Leids Universitair
Medisch Centrum

Niet-selectieve bètablockers bij gedecompenseerde levercirrose

Medicatiegebruik en leverziektes: gunstig of schadelijk?
DLW 2017

Dr. M.J. Coenraad

Maag- Darm- en Leverziekten

LEIDEN

No disclosures

Casus: vrouw 56 jaar

Voorgeschiedenis:

2014 Alcoholische levercirrose

2015 Hoge tractus digestivusbloeding uit reflux oesofagitis graad 2, bulbitis

2017 Refractaire ascites, Child Pugh B cirrose

Verwezen voor evaluatie voor levertransplantatie na > 6 maanden abstinentie

Tussentijdse presentatie op polikliniek wegens massale ascites

In 4 dagen +9 kg gewichtstoename

Ernstige mechanische bezwaren

Medicatie: o.a. furosemide 2x 40 mg, spironolacton 200 mg, thiamine, propranolol 2x40 mg

Opname voor ontlastende paracentese

Vraag: wat te doen met propranolol?

1. Direct stoppen
2. Afbouwen tot stop in 5-7 dagen
3. Dosis halveren (2x20 mg)
4. Gewoon doorgaan met zelfde dosis
5. Ik weet het niet

Aanvullende gegevens casus

RR 130/63 mmHg

Pols 60/min

Lengte 165 m, gewicht 60 kg

Graad 3 ascites, caput medusae

Lab:

Na 132 mmol/l

creatinine 87 µmol/l

Bilirubine 19 µmol/l

Albumine 25 g/l

INR 1.3

Echo bovenbuik:

Bekende levercirrose met kenmerken van portale hypertensie en ascites. Geen aanwijzingen voor HCC. Vena portae open. Graciele venae hepatica.

Nonselective beta-blockers

Non-selective betablockers (NSBBs) represent the cornerstone of pharmacological treatment of portal hypertension since 1980

Inhibition of

B_1 reduction heart rate, cardiac output, renin excretion

B_2 peripheral vasoconstriction, reduction norepinephrin

Carvedilol: α_1 vasodilation and reduction renin

Consequence:

1. reduction cardiac output
2. Bradycardia
3. Hypotension
4. reduction in renin concentration

Patients with medium-large varices (unchanged)

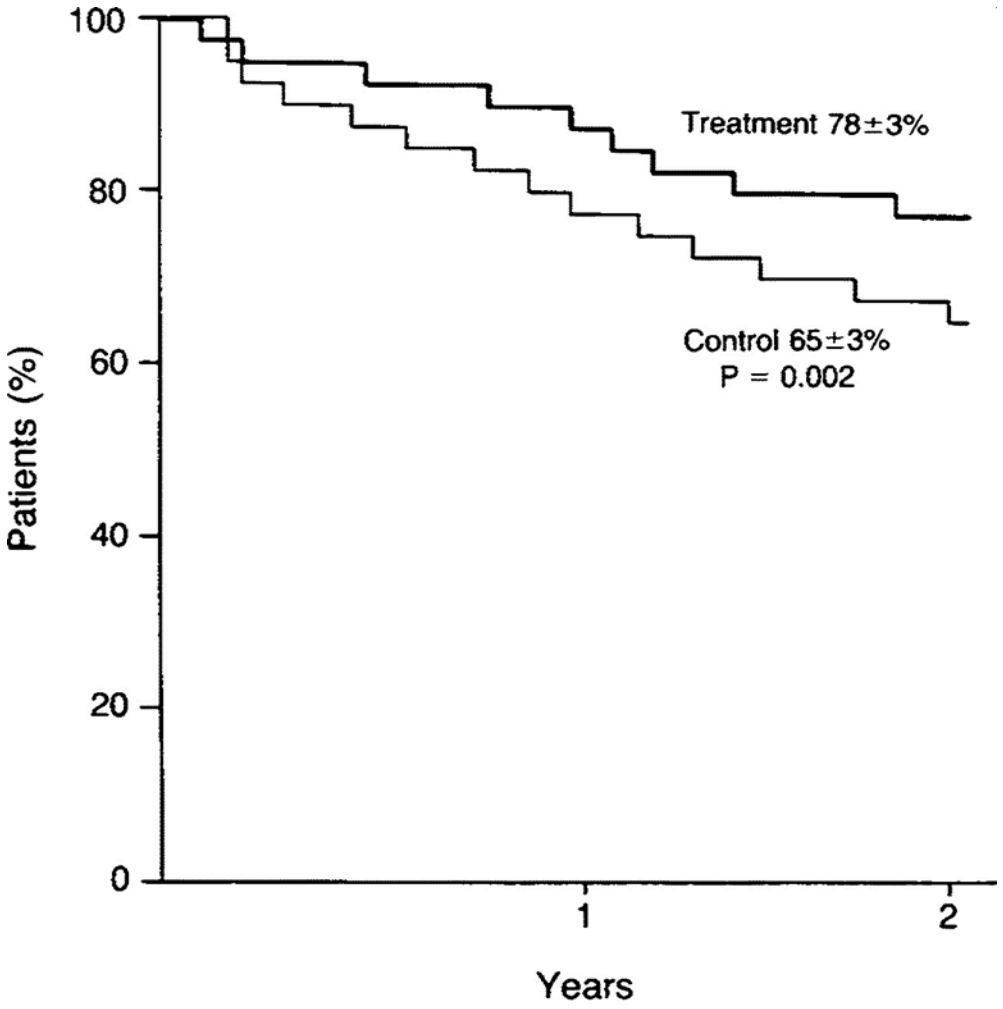
- Either NSBB or endoscopic band ligation is recommended

for the prevention of the first variceal bleeding of medium or large varices (1a;A).

- The choice of treatment should be based on local

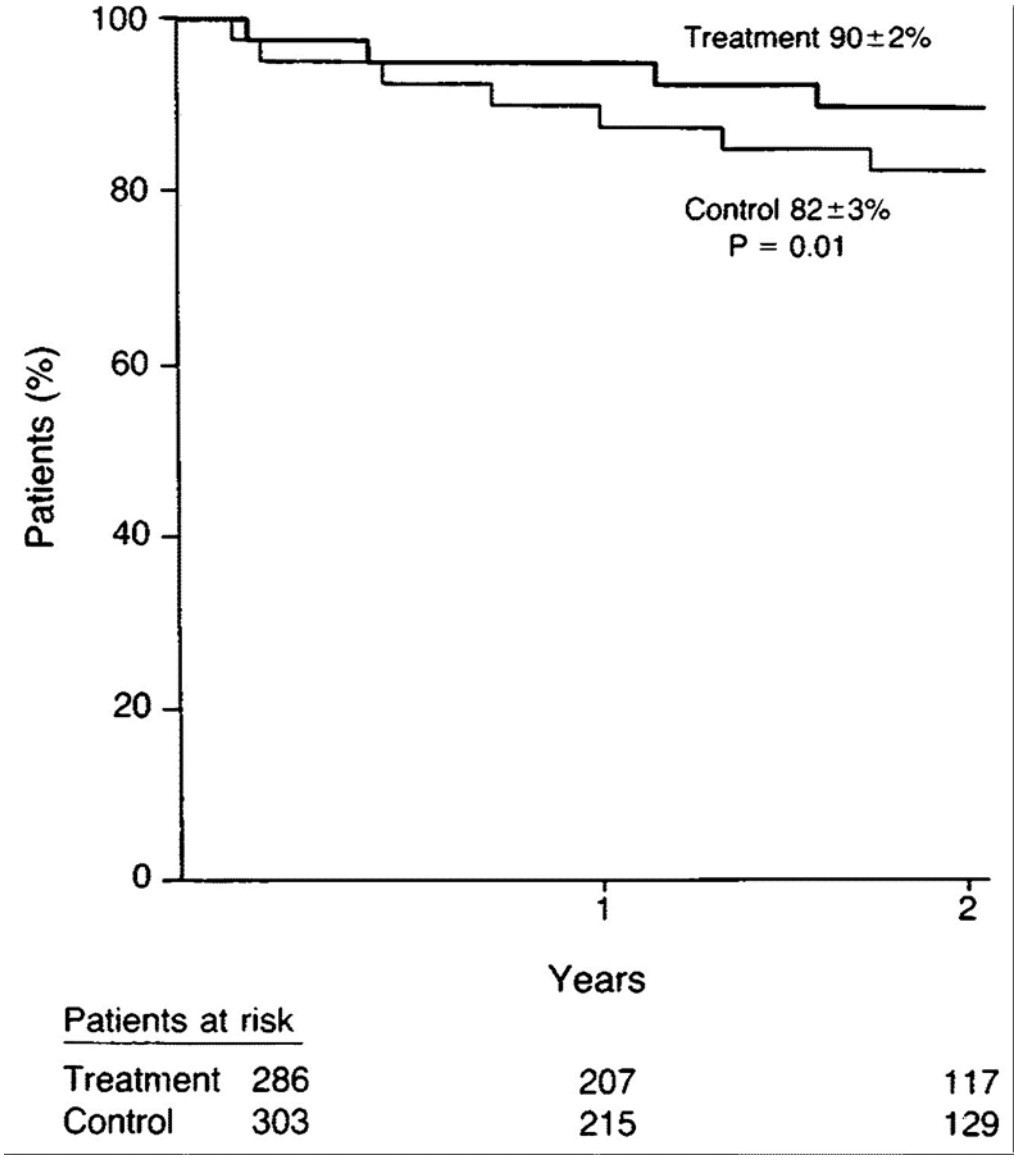
resources and expertise, patient preference and characteristics, contraindications and adverse events (5;D)

