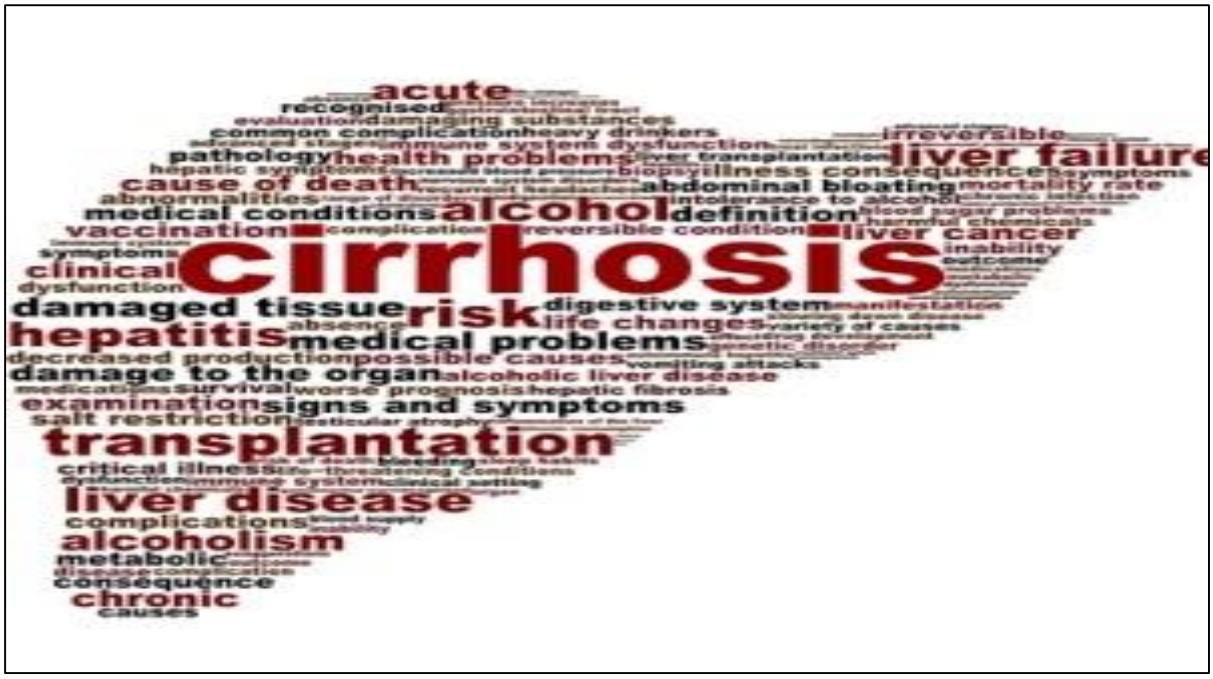
Non-selective Beta-blockers in Patients with Ascites: Friend or Foe?



http://www.health24.com/Medical/Liver-Health/Cirrhosis-of-the-liver/Cirrhosis-of-the-liver-20120721

Jenna Snoga, Pharm.D.
PGY-1 Pharmacotherapy Resident
University of the Incarnate Word Feik School of Pharmacy
San Antonio, TX
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Learning Objectives:

1. Identify the benefits of non-selective beta-blockers in patients with cirrhosis.
2. Describe the mechanism of non-selective beta-blockers and how they affect the circulatory function of a cirrhotic patient.
3. Evaluate current literature for non-selective beta-blocker use in patients with ascites.
4. Determine when non-selective beta-blockers can be safely used in patients with ascites.

- Definition[1]
  - Histological development of regenerative nodules surrounded by fibrous bands in response to chronic liver injury
  - End stage of any chronic liver disease

- Etiologies of Cirrhosis[1,2]
  - Alcoholism
  - Chronic hepatitis B virus (HBV)
  - Hepatitis C virus (HCV)
  - Non-alcoholic steatohepatitis (NASH)
  - Non-alcoholic fatty liver disease (NAFLD)

- Natural History of Chronic Liver Disease[2,3]

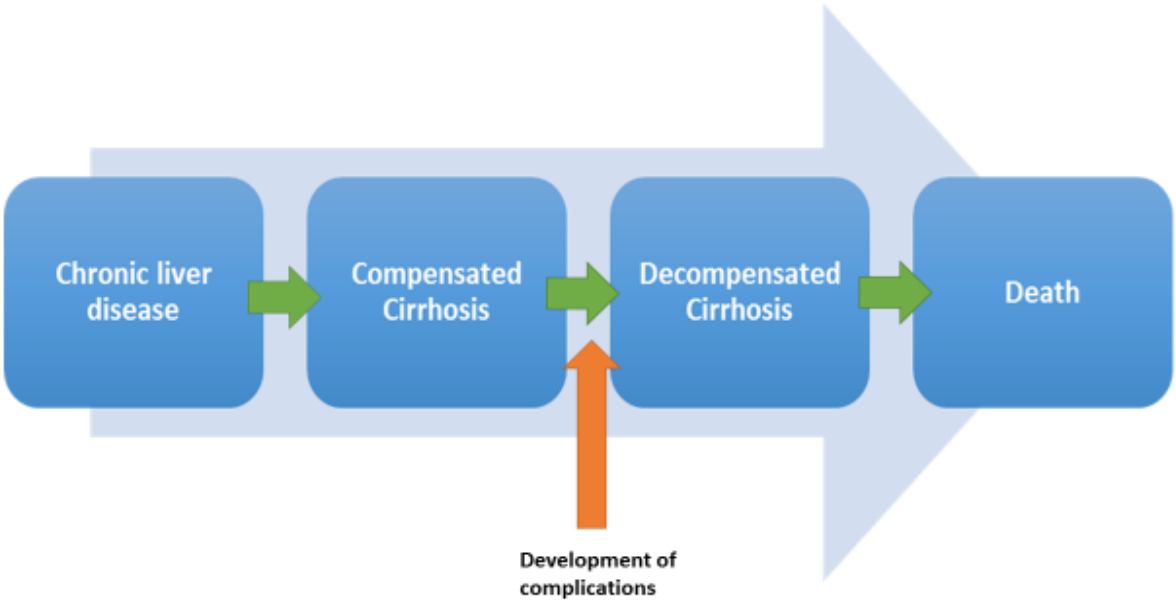


Figure 1: The natural history of cirrhosis

- Complications of Cirrhosis[2]
  - Variceal hemorrhage
  - Ascites
  - Spontaneous bacterial peritonitis
  - Hepatorenal syndrome
  - Encephalopathy
  - Jaundice
  - Coagulopathies
  - Hepatocellular carcinoma

