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

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BACKGROUND & AIDS: Nonselective β blockers (NSBBs) reduce portal pressure and the risk for variceal hemorrhage in patients with cirrhosis. However, development of spontaneous bacterial peritonitis (SBP) in these patients could preclude treatment with NSBBs because of their effects on the circulatory reserve. We investigated the effects of NSBBs in patients with cirrhosis and ascites with and without SBP. METHODS: We performed a retrospective analysis of data from 607 consecutive patients with cirrhosis who had their first paracentesis at the Medical University of Vienna from 2006 through 2011. Cox models were calculated to investigate the effect of NSBBs on transplant-free survival time and adjusted for Child-Pugh stage and presence of varices. RESULTS: NSBBs increased transplant-free survival in patients without SBP (hazard ratio = 0.75; 95% confidence interval: 0.581–0.968; P = .027) and reduced days of nonselective hospitalization (19.4 days/year for patients on NSBBs vs 23.9 days/year for patients not taking NSBBs). NSBBs had only moderate effects on systemic hemodynamics at patients’ first paracentesis. However, at the first diagnosis of SBP, the proportion of hemodynamically compromised patients with systolic arterial pressure <100 mm Hg was higher among those who received NSBBs (38% vs 18% of those not taking NSBBs; P = .002), as was the proportion of patients with arterial pressure <82 mm Hg (64% of those taking NSBBs vs 44% of those not taking NSBBs; P = .006). Among patients with SBP, NSBBs reduced transplant-free survival (hazard ratio = 1.58; 95% confidence interval: 1.098–2.274; P = .014) and increased days of nonelective hospitalization (29.6 days/person-year in patients on NSBBs vs 23.7 days/person-year in those not taking NSBBs). A higher proportion of patients on NSBBs had hepatorenal syndrome (24% vs 11% in those not taking NSBBs; P = .027) and grade C acute kidney injury (20% vs 8% for those not taking NSBBs; P = .021). CONCLUSIONS: Among patients with cirrhosis and SBP, NSBBs increase the proportion who are hemodynamically compromised, time of hospitalization, and risks for hepatorenal syndrome and acute kidney injury. They also reduce transplant-free survival. Patients with cirrhosis and SBP should not receive NSBBs.

Keywords: Liver Fibrosis; Bacterial Infection; Mortality; β Blocker; Adrenergic Receptor.

Cirrhosis accounts for 1.8% of all deaths in Europe1 and is the 12th leading cause of death in the United States, and a recent report suggests that even this might be an underestimation.2

According to a prognostic model proposed by D’Amico et al.,3 the occurrence of varices initiates the second stage of cirrhosis, and the third stage is defined by the development of ascites. Variceal hemorrhage, the most common lethal complication of cirrhosis, results directly from portal hypertension and triggers the fourth stage of cirrhosis.

Abbreviations used in this paper: AKI, acute kidney injury; CI, confidence interval; CPS, Child-Pugh score; DAP, diastolic arterial pressure; HR, hazard ratio; HRS, hepatorenal syndrome; IQR, interquartile range; MAP, mean arterial pressure; NSBB, nonselective β blocker; PMN, polymorphonuclear neutrophil; SAP, systemic arterial pressure; SBP, spontaneous bacterial peritonitis.
Nonselective β blockers (NSBBs) have been shown to reduce the hepatic venous portal pressure gradient by lowering cardiac output and splanchic vasoconstriction through the inhibition of the binding of catecholamines to β₁ and β₂ adrenoreceptors.4

Based on a broad body of evidence, current guidelines5–7 recommend NSBB treatment for the prevention of the first variceal hemorrhage and rebleeding. NSBBs are among the most widely used drugs in patients with cirrhosis and have even been referred to as “the aspirin of hepatologists.”8

However, the role of β blockers appears to have changed over the years.9 Although the efficacy of NSBB treatment in prevention of variceal hemorrhage was established as early as 1981,9 recent studies suggest additional beneficial effects of NSBB treatment. In patients with compensated cirrhosis, hemodynamic response to NSBBs has been shown to reduce the risk of developing ascites, refractory ascites, and hepatorenal syndrome (HRS).10 In addition, NSBB treatment has been shown to decrease intestinal permeability independently of hemodynamic response10 and to prevent the development of spontaneous bacterial peritonitis (SBP).11 In contrast, a recent study by Serste et al12 has demonstrated a detrimental effect of NSBB treatment in patients with cirrhosis and refractory ascites and has initiated an intense debate on whether the use of NSBBs should be contraindicated in this group of patients.

The window hypothesis,13 proposed by Krag et al, is consistent with these results and implies the existence of a therapeutic window for NSBB treatment, which closes late in the natural course of cirrhosis. As meta-analysis has shown that the reduction of the risk of variceal hemorrhage by NSBB treatment is significantly lower among patients with ascites,14 the end of this therapeutic window might be expected at some point after the first development of ascites.

