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Terlipressin versus placebo or no intervention for people with cirrhosis and hepatorenal syndrome (Review)

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[Intervention Review]

Terlipressin versus placebo or no intervention for people with cirrhosis and hepatorenal syndrome

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ABSTRACT

Background

Hepatorenal syndrome is a potentially reversible renal failure associated with severe liver disease. The disease is relatively common among people with decompensated cirrhosis. Terlipressin is a drug that increases the blood flow to the kidneys by constricting blood vessels. The previous version of this systematic review found a potential beneficial effect of terlipressin on mortality and renal function in people with cirrhosis and hepatorenal syndrome.

Objectives

To assess the beneficial and harmful effects of terlipressin versus placebo/no intervention for people with cirrhosis and hepatorenal syndrome.

Search methods

We identified eligible trials through searches of the Cochrane Hepato-Biliary Group Controlled Trials Register, the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, MEDLINE, Embase, and Science Citation Index Expanded, and manual searches until 21 November 2016.

Selection criteria

Randomised clinical trials (RCTs) involving participants with cirrhosis and type 1 or type 2 hepatorenal syndrome allocated to terlipressin versus placebo or no intervention. We allowed co-administration with albumin administered to both comparison groups.

Data collection and analysis

Two review authors independently extracted data from trial reports and undertook correspondence with the authors. Primary outcomes were mortality, hepatorenal syndrome, and serious adverse events. We conducted sensitivity analyses of RCTs in which participants received albumin, subgroup analyses of participants with type 1 or type 2 hepatorenal syndrome, and Trial Sequential Analyses to control random errors. We reported random-effects meta-analyses with risk ratios (RR) and 95% confidence intervals (CI). We assessed the risk of bias based on the Cochrane Hepato-Biliary Group domains. We graded the quality of the evidence using GRADE.

Main results

We included nine RCTs with a total of 534 participants with cirrhosis and ascites. One RCT had a low risk of bias for mortality and a high risk of bias for the remaining outcomes. All included trials had a high risk of bias for non-mortality outcomes. In total, 473 participants had type 1 hepatorenal syndrome. Seven RCTs specifically evaluated terlipressin and albumin. Terlipressin was associated with a beneficial effect on mortality when including all RCTs (RR 0.85, 95% CI 0.73 to 0.98; 534 participants; number needed to treat for an additional beneficial outcome (NNTB) 10.3 people; low-quality evidence). Trial Sequential Analysis including all RCTs also found a beneficial effect of terlipressin. Additional analyses showed a beneficial effect of terlipressin and albumin on reversal of hepatorenal syndrome (RR 0.63, 95% CI 0.48 to 0.82; 510 participants; 8 RCTs; NNTB 4 people; low-quality evidence). Terlipressin increased the risk of serious cardiovascular adverse events (RR 7.26, 95% CI 1.70 to 31.05; 234 participants; 4 RCTs), but it had no effect on the risk of serious adverse events when analysed as a composite outcome (RR 0.91, 95% CI 0.68 to 1.21; 534 participants; 9 RCTs; number needed to treat for an additional harmful outcome 24.5 people; low-quality evidence). Non-serious adverse events were mainly gastrointestinal, including diarrhoea (RR 5.76, 95% CI 2.19 to 15.15; 240 participants; low-quality evidence) and abdominal pain (RR 1.54, 95% CI 0.97 to 2.43; 294 participants; low-quality evidence).

We identified one ongoing trial on terlipressin versus placebo in participants with cirrhosis, ascites, and hepatorenal syndrome type 1.

Three RCTs reported funding from a pharmaceutical company. The remaining trials did not report funding or did not receive funding from pharmaceutical companies.

Authors' conclusions

This review suggests that terlipressin may be associated with beneficial effects on mortality and renal function in people with cirrhosis and type 1 hepatorenal syndrome, but it is also associated with serious adverse effects. We downgraded the strength of the evidence due to methodological issues including bias control, clinical heterogeneity, and imprecision. Consequently, additional evidence is needed.

PLAIN LANGUAGE SUMMARY

Terlipressin versus placebo/no intervention for people with cirrhosis and hepatorenal syndrome

Background

Cirrhosis is a chronic disorder of the liver where scar tissue replaces the normal liver. People with cirrhosis can develop a kidney disease known as hepatorenal syndrome. The disease may develop when the blood flow to the kidneys becomes insufficient. Increasing the blood flow to the kidneys may therefore benefit people with hepatorenal syndrome. There are two types of hepatorenal syndrome: type 1 occurs rapidly, and type 2 has a slower onset. Terlipressin is a drug that increases the blood flow to the kidneys by constricting blood vessels. The drug may therefore help people with cirrhosis and hepatorenal syndrome.

Review question

Is terlipressin better than inactive placebo/no treatment for people with hepatorenal syndrome?

Search date

November 2016.

Study characteristics

The review includes nine randomised clinical trials (RCTs) and a total of 534 participants. The trials originated from six countries. Seven trials included only participants with type 1 hepatorenal syndrome. Two trials included a total of 96 participants with type 1 or type 2 hepatorenal syndrome.

Study funding sources

Three RCTs reported funding from a pharmaceutical company. The remaining trials did not report funding or did not receive funding from pharmaceutical companies.

Key results

People who received terlipressin had a lower risk of dying than people who received inactive placebo or no treatment. Terlipressin was also associated with a beneficial effect on renal function. Terlipressin increased the risk of serious circulation and heart problems (so-called cardiovascular events). Other adverse events included diarrhoea and abdominal pain.

The analyses mainly included people with type 1 hepatorenal syndrome. No beneficial or harmful effects of terlipressin were found when analysing participants with type 2 hepatorenal syndrome (possibly due to the small number of participants).

Quality of the evidence

We considered the evidence to be of low quality.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Terlipressin versus placebo or no intervention for hepatorenal syndrome

Terlipressin versus placebo or no intervention for hepatorenal syndrome. Administration of albumin allowed if administered to both the intervention and comparison group

Patient or population: people with hepatorenal syndrome

Setting: hospital

Intervention: terlipressin alone or terlipressin plus albumin

Comparison: placebo or no intervention or albumin

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo or no intervention	Risk with terlipressin				
Mortality	Study population		RR 0.85 (0.73 to 0.98)	534 (9 RCTs)	⊕⊕⊕⊖ LOW ¹	Downgraded because of i) clinical heterogeneity and ii) the results of the Trial Sequential Analysis
	688 per 1000	536 per 1000 (433 to 660)				
	Moderate					
	625 per 1000	488 per 1000 (394 to 600)				
Hepatorenal syndrome	Study population		RR 0.63 (0.48 to 0.82)	510 (7 RCTs)	⊕⊕⊕⊖ LOW	Downgraded because of i) clinical heterogeneity and ii) all trials are judged as 'high risk of bias'.
	879 per 1000	510 per 1000 (431 to 606)				
	Moderate					
	875 per 1000	507 per 1000 (429 to 604)				
Serious adverse events	Study population		RR 0.91 (0.68 to 1.21)	534 (9 RCTs)	⊕⊕⊕⊖ LOW	Downgraded because of i) clinical heterogeneity and ii) all RCTs are judged as high risk of bias.
	85 per 1000	212 per 1000 (131 to 344)				

Serious cardiovascular adverse events	Study population		RR 7.26 (1.70 to 31.05)	234 (4 RCTs)	⊕⊕⊕⊕ LOW	Downgraded because of i) clinical heterogeneity and ii) all RCTs are judged as high risk of bias
	16 per 1000	111 per 1000				
Abdominal pain	Study population		RR 1.54 (0.97 to 2.43)	294 (4 RCTs)	⊕⊕⊕⊕ LOW ¹	Downgraded because of i) clinical heterogeneity and ii) all RCTs are judged as high risk of bias
	149 per 1000	229 per 1000				
Diarrhoea	Study population		RR 5.76 (2.19 to 15.15)	240 (2 RCTs)	⊕⊕⊕⊕ LOW	Downgraded because of i) clinical heterogeneity and ii) all RCTs are judged as high risk of bias
	33 per 1000	190 per 1000				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

¹Not confirmed in analyses of randomised clinical trials (RCTs) with a low risk of bias.

