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Simvastatin and Rifaximin in Decompensated Cirrhosis
A Randomized Clinical Trial

Elisa Pose, MD; César Jiménez, MD; Giacomo Zaccherini, MD; Daniela Campion, MD; Salvatore Piano, MD; Frank Erhard Uschner, MD; Koos de Wit, MD; Olivier Roux, MD; Kohilan Gananandan, MD; Wim Laleman, MD; Cristina Solé, MD; Sonia Alonso, MD; Berta Cuyàs, MD; Xavier Ariza, MD; Adrià Juanola, MD; Ann T. Ma, MD; Laura Napoleone, MD; Jordi Gratacós-Ginès, MD; Marta Tonon, MD; Enrico Pompili, MD; Jordi Sánchez-Delgado, MD; Andrew S. Allegretti, MD; Manuel Morales-Ruiz, MD; Marta Carol, PhD; Martina Pérez-Guasch, MSc; Núria Fabrellas, PhD; Judit Pich, BSc; Claudia Martell, MSc; María Joyera, MSc; Gemma Domenech, PhD; José Ríos, PhD; Ferrán Torres, MD; Miquel Serra-Burriel, PhD; Rubén Hernáez, MD; Elsa Solà, MD; Isabel Graupera, MD; Hugh Watson, MD; Germán Soriano, MD; Rafael Bañares, MD; Rajeshwar P. Mookerjee, MD; Claire Francoz, MD; Ulrich Beuers, MD; Jonel Trebicka, MD; Paolo Angeli, MD; Carlo Alessandria, MD; Paolo Caraceni, MD; Víctor M. Vargas, MD; Juan G. Abraldes, MD; Patrick S. Kamath, MD; Pere Ginès, MD; for the LIVERHOPE Consortium

IMPORTANCE There are no useful treatments to prevent the development of severe complications of liver cirrhosis. Simvastatin and rifaximin have shown beneficial effects in liver cirrhosis.

OBJECTIVE To assess whether simvastatin combined with rifaximin improves outcomes in patients with decompensated cirrhosis.

DESIGN, SETTING, AND PARTICIPANTS Double-blind, placebo-controlled, phase 3 trial conducted among patients with decompensated cirrhosis in 14 European hospitals between January 2019 and December 2022. The last date of follow-up was December 2022.

INTERVENTIONS Patients were randomly assigned to receive simvastatin, 20 mg/d, plus rifaximin, 1200 mg/d (n = 117), or identical-appearing placebo (n = 120) for 12 months in addition to standard therapy, stratified according to Child-Pugh class B or C.

MAIN OUTCOMES AND MEASURES The primary end point was incidence of severe complications of liver cirrhosis associated with organ failure meeting criteria for acute-on-chronic liver failure. Secondary outcomes included transplant or death and a composite end point of complications of cirrhosis (ascites, hepatic encephalopathy, variceal bleeding, acute kidney injury, and infection).

RESULTS Among the 237 participants randomized (Child-Pugh class B: n = 194; Child-Pugh class C: n = 43), 72% were male and the mean age was 57 years. There were no differences between the 2 groups in terms of development of acute-on-chronic liver failure (21 [17.9%] vs 17 [14.2%] patients in the treatment and placebo groups, respectively; hazard ratio, 1.23; 95% CI, 0.65-2.34; *P* = .52); transplant or death (22 [18.8%] vs 29 [24.2%] patients in the treatment and placebo groups, respectively; hazard ratio, 0.75; 95% CI, 0.43-1.32; *P* = .32); or development of complications of cirrhosis (50 [42.7%] vs 55 [45.8%] patients in the treatment and placebo groups, respectively; hazard ratio, 0.93; 95% CI, 0.63-1.36; *P* = .70). Incidence of adverse events was similar in both groups (426 vs 419; *P* = .59), but 3 patients in the treatment group (2.6%) developed rhabdomyolysis.

CONCLUSIONS AND RELEVANCE The addition of simvastatin plus rifaximin to standard therapy does not improve outcomes in patients with decompensated liver cirrhosis.

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Visual Abstract

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Authors: Pere Ginès, MD, PhD (pgines@clinic.cat), and Elisa Pose, MD, PhD (epose@clinic.cat), Liver Unit, Hospital Clínic of Barcelona, 170 Villarroel St, 08036 Barcelona, Spain.

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Decompensated liver cirrhosis is characterized by complications such as ascites, hepatic encephalopathy, variceal bleeding, bacterial infection, or acute kidney injury. Decompensated cirrhosis is associated with recurrent hospitalizations, high health care costs, lower quality of life, and increased mortality.[1-3] Patients with decompensated cirrhosis are typically classified into either Child-Pugh class B or class C disease severity groups, with class C indicating worse severity.[4] Acute-on-chronic liver failure (ACLF) is a complication of cirrhosis characterized by failure of the liver and/or extrahepatic organs that occurs as disease progresses, in the context of increased systemic inflammation, and is a major cause of death.[5,6] Currently, there are no treatments to prevent ACLF.

Statins are 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors that reduce serum cholesterol levels[7] and also have pleiotropic effects due to their anti-inflammatory properties,[8-11] which make them an attractive option in the treatment of decompensated cirrhosis.[12] Statins reduced portal pressure in patients with cirrhosis and may reduce the risk of complications of cirrhosis and increase survival.[13-18] Cirrhosis is also characterized by marked abnormalities in the gut microbiome, increased permeability of gut mucosa, and increased bacterial translocation.[19] These alterations trigger complications of cirrhosis, such as hepatic encephalopathy, bacterial infection, and ACLF. Rifaximin, a poorly absorbed antibiotic with broad-spectrum antibacterial activity, has been shown to reduce the risk of recurrence of hepatic encephalopathy and modulate the gut microbiome.[20-22]

With this background, the LIVERHOPE study aimed to investigate whether the combination of simvastatin and rifaximin, when added to standard therapy, could reduce the occurrence of ACLF as well as other complications in patients with decompensated cirrhosis.

Key Points

Question Is the combination of simvastatin and rifaximin useful to prevent severe complications of liver cirrhosis?

Findings In this randomized clinical trial that included 237 patients with decompensated cirrhosis, no significant differences were found in terms of the incidence of severe complications of cirrhosis associated with organ failure (acute-on-chronic liver failure); transplant or death; and complications of cirrhosis.

Meaning The combination of simvastatin and rifaximin in patients with decompensated cirrhosis did not prevent severe complications of liver cirrhosis.

Methods

Study Design

In this multicenter, parallel-group, placebo-controlled trial, participants were randomly assigned in a 1:1 ratio to receive either oral simvastatin, 20 mg once per day, and rifaximin, 400 mg 3 times per day, or identical-appearing placebo of both medications for 12 months. Patients were recruited from 14 European hospitals. The dose of simvastatin was selected based on a previous safety study comparing simvastatin, 20 mg/d, vs simvastatin, 40 mg/d, or placebo, in association with rifaximin, that showed that simvastatin, 40 mg/d, was associated with a higher frequency of rhabdomyolysis, whereas simvastatin, 20 mg/d, was safe.[23] The pharmaceutical formulation of rifaximin (rifaximin extended intestinal release, 400 mg) used in this study is slightly different from the commercially available product in that the rifaximin is coated with a gastroresistant polymer that allows a higher bioavailability of the drug in the intestine compared with the commercial formulation.

