

MÁSTER EN HEPATOLOGÍA

UAM
Universidad Autónoma
de Madrid

 Universidad
de Alcalá

Asignatura: Cirrosis II

“Hemorragia aguda por varices”

Rafael Bañares

Agustín Albillos

Caso clínico

Varón, 51 años

Cirrosis de etiología alcohólica

Hemorragia por varices esofágicas en 2019

Profilaxis con propranolol (20 mg/12h) y LEB (última sesión 19/09/19)

Trombosis vena esplénica tratada con HBPM durante 8 meses

Día 0

Melena, rectorragia y síncope

Ibuprofeno desde 1 sem antes por infección VRA

TA 95/58, 64 lpm

No asterixis.

Hb 6 g/dl, plaq 49000

bilir 0.90 mg/dl, INR 1.2, crea 0.8 mg/dl, albúmina 3.2 g/dl

Child B-7

ECO: ascitis, porta permeable, trombosis parcial crónica vena esplénica

PEO: VE con pezones de fibrina, LE 4 bandas

GOV2 sin estigmas hemorragia

Tratamiento:

- LEB

- Somatostatina bolo + perfusión, ceftriaxona 1 g, pantoprazol perfusión

- Transfusión 3 conc hematíes

Caso clínico

Día 3

Hematemesis masiva y shock
Traslado a UCI
IOT → PEO → extubación

PEO: VE grandes, sangre en esófago que dificulta visión
Colocación prótesis Danis

Transfusión 6 CH
Estabilización hemodinámica

Indica **TIPS rescue**

TAC: confirma hallazgos ECO

Día 4

TIPS: prótesis cubierta, presión porta/VCI final 17/7 mmHg

Día 5

Retirada prótesis Danis
Continua con profilaxis con ceftriaxona IV

Día 11

Alta a planta

Día 12

Somnolencia y disnea
Neumonía broncoaspirativa
Piperacilina-tazobactam IV

Baveno VII

- All patients with AVB should undergo abdominal imaging, preferably contrast-enhanced cross-sectional imaging (CT or MRI) to exclude splanchnic vein thrombosis, hepatocellular carcinoma and to map portosystemic collaterals in order to guide treatment (D1) (New)

Caso clínico

Preguntas

¿Optimización del tratamiento estándar?

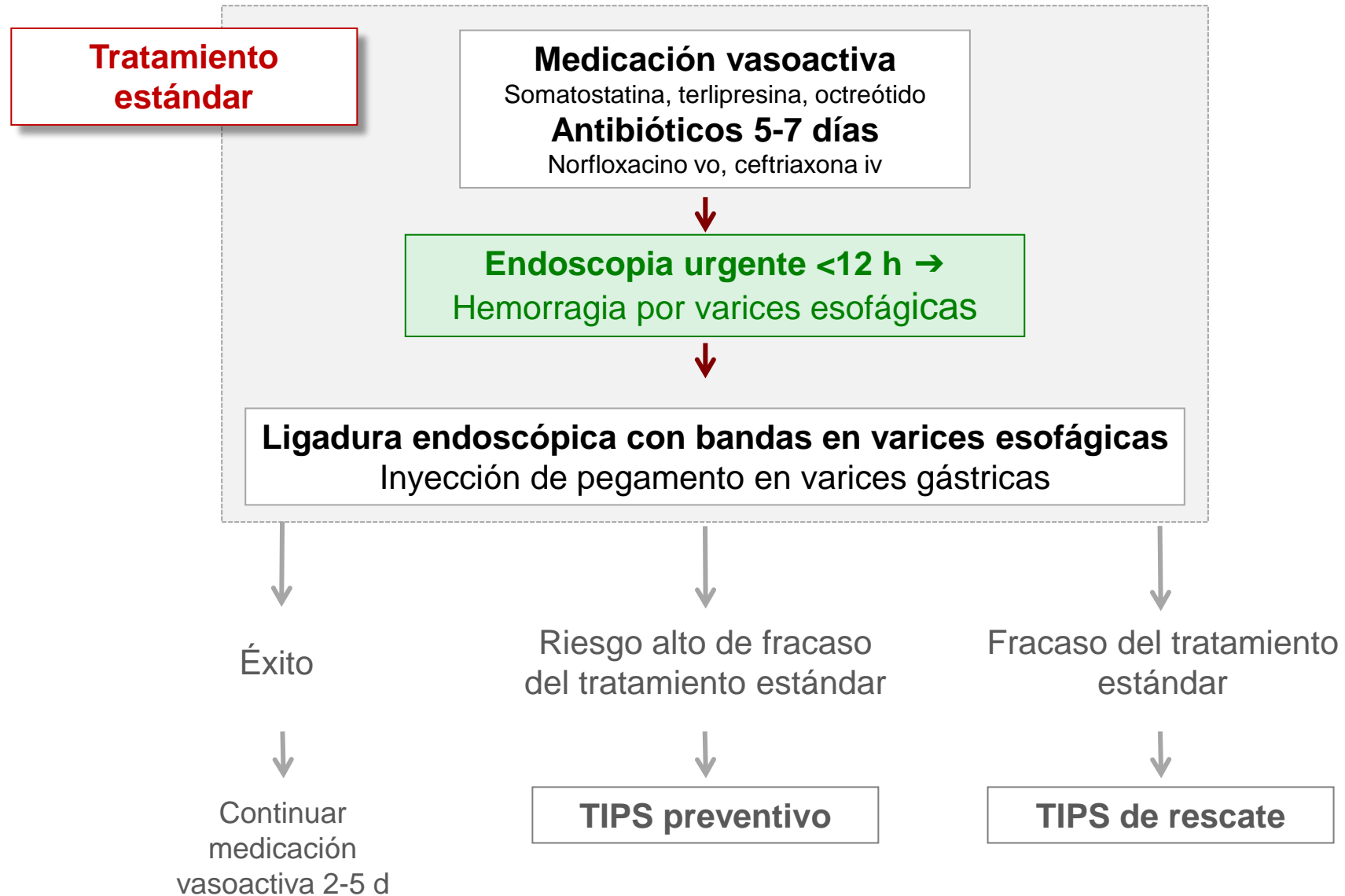
¿Están indicados los IBP?

¿Cuál es el mejor antibiótico?

¿Balón vs. prótesis de Danis?

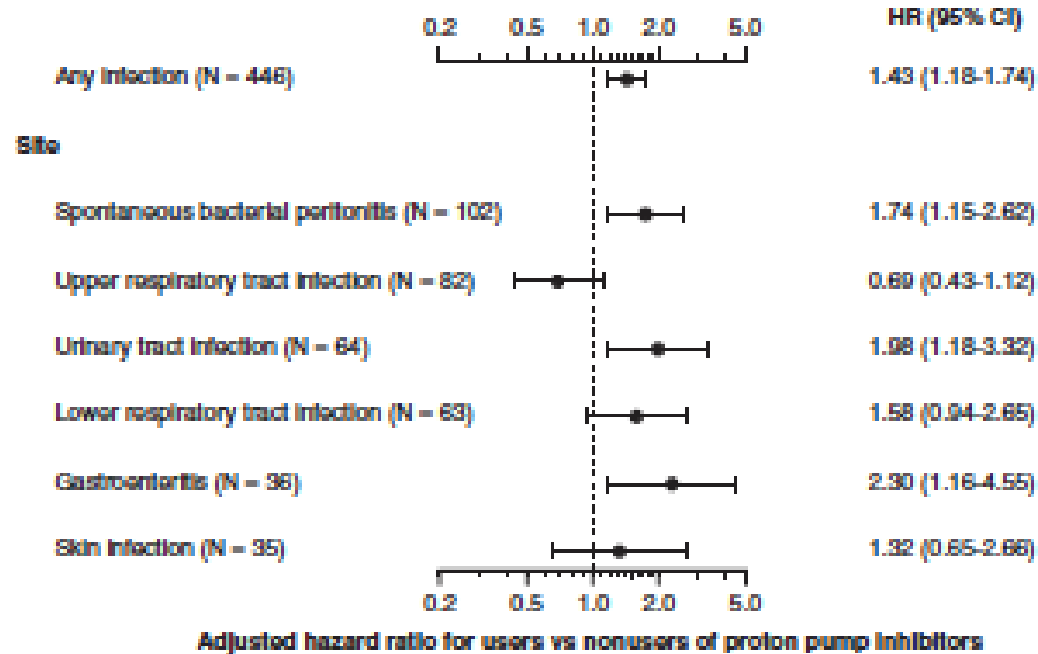
¿Indicación de TIPS preventivo?

Tratamiento de la hemorragia aguda por varices esofagogástricas



Riesgo de infección y encefalopatía en pacientes con cirrosis tratados con IBP

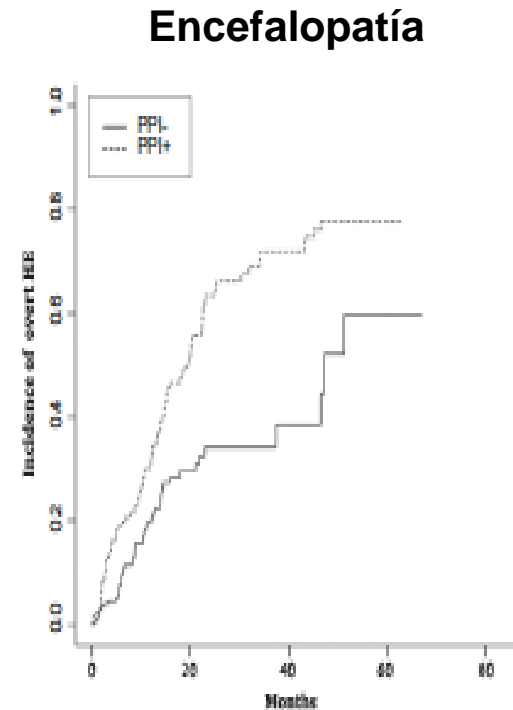
Hazard ratio ajustado de infección IBP vs. no IBP en cirrosis con ascitis



40% usan IBP

G Dam et al. *Liv Int* 2018

Riesgo encefalopatía en pacientes con cirrosis tratados con IBP



S Nardelli et al.
Hepatology 2019

Estratificados por IBP

	Risk of hepatic encephalopathy		
	Users, n (%)	Nonusers, n (%)	OR (95% CI) ^a
Pantoprazole	120 (10.3)	42 (3.6)	2.05 (1.39-3.03)
Lansoprazole	193 (16.6)	100 (8.6)	1.40 (1.05-1.87)
Omeprazole	125 (10.7)	64 (5.5)	1.38 (1.03-1.96)
Esomeprazole	176 (15.1)	95 (8.1)	1.35 (1.01-1.71)
Rabeprazole	57 (4.9)	28 (2.4)	1.43 (0.87-2.34)

Riesgo dosis dependiente

CH Tsai et al.
Gastroenterology 2017

Baveno VII

- PPIs, when started before endoscopy, should be stopped immediately after the procedure unless there is a strict indication to continue them (D2) (New)

Riesgo de infección bacteriana respiratoria en pacientes con hemorragia por varices en profilaxis antibiótica

- Estudio observacional, 2011-2015
- 1656 (**94%**) profilaxis antibiótica (76%C3G, FQ)

