SESIÓN BIBLIOGRÁFICA 5 mayo 2023

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Efficacy and Safety of Drugs for Gastroparesis: Systematic Review and Network Meta-analysis

Gastroenterology 2023;164:642–654

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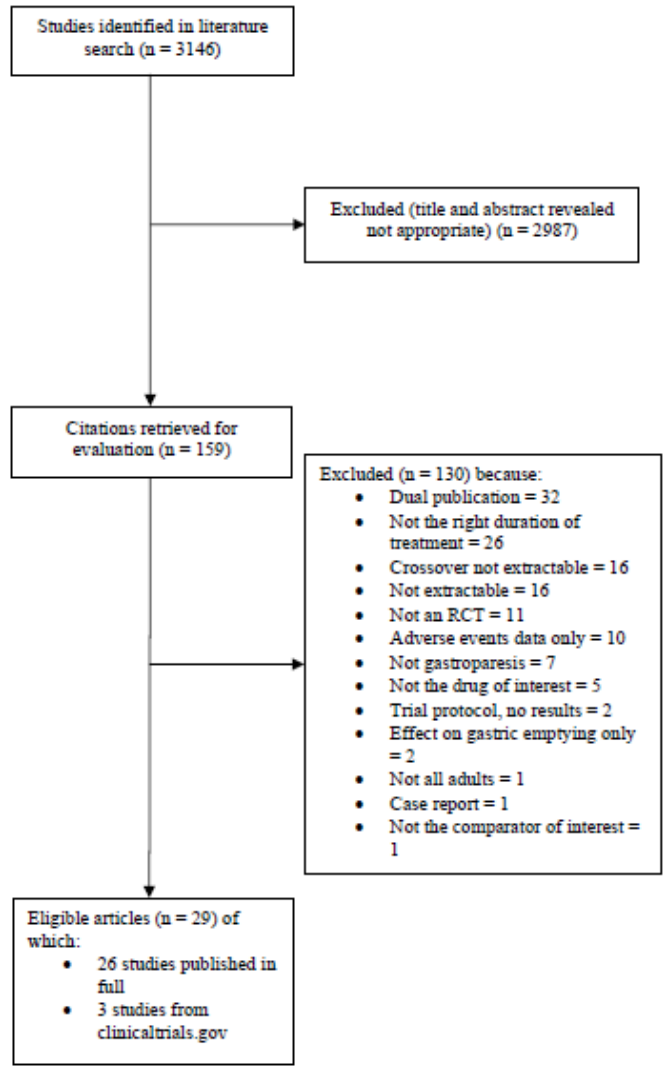
- Gastroparesia: retraso en vaciamiento gástrico de sólidos, asociado a síntomas (típicamente dolor en parte superior de abdomen, náuseas, vómitos, saciedad precoz, distensión abdominal), en ausencia de obstrucción mecánica en estómago o duodeno
- Puede confirmarse mediante gammagrafía, pruebas del aliento con isótopos estables (13C-espirulina) o telemetría mediante cápsula
- Etiología: 3 subtipos: diabético (60%), iatrógeno (15%) e idiopático (10%)
- En encuesta global de síntomas Fundación Roma: prevalencia 0.9%, en diabéticos 1.3%
- En revisión sistemática: prevalencia entre 13.8 y 267.7:100000 adultos, e incidencia 1.9 a 6.3:100000 años-persona
- Metoclopramida es el único fármaco aprobado por la FDA, durante un período máximo de 12 semanas, en menores de 65 años
- Revisión sistemática y metaanálisis en red de ECA que evaluaron eficacia y seguridad de todos los fármacos probados en pacientes con gastroparesia, definida según los síntomas típicos, con o sin evidencia de retraso en el vaciamiento gástrico

- Criterio principal: eficacia de todos los fármacos comparados entre sí o con placebo en términos de fracaso en lograr mejoría global en los síntomas de gastroparesia

- Criterios secundarios: eficacia en términos de fracaso para mejorar los síntomas individuales: náuseas, vómitos, saciedad, distensión y dolor abdominal

- Otros resultados secundarios: número de pacientes que presentaron al menos un efecto adverso, número de retiradas del estudio por efectos adversos

Supplementary Figure 1. Flow Diagram of Assessment of Studies Identified in the Systematic Review.



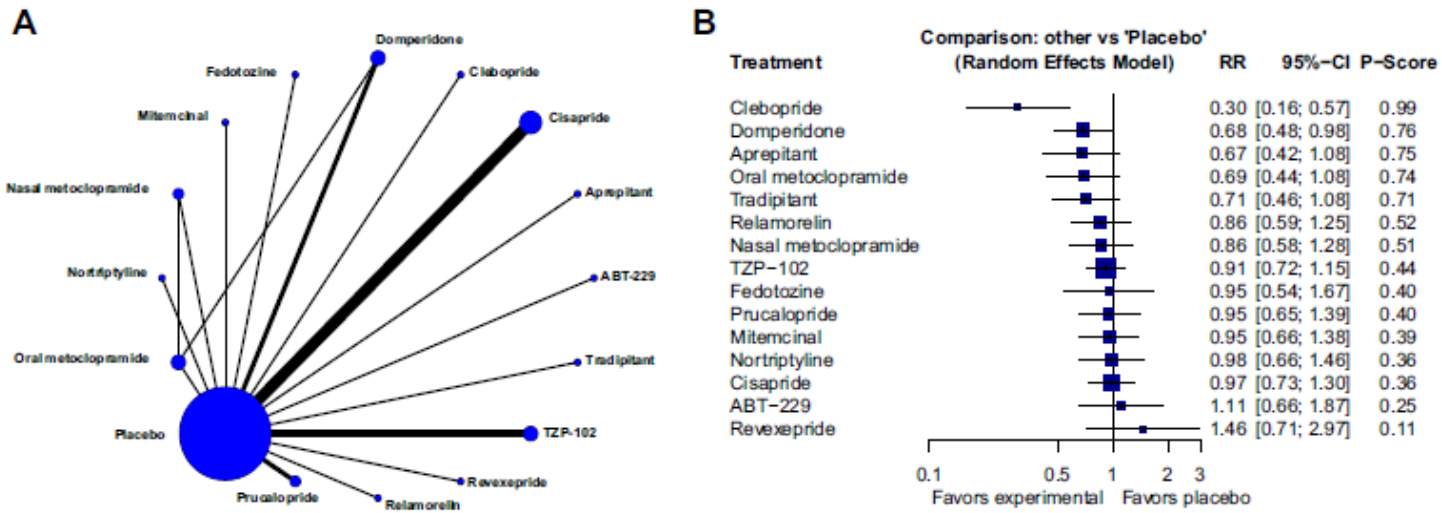


Figure 1. (*A*) Network plot for failure to achieve an improvement in global gastroparesis symptoms: all RCTs. *Circle* (node) size is proportional to the number of study participants assigned to receive each intervention. The *line width* (connection size) corresponds to the number of studies comparing the individual interventions. (*B*) Forest plot for failure to achieve an improvement in global gastroparesis symptoms: all RCTs. The P-score is the probability of each intervention being ranked as best in the network.

Table 1. League Table for Failure to Achieve an Improvement in Global Gastroparesis Symptoms: All RCTs