- Portal Hypertension Pathophysiology

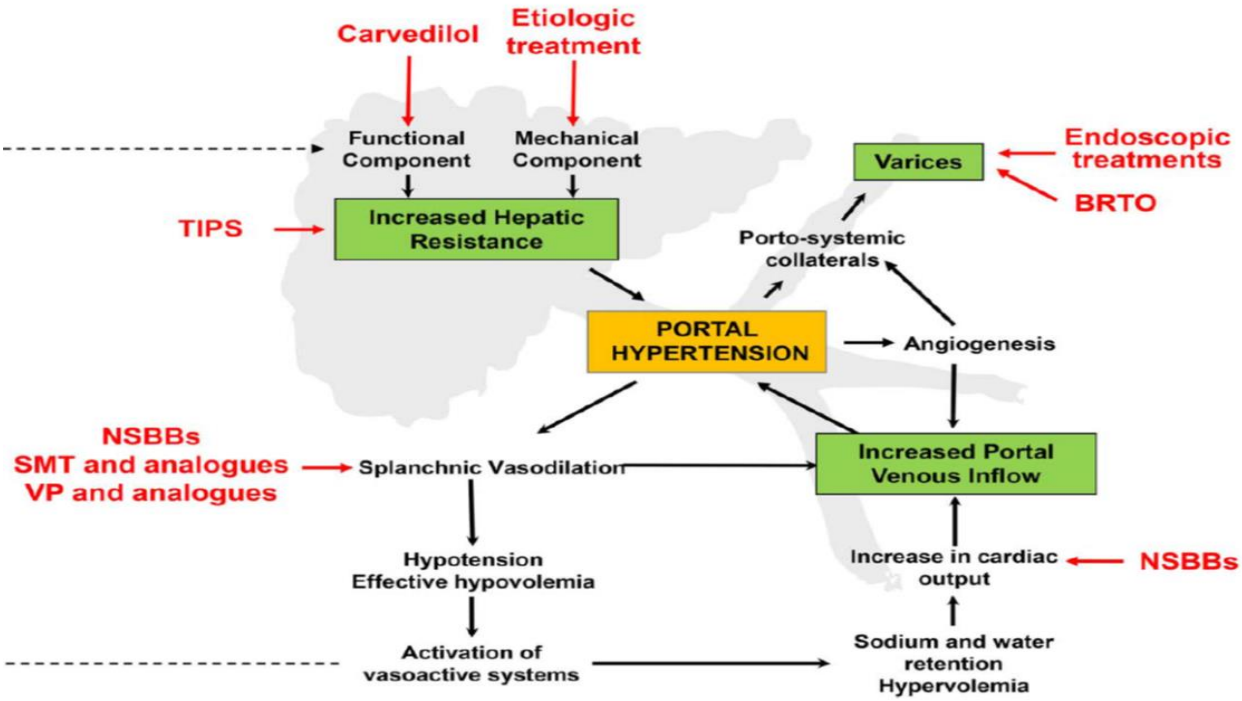


Figure 2: Pathogenesis of Portal Hypertension[3]

- Portal Hypertension Severity

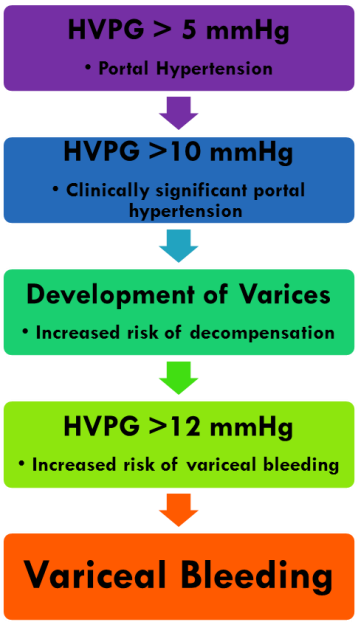


Figure 3: Portal Hypertension and varices at various degrees of severity[2,3]

- Guideline Recommendations for Non-selective Beta-blockers (NSBBs)

Table 1: Prevention and Management of Gastroesophageal Varices in Cirrhosis				
Treatment	**AASLD Guidelines[3,4]**		**Baveno VI Consensus Guidelines[5]**	
Primary Prevention	No varices	NSBB not recommended	No varices	NSBB not recommended
	Small varices	NSBB optional, but further studies are needed to confirm benefit	Small varices	NSBB optional, but further studies are needed to confirm benefit
	Small varices with increased risk of bleeding (red wale marks or Child-Pugh B/C)	NSBB recommended	Small varices with an increased risk of bleeding (red wale marks or Child-Pugh C)	NSBB recommended
	Medium-large varices	NSBB or EVL	Medium-large varices	NSBB or EVL
Secondary Prevention	Combination of NSBB plus EVL		NSBB (propranolol or nadolol) plus EVL	
American Association for the Study of Liver Diseases (AASLD), Endoscopic variceal ligation (EVL), non-selective beta-blocker (NSBB)				

- NSBBs for the Prevention and Management of Gastroesophageal Varices in Cirrhosis