Written informed consent was obtained from all participants. The institutional review board at each center approved the study protocol. The trial protocol is available, together with the statistical analysis plan, in Supplement 1. The study drugs, simvastatin, rifaximin, and placebo, were manufactured, prepared, and supplied by AlphaSigma (Bologna, Italy). This report followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Study Population

We enrolled patients 18 years of age or older who had a clinical diagnosis of decompensated cirrhosis, namely Child-Pugh class B or C; these patients have a high risk of developing complications of cirrhosis as well as mortality (eTable 1 in Supplement 2 describes the Child-Pugh classification). We excluded patients with severe liver impairment, defined as (1) presence of ACLF at enrollment; (2) serum bilirubin greater than 5 mg/dL (>85.5 µmol/L); (3) international normalized ratio of 2.5 or greater; (4) severe alcohol-associated hepatitis requiring corticosteroid therapy; (5) overt hepatic encephalopathy; and (6) Child-Pugh score of 13 points or greater. Patients with hepatocellular carcinoma or with severe extrahepatic comorbidities, including congestive heart failure (New York Heart Association class III/IV), chronic obstructive pulmonary disease (Global Initiative for Chronic Obstructive Lung Disease group 2 or higher), serum creatinine of 2 mg/dL or greater (≥176.8 µmol/L), or receiving kidney replacement therapy, were also excluded. Importantly, patients receiving treatment with rifaximin or statins or with indication to start simvastatin or rifaximin therapy (eg, patients with recurrent hepatic encephalopathy) or those with increased risk of adverse events related to the study medications (eg, treatment with potent inhibitors of cytochrome P450 3A4) were excluded. Patients unable to provide informed consent or with anticipated poor adherence and/or alcohol consumption of 3 units per day or greater were also excluded.

Information on race and ethnicity was collected by self-report at the baseline visit. Several predefined categories were established and patients self-identified the category they considered to be their own.

Outcomes

The primary outcome was the incidence of ACLF. Secondary outcomes included transplant or death, severity of ACLF, a composite end point of complications of cirrhosis (ascites,

hepatic encephalopathy, variceal bleeding, acute kidney injury, and infection), and changes in liver function tests and Model for End-Stage Liver Disease (MELD) score.[24] ACLF was defined using the European Association for the Study of the Liver-Chronic Liver Failure (EASL-CLIF) criteria and classified into 3 grades of increasing severity[25] (eTable 2 in Supplement 2). Definitions of complications of cirrhosis (ascites, acute kidney injury, gastrointestinal bleeding, hepatic encephalopathy, and bacterial infection) were per the EASL clinical practice guidelines for the management of decompensated cirrhosis and are detailed in eTable 3 in Supplement 2.[26]

Study Visits and Safety Analysis

Participants had follow-up visits at months 1, 3, 6, 9, and 12, at which time clinical data, standard laboratory test results, complications of cirrhosis, and adverse events were documented. Adherence to study drug therapy was determined by direct counting of the pills returned by the patients at each study visit. Treatment was temporarily discontinued among patients who developed ACLF or other complications of cirrhosis and was restarted after recovery. Treatment was permanently withdrawn among patients who developed severe treatment-related adverse effects and those who developed recurrent hepatic encephalopathy, which is an indication for rifaximin therapy.[27] The main safety outcome measures were assessed by an independent data and safety monitoring board, which held 2 meetings during the study (November 2019 and September 2020) and provided written reports. No major safety concerns were raised.

Statistical Analysis and Sample Size Calculation

Sample size and power considerations were based on the incidence of ACLF. The estimated incidence of ACLF in the placebo group was 25% overall, 18% in patients with Child-Pugh class B disease and 45% in those with Child-Pugh class C disease.[28] Accordingly, 75% of patients included had Child-Pugh class B disease and 25% had Child-Pugh class C disease. We calculated that 105 patients per group were required with 31 ACLF events in total to achieve 80% statistical power to detect an absolute risk reduction of 15% in the incidence of ACLF in the treatment group, with a 2-sided α error of .05. An overall sample size of 240 patients was predefined, allowing for a 12% dropout rate. No interim analyses were planned.

All patients who underwent randomization were followed up until the end of the study. For the main outcome, the Fine and Gray Cox model approach using the randomization Child-Pugh strata under a competing risk strategy (death and transplant) was used to estimate cumulative incidence function, subdistribution hazard ratios, and their 95% CIs.[29] Other events were analyzed by the same method, except for transplant or death, which were analyzed without competing risk. The annual rate of ACLF and the rate ratio between treatment groups were assessed using a Poisson regression model adjusted by Child-Pugh strata with 95% CI estimation. We analyzed longitudinal continuous variables by assessing the individual laboratory parameters (serum bilirubin, creatinine, international normalized ratio, albumin, MELD score, C-reactive protein, and total, low-density lipoprotein, and high-density lipoprotein cholesterol) with mixed models for repeated measurements, including the Child-Pugh stratum and the baseline measurement. We handled missing data for longitudinal variables through the strategy of mixed models for repeated measurements, which assumes that missing observations are independent of unobserved data. Baseline characteristics are described by means of appropriate descriptives: numbers and percentages for categorical variables, means and standard deviations for continuous variables with a normal distribution, and medians and interquartile ranges for continuous variables with a nonnormal distribution (normality was evaluated by graphical methods).

Herein, we report outcomes in the intention-to-treat population instead of the modified intention-to-treat population outlined in the statistical analysis plan. In the intention-to-treat population, all patients were analyzed for the complete duration of follow-up except those who were lost to follow-up, withdrew consent, or had competing events such as death or transplant. In the modified intention-to-treat population, patients who stopped treatment because of adverse events, patient decision, or medical decision were analyzed until the end of treatment instead of the end of study follow-up. The primary outcome of the study is also reported for the per-protocol population, which included participants from the intention-to-treat population who did not present major protocol deviations (follow-up <1 month, medication fulfillment <75%, and/or fulfillment of exclusion criteria). A post hoc analysis was also done including patients who underwent randomization but who, due to varying reasons, did not start study medication.