Mean (±SE) Percentage of Patients with Cirrhosis Who Had No Upper Gastrointestinal Bleeding during the Two-Year Treatment Period

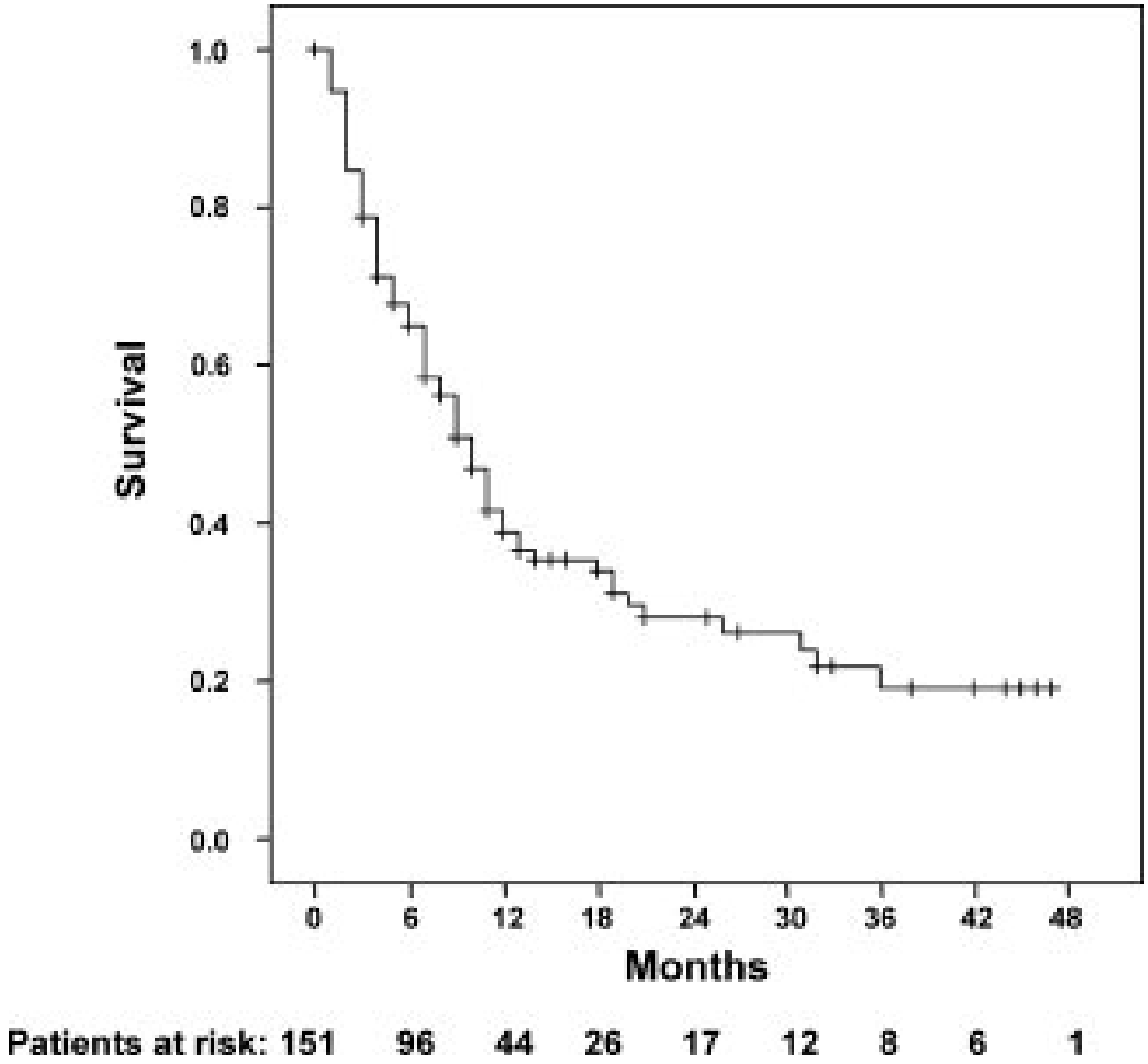


Patients at risk			
Treatment	286	192	98
Control	303	183	94

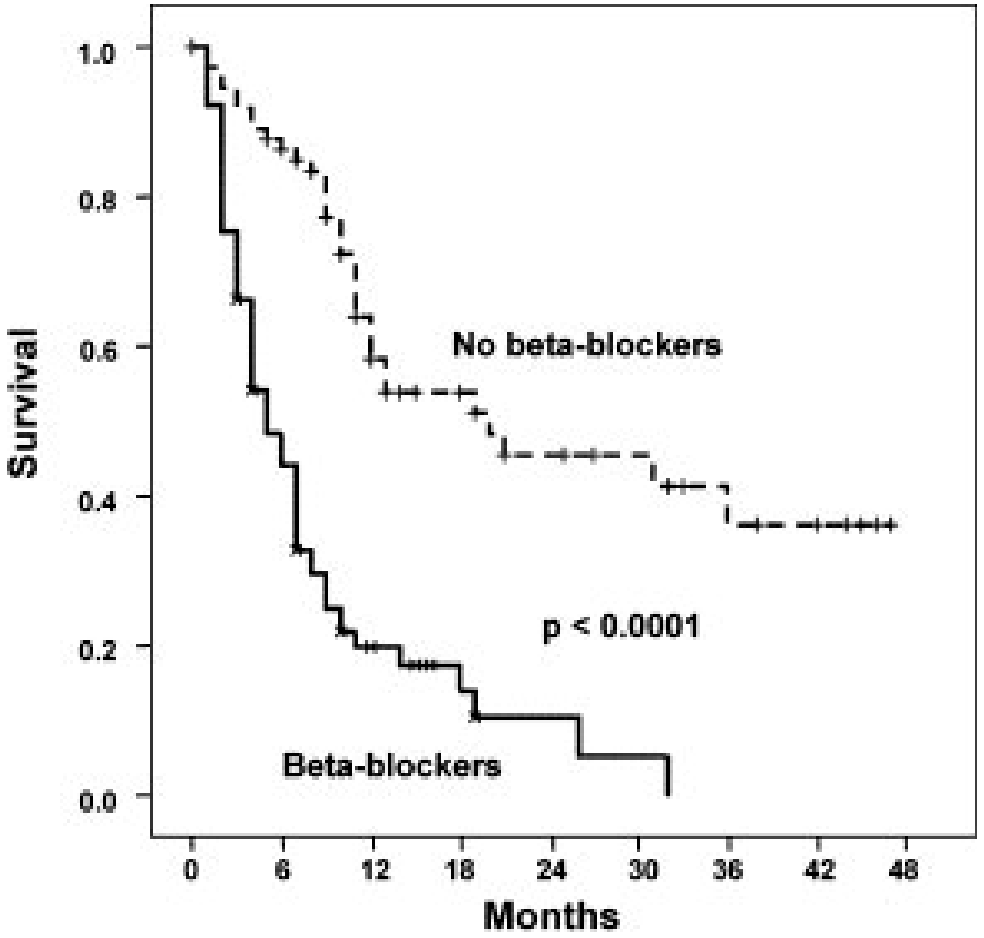
Mean (±SE) Percentage of Patients with Cirrhosis Who Did Not Die of Bleeding during the Two-Year Treatment Period



Deleterious effects of beta-blockers on survival in patients with cirrhosis and refractory ascites



Deleterious effects of beta-blockers on survival in patients with cirrhosis and refractory ascites



Patients at risk : (No beta-blockers)	74	63	34	21	15	11	8	6	1
Patients at risk : (Beta-blockers)	77	33	10	5	2	1			

Vervolg casus

Propranolol en overige medicatie gecontinueerd

Ontlastende paracentese: 12 liter

Albumine 8-10 g per liter infusie

Na paracentese RR 95/49 mmHg (was 130/63 mmHg)

Vraag: NSBB nu staken?

