Refractory ascites

Hepatology Day

Beirut, May 28, 2011

Alexandre Pariente, Pau, France

Thanks to Christophe Bureau, Toulouse

Plan

- Definition
- Incidence and Prognosis
- General Measures
- Specific measures
  - Liver Transplantation
  - Large Volume Paracentesis (LVP)
  - Transjugular Intra Hepatic Shunt (TIPS)
- Recommendations
- 2 news about βblockers and clonidine

Definition

- “Ascites that cannot be mobilized or the early recurrence of which cannot be prevented by medical therapy”
- **1 Diuretic-resistant ascites :** lack of response to dietary sodium and intensive diuretic treatment (400 mg of spironolactone and 160 mg of furosemide)
- **2 Diuretic-intractable ascites :** diuretics can not be used because of the development of complications (encephalopathy, renal impairment, hyponatremia, hyperkaliemia or hypokalemia…) that preclude the use of an effective diuretic dosage

Moore KP et al. Hepatology 2003;38:258-66

Definition

Treatment duration : at least 1 week

Lack of response : mean weight loss < 0.8 kg over 4 days and urinary sodium output less than the sodium intake

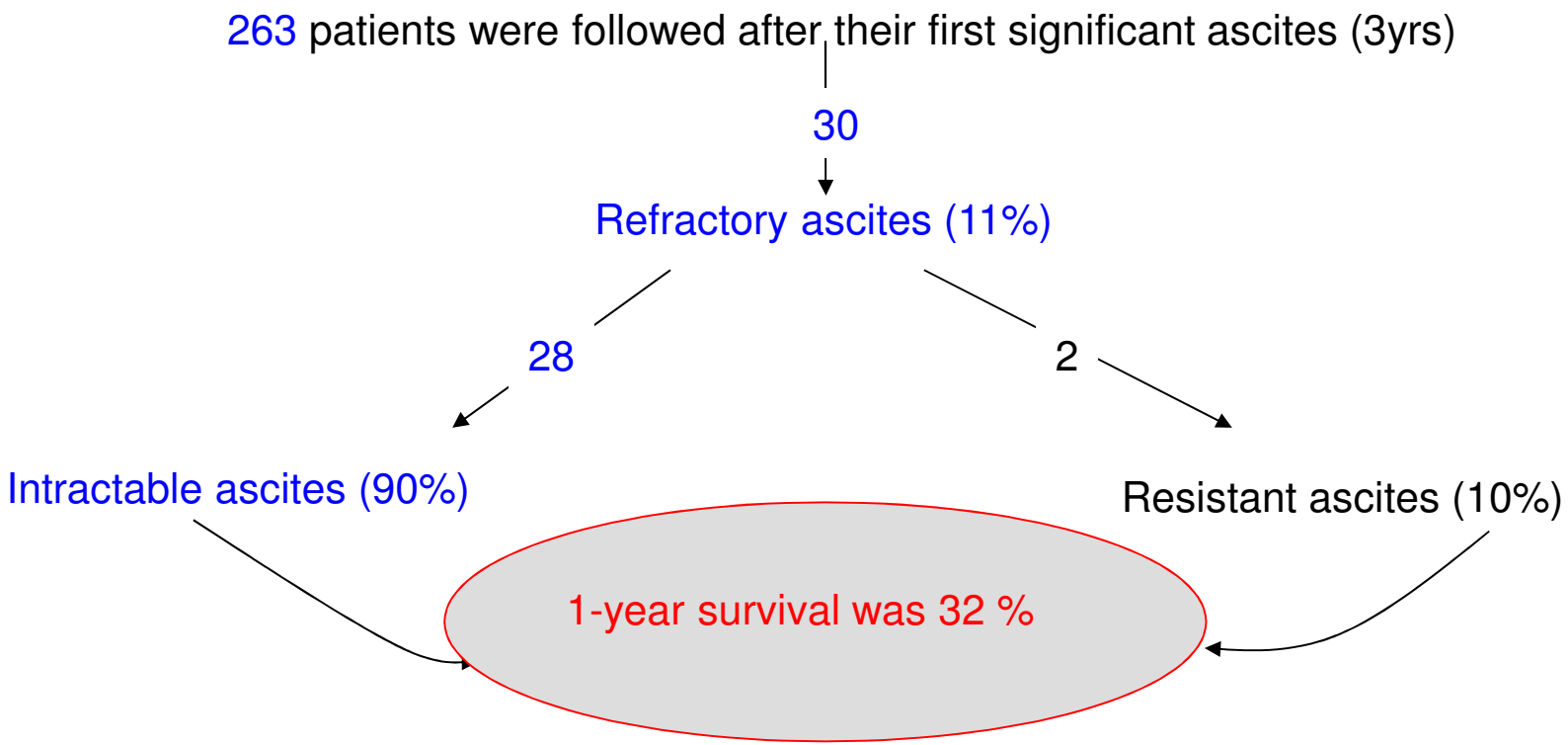
Early ascites recurrence : recurrence of grade 2 or 3 ascites within 4 weeks after initial mobilization

Diuretic-induced complications :

- encephalopathy in the absence of any other precipitating factors
- ↑ serum creatinine by >100 % to a value >2 mg/dl (177 uM
- ↓serum sodium by >10 mmol to a serum sodium <125 mmol/l
- serum potassium < 3 mmol/l or > 6 mmol/l

Moore KP et al. Hepatology 2003;38:258-66

RA is rare and severe



Planas R et al. Clin Gastroenterol Hepatol 2006;4:1385

…and in France

- 93 % intractable-ascites
- 7 % resistant-ascites
- 1 yr survival : 52 %
- Survival predictive factors
  - –Age, HCC, diabetes, persistance of alcohol

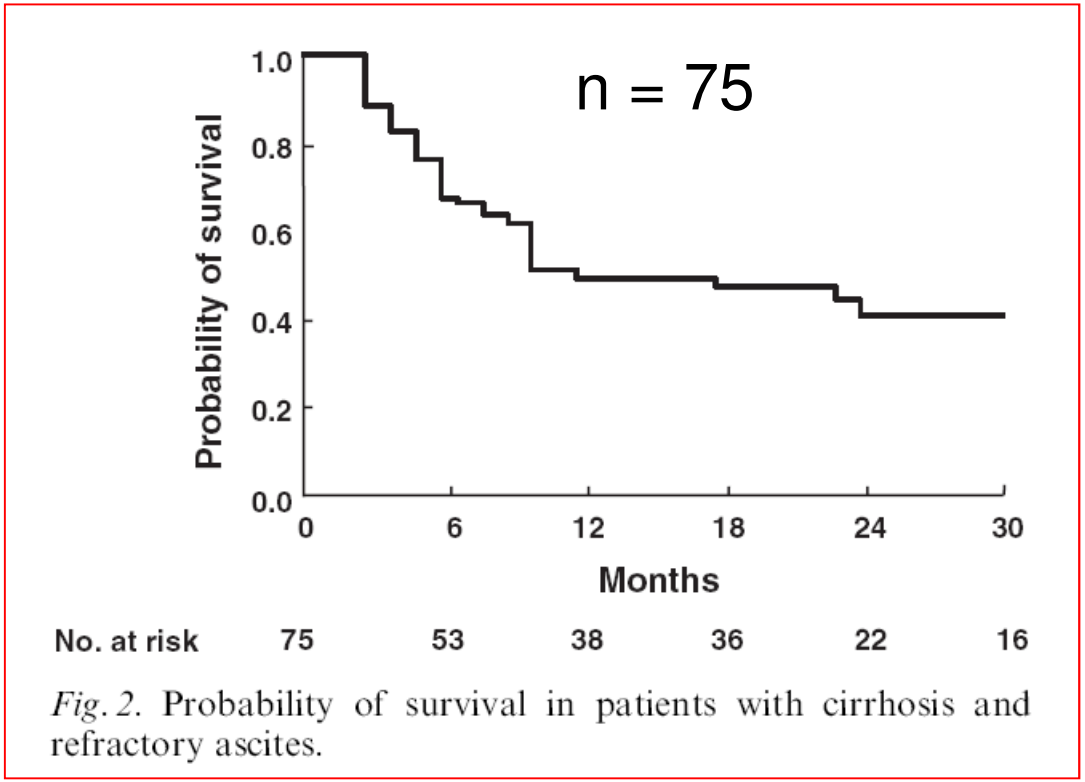


Fig. 2. Probability of survival in patients with cirrhosis and refractory ascites.

Moreau R et al. Liver Int 2004;24:467

Don’t forget…

- To eliminate other causes of « refractory » ascites (cardiac ascites, pancreatitis, tuberculosis, malignant ascites and hypothyroidism…)
- To evaluate the heart
- To look for PVT and HCC
- To measure natriuresis

So, Refractory Ascites is

- diuretic-intractable ascites in most cases
- a severe complication occuring in 10 % of patients
- resulting in poor quality of life, high risk of spontaneous bacterial peritonitis and hepatorenal syndrome
- a sign of end stage liver disease associated with poor survival

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General measures

- Ascitic fluid should be examined to rule out SBP
- The cause of cirrhosis must be treated (alcohol withdrawal, antiviral therapy etc…)
- A precipitating factor must be looked for (PVT,HCC)
- Patients should be maintained on a low sodium diet (90 mmol/d)
- Diuretics can be discontinued (sodium urinary excretion <30 mmol/d)

  SBP and HRS must be prevented (nephrotoxic antibiotics, NSAID's, hypotensive agents, iodine contrast media)