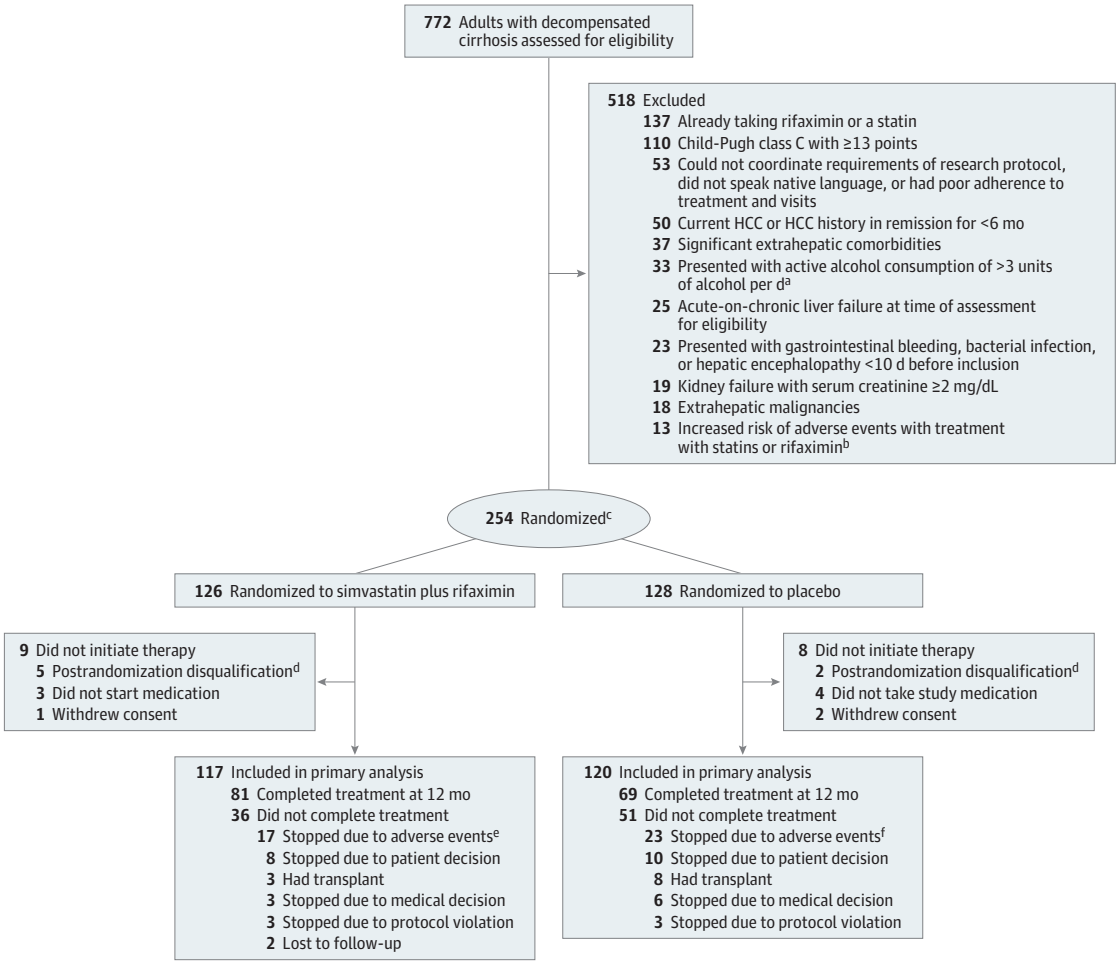
The analysis of the results was performed in a blinded manner using SAS software, version 9.4 (SAS Institute Inc).

Results

Study Population

Between January 2019 and December 2021, 772 patients with decompensated cirrhosis were assessed for eligibility and 254 patients were randomized into the 2 study groups. Of those, 17 were excluded due to varying reasons, leading to 237 patients being included in either the simvastatin plus rifaximin group (n = 117) or the placebo group (n = 120). Of all patients included, 150 (63%) completed the study protocol. **Figure 1** summarizes the study flow. Reasons for not completing the study protocol were occurrence of adverse events (complications causing death, recurrent hepatic encephalopathy, or rhabdomyolysis; 40 patients), patient decision (18 patients), liver transplant (11 patients), medical decision (9 patients), protocol violation (6 patients), and loss to follow-up (3 patients). Median follow-up was 365 days (IQR, 365-369 days) in the simvastatin plus rifaximin group and 365 days (IQR, 350-369 days) in the placebo group, and median treatment duration was 360 days (IQR, 274-369 days) in the simvastatin plus rifaximin group and 350 days (IQR, 119-369 days) in the placebo group. Baseline characteristics of the patients were similar in the 2 groups (**Table 1**). Patients had a mean age of 57.0 (SD, 9.7) years, the majority were male (72%), and alcohol-related cirrhosis was the most common etiology (80%).

Figure 1. Flow of the Study Population



HCC indicates hepatocellular carcinoma.

[a]One unit is equivalent to 10 g of alcohol.

[b]Creatine kinase levels of more than 50% of the upper limit of normal at inclusion, history of rhabdomyolysis, history of intestinal obstruction, or contraindication or known sensitivity to statins or rifaximin.

[c]Patients were stratified according to Child-Pugh class B or C.

[d]Patients met the inclusion criteria and none of the exclusion criteria at the screening visit, but at the randomization visit did not meet inclusion criteria or did meet some of the exclusion criteria.

[e]Three were episodes of recurrent hepatic encephalopathy.

[f]Eight were episodes of recurrent hepatic encephalopathy.

Development of ACLF

A total of 38 patients presented with at least 1 episode of ACLF, 21 patients in the simvastatin plus rifaximin group and 17 patients in the placebo group (hazard ratio, 1.23; 95% CI, 0.65-2.34) (**Table 2**; eTable 4 in Supplement 2). Cumulative incidence of ACLF during the study period is shown in **Figure 2**. Similar results were found in the modified intention-to-treat and per-protocol populations and in the post hoc analysis including 7 patients who were randomized but did not start study medication (4 who were lost to follow-up and 3 who had major intercurrent clinical events before baseline) (Figure 2).

The severity grade of ACLF was similar between the 2 groups: 8 (38.1%; 95% CI, 18.1%-61.6%), 9 (42.9%; 95% CI, 21.8%-66.0%), and 4 (19%; 95% CI, 5.4%-41.9%) episodes each of ACLF grades I, II, and III in the simvastatin plus rifaximin group, and 9 (52.9%; 95% CI, 27.8%-77%), 5 (29.4%; 95% CI, 10.3%-56%), and 3 (17.6%; 95% CI, 3.8%-43.4%) episodes, respectively, in the placebo group (P = .70). There were no significant differences between the 2 groups with respect to the prevalence of organ failure (eTable 5 in Supplement 2). The annual rate of ACLF was 23.58 (95% CI, 14.98-37.12) vs 19.48 (95% CI, 11.86-32.01) episodes per 100 patient-years in the simvastatin plus rifaximin and placebo groups, respectively, with a rate ratio of 1.21 (95% CI, 0.64-2.29) and no significant differences between study groups (P = .56).

Mortality, Complications of Cirrhosis, and Effects on Cholesterol Levels

Twenty-two patients (19%) died (n = 17) or received liver transplants (n = 5) in the simvastatin plus rifaximin group vs 29 (25%) in the placebo group (17 died; 12 had transplants) (hazard

Table 1. Baseline Characteristics of the Study Population

Characteristics	Simvastatin plus rifaximin (n = 117)	Placebo (n = 120)
Age, y	58 (9)	56 (10)
Sex, No. (%)		
Female	29 (24.8)	38 (31.7)
Male	88 (75.2)	82 (68.3)
Race, No. (%)		
Arab	1 (0.9)	0
Asian	1 (0.9)	1 (0.8)
Black	3 (2.6)	0
Hispanic	4 (3.5)	4 (3.3)
Turkish	0	2 (1.6)
White	108 (92.4)	113 (94.2)
Alcohol consumption, No. (%)		
Current	12 (11.4)	17 (16.5)
Previous	86 (81.9)	77 (74.8)
None	7 (6.7)	9 (8.7)
Comorbidities, No. (%)		
Type 2 diabetes	28 (23.9)	24 (20.5)
Arterial hypertension	26 (22.2)	37 (31.6)
Obesity	20 (17.0)	17 (14.5)
Hypercholesterolemia	6 (5.1)	10 (8.5)
Chronic kidney disease	4 (3.4)	5 (4.3)
Chronic obstructive pulmonary disease	2 (1.7)	5 (4.3)
Medications for liver disease, No. (%)		
Lactulose	67 (57.3)	58 (48.3)
β-Blockers[a]	60 (51.3)	56 (46.6)
Norfloxacin	9 (7.7)	13 (10.8)
Etiological factors of cirrhosis, No. (%)		
Alcohol consumption	97 (82.9)	92 (76.7)
MASLD	15 (12.8)	24 (20.0)
Hepatitis C	13 (11.1)	6 (5.0)
Hepatitis B	6 (5.1)	8 (6.7)
Cryptogenic	5 (4.3)	3 (2.5)
Autoimmune hepatitis	2 (1.7)	5 (4.2)
Primary biliary cholangitis	2 (1.7)	4 (3.3)
Hemochromatosis	2 (1.7)	1 (0.8)
Hepatitis delta	1 (0.8)	3 (2.5)
Primary sclerosing cholangitis	0	2 (1.7)
Other[b]	0	2 (1.7)
Ascites grade, No. (%)[c]	68 (58.1)	59 (49.2)
I	24 (20.5)	23 (19.2)
II	35 (29.9)	24 (20.0)
III	9 (7.7)	12 (10.0)
Previous decompensations, No. (%)		
Ascites	105 (89.7)	104 (86.7)
Bacterial infection	40 (34.2)	31 (25.8)
Hepatic encephalopathy	34 (29.1)	37 (30.8)
Gastrointestinal bleeding	32 (27.4)	33 (27.5)
Child-Pugh class, No. (%)[d]		
B	97 (82.9)	97 (80.8)
C	20 (17.0)	23 (19.2)
MELD score, mean (SD)[e]	14 (3.6)	14 (3.2)

