Vasopressors for hypotensive shock (Review)

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[Intervention Review]

Vasopressors for hypotensive shock

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ABSTRACT

Background

Initial goal directed resuscitation for shock usually includes the administration of intravenous fluids, followed by initiating vasopressors. Despite obvious immediate effects of vasopressors on haemodynamics their effect on patient relevant outcomes remains controversial. This review was originally published in 2004 and was updated in 2011.

Objectives

Our primary objective was to assess whether particular vasopressors reduce overall mortality, morbidity, and health-related quality of life.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2010, Issue 2), MEDLINE, EMBASE, PASCAL BioMed, CINAHL, BIOSIS, and PsycINFO (from inception to March 2010). The original search was performed in November 2003. We also asked experts in the field and searched meta-registries for ongoing trials.

Selection criteria

Randomized controlled trials comparing various vasopressor regimens for hypotensive shock.

Data collection and analysis

Two authors abstracted data independently. Disagreement between the authors was discussed and resolved with a third author. We used a random-effects model for combining quantitative data.

Main results

We identified 23 randomized controlled trials involving 3212 patients, with 1629 mortality outcomes. Six different vasopressors, alone or in combination, were studied in 11 different comparisons.

All 23 studies reported mortality outcomes; length of stay was reported in nine studies. Other morbidity outcomes were reported in a variable and heterogeneous way. No data were available on quality of life or anxiety and depression outcomes. We classified 10 studies as being at low risk of bias for the primary outcome mortality; only four studies fulfilled all trial quality items.

In summary, there was no difference in mortality in any of the comparisons between different vasopressors or combinations. More arrhythmias were observed in patients treated with dopamine compared to norepinephrine. Norepinephrine versus dopamine, as the largest comparison in 1400 patients from six trials, yielded almost equivalence (RR 0.95, 95% confidence interval 0.87 to 1.03). Vasopressors used as add-on therapy in comparison to placebo were not effective either. These findings were consistent among the few large studies as well as in studies with different levels of within-study bias risk.

Authors' conclusions

There is some evidence of no difference in mortality between norepinephrine and dopamine. Dopamine appeared to increase the risk for arrhythmia. There is not sufficient evidence of any difference between any of the six vasopressors examined. Probably the choice of vasopressors in patients with shock does not influence the outcome, rather than any vasoactive effect per se. There is not sufficient evidence that any one of the investigated vasopressors is clearly superior over others.

PLAIN LANGUAGE SUMMARY

Vasopressors for shock

Circulatory shock is broadly defined as circulatory failure resulting in the body's inability to maintain organ perfusion and to meet oxygen demands. It usually presents with low blood pressure. Up to every third patient with circulatory shock may be admitted to the intensive care unit because of circulatory failure, and mortality in the intensive care unit ranges from 16% to 60%. For treatment, fluid replacement is followed by vasopressor agents, if necessary. A vasopressor agent is an agent that causes a rise in blood pressure. Vasopressor therapy is an important part of haemodynamic support in patients with shock (where haemodynamics is defined as the flow of blood in the circulatory system). A number of different vasopressors are available.

This systematic review included 23 randomized controlled trials. Overall 3212 patients, with 1629 deaths, were analysed. Six different vasopressors alone or in combination with dobutamine or dopexamine were studied in 11 different comparisons. The strength of evidence differed greatly between several comparisons and the most data are available for norepinephrine. Dopamine seems to increase the risk for heart arrhythmias. In summary, there is not sufficient evidence to prove that any of the vasopressors, in the assessed doses, were superior to others. The choice of a specific vasopressor may therefore be individualized and left to the discretion of the treating physicians.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

norepinephrine compared to dopamine for hypotensive shock

Patient or population: hypotensive shock
Settings:
Intervention: norepinephrine
Comparison: dopamine

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	dopamine	norepinephrine				
Mortality Follow-up: 12 months[1]	**Study population**[2]		**RR 0.95** (0.87 to 1.03)	1400 (6 studies)	⊕⊕⊕⊕ **high**[3,4]	
	61 per 100	**58 per 100** (53 to 63)				
	Medium risk population[2]					
	38 per 100	**36 per 100** (33 to 39)				
Arrhythmia Follow-up: 28 days	**Study population**[5,6]		**RR 0.43** (0.26 to 0.69)	1931 (2 studies)	⊕⊕⊕⊕ **high**[7]	
	260 per 1000	**112 per 1000** (68 to 179)				
	Low risk population[5,6]					
	122 per 1000	**52 per 1000** (32 to 84)				
	Medium risk population[5,6]					

	176 per 1000	**76 per 1000** (46 to 121)			
Length of stay in intensive care unit Days in ICU. Scale from: 5 to 6.8.	The mean length of stay in intensive care unit in the control groups was **5 days in ICU**	The mean Length of stay in intensive care unit in the intervention groups was **0.09 higher** (0.57 lower to 0.75 higher)		1931 (2 studies)	⊕⊕⊕⊕ **high**[7]
Length of stay in hospital Days in hospital. Scale from: 11 to 14.	The mean length of stay in hospital in the control groups was **11 days in hospital**	The mean Length of stay in hospital in the intervention groups was **0.66 higher** (0.96 lower to 2.29 higher)		1931 (2 studies)	⊕⊕⊕⊕ **high**[7]
Health related quality of life - not reported	See comment	See comment	Not estimable	-	See comment
Anxiety and depression - not reported	See comment	See comment	Not estimable	-	See comment

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] The largest study reported 12 Mo mortality, one study reported 28day mortality and one hospital mortality. For the remaining 3 studies the time-point of mortality assessment was undetermined. A sensitivity analysis does indicate no influence on the effects by differences in mortality definition.
[2] Sakr 2006

[3] There are 4 smaller studies with up to 50 patients each which do not fulfil some of the quality criteria and one high risk of bias study that contributes 252 patients . However, the summary result is mainly made up by the biggest study of over 1000 patients that fulfils all low bias risk criteria.

[4] The main outcome of the four smaller studies are haemodynamics and metabolic measures. Mortality is only reported at the end of the results and often unclear timepoint-wise. However the study by De Baker (which contributes mainly to the summary result) clearly defines mortality endpoints.

[5] Reinelt P Karth DG, Geppert A, Heinz G. Intens Care Med 2001;27:1466-73

[6] Annane J, Sebille V, Duboc D, et al. Am J Resp Crit Care Med 2008;178:20-25

[7] Information comes from 992 patients where 86% of these patients were studied in a low risk of bias study (DeBacker 2010) and the remaining patients come from a high risk of bias study (Patel 2010). The effects show into the same direction.

BACKGROUND

Description of the condition

Shock is a state of severe systemic deterioration in tissue perfusion, characterized by decreased cellular oxygen delivery and utilization as well as decreased removal of waste byproducts of metabolism. Hypotension, although common in shock, is not synonymous to shock. One can have hypotension and normal perfusion or shock without hypotension in a patient who is usually very hypertensive. Shock is the final pre-terminal event in many diseases. Progressive tissue hypoxia results in loss of cellular membrane integrity, reversion to a catabolic state of anaerobic metabolism, and a loss of energy-dependent ion pumps and chemical and electrical gradients. Mitochondrial energy production begins to fail. Multiple organ dysfunction follows localized cellular death, followed by organism death (Young 2008). A widely used classification for mechanisms of shock is hypovolaemic, cardiogenic, obstructive and distributive (Hinshaw 1972).

Currently the definition of septic shock is more pragmatic because hypotension instead of hypoperfusion is the main clinical criterion. The current standard definition for septic shock (Dellinger 2008) in adults refers to a state of acute circulatory failure characterised by persistent arterial hypotension that is unexplained by other causes. Hypotension is defined by systolic blood pressure < 90 mm Hg, mean arterial pressure < 60 mm Hg, or a reduction in systolic blood pressure of > 40 mm Hg despite adequate volume resuscitation in the absence of other causes for hypotension (Levy 2003). A large study recently defined shock even more pragmatically, as haemodynamic compromise necessitating the administration of vasopressor catecholamines (Sakr 2006).

Estimates of the incidence of shock in the general population vary considerably. From an observational study, 31 cases of septic shock per 100,000 population/year (Esteban 2007) were reported. Many patients develop shock from severe sepsis, which has an incidence of 25 to 300 cases per 100,000 population/year (Angus 2001; Blanco 2008; Sundararajan 2005); among those 30% are expected to develop septic shock (Esteban 2007).

The frequency of shock at healthcare facilities is somewhat better described. In the large observational SOAP study, in 3147 critically ill patients from 198 intensive care units (ICUs), 34% had shock; among those 15% had septic shock (Sakr 2006). In another large European ICU cohort study 32% were found to have septic shock. In a prospective observational study in 293,633 patients with ST-elevation myocardial infarction from 775 US hospitals, 9% developed cardiogenic shock (Babaev 2005). From an observational study on 2445 patients admitted to a trauma level I centre, 22% were reported to already have shock on admission in the emergency department (ED) (Cannon 2009).

Hospital mortality is high, at around 38% (Sakr 2006), in patients with shock but seems to depend much on shock type. For patients with septic shock mortality ranges from 46% (Esteban 2007; Sakr 2006) up to 61% (Alberti 2005). Mortality in patients with traumatic shock was somewhat lower at 16% (Cannon 2009). Whereas the incidence of cardiogenic shock was almost constant between 1995 and 2004, mortality has decreased from 60% in 1995 to 48% over the years (Babaev 2005).

Description of the intervention

Vasopressors are a heterogenous class of drugs with powerful and immediate haemodynamic effects. Vasopressors can be classified according to their adrenergic and non-adrenergic actions.

Catecholamines are sympathomimetics that act directly or indirectly on adrenergic receptors. Their haemodynamic effects depend on their varying pharmacological properties. They may increase the contractility of the myocardial muscle fibres and heart rate (via beta-adrenergic receptors) but they may also, and sometimes exclusively, increase vascular resistance (via alpha-adrenergic receptors). There are many good textbooks outlining the detailed mechanisms of action (see, for example, Hoffman 1992; Zaritsky 1994).

The haemodynamic properties of vasopressin, a neurohypophysial peptide hormone, were first reported in 1926 (Geiling 1926). Vasopressin and analogues like terlipressin display their vasopressor effects via vasopressin receptors and are newer drugs for the treatment of shock (Levy 2010).

Utilisation of different vasopressors was described recently in a large European multicentre cohort study in 198 ICUs (Sakr 2006). The most frequently used vasopressor was norepinephrine (80%), followed by dopamine (35%), and epinephrine (23%) alone or in combination. Single agent use was reported for norepinephrine (32%), dopamine (9%), and epinephrine (5%). A combination of norepinephrine, dopamine, and epinephrine was used in only 2% of patients with shock. Vasopressin and terlipressin were not contained in this report. Currently the choice of vasopressors seems mainly based on physicians' preferences (Leone 2004).

How the intervention might work

Initial goal directed resuscitation to support vital functions are essential in the management of shock. The first-line treatment for the manifestation of circulatory failure is usually the administration of intravenous fluids. If fluid treatment does not restore circulatory function, vasopressors such as norepinephrine, dopamine, epinephrine, and vasopressin are recommended.

Why it is important to do this review

The effects of vasopressors on the cardiovascular system are largely undisputed. It is, however, unclear if there is a vasopressor of choice, either for the treatment of particular forms of shock or for the treatment of shock in general.