- Ja
- Nee
- Weet niet

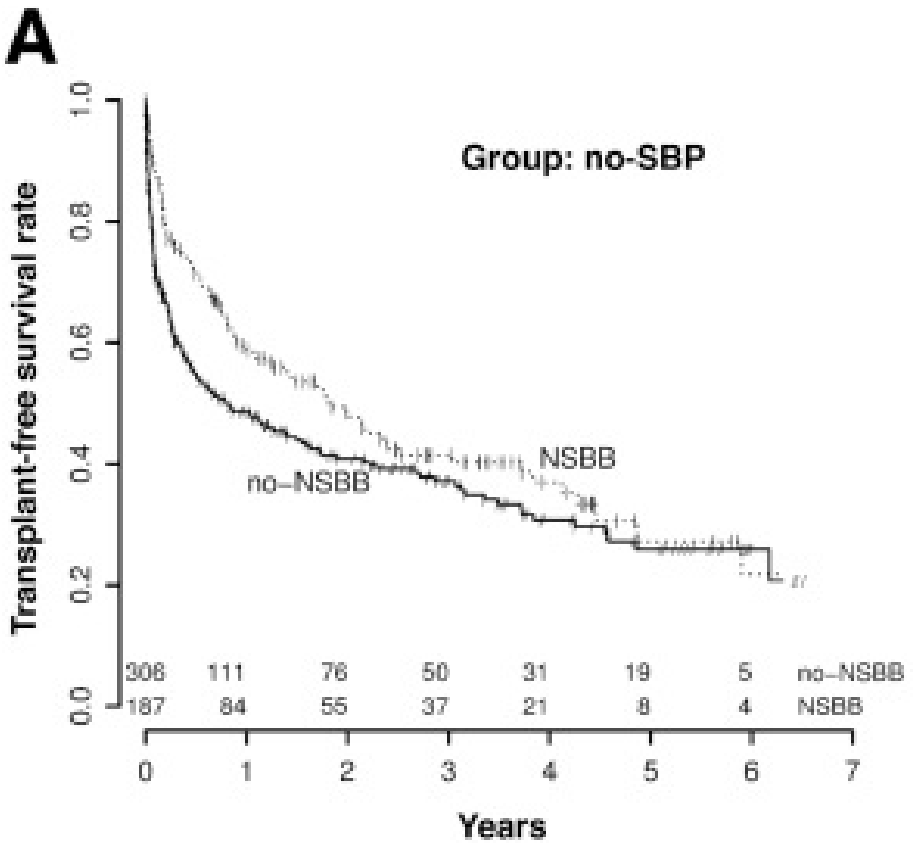
Vraag: NSBB nu staken?

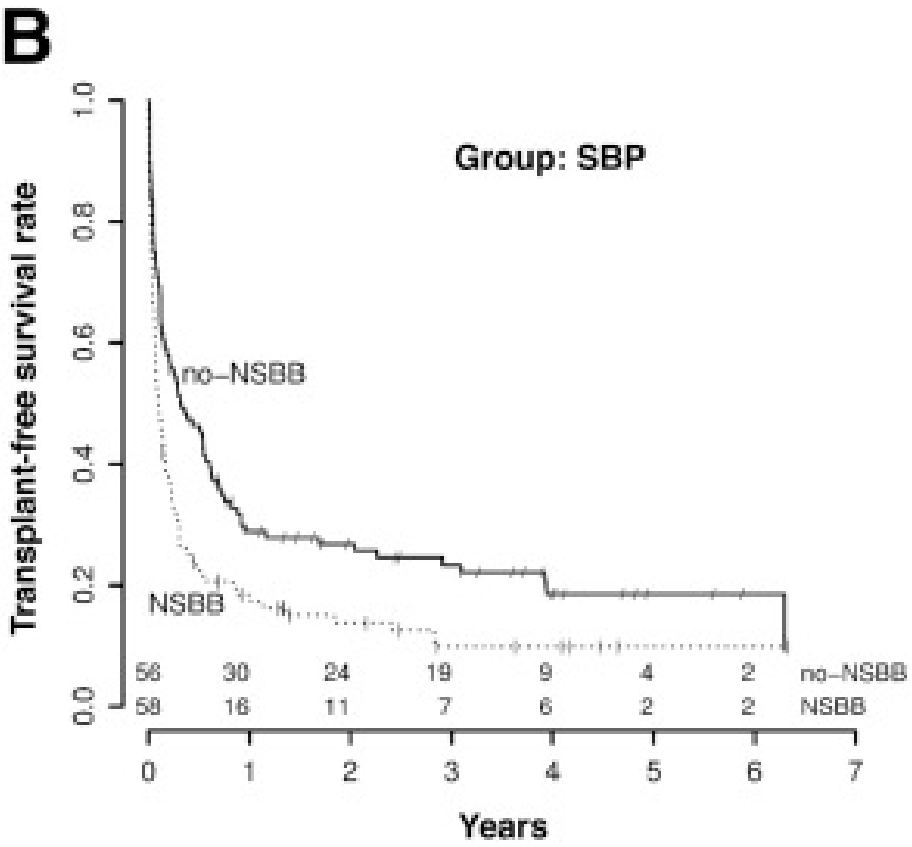
- Ja
- Nee
- Weet niet

Ascites

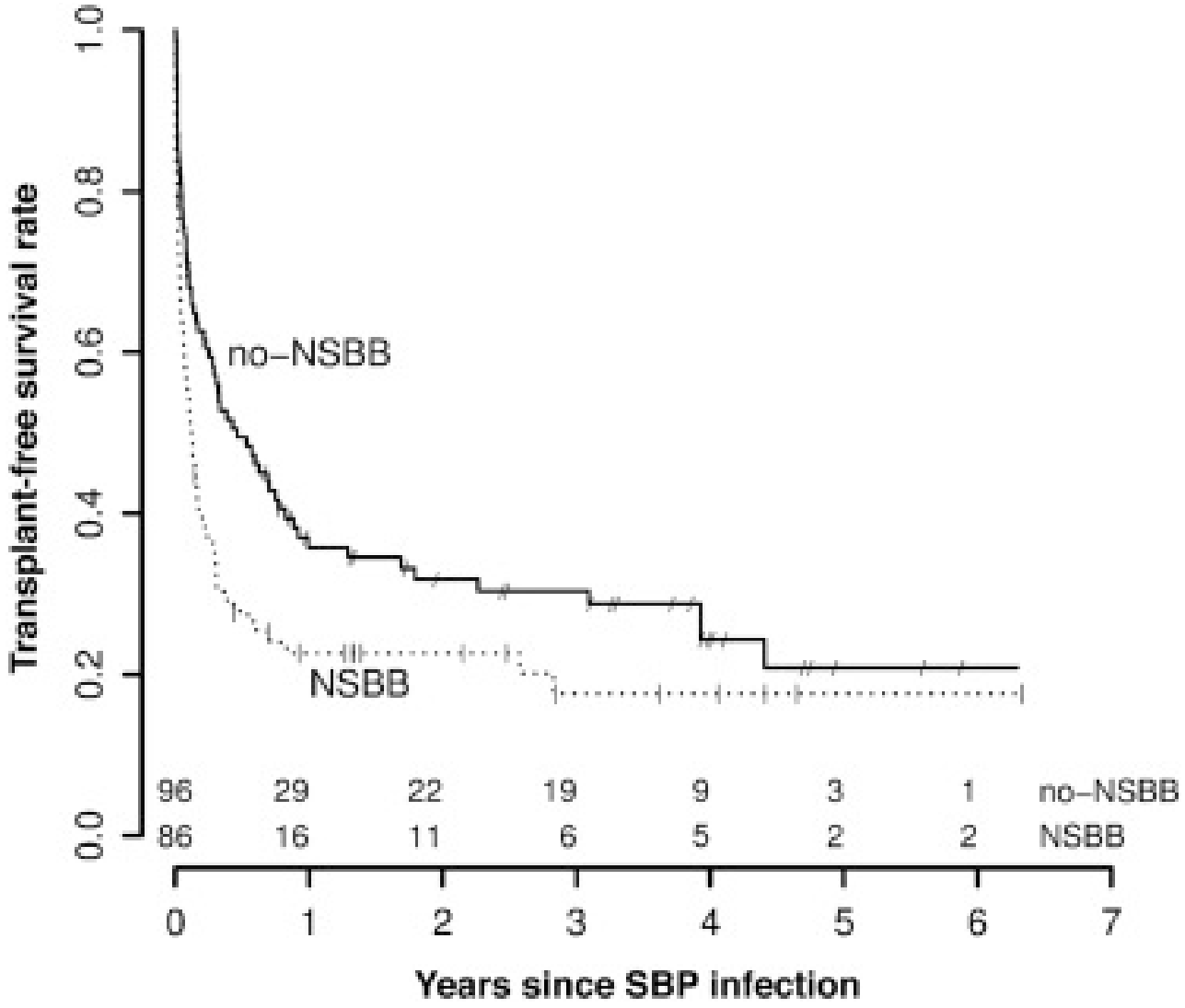
- Saag 18
- Ascites Granulocytes 0.05 x 109/l