CLE													**0.30 (0.16–0.57)**			
0.44 (0.21–0.93)	DOM		0.92 (0.58–1.46)										0.72 (0.48–1.08)			
0.45 (0.20–1.00)	1.01 (0.56–1.83)	APR											0.67 (0.42–1.08)			
0.44 (0.20–0.96)	0.99 (0.67–1.47)	0.98 (0.51–1.89)	Oral MET			1.97 (0.38–10.32)							**0.48 (0.23–0.99)**			
0.43 (0.20–0.92)	0.96 (0.55–1.67)	0.95 (0.50–1.80)	0.97 (0.52–1.80)	TRA									0.71 (0.46–1.08)			
0.35 (0.17–0.74)	0.80 (0.47–1.34)	0.79 (0.43–1.44)	0.80 (0.45–1.44)	0.83 (0.47–1.46)	REL								0.86 (0.59–1.25)			
0.35 (0.17–0.74)	0.79 (0.47–1.33)	0.78 (0.42–1.45)	0.80 (0.45–1.42)	0.82 (0.46–1.47)	0.99 (0.58–1.71)	Nasal MET							0.91 (0.61–1.36)			
0.33 (0.17–0.65)	0.75 (0.49–1.14)	0.74 (0.43–1.25)	0.75 (0.45–1.25)	0.78 (0.48–1.26)	0.94 (0.60–1.46)	0.94 (0.60–1.49)	TZP-102						0.91 (0.72–1.15)			
0.32 (0.14–0.74)	0.72 (0.37–1.40)	0.71 (0.34–1.48)	0.72 (0.35–1.48)	0.75 (0.37–1.51)	0.90 (0.46–1.77)	0.91 (0.46–1.80)	0.96 (0.52–1.76)	FED					0.95 (0.54–1.67)			
0.32 (0.15–0.67)	0.72 (0.42–1.22)	0.71 (0.39–1.31)	0.72 (0.40–1.31)	0.75 (0.42–1.33)	0.90 (0.53–1.55)	0.91 (0.53–1.57)	0.96 (0.62–1.51)	1.00 (0.51–1.98)	PRU				0.95 (0.65–1.39)			
0.32 (0.15–0.67)	0.72 (0.43–1.20)	0.71 (0.39–1.30)	0.72 (0.40–1.30)	0.75 (0.42–1.31)	0.90 (0.53–1.53)	0.91 (0.53–1.56)	0.96 (0.62–1.49)	1.00 (0.51–1.97)	1.00 (0.58–1.70)	MIT			0.95 (0.66–1.38)			
0.31 (0.14–0.66)	0.70 (0.41–1.19)	0.69 (0.37–1.28)	0.70 (0.38–1.28)	0.72 (0.40–1.30)	0.87 (0.50–1.52)	0.88 (0.50–1.54)	0.93 (0.59–1.48)	0.97 (0.49–1.94)	0.97 (0.56–1.68)	0.97 (0.56–1.68)	NOR		0.98 (0.66–1.46)			
0.31 (0.15–0.63)	0.70 (0.44–1.11)	0.69 (0.40–1.21)	0.71 (0.41–1.20)	0.73 (0.44–1.22)	0.88 (0.55–1.42)	0.89 (0.54–1.44)	0.94 (0.65–1.36)	0.98 (0.52–1.84)	0.97 (0.60–1.57)	0.98 (0.61–1.56)	1.01 (0.61–1.65)	CIS	0.97 (0.73–1.30)			
0.30 (0.16–0.57)	**0.68 (0.48–0.98)**	0.67 (0.42–1.08)	0.69 (0.44–1.08)	0.71 (0.46–1.08)	0.86 (0.59–1.25)	0.86 (0.58–1.28)	0.91 (0.72–1.15)	0.95 (0.54–1.67)	0.95 (0.65–1.39)	0.95 (0.66–1.38)	0.98 (0.66–1.46)	0.97 (0.73–1.30)	PLA	0.90 (0.54–1.52)	0.69 (0.34–1.40)	
0.27 (0.12–0.62)	0.61 (0.33–1.16)	0.61 (0.30–1.23)	0.62 (0.31–1.23)	0.64 (0.33–1.25)	0.77 (0.41–1.47)	0.78 (0.41–1.49)	0.82 (0.47–1.46)	0.86 (0.40–1.85)	0.86 (0.45–1.63)	0.86 (0.45–1.63)	0.88 (0.46–1.70)	0.88 (0.48–1.59)	0.90 (0.54–1.52)	ABT-229		
0.21 (0.08–0.54)	0.47 (0.21–1.04)	0.46 (0.20–1.09)	0.47 (0.20–1.10)	0.49 (0.21–1.12)	0.59 (0.26–1.32)	0.59 (0.26–1.33)	0.63 (0.30–1.33)	0.65 (0.26–1.62)	0.65 (0.29–1.46)	0.65 (0.29–1.46)	0.67 (0.30–1.52)	0.67 (0.31–1.44)	0.69 (0.34–1.40)	0.76 (0.32–1.84)	REV	

NOTE. RR with 95% CIs in parentheses. Comparisons, column vs row, should be read from left to right, and are ordered relative to their overall efficacy. The intervention in the top left position is ranked as best after the network meta-analysis of direct and indirect effects. Direct comparisons are provided above the drug labels, and indirect comparisons are below. Bold values denote a statistically significant difference.
APR, aprepitant; CIS, cisapride; CLE, clebopride; DOM, domperidone; FED, fedotozine; MET, metoclopramide; MIT, mitemcinal; NOR, nortriptyline; PLA, placebo; PRU, prucalopride; REL, relamorelin; REV, revexepride; TRA, tradipitant.

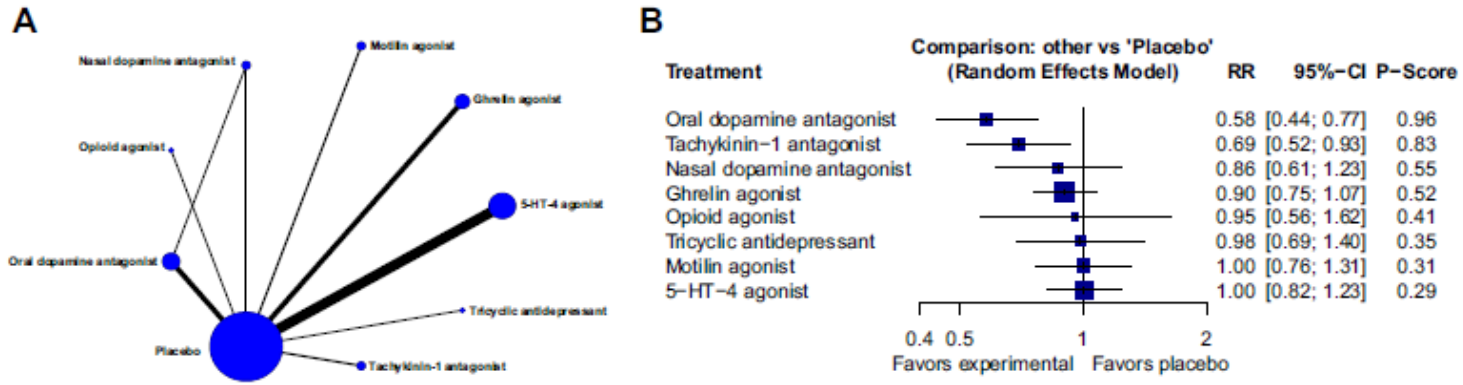


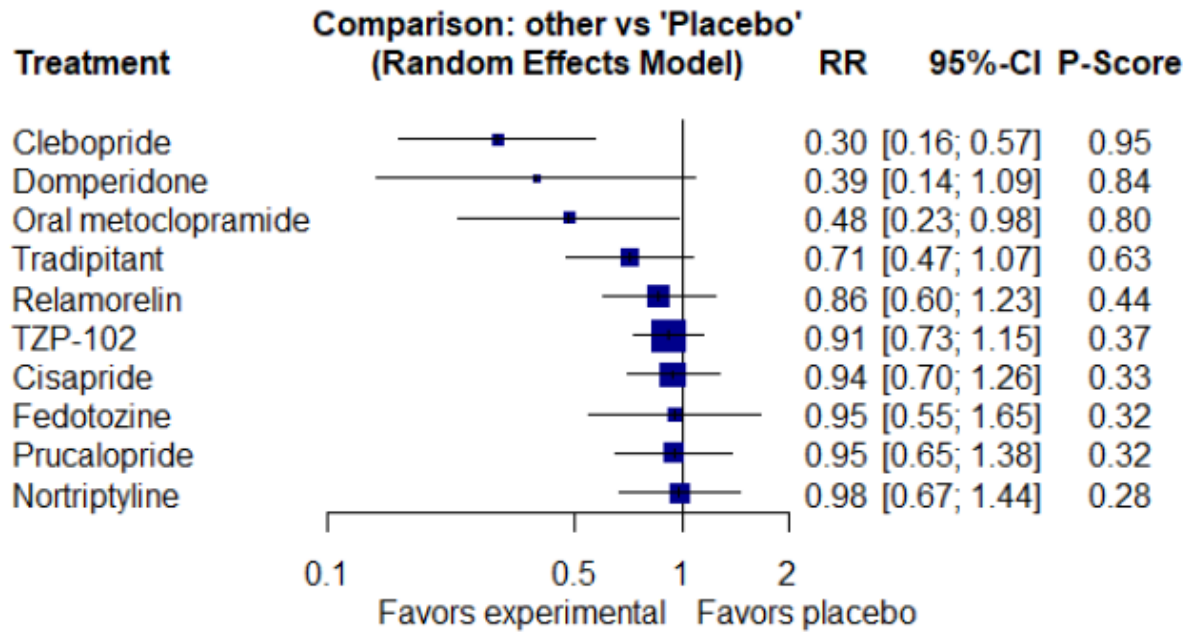
Figure 2. (*A*) Network plot for failure to achieve an improvement in global gastroparesis symptoms: according to drug class. *Circle* (node) size is proportional to the number of study participants assigned to receive each intervention. The *line width* (connection size) corresponds to the number of studies comparing the individual interventions. (*B*) Forest plot for failure to achieve an improvement in global gastroparesis symptoms: according to drug class. The P-score is the probability of each intervention being ranked as best in the network.

