STANFORD SCHOOL OF MEDICINE

Beta Blockers in Patients with Advanced Cirrhosis and Ascites

W Ray Kim, MD
Professor and Chief
Gastroenterology and Hepatology
Stanford University School of Medicine

Case

A 59-year old man referred for abnormal liver enzymes

- History of hypertension and 'borderline' diabetes
- Moderate alcohol consumption: 2 beers 3-4 times a week
- Examination: BMI 33 with truncal obesity, palpable liver edge
- Ultrasonography:
  - Nodular surface of the liver, no mass
  - Small amount of perihepatic fluid, spleen diameter 12cm
- Laboratory
  - T Bilirubin: 1.2 mg/dL
  - Creatinine: 1.0 mg/dL
  - Platelets: 165,000
  - INR: 1.0
  - Albumin: 3.9 g/dL
- Elastography: 18.4 kPa

What is the most appropriate action?

1. Perform upper endoscopy and ligate varices to eradication.
2. Initiate surveillance for hepatocellular carcinoma.
3. Start carvedilol 3.125mg daily.
4. Start furosemide 80mg daily.
5. Start lactulose 20g twice daily.

AASLD Guidance: Compensated Cirrhosis

Disease Stage	Compensated		
HVPG	<10 mm Hg	≥10 mm Hg (CSPH)	
Varices	Absent	Absent	Present
Complications of PH	Absent	Absent	Absent
Goals of therapy	Prevent CSPH	Prevent decompensation	Prevent decompensation (first bleeding episode)

- No EGD if liver stiffness <20 kPa and platelet count >150,000/mm^3
  - Very low probability (<5%) for high-risk varices

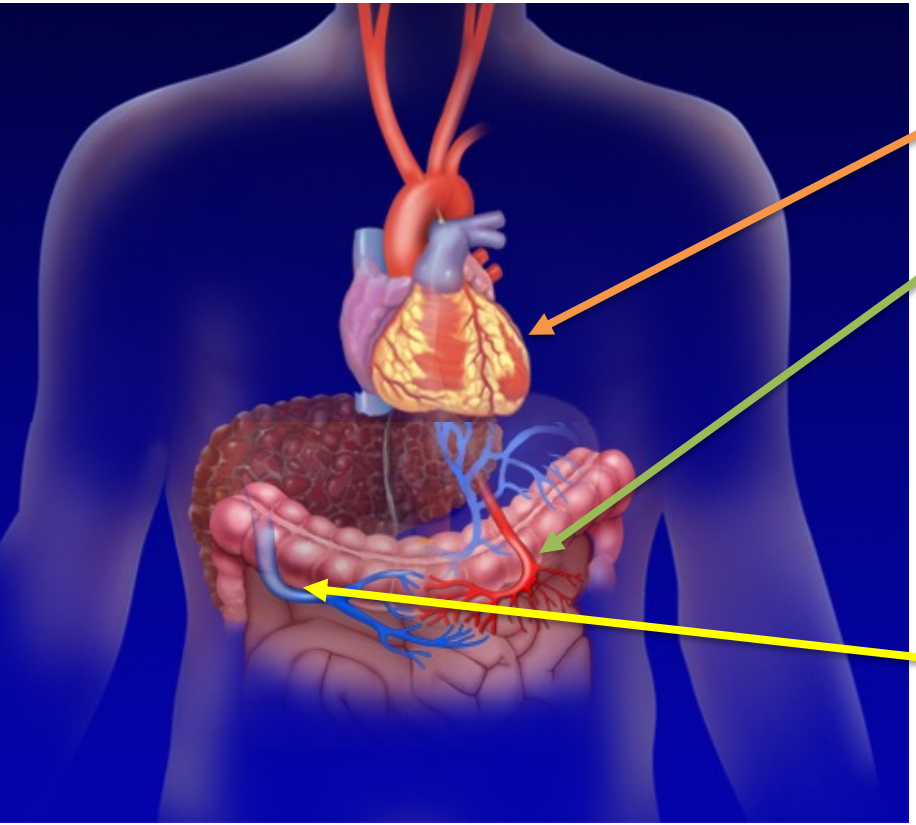
Garcia-Tsao. Hepatology 2017;65:310

AASLD Guidance: Objectives of Treatment in Compensated Cirrhosis

- Mild pHTN:
  - Prevent development of clinically significant portal hypertension or decompensation
  - Achieve regression (or delay progression) of cirrhosis:
    - Elimination of the etiologic agent
  - NSBBs:
    - Mostly ineffective
    - Hyperdynamic circulatory state not fully developed
- Clinically significant pHTN (>10 mmHg) without varices:
  - Prevent clinical decompensation
  - No evidence to recommend the use of NSBBs in preventing formation of varices

Garcia-Tsao. Hepatology 2017;65:310

NSBBs in Cirrhosis



- β1 (cardiac) receptors
  - β1 blockade reduces the cardiac output.
- β2 (peripheral) receptors
  - β2 blockade leads to splanchnic vasoconstriction.
- Combined β1 and β2 blockade needed for reduction in portal pressure.
- Carvedilol
  - Potent β blocker
  - Mild α adrenergic blocker
    - Decreases portal venous resistance
    - Can also reduce MAP

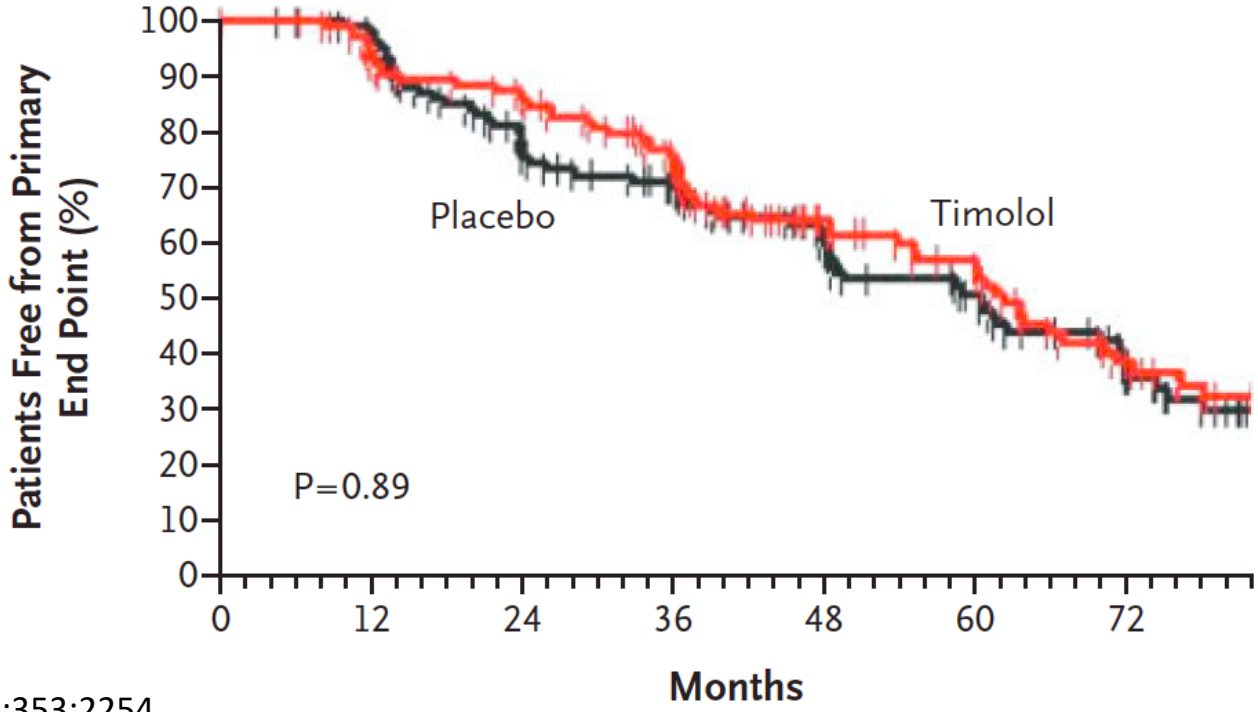
Beta Blockers

Drug	Starting dose (per day)	Max dose (per day)	Monitoring parameters
Propranolol	20-40mg bid	320mg (no ascites) 160mg (ascites)	Resting HR: 55-60 /min Systolic BP> 90 mmHg
Nadolol	20-40mg qd	160mg (no ascites) 80mg (ascites)	
Carvedilol	6.25mg qd	12.5mg	Systolic BP> 90 mmHg

Garcia-Tsao. Hepatology 2017;65:310

NSBB in Preventing Varices

- Multicenter, randomized, placebo-controlled trial of timolol (NSBB) vs. placebo
- Primary end point: Prevention of development of varices

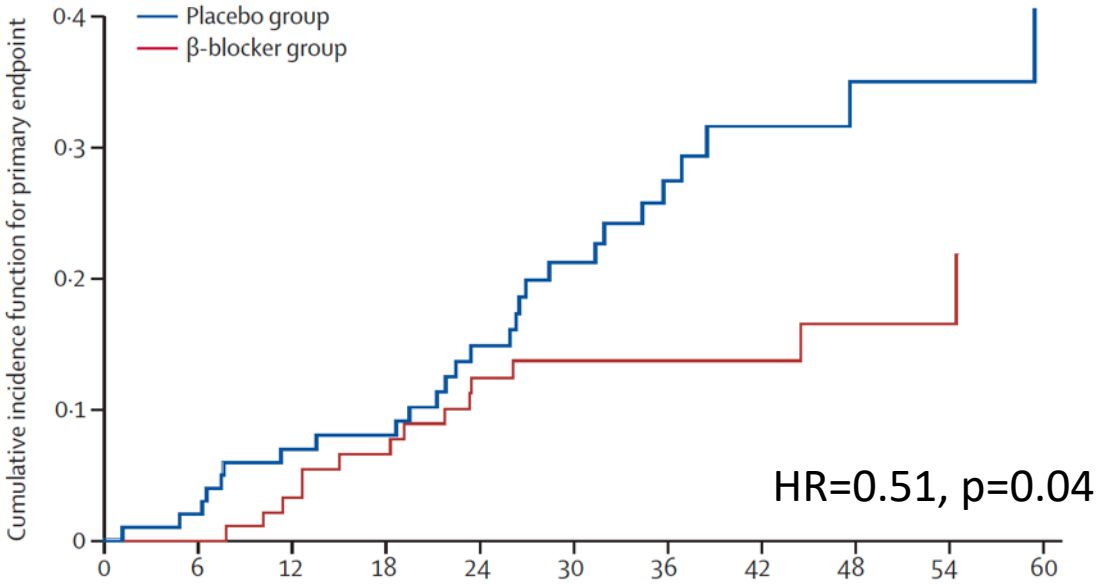


Groszman. NEJM 2005;353:2254

NSBB Prevents Hepatic Decompensation

- Spanish multicenter placebo-controlled trial
- Primary end point: Death or decompensation

  Decompensation: ascites, portal hypertensive GI bleeding, or overt HE

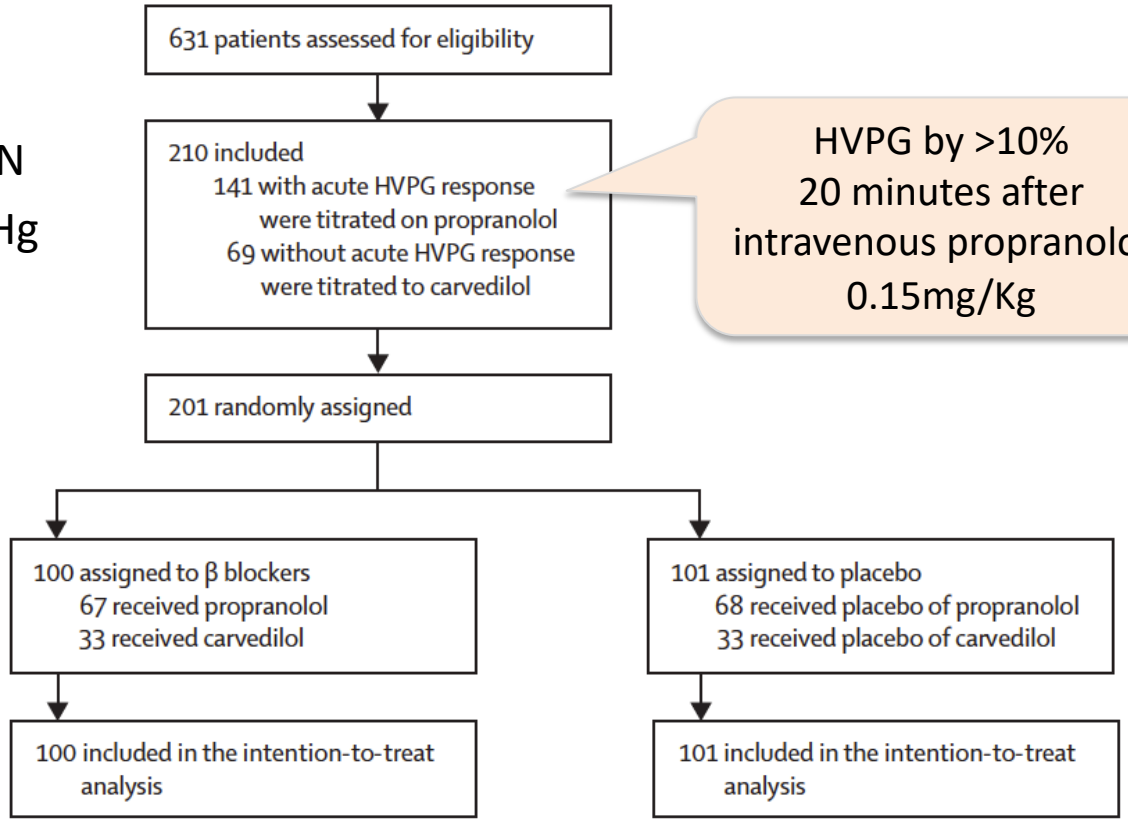


Villanueva. Lancet 2019;393:1597-1608

Beta Blockers to Prevent Hepatic Decompensation

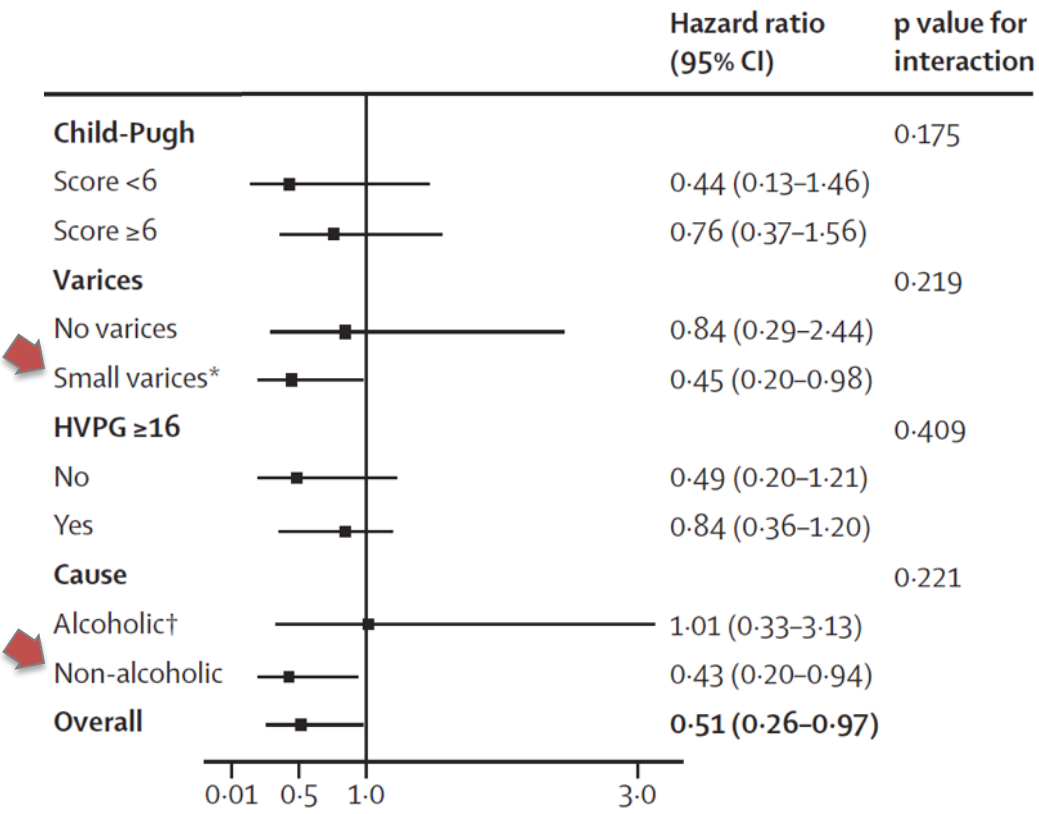
Patients

- Compensated cirrhosis
- Clinically significant portal HTN
  - HVPG measured ≥ 10 mmHg
  - No varices or small varices without red signs
- Exclusion
  - T bilirubin > 3 mg/dL
  - Platelets < 30,000
  - INR > 2.7
  - Creatinine > 2 mg/dL



Villanueva. Lancet 2019;393:1597-1608

Subgroup Analysis



Primary end points in HVPG responders

- Propranolol (n=67): 19%
- Placebo (n=68): 26%
- HR=0.69 (p=0.29)

Median dose= 80mg/d (IQR 40-120)

