selonsertib
Emricasan

Disbiosis:
IMM-124E(NCT02316717)
Solithromycin(NCT2510599)
JKB-121(NCT02442687)

FIBROSIS

Cenicriviroc
Simtuzumab
GR-MD-02
Selonsertib +
Simtuzumab
Tipelukast
Emricasan*
VAP1-inhibit
MT3995

* Con HTP

Yomeda M, J Gastroenterol 2018.Chalasani N; Hepatology

Mecanismo de acción Fase III

Drug name	Mechanism of action	Pharmaceutical company	Phase of clinical trial
Obeticholic Acid (OCA)	Farnesoid X receptor agonist	Intercept pharmaceuticals	3
Selonsertib	Apoptosis signal-regulating kinase-1 inhibitor	Gilead	3
Elafibranor	PPAR α/δ activator	Genfit	3
Cenicriviroc	CCR2/CCR5 antagonist	Allergan	3

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Fármacos en Fase III

Drug (Alias)	Mechanism	Study Name (ClinicalTrials.gov ID; Sponsor)	Target Completion Date*	Target Enrollment	Inclusion Criteria			Primary Outcome Measures
					NAS	Fibrosis Stage	Diagnosis	
Obeticholic acid (OCA) **(REGENERATE)**	FXR ligand	REGENERATE (NCT02548351; Intercept Pharmaceuticals, New York, NY, USA)	Oct 2021	2000	≥4, with ≥1 of each component of the score	F1–3†	Biopsy	• Histologic improvement - improvement in liver fibrosis and resolution of NASH at 18 months • Composite outcome - death, MELD ≥15, cirrhosis, transplant, HCC, hospitalization, others at 6 years (est.)
Elafibranor (GFT505) **(RESOLVE-IT)**	PPAR-α/δ agonist	RESOLVE-IT (NCT02704403; Genfit, Loos, France)	Dec 2021	2000	≥4, with ≥1 of each component of the score	F1–3‡	Biopsy	• Histologic improvement - resolution of NASH without worsening of fibrosis at 72 weeks • Composite outcome - all-cause mortality, cirrhosis, "liver-related clinical outcomes" at 4 years (est.)
Selonsertib (GS-4997)	ASK-1 inhibitor	STELLAR-3 and STELLAR-4 (NCT03053050 and NCT03053063; Gilead Sciences, Foster City, CA, USA)	Jan 2020	800 (each)	–	F3 (STELLAR-3) F4 (STELLAR-4)	Biopsy	• Histologic improvement - ≥1 stage improvement in fibrosis without worsening of NASH at 48 weeks • Event-free survival at 240 weeks
Cenicriviroc (CVC) **(AURORA)**	Dual CCR2/ CCR5 antagonist	AURORA (NCT03028740; Tobira Therapeutics, South San Francisco, CA, USA)	Jul 2019	2000	–	F2–3	Biopsy	• Histologic improvement - ≥1 stage improvement in fibrosis without worsening of NASH at 12 months • Composite outcome - cirrhosis on histology, liver-related clinical outcomes, and all-cause mortality at 5 years (est.)
Liraglutide§	GLP-1 analogue	CGH-LiNASH (NCT02654665; Changi General Hospital, Singapore)	Sep 2017	36	–	–	Liver chemistries, ultrasound, ± biopsy	• Improvement in NASH at 12 months • Reduction/normalization in aminotransferases, liver fat at 12 months
Metadoxine	Antioxidant (glutathione source)	(NCT02541045; Hospital General de Mexico, Mexico City, Mexico)	Aug 2018	108	≥3, with ≥1 of each component of the score	F0–2	Biopsy	• Improvement in NAS at 6 months
Hydroxytyrosol and vitamin E¶	Antioxidant	(NCT02842567; Bambino Gesù Hospital and Research Institute, Rome, Italy)	Apr 2017	80	–	–	Biopsy	• Laboratory markers of inflammation and oxidative stress at 4 months • Laboratory markers of metabolic syndrome at 4 months

Connolly JJ, et al. J Clin Transl Hepatol. 2018 Sep 28;6(3):264-275.