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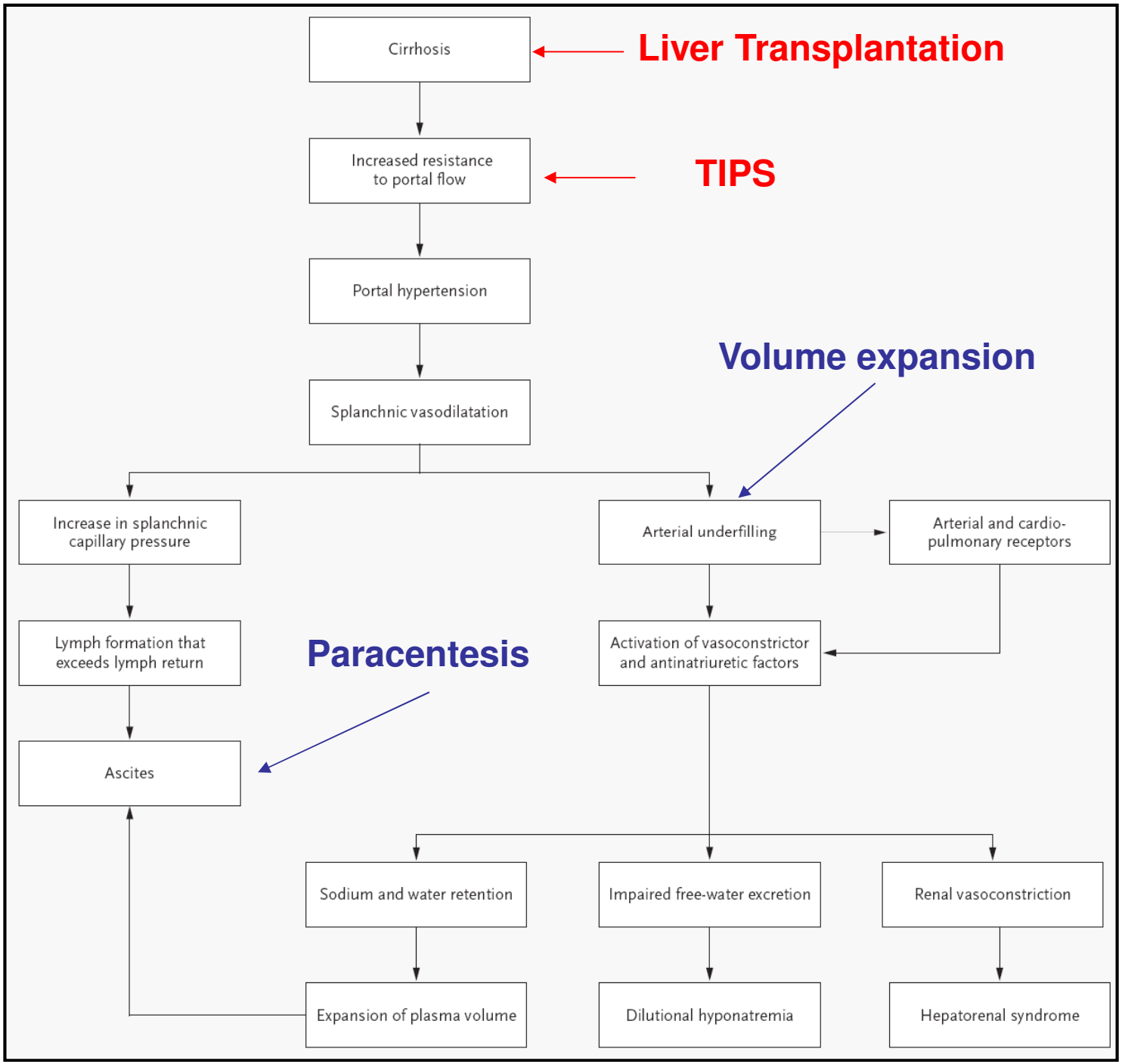
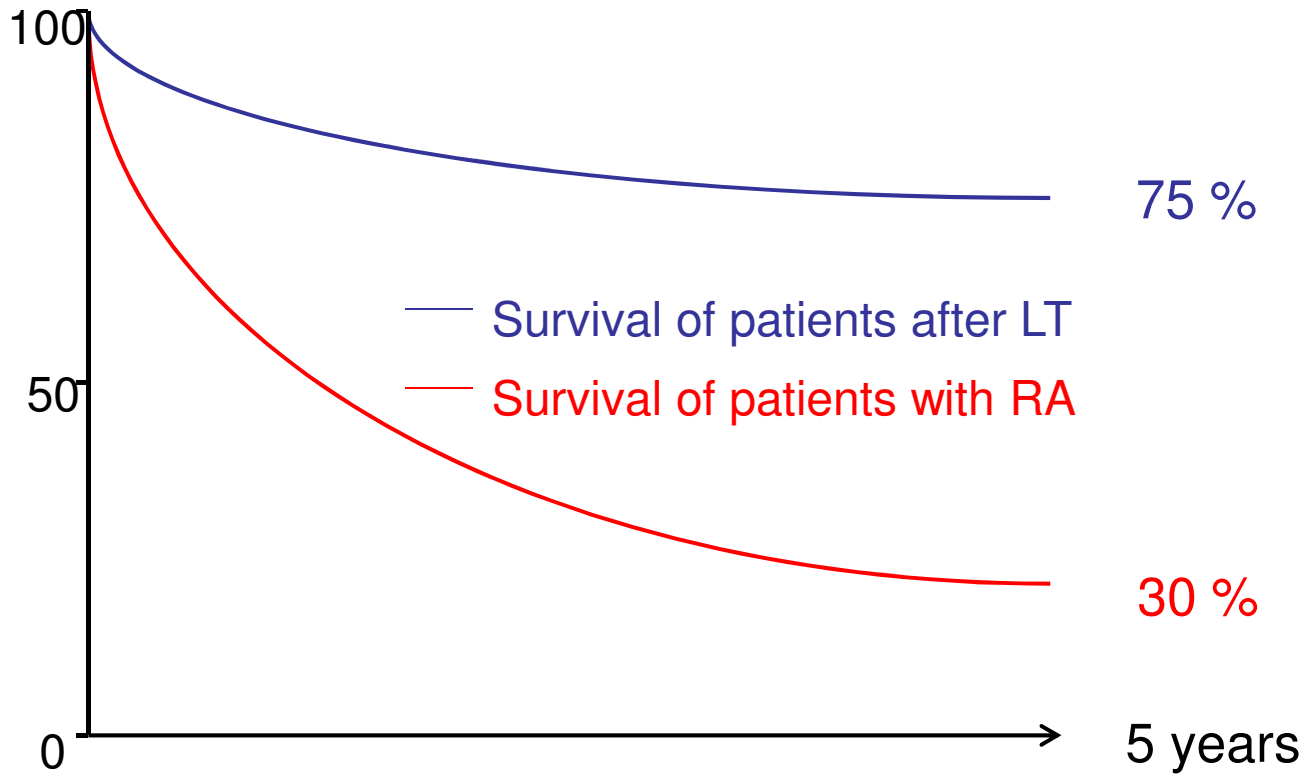
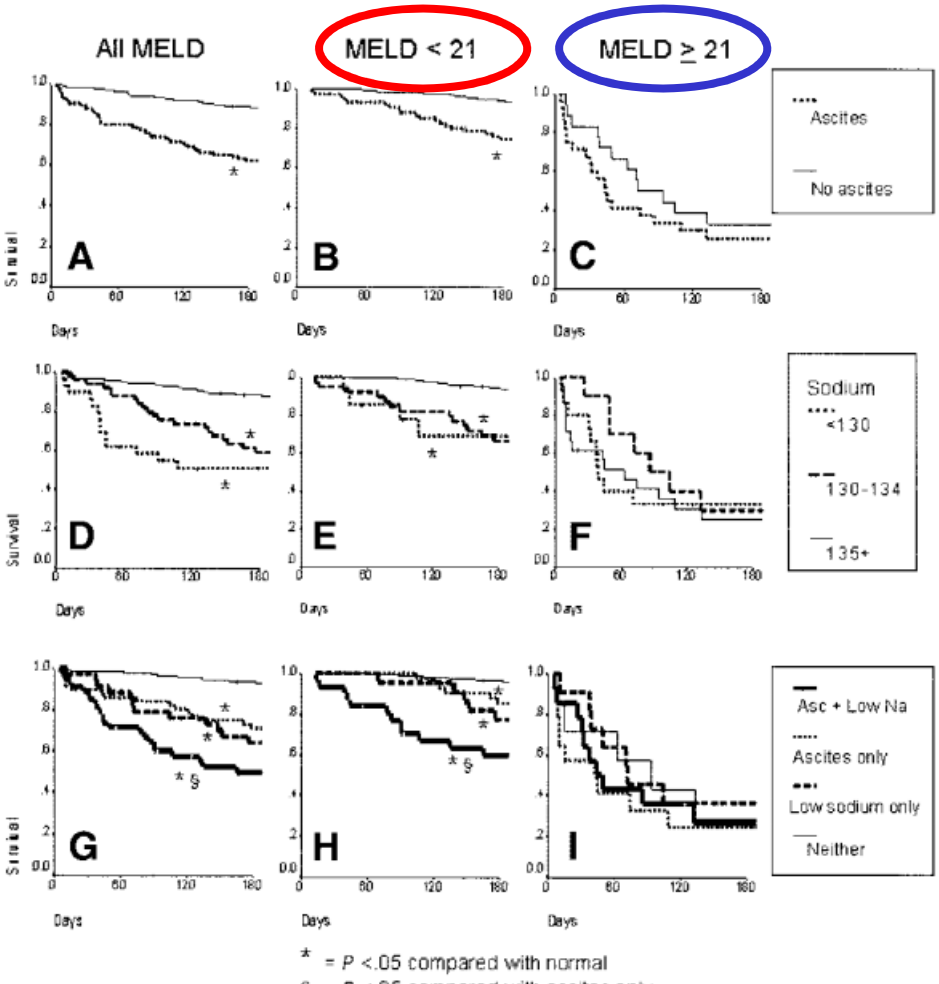

Cirrhosis
Liver Transplantation
Increased resistance to portal flow
TIPS
Portal hypertension
Volume expansion
Splanchnic vasodilatation
Increase in splanchnic capillary pressure
Arterial underfilling
Arterial and cardio-pulmonary receptors
Lymph formation that exceeds lymph return
Paracentesis
Activation of vasoconstrictor and antinatriuretic factors
Ascites
Sodium and water retention
Impaired free-water excretion
Renal vasoconstriction
Expansion of plasma volume
Dilutional hyponatremia
Hepatorenal syndrome

Liver Transplantation



MELD underestimates early mortality in patients with Refractory Ascites

- 507 cirrhotics on TList
- 61/296 (21%) death < J180
  - Mean MELD 21



Heuman DM et al. Hepatology 2005;40:802-10

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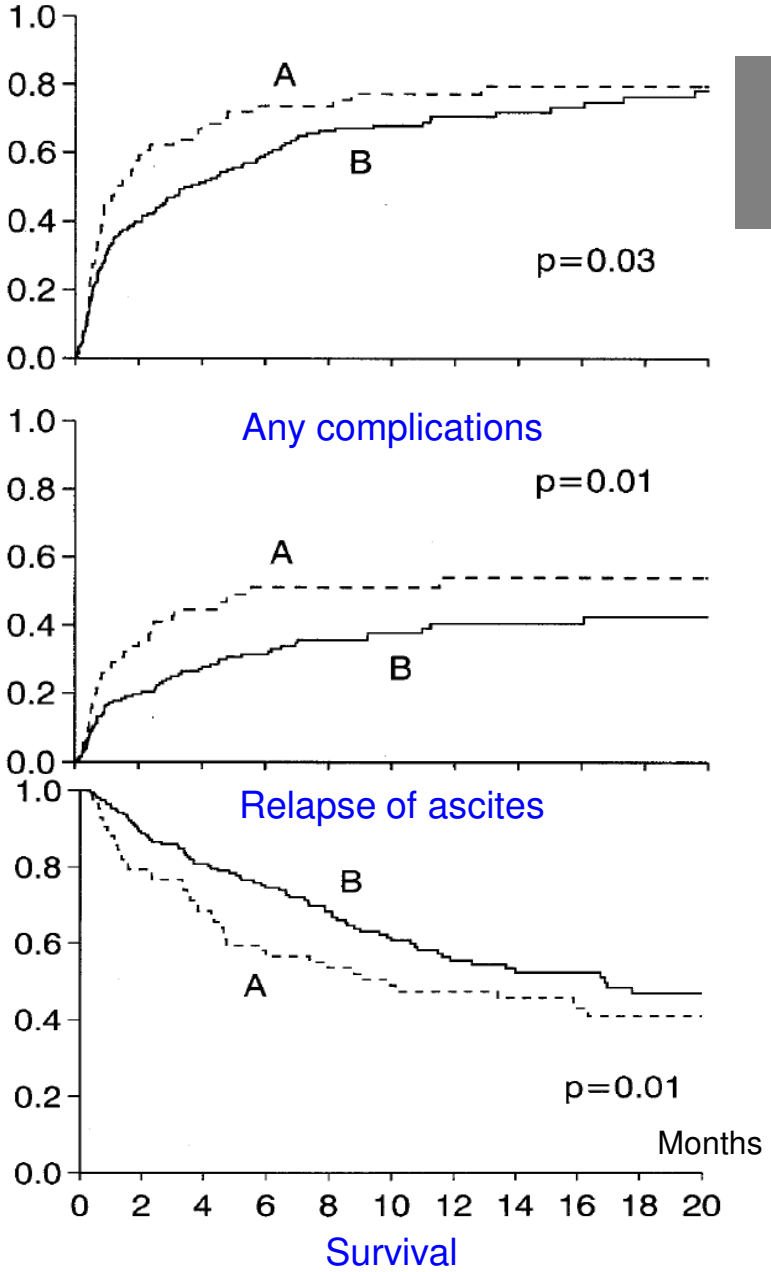
  - Vasocontrictors
  - Beta-blockers

