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The Use of Rifaximin in the Prevention of Overt Hepatic Encephalopathy After Transjugular Intrahepatic Portosystemic Shunt

A Randomized Controlled Trial

Christophe Bureau, MD, PhD; Dominique Thabut, MD, PhD; Caroline Jezequel, MD; Isabelle Archambeaud, MD; Louis D'Alteroche, MD, PhD; Sêbastien Dharancy, MD, PhD; Patrick Borentain, MD; Frédéric Oberti, MD, PhD; Aurélie Plessier, MD; Victor De Ledinghen, MD, PhD; Nathalie Ganne-Carrié, MD, PhD; Nicolas Carbonell, MD; Vanessa Rousseau, PhD; Agnès Sommet, MD, PhD; Jean Marie Péron, MD, PhD; and Jean Pierre Vinel, MD

Background: The efficacy of rifaximin in the secondary prevention of overt hepatic encephalopathy (HE) is well documented, but its effectiveness in preventing a first episode in patients after transjugular intrahepatic portosystemic shunt (TIPS) has not been established.

Objective: To determine whether rifaximin prevents overt HE after TIPS compared with placebo.

Design: Randomized, double-blind, multicenter, placebo-controlled trial. (ClinicalTrials.gov: NCT02016196)

Participants: 197 patients with cirrhosis undergoing TIPS for intractable ascites or prevention of variceal rebleeding.

Intervention: Patients were randomly assigned to receive rifaximin (600 mg twice daily) or placebo, beginning 14 days before TIPS and continuing for 168 days after the procedure.

Measurements: The primary efficacy end point was incidence of overt HE within 168 days after the TIPS procedure.

Results: An episode of overt HE occurred in 34% (95% CI, 25% to 44%) of patients in the rifaximin group ($n = 93$) and 53% (CI, 43% to 63%) in the placebo group ($n = 93$) during the postprocedure period (odds ratio, 0.48 [CI, 0.27 to 0.87]). Neither the incidence of adverse events nor transplant-free survival was significantly different between the 2 groups.

Limitations: The study's conclusion applies mainly to patients with alcoholic cirrhosis, who made up the study population. The potential benefit of rifaximin 6 months after TIPS and beyond remains to be investigated.

Conclusion: In patients with cirrhosis treated with TIPS, rifaximin was well tolerated and reduced the risk for overt HE. Rifaximin should therefore be considered for prophylaxis of post-TIPS HE.

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For author, article, and disclosure information, see end of text.
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In patients with cirrhosis, transjugular intrahepatic portosystemic shunt (TIPS) is now a standard procedure for treating portal hypertension–related complications (1). The main indications for TIPS include recurrent ascites and variceal bleeding, either to treat refractory bleeding or to prevent rebleeding.

Historically, the main drawbacks of TIPS have been shunt dysfunction and the development of hepatic encephalopathy (HE). The rate of shunt dysfunction has been dramatically reduced by the use of polytetrafluoroethylene-covered stents (2, 3), which are not associated with an increased risk for HE compared with bare stents (3–6). Nevertheless, HE remains the main side effect of TIPS, despite the procedure being contraindicated in patients with a high risk for this complication. On average, an episode of overt HE occurs in 35% to 50% of patients after TIPS (7, 8). According to U.S. and European guidelines published in 2014, no prophylactic therapy is recommended to prevent overt HE after TIPS placement in these patients (9). Indeed, one study failed to show any benefit of lactulose or rifaximin in preventing a first post-TIPS HE episode (10). However, the sample size and length of follow-up were limited, precluding any definitive conclusion.

Rifaximin is a poorly absorbed antibiotic commonly used as secondary prophylaxis against HE in patients with cirrhosis (11, 12). In a pivotal study conducted by Bass and colleagues (13) in patients with a history of recurrent HE, the hazard ratio for an episode of HE was 0.42 (95% CI, 0.28 to 0.64) in those receiving rifaximin compared with the control group over 168 days. Hence, rifaximin is now approved for the secondary prevention of overt HE (9).

Therefore, we conducted this large double-blind, multicenter, randomized study to determine whether rifaximin prevents overt HE after TIPS compared with placebo.

Methods

Study Patients

Expert hepatologists recruited patients in tertiary university care centers to participate in the study. Potentially eligible patients had cirrhosis, were at least 18 years of age, and were planning to have TIPS placement to treat intractable ascites (1) or to prevent variceal rebleeding.

See also:

Web-Only
Supplement

Cirrhosis was diagnosed by liver biopsy or the usual clinical, biochemical, and endoscopic parameters. All patients were evaluated for HE at study entry and during follow-up according to the same West Haven modified criteria provided in the case report form and described in Supplement Table 2 (available at Annals.org). A list of all exclusion criteria is provided on page 26 of the Supplement (available at Annals.org) . The main exclusion criteria were a Child–Pugh score above 12, hepatocellular carcinoma beyond Milan criteria, recurrent or persistent overt HE (grade 2 or higher according to West Haven modified criteria), and a known allergy to rifaximin. All patients or their legal representative provided written informed consent.

