Optimisation de la prise en charge de l'ascite ez le cirrhotique

M. Benazzouz

Rabat

Paris 30 Janvier 2017

Objectifs

Ascite chez le cirrhotique

- Quand ponction exploratrice
- Quels traitements diurétiques
- Critères d'échec d'un traitement diurétique
- Intérêt du traitement de la cause de la cirrhose pour contrôler l'ascite
- Quand Albumine et comment
- Place des Vaptans si ascite + hyponatrémie
- Y-a-t-il un risque si usage des B.Bloquants en cas ascite

Cas clinique

- BN ,âgé de 61 ans
- Sans ATCD
- Consulte pour asthénie + OMI
- Examen physique : ascite moyenne abondance , OMI , CVC,SPG, apyrétique
- Poids : 72 Kg
- Biologie
  - Cytolyse 2.3 x N
  - Ferritine, GGT: Nx
  - Bili: 14 mg/l
  - TP : 63%, Plaquettes 102.000/mm3
  - Alb 29g/l
  - Natrémie : 135 meq/L Kaliémie 4,3 meq/l , Créat: 6 mg/l
  - Glycémie , cholestérol , TG : normaux
  - Ag HBs +, Ag HBe -, Ac anti Hbe +, ADN VHB : 54 240 UI/ml
  - Sérologies VIH, VHC, VHD négatives
- Echographie abdominale : Foie dysmorphique sans nodule + ascite + SPG

Cas clinique

- Que faire ?
  - Faire une ponction exploratrice avec : dosage protéine et Alb , contage de PNN, étude cytologique et culture
  - Faire ponction avec contage de PNN ,Alb et protéine
  - Traiter sans faire de ponction

Ponction diagnostique si ascite

Recommendations

1. ***Diagnostic abdominal paracentesis should be performed and ascitic fluid should be obtained from inpatients and outpatients with clinically apparent new-onset ascites. (Class I, Level C)***

AASLD - Hepatology - fevrier 2013

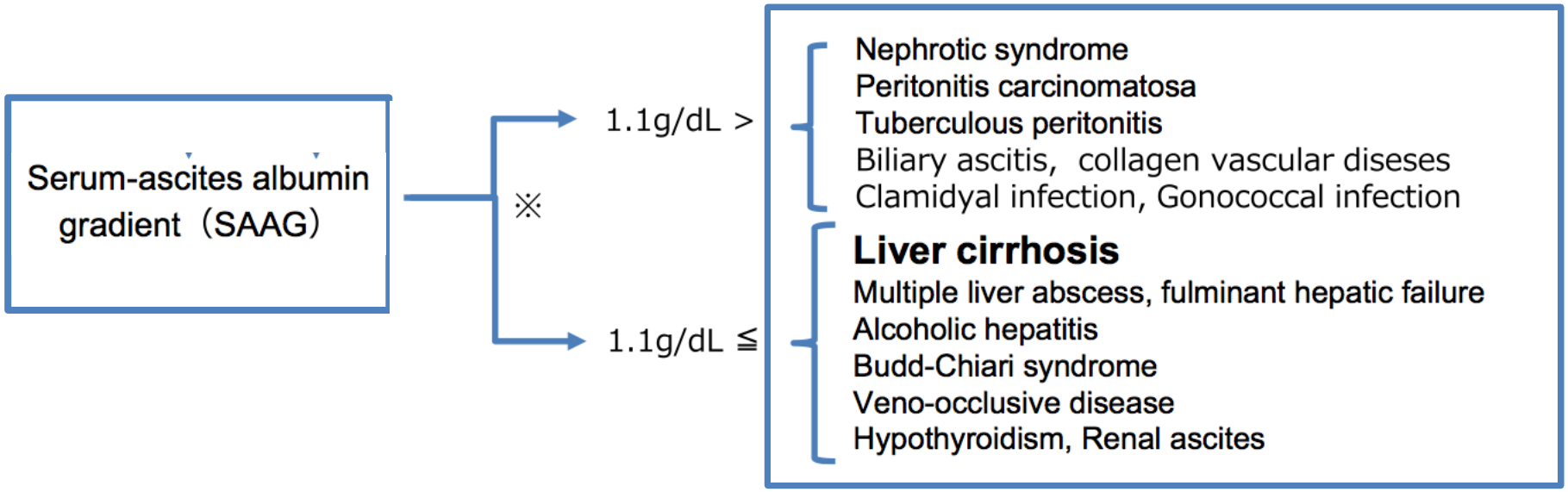
Ponction diagnostique si ascite

Routine	Optional (When There is Suspicion of Infection)	Unusual	Unhelpful
Cell count and differential	Culture in blood culture bottles	AFB smear and culture	pH
Albumin	Glucose	Cytology	Lactate
Total protein	Lactate dehydrogenase	Triglyceride	Cholesterol
	Amylase	Bilirubin	Fibronectin
	Gram's stain		Glycosaminoglycans

Abbreviation: AFB, acid-fast bacteria.

AASLD - Hepatology - fevrier 2013

Intérêt du SAAG



H Fukui , J Gastroenterol (2016)

Cas clinique

- Pour le traitement de l’ascite ?
  - Spironolactone 100 mg
  - Furosémide 40 mg
  - Association des deux
  - Ponction d’ascite évacuatrice

Traitement de l'ascite non compliquée chez le cirrhotique

Grade of ascites	Definition	Treatment
Grade 1 ascites	Mild ascites only detectable by ultrasound	No treatment
Grade 2 ascites	Moderate ascites evident by moderate symmetrical distension of abdomen	Restriction of sodium intake and diuretics
Grade 3 ascites	Large or gross ascites with marked abdominal distension	Large-volume paracentesis followed by restriction of sodium intake and diuretics (unless patients have refractory ascites)

EASL 2010

Combined versus sequential diuretic treatment of ascites in non-azotaemic patients with cirrhosis: results of an open randomised clinical trial

P Angeli, S Fasolato, E Mazza, et al.

	Group A (n = 50)	Group B (n = 50)	p Value
Number of patients who did not reach the effective diuretic step (%)	6 (12%)	2 (4%)	NS
because of the development of adverse effects	5	2	
because of resistant ascites	1	0	
Number of patients with excessive diuretic response while on treatment with the effective diuretic step (%)	2 (4%)	2 (4%)	NS
Number of patients with adverse effects while on treatment with the effective diuretic step (%)	14 (32%)	8 (17%)	<0.05
Total number of treatment failures	22 (44%)	12 (24%)	<0.05

Gut 2010

Recommandations UK/EASL/AASLD

British Society of Gastroenterology [5]	European Association for the Study of the Liver [1]	American Association for the Study of Liver Diseases [10,15,16]
100 mg spironolactone, increasing to a maximum of 400 mg/day, as first-line treatment Addition of furosemide at a dose up to 160 mg/day as second-line treatment No limit in patients with severe oedema	An aldosterone antagonist e.g. spironolactone started at 100 mg/day and increasing stepwise every 7 days by 100 mg to a maximum of 400 mg/day In non-responders, Furosemide added at a dose of 40 mg/day increasing stepwise to a	100 mg/day spironolactone and 40 mg/day furosemide (single-agent use of spironolactone only in patients with minimal fluid overload) The doses of both drugs can be increased simultaneously every 3–5 days

M Pericleous ,European Journal of Gastroenterology & Hepatology 2

The Japanese Society of Gastroenterology

CQ: Is spironolactone alone or in combination with loop diuretics better for treatment of cirrhotic patients with ascites?