(continued)

Table 1. Baseline Characteristics of the Study Population (continued)

Characteristics	Simvastatin plus rifaximin (n = 117)	Placebo (n = 120)
Albumin, median (IQR), g/dL	3.4 (3.0-3.7)	3.4 (3.0-3.7)
Bilirubin, median (IQR), mg/dL	2.1 (1.4-3.0)	2.5 (1.5-3.2)
Creatinine, median (IQR), mg/dL	0.8 (0.72-1.0)	0.7 (0.6-0.9)
Platelet count, median (IQR), × 10^9/μL	104.0 (67.0-153.0)	109.0 (72.5-140.5)
Hemostasis: INR, median (IQR)	1.3 (1.2-1.5)	1.4 (1.2-1.5)

Abbreviations: INR, international normalized ratio; MASLD, metabolic dysfunction–associated steatotic liver disease.

SI conversion factor: To convert creatinine to micromoles per liter, multiply by 88.4.

[a] In the simvastatin plus rifaximin group, 40 participants were receiving treatment with propranolol and 20 with carvedilol; in the placebo group, 39 participants were receiving treatment with propranolol and 17 with carvedilol.

[b] One patient had toxic steatohepatitis and 1 patient had secondary biliary cirrhosis.

[c] Ascites is classified into 3 grades: I corresponds to ascites that can be diagnosed only by abdominal ultrasound; II is ascites that can be identified on physical examination and occupies the abdominal flanks; and III is tense ascites that occupies and distends the abdominal cavity.

[d] The Child-Pugh classification of liver dysfunction in patients with cirrhosis uses clinical findings (ascites and hepatic encephalopathy) and laboratory values (bilirubin, albumin, and INR). It ranges from 5 to 15 points and is divided into 3 categories of increasing severity: class A, 5 to 6 points; class B, 7 to 9 points; and class C, 10 to 15 points.

[e] The Model for End-Stage Liver Disease (MELD) score uses 3 laboratory values to measure the severity of liver dysfunction: bilirubin, creatinine, and INR. It ranges from 6 to 40 points, with higher scores indicating increasing severity.

Table 2. Incidence of ACLF, Death, Transplant, and Complications of Cirrhosis[a]

	No. (%)			
	Simvastatin plus rifaximin (n = 117)	Placebo (n = 120)	Absolute difference in proportions (95% CI)	Subdistribution hazard ratio (95% CI)[b]
Primary outcome				
ACLF[c]	21 (17.9)	17 (14.2)	3.78 (−9.15 to 16.60)	1.23 (0.65-2.34)
Secondary outcomes				
Death	17 (14.5)	17 (14.2)	0.36 (−12.55 to 13.19)	1.12 (0.56-2.26)
Transplant	5 (4.3)	12 (10.0)	−5.73 (−18.52 to 6.87)	0.41 (0.45-1.15)
Complications of cirrhosis[d]	50 (42.7)	55 (45.8)	−3.10 (−15.98 to 9.65)	0.93 (0.63-1.36)
Ascites	34 (29.1)	38 (31.7)	−2.61 (−15.23 to 10.22)	0.92 (0.58-1.47)
New	10/12 (83.3)	10/16 (62.5)	0.21 (−12.69 to 12.82)	0.92 (0.38-2.23)
Worsening	28/105 (26.7)	30/104 (28.8)	−1.07 (−13.68 to 11.85)	1.01 (0.60-1.68)
Bacterial infection[e]	28 (23.9)	31 (25.8)	−1.9 (−14.49 to 11.02)	0.94 (0.57-1.57)
Hepatic encephalopathy	21 (17.9)	22 (18.3)	−0.38 (−13.23 to 12.52)	1.09 (0.60-1.98)
Acute kidney injury[f]	18 (15.4)	22 (18.3)	−2.95 (−15.79 to 9.97)	0.75 (0.40-1.41)
Gastrointestinal bleeding	5 (4.3)	8 (6.7)	−2.39 (−15.22 to 10.22)	0.62 (0.21-1.88)
Additional outcomes				
ACLF, transplant, or death	30 (25.6)	36 (30.0)	−4.36 (−16.89 to 8.54)	0.80 (0.49-0.30)

Abbreviation: ACLF, acute-on-chronic liver failure.

[a] Cox model with competing risk adjusted by ACLF stratum (considering transplant or death competing events) for all complications of cirrhosis (considering other complications of cirrhosis competing events). The end points of transplant or death and ACLF, transplant, or death were calculated with a Cox model without considering competing risk adjusted by stratum.

[b] Primary, secondary, and additional outcomes were adjusted by Child-Pugh stratum.

[c] ACLF is a severe decompensation of cirrhosis characterized by failure of 1 or more organs or systems (including liver, kidney, brain, respiratory system, circulatory system, and coagulation) and associated with a poor short-term and mid-term prognosis.

[d] New ascites, worsening of ascites, hepatic encephalopathy, acute kidney injury, bacterial infection, and variceal bleeding.