Study Design and Procedure

The study protocol was approved by the French National Ethics Committee (2 May 2013) and is available in the Supplement. After the inclusion and exclusion criteria were checked by one of the center investigators, the trial methodologist randomly assigned participants to receive rifaximin or placebo (1:1 ratio) according to a computer-generated randomization list available on a dedicated website. Randomization was centralized and stratified with respect to the presence or absence of a history of overt HE before TIPS and to Child–Pugh classification (A+B or C). The chosen block size was random. The list was generated by using the command *ralloc* in Stata, version 14.0 (StataCorp). Details about the randomization, allocation, and blinding procedures are provided in the Supplement. The investigational treatments were prepared by the Toulouse University Hospital pharmacy. Both treatments were similar in all aspects (appearance, size, and color). The packaging followed the randomization list and allowed blinding to be maintained. Three capsules of rifaximin, 200 mg, or placebo were given twice a day (morning and evening) for 2 weeks before TIPS and for 168 days after the procedure. After 14 days of treatment, the TIPS procedure was carried out under sedation as previously described (5). All patients received 10-mm covered stents (Viatorr TIPS Endoprosthesis [W.L. Gore & Associates]), dilated to 8 or 10 mm according to hemodynamic response. The aim was to reduce the portosystemic pressure gradient below 12 mm Hg (difference between the portal vein pressure and the vena cava pressure after the prosthesis was released).

Treatment was maintained for 182 days (14 days before TIPS plus 168 days afterward). Lactulose for HE prevention was not allowed, although it could be used to treat an episode of overt HE during follow-up. For patients with at least 2 relapses, study medication was stopped and open-label rifaximin was prescribed according to current guidelines. The dosage and duration of any new medication initiated during the study period were recorded.

Efficacy and Safety Assessment

Planned visits occurred on days 0 and 14 before the TIPS procedure; then every 28 days for 168 days (at which point the study medication was discontinued); and then every 3 months until 1 year, death, or liver transplantation. At each visit, clinical and laboratory parameters were assessed. Liver disease–related complications and treatment modifications were recorded. Safety and adherence were systematically assessed by questioning the patients. At each visit, planned or otherwise, patients were evaluated for symptoms of overt HE. Asterixis was assessed by asking patients to extend their arms with wrists flexed backward and fingers spread wide for 30 seconds. If asterixis was the only manifestation of HE, it was referred to as "isolated" asterixis. Overt HE was defined as HE grade 2 or higher according to West Haven modified criteria (9), with grade 2 including isolated asterixis. In the absence of overt HE, the Psychometric Hepatic Encephalopathy Score (PHES) was assessed (14). Patients were classified as having minimal HE if their PHES was less than −4. Information on overt HE episodes that may have occurred since the previous visit was also collected.

Adverse events reported by participants were recorded at each visit. Serious adverse events were those that resulted in death, were life threatening, required hospitalization or prolongation of hospitalization, resulted in substantial or persistent disability or incapacity, represented a congenital anomaly or malformation, or were considered medically serious. The definition of *serious adverse event* is provided in the study protocol (Supplement).

The primary end point was incidence of overt HE occurring during the 168 days after TIPS. Overt HE was defined as HE of grade 2 or higher according to West Haven modified criteria, with grade 2 including isolated asterixis (asterixis as the only manifestation of HE).

Secondary end points were the incidence of other liver disease–related complications (gastrointestinal bleeding, acute kidney injury, and hepatocellular carcinoma), transplant-free survival at 168 days, and duration and severity of the first overt HE episode. Post hoc exploratory analyses were added to assess the incidence of heart failure and infections after the TIPS procedure. The incidence of adverse events and serious adverse events were safety end points.

Sample Size

Sample size calculation was based on the assumption that 17% and 35% of the patients receiving rifaximin and placebo, respectively, would have at least 1 episode of overt HE within the first 168 days after TIPS. To detect such a difference with a statistical power of greater than 80% and anticipating a 5% loss to follow-up, including patients who did not receive TIPS, a minimum of 89 patients per group was needed (2-sided test, $\alpha < 0.050$).

Intention-to-Treat and Safety Populations

Analysis of the primary end point, incidence of overt HE occurring within 168 days after TIPS, was carried out in the sample of patients who had actually been treated with TIPS (intention-to-treat analysis). Safety analysis was performed for all patients who had received at least 1 dose of the study medications.

Statistical Analysis

Quantitative variables are presented as means and SDs or medians and interquartile ranges, and categorical

variables are presented as numbers and percentages with 95% CIs. Categorical variables were compared between the 2 treatment groups by using the χ^2 test (or Fisher exact test, as appropriate); quantitative variables were compared by using the Wilcoxon–Mann–Whitney test. For all outcomes (primary, secondary, and safety), the treatment effect was estimated by the difference in proportions between the 2 treatment groups and its 95% CI.

For the primary outcome, a logistic regression model was used to estimate the association between treatment group and an episode of overt HE after TIPS (within 168 days). This model was stratified by Child–Pugh class and the presence of a previous HE episode. The Wald method was used to calculate the binomial proportion CIs.

To account for time to the first episode of overt HE in the 168 days after TIPS, survival analysis was used. A cumulative incidence plot shows the probability of overt HE obtained from the inverses of Kaplan–Meier estimates. The distributions of time to overt HE were compared by using a log-rank test stratified by Child–Pugh class and the presence of a previous HE episode.

Likewise, sensitivity survival analyses were conducted for some patient subgroups: patients with and without a previous HE episode, those with minimal HE at baseline (defined according to PHES), and those without isolated asterixis. Finally, a sensitivity analysis was done to estimate the probability of minimal HE in the 168 days after TIPS.

All tests were 2-sided and considered significant at an α level of 0.050. Statistical analyses were conducted by 2 of the authors (V.R. and A.S.) using SAS software, version 9.4 (SAS Institute). PROC LOGISTIC was used for the logistic regression analysis; the macro *newsurv* (http://bioinformaticstools.mayo.edu/research/newsurv) was used for the survival analyses (see the **Supplement** for a list of SAS procedures used).

