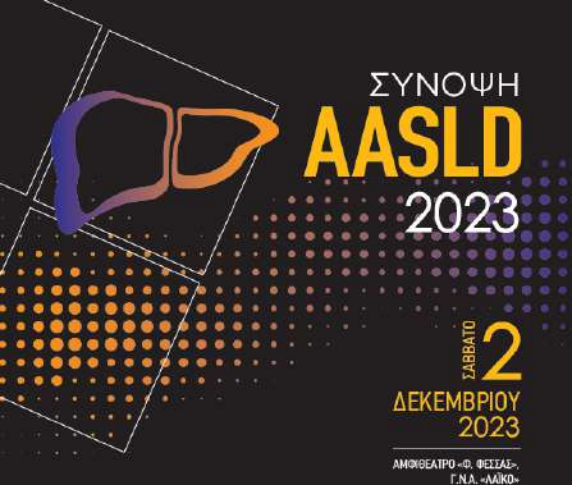


Ίνωση – Κίρρωση – Πυλαία υπέρταση

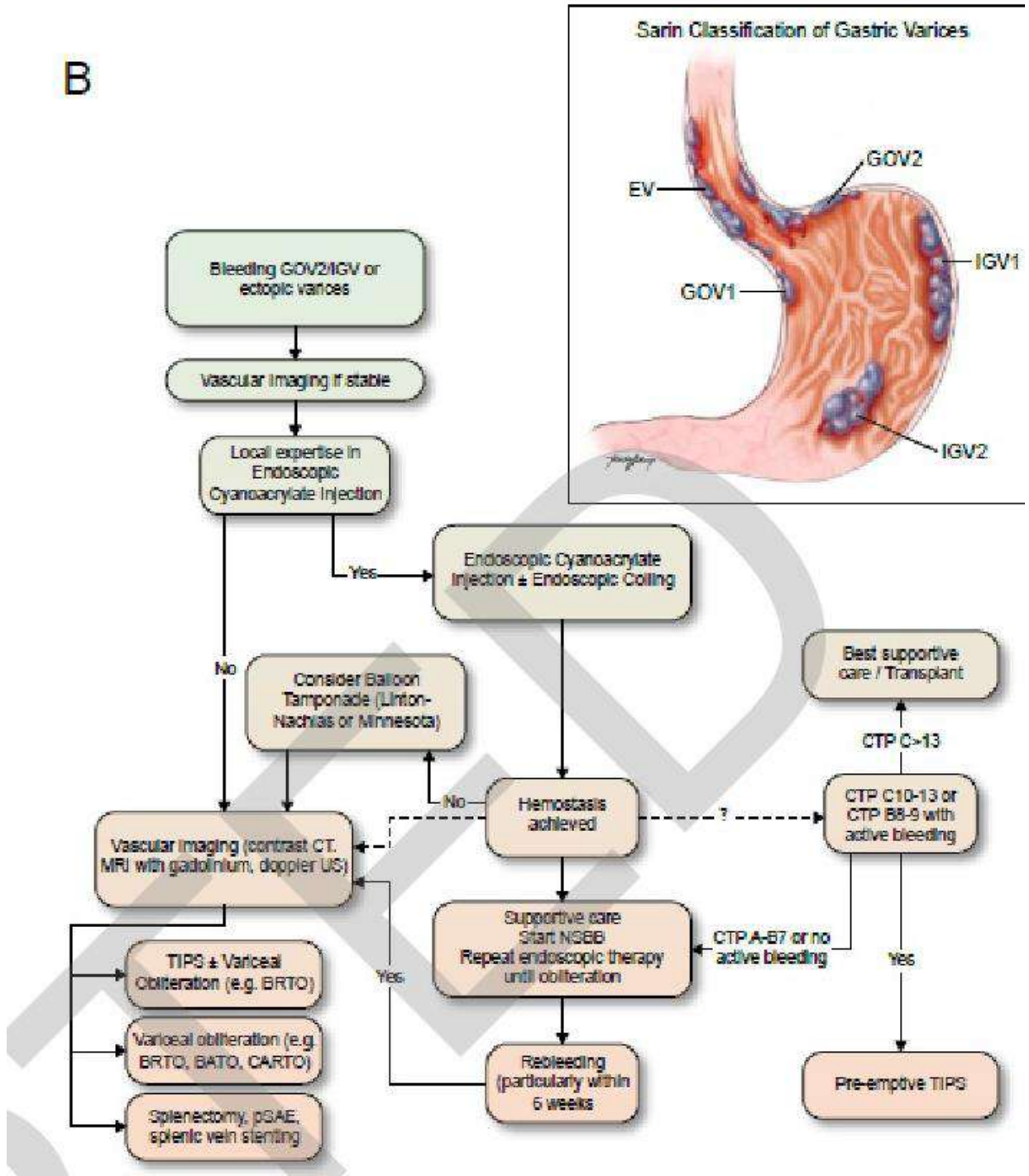
Χ.Τριάντος
Αναπληρωτής Καθηγητής Παθολογίας-Γαστρεντερολογίας
Ιατρικό τμήμα, Πανεπιστήμιο Πατρών

Serial endoscopic injection sclerotherapy with N-butyl cyanoacrylate glue versus radiological intervention for secondary prophylaxis of gastric variceal hemorrhage in patients with liver cirrhosis (CRISP-GV): A randomized controlled trial

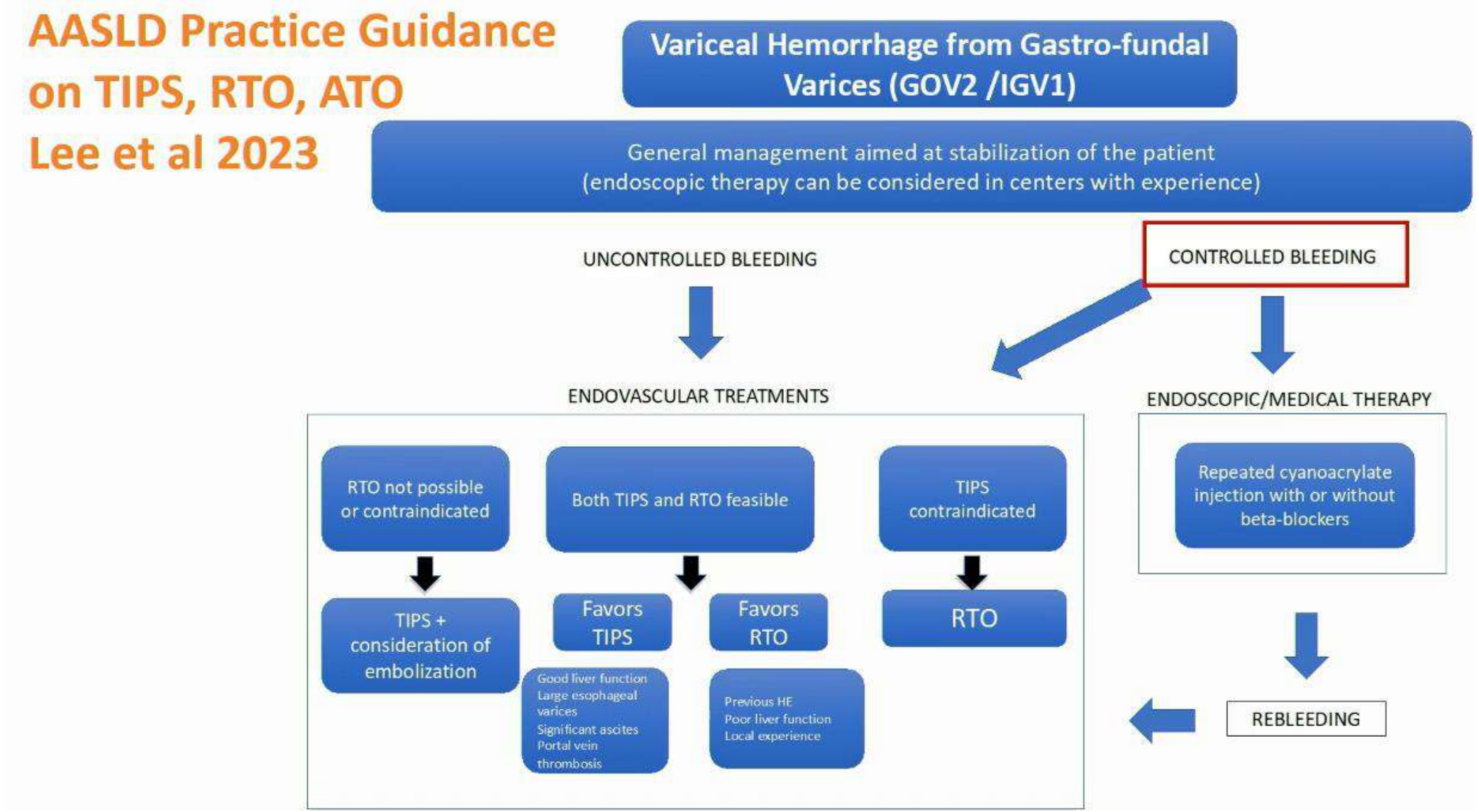
Biswas S, Vaishnav M, Swaroop S, Arora U, Aggarwal A, Elhence A, Gunjan D, Kedia S, Mahapatra SJ, Gamanagatti S, Shalimar*

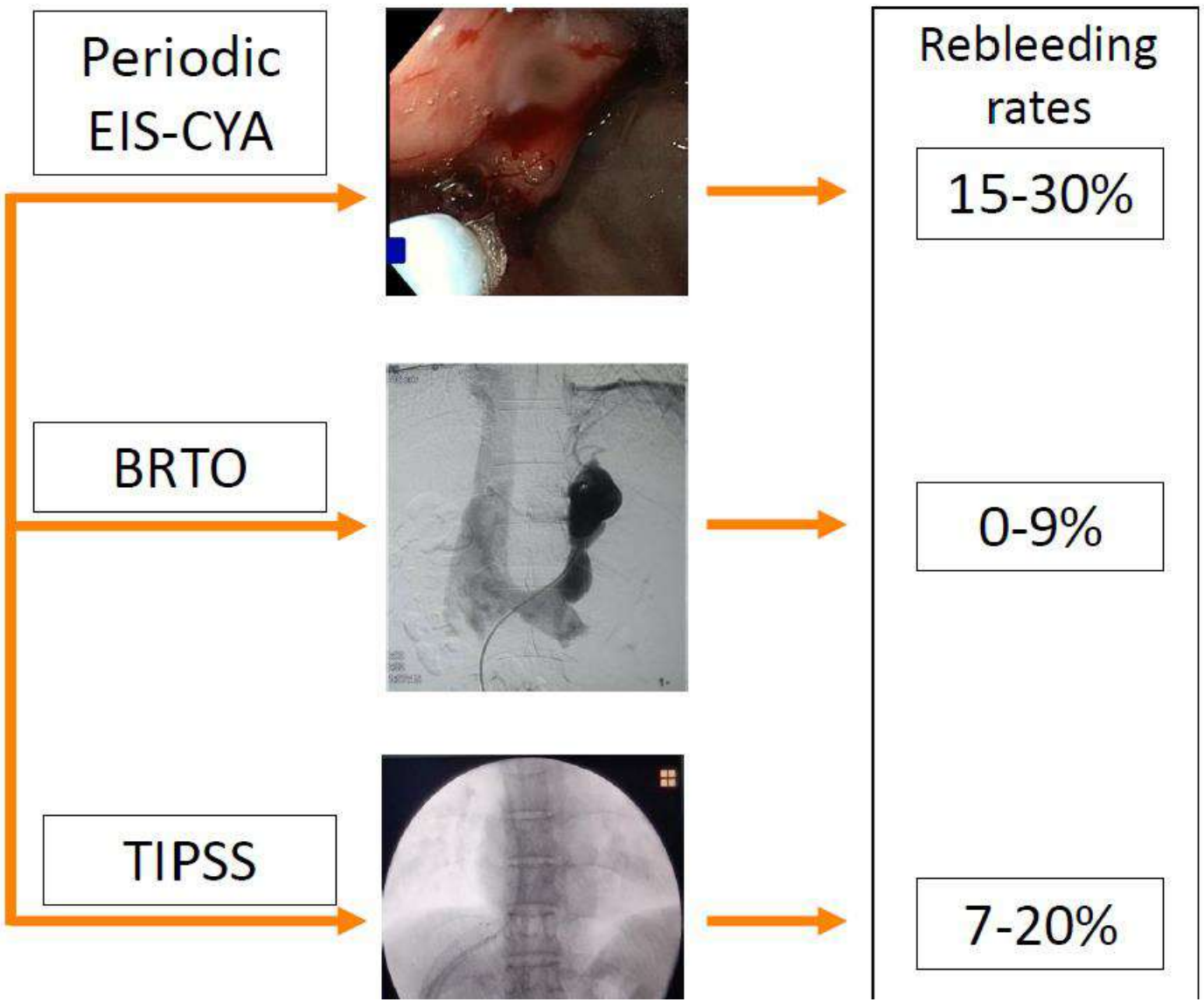
All India Institute of Medical Sciences, New Delhi

AASLD 2023 Guidelines



AASLD Practice Guidance on TIPS, RTO, ATO Lee et al 2023




Periodic EIS-CYA
BRTO
TIPSS
Rebleeding rates
15-30%
0-9%
7-20%

Society	Year	Recommendations	Choice between modalities
American Gastroenterology Association (AGA)	2021	BRTO=TIPSS	BRTO > TIPSS in the presence of GRS?
Baveno VII Consensus	2022	BRTO alternative to TIPSS	Based on shunt anatomy
American Association for the Study of Liver Diseases (AASLD)	2023	BRTO- if TIPSS contraindicated	Based on- anatomy, expertise, clinical profile

Υπόθεση

Radiologic intervention (BRTO/TIPSS) compared to periodic surveillance endoscopy with injection sclerotherapy using N-butyl cyanoacrylate glue is associated with a reduction in GV rebleeding rate from 25% to 2.5% over 1-year among cirrhosis patients with acute gastric variceal bleeding after primary hemostasis

Σκοπός της μελέτης

Primary Objective

- To compare the gastric variceal rebleeding rates between the Endoscopic and Radiologic Intervention arms at 1 year

Secondary Objectives

- Overall and GV rebleeding related mortality
- All-cause rebleed rates
- Complications
- Aggravation of portal hypertension
- Changes in liver function

All secondary objectives were assessed at 1 year from date of randomization

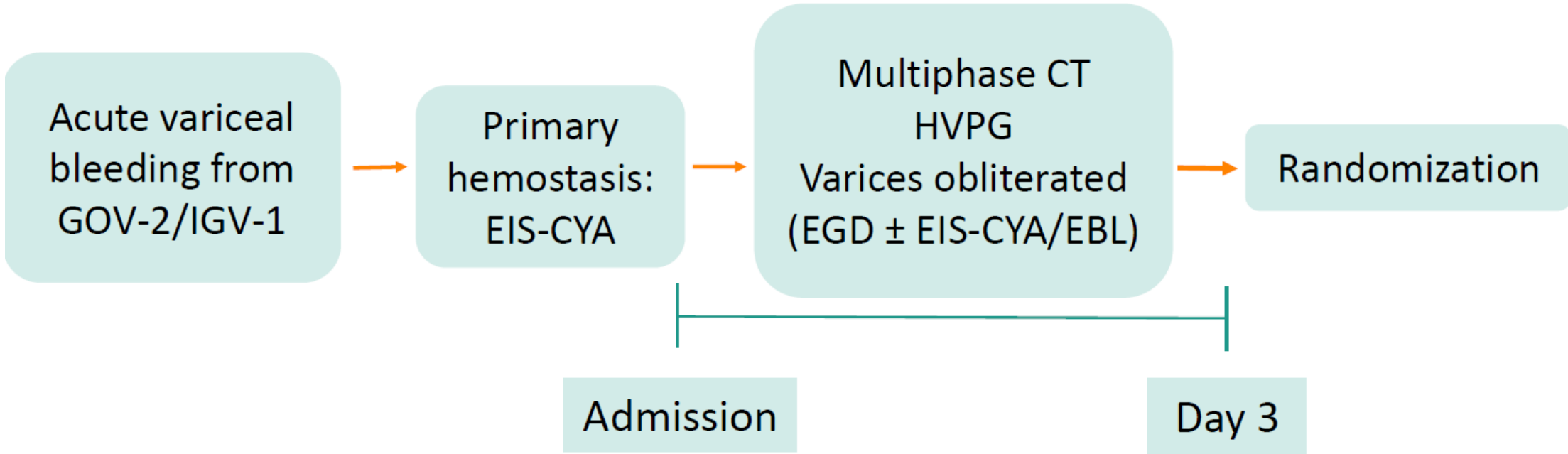
Κριτήρια

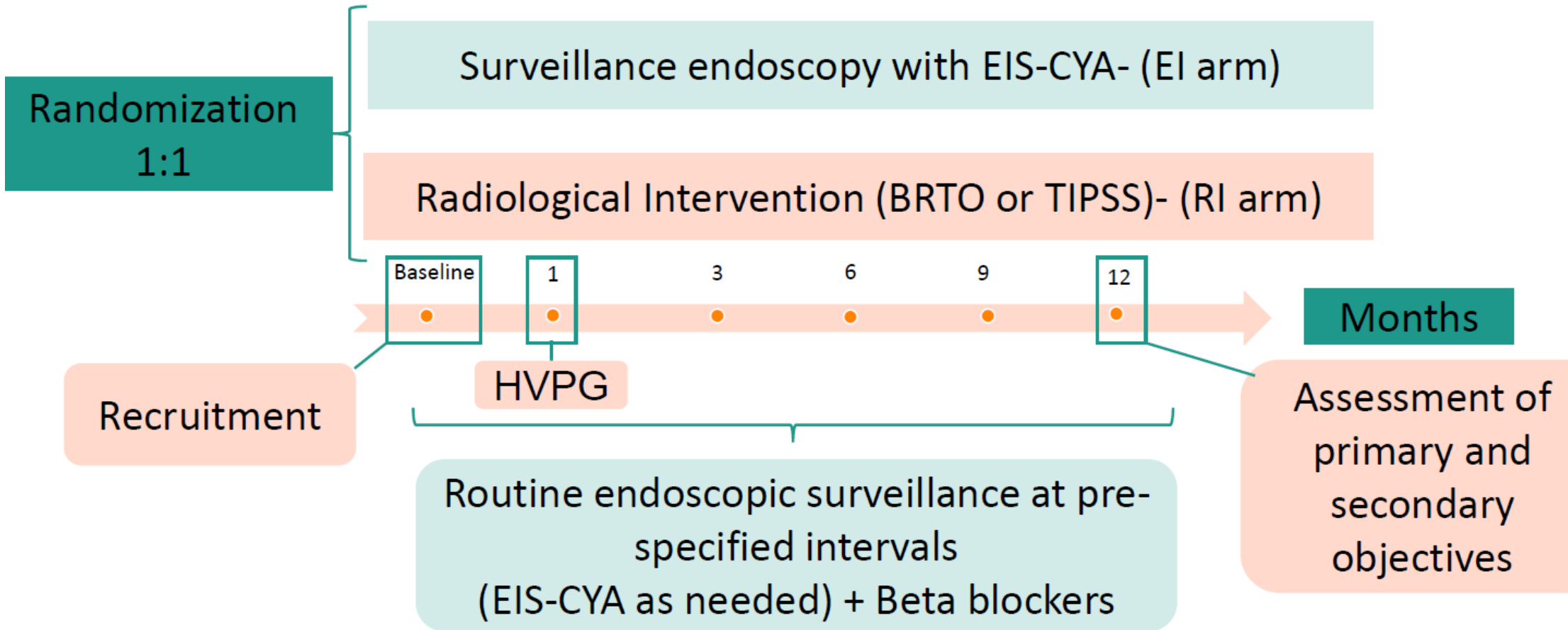
Inclusion Criteria

- Patients with cirrhosis of liver
- Acute variceal bleeding from GOV-2/IGV-1
- Age >18 years or <65 years

Exclusion Criteria

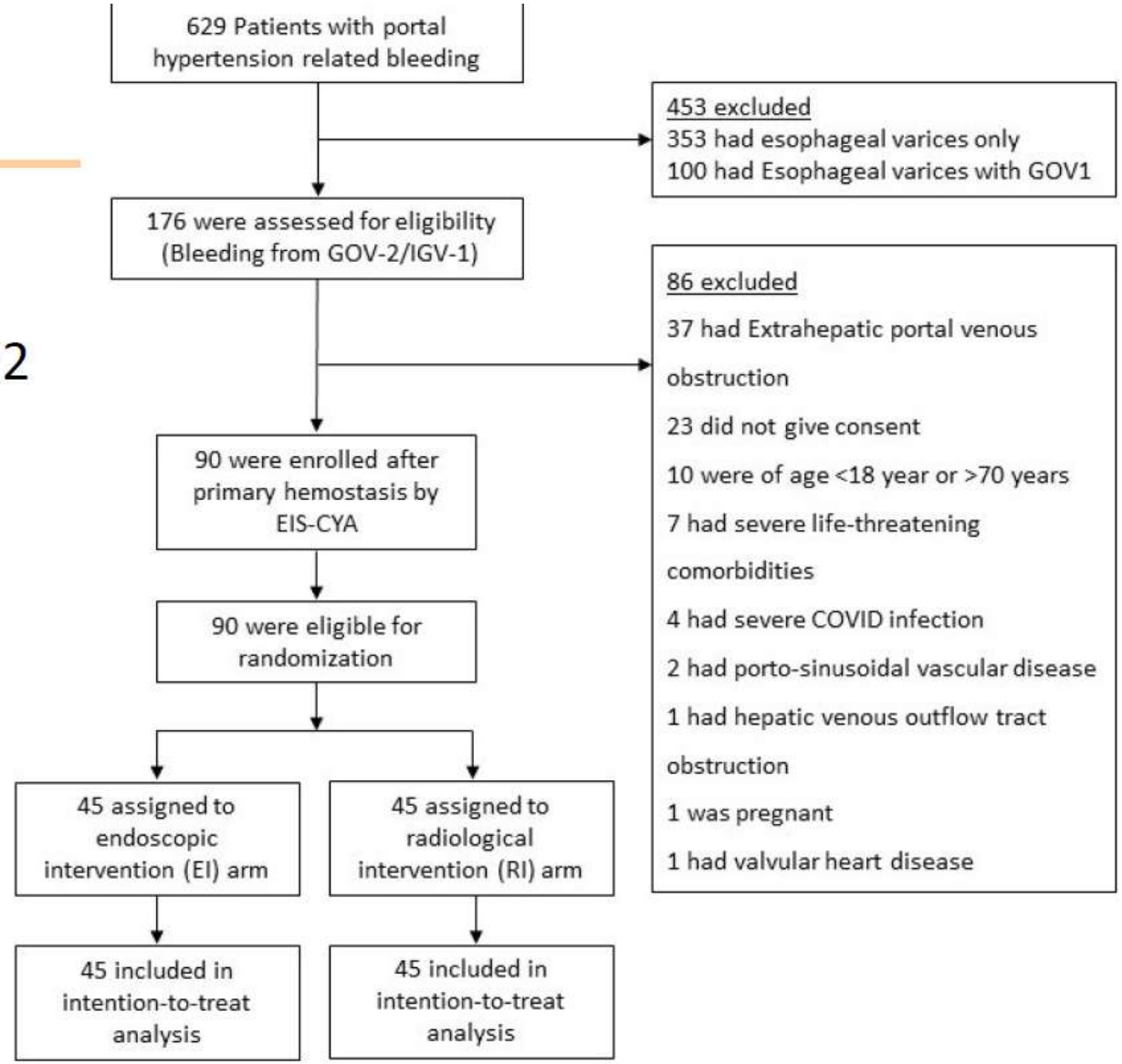
- Failure of primary hemostasis
- Porto sinusoidal vascular disorders
- Portal vein thrombosis
- Hepatocellular carcinoma
- Overt hepatic encephalopathy
- Contraindications to TIPSS/BRTO
- Chronic Kidney Injury or Creatinine >1.5
- MELD >20
- Pregnancy
- Acute-on-Chronic liver failure


Acute variceal bleeding from GOV-2/IGV-1
Primary hemostasis: EIS-CYA
Multiphase CT
HVPG
Varices obliterated
(EGD ± EIS-CYA/EBL)
Randomization
Admission
Day 3

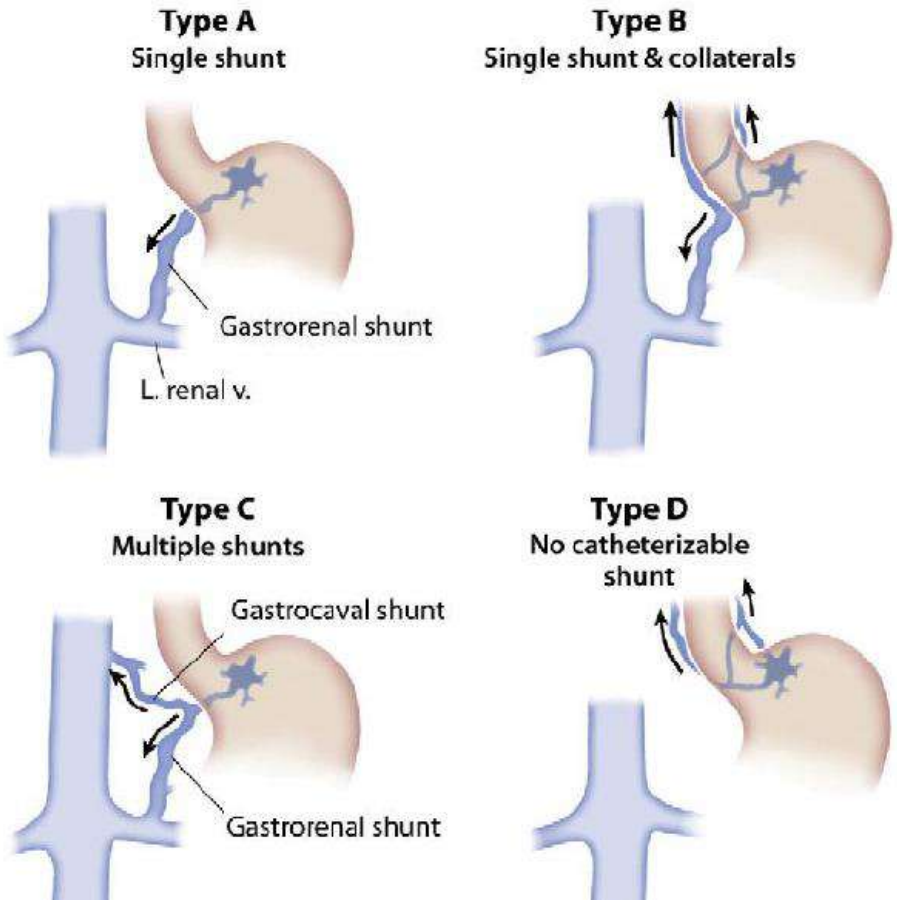

Randomization 1:1
Surveillance endoscopy with EIS-CYA- (EI arm)
Radiological Intervention (BRTO or TIPSS)- (RI arm)
Baseline
1
3
6
9
12
Months
Recruitment
HVPG
Routine endoscopic surveillance at pre-specified intervals
(EIS-CYA as needed) + Beta blockers
Assessment of primary and secondary objectives

Patient Flow

Duration: February 2021- July 2022



Απόφαση BRTO/TIPS

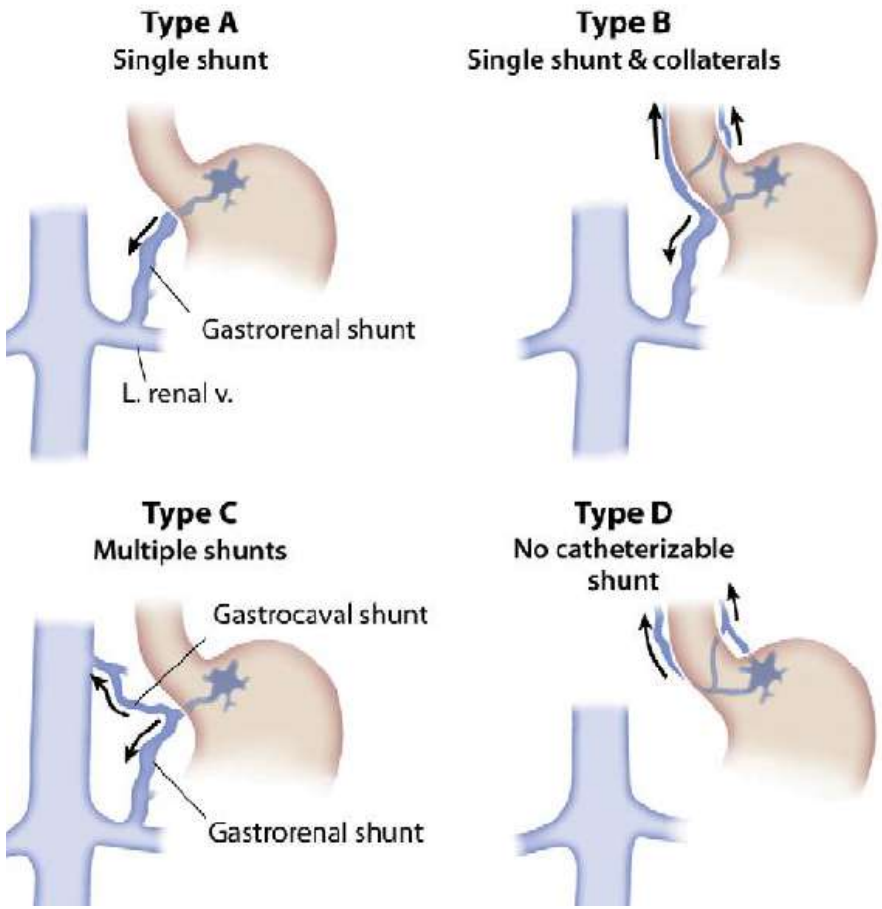


TIPSS performed with Type A/B/C pathway if BRTO not amenable/technically difficult- Decision by IR team

ΧΑΡΑΚΤΗΡΙΣΤΙΚΑ

Variables	Endoscopic Intervention (EI) arm (n=45)	Radiologic Intervention (RI) arm (n=45)
Age (years) (mean ± SD)	45·2 ± 12·8	45·6 ± 12·1
Etiology		
Alcohol	18 (40%)	15 (33.3%)
NAFLD	9 (20%)	14 (31.1%)
Others	18 (40%)	16 (35.6%)
Child's score	7·0 (6·0-8·0)	7·0 (6·0-8·0)
MELD score	12·4 (9·9-14·4)	11·7 (9·4-14·7)
Ascites		
Grade I-II : III	18 (40%) : 1 (2.2%)	20 (44.4%) : 3 (6.6%)
Hepatic Encephalopathy (Grade I)	8 (17.7%)	4 (8.8%)
Coexistent esophageal varices		
Small : Medium-Large	29 (64.4%) : 9 (20%)	31 (68.8%) : 3 (6.6%)
Median follow up time (months)	17.9 (6.7-22.9)	16.4 (12.9-21.8)

Values provided as median (IQR) or n (%) unless stated otherwise



Outflow pathway	Type A	Type B	Type D
BRTO (n=25)	23 (92%)	2 (8%)	0
TIPSS (n=20)	14 (70%)	0	6 (30%)

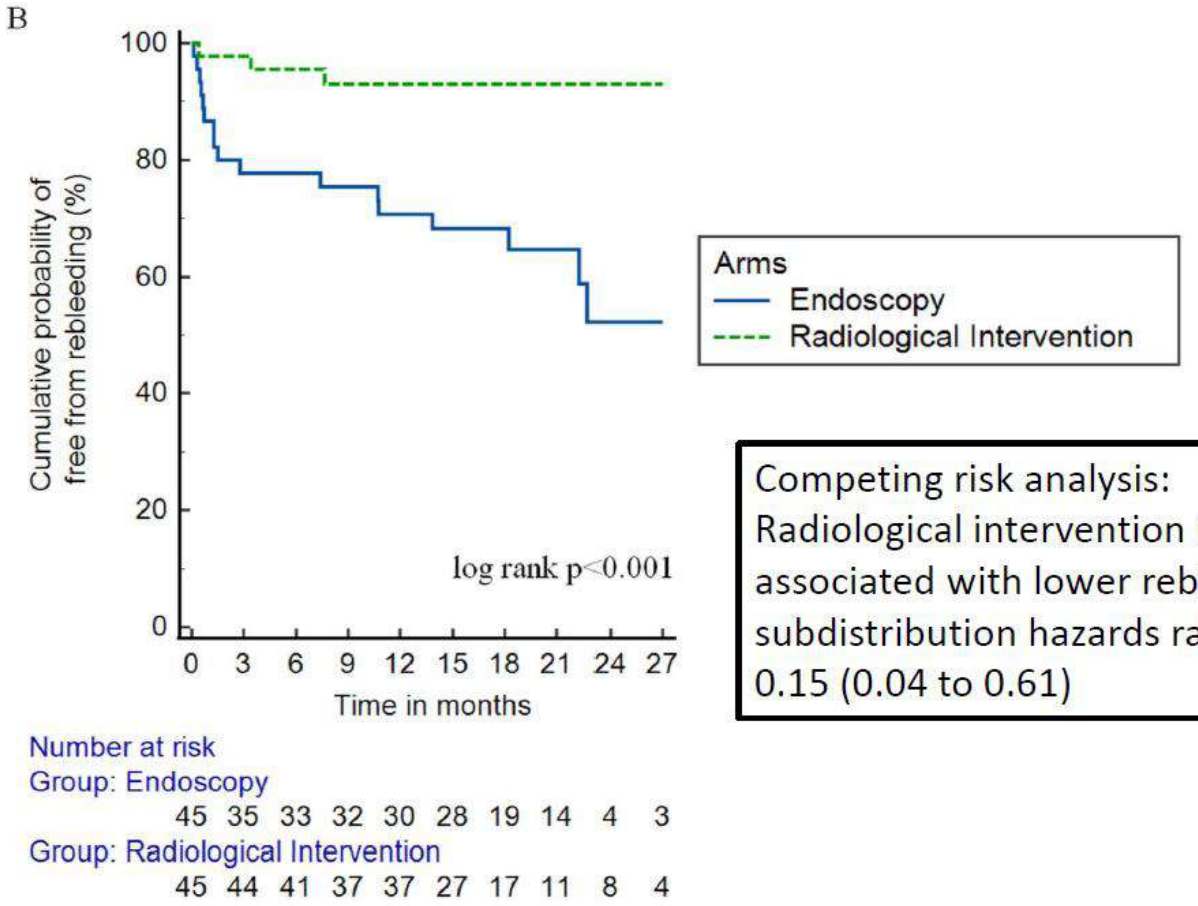
TIPSS performed with Type A pathway if BRTO not amenable/technically difficult- Decision by IR team