OBJECTIVES

Our objective was to assess the effect of one vasopressor regimen (vasopressor alone, or in combination) compared to another vasopressor regimen on mortality in critically ill patients with shock. We further aimed to investigate effects on other patient relevant outcomes and to assess the influence of bias on the robustness of our effect estimates.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized controlled trials (RCTs) investigating the effect of vasopressors for the treatment of any kind of circulatory failure. For simplicity, we refer to circulatory failure as 'shock' (see also search terms for shock). We were exclusively interested in patient relevant outcomes (see below). Such endpoints, particularly death, can only be assessed with parallel group trials. Therefore we excluded crossover trials.

Types of participants

We included trials with acutely and critically ill adult and paediatric patients. We excluded trials looking at pre-term infants with hypotension as this patient group is covered in another Cochrane Review (Subhedar 2003). We excluded animal experiments. The definition of 'shock' was as used as given by the study authors.

Types of interventions

The intervention was the administration of different vasopressors, vasopressors versus intravenous fluids, and vasopressors versus placebo.

Types of outcome measures

Primary outcomes

We looked at total mortality (in the ICU, in hospital, and at one year) as the main endpoint. If mortality was assessed at several time points in a study we used data from the latest follow-up time.

Secondary outcomes

Other pre-defined outcomes were morbidity (given as length of ICU stay; length of hospital stay; duration of vasopressor treatment; duration of mechanical ventilation; renal failure (as defined by authors: such as oliguria or need for renal replacement therapy)); measures of health-related quality of life at any given time; and measures of anxiety and depression (together or separately) at any given time.

Search methods for identification of studies

We did not apply language restrictions.

Electronic searches

We searched MEDLINE (1966 to March 2010) (see Appendix 1); the Cochrane Central Register of Controlled Trials (*The Cochrane Library* 2010, Issue 2) (see Appendix 2, Search filter for CENTRAL); EMBASE (1989 to March 2010) (see Appendix 3, Search filter for EMBASE); PASCAL BioMed (1996 to March 2010); and BIOSIS (1990 to March 2010) (see Appendix 4 and Appendix 5, Search filter for PASCAL BioMed, CINAHL, and BIOSIS); PsycINFO (1978 to March 2010) (see Appendix 6, Search filter for PsychINFO) using the Ovid platform. CINAHL (1984 to March 2010) was searched via EBCSO. We searched for key words describing the condition or describing the intervention and combined the results with a methodological filter (RCT filter).
We used a validated RCT filter for MEDLINE and EMBASE (Higgins 2011).

Searching other resources

We searched ongoing clinical trials and unpublished studies via the Internet (date of latest search 29 June 2010) on www.controlled-trials.com using the multiple database search option metaRegister of Controlled Trials. This register includes the ISRCTN Register, Action Medical Research, Leukaemia Research Fund, Medical Reserch Council (UK), NHS Research and Development HTA Programme, ClinicalTrials.gov, Wellcome Trust, and UK Clinical Trials Gateway.
Further, we searched textbooks and references of papers selected during the electronic search for relevant references. Finally, we contacted experts in the field to identify further trials (see 'Acknowledgements').

Data collection and analysis

Selection of studies

We entered all search results into a bibliographic software (Endnote X1, The Thomson Corp, USA) then we removed duplicates.

Two authors independently screened the studies by title and abstract for exclusion using a template with inclusion and exclusion criteria. We recorded the reasons for exclusion. For the remaining studies, full papers were retrieved. Two authors independently recorded the inclusion and exclusion criteria using the first section of the data extraction form. We resolved all disagreements through arbitration by a third author.

Data extraction and management

Two authors abstracted data independently onto a pre-defined data extraction form and entered the data into RevMan 5.1. The results were compared and disagreements were resolved by discussion amongst at least three review authors.

Besides data on intervention and outcome, we also recorded study characteristics such as: age; gender; severity of illness, as given (for example acute physiology and chronic health evaluation (APACHE), multiple organ failure (MOF) score, simplified acute physiology score (SAPS)); underlying diagnosis and particular type of shock, given definition of shock; duration of ICU stay before enrolment into study; duration of mechanical ventilation before enrolment; and study setting.

Assessment of risk of bias in included studies

Two authors independently abstracted data to a pre-defined data extraction form. We abstracted whether adequate methods were used to generate a random sequence, that allocation to treatment was concealed, whether inclusion and exclusion criteria were explicit, if the data were analysed by intention to treat, whether patient descriptions were adequate, whether care during the study period was identical in both groups, whether the outcome description was adequate, whether the involved clinical staff were blinded to the intervention, and whether the assessor of the outcome was blinded to the intervention. The results were compared and disagreements were resolved by discussion amongst at least three review authors. Data were then entered into RevMan. We produced a risk of bias graph and a risk of bias table.

Assessment of reporting biases

We planned to assess reporting bias and small study effects graphically using funnel plots of standard errors versus effect estimates for the primary outcome. We also planned to formally test funnel plot asymmetry by using the arcsine test (Rucker 2008) if at least 10 studies per comparison for the primary outcome were available.

Data synthesis

We combined data quantitatively only if clinical heterogeneity was assumed to be negligible. Statistical heterogeneity was assessed with the I^2 statistic and the Cochrane Q tests for heterogeneity. We used a random-effects model to combine relative risks by default because we expected a number of different comparisons with at least some heterogeneity. In two trials (Dünser 2003; Martin 1993), some participants crossed over to the other treatment; these patients were analysed according to the intention-to-treat principle, that is according to the group to which they were initially assigned.

We did not plan any a priori subgroup analyses.

Sensitivity analysis

We planned a sensitivity analysis to assess the influence of the risk of bias on the main effect of the interventions, and thereby the robustness of our estimates. We classified studies as 'low risk of bias' and 'no low risk of bias'. Studies were classified as having low risk of bias if they have adequate allocation concealment and if the other bias items in the summary were not believed to have a major influence on the robustness of the single study effect. Unclear or inadequate allocation concealment in any case resulted in classification as 'study with no low risk of bias'. Our primary outcome was mortality, which was generally considered robust against outcome assessor knowledge of treatment allocation. Lack of blinding of the outcome assessors therefore had smaller weight on the bias risk assessment for this outcome. On the contrary this bias risk item had strong weight for outcomes where the assessment included individual judgement, as for measures of quality of life. In the sensitivity analysis we grouped studies according to our classification of 'low risk of bias' and 'no low risk of bias' in a forest plot.

We also performed a post hoc sensitivity analysis to investigate the influence of different time points on the mortality outcome assessment.

RESULTS

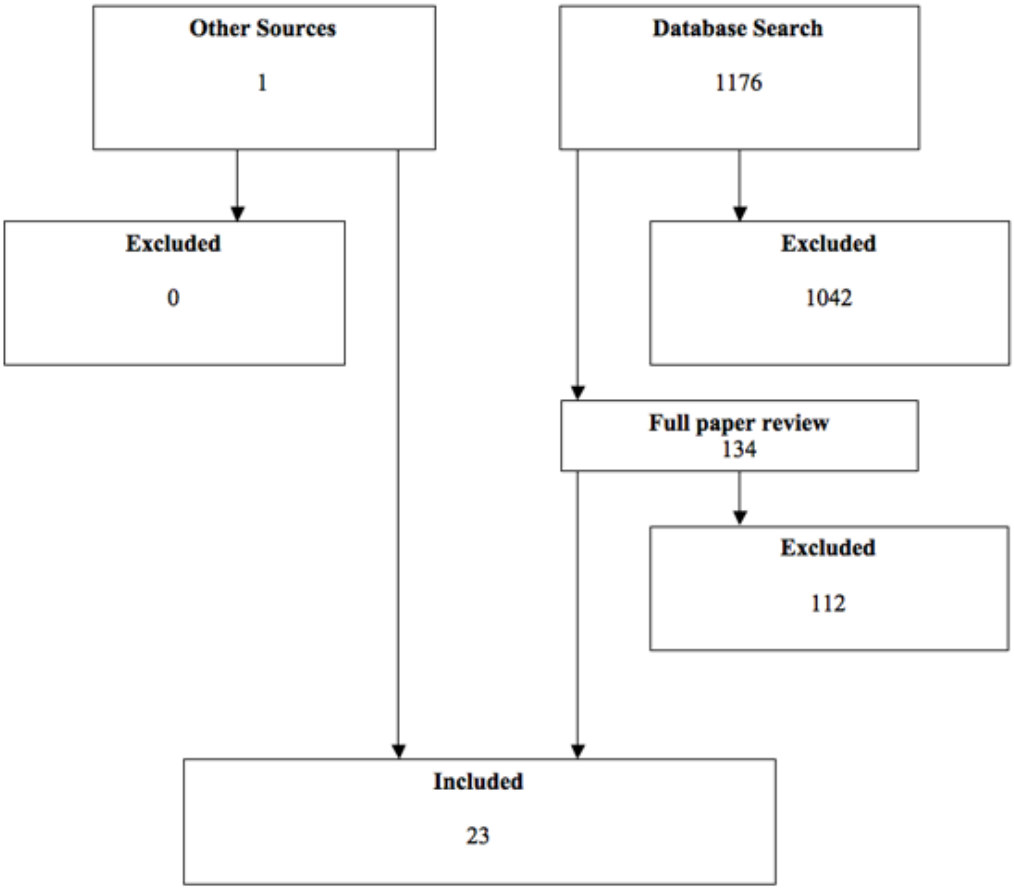
Description of studies

Results of the search

Search result

The electronic search resulted in 1176 hits after removing duplicates with the bibliographic software (Figure 1). We identified and retrieved 134 potentially relevant articles (this number included 12 articles identified from reading the references of potentially relevant articles and writing to 14 specialists in the field, of whom five replied, see 'Acknowledgements'). Two trials were not retrievable (Hai Bo 2002; Singh 1966). Of these 134 articles, after closer inspection 101 failed our inclusion criteria due to the following reasons:

Figure 1. Trial flow chart



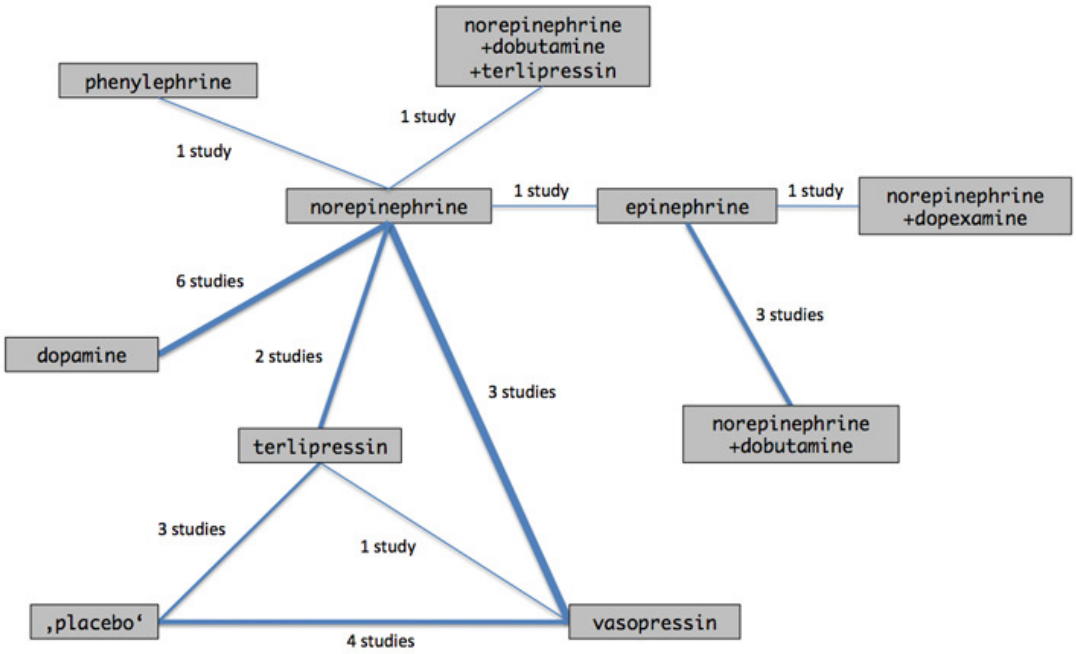
- 39 trials were about other interventions;
- 35 were not randomized;
- 23 were crossover trials;
- 3 were animal studies;
- 1 trial was a duplicate (abstract presented at a scientific meeting and then report subsequently published) (Martin 1993).

