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# Reversal of hepatorenal syndrome type 1 with terlipressin plus albumin vs. placebo plus albumin in a pooled analysis of the OT-0401 and REVERSE randomised clinical studies

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## SUMMARY

### Background
The goal of hepatorenal syndrome type 1 (HRS-1) treatment is to improve renal function. Terlipressin, a synthetic vasopressin analogue, is a systemic vasoconstrictor used for the treatment of HRS-1, where it is available.

### Aim
To compare the efficacy of terlipressin plus albumin vs. placebo plus albumin in patients with HRS-1.

### Methods
Pooled patient-level data from two large phase 3, randomised, placebo-controlled studies were analysed for HRS reversal [serum creatinine (SCr) value $\leq 133$ µmol/L], 90-day survival, need for renal replacement therapy and predictors of HRS reversal. Patients received intravenous terlipressin 1–2 mg every 6 hours plus albumin or placebo plus albumin up to 14 days.

### Results
The pooled analysis comprised 308 patients (terlipressin: $n = 153$; placebo: $n = 155$). HRS reversal was significantly more frequent with terlipressin vs. placebo (27% vs. 14%; $P = 0.004$). Terlipressin was associated with a more significant improvement in renal function from baseline until end of treatment, with a mean between-group difference in SCr concentration of $-53.0$ µmol/L ($P < 0.0001$). Lower SCr, lower mean arterial pressure and lower total bilirubin and absence of known precipitating factors for HRS were independent predictors of HRS reversal and longer survival in terlipressin-treated patients.

### Conclusions
Terlipressin plus albumin resulted in a significantly higher rate of HRS reversal vs. albumin alone in patients with HRS-1. Terlipressin treatment is associated with improved renal function. (ClinicalTrials.gov identifier: OT-0401, NCT00089570; REVERSE, NCT01143246).

## INTRODUCTION

Hepatorenal syndrome type 1 (HRS-1) is a rapidly progressive but potentially reversible form of renal failure that may develop in patients with cirrhosis and ascites, acute liver failure, or alcoholic hepatitis.[1] In patients with HRS-1, serum creatinine (SCr) increases to >226 µmol/L within 2 weeks, frequently after a precipitating event, such as an infection or gastrointestinal bleeding.[1, 2] Renal failure develops subsequent to a series of pathophysiologic haemodynamic changes. Splanchnic arterial vasodilation consequent upon the presence of portal hypertension leads to a reduction in effective arterial blood volume. This in turns activates the renin-angiotensin-aldosterone system and the sympathetic nervous system, resulting in intense renal vasoconstriction and a reduction in the glomerular filtration rate (GFR), followed by renal sodium and water retention, which ultimately leads to ascites and oedema.[3]

Without effective treatment, HRS-1 is rapidly fatal, with a median survival of 1 month.[4] The definitive therapy for HRS-1 is liver transplantation, which eliminates the liver dysfunction, portal hypertension, and splanchnic arterial vasodilation that led to the renal consequences.[5] The presence of renal insufficiency at the time of liver transplantation may reduce post-transplant survival.[6–9] In addition, liver transplantation is not possible for all patients with HRS-1. Current recommended first-line therapies for HRS-1 are vasoconstrictors coupled with albumin; among the vasoconstrictors, terlipressin is recommended in clinical practice guidelines as first-line therapy for HRS-1, where it is available.[10] Terlipressin is a synthetic vasopressin analogue that produces systemic vasoconstriction through its $V_1$ receptor agonist activity.[11] In several small, randomised, controlled studies, terlipressin treatment was shown to improve renal function in patients with HRS-1 by significantly reducing SCr.[12–16] Meta-analyses of these studies of terlipressin in HRS-1 support the beneficial effect of terlipressin on renal function.[17, 18]

OT-0401 and REVERSE are two large, similarly designed phase 3 clinical studies comparing treatment with terlipressin plus albumin vs. placebo plus albumin in patients with HRS-1. Given the very limited sample sizes in the majority of previously published studies in this therapeutic area, a pooled analysis of individual patient-level data from these two studies was performed to assess the effects of terlipressin in the overall population and allow a robust analysis of predictive factors using a large database. Here, we present the results of the pooled analysis of the OT-0401 and REVERSE studies.

## MATERIALS AND METHODS

The study designs, including eligibility criteria, procedures, treatments and statistical analyses, have been reported previously.[11, 16, 19]

### Patients

Briefly, eligible patients in both studies were aged 18 years or older and had a diagnosis of HRS-1. In the OT-0401 study, the diagnosis was based on the 1996 International Club of Ascites criteria.[20] In the REVERSE study, the diagnosis was based on International Club of Ascites criteria, which were updated in 2007.[1] The OT-0401 study comprised patients with chronic liver disease or acute (de novo onset within 6 weeks) viral and/or alcoholic hepatitis, and the REVERSE study comprised patients with cirrhosis and ascites, with or without superimposed alcoholic hepatitis.

All patients were required to have rapidly progressive reduction in renal function. In the OT-0401 study, reduction in renal function was defined as a doubling of SCr to ≥226 µmol/L within 2 weeks or a 50% reduction in the initial 24-h creatinine clearance to <20 mL/min in the absence of other causes of renal impairment. In the REVERSE study, reduction in renal function was defined as SCr ≥226 µmol/L and/or a doubling of SCr within 2 weeks.

Both studies required that patients have no sustained improvement in renal function during the pre-enrolment screening phase. However, in the REVERSE study, these criteria were extended and refined; all patients underwent fluid challenge with intravenous albumin to demonstrate that volume expansion was insufficient to correct renal failure, and specific inclusion criteria were applied for the SCr response 48 h after diuretic withdrawal and albumin administration (<20% decrease in SCr and SCr ≥199 µmol/L) to avoid enroling patients who quickly responded to albumin alone.

The OT-0401 study had no upper limit of baseline SCr values for patient exclusion; the REVERSE study excluded patients with SCr values ≥619 µmol/L based on the absence of response in these patients observed in the OT-0401 study. Both studies excluded patients with ongoing shock or uncontrolled bacterial infection. Patients receiving octreotide, midodrine, vasopressin, dopamine or other vasopressors within 48 h, as well as patients who received <2 days of anti-infective therapy

for suspected or documented infection, were excluded in the REVERSE study.