ΑΠΟΤΕΛΕΣΜΑΤΑ

Parameter	Endoscopic Intervention (EI) arm (n=45)	Radiologic Intervention (RI) arm (n=45)	p value	Absolute risk difference (%) with 95% CI	Numbers needed to treat (95 % CI)
Gastric varices rebleeding	11 (24·4%; 12·9-39·5)	1 (2·2%; 0·1-11·8)	**0.004**	22.2 (8.4-36.6)	**4.5** (2.7-11.9)
Esophageal varices	0 (0-7·9)	2 (4·4%; 0·5-15·1)	0.494	-4.4 (-14.8 to 4.1)	-22.5 (-24.7 to 6.7)
All-cause rebleeding	13 (28·9%; 16·4-44·3)	3 (6·7%; 1·4-18·3)	**0·011**	22.2 (6.4-37.3)	4.5 (2.7-15.6)
Rescue therapy	8 EIS-CYA, 2 BRTO 1 TIPSS	1 BRTO			

In the EI arm, source of rebleed was unknown in 2 patients
Note: All values presented as n (%; 95% CI)

ΑΠΟΤΕΛΕΣΜΑΤΑ



Competing risk analysis:
Radiological intervention independently associated with lower rebleeding subdistribution hazards ratio (sHR):
0.15 (0.04 to 0.61)

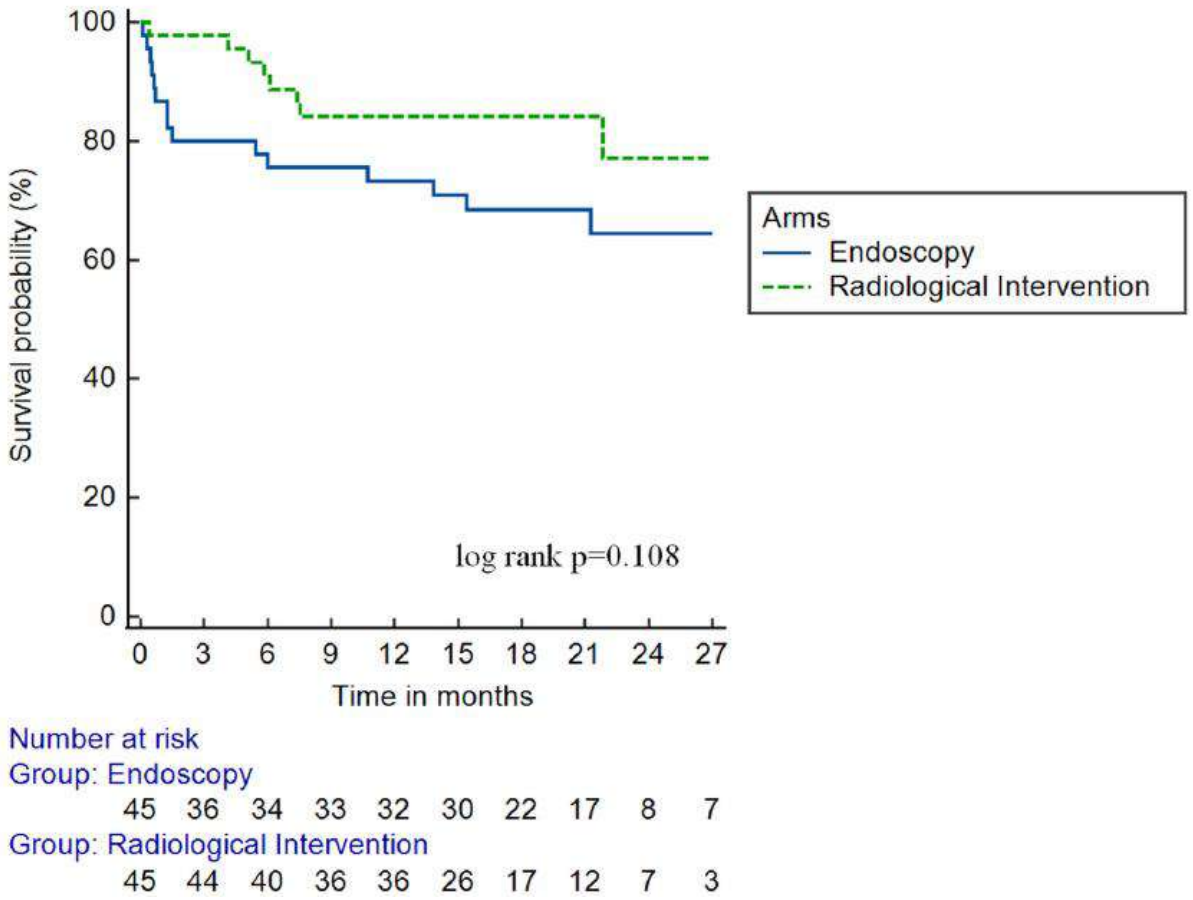
ΑΠΟΤΕΛΕΣΜΑΤΑ

Parameter	Endoscopic Intervention (EI) arm (n=45)	Radiologic Intervention (RI) arm (n=45)	p value	Absolute risk difference (%) with 95% CI	Numbers needed to treat (95 % CI)
Gastric variceal rebleed related mortality	8 (17·8%; 8·0-32·1)	1 (2·2%; 0·1-11·8)	**0·030**	15.6 (2.9-29.2)	**6.4** (3.4-34.1)
All-cause 1-year mortality	12 (26·7%; 14·6-41·9)	7 (15·6%; 6·5-29·5)	0·302	11.1 (5.9-27.5)	9 (-3.6 to 16.9)
Cause of death	GV rebleeding: 8 Sepsis: 2 AMI: 2	GV rebleed: 1 Sepsis: 1, ARDS: 1 ACLF: 4			

Note: All values presented as n (%; 95% CI)

AMI: Acute myocardial infarction; ACLF: Acute on chronic liver failure; ARDS: Acute respiratory distress syndrome

ΑΠΟΤΕΛΕΣΜΑΤΑ



ΑΠΟΤΕΛΕΣΜΑΤΑ

Parameter	EIS-CYA (n=45)	BRTO (n=25)	TIPSS (n=20)	EIS-CYA vs BRTO p value	EIS-CYA vs TIPSS p value	TIPSS vs BRTO p value
New onset/ aggravation of esophageal varices	5 (11·1%; 3·7-24·1)	6 (24·0%; 9·4-45·1)	1 (5·0%; 0·1-24·9)	0·183	0·657	0·112
New onset/ aggravation of portal hypertensive gastropathy	16 (35·6%; 21·9-51·2)	12 (48·0%; 27·8-68·7)	1 (5·0%; 0·1-24·9)	0·323	**0·013**	**0·002**
Median change in HVPG values after 1 month*	-1·0 (-5·0 to 1·0)	-2·0 (-4·5 to 5·0)[#]		0·715		

Note: All values presented as n (%; 95% CI)

*Comparison between EIS-CYA and BRTO

[#]Change in HVPG= HVPG at baseline-HVPG at 1 month

ΕΠΙΠΛΟΚΕΣ

Parameter	EIS-CYA (n=45)	BRTO (n=25)	TIPSS (n=20)	EIS-CYA vs BRTO p value	EIS-CYA vs TIPSS p value	TIPSS vs BRTO p value
New onset/worsening of pre-existing hepatic encephalopathy (HE)	3 (6.7%; 1.4-18.3)	2 (8.0%; 1.0-26.0)	6 (30.0%; 11.9-54.3)	1.0	**0.020**	0.113
New onset/worsening of pre-existing ascites	2 (4.4%; 0.5-15.1)	9 (36.0%; 18.0-57.5)	3 (15.0%; 3.2-37.9)	**0.001**	0.165	0.177
New onset/worsening of pre-existing pleural effusion	1 (2.2%; 0.1-11.8)	4 (16.0%; 4.5-36.1)	1 (5.0%; 0.1-24.9)	0.051	0.524	0.362

Parameter	EIS-CYA (n=45)	BRTO (n=25)	TIPSS (n=20)	EIS-CYA vs BRTO p value	EIS-CYA vs TIPSS p value	TIPSS vs BRTO p value
Median change in CTP score over 1 year	0 (-0·5 to 1·0)	1 (0-3·0)	1 (0-2·0)	0·274	0·176	0·082
Median change in MELD score over 1 year	-1·9 (-5·1 to 0·9)	0·7 (-2·1 to 1·8)	0 (-1·6 to 1·5)	**0·046**	0·068	0·940

Note: All values presented as median difference (IQR)

Note: Change in CTP/MELD score= CTP/MELD at Baseline- CTP/MELD at 1 year

BRTO VS TIPSS

Parameter	BRTO (n=25)	TIPSS (n=20)	p value
All cause rebleed at 1-year (n=3)	2 (8·0%; 1·0 to 26·0)	1 (5·0%; 1·0 to 24·9)	1·0
GV rebleed	1 (4·0%; 0·1 to 20·4)	0 (0; 0 to 16·8)	
EV rebleed	1 (4·0%; 0·1 to 20·4)	1 (5·0%; 0·1 to 24·9)	
All-cause mortality at 1-year (n=7)	4 (16·0%; 4·5 to 36·1)	3 (15·0%; 3·2 to 37·9)	1·0
Causes of death GV rebleed	1	0	
Acute-on-chronic liver failure	2	2	
Sepsis with septic shock	1	0	
Pneumonia with ARDS	0	1	
Need for rescue therapy	2 (8·0%; 1·0 to 26·0)	0 (0; 0 to 16·8)	0·495

Note: No difference in demographics between patients undergoing BRTO and TIPSS

ΣΥΜΠΕΡΑΣΜΑΤΑ

- Patients with Gastric variceal bleeding may benefit from Radiological Interventions (BRTO/TIPSS) for secondary prophylaxis
- Choice of radiologic procedure (BRTO/TIPSS) should be guided by available technical experience
- Longer follow-up required for impact on overall survival?

ΣΥΜΠΕΡΑΣΜΑΤΑ

Radiological intervention (BRTO/TIPS) compared to Endoscopic-CYA alone for secondary prophylaxis decreases GV related rebleeding and mortality at 1 year in patients with gastric variceal hemorrhage

HIGH DOSES OF ALBUMIN INCREASES MORTALITY AND COMPLICATIONS IN TERLIPRESSIN TREATED PATIENTS WITH CIRRHOSIS: INSIGHTS FROM THE ATTIRE TRIAL

Nikolaj Torp[1,2], Louise China[3], Mads Israelsen[1], Aleksander Krag[1,2] and Alastair O'Brien[3,4]

1) Odense University Hospital, Denmark 2) University of Southern Denmark 3) Royal Free Hospital London, United Kingdom 4) University College London, United Kingdom

ΣΚΟΠΟΣ

A post-hoc analysis of ATTIRE trial data comparing safety of serum targeted albumin infusions to standard of care in patients with cirrhosis recieving terlipressin

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of Albumin Infusions in Hospitalized Patients with Cirrhosis

Louise China, Ph.D., Nick Freemantle, Ph.D., Ewan Forrest, M.D., Yiannis Kallis, Ph.D., Stephen D. Ryder, D.M., Gavin Wright, Ph.D., Andrew J. Portal, M.D., Natalia Becares Salles, Ph.D., Derek W. Gilroy, Ph.D., and Alastair O'Brien, Ph.D., for the ATTIRE Trial Investigators*

Table 3. Serious Adverse Events.*

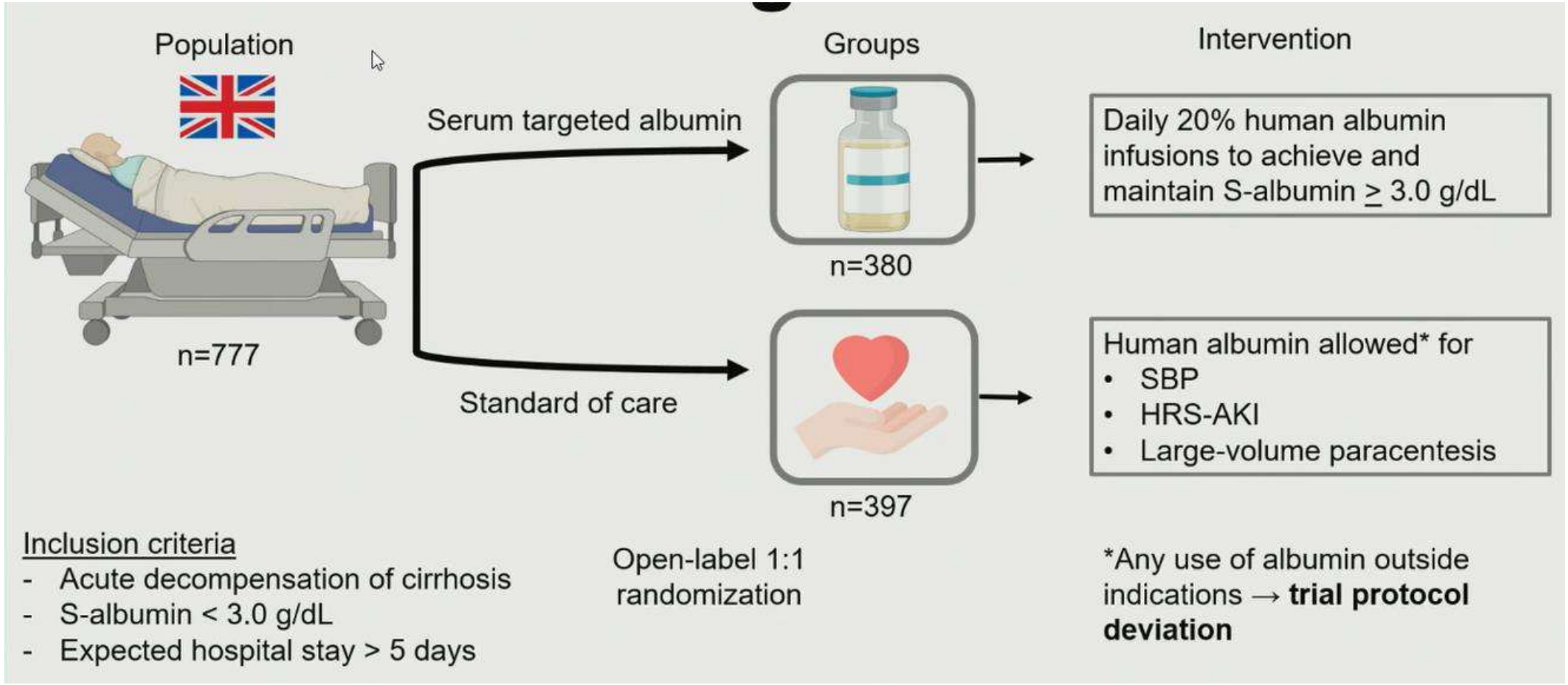
Event	Albumin Group (N=380)	Standard-Care Group (N=397)	All Patients (N=777)
		number of events	
All serious adverse events that included pulmonary edema or gastrointestinal bleeding‡			
Any pulmonary edema or fluid overload	23	8	31

ATTIRE

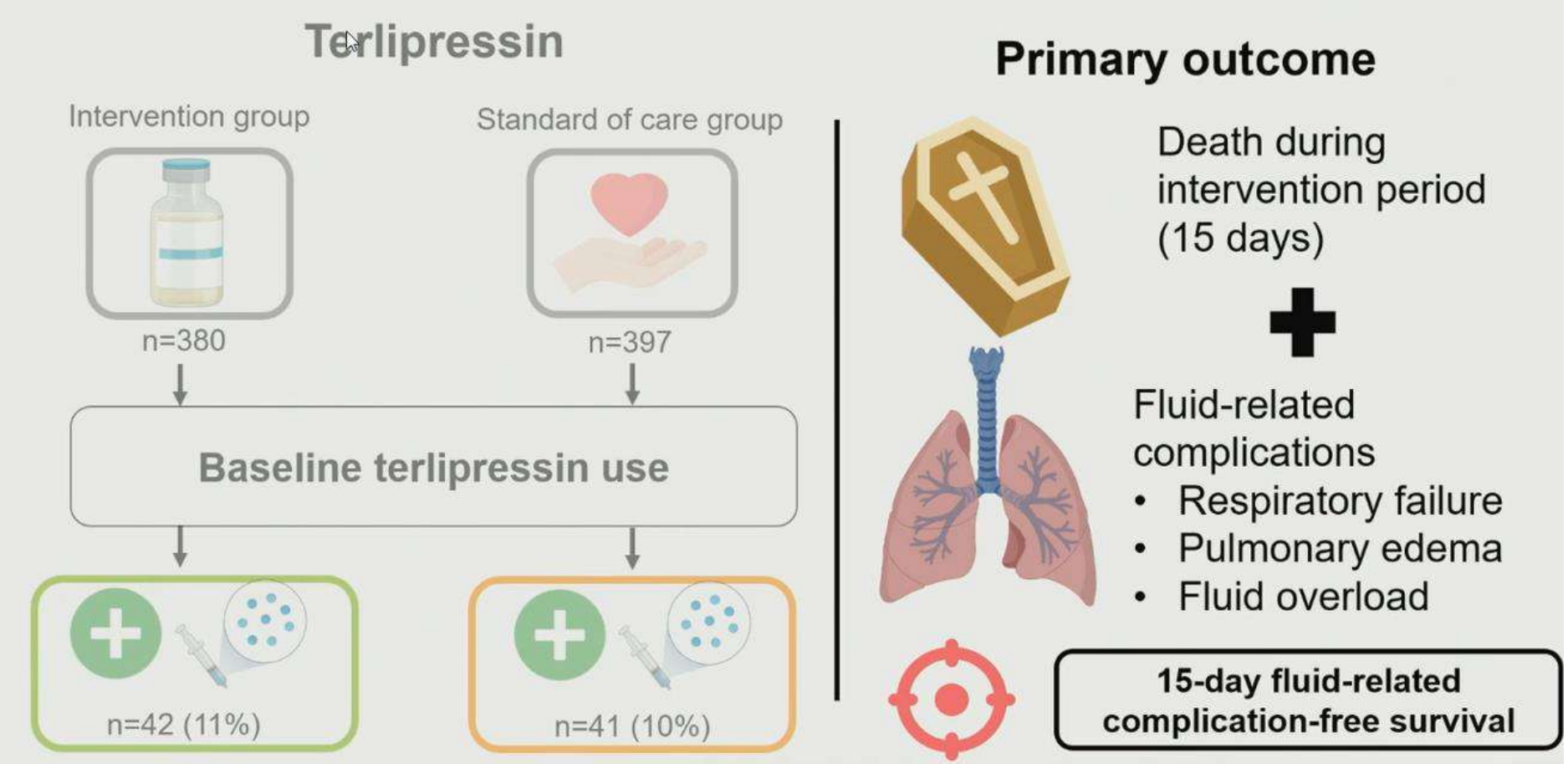
- Investigator-initiated - **1:1** RCT of **human albumin** - **n=777** w/**acute decompensation** of cirrhosis
- **Negative** primary outcome (infection, kidney dysfunction or death)
- Albumin group → **Pulmonary edema** & **fluid overload**↑

China et al. NEJM 2021

ATTIRE


Population
Groups
Intervention
Serum targeted albumin
n=777
n=380
Daily 20% human albumin infusions to achieve and maintain S-albumin ≥ 3.0 g/dL
Standard of care
n=397
Human albumin allowed* for
• SBP
• HRS-AKI
• Large-volume paracentesis
Inclusion criteria
- Acute decompensation of cirrhosis
- S-albumin < 3.0 g/dL
- Expected hospital stay > 5 days
Open-label 1:1 randomization
*Any use of albumin outside indications → **trial protocol deviation**

ATTIRE

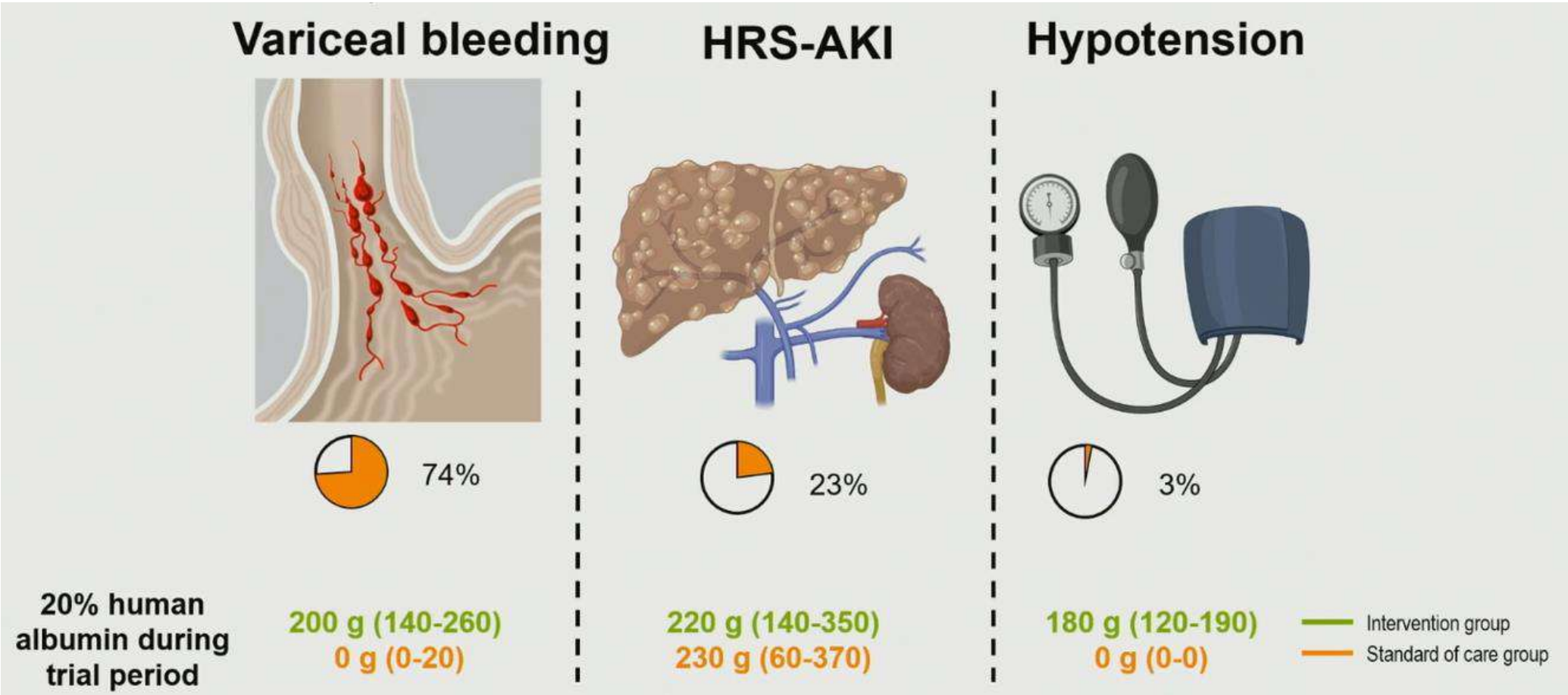

Terlipressin
Intervention group
Standard of care group
n=380
n=397
Baseline terlipressin use
n=42 (11%)
n=41 (10%)
Primary outcome
Death during intervention period (15 days)
+
Fluid-related complications
• Respiratory failure
• Pulmonary edema
• Fluid overload
15-day fluid-related complication-free survival

ATTIRE

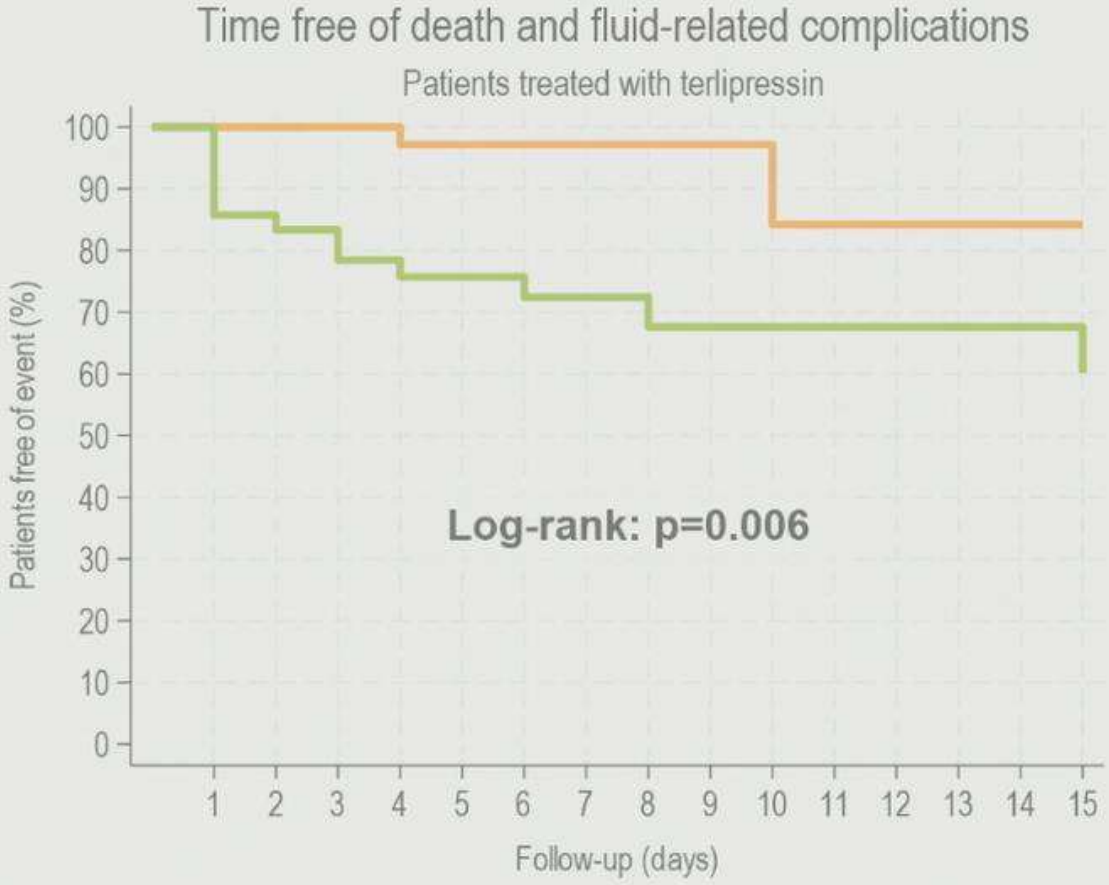
	Intervention group (n=42)	Standard of care group (n=41)
Sex (male), n	31 (74%)	31 (76%)
Age, years	53.6 (± 9.9)	55.8 (± 12.3)
Alcohol-related cirrhosis, n	37 (88%)	34 (83%)
MELD	19 (15-23)	18 (14-24)
Albumin (g/dL)	2.4 (2.1-2.5)	2.4 (2.2-2.6)
INR	1.6 (1.4-1.9)	1.5 (1.4-1.8)
Creatinine (mg/dL)	0.9 (0.7-1.5)	1.0 (0.7-1.6)
Bilirubin (mg/dL)	3.6 (2.6-7.5)	3.7 (1.8-6.1)
Sodium (mmol/L)	135 (130-137)	135 (132-138)
White blood cells (10^9/L)	7.0 (5.2-10.3)	7.5 (4.9-11.0)
CRP (mg/L)	2.4 (1.3-7.1)	1.4 (1.0-4.5)

Data are presented as mean (±SD) or median (IQR) for continuous measures, and n (%) for categorical measures.

Ενδείξεις χορήγησης τερλιπρεσσίνης



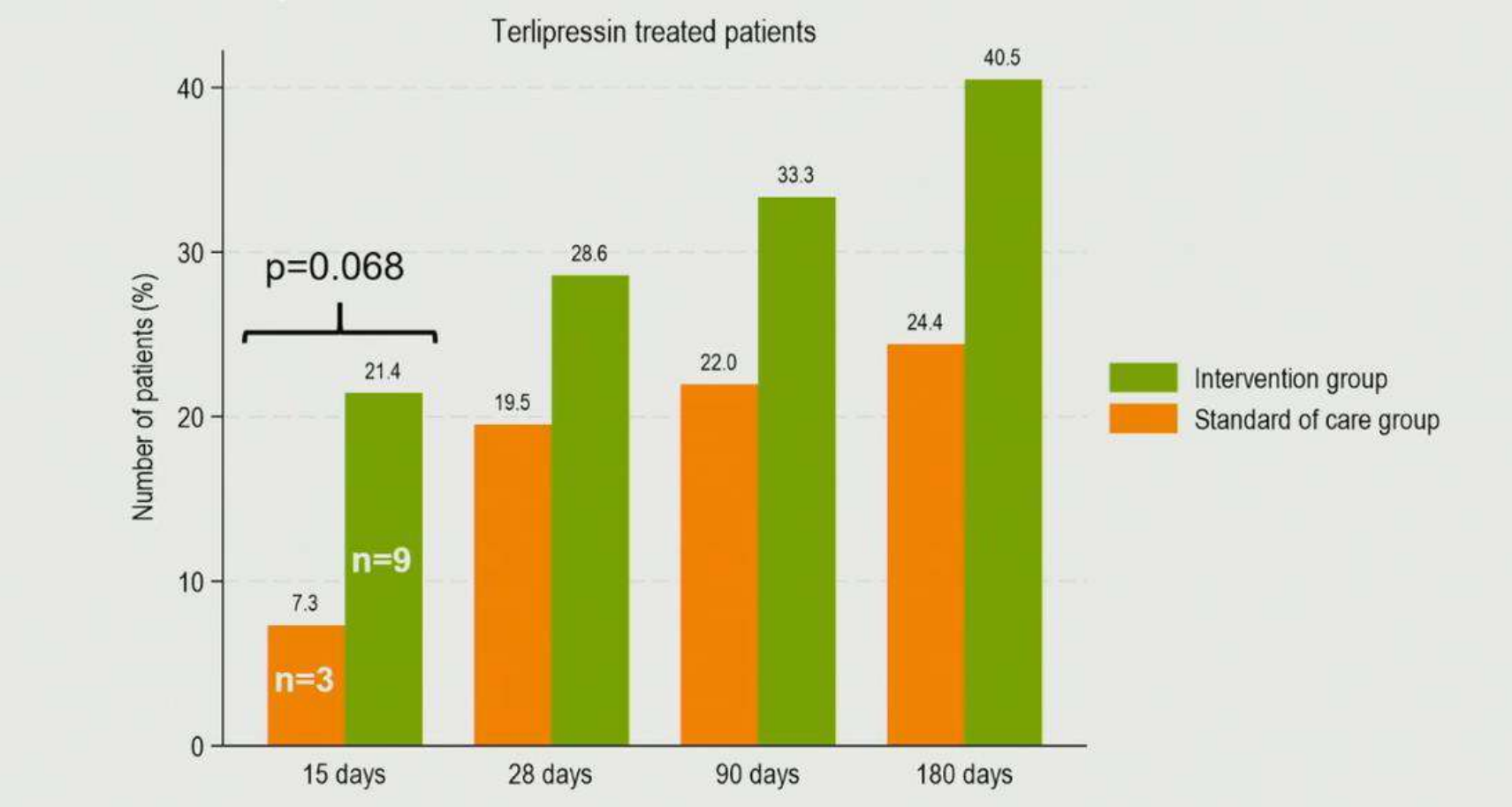
Πρωτογενές καταληκτικό σημείο



Cox regression

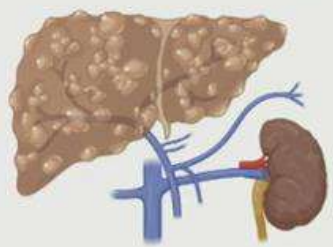
Variable	aHR	95% CI	P-value
Intervention group, yes	5.63	1.60-19.86	0.007
Baseline MELD	1.05	1.02-1.08	0.002

Θνητότητα


Terlipressin treated patients
Number of patients (%)
40
30
20
10
0
p=0.068
7.3
21.4
n=3
n=9
19.5
28.6
22.0
33.3
24.4
40.5
15 days
28 days
90 days
180 days
Intervention group
Standard of care group

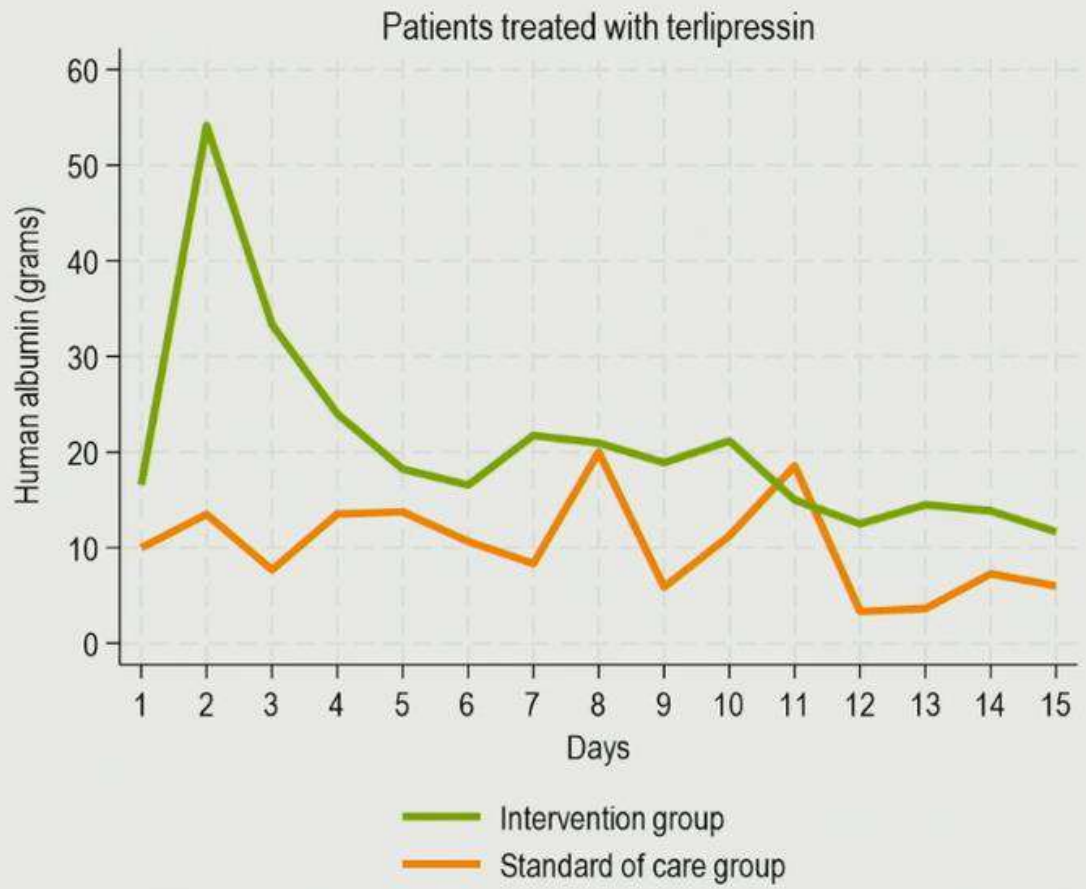
Death or fluid-related complication

Variceal bleeding
Intervention group: **n = 6**
Standard of care group: **n = 0**