Role of the Funding Source

The French Public Health Ministry had no role in the design of the study; collection, analysis, or interpretation of the data; writing, review, or approval of the manuscript; or the decision to submit the manuscript for publication.

RESULTS

Study Patients

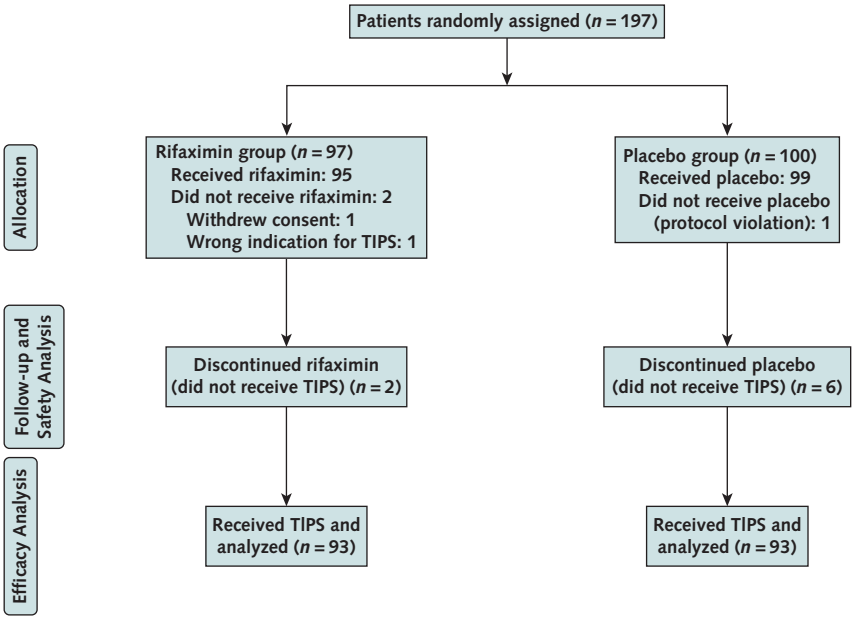
Between October 2013 and June 2016, a total of 197 patients were randomly assigned to receive a study drug at 12 investigative sites (**Table 1**). Of these patients, 194 received at least 1 dose of rifaximin or placebo (population for safety analysis) and 186 had TIPS placement (population for efficacy analysis) (**Figure 1**).

Table 1. Baseline Characteristics of 197 Randomly Assigned Patients

Characteristics	Rifaximin Group (*n* = 97)	Placebo Group (*n* = 100)	Total (*n* = 197)
Mean age (SD), *y*	61 (9)	58 (8)	60 (8)
Male sex, *n (%)*	73 (75)	79 (79)	152 (77)
Alcohol-related liver disease, *n (%)*	83 (86)	87 (87)	170 (86)
Active drinker, *n (%)*	9 (9)	12 (12)	21 (11)
Previous liver disease–related complications, *n (%)*			
PHT-related bleeding	32 (33)	41 (41)	73 (37)
Ascites	93 (96)	92 (92)	185 (94)
Jaundice	30 (31)	25 (25)	55 (28)
HCC	6 (6)	8 (8)	14 (7)
Hepatorenal syndrome	14 (14)	13 (13)	27 (14)
Overt HE	12 (12)	13 (12)	25 (13)
Chronic renal injury, *n (%)*	13 (13)	13 (13)	26 (13)
Diabetes, *n (%)*	42 (43)	34 (34)	76 (39)
Mean serum sodium level (SD), *mmol/L*	135 (4)	135 (5)	135 (4)
Mean serum creatinine level (SD)			
μmol/L	91 (31)	97 (40)	94 (36)
mg/dL	1.0 (0.3)	1.1 (0.5)	1.1 (0.4)
Mean serum albumin level (SD), *g/L*	33 (5)	33 (5)	33 (5)
Mean INR (SD)	1.3 (0.3)	1.4 (0.5)	1.4 (0.4)
Mean serum bilirubin level (SD)			
μmol/L	24 (16.0)	22 (14.0)	23 (15.0)
mg/dL	1.4 (1.0)	1.3 (0.8)	1.3 (0.9)
Mean platelet count (SD), $\times 10^9$/*L*	153 (59)	155 (83)	154 (72)
Mean ammonia level (SD), *mmol/L*	48 (22)	50 (30)	49 (26)
Mean Child–Pugh score (SD)*	8 (1)	8 (1)	8 (1)
Mean MELD score (SD)†	12 (4)	12 (4)	12 (4)
TIPS indication: ascites, *n (%)*	82 (85)	78 (78)	160 (81)
Mean PPG (SD), *mm Hg*			
Before TIPS	16 (4)	17 (5)	16 (5)
After TIPS	6 (3)	6 (2)	6 (2)
Mean shunt diameter (SD), *mm*	9.2 (1.1)	9.3 (1.0)	9.2 (1.1)
Minimal HE at baseline, *n (%)*	10 (10)	13 (13)	23 (12)

HCC = hepatocellular carcinoma; HE = hepatic encephalopathy; INR = international normalized ratio; MELD = Model for End-Stage Liver Disease; PHT = portal hypertension; PPG = portal pressure gradient; TIPS = transjugular intrahepatic portosystemic shunt.
* Child–Pugh scores range from 5 to 15, with higher scores indicating more severe disease.
† MELD scores range from 6 to 40, with higher scores indicating more severe disease.

Figure 1. Flow chart of the study.



