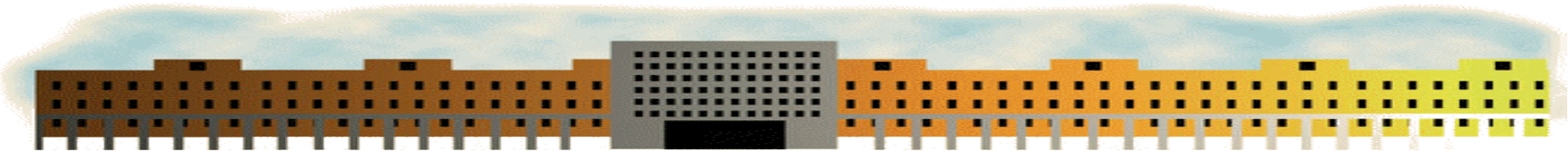
Tratamiento de la EHGNA en 2019.

XVIII Jornadas de Avances en Hepatología

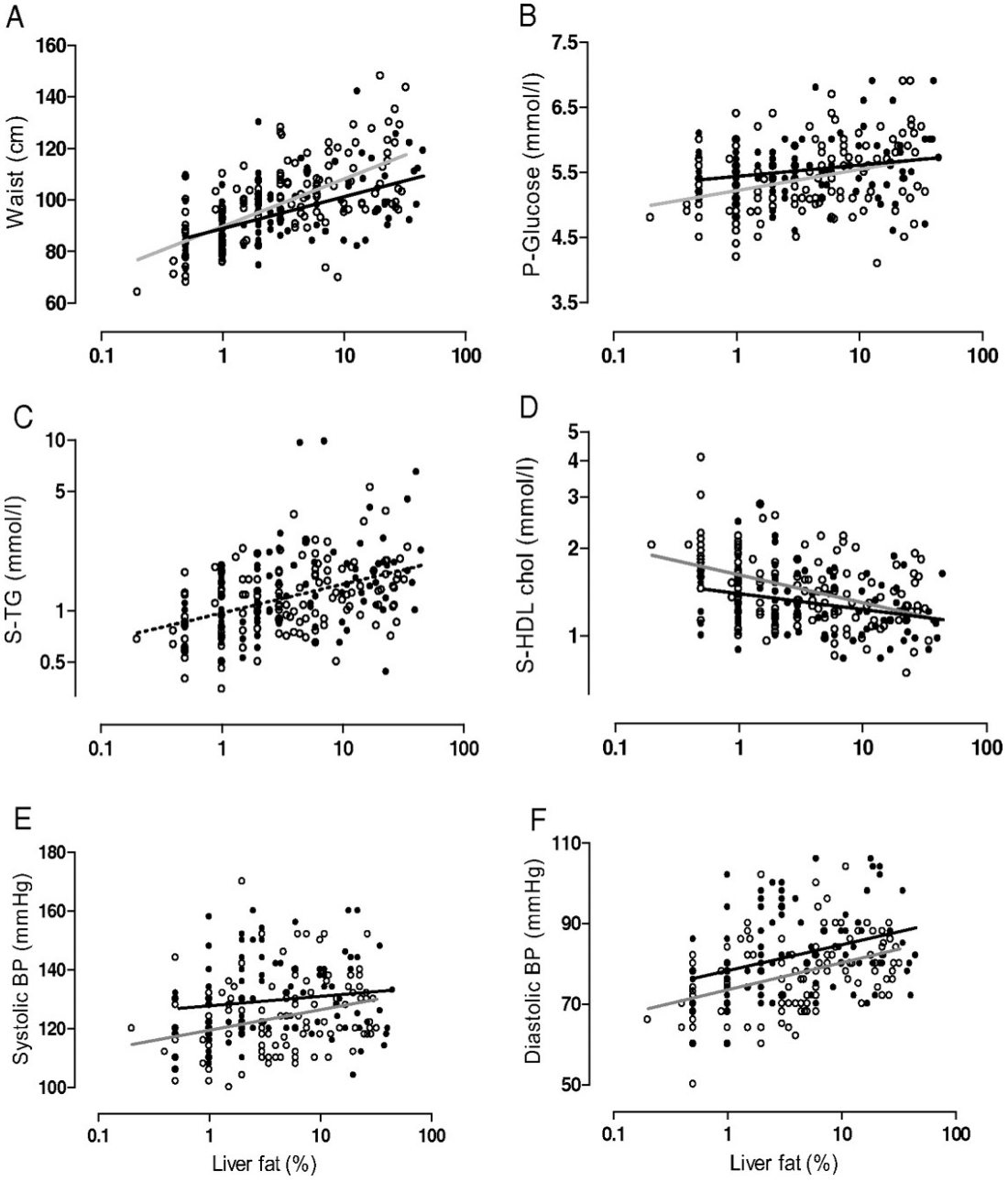
Conrado Fernández Rodríguez
S. Aparato Digestivo. Hospital Universitario Fundación Alcorcón.
Málaga, 23 y 24 de Mayo de 2019.



Sinopsis

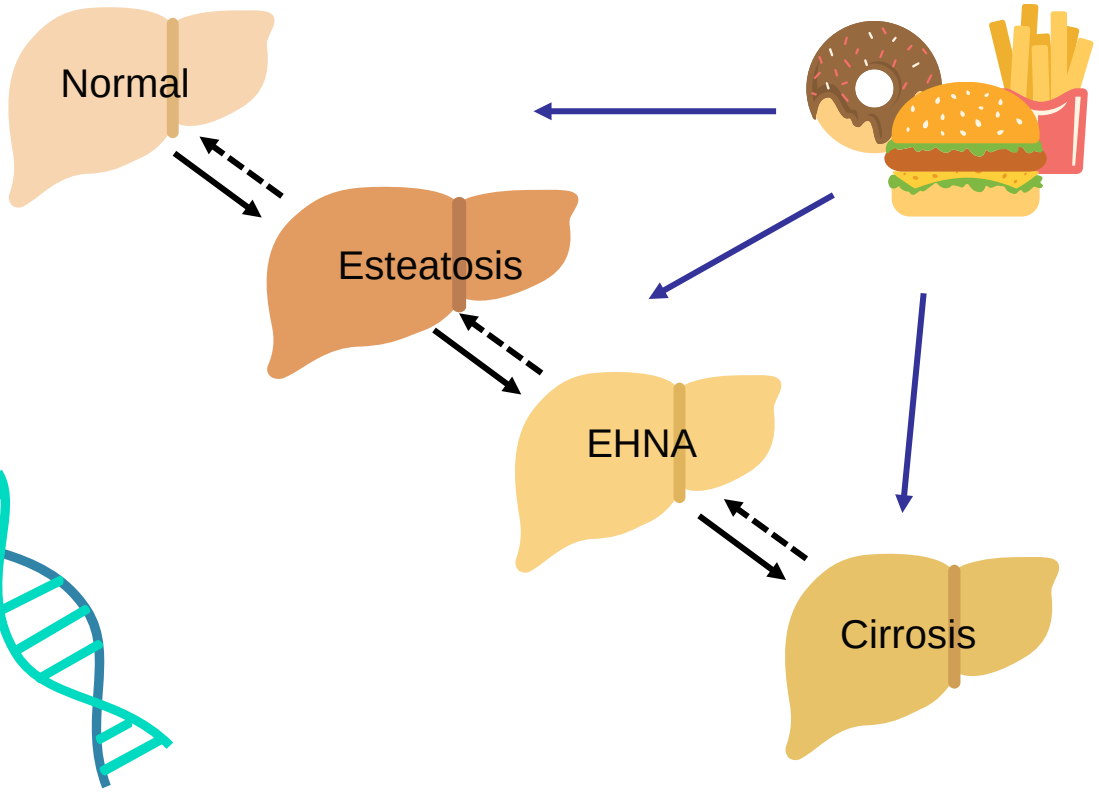
- Cambios en el estilo de vida.
- Fármacos disponibles.
- Endoscopia metabólica.
- Fármacos en desarrollo.

Relationships between liver fat and components of the metabolic syndrome. Liver fat is associated with waist .



The Journal of Clinical Endocrinology & Metabolism, Volume 92, Issue 9, 1 September 2007, Pages 3490–3497, https://doi.org/10.1210/jc.2007-0482 .

EHGNA se produce por una compleja interaccion entre factores geneticos y modificadores ambientales

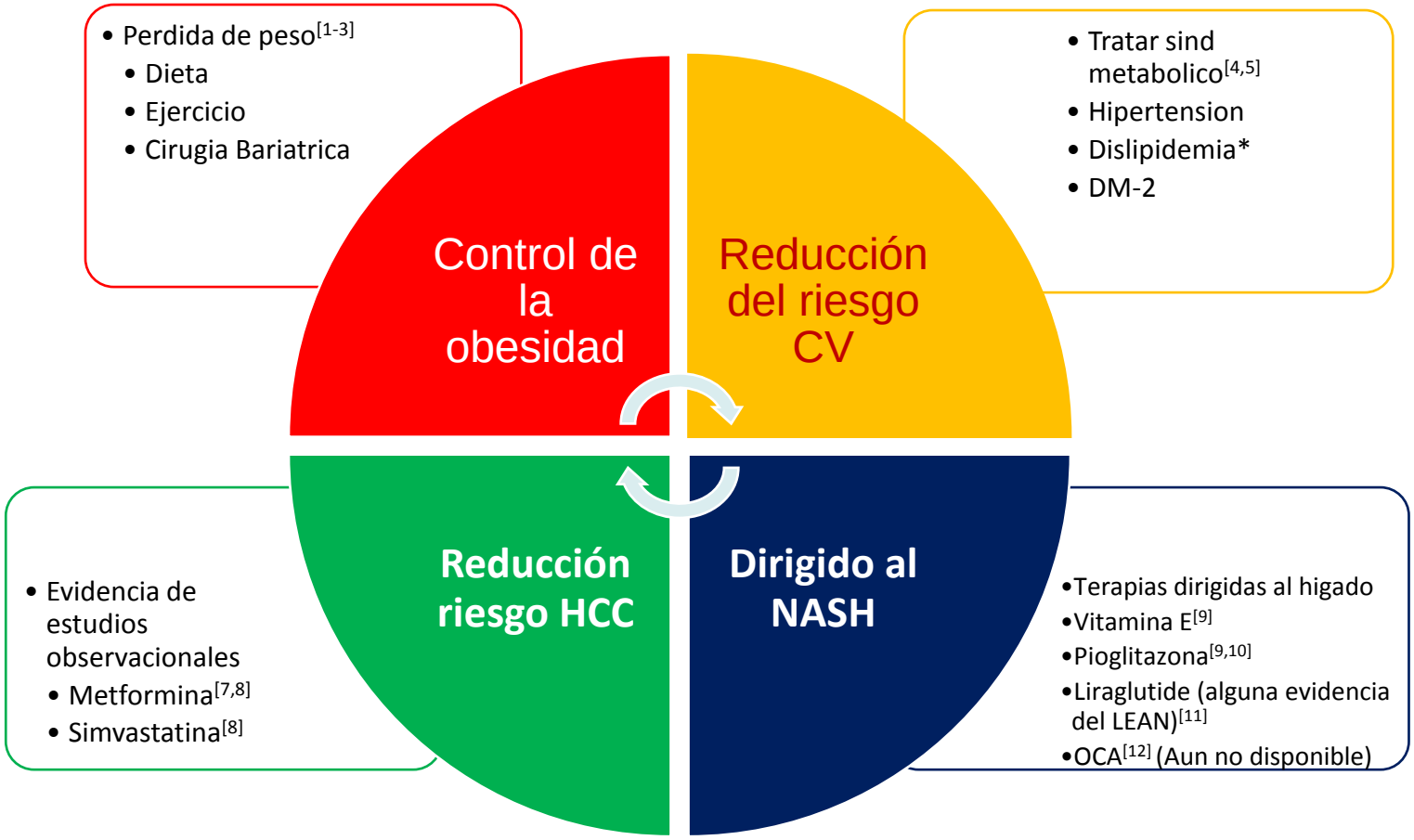


Ambientales
Sedentarismo
“Picoteo”,
comidas rapidas
Grasas trans y saturadas
Carnes rojas procesadas

Genes
PNPLA3
TM6SF2
GCKR
SOD2
MBOAT7

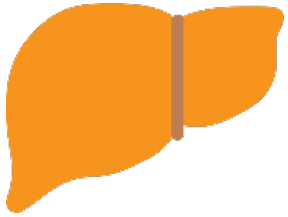
Slide credit: clinicaloptions.com

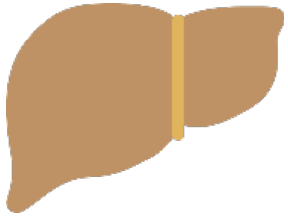
Objetivos del manejo de la EHGNA con los tratamientos actualmente disponibles

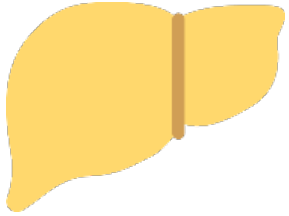


1. Promrat. Hepatology. 2010;51:121. 2. Vilar-Gomez. Gastroenterology. 2015;149:367. 3. Lassailly. Gastroenterology. 2015;149:379.
4. Musso. Hepatology. 2010;52:79. 5. Ratziu. J Hepatol. 2010;53:372. 6. Bril. J Clin Endocrinol Metab. 2017;102:2950. 7. Zhang. Scand J Gastroenterol. 2013;48:78. 8. Chen. Medicine (Baltimore). 2015;94:e1013. 9. Sanyal. NEJM. 2010;362:1675. 10. Cusi. Ann Intern Med. 2016;165:305. 11. Armstrong. Lancet. 2016;387:679. 12 Younossi. EASL 2019. Abstr GS-06

Enfoque a los procesos fisiopatológicos.







Targets related to insulin resistance and/or lipid metabolism

Targets related to lipotoxicity and oxidative stress

Targets related to inflammation and immune activation

Targets related to cell death (apoptosis and necrosis)

Targets related to fibrogenesis and collagen turnover

PPAR γ Pioglitazone
GLP-1: Liraglutide, Semaglutide
ACC: GS-0976, PF-05221304
SCD1: Aramchol
SGLT1/2: LIK066
FGF21: BMS-986036
THR-β: MGL-3196

PPARα/∂: Elafibranor
PPARα/∂/γ: IVA337
PPARα/γ: Saroglitazar
mTOT: MSDC-0602K
FXR: OCA, GS-9674, LJN-452, LMB-763
TGR5: INT-767, INT-777
ASBT: Volixibat
FGF19: NGM282
Vitamin E

CCR2/5: Cenicriviroc
AOC3: BI 1467335
TLR4: JKB-121

ASK1: Selonsertib
Caspases: Emricasan

LOXL2: Simtuzumab
Galectin: GR-MD-02

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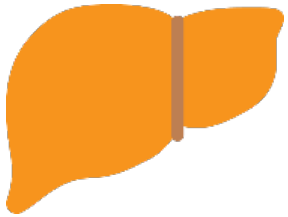
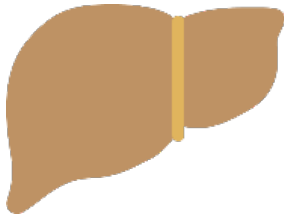
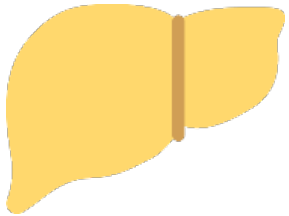
Enfoque a los procesos fisiopatológicos







Targets related to insulin resistance and/or lipid metabolism

Targets related to lipotoxicity and oxidative stress

Targets related to inflammation and immune activation

Targets related to cell death (apoptosis and necrosis)

Targets related to fibrogenesis and collagen turnover

PPAR γ
GLP-1:

ACC:

SCD1:
SGLT1/2:
FGF21:
THR-β:

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

PPARα/∂:
PPARα/∂/γ:
PPARα/γ:
mTOT:
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TGR5:
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FGF19:

Elafibranor
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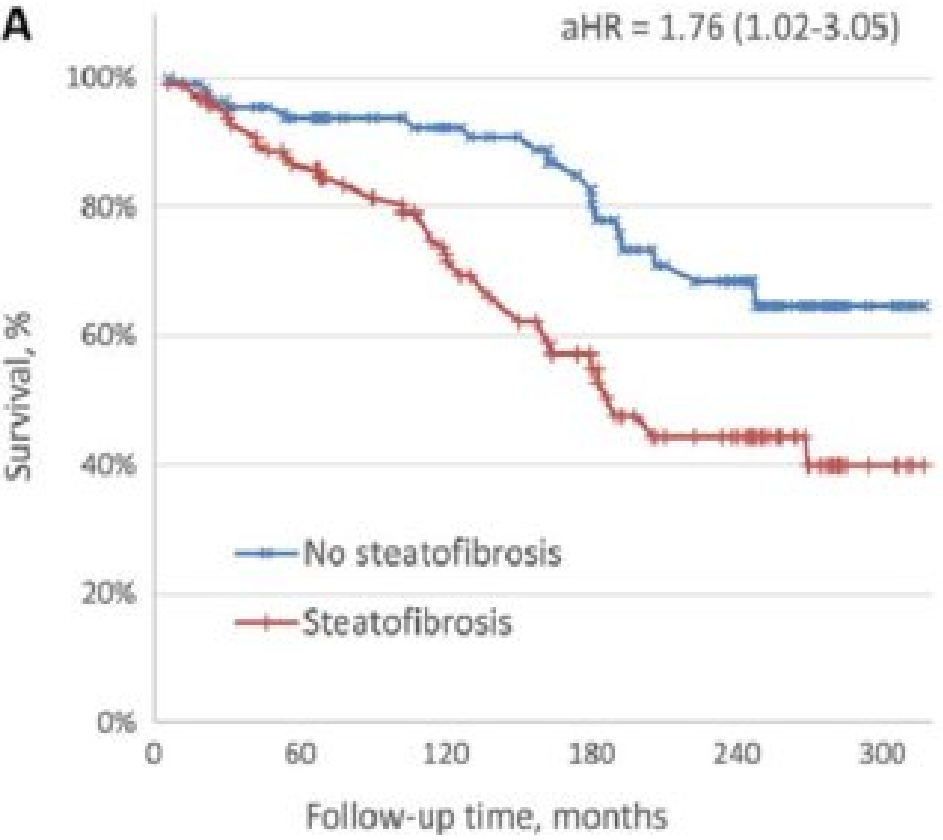
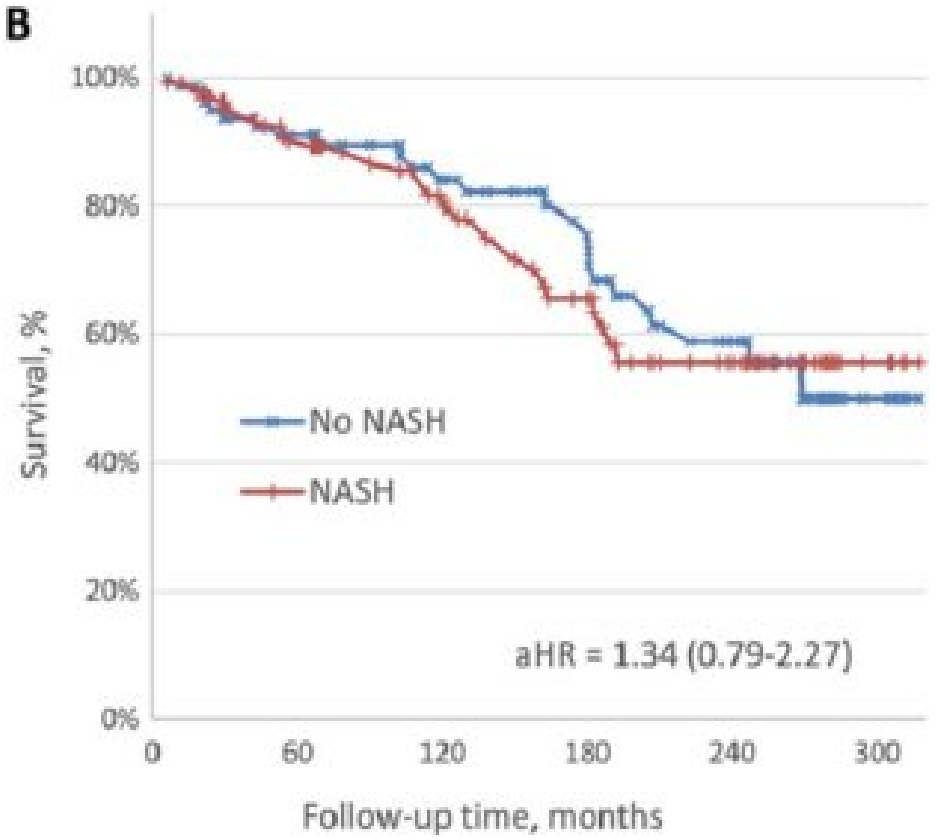
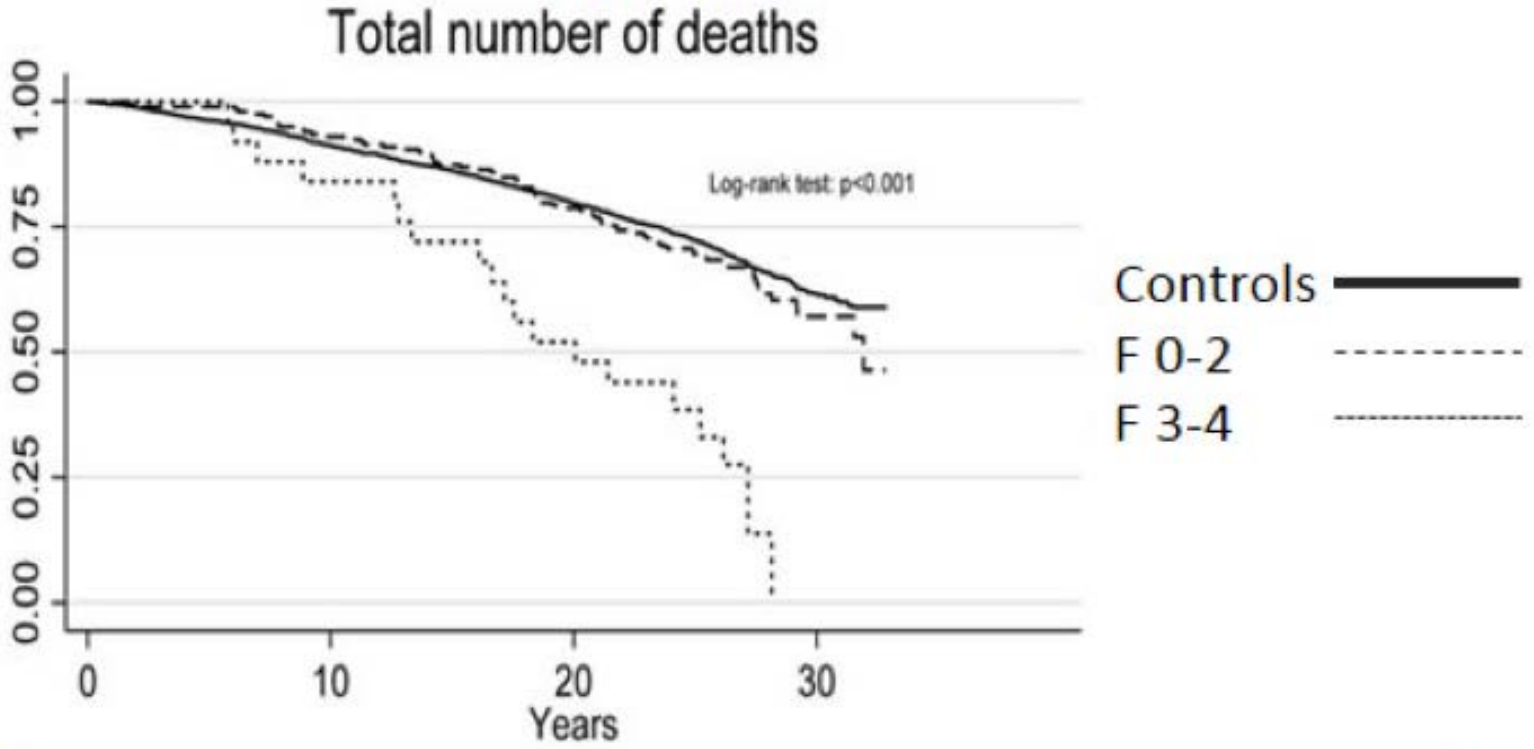
EHNA: La importancia pronóstica de la fibrosis.





Younossi Z et al Hepatol Commun. 2017; 1: 421–428.

Strongest predictor for disease-specific mortality in NAFLD[b]



# at Risk	0	10 y	20 y	30 y
Cont.	2286	2085	1818	387
F 0-2	198	184	156	28
F 3-4	25	21	13	0

Ekstedt M Hepatology 2015; 61:1547-1554

FDA: Los objetivos de mejoría histológica predicen beneficio clinico.

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

Porcentaje de reducción ponderal asociado a mejoría histológica en la EHGNA.

Perdida de peso	Resultado en pacientes que pierden peso	Resultado en los que mantienen la perdida a 1 año
≥10% [1]	Regresión de la fibrosis (45%)	<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*)	No publicado

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.

Table 4. *Factors associated with non-alcoholic steatohepatitis in overweight patients with NAFLD*

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p-value	OR (95% CI)	p value
Age (years)	1.067 (1.019-1.117)	0.005		
Male sex	0.250 (0.073-0.855)	0.027		
Body mass index (kg/m^2)	1.184 (0.942-1.488)	ns		
Waist circumference, cm	1.018 (0.955-1.084)	ns		
Systolic blood pressure, mmHg	1.073 (1.032-1.116)	0.001		
Diastolic blood pressure, mmHg	1.073 (1.032-1.115)	0.001		
Total cholesterol, mg/dl	0.997 (0.987-1.007)	ns		
Triglycerides, mg/dl	1.005 (0.999-1.012)	ns		
ALT, IU/l	1.008 (0.998-1.019)	ns		
AST, IU/l	1.016 (0.998-1.035)	ns		
GGT, IU/l	0.994 (0.986-1.003)	ns		
Fasting plasma glucose, mg/dl	1.038 (1.004-1.074)	0.03		
HOMA-IR	2.036 (1.305-3.176)	0.002		
LDL-chol, mg/dl	1.001 (0.987-1.015)	ns		
HDL-chol, mg/dl	0.975 (0.939-1.013)	ns		
Platelet count, $\times 10^3$/µl	0.992 (0.984-1.001)	ns		
PNPLA3 G carrier	1.810 (0.511-6.403)	ns		
TNFA-α A carrier	0.483 (0.105-2.220)	ns		
History of diabetes	8.571 (0.937-78.405)	0.057		
History of hypertension	8.156 (2.601-15.577)	0.001		
Metabolic syndrome	0.201 (0.068-0.598)	0.004		
MEDAS	0.667 (0.501-0.890)	0.006	0.7 (0.5-0.8)	0.002

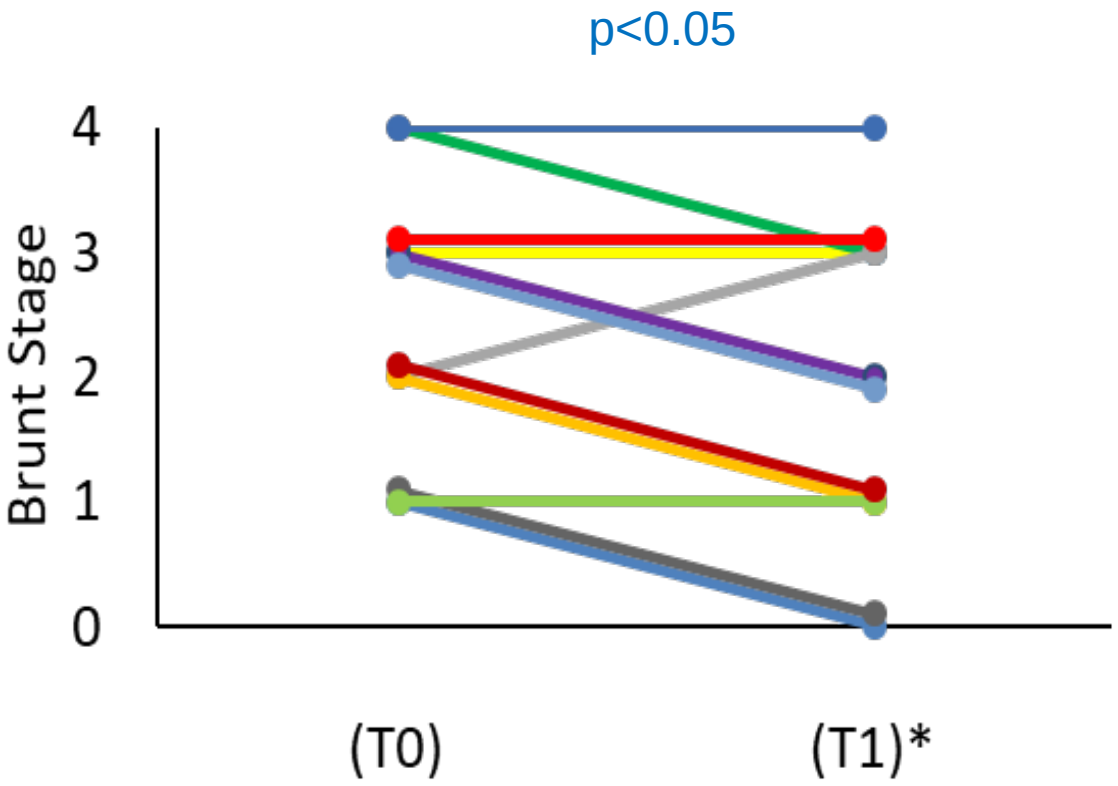
ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyltransferase; HOMA-IR: homeostasis model assessment of insulin resistance; LDL-chol: low-density lipoprotein cholesterol; HD-chol: high-density lipoprotein cholesterol; PNPLA3: patatin-like phospholipase domain containing protein 3; TNF-α: tumor necrosis factor-alpha.

Table 5. *Factors associated with liver fibrosis in overweight patients with NAFLD*

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p-value	OR (95% CI)	p value
Age (years)	1.049 (1.005-1.094)	0.028		
Male sex	4 (1.169-13.683)	0.027		
Body mass index (kg/m^2)	0.951 (0.767-1.179)	ns		
Waist circumference, cm	0.97 (0.91-1.035)	ns		
Systolic blood pressure (mmHg)	1.029 (0.999-1.060)	ns		
Diastolic blood pressure (mmHg)	1.018 (0.988-1.049)	ns		
Creatinine, mg/dl	0.157 (0.006-3.874)	ns		
Total bilirubin, mg/dl	1.229 (0.657-2.297)	ns		
ALT, IU/l	1.016 (1.003-1.030)	0.019		
AST, IU/l	1.031 (1.004-1.059)	0.022		
GGT, IU/l	1.002 (0.994-1.010)	ns		
Fasting plasma glucose, mg/dl	1.022 (0.994-1.049)	ns		
HOMA-IR	1.423 (1.057-1.916)	0.020	1.8 (1.1-2.8)	0.007
Total cholesterol, mg/dl	0.992 (0.981-1.002)	ns		
LDL-chol, mg/dl	0.996 (0.982-1.010)	ns		
HDL-chol, mg/dl	0.978 (0.942-1.015)	ns		
Triglycerides, mg/dl	1.001 (0.995-1.007)	ns		
Platelet count, $\times 10^3$/µl	0.996 (0.988-1.004)	ns		
PNPLA3 rs 738409 carrier	0.857 (0.263-2.792)	ns		
TNF-α	0.179 (0.032-0.996)	0.049		
History of diabetes	8.571 (0.937-18.405)	ns		
History of hypertension	3.223 (1.128-9.21)	0.029		
Metabolic syndrome	0.632 (0.227-1.761)	ns		
MEDAS	0.695 (0.528-0.915)	0.010	0.7 (0.5-0.8)	0.001

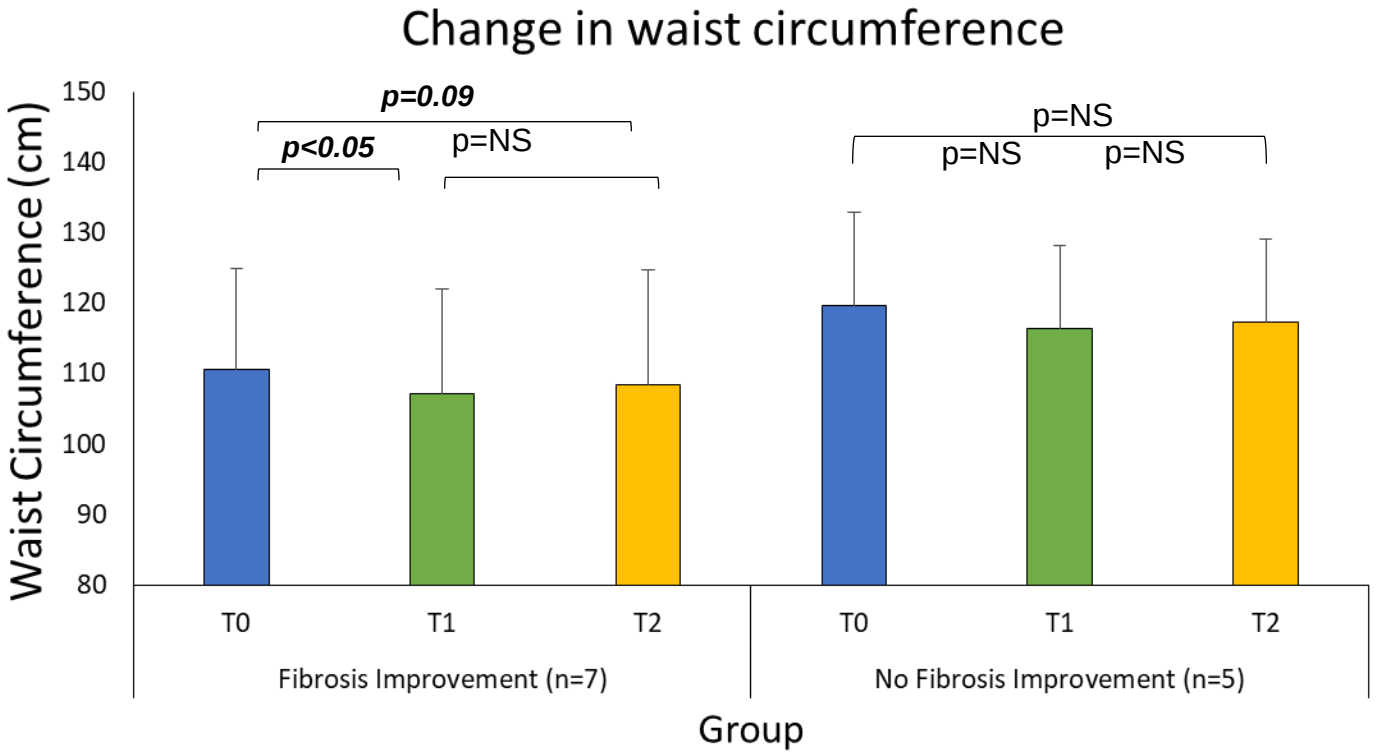
ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyltransferase; HOMA-IR: homeostasis model assessment of insulin resistance; LDL: low-density lipoprotein; HDL: high-density lipoprotein; PNPLA3: patatin-like phospholipase domain containing protein 3; TNF-α: tumor necrosis factor-alpha.