HRS-AKI
Intervention group: **n = 5**
Standard of care group: **n = 3**

Hypotension
Intervention group: **n = 2**
Standard of care group: **n = 0**



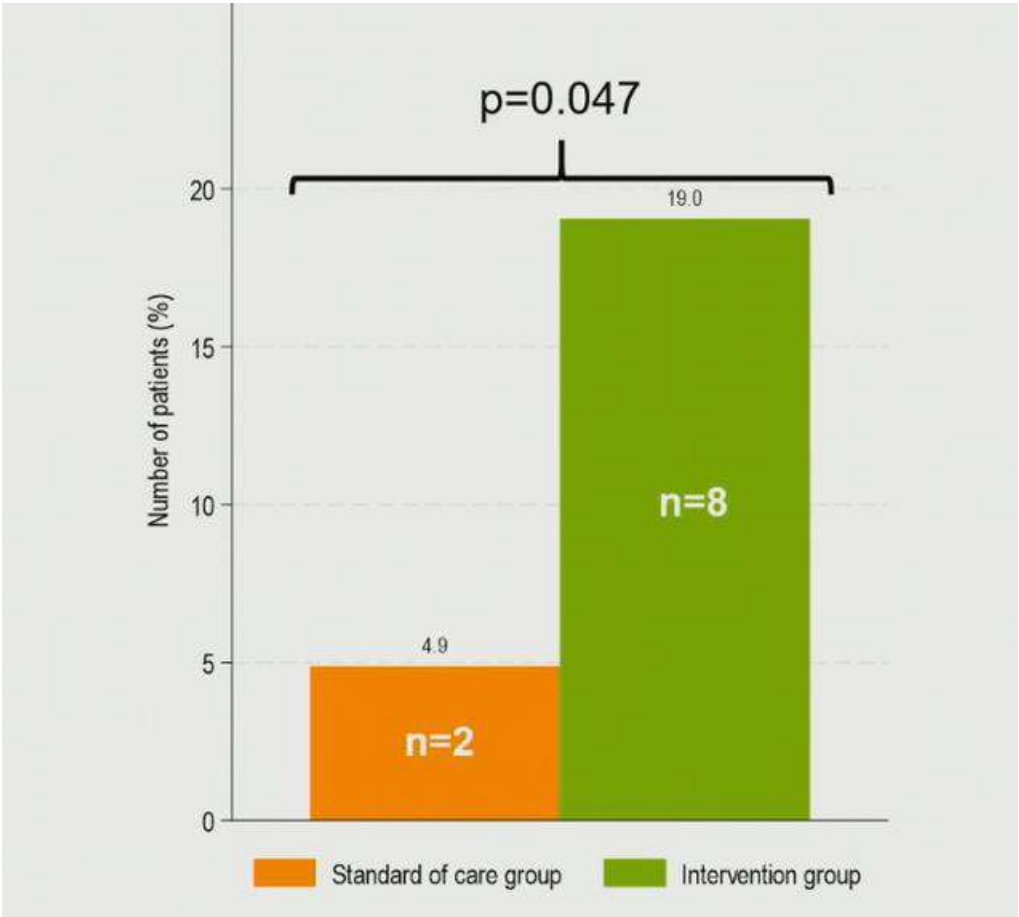
Amount of 20% human albumin (mean)

Intervention	Standard of care
209 grams	96 grams

Δ

p<0.001

Επιπλοκές σχετικά με τη χορήγηση υγρών



Περιορισμοί

- Low numbers and a **post-hoc analysis** of trial data
- Cannot attribute the **mode of administration** (bolus or continous infusion) or **dosing** for terlipressin to outcomes
- **No** available **information** on **fluid treatment** regimens for patients **prior** to **trial inclusion**

Συμπεράσματα

- **High albumin doses** – as a result of a serum albumin guided treatment strategy – was associated with an **increased risk of death and fluid-related complications** in patients with cirrhosis recieving **terlipressin**
- Findings were **independent** of the patients **disease severity** (MELD score)

Key take-away

Patients with **variceal bleeding** treated with terlipressin, seems especially **prone** to **unfavorable outcomes** when treated with concomitant **20% human albumin**

Albumin Dosing With Terlipressin for the Treatment of HRS-AKI: A Double-Edged Sword

Florence Wong[1], S. Chris Pappas[2], Michael P. Curry[3], Pratima Sharma[4], Khurram Jamil [5]

[1] Department of Medicine, University of Toronto, Toronto, Ontario, Canada; [2] Orphan Therapeutics, LLC, Longboat Key, FL, USA; [3] Department of Medicine, Beth Israel Deaconess Medical Centre, Boston, MA, USA; [4] University of Michigan Medical Center, Ann Arbor, MI, USA; [5] Mallinckrodt Pharmaceuticals, Bridgewater, NJ, USA

Σκοπός

- To evaluate the optimal dose of albumin with respect to efficiency and safety, based on the pooled analysis of the 2 largest randomized controlled trials of terlipressin plus albumin versus placebo in patients with HRS type 1

Μέθοδος

- Data were pooled from 2 Phase III randomized, placebo-controlled studies in patients with cirrhosis, ascites & HRS1:
  - CONFIRM[1] (NCT02770716; n = 300)
  - REVERSE[2] (NCT01143246; n = 196)
- Patients were divided into albumin dose quartiles and compared

1. Wong F et al. *N Engl J Med*. 2021;384(9):818–828. 2. Boyer TD et al. *Gastroenterology*. 2016;150(7):1579–1589.

Τερλιπρεσσίνη με αλβουμίνη στην αντιμετώπιση του HRS type 1: δεδομένα από RCT φάσης III

Albumin was administered in 165 patients (83%) in the terlipressin group (mean [±SD] total dose per person, 199.4±146.8 g over a median of 5.0 days) and 92 patients (91%) in the placebo group (mean total dose, 239.5±183.6 g over a median of 5.5 days).

Τυχαιοποίηση 2:1 για να λάβουν **τερλιπρεσσίνη ή placebo** έως και 14 d

Και στις δύο ομάδες→ ισχυρή ένδειξη για **συγχορήγηση αλβουμίνης**

End Point	Terlipressin	Placebo	P Value
	number/total number of patients (percent)		
Primary end point of verified reversal of HRS†			0.006
Clinical success	63/199 (32)	17/101 (17)	
Clinical failure	121/199 (61)	81/101 (80)	
Competing event‡			
Liver transplantation	10/199 (5)	2/101 (2)	
Death	5/199 (3)	0/101	

Η τερλιπρεσσίνη ήταν αποτελεσματικότερη στη βελτίωση της νεφρικής λειτουργίας, αλλά συσχετίστηκε με **ανεπιθύμητες ενέργειες**, συμπεριλαμβανομένης της **αναπνευστικής ανεπάρκειας.**

Event	Terlipressin (N=200)	Placebo (N=99)
	number of patients (percent)	
Adverse events of any grade†	176 (88)	88 (89)
Adverse events leading to discontinuation of the trial regimen	24 (12)	5 (5)
Serious adverse events with an incidence of ≥3% in either trial group‡		
Any	130 (65)	60 (61)
Cardiac disorders	8 (4)	6 (6)
Atrial fibrillation	1 (<1)	3 (3)
Gastrointestinal disorders	30 (15)	6 (6)
Abdominal pain	10 (5)	1 (1)
Gastrointestinal hemorrhage	8 (4)	0
General disorders and administration-site conditions	11 (6)	6 (6)
Multiple organ dysfunction syndrome	9 (4)	3 (3)
Hepatobiliary disorders	37 (18)	29 (29)
Chronic hepatic failure	9 (4)	8 (8)
Alcoholic cirrhosis	4 (2)	3 (3)
Hepatic cirrhosis	6 (3)	2 (2)
Hepatic failure	9 (4)	10 (10)
Worsening of HRS	3 (2)	3 (3)
Infections and infestations	19 (10)	5 (5)
Pneumonia	4 (2)	3 (3)
Sepsis	9 (4)	0
Nervous system disorders	13 (6)	3 (3)
Hepatic encephalopathy	9 (4)	3 (3)
Respiratory, thoracic, and mediastinal disorders§	33 (16)	8 (8)
Acute respiratory failure	8 (4)	2 (2)
Respiratory failure	20 (10)	3 (3)
Vascular disorders	10 (5)	4 (4)
Shock	5 (2)	3 (3)

Wong F, et al. *N Engl J Med*. 2021;384(9):818-828.

Gastroenterology 2016;150:1579–1589

CLINICAL—LIVER

Terlipressin Plus Albumin Is More Effective Than Albumin Alone in Improving Renal Function in Patients With Cirrhosis and Hepatorenal Syndrome Type 1

Thomas D. Boyer,[1] Arun J. Sanyal,[2] Florence Wong,[3] R. Todd Frederick,[4] John R. Lake,[5] Jacqueline G. O'Leary,[6] Daniel Ganger,[7] Khurram Jamil,[8] Stephen Chris Pappas,[9] and the REVERSE Study Investigators

[1]*Department of Medicine, University of Arizona, Tucson, Arizona;* [2]*Department of Medicine, Virginia Commonwealth University, Richmond, Virginia;* [3]*Department of Medicine, University of Toronto, Toronto, Ontario, Canada;* [4]*Department of Medicine, California Pacific Medical Center, San Francisco, California;* [5]*Department of Medicine, University of Minnesota, Minneapolis, Minnesota;* [6]*Department of Medicine, Baylor University Medical Center, Dallas, Texas;* [7]*Department of Medicine, Northwestern University, Chicago, Illinois;* [8]*Ikaria Therapeutics, LLC, a Mallinckrodt Company, Hampton, New Jersey;* [9]*Orphan Therapeutics, Lebanon, New Jersey*

See editorial on page 1525.

BACKGROUND & AIMS: Hepatorenal syndrome type 1 (HRS-1) in patients with cirrhosis and ascites is a functional, potentially reversible, form of acute kidney injury characterized by rapid (<2 wk) and progressive deterioration of renal function. Terlipressin is a synthetic vasopressin analogue that acts, via vascular vasopressin V1 receptors, as a systemic vasoconstrictor. We performed a phase 3 study to evaluate the efficacy and safety of intravenous terlipressin plus albumin vs placebo plus albumin in patients with HRS-1. **METHODS:** Adult patients with cirrhosis, ascites, and HRS-1 (based on the 2007 International Club of Ascites criteria of rapidly deteriorating renal function) were assigned randomly to groups given intravenous terlipressin (1 mg, n = 97) or placebo (n = 99) every 6 hours with concomitant albumin. Treatment continued through day 14 unless the following occurred: confirmed HRS reversal (CHRSR, defined as 2 serum creatinine [SCr] values ≤1.5 mg/dL, at least 40 hours apart, on treatment without renal replacement therapy or liver transplantation) or SCr at or above baseline on day 4. The primary end point was the percentage of patients with confirmed CHRSR. Secondary end points included the incidence of HRS reversal (defined as at least 1 SCr value ≤1.5 mg/dL while on treatment), transplant-free survival, and overall survival. The study was performed at 50 investigational sites in the United States and 2 in Canada, from October 2010 through February 2013. **RESULTS:** Baseline demographic/clinical characteristics were similar between groups. CHRSR was observed in 19 of 97 patients (19.6%) receiving terlipressin vs 13 of 99 patients (13.1%) receiving placebo ($P = .22$). HRS reversal was achieved in 23 of 97 (23.7%) patients receiving terlipressin vs 15 of 99 (15.2%) receiving placebo ($P = .13$). SCr decreased by 1.1 mg/dL in patients receiving terlipressin and by only 0.6 mg/dL in patients receiving placebo ($P < .001$). Decreases in SCr and survival were correlated ($r^2 = .882$; $P < .001$). Transplant-free and overall survival were similar between groups. A significantly greater proportion of patients with CHRSR who received terlipressin survived until day 90 than patients who did not have CHRSR after receiving terlipressin ($P < .001$); this difference was not observed in patients who did vs did not have CHRSR after receiving placebo ($P = .28$). There were similar numbers of adverse events in each group, but patients in the terlipressin group had more ischemic events. **CONCLUSIONS:** Terlipressin plus albumin was associated with greater improvement in renal function vs albumin alone in patients with cirrhosis and HRS-1. Patients had similar rates of HRS reversal with terlipressin as they did with albumin. ClinicalTrials.gov no: NCT01143246.

Keywords: REVERSE Study; Acute Kidney Injury; Clinical Trial; Large-Volume Paracentesis.

Hepatorenal syndrome type 1 (HRS-1) in patients with cirrhosis and ascites is a functional, potentially reversible, form of acute kidney injury characterized by rapid (<2 wk) and progressive deterioration of renal function (serum creatinine [SCr] >2.5 mg/dL).[1] HRS reportedly occurs in 7%–15% of patients with advanced cirrhosis and ascites; the estimated annual incidence of HRS in the United States is approximately 9,000–14,000 patients.[2–4] The prognosis for HRS-1 is poor, with more than 80% mortality within 3 months and a median survival time of only 2–4 weeks if left untreated,[1,5–7] highlighting the need for effective pharmacologic treatment to improve renal function.

Increased understanding of HRS-1 pathophysiology has shown that vasoconstrictive drug therapy may improve

Abbreviations used in this paper: **AE, adverse event; CHRSR, confirmed hepatorenal syndrome reversal; CLIF-SOFA, chronic liver failure–sequential organ failure assessment; DSMB, Data Safety Monitoring Board; HRS-1, hepatorenal syndrome type 1; LVP, large-volume paracentesis; MAP, mean arterial pressure; REVERSE, Randomized, placEbo-controlled, double-blind study to confirm the reVERSal of hepatorenal syndromE type 1 with terlipressin; RRT, renal replacement therapy; SCr, serum creatinine.**

Most current article

0016-5085/$36.00
http://dx.doi.org/10.1053/j.gastro.2016.02.026

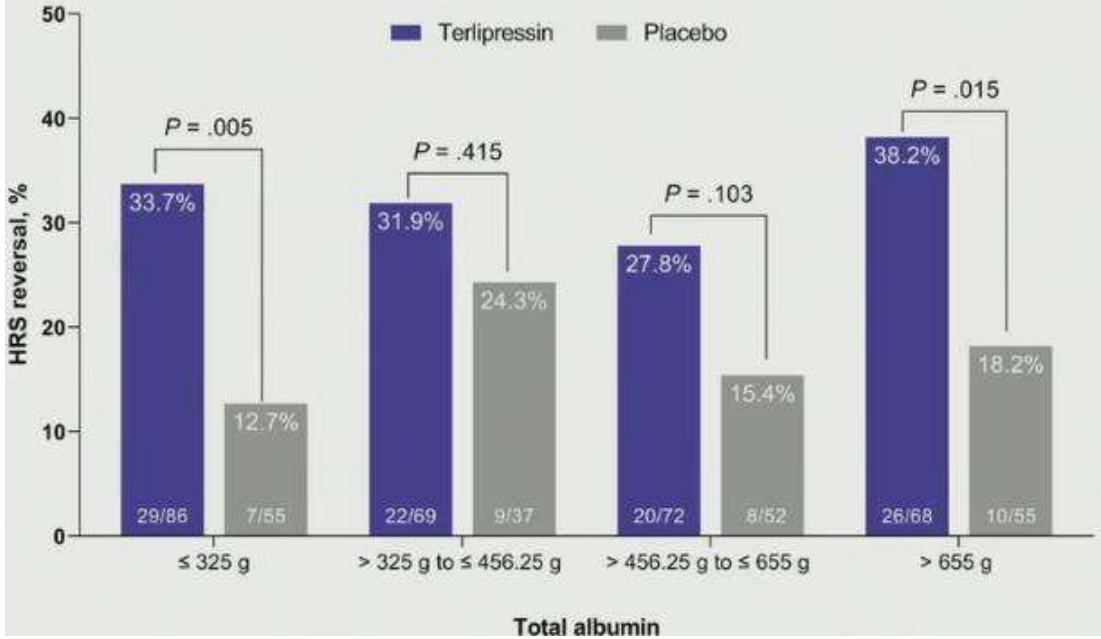
- The following clinical outcomes were assessed by total albumin quartiles:
  - Incidence of HRS reversal, defined as SCr ≤ 1.5 mg/dL by Day 14 or discharge
  - Transplant-free survival (TFS), analyzed using a Kaplan-Meier product limit method
- Total albumin included albumin administered up to 14 days prior to randomization, and concomitant albumin administered during study treatment

Αποτελέσματα

	Terlipressin					Placebo				
Albumin dose	≤325g	>325 – 456.25g	>456.25-655g	>655g	P value	≤325g	>325 – 456.25g	>456.25-655g	>655g	P value
n	86	69	72	68		55	37	52	55	
Age	55.3±10.0	55.2±11.9	53.7±10.7	53.8±9.4	0.388	54.4±10.0	56.7±10.4	51.8±11.0	54.8±9.7	0.294
M (%)	47 (57%)	34 (49%)	43 (60%)	46 (68%)	0.182	32 (58%)	21 (57%)	34 (65%)	38 (69%)	0.555
Na	132 ±5.7	132±6.8	133±5.4	134±5.9	0.596	132±5.1	132±5.8	133±6.2	134±5.7	0.402
Creatinine	3.4±0.97	3.5±1.05	3.6±1.03	3.6±1.06	0.403	3.6±1.12	3.7±1.03	3.6±1.17	3.6±1.03	0.834
INR	2.2±0.74	2.2±0.76	2.4±0.85	2.2±0.90	0.506	2.2±0.71	2.3±1.10	2.7±3.41	2.2±0.73	0.883
Bilirubin	12.3±12.2	13.6±13.3	13.2±13.1	10.4±11.7	0.285	13.6±13.1	15.7±19.3	14.1±13.9	11.3±11.9	0.917
Albumin	3.4±0.73	3.5±0.63	3.8±0.69	4.0±0.71	**<0.001**	3.3±0.63	3.6±0.61	3.7±0.78	4.4±3.4	**<0.001**
MELD-Na	32.9±6.4	33.4±5.8	33.5±6.5	31.8±7.3	0.578	32.9±5.4	32.8±6.8	33.0±6.1	32.7±5.5	0.973

Αντιστροφή ΗΝΣ

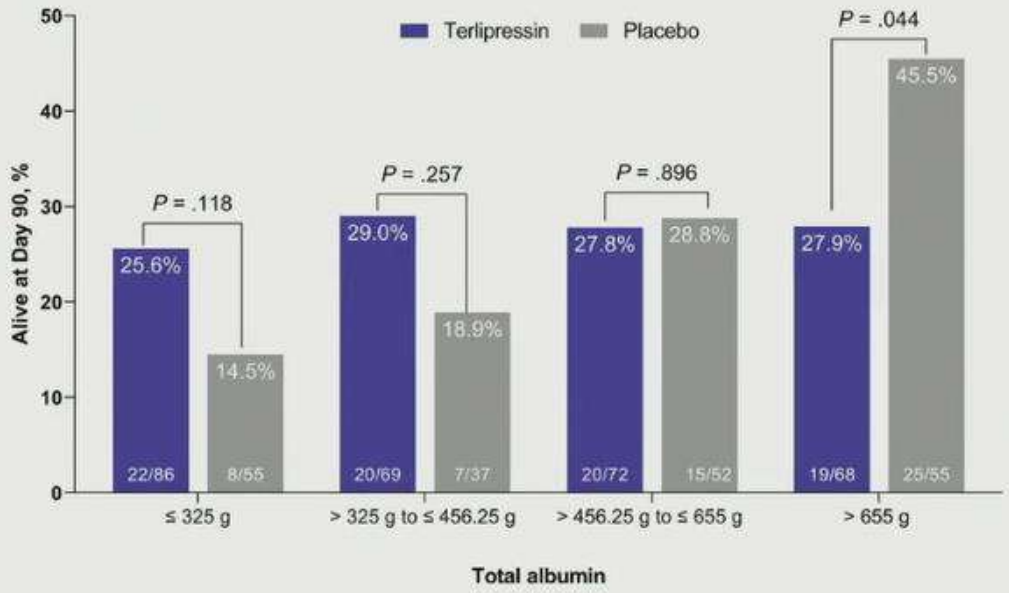
Incidence of HRS reversal by Day 90 by quartiles of total albumin and treatment group; ITT population[a]



- The incidence of HRS reversal was numerically higher among patients in the terlipressin group (vs placebo) across all albumin subgroup levels
- There was no dose-response relationship between total albumin use and HRS reversal for either treatment group

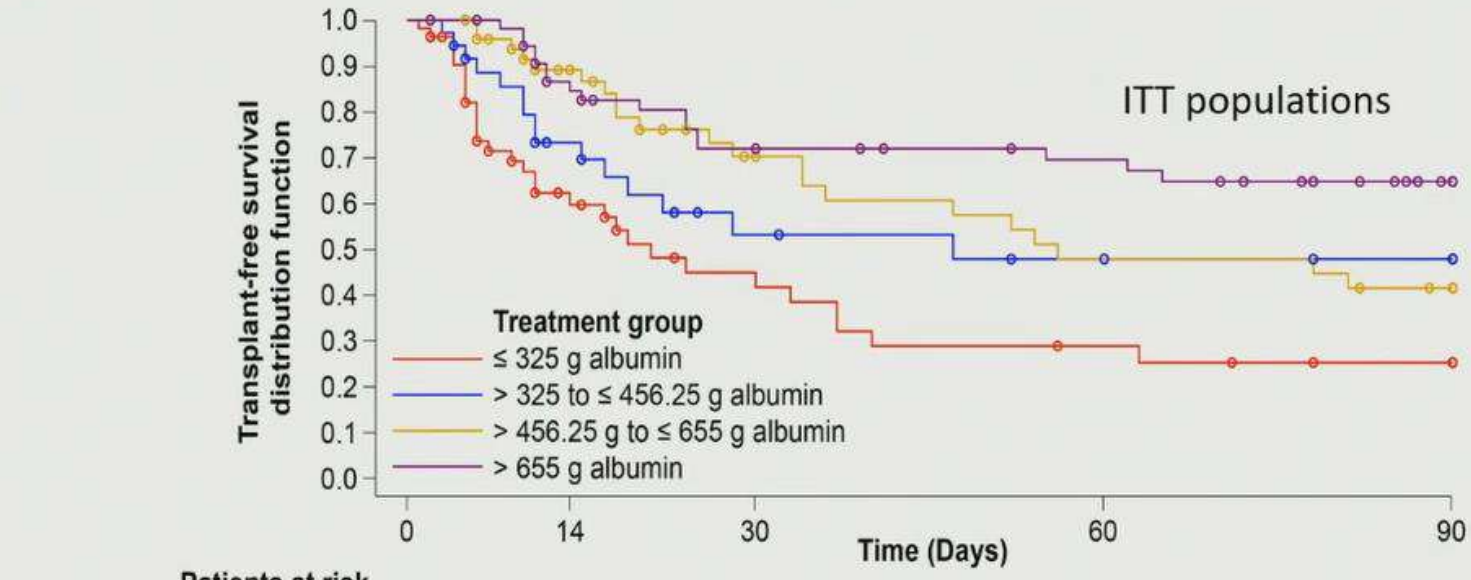
Επιβίωση (χωρίς μεταμόσχευση) – Ημ 90

Incidence of survival by Day 90 without a liver transplant by quartiles of total albumin; ITT population[a]



- In the highest albumin quartile (ie, > 655 g), significantly more patients were alive without a transplant in the placebo group (vs terlipressin group) by Day 90
- No such differences were observed among the terlipressin patients between the albumin quartiles

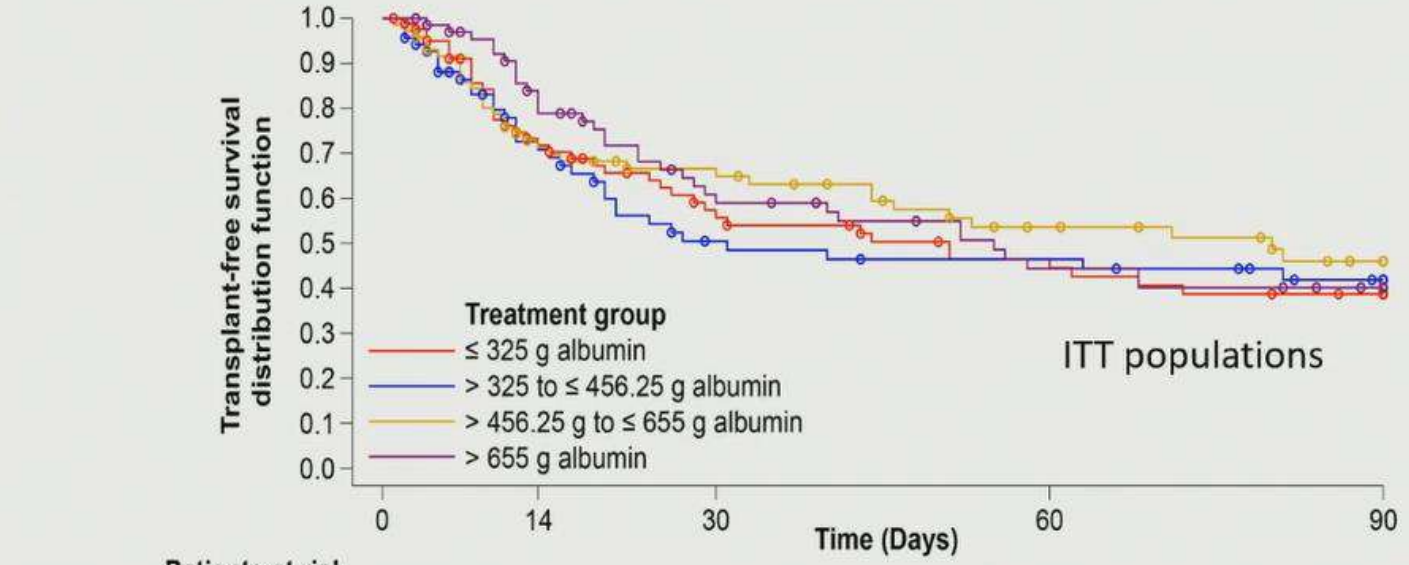
Επιβίωση (χωρίς μεταμόσχευση) – Ημ90
PLACEBO



Patients at risk					
≤ 325 g albumin	55	24	14	8	5
> 325 to ≤ 456.25 g albumin	37	20	11	8	6
> 456.25 g to ≤ 655 g albumin	52	36	23	15	10
> 655 g albumin	55	43	34	29	14

In the placebo group, transplant free survival increased with increasing albumin

Επιβίωση (χωρίς μεταμόσχευση) – Ημ 90 TERLIPRESSIN



Patients at risk					
≤ 325 g albumin	86	50	34	24	18
> 325 to ≤ 456.25 g albumin	69	41	25	22	15
> 456.25 g to ≤ 655 g albumin	72	47	39	25	14
> 655 g albumin	68	50	33	21	15

There was no clear relationship between total albumin use and TFS in the terlipressin group

AE - θάνατος – Ημ 30

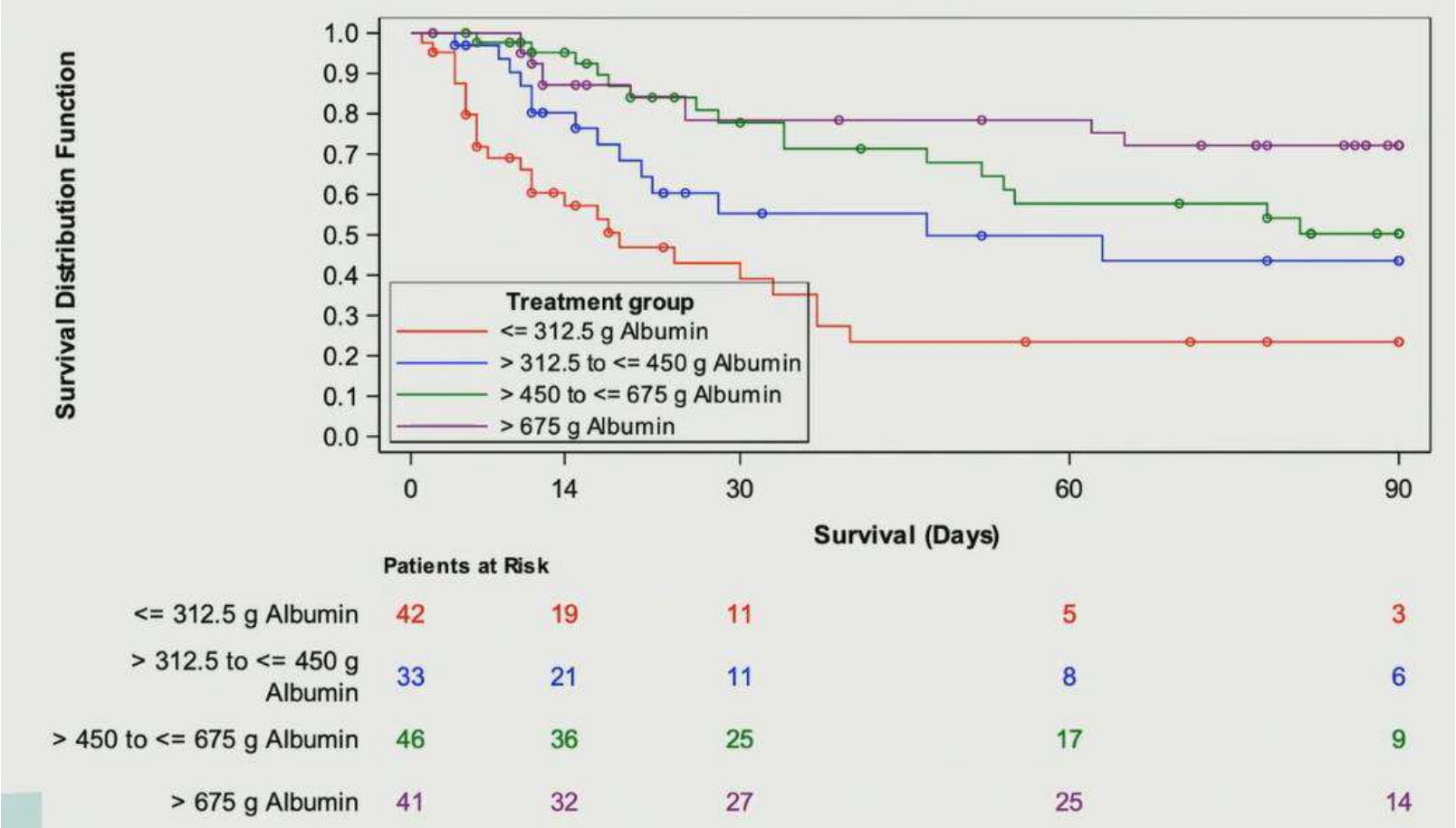
AEs leading to death reported up to 30 days posttreatment (≥ 3%); Safety population

	CONFIRM[1]		REVERSE[2]	
	Terlipressin (n = 200)	Placebo (n = 99)	Terlipressin (n = 93)	Placebo (n = 95)
Total AE leading to death	83 (41.5)	40 (40.4)	35 (37.6)	34 (35.8)
MODS	9 (4.5)	3 (3.0)	8 (8.6)	5 (5.3)
Chronic hepatic failure	9 (4.5)	8 (8.1)	9 (9.7)	5 (5.3)
Hepatic failure	9 (4.5)	9 (9.1)	1 (1.1)	5 (5.3)
Respiratory failure	**11 (5.5)**	**0 (0.0)**	**4 (4.3)**	**1 (1.1)**
Sepsis	**4 (2.0)**	**0 (0.0)**	**3 (3.2)**	**2 (2.1)**
Acute respiratory failure	**6 (3.0)**	**1 (1.0)**	**2 (2.2)**	**1 (1.1)**
Septic shock	**4 (2.0)**	**0 (0.0)**	**3 (3.2)**	**1 (1.1)**
Hepatorenal syndrome	2 (1.0)	3 (3.0)	4 (4.3)	2 (2.1)
Hepatic cirrhosis	6 (3.0)	1 (1.0)	0 (0.0)	1 (1.1)
Renal failure	3 (1.5)	0 (0.0)	2 (2.2)	1 (1.1)
Alcoholic cirrhosis	4 (2.0)	3 (3.0)	1 (1.1)	1 (1.1)

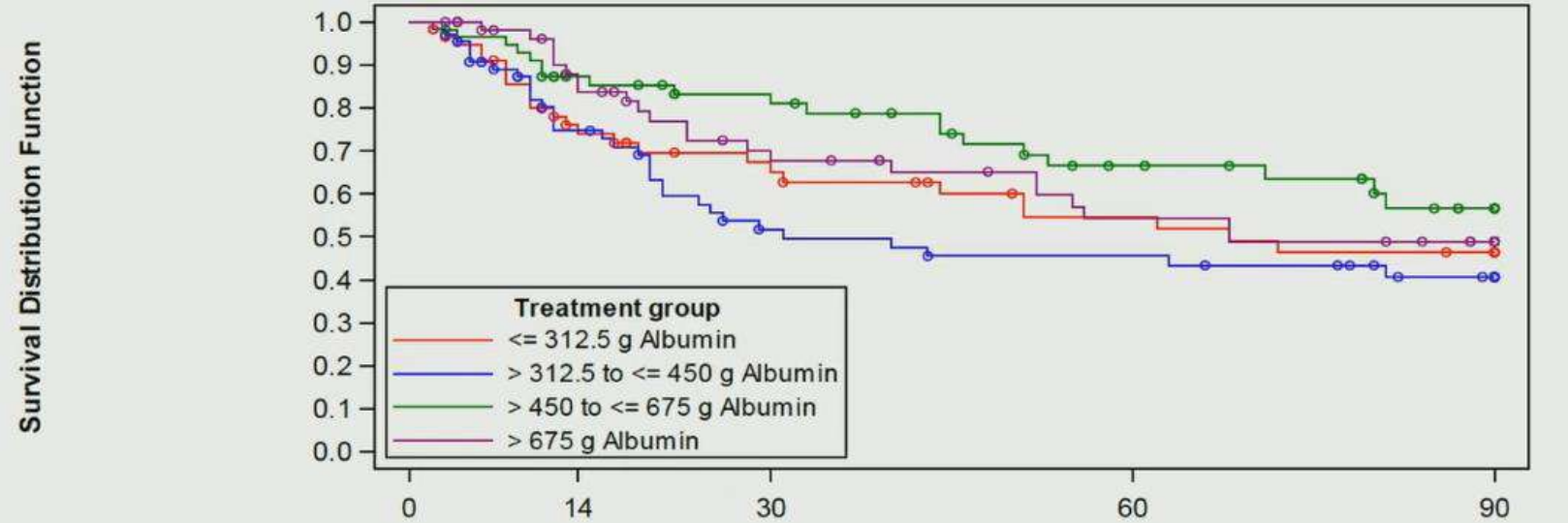
Data are presented as n (%).