Table 2: Types of Non-selective Beta-blockers in Portal Hypertension[3,4,5]			
	Propranolol	**Nadolol**	**Carvedilol**
Primary prevention	Yes	Yes	Yes
Secondary prevention	Yes	Yes	No
Proposed mechanism of action	β-1 activity: reduce cardiac output β-2 activity: produces splanchnic vasoconstriction which reduces portal blood flow		β-1 activity: reduce cardiac output β-2 activity: produces splanchnic vasoconstriction which reduces portal blood flow α-1 adrenergic activity
Adverse reactions	Bradycardia, hypotension, dizziness, fatigue		
Initial Dose (PO)	20 mg BID	20 mg daily	6.25 mg daily
Max Dose (PO)	160 mg BID	160 mg daily	12.5 mg daily

- Duration of NSBB Therapy
  - Therapy should be continued indefinitely[3,4]

- Clinical Questions
    - What role do NSBBs play on mortality in patients with refractory ascites?
    - What adverse effects of NSBBs may occur in patients with refractory ascites?
    - Should patients with refractory ascites continue NSBB therapy?

- Literature Characteristics
    - Current evidence evaluating the effects of NSBB therapy in patients with refractory ascites is conflicting
    - Current evidence is limited to observational studies rather than randomized controlled trials

- The Window Hypothesis

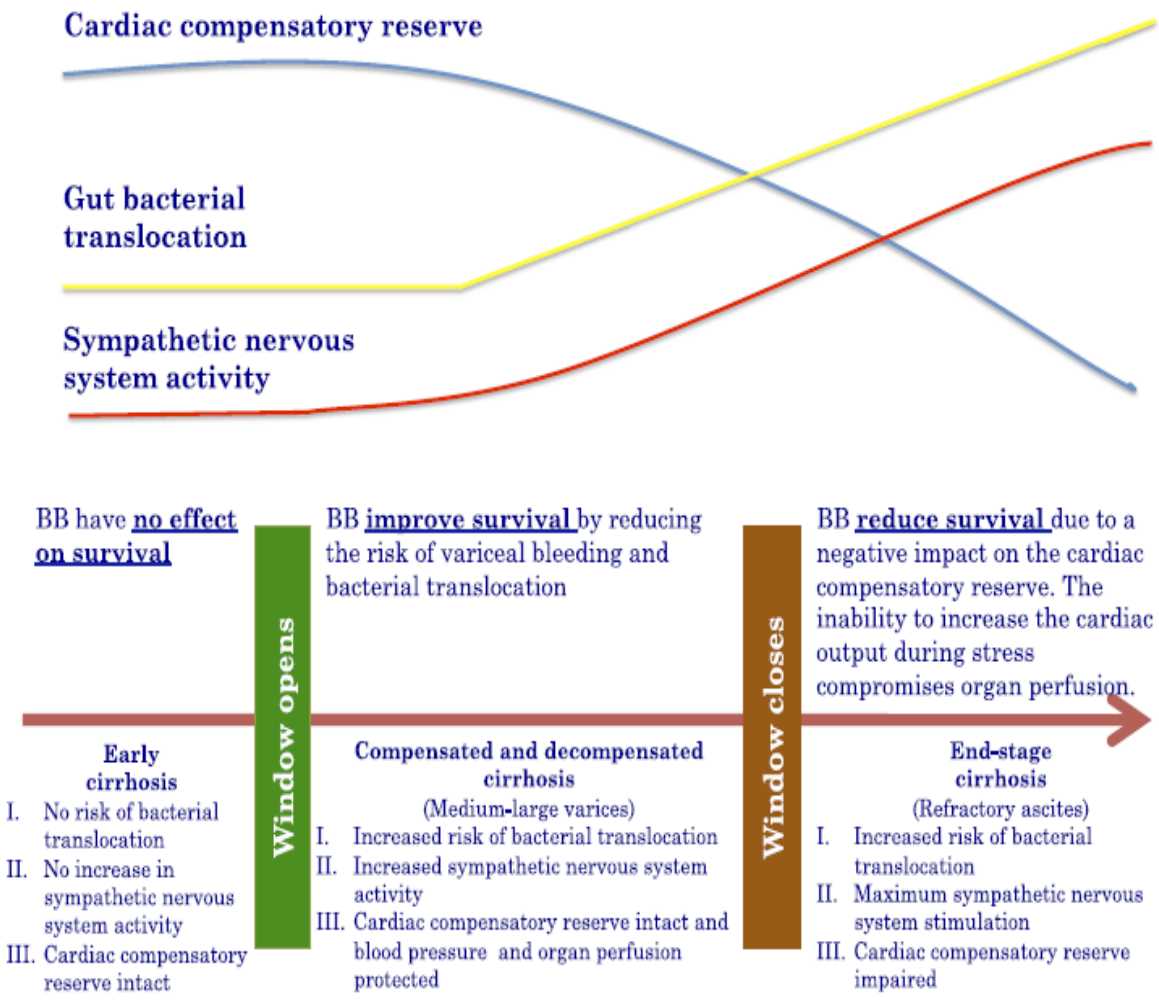


Figure 4: Window Hypothesis for NSBB therapy in cirrhosis[6]

- Previous Studies Evaluating Blood Pressure and Survival

Table 3: Studies evaluating survival and hemodynamics in cirrhosis		
Study	**Objectives**	**Results**
LLach, et al (1988)[8]	• Identify prognostic factors in cirrhotic patients	• MAP is an independent predictor of survival • MAP of ≤ 82 mmHg- Survival rate at 24 months was approximately 20% and at 48 months was 0% • MAP > 82 mmHg- Survival rate at 24 months was approximately 70% and at 48 months was 50%
Krag, et al (2010)[7]	• Investigate the relationship between cardiac and renal function in patients with cirrhosis and ascites • Investigate the impact of cardiac systolic function on survival	• Patients with a CI < 1.5 L/min/m^2 had poorer survival at 3, 9, and 12 months vs. those with a CI > 1.5 L/min/m^2, p <0.05 • Patients with a MAP < 80 mmHg had lower survival at 12 months versus those with a MAP > 80 mmHg • Rate of HRS within 3 months was higher in the group with the low CI vs. high CI (43% vs 5%, p=0.04)
Cardiac Index (CI), mean arterial pressure (MAP), hepatorenal syndrome (HRS)		