The occurrence of bacterial infections, even with recovery, can establish an additional fifth stage of cirrhosis, termed the critically ill patient with cirrhosis.15 These bacterial infections predominately occur in advanced cirrhosis, which is associated with profound changes in systemic hemodynamics, most importantly peripheral vasodilation with an impaired responsiveness to vasoconstrictors16 and a simultaneous increase in cardiac output to maintain adequate organ perfusion.13 However, parallel to the progression of hyperdynamic circulation, the cardiac compensatory reserve gradually decreases, resulting in an impaired adaptive response to acute circulatory stress, such as SBP. Development of SBP has been shown to be associated with pronounced portal and systemic hemodynamic derangements, as bacteremia has been found to decrease systemic vascular resistance17 and patients with low cardiac output have been shown to be at high risk for development of HRS,18 a major complication of SBP that further reduces survival. In patients with ascites, impaired cardiac output has been found to be associated with substantially increased mortality.19

We therefore hypothesized that the development of SBP closes the window of opportunity for NSBB treatment, as maintaining the circulatory reserve is crucial in critically ill patients with cirrhosis. The main adaptive mechanism to circulatory stress is the increase in heart rate mediated by β₁ adrenoreceptors that are down-regulated and desensitized in patients with advanced cirrhosis.20 Additional pharmaceutical blockade induces chronotropic incompetence,20 decreases cardiac output,21 and blood pressure and can increase the rate of HRS development after an SBP episode, resulting in worse survival.

The aim of this study was to assess the influence of NSBB treatment on SBP incidence and the impact of SBP development on the effect of NSBB treatment on hospitalization and transplant-free survival. In addition, rates of HRS and acute kidney injury (AKI) development after the first SBP diagnosis were assessed in patients with NSBB treatment and without.

### Patients and Methods

#### Study Design

A total of 607 consecutive patients with cirrhosis who underwent their first paracentesis at the Medical University of Vienna between 2006 and 2011, had bacterial cultures from ascites, and did not display any exclusion criteria, were included in this retrospective study. Patients with other causes of ascites, such as severe cardiovascular disease, renal insufficiency, extrahepatic malignancies, and noncirrhotic portal hypertension, were excluded from the study.

#### Assessed Parameters

Epidemiological characteristics, etiology of cirrhosis, presence of varices, and information on previous variceal bleeding, as well as follow-up variceal bleeding and liver transplantation, were assessed from patient medical history. In addition, information on NSBB and rifaximin treatment, as well as systemic hemodynamics, was obtained from patient medical history. The following laboratory parameters were assessed at the time of the first paracenteses and the first diagnosis of SBP: platelet count, albumin, bilirubin, international normalized ratio, creatinine, and ascitic fluid neutrophil count. Hepatic venous portal pressure gradient measurements were performed as described previously.22 The model for end-stage liver disease23 and Child-Pugh score (CPS)24 were calculated based on laboratory parameters and patients’ medical history.

#### Paracenteses and Diagnosis of Spontaneous Bacterial Peritonitis

Paracenteses were performed either in a diagnostic or therapeutic setting. In accordance with national guidelines,5,25 albumin was administered in all large-volume paracenteses. SBP was diagnosed if the ascitic fluid neutrophil count was >250 mL without an evident intra-abdominal source of infection or another explanation for an elevated ascitic fluid neutrophil count.5,26,27 Patients with SBP were receiving albumin in addition to antibiotic treatment, as recommended by national guidelines during the full study period.5,25

#### Diagnosis of Hepatorenal Syndrome and Acute Kidney Injury

The diagnosis of HRS was established if creatinine levels increased to >1.5 mg/dL or doubled to a level of >2.5 mg/dL in the absence of evidence for shock or hypovolemia5,26,27 within
90 days after the first SBP diagnosis. Patients with a history of chronic kidney disease other than HRS or evidence for parenchymal kidney disease, such as proteinuria, microhematuria, or abnormal renal ultrasonography were excluded from this analysis.

AKI was diagnosed if a patient fulfilled the criteria of group C of the modified AKI classification proposed by Fagundes et al.²⁸ comprising both stages 2 and 3 of the Acute Kidney Injury Network criteria.²⁹ AKI was defined as an increase of serum creatinine >2-fold from baseline or a serum creatinine >4.0 mg/dL with an acute increase >0.5 mg/dL. In addition, urine output <0.5 mL/kg per hour for >12 hours was considered as AKI.

Statistics

Statistical analyses were conducted using IBM SPSS Statistics 21 (SPSS Inc., Armonk, NY) and R.3.0.1 (R Development Core Team 2008, The R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were reported as mean ± standard deviation (SD) or median (interquartile range [IQR]), and categorical variables were reported as number (n) of patients with the certain characteristic (proportion of patients with the certain characteristic [%]). Student t test was used for group comparisons of continuous variables when applicable. Otherwise, Mann-Whitney U test was applied. Group comparisons of categorical variables were performed using either Pearson’s χ² or Fisher’s exact test. The impact of NSBB treatment on SBP incidence and transplant-free survival was analyzed using semi-parametric proportional hazard Cox models. The proportional hazard assumption was verified by inspecting the cumulative hazard plot for parallel curves.

