



# Management of Difficult Ascites

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Speakers: Dr C Francoz, Pr D Thabut

# Mr A.E., 55 years old, referred for ascites

- Past medical history : HCV infection, never treated (« normal ALT »)
- Ongoing treatments: none
- Recent medical history :
  - In 2014 : « cirrhosis » (FT=0.75 and FS=27kPa), work-up not performed
  - No history of decompensation
  - GP for weight increase, ultrasound examination: ascites

# Mr A.E., 55 years old, referred for ascites

- Clinical examination:
  - Weight : 80kg/ 1m70 ;
  - Moderate ascites
  - No jaundice, no HE
- Lab tests :
  - Hb: 12.9g/dL, leucocytes: 3800/mm<sup>3</sup>, platelets count : 151.000/mm<sup>3</sup>
  - ASAT : 56 UI/L, ALAT : 49 UI/L, GGT : 59 UI/L, BiliT : 19 µmol/L, Albumin : 34 g/l
  - PT : 67%, INR: 1.1
  - Na<sup>+</sup>=134 mmol/l, creatinin: 89 µmol/L
  - HCVPCR=6 logUI/ml, G1a
  - Child B8, MELD = 8

# How would you manage this patient?

- Diuretics prescription and diet with low-sodium content (4-6 g/j)
- Diuretics prescription and diet with very low-sodium content (<2g/j)
- HCV Tx
- Upper endoscopy
- Discussion for LT

# How would you manage this patient?

- **Diuretics prescription and diet with low-sodium content (4-6 g/j)**
- Diuretics prescription and diet with very low-sodium content (<2g/j)
- **HCV Tx ???**
- **Upper endoscopy**
- Discussion for LT

# Screening of EV in cirrhotic patients

Position Paper



## **Expanding consensus in portal hypertension Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension**

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- ❖ cACLD= compensated advanced chronic liver disease
- ❖ Screening endoscopy except if FS < 20 kPa and plt > 150000

# Treatment of uncomplicated ascites

Clinical Practice Guidelines

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## EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis<sup>☆</sup>

### Recommendations

- A moderate restriction of sodium intake (80–120 mmol/day, corresponding to 4.6–6.9 g of salt) is recommended in patients with moderate, uncomplicated ascites. This is generally equivalent to a no added salt diet and avoidance of pre-prepared meals. Adequate nutritional education of patients on how to manage dietary sodium is also recommended (II-2;1).
- Diets with a very low sodium content (<40 mmol/day) should be avoided, as they favour diuretic-induced complications and can endanger a patient's nutritional status (II-2;1).

### Recommendations

- Patients with the first episode of grade 2 (moderate) ascites should receive an anti-mineralocorticoid drug alone, starting at 100 mg/day with stepwise increases every 72 h (in 100 mg steps) to a maximum of 400 mg/day if there is no response to lower doses (I;1).
- In patients who do not respond to anti-mineralocorticoids, as defined by a body weight reduction of less than 2 kg/week, or in patients who develop hyperkalemia, furosemide should be added at an increasing stepwise dose from 40 mg/day to a maximum of 160 mg/day (in 40 mg steps) (I;1).
- Patients with long-standing or recurrent ascites should be treated with a combination of an anti-mineralocorticoid drug and furosemide, the dose of which should be increased sequentially according to the response, as explained (I;1).

# Treatment of the cause of liver disease

Clinical Practice Guidelines

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## **EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis<sup>☆</sup>**

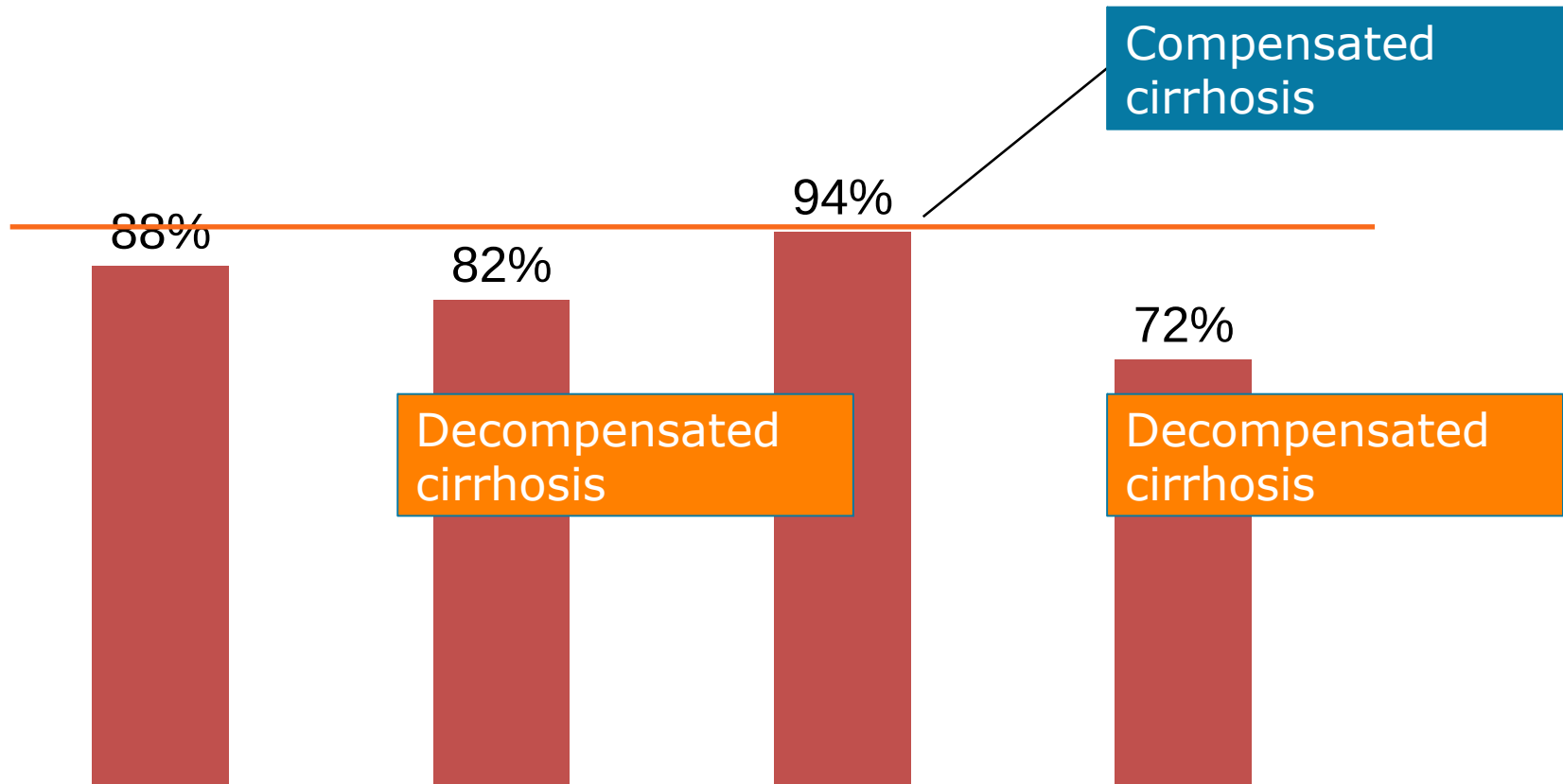
European Association for the Study of the Liver\*

### **Recommendations**

- In patients with decompensated cirrhosis, the aetiological factor, should be removed, particularly alcohol consumption and hepatitis B or C virus infection as this strategy is associated with decreased risk of decompensation and increased survival (II-2,1).