Carvedilol versus placebo

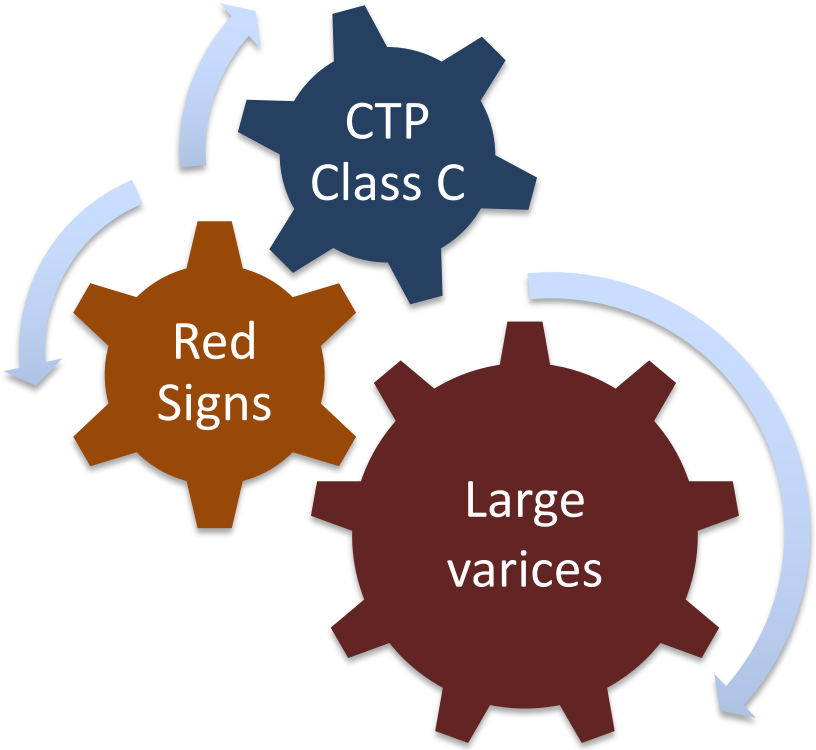
(HVPG non-responders)

- Carvedilol (n=33): 9%
- Placebo (n=33): 27%
- HR=0.39 (p=0.16)

Median dose= 18.8mg/d (IQR 12.5-25)

Villanueva. Lancet 2019;393:1597-1608

Risk Stratification for Variceal Bleeding



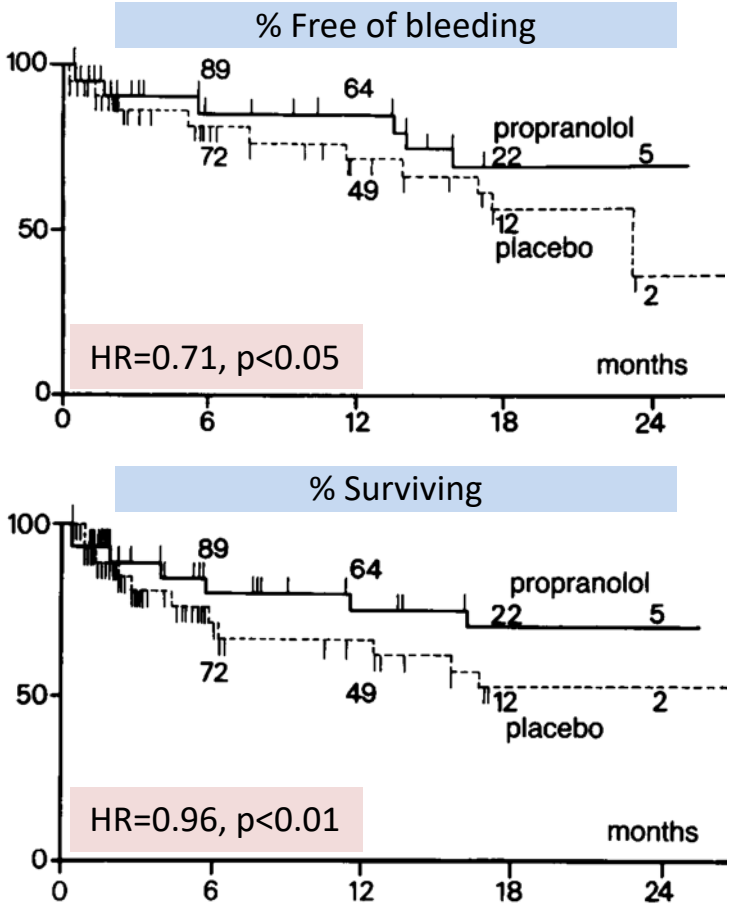
CTP: Child Turcotte Pugh

Propranolol to Prevent First Bleeding

French multicenter RCT

	CTP A/B		CTP C	
	Propranolol	Placebo	Propranolol	Placebo
n	44	44	74	68
Large varices	7%	8%	20%	17%
ALD	91%	84%	93%	90%
Bilirubin	2.4 mg/dl	1.8 mg/dl	4.4 mg/dl	3.2 mg/dl
Creatinine	1.0 mg/dl	1.0 mg/dl	0.9 mg/dl	0.9 mg/dl

- Average daily propranolol dose:
  162 ± 85 mg
- Heart rate reduction:
  24 ± 8 %



Pascal. NEJM 1987;317:856-61

Nadolol to Prevent First Bleeding

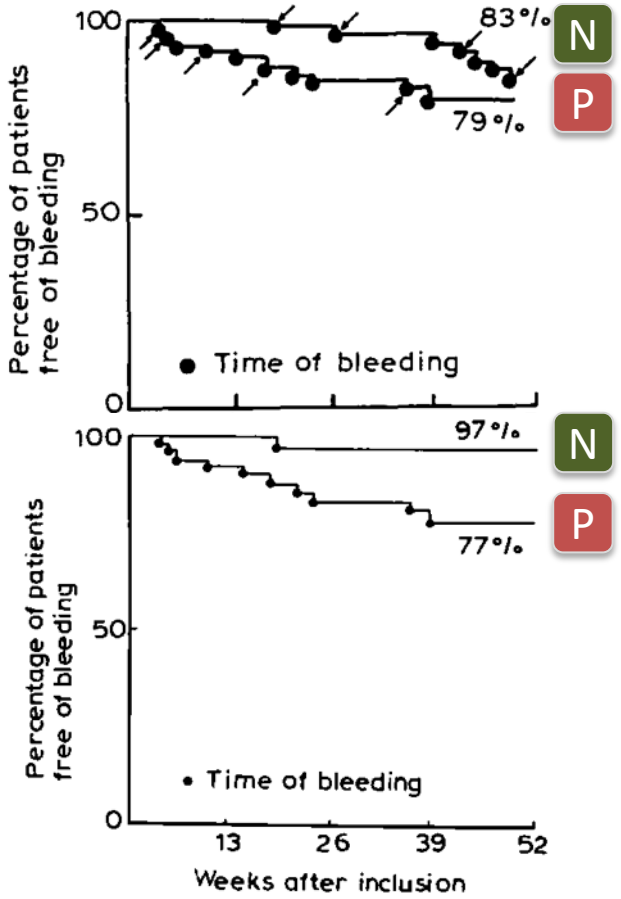
French multicenter RCT

	nadolol ($n = 53$)	placebo ($n = 53$)
Age (yr)	55 ± 2[a]	57 ± 2
Sex (male/female)	39/14	40/13
Causes of cirrhosis		
alcoholism	39	39
chronic hepatitis B infection	6	6
primary biliary cirrhosis	3	1
cryptogenic	5	7
Severity of cirrhosis		
grade A[b]	33	29
grade B	20	24

- Daily nadolol dose (Guided by HR):
  80 mg (n=39), 120-160 mg (n=14)
- 40/53 (75%) remained compliant.
- No difference in survival.

Intent-to-treat

Per-Protocol

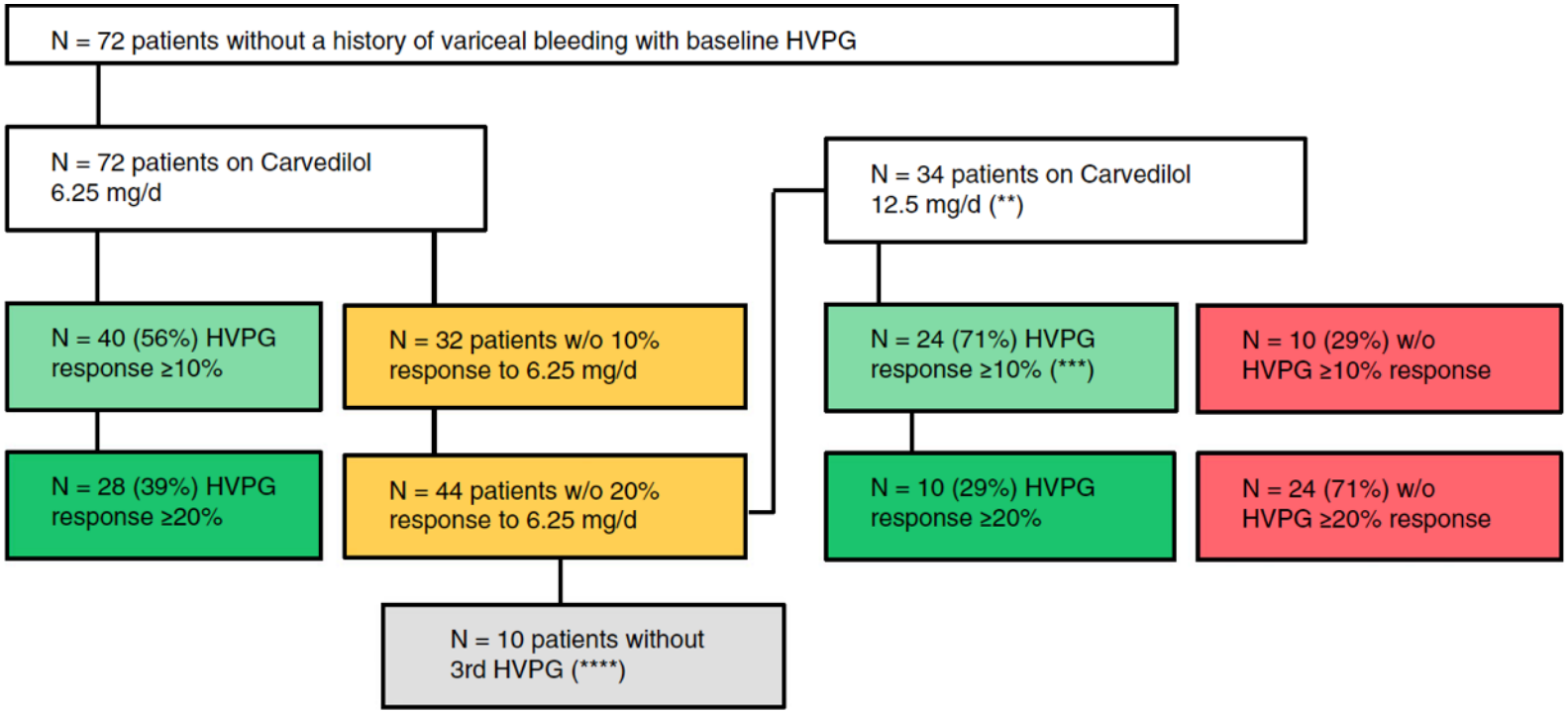


Lebrec. J Hep 1988;7:118-125

Optimal Dosing for Carvedilol

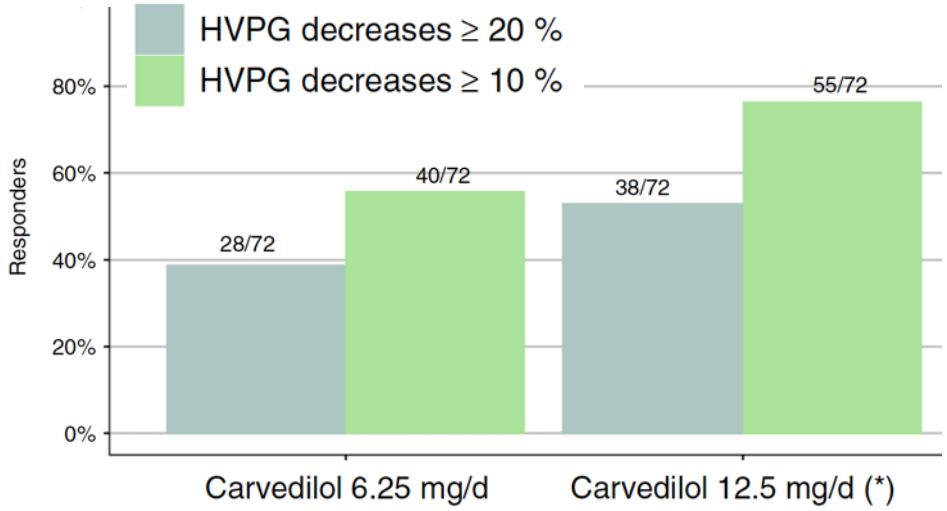
- Single center (U Vienna) retrospective cohort with HVPG data (n=676)

  Response: HVPG reduction by ≥ 20% or to <12 mmHg



Schwarzer. AP&T 2018;47:1162-1169

Optimal Dosing for Carvedilol



- Changes in pulse rate or arterial blood pressure do not predict HVPG response to carvedilol.
- Patients with ascites had less hemodynamic benefit and poorer tolerance of carvedilol.

Schwarzer. AP&T 2018;47:1162-1169

	Responders[a] (n = 38)	Nonresponders (n = 34)	*P* value
Median Child-Pugh score (IQR)	7.0 (5.0-8.0)	8.0 (6.0-10.8)	0.092
Median MELD (IQR)	12 (9-15)	12 (10-16)	0.184
Ascites (n, %)	17 (45%)	21 (62%)	0.226
Hepatic encephalopathy (n, %)	5 (13%)	12 (35%)	0.053
HVPG	20 (16-23)	18 (16-22)	0.230
Systolic arterial pressure (mm Hg)	128 (118-144)	126 (117-136)	0.487
Mean arterial pressure (mm Hg)	95 (87-105)	94 (88-98)	0.229
Decompensation (ascites or hepatic encephalopathy	18 (47%)	21 (62%)	0.323
Size of varices (n=66)			
Small varices	22 (58%)	16 (47%)	0.494
Large varices	16 (42%)	18 (53%)	

Efficacy of carvedilol, endoscopic variceal ligation (EVL), or a combination for the prevention of first variceal bleed in Child B and C cirrhosis with high risk varices: a randomized controlled trial (NCT03069339)

Aim:

To evaluate the efficacy and safety of carvedilol or endoscopic variceal ligation (EVL) alone or in combination to prevent first variceal bleed in advanced cirrhotics with 'high risk' varices

Methods:

- A randomized prospective controlled trial
- 270 Child B and C cirrhotics with high risk varices [large (>5 mm) (n=132; 48.9%) or small (<5 mm, with significant red color signs) (n=138; 51.1%)] were prospectively randomized (90 per group) to receive carvedilol (Gr I) or EVL (Gr II) or combination (Gr III). The mean age and CTP score in the three groups were 50.98 ± 11.5; 50.93 ± 10.7; and 51.7 ± 9.95 years (p=0.84); 8.9 ± 1.1; 9.18 ± 1.18; and 9.1 ± 1.19 (p=0.51).

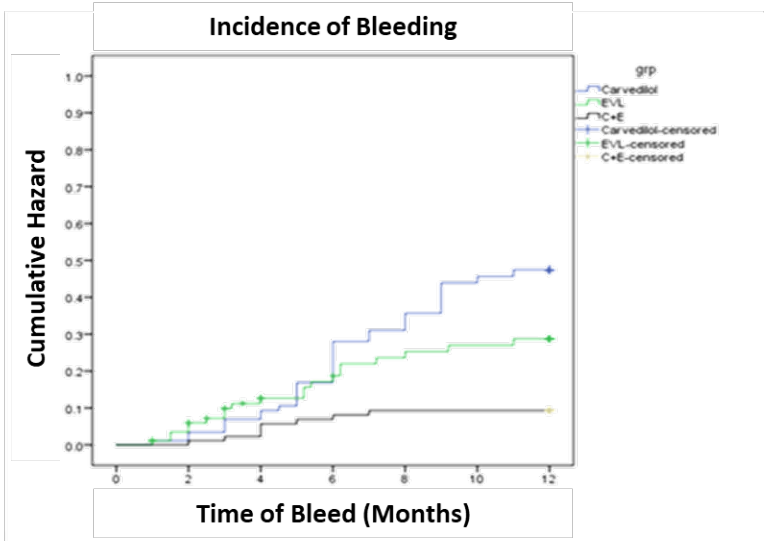
Main Findings:

The actuarial probability of first bleeding during a mean follow-up of 10.42 (10-10.8) months was 37.8%; 22.2%; and 8.9 % in groups I, II, and III, respectively (p<0.04, I vs II and <0.001 I vs III).

Conclusions:

Combination of carvedilol and EVL is more effective than either therapy alone for primary prevention of first variceal bleed in high risk varices in advanced cirrhosis.

Pande A, et al., Abstract 145



Arm		0	2	4	6	8	10	12
Carvedilol	Affected	0	3	6	22	27	33	34
	At risk	90	87	84	68	63	57	56
EVL	Affected	0	5	10	14	18	19	20
	At risk	90	85	80	76	72	71	70
Carvedilol + EVL	Affected	0	1	5	7	8	8	8
	At risk	90	89	85	83	82	82	82

Case - continued

- The patient was lost to follow-up until being brought into ED 2 years later with hematemesis.
- An emergency endoscopy showed 3 trunks of large distal esophageal varices with red signs. Band ligation was successfully performed.
- Examination after stabilization
  - BP 121/71 (MAP 88)
  - Pulse 82
  - A few spider angiomata.
  - No asterixis
- Ultrasonography
  - Cirrhotic liver, no mass
  - Moderate amount of ascites
- Laboratory
  - T Bilirubin: 1.9 mg/dL
  - INR: 1.3
  - Creatinine: 1.0 mg/dL
  - Albumin: 3.6 g/dL
  - Sodium: 133 mEq/L

Case - continued

The following medical therapy is planned/instituted. Which has been shown to improve survival?