Patients entered the SBP incidence model (Model 1) with their first paracentesis and were followed until their last paracentesis. In liver transplant recipients and in case of death, the last paracentesis before the liver transplantation or death was the end of follow-up. Patients who had only one paracentesis, as well as patients with SBP at their first paracentesis, were excluded from this analysis. NSBB treatment and CPS stage were considered as covariates. In addition, SBP incidence rates among patients with NSBB treatment, and without, as well as the SBP incidence rate ratio were calculated.

The rates of follow-up paracentesis and variceal bleeding after the first paracentesis were calculated for NSBB and no-NSBB patients. Similarly, follow-up paracentesis and bleeding rates after the first development of SBP were calculated.

Patients entered the first transplant-free survival model (Model 2) with their first paracentesis and were followed until 2013. Transplant-free survival time was defined as the time to liver transplantation, death, or end of follow-up. Patients who received a liver transplantation were censored at the day of surgery. Besides NSBB treatment, the model included presence of varices, CPS stage, and SBP status as covariates. The latter variable was treated as a time-dependent covariate in the following fashion: The first development of SBP in patients without SBP at the first paracentesis separated the follow-up into 2 adjoining time intervals. In the first (right censored) interval the SBP status is negative, and it is positive in the second (left or interval censored) time period. To assess the modulating effect of SBP development on the impact of NSBB treatment on transplant-free survival, the interaction term NSBB × SBP was incorporated into the model.

A second transplant-free survival model (Model 3) restricted to SBP patients was calculated with patients entering the model with the first development of SBP and NSBB treatment, presence of varices and CPS stage at the time of SBP diagnosis as covariates. Kaplan-Meier curves are shown for all models.

P values <.05 were considered as statistically significant. No adjustment for multiplicity was performed.

Ethics

This study was conducted in accordance with the Declaration of Helsinki and approved by the local ethics committee of the Medical University of Vienna (EK Nr. 1008/2011).

Results

Patient Characteristics and Systemic Hemodynamics at the First Paracentesis

Except for a higher proportion of female subjects (NSBB: 34% vs no-NSBB: 27%; P = .048) and patients with varices (NSBB: 90% vs no-NSBB: 62%; P < .001) in the NSBB group, no statistically significant differences in patient characteristics between patients with NSBB treatment, and without, were observed (Table 1).

Although the mean heart rate (NSBB: 77.5 ± 16.5 beats/min vs no-NSBB: 83.9 ± 15.5 beats/min; P < .001) and systolic arterial pressure (SAP) (NSBB: 114 ± 18 vs no-NSBB: 117 ± 18 mm Hg; P = .05) (Figure 1) were lower among patients with NSBB treatment than in patients without, no differences in diastolic arterial pressure (DAP) and mean arterial pressure (MAP) (Figure 1B) were observed. The proportion of hemodynamically compromised patients, as defined by a SAP <100 mm Hg (NSBB: 18% vs no-NSBB: 15%; P = .391) (Figure 1C) or an MAP <82 mm Hg (NSBB: 39% vs no-NSBB: 38%; P = .757) (Figure 1D), was comparable between the NSBB treatment groups at the first paracentesis.

In the NSBB group, daily propranolol doses ranged between 20 mg and 120 mg (20 mg: 10%; 30 mg: 4%; 40 mg: 25%; 50 mg: 1%; 60 mg: 12%; 80 mg: 17%; 100 mg: 1%; 120 mg: 4%), and the administered carvedilol doses ranged between 6.25 mg and 25 mg (6.25 mg: 7%, 12.5 mg: 18%, 25 mg: 4%).

Influence of Nonselective β Blocker Treatment on Spontaneous Bacterial Peritonitis Incidence

NSBB treatment (hazard ratio [HR] = 0.699; 95% confidence interval [CI]: 0.427–1.146; P = .156) and CPS stage (stage B: HR = 1.211; 95% CI: 0.283–5.192; P = .796 and stage C: HR = 2.033; 95% CI: 0.485–8.519; P = .332) were not associated with SBP incidence in univariate analysis (Model 1, Supplementary Figure 1).

In multivariate analysis, neither NSBB treatment (HR = 0.728; 95% CI: 0.422–1.198; P = .211) nor CPS stage (stage B: HR = 1.082; 95% CI: 0.25–4.686; P = .916 and stage C: HR = 1.792; 95% CI: 0.422–7.611; P = .429) were associated with SBP development (Model 1, Supplementary Figure 1).