# Efficacy of DAAs in cirrhotic patients



(1) Charlton M. Gastroenterology 2015; (2) Poordad F, Hepatology 2016 Abs. L08; (3) Poordad F NEJM 2014 (4) Saxena V, Hepatology 2015

# 3D + RBV in Child B patients

- *Phase IIIb study, G1a et G1b, n=11, SVR=100%*
- *Side effects in 5 patients, decompensation, hyperbilirubinemia and anemia*



U.S. Food and Drug Administration  
Protecting and Promoting Your Health

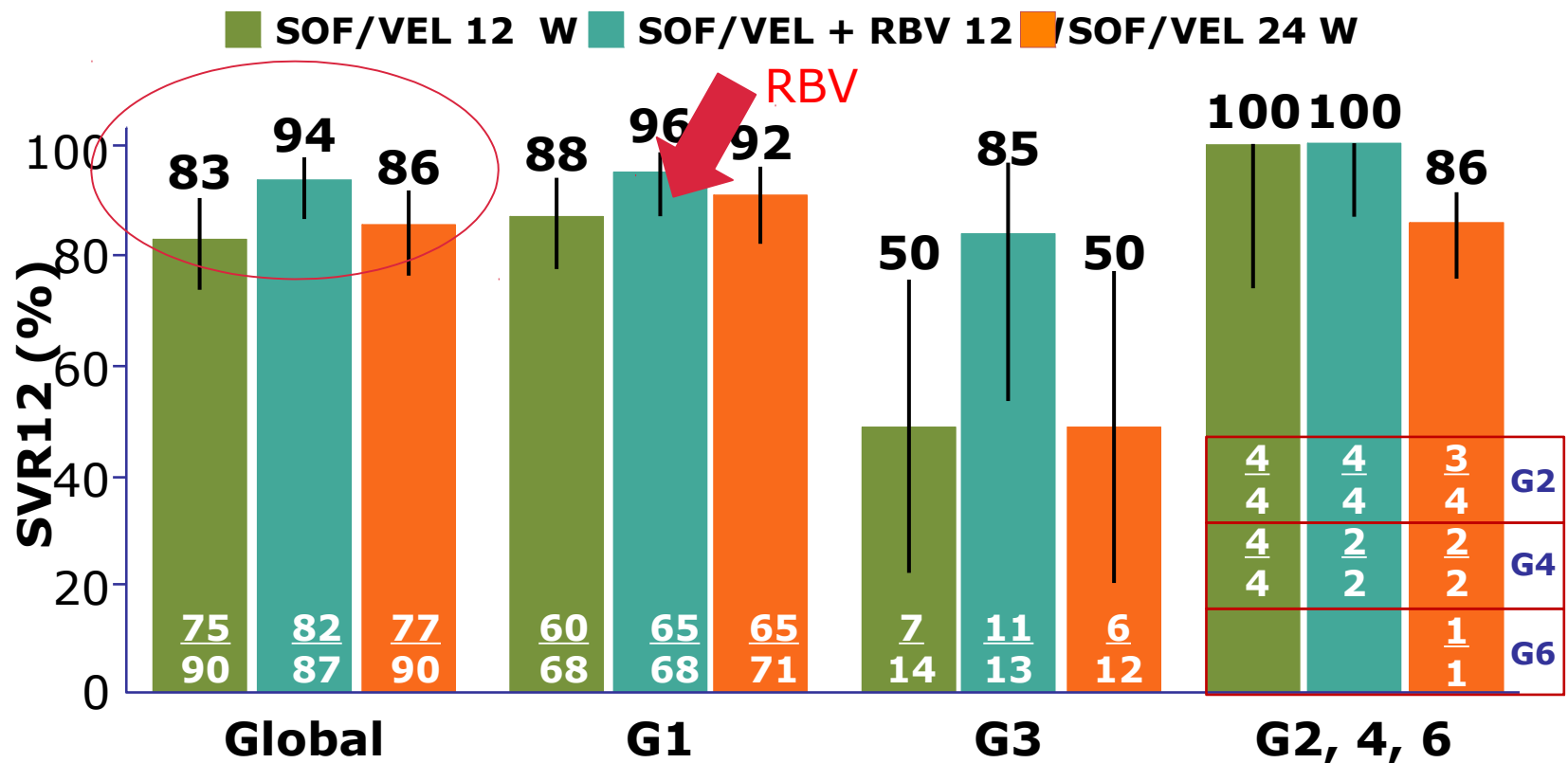
## Drug Safety Communications

**FDA Drug Safety Communication: FDA warns of serious liver injury risk with hepatitis C treatments Viekira Pak and Technivie**

- *3D + RBV treatment is effective in Child B patients but side effects are frequent and severe*
  - Protease inhibitors are contra-indicated in Child C pts

# New generation of DAAs in Child B cirrhotic patients

ASTRAL 4 : sofosbuvir/velpatasvir

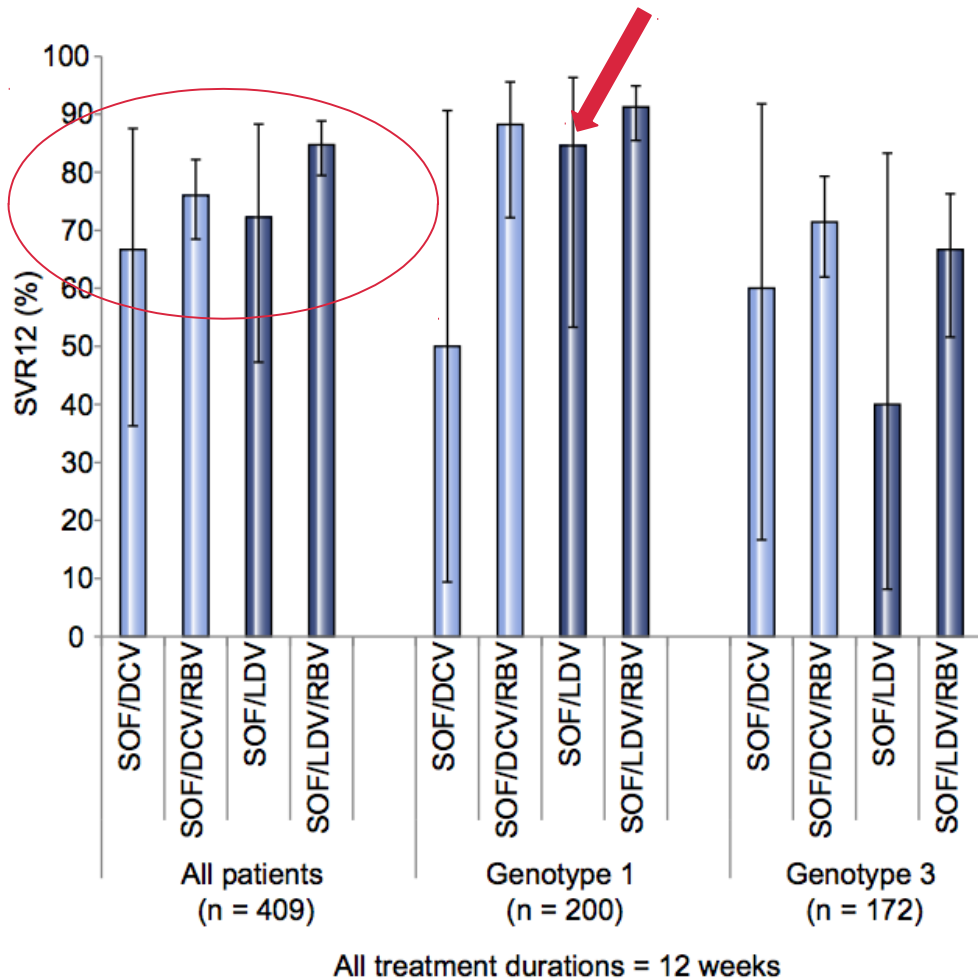


➤ SVR 85%, RBV, 24 sem not better

Curry et al. N Engl J Med. 2015

# Efficacy of DAAs in patients with decompensated cirrhosis

- Early Access Program UK
- 409 pts with decompensated cirrhosis Child >B7
- Sof, Dcv, Ldv 12 sem
- SVR: 91% G1, 68% G3
- Efficacy < other pts
- 12 sem with RBV
- Pb of GT3