TIPS = transjugular intrahepatic portosystemic shunt.

The main cause of cirrhosis was alcohol use disorder. The main indication for nonurgent TIPS was intractable ascites. Twenty-five patients (13%) had a history of an overt HE episode; 76 (39%) had diabetes at baseline. The mean Model for End-Stage Liver Disease score was 12 (SD, 4). The median duration of treatment was 181 days (interquartile range [IQR], 177 to 183 days) in the rifaximin group and 178 days (IQR, 59 to 181 days) in the placebo group. Early withdrawal occurred after a median of 50 days (IQR, 17 to 117 days) in 8 patients in the rifaximin group and 35 days (IQR, 23 to 49 days) in 9 patients in the placebo group.

Occurrence of Overt HE

During the treatment period, an episode of overt HE was observed in 32 of 93 patients in the rifaximin group (34% [CI, 25% to 44%]) and 49 of 93 patients in the placebo group (53% [CI, 43% to 63%]), with an estimated risk difference of −18 percentage points (CI, −32 to −4 percentage points [$P = 0.012$]). The odds ratio for the risk for an overt HE episode after TIPS was 0.48 (CI, 0.27 to 0.87 [$P = 0.015$]) in the rifaximin group compared with the placebo group, stratified according to Child–Pugh class and the presence of a previous HE episode. The cumulative incidence of overt HE during the 168-day treatment period, according to treatment group, is presented in **Figure 2**. The characteristics of the first episode of overt HE during the treatment period (grade, duration, and presence of a possible precipitating factor) are listed in **Table 2** and **Appendix Table 1** (available at Annals.org). In a post hoc analysis of the subset of 24 patients with a previous HE episode, the cumulative incidence of overt HE after TIPS was 33% (CI, 1% to 55%) with rifaximin versus 83% (CI, 41% to 95%) with placebo (**Appendix Figure**, *top*, available at Annals.org). In a post hoc analysis in the subgroup of patients without a previous episode of overt HE (162 patients; **Appendix Figure**, *bottom*, available at Annals.org), the incidence of overt HE at 168 days was 35% (CI, 24% to 45%) in the rifaximin group versus 51% (CI, 38% to 61%) in the placebo group (stratified log-rank $P = 0.070$).

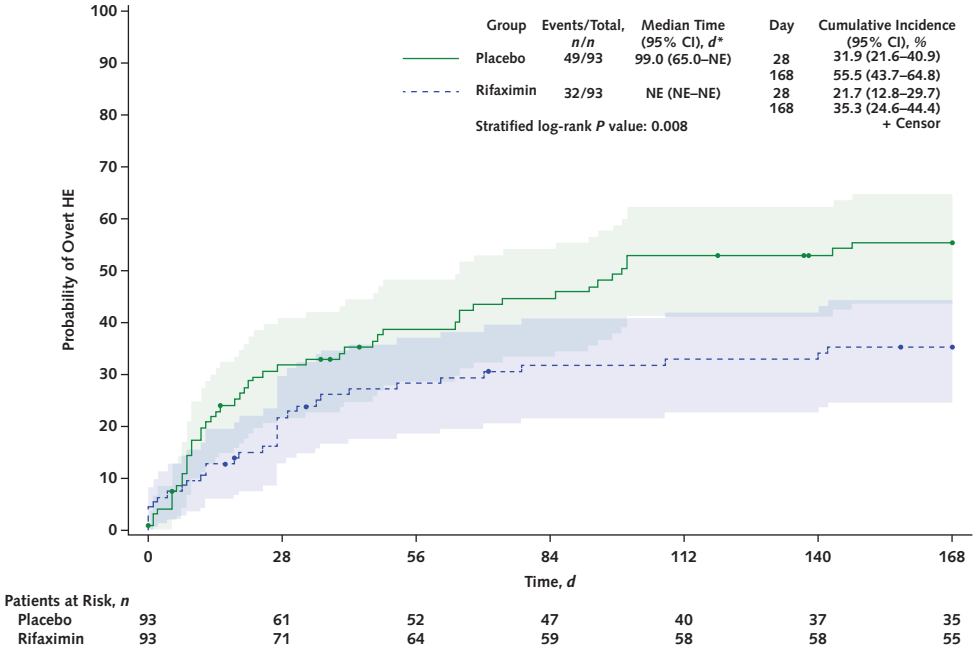
Results in patients with minimal HE at baseline ($n = 23$) and the effect of rifaximin in preventing minimal HE ($n = 186$) are presented in the **Appendix** (available at Annals.org).

Secondary Outcomes and Safety Analysis

The incidence of other liver disease–related complications did not differ between the treatment groups (**Table 3**). A total of 22 patients died during the initial 168 days (10 in the rifaximin group and 12 in the placebo group). Causes of death are listed in **Appendix Table 2** (available at Annals.org). Seven patients received a transplant during the first 168 days (2 in the rifaximin group and 5 in the placebo group). As a whole, the probability of 168-day transplantation-free survival was 87% (CI, 80% to 94%) in the rifaximin group versus 81% (CI, 73% to 90%) in the placebo group ($P = 0.27$).

In the 182 days after the first day of treatment, 182 of 194 patients (94% [CI, 90% to 97%]) had at least 1 adverse event; 107 of 194 (55% [CI, 48% to 62%]) had a serious adverse event (**Table 4**). The incidence of adverse events reported was similar in the rifaximin group (88 of 95 patients [93%]) and the placebo group (94 of 99 patients [95%]) ($P = 0.99$), as was the incidence of serious adverse events (53 of 95 patients [56%] and 54

Figure 2. Cumulative incidence of post-TIPS overt HE at 168 days, according to treatment group.