- Although outpatients can be first treated with spironolactone alone, the combination therapy is rather proposed for inpatients receiving intensive therapy to prevent side effects. (Evidence level C, strength 2)

J Gastroenterol (2016)

Cas clinique

- J7 : sous 100 mg de spironolactone et 40 mg de furosémide
- Ascite ++
- Poids : 69 Kg
- Na : 129 meq/l K et créat : Nx
- Que faire ?
  - Arrêter diurétique et ponction
  - Continuer diurétique et contrôler Iono

Critères d’efficacité

- Une perte de poids maximale de 0,5 kg/jour chez les patients sans œdème
- 1 kg/jour chez les patients avec œdème
- Inefficacité
  - Si perte pondérale < 2g /s
  - Arrêt des diurétiques si pas de réponse clinique et Na urinaire < 30meq/j

Recommandations UK/EASL/AASLD

Que faire si hyponatrémie sous diurétiques

British Society of Gastroenterology [5]	European Association for the Study of the Liver [1]	American Association for the Study of Liver Diseases [10,15,16]
Na ≥ 126 mmol/l: continue diuretics with no water restriction Na 121–125 mmol/l with a normal creatinine level: consider stopping diuretics or continue with caution Na ≤ 121–125 mmol/l with an increasing in creatinine: stop diuretics and give volume expansion Na ≤ 120 mmol/l: stop diuretics and give volume expansion. Avoid increasing serum Na > 12 mmol/l per 24 h	Stop diuretics if: Na < 120 mmol/l Progressive renal failure Worsening hepatic encephalopathy Incapacitating muscle cramps	Stop diuretics if: Na < 120 mmol/l despite fluid restriction Serum creatinine > 2.0 mg/dl recurrent or uncontrolled encephalopathy

M Pericleous ,European Journal of Gastroenterology & Hepatology 2016

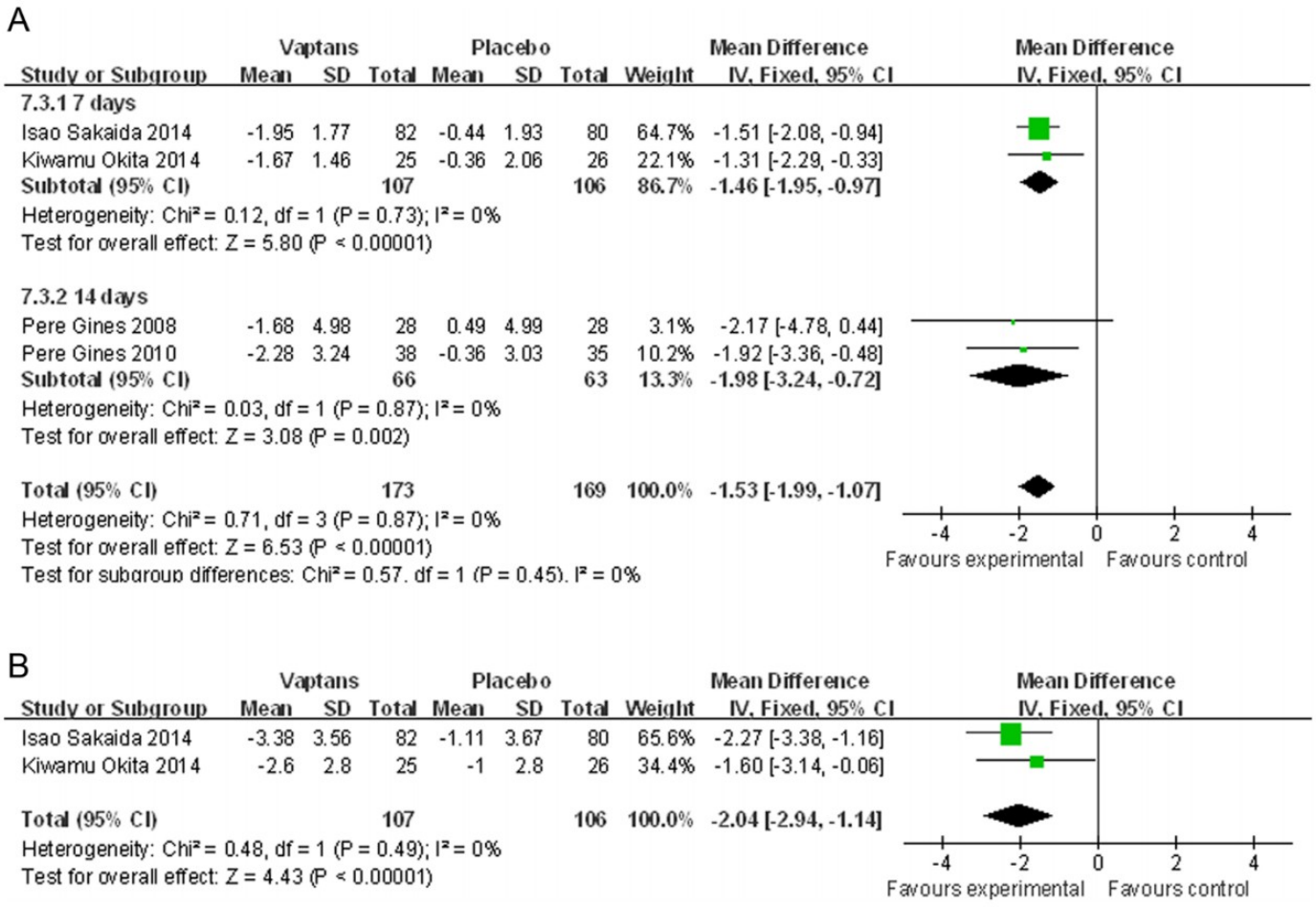
Cas clinique

- J14 : Malgré 200 mg de spironolactone + 80 mg de Furosémide :
  - Toujours ascite +
  - Poids : 67 kg
  - Iono sanguin : Na 128 meq/l -K - Cérat : Nx
  - Iono urinaire : Na 42 mmol/j
- Que faire ?
  - Augmenter encore les doses de diurétiques
  - Faire ponction
  - Ajouter un Vaptan

The treatment of vasopressin V2-receptor antagonists in cirrhosis patients with ascites: a meta-analysis of randomized controlled trials

Long Yan[1†], Feng Xie[1†], Jiongjiong Lu[1], Qingqiang Ni[1], Changying Shi[1], Caixi Tang[2] and Jiamei Yang[1*]

Impact sur poids te PO



Yan et al. BMC Gastroenterology (2015)