- Incidence of death from respiratory failure/sepsis/septic shock in the pooled population:
  - Terlipressin: 12.6% (37/293)
  - Placebo: 3.0% (6/194)

Επιβίωση (χωρίς μεταμόσχευση) – Ημ90 χωρίς ACLF3- PLACEBO

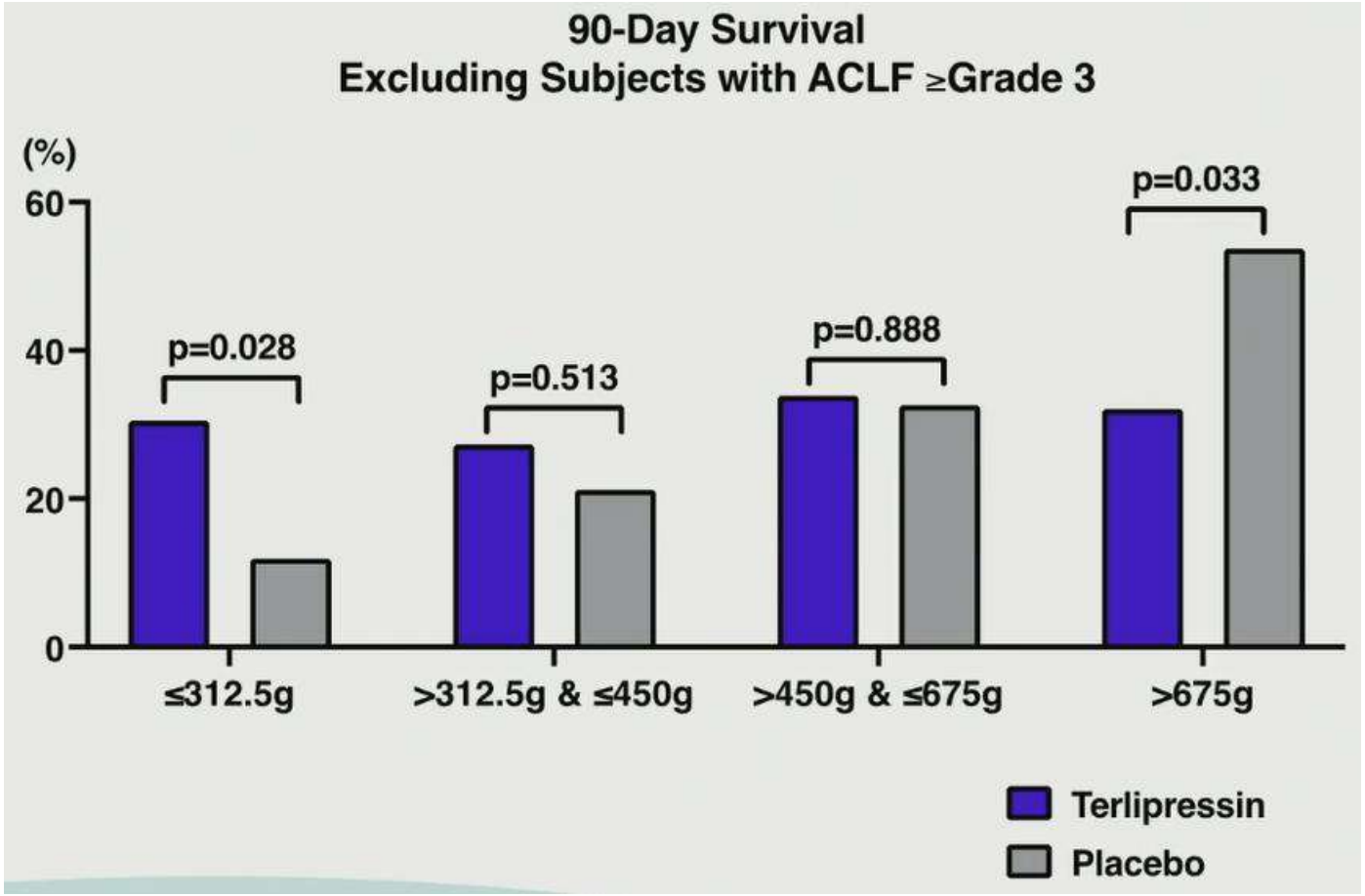


Επιβίωση (χωρίς μεταμόσχευση) – Hμ90 χωρίς ACLF3- TERLIPRESSIN



Patients at Risk					
<= 312.5 g Albumin	59	37	29	20	16
> 312.5 to <= 450 g Albumin	66	41	25	21	13
> 450 to <= 675 g Albumin	56	44	38	24	13
> 675 g Albumin	56	42	30	20	14

Επιβίωση (χωρίς μεταμόσχευση) – Ημ90 χωρίς ACLF3



ΣΥΜΠΕΡΑΣΜΑΤΑ

- Although albumin has many beneficial effects, it is not "the more the merrier"
- When excluding patients with ACLF ≥grade 3, the use of lower doses of albumin with terlipressin provides a survival advantage over placebo
- Higher doses of albumin are not necessarily useful with terlipressin use.

ΣΥΜΠΕΡΑΣΜΑΤΑ

- The relationship between albumin use and the balance between efficacy and safety is complex

- This *"double-edged sword"* underscores the need for careful patient selection and monitoring of albumin use to avoid volume overload

Ένδειξη	Δοσολογία	Level of Evidence/ Grade of Recommendation	Σχόλια
Παρακέντηση μεγάλου όγκου (>5L) ασκίτη	8g ανά λίτρο ασκίτη που αφαιρείται	I;1	Θα μπορούσε να εξεταστεί το σε κιρρωτικούς ασθενείς με ACLF ή AKI που υποβάλλονται σε παρακέντηση <5L
Αυτόματη βακτηριακή περιτονίτιδα	1.5g/kg κατά τη διάγνωση και 1g/kg την 3η ημέρα	I;1	Ιδιαίτερα σε ασθενείς με baseline T.Bil >4 mg/dl ή sCr>1 mg
AKI stage>1A	1 g/kg (με μέγιστη δόσης τα 100 g) για δύο συνεχόμενες ημέρες	III;1	Εγχυση αλβουμίνης→θα πρέπει να χρησιμοποιείται για τη δ.δ. του HRS.
HRS-AKI	20–40 g/ημέρα (μέχρι cr <1.5 mg/dl) ή 14 d)	II-2;1	

EASL Guidelines. J Hepatol. 2018;69(2):406-460.

Ένδειξη	Δοσολογία
Μακροχρόνια χορήγηση σε ασθενείς με μη επιπλεγμένο ασκίτη υπό αντιδιουρητική αγωγή	40g/εβδομάδα με στόχο επίτευξης 4g/L στον ορό
Ηπατική εγκεφαλοπάθεια	20–40 g/ημέρα
Υπονατριαιμία	Εξατομίκευση
Σηπτικό σοκ σε κίρρωση	250 ml δ/ματος 5% HA i.v. σε διάστημα 15–30 min, και μετά έγχυση συντήρησης 50 ml/h έως ότου επέλθει αιμοδυναμική σταθεροποίηση

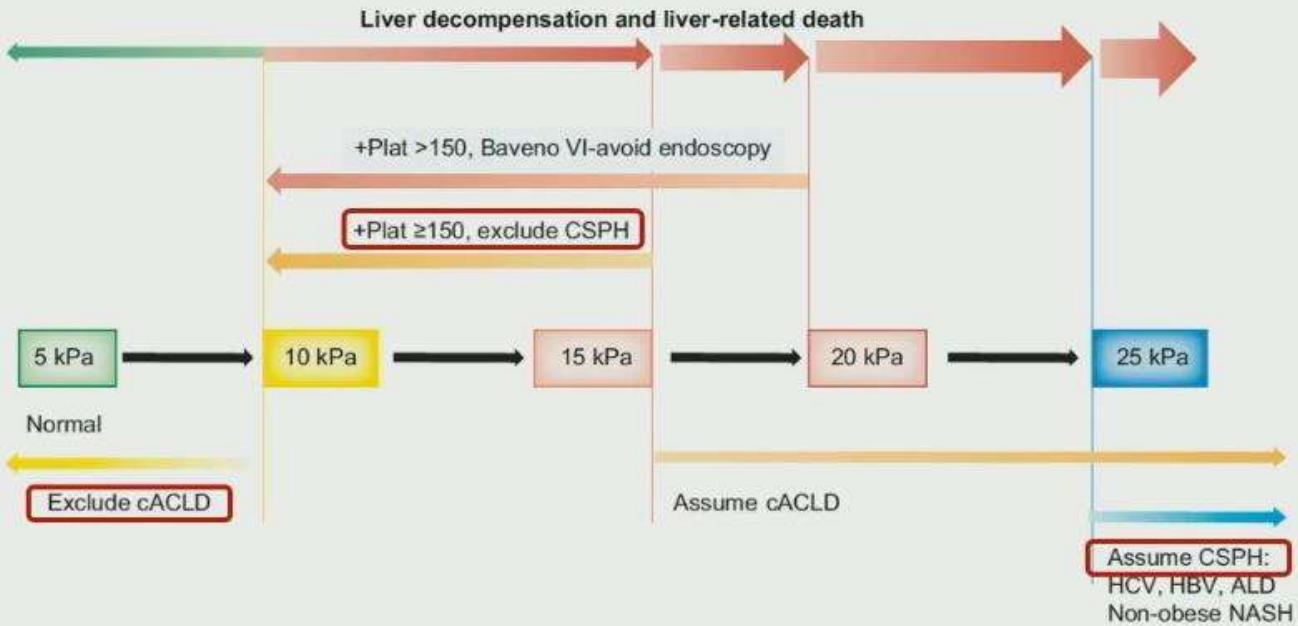
Bai Z. An international position statement. *JHEP Rep*. 2023;5(8):100785.

Risk and predictors of hepatic decompensation in grey zone patients by the Baveno VII criteria: A competing risk analysis

Huapeng Lin, Jimmy Lai, Grace Wong, Adèle Delamarre, Sang Hoon Ahn, Guanlin Li, Beom Kyung Kim, Lilian Liang, Hye Won Lee, Sherlot Song, Henry Chan, Vincent Wong, Victor de Lédinghen, Seung Up Kim, Terry Yip

Department of Medicine and Therapeutics, The Chinese University of Hong Kong

Combination of liver stiffness measurement (LSM) by transient elastography and platelet count in identifying compensated advanced chronic liver disease (cACLD) patients with CSPH **(Baveno VII consensus)**



Grey zone = LSM 15–24.9 kPa and/or platelet count <150 x 10^9/L

Problems with patients in the grey zone

- Around 40% of cACLD patients
- The natural history and risk of hepatic decompensation are not well-defined

Σκοπός

Evaluate the risk and predictors of hepatic decompensation in cACLD patients in Baveno VII grey zone

Validate the Baveno VII-SSM combination in predicting the risk of decompensation

Three prospective cohorts ***(Hong Kong, South Korea and France)*** of adult patients with chronic liver disease receiving transient elastography examination from 2003 - 2021

Exclusion criteria

- Hepatic decompensation or hepatocellular carcinoma (HCC) before baseline or within 6 months after baseline
- Unreliable LSM (<10 successful measurement or IQR to median ratio > 0.3)
- Missing platelet count
- Lost to follow-up

Low-risk group = LSM < 15 kPa and platelet count ≥150 x 10^9/L

High-risk group = LSM ≥ 25 kPa

Grey zone = LSM 15–24.9 kPa and/or platelet count <150 x 10^9/L

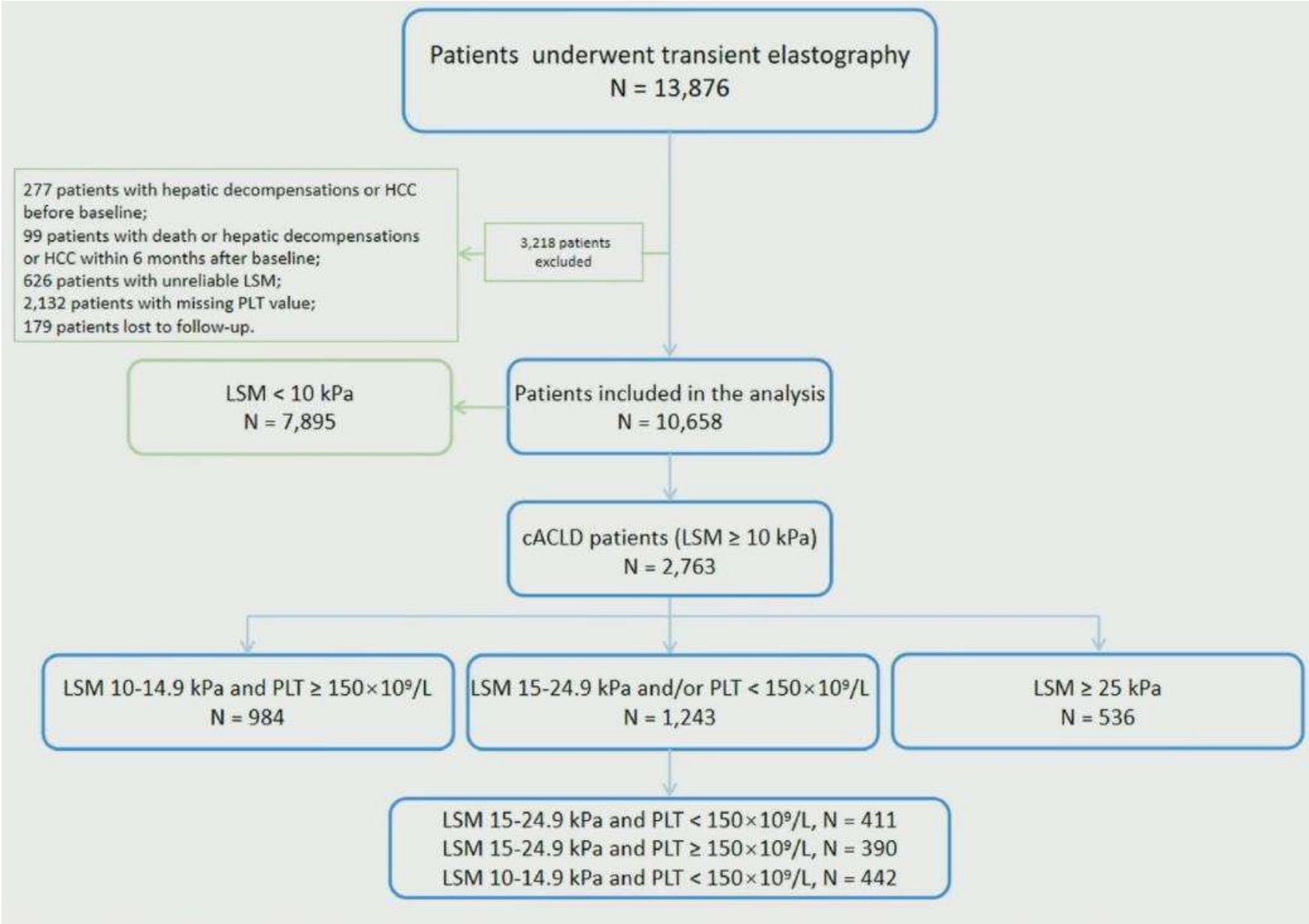
Control group = LSM < 10 kPa

Primary outcome

- Incident hepatic decompensation
  - ❖ Defined as ascites, variceal bleeding, hepatic encephalopathy and/or cirrhotic complication-related mortality

Secondary outcome

- Incident HCC
  - ❖ Confirmed by histology or typical radiological features

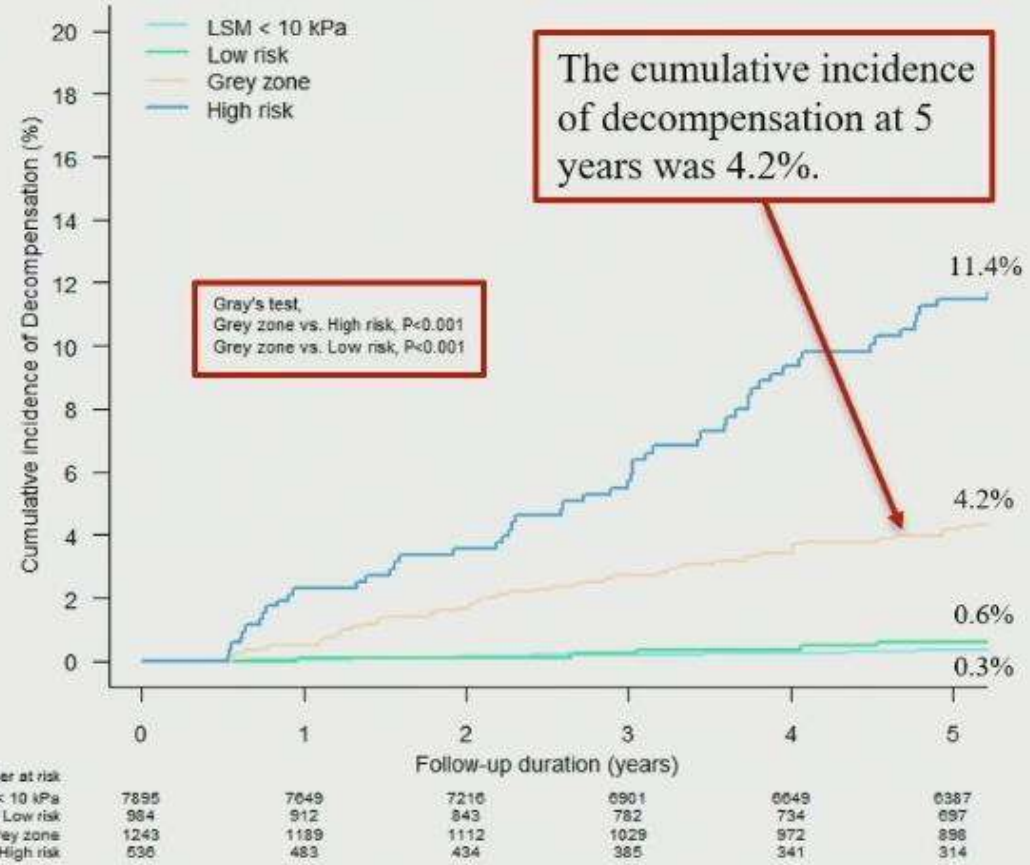

Patients underwent transient elastography
N = 13,876
277 patients with hepatic decompensations or HCC before baseline;
99 patients with death or hepatic decompensations or HCC within 6 months after baseline;
626 patients with unreliable LSM;
2,132 patients with missing PLT value;
179 patients lost to follow-up.
3,218 patients excluded
LSM < 10 kPa
N = 7,895
Patients included in the analysis
N = 10,658
cACLD patients (LSM ≥ 10 kPa)
N = 2,763
LSM 10-14.9 kPa and PLT ≥ 150×10⁹/L
N = 984
LSM 15-24.9 kPa and/or PLT < 150×10⁹/L
N = 1,243
LSM ≥ 25 kPa
N = 536
LSM 15-24.9 kPa and PLT < 150×10⁹/L, N = 411
LSM 15-24.9 kPa and PLT ≥ 150×10⁹/L, N = 390
LSM 10-14.9 kPa and PLT < 150×10⁹/L, N = 442

Baseline

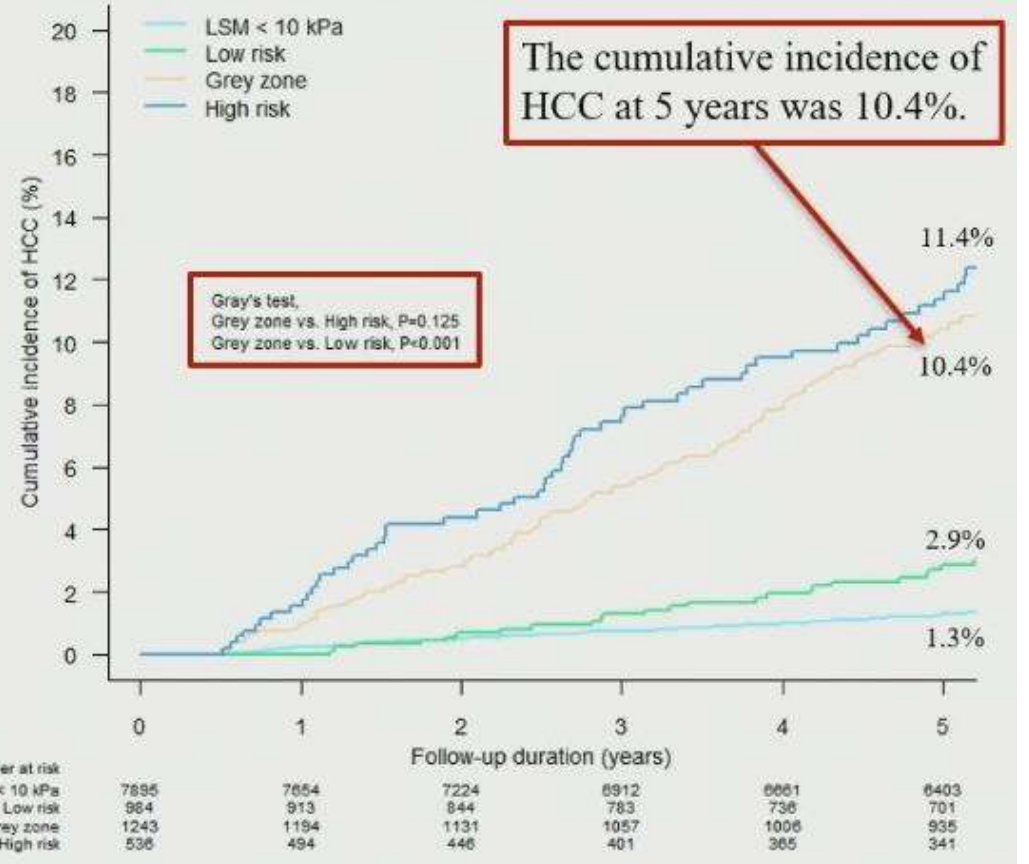
Characteristics	LSM < 10 kPa	cACLD (N = 2763)			*P* value
		LSM 10-14.9 kPa and PLT ≥ 150×10^9/L	LSM 15-24.9 kPa and/or PLT < 150×10^9/L	LSM ≥ 25 kPa	
	N = 7895	N = 984	N = 1243	N = 536	
Age (years)	52.4	53.3	55.6	56.0	<0.001
Male sex, %	56.0	59.0	59.9	64.4	0.111
HBV infection, %	36.0	30.3	55.3	35.8	<0.001
HCV infection, %	1.8	2.4	8.5	8.6	<0.001
MASLD, %	38.3	45.5	21.7	26.7	<0.001
ALD, %	12.3	16.6	10.9	25.2	<0.001
ALT (IU/L)	28	49	43	50	0.004
AST (IU/L)	30	47	45	62	<0.001
ALBI score	-3.0	-3.0	-2.9	-2.5	<0.001
ALP (IU/L)	66	73	78	100	<0.001
AFP (μg/L)	2.6	3.5	4.6	9.1	<0.001
Platelet ($\times10^9$/L)	217	215	130	130	<0.001
Creatinine (μmol/L)	72.5	72.0	72.0	69.0	0.005
LSM (kPa)	5.8	11.8	16.5	38.2	<0.001

Αποτελέσματα

Hepatic decompensation



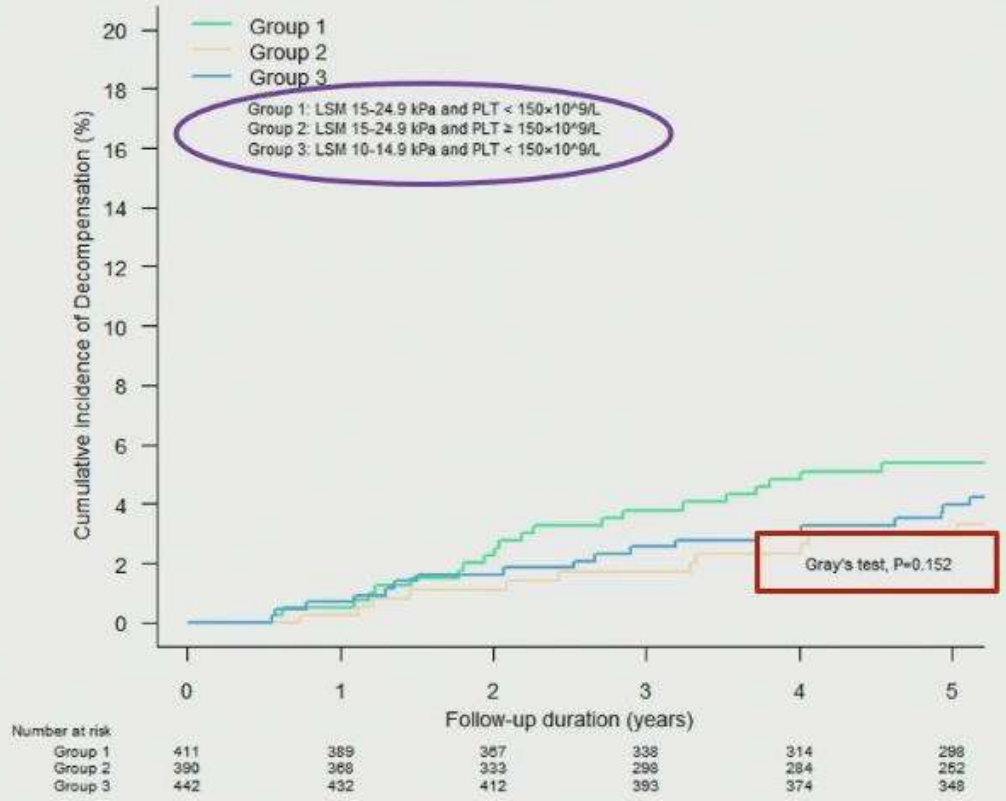
HCC



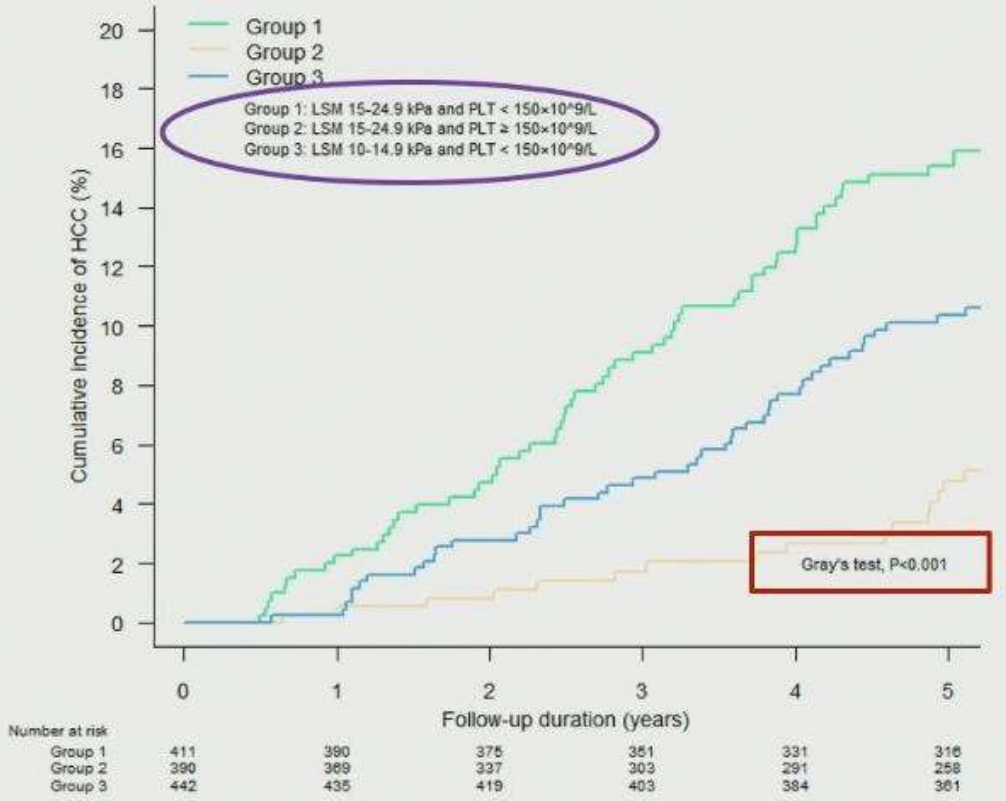
Αποτελέσματα

Incidences by Baveno VII grey zone categories

Hepatic decompensation



HCC



Risk factors associated with hepatic decompensation in patients in grey zone

Parameters	Univariate Analysis		Multivariable Analysis	
	SHR (95% CI)	*P*	SHR (95% CI)	*P*
MASLD (vs. viral hepatitis)	1.74 (1.03-2.91)	0.037	1.57 (0.92-2.69)	0.101
ALD (vs. viral hepatitis)	2.16 (1.12-4.18)	0.021	2.05 (1.05-3.99)	**0.035**
ALBI score (per unit increase)	2.16 (1.26-3.69)	0.005	1.80 (1.06-3.04)	**0.028**
ALP (per multiples of UL increase)	1.91 (1.37-2.66)	<0.001	1.60 (1.09-2.32)	**0.014**

Baveno VII-SSM combinations classify fewer patients in grey zone

Sequential Baveno VII-SSM Model

→ Sequential application of SSM cut-offs of <21 kPa and >50 kPa to rule out and rule in CSPH in patients within the grey zone group

Combined Baveno VII-SSM Model

→ Low risk of CSPH if at least <u>two</u> of the followings were present
- LSM ≤ 15 kPa
- Platelet count ≥150 x 10^9/L
- SSM ≤ 40 kPa

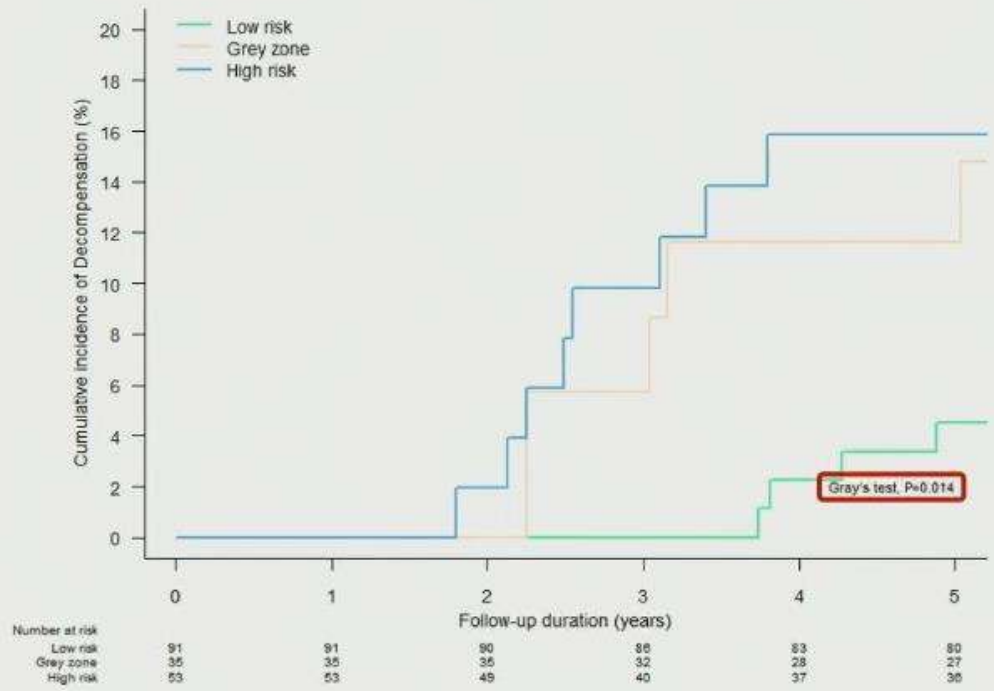
→ High risk of CSPH if at least <u>two</u> of the followings were present
- LSM > 25 kPa
- Platelet count <150 x 10^9/L
- SSM > 40 kPa

Models	Incident decompensation N (%)	Incidence of decompensation at 5 years % and 95%CI
	Baveno VII Model	
Low risk group: LSM ≤ 15 kPa + PLT ≥ 150×10^9/L	4 (5.3)	2.6 (0.4-8.4)
Grey zone group	12 (15.3)	7.7 (3.1-15.0)
High risk group: LSM > 25 kPa	7 (26.9)	15.3 (4.6-31.9)
	Sequential Baveno VII-SSM Model	
Low risk group: 1°: LSM ≤ 15 kPa + PLT ≥ 150×10^9/L 2°: SSM < 21 kPa	6 (6.5)	4.4 (1.4-10.2)
Grey zone group	5 (14.2)	11.6 (3.5-24.8)
High risk group: 1°: LSM > 25 kPa 2°: SSM > 50 kPa	12 (22.6)	15.8 (7.3-27.2)
	Combined Baveno VII-SSM Model	
Low risk group: Two out of: LSM ≤ 15 kPa PLT ≥ 150×10^9/L SSM ≤ 40 kPa	3 (3.2)	2.2 (0.4-7.2)
Grey zone group	4 (17.3)	13.6 (3.3-31.3)
High risk group: Two out of: LSM > 25 kPa PLT < 150×10^9/L SSM > 40 kPa	16 (24.6)	17.6 (9.3-28.0)

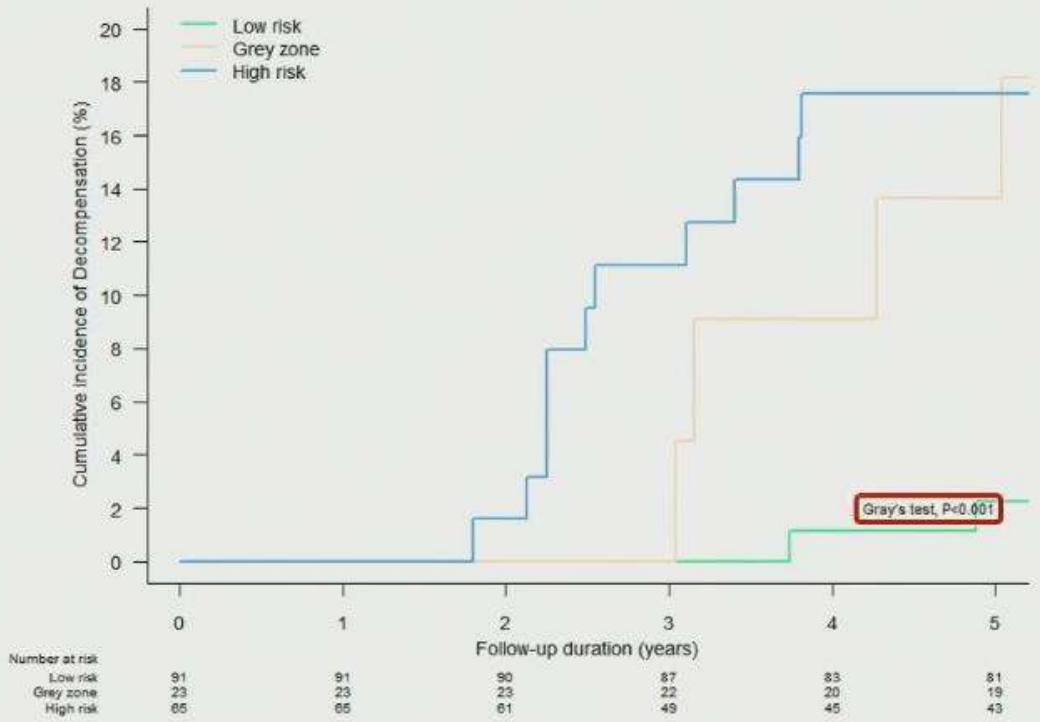
Αποτελέσματα

Baveno VII-SSM combinations distinguish patients with different risk of hepatic decompensation

Sequential Baveno VII-SSM Model



Combined Baveno VII-SSM Model



Συμπεράσματα

Patients in grey zone of Baveno VII criteria remain at high risk of hepatic decompensation

Clinical risk factors and spleen stiffness can further stratify the risk in these patients

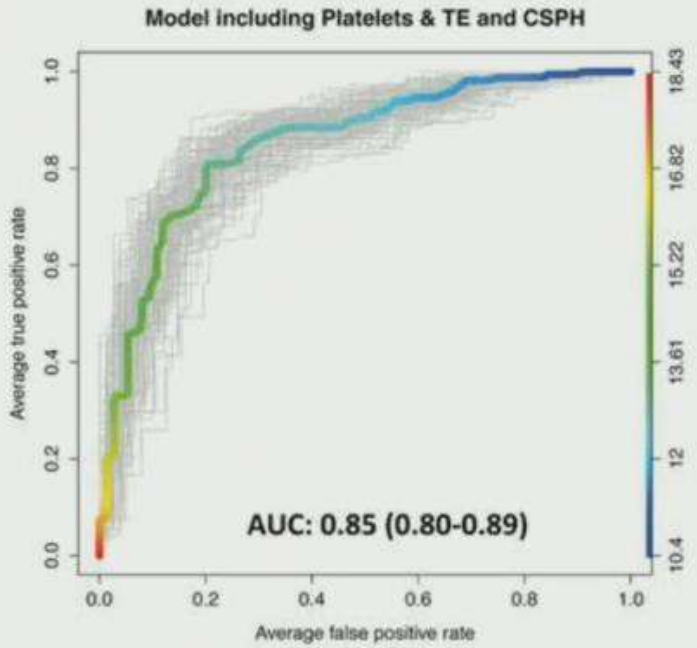
Spleen stiffness measurement by a dedicated 100hz VCTE probe improves the non-invasive diagnosis of clinically significant portal hypertension

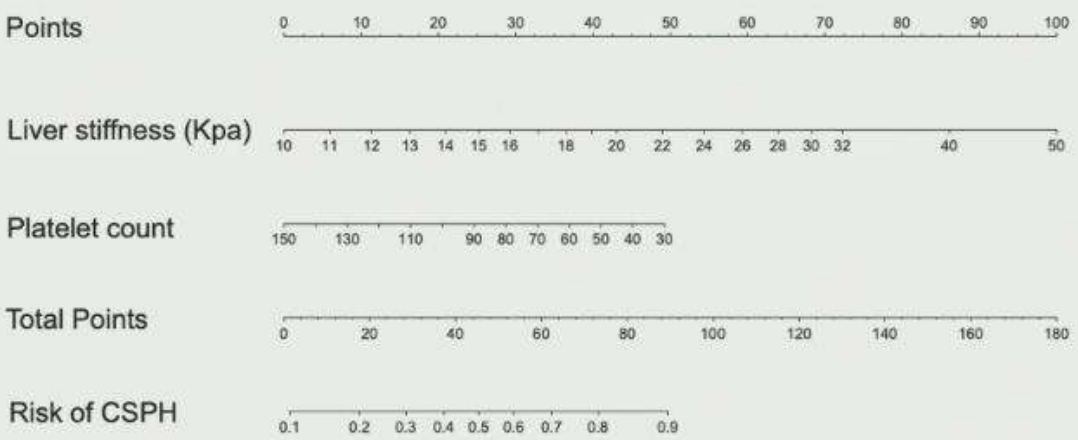
Interim results from an ongoing prospective multicenter study

Mathias Jachs, M.D.

