

A scites to Z

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Disclosures

- ◆ **Consultant: Mallinckrodt, PharmaIN, Biovie, Sequana, Novo Nordisk, Astra Zeneca, Kezar, Amgen**
- ◆ **I will be discussing off-label uses of the following medications:**
 - Albumin
 - Rifaximin
 - Carvedilol/Propranolol
 - Terlipressin
 - Ciprofloxacin

Ascites **to** **Z**

A – At Risk

D – Diagnosis (paracentesis)

E – Eating (Salt restriction)

F – Furosemide (medications)

R – Recurrent/Refractory Ascites

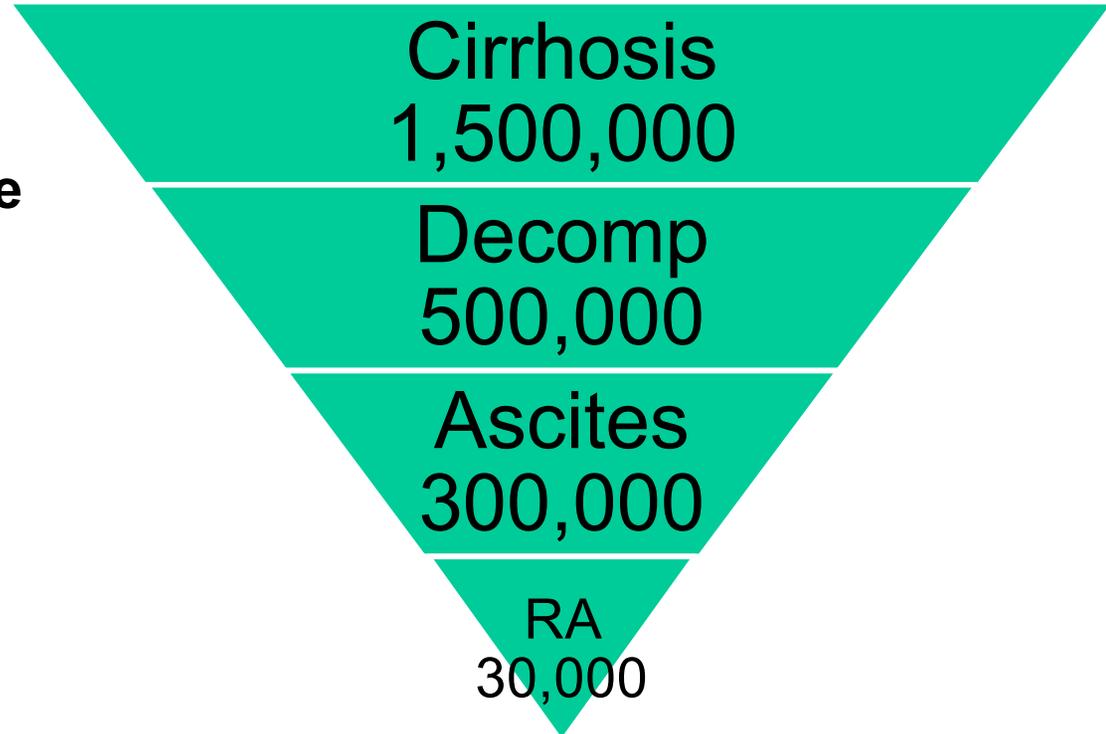
S – Spontaneous Bacterial Peritonitis (SBP)

T – Thoracentesis (Hepatic Hydrothorax)

Z – ‘Ze Hepatorenal Syndrome

How many Americans have Ascites?

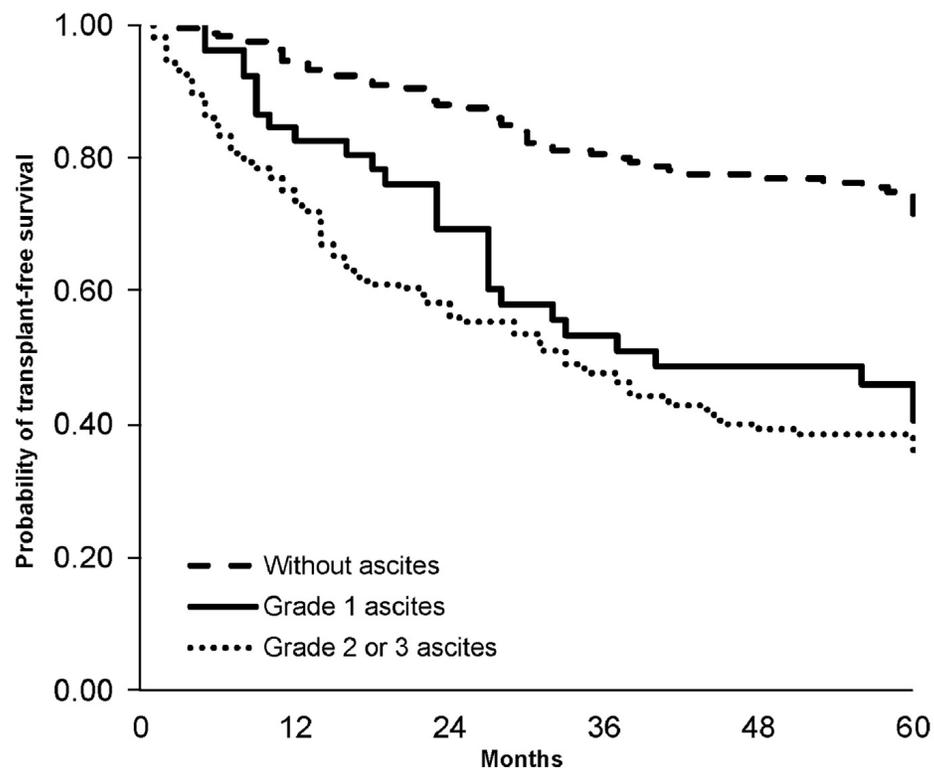
- ◆ **Cirrhosis Prevalence – 270**
– 1058 per 100,000 people
- ◆ **Estimate 900k – 3.4M; My guess is 1.5M and rising**
- ◆ **25 – 40% with cirrhosis are decompensated (500k)**
- ◆ **Ascites is present in 20% patients with cirrhosis; 67% with decompensated cirrhosis (300k)**
- ◆ **Recurrent/Refractory ascites in ~10% (30k)**



AM Moon, AG Singal, EB Tapper, CGH 2020.
E Orman et al JAMA Network Open, 2019
DP Ladner et al Plos One, 2024

Ascites - Outcomes and Mortality

- ◆ Ascites of any grade foreshadows poor outcome



No at risk	0	12	24	36	48	60
Without ascites	259	224	178	139	123	110
Grade 1 ascites	54	45	32	24	20	17
Grade 2 ascites	234	145	98	65	53	47

M Tonon et al CGH, 2021.

Ascites A to Z

A – At Risk

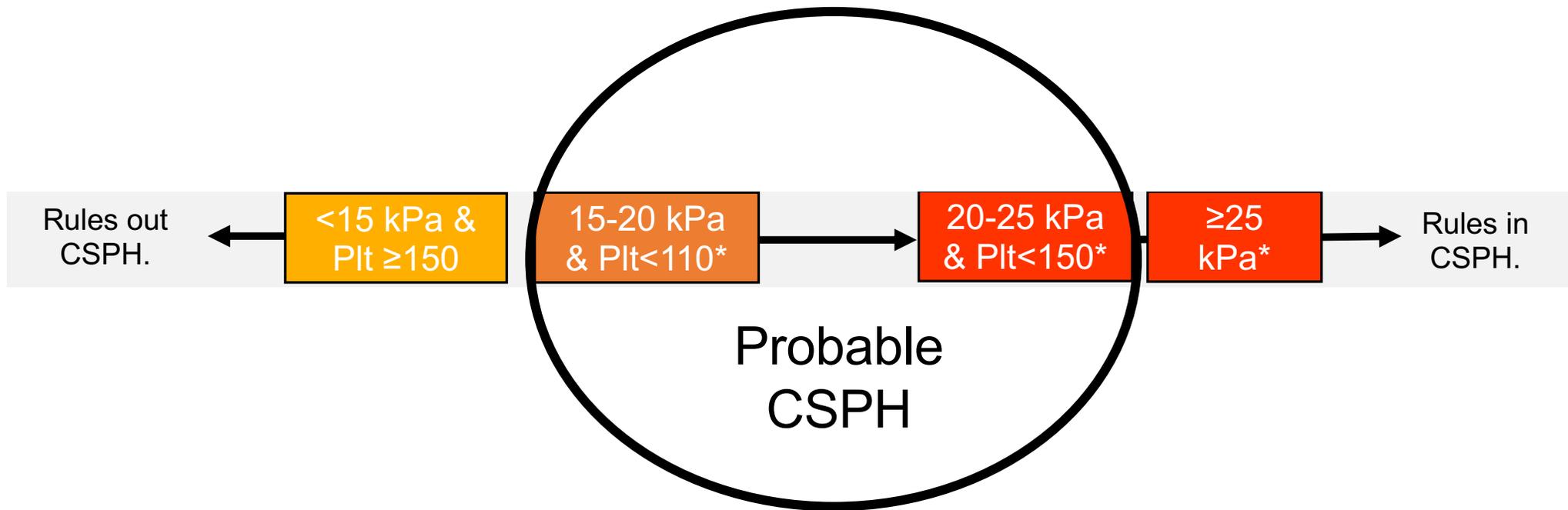


Prevention of Ascites Development

◆ At risk

Patients with Clinically Significant Portal Hypertension (CSPH)