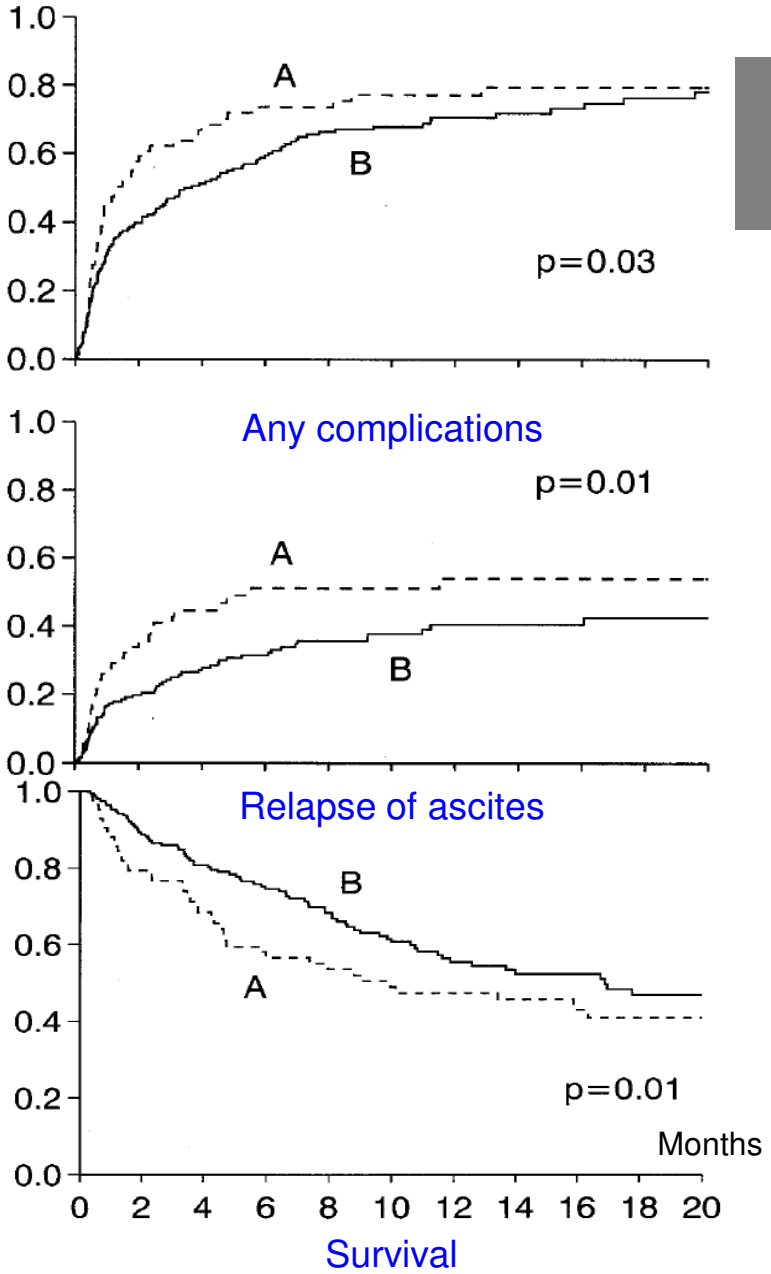
LVP and post-paracentesis induced circulatory dysfunction



A : Patients with circulatory dysfunction
B : Patients without circulatory dysfunction

Ginès P et al Gastroenterology 1996;111:1002

LVP and post-paracentesis induced circulatory dysfunction



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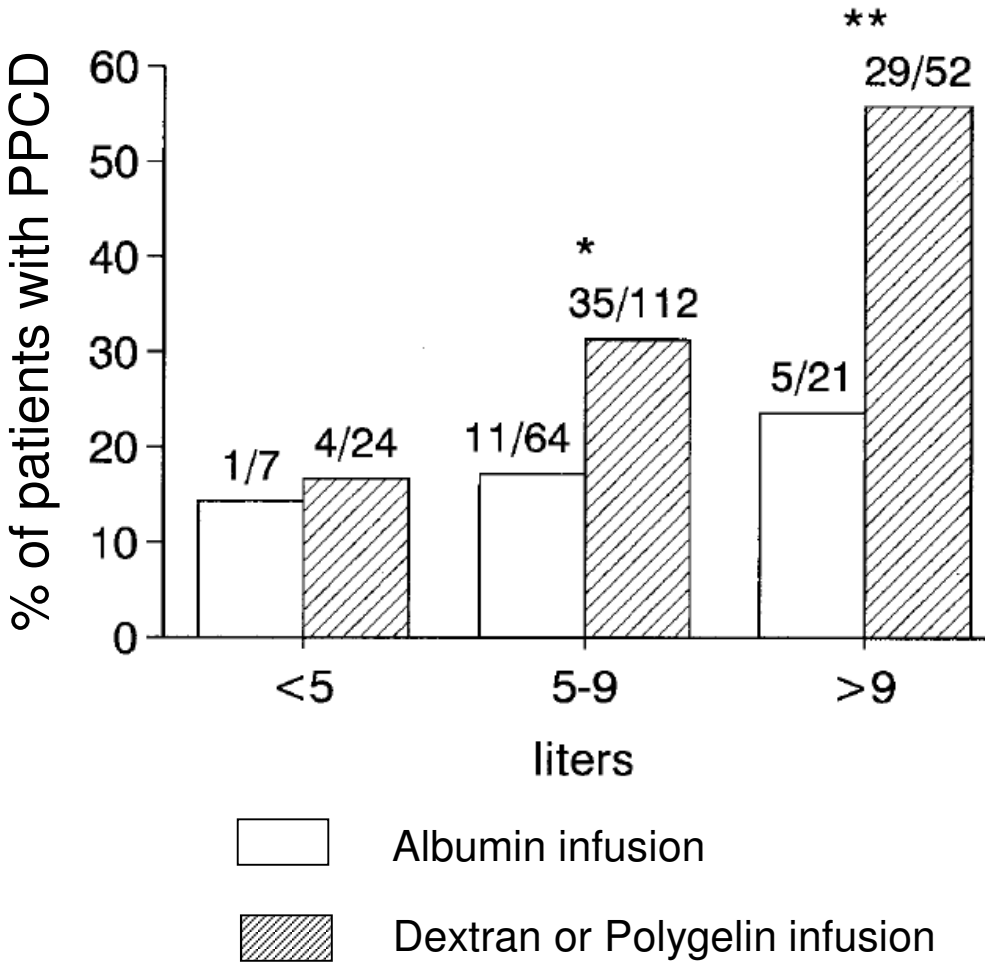

Ginès P et al Gastroenterology 1996;111:1002

Diuretics

- Inefficacy in > 90% of patients
  - Stop definitely if complications
  - Pursue if natriuresis is > 30 mM/d