Of the remaining 34 potentially relevant clinical trials we excluded 11 studies (Characteristics of excluded studies). Finally we included 23 studies in our review (Characteristics of included studies).

Included studies

In our original review (Müllner 2004) we included eight studies. In this updated review we included 15 new studies. In total we have included 23 studies investigating several comparisons (Figure 2). Details are presented in the table 'Characteristics of included studies'. Among these studies seven were multicentre studies (Annane 2007; Choong 2009; De Backer 2010; Lauzier 2006; Malay 1999; Myburgh 2008; Russell 2008) and all but three (Annane 2007; Malay 1999; Myburgh 2008) were performed in university hospitals only.

Figure 2. Comparison of vasopressor identified from the systematic review. The 26 comparisons come from 23 studies. Line thickness is proportional to the number of included patients.



Fifteen studies were performed in patients with septic shock (Albanese 2005; Annane 2007; Lauzier 2006; Malay 1999; Marik 1994; Martin 1993; Morelli 2008a; Morelli 2008b; Morelli 2009; Ruokonen 1993; Russell 2008; Seguin 2002; Seguin 2006; Yildizdas 2008; Patel 2010). Three studies included patients with peri-operative shock (Boccara 2003; Dünser 2003; Luckner 2006). Two studies were performed in paediatric patients (Choong 2009; Yildizdas 2008).

Fifteen studies had norepinephrine as an intervention (Albanese 2005; Boccara 2003; De Backer 2010; Dünser 2003; Lauzier 2006; Luckner 2006; Marik 1994; Martin 1993; Mathur 2007; Morelli 2008a; Morelli 2008b; Myburgh 2008; Ruokonen 1993; Russell 2008; Patel 2010), another three studies examined the combination of norepinephrine plus dobutamine (Annane 2007; Levy 1997; Seguin 2002), and one study used the combination of norepinephrine plus dopexamine (Seguin 2006).

Dopamine was used in six studies (De Backer 2010; Marik 1994; Martin 1993; Mathur 2007; Patel 2010; Ruokonen 1993), and epinephrine was used in five studies (Annane 2007; Levy 1997; Myburgh 2008; Seguin 2002; Seguin 2006). Vasopressin was used in seven studies (Choong 2009; Dünser 2003; Lauzier 2006; Luckner 2006; Malay 1999; Morelli 2009; Russell 2008), and another five studies used terlipressin (Albanese 2005; Boccara 2003; Morelli 2008a; Morelli 2009; Yildizdas 2008). Phenylephrine (Morelli 2008b) was used in one study. Three studies compared vasopressors to placebo as an add-on therapy (Choong 2009; Malay 1999; Yildizdas 2008).

Excluded studies

In our original review we excluded nine studies (Müllner 2004). In this updated version we excluded two new studies (Schmoelz 2006; Sperry 2008). In total we excluded 11 studies from our review. Some detail of the excluded studies is presented in the table 'Characteristics of excluded studies'. Eight studies were excluded because they did not report on any of our pre-defined endpoints but haemodynamic variables and other surrogate endpoints instead (Argenziano 1997; Hentschel 1995; Kinstner 2002; Levy 1999; Majerus 1984; Patel 2002; Totaro 1997; Zhou 2002). We excluded one trial looking at pre-term infants with hypotension (Rozé 1993) as this topic is covered in another Cochrane Review (Subhedar 2003). One study was a non-randomized multicentre prospective cohort study and was therefore excluded (Sperry 2008). Another study compared low dopamine to dopexamine and to placebo added to norepinephrine with the intention of improving renal and splanchnic blood flow. Low dose dopamine at

3 µg/kg/min is not considered to have relevant vasopressor properties, therefore we excluded this study too (Schmoelz 2006).

Studies waiting to be assessed

There are two studies that we have not yet been able to retrieve. One, which was published in 1966 (Singh 1966), is a 'comparative study of angiotensin and norepinephrine in hypotensive states' according to the title. As there is no abstract available, we do not know how many patients were enrolled. The second study, published in the journal *Critical Care Shock* in 2002 (Hai Bo 2002), was also not retrievable. This paper is on the 'renal effect of dopamine, norepinephrine, epinephrine, or norepinephrine-dobutamine in septic shock'. We do not know if this study contained original data of human experiments, if it was randomized and, if so, whether relevant outcomes were reported.

Ongoing studies

Our search resulted in 52 potentially relevant ongoing studies. Three ongoing studies were considered relevant (Characteristics of ongoing studies).

Risk of bias in included studies

Methodological quality of included studies

Risk of bias is presented in Figure 3 and Figure 4.

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

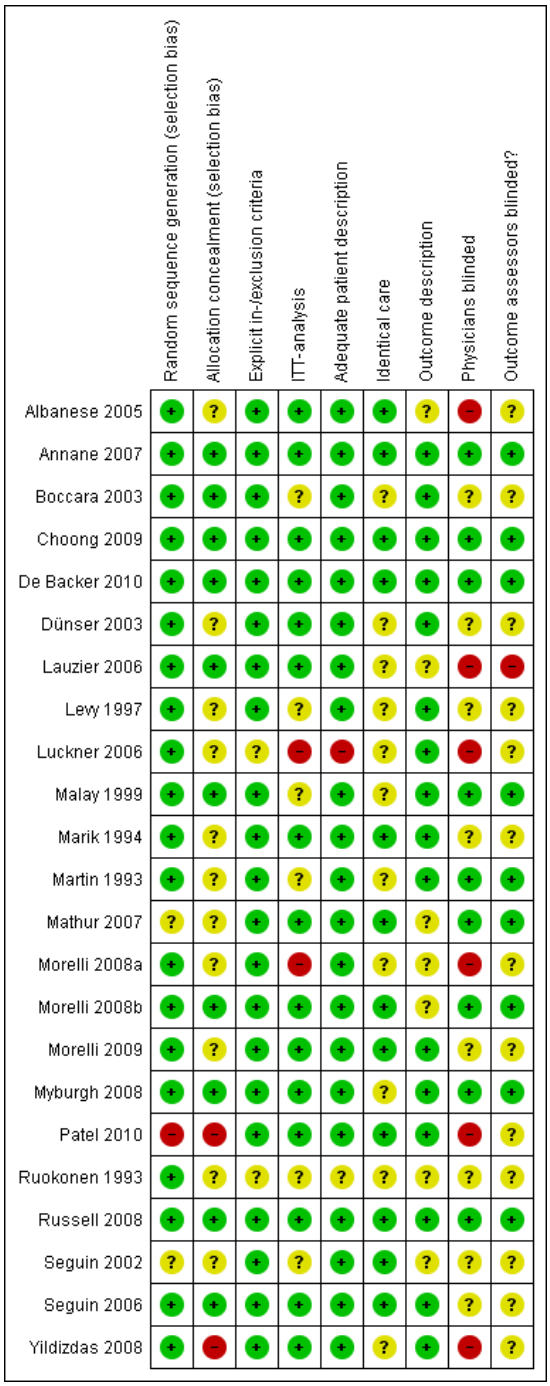
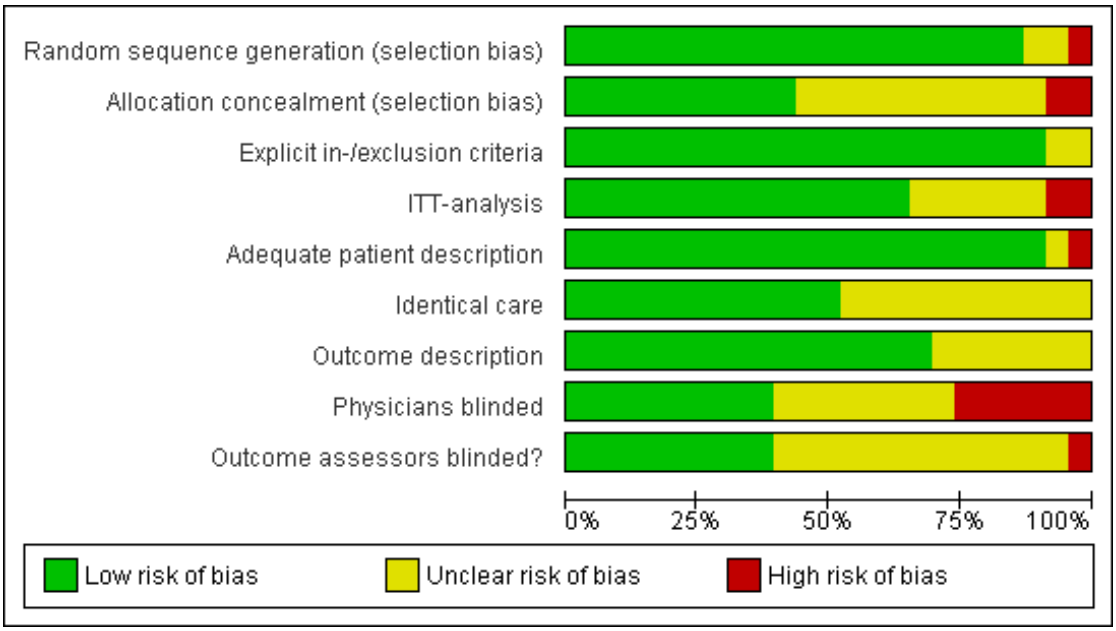


Figure 4. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Generally the risk of bias in the included studies was moderate to low. Random sequence generation was reported in all but three studies (Mathur 2007; Patel 2010; Seguin 2002). Allocation concealment was appropriate in 10 studies (Annane 2007; Boccara 2003; Choong 2009; De Backer 2010; Lauzier 2006; Malay 1999; Morelli 2008b; Myburgh 2008; Russell 2008; Seguin 2006) and not appropriate in two studies (Yildizdas 2008; Patel 2010). All but two studies described inclusion and exclusion criteria explicitly (Boccara 2003; Ruokonen 1993). All but eight studies presented intention-to-treat analyses; for six studies this item was unclear (Boccara 2003; Levy 1997; Malay 1999; Martin 1993; Ruokonen 1993; Seguin 2002) and for two studies this was not fulfilled (Luckner 2006; Morelli 2008a). Patients were adequately described in all but two studies (Luckner 2006; Ruokonen 1993). From the available information identical care for intervention group and control group could be assumed for 12 studies (Albanese 2005; Annane 2007; Choong 2009; De Backer 2010; Marik 1994; Mathur 2007; Morelli 2008b; Morelli 2009; Russell 2008; Seguin 2002; Seguin 2006; Patel 2010). An appropriate outcome description was present in 16 studies; for the remaining studies this was unclear (Albanese 2005; Lauzier 2006; Mathur 2007; Morelli 2008a; Morelli 2008b; Ruokonen 1993; Seguin 2002). Treating personnel were blinded in nine studies (Annane 2007; Choong 2009; De Backer 2010; Malay 1999; Martin 1993; Mathur 2007; Morelli 2008b; Myburgh 2008; Russell 2008). In the same nine studies outcome assessors were blinded too.

