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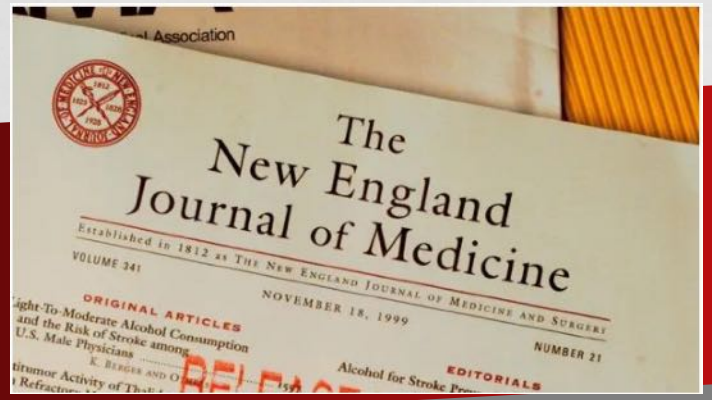


Noelia Carracedo Falagán

Medicina Interna

12 de abril de 2024.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cefepime–Taniborbactam in Complicated Urinary Tract Infection

Florian M. Wagenlehner, M.D., Leanne B. Gasink, M.D., Paul C. McGovern, M.D., Greg Moeck, Ph.D., Patrick McLeroth, M.D., MaryBeth Dorr, Ph.D., Aaron Dane, M.Sc., and Tim Henkel, M.D., Ph.D., for the CERTAIN-1 Study Team*

INTRODUCCIÓN

✓ Infecciones urinarias complicadas y pielonefritis agudas.

- Causa de **600.000 ingresos USA** y **elevado coste sanitario**.

Tabak YP et al. "Attributable clinical and economic burden of carbapenem non susceptible Gram negative infections in patients hospitalized with complicated urinary tract infectiones". **J. Hosp Infect 2019;102:37-44.**

Vallejo Torres L et al. "Cost of hospitalised patients due to complicated urinary tract infections: a retrospective observational study in countries with high prevalence of multidrug resistant Gram megative bacteria: the COMBACT-MAGNET, RESCUING study". **BMJ Open 2018;8(4):e020251.**

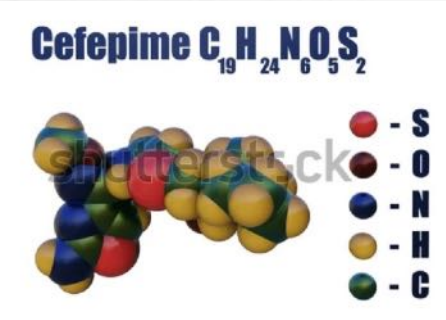
✓ **Resistencias** emergentes a **β-lactámicos** complica el tratamiento.

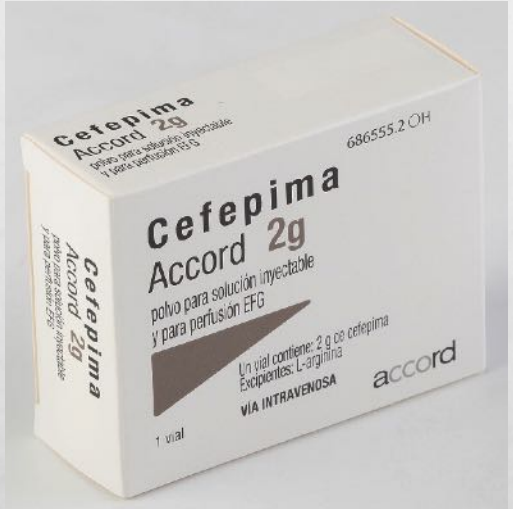
"Antimicrobial resistance in the EU/EEA R-Net): anual epidemiological report for 2021. Stockholm: European Centre for Disease Prevention and Control", **November 2022.**

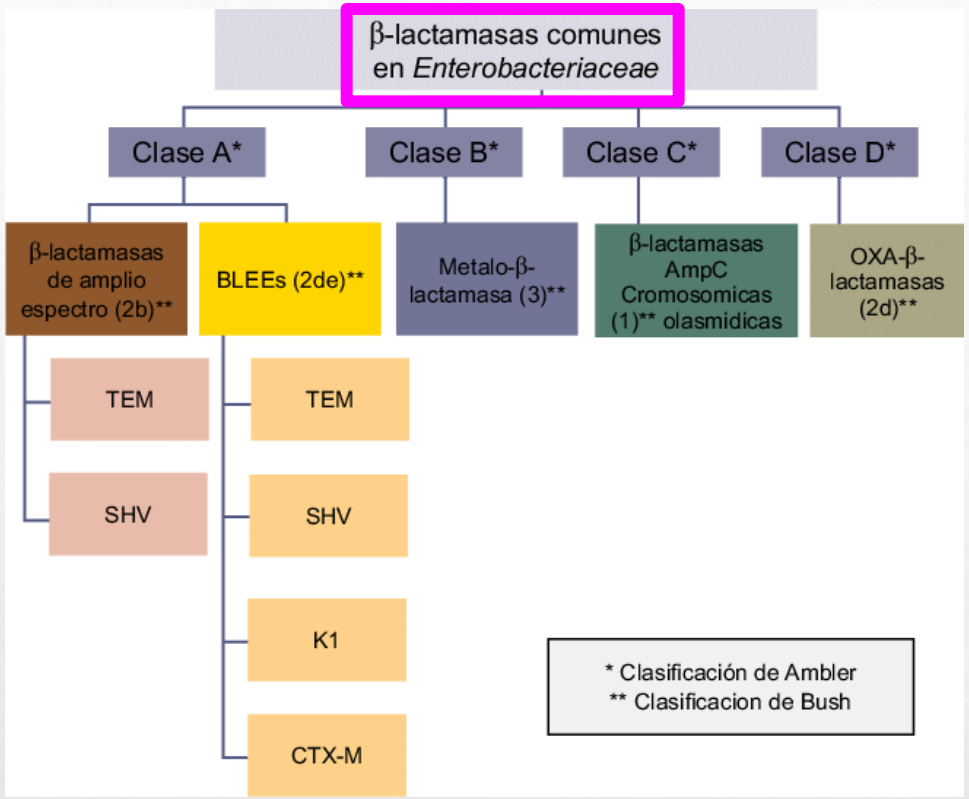
"No time to wait: securing the future from durg-resistant infections: report to the Secretary General of the United Nations. **Geneva: World Health Organization", April 29, 2019.**

Bush K et al . "Epidemiology of b-lactamase producing pathogens". **Clin Microbiol Rev 202;33 (2): e00047-19.**

INTRODUCCIÓN







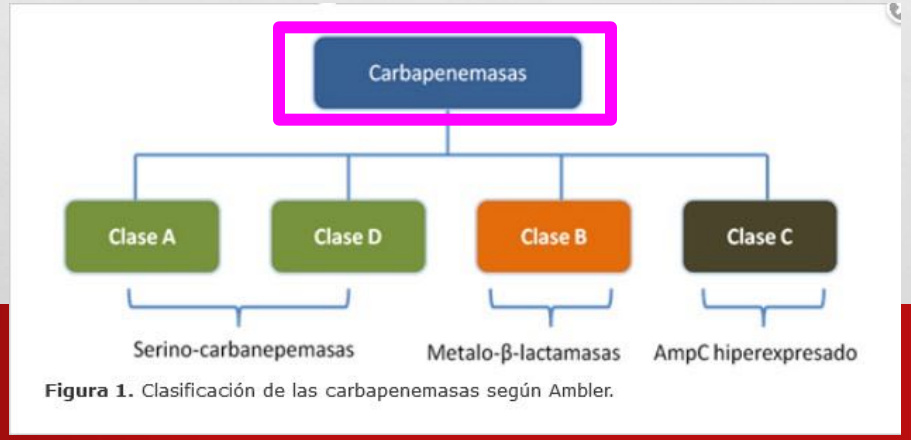


Figura 1. Clasificación de las carbapenemasas según Ambler.

Isler B et al. "An update oncefepime and its future role in combination with novel B-lactamase inhibitors for MDR Enterobacterales and Pseudomonas aeroginosa". **J. Antimicrob. Chemoter 2021;76:550-60.**

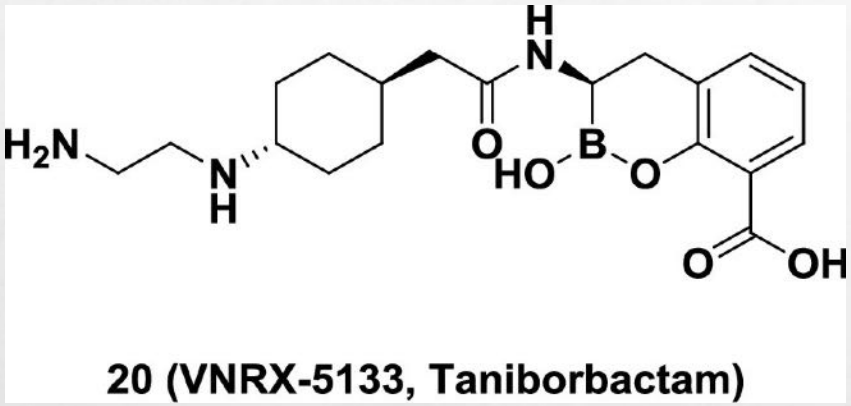
European Centre for Disease Prevention and Control. Antimicrobial resistance surveillance in Europe 2022-2020 data. **Copenhagen: WHO Regional Office for Europe, 2022.**

Grupo funcional	Clase molecular	Sustrato	Enzimas	Inhibida por Ácido clavulánico o tazobactam	Inhibida por EDTA	Aztreonam
1	C	Cefalosporinas	AmpC, P99, ACT-1, CMY-2, FOX-1, MIR-1	No	No	-
1e	C	Cefalosporinas	CG1, CMY-37	No	No	-
2df	D	Cloxacilina, Carbapenémicos.	OXA-23, OXA-48	Variable	No	S
2f	A	Carbapenémicos, Oxoamino-β-lactámicos, Cefamicinas.	SME-1, IMI-1, KPC-2	Sí	No	R
3a	B (B1)	Carbapenémicos	IMP-1, VIM-1, CcrA, INN-1	No	Sí	S/R
3b	B (B2)	Carbapenémicos	CphA, Shf-1	No	Sí	S/R
3c	B (B3)	Carbapenémicos	L1, CAU-1, GOB-1, FEZ-1	No	Sí	S/R

EDTA: ácido etilen-diamino-tertra-acético.
KPC: *Klebsiella pneumoniae* productora de carbapenemasas.

Tabla 1. Clasificación de las carbapenemasas según Ambler & Bush, adaptado de Bush Jacoby [5].

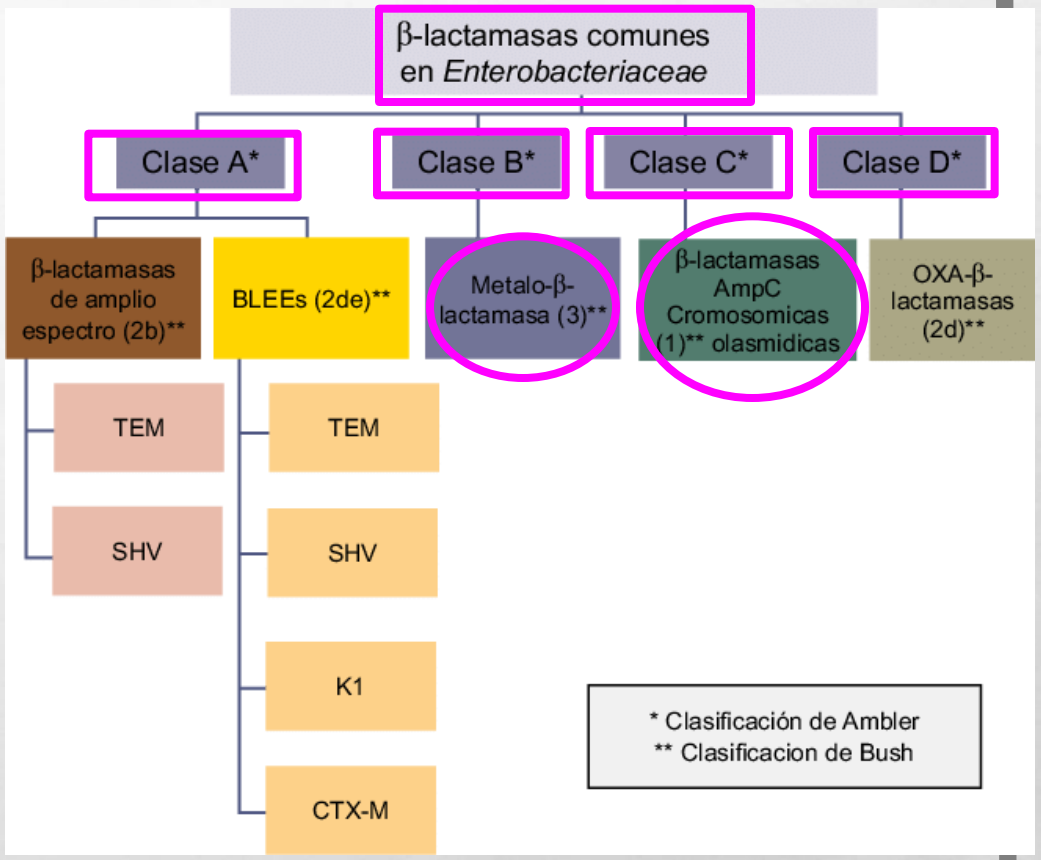
INTRODUCCIÓN



20 (VNRX-5133, Taniborbactam)

- ✓ <u>Boronato bicíclico</u> inhibidor de B-lactamasa.

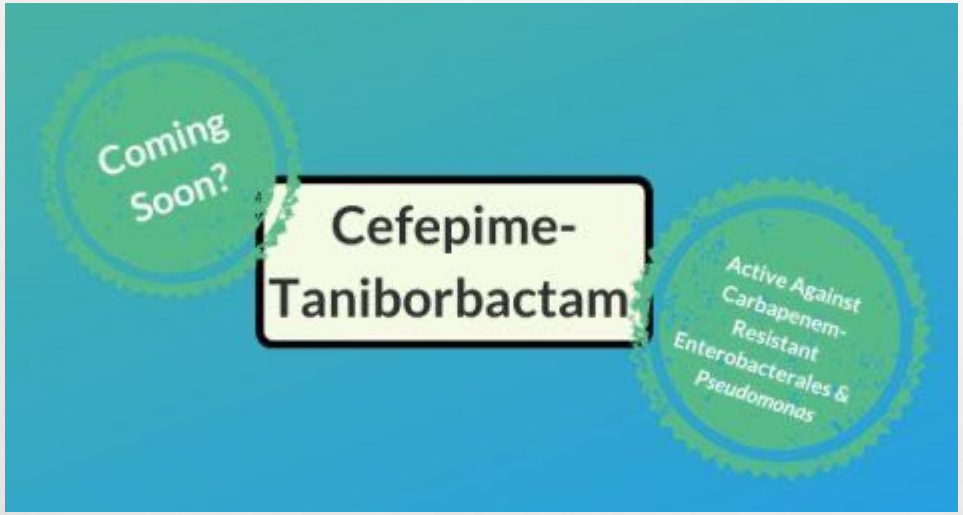
- ➢ DIRECTA.
- ➢ POTENTE.
- ➢ SELECTIVA.



Lui B et al. "Discovery of taniborbactma (VNRX-5133): a borad-spectrum serine and metallo B-lactamase inhibitor for carbapenem riesistant bacterial infections". **J. Med. Chem 2020; 63:2789-801.**

Hamrick JC et al. "VNRX-5133 (taniborbactam), a broad-spectrum inhibitor of serine and metallo B-lactamases, restores activity of cefepime in Enterobacterales and Pseudomonas aeroginosa". **Antimicrob Agent; Chemother 2020; 64(3): 301963-19.**

INTRODUCCIÓN



- ✓ Perfil **seguridad** en **voluntarios sanos.**
- ✓ **Eliminación renal** 80%.

ACTIVIDAD "IN VITRO"	ACTIVIDAD "IN VIVO"
❑ Enterobacterias R a carbapenémicos.	❑ Enterobacterias R a carbapenémicos y cefepime.
❑ P. aeroginosa multi-R.	❑ P. aeroginosa R a carbapenémicos y cefepime.
❑ Enterobacterias y P. aeroginosa R a: - Ceftolozano-tazobactam. - Ceftazidima-avibactam.	

Golden AR et al. "Activity of cefepime/taniborbactam and comparators against whole genome sequenced ertapenem non suceptible Enterobacterales clinical isolates: **CANWARD 2007-2019. JAC Antimicrob Resist 2022; 4(1): dlab197.**

Hernández García M et al. "In vitro activity of cefepime-taniborbactam against carbapenemase-producing and Pseudomonas aeroginosa isolates recovered in Spain". **Antimicrob Agents Chemother 2022;66(3):e0216121.**

Karlowsky JA et al. "In vitro activity of cefepime-taniborbactam and comparators against clinical isolates of Gram-negative bacilli from 2018 to 2020: results form the Global Evaluation of Antimicrobial Resistance via Surveillance (GEARS) program". **Antimicrob Agents Chemother 2023;67(1):e0128122.**

Abdelraouf K et al. "In vivo pharmacodynamics of new generation B-lactamase inhibitor toniborbactam (formerly VNRX-5133) in combination with cefepime against serine B-lactamasa producing Gram negative bacteria". **J Antimicrob Chemoter 2020;75:3601-10.**

Abdelraouf K et al. "In vivo Pharmacokinetic/pharmacodynamic evaluation of cefepime/taniborbactam combination against cefepime non susceptible Enterobacterales and Pseudomonas aeroginosa ina murine pneumonia model". **J Antimicrob Chemother 2023;78:692-702.**

MATERIAL Y MÉTODOS

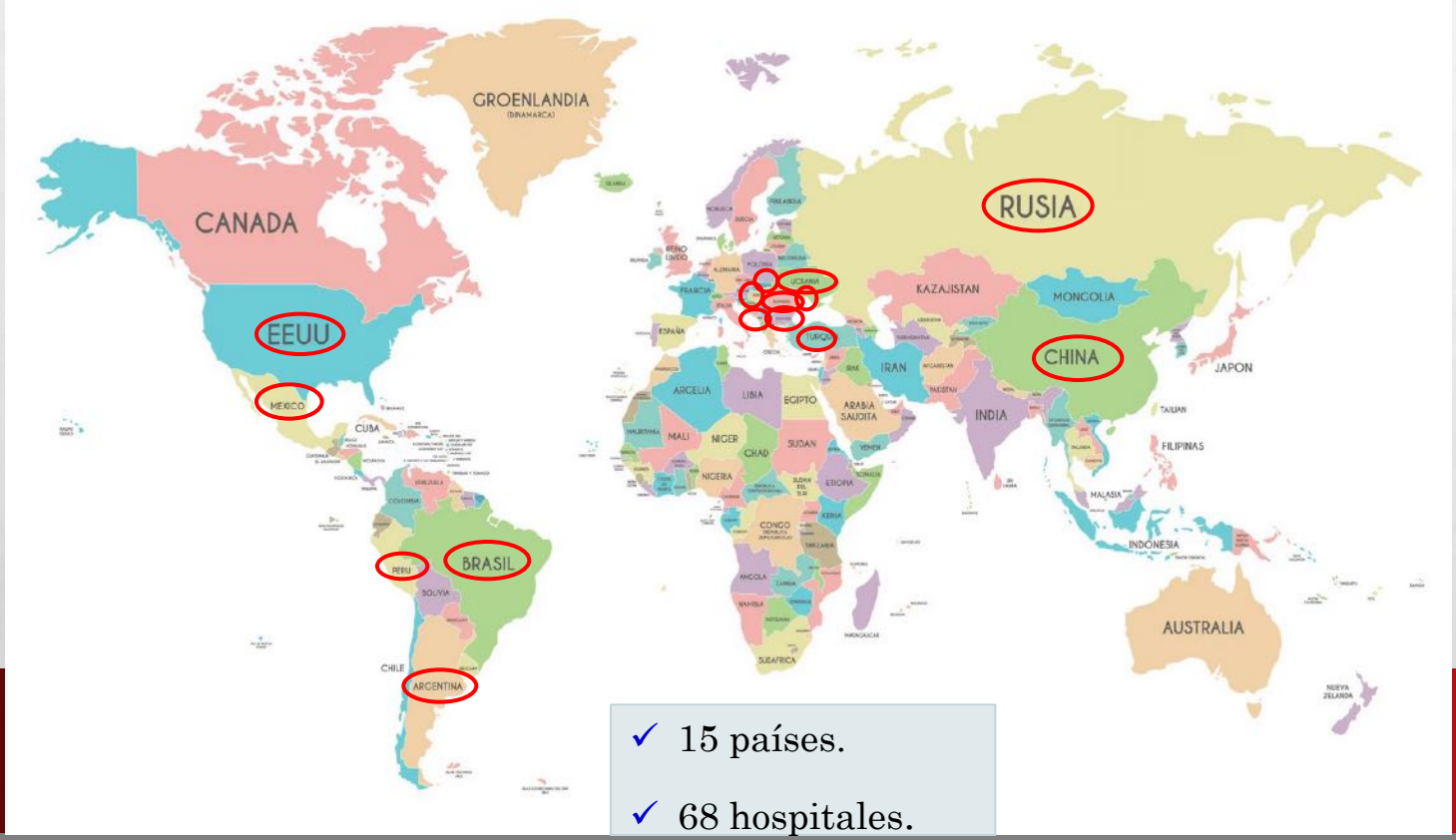
DISEÑO DEL ENSAYO

✓ CERTAIN-1

- Ensayo fase 3 para evaluar seguridad y eficacia de **CEFEPIME-TANIBORBACTAM** vs MEROPENEM en pacientes hospitalizados con **ITUs complicadas**.

✓ Ensayo clínico, aleatorizado, doble ciego, doble simulación controlado con tratamiento activo.

✓ Agosto 2019 a Diciembre 2021.



✓ 15 países.

✓ 68 hospitales.

Venatorx PHARMACEUTICALS

Junta de Castilla y León Consejería de Sanidad · Sacyl · Complejo Asistencial Universitario de León

MATERIAL Y MÉTODOS

CRITERIOS DE SELECCIÓN

CRITERIOS DE INCLUSIÓN	CRITERIOS DE EXCLUSIÓN
Adultos mayores de 18 años con dco:	❑ Antibioterapia > 24 horas previas a la aleatorización.
1. ITU complicada: - Piuria. - >/ 1 signo sistémico (naúseas/vómitos, escalofríos/tiritona/fiebre). - >/ 1 signo/síntoma local (disuria, polaquiuria, tenesmo, dolor suprapúbico). - >/ 1 factor de complicación (anomalía anatómica o funcional del tracto urinario).	❑ Antecedente ITU con patógeno R a meropenem. ❑ Tratamiento AB previo sin indicación filiada. ❑ FG < 30 ml/1.73 m2. ❑ Prostatitis. ❑ Absceso renal o peri-renal. ❑ Insuficiencia hepática grave. ❑ Hipersensibilidad a cualquier β-lactámico.
2. **Pielonefritis aguda:** - Piuria. - >/ 1 síntoma sistémico (náuseas/vómitos, escalofríos/tiritona/fiebre). -Dolor en flanco o hipersensibilidad en ángulo costovertebral.	❑ Transplante renal.

MATERIAL Y MÉTODOS

ALEATORIZACIÓN Y TRATAMIENTO

Aleatorización

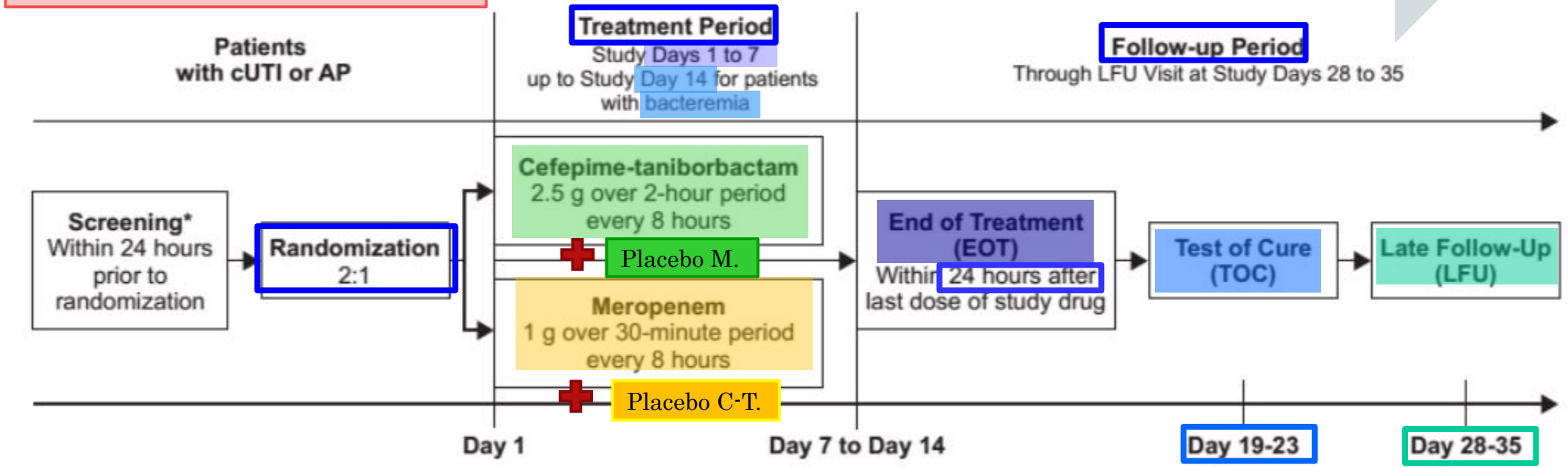
Tipo infección
- ITU.
- PA.

Región
- Norte-América.
- Europa occidental.
- Europa del Este.
- Resto mundo.

Desescalar AB oral.

Aleatorización previa resultado urinocultivo.

Figure S1. Overview of Study Design



AP = acute pyelonephritis; cUTI = complicated urinary tract infection; EOT = end of treatment; TOC = test of cure; LFU = late follow-up.
*Samples taken for determination of eligibility in primary analysis population (microbiologic intent-to-treat [microITT]).

MATERIAL Y MÉTODOS

POBLACIÓN DEL ENSAYO

Población por intención de tratar (ITT)

- Todos los pacientes aleatorizados.

Población microbiológica por intención de tratar (micro-ITT)

- Pacientes UC positivo (100.000 UFC/ml) para Gram – ⇨ S a Cefep-tanibor y Meropenem.
- Aislamiento no superior a 2 bacterias.
- Monomicrobiano G + ⇨ excluidos.

Población microbiológica extendida por intención de tratar (extended micro-ITT)

- Toda población micro-ITT + pacientes con UC positivo para Gram - S a sólo un F (C-T o M).

POBLACIÓN micro-ITT:

✓ Utilizada en los ensayos con ANTIBIÓTICOS para evaluar la **NO INFERIORIDAD** y que el componente MICROBIOLÓGICO del objetivo primario pueda ser evaluado.

MATERIAL Y MÉTODOS

POBLACIÓN DEL ENSAYO

END POINT PRIMARIO

Compuesto de: respuesta clínica y microbiológica (micro-ITT) en "periodo de curación" desde los días 19 a 23.

MEJORIA CLÍNICA:

-Resolución de síntomas y signos sin necesidad de otros AB adicionales.

MEJORIA MICROBIOLÓGICA:

- ↓Patógenos basales ≤ 1000 UFC/ml.

END POINT SECUNDARIOS

Compuesto de: mejoria clínica y microbiológica (micro-ITT y micro-ITT extendida) al final del tratamiento y seguimiento tardío.

