A Prognostic Strategy Based on Stage of Cirrhosis and HVPG to Improve Risk Stratification After Variceal Bleeding

Vincenzo La Mura, Marta Garcia-Guix, Annalisa Berzigotti, Juan G. Abraldes, Juan Carlos García-Pagán, Candid Villanueva, and Jaime Bosch

BACKGROUND AND AIMS: A hepatic venous pressure gradient (HVPG) decrease of 20% or more (or ≤12 mm Hg) indicates a good prognosis during propranolol/nadolol treatment but requires two HVPG measurements. We aimed to simplify the risk stratification after variceal bleeding using clinical data and HVPG.

METHODS: A total of 193 patients with cirrhosis (62% with ascites and/or hepatic encephalopathy [HE]) who were within 7 days of bleeding had their HVPG measured before and at 1-3 months of treatment with propranolol/nadolol plus endoscopic band ligation. The endpoints were rebleeding and rebleeding/transplantation-free survival for 4 years. Another cohort (n = 231) served as the validation set.

RESULTS: During follow-up, 45 patients had variceal bleeding and 61 died. The HVPG responders (n = 71) had lower rebleeding risk (10% vs. 34%, \( P = 0.001 \)) and better survival than the 122 nonresponders (61% vs. 39%, \( P = 0.001 \)). Patients with HE (n = 120) had lower survival than patients without HE (40% vs. 63%, \( P = 0.005 \)). Among the patients with ascites/HE, those with baseline HVPG ≤ 16 mm Hg (n = 16) had a low rebleeding risk (13%). In contrast, among patients with ascites/HE and baseline HVPG > 16 mm Hg, only the HVPG responders (n = 32) had a good prognosis, with lower rebleeding risk and better survival than the nonresponders (n = 72) (respective proportions: 7% vs. 39%, \( P = 0.018 \); 56% vs. 30% \( P = 0.010 \)). These findings allowed us to develop a strategy for risk stratification in which HVPG response was measured only in patients with ascites and/or HE and baseline HVPG > 16 mm Hg. This method reduced the “gray zone” (i.e., high-risk patients who had not died on follow-up) from 46% to 35% and decreased the HVPG measurements required by 42%. The validation cohort confirmed these results.

CONCLUSIONS: Restricting HVPG measurements to patients with ascites/HE and measuring HVPG response only if the patient’s baseline HVPG is over 16 mm Hg improves detection of high-risk patients while markedly reducing the number of HVPG measurements required. (Hepatology 2020;72:1353-1365).

Variceal bleeding is a major complication of cirrhosis, with a high risk of rebleeding and high mortality in untreated patients. This makes it mandatory to implement effective therapy, which nowadays consists of the combination of nonselective beta-blockers (NSBBs) and repeat endoscopic band ligation sessions.\(^1\,\,^2\) The hepatic venous pressure gradient (HVPG) provides valuable prognostic information in patients with cirrhosis during the prevention of recurrent variceal bleeding.\(^3\,\,^4\) Many studies\(^5\,\,^8\) and meta-analyses\(^9\,\,^10\) have consistently
have a high mortality risk, which has led to the recommendation that the main goal of therapy in such cases be survival. Current recommended therapy for the prevention of variceal rebleeding is the combination of NSBBs plus endoscopic band ligation (EBL) for patients with or without ascites/HE. This study explores in a large cohort of patients receiving the recommended treatment for prevention of variceal rebleeding whether considering the presence/absence of ascites and/or HE and adding the finding of a baseline HVPG below or over 16 mm Hg to the traditional criteria of hemodynamic response may improve risk stratification and simplify the use of HVPG-based therapeutic decisions.