1. Endoscopic band ligation of varices to eradication
2. Carvedilol 6.25mg daily
3. Spironolactone 100mg daily
4. Liver transplant
5. All of above

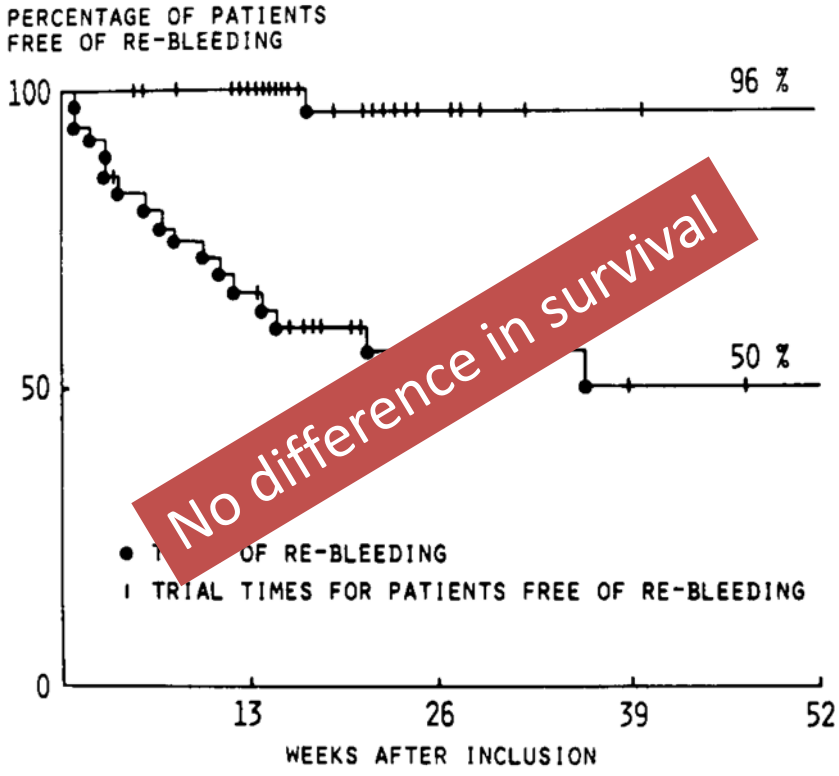
AASLD Guidance: Stages of Cirrhosis

Disease Stage	Compensated			Decompensated*		
HVPG	<10 mm Hg	≥10 mm Hg (CSPH)		≥12 mm Hg		
Varices	Absent	Absent	Present	Present		
Complications of PH	Absent	Absent	Absent	Acute VH	Previous VH without other complications†	Previous VH with other complications
Goals of therapy	Prevent CSPH	Prevent decompensation	Prevent decompensation (first bleeding episode)	Control bleeding, prevent early rebleeding and death	Prevent further decompensation (further bleeding) and other complications†	Prevent further decompensation and death/OLT

Garcia-Tsao. Hepatology 2017;65:310

Propranolol to Prevent Rebleeding

- French RCT recruiting patients surviving >2 weeks after UGI bleeding



No difference in survival

Lebrec. NEJM 1981;305:1371-4

- Transfusion first 24 hours <50
- No chronic illness other than ci sis

Propranolol:
Increasing doses until HR reduced by 25%
Dose range: 20-180 mg twice a day

	PROPRANOLOL	PLACEBO
No. of patients	38	36
Source of bleeding for which		
Ruptured varices	28	28
Acute gastric erosions	10	8
Causes of cirrhosis (no. of patients)		
Alcoholism	33 ‡	32 ‡
Chronic hepatitis B infection	3	2
Cryptogenic	2	2
Serum studies †		
Bilirubin (mg/dl) §	1.87±1.25	2.12±1.95
Albumin (g/dl)	3.40±0.64	3.21±0.53
Alanine aminotransferase (IU) ‖	26.1±14.5	25.1±14.1
Creatinine (mg/dl) ¶	0.94±0.15	0.91±0.43

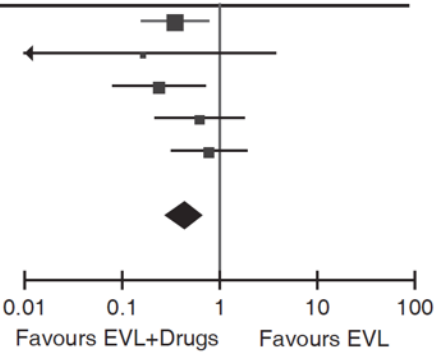
Meta-analysis: Prevention of Rebleeding

EVL+NSBB versus EVL

	EVL + Drugs Events	EVL + Drugs Total	EVL Events	EVL Total	Weight	Risk Ratio M-H,Random,95%CI
2000 Lo	14	60	29	62	37.3%	0.35 [0.16, 0.75]
2004 Sollano	0	16	2	15	4.3%	0.16 [0.01, 3.72]
2005 De la Peña	6	43	15	37	23.7%	0.24 [0.08, 0.79]
2009 Ahmad	8	37	12	39	15.6%	0.62 [0.22, 1.75]
2009 Kumar *	11	72	13	69	19.2%	0.78 [0.32, 1.87]
Total (95% CI)		**228**		**222**	**100.0%**	**0.44 [0.28, 0.69]**
Total events	39		39			

Heterogeneity: $X^2 = 4.01$, df= 4 ($P = 0.40$); $I^2 = 0\%$

Test for overall effect: $Z = 3.60$ ($P = 0.0003$)

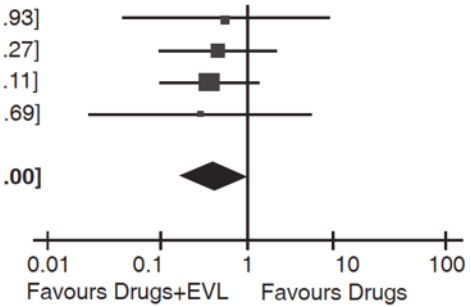


EVL+NSBB versus NSBB

	EVL + Drugs Events	EVL + Drugs Total	Drugs Events	Drugs Total	Weight	Risk Ratio M-H,Random,95%CI
2009 Ahmad	8	37	9	35	10.8%	0.84 [0.37, 1.93]
2009 Garcia Pagán	22	80	27	78	34.0%	0.79 [0.50, 1.27]
2009 Lo	23	60	31	60	45.9%	0.74 [0.50, 1.11]
2009 Villanueva	6	29	9	30	9.3%	0.69 [0.28, 1.69]
Total (95% CI)		**206**		**203**	**100.0%**	**0.76 [0.58, 1.00]**
Total events	59		76			

Heterogeneity: $X^2 = 0.15$, df = 3 ($P = 0.99$); $I^2 = 0\%$

Test for overall effect: $Z = 1.92$ ($P = 0.05$)



Puente. Liver Int. 2014:34:823–833

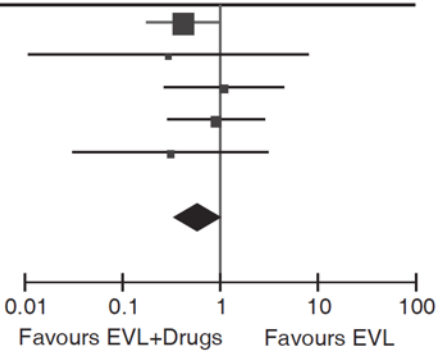
Meta-analysis: Survival

EVL+NSBB versus EVL

	EVL + Drugs Events	Total	EVL Events	Total	Weight	Risk Ratio M-H,Random,95%CI
2000 Lo	10	60	20	62	52.8%	0.42 [0.18, 1.00]
2004 Sollano	0	16	1	15	4.8%	0.29 [0.01, 7.76]
2005 De la Peña	5	43	4	37	12.2%	1.09 [0.27, 4.38]
2009 Ahmad	7	37	8	39	20.4%	0.90 [0.29, 2.80]
2009 Kumar *	1	72	3	69	9.7%	0.31 [0.03, 3.05]
Total (95% CI)		**228**		**222**	**100.0%**	**0.58 [0.33, 1.03]**
Total events	23		36			

Heterogeneity: $X^2 = 2.36$, df = 4 ($P = 0.67$); $I^2 = 0\%$

Test for overall effect: $Z = 1.84$ ($P = 0.07$)

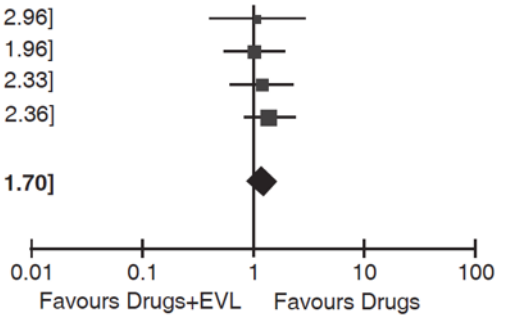


EVL+NSBB versus NSBB

	EVL + Drugs Events	Total	Drugs Events	Total	Weight	Risk Ratio M-H,Random,95%CI
2009 Ahmad	7	37	6	35	10.2%	1.10 [0.41, 2.96]
2009 Garcia Pagán	16	80	15	78	25.0%	1.04 [0.55, 1.96]
2009 Lo	16	60	13	60	24.5%	1.23 [0.65, 2.33]
2009 Villanueva	18	29	13	30	40.2%	1.43 [0.87, 2.36]
Total (95% CI)		**206**		**203**	**100.0%**	**1.24 [0.90, 1.70]**
Total events	57		47			

Heterogeneity: $X^2 = 0.70$, df = 3 ($P = 0.87$); $I^2 = 0\%$

Test for overall effect: $Z = 1.34$ ($P = 0.18$)



Puente. Liver Int. 2014:34:823–833

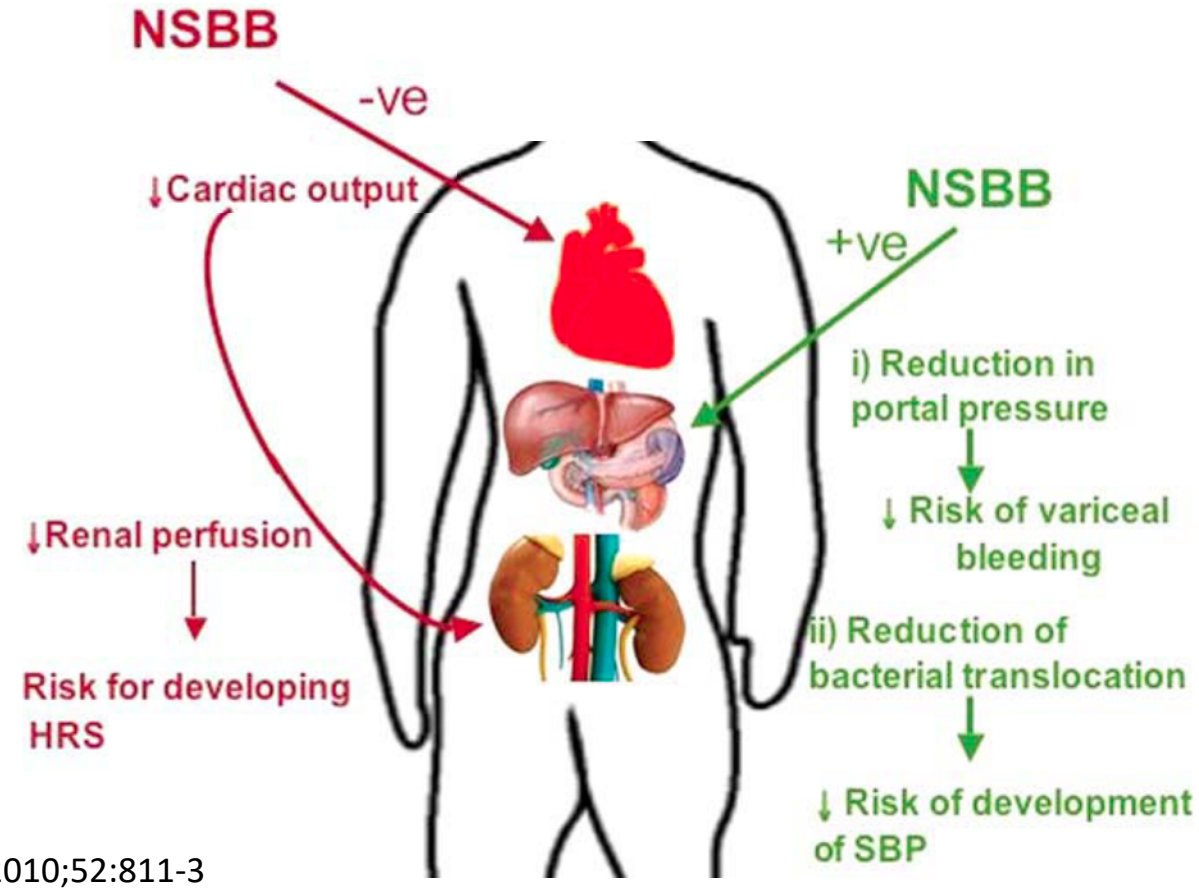
Case - continued

- The patient is managed with EVL, nadolol, and diuretics.
- Over time, he develops increasing ascites and peripheral edema.
- Now, the patient returns to the clinic, feeling unwell with fevers (100F).
- Medications:
  - Furosemide 80mg + Spironolactone 200mg daily
  - Nadolol 80mg daily
- Exam: BP 98/65, Large ascites and small umbilical hernia
- Lab:
  - T. bili: 2.5 mg/dL
  - INR: 1.5
  - Na: 128 mEq/L
  - Albumin: 2.9 g/dL
  - Creatinine: 2.1 mg/dL
  - Paracentesis: PMN 430 /mm^3

Case - continued

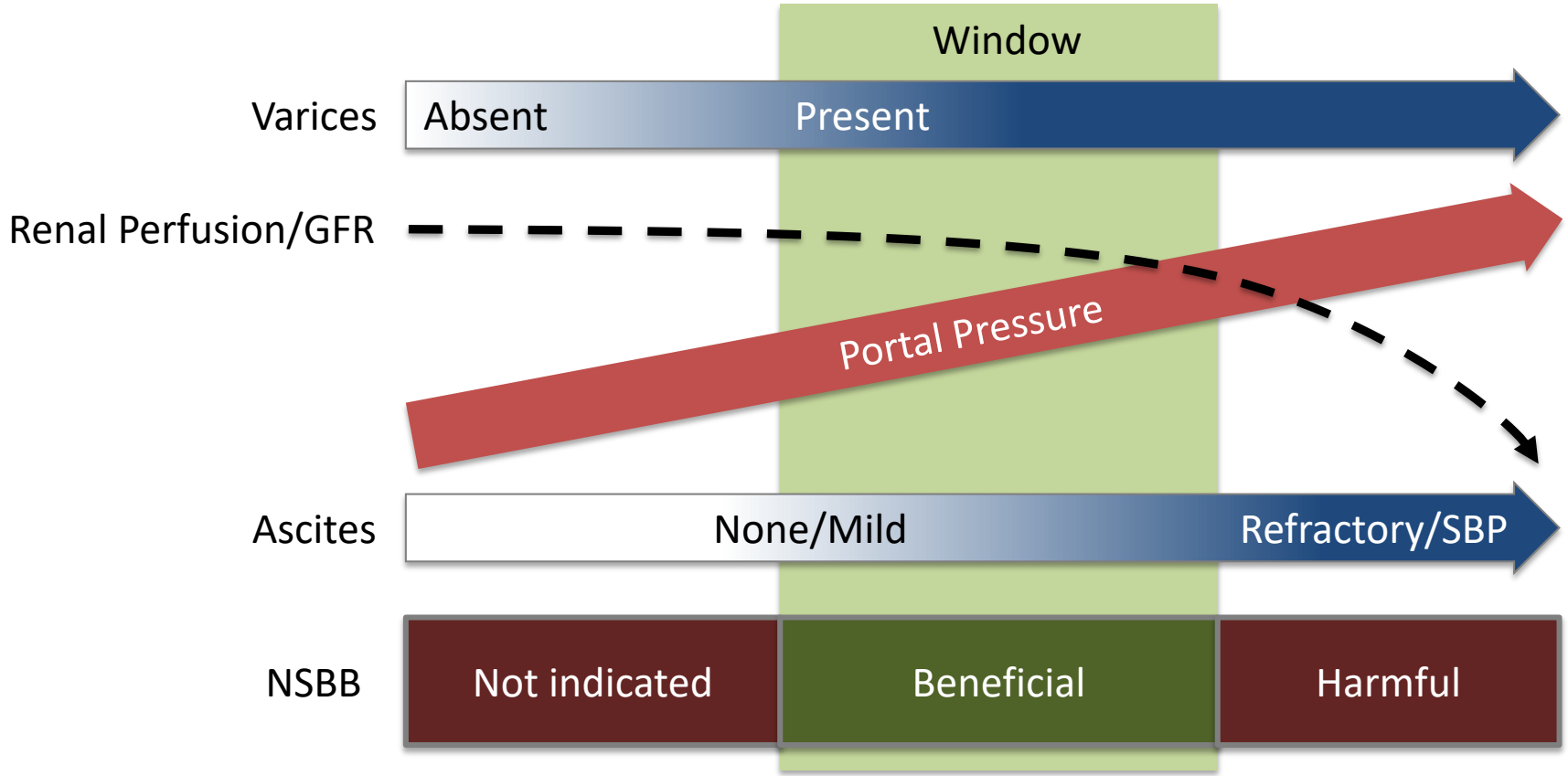
- Which is true for NSBB in this setting?
  1. May be responsible for his AKI
  2. Improves survival
  3. Improves cardiac function
  4. Should be continued regardless of systemic blood pressure
  5. All of above