## Study design

OT-0401 (NCT00089570) and REVERSE (NCT01143246) were phase 3, multicentre, randomised, double-blind, placebo-controlled studies. OT-0401 was conducted at 35 medical centres across the USA ($n = 30$), Germany ($n = 2$) and Russia ($n = 3$) from June 2004 through September 2006.[19] REVERSE was conducted at 52 medical centres in the USA ($n = 50$) and Canada ($n = 2$) during October 2010 through February 2013[16]; eligible patients were randomised (1:1) to receive terlipressin or placebo, stratified by presence or absence of alcoholic hepatitis (see Supporting Information for a complete list of the OT-0401 and REVERSE investigators). REVERSE also stratified patients by SCr <318 μmol/L or ≥318 μmol/L, based on the identification of lower baseline SCr as a predictor of HRS reversal and survival observed in the OT-0401 study. Concomitant use of albumin was strongly recommended for the two treatment arms in both studies if clinically appropriate (OT-0401: 100 g on day 1 and 25 g daily until end of treatment; REVERSE: 20–40 g/day). OT-0401 and REVERSE included three periods: pre-study, 14-day active treatment, and 180-day (OT-0401) and 90-day (REVERSE) follow-up. Both studies were conducted in accordance with the ethical principles of the Declaration of Helsinki and were in compliance with good clinical practice and all applicable regulatory guidelines. The protocols were approved by an institutional review board and/or independent ethics committee at each study site, and all patients or their surrogates provided written informed consent.

In both studies, slow intravenous bolus injections of terlipressin or placebo were administered over 2 min four times daily. A terlipressin starting dose of 1 mg every 6 h (4 mg/day) could be doubled to 2 mg every 6 h (8 mg/day) in patients who achieved a < 30% decrease in SCr after either a minimum of 12 doses (OT-0401) or a minimum of 10 doses (REVERSE). However, the REVERSE study did not permit dose escalation in patients with known coronary artery disease or in the clinical setting of circulatory overload, pulmonary oedema or treatment-refractory bronchospasm. In addition, both studies required permanent discontinuation in the case of renal replacement therapy or liver transplantation, or if SCr remained at or above baseline either on day 4 after a minimum of 10 doses (REVERSE) or on day 7 or later (OT-0401); dosing could be interrupted for an adverse event and then decreased to a lower dose (0.5 mg every 6 h). In OT-0401, a less frequent dosing interval (1 mg every 8–12 h) could be resumed. Interruption for an ischaemic adverse event mandated permanent discontinuation in REVERSE. Study medication was continued for 2 days after a first value of SCr <133 μmol/L had been obtained or up to a maximum of 14 days in either study.

The primary endpoint in the OT-0401 study was treatment success at day 14, defined as SCr <133 μmol/L on two occasions at least 48 (±8) h apart, followed by an additional SCr value <226 μmol/L measured on day 14, without intervening liver transplant, dialysis or HRS recurrence. The primary endpoint of the REVERSE study was confirmed HRS reversal, defined as at least two on-treatment SCr values <133 μmol/L at least 48 (±8) h apart and without intervening renal replacement therapy or liver transplant.

## Pooled analysis

HRS reversal was chosen as the main outcome of interest for the pooled analysis because its definition was identical in OT-0401 and REVERSE. In each study, the incidence of HRS reversal was defined as the percentage of patients with at least one SCr value <133 μmol/L on treatment (up to 24 h after the last dose of study medication). Other parameters assessed for the current analysis included change from baseline in SCr, estimated GFR (eGFR) (calculated using the Cockcroft-Gault equation), and mean arterial pressure (MAP), as well as transplant-free survival, overall survival and use of renal replacement therapy.

## Statistical analyses

The intent-to-treat (ITT) population, defined as all randomised patients who had at least one baseline assessment, was used in the pooled analysis. Differences between treatment groups in the incidence of HRS reversal were analysed with the Cochran-Mantel-Haenszel test for general association adjusted for alcoholic hepatitis (present or not present).

To evaluate changes from baseline in SCr and eGFR, least-squares (LS) means were calculated from repeated-measures analysis of variance, with factors of treatment, alcoholic hepatitis, day and treatment by day interaction in the pooled analysis. The LS mean treatment difference between groups was calculated as the terlipressin LS mean change from baseline minus the placebo LS mean change from baseline. MAP changes were evaluated with an analysis of variance comparing the change from baseline values.

The estimated transplant-free survival and overall survival rates were compared with $P$ values derived from a two-sample log-rank test stratified by alcoholic hepatitis (present or not present).

Baseline prognostic factors were evaluated by univariate and multivariate logistic regression analysis. For multivariate analyses, two models with a combination of four baseline variables and one model with a combination of three baseline variables were used; for each analysis, all significant univariate results were added to the model, and step-wise selection was used to obtain the final model.

## RESULTS

### Patients

The pooled analysis population comprised 308 patients (terlipressin plus albumin: $n = 153$; placebo plus albumin: $n = 155$). The baseline patient disposition for both studies is shown in Figure 1. Overall, baseline patient demographic and clinical characteristics were typical of a severely ill HRS-1 population (>60% Child–Pugh Class C, mean baseline Model for End-Stage Liver Disease [MELD] scores of 32–34, and >90% with ascites) and were generally similar between treatment groups (Table 1).

### Treatment

Mean duration of treatment was 6.1 days in the terlipressin and placebo groups, and mean total exposure to study drug was 26.2 mg with terlipressin and 27.6 mg with placebo. The standard dose level (1 mg) was used by 73% (112/153) of patients receiving terlipressin and 64% (99/155) of patients receiving placebo, while a high dose level (at least one 2-mg dose) was used by 24% (37/153) and 33% (51/155) of patients, respectively. The proportion of patients with concomitant albumin use from the start to the end of treatment was similar between groups [terlipressin: 87.6% (134/153); placebo: 87.1% (135/155)]. Mean duration of concomitant albumin use was 4.9 days and total exposure to concomitant albumin was 225 g in patients receiving terlipressin and 5.5 days and 244 g, respectively, in patients receiving placebo ($P = $ NS).

### Changes in renal function

As shown in Figure 2, the incidence of HRS reversal was significantly higher among patients receiving terlipressin [42/153 (27%)] compared with patients receiving placebo [22/155 (14%)]; $P = 0.004$]. In the pooled analysis, mean

(standard deviation) time from randomisation to HRS reversal was 6.6 (3.5) days in patients receiving terlipressin and 6.4 (3.2) days in patients receiving placebo.