◆ CSPH – HVPG ≥ 10 mm Hg



Prevention of Ascites Development

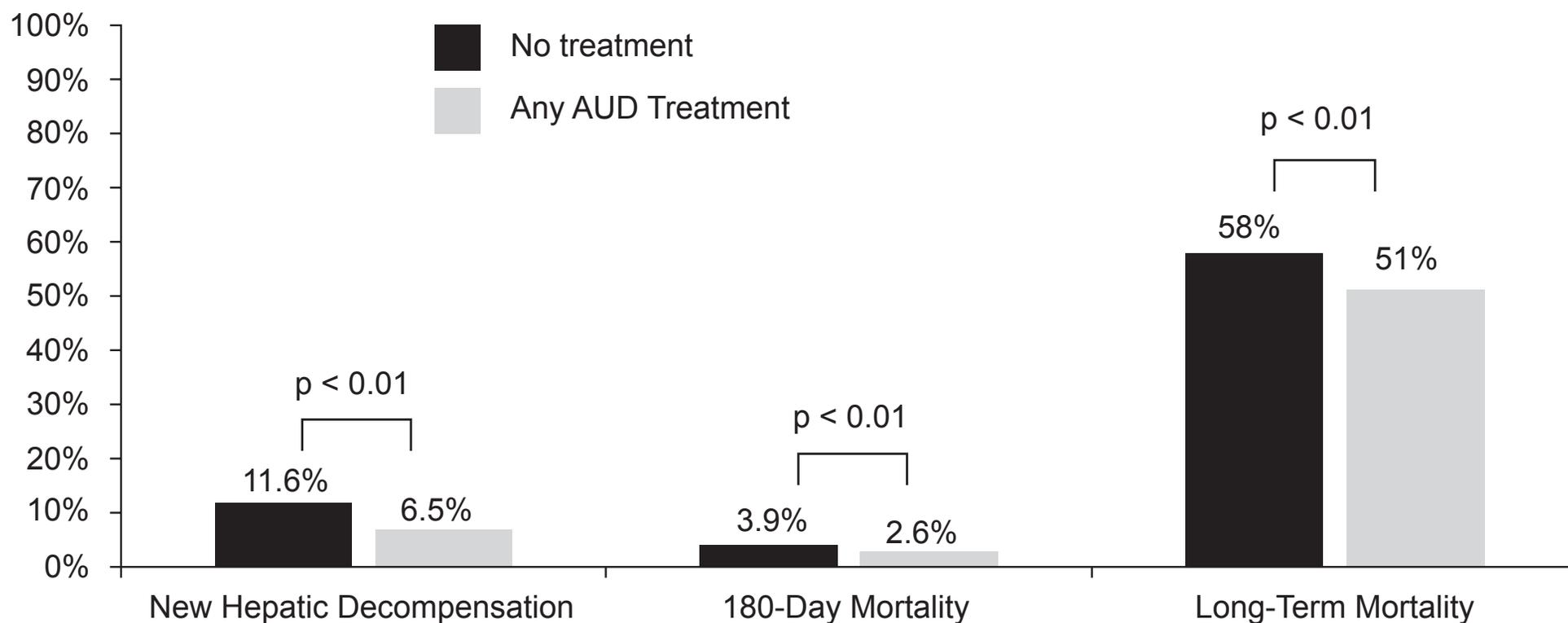
Treat the underlying liver disease

Sofosbuvir

Tenofovir

Ursodiol

Naltrexone

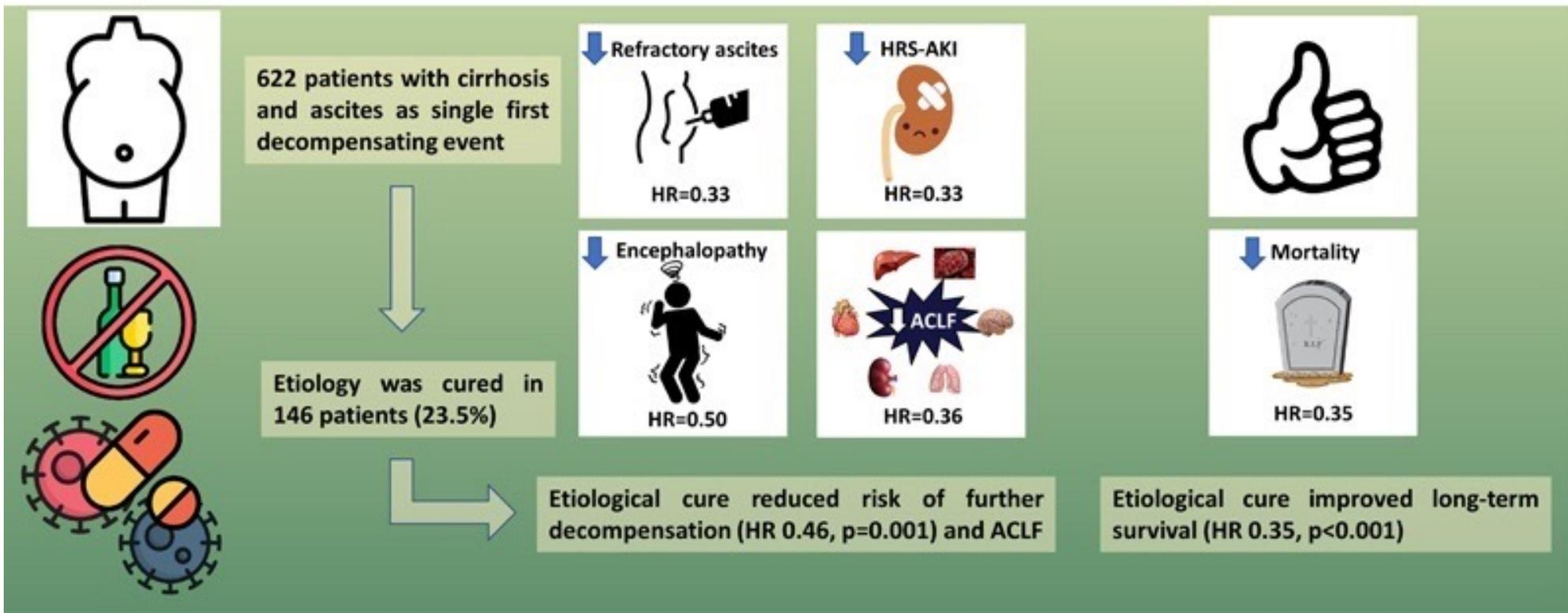


S Lens et al Journal of Hepatology, 2020 (HCV)
P Marcellin et al Lancet, 2013 (HBV)

S Rogal et al Hepatology, 2020 (ALD)
BV John et al AJG, 2021 (PBC)

Prevention of Ascites Development

Etiological cure prevents further decompensation and mortality in cirrhotic patients with ascites as the single first decompensating event



Tonon M, Balcar L, et al. *Hepatology*.

HEPATOLOGY

NSBB prevent Ascites in CSPH

- ◆ PREDESCI study – PREvent DEcompensation in Cirrhosis
- ◆ Compensated cirrhosis with CSPH without high-risk varices
- ◆ NSBB (propranolol/carvedilol) vs placebo, 1:1
- ◆ Eight centers in Spain, 2010 – 2013
- ◆ 1° endpoint: Composite of death/hepatic decompensation
- ◆ Followed for up to 5 years
- ◆ BOPPP study in UK to follow (740 pts, 36 months)

	Placebo group (n=101)	β-blockers group (n=100)	Risk (95% CI)*	p value†
Decompensation or death				
Overall‡	27 (27%)	16 (16%)	0.51 (0.26–0.97)	0.0412
Secondary outcomes				
Ascites	20 (20%)	9 (9%)	0.42 (0.19–0.92)	0.030

Villaneuva C, et al. Lancet 2019

Ascites A to Z

D – Diagnosis (paracentesis)

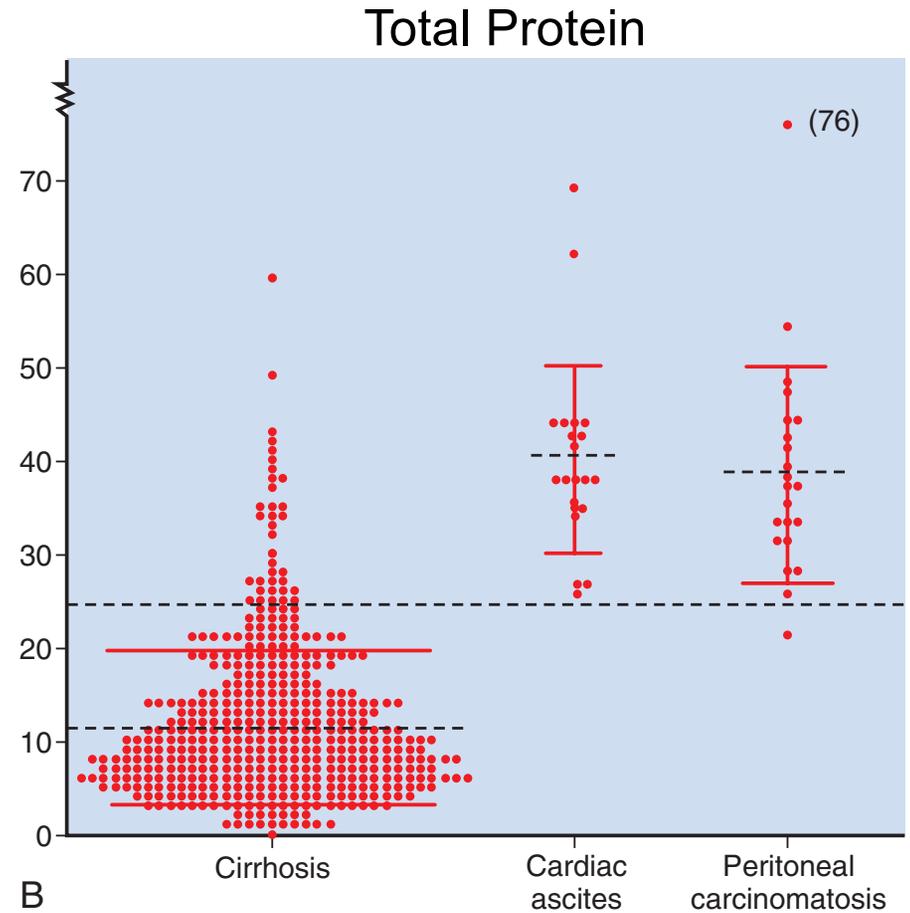
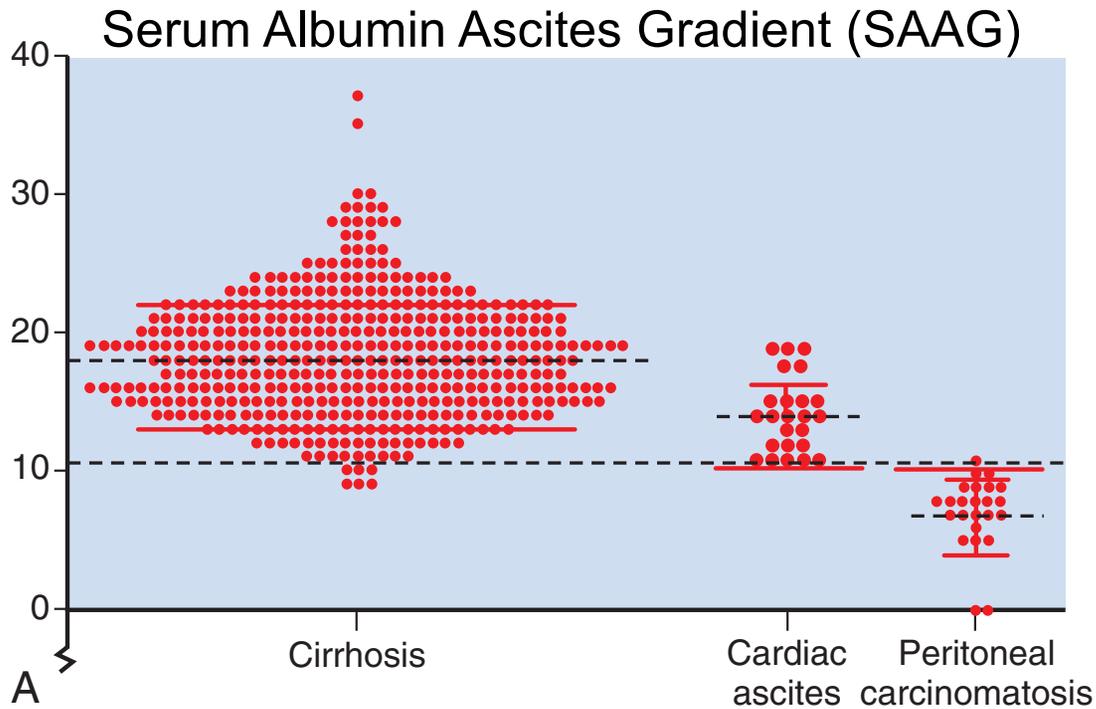
E – Eating (Salt restriction)

F – Furosemide (medications)



Diagnosis

- ◆ Cirrhosis causes >75% of ascites
- ◆ “High SAAG, Low Protein”



G Garcia-Tsao in Zakim & Boyer, 7th ed, 2018
WG Rector & TB Reynolds, AJM, 1984

B Runyon et al, Annals of Internal Medicine, 1992

Low-Salt Diet

- ◆ What does this mean?
- ◆ Does it work?
- ◆ What are the consequences?



Low-Salt Diet

◆ What does this mean?

- Na 2000mg or 90mmol per day



~600mg Na



~1500mg Na

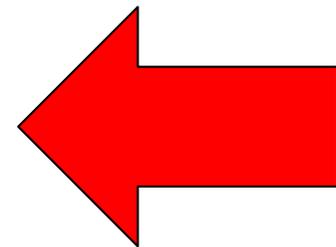
Parameter	Sodium in foods (mmol/day)
Group A ($n = 37$)	58.9 ± 3.3
Group B ($n = 83$)	103.3 ± 5.3*
Subgroup B1 ($n = 54$)	106.6 ± 6.9†
Subgroup B2 ($n = 29$)	97.0 ± 7.7

Low-Salt Diet

◆ Does it work?

