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CLINICAL LIVER

Addition of Simvastatin to Standard Therapy for the Prevention of Variceal Rebleeding Does Not Reduce Rebleeding but Increases Survival in Patients With Cirrhosis

Juan G. Abraldes,[1,*] **Candid Villanueva**,[2,*] Carles Aracil,[3] Juan Turnes,[4] Manuel Hernandez-Guerra,[5] Joan Genesca,[6] Manuel Rodriguez,[7] Jose Castellote,[8] Juan Carlos García-Pagán,[1] Ferran Torres,[9] Jose Luis Calleja,[10] Agustin Albillos,[11] and Jaime Bosch,[1,12] for the BLEPS Study Group

[1]Barcelona Hepatic Hemodynamic Laboratory, Liver Unit, Hospital Clínic-Institut D'Investigacions Biomédiques August Pi i Sunyer, University of Barcelona, Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas, Spain; [2]Department of Gastroenterology, Hospital de Sant Pau, Barcelona, Universidad Autònoma de Barcelona, Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas, Spain; [3]Servicio de Gastroenterología, Hospital Universitario Arnau de Vilanova, Institut de Recerca Biomedica, Lleida, Spain; [4]Department of Gastroenterology, Complejo Hospitalario Universitario de Pontevedra, Instituto de Investigación Biomédica, Pontevedra, Spain; [5]Gastroenterology Department, University Hospital of the Canary Islands, Tenerife, Spain; [6]Liver Unit, Hospital Universitari Vall d'Hebron, Vall d'Hebron Institute of Research, Universidad Autònoma de Barcelona, Barcelona, Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas, Instituto de Salud Carlos III, Madrid, Spain; [7]Liver Unit, Hospital Universitario Central de Asturias, Oviedo, Spain; [8]Unidad de Hepatología, Servicio de Aparato Digestivo, Institut d'Investigació Biomèdica de Bellvitge: Hospital Universitari de Bellvitge, L'Hospitalet de Llobregat, Spain; [9]Biostatistics and Data Management Core Facility, Institut D'Investigacions Biomédiques August Pi i Sunyer, Hospital Clinic Barcelona, Spain and Biostatistics Unit, Faculty of Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain; [10]Liver Unit. Hospital U. Puerta de Hierro. Universidad Autònoma de Madrid, Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas, Spain; [11]Department of Gastroenterology, Hospital Universitario Ramón y Cajal, Instituto Ramón y Cajal de Investigación Sanitaria, University of Alcalá, Madrid, Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas, Spain; [12]Swiss Liver Center, Inselspital, Bern, Switzerland

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BACKGROUND & AIMS: The combination of β-blockers and band ligation is the standard approach to prevent variceal rebleeding, but bleeding recurs and mortality is high. The lipid-lowering drug simvastatin decreases portal pressure, improves hepatocellular function, and might reduce liver fibrosis. We assessed whether adding simvastatin to standard therapy could reduce rebleeding and death after variceal bleeding in patients with cirrhosis. **METHODS:** We performed a multicenter, double-blind, parallel trial of 158 patients with cirrhosis receiving standard prophylaxis to prevent rebleeding (a β-blocker and band ligation) in Spain from October 2010 through October 2013. Within 10 days of bleeding, subjects were randomly assigned, but stratified by Child-Pugh class of A or B vs C, to groups given simvastatin (20 mg/d the first 15 days, 40 mg/d thereafter; n = 69) or placebo (n = 78). Patients were followed for as long as 24 months. The primary end point was a composite of rebleeding and death, and main secondary end points were the individual components of the composite (death and rebleeding). **RESULTS:** The primary end point was met by 30 of 78 patients in the placebo group and 22 of 69 in the simvastatin group ($P = .423$). Seventeen patients in the placebo group died (22%) vs 6 patients in the simvastatin group (9%) (hazard ratio for adding simvastatin to therapy = 0.39; 95% confidence interval: 0.15–0.99; $P = .030$). Simvastatin did not increase survival of patients with Child-Pugh class C cirrhosis. Rebleeding occurred in 28% of patients in the placebo group and 25% in the simvastatin group ($P = .583$). Serious adverse events occurred in 53% of patients in the placebo group and 49% in the simvastatin group ($P = .752$); the percentages of serious adverse events related to therapy were 11% in the placebo group vs 8% in the in the simvastatin group ($P = .599$). Two patients in the simvastatin group, each with advanced liver disease, developed rhabdomyolysis. **CONCLUSIONS:** In a randomized controlled trial, addition of simvastatin to standard therapy did not reduce rebleeding, but was associated with a survival benefit for patients with Child-Pugh class A or B cirrhosis. Survival was not the primary end point of the study, so these results require validation. The incidence of rhabdomyolysis in patients receiving 40 mg/d simvastatin was higher than expected. European Clinical Trial Database ID: EUDRACT 2009-016500-24; ClinicalTrials.gov ID: NCT01095185.

Keywords: Liver Disease; Fibrosis; Treatment; Muscle Effects.

*Authors share co-first authorship.

Abbreviations used in this paper: CI, confidence interval; HR, hazard ratio; IQR, interquartile range; MELD, Model for End-Stage Liver Disease; NSBB, nonselective β-blocker.

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Variceal bleeding is a major complication of cirrhosis, with a 6-week mortality rate of 10%–20%. After a variceal bleeding episode, the risk of rebleeding is around 60% during the first year, if the patient is left untreated. The current first-line standard treatment after variceal bleeding is the combination of nonselective β-blockers (NSBBs) and repeated endoscopic variceal ligation until variceal eradication. With this treatment, the 2-year risk of rebleeding (30%) and mortality (25%) are still high.[1] Therefore, there is clearly a need for more effective therapies for the management of these patients.

The major determinants of prognosis after variceal bleeding are the magnitude of the decrease in portal pressure achieved with pharmacologic treatment and the degree of liver dysfunction.[2–6] Therefore, to improve prognosis in patients with variceal bleeding, new treatments should be able to improve liver function and/or further decrease portal pressure.

Several preclinical studies in rodent models of cirrhosis showed a potential benefit of statins on portal hypertension.[7–12] In addition, an initial pilot study in patients with cirrhosis showed that a single dose of oral simvastatin induced an acute decrease in hepatic vascular resistance.[13] A subsequent multicenter randomized placebo-controlled proof-of-concept study showed that 1-month simvastatin treatment induced a decrease in portal pressure and improved indocyanine green clearance, a quantitative test of liver function.[14] These results suggested that simvastatin could improve the outcomes of patients with cirrhosis after acute variceal bleeding by having an impact on the 2 major determinants of prognosis—portal pressure and liver function.

Here we report the results of a randomized double-blind multicenter trial comparing simvastatin with placebo added to standard therapy (endoscopic variceal ligation and NSSBs) to assess if this could decrease rebleeding and death after variceal bleeding in patients with cirrhosis.

Methods

Study Design and Oversight

The BLEPS (Bleeding Prevention With Simvastatin) study was an investigator-initiated multicenter, randomized (1:1), placebo-controlled, double-blind, parallel group trial that enrolled patients from 14 Spanish academic centers. The study protocol and amendments were approved by the Spanish national regulatory authority and the Institutional Review Board or Ethics Committee for Clinical Research at each participating center and the coordinating center. Written informed consent was obtained from all participants and informants, based on local Institutional Review Board requirements. A data monitoring committee composed by a pharmacologist, a biostatistician, and a hepatologist was appointed at the onset of the study and had access to the adverse event reports and the interim analysis. The study was independently monitored by the Clinical Trials Unit at the University of Barcelona. The Spanish Ministry of Health funded the trial through a competitive peer-reviewed grant. The funding agency had no role in the collection, analysis, or interpretation of the data. The trial was registered at European Clinical Trial Database (EUDRACT 2009-016500-24) and at ClinicalTrials.gov (NCT01095185). All authors had access to the study data and had reviewed and approved the final manuscript.