BACKGROUND

Description of the condition

Hepatorenal syndrome is a potentially reversible renal failure associated with severe liver disease (Arroyo 1996). The disease is relatively common among people with decompensated cirrhosis. Over 20% of people with decompensated cirrhosis become hospitalised with renal failure, among whom up to 20% have hepatorenal syndrome (Gines 1993; Garcia-Tsao 2008; Israelsen 2015b). The diagnosis includes cirrhosis and ascites plus impaired renal function after exclusion of parenchymal renal disease and factors that may precipitate renal dysfunction in cirrhosis (Salerno 2007). Hepatorenal syndrome is divided into two types, with type 1 having the most rapid course of development. Without treatment, type 1 has a median survival of about two weeks and type 2 a median survival of about six months (Arroyo 1996; Gines 2003; Salerno 2007).

Description of the intervention

The development of hepatorenal syndrome is associated with the circulatory changes seen in cirrhosis of the liver subsequent to portal hypertension and vasodilation of the splanchnic vasculature (Cardenas 2003). This vasodilation results in effective underfilling of the renal arteries and activation of the renin-angiotensin-aldosterone, the arginine-vasopressin, and the sympathetic nervous systems (Pasqualetti 1998; Moller 2004; Ruiz del Arbol 2005). Activation of these systems may in turn lead to severe vasoconstriction of the renal arteries and hepatorenal syndrome (Cardenas 2003). Current treatments focus on improvement of renal blood flow and effective arterial circulation. This is done with volume expanders (such as intravenous albumin) or with vasoactive drugs that preferentially constrict the splanchnic circulation, such as terlipressin.

How the intervention might work

Vasoactive drugs that increase the splanchnic arterial tone may reverse hepatorenal syndrome. Vasopressin is a potential candidate, but may lead to severe ischaemia of the mesenteric mucosa, skin, and myocardium (Obritsch 2004). A controlled trial found that the vasopressin analogue terlipressin may be a safer alternative (Freeman 1982). Terlipressin is administered intravenously either by bolus or continuous infusion. It is commonly titrated based on desired change in mean arterial pressure. It has both systemic and splanchnic constrictive effects, so adverse events include sequelae of vasoconstriction, such as mild gastrointestinal symptoms (e.g. diarrhoea and abdominal pain) or more severe evidence of ischaemia.

Why it is important to do this review

Two initial randomised clinical trials (RCTs) evaluated terlipressin for participants with hepatorenal syndrome; however, they were small and had short-term follow-up (Hadengue 1998; Solanki 2003). Three subsequent larger RCTs found no convincing effects on mortality (Martín-Llahí 2008; Neri 2008; Sanyal 2008). Three meta-analyses of RCTs and observational studies reached equivocal findings (Fabrizi 2009; Dobre 2010; Sagi 2010). In the previous version of this systematic review, we found a potential beneficial effect of terlipressin on mortality and reversal of hepatorenal syndrome (Gluud 2006), but we also identified

potential methodological concerns. We updated the review to include the currently available evidence.

OBJECTIVES

To assess the beneficial and harmful effects of terlipressin versus placebo or no intervention for people with cirrhosis and hepatorenal syndrome.

METHODS

Criteria for considering studies for this review

Types of studies

We included RCTs irrespective of blinding, publication status, or language. We included the first period from cross-over RCTs. In addition, we planned to include quasi-randomised studies and observational studies in our assessment of serious adverse events (Higgins 2011), although this is a known limitation making us focus more on benefits than on harms (Gluud 2017).

Types of participants

We included people with cirrhosis and type 1 or type 2 hepatorenal syndrome (defined as an increase in creatinine in people with ascites and no other causes of renal disease).

Types of interventions

We included RCTs comparing terlipressin (any dose or duration) versus placebo or no intervention. We allowed co-administration of albumin given to both comparison groups.

Types of outcome measures

We assessed all outcomes at the maximum duration of follow-up.

Primary outcomes

1. Mortality.
2. Hepatorenal syndrome (number of participants who did not achieve reversal of hepatorenal syndrome).
3. Serious adverse events: any untoward medical occurrence that led to death, was life-threatening, or required hospitalisation or prolongation of hospitalisation (ICH-GCP 1997). We analysed serious adverse events as a composite outcome (Gluud 2017).

Secondary outcomes

1. Health-related quality of life: the overall score based on the quality of life questionnaires used in individual trials.
2. Non-serious adverse events: all adverse events that did not fulfil the criteria for serious adverse events.

Search methods for identification of studies

Electronic searches

We performed electronic searches in the Cochrane Hepato-Biliary Group Controlled Trials Register, the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, MEDLINE (OvidSP), Embase (OvidSP), and Science Citation Index Expanded (Web of Science) (Royle 2003). The search strategies with the timespan of the searches are given in Appendix 1. We updated searches as of 21 November 2016.

Searching other resources

Manual searches included scanning of reference lists in relevant articles and conference proceedings. We also searched trial registers through the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) search portal (www.who.int/ictcp/search/en/) (21 November, 2016).

Data collection and analysis

Selection of studies

Two review authors (AA and MI) independently selected trials eligible for inclusion from the updated literature searches and listed excluded with the reasons for exclusion.

Data extraction and management

Two review authors (AA and MI) independently extracted data. All disagreements were resolved through discussion before analyses. In case of disagreements, a third review author (LG) acted as ombudsman. We wrote to authors of the included trials to obtain additional information not described in the published reports, including missing data.

Assessment of risk of bias in included studies

We assessed the risk of bias using the domains described in the Cochrane Hepato-Biliary Group Module ([Gluud 2017](#)).

Allocation sequence generation

- Low risk of bias: the study authors performed sequence generation using computer random number generation or a random number table. Drawing lots, tossing a coin, shuffling cards, and throwing dice were adequate if an independent person not otherwise involved in the study performed them.
- Unclear risk of bias: not specified.
- High risk of bias: the sequence generation was not random. We planned to include such studies for assessment of harms.

Allocation concealment

- Low risk of bias: the participant allocations could not have been foreseen in advance of, or during, enrolment. Allocation was controlled by a central and independent randomisation unit. The allocation sequence was unknown to the investigators (e.g. if the allocation sequence was hidden in sequentially numbered, opaque, and sealed envelopes).
- Unclear risk of bias: the method used to conceal the allocation was not described so that intervention allocations may have been foreseen in advance of, or during, enrolment.
- High risk of bias: the allocation sequence was likely to be known to the investigators who assigned the participants.

Blinding of participants and personnel

- Low risk of bias: i) the outcome was mortality, which according to previous empirical evidence is not likely to be influenced by lack of blinding ([Hróbjartsson 2001](#); [Savović 2012](#)); or ii) blinding of participants and key study personnel ensured, and it is unlikely that the blinding could have been broken.
- Unclear risk of bias: insufficient information to permit judgement of 'low risk' or 'high risk'.

- High risk of bias: no blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding (non-mortality outcomes).

Blinding of outcome assessors

- Low risk of bias: i) the outcome was mortality, which according to previous empirical evidence is not likely to be influenced by lack of blinding ([Hróbjartsson 2001](#); [Savović 2012](#)); or ii) blinding of outcome assessment ensured, and it is unlikely that the blinding could have been broken.
- Unclear risk of bias: insufficient information to permit judgement of 'low risk' or 'high risk'.
- High risk of bias: no blinding or inadequate blinding (e.g. intravenous versus orally administered drugs), and the outcome is likely to be influenced by lack of blinding (non-mortality outcomes).

Incomplete outcome data

- Low risk of bias: missing data were unlikely to make treatment effects depart from plausible values. The investigators used sufficient methods, such as intention-to-treat analyses with multiple imputations or carry-forward analyses, to handle missing data.
- Unclear risk of bias: there was insufficient information to assess whether missing data in combination with the method used to handle missing data induced bias on the results.
- High risk of bias: the results were likely to be biased due to missing data.

Selective outcome reporting

- Low risk of bias: the trial reported clinically relevant outcomes (mortality, hepatic encephalopathy, and serious adverse events). If we had access to the original trial protocol, the outcomes should have been those called for in that protocol. If we obtained information from a trial registry (such as www.clinicaltrials.gov), we only used the information if the investigators registered the trial before inclusion of the first participant.
- Unclear risk of bias: predefined outcomes were not reported fully.
- High risk of bias: one or more predefined outcomes were not reported.

For-profit bias

- Low risk of bias: the trial appears to be free of industry sponsorship or other type of for-profit support.
- Unclear risk of bias: no information on clinical trial support or sponsorship was available.
- High risk of bias: the trial was sponsored by industry, received support in the form of terlipressin or placebo, or received any other type of support.

Other bias

- Low risk of bias: the trial appeared to be free of other biases including medicinal dosing problems or follow-up (as defined below).
- Unclear risk of bias: the trial may or may not have been free of other factors that could put it at risk of bias.