FINAL TRATAMIENTO:

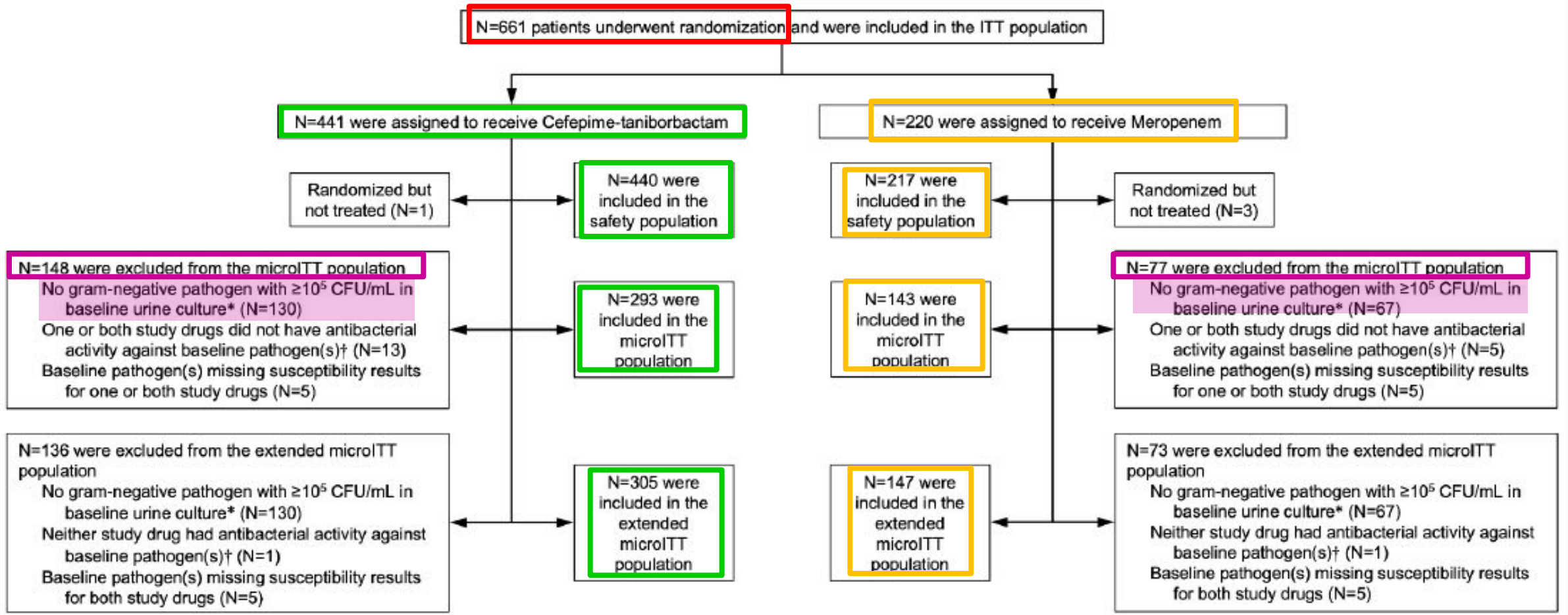
-Primeras 24 horas tras última dosis AB.

SEGUIMIENTO TARDIO:

-Días 28 a 35.

RESULTADOS

Figure S2. Patient Disposition – CONSORT Diagram



RESULTADOS

- ✓ La **mayoría finalizó tratamiento AB** ⇨ 93.9% vs 96.4%.
- ✓ La **mayoría completó ensayo** ⇨ 96.6% vs 97.3%.
- ✓ Duración media de tratamiento ⇨ **7 días** (1 a 15).
- ✓ Mediana duración tto en **bacteriemia** fue similar (**12-14 días**).

Table S5. Gram-negative Baseline Pathogens in at least 10 Patients across Both Treatment Groups (Microbiologic Intent-to-Treat Population)

	Cefepime-taniborbactam (N=293) n (%)	Meropenem (N=143) n (%)	Total (N=436) n (%)
Enterobacterales	281 (95.9%)	137 (95.8%)	418 (95.9%)
Enterobacter cloacae complex	14 (4.8%)	3 (2.1%)	17 (3.9%)
Escherichia coli	202 (68.9%)	99 (69.2%)	301 (69.0%)
Klebsiella pneumoniae	40 (13.7%)	20 (14.0%)	60 (13.8%)
Proteus mirabilis	10 (3.4%)	10 (7.0%)	20 (4.6%)
Pseudomonas aeruginosa	12 (4.1%)	6 (4.2%)	18 (4.1%)

The denominator for percentages is the number of patients in each treatment group (N).
Patients may have more than one pathogen at baseline.
Multiple isolates of the same pathogen (i.e., species) from the same patient are counted only once.

Table 1. Characteristics of the Patients at Baseline (Microbiologic Intention-to-Treat Population).*

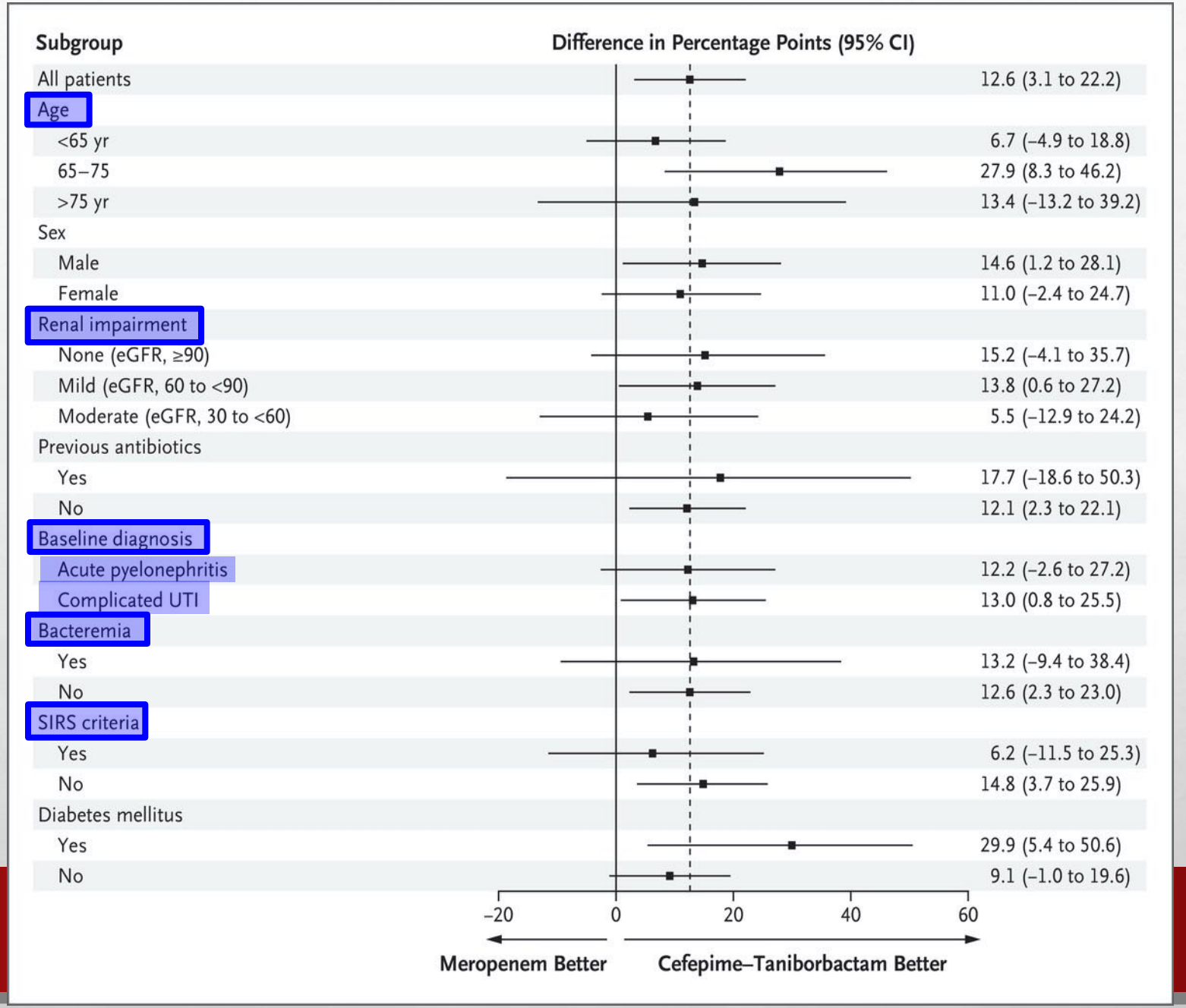
Characteristic	Cefepime–Taniborbactam (N=293)	Meropenem (N=143)
Age		
Mean	56.5±17.6	55.8±17.9
Distribution — no. (%)		
<65 yr	180 (61.4)	90 (62.9)
65 to 75 yr	72 (24.6)	35 (24.5)
>75 yr	41 (14.0)	18 (12.6)
Female sex — no. (%)	161 (54.9)	69 (48.3)
Race or ethnic group — no. (%)†		
American Indian or Alaska Native	3 (1.0)	0
Asian	26 (8.9)	6 (4.2)
Black	1 (0.3)	0
White	257 (87.7)	131 (91.6)
Other	6 (2.0)	6 (4.2)
Hispanic or Latino ethnic group — no. (%)†		
Yes	29 (9.9)	12 (8.4)
No	263 (89.8)	130 (90.9)
Missing data	1 (0.3)	1 (0.7)
Geographic region — no. (%)		
North America or western Europe	14 (4.8)	8 (5.6)
Eastern Europe	236 (80.5)	121 (84.6)
Rest of world	43 (14.7)	14 (9.8)
Body-mass index — no. (%)‡		
<18.5	10 (3.4)	3 (2.1)
18.5 to 24.9	89 (30.4)	45 (31.5)
25 to 29.9	113 (38.6)	54 (37.8)
≥30	81 (27.6)	39 (27.3)
Missing data	0	2 (1.4)
Status for eGFR — no. (%)§		
Normal: ≥90 ml/min/1.73 m²	66 (22.5)	29 (20.3)
Mild impairment: 60 to <90 ml/min/1.73 m²	138 (47.1)	75 (52.4)
Moderate impairment: 30 to <60 ml/min/1.73 m²	84 (28.7)	38 (26.6)
Severe impairment: <30 ml/min/1.73 m²	5 (1.7)	1 (0.7)
Infection type — no. (%)		
Complicated UTI	167 (57.0)	85 (59.4)
Acute pyelonephritis	126 (43.0)	58 (40.6)
Bacteremia — no. (%)	38 (13.0)	19 (13.3)
SIRS criteria — no. (%)¶	70 (23.9)	36 (25.2)
Diabetes — no. (%)	49 (16.7)	24 (16.8)
Gram-negative pathogen — no. (%)	293 (100)	143 (100)
Enterobacterales species		
Any	281 (95.9)	137 (95.8)
Cefepime-resistant	66 (22.5)	30 (21.0)
ESBL-producing	76 (25.9)	40 (28.0)
Multidrug-resistant**	100 (34.1)	55 (38.5)

RESULTADOS

Table 2. Primary and Secondary Efficacy Outcomes.*

Outcome, Population, and Time of Assessment	Cefepime–Taniborbactam	Meropenem	Treatment Difference (95% CI)
	no./total no. of patients (%)		*percentage points*
Microbiologic intention-to-treat population			
Primary outcome†			
Composite success at test of cure	207/293 (70.6)	83/143 (58.0)	12.6 (3.1 to 22.2)‡
Microbiologic§	229/293 (78.2)	95/143 (66.4)	11.7 (2.9 to 21.0)
Clinical¶	251/293 (85.7)	116/143 (81.1)	4.5 (–2.6 to 12.6)
Secondary outcome‖			
Composite success at end of treatment	261/293 (89.1)	123/143 (86.0)	3.1 (–3.2 to 10.4)
Microbiologic§	284/293 (96.9)	139/143 (97.2)	–0.3 (–3.5 to 4.1)
Clinical¶	265/293 (90.4)	127/143 (88.8)	1.6 (–4.1 to 8.5)
Composite success at late follow-up	187/293 (63.8)	74/143 (51.7)	12.1 (2.2 to 21.9)
Microbiologic§	207/293 (70.6)	90/143 (62.9)	7.7 (–1.6 to 17.3)
Clinical¶	238/293 (81.2)	102/143 (71.3)	9.9 (1.5 to 18.8)
Extended microbiologic intention-to-treat population			
Secondary outcome			
Composite success at test of cure	216/305 (70.8)	86/147 (58.5)	12.3 (3.0 to 21.8)
Microbiologic§	238/305 (78.0)	98/147 (66.7)	11.4 (2.7 to 20.5)
Clinical¶	262/305 (85.9)	119/147 (81.0)	4.9 (–2.1 to 12.9)

RESULTADOS


Subgroup
Difference in Percentage Points (95% CI)
All patients
12.6 (3.1 to 22.2)
Age
<65 yr
6.7 (–4.9 to 18.8)
65–75
27.9 (8.3 to 46.2)
>75 yr
13.4 (–13.2 to 39.2)
Sex
Male
14.6 (1.2 to 28.1)
Female
11.0 (–2.4 to 24.7)
Renal impairment
None (eGFR, ≥90)
15.2 (–4.1 to 35.7)
Mild (eGFR, 60 to <90)
13.8 (0.6 to 27.2)
Moderate (eGFR, 30 to <60)
5.5 (–12.9 to 24.2)
Previous antibiotics
Yes
17.7 (–18.6 to 50.3)
No
12.1 (2.3 to 22.1)
Baseline diagnosis
Acute pyelonephritis
12.2 (–2.6 to 27.2)
Complicated UTI
13.0 (0.8 to 25.5)
Bacteremia
Yes
13.2 (–9.4 to 38.4)
No
12.6 (2.3 to 23.0)
SIRS criteria
Yes
6.2 (–11.5 to 25.3)
No
14.8 (3.7 to 25.9)
Diabetes mellitus
Yes
29.9 (5.4 to 50.6)
No
9.1 (–1.0 to 19.6)
–20
0
20
40
60
Meropenem Better
Cefepime–Taniborbactam Better

RESULTADOS

Table 3. Composite, Microbiologic, and Clinical Success at Test of Cure, According to Pathogen (Microbiologic Intention-to-Treat Population).*

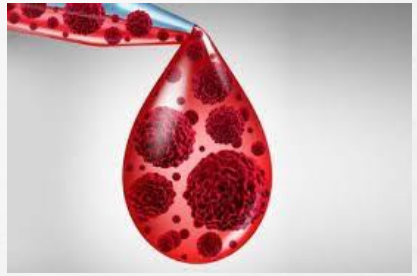
Baseline Pathogen and Outcome	Cefepime–Taniborbactam	Meropenem
	no./total no. of patients (%)	
Composite success		
Enterobacterales species or category	202/281 (72)	80/137 (58)
Enterobacter cloacae complex	11/14 (79)	1/3 (33)
Escherichia coli	147/202 (73)	58/99 (59)
Klebsiella pneumoniae	24/40 (60)	12/20 (60)
Proteus mirabilis	8/10 (80)	4/10 (40)
Cefepime-resistant	47/66 (71)	16/30 (53)
ESBL-producing	54/76 (71)	22/40 (55)
Multidrug-resistant	68/100 (68)	33/55 (60)
Pseudomonas aeruginosa	5/12 (42)†	3/6 (50)
Microbiologic success		
Enterobacterales species or category	224/281 (80)	91/137 (66)
E. cloacae complex	11/14 (79)	1/3 (33)
E. coli	163/202 (81)	67/99 (68)
K. pneumoniae	27/40 (68)	14/20 (70)
P. mirabilis	9/10 (90)	4/10 (40)
Cefepime-resistant	50/66 (76)	18/30 (60)
ESBL-producing	57/76 (75)	25/40 (62)
Multidrug-resistant	71/100 (71)	38/55 (69)
P. aeruginosa	5/12 (42)†	4/6 (67)
Clinical success		
Enterobacterales species or category	241/281 (86)	111/137 (81)
E. cloacae complex	14/14 (100)	3/3 (100)
E. coli	177/202 (88)	80/99 (81)
K. pneumoniae	29/40 (72)	14/20 (70)
P. mirabilis	9/10 (90)	9/10 (90)
Cefepime-resistant	54/66 (82)	25/30 (83)
ESBL-producing	64/76 (84)	32/40 (80)
Multidrug-resistant	87/100 (87)	46/55 (84)
P. aeruginosa	10/12 (83)	5/6 (83)

RESULTADOS

Table S6. Composite, Microbiologic, and Clinical Success at the Late Follow-up Visit According to Pathogen (Microbiologic Intent-to-Treat Population)

Baseline Pathogen*	Cefepime-Taniborbactam	Meropenem
	no. of patients with success/no. of patients (%)	
Composite Success		
Enterobacterales	182/281 (64.8)	71/137 (51.8)
Enterobacter cloacae complex	11/14 (78.6)	1/3 (33.3)
Escherichia coli	127/202 (62.9)	48/99 (48.5)
Klebsiella pneumoniae	26/40 (65.0)	11/20 (55.0)
Proteus mirabilis	7/10 (70.0)	5/10 (50.0)
Pseudomonas aeruginosa	5/12 (41.7)	3/6 (50.0)
Cefepime-resistant Enterobacterales†	45/66 (68.2)	13/30 (43.3)
ESBL-producing Enterobacterales‡	51/76 (67.1)	19/40 (47.5)
Multidrug-resistant Enterobacterales§	62/100 (62.0)	28/55 (50.9)
Microbiologic Success		
Enterobacterales	202/281 (71.9)	86/137 (62.8)
Enterobacter cloacae complex	11/14 (78.6)	1/3 (33.3)
Escherichia coli	140/202 (69.3)	61/99 (61.6)
Klebsiella pneumoniae	30/40 (75.0)	13/20 (65.0)
Proteus mirabilis	8/10 (80.0)	5/10 (50.0)
Pseudomonas aeruginosa	5/12 (41.7)	4/6 (66.7)
Cefepime-resistant Enterobacterales†	48/66 (72.7)	16/30 (53.3)
ESBL-producing Enterobacterales‡	54/76 (71.1)	23/40 (57.5)
Multidrug-resistant Enterobacterales§	69/100 (69.0)	35/55 (63.6)
Clinical Success		
Enterobacterales	230/281 (81.9)	97/137 (70.8)
Enterobacter cloacae complex	14/14 (100)	1/3 (33.3)
Escherichia coli	166/202 (82.2)	71/99 (71.7)
Klebsiella pneumoniae	29/40 (72.5)	13/20 (65.0)
Proteus mirabilis	9/10 (90.0)	6/10 (60.0)
Pseudomonas aeruginosa	8/12 (66.7)	5/6 (83.3)
Cefepime-resistant Enterobacterales†	49/66 (74.2)	20/30 (66.7)
ESBL-producing Enterobacterales‡	59/76 (77.6)	28/40 (70.0)
Multidrug-resistant Enterobacterales§	76/100 (76.0)	39/55 (70.9)

RESULTADOS



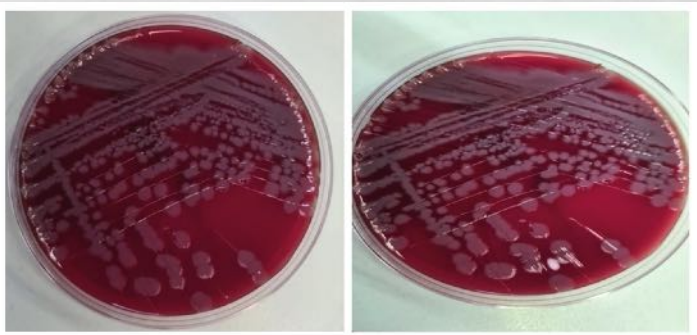
BACTERIEMIAS

- ✓ HEMOCULTIVOS de control :
  - Fueron negativos en todos los pacientes con bacteriemia inicial en grupo Cefepime/Taniborbactam.

- ✓ OBJETIVO PRIMARIO (compuesto respuesta clínica y microbiológica en "periodo de curación")
  - Fue **81.6% Cefepime/Taniborbactam** vs 68.4% Meropenem.

POBLACIÓN MICRO-ITT EXTENDED

- ✓ CEFEPIME-TANIBORBACTAM se cumplió el objetivo primario.
  - 8 de 10 pacientes **RESISTENTES al MEROPENEM**
    - *K. pneumoniae*: 6 pacientes de 7.
    - *P. aeroginosa*: 1 paciente de 2.
    - *Serratia marcescens*: 1 paciente.



RESULTADOS

SEGURIDAD

Table 4. Summary of Adverse Events (Safety Population).*

Event	Cefepime–Taniborbactam (N=440)	Meropenem (N=217)
Any adverse event — no. of patients (%)	156 (35.5)	63 (29.0)
No. of adverse events	341	114
Mild — no./total no. (%)	226/341 (66.3)	82/114 (71.9)
Moderate — no./total no. (%)	100/341 (29.3)	25/114 (21.9)
Severe — no./total no. (%)	15/341 (4.4)	7/114 (6.1)
Adverse event related to a trial drug — no. of patients (%)†	59 (13.4)	19 (8.8)
Adverse event reported in ≥1% of patients in either treatment group — no. of patients (%)‡		
Headache	27 (6.1)	8 (3.7)
Diarrhea	18 (4.1)	5 (2.3)
Constipation	14 (3.2)	3 (1.4)
Hypertension	10 (2.3)	2 (0.9)
Nausea	9 (2.0)	2 (0.9)
Abdominal distention	7 (1.6)	3 (1.4)
Anemia	7 (1.6)	3 (1.4)
Dizziness	7 (1.6)	1 (0.5)
Hypokalemia	7 (1.6)	1 (0.5)
Phlebitis	6 (1.4)	1 (0.5)
Vomiting	6 (1.4)	1 (0.5)
Cough	5 (1.1)	2 (0.9)
Pyrexia	5 (1.1)	3 (1.4)
Increased alanine aminotransferase	4 (0.9)	5 (2.3)
Vulvovaginal candidiasis	3 (0.7)	3 (1.4)
Discontinuation of trial drug — no. (%)§	13 (3.0)	2 (0.9)
Serious adverse event — no. of patients (%)¶		
Any	9 (2.0)	4 (1.8)
Related to a trial drug†	2 (0.5)	0

C. difficile: 3 pacientes.

RESULTADOS

SEGURIDAD

Table S10. Treatment-emergent Adverse Events Leading to Discontinuation of Study Drug by System Organ Class and Preferred Term (Safety Analysis Population)

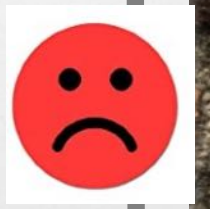
System Organ Class Preferred Term	Cefepime-taniborbactam (N=440) n (%)	Meropenem (N=217) n (%)
Patients with any TEAE leading to discontinuation of study drug	13 (3.0%)	2 (0.9%)
Gastrointestinal disorders	2 (0.5%)	0
Abdominal pain	1 (0.2%)	0
Glossitis	1 (0.2%)	0
General disorders and administration site conditions	1 (0.2%)	0
Generalized oedema	1 (0.2%)	0
Infections and infestations	4 (0.9%)	1 (0.5%)
COVID-19	1 (0.2%)	0
Endocarditis	1 (0.2%)	0
Gastrointestinal candidiasis	1 (0.2%)	0
Renal abscess	1 (0.2%)	0
Tubo-ovarian abscess	0	1 (0.5%)
Injury, poisoning and procedural complications	1 (0.2%)	0
Procedural dizziness	1 (0.2%)	0
Procedural nausea	1 (0.2%)	0
Musculoskeletal and connective tissue disorders	1 (0.2%)	0
Muscle spasms	1 (0.2%)	0
Skin and subcutaneous tissue disorders	3 (0.7%)	1 (0.5%)
Urticaria	1 (0.2%)	1 (0.5%)
Angioedema	1 (0.2%)	0
Rash	1 (0.2%)	0
Vascular disorders	1 (0.2%)	0
Thrombophlebitis	1 (0.2%)	0

DISCUSIÓN

FORTALEZAS

- ✓ Mayores tasas de **respuesta compuesta** (C+M) y **mantenida en el seguimiento.**
  - Teniendo en cuenta patógenos eran S a ambos F.
  - Criterio mixto y características del microbiológicos más estrictos que usados en ensayos previos de AB aprobados.
- ✓ Resultados **concordantes** en los **diferentes subgrupos**, incluidos: enfermedad grave (bacteriemia y SIRS), según patógeno inicial y en grupos resistentes.
- ✓ Efectos adversos **similares:**
  - A pesar de dosis máximas de Cefepime: 2 gr/8 h.
- ✓ Caracteríticas basales y microbiológicas **similares** en ambos grupos.
  - **SUPERIORIDAD no** explicada por diferencias.
- ✓ **NO** desescalaje a **ANTIBIOTERAPIA ORAL** evita posible factor de confusión de AB adicional.
- ✓ Duración tratamiento ⇨ **7 días** (sin bacteriemia).
  - Consistente con guias actuales "duración corta" tto.
- ✓ **Generalización resultados:**
  - Representativos por incluir patógenos **multiR** (incluida P. aeroginosa).

LIMITACIONES



- ❑ Interrupción tratamiento por **ef. adversos graves** fue **superior**: 3% (C-T) vs 0.9% (M).
  - Heterogéneos….
  - < 5%.
- ❑ **NO** reflejo práctica clínica a nivel mundial:
  - Ausencia **tto oral**, **duración** fija **iv** y necesidad **hospitalización**.
- ❑ **81.9%** pacientes ⇨ **EUROPA del ESTE.**
  - Diferencias regionales en patrones de S.
  - Ubicación geográfica **no alteró**: caract. fisiopatológicas ITUc ni respuesta esperada a AB porque la **población incluida** eran bacterias **S a ambos fármacos.**
- ❑ Resultados de objetivo primario compuesto:
  - Fue más estricto que utilizados en ensayos previos.
  - Incluye pacientes con **bacteriuria asintomática** como un **fallo compuesto**, requeriría análisis complementario de respuesta clínica solamente.

CONCLUSIONES

1

- ✓ En pacientes con **infecciones urinarias complicadas** **CEFEPIME/TANIBORBACTAM** fue **SUPERIOR** a **MEROPENEM** en alcanzar tanto **respuesta CLÍNICA** como **MICROBIOLÓGICA** de **curación.**

2

- ✓ **Respuesta compuesta** y **respuesta clínica** fue **superior en grupo CEFEPIME/TANIBORBACTAM** al **FINAL del SEGUIMIENTO**.

3

- ✓ Ambos fármacos tienen un **perfil de SEGURIDAD SIMILAR.**

4

- ✓ **CEFEPIME/TANIBORBACTAM** es una **opción terapéutica** en pacientes con **ITUc y PIELONEFTRITIS AGUDA** causada por ***Enterobacteriae sp*** y ***P. aeroginosa*** incluidas cepas **resistentes**.

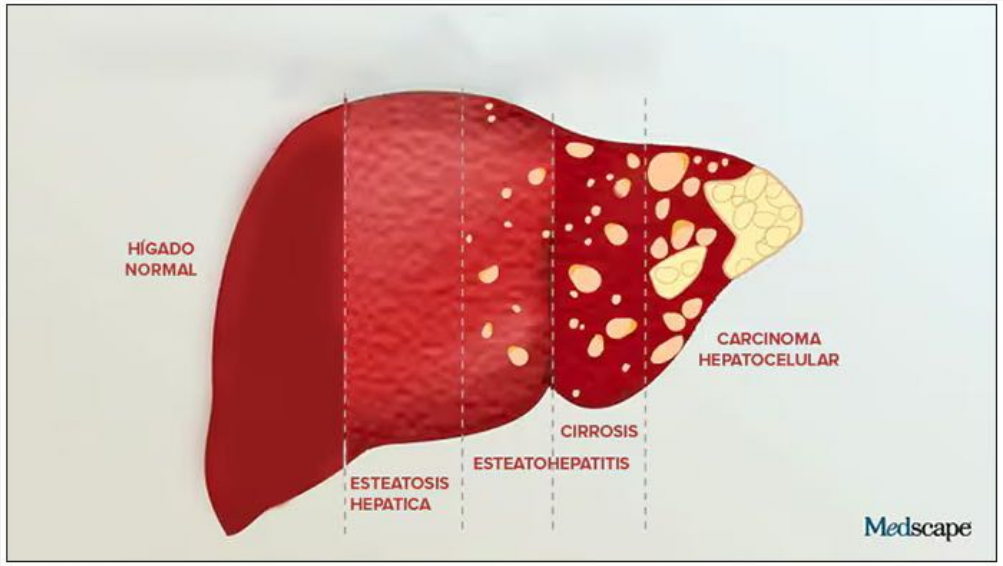
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 8, 2024 VOL. 390 NO. 6

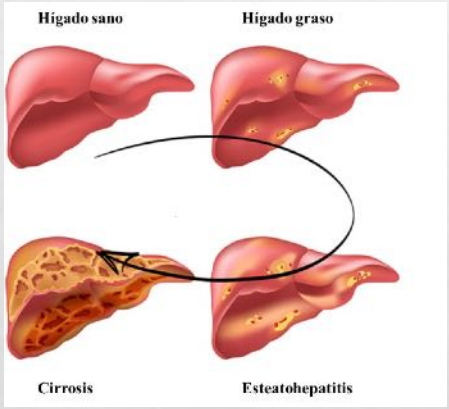
A Phase 3, Randomized, Controlled Trial of Resmetirom in NASH with Liver Fibrosis

S.A. Harrison, P. Bedossa, C.D. Guy, J.M. Schattenberg, R. Loomba, R. Taub, D. Labriola, S.E. Moussa, G.W. Neff, M.E. Rinella, Q.M. Anstee, M.F. Abdelmalek, Z. Younossi, S.J. Baum, S. Francque, M.R. Charlton, P.N. Newsome, N. Lanthier, I. Schiefke, A. Mangia, J.M. Pericàs, R. Patil, A.J. Sanyal, M. Noureddin, M.B. Bansal, N. Alkhouri, L. Castera, M. Rudraraju, and V. Ratziu, for the MAESTRO-NASH Investigators*

INTRODUCCIÓN



✓ESTEATOHEPATITIS NO ALCOHÓLICA (NASH)



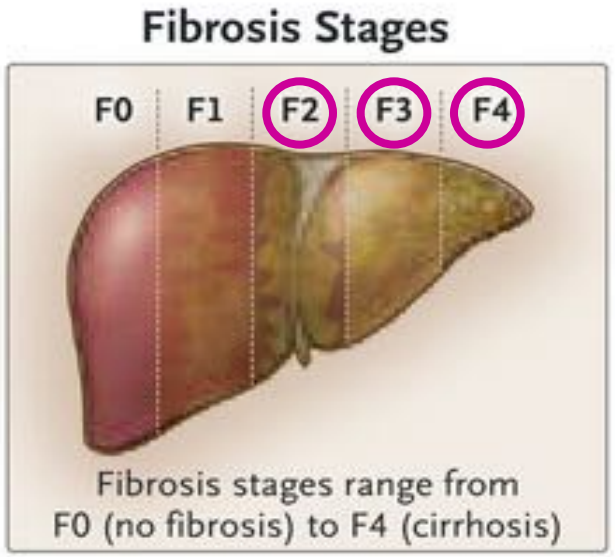
✓ Esteatosis hepática ≥ 5%.