A sensitivity analysis was performed to determine the generalisability of the data. The incidence of HRS reversal in subgroup analyses was generally higher among patients receiving terlipressin compared with those receiving placebo; however, when analysed by gender, HRS reversal was achieved by 29% of male patients receiving terlipressin vs. 13% receiving placebo ($P = 0.006$) but only by 25% of female patients receiving terlipressin vs. 16% receiving placebo ($P = 0.27$). Terlipressin treatment resulted in higher rates of HRS reversal vs. placebo in patients with less severe disease, such as those with baseline SCr <265 μmol/L (47% vs. 21%; $P = 0.008$), lower (<34) baseline MELD score (42% vs. 17%; $P = 0.0008$), and baseline MAP ≥70 mmHg (27% vs. 12%; $P = 0.008$). The incidence of HRS reversal in patients with Child–Pugh Class C disease was significantly higher with terlipressin vs. placebo (28% vs. 12%; $P = 0.005$). In patients receiving >10 doses of study medication, the incidence of HRS reversal was approximately twofold greater with terlipressin vs. placebo (43% vs. 20%; $P = 0.0004$), as was the incidence of HRS reversal in patients who received >12 doses of study medication (50% vs. 26%; $P = 0.0013$); however, these results could have been confounded because dosing could be discontinued if patients did not demonstrate early response to study drug. The incidence of HRS reversal in patients with dose increases also was significantly higher with terlipressin vs. placebo (32% vs. 10%; $P = 0.008$).

The repeated-measures LS mean changes in SCr concentration from baseline to the end of treatment are shown in Figure 3. The SCr concentration decreased over time in the terlipressin and placebo groups, with a mean treatment difference between groups of −53.0 μmol/L ($P < 0.0001$) in the pooled analysis; the mean between-group difference also was significant in the individual studies. In addition, eGFR increased over time in both groups and was significantly greater with terlipressin (28.0 mL/min) vs. placebo (13.8 mL/min) in the pooled analysis, for a repeated-measures LS mean between-group difference of 14.2 mL/min ($P < 0.0001$); the mean treatment difference between groups in the individual studies was also significant.

### Mean arterial pressure

From baseline to the end of treatment, MAP increased by 4.1 mmHg in patients receiving terlipressin and decreased by 1.8 mmHg in patients receiving placebo in
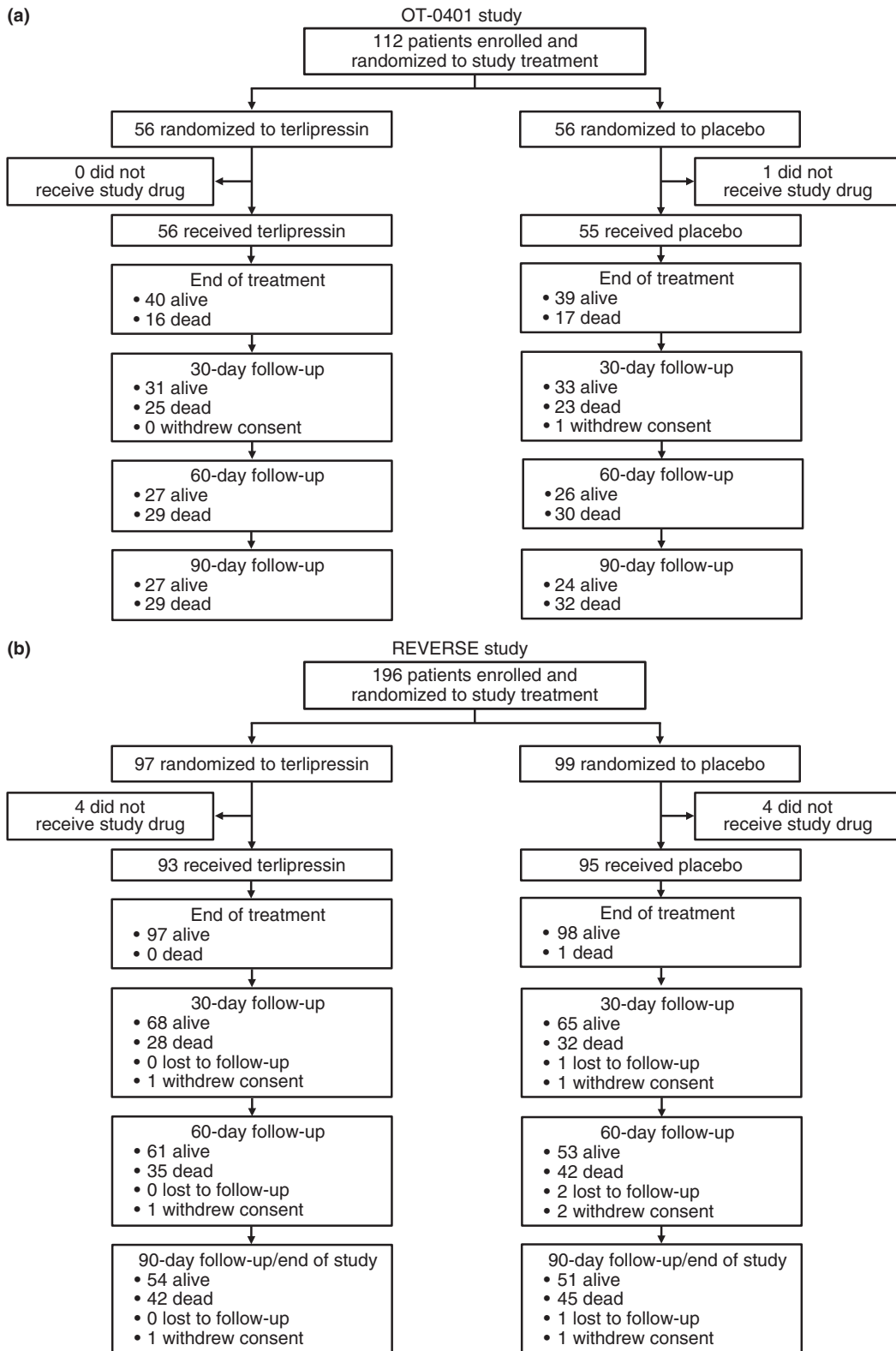
**(a)**

OT-0401 study

112 patients enrolled and
randomized to study treatment

56 randomized to terlipressin

0 did not
receive study drug

56 received terlipressin

End of treatment
• 40 alive
• 16 dead

30-day follow-up
• 31 alive
• 25 dead
• 0 withdrew consent

60-day follow-up
• 27 alive
• 29 dead

90-day follow-up
• 27 alive
• 29 dead

56 randomized to placebo

1 did not
receive study drug

55 received placebo

End of treatment
• 39 alive
• 17 dead

30-day follow-up
• 33 alive
• 23 dead
• 1 withdrew consent

60-day follow-up
• 26 alive
• 30 dead

90-day follow-up
• 24 alive
• 32 dead

**(b)**

REVERSE study

196 patients enrolled and
randomized to study treatment

97 randomized to terlipressin

4 did not
receive study drug

93 received terlipressin

End of treatment
• 97 alive
• 0 dead

30-day follow-up
• 68 alive
• 28 dead
• 0 lost to follow-up
• 1 withdrew consent

60-day follow-up
• 61 alive
• 35 dead
• 0 lost to follow-up
• 1 withdrew consent

90-day follow-up/end of study
• 54 alive
• 42 dead
• 0 lost to follow-up
• 1 withdrew consent