Impact of NSBB treatment on transplant-free survival according to SBP status

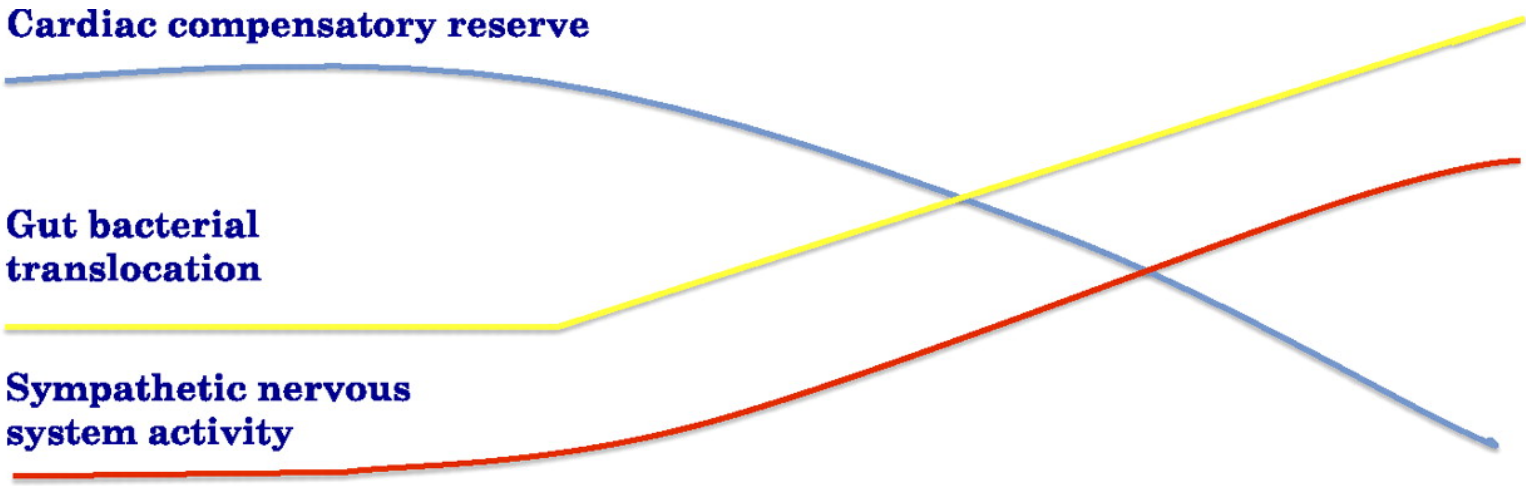




Influence of NSBB treatment on transplant-free survival after the first SBP diagnosis



Hypothesis of the therapeutic window for non-selective β-blockers (BB) in cirrhosis



BB have **no effect on survival**

Early cirrhosis

I. No risk of bacterial translocation
II. No increase in sympathetic nervous system activity
III. Cardiac compensatory reserve intact

Window opens

BB **improve survival** by reducing the risk of variceal bleeding and bacterial translocation

Compensated and decompensated cirrhosis
(Medium-large varices)

I. Increased risk of bacterial translocation
II. Increased sympathetic nervous system activity
III. Cardiac compensatory reserve intact and blood pressure and organ perfusion protected

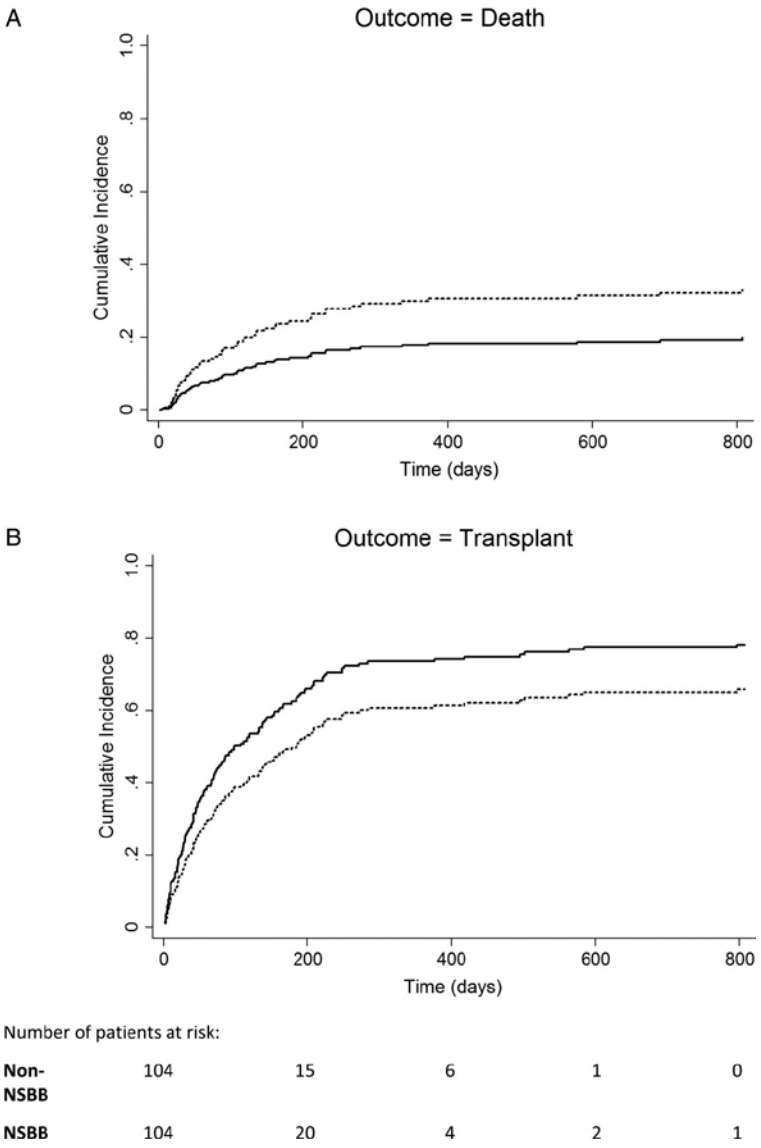
Window closes

BB **reduce survival** due to a negative impact on the cardiac compensatory reserve. The inability to increase the cardiac output during stress compromises organ perfusion.