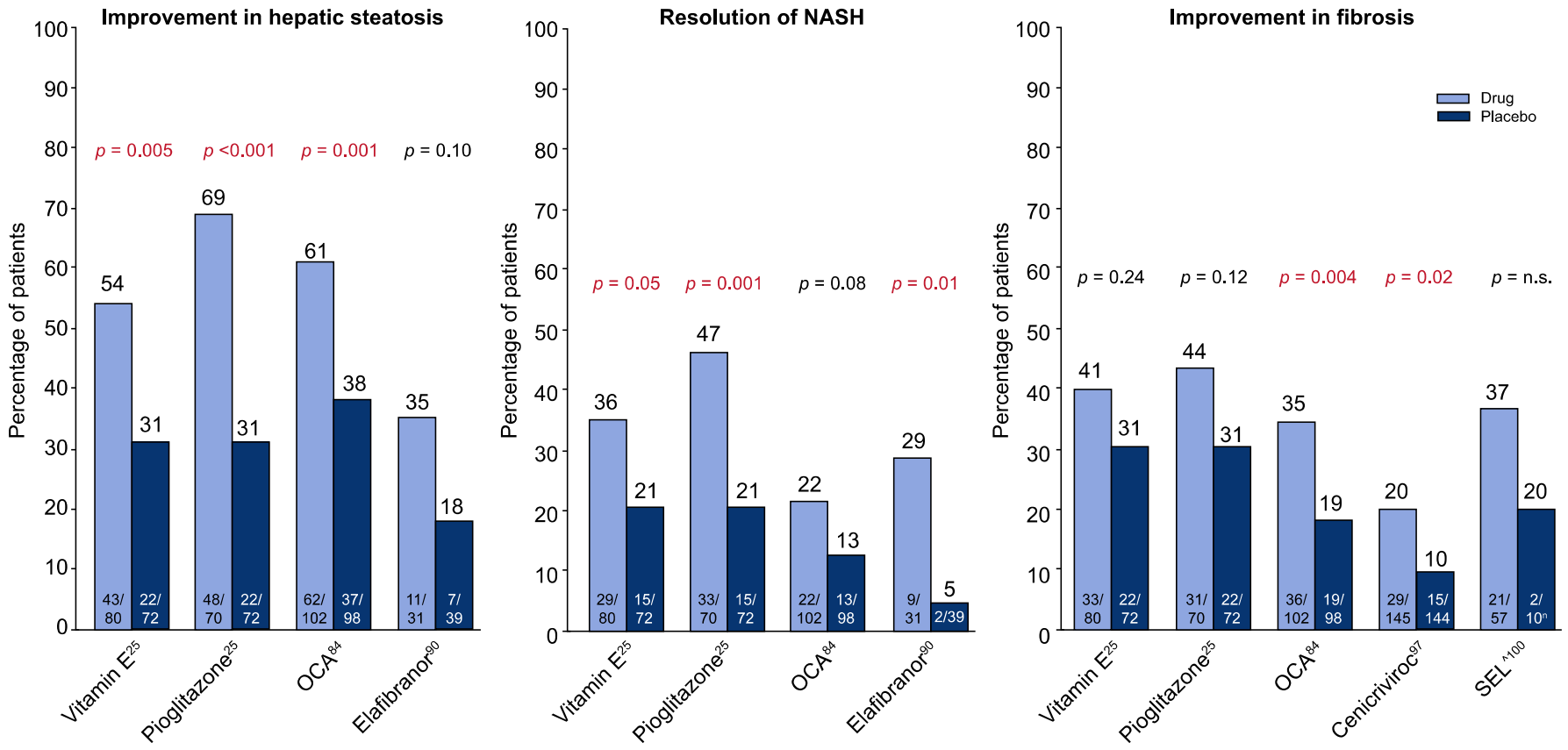
Resultados de Trabajos Fase III

Drug (Alias)	Mechanism	Study Name[Ref]	Study Design	Population	Results
Obeticholic acid (OCA) **(REGENERATE)**	FXR ligand	FLINT[47]	Phase 2b U.S. multicenter, double-blind, RCT comparing obeticholic acid 25 mg daily to placebo for 72 weeks (n = 283)	Adults with biopsy-proven, non-cirrhotic NASH with NAS ≥4, with ≥1 of each component of the score*	• Primary endpoint (improvement in NAS ≥2 points without worsening of fibrosis) met in 50/110 (45%) patients in the intervention arm vs. 23/109 (23%) patients in the placebo arm ($p < 0.001$) • Fibrosis improved in 36/102 (35%) patients i the intervention arm vs. 19/98 (19%) patient in the placebo arm ($p = 0.004$)
Elafibranor (GFT505) **(RESOLVE-IT)**	PPAR-α/δ agonist	GOLDEN-505[52]	Phase 2b USA and Europe multicenter, double-blind, RCT comparing elafibranor 80 mg and 120 mg daily to placebo for 52 weeks (n = 276)	Adults with biopsy-proven, non-cirrhotic NASH with NAS ≥3, with ≥1 of each component of the score*	• Protocol-defined primary outcome (reversal of NASH defined by the absence of at least 1 of steatosis, ballooning, and inflammation without progression to bridging fibrosis or cirrhosis) not significantly different between arms • Modified definition of response (resolution o NASH as defined by disappearance of ballooning with disappearance or mild persistence of lobular inflammation and a pathologic diagnosis of steatosis ± mild inflammation and no worsening of fibrosis) met in 17/89 (19%) patients in the 120 mg arm vs. 11/92 (12%) in the placebo arm ($p = 0.045$) • Fibrosis stage was significantly reduced in responders (based on the modified definition to 120 mg vs. non-responders
Selonsertib (GS-4997) **(AURORA)**	ASK-1 inhibitor	[54]	Phase 2 U.S. and Canada multicenter, open-label, RCT comparing selonsertib 6 mg and 18 mg daily ± simtuzumab to simtuzumab monotherapy for 24 weeks (n = 72)	Adults with biopsy-proven F2–3 NASH with NAS ≥5	• Fibrosis improved in 13/30 (43%) patients in the 18 mg ± simtuzumab arm vs. 8/27 (30%) patients in the 6 mg ± simtuzumab arm vs. 2/10 (20%) patients receiving simtuzumab monotherapy • Mostly dose-dependent trends observed in ≥15% reduction in MRE stiffness, ≥30% reduction in MRI-PDFF, ≥2 point improvement in NAS, and less likely progression to cirrhosis
Cenicriviroc (CVC)	Dual CCR2/CCR5 antagonist	CENTAUR[58]	Phase 2b multinational multicenter, double-blind, RCT comparing cenicriviroc 150 mg daily to placebo for 2 years (n = 289)	Adults with biopsy-proven F1–3 NASH with NAS ≥4 and diabetes or metabolic syndrome	• Pre-specified primary endpoint (≥2 point improvement in NAS [with ≥1-point reduction in lobular inflammation or ballooning] and no worsening of fibrosis) not met at 1 year interim analysis • Fibrosis improved (without worsening of steatohepatitis) in 29/145 (20%) patients in the intervention arm vs. 15/144 (10%) patients in the placebo arm ($p = 0.023$), mos pronounced in subjects with higher disease activity and stage, at 1 year interim analysis

*NAS (NAFLD activity score) scored as steatosis 0–3, ballooning 0–2, and lobular inflammation 0–3.