Effects of interventions

See: **Summary of findings for the main comparison** Norepinephrine compared to dopamine for hypotensive shock

In total, six vasopressors were compared in several combinations and directions (Figure 2). We have therefore organized our comparisons to present each vasopressor against all comparators in a separate analysis per outcome. Vasopressors that were used in both study arms were considered as constant between groups and were generally not explicitly described in the analyses. For studies with more than two study arms we used each comparison separately. We refrained from overall summary effects within the analyses because of considerable clinical heterogeneity due to major differences in comparators and additionally, where applicable, to avoid a unit of analysis error.

A) Mortality

Mortality was assessed in all included studies. If mortality was assessed at several time points in a study we used data from the latest follow-up time. Mortality was assessed at an undetermined time point in Boccara 2003, Levy 1997, Marik 1994, Mathur 2007, Seguin 2002, and Ruokonen 1993.

- Norepinephrine was compared to dopamine, epinephrine, terlipressin, vasopressin, phenylephrine, and norepinephrine + terlipressin + dobutamine (Analysis 1.1). In addition Morelli 2009 compared norepinephrine to norepinephrine plus vasopressin and norepinephrine to norepinephrine plus terlipressin and found no difference for both comparisons (RR 1.25, 95% CI 0.69 to 2.26; and RR 1.43, 95% CI 0.75 to 2.70). Overall 1359 deaths were observed in 2593 patients. Studies were performed in patients with septic shock (Albanese 2005; Lauzier 2006; Levy 1997; Marik 1994; Martin 1993; Mathur 2007; Morelli 2008a; Morelli 2008b; Morelli 2009; Patel 2010; Ruokonen 1993; Russell 2008; Seguin 2002; Seguin 2006), in critically ill patients (De Backer 2010; Myburgh 2008), in patients with refractory hypotension after anaesthesia (Boccara 2003), and in adult post-operative patients (Luckner 2006). In none of the comparisons a significant difference was found.

-Epinephrine was compared to norepinephrine, norepinephrine + dobutamine, and norepinephrine + dopexamine (Analysis 2.1). Overall 289 deaths were observed in 673 patients. Studies were performed in patients with septic shock (Annane 2007; Levy 1997; Seguin 2002; Seguin 2006) and in critically ill patients (Myburgh 2008). In none of the comparisons a significant difference was found.

-Vasopressin was compared to placebo, terlipressin, and norepinephrine (Analysis 3.1). In the comparisons described as 'versus placebo' two studies actually used a placebo (Choong 2009; Malay 1999), in two studies (Dünser 2003; Morelli 2009) fixed dose vasopressin + variable dose norepinephrine was compared to variable dose norepinephrine. Overall 442 deaths were observed in 999 patients. Studies were performed in patients with septic shock (Dünser 2003; Lauzier 2006; Malay 1999; Morelli 2009; Russell 2008), adult post-operative patients (Luckner 2006), and paediatric vasodilatory shock (Choong 2009). In none of the comparisons a significant difference was found.

-Terlipressin was compared to placebo, norepinephrine, and vasopressin (Analysis 4.1). In the comparisons described as 'versus placebo' one study actually used a placebo (Yildizdas 2008), in two studies (Morelli 2008a; Morelli 2009) fixed dose terlipressin + variable dose norepinephrine was compared to variable dose norepinephrine. Overall 107 deaths were observed in 197 patients. Studies were performed in patients with septic shock (Albanese 2005; Morelli 2008a; Morelli 2009), in catecholamine-resistant shock in children (Yildizdas 2008), and in patients with refractory hypotension after anaesthesia (Boccara 2003). In none of the comparisons a significant difference was found.

-Dopamine was compared to norepinephrine (Analysis 5.1). Overall 838 deaths were observed in 1400 patients. Studies were performed in patients with septic shock (Marik 1994; Martin 1993; Mathur 2007, Patel 2010; Ruokonen 1993) and in patients with several causes of shock (De Backer 2010). In none of the comparisons a significant difference was found.

-Phenylephrine was compared to norepinephrine in patients with septic shock (Morelli 2008b). Out of 16 patients 10 died in the phenylephrine infusion group compared to 9 of 16 patients in the norepinephrine group (RR 1.11, 95% CI 0.63 to 1.97).

B) Morbidity

Morbidity was assessed as length of ICU stay; length of hospital stay; duration of vasopressor treatment; duration of mechanical ventilation; and renal failure (as defined by authors: such as oliguria or renal replacement therapy). Renal outcomes are presented separately in Table 1.

-Norepinephrine was compared to dopamine, vasopressin, phenylephrine, and norepinephrine + terlipressin + dobutamine in terms of ICU length of stay (Analysis 1.2). All studies included patients with septic shock. There was no difference in ICU and hospital length of stay (Analysis 1.2 and Analysis 1.3). Additionally Russell 2008 compared norepinephrine versus vasopressin and found no significant difference in hospital length of stay (difference 1.00 day, 95% CI -3.01 to 5.01). Further there was no significant difference in days alive free of mechanical ventilation (6, interquartile range (IQR) 0 to 20 versus 9, IQR 0- to 20; P = 0.24), vasopressor use (17, IQR 0 to 24 versus 19, IQR 0 to 24; P = 0.61). Myburgh 2008 compared norepinephrine with epinephrine and found no difference in the number of vasopressor-free days (25 days, IQR 14 to 27 versus 26 days, IQR 19 to 27; P = 0.31). De Backer 2010 compared norepinephrine to dopamine and found no difference in days free of mechanical ventilation within 28 days (9.5 ± 11.4 days versus 8.5 ± 11.2 days; P = 0.13). There was a small difference in days free of any vasopressor therapy within 28 days (14.2 ± 12.3 days versus 12.6 ± 12.5 days; P = 0.007). The largest study by De Backer 2010 and a smaller study by Patel 2010 compared dopamine versus norepinephrine and found a significant difference in arrhythmia (Analysis 1.4), including mostly sinus tachycardia (Patel 2010): 25% versus 6%; atrial fibrillation: 21% versus 11% (De Backer 2010), 13% versus 3% (Patel 2010); ventricular tachycardia (De Backer 2010): 2.4% versus 1.0%; and ventricular fibrillation (De Backer 2010): 1.2% versus 0.5%. Boccara 2003 compared noradrenaline to terlipressin and found no difference in length of hospital stay (5 days, IQR 4 to 7 versus 5 days, IQR 4 to 7).

-Epinephrine was compared to norepinephrine + dobutamine in terms of ICU length of stay in patients with septic shock (Annane 2007). No significant difference in ICU length of stay was found (difference 1.00 day, 95% CI -3.01 to 5.01). In another study (Annane 2007) the number of vasopressor-free days until day 90 was reported as a median 53 days (IQR 0 to 86) in the epinephrine

group and 66 days (IQR 6 to 86) in the norepinephrine + dobutamine group (P = 0.18). In the same study, duration of vasopressor support was presented as a Kaplan Meier plot (logrank test P = 0.09). Myburgh 2008 compared epinephrine with norepinephrine and found no difference in the number of vasopressor-free days (26 days, IQR 19 to 27 versus 25 days, IQR 14 to 27; P = 0.31).
-Vasopressin was compared to placebo, terlipressin, and norepinephrine in terms of ICU length of stay (Analysis 3.2). Studies were performed in patients with septic shock (Morelli 2009; Russell 2008) and paediatric vasodilatory shock (Choong 2009). In none of the comparisons a significant difference was found. Vasopressin was compared to norepinephrine in terms of hospital length of stay in one study (Russell 2008) and no significant difference was found (difference 1.00 day, 95% CI -3.01 to 5.01). Further there was no significant difference in days alive free of mechanical ventilation (9, IQR 0 to 20 versus 6, IQR 0 to 20; P = 0.24), vasopressor use (19, IQR 0 to 24 versus 17, IQR 0 to 24; P = 0.61). Choong 2009 compared vasopressin to placebo and found no difference in time to vasopressors discontinuation (50 hours, IQR 30 to 219 versus 47, IQR 26 to 87; P = 0.85), and mechanical ventilation-free days until day 30 (17 days, IQR 0 to 24 versus 23 days, IQR 13 to 26; P = 0.15).
-Terlipressin was compared to placebo and vasopressin in terms of ICU length of stay (Analysis 4.2). In the comparisons described as 'versus placebo' one study actually used a placebo (Yildizdas 2008), in two studies (Morelli 2008a; Morelli 2009) fixed dose terlipressin + variable dose norepinephrine was compared to variable dose norepinephrine. Studies were performed in patients with septic shock (Morelli 2008a; Morelli 2009) and in catecholamine-resistant shock in children (Yildizdas 2008). In none of these comparisons a significant difference was found. One study also assessed duration of mechanical ventilation (Yildizdas 2008). In the terlipressin group the mean duration was 4.4 ± 1.4 days versus 4.8 ± 1.5 days in the control group (-0.40 days, 95% CI -1.15 to 0.35). Boccara 2003 compared terlipressin to noradrenaline and found no difference in length of hospital stay (5 days, IQR 4 to 7 versus 5 days, IQR 4 to 7).
-Dopamine was compared to norepinephrine. De Backer 2010 and Patel 2010 compared dopamine to norepinephrine and found no difference in ICU and hospital length of stay (Analysis 5.2 and Analysis 5.3). Further De Backer 2010 assessed days free of mechanical ventilation within 28 days (8.5 ± 11.2 days versus 9.5 ± 11.4 days; P = 0.13). There was a small difference in days free of any vasopressor therapy within 28 days (12.6 ± 12.5 days versus 14.2 ± 12.3 days; P = 0.007). The largest study by De Backer 2010 and a smaller study by Patel 2010 compared dopamine versus norepinephrine and found a significant difference in arrhythmias (Analysis 5.4), including mostly sinus tachycardia (Patel 2010): 25% versus 6%; atrial fibrillation: 21% versus 11% (De Backer 2010), 13% versus 3% (Patel 2010); ventricular tachycardia (De Backer 2010): 2.4% versus 1.0%; and ventricular fibrillation (De Backer 2010): 1.2% versus 0.5%.
-Phenylephrine was compared to norepinephrine in patients with septic shock (Morelli 2008b). Mean length of ICU stay was 16 ± 13 versus 16 ± 10 days (difference 0.00 days, 95% CI -8.27 to 8.27).

C) Health-related quality of life

In none of the studies health-related quality of life was assessed.

D) Anxiety and depression

In none of the studies measures of anxiety and depression were assessed.