Participants and Eligibility Criteria

The target population of the study was patients with cirrhosis who recovered from a variceal bleeding. Inclusion criteria were age between 18 and 80 years; previous diagnosis of liver cirrhosis; index variceal bleeding within the previous 5–10 days; plan to start standard treatment for the prevention of variceal rebleeding; and, in woman, documented absence of pregnancy and commitment to use adequate contraception, if applicable. Exclusion criteria were pregnancy or lactation; multifocal hepatocellular carcinoma or a single nodule >5 cm in diameter; creatinine >2 mg/dL; Child-Pugh score >13 points; contraindication for statins; HIV infection on protease inhibitors; pretreatment with portosystemic shunt (surgical or percutaneous); index bleeding due to gastric varices; complete portal vein thrombosis or portal vein cavernomatosis; previous treatment with the combination of endoscopic banding ligation and NSBB (before the index episode); and previous treatment with statins within 1 month of randomization.

The study was conducted between October 2010 and October 2013.

Interventions

All patients were started with the standard secondary prophylaxis of variceal bleeding combining endoscopic variceal ligation and NSBB. Treatment with NSBB was initiated at day 5/6 from admission and either propranolol or nadolol were used (depending on each center preference) up to the maximum tolerated dose. The first endoscopic variceal ligation session was performed to treat acute bleeding and sessions were repeated at 2- to 4-week intervals until variceal eradication.

Between days 5 and 10 from the index bleeding, participants were randomized in a 1:1 ratio to receive simvastatin or identical placebo stratified by Child-Pugh class (A/B vs C). Target dose of simvastatin was 40 mg/d as a single dose (2 capsules), with planned titration from a starting dose of 20 mg (1 capsule) and subsequent increase to 2 capsules (40 mg) at day 15 if the initial dose was tolerated. Treatment was maintained for up to 2 years. Patients were followed at day 15, and at months 3, 6, 9, 12, 18, and 24 after randomization. In our previous study,[14] we did not observe any signal of a correlation between baseline cholesterol or changes in cholesterol and hemodynamic effects/adverse events of simvastatin. On these bases, to maintain the blindness throughout the study, cholesterol levels were not measured in the follow-up.

The study medication was stopped if the patients developed the primary end point, underwent liver transplantation, or developed toxicity associated with the medication. An asymptomatic increase in alanine aminotransferase, aspartate aminotransferase, or creatine kinase >3-fold baseline was considered significant drug toxicity. Patients developing a significant episode of variceal rebleeding were treated according to the international guidelines, which recommend the performance of a transjugular intrahepatic portosystemic shunt in the absence of contraindications. Patients were considered compliant with the study protocol if they attended all the study visits, and they brought the empty medication bottles back to the office.

Outcome Measures

The primary efficacy outcome measure was a composite end point defined as all-cause rebleeding (defined as hematemesis or melena leading to hospitalization and diagnosed by a physician) or all-cause death. Two major secondary end points were all-cause death and all-cause rebleeding.

Because this was the first randomized trial assessing the clinical effects of simvastatin in decompensated cirrhosis, we identified the following exploratory secondary end points: recurrent variceal bleeding; number of packed red blood cells transfusions from the first dose of medication; proportion of patients requiring alternative treatment (transjugular intrahepatic portosystemic shunt or portocava shunt surgery; incidence of other decompensations of portal hypertension, defined as ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome; proportion of patients developing de novo or worsening ascites (sustained increase over 2 weeks of diuretics requirements); proportion of patients who develop spontaneous bacterial peritonitis; proportion of patients who develop hepatorenal syndrome; proportion of patients developing de novo or progressed thrombosis in the mesenteric–splenoportal axis; death or transplantation; proportion of patients with any adverse event related to the study drugs; proportion of patients with serious adverse events related to the study drugs; proportion of patients who discontinued the study due to adverse events; and changes in Model for End-Stage Liver Disease (MELD) score at 6 months after starting treatment.

Relevant Amendments to the Study Protocol

After the onset of the trial the period of inclusion was extended from a maximum of 7 days after the index bleeding to 10 days after the index bleeding because it was logistically challenging to get the study medication to the centers by day 7. In addition, the follow-up period was extended from 1 year to 2 years. This was a technicality, determined by the initial funding call, which was for 1-year period.

Sample Size

The probability of death or hemorrhage in patients treated with standard therapy was 36% per year in a very recent Spanish multicenter study.[1] We calculated that 31 events were required to achieve an 80% statistical power to detect an improvement by 21% in the risk of death or bleeding with the addition of simvastatin, with a 4.8% 2-sided adjusted α (5% overall considering the interim analyses, see statistical analysis), and assuming a loss of follow-up of about 5%. According to the expected rates of events, a sample size of 158 patients was estimated.[15]

Randomization

The randomization codes were generated with PROC PLAN of the SAS system at the Pharmacy Department, Hospital Clinic, University of Barcelona. Randomization was stratified by Child-Pugh (A/B vs C). Treatment was assigned through a website-based case report form.

Blinding

All investigators, staff, and participants were masked to treatment assignment. Simvastatin was purchased in 20-mg pills from Ratiopharm Laboratories (Madrid, Spain), and excipients for placebo preparation from Fragon Iberica (Terrasa, Barcelona, Spain). Simvastatin pills (or the corresponding excipients) were encapsulated in 20-mg doses, so that the pills were identical in appearance and organoleptic properties.

Statistical Analysis

The analysis was conducted with the SAS System (version 9.2, SAS Institute, Inc, Cary, NC) according to the general regulatory recommendations given in the guideline International Conference on Harmonization topic E9 about statistical principles for clinical trial guidance,[16] as well as other specific guidance on methodological and statistical issues.[17] A statistical analysis plan was defined between the project statistician (FT) and the study investigators before the conclusion of the study. A data blind review was conducted between the statistician, the leading study monitor, the electronic CRF manager and 2 leading investigators (JGA, JB) before the database lock.

The primary outcome was analyzed as a time to event variable, the survival function was estimated by means of the Kaplan-Meier method and groups were compared with the stratified log-rank test and hazard ratios (HRs) (95% confidence interval [CI]), calculated using the Cox model adjusting by the strata predefined in the design (Child-Pugh A/B vs C). The cutoff point for the statistical significance of the main outcome was set at $P \leq .048$ (α adjustment due to the 2 interim analyses).

Secondary end points. Time-to-event variables were analyzed as detailed for the primary outcome. For binary secondary outcomes, stratum-adjusted rates and P values were estimated from a log-binomial regression adjusting by the predefined strata. The number of packed red blood cell transfusions was compared using the stratified nonparametric van Elteren test using the same predefined strata. Median (95% CI) difference between groups was calculated using the Hodges-Lehmann methods. MELD, as a continuous variable measured repeatedly over time was analyzed through mixed models for repeated measurements.