SBP incidence rates were comparable between patients with (0.107 per person-year; 95% CI: 0.071–0.15) and...
<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>At the first paracentesis</th>
<th>At the first development of SBP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All (n = 607)</td>
<td>No NSBB (n = 362)</td>
</tr>
<tr>
<td>Age, y, mean ± SD</td>
<td>57.5 ± 11.8</td>
<td>57.2 ± 12.1</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>426 (70)</td>
<td>265 (73)</td>
</tr>
<tr>
<td>Female</td>
<td>181 (30)</td>
<td>97 (27)</td>
</tr>
<tr>
<td>Etiology, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALD</td>
<td>336 (55)</td>
<td>192 (53)</td>
</tr>
<tr>
<td>Viral</td>
<td>113 (19)</td>
<td>70 (19)</td>
</tr>
<tr>
<td>ALD and viral</td>
<td>49 (8)</td>
<td>27 (7)</td>
</tr>
<tr>
<td>Other</td>
<td>109 (18)</td>
<td>73 (20)</td>
</tr>
<tr>
<td>HCC, n (%)</td>
<td>129 (21)</td>
<td>74 (20)</td>
</tr>
<tr>
<td>Previous variceal bleeding, n (%)</td>
<td>98 (16)</td>
<td>54 (15)</td>
</tr>
<tr>
<td>Varices, n (%)</td>
<td>443 (73)</td>
<td>223 (62)</td>
</tr>
<tr>
<td>HVPG, mm Hg, mean ± SD</td>
<td>18.7 ± 6.5</td>
<td>18.3 ± 7.1</td>
</tr>
<tr>
<td>MELD, median (IQR)/mean ± SD</td>
<td>17.5 (10.6)</td>
<td>17.8 (11)</td>
</tr>
<tr>
<td>CPS stage, n (%)</td>
<td>.961</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>22 (4)</td>
<td>13 (4)</td>
</tr>
<tr>
<td>B</td>
<td>281 (46)</td>
<td>166 (46)</td>
</tr>
<tr>
<td>C</td>
<td>304 (50)</td>
<td>183 (51)</td>
</tr>
<tr>
<td>Platelet count, 109/L, median (IQR)</td>
<td>117 (107)</td>
<td>117 (108)</td>
</tr>
<tr>
<td>Albumin, g/L, mean ± SD</td>
<td>27.2 ± 5.7</td>
<td>27 ± 5.4</td>
</tr>
<tr>
<td>Bilirubin, mg/dL, median (IQR)</td>
<td>3.2 (6.02)</td>
<td>3.05 (6.98)</td>
</tr>
<tr>
<td>INR, median (IQR)</td>
<td>1.38 (0.58)</td>
<td>1.41 (1.19)</td>
</tr>
<tr>
<td>Creatinine, mg/dL, median (IQR)</td>
<td>1.14 (0.78)</td>
<td>1.14 (0.83)</td>
</tr>
<tr>
<td>Rifaximin treatment, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>69 (11)</td>
<td>36 (10)</td>
</tr>
<tr>
<td>Before first paracentesis</td>
<td>14 (2)</td>
<td>8 (2)</td>
</tr>
<tr>
<td>After the first paracentesis</td>
<td>63 (10)</td>
<td>34 (9)</td>
</tr>
<tr>
<td>Heart rate, beats/min, mean ± SD</td>
<td>81.2 ± 16.2</td>
<td>83.9 ± 15.5</td>
</tr>
<tr>
<td>SAP, mm Hg, mean ± SD</td>
<td>115 ± 18</td>
<td>117 ± 18</td>
</tr>
<tr>
<td>SAP &lt; 100 mm Hg, n (%)</td>
<td>98 (16)</td>
<td>55 (15)</td>
</tr>
<tr>
<td>DAP, mm Hg, mean ± SD</td>
<td>70.5 ± 12.5</td>
<td>71 ± 12.5</td>
</tr>
<tr>
<td>MAP, mm Hg, mean ± SD</td>
<td>85.4 ± 13.3</td>
<td>86.2 ± 13.2</td>
</tr>
<tr>
<td>MAP &lt; 82 mm Hg, n (%)</td>
<td>228 (38)</td>
<td>135 (38)</td>
</tr>
</tbody>
</table>

ALD, alcoholic liver disease; CPS, Child-Pugh score; DAP, diastolic arterial pressure; HCC, hepatocellular carcinoma; HVPG, hepatic venous pressure gradient; INR, international normalized ratio; MAP, mean arterial pressure; MELD model for end-stage liver disease; SAP, systolic arterial pressure.

*Available in 220 patients.
**Available in 82 patients.
†Available in 395 patients.
‡Available in 109 patients.
§Available in 595 patients.
without NSBB treatment (0.117 per person-year; 95% CI: 0.084–0.156), with an incidence rate ratio of 0.915 (95% CI: 0.565–1.483).

**Influence of Nonselective β Blocker Treatment on Spontaneous Bacterial Peritonitis Development, Paracentesis and Variceal Bleeding Rates, Hospitalization as Well as Transplant-Free Survival**

A total of 607 patients were followed for 660 person-years after their first paracentesis. There was a trend toward a lower paracentesis rate among patients with (2.45 per person-year; 95% CI: 2.27–2.63), when compared with patients without NSBB treatment (2.76 per person-year; 95% CI: 2.6–2.94).

Thirty-three episodes of variceal bleeding were observed during follow-up. Bleeding rates were comparable between patients with (0.059 per person-year; 95% CI: 0.034–0.068) and without NSBB treatment (0.043 per person-year; 95% CI: 0.025–0.067). The proportions of patients receiving a liver transplant were 12% and 10% in the NSBB and no-NSBB group, respectively (P = .46).