# Safety in severe patients

## Pharmacokinetics of DAAS

	Hepatic function impairment			Avoid
	Mild	Moderate	Severe	
Simeprevir <sup>1</sup>		+ 2.44	+ 5.22	Child C
Sofosbuvir <sup>2</sup>		+ 1.26	+ 1.43	
Ledipasvir <sup>3</sup>	No adjustment			
Paritaprevir/r <sup>4</sup>	- 0.71	+ 1.62	+ 10.23	Child C
Ombitasvir <sup>4</sup>	+ 0.92	+ 0.70	+ 0.45	
Dasabuvir <sup>4</sup>	+ 1.17	+ 0.84	+ 4.19	Child C?
Asunaprevir <sup>5</sup>	- 0.79	+ 9.8	+ 32	Child B/C
Daclatasvir <sup>5</sup>	- 0.57	- 0.62	- 0.64	

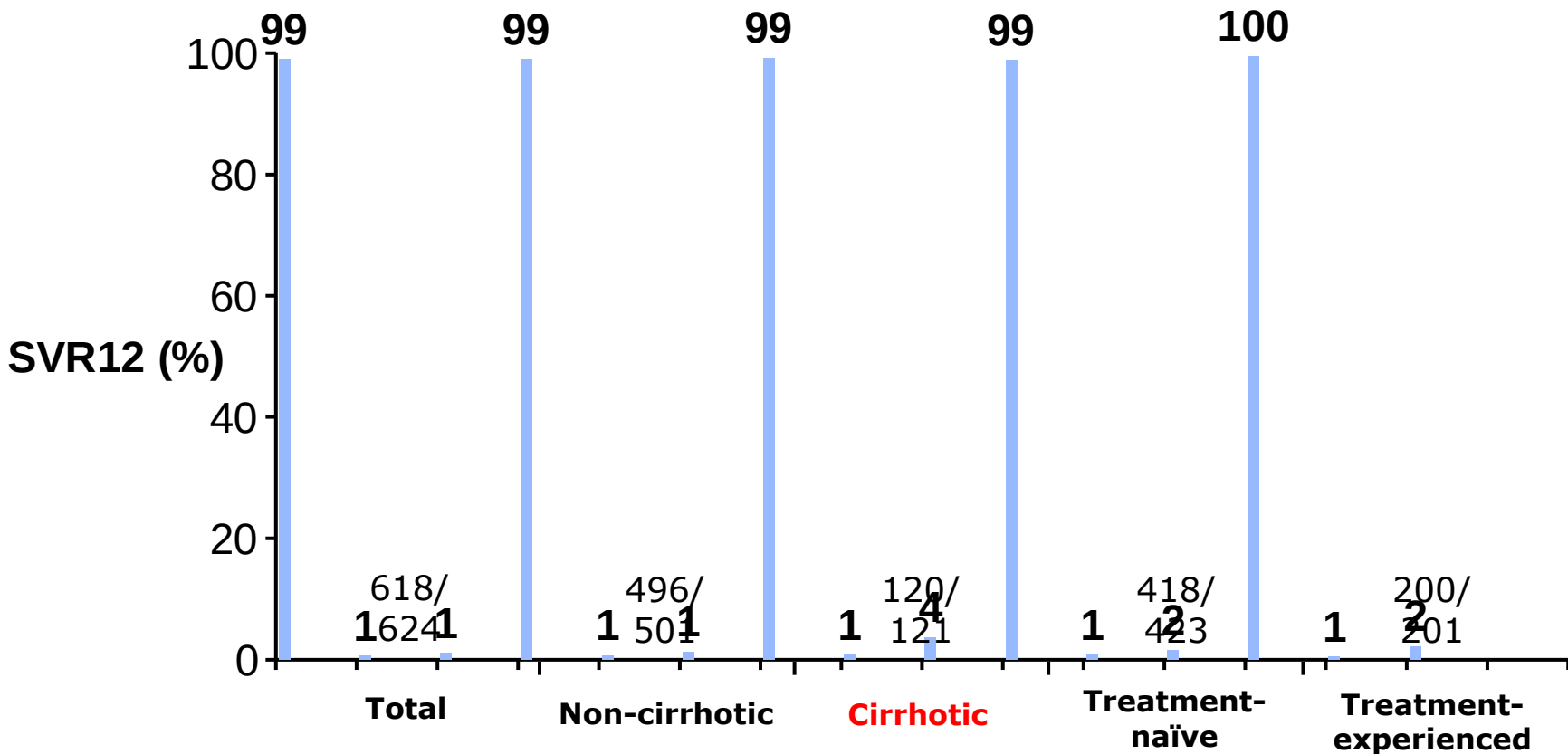
➤ 24% AE, related to R

1. Ouwerkerk-Mahadeva S, et al. AASLD 2013. Oral #65; 2. Gilead Sciences Europe. SOVALDI (sofosbuvir), Summary of Product Characteristics, January 2014; 3. German P, et al. AASLD. 2013. Oral #52; 4. Khatri A, et al. AASLD. 2012. Oral #66; 5. Bifano M, et al. AASLD. 2011. Oral #78.

# DAAs in most severe patients

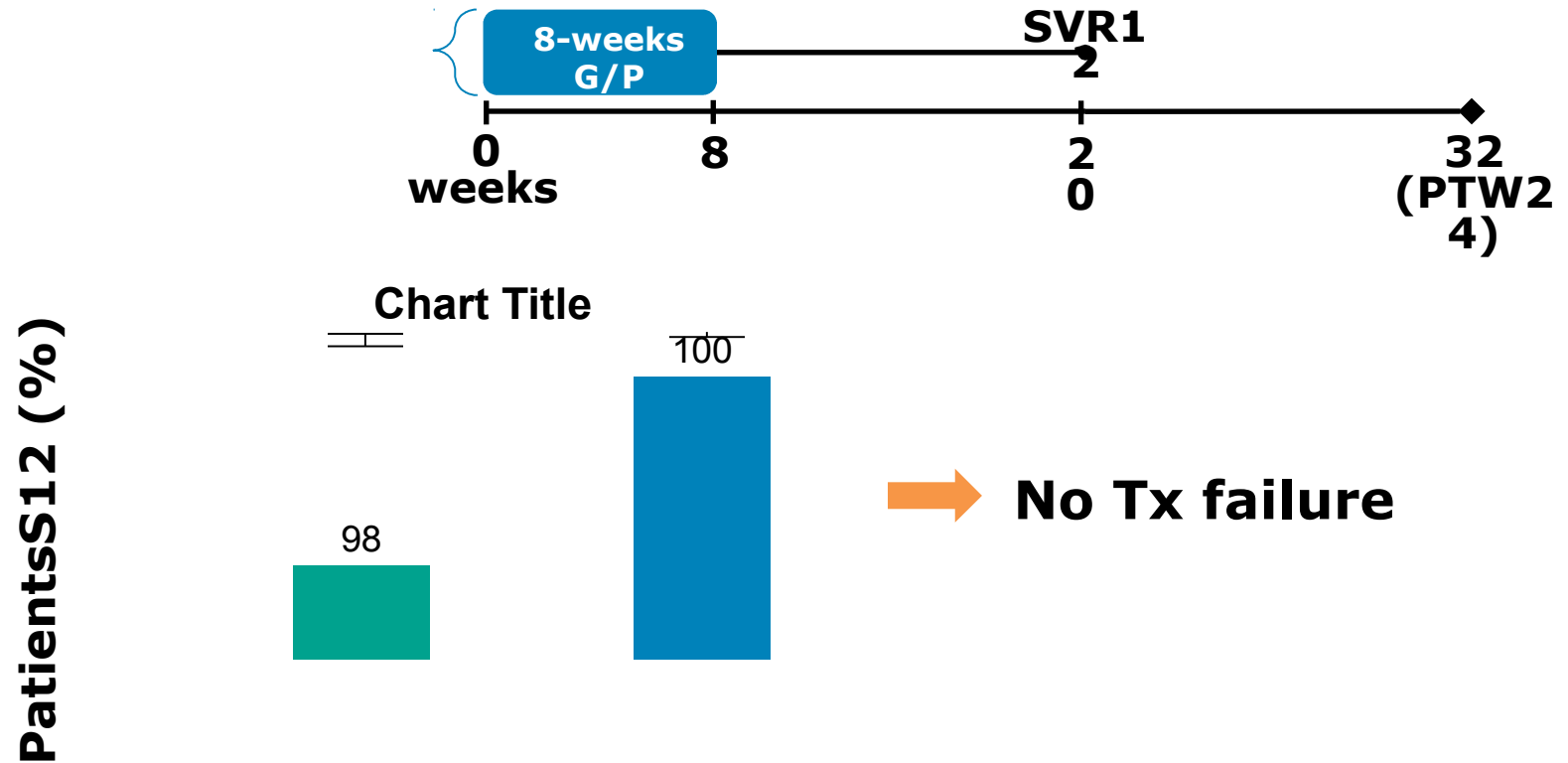
- DAAs and decompensated cirrhosis
  - Good efficacy, inferior to non decompensated pts
  - RBV is mandatory
  - Safety OK
  - No PI (new DAAs)