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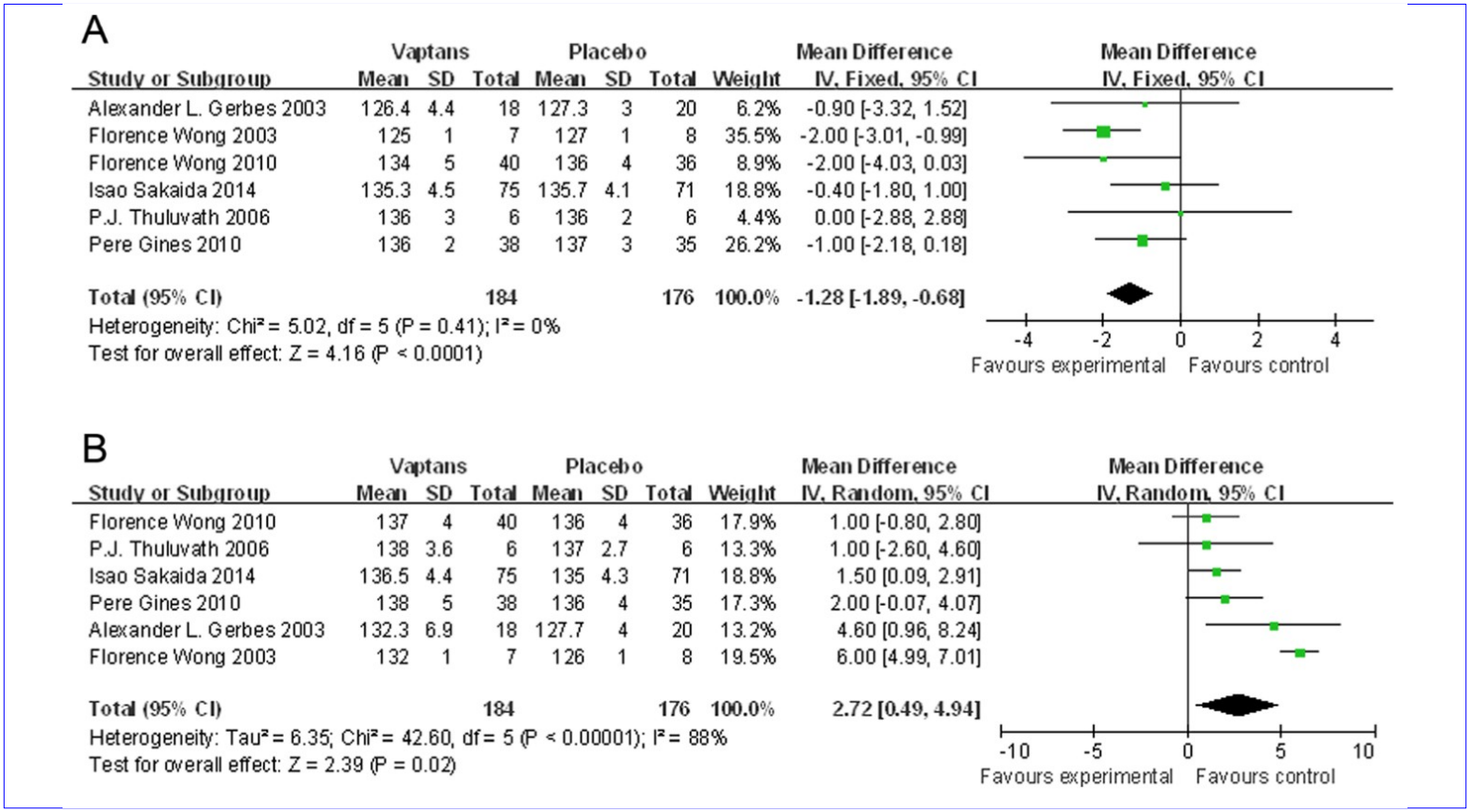
A: Natremie en cours du Tx B: Natermie après arrêt



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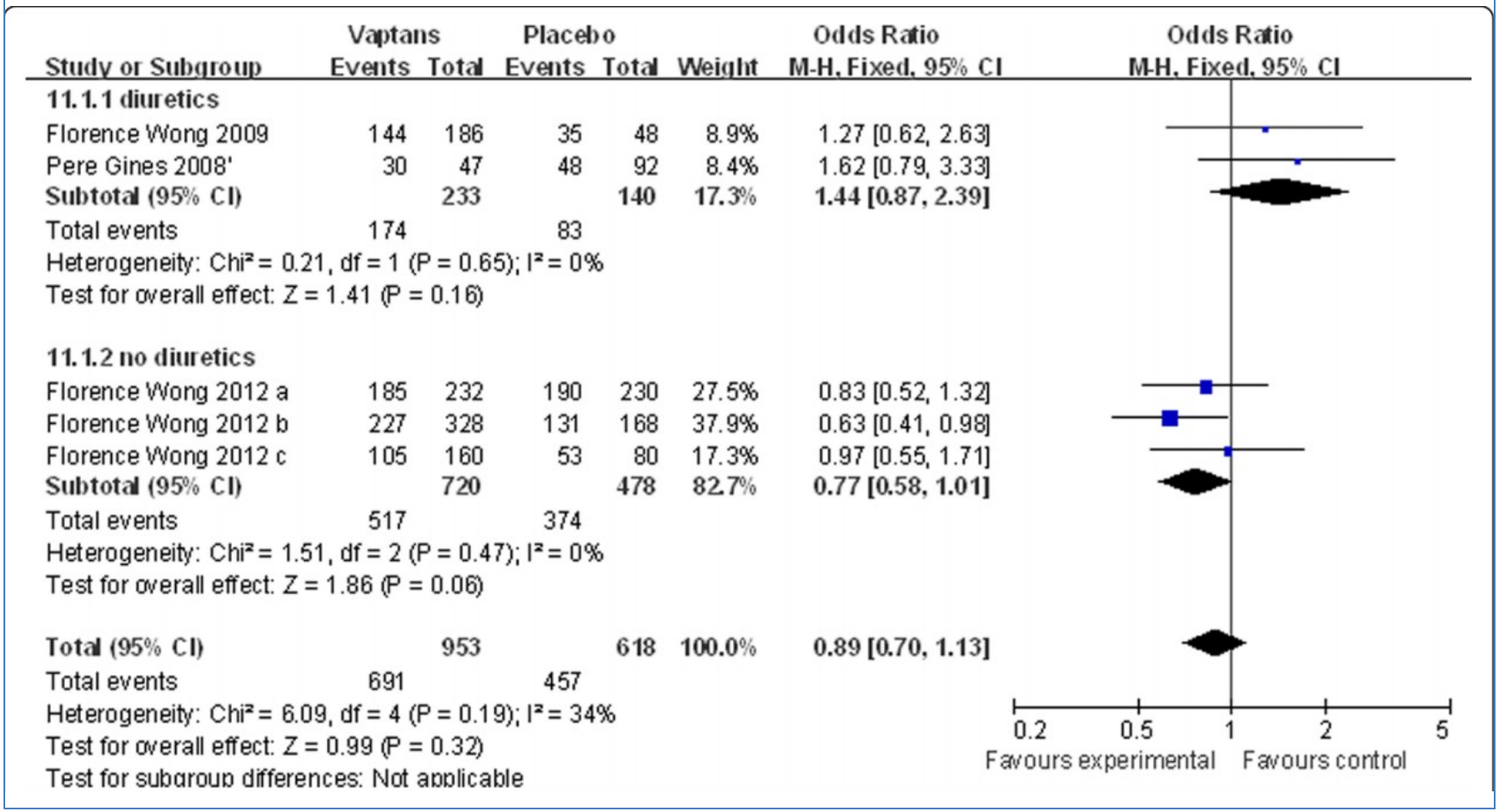
Impact sur la survie



