**TABLE .** Long-term outcomes in the two groups \*

|  | **SURGERY**  **Group**  (N = ) | **CONTROL**  **Group**  (N = ) | **Risk (95% CI)** \* | **P value** † |
| --- | --- | --- | --- | --- |
| Decompensation and/or death |  |  |  |  |
| Overall  At 12-months |  |  |  |  |
| Decompensation  Overall  At 12 months |  |  |  |  |
| Death from any cause  Overall  At 12 months |  |  |  |  |
| Ascites  Overall  At 12 months |  |  |  |  |
| Gastrointestinal bleeding  Overall  At 12 months |  |  |  |  |
| Variceal bleeding  Overall  At 12 months |  |  |  |  |
| Overt hepatic encephalopathy  Overall  At 12 months |  |  |  |  |
| SBP  Overall  At 12 months |  |  |  |  |
| Other Bacterial infections §  Overall  At 12 months |  |  |  |  |
| Hepatorenal Syndrome  Overall  At 12 months |  |  |  |  |
| Hepatocellular carcinoma  Overall  At 12 months |  |  |  |  |

**LEGEND FOR TABLE :**

Percentages are crude rates of events occurring at any time during the follow-up.

\* Values indicate the hazard ratio (or odds ratio for adverse events) of an outcome in the surgery group as compared to control group. CI stands for confidence interval.

† Comparison of cumulative incidences by competing-risk analysis (differences assessed by Gray’s test).

‡.

§ Include SBP and other documented bacterial infections during follow-up.

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**TABLE 4.** Causes of death

|  | **PLACEBO**  **Group**  **(N = 101)** | **β-BLOCKERS**  **Group**  **(N = 100)** | **Hazard Ratio**  **(95% CI)** \* | **P value** |
| --- | --- | --- | --- | --- |
| Overall | 11 (11%) | 8 (8%) | 0.54 (0.20–1.48) | 0.230 |
| Related to cirrhosis †  Bacterial infection ‡ | 11 (11%)  3 | 6 (6%)  2 | 0.55 (0.20-1.49) | 0.252 |
| Variceal Bleeding | 2 | 1 |  |  |
| Hepatocellular carcinoma  Cholangiocarcinoma  Hemoperitoneum  Other with liver failure § | 3  1  0  2 | 2  0  1  0 |  |  |
| Not related to cirrhosis  Myocardial infarction  Hemorrhagic stroke | 0 | 2 (2%)  1  1 |  |  |

**LEGEND FOR TABLE 4:**

\* Values indicate the hazard ratio of each cause of mortality in the guided-therapy group as compared to the control group. CI stands for confidence interval.

† 9 patients in the placebo group and 4 in the β-blockers group died after developing decompensation of cirrhosis. In the pacebo group, 2 patients died of liver-related causes with compensated cirrhosis: 1 from an advanced hepatocellular carcinoma and 1 from a cholangiocarcinoma. In the β-blockers group, 2 patients died of liver-related causes with compensated cirrhosis: 1 from an advanced hepatocellular carcinoma and 1 from a hemoperitoneum.

‡ In the placebo group, 1 patient died of SBP, 1 patient died of necrotizing pneumonia and 1 patient died of a urinary tract sepsis. In the β-blockers group, 1 patient died of a urinary tract sepsis and 1 patient died of a postoperative septic shock.

§ In 2 patients of the placebo group, the cause of death was not specified. At the time of death, these 2 patients had decompensated cirrhosis and were Child-Pugh C with MELD score >20.

**Authors and contributors**

All authors contributed to the design, vouch for integrity and accuracy of analysis, for fidelity to the protocol and to draft the manuscript and submission for publication. The trial was monitored by an independent data-and-safety monitoring board. No one who is not an author contributed to the manuscript.

All the authors meet all four criteria for authorship in the ICMJE Recommendations:

All had substantial contributions to the conception or design of the work and the acquisition, analysis, or interpretation of data for the work. All contribute to drafting the work and/or revising it critically for important intellectual content, they all gave final approval of the version to be published and they all agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

**FIGURE LEGENDS**

**Figure 1**

*Title: “Screening, Randomization and Follow-up”*

During the study period, 631 patients with compensated cirrhosis were screened and 237 had one or more exclusion criteria (35 had previous decompensation of cirrhosis, 34 presence of high-risk esophageal varices, 13 previous treatment with β-blockers, 20 contraindication to β-blockers, 16 were on anticoagulants, 16 had an age <18 years or >80 years, 14 had baseline bilirubin>3 mg/dl, 7 had co-morbidity with life expectancy <12 months, 26 had more than one of the previous criteria and 56 had other reasons). Of the 394 eligible patients, 101 refused to participate in the study and 83 had no CSPH. Finally, 210 were included and of these, 141 patients were titrated on propranolol and 69 patients were titrated on carvedilol. Of the 210 patients initially included, 9 were withdrawn during the titration period because they were found to be ineligible. Finally, 201 patients were randomized, 101 of them were treated with placebo and 100 were treated with β-blockers (67 of them received propranolol and 33 received carvedilol).