Yin and Yang of NSBB



Wong. Hepatology 2010;52:811-3

The Window Theory



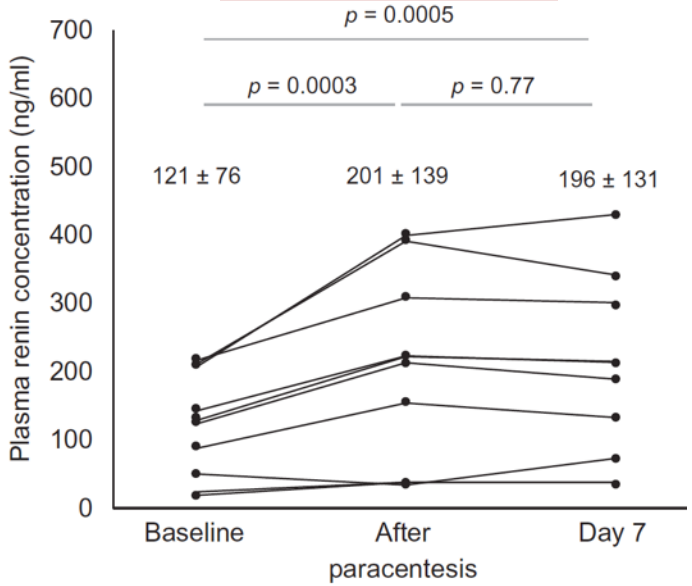
Kim. Liver Transplant 2017;23:733–40

NSBB and Paracentesis-Induced Circulatory Dysfunction (PICD)

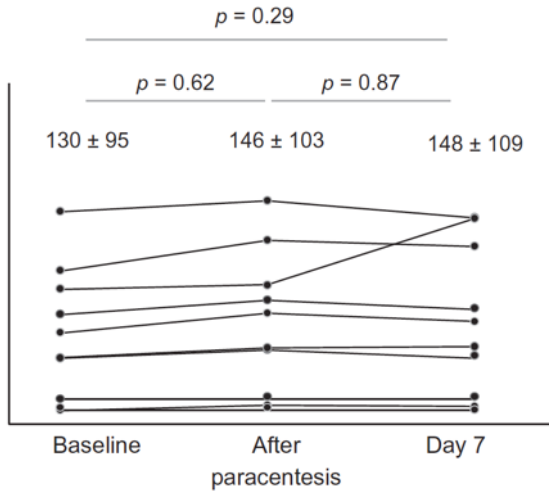
- Refractory ascites (LVP x2/mo), n=10
- Hemodynamic changes after LVP with and without propranolol

Propranolol dose
160mg (n=7)
80mg (n=2)
40mg (n=1)

On Propranolol
PICD: 8/10



Off Propranolol
PICD: 1/10



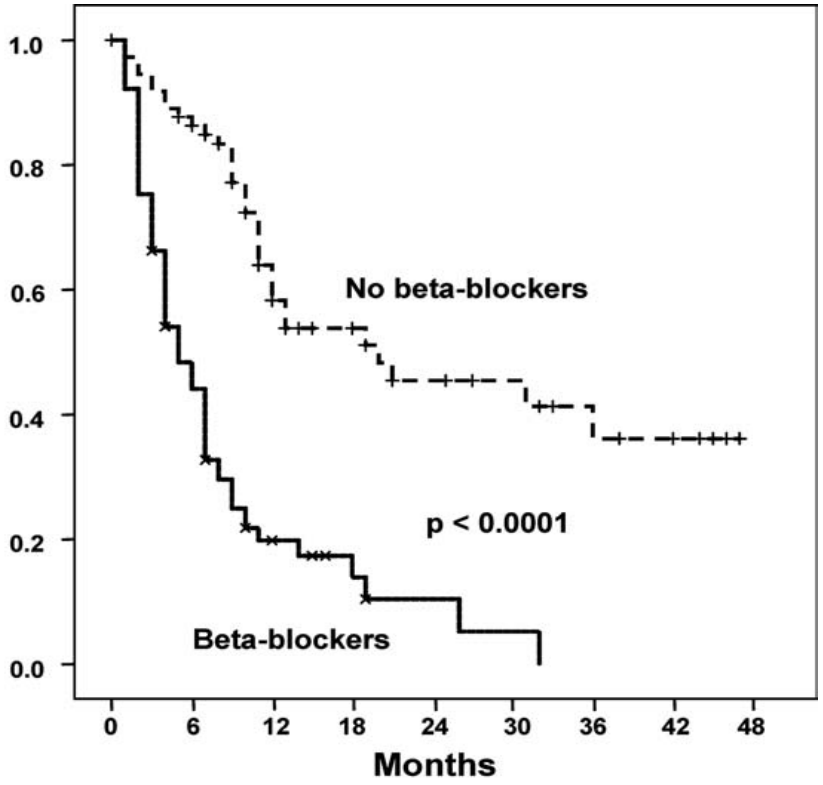
Serste. J Hep 2011;55:794-9

Harm of NSBB in Patients with Refractory Ascites

Single-center cohort of patients regularly requiring LVP (n=151)

- Mean MELD=18.8
- 51% (n=77) on propranolol
  - 48% 120-160 mg
  - 52% 40-80 mg

	No NSBB	NSBB
Varices	4%	100%
CTP-C	61%	74%
T bilirubin (mg/dl)	2.8	3.3
Creatinine (mg/dl)	0.86	0.89
Na (mmol/l)	133	125
MELD-Na	22	22



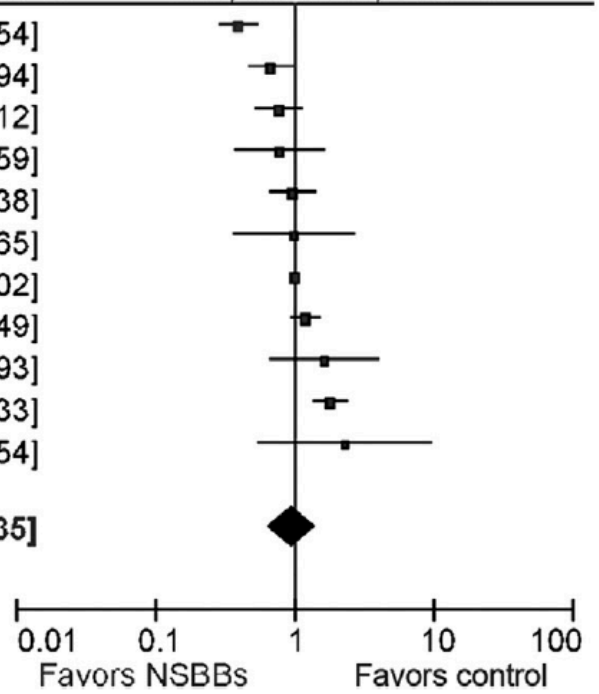
Serste. Hepatology 2010;52:1017-22

NSBB and Survival in Cirrhotic Patients with Ascites

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)

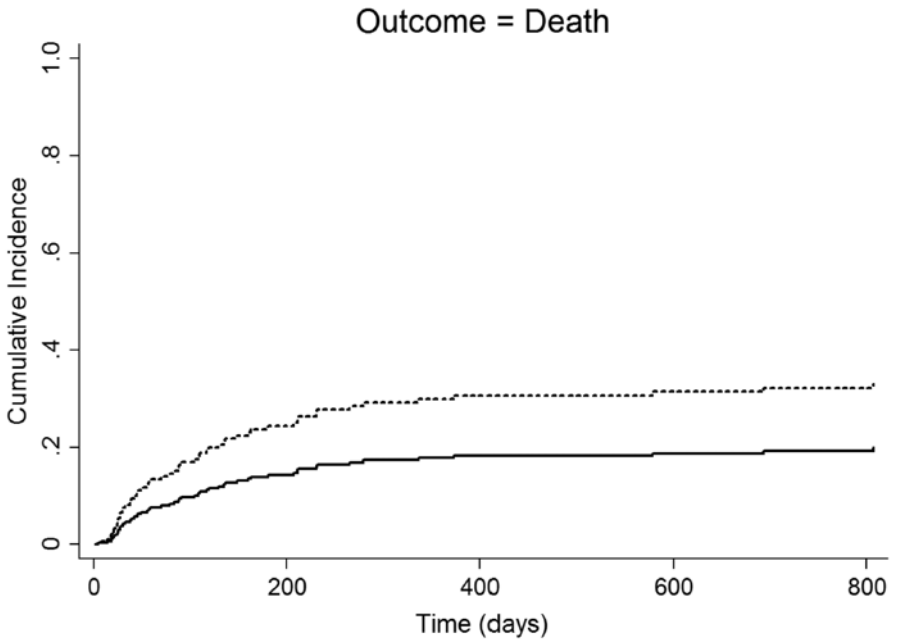


Chirapongsathorn. CGH 2016;14:1096-1104

NSBB and Waitlist Outcome

- UK single center retrospective cohort of LTx candidates with ascites (n=322)
- No uniform protocol for NSBB administration

	No NSBB	NSBB
n	163	159
Refractory ascites	37%	35%
Variceal bleeding	25%	40%
T bilirubin (mg/dl)	3.2	3.0
Creatinine (mg/dl)	0.86	0.89
Na (mmol/l)	134	136
MELD	17	16

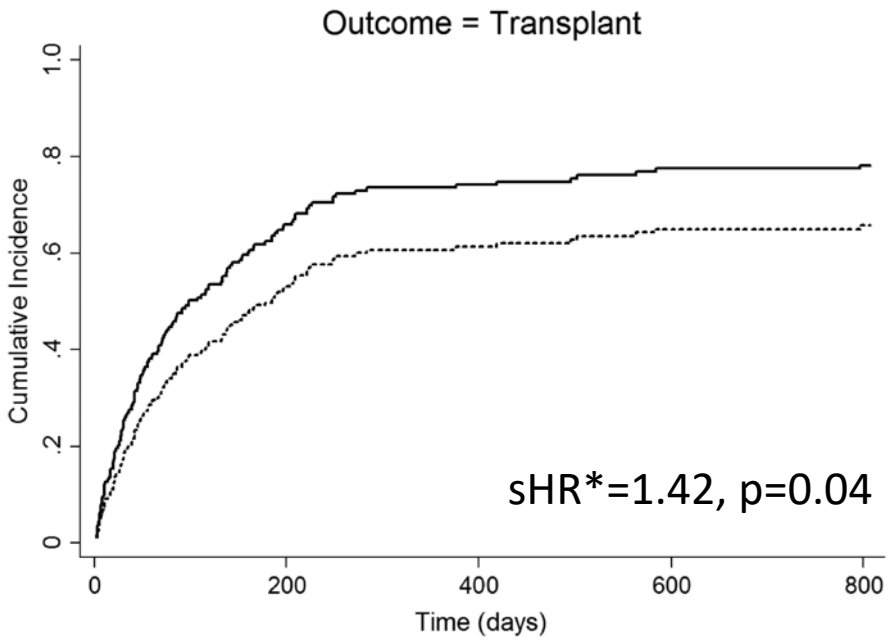


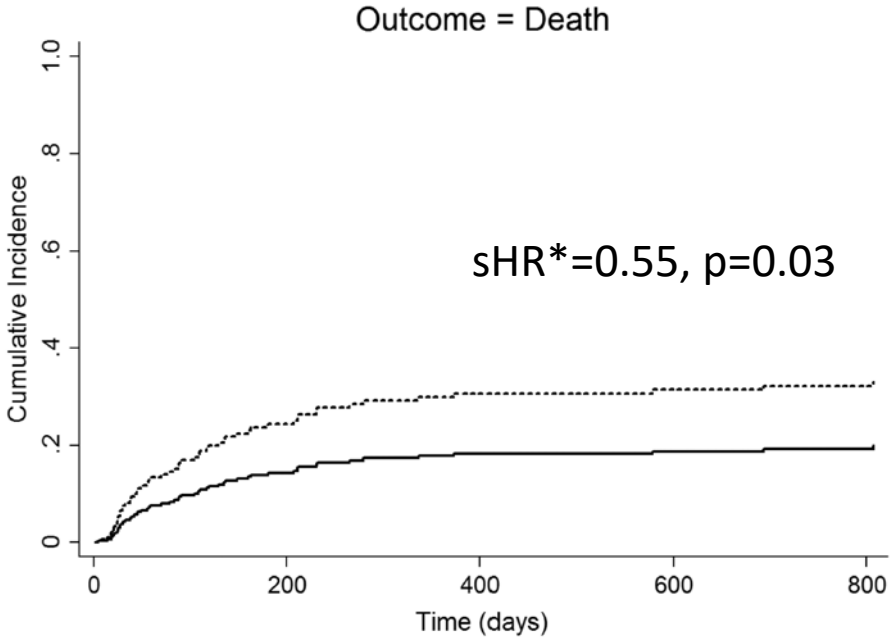
- Propensity score matching

Leithead. Gut 2015;64:1111-9

NSBB and Waitlist Outcome

- UK single center retrospective cohort of LTx candidates with ascites (n=322)
- No uniform protocol for NSBB administration





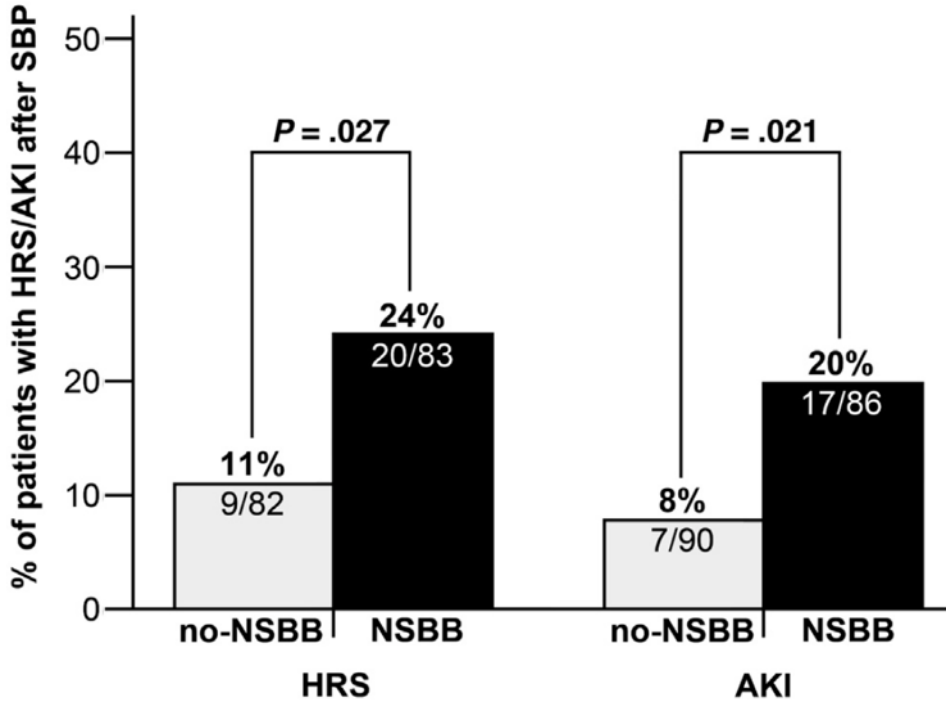
Leithead. Gut 2015;64:1111-9

*Propensity-score-matched, multivariable-adjusted

NSBB in Patients with SBP

- Single center study of cirrhotic patients undergoing paracentesis (n=607)
  - Mean MELD= 17.5, Child C= 50%
  - 182 (30%) with SBP
  - 245 (40%) receiving NSBB
  - Among patients with SBP:

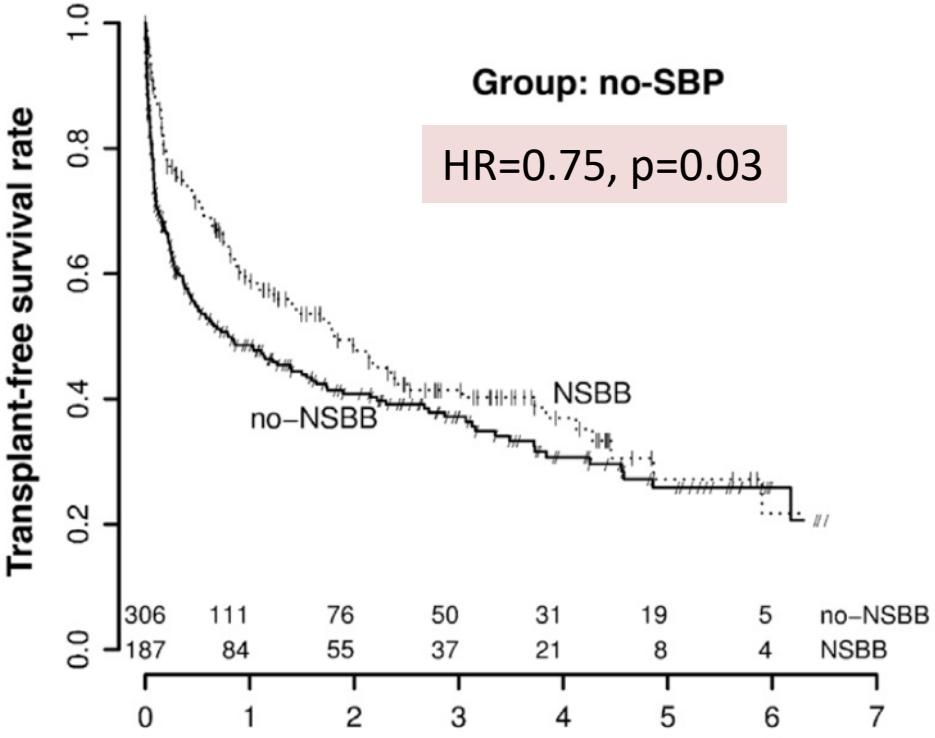
    NSBB was associated with
    - HRS
    - AKI