✓ Daño hepatocelular.

✓ Inflamación.

INTRODUCCIÓN

✓ **NASH**: Esteatohepatitis no alcohólica.



Angulo et al. "Liver fibrosis, but no other histologic features, associates with ong term outcomes of patients with nonalcoholic fatty liver disease". **Gastroenterology 2015; 149(2):389-97.e10.**

Huang DQ et al. "Fibrosis progression rate in biopsy-proven nonalcoholic fatty liver disease among people with diabetes versus people without diabetes: a multicenter study" **Gastroenterology 2023;165(2):463-472 e5.**

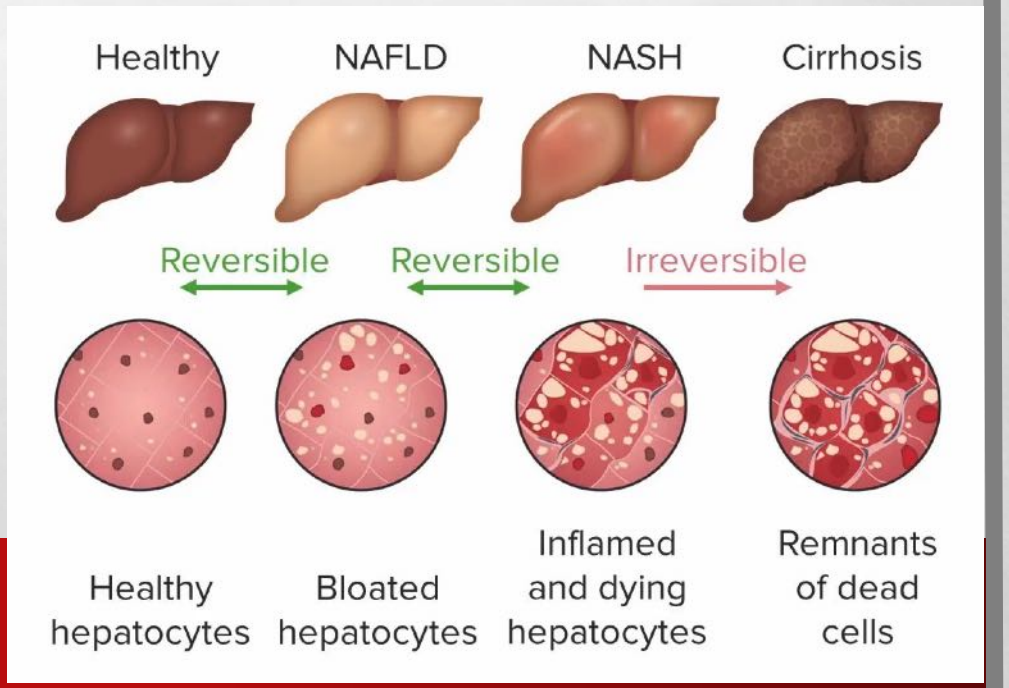
Targher G et al. "Nonalcoholic fatty liver disease: amultisystem disease requiring a multidisciplinary and holistic approach" **Lancet Gastroenterol Hepatol 2021;6:578-88.**

✓ Aumenta significativamente el riesgo de complicaciones hepáticas, especialmente en **DM 2** y **obesidad** (70%).

✓ **NAFLD**: hígado graso no alohólico

- Estudio prospectivo indicó que sólo F3 y F4 se asociaban con muerte por enfermedad hepática.

Sanyal AJ et al. "Prospective study of outcomes in adults wih nonalcoholic fatty liver disease". **NEJM 2021;385:1559-69.**



INTRODUCCIÓN

- ✓ Prevalencia mundial NASH ⇨ 4- 6%.
  - ❖ Elevados costes sociosanitarios.

- ✓ Opciones tratamiento NASH.
  - ❖ **Tto OBESIDAD** ⇨ dieta y ejercicio y/o aGLP-1.
  - ❖ **Tto DM 2** ⇨ glitazonas.

Schattenberg JM et al. "Disease burden and economic impact of diagnosed non alcoholic steatohepatitis in five European countries in 2018: a cost of illness analysis". **Liver Int 2021;41:1227-42.**

Younossi ZM et al. "The economic and economic and clinical burden of nonalcoholic fatty liver disease in the United States and Europe". **Hepatology 2016; 64:1577-86.**

- ✓ En la actualidad **NO** hay **NINGÚN FÁRMACO APROBADO** para el **TRATAMIENTO.**

- ✓ Necesidad imperiosa terapéutica ⇨**FDA** aprobaría un F condicionado a:
  - ❖ Criterios histológicos: mejoría estadio fibrosis.
  - ❖ Beneficio clínico traducido como:
    - ❑ ↓ mortalidad por cualquier causa.
    - ❑ ↓ necesidad transplante hepático.
    - ❑ ↓ descompensación hidrópica.

Omokaro SO et al. "FDA regulatory considerations for NASH clinical trial endpoints". Silver Spring, MD: **Food and Drug Administration; February 26, 2018.**

Omokaro SO et al. "FDA regulatory considerations for NASH clinical trial endpoints". Silver Spring, MD: **Food and Drug Administration; February 26, 2018.**

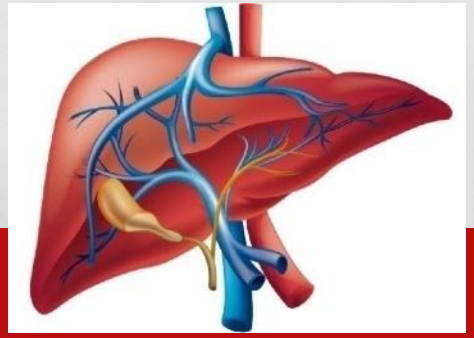
INTRODUCCIÓN

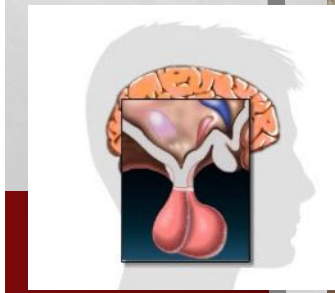
- ✓ **TSH modula:**
  - ❖ Glucosa hepática.
  - ❖ Metabolismo lipídico.

→

- ✓ **Hipotiroidismo** se asocia a **esteatosis hepática**.

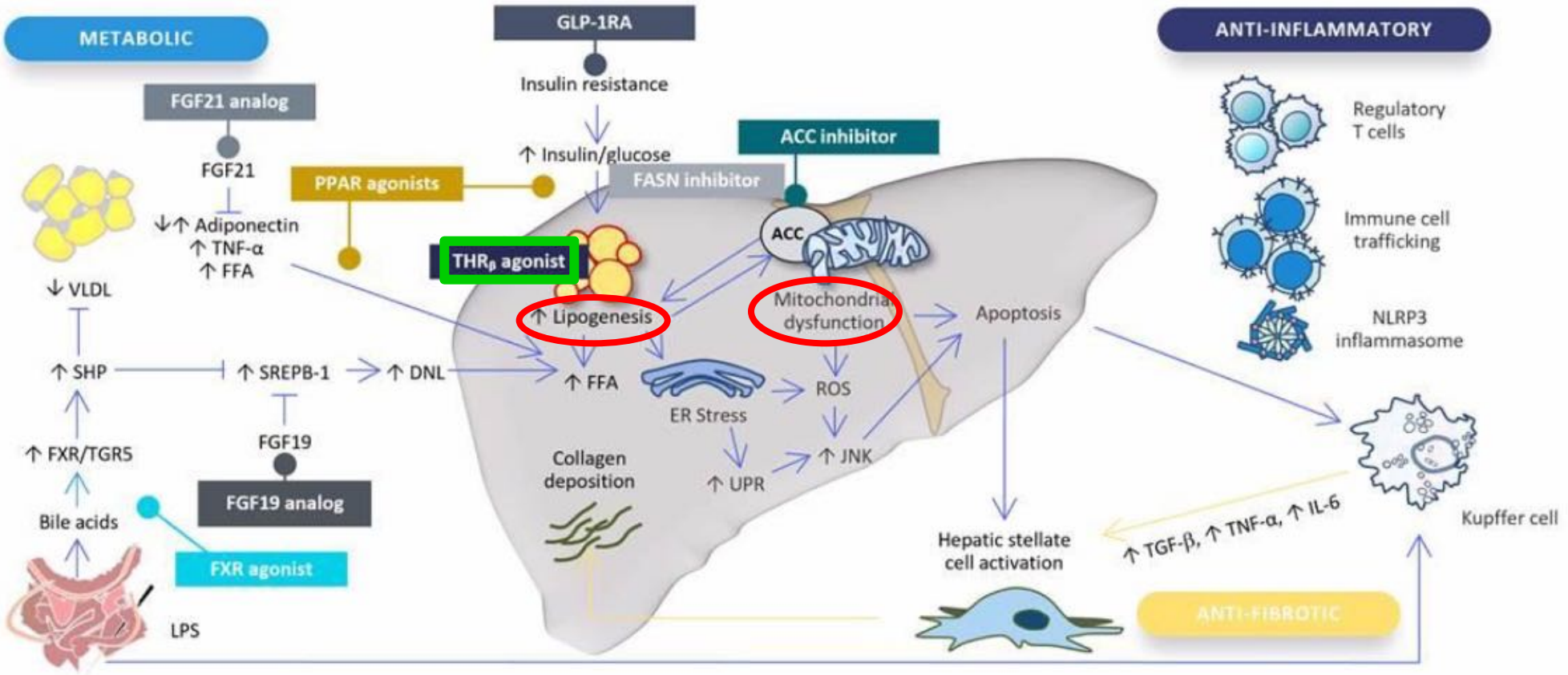
- ✓ **TRH**
  - ✓ **TRH-α**
  - ✓ **TRH-β**





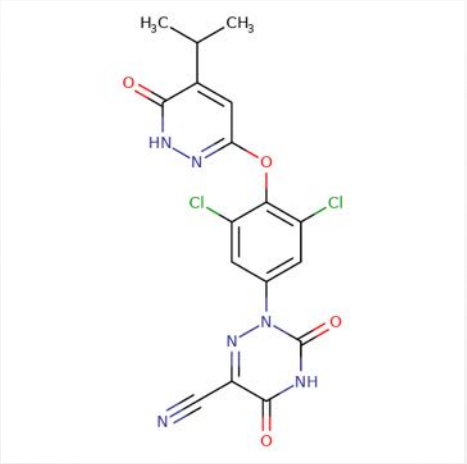
INTRODUCCIÓN

Pathways that contribute to NASH



Adapted from Konerman et al. J Hepatol. 2017; 68:362–375

INTRODUCCIÓN



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Contents lists available at ScienceDirect

Atherosclerosis

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

Lipid lowering in healthy volunteers treated with multiple doses of MGL-3196, a liver-targeted thyroid hormone receptor-β agonist

Rebecca Taub[a,*], Edward Chiang[a], Malorie Chabot-Blanchet[b], Martha J. Kelly[a], Richard A. Reeves[c], Marie-Claude Guertin[b], Jean-Claude Tardif[d]

[a] Madrigal Pharmaceuticals, Fort Washington, PA, USA
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[c] RAR Consulting LLC, Pennington, NJ, USA
[d] Montreal Heart Institute, Université de Montréal, Montreal, Canada

nature medicine

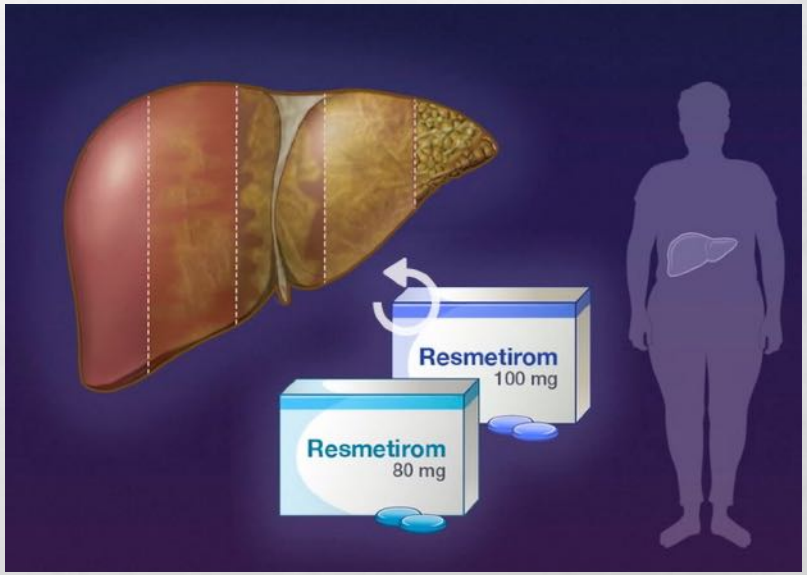
Article

https://doi.org/10.1038/s41591-023-02603-1

Resmetirom for nonalcoholic fatty liver disease: a randomized, double-blind, placebo-controlled phase 3 trial

Nature Medicine | Volume 29 | November 2023 | 2919–2928

- ✓ MAESTRO-NASH
  - Ensayo en fase 3 de eficacia y seguridad de RESMETIROM en adultos con NASH confirmada por biopsia con resultados a 52 semanas.



MÉTODOS

DISEÑO

- ✓ Ensayo clínico en fase 3, aleatorizado, doble ciego y controlado con placebo.
- ✓ 15 países, 245 centros.
- ✓ Duración del ensayo: 54 meses.
  - ❖ Evaluación inicial a los **52 semanas**.

Madrigal Pharmaceuticals

MÉTODOS

CRITERIOS DE SELECCIÓN

CRITERIOS DE INCLUSIÓN

✓3 de 5 criterios síndrome metabolico (IFD)

✓Fibroscan realizado en los 3 meses previos.
- CAP ≥ 280dB
- Rigidez ≥ 8.5 kPa

o

✓Biopsia hepática realizada en los 6 meses previos.

✓Bioposia hepática: AP compatible NASH
- Score NAFLD ≥ 4 puntos.
- Grados fibrosis
  - ≥ 50% F3.
  - ≤ 15% F1
    - F1B: principalmente
    - F1A o F1C ≤ 3%.

✓Peso estable últimos 3 meses (variaciones <5%)

✓Dosis aGLP1 sin cambios últimos 6 meses.

Table 5 International Diabetes Federation metabolic syndrome world-wide definition

Central obesity	Waist circumference*†—ethnicity specific (see Table 7) plus any two of the following:
Raised triglycerides	≥ 1.7 mmol/l (150 mg/dl) or specific treatment for this lipid abnormality
Reduced HDL-cholesterol	< 1.03 mmol/l (40 mg/dl) in males < 1.29 mmol/l (50 mg/dl) in females or specific treatment for this lipid abnormality
Raised blood pressure	Systolic: ≥ 130 mmHg or Diastolic: ≥ 85 mmHg or treatment of previously diagnosed hypertension
Raised fasting plasma glucose‡	Fasting plasma glucose ≥ 5.6 mmol/l (100 mg/dl) or previously diagnosed Type 2 diabetes If > 5.6 mmol/l or 100 mg/dl, oral glucose tolerance test is strongly recommended but is not necessary to define presence of the syndrome

MÉTODOS

CRITERIOS DE SELECCIÓN

CRITERIOS DE INCLUSIÓN

✓3 de 5 criterios **síndrome metabolico** (IFD)

✓**Fibroscan** realizado en los **3 meses previos.**

- CAP ≥ 280dB
- Rigidez ≥ 8.5 kPa

o

✓**Biopsia hepática** realizada en los **6 meses previos.**

✓Bioposia hepática: AP compatible **NASH**

- **Score NAFLD** ≥ 4 puntos.
- **Grados fibrosis**
  - ≥ 50% **F3.**
  - ≤ 15% F1
    - F1B: principalmente
    - F1A o F1C ≤ 3%.

✓**Peso estable** últimos 3 meses (variaciones <5%)

✓Dosis **aGLP1** sin cambios últimos 6 meses.

Tabla 1. Clasificación histológica de actividad de hígado graso no alcohólico (adaptado de Kleiner et al. 2005)[5]

NAFLD *Activity Score* (NAS) (0-8)	Suma de los puntajes de esteatosis, inflamación lobular y balonización hepatocelular
Esteatosis (0-3)	0 = < 5% hepatocitos comprometidos 1 = 5-33% hepatocitos comprometidos 2 = 33-66% hepatocitos comprometidos 3 = > 66% hepatocitos comprometidos
Inflamación lobular (0-3)	0 = ninguna 1 = < 2 focos por campo óptico x200 2 = 2-4 focos por campo óptico x200 3 = > 4 focos por campo óptico x200
Balonización de hepatocitos (0-2)	0 = ninguno 1 = pocas células balonizadas 2 = muchas células/balonización prominente
Correlación entre el total de puntaje NAS y el diagnóstico global histológico de esteatohepatitis	
NAFLD *activity score*	Diagnóstico histológico de esteatohepatitis
≥ 5	EHNA probable o definitivo
3-4	Indeterminado
≤ 2	No EHNA
Puntuación de fibrosis	1 Perisinusoidal o periportal 1A Leve fibrosis perisinusoidal en zona 3 1B Moderada fibrosis perisinusiodal en la zona 3 1C Sólo fibrosis portal/periportal 2 Fibrosis perisinusoidal en la zona 3, con fibrosis portal/periportal 3 Puentes de fibrosis 4 Cirrosis

MÉTODOS

CRITERIOS DE SELECCIÓN

CRITERIOS DE EXCLUSIÓN

- Consumo de alcohol:
  - Mujeres > 20 gr/día.
  - Hombres > 30 gr/día.
- HbA1C > 9%.
- Otras causas de hepatopatía crónica sin cirrosis diferentes NASH .

MÉTODOS

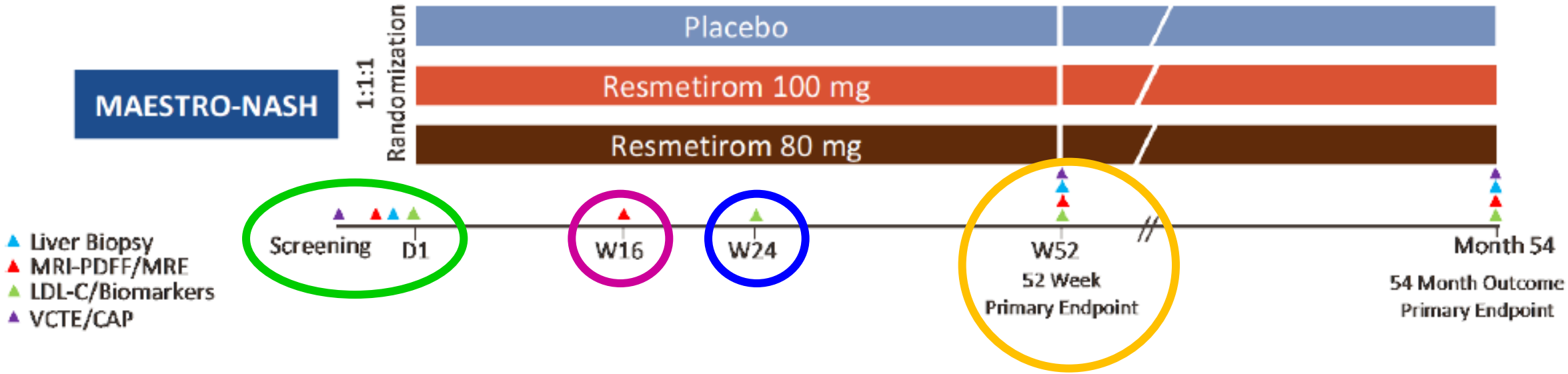
ALEATORIZACIÓN

- ✓ 1:1:1.
  - ❖ DM 2 (presencia o ausencia).
  - ❖ Estadío de fibrosis: F1, F2, F3.

Supplementary Figures and Tables

Figure S1. Study Design

CAP, controlled attenuation parameter; LDL-C, low-density lipoprotein cholesterol; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; VCTE, vibration-controlled transient elastography.



MÉTODOS

OBJETIVOS

OBJETIVO PRIMARIO

Resolución NASH:

- Balonización hepatocitos: 0.
- Inflamación lobulillar: 0-1.
- Reducción score NAFLD ≥ 2 puntos.

Reducción fibrosis en al menos 1 estadio sin empeoramiento score **NAFLD.**

OBJETIVO SECUNDARIO

Reducción niveles **LDLc** en la semana 24.

OBJETIVOS DE SEGURIDAD

Eventos adversos (Graves):

- Muerte.
- Eventos CV.
- Toxicidad hepática.

Criterios clínicos.

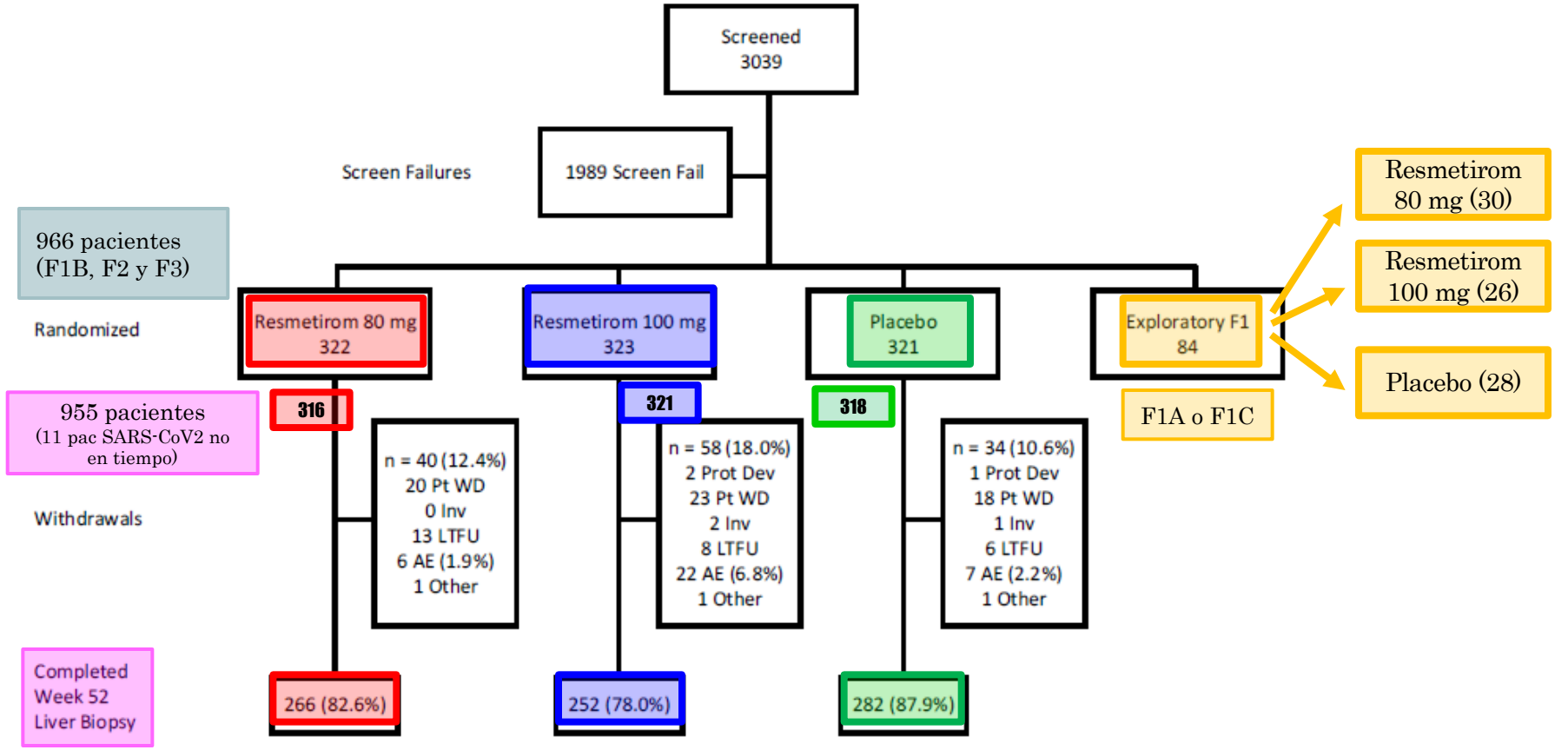
Criterios BQ.

RESULTADOS

- ✓ Marzo 2019 a julio 2021.
- ✓ 1050 pacientes.

Figure S3. Patient Disposition

AE, adverse event; LTFU, lost to follow up. The primary reasons for screen failure included biopsy, withdraw of consent, MRI-PDFF <8%, HbA1c >9. The exploratory F1 group included baseline F1a/F1c patients (n = 84) that were considered only for exploratory efficacy and safety analyses. These patients received treatment but as prespecified in the statistical analysis plan, were not included in the primary analysis population.



RESULTADOS

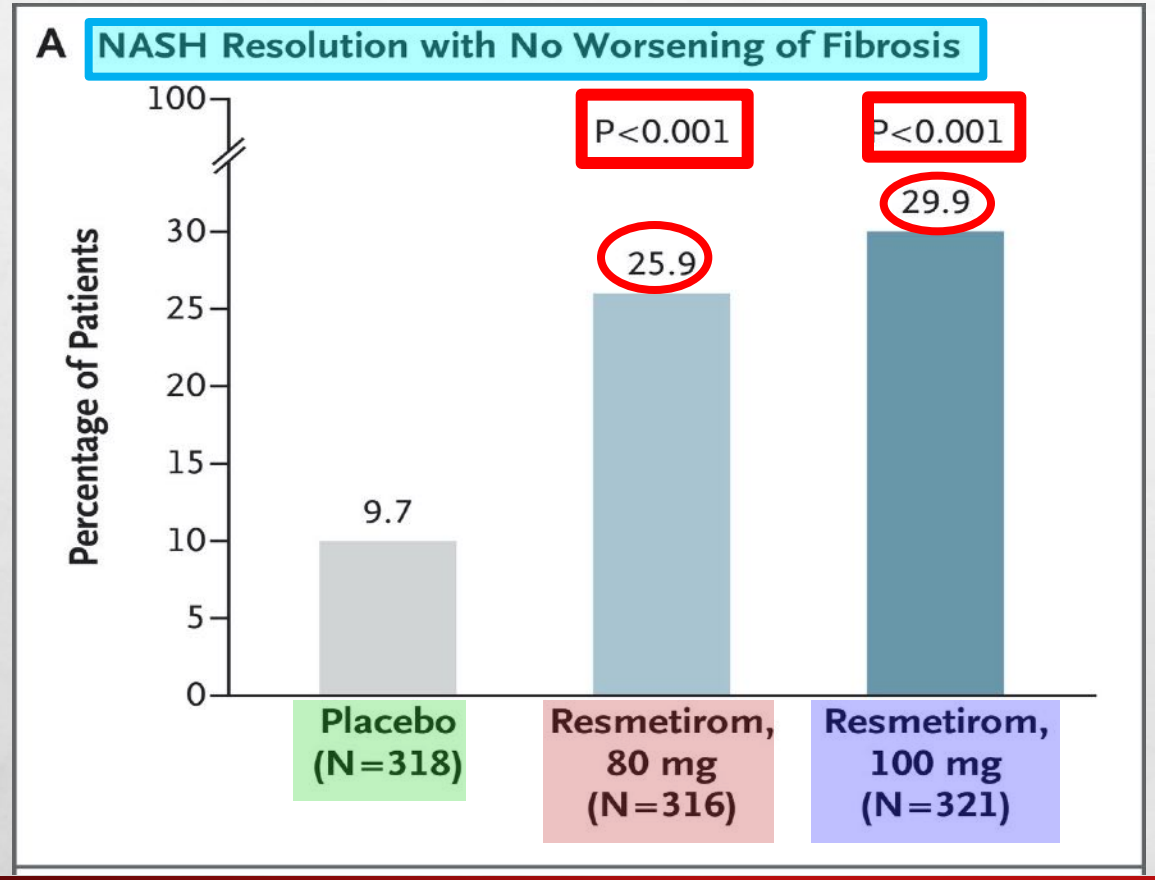
- ✓ **Semana 52 de evaluación** objetivos:
  - 92% cumplimiento.
  - 80% adherencia.