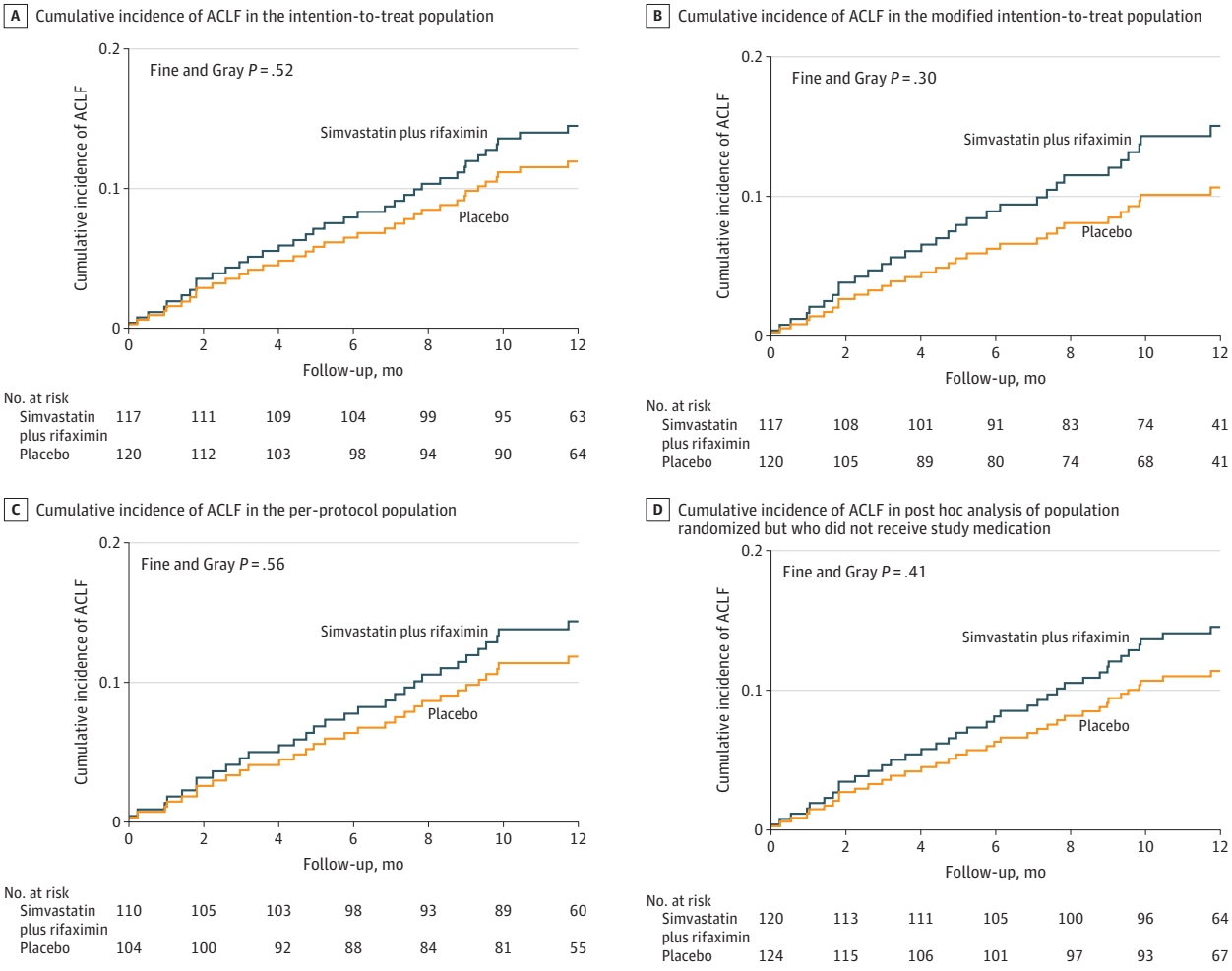
[e] Bacterial infection includes spontaneous bacterial peritonitis, spontaneous bacterial empyema, urinary tract infection, respiratory tract infection, skin infection, and bacteremia.

[f] Acute kidney injury in patients with cirrhosis defined as an increase in serum creatinine ≥0.3 mg/dL within 48 hours or ≥50% from baseline to a value of 1.5 mg/dL or higher, known or presumed to have occurred within the prior 7 days.

ratio, 0.75; 95% CI, 0.43-1.32; P = .32). Causes of death were related to ACLF/complications of cirrhosis in most cases (13/17 in the simvastatin plus rifaximin group and 12/17 in the placebo group (eTable 6 in Supplement 2). Moreover, ACLF-related mortality was not significantly different between the 2 groups (13/21 [40%] vs 12/17 [54%], respectively; P = .56).

Fifty patients (43%) developed at least 1 complication of cirrhosis other than ACLF in the simvastatin plus rifaximin group compared with 55 patients (46%) in the placebo group (hazard ratio, 0.93; 95% CI, 0.63-1.36). The incidence of the complications was similar between the 2 groups (Table 2). At the end of follow-up, mean MELD scores were 13 (SD, 4.8) and 12 (SD, 3.6) in the simvastatin plus rifaximin and placebo groups, respectively (adjusted mean difference, −0.42; 95% CI, −1.27 to 0.42). There were no significant differences in liver function tests or C-reactive protein levels between the 2 study

Figure 2. Cumulative Incidence of ACLF According to Study Group



Cumulative incidence of acute-on-chronic liver failure (ACLF) is shown for (A) the intention-to-treat population (primary analysis), (B) the modified intention-to-treat population, (C) the per-protocol population, and (D) the post hoc analysis including the population that was randomized but did not receive the study medication. The diagnosis of ACLF was based on the criteria of the European Association for the Study of the Liver–Chronic Liver Failure consortium. ACLF is a severe decompensation of cirrhosis accompanied by failure of 1 or more organs or systems (including liver, kidney, brain, respiratory system, circulatory system, and coagulation) and is associated with poor short-term and mid-term prognosis. The Fine and Gray Cox model approach using the randomization Child-Pugh strata under a competing risk strategy (death and transplant) was used to estimate cumulative incidence of ACLF. Median observation time was 365 days (IQR, 360-365 days).

groups (eTable 7 in Supplement 2). At the end of treatment, total serum cholesterol levels were 138 mg/dL (95% CI, 131-144 mg/dL) in patients in the simvastatin plus rifaximin group compared with 152 mg/dL (95% CI, 145-159 mg/dL) in the placebo group (adjusted absolute difference, 14.16 mg/dL [SEM, 4.64 mg/dL; 95% CI, 5.05-23.28 mg/dL]; P = .002). Corresponding values of serum low-density lipoprotein cholesterol were 70 mg/dL (95% CI, 66-76 mg/dL) vs 88 mg/dL (95% CI, 82-93 mg/dL), respectively (adjusted absolute difference, 17.10 mg/dL [SEM, 3.51 mg/dL; 95% CI, 10.20-24.00 mg/dL]; P < .001). (To convert total and low-density lipoprotein cholesterol to millimoles per liter, multiply by 0.259.)

The annual rate of hospitalizations was 50 (95% CI, 36.7-68.1) vs 58 (95% CI, 43.3-77.4) per 100 patient-years in the simvastatin plus rifaximin and placebo groups, respectively, with a rate ratio of 0.86 (95% CI, 0.58-1.29) and no significant differences between study groups.

Adverse Events

Adverse events were common in both groups (426 events in 101 patients in the simvastatin plus rifaximin group and 419 events in 100 patients in the placebo group) (Clopper-Pearson interval, −9.89 to 15.85; P = .59). There were no significant differences between groups in the different types of adverse events (**Table 3**). The incidences of serious adverse events (44 [37.6%] vs 50 [41.7%]; absolute difference in proportions, −4.06; 95% CI, −16.61 to 8.55; P = .79) and fatal adverse events (17 [14.5%] vs 17 [14.2%]; absolute difference in proportions, −0.51; 95% CI, −9.39 to 8.55; P > .99) were similar between groups. Of note, 3 patients (2.6%) in the simvastatin

