**Title:** Systematic review with meta-analysis: vasoactive drugs for the treatment of hepatorenal syndrome type 1

**Authors**

Dr F.J. Gifford, Clinical Research Fellow and Specialist Registrar in Nephrology, Royal Infirmary of Edinburgh, Edinburgh, UK.

Dr J.R. Morling, Clinical Lecturer in Public Health, Division of Epidemiology and Public Health, School of Medicine, University of Nottingham, Nottingham, UK.

Dr J.A. Fallowfield, NHS Research Scotland Senior Clinical Fellow and Honorary Consultant Hepatologist, MRC Centre for Inflammation Research, University of Edinburgh, Edinburgh, UK.

Correspondence to: Dr Fiona Gifford

Department of Hepatology

Royal Infirmary of Edinburgh

51 Little France Crescent

Edinburgh, EH16 4SA

Tel: +44(0)1312421626

Email: Fiona.gifford@nhslothian.scot.nhs.uk

Keywords: Hepatorenal syndrome, vasoactive drugs, terlipressin, noradrenaline, systematic review, meta-analysis.

Word Count: 3669 words (Abstract 250)

**Abstract**

**Background**

Hepatorenal syndrome type 1 (HRS1) is a functional, rapidly progressive, potentially reversible form of acute kidney injury occurring in patients with cirrhosis. Characterised by intense renal arterial vasoconstriction, it carries a very poor prognosis. There is a significant unmet need for a widely approved, safe and effective pharmacological treatment.

**Aim**

To re-evaluate efficacy and safety of pharmacological treatments for HRS1, in light of recently published randomised controlled trials (RCTs).

**Methods**

MEDLINE(OvidSP), EMBASE, PubMed and Cochrane registers were searched for RCTs reporting efficacy and adverse events related to pharmacological treatment of HRS1. Search terms included: 'hepatorenal syndrome', 'terlipressin', 'noradrenaline', 'octreotide', 'midodrine', 'vasopressin', 'dopamine', 'albumin' and synonyms. Comparison of vasoactive drugs versus placebo/no treatment, and two active drugs were included. Meta-analysis was performed for HRS1 reversal, creatinine improvement, mortality and adverse events.

**Results**

12 RCTs enrolling 700 HRS1 patients were included. Treatment with terlipressin and albumin led to HRS1 reversal more frequently than albumin alone or placebo (RR:2.54,95%CI:1.51-4.26). Noradrenaline was effective in reversing HRS1, but trials were small and non-blinded. Overall, there was mortality benefit with terlipressin (RR:0.79,95%CI:0.63-1.01), but

sensitivity analysis including only trials with low risk of selection bias weakened this relationship (RR:0.87,95%CI:0.71-1.06). Notably, there was a significant risk of adverse events with terlipressin therapy (RR4.32,95%CI:0.75-24.86).

**Conclusion**

Terlipressin treatment is superior to placebo for achieving HRS1 reversal, but mortality benefit is less clear. Terlipressin is associated with significant adverse events, but infusion regimens may be better tolerated. There is continued need for safe and effective treatment options for hepatorenal syndrome.

## Introduction

Hepatorenal syndrome (HRS) is a severe form of acute kidney injury (AKI) that typically occurs in patients with decompensated liver cirrhosis, but is also a frequent complication of fulminant hepatic failure and acute alcoholic hepatitis. HRS remains a diagnosis of exclusion[1] and is associated with a dismal prognosis.[2] With an estimated annual incidence in the United States of 9,000–14,000 patients, HRS is present in approximately 15% of patients admitted to hospital with ascites and develops in more than 50% of cirrhotics who die.[3]

Clinically there are two distinct types of HRS. Type-1 HRS (HRS1) is characterized by rapidly progressive kidney failure, which is most frequently precipitated by acute bacterial infection and a dysregulated systemic inflammatory response. If left untreated, HRS1 has a 2-week mortality rate of ~80%.[4] In contrast, renal impairment in type-2 HRS (HRS2) is slower in onset and progression and typically occurs in patients with refractory ascites. The median survival of HRS2 is around 6 months without liver transplantation.[4]

Intense renal arterial vasoconstriction is thought to be the central mechanism underlying the functional renal failure that characterizes HRS.[5] In cirrhosis, HRS occurs in response to portal hypertension and splanchnic arterial vasodilatation that results in a reduction in effective circulating volume. The development of a hyperdynamic circulation and activation of homeostatic neurohormonal mechanisms (such as the renin-angiotensin-aldosterone system, vasopressin and the sympathetic nervous system) maintain arterial blood pressure via increased cardiac output and heart rate, heightened systemic vascular tone, and sodium and water retention, but also causes renal vasoconstriction.[6] Pooling of blood in the splanchnic circulation also alters gut permeability and enhances bacterial translocation, with the release of endotoxin and increase in pro-inflammatory cytokines leading to amplification of

circulatory dysfunction.[7] As cirrhosis and splanchnic vasodilation progress, cardiac output is no longer able to compensate and systemic hypotension occurs.[6] The combination of hypotension and peripheral vasoconstriction leads to reduced tissue perfusion in extra-splanchnic organs including the kidneys and brain.[8] This 'splanchnic steal phenomenon' leaves patients vulnerable to episodes of non-HRS AKI, HRS and hepatic encephalopathy. HRS develops when renal blood flow falls below the level required to maintain glomerular filtration rate.

The optimum treatment for HRS is liver transplantation, but this is limited by donor availability and patients often die before transplantation can occur. Interestingly, renal artery resistive indices can take up to a year to return to normal following transplant[9] and recovery of renal function is not universal.[10] Indeed, complete recovery of kidney function only occurred in 58% of patients within 4-110 days of liver transplantation, 15% partially recovered, and 25% never recovered.[10] Effective pharmacological therapy for HRS1 is therefore an important requirement. Evidence suggests that HRS1 is potentially reversible if haemodynamic derangements are corrected in a timely fashion. However, if uncorrected, prolonged renal arteriolar vasoconstriction and parenchymal ischaemia may result in acute tubular necrosis.[11] Vasoconstrictor drugs and albumin infusion currently form the mainstay of treatment for HRS1. Such vasoconstrictors induce systemic and splanchnic vasoconstriction, thereby increasing systolic blood pressure and augmenting effective arterial blood volume. In theory, increased renal perfusion follows as systolic blood pressure rises and neurohormonal systems are attenuated. Three classes of vasoconstrictor have been studied in HRS1. Vasopressin analogues such as ornipressin and terlipressin act upon vasopressin-1 receptors on the vascular smooth muscle causing vasoconstriction. Additionally, these drugs

reduce portal pressure. Terlipressin is used in many countries for the treatment of HRS1 but it is not approved by the Food and Drug Administration for use in the USA and Canada. Noradrenaline and midodrine are $\alpha$-adrenergic agonists that similarly lead to constriction of vascular smooth muscle and increase systemic vascular resistance. Midodrine is often used in combination with octreotide, a somatostatin analogue that inhibits the release of systemic vasodilators such as glucagon.

Many previous studies evaluating the efficacy and safety of these agents were small, uncontrolled, non-blinded and poorly designed. In the last decade several randomised controlled trials (RCTs) have been published with varying conclusions. Some of these trials combined patients with HRS1 and HRS2 despite significant differences in the severity, rate of progression, and prognosis of these conditions. More recently a number of appropriately powered, well-designed RCTs in patients with HRS1 alone have been reported.

In light of recent advancements in the literature, the aim of this systematic review and meta-analysis was to re-evaluate the efficacy and safety of available pharmacological treatments for HRS1.

## Methods

### Study design

This systematic review and meta-analysis was registered in the PROSPERO international prospective register of systematic reviews (CRD42016042921) and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[12]

Search strategy and study selection

An electronic search was performed through to June 2016 using MEDLINE(OvidSP), EMBASE, PubMed and both the Cochrane Central Register of Controlled Trials, and the Cochrane Hepatobiliary Group Register. Manual searches of selected speciality journals and conference proceedings *(Appendix 1, Supplementary material (Supp Material))* were performed to identify all pertinent literature. Similarly, reference lists from published clinical trials and previous systematic reviews were examined. Our search was limited to human studies that were published in English. No date limitation was applied.

Search terms included 'hepatorenal syndrome', 'terlipressin', 'noradrenaline', 'octreotide', 'midodrine', 'vasopressin', 'dopamine', 'albumin' and their synonyms. Studies deemed eligible for inclusion were RCTs in adults (≥18 years) with HRS1 as defined by the International Ascites Club in 2007.[13] Comparisons between two pharmacological agents, or one active drug and placebo/no treatment were included. Moreover, papers were excluded if they did not report one or more of the outcomes of interest, as outlined in Table 1. One investigator (FJG) performed an initial review of all titles in order to exclude duplicates and non-relevant literature. Two investigators (JAF and FJG) then independently judged eligibility of all abstracts. A third investigator (JRM) reviewed a subset (10%) of studies to check the accuracy of selection and data extraction, and to resolve any disagreements that emerged.