Table 3 *Clinical and biochemical data on 14th day of treatment*

	<i>Salt restricted diet</i>	<i>Unrestricted diet</i>	
Patients under treatment	74	61	
Ascites			
Complete disappearance (%)	42	23	NS
Partial disappearance (%)	57	60.6	NS
No disappearance (%)	1	16.4	p<0.01
Loss of weight (kg)	8±4.3	5.4±4	p<0.001
Decrease in abdominal girth (cm)	9.9±6	5.8±4	p<0.001
Appetite			
Equal or less (%)	63.5	82	
Improve (%)	36.5	18	p<0.02
% of patients taking maximum spironolactone dose	12	26	p<0.04
Blood urea (mmol/l)	4.7±2.2	5.3±5.7	NS
Difference 14th day – 1st day	*1±1.8	*0.7±1.6	NS
Serum sodium (mmol/l)	132±4	133±4	NS
Difference 14th day – 1st day	†4±4.3	†2.4±3.6	S (p=0.025)
Serum potassium (mmol/l)	4.5±0.5	4.3±0.4	NS
Difference 14th day – 1st day	*0.6±0.6	*0.5±0.5	NS
Urine volume (ml/24 h)	*699±674	*521±654	NS
Urine sodium (mmol/24 h)	84.7±117.5	99±129.4	NS
Urine potassium (mmol/24 h)	*29.4±44.9	*17.6±50.5	NS

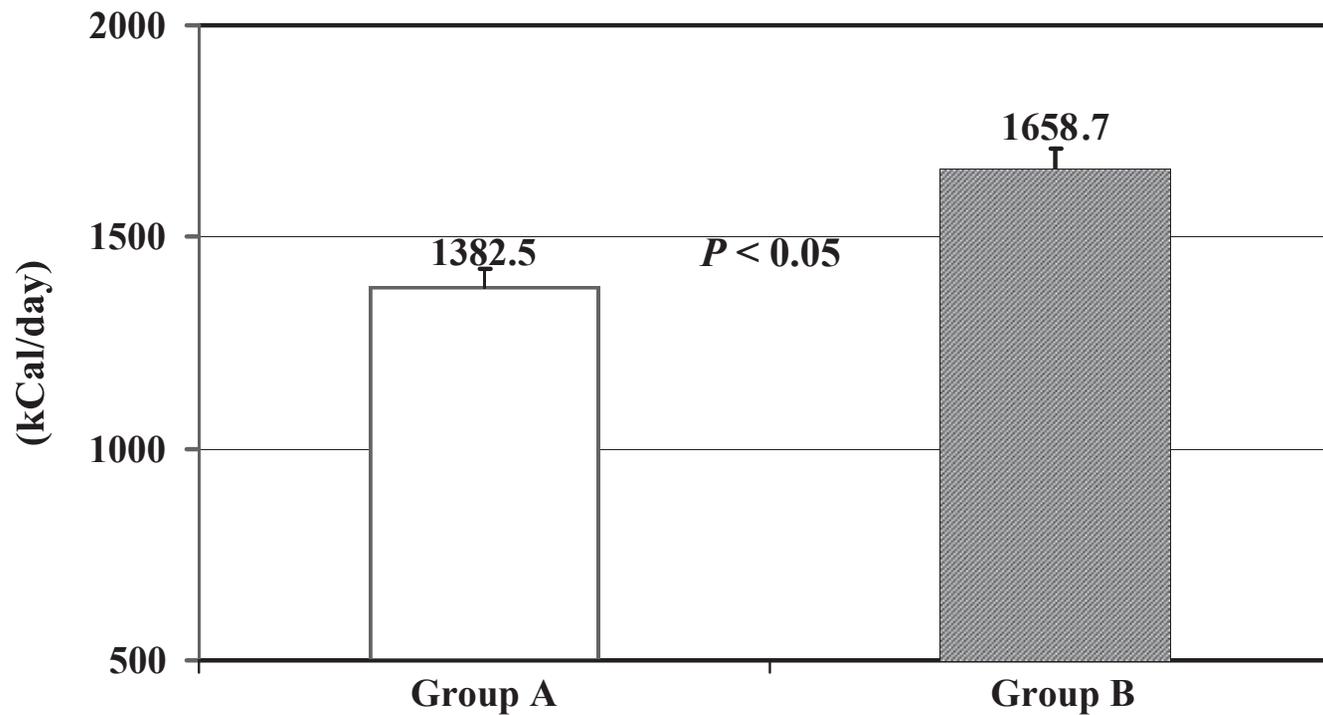


* representing an increase.
 † a decrease from the initial value.

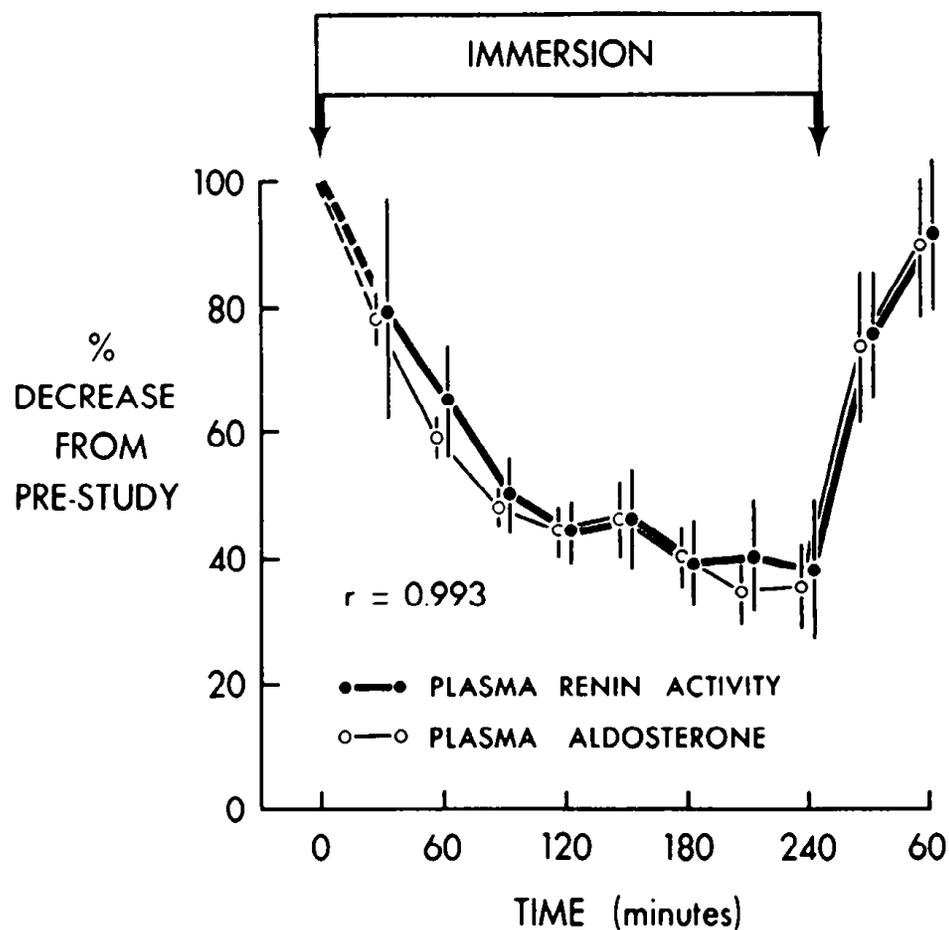
A Gauthier et al Gut, 1986

Low-Salt Diet

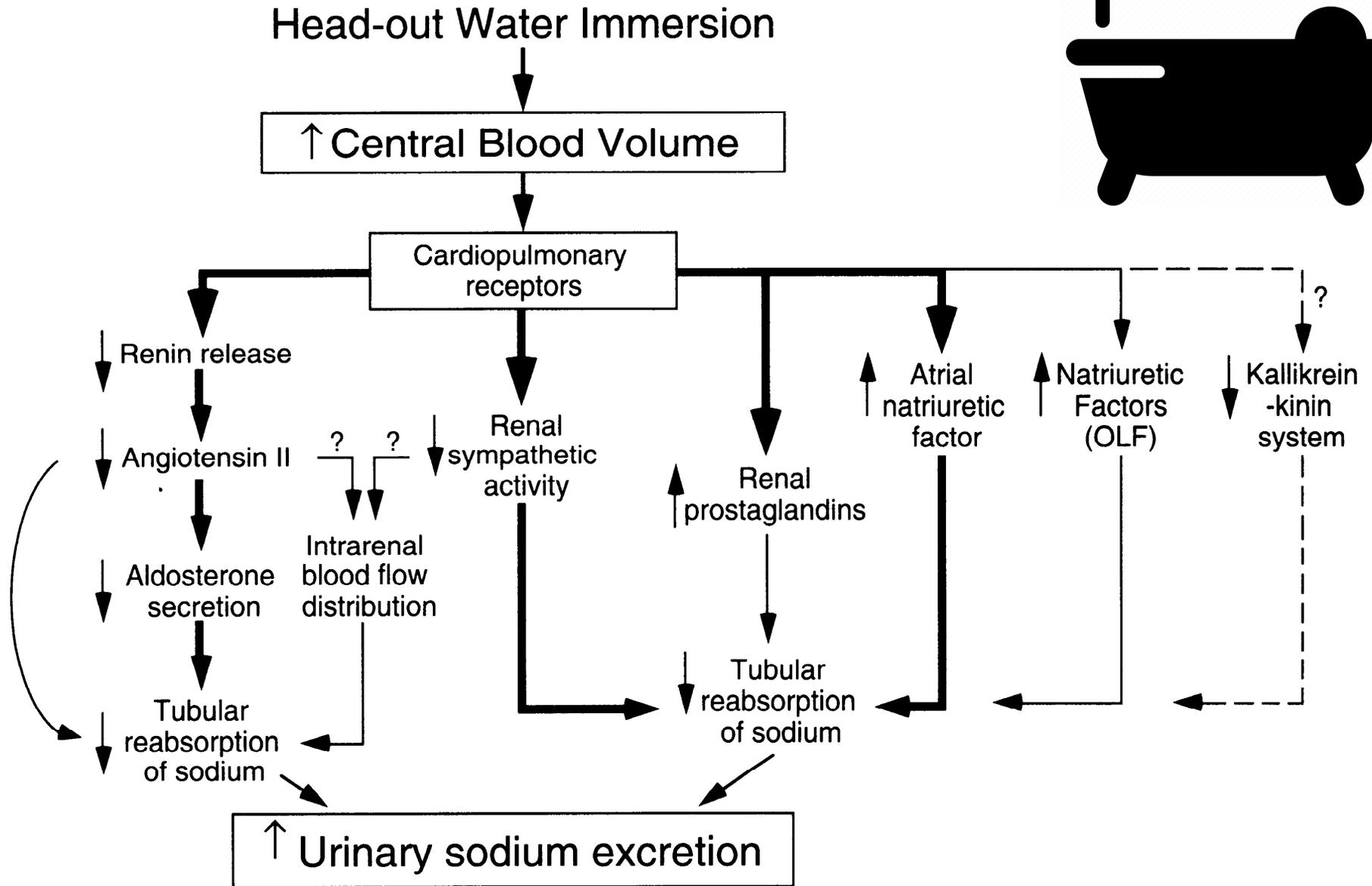
◆ What are the consequences?



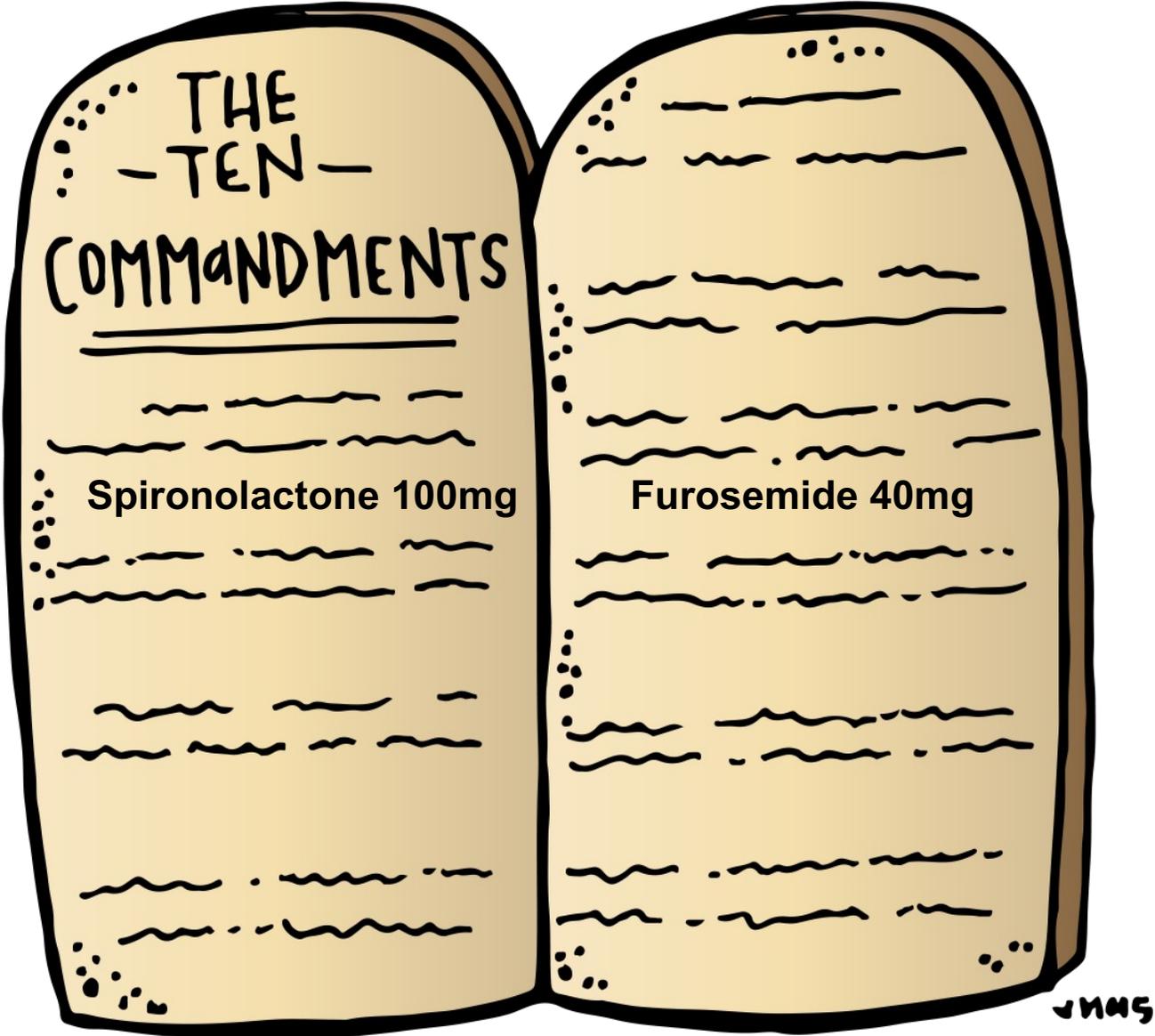
Head-out water immersion (HWI)