**Patients and Methods**

**STUDY COHORTS**

The study cohort consisted of n = 193 patients with cirrhosis receiving NSBBs and EBL for preventing variceal rebleeding at the Liver Unit, Hospital Clinic, Barcelona, and at the Gastroenterology Division, Hospital de Sant Pau, Barcelona, in whom HVPG response to NSBBs (after 1-3 months on NSBBs) was evaluated and who were included in previously published studies. This study is a nested retrospective analysis using the initial database. Inclusion criteria for the present study were diagnosis of cirrhosis (based on liver biopsy and/or unequivocal clinical data and compatible findings on imaging techniques), admission for variceal bleeding within the previous 7 days, baseline...
HVPG values of at least 12 mm Hg, subsequent long-term treatment with NSBBs (propranolol or nadolol) combined with repeated EBL sessions, and a second HVPG measurement after 1-3 months of continued pharmacological therapy. Patients with hepatocellular carcinoma at baseline, portal vein thrombosis, contraindications to beta-blockers, previous transjugular intrahepatic porto-systemic shunt (TIPS) or surgical shunts, or cholestatic liver disease were excluded. A total of 231 patients who received NSBBs without concomitant EBL, who were included in previous studies from the same institutions,\(^{5,30,34,35}\) and who had baseline and repeat HVPG measurements served as a validation cohort of the proposed strategy for risk stratification. Both in the training and validation cohorts, patients were considered positive for ascites if they presented clinical evidence of ascites at inclusion or if they had clinically evident ascites confirmed by paracentesis in the previous 12 months. HE was considered to be present when clinically evident (grade ≥ 2 in the West Haven scale) and diagnosed by a physician during hospital admission or at an outpatient visit. All included patients gave their informed consent to the initial studies. The retrospective collection of clinical and hemodynamic data for the current study was approved by the ethical committee for clinical investigation of the Hospital Clinic in Barcelona.

HEMODYNAMIC MEASUREMENTS

Baseline hemodynamic studies were performed before starting NSBBs for prevention of variceal rebleeding. The study was performed after the patients were in stable conditions, at days 4-7 after admission for variceal bleeding. Briefly, under local anesthesia, a venous introducer was placed in the right internal jugular vein using the Seldinger technique. Under fluoroscopy, a 7F balloon-tipped catheter was advanced into the main right hepatic vein for measuring wedged hepatic venous pressure (WHVP) and free hepatic venous pressure (FHVP) as previously described.\(^{6}\) WHVP was measured after verifying adequate occlusion of the hepatic vein by the inflated balloon, while FHVP was measured at 2-3 cm of the outlet of the hepatic vein into the inferior vena cava. All measurements were taken in triplicate. Permanent tracings were obtained in a multichannel recorder (Mac-Lab, GE Healthcare [Freiburg, Germany] for Hospital Clinic; PowerLab 8SP, ADInstruments [Sydney, Australia] for Hospital Sant Pau), and were reviewed specifically for this study by experienced investigators (V.L.M., J.G.A., J.C.G.P., J.B., and C.V.) who were unaware of the clinical data of the patients.

HVPG was calculated as the mean of triplicate measurements of WHVP and FHVP. The second hemodynamic study to evaluate the hemodynamic response to NSBBs was performed 1-3 months later, after the patient had reached a stable dose of the NSBBs for at least 2 weeks.

TITRATION OF NSBBs AND FOLLOW-UP

After the hemodynamic evaluation, all patients were started on oral propranolol (20 mg twice daily) or nadolol (20 to 80 mg once daily), which were increased stepwise, if clinically tolerated, until heart rate had fallen to 50-55/minute, and systolic blood pressure was > 90 mm Hg up to a maximum of 320 mg/day for propranolol or 240 mg/day for nadolol.

The first EBL session was performed at admission for the control of acute variceal bleeding. Sessions were repeated every 3-4 weeks until variceal eradication.\(^{29}\) Follow-up endoscopies were scheduled at 3 months, 6 months, and every 12 months thereafter. In case of variceal recurrence, additional EBL sessions were performed. All patients were followed up in the outpatient clinic at 1, 3, and 6 months, and every 3-6 months thereafter. Medical history, physical examination, biochemistry, hematologic tests, and abdominal ultrasound were performed every 6 months. Follow-up data were collected for up to 4 years (follow-up was extended for those patients censored at 2 years in the original studies), or until death or orthotopic liver transplantation (OLT). Patients who stopped NSBBs were censored the day of drug withdrawal (per treatment-received analysis). Clinical events assessed were rebleeding, death, or liver transplantation defined according to Baveno criteria.\(^{2}\) Patients who discontinued propranolol/nadolol were censored at the time of treatment discontinuation; the same was done for patients who received TIPS during the follow-up.