- Medical University of Vienna
- Resident Internal Medicine/ GI & Hep
- PhD student
  (supervisor: Mattias Mandorfer, M.D. PhD)
- Focus: treatment of and NIT for CSPH

NIT for CSPH - ANTICIPATE

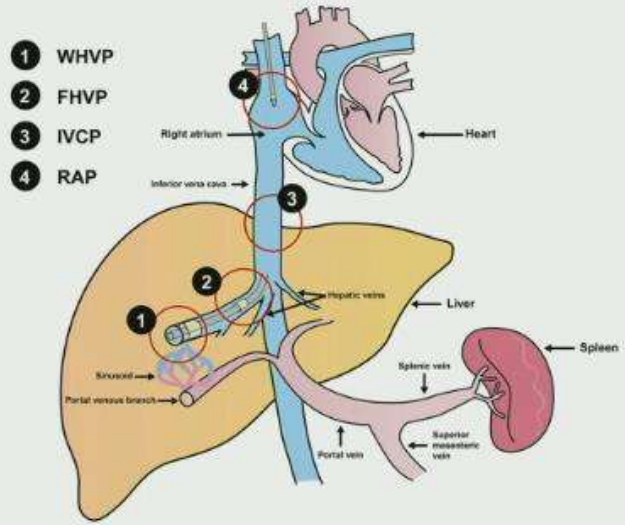


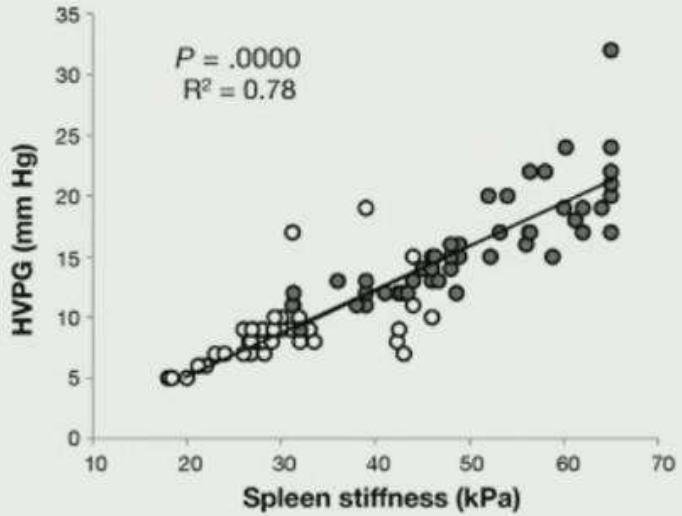


Abraldes J, Hepatology 2016

Spleen stiffness (SSM) - emerging NIT for CSPH

- Mostly single-center studies
- Predominant etiology: HCV
- Limitation: 50Hz probe
  - failure rate up to 24%
- Added value to ANTICIPATE/ existing NIT to be determined

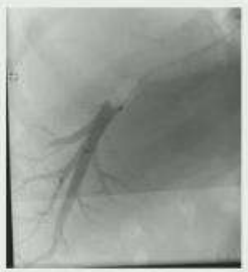




Reiberger T. Hepatol Commun 2022. & Colecchia et al. Gastroenterology 2012.

Our European multicenter Study

- 16 European specialized centers
- Enrolment: 2021 – 2023
- Prospective characterization
  - Paired HVPG, LSM, SSM and lab
  - VCTE: FibroScan ® Expert 630 (SSM-100Hz)



- Aim 1: Value of SSM-100Hz as NIT for CSPH & refinement of non-invasive CSPH diagnosis
- Aim 2: Value of SSM-100Hz for predicting NSBB-response & Aim 3: Prognostic value of SSM-100Hz in ACLD

Interim results: a contemporary patient cohort

- 244 cACLD patients from 12 centers (until 03/2023)
  - Inclusion: ≥18 years, suspicion of cACLD (LSM ≥10 kPa or F3/F4 fibrosis), CTP-A
  - Exclusion: PSVD, PVT, TIPS, history of transplant/HCC, invalid HVPG
  - NAFLD/MASLD: 40%, ArLD: 36%, viral: 15%, other etiology: 9%
  - BMI: 28.9 (24.8-33.6) kg/m^2, obese (BMI ≥30): 43%
- HVPG: 11 (8-15) mmHg, CSPH: 64.8%, SSM-100Hz success rate: approx. 96.5%
- LSM: 22.5 (14.8-33.2) kPa, SSM: 45.6 (33.0-66.5) kPa, PLT: 129 (92-183) G/L

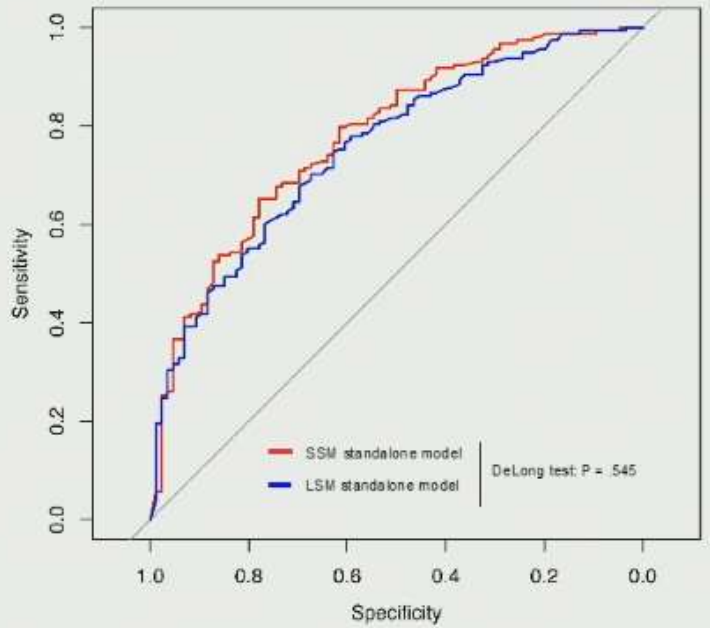
SSM-100Hz vs. LSM

- SSM standalone model:

  AUC 0.778 (0.718-0.839)

- LSM standalone model:

  AUC 0.755 (0.639-0.817)



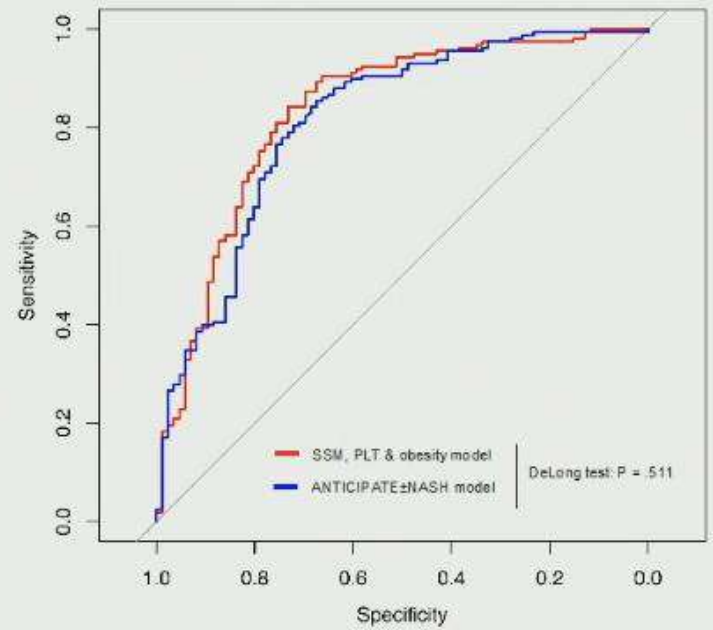
SSM-100Hz, PLT & obesity vs. ANTICIPATE±NASH

- SSM, PLT & obesity:

  AUC 0.834 (0.777-0.890)

- ANTICIPATE±NASH:

  AUC 0.814 (0.756-0.872)



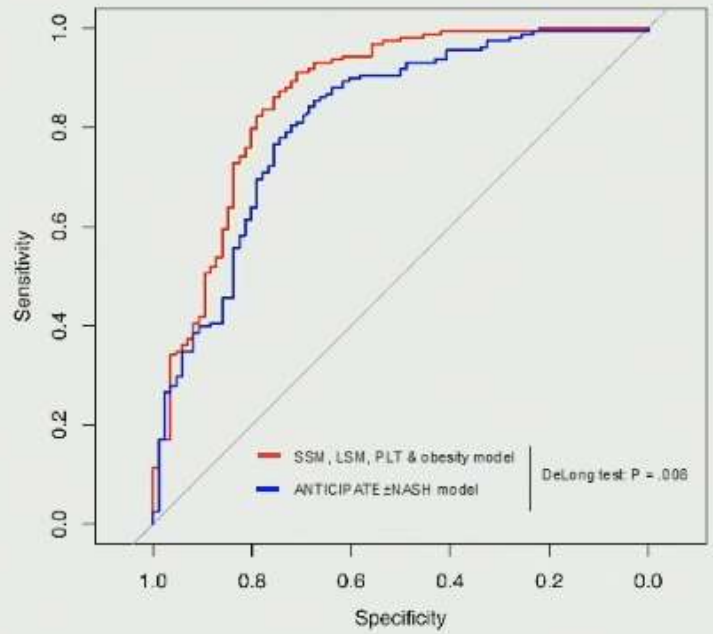
Addition of SSM-100Hz to LSM, PLT & BMI

- SSM, LSM, PLT & obesity:

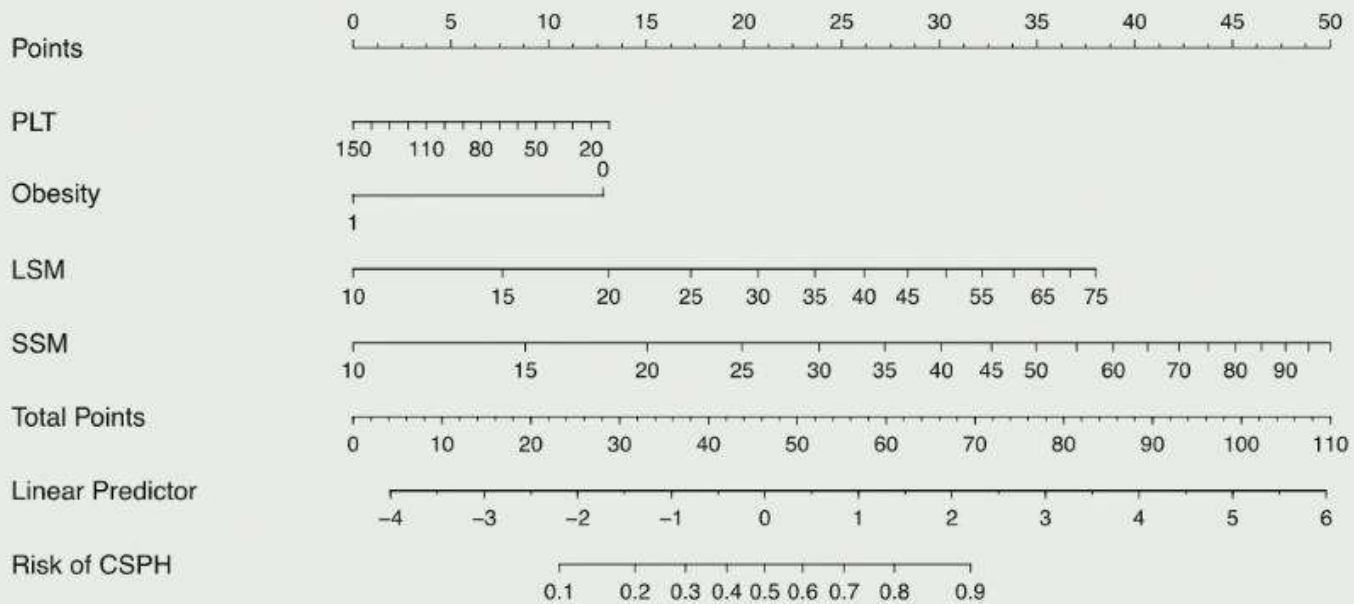
  AUC 0.864 (0.812-0.916)

- ANTICIPATE±NASH:

  AUC 0.814 (0.756-0.872)



Nomogram for individual CSPH risk assessment



Συμπεράσματα

- Established NIT for CSPH require reevaluation in contemporary cohorts
- Addition of SSM(-100Hz) to existing NIT improves the non-invasive diagnosis of CSPH
- Final results coming soon – including validation cohort (calibration) and subgroup analyses

Addition of Rifaximin to broad-spectrum antibiotics has no beneficial role in critically ill cirrhosis patients- a double-blind RCT (ARiE)

ANAND V KULKARNI, Mahathi Avadhanam, Puja Karandikar, Kalyan Rakam, Anand Gupta, Venu Simhadri, Madhumita Premkumar, Asim Ahmed Zuberi, Mithun Sharma[1], Sowmya Iyengar[1], Manasa Alla, Shantan Venishetty, D. Nageshwar Reddy, P. N. Rao

DEPT. OF HEPATOLOGY AND LIVER TRANSPLANTATION

AIG HOSPITALS, HYDERABAD, INDIA

Σκοπός

- To assess safety and efficacy of rifaximin in treating overt HE in critically ill cirrhosis patients who are on broad-spectrum antibiotics

Primary	Secondary
✓ to compare the proportion of patients achieving 2-grade reduction and/or complete resolution of HE among patients receiving antibiotics alone vs. antibiotics+rifaximin	✓ in-hospital survival ✓ duration of hospital stay ✓ incidence of nosocomial infections ✓ change in endotoxin levels ✓ predictors of HE resolution ✓ sub-group analysis: comparing decompensated cirrhosis vs. ACLF

Κριτήρια

- Single-center, double-blind RCT
- AIG Hospitals, Hyderabad, India, from February 28, 2022, to April 3, 2023
- Consecutive adult patients with cirrhosis and ≥ grade 2 HE were screened for inclusion within 24 hours of ICU admission

Exclusion criteria

- ALF
- Blood urea level> 150 mg/dl/West-Haven grade 1 HE
- Known CKD/HCC
- Patients with an underlying neuropsychiatric disease or those receiving antidepressants or antipsychotics medications
- Patients with acute cerebrovascular events
- Patients with recent (<1 week) history of alcohol consumption
- Those who died within 24 hours of ICU admission were excluded

Μέθοδος

- SMT: correct underlying cause
- Lactulose solution/enema to ensure 2-3 soft stool per day
- Rifaximin 550 mg twice daily for 14 days or until death or discharge
- Grade IV HE underwent CT brain to rule out other causes
- Daily HE assessment by two separate individuals
- If no consensus third investigator would assess
- For those on mechanical ventilation: withdraw sedatives and assess HE

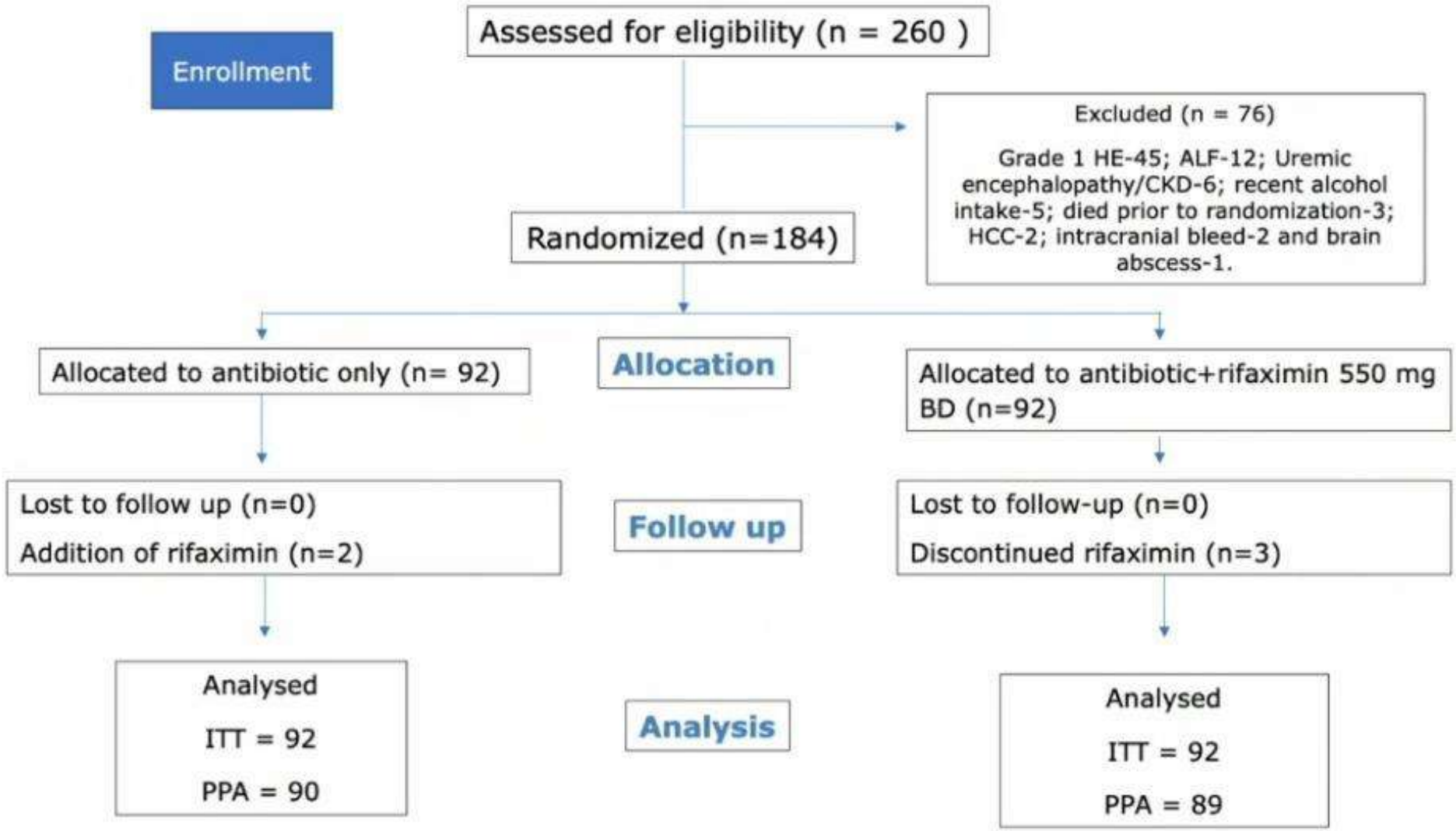
ΟΡΙΣΜΟΙ

- HE-West Haven criteria
- Cephalosporins, penicillin with beta-lactamase inhibitors, carbapenems, fluoroquinolones, macrolides, and glycopeptides were considered broad-spectrum antibiotics.
- ACLF as per APASL definition

ΥΠΟΛΟΓΙΣΜΟΣ ΔΕΙΓΜΑΤΟΣ

- 92.5% of patients receiving rifaximin, LOLA and lactulose
- Considering that this combination, in addition to broad-spectrum antibiotics, will be as effective as broad-spectrum antibiotics alone (or at least non-inferior) with a power of 90%; an alpha error of 5% and with a margin of 15% in HE resolution, we needed to enrol 88 patients in each arm
- 5% attrition rate= 92 patients in each arm (184 total)

Jain et al. Hepatology. 2021



Adverse events
2-itching
1-bloating and loose stools

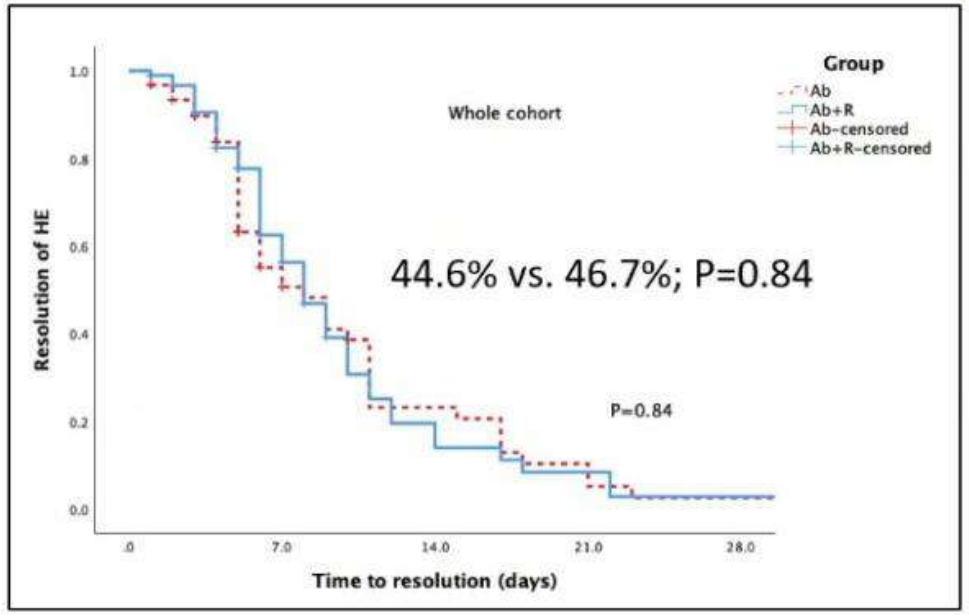
Variables	Antibiotics-only (n=92)	Antibiotics+rifaximin (n=92)
Age	48.11±11.42	47.54±12.1
Females	11 (12%)	10 (11%)
Alcohol/MASH	59/13	63/16
First episode of HE Recurrent HE	74 (80.4%) 18 (19.6%)	77 (83.7%) 15 (16.3%)
Prior lactulose	31 (33.7%)	35 (38%)
Prior rifaximin	11 (12%)	13 (14.1%)
Grade of HE (II/III/IV)	27/55/10	19/65/8
Infection at baseline	42 (45.7%)	37 (40.2%)
AKI at baseline	56 (61%)	46 (50%)

Variables	Antibiotics-only (n=92)	Antibiotics+rifaximin (n=92)
Precipitant of HE Constipation + dyselectrolytemia	37	38
Constipation	10	10
Dyselectrolytemia	14	12
Infection		
Constipation+infection	12	11
	3	0
Dyselectrolytemia + infection	7	9
Constipation+ dyselectrolytemia + infection	0	2
	2	1
GI bleed	0	1
Dyselectrolytemia infection + GI bleed	7	8
Spontaneous		

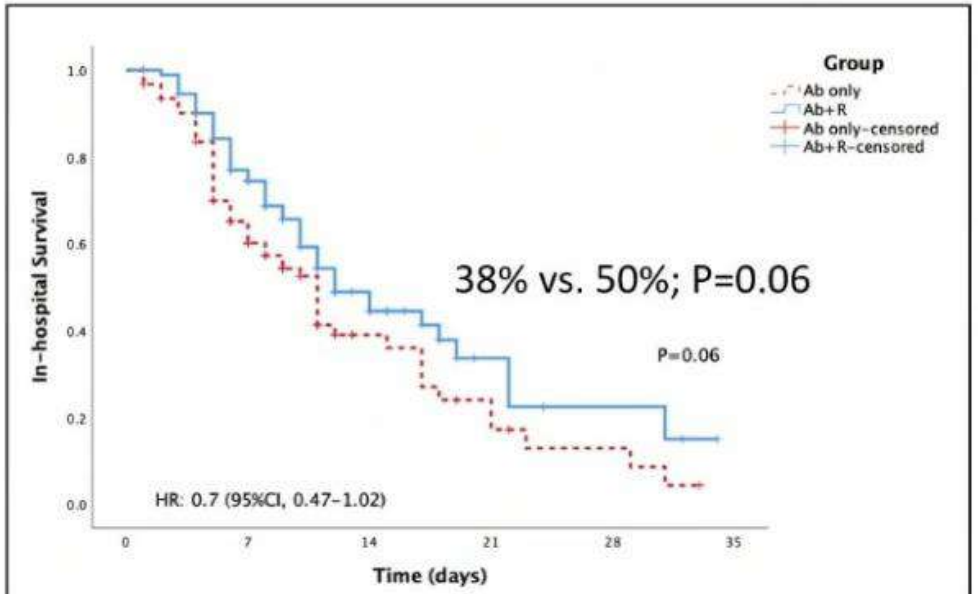
Variables	Antibiotics-only (n=92)	Antibiotics+ Rifaximin (n=92)
Mechanical ventilation	30 (32.6%)	26 (28.3%)
Antibiotics at baseline		
Carbapenems	33 (36%)	37 (40.2%)
Cephalosporin+beta-lactamase inhibitor	36 (39%)	32 (34.8%)
Penicillin+beta-lactamase inhibitor	15 (16.3%)	20 (21.7%)
Cephalosporin	8 (8.7%)	3 (3.3%)
LOLA used	38 (41.3%)	46 (50%)
Endotoxin levels (EU/ml)	1.22±0.72 (n=17)	1.3±0.86 (n=15)
Arterial ammonia levels (μmol/L)	98.4±56.3	93.7±46.4
MELD NA	31.4±8.3	31±8
SOFA score	8.9±3.41	8.8±3.37

ΑΠΟΤΕΛΕΣΜΑΤΑ

HE reduction 2 grade or resolution



In-hospital survival



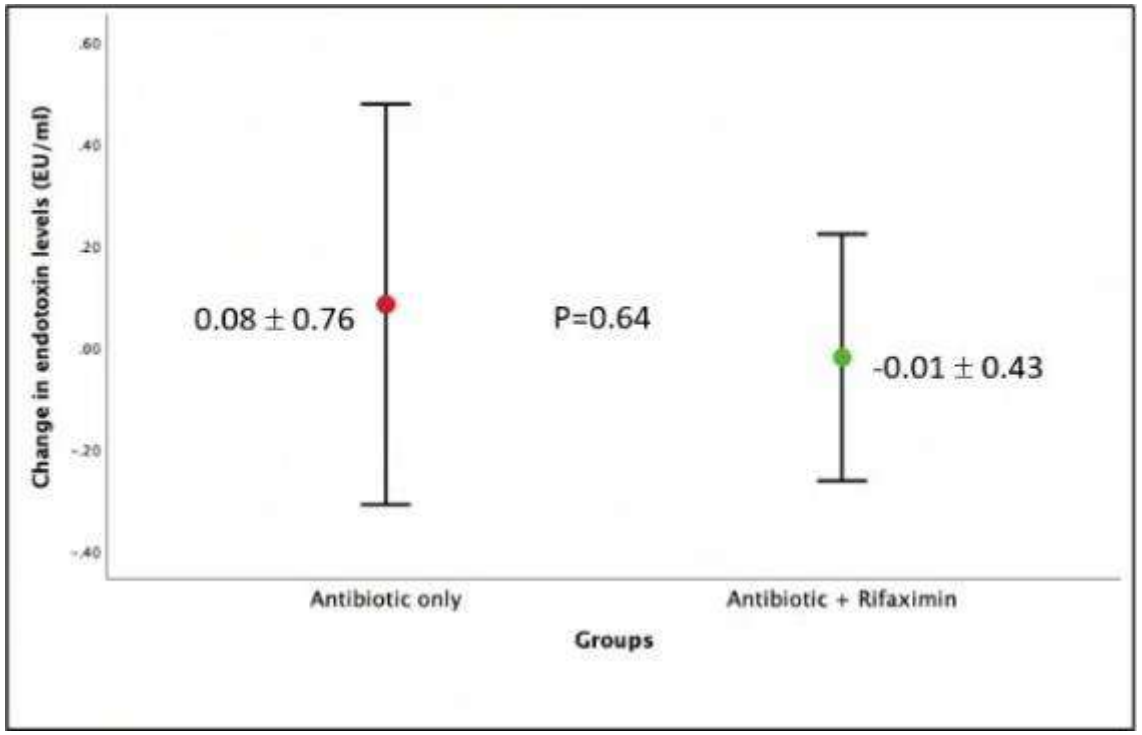
Number at risk	Day 0	Day 7	Day 14	Day 21	Day 28	Day 35
Ab	92	57	45	38	36	35
Ab+R	92	70	52	49	47	46

Objectives	Ab alone	Ab+R	P
Hospital stay	8.9± 6.38	10.15± 6.52	0.18
Infection resolution	40.5% (17/42)	43.2% (16/37)	0.49
Nosocomial infections	6.5% (n=6)	13% (n=12)	0.21

ΛΟΙΜΩΞΕΙΣ

	Ab only	Ab+R	P
Site			
Pneumonia	4	5	0.47
Bacteremia	2	2	
UTI	0	1	
SBP	0	1	
SSTI	0	3	
Organism			
Klebsiella	2	4	0.43
E.Coli	0	1	
Enterococcus	1	1	
MSSA	0	1	
Candida albicans	1	0	

ΕΝΔΟΤΟΞΙΝΗ

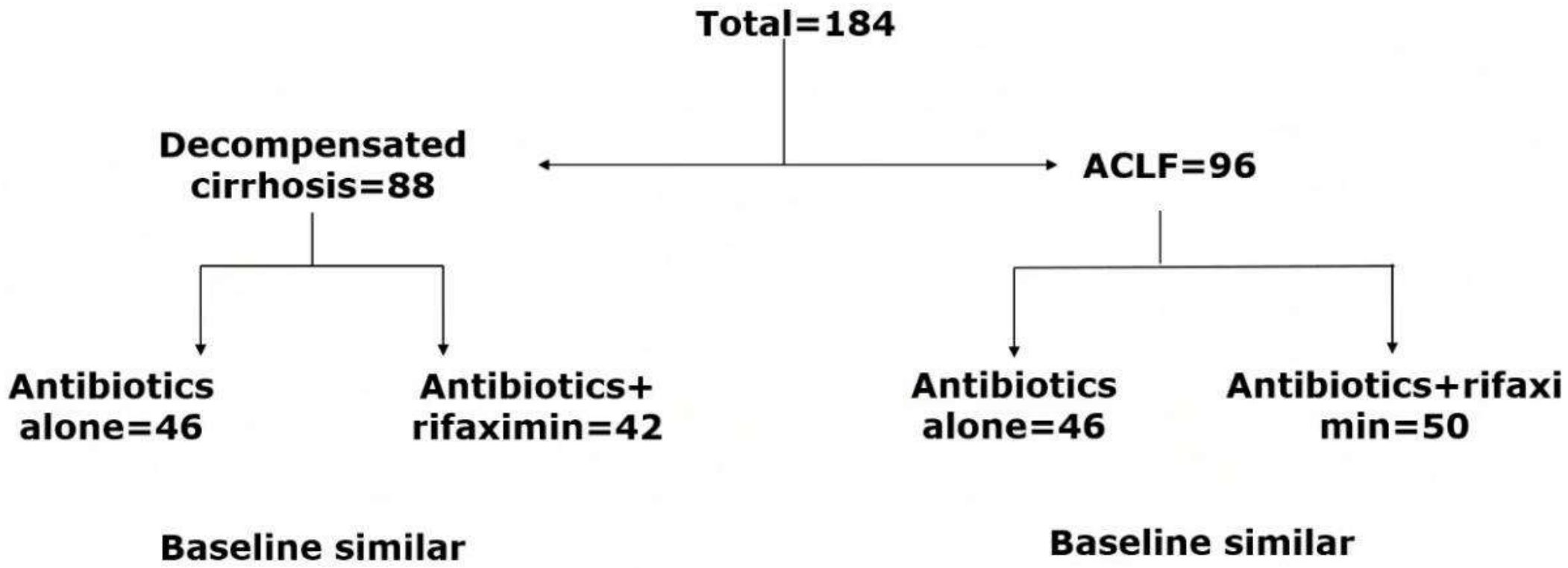

Change in endotoxin levels (EU/ml)
.60
.40
.20
.00
-.20
-.40
0.08 ± 0.76
P=0.64
-0.01 ± 0.43
Antibiotic only
Antibiotic + Rifaximin
Groups