Yan et al. BMC Gastroenterology (2015)

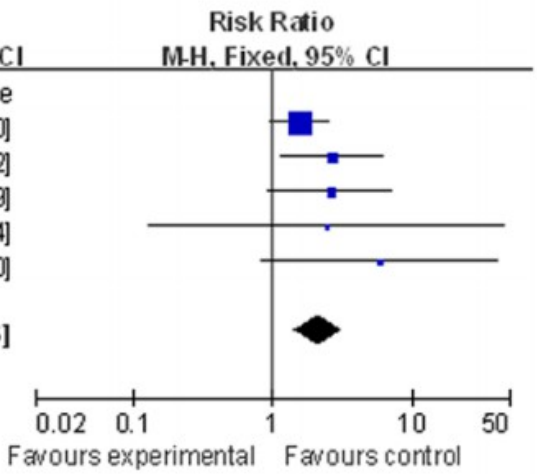
Effet secondaires sérieux sous vaptans

B

Study or Subgroup	Vaptans Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Andres Cardenas 2012	0	63	0	57		Not estimable
Florence Wong 2012 a	35	232	22	230	58.7%	1.58 [0.96, 2.60]
Florence Wong 2012 b	31	328	6	168	21.1%	2.65 [1.13, 6.22]
Florence Wong 2012 c	21	160	4	80	14.2%	2.63 [0.93, 7.39]
Pere Gines 2008	3	82	0	28	2.0%	2.45 [0.13, 45.94]
Pere Gines 2010	19	113	1	35	4.1%	5.88 [0.82, 42.40]
Total (95% CI)		**978**		**598**	**100.0%**	**2.14 [1.45, 3.16]**
Total events	109		33			

Heterogeneity: Chi² = 2.83, df = 4 (P = 0.59); I² = 0%

Test for overall effect: Z = 3.84 (P = 0.0001)



Yan et al. BMC Gastroenterology (2015)

Place des Vaptans

The Japanese Society of Gastroenterology

CQ: Are vasopressin V_2 receptor antagonists effective for management of ascites or water retention in cirrhotic patients?

- A vasopressin V_2 receptor antagonist combined with loop diuretics and aldosterone antagonists is recommended for such patients on the basis of its effectiveness on hyponatremia and ascites. (Evidence level A, strength 1)

Dose 3.75–7.5 mg/J

J Gastroenterol (2016)

Place des Vaptans

11. *Vaptans may improve serum sodium in patients with cirrhosis and ascites. However their use does not currently appear justified in view of their expense, potential risks, and lack of evidence of efficacy in clinically meaningful outcomes. (Class III, Level A)*

AASLD 2013

Cas clinique

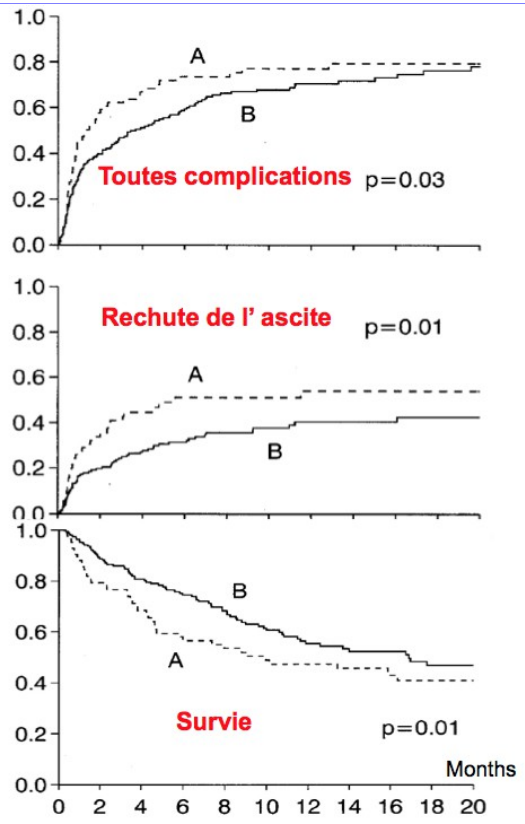
- Augmentation de la dose des diurétiques
- Le patient se présente en consultation avec une ascite tendue ,on décide de faire une ponction d'ascite:
  - ponction d'ascite et retirer le Max de liquide
  - Ne pas dépasser 5 l
  - Passer de l'alb quelque soit le volume retiré
  - Passer Alb si volume > 5 l
  - Passer du dextran si volume < 5l

Ascite chez le cirrhotique
EASL 2010

Recommendations **Large-volume paracentesis (LVP) is the first-line therapy in patients with large ascites (grade 3 ascites) (Level A1). LVP should be completed in a single session (Level A1).**

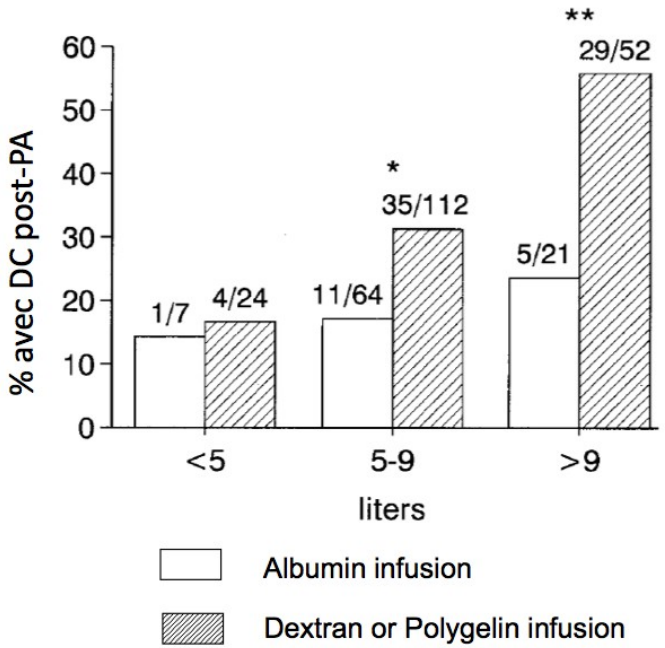
LVP should be performed together with the administration of albumin (8 g/L of ascitic fluid removed) to prevent circulatory dysfunction after LVP (Level A1).

