Leids Universitair
Medisch Centrum

Acute decompensatie van cirrose en acuut op chronisch leverfalen

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Maag, Darm en Leverziekten

LEIDEN

Disclosure

Advisory board Ferring Pharmaceuticals

Beethoven's autopsy report

…The abdominal cavity was filled with four quarts of a reddish, cloudy fluid. The liver was half of its usual size. It was compact and leathery in consistency, blue-green in color, and its surface was covered by nodules the size of a bean. …

…The spleen appeared twice its usual size…

…Both kidneys were pale red and soft …

…The hair contained an average of 60 parts per million of lead. The authors concluded that Beethoven had 'plumbism' (lead poisoning) and that this had contributed to his death.

Outline

Mechanisms of portal hypertension

Spontaneous bacterial peritonitis

Hepatorenal Syndrome

Hepatic Encephalopathy

AD/ACLF

Bacterial translocation

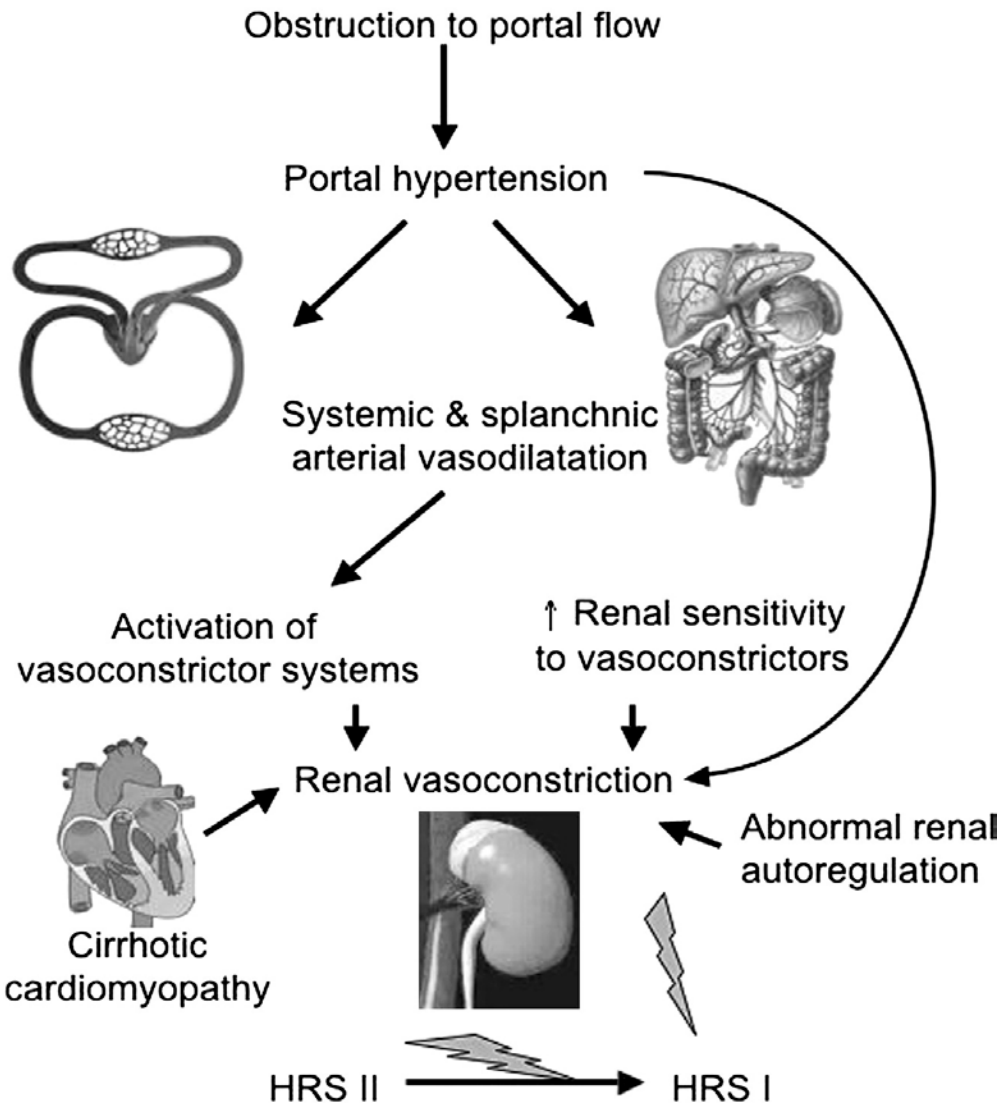
Innate immunity activation

Rifaximin

Farnesoid X Receptor agonist

Statins

TLR4 antagonists



Loop diuretics

Aldosterone antagonists

V1 agonists

V2 antagonists

Albumin

Outline

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Mechanisms of portal hypertension

Spontaneous bacterial peritonitis

Hepatorenal Syndrome

Hepatic Encephalopathy

AD/ACLF

Spontaneous bacterial peritonitis

Bacterial translocation: intestinal bacterial overgrowth, mucosal barrier, immunity

Prevalence: 10-30% hospitalized, 3.5% outpatients

Diagnostic paracentesis at admission!

Ascites neutrophil count $\geq 250/mm^3$ ($0.25x10^9/l$)

40% Ascites culture negative (bedside inoculation)

Intestinal-type flora:

70% gram negative, 25% gram positive, 5% anaerobic

SBP treatment

Third generation cefalosporin and albumin*

Confirm resolution SBP by decrease neutrophil count

Follow-up paracentesis after 2 days of AB to guide therapy

Secondary prophylaxis using norfloxacin

Outcome SBP:

SBP resolution 80-95%

In-hospital mortality: 30%

Hepatorenal syndrome: 30%

*Sort NEJM: lower rate of renal impairment and mortality

SBP treatment

Third generation cefalosporin and albumin*

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*Sort NEJM: lower rate of renal impairment and mortality

Use of norfloxacin in advanced cirrhosis?

THE ILC 2017
Amsterdam, The Netherlands
April 20, 2017

A Randomized Trial of 6-Month Norfloxacin Therapy in Patients with Child-Pugh class C Cirrhosis

Richard Moreau, Laure Elkrief, Christophe Bureau,
Jean-Marc Pérarnau, Thierry Thévenot, Faouzi Saliba,
Isabelle Ollivier-Hourmand, Alexandre Louvet, Pierre Nahon,
Frédéric Oberti, Rodolphe Anty, Sophie Hillaire, Blandine Pasquet,
Violaine Ozenne, Marika Rudler, Marie-Angèle Robic,
Louis d'Alteroche, Vincent Di Martino,
Pierre-Emmanuel Rautou, Nathalie Gault, Didier Lebrec
For the NORFLOCIR Study Group

Background and aim

- **Fluoroquinolones include norfloxacin, ciprofloxacin**

- **Long-term oral fluoroquinolone therapy to improve outcomes in patients with cirrhosis is debated**

Aim: to study the effects of norfloxacin administration on survival in a large series of patients with Child-Pugh class C cirrhosis.

Study Design

National, multicenter (18), randomized, double-blind, placebo-controlled trial of norfloxacin (Sponsor: French Gov.)