# ASTRAL-1: SOF/VEL for 12 weeks is effective regardless of cirrhosis and treatment experience



# Glecaprevir +Pibrentasvir for 8 weeks in cirrhotic patients

➔ **280 naïve pts, Child-Pugh A cirrhosis, genotype non 3 (1a : 34 %, 1b : 49 %)**





# 2 months after...

- HCV Tx prescribed (Sof/Vel/RBV)
- Spironolactone 75 mg/j, then Furosemide 40 mg/j started
- Upper endoscopy: grade 2 EV; propranolol 80 mg/day
- Currently 150 mg/120 mg diuretics
- No weight loss, was tapped 3 times in outpatient clinics (14 liters)
- Did not take HCV Tx
- Lab tests:
  - creat: 135  $\mu$ mol/L, Na<sup>+</sup>: 131 mmol/l, Bilirubin : 20  $\mu$ mol/L, Albumin : 31 g/l
  - PT : 67%, INR: 1.1
  - Plt=100000/mm<sup>3</sup>
- Child B8, MELD: 12

# How would you manage this patient?

- Increase diuretics
- TIPS
- HCV Tx (sofosbuvir-velpatasvir-RBV)
- HCV Tx (Glipaprevir-Pibrentasvir)
- Discussion for LT

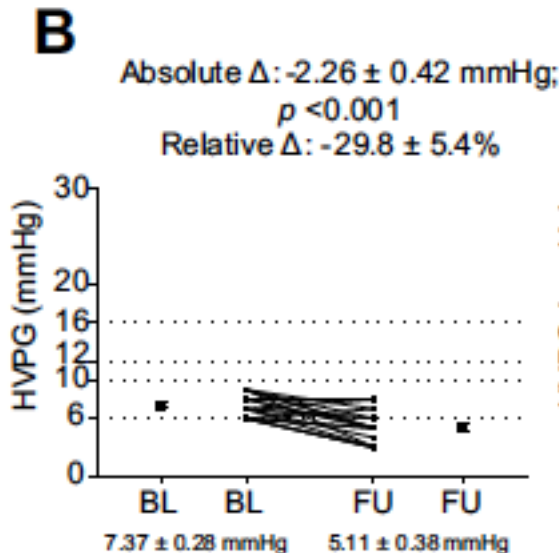
# How would you manage this patient?

- Increase diuretics
- TIPS
- **HCV Tx (sofosbuvir-velpatasvir-RBV)**
- HCV Tx (Glipaprevir-Pibrentasvir)
- Discussion for LT

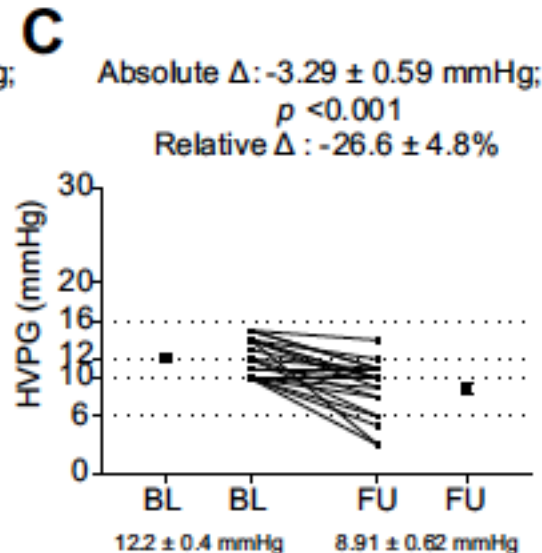
# Effects of HCV Therapy on HVPG

- ❖ 50 pts with viral C cirrhosis and PHT (HVPG)  $\geq 6$  mmHg; SVR 12=92% (DAAs)

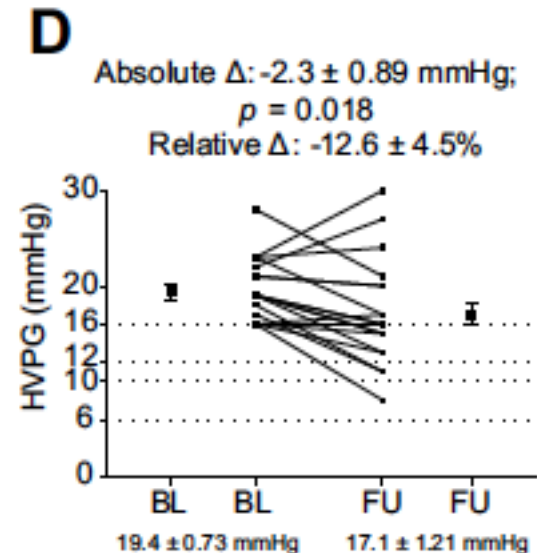
## HVPG variations



HVPG: 6-9 mmHg



HVPG: 10-15 mmHg

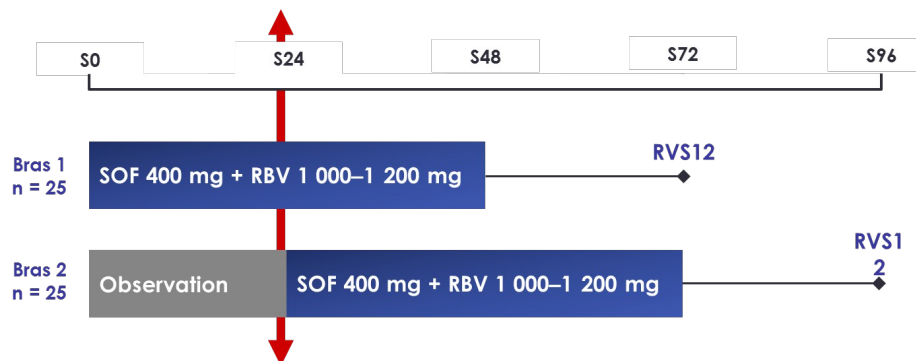


HVPG > 15 mmHg

Mandorfer M, et al., J Hepatol 2016  
 Lens S et al., Gastroenterology 2017

# Clinical effects of virosuppression on PHT

- ❖ 50 pts with « decompensated » cirrhosis Child-Pugh A or B, HVPg > 6 mmHg,
- ❖ EV or gastric varices (78% pts with HVPg > 12)
- ❖ Median HVPg = 16 mmHg (IQR = 16)