12 semanas de ejercicio aeróbico en 12 pacientes sin reducción significativa de peso



O`Gorman P et al ILC 2019, PS-105

12 semanas de ejercicio aeróbico mejoro el perímetro abdominal y la histología, pese a que solo 3 de 12 redujeron ≥ 5% el peso



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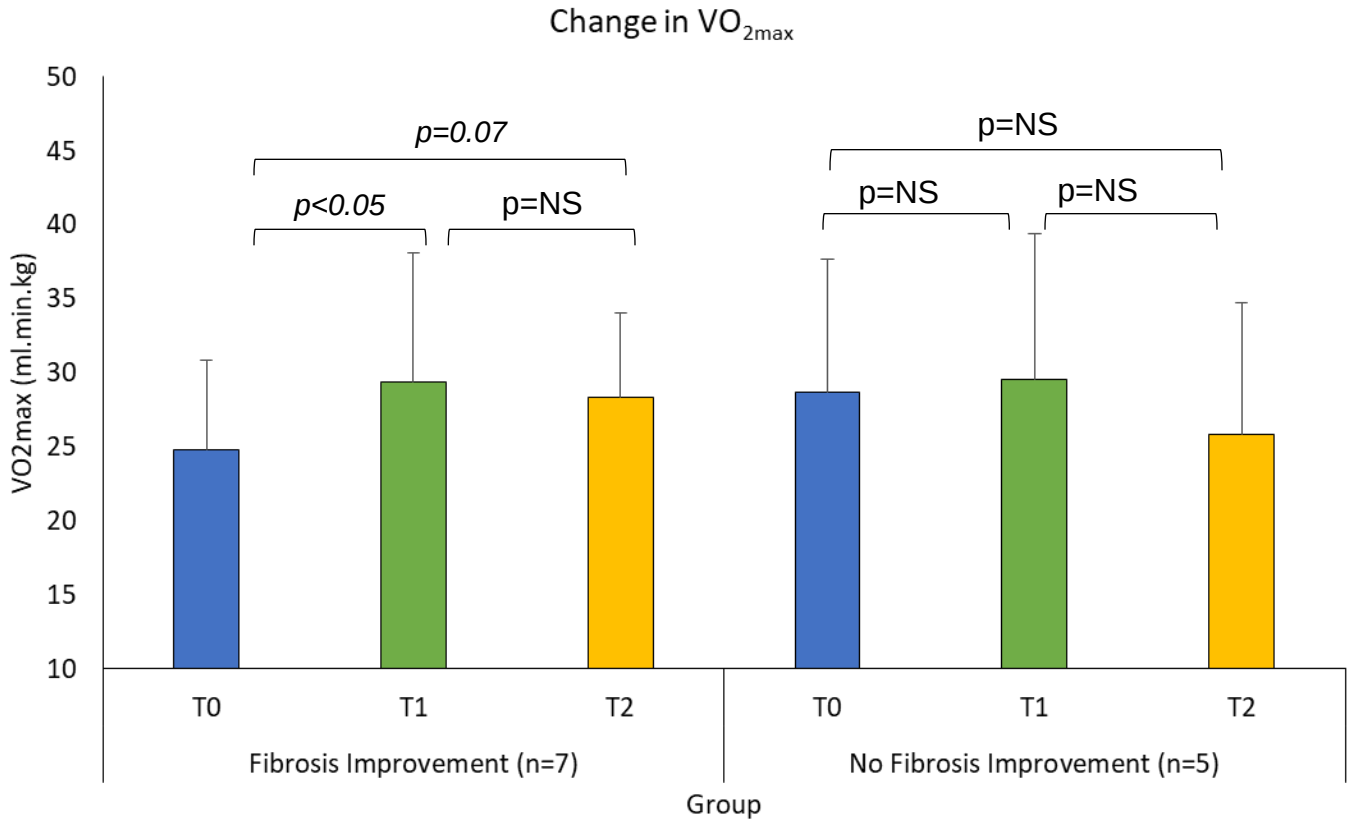
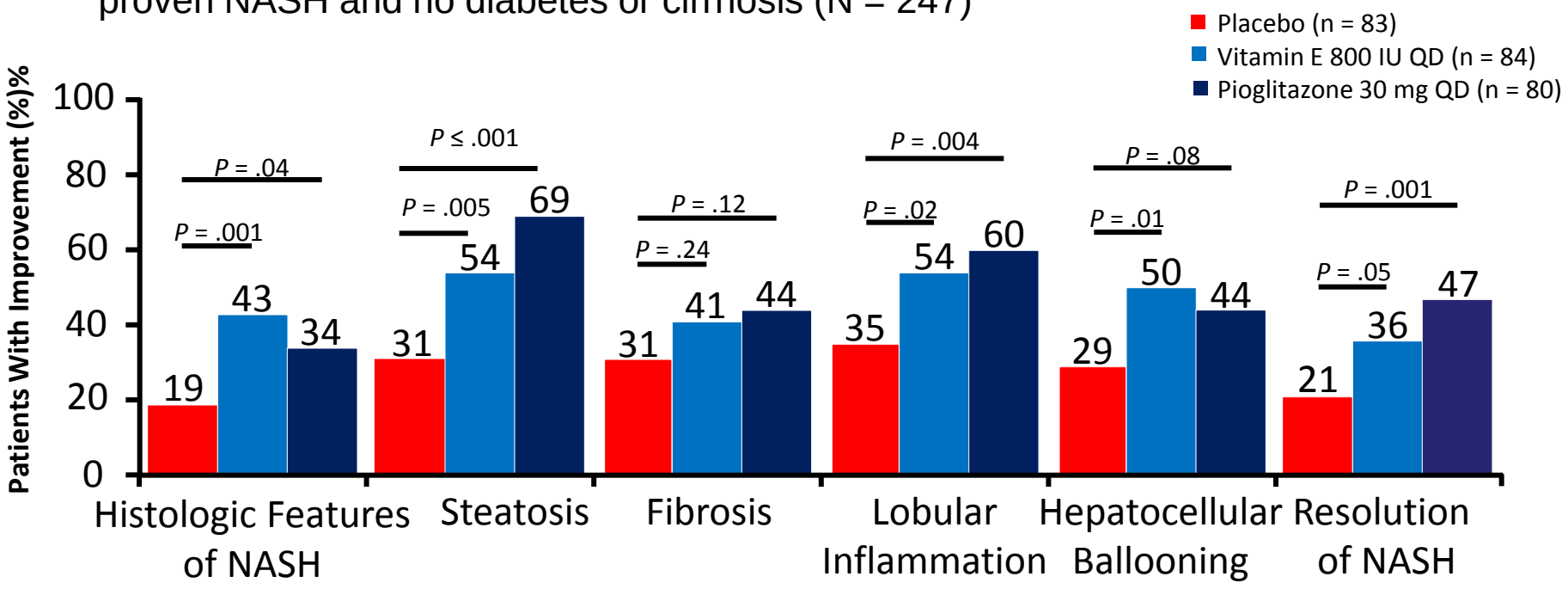


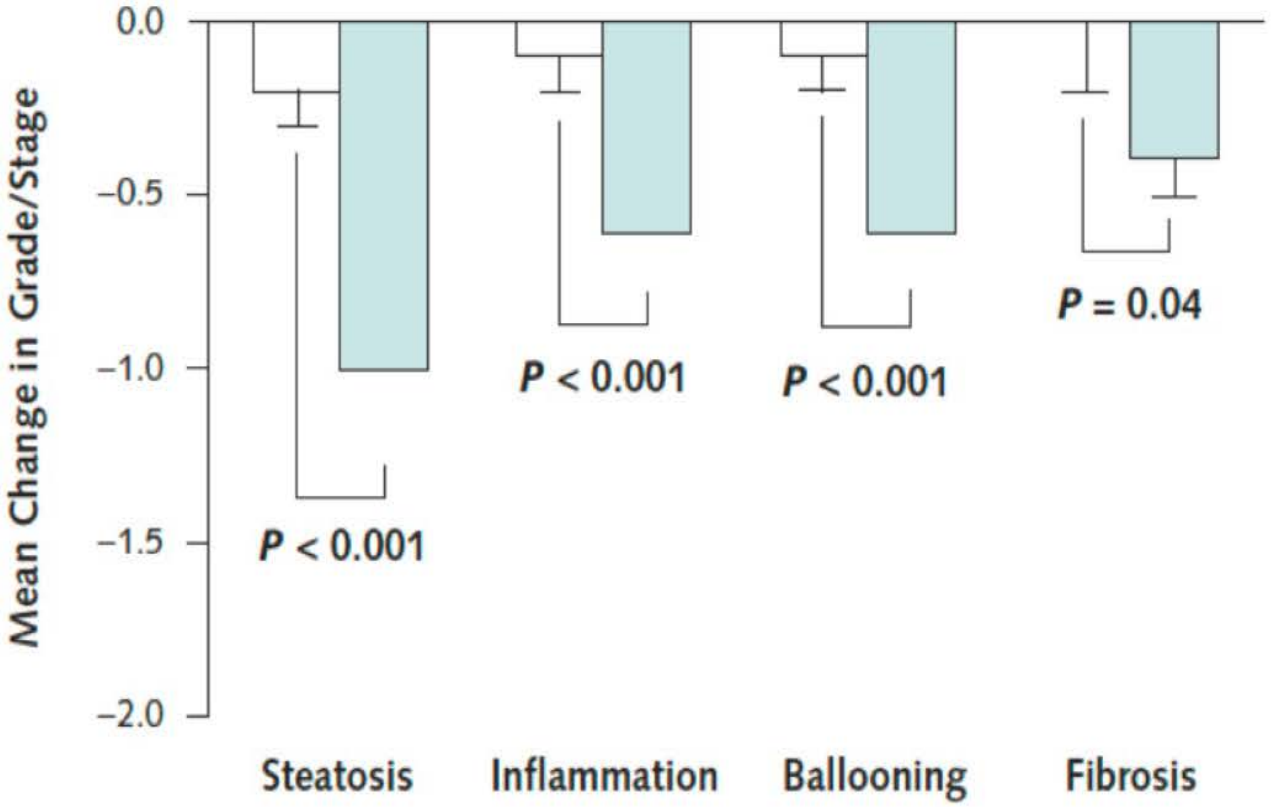
O`Gorman P et al ILC 2019, PS-105

PIVENS: 96-Wk Results of Pioglitazone and Vitamin E in Patients With NASH

- Double-blind, placebo-controlled, randomized phase III study in adults with biopsy-proven NASH and no diabetes or cirrhosis (N = 247)



Sanyal. NEJM. 2010;362:1675.



Primary outcome: ≥2-point decrease in NAS without worsening of fibrosis

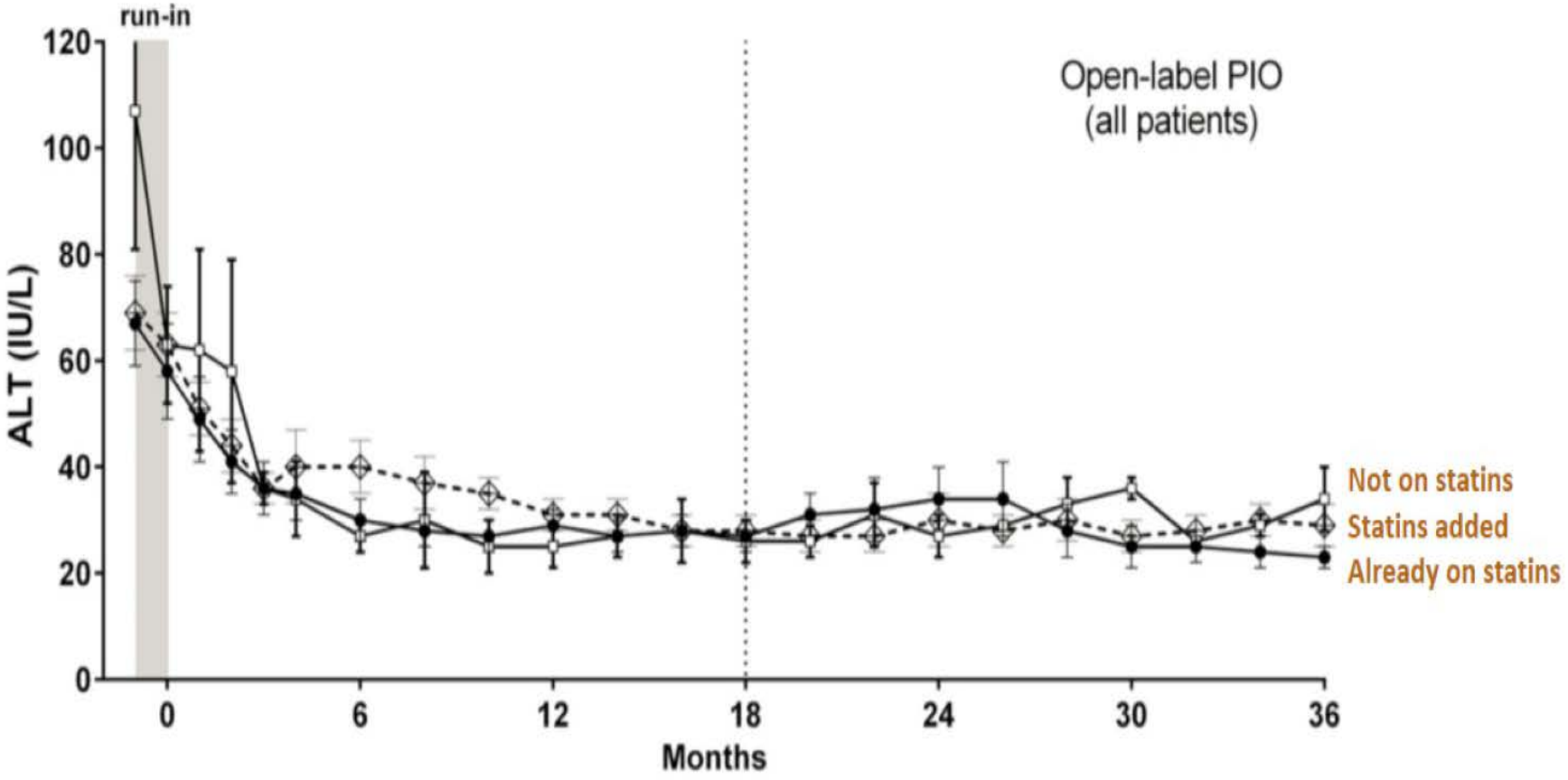
Secondary outcomes: ≥1-point improvement

- Steatosis
- Inflammation
- Ballooning
- Fibrosis

Note: In patients with paired biopsies; white bars represent placebo. Blue bars represent pioglitazone.