Inclusion

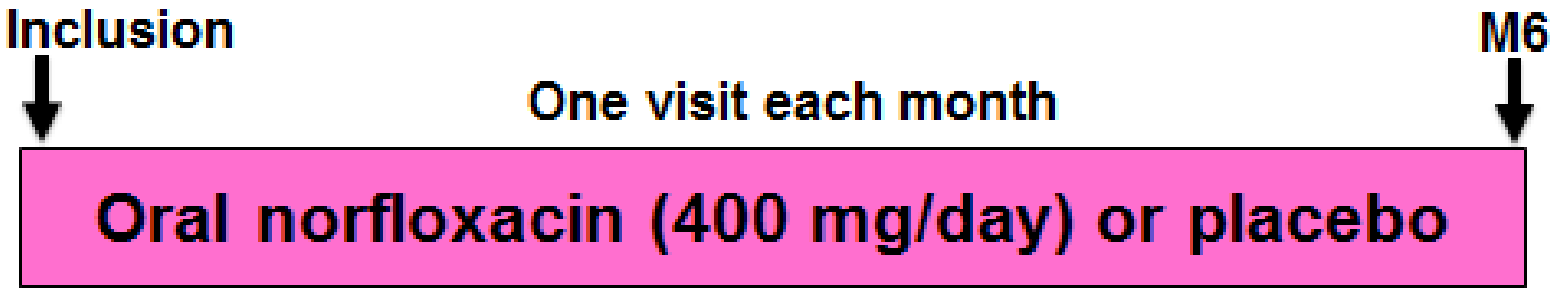
- Child-Pugh class C cirrhosis

Non-inclusion

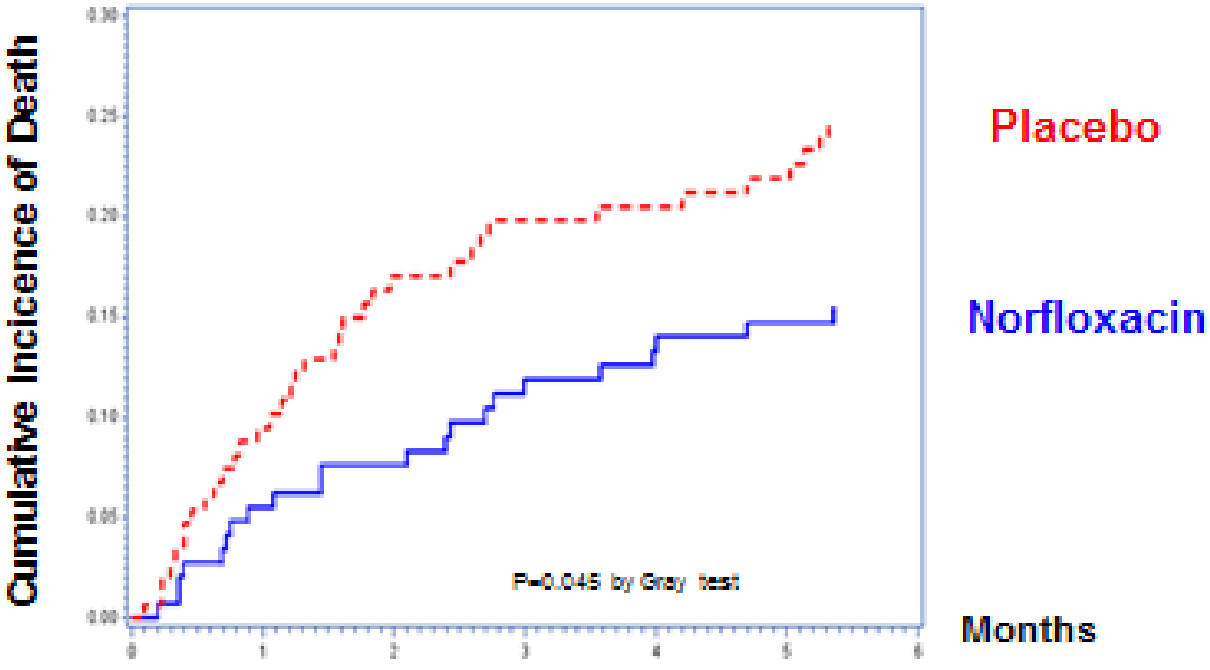
- HIV
- HCC outside Milan
- Fluoroquinolone therapy during the last month

Outcomes

- Primary: 6-month mortality
- Secondary:
  - Development of liver-related complications: kidney dysfunction, encephalopathy, variceal hemorrhage
  - Liver transplantation



Primary Outcome: 6-Month Mortality



	SHR*	95% CI	P
Unadjusted	0.586	0.346 to 0.992	0.0467
Adjusted**	0.575	0.338 to 0.979	0.0415

*Fine & Gray model. **For nonselective β-blockers and corticosteroids

Results

Secondary Outcomes at 6 Months: Infections

Outcome	Norfloxacin (N=144)	Placebo (N=147)	P (log-rank test)
	Cumulative incidence (%)		
SBP	7.9	14.3	0.15
Any infection	23.9	35.0	0.04
Gram-negative	3.2	13.0	0.005
Gram-positive	3.4	8.1	0.08
Septic shock	6.2	5.2	0.79

Conclusions

- In this trial involving patients with Child-Pugh class C cirrhosis without recent history of fluoroquinolone therapy, 6-month mortality (primary outcome) was significantly lower among patients who received norfloxacin than among those who received placebo.

- Norfloxacin also reduced the risk of infections but not that of SBP, and had no effect on the development of any other liver-related complication.

Outline

Mechanisms of portal hypertension

Spontaneous bacterial peritonitis

Hepatorenal Syndrome

Hepatic Encephalopathy

AD/ACLF

HRS and acute kidney injury in cirrhosis

Cirrhosis with ascites

Serum creatinin > 133 µmol/l

No improvement after 2 days diuretics withdrawal and albumin administration

Absence of shock, no nephrotoxic drugs, no renal parenchymatous disease

Acute kidney injury (AKI): new definition

Stage 1: ↑ SCr ≥ 26 µmol/l or ≥1.5-2.0 x from baseline

Stage 2: or ≥2.0-3.0 x from baseline

Stage 3: ≥3 x from baseline

HRS-AKI

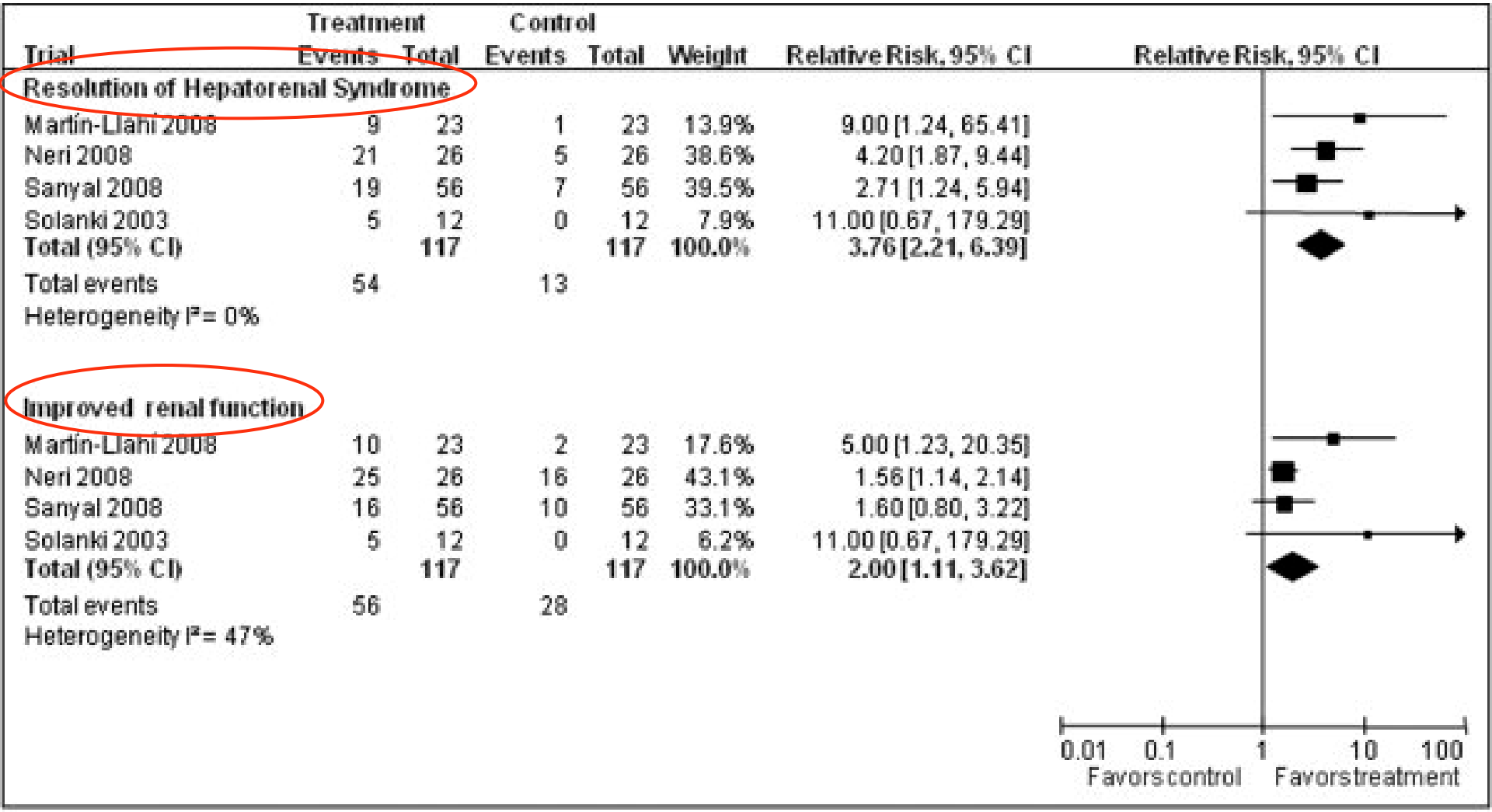
HRS and acute kidney injury in cirrhosis