STATISTICAL ANALYSIS

Statistical analysis was performed with SPSS 19.0 package (SPSS, Chicago, IL) and R (http://www.r-project.org). Data are reported as frequencies or means
with SD. Comparisons for continuous and categorical data were performed with unpaired Student t-test, Mann-Whitney U test, or Fisher’s exact test as appropriate. For the survival analysis, we considered two clinical endpoints: rebleeding and rebleeding/OLT-free survival. Rebleeding risk was tested as cumulative incidence function, which takes into account death or liver transplantation as competing risks. Rebleeding and OLT-free survival on follow-up are depicted using Kaplan-Meier curves. The log-rank test was used to compare the groups considered in this analysis. The hazard ratios (HRs) of association with rebleeding and survival were adjusted by introducing independent variables in the Fine-Gray model for competing risk analysis and the multivariable Cox proportional hazards model, respectively. Redundant variables were not introduced in the final analysis. The contribution of each variable was estimated by the HR with its 95% confidence intervals (CIs). Comparison of the number of patients misclassified as belonging to a high-risk category by traditional criteria and by the criteria derived from the study was done using the McNemar test. A strategy for risk stratification based on baseline HVPG, presence/absence of ascites/HE, and HVPG response were constructed. Significance was established at $P < 0.05$.

**Results**

**CLINICAL AND HEMODYNAMIC CHARACTERISTICS OF PATIENTS INCLUDED IN THE STUDY**

A total of 193 patients were included in the study cohort. Clinical characteristics and hemodynamic data of the patients are reported in Table 1. Seventy-one (37%) patients exhibited a fall in HVPG below 12 mm Hg or at least 20% of the baseline value and were considered “HVPG-responders” to continued administration of NSBBs; 122 (63%) patients were nonresponders. As per current recommendations, both responders and nonresponders were kept on NSBBs treatment and continued EBL. For 73 patients (38%), bleeding alone was the index manifestation of clinical decompensation, whereas for 120 patients (62%), bleeding occurred as a further decompensation on top of ascites (n = 74; 38%), HE (n = 5; 3%), or ascites plus HE (n = 41; 21%). Because the number of patients with HE alone (on top of bleeding) were only 5, these were added to the other 74 patients with ascites alone to make up a group of 79 patients with bleeding + ascites/HE (41%). A comparison of the clinical characteristics and hemodynamics in these different stages of decompensation is summarized in Table 1. As indicated, patients presenting only with bleeding had better liver function, lower portal pressure, and were more frequently HVPG-responders to continued administration of NSBBs than the other groups.

**PROGNOSIS ACCORDING TO HVPG RESPONSE**

During follow-up (median of 31 months), 45 patients experienced variceal rebleeding, 61 patients died, and 10 were transplanted in accordance with the local transplantation policy based on Model for End-Stage Liver Disease (MELD) score and at least 6 months of verified abstinence from alcohol. Rebleeding occurred in 39 of 122 nonresponders versus 6 of 71 HVPG responders (cumulative 4-year rebleeding risk: 34% vs. 10%; HR: 4.332, 95% CI: 1.854-10.075; $P = 0.001$) (Fig. 1A-C). According to HVPG response, 83 of 122 (68%) nonresponders (representing 43% of the cohort) were misclassified as high risk, as they did not rebleed on follow-up (gray zone). The cumulative 4-year OLT-free survival was 61% in responders versus 39% in nonresponders (HR: 2.142, 95% CI: 1.321-3.474; $P = 0.002$).