Table 3. Adverse Events According to Study Group

System organ classification	Simvastatin plus rifaximin		Placebo		Absolute difference in proportions (95% CI)
	Events, No.	Participants, No. (%) [n = 117]	Events, No.	Participants, No. (%) [n = 120]	
All	426	101 (86.3)	419	100 (83.3)	2.99 (−9.89 to 15.85)
Hepatobiliary disorders	85	44 (37.6)	91	46 (38.3)	−0.73 (−13.56 to 11.89)
Gastrointestinal disorders	53	35 (29.9)	62	40 (33.3)	−3.42 (−16.06 to 9.39)
Infection	64	33 (28.2)	45	33 (27.5)	0.71 (−11.89 to 13.55)
Musculoskeletal and connective tissue disorders[a]	39	32 (27.4)	30	26 (21.7)	5.68 (−6.99 to 18.50)
Metabolism and nutrition disorders	33	21 (17.9)	26	19 (15.8)	2.12 (−10.79 to 14.97)
Kidney and urinary disorders	31	19 (16.2)	32	21 (17.5)	−1.26 (−14.12 to 11.64)
Nervous system disorders	18	14 (12.0)	7	7 (5.8)	6.13 (−6.83 to 18.67)
General disorders	13	12 (10.3)	30	23 (19.2)	−8.91 (−21.66 to 3.99)
Blood and lymphatic system disorders	14	10 (8.5)	17	14 (11.7)	−3.12 (−15.99 to 9.59)
Skin and subcutaneous tissue disorders	11	10 (8.5)	11	9 (7.5)	1.05 (−11.86 to 13.62)
Reproductive system and breast disorders	11	10 (8.5)	8	7 (5.8)	2.71 (−10.20 to 15.23)
Respiratory and thoracic and mediastinal disorders	11	10 (8.5)	11	6 (5.0)	3.55 (−9.37 to 16.06)
Neoplasms	9	9 (7.7)	7	6 (5.0)	2.69 (−10.21 to 15.23)
Injury, poisoning, and procedural complications	11	9 (7.7)	5	5 (4.2)	3.53 (−9.38 to 16.06)
Investigations[b]	4	4 (3.4)	8	7 (5.8)	−2.41 (−15.22 to 10.22)
Surgical and medical procedures	4	4 (3.4)	7	5 (4.2)	−0.75 (−13.56 to 11.89)
Cardiac disorders	4	4 (3.4)	5	5 (4.2)	−0.75 (−13.56 to 11.89)
Vascular disorders	4	4 (3.4)	4	4 (3.3)	0.09 (−12.73 to 12.73)
Eye disorders	4	3 (2.6)	2	2 (1.7)	0.90 (−11.89 to 13.56)
Psychiatric disorders	2	2 (1.7)	8	7 (5.8)	−4.12 (−16.88 to 8.55)
Immune system disorders	1	1 (0.9)	3	3 (2.5)	−1.65 (−14.39 to 11.06)

[a] Three patients in the simvastatin plus rifaximin group presented with 1 episode of rhabdomyolysis (2.5%) vs zero episodes in zero patients in the placebo group.

[b] Adverse events that happened at the time of the study visit (eg, a patient had a fever at the visit).

plus rifaximin group developed self-limited rhabdomyolysis vs no patients in the placebo group.

Discussion

In this large, international, multicenter, randomized, placebo-controlled trial, 20 mg of simvastatin plus 1200 mg of rifaximin daily did not reduce the development or severity of ACLF in patients with decompensated cirrhosis. Simvastatin plus rifaximin had no effect on transplant or death or incidence of other complications of cirrhosis. The rate of adverse events was similarly high in the 2 study groups.

Studies assessing statins in prevention of cirrhosis progression have shown conflicting results.[26,30] The rationale for the use of statins in cirrhosis is based on prospective studies showing that statins reduce portal pressure[31-33] and retrospective studies showing that treatment with statins was associated with beneficial effects on liver outcomes.[13-17,34,35] A randomized, double-blind clinical trial of simvastatin, 40 mg/d, vs placebo in patients with cirrhosis after variceal bleeding was negative with respect to the primary composite end point of rebleeding and death but was positive in a secondary end point of death alone.[18] Our study did not show significant differences in survival between patients treated with placebo and those treated with simvastatin plus rifaximin. Reasons for the discrepant findings may be related to differences in populations evaluated (less severe impairment in liver function in the former study, with MELD scores of 10 vs 14), duration of therapy (24 months in the former vs 12 months in the latter), and dose of simvastatin used (40 mg/d vs 20 mg/d, respectively). However, our study did not show significant differences in the rate and severity of ACLF or in the most relevant complications of cirrhosis, including ascites, variceal bleeding, hepatic encephalopathy, bacterial infection, and acute kidney injury. Finally, treatment with simvastatin plus rifaximin was not associated with an improvement in liver or kidney function tests or MELD score.

Simvastatin was chosen for this study because it is one of the most widely used statins for cardiovascular prevention and has been extensively investigated in cirrhosis. The dose of simvastatin of 20 mg/d was chosen on the basis of a previous randomized placebo-controlled study comparing doses of 20 mg/d and 40 mg/d, which showed a high frequency of rhabdomyolysis in patients treated with 40 mg/d but not in those treated with 20 mg/d.[23]

In the current study, simvastatin was given in combination with rifaximin.[21,36,37] Rifaximin is recommended in patients with cirrhosis for prevention of recurrent hepatic encephalopathy.[27] In this study, no beneficial effects of

rifaximin on preventing ACLF or other complications was observed when given in combination with simvastatin. Our results therefore do not support the use of rifaximin in the management of patients with decompensated cirrhosis for indications other than prevention of recurrent hepatic encephalopathy.

Limitations

Our study has some limitations. First, most patients had alcohol-related cirrhosis, whereas less than one-fifth had cirrhosis related to metabolic dysfunction-associated steatotic liver disease (MASLD) and an even lower proportion had hepatitis C- or hepatitis B-associated cirrhosis. Therefore, we do not know if the same findings would apply to a population with a higher percentage of viral hepatitis-associated or MASLD-related cirrhosis. Second, the dose of simvastatin of 20 mg/d is in the low range of doses for lipid-lowering effects; however, this dose has similar anti-inflammatory effects compared with higher doses in patients with diabetes or cardiovascular disease.[38,39] Finally, the participants of this study had cirrhosis with moderate to severe liver function impairment, and it is unclear whether our findings would apply to patients with less advanced cirrhosis.

Conclusions

In conclusion, the LIVERHOPE trial did not find that addition of simvastatin plus rifaximin to standard therapy reduced the occurrence of ACLF in patients with decompensated cirrhosis at high risk of clinical complications. Furthermore, simvastatin plus rifaximin had no effect on other complications of cirrhosis, survival, or liver function tests. Thus, our study does not support the combined use of simvastatin plus rifaximin to improve outcomes in patients with decompensated cirrhosis.