Infección bacteriana en ~20%

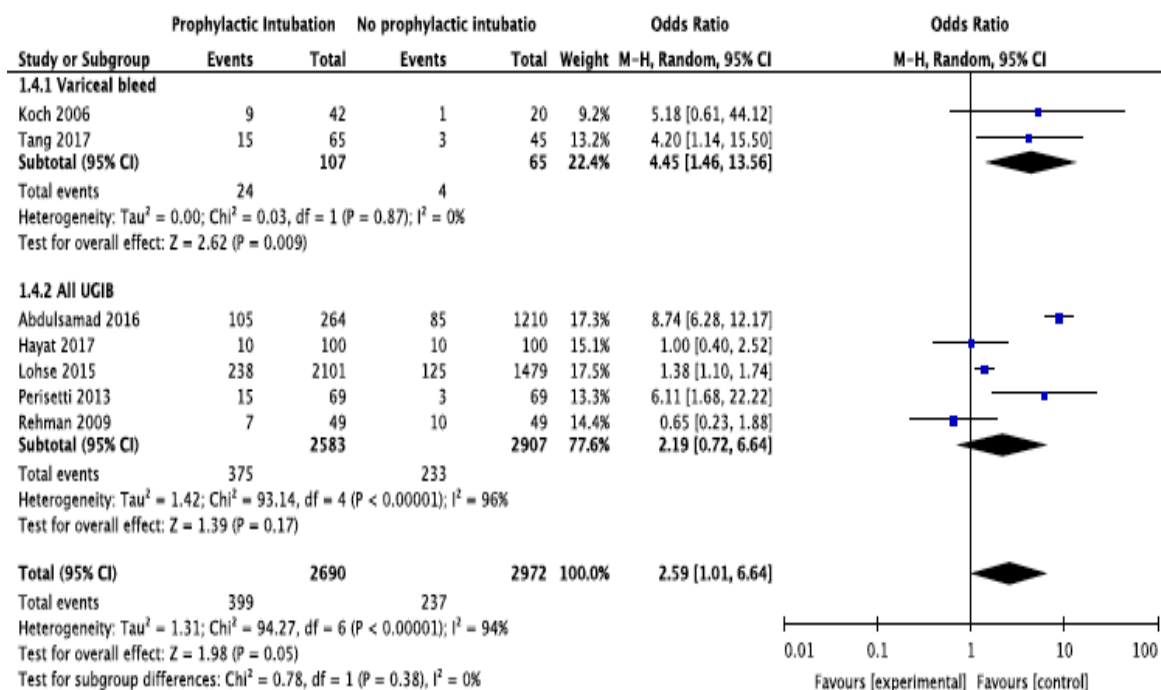
Type of infection	N (%)
Respiratory	163 (43%)
Urinary tract	54 (14%)
Spontaneous bacteriemia	47 (12%)
Spontaneous bacterial peritonitis	30 (8%)
Soft-tissue	21 (6%)
Other	64 (17%)

Factores de riesgo al ingreso de infección respiratoria

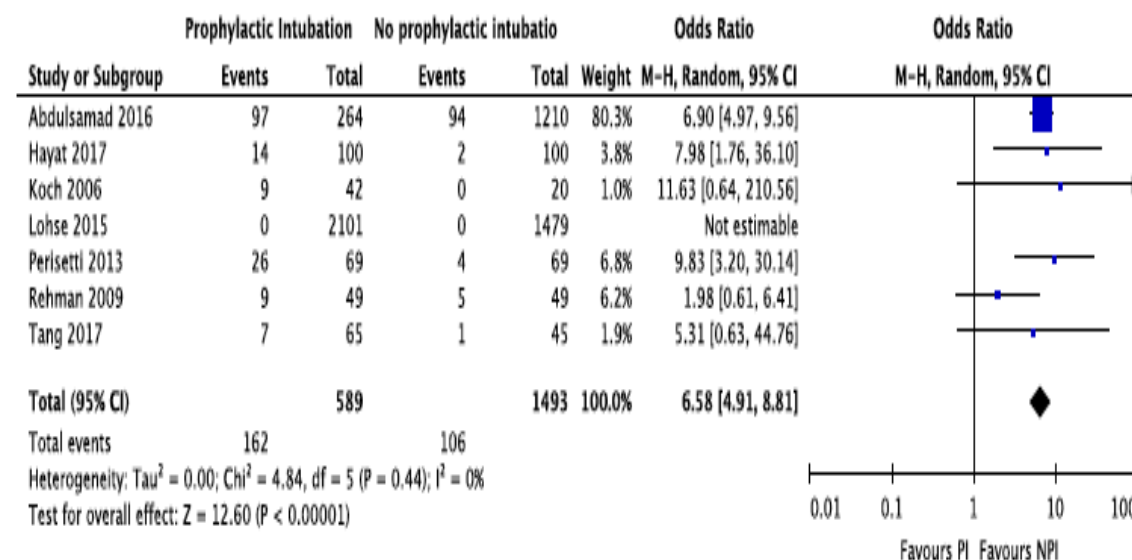
	OR	IC95%
Child C	3.1	1.4-4.9
Encefalopatía grave (III-IV)	2.8	1.4-4.9
Intubación para endoscopia	2.6	1.8-3.7
Taponamiento con balón	2.4	1.2-4.9
Sonda nasogástrica	1.7	1.2-2.4

Intubación orotraqueal profiláctica en pacientes críticos con hemorragia digestiva alta

Mortalidad



Neumonía aspirativa



Prevención de infección respiratoria en pacientes cirróticos con hemorragia digestiva

Factores de riesgo

- Encefalopatía hepática
- Intubación orotraqueal para endoscopia
- Sonda nasogástrica

Medidas preventivas

- Oxigenoterapia y pulsioximetría
- Aspiración de sangre y secreciones de la vía aérea
- Intubación orotraqueal sólo si encefalopatía o vómitos
- Evitar sonda nasogástrica

Baveno VII

- Manipulation of airway, including use of nasogastric tube, should be performed with caution because of the risk of pulmonary infection (D2) (New)
- Intubation is recommended before endoscopy in patients with altered consciousness and those actively vomiting blood (D1) (New)

Profilaxis antibiótica

Elección del antibiótico

Quinolonas vo/iv (norfloxacin 400 mg/12 h vo)

- Recomendación del consenso (Baveno V, 2010)

Cefalosporinas 3ª generación (ceftriaxona 1 g/24 h iv)

Abordaje pragmático

... Pero selecciona cepas resistentes a β -lactámicos

Indicación (Baveno V, 2010):

- Cirrosis avanzada (Child C)
- Prevalencia elevada de resistencia a quinolonas
- Pacientes en profilaxis con quinolonas

Profilaxis con **antibióticos activos frente a MDR bacterias**,
si infección reciente por Enterobacterias BLEE

Baveno V, VI, VII

Prótesis metálicas auto-expandibles en hemorragia por varices no controlada

Hemorragia por varices refractaria
Taponamiento con balón, n=15
Prótesis esofágica, n=13

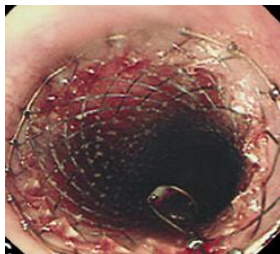
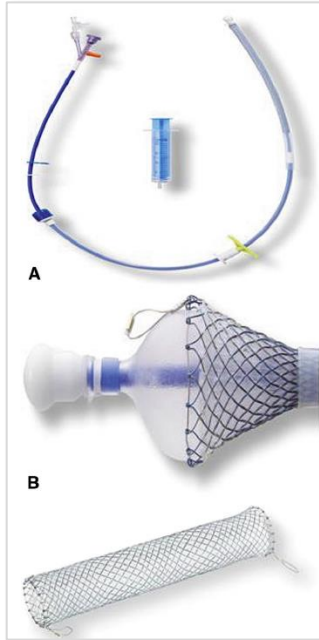
Variable	Esophageal Stent (n = 13)	Balloon Tamponade (n = 15)	P Value	Variable	Esophageal Stent (n = 13)	Balloon Tamponade (n = 15)	P Value
Inclusion criteria, n (%)			0.93	Total number of AEs, n	6	14	
Failure of combined therapy	8 (62)	9 (60)		SAEs, n			
Massive bleeding	5 (38)	6 (40)		Cardiorespiratory arrest	1	1	
Interval admission-inclusion, days*	1.5 (0-7)	1 (0-25)	0.60	Aspiration pneumonia	0	5	
Success of therapy, n (%)	8 (66)	3 (20)	0.025	Esophageal rupture	0	1	
Absence of bleeding, 15 days, n (%)	11 (85)	7 (47)	0.037	SBP and hepatorenal syndrome	1	0	
Absence of SAEs, n (%)	11 (84)	8 (53)	0.077	Mild AEs, n			
Survival at 15 days, n (%)	9 (69)	8 (47)	0.39	Infections	2	1	
Absence of bleeding, 6 weeks, n (%)	7 (54)	7 (47)	0.25	Esophageal ulcer (not bleeding)	1	1	
Absence of device-related SAE, n (%)	12 (92)	9 (60)	0.049	Bronchoaspiration not causing pneumonia	1	3	
Causes of death (15 days; n)			0.044	Seizures	0	1	
Hypovolemic shock	1	6†		Transitory acute stroke	0	1	
MOF after sepsis	3	1		Patients with at least one AE, n (%)	4 (31)	11 (73)	0.024
Survival at 6 weeks, n (%)	7 (54)	6 (40)	0.46	Patients with at least one SAE, n (%)	2 (15)	7 (47)	0.077
Use of additional resources (during the hospital stay), n (%)	4 (31)	11 (73)	0.059	Patients with at least one device-related SAE, n (%)	1 (8)	6 (40)	0.049

Prótesis metálicas auto-expandibles en hemorragia por varices no controlada

13 estudios

(12 observacionales, 1 controlado con balón SB)

361 pacientes



	Frecuencias estimadas acumuladas (%)		
	Frecuencia del evento	Límite inferior	Límite superior
Muerte	39	31	48
Muerte en 30 d	36	26	46
Fallo en el control sangrado	18	10	29
Migración de la prótesis	28	16	43

Frecuencia estimada de acceso a TIPS 26%

Taponamiento esofágico en hemorragia por varices no controlada: Balón vs. Prótesis metálica auto-expandible

	Balón	Prótesis
Tratamiento temporal	Sí	Sí
Duración máxima	<24-48 h	7-14 d
Hemostasia inicial	90%	70-100%
Complicaciones graves	20-60%	~10%
Complicaciones, tipo	Neumonía aspiración Úlcera/rotura esofágica	Mal posición/ migración

Baveno VII

- In refractory variceal bleeding, balloon tamponade (BT) or self-expandable metal stents (SEMS) should be used as a bridge therapy to a more definite treatment such as PTFE-covered TIPS. SEMS are as efficacious as BT and a safer option (B1) (Changed)



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Nuevas recomendaciones de Baveno 7 en relación con la hemorragia por varices Parte 2