Data extraction and study quality assessment

Two investigators (JAF and FJG) independently extracted data using a standardised data collection form in Microsoft Excel version 15.20. Extracted data included patient characteristics, treatment arm, comparator groups, and selected outcomes. Additionally, country of origin, single or multi-centre status, randomisation and blinding procedures,

funding source, duration of follow-up, number of patient withdrawals, and appropriate powering of the study were noted. Where possible, data was extracted as intention-to-treat analyses.

The quality of included studies was appraised using the Cochrane Collaboration's tool for assessing the risk of bias.[14] Risk of bias was judged as low, high or unclear within seven domains: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, missing outcome data, selective reporting and other sources of bias.

Study outcomes and statistical analysis

Outcomes of interest included HRS1 reversal (as defined by each individual trial), improved serum creatinine (sCr), and all–cause mortality. Additionally, data was recorded on adverse events, focussing specifically on ischaemic adverse events. The relative risk (RR) and 95% confidence intervals (95% CI) were calculated for each outcome. Meta-analysis was performed using a Mantel-Haenszel random-effects model in view of the expected heterogeneity between trials (varying inclusion criteria, treatment dose, duration and definition of outcomes). The heterogeneity between studies was quantified using the $I^2$ statistic with $I^2$ <25% representing low heterogeneity, 25-50% moderate and >50% $I^2$ high inter-trial heterogeneity. Each therapeutic method was analysed separately. A sensitivity analysis of treatment effect was undertaken using only trials judged as having low risk of selection bias on the grounds of sequence generation and allocation concealment.[15] All analyses were performed using REVMAN version 5.3 (Nordic Cochrane Centre, Copenhagen, Denmark).

## Results

### Study characteristics and risk of bias

The literature search identified a total of 2739 manuscripts. 894 papers were duplicates, and 1629 citations were removed after screening of titles. A further 169 publications were excluded after abstract review, leaving 24 full text articles. 12 studies were excluded: 6 as after contacting the primary authors for further information only an abstract was available; 2 were not RCTs; 3 did not separate HRS1 and HRS2 patients when reporting their results; and one further study (*Hadengue et al*, 1998)[16] was later excluded due to insufficient outcome reporting.

A total of 12 papers were included in the final analysis (Figure 1).[17-28] All included studies were RCTs. Treatment comparisons included terlipressin, noradrenaline, octreotide and midodrine, low dose dopamine, and placebo. All trials used albumin or a similar plasma expander in both treatment and comparator groups. Four studies included both HRS1 and HRS2 patients, but reported results for the HRS1 subgroup independently.[19,26-28] Study characteristics are shown in Table 2.

A total of 700 participants with HRS1 were included in our series. Mean age was 53 years, and participants were 74% male (*Silawat et al*[23] did not publish the age or sex of their participants). Overall treatment time varied between 5 and 19 days, with a mean of 14 days. Average albumin dose was 12.5–40g/day. In two multi-centre studies, concomitant albumin use was recommended but not universally applied.[17,21] Four studies allowed paracentesis for tense ascites when required.[22,25,26,28] Two of these stated that additional albumin therapy was given during paracentesis.[22,28] Length of follow-up varied between 15 and 180 days. 5 studies (45%) had 90-day follow up (Table 2). *Silawat et al*[23] did not define length of follow-up.

In studies examining the use of terlipressin, the initial terlipressin dose varied from 1mg/day to 6mg/day. 6 of the 10 studies increased the terlipressin dose on day 3-5 if only a partial response was seen.[17-19,21,22,24] The maximum dose of terlipressin was 8-12mg/day. *Neri et al*[20] routinely reduced terlipressin dose on day 5 from 3mg/day to 1.5mg/day. In studies using noradrenaline, the dose was recorded as 0.5-3mg/hour[22,24] or 0.1-0.7μg/kg/min.[27,28]

Bias

17% studies had high risk of bias for allocation concealment, 83% for blinding of participants and 58% for blinding of outcome assessment. Two trials were double-blinded (18%).[17,21] One was reported to be single-blinded, however it did not state if the blinding referred to the patient or investigator.[25] 9 studies (75%) were non-blinded, although one open-label study reported that outcome assessors were blinded.[26] 25% of included studies were judged to have a high risk of bias due to incomplete outcome data and a further 8% for selective reporting. 58% of trials published a sample size calculation. *Boyer et al* amended the recruitment target mid-trial, then continued to recruit until 30 patients had achieved complete HRS1 reversal.[17] The trial by *Martin-Llahi et al* was terminated early after interim analysis revealed an unexpectedly low event rate.[19] Similarly, the study by *Srivastava et al* was deemed to be significantly underpowered,[26] although sample size calculations are not included in the risk of bias domains defined by Cochrane.[14] The paper by *Silawat et al* had a high risk of bias in 5 of 7 domains.[23] Sensitivity analysis was subsequently performed incorporating only low risk trials. Assessment of Cochrane risk of bias is outlined in Table 3.

Results of data analysis by comparison:

The definition of HRS1 reversal varied across studies and for two trials the diagnostic criteria was not specified.[23,25] Only two studies used the existing gold standard definition of 'two sCr measurements of ≤ 132µmol/L on 2 occasions, at least 48 hours apart without death, renal replacement therapy or HRS1 recurrence'.[17,21] For the purpose of meta-analysis, the definition of HRS1 reversal was taken as a sCr ≤ 132µmol/L on at least one occasion.

11 of the 12 included trials reported mortality data for HRS1 patients. *Martin-Llahi et al* did not sub-divide mortality data by HRS1 and HRS2 and therefore this study was not included in this analysis.[19]

Reporting of adverse events was also variable between studies. Frequently listed complaints included abdominal pain/presumed intestinal ischaemia, myocardial infarction, arrhythmias, electrocardiogram (ECG) changes and digital ischaemia. The study by *Alessandria et al* was unclear with regard to adverse event rates, stating that 'most' patients treated with terlipressin experienced transient abdominal cramps and watery diarrhoea. Consequently, adverse event data from this study was included in the meta-analysis for ischaemic adverse events only.[28]

**Terlipressin + albumin vs no intervention/placebo + albumin**

Terlipressin plus albumin significantly increased the chance that a patient would achieve HRS1 reversal (RR 2.54, 95% CI 1.51 to 4.26; $I^2$ 52%; Figure 2) compared to albumin alone, or with placebo. A similar, but more modest result was obtained when the analysis was restricted to papers with low risk of selection bias (RR 2.11, 95% CI 1.28 to 3.49; $I^2$ 40%; *Analysis 1.3 Supp Material).* Three studies provided additional information on patients who showed a partial

response to vasoconstrictor therapy *(drop by >50% from baseline sCr)*.[18-20] Analysis of all patients with improved sCr favoured the use of terlipressin versus placebo (RR: 1.66, 95% CI 1.07 to 2.57*,* Figure 2).

Terlipressin reduced the risk of mortality when compared with placebo/no intervention (RR: 0.79, 95% CI 0.63 to 1.01, $I^2$ 53%, *Analysis 1.1 Supp Material*). However sub-group analysis including only papers with low risk of selection bias weakened this relationship with a RR of 0.87 (95% CI 0.71 to 1.06, *Analysis 1.2 Supp Material*). Repeat meta-analysis after omitting the trial by *Solanki et al* (low risk of selection bias but high risk of detection bias) revealed a RR of 0.93 (95% CI 0.80 to 1.09).

The use of terlipressin significantly increased the risk of *all* adverse events when compared to placebo (RR 4.32, 95% CI 0.75 to 24.86, Figure 3). Further analysis showed the RR of an *ischaemic* adverse event whilst using terlipressin to be 3.56 (95% CI 1.64 to 7.72) compared to placebo.

**Terlipressin infusion vs terlipressin bolus**

*Cavallin et al* compared terlipressin infusion with bolus therapy and showed that HRS1 reversal was more likely with terlipressin infusion (RR: 1.22, 95% CI 0.77 to 1.93, *Analysis 2.1 Supp Material*).[18] Moreover, terlipressin infusion led to greater sCr improvement (RR: 1.18, 95% CI 0.87 to 1.59, *Analysis 2.2 Supp Material*), reduced the risk of all adverse events (RR 0.48, 95% CI 0.22 to 1.01, *Analysis 2.4 Supp Material*), and specifically ischaemic adverse events (RR 0.63, 95% CI 0.28 to 1.42) compared with bolus therapy. Despite this, infusion of

terlipressin was inferior to bolus therapy with respect to mortality rate (RR: 1.58, 95% CI 0.86 to 2.91, *Analysis 2.3 Supp Material*).

**Terlipressin + albumin vs noradrenaline + albumin**

Terlipressin and noradrenaline treatment performed equally with regard to HRS1 reversal (RR: 0.99, 95% CI 0.67 to 1.45, *Analysis 3.1 Supp Material*). However, mortality rate with terlipressin was marginally worse compared with noradrenaline (RR: 1.04, 95% CI 0.74 to 1.47, *Analysis 3.2 Supp Material*). The use of terlipressin significantly increased the risk of *all* adverse events when compared with noradrenaline (RR: 2.14, 95% CI 0.81 to 5.69, *Analysis 3.3 Supp Material*). However, terlipressin induced fewer *ischaemic* adverse events than noradrenaline, although numbers were small (RR: 0.63, 95% CI 0.15 to 2.59).