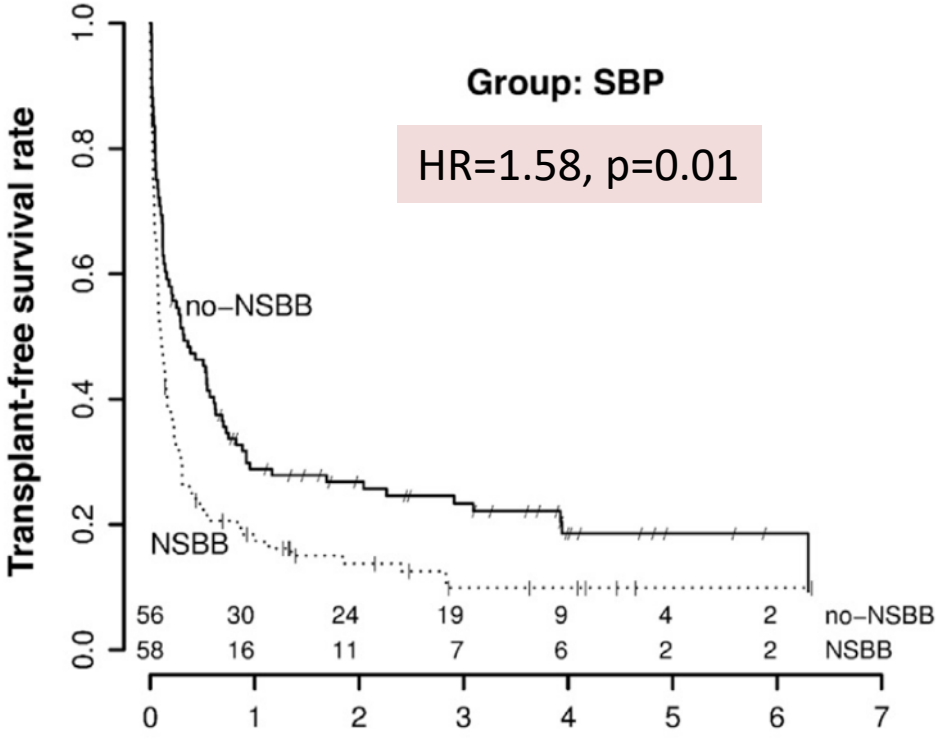


Mandorfer. Gastroenterology 2014;146:1680–90

NSBB in Patients with SBP

- Impact of NSBB on survival changes depending on SBP

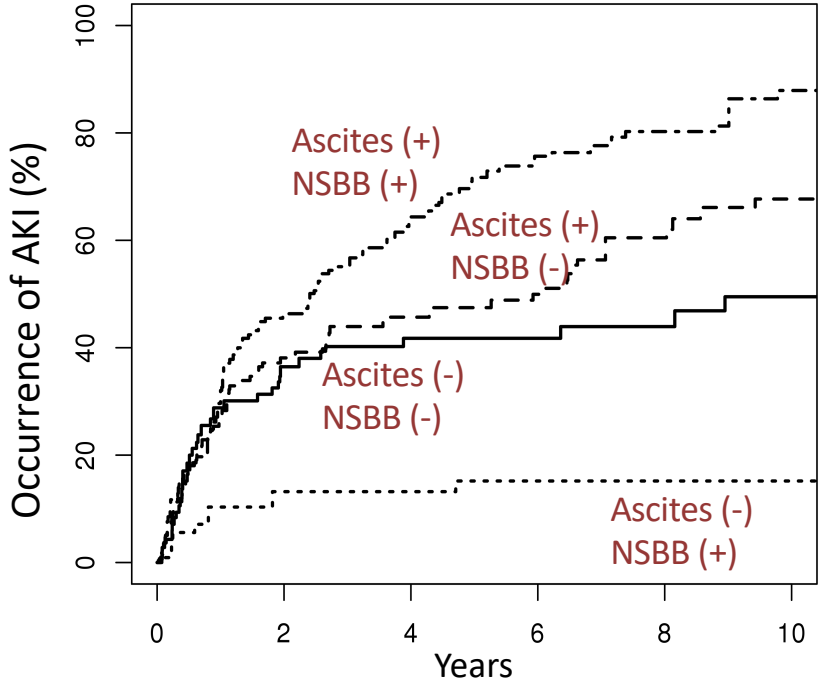




Mandorfer. Gastroenterology 2014;146:1680–90

Incidence of AKI

- Single center LTx waitlist data (n=2,361)
- AKI developed in 205 while waiting: NSBB use was higher in AKI (46% versus 375)



Predictors of AKI

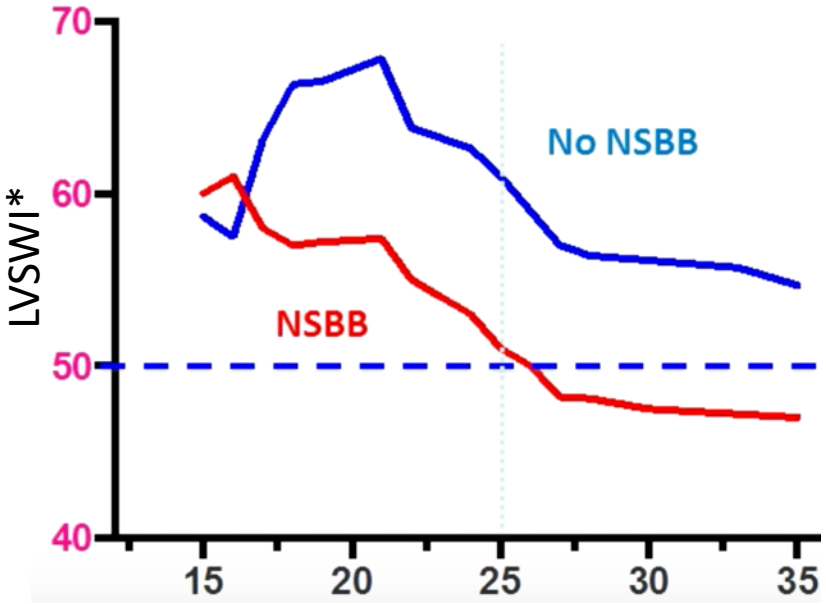
	HR	p
MELD-Na at Baseline	1.66 (1.36-2.02)	<0.01
NSBB - No Ascites	0.19 (0.06-0.60)	<0.01
NSBB – Ascites	3.31 (1.57-6.95)	<0.01

* Cox proportional hazards model stratifying on matched pairs and adjusting for age, sex, race, etiology of cirrhosis, presence of HCC

Kim. Liver Transplant 2017;23:733–40

NSBB, Refractory Ascites and Cardiac Dysfunction

Waitlist registrants with right heart catheterization data (1999-2014, n=584)



- Refractory ascites (33%): Lower LVSWI
- Higher mortality in patients with low LVSWI receiving NSBB.
- Predictors of waitlist mortality

Variable	sHR	p
MELD	1.03 (1.00-1.06)	0.03
Sodium	0.97 (0.93-1.01)	0.19
Refractory Ascites	1.52 (1.01-2.28)	0.04
NSBB and LVSWI*<64 g.m/m^2	1.96 (1.32-2.90)	<0.01

*Left ventricular systolic work index: Indicator of global cardiac performance
LVSWI=13.6*(MAP-PCWP)*CI/HR*

Giannelli. J Hep 2019; in press

Take Home

Compensated with no pHTN	No role for NSBB
Compensated with significant pHTN and no/low risk varices	Carvedilol (> other NSBB) to prevent decompensation
Compensated or mildly decompensated with high risk varices	NSBB, EVL or combo (?) to prevent bleeding
Compensated or mildly decompensated with bleeding history	NSBB+EVL (> mono therapy) to prevent rebleeding
Decompensated with refractory ascites, SBP, or cardiac dysfunction	Discontinue NSBB in sick ESLD patients. EVL as needed.

AASLD
THE LIVER MEETING®
NOVEMBER 8-12 2019 BOSTON

THE BEST OF THE LIVER MEETING® 2019

Portal Hypertension / Cirrhosis

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

The CONFIRM study: a North American randomized controlled trial of terlipressin plus albumin for the treatment of HRS-1

Aim:

To confirm the efficacy and safety of terlipressin + albumin vs albumin alone in patients with HRS-1 (based on ICA criteria*)

Methods:

- Double-blind, prospective trial with 300 patients randomized 2:1 to terlipressin (1 mg IV q6h) or placebo (plus albumin in both groups)
- Primary endpoint: VHRSR† defined as 2 consecutive SCr values ≤1.5 mg/dL ≥2 h apart, by Day 14 or discharge; subjects must be alive without RRT for ≥10 days after achieving VHRSR

Results:

- Significant improvements in renal function were observed with terlipressin.
- The incidence of RRT post-liver transplant was 19.6% with terlipressin plus albumin versus 44.8% with albumin alone (*P*=0.036).

Conclusions:

Terlipressin is effective in improving renal function and achieving HRS reversal in patients with HRS-1 and progressive advanced liver disease.

Wong F, et al., Abstract LO5

Outcome, n (%)	Terlipressin n=199	Placebo n=101	*P* Value
Primary endpoint: VHRSR†	58 (29.1)	16 (15.8)	0.012
HRSR‡	72 (36.2)	17 (16.8)	<0.001
Durability of HRSR (no RRT to Day 30)	63 (31.7)	16 (15.8)	0.003
HRSR in the SIRS subgroup	28 (33.3)	3 (6.3)	<0.001
VHRSR with no recurrence of HRS by Day 30	48 (24.1)	16 (15.8)	0.092
Alive and Transplant-free at Day 90, % (n)	26.1 (52)	26.7 (27)	0.78

*International Club of Ascites
†VHRSR, verified HRS reversal
‡HRSR, hepatorenal syndrome reversal (decrease in SCr to ≤1.5 mg/dL).
RRT, renal replacement therapy; SCr, serum creatinine; SIRS, systemic inflammatory response syndrome.

Rifaximin for the prevention of hepatic encephalopathy in patients treated by TIPS: a multicentre RCT

Objective:

The efficacy of rifaximin in secondary prevention of clinical hepatic encephalopathy (HE) is well documented, but its efficacy for prevention of a first episode in patients treated by TIPS is not established.

Methods:

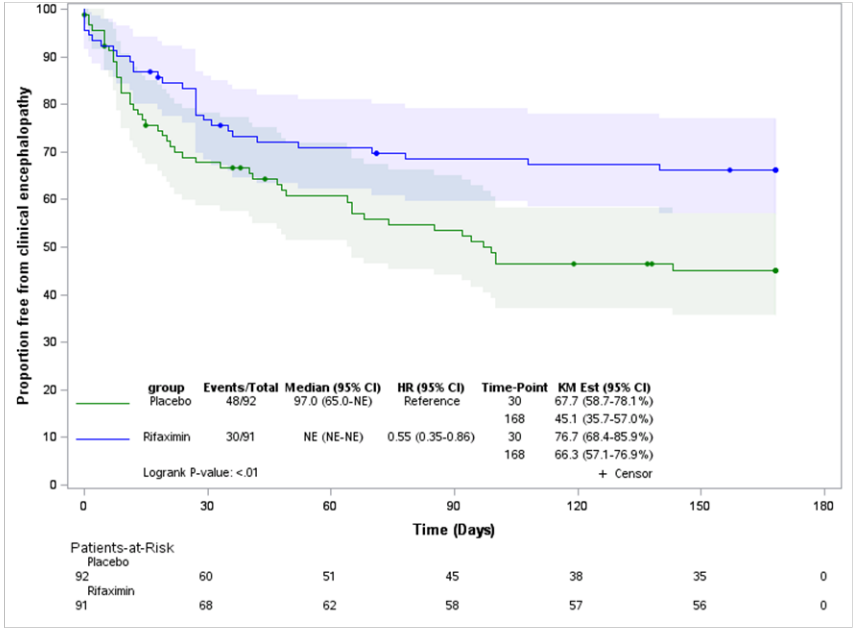
We randomly assigned 183 patients who were treated by TIPS to receive either rifaximin, at a dose of 600 mg twice daily or placebo, started 15 days before TIPS and for 6 months after the procedure. The primary outcome was the occurrence of at least one episode of HE within 6 months (double blind assessment).

Main Findings:

The 6-month probability of being free of HE was 66.3 % in the rifaximin group compared to 45.1 % in the placebo group (p<0.01). Stratified OR on Child Pugh Class and a previous episode of HE before TIPS was 0.48 IC 95% [0.27-0.87; p=0.01].

Conclusion:

In patients treated by TIPS, we showed that the use of preventive rifaximin is associated with a lower risk of clinical HE.



Bureau C, et al., Abstract 14

Long-term effect of growth hormone therapy in decompensated cirrhosis

Aim:

To study the safety and efficacy of Growth Hormone (GH) therapy and its effect on malnutrition, nitrogen metabolism, and hormonal changes in patients with decompensated cirrhosis (DC)

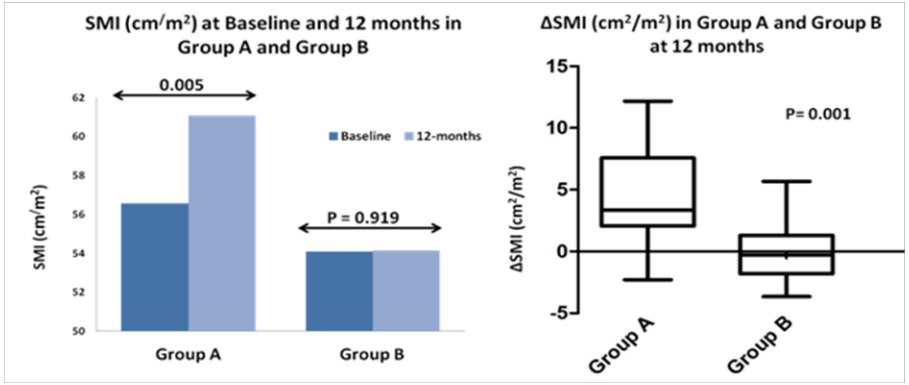
Methods:

- Thirty-four patients with DC were openly randomized to either standard medical therapy (SMT) plus GH (1 IU/day subcutaneously and increased to 2 IU/day by titrating the dose according to IGF-1 levels) (Group A; n=17) or SMT alone (Group B; n=17).
- Malnutrition parameters [skeletal muscle index (SMI), body mass index (BMI), mid-arm muscle circumference (MAMC), hand grip strength (HGS)], hormonal changes, and nitrogen balance were studied at baseline, 3, 6, 9, and 12 months.

Conclusions:

- GH therapy is safe and effective in patients with DC.
- Long-term use of GH improves malnutrition (SMI, BMI, MAMC, and HGS) and nitrogen balance and decreases GH resistance.

Kumari S, et al., Abstract 50



Various Parameters at Baseline and 12 Months

Parameters	Group A			Group B		
	Baseline	12-months	*P*-value	Baseline	12-months	*P*-value
BMI(Kg/m²)	22.9±3.0	25.7±3.2	0.02	21.2±5.8	22.6±4.2	0.87
MAMC (cm)	22.6±2.5	27.5±8.1	0.02	22.7±7.8	23.79±8.9	0.89
Handgrip strength (Kg)	21.1±5.8	27.5±6.4	0.01	22.5±5.9	23.7±6.6	0.58
IGF-1(ng/ml)	0.3±0.1	6.2±4.5	0.00	0.4±0.1	0.5±1.5	0.68
GH(IU/ml)	565.7±355.1	185.1±120.6	0.04	498.8±355.1	402.1±150.6	0.67
Nitrogen Balance (g/day)	3.02±6.4	8.43.±6.2	0.09	2.98±5.9	3.58±6.3	0.45

Comparison of the efficacy of granulocyte macrophage-colony stimulating factor (GM-CSF) and norfloxacin for secondary prophylaxis of spontaneous bacterial peritonitis – a randomized controlled trial

Aim:

To compare immunostimulatory therapy using GM-CSF with norfloxacin for secondary prophylaxis of SBP

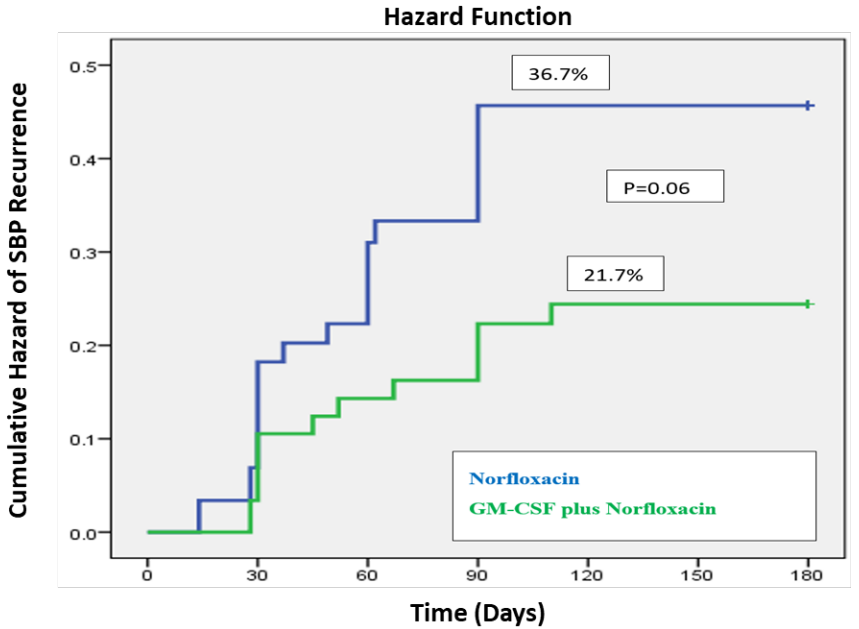
Methods:

- In an open-label, randomized trial, decompensated cirrhotic patients (n=120) with complete resolution of SBP on standard antibiotic therapy received oral norfloxacin 400 mg/day [Group A, n=60] or in addition GM-CSF 1.5 mcg/kg infusion over 4 hours every 15 days [Group B, n=60].
- Recurrence of SBP at 6 months, new onset complications, overall survival and adverse effects of the drugs were studied.

Conclusions:

Fortnightly GM-CSF was safe and more effective in preventing recurrence than daily norfloxacin therapy (p=0.06).

Recurrence of SBP in Both Groups Based on Intention to Treat Analysis



Mishra M, et al., Abstract 97

G-CSF to treat acute-on-chronic liver failure (GRAFT trial): interim analysis of the first European multicentre trial

Hypothesis:

Granulocyte-colony stimulating factor (G-CSF) mitigates organ injury in acute-on-chronic liver failure (ACLF).