Literature Review

Table 4: 2010 Sersté T et al.[9] Deleterious effects of beta-blockers on survival in patients with cirrhosis and refractory ascites. Hepatology. 2010;52(3):1017-22.	
Objectives	Evaluate the effect of NSBB therapy on long-term survival in patients with cirrhosis and refractory ascites Assess predictive factors of mortality
Methods	
Study Design	Single-center, observational, case-only, prospective January 2004 to December 2008
Patient Selection	Inclusion Criteria: • Cirrhosis • Greater than 18 years old • Refractory ascites ○ Criteria based on International Ascites Club criteria: diuretic-resistant[a] or diuretic-intractable[b] Exclusion Criteria: Not meeting inclusion criteria above

Treatment	Time of entry was date on which the criteria for refractory ascites was first fulfilled • Beta-blocker group: propranolol 40 mg to 160 mg as a total daily dose • No Beta-blocker group
Outcomes	Analysis of patients who received NSBB versus no therapy • Renal dysfunctional development, liver transplantation, and death • Predictive factors of mortality

Statistical Analysis	• Kaplan-Meier nonparametric survivorship function: to assess survival
	  ○ Group comparisons were made with the log rank test
	• Continuous data that were not normally distributed reported as median and ranges
	  ○ Shapiro-Wilk test: distribution of variables
	  ○ Wilcoxon-Mann-Whitney test: group comparisons
	• Categorical data reported as counts or percentages
	  ○ χ^2 test or Fischer's exact test: group comparisons
	• Univariate and multivariate Cox regression analyses: detect independent predictors of survival
	• P value <0.05 considered statistically significant

Results

Baseline Characteristics

	NSBB (N=77)	No NSBB (N=74)	P Value
Gender	62 (80.5)	60 (81.1)	0.93
Age	60.9 ± 12.2	59.8 ± 11.4	0.56
Heart rate, bpm	65 (54-79)	77 (63-89)	<0.0001
Systolic BP, mm Hg	103 (91-119)	123 (11-139)	<0.0001
Diastolic BP, mm Hg	73 (55-89)	73 (64-89)	0.95
Child-Pugh Score B	20 (26.0)	29 (39.2)	0.083
Child-Pugh Score C	57 (74)	45 (60.8)	0.083
Creatinine, mg/dL	0.89 (0.42-2.56)	0.86 (0.45-3.40)	0.83
Serum sodium, mmol/L	125 (112-145)	133 (118-140)	0.09
Serum albumin, g/L	26 (4-47)	29 (20-42)	0.12
Total bilirubin, mg/dL	56 (17-125)	48 (11-340)	0.01
MELD	18.8	18.9	0.89
MELD-Na	22 (14-30)	22 (11-31)	0.69
Platelets, $x10^{-3}/mm^3$	78 (27-270)	74 (29-359)	0.92
AST, U/L	58 (22-142)	54 (21-360)	0.16
ALT, U/L	49 (11-156)	45 (12-183)	0.68
INR	1.8 (1-2.5)	1.8 (1-2.5)	0.15
Renal dysfunction	21 (27.3)	30 (41)	0.07
Presence of HE	33 (42.8)	24 (32.4)	0.38
Presence of HCC	24 (31.2)	17 (23)	0.26
Presence of varices	77 (100)	3 (4.1)	<0.001

Study Outcomes	<u>Patient characteristics</u>
	• 104 (68.9%) diuretic-intractable ascites, 47 (31.1%) diuretic-resistant ascites
	• 77 (51%) were treated with propranolol
	  ○ 40 mg per day: 11.7%
	  ○ 80 mg per day: 40.3%
	  ○ 120 mg per day: 1.3%
	  ○ 160 mg per day: 46.7%
	
	<u>Outcome and follow-up of the whole group of patients</u>
	• Median time to follow-up: 8 months (1-47 months)
	• Median survival time: 10 months
	• Probability of survival: 41% at 1 year and 28% at 2 years
	• 97 (64.2%) patients died
	  ○ Sepsis: 50 patients (SBP in 11 cases)
	  ○ Progression to hepatocellular carcinoma: 13 patients
	  ○ Unknown cause: 25 patients
	
	<u>Outcome according to NSBB therapy: NSBB vs. no NSBB therapy</u>
	• Median survival time: 5 months vs. 20 months (p< 0.0001)
	• 1 year probability of survival: 19% vs. 64%
	• 2 year probability of survival: 9% vs. 45%
	
	<u>Factors Associated with Mortality</u>
	• Child-Pugh class C: 1.76 (HR 1.09-2.8)
	• Hepatocellular Carcinoma: 1.94 (HR 1.25-3.02)
	• Treatment with NSBB: 2.61 (HR 1.63-4.19)
	• Etiology of refractory ascites
	  ○ Renal impairment: 3.27 (HR 1.73-6.17)
	  ○ Hyponatremia: 7.07 (HR 3.77-13.25)

Conclusion and Evaluation	
Author's conclusions	Use of NSBBs in patients with cirrhosis and refractory ascites was associated with a significantly higher mortality rate
Strengths	• Standardized definition for refractory ascites: defined by the International Ascites Club criteria • Reasonable sample size for study design • Propranolol dose described • Reported presence of esophageal varices
Weaknesses	• Observational data (lack of randomization), single-center • Baseline characteristic not similar between the two groups (Child-Pugh class C, history of varices, total bilirubin, serum sodium, HR, and BP) • Adherence and side effects not discussed • Propranolol dose titrations not described • Cause of death reports were vague • No information provided regarding alcohol use or antibiotic prophylaxis • Outcome measures not clearly stated • Liver transplantation may have affected study outcomes