- High risk of bias: there were other factors in the trial that could put it at risk of bias, such as the administration of inappropriate treatments to the controls (e.g. an inappropriate dose) or follow-up (e.g. the trial included different follow-up schedules for participants in the allocation groups), or premature discontinuation of the trial.

Overall bias assessment

- Low risk of bias: all domains were classified as low risk of bias using the definitions described above.
- High risk of bias: one or more of the bias domains were classified as unclear or high risk of bias.

Measures of treatment effect

We expressed outcomes using risk ratios (RR) with 95% confidence intervals (CI). For primary outcomes, we calculated the number needed to treat (NNT) using the inverse of the risk difference (RD). Based on the control group event rate, we repeated the analyses using odds ratios (OR) and RD. The analyses using OR and RD had no influence on the results of the review.

Unit of analysis issues

We included data from the first treatment period of cross-over trials.

Dealing with missing data

We planned to evaluate the importance of missing data in a worst-case scenario analysis (with inclusion of missing outcomes as treatment failures) and an extreme worst-case scenario analysis (including missing outcomes as failures in the experimental group and successes in the control group). However, we did not identify participants with missing outcome data and were therefore unable to conduct these analyses.

Assessment of heterogeneity

We expressed heterogeneity as I^2 values using the following thresholds: 0% to 40% (unimportant), 40 to 60% (moderate), 60 to 80% (substantial), and > 80% (considerable). We have included this information in the 'Summary of findings' tables (GRADEpro).

Assessment of reporting biases

For meta-analyses with at least 10 RCTs, we planned to assess reporting biases through regression analyses.

Data synthesis

We performed the analyses in Review Manager 5 (RevMan 2014), STATA (STATA), and Trial Sequential Analysis (TSA 2011), and used GRADEpro software to prepare 'Summary of findings' tables (GRADEpro).

Meta-analysis

We initially conducted fixed-effect and random-effects meta-analyses (Higgins 2011). If the estimates of the fixed-effect and random-effects meta-analyses were similar, then we assumed that any small-study effects had little effect on the intervention effect estimate. If the random-effects estimate was more beneficial, we planned to re-evaluate whether it was reasonable to conclude that the intervention was more effective in the smaller studies. We originally planned to evaluate if the larger RCTs tended to be

conducted with greater methodological rigour, or conducted in circumstances more typical of the use of terlipressin in clinical practice. Had we found this scenario, we planned to report the results of meta-analyses restricted to the larger, more rigorous studies. However, this scenario did not occur.

Based on the expected clinical heterogeneity, we expected that a number of analyses would display statistical heterogeneity ($I^2 > 0\%$). For random-effects models, precision will decrease with increasing heterogeneity and confidence intervals will widen correspondingly. We therefore expected that the random-effects model would give the most conservative (and a more correct) estimate of the intervention effect. Accordingly, we have reported the results of our analyses based on random-effects meta-analyses.

Trial Sequential Analysis

We performed Trial Sequential Analysis to control the risks of type 1 and type 2 errors and to evaluate futility in the assessment of our primary outcomes (TSA 2011; Gluud 2017). We defined the required information size (also known as the diversity-adjusted required information size) as the number of participants needed to detect or reject an intervention effect based on the relative risk reduction (RRR) and control group risk (CGR). Firm evidence was established if the Z-curve crossed the monitoring boundary (also known as the trial sequential monitoring boundary) before reaching the required information size. Based on previous evidence (Krag 2008), we performed the analyses with alpha set to 3%, power to 90%, and the RRR, CGR, and heterogeneity correction to 25%, 61.5%, and 30% for mortality; 25%, 87.5%, and 70% for hepatorenal syndrome; and 25%, 15%, and 20% for serious cardiovascular adverse events. We repeated the analyses with the RRR reduced to 20% for mortality, hepatorenal syndrome, and serious cardiovascular adverse events. In the analyses of serious cardiovascular events, we also reduced the CGR to 5%.

Subgroup analysis and investigation of heterogeneity

We conducted subgroup analyses to investigate heterogeneity associated with the type of hepatorenal syndrome and use of albumin.

Sensitivity analysis

We did not evaluate the influence of bias because only one RCT was at low risk of bias for mortality and no randomised clinical trials were at low risk of bias for the remaining outcomes.

Summary of findings tables

We used GRADEpro to generate a 'Summary of findings' table with information about outcomes, risk of bias, and the results of the meta-analyses (GRADEpro). We used the GRADE system to evaluate the quality of the evidence for outcomes reported in the review considering the within-study risk of bias (methodological quality), indirectness of evidence, heterogeneity, imprecision of effect estimate, and risk of publication bias.

RESULTS

Description of studies

We included nine randomised clinical trials in the quantitative and qualitative analyses (see Characteristics of included studies). We also identified one ongoing trial (NCT01143246).

Results of the search

The electronic searches revealed 619 potentially eligible references and the manual searches three additional references (Figure 1). After scanning the titles and abstracts, we retrieved and listed 25 records. We had to exclude 10 of these that referred to randomised clinical trials on participants with hepatorenal syndrome because they did not evaluate the interventions assessed in the present review (Chelarescu 2003; Pomier 2003; Alessandria 2007; Angeli

2008; Sharma 2008; Silawat 2011; Cavallin 2012; Indrabi 2013; Wan 2014; Cavallin 2015; Nguyen-Tat 2015). The remaining references referred to nine RCTs that fulfilled our inclusion criteria (Hadengue 1998; Yang 2001; Solanki 2003; Martín-Llahí 2008; Neri 2008; Pulvirenti 2008; Sanyal 2008; Boyer 2016). One trial used a cross-over design (Hadengue 1998), and the remaining a parallel-group design (Hadengue 1998; Solanki 2003; Martín-Llahí 2008; Neri 2008; Pulvirenti 2008; Sanyal 2008; Zafar 2012; Boyer 2016).

Figure 1. Study flow diagram.

Included studies

Trial characteristics

One RCT was published in abstract form (Zafar 2012) and the remaining RCTs as full-paper articles ([Characteristics of included studies](#)). The language of trial publications was Chinese (Yang 2001), Italian (Pulvirenti 2008), or English (Hadengue 1998; Solanki 2003; Martín-Llahí 2008; Neri 2008; Sanyal 2008; Zafar 2012; Boyer 2016). The trials were conducted in the United States, Italy, Spain, Canada, India, China, Germany, and Russia. The trial investigators performed the trials in specialised units in an intensive or semi-intensive setting. Three trials were multicenter trials (Neri 2008; Sanyal 2008; Boyer 2016), and the remaining trials were single-centre trials (Hadengue 1998; Yang 2001; Solanki 2003; Martín-Llahí 2008; Pulvirenti 2008; Zafar 2012).

The duration of follow-up was six months in two trials (Pulvirenti 2008; Sanyal 2008), three months in one RCT (Boyer 2016), and end of treatment in the remaining trials (Hadengue 1998; Yang 2001; Solanki 2003; Martín-Llahí 2008; Neri 2008; Zafar 2012).

Participant characteristics

The total number of participants was 534 participants. Included participants had cirrhosis, ascites, and hepatorenal syndrome with serum creatinine > 133 µmol/L (1.5 mg/dL) after diuretic withdrawal and volume expansion. None of the participants had evidence of shock, parenchymal renal disease, treatment with nephrotoxic drugs, or other potential causes of kidney disease. In total, 473 participants had type 1 hepatorenal syndrome. One RCT included 11 participants with type 2 hepatorenal syndrome (Martín-Llahí 2008). One RCT with 50 participants did not describe if participants had type 1 or type 2 hepatorenal syndrome (Zafar 2012). The mean age in the terlipressin and control groups ranged from 51 to 59 years and 52 to 60 years. The proportion of men ranged from 40% to 71%, and the proportion with alcoholic liver disease from 13% to 72%.

Intervention characteristics

The median initial dose of terlipressin was 1 mg four times daily. The RCTs used a fixed dose of terlipressin (Hadengue 1998; Yang 2001; Solanki 2003; Pulvirenti 2008), or increased the dose after three days in non-responders to a maximum of 2 mg four to six times daily (Martín-Llahí 2008; Neri 2008; Sanyal 2008; Zafar 2012; Boyer 2016). One trial used continuous administration of terlipressin for the first day before switching to bolus dosing (Pulvirenti 2008). The duration of terlipressin administration ranged from two days, in Hadengue 1998, to 19 days, in Neri 2008, with a median treatment duration of 15 days. Two trials did not use albumin (Hadengue 1998; Yang 2001). All participants in the experimental and control groups of the remaining trials received comparable albumin (Solanki 2003; Martín-Llahí 2008; Neri 2008; Pulvirenti 2008; Sanyal 2008; Zafar 2012; Boyer 2016).