Table 2. League Table for Failure to Achieve an Improvement in Global Gastroparesis Symptoms: According to Drug Class

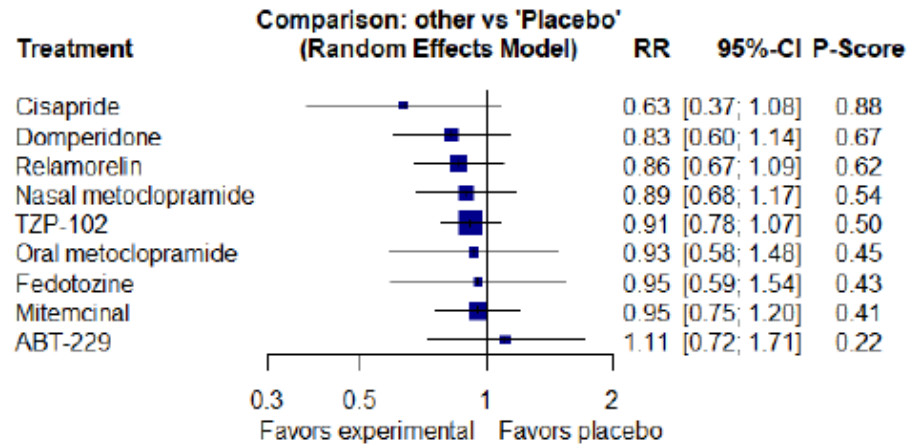
Oral dopamine antagonist		1.97 (0.38–10.22)						**0.56 (0.42–0.75)**
0.84 (0.56–1.25)	Tachykinin-1 antagonist							**0.69 (0.52–0.93)**
0.67 (0.43–1.05)	0.80 (0.51–1.27)	Nasal dopamine antagonist						0.91 (0.63–1.30)
0.65 (0.46–0.90)	0.77 (0.55–1.09)	0.96 (0.65–1.43)	Ghrelin agonist					0.90 (0.75–1.07)
0.61 (0.33–1.11)	0.73 (0.40–1.34)	0.91 (0.48–1.72)	0.94 (0.54–1.65)	Opioid agonist				0.95 (0.56–1.62)
0.59 (0.37–0.94)	0.71 (0.45–1.12)	0.88 (0.53–1.46)	0.92 (0.61–1.37)	0.97 (0.51–1.85)	Tricyclic antidepressant			0.98 (0.69–1.40)
0.58 (0.39–0.86)	0.70 (0.47–1.04)	0.87 (0.56–1.35)	0.90 (0.65–1.25)	0.96 (0.53–1.74)	0.98 (0.63–1.54)	Motilin agonist		1.00 (0.76–1.31)
0.58 (0.41–0.82)	**0.69 (0.49–0.99)**	0.86 (0.57–1.30)	0.90 (0.68–1.18)	0.95 (0.54–1.68)	0.98 (0.65–1.48)	1.00 (0.71–1.40)	5-HT-4 agonist	1.00 (0.82–1.23)
0.58 (0.44–0.77)	**0.69 (0.52–0.93)**	0.86 (0.61–1.23)	0.90 (0.75–1.07)	0.95 (0.56–1.62)	0.98 (0.69–1.40)	1.00 (0.76–1.31)	1.00 (0.82–1.23)	Placebo

NOTE. RR with 95% CIs in parentheses. Comparisons, column vs row, should be read from left to right, and are ordered relative to their overall efficacy. The intervention in the top left position is ranked as best after the network meta-analysis of direct and indirect effects. Direct comparisons are provided above the drug labels, and indirect comparisons are below. Bold values denote a statistically significant difference.

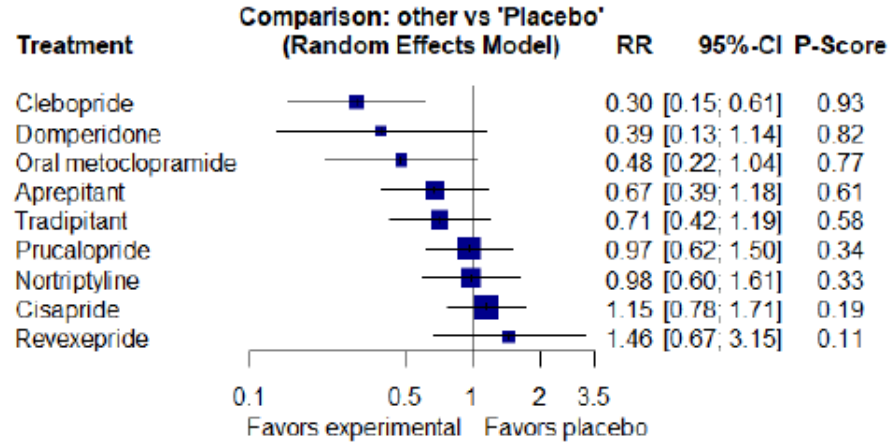
Supplementary Figure 4. Forest Plot for Failure to Achieve an Improvement in Global Gastroparesis Symptoms: Including Only Randomized Controlled Trials That Confirmed Delayed Gastric Emptying in All Patients.



Supplementary Figure 5. Forest Plot for Failure to Achieve an Improvement in Global Gastroparesis Symptoms: Including Randomized Controlled Trials Recruiting Diabetic Gastroparesis Patients Exclusively.



Supplementary Figure 6. Forest Plot for Failure to Achieve an Improvement in Global Gastroparesis Symptoms: Including Only Randomized Controlled Trials Recruiting Idiopathic or Mixed Etiology Gastroparesis Patients.



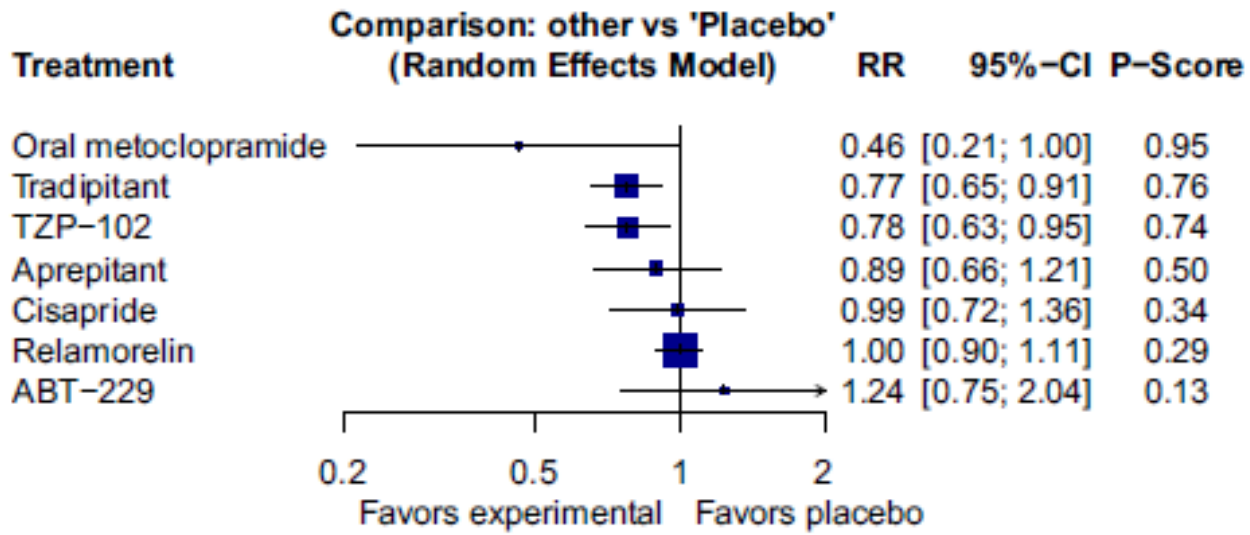
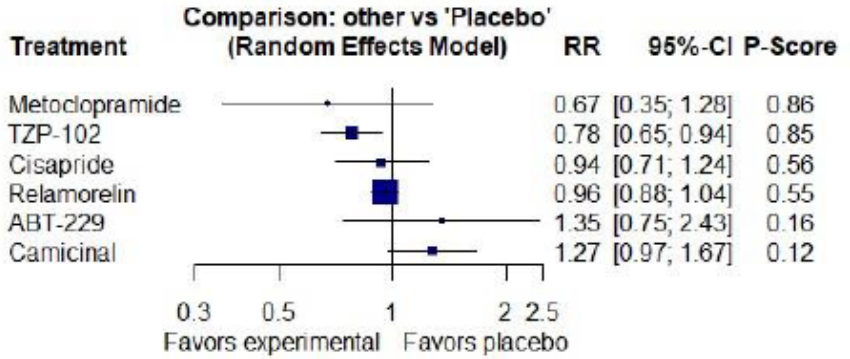
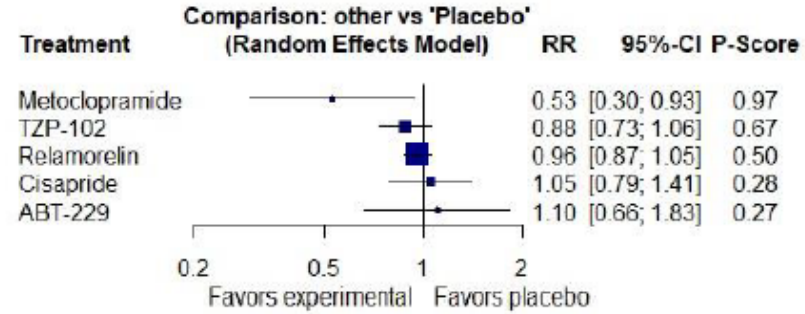


Figure 3. Forest plot for failure to achieve an improvement in nausea. The P-score is the probability of each intervention being ranked as best in the network.