Head-out water immersion (HWI)



Diuretics



Diuretics

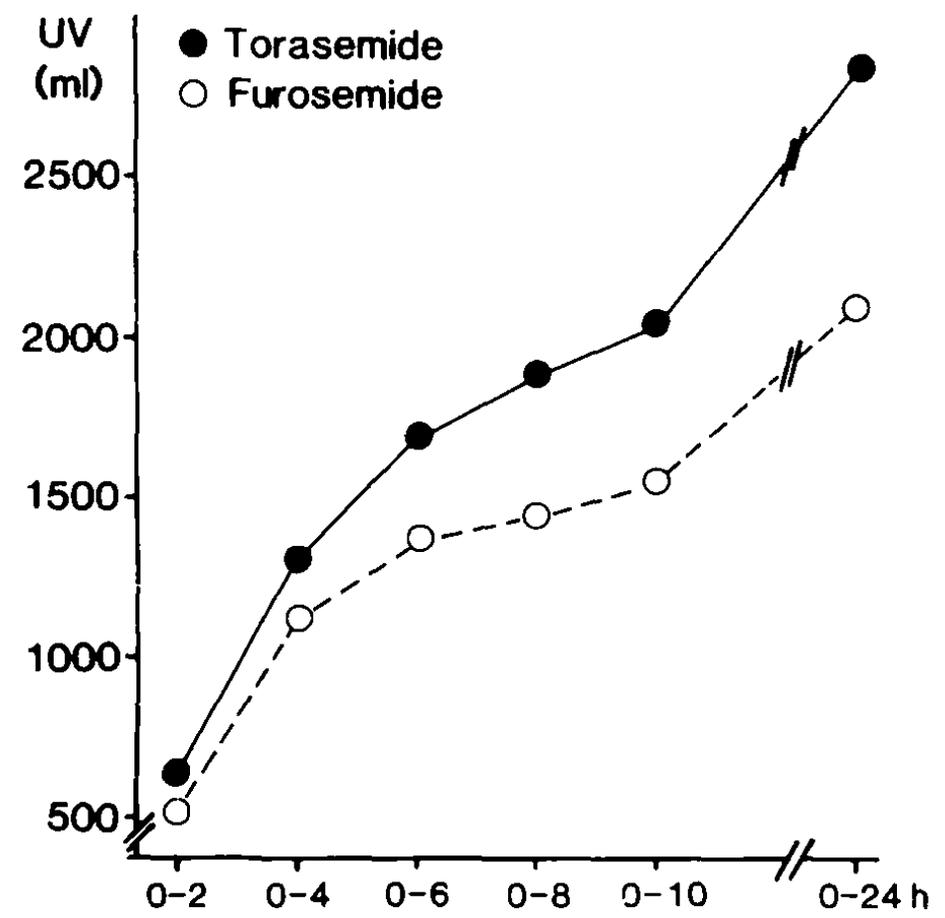
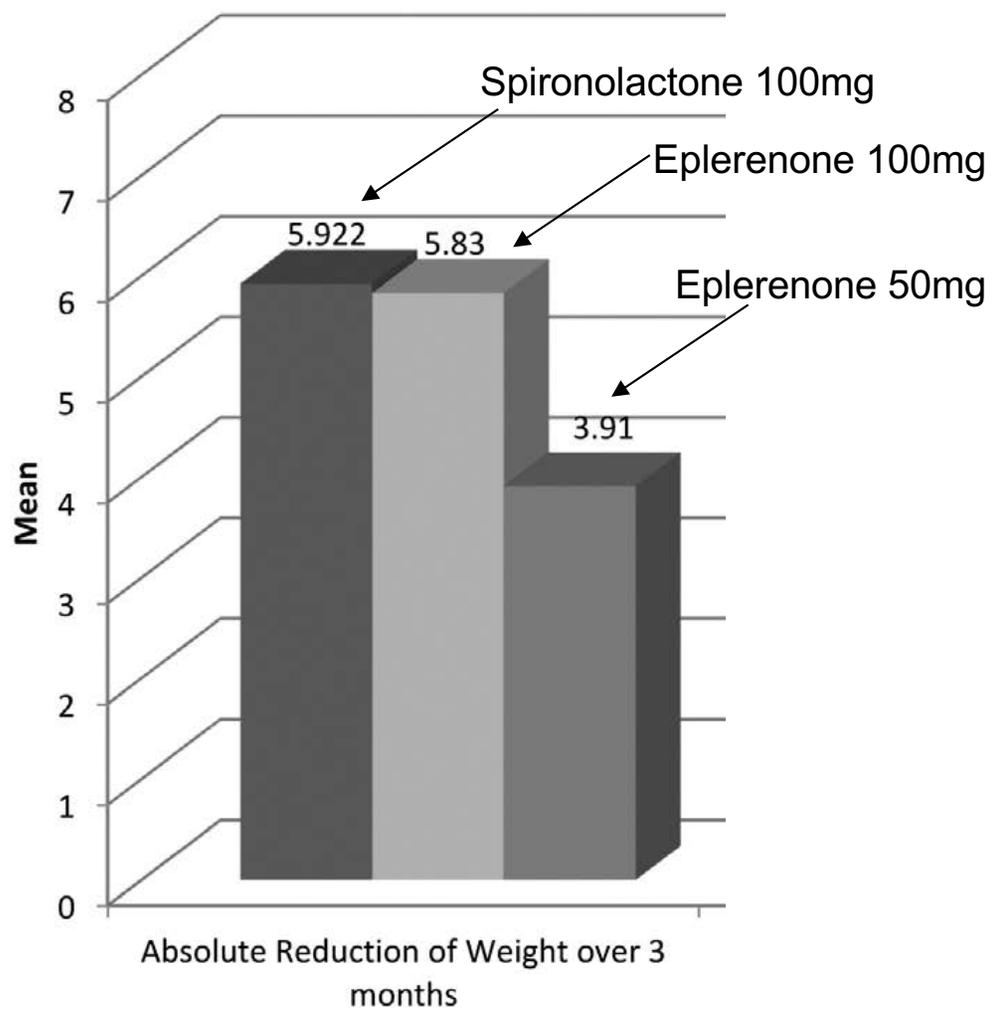
- ◆ For mild to moderate ascites, can use spironolactone alone
- ◆ Single center study in Spain
- ◆ Grade 2 ascites – visible on PE, but LVP not needed
- ◆ 100 patients – 1:1, spiro+furosemide vs spiro alone
- ◆ Increase in diuretic dose every 4 days as needed to achieve Grade 1 ascites

	Group 1: S + F (n = 47)	Group 2: S (n = 47)	P value
Loss of body weight (kg)	7.5 (2–17)	6.6 (2–15)	NS
Time to obtain of response (days)	9.8 (4–35)	10.3 (4–32)	NS
Response or Mobilization of ascites (n/%)	46/98	44/94	NS
Side effects (n/%)	3/7.7	6 ^b /13.2	NS
Need to reduce the diuretic dosage (n/%)	32/68	16/34	0.002
Spironolactone (mg)			
Cumulative dose	1934 (400–7700)	2445 (400–7800)	NS
Dose/day	148 (83–233)	170 (100–325)	0.037
Dose/liter of ascites	311 (125–1405)	407 (118–1300)	NS
Cumulative dose of furosemide (mg)	480 (80–3080)	240 and 640 ^c	-

J Satos et al Journal of Hepatology, 2003.

Diuretics

- ◆ Eplerenone may work as well as spironolactone (1:1)
- ◆ Bumetanide/Torsemide are more potent than furosemide

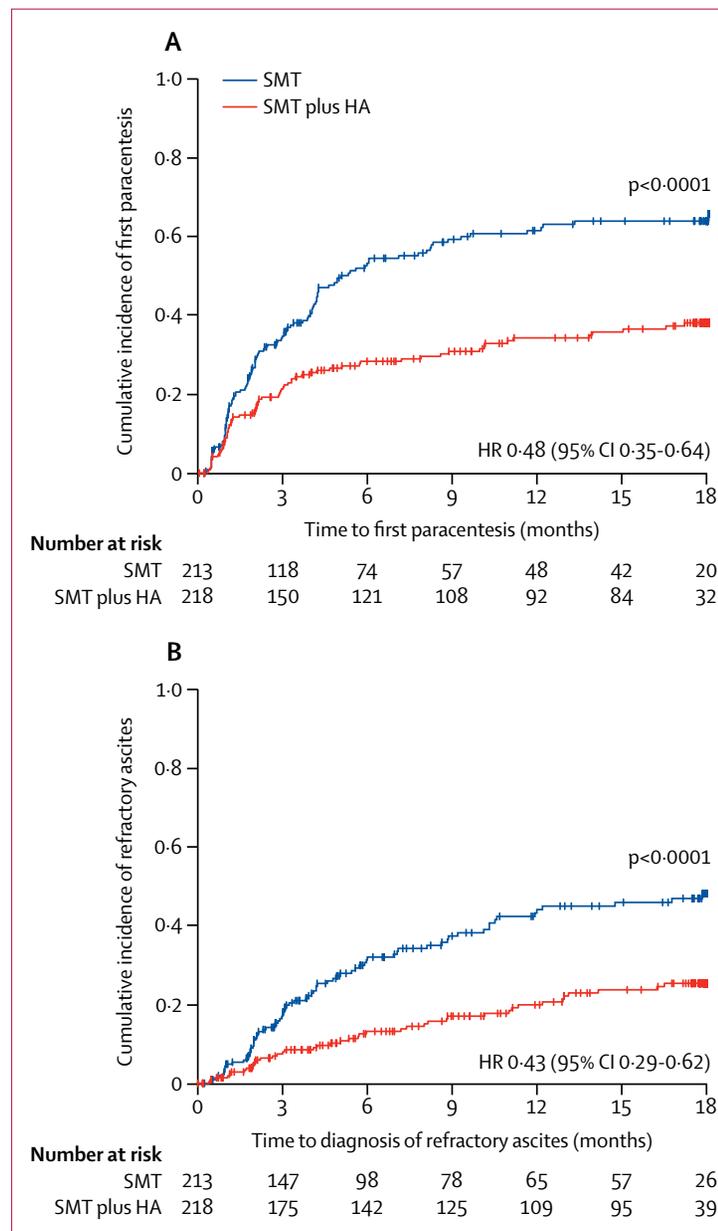
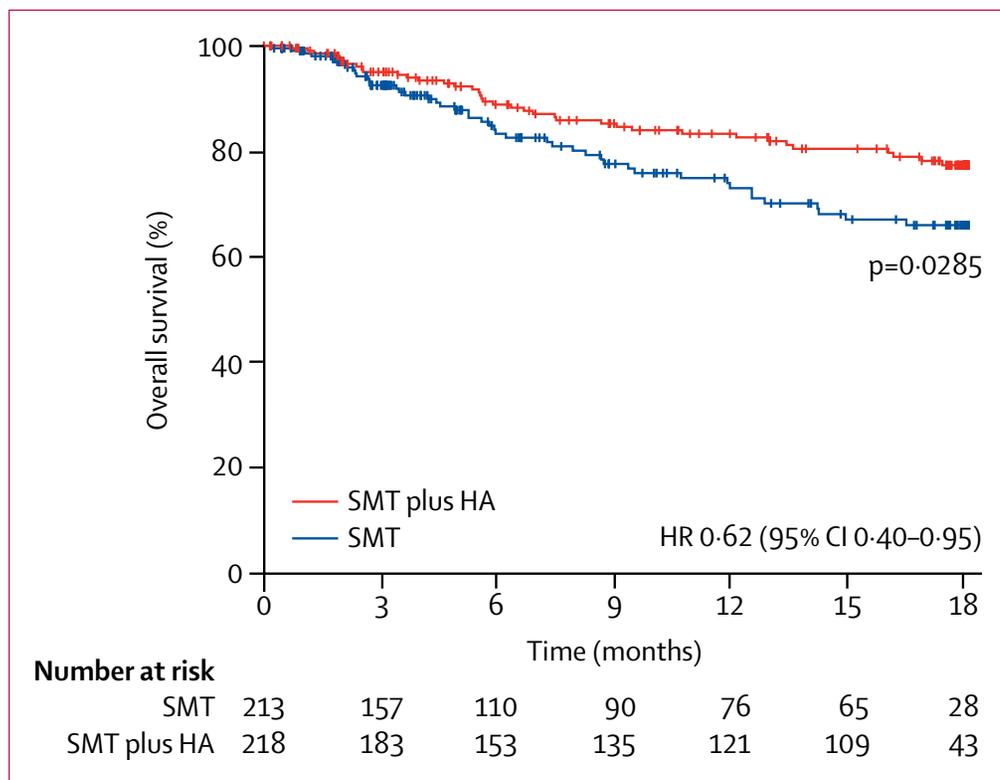