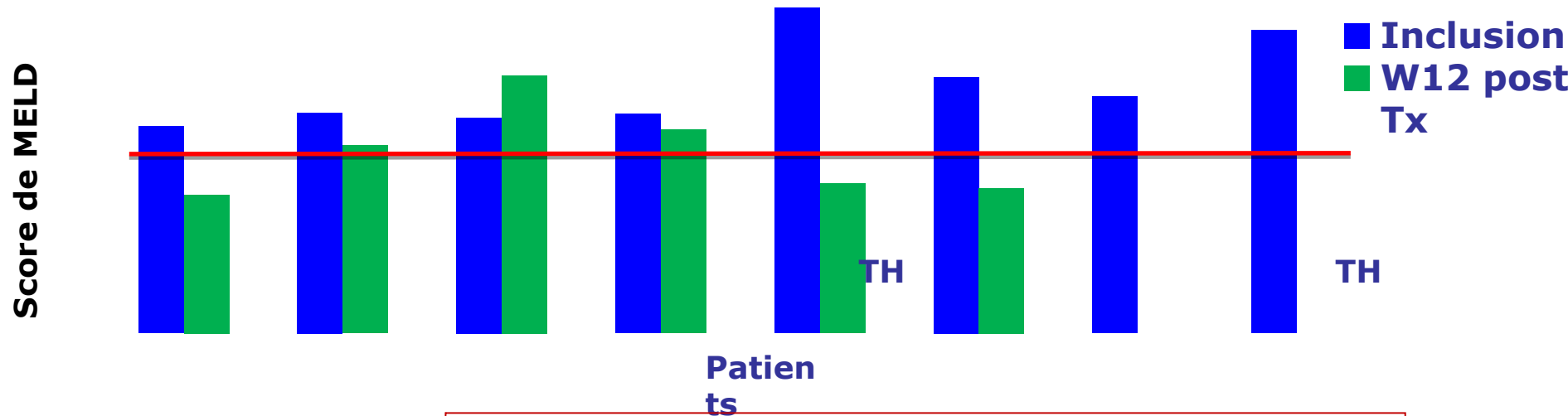


	Ascite		Encéphalopathie hépatique	
Patients , n	SOF + RBV (n = 25)	Observation (n = 25)	SOF + RBV (n = 25)	Observation (n = 25)
Initial	6	9	5	2
Semaine 12	5	8	3	3
Semaine 24	0	7	0	4

# DAAAs in Decompensated Pts

- ❖ 77 patients, decompensated cirrhosis, awaiting OLT (no CHC, MELD=12 ± 5 ; Child A (19 %), B (38 %) and C (40 %))
- ❖ SOF/LDV +/- RBV or SOF/DCV +/- RBV or SOF/SMV +/- RBV
- ❖ SVR12 = 88 % ; Clinical and biochemical response: 31/72 patients (42 %)

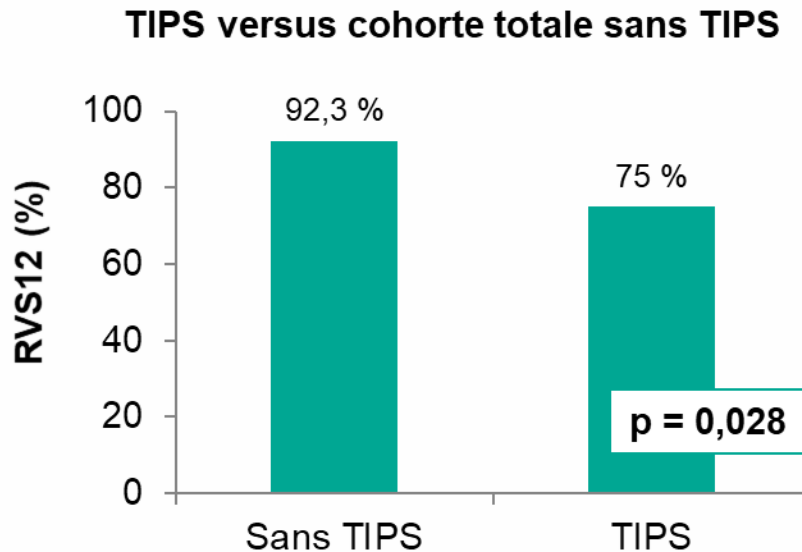
## Outcome of 8 patients with MELD ≥ 20 before treatment



**Disappearance of ascites in 73% of cases**  
**16 % of pts delisted for improvement**

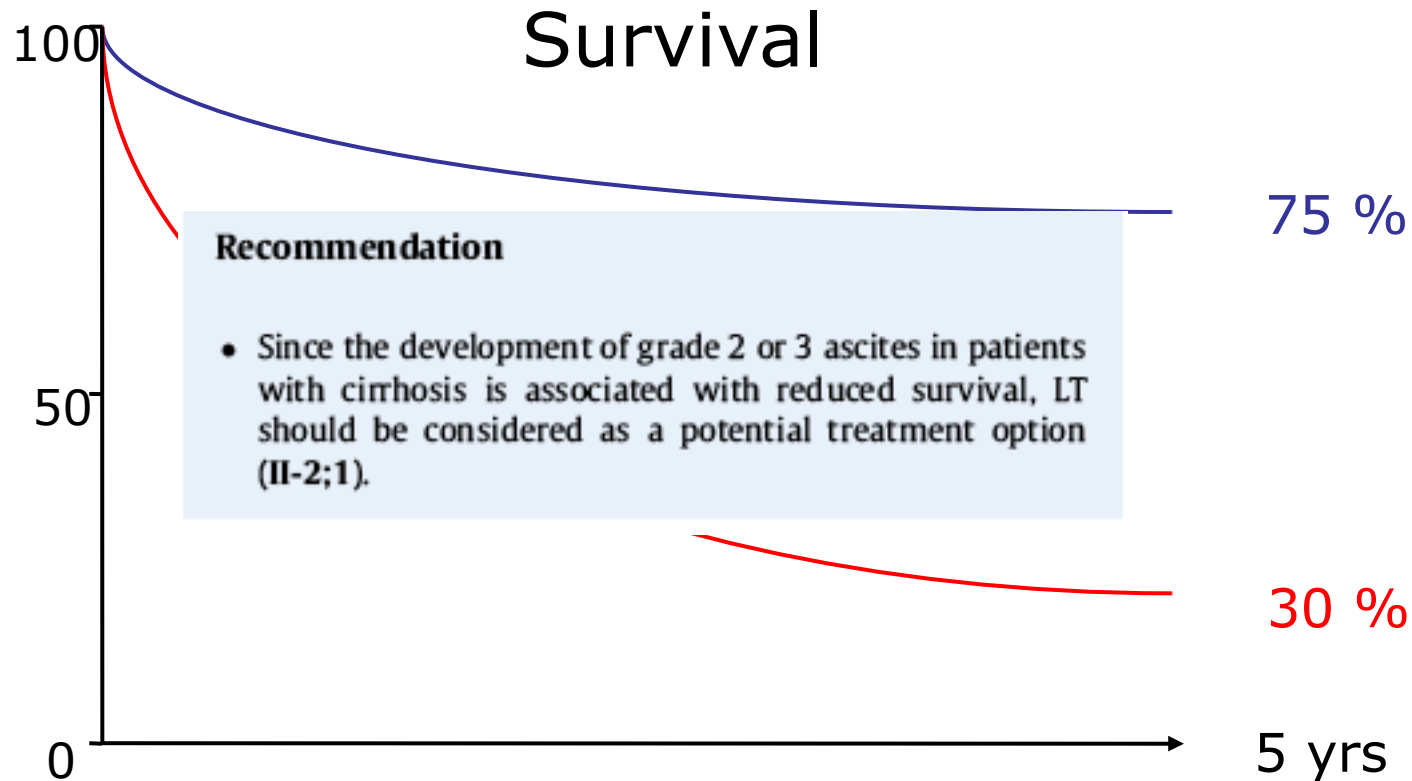
# TIPS and antiviral therapy

- ❖ 16 decompensated pts with TIPS vs 32 without TIPS



- Pts with TIPS have lower SVR12

# Prognosis of refractory ascites



— Pts with refractory ascites after LT

— Pts with refractory ascites without LY



# 6 months after...

- SVR12 obtained
- Tense ascites, one paracentesis/month
- No diuretics
- Lab tests:
  - creat: 110  $\mu\text{mol/L}$ ,  $\text{Na}^+$ : 134 mmol/l, BiliT : 23  $\mu\text{mol/L}$ , Albumin : 26 g/l
  - PT : 62%, INR: 1.2
  - Plt=75000/mm<sup>3</sup>
- Child B8, MELD: 12