ΠΡΟΓΝΩΣΤΙΚΟΙ ΠΑΡΑΓΟΝΤΕΣ ΗΕ RESOLUTION

Variables	Univariate (HR,95%CI)	P
Age	1.01 (0.99-1.03)	0.08
Females	0.83 (0.44-1.58)	0.58
LOLA used	1.75 (1.13-2.71)	0.01
Infection at baseline	0.54 (0.34-0.86)	0.01
Hemoglobin (g/dl)	1.05 (0.93-1.17)	0.37
TLC(cells/mm^3)	1	0.02
Platelets (x10^9/L)	1	0.7
INR	066 (0.51-0.87)	0.003
Blood urea nitrogen (mg/dl)	0.99 (0.98-0.99)	0.03
Serum creatinine (mg/dl)	0.89 (0.76-1.03)	0.12
Serum sodium (meq/dl)	1 (0.97-1.02)	0.97
Serum potassium (meq/dl)	0.94 (0.74-1.2)	0.65
Endotoxin levels (EU/ml)	0.74 (0.41-1.32)	0.31
Arterial ammonia levels (μmol/L)	1.002 (0.99-1.006)	0.41
Use of rifaximin	0.98 (0.64-1.5)	0.92
DC vs. ACLF	0.52 (0.33-0.8)	0.003
MELD	0.95 (0.93-0.97)	<0.001
MELD NA	0.95 (0.93-0.98)	<0.001
Total bilirubin (mg/dl)	0.96 (0.94-0.98)	<0.001
Albumin (g/dl)	1.88 (1.24-2.85)	0.003
SOFA score	0.84 (0.77-0.91)	<0.001

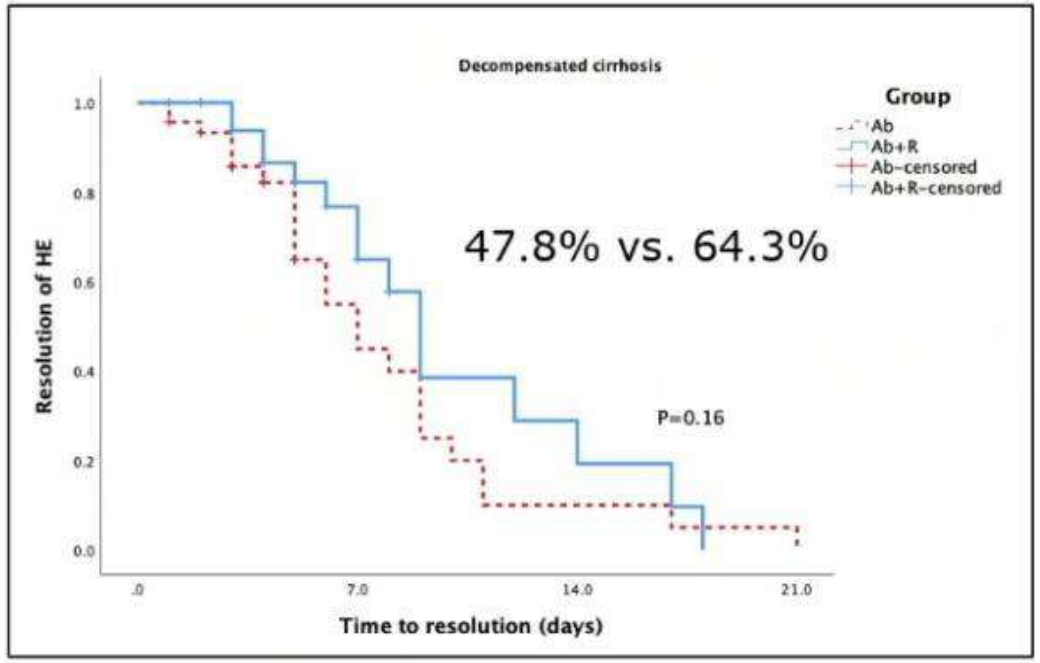
Variables	**Multivariate (HR, 95%CI)**	**P**
Total bilirubin (mg/dl)	**0.96 (0.94-0.99)**	**0.005**
Albumin (g/dl)	**1.68 (1.12-2.5)**	**0.01**
SOFA score	**0.88 (0.82-0.95)**	**0.002**

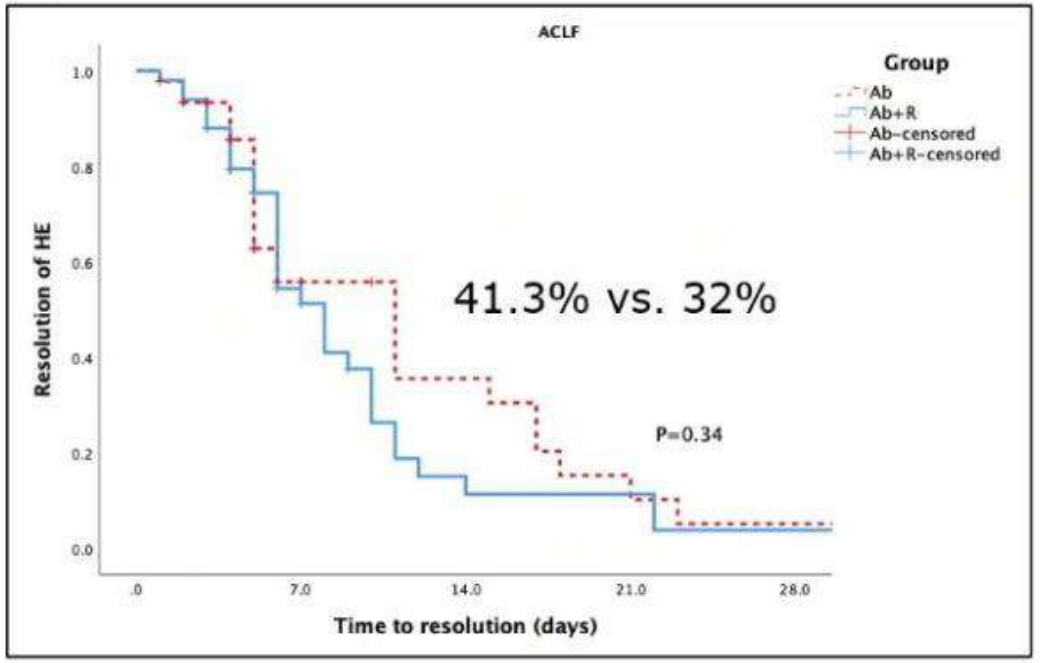
ΥΠΟΟΜΑΔΕΣ


Total=184
Decompensated cirrhosis=88
ACLF=96
Antibiotics alone=46
Antibiotics+ rifaximin=42
Antibiotics alone=46
Antibiotics+rifaxi min=50
Baseline similar
Baseline similar

Μη αντιρροπούμενη κίρρωση vs APASL ACLF

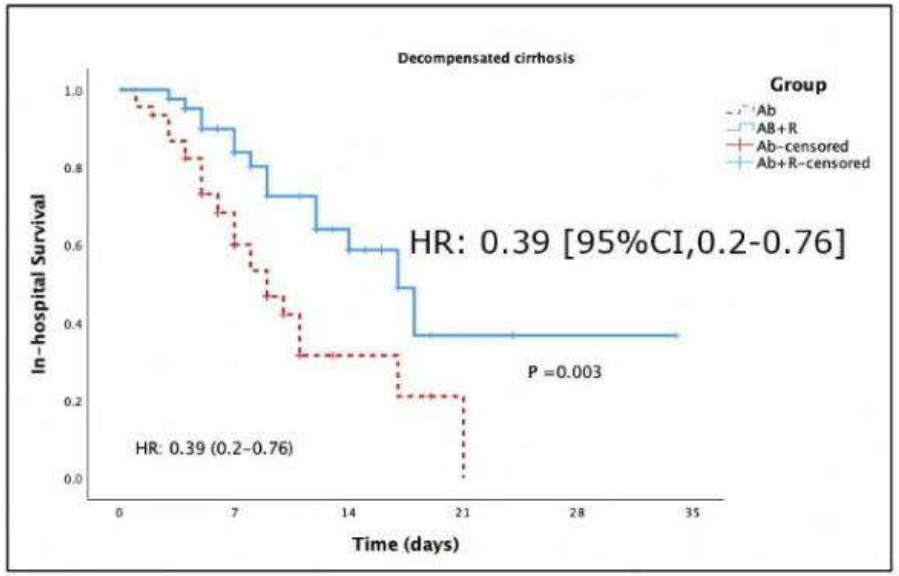
No effect on HE resolution in either groups





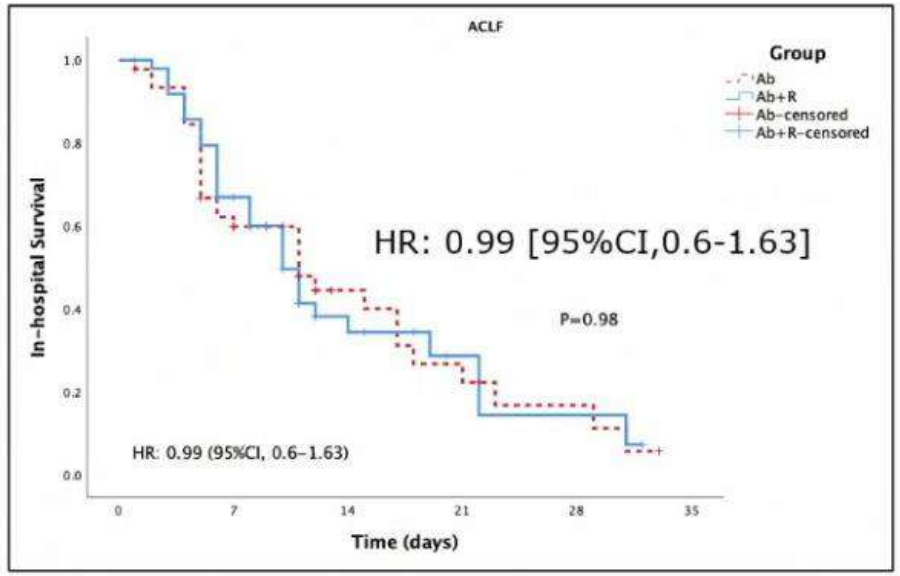
Μη αντιρροπούμενη κίρρωση vs APASL ACLF

a. Improved survival in DC



Number at risk	Day 0	Day 7	Day 14	Day 21	Day 28	Day 35
Ab	46	29	22	20	20	20
Ab+R	42	36	30	28	28	28

b. No effect on ACLF



Number at risk	Day 0	Day 7	Day 14	Day 21	Day 28	Day 35
Ab	46	28	23	18	17	15
Ab+R	50	34	22	21	19	18

Ab-antibiotic
R-Rifaximin

Μειωμένες νοσοκομειακές λοιμώξεις σε ΜΑΚ

	Decompensated cirrhosis			ACLF		
	Ab alone	**Ab+R**	**P**	**Ab alone**	**Ab+R**	**P**
Nosocomial infections	10.86%	0	0.02	9%	18%	0.23
Mortality due to nosocomial infection	60%	-	-	100%	100%	-

ΣΥΜΠΕΡΑΣΜΑΤΑ

- ✓Rifaximin doesn't have any effect on HE resolution in patients admitted to ICU who are broad-spectrum antibiotics
- ✓Rifaximin may reduce mortality in patients with decompensated cirrhosis, probably by preventing nosocomial infections.
- ✓No survival benefit in patients with ACLF

- ✓Limitations: Included sick ICU patients (mean MELD Na-31)

No placebo

Alcohol-related cirrhosis portends lower 6-week mortality after acute variceal bleeding compared to other etiologies

Results from a large propensity score matched international cohort

The Liver Meeting
11.12.2023

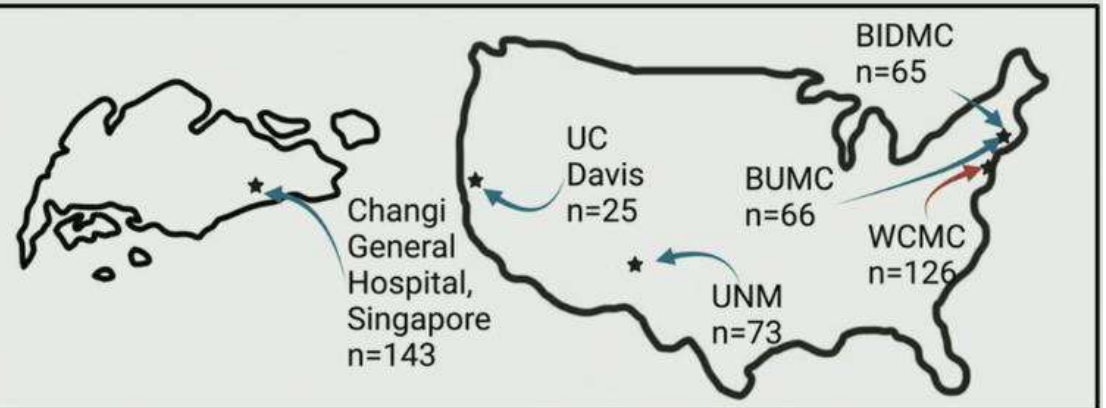
Adam Buckholz, MD MSc
Assistant Professor of Gastroenterology and Hepatology
Weill Cornell Medical Center

ΣΚΟΠΟΣ

- To determine whether there is a differential impact of alcohol-related cirrhosis on 6-week mortality after variceal bleed
- **Relevance:** If disease etiology impacts outcomes, but is not accounted for in current predictive models (CTP, MELD, MELD 3.0), risk assessment as a tool to guide management may need refinement

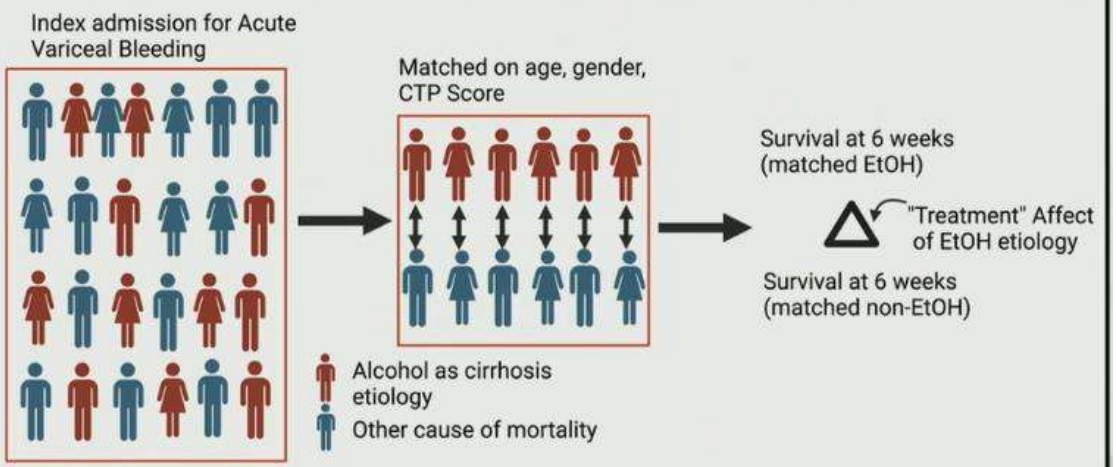
ΣΧΕΔΙΑΣΜΟΣ - ΜΕΘΟΔΟΛΟΓΙΑ

Study Population: Index variceal bleed excluding advanced HCC and those managed with pre-emptive TIPS or transplant



Analytical Plan: Quasi-experimental **propensity score model** matching patients based on age, gender and CTP

Primary outcome: 6-week mortality as outlined in Baveno consensus



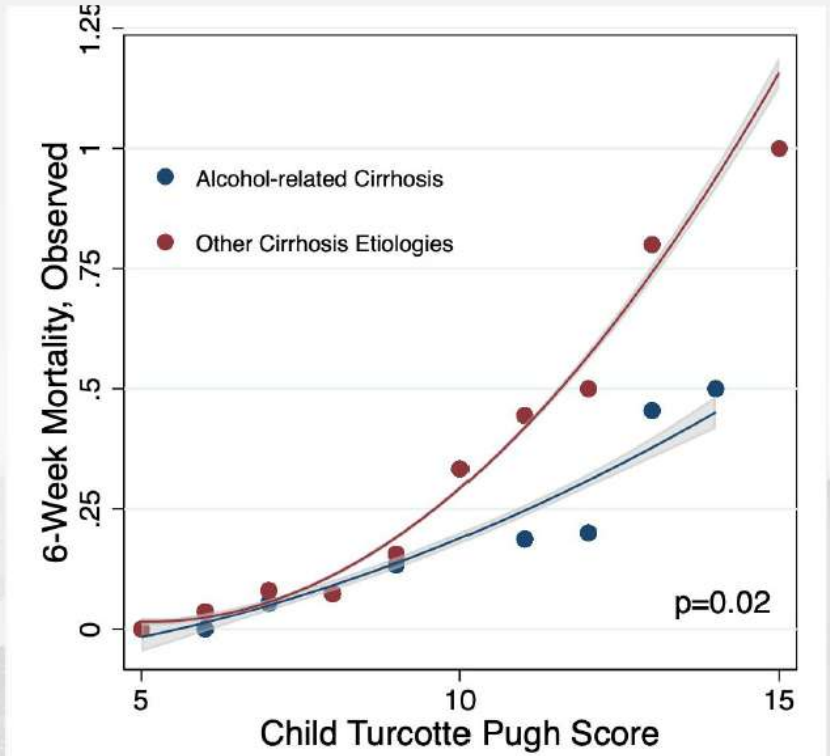
Hypothesis: 6-week mortality after acute variceal bleed is higher in those with non-alcohol related disease

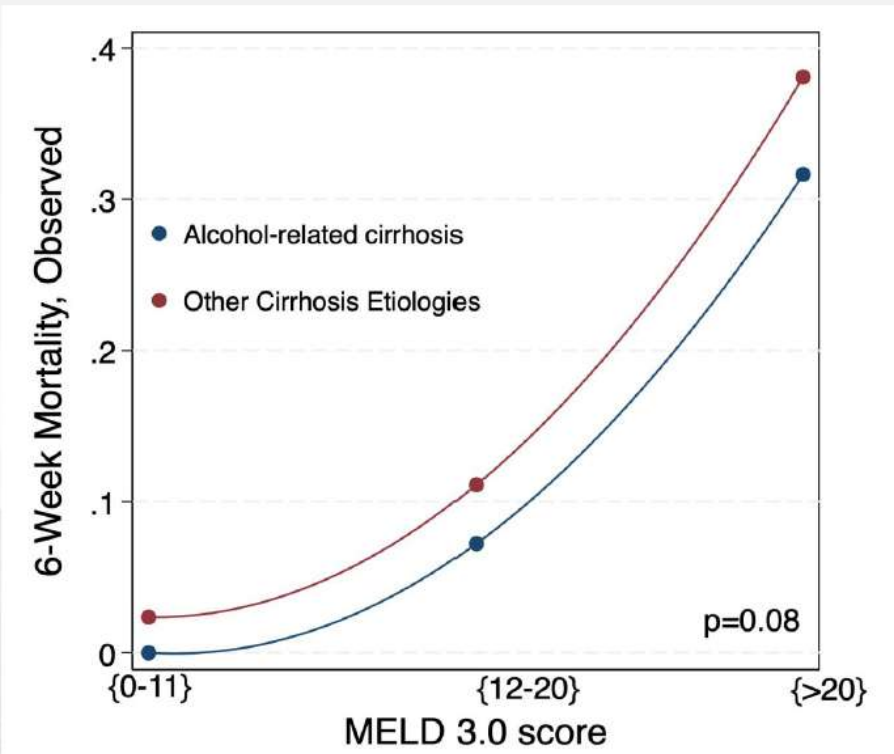
BASELINE

Etiology	Frequency, n (% of total)
Alcohol	157 (33.5%)
Alcohol plus HBV or HCV*	47 (10.0%)
MASLD	64 (13.7%)
HBV	45 (9.6%)
HCV	84 (17.9%)
Cryptogenic	22 (4.7%)
Other (AIH, etc)	50 (10.7%)
Total	**469**

	Alcohol (n=204)	Non-alcohol (n=265)	Total (n=469)	p value
Gender, M (%)	160 (78%)	175 (66%)	335 (71%)	<0.01
Age, mean (SD)	52.4 (11.0)	61.0 (11.1)	57.3 (11.9)	<0.01
Admission MELD	18.1	13.8	15.7	<0.01
Admission CTP	9.12	7.80	8.37	<0.01
Admission MELD 3.0	19.5	15.9	17.5	<0.01
6-week Mortality, n (%)	**32 (15.7%)**	**39 (14.7%)**	**71 (15.1%)**	**0.77**

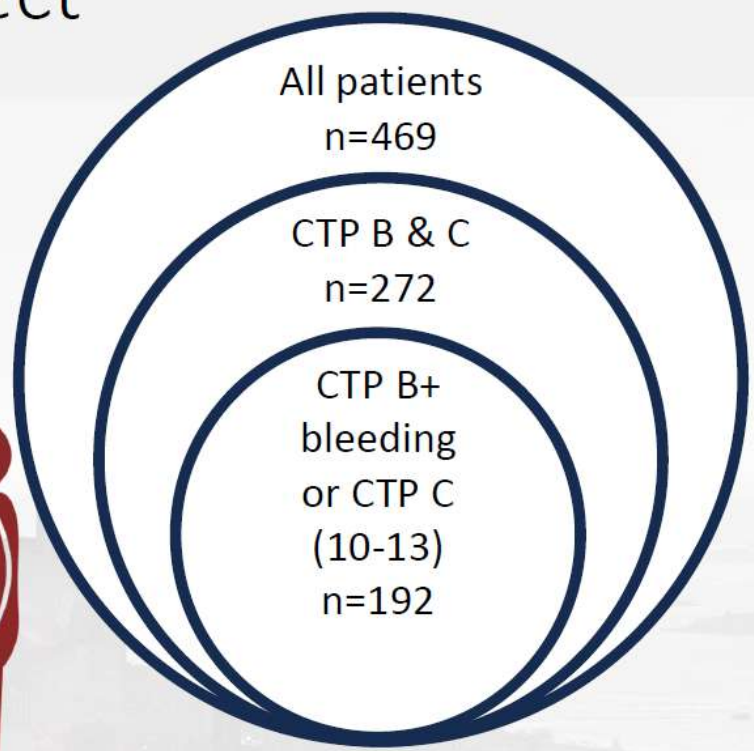
Observed Disparity in Mortality in ALD





In propensity matched model, alcohol had a "protective" treatment effect

- All patients ATET = ↓ 10%
  - *p*=0.054 95% CI -0.002, 0.21
- CTP B & C ATET = ↓ 15%
  - *p*=0.04 95% CI 0.01, 0.31
- CTP B + active bleed or CTP C (10-13) ATET= ↓ 17%
  - *p*=0.03 95% CI 0.02, 0.32



- In a large multicenter study of patients with cirrhosis, when adjusted for disease severity, age and gender, patients with **alcohol-associated cirrhosis** had reduced mortality at 6-weeks after variceal bleed.
- Consideration of patient-based factors may improve risk stratification and management of those with acute variceal bleeding
  - TIPS or no TIPS
  - Transplant candidacy/urgency
  - Need for endoscopic or pharmacologic interventions

Carvedilol plus NUCs to prevent the progression of esophageal varices in compensated HBV-cirrhosis patients under virological suppression: RCT study

Bingqiong Wang

Liver Research Center

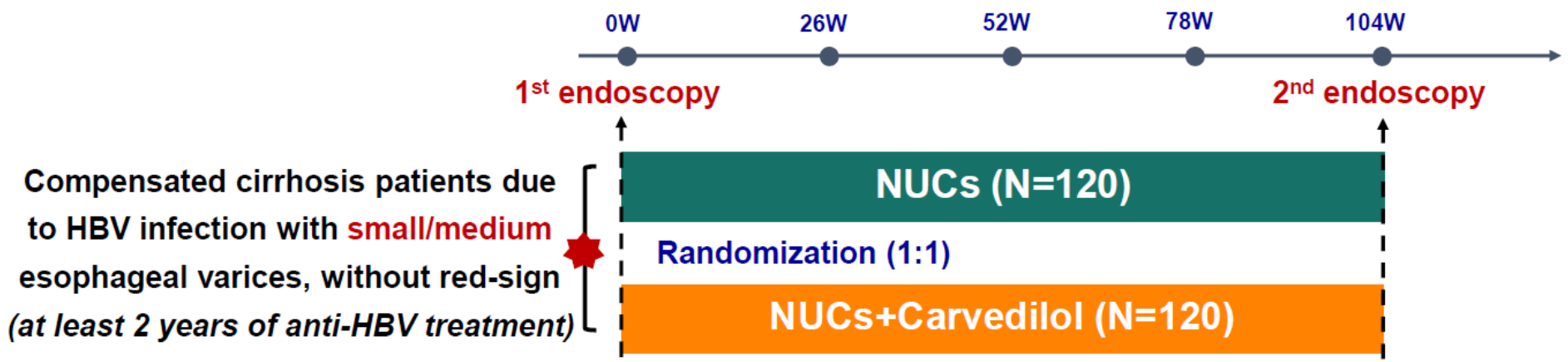
Beijing Friendship Hospital

Capital Medical University, Beijing, China

2023-11-12

- Beijing Friendship Hospital, Capital Medical University
- Peking University First Hospital
- Zhongshan Hospital, Fudan University
- Beijing Youan Hospital, Capital Medical University
- Affiliated Hospital of Yanbian University
- Tianjin Third Central Hospital
- Peking University People's Hospital
- Beijing Ditan Hospital, Capital Medical University
- Shanghai General Hospital, Shanghai Jiaotong University School of Medicine
- Tianjin Second People's Hospital
- Shanghai Public Health Clinical Center
- Xinjiang Uygur Autonomous Region Traditional Chinese Medicine Hospital

- **Study design:** A prospective, open-label, randomized, controlled, multi-center study
- **Aims: Carvedilol combined with NUCs could yield more benefits in delaying progression of esophageal varices in cirrhotic patients under virological suppression (NCT 03736265)**

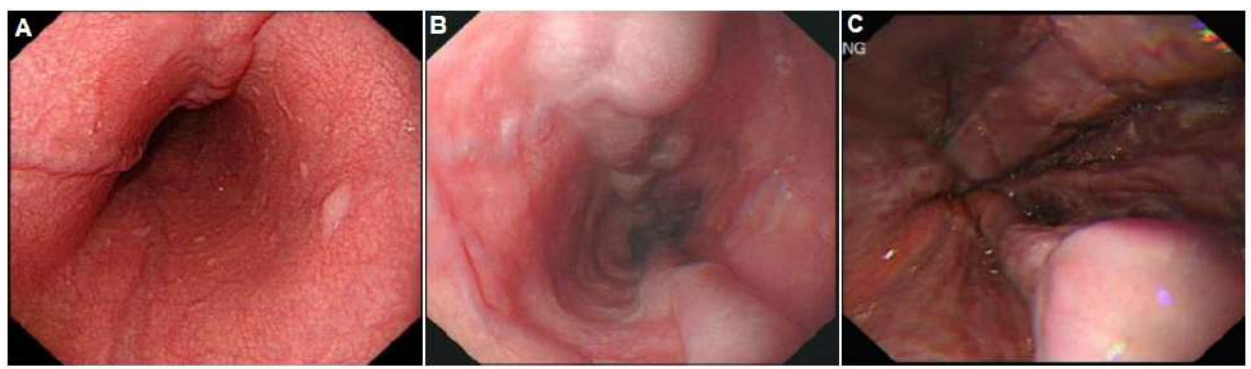


Carvedilol: 6.25mg/day for one week, then increase to 12.5mg/day if tolerated

Primary Endpoint

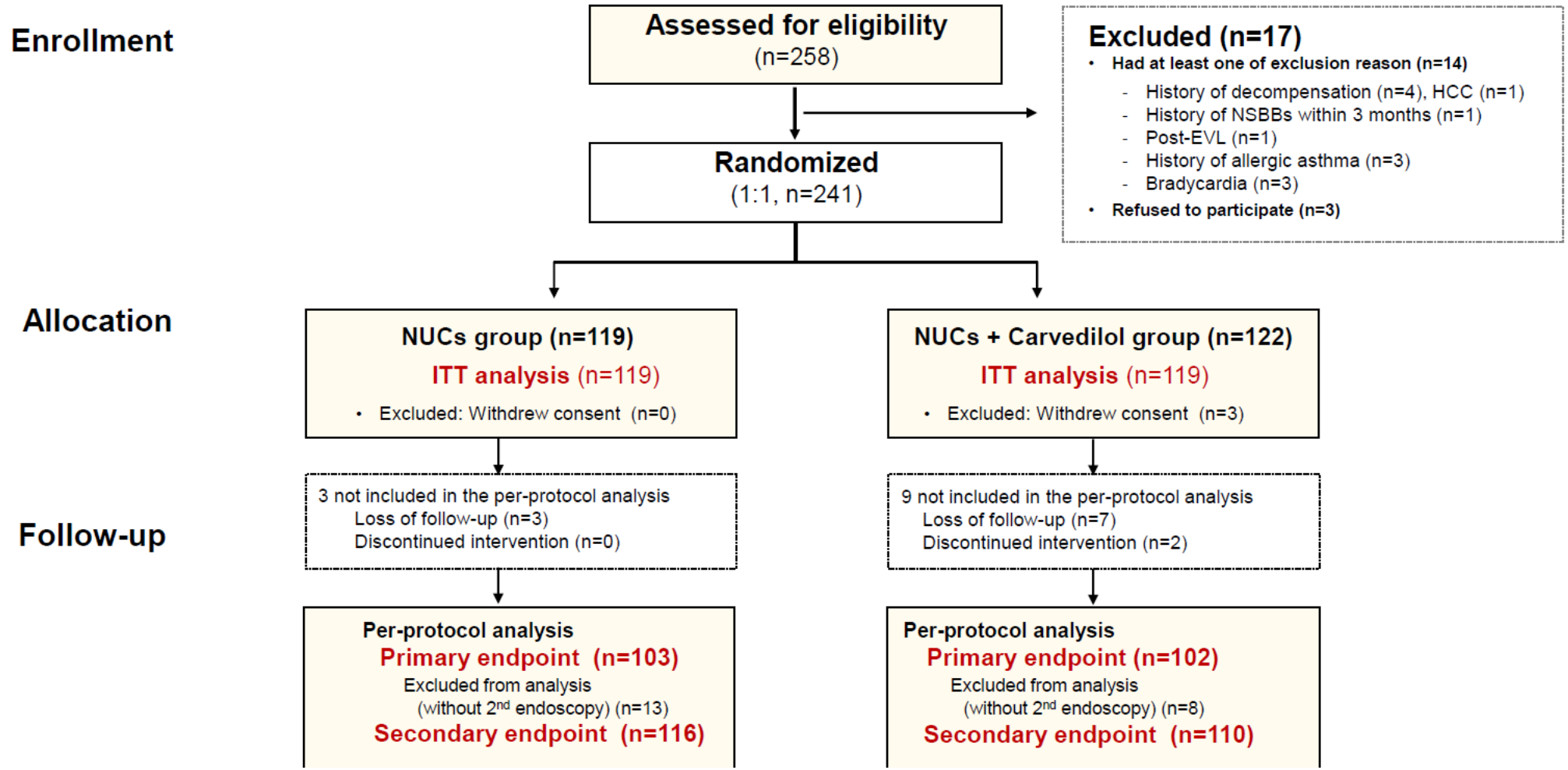
Progression rate of esophageal varices after 2 years of treatment

- ✓ Progression from small (grade 1) to medium or large (grade 2/3).
- ✓ Progression from medium (grade 2) to large (grade 3).
- ✓ Bleeding from esophageal varices.