99 randomized to placebo

4 did not
receive study drug

95 received placebo

End of treatment
• 98 alive
• 1 dead

30-day follow-up
• 65 alive
• 32 dead
• 1 lost to follow-up
• 1 withdrew consent

60-day follow-up
• 53 alive
• 42 dead
• 2 lost to follow-up
• 2 withdrew consent

90-day follow-up/end of study
• 51 alive
• 45 dead
• 1 lost to follow-up
• 1 withdrew consent

**Figure 1 |** Patient disposition in the (a) OT-0401 and (b) REVERSE studies. The REVERSE study patient disposition is reprinted from *Gastroenterology*, 150, Boyer TD, Sanyal AJ, Wong F, *et al.*, Terlipressin plus albumin is more effective than albumin alone in improving renal function in patients with cirrhosis and hepatorenal syndrome type 1, 1579–1589, copyright 2016, with permission from Elsevier.

**Table 1 |** Summary of baseline demographics and measures (intent-to-treat population)

| | OT-0401 + REVERSE | |
| --- | --- | --- |
| | Terlipressin $n = 153$ | Placebo $n = 155$ |
| Age, years, mean (SD) | 53.9 (9.5) | 54.2 (9.6) |
| Female, n (%) | 60 (39.2) | 49 (31.6) |
| White, n (%) | 136 (88.9) | 141 (91.0) |
| Child–Pugh Class, n (%) | | |
|    Class A (5–6) | 2 (1.3) | 1 (0.6) |
|    Class B (7–9) | 32 (20.9) | 39 (25.2) |
|    Class C (10–15) | 109 (71.2) | 107 (69.0) |
| MELD score, mean (SD) | 33.4 (6.1) | 32.9 (5.8) |
| Encephalopathy stage, mean (SD) | 1.5 (0.8) | 1.4 (0.9) |
| SCr, µmol/L, mean (SD) | 327.1 (144.1) | 327.1 (97.2) |
| Alcoholic hepatitis, n (%) | 40 (26.1) | 45 (29.0) |
| Possible precipitating factors for HRS, n (%) | | |
|    Diuretic treatment | 25 (16.3) | 23 (14.8) |
|    Gastrointestinal bleeding | 7 (4.6) | 10 (6.5) |
|    Infection | 32 (20.9) | 29 (18.7) |
|    LVP | 23 (15.0) | 20 (12.9) |
|    Other | 7 (4.6) | 13 (8.4) |
| Cirrhosis due to, n (%) | | |
|    Alcohol | 78 (51.0) | 83 (53.5) |
|    Hepatitis B | 7 (4.6) | 4 (2.6) |
|    Hepatitis C | 59 (38.6) | 61 (39.4) |
|    Non-alcoholic steatohepatitis | 10 (6.5) | 12 (7.7) |
|    Autoimmune hepatitis | 3 (2.0) | 4 (2.6) |
|    Primary biliary cirrhosis | 6 (3.9) | 4 (2.6) |
| Hepatocellular carcinoma, n (%) | 11 (7.2) | 18 (11.6) |
| Oesophageal varices, n (%) | 87 (56.9) | 86 (55.5) |
| Ascites, n (%) | 147 (96.1) | 146 (94.2) |
| Mean arterial pressure, mmHg (SD) | 75.6 (11.6) | 76.1 (11.7) |
| Concomitant use of beta blockers, n (%) | 41 (26.8) | 41 (26.5) |
| Prior rifaximin use, n (%) | 72 (47.1) | 67 (43.2) |

HRS, hepatorenal syndrome; LVP, large volume paracentesis; MELD, model for end-stage liver disease; SCr, serum creatinine; SD, standard deviation.

the pooled analysis ($P = 0.0003$). Similar results were observed for the individual studies.

## Survival

In the terlipressin group, 31% (48/153) of patients received a liver transplant up to day 90 compared with 30% (47/155) in the placebo group; 26% (40/153) in the terlipressin group and 23% (35/155) in the placebo group were alive and transplant-free at day 90. No effects of terlipressin on transplant-free survival or overall survival at day 90 were identified in the pooled analysis (Figure 4a and b). The estimated transplant-free survival rates at day 90 (death as an event) were 43.8% in patients receiving terlipressin and 37.9% in patients receiving placebo ($P = 0.7162$). The estimated overall survival rates at day 90 were 54.2% in patients receiving terlipressin and 49.5% in patients receiving placebo

($P = 0.5588$). As shown in Figures 4c and d, both transplant-free and overall survival rates up to 90 days were significantly higher in patients with HRS reversal vs. those without HRS reversal, regardless of treatment received (transplant-free survival with terlipressin: 78.7% vs. 26.0%, $P < 0.0001$; transplant-free survival with placebo: 67.0% vs. 31.2%, $P = 0.0026$; overall survival with terlipressin: 81.0% vs. 44.1%, $P < 0.0001$; overall survival with placebo: 68.2% vs. 46.4%, $P = 0.036$).

In subgroup analyses, overall survival at day 90 was significantly lower in females vs. males (43.1% vs. 56.7%; $P = 0.021$). However, overall survival at 90 days trended higher in females receiving terlipressin vs. placebo (50.0% vs. 34.7%; $P = 0.0658$) and was similar to that in males (57.0% vs. 56.4%; $P = 0.774$). Regarding the assessment of overall survival in other subgroups, a larger proportion of patients with baseline MAP
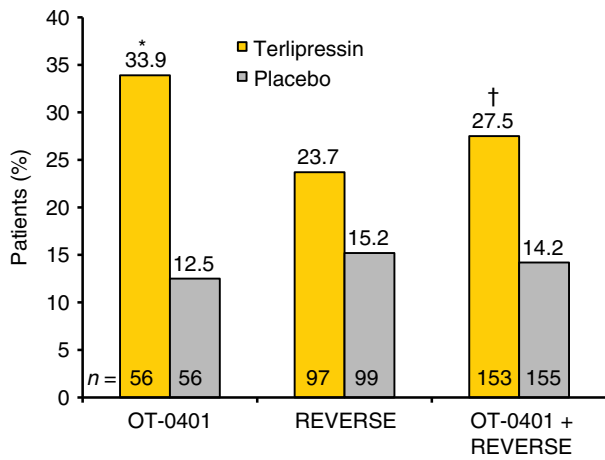
**Figure 2 | Incidence of hepatorenal syndrome reversal in the pooled analysis and in the individual OT-0401 and REVERSE studies. \*P = 0.008 vs. placebo. †P = 0.004 vs. placebo.**

<70 mmHg who received terlipressin survived vs. patients who received placebo (71% vs. 41%; $P = 0.004$). Patients taking concomitant beta blockers who received terlipressin also had a significantly higher overall survival

rate vs. those who received placebo (70% vs. 39%; $P = 0.036$).