Interim analysis. Given that this was the first long-term study in cirrhosis with statins, 2 interim analyses were planned, after achieving 10 and 20 events following the Peto-Haybittle approach. The statistical rules for stopping the study were P values $\leq$.001 in the first and second interim analysis for overwhelming superiority and the adjusted α level for the final analysis was .048. The independent Data Monitoring Committee reviewed both interim analysis and recommended the continuation of the trial in both instances. Only the decision of continuing with the study was communicated to the investigators.

Subgroup analysis. Only one subgroup analysis was preplanned based on the randomization strata (Baseline Child-Pugh $\leq$9 vs $\geq$10). Three consecutive criteria were considered for confirmatory evidence: test of the overall treatment effect, test of the treatment-by-subgroup interaction at the 10% level of significance, and test of the treatment effect in each subgroup category. It was predefined that the fulfillment of the 3 criteria would be required for assigning an appropriate level of evidence for this exploratory analysis.

Results

The study enrolled 158 participants who were randomized a median of 6 days after the index bleeding

(interquartile range [IQR], 5–7 days). Eighty-three were assigned to receive placebo and 75 simvastatin. Supplementary Figure 1 shows the disposition of the patients. During the data blind review, 9 patients were excluded from the safety population (n = 149) because they never received the study medication (6 consent withdrawal before starting treatment, 1 immediate death, 1 immediate rebleeding, and 1 no trial medication available), and 2 additional patients were considered wrong inclusions (1 known advanced hepatocellular carcinoma and 1 non-variceal index bleeding) and were excluded from the full-analysis set (n = 147) (Supplementary Table 1 provides the results from all populations defined in the study protocol). All exclusions were in full agreement with International Conference on Harmonization E9 guidelines. In addition, during the study, 7 patients in the placebo group (9%) and 6 patients in the simvastatin group (9%) were lost to follow-up.

Baseline characteristics were comparable between the study groups (Table 1). The most frequent etiology was alcohol liver disease, and up to 50% of those patients were actively drinking at the time of bleeding. Most patients had moderately impaired liver function: mean MELD score was 10 and only 15% of the patients were Child-Pugh C class. The proportion of patients with ascites was slightly higher in the simvastatin group as compared with placebo group (46% vs 33%). Median follow-up was 382 days in the placebo group (IQR, 174–561 days) and 371 days (IQR, 188–656 days) in the simvastatin group.

Treatments

Patients in the placebo group were on the study drug for a median of 329 days (IQR, 137–498 days) and patients in the simvastatin group were treated for a median of 337 days (IQR, 135–628 days). In all patients reaching day 15 of the study, the dose of the study medication was increased to 2 capsules (40-mg dose of simvastatin or identical placebo). The median number of endoscopic variceal ligation sessions to achieve eradication was 3 (IQR, 1–5) in the placebo group, and 3 (IQR, 2–5) in the simvastatin group. Sixty-five percent of the patients were initially treated with propranolol and 35% with nadolol. Median daily doses of propranolol were 80 mg (IQR, 40–120 mg) in the placebo group and 80 mg (IQR, 40–160 mg) in the simvastatin group. The median doses of nadolol were 80 mg (IQR, 40–100 mg) in the placebo group and 80 mg (IQR 40–120 mg) in the simvastatin group. In 23% of the patients in the placebo group, NSBBs were discontinued due to intolerance, and this occurred in 17% in the simvastatin group. Seventy-two percent of patients in the placebo group and 83% in simvastatin were considered fully compliant with the study protocol.

Primary Outcome

The primary end point (rebleeding or death) was reached by 30 of 78 (39%) patients in the placebo group and 22 of 69 (32%) in the simvastatin group (HR for simvastatin = 0.822; 95% CI: 0.473–1.427; stratified log-rank $P = .423$). Therefore, the addition of simvastatin to standard therapy was not statistically superior to placebo in preventing rebleeding or death after a variceal bleeding episode (Figure 1).

Key Secondary Outcomes

Mortality. Seventeen (22%) patients died in the placebo group as compared with 6 (9%) in the simvastatin group (HR = 0.387; 95% CI: 0.152–0.986; stratified log-rank $P = .030$). Therefore, treatment with simvastatin was associated with a 61% reduction in the relative risk of death as compared with placebo (Figure 2*A*). Causes of death are detailed in Table 2. Rebleeding, spontaneous bacterial peritonitis, and progression of liver disease were the most frequent cause of death in the placebo group (5, 3, and 3 patients, respectively), and only 1 patient in the simvastatin group died from rebleeding, none from spontaneous bacterial peritonitis, and 3 from progression of liver disease.

Rebleeding. In the placebo group, 22 patients developed rebleeding (28%) compared with 17 patients in the simvastatin group (25%). The rebleeding rate was not significantly decreased by the addition of simvastatin to the standard therapy (HR = 0.858; 95% CI: 0.455–1.620; stratified log-rank $P = .583$) (Figure 2*B*).

Additional Secondary Outcomes

Table 3 shows the rate of additional secondary outcomes in the study groups. There were no differences in the rate of variceal rebleeding (HR = 0.827; 95% CI: 0.410–1.668), ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, portal vein thrombosis, need for rescue shunting, or need for transfusion between the 2 groups. Two patients received liver transplantation, both in the simvastatin group. The rate of death or transplantation was not significantly different between both groups ($P = .093$). There were no significant differences in the MELD score between the 2 groups during the study period (Supplementary Figure 2).

Preplanned Subgroup Analysis

There was not statistical heterogeneity across predefined Child-Pugh class strata (A/B vs C) on the effects of simvastatin on the primary end point (rebleeding or death: $P = .133$) or the major secondary end points (rebleeding: $P = .729$; death: $P = .341$) (Supplementary Figure 3). However, the effects of simvastatin on survival were qualitatively different in Child-Pugh A/B patients than in Child-Pugh C. In Child-Pugh A/B patients, there was a significant decrease in mortality with simvastatin, which was not observed in Child-Pugh C patients (Supplementary Figure 3).

Safety

A total of 117 of the 149 patients included in the safety population (78.5%) reported adverse events, with no statistically significant differences between treatment groups (60 patients on placebo group vs 57 on simvastatin group;