(A) Small, Grade 1 (B) Medium, Grade 2 (C) Large, Grade 3

Flow chart of our study

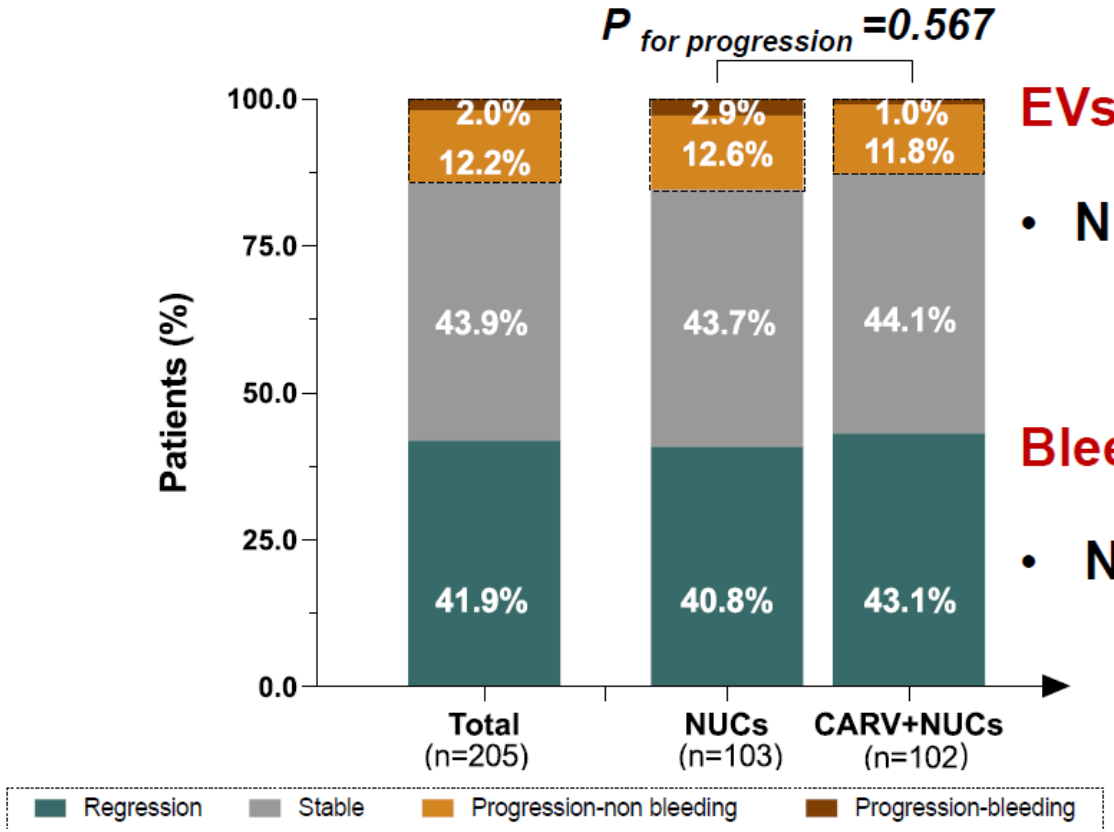


Baseline

Parameters	Total (N=238)	NUCs (N=119)	CARV+NUCs (N=119)
Gender, male, n (%)	176 (73.9)	85 (71.4)	91 (76.5)
Age, year	51 ± 10	49 ± 10	51 ± 10
Duration of treatment, y	4.0 (2.0, 7.3)	4.0 (2.0, 6.0)	4.5 (2.0, 8.0)
HBeAg (+), n (%) *	61/237 (25.7)	30/118 (25.4)	31/119 (26.1)
HBV-DNA <100 IU/mL, n (%)	226 (95.0)	110 (92.4)	116 (97.5)
EVs, small, n (%)	184 (77.3)	92 (77.3)	92 (77.3)
PLT, 10^9/L	115.2 (67.0, 166.5)	112.0 (64.4, 166.0)	118.0 (69.0, 168.0)
ALT, U/L	23.3 (18.0, 31.7)	23.4 (18.0, 34.0)	23.0 (18.7, 31.0)
AST, U/L	25.0 (21.0, 31.1)	25.0 (20.0, 31.1)	25.0 (21.0, 31.2)
TBIL, umol/L	18.6 (14.5, 24.4)	19.0 (14.4, 28.7)	17.6 (14.5, 22.5)
ALB, g/L	45.9 (42.0, 48.7)	45.7 (40.6, 48.4)	46.3 (43.0, 49.0)
INR	1.1 (1.0, 1.2)	1.1 (1.0, 1.2)	1.1 (1.0, 1.2)
LSM, kPa	10.6 (6.9, 16.2)	10.4 (6.8, 16.1)	10.9 (7.3, 16.3)
MELD score	8.0 (7.0, 9.0)	8.0 (7.0, 9.8)	8.0 (7.0, 9.0)

Η ομάδα καρβεντιλόλης δεν έδειξε υπεροχή συνολικά

- **Total of all enrolled patients**



EVs progression rate

- **NUCs 15.5% vs. CARV+ NUCs 12.7%**

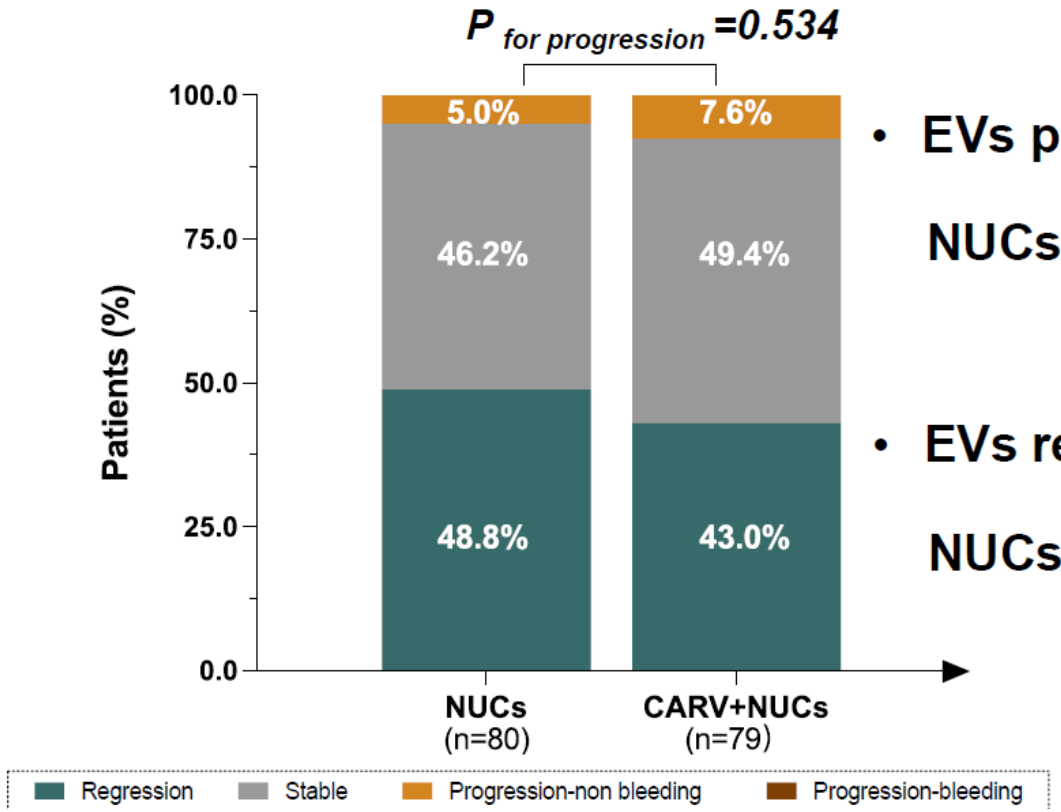
  RR = 0.79 (0.36-1.75), *P* = 0.567

Bleeding:

- **NUCs 2.9% vs. CARV+ NUCs 1.0%**

Μικροί κιρσοί

- **Patients with small EVs**



- **EVs progression rate:**

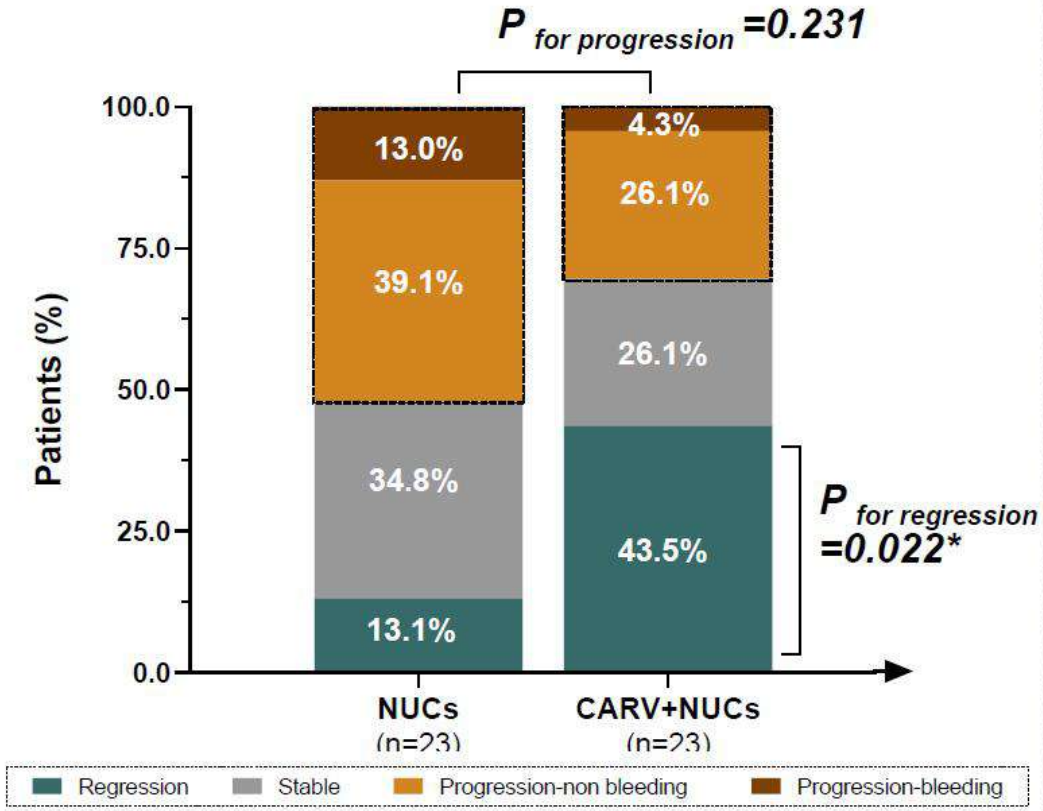
  NUCs 5.0% vs. CARV+ NUCs 7.6%

- **EVs regression rate:**

  NUCs 48.8% vs. CARV+ NUCs 43.0%

Κιρσοί μεσαίου μεγέθους

- **Patients with medium EVs**



- **EVs progression rate:**

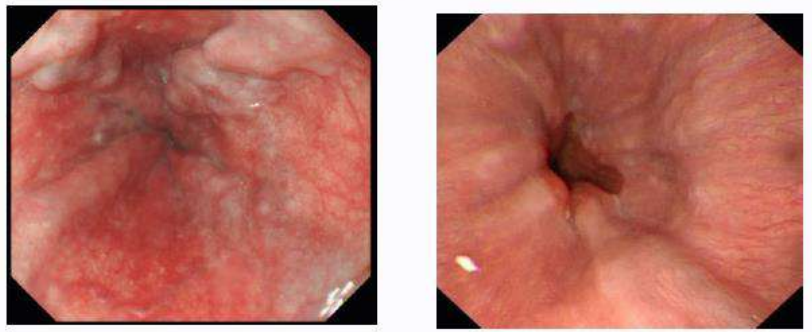
  NUCs **52.2%** vs. CARV+ NUCs **30.4%**

- **EVs regression rate:**

  NUCs **13.1%** vs. CARV+ NUCs **43.5%**

  P for regression=0.022

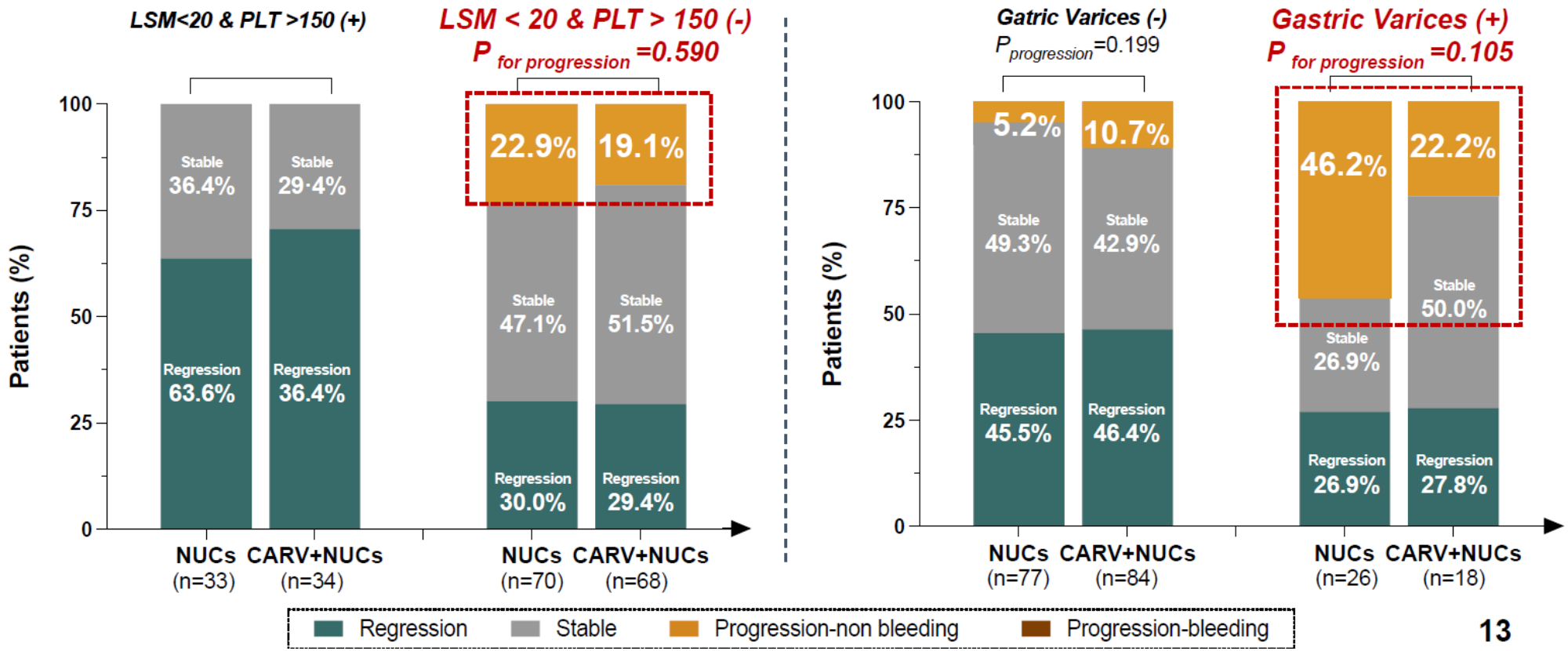
Pre-treatment (medium EVs) **Post-treatment (small EVs)**



Regression of EVs (on CVD)

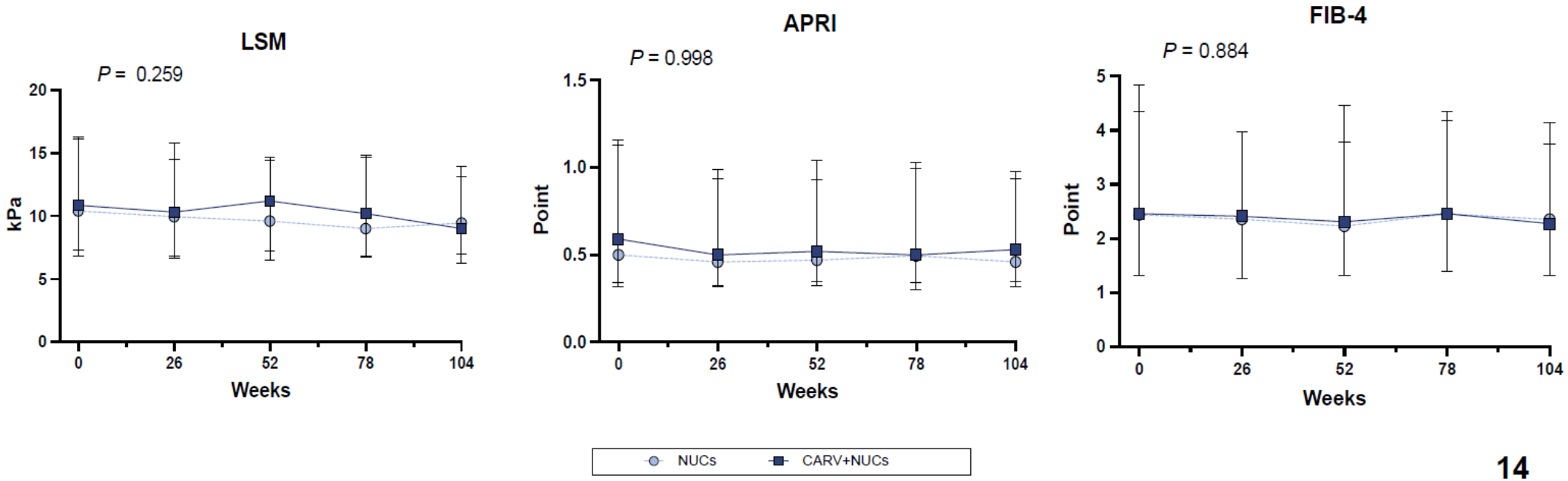
Subgroup analysis showed potential benefit of carvedilol in patients with suspected CSPH

- **Based on Baveno VI criteria**
- **Based on gastric varices**



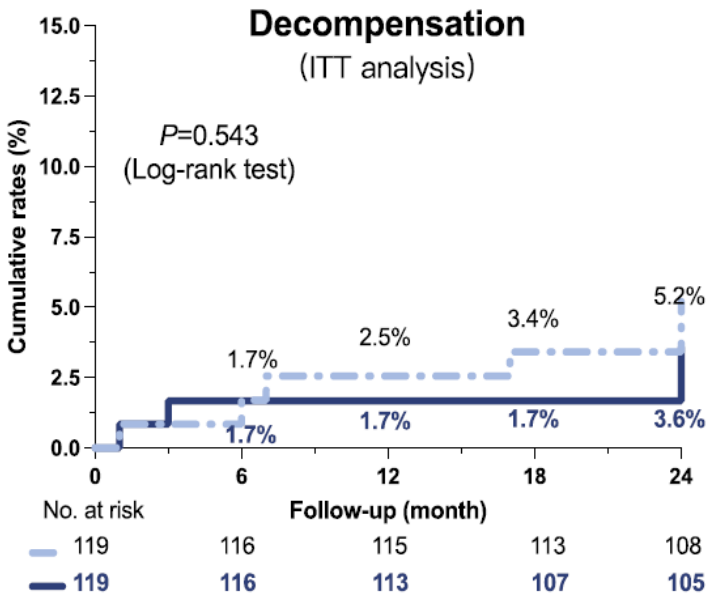
Ηπατική ίνωση

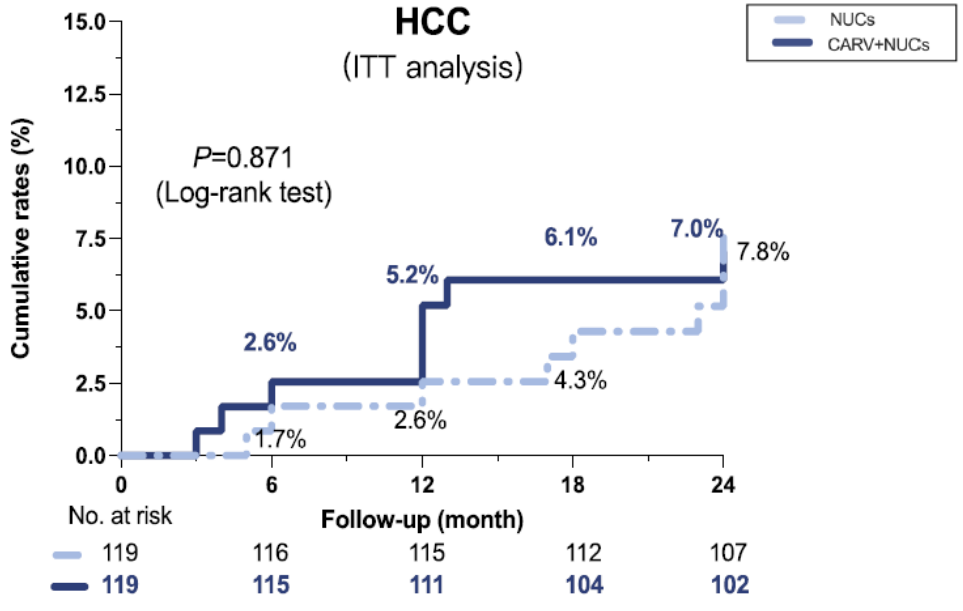
- **Non-invasive measurement of liver fibrosis**
- **There were no statistically significant difference**



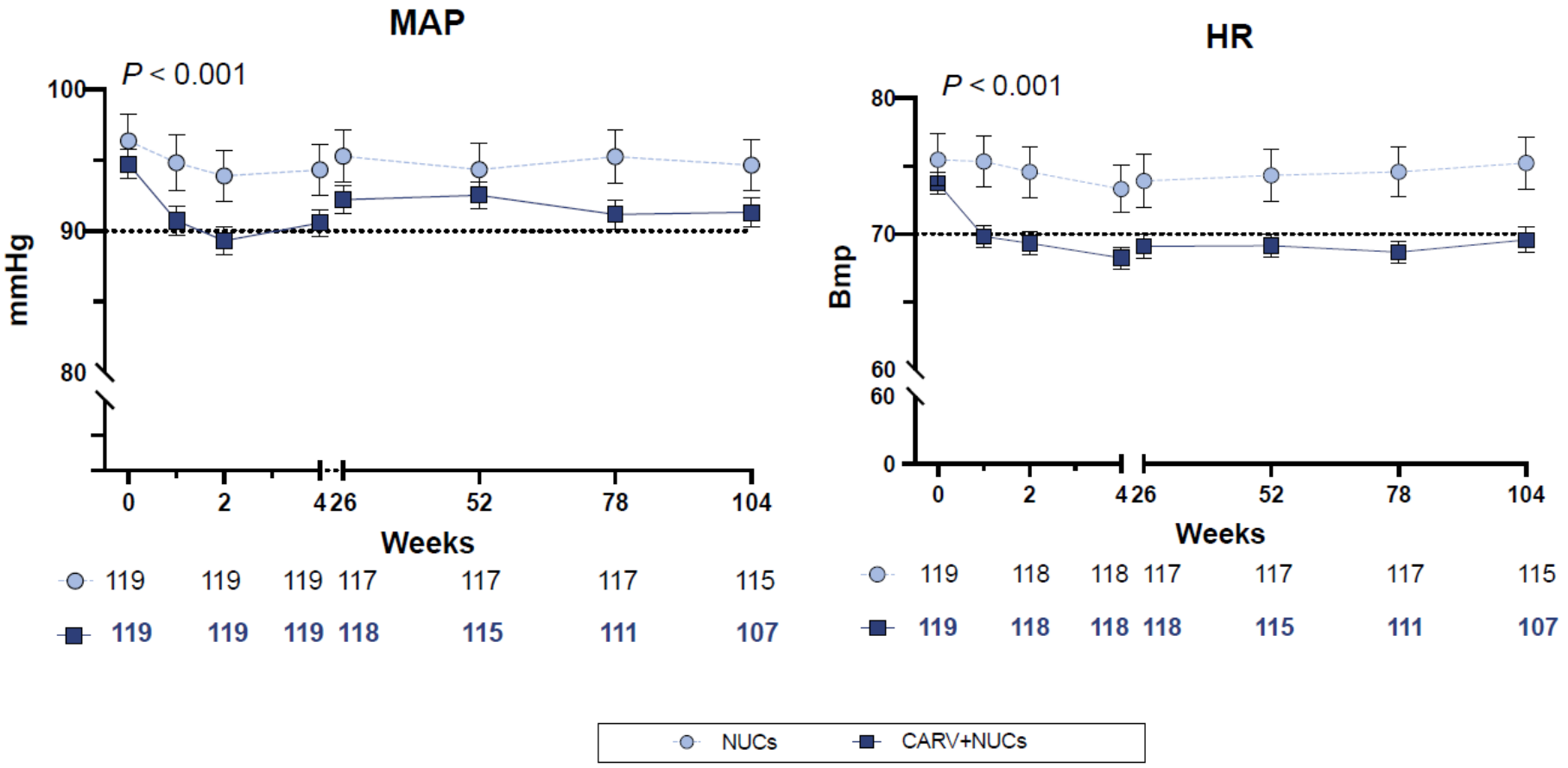
LREs

- No. LREs (decompensation, HCC, and death/LTx): **25 patients**
- The cumulative incidence of LREs: NUCs **11.2%** vs. CARV+ NUCs **10.4%**
- There were no statistically significant differences (*P* = 0.881)





Μείωση MAP και HR τις πρώτες δύο εβδομάδες στην ομάδα καρβεντιλόλης



Περισότερες NSAE στην ομάδα καρβεντιλόλης

Adverse events*	NUCs (n=119)	CARV+NUCs (n=119)	*P* value ‡
Total number of adverse events (AE)	7 (7 patients, 5.9%)	24 (17 patients, 14.3%)	***0.031***
Serious adverse events (SAE) †	5 events (5 patients)	5 events (4 patients)	1.000
Cerebrovascular accident	0	2	
Acute coronary syndrome	0	1	
Bacterial infection	1	0	
Herpes zoster virus infection	0	1	
Neoplasms malignant and unspecified	2	0	
Cholelithiasis with cholecystitis	1	0	
Ureteral stone with hydronephrosis	0	1	
Bone fracture	1	0	
Non-serious adverse events	**2 events (2 patients)**	**19 events (13 patients)**	***0.003***
Dizzy	**1**	**5**	
Bradycardia	**0**	**5**	
Hypotension	**0**	**3**	
Diarrhea	0	1	
Edema	0	1	
Rash	0	1	
Infection	0	3	
Chest Congestion	1	0	

† Serious adverse events: CTCAE grade above 3.

‡ *P* value was calculated by comparing the number of patients with one or more event between NUCs and CARV+NUCs group.

Συμπεράσματα

- Even with virological suppression, 15% of patients with compensated HBV-cirrhosis still experienced EVs progression.
- Overall, the added carvedilol strategy did not show more benefits than NUCs monotherapy in preventing EVs progression.
- However, carvedilol-added approach might improve outcomes for patients with medium EVs, especially in reversing EVs degree.

RIVET TRIAL: PHASE 2 RCT OF RIFAMYCIN SV MMX, A NOVEL RIFAMPIN ANALOGUE, ON GUT-BRAIN AXIS CHANGES IN CIRRHOSIS AND MINIMAL HEPATIC ENCEPHALOPATHY

Jasmohan S. Bajaj1,2, Andrew Fagan2, Edith A. Gavis2, Mary Leslie Gallagher2, Travis Mousel2, Puneet Puri1,2, Michael Fuchs2, Brian C. Davis2, Vishwadeep Ahluwalia3, Robert Cadrain3, Masoumeh Sikaroodi4, Patrick M Gillevet4.

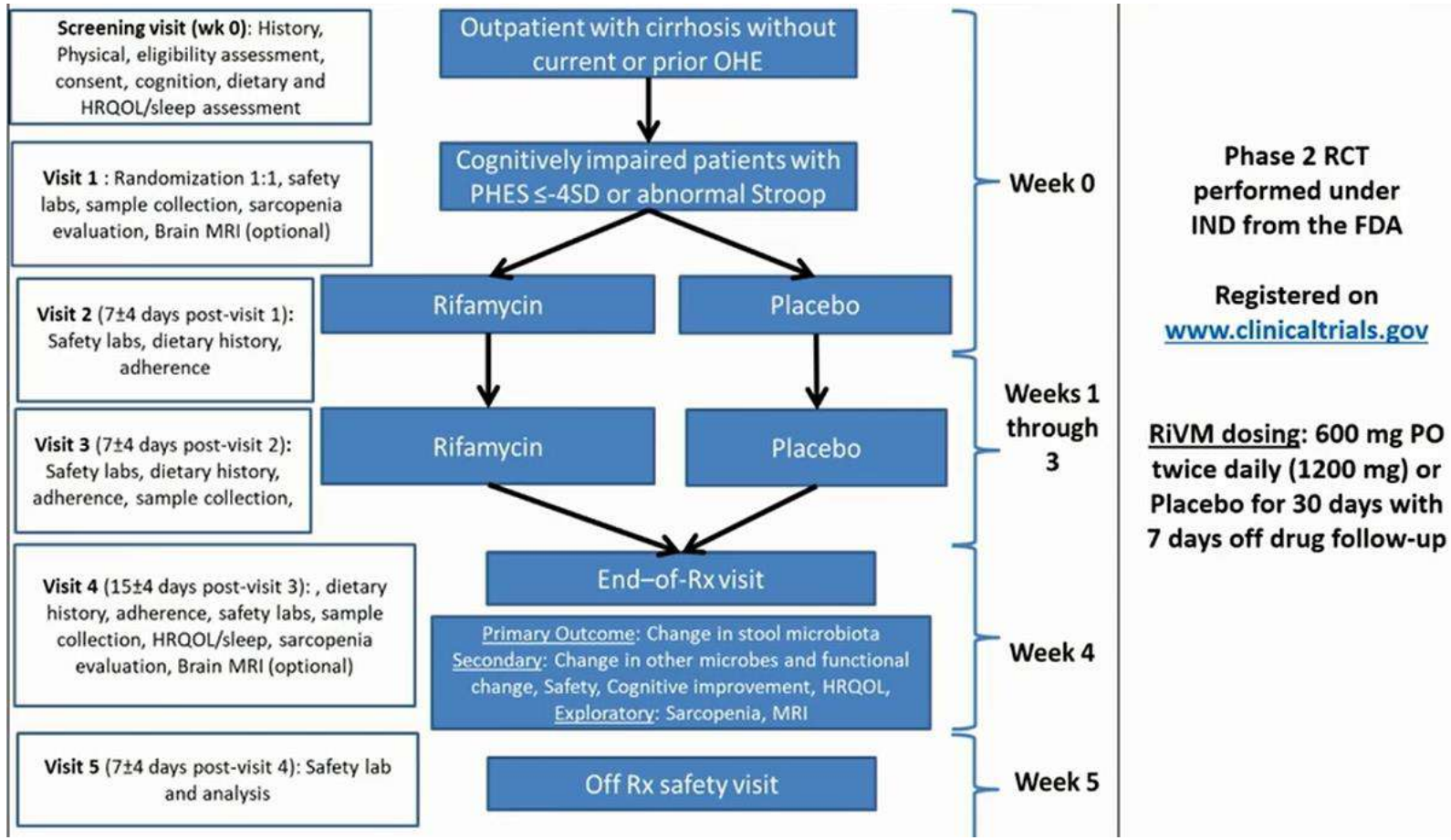
(1) Gastroenterology, Hepatology and Nutrition, Virginia Commonwealth University, Richmond, VA
(2) GI Section, Richmond VA Medical Center, Richmond, VA
(3) Collaborative Advanced Research Imaging Center, Virginia Commonwealth University, Richmond, VA
(4) Microbiome Analysis Center, George Mason University, Manassas, VA

- Patient-reported outcomes in cirrhosis span psycho-social and physical domains, which impair overall quality of life
- Minimal hepatic encephalopathy (MHE), cognitive impairment related to cirrhosis, affects clinical and psychosocial outcomes.
- Sarcopenia, and altered muscle function also affect outcomes such as falls and survival.
- Gut-brain axis alterations in cirrhosis link with several of these complications and medications such as lactulose and rifaximin have been studied in MHE.
- However, treatment for MHE is not standard of care and is decided on a case-by-case basis.
- Rifamycin SV MMX (RiVM) is a gut-targeted antibiotic, which is approved for traveler's diarrhea that starts acting in the colon.

Kaplan et al Curr Gastro Rep 2022, Vilstrup et al AASLD/EASL HE Guidelines Hepatology 2014, Lai & Tapper et al Hepatolgoy 2021, Bajaj et al Gastro 2010, Steffen et al J Travel Med 2018

Σκοπός

Evaluate impact of RiVM on the microbiome, safety, gut-brain axis, and gut-muscle axis in a double-blind, placebo-controlled randomized trial in patients with cirrhosis and MHE



Phase 2 RCT performed under IND from the FDA

Registered on www.clinicaltrials.gov

RiVM dosing: 600 mg PO twice daily (1200 mg) or Placebo for 30 days with 7 days off drug follow-up

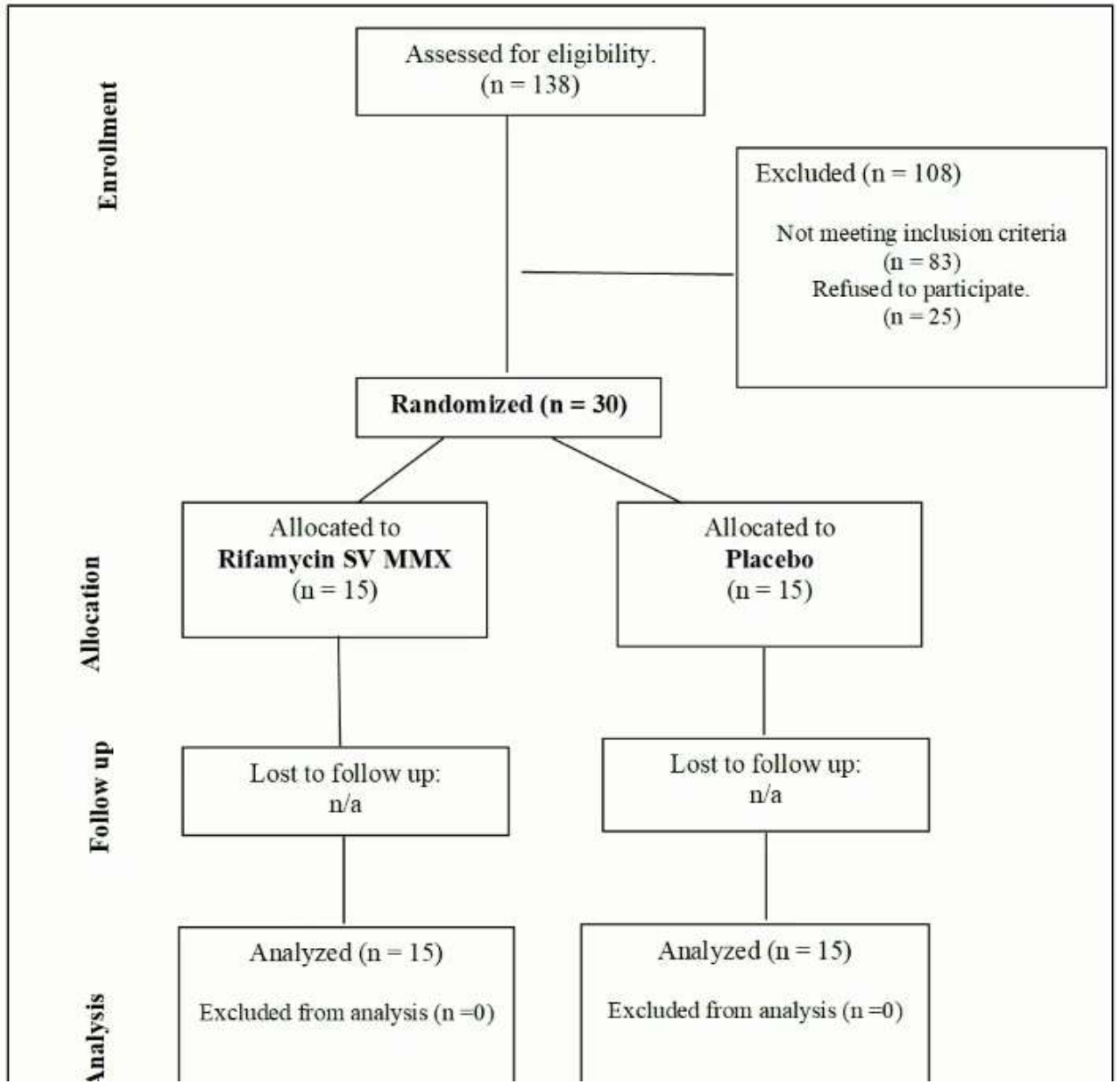
- Inclusion criteria
  - Age 18-75 years
  - Cirrhosis confirmed using biopsy, imaging characteristics, or non-invasive tests
  - Stable liver function 2-12 weeks prior to enrollment
  - Cognitive impairment (minimal HE) on screening: Impairment on any of the 2 tests: PHES <-4SD or MHE on EncephalApp Stroop (per US-based norms)
- Exclusion criteria
  - Prior HE
  - Allergic reactions to rifampin analogues
  - Advanced liver disease (MELD>20, Na<125, CTP>8)
  - Alcohol or illicit drug use within the last 3 months
  - Antibiotic/probiotic use within the last 1 month
  - Congestive heart failure and other end-organ failures
  - <3 month on statins if on statin therapy
  - Unable to consent or follow-up over 6 weeks
  - Post-transplant status

- **Primary Outcome:**
  - Change in Stool Cirrhosis Dysbiosis Ratio (CDR) calculated as

    Lachnospiraceae + Ruminococcaceae + Veillonellaceae/Enterobacteriaceae + Bacteroidaceae
- **Secondary Outcomes:**
  - Safety and tolerability, including MELD score and CPK (due to potential for rhabdomyolysis per FDA)
  - Microbiota composition: α/β diversity and individual microbes in stool and saliva
  - Microbial function: Short-chain fatty acids and Bile acids in stool, serum and urine
  - Cognitive function: PHES and Stroop
  - Inflammation: Stool calprotectin and serum cytokines
  - Sarcopenia and muscle function: handgrip strength and InBody measurement using bioelectric impedance
  - PROs: Sickness impact profile (SIP: higher=bad, physical and psychosocial domains)
  - Exploratory: brain MRS