### Renal replacement therapy

The cumulative incidence of renal replacement therapy was slightly lower in the terlipressin group than in the placebo group through day 90 (Figure 5a). By day 90 of follow-up, 5% (2/42) of patients receiving terlipressin who experienced HRS reversal required renal replacement therapy compared with 14% (3/22) of patients receiving placebo. Among patients who did not experience HRS reversal, renal replacement therapy was required by 47% (52/111) of patients receiving terlipressin and 42% (56/133) receiving placebo. The proportion of patients with HRS reversal who did not require renal replacement therapy and who were alive at day 90 was 76% (32/42) with terlipressin and 55% (12/22) with placebo ($P = 0.094$) (Figure 5b).

### Predictive factors for HRS reversal and survival

Baseline factors predictive of HRS reversal by univariate analysis in the patients treated with terlipressin were lower international normalised ratio, lower MELD score,
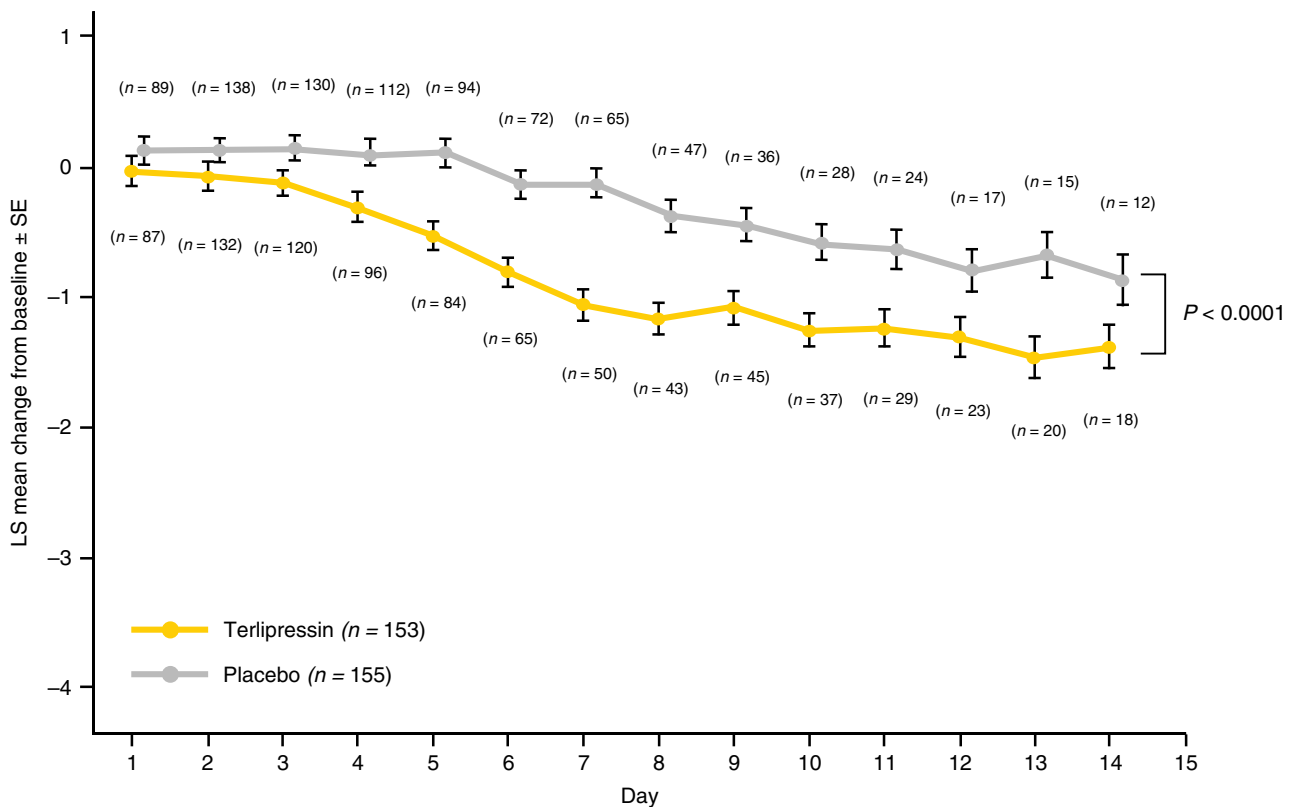


**Figure 3 | Mean change in serum creatinine from baseline to the end of treatment in the pooled analysis of the OT-0401 and REVERSE studies. LS, least-squares mean; SE, standard error.**
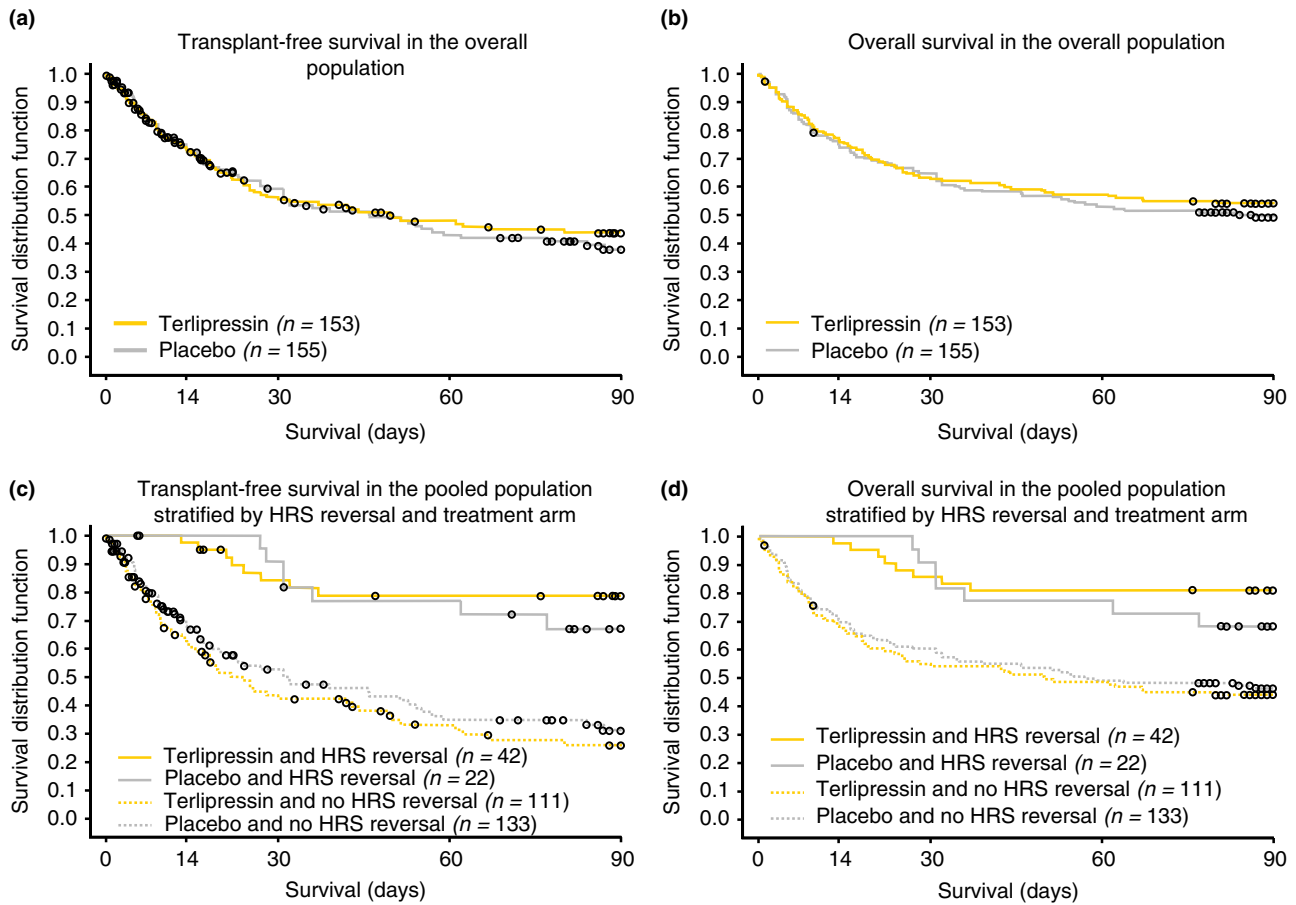
**(a)**