**PROGNOSIS ACCORDING TO PRESENCE OF ASCITES/HE AND TO BASELINE HVPG > 16 MM HG**

As expected, the presence of other manifestations of clinical decompensation at the moment of bleeding (ascites and/or HE; n = 120) markedly influenced 4-year survival (40% vs. 63%, $P = 0.005$). The rebleeding risk increased and survival progressively worsened with increasing number of manifestations of decompensation (e.g., patients with bleeding as the only decompensation event vs. patients with bleeding + ascites/HE vs. patients with bleeding + ascites + HE). Specifically, in the 79 patients presenting with bleeding + ascites/HE, 4-year rebleeding was 21% and survival was 48%, which were better than those observed in the 41 patients presenting with...
|                          | Overall | Bleeding as Only Decompensation | Bleeding + Ascites/HE | Bleeding + Ascites + HE | P Linear Trend | Bleeding + Ascites and/or HE | P* |
|--------------------------|---------|---------------------------------|----------------------|------------------------|---------------|-------------------------------|-----|
| Number of patients       | 193     | 73                              | 79                   | 41                     | —             | 120                           | —   |
| Age (years)              | 58 (12) | 56 (12)                         | 60 (10)              | 57 (13)                | 0.447         | 59 (11)                       | 0.081 |
| Sex (% male)             | 75      | 74                              | 73                   | 78                     | 0.680         | 75                            | 0.866 |
| Alcohol etiology (% of patients) | 60 | 52                              | 65                   | 66                     | 0.108         | 65                            | 0.095 |
| Active alcoholism (% of patients) | 50 | 45                              | 50                   | 56                     | 0.264         | 52                            | 0.375 |
| MELD score              | 13.2 (4.3) | 11.4 (2.5)                     | 13.2 (4.0)           | 16.7 (5.2)             | <0.001        | 14.4 (4.7)                    | <0.001 |
| Ascents (% of patients)  | 60      | 0                               | 94                   | 100                    | <0.001        | 96                            | <0.001 |
| Hepatic encephalopathy (% of patients) | 24 | 0                               | 6                    | 100                    | <0.001        | 38                            | <0.001 |
| Albumin (g/L)            | 28.4 (5.4) | 30.5 (4.9)                     | 28.9 (4.6)           | 23.3 (4.5)             | <0.001        | 27.0 (5.2)                    | <0.001 |
| Bilirubin (mg/dL)        | 2.5 (2.7) | 1.9 (1.2)                      | 2.3 (1.8)            | 4.2 (4.9)              | <0.001        | 2.9 (3.3)                     | 0.007 |
| Creatinine (mg/dL)       | 1.00 (0.74) | 0.83 (0.20)                    | 1.05 (0.75)          | 1.21 (1.17)            | 0.008         | 1.11 (0.92)                   | 0.002 |
| Hematocrit (%)           | 27.8 (5.4) | 29.8 (4.5)                     | 27.2 (5.6)           | 25.3 (5.3)             | <0.001        | 26.6 (5.5)                    | <0.001 |
| Sodium (mEq/L)           | 137 (4)  | 137 (4)                         | 136 (5)              | 137 (6)                | 0.475         | 136 (5)                       | 0.154 |
| Platelets (10^9/mm^3)    | 96.9 (49.0) | 89.7 (46.5)                    | 101.4 (45.8)         | 101.3 (57.9)           | 0.166         | 101.4 (50.1)                  | 0.109 |
| Prothrombin activity (%) | 6.2 (14) | 68.1 (13.0)                    | 62.1 (13.6)          | 54.7 (11.7)            | <0.001        | 59.5 (13.4)                   | <0.001 |
| Small/large varices (% of patients) | 694 | 10/90                           | 4/96                 | 5/95                   | 0.225         | 4/96                          | 0.136 |
| % of patients who stopped NSBBs | 7 | 6                               | 9                    | 5                      | 0.944         | 8                             | 0.773 |
| Basal HVPG (mm Hg)       | 20.8 (4.7) | 19.6 (4.9)                     | 21.4 (4.4)           | 22.0 (4.8)             | 0.007         | 21.6 (4.5)                    | 0.006 |
| Patients with basal HVPG ≤ 16 mm Hg (%) | 18 | 25                              | 14                   | 12                     | 0.064         | 13                            | 0.053 |
| HVPG decrease (%) during NSBBs | 12.6 (17.2) | 14.4 (19.1)                    | 13.1 (15.6)          | 8.2 (16.5)             | 0.084         | 11.5 (16.0)                   | 0.254 |
| HVPG-responders (%)      | 37      | 47                              | 37                   | 20                     | 0.005         | 31                            | 0.032 |