Excluded studies

The excluded RCTs compared terlipressin and albumin versus other vasoactive drugs for hepatorenal syndrome (see [Characteristics of excluded studies](#)).

Risk of bias in included studies

We identified several sources of bias (Figure 2). For the outcome mortality, we classified one trial as at 'low risk of bias' (Martín-Llahí 2008), and the remaining trials as at 'high risk of bias' (Hadengue 1998; Yang 2001; Solanki 2003; Neri 2008; Pulvirenti 2008; Sanyal 2008; Zafar 2012; Boyer 2016). For non-mortality outcomes, we classified all RCTs as at 'high risk of bias'. No single study lacked bias across all assessed domains, including randomisation/sequence allocation, blinding, and for-profit funding sources. We deemed Martín-Llahí 2008 as at 'low risk of bias' for mortality because its sources of bias were only around blinding, which was less likely to have an influence on a purely objective outcome like mortality.

Figure 2. Methodological quality summary: review authors' judgments about each methodological quality item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	For-profit funding	Other bias	Overall risk of bias (mortality)	Overall risk of bias (non-mortality outcomes)
Boyer 2016	+	+	+	+	+	+	-	+	-	-
Hadengue 1998	?	+	+	+	-	+	-	+	-	-
Martín-Llahí 2008	+	+	-	-	+	+	+	+	+	-
Neri 2008	+	+	-	-	+	+	?	+	-	-
Pulvirenti 2008	+	+	-	-	+	+	?	+	-	-
Sanyal 2008	+	+	+	+	+	+	-	+	-	-
Solanki 2003	+	+	?	?	+	+	?	+	-	-
Yang 2001	?	?	-	-	?	+	?	+	-	-
Zafar 2012	?	?	-	-	?	+	?	+	-	-

Figure 3 presents review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Allocation

Three RCTs did not describe the allocation sequence generation (Hadengue 1998; Yang 2001; Zafar 2012), and two RCTs did not describe the allocation concealment (Yang 2001; Zafar 2012). Accordingly, we classified six RCTs as 'low risk' of selection bias (Solanki 2003; Martín-Llahí 2008; Neri 2008; Pulvirenti 2008; Sanyal 2008; Boyer 2016).

Blinding

We considered three RCTs that were double-blind as 'low risk' of performance and detection bias (Hadengue 1998; Sanyal 2008; Boyer 2016). We assessed the remaining RCTs as 'unclear', Solanki 2003, or 'high risk' of performance and detection bias (Yang 2001; Martín-Llahí 2008; Neri 2008; Pulvirenti 2008; Zafar 2012).

Incomplete outcome data

Six RCTs had no missing outcome data and included all participants in the analyses (Solanki 2003; Martín-Llahí 2008; Neri 2008; Pulvirenti 2008; Sanyal 2008; Boyer 2016). We classified these RCTs as low risk of attrition bias and the remaining three RCTs as 'unclear risk', Yang 2001, Zafar 2012, or 'high risk' of attrition bias (Hadengue 1998).

Selective reporting

All RCTs reported clinically relevant outcomes (Hadengue 1998; Yang 2001; Solanki 2003; Martín-Llahí 2008; Neri 2008; Pulvirenti 2008; Sanyal 2008; Zafar 2012; Boyer 2016). We identified no discrepancies between registered protocols (for those available) and trial publications.

For-profit funding

One RCT did not receive external funding (Martín-Llahí 2008). Three RCTs received funding from a pharmaceutical company (Hadengue 1998; Sanyal 2008; Boyer 2016). The remaining RCTs did not report funding (Yang 2001; Solanki 2003; Neri 2008; Pulvirenti 2008; Zafar 2012).

Other potential sources of bias

One study was stopped early due to low event rates (Martín-Llahí 2008).

Effects of interventions

See: [Summary of findings for the main comparison Terlipressin versus placebo or no intervention for hepatorenal syndrome](#)

Primary outcomes

We were able to gather mortality data from all RCTs (Analysis 1.1). Terlipressin was associated with reduced mortality compared with placebo/no intervention when including all RCTs (risk ratio (RR) 0.85, 95% confidence interval (CI) 0.73 to 0.98; 534 participants; 9 RCTs; $I^2 = 14\%$; number needed to treat for an additional beneficial outcome (NNTB) to prevent one death was 10; low-quality evidence). In Trial Sequential Analysis including all RCTs (Figure 4), the cumulative Z-curve did not cross the monitoring boundary for benefit. We planned to conduct worst-case scenario analyses. However, as six of the included RCTs did not have missing outcome data (Solanki 2003; Martín-Llahí 2008; Neri 2008; Pulvirenti 2008; Sanyal 2008; Boyer 2016), and we were unable to extract the number of participants with missing outcomes

from the remaining three RCTs (Hadengue 1998; Yang 2001; Zafar 2012), we were therefore unable to conduct the analysis. Subgroup analyses found an effect of terlipressin in the RCTs evaluating type 1 hepatorenal syndrome (RR 0.78, 95% CI 0.63 to 0.98; 438 participants; 7 RCT; $I^2 = 30\%$; Analysis 1.1). We were unable to

gather separate outcome data on participants with type 1 or type 2 hepatorenal syndrome from two RCTs (RR 0.92, 95% CI 0.75 to 1.14; 96 participants; $I^2 = 0\%$). An additional subgroup analysis found no beneficial or harmful effect of the terlipressin and albumin (RR 0.82, 95% CI 0.67 to 1.01; 510 participants; $I^2 = 22\%$; Analysis 1.2).

Figure 4. Trial Sequential Analysis of eight randomised clinical trials (525 participants) evaluating terlipressin versus placebo or no intervention for people with hepatorenal syndrome on mortality. Data from Hadengue 1998 is not included due to lack of events. The analysis is made with power 90%, alpha 3%, a relative risk reduction (RRR) of 25%, a control group risk (CGR) of mortality of 61.5%, and a model variance-based heterogeneity correction of 30%. The risk ratio is 0.85 (95% confidence interval 0.70 to 1.02). The cumulative Z-curve (blue line) does not cross the diversity-adjusted trial monitoring boundary for benefit.

Two RCTs did not report the number of participants without reversal of hepatorenal syndrome (Hadengue 1998; Yang 2001). Analysis of the remaining seven RCTs showed a beneficial effect of terlipressin on this outcome measure (RR 0.63, 95% CI 0.48 to 0.82; 510 participants; $I^2 = 75\%$; low-quality evidence; Analysis 1.3). In Trial Sequential Analysis including these seven RCTs (Figure 5), the cumulative Z score crossed the monitoring boundary for benefit. The NNTB to reverse one case of hepatorenal syndrome was 4. All RCTs included in this analysis evaluated terlipressin and

albumin. In Trial Sequential Analysis including all RCTs regardless of bias control (Figure 6), the cumulative Z-curve crossed the monitoring boundary for benefit. Subgroup analyses showed a beneficial effect of terlipressin on type 1 hepatorenal syndrome based on six RCTs (RR 0.64, 95% CI 0.47 to 0.87; 449 participants; $I^2 = 80\%$), but not in participants with type 2 hepatorenal syndrome (RR 0.39, 95% CI 0.14 to 1.08; 11 participants; 1 RCT) or the trial including participants with type 1 or type 2 hepatorenal syndrome (RR 0.65, 95% CI 0.46 to 0.92; 50 participants).

Figure 5. Trial Sequential Analysis of seven randomised clinical trials (510 participants) evaluating terlipressin versus placebo/no intervention for people with hepatorenal syndrome on lack of reversal of hepatorenal syndrome. The analysis is made with power 90%, alpha 3%, a relative risk reduction (RRR) of 25%, a control group risk (CGR) of lack of reversal of hepatorenal syndrome of 88%, and a heterogeneity correction of 70%. The risk ratio is 0.64 (95% confidence interval 0.46 to 0.89). The cumulative Z-curve (blue line) crosses the diversity-adjusted trial monitoring boundary for benefit during the fourth trial.