Rafael Bañares

Madrid, 17 de diciembre de 2021



Hospital General Universitario
Gregorio Marañón



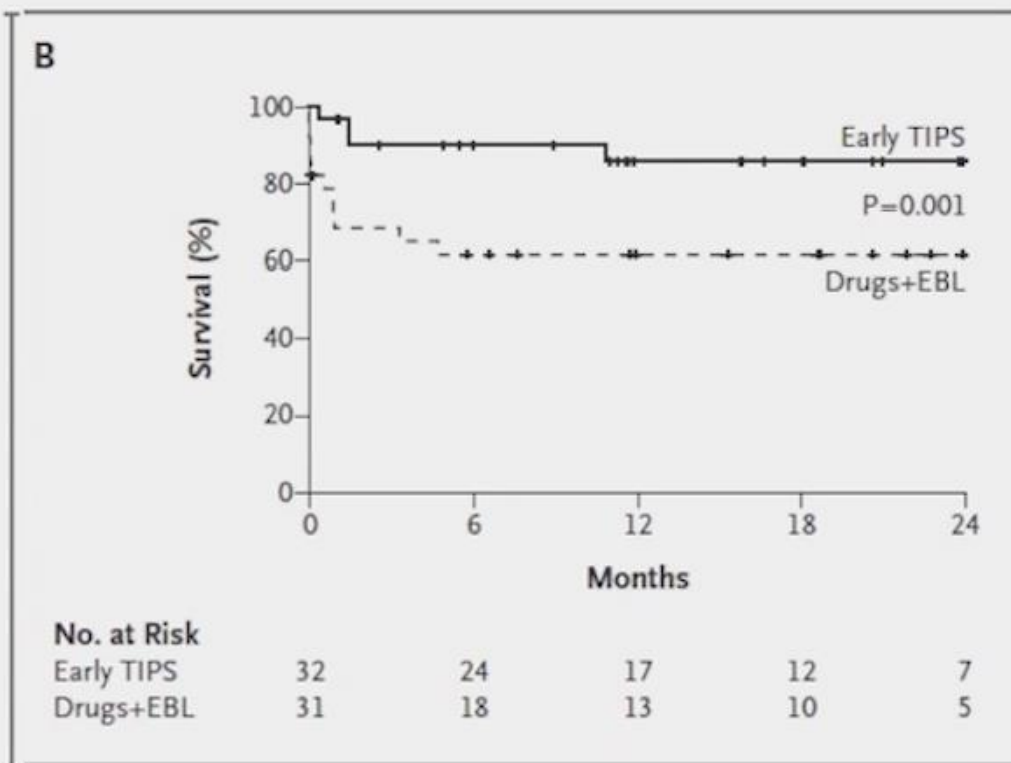
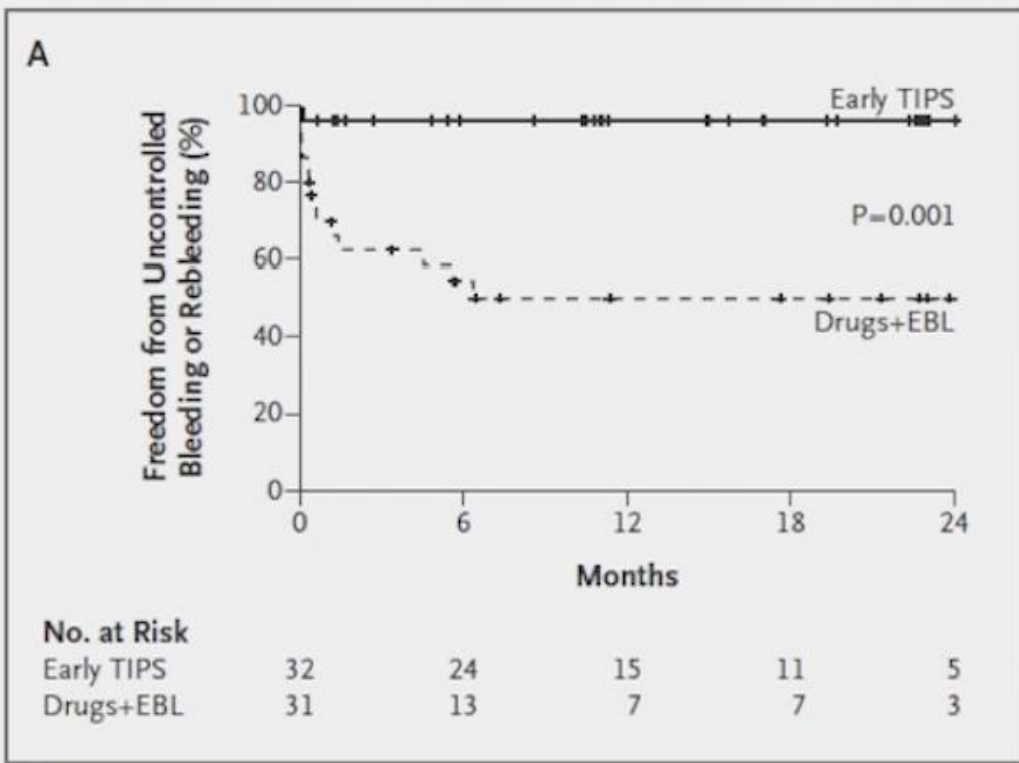
Statement 6.9

Pre-emptive TIPS with PTFE-covered stents within 72 hours (ideally <24hours) is indicated in patients bleeding from EV, GOV1 and GOV2 who meet any of the following criteria: Child Pugh class C<14 points or Child class B >7 with active bleeding at initial endoscopy or HVPG >20 mmHg at time of hemorrhage (A1) (Changed)

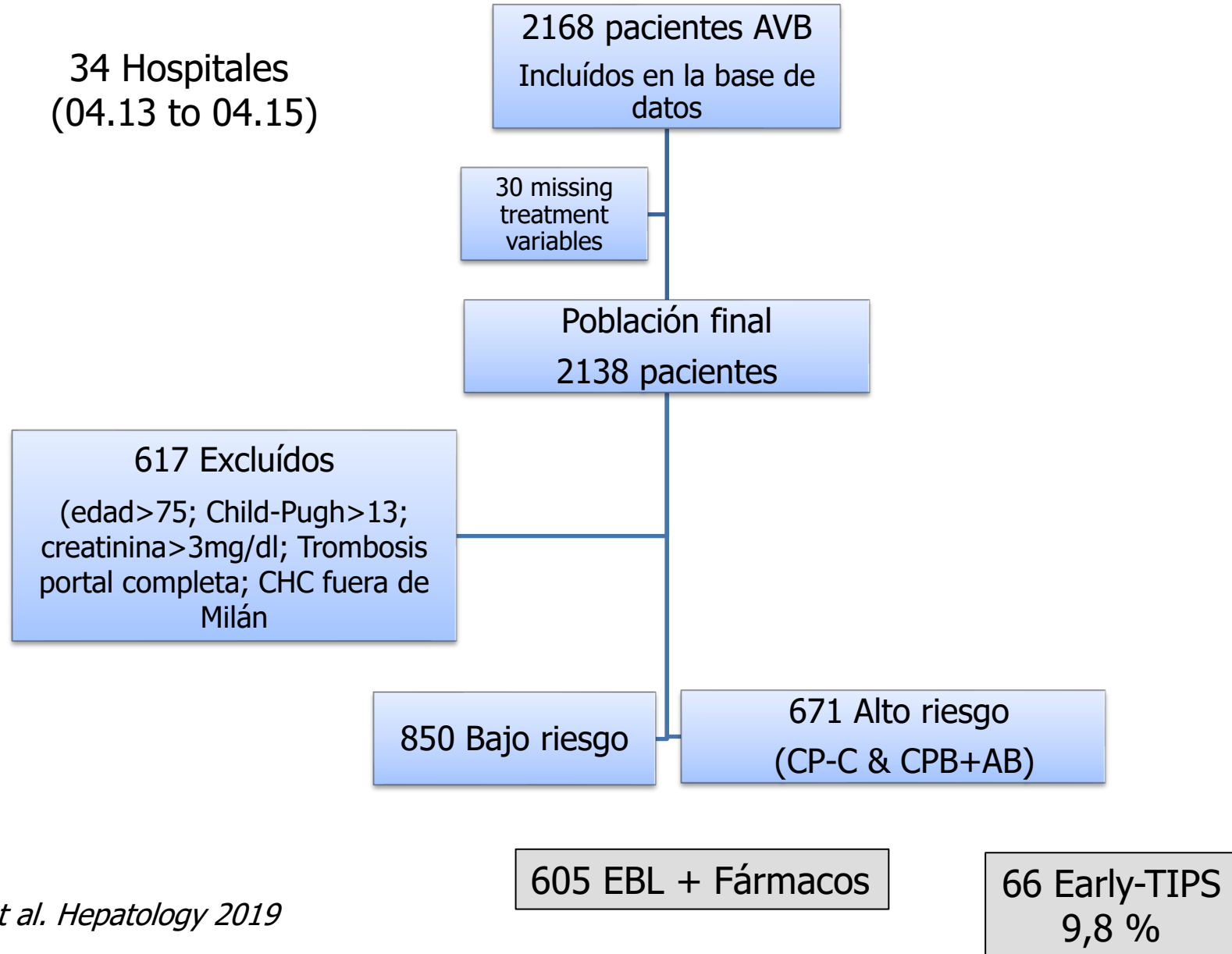
Ensayos aleatorizados: TIPS preventivo

Autor	Tamaño de la muestra Intervención y comparador	Criterios de inclusión principales	Criterios de exclusión principales	Seguridad	Eficacia
Monescillo et al. <i>Hepatology 2004</i>	134 pacientes consecutivos 116 con medida del GPVH 52 pacientes aleatorizados 1:1	GPVH ≥ 20 mmHg	Edad < 18 y > 75 CHC; HIV; IRC; IC En 5 casos no HVPG TIPS previo	No aumento de HE de novo Complicaciones relacionadas con TIPS n=5	Mejora en el control HD Mortalidad hospitalaria 11% Vs 31% Mortalidad HD 19 % Vs 38% Mortalidad 1 año 38% Vs 65%
Garcia-Pagan et al <i>NEJM 2010</i>	359 pacientes consecutivos 63 pacientes aleatorizados 1:1	Child-Pugh B con hemorragia activa (51 %) Child C ≤ 13 puntos (49 %)	Edad < 18 y > 75 CHC fuera de Milán Trombosis portal oclusiva TIPS previo IRC; IC	No aumento de HE de novo ni en el seguimiento Complicaciones relacionadas con TIPS n=5	Mejora en el control HD 3% Vs 50 % Mortalidad 1 año 14% Vs 39% Tendencia a menor desarrollo de ascitis
Lv et al. <i>Lancet Gastroenterol Hepatol 2019</i>	373 pacientes consecutivos 132 pacientes aleatorizados 2:1	Child-Pugh B sin hemorragia activa: 57 % Child-Pugh B con hemorragia activa: 21 % Child C ≤ 13 puntos 22 %	Edad < 18 y > 75 CHC fuera de Milán Trombosis portal oclusiva TIPS previo IRC; IC EH "overt"	No aumento de HE	Mejora en el control HD 11% Vs 34 % Mortalidad 1 año 38% Vs 65% Ascitis de novo o empeoramiento 11% Vs 43 %

Pre-Emptive (early) TIPS in High-Risk Variceal Bleeders: (Child C (<14) or Child B + Active Bleeding)



International Variceal Bleeding Observational Study





Cirrhotic patients with portal hypertension-related bleeding and an indication for early-TIPS: A large multicentre audit with real-life results

Dominique Thabut^{1,*}, Arnaud Pauwels², Nicolas Carbonell³, Andre Jean Remy⁴, Pierre Nahon⁵,

Academic centres with PHT-related bleeding 600 cirrhotic patients

Study population with PHT-related bleeding 964 cirrhotic patients

Non-academic centres with PHT-related bleeding 364 cirrhotic patients

Child-Pugh C or B + active bleeding at endoscopy
n = 301

Child-Pugh C or B + active bleeding at endoscopy
n = 460

Child-Pugh C or B + active bleeding at endoscopy
n = 159

Patients eligible for early-TIPS
n = 207

Patients eligible for early-TIPS
n = 326

Patients eligible for early-TIPS
n = 119

Early-TIPS placement
n = 19

Early-TIPS placement
n = 22

Early-TIPS placement
n = 3

Razones para no realizar TIPS

No disponibilidad local (45 %)