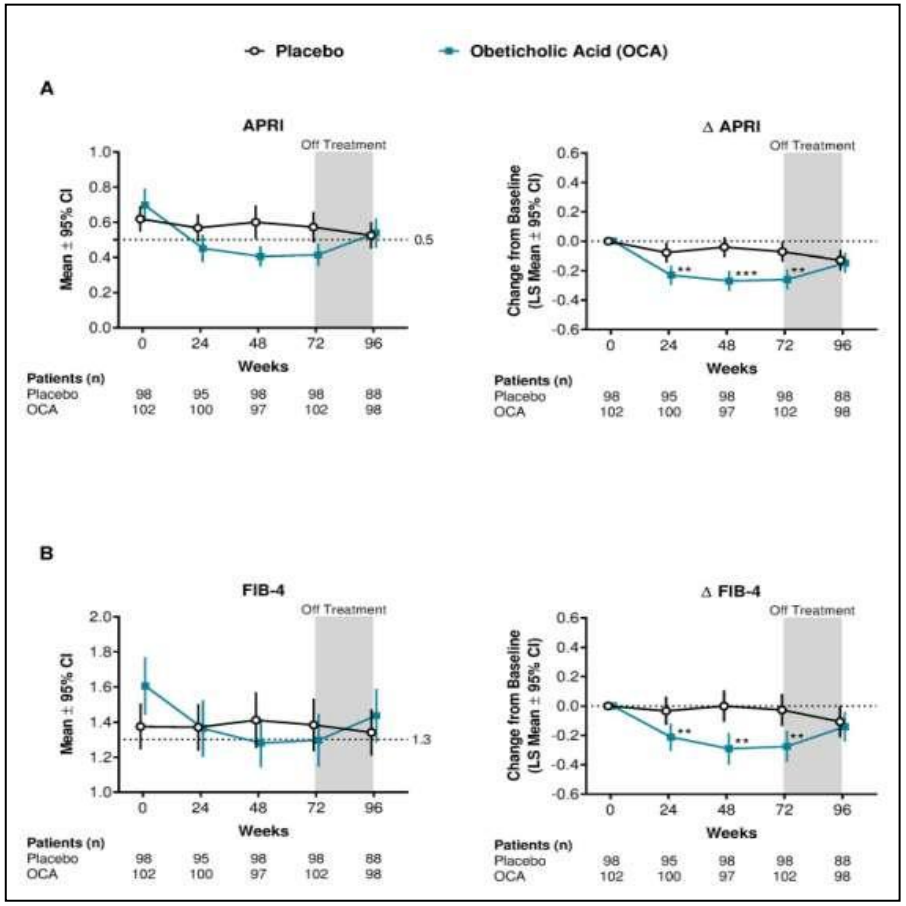
Connolly JJ, et al. J Clin Transl Hepatol. 2018 Sep 28;6(3):264-275.