**Terlipressin + albumin vs dopamine + standard care**

For HRS1 reversal, the evaluation of terlipressin versus low dose dopamine favoured terlipressin (RR 2.00, 95% CI 1.14 to 3.52, *Analysis 4.1 Supp Material*). However, in this comparison terlipressin treatment did not show a significant survival benefit (RR: 0.98, 95% CI 0.76 to 1.26, *Analysis 4.2 Supp Material*), although participant numbers were small. Terlipressin significantly increased the risk of *all* adverse events (RR 4.79, 95% CI 0.46 to 49.60, *Analysis 4.3 Supp Material*) and *ischaemic* adverse events (RR:2.18, 95% CI 0.51 to 9.34) when compared with low dose dopamine.

**Noradrenaline + albumin vs Octreotide, Midodrine + albumin**

Noradrenaline performed better than midodrine and octreotide for achieving HRS1 reversal (RR: 1.25, 95% CI 0.70 to 2.24, *Analysis 5.1 Supp Material*), but was found to be inferior in reducing mortality (RR: 1.50, 95% CI 0.60 to 3.78, *Analysis 5.2 Supp Material*). No adverse events were reported for either treatment in this study.

## Discussion

HRS1 is a rapidly fatal disease if left untreated. Until recently, a significant proportion of the literature consisted of poorly designed, non-blinded studies with incomplete outcome reporting. Additionally, some studies had pooled both HRS1 and HRS2 patients together. Given the significant disparity in speed of onset and progression, severity, and outcomes related to these two conditions, we believe that they should be considered separately. Recently, larger well designed and appropriately powered RCTs have shed further light on this important area.[17,18] A prior systematic review (Cochrane 2012)[29] reported that treatment with terlipressin alone or in combination with albumin achieved reversal of HRS1 more frequently than albumin alone (RR: 3.76, 95% CI 2.21 to 6.39). Moreover, terlipressin reduced mortality in patients with HRS1, compared to no intervention or placebo ± albumin (RR: 0.75, 95% CI 0.59 to 0.97). This relationship was maintained when studies with low risk of selection bias were analysed. Our present review concords that terlipressin is more effective than albumin, alone or with placebo, for achieving HRS1 reversal. Furthermore, a similar reduction in mortality rate was seen with terlipressin in meta-analysis of all studies (RR:0.79, 95% CI 0.63 to 1.01). However, when the analysis was repeated including only trials with low risk of selection bias this relationship weakened (RR: 0.87, 95% CI 0.71 to 1.06). In keeping with previous studies, we identified a significant risk of adverse events (RR 4.32, 95% CI 0.75 to

24.86), especially ischaemic adverse events (RR: 3.56, 95% CI 1.64 to 7.72) with terlipressin treatment. Indeed, terlipressin caused more serious adverse events than any other vasoconstrictor. Prior to study recruitment, potential participants were screened for significant cardiovascular risk factors, so this may in fact be an under-estimate of the true population risk. Recording of adverse events was unreliable in several studies, with possible reporting bias and the suggestion that low adverse event rates were related to lower doses of terlipressin.

Pooled data comparing terlipressin and noradrenaline showed no evidence of superiority of terlipressin over noradrenaline for achieving HRS1 reversal (RR: 0.99, 95% CI 0.67 to 1.45. Terlipressin appeared marginally inferior to noradrenaline with regard to mortality (RR: 1.04, 95% CI 0.74 to 1.47). Notably, the confidence intervals for both of these results crossed 1, so the validity of this data is uncertain. Furthermore, the three trials comparing noradrenaline and terlipressin were small, non-blinded, single centre studies.[22,24,28] Meta-analysis suggested fewer ischaemic adverse events with noradrenaline, although patient numbers were small and confidence intervals broad. Noradrenaline was superior to octreotide and midodrine with respect to HRS1 reversal, but not survival or adverse event rate.

Interestingly, *Matto et al* recently compared both the efficacy and cost of terlipressin and noradrenaline therapy.[30] Their study reinforced previous literature concluding that neither vasoconstrictor was superior with respect to HRS1 reversal or 30-day mortality. However, unlike other economic analyses where only the cost of the vasoconstrictor drug was considered, *Matto et al* calculated all direct medical costs involved in a hypothetical hospitalisation using each of the studied medications. These calculations included the costs accrued in the intensive care unit, where a patient must be monitored if noradrenaline is

infused. This economic evaluation is arguably a more accurate assessment of real-world costs, and suggested that terlipressin is a more cost-effective treatment than noradrenaline.

Additionally, *Salerno et al* recently published a meta-analysis of 19 studies (8 RCTs, 8 prospective and 3 retrospective studies) suggesting a dose-response relationship between albumin therapy and survival in HRS1 patients.[31] As cumulative albumin dose increased in 100g increments, survival improved significantly (hazard ratio (HR) 1.15, CI: 1.02-1.31, p=0.02). A similar relationship was shown for reversal of HRS1, however these results did not reach statistical significance (HR: 1.15, CI: 0.97-1.37, p=0.10). Although the included studies were not powered to demonstrate a relationship between albumin dose and outcomes, this meta-analysis highlights its potential importance.

Despite restricting our analysis to only HRS1 patients, and performing repeat analysis of low risk trials, there remain some limitations to this review. The overall sample size was small and many studies had inadequate blinding and did not report sample size calculations. Moreover, true HRS1 is a relatively infrequent diagnosis, even in large tertiary referral centres. This is evidenced by the three most recent multi-centre studies where *Boyer et al* recruited 196 patients from 52 sites over 2.5 years, *Cavallin et al* recruited 78 patients from 3 centres over 7 years, and *Sanyal et al* recruited 112 patients from 35 centres over 2.5 years. In stark contrast to this, *Silawat et al* recruited 60 HRS1 patients from a single centre in 6 months. This disparity suggests that strict diagnostic criteria may not have been adhered to. Indeed, some patients labelled as HRS1 were reported to have “refractory ascites”, which is more typically associated with HRS2. This may, in part, explain the variation seen in historical meta-analyses of vasoconstrictor therapies for HRS. The use of stringent criteria for study inclusion and the

addition of recent high quality studies, may arguably render the results of our updated meta-analysis more reliable.

A recent meta-analysis by *Belcher et al* suggested that improvement in sCr, when taken as a continuous variable, was a valid surrogate marker for mortality.[32] This implies that even partial improvement in sCr may lead to improved short-term survival. Importantly, some patients now survive long enough to undergo liver transplantation. Furthermore, as pre-transplant renal dysfunction is associated with increased morbidity and mortality after liver transplantation, any increase in renal function (whether complete or partial HRS reversal) may improve outcomes.[33] In contrast, survival in HRS1 'non-responders' is extremely low.[34] In view of the severity of this condition and limitations of currently available drug therapy, the Food and Drug Administration recently granted HRS orphan disease status in an attempt to accelerate the development of more effective treatments.

An ideal treatment for HRS1 would theoretically consist of a drug with selective vasodilator activity in the renal circulation but without significant vasodilator effects in other vascular beds, especially the splanchnic circulation. However, nitrates may have potentially deleterious effects on renal function in cirrhosis.[35] Fenoldopam, a selective dopamine-1 receptor agonist with renoprotective properties, has been evaluated in patients with post-operative AKI[36] but randomized placebo-controlled studies in cirrhosis are lacking. Other investigational agents such as the thromboxane receptor antagonist ifetrobam (ClinicalTrials.gov: NCT01436500) and the relaxin family peptide receptor-1 agonist serelaxin (ClinicalTrials.gov: NCT01640964) are in clinical development and may have therapeutic potential for the treatment of portal hypertension and/or renal dysfunction in cirrhosis.

## Authorship

*Guarantor of article*: JA Fallowfield.

*Specific author contributions*: FJ Gifford and JA Fallowfield performed the research, collected and analysed the data. JR Morling contributed to the design of the study, analysed the data and contributed to the manuscript. FJ Gifford and JA Fallowfield wrote the paper. All authors approved the final version of the article, including the authorship list.

## References


1. Angeli P, Gines P, Wong F, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: Revised consensus recommendations of the International Club of Ascites. *Gut* 2015; 64: 531-7.
2. Martin-Llahi M, Guevara M, Torre A, et al. Prognostic importance of the cause of renal failure in patients with cirrhosis. *Gastroenterology* 2011; 140: 488-96.e4.
3. Besso J PC, Padron J, Plaz J. Hepatorenal syndrome. In: Gullo A, LD, ed. Intensive and Critical Care Medicine: Reflection, Recommendations and Perspectives: Springer-Verlag; 2007: 9-27.
4. Arroyo V, Gines P, Gerbes AL, et al. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. International Ascites Club. *Hepatology* 1996; 23: 164-76.
5. Platt JF, Ellis JH, Rubin JM, et al. Renal duplex Doppler ultrasonography: a noninvasive predictor of kidney dysfunction and hepatorenal failure in liver disease. *Hepatology* 1994; 20: 362-9.
6. Ruiz-del-Arbol L, Monescillo A, Arocena C, et al. Circulatory function and hepatorenal syndrome in cirrhosis. *Hepatology* 2005; 42: 439-47.
7. Fernández J, Navasa M, Planas R, et al. Primary prophylaxis of spontaneous bacterial peritonitis delays hepatorenal syndrome and improves survival in cirrhosis. *Gastroenterology* 2007; 133: 818-24.
8. Newby DE, Hayes PC. Hyperdynamic circulation in liver cirrhosis: Not peripheral vasodilatation but 'splanchnic steal'. *QJM - Monthly Journal of the Association of Physicians* 2002; 95: 827-30.
9. Navasa M, Feu F, Garcia-Pagan JC, et al. Hemodynamic and humoral changes after liver transplantation in patients with cirrhosis. *Hepatology* 1993; 17: 355-60.
10. Marik PE, Wood K, Starzl TE. The course of type 1 hepato-renal syndrome post liver transplantation. *Nephrology Dialysis Transplantation* 2006; 21: 478-82.
11. Mandal AK, Lansing M, Fahmy A. Acute tubular necrosis in hepatorenal syndrome: an electron microscopy study. *American Journal of Kidney Diseases* 1982; 2: 363-74.
12. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015; 4: 1.