Falta de confianza del médico en el beneficio del TIPS preventivo (34 %)

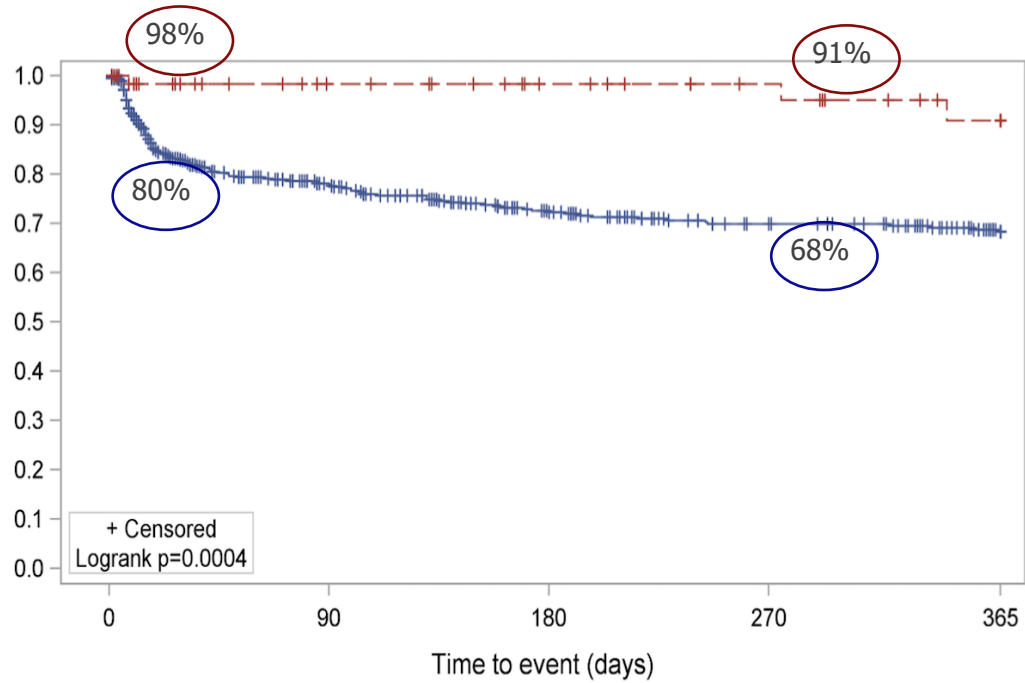
Otras razones (21 %)

Tiempo máximo de ambulancia entre centros: 90 minutos

Aumento de la información y de la evaluación del riesgo

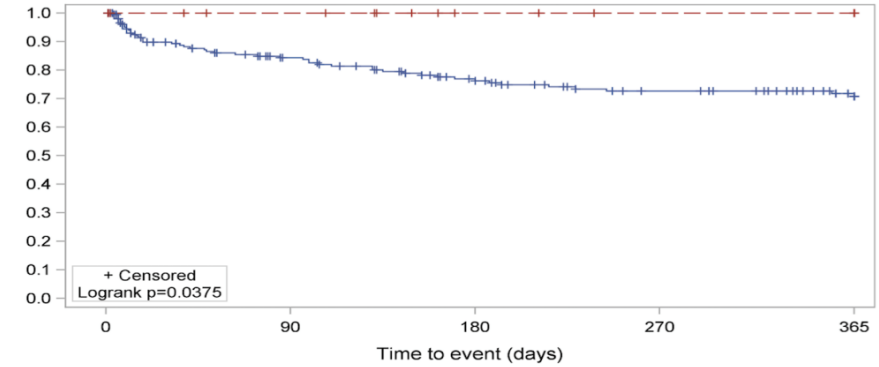
Logística

Mejor control de la hemorragia y menor recidiva precoz



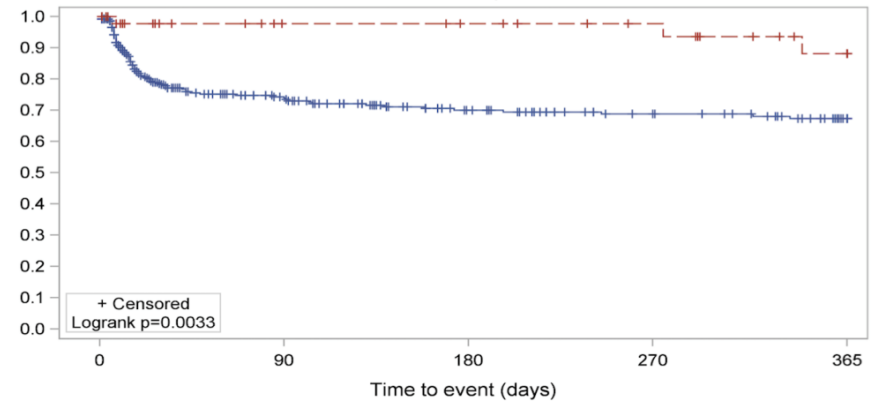
	Early TIPS (placed within first 72h in high-risk patients after initial control of bleeding)?										
	No					Yes					
No	605	367	331	294	265	236	212	197	192	180	152
Yes	66	50	47	43	41	36	33	31	28	25	22

Child-Pugh B + hemorragia activa



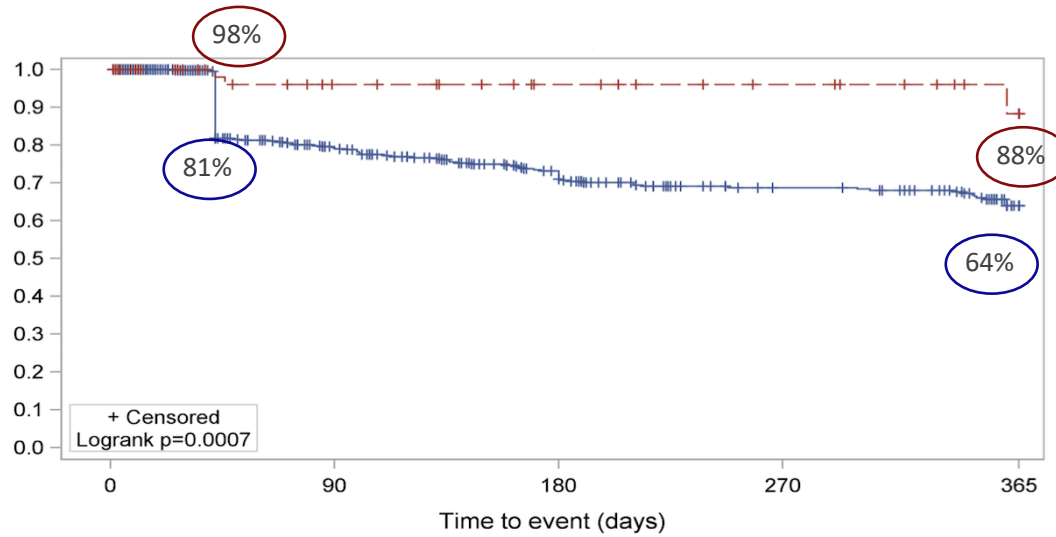
	Early TIPS (placed within first 72h in high-risk patients after initial control of bleeding)?										
	No					Yes					
No	218	163	152	137	126	112	102	95	93	87	75
Yes	19	16	14	13	11	8	7	6	6	6	6

Child C



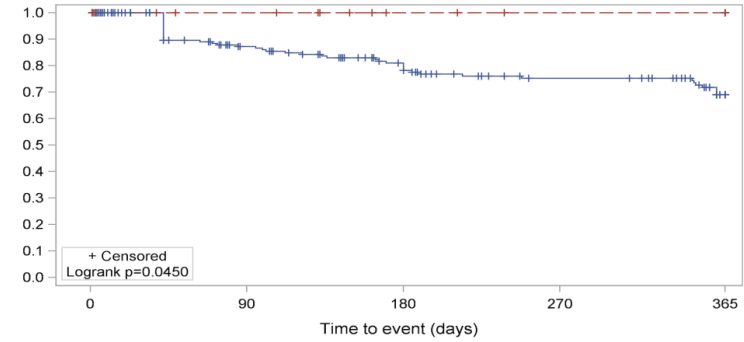
	Early TIPS (placed within first 72h in high-risk patients after initial control of bleeding)?										
	No					Yes					
No	387	204	179	157	139	124	110	102	99	93	77
Yes	47	34	33	30	30	28	26	25	22	19	16

Desarrollo de Ascitis



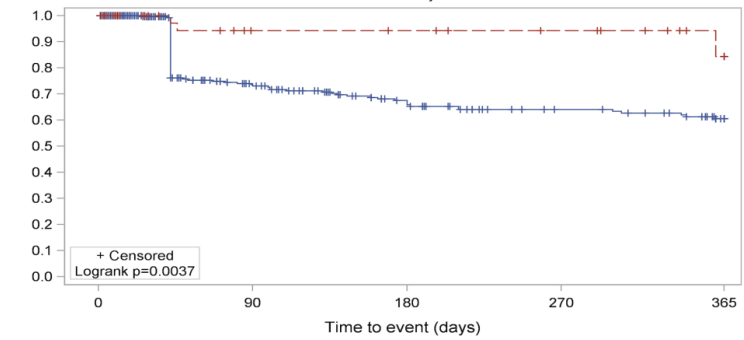
	Early TIPS (placed within first 72h in high-risk patients after initial control of bleeding)?										
	— No — Yes										
No	605	436	326	291	261	228	204	192	190	181	130
Yes	66	51	46	42	40	36	33	32	30	28	23

Child-Pugh B + Active Bleeding



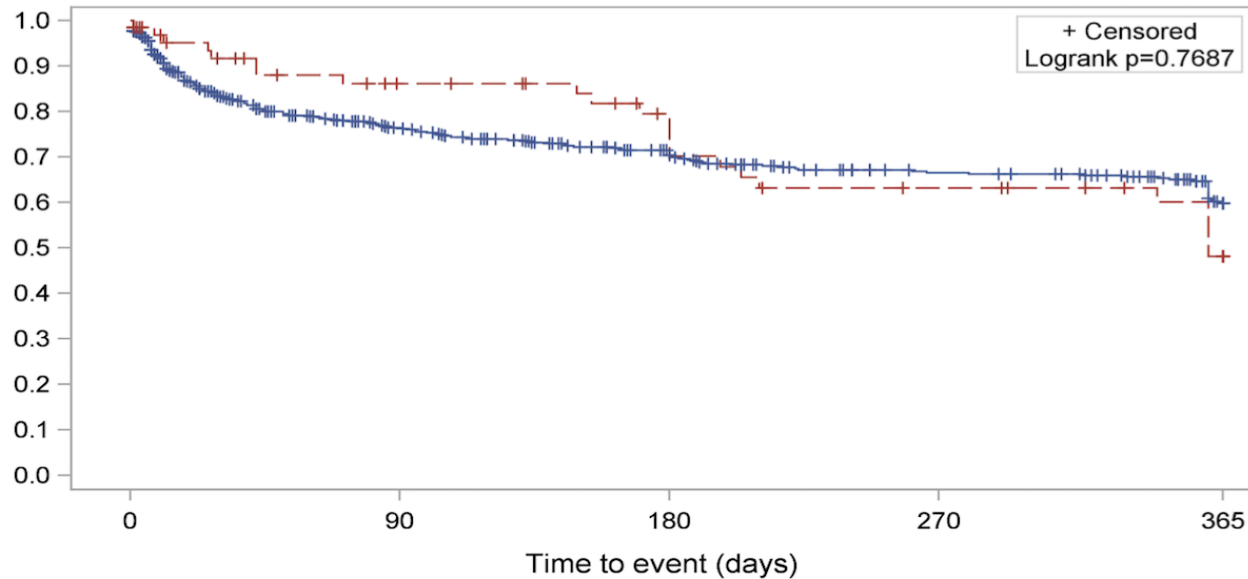
	Early TIPS (placed within first 72h in high-risk patients after initial control of bleeding)?										
	— No — Yes										
No	218	182	155	140	129	113	102	95	95	91	64
Yes	19	16	14	13	11	8	7	6	6	6	6