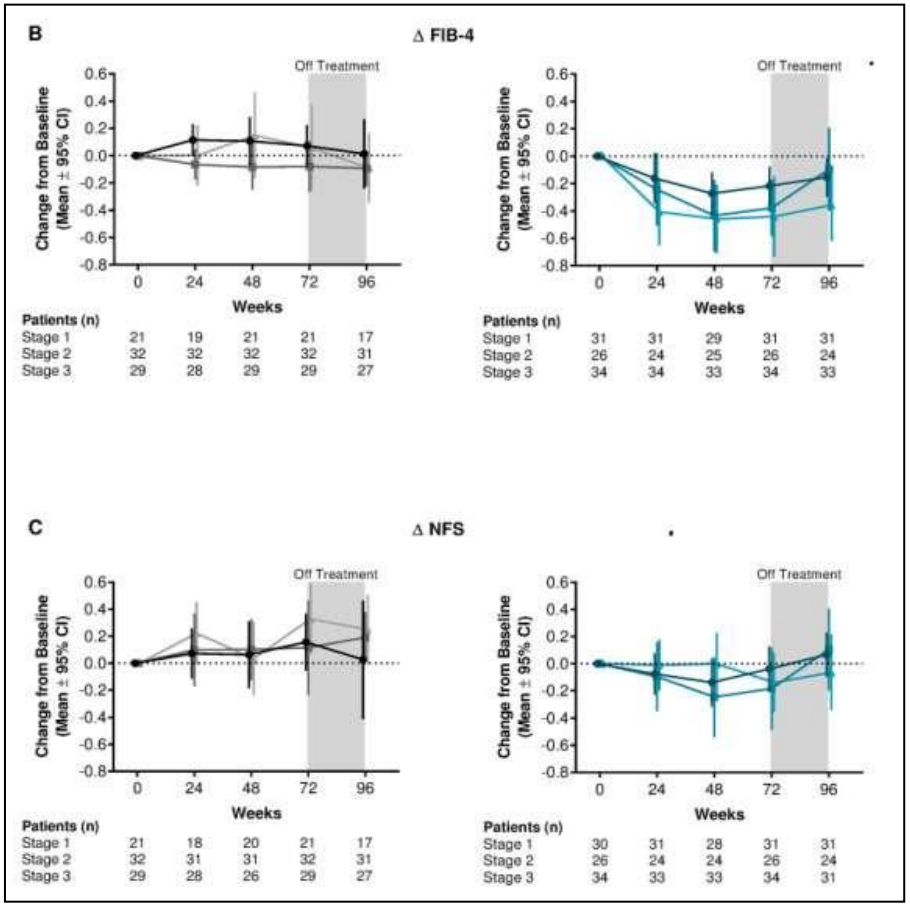
Efecto Farmacológico en NASH



Konerman M, et al. J Hepatol 2018 vol 68:362-375

OCA. Mejoría de Scores Clásicos

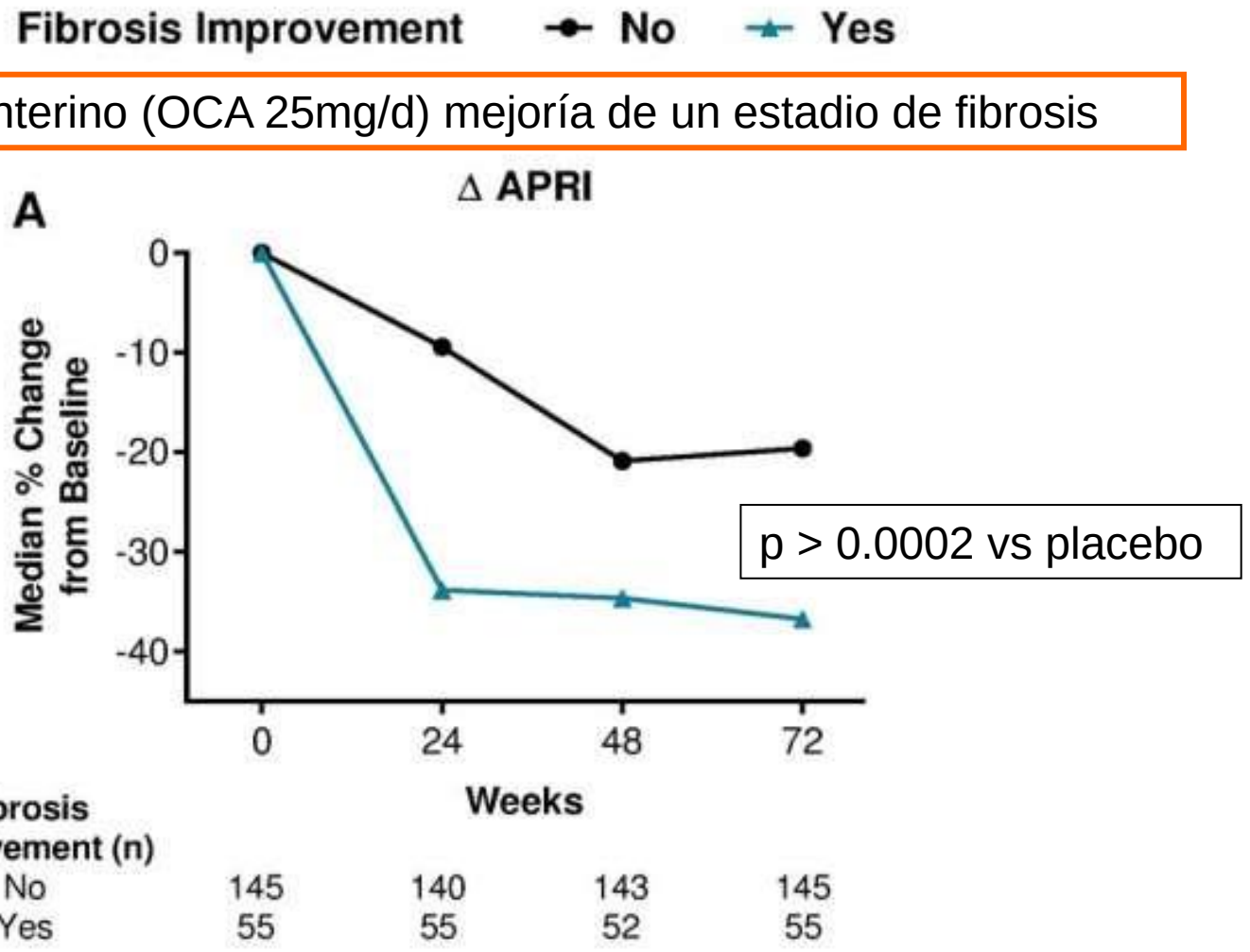




Sanyal AJ. Liver Int. 2018 Sep 25.

OCA. Mejoría de Scores Clásicos

REGENERATE TRIAL



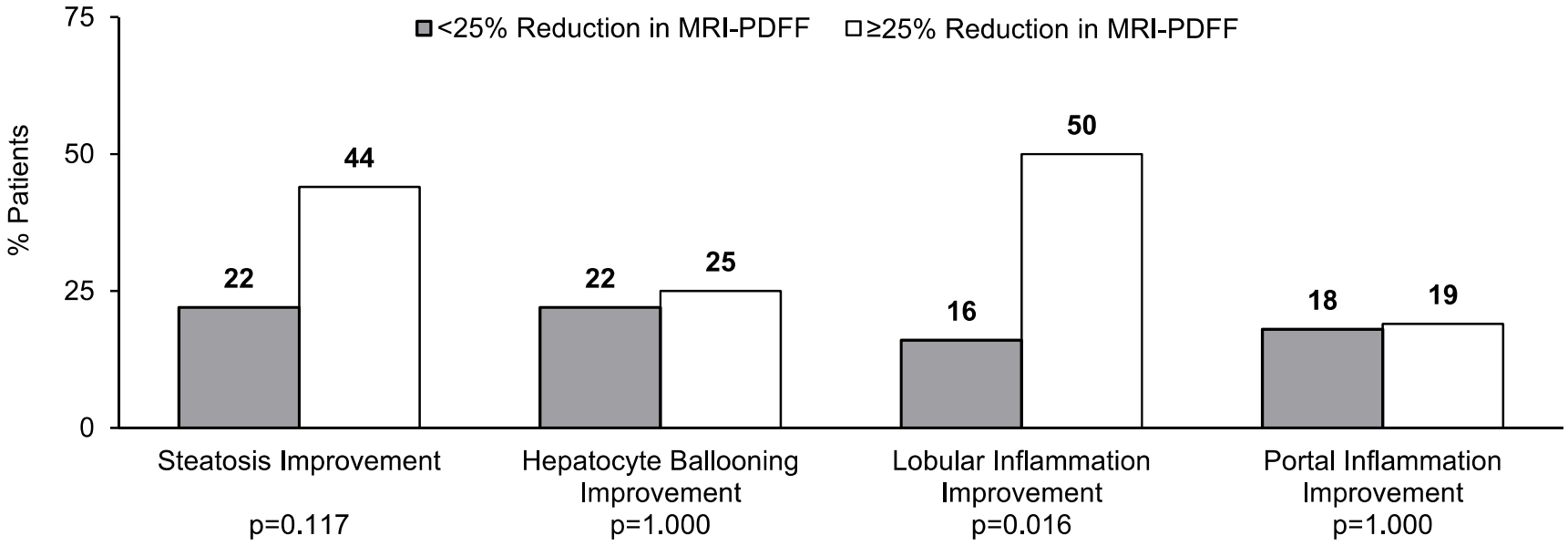
Análisis interino (OCA 25mg/d) mejoría de un estadio de fibrosis