Efecto de la pioglitazona a los 18 meses de tratamiento en pacientes con DM2 o prediabetes.

Patients on Pioglitazone During the PIO Trial



Reprinted from *J Clin Endo Metab*, 102, Bril F, et al. Liver Safety of Statins in Prediabetes or T2DM and Nonalcoholic Steatohepatitis: Post-hoc Analysis of a Randomized Trial , 2950-2961, Copyright 2017, with permission from Elsevier.

Vitamina E

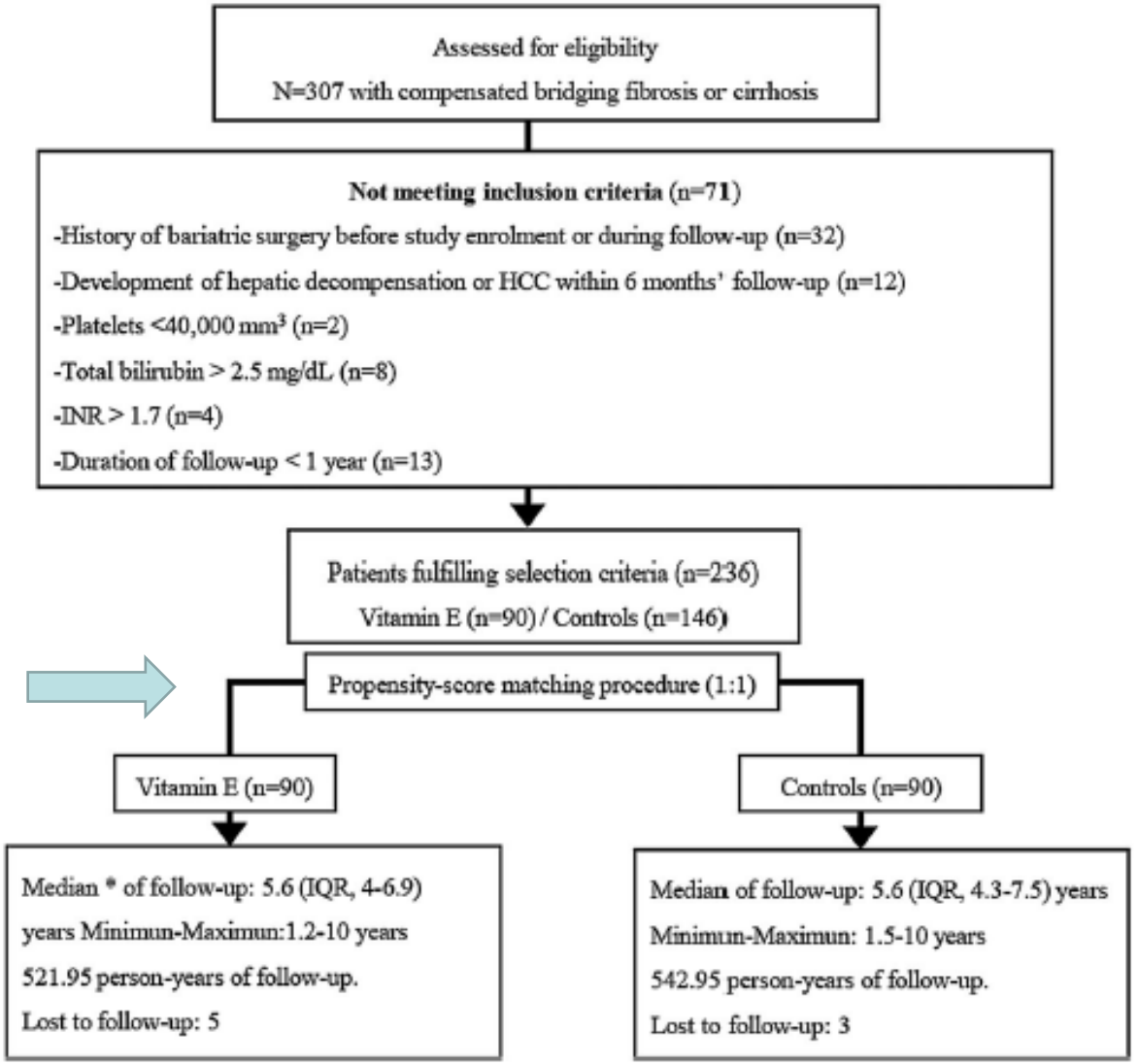
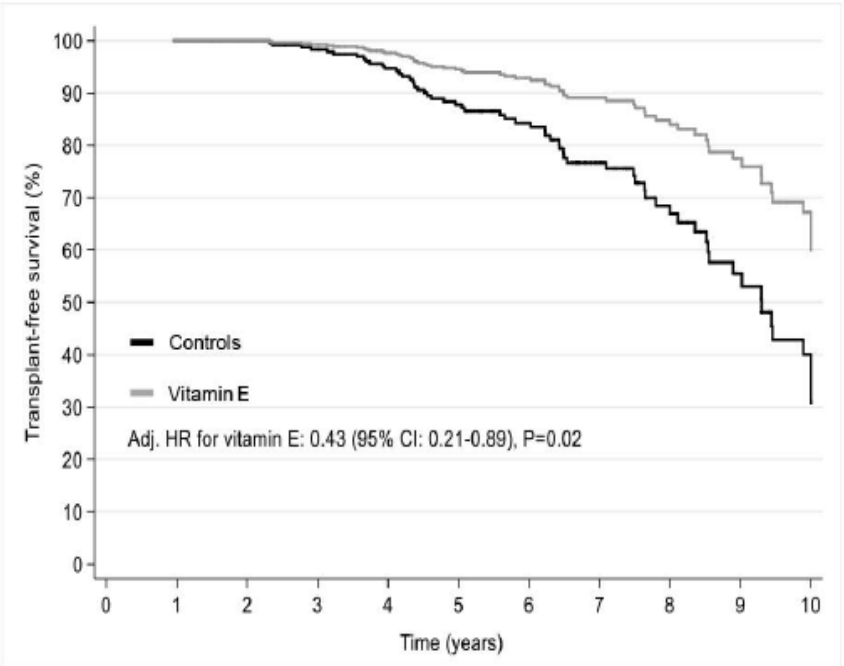
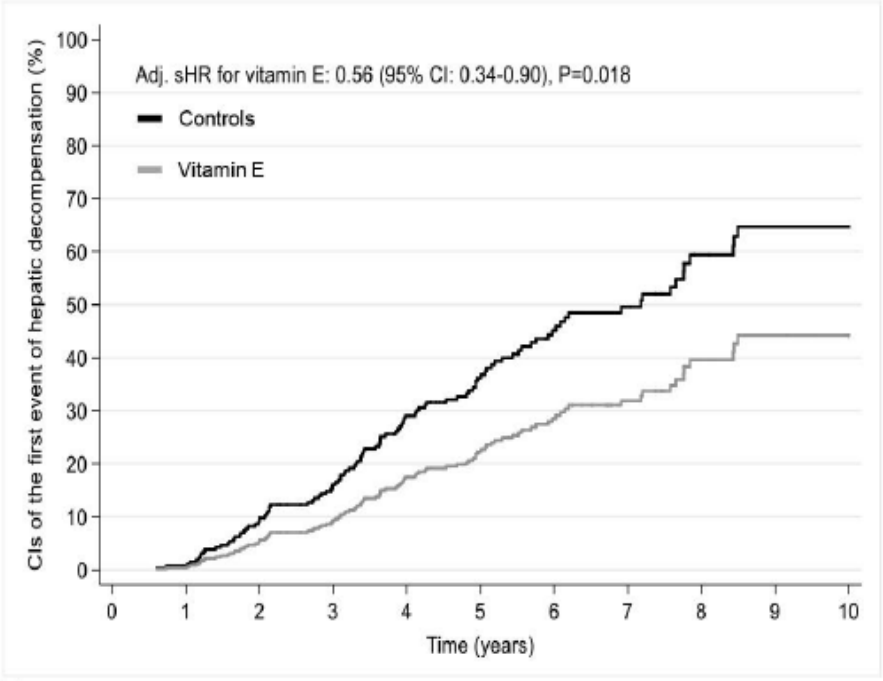


FIG. 1. Flowchart of patients through the study cohort. *Median follow-up after vitamin E was initiated.

Vilar-Gomez E et al Hepatology. 2018 Dec 1. doi: 10.1002/hep.30368. [Epub ahead of print]

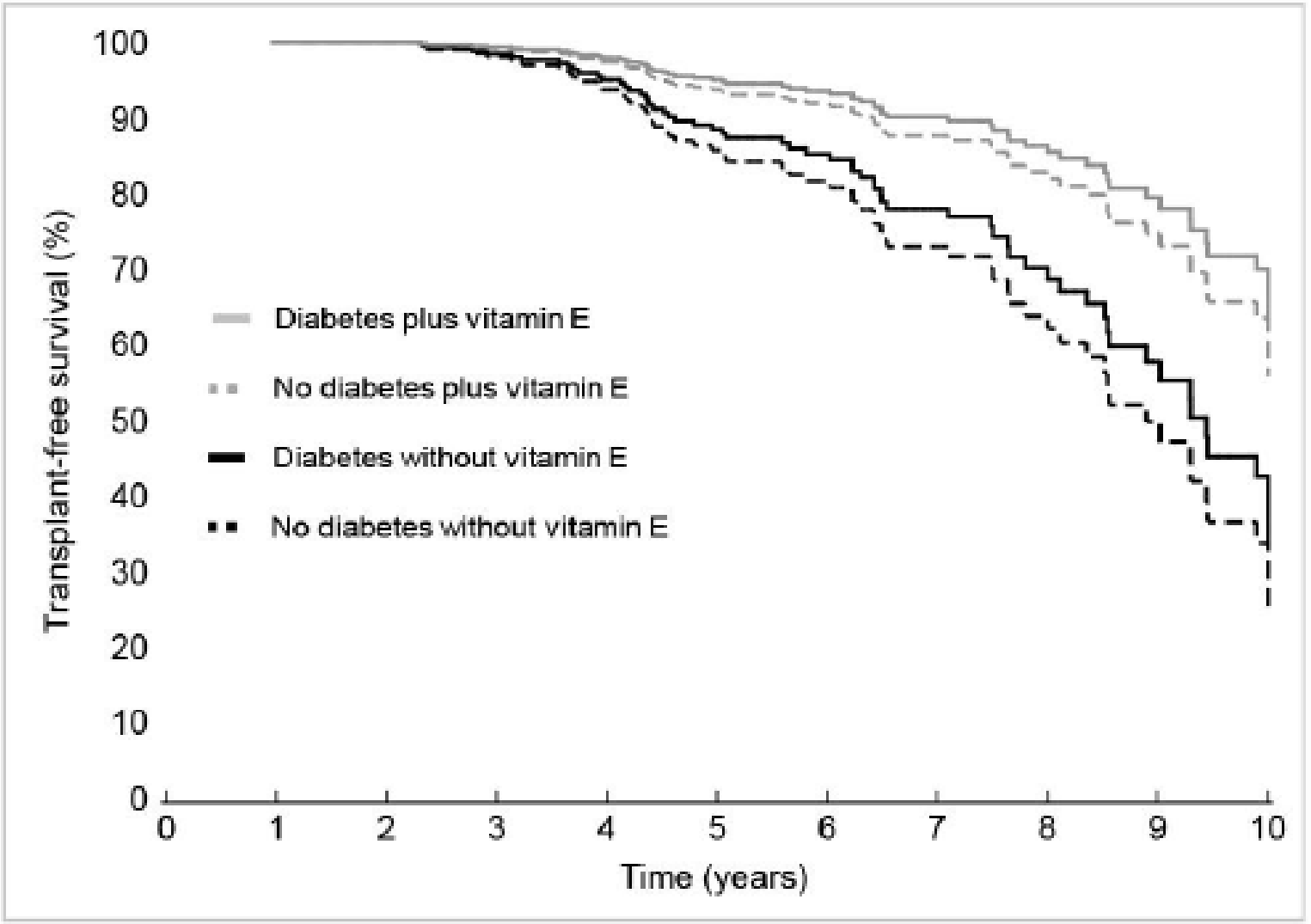


No. at risk											
Vitamin E	90	89	84	77	67	55	38	21	13	10	8
Controls	146	146	145	139	126	101	83	62	43	27	15



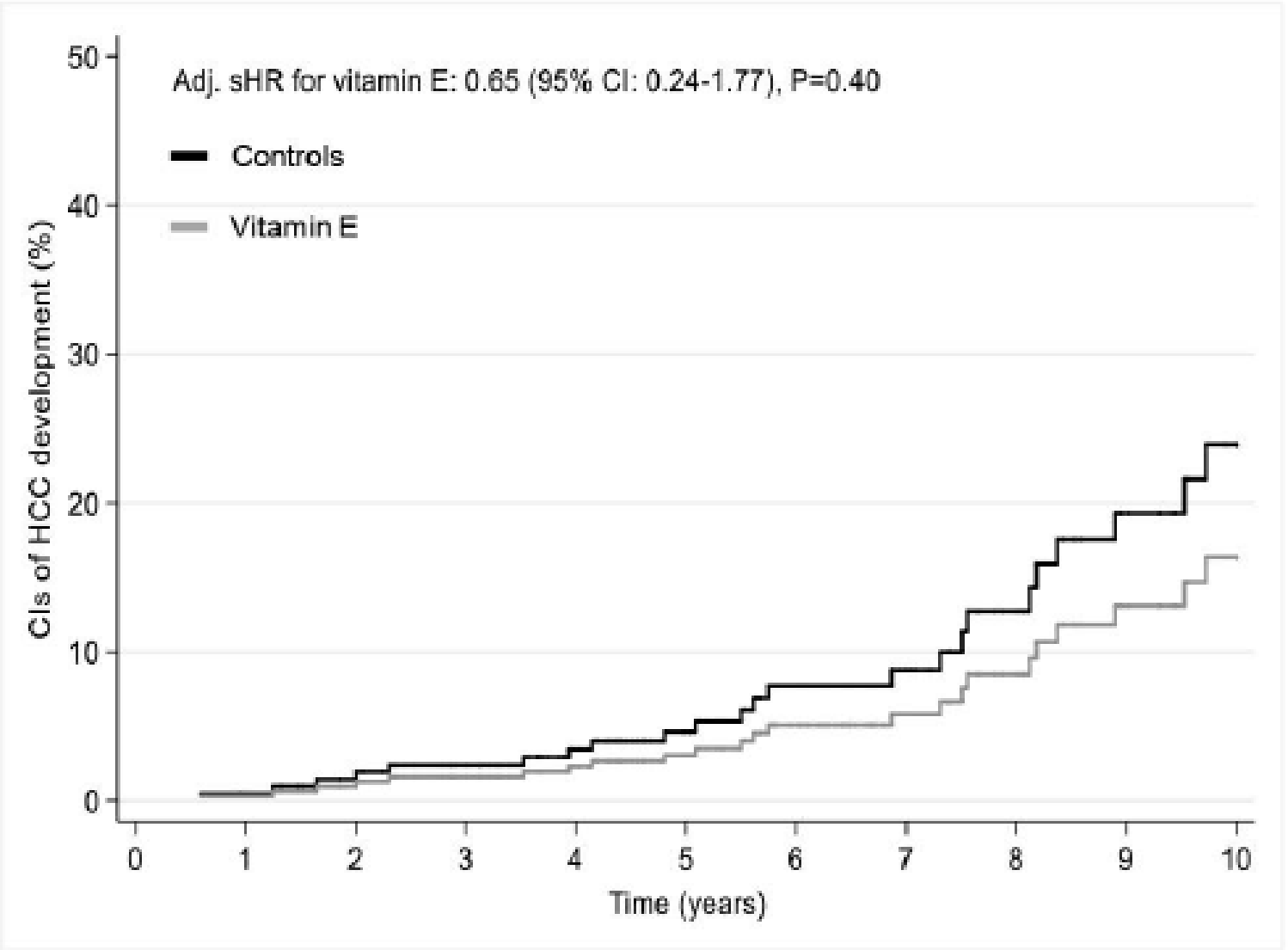
No. at risk											
Vitamin E	90	88	75	68	55	43	26	19	12	9	6
Controls	146	146	130	114	85	57	37	24	10	7	7

Vilar-Gomez E et al Hepatology. 2018 Dec 1. doi: 10.1002/hep.30368. [Epub ahead of print]