ARTICLE INFORMATION

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Author Affiliations: Liver Unit, Hospital Clínic de Barcelona, Barcelona, Spain (Pose, Juanola, Napoleone, Gratacós-Ginès, Pompili, Pérez-Guasch, Graupera, Ginès); Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain (Pose, Juanola, Napoleone, Gratacós-Ginès, Carol, Pérez-Guasch, Fabrellas, Graupera, Ginès); Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEReHD), Madrid, Spain (Pose, Solé, Alonso, Juanola, Napoleone, Gratacós-Ginès, Sánchez-Delgado, Morales-Ruiz, Carol, Pérez-Guasch, Fabrellas, Graupera, Soriano, Bañares, Vargas, Ginès); Liver Unit, Hospital Universitari Vall d'Hebron, Barcelona, Spain (Jiménez, Vargas); Vall d'Hebron Institut de Recerca, Liver Unit, Universitat Autonoma de Barcelona, Department of Medicine, Barcelona, Spain (Jiménez); Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy (Zaccherini, Pompili, Caraceni); Unit of Semeiotics, Liver and Alcohol-Related Diseases, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy (Zaccherini, Caraceni); Division of Gastroenterology and Hepatology, A. O. U. Città della Salute e della Scienza di Torino, University of Turin, Turin, Italy (Campion, Alessandria); Unit of Internal Medicine and Hepatology, Department of Medicine–DIMED, University and Hospital of Padova, Padova, Italy (Piano, Tonon, Angeli); Department of Internal Medicine I, University Hospital Frankfurt, Frankfurt am Main, Germany (Uschner); Department of Internal Medicine B, University Hospital Münster, Münster, Germany (Uschner, Laleman, Trebicka); Department of Gastroenterology and Hepatology, Amsterdam UMC, University of Amsterdam, Amsterdam Gastroenterology Endocrinology Metabolism, Amsterdam, the Netherlands (de Wit, Beuers); Service d'Hépatologie, AP-HP, Hôpital Beaujon, DMU DIGEST, Centre de Référence des Maladies Vasculaires du Foie, Clichy, France (Roux, Francoz); Centre de Recherche sur l'Inflammation, Inserm, UMR, Paris, France (Roux, Francoz); Institute for Liver and Digestive Health, University College London, London, United Kingdom (Gananandan, Mookerjee); Department of Gastroenterology and Hepatology, Cluster of Liver and Biliopancreatic Disorders and Liver Transplantation, University Hospitals Leuven, KU Leuven, Leuven, Belgium (Laleman); Department of Gastroenterology and Hepatology, Parc Tauli Hospital Universitari, Institut d'Investigació i Innovació Parc Taulí (I3PT-CERCA), Universitat Autònoma de Barcelona, Sabadell, Spain (Solé, Sánchez-Delgado); Digestive Department, Hospital General Universitario Gregorio Marañón, Madrid, Spain (Alonso, Bañares); Department of Gastroenterology, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain (Cuyàs, Soriano); Digestive Diseases Unit, Hospital Moisès Broggi, Sant Joan Despí, Barcelona, Spain (Ariza); Toronto Centre for Liver Disease, University Health Network, Toronto, Ontario, Canada (Ma); Division of Nephrology, Department of Medicine, Massachusetts General Hospital, Boston (Allegretti); Biochemistry and Molecular Genetics Department, Hospital Clínic of Barcelona, Barcelona, Spain (Morales-Ruiz); Biomedicine Department, University of Barcelona, Barcelona, Spain (Morales-Ruiz); Faculty of Nursing, University of Barcelona, Barcelona, Spain (Carol, Fabrellas); Clinical Trial Unit, Hospital Clínic of Barcelona, Barcelona, Spain (Pich, Martell, Joyera); Biostatistics and Data Management Core Facility, Institut D'Investigacions Biomédiques August Pi i Sunyer (IDIBAPS), Hospital Clínic of Barcelona, Barcelona, Spain (Domenech, Ríos); Biostatistics Unit, Faculty of Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain (Ríos, Torres); Epidemiology, Biostatistics, and Prevention Institute, University of Zurich, Zurich, Switzerland (Serra-Burriel); Section of Gastroenterology, Michael E. DeBakey Veterans Affairs Medical Center, Houston, Texas (Hernáez); VA Health Services Research and Development, Center for Innovations in Quality, Effectiveness, and Safety, Michael E. DeBakey Veterans Affairs Medical Center, Houston, Texas (Hernáez); Section of Gastroenterology and Hepatology, Department of Medicine, Baylor College of Medicine, Houston, Texas (Hernáez); Institute for Immunity, Transplantation, and Infection, Stanford University, Stanford, California (Solà); School of Medicine and Health Sciences, University of Barcelona, Barcelona, Spain (Graupera, Ginès); Medical Development and Translational Science, Evotec, Lyon, France (Watson); Department of Hepatology and Gastroenterology, Aarhus University, Aarhus, Denmark (Watson, Mookerjee); Instituto de Investigación Sanitaria Gregorio Marañón (IISGM), Facultad de Medicina, Universidad Complutense de Madrid, Madrid, Spain (Bañares); Division of Gastroenterology, Liver Unit, University of Alberta, Edmonton, Canada (Abraldes); Division of Gastroenterology and Hepatology, Mayo Clinic College of Medicine and Science, Rochester, Minnesota (Kamath).

Author Contributions: Drs Pose and Ginès had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Pose, Piano, Juanola, Morales-Ruiz, Pich, Domenech, Ríos, Torres, Serra-Burriel, Hernáez, Solà, Graupera, Beuers, Trebicka, Angeli, Vargas, Kamath, Ginès.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Pose, Ginès.
Critical review of the manuscript for important intellectual content: Pose, Jiménez, Zaccherini, Campion, Piano, Uschner, de Wit, Roux, Gananandan, Laleman, Solé, Alonso, Cuyàs, Ariza, Juanola, Ma, Napoleone, Gratacós-Ginès, Tonon, Pompili, Sánchez-Delgado, Allegretti, Morales-Ruiz, Carol, Fabrellas Padres, Martell, Ríos, Torres, Serra-Burriel, Hernáez, Solà, Graupera, Watson, Soriano, Bañares, Mookerjee, Francoz, Beuers, Trebicka, Angeli, Alessandria, Caraceni, Vargas, Abraldes, Kamath, Ginès.
Statistical analysis: Domenech, Ríos, Torres, Serra-Burriel, Ginès.
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Administrative, technical, or material support: Campion, Piano, Uschner, Ariza, Juanola, Ma, Napoleone, Carol, Pérez-Guasch, Pich, Martell, Hernáez, Graupera, Mookerjee, Trebicka, Ginès.

Supervision: Pose, Laleman, Solé, Ariza, Juanola, Morales-Ruiz, Carol, Fabrellas Padres, Pich, Serra-Burriel, Graupera, Watson, Mookerjee, Francoz, Beuers, Trebicka, Vargas, Abraldes, Ginès.

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REFERENCES

1. Sepanlou SG, Safiri S, Bisignano C, et al; GBD 2017 Cirrhosis Collaborators. The global, regional, and national burden of cirrhosis by cause in 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Gastroenterol Hepatol*. 2020;5(3):245-266. doi:10.1016/S2468-1253(19)30349-8

2. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. *J Hepatol*. 2006;44(1):217-231. doi:10.1016/j.jhep.2005.10.013

3. Ginès P, Krag A, Abraldes JG, Solà E, Fabrellas N, Kamath PS. Liver cirrhosis. *Lancet*. 2021;398 (10308):1359-1376. doi:10.1016/S0140-6736(21)01374-X

4. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg*. 1973;60 (8):646-649. doi:10.1002/bjs.1800600817

5. Hernaez R, Solà E, Moreau R, Ginès P. Acute-on-chronic liver failure: an update. *Gut*. 2017;66(3):541-553. doi:10.1136/gutjnl-2016-312670

6. Arroyo V, Moreau R, Jalan R. Acute-on-chronic liver failure. *N Engl J Med*. 2020;382(22):2137-2145. doi:10.1056/NEJMra1914900

7. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2019;73(24):3168-3209. doi:10.1016/j.jacc.2018.11.002

8. Kinlay S, Schwartz GG, Olsson AG, et al; Myocardial Ischemia Reduction With Aggressive Cholesterol Lowering Study Investigators. High-dose atorvastatin enhances the decline in inflammatory markers in patients with acute coronary syndromes in the MIRACL study. *Circulation*. 2003;108(13):1560-1566. doi:10.1161/01.CIR.0000091404.09558.AF

9. Hothersall E, McSharry C, Thomson NC. Potential therapeutic role for statins in respiratory disease. *Thorax*. 2006;61(8):729-734. doi:10.1136/thx.2005.057976

10. Wagner AH, Schwabe O, Hecker M. Atorvastatin inhibition of cytokine-inducible nitric oxide synthase expression in native endothelial cells in situ. *Br J Pharmacol*. 2002;136(1):143-149. doi:10.1038/sj.bjp.0704678

11. Huang KC, Chen CW, Chen JC, Lin WW. HMG-CoA reductase inhibitors inhibit inducible nitric oxide synthase gene expression in macrophages. *J Biomed Sci*. 2003;10(4):396-405. doi:10.1007/BF02256431