13. Salerno F, Gerbes A, Gines P, et al. Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. *Gut* 2007; 56: 1310-8.

14. Green JPHaS. Cochrane Handbook for Systematic Reviews of Interventions. . Version 5.1.0 ed.

15. Wood L, Egger M, Gluud LL, et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. *BMJ* 2008; 336: 601-5.

16. Hadengue A, Gadano A, Moreau R, et al. Beneficial effects of the 2-day administration of terlipressin in patients with cirrhosis and hepatorenal syndrome. *J Hepatol* 1998; 29: 565-70.

17. 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. *Gastroenterology* 2016; 150: 1579-89.

18. Cavallin M, Piano S, Fasolato S, et al. Terlipressin given by continuous intravenous infusion versus terlipressin given by intravenous boluses in the treatment of hepatorenal syndrome in patients with cirrhosis: Final results of a controlled clinical study. *Hepatology* 2015; 62: 284A.

19. Martin-Llahi M, Pepin M, Guevara M, et al. Terlipressin and Albumin vs Albumin in Patients With Cirrhosis and Hepatorenal Syndrome: A Randomized Study. *Gastroenterology* 2008; 134: 1352-9.

20. Neri S, Pulvirenti D, Malaguarnera M, et al. Terlipressin and albumin in patients with cirrhosis and type I hepatorenal syndrome. *Digestive diseases and sciences* 2008; 53: 830-5.

21. Sanyal AJ, Boyer T, Garcia-Tsao G, et al. A Randomized, Prospective, Double-Blind, Placebo-Controlled Trial of Terlipressin for Type 1 Hepatorenal Syndrome. *Gastroenterology* 2008; 134: 1360-8.

22. Sharma P, Kumar A, Shrama BC, et al. An open label, pilot, randomized controlled trial of noradrenaline versus terlipressin in the treatment of type 1 hepatorenal syndrome and predictors of response. *American Journal of Gastroenterology* 2008; 103: 1689-97.

23. Silawat FNS, M.K; Lohana, R.K et al Efficacy of Terlipressin and Albumin in the Treatment of Hepatorenal Syndrome. *World Applied Sciences Journal* 2011; 12: 1946-50.

24. Singh V, Ghosh S, Singh B, et al. Noradrenaline vs. terlipressin in the treatment of hepatorenal syndrome: a randomized study. *Journal of Hepatology* 2012; 56: 1293-8.

25. Solanki P, Chawla A, Garg R, et al. Beneficial effects of terlipressin in hepatorenal syndrome: a prospective, randomized placebo-controlled clinical trial. *J Gastroenterol Hepatol* 2003; 18: 152-6.

26. Srivastava S, Shalimar, Vishnubhatla S, et al. Randomized Controlled Trial Comparing the Efficacy of Terlipressin and Albumin with a Combination of Concurrent Dopamine, Furosemide, and Albumin in Hepatorenal Syndrome. *Journal of Clinical and Experimental Hepatology* 2015; 5: 275-86.

27. Tavakkoli H, Yazdanpanah K, Mansourian M. Noradrenalin versus the combination of midodrine and octreotide in patients with hepatorenal syndrome: Randomized clinical trial. *International Journal of Preventive Medicine* 2012; 3: 764-9.

28. Alessandria C, Ottobrelli A, Debernardi-Venon W, et al. Noradrenalin vs terlipressin in patients with hepatorenal syndrome: a prospective, randomized, unblinded, pilot study. *J Hepatol* 2007; 47: 499-505.

29. Gluud LL, Christensen K, Christensen E, et al. Terlipressin for hepatorenal syndrome. *Cochrane Database of Systematic Reviews* 2012; 9: CD005162.

30. Mattos AZ, Mattos AA, Ribeiro RA. Terlipressin versus noradrenaline in the treatment of hepatorenal syndrome - Systematic review with meta-analysis and full economic evaluation. *Value in Health* 2015; 18 : A866.

31. Salerno F, Navickis RJ, Wilkes MM. Albumin treatment regimen for type 1 hepatorenal syndrome: A dose-response meta-analysis. *BMC Gastroenterology* 2015; 15 .

32. Belcher JM, Coca SG, Parikh CR. Creatinine Change on Vasoconstrictors as Mortality Surrogate in Hepatorenal Syndrome: Systematic Review & Meta-Analysis. *PLoS ONE [Electronic Resource]* 2015; 10: e0135625.

33. Belcher JM, Sanyal AJ, Peixoto AJ, et al. Kidney biomarkers and differential diagnosis of patients with cirrhosis and acute kidney injury. *Hepatology* 2014; 60: 622-32.

34. Schepke M, Appenrodt B, Heller J, et al. Prognostic factors for patients with cirrhosis and kidney dysfunction in the era of MELD: Results of a prospective study. *Liver International* 2006; 26: 834-9.

35. Salmeron JM, Ruiz del Arbol L, Gines A, et al. Renal effects of acute isosorbide-5-mononitrate administration in cirrhosis. *Hepatology* 1993; 17: 800-6.

36. Gillies MA, Kakar V, Parker RJ, et al. Fenoldopam to prevent acute kidney injury after major surgery-a systematic review and meta-analysis. *Crit Care* 2015; 19: 449.

## Acknowledgements

The authors are grateful to Sharon Tuck (Epidemiology and Statistics Core, Edinburgh Clinical Research Facility) for statistical advice.

*Authors' declaration of personal interests*:

JA Fallowfield has served as a speaker, a consultant and an advisory board member for Novartis and as a speaker and consultant for Merck. JA Fallowfield has received research funding from GlaxoSmithKline.

*Declaration of funding interests*:

JA Fallowfield is funded by the Scottish Funding Council through a NHS Research Scotland Senior Clinical Fellowship.

## Figure legends

**Table 1.** Eligibility criteria
Table 1. USS; ultrasound, sCr; serum creatinine, TIPS; transjugular intrahepatic portosystemic shunt, HRS; hepatorenal syndrome.

**Table 2.** Study characteristics

**Table 3.** Risk of bias summary: review authors' judgements about each risk of bias item for each included study.
Risk of bias: Green; low risk of bias, Red; high risk of bias, Orange; unclear risk of bias
1. Insufficient information provided. 2. Non-blinded. 3. Trial terminated after preliminary analysis.
4. Randomisation chart used- possibility for selection bias. 5. Outcome data incomplete. 6. Primary outcome not defined or reported. 7. Missing detail: duration of treatment/follow up, possibility of lenient inclusion criteria. 8. Single blinded.

**Figure 1**. Flow chat of study selection

**Figure 2.** Terlipressin +/- albumin vs no intervention/placebo +/- albumin.
Outcomes: HRS reversal and improved sCr

**Figure 3.** Terlipressin +/- albumin vs no intervention/placebo +/- albumin.
Outcome: Adverse events

**Table 1**

| |
|---|
| - Randomised, controlled trials<br>- Published in English<br>- Adults (≥18 years) |
| - Type 1 hepatorenal syndrome:<br>• Liver cirrhosis (clinical, biochemical, USS, biopsy, or endoscopy diagnosis)<br>• sCr >133μmol/L (>1.5mg/dL)<br>• No improvement in sCr after 2 days diuretic withdrawal + volume expansion<br>• Absence of shock (doctor defined)<br>• No current or recent nephrotoxin use<br>• No macroscopic signs of structural kidney injury (urine dipstick/USS)<br>- Excluding patients with previous TIPS or liver transplant |
| - Outcomes include one or more of the following:<br>• HRS reversal (as defined by individual author)<br>• Improved renal function<br>• Mortality<br>• All serious adverse events<br>• Cardiovascular adverse events |