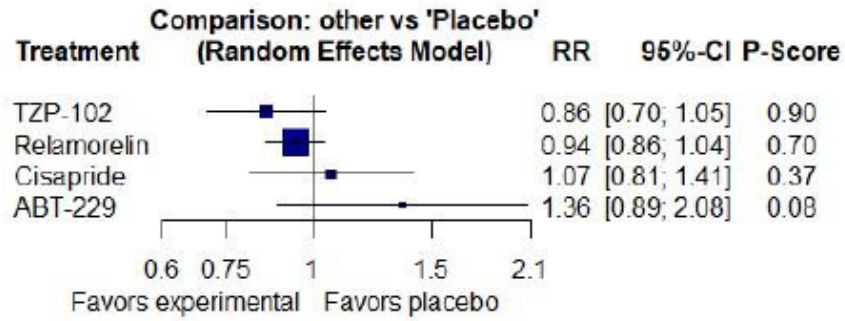
Supplementary Figure 7. Forest Plot for Failure to Achieve an Improvement in Fullness.



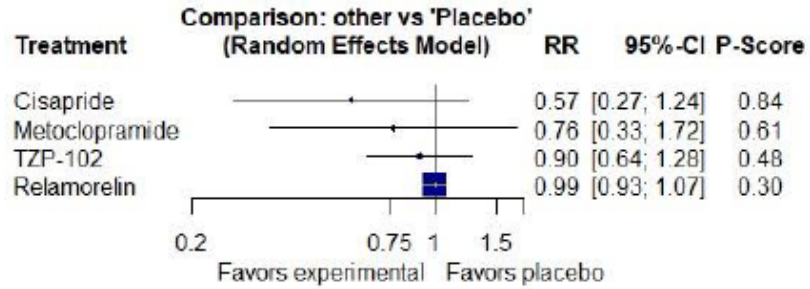
Supplementary Figure 8. Forest Plot for Failure to Achieve an Improvement in Bloating.



Supplementary Figure 9. Forest Plot for Failure to Achieve an Improvement in Abdominal Pain.



Supplementary Figure 10. Forest Plot for Failure to Achieve an Improvement in Vomiting.



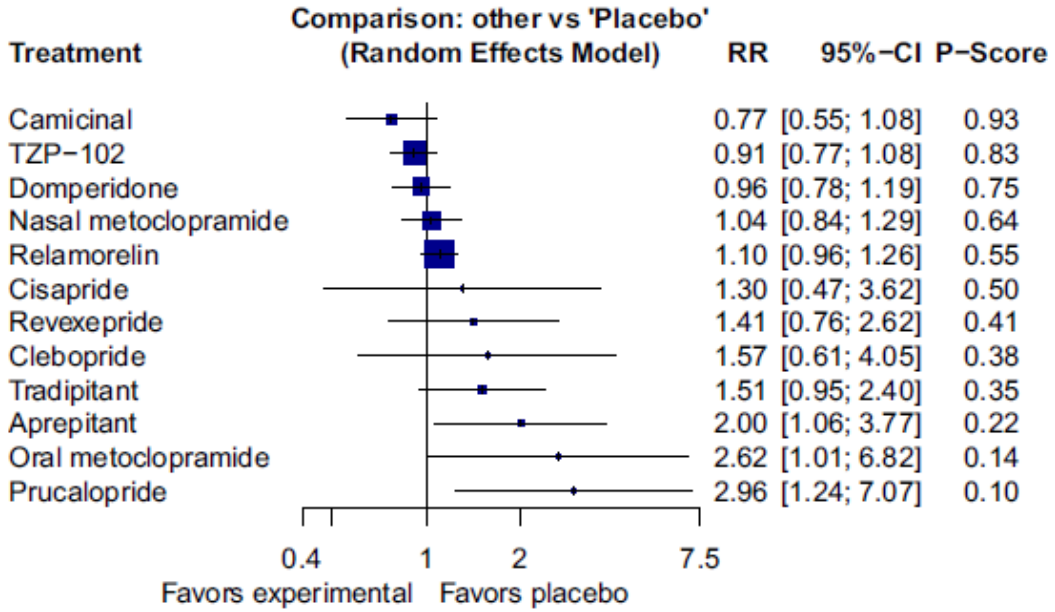
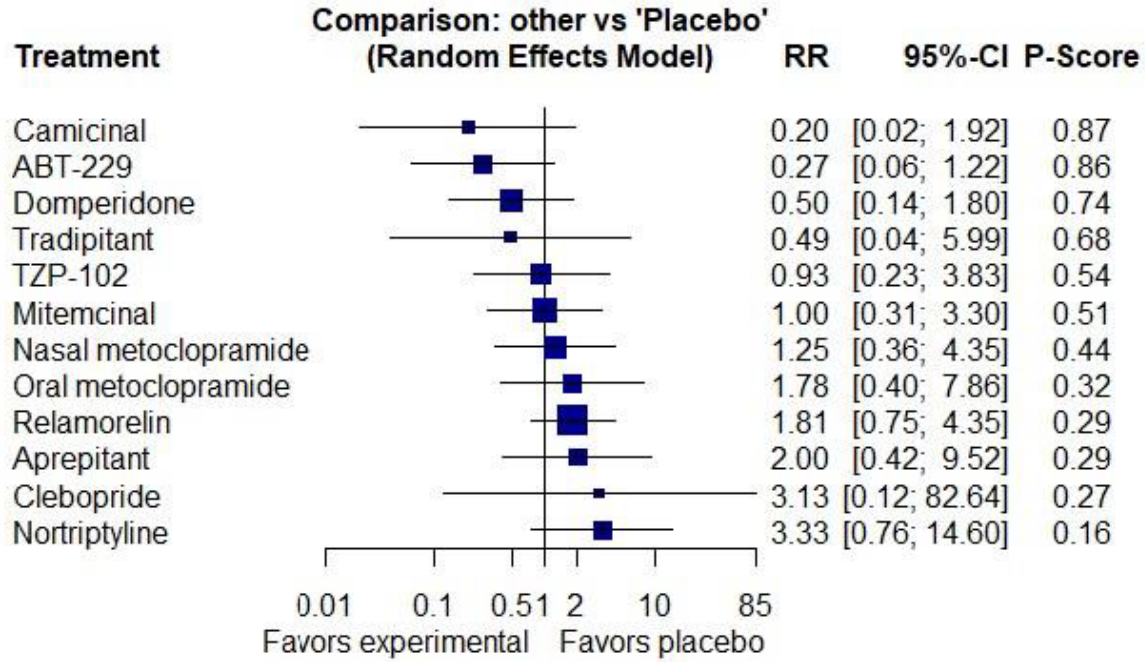


Figure 4. Forest plot for adverse events. The P-score is the probability of each intervention being ranked as best in the network.

Supplementary Figure 11. Forest Plot for Adverse Events Leading to Withdrawal From the Study.