Sensitivity analysis

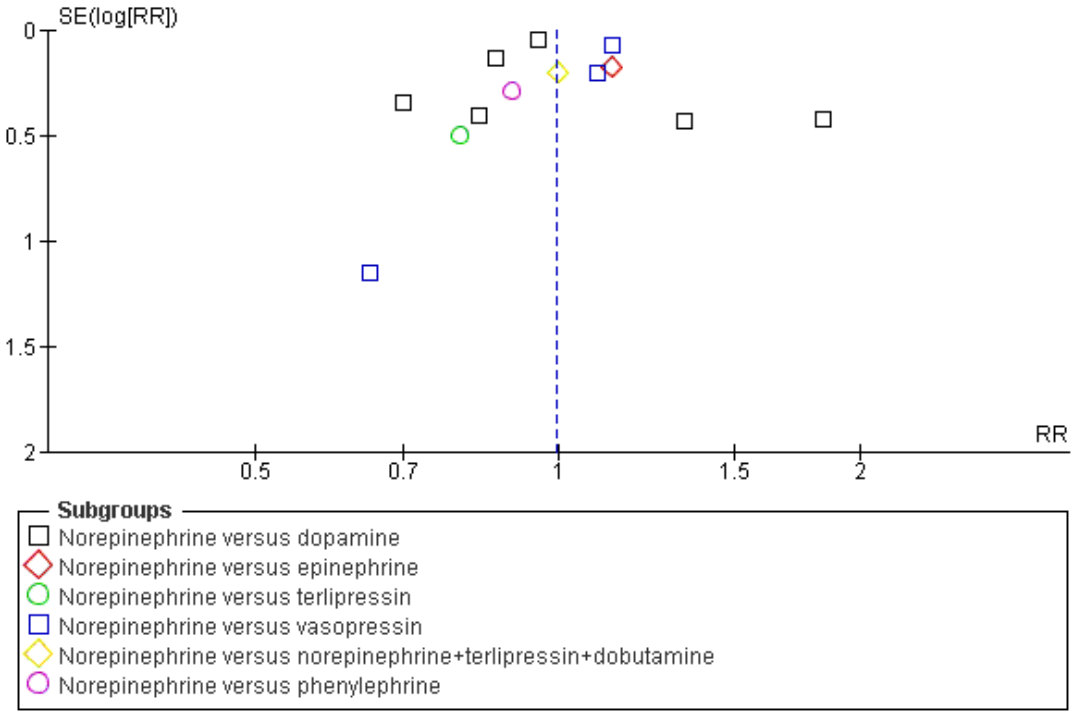
We classified 10 studies as being at low risk of bias for the primary outcome, mortality (Annane 2007; Boccara 2003; Choong 2009; De Backer 2010; Lauzier 2006; Malay 1999; Morelli 2008b; Myburgh 2008; Russell 2008; Seguin 2006); for the remaining studies at least some risk of bias could not be excluded due to the lack of information or if we had an indication of high risk of bias due to the study design.
In none of the comparisons within-study bias risk seemed to affect the overall estimates (Analysis 6.1; Analysis 7.1; Analysis 8.1; Analysis 9.1; Analysis 10.1).
In four comparisons we included heterogenous mortality outcomes (Analysis 1.1; Analysis 2.1; Analysis 3.1; Analysis 5.1).
For the comparison of norepinephrine versus dopamine (Analysis 1.1; Analysis 5.1) the effect of using the latest mortality outcome gave a RR of 0.95 (95% CI 0.87 to 1.03) as compared to a RR of 0.92 (95% CI 0.85 to 1.01) if acknowledging 28-day mortality, hospital mortality and undetermined periods.
For the comparison of epinephrine versus norepinephrine + dobutamine (Analysis 2.1) the effect from using the latest mortality outcome was RR 1.04 (95% CI 0.85 to 1.26) as compared to a RR of 1.19 (95% CI 0.92 to 1.54) if acknowledging 28-day mortality and undetermined periods.
For the comparison of vasopressin versus placebo (Analysis 3.1) the effect from using the latest mortality outcome was an RR of 1.00 (95% CI 0.60 to 1.66) as compared to RR 0.90 (95% CI 0.06 to 12.64) if restricted to studies reporting 24-hour mortality (Dünser 2003; Malay 1999) and RR of 1.05 (95% CI 0.63 to 1.75) restricted to studies reporting 30-day or ICU mortality (Choong 2009; Dünser 2003; Morelli 2009).
For the comparison of norepinephrine versus vasopressin (Analysis 1.1; Analysis 3.1) the effect of using the latest mortality outcome was an RR of 1.12 (95% CI 0.98 to 1.29) as compared to RR of 1.10 (95% CI 0.94 to 1.30) if acknowledging 28-day mortality and ICU mortality.

In summary the estimates remained virtually unchanged if definitions of mortality were changed or studies with different mortality definitions were compared.

Reporting bias

Funnel plots of the primary outcome of all comparisons did not suggest major asymmetry. We present the funnel plot for comparison 1.1 (Figure 5). We had too few studies per comparison to sensibly perform a formal test for funnel plot asymmetry. Overall, however, reporting bias does not seem to be a major problem in this review and in particular does not explain the results.

Figure 5. Funnel plot of comparison: 1 norepinephrine, outcome: 1.1 mortality.



DISCUSSION

Summary of main results

We found 23 studies fulfilling our inclusion criteria. Overall 3212 patients with 1629 mortality outcomes were analysed. Information comes mainly from five studies (Annane 2007; De Backer 2010; Myburgh 2008; Patel 2010; Russell 2008). These five studies reported on 2658 patients (82% of total) and 1402 mortality outcomes (85% of total mortality outcomes). Six different vasopressors, alone or in combination with dobutamine or dopexam-

ine, were compared in 11 different combinations.

All 23 studies reported mortality outcomes. Length of stay was reported in 10 studies (Annane 2007; Choong 2009; Boccara 2003; De Backer 2010; Morelli 2008a; Morelli 2008b; Morelli 2009; Patel 2010; Russell 2008; Yildizdas 2008). Other morbidity outcomes were reported in a variable and heterogeneous way. No data were available on quality of life or anxiety and depression outcomes.

In summary there was no difference in mortality outcome in any of the studies comparing different vasopressors or combinations. In particular, for the comparison between dopamine and norepinephrine, which included most patients, there was no difference in mortality (Summary of findings for the main comparison).

The two studies De Backer 2010 and Patel 2010 comparing dopamine versus norepinephrine found a higher risk of arrhythmia in the dopamine group (Analysis 1.4). In total 347 arrhythmia episodes were documented in 1891 patients (Summary of findings for the main comparison). Other adverse events like new infectious episodes, skin ischaemias and arterial occlusion did not differ between the intervention groups.

We found no difference in other relevant morbidity outcomes within any of the comparisons. This finding was consistent among the few large studies as well as in studies with different levels of within-study bias risk.

In our review we had no pre-defined subgroup analyses, therefore we cannot make inferences about whether the effect of vasopressors differs across populations with different causes of shock. However in one of the large trials comparing norepinephrine with dopamine (De Backer 2010) a pre-defined subgroup analysis according to shock type revealed a beneficial effect on 28-day mortality in patients with cardiogenic shock if treated with norepinephrine. However, although the subgroups were pre-defined, randomization was not stratified and moreover the test for subgroup differences (P = 0.87) suggests that this subgroup effect can be explained by chance alone.

Probably the choice of vasopressor in patients with shock does not influence outcome, rather than any vasoactive effect per se. There is no evidence that any of the investigated vasopressors are clearly superior over others.

Seven studies can be regarded as placebo controlled add-on studies. Morelli 2008a and Morelli 2009 compared norepinephrine versus norepinephrine plus terlipressin and dobutamine, which might be seen as an add-on therapy of terlipressin plus dobutamine versus no extra vasopressor in patients receiving norepinephrine. No difference in mortality or length of stay was reported. Likewise Morelli 2009 included a vasopressin + norepinephrine arm compared to norepinephrine alone. This add-on vasopressin therapy did not have an effect. Yildizdas 2008 compared terlipressin with placebo in paediatric septic shock patients who did not respond to fluid resuscitation and high dose catecholamines and found no difference in mortality but a significant reduction of length of stay. This effect was no longer found if data were combined with the Morelli 2008a study. Malay 1999 studied vasopressin versus placebo in patients with septic shock who were already on catecholamines; Dünser 2003 compared norepinephrine versus norepinephrine plus vasopressin; and Choong 2009 compared vasopressin with placebo in paediatric vasodilatory shock after volume resuscitation under catecholamines. In none of these comparisons could a significant effect on mortality or morbidity be found. This result must not be interpreted as no effect of vasopressors versus placebo in terms of no absolute effect of vasopressors. Moreover, these results indicate that in patients requiring massive vasoactive support additional vasopressors have no major effect. It is noteworthy that this evidence on placebo comparisons comes from a few small studies only and must therefore be interpreted with caution.

Overall completeness and applicability of evidence

Even though 23 studies met inclusion criteria, a large number of comparisons were necessary. Accordingly the actual number of studies per comparison, as well as the number of patients in the majority of studies, was small. Therefore some of the comparisons resulted in under-powered effects. Also no subgroup analyses could be performed to investigate potential sources of heterogeneity.

Quality of the evidence

Only four studies (Annane 2007; Choong 2009; De Backer 2010; Russell 2008) fulfilled all criteria in the risk of bias assessment (Figure 3). However, considering only bias items that assumably strongly influence the effects, 11 studies were classified as low risk of bias studies. Small study bias usually tends to overestimate a true effect but on the other hand, in the case of a null effect, the limited power to exclude the absence of an effect may matter more. Therefore many of the comparisons must be interpreted with caution. In summary, however, within study bias does not seem to explain our findings.

There were too few studies to examine reporting bias in detail. However, taking into account that here was no obvious asymmetry in the funnel plots and considering the comprehensive search strategy using several electronic databases without restrictions, searching trial registers, and contacting experts in the field, reporting bias may not be a major source of distortion.

Agreements and disagreements with other studies or reviews

Several cohort studies have come to different conclusions about the effects of different vasopressors.

In a university hospital-based cohort study Martin 2000 studied 97 patients with septic shock. Patients were treated with a mix of catecholamines, mainly comparing high dose dopamine versus norepinephrine in a non-randomized design. Norepinephrine in

comparison to other vasopressors was significantly associated with a better outcome. This effect was adjusted for many potential confounders but still treatment allocation may have been poorly controlled.

In a multicentre cohort study in 198 European ICUs (Sakr 2006) (SOAP study) the effect of norepinephrine, dopamine, dobutamine and epinephrine was assessed in 1058 patients with shock. Epinephrine and in particular dopamine were found to worsen the outcome. In a smaller subset of patients with septic shock epinephrine was associated with a poor outcome and dopamine showed a trend towards a poor outcome. These data come from a very heterogenous sample and, despite extensive multivariable adjustments, residual confounding may explain the effect.

Povoa 2009 (SACiUCI study) reported a multicentre cohort study from 17 Portuguese ICUs, where 897 patients with community acquired sepsis were studied. In this population norepinephrine and dobutamine were associated with worse outcomes, whereas dopamine was a predictor for a better outcome. In particular when comparing patients who received dopamine only to patients who received norepinephrine only, the latter had a significantly worse outcome. This effect was adjusted for age, sex, admission diagnosis, SAPS II, SOFA score, and inotropic support but residual confounding cannot reasonably be excluded. Specifically, there was a concern that the choice of vasopressors was driven by disease severity, simply that sicker patients were more likely to receive norepinephrine than dopamine.