Figure 6. Trial Sequential Analysis of four randomised clinical trials (234 participants) evaluating terlipressin versus placebo or no intervention for people with hepatorenal syndrome on cardiovascular adverse events. The analysis is made with power 90%, alpha 3%, a relative risk reduction (RRR) of 25%, a control group risk (CGR) of cardiovascular adverse events of 15%, and a heterogeneity correction of 20%. The risk ratio is 7.26 (95% confidence interval 1.70 to 31.05). The diversity-adjusted trial monitoring boundary for harm is not included in the figure due to insufficient information. The estimated required information size is 4831 participants. Accordingly, with an accrued number of participants of 234, only 4.8% of the required number of participants has been achieved.

Overall, terlipressin did not influence the risk of serious adverse events when analysed as a composite outcome (RR 0.91, 95% CI 0.68 to 1.21; participants = 534; 9 RCTs; $I^2 = 71\%$; [Analysis 1.4](#)). The number needed to treat for an additional harmful outcome to cause one serious adverse event was 24.5. A Trial Sequential Analysis also found a detrimental effect of terlipressin on this outcome ([Figure 6](#)). As expected, the most common serious adverse events were cardiovascular (RR 7.26, 95% CI 1.70 to 31.05; [Analysis 1.5](#)). Other serious adverse events included circulatory overload, gastrointestinal bleeding, hepatic encephalopathy, respiratory distress/acidosis, and bacterial infections.

We repeated the Trial Sequential Analyses with power increased to 90% and the relative risk reduction reduced to 10% for mortality and 20% for hepatorenal syndrome and serious cardiovascular adverse events. In the analyses of serious cardiovascular events, we also reduced the control group risk to 15%. All analyses found insufficient evidence to support or refute beneficial or harmful effects of terlipressin versus placebo/no intervention.

Secondary outcomes

None of the included trials assessed health-related quality of life. Non-serious adverse events were similar when comparing terlipressin with placebo or no intervention (RR 1.25, 95% CI 0.58 to 2.68; 406 participants; 5 RCTs; $I^2 = 17\%$; [Analysis 1.6](#)). The most frequent adverse events were gastrointestinal, including abdominal pain and diarrhoea.

Quality of the evidence

We downgraded the quality of the evidence for all outcomes due to risk of bias, clinical heterogeneity, and imprecision according to the Trial Sequential Analyses ([Summary of findings for the main comparison](#)).

DISCUSSION

Summary of main results

This review found that terlipressin may reduce mortality and have a beneficial effect on renal function in type 1 hepatorenal syndrome,

but an increased risk of serious cardiovascular adverse events was also noted. Other studies also show that terlipressin may be associated with severe adverse effects (Shawcross 2004; Krag 2008), therefore the intervention should be closely monitored. In addition, only one RCT had a low risk of bias in the overall assessment and most of the included RCTs only followed participants to the end of treatment. Accordingly, the quality of the evidence was low and additional RCTs may be needed.

The evidence on the use of terlipressin alone and intervention benefits in type 2 hepatorenal syndrome was scarce. Only two of the included trials assessed terlipressin alone (Hadengue 1998; Yang 2001); the trials were small and the findings were inconclusive. Likewise, only two RCTs on terlipressin included participants with type 2 hepatorenal syndrome (Martín-Llahí 2008; Zafar 2012), and the number of participants with type 2 hepatorenal syndrome was relatively small. Accordingly, we identified no clear intervention effects for this patient group.

Overall completeness and applicability of evidence

We found little evidence of clinical intertrial heterogeneity. The mean control group Child-Pugh scores were remarkably similar (11 in three trials) (Martín-Llahí 2008; Neri 2008; Sanyal 2008). Likewise, the included trials used similar criteria to diagnose hepatorenal syndrome, based on previous recommendations (Arroyo 1996). Diagnostic criteria included presence of cirrhosis, ascites, elevated serum creatinine after at least 48 hours of diuretic withdrawal and volume expansion combined with absence of shock, treatment with nephrotoxic drugs, and parenchymal renal disease (Salerno 2007). Updated criteria in 2015 now use a lower threshold of increased creatinine to diagnose hepatorenal syndrome (Angeli 2015). Less emphasis is placed on the labels of type 1 hepatorenal syndrome (defined as serum creatinine increasing to 226 µmol/L (2.5 mg/dL) within two weeks) and type 2 hepatorenal syndrome (defined as a moderate to slowly progressive renal failure with serum creatinine between 133 and 226 µmol/L (1.5 to 2.5 mg/dL)). Although the included trials used previously established criteria, the evidence is likely to be applicable today. However, it may be argued that there is still room for trials on terlipressin using the current diagnostic criteria, as the current criteria are more sensitive to detection of less severe acute kidney injury. Future trials would likely benefit from adoption of a standardised treatment algorithm of terlipressin dosing and sample-sized calculations based on mortality rates, rather than rates of reversal of hepatorenal syndrome. Notably, dosing of intravenous terlipressin varied widely among studies, ranging from 1 mg twice daily, in Yang 2001, to up to 2 mg six times per day for non-responders in Boyer 2016, thus making direct comparisons between trials more challenging.

The duration of the effect of terlipressin on mortality should be considered when deciding whether or not to treat a patient with hepatorenal syndrome (Gluud 2010). Some participants may die in spite of a clear improvement in renal function (Martín-Llahí 2008; Sanyal 2008). The duration of treatment varied among the included trials, ranging from two days, in Hadengue 1998, to 19 days, in Neri 2008, with a median duration of 15 days. This may affect the intervention effect estimates. After an initial complete normalisation of renal function, hepatorenal syndrome may reappear. We attempted to perform a post hoc analysis to determine the effect of treatment on recurrence of hepatorenal syndrome but were unable to extract the necessary data.

Quality of the evidence

The present review identified a number of methodological concerns, including lack of sample size calculations, unclear randomisation, and lack of blinding. We downgraded evidence due to high risk of bias within individual trials, heterogeneity across trials, and imprecision (wide confidence intervals) of outcomes. As a result, the evidence for each of the primary and secondary analyses received a low quality rating. One of the included trials reporting sample size calculations was terminated prematurely due to unexpectedly low event rates (Martín-Llahí 2008). The trial assessed terlipressin plus albumin versus albumin and was terminated after an interim analysis suggested that 2000 participants would be required to achieve sufficient statistical power. Whether the interim results reflect a true (low) intervention effect, a random error, or the inclusion criteria is difficult to assess. One possible explanation could be that a number of the included participants had type 2 hepatorenal syndrome; overall, there is little evidence on this patient group.

Potential biases in the review process

One of the main limitations of the present review concerns the relatively low overall sample size. Identification of participants who clearly fulfil the diagnostic criteria for hepatorenal syndrome may be difficult, as is the recruitment of critically ill people in clinical trials. Accordingly, the largest trials were multicentred and multinational (Sanyal 2008). This involvement of several clinical sites in more than one geographical region increases the clinical heterogeneity. On the other hand, the heterogeneity also increases the external validity, making it possible to extrapolate the results to larger patient populations in similar specialised centres. The heterogeneity increases the need for additional subgroup and sensitivity analyses. Analysis of individual patient data would have increased the possibilities of performing such analyses. Unfortunately, the available data did not allow detailed analyses of potential sources of heterogeneity. In addition, we have reversed the definition of an event in Analysis 1.3 compared to prior versions of this review, which resulted in a high event rate, potentially introducing bias through the use of risk ratios as our effect measure. We felt the analysis of 'reversal of hepatorenal syndrome' was easier to interpret clinically than 'non-reversal'. This also obviated the need to perform a separate analysis for 'improvement in renal function'.

We did not search specifically for harms reported in quasi-randomised and observational studies, which is a weakness of this review that may bias our assessments of the balance between benefits and harms.

We did not search databases of regulatory authorities, and so may have overlooked unpublished trials. This could also have hampered our assessments of the balance between benefits and harms.

Agreements and disagreements with other studies or reviews

Three of the included trials found that baseline serum creatinine was an independent predictor of survival (Martín-Llahí 2008; Neri 2008; Sanyal 2008). In our analyses, the baseline creatinine in the control groups of the trials on terlipressin plus albumin ranged from 194 to 362 µmol/L (2.2 to 4.1 mg/dL). All trials found similar baseline values for the treatment and control groups. In agreement with previous findings, our analyses suggest that the

treatment effect was the largest in the trial with the lowest baseline serum creatinine (Solanki 2003). This may suggest that treatment should be administered early and that a protracted deterioration in renal function impedes recovery. Inclusion of non-randomised, observational studies would have increased our ability to detect rare adverse events. However, we found no observational studies that reported adverse events to include in these analyses.