- Globalmente, solo cleboprida y domperidona resultaron superiores a placebo
- En el análisis por clases de fármacos, solo los antagonistas orales de dopamina y los antagonistas de taquiquinina 1
- En estudios con retraso del vaciamiento confirmado, solo cleboprida y metoclopramida
- En gastroparesia diabética, ninguno fue superior a placebo
- En idiopática y mixta, solo cleboprida

Greater Transplant-Free Survival in Patients Receiving Obeticholic Acid for Primary Biliary Cholangitis in a Clinical Trial Setting Compared to Real-World External Controls

Gastroenterology 2022;163:1630–1642

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- Colangitis biliar primaria (CBP): es una enfermedad hepática autoinmune, crónica, rara y grave, de etiología desconocida, que afecta predominantemente a mujeres mayores de 40 años (6:1000). Se caracteriza por una inflamación y destrucción progresiva de origen autoinmune de los pequeños conductos biliares intrahepáticos, que da lugar a una obstrucción del flujo biliar, provocando daño en el tejido hepático por la acumulación de ácidos biliares en los hepatocitos. Esta inflamación y destrucción de los conductos biliares da lugar a un cuadro clínico de colestasis, que puede progresar a fibrosis, y finalmente cirrosis e insuficiencia hepática que puede llevar a descompensación hepática y muerte a menos que reciban un trasplante hepático.
- Tratamiento de primera línea: ácido ursodeoxicólico (UDCA), mejora supervivencia libre de transplante
- >40 % respuesta inadecuada, requieren segunda línea: ácido obeticólico (OCA), agonista selectivo del receptor X farnesoide (FXR), demostró reducción sostenida de ALP y bilirrubina (estudio POISE), pero está pendiente de demostrar beneficio clínico
- En POISE, tras fase doble ciego de 12 meses, se pasó a extensión abierta: el brazo placebo recibe UDCA, el otro mantiene OCA. Grupo de control externo no tratado con OCA con respuesta inadecuada a UDCA (registros Global PBC y UK PBC). Seguimiento 5 años
- Objetivo primario: eficacia a largo plazo de OCA comparando tiempo hasta transplante hepático o muerte. Objetivo secundario: descompensación hepática (ascitis, encefalopatía, PBE, hemorragia por varices)

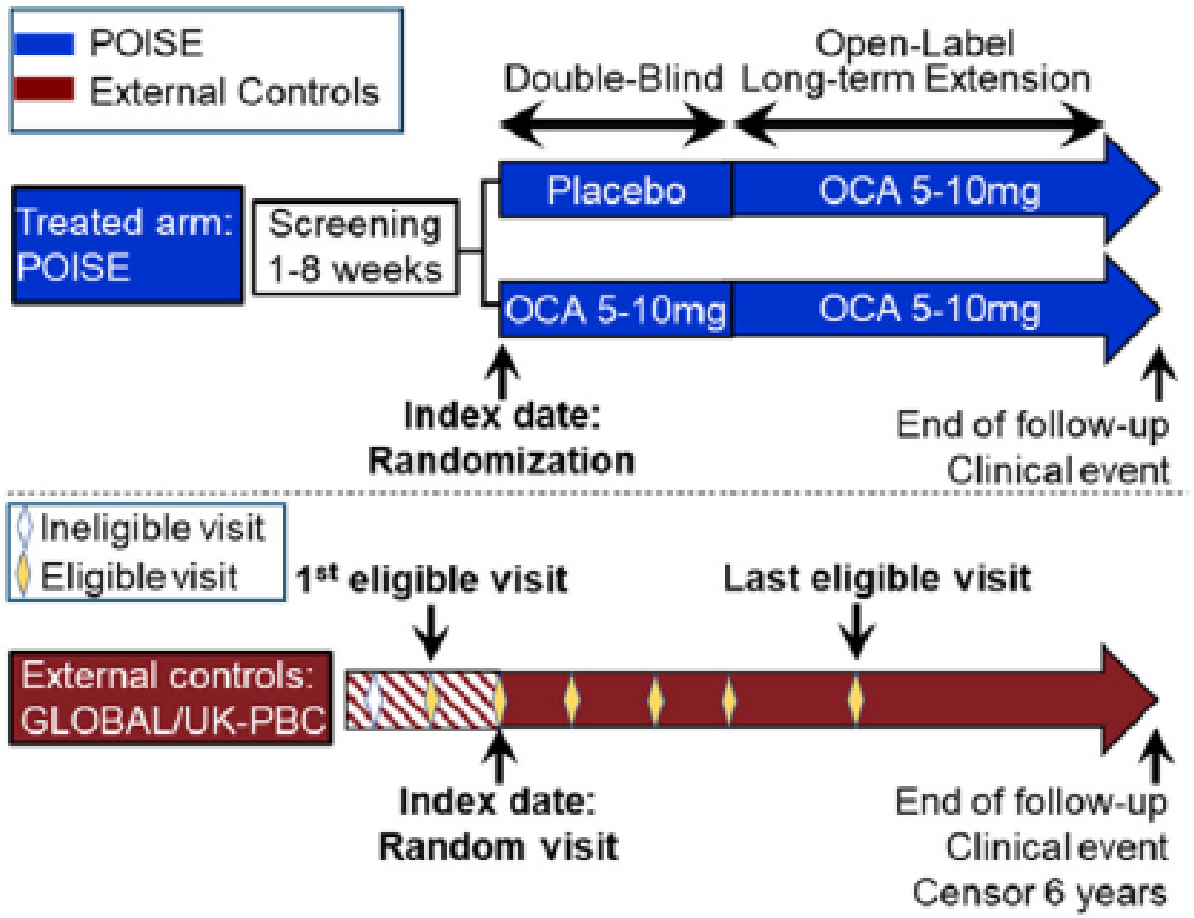
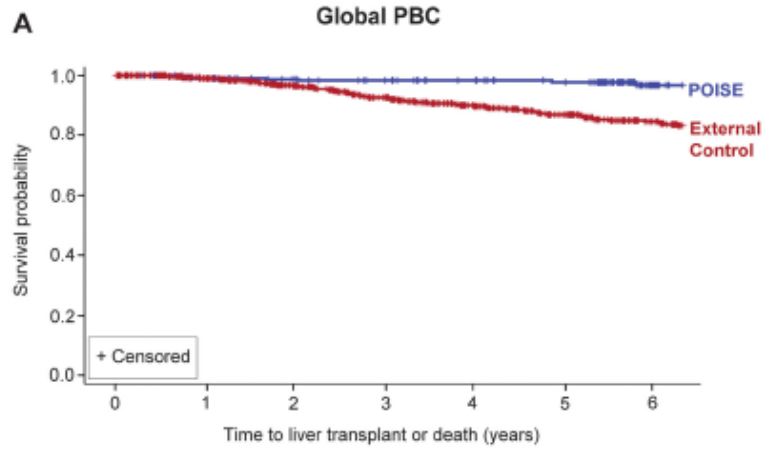

POISE
External Controls
Double-Blind
Open-Label
Long-term Extension
Treated arm:
POISE
Screening
1-8 weeks
Placebo
OCA 5-10mg
OCA 5-10mg
OCA 5-10mg
Index date:
Randomization
End of follow-up
Clinical event
Ineligible visit
Eligible visit
1st eligible visit
Last eligible visit
External controls:
GLOBAL/UK-PBC
Index date:
Random visit
End of follow-up
Clinical event
Censor 6 years

Table 1. Baseline (Unmatched) Characteristics of the POISE Open-Label Extension, Global PBC, and UK-PBC Cohorts

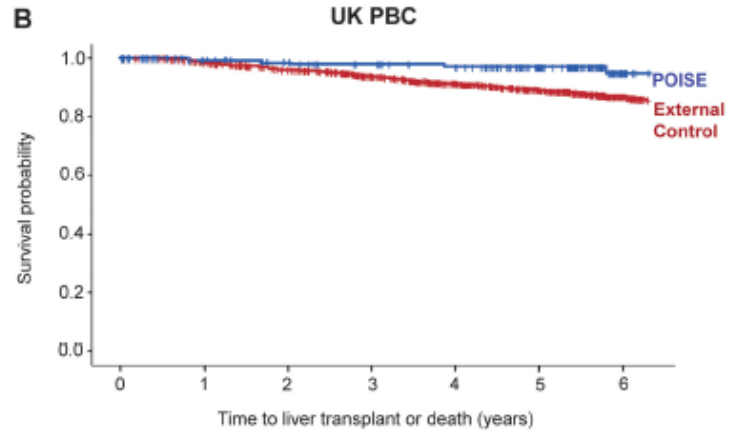
Characteristic	POISE OLE (n = 209)	Global PBC (n = 1381)	UK-PBC (n = 2135)
Female, n (%)	190 (90.9)	1253 (90.7)	1907 (89.3)
UDCA, n (%)	197 (94.3)	1265 (91.6)	1849 (86.6)
UDCA dose, *mg*, median (IQR)[a]	1000 (900–1250)	900 (750–1050)	1000 (750–1000)
Duration of UDCA treatment, *mo*, median (IQR)	46 (20–95)	40 (16–90)	48 (12–89)
Year of diagnosis, median (IQR)	2005 (2000–2009)	1999 (1994–2003)	2004 (2000–2009)
Year of visit, median (IQR)	2012 (2012–2012)	2005 (2000–2009)	2011 (2006–2015)
Age, *y*, mean (SD)	55.7 (10.6)	56.9 (12.3)	60.55 (11.6)
Duration of disease, *y*, median (IQR)	7.8 (3.6–12.6)	4.5 (2.1–7.9)	4.5 (1.7–9.1)
ALP, ×*ULN*, median (range)	2.41 (2.00–3.15)	2.08 (1.75–2.81)	2.16 (1.78–3.03)
Bilirubin, ×*ULN*, median (range)	0.47 (0.34–0.67)	0.67 (0.45–1.09)	0.57 (0.40–1.00)
AST, ×*ULN*, median (range)	1.68 (1.20–2.36)	1.20 (0.88–1.78)	—
ALT, ×*ULN*, median (range)	2.09 (1.44–3.02)	—	1.16 (0.74–1.84)
Cirrhosis at inclusion, n (%)	36 (17.2)	197 (14.3)	—

NOTE. The samples were closely aligned on baseline characteristics before propensity scoring. Year of index visit was earlier for the Global PBC cohort and duration of disease was higher for the POISE group. Both variables were included in the propensity score.