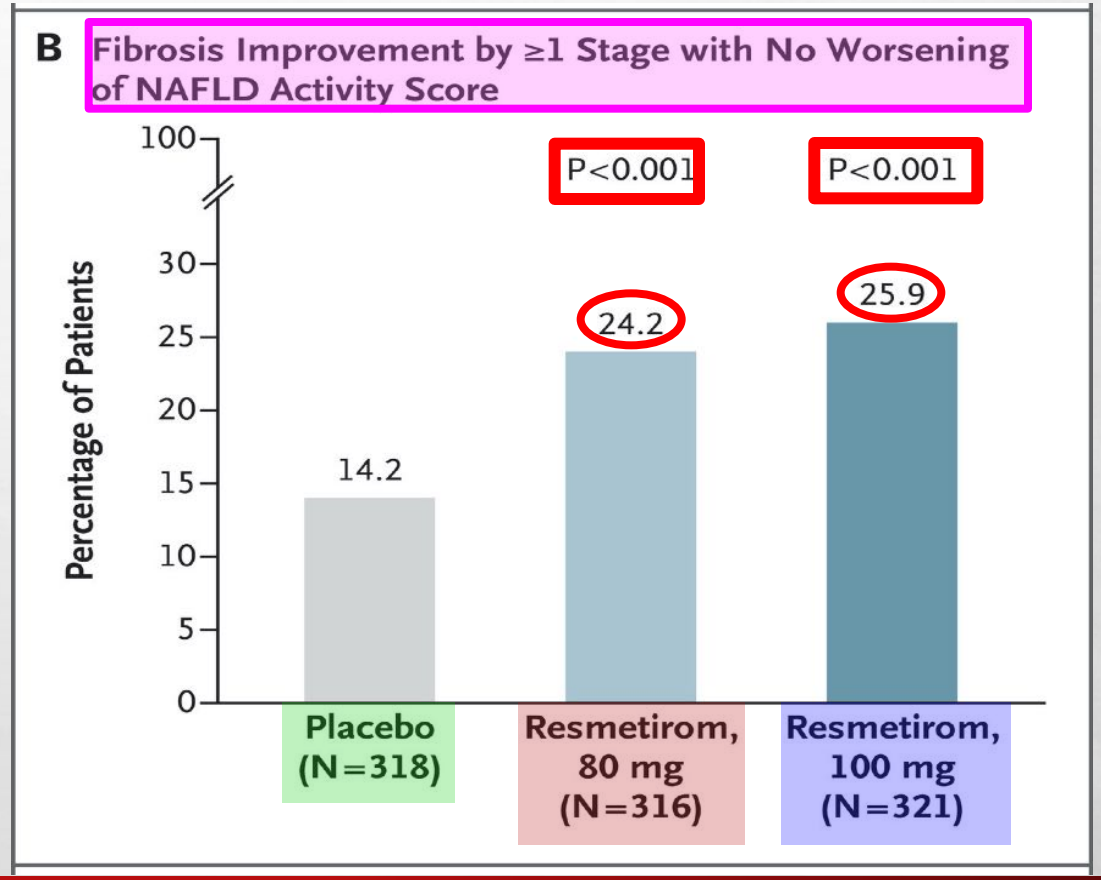
Table 1. Demographic and Clinical Characteristics of the Patients at Baseline (Primary Population).*

Characteristic	Resmetirom, 80 mg (N=322)	Resmetirom, 100 mg (N=323)	Placebo (N=321)
Age — yr	55.9±11.5	57.0±10.8	57.1±10.5
Male sex — no. (%)†	140 (43.5)	141 (43.7)	143 (44.5)
Race or ethnic group — no. (%)†			
White	291 (90.4)	291 (90.1)	281 (87.5)
Black	5 (1.6)	5 (1.5)	9 (2.8)
Asian	10 (3.1)	9 (2.8)	9 (2.8)
Other‡	12 (3.7)	11 (3.4)	18 (5.6)
Missing data	4 (1.2)	7 (2.2)	4 (1.2)
Hispanic or Latino ethnic group — no. (%)†	71 (22.0)	81 (25.1)	52 (16.2)
Body weight — kg	100.1±22.3	101.9±22.9	100.2±23.1
Body-mass index	35.5±6.4	36.2±7.4	35.3±6.5
Type 2 diabetes — no. (%)	224 (69.6)	213 (65.9)	210 (65.4)
Hypertension — no. (%)	243 (75.5)	254 (78.6)	257 (80.1)
Dyslipidemia — no. (%)	229 (71.1)	236 (73.1)	224 (69.8)
Hypothyroidism — no. (%)§	39 (12.1)	46 (14.2)	45 (14.0)
History of ASCVD — no. (%)	20 (6.2)	23 (7.1)	14 (4.4)
Estimated 10-yr risk of ASCVD — %¶	14.7±12.0	14.5±12.1	15.4±11.6
FibroScan liver-stiffness measurement — kPa‖			
Mean	13.3±6.8	13.6±7.1	12.9±5.5
Median (IQR)	11.5 (9.5–14.9)	11.9 (9.5–15.9)	11.7 (9.4–14.8)
FibroScan controlled attenuation parameter — dB/m**	346.1±37.2	349.4±38.7	347.2±37.0
MRI-PDFF — %††	18.2±6.8	17.2±6.6	17.8±6.8
Liver stiffness on MRE — kPa	3.5±0.9	3.7±1.1	3.5±1.0
Fibrosis-4 index score‡‡	1.4±0.7	1.5±0.7	1.4±0.7
LDL cholesterol level — mg/dl	106.6±37.4	103.0±36.8	106.8±41.1
Alanine aminotransferase level — U/liter	52.8±27.3	56.3±34.0	54.7±34.8
Aspartate aminotransferase level — U/liter	38.2±19.3	42.5±25.2	40.7±24.6
γ-Glutamyltransferase level — U/liter	84.3±111.3	84.6±99.0	75.7±85.0
Liver-biopsy findings — no. (%)			
NAFLD activity score ≥5§§	266 (82.6)	288 (89.2)	253 (78.8)
Fibrosis stage¶¶			
F1B	16 (5.0)	15 (4.6)	18 (5.6)
F2	107 (33.2)	100 (31.0)	112 (34.9)
F3	199 (61.8)	208 (64.4)	191 (59.5)

RESULTADOS

END POINT PRIMARIO





RESULTADOS

END POINT PRIMARIO

Table 2. Biopsy End Points.*

End Point	Resmetirom, 80 mg (N=316)	Resmetirom, 100 mg (N=321)	Placebo (N=318)	Difference between Resmetirom, 80 mg, and Placebo (95% CI)†	P Value	Difference between Resmetirom, 100 mg, and Placebo (95% CI)†	P Value
	percent with response			*percentage points*		*percentage points*	
Primary end points							
NASH resolution with no worsening of fibrosis	25.9	29.9	9.7	16.4 (11.0–21.8)	<0.001	20.7 (15.3–26.2)	<0.001
Fibrosis improvement by ≥1 stage with no worsening of NAFLD activity score	24.2	25.9	14.2	10.2 (4.8–15.7)	<0.001	11.8 (6.4–17.2)	<0.001
Other end points							
≥2-Point improvement in NAFLD activity score, including ≥1-point improvement in hepatocellular ballooning or lobular inflammation, with no worsening of fibrosis	41.3	44.9	21.2	20.2 (13.8–26.5)		23.8 (17.4–30.2)	
≥2-Point improvement in NAFLD activity score, including ≥1-point improvement in hepatocellular ballooning or lobular inflammation, with improvement in fibrosis	18.8	21.2	8.5	10.5 (5.8–15.3)		13.0 (8.3–17.7)	
Improvement in each component of NAFLD activity score	23.3	27.9	7.2	16.1 (11.1–21.0)		20.9 (15.8–25.9)	
Improvement in fibrosis by ≥2 stages	8.3	10.1	2.8	5.6 (2.5–8.7)		7.4 (3.9–10.8)	
Both NASH resolution and fibrosis improvement by ≥1 stage	14.2	16.0	4.9	9.5 (5.4–13.6)		11.6 (7.5–15.8)	

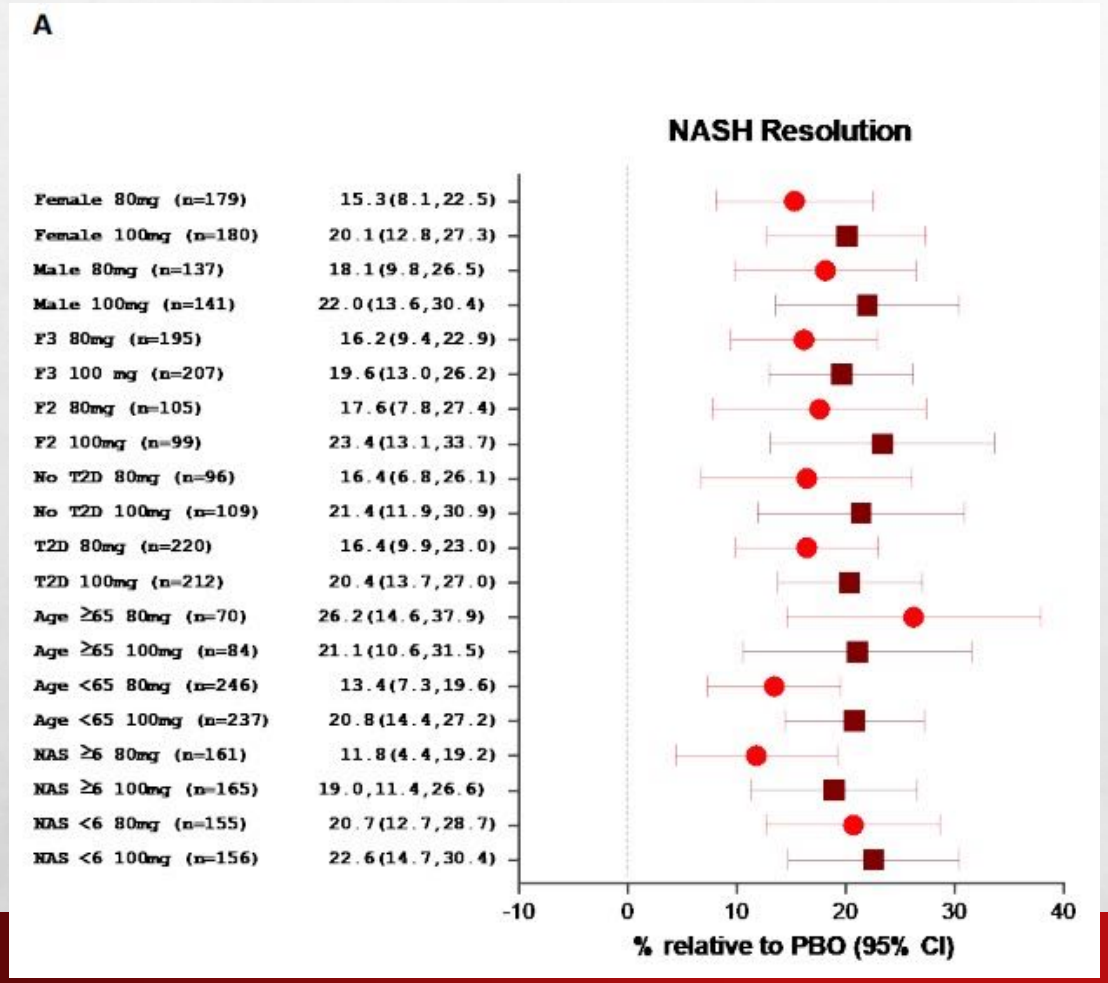
* Of the 966 patients in the primary population, 11 patients (6 in the 80-mg resmetirom group, 3 in the 100-mg resmetirom group, and 2 in the placebo group) had a delay in their week 52 biopsy for reasons related to coronavirus disease 2019 (Covid-19) and were not evaluated for the end points shown here. NASH resolution was defined as a hepatocellular ballooning score of 0, a lobular inflammation score of 0 or 1, and a reduction in the NAFLD activity score by at least 2 points.

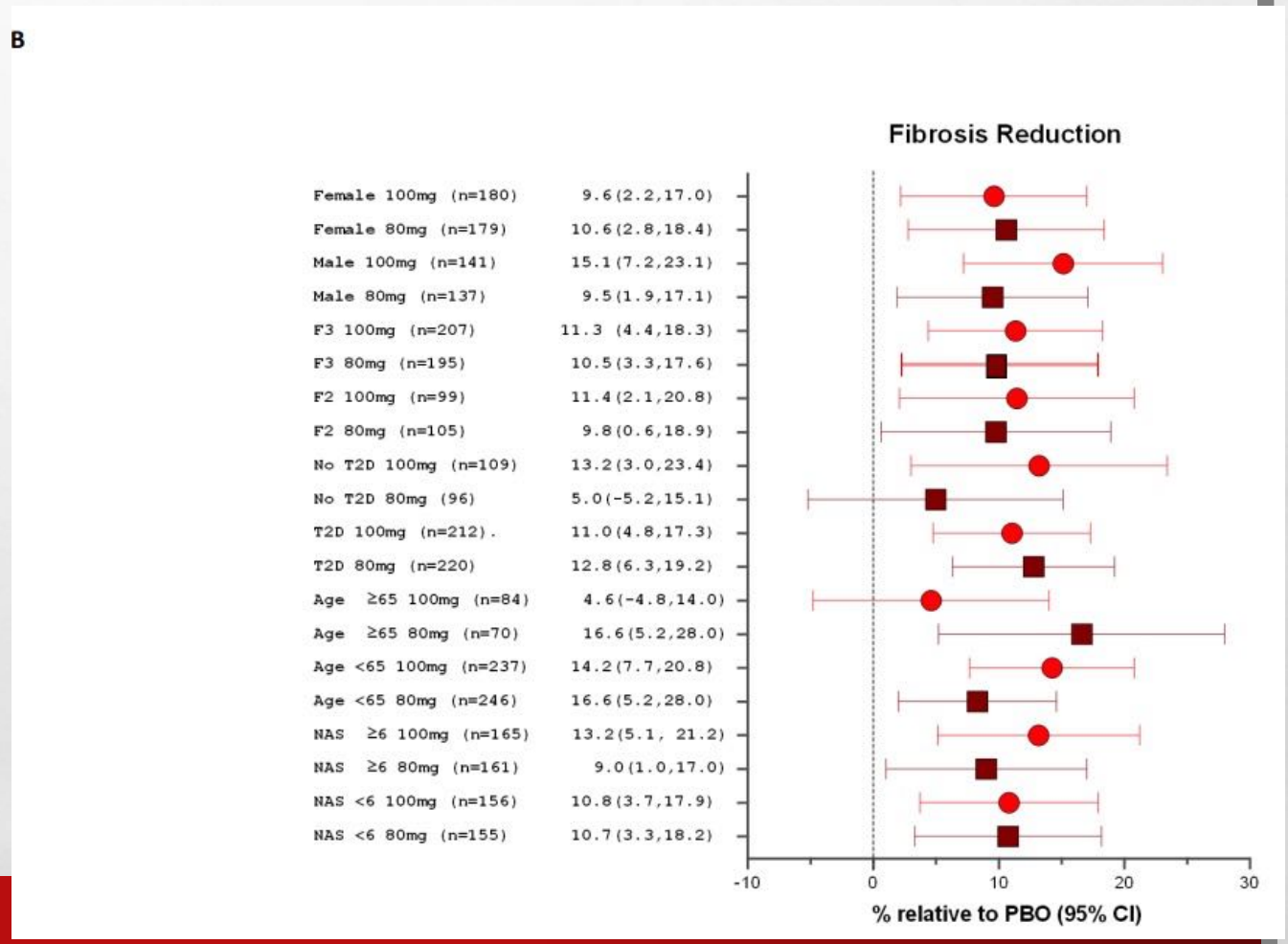
† The widths of the confidence intervals have not been adjusted for multiplicity and may not be used for hypothesis testing.

RESULTADOS

ANÁLISIS POR SUBGRUPOS

Figure S4. Subgroup analyses of the dual primary endpoints at Week 52





RESULTADOS

ANÁLISIS POR SUBGRUPOS

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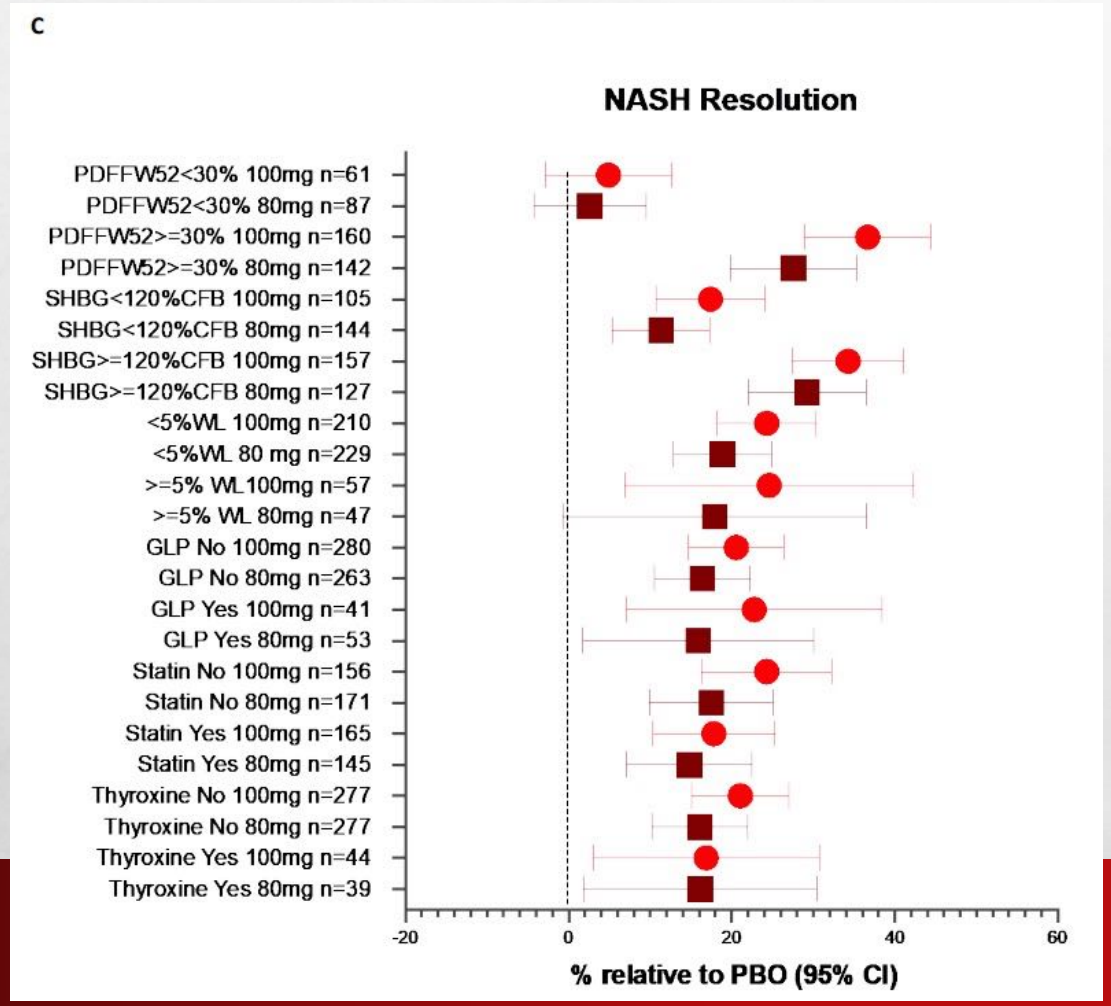
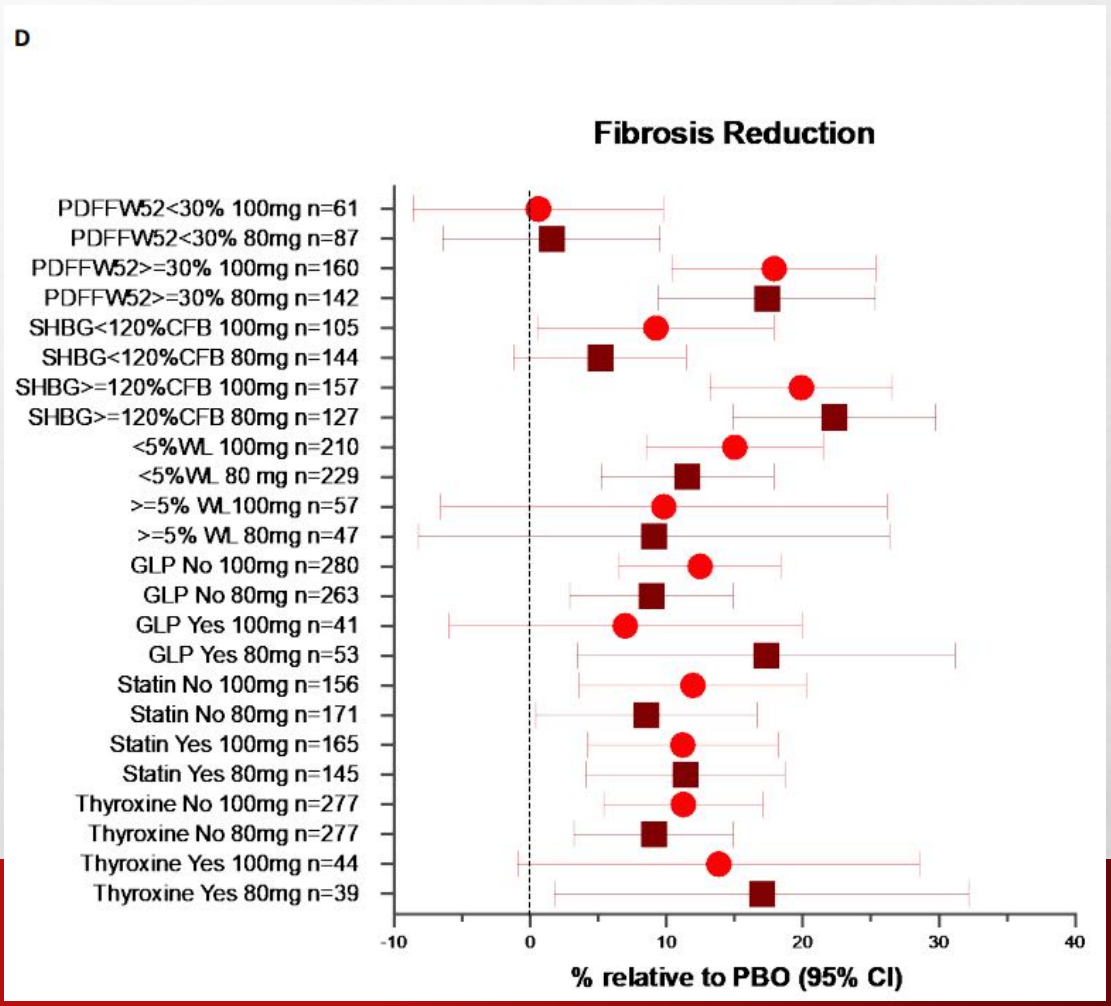
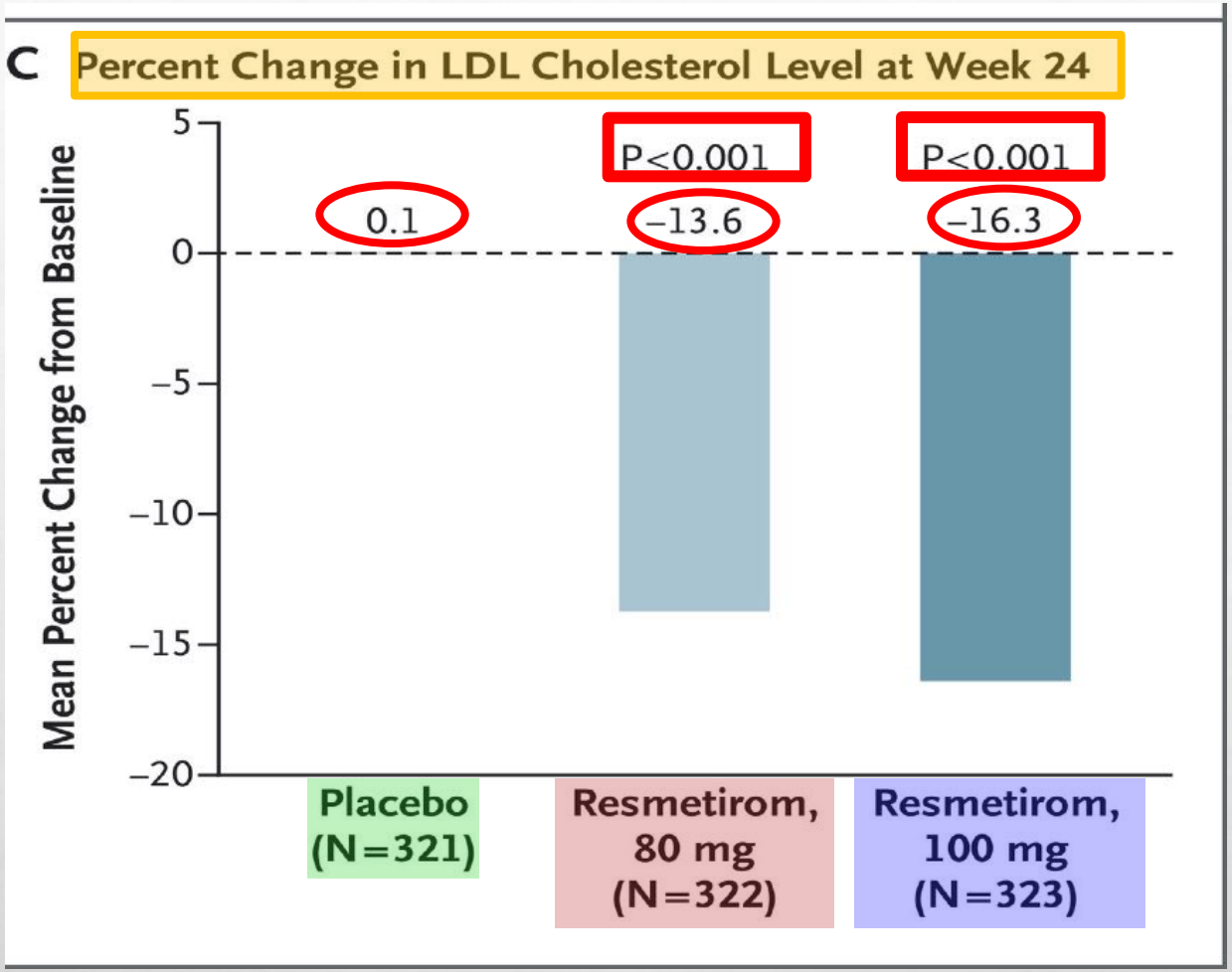




RESULTADOS

END POINT SECUNDARIO



RESULTADOS

END POINT SECUNDARIO

Table 3. Key Secondary and Other Secondary End Points (Primary Population).*

Measurement	Resmetirom, 80 mg (N=322)	Resmetirom, 100 mg (N=323)	Placebo (N=321)	Difference between Resmetirom, 80 mg, and Placebo (95% CI)†	Difference between Resmetirom, 100 mg, and Placebo (95% CI)†
	least-squares mean percent change from baseline			*percentage points*	
LDL cholesterol level at wk 24‡§	−13.6±1.7	−16.3±1.7	0.1±1.7	−13.7 (−17.5 to −10.0)¶	−16.4 (−20.1 to −12.6)¶
Apolipoprotein B level at wk 24§	−16.8±1.3	−19.8±1.3	0.39±1.3	−17.2 (−20.0 to −14.4)	−20.2 (−22.9 to −17.4)
Triglyceride level at wk 24§‖	−22.7±4.0	−21.7±4.3	−2.6±4.1	−20.1 (−28.3 to −11.8)	−19.1 (−27.8 to −10.3)
Lipoprotein(a) level at wk 24§**	−30.4±3.8	−35.9±4.0	−0.84±3.5	−29.5 (−37.6 to −21.5)	−35.1 (−43.5 to −26.6)
MRI-PDFF at wk 52	−35.4±2.8	−46.6±2.8	−8.7±2.7	−26.7 (−32.9 to −20.6)	−37.9 (−44.2 to −31.7)
Alanine aminotransferase level at wk 48††	−26.6±3.7	−33.2±3.9	−6.9±3.8	−19.7 (−27.7 to −11.6)	−26.3 (−34.5 to −18.1)
Aspartate aminotransferase level at wk 48††	−22.1±3.9	−28.3±3.9	−2.9±3.8	−19.3 (−27.2 to −11.3)	−25.4 (−33.5 to −17.4)
γ-Glutamyltransferase level at wk 48††	−25.0±5.5	−31.9±6.3	3.3±5.2	−28.3 (−37.3 to −19.3)	−35.2 (−45.5 to −25.0)

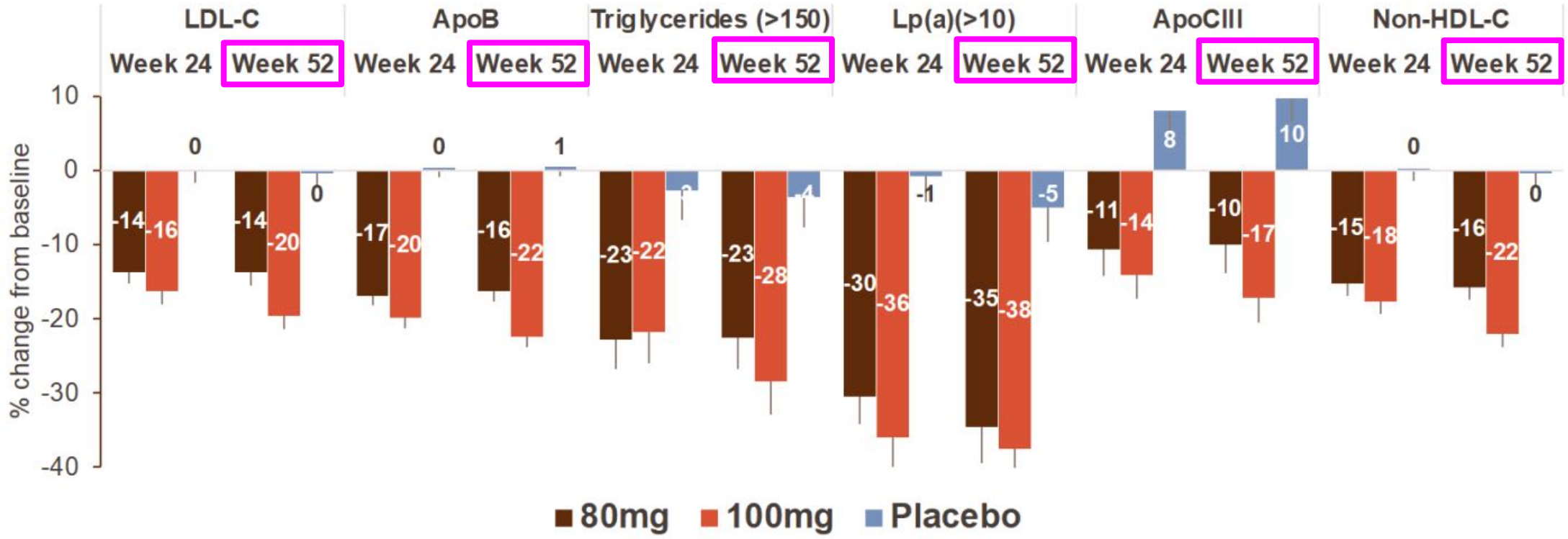
* Multiple imputation analyses were used for lipids and liver enzymes. Details on the change from baseline in levels of lipids, lipoproteins, and lipid particles at weeks 24 and 52 are provided in Table S11.
† The widths of the confidence intervals have not been adjusted for multiplicity and may not be used for hypothesis testing.
‡ The key secondary end point was the percent change from baseline in the LDL cholesterol level at week 24. LDL cholesterol was directly measured.
§ Data were missing for one patient in the 80-mg resmetirom group.
¶ P<0.001.
‖ Data are for patients with a baseline triglyceride level of more than 150 mg per deciliter.
** Data are for patients with a baseline lipoprotein(a) level of more than 10 nmol per liter.
†† Data are for patients with a baseline alanine aminotransferase level of 30 U per liter or more.