**Table 2**

| | Single/Multi-centre | Treatment 1 | Dose | Treatment 2 | Dose | Treatment duration | Length of follow up |
|---|---|---|---|---|---|---|---|
| **Alessandria (2007)** | Single *(Italy)* | Terlipressin + albumin (n = 5) | 1-2mg/4h | Noradrenaline + albumin (n = 4) | 0.1-0.7μg/kg/min | ≤14 days | 180 days |
| **Boyer (2016)** | Multi *(USA/Canada)* | Terlipressin + albumin (n = 97) | 1-2mg/6h | Placebo + albumin (n = 99) | N/A | ≤14 days | 90 days |
| **Cavallin (2015)** | Multi *(Italy)* | Terlipressin infusion + albumin (n = 34) | 2-12mg/day | Terlipressin bolus + albumin (n = 37) | 0.5-2mg/4h | ≤15 days | 90 days |
| **Martin-Llahi (2008)** | Multi *(Spain)* | Terlipressin + albumin (n = 17) | 1-2mg/4h | Albumin alone (n = 18) | N/A | ≤15 days | 90 days |
| **Neri (2008)** | Single *(Italy)* | Terlipressin + albumin (n = 26) | 1mg/8h (5days) then 0.5mg/8h (14 days) | Albumin alone (n = 26) | N/A | 19 days | 90 days |
| **Sanyal (2008)** | Multi *(USA/Germany/Russia)* | Terlipressin + albumin (n = 56) | 1-2mg/6h | Placebo + albumin (n = 56) | N/A | ≤14 days | 180 days |
| **Sharma (2008)** | Single *(India)* | Terlipressin + albumin (n = 20) | 0.5-2mg/6h | Noradrenaline + albumin (n = 20) | 0.5-3mg/h | 15 days | 15 days |
| **Silawat (2011)** | Single *(Pakistan)* | Terlipressin + albumin (n = 30) | 0.5-1mg/12h | Low dose dopamine + plasma expanders (n = 30) | 4μg/min | Not stated | Not stated |
| **Singh (2012)** | Single *(India)* | Terlipressin + albumin (n = 23) | 0.5-2mg/6h | Noradrenaline + albumin (n = 23) | 0.5-3mg/h | 15 days | 30 days |
| **Solanki (2003)** | Single *(India)* | Terlipressin + albumin (n = 12) | 1mg/12h | Placebo + albumin (n = 12) | N/A | 15 days | 15 days |
| **Srivastava (2015)** | Single *(India)* | Terlipressin + albumin (n = 20) | 0.5mg/6h | Low dose dopamine, furosemide + albumin (n = 20) | 2μg/kg/min | 5 days | 30 days |
| **Tavakkoli (2012)** | Single *(Iran)* | Noradrenaline + albumin (n = 6) | 0.1-0.7μg/kg/min | Octreotide, Midodrine + albumin (n = 9) | 100-200μg/8h 5-15mg/8h | ≤15 days | 90 days |

**Table 3**

| | Sequence generation | Allocation concealment | Blinding of participants/personnel | Blinding of outcome assessment | Incomplete outcome data | Selective reporting | Other sources of bias | Study comparison |
|---|---|---|---|---|---|---|---|---|
| Alessandria et al | 1 | | 2 | 2 | | 1 | 1 | Terlipressin vs noradrenaline |
| Boyer et al | | | | 1 | | | | Terlipressin vs placebo |
| Cavallin et al | | | 2 | 2 | | | | Terlipressin infusion vs terlipressin bolus |
| Martin-Llahi et al | | | 2 | 2 | | 1 | 3 | Terlipressin vs albumin alone |
| Neri et al | | 1 | 2 | 2 | | | 1 | Terlipressin vs albumin alone |
| Sanyal et al | | | | 1 | | | | Terlipressin vs placebo |
| Sharma et al | | 4 | 2 | 1 | 5 | 1 | 1 | Terlipressin vs noradrenaline |
| Silawat et al | 1 | | 2 | 2 | 5 | 6 | 7 | Terlipressin vs low dose dopamine |
| Singh et al | | | 2 | 1 | | | | Terlipressin vs noradrenaline |
| Solanki et al | | | 8 | 8 | | 1 | 1 | Terlipressin vs placebo |
| Srivastava et al | | 2 | 2 | | | | 1 | Terlipressin vs low dose dopamine |
| Tavakkoli et al | | 1 | 2 | 2 | 5 | 1 | 1 | Noradrenaline vs octeoride + midodrine |

**Figure 1**

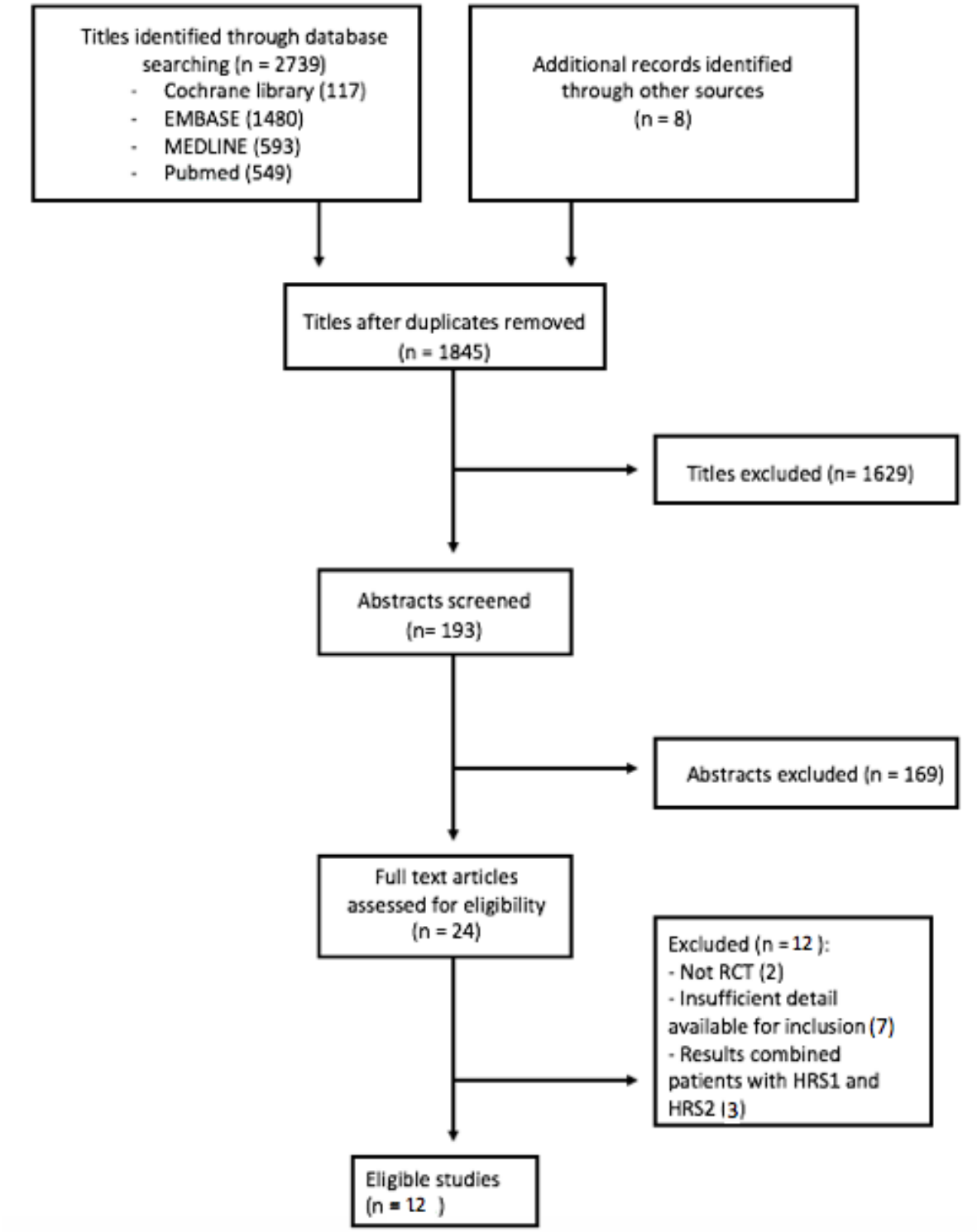
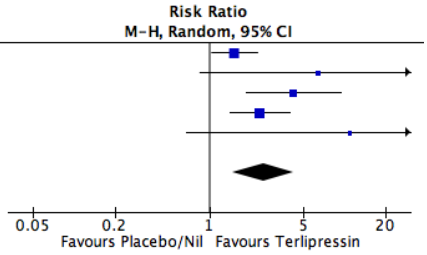

Titles identified through database searching (n = 2739)
- Cochrane library (117)
- EMBASE (1480)
- MEDLINE (593)
- Pubmed (549)
Additional records identified through other sources (n = 8)
Titles after duplicates removed (n = 1845)
Titles excluded (n= 1629)
Abstracts screened (n= 193)
Abstracts excluded (n = 169)
Full text articles assessed for eligibility (n = 24)
Excluded (n = 12 ):
- Not RCT (2)
- Insufficient detail available for inclusion (7)
- Results combined patients with HRS1 and HRS2 (3)
Eligible studies (n = 12 )

**Figure 2**

HRS reversal

| Study or Subgroup | Terlipressin Events | Terlipressin Total | Placebo/ no intervention Events | Placebo/ no intervention Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Boyer 2016 | 42 | 97 | 28 | 99 | 36.9% | 1.53 [1.04, 2.26] |
| Martin-Llahi 2008 | 6 | 17 | 1 | 18 | 5.8% | 6.35 [0.85, 47.44] |
| Neri 2008 | 21 | 26 | 5 | 26 | 21.8% | 4.20 [1.87, 9.44] |
| Sanyal 2008 | 33 | 56 | 14 | 56 | 32.3% | 2.36 [1.42, 3.90] |
| Solanki 2003 (1) | 5 | 12 | 0 | 12 | 3.2% | 11.00 [0.67, 179.29] |
| **Total (95% CI)** | | **208** | | **211** | **100.0%** | **2.54 [1.51, 4.26]** |
| Total events | 107 | | 48 | | | |

Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 8.35$, df = 4 (P = 0.08); $I^2 = 52\%$
Test for overall effect: Z = 3.52 (P = 0.0004)




Footnotes
(1) Solanki - definition of HRS reversal not given

Improved sCr

| Study or Subgroup | Terlipressin Events | Terlipressin Total | Placebo/ no intervention Events | Placebo/ no intervention Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Martin-Llahi 2008 | 6 | 17 | 2 | 18 | 8.5% | 3.18 [0.74, 13.63] |
| Neri 2008 | 25 | 26 | 16 | 26 | 91.5% | 1.56 [1.14, 2.14] |
| **Total (95% CI)** | | **43** | | **44** | **100.0%** | **1.66 [1.07, 2.57]** |
| Total events | 31 | | 18 | | | |

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 1.10$, df = 1 (P = 0.29); $I^2 = 9\%$
Test for overall effect: Z = 2.28 (P = 0.02)

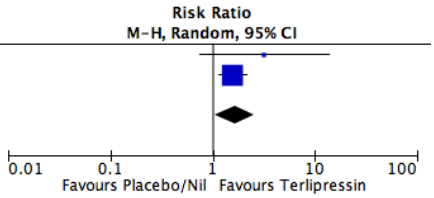
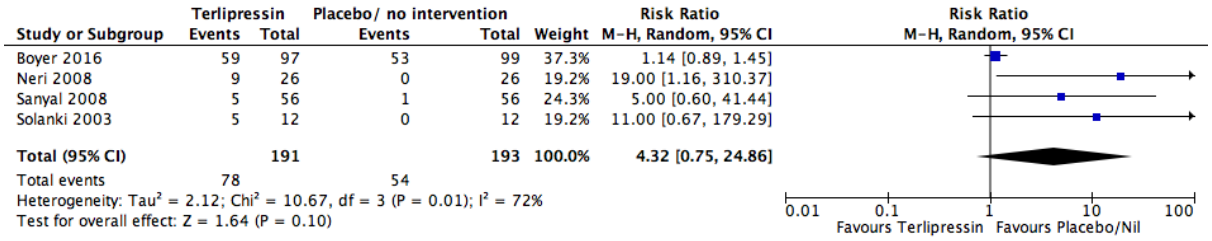
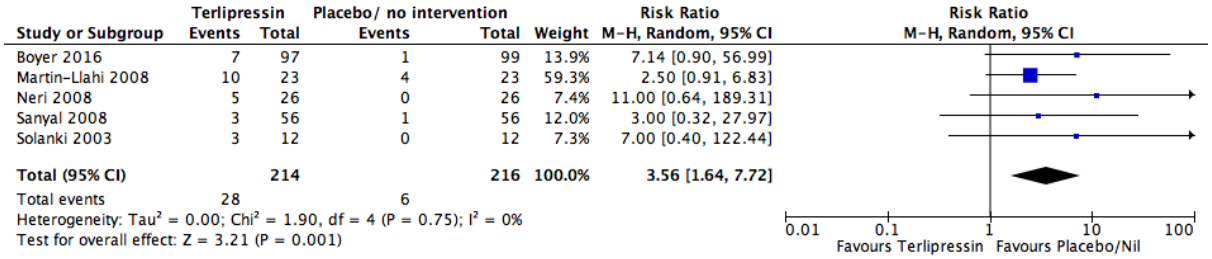


**Figure 3**

All adverse events




Ischaemic adverse events



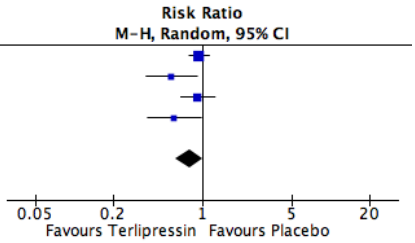
## Supplementary material

## 1. Terlipressin +/- albumin vs no intervention/placebo +/- albumin

### 1.1 All studies - Mortality

| Study or Subgroup | Terlipressin Events | Total | Placebo/ no intervention Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Boyer 2016 (1) | 67 | 97 | 73 | 99 | 38.7% | 0.94 [0.78, 1.12] |
| Neri 2008 (2) | 12 | 26 | 21 | 26 | 17.6% | 0.57 [0.36, 0.90] |
| Sanyal 2008 (3) | 32 | 56 | 35 | 56 | 27.3% | 0.91 [0.67, 1.24] |
| Solanki 2003 (4) | 7 | 12 | 12 | 12 | 16.5% | 0.60 [0.37, 0.97] |
| **Total (95% CI)** | | **191** | | **193** | **100.0%** | **0.79 [0.63, 1.01]** |
| Total events | 118 | | 141 | | | |

Heterogeneity: Tau² = 0.03; Chi² = 6.34, df = 3 (P = 0.10); I² = 53%
Test for overall effect: Z = 1.91 (P = 0.06)



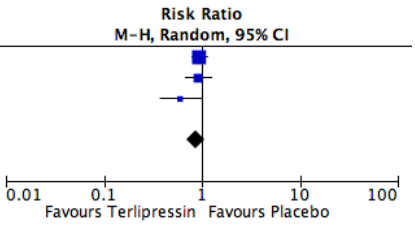

Footnotes
(1) 90-day transplant-free mortality
(2) 90 day mortality
(3) Overall survival
(4) 15 day mortality

***Low risk of selection bias based on the assessment of allocation methods (sequence generation and allocation concealment)***

### 1.2 Low risk studies – Mortality

| Study or Subgroup | Terlipressin Events | Total | No intervention/placebo Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Boyer 2016 | 67 | 97 | 73 | 99 | 54.9% | 0.94 [0.78, 1.12] |
| Sanyal 2008 | 32 | 56 | 35 | 56 | 30.1% | 0.91 [0.67, 1.24] |
| Solanki 2003 | 7 | 12 | 12 | 12 | 15.0% | 0.60 [0.37, 0.97] |
| **Total (95% CI)** | | **165** | | **167** | **100.0%** | **0.87 [0.71, 1.06]** |
| Total events | 106 | | 120 | | | |

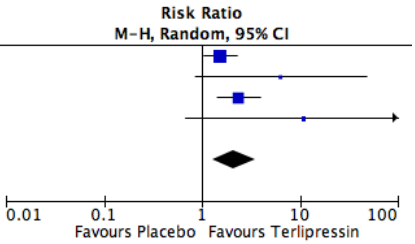
Heterogeneity: Tau² = 0.01; Chi² = 2.96, df = 2 (P = 0.23); I² = 32%
Test for overall effect: Z = 1.36 (P = 0.18)




### 1.3 Low risk studies - HRS reversal (sCr<132micromol/L)

| Study or Subgroup | Terlipressin Events | Total | No intervention/placebo Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Boyer 2016 | 42 | 97 | 28 | 99 | 49.8% | 1.53 [1.04, 2.26] |
| Martin-Llahi 2008 | 6 | 17 | 1 | 18 | 5.8% | 6.35 [0.85, 47.44] |
| Sanyal 2008 | 33 | 56 | 14 | 56 | 41.4% | 2.36 [1.42, 3.90] |
| Solanki 2003 | 5 | 12 | 0 | 12 | 3.1% | 11.00 [0.67, 179.29] |
| **Total (95% CI)** | | **182** | | **185** | **100.0%** | **2.11 [1.28, 3.49]** |
| Total events | 86 | | 43 | | | |

Heterogeneity: Tau² = 0.09; Chi² = 4.98, df = 3 (P = 0.17); I² = 40%
Test for overall effect: Z = 2.91 (P = 0.004)

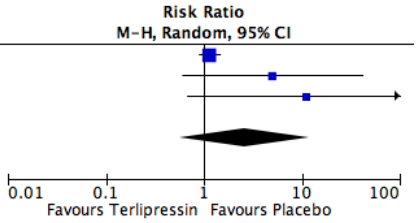


## 1.4 Low risk studies - Adverse events

## All adverse events

| Study or Subgroup | Terlipressin Events | Total | No intervention/placebo Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Boyer 2016 | 59 | 97 | 53 | 99 | 53.8% | 1.14 [0.89, 1.45] |
| Sanyal 2008 | 5 | 56 | 1 | 56 | 26.7% | 5.00 [0.60, 41.44] |
| Solanki 2003 | 5 | 12 | 0 | 12 | 19.4% | 11.00 [0.67, 179.29] |
| **Total (95% CI)** | | **165** | | **167** | **100.0%** | **2.62 [0.57, 12.13]** |
| Total events | 69 | | 54 | | | |

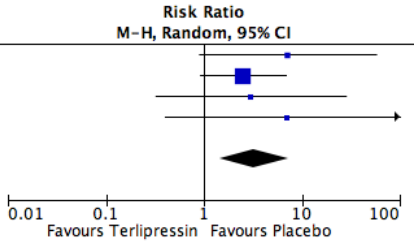
Heterogeneity: $Tau^2 = 1.12$; $Chi^2 = 4.98$, df = 2 (P = 0.08); $I^2 = 60\%$
Test for overall effect: Z = 1.23 (P = 0.22)