Child-Pugh C



	Early TIPS (placed within first 72h in high-risk patients after initial control of bleeding)?										
	— No — Yes										
No	387	254	171	151	132	115	102	97	95	90	66
Yes	47	35	32	29	29	28	26	26	24	22	17

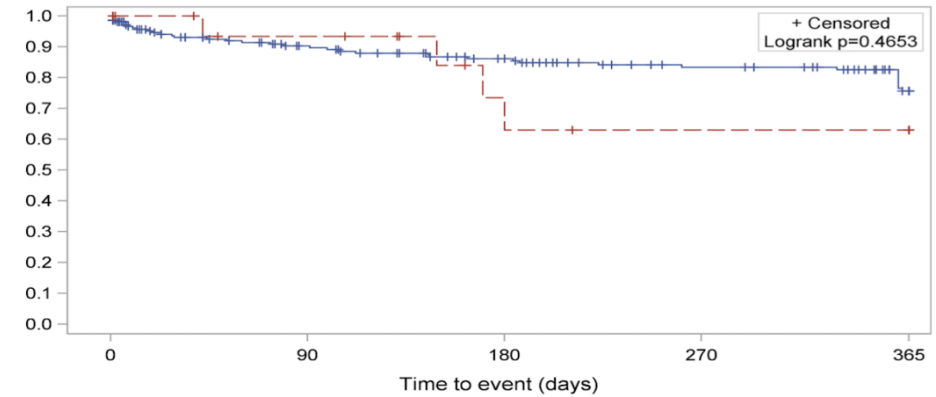
Desarrollo de Encefalopatía Hepática



Early TIPS (placed within first 72h in high-risk patients after initial control of bleeding)?
 — No — Yes

No	605	399	356	319	294	265	240	227	222	213	171
Yes	66	51	46	42	40	30	26	26	24	22	16

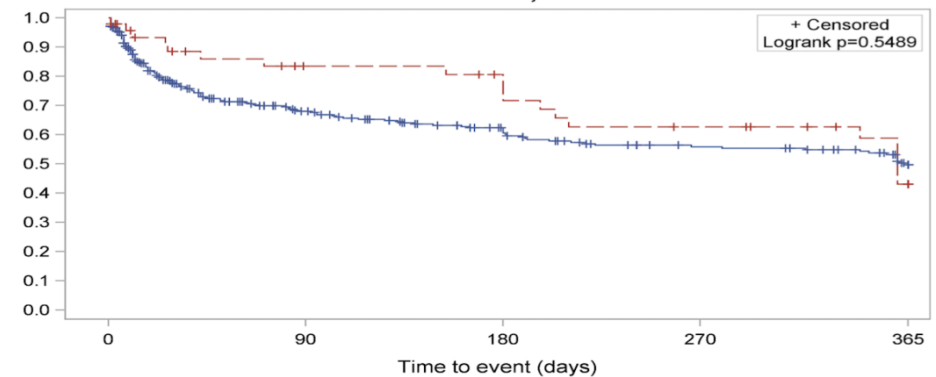
Child-Pugh B + Active Bleeding



Early TIPS (placed within first 72h in high-risk patients after initial control of bleeding)?
 — No — Yes

No	218	174	165	151	143	133	121	115	113	109	86
Yes	19	16	13	12	10	6	5	5	5	5	5

Child-Pugh C

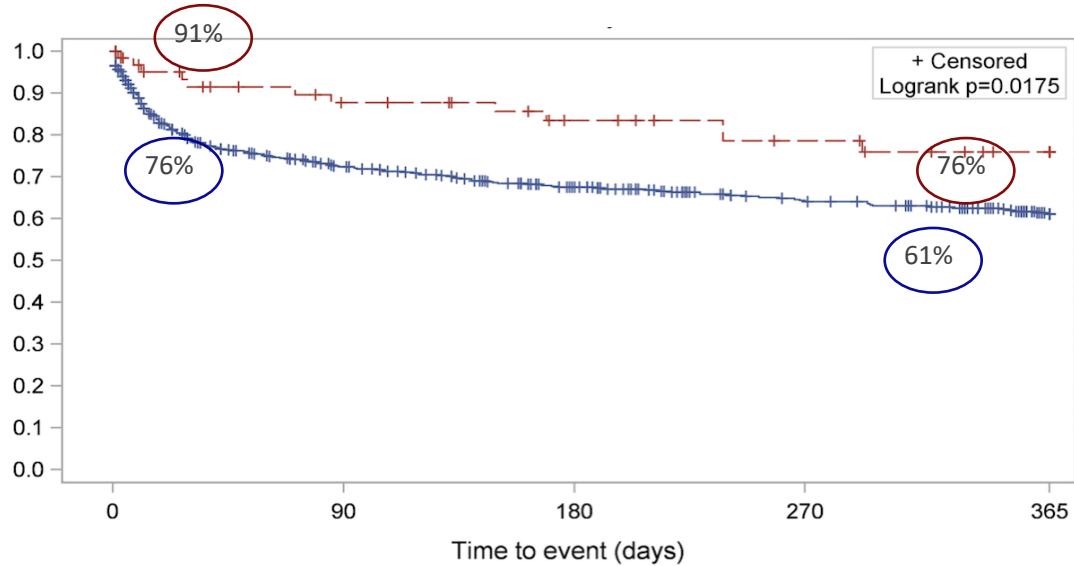


Early TIPS (placed within first 72h in high-risk patients after initial control of bleeding)?
 — No — Yes

No	387	225	191	168	151	132	119	112	109	104	85
Yes	47	35	33	30	30	24	21	21	19	17	11

Supervivencia libre de trasplante

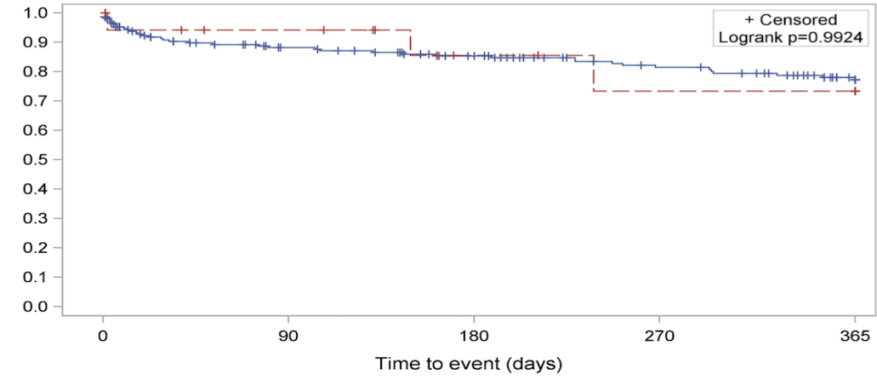
Child-Pugh B + Hemorragia activa



Early TIPS (placed within first 72h in high-risk patients after initial control of bleeding)?

— No — Yes

No	605	412	379	350	325	300	274	257	249	234	197
Yes	66	51	48	44	42	37	34	32	30	27	24

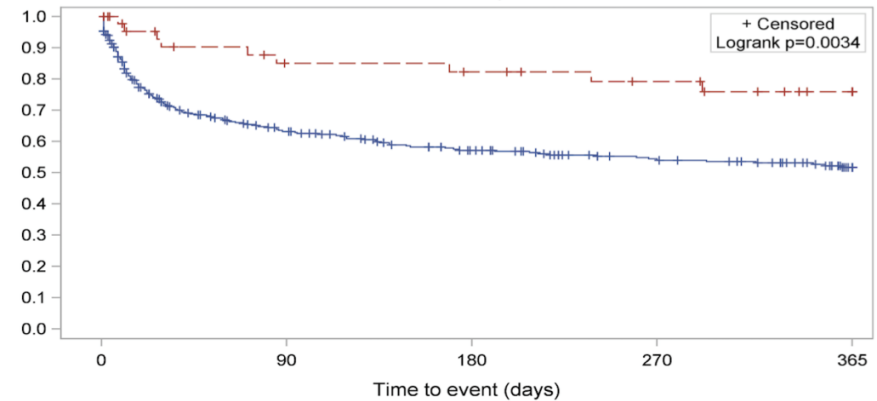


Early TIPS (placed within first 72h in high-risk patients after initial control of bleeding)?

— No — Yes

No	218	176	169	159	152	142	131	124	121	113	97
Yes	19	16	14	13	8	7	6	6	6	6	6

Child Pugh C



Early TIPS (placed within first 72h in high-risk patients after initial control of bleeding)?

— No — Yes

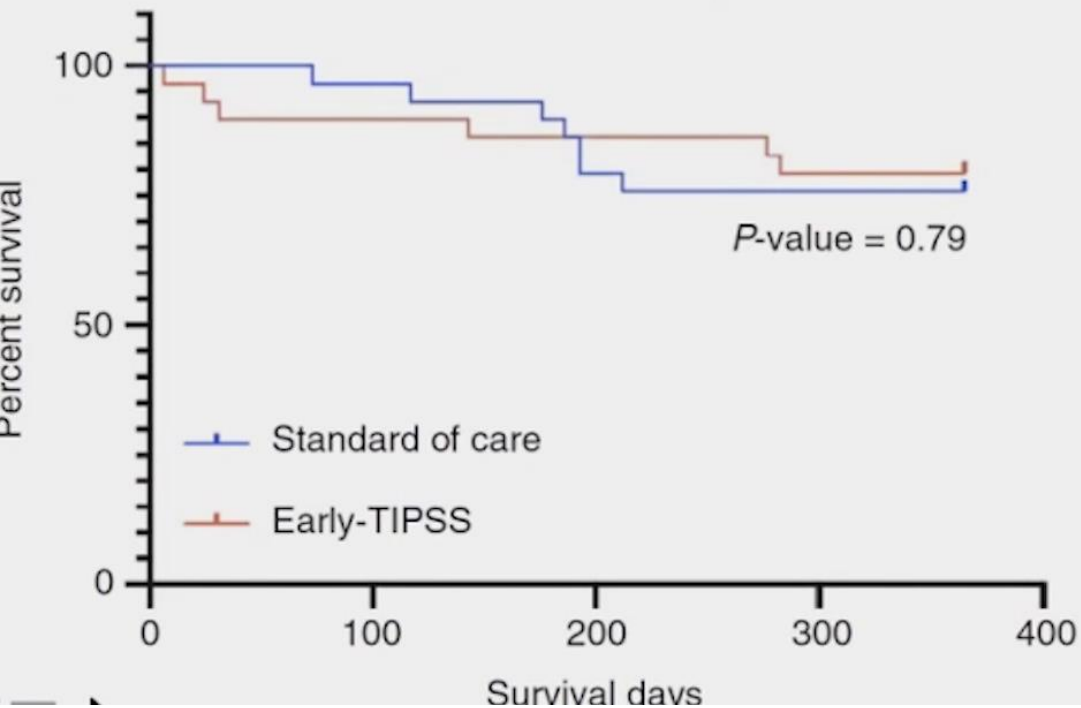
No	387	236	210	191	173	158	143	133	128	121	100
Yes	47	35	34	31	31	29	27	26	24	21	18