AASLD. J Hepatol 2010;53:397-417

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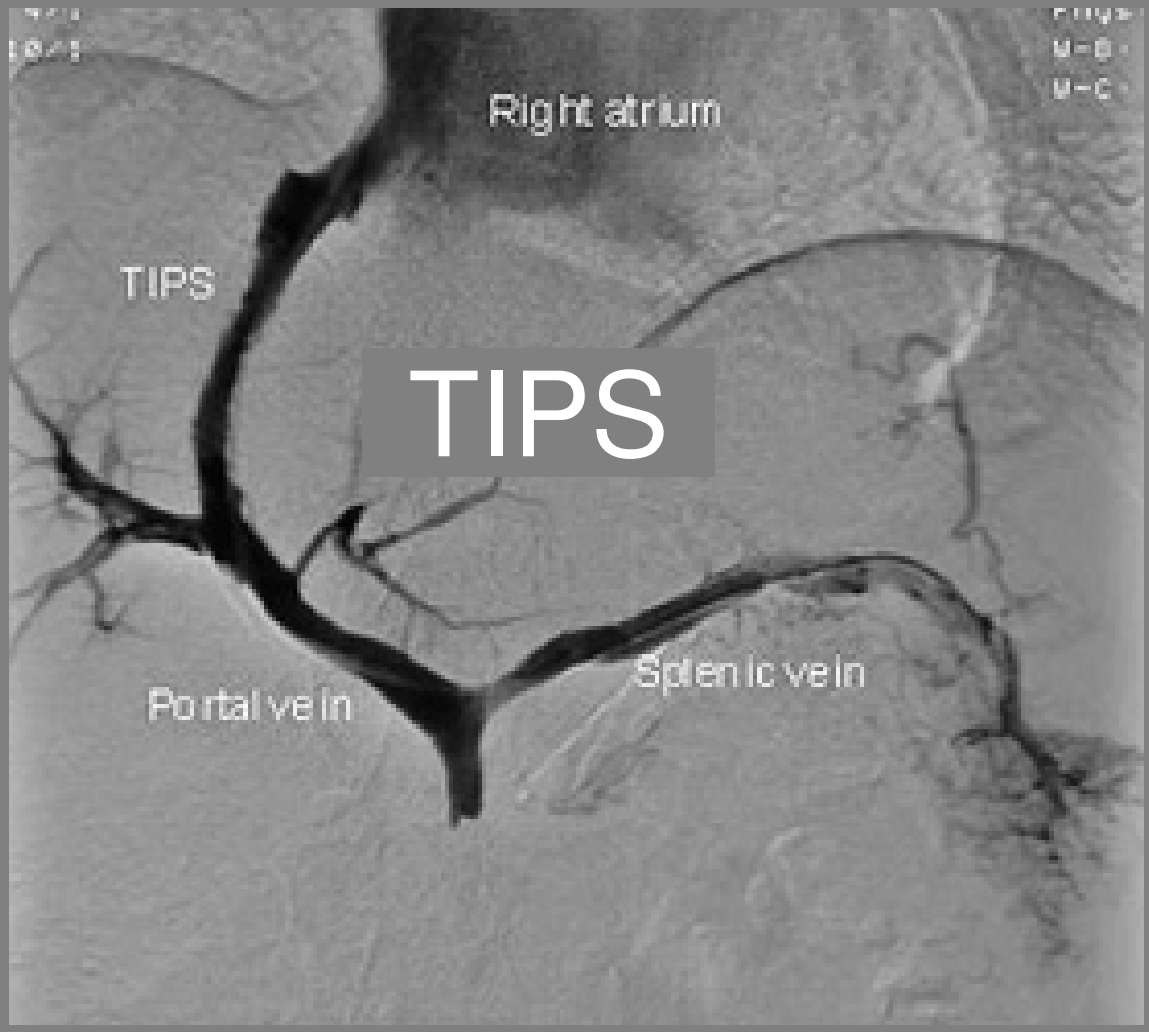
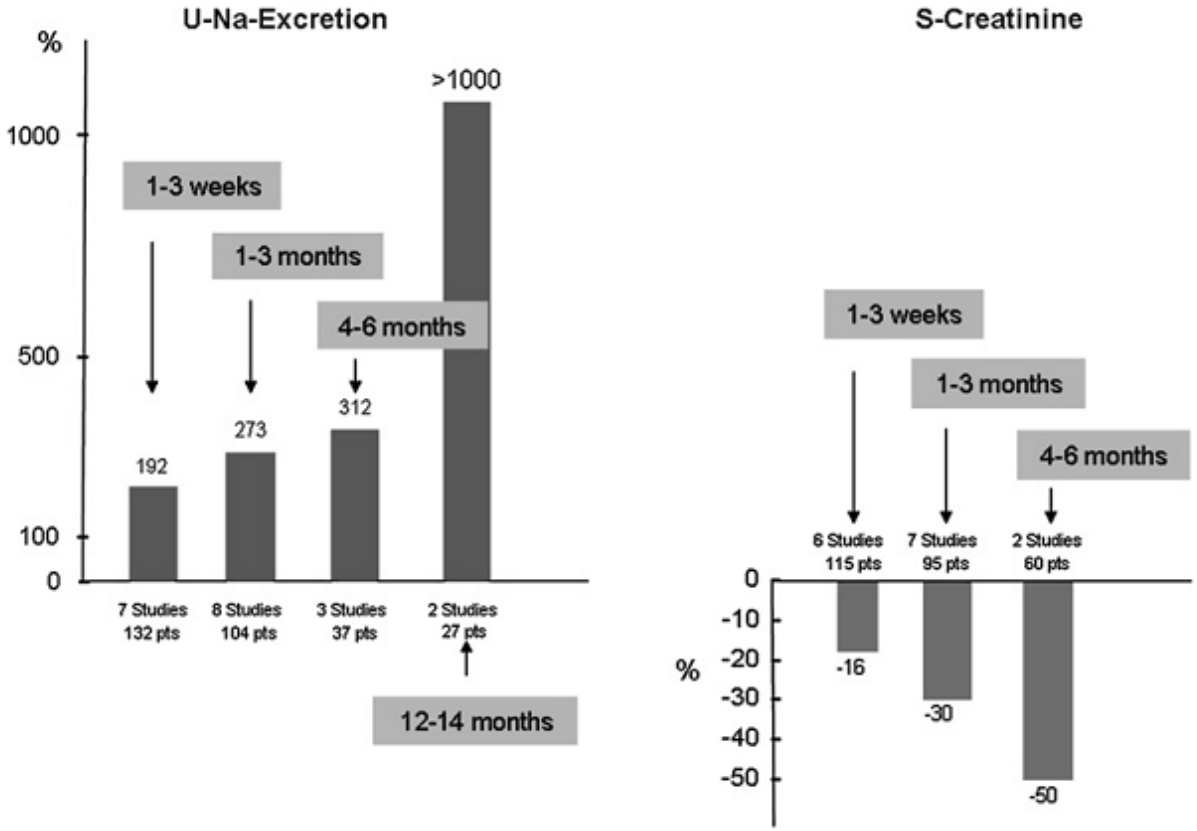
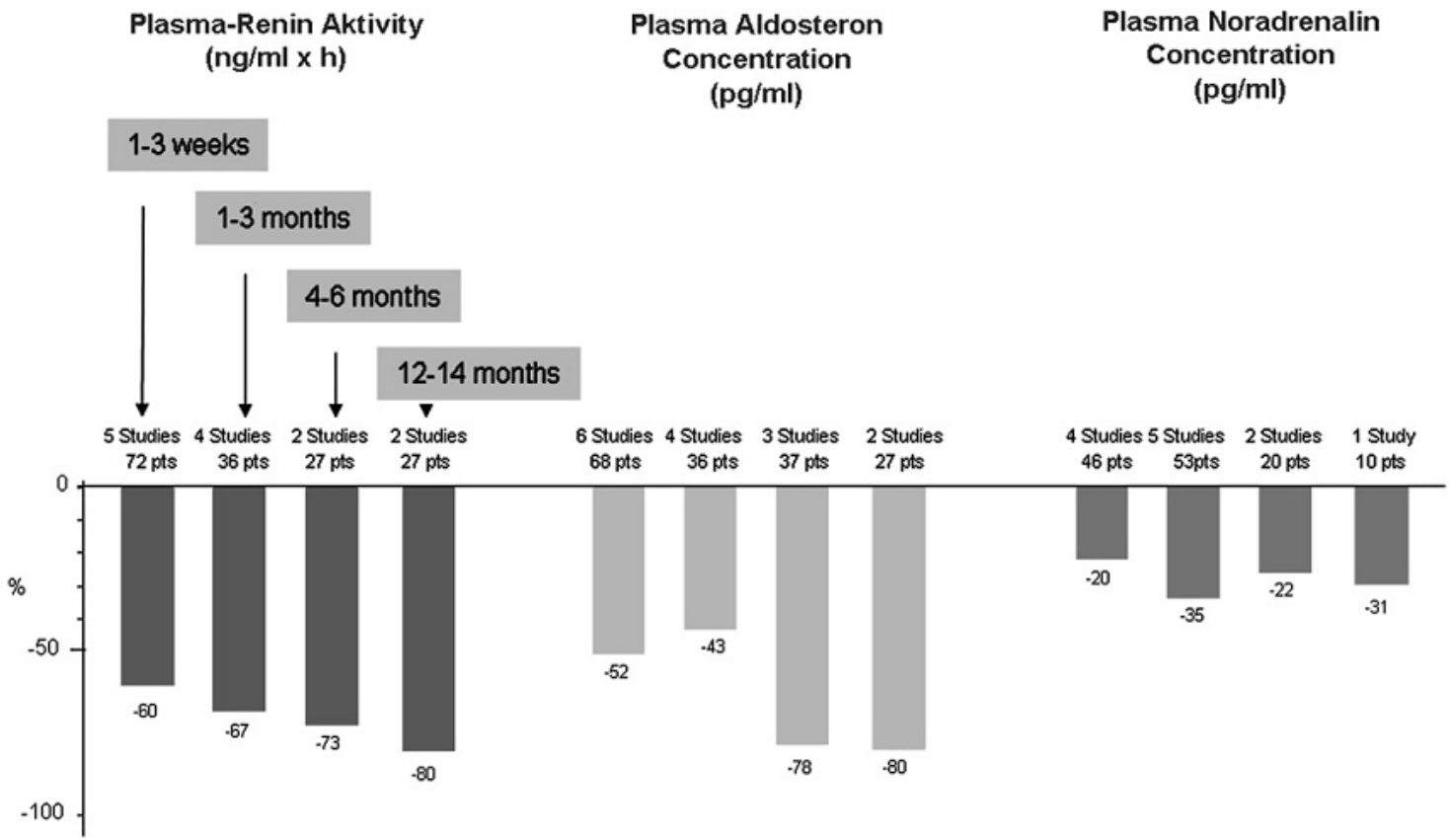

Right atrium
TIPS
TIPS
Portal vein
Splenic vein

TIPS effects



Rössle M, Gerbes AL. Gut 2010;59:988-1000

TIPS effects [2]



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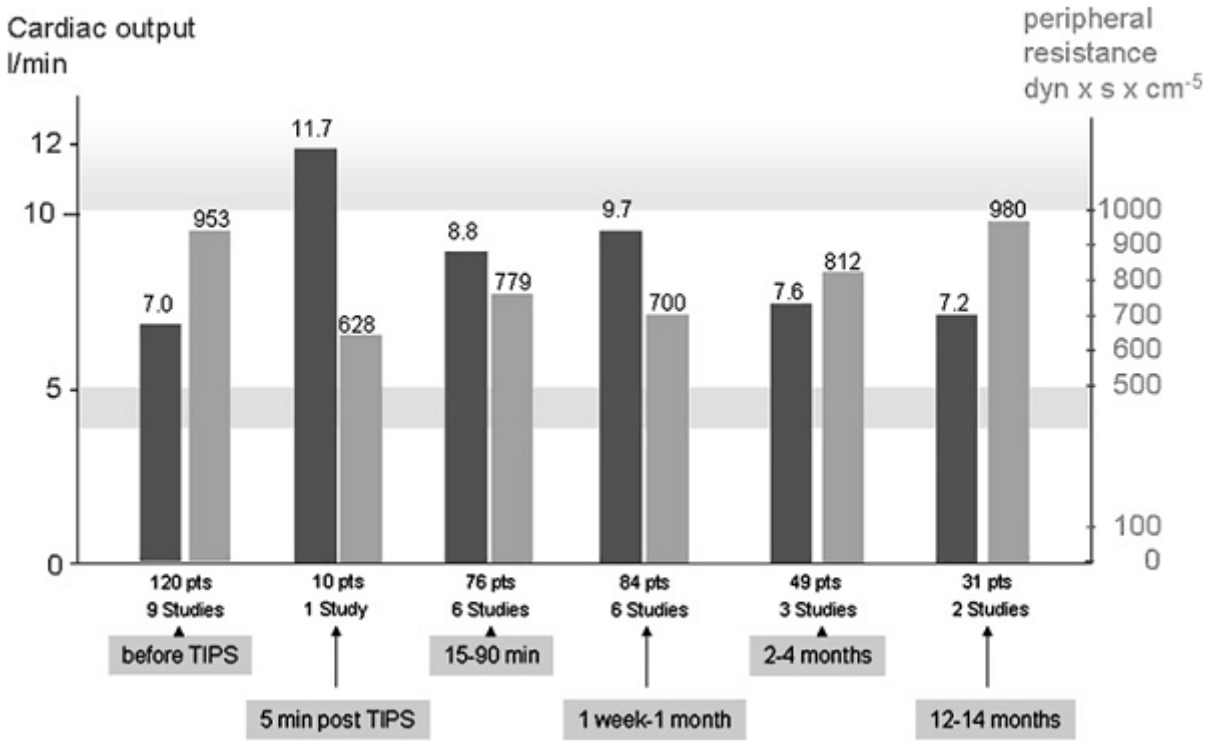
TIPS effects [3]



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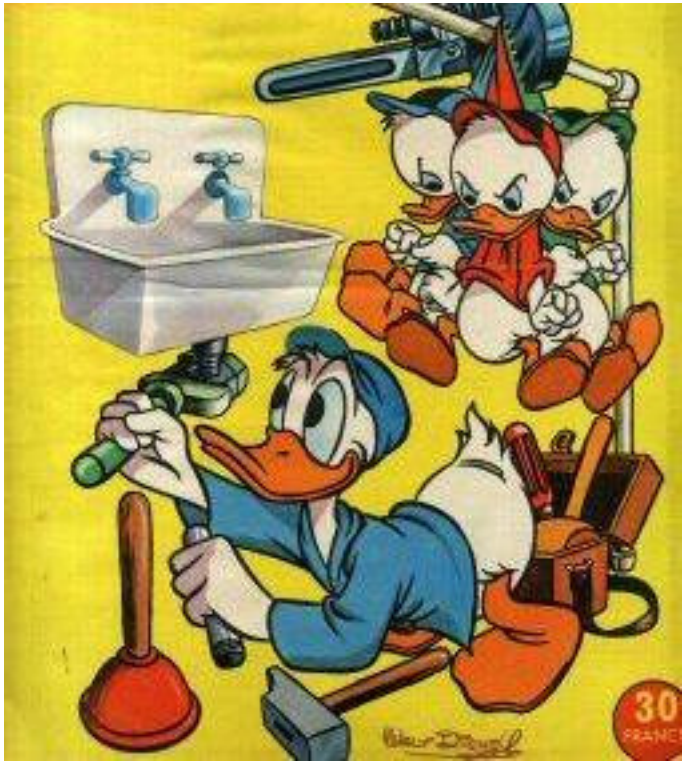
Paracentesis

or TIPS ?