[a]UDCA baseline dose data were available for 1169 patients in Global PBC and 201 patients in UK-PBC.



HR = 0.29
95% CI 0.10, 0.83
P = 0.02



HR = 0.30
95% CI 0.12, 0.75
P < 0.01

Total Number of Events	POISE (n=5)	Global PBC (n=135)	UK PBC (n=281)
Liver transplantation	2	51	119
Death	3	84	162

Figure 3. Kaplan-Meier curves for transplant-free survival comparing POISE with Global PBC (*A*) and UK-PBC (*B*) external controls. *UK-PBC: ALT included as a covariate. Kaplan-Meier curves for transplant-free survival comparing POISE with Global PBC (*A*) and UK-PBC (*B*) begin separating at 12–18 months. During the 6-year follow-up period, there were 5 composite events in 209 subjects in the POISE study, 135 events in 1381 patients in the Global PBC external control group, and 281 events in 2135 patients in the UK-PBC control group.

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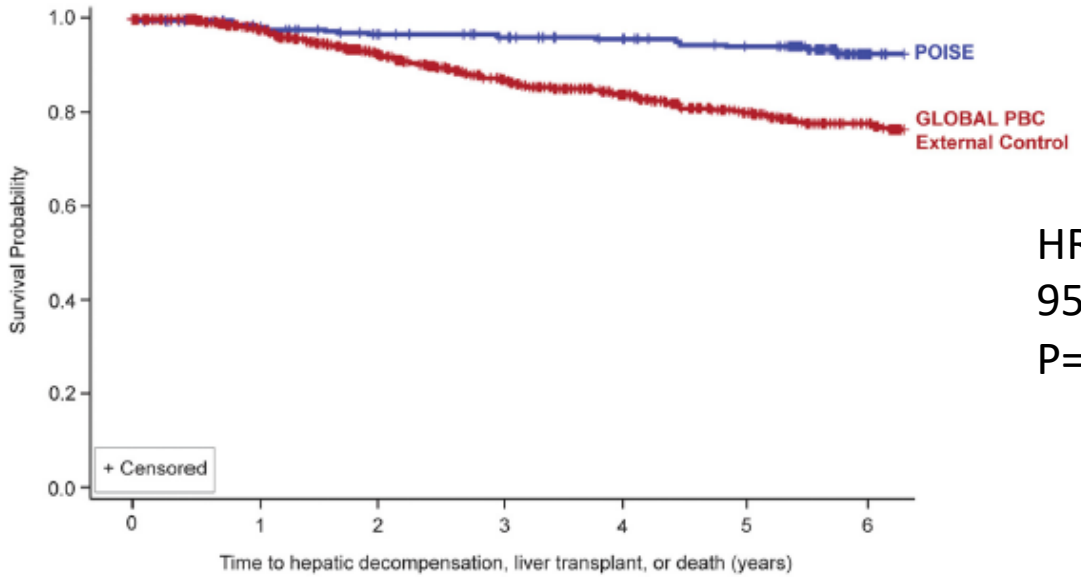
Figure 5. Kaplan-Meier curves for time to first occurrence of hepatic decompensation, liver transplantation, or death comparing POISE with Global PBC external controls (random visit). *Of the 2 patients with liver transplantation in the primary outcomes analysis, 1 had hepatic decompensation before the transplantation in the secondary outcomes analysis. Patients treated with OCA in a trial setting had significantly greater event-free survival (composite end point of decompensation, liver transplantation, or death) than patients in the Global PBC external control group (HR, 0.42; 95% CI, 0.21–0.85; $P = .02$).



FIRST EVENT	POISE (n=16)	Global PBC (n=212)
Decompensation	12	126
Liver Transplant*	1	23
Death	3	63

HR=0,42
95% CI, 0.21-0.86
P=0.02

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- Conclusión: OCA se asocia a una reducción en muerte, transplante hepático o descompensación en pacientes con CBP
- Recomendación: iniciar tratamiento de segunda línea con OCA en pacientes que no toleran UDCA o presentan una respuesta inadecuada a los 6-12 meses de tratamiento

- Limitaciones:
  - no aleatorización
  - posibilidad de sesgo de selección en POISE (pacientes menos enfermos)
  - escaso número de eventos
  - información limitada sobre la estabilidad de dosis de UDCA en cohorte UK-PBC

Vonoprazan Versus Lansoprazole for Healing and Maintenance of Healing of Erosive Esophagitis: A Randomized Trial

Gastroenterology 2023;164:61–71

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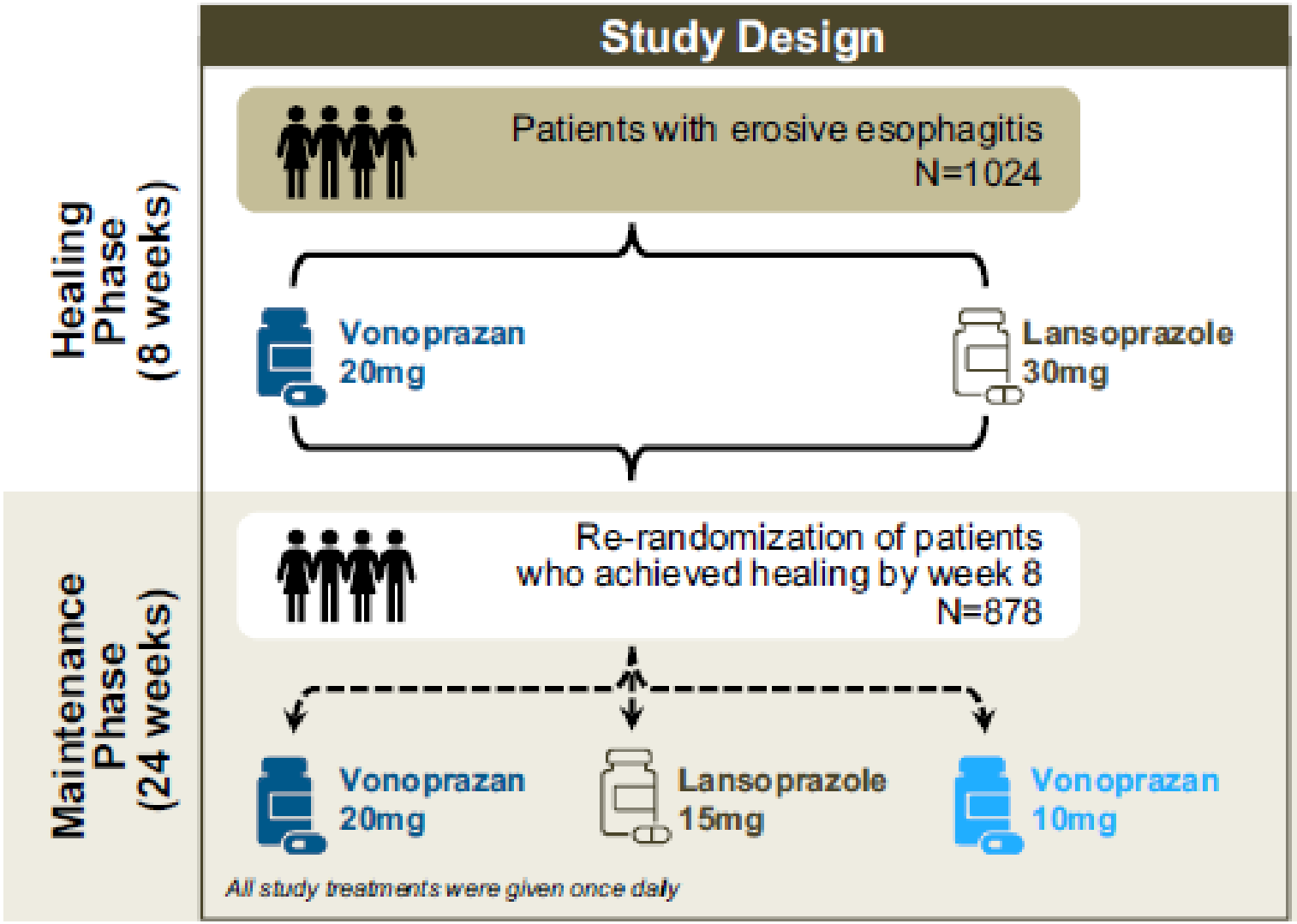
- ERGE: prevalencia estimada EEUU 21%
- Complicación más común: esofagitis erosiva (en 25 a 50%)
- Tratamiento de elección: IBP, mantenido en esofagitis severas (grados C y D de Los Angeles)
- Fracaso terapéutico en 5-20%, hasta 30% en casos severos, y recurrencia a los 12 meses en 10 a 45%
- IBP solo inhiben bombas de protones activas, son ácido-lábiles, precisan cubierta entérica, tienen una vida media corta (1-2 horas), por lo que deben tomarse 30-60 minutos antes de una comida, requieren varios días para alcanzar la máxima supresión ácida
- Vonoprazan: bloqueante competitivo de los canales de potasio, ácido estable, alcanza concentraciones altas y sostenidas rápidamente (vida media de 9 horas) con lo que consigue una supresión ácida máxima después de una sola dosis
- No se metaboliza por CYP2C19 y CYP3A4, con menos interacciones y variación individual