RESULTADOS

END POINT SECUNDARIO

Figure S7. Percent Change from Baseline in Lipids and Lipoproteins at Weeks 24 and 52

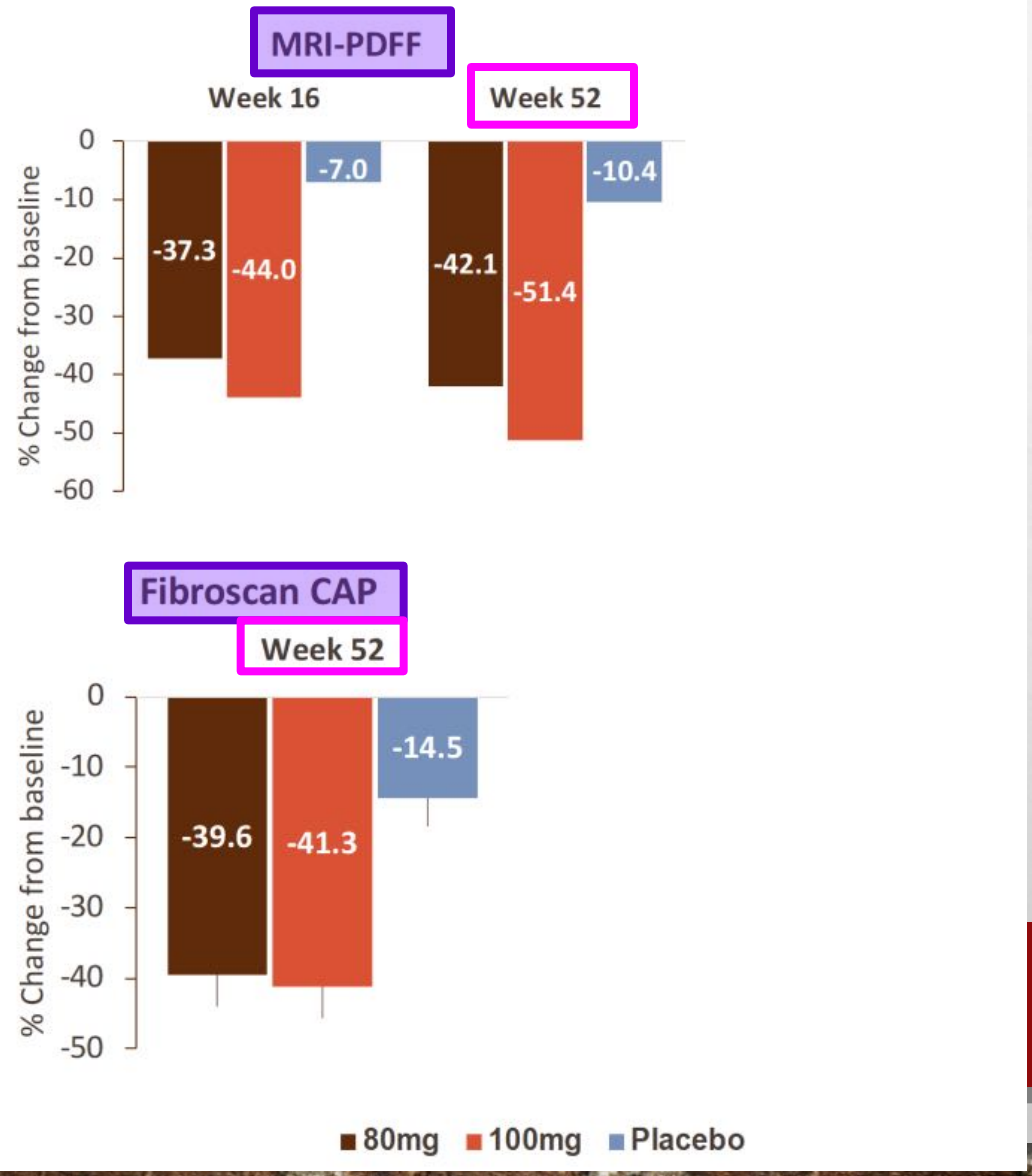
ApoB, apolipoprotein B; ApoCIII, apolipoprotein CIII; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein a; non-HDL-C, non–high-density lipoprotein cholesterol. 80mg, 100 mg, resmetirom.



RESULTADOS

Figure S8. Percent Change from Baseline in Hepatic Fat as Measured by Magnetic Resonance Imaging-Proton Density Fat Fraction at Weeks 16 and 52, and Steatosis as Measured by FibroScan Controlled Attenuation Parameter at Week 52

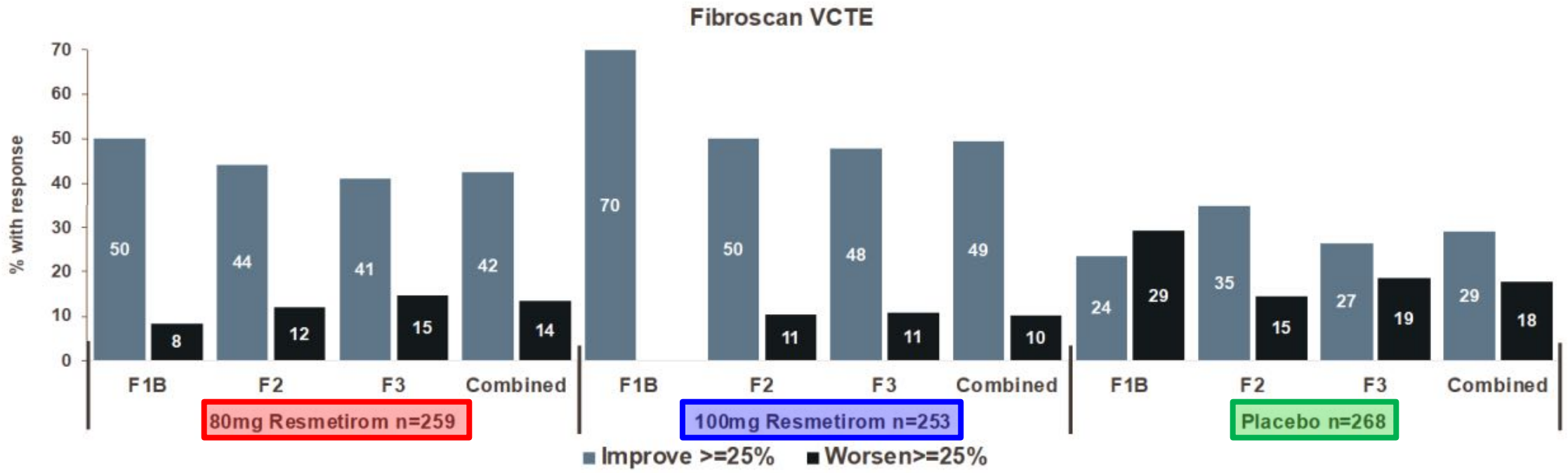
80 mg, 100 mg: resmetirom, based on observed data, patients with a baseline and Week 52 assessment.



RESULTADOS

Figure S9. Percentage of Patients Achieving a ≥25% Reduction from Baseline in Liver Stiffness as Measured by FibroScan Vibration-controlled Transient Elastography at Week 52

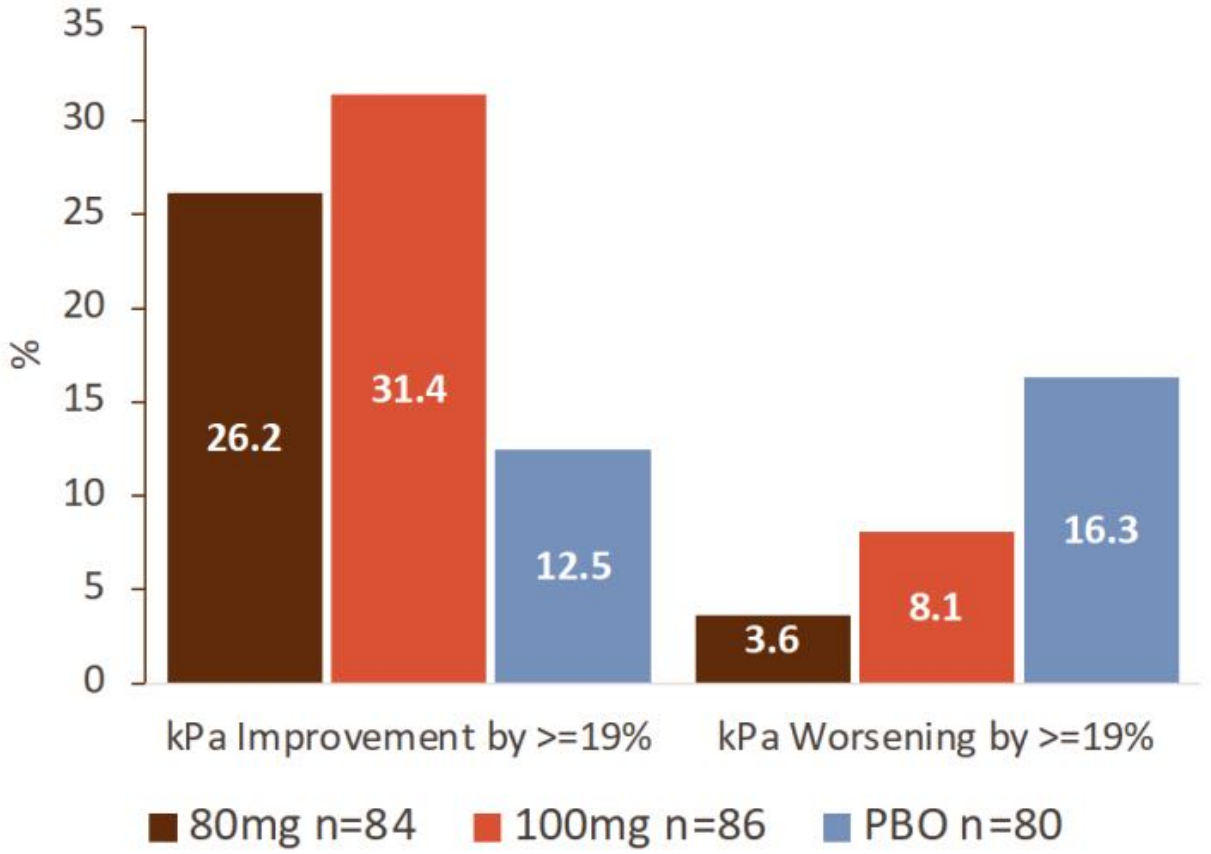
Based on observed data, patients with a baseline and Week 52 assessment.



RESULTADOS

Figure S10. Improvement or Worsening from Baseline in Liver Stiffness As Measured by Magnetic Resonance Elastography at Week 52

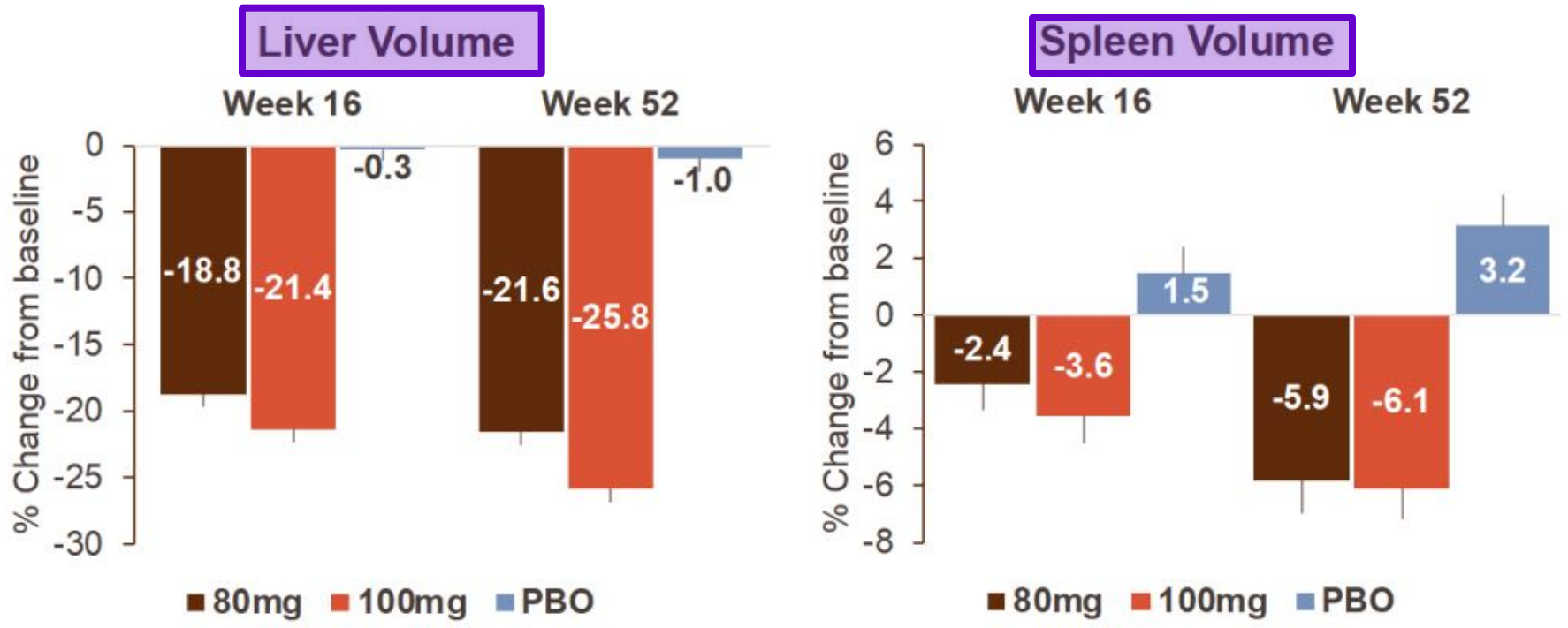
80 mg, 100 mg resmetirom, based on observed data, patients with a baseline and Week 52 assessment.



RESULTADOS

Figure S11. Percent Change from Baseline in Liver and Spleen Volume at Weeks 16 and 52

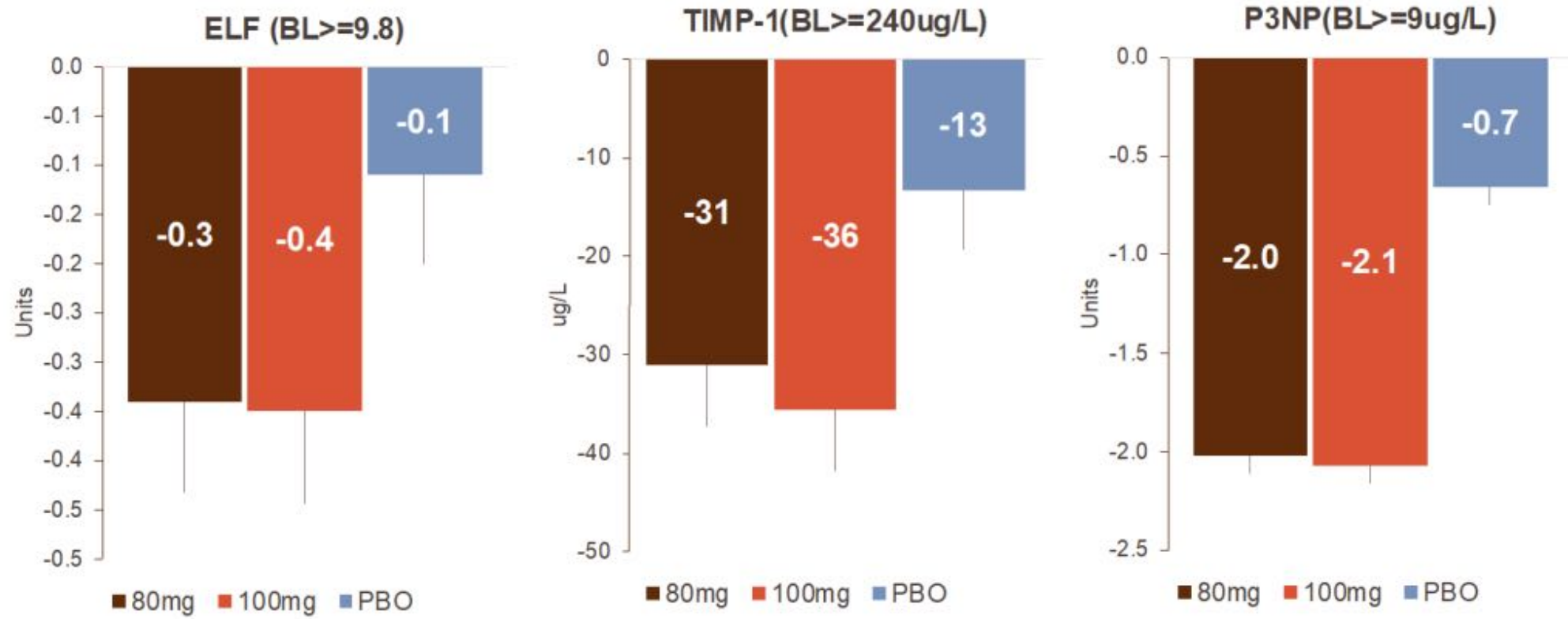
80 mg, 100 mg: resmetirom, based on observed data, patients with a baseline and Week 52 assessment.



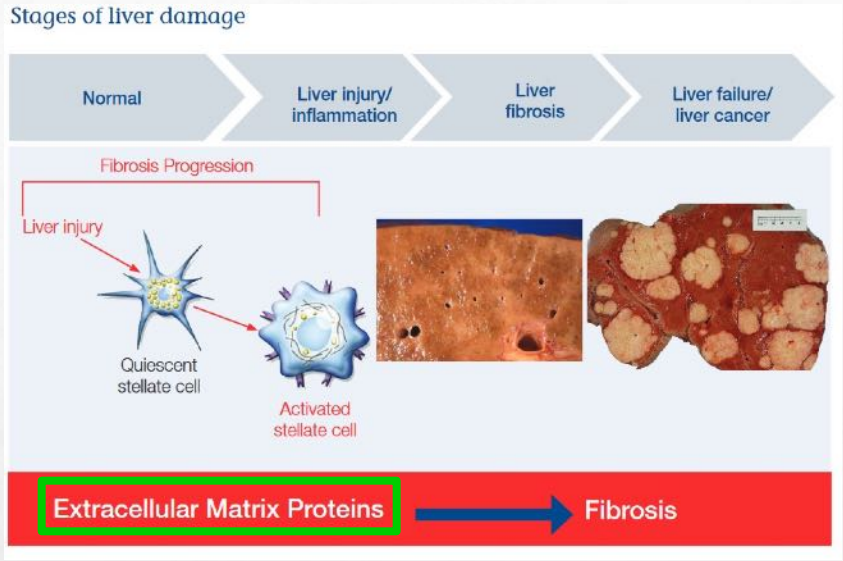
RESULTADOS

Figure S12. Change from Baseline in the Enhanced Liver Fibrosis Score, P3NP, and TIMP-1

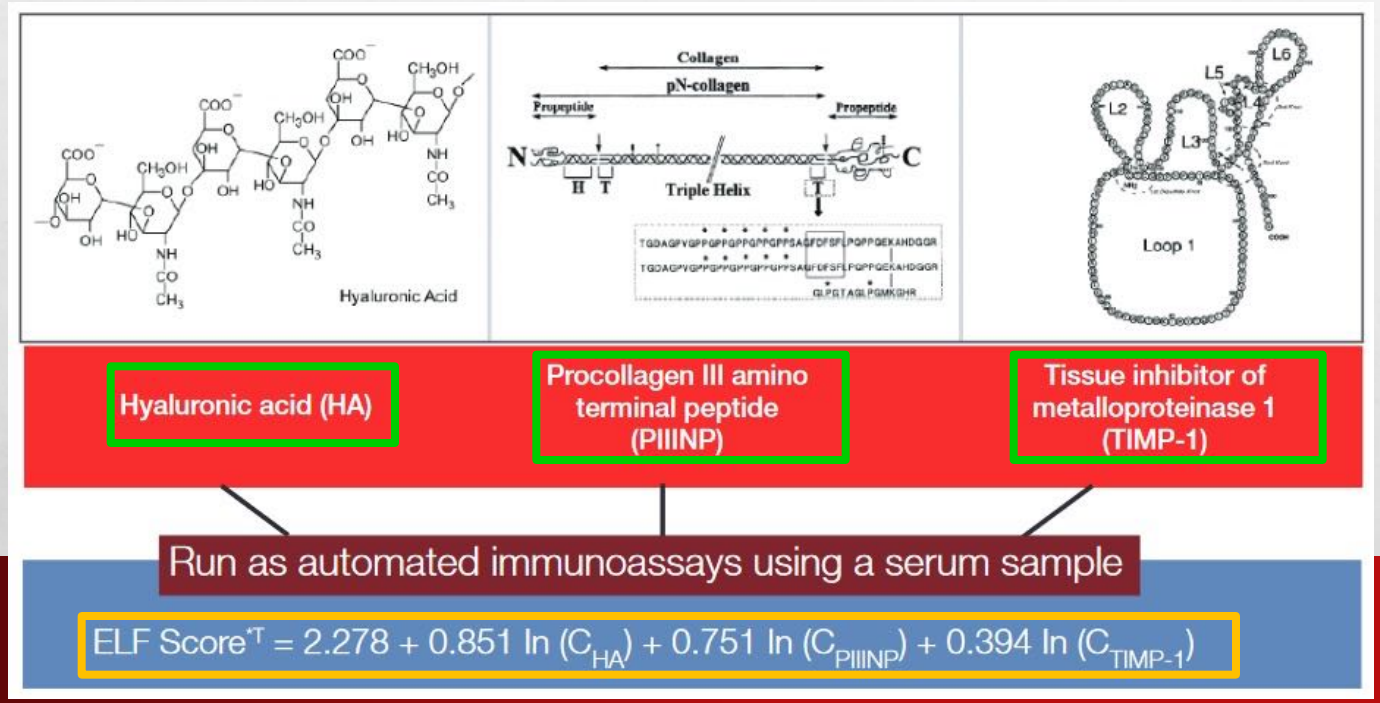
80mg, 100mg: resmetirom. Based on observed data



RESULTADOS



- ✓ Elevado **VPN.**
- ✓ <u>Equipable</u> a <u>fibroscan.</u>



- < 7.7: no to mild fibrosis
- ≥ 7.7 — < 9.8: Moderate fibrosis
- ≥ 9.8 — < 11.3: Severe fibrosis
- ≥ 11.3: Cirrhosis

RESULTADOS

END POINT SEGURIDAD

- ✓ No tuvo efectos en: FC y peso.
- ✓ Ligera hipoPA.
- ✓ Reducción niveles hh sexuales.
- ✓ No aumento fracturas ni cambios puntuación T densidad mineral ósea.
- ✓ **Reducción** niveles **T4** ⇨16-19%.
  - ❖ Independientemente si/no levotirosina.
  - ❖ No afectación TSH ni T3.

Table 4. Safety Summary (Primary Population).

Event	Resmetirom, 80 mg (N=322)	Resmetirom, 100 mg (N=323)	Placebo (N=321)
	number of patients (percent)		
≥1 Adverse event	296 (91.9)	296 (91.6)	298 (92.8)
Grade 1: mild	73 (22.7)	66 (20.4)	77 (24.0)
Grade 2: moderate	180 (55.9)	183 (56.7)	169 (52.6)
Grade 3 or higher: severe	43 (13.4)	47 (14.6)	52 (16.2)
≥1 Adverse event attributed to resmetirom or placebo*	124 (38.5)	134 (41.5)	88 (27.4)
≥1 Serious adverse event	35 (10.9)	41 (12.7)	37 (11.5)
≥1 Serious adverse event attributed to resmetirom or placebo*	2 (0.6)	0	1 (0.3)
Adverse event leading to trial discontinuation before wk 52†	6 (1.9)	22 (6.8)	7 (2.2)
Adverse event leading to trial discontinuation during entire treatment period†	9 (2.8)	25 (7.7)	11 (3.4)
Fatal adverse event	1 (0.3)	2 (0.6)	1 (0.3)
Major adverse cardiovascular event‡	1 (0.3)	1 (0.3)	1 (0.3)
Other cardiovascular event‡	0	1 (0.3)	3 (0.9)
Adverse events affecting >10% of patients in any group			
Diarrhea	87 (27.0)	108 (33.4)	50 (15.6)
Covid-19	69 (21.4)	54 (16.7)	66 (20.6)
Nausea	71 (22.0)	61 (18.9)	40 (12.5)
Arthralgia	48 (14.9)	35 (10.8)	40 (12.5)
Back pain	35 (10.9)	27 (8.4)	38 (11.8)
Urinary tract infection	33 (10.2)	27 (8.4)	27 (8.4)
Fatigue	33 (10.2)	26 (8.0)	28 (8.7)
Pruritus	26 (8.1)	37 (11.5)	22 (6.9)
Vomiting	28 (8.7)	35 (10.8)	17 (5.3)

* Shown are events that were considered by investigators to be related to resmetirom or placebo.
† Data are for events that emerged after the first dose of resmetirom or placebo and within 30 days after the last dose.
‡ Major adverse cardiovascular events were defined as nonfatal stroke, nonfatal myocardial infarction, and death from cardiovascular causes. All cardiovascular events were adjudicated.

DISCUSIÓN

FORTALEZAS

- ✓ **Resmetirom** superior a placebo en resultados histológicos y mejoría fibrosis.
  - Cumplen estándares FDA.
  - Resultados consistentes en subgrupos.
- ✓ Mejoria en parámetros pruebas no invasivas (imagen como séricos) lo respalda.
- ✓ Mejoria todo el perfil lipídico
  - **Reducción RCV** ?? ⇨ ↓↓ Apo B y LDLc
- ✓ Interrupción mayor ⇨ Resmetirom 100 mg.
  - Ef. adversos graves **similares** en todos los grupos.
  - Ef. adversos más comunes: **GI** (autolimitado).
- ✓ Paradigma ⇨ p. no invasivas **dco** NASH y monitorizar **respuesta tto.**
  - ↓ 30% grasa hepática (MRI-PDFF) y/o ↑120% globulina fijadora hh sexuales ⇨ se asocia a respuesta anatomo-patológica.