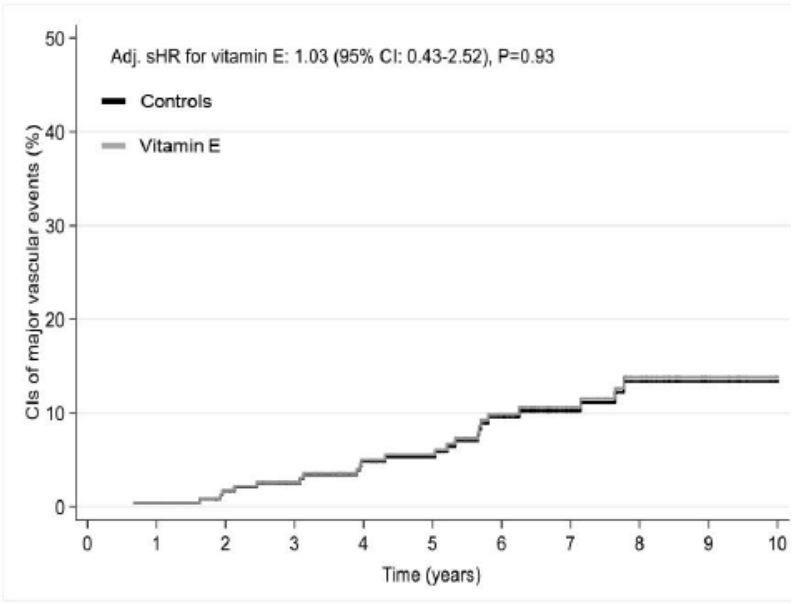
No. at risk											
T2D + vit E	56	55	50	49	43	34	23	10	6	5	3
T2D + no vit E	108	108	107	104	96	79	63	48	33	23	12
No T2D + vit E	34	34	34	28	24	21	15	11	7	5	5
No T2D + no vit E	38	38	38	35	30	22	20	14	10	4	3

Vilar-Gomez E et al Hepatology. 2018 Dec 1. doi: 10.1002/hep.30368. [Epub ahead of print]

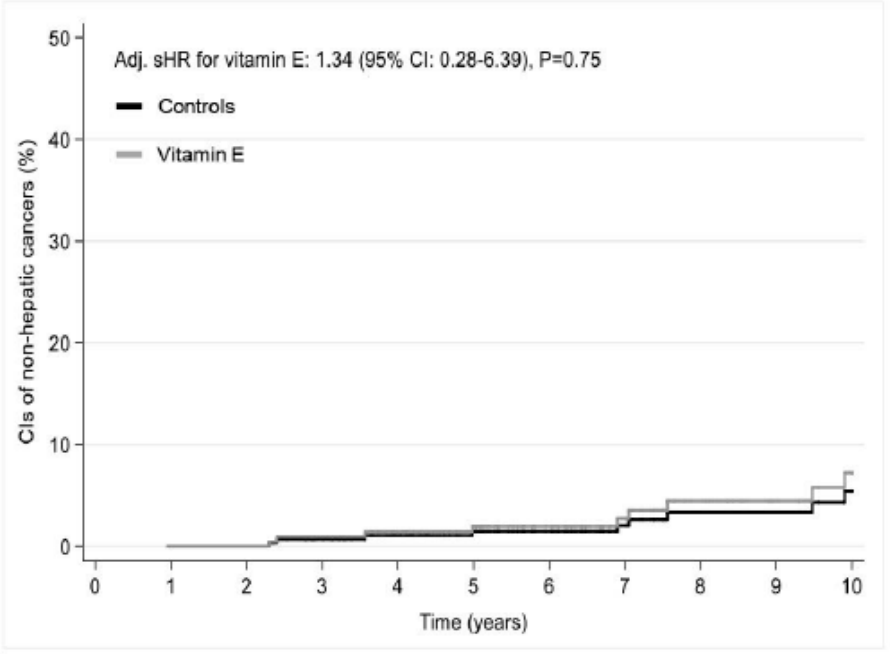


No. at risk											
Vitamin E	90	88	82	75	66	54	36	20	13	9	7
Controls	146	146	143	137	123	100	81	60	42	25	14

Vilar-Gomez E et al Hepatology. 2018 Dec 1. doi: 10.1002/hep.30368. [Epub ahead of print]



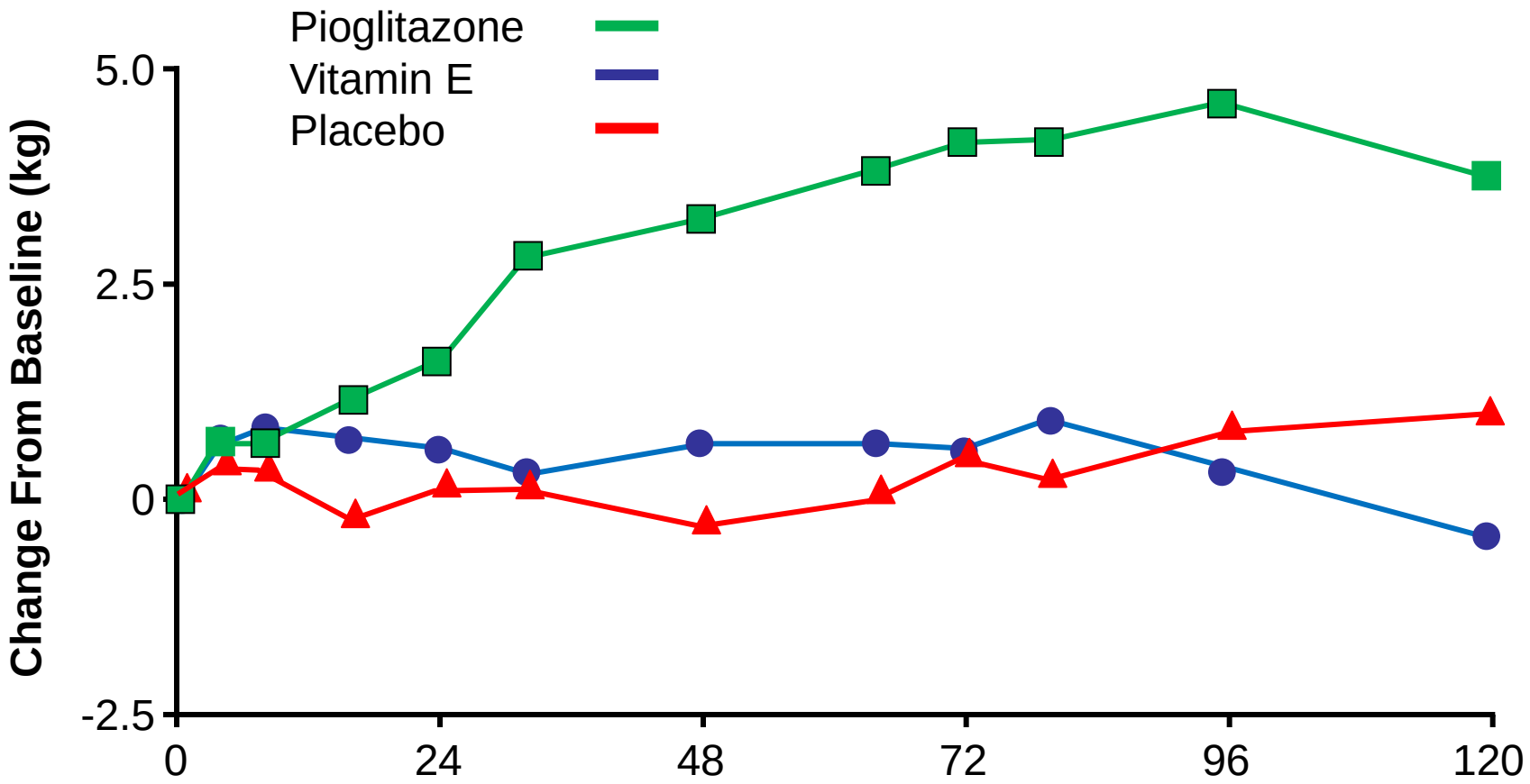
No. at risk											
Vitamin E	90	88	83	74	64	53	36	21	12	9	7
Controls	146	146	143	137	121	99	79	58	39	23	15



No. at risk											
Vitamin E	90	89	84	76	66	53	37	20	13	10	8
Controls	146	146	145	138	124	100	82	61	41	25	12

Vilar-Gomez E et al Hepatology. 2018 Dec 1. doi: 10.1002/hep.30368. [Epub ahead of print]

PIVENS: Change in Weight by Treatment



Sanyal AJ, et al. N Engl J Med. 2010;362:1675-1685.

Tolerancia y seguridad de los tratamientos recomendados (Fuera de ficha tecnica)

Vitamin E (800 IU/day)

- Possible all-cause mortality risk at > 800 IU/day[1]
- Increased hemorrhagic stroke risk[2]
  - Also shows reduced ischemic stroke risk
- Increased prostate carcinoma risk (HR vs placebo: 1.17; 99% CI: 1.004-1.36; *P* = .008)[3]

Pioglitazone

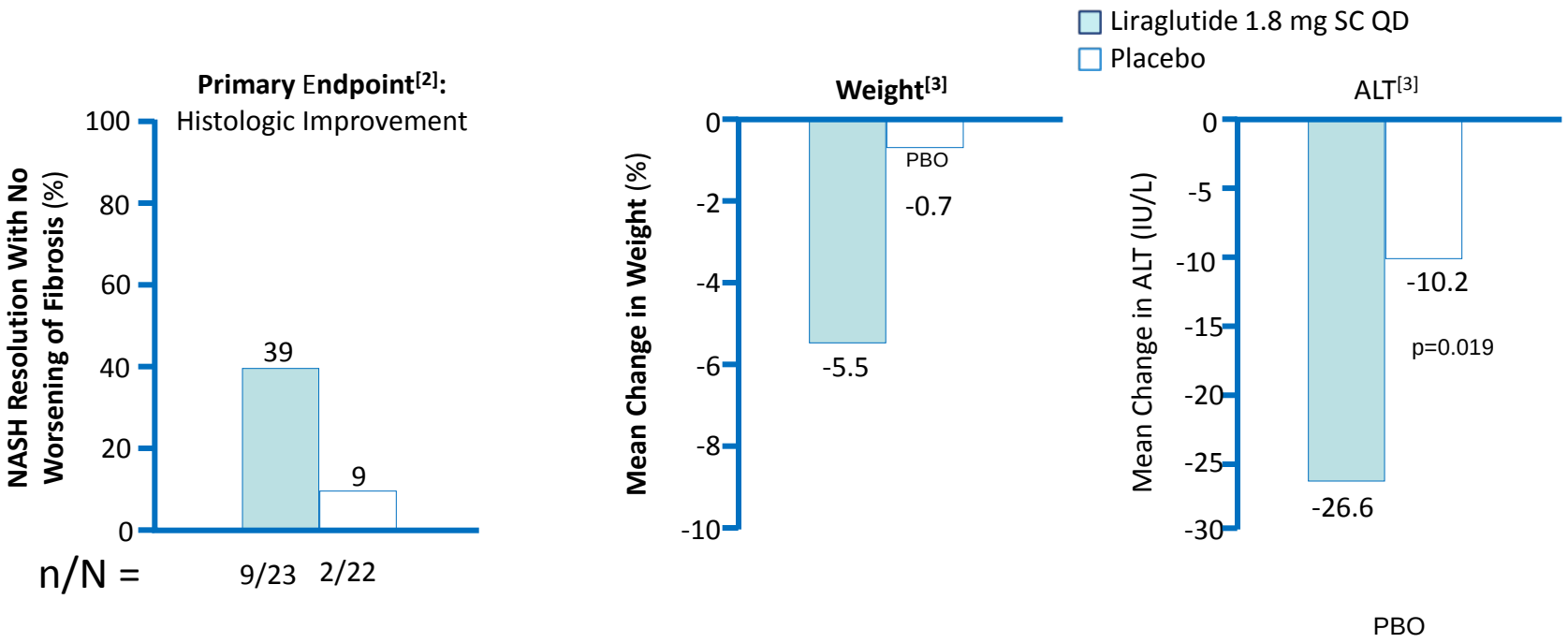
- Edema, weight gain (~ 2-3 kg over 2-4 yrs)[4]
- Risk of osteoporosis in women[5]
- Equivocal bladder cancer risk
  - Increased in some studies[6]
  - No association in most studies[7,8]

Use of these agents should be personalized for selected patients with histologically confirmed NASH after careful consideration of risk/benefit ratio

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.

LEAN: 48-Wk Results of Liraglutide vs Placebo in Overweight Patients With NASH

- Randomized, double-blind phase II study[1]



Semaglutide also associated with ALT reduction and weight loss in nondiabetic adults with NASH and obesity[3]

1. Armstrong. BMJ Open. 2013;3:e003995. 2. Armstrong. Lancet. 2016;387:679. 3. Armstrong. EASL 2015. Abstr G01.

NASH Treatments Currently in Phase III Investigations

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]	2370	≥ 1 stage fibrosis improvement with no NASH worsening; resolution of NASH with no fibrosis worsening	18 mos
		REVERSE[4]	540	≥ 1 stage fibrosis improvement with no NASH worsening	12 mos
Selonsertib	ASK1 inhibitor	STELLAR 3[5]	808	≥ 1 stage fibrosis improvement with no NASH worsening; event-free survival	48 wks
		STELLAR 4[6]	883	NASH with compensated cirrhosis	240 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. NCT02548351. 4. NCT03439254. 5. NCT03053050. 6. NCT03053063.

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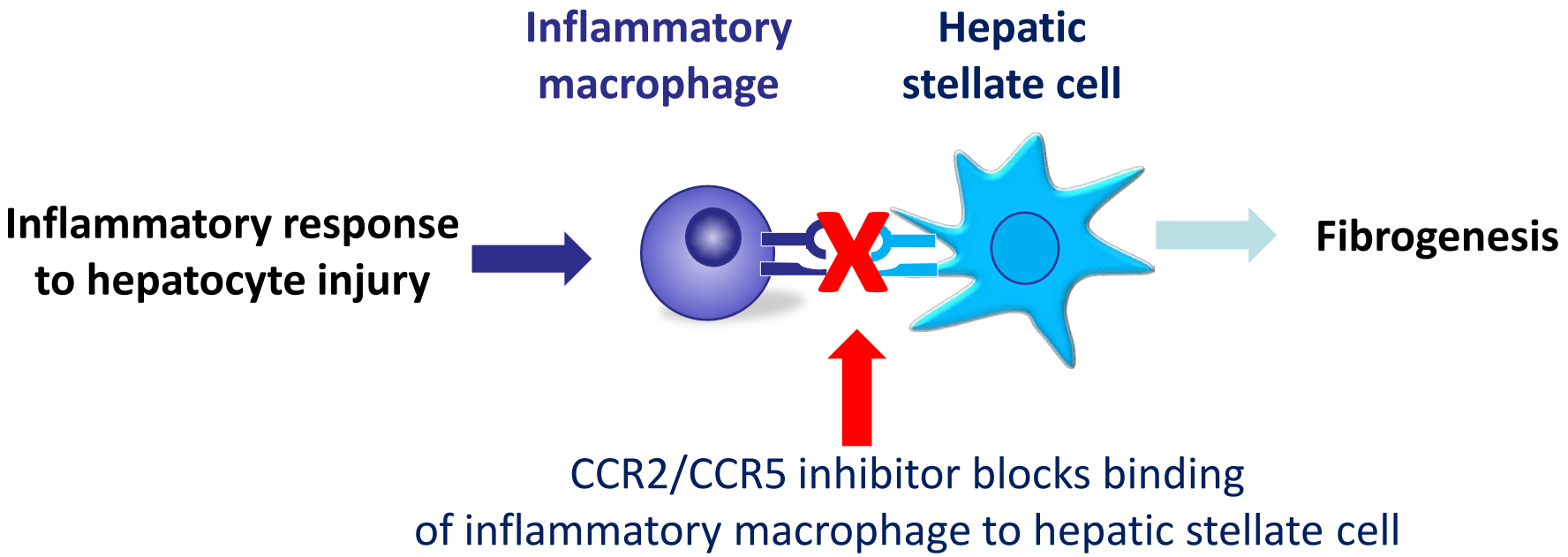
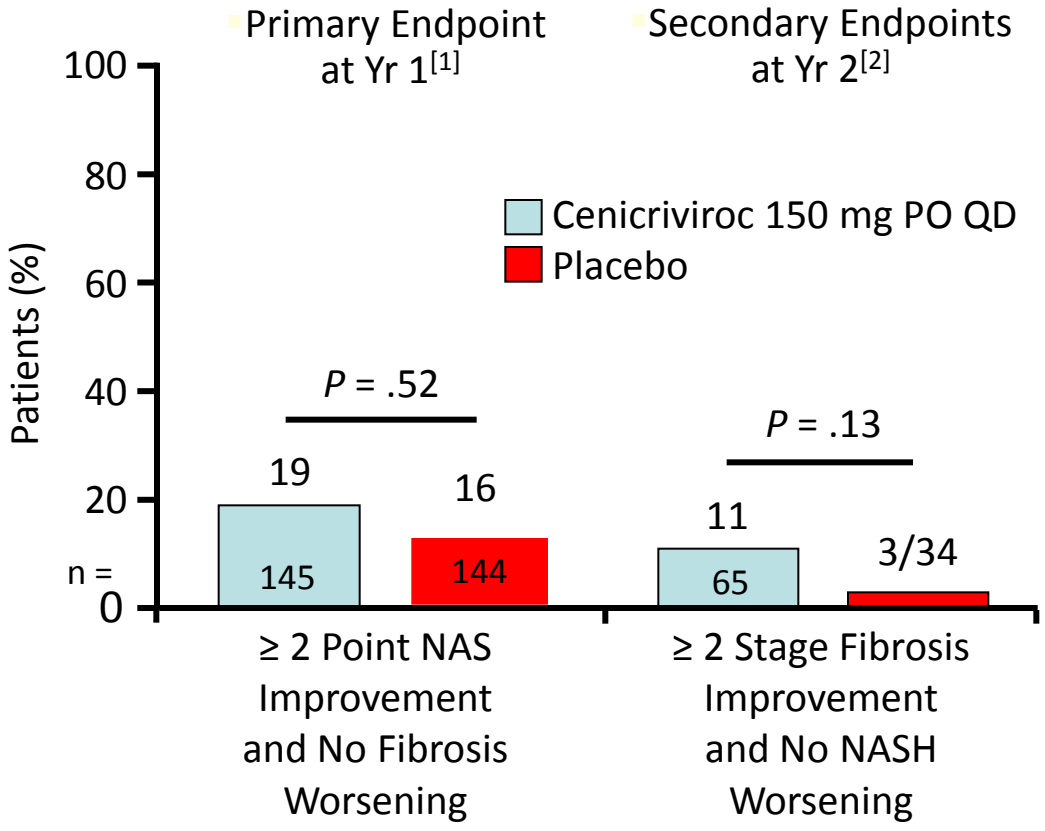
Cenicriviroc: CCR2/CCR5 Inhibitor