In contrast to the observational evidence recent reviews (Beale 2004; Holmes 2009; Leone 2008) are conservative in stating differences between several vasopressors, where norepinephrine and dopamine are mostly considered to be the vasopressors of choice in patients with shock.

AUTHORS' CONCLUSIONS

Implications for practice

Vasopressor therapy is an important part of haemodynamic support in patients with shock. A number of different vasopressors are available, and for six vasopressors the effect was assessed in randomised controlled trials. The strength of evidence differs greatly between several comparisons but, in summary, there is not sufficient evidence to prove that any of the vasopressors in the assessed doses are superior over others in terms of mortality. Dopamine appears to increase the risk for arrhythmia. The most data are available for norepinephrine. The choice of the specific vasopressor may therefore be individualized and left to the discretion of the treating physicians. Factors like experience, physiological effects (for example heart rate, intrinsic inotropic effects, splanchnic perfusion), drug interaction with other therapeutics, availability, and cost should be considered.

Implications for research

A large number of randomised trials are available now, but still the sample size population for specific comparisons is small. We hope that our review encourages the scientific community to design future studies in a way that outcomes which matter to patients, such as survival, but also long-term health-related quality of life, can be evaluated. Such studies ideally would be large, multicentre trials following simple and pragmatic study protocols. Such studies are also needed to evaluate whether surrogate endpoints, such as filling pressures, are of any clinical use and, if so, how they should be used. Maybe a more suitable approach to the treatment of shock is not the choice of a specific vasopressor but a goal directed approach (Rivers 2001). To the best of our knowledge this has not yet been assessed in a systematic way.

As with all Cochrane Reviews, this review will be updated regularly. Hopefully answers to the questions under study will be found over the next few years.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Albanese 2005

Methods	Single centre, open label randomized controlled study in a tertiary care university hospital
Participants	Adult patients with hyperdynamic septic shock after fluid resuscitation Mean age=66yrs, 35% female APACHE II score = 28.5 (N=20)
Interventions	Norepinephrine started with 0.3mcg/kg and increased by 0.3mcg/kg every 4 min until MAP 65-75mmHg versus Terlipressin 1mg bolus, followed by second bolus of 1mg if MAP<65mmHg
Outcomes	In-hospital mortality, renal function (urine flow, creatinine clearance up to 8 hours - presented in a graph only, no numbers provided), haemodynamic parameters, blood gas, lactate at 6 hours For the mortality analysis we used data on in-hospital mortality
Notes	No explicit primary outcome defined

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated randomization schedule
Allocation concealment (selection bias)	Unclear risk	Unclear if allocation was concealed
Explicit in-/exclusion criteria	Low risk	
ITT-analysis	Low risk	
Adequate patient description	Low risk	
Identical care	Low risk	Only for 6 hours
Outcome description	Unclear risk	Implicitly described
Physicians blinded	High risk	Open label
Outcome assessors blinded?	Unclear risk	Not reported

Annane 2007

Methods	Multicentre versus double-blinded randomized controlled trial in 19 ICUs (CATS study)
Participants	Adult patients with septic shock (authors' definition) Mean age=63, 39% female SAPS II score=53, SOFA score=11 (N=330)
Interventions	Epinephrine infusion 0.2mcg/kg/min (N=161) versus Norepinephrine infusion 0.2mcg/kg/min and dobutamine 5mcg/kg/min (N=169) Both adjusted according to MAP, pulmonary arterial wedge pressure, cardiac index and response to fluid challenge
Outcomes	28-day mortality (primary), 7,14,90 day- ICU-, and hospital-mortality, duration of vasopressor therapy, time to haemodynamic success, adverse events For the mortality analysis we used data on 90-day mortality.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer randomization sequence, stratified by centre, 1:1, blocks of 6
Allocation concealment (selection bias)	Low risk	Double blind, double dummy
Explicit in-/exclusion criteria	Low risk	
ITT-analysis	Low risk	
Adequate patient description	Low risk	
Identical care	Low risk	
Outcome description	Low risk	
Physicians blinded	Low risk	
Outcome assessors blinded?	Low risk	

Boccara 2003

Methods	Single centre; university hospital
Participants	Adult patients scheduled for carotid endarterectomy and refractory perioperative hypotension (N=20)

Boccara 2003 (*Continued*)

Interventions	Goal directed (terlipressin infused in 1 mg intravenous boluses up to 3 mg versus norepinephrine (50 mcg/ml) initial rate of 10 ml/h, incrementally by 2 ml/h)
Outcomes	Death, stroke, myocardial ischemias; renal failure; hospital stay For the mortality analysis we used data on undetermined mortality
Notes	It is unclear when patients died (peri-operative or in-hospital)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	Envelopes
Explicit in-/exclusion criteria	Low risk	
ITT-analysis	Unclear risk	Not reported
Adequate patient description	Low risk	
Identical care	Unclear risk	Not reported
Outcome description	Low risk	
Physicians blinded	Unclear risk	Not reported
Outcome assessors blinded?	Unclear risk	Not reported

Choong 2009

Methods	Multicentre versus double-blind randomized controlled trial, university hospital PCCUs (Paediatric Critical Care Unit)
Participants	Pediatric patients with vasodilatory shock (authors' definition) Mean age= 10yrs, 48% female PRISM III score=13, MODS score=3; PELOD score=10.5 (N=69)
Interventions	Vasopressin infusion 0.0005U/kg/min, increased every 5 min up to 0.002U/kg/min (max. dose 0.05U/min) to maintain target MAP for age versus Saline placebo

Choong 2009 (*Continued*)

Outcomes	Time to vasopressors discontinuation (primary), 30 day mortality, organ dysfunction, urine output, haemodynamics, vasopressor dose, vasopressin serum levels, vasopressor free days until day 30, organ failure free days until day 30, mechanical ventilation free days until day 30, length of PCCU stay, adverse events For the mortality analysis we used data on 30 day mortality.
Notes	All other vasopressors were open label and up to the treating physician's discretion

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer randomization sequence, 1:1, stratified by centre, permuted blocks within strata
Allocation concealment (selection bias)	Low risk	Central telephone-based randomization
Explicit in-/exclusion criteria	Low risk	
ITT-analysis	Low risk	
Adequate patient description	Low risk	
Identical care	Low risk	
Outcome description	Low risk	
Physicians blinded	Low risk	Identical syringes
Outcome assessors blinded?	Low risk	

De Backer 2010

Methods	Multicentre versus randomized blinded controlled trial, 8 university hospitals (SOAP II study)
Participants	Adult patients with shock (authors´ definition) Mean age=68yrs, 57%female APACHE II score = 20, SOFA score =9 (N=1679)
Interventions	Dopamine incrementally increased dose by 2 mcg/kg/min (max 20 mcg) versus Norepinephrine incrementally increased dose by 0.02 mcg/kg/min (max 0.19 mcg)
Outcomes	28 day mortality (primary), 6 months-12 months- ICU-, and hospital-mortality, length of stay ICU, length of stay in hospital, number of days without need of organ support

De Backer 2010 (*Continued*)

	(vasopressors, ventilators, renal replacement therapy), time to reach MAP>65 mmHg, adverse events (arrhythmia, myocardial necrosis, skin necrosis, ischemias in limbs or distal extremities, secondary infections) For the mortality analysis we used data on 12 months mortality
Notes	If patients hypotensive after max dosage, open label norepinephrine

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated permuted blocks of 6-10, stratified to centres
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes
Explicit in-/exclusion criteria	Low risk	
ITT-analysis	Low risk	
Adequate patient description	Low risk	
Identical care	Low risk	
Outcome description	Low risk	
Physicians blinded	Low risk	Identical syringes
Outcome assessors blinded?	Low risk	

Dünser 2003

Methods	Single centre; university hospital
Participants	Adult surgical and medical patients with vasodilatory shock (N=48)
Interventions	Fixed dose of vasopressin (4 U/h) plus goal directed norepinephrine (MAP>=70mmHg) versus goal directed norepinephrine (MAP≥70mmHg)
Outcomes	24h mortality; 48h mortality; ICU mortality; length of ICU stay For the mortality analysis we used data on ICU mortality.
Notes	Patients were allowed to receive vasopressin in the norepinephrine group if "failed"

Risk of bias

Dünser 2003 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	'patients were randomly assigned into and AVP group and an NE group'
Allocation concealment (selection bias)	Unclear risk	Not reported
Explicit in-/exclusion criteria	Low risk	Implicitly described
ITT-analysis	Low risk	
Adequate patient description	Low risk	
Identical care	Unclear risk	Not reported
Outcome description	Low risk	Implicitly described
Physicians blinded	Unclear risk	Not reported
Outcome assessors blinded?	Unclear risk	Not reported

Lauzier 2006

Methods	Multicentre versus open label randomized controlled at university hospitals
Participants	Adult patients with septic shock (ACCP/SCCM Definition ACCP/SCCM 1992) mean age=55yrs, 39% female Mean APACHE II score = 23.15, mod. SOFA score =8.9 (N=23)
Interventions	Arginine-vasopression (AVP) infusion 0.04 to 0.2U/min (N=13), at doses >0.2U/min rescue therapy with norepinephrine or additional AVP allowed versus Norepinephrine 0.1-2.8mcg/kg/min (N=10), at doses >2.8mcg/kg/min rescue therapy with norepinephrine or additional AVP allowed both for 48 hours to achieve MAP>70mmHg
Outcomes	Hemodynamic parameters, organ dysfunction, kreatinine clearance based on two hour collection 24h after randomisation, ICU mortality For the mortality analysis we used data on ICU mortality.
Notes	Dobutamine allowed if cardiac index < 3l/min/m^2

Risk of bias

Bias	Authors' judgement	Support for judgement

Lauzier 2006 (*Continued*)

Random sequence generation (selection bias)	Low risk	Computer generated block randomisation list, stratified by centre
Allocation concealment (selection bias)	Low risk	Sequentially numbered opaque sealed envelopes
Explicit in-/exclusion criteria	Low risk	
ITT-analysis	Low risk	
Adequate patient description	Low risk	
Identical care	Unclear risk	Groups differ in steroid therapy and baseline vasopressor support
Outcome description	Unclear risk	Only implicitly described, no primary outcome
Physicians blinded	High risk	Open label
Outcome assessors blinded?	High risk	

Levy 1997

Methods	Single centre; university hospital
Participants	Adult surgical and medical patients with septic shock (N=30)
Interventions	Goal directed epinephrine versus norepinephrine + fixed dobutamine (5 mcg/kg/min)
Outcomes	Survival (not further clarified); haemodynamics, tonometry For the mortality analysis we used data undetermined mortality
Notes	It is unclear when patients died

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	'according to a randomisation code'
Allocation concealment (selection bias)	Unclear risk	Not reported
Explicit in-/exclusion criteria	Low risk	Explicitly described

Levy 1997 (*Continued*)

ITT-analysis	Unclear risk	Not reported
Adequate patient description	Low risk	
Identical care	Unclear risk	Not reported
Outcome description	Low risk	Implicit
Physicians blinded	Unclear risk	Not reported
Outcome assessors blinded?	Unclear risk	Not reported