## Ischaemic adverse events

| Study or Subgroup | Terlipressin Events | Total | No intervention/placebo Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Boyer 2016 | 7 | 97 | 1 | 99 | 15.0% | 7.14 [0.90, 56.99] |
| Martin-Llahi 2008 | 10 | 23 | 4 | 23 | 64.1% | 2.50 [0.91, 6.83] |
| Sanyal 2008 | 3 | 56 | 1 | 56 | 13.0% | 3.00 [0.32, 27.97] |
| Solanki 2003 | 3 | 12 | 0 | 12 | 7.9% | 7.00 [0.40, 122.44] |
| **Total (95% CI)** | | **188** | | **190** | **100.0%** | **3.25 [1.45, 7.27]** |
| Total events | 23 | | 6 | | | |

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.17$, df = 3 (P = 0.76); $I^2 = 0\%$
Test for overall effect: Z = 2.87 (P = 0.004)



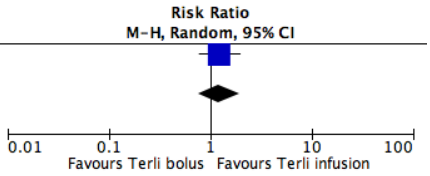
## Supplementary material

## 2. Terlipressin infusion vs terlipressin bolus *(Forest plot of comparison)*

### 2.1 HRS reversal (sCr<132micromol/L)

| Study or Subgroup | Terlipressin infusion Events | Total | Terlipressin bolus Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Cavallin 2016 | 19 | 34 | 17 | 37 | 100.0% | 1.22 [0.77, 1.93] |
| **Total (95% CI)** | | **34** | | **37** | **100.0%** | **1.22 [0.77, 1.93]** |
| Total events | 19 | | 17 | | | |

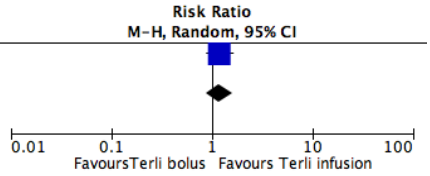
Heterogeneity: Not applicable
Test for overall effect: Z = 0.83 (P = 0.40)




### 2.2 Improved serum creatinine

| Study or Subgroup | Terlipressin infusion Events | Total | Terlipressin bolus Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Cavallin 2016 | 26 | 34 | 24 | 37 | 100.0% | 1.18 [0.87, 1.59] |
| **Total (95% CI)** | | **34** | | **37** | **100.0%** | **1.18 [0.87, 1.59]** |
| Total events | 26 | | 24 | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 1.07 (P = 0.28)

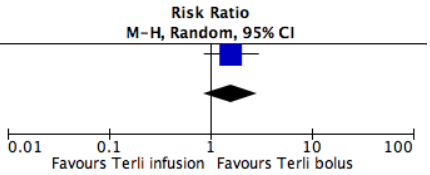



### 2.3 Mortality

| Study or Subgroup | Terlipressin infusion Events | Total | Terlipressin bolus Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Cavallin 2016 (1) | 16 | 34 | 11 | 37 | 100.0% | 1.58 [0.86, 2.91] |
| **Total (95% CI)** | | **34** | | **37** | **100.0%** | **1.58 [0.86, 2.91]** |
| Total events | 16 | | 11 | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 1.47 (P = 0.14)

Footnotes
(1) 90-day mortality

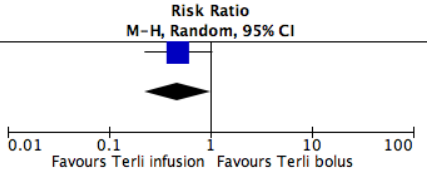



### 2.4 Adverse events

#### All adverse events

| Study or Subgroup | Terlipressin infusion Events | Total | Terlipressin bolus Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Cavallin 2016 | 7 | 34 | 16 | 37 | 100.0% | 0.48 [0.22, 1.01] |
| **Total (95% CI)** | | **34** | | **37** | **100.0%** | **0.48 [0.22, 1.01]** |
| Total events | 7 | | 16 | | | |

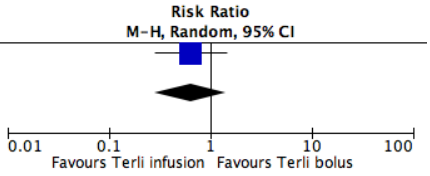
Heterogeneity: Not applicable
Test for overall effect: Z = 1.92 (P = 0.05)




#### Ischaemic adverse events

| Study or Subgroup | Terlipressin infusion Events | Total | Terlipressin bolus Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Cavallin 2016 | 7 | 34 | 12 | 37 | 100.0% | 0.63 [0.28, 1.42] |
| **Total (95% CI)** | | **34** | | **37** | **100.0%** | **0.63 [0.28, 1.42]** |
| Total events | 7 | | 12 | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 1.10 (P = 0.27)



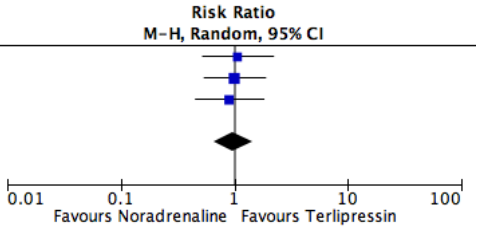
## Supplementary material

## 3. Terlipressin vs Noradrenaline (*Forest plot of comparison)*

### 3.1 HRS reversal (sCr<132micromol/L)

| Study or Subgroup | Terlipressin Events | Terlipressin Total | Noradrenaline Events | Noradrenaline Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Alessandria 2007 | 4 | 5 | 3 | 4 | 29.3% | 1.07 [0.52, 2.18] |
| Sharma 2008 | 10 | 20 | 10 | 20 | 39.1% | 1.00 [0.54, 1.86] |
| Singh 2012 | 9 | 23 | 10 | 23 | 31.5% | 0.90 [0.45, 1.80] |
| **Total (95% CI)** | | **48** | | **47** | **100.0%** | **0.99 [0.67, 1.45]** |
| Total events | 23 | | 23 | | | |

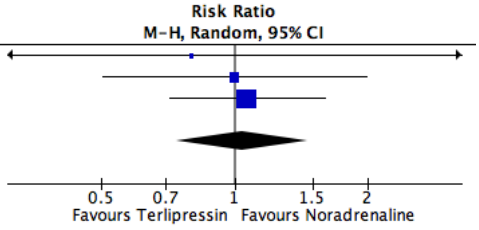
Heterogeneity: Tau² = 0.00; Chi² = 0.13, df = 2 (P = 0.94); I² = 0%
Test for overall effect: Z = 0.07 (P = 0.94)




### 3.2 Mortality

| Study or Subgroup | Terlipressin Events | Terlipressin Total | Noradrenaline Events | Noradrenaline Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Alessandria 2007 | 1 | 5 | 1 | 4 | 2.0% | 0.80 [0.07, 9.18] |
| Sharma 2008 | 9 | 20 | 9 | 20 | 25.2% | 1.00 [0.50, 1.98] |
| Singh 2012 | 16 | 23 | 15 | 23 | 72.9% | 1.07 [0.71, 1.60] |
| **Total (95% CI)** | | **48** | | **47** | **100.0%** | **1.04 [0.74, 1.47]** |
| Total events | 26 | | 25 | | | |

Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 2 (P = 0.96); I² = 0%
Test for overall effect: Z = 0.24 (P = 0.81)

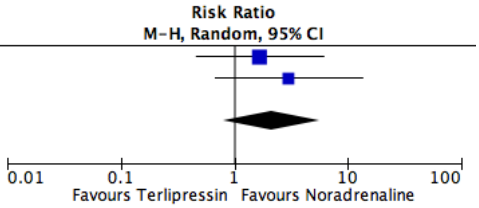



### 3.3 Adverse events

### All adverse events

| Study or Subgroup | Terlipressin Events | Terlipressin Total | Noradrenaline Events | Noradrenaline Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Sharma 2008 | 5 | 20 | 3 | 20 | 57.2% | 1.67 [0.46, 6.06] |
| Singh 2012 | 6 | 23 | 2 | 23 | 42.8% | 3.00 [0.67, 13.34] |
| **Total (95% CI)** | | **43** | | **43** | **100.0%** | **2.14 [0.81, 5.69]** |
| Total events | 11 | | 5 | | | |

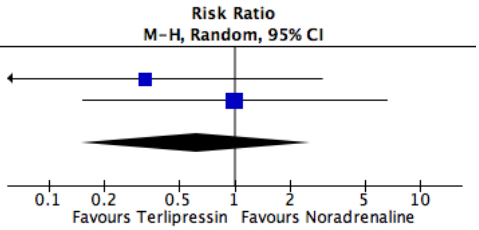
Heterogeneity: Tau² = 0.00; Chi² = 0.34, df = 1 (P = 0.56); I² = 0%
Test for overall effect: Z = 1.53 (P = 0.13)