Management HRS-AKI:

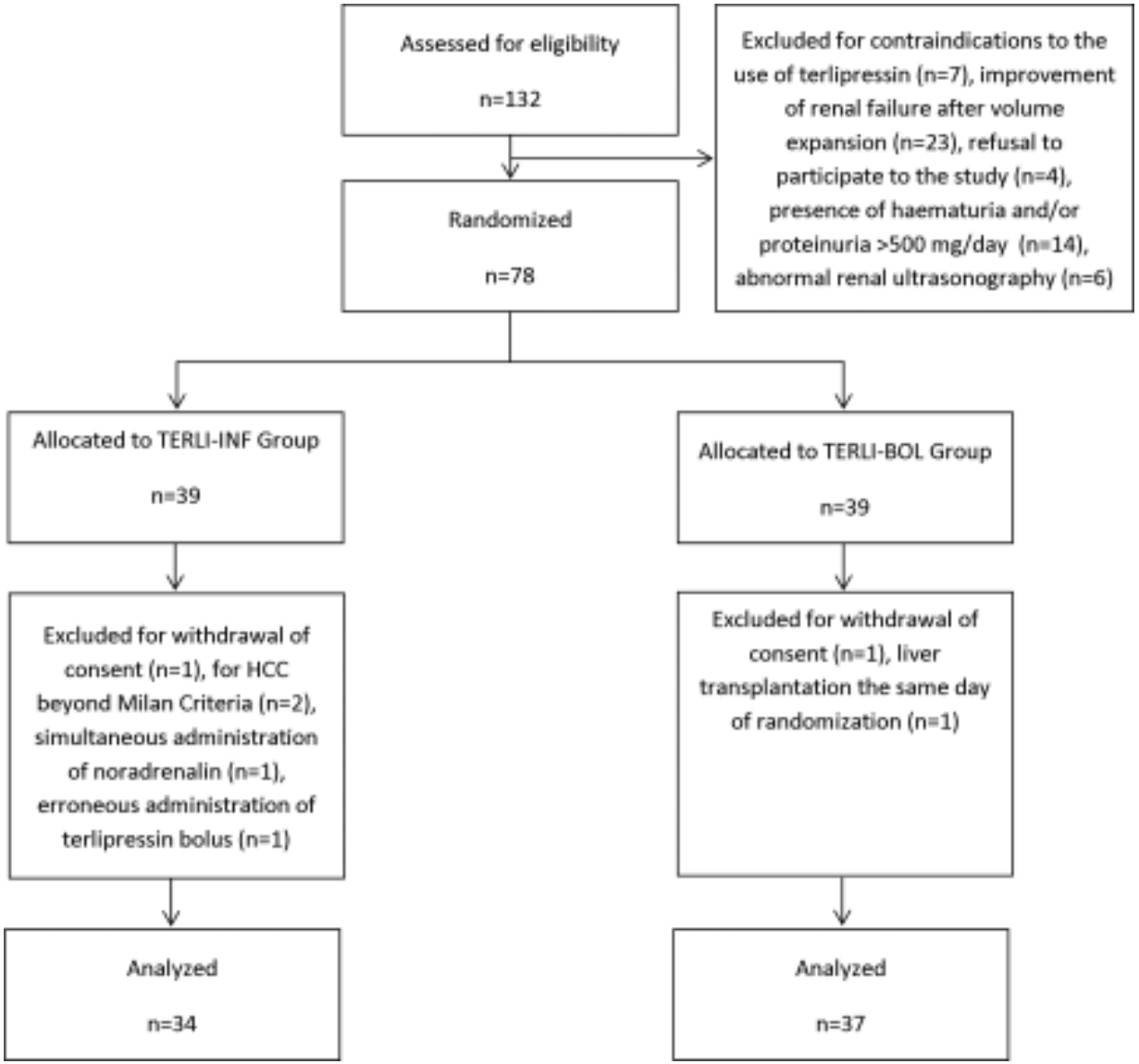
Stop all diuretics, remove precipitating event, volume expansion with albumin

V1 agonist Terlipressin: HRS reversal: 34% vs 13% albumin alone (p=0.008)

Meta-analysis: terlipressin plus albumin versus albumin for patients with HRS.



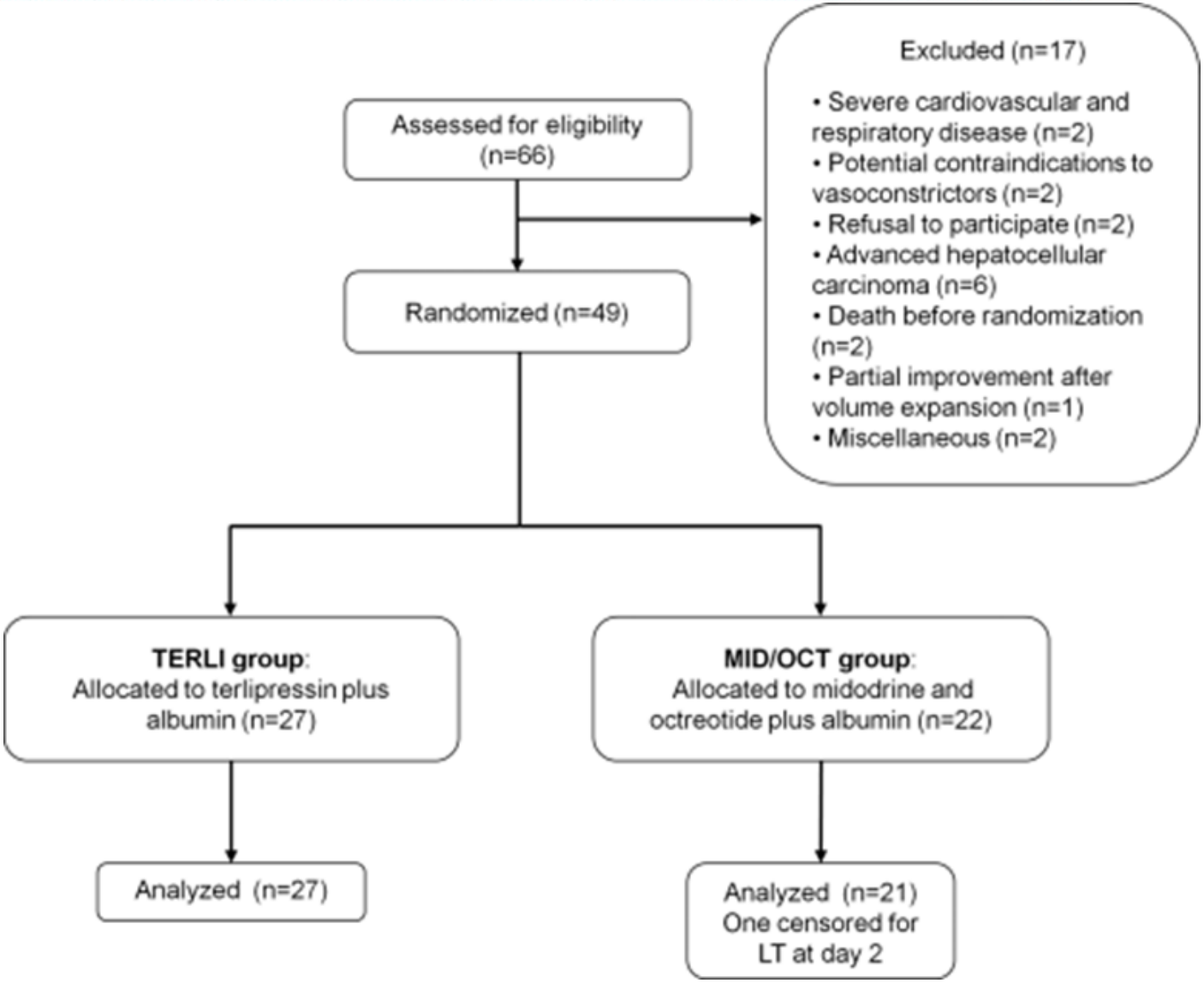
Terlipressin boluses or continuous infusion?



Terlipressin boluses or continuous infusion?