Luckner 2006

Methods	Single centre randomized controlled trial, university hospital
Participants	Adult postoperative patients (major surgery or cardiac surgery) with MAP<65mmHg and norepinephrine support>0.5mcg/kg/min Mean age=69yrs, 39% female Modified Goris score=12.3 (N=18)
Interventions	Arginine vasopressin-infusion 4U/h and norepinephrine-infusion to achieve and maintain MAP>65mmHg versus Norepinephrine-infusion to achieve and maintain MAP>65mmHg
Outcomes	Cutaneous vascular reactivity and flow motion at 1 hour (primary), haemodynamics, metabolic variables, ICU mortality For the mortality analysis we used data on ICU mortality.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random number generating computer program
Allocation concealment (selection bias)	Unclear risk	No sufficient detail reported
Explicit in-/exclusion criteria	Unclear risk	No sufficient detail reported
ITT-analysis	High risk	The analysis was performed 'as treated'
Adequate patient description	High risk	No sufficient detail reported

Luckner 2006 (*Continued*)

Identical care	Unclear risk	No sufficient detail reported, in particular on catecholamine therapy
Outcome description	Low risk	
Physicians blinded	High risk	
Outcome assessors blinded?	Unclear risk	Not reported

Malay 1999

Methods	Multicentre
Participants	Adult surgical and trauma patients with septic shock (N=10)
Interventions	Fixed dose of vasopressin (0.04 U/min) versus placebo
Outcomes	24h mortality For the mortality analysis we used data on 24h mortality.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated list
Allocation concealment (selection bias)	Low risk	Pharmacy controlled
Explicit in-/exclusion criteria	Low risk	
ITT-analysis	Unclear risk	Not reported
Adequate patient description	Low risk	
Identical care	Unclear risk	Not reported
Outcome description	Low risk	
Physicians blinded	Low risk	
Outcome assessors blinded?	Low risk	

Marik 1994

Methods	Single centre; university hospital	
Participants	Adult patients with septic shock; unclear whether medical or surgical (N=20)	
Interventions	Goal directed norepinephrine (to achieve a MAP>75mmHg) versus dopamine ("... and in case of dopamine … to keep pulse rate <150/min")	
Outcomes	Death For the mortality analysis we used data on undetermined mortality	
Notes	It is unclear when patients died	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random number generator
Allocation concealment (selection bias)	Unclear risk	Not reported
Explicit in-/exclusion criteria	Low risk	
ITT-analysis	Low risk	
Adequate patient description	Low risk	
Identical care	Low risk	
Outcome description	Low risk	Implicit
Physicians blinded	Unclear risk	Not reported
Outcome assessors blinded?	Unclear risk	Not reported

Martin 1993

Methods	Single centre; university hospital
Participants	Adult patients with septic shock; unclear whether medical or surgical (N=32)
Interventions	Goal directed dopamine (max 25 mcg/kg/min; if goal not reached, addition of norepinephrine) versus norepinephrine (max 5 mcg/kg/min; if goal not reached addition of dopamine)

Martin 1993 (*Continued*)

Outcomes	Hospital mortality For the mortality analysis we used data on hospital mortality
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	'according to the randomisation code'
Allocation concealment (selection bias)	Unclear risk	Not reported in sufficient detail
Explicit in-/exclusion criteria	Low risk	
ITT-analysis	Unclear risk	Not reported
Adequate patient description	Low risk	
Identical care	Unclear risk	Not reported
Outcome description	Low risk	
Physicians blinded	Low risk	
Outcome assessors blinded?	Low risk	

Mathur 2007

Methods	Single centre, randomized controlled trial; university hospital
Participants	Adult patients with septic shock (authors' definition) Mean age=54yrs, 36% female APACHE II score=25 (N=50)
Interventions	Dopamine-infusion 10mcg/kg/min, increase by 2.5mcg/kg/min every 15 min (up to 25mcg/kg/min) to achieve goal versus Norepinephrine-infusion 0.5mcg/kg/min, increase by 0.25mcg/kg/min every 15 min (up to 2.5mcg/kg/min) to achieve goal Goal (to be achieved and maintained for 6 hours): SBP>90mmHg and SVRI>1100dynes*s/cm5*m2 and CI>4l/min/m2 and IDO2>550ml/min/m2 and IVO2>150ml/min/m2
Outcomes	Haemodynamic parameters, haemodynamic response (goal achieved), urine output, mortality

Mathur 2007 (*Continued*)

	For the mortality analysis we used data on undetermined mortality
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'were randomly allocated into two groups'
Allocation concealment (selection bias)	Unclear risk	Not reported
Explicit in-/exclusion criteria	Low risk	
ITT-analysis	Low risk	
Adequate patient description	Low risk	
Identical care	Low risk	
Outcome description	Unclear risk	Implicitly described
Physicians blinded	Low risk	
Outcome assessors blinded?	Low risk	

Morelli 2008a

Methods	Single centre open label randomized controlled pilot study, university hospital
Participants	Adult patients with septic shock (ACCP/SCCM 1992 ACCP/SCCM 1992) and norepinephrine support >0.9mcg/kg/min Mean age=66yrs, 27% female SAPS score=60 (N=59)
Interventions	1) Norepinephrine infusion incrementally to achieve MAP 65-75 versus 2) Terlipressin 1mg (bolus) and norepinephrine infusion to achieve MAP 65-75 versus 3) Terlipressin 1mg (bolus) and dobutamine infusion 3mcg/kg/min (increasing by 1-3mcg/kg/min up to 20mcg/kg/min to maintain mixed venous oxygen saturation at baseline) and norepinephrine infusion to achieve MAP 65-75 We used the comparisons 1 versus 2 and 1 versus 3, but not 2 versus 3, because this is virtually a comparison of dobutamine versus control. Dobutamine is not considered a vasopressor

Morelli 2008a (*Continued*)

Outcomes	Organ dysfunction, urine output two and four hours after study start, haemodynamics, vasopressor requirements, length of ICU stay, ICU mortality For the mortality analysis we used data on ICU mortality.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer based procedure reported
Allocation concealment (selection bias)	Unclear risk	No means to conceal the allocation is reported
Explicit in-/exclusion criteria	Low risk	
ITT-analysis	High risk	One patient with inappropriate noradrenaline dosing was excluded from the analysis
Adequate patient description	Low risk	
Identical care	Unclear risk	Not reported in sufficient detail
Outcome description	Unclear risk	Not reported in sufficient detail
Physicians blinded	High risk	
Outcome assessors blinded?	Unclear risk	Not reported

Morelli 2008b

Methods	Single centre double blind randomized controlled study, university hospital
Participants	Adult patients with septic shock (Surviving Sepsis Campaign 2008 criteria Dellinger 2008) Mean age=70yrs, 34% female Simplifies APACHE II score=56 (N=32)
Interventions	Norepinephrin infusion to achieve MAP 65-75mmHg versus Phenylephrine infusion to achieve MAP 65-75mmHg For both arms explicit dosing schemes are not reported.

Morelli 2008b (*Continued*)

Outcomes	Plasma disappearance rate of indocyanine green (PDR) and blood clearance of indocyanine green (CBI) (primary), haemodynamics, organ function, length of ICU stay, ICU mortality. Creatinine clearance and urine output are presented only graphically, P values are reported For the mortality analysis we used data on ICU mortality.
Notes	Noradrenaline dose at baseline was 0.8±0.7mcg/kg/min Dobutamine was added to achieve mixed venous oxygen saturation >64% if necessary

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer based procedure
Allocation concealment (selection bias)	Low risk	Double blind study drug
Explicit in-/exclusion criteria	Low risk	
ITT-analysis	Low risk	
Adequate patient description	Low risk	
Identical care	Low risk	
Outcome description	Unclear risk	Only primary outcome described in the methods
Physicians blinded	Low risk	
Outcome assessors blinded?	Low risk	

Morelli 2009

Methods	Single centre randomized controlled trial, university hospital
Participants	Adult patients with septic shock (Surviving Sepsis Campaign criteria 2008 Dellinger 2008) Mean age 66yrs, 27% female SAPS II score=60 (N=45)
Interventions	Terlipressin infusion 1.3mcg/kg/h versus Arginine vasopressin infusion 0.03U/min versus Norepinephrine infusion 15mcg/min

Morelli 2009 (*Continued*)

	For all groups open label norepinephrine was added to achieve MAP 65-75mmHg
Outcomes	Norepinephrine requirements (primary), haemodynamics, metabolic parameters, blood gas, cytokine levels, ICU mortality, length of ICU stay, adverse events, renal replacement therapy, creatinine clearance and urine output at 48hrs (data presented in a graph only, with intra-group comparisons) For the mortality analysis we used data on ICU mortality.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer based procedure
Allocation concealment (selection bias)	Unclear risk	No concealment procedure reported
Explicit in-/exclusion criteria	Low risk	
ITT-analysis	Low risk	
Adequate patient description	Low risk	
Identical care	Low risk	
Outcome description	Low risk	
Physicians blinded	Unclear risk	Not explicitly reported
Outcome assessors blinded?	Unclear risk	Not explicitly reported

Myburgh 2008

Methods	Multicenter versus double blind randomized controlled trial, four multidisciplinary university hospital ICUs
Participants	Adult ICU patients requiring vasopressors for any reason Mean age=60yrs, 39% female APACHE II score=22 (N=280)
Interventions	Switch from the vasopressor at inclusion to either Epinephrine (no dosing scheme reported) or Norepinephrine (no dosing scheme reported) To achieve MAP>70mmHg (or individualised by treating physicians), no restriction on other vasopressors except the study drugs

Myburgh 2008 (*Continued*)

Outcomes	Time to achieve MAP goal, drug free days from randomization (primary); mortality at days 28, 90 For the mortality analysis we used data on 90 day mortality.
Notes	Subgroup analysis: septic shock, circulatory failure; 22 patients withdrawn by treating physicians due to adverse events

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random number generator (StatMate, GraphPad), stratified by centre in invariable blocks
Allocation concealment (selection bias)	Low risk	Independently prepared double blind study drugs
Explicit in-/exclusion criteria	Low risk	
ITT-analysis	Low risk	
Adequate patient description	Low risk	
Identical care	Unclear risk	Sufficient detail not described
Outcome description	Low risk	
Physicians blinded	Low risk	
Outcome assessors blinded?	Low risk	

Patel 2010

Methods	Single centre (university hospital), prospective, quasi-randomized, open label, clinical trial in a medical intensive care unit
Participants	Adult fluid-resuscitated patients with septic shock Age not stated, 54% female APACHE II score=28 SOFA score=12, (N=252)
Interventions	Dopamine 5-20 mcg/kg/min to pre-determined max of 20 mcg/kg/min versus Norepinephrine 5-20 mcg/min, to a pre-determined max of 20 mcg/kg/min as the initial vasopressor If haemodynamic goal was not achieved (MAP > 60 mmHg and/or SBP > 90mmHg):

Patel 2010 (*Continued*)

	add (1) vasopressin 0.04 U/min and (2) phenylephrine (25-200 mcg/min) If ScvO2 < 70%: add dobutamine	
Outcomes	Primary: all-cause 28 day mortality. Secondary: organ dysfunction, hospital and intensive care unit length of stay, and safety (primarily occurrence of arrhythmias) For the mortality analysis we used data on 28 day mortality.	
Notes	SOFA score as secondary outcome not explicitly presented	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Even and odd calender day enrolment
Allocation concealment (selection bias)	High risk	
Explicit in-/exclusion criteria	Low risk	
ITT-analysis	Low risk	
Adequate patient description	Low risk	But age not stated
Identical care	Low risk	
Outcome description	Low risk	
Physicians blinded	High risk	
Outcome assessors blinded?	Unclear risk	But not explicitly reported