Methods:

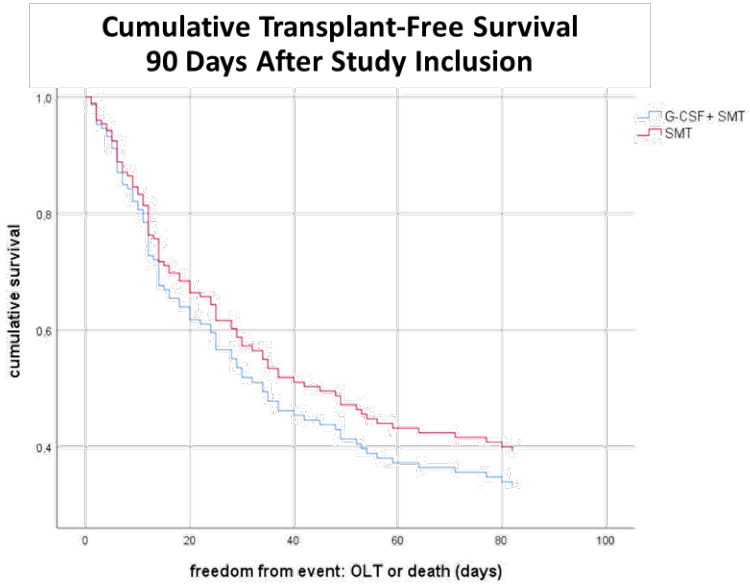
Controlled, prospective, open-label 2-arm study in 163 patients comparing the efficacy of G-CSF against standard medical therapy (SMT) in patients with ACLF

Main Findings:

Patients treated with G-CSF had a 90-day transplant-free survival of 40.7%, which was not different to 48.8% in SMT with a hazard ratio of 1.177 (95% CI 0.778; 1.782) (p=0.44).

Conclusions:

Unlike previous publications from smaller clinical trials these results show that G-CSF has no beneficial effect on the outcome of patients with ACLF.



Patients at risk

G-CSF + SMT	81	48	28	21	20
SMT	82	44	32	27	25

Engelmann C, et al., Abstract 17

AASLD
THE LIVER MEETING®
NOVEMBER 8-12 2019 BOSTON

THE BEST OF THE LIVER MEETING® 2019

Portal Hypertension / Cirrhosis

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

HRS: 2007 International Ascites Club Definition

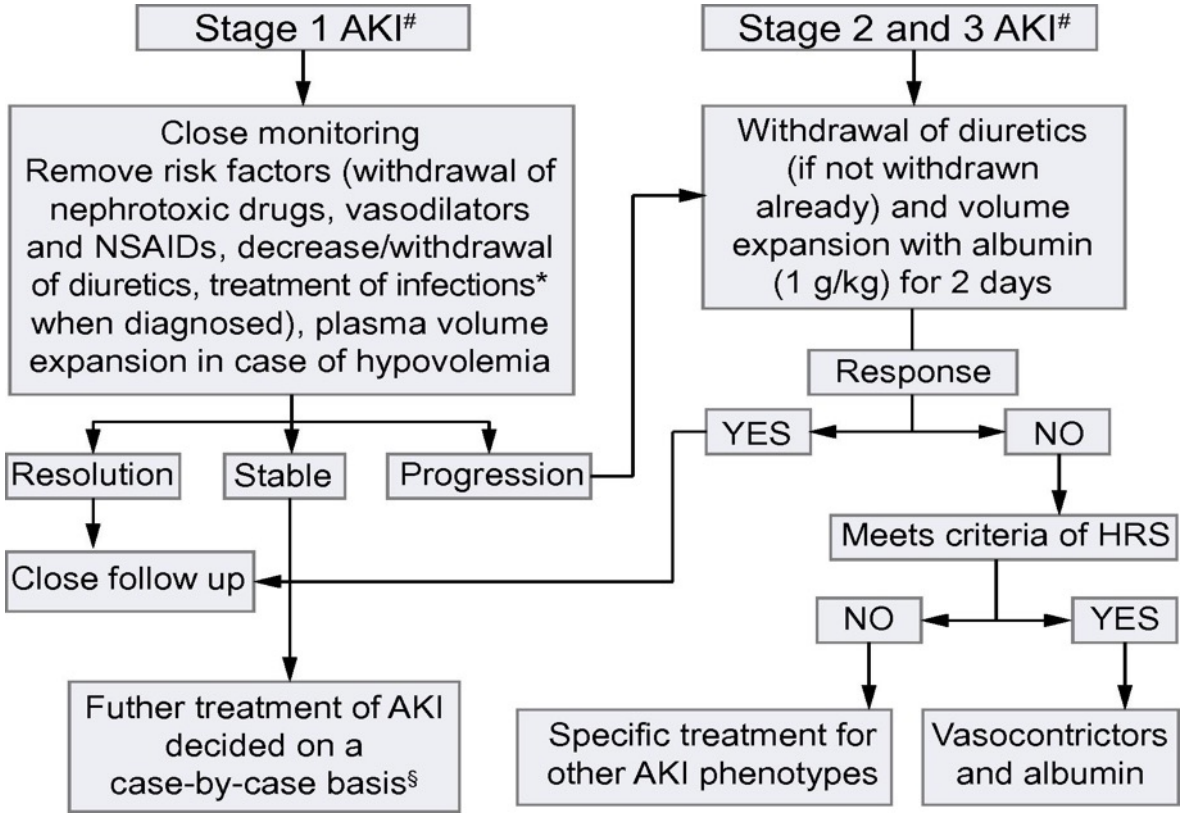
- Cirrhosis with ascites
- Serum creatinine > 1.5 mg/dl
- No improvement in serum creatinine (decrease 1.5 mg/dl) after at least 2 days of diuretic withdrawal and volume expansion with albumin*.
- Absence of shock
- No current or recent treatment with nephrotoxic drugs
- Absence of parenchymal kidney disease (proteinuria, microhematuria and/or abnormal renal ultrasonography)

- * recommended albumin dose: 1 g/kg/day (max 100 g/day)

Salerno. Gut 2007;1310

Consensus Recommendation: Management of AKI

Stage	Criteria
1	Cr ≥ 0.3 mg/dL and < x2 baseline
2	x2-3 baseline
3	x3 baseline, Cr ≥ 4.0 mg/dL or dialysis



Angeli. Gut 2015

Question

Does the patient have hepatorenal syndrome (HRS)?

1. Yes
2. No
3. Need more data

Cirrhotic Cardiomyopathy and NSBB

Prevalence of Cardiomyopathy and Impact of the Use of Non-Selective Beta Blockers in End Stage Liver Disease

- Retrospective study of liver transplant candidates (n=526)

  77% male, mean age 53 years old

  49% Alcohol, 27% HCV and 12% HBV

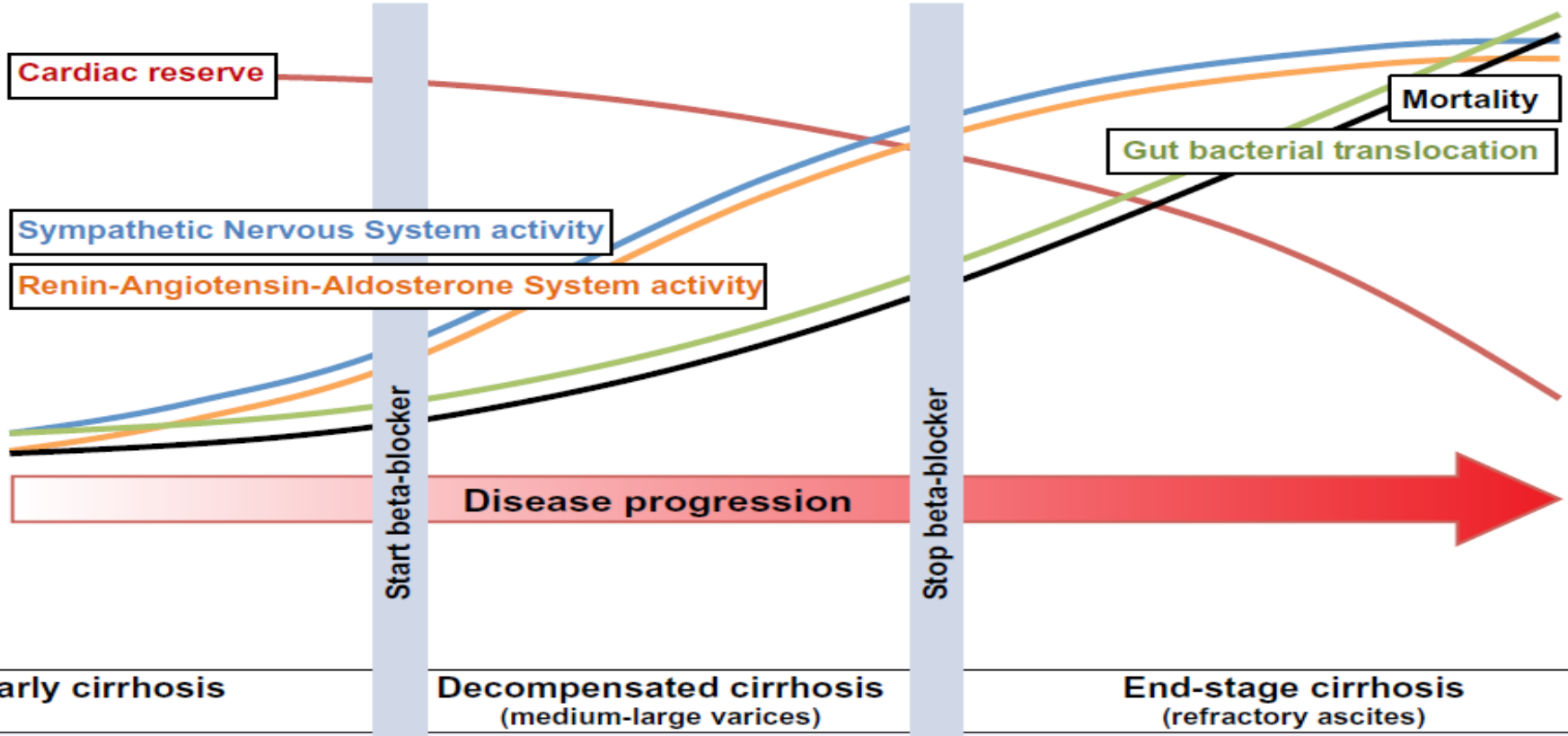
MELD Category	n	NSBB	Myocardial Dysfunction
MELD <15	246	47%	32%
MELD 16-25	215	58%	35%
MELD >25	60	50%	37%

- Severity of cardiomyopathy measured by

  Left ventricular stroke work index (LVSWI): Normal > 50

Giannelli. EASL PS062

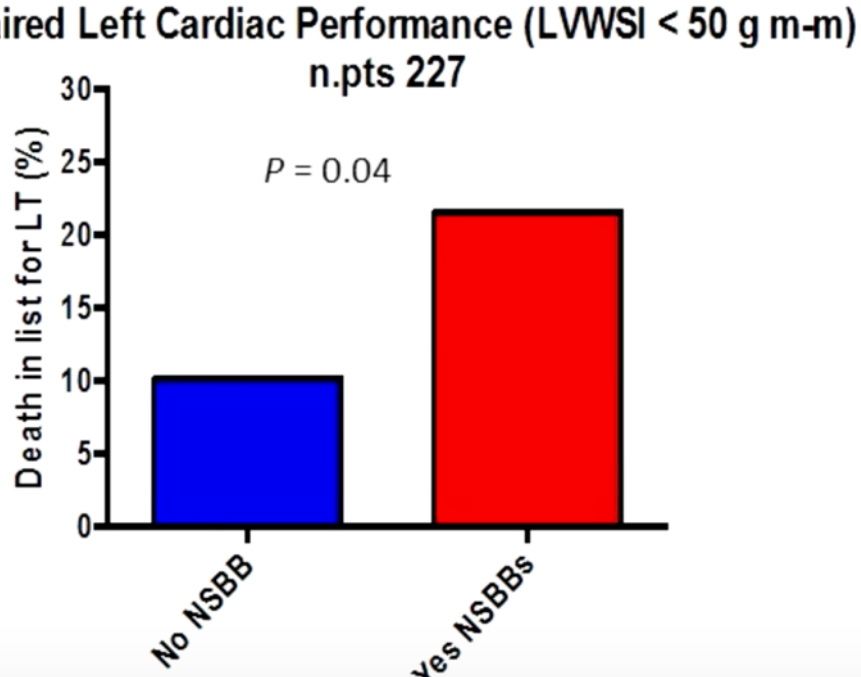
Window Theory



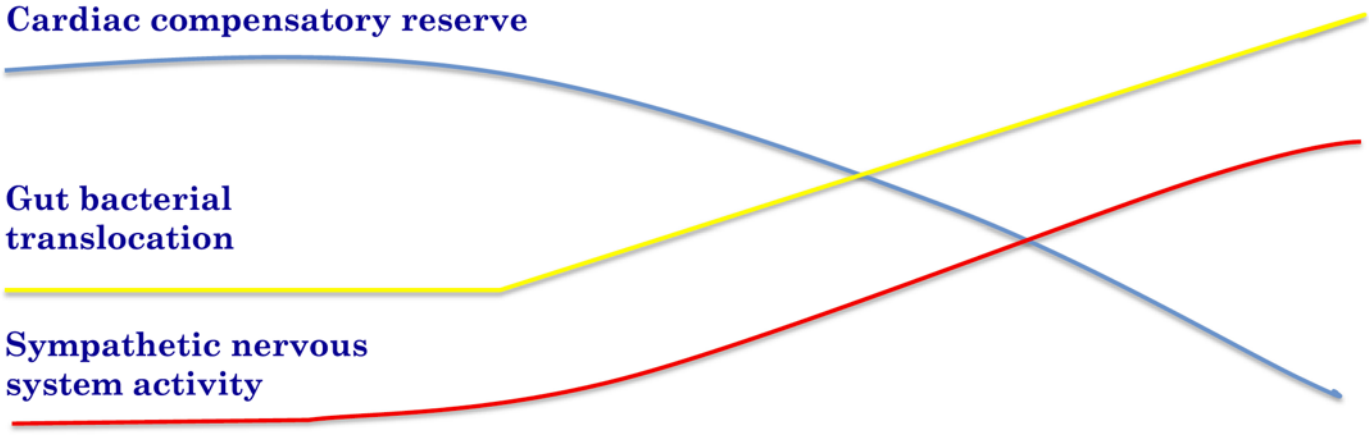
Am J Gastroenterol 2012; 107:418–427

Impact on Mortality

Mortality among Patients with LVSWI < 50



Giannelli. EASL PS062



BB have **no effect on survival**

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

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.

Window opens

Window closes

Early cirrhosis

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

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

End-stage cirrhosis

(Refractory ascites)

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

Use of TIPS for Variceal Bleeding

- Controlling acute bleeding:
- Preemptive TIPS (within 72 hours from EVL)
  - High risk of failure or rebleeding
  - No contraindications for TIPS
- Refractory or rebleeding despite vasoactive therapy and EVL
- Treatment of choice for cardiofundal varices (GOV2 or IGV1)

Garcia-Tsao. Hepatology 2017;65:310

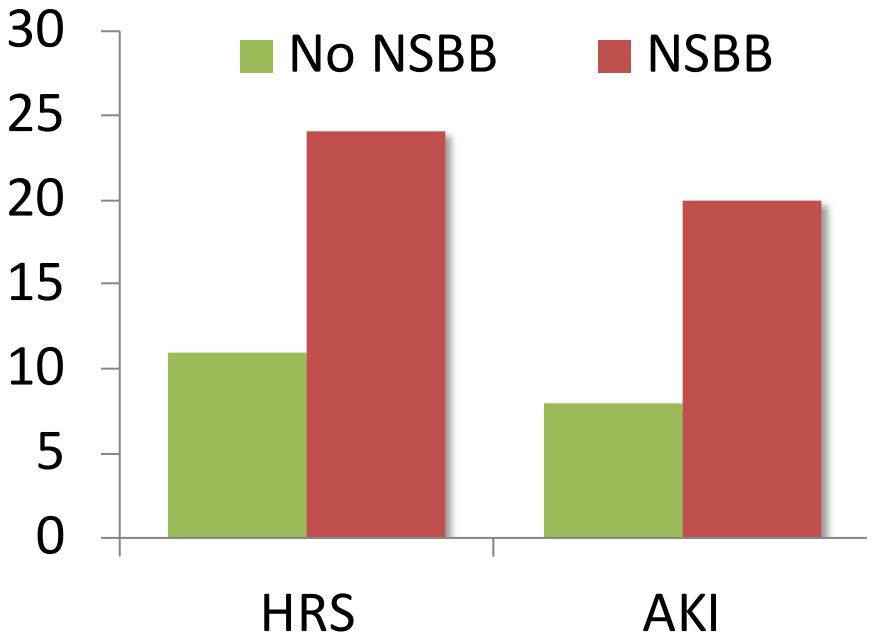
AASLD Guideline: Spontaneous Bacterial Peritonitis

- Community-acquired SBP:
- Empiric antibiotic therapy with third-generation cephalosporin
- Cefotaxime 2 g every 8 hours
- Oral ofloxacin 400 mg twice per day may be used in stable patients
- Nosocomial SBP or recent B-lactam antibiotic exposure:
- Antibiotic therapy based on local susceptibility profile
- Albumin infusion
- Creatinine >1 mg/dL, blood urea nitrogen >30 mg/dL, or total bilirubin >4 mg/dL
- 1.5 g/kg within 6 hours of detection and 1.0 g/kg on day 3
- Long-term prophylaxis
- Norfloxacin (if available) 400mg or ciprofloxacin 500mg daily
- Trimethoprim/sulfamethoxazole double strength daily or 5 times a week

Runyon. Hepatology 2013

NSBBs in Patients with Severe Hepatic Decompensation

Austrian study (n=182)
Patients with SBP



- AASLD Guidance
- Refractory ascites and SBP are not absolute contraindications for NSBBs.
- Avoid high doses of NSBBs
  - >160 mg/day of propranolol or
  - >80 mg/day of nadolol
- Hold or decrease the dose of NSBBs in patients with refractory ascites and
  - Systolic blood pressure < 90mmHg
  - Serum sodium <130 meq/L, or
  - HRS