# How would you manage this patient?

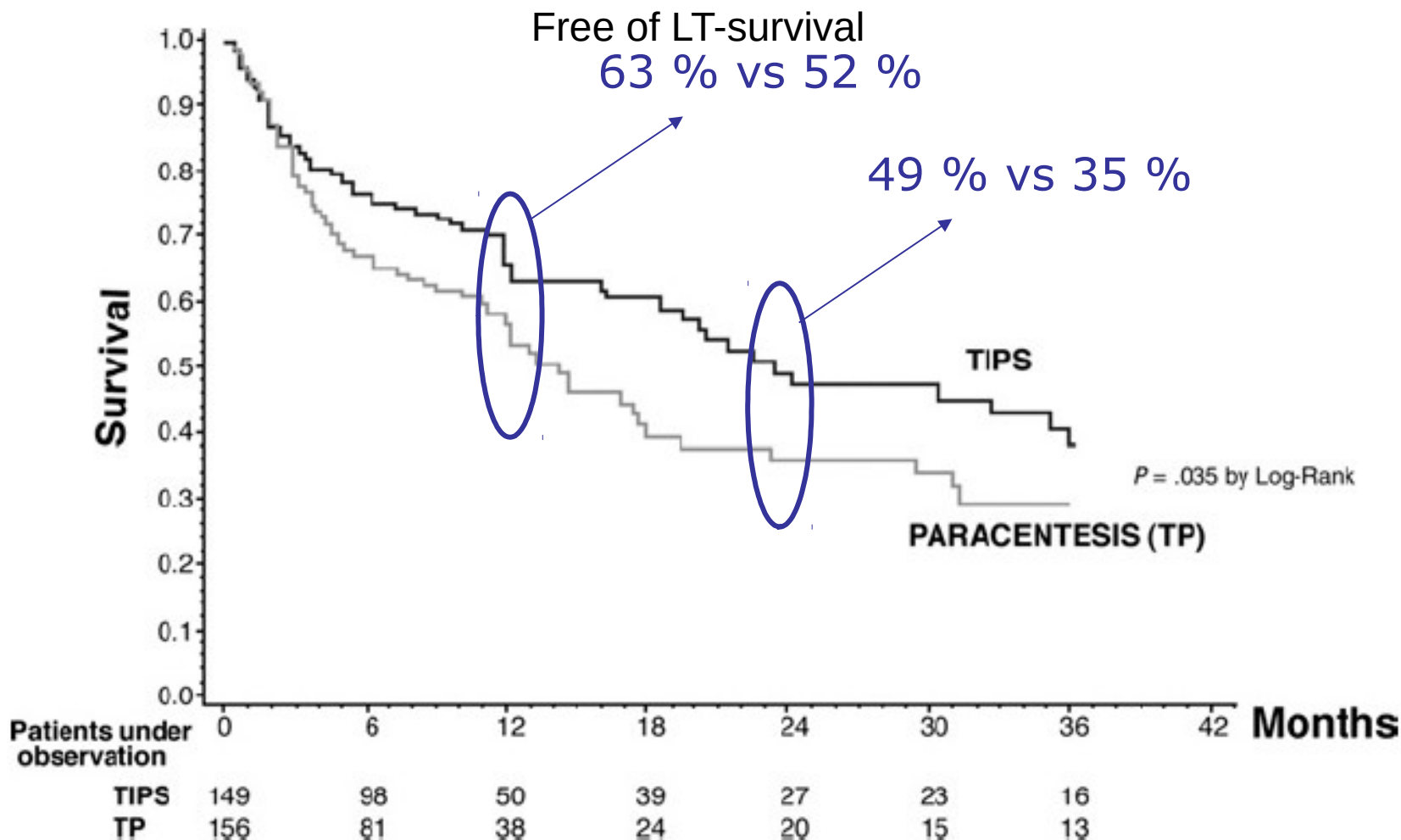
- Reintroduction of diuretics
- TIPS
- LT
- Alfapump
- LVP

# How would you manage this patient?

- Reintroduction of diuretics
- **TIPS**
- LT
- Alfapump
- LVP

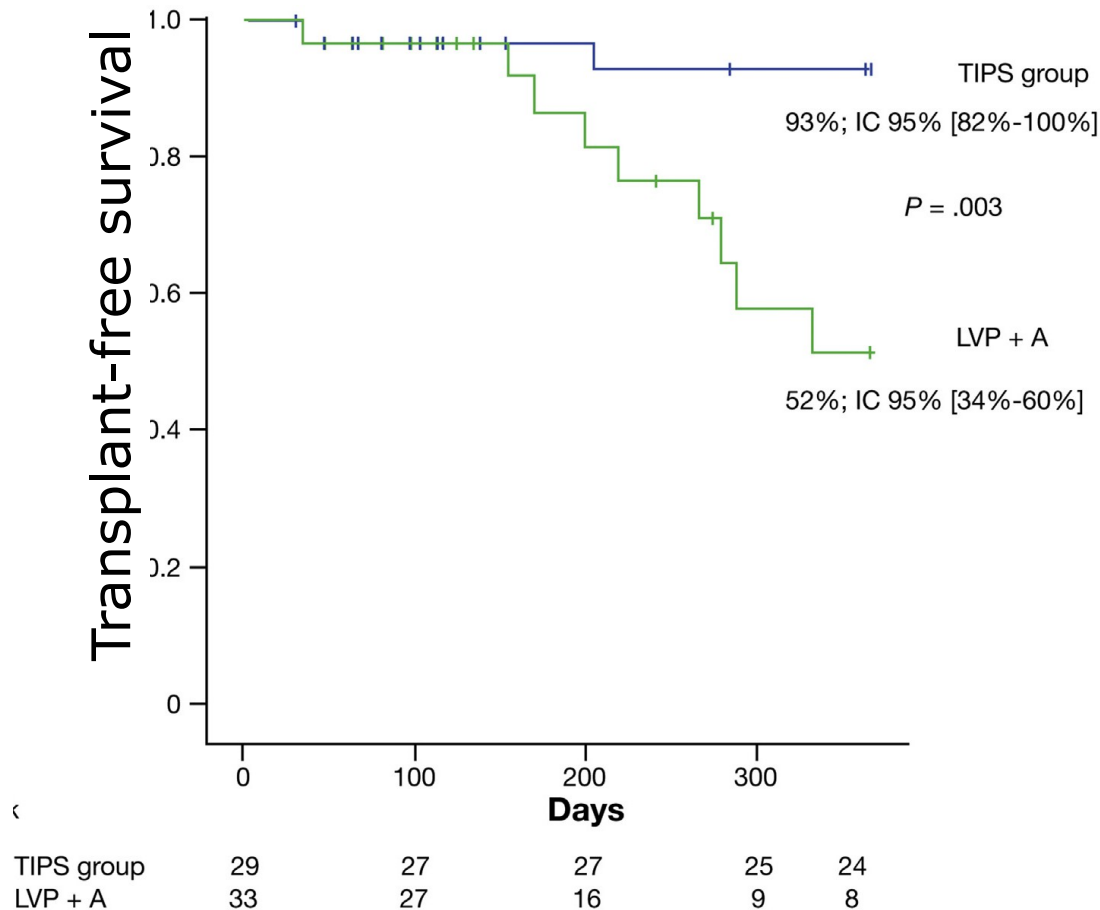
# Meta-analyse TIPS vs LVP, individual data