LIMITACIONES

- ❑ Falta de correlación entre datos clínicos y datos anatomo-patológicos.
- ❑ **No** evaluada **seguridad a largo plazo.**
  - Previsto ensayo a 54 meses.

CONCLUSIONES

✓**RESMETIROM** puede proprocionar <u>beneficios</u> a pacientes con **<u>ESTEATOHEPATITIS NO ALCOHÓLICA</u>** (NASH) y datos de **<u>FIBROSIS HEPÁTICA</u>**.

✓Tanto dosis de <u>80 mg</u> como dosis de <u>100 mg</u> fueron <u>eficaces</u> para ambos <u>objetivos primarios</u> (mejorar score actividad NAFLD y reducir fibrosis en 1 estadio).

EDITORIALS

Selective Agonists of Thyroid Hormone Receptor Beta for the Treatment of NASH

Kenneth Cusi, M.D.

N ENGL J MED 390;6 NEJM.ORG FEBRUARY 8, 2024

RESMETIROM

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- ✓ Superior a placebo en ambos objetivos primarios.
- ✓ Mejoro DL aterogénica.
- ✓ Efecto neutro en peso, resistencia a insulina, cifras de glucemia, FC y PA.
- ✓ Perfil aceptable ef. adversos: náuses, vómitos y diarrea.

- ✓ **↑ niveles globulina fijadora de hh sexuales ⇨ ↑ estradiol y testosterona totales.**
  - ❖ No parece afectar a niveles testosterona libres.
  - ❖ No datos niveles libres.

- ✓ Necesario **seguimiento clínico** y **medición precisa** niveles hh libres.

RESMETIROM

EDITORIALS

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- ✓ Afectación **eje hipofisario-tiroides**
  - ↓ T4 (17-21%).
  - ↓ TSH media.
  - Niveles T3 se mantuvieron normales.

- ✓ **PROMOVER HIPOTIROIDISMO** de difícil diagnóstico.

- ✓ Necesario **seguimiento clínico** y **medición precisa** niveles hh libres.

RESMETIROM

END POINT PRIMARIO

EDITORIALS

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≥2-Point improvement in NAFLD activity score, including ≥1-point improvement in hepatocellular ballooning or lobular inflammation, with no worsening of fibrosis	41.3	44.9	21.2	20.2 (13.8–26.5)		23.8 (17.4–30.2)	
≥2-Point improvement in NAFLD activity score, including ≥1-point improvement in hepatocellular ballooning or lobular inflammation, with improvement in fibrosis	18.8	21.2	8.5	10.5 (5.8–15.3)		13.0 (8.3–17.7)	
Improvement in each component of NAFLD activity score	23.3	27.9	7.2	16.1 (11.1–21.0)		20.9 (15.8–25.9)	
Improvement in fibrosis by ≥2 stages	8.3	10.1	2.8	5.6 (2.5–8.7)		7.4 (3.9–10.8)	
Both NASH resolution and fibrosis improvement by ≥1 stage	14.2	16.0	4.9	9.5 (5.4–13.6)		11.6 (7.5–15.8)	

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† The widths of the confidence intervals have not been adjusted for multiplicity and may not be used for hypothesis testing.

- ✓ 2 de cada 10 pacientes tratados.
- ✓ 1 de cada 10 pacientes tratados.

- ✓ NECESARIO TTO COMBINADO:
  - aGLP1.
  - Pioglitazona.

RESMETIROM

EDITORIALS

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N ENGL J MED 390;6 NEJM.ORG FEBRUARY 8, 2024

- ✓ USA ⇨ 11.6 millones de personas NASH
  - F2-F3 en DM2 ⇨ mayor riesgo cirrosis ⇨ **12-15% ⇨ 4-5 millones personas.**
  - Monitorización acceso y respuesta al tratamiento.
  - Interrupción si no respuesta y futilidad.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Microplastics and Nanoplastics in Atheromas and Cardiovascular Events

R. Marfella, F. Prattichizzo, C. Sardu, G. Fulgenzi, L. Graciotti, T. Spadoni, N. D'Onofrio, L. Scisciola, R. La Grotta, C. Frigé, V. Pellegrini, M. Municinò, M. Siniscalchi, F. Spinetti, G. Vigliotti, C. Vecchione, A. Carrizzo, G. Accarino, A. Squillante, G. Spaziano, D. Mirra, R. Esposito, S. Altieri, G. Falco, A. Fenti, S. Galoppo, S. Canzano, F.C. Sasso, G. Matacchione, F. Olivieri, F. Ferraraccio, I. Panarese, P. Paolisso, E. Barbato, C. Lubritto, M.L. Balestrieri, C. Mauro, A.E. Caballero, S. Rajagopalan, A. Ceriello, B. D'Agostino, P. Iovino, and G. Paolisso

INTRODUCCIÓN

✓ Producción **plásticos** en **aumento** y esperable hasta el 2050.

✓ **Contaminación** del **medio ambiente** ⇨ amplia distribución.

Wang S et al. "Microplastic abundance, distribution and composition in the mid-west Pacific Ocean". **Environ Pollut 2020;264:114125.**

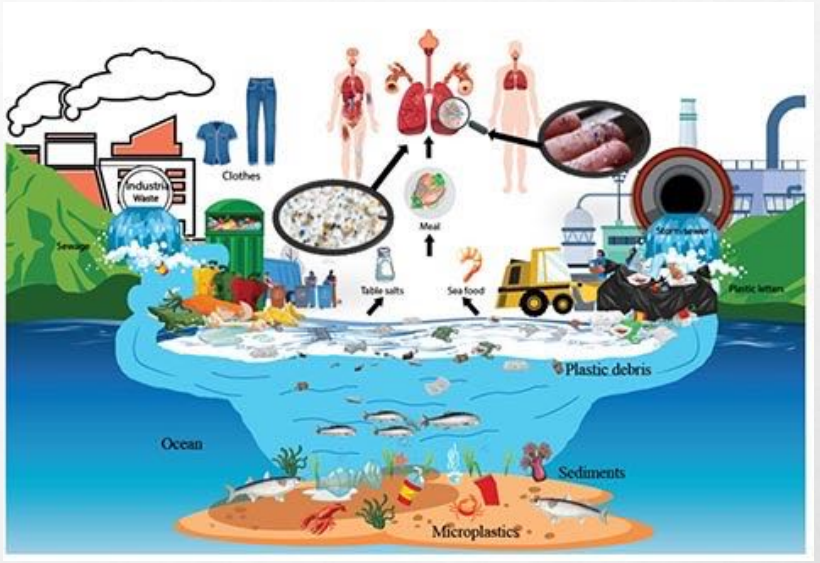
Collignosn A et al. "Neustonic microplastic and zooplankton in the north western Mediterranean Sea". **Mar Pollut Bull 2012;64:861-4.**

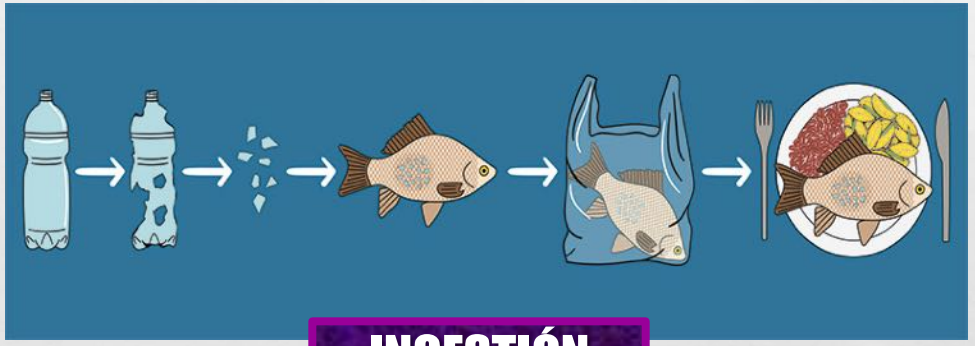
✓ Una vez liberados naturaleza ⇨ **DEGRADADOS**

✓ **MICROPLÁSTICOS:** < 5 mm.

✓ **NANOPLÁSTICOS:** < 1000 nm.

INTRODUCCIÓN



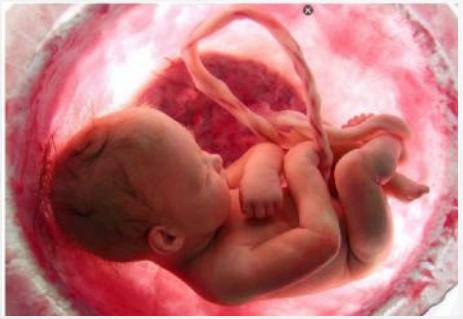


INGESTIÓN

INHALACIÓN

PIEL

INTRODUCCIÓN



Contents lists available at ScienceDirect

Environment International

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

Plasticenta: First evidence of microplastics in human placenta

Antonio Ragusa [a], Alessandro Svelato [a,*], Criselda Santacroce [b], Piera Catalano [b], Valentina Notarstefano [c], Oliana Carnevali [c], Fabrizio Papa [b], Mauro Ciro Antonio Rongioletti [b], Federico Baiocco [d], Simonetta Draghi [d], Elisabetta D'Amore [e], Denise Rinaldo [f], Maria Matta [f], Elisabetta Giorgini [c]

[a] Department of Obstetrics and Gynecology, San Giovanni Calibita Fatebenefratelli Hospital, Isola Tiberina, Via di Ponte Quattro Capi, 39, 00186 Rome, Italy
[b] Department of Pathological Anatomy, San Giovanni Calibita Fatebenefratelli Hospital, Isola Tiberina, Via di Ponte Quattro Capi, 39, 00186 Rome, Italy
[c] Department of Life and Environmental Sciences, Università Politecnica delle Marche, via Brecce Bianche, 60131 Ancona, Italy
[d] Department of Obstetrics and Gynecology, ASST Bergamo Est, Bolognini Hospital, Seriate, Via Paderno, 21, 24068 Bergamo, Italy
[e] Human Medical and Surgery Course, University of Pavia, Corso Strada Nuova 65, 27100 Pavia, Italy

Microplastics detected in cirrhotic liver tissue

Thomas Horvatits,[a,*] Matthias Tamminga,[b] Beibei Liu,[a] Marcial Sebode,[c] Antonella Carambia,[d] Lutz Fischer,[c] Klaus Püschel,[d] Samuel Huber,[a] and Elke Kerstin Fischer [b,**]

[a] I. Department of Medicine, Gastroenterology and Hepatology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[b] Center for Earth System Research and Sustainability (CEN), University of Hamburg, Hamburg, Germany
[c] Department of Transplant Surgery, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[d] Institute of Legal Medicine, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany

eBioMedicine
Part of THE LANCET Discovery Science

www.thelancet.com Vol 82 Month August, 2022

toxics Toxics 2023, 11, 40 MDPI

Article

First Evidence of Microplastics in Human Urine, a Preliminary Study of Intake in the Human Body

Concetta Pironti [1,†], Valentina Notarstefano [2,†], Maria Ricciardi [3], Oriana Motta [1,*], Elisabetta Giorgini [2] and Luigi Montano [4,5,*]

Science of the Total Environment 831 (2022) 154907

Contents lists available at ScienceDirect

Science of the Total Environment

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

Detection of microplastics in human lung tissue using μFTIR spectroscopy

Lauren C. Jenner [a], Jeanette M. Rotchell [b], Robert T. Bennett [c], Michael Cowen [c], Vasileios Tentzeris [c], Laura R. Sadofsky [a,*]

[a] Hull York Medical School, University of Hull, Hull HU6 7RX, United Kingdom
[b] Department of Biological and Marine Sciences, University of Hull, Hull HU6 7RX, United Kingdom
[c] Department of Cardiothoracic Surgery, Castle Hill Hospital, Cottingham HU16 5JQ, United Kingdom

polymers Polymers 2022, 14, 2700 MDPI

Article

Raman Microspectroscopy Detection and Characterisation of Microplastics in Human Breastmilk

Antonio Ragusa [1], Valentina Notarstefano [2,*], Alessandro Svelato [3], Alessia Belloni [2], Giorgia Gioacchini [2], Christine Blondeel [3], Emma Zucchelli [3], Caterina De Luca [3], Sara D'Avino [3], Alessandra Gulotta [4], Oliana Carnevali [2] and Elisabetta Giorgini [2]

Contents lists available at ScienceDirect

Environment International

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

Full length article

Discovery and quantification of plastic particle pollution in human blood

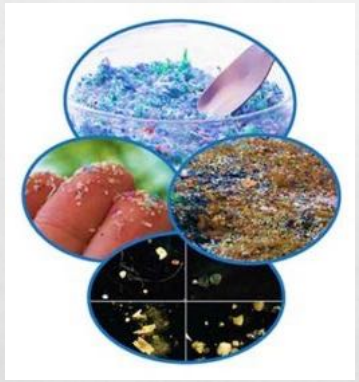
Heather A. Leslie [a], Martin J.M. van Velzen [a], Sicco H. Brandsma [a], A. Dick Vethaak [a,b], Juan J. Garcia-Vallejo [c], Marja H. Lamoree [a,*]

[a] Dept. of Environment and Health, Faculty of Science, Vrije Universiteit Amsterdam, De Boelelaan 1108, 1081 HZ Amsterdam, the Netherlands
[b] Deltares, Delft, the Netherlands
[c] Cancer Center Amsterdam and Amsterdam Infection and Immunity, Amsterdam University Medical Center (VUmc location), De Boelelaan 1108, 1081 HZ Amsterdam, the Netherlands

Environment International 163 (2022) 107199

Junta de Castilla y León Consejería de Sanidad · Sacyl · Complejo Asistencial Universitario de León

INTRODUCCIÓN



Environment International 171 (2023) 107662

Contents lists available at ScienceDirect

Environment International

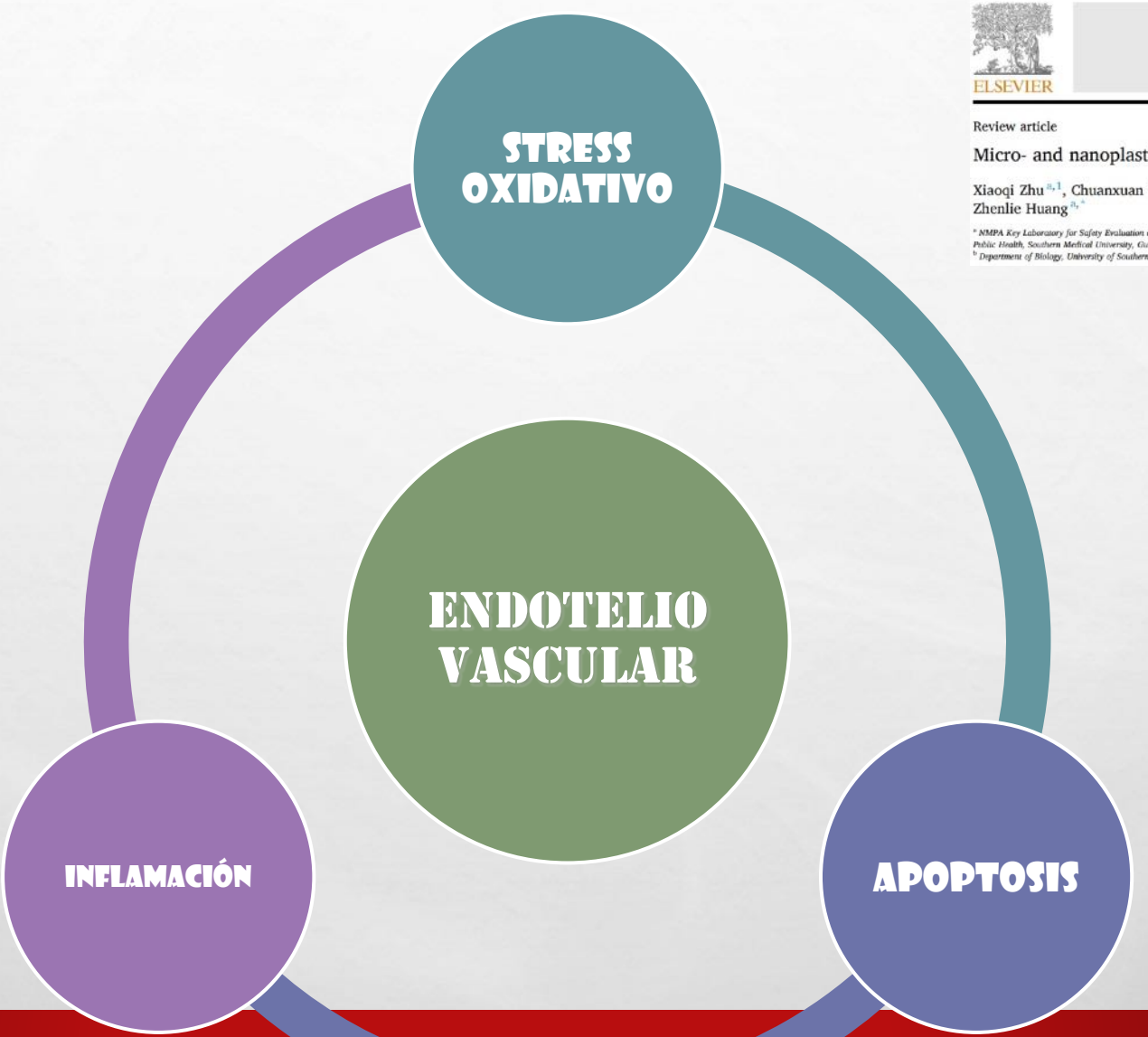
journal homepage: www.elsevier.com/locate/envint

Review article

Micro- and nanoplastics: A new cardiovascular risk factor?

Xiaoqi Zhu [a,1], Chuanxuan Wang [a,1], Xiaoyu Duan [b], Boxuan Liang [a], Elvis Genbo Xu [b,*], Zhenlie Huang [a,*]

[a] NMPA Key Laboratory for Safety Evaluation of Cosmetics, Guangdong Provincial Key Laboratory of Tropical Disease Research, Department of Toxicology, School of Public Health, Southern Medical University, Guangzhou 510515, China
[b] Department of Biology, University of Southern Denmark, Odense 5230, Denmark



MODELOS ANIMALES

- FC.
- ↓ FE.
- Fibrosis miocárdica.
- Disfunción endotelial.

MÉTODOS

DISEÑO DEL ESTUDIO

- ✓ Determinar si **MNP** son **detectables en la placa ateroesclerótica** y si la **carga** de MNP se **asocia a ECV.**
  - ❖ Mediante cromatografia de gases acoplado a espectrometria de masas, análisis de isótopos estables y microscopia electrónica en a. carótida (endarterectomia).
- ✓ Estudio observacional, prospectivo y multicéntrico.
- ✓ 1 agosto 2019 a 31 julio 2020.

Università degli Studi della Campania *Luigi Vanvitelli*

University of Napoli Luigi Vanvitelli

UNIVERITÀ DEGLI STUDI DI SALERNO

Junta de Castilla y León · Sacyl · Complejo Asistencial Universitario de León

MÉTODOS

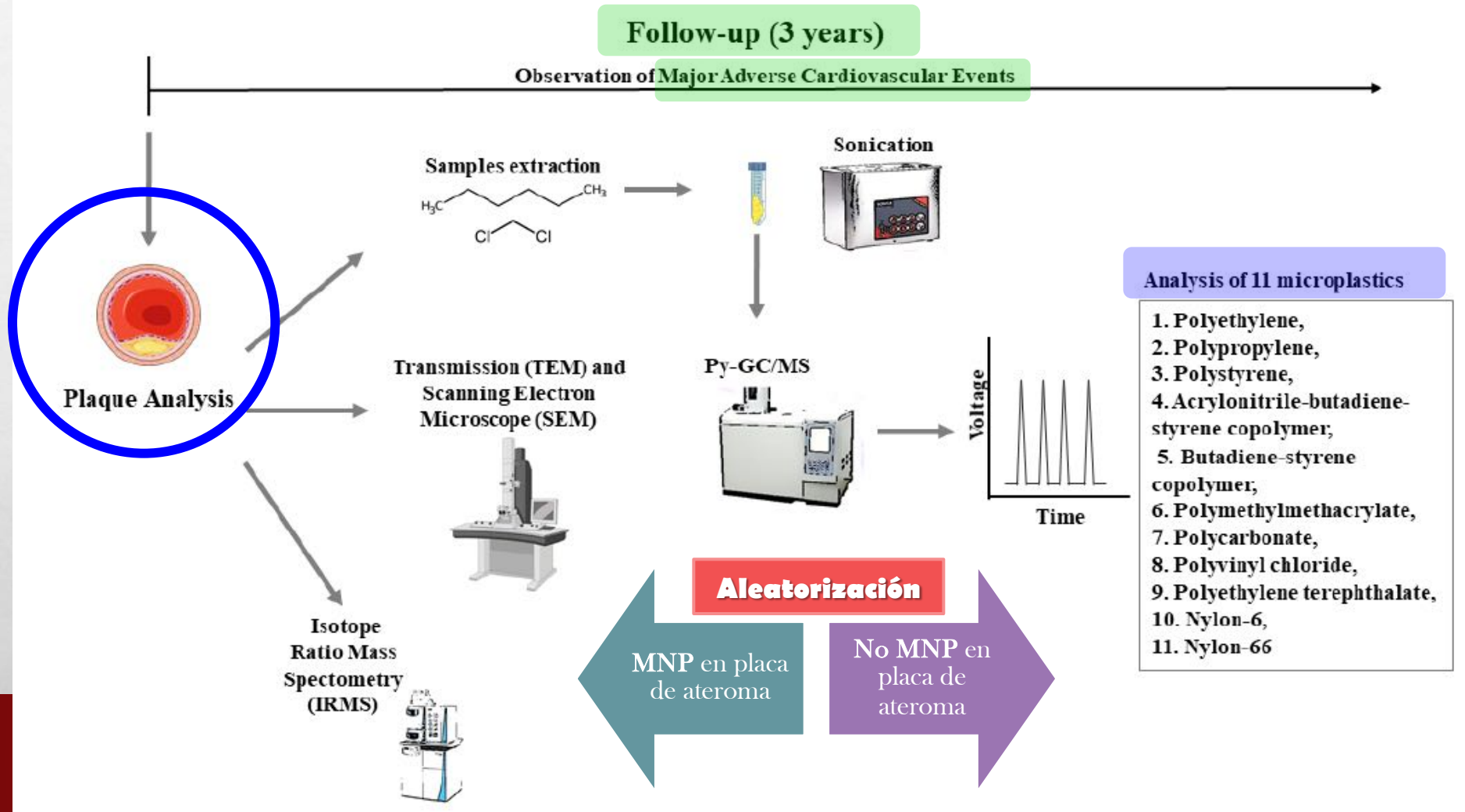
CRITERIOS DE SELECCIÓN

CRITERIOS DE INCLUSIÓN	CRITERIOS DE EXCLUSIÓN
✓Pacientes entre 18 a 75 años: -Estenosis carotida interna significativa (>70%) asintomáticos programados para endarterectomía.	❑ Insuficiencia Cardiaca. ❑ Valvulopatías. ❑ Neoplasias . ❑ HTA de causa secundaria. ❑ Complicaciones en post-operatorio inmediato: -Datos incompletos. -Pérdida durante el seguimiento.

MÉTODOS

DISEÑO DEL ESTUDIO

Supplementary Figure S1. Design of the study.



MÉTODOS

GC-MS

ISÓTOPOS ESTABLES

MÉTODOS

OBJETIVOS

OBJETIVO PRIMARIO

- Compuesto de:
  - IAM no fatal.
  - Ictus no fatal.
  - Muerte por cualquier causa.

→ Placa con MNP

→ Placa sin MNP

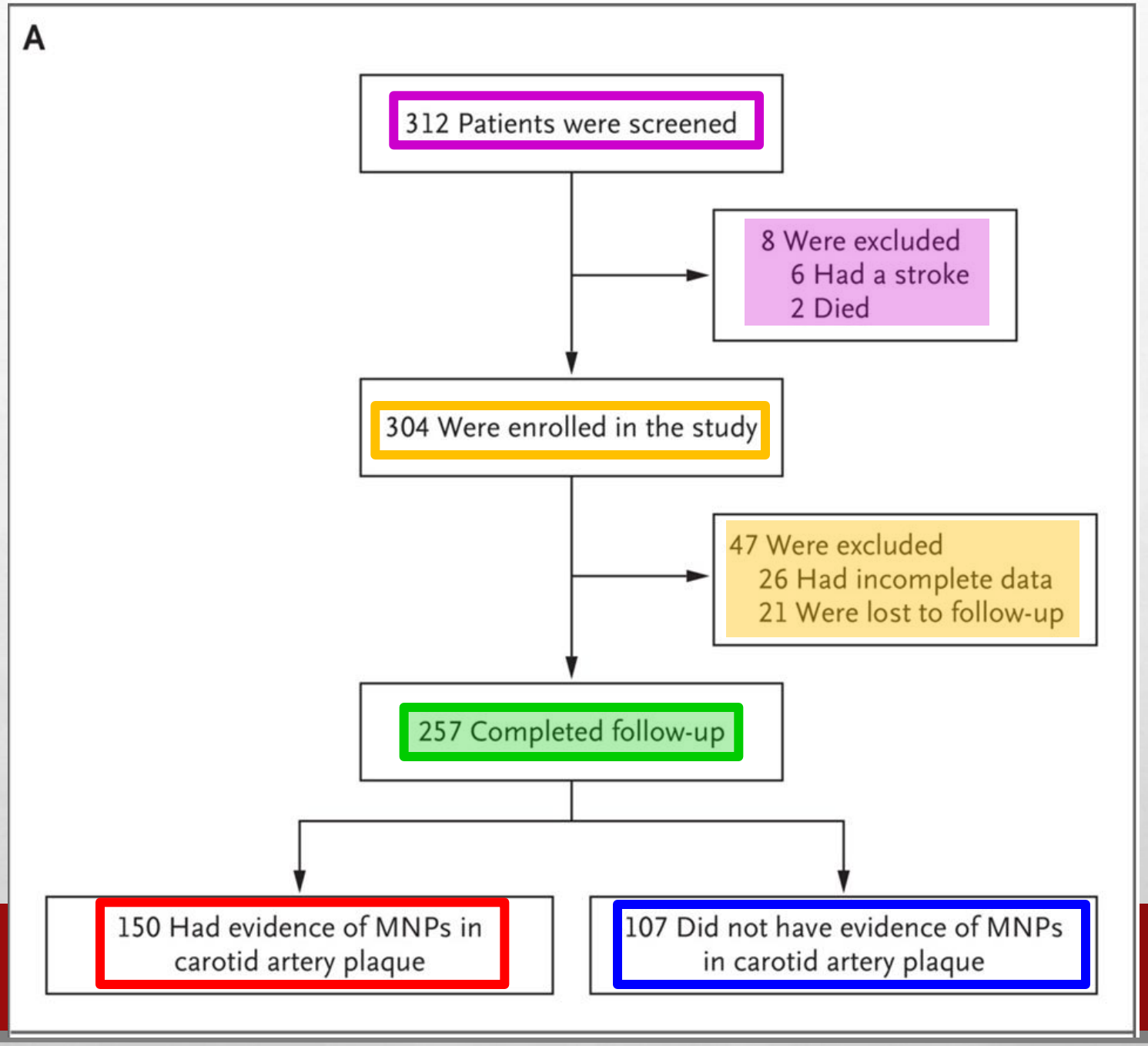
OBJETIVOS SECUNDARIOS

- Niveles de biomarcadores tisulares:
  - IL 18.
  - IL 1B.
  - TNF-a.
  - IL 6.
  - CD 68.
  - CD 3.
  - Colágeno