The light shading around the green and purple lines indicates confidence bands; the dark shading indicates overlap of the bands. The symbols on the lines indicate censoring. HE = hepatic encephalopathy; NE = not estimable; TIPS = transjugular intrahepatic portosystemic shunt.
* Median time until 50% of patients had the event of interest.

of 99 patients [55%], respectively; $P = 0.47$). Among the adverse events of interest, at least 1 episode of infection occurred in 37 of 93 patients (40% [CI, 30% to 50%]) in the rifamixin group and 38 of 93 (41% [CI, 31% to 51%]) in the placebo group ($P = 0.88$), and at least 1 episode of heart failure occurred in 13 of 93 (14% [CI, 7% to 21%]) and 16 of 93 (17% [CI, 10% to 25%]), respectively ($P = 0.54$).

Discussion

This double-blind, placebo-controlled, randomized, multicenter trial showed that rifaximin reduced the incidence of post-TIPS overt HE compared with placebo.

The main drawback of TIPS is still HE, which is reported in 30% to 50% of patients within 6 months after TIPS (7, 8). This complication has been treated successfully with lactulose, rifaximin, or both (12, 15). However, so far no treatment has been found to be effective for preventing HE; therefore, no prophylactic therapy is recommended currently (9). Nevertheless, a preventive treatment would be useful, because HE is associated with increased mortality (7); greatly alters the quality of life of patients and their families (15); and requires costly hospitalizations (16), which carry a high risk for nosocomial complications in these vulnerable patients.

Two previously published randomized trials, 1 in patients with decompensated cirrhosis (17) and the other in patients treated with TIPS (10), failed to find any efficacy for rifaximin in preventing overt HE. These negative results might be explained on several grounds. First, both studies included only 75 patients in total, so the risk for a β-type error was substantial. Rifaximin was prescribed immediately after the shunt procedure in the study by Riggio and colleagues (10), although it might be hypothesized that regardless of mode of action, several days of treatment might be needed before the drug is fully effective. Accordingly, treatment was initiated 2 weeks before TIPS in the present trial. Finally, in the study by Riggio and colleagues, patients were followed for only 1 month. In our study, the cumulative incidence curves for overt HE (Figure 2) show that rifaximin's superiority over placebo was observed mainly after 1 month.

Table 2. Characteristics of the First Episode of Overt HE, According to Treatment Group, in 81 Patients Who Had Overt HE During the 168 Days

Characteristics	Rifaximin Group ($n = 32$)	Placebo Group ($n = 49$)
Grade, according to West Haven criteria, *n (%)*		
2	25 (78)	34 (69)
3	5 (16)	12 (25)
4	2 (6)	3 (6)
Median duration of first episode (IQR), *d*	4 (2–8)	4 (2–7)
Precipitating factors, *n (%)**	11 (34)	14 (29)

HE = hepatic encephalopathy; IQR = interquartile range.
* Described in Appendix Table 1 (available at Annals.org).

Table 3. Incidence of Secondary Outcomes, According to Treatment Group

Secondary Outcome	Rifaximin Group (*n* = 93), *n* (%)	Placebo Group (*n* = 93), *n* (%)	Proportion Difference (95% CI), %*
Gastrointestinal bleeding	1 (1)	3 (3)	−2 (−6 to 2)
AKI	23 (25)	27 (29)	−4 (−17 to 8)
HCC	2 (2)	3 (3)	−1 (−5 to 4)
Liver transplantation	2 (2)	5 (5)	−3 (−9 to 2)
Death	10 (11)	12 (13)	−2 (−11 to 7)

AKI = acute kidney injury; HCC = hepatocellular carcinoma.
* Differences between groups for each event were tested for significance with a χ^2 or Fisher exact test. None of the differences was statistically significant.

In our placebo group, the incidence of post-TIPS overt HE was 53%, which is among the highest percentages reported in the literature. The reason for this high incidence may be related to the follow-up protocol, which required investigators to look for symptoms of overt HE systematically every month, whereas in most reported series, this was done only in patients who were hospitalized. Furthermore, we classified HE as grade 2 if asterixis was the only symptom (9), whereas other investigators classified it as grade 1. Because this study was double-blinded and the same grading was used for all participants, such a discrepancy should not have influenced the results.

It is noteworthy that similar incidences of overt HE were observed in the subgroup of patients with minimal encephalopathy according to PHES, regardless of whether they received rifaximin or placebo. Although this subgroup was too small to draw any definitive conclusion, this finding is in line with results of a previous study (18). Finally, some recent data incriminate the shunt diameter: The larger the shunt, the higher the risk for overt HE (19, 20). Whether this may have influenced the incidence of overt HE observed in this study remains possible.

Our study has several limitations. Most participants had alcoholic cirrhosis and were selected according to known risk factors for post-TIPS overt HE. The results, therefore, are limited to this specific subgroup and may not be generalizable to patients with cirrhosis of other causes. Treatment was initiated 15 days before TIPS; 11 patients could not be treated with TIPS and therefore could not be included in the efficacy analysis. However, the 5% withdrawal rate we expected in calculating the sample size compensated for this number of patients. Furthermore, initiating treatment before TIPS limits the scope of our results to patients who do not receive treatment under emergency conditions. Finally, treatment was given for 168 days after TIPS, so whether rifaximin prophylaxis against overt HE should be maintained beyond that time is unknown.