Table 1. Baseline Characteristics of Patients From the Full-Analysis Set

Demographic and clinical basal data	Placebo (n = 78)	Simvastatin (n = 69)
Age, *y*, mean (SD)	57.62 (10.59)	57.42 (11.31)
Male sex, n (%)	53 (67.9)	45 (65.2)
Anthropometric data, mean (SD)		
Weight, *kg*	74.62 (16.57)	71.46 (13.63)
Body mass index, kg/m^2	26.62 (5.95)	26.29 (4.31)
Etiology of cirrhosis,[a] n (%)		
Alcohol (active or past significant consumption)	55 (71.4)	49 (71.0)
Hepatitis C	17 (22.1)	19 (27.5)
Hepatitis B	2 (2.6)	1 (1.4)
Primary biliary cirrhosis	0 (0.0)	3 (4.3)
Non-alcoholic steatohepatitis	4 (5.2)	1 (1.4)
Other	7 (9.1)	5 (7.2)
Toxics habits, n (%)		
Active alcohol consumption	36 (46.2)	35 (50.7)
Active smokers	26 (33.3)	28 (40.6)
Comorbidities, n (%)		
VIH	1 (1.3)	1 (1.4)
Diabetes Mellitus	29 (37.7)	22 (31.9)
Hypercholesterolemia	3 (3.9)	3 (4.3)
Hypertension	27 (35.1)	16 (23.2)
Liver function		
Basal Child-Pugh score, mean (SD)	7.68 (1.78)	7.93 (1.64)
Proportion of Child-Pugh A/B/C patients, %	24/62/14	15/68/17
Basal MELD score, mean (SD)	10.03 (5.32)	10.15 (4.40)
Clinical complications of cirrhosis, n (%)		
Ascites (responsive to treatment)	22 (28.2)	26 (37.7)
Refractory ascites	4 (5.1)	6 (8.7)
Edema	20 (25.6)	11 (15.9)
Encephalopathy	3 (3.8)	2 (2.9)
Hepatocellular carcinoma	5 (6.4)	3 (4.3)
Vital signs, mean (SD)		
Systolic blood pressure, *mmHg*	109.26 (22.94)	113.03 (20.97)
Diastolic blood pressure, *mmHg*	71.72 (17.38)	69.10 (14.63)
Mean arterial pressure, *mmHg*	84.41 (12.85)	83.23 (13.48)
Heart rate, *bpm*	74.38 (12.69)	78.17 (15.32)
Laboratory data, mean (SD)		
Sodium, *mEq/L*	137.18 (4.09)	136.34 (4.11)
Hemoglobin, g/dL	9.43 (1.42)	9.07 (1.34)
Platelets, $\times 10^3/\mu L$	96.05 (046.76)	98.44 (60.89)
INR	1.42 (0.35)	1.41 (0.32)
Bilirubin, *mg/dL*	2.20 (2.60)	2.34 (2.58)
Albumin, *g/dL*	2.94 (0.53)	2.82 (0.47)
Aspartate aminotransferase, *U/L*	67.39 (50.99)	78.18 (87.83)
Alanine aminotransferase, *U/L*	41.39 (33.09)	48.77 (47.38)
Baseline lipid profile, *mg/dL*, median (IQR)		
Total cholesterol	118 (97–148)	115 (93–130)
LDL cholesterol	79 (60–107)	69 (58–84)
HDL cholesterol	28 (17–33)	25 (21–32)
Triglycerides	85 (63–110)	81 (65–95)
Follow-up, *d*, median (IQR)	382 (174–561)	371 (188–656)

[a]Some patients had more than one etiologic factor.

$P = .718$). The most frequent adverse events were those related to complications of cirrhosis: gastrointestinal hemorrhage (15.1% placebo and 14.2% simvastatin), ascites (11.3% vs 15.7% in placebo and simvastatin, respectively) and hepatic encephalopathy (10.1% placebo and 10.0% simvastatin). Asthenia was reported in 11.3% of patients on placebo and in 7.1% on simvastatin. The remaining adverse events occurred in <10% of patients in each treatment group. Adverse events considered by the investigator to be possibly or probably related to drug treatment occurred in 14 patients on placebo and in 16 patients on simvastatin ($P = .547$). Forty-four patients in the placebo group and 37 in the simvastatin group reported serious adverse event ($P = .752$), which were considered related to the study medication in 11% and 8% of the cases in the placebo and simvastatin group, respectively ($P = .599$). A summary of

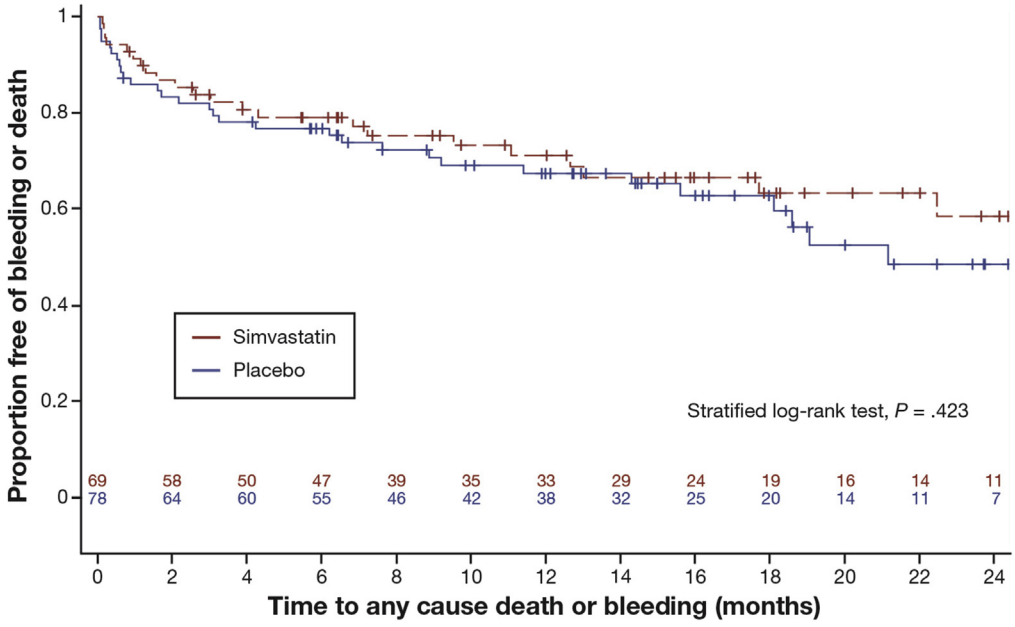

Figure 1. Kaplan-Meier curve showing the probability of developing the primary end point (rebleeding or death) in patients from simvastatin (*red*) and placebo (*blue*) groups. There were no differences between the study groups.

adverse events, including treatment-related adverse event experienced by at least 2% of patients in any study group, is shown in Table 4. No new safety signals for simvastatin were detected during this trial in the specific population of cirrhotic patients.

Two adverse events were specifically monitored during the study: increase in liver transaminases and rhabdomyolysis. In 1 patient from the simvastatin group, the study medication was stopped due to a >3-fold increase in liver transaminases. This patient did not show signs of worsening liver function as assessed clinically or by bilirubin and international normalized ratio. Liver transaminases returned to baseline after discontinuation of simvastatin. Two episodes of rhabdomyolysis were reported, both from the simvastatin group (1 male and 1 female), and were classified as serious adverse events. Rhabdomyolysis was detected 15 and 85 days after the initiation of simvastatin. Both patients were symptomatic (myalgias and asthenia). Peak creatine kinase levels were 7823 and 3500 IU/L. None developed acute kidney injury and both recovered completely (normal creatine kinase levels) 14 and 19 days after stopping the study medication, respectively. These 2 patients had deteriorated liver function at baseline, with a bilirubin >5 mg/dL, and their baseline kidney function was normal. There were no drug-to-drug interactions that could explain an increased risk of rhabdomyolysis.

Discussion

In this multicenter double-blind randomized trial in patients with cirrhosis after variceal bleeding, treatment with simvastatin resulted in longer survival than placebo administration (given above standard of care therapy). Simvastatin, however, failed to show superiority over placebo in decreasing the rate of rebleeding or other complications of cirrhosis. The increase in survival achieved by simvastatin was mainly determined by a decrease in mortality derived from rebleeding and infections, suggesting that simvastatin, although unable to prevent those complications, attenuated the deleterious effect of these events on the course of the disease. In addition, this study provides thorough information of the safety of long-term simvastatin in patients with decompensated cirrhosis. We have observed a similar rate of adverse events between the placebo and simvastatin group. However, 2 patients developed rhabdomyolysis in the simvastatin group, an incidence much higher than expected with the dose used in the present trial.