After their first paracentesis, patients with NSBB treatment were hospitalized for 26.7 days per person-year (95% CI: 26.1–27.3), and patients without NSBB treatment were hospitalized for 30.9 days per person-year (95% CI: 30.4–31.5). Although the duration of elective hospitalizations was similar (NSBB: 7.37 days per person-year; 95% CI: 7.07–7.69 vs no-NSBB: 6.98 days per person-year; 95% CI: 6.72–7.26), the duration of nonelective hospitalization was lower among patients with (19.4 days per person-year; 95% CI: 18.9–19.9) when compared with patients without NSBB treatment (23.9 days per person-year; 95% CI: 23.4–24.4).

NSBB treatment was associated with higher transplant-free survival (HR = 0.771; 95% CI: 0.598–0.993; P = .044) in multivariate analysis, when adjusting for the presence of varices (HR = 0.983; 95% CI: 0.783–1.235; P = .886), CPS stage (stage B: HR = 1.134; 95% CI: 0.615–2.09; P = .687 and stage C: HR = 2.24; 95% CI: 1.222–4.107; P = .009), and SBP development (HR = 1.401; 95% CI: 1.056–1.857; P = .019) (Model 2, Table 2). In addition, the interaction term NSBB × SBP (HR = 1.917; 95% CI: 1.252–2.924; P = .003) was statistically significantly associated with transplant-free survival. This suggests that the development of SBP modulates the effect of NSBB treatment on transplant-free survival warranting additional subgroup analysis.

**Impact of Spontaneous Bacterial Peritonitis Development on the Effect of Nonselective β Blocker Treatment on Transplant-Free Survival**

Up to the development of SBP, NSBB treatment had a beneficial effect on transplant-free survival (HR = 0.75; 95% CI: 0.581–0.968; P = .027) when adjusting for the presence of varices and CPS stage (Model 2, Table 2, Figure 2A) and was associated with a reduction in mortality risk of 25%. In contrast, once a patient developed SBP, NSBB treatment was associated with lower transplant-free survival (HR = 1.58; 95% CI: 1.098–2.274; P = .014) when
adjusting for the same variables (Model 2, Table 2, Figure 2B). NSBB treatment was associated with an increase of 58% in mortality risk once a patient developed SBP.

**Patient Characteristics and Systemic Hemodynamics at First Development of Spontaneous Bacterial Peritonitis**

A total of 182 patients developed at least one SBP episode. Comparing NSBB and no-NSBB patient characteristics revealed no statistically significant differences except for a higher prevalence of varices (NSBB, 94% vs no-NSBB, 60%; \( P < .001 \)) and higher median bilirubin levels (NSBB: 5.11 mg/dL [IQR, 9.32 mg/dL] vs no-NSBB: 3 mg/dL [IQR, 5 mg/dL]; \( P = .024 \)) in the NSBB group. In addition, there was a trend toward a higher proportion of female patients (NSBB: 33% vs no-NSBB: 21%; \( P = .073 \)), as well as patients with alcoholic etiology (NSBB: 60% vs no-NSBB: 44%; \( P = .07 \)) and CPS stage C (NSBB: 67% vs no-NSBB: 53%; \( P = .107 \)) among patients with NSBB treatment.

Patients with NSBB treatment had a lower mean heart rate (NSBB: 76.2 ± 15.7 beats/min vs no-NSBB: 82.9 ± 15.7 beats/min; \( P = .027 \)), SAP (NSBB: 104 ± 17 mm Hg vs no-NSBB: 113 ± 18 mm Hg; \( P < .001 \)) (Figure 1A), and MAP (NSBB: 77.2 ± 13.1 mm Hg vs no-NSBB: 82.6 ± 12.5 mm Hg; \( P = .005 \)) (Figure 1B). In addition, DAP tended to be lower among patients with NSBB treatment (NSBB: 63.8 ± 12.3 mm Hg vs no-NSBB: 67.3 ± 12.5 mm Hg; \( P = .06 \)). Similarly, the proportion of patients with SAP <100 mm Hg (NSBB: 38% vs no-NSBB: 18%; \( P = .002 \)) (Figure 1C) or MAP <82 mm Hg (NSBB: 64% vs no-NSBB: 44%; \( P = .006 \)) (Figure 1D) was substantially higher among patients with NSBB treatment.

**Impact of Nonselective \( \beta \) Blocker Treatment on Paracentesis and Variceal Bleeding Rates, Hospitalization as Well as Transplant-Free Survival After the First Spontaneous Bacterial Peritonitis Diagnosis**

After SBP development, 182 patients were followed for a total of 147 person-years. The paracentesis rate was comparable between no-NSBB (3.67 per person-year; 95% CI: 3.29–4.08) and NSBB patients (3.36 per person-year; 95% CI: 2.9–3.84).