End-stage cirrhosis
(Refractory ascites)

I. Increased risk of bacterial translocation
II. Maximum sympathetic nervous system stimulation
III. Cardiac compensatory reserve impaired

Cumulative incidence of (A) death and (B) transplantation in propensity risk score-matched patients with ascites listed for liver transplantation



NSBB (solid line)

absence of NSBB (dashed line)

Non-selective beta-blockers are not associated with increased mortality in cirrhotic patients with ascites

Single center retrospective study in Royal Free Hospital, London UK

N=316 cirrhotic patients with ascites (39% refractory)

NSBBs (n=128, 40.5%)

Median follow-up: 7 months.

Mortality 20 (16%) in NSBB group vs. 60 (32%) in non-NSBB group (*P*=.002).

Multivariate competing risk Cox regression analysis:

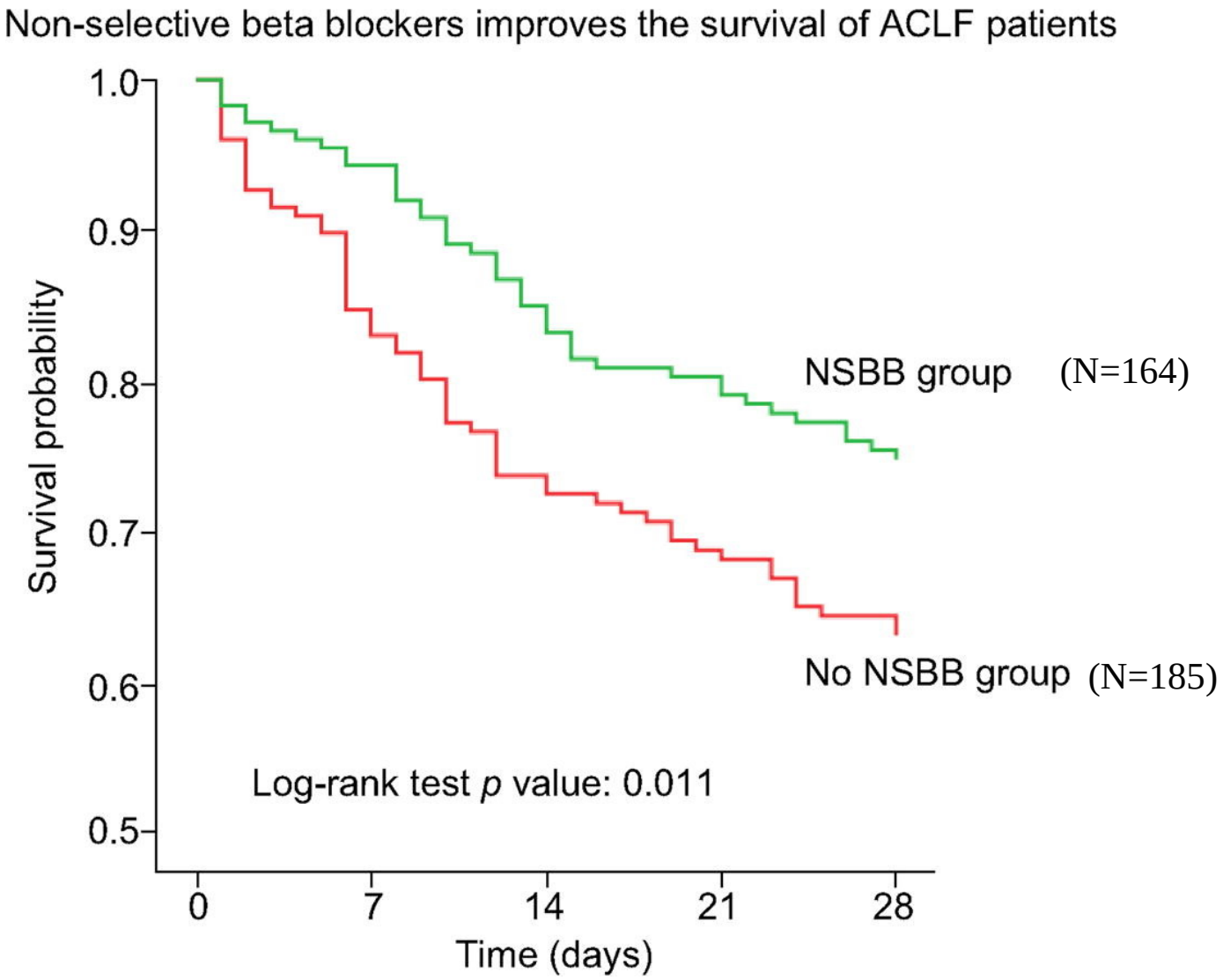
NSBB use (HR=0.55, 95% CI=0.33-0.94)

prophylactic antibiotic use (HR=0.33, 95% CI=0.14-0.74)

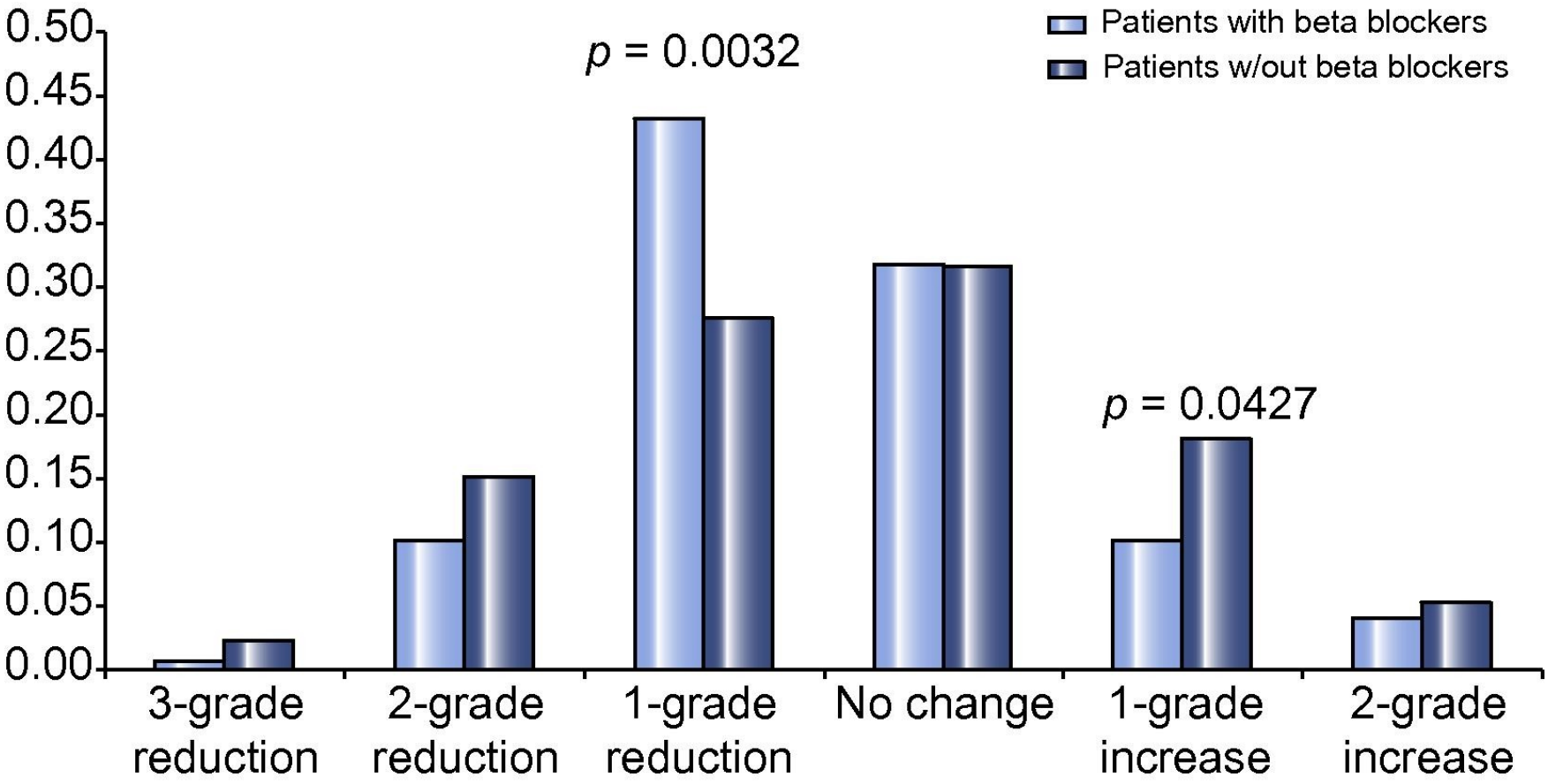
MELD score (HR=1.10, 95% CI=1.06-1.14)

sodium levels (HR=0.94, 95% CI: 0.89-0.98).