The results of this study raise several questions. One question is how long treatment should continue for optimal results. In the current study, several patients had an episode of overt HE soon after discontinuing rifaximin treatment. The number of patients still at risk at that time was too low to draw any firm conclusion; further studies clearly are needed to assess whether patients should be maintained on therapy, considering the safety profile of rifaximin (21, 22). Another question is how to select patients for TIPS. In our study, patients were selected on the basis of established risk factors for post-TIPS overt HE, namely age older than 65 years, Child–Pugh score above 12, and a history of recurrent episodes of overt HE (8). Could prophylactic rifaximin change these

Table 4. Safety Report*

AEs†	Rifaximin Group (*n* = 95), *n* (%)	Placebo Group (*n* = 99), *n* (%)	Proportion Difference (95% CI), %
Any AE	88 (93)	94 (95)	−2 (−9 to 5)
Any serious AE	53 (56)	54 (55)	1 (−13 to 15)
Any serious AE leading to discontinuation of treatment	5 (5)	5 (5)	0 (−6 to 6)
Death	10 (11)	12 (12)	−1 (−11 to 7)
Common AEs occurring in >5% of patients‡			
Shunt revision	6 (6)	7 (7)	−1 (−8 to 6)
Strangulated umbilical hernia	2 (2)	8 (9)	−6 (−12 to 0)
Adverse events of interest‡			
Infections	37 (40)	38 (41)	−1 (−15 to 13)
Heart failure	13 (14)	16 (17)	−3 (−14 to 7)

AE = adverse event; TIPS = transjugular intrahepatic portosystemic shunt.
* The number of patients with AEs was calculated from the 194 patients who received at least 1 dose of the treatment (except for shunt revision, strangulated hernia, heart failure, and infections [*n* = 186]). The period considered was 182 d: 14 d before the TIPS procedure + 168 d after it (except for shunt revision and infections: 168 d after the TIPS procedure).
† AEs were described according to MedDRA (Medical Dictionary for Regulatory Activities). MedDRA, a dictionary of international medical terminology, is clinically validated and used by regulatory authorities as well as the regulated biopharmaceutical industry (preferred term, fourth level of terminology).
‡ *n* = 93 in each group.

thresholds; if so, to what extent? This point also requires further study. Transjugular intrahepatic portosystemic shunt is not the only factor known to precipitate overt HE. Whether rifaximin might be used to prevent overt HE in high-risk situations other than TIPS should also be evaluated. Of interest, the effect of rifaximin was observed in patients with a previous episode of overt HE. Contrary to previously published work (12), rifaximin was not administered in conjunction with lactulose in our trial; therefore, prevention of overt HE must be ascribed to rifaximin only. Whether rifaximin's beneficial effect would have been greater if the drug was combined with a nonabsorbable disaccharide, such as lactulose or lactitol, remains to be assessed. Lastly, medicoeconomic studies are lacking, precluding the assessment of whether using rifaximin to prevent overt HE is cost-effective.

Like other antibiotics used to treat overt HE, such as neomycin (23) and vancomycin (24), rifaximin is poorly absorbed in the gut. However, it has several advantages over the other antibiotics: It is neither nephrotoxic nor ototoxic, thus it is not contraindicated for long-term prescription; it has broad-spectrum activity against both gram-negative and gram-positive aerobic and anaerobic bacteria; and it carries a low risk for inducing bacterial resistance. Therefore, the safety profile of rifaximin should not preclude its use in patients with cirrhosis. Indeed, in the present study, the incidence of adverse events was similar whether patients received rifaximin or placebo, which is in accordance with the trial by Bass and colleagues (13).

Rifaximin's mechanism of action remains unclear. The drug has been used to treat or prevent several conditions, including inflammatory bowel disease, irritable bowel syndrome, and complications of chronic liver disease (hepatorenal syndrome, overt as well as minimal HE, spontaneous bacterial peritonitis, and nonalcoholic steatohepatitis) (25). These effects are ascribed to modifications in the functionality of gut microbiota, with a shift toward a decrease in production of proinflammatory molecules, such as lipopolysaccharides, or secondary bile acids (26) rather than to changes in the overall microbiota composition (27), although this issue is still under debate (28, 29). Rifaximin treatment induces a decrease in circulating plasma renin activity and plasma endotoxin, interleukin-6, and tumor necrosis factor-α levels (30), which is in line with the results of recent studies establishing the importance of neuroinflammation in the development of HE (31). Rifaximin has also been found to have effects independent of its ability to alter gut microbiota (32). Whether the pathways involved in these effects play a role in the prevention or treatment of HE remains to be assessed.

In conclusion, this study supports the use of rifaximin to prevent post-TIPS overt HE in patients with cirrhosis.

From University Hospital of Toulouse and Toulouse III Paul Sabatier University, Toulouse, France (C.B., J.M.P., J.P.V.); Groupe Hospitalier Pitié-Salpêtrière, Paris, France (D.T.); Centre d'Investigation Clinique de Rennes, Rennes, France (C.J.); Centre Hospitalier Universitaire de Nantes, Nantes, France (I.A.); Trousseau University Hospital of Tours, Tours, France (L.D.M.); Centre Hospitalier Universitaire de Lille, Lille, France (S.D.); Centre Hospitalo-Universitaire Timone, Marseille, France (P.B.); Centre Hospitalier Universitaire d'Angers, Angers, France (F.O.); Beaujon Hospital, Clichy, France (A.P.); Centre Hospitalier Universitaire de Bordeaux, Bordeaux, France (V.D.); Hôpitaux Universitaires Paris Seine-Saint-Denis, Bondy, and Université Paris 13, Sorbonne Paris Cité et INSERM UMR 1162, Paris, France (N.G.); Hôpital Saint-Antoine, Paris, France (N.C.); and Toulouse University Hospital, Toulouse, France (V.R., A.S.).