A number of meta-analyses have assessed the effect of terlipressin for hepatorenal syndrome (Fabrizi 2009; Dobre 2010; Sagi 2010). The results concerning mortality are equivocal. One meta-analysis found that terlipressin increases survival among participants with type 1 hepatorenal syndrome (Sagi 2010). The two remaining meta-analyses found no clear effect of terlipressin on survival, although only one performed a meta-analysis addressing this question (Fabrizi 2009). In agreement with our findings, all reviews found that terlipressin seems to improve renal function but also increases the risk of cardiovascular and ischaemic adverse events. The differences between the conclusions in the different reviews are mainly related to the inclusion criteria. For example, one review only included placebo-controlled trials (Fabrizi 2009). This decision is not clearly supported by previous evidence on the importance of bias control in RCTs (Gluud 2006; Wood 2008). Although lack of blinding may affect the risk of bias, there is no clear or consistent evidence to support the exclusion of open trials from meta-analyses since the effect of blinding is inconsistent across trials. The extent, as well as the effect, of bias associated with lack of blinding is unpredictable and does not support the a priori exclusion of trials based on this component alone.

AUTHORS' CONCLUSIONS

Implications for practice

This review includes RCTs evaluating people with cirrhosis and hepatorenal syndrome. The main body of evidence evaluated terlipressin and albumin for participants with type 1 hepatorenal syndrome. The number of RCTs evaluating terlipressin without albumin and the number of participants with type 2 hepatorenal syndrome were small. The analyses suggest a potential beneficial effect of terlipressin on mortality and hepatorenal syndrome, but also an increased risk of serious cardiovascular adverse events and gastrointestinal events such as diarrhoea.

Implications for research

We used the EPICOT format in the definition of implications for research (Brown 2006):

Evidence (what is the current state of the evidence?): this review includes seven RCTs and found low-quality evidence that combined terlipressin and albumin has both beneficial and harmful effects in the management of people with type 1 hepatorenal syndrome. Additional research is needed to further evaluate the effect of the intervention in type 2 hepatorenal syndrome.

Participants (what is the population of interest?): the largest body of evidence evaluated people with cirrhosis and type 1 hepatorenal syndrome. Future RCTs should consider evaluating participants with hepatorenal syndrome defined using current guidelines.

Interventions (what are the interventions of interest?): the interventions assessed included terlipressin in doses ranging from 1 mg twice a day up to 2 mg six times a day for a median duration of 15 days (range 2 to 19 days).

Comparisons (what are the comparisons of interest?): placebo or no intervention.

Outcomes (what are the outcomes of interest?): RCTs should include an assessment of mortality, hepatorenal syndrome, and adverse events. Additional evidence evaluating the effect on health-related quality of life is also needed.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Boyer 2016

Methods	Double-blind, multicentre RCT
Participants	Participants had cirrhosis and type 1 hepatorenal syndrome based on the 2007 International Club of Ascites criteria.
Interventions	<p>Terlipressin/albumin versus placebo/albumin for a maximum of 14 days. The investigators discontinued treatment if serum creatinine was below 1.5 mg/dL at the initiation of renal replacement therapy or liver transplantation.</p> <p>Terlipressin</p> <ul style="list-style-type: none"> 1 mg 4 times daily increased to 2 mg 6 times daily in non-responders (participants without improved renal function). <p>Albumin</p> <ul style="list-style-type: none"> 20 to 40 g/day.
Outcomes	Duration of follow-up: 90 days
Country of origin	United States and Canada
Inclusion period	October 2010 to February 2013
Proportion with type 1 hepatorenal syndrome	100%
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Central randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants and personnel using placebo
Blinding of outcome assessment (detection bias)	Low risk	Blinding of outcome assessors using placebo

Terlipressin versus placebo or no intervention for people with cirrhosis and hepatorenal syndrome (Review)

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Boyer 2016 (Continued)

All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in the analyses based on the intention-to-treat principle. Information about clinical outcomes was available for all participants.
Selective reporting (reporting bias)	Low risk	Clinically relevant outcomes reported as described in the protocol and online trial registration.
For-profit funding	High risk	Ikaria Therapeutics LLC funded the trial.
Other bias	Low risk	No other biases identified.
Overall risk of bias (mortality)	High risk	High risk of bias
Overall risk of bias (non-mortality outcomes)	High risk	High risk of bias

Hadengue 1998

Methods	Double-blind, single-centre RCT.	
Participants	<ul style="list-style-type: none"> Mean age: <ul style="list-style-type: none"> terlipressin group: 53 years placebo group: 53 years Proportion of men: 56% Proportion with alcoholic liver disease: 78% 	
Interventions	Terlipressin versus placebo Terlipressin <ul style="list-style-type: none"> 1 mg twice daily for 2 days. 	
Outcomes	Duration of follow-up: end of treatment	
Country of origin	France	
Inclusion period	Not described	
Proportion with type 1 hepatorenal syndrome	100%	
Notes	We did not include the trial in our analyses of hepatorenal syndrome because we did not have information about the outcome measure from the first period.	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described

Hadengue 1998 (Continued)

Allocation concealment (selection bias)	Low risk	Identical coded drug containers
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants and personnel achieved through double-blinding using terlipressin placebo.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment achieved through double-blinding using terlipressin placebo.
Incomplete outcome data (attrition bias) All outcomes	High risk	The trial report states that the analyses excluded 3 participants.
Selective reporting (reporting bias)	Low risk	Clinically relevant outcomes reported.
For-profit funding	High risk	The trial received funding from Ferring S.A., France.
Other bias	Low risk	No other biases identified.
Overall risk of bias (mortality)	High risk	High risk of bias
Overall risk of bias (non-mortality outcomes)	High risk	High risk of bias

Martín-Llahí 2008

Methods	Open, multicentre RCT
Participants	<ul style="list-style-type: none"> Mean age: <ul style="list-style-type: none"> terlipressin/albumin group: 59 years albumin group: 52 years Proportion of men: 63% Proportion with alcoholic liver disease: 72%
Interventions	Terlipressin/albumin versus albumin for a maximum of 15 days Terlipressin <ul style="list-style-type: none"> 1 mg 6 times daily. If no improvement in renal function was observed, the dose was increased to 2 mg 6 times daily. Albumin <ul style="list-style-type: none"> 1 g/kg for 24 hours then 40 g/day adjusted according to the central venous pressure.
Outcomes	Duration of follow-up: 3 months after treatment
Country of origin	Spain
Inclusion period	January 2002 to February 2006

Martín-Llahí 2008 (Continued)

Proportion with type 1 hepatorenal syndrome 56%

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Central randomisation
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding of participants or personnel (open trial)
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of outcome assessment (open trial)
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up, and all participants included in the analyses.
Selective reporting (reporting bias)	Low risk	Clinically relevant outcome measures reported. Primary outcome measures: <ul style="list-style-type: none"> • mortality after 3 months; and • improvement in renal function.
For-profit funding	Low risk	The trial did not receive funding from pharmaceutical companies (reported in the discussion).
Other bias	Low risk	No other biases identified.
Overall risk of bias (mortality)	Low risk	Low risk of bias
Overall risk of bias (non-mortality outcomes)	High risk	High risk of bias

Neri 2008

Methods	Open, multicentre RCT
Participants	<ul style="list-style-type: none"> • Mean age: <ul style="list-style-type: none"> ◦ terlipressin and albumin group: 59 years ◦ albumin group: 60 years • Proportion of men: 40% • Proportion with alcoholic liver disease: 13%

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Neri 2008 (Continued)

Interventions	Terlipressin/albumin versus albumin for 19 days Terlipressin <ul style="list-style-type: none"> 1 mg 4 times daily for 5 days then 0.5 mg 4 times daily for 14 days. Albumin <ul style="list-style-type: none"> 1 g/kg for 24 hours then 40 to 80 g/day.
Outcomes	Duration of follow-up: 6 months after hospital discharge
Country of origin	Italy
Inclusion period	December 2002 to December 2005
Proportion with type 1 hepatorenal syndrome	100%
Notes	Participants with recurrence of hepatorenal syndrome after the initial treatment received terlipressin and albumin.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated list of random numbers
Allocation concealment (selection bias)	Low risk	Central randomisation
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding of participants or personnel (open trial)
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of outcome assessment (open trial)
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up
Selective reporting (reporting bias)	Low risk	Clinically relevant outcome measures reported. Primary outcome measure: resolution of hepatorenal syndrome defined as normalisation of creatinine.
For-profit funding	Unclear risk	Funding not reported. Email requesting information about funding sent 17 February 2016.
Other bias	Low risk	No other biases
Overall risk of bias (mor-tality)	High risk	High risk of bias