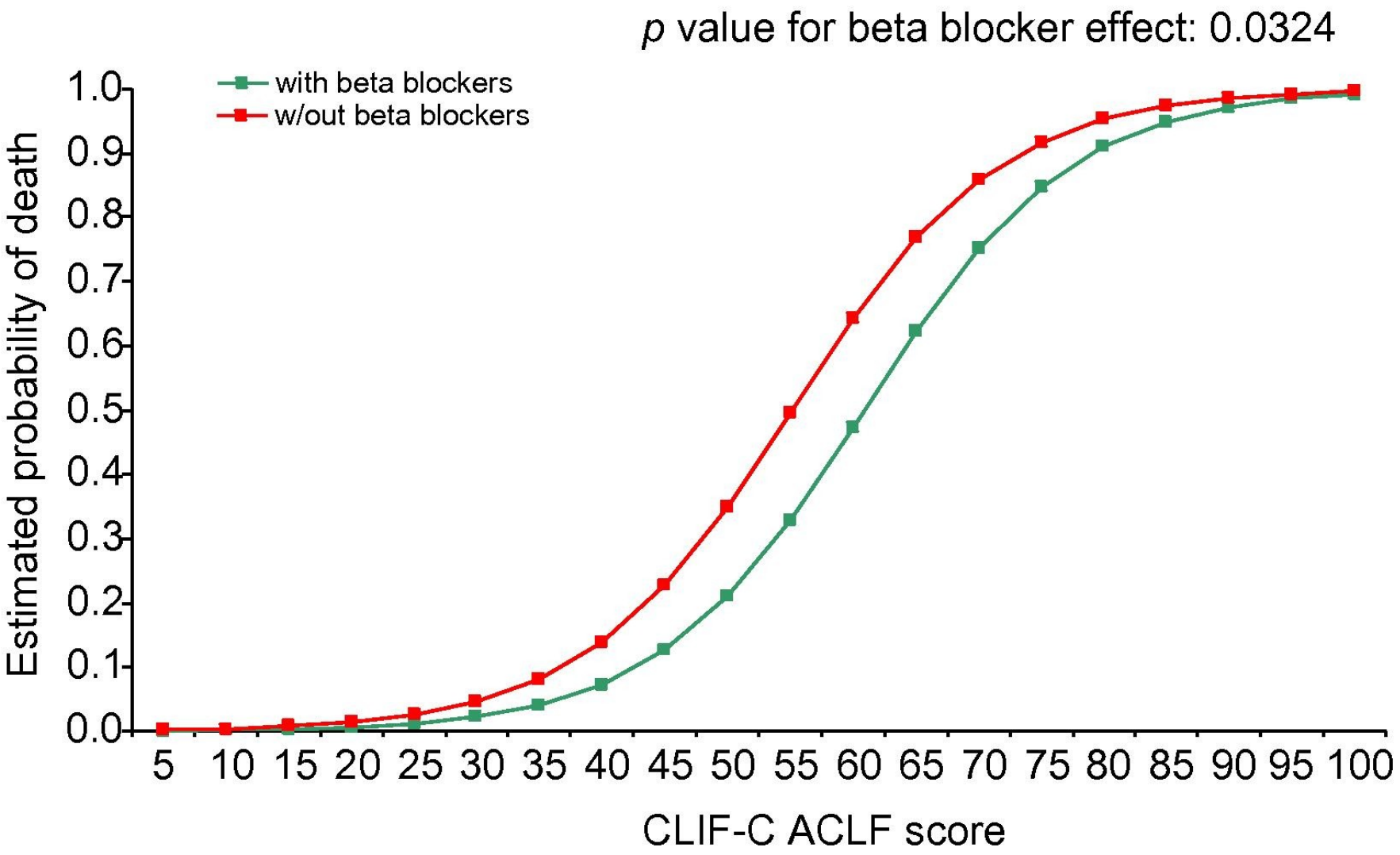
Survival curves at 28 days after diagnosis ACLF in relation to NSBB use



Evolution of ACLF grade up to one week after its first onset according to treatment with NSBBs



Estimated probability of death at 28 days from logistic regression model in ACLF patients

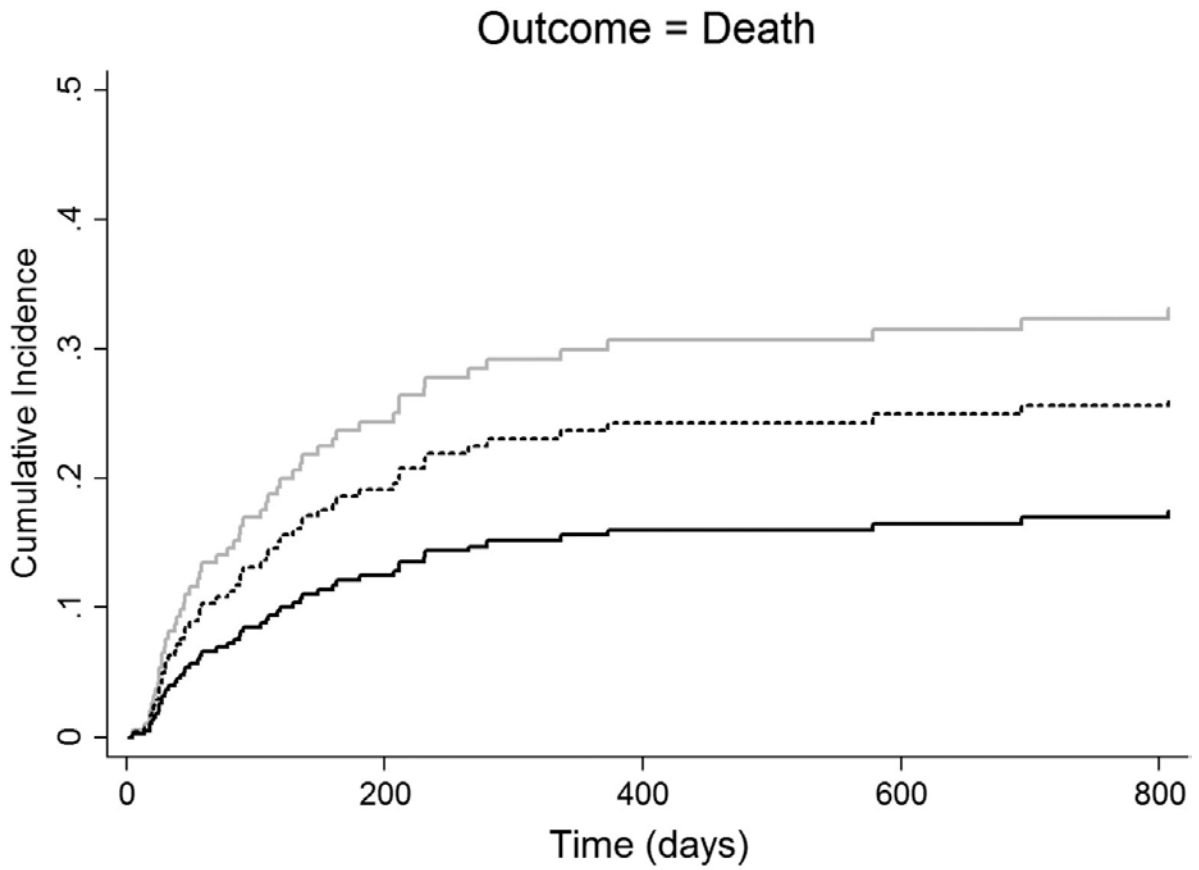


Does type of NSBB matter?