Take Away Summary	In patients with cirrhosis and refractory ascites, the use of NSBBs may increase mortality. However, the NSBB users may have had a poorer condition at baseline compared to the nonusers. It is also important to point out that 46.7% of patients received 160 mg of propranolol per day, which may have altered the study outcomes.
Footnotes	a. Diuretic-resistant: ascites could not be stabilized despite intensive diuretic therapy (e.g. 400 mg of spironolactone with 160 mg of furosemide per day) associated with dietary sodium restriction (90 mmol of sodium per day) b. Diuretic-intractable: metabolic disturbances made it impossible to administered or increase diuretic therapy 1. Diuretic induced hepatic encephalopathy 2. Hyponatremia (serum sodium level ≤125 mmol/L) 3. Renal impairment (serum creatinine level ≥1.5 mg/dL) 4. Abnormal potassium levels (serum potassium ≤3 or ≥6 mmol/L)

Table 5: Bossen, et al.[10] Nonselective β-blockers do not affect mortality in cirrhosis patients with ascites: Post Hoc analysis of three randomized controlled trials with 1198 patients. Hepatology. 2016;63(6):1968-76.	
Objective	Investigate whether NSBB therapy is associated with increased mortality in patients with cirrhosis and ascites (including subgroups of decompensated cirrhosis (eg, patients with refractory ascites))
Methods	
Study Design	Post Hoc analysis: data from three multicenter, randomized, controlled trials conducted to examine the efficacy of satavaptan in treating ascites in cirrhosis July 2006 and December 2008
Patient Selection	Inclusion Criteria • Diuretic manageable ascites[a] • Ascites managed with diuretics and occasional therapeutic paracentesis[b] • Diuretic resistant ascites managed primarily with therapeutic paracentesis[b] Exclusion Criteria • SBP or variceal bleed within 10 days before randomization • Functional transjugular intrahepatic portosystemic shunt • Lab abnormalities: serum creatinine >150 µmol/L, serum potassium >5.0 mmol/L, serum sodium >143 mmol/ L, serum bilirubin >150 µmol/L, international normalized ratio >3.0, platelets <30,000/mm^3, neutrophils <1000/mm^3 • Systolic arterial pressure <80 mm Hg or symptomatic orthostatic hypotension • Hepatocellular carcinoma exceeding the Milan criteria • Use of a potent modifier of the cytochrome P450 3A pathway
Treatment	• NSBB therapy (propranolol or carvedilol) vs. no NSBB therapy
Outcomes	Analysis of patients who received NSBB therapy vs. no NSBB therapy • All-cause mortality • Cirrhosis-related mortality • Cause of death (cirrhosis-related or other known causes) • Combined endpoint of hospitalization or death • Clinical events predicting that a patient would stop the NSBB • Discontinuation of NSBB therapy

Statistical Analysis

- Kaplan-Meier estimates: cumulative mortality
- Cox proportional hazards regression: estimate the effect of NSBB use on mortality
- Adjusted for confounding by patient gender, age, cirrhosis etiology, MELD score, Child-Pugh score, serum sodium, history of variceal bleeding (yes or no), and severity of ascites

Results

Baseline Characteristics

- N= 1188
- 588 patients with refractory ascites and 600 with diuretic-responsive ascites

	NSBB (N=559)	No NSBB (N=629)
Gender, Men	394 (70%)	432 (69%)
Age	57 (51-64)	57 (50-64)
Child-Pugh Score A/B/C	8%/68%/24%	8%/64%/28%
Child-Pugh Score (mean)	8.45	8.57
MELD (median)	12 (8-15)	11 (8-15)
MELD score >18	64 (11%)	69 (11%)
Serum sodium mmol/L (mean)	137	136
Serum sodium < 135 mmol/L	156 (28%)	220 (35%)
Serum Albumin, g/dL	3.3	3.4
Total bilirubin, mg/dL	1.46	1.40
Platelets	115 (79-167)	130 (89-187)
INR	1.4 (1.2-1.6)	1.3 (1.2-1.5)
Previous/current variceal bleed	168 (30%)	82 (13%)
Previous/current SBP	89 (16%)	87 (14%)
HCC	19 (3%)	24 (4%)
Refractory ascites	258 (46%)	330 (52%)
MAP mm Hg (median)	83 (73-90)	85 (76-93)
MAP <71 mm Hg	70 (13%)	63 (10%)
MAP 71-80 mm Hg	189 (34%)	171 (27%)
MAP 81-90 mm Hg	169 (30%)	197 (31%)

Study Outcomes

- 286 patients died during follow up
- Median follow-up survival: 52.5 weeks

<u>NSBB vs. no NSBB therapy:</u>

- 52-week cumulative mortality: 23.2% vs. 25.3%, adjusted HR 0.92 (0.72-1.18)
- Hospitalization or death (1-year cumulative risk): 57.1% vs. 63.9%, adjusted HR 0.83 (0.71-0.97)
- Cirrhosis-related mortality: adjusted HR 1.00 (0.76-1.31)

<u>NSBB vs. no NSBB therapy in patients with ascites:</u>

- 52-week cumulative mortality in refractory ascites: 30.5% vs. 30.9%, adjusted HR 1.02 (0.74-1.39)
- 52-week cumulative mortality in diuretic responsive ascites: 17% vs. 19.5%, adjusted HR 0.78 (0.53-1.16)
- Cirrhosis-related mortality in refractory ascites: HR 1.20 (0.84-1.72)
- Cirrhosis-related mortality in diuretic responsive ascites: HR 0.75 (0.48-1.15)