No todo es de color rosa

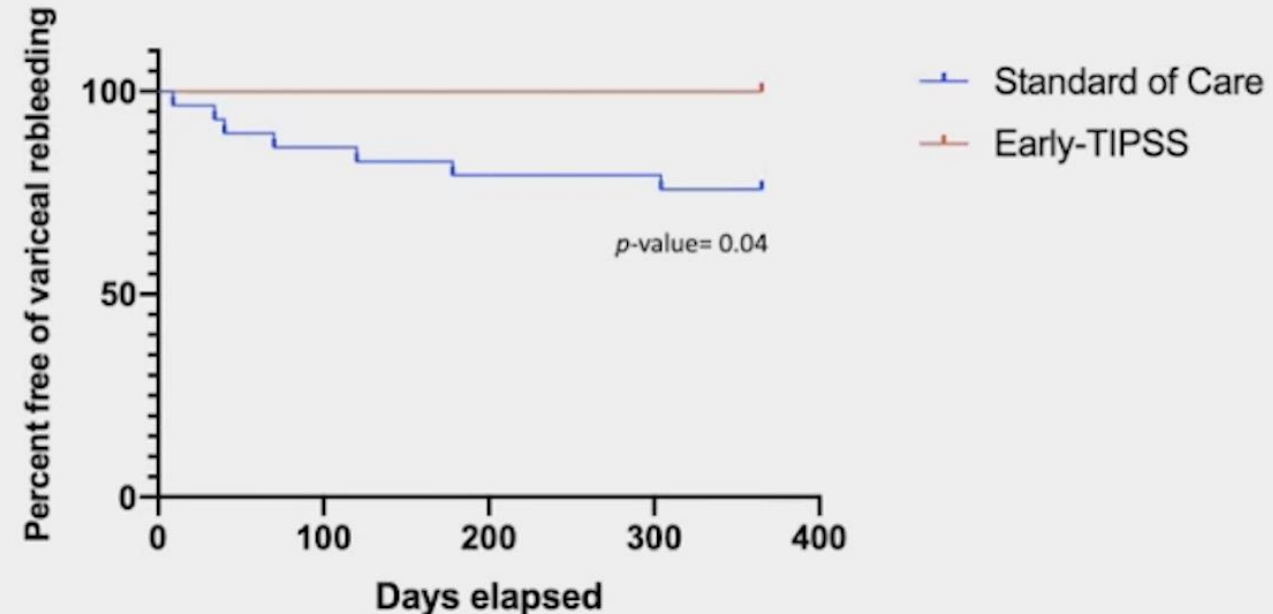
Randomised clinical trial: standard of care versus early-transjugular intrahepatic porto-systemic shunt (TIPSS) in patients with cirrhosis and oesophageal variceal bleeding

Philip D. J. Dunne¹ | Rohit Sinha¹ | Adrian J. Stanley² | Neil Lachlan² |
Hamish Ireland³ | Aman Shams^{1,4} | Ram Kasthuri⁵ | Ewan H. Forrest² | Peter C. Hayes¹

No SV benefit when all patients included



Benefit in preventing variceal rebleeding when considering pTIPS placed in the first 72h (no data on SV)



Statement 6.10

In patients fulfilling pre-emptive TIPS criteria, ACLF, HE at admission and hyperbilirubinemia at admission should not be considered as contra-indications to pTIPS (B1) (New)

Meta-análisis de datos individuales

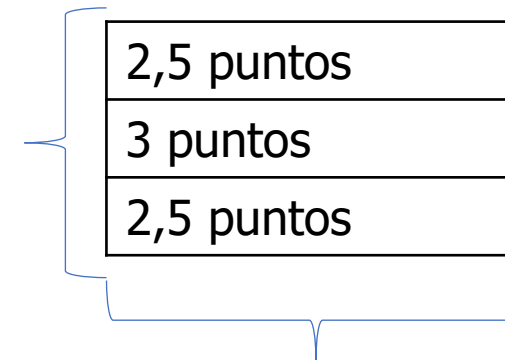
- Monescillo A al. RCT. 2004
- Garcia-Pagan JC et al. RCT 2010
- Garcia-Pagan JC et al. Observational 2013
- Rudler et al. Observational * 2014
- Yong Lv et al. Observational * 2018
- Hernandez-Gea et al. Observational 2019
- Yong Lv et al. RCT * 2019

* Only the subgroup of high-risk patients

1327 high-risk pts: 310 p-TIPS and 1017 Drugs+Endo
602 (45.3%) were CP-B+AB and 725 (54.7%) CP-C (<14)

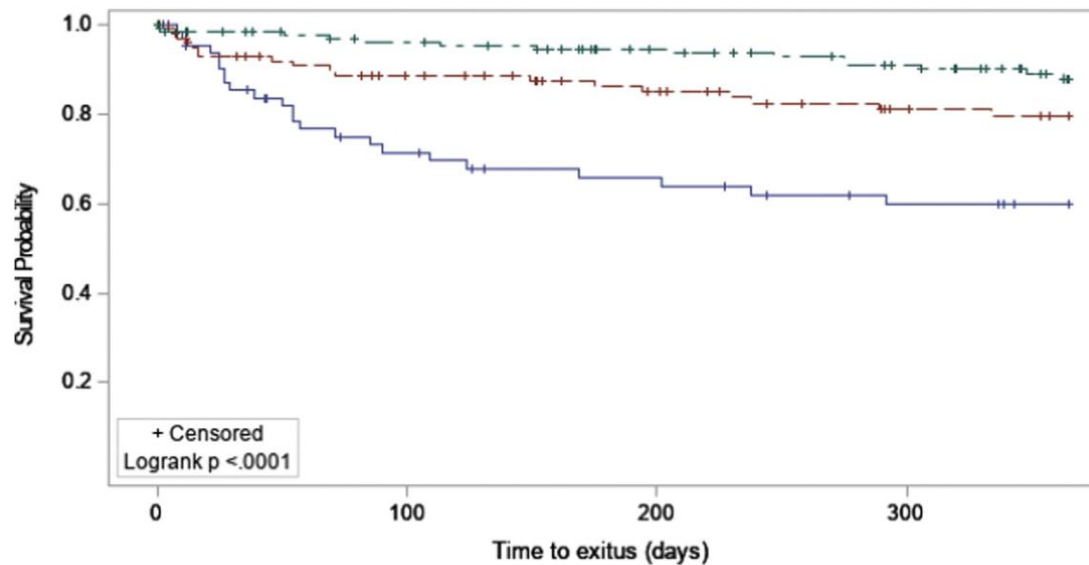
Identificación de grupos de riesgo en pacientes de alto riesgo receptores de p-TIPS

	Variables	HR (95 % CI)
Modelo 1	Edad > 55	2,769 (1,480-5,180)
	Child Pugh > 11	3,338 (1,728-6,449)
	Creatinina \geq 1,3 mg/dl	2,461 (1,228-4,929)
Modelo 2	Edad > 55	2,855 (1,526-5,343)
	MELD \geq 19	2,341 (1,272-4,308)
Modelo 3	Edad > 55	2,283 (1,396-3,734)
	Bilirrubina \geq 3 mg/dl	2,155 (1,331-3,492)
	Creatinina \geq 1,3 mg/dl	2,051 (1,167-3,604)
	Albúmina \leq 27 g/L	1,656 (0,982-2,795)



Bajo Riesgo	0 puntos	142
Riesgo medio	0-2,5 puntos	103
Alto Riesgo	>2,5 puntos	65

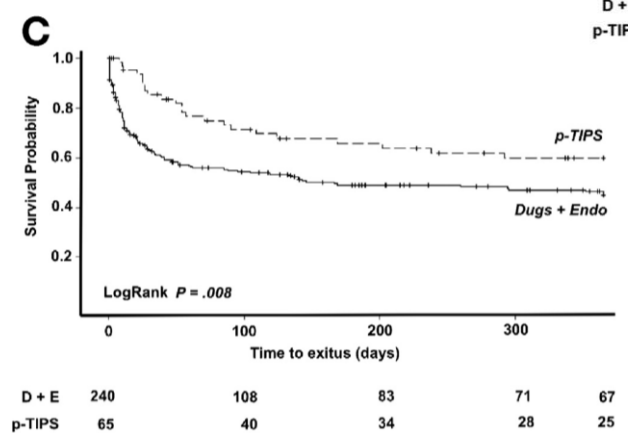
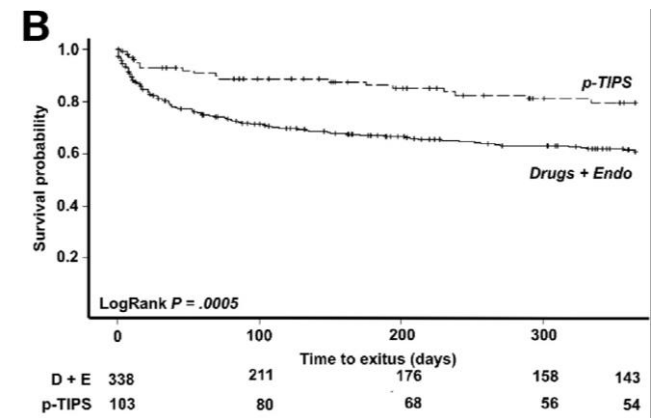
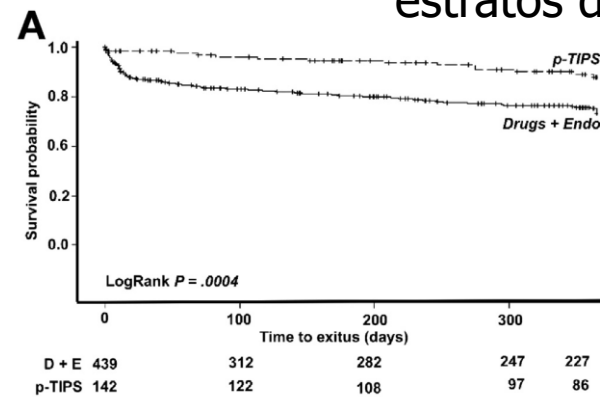
La puntuación de riesgo funciona



risk — 1: High risk — 2: Intermediate risk — 3: Low risk

1	65	48	40	35	34	30	28	25
2	103	87	80	75	68	61	56	54
3	142	127	122	119	108	102	97	86