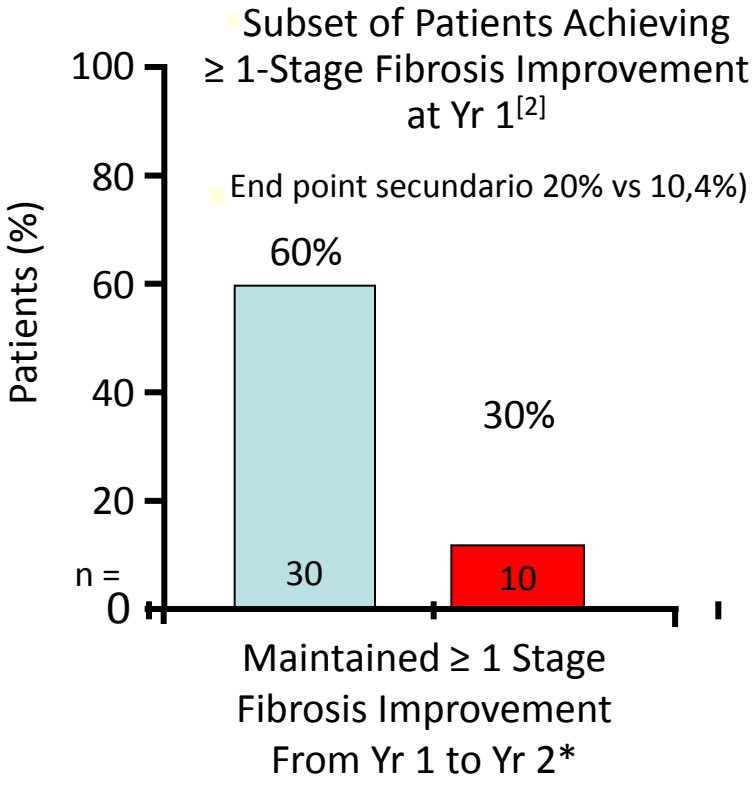


Friedman. Hepatology. 2018;67:1754.

CENTAUR: Cenicriviroc vs Placebo in Patients With NASH at Yr 1 and 2

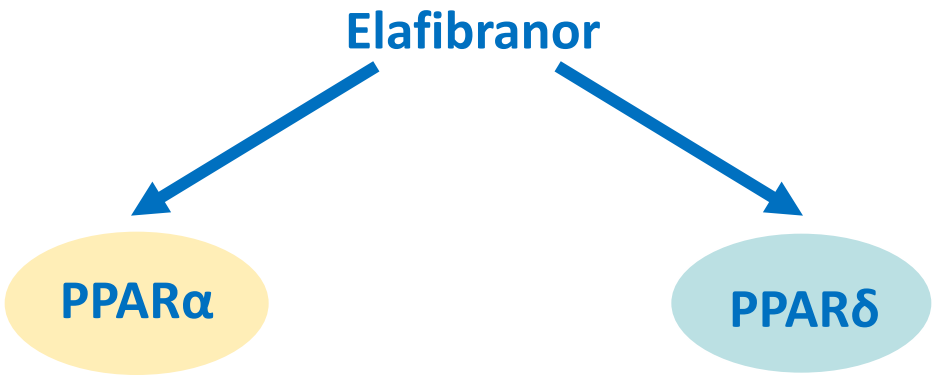
Randomized, double-blind, phase IIb study in pts with NASH, NAS ≥ 4 and F1-F3 fibrosis (N = 289)[1]





1. Friedman. Hepatology. 2018;67:1754. 2. Ratziu. EASL 2018. Abstr GS-002.

Elafibranor: PPARα/δ Agonist



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

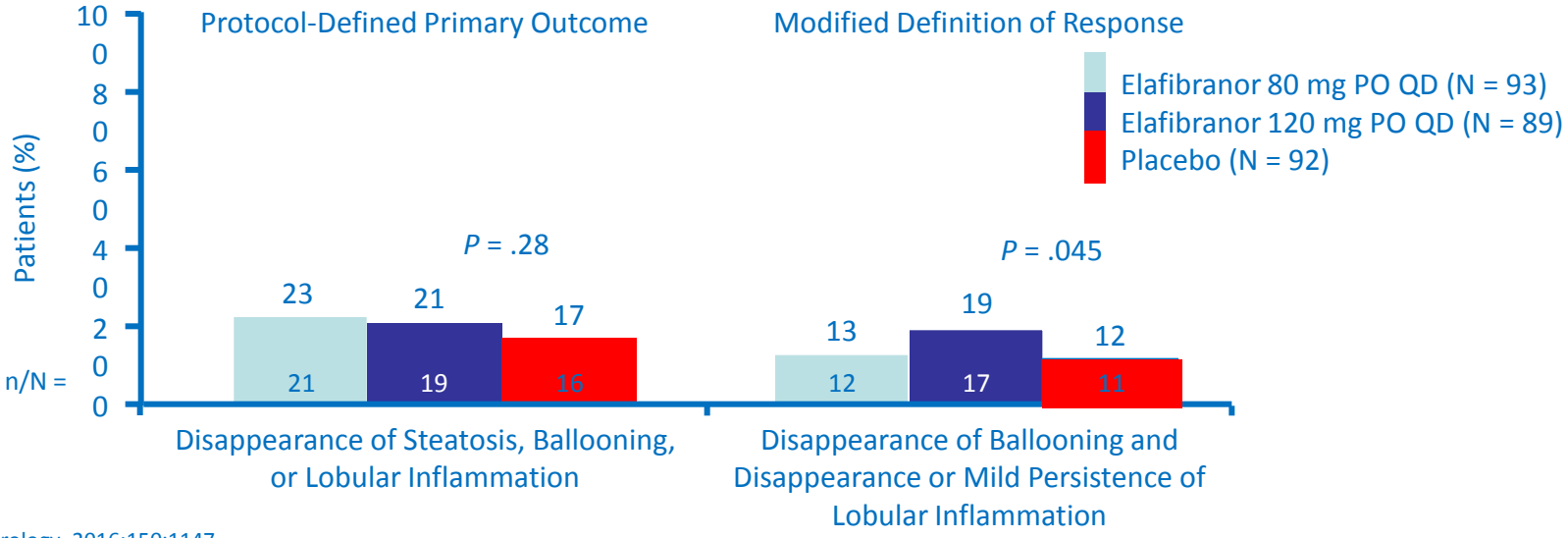
- Lipoprotein metabolism
- Glucose homeostasis
- Energy metabolism
- Inflammation

Liver

Slide courtesy of Bart Staels, MD

GOLDEN-505: Elafibranor vs Placebo in Patients With NASH at Wk 52

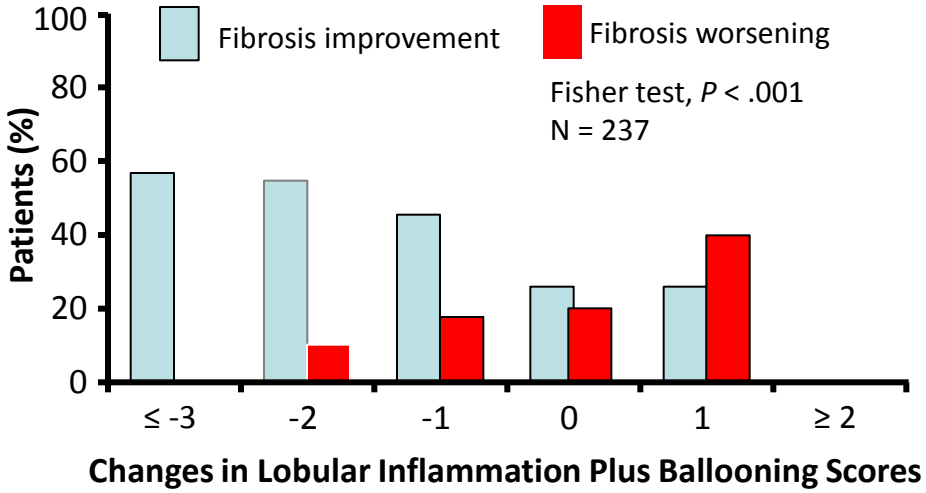
- Double-blind, placebo-controlled, randomized, international phase IIb study in patients with noncirrhotic NASH (N = 276)
  - Primary endpoint: resolution of NASH without fibrosis worsening at Wk 52



Ratziu. Gastroenterology. 2016;150:1147.

GOLDEN-505: Correlation Between NASH Histology and Fibrosis at Wk 52, Tolerability

- Changes in hepatocyte ballooning and lobular inflammation correlated with changes in fibrosis stage ($P = .04$ and $P < .001$, respectively)[1]
  - Changes in steatosis did not correlate with changes in fibrosis stage

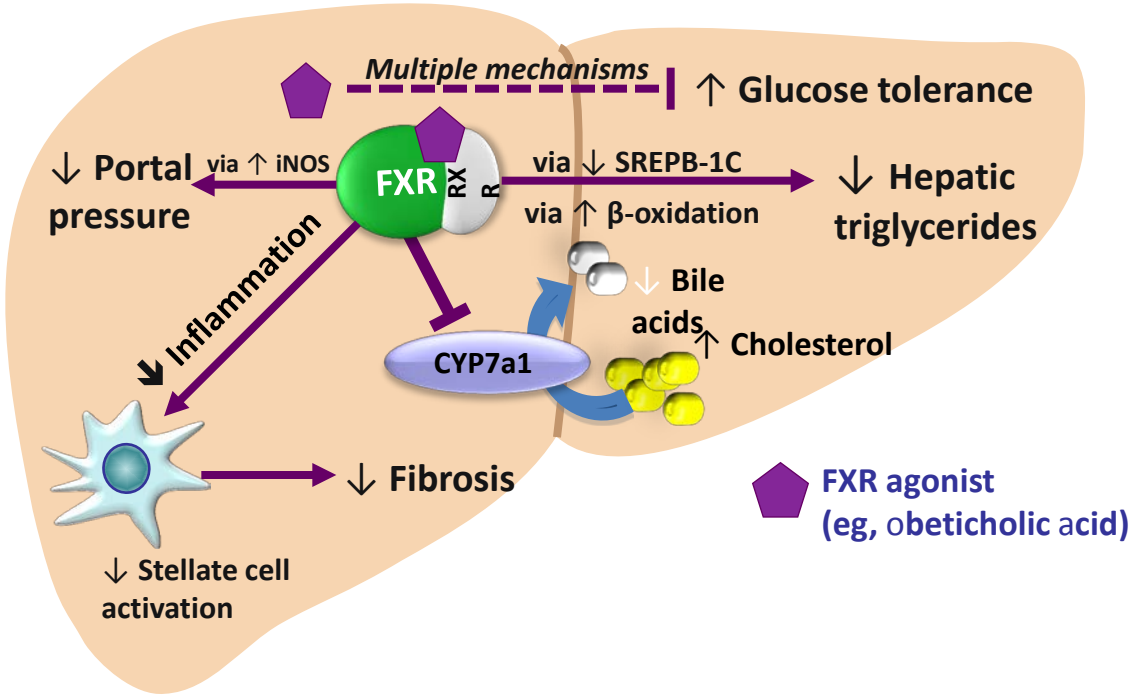


- Liver enzymes, lipids, glucose profiles, and markers of systemic inflammation significantly lower in elafibranor 120-mg group vs the placebo group[2]
- Elafibranor well tolerated; no weight gain or cardiac events[2]
- Mild, reversible increase in serum creatinine (effect size vs placebo: increase of 4.31 ± 1.19 mmol/L; $P < .001$)[2]

1. Ratziu. AASLD 2016. Abstr LB-37. 2. Ratziu. Gastroenterology. 2016;150:1147.

Obeticholic Acid: FXR Agonist

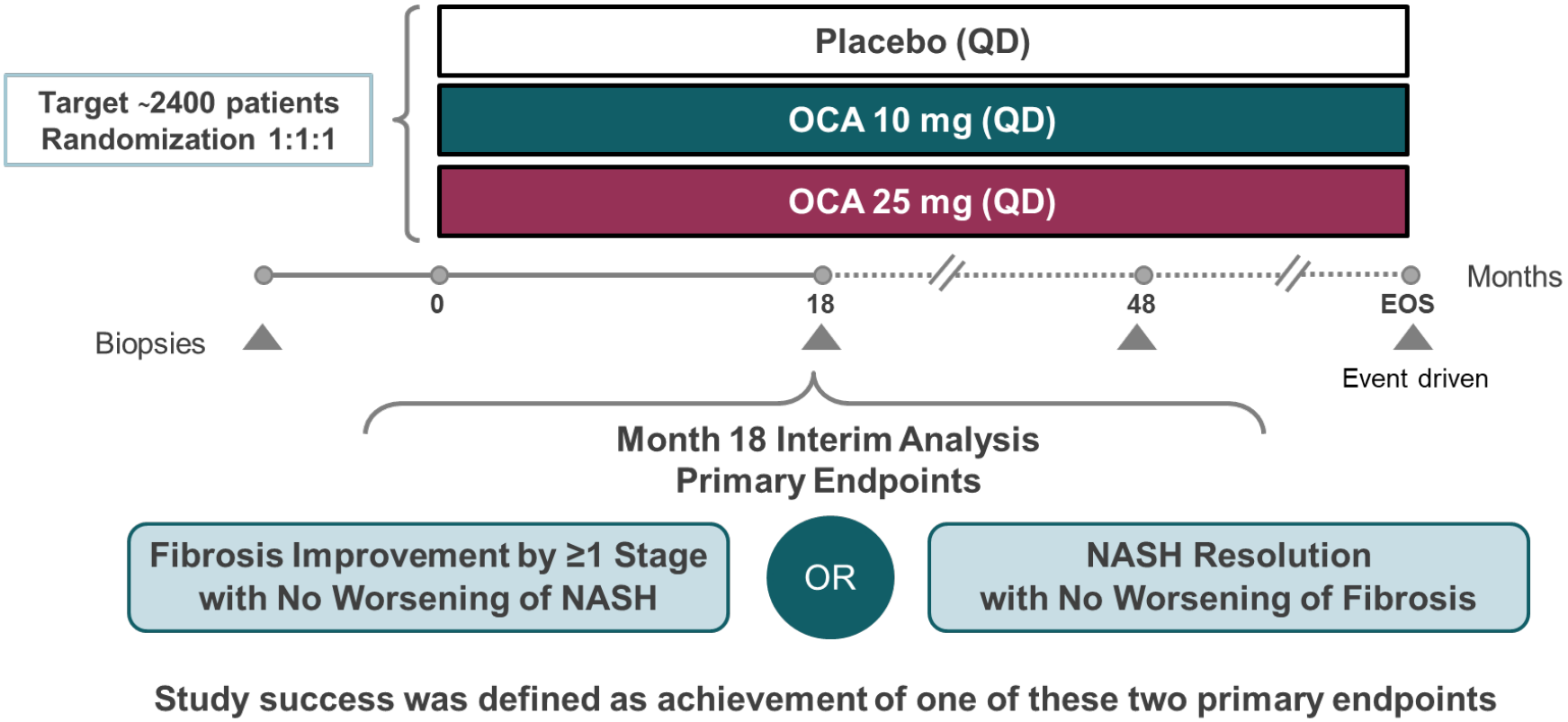
FXR central to multiple key pathways in animal models



1. Cariou. Diabetes Metab. 2008;34:685. 2. Calkin. Nat Rev Mol Cell Biol. 2012;13:213. 3. Verbeke. Hepatology. 2014;59:2286.