	<u>Causes of death:</u> • Cirrhosis-related causes: 226 (79%) • Other known causes: 33 (12%) • Unknown causes: 27 (9%) <u>Discontinuation of NSBB:</u> • Total discontinuation: 29% during the follow-up period • Discontinuation before first hospitalization: 13% • Discontinuation of NSBBs was associated with a sharp rise in mortality hazard: adjusted HR 5.13 (2.28-11.55) • Predictors of NSBB discontinuation: admission to the hospital, variceal bleeding, bacterial infection, hepatorenal syndrome, high Child-Pugh score, and refractory ascites
Conclusion and Evaluation	
Author's Conclusions	NSBBs did not increase all-cause or cirrhosis-related mortality in the overall cohort of cirrhotic patients with ascites or in the subgroup of patients with refractory ascites. NSBBs were frequently discontinued and the impact of discontinuation cannot be determined. These findings suggest that clinicians can continue to use NSBBs.
Strengths	• Large sample size based on prospective study design • Data prospectively collected in the context of randomized controlled trials

Weaknesses	• Baseline characteristic not similar between the two groups in regards to potential predictors of cirrhosis mortality
	  ○ History of variceal bleeding and lower MAP more common in NSBB group
	  ○ Did not list p values
	• Lack of standardized definition for refractory ascites classification
	• Lack of information on diuretics or antibiotics used
	• NSBB dose and dose titrations were not described
	• Adherence not addressed
	• High NSBB discontinuation rate could potentially alter outcomes
	• Confounders: no mention of EVL or presence of varices
	• Outcome measures not specifically stated
	• Clarity of study design

Take Away Summary	In cirrhotic patients with ascites, NSBB therapy did not increase mortality and may be considered safe. However, the results of this study should be interpreted with caution since the study did not report the dose of NSBB used. It is also important to note that there was a high NSBB discontinuation rate which could have altered study outcomes.
Footnotes	a. Diuretic-manageable ascites: permitted one or two paracenteses within 6 months before inclusion as long as the interval between them exceeded three months. b. Classification into refractory or diuretic-responsive ascites was done by the managing clinician at each participating center.

Table 6: Leithead, et al.[11] **Non-selective β-blockers are associated with improved survival in patients with ascites listed for liver transplantation. Gut. 2015;64(7):1111-9.**	
Objective	Determine whether NSBB use is a risk factor for mortality in patients with ascites awaiting liver transplantation
Methods	
Study Design	Single-center, retrospective study January 2007 and June 2011
Patient Selection	Inclusion Criteria: • Cirrhosis and ascites listed for their first elective liver transplantation Exclusion Criteria: • Acute liver failure • Listed for combined liver-kidney transplantation or retransplantation • Transjugular porto-systemic shunt *in situ* • Prescribed a selective beta-blocker
Treatment	• NSBB (propranolol or carvedilol) vs. no NSBB
Outcomes	Analysis of NSBB therapy vs. no NSBB therapy • Mortality • Transplantation rate • Median time to death • Median time to transplantation
Statistical Analysis	• Student t test: normally distributed continuous variables • Mann-Whitney test: non-parametric continuous variables • Fisher's exact test and χ^2 analysis: categorical data • Cox proportional hazards analysis: survival modeling • Utilized competing risk Cox regression analysis • Utilized propensity risk scores to control for selection bias

Results

Baseline Characteristics

Prematch

	NSBB (N=159)	No NSBB (N=163)	P Value
Age	55	53.2	0.107
Gender, Male	97 (61%)	112 (68.7%)	0.147
Etiology- Alcohol	60 (37.7%)	62 (38%)	0.956
Etiology- Hepatitis C	30 (18.9%)	33 (20.2%)	0.755
Etiology- NAFLD	22 (13.8)	20 (12.3%)	0.676
HCC	15 (9.4%)	23 (14.1%)	0.193
Bilirubin, mg/dL	2.98	3.22	0.164
Albumin, g/dL	3.10	3.10	0.803
INR	1.4	1.4	0.453
Creatinine, mg/dL	1.01	1.0	0.681
GFR (mL/min/1.73m^2)	75	78	0.266
Sodium, mmol/L	136	134	0.016
MELD score	16	17	0.168
Refractory ascites	56 (35.2%)	61 (37.4%)	0.681
Previous Variceal Bleed	64 (40.3%)	40 (24.5%)	0.003
Hepatorenal syndrome (type 2)	7 (4.4%)	8 (4.9%)	0.830

Propensity Risk Score Matched

	NSBB (N=104)	No NSBB (N=104)	P Value
Age	54.7	53.4	0.375
Gender, Male	74 (71.2%)	70 (67.3%)	0.659
Etiology- Alcohol	42 (40.4%)	41 (39.4%)	1.00
Etiology- Hepatitis C	24 (23.1%)	21 (20.2%)	0.743
Etiology- NAFLD	10 (9.6)	13 (12.5%)	0.664
HCC	11 (10.6%)	12 (11.5%)	1.00
Bilirubin, mg/dL	3.10	3.16	0.722
Albumin, g/dL	3.00	3.10	0138
INR	1.5	1.4	0.397
Creatinine, mg/dL	1.03	1.03	0.902
GFR (mL/min/1.73m^2)	74	76	0.930
Sodium, mmol/L	135	135	0.814
MELD score	17	17	0.810
Refractory ascites	39 (37.5%)	37 (35.6%)	0.885
Previous Variceal Bleed	29 (27.9%)	29 (27.9%)	1.00
Hepatorenal syndrome (type 2)	5 (4.8%)	6 (5.89%)	1.00

Study Outcomes

Overall cohort:

- Death: 82 patients (25.5%)
- Transplantation: 221 patients (68.6%)
- Causes of death: liver failure (46), sepsis (14), multiorgan failure cause unspecified (7), cardiac (4), tumor (2), gastrointestinal hemorrhage (1)
- Median propranolol dose: 80 mg per day (10-240 mg)
- Median carvedilol dose: 6.25 mg per day (3.125-12.5 mg)