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* Clinical investigators involved in recruitment and clinical follow-up of patients.

† Clinical research assistant.

‡ Study coordinator for monitoring.

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Corresponding Author: Christophe Bureau, MD, PhD, Hepatology Unit, University Hospital of Toulouse France and Toulouse III Paul Sabatier University, 1 avenue Jean Poulhes 31059, Toulouse Cedex, France; e-mail: bureau.c@chu-toulouse.fr.

Current author addresses and author contributions are available at Annals.org.

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Current Author Addresses: Dr. Bureau: Hepatology Unit, University Hospital of Toulouse France and Toulouse III Paul Sabatier University, 1 avenue Jean Poulhes 31059, Toulouse Cedex, France.
Dr. Thabut: APHP Sorbonne Université, Site Pitié-Salpêtrière, Service d'hépato-gastroentérologie, 83 boulevard de l'hôpital, 75013 Paris, France.
Dr. Jezequel: Service des maladies du foie, CHU de Rennes - Hôpital Pontchaillou, 2, rue Henri Le Guilloux, 35033 Rennes Cedex 9, France.
Dr. Archambeaud: Service Hépato-Gastroentérologie et cancérologie digestive, CHU Hôtel Dieu, 1 place Alexis Ricordeau, 44093 Nantes Cedex 1, France.
Dr. D'Alteroche: Department of Hepatology, Hôpital Trousseau, Tours University, 37044 Tours Cedex, France.
Dr. Dharancy: Service des Maladies de l'appareil digestif, Hôpital Huriez, Lille, France.
Dr. Borentain: Service d'Hépato-Gastro-Enterologie, AP-HM, Centre Hospitalo-Universitaire Timone, 264, rue Saint-Pierre, Marseille Cedex 0 513 385, France.
Dr. Oberti: Liver-Gastroenterology Department, University Hospital, HIFIH Laboratory, Angers, France.
Dr. Plessier: Department of Hepatology, Hôpital Beaujon, 100 boulevard du général Leclerc, 92110 Clichy, France.
Dr. De Ledinghen: Service d'hépatologie et de transplantation hépatique, Hôpital Haut-Lévêque, 33600 Pessac, France.
Dr. Ganne-Carrié: Hôpital Avicenne, APHP, Université Sorbonne Paris Nord, INSERM UMR S-1138, équipe FunGeST, Centre de Recherche des Cordeliers, Sorbonne Université, F-75006 Paris, France.
Dr. Carbonell: Hôpital saint Antoine, 184 rue du faubourg Saint Antoine, 75012 Paris, France.
Drs. Rousseau and Sommet: Service de Pharmacologie Médicale et Clinique - 37, Allées Jules Guesde, 31000 Toulouse, France.
Drs. Péron and Vinel: University Hospital of Toulouse Rangueil, 1 avenue Jean Poulhes, 31059 Toulouse Cedex, France.

Author Contributions: Conception and design: C. Bureau, A. Sommet, J.P. Vinel.
Analysis and interpretation of the data: C. Bureau, V. Rousseau, A. Sommet, J.M. Péron, J.P. Vinel.
Drafting of the article: C. Bureau, J.P. Vinel.
Critical revision for important intellectual content: C. Bureau, D. Thabut, S. Dharancy, F. Oberti, A. Plessier, N. Ganne-Carrié, N. Carbonell, J.M. Péron, J.P. Vinel.
Final approval of the article: C. Bureau, D. Thabut, C. Jezequel, I. Archambeaud, L. D'Alteroche, S. Dharancy, P. Borentain, F. Oberti, A. Plessier, V. De Ledinghen, N. Ganne-Carrié, N. Carbonell, V. Rousseau, A. Sommet, J.M. Péron, J.P. Vinel.
Provision of study materials or patients: C. Bureau, D. Thabut, C. Jezequel, I. Archambeaud, L. D'Alteroche, S. Dharancy, P. Borentain, F. Oberti, A. Plessier, V. De Ledinghen, N. Ganne-Carrié, N. Carbonell, J.M. Péron.
Statistical expertise: V. Rousseau, A. Sommet.
Obtaining of funding: C. Bureau.
Administrative, technical, or logistic support: C. Bureau, J.M. Péron, J.P. Vinel.
Collection and assembly of data: C. Bureau, D. Thabut, C. Jezequel, I. Archambeaud, L. D'Alteroche, S. Dharancy, P. Borentain, F. Oberti, A. Plessier, V. De Ledinghen, N. Ganne-Carrié, N. Carbonell, J.M. Péron.

Appendix: Sensitivity Analyses

In 23 of 186 patients (12%) with minimal HE at baseline, according to the results of the PHES, the incidence of overt HE was 33% (3 of 10) in the rifaximin group and 46% (6 of 13) in the placebo group. The presence of minimal HE at baseline in these 23 patients was not associated with the risk for overt HE after the TIPS procedure: 9 of 23 patients (39% [CI, 19% to 59%]) versus 72 of 163 (44% [CI, 37% to 52%]) without minimal HE at baseline. Rifaximin use was not associated with a decreased incidence of minimal HE: 25 of 93 (27% [CI, 18% to 36%]) versus 27 of 93 patients (29% [CI, 20% to 38%]) in the rifaximin and placebo groups, respectively ($P = 0.74$). Finally, during follow-up of the 186 patients, if those with only isolated asterixis were not graded as having overt HE, the difference observed would remain statistically different between the 2 treatment groups (37 of 93 [40%] vs. 19 of 93 [20%] in the placebo and rifaximin groups, respectively; $P = 0.010$).