n = 305



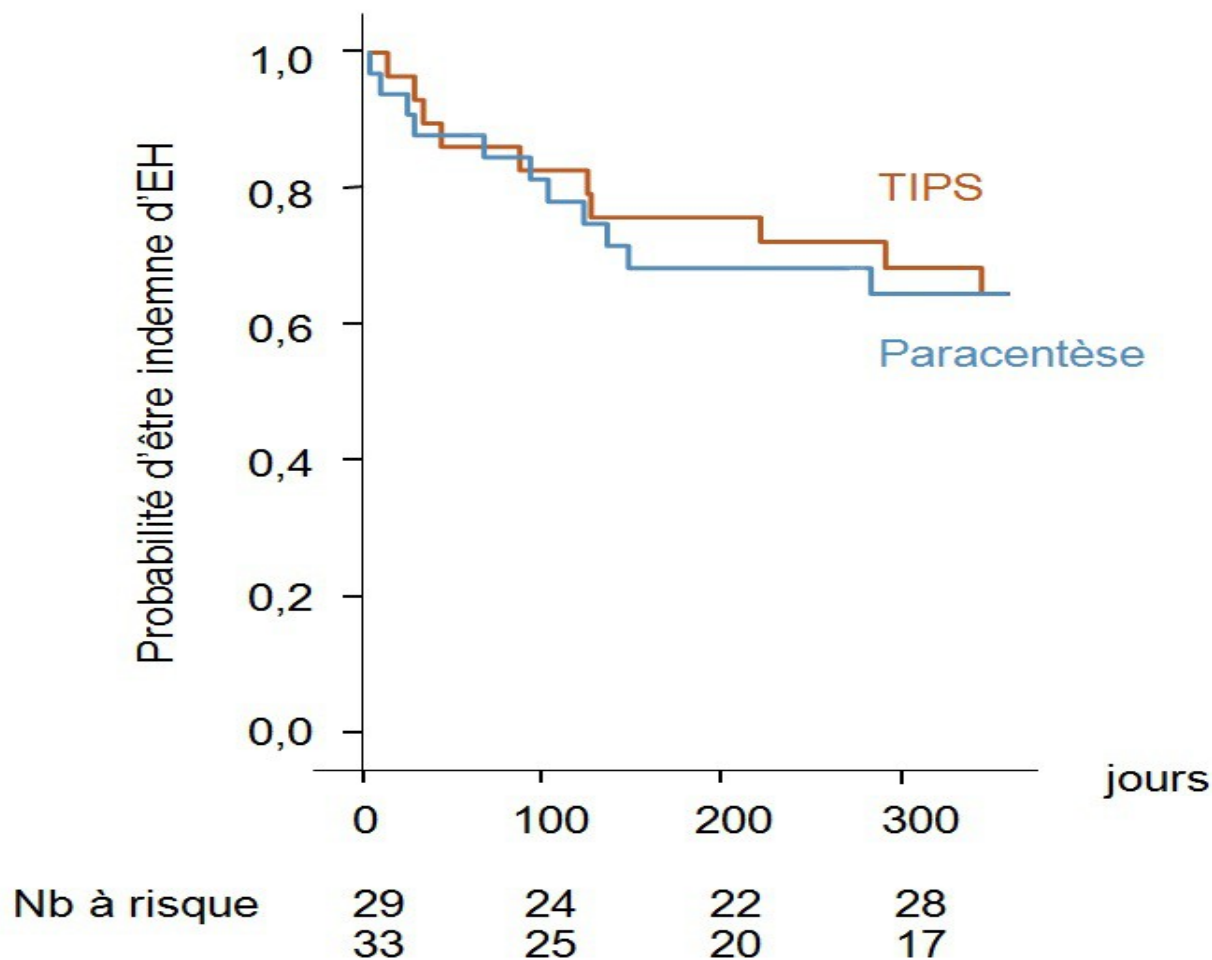
# Covered TIPS in Pts with Refractory Ascites

- Patients with  $\geq 2$  LVP within min. 3weeks, but  $\leq 6$  LVP in the last 3 months