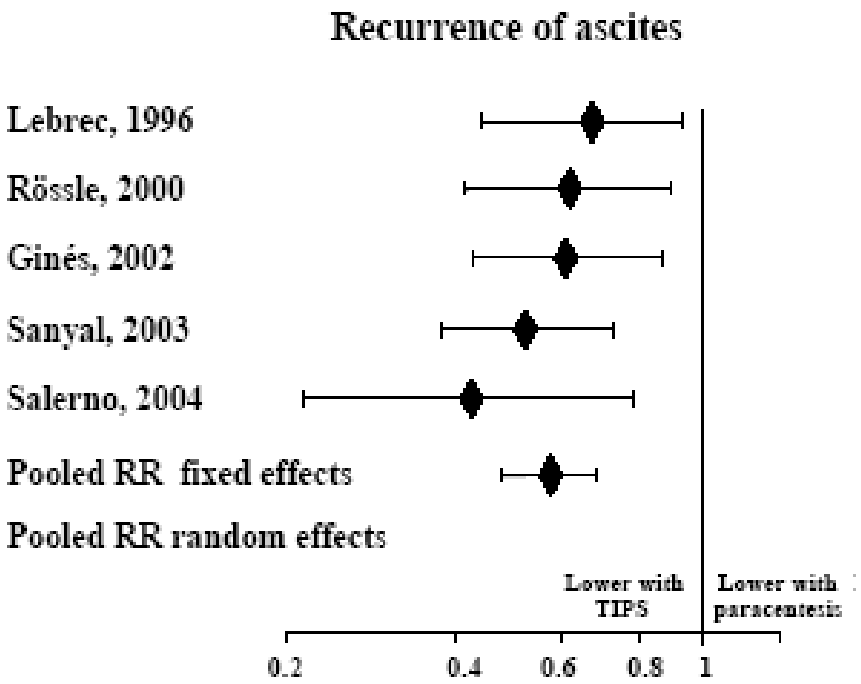


TIPS vs PA

5 trials, 4 metaanalyses

N=330

42 % vs 80 %



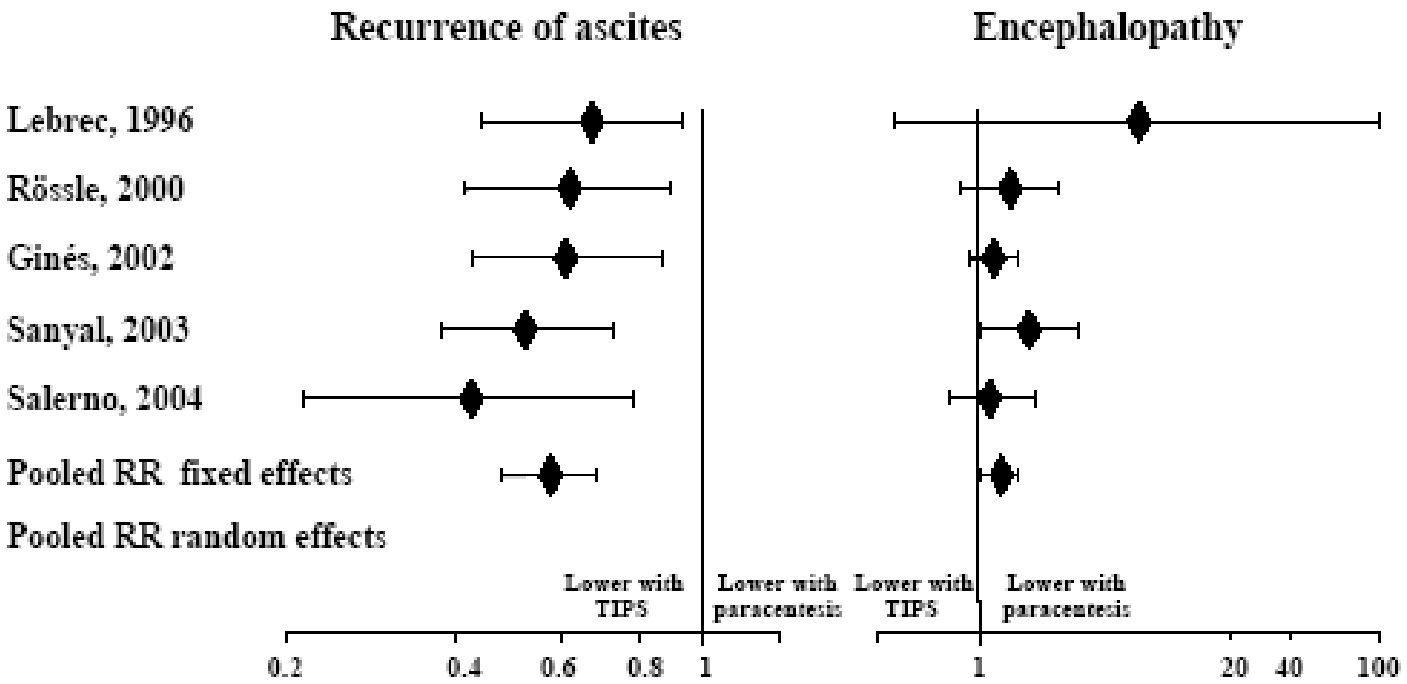
Albillos A et al. J Hepatol 2005;43:986

TIPS vs PA

5 trials, 4 metaanalyses

N=330

54 % vs 36 %



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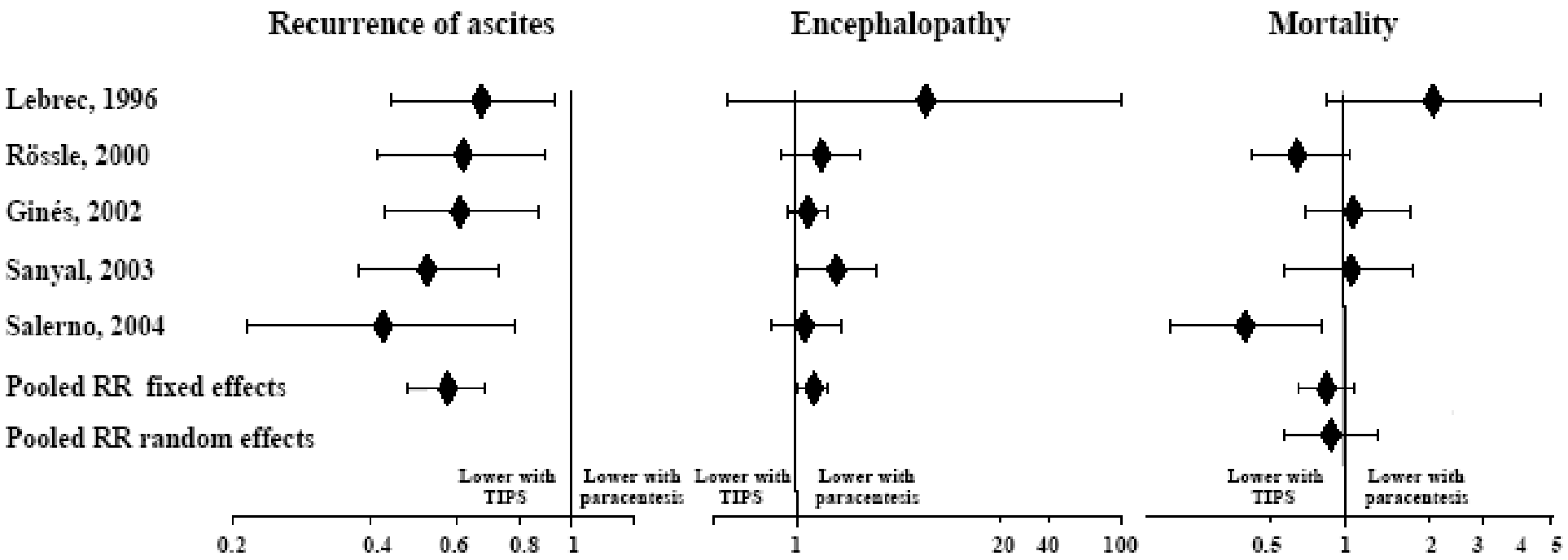
TIPS vs PA