Appendix Table 1. Precipitating Factors Suspected at the Time of the First Episode of Overt HE ($n = 25$)

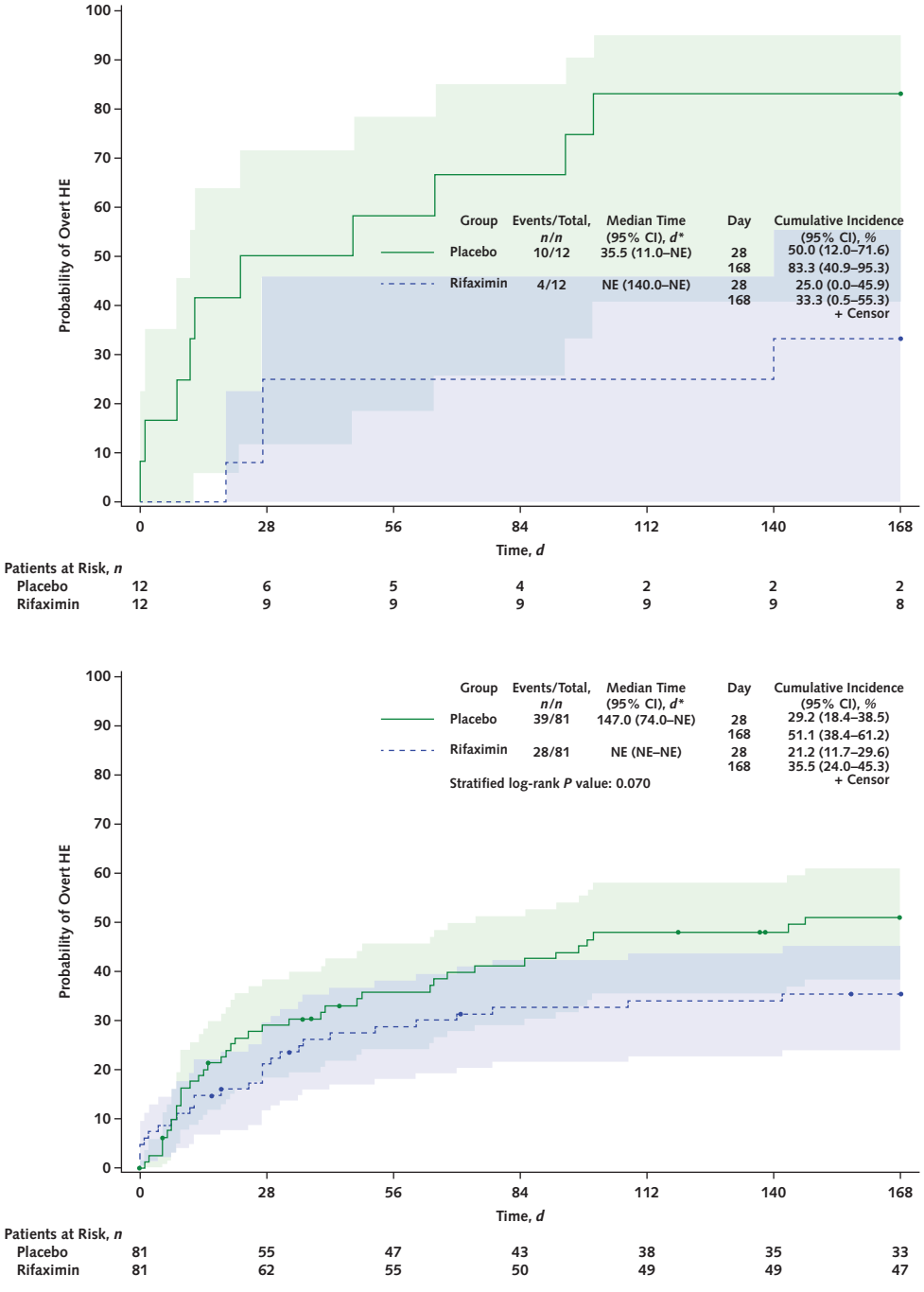
Precipitating Factor	Rifaximin Group ($n = 11$), n	Placebo Group ($n = 14$), n
Dehydration and/or diuretic intolerance	3	4
Gastrointestinal bleeding	2	0
Infection	2	3
Drug induced	3	5
Constipation	1	0
Intestinal obstruction/surgery	0	2

HE = hepatic encephalopathy.

Appendix Table 2. Causes of Death in 22 Patients Who Died Before the 168-Day Period

Cause of Death	Rifaximin Group ($n = 10$), n	Placebo Group ($n = 12$), n
Liver failure	3	3
Heart failure	3	2
Septic shock	1	3
Bleeding	1	2
Pulmonary embolism or respiratory failure	1	1
Syncope	0	1
Unknown	1	0

Appendix Figure. Cumulative incidence of post-TIPS overt HE at 168 days in the subgroups of patients with (*top*) and without (*bottom*) a previous episode of HE at baseline, according to treatment group.



The light shading around the green and purple lines indicates confidence bands; the dark shading indicates overlap of the bands. The symbols on the lines indicate censoring. HE = hepatic encephalopathy; NE = not estimable; TIPS = transjugular intrahepatic portosystemic shunt.
* Median time until 50% of patients had the event of interest.