Ponction d'ascite et dysfonction circulatoire



A : Patients avec dysfonction circulatoire
B : Patients sans dysfonction circulatoire

Dysfonction circulatoire après grande ponction d' ascite



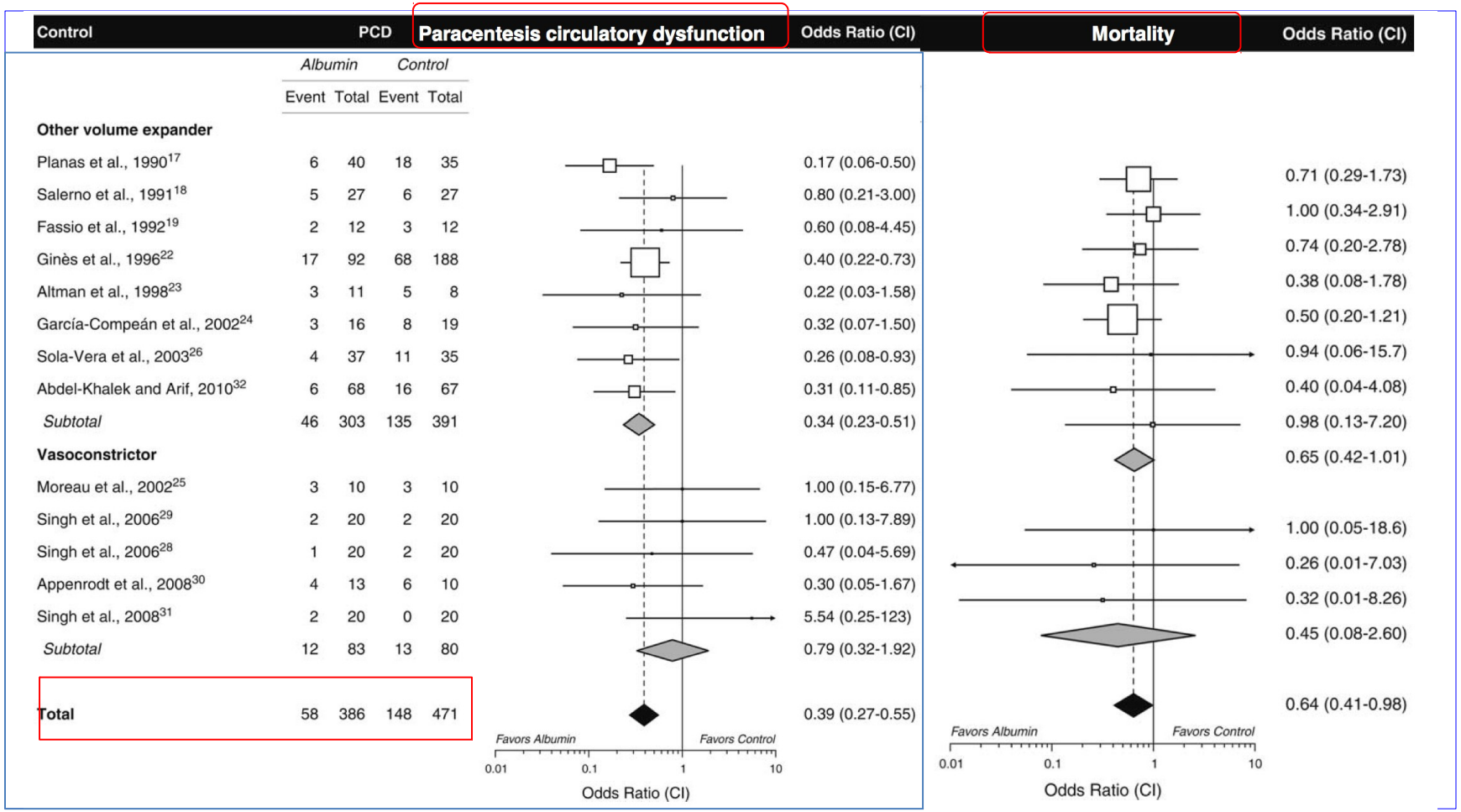
Ginès P et al Gastroenterology 1996;111:1002

Alb et amélioration de la fonction rénale

	Group 1 (Albumin) N=10			Group 2 (Hydroxyethyl Starch) N=10		
	At Diagnosis	At Resolution	*P*	At Diagnosis	At Resolution	*P*
Systemic hemodynamics						
Mean arterial pressure (mmHg)	76 ± 9	85 ± 13	.01	80 ± 15	81 ± 8	.36
Cardiac index (L/min/m^2)	4.9 ± 0.7	4.6 ± 0.9	.21	4.8 ± 1.0	4.9 ± 1.4	.44
Systemic vascular resistance (dyn·sec/cm^5)	668 ± 134	803 ± 197	.03	777 ± 239	778 ± 290	.96
Systolic volume (mL)	97 ± 20	104 ± 17	.05	83 ± 15	92 ± 23	.12
Heart rate (beats/min)	91 ± 14	80 ± 13	.01	90 ± 10	84 ± 9	.01
Stroke work index (g·m/m^2)	51 ± 17	59 ± 17	.01	48 ± 13	53 ± 13	.24
Right atrial pressure (mmHg)	8 ± 2	9 ± 2	.03	7 ± 3	7 ± 3	1.0
Pulmonary artery pressure (mmHg)	17 ± 4	21 ± 5	.01	18 ± 6	18 ± 7	.88
Pulmonary capillary pressure (mmHg)	11 ± 3	14 ± 4	.03	10 ± 4	11 ± 5	.51
Plasma hormonal systems						
Plasma renin activity (ng·mL/h)	5.7 ± 4.7	3.1 ± 3.4	.04	8.5 ± 7.3	16.8 ± 24.6	.65
Atrial natriuretic factor (fmol/mL)	55 ± 21	85 ± 37	.05	45 ± 32	28 ± 18†	.51
Splanchnic and renal hemodynamics						
Wedged hepatic venous pressure (mmHg)	30.6 ± 2.9	31.9 ± 4.0	.31	30.6 ± 5.6	31.6 ± 5.2	.29
Free hepatic venous pressure (mmHg)	12.8 ± 3.0	13.4 ± 2.1	.47	10.5 ± 3.5	11.0 ± 2.7	.57
HVPG (mmHg)	17.8 ± 2.5	18.5 ± 3.1	.31	20.1 ± 4.3	20.6 ± 4.6	.59
Hepatic blood flow (L.min^{-1})*	0.8 ± 0.2	1.0 ± 0.3	.14	0.9 ± 0.4	1.2 ± 0.5	.71
Renal resistive index	0.80 ± 0.04	0.78 ± 0.04	.11	0.80 ± 0.02	0.81 ± 0.04	.44
Renal function						
Serum creatinine (mg/dL)	1.6 ± 0.8	1.0 ± 0.3	.01	1.2 ± 0.5	1.0 ± 0.2	.02

Fernandez. Hepatology 2005

Ponction d'ascite et dysfonction circulatoire/mortalité



M Bernardi HEPATOLOGY 2012

Alb et infection du liquide d'ascite

Outcome Variable	Cefotaxime (N=63)	Cefotaxime plus Albumin (N=63)	P Value
Resolution of infection — no. (%)†	59 (94)	62 (98)	0.36
Duration of antibiotic therapy — days	6±1	5±1	0.48
Paracentesis for ascites after resolution of infection — no. (%)‡	16 (25)	14 (22)	0.83
Hospital stay — days	13±1	14±1	0.48
Renal impairment — no. (%)	21 (33)	6 (10)	0.002
Death — no. (%)			
In hospital§	18 (29)	6 (10)	0.01
At three months¶	26 (41)	14 (22)	0.03

Utilité albumine iv ajouté aux antibiotiques dans autres infections?