Neri 2008 (Continued)

Overall risk of bias (non-mortality outcomes)	High risk	High risk of bias
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Pulvirenti 2008

Methods	Open, single-centre RCT.
Participants	<ul style="list-style-type: none"> Mean age: <ul style="list-style-type: none"> terlipressin group: 58 years albumin group: 61 years Proportion of men: 37% Proportion with alcoholic liver disease: 13%
Interventions	Terlipressin/albumin versus albumin for a maximum of 15 days Terlipressin <ul style="list-style-type: none"> 1 mg/hour for the first day, then 0.5 mg/8 hours for the next 12 days. Albumin <ul style="list-style-type: none"> 1 g/kg/day for 5 days.
Outcomes	Duration of follow-up: 180 days after treatment
Country of origin	Italy
Inclusion period	June 2004 to March 2006
Proportion with type 1 hepatorenal syndrome	100%
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated list of random numbers
Allocation concealment (selection bias)	Low risk	Central randomisation
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding of participants or personnel (open trial)
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of outcome assessment (open trial)
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up

Pulvirenti 2008 (Continued)

Selective reporting (reporting bias)	Low risk	Clinically relevant outcome measures reported.
For-profit funding	Unclear risk	Funding not reported. Email requesting information about funding sent 17 February 2016.
Other bias	Low risk	No other biases
Overall risk of bias (mortality)	High risk	High risk of bias
Overall risk of bias (non-mortality outcomes)	High risk	High risk of bias

Sanyal 2008

Methods	Double-blind, multicentre RCT
Participants	<ul style="list-style-type: none"> Mean age: <ul style="list-style-type: none"> terlipressin/albumin group: 51 years placebo/albumin group: 53 years Proportion of men: 71% Proportion with alcoholic liver disease: 36%
Interventions	Terlipressin/albumin versus placebo/albumin for a maximum of 14 days Terlipressin <ul style="list-style-type: none"> 1 mg 4 times daily increased to 2 mg 4 times daily if serum creatinine had not decreased by at least 30%. Albumin <ul style="list-style-type: none"> 100 g for 24 hours then 25 g daily.
Outcomes	Duration of follow-up: 6 months
Country of origin	United States, Germany, and Russia
Inclusion period	June 2004 to September 2006
Proportion with type 1 hepatorenal syndrome	100%
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Central randomisation

Sanyal 2008 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants and personnel achieved through double-blinding using terlipressin placebo.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment achieved through double-blinding using terlipressin placebo.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analyses including all participants randomised are reported. No outcomes reported after censoring.
Selective reporting (reporting bias)	Low risk	Clinically relevant outcome measures reported. Primary outcome measure: treatment success at day 14 defined as normalisation of serum creatinine on 2 measurements with at least 48-hour intervals and no dialysis, death, or recurrence of hepatorenal syndrome type 1 before day 15
For-profit funding	High risk	Industry funding (Orphan Therapeutics)
Other bias	Low risk	No other biases
Overall risk of bias (mortality)	High risk	High risk of bias
Overall risk of bias (non-mortality outcomes)	High risk	High risk of bias

Solanki 2003

Methods	Open, single-centre RCT
Participants	<ul style="list-style-type: none"> Mean age: <ul style="list-style-type: none"> terlipressin/albumin group: 51 years albumin group: 52 years Proportion of men: 71% Proportion with alcoholic liver disease: 33%
Interventions	Terlipressin/albumin versus placebo/albumin for 15 days Terlipressin <ul style="list-style-type: none"> 1 mg twice daily. Albumin <ul style="list-style-type: none"> 20 g daily.
Outcomes	Duration of follow-up: end of treatment
Country of origin	India
Inclusion period	Not described

Solanki 2003 (Continued)

Proportion with type 1 hepatorenal syndrome 100%

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random-number table
Allocation concealment (selection bias)	Low risk	Centralised randomisation through an independent statistician
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The authors state that the trial is single-blind, but do not describe the method of blinding.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The authors state that the trial is single-blind, but do not describe the method of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no losses to follow-up.
Selective reporting (reporting bias)	Low risk	Clinically relevant outcome measures reported.
For-profit funding	Unclear risk	Funding not reported.
Other bias	Low risk	No other biases
Overall risk of bias (mortality)	High risk	High risk of bias
Overall risk of bias (non-mortality outcomes)	High risk	High risk of bias

Yang 2001

Methods	Open, single-centre RCT
Participants	Participant characteristics (n = 50) not reported.
Interventions	Terlipressin versus no intervention for 15 days Terlipressin <ul style="list-style-type: none"> 1 mg twice daily.
Outcomes	Duration of follow-up: 15 days

Yang 2001 (Continued)

Country of origin	China
Inclusion period	Not reported
Proportion with type 1 hepatorenal syndrome	100%
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding of participants or personnel (open trial)
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of outcome assessment (open trial)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear reporting of losses to follow-up
Selective reporting (reporting bias)	Low risk	Clinically relevant outcome measures reported. Primary outcome measure: reversal of hepatorenal syndrome
For-profit funding	Unclear risk	Funding not reported.
Other bias	Low risk	No other biases
Overall risk of bias (mortality)	High risk	High risk of bias
Overall risk of bias (non-mortality outcomes)	High risk	High risk of bias

Zafar 2012

Methods	Open, multicentred RCT.
Participants	Participant characteristics not reported.
Interventions	Terlipressin/albumin versus albumin for 10 days (range 8 to 12 days) <ul style="list-style-type: none"> Terlipressin (1 mg/4 hourly).

Zafar 2012 (Continued)

- Albumin (1 g/kg followed by 20 to 40 g/day).

Outcomes	Not reported
Country of origin	Pakistan
Inclusion period	Not reported
Proportion with type 1 hepatorenal syndrome	Not reported
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding of participants or personnel (open trial)
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of outcome assessment (open trial)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described
Selective reporting (reporting bias)	Low risk	Clinically relevant outcome measures reported.
For-profit funding	Unclear risk	Not described
Other bias	Low risk	No other biases
Overall risk of bias (mortality)	High risk	High risk of bias
Overall risk of bias (non-mortality outcomes)	High risk	High risk of bias

RCTs: randomised clinical trial

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Alessandria 2007	RCT on noradrenaline/albumin versus terlipressin/albumin for hepatorenal syndrome.

Study	Reason for exclusion
Angeli 2008	RCT comparing different modes of administering terlipressin/albumin for hepatorenal syndrome.
Cavallin 2012	RCT on terlipressin/albumin versus midodrine/octreotide/albumin for hepatorenal syndrome.
Cavallin 2015	RCT comparing terlipressin versus midodrine/octreotide for people with hepatorenal syndrome.
Chelarescu 2003	RCT comparing captopril/octreotide versus octreotide published in abstract form.
Indrabi 2013	RCT on noradrenalin/albumin versus terlipressin/albumin for hepatorenal syndrome.
Nguyen-Tat 2015	Observational study on terlipressin for hepatorenal syndrome.
Pomier 2003	Cross-over trial on octreotide for hepatorenal syndrome.
Sharma 2008	RCT on noradrenalin/albumin versus terlipressin/albumin for hepatorenal syndrome.
Silawat 2011	RCT on dopamine versus terlipressin/albumin for hepatorenal syndrome.
Wan 2014	RCT comparing low and high-dose of terlipressin for hepatorenal syndrome type 1.