Yes

No

Cumulative incidence of death in propensity risk score-matched patients with ascites listed for liver transplantation



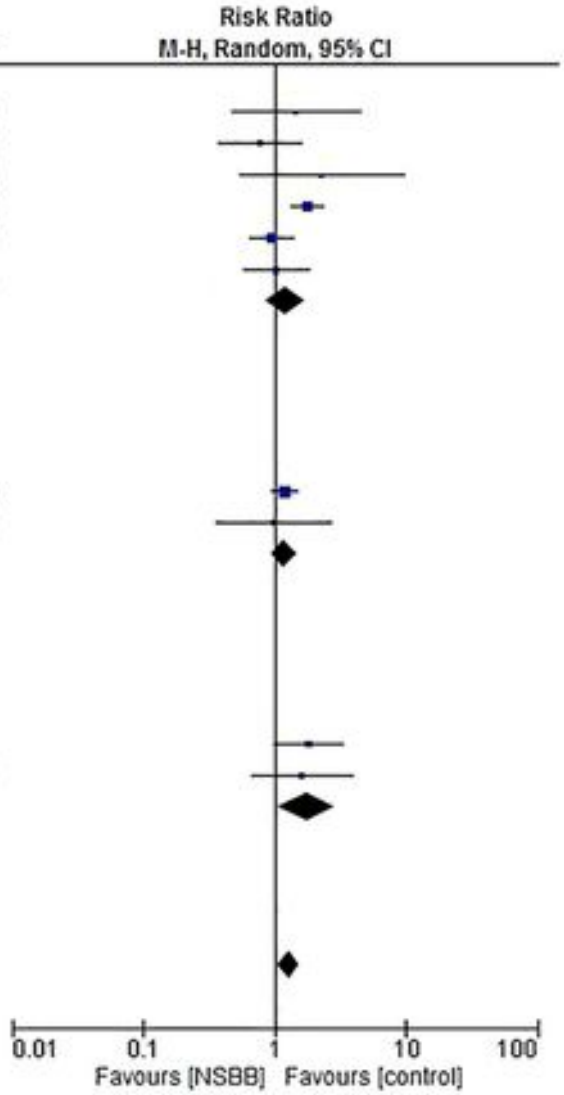
Number of patients at risk:

(solid grey)	**Non-NSBB**	104	15	6	1	0
(dashed)	**Carvedilol**	26	5	2	2	1
(solid black)	**Propanolol**	78	15	2	0	0

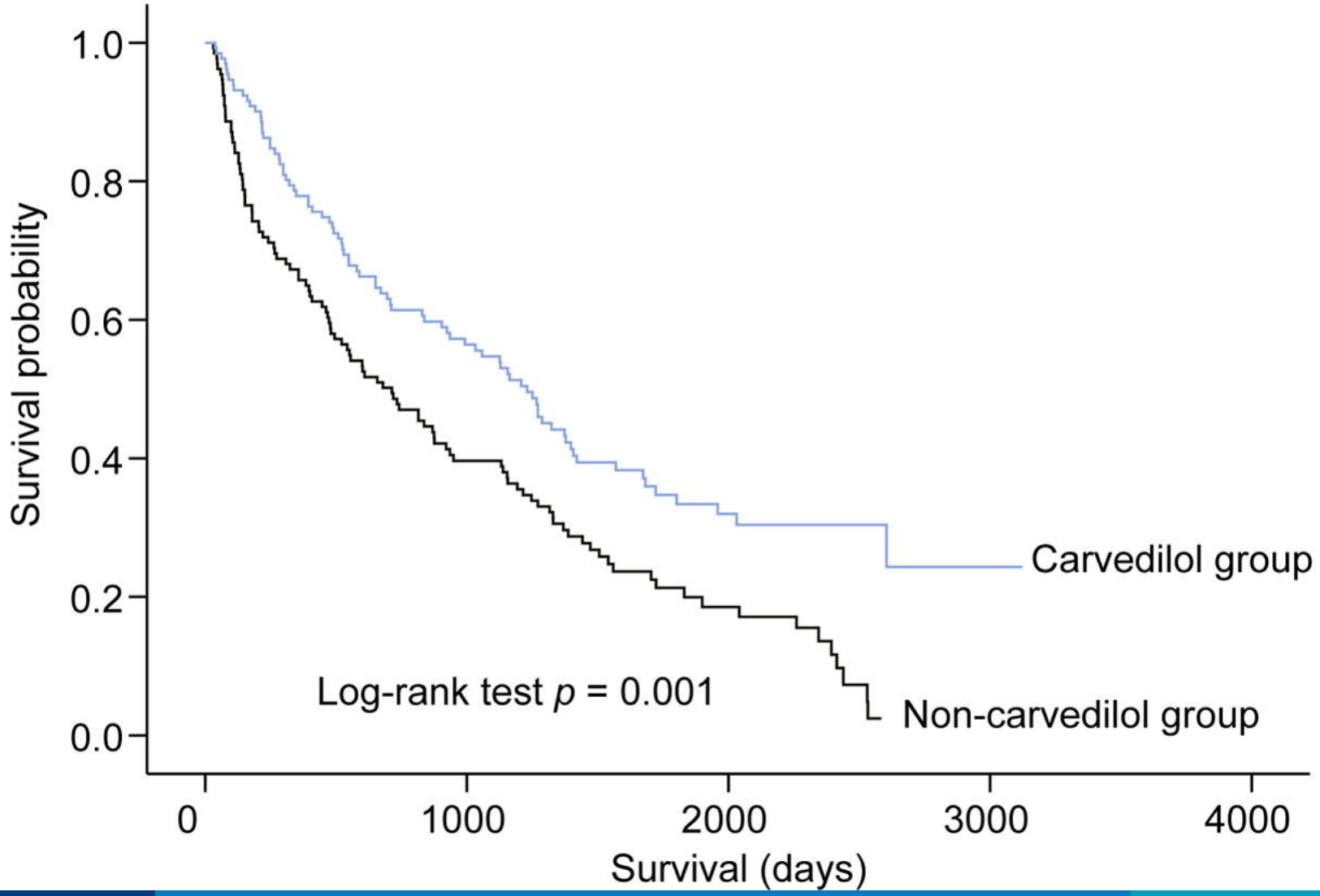
Meta-analysis by type of NSBB use and all-cause mortality of patients with cirrhosis and ascites

B

Study or Subgroup	NSBB Events	NSBB Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
1.2.1 Propranolol							
Groszmann 1990	5	22	5	32	3.1%	1.45 [0.48, 4.43]	1990
Escorsell 2002	7	19	11	23	6.5%	0.77 [0.37, 1.59]	2002
Cholongitas 2006	14	101	2	33	2.0%	2.29 [0.55, 9.54]	2006
Serste 2010	63	77	34	74	21.6%	1.78 [1.36, 2.33]	2010
Kimer 2015	15	23	26	38	16.3%	0.95 [0.66, 1.38]	2014
Leithead 2015	17	78	22	104	9.7%	1.03 [0.59, 1.81]	2014
Subtotal (95% CI)		**320**		**304**	**59.2%**	**1.22 [0.86, 1.73]**	
Total events	121		100				
Heterogeneity: Tau² = 0.09; Chi² = 11.22, df = 5 (P = 0.05); I² = 55%							
Test for overall effect: Z = 1.11 (P = 0.27)							
1.2.2 Nadolol							
Borroni 2002	23	25	21	27	23.8%	1.18 [0.94, 1.49]	2002
Lo 2004	5	17	6	20	3.8%	0.98 [0.36, 2.65]	2004
Subtotal (95% CI)		**42**		**47**	**27.6%**	**1.17 [0.93, 1.47]**	
Total events	28		27				
Heterogeneity: Tau² = 0.00; Chi² = 0.19, df = 1 (P = 0.67); I² = 0%							
Test for overall effect: Z = 1.37 (P = 0.17)							
1.2.3 Carvedilol							
Shah 2014	10	26	22	104	8.5%	1.82 [0.99, 3.35]	2014
Leithead 2015	10	33	6	32	4.7%	1.62 [0.67, 3.93]	2014
Subtotal (95% CI)		**59**		**136**	**13.2%**	**1.75 [1.06, 2.90]**	
Total events	20		28				
Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.83); I² = 0%							
Test for overall effect: Z = 2.18 (P = 0.03)							
Total (95% CI)		**421**		**487**	**100.0%**	**1.28 [1.04, 1.57]**	
Total events	169		155				
Heterogeneity: Tau² = 0.03; Chi² = 13.85, df = 9 (P = 0.13); I² = 35%							
Test for overall effect: Z = 2.31 (P = 0.02)							
Test for subgroup differences: Chi² = 2.05, df = 2 (P = 0.36), I² = 2.5%							