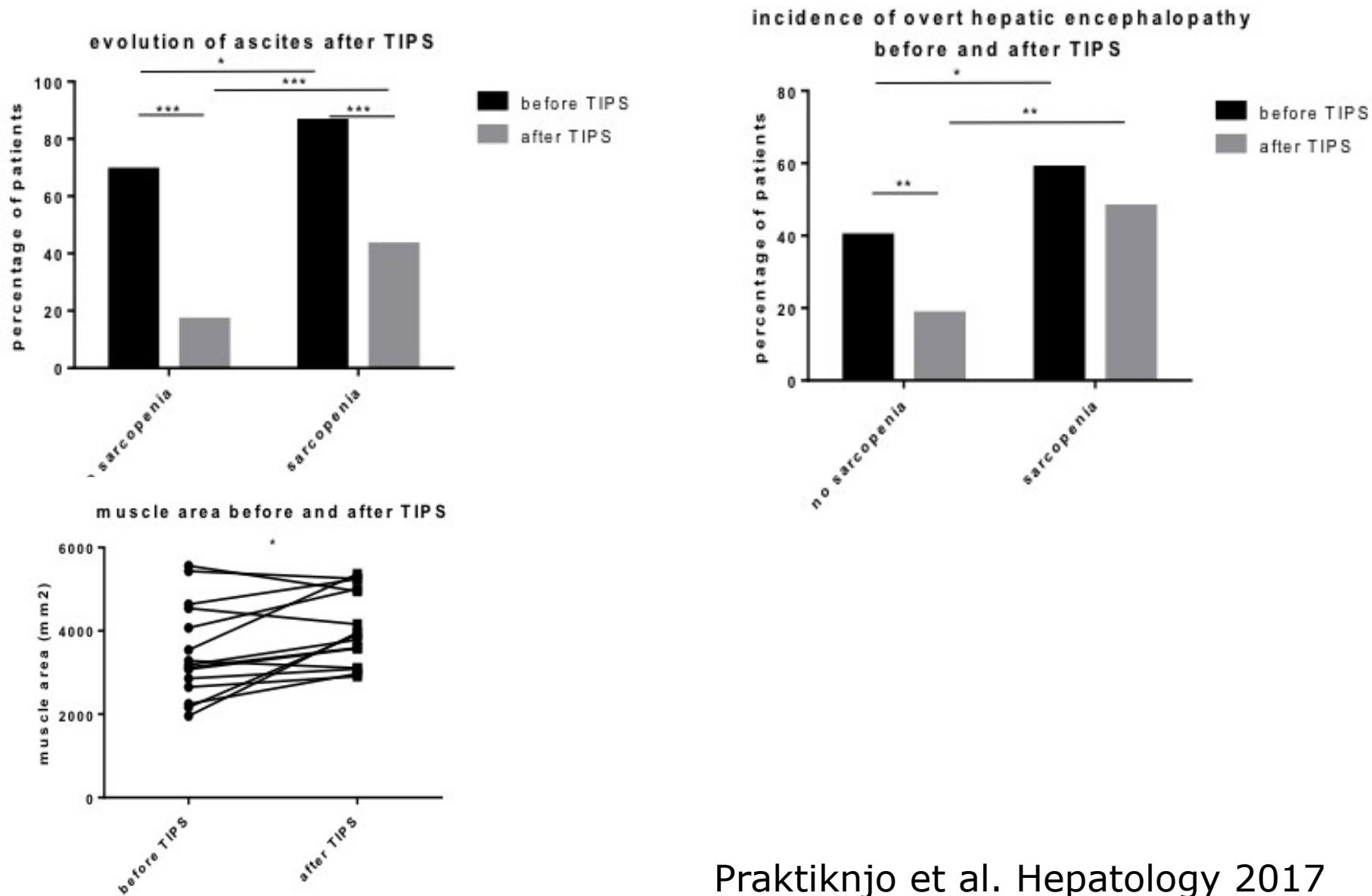


Bureau et al., Gastroenterology 2017

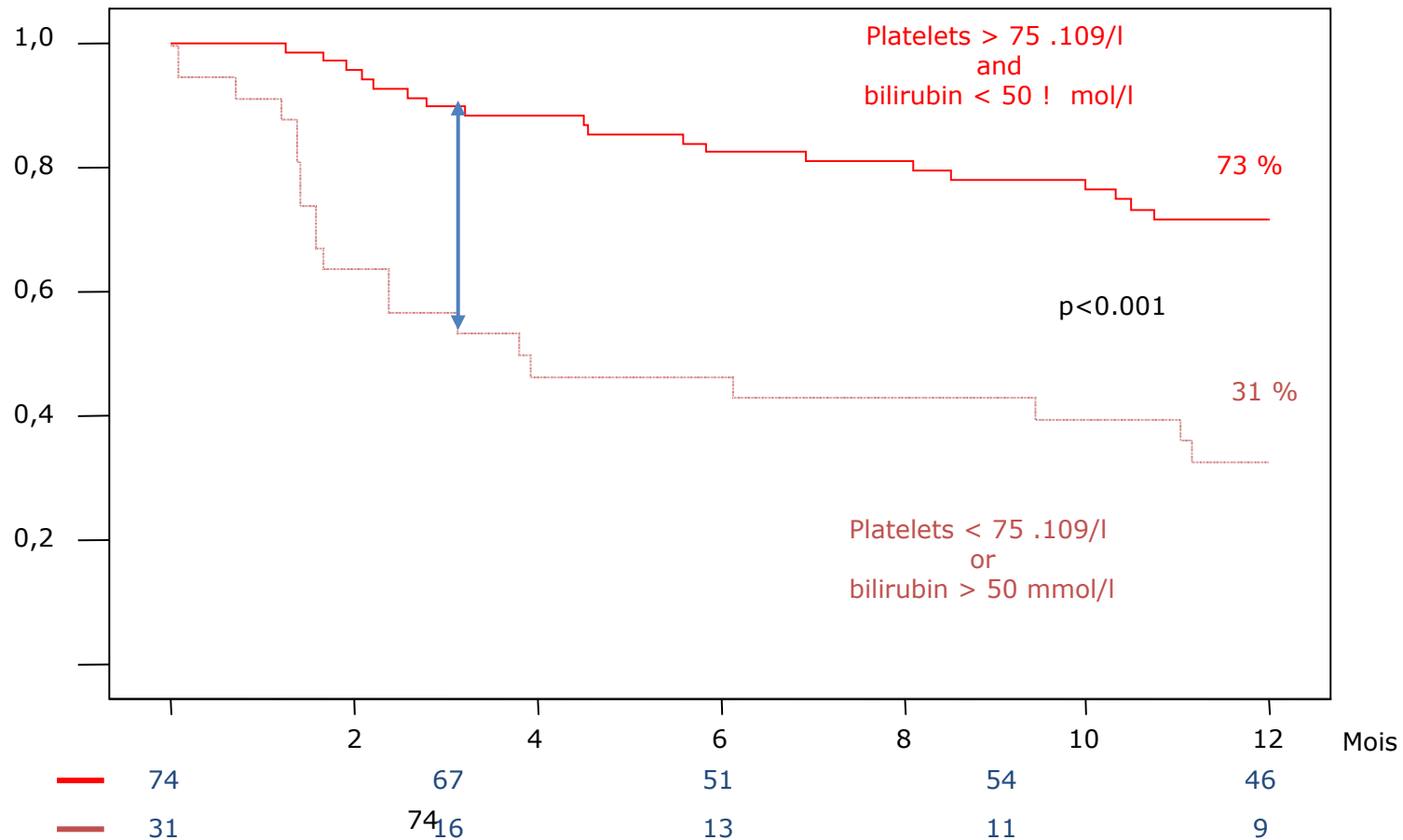
# Covered TIPS in Pts with Refractory Ascites: occurrence of HE



# Sarcopenia related to HE and ascites, TIPS increases muscle mass.



# TIPS in refractory ascites: it's all about patients'selection ...





# TIPS in refractory ascites: it's all about patients'selection ...

Characteristic	TIPS (n = 29)	LVP+A (n = 33)	P value
Sex, male/female, n	17/12	27/6	.06
Age, y	56.7 ± 5.7	56.4 ± 7.9	.868
Weight, kg	67 ± 13	72 ± 13	.132
BMI, kg/m	23.6 ± 4.3	24.3 ± 3.3	.465
Etiology, %			
Alcohol	90	85	1.00
Stopped alcohol use	70	80	1.00
Chronic hepatitis C	3	9	.616
Other	7	6	1.00
History of SBP, %	7	15	.432
History of OHE, %	0	3	1.00
History of variceal bleeding, %	28	30	1.00
History of renal failure, %	21	18	1.00
No. of paracentesis, last 3 mo	4.5 ± 1.4	4.2 ± 1.3	.377
Duration of cirrhosis, y	3.7 ± 4.1	2.9 ± 3.4	.364
Trail making test A, s	71 ± 33	66 ± 44	.614
Bilirubin, $\mu\text{mol/L}$	17.8 ± 10.7	17.5 ± 10.1	.688
INR	1.39 ± 0.27	1.46 ± 0.30	.382
Albumin, g/L	30.7 ± 5.5	33.4 ± 5.4	.06
Serum creatinine, $\mu\text{mol/L}$	84.6 ± 30.1	85.6 ± 21.4	.888
Serum sodium, mmol/L	134 ± 4	132 ± 4	.06
Hemoglobin, g/dL	11.5 ± 1.7	11.8 ± 1.7	.543
Platelets, $10^3/\text{mm}^3$	178 ± 84	188 ± 88	.687
ASAT, UL/N	1.69 ± 0.79	1.63 ± 0.85	.771
ALAT, UL/N	1.09 ± 0.28	1.12 ± 0.38	.711
Child-Pugh score	9.1 ± 1.4	9.0 ± 1.6	.922
Child-Pugh class: B/C, n	19/10	22/11	1.00

# Tips and ascites

Clinical Practice Guidelines

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## EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis<sup>☆</sup>

European Association for the Study of the Liver\*

- Patients with refractory or recurrent ascites (I;1), or those for whom paracentesis is ineffective (e.g. due to the presence of loculated ascites) should be evaluated for TIPS insertion (III;1).
- TIPS insertion is recommended in patients with recurrent ascites (I;1) as it improves survival (I;1) and in patients with refractory ascites as it improve the control of ascites (I;1).
- The use of small-diameter PTFE-covered stents in patients is recommended to reduce the risk of TIPS dysfunction and hepatic encephalopathy with a high risk of hepatic encephalopathy is recommended (I;1).
- Careful selection of patients for elective TIPS insertion is crucial, as is the experience of the centre performing this procedure. TIPS is not recommended in patients with serum bilirubin > 3 mg/dl and a platelet count lower than  $75 \times 10^9/L$ , current hepatic encephalopathy grade  $\geq 2$  or chronic hepatic encephalopathy, concomitant active infection, progressive renal failure, severe systolic or diastolic dysfunction, or pulmonary hypertension (III;1).

# 6 months after...

- TIPS effective
- Disappearance of ascites
- Diuretics stopped
- Not listed for LT
- Child A
- Screening for HCC