R Seghal et al EJGH, 2020.

AL Gerbes et al Journal of Hepatology, 1993.

Ascites and Long-term Albumin Infusion

- ◆ Randomized trial for patients with diuretic-responsive ascites
- ◆ Standard medical treatment (SMT) vs SMT + regular albumin infusions
- ◆ ANSWER Trial
- ◆ Italy, 33 centers, 18 months



P Caraceni et al 2018.

Ascites A to Z

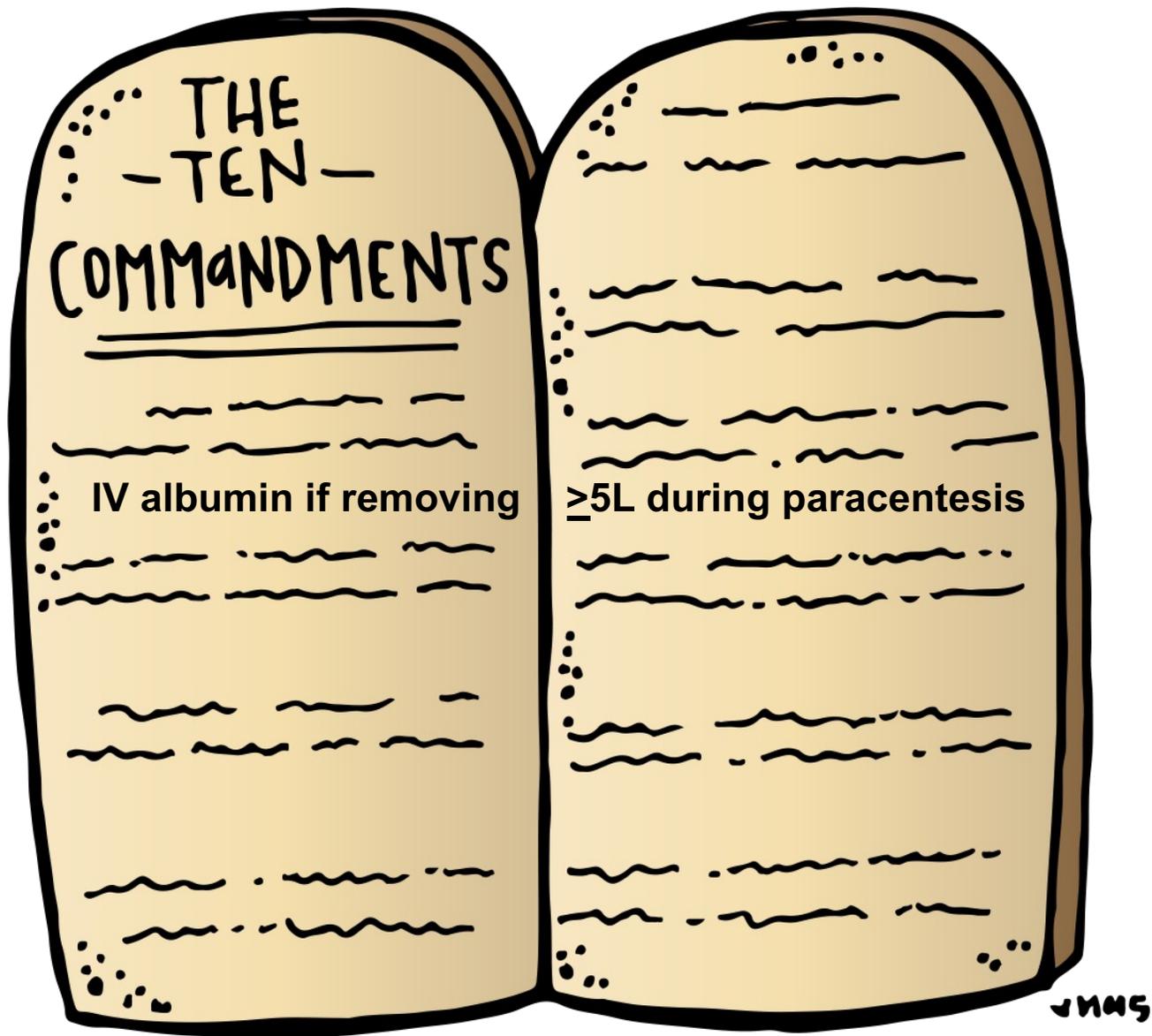
R – Recurrent/Refractory Ascites

S – Spontaneous Bacterial Peritonitis (SBP)

T – Thoracentesis (Hepatic Hydrothorax)



Recurrent Ascites - Paracentesis



Large Volume Ascites

- ◆ **Grade 3 Ascites** – Large ascites that cannot be mobilized OR early recurrence after LVP that is not prevented with diuretics
- ◆ **Recurrent Ascites** – Recurs at least 3x within one year despite Na restriction and diuretics
- ◆ **Refractory Ascites**
 - Diuretic resistant – large ascites persists despite furosemide 160mg and spironolactone 400mg daily (rare)
 - Diuretic intractable – side effects of diuretics (Na, Cr, K, CO₂) preclude the use of maximum doses (common)

Recurrent Ascites - TIPS

Contraindications to Placement of a TIPS

Absolute

- Primary prevention of variceal bleeding
- Congestive heart failure
- Multiple hepatic cysts
- Uncontrolled systemic infection or sepsis
- Unrelieved biliary obstruction
- Severe pulmonary hypertension

Relative

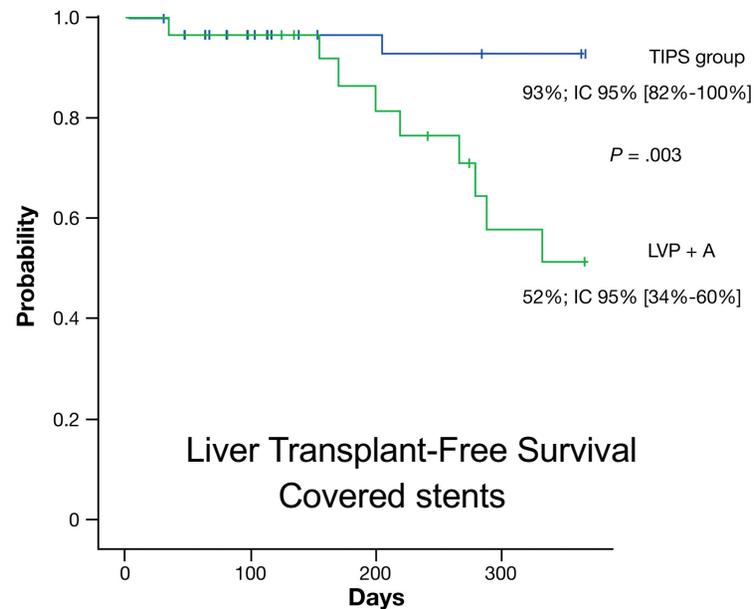
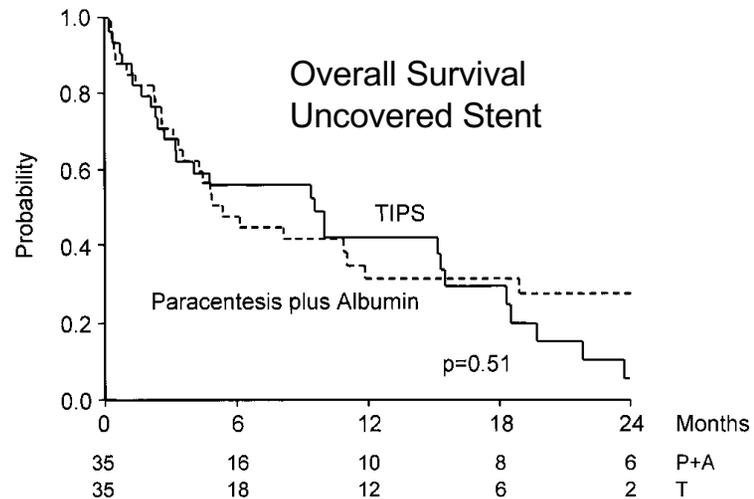
- Hepatoma especially if central
- Obstruction of all hepatic veins
- Portal vein thrombosis
- Severe coagulopathy (INR > 5)
- Thrombocytopenia of < 20,000/cm³
- Moderate pulmonary hypertension

Other relative contraindications:
 Age (>60)
 Overt Hepatic Encephalopathy
 Advanced Kidney Disease
 MELD > 18

C Bureau et al Gastroenterology 2017.

Boyer & Haskal, 2009.

P Gines et al 2002.



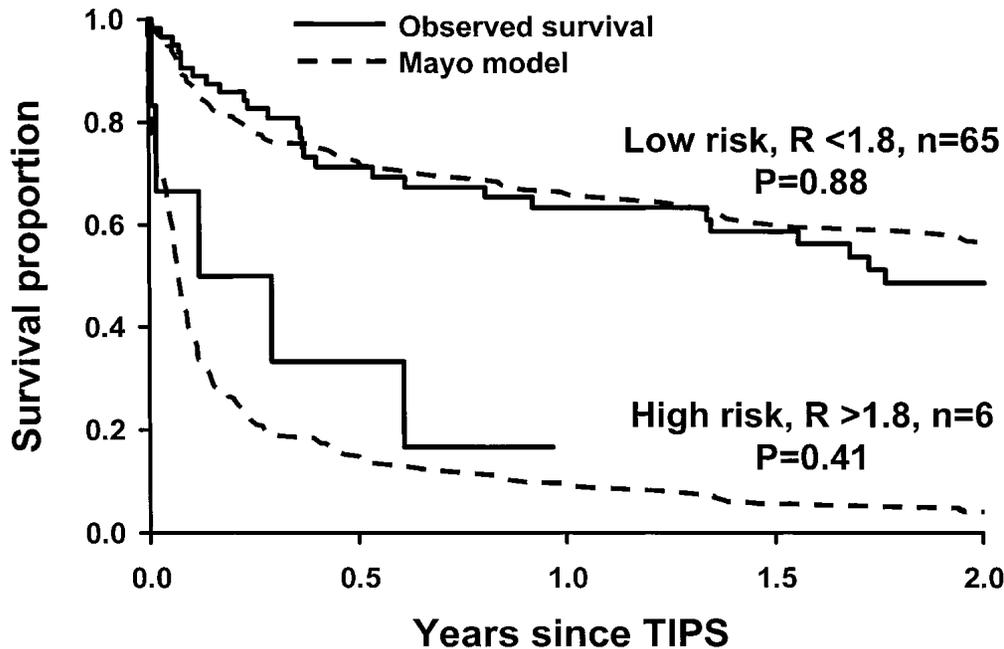
TIPS group	29	27	27	25	24
LVP + A	33	27	16	9	8

TIPS – Candidate selection

Who is safe to undergo TIPS?