p > 0.0002 vs placebo

Sanyal AJ. Liver Int. 2018. EASL19, Abstract.

Selonsertib. Cambios Histológicos

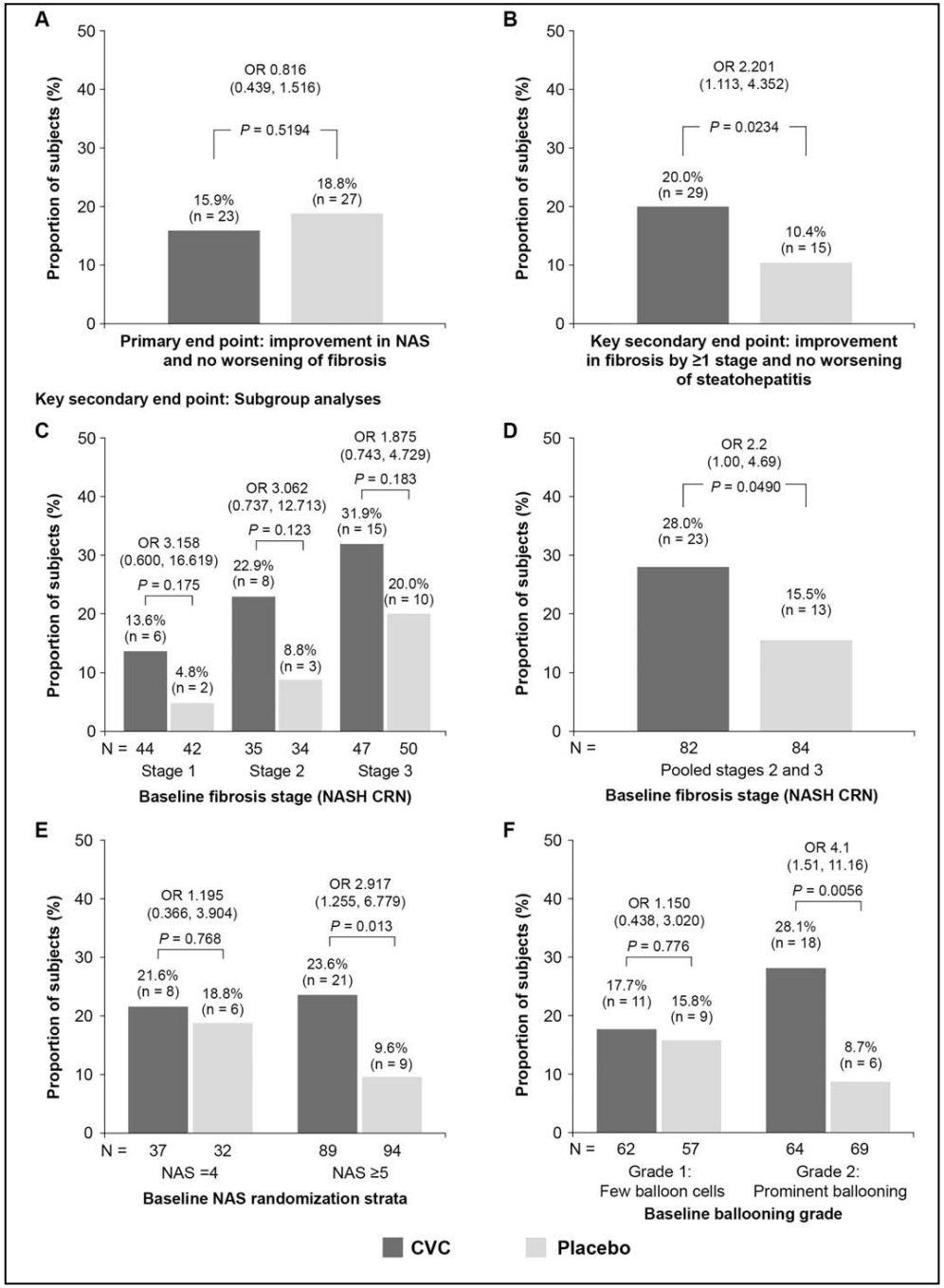
STELLAR-3 y STELLAR-4, suspendido en análisis interino por falla en end-point primario