NSBB and no NSBB therapy:

- Blood pressure data available for 81 patients (25%)
  - Baseline SBP: 115 mmHg vs. 122 mmHg
  - Baseline DBP: 71 mmHg vs. 73 mmHg
- Death: 22.0% vs. 28.8%
- Transplantation: 73.6% vs. 63.8%
- Median time to death: 150 days vs. 54 days
- Median time to transplantation: 76 days vs. 44 days

Predictors of death after listing for liver transplantation in ascites:

- MELD score, hyponatremia, HCC, previous variceal hemorrhage, prophylactic antibiotics, and NSBB use were associated with death on univariate analysis

Multivariate Cox regression analysis of variables associated with death after listing for liver transplantation in all patients with ascites

	Cox regression analysis		**Competing risk Cox regression analysis**			
	Outcome Death (censored at transplant)		**Outcome Death**		**Outcome Transplant**	
	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value
NSBB	0.53 (0.34-0.84)	0.007	0.70 (0.45-1.10)	0.119	1.21 (0.92-1.59)	0.172

Multivariate Cox regression analysis of variables associated with death after listing for liver transplantation in PRS-matched patients with ascites

	Cox regression analysis		**Competing risk Cox regression analysis**			
	Outcome Death (censored at transplant)		**Outcome Death**		**Outcome Transplant**	
	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value
NSBB	0.47 (0.26-0.83)	0.009	0.55 (0.32-0.95)	0.032	1.42 (1.01-1.99)	0.041

Predictors of death after listing for transplantation in refractory ascites (NSBB vs. no NSBB):

- Patients with refractory ascites (N= 117)
- Death: 23.2% vs. 34.8%
- Transplantation: 73.2% vs. 59.0%
- Median time till death: 159 days vs. 52 days
- Median time till transplantation: 67 days vs. 46 days

Multivariate Cox regression analysis of variables associated with death after listing for liver transplantation in all patients with refractory ascites

	Cox regression analysis		Competing risk Cox regression analysis	
	Outcome Death (censored at transplant)		Outcome Death	
	HR (95% CI)	P Value	HR (95% CI)	P Value
NSBB	0.46 (0.32-0.98)	0.045	0.49 (0.25-0.96)	0.038

Multivariate Cox regression analysis of variables associated with death after listing for liver transplantation in PRS-matched patients with refractory ascites

	Cox regression analysis		Competing risk Cox regression analysis	
	Outcome Death (censored at transplant)		Outcome Death	
	HR (95% CI)	P Value	HR (95% CI)	P Value
NSBB	0.33 (0.12-0.89)	0.028	0.35 (0.14-0.86)	0.022

Conclusion and Evaluation

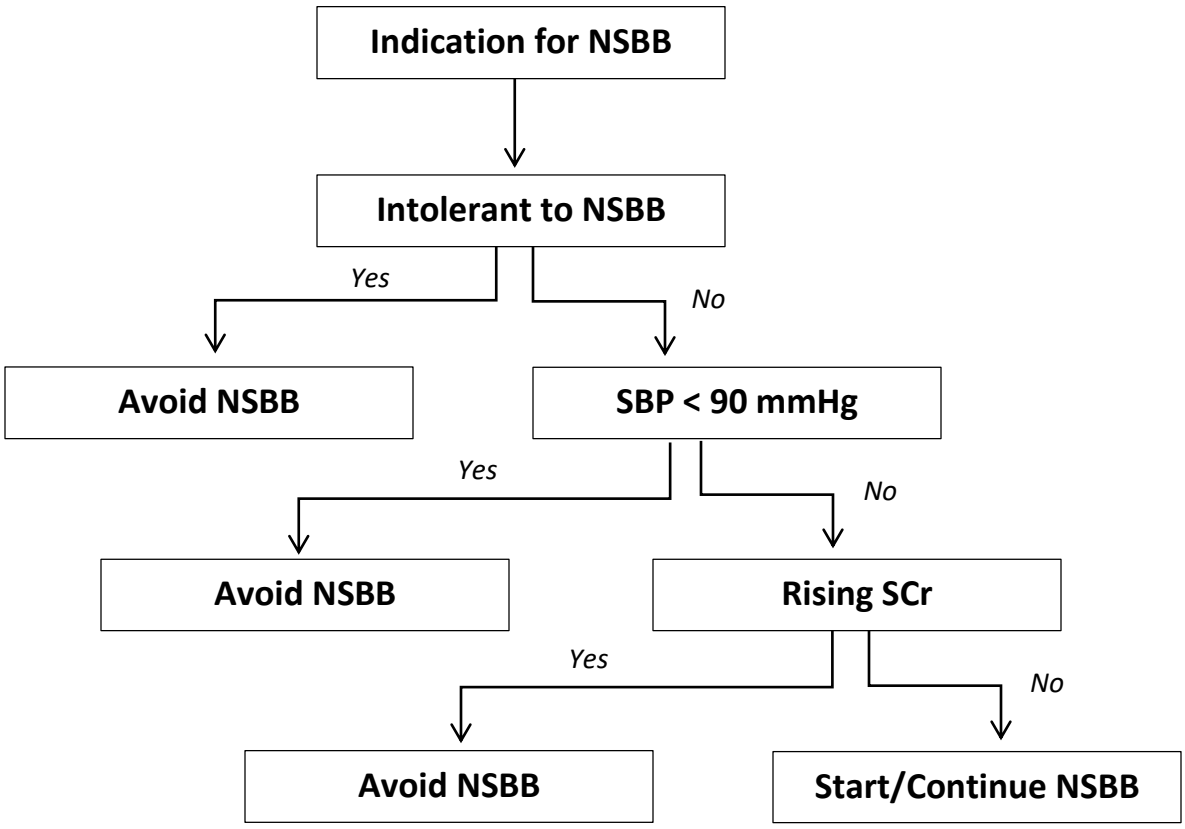
Author's conclusions	NSBB therapy in cirrhotic patients with ascites and refractory ascites listed for liver transplantation is not detrimental, and instead is associated with reduced mortality. The therapeutic "window" remains open in such patients and that alternative markers of circulatory failure (ie. hypotension and reduced glomerular filtration rate) may be more appropriate.
Strengths	• Large sample size for retrospective study • Utilization of a propensity risk score matched analysis to control for selection bias • Reported median dose of beta-blocker therapy • Reported causes of death unlike other studies • Utilized the International Ascites Club definition for refractory ascites • Transplantation was recognized as a competing risk factor
Weaknesses	• Observational data (lack of randomization) • Single-center study • Patient population only included those on the transplant waiting list • NSBB therapy adherence not addressed • BP data only available in 81 patients (25%) of the cohort • Confounders: no mention of EVL or presence of varices • Outcome measures not specifically stated
Take Away Summary	In cirrhotic patients with ascites or refractory ascites, NSBB therapy at moderate doses (eg, propranolol 80mg/day and carvedilol 6.25 mg/day) does not appear to increase mortality. Other factors of circulatory function should be considered to determine if NSBBs should be discontinued in patients with refractory ascites.