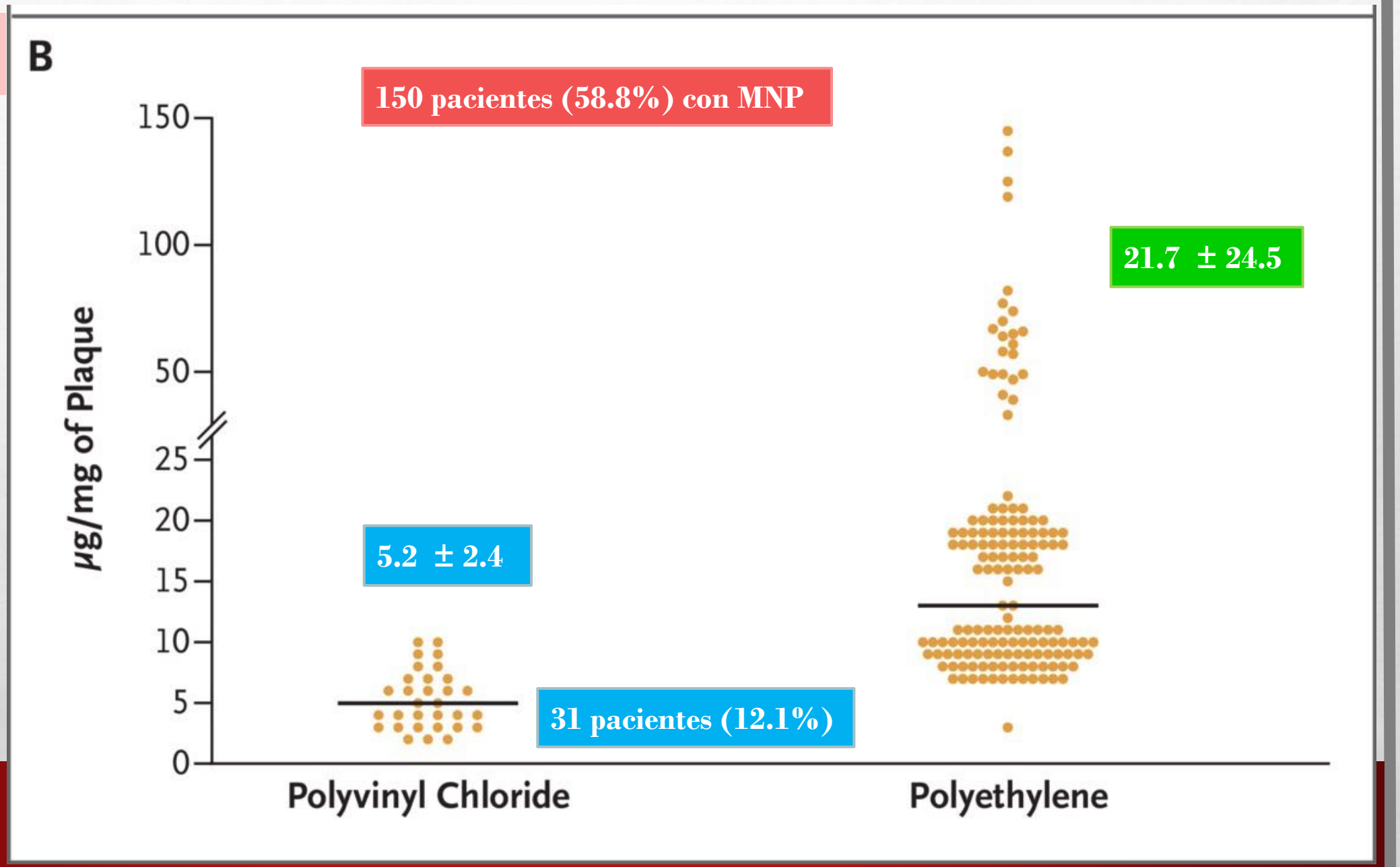
→ Placa con MNP

→ Placa sin MNP

RESULTADOS


A
312 Patients were screened
8 Were excluded
6 Had a stroke
2 Died
304 Were enrolled in the study
47 Were excluded
26 Had incomplete data
21 Were lost to follow-up
257 Completed follow-up
150 Had evidence of MNPs in carotid artery plaque
107 Did not have evidence of MNPs in carotid artery plaque

RESULTADOS


B
150 pacientes (58.8%) con MNP
21.7 ± 24.5
5.2 ± 2.4
31 pacientes (12.1%)
µg/mg of Plaque
150
100
50
25
20
15
10
5
0
Polyvinyl Chloride
Polyethylene

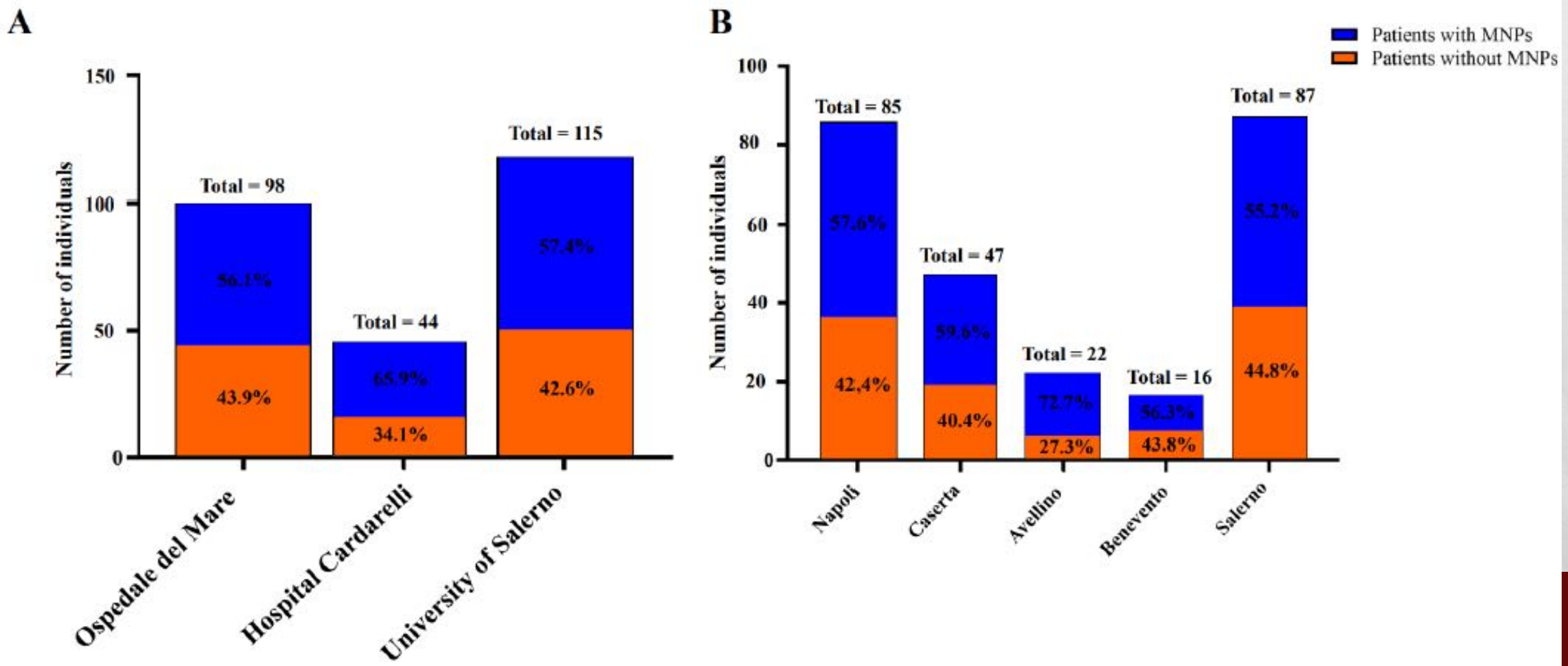
RESULTADOS

Table 1. Characteristics of the Patients at Baseline.*

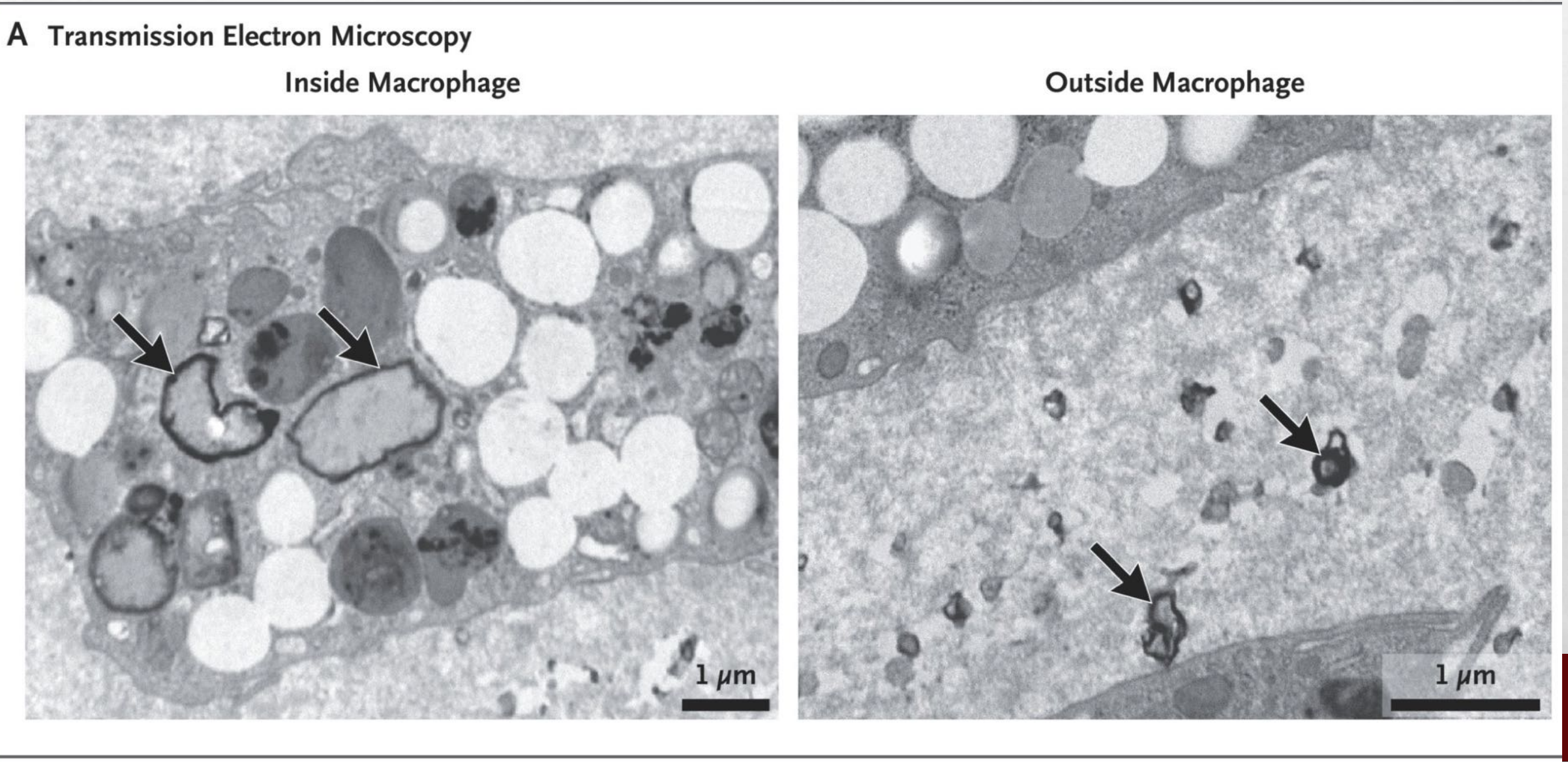
Variable	MNPs Present (N=150)	MNPs Not Present (N=107)
Age (IQR) — yr	71 (65–75)	73 (67–77)
Male sex — no. (%)	116 (77.3)	79 (73.8)
Body-mass index (IQR)†	28 (27–29)	28 (26–29)
Hypertension — no. (%)	78 (52.0)	69 (64.5)
Systolic blood pressure (IQR) — mm Hg	124 (118–130)	127 (118–129)
Diastolic blood pressure (IQR) — mm Hg	78 (75–83)	77 (75–85)
Heart rate (IQR) — beats/min	85 (79–91)	81 (76–86)
Stenosis severity (IQR) — %	77 (73–83)	78 (73–83)
Diabetes — no. (%)	36 (24.0)	32 (29.9)
Cardiovascular disease — no. (%)‡	50 (33.3)	35 (32.7)
Dyslipidemia — no. (%)	55 (36.7)	40 (37.4)
Total cholesterol (IQR) — mg/dl	150 (145–158)	147 (139–158)
LDL cholesterol (IQR) — mg/dl	77 (69–84)	74 (69–82)
HDL cholesterol (IQR) — mg/dl	42 (40–43)	42 (40–44)
Triglycerides (IQR) — mg/dl	178 (165–192)	182 (163–193)
Creatinine (IQR) — mg/dl	1.00 (0.90–1.10)	0.96 (0.96–1.06)
Smoker — no. (%)	24 (16.0)	17 (15.9)
Medication use — no. (%)		
Beta-blockers	48 (32.0)	35 (32.7)
ACE inhibitors	75 (50)	53 (49.5)
ARBs	35 (23.3)	31 (29.0)
Calcium-channel blockers	13 (8.7)	8 (7.5)
Diuretics	17 (11.3)	16 (15.0)
Heparin	12 (8.0)	10 (9.3)
Antiplatelet drugs	146 (97.3)	105 (98.1)
Statin	143 (95.3)	101 (94.4)
Ezetimibe	26 (17.3)	20 (18.7)

RESULTADOS

Figure S2. Proportion of individuals with MNPs among different centers of recruitment (A) and areas of living (B).

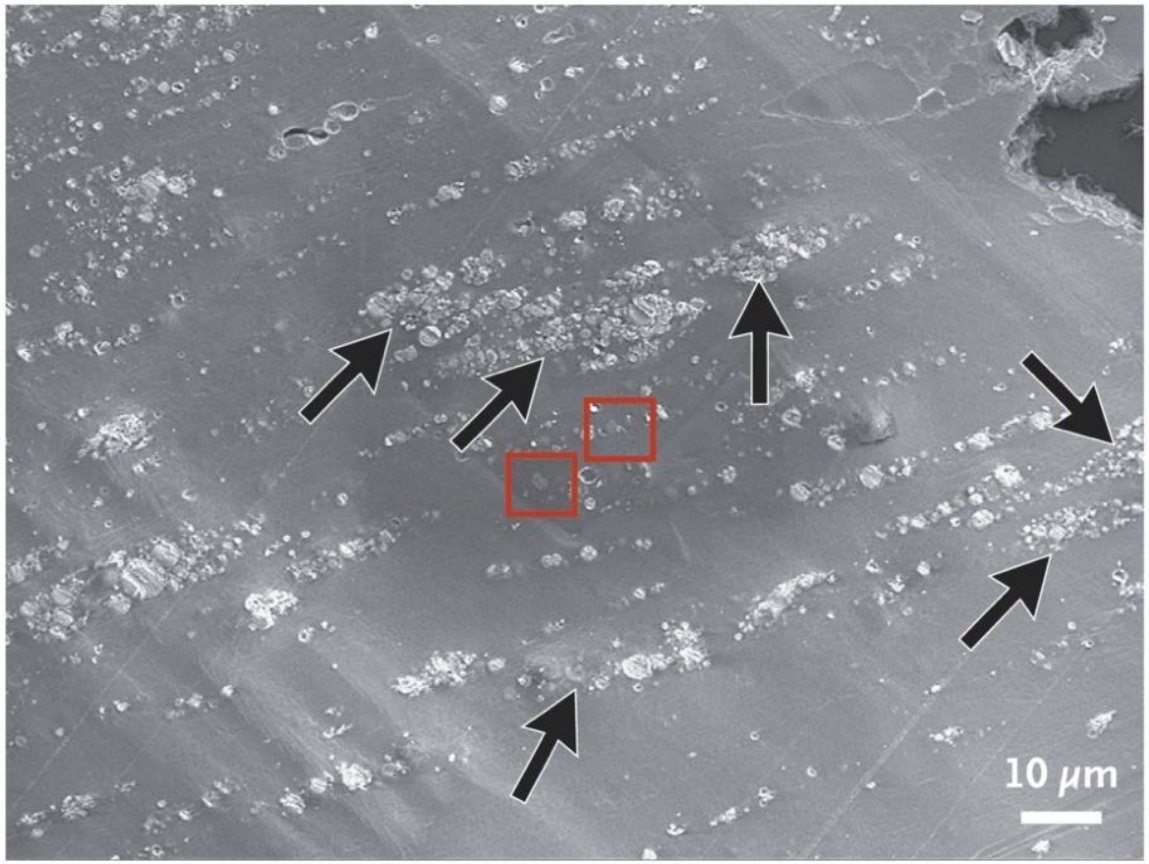


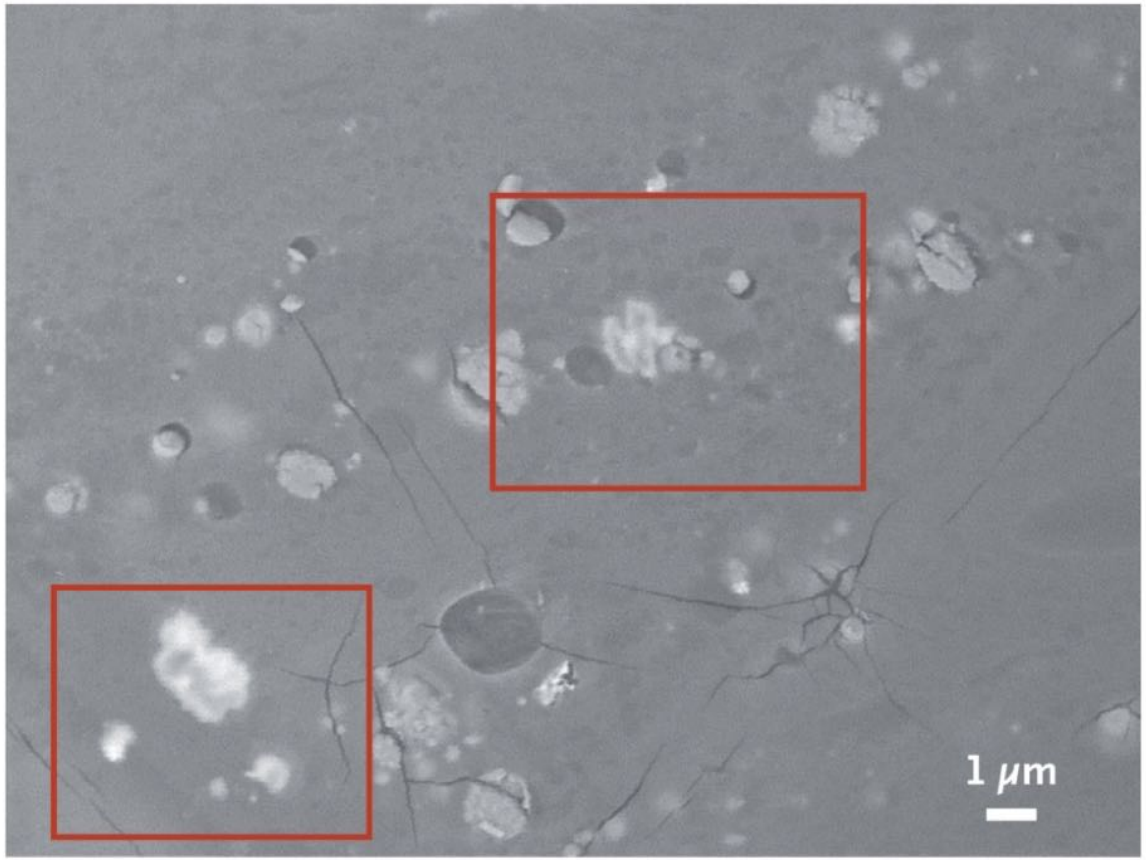
RESULTADOS


A Transmission Electron Microscopy
Inside Macrophage
Outside Macrophage
1 μm
1 μm

RESULTADOS

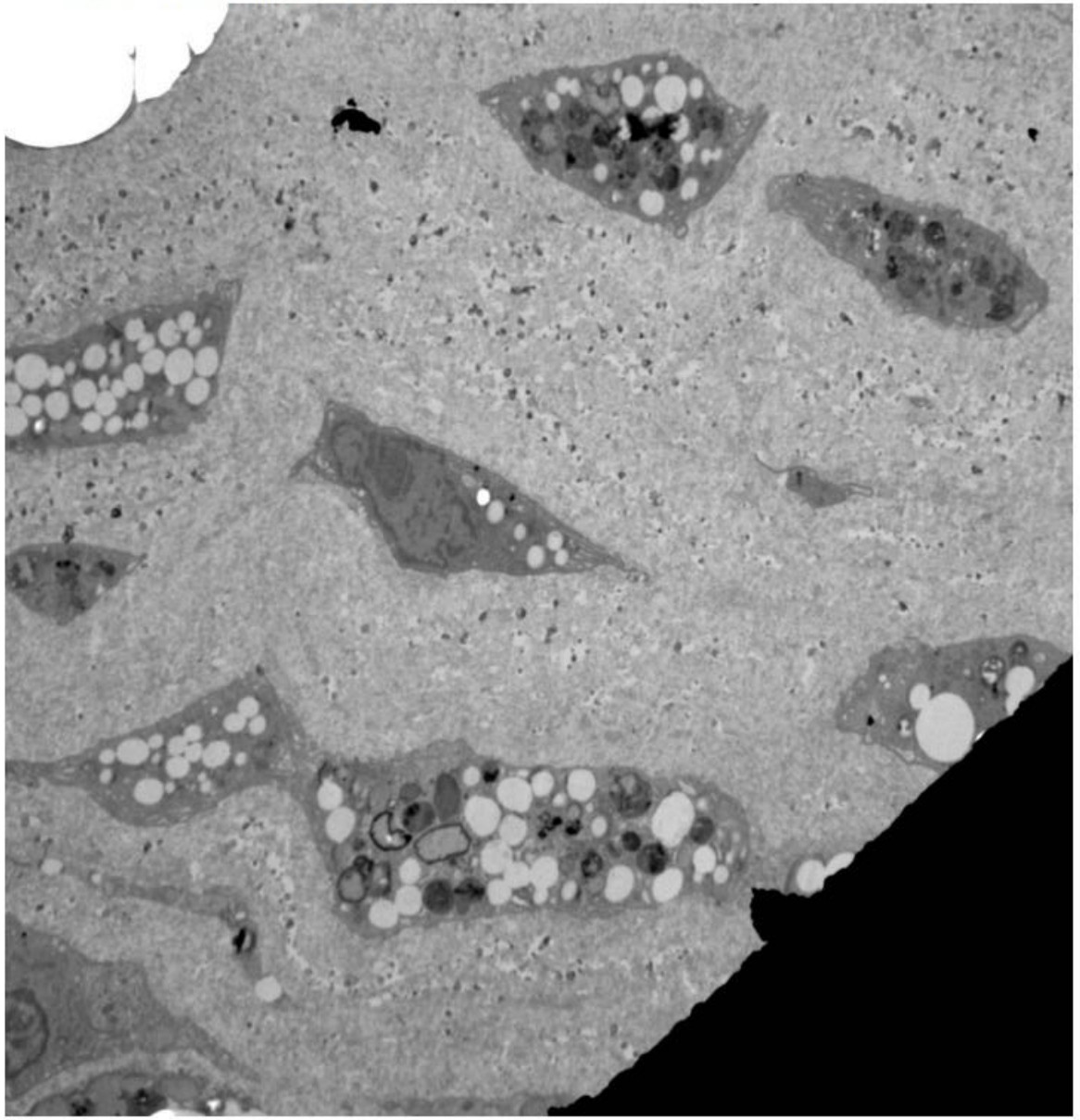
B Scanning Electron Microscopy Using Back-Scattered Electrons





RESULTADOS

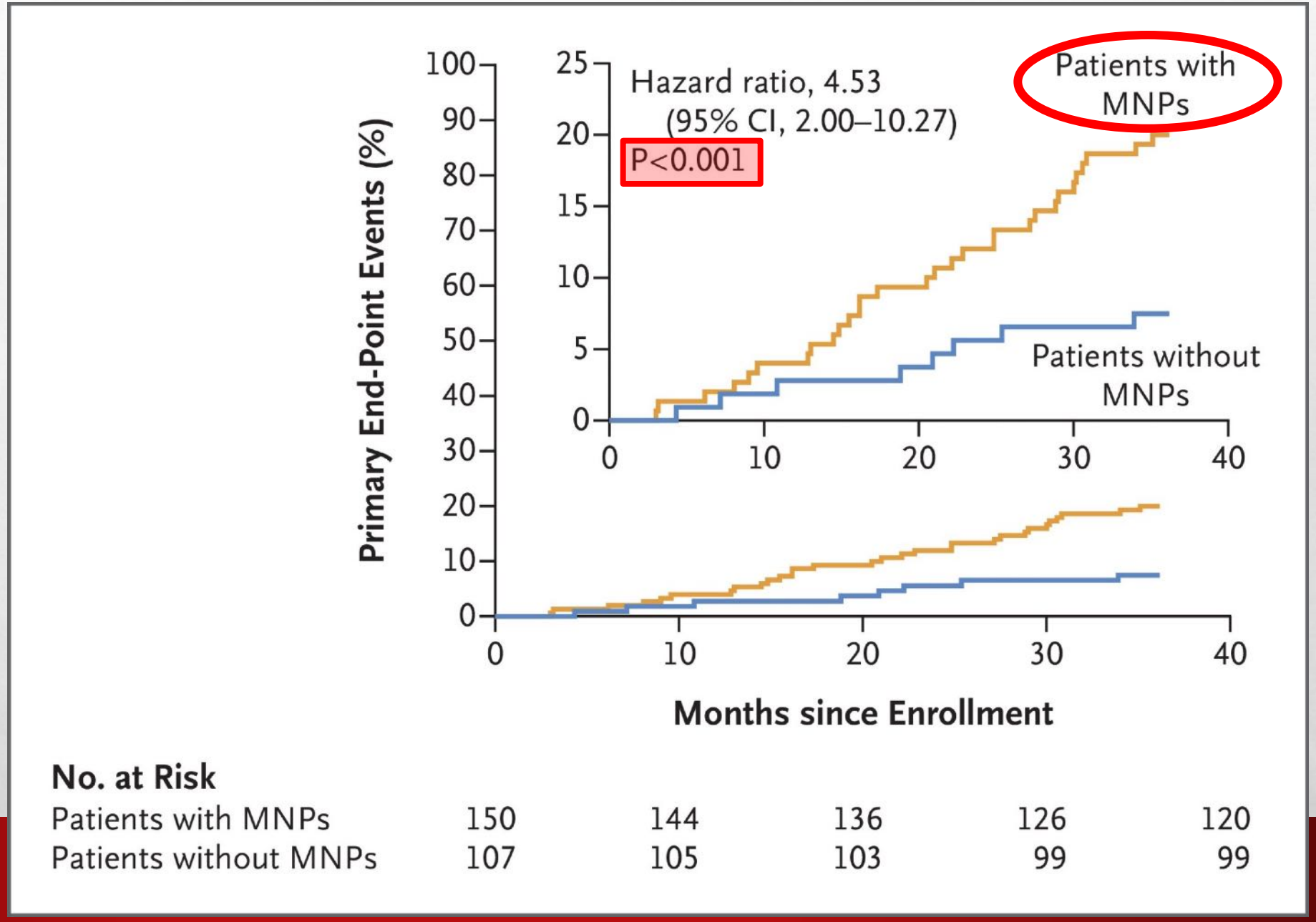
Figure S3A. Lower magnification of the trasmission electron microscopy (TEM) image of the atheroma showing living cells with vacuoles dispersed in the plaque (relative to Figure 2A).



RESULTADOS

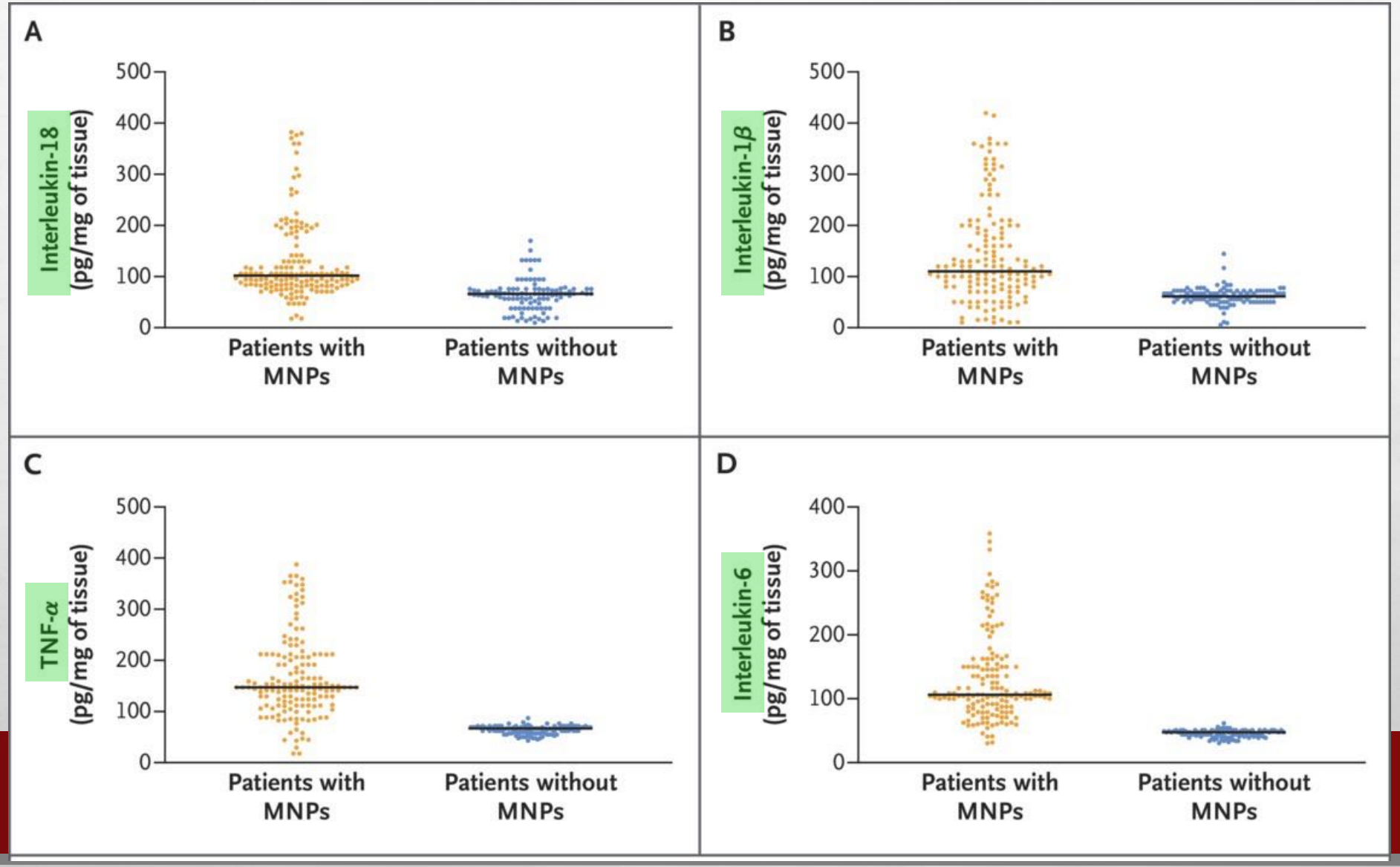
OBJETIVO PRIMARIO

- ✓ **Análisis de regresión** ajustado por FRCV:
  - Edad.
  - Sexo.
  - IMC.
  - CT.
  - TG.
  - HDLc.
  - LDLc.
  - Cr.
  - DM.
  - HTA.
  - ECV previa.