12. Bosch J, Gracia-Sancho J, Abraldes JG. Cirrhosis as new indication for statins. *Gut*. 2020;69(5):953-962. doi:10.1136/gutjnl-2019-318237

13. Chang FM, Wang YP, Lang HC, et al. Statins decrease the risk of decompensation in hepatitis B virus- and hepatitis C virus-related cirrhosis: a population-based study. *Hepatology*. 2017;66(3):896-907. doi:10.1002/hep.29172

14. Bang UC, Benfield T, Bendtsen F. Reduced risk of decompensation and death associated with use of statins in patients with alcoholic cirrhosis: a nationwide case-cohort study. *Aliment Pharmacol Ther*. 2017;46(7):673-680. doi:10.1111/apt.14243

15. Mohanty A, Tate JP, Garcia-Tsao G. Statins are associated with a decreased risk of decompensation and death in veterans with hepatitis C-related compensated cirrhosis. *Gastroenterology*. 2016;150(2):430-440. doi:10.1053/j.gastro.2015.10.007

16. Kumar S, Grace ND, Qamar AA. Statin use in patients with cirrhosis: a retrospective cohort study. *Dig Dis Sci*. 2014;59(8):1958-1965. doi:10.1007/s10620-014-3179-2

17. Motzkus-Feagans C, Pakyz AL, Ratliff SM, Bajaj JS, Lapane KL. Statin use and infections in veterans with cirrhosis. *Aliment Pharmacol Ther*. 2013;38(6):611-618. doi:10.1111/apt.12430

18. Abraldes JG, Villanueva C, Aracil C, et al; BLEPS Study Group. Addition of simvastatin to standard therapy for the prevention of variceal rebleeding does not reduce rebleeding but increases survival in patients with cirrhosis. *Gastroenterology*. 2016;150(5):1160-1170. doi:10.1053/j.gastro.2016.01.004

19. Trebicka J, Macnaughtan J, Schnabl B, Shawcross DL, Bajaj JS. The microbiota in cirrhosis and its role in hepatic decompensation. *J Hepatol*. 2021;75(suppl 1):S67-S81. doi:10.1016/j.jhep.2020.11.013

20. Bass NM, Mullen KD, Sanyal A, et al. Rifaximin treatment in hepatic encephalopathy. *N Engl J Med*. 2010;362(12):1071-1081. doi:10.1056/NEJMoa0907893

21. Patel VC, Lee S, McPhail MJW, et al. Rifaximin-α reduces gut-derived inflammation and mucin degradation in cirrhosis and encephalopathy: RIFSYS randomised controlled trial. *J Hepatol*. 2022;76(2):332-342. doi:10.1016/j.jhep.2021.09.010

22. Caraceni P, Vargas V, Solà E, et al; LIVERHOPE Consortium. The use of rifaximin in patients with cirrhosis. *Hepatology*. 2021;74(3):1660-1673. doi:10.1002/hep.31708

23. Pose E, Napoleone L, Amin A, et al. Safety of two different doses of simvastatin plus rifaximin in decompensated cirrhosis (LIVERHOPE-SAFETY): a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Gastroenterol Hepatol*. 2020;5(1):31-41. doi:10.1016/S2468-1253(19)30320-6

24. Kamath PS, Wiesner RH, Malinchoc M, et al. A model to predict survival in patients with end-stage liver disease. *Hepatology*. 2001;33(2):464-470. doi:10.1053/jhep.2001.22172

25. Moreau R, Jalan R, Ginès P, et al; CANONIC Study Investigators of the EASL–CLIF Consortium. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. *Gastroenterology*. 2013;144(7):1426-1437. doi:10.1053/j.gastro.2013.02.042

26. Angeli P, Bernardi M, Villanueva C, et al; European Association for the Study of the Liver. EASL clinical practice guidelines for the management of patients with decompensated

cirrhosis. *J Hepatol*. 2018;69(2):406-460. doi:10.1016/j.jhep.2018.03.024

27. Montagnese S, Rautou PE, Romero-Gómez M, et al; European Association for the Study of the Liver. EASL clinical practice guidelines on the management of hepatic encephalopathy. *J Hepatol*. 2022;77(3):807-824. doi:10.1016/j.jhep.2022.06.001

28. Piano S, Tonon M, Vettore E, et al. Incidence, predictors and outcomes of acute-on-chronic liver failure in outpatients with cirrhosis. *J Hepatol*. 2017;67(6):1177-1184. doi:10.1016/j.jhep.2017.07.008

29. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94:496-509. doi:10.1080/01621459.1999.10474144

30. de Franchis R, Bosch J, Garcia-Tsao G, Reiberger T, Ripoll C; Baveno VII Faculty. Baveno VII—renewing consensus in portal hypertension. *J Hepatol*. 2022;76(4):959-974. doi:10.1016/j.jhep.2021.12.022

31. Abraldes JG, Albillos A, Bañares R, et al. Simvastatin lowers portal pressure in patients with cirrhosis and portal hypertension: a randomized controlled trial. *Gastroenterology*. 2009;136(5):1651-1658. doi:10.1053/j.gastro.2009.01.043

32. Pollo-Flores P, Soldan M, Santos UC, et al. Three months of simvastatin therapy vs. placebo for severe portal hypertension in cirrhosis: a randomized controlled trial. *Dig Liver Dis*. 2015;47(11):957-963. doi:10.1016/j.dld.2015.07.156

33. Bishnu S, Ahammed SM, Sarkar A, et al. Effects of atorvastatin on portal hemodynamics and clinical outcomes in patients with cirrhosis with portal hypertension: a proof-of-concept study. *Eur J Gastroenterol Hepatol*. 2018;30(1):54-59. doi:10.1097/MEG.0000000000001006

34. Vijayaraghavan R, Jindal A, Arora V, Choudhary A, Kumar G, Sarin SK. Hemodynamic effects of adding simvastatin to carvedilol for primary prophylaxis of variceal bleeding: a randomized controlled trial. *Am J Gastroenterol*. 2020;115(5):729-737. doi:10.14309/ajg.0000000000000551

35. Kronborg TM, Schierwagen R, Trošt K, et al. Atorvastatin for patients with cirrhosis: a randomized, placebo-controlled trial. *Hepatol Commun*. 2023;7(12):7. doi:10.1097/HC9.0000000000000332

36. Kalambokis GN, Mouzaki A, Rodi M, et al. Rifaximin improves systemic hemodynamics and renal function in patients with alcohol-related cirrhosis and ascites. *Clin Gastroenterol Hepatol*. 2012;10(7):815-818. doi:10.1016/j.cgh.2012.02.025

37. Kimer N, Pedersen JS, Tavenier J, et al; CoRif Study Group. Rifaximin has minor effects on bacterial composition, inflammation, and bacterial translocation in cirrhosis: a randomized trial. *J Gastroenterol Hepatol*. 2018;33(1):307-314. doi:10.1111/jgh.13852

38. Plenge JK, Hernandez TL, Weil KM, et al. Simvastatin lowers C-reactive protein within 14 days: an effect independent of low-density lipoprotein cholesterol reduction. *Circulation*. 2002;106(12):1447-1452. doi:10.1161/01.CIR.0000029743.68247.31

39. Hernandez TL, Capell WH, Wolfe P, Gerard LA, Eckel RH. Time course of C-reactive protein reduction with simvastatin therapy in patients with type 2 diabetes mellitus. *Am J Cardiol*. 2006;98(12):1656-1659. doi:10.1016/j.amjcard.2006.07.047