Mayo TIPS Model, 1998

Total Bilirubin
Creatinine
Disease
INR

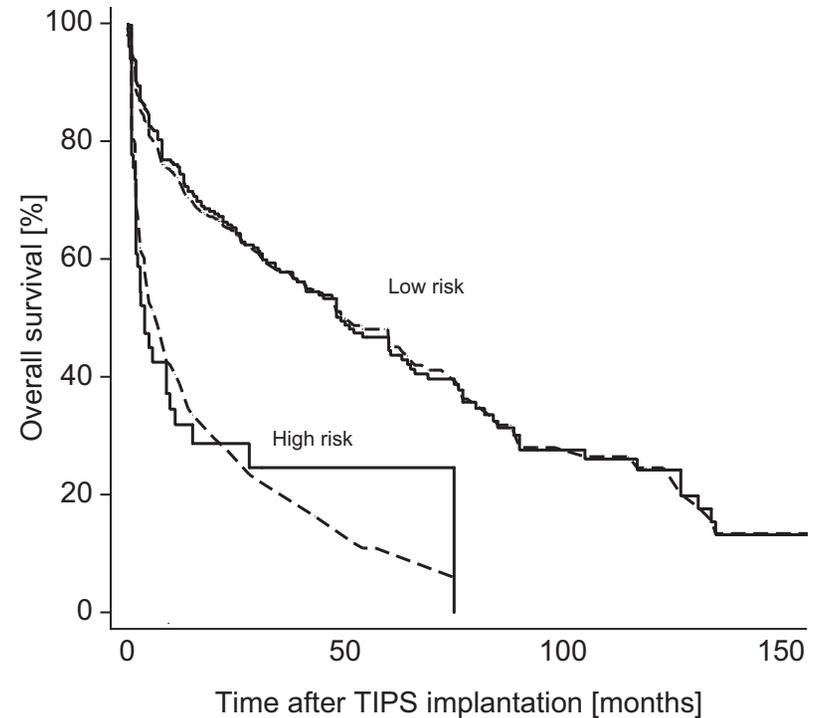


mayo
CP873252B-1

Freiburg Index of Post-TiPS Survival (FIPS), 2021

Total Bilirubin
Creatinine
Albumin
Age

Validation set ($n = 375$)



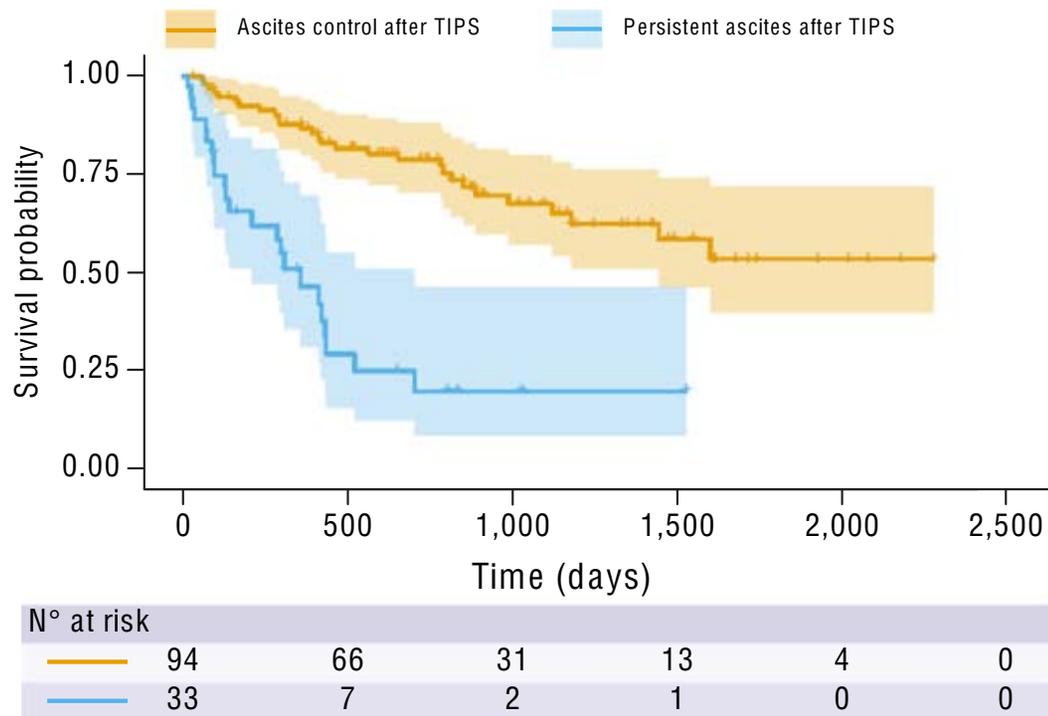
<https://jscalculator.io/calc/Jfucjdw1Y6pN518B>

D Bettinger et al Journal of Hepatology 2021.

M Malinchoc et al Hepatology, 1998

TIPS - Timing

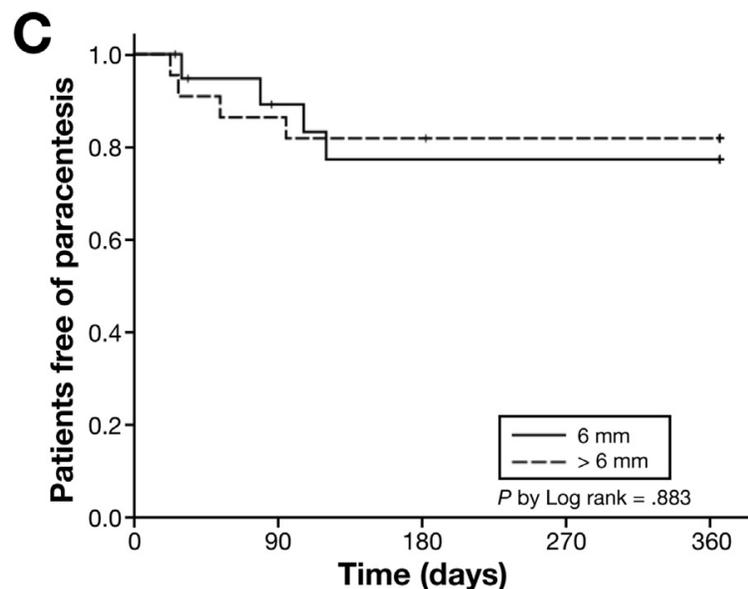
- ◆ Retrospective study of TIPS for Refractory Ascites (n=128)
- ◆ LVP Frequency prior to TIPS predicted post-TIPS ascites
- ◆ Controlled ascites vs persistent ascites: 2.2 vs 3.6 / month prior to TIPS
- ◆ Controlled ascites after TIPS predict post-TIPS survival



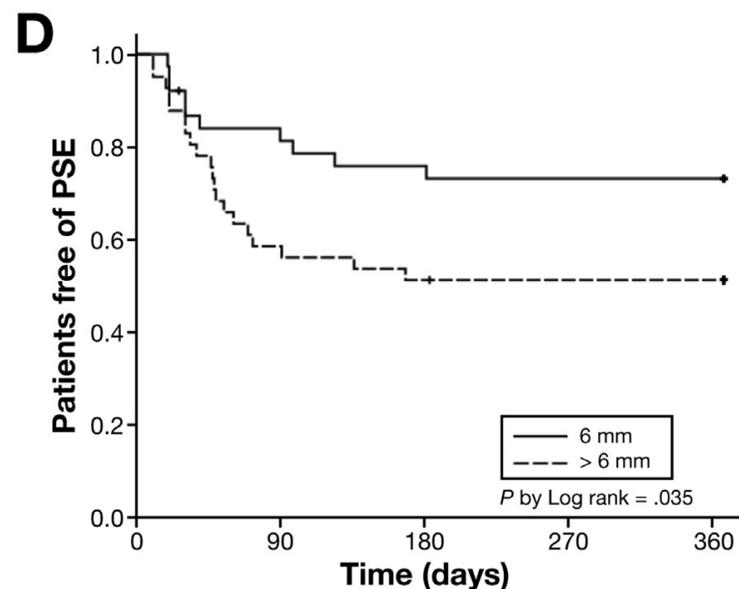
F Pecha et al JHEP Reports, 2019.

TIPS – smaller diameter

- ◆ Most common concern & AE is post-TIPS encephalopathy
- ◆ Prospective, non-randomized study at 2 centers in Italy
- ◆ 3 groups: Standard - 8mm, Under-dilated - 6-7mm & 6mm
- ◆ MV model: HE pre-TIPS, >6mm diameter, post TIPS <10mm Hg, older age, female
- ◆ BD ARCH study ongoing for 6mm stent



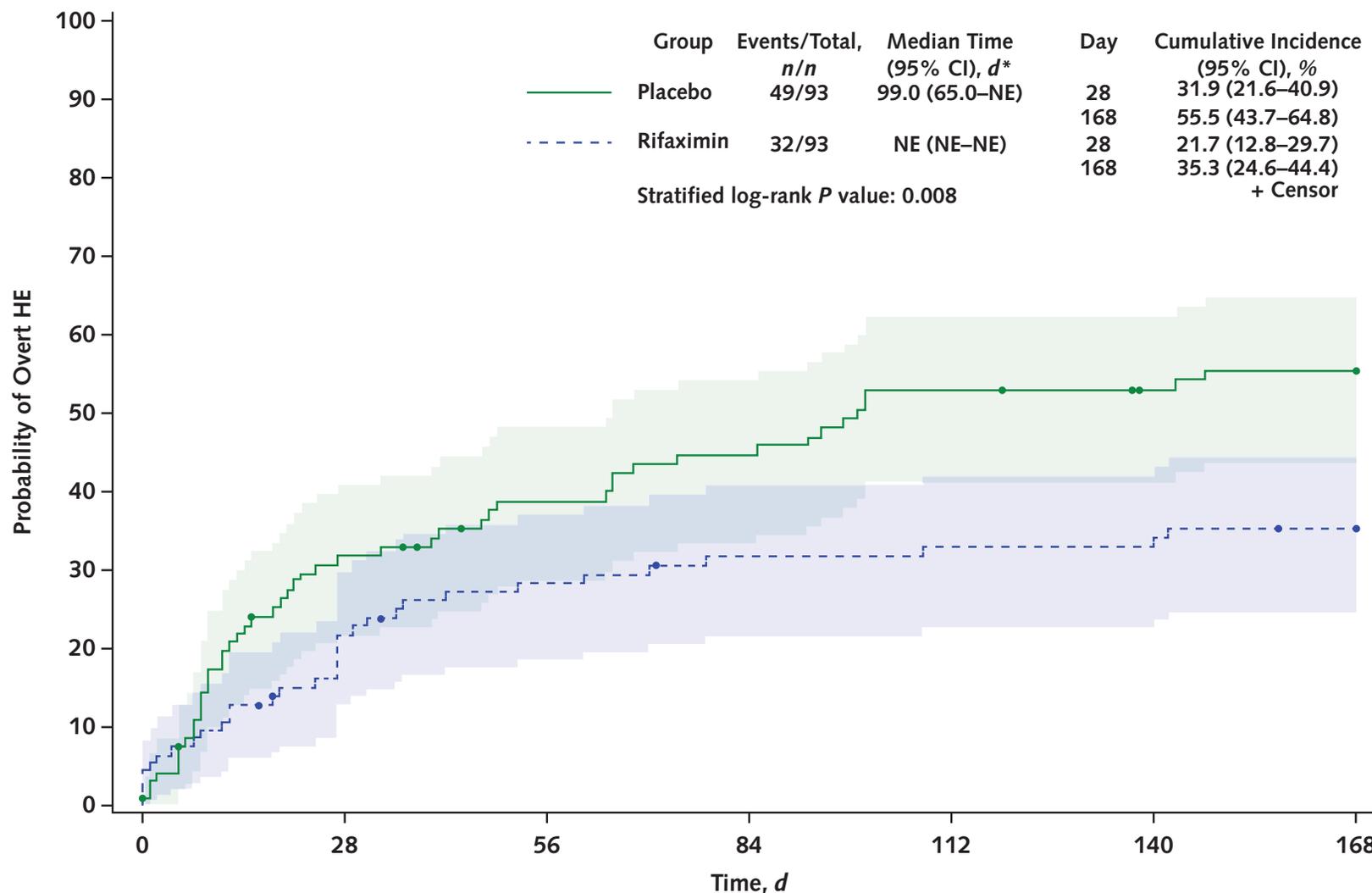
No. at risk	0	90	180	270	360
— 6 mm	20	15	12	12	12
- - - > 6 mm	22	19	18	17	17



No. at risk	0	90	180	270	360
— 6 mm	38	30	27	27	27
- - - > 6 mm	41	23	21	20	20

F Schepis et al CGH, 2018.