	TERLI-INF Group (n = 26)	TERLI-BOL Group (n = 24)	*P*
Response to treatment	76.5%	64.9%	NS
Maximum daily dose of terlipressin, mg	2.62 ± 1.06	4.50 ± 3.06	0.0001
Mean daily dose of terlipressin, mg	2.23 ± 0.65	3.51 ± 1.77	0.0001
Severe treatment associated AEs, no of patients (%)	7 (20.59)	16 (43.24)	<0.05

Terlipressin plus albumin versus midodrine and octreotide plus albumin in the treatment of HRS: A RCT



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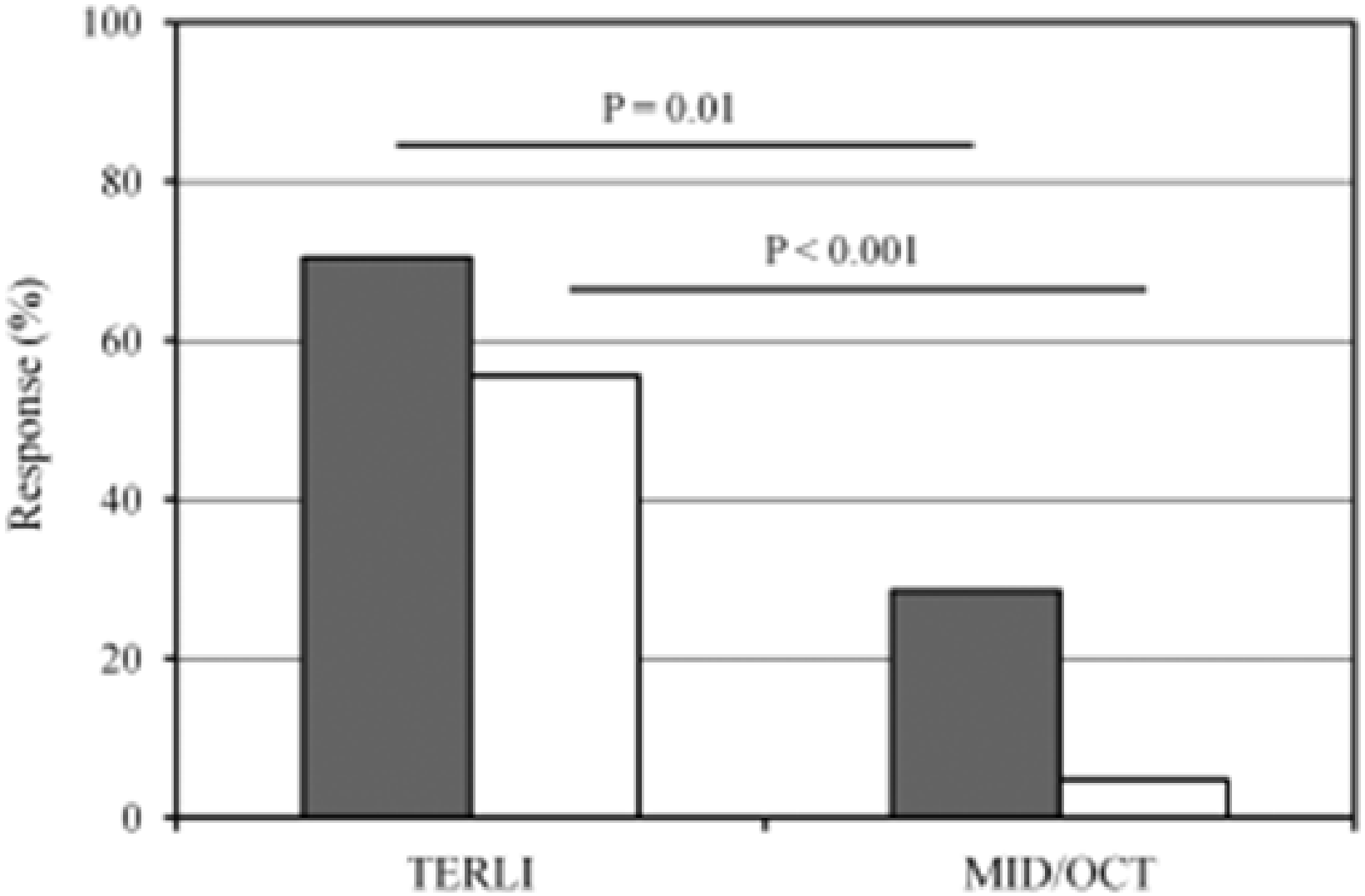

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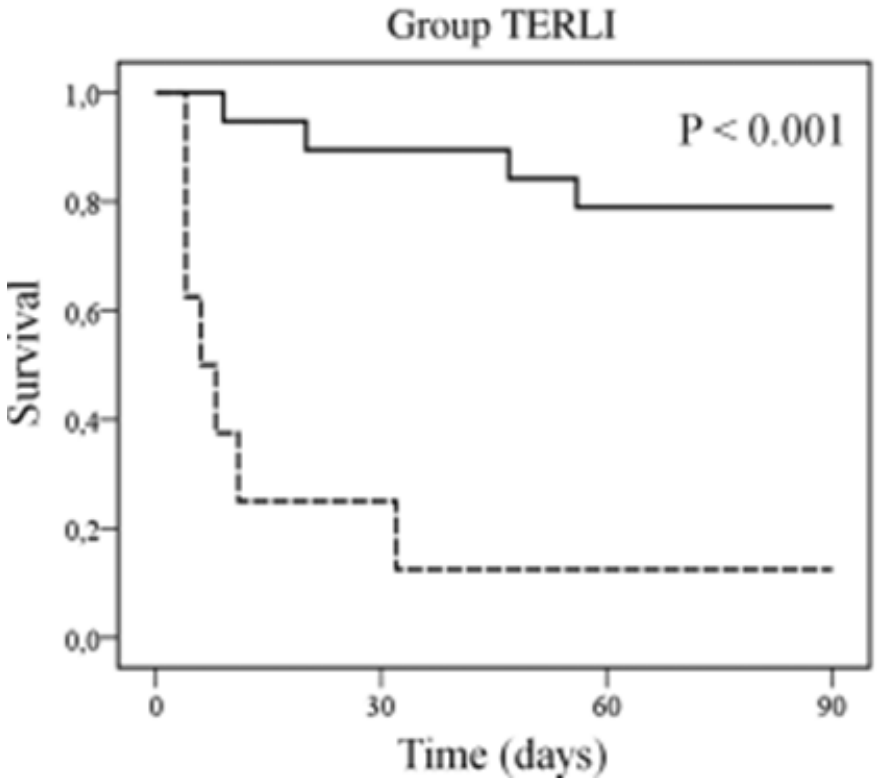

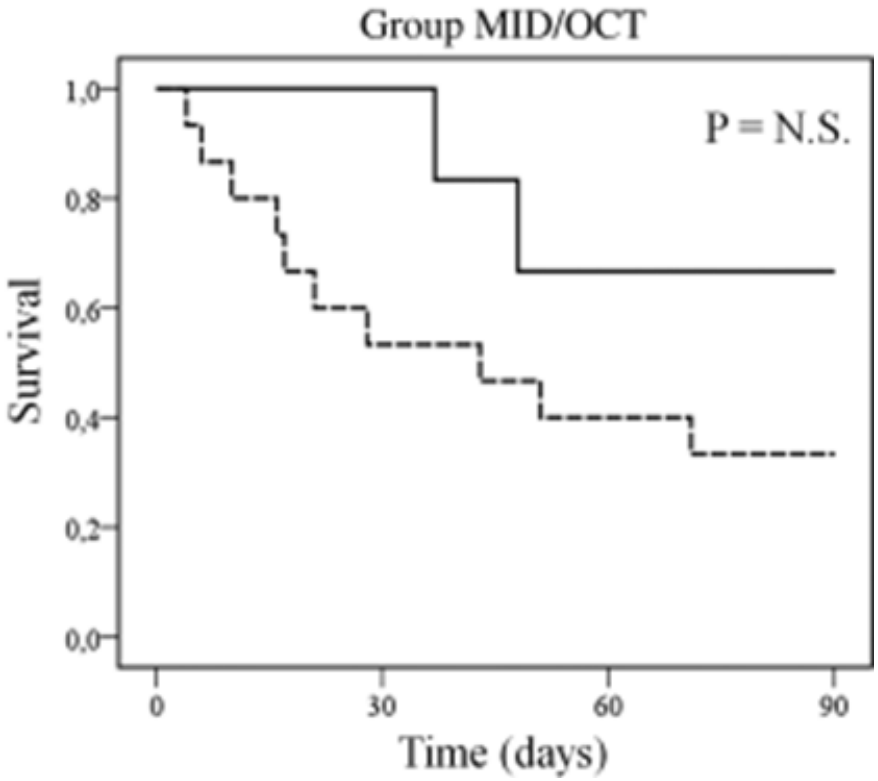

Albumin for other indications?