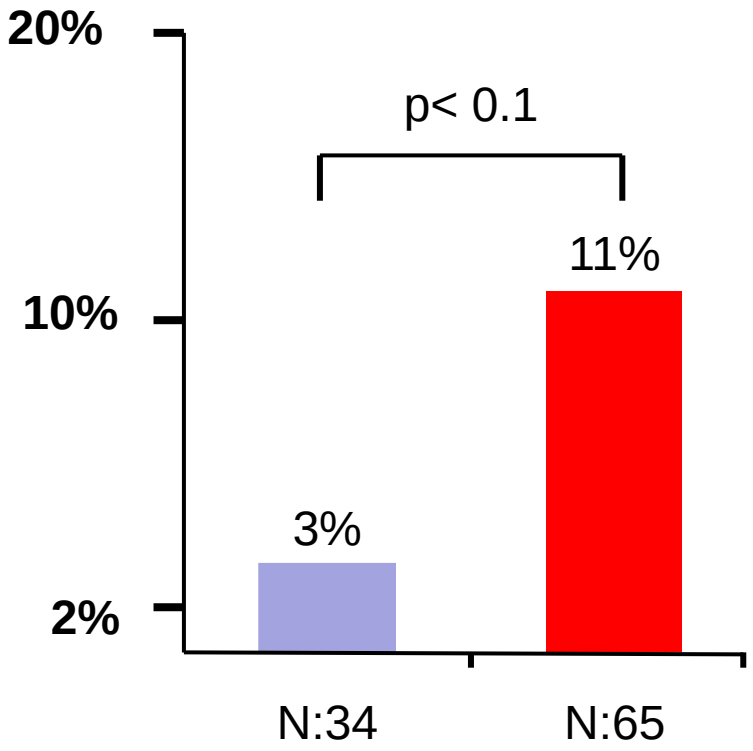
Jayakumar S, et al. J Hepatol. 2018. www.gilead.com/news-stellar-3, 2019.

Cenicriviroc

Fase III-AURORA- Sep. 2020



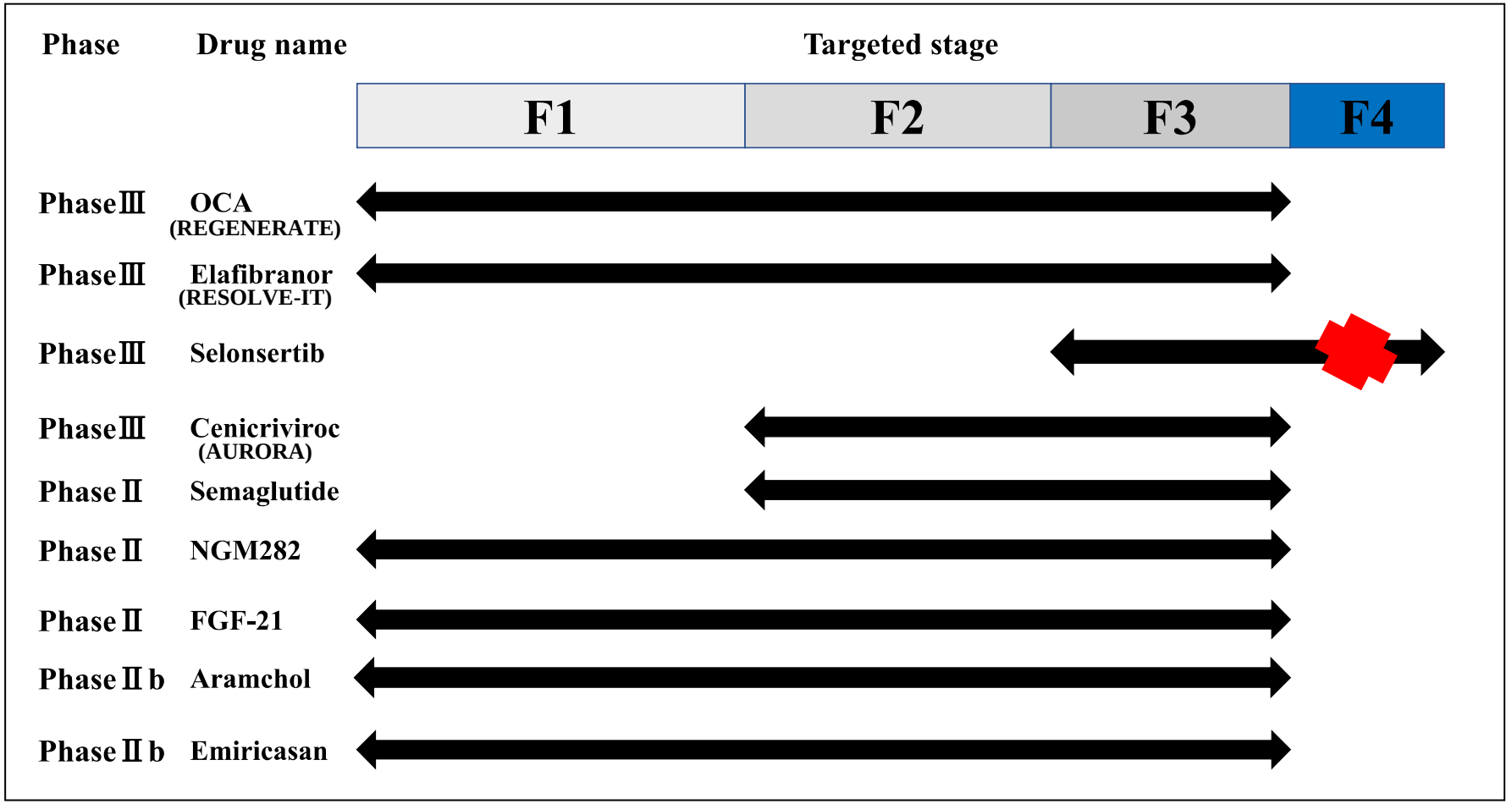
Mejoría del estadio de fibrosis (>2) en el Fase II (CENTAUR)