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**Table 2. Impact of Spontaneous Bacterial Peritonitis Development on the Effect of Nonselective \( \beta \) Blocker Treatment on Transplant-Free Survival (Model 2): Univariate and Multivariate Analyses Including All patients and Multivariate Analysis According to Spontaneous Bacterial Peritonitis Status**

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>HR</th>
<th>95% CI</th>
<th>P value</th>
<th></th>
<th>HR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lower</td>
<td>Upper</td>
<td></td>
<td></td>
<td>Lower</td>
<td>Upper</td>
<td></td>
</tr>
<tr>
<td>Varices, yes</td>
<td>1.047</td>
<td>0.841 1.303</td>
<td>.682</td>
<td></td>
<td>0.983</td>
<td>1.235 .869</td>
<td>.886</td>
</tr>
<tr>
<td>CPS stage B</td>
<td>1.076</td>
<td>0.584 1.983</td>
<td>.814</td>
<td></td>
<td>1.134</td>
<td>2.09 .687</td>
<td>.009</td>
</tr>
<tr>
<td>CPS stage C</td>
<td>2.203</td>
<td>1.203 4.035</td>
<td>.011</td>
<td></td>
<td>2.24</td>
<td>4.107 .009</td>
<td>.019</td>
</tr>
<tr>
<td>SBP, yes</td>
<td>1.893</td>
<td>1.538 2.328</td>
<td>&lt;.001</td>
<td></td>
<td>1.401</td>
<td>1.857 .019</td>
<td>.019</td>
</tr>
<tr>
<td>NSBB, yes</td>
<td>0.945</td>
<td>0.775 1.152</td>
<td>.578</td>
<td></td>
<td>0.771</td>
<td>0.993 .044</td>
<td>.044</td>
</tr>
<tr>
<td>NSBB ( \times ) SBP</td>
<td>1.917</td>
<td>1.256 2.924</td>
<td>.003</td>
<td></td>
<td>1.269</td>
<td>10.68 .098</td>
<td>.098</td>
</tr>
</tbody>
</table>

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**Figure 2. Impact of NSBB treatment on transplant-free survival according to SBP status.** Patients without SBP at first diagnosis started in (A) (no-SBP), while Patients with SBP at the first paracentesis started in (B) (SBP). At the first SBP diagnosis, patients were censored in (A) (no-SBP), entered (B) (SBP), and remained in this group.
Thirteen episodes of variceal bleeding were observed after the first SBP diagnosis. Bleeding rates were similar among patients with (0.086 per person-year; 95% CI: 0.028–0.175) and without NSBB treatment (0.09 per person-year; 95% CI: 0.039–0.162). In addition, the proportion of patients receiving a liver transplantation did not vary statistically significantly throughout the NSBB treatment groups (no-NSBB: 9% vs NSBB: 13%; \( P = .462 \)).

After the first diagnosis of SBP, the duration of hospitalization was higher in the NSBB group (NSBB: 33.4 days per person-year; 95% CI: 31.9–34.9 vs no-NSBB: 28.8 days per person-year; 95% CI: 27.6–29.9). The duration of elective hospitalizations was comparable between both treatment groups (NSBB: 3.6 days per person-year; 95% CI: 3.1–4.1 vs no-NSBB: 3.9 days per person-year; 95% CI: 3.5–4.3). In contrast, a higher duration of nonelective hospitalizations was observed in the NSBB group (NSBB: 29.6 days per person-year; 95% CI: 28.2–31 vs no-NSBB: 23.7 days per person-year; 95% CI: 22.7–24.8).

In multivariate analysis, NSBB treatment was associated with impaired transplant-free survival after SBP diagnosis (HR = 1.644; 95% CI: 1.145–2.361; \( P = .007 \)), after adjusting for CPS stage (stage B: HR = 1.642; 95% CI: 0.507–5.314; \( P = .408 \)); stage C: HR = 3.318; 95% CI: 1.036–10.627; \( P = .043 \)) and the presence of varices (HR = 0.695; 95% CI: 0.457–1.057; \( P = .089 \)) at the time of SBP development (Model 3, Table 3, Figure 3). Rates of transplant-free survival after SBP development are shown in Table 3.

**Influence of Nonselective \( \beta \) Blocker Treatment on Hepatorenal Syndrome and Acute Kidney Injury Development After the First Spontaneous Bacterial Peritonitis Diagnosis**

A total of 11 patients were excluded from the analysis of HRS development because of evidence for shock, hypovolemia, or chronic kidney disease other than HRS. In addition, 6 patients without HRS, liver transplantation, or death were excluded because of a follow-up period of <90 days after the first SBP diagnosis. Among the remaining 165 patients, HRS was observed in 18% (29 of 165) of patients within 90 days after the SBP diagnosis. The rate of HRS development was significantly higher in patients with (24% [20 of 83]) when compared with patients without NSBB treatment (11% [9 of 82]; \( P = .027 \)) (Figure 4).

Eighty percent (16 of 20) of patients with NSBB treatment developing HRS died within 90 days after the HRS diagnosis.