- Ensayo doble ciego, randomizado, grupos paralelos comparando dos dosis de vonoprazam frente a las dosis aprobadas de lansoprazol para la curación y el mantenimiento de la curación en pacientes con esofagitis erosiva en Europa y EEUU

- Incluyen: adultos con esofagitis erosiva en endoscopia

- Excluyen: infección por *Helicobacter pylori,* esófago de Barrett e infección COVID 19


Study Design
Healing Phase (8 weeks)
Patients with erosive esophagitis
N=1024
Vonoprazan 20mg
Lansoprazole 30mg
Maintenance Phase (24 weeks)
Re-randomization of patients who achieved healing by week 8
N=878
Vonoprazan 20mg
Lansoprazole 15mg
Vonoprazan 10mg
All study treatments were given once daily

Healing Phase

Primary Endpoint
Non-inferiority: The % of subjects who had complete healing of erosive esophagitis by week 8

Non-inferiority: The % of 24-hour heartburn-free days over the healing phase

Superiority: The % of LA Grade C/D subjects who had healing at week 2

Superiority: The % of subjects with onset of sustained resolution of heartburn by day 3

Superiority: The % of LA Grade C/D subjects who had healing by week 8

Superiority: The % of subjects (all grades) who had healing at week 2

Maintenance Phase

Primary Endpoint* – Vonoprazan 10mg and 20mg
Non-inferiority: The % of subjects (all grades) who maintained healing at week 24

Vonoprazan 20mg

Superiority: The % of LA Grade C/D subjects who maintained healing at week 24

Vonoprazan 20mg

Superiority: The % of subjects (all grades) who maintained healing at week 24

Vonoprazan 20mg

Non-inferiority: The % of 24-hour heartburn-free days through week 24

Vonoprazan 10mg

Superiority: The % of LA Grade C/D subjects who maintained healing at week 24

Vonoprazan 10mg

Superiority: The % of subjects (all grades) who maintained healing at week 24

Vonoprazan 10mg

Non-inferiority: The % of 24-hour heartburn-free days through week 24

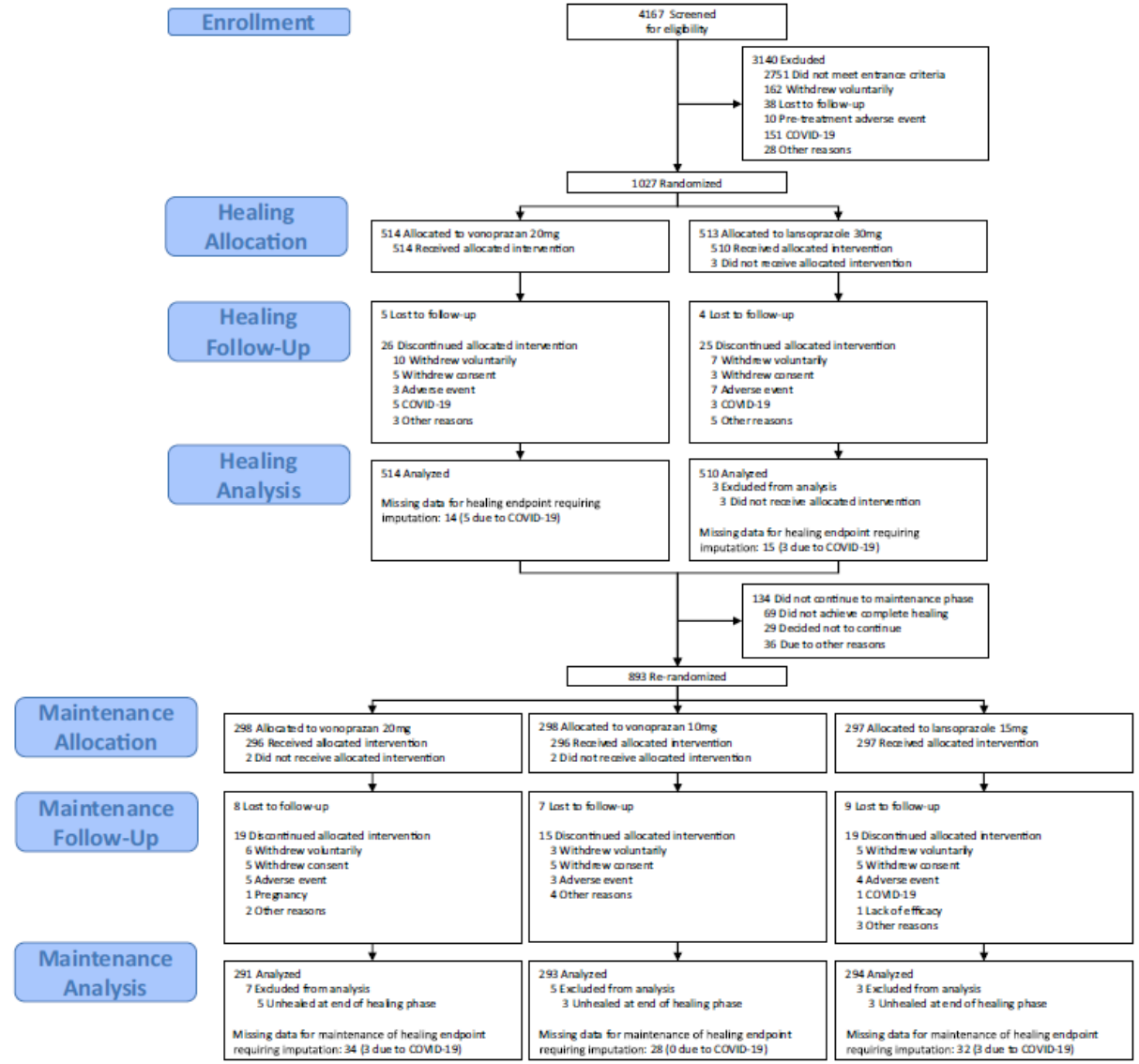


Figure 2. Flow diagram showing progression of patients through the study.