INFECIR-2 Albumin prevention study: European multicenter RCT

Aim: Evaluate whether albumin administration improves short-term survival in patients with advanced cirrhosis and bacterial infections other than SBP

Human Albumin for the Treatment of Ascites in Patients With Hepatic Cirrhosis **(ANSWER):** Italian RCT

Aim: define the effectiveness of the prolonged administration of human albumin in the treatment of liver cirrhosis with ascitic decompensation

Wk 1 and 2: 40 grams twice a week followed by 1/week 40 gr

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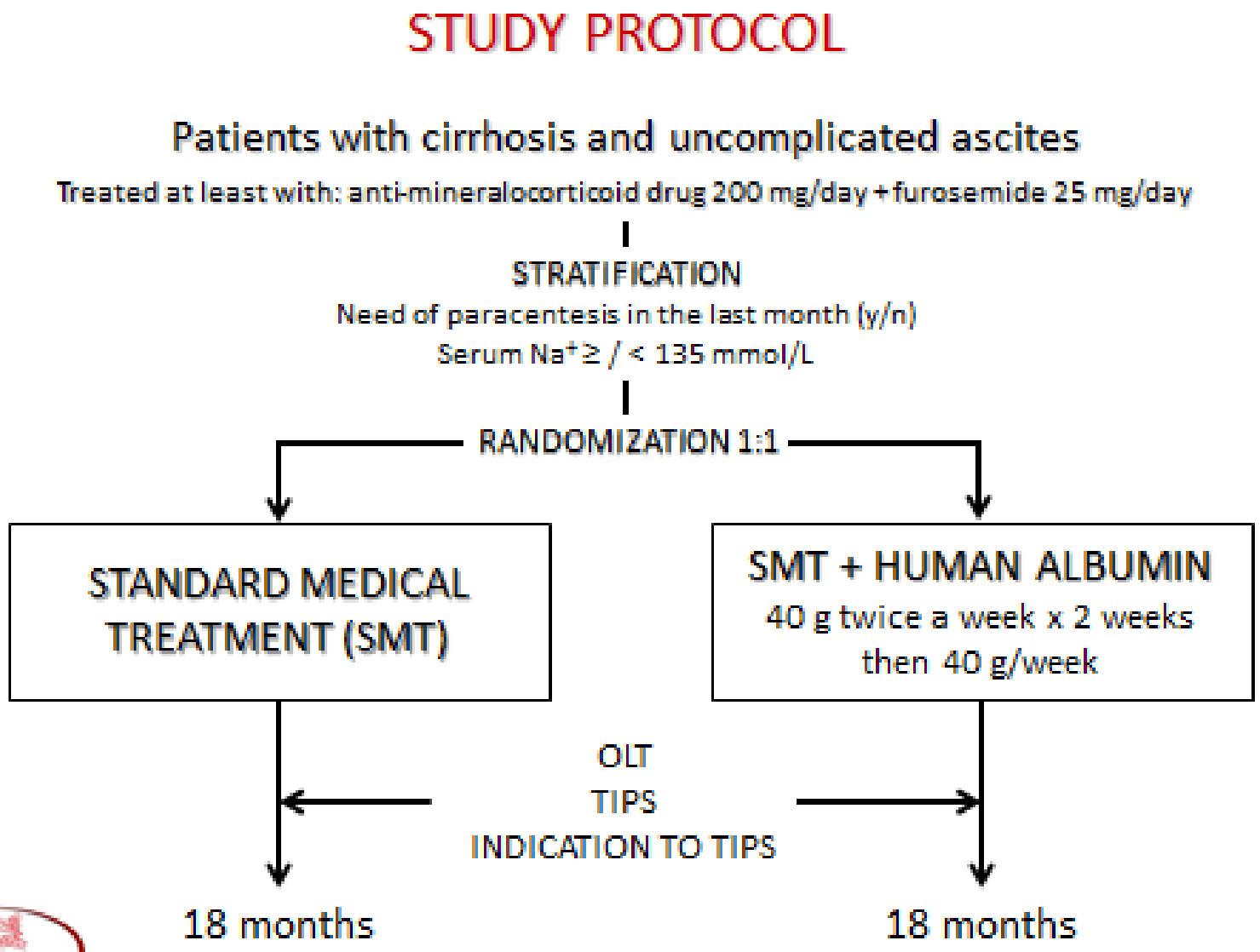
LONG-TERM ALBUMIN ADMINISTRATION IMPROVES SURVIVAL IN PATIENTS WITH DECOMPENSATED CIRRHOSIS

FINAL RESULTS OF THE "ANSWER" STUDY

The ANSWER Study Investigators

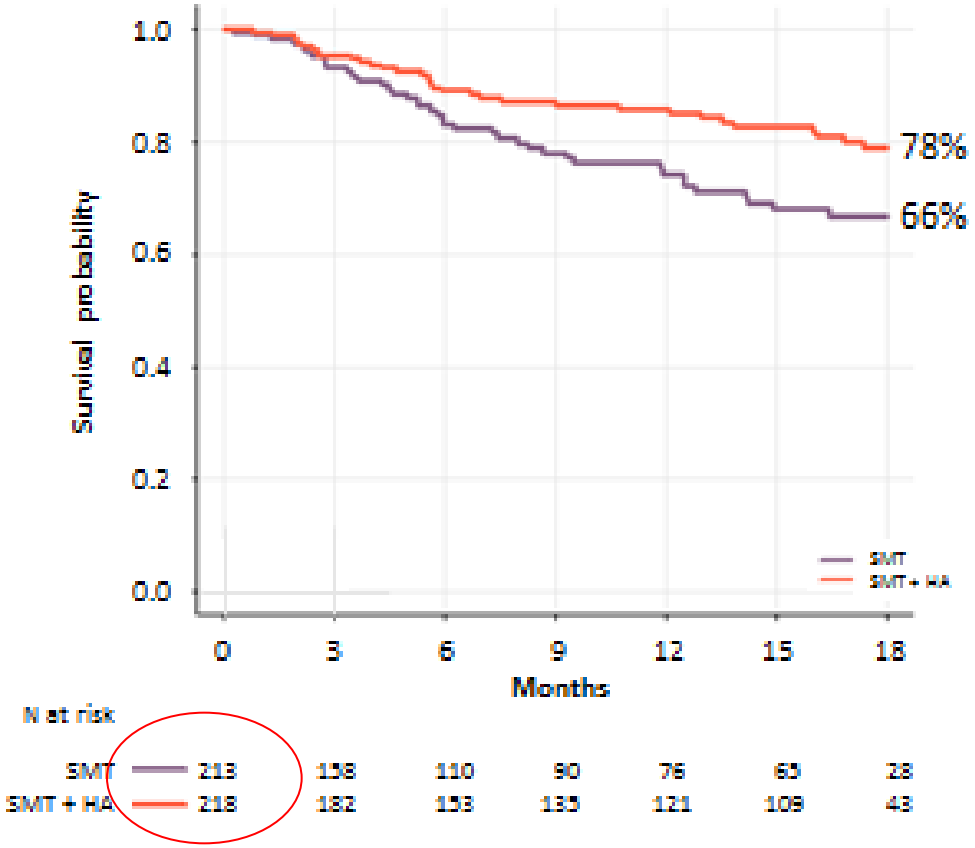
ANSWER

Methods


STUDY PROTOCOL
Patients with cirrhosis and uncomplicated ascites
Treated at least with: anti-mineralocorticoid drug 200 mg/day + furosemide 25 mg/day
STRATIFICATION
Need of paracentesis in the last month (y/n)
Serum Na+ ≥ / < 135 mmol/L
RANDOMIZATION 1:1
STANDARD MEDICAL TREATMENT (SMT)
SMT + HUMAN ALBUMIN
40 g twice a week x 2 weeks
then 40 g/week
OLT
TIPS
INDICATION TO TIPS
18 months
18 months