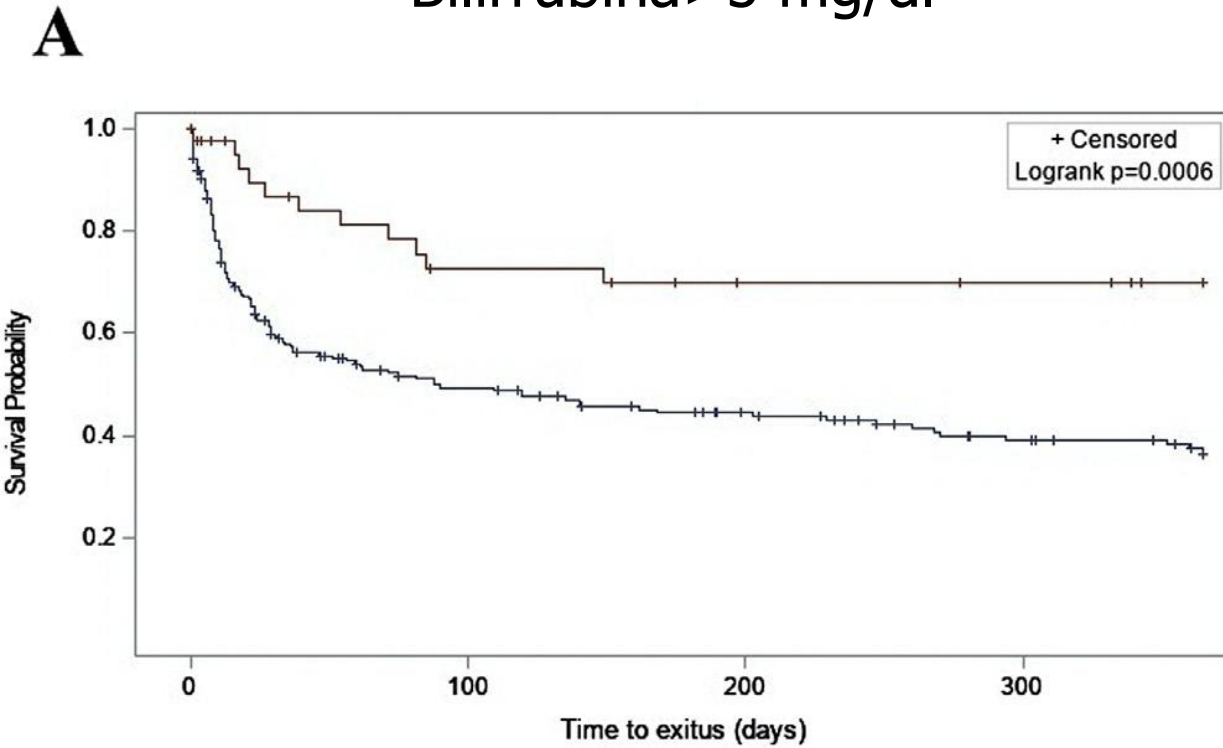
p-TIPS mejora el pronóstico en todos los estratos de riesgo



Y, ¿en pacientes muy malos?

El p-TIPS mejora el pronóstico en pacientes con hiperbilirrubinemia

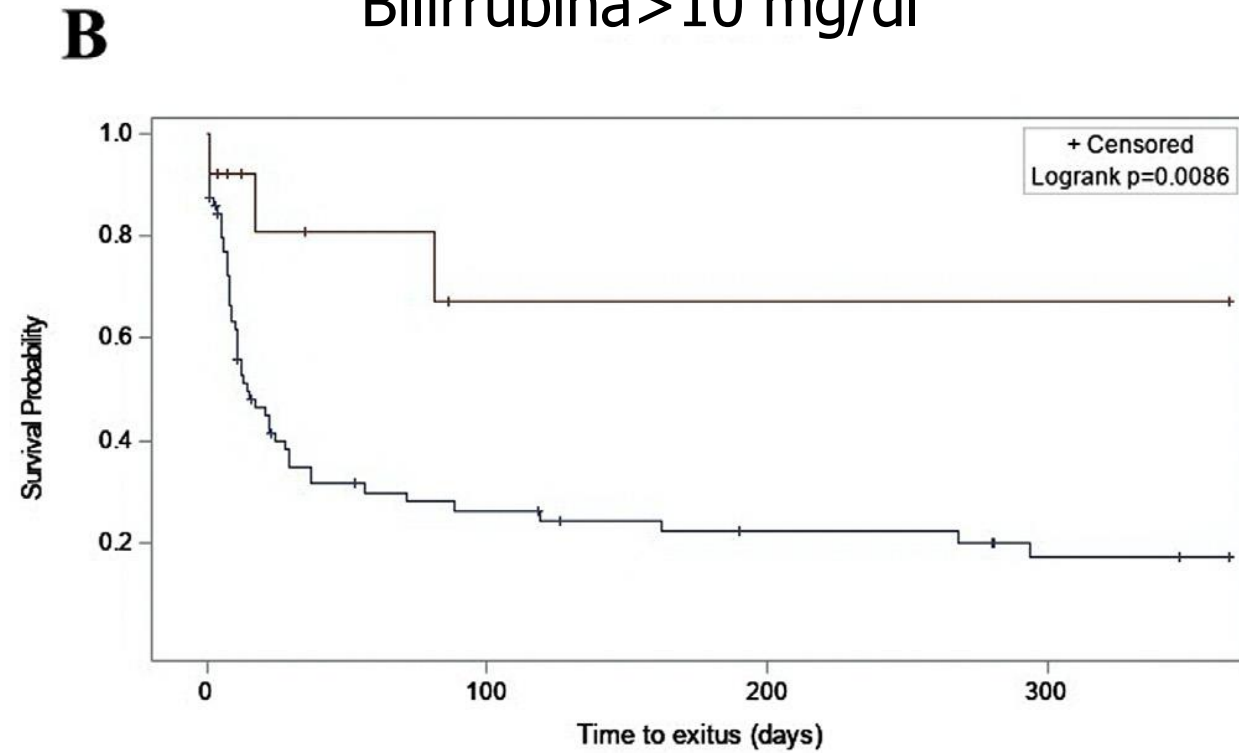
A Bilirrubina > 5 mg/dl



Treatment — Drug+Endo — p-TIPS

Drug+Endo	208	100	84	73	65	56	49	45
p-TIPS	43	30	25	24	21	21	20	17

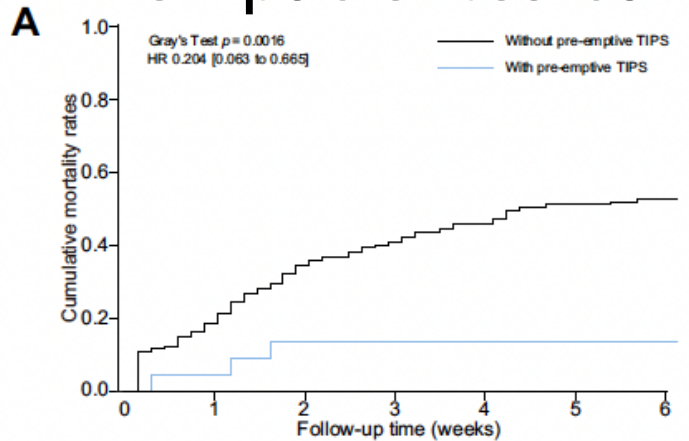
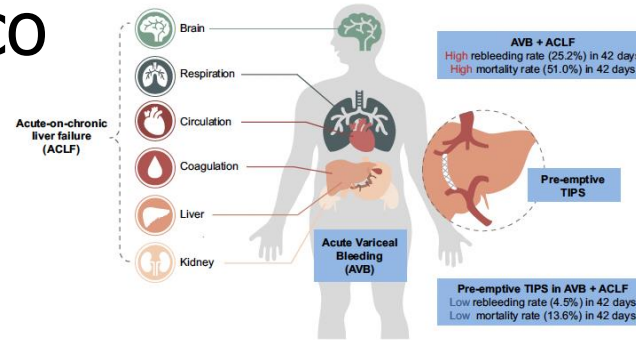
B Bilirrubina > 10 mg/dl



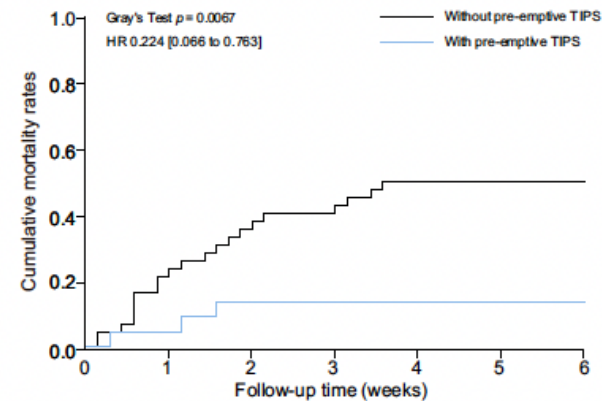
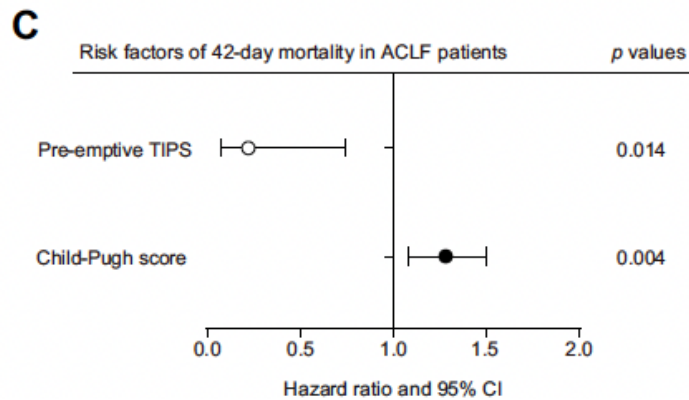
Treatment — Drug+Endo — p-TIPS

Drug+Endo	71	19	15	12	10	10	6	5
p-TIPS	13	6	4	4	4	4	4	4

p-TIPS mejora el pronóstico en pacientes con ACLF

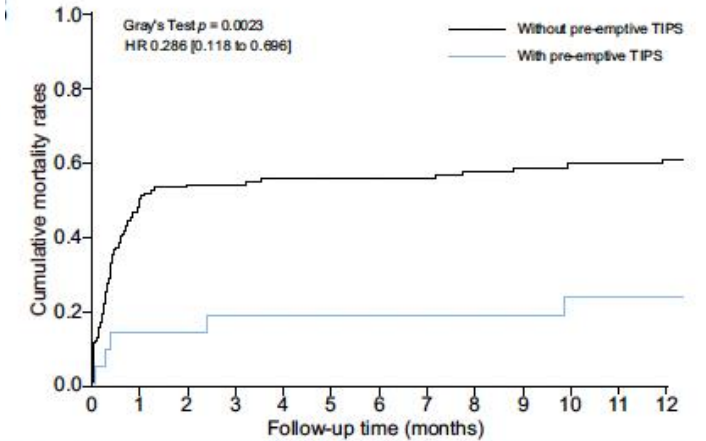


N° at risk	0	1	2	3	4	5	6
No pTIPS	147	110	86	75	65	59	56
pTIPS	22	20	19	18	17	16	16