5 trials, 4 metaanalyses

N=330

46 % vs 50 %



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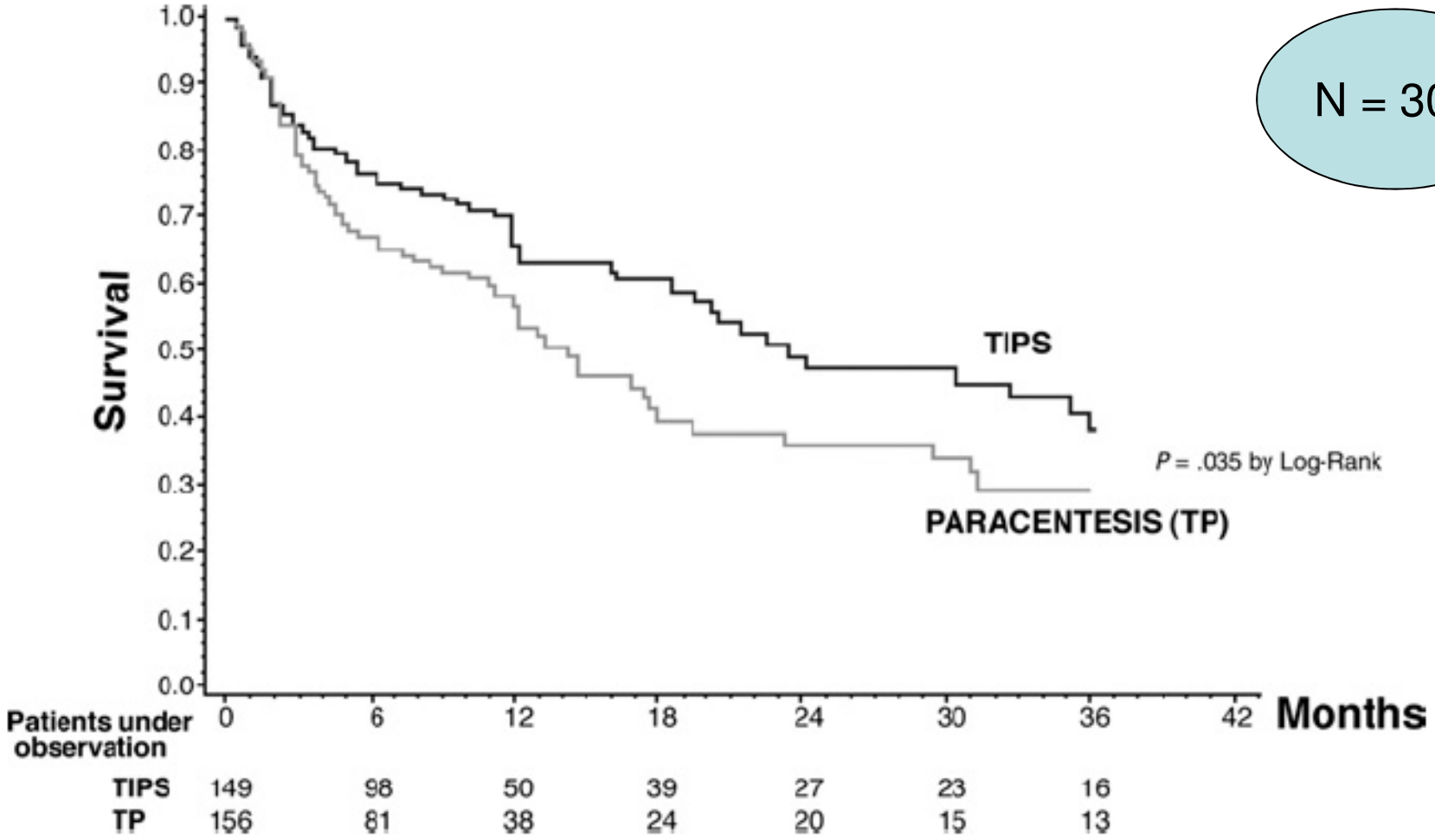
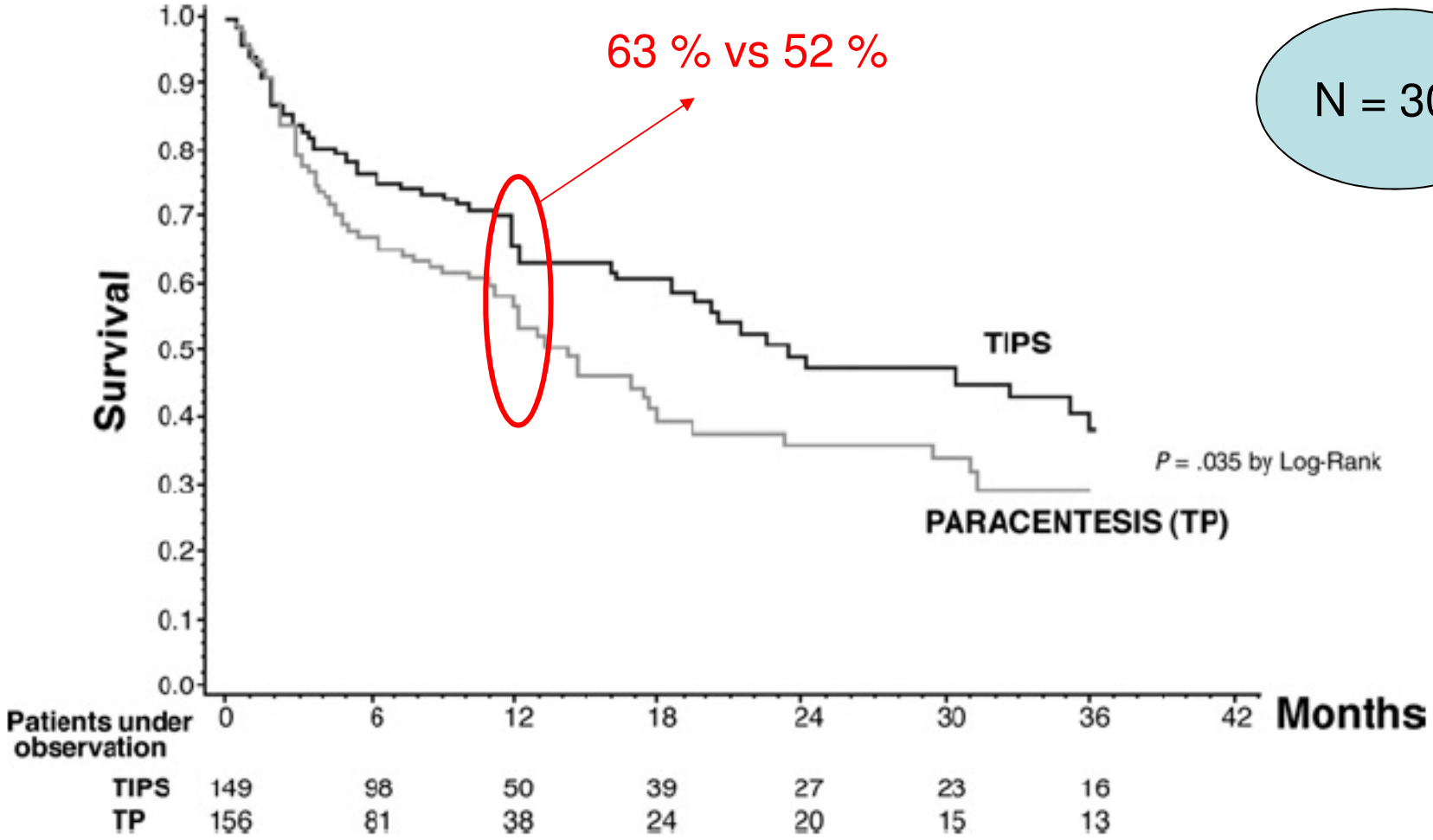
Meta-analysis according to individual data



Cumulative probability of transplant-free survival according to treatment allocation

Salerno F et al. Gastroenterology 2007;133:825

Meta-analysis according to individual data



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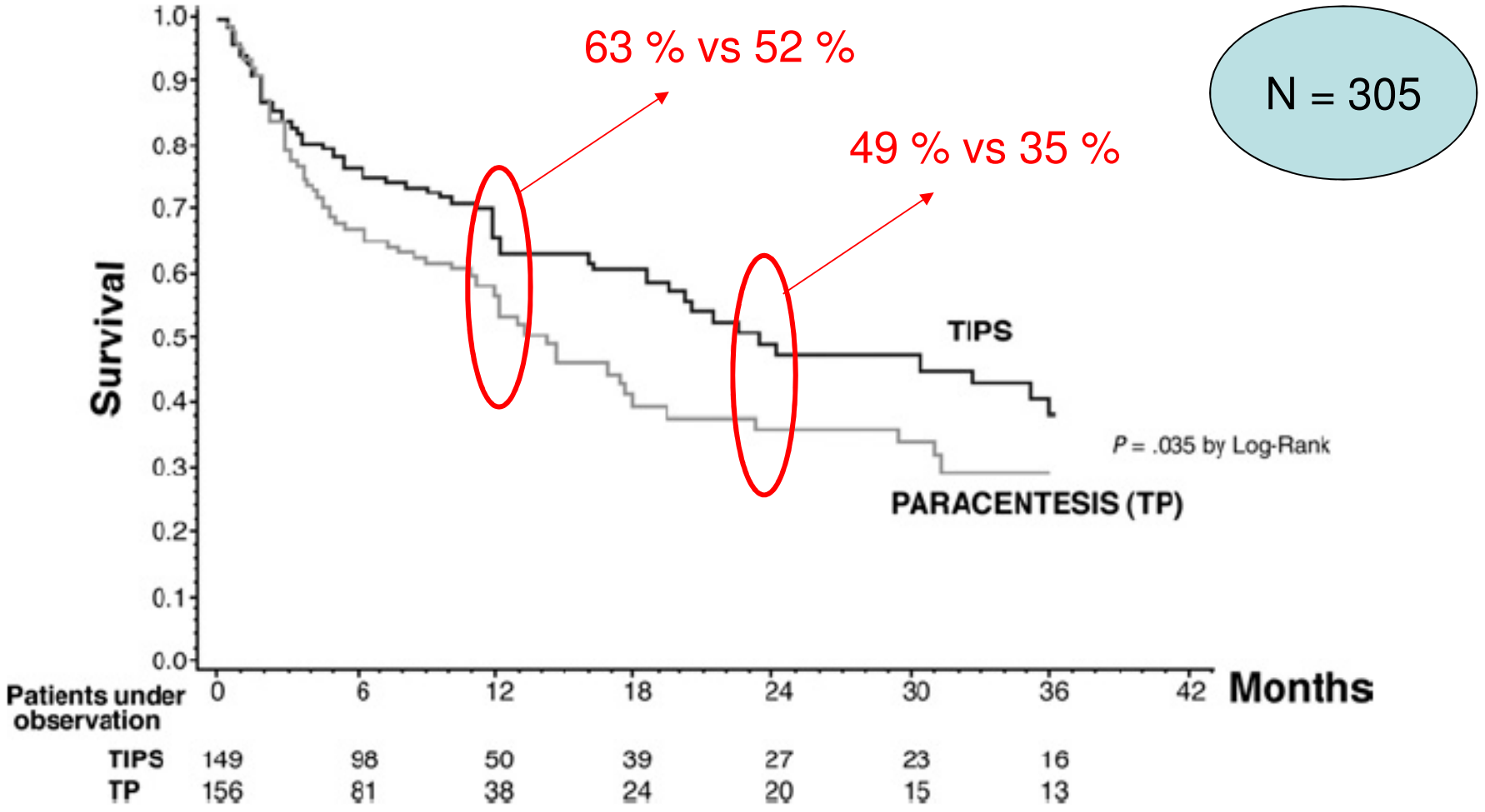