Table 11: Overview of Other Available Studies				
Study	**Type of patients**	**Conclusion**	**Strengths**	**Limitations**
Chirapongsathorn, et al (2016)[12] **Systematic Review and Meta-analysis**	Patients with ascites and refractory ascites	The use of NSBB therapy was not associated with a significant increase in all-cause mortality in patients with cirrhosis and ascites or refractory ascites	• Meta-analysis of 11 trials • Rigorous search process to find and review potential articles for inclusion into meta-analysis	• Most studies included were observational • Significant heterogeneity across studies • Drug, dose, and duration of NSBB was not explored • Most studies included were considered to have medium to high risk of bias
Serste, et al (2011)[13] **Prospective cross-over study**	Patients with refractory ascites (N= 10)	Beta-blocker therapy may be associated with a high risk of paracentesis-induced circulatory dysfunction in patients with refractory ascites	• Definition of refractory ascites was based on the International Ascites Club criteria • Propranolol dose was reported: 7 patients received 160 mg/day	• Small study • Observational study • Hard outcomes (ie. Death) were not assessed
Robins, et al (2014)[14] **Letter/retrospective study**	Patients undergoing regular paracentesis (N= 114)	Median survival was 18 months in the NSBB group vs. 11 months in the no NSBB group, with no significant difference (p= 0.93)	• Propranolol dose was reported: mean total daily dose of 48.9 mg • Reported history of variceal bleeding and presence of varices	• Letter/retrospective study • Definition for refractory ascites
Kimer, et al (2015)[15] **Retrospective study**	Patients with cirrhosis and refractory ascites (N= 61)	Survival analysis revealed no significant difference in survival (P= 0.69)	• Propranolol dose was reported: 80 mg (40-200) per day	• Retrospective • Refractory ascites defined as: paracentesis 2 times or more yearly in spite of diuretic treatment

- In patients with refractory ascites, NSBB (propranolol or nadaolol) should be used with caution
    - Closely monitor blood pressure, serum creatinine, and serum sodium
- NSBB therapy should be reduced/discontinued if a patient with refractory ascites develops:
    - Systolic blood pressure < 90 mmHg
    - Hyponatremia (<130 mEq/L)
    - Acute kidney injury
- If there was a clear precipitant for these events (e.g. acute variceal bleed), reinitiation of NSBB should be considered after these abnormal parameters return to baseline values
    - If reinitiating NSBB, start at the lowest dose and titrate upward

Conclusion and Recommendations

- Treatment Algorithm



- Considerations
  - Monitoring: Blood pressure and serum creatinine should be monitored more frequently in patients with refractory ascites
  - NSBB choice: Avoid carvedilol in patients with refractory ascites due to the more pronounced hemodynamic effects
  - NSBB dose: Avoid propranolol doses greater than 160mg/day

Concluding Remarks

- There is conflicting evidence about the potentially detrimental effects of NSBBs in patients with advanced cirrhosis, especially in patients with refractory ascites.
- There is a clear rationale to assume that NSBB therapy might be detrimental in patients with refractory ascites due to the circulatory dysfunction.
- Randomized controlled trials are needed to determine whether or not NSBB therapy is beneficial in patients with refractory ascites.
- Until further studies are available, NSBB therapy should be used with caution in patients with refractory ascites.

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Appendices:

Appendix A: Child-Pugh Score[16]			
Score	**1**	**2**	**3**
Total bilirubin (mg/dL)	<2	2-3	>3
Albumin (g/dL)	>3.5	2.8-3.5	<2.8
Ascites	None	Mild	Moderate
Encephalopathy (grade)	None	1 and 2	3 and 4
Prothrombin time (seconds prolonged)	<4	4-6	>6

Appendix B: Child-Pugh Class (total points)[16]	
Class A	5-6 points
Class B	7-9 points
Class C	10-15 points

Appendix C: Model for end-stage liver disease (MELD) score[16]	
International normalized ratio (INR)	0.957× log (creatinine) + 0.378 × log (total bilirubin) + 1.120 log (INR) + 0.6431
Serum Creatinine	
Serum Bilirubin	
Dialysis at least twice in the past week	
Range = 6 (lowest risk) to 40 (highest risk)	

Appendix D: Model for end-stage liver disease (MELD-Na) score[16]	
International normalized ratio (INR)	MELD-Na Score = MELD + 1.59 X (135-Na [mEq/L])
Serum Creatinine	
Serum Bilirubin	
Serum Sodium	
Dialysis at least twice in the past week	
Range = 6 (lowest risk) to 40 (highest risk)	