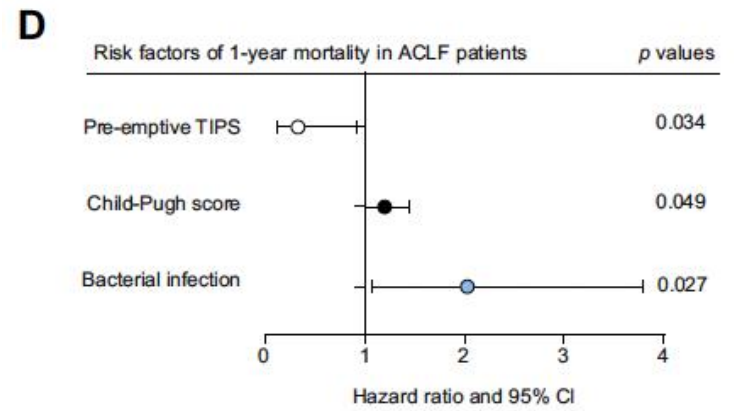


N° at risk	0	1	2	3	4	5	6
No pTIPS	44	37	30	23	16	9	8
pTIPS	22	20	19	18	17	16	16

Ajustado por propensity score

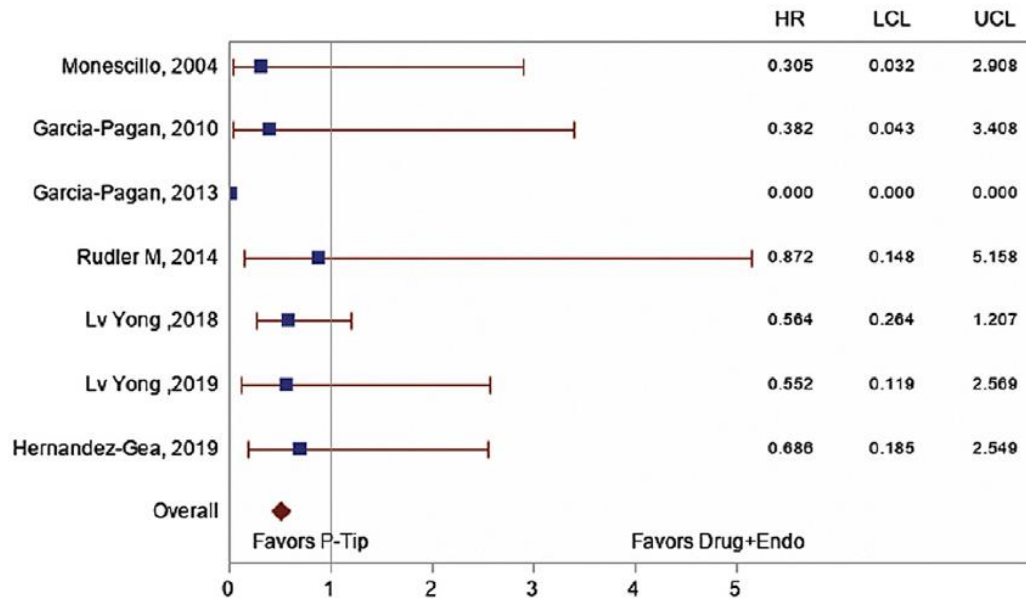


N° at risk	0	1	2	3	4	5	6	7	8	9	10	11	12
No pTIPS	147	60	55	53	49	46	46	43	37	36	34	34	31
pTIPS	22	17	17	15	15	15	14	13	13	13	11	10	9



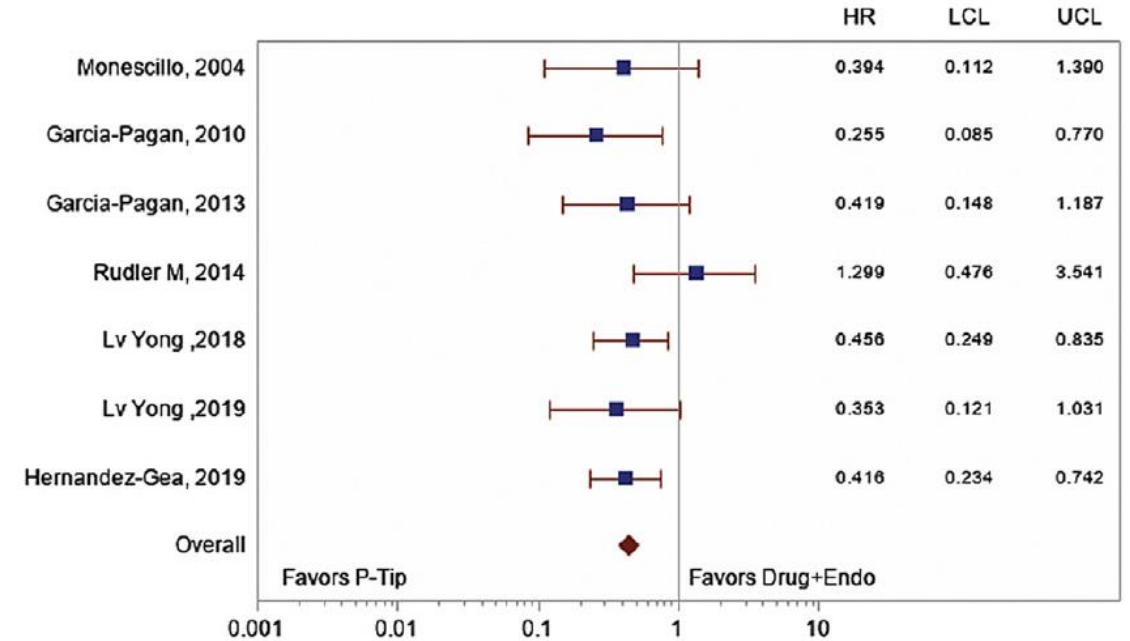
Impact of Treatment on mortality by Study (Child-B patients)

Hazard Ratio and 95% CL



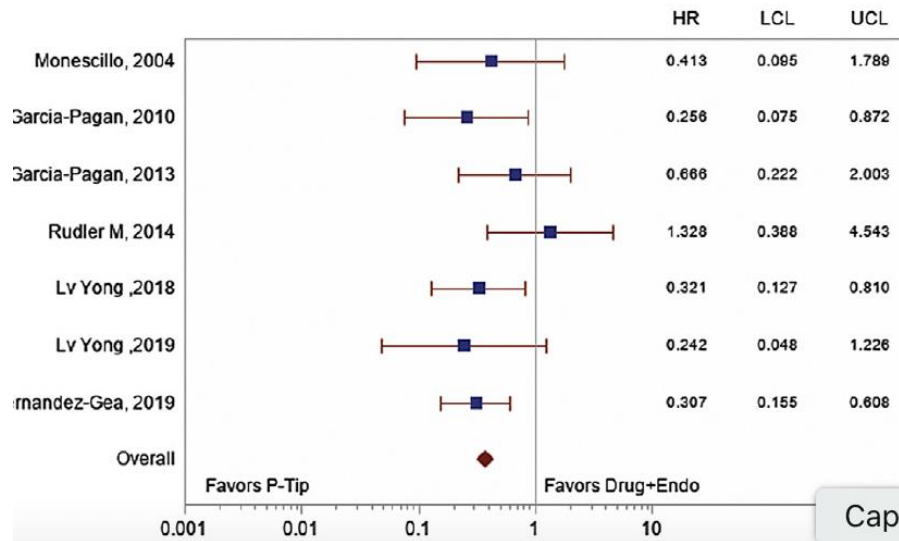
Impact of Treatment on mortality by Study (All patients)

Hazard Ratio and 95% CL



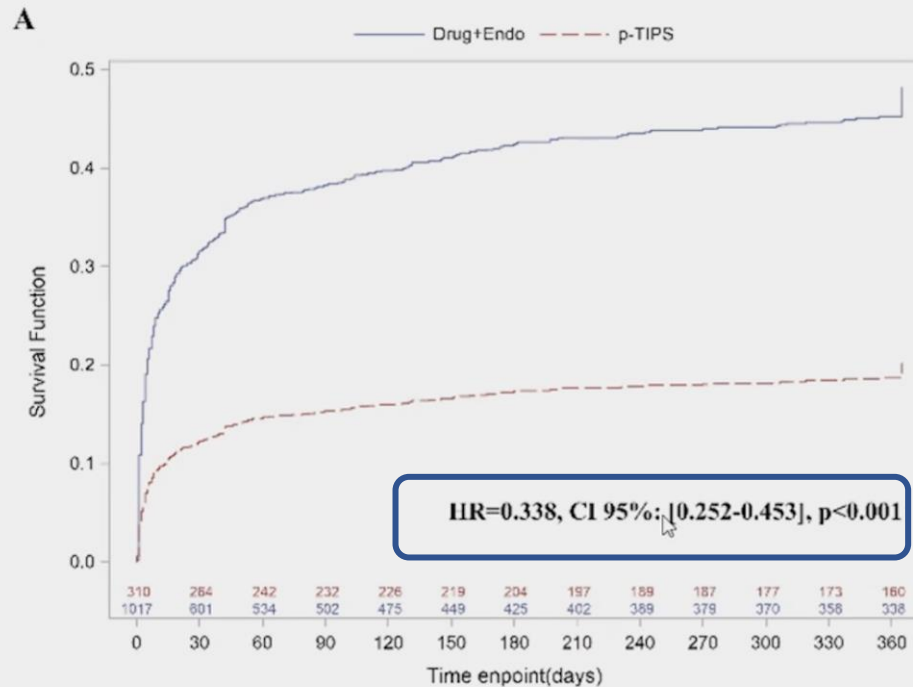
Impact of Treatment on mortality by Study (Child-C patients)

Hazard Ratio and 95% CL



¿Realmente aporta tanto beneficio?

Magnitud del beneficio



Nicoara-Farcau et al Gastroenterology 2021

- NNT p-TIPS Vs. Tratamiento estándar para prevenir una muerte al año=4
- NNT Tratamiento directo sobre las coronarias Vs. trombolisis para prevenir una muerte=31.8

- La cirrosis es una enfermedad de segunda división

Statement 6.11

Failure to control variceal bleeding despite combined pharmacological and endoscopic therapy is best managed by salvage PTFE-covered TIPS (B1)

(Changed)

TIPS as a Salvage for Variceal Bleeding

Author	N pts	% Pugh's C	Immediate control (%)	Previous endoscopic therapy	% rebleeding	Interval of rebleeding (days)	Site of rebleeding ^a	Mortality (%)
LaBerge et al. [3]	32	NG	97	Sclerotherapy	NG	NG	NG	NG
Haag et al. [4]	19	68	100	NG	11	10	SU	26 (30 days)
Helton et al. [5]	23	78	NG	Sclerotherapy	NG	NG	NG	56 (in hospital)
Le Moine et al. [6]	4	NG	NG	Sclerotherapy	NG	NG	NG	75 (30 days)
Rubin et al. [7]	12	NG	75	Sclerotherapy	NG	NG	NG	NG
				Band ligation				
Jalan et al. [8]	19	68	100	Sclerotherapy	15.6	30	V-SU	42 (30 days)
Jabbour et al. [9]	25	48	96	Sclerotherapy	NG	NG	V-SU-DU	44 (30 days)
Sanyal et al. [10]	30	73	100	Sclerotherapy	7	14	V-GU	40 (6 weeks)
Perarnau [11]	48	56	92	Sclerotherapy	8.5	NG	NG	25 (30 days)
Banares et al. [12]	56	41	95	Sclerotherapy	14	30	V	15 (30 days)
Gerbes et al. [13]	11	64	91	Sclerotherapy	27	14	NG	27 (30 days)
				Band ligation				
Chau et al. [2] ^b	112	71	96	Sclerotherapy	13 EV	7	EV-GV-SU	37 (30 days)
	EV 84	EV 75			14 GV			EV 34
	GV 28	GV 61						GV 42
Barange et al. [14] ^c	32	47	90	Sclerotherapy	14		NG	25 (30 days)
Bizollon et al. [15]	28	61	96	Sclerotherapy	8	14	V-SU	25 (40 days)
				Band ligation				
Azoulay et al. [1]	58	81	90	Sclerotherapy	6	14	V-GU	29 (30 days)

95%

Vangeli et al. J Hepatol 2002

26-75%

Statement 6.11

TIPS may be futile in patients with Child-Pugh ≥ 14 cirrhosis, or with a MELD score > 30 and lactate > 12 mmol/L, unless liver transplantation is envisioned in the short-term (B1)

The decision to perform TIPS in such patients should be taken on a case-by-case basis D1

(New)



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