Six patients without HRS, liver transplantation, or death were excluded from the analysis of AKI development because of a follow-up period of <90 days after the first SBP diagnosis. Grade C AKI was observed in 14% (24 of 176) of the patients included in this analysis. Patients with NSBB treatment (20% [17 of 86]) showed a higher rate of grade C AKI development when compared with patients without NSBB

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**Table 3. Influence of Nonselective \( \beta \) Blocker Treatment on Transplant-Free Survival After the First Spontaneous Bacterial Peritonitis Diagnosis (Model 3) and Survival Rates After Spontaneous Bacterial Peritonitis Development**

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>95% CI</th>
<th>( P ) value</th>
<th>95% CI</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate (( n = 182 ))</td>
<td></td>
<td>Multivariate (( n = 182 ))</td>
<td></td>
</tr>
<tr>
<td>Varices, yes</td>
<td>0.97</td>
<td>0.657–1.432</td>
<td>.88</td>
<td>0.695</td>
</tr>
<tr>
<td>CPS stage B</td>
<td>1.478</td>
<td>0.459–4.757</td>
<td>.512</td>
<td>1.642</td>
</tr>
<tr>
<td>CPS stage C</td>
<td>2.954</td>
<td>0.932–9.365</td>
<td>.066</td>
<td>3.318</td>
</tr>
<tr>
<td>NSBB, yes</td>
<td>1.539</td>
<td>1.095–2.164</td>
<td>.013</td>
<td>1.644</td>
</tr>
<tr>
<td></td>
<td>no-NSBB (( n = 96 ))</td>
<td></td>
<td>NSBB (( n = 86 ))</td>
<td></td>
</tr>
<tr>
<td><strong>Time point</strong></td>
<td><strong>Estimate</strong></td>
<td><strong>95% CI</strong></td>
<td><strong>Estimate</strong></td>
<td><strong>95% CI</strong></td>
</tr>
<tr>
<td>1 month</td>
<td>0.713</td>
<td>0.627–0.81</td>
<td>0.566</td>
<td>0.47–0.682</td>
</tr>
<tr>
<td>6 month</td>
<td>0.495</td>
<td>0.403–0.608</td>
<td>0.279</td>
<td>0.198–0.393</td>
</tr>
<tr>
<td>12 month</td>
<td>0.358</td>
<td>0.271–0.472</td>
<td>0.227</td>
<td>0.152–0.338</td>
</tr>
</tbody>
</table>

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![Figure 3. Influence of NSBB treatment on transplant-free survival after the first SBP diagnosis.](image-url)
follow-up duration was limited to the last paracentesis for statistical reasons, a lack of statistical power of Model 1 to detect a clinically significant effect of NSBB treatment on SBP development cannot be excluded. However, these limitations do not apply to the analyses of SBP incidence rates, which were comparable between patients with and without NSBB treatment. The proportion of CPS stage C patients in our study was substantially higher when compared with previous studies designed for the assessment of the effect of NSBB treatment on variceal bleeding,13 and all patients included in our study had previously developed ascites. As NSBB treatment has been shown to reduce the risk of developing ascites in patients with compensated cirrhosis,9 the overall effect of NSBB treatment initiated before the first decompensation cannot be assessed in our study. Our results provide a rationale for additional meta-analyses assessing the effect of NSBB treatment on SBP development in patients with more advanced stages of cirrhosis.

Nearly half of the patients included in the study by Serste et al12 received a comparatively high daily propranolol dose of 160 mg. In a consecutive crossover study, propranolol treatment was found to be associated with a higher risk for paracentesis-induced circulatory dysfunction in patients with refractory ascites and cirrhosis.20 Seven of 10 patients included in this study received 160 mg propranolol. Because high NSBB doses have profound effects on systemic circulation and might not be well tolerated by hemodynamically compromised patients, such as patients with advanced cirrhosis, Robins et al12 suggested that the use of lower NSBB doses is safe among patients with refractory ascites. In contrast, substantially lower NSBB doses were administered in our study. However, carvedilol might not only be more efficient in decreasing portal pressure by additional α1 adrenoreceptor inhibition,16,37 it might also lead to a more pronounced decrease in MAP.36

The efficacy of NSBB treatment for the prevention of variceal bleeding has primarily been studied in patients without ascites, and meta-analysis suggests that the beneficial effect in the prevention of variceal bleeding might be lower among patients with ascites.11 The characteristics or our study population might explain the low rates of variceal bleeding during follow-up observed in our study. There was a significant proportion of patients without varices in the no-NSBB group, and the proportion of patients with previous variceal bleeding included in this study was low. When comparing bleeding rates between patients with and without NSBB treatment, the unequal distribution of varices has to be considered.

Patients with more advanced liver disease, such as patients with cirrhosis and refractory ascites or bacterial infections have yet not been specifically addressed in clinical trials investigating the effectiveness of NSBB treatment.4 Our study assessed the effect of NSBB treatment in a cohort of patients with cirrhosis undergoing their first paracentesis and considered the incidence of SBP as a time-dependent covariate. Thus, our study comprised an internal control group of patients with ascites who yet have not developed SBP. This study design is in accordance with the

Discussion

A recent landmark study by Serste et al12 demonstrated reduced survival in patients with refractory ascites who were treated with NSBBs and has initiated a lively debate among gastroenterologists on the appropriate use of NSBBs in patients with advanced cirrhosis. In summary, the editorial10 and various other responses to this study brought up concerns about the unequal distribution of esophageal varices between the NSBB and no-NSBB group. In addition, the trends toward a higher prevalence of CPS stage C and HCC in patients with NSBB treatment31,32 and the lack of consecutive patient enrollment33 were highlighted as factors significantly limiting the conclusions drawn within the study. We aimed to address these limitations in our study by adjusting for the presence of varices in all analyses of transplant-free survival. In addition, all analyses were adjusted for CPS stage, as at the first SBP diagnosis, there was a trend toward a lower prevalence of CPS stage B and a higher prevalence of CPS stage C among patients with NSBB treatment. Except for a higher proportion of females in the NSBB group at the first paracentesis and higher bilirubin levels in the NSBB group at the first SBP diagnosis, no other statistically significant differences in patient characteristics were observed. In order to avoid multicollinearity, bilirubin was not considered as a covariate, as it is a component of the CPS. As our study population comprises consecutive patients meeting the inclusion and exclusion criteria of this study, our results are based on a large, representative cohort treated at a single academic center.