Table 1. Selected Baseline Characteristics of Treatment Groups

Characteristics	Healing phase		Maintenance phase		
	Vonoprazan, 20 mg (n = 514)	Lansoprazole, 30 mg (n = 510)	Vonoprazan, 20 mg (n = 291)	Vonoprazan, 10 mg (n = 293)	Lansoprazole, 15 mg (n = 294)
Age, mean (SD), *y*	51.0 (13.4)	51.7 (14.1)	51.0 (14.5)	52.3 (13.8)	51.0 (13.0)
Female sex	256 (49.8)	287 (56.3)	146 (50.2)	159 (54.3)	171 (58.2)
Geographic region					
US	325 (63.2)	316 (62.0)	159 (54.6)	178 (60.8)	195 (66.3)
Europe	189 (36.8)	194 (38.0)	132 (45.4)	115 (39.2)	99 (33.7)
Race					
White	474 (92.2)	455 (89.2)	269 (92.4)	267 (91.1)	265 (90.1)
Black	23 (4.5)	41 (8.0)	17 (5.8)	15 (5.1)	20 (6.8)
Asian	7 (1.4)	6 (1.2)	3 (1.0)	4 (1.4)	3 (1.0)
Other/unknown	10 (1.9)	8 (1.6)	2 (0.7)	7 (2.4)	6 (2.0)
Latin American ethnicity	62 (12.1)	58 (11.4)	33 (11.3)	31 (10.6)	31 (10.5)
BMI, mean (SD), kg/m^2	30.8 (6.0)	31.5 (6.6)	31.0 (6.7)	31.6 (6.8)	31.1 (6.1)
Current smoker	77 (15.0)	70 (13.7)	38 (13.1)	39 (13.3)	42 (14.3)
Any alcohol use	313 (60.9)	315 (61.8)	187 (64.3)	183 (62.5)	180 (61.2)
PPI use	163 (31.7)	164 (32.2)	86 (29.6)	94 (32.1)	94 (32.0)
Cytochrome P450 2C19 status					
Extensive metabolizer	411 (80.0)	402 (78.8)	238 (81.8)	245 (83.6)	242 (82.3)
Poor metabolizer	9 (1.8)	9 (1.8)	6 (2.1)	4 (1.4)	6 (2.0)
Missing	94 (18.3)	99 (19.4)	47 (16.2)	44 (15.0)	46 (15.6)
Baseline erosive esophagitis					
LA Grade A	168 (32.7)	184 (36.1)	106 (36.4)	110 (37.5)	101 (34.4)
LA Grade B	169 (32.9)	152 (29.8)	93 (32.0)	88 (30.0)	97 (33.0)
LA Grade C	154 (30.0)	156 (30.6)	81 (27.8)	86 (29.4)	92 (31.3)
LA Grade D	23 (4.5)	18 (3.5)	11 (3.8)	9 (3.1)	4 (1.4)
Mean heartburn severity score (0-4)[a]	1.3 (0.8–2.0)	1.3 (0.6–1.9)	1.2 (0.7–1.8)	1.3 (0.6–1.9)	1.3 (0.6–2.0)
Days with heartburn	7 (5–7)	6 (4–7)	6 (4–7)	6 (4–7)	6 (4–7)
Serum gastrin ≥200 pg/mL	6 (1.2)	8 (1.6)	5 (1.7)	2 (0.7)	5 (1.7)
Serum gastrin, mean (SD), *pg/mL*	29.8 (45.6)	32.3 (62.8)	124.8 (158.6)	125.0 (147.7)	117.5 (121.4)

NOTE. Data are presented as n (%) or median (interquartile range), unless indicated otherwise.
SD, standard deviation.
[a]Mean severity of heartburn was calculated for each patient using the highest severity of heartburn (daytime or nighttime) recorded for each of the 7 days before treatment initiation. The median of the mean severities across the treatment group is presented.

Table 2. Primary and Secondary Efficacy End Points in Predefined Fixed-Sequence Analyses for Healing Phase

Efficacy end point	Vonoprazan, 20 mg (n = 514)	Lansoprazole, 30 mg (n = 510)	Difference (95% CI)
Healing by week 8, %	92.9	84.6	8.3 (4.5–12.2)[a,b]
24-hour heartburn-free days, mean (SD), %	66.8 (34.6)	64.1 (35.5)	2.7 (−1.6 to 7.0)[c]
Healing at week 2 in LA Grade C/D, %[d]	70.2	52.6	17.6 (7.4–27.4)[e]
Onset of sustained resolution of heartburn by day 3, n (%)	177 (34.4)	164 (32.2)	2.3 (−3.5 to 8.0)
Healing by week 8 in LA Grade C/D, %[d,f]	91.7	72.0	19.6 (11.8–27.6)
Healing at week 2, %[f]	74.3	68.2	6.1 (0.5–11.6)

SD, standard deviation.
[a]Noninferiority established in primary analysis (noninferiority margin was 10%, which required lower bound of 95% CI to be −10%; *P* for noninferiority .0001).
[b]*P* .0001 for superiority in predefined exploratory analysis performed after noninferiority established in primary analysis.
[c]Noninferiority established in predefined fixed-sequence analysis of secondary end point (noninferiority margin was 15%, which required lower bound of 95% CI to be −15%).
[d]Number for LA Grade C/D end points was 177 for vonoprazan and 174 for lansoprazole.
[e]*P* = .0008 for superiority in predefined fixed-sequence analysis of the secondary end point.
[f]Hypothesis testing was not performed because prior end point (sustained heartburn resolution) did not show superiority in fixed-sequence analysis.

Table 3. Primary and Secondary Efficacy End Points in Predefined Fixed-Sequence Analyses for Maintenance Phase

Efficacy end point	Vonoprazan, 20 mg(n = 291)	Vonoprazan, 10 mg(n = 293)	Lansoprazole, 15 mg(n = 294)	Difference (95% CI) vonoprazan, 20 mg, vs lansoprazole, 15 mg	Difference (95% CI) vonoprazan, 10 mg, vs lansoprazole 15 mg
Healing maintained, %	80.7	79.2	72.0	8.7 (1.8–15.5)[a,b]	7.2 (0.2–14.1)[a,b]
Healing maintained in LA Grade C/D, %[c]	77.2	74.7	61.5	15.7 (2.5–28.4)[d]	13.3 (0.02–26.1)[d]
24-hour heartburn-free days, mean (SD), %	80.6 (30.0)	80.9 (28.6)	78.6 (27.5)	2.0 (−2.6 to 6.7)[e]	2.3 (−2.3 to 6.8)[e]

SD, standard deviation.
[a]Noninferiority established in primary analyses (noninferiority margin was 10%, which required lower bound of 95% CI to be −10%; *P* for noninferiority .0001).
[b]*P* values for superiority were .014 for 20 mg and .044 for 10 mg in predefined fixed-sequence analyses performed after noninferiority established in primary analyses.
[c]Number for LA Grade C/D end point was 95 for vonoprazan, 10 mg, 92 for vonoprazan, 20 mg, and 96 for lansoprazole.
[d]*P* values for superiority were .020 for 20 mg and .049 for 10 mg in predefined fixed-sequence analyses of secondary end point.
[e]Noninferiority established in predefined fixed-sequence analyses of secondary end point (noninferiority margin was 15%, which required lower bound of 95% CI to be −15%).

Table 4. Safety and Tolerability of Treatment Groups in Patients Receiving at Least 1 Dose of Study Medication

	Healing phase		Maintenance phase		
Variable	Vonoprazan, 20 mg (n = 514)	Lansoprazole, 30 mg (n = 510)	Vonoprazan, 20 mg (n = 296)	Vonoprazan, 10 mg (n = 296)	Lansoprazole, 15 mg (n = 297)
Adverse events	155 (30.2)	149 (29.2)	167 (56.4)	160 (54.1)	150 (50.5)
Severe adverse events	2 (0.4)	4 (0.8)	17 (5.7)	8 (2.7)	8 (2.7)
Serious adverse events	3 (0.6)	3 (0.6)	14 (4.7)	10 (3.4)	7 (2.4)
Adverse event leading to treatment discontinuation	5 (1.0)	11 (2.2)	8 (2.7)	2 (0.7)	2 (0.7)
COVID-19	11 (2.1)	9 (1.8)	30 (10.1)	18 (6.1)	20 (6.7)
Clostridium difficile infection	0	0	0	0	0
Bone fracture	1 (0.2)	0	4 (1.4)	2 (0.7)	1 (0.3)
ALT or AST 3× upper limit of normal	2 (0.4)	1 (0.2)	1 (0.3)	3 (1.0)	6 (2.0)
Serum gastrin, mean (SD), *pg/mL*	158.3 (143.6)	64.1 (68.6)	223.0 (216.6)	166.0 (189.8)	74.1 (96.1)
Serum gastrin 500 pg/mL	22 (4.3)	7 (1.4)	47 (15.9)	33 (11.1)	4 (1.3)

NOTE. Data are presented as n (%) unless indicated otherwise.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; SD, standard deviation.

Results

Vonoprazan 20mg

Lansoprazole 30mg

Difference between arms (95% CI)

92.9%	8.3% (4.5–12.2)	84.6%	All patients
91.7%	19.6% (11.8–27.6)	72.0%	LA Grades C/D

Vonoprazan 20mg

Lansoprazole 15mg

Vonoprazan 10mg

Difference between arms (95% CI)				Difference between arms (95% CI)		
80.7%	8.7% (1.8–15.5)	72.0%	All patients	72.0%	7.2% (0.2–14.1)	79.2%
77.2%	15.7% (2.5–28.4)	61.5%	LA Grades C/D	61.5%	13.3% (0.02–26.1)	74.7%

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- Conclusión:

- vonoprazan resultó no inferior a lansoprazol para la curación y mantenimiento de la curación en pacientes con esofagitis erosiva, y alcanzó mayores tasas de curación y mantenimiento de la curación, sobre todo en esofagitis más severas (C y D de Los Angeles), y ya a partir de la segunda semana de tratamiento

- Limitaciones: población de estudio (fundamentalmente blancos europeos y EEUU), no generalizable a *H. pylori*