*P value < 0.05 indicates a significant difference between the cohort presenting with bleeding as the only decompensation event versus bleeding on top of ascites and/or HE.
**FIG. 1.** Traditional method of using HVPG response (A) to stratify the rebleeding risk at 4 years (B) and rebleeding/OLT-free survival (C).
bleeding + ascites + HE who had greater rebleeding risk (38%) \( (P = 0.062) \) and worse survival (24%) \( (P = 0.036) \).

As for baseline HVPG, 34 patients (18%) had a pretreatment HVPG ≤ 16 mm Hg. This was associated with a low rebleeding risk even in patients with poor prognostic indicators. Indeed, rebleeding was low and similar in the 16 patients with baseline HVPG ≤ 16 mm Hg presenting with bleeding + ascites and/or HE as in the 19 HVPG non-responders with baseline HVPG ≤ 16 mm Hg (13% and 12%, respectively). The corresponding survival figures were also similar: 47% and 52%.

In contrast, in patients with a combination of negative prognostic markers, such as patients presenting with bleeding plus ascites and/or HE who had a baseline HVPG > 16 mm Hg, the HVPG response to NSBBs strongly correlated with the outcomes. In this subgroup, nonresponders \( (n = 72) \) had a 39% rebleeding risk, much higher than the 7% observed in hemodynamic responders \( (n = 32) \) and the 13% of rebleeding risk already shown in patients presenting with bleeding plus ascites and/or HE who had baseline HVPG ≤ 16 mm Hg \( (n = 16) \) \( (P = 0.018) \) (Supporting Fig. S1A). Survival was also worse in patients presenting with bleeding plus ascites and/or HE together with a baseline HVPG > 16 mm Hg and who were nonresponders to NSBBs (30%), as compared with patients in the same category who were either HVPG responders (56%) or who had a baseline HVPG ≤ 16 mm Hg (47%) \( (P = 0.010) \) (Supporting Fig. S1B).

**REFINING RISK STRATIFICATION IN CIRRHOSIS: A CLINICAL AND HEMODYNAMIC APPROACH**

These data allow us to establish an approach for risk stratification in patients with cirrhosis surviving an episode of variceal bleeding. Given the high survival (63%) of patients with only variceal bleeding, this approach takes into account, first of all, the presence of ascites and/or HE in addition to bleeding, and secondly, the baseline HVPG. This restricts the measurement of baseline HVPG to patients with ascites and/or HE when admitted for bleeding and restricts the assessment of the hemodynamic response to those with ascites and/or HE who have a baseline HVPG > 16 mm Hg (Fig. 2A). Using this approach, rebleeding occurred in 27 of 72 of patients classified as “high risk” (i.e., those with ascites and/or HE, baseline HVPG > 16 mm Hg, and absence of hemodynamic response) versus 18 of 121 of the “low-risk patients” (cumulative 4-year rebleeding risk: 39% vs. 17%; HR: 2.882, 95% CI: 1.609-5.164; \( P < 0.001 \)) (Fig. 2B).