Another response by Senzolo et al11 addressed a potential beneficial effect of NSBB treatment on SBP development, highlighting a positive meta-analysis by the same author.11 In our study, no statistically significant effect of NSBB treatment on SBP incidence was observed. As patients who had only one paracentesis and patients with SBP at their first paracentesis were excluded and the

Figure 4. Influence of NSBB treatment on HRS and grade C AKI development within 90 days after the first SBP diagnosis.
common understanding of cirrhosis as a dynamic process and facilitates the design of prospective studies to validate our observations. Although up to the development of SBP, NSBB treatment had a beneficial effect on transplant-free survival and was associated with a reduction in mortality risk of 25%, transplant-free survival was worse in SBP patients receiving NSBB treatment with an increase in mortality risk of 58%. We also confirmed this observation in an additional analysis with patients entering the model with the first development of SBP. These observations suggest that NSBB treatment should be discontinued at the first development of SBP, raising the question of whether to permanently discontinue or to restart NSBB treatment after resolving the SBP episode. Based on the slope of the Kaplan-Meier curves, the higher hazard in the NSBB patients was limited to the first 6 months after SBP development, with curves converging toward the end of follow-up. However, this observational data must be interpreted with caution, as significant bias can arise from the high rate of early mortality observed in the NSBB group, leading to the selection of patients with better prognosis and therefore lower hazard or with improvement of hepatic function during follow-up. In addition, the development of additional SBP episodes was not considered in this model. Arvaniti et al have demonstrated that following the occurrence of bacterial infections, 30% of patients with cirrhosis patients die within 1 month, and another 30% die within 1 year. The development of bacterial infections might define a distinct group of critically ill patients with cirrhosis with a highly restricted prognosis in which maintaining the circulatory reserve is crucial not only during the acute phase of infection but also later on. This hypothesis is supported by recent data on mortality in patients with cirrhosis admitted to the intensive care unit for severe sepsis or septic shock in which NSBB treatment was discontinued during the period of hemodynamic instability. Although intensive care unit mortality was comparable, higher mortality rates at 3 and 6 months were observed among patients discharged from the intensive care unit with re-established NSBB treatment.

Similar to our observations on transplant-free survival, NSBB treatment had a detrimental effect on nonelective and overall hospitalization after SBP development. NSBB treatment might not only lead to increased mortality, but also to increased morbidity and burden of disease in this subgroup of patients.

NSBB treatment had only a moderate effect on systemic hemodynamics at the time of the first paracentesis and therefore did not increase the proportion of hemodynamically compromised patients. In contrast, at the time of the first SBP diagnosis, there was a substantially increased proportion of hemodynamically compromised patients in the NSBB group, defined as SAP <100 mm Hg or MAP <82 mm Hg, MAP <82 mm Hg or impaired cardiac output have been found to be associated with substantially increased mortality in patients with cirrhosis or both cirrhosis and ascites, respectively. Also, patients with SBP and low cardiac output have been shown to be at high risk for HRS, and NSBB treatment has previously been found to further deteriorate cardiac output in patients with cirrhosis. These results provide a pathophysiologic explanation for the detrimental effect of NSBB treatment after SBP development, compromising systemic hemodynamics and predisposing for HRS and AKI development, as observed in our study population. Our study supports previous hypotheses with observational data. Because we only considered group C AKI in our analyses, there was a substantial overlap of AKI and HRS. However, the proportion of patients who fulfilled the criteria for group C AKI was numerically smaller than the proportion of patients with HRS, which might be explained by the restrictive time criterion included in the diagnostic criteria of AKI and the higher creatinine increase threshold for the diagnosis of group C AKI.

The main limitations of our study arise from the retrospective design. As patients have not been prospectively followed, drug adherence and intermittent interruptions in NSBB treatment cannot be ruled out entirely. However, the beneficial effect of transplant-free survival in the no-SBP group can serve as an internal validation for our approach. This is the first study to provide observational evidence for the detrimental effect of NSBB treatment after SBP development. It supports the pathophysiologically compelling window hypothesis by Krag et al defining SBP as a clinical event that closes the therapeutic window for NSBB treatment. However, whether the therapeutic window for NSBB treatment reopens after resolving the SBP episode remains unclear. Prospective studies are highly encouraged to investigate the appropriate, stage-dependent use of this cornerstone in the treatment of portal hypertension.

**Supplementary Material**

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2014.03.005.

**References**


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Conflicts of interest
The authors disclose no conflicts.
Supplementary Figure 1. Influence of NSBB treatment on SBP incidence.