Mandorfer. Gastroenterology 2014;146:1680–1690
Garcia-Tsao. Hepatology 2017;65:310

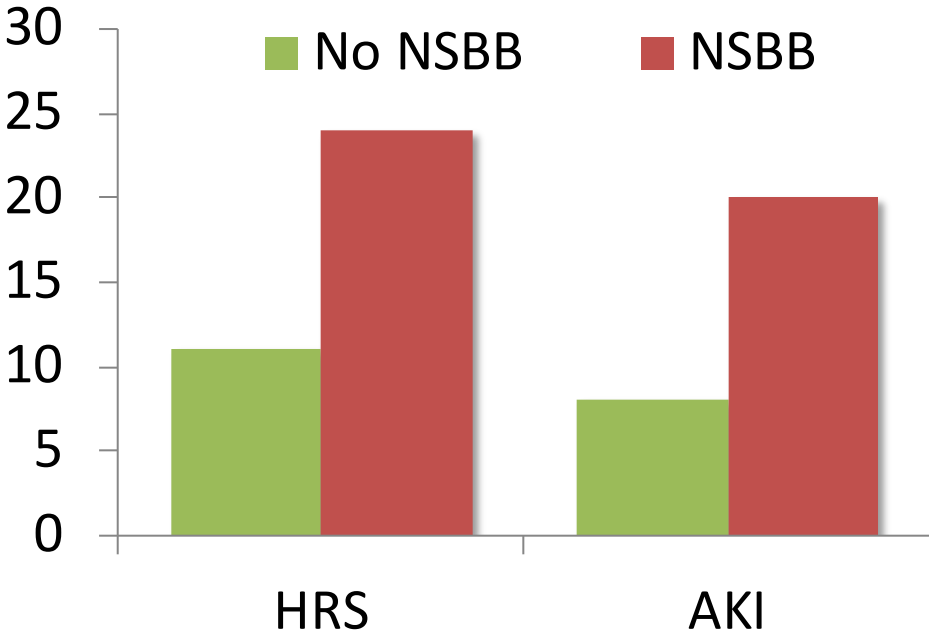
Take Home

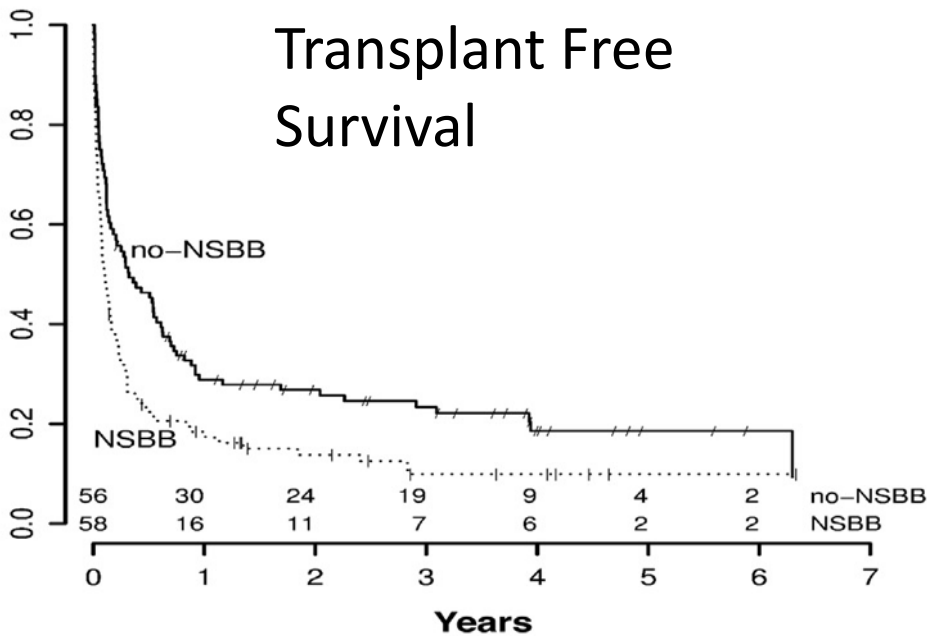
- Stages of cirrhosis:
  - Compensated cirrhosis with or without clinically significant portal hypertension
  - Decompensated cirrhosis with variceal hemorrhage and end stage liver disease
- Prevention of variceal hemorrhage
  - Primary: beta blockade or variceal band ligation
  - Secondary: beta blockade and ligation
- TIPS for variceal bleeing
  - Refractory bleeding, prevention of rebleeding if high risk, cardiofundal varices
- SBP
  - Antibiotics plus albumin followed by antibiotic prophylaxis
- HRS and AKI
  - Restoration of renal perfusion (albumin + vasocontrictor)
- Potential harm of NSBB in far advanced patients

Potential Harm of NSBB in Patients with SBP

Single center study (Austrian, n=607, 182 with SBP)

Mean MELD= 17.5, Child C= 50%





Mandorfer Gastroenterology 2014;146:1680–1690

The CONFIRM Study: Terlipressin for HRS-1

Aim:

To confirm the efficacy and safety of terlipressin + albumin vs albumin alone in patients with HRS-1 (based on ICA criteria*)

Methods:

- Double-blind, prospective trial with 300 patients randomized 2:1 to terlipressin (1 mg IV q6h) or placebo (plus albumin in both groups)
- Primary endpoint: VHRSR† defined as 2 consecutive SCr values ≤1.5 mg/dL ≥2 h apart, by Day 14 or discharge; subjects must be alive without RRT for ≥10 days after achieving VHRSR

Results:

- Significant improvements in renal function were observed with terlipressin.
- The incidence of RRT post-liver transplant was 19.6% with terlipressin plus albumin versus 44.8% with albumin alone (*P*=0.036).

Conclusions:

Terlipressin is effective in improving renal function and achieving HRS reversal in patients with HRS-1 and progressive advanced liver disease.

Wong F, et al., Abstract LO5

Outcome, n (%)	Terlipressin n=199	Placebo n=101	*P* Value
Primary endpoint: VHRSR†	58 (29.1)	16 (15.8)	0.012
HRSR‡	72 (36.2)	17 (16.8)	<0.001
Durability of HRSR (no RRT to Day 30)	63 (31.7)	16 (15.8)	0.003
HRSR in the SIRS subgroup	28 (33.3)	3 (6.3)	<0.001
VHRSR with no recurrence of HRS by Day 30	48 (24.1)	16 (15.8)	0.092
Alive and Transplant-free at Day 90, % (n)	26.1 (52)	26.7 (27)	0.78

*International Club of Ascites
†VHRSR, verified HRS reversal
‡HRSR, hepatorenal syndrome reversal (decrease in SCr to ≤1.5 mg/dL).
RRT, renal replacement therapy; SCr, serum creatinine; SIRS, systemic inflammatory response syndrome.

Glass half-full?: Response in 1/3
Biomarker for response
Precision, cost-effective delivery

RESULTS

- Sixty-five (39%) of 168 consecutive patients evaluated for liver transplantation were, and 103 (61%) were not taking NSBBs at the time of initial evaluation.
- Patients taking NSBBs had higher Model for End-Stage Liver Disease and (MELD) Childs Pugh Scores (CPS), and more frequent refractory ascites and large/previously bleeding esophageal varices (Table 1). Although resting heart rate was lower in patients taking NSBBs, mean arterial pressure (MAP) was not significantly lower.
- Ninety day outcomes from the date of initial evaluation were compared in patients taking and not taking NSBBs (Table 2). Patients taking NSBBs had higher rates of acute kidney injury (22% vs. 5%, p=0.001), but a lower 90 day mortality (5% vs 15%, p = 0.04). However there was no difference in overall transplant free survival (Figure 1). The 14 patients taking NSBBs and developing acute kidney injury within 90 days had significantly higher MELD (19 (17-25(vs. 13-18), p=0.002), related to higher creatinine (3.1 (2.3 -4.1) vs. 1.1 (0.8-1.3), p=0.09) and numerically lower MAP (79 (71-86) vs. 85 (77-93) p=0.19).
- Similar proportions of patients who were and were not taking NSBBs completed liver transplant evaluation with no differences in transplant candidacy rates or overall liver transplant rates (Table 2).
- The predictors of 90 day mortality on multiple logistic regression analysis are described below (Table 3). The use of NSBB was independently associated with decreased 90-day mortality, as were higher MAP and lower MELD.
- The continued use of NSBBs in the 65 patients taking NSBBs at initial liver transplant evaluation was characterized in 45 (69%) with available follow up between 90 and 180 days after initial evaluation (Table 4). Thirteen of the 45 (29%) had discontinued NSBB during that interval, and they had numerically lower MAP and a trend towards higher MELD compared with the 32 patients still taking NSBBs. Twenty-five of the 32 (78%) had available follow-up between 180 and 270 days after initial evaluation (Table 4). Similarly, 8 of them (32%) had discontinued NSBBs during that interval, and they had numerically lower MAP, and significantly higher MELD compared with the 17 patients still taking NSBBs. The reasons for discontinuation of NSBBs included fatigue, hemodynamic concerns of hypotension (non-uniform) and acute kidney injury, but not refectory ascites of spontaneous bacterial peritonitis.

Table 2

Table 2. Clinical outcomes of patients taking and not taking NSBBs at liver transplant evaluation			
	On NSBBs n=65	**Not on NSBBs n=103**	**P value**
Acute kidney injury within 90 days	14 (22%)	5 (5%)	0.001
*Gastrointestinal bleeding within 90 days	None	None	NA
Spontaneous bacterial peritonitis within 90 days	4 (6%)	2 (2%)	0.14
Hospitalized within 90 days	19 (29%)	23 (22%)	0.3
Liver transplant within 90 days	1 (1%)	5 (5%)	0.3
Died within 90 days	3 (5%)	5 (15%)	0.04
Liver transplant committee decision Listed Non-candidate Additional evaluation/treatment needed	 27 (66%) 7 (17%) 7 (17%)	 34 (61%) 12 (21%) 10 (18%)	0.8
Follow-up interval (days)	283 (124 – 687)	235 (100 – 488)	0.01
Total number of hospitalizations	1 (0-3)	1 (0-2)	0.7
Overall survival and transplant outcomes Alive Underwent liver transplantation Died	 22 (34%) 21 (32%) 22 (34%)	 33 (32%) 32 (31%) 39 (37%)	0.9

Values shown as median (interquartile range) or number (percentage)

Abbreviations: NSBBs, Non-selective beta blockers; NA, not applicable.

Footnotes

* Related to portal hypertension

Table 3

Table 3. Predictors of 90-day Mortality		
	Odds Ratio (95% CI)	**P value**
Model for End-Stage Liver Disease	1.2 (1.1-1.4)	<0.001
Mean arterial pressure	0.9 (0.8 - 1)	0.006
NSBB use	0.08 (0.01 - 0.5)	0.008
Gender (male)	6.4 (0.9 - 47)	0.07
Childs Pugh Score	1.04 (0.7 - 1.5)	0.8

Abbreviations: CI, confidence interval

Factors that were not predictive of 90-day mortality on simple logistic regression were age, race, etiology of liver disease, serum sodium and body mass index.

Predictors of AKI – Multivariable Analysis*

	HR	95% CI		p	Interaction
MELD-Na at Baseline	1.66	(1.36	- 2.02)	<0.001	
NSBB and ascites (-)	0.16	(0.06	- 0.48)	0.001	<.001
NSBB and ascites (+)	3.78	(1.93	- 7.39)	<0.001	

* Cox proportional hazards model stratifying on matched pairs and adjusting for age, sex, race, etiology of cirrhosis, presence of HCC

Kim AASLD 2014

Use of Non-selective β-Blockade (NSBB) in ESLD

- Effect of NSBB on portal hypertension (pHTN)
  - Single center study, 294 patients with cirrhosis
  - Propranolol i.v. 0.15 mg/Kg

	Mild pHTN (n=81)	Significant pHTN (n=194)
Baseline	HVPG > 10 mmHg	HVPG 6-10 mmHg Small varices (n=114) No varices (n=80)
Liver stiffness MELD Splenomegaly Systemic vascular resistance Cardiac index	19 kPa 5.6 40% 1469 dyne.s.cm 2.8	30kPa 6.5 63% 1336 dyne.s.cm 3.3
HVPG response to propranolol		
Pre-Post change	7.3 – 6.6 mmHg (-8%)	14.7 - 12.2 mmHg (-16%)
>20% reduction	12%	40%

Villanueva. AASLD 2014 Abstract 2036

Benefits of β-blockade in Cirrhosis

Non-selective β-blocker (NSBB) is beneficial in patients with cirrhosis and esophageal varices.

- Reduced incidence of variceal hemorrhage
- Reduced incidence of ascites
- Improved survival

Current AASLD Guideline (2007) recommends NSBB for:

- Primary prophylaxis in patients with low risk bleeding (Child A, no red signs) and medium/large varices
- Primary prophylaxis in patients at high risk of bleeding (e.g., Child B/C) regardless of the variceal size
- Secondary prophylaxis (in conjunction with variceal ligation)

Am J Gastroenterol 2012; 107:418–427

Potential Harm of NSBB

- NSBBs are associated with paracentesis-induced circulatory dysfunction in patients with cirrhosis and refractory ascites
- NSBBs are associated with poor survival in patients with refractory ascites
- Among patients with cirrhosis and SBP, NSBBs increased risk for hepatorenal syndrome and acute kidney injury and reduced transplant-free survival.

J Hepatol 2011;55:794-9; HEPATOLOGY 2010;52:1017-1022; Gastroenterology 2014;146:1680–1690

NSBB and Short Term Survival

Non-selective Beta Blocker use is Associated with Improved Short term Survival in Patients Referred for Liver Transplantation

	On NSBBs n=65	Not on NSBBs n=103	P
Age, years	59 (55 - 64)	58 (53 - 63)	0.5
Male gender	43 (66%)	63 (61%)	0.5
Heart rate beats/min	65 (60 - 72)	79 (70 - 88)	<0.01
Systolic BP, mmHg	112 (101 – 127)	118 (104 – 129)	0.2
Diastolic BP, mmHg	67 (60 -76)	70 (60 – 79)	0.3
Cirrhosis Etiology			
Hepatitis C	28 (43%)	56 (54%)	0.2
Alcohol	23 (35%)	31 (30%)	0.4
NASH	19 (29%)	22 (21%)	0.2
Creatinine (mg/dL)	1.05 (0.8 – 1.4)	0.9 (0.7 – 1.2)	0.06
MELD	16 (14 - 19)	14 (10 - 19)	0.02

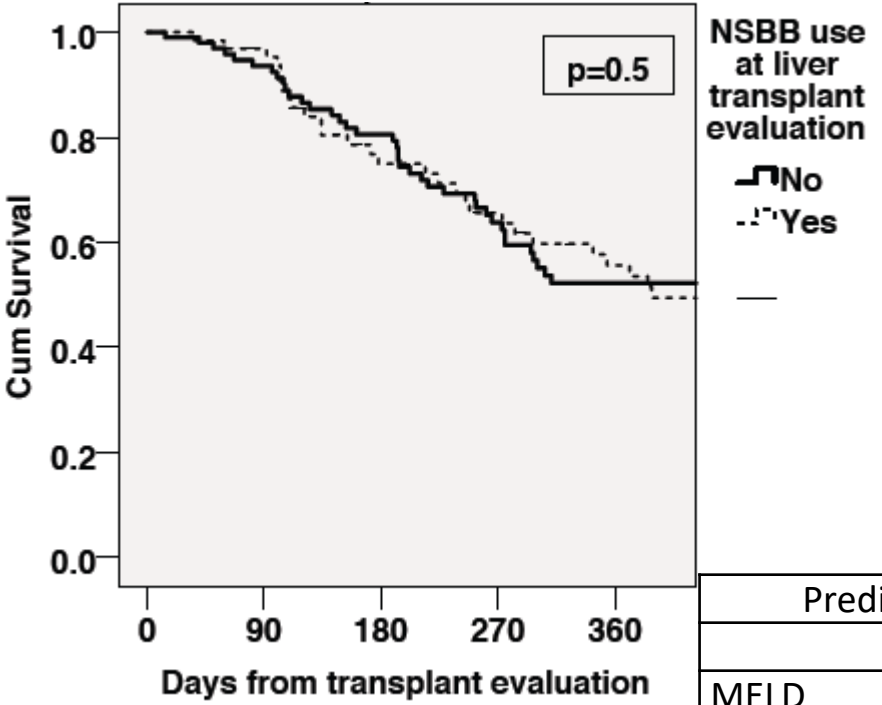
Ngwa. DDW 2016. Abst Sa1649

NSBB and Short Term Survival

	On NSBBs	Not on NSBBs	P
Childs Pugh class			
A	3 (5%)	15 (14%)	
B	24 (37%)	50 (48%)	0.01
C	38 (58%)	39 (37%)	
Esophageal varices			
None or small	30 (46%)	71 (69%)	
Non-bleeding large	17 (26%)	22 (21%)	0.003
Prior bleeding	18 (28%)	10 (10%)	
Ascites			
None	11 (17%)	31 (30%)	
Controlled	36 (55%)	52 (50%)	0.1
Refractory	18 (28%)	21 (20%)	
Prior SBP	2 (3%)	3 (3%)	0.9

Ngwa. DDW 2016. Abst Sa1649

Transplant Free Survival



Predictors of 90-day Mortality		
	Odds Ratio (95% CI)	p
MELD	1.2 (1.1-1.4)	<0.01
MAP	0.9 (0.8 - 1)	0.006
NSBB	0.08 (0.01 - 0.5)	0.008
Male	6.4 (0.9 - 47)	0.07
CTP Score	1.04 (0.7 - 1.5)	0.8