Transplant-free survival in the overall population



**(b)**

Overall survival in the overall population



**(c)**

Transplant-free survival in the pooled population stratified by HRS reversal and treatment arm



**(d)**

Overall survival in the pooled population stratified by HRS reversal and treatment arm



**Figure 4 |** (a) Transplant-free survival up to 90 days in the overall pooled population from the OT-0401 and REVERSE studies (intent-to-treat population); (b) overall survival up to 90 days in the overall pooled population from the OT-0401 and REVERSE studies (intent-to-treat population); (c) transplant-free survival up to 90 days in the pooled population from the OT-0401 and REVERSE studies stratified by HRS reversal status and treatment arm; and (d) overall survival up to 90 days in pooled population from the OT-0401 and REVERSE studies stratified by HRS reversal status and treatment arm.

lower SCr and lack of prior use of rifaximin (Table 2). For transplant-free survival, univariate baseline predictors in patients treated with terlipressin were lower MELD score, lower SCr, lower MAP and lower bilirubin and absence of precipitating factors for HRS (Table 3). Similar to transplant-free survival, lower MELD score, lower SCr, lower MAP and lower bilirubin and absence of precipitating factors for HRS were significantly predictive of overall survival in terlipressin-treated patients in the univariate analysis (Table 3).

In the placebo group, no baseline factors were found to be significantly predictive of HRS reversal by univariate analysis; however, there was a non-significant trend for lower baseline MELD score. Absence of alcoholic hepatitis and male sex were shown to be predictive of longer transplant-free survival by univariate analysis in

the placebo group; only the absence of alcoholic hepatitis and male sex were predictive of longer overall survival.

Multiple models were prepared to carry out multivariate analyses to verify the independent predictive value of the various baseline parameters on HRS reversal, 90-day transplant-free survival and 90-day overall survival. For HRS reversal, results from the univariate analysis were confirmed by the multivariate analyses (see Supporting Information). For 90-day transplant-free survival, lower SCr, lower MAP, and lower total bilirubin and absence of precipitating factors remained independent predictors of longer transplant-free survival in the terlipressin group (see Supporting Information). As in the univariate analysis, absence of alcoholic hepatitis and male sex were independently predictive of longer transplant-free survival in the placebo group. Lower SCr, lower MAP, and
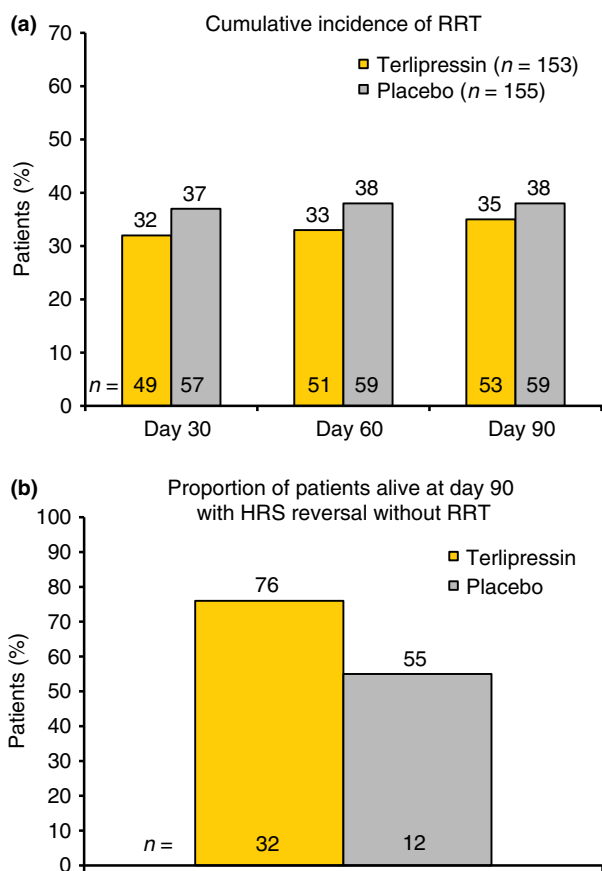
**(a)**



**(b)**



**Figure 5** | (a) Cumulative incidence of RRT in the pooled terlipressin and placebo populations from the OT-0401 and REVERSE studies. (b) Proportion of patients alive at day 90 with HRS reversal without RRT. RRT, renal replacement therapy.

lower total bilirubin and absence of precipitating factors were found by multivariate analysis to be independent predictors of longer overall survival in the terlipressin group; absence of alcoholic hepatitis and male sex were independent predictors in the placebo group (see Supporting Information).

## Safety

Details regarding the observed safety profiles for each individual study have been previously reported.[16, 19] Overall, the incidence of adverse events was similar in the two treatment groups [terlipressin, 142/149 (95%); placebo, 137/150 (91%)], as was the incidence of serious adverse events [terlipressin, 96/149 (64%); placebo, 89/150 (59%)]. A total of 71 patients (48%) in the terlipressin group experienced treatment-related adverse events compared with 42 (28%) in the placebo group.