Results

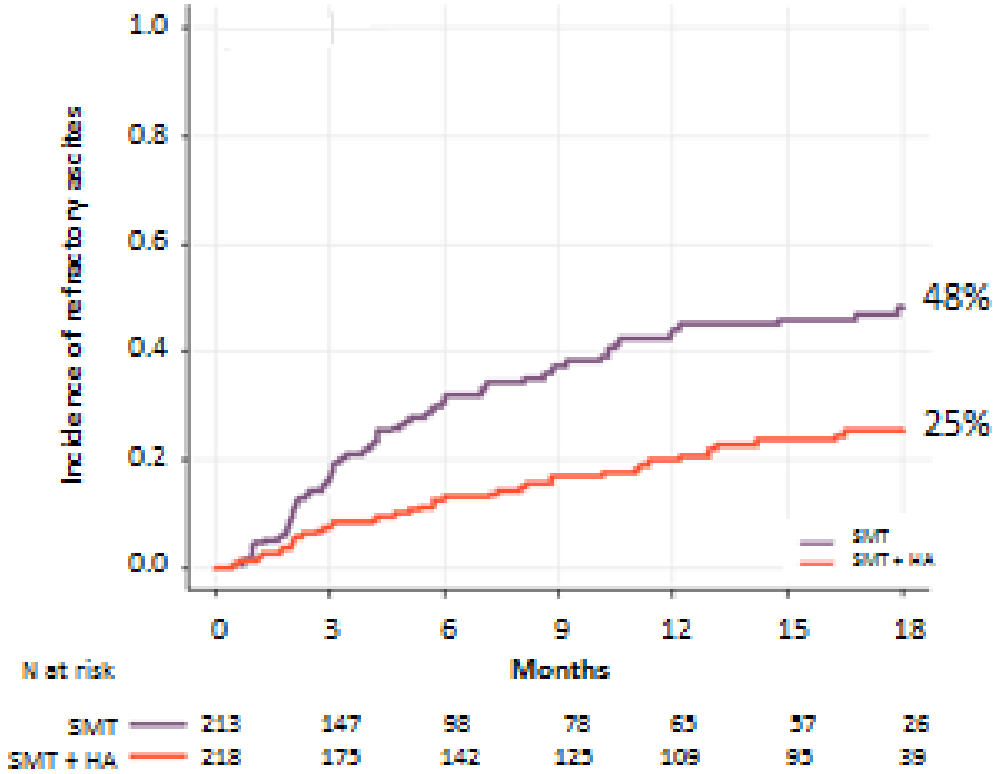
OVERALL SURVIVAL



Hazard Ratio (HA+SMT vs SMT)	Log-rank P value
0.62 (95% CI 0.40-0.95) (−38%)	0.0285

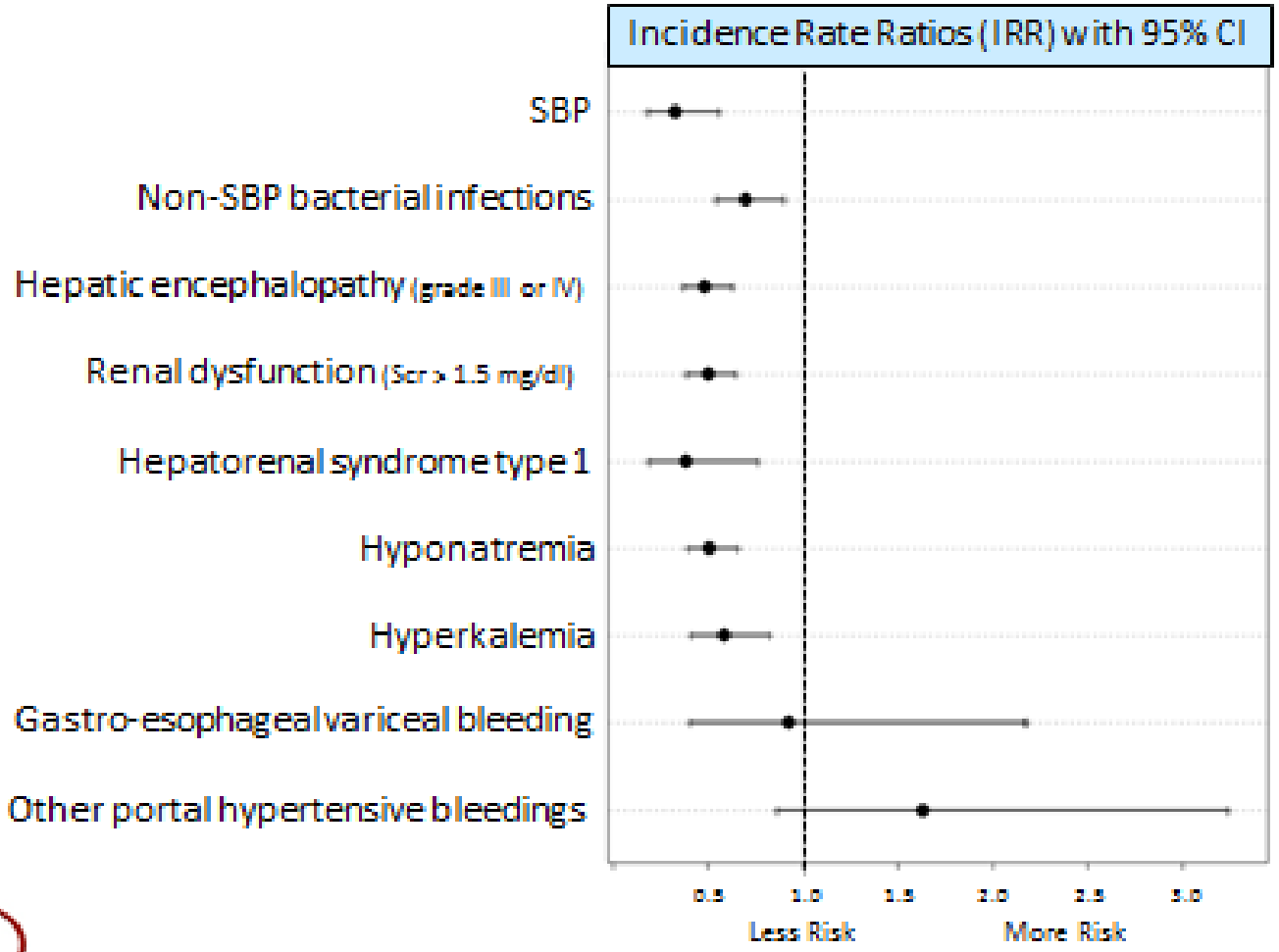
Results

INCIDENCE OF REFRACTORY ASCITES



Hazard Ratio (HA+SMT vs SMT)	Log-rank P value
0.54 (95% CI 0.29-0.62) (−46%)	< 0.0001

INCIDENCE OF COMPLICATIONS



CONCLUSIONS

Long-term albumin administration to patients with cirrhosis and ascites:

- Facilitates the management of ascites
- Improves survival and the quality of life
- Reduces the incidence of severe complications of cirrhosis
- Reduces the number of hospitalizations
- It is generally well tolerated

Long-term albumin administration to patients with decompensated cirrhosis could be seen as a disease-modifying treatment

Change in paradigm in cirrhosis

TRADITIONAL: stepwise progression of cirrhosis

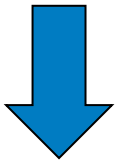
Ascites

Variceal bleeding

Hepatic encephalopathy

Hepatorenal syndrome

....



Acute decompensation - Acute on chronic liver disease (ACLF)

Vraag

Welke van de volgende stellingen over acuut op chronisch leverfalen (ACLF) is juist?

A. ACLF wordt gekenmerkt door sterk verhoogde aminotransferasen bij patiënten met eindstadium levercirrose
B. ACLF is reversibel in ongeveer 50% van de patiënten
C. ACLF ontstaat in 50% van de gevallen na een acute tractus digestivusbloeding
D. Patienten met ACLF die niet-selectieve betablockers gebruiken, hebben een verhoogde kans op mortaliteit vergeleken met patiënten die dat niet gebruiken

Acute on Chronic Liver Failure

Hepatic and systemic inflammation lead to acute deterioration of liver function

Regardless of underlying stage of cirrhosis

Due to superimposed injury or precipitating infection

Organ failures

High mortality rate

Acute on chronic liver failure: CANONIC study

Prospective observational study in 1343 hospitalized patients with cirrhosis and acute decompenstion (AD) from February to September 2011 at 29 liver units in 8 European countries

303 had ACLF at inclusion	; 28-day mortality 34%
112 developed ACLF during admission	: mortality 30%
928 did not have ACLF	: mortality 2%