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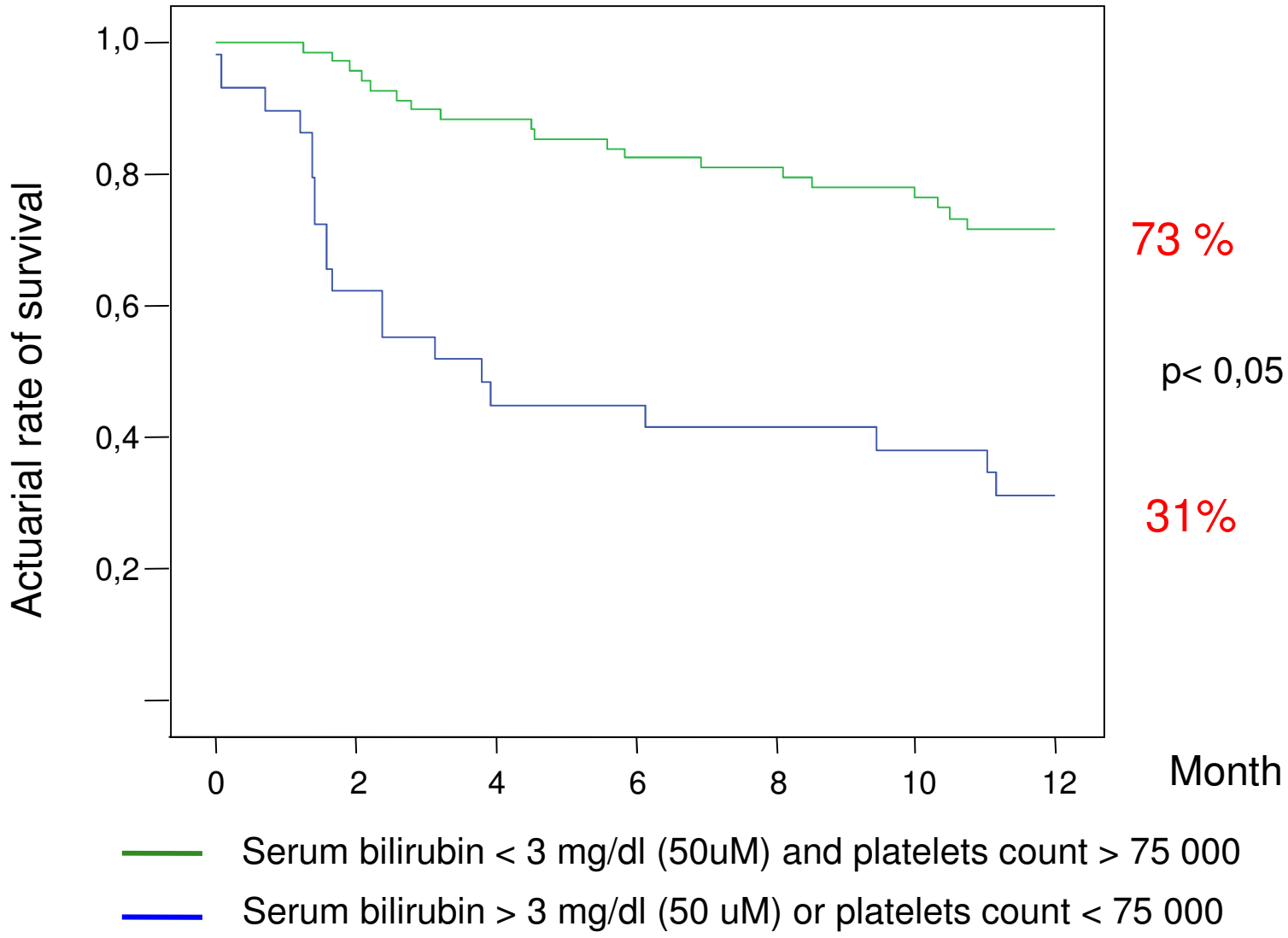
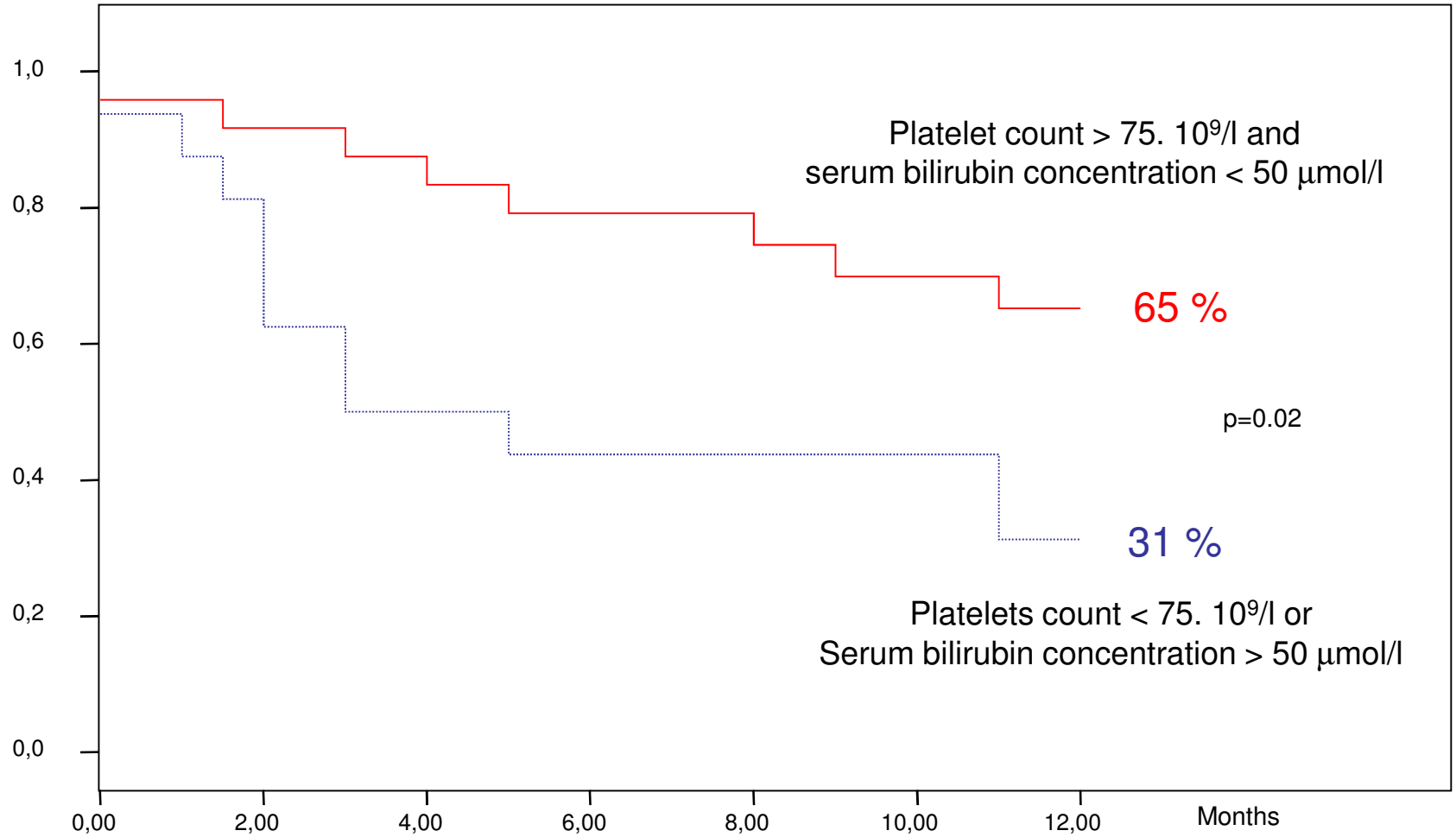
1-year survival in 105 patients treated by TIPS for RA



Bureau C et al. J Hepatol 2011

Prospective validation



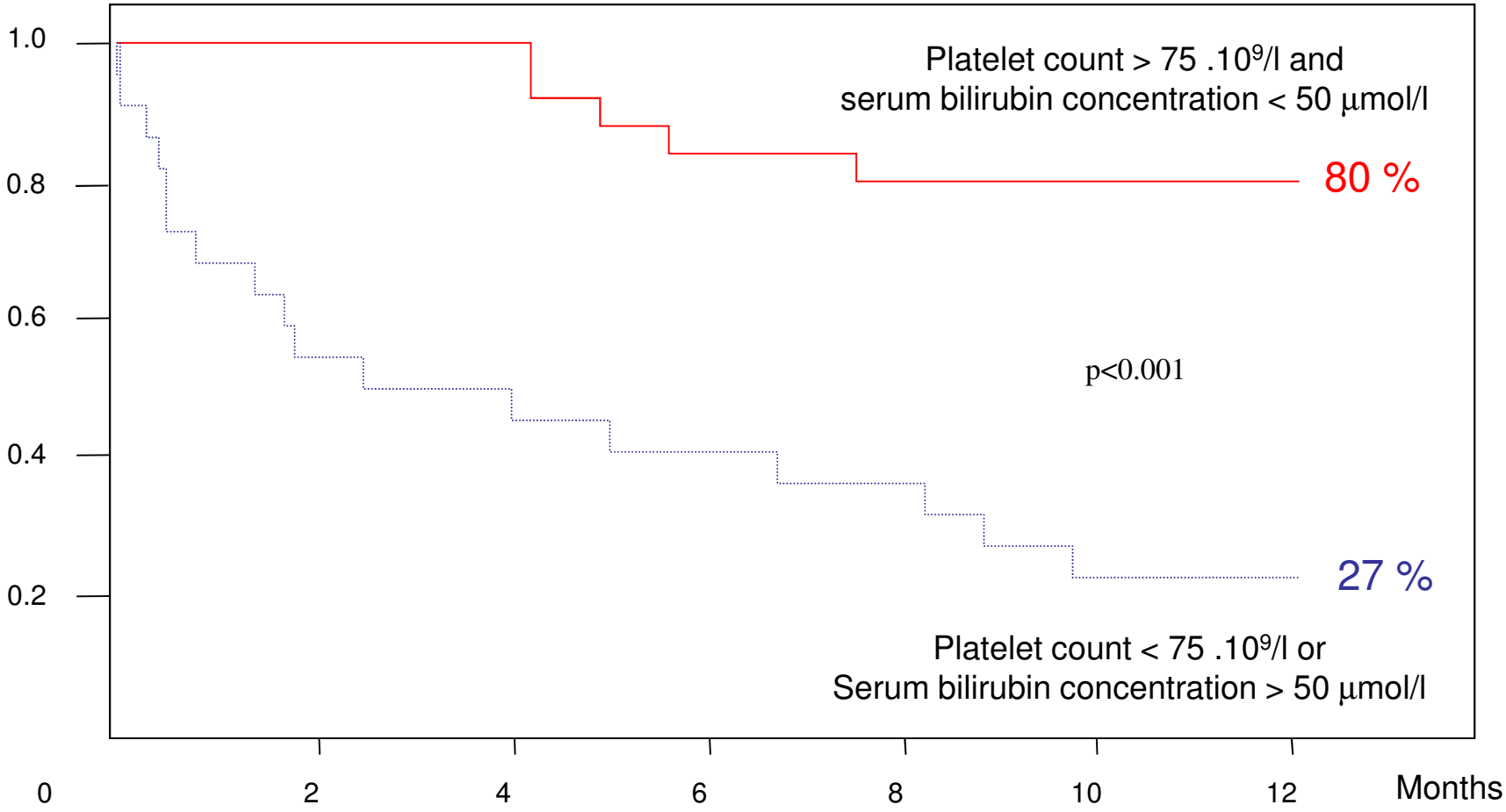
AUROC - Bilirubine 0.668
- Plaquettes 0.823

< 50 µmol/l bilirubine : sensibilité 95 % - spécificité of 31 %

Plaquettes > 75 000 : sensibilité 95 %, spécificité 32 %

External validation (Barcelone)