It is worth noting that a sensitivity analysis demonstrated that a range of baseline HVPG from 15 to 17 mm Hg performed similarly, but 16 mm Hg was the best cutoff to use as an additional prognostic criterion on top of ascites/HE. This indicates that our finding is robust, as the variability of HVPG measurements is below 1 mm Hg.\(^{(38)}\) We also performed an exploratory analysis comparing patients with and without active alcohol consumption (patients with active alcohol intake: \( n = 58 \) low risk, \( n = 37 \) high risk; patients without active alcohol consumption: \( n = 63 \) low risk, \( n = 34 \) high risk), and the discriminative ability of the algorithm for survival did not change (data not shown).

The proposed approach reduced the number of patients incorrectly classified as high risk for rebleeding. The number and relative proportion of patients who did not rebleed on follow-up among the group classified as high risk using the traditional and the proposed strategies were, respectively, 83 of 122 (68%, corresponding to 43% of the total cohort) and 45 of 72 (62%, corresponding to 23% of the total cohort) \( (P < 0.001; \) McNemar test), whereas the number of patients who rebled among the low-risk group were 6 of 71 (8.4%) for the old strategy and 18 of 121 (14.8%) for the proposed strategy (corresponding to 3% and 9% of the total cohort, respectively). This suggests that the proposed strategy performs better among high-risk patients. Similar findings were observed for survival. Indeed, the number of patients misclassified as high risk for the old and the proposed strategy for this endpoint was 56 of 122 (46%, or 29% of the total cohort) versus 25 of 72 (35%, or 13% of the total cohort), respectively \( (P < 0.001, \) McNemar test). The corresponding numbers of misclassified low-risk patients with regard to mortality were 22 of 71 (31%) using the traditional strategy, and of 41 of 122 (33%) when using the proposed strategy.

Moreover, the proposed strategy allowed a markedly decreasing number of hemodynamic measurements needed for risk stratification. Thus, 73 patients without ascites/HE would not need any measurement, 16 patients with ascites and/or HE and a baseline
FIG. 2. Proposed method of using ascites and/or HE, basal HVPG of 16 mm Hg, and HVPG response (A) to stratify the rebleeding risk at 4 years (B) and rebleeding/OLT-free survival (C).
HVPG $\leq 16$ mm Hg would need only one measurement, and 104 with ascites and/or HE and a baseline HVPG $>16$ mm Hg would need two measurements, for a total of 224 HVPG measurements versus 386 using the traditional HVPG response-based risk assessment, thus saving 42% of HVPG measurements (Fig. 3).

The proposed strategy had an excellent prognostic value for survival free of rebleeding or OLT. This was analogous to that obtained by measuring the HVPG response (Fig. 2C), but saving 42% of the HVPG examinations.

Variables that in univariate analysis were found to be significantly associated with being a high-risk patient (Supporting Table S1) and with rebleeding and survival on follow-up (Supporting Table S2) were introduced in a multivariate analysis (Table 2). Belonging to the high-risk group was the only independent predictor of rebleeding (HR: 2.739, 95% CI: 1.436-5.226; $P = 0.002$) and the strongest predictor of survival free of rebleeding/OLT (HR: 2.539, 95% CI: 1.546-4.169; $P < 0.001$), followed by low serum sodium levels (HR: 0.943, 95% CI: 0.899-0.990; $P = 0.018$).

### Table 2. Multivariate Analysis for Rebleeding and Rebleeding/OLT-Free Survival

| Independent Variables                          | Rebleeding                        | Survival (Free of Rebleeding/OLT) |
|------------------------------------------------|-----------------------------------|-----------------------------------|
|                                                | Competing Risk Analysis/Fine-Gray Model | Cox Proportional Hazard Model |
| Age (per year of increase)                      | HR 95% CI $P$                      | HR 95% CI $P$                      |
| MELD score (per one unit of increase)           | 1.000 0.934-1.071 1.000          | 1.042 0.993-1.095 0.097          |
| Hematocrit (per % of increase)                  | 0.984 0.926-1.045 0.623          | 0.989 0.942-1.038 0.657          |
| Albumin (per g/L of increase)                   | 0.997 0.935-1.063 0.593          | 1.003 0.957-1.052 0.886          |
| Sodium (per mEq/L of increase)                  | NA NA NA                         | 0.943 0.899-0.990 0.018          |
| High risk (ascites/HE, HVPG $>16$ mm Hg, and HVPG nonresponders) | 2.739 1.436-5.226 0.002 | 2.539 1.546-4.169 <0.001 |