Several studies in rodent models provided a strong rationale for the clinical assessment of the effects of statins in cirrhosis.[7–12] In 2 different models of cirrhosis, treatment with oral simvastatin or atorvastatin improved liver microvascular dysfunction and portal pressure.[7,8] In addition, statins showed robust anti-inflammatory[10,11,18] and anti-fibrotic[9,12] effects in the liver that could also be of benefit in decompensated cirrhosis. The beneficial effect of statins on portal pressure was subsequently confirmed in a multicenter randomized study in humans comparing simvastatin and placebo.[14] The decrease in portal pressure with simvastatin was mild (8%), but was observed in patients with or without β-blocker treatment, suggesting that the effects of simvastatin could be additive to those of β-blockers, the current standard drug therapy for portal hypertension.[19] The study further showed that the decrease in portal pressure was achieved without any decrease in liver blood flow, suggesting a diminished vascular resistance in the liver microcirculation. This was associated with a significant improvement in quantitative liver function tests.

Recent observational studies also suggested a potential clinical benefit of statins in cirrhosis. In a small

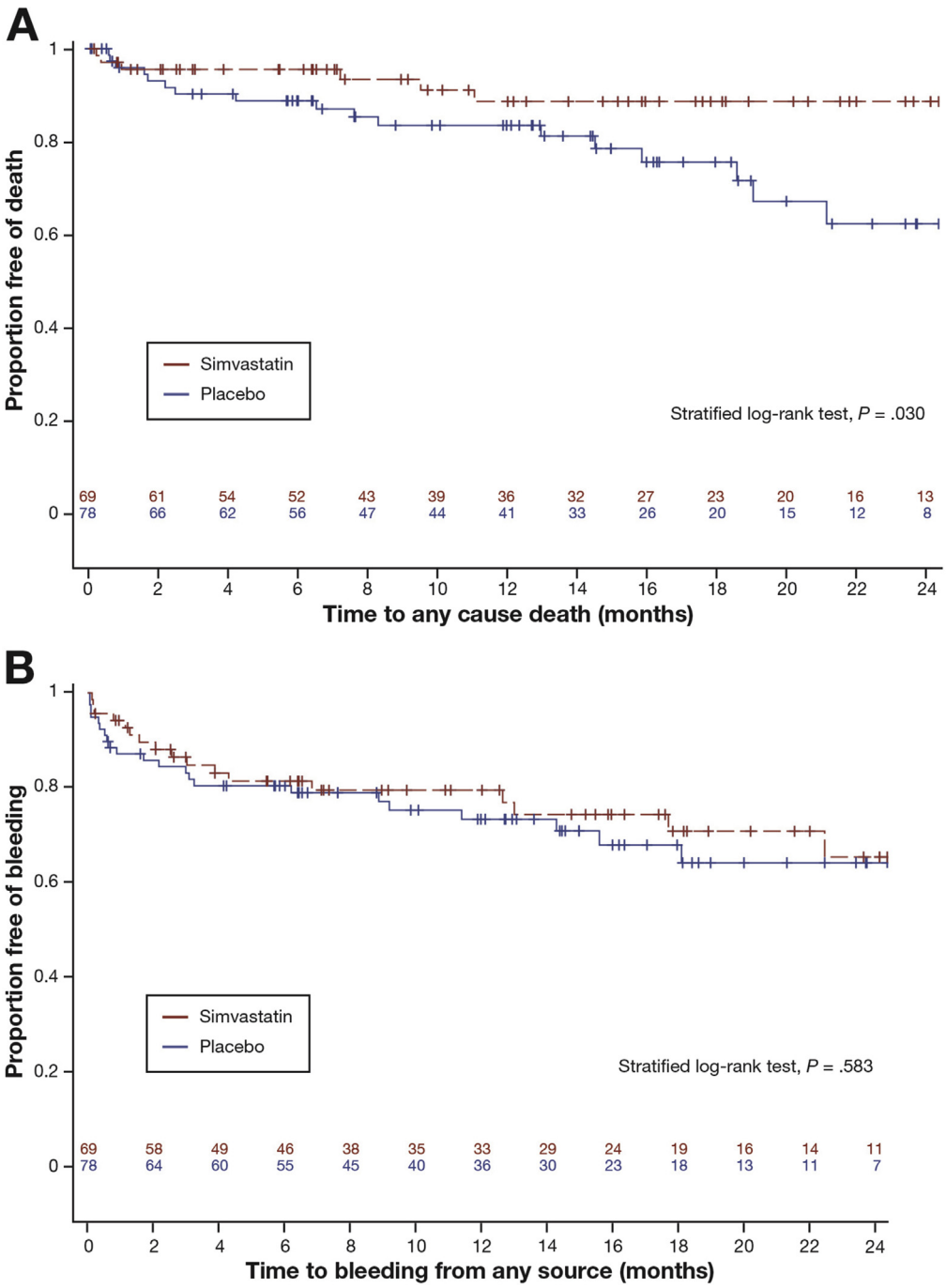

Figure 2. (*A*) Kaplan-Meier curve showing that patients in simvastatin arm (*red*) had a significantly greater survival than patients in the placebo arm (*blue*). (*B*) Kaplan-Meier curve showing the rate of rebleeding. There were no differences between the treatment arms.

retrospective cohort study in patients with biopsy-proven cirrhosis, statin treatment was associated with improved survival[20] and in large observational study-based Veterans Health Administration databases, patients with cirrhosis treated with statins had a lower risk of infections,[21] lower risk of decompensation, and lower mortality.[22] Studies in patients with hepatitis C also suggested a benefit from statin therapy delaying fibrosis progression and hepatic decompensation, and decreasing the incidence of hepatocellular carcinoma.[23–25] However, no randomized trial has, so far, directly addressed these questions. This is of special concern because although several observational studies showed a benefit from statins in other acute and chronic conditions, these were not subsequently confirmed in randomized trials. Indeed, statins failed to show benefit in randomized trials for chronic obstructive pulmonary disease,[26–28] acute respiratory distress syndrome,[29] severe sepsis,[30,31] ventilator-associated pneumonia,[32] ulcerative colitis,[33] Alzheimer disease,[34,35] multiple sclerosis,[36–38] and several cancers.[39–43] Therefore, the present double-blind multicenter randomized trial addresses for the first time a relevant gap of knowledge, which is whether statins might improve relevant outcomes in patients with cirrhosis, specifically after a variceal bleeding.

Table 2. Causes of Death

Cause of death	Placebo (n = 78)	Simvastatin (n = 69)
Overall	17 (21.5)	6 (8.6)
Bleeding	5 (6.4)	1 (1.4)
Spontaneous bacterial peritonitis	3 (3.8)	0 (0)
Other infections	0 (0)	1 (1.4)
Alcoholic hepatitis	0 (0)	1 (1.4)
Progression of liver disease	3 (3.8)[a]	3 (4.3)
Hemoperitoneum	1 (1.3)	0 (0)
Cholangiocarcinoma	1 (1.3)	0 (0)
Lymphoproliferative disease	1 (1.3)	0 (0)
Small-cell lung cancer	1 (1.3)	0 (0)
Cerebral edema post correction of severe hyperglycemia	1 (1.3)	0 (0)
Incarcerated umbilical hernia secondary to tense ascites	1 (1.3)	0 (0)

NOTE. Data are presented as n (%).
[a]One patient died from advanced hepatocellular cancer.