Seguimiento a 2 años

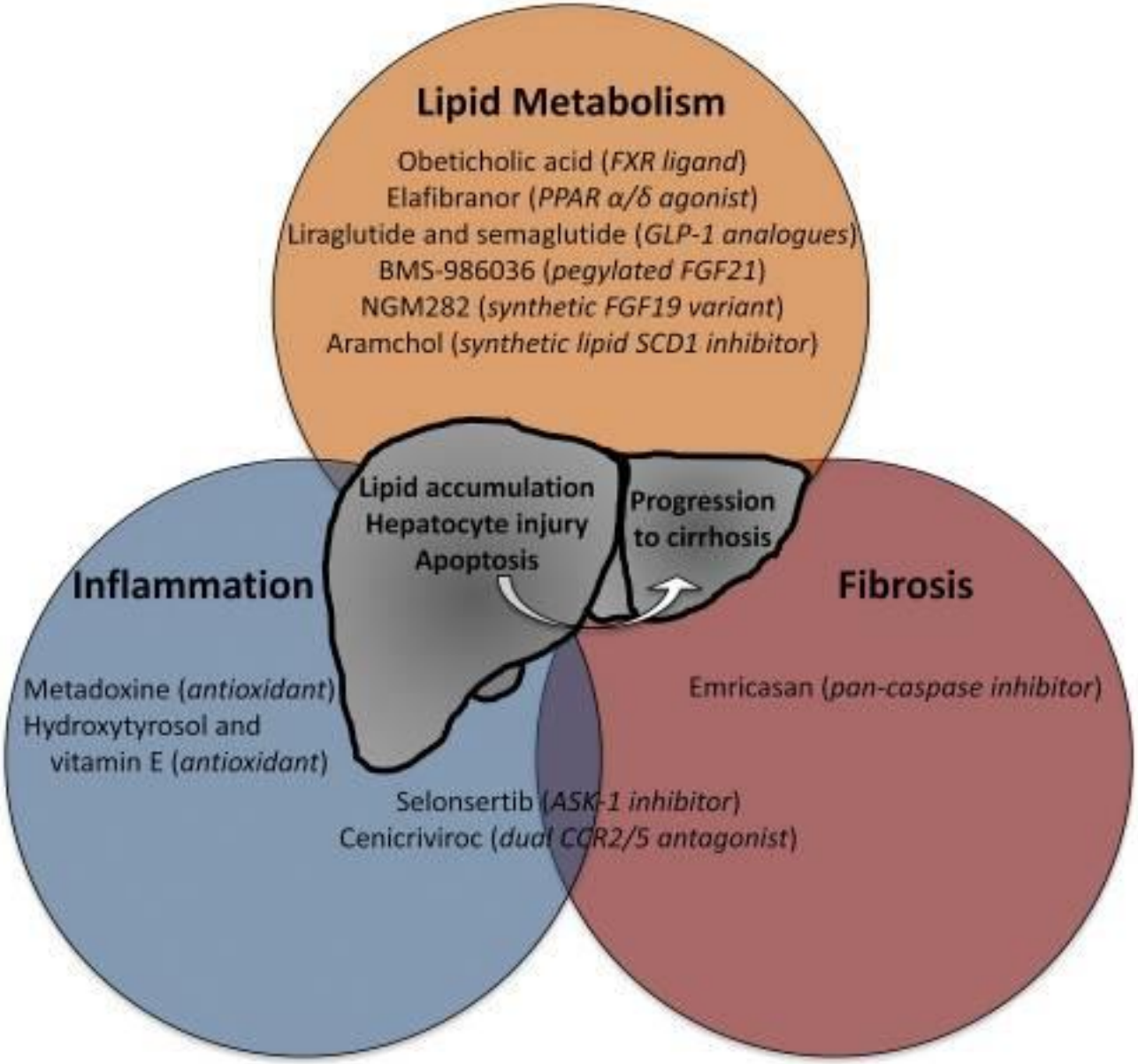
Friedman SL, et al. Hepatology 2018.