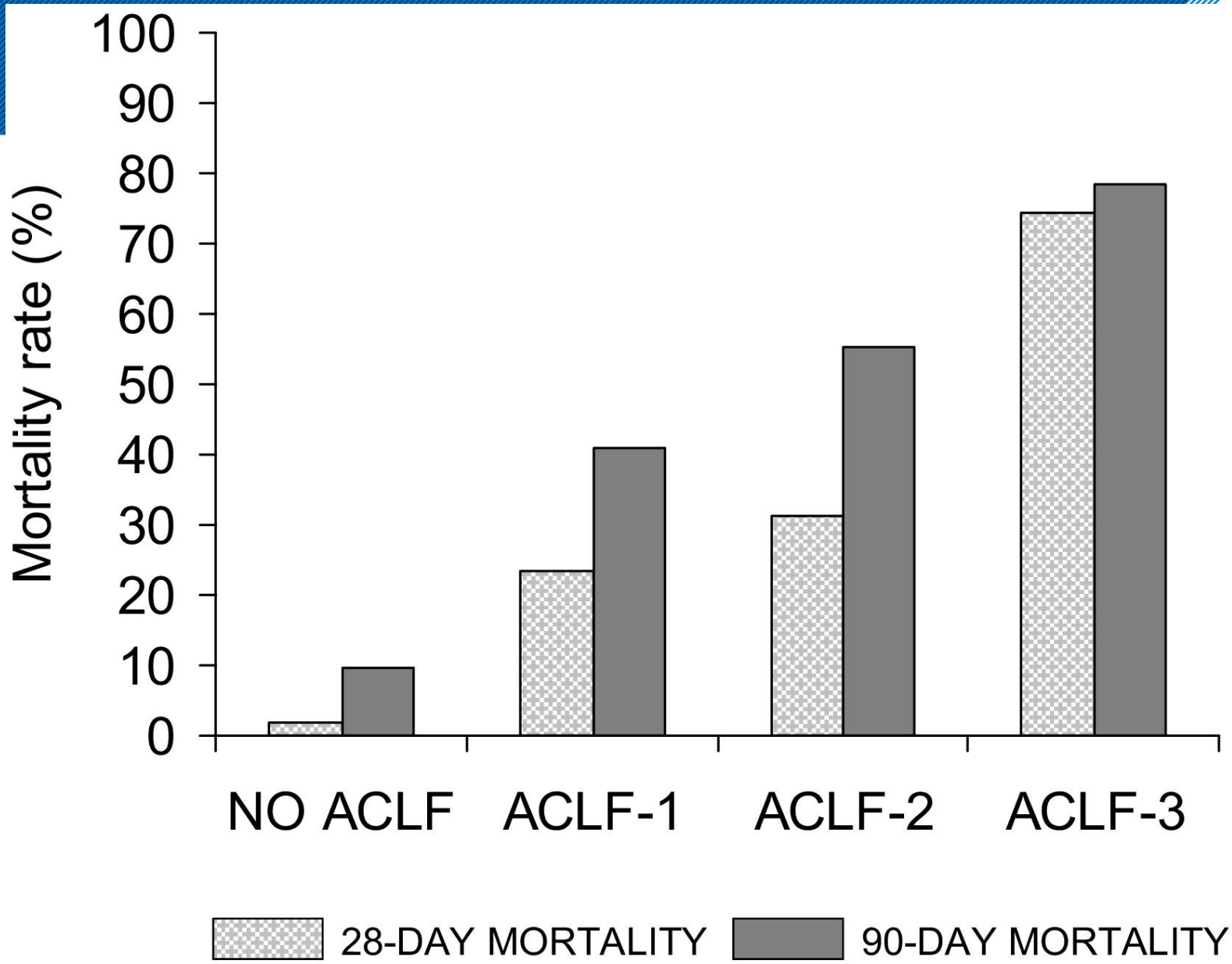
ACLF: organ failure(s)

CLIF-SOFA Score

Organ/system	0	1	2	3	4
Liver (TBil, mg/L)	<1.2	≥1.2 to < 2.0	≥2.0 to < 6.0	≥6.0 to< 12.0	≥12.0
Kidney (Cr, mg/dl)	<1.2	≥1.2 to < 2.0	≥2.0 to < 3.5	≥3.5 to< 5.0	≥5.0
Cerebral (HE grade)	No HE	I	II	III	IV
Coagulation (INR)	<1.1	≥1.1 to < 1.25	≥1.25 to < 1.5	≥1.5 to< 2.5	≥2.5 or PLT≤20 ×10⁹/L
Circulation (MAP, mmHg)	≥70	< 70	DA ≤5 or DOB or Terlipressin	DA >5 or E ≤0.1 or NE ≤0.1	DA >15 or E > 0.1 or NE > 0.1
Lung PaO_2/FiO_2	>400	>300 ≤400	> 200 to≤300	> 100 to ≤200	≤100
or SpO_2/FiO_2	>512	>357 to ≤512	> 214 to ≤357	>89 to ≤ 214	≤89

[Clif Research > Tools - Calculators](https://www.clifresearch.com/ToolsCalculators.aspx)

https://www.clifresearch.com/ToolsCalculators.aspx



ACLF-1: single kidney failure (creat>2.0 mg/dl) or single organ failure and creatinin 1.5-1.9 mg/dl and/ or mild-moderate hepatic encephalopathy

Development of ACLF

50% of cases have precipitating event (bacterial infection, active alcoholism) as initiator of AD/ACLF

Associated with **systemic inflammation**, even without precipitating event

Circulatory failure

…role in pathogenesis/ prognosis of AD/ ACLF…

Renin and Copeptin (cleavage product of pre-pro-AVP secreted equimolarly), biomarkers of hemodynamic derangement associated with mortality

Clinical course of ACLF syndrome and effects on prognosis

Goal: improve management and minimize futile care

Overall course of ACLF

49% ACLF resolution or improvement

30% fluctuating course, unchanged final ACLF grade

20% worsening ACLF

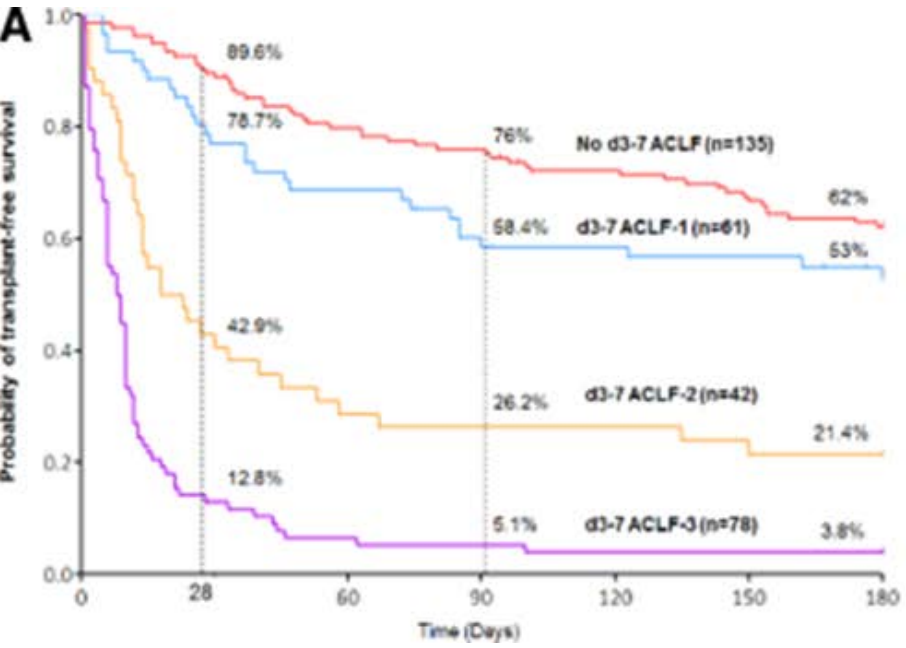
Resolution of ACLF < 28 days occurs in 42% of patients