Characteristics of ongoing studies *[ordered by study ID]*

NCT01143246

Trial name or title	A placebo-controlled, double-blind study to confirm the reversal of hepatorenal syndrome type 1 with terlipressin
Methods	Study type: interventional Study design: allocation: randomised Endpoint classification: safety/efficacy study Intervention model: parallel assignment Masking: double-blind (participant, investigator) Primary purpose: treatment
Participants	Cirrhosis, ascites, and hepatorenal syndrome type 1
Interventions	Drug: terlipressin Blinded terlipressin reconstituted with 5 mL of sterile 0.9% sodium chloride solution for injection will be administered intravenously as a slow bolus injection over 2 minutes at a dose of 1 mg (1 vial) every 6 hours (4 mg/day). Other name: Lucassin Drug: placebo Lyophilised mannitol reconstituted with 5 mL of sterile 0.9% sodium chloride solution administered intravenously as a slow bolus injection over 2 minutes at a dose of 1 mg (1 vial) every 6 hours (4 mg/day).
Outcomes	Confirmed hepatorenal syndrome reversal: the percentage of participants with 2 serum creatinine values of $\leq 133 \mu\text{mol/L}$ (1.5 mg/dL) at least 48 hours apart, on treatment, and without intervening renal replacement therapy or liver transplant.
Starting date	September 2010
Contact information	Diane Stebbins diane.stebbins@ikaria.com

NCT01143246 (Continued)

Notes

Estimated enrolment: 180

DATA AND ANALYSES

Comparison 1. Terlipressin alone or with albumin versus no intervention or albumin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	9	534	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.73, 0.98]
1.1 Type 1 hepatorenal syndrome	7	438	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.63, 0.98]
1.2 Type 1 or 2 hepatorenal syndrome	2	96	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.75, 1.14]
2 Mortality in randomised clinical trials evaluating terlipressin and albumin	7	510	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.67, 1.01]
3 Hepatorenal syndrome	7	510	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.48, 0.82]
3.1 Type 1 hepatorenal syndrome	6	449	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.47, 0.87]
3.2 Type 2 hepatorenal syndrome	1	11	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.14, 1.08]
3.3 Type 1 or 2 hepatorenal syndrome	1	50	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.46, 0.92]
4 Serious adverse events, total number	9	534	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.68, 1.21]
5 Serious adverse events, types	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Cardiovascular adverse events	4	234	Risk Ratio (M-H, Random, 95% CI)	7.26 [1.70, 31.05]
5.2 Circulatory overload	1	46	Risk Ratio (M-H, Random, 95% CI)	1.75 [0.59, 5.17]
5.3 Gastrointestinal bleeding	1	46	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.22, 2.05]
5.4 Hepatic encephalopathy	1	46	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.68, 1.47]
5.5 Respiratory distress/acidosis	2	300	Risk Ratio (M-H, Random, 95% CI)	1.97 [0.84, 4.60]
5.6 Bacterial infections	1	46	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.39, 1.43]
6 Non-serious adverse events	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Total number	5	406	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.58, 2.68]
6.2 Abdominal pain	4	294	Risk Ratio (M-H, Random, 95% CI)	1.54 [0.97, 2.43]
6.3 Chest pain	1	52	Risk Ratio (M-H, Random, 95% CI)	5.00 [0.25, 99.34]
6.4 Livedo reticularis	1	112	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.12, 72.10]
6.5 Diarrhoea	2	240	Risk Ratio (M-H, Random, 95% CI)	5.76 [2.19, 15.15]

Analysis 1.1. Comparison 1 Terlipressin alone or with albumin versus no intervention or albumin, Outcome 1 Mortality.

Analysis 1.2. Comparison 1 Terlipressin alone or with albumin versus no intervention or albumin, Outcome 2 Mortality in randomised clinical trials evaluating terlipressin and albumin.

Analysis 1.3. Comparison 1 Terlipressin alone or with albumin versus no intervention or albumin, Outcome 3 Hepatorenal syndrome.

Analysis 1.4. Comparison 1 Terlipressin alone or with albumin versus no intervention or albumin, Outcome 4 Serious adverse events, total number.

Analysis 1.5. Comparison 1 Terlipressin alone or with albumin versus no intervention or albumin, Outcome 5 Serious adverse events, types.

Analysis 1.6. Comparison 1 Terlipressin alone or with albumin versus no intervention or albumin, Outcome 6 Non-serious adverse events.

APPENDICES

Appendix 1. Search strategies

Database	Timespan	Search strategy
Cochrane Hepato-Biliary Group Controlled Trials Register	November 2016	(terlipressin* OR glypressin* OR vasoconstric*) AND 'hepatorenal syndrom*'

(Continued)

Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library	2016, Issue 11	#1 MeSH descriptor Vasoconstrictor Agents explode all trees
		#2 terlipressin* OR glypressin* OR vasoconstrict*
		#3 (#1 OR #2)
		#4 MeSH descriptor Hepatorenal Syndrome explode all trees
		#5 hepatorenal syndrom*
		#6 (#4 OR #5)
		#7 (#3 AND #4)
MEDLINE (OvidSP)	1946 to November 2016	1. exp Vasoconstrictor Agents/
		2. (terlipressin* or glypressin* or vasoconstrict*).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
		3. 1 or 2
		4. exp Hepatorenal Syndrome/
		5. hepatorenal syndrom*.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
		6. 4 or 5
		7. 6 and 3
		8. (random* or blind* or placebo* or meta-analysis).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
		9. 8 and 7
Embase (OvidSP)	1974 to November 2016	1. exp Terlipressin/
		2. exp Vasoconstrictor Agent/
		3. (terlipressin* or glypressin* or vasoconstrict*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
		4. 1 or 3 or 2
		5. exp Hepatorenal Syndrome/
		6. hepatorenal syndrom*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
		7. 6 or 5
		8. 4 and 7
		9. (random* or blind* or placebo* or meta-analysis).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
		10. 8 and 9
Science Citation Index Expanded (Web of Science)	1900 to November 2016	# 5 #4 AND #3
		# 4 TS=(random* or blind* or placebo* or meta-analysis)

(Continued)

3 #1 AND #2

2 TS=(hepatorenal syndrom*)

1 TS=(terlipressin* or glypressin* or vasoconstrict*)

WHAT'S NEW

Date	Event	Description
17 February 2016	New search has been performed	Based on peer review comments, the outcomes now include health-related quality of life and the total number of serious adverse events. We now only include trials with a placebo or no intervention comparison. Trials with active comparators are included in a separate review (Israelsen 2015a). We have updated the methods based on the latest recommendations from Cochrane and the Cochrane Hepato-Biliary Group. The updates include the statistical analyses and the bias assessment.
17 February 2016	New citation required but conclusions have not changed	We included three additional randomised clinical trials (RCTs). Our overall conclusions did not change.

CONTRIBUTIONS OF AUTHORS

Two authors (AA and MI) updated the searches, listed potentially eligible trials, and extracted data. Four authors participated in the final selection of trials (AA, MI, AK, LG), and three conducted the analyses (AA, MI, LG). Three authors (AA, MI, LG) participated in the interpretation of data and revision of the review. All authors approved the final version.

DECLARATIONS OF INTEREST

Andrew S Allegretti: served on a Scientific Advisory Board for Ferring Pharmaceuticals (makers of terlipressin in Europe) after the submission of this manuscript.

Mads Israelsen: no conflicts of interest.

Aleksander Krag: Served on a Scientific Advisory Board for Norgine, planned scientific meetings for Norgine and Intercept, and received funding for research from Norgine. Manol Jovani: no conflicts of interest.

Alison H Goldin: no conflicts of interest.

Allison R Schulman: no conflicts of interest.

Rachel W Winter: no conflicts of interest.

Lise Lotte Gluud: acted as investigator in studies funded by AbbVie, Intercept, Merck and Norgine, received funding for travel expenses and consultancy from Novo Nordisk, and for scientific presentations at meetings funded by Norgine and Eli Lilly.

SOURCES OF SUPPORT

Internal sources

- No internal funding received, Other.

External sources

- No external funding received, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- We have updated the criteria for assessment of the outcome measures, bias control, and statistical analyses including the Trial Sequential Analysis.
- Based on the latest criteria (described by the International Club of Ascites (www.icascites.org)) and the recommendation of the Cochrane Hepato-Biliary Group, we have excluded urine output and creatinine clearance from our analyses.

- We originally planned to include trials comparing different vasoactive drugs, but excluded these analyses based on review comments.
- In keeping with updates to Cochrane review protocols, we changed the title and objectives to include the term "people with cirrhosis", though this did not affect the inclusion of studies.
- We have changed the term "reversal of hepatorenal syndrome and improved renal function" to "number of participants who did not achieve reversal of hepatorenal syndrome", in order to be consistent with the other primary outcome (mortality), which is also framed in the negative. We removed "improved renal function", as it replicates the same analysis as "reversal of hepatorenal syndrome".
- We have added calculations of number needed to treat for primary outcomes.
- We have moved health-related quality of life to the secondary outcomes.
- We did not perform Egger's test to assess the effect of small study size.

INDEX TERMS

Medical Subject Headings (MeSH)

Abdominal Pain [chemically induced]; Albumins [therapeutic use]; Diarrhea [chemically induced]; Hepatorenal Syndrome [classification] [*drug therapy] [mortality]; Lypressin [adverse effects] [*analogs & derivatives] [therapeutic use]; Randomized Controlled Trials as Topic; Terlipressin; Vasoconstrictor Agents [adverse effects] [*therapeutic use]

MeSH check words

Humans