TIPS – Rifaximin prevents Encephalopathy



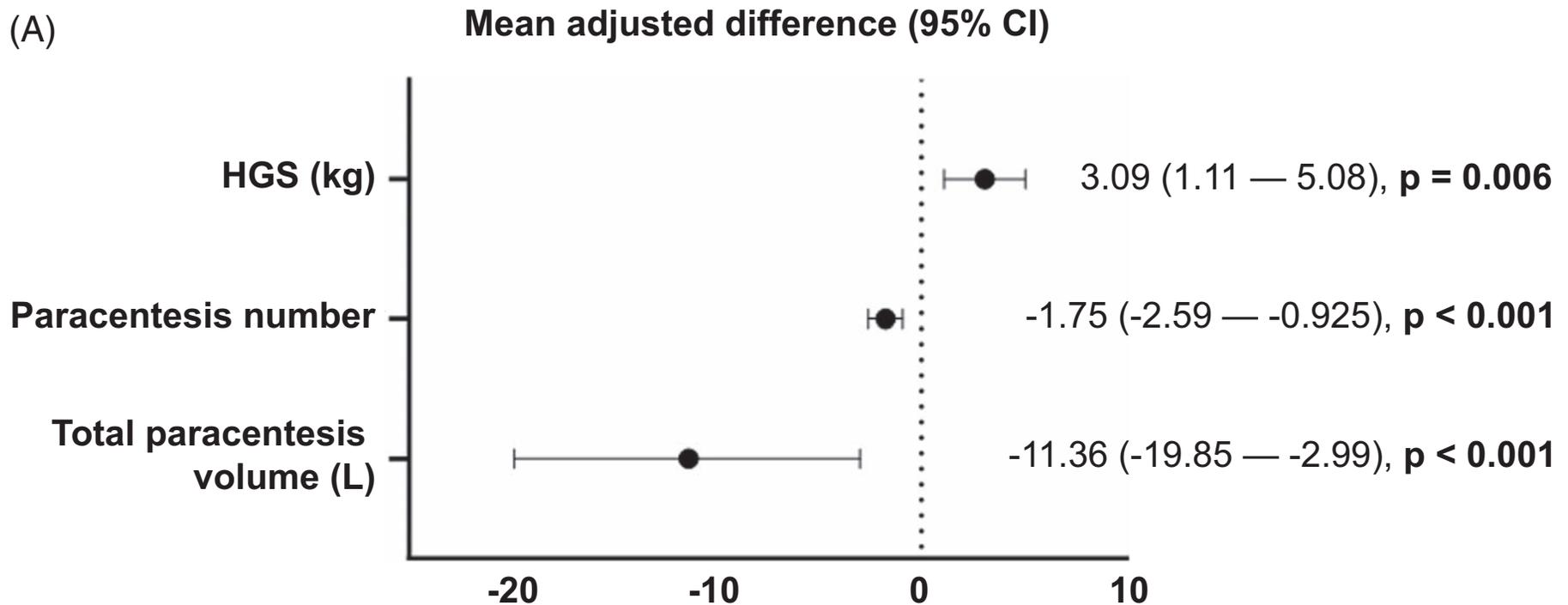
Patients at Risk, *n*

Placebo	93	61	52	47	40	37	35
Rifaximin	93	71	64	59	58	58	55

C Bureau et al Annals of Internal Medicine 2021.

Refractory ascites – Continuous Terlipressin

- ◆ Victorian Liver Transplant Unit in Melbourne, Australia
- ◆ Pioneered continuous terlipressin infusion (CTI) for LT waitlist
- ◆ 30 patients – Crossover, CTI 12 weeks, SOC 12 weeks
- ◆ 4mg Terlipressin delivered over 24 hrs via PICC

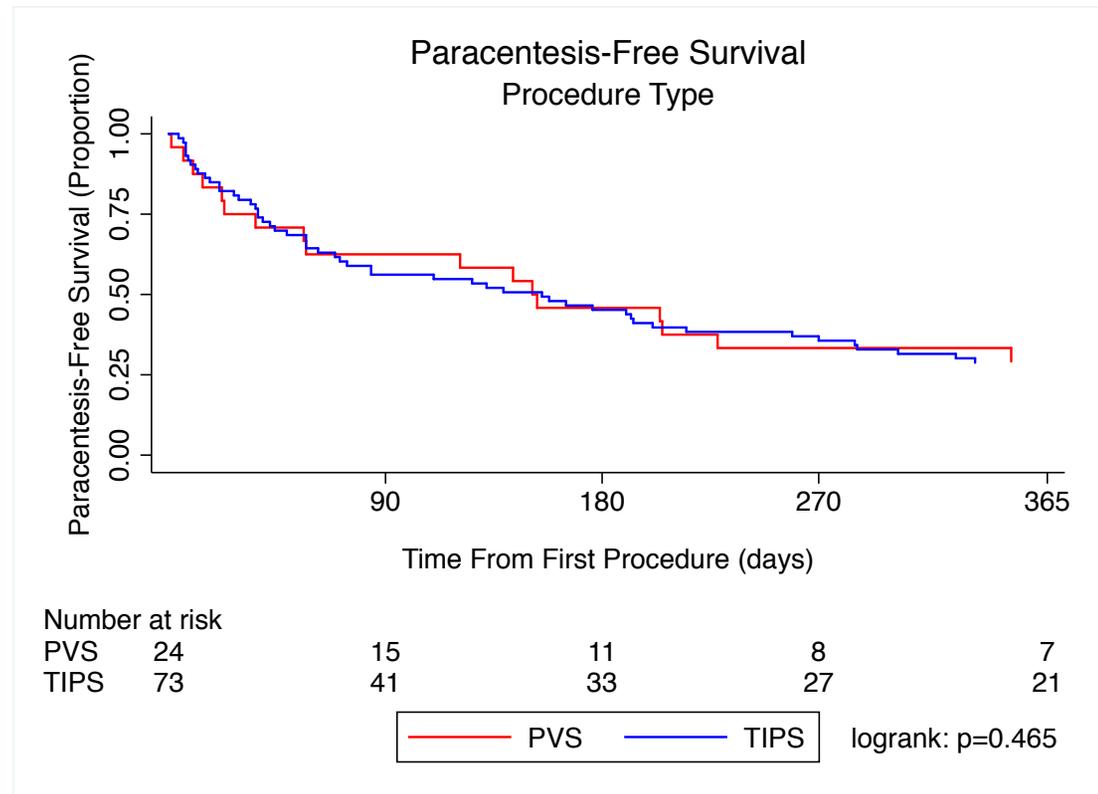


R Terbah at al Hepatology, 2024.

Refractory Ascites and not TIPS candidate

Peritoneovenous Shunt

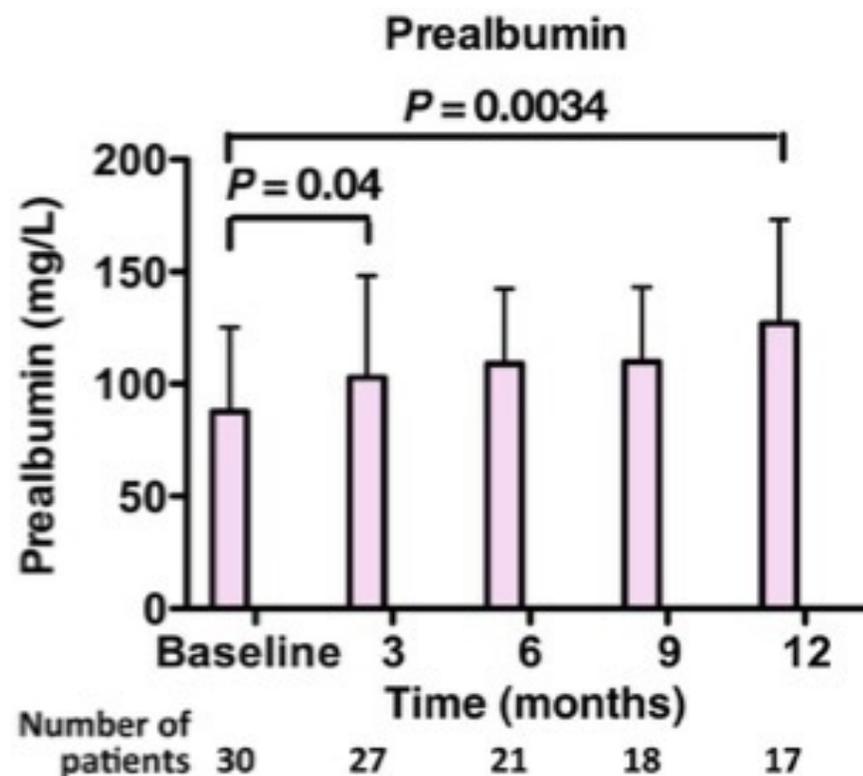
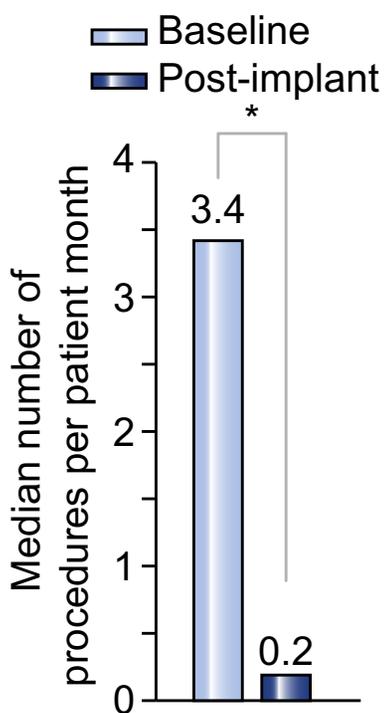
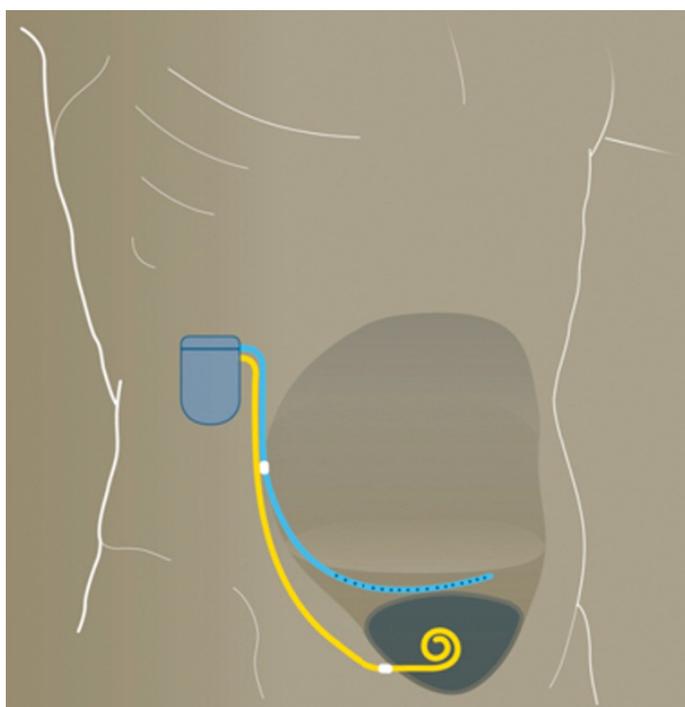
- ◆ Denver or LeVeen shunt
- ◆ More commonly used prior to advent of TIPS (1970s)
- ◆ Poor long-term patency
- ◆ Improves quality of life
- ◆ Decreases hospital visits