In the design of this trial, we decided to use a composite end point—rebleeding or death. The reasons for this choice were that patients with decompensated cirrhosis have high rates of mortality, which competes with the assessment of rebleeding, and we postulated that simvastatin could improve both rebleeding and death by decreasing portal pressure and by improving liver function, respectively. Although we are aware of the limitations of the use of composite end points,[44] this strategy is widely used in trial design for hypothesizing an effect size and sample size calculations. We think these limitations were overcome by assessing the individual components of the main end point as major secondary end points.

The main result of this study is that simvastatin increases survival in decompensated cirrhotic patients after a variceal bleeding, but it does not prevent further complications of portal hypertension. It has been shown that a pharmacologic reduction in portal pressure by >20% from baseline or to <12 mmHg is associated with protection from all complications of cirrhosis.[4,5,45] The results of the present study suggest that the additional mild reduction in portal pressure described for simvastatin (on top of that achieved by β-blockers) was not of enough magnitude to prevent further cirrhosis complications after a variceal bleeding episode. However, simvastatin achieved a major improvement in survival, which, without doubt, is hierarchically the most relevant end point in patients with decompensated cirrhosis.[46] Although classifying deaths as liver or non–liver-related is problematic, an exploratory analysis showed that the improvements in mortality were mainly related to a decrease in liver-related deaths (14 in placebo, and 6 events in simvastatin; absolute risk reduction = 10.39% (95% CI: 0.26%–20.51%). The pragmatic nature of this study makes that the mechanisms mediating improved survival remain conjectural. On the one hand, simvastatin has been shown to improve quantitative test of liver function in cirrhosis.[14] However, we could not detect a signal of a beneficial effect of simvastatin on liver function because simvastatin did not modify the MELD trajectory during the trial. These results, however, might be confounded by the fact that the higher mortality in the placebo group would progressively select better MELD scores in the placebo arm. On the other hand, preclinical studies in animal models have shown that simvastatin prevents liver injury induced by endotoxemia,[10] bleeding,[11] and ischemia/reperfusion[47] by supporting liver microcirculation and by attenuating liver inflammation. This would be in keeping with the observed decrease in mortality related to bleeding and related to infections, but further mechanistic studies should clarify these questions.

In this study, we provide valuable data on the long-term safety of simvastatin in decompensated cirrhosis, at least for up to 2 years of treatment. The number of severe adverse effects was not different between the study groups. It is important to note that only 1 patient developed a significant increase in transaminases requiring treatment withdrawal. A more concerning issue is that 2 patients on simvastatin developed rhabdomyolysis, which warrants a word of caution in the use of simvastatin in the most advanced

Table 3. Summary of Additional Secondary Outcomes

Outcomes	Placebo (n = 78)	Simvastatin (n = 69)	*P* value[a]
Variceal bleeding	18 (23.1)	14 (20.3)	.699 (.551[b])
Other complications of portal hypertension	16 (20.5)	15 (21.7)	.808
New ascites or worsening ascites	16 (20.5)	15 (21.7)	.808
Spontaneous bacterial peritonitis	4 (5.1)	0 (0.0)	.123
Hepatorenal syndrome	0 (0.0)	1 (1.4)	.835
New PVT or progression of previous partial PVT	2 (2.6)	4 (5.8)	.594
Need for rescue treatment (TIPS or surgical shunt)	3 (3.8)	5 (7.2)	.475
Death or transplantation	17 (21.8)	8 (11.6)	.036 (.093[b])
Blood transfusion during the study period, n, median (IQR)	0 (0–8)	0 (0–7)	.393[c]

NOTE. Descriptive data are n (%) or otherwise specified.
PVT, portal vein thrombosis; TIPS, transjugular intrahepatic portosystemic shunt.
[a]*P* value form the stratum-adjusted binomial regression or otherwise specified.
[b]*P* value form the stratified log-rank test.
[c]*P* value from the Stratified Van Elteren test.

Table 4. Summary of Treatment-Related Adverse Events Experienced by At Least ≥2% of the Subjects in Any of the Study Groups (Safety Population n = 149)

Adverse event	Placebo (n = 79)	Simvastatin (n = 70)
Any adverse event	60 (75.9)	57 (81.4)
Serious adverse events	44 (55.6)	37 (52.8)
Serious and related adverse events	9 (10.8)	6 (8.0)
Treatment-related adverse events	14 (17.7)	16 (22.8)
Abdominal pain	3 (3.8)	0 (0.0)
Ascites	2 (2.5)	2 (2.8)
Asthenia	3 (3.8)	2 (2.8)
Gastrointestinal hemorrhage	2 (2.5)	1 (1.4)
Gynecomastia	0 (0.0)	2 (2.8)
Hepatic encephalopathy	1 (1.2)	3 (4.2)
Iron-deficiency anemia	0 (0.0)	2 (2.8)
Rhabdomyolysis	0 (0.0)	2 (2.8)
Toxicity to various agents	0 (0.0)	2 (2.8)

NOTE. Data are presented as n (%). All *P* values >.05, lowest *P* value = .247 for the related treatment-related abdominal pain.

patients (both patients had a bilirubin >5 mg/dL). In previous studies, chronic liver disease was found to be a risk factor for myopathy, but only in woman.[48] However, these studies were unlikely to include patients with advanced liver disease. In addition, rhabdomyolysis has been particularly associated with higher doses of simvastatin (80 mg, which are no longer recommended) that the one used in this study (40 mg).[49,50] This suggests that patients with severely deteriorated liver function might develop rhabdomyolysis at lower doses than the general population. Along these lines, very recent studies showed that progressive liver disease (at least of alcoholic etiology) is associated with decreased expression of SLCO1B, an organic anion transporter that regulates the hepatic uptake of statins.[51,52] Indeed, a loss-of-function single nucleotide polymorphism in SLCO1B1 has been associated with statin-induced myopathy.[53,54] Of note, in subsequent studies, SLCO1B1 polymorphism was not associated with myopathy in patients taking atorvastatin.[54,55] Altogether, this calls for a close monitoring of muscle enzymes in this particular group of patients, and for testing either atorvastatin or lower doses of simvastatin in future studies including patients with advanced cirrhosis.

It is important to note that the results of this study cannot be generalized to all patients that recover from variceal bleeding, because those with advanced liver dysfunction (Child-Pugh >13) or with creatinine >2 mg/d, and patients with complete portal vein thrombosis were excluded from this study. In addition, simvastatin benefits were observed in one of the major secondary end points, but not on the primary end point, which increases the chances of type I error. In addition, because 11 patients were excluded from the efficacy analysis, our study might have been underpowered to assess the study hypothesis. An additional limitation of this study is the lack of data on the potential impact of alcohol abstinence on the study outcomes.

In conclusion, in patients with cirrhosis who recover from an acute variceal bleeding episode, the BLEPS trial showed that addition of simvastatin to NSBBs and endoscopic variceal ligation improves survival without reducing the rate of other complications of cirrhosis. Because survival was not the primary end point of the study, these results would require further validation in new randomized controlled trials. These new trials should not necessarily focus on patients with previous variceal bleeding, because variceal rebleeding was not prevented, but could target a wider cirrhosis population. In addition, because no survival benefit was observed in Child-Pugh C patients, new trials should focus on less-advanced patients (Child-Pugh A and B).

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.2016.01.004.

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Author names in bold designate shared co-first authorship.