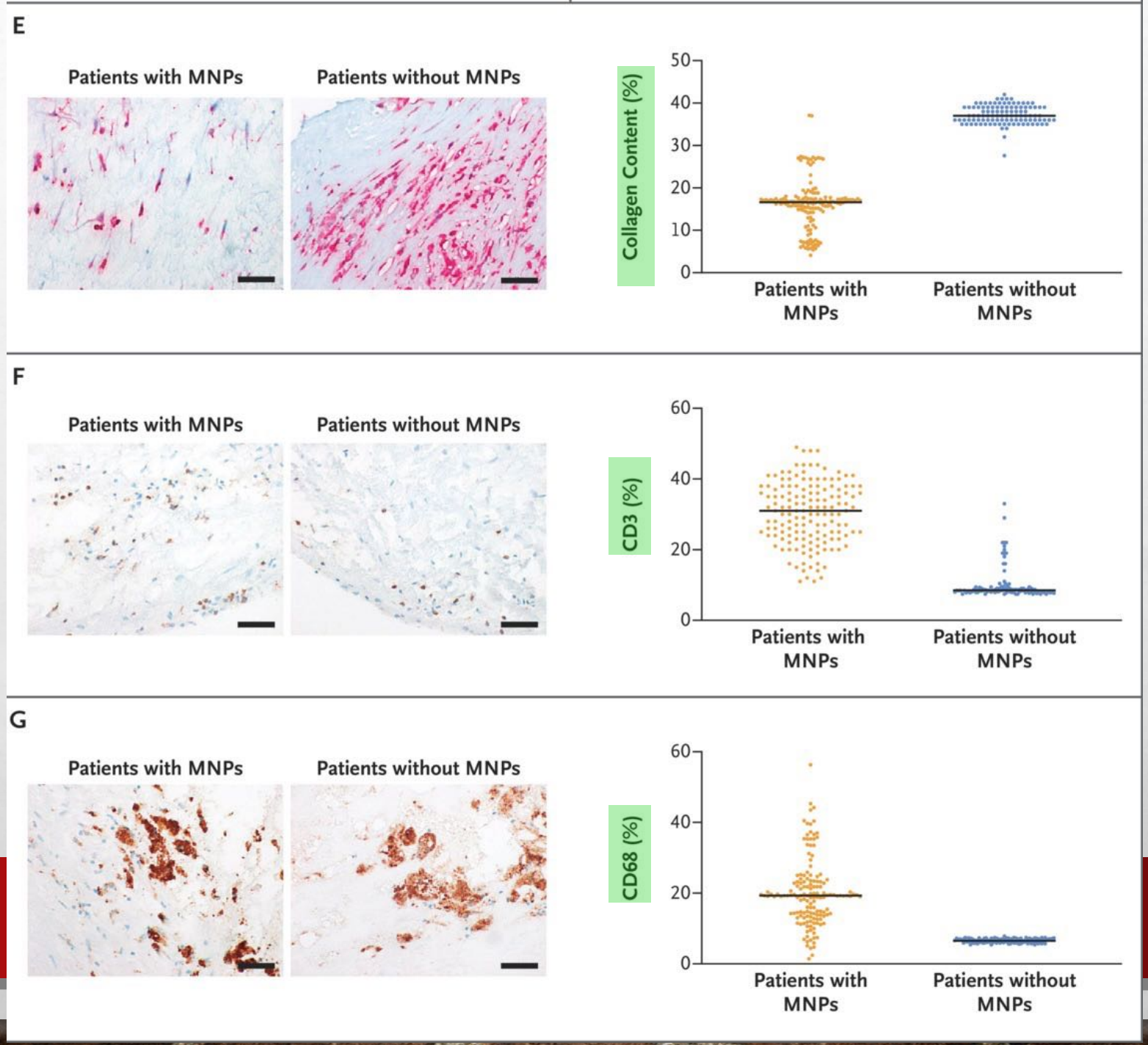
RESULTADOS

MARCADORES INFLAMATORIOS



RESULTADOS

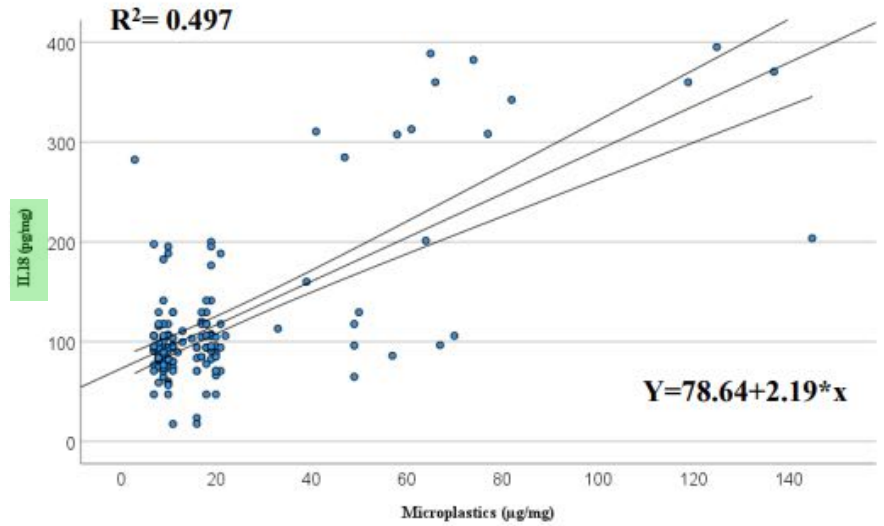
MARCADORES INFLAMATORIOS

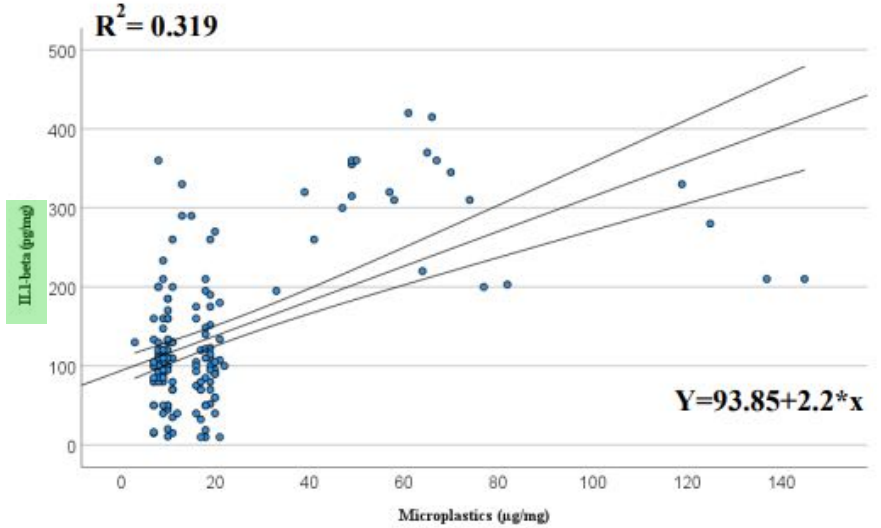


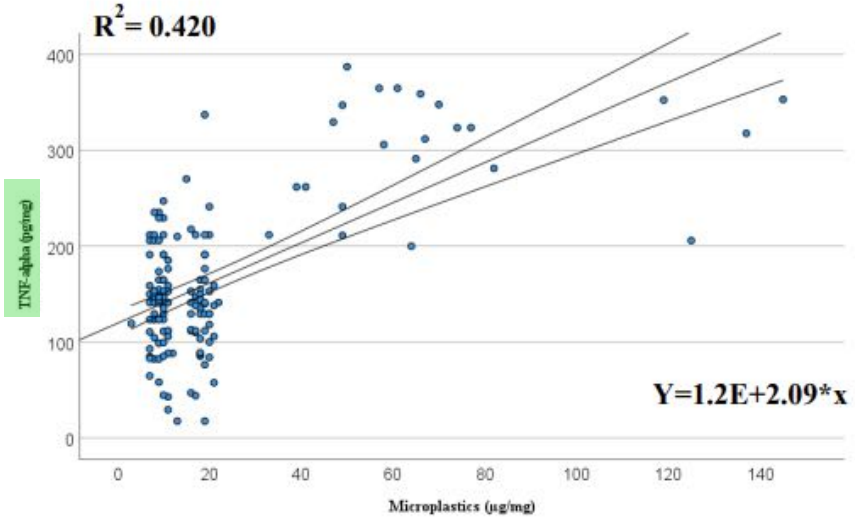
RESULTADOS

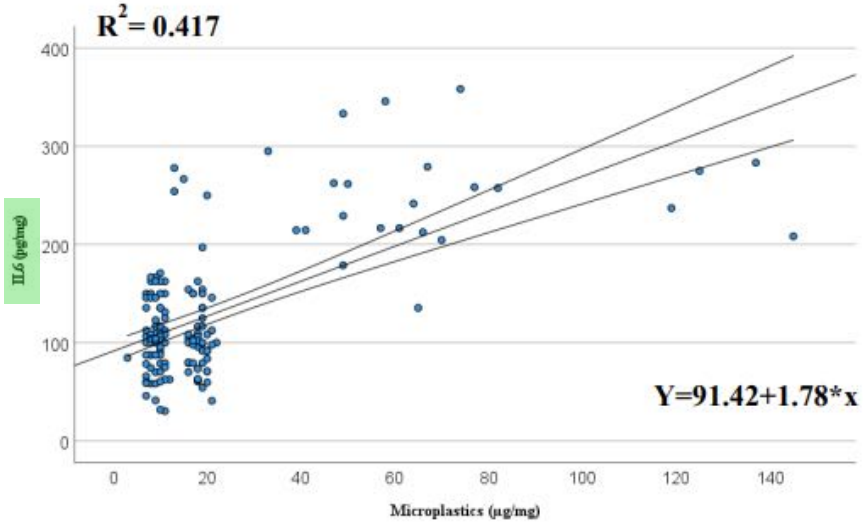
MARCADORES INFLAMATORIOS

Figure S5. Relationship between micronanoplastics levels and plaque biomarkers.



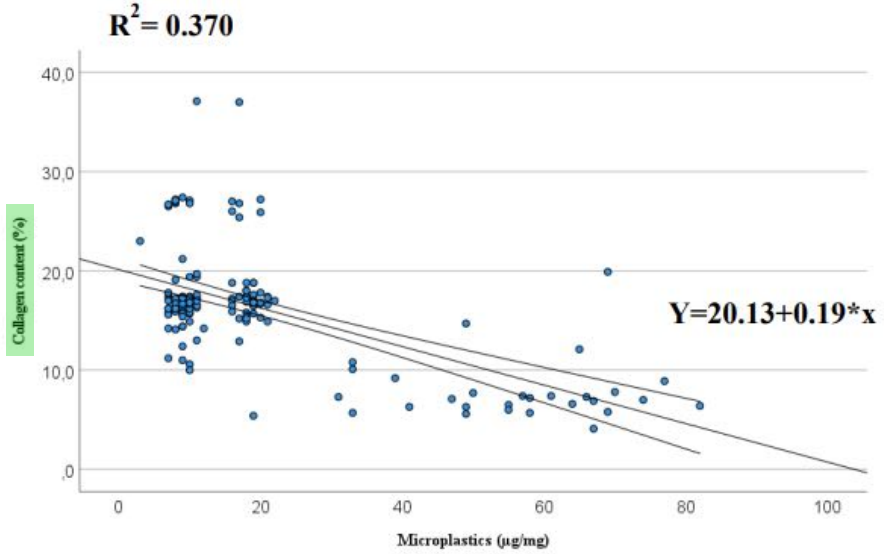


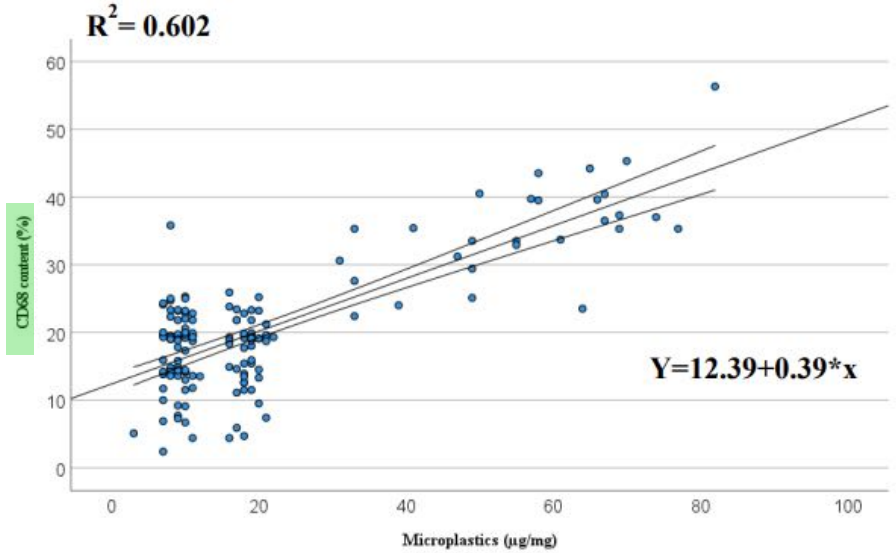


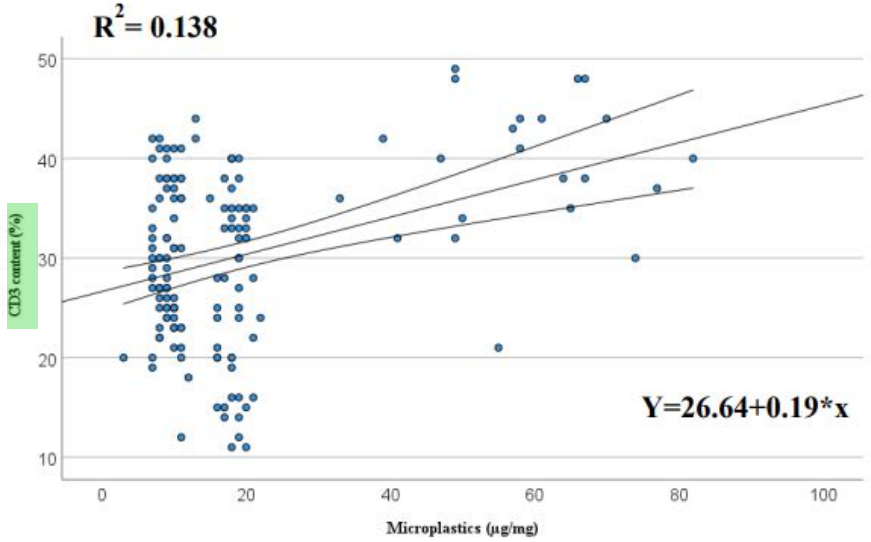


RESULTADOS

MARCADORES INFLAMATORIOS



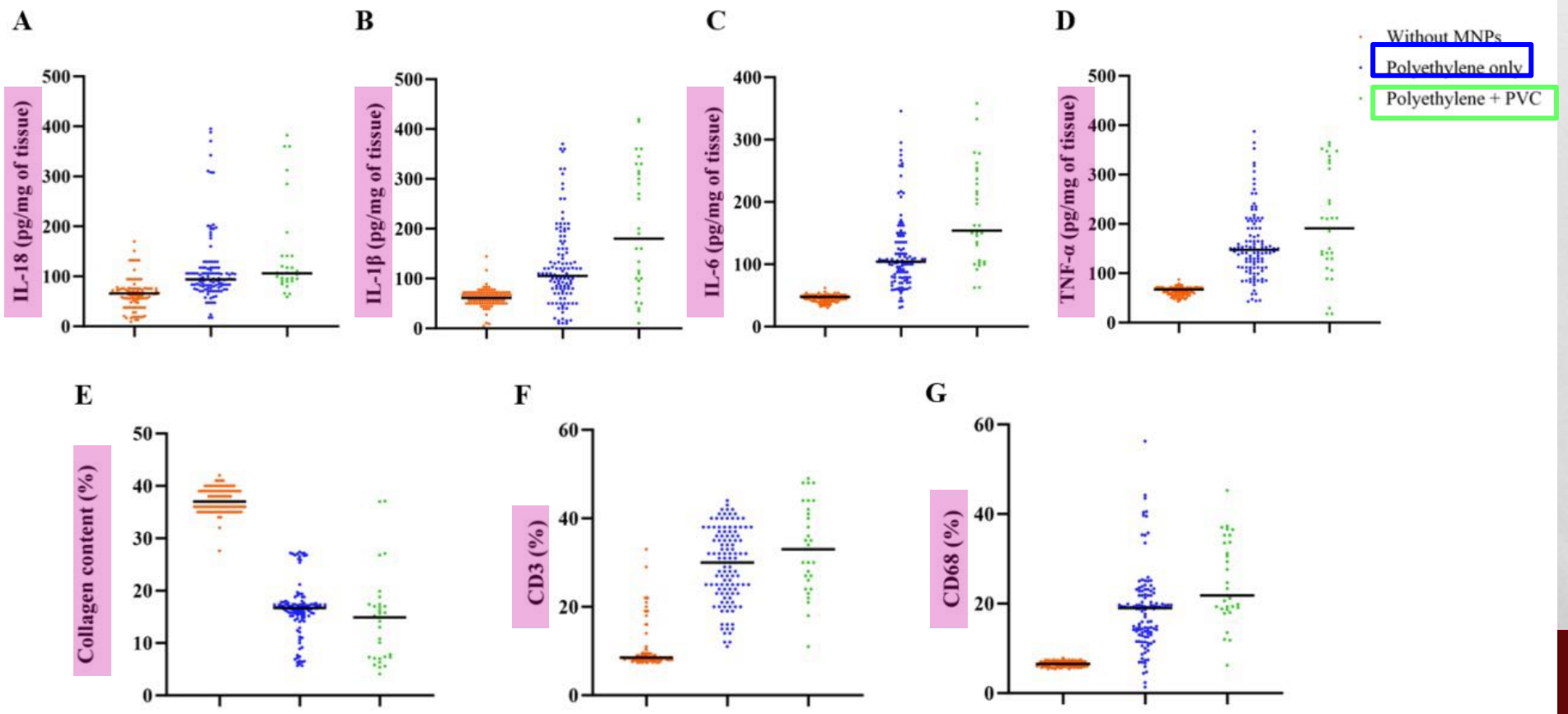




RESULTADOS

MARCADORES INFLAMATORIOS

Figure S6. Expression of plaque markers in the three groups of patients without evidence of micronanoplastics in the plaque, with evidence of polytheylene only, or with evidence of both polyethylene and polyvinylchloride.



DISCUSIÓN

FORTALEZAS

- ✓ Estudios preclínicos previos se evaluaban **MNP de tamaños superiores.**
  - Difícil extrapolar hallazgos a humanos.

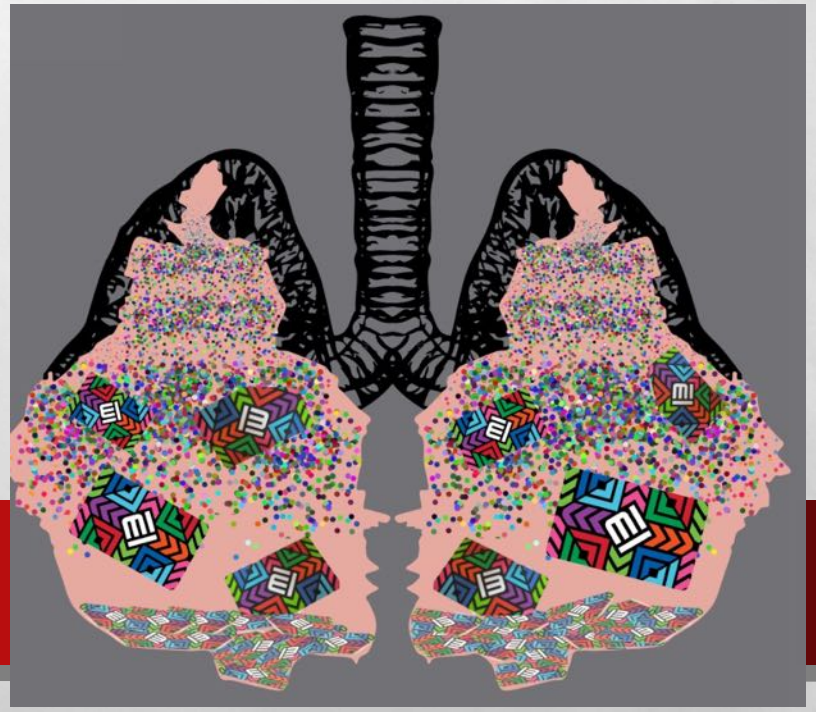
  - Según OMS: MNP > 150 µm y 10 µm de diámetro no se absorben en sangre no penetran en los tejidos.

LIMITACIONES

- ❑ Sólo detectados en la placa: **polietileno** y **cloruro de polivinilo** (2 de 11).
  - Más estudios: preferencia ateroesclerosis y/o patogenicidad.
- ❑ Resultados **no** demuestran **CAUSALIDAD**
  - Variables de confusión no estudiadas (tipo/cantidad exposión, estilo de vida...)
- ❑ No mediciones **polución ambiental**: FRCV.
  - PM 2,5 y PM10.
- ❑ Posible riesgo residual de contaminación del laboratorio.
  - Recogida y análisis de las muestras escrupulosos.
- ❑ **No** valoración **nivel socio-económico.**
- ❑ **Población "seleccionada"** datos no extrapolables.
- ❑ No estudiadas variables de alimentación-agua consumida.
- ❑ **"Papel light"** en **enfermedad cardiovascular** ???
  - ↑ exposición a plásticos en décadas y ↓ tasa ECV .

Cosmética

La UE impondrá tasas a las empresas de cosmética para reducir los microplásticos



The NEW ENGLAND JOURNAL of MEDICINE

Plastics, Fossil Carbon, and the Heart

Philip J. Landrigan, M.D.

N ENGL J MED 390;10 NEJM.ORG MARCH 7, 2024

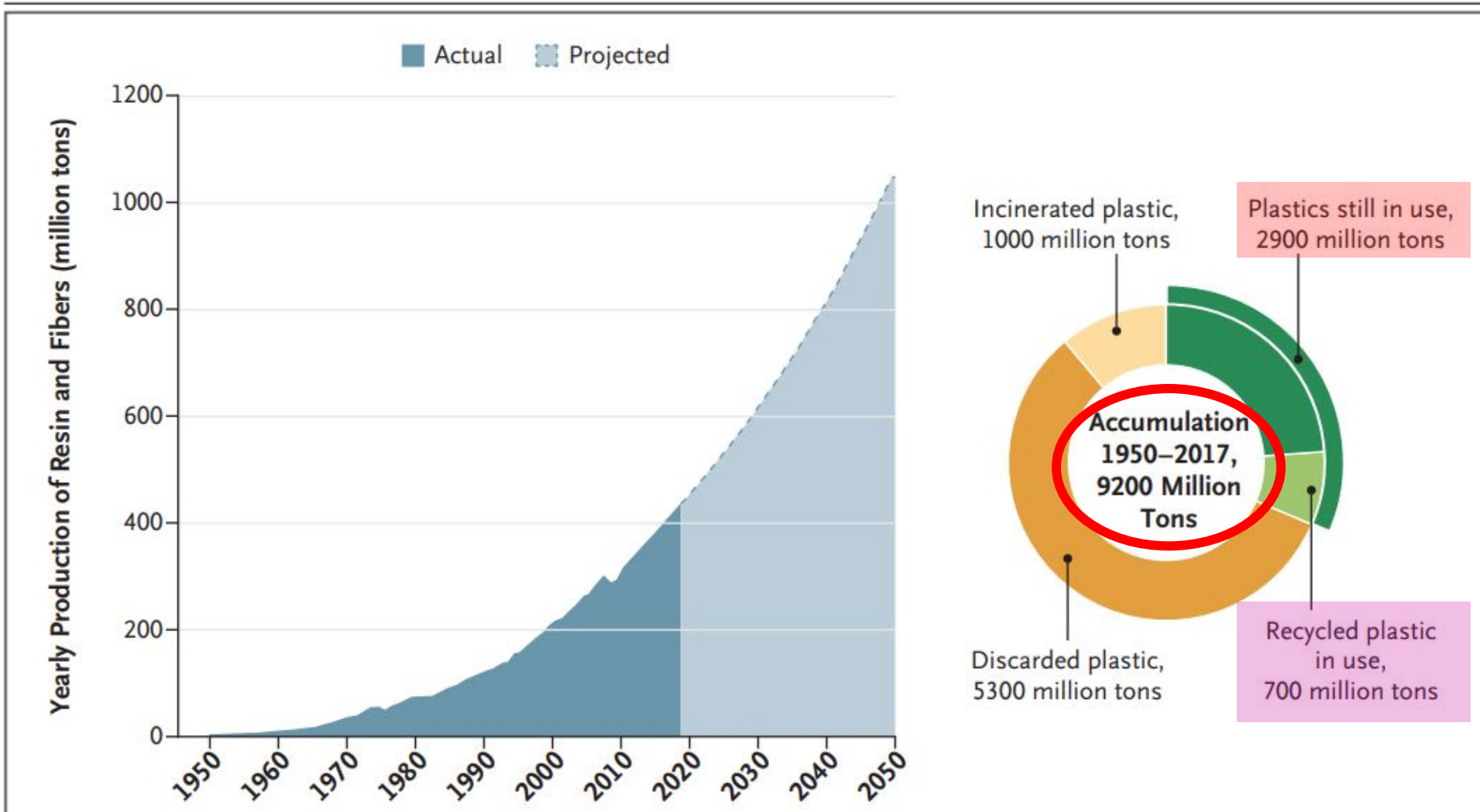


Figure 1. Global Plastic Production, Accumulation, and Trends.

Adapted with permission from GRID–Arendal.

Plastics, Fossil Carbon, and the Heart

Philip J. Landrigan, M.D.

✓ **40%** producción actual ⇨ artículos desechables de **un solo uso.**

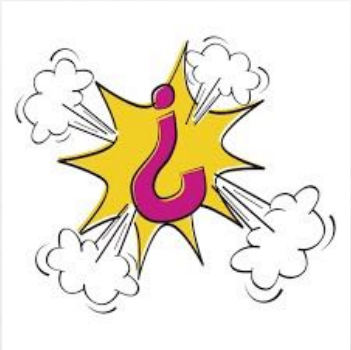
✓ Aditivos tóxicos:

- Carcinógenos.
- Neurotóxicos.
- Sustancias fluoradas/bifenoles alteran metabolismo lípidos, aumentan riesgo de: DM, ictus y enfermedades CV.

✓ Descritos casos en trabajadores:

- Angiosarcoma hepático ⇨ cloruro de polivinilo.
- EPID ⇨ flocado de nailon (textil).

- ¿Debería considerarse **como** un **factor de RCV?**



- ¿Qué más **órganos** están **en riesgo**?

- ¿Podemos **reducir su exposición**?

- Patrones actuales de producción, uso y eliminación **NO** son **SOSTENIBLES**.

ABC del tratado sobre el plástico que se está debatiendo esta semana en París

Tratado de Contaminación por Plásticos de la ONU “está más cerca" de hacerse realidad

Los negociadores en París acuerdan comenzar a desarrollar un borrador de tratado con reglas globales para frenar la contaminación por plásticos

Nueva ronda de negociaciones sobre un tratado mundial contra la contaminación por plástico

Tratado ONU sobre el plástico: el instrumento internacional ambiental más importante desde el Acuerdo de París

Lucha por la salud de nuestro planeta

Tratado global contra la contaminación por plásticos

Ciencia y Medio Ambiente

El mundo se une contra el plástico

El Tratado Global de Plásticos: antecedentes normativos y objetivo común

Pedimos la prohibición mundial de plásticos de un solo uso "dañinos e innecesarios"

QUE NO TE LO CUENTEN.

Ven y descúbrelo tú mismo