The most commonly reported adverse events were abdominal pain [terlipressin, 36/149 (24%); placebo, 24/150 (16%)], nausea [terlipressin, 20/149 (13%); placebo, 20/150 (13%)], hypotension [terlipressin, 23/149 (15%); placebo, 13/150 (9%)], and diarrhoea [terlipressin, 26/149 (17%); placebo, 6/150 (4%)]. Twenty-two patients (15%) in the terlipressin group and 8 (5%) in the placebo group discontinued from the study due to adverse events.

## DISCUSSION

The results of this pooled analysis of individual patient-level data from the phase 3 OT-0401 and REVERSE studies demonstrate that the addition of terlipressin to albumin provides a significant benefit in terms of HRS reversal in patients with HRS-1. The significant increase in the frequency of HRS reversal observed with terlipressin is consistent with a significant improvement in renal function, as reflected by reductions in SCr and increases in eGFR. In addition, observed increases from baseline in MAP with terlipressin treatment are consistent with published findings of vasoconstrictor therapy in HRS-1 in which increases in MAP have been associated with improved clinical outcomes.[21]

Our findings also demonstrate the importance of keeping patients on treatment and minimising withdrawals due to adverse events, as well as the benefits of increasing the dose of terlipressin if necessary; subgroup analyses indicated significantly higher rates of HRS reversal for patients who received >10 and >12 doses of medication and those who had dose increases. Also, the need for early recognition and treatment of HRS-1 is also apparent from these data, as patients did better if treatment commenced at a lower SCr.

Overall, the observed rates of transplant-free survival and overall survival up to day 90 were similar in the two treatment groups. The lack of an effect of terlipressin on survival in this pooled analysis is not surprising. Although terlipressin has been shown to improve renal function, it does not affect the underlying liver disease; therefore, terlipressin would not be expected to have more than a modest effect on survival, which would be difficult to demonstrate even in large studies. For example, in OT-0401 ($N = 112$), a relative difference of 14% in overall survival was observed in favour of terlipressin by the 180-day follow-up visit (42.9% for terlipressin patients vs. 37.5% for placebo patients; $P = 0.839$).[19] Given the observed overall relative survival difference of 14%, a much larger sample size (~2000 patients) would be required to

**Table 2 |** Pooled univariate logistic regression analysis of effects of baseline characteristics on HRS reversal by treatment group (intent-to-treat population)

| Baseline parameter* | Terlipressin | | | | Placebo | | | |
|---|---|---|---|---|---|---|---|---|
| | N | RR | 95% CI | P value | N | RR | 95% CI | P value |
| Age <65 years | 153 | 1.05 | 0.47–2.34 | 0.9063 | 155 | 0.83 | 0.27–2.54 | 0.7465 |
| Alcoholic hepatitis not present | 153 | 0.71 | 0.42–1.20 | 0.2021 | 155 | 1.09 | 0.46–2.61 | 0.8449 |
| Child–Pugh score | 143 | 0.97 | 0.85–1.10 | 0.6128 | 147 | 0.91 | 0.73–1.14 | 0.4009 |
| INR | 144 | 0.61 | 0.42–0.90 | 0.0121 | 148 | 0.76 | 0.42–1.36 | 0.3506 |
| MAP | 153 | 0.99 | 0.97–1.02 | 0.6466 | 154 | 1.00 | 0.97–1.04 | 0.8498 |
| MELD score | 138 | 0.93 | 0.90–0.97 | <0.0001 | 140 | 0.94 | 0.88–1.00 | 0.0571 |
| Serum creatinine | 153 | 0.61 | 0.45–0.82 | 0.0011 | 155 | 0.70 | 0.46–1.05 | 0.0843 |
| Serum sodium | 153 | 1.00 | 0.97–1.04 | 0.8905 | 155 | 1.00 | 0.95–1.07 | 0.8738 |
| Total bilirubin | 150 | 0.98 | 0.95–1.01 | 0.1258 | 150 | 0.98 | 0.94–1.01 | 0.2294 |
| Male sex | 153 | 1.16 | 0.68–2.00 | 0.5882 | 155 | 0.81 | 0.36–1.80 | 0.6035 |
| Precipitating factor for HRS | 153 | 0.79 | 0.46–1.33 | 0.3697 | 155 | 1.31 | 0.60–2.86 | 0.4920 |
| Prior rifaximin | 153 | 0.56 | 0.32–0.98 | 0.0431 | 155 | 0.61 | 0.26–1.42 | 0.2528 |

CI, confidence interval; HRS, hepatorenal syndrome; INR, international normalised ratio; MAP, mean arterial pressure; MELD, model for end-stage liver disease; RR, relative risk.

* Baseline parameters for which data were available in both the OT-0401 and REVERSE studies were included in the analysis.

**Table 3 |** Pooled univariate logistic regression analysis of effects of baseline characteristics on 90-day transplant-free survival and overall survival by treatment group (intent-to-treat population)