Sort. NEJM 1999
Fernandez. J Hepatology 2012

Low dose albumin for the prevention of renal impairment following large volume paracentesis in cirrhosis

Waqar Hussain[1], Abdullah Bin Khalid[2], Tayyab Usmani[3], Aiman Ghufran[4], Hasnain Shah[5]

	Group A (25gram Albumin) (n=108)		*Group B (50gram Albumin) (n=31)*		*P value*
	Pre LVP	*Post LVP*	*Pre LVP*	*Post LVP*	
Serum Cr (mg/dl)	1.04± 0.24	1.07±0.35	1.11± 0.23	1.41± 0.94	0.35
Sodium (meq/lit)	130 ± 5.6	129.6±5.9	127.6 ± 5.8	128 ±6.2	0.14

Conclusion: This study suggests that 4 grams of albumin per litre of ascitic fluid drained is effective in preventing the PICD related renal impairment following large volume paracentesis in cirrhosis

Pak J Med Sci 2015

Usage de faible dose d'Alb après ponction d'ascite ?

Dig Dis Sci (2015) 60:2190–2195
DOI 10.1007/s10620-015-3578-z

ORIGINAL ARTICLE

Reduced Albumin Dosing During Large-Volume Paracentesis Is Not Associated with Adverse Clinical Outcomes

Kara B. Johnson · Jessica L. Mueller · Tracey G. Simon · Hui Zheng · Lindsay Y. King · Robert S. Makar · Debra A. Gervais · Raymond T. Chung

Contents lists available at ScienceDirect

Digestive and Liver Disease 2011

journal homepage: www.elsevier.com/locate/dld

Liver, Pancreas and Biliary Tract

Prevention of paracentesis-induced circulatory dysfunction in cirrhosis: Standard vs half albumin doses. A prospective, randomized, unblinded pilot study☆

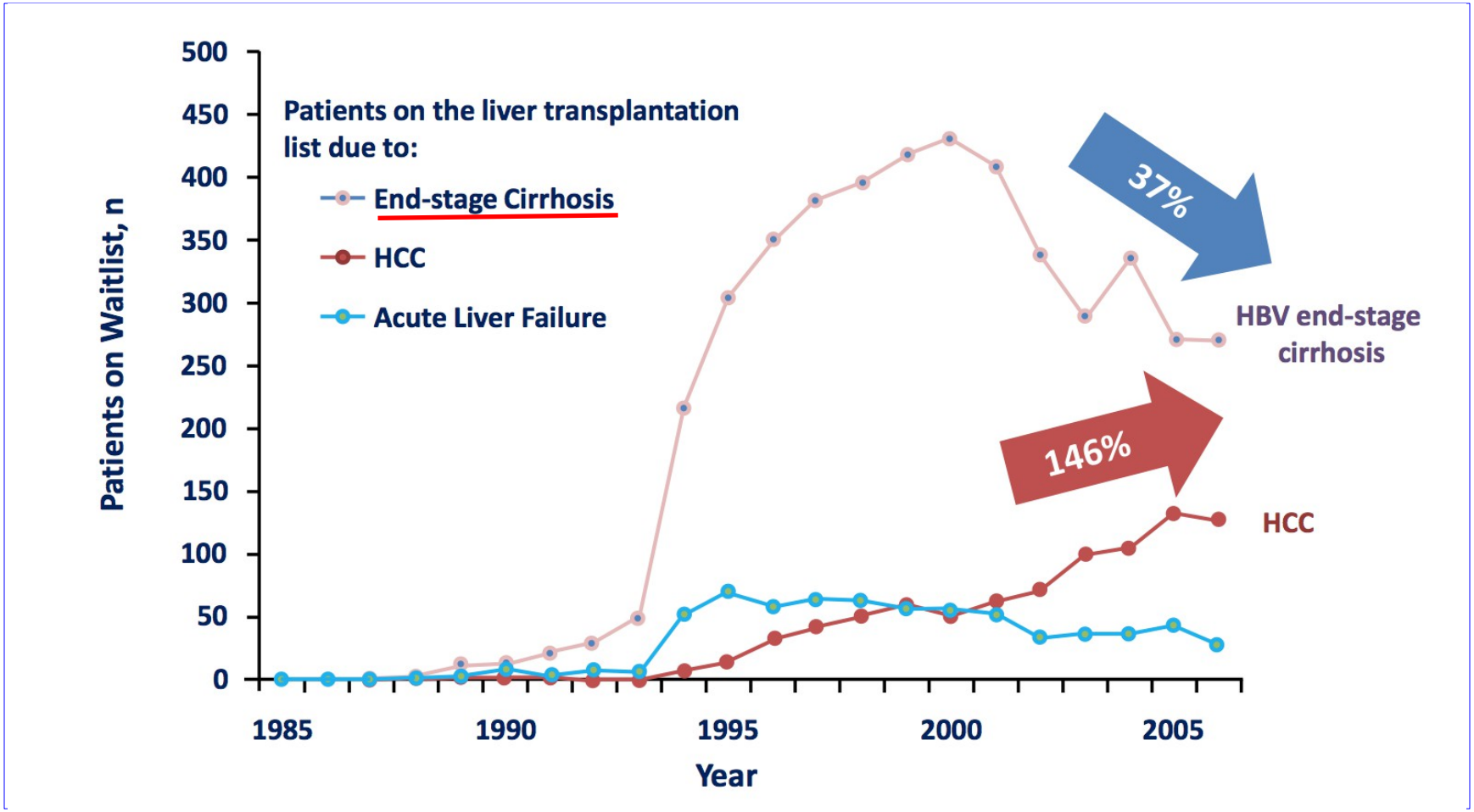
Carlo Alessandria*, Chiara Elia, Lavinia Mezzabotta, Alessandro Risso, Alida Andrealli, Maurizio Spandre, Anna Morgando, Alfredo Marzano, Mario Rizzetto

Division of Gastroenterology and Hepatology, San Giovanni Battista Hospital – University of Turin, Turin, Italy

Cas clinique

- Le patient est mis sous entecavir
- Pensez vous que la viro-supression sous NUC contribuerait-elle à un meilleur contrôle de l’ascite
  - Oui
  - Non