### Ischaemic adverse events

| Study or Subgroup | Terlipressin Events | Terlipressin Total | Noradrenaline Events | Noradrenaline Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Alessandria 2007 | 0 | 5 | 0 | 4 | | Not estimable |
| Sharma 2008 | 1 | 20 | 3 | 20 | 42.5% | 0.33 [0.04, 2.94] |
| Singh 2012 | 2 | 23 | 2 | 23 | 57.5% | 1.00 [0.15, 6.51] |
| **Total (95% CI)** | | **48** | | **47** | **100.0%** | **0.63 [0.15, 2.59]** |
| Total events | 3 | | 5 | | | |

Heterogeneity: Tau² = 0.00; Chi² = 0.57, df = 1 (P = 0.45); I² = 0%
Test for overall effect: Z = 0.65 (P = 0.52)



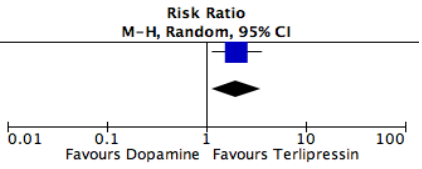
## Supplementary material

## 4. Terlipressin + albumin vs Dopamine + standard care (*Forest plot of comparison)*

### 4.1 HRS reversal (sCr<132micromol/L)

| Study or Subgroup | Terlipressin Events | Total | Dopamine + standard care Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Silawat 2011 (1) | 20 | 30 | 10 | 30 | 100.0% | 2.00 [1.14, 3.52] |
| **Total (95% CI)** | | **30** | | **30** | **100.0%** | **2.00 [1.14, 3.52]** |
| Total events | 20 | | 10 | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 2.40 (P = 0.02)

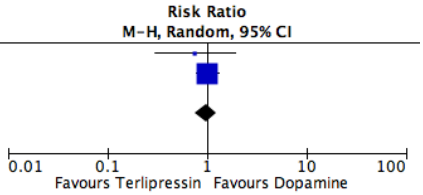



Footnotes
(1) silawat- not defined ('recovered')

### 4.2 Mortality

| Study or Subgroup | Terlipressin Events | Total | Dopamine + standard care Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Silawat 2011 (1) | 6 | 30 | 8 | 30 | 7.3% | 0.75 [0.30, 1.90] |
| Srivastava 2015 (2) | 17 | 20 | 17 | 20 | 92.7% | 1.00 [0.77, 1.30] |
| **Total (95% CI)** | | **50** | | **50** | **100.0%** | **0.98 [0.76, 1.26]** |
| Total events | 23 | | 25 | | | |

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.58$, df = 1 (P = 0.45); $I^2 = 0\%$
Test for overall effect: Z = 0.16 (P = 0.87)



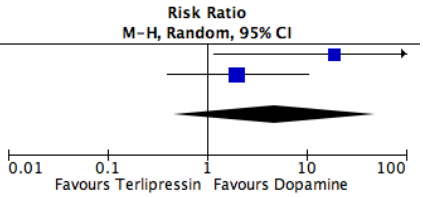

Footnotes
(1) no timescale given for survival
(2) 30 day mortality

### 4.3 Adverse events

### All adverse events

| Study or Subgroup | Terlipressin Events | Total | Dopamine + standard care Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Silawat 2011 | 9 | 30 | 0 | 30 | 38.8% | 19.00 [1.16, 312.42] |
| Srivastava 2015 | 4 | 40 | 2 | 40 | 61.2% | 2.00 [0.39, 10.31] |
| **Total (95% CI)** | | **70** | | **70** | **100.0%** | **4.79 [0.46, 49.60]** |
| Total events | 13 | | 2 | | | |

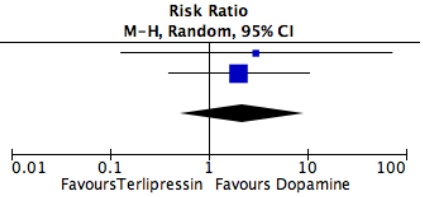
Heterogeneity: $Tau^2 = 1.62$; $Chi^2 = 2.18$, df = 1 (P = 0.14); $I^2 = 54\%$
Test for overall effect: Z = 1.31 (P = 0.19)




### Ischaemic adverse events

| Study or Subgroup | Terlipressin Events | Total | Dopamine + standard care Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Silawat 2011 | 1 | 30 | 0 | 30 | 21.2% | 3.00 [0.13, 70.83] |
| Srivastava 2015 | 4 | 40 | 2 | 40 | 78.8% | 2.00 [0.39, 10.31] |
| **Total (95% CI)** | | **70** | | **70** | **100.0%** | **2.18 [0.51, 9.34]** |
| Total events | 5 | | 2 | | | |

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.05$, df = 1 (P = 0.82); $I^2 = 0\%$
Test for overall effect: Z = 1.05 (P = 0.29)



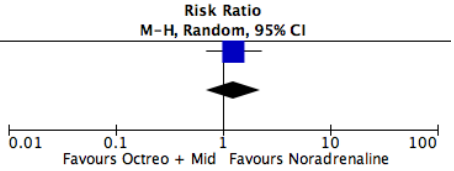
## Supplementary material

**5. Noradrenaline + albumin vs Octreotide + Midodrine + albumin** (*Forest plot of comparison*

### 5.1 HRS reversal (sCr<132micromol/L)

| Study or Subgroup | Noradrenaline Events | Noradrenaline Total | Octreotide + midodrine Events | Octreotide + midodrine Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Tavakkoli 2012 | 5 | 6 | 6 | 9 | 100.0% | 1.25 [0.70, 2.24] |
| **Total (95% CI)** | | **6** | | **9** | **100.0%** | **1.25 [0.70, 2.24]** |
| Total events | 5 | | 6 | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.75 (P = 0.45)

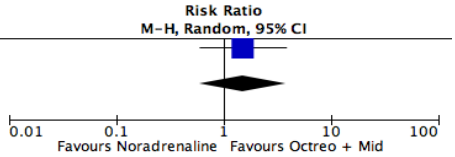



### 5.2 Mortality

| Study or Subgroup | Noradrenaline Events | Noradrenaline Total | Octreotide + midodrine Events | Octreotide + midodrine Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Tavakkoli 2012 (1) | 4 | 6 | 4 | 9 | 100.0% | 1.50 [0.60, 3.78] |
| **Total (95% CI)** | | **6** | | **9** | **100.0%** | **1.50 [0.60, 3.78]** |
| Total events | 4 | | 4 | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.86 (P = 0.39)

Footnotes
(1) 90 day mortality



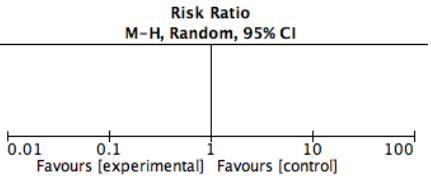

### 5.3 Adverse events

### All adverse events

| Study or Subgroup | Noradrenaline Events | Noradrenaline Total | Octreotide + midodrine Events | Octreotide + midodrine Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Tavakkoli 2012 (1) | 0 | 6 | 0 | 9 | | Not estimable |
| **Total (95% CI)** | | **6** | | **9** | | **Not estimable** |
| Total events | 0 | | 0 | | | |

Heterogeneity: Not applicable
Test for overall effect: Not applicable

Footnotes
(1) nil reported

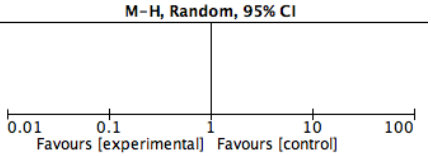



### Ischaemic adverse events

| Study or Subgroup | Noradrenaline Events | Noradrenaline Total | Octreotide + midodrine Events | Octreotide + midodrine Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Tavakkoli 2012 (1) | 0 | 6 | 0 | 9 | | Not estimable |
| **Total (95% CI)** | | **6** | | **9** | | **Not estimable** |
| Total events | 0 | | 0 | | | |

Heterogeneity: Not applicable
Test for overall effect: Not applicable

Footnotes
(1) nil reported



## Supplementary material

**Appendix 1**

List of speciality journals included in manual search for additional pertinent literature

1. Journal of Hepatology
2. Gastroenterology
3. Journal of Gastroenterology and Hepatology
4. American Journal of Gastroenterology
5. Hepatology
6. European Journal of Gastroenterology and Hepatology
7. Alimentary, Pharmacology and Therapeutics
8. Liver International
9. Digestive Diseases and Sciences
10. Nephrology Dialysis Transplantation
11. GUT
12. Nature Reviews Gastroenterology and Hepatology

Conference proceedings

1. AASLD: American Association for the Study of Liver Diseases (Hepatology)
2. EASL: European Association for the Study of the Liver (Journal of Hepatology)
3. ERA-EDTA: European Renal Association- European Dialysis and Transplant Association (Nephrology Dialysis Transplantation)

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 2-3 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 4-6 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 7 |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | 6-7 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 7, Table 1 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 7 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 7 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 7-8 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 7-8 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 8 |

| | | | |
|---|---|---|---|
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 8 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 8 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | 8 |



| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 8 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 8 |
| **RESULTS** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 9 Figure 1 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 9-10, Table 2 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 10, Table 3 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 10-13, Supp material p30-35 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | Supp material p30-35 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | 10-13 |

| | | | |
|---|---|---|---|
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | 10-13, Supp material p30-35 |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 13-14 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 14-15 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 15-16 |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 21 |

*From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097