Ngwa. DDW 2016. Abst Sa1649

Other Outcomes

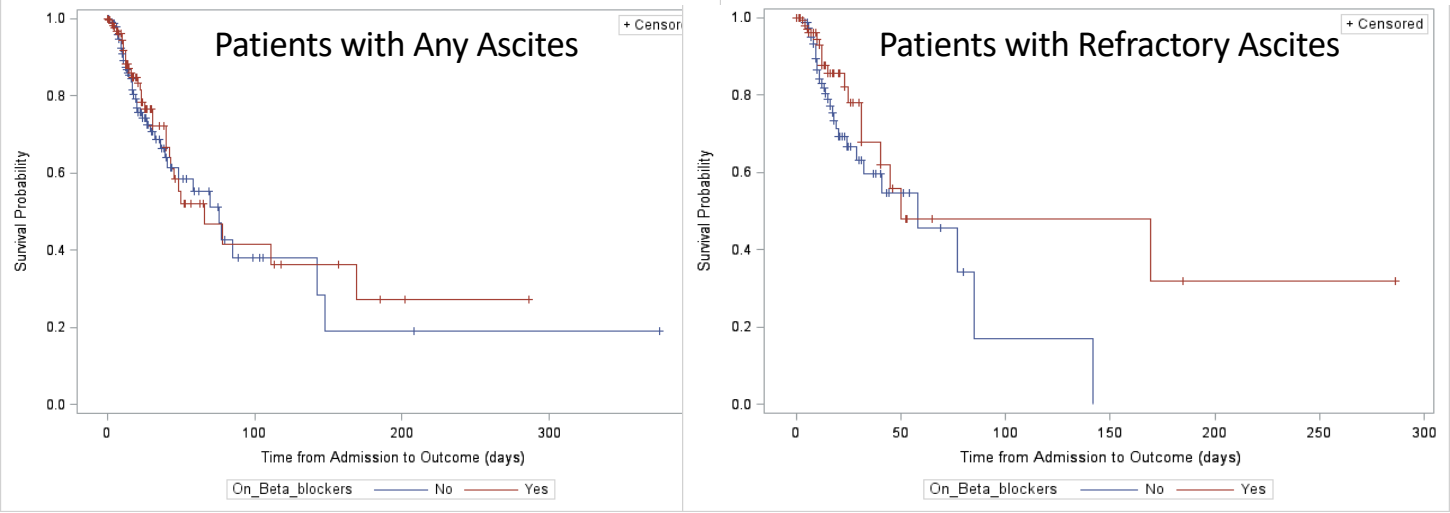
Clinical outcomes of patients taking and not taking NSBBs at liver transplant evaluation			
	On NSBBs n=65	**Not on NSBBs n=103**	**P value**
Acute kidney injury within 90 days	14 (22%)	5 (5%)	0.001
SBPwithin 90 days	4 (6%)	2 (2%)	0.14
Hospitalized within 90 days	19 (29%)	23 (22%)	0.3
Liver transplant within 90 days	1 (1%)	5 (5%)	0.3
Died within 90 days	3 (5%)	5 (15%)	0.04
Follow-up interval (days)	283 (124 – 687)	235 (100 – 488)	0.01
Total number of hospitalizations	1 (0-3)	1 (0-2)	0.7
Overall survival and transplant outcomes			
Alive	22 (34%)	33 (32%)	0.9
Underwent liver transplantation	21 (32%)	32 (31%)	
Died	22 (34%)	39 (37%)	

Ngwa. DDW 2016. Abst Sa1649

NSBB and Survival

Beta-blocker (BB) Use In Hospitalized Cirrhotic Patients With Ascites Does Not Affect Survival And Is Associated With Less Inflammation

- Sub-analysis of the NACSELD (North American Consortium for the Study of End-Stage Liver Disease) database of patients with cirrhosis hospitalized in 16 centers across the US and Canada



Bhutta. DDW 2016. Abst Sa1645

Patients with Any Ascites

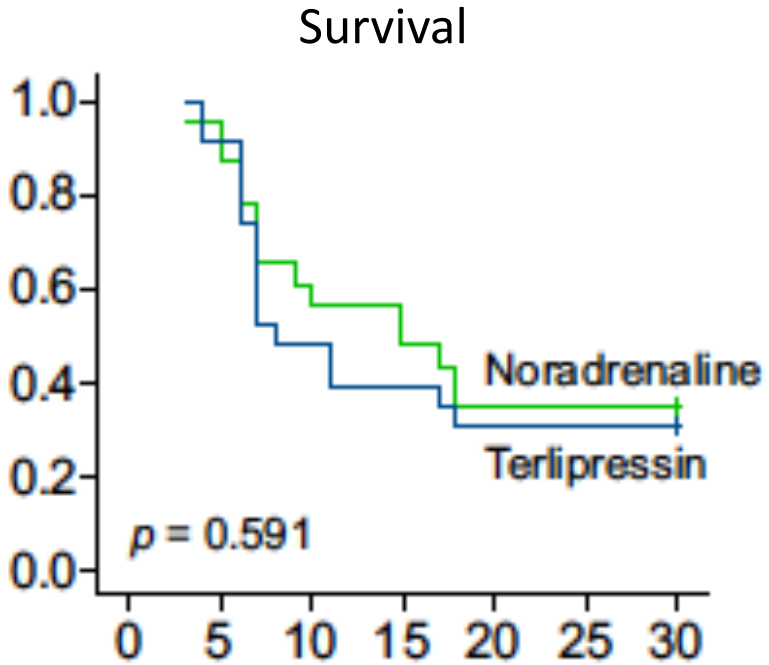
	NSBB (n=307)	No NSBB (n=411)	p
Age (years)	58 ±10	56 ±10	0.06
Gender (% male)	68%	62%	0.10
Diabetes (%)	37%	28%	0.007
History of variceal hemorrhage (%)	33%	16%	<0.001
Heart rate (bpm)	80 ± 17	90 ± 16	<0.001
WBC	7.4 ± 4.4	8.7 ± 5.8	<0.001
Platelet count (x 1,000)	104 ± 66	119 ± 76	0.004
Serum Na (mEq/L)	134 ± 6	133 ± 6	0.029
SIRS present (%)	21%	33%	<0.001
Child score	10 ±2	10 ± 2	0.66
MELD	20 ± 8	20 ± 8	0.11
Medium/large varices	42%	26%	<0.001

Bhutta. DDW 2016. Abst Sa1645

Norepinphrine versus Terlipressin for HRS-1

Randomized controlled (open label) trial

- Norepinephrine versus Terlipressin
  (Total n=46, 23 in each group)
- Both in combination with albumin, 20g/d
- Goal (Up to 15 days):
  - ⇧MAP by >10 mmHg or
  - ⇧4-h urine output by > 200 ml
- Norepinephrine: 0.5mg/h increased by 0.5mg/h every 4 hours
  Maximum: 3mg/h
- HRS reversal (primary end point):
  Norepinephrine: 43.4%
  Terlipressin: 39.1%, p = 0.76



Singh. J Hep 2012;56:1293–1298

Stanford Norepinephrine Protocol (Proposal)

Inclusion criteria

- Adult inpatients with end-stage liver disease and ascites
- Serum creatinine ≥ 1.5 mg/dL and ≥ 0.3 mg/dL above baseline
- No improvement in renal function following diuretic withdrawal and plasma volume expansion with albumin 1 g/kg for 2 days.

Exclusion criteria

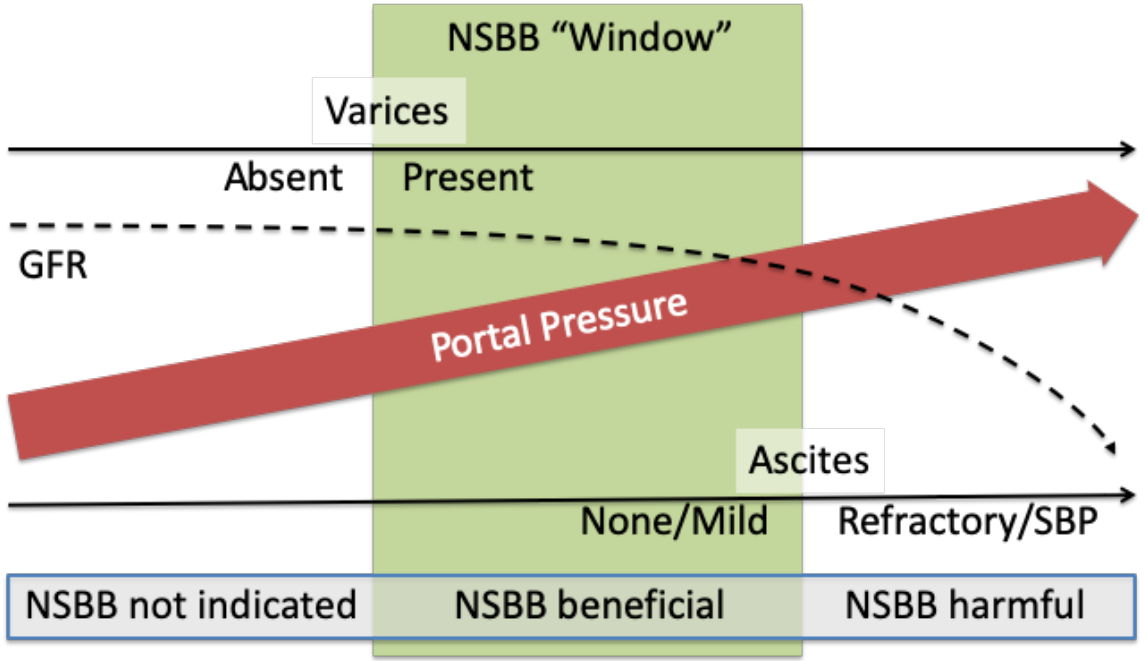
- On-going coronary artery disease, cardiomyopathy, and arrhythmia
- Proteinuria greater than 500 mg/24 hours
- Ultrasound evidence of renal parenchymal disease or obstructive uropathy
- A positive sepsis screen, i.e. 2 or more of the following: T>38 or T<36, WBC>12, HR>90, RR>20.

Stanford Norepinephrine Protocol (Proposal)

- Participants to be identified by hepatology and nephrology consultation services
- Starting dose: continuous infusion of low-dose NE (5 mcg/min)
- Dose adjustment: up by 2.5 mcg/min every 4 hours
- Maximum dose: 10 mcg/min
- Target: to increase the mean arterial pressure (MAP) by 10 mm Hg above baseline
- Monitoring
  - VS (BP, P and Temp) q2 hours until the target MAP is reached
  - Once a stable NE dose is achieved, VS monitoring q4 hours
  - Team to be notified for SBP > 140 mmHg or a change in SBP> 20 mmHg
- Daily dose of 25 grams of albumin
- Response:
  - Failure to achieve MAP target: midodrine and octreotide may be added back
  - Discontinuation:

Beta Blockers in Patients with Ascites

- Risk of NSBB in advanced cirrhosis
  - SBP: ↑AKI/HRS, ↓LT-free survival
  - Refractory ascites: ↓Survival
- Reduce or discontinue NSBB in patients with refractory ascites or SBP, especially if hypotension or renal impairment



Use of Non-selective β-Blockade (NSBB) in ESLD

- Effect of NSBB on portal hypertension (pHTN)
  - Single center study, 294 patients with cirrhosis
  - Propranolol i.v. 0.15 mg/Kg

	Mild pHTN (n=81)	Significant pHTN (n=194)
Baseline	HVPG 6-10 mmHg	HVPG >10 mmHg Small varices (n=114) No varices (n=80)
Liver stiffness MELD Splenomegaly Systemic vascular resistance Cardiac index	19 kPa 5.6 40% 1469 dyne.s.cm 2.8	30kPa 6.5 63% 1336 dyne.s.cm 3.3
HVPG response to propranolol		
Pre-Post change	7.3 – 6.6 mmHg (-8%)	14.7 - 12.2 mmHg (-16%)
>20% reduction	12%	40%

Villanueva. AASLD 2014 Abstract 2036

Benefits of β-blockade in Cirrhosis

Non-selective β-blocker (NSBB) is beneficial in patients with cirrhosis and esophageal varices.

- Reduced incidence of variceal hemorrhage
- Reduced incidence of ascites
- Improved survival

Current AASLD Guideline (2007) recommends NSBB for:

- Primary prophylaxis in patients with low risk bleeding (Child A, no red signs) and medium/large varices
- Primary prophylaxis in patients at high risk of bleeding (e.g., Child B/C) regardless of the variceal size
- Secondary prophylaxis (in conjunction with variceal ligation)

Am J Gastroenterol 2012; 107:418–427

Potential Harm of NSBB

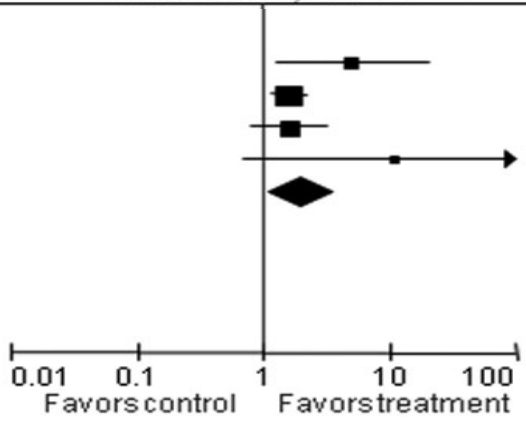
- NSBBs are associated with paracentesis-induced circulatory dysfunction in patients with cirrhosis and refractory ascites.
- NSBBs are associated with poor survival in patients with refractory ascites.
- Among patients with cirrhosis and SBP, NSBBs increase risk for hepatorenal syndrome and acute kidney injury and reduce transplant-free survival.

J Hepatol 2011;55:794-9; HEPATOLOGY 2010;52:1017-1022; Gastroenterology 2014;146:1680–1690

Vasoconstrictor Therapy for HRS-1

- Terlipressin therapy is associated with improved renal function, reversal of HRS and longer survival.

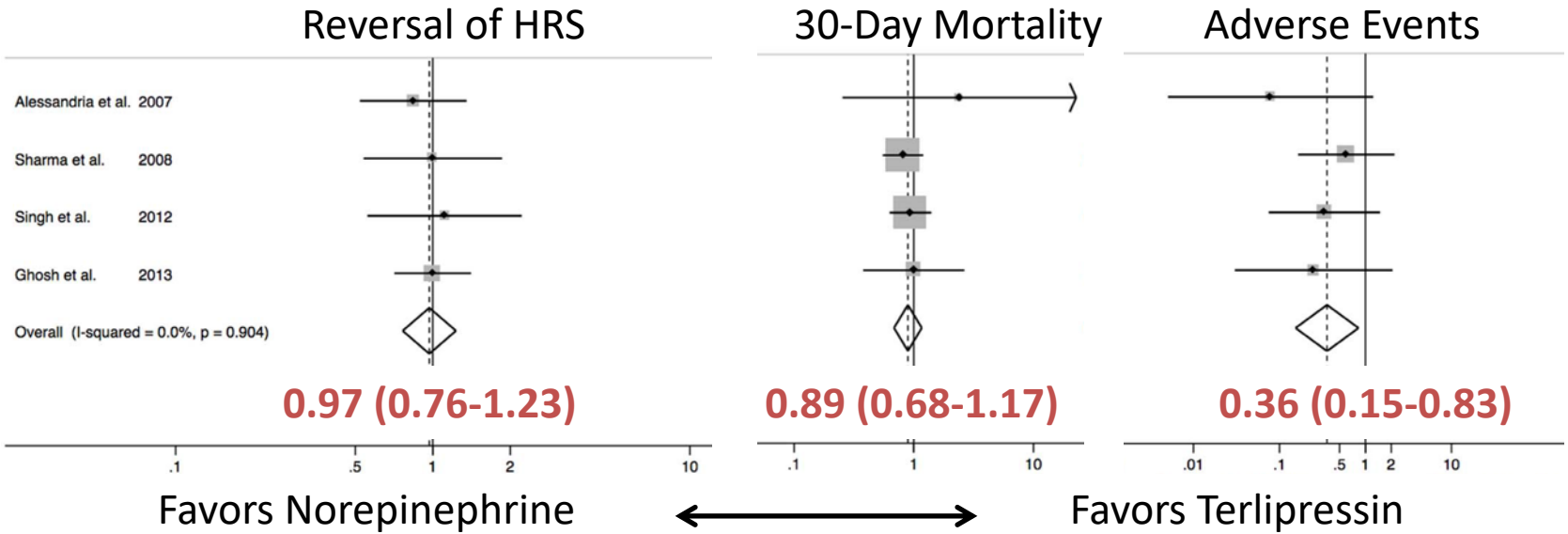
Trial	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Relative Risk, 95% CI
Improved renal function						
Martín-Llahí 2008	10	23	2	23	17.6%	5.00 [1.23, 20.35]
Neri 2008	25	26	16	26	43.1%	1.56 [1.14, 2.14]
Sanyal 2008	16	56	10	56	33.1%	1.60 [0.80, 3.22]
Solanki 2003	5	12	0	12	6.2%	11.00 [0.67, 179.29]
Total (95% CI)		**117**		**117**	**100.0%**	**2.00 [1.11, 3.62]**
Total events	56		28			
Heterogeneity I^2= 47%						



- Smaller studies support the use of midodrine+octerotide +albumin:
  - Octreotide target dose of 200ug sc tid
  - Midodrine titrated up to max of 12.5mg po tid (goal increase in MAP by 15 mmHg)

Gluud. Hepatology 2010;576

- Meta-analysis of Norepinephrine versus Terlipressin (n=4 studies)



Norepinephrine	Terlipressin
Chest pain (n=3); ST segment depression (n=1); Extrasystoles (n=2)	Abdominal cramps and diarrhea (n=17); Cyanosis (n=2); Extrasystoles (n=2); ST segment depression (n=1)

Nassar. PLOS One 2014:9;e107466

AASLD Guidance: Prophylaxis of Variceal Hemorrhage

- Primary prophylaxis
  - NSBBs (propranolol, nadolol), carvedilol, or endoscopic ligation (EVL)
  - Once on a NSBB or carvedilol, no need for serial EGD
- Secondary prophylaxis
  - Combination of NSBB and EVL
  - TIPS: No need for NSBB or EVL

Garcia-Tsao. Hepatology 2017;65:310