Figure 4: Actuarial rates of survival in the 40 patients with cirrhosis and refractory ascites treated with TIPS according to serum bilirubin concentration and platelet count



AUROC - Bilirubine 0.803
- Plaquettes 0.750

< 50 µmol/l bilirubine : sensibilité 89 % - spécificité of 46 %

Plaquettes > 75 000 : sensibilité 77 %, spécificité 68 %

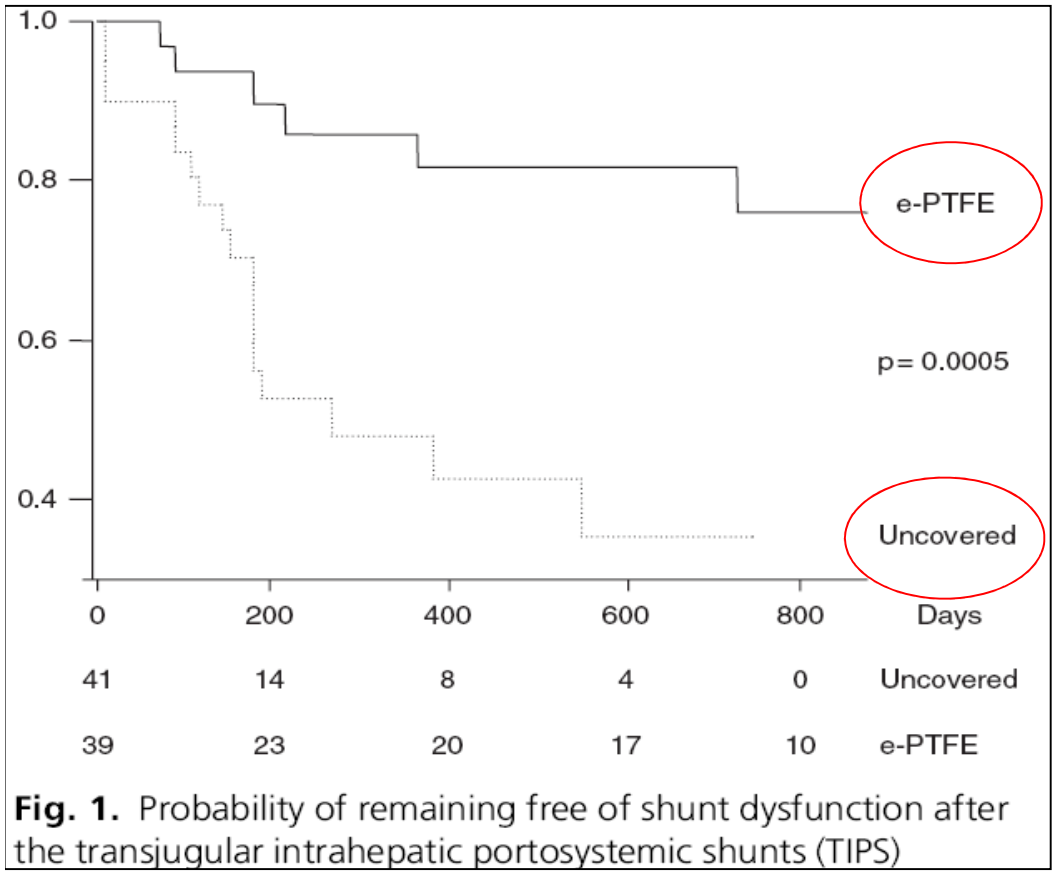
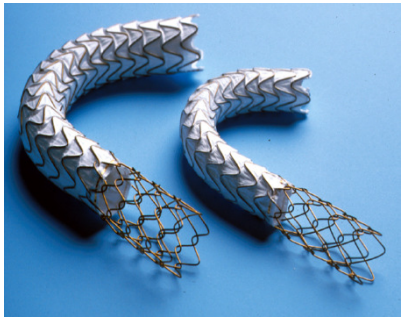


Fig. 1. Probability of remaining free of shunt dysfunction after the transjugular intrahepatic portosystemic shunts (TIPS)



Covered stents for TIPS

C Bureau et al. Gastroenterology 2004

Covered stents for TIPS

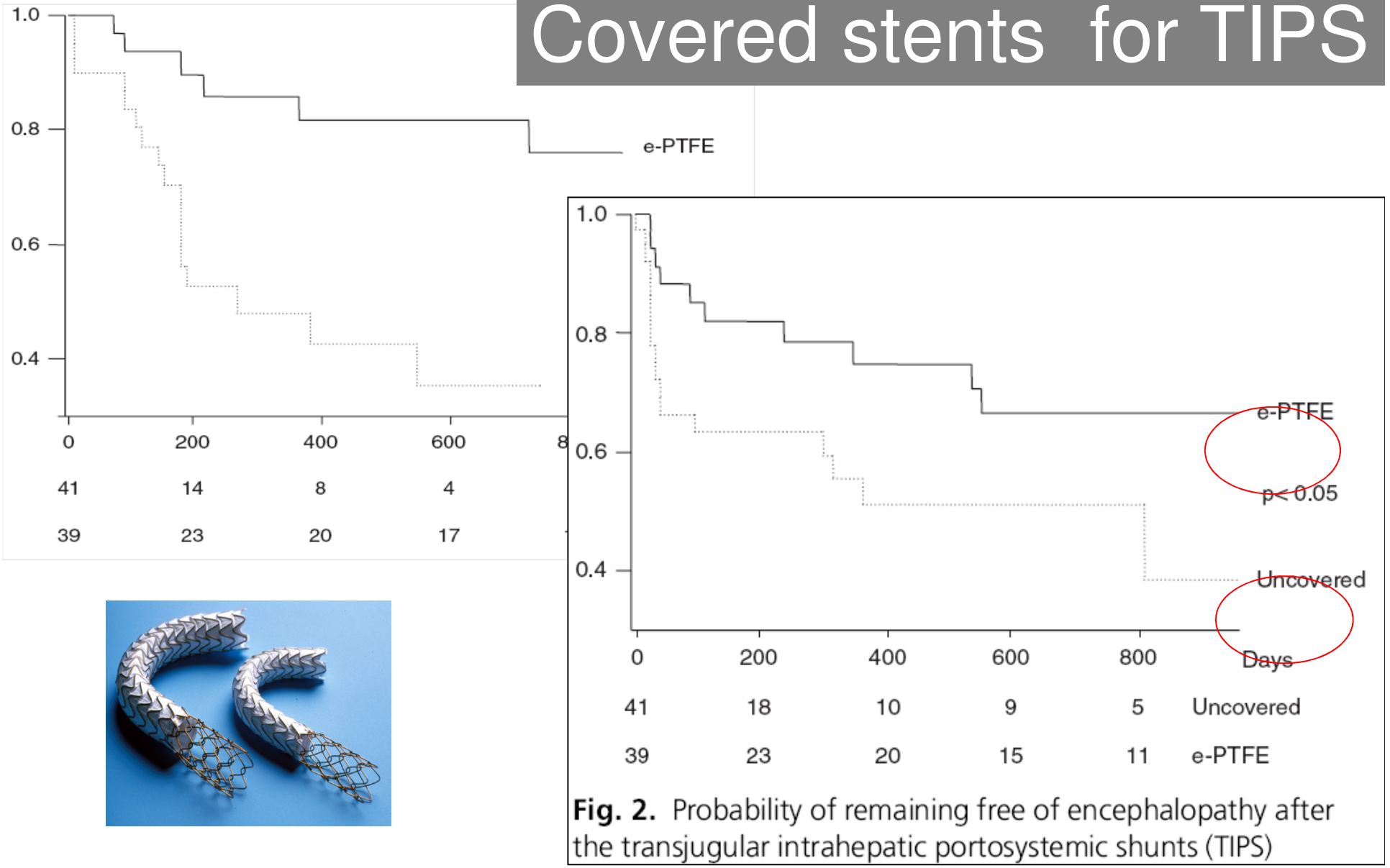


Fig. 2. Probability of remaining free of encephalopathy after the transjugular intrahepatic portosystemic shunts (TIPS)

Bureau C et al. Liver International 2007

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Recommendations

- Repeated LVP with albumin infusion (8 g/L of ascites removed) is the first line of treatment for refractory ascites (A1). Diuretics should be discontinued in patients with RA who do not excrete
  > 30 mM of sodium under treatment.

AASLD. J Hepatol 2010;53:397-417

Recommendations 2

- TIPS is effective in the management of RA but is associated with a high risk of encephalopathy ans studies have not been shown to convincingly improve survival compared with LVP (A1).
- TIPS could be considered in patients with very frequent requirement of LVP, or in those in whom paracentesis is inffective (e.g. due to the presence of loculated ascites (B1)

AASLD. J Hepatol 2010;53:397-417

Recommendations 3

- Resolution of ascites after TIPS is slow and most patients require continued administration of diuretics and salt restriction (B1)
- TIPS cannot be recommended in patients with severe liver failure (serum bilirubin > 5 mg/dL, INR >2 or Child-Pugh score > 11, current encephalopathy >1 or chronic hepatic encephalopathy), concomitant active infection, progressive renal failure, or severe cardiopulmonary disease (B1)

AASLD. J Hepatol 2010;53:397-417

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Deleterious effect of propranolol in patients with RA ?

- Observational single-center study
- 151 patients with refractory ascites
- LVP with albumin
- 77 took beta blockers for the prevention of GI bleeding
- Median follow-up 8 months
- 1-year survival 41 %
  - Propranolol 19% (IC 95%: 8-29%)
  - Non Propranolol 64% (IC 95%: 52-76%)

QuickTime™ et un
décompresseur
sont requis pour visionner cette image.

Sersté T et al. Hepatology 2010;52:1017-22

Deleterious effect of propranolol in patients with RA ?

- Independent factors of mortality

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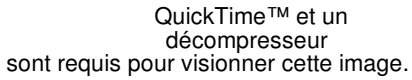
Sersté T et al. Hepatology 2010;52:1017-22

Propranolol and Post-Paracentesis Circulatory Dysfunction

- 10 patients with RA treated with propranolol
- Self control cross over study
- Before, D0 and D7
- Then eradication of VO by banding, and new identical study without propranolol
- PPCD
  - 80% on propranolol
  - 20% off propranolol

On



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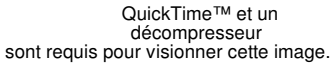

Sersté T et al. J Hepatol 2011, in press

Clonidine in Refractory Ascites

- RCT, 270 patients with RA
- ß blockers 35 vs 37%
- Spironolactone and furosemide on individual basis
- Clonidine 0,075 mg x 2 /d/3 months *vs* nothing
- Response : 20% decrease in body weight and 20% increase in $U_{Na}V$ at 1 and 3 months

Yang YY et al. Gut 2010;59:1545-53

Clonidine in Refractory Ascites

- ↓Aldosterone, PRA, Norepi
- ↑ UNaV, GFR
- Response :
  - 1 month 55%
  - 3 months 60%
- Responders:
  - ↓Paracentesis

  (9 vs 13/3m)

QuickTime™ et un décompresseur sont requis pour visionner cette image.

Yang YY et al. Gut 2010;59:1545-53


Thank you for your attention