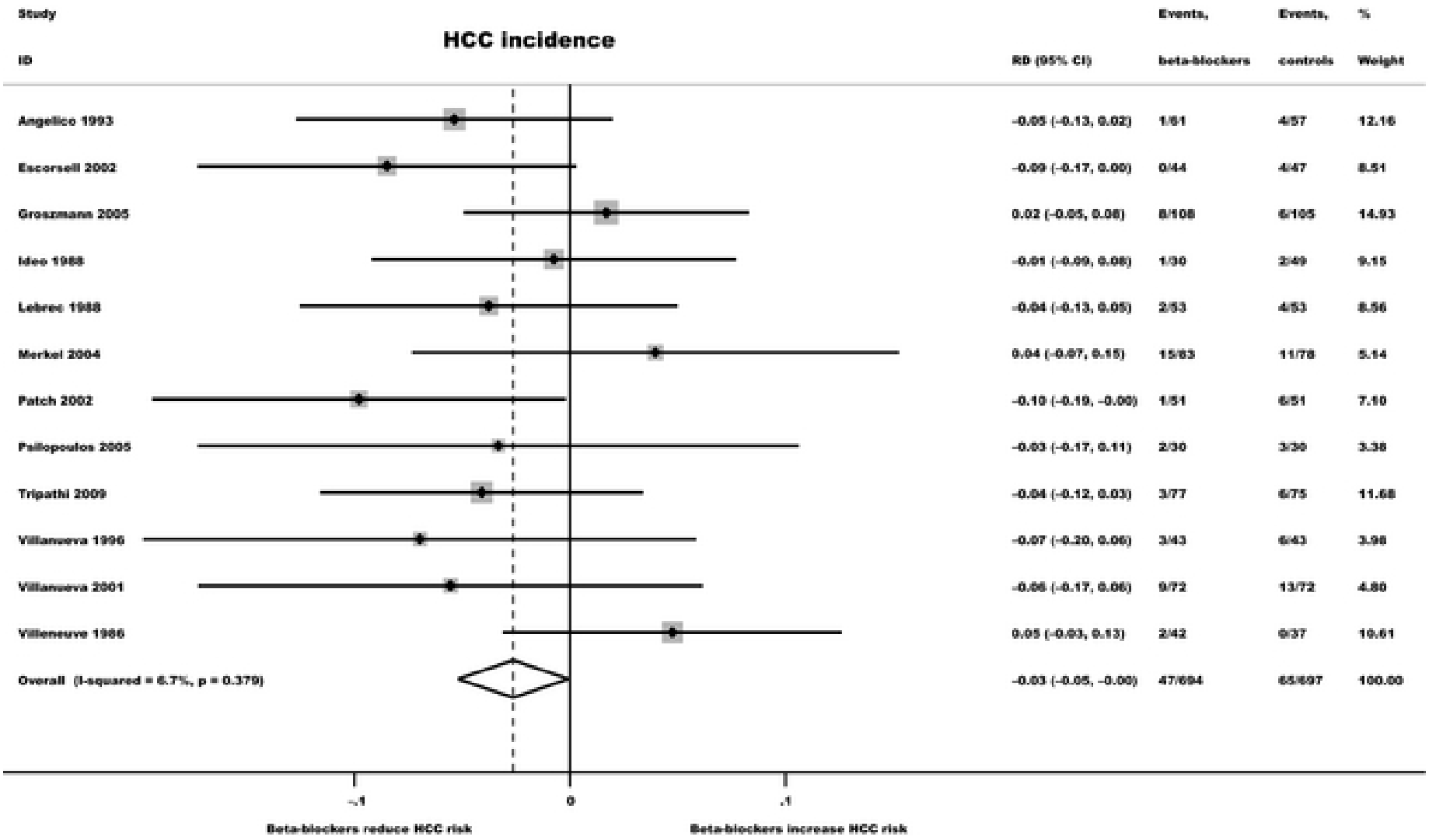
Carvedilol use is associated with improved survival in patients with liver cirrhosis and ascites.



Other potential beneficial effects of NSBB?

- Gut motility
- Gut permeability
- Bacterial translocation
- Systemic inflammation
- Inhibition of angiogenesis
- ….

Non-selective beta-blockers may reduce risk of hepatocellular carcinoma: a meta-analysis of randomized trials



Use of NSBB in patients with end-stage liver disease (new)

- The safety of NSBB in subgroups with end-stage disease (refractory ascites and/or spontaneous bacterial peritonitis) has been questioned (2b;B).
- NSBB contraindications may be absent when the therapy is firstly prescribed but need to be monitored during the evolution of the disease (5;D).
- Close monitoring is necessary in patients with refractory ascites, and reduction of dose or discontinuation can be considered in those who develop low blood pressure and impairment in renal function (4;C).
- If NSBB are stopped endoscopic band ligation should be performed (5;D).

Take home messages

- Randomized controlled studies are lacking

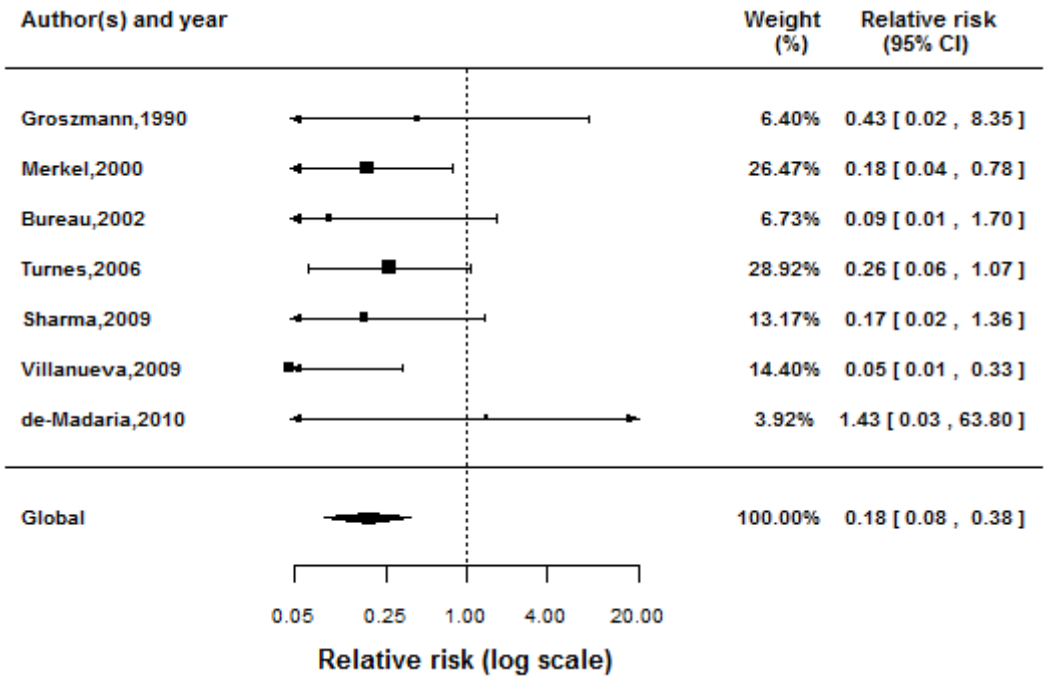
- Conflicting evidence from retrospective/observational studies

Baveno consensus:

- Close monitoring in patients with refractory ascites using NSBB
- Consider dose reduction or discontinuation in progressive low systolic blood pressure or impairment in renal function

- If vasopressors are indicated: stop NSBB

- Don’t forget to provide alternative prophylactic measures (endoscopic band ligation/ TIPS) for variceal bleeding


Author(s) and year
Weight (%)
Relative risk (95% CI)
Groszmann,1990
6.40%
0.43 [0.02 , 8.35]
Merkel,2000
26.47%
0.18 [0.04 , 0.78]
Bureau,2002
6.73%
0.09 [0.01 , 1.70]
Turnes,2006
28.92%
0.26 [0.06 , 1.07]
Sharma,2009
13.17%
0.17 [0.02 , 1.36]
Villanueva,2009
14.40%
0.05 [0.01 , 0.33]
de-Madaria,2010
3.92%
1.43 [0.03 , 63.80]
Global
100.00%
0.18 [0.08 , 0.38]
0.05
0.25
1.00
4.00
20.00
Relative risk (log scale)

Leids Universitair
Medisch Centrum