Refractory Ascites and not TIPS candidate

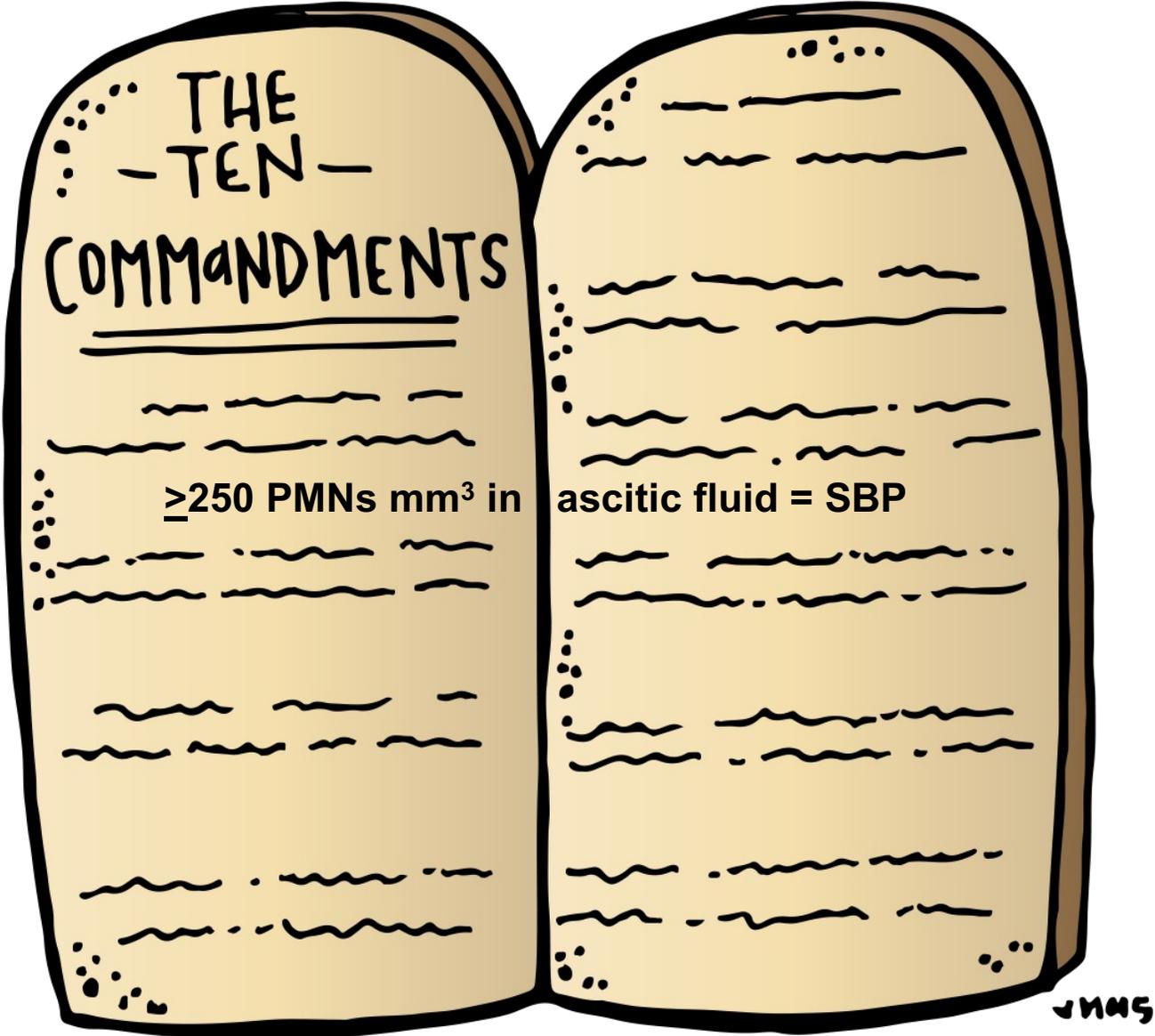
Automated Low-Flow Pump – Alfa Pump

- ◆ Approved for use in EU in 2013; FDA approved in December 2024
- ◆ May need serial albumin infusion if large weekly volumes



P Bellot et al Journal of Hepatology, 2013.
F Wong et al Liver Transplantation, 2020.

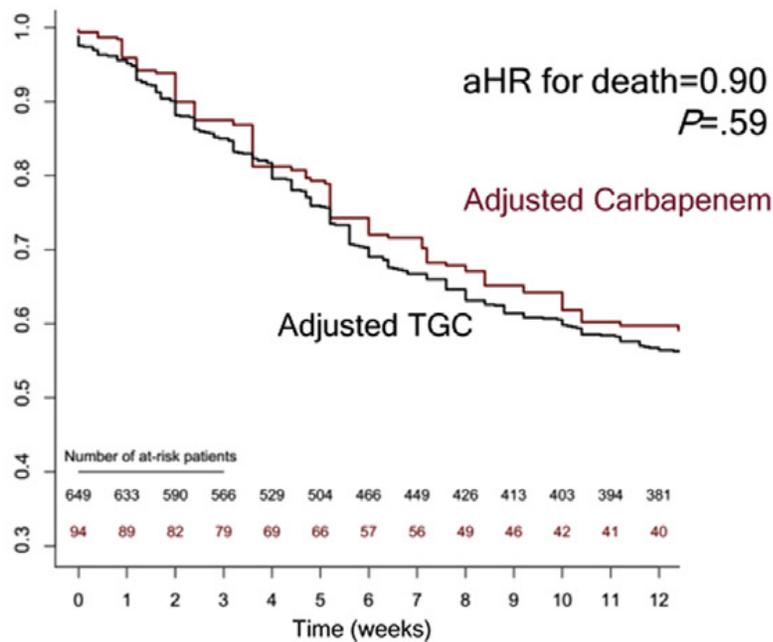
Peritonitis



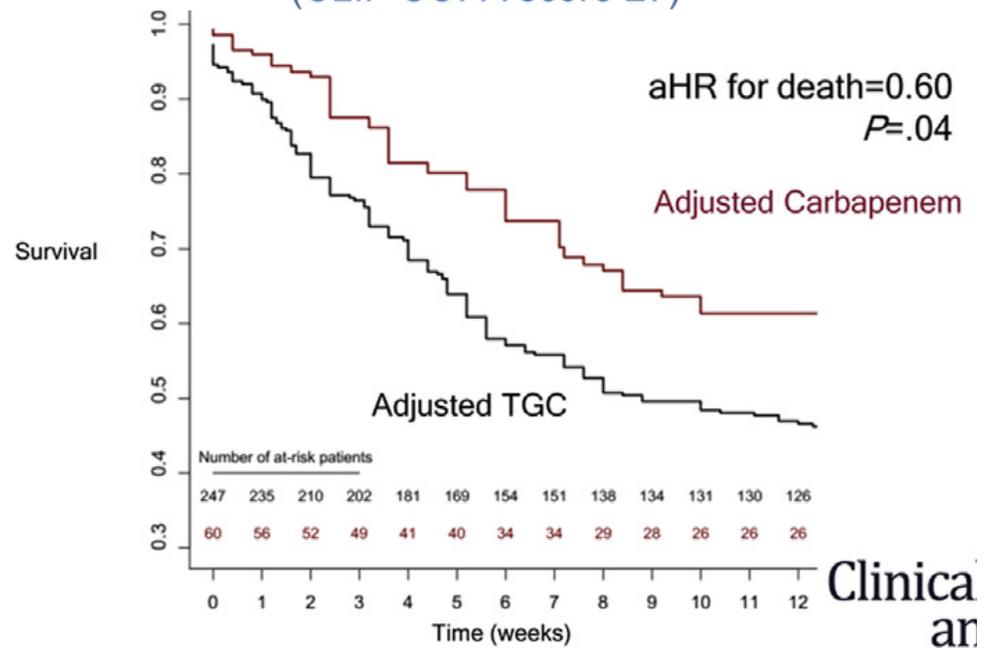
Peritonitis

- ◆ 3rd generation cephalosporin is SOC for SBP
- ◆ Severely ill may benefit from carbapenem as first-line
- ◆ If SBP develops while in hospital (nosocomial), start with daptomycin + meropenem

Overall SBP



SBP with Severe Organ Dysfunction (CLIF-SOFA score ≥ 7)



SW Kim et al CGH, 2021.
S Piano et al Hepatology, 2016.

SBP Prophylaxis

- ◆ 2° prophylaxis prevents recurrent infection.
- ◆ 1° prophylaxis – more questions
 - Who?
 - Ascites Total protein <1.5g/dL + one of the following: Cr_≥1.2, BUN_≥25, Na_≤130, CTP9 + Tbili_≥3
 - With what?
 - Ciprofloxacin, TMP/SMX
 - How long?
 - Until LT, death, or ascites resolution
 - Pros/Cons
 - Possibly improved morbidity/mortality
 - Increased MDRO
 - **ASEPTIC trial (NCT04395365)**

TABLE 1 Comparison between patients on primary prophylaxis versus those who did not develop their first SBP episode using the CDW analysis

	On primary prophylaxis (n = 1367), n (%)	Not on primary prophylaxis (n = 6192), n (%)	p
Age	62.1 ± 8.6	62.7 ± 9.0	0.02
Sex (M)	1300 (97.1)	5894 (97.7)	0.26
MELD-Na on admission	15.8 ± 8.9	15.9 ± 9.0	0.80
Culture positive	220 (16.1)	861 (13.9)	0.04
Organism isolated (first SBP)			
Fungus	5 (<1)	1 (<1)	—
Gram positive	104 (47.3)	378 (43.9)	0.37
Gram negative	115 (52.3)	478 (55.5)	0.39
Fluoroquinolone resistance	56 (25.5)	113 (13.1)	< 0.0001
TMP-SMX resistance	49 (22.3)	101 (11.7)	< 0.0001
Outcomes			
LOS (d)	13.6 ± 9.0	11.8 ± 8.4	< 0.0001
ICU transfer	276 (20.1)	1183 (19.1)	0.36
Death (during hospitalization or sent to hospice)	240 (17.6)	1201 (19.4)	0.12

M Kaltenbach, Why? Series, 2021.
BD Badal et al Hepatology, 2023.

Hepatic Hydrothorax

- ◆ TIPS for HHT that does not respond to diuretics
- ◆ Scoring systems, response rates, and survival are similar to refractory ascites

Table 3 Outcomes data after transjugular intrahepatic portosystemic shunt placement.

	Hepatic hydrothorax cohort (%)	Ascites cohort (%)	P-value
<i>Ascites/pleural fluid at 1 month</i>			0.33
Completely resolved	6/31 (19.4%)	35/103 (34%)	
Partially resolved	11/31 (35.5%)	30/103 (29.1%)	
No response	14/31 (45.1%)	38/103 (36.9%)	
<i>Ascites/pleural fluid at 3 months</i>			0.19
Completely resolved	11/27 (40.8%)	58/98 (59.2%)	
Partially resolved	7/27 (25.9%)	20/98 (20.4%)	
No response	9/27 (33.3%)	20/98 (20.4%)	
<i>Ascites/pleural fluid at 6 months</i>			0.28
Completely resolved	14/28 (50%)	59/98 (59.8%)	
Partially resolved	4/28 (14.3%)	19/98 (19.6%)	
No response	10/28 (35.7%)	20/98 (20.6%)	

A scites to Z

Z – ‘Ze Hepatorenal Syndrome



Hepatorenal Syndrome (HRS)

- ◆ **Basic Definition**

1. **Cirrhosis with ascites**

2. **AKI that is not responsive to diuretic withdrawal, volume expansion, and cannot be explained by other diagnosis (ATN, AIN, etc)**

- ◆ **Terlipressin approved for use in Sept 2022**

- ◆ **AKI in cirrhosis and HRS-AKI require separate talk**

Old	New
HRS-1 - acute	HRS-AKI – acute
HRS-2 - chronic	HRS-AKD – acute-to-chronic
	HRS-CKD - chronic

Simonetto *et al*, BMJ 2020.

Take Away Points

- ◆ **Best treatment of ascites - prevention**
- ◆ **Low salt diet - Teach your patients + refer to a nutritionist**
- ◆ **More baths**
- ◆ **Eplerenone is not cost-prohibitive**
- ◆ **Bumetanide/Torsemide are more potent**
- ◆ **Place TIPS early after development of Refractory Ascites**
- ◆ **Tell your IR person about “small TIPS”**
- ◆ **Primary SBP prophylaxis is not straight-forward**

Thank you!