Antifibróticos Fase II y III

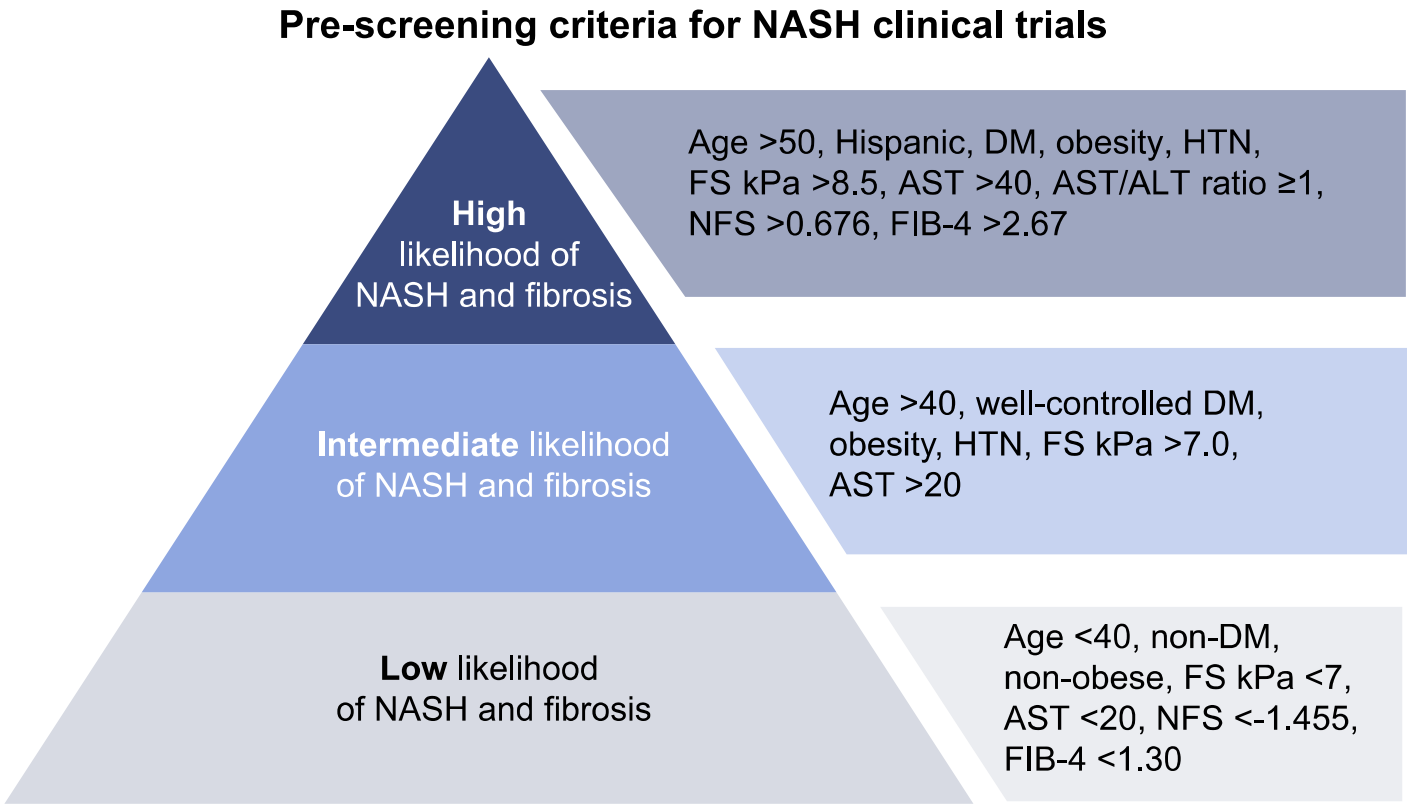


Yomeda M, J Gastroenterol 2018

Tratamientos Futuros en NASH



El problema del enrolamiento en los protocolos de investigación



Tasa de screening faillure > **65%**.....nos faltan predictores de fibrosis mas sensibles?

Tratamiento Quirúrgico

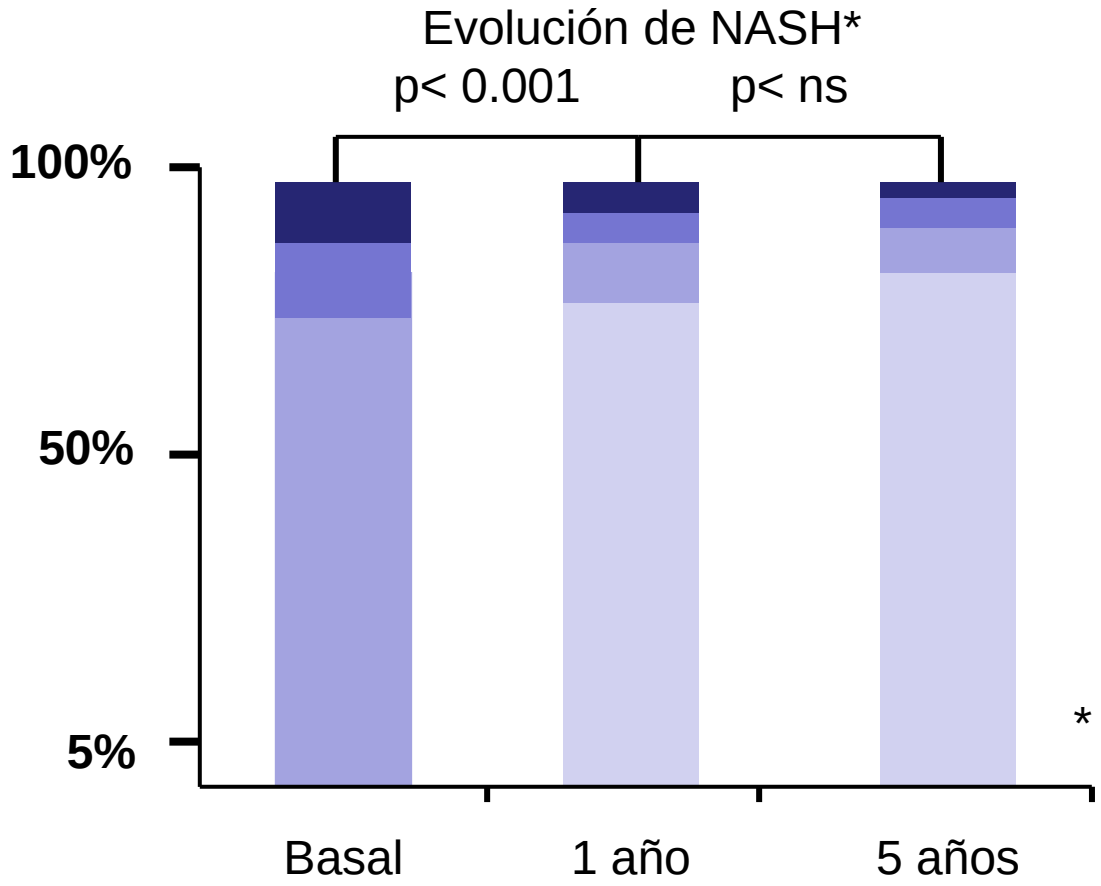
Cirugía bariática por obesidad mórbida (cinturón gástrico o derivación yeyuno-ileal por laparoscopía)

Pérdida significativa de peso

<u>Mejoría histológica</u>

- **Esteatosis**
- **Inflamación**
- **Fibrosis**

Efecto Histológico de la Cirugía Bariátrica



Lassailly G, et al. EASL 2018, Paris. #484.

Conclusiones

- El tratamiento se basa en múltiples conductas.
- El descenso de peso y la actividad física son pilares fundamentales del tratamiento.
- Existe evidencia discutida sobre los tratamientos especificos existentes en el mercado.
- El futuro permitirá establecer el mejor tratamiento para cada caso seleccionando el los fármacos mas adecuados.