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Reprint requests
Address requests for reprints to: Jaime Bosch, MD, Hepatic Hemodynamic Laboratory, Hospital Clínic, C. Villarroel 170, 08036 Barcelona, Spain. e-mail: jbosch@clinic.ub.es; fax: +34 93-227-98-56; or Juan G. Abraldes, MD, Division of Gastroenterology, University of Alberta, 1-38 Zeidler Ledcor Centre, Edmonton, AB, T6G 2X8, Canada. e-mail: juan.g.abraldes@ualberta.ca; fax: +1 780-492-9873.

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Additional BLEPS Study Investigators: Hospital Vall d'Hebron (Barcelona): Salvador Augustin; Hospital Puerta de Hierro (Madrid): Elba Llop; Hospital Universitario de Canarias (Tenerife): Dalia Morales Arraez, Goretti Hernández Mesa; Hospital Ramon y Cajal (Madrid): Javier Martinez; Hospital Clinic (Barcelona): Enric Reverter, Susana Seijo, Fanny Turon; Hospital Arnau de Vilanova (Lleida): Josep Miñana, Juan Buenestado, Josep M. Reñe; Hospital Central de Asturias: Carmen A. Navacués; Hospital Germans Trias i Pujol: Ramon Planas, Rosa M. Morillas; Hospital Universitario de Alicante: Pau Bellot, Jose Such; Hospital Parc Tauli (Sabadell): Mercedes Vergara; Hospital Marques de Valdecilla (Santander): Angela Puente, Joaquin de la Pena; Complejo Hospitalario de Pontevedra: José Mera Calviño, Laura Rivas Moral; Hospital de Sant Pau (Barcelona): Oana Pavel, Edilmar Alvarado y Alba Ardevol; Hospital de Bellvitge (L'Hospitalet de Llobregat): Anna Girbau y Alba Cachero; Clinical Trials Unit, Hospital Clinic, University of Barcelona, Spain: Joan Albert Arnaiz, Annalisa Berzigotti, Judit Pich, Jose Rios; Site Coordinators: Rosa Saenz, Laura Millan; Monitors: Helena Beleta y Núria Ramos.

Conflicts of interest
The authors disclose no conflicts.

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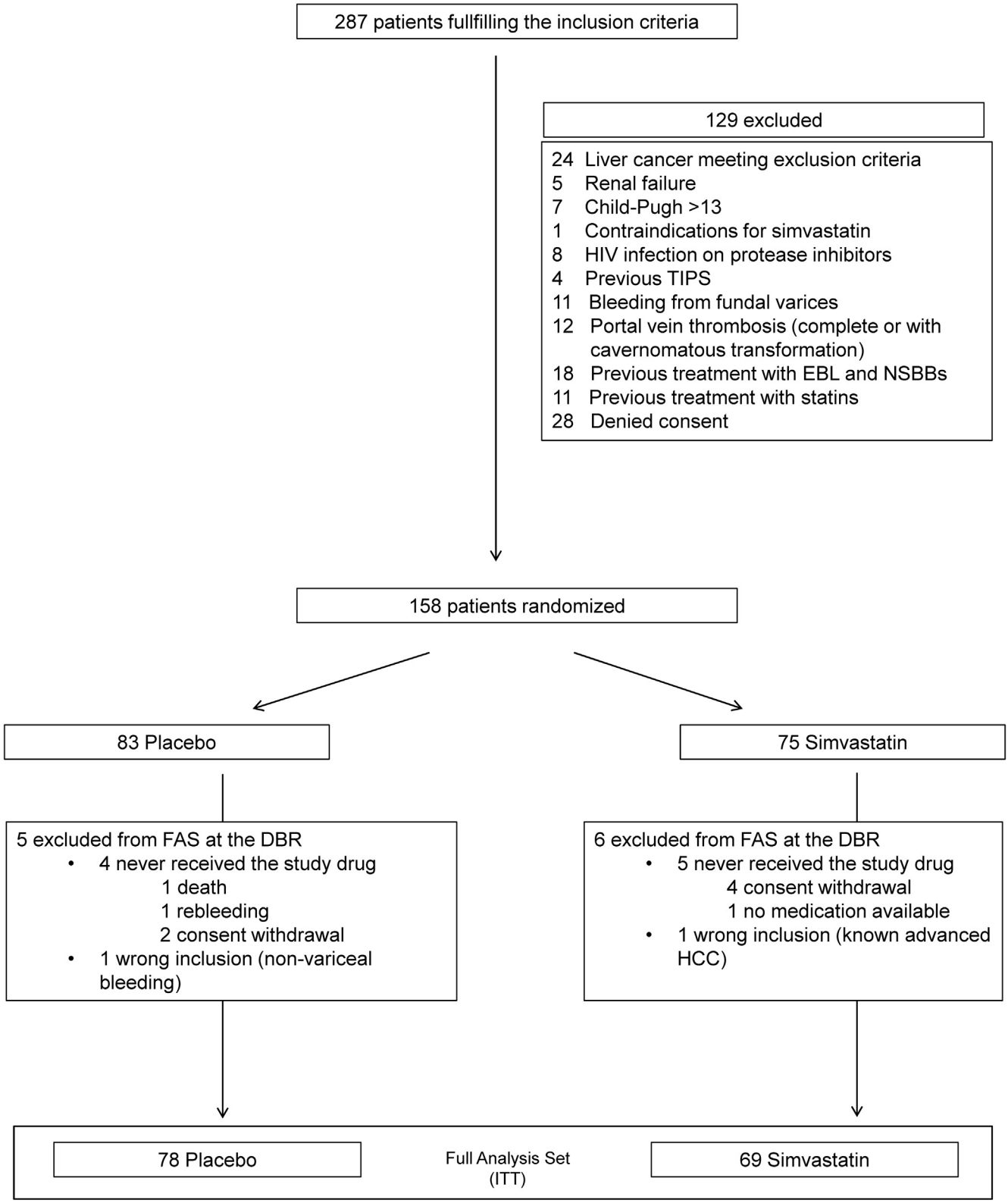
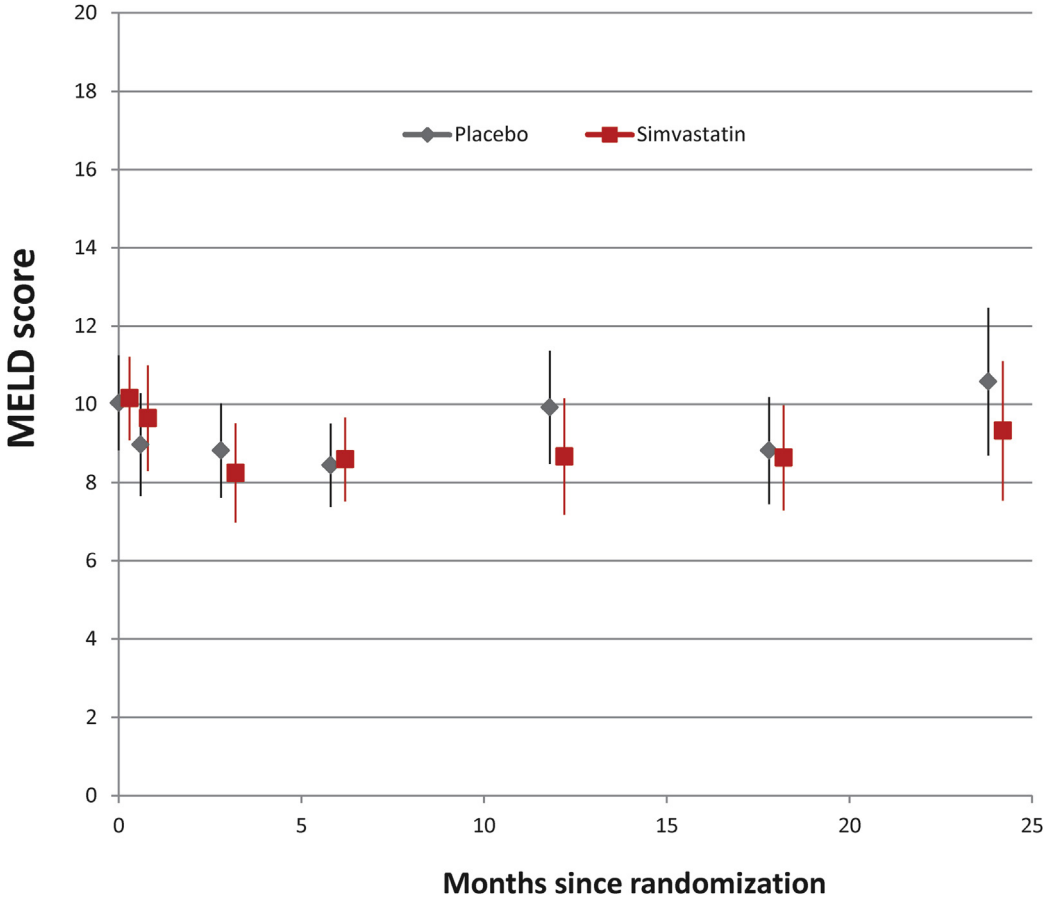
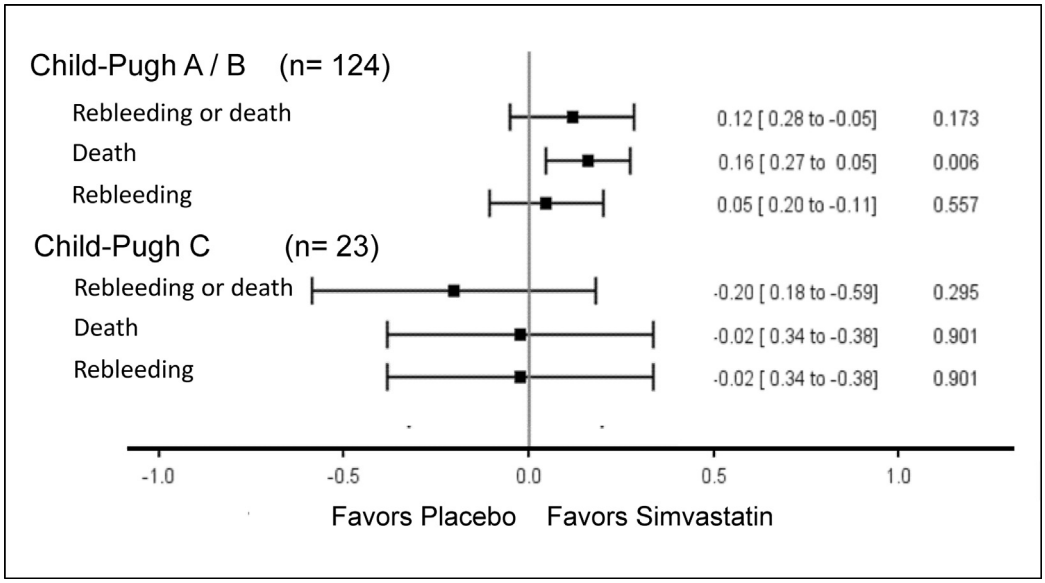