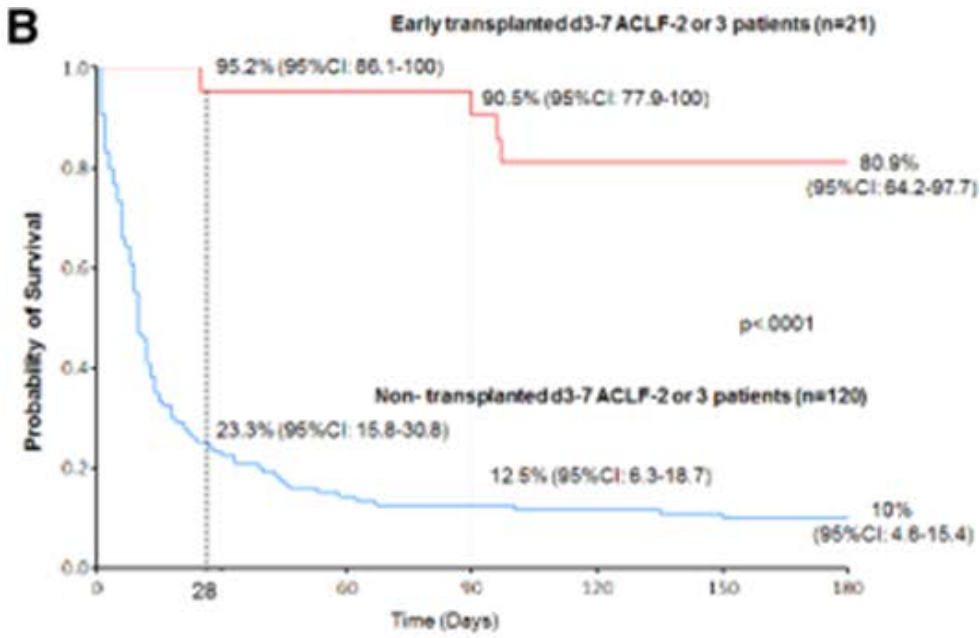
ACLF-1 55%

ACLF-2 35%

ACLF-3 16%

Clinical course of ACLF syndrome and effects on prognosis





Intensive care of patients with ACLF should be continued during the first 7 days after ACLF diagnosis

Take home messages

Chronic inflammation (bacterial translocation, innate immunity activation) central role in portal hypertension

ACLF very dynamic syndrome

CLIF-AD and CLIF-ACLF score for prognosis

Intensive care of patients with ACLF should be continued during the first 7 days after ACLF diagnosis

Inflammation/ circulatory dysfunction in pathogenesis of ACLF
… implications for new treatment options

Vraag

Welke van de volgende stellingen over acuut op chronisch leverfalen (ACLF) is juist?

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B. ACLF is reversibel in ongeveer 50% van de patiënten
C. ACLF ontstaat in 50% van de gevallen na een acute tractus digestivusbloeding
D. Patienten met ACLF die niet-selectieve betablockers gebruiken, hebben een verhoogde kans op mortaliteit vergeleken met patiënten die dat niet gebruiken

TIPS versus paracentesis: 5 meta-analyses

Ref	ascites recurrence	encephalopathy	survival
Albillos 2005	lower	higher	no difference
Deltenre 2005	lower	higher	no difference
D´Amico 2005	lower	higher	no difference
Saab 2006	lower	higher	no difference
Salerno 2007	lower	higher	better in TIPS

Cautious selection of patients for TIPS treatment

Contraindications: bilirubin > 85 µmol/l, INR>2, CP score >11, HE ≥grade 2, active infection, renal failure or cardiopulmonary disease

Revised classification system of renal dysfunction

Goal: broaden diagnosis of renal dysfunction in cirhosis

AKI: acute deterioration of renal function (>50% increase or > 26 µmol/l rise < 48 h)

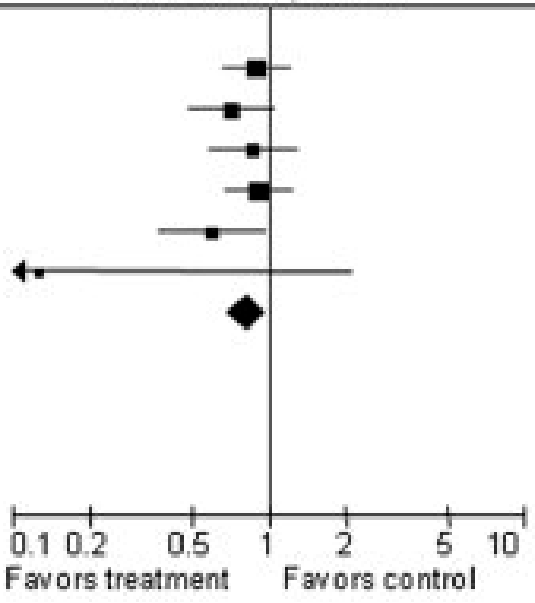
Chronic renal disease: GFR < 60 ml/min for > 3 months

Acute on chronic kidney disease: AKI superimposed on chronic

Future treatment strategies…..

Meta-analysis: vasoconstrictor drugs alone or with albumin versus no intervention or albumin for HRS

Trial	Treatment Events	Total	Control Events	Total	Weight	Relative Risk, 95% CI
Mortality						
Martin-Llahi 2008	17	23	19	23	27.3%	0.89 [0.66, 1.22]
Neri 2008	15	26	21	26	17.9%	0.71 [0.49, 1.04]
Pomier 2003	7	9	9	10	15.6%	0.86 [0.58, 1.30]
Sanyal 2008	32	56	35	56	27.7%	0.91 [0.67, 1.24]
Solanki 2003	7	12	12	12	11.2%	0.60 [0.37, 0.97]
Yang 2001	0	8	3	7	0.3%	0.13 [0.01, 2.10]
Total (95% CI)		**134**		**134**	**100.0%**	**0.82 [0.70, 0.96]**
Total events	78		99			
Heterogeneity $I^2 = 0\%$						



Vraag 1

Welke van de volgende factoren speelt GEEN rol in het ontstaan van portale hypertensie?

A. Angiogenese
B. Bacteriële translocatie
C. Vasodilatatie in splanchnicusgebied
D. Verlaagde serum aldosteron concentratie

Table 3. Patient Characteristics at Enrollment

Characteristic	No ACLF (n = 1040)	ACLF all grades (n = 303)	*P* value[a]	ACLF grade 1 (n = 148)	ACLF grade 2 (n = 108)	ACLF grade 3 (n = 47)	*P* value[b]
Age (*y*)	58 ± 12	56 ± 11	.02	58 ± 12	54 ± 11	52 ± 12	<.01
Male sex	655 (63.0)	195 (64.4)	.66	104 (70.3)	66 (61.1)	25 (53.2)	.14
Ascites	656 (63.4)	236 (78.7)	<.001	112 (76.2)	87 (82.1)	37 (78.7)	.08
Mean arterial pressure (*mm Hg*)	85 ± 12	79 ± 13	<.001	81 ± 13	79 ± 13	72 ± 10	<.001
Cause of cirrhosis							
Alcohol	483 (49.2)	170 (60.3)	<.01	86 (61.9)	64(59.8)	26 (56.5)	<.01
Hepatitis C virus	210 (21.4)	38 (13.0)	<.01	15 (10.8)	17 (15.9)	6 (13.0)	.01
Alcohol plus hepatitis C virus	95 (9.7)	27 (9.3)	.83	14 (10.1)	9 (8.5)	4 (8.7)	.97
Potential precipitating events of ACLF							
Bacterial infection	226 (21.8)	98 (32.6)	<.001	44 (29.9)	33 (30.8)	21 (44.7)	<.001
Gastrointestinal hemorrhage	180 (17.3)	40 (13.2)	.09	15 (10.1)	14 (13.0)	11 (23.4)	.06
Active alcoholism within the past 3 months	147 (14.9)	69 (24.5)	<.001	22 (16.1)	28 (28.6)	19 (40.4)	<.001
Other precipitating event[c]	34 (3.5)	25 (8.6)	<.001	12 (8.5)	10 (9.6)	3 (6.7)	<.01
No precipitating event[d]	584 (58.9)	126 (43.6)	<.001	73 (51.4)	40 (40.0)	13 (27.3)	<.001
More than one precipitating event[e]	56 (5.7)	39 (13.5)	<.001	17 (12.0)	14 (14.0)	8 (17.0)	<.001
Organ failures							
Liver	75 (7.2)	132 (43.6)	<.001	37 (25.2)	65 (60.2)	30 (63.8)	<.001
Kidney	0 (0)	169 (55.8)	<.001	87 (58.8)	49 (45.4)	33 (70.2)	<.001
Cerebral	26 (2.5)	73 (24.1)	<.001	5 (3.4)	35 (32.4)	33 (70.2)	<.001
Coagulation	21 (2.0)	84 (27.7)	<.001	11 (7.4)	42 (38.9)	31 (66.0)	<.001
Circulation	13 (1.3)	51 (16.8)	<.001	3 (2.0)	18 (16.7)	30 (63.8)	<.001
Lungs	4 (0.4)	28 (9.2)	<.001	5 (3.4)	7 (6.5)	16 (34.0)	<.001
Kidney dysfunction	96 (9.2)	40 (13.2)	.04	26 (17.6)	8 (7.4)	6 (12.8)	.01