HVB : Réduction du risque de décompensation sous NUC



Kim WR. *Hepatology* 2009;49:S28-S34

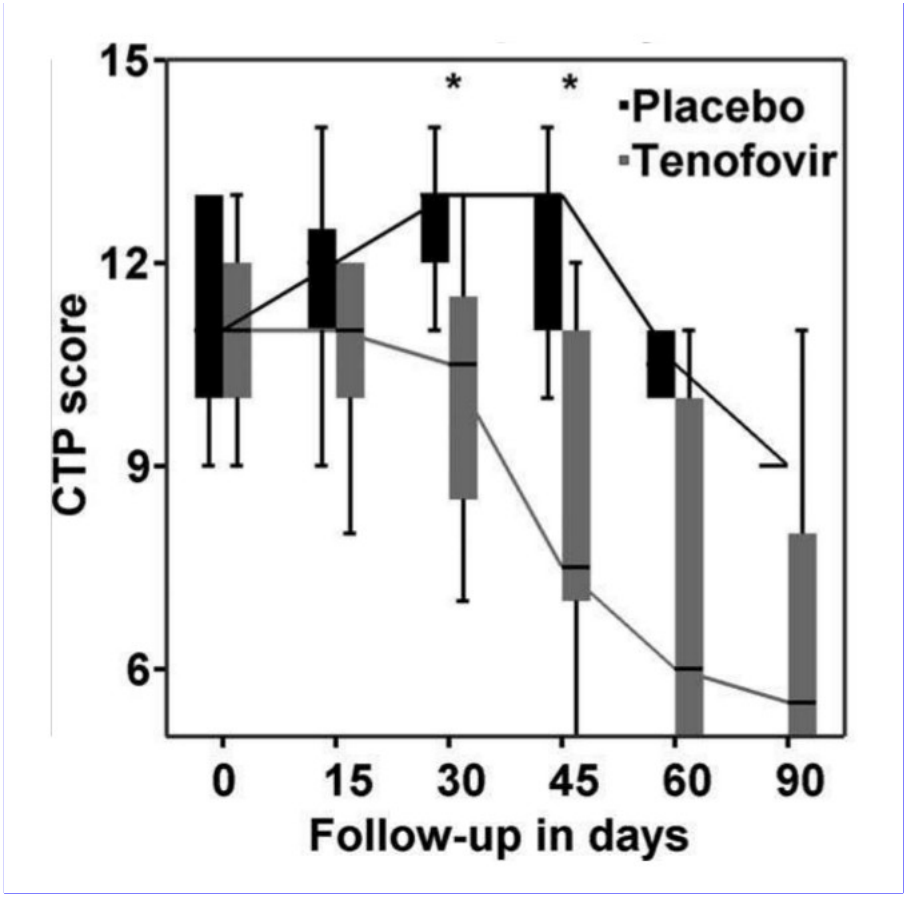
Cirrhose décompensé :Lam vs contrôle
Meta-analyse

	Lamivudine			No treatment		Effect size	
	Studies (N)	Sample size	Events	Sample size	Events	OR (95% CI)	*P*
↓ CTP ≥ 2 pts	2	53	27	53	0	117 (915–921)	<0.0001
Normal ALT	2	51	38	60	0	173 (22–1376)	<0.0001
Undetectable DNA	4	149	115	193	29	117 (2–6574)	0.02
HBeAg loss	3	82	25	156	10	14 (0.3–563)	0.16
HBeAg seroconversion	1	16	1	23	0	4.6 (0.2–12)	0.36
Off OLT list	2	185	14	170	7	2 (1–5)	0.22
LT	2	185	97	170	101	0.38 (0.1–3)	0.34
HCC	1	30	2	30	2	1 (0.1–8)	0.17
OLT free survival	4	245	155	216	87	5 (1.5–15)	0.022
Overall survival	4	245	214	216	87	14 (2–119)	0.017
Drug resistance	4	223	28	205	0	16 (4–72)	<0.0001

CTP, child Turcotte Pugh; HCC, hepatocellular carcinoma; LT, liver transplantation; OR, odds ratio.

A. K. Singal* & R. J. Fontana† *Aliment Pharmacol Ther* 2012; **35**: 674–689

Tenofovir Improves the Outcome in Patients with Spontaneous Reactivation of Hepatitis B Presenting as Acute-On-Chronic Liver Failure

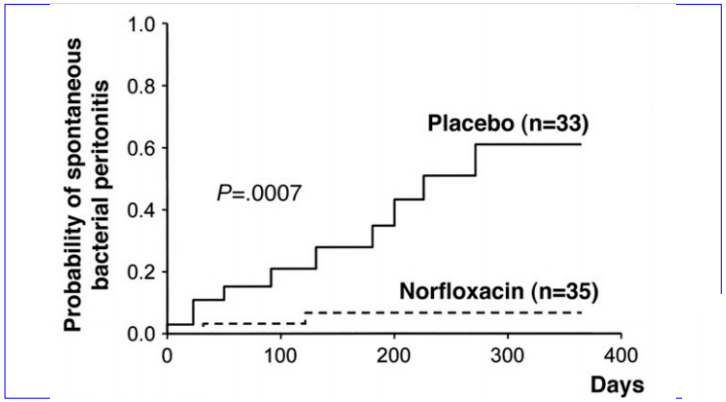


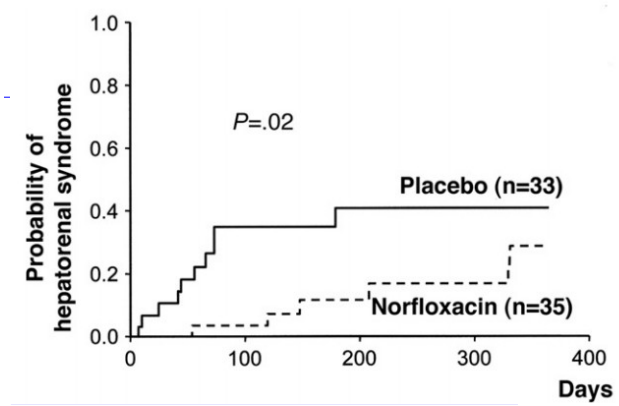
HEPATOLOGY 2011

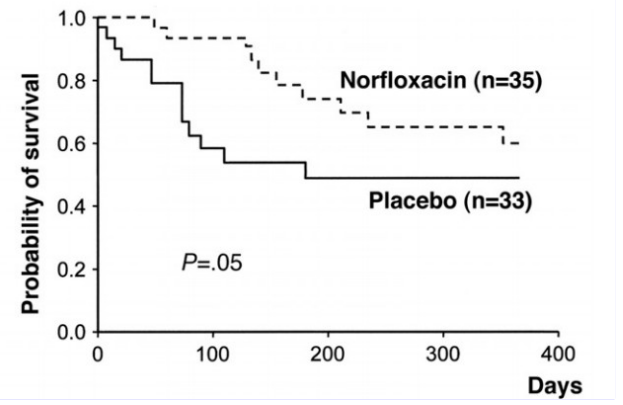
Cas clinique

- Taux de protéine dans le liquide d’ascite est à 9 g /l
  - Antibioprophylaxie primaire de l’infection spontané liquide d’ascite :
    - Oui ?
    - Non ?

Primary Prophylaxis of Spontaneous Bacterial Peritonitis Delays Hepatorenal Syndrome and Improves Survival in Cirrhosis







JAVIER FERNÁNDEZ GASTROENTEROLOGY 2007

Quand prophylaxie si liquide d'ascite pauvre en protéine

In patients with cirrhosis and ascites, longterm use of norfloxacin (or trimethoprim/sulfamethasoxazole) can be justified if the ascitic fluid protein <1.5 g/dL along with impaired renal function (creatinine ≥1.2, BUN ≥25 or serum Na ≤130) or liver failure (Child score ≥9 and bilirubin ≥3). (Class I, Level A)

AASLD 2013

Cas clinique

- Notre patient est pris en charge en ambulatoire diurétiques / ponction d'ascite
- Mis sur liste de TH
- Pour le propranolol
  - arrêt et ligature de VO
  - continuer sans réduction de dose
  - réduire la dose

Deleterious Effects of Beta-Blockers on Survival in Patients With Cirrhosis and Refractory Ascites

Thomas Sersté,[1,2,3] Christian Melot,[4] Claire Francoz,[1,2,5] François Durand,[1,2,5] Pierre-Emmanuel Rautou,[1,2] Dominique Valla,[1,2,5] Richard Moreau,[1,2,5*] and Didier Lebrec,[1,2,5*]