| Baseline parameter* | 90-Day transplant-free survival | | | | | | | | 90-Day overall survival | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Terlipressin | | | | Placebo | | | | Terlipressin | | | | Placebo | | | |
| | N | RR | 95% CI | P value | N | RR | 95% CI | P value | N | RR | 95% CI | P value | N | RR | 95% CI | P value |
| Age <65 years | 153 | 1.56 | 0.85–2.86 | 0.1509 | 155 | 1.08 | 0.66–1.76 | 0.7560 | 153 | 1.54 | 0.84–2.82 | 0.1636 | 155 | 1.15 | 0.37–1.98 | 0.6140 |
| Alcoholic hepatitis not present | 153 | 1.21 | 0.84–1.74 | 0.3003 | 155 | 1.86 | 1.20–2.88 | 0.0058 | 153 | 1.19 | 0.83–1.72 | 0.3429 | 155 | 1.72 | 1.10–2.68 | 0.0168 |
| Child–Pugh score | 143 | 0.95 | 0.88–1.02 | 0.1546 | 147 | 0.92 | 0.85–1.00 | 0.0591 | 143 | 0.94 | 0.87–1.01 | 0.0760 | 147 | 0.92 | 0.84–1.01 | 0.0807 |
| INR | 144 | 0.90 | 0.74–1.08 | 0.2570 | 148 | 0.91 | 0.76–1.10 | 0.3421 | 144 | 0.86 | 0.71–1.05 | 0.1428 | 148 | 0.91 | 0.75–1.11 | 0.3688 |
| MAP | 153 | 0.98 | 0.97–0.99 | 0.0009 | 154 | 1.00 | 0.99–1.01 | 0.9823 | 153 | 0.98 | 0.97–0.99 | 0.0004 | 154 | 1.00 | 0.99–1.01 | 0.7042 |
| MELD score | 138 | 0.96 | 0.94–0.99 | 0.0012 | 140 | 0.99 | 0.97–1.01 | 0.3753 | 138 | 0.96 | 0.94–0.99 | 0.0011 | 140 | 0.99 | 0.97–1.02 | 0.4905 |
| Serum creatinine | 153 | 0.82 | 0.72–0.93 | 0.0024 | 155 | 1.00 | 0.88–1.14 | 0.9931 | 153 | 0.82 | 0.72–0.94 | 0.0033 | 155 | 0.98 | 0.85–1.12 | 0.7590 |
| Serum sodium | 153 | 1.00 | 0.98–1.02 | 0.6355 | 155 | 0.99 | 0.97–1.01 | 0.2980 | 153 | 0.99 | 0.97–1.01 | 0.5084 | 155 | 0.99 | 0.97–1.01 | 0.3957 |
| Total bilirubin | 150 | 0.98 | 0.96–0.99 | 0.0038 | 150 | 0.99 | 0.98–1.00 | 0.1085 | 150 | 0.98 | 0.96–0.99 | 0.0040 | 150 | 0.99 | 0.98–1.01 | 0.2436 |
| Male sex | 153 | 1.10 | 0.82–1.49 | 0.5242 | 155 | 1.46 | 1.00–2.11 | 0.0477 | 153 | 1.14 | 0.84–1.55 | 0.4059 | 155 | 1.66 | 1.09–2.52 | 0.0175 |
| No precipitating factor for HRS | 153 | 1.40 | 1.05–1.87 | 0.0232 | 155 | 1.30 | 0.96–1.74 | 0.0849 | 153 | 1.37 | 1.02–1.83 | 0.0358 | 155 | 1.34 | 0.98–1.84 | 0.0660 |
| Prior rifaximin | 153 | 1.24 | 0.93–1.65 | 0.1461 | 155 | 1.11 | 0.83–1.49 | 0.4875 | 153 | 1.21 | 0.90–1.62 | 0.2002 | 155 | 0.96 | 0.70–1.32 | 0.8169 |
| Race group (white vs. non-white) | 152 | 1.12 | 0.67–1.87 | 0.6704 | 155 | 1.96 | 0.85–4.55 | 0.1166 | 152 | 1.10 | 0.66–1.84 | 0.7081 | 155 | 1.84 | 0.79–4.27 | 0.1574 |

CI, confidence interval; HRS, hepatorenal syndrome; INR, international normalised ratio; MAP, mean arterial pressure; MELD, model for end-stage liver disease; RR, relative risk.

* Baseline parameters for which data were available in both the REVERSE and OT-0401 studies were included in the analysis.

adequately power a study to demonstrate a survival difference.

Lower MELD score, lower SCr, lower MAP, and lower total bilirubin and absence of precipitating factors for HRS at baseline were predictive of longer transplant-free survival in the univariate analysis of the terlipressin group. It is not surprising that those with less severe liver disease and renal impairment had a higher chance of surviving without liver transplantation. The findings of lower MAP and absence of precipitating factors being predictive of improved survival in the terlipressin group were unexpected and merit further evaluation. For the placebo group, only the absence of alcoholic hepatitis and male sex were predictive of both longer transplant-free survival and longer overall survival. While absence of alcoholic hepatitis is a known predictive factor for better survival,[22] the finding of male sex as a predictor should be examined further. Overall survival at day 90 was significantly lower in females than in males; however, females receiving terlipressin showed a trend towards improved survival compared with those receiving placebo, and the survival estimate was similar to that for males.

Our observations regarding factors predictive of HRS reversal and survival essentially confirm what has been observed in previous studies,[22–27] with the exception of the absence of a precipitating cause for HRS-1, absence of prior rifaximin use in the terlipressin group, and male sex in the placebo group – all new observations. The absence of prior rifaximin use as a factor predictive of HRS reversal in the terlipressin group is of interest; it is possible that patients without prior rifaximin exposure are less ill than those receiving rifaximin. However, the effect of rifaximin exposure remained in the multivariate model that adjusted for the commonly recognised factors previously shown to be predictive of HRS reversal (e.g. lower SCr, lower MELD score). Low patient numbers restricted prior studies in their ability to explore multiple predictive factors. Use of our larger pooled database, derived from individual patient data, demonstrates the value of such pooling to explore and identify previously unreported factors that may be important in predicting therapeutic response and survival in patients with HRS-1[16, 19] and which require further study.

More patients experiencing HRS reversal with terlipressin plus albumin than with placebo plus albumin were alive without renal replacement therapy at day 90 (76% vs. 55%, respectively). Thus, patients who achieve HRS reversal with terlipressin plus albumin may have better outcomes than patients who achieve HRS reversal with albumin alone.

Previous studies have shown that for HRS reversal to occur, a rise in MAP in response to treatment is required, which was also observed in the current report. The investigators proposed that the correlation between changes in MAP and improvement in renal function with terlipressin may be a result of terlipressin-induced reduction in splanchnic vasodilation, which does not occur with albumin alone.[22]

This pooled analysis has the usual limitations. The studies were not designed for a pre-specified pooled analysis. Although the studies were similar in patient population, design, and dosing regimen, some differences may have influenced the results and/or interpretation of the results. These include the retrospective nature of the analysis and unbalanced numbers of patients in some of the subgroups. Nevertheless, we believe that our rigorous approach using patient-level data analyses of the combined populations from these large studies allows for a higher degree of confidence in the results observed regarding treatment-related effects of terlipressin compared with results observed via a standard meta-analysis.

In conclusion, in this pooled population of patients with HRS-1, terlipressin plus albumin achieved a significantly higher rate of HRS reversal than placebo plus albumin. More patients achieving HRS reversal with terlipressin were alive without the need for renal replacement therapy at 90 days compared with placebo. Our findings confirm that patients with HRS-1 who receive terlipressin plus albumin achieve HRS reversal more frequently, and have a greater degree of improvement in renal function than patients who receive albumin alone.

## SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

**Data S1.** The OT-0401 trial investigators.

**Data S2.** The REVERSE trial investigators.

**Table S1.** Pooled multivariate logistic regression analysis of effects of baseline characteristics on HRS reversal in the terlipressin group (intent-to-treat population).

**Table S2.** Pooled multivariate logistic regression analysis of effects of baseline characteristics on 90-day transplant-free survival by treatment group (intent-to-treat population).

**Table S3.** Pooled multivariate logistic regression analysis of effects of baseline characteristics on 90-day overall survival by treatment group (intent-to-treat population).

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