Reasons for discontinuation of the trial did not differ significantly between the two groups. A total of 17 patients in the β-blocker-group were lost to follow-up or withdrew, as did 13 in the placebo-group (P = 0.435). In the β-blocker-group 2 patients were withdrawn by the attending physician to receive antiviral therapy for HCV with DAA and 6 withdrew consent. In the placebo-group these figures were 3 and 6, respectively.

**Figure 2**

*Title: Heart rate and HVPG throughout the study*

\* P ≤0.05 vs baseline value within the group; † P ≤0.01 vs baseline value within the group; ‡ P ≤0.05 between values of both groups; § P ≤0.01 between values of both groups.

Panel A shows the Heart Rate (mean [95%CI]) in both groups at each control during the follow-up. Patients in the NSBB-group had a significant decrease at each control visit, which was not observed with placebo. Patients in the NSBB-group had an average reduction from baseline of 17%. Patients in the placebo-group had an average increase of 4%.

Panel B shows the HVPG (mean [95%CI]) in both groups at baseline and at each year control. HVPG had a significant decrease throughout each control in the NSBB-group which was not observed with placebo. In the NSBB-group, the HVPG had an average reduction from baseline of 11% [6% to 15%] and in the placebo group had an average increase of 1% [-2% to 5%].

Panel C shows percentage changes of HVPG (mean [95%CI]) from baseline at each year control in the overall series of patients (whatever the treatment received), comparing those who developed the primary end-point (red dashed line) vs those who did not (solid blue line). Patients developing the outcome had an average, not significant, increase in HVPG from baseline of 2% [-5% to 10%]. Patients without the primary outcome had a significant decrease throughout each year control, with an average reduction of 7% [2% to 10%].

**Figure 3**

*Title: Primary end-point (decompensation or death) according to treatment group*

Panel A shows the cumulative incidence of developing decompensation and/or death during follow-up in both groups. The risk was significantly lower in the NSBB-group than in the placebo-group (HR= 0.51, 95% CI= 0.27 to 0.97; P=0.041 by Gray test). The numbers of patients at risk at the start of each 6-months period of follow-up are shown, along with the numbers of patients with primary outcome (with the number of those who died within brackets) and the numbers of patients with censoring events. Two non-liver related deaths in the NSBB-group occurred at months 3 (hemorrhagic stroke) and 13 (myocardial infarction). 77 patients in the NSBB-group and 68 in the placebo-group were censored due to: 13 lost to follow-up (9 in NSBB-group), 12 withdrawn consent (6 in each group), 5 were withdrawn by a physician to receive antiviral therapy (2 in NSBB-group) and the remaining were censured due to the end of the study. Censoring events are detailed in the supplementary appendix.

Panel B shows the Forest plots with hazard ratios and the 95% CI for the primary end-point (decompensation and/or death) according to pre-specified subgroups. The benefit of NSBB therapy was consistent across pre-specified subgroups and appeared to be particularly pronounced in patients with small varices and in patients with non-alcoholic cirrhosis.

**Figure 4**

*Title: Risk of ascites according to treatment group and primary end-point according to hemodynamic response*

Panel A shows the cumulative incidence of developing ascites during follow-up in the two treatment groups by competing risk analysis, considering non-liver related deaths as competing events. The risk was significantly lower in the NSBB-group than in the placebo-group (HR= 0.42, 95% CI= 0.19 to 0.92; P=0.030 by Gray test).

Panel B shows the cumulative incidence of developing the primary end-point (decompensation and/or death) during follow-up in patients who at 1-year had a decrease in HVPG >10% from baseline or to <10mmHg Vs patients without such HVPG response. Six of 63 patients (9%) with such an HVPG decrease and 26 of the 93 patients (28%) without the HVPG decrease developed the primary end-point (HR= 0.32, 95% CI= 0.13 to 0.75; P=0.008 by Gray test).