Note: In the proposed strategy, the HRs for the condition of being high risk were adjusted for all variables differently distributed in high-risk versus low-risk patients and associated with the event at the univariate analysis with a $P < 0.1$ for each clinical endpoint (see Supporting Tables S1 and S2).

Abbreviation: NA, not applicable.
P = 0.018) and with a residual trend for MELD score (HR: 1.042, 95% CI: 0.993-1.095; P = 0.097).

**VALIDATION SET**

Supporting Table S3 reports the clinical characteristic of the 231 patients included in the validation set. Over the 4-year follow-up, 65 patients experienced variceal rebleeding, 57 patients died, and 18 were transplanted.

As depicted in Fig. 4, the prognostic performance of the proposed strategy was successfully validated both for risk of rebleeding (Fig. 4A) and survival (Fig. 4B).

**Discussion**

In this study we present an approach that simplifies and improves the risk stratification in patients with cirrhosis who receive the recommended treatment with NSBBs and EBL to prevent recurrent variceal bleeding. This strategy, derived from a thorough analysis of two large cohorts of patients (training and validation sets), is based on incorporating data on the stage of decompensation of cirrhosis and the results of baseline HVPG measurements. In this approach, HVPG measurements are performed at time of the index bleed only in patients with ascites and/or HE, and assessment of the HVPG response to NSBBs is performed only if the baseline HVPG is over 16 mm Hg. Therefore, low-risk patients are considered those with variceal bleeding who have no ascites/HE, as well as patients with ascites and/or HE but with baseline HVPG ≤ 16 mm Hg. In contrast, the proposed method considers high-risk patients as those with variceal bleeding who also have all of the following: (1) ascites and/or HE, (2) HVPG > 16 mm Hg before starting NSBBs, and (3) lack of an adequate hemodynamic response to continued NSBBs (failure to decrease HVPG by at least 20% of baseline or ≤ 12 mm Hg).

This strategy is superior to the traditional one in several ways. First, it have obviated any hemodynamic measurements in 38% of our patients (i.e., those without ascites or HE at time of the index variceal bleeding) and would have restricted measuring the HVPG response to NSBBs in 54% of patients (instead of 100% in the traditional strategy). This reduces the

![Validation set (n = 231 patients who received NSBBs for rebleeding prophylaxis): The prognostic performance of the proposed strategy, which considers patients to be at high risk if they present with ascites and/or HE, basal HVPG > 16 mm Hg, and nonresponsive to NSBBs, was excellent both with regards to Rebleeding (panel A) and Survival (panel B).](image-url)
number of hepatic vein catheterization studies to be performed by almost half, thus halving the economic cost, health care burden, and patient discomfort required in the previous strategy of risk stratification. Second, this strategy is associated with an improved accuracy of the prediction of patients at high risk of rebleeding or death during a 4-year follow-up. With regard to rebleeding, the number of patients classified as high risk but who do not bleed during the follow-up (the so-called “gray zone”) decreased from 83 with the traditional strategy to 45 with the proposed strategy (from 43% to 23% of the total cohort). Third, this approach also predicted survival free of OLT and rebleeding, an endpoint that is more important than rebleeding alone in patients with advanced liver failure, particularly when bleeding occurs in patients with ascites and/or HE, a subgroup in whom death is frequent and the most relevant event.\(^{(2,28,29)}\)