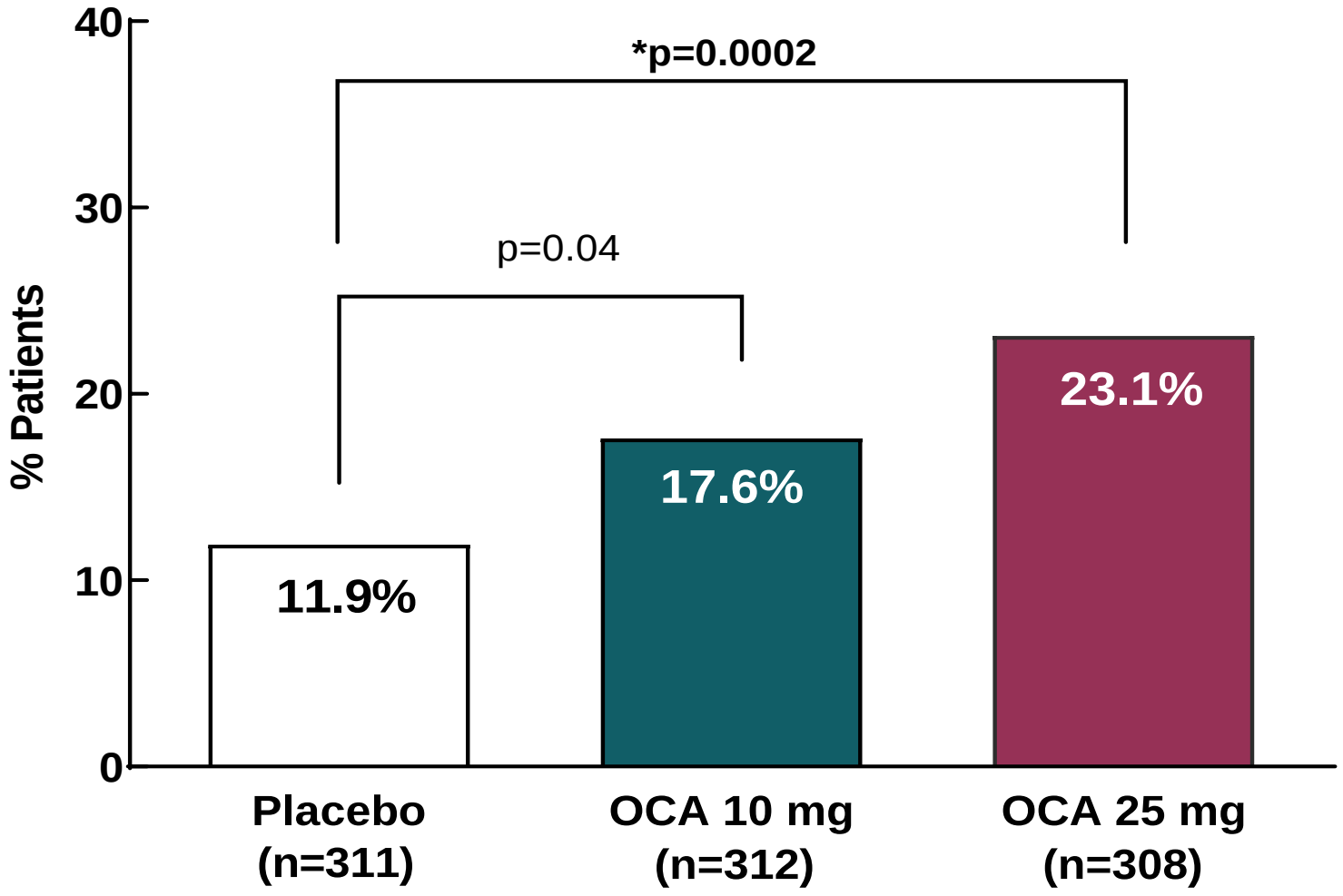
Slide credit: clinicaloptions.com

REGENERATE: A phase 3 international, randomized, placebo-controlled study of obeticholic acid treatment for NASH



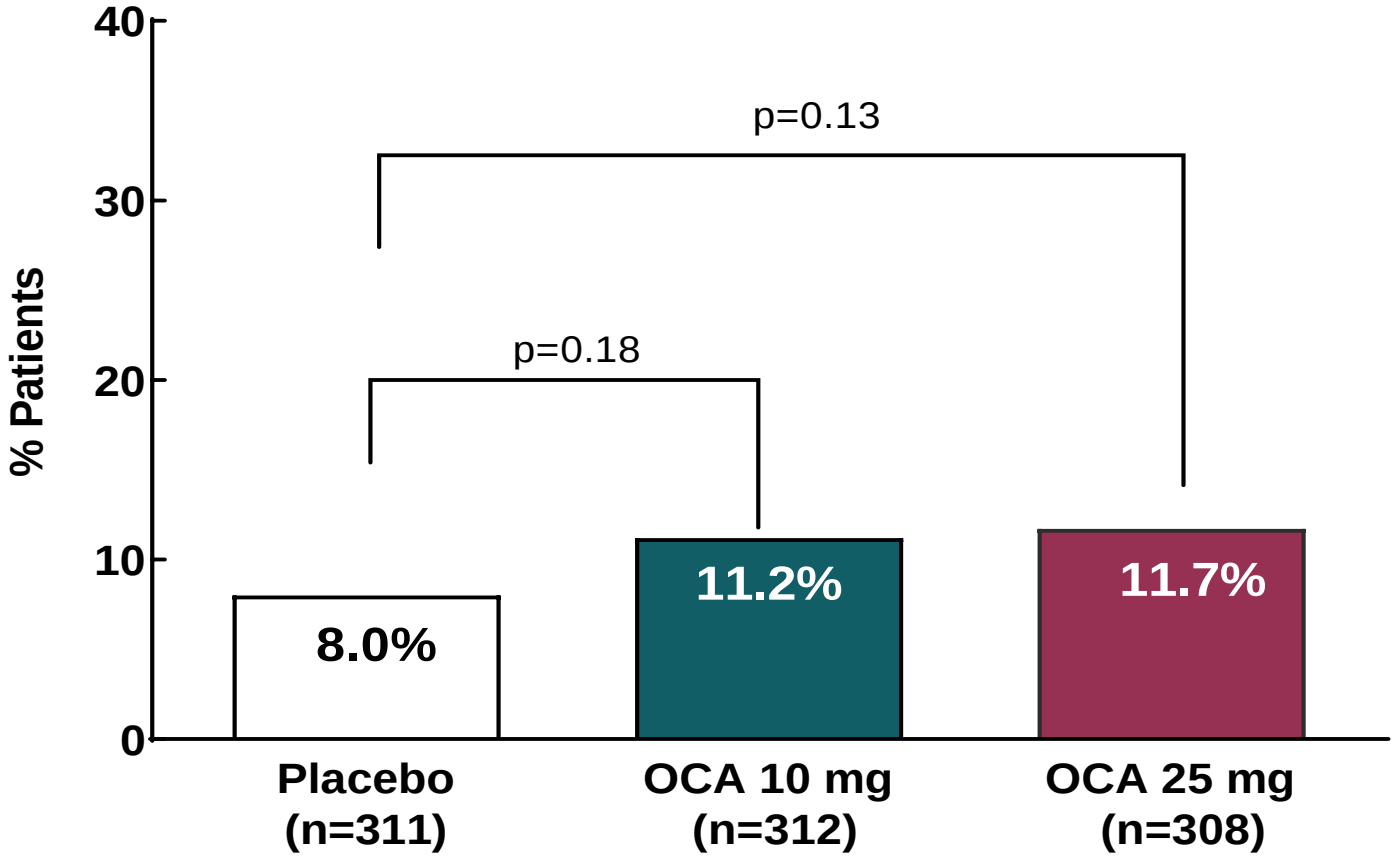
Study success was defined as achievement of one of these two primary endpoints

Primary endpoint (ITT): fibrosis improvement by ≥1 stage with no worsening of NASH



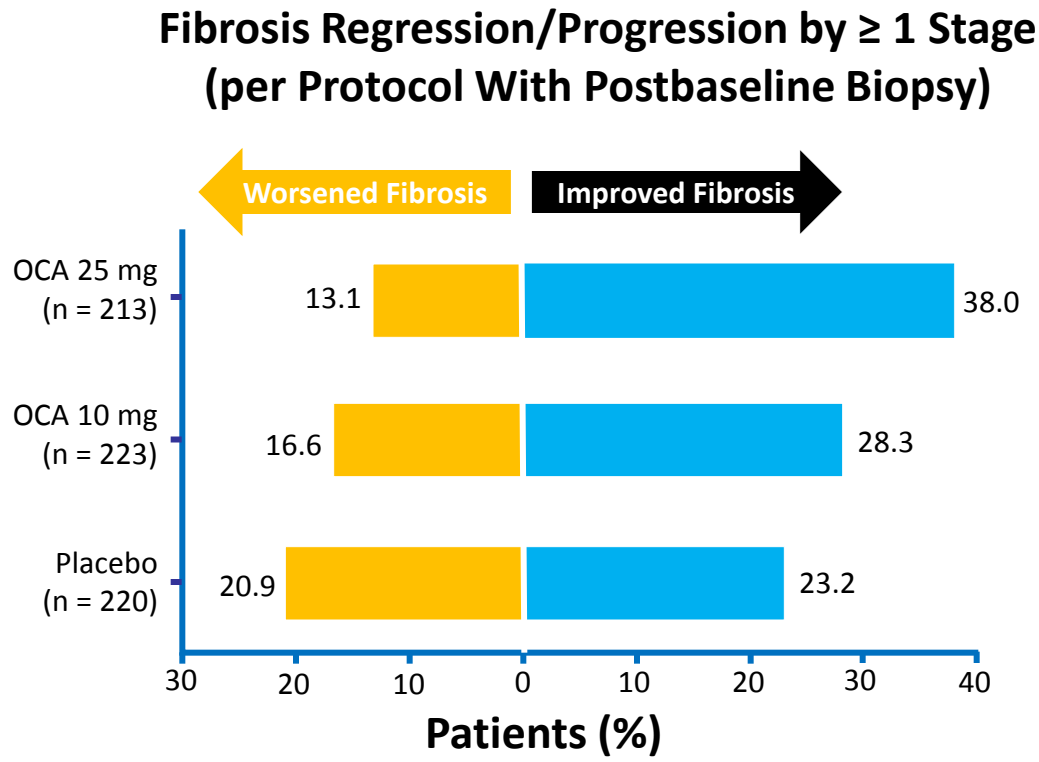
Younossi. EASL 2019. Abstr GS-06.

Primary endpoint (ITT): NASH resolution with no worsening of fibrosis



Younossi. EASL 2019. Abstr GS-06.

REGENERATE Secondary Endpoints: Changes in Fibrosis



Younossi. EASL 2019. Abstr GS-06.

- OCA also associated with improvement in fibrosis staging, NAS parameters, ALT, AST, GGT

REGENERATE: Seguridad.

- **Pruritus** incidence peaked within first 3 mos before declining
- In OCA 25 mg arm, 9% discontinued due to pruritus, mostly protocol driven
  - Rates comparable between arms
- **Cardiovascular AE rates** ≤ 2% in all arms
- **LDL increased** and **HDL decreased** early with OCA; recovered with clinical management
- **Hepatic TEAE** rates similar across arms
  - Hepatic serious AEs in < 1%, numerically more cases in OCA 25 mg arm
  - Low rates of cholelithiasis, cholecystitis AEs

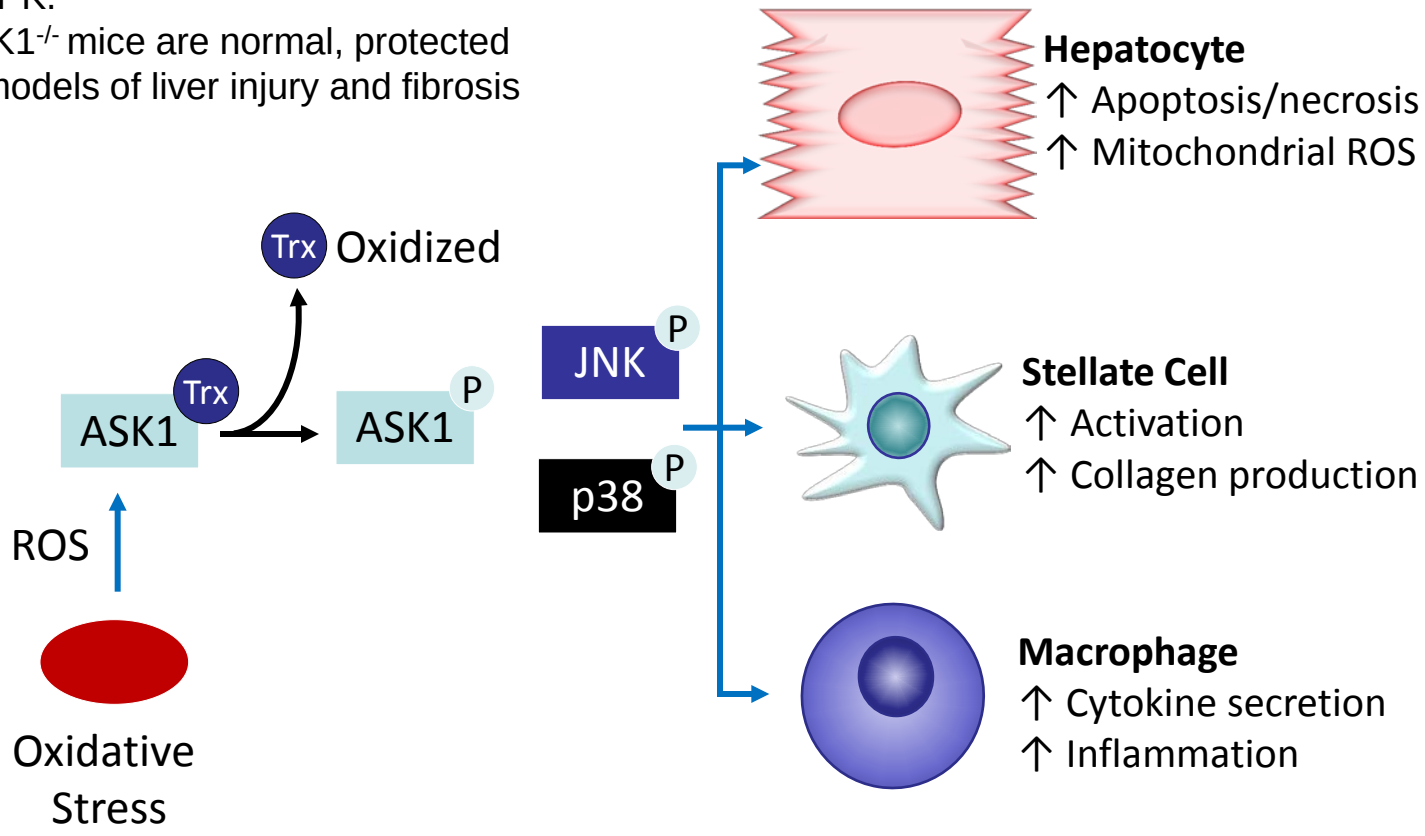
TEAEs Occurring in ≥ 10% of Patients in Any Arm, n (%)	**OCA 10 mg (n = 653)**	**OCA 25 mg (n = 658)**	**Placebo (n = 657)**
Pruritus	183 (28)	336 (51)	123 (19)
LDL increased	109 (17)	115 (17)	47 (7)
Nausea	72 (11)	83 (13)	77 (12)
Fatigue	78 (12)	71 (11)	88 (13)
Constipation	65 (10)	70 (11)	36 (5)
Abdominal pain	65 (10)	67 (10)	62 (9)
Diarrhea	44 (7)	49 (7)	79 (12)

Younossi. EASL 2019. Abstr GS-06.