Supplementary Figure 1. Flowchart showing the disposition of the patients. DBR, data blind review; EBL, endoscopic banding ligation; FAS, full analysis set; HCC, hepatocellular carcinoma; ITT, intention to treat; TIPS, transjugular intrahepatic portosystemic shunt.



Supplementary Figure 2. MELD trajectory during the study period in the placebo and simvastatin group (least square means and 95% CI from the mixed models for repeated measurements analysis).



Supplementary Figure 3. Forest plot showing the effects of simvastatin on the primary and main secondary end points, according to the predefined Child-Pugh class strata (A/B vs C). Statistics are rate differences (95% CI) and *P* values from the log-binomial regression model. There was no statistical heterogeneity in the effects of simvastatin across the strata. However, in Child-Pugh A/B patients there was a significant decrease in mortality with simvastatin, which was not observed in Child-Pugh C patients.

Supplementary Table 1. Post-Hoc Analysis Showing the Number of Events and *P* Values in the Different Populations Defined in the Study Protocol

Population	Variable	Events in the placebo group, n (%)	Events in the simvastatin group, n (%)	Difference[a]		Survival analysis[b]	
				% Difference (95% CI)	*P* value	HR (95% CI)	*P* value
Randomized[c] (83 + 75 = 158)	Death or hemorrhage	33 (39.8)	22 (29.3)	10.54 (−4.22 to 25.29)	.162	0.745 (0.434 to 1.280)	.227
	Death	18 (21.7)	6 (8.0)	14.42 (4.23 to 24.61)	.006	0.366 (0.145 to 0.925)	.018
Safety[d] (79 + 70 = 149)	Death or hemorrhage	30 (38.0)	22 (31.4)	6.58 (−8.73 to 21.89)	.399	0.813 (0.468 to 1.413)	.399
	Death	17 (21.5)	6 (8.6)	14.21 (3.59 to 24.82)	.009	0.384 (0.151 to 0.977)	.028
FAS[e] (78 + 69 = 147)	Death or hemorrhage	30 (38.5)	22 (31.9)	6.58 (−8.88 to 22.04)	.404	0.822 (0.473 to 1.427)	.423
	Death	17 (21.8)	6 (8.7)	14.37 (3.62 to 25.12)	.009	0.387 (0.152 to 0.986)	.030
PP[f] (76 + 69 = 145)	Death or hemorrhage	30 (39.5)	22 (31.9)	7.82 (−7.77 to 23.42)	.325	0.785 (0.452 to 1.361)	.364
	Death	17 (22.4)	6 (8.7)	14.99 (4.13 to 25.85)	.007	0.355 (0.140 to 0.903)	.019

NOTE. These populations were defined in the data blind review according to the definitions in the statistical analysis plan and reproduced below.
FAS, full-analysis set; PP, per protocol.
[a]Treatment effect and *P* values from the stratum adjusted binomial regression.
[b]Treatment effect from the Cox model and *P* values from the stratified log-rank test.
[c]All study patients who were randomized.
[d]Safety population defined as all randomized subjects who took the study medication.
[e]FAS defined as all patients who were randomized into the study and who initiated the study medication. The accepted exclusions, as per the International Conference on Harmonization E9, were predefined as follows and verified during the data blind review: subjects who failed to satisfy an entry criterion were excluded from the analysis if the entry criterion was measured before randomization; detection of the relevant eligibility violations could be made completely objectively; all subjects received equal scrutiny for eligibility violations; and all detected violations of the particular entry criterion are excluded.
[f]PP defined as those patients included in the FAS who took the study medication without major protocol deviations that might impact the study's main assessments. These deviations were assessed during the data blind review before database lock.