For all of these reasons, it is possible that this strategy for risk stratification, with much better cost-effectiveness than the traditional one, might lead to changes in the approach to treatment. This is particularly likely considering that HVPG-guided therapy improved the outcome of therapy in a recent trial.\(^{(39)}\) High-risk patients are usually considered for TIPS or liver transplantation at tertiary care centers. It is likely that in these circumstances it would be easier to implement a therapeutic protocol including stratification based on clinical data and HVPG. The practical implication of applying this method can only be addressed by an adequately designed study. However, this strategy has the potential to be a better selector of the group of high-risk patients, by markedly reducing its number and by having lower gray zones for rebleeding and death (i.e., patients included in the high-risk group category who do not bleed or die on follow-up).\(^{(11)}\) It is possible that this high-risk group of patients could benefit from a more aggressive therapeutic approach, such as by using TIPS. As shown in previous studies both for acute bleeding\(^{(40)}\) and for “difficult ascites,”\(^{(41)}\) advancing a decision for TIPS (instead of using it as rescue therapy after failure of standard treatment) may be life-saving. Therefore, it may be worth trying this approach in the high-risk population as defined by patients with ascites, HVPG > 16 mm Hg, and nonresponders to propranolol.

Importantly, the concept that patients with several decompensating events (e.g., bleeding + ascites and/or HE) have the worst prognosis is in line with the recent survival models proposed for the natural history of cirrhosis.\(^{(27,29)}\) The prognostic information provided by the cutoff of 16 mm Hg is not entirely new, as five previous studies showed it to be a predictor of survival.\(^{(8,23-26)}\) However, none of these studies investigated its prognostic value in the context of the medical treatment of portal hypertension.

Our study has strengths and limitations. A major strength is that it is based on large number of patients, both for the training and the validation cohorts, and mostly included in prospective clinical trials in two expert centers, so the results are robust. Among the limitations, the subgroup of patients with only HE on top of variceal bleeding was quite small (n = 5), so its role in aggravating the prognosis of patients with bleeding and ascites could not be fully characterized. This is why we pooled these patients with those with ascites on top of bleeding. Second, from this study we cannot extrapolate whether the prognostic value of the proposed approach would extend to patients treated prophylactically, before the first bleeding or clinical decompensation, who have a much lower risk of bleeding and death. Finally, the fact that the strategy still includes HVPG measurements in some of the patients also constitutes a limitation, as the cost and invasive nature of the technique may be prohibitive. However, noninvasive methods are evolving and may in the future substitute invasive HVPG measurements for risk stratification.\(^{(42)}\)

In summary, we have demonstrated in a large cohort of patients with cirrhosis presenting with a recent episode of variceal bleeding that the absence of ascites/HE and the finding of a baseline HVPG < 16 mm Hg represent additional criteria of good outcome during subsequent treatment with the standard of care (NSBBs plus EBL). Restricting the measurement of HVPG response to patients presenting with ascites and/or HE at the time of bleeding, who have a basal HVPG > 16 mm Hg, significantly decreases the gray zone, and reduces the number of HVPG measurements required for risk stratification by 42%. Therefore, this strategy has advantages over the previously defined criteria for a good hemodynamic response to beta-blockers and may facilitate adopting therapeutic decisions based on expected outcomes and risk stratification.

Acknowledgment: We thank Drs. Eyal Ashkenazi, Andrea Ribeiro de Souza, and Oana Pavel for helping
during the initial steps of data collection, and Rosa Saez, Angels Barinco, and Laura Rocabert for their expert technical support.

**Author Contributions:** J.B. and V.L.M. were responsible for the study concept and design. V.L.M. and M.G.G. were responsible for the data acquisition. V.L.M., J.G.A., A.B., J.C.G.P., C.V., and J.B. were responsible for the analysis and interpretation of data. V.L.M. and J.B. were responsible for drafting the manuscript. J.B., C.V., J.C.G.P., A.B., and J.G.A. were responsible for critical revision of the manuscript for important intellectual content. V.L.M., J.G.A., and A.B. were responsible for the statistical analysis. J.B. was responsible for the study supervision and obtaining funding.

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Author names in bold designate shared co-first authorship.

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