HEPATOLOGY 201

Nonselective β Blockers Increase Risk for Hepatorenal Syndrome and Death in Patients With Cirrhosis and Spontaneous Bacterial Peritonitis

Mattias Mandorfer,[1,2] Simona Bota,[1,2] Philipp Schwabl,[1,2] Theresa Bucsics,[1,2]

Gastroenterology 20

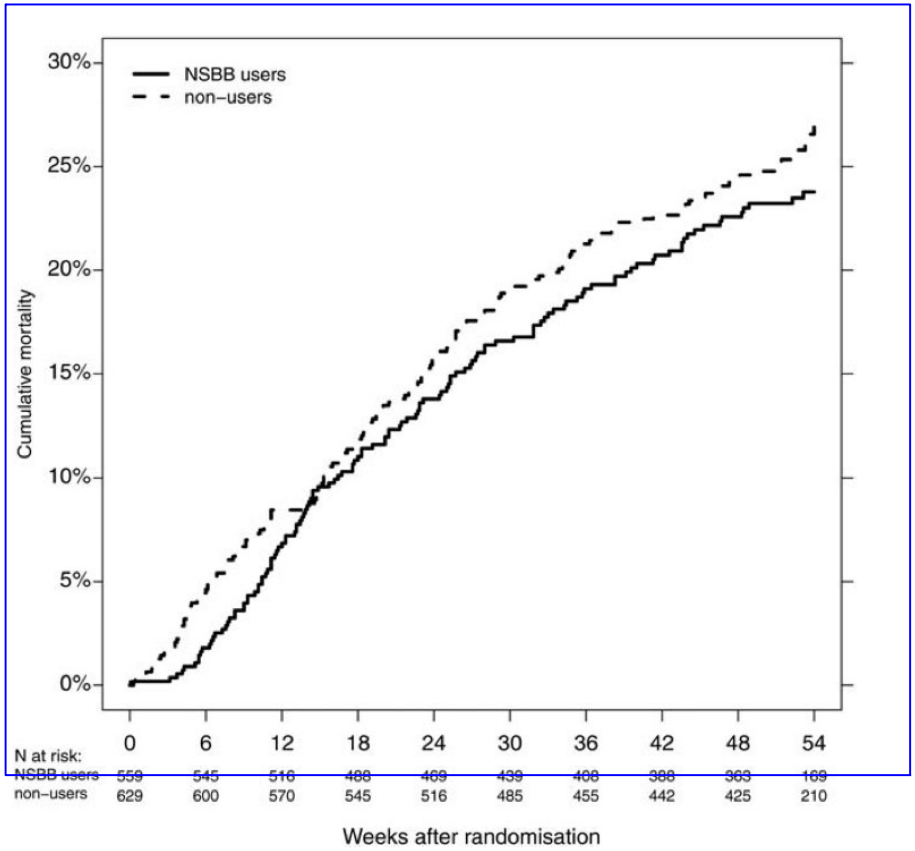
The deleterious effects of non-selective beta-blockers on cirrhotic patients: the confused clinician!

Anca Trifan1,2, Carol Stanciu

J Gastrointestin Liver Dis, December 2014

Nonselective β-Blockers Do Not Affect Mortality in Cirrhosis Patients With Ascites: Post Hoc Analysis of Three Randomized Controlled Trials With 1198 Patients

Lars Bossen,[1,2] Aleksander Krag,[3] Hendrik Vilstrup,[1] Hugh Watson,[4] and Peter Jepsen[1,2]



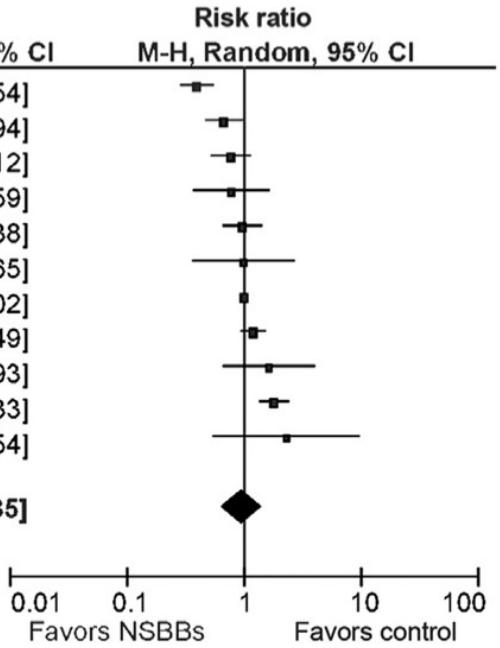
Chez les 29% des patients avec arrêt des BB : augmentation des complications et de la mortalité mortality hazard (adjusted HR 5 5.13, 95% CI 2.28- 11.55)

BOSSEN ET AL

Nonselective β-Blockers and Survival in Patients With Cirrhosis and Ascites: A Systematic Review and Meta-analysis

Study	NSBBs Events	NSBBs Total	Control Events	Control Total	Weight	Risk ratio M-H, Random, 95% CI
Mazhar 2013	43	619	167	941	10.6%	0.39 [0.28, 0.54]
Robins 2012	18	36	59	78	10.5%	0.66 [0.47, 0.94]
Leithead 2014	35	159	47	163	10.3%	0.76 [0.52, 1.12]
Escorsell 2002	7	19	11	23	7.8%	0.77 [0.37, 1.59]
Kimer 2014	15	23	26	38	10.3%	0.95 [0.66, 1.38]
Lo 2004	5	17	6	20	6.1%	0.98 [0.36, 2.65]
Mandorfer 2014	239	245	355	362	11.6%	0.99 [0.97, 1.02]
Borroni 2002	23	25	21	27	11.1%	1.18 [0.94, 1.49]
Shah 2014	10	33	6	32	6.7%	1.62 [0.67, 3.93]
Serste 2010	63	77	34	74	10.9%	1.78 [1.36, 2.33]
Cholongitas 2006	14	101	2	33	4.0%	2.29 [0.55, 9.54]
Total (95% CI)		**1354**		**1791**	**100.0%**	**0.95 [0.67, 1.35]**
Total events	472		734			

Heterogeneity: Tau² = 0.28; Chi² = 155.49, df = 10 (*P* < .00001)
I² = 94%; Test for overall effect: Z = 0.28 (*P* = .078)



The use of NSBBs was not associated with a significant increase in all-cause mortality in patients with cirrhosis and ascites or refractory ascites. Certainty in the available estimates is low; a randomized trial of only patients with ascites is needed to answer this question. This meta-analysis does not support the position that NSBBs routinely be withheld from patients with ascites.

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Clinical Gastroenterology and Hepatology 2016

AASLD 2013

The risks versus benefits of beta blockers must be carefully weighed in each patient with refractory ascites. Systemic hypotension often complicates their use. Consideration should be given to discontinuing or not initiating these drugs in this setting. (Class III, Level B)

Baveno VI

- Ascite réfractaire et infection du liquide d'ascite

  Problème de sécurité BB posé (2b;B).

- Peut être Pas de contre-indications des BB si prescription première faite mais surveillance (5;D).
- si ascite réfractaire :

  Surveillance++ ,réduction de dose si TA basse ou IR(4;C).
- si arrêt BB : ligature VO (5;D).

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