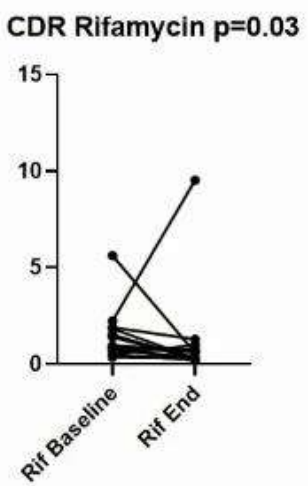
Subject Flow & Course

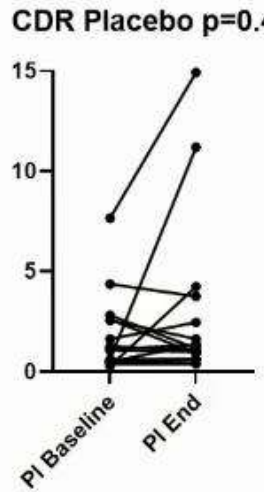
- **No SAEs** for RiVM and one unrelated SAE in the placebo group (chest pain)
- **5 RiVM & 5 placebo patients developed AEs**.
- **RiVM patients**: 3 with self-limited digestive symptoms, 1 with cough and 1 dizziness
- **Placebo patients**: 2 with self-limited digestive symptoms, 1 jaw pain, 1 shoulder pain & 1 high CPK.
- No discontinuation or interruption of study drug
- None developed overt HE or other decompensating event

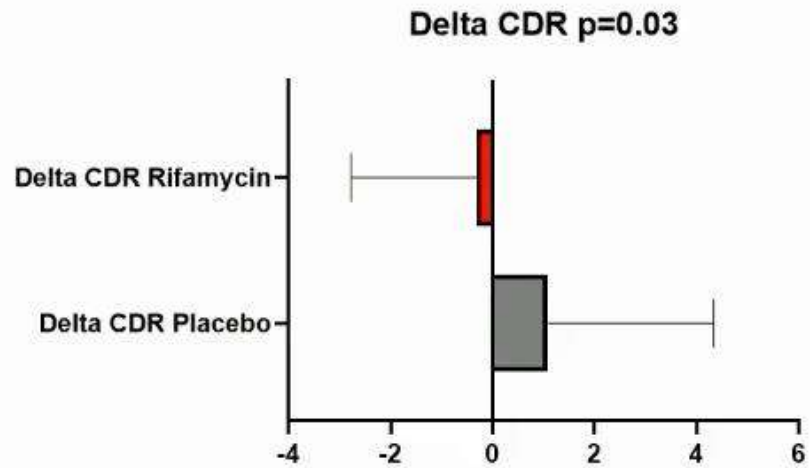


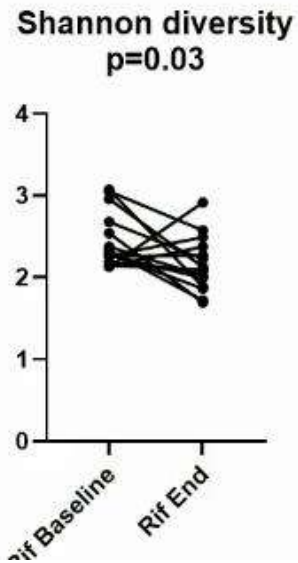
BASELINE COMPARISONS	Placebo (n=15)	Rifamycin (n=15)
Age	67.1±4.8	66.8±6.2
Male Gender	14	14
Race (Caucasian/ African-American)	10/5	8/7
Years of education	13.4±3.4	12.6±1.5
Cirrhosis details		
MELD-Na	7.7±2.0	8.7±3.0
Etiology (HCV/Alcohol/ HCV+Alcohol /MASH)	4/3/6/4	3/3/4/5
AST	30.4±16.6	34.5±17.5
ALT	29.0±7.9	33.1±9.3
ALP	94.7±24.9	110.2±44.8
Bilirubin	0.6±0.3	0.6±0.4
INR	1.1±0.3	1.1±0.2
Creatinine	1.0±0.2	1.1±0.5
Ammonia	**26.5±10.4**	**52.1±31.9***
Albumin	3.7±0.4	3.6±0.4
Sodium	138.8±2.1	139.5±2.1
Other labs		
WBC	6.5±1.9	5.4±2.1
Hgb	14.0±1.4	13.8±1.6
Platelet count	192.2±77.2	175.9±98.4
CPK	208±202	135±51

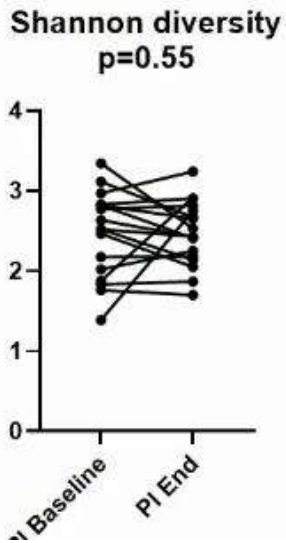
Primary Outcome: Change in CDR and microbial diversity

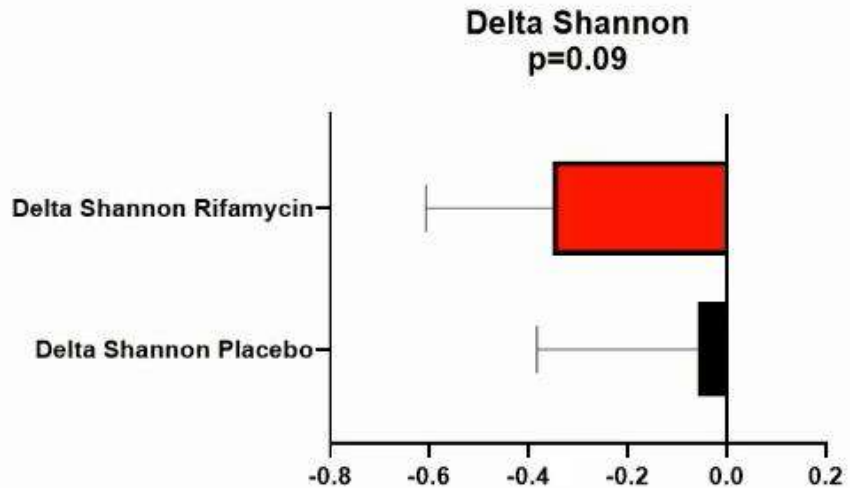










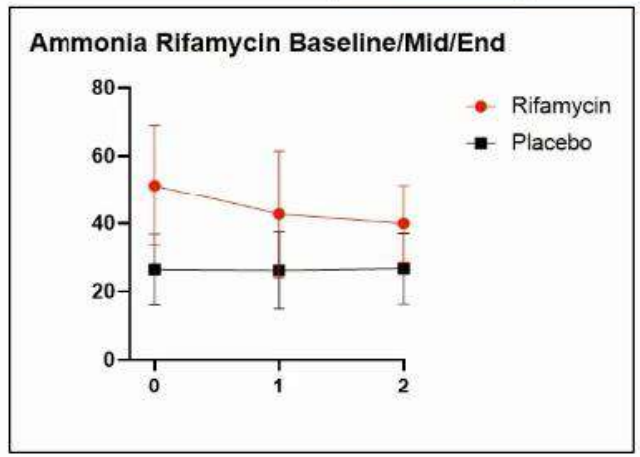


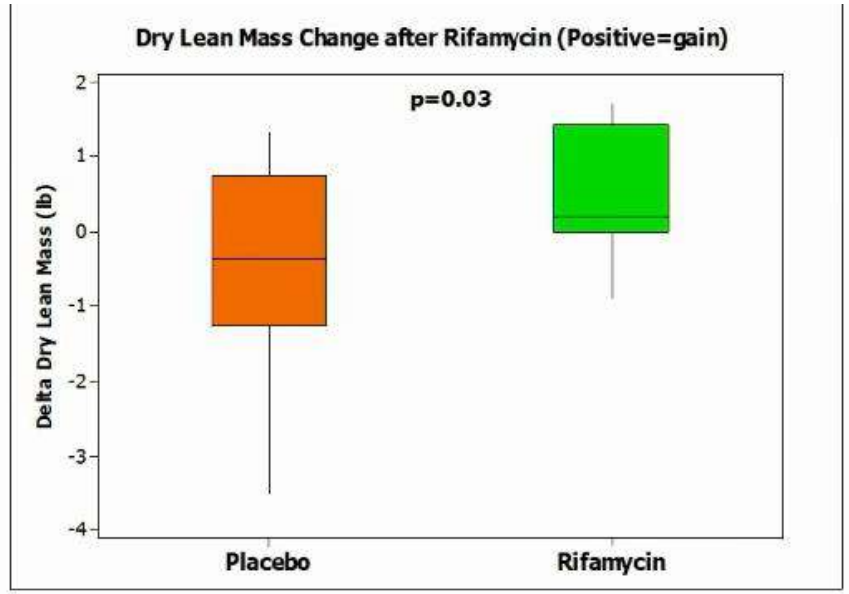
Cognitive, PROs and clinical variables	Rifamycin SV MMX (n=15)		Placebo (n=15)	
	Baseline	Drug-end	Baseline	Drug-end
MELD-Na	9.0±3.0	8.7±2.7	7.7±2.0	8.4±3.1
Ammonia (umol/L)	**52.1±31.9†**	**39.9±20.1*‡**	26.5±10.4	26.8±10.3
Cognitive testing				
PHES (high=good)	-5.3±2.3	-5.0±2.9	-4.0±2.9	-3.6±3.3
NCT A (low=good)	55.8±26.4	52.2±24.9	48.0±17.2	45.5±15.3
NCT B(low=good)	137.3±55.5	157.1±77.6	127.5±60.2	124.9±51.9
DST (high=good)	37.9±6.6	37.2±7.6	46.6±11.6	47.4±11.0
SDT (low=good)	**80.7±15.5**	**72.4±16.5***	73.7±16.6	70.9±18.4
LTT errors (low=good)	43.0±22.9	48.6±27.9	32.5±12.0	33.6±14.7
LTT time(low=good)	82.1±25.8	83.0±32.1	81.3±18.7	73.1±25.3
Stroop (low=good)				
Total time	218.5±47.2	229.3±49.9	196.9±34.7	198.8±42.9
OffTime	99.4±21.5	103.4±29.0	90.1±15.3	91.7±21.4
OnTime	119.1±29.4	121.7±29.9	106.8±21.2	108.1±23.8
Patient reported outcomes				
SIP total (low=good)	18.4±13.3	15.5±10.4	12.2±10.5	12.8±11.3
SIP physical (low=good)	**16.8±10.2†**	**13.2±10.1*‡**	9.7±11.3	10.3±11.2
SIP psychological (low=good)	18.9±18.2	15.6±14.6	13.6±13.0	14.4±14.7

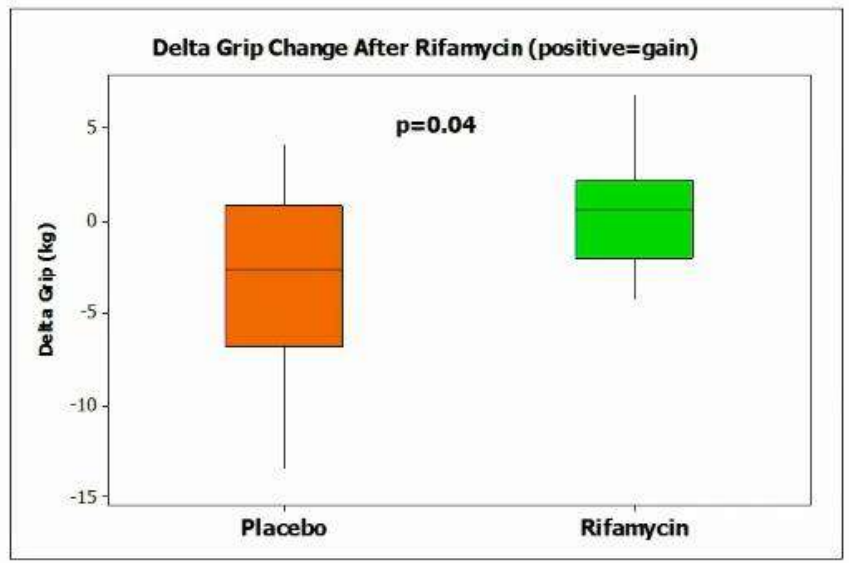
serial dotting test (SDT), Sickness Impact Profile (**SIP**)

	Rifamycin SV MMX (n=15)		Placebo (n=15)	
	Baseline	**Drug-end**	**Baseline**	**Drug-end**
Sarcopenia Median (IQR)				
Grip Strength (kg)	27.0 (16.5)	32.0 (19.0)	33.0 (18.3)	27.4 (19.0)
BMI	28.7 (6.8)	27.8 (7.3)	28.2(8.1)	28.9 (6.4)
Dry lean mass (lb)	**29. 9 (5.3)**	**31.9 (9.9)***	33.5 (10.9)	33.5 (10.2)
Intracellular water (lb)	52.7 (9.5)	53.2 (16.4)	57.1(20.9)	57.1 (16.9)
Extracellular water (lb)	34.4 (6.3)	34.6 (10.2)	37.5 (11.4)	36.2 (10.2)
Body fat mass%	63.6 (32.3)	60.1(35.9)	56.0 (46.6)	54.5 (42.3)
Inflammation Median (IQR)				
IL-1β (pg/ml)	**0.10 (0.12)**	**0.05 (0.0)***	0.10 (0.0)	0.10 (0.0)
IL-6 (pg/ml)	4.41 (9.51)	3.31 (7.96)	3.31 (3.89)	2.24 (2.33)
TNF-α (pg/ml)	3.10 (3.89)	2.65 (2.27)	3.09 (3.01)	2.61 (2.77)
LBP (ng/ml)	7142 (3251)	6961 (4360)	6628 (4245)	6840 (3113)
Stool Calprotectin (mcg/g) mean±SD	**346±766**	**82.6±57.3***	116.2±124.2	97.5±93.4

Delta (End minus Baseline)	Placebo	Rifamycin	P value
Labs			
MELD-Na	0.71±1.90	-0.07±1.53	0.21
Ammonia (umol/L)	0.24±8.56	-11.4±19.8	**0.05**
Calprotectin (mcg/g)	-14.4±61.6	-263±777	0.24
Cognition & Patient reported outcomes			
PHES	0.53±1.50	0.33±1.99	0.62
Stroop Off+OnTime	1.9±18.6	12.8±29.1	0.11
SIP total	0.65±5.86	-2.87±6.50	0.12
SIP physical	1.62±5.76	-2.76±5.44	**0.03**
SIP psychosocial	0.9±12.4	-3.34±9.26	0.28
Sarcopenia and body composition			
Lean mass change lb (median IQR)	-0.35 (2.0)	0.20 (1.4)	**0.03**
Handgrip kg (median IQR)	-2.6 (7.6)	0.6 (4.10)	**0.04**







Συμπεράσματα

- ✓RiVM was safe and well-tolerated
- ✓Lowered venous ammonia
- ✓Changes in stool microbiota composition and function focused on beneficial bile acids and short-chain fatty acids.
- ✓Improvement in several aspects of physical function, including handgrip, lean body mass, serial dotting test, and personal physical function evaluation.
- ✓Reduction in systemic and colonic inflammatory markers
- ✓No change in cognitive testing overall
- ✓ Reduction in brain oxidative stress

Συμπεράσματα

- In this phase 2 double-blind, placebo-controlled RCT of rifamycin SV-MMX in patients with cirrhosis and MHE, we found no safety concerns and a unique profile of changes across multiple systems.
- RiVM treatment lowered gut microbial α-diversity and cirrhosis dysbiosis ratio in stool without changes in saliva.
- Favorable changes in gut-brain axis and gut-muscle axis were noted with RiVM therapy but no change in cognitive testing.
- RiVM, with predominant colonic action, may have an important gut-brain axis and gut-muscle modulatory impact in cirrhosis and MHE.

Prevention of Bleeding Events After Endoscopic Variceal Ligation with Proton Pump Inhibitors: Benefit or Risk?

Ricardo Albarran-Anguiano[1]; Themistoklis Kourkoumpetis[1,2]; Shivang S. Mehta[1,2]; Saleh Elwir[2]; Apurva A. Modi[1,2]; James F. Trotter[2]; Stevan A. Gonzalez[1,2]

[1]Burnett School of Medicine at TCU, Internal Medicine; [2]Baylor Simmons Transplant Institute, Baylor Scott & White All Saints Medical Center Fort Worth and Baylor University Medical Center Dallas

Background

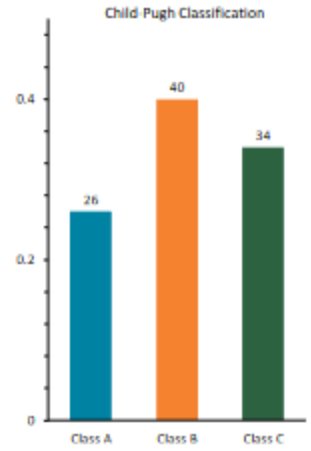
- Esophageal varices
  - Present in up to 50% of compensated & 85% in decompensated cirrhosis
  - Indicate clinically significant portal HTN
- Esophageal variceal hemorrhage (EVH) conveys up to 20% mortality within 30 days of the first bleeding episode
  - Rebleeding risk is 60% if untreated
- Proton pump inhibitors (PPI) may decrease post-banding ulcer size
  - However, impact on post-EVL bleeding risk is not well defined
- Current AASLD guidelines do not provide specific guidance on use of PPI therapy for EVL

Methods

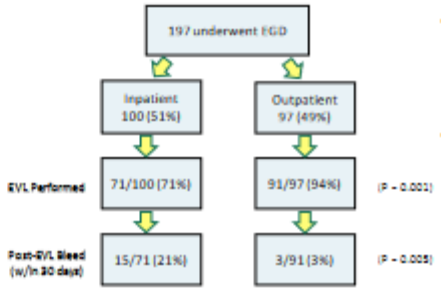
- Retrospective cohort study, January 2021 to October 2022
- Single-center, large tertiary care hepatology practice affiliated with liver transplant program
- Inclusion criteria:
  - Consecutive patients who underwent esophagogastroduodenoscopy (EGD)
  - Diagnosed with cirrhosis and esophageal varices
- Exclusion criteria:
  - Portal hypertension or varices from non-cirrhotic causes

Patient Characteristics

Demographic/Clinical (n=197)	
Age	58 (30-85)
Gender	
Male	58%
Female	42%
Race/Ethnicity	
White	63%
Hispanic	31%
Other	6%
Primary Diagnosis	
Alcohol-related liver disease	40%
NAFLD/cryptogenic	29%
Hepatitis C	21%
Other	10%
Ascites	65%
Encephalopathy	46%
MELD-Na	14 (6-40)
Platelets	
<50	15%
<75	39%
INR	1.4 (0.9-7.8)



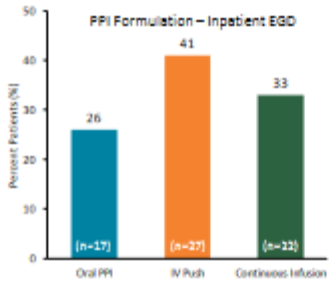
Post-EVL Bleeding Episodes



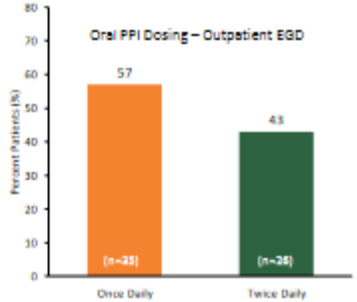
- 18/162 (11%) post-EVL bleeding within 30 days
- At f/u EGD #2:
  - Post-banding ulcers in 11/18 (61%)
  - Active bleeding in 9/18 (50%)

Hospitalized Patients vs Outpatient EVL

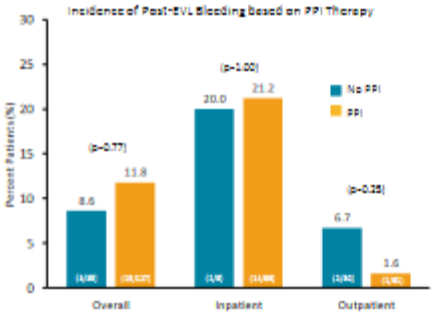
- **Hospitalized patients** more frequently had non-variceal sources of bleeding (20% vs. 5%, p=0.002)
- 88/100 (88%) underwent EGD for acute bleeding
- EGD + EVL: 66/71 (93%) received PPI therapy



- **Outpatients** received PPI therapy in 61/91 (67%)
  - Less frequent compared with hospitalized patients (p<0.001)
- 2/67 (3%) received at least 7 days PPI
- 41/61 (67%) received at least 14 days PPI



Impact of PPI Therapy



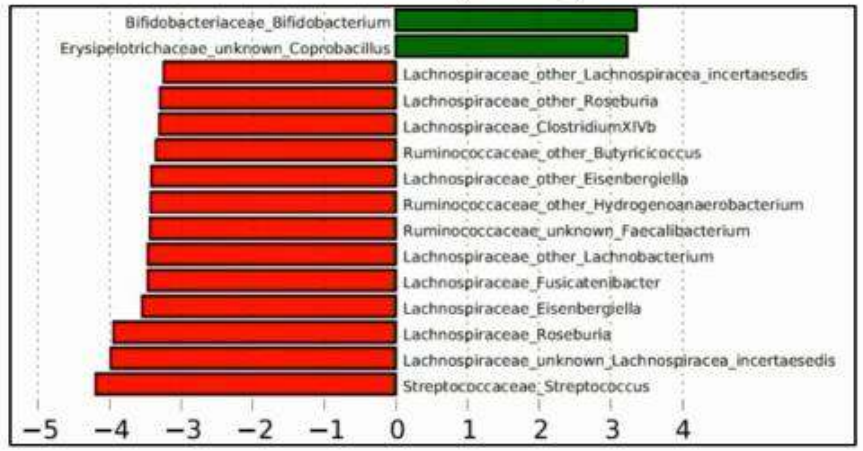
Conclusions

- PPI therapy at the time of EVL may not decrease the risk of post-EVL bleeding
  - Regardless of hospitalization status or PPI formulation, dose, or duration
- Risk-benefit of PPI use should be assessed prior to decision on initiating therapy
- Benefit in hospitalized patients will require further study

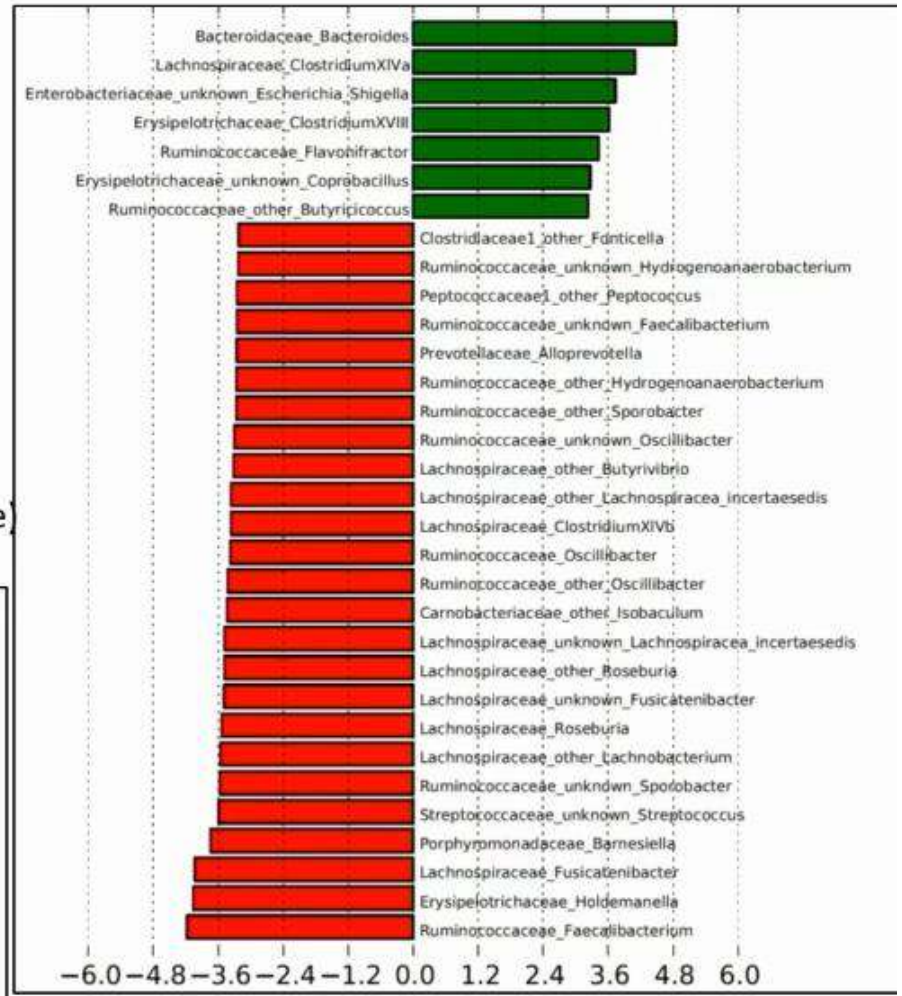

TD GARDEN

Stool Microbiota Comparisons between RiVM baseline versus end and RiVM Versus Placebo End.

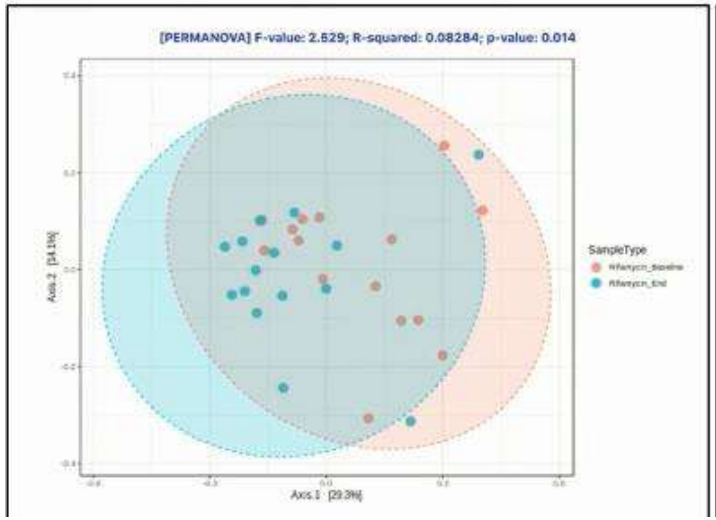
A. LEfSe results Rifamycin Baseline (Red) versus End (Green)



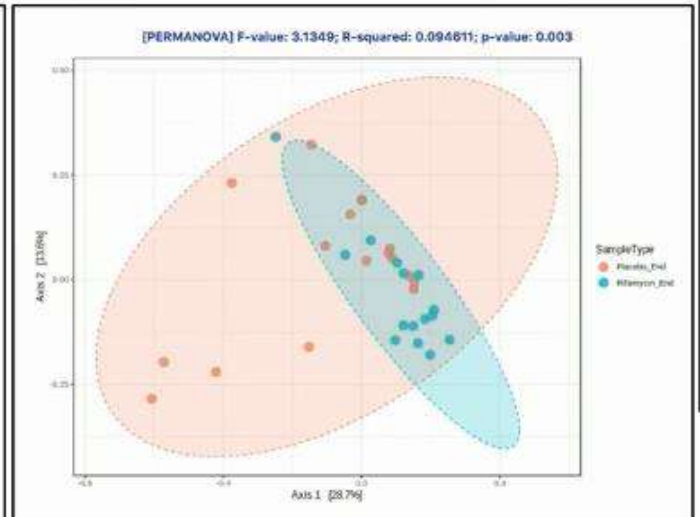
B. LEfSe results Placebo End (Red) versus Rifaximin End (Green)



C. Rifamycin Baseline (Pink) vs End (Blue)
PERMANOVA F-value 2.529, p=0.014)



D. Placebo End (Pink) vs Rifamycin End (Blue)
PERMANOVA F-value 3.349, p=0.003)



Stool Bile Acids

Red decreased Blue increased	Rifamycin SV MMX (n=15)		Placebo (n=15)	
	Baseline	**Drug-end**	**Baseline**	**Drug-end**
Serum C4 (nmol/L)	83.7±50.2	70.7±65.5	65.8±46.6	107.9±96.7
Stool BA profile (nmol/g)				
DCA	7717±7909	6557±9371	6440±4795	6933±6743
GDCA	**21.5±20.8**	**7.8±20.4***	21.5±39.3	66.8±54.5
TDCA	**64.4±222.0**	**4.9±9.9***	12.4±28.9	34.0±36.4
HDCA	3.3±6.8	12.4±36.2	2.0±4.0	4.1±13.5
7Keto DCA	**74.1±89.2**	**405±429*‡**	107±240	64±213
IsoDCA	**338±276**	**227±249***	316±241	377±304
LCA	**3323±2342**	**2172±2200***	3615±14593	3725±2595
GLCA	**5.7±3.2**	**3.6±2.4***	4.2±1.8	4.1±2.5
TLCA	5.3±18.2	1.9±5.6	0.9±2.7	0.31±0.9
IsoLCA	**951±1008**	**430±526***	933±493	1061±937
7Keto LCA	**88.8±92.9**	**433.0±728.1***	121.0±216.0	49.3±87.8
12Keto LCA	2408±3387	1997±2082	2991±2368	2895±1980
UDCA	**175.0±314.2**	**690.0±1082.0*‡**	156.2±179.0	71.0±142.3
GUDCA	19.0±48.4	3.5±9.9	7.4±14.1	3.5±8.9
TUDCA	**1.1±2.8**	**1.8±0.58‡**	1.1±4.5	0.0±0.0
Hyocholic acid	**5.2±13.7**	**58.9±113*‡**	4.3±12.1	0.0±0.0
HDCA	3.3±6.8	12.4±36.2	2.0±4.0	4.1±13.5

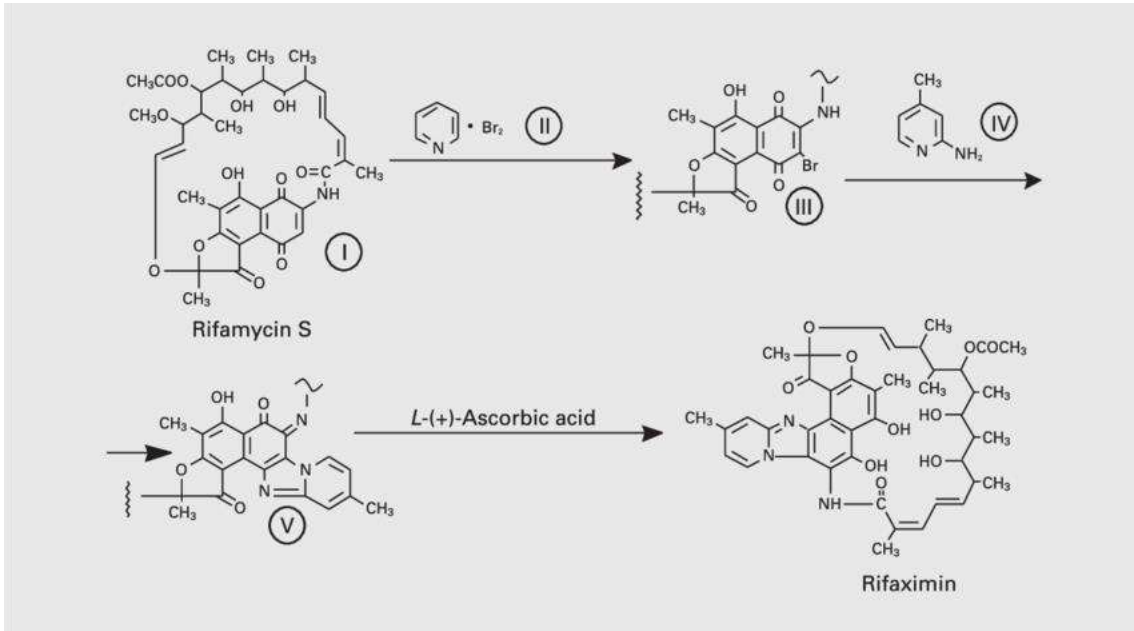
Stool Short Chain Fatty Acids

Blue increased	Rifamycin SV MMX (n=15)		Placebo (n=15)	
	Baseline	Drug-end	Baseline	Drug-end
Stool SCFA (ng/g)				
Acetate	**597757±332701**	**833786±430656***	851712±487717	841161±306433
Propionate	**322710±148804**	**398580±187176***	380264±144946	403190±156648
Butyrate	**243417±113507**	**330814±194092***	445887±375342	396597±244928
Isobutyrate	**221313±128638**	**298040±154782***	295937±149022	327493±136848
Valerate	**118052±67957**	**1455993±72215***	161802±126082	168123±98864
Hexanoate	18224±23822	16502±15901	49406±99621	43690±50161
Isovalerate	**164860±94499**	**220997±115984***	224782±113130	232616±120753
2 methylbutyrate	151752±107292	176981±115483	202002±123302	232573±137624
Isocaproate	1859±1830	2977±3320	3035±4180	5228±11590

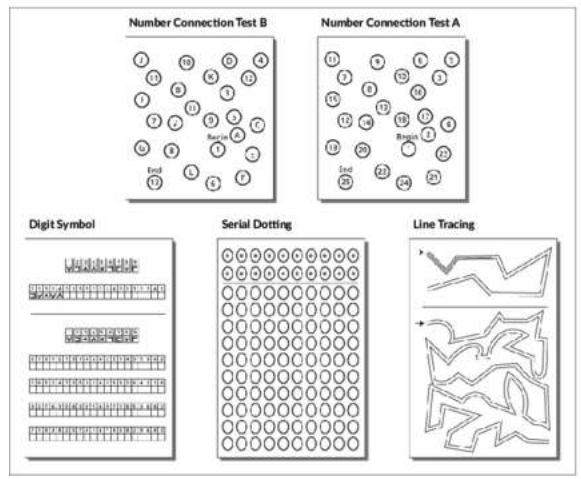
In the subset that underwent brain MRS pre/post Rx, Glutathione increased post-rifaximin and reduced after placebo

Weighted mean±SEM	Glu+Gln	NAA+NAAG	GPC+PCh	Ins	GSH
placebo-baseline (n=11)	1.764±0.01	1.201±0.00	0.195±0.00	0.801±0.00	0.284±0.00
placebo-study end (n=11)	1.744±0.01	1.178±0.00	0.188±0.00	0.789±0.00	0.277±0.00
Rifamycin-baseline (n=5)	1.919±0.02	1.208±0.01	0.195±0.00	0.725±0.01	0.307±0.01
Rifamycin-study end (n=5)	1.976±0.02	1.169±0.01	0.198±0.00	0.754±0.01	0.321±0.01
Conc. Ratios (/Cr) T-TEST p-values					
placebo (within group p value)	0.277	0.144	0.219	0.185	**0.000**
Rifamycin (within group p value)	0.306	0.112	0.445	0.086	**0.016**

Glu+Gln: glutamate+glutamine, NAA+NAAG: N-acetyl aspartate+N-acetyl-aspartyl-glutamate, GPC: glycerophosphocholine and phosphocholine, Ins: inositol, GSH: glutathione


Rifamycin S
L-(+)-Ascorbic acid
Rifaximin

Psychometric Hepatic Encephalopathy Score



Test	Description
Number connection test A (NCT-A)	Randomly dispersed numbers are to be connected with each other in serial order as quickly as possible.
Number connection test A (NCT-B)	Randomly dispersed numbers and letters are to be connected in alternating series (1-A-2-B...) as quickly as possible.
Digit-symbol	Digits from 1 to 9 are assigned respective symbols. Under each digit the corresponding symbol is to be written within a given time.
Serial dotting	Draw a dot inside each circle as quickly as possible.
Line tracing	A given line is to be traced as quickly as possible.