Selonsertib: ASK1 Inhibitor

ASK1: Apoptosis Signal-Regulating Kinase

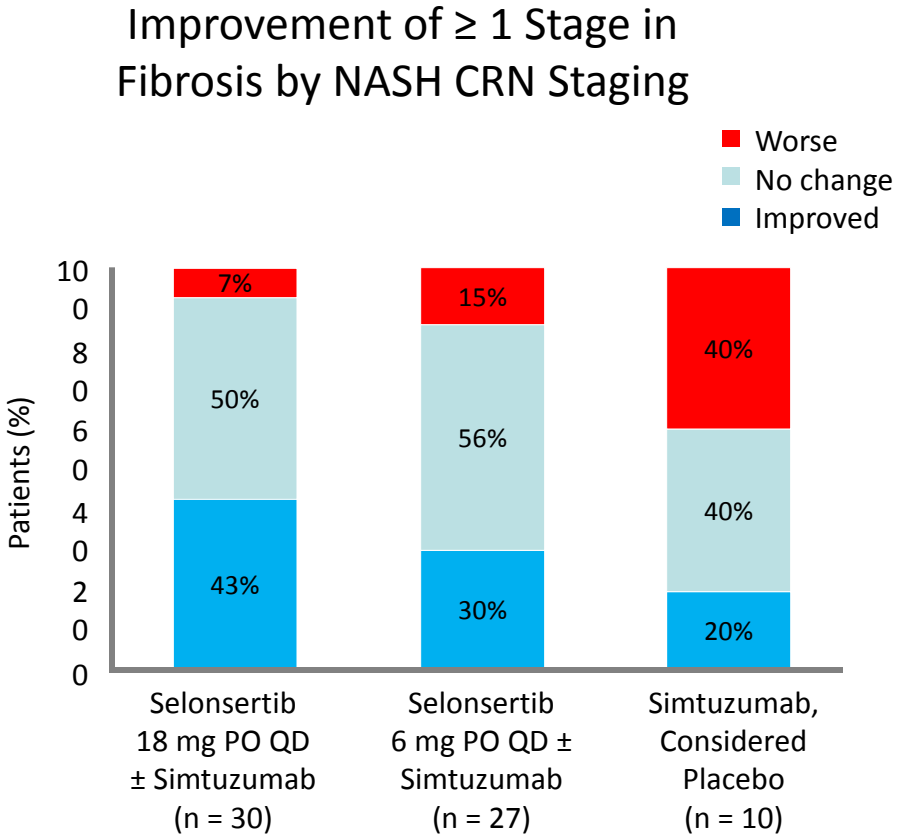
- Activated by oxidative stress. **Promotes cell death,** fibrosis, and inflammation via JNK and p38 MAPK.
- ASK1$^{-/-}$ mice are normal, protected in models of liver injury and fibrosis



Loomba. Hepatology. 2018;67:549.

Selonsertib: ASK1 Inhibitor in Patients With NASH at Wk 24

- Open-label phase II study in patients with biopsy-proven NASH, NAS ≥ 5, F2-F3 fibrosis (N = 72)
- Improvement in fibrosis associated with:
  - Reduction in liver stiffness by MR
  - Reduction in collagen content and lobular inflammation on liver biopsy
  - Improvements in serum biomarkers of apoptosis and necrosis



Loomba. Hepatology. 2018;67:549.

Double-blind, placebo-controlled, randomized trial of emricasan in subjects with NASH cirrhosis and severe portal hypertension

BACKGROUND & AIMS

- Severe PH is a key driver of decompensation and worse clinical outcomes
  - Lowering HVPG associated with clinical benefit
- **Aim**: To establish if emricasan reduces HVPG in cirrhosis patients with HVPG ≥12 mmHg (open-label study)

METHODS

- Patients with NASH cirrhosis and BL HVPG ≥12 mmHg randomized 1:1:1:1 to emricasan 5, 25, 50 mg or placebo orally twice daily for 48 wks
  - Primary endpoint: 1 follow-up HVPG at Wk 24
  - All HVPG tracings evaluated by central reader

RESULTS

- 263 subjects randomized (59 US/EU sites)
  - 13 discontinued prior to Wk 24
  - 7 had no/unevaluable Wk 24 HVPG
- Treatment groups were generally balanced

Population characteristics	%	Population characteristics	Mean (SD)
Sex, female	57	Age, years	60.8 (8.8)
Race, Caucasian	91	BMI, kg/m^2	35.3 (6.9)
Type 2 diabetes	84	MELD	9.0 (2.5)
Compensated	76	HVPG, mmHg	17.0 (3.6)
Early decompensated	24		

Double-blind, placebo-controlled, randomized trial of emricasan in subjects with NASH cirrhosis and severe portal hypertension

RESULTS

- HVPG was reduced in subsets of patients (*Table*)*
- TEAEs: 81.6% combined emricasan vs. 82.1% pbo
- SAEs: 17.9% emricasan vs. 11.9% pbo
- No imbalance in routine labs, vitals, ECGs

Least squares mean change† from baseline at Wk 24	Emricasan 5 mg N=65	Emricasan 25 mg N=65	Emricasan 50 mg N=66	Placebo N=67
HVPG (overall)	-0.6; p=0.96	-0.8; p=0.79	-1.0; p=0.65	-0.4
HVPG (compensated)	-0.8; p=0.10	-0.9; p=0.09	-0.5; p=0.27	+0.2
HVPG (compensated HVPG ≥16 mmHg)‡	-1.6; p=0.01	-1.7; p<0.01	-1.5; p=0.02	+0.5
Caspase 3/7	-4%; p=0.90	-31%; p<0.01	-37%; p<0.01	-4%
cCK18	-27%; p<0.01	-32%; p<0.01	-34%; p<0.01	-13%
ALT	-8; p<0.01	-8; p<0.01	-6; p=0.02	-3
AST	-6; p<0.01	-7; p<0.01	-3; p=0.18	-1

CONCLUSIONS Primary endpoint was not met. Data suggest that emricasan for 24 wks reduced portal pressure in compensated NASH cirrhosis patients with severe PH (especially higher BL HVPG). Decreases in transaminases suggest an intrahepatic effect with reduction of liver injury. Clinical outcomes and full safety data will be evaluated after the 48-wk study

*p-values (descriptive) for difference in least squares mean vs. placebo;
†Adjusting for baseline value, cirrhosis status, and/or NSBB use (multiple imputation for overall, observed case for rest);
‡Post-hoc.
Garcia-Tsao G, et al. ILC 2019; LB-01

NASH Clinical Trial Endpoints in Early Phase II Development

ALT

- **10 U/L reduction associated with histologic improvement or resolution of NASH[1]**
- **≥ 17 U/L reduction predicts histologic response[2]**

Liver Fat Fraction (MRI-PDFF)

- ≥ 5% absolute reduction associated with improvement in steatosis[3]
- ≥ 30% relative reduction associated with improvement in NAFLD activity score without fibrosis worsening[4]

1. Vuppalanchi. Clin Gastroenterol Hepatol. 2014;12:2121. 2. Loomba. Gastroenterology. 2019;156:88.
3. Middleton. Gastroenterology. 2017;153:753. 4. Patel. Therap Adv Gastro 2016;9:692.

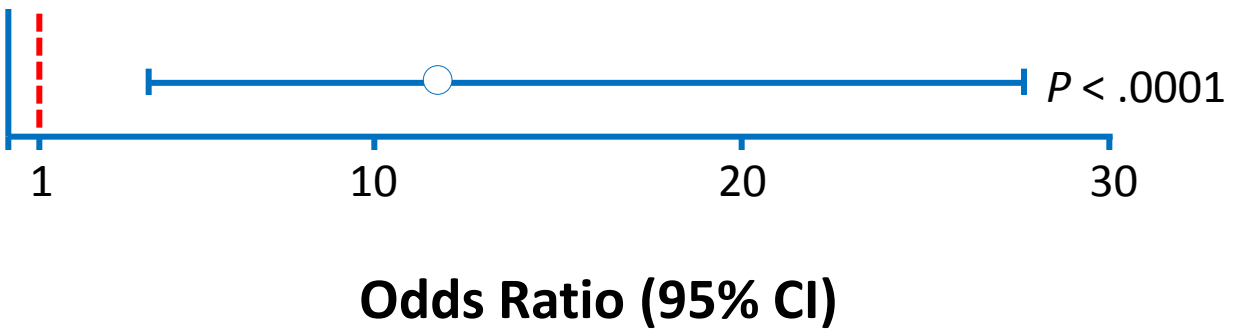
Slide credit: clinicaloptions.com

ALT: Correlation With Histologic Response

Logistic regression model of factors associated with histologic response in a 72-wk study of obeticholic acid in adults with NASH (N = 283)

Histologic response: decrease in NAS by ≥ 2 points with no fibrosis worsening

ALT Decrease ≥ 17 U/L as Predictor of Histologic Response



Loomba. Gastroenterology. 2019;156:88.

NASH Objetivos adaptados para ensayos clinicos.

Phase III

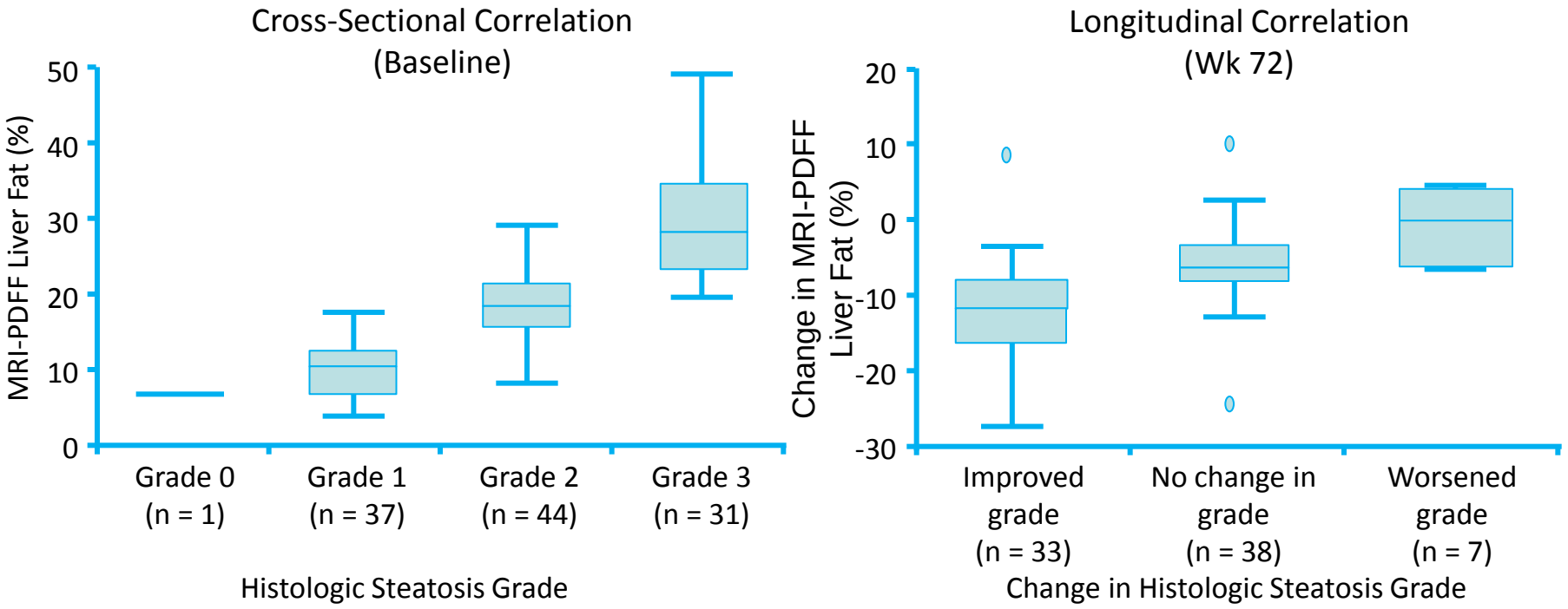
- **NASH resolution with no worsening of fibrosis**
- **Fibrosis improvement with no worsening of NASH**

Phase II

- ALT reduction
- Liver fat reduction by MRI-PDFF

Konerman. J Hepatol. 2018;68:362.

Liver Fat by MRI-PDFF: Correlation With Steatosis Grade at Baseline and After Treatment



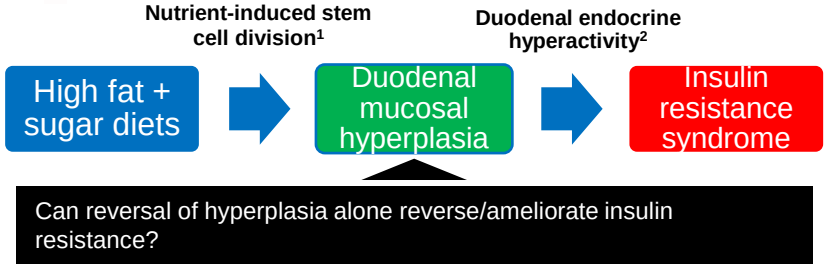
Median values given with IQRs, dots are outliers.

Middleton. Gastroenterology. 2017;153:753.

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

BACKGROUND & AIMS

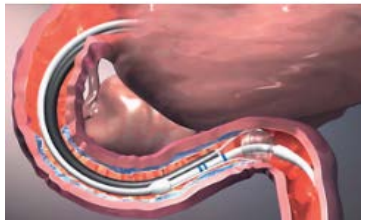
Putative role of duodenal mucosal hyperplasia in metabolic disease



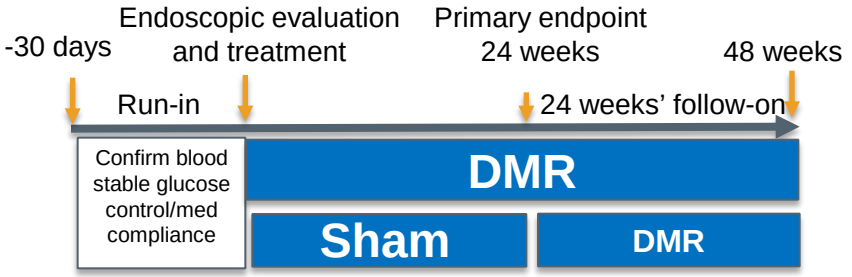
Aim: Evaluate effect of DMR on glycaemia, hepatic fat, and mechanistic endpoints

DMR: REVITA single catheter

Schematic of DMR



METHODS



- 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

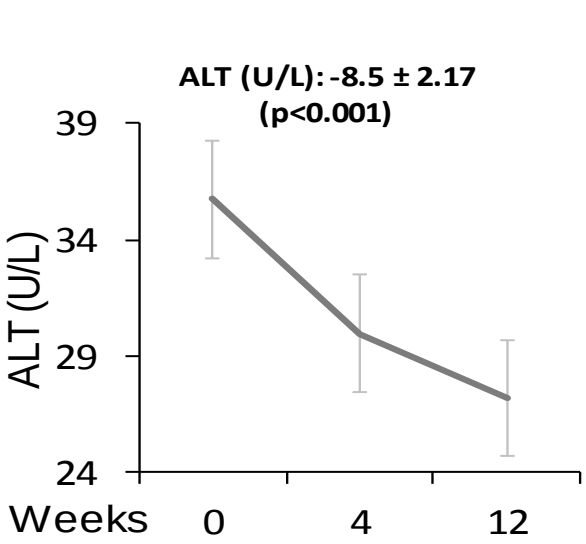
Endoscopic duodenal mucosal resurfacing improves hepatic fat fraction, glycaemic and lipid profiles in type 2 diabetes

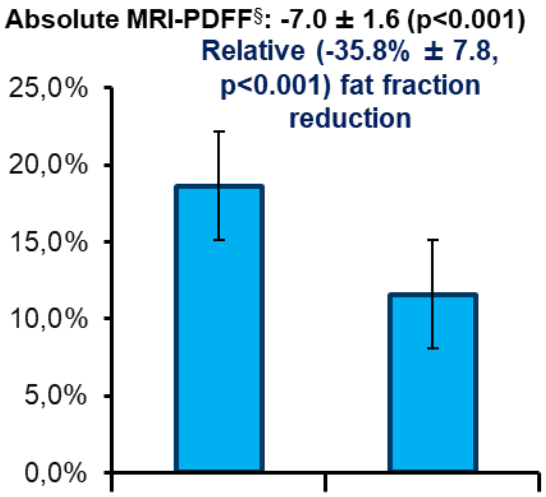
Baseline and 12-week metabolic and glycaemic values*

RESULTADOS

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*





CONCLUSIONS 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

Resumen

- La reduccion ponderal y cambios de estilo de vida son la piedra angular del manejo de la EHGNA
- Vitamina E, liraglutide y Pioglitazona ofrecen resultados positivos. Se desconoce su seguridad a largo plazo.
- Multiples dianas farmacologicas en desarrollo
- Los 2 objetivos histologicos para los ensayos **fase III** son:
  - **Resolución del NASH** sin empeoramiento de la fibrosis
  - **Mejoria de la fibrosis** sin empeoramiento del NASH
- Los ensayos clinicos de diseño “adaptado” (Fase 2) aportan la oportunidad de acelerar el desarrollo.
- El OCA es el primero de los ensayos Fase III en ofrecer resultados positivos.