Ruokonen 1993

Methods	Single centre; university hospital
Participants	Adult, medical patients with septic shock (N=10)
Interventions	Goal directed norepinephrine versus dopamine Patients in the norepinephrine group received additional low-dose dopamine (not considered as vasopressor)
Outcomes	Death For the mortality analysis we used data on undetermined mortality
Notes	It is unclear when patients died; duration of the intervention is unclear

Ruokonen 1993 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	'patients received in random order ...'
Allocation concealment (selection bias)	Unclear risk	Not reported
Explicit in-/exclusion criteria	Unclear risk	Not reported
ITT-analysis	Unclear risk	Not reported
Adequate patient description	Unclear risk	Not reported
Identical care	Unclear risk	Not reported
Outcome description	Unclear risk	Not reported
Physicians blinded	Unclear risk	Not reported
Outcome assessors blinded?	Unclear risk	Not reported

Russell 2008

Methods	Multicentre versus double blind randomized controlled trial, university hospitals (VASST study)
Participants	Adult patients with septic shock defined by ACCP/SCCM 1992 criteria (ACCP/SCCM 1992) Mean age 61yrs, 39% female APACHE score=27 (N=778)
Interventions	Vasopressine infusion 0.01U/min, increased by 0.005U/min every 10 min (max 0.03U/min) until MAP 65-75 mmHg versus Norepinephrine infusion 5mcg/min, increased by 2.5mcg/min every 10 min (max 15mcg/min) until MAP 65-75 mmHg Additional open label vasopressors were allowed if MAP not reached at maximum doses of study drugs
Outcomes	28day mortality (primary), 90 days mortality, days alive and organ dysfunction free (renal replacement therapy, mechanical ventilation) until day 28, days alive and free of SIRS until day 28, days alive and free of corticosteroids until day 28, length of stay in ICU and hospital, serious adverse events For the mortality analysis we used data on 90 day mortality.

Russell 2008 (*Continued*)

Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated procedure, stratified by centre and severity of shock, variable permutated blocks (size 2-6)
Allocation concealment (selection bias)	Low risk	Central telephone-based allocation system
Explicit in-/exclusion criteria	Low risk	
ITT-analysis	Low risk	
Adequate patient description	Low risk	
Identical care	Low risk	
Outcome description	Low risk	
Physicians blinded	Low risk	
Outcome assessors blinded?	Low risk	

Seguin 2002

Methods	Single centre; university hospital	
Participants	Adult patients with septic shock; unclear whether medical or surgical (N=22)	
Interventions	Goal directed epinephrine versus norepinephrine + fixed dobutamine (5 microgram/kg/min)	
Outcomes	Death For the mortality analysis we used data on undetermined mortality	
Notes	It is unclear when patients died	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	'the patient was randomised to either epinephrine or dobutamine-norepinephrine..'

Seguin 2002 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Not reported
Explicit in-/exclusion criteria	Low risk	
ITT-analysis	Unclear risk	Not reported
Adequate patient description	Low risk	
Identical care	Low risk	
Outcome description	Unclear risk	Not reported
Physicians blinded	Unclear risk	Not reported
Outcome assessors blinded?	Unclear risk	Not reported

Seguin 2006

Methods	Single centre, randomised controlled trial, university hospital
Participants	Adult patients with septic shock (authors' definition) Mean age= 66yrs, 23% female SAPS II score=54, SOFA score =10 (N=22)
Interventions	Dopexamine(DX) infusion 0.5mcg/kg/min and norepinephrine(NE)-infusion 0.2 mcg/kg/min If cardiac index>3l/kg/min NE increased by 0.2mcg/kg/min every 3 min until MAP 70 to 80 mmHg If cardiac index <3l/kg/min DX increased by 0.5mcg/kg/min every 3 min until MAP 70 to 80 mmHg versus Epinephrine infusion 0.2mcg/kg/min. Icreased by 0.2mcg/kg/min every 3 min until MAP 70 to 80 mmHg
Outcomes	Gastro mucosal blood flow (primary), haemodynamics, 28 day mortality, 90 day mortality For the mortality analysis we used data on 90 day mortality.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated randomisation list, unequal blocks

Seguin 2006 (*Continued*)

Allocation concealment (selection bias)	Low risk	By independent pharmacist
Explicit in-/exclusion criteria	Low risk	
ITT-analysis	Low risk	
Adequate patient description	Low risk	
Identical care	Low risk	
Outcome description	Low risk	
Physicians blinded	Unclear risk	Independent pharmacist involved, but masking not described
Outcome assessors blinded?	Unclear risk	Not described

Yildizdas 2008

Methods	Single centre randomized controlled trial, university hospital PICUs (Paediatric Intensive Care Unit)
Participants	Pediatric patients with septic shock (Hayden 1994,ACCP/SCCM 1992) and non-response to fluid resuscitation and high dose catecholamines Mean age= 28months, 47% female PRISM score=29 (N=58)
Interventions	Terlipressin bolus 20mcg/kg every 6 hours up to 96 hours (if MAP <2SD for age and at treating physicians discretion) versus Placebo
Outcomes	ICU mortality. length of ICU stay, biochemical markers, mechanical ventilation, haemodynamics, adverse events (digital ischemias). Urine output was narratively described as unchanged within the intervention group, but no numbers or between-group comparisons are presented) For the mortality analysis we used data on ICU mortality.
Notes	Placebo administration is not described in sufficient detail

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Open random table

Yildizdas 2008 (*Continued*)

Allocation concealment (selection bias)	High risk	Open random table
Explicit in-/exclusion criteria	Low risk	
ITT-analysis	Low risk	
Adequate patient description	Low risk	
Identical care	Unclear risk	Catecholamine therapy not described in sufficient detail
Outcome description	Low risk	
Physicians blinded	High risk	
Outcome assessors blinded?	Unclear risk	Not reported

h, hour; ICU, intensive care unit; PCCU, paediatric critical care unit; PICU, paediatric intensive care unit; MAP, mean arterial pressure; SBP, systolic blood pressure; U, units;

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

Study	Reason for exclusion
Argenziano 1997	No relevant endpoints (Study population: vasodilatory shock after left ventricular assist device placement) Intervention: vasopressin or saline placebo
Hentschel 1995	No relevant endpoints and other population (Study population: hypotensive preterm infants) Intervention: dobutamine or dopamine
Kinstner 2002	No relevant endpoints (Study population: adult patients with septic shock) Intervention: arginine-vasopressin, or placebo Study population: adults with septic shock NB only published as abstract
Levy 1999	No relevant endpoints (Study population: adult patients with septic shock) Intervention: dobutamine or dopexamine

(*Continued*)

Majerus 1984	No relevant endpoints (Study population: adult patients after abdominal surgery with septic shock) Intervention: dopamine or dobutamine
Patel 2002	No relevant endpoints (Study population: adult patients with severe septic shock) Intervention: norepinephrine or vasopressin
Rozé 1993	Other population (Study population: preterm infants with refractory shock) Intervention: dopamine versus dobutamine
Schmoelz 2006	Patients with septic shock treated with norepinephrine received either dopexamine (2mcg/kg/min), dopamine (3mcg/kg/min), or saline placebo The comparison between dopamine and saline placebo as add-on therapy was initially considered relevant. However, the dopamine dose (3mcg/kg/min) is not considered to have vasopressor properties and accordingly does not fulfil our inclusion criteria of vasopressor versus placebo
Sperry 2008	Data from a multicentre prospective cohort study in patients with blunt injury and haemorrhagic shock, not randomized study
Totaro 1997	No relevant endpoints (Study population: adult patients with hypotension after cardiopulmonary bypass) Intervention: epinephrine or norepinephrine
Zhou 2002	No relevant endpoints (Study population: adults with septic shock) Intervention: norepinephrine, epinephrine, and norepinephrine-dobutamine in a crossover fashion

Characteristics of studies awaiting assessment *[ordered by study ID]*

Hai Bo 2002

Methods	Not available
Participants	Not available
Interventions	Not available
Outcomes	Not available
Notes	Not available

Singh 1966

Methods	Not available
Participants	Not available
Interventions	Not available
Outcomes	Not available
Notes	Not available

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

Cohn 2007

Trial name or title	Prospective randomized double blind multicentre trial of low dose vasopressin versus placebo in traumatic shock resuscitation
Methods	Randomized, placebo controlled parallel group efficacy study
Participants	age 18+, systolic blood pressure <90mmHg, clinical evidence of acute traumatic injury, infusion of study drug within 1 hour after shock onset
Interventions	Vasopressin bolus 4U, followed by continuous infusion 2.4U/h for 5 hours versus Placebo
Outcomes	Organ dysfunction, 28-day mortality
Starting date	February 2007
Contact information	Stephen Cohn, MD, University of Texas San Antonio
Notes	Estimated enrolment: 333 patients NCT00420407

Fernandez 2006

Trial name or title	Terlipressin in Septic Shock in Cirrhosis; Effects on Survival of Terlipressin Administration in Cirrhotic Patients With Severe Sepsis or Septic Shock. A Randomized, Open Labelled Controlled Trial
Methods	Treatment, Randomized, Open Label, Uncontrolled, Single Group Assignment, Safety/Efficacy Study
Participants	Adults with liver cirrhosis and septic shock
Interventions	Terlipressin 1, 1.5 and 2 mg/4h intravenously in patients with body weight < 50 kg, between 50 and 70 Kg and > 70 Kg respectively until 24h after shock resolution plus Dopamine (1-20 µg/Kg/min) and/or norepinephrine (0.05-4 µg/Kg/min) until shock resolution

Fernandez 2006 (*Continued*)

	versus Dopamine (1-20 µg/Kg/min) and/or norepinephrine (0.05-4 µg/Kg/min) until shock resolution
Outcomes	Hospital survival (primary), Refractory shock, Variceal bleeding, Hepatorenal syndrome
Starting date	October 2006
Contact information	Javier Fernandez, MD Jfdez@clinic.ub.es Hospital Clinic Barcelona, Catalonia, Spain
Notes	NCT00628160

Lienhart 2007

Trial name or title	Vasopressin for the therapy of persistent traumatic hemorrhagic shock. The VITRIS.at study
Methods	European multicentre randomized controlled study in the pre-hospital emergency medical helicopter setting
Participants	Adult pre-hospital traumatic haemorrhagic shock despite standard treatment within 60 min
Interventions	Vasopressin (10IU IV) versus saline placebo up to 3 injections at least 5 min apart
Outcomes	Hospital admission rate (primary), haemodynamics, fluid requirements, hospital discharge rate
Starting date	Jan 2009
Contact information	www.vitris.at
Notes	NCT 00379522 EudraCT-Nummer 2006-004252-20

DATA AND ANALYSES

Comparison 1. Norepinephrine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	14		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Norepinephrine versus dopamine	6	1400	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.87, 1.03]
1.2 Norepinephrine versus epinephrine	1	269	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.80, 1.60]
1.3 Norepinephrine versus terlipressin	2	40	Risk Ratio (M-H, Random, 95% CI)	0.8 [0.30, 2.13]
1.4 Norepinephrine versus vasopressin	3	812	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.98, 1.29]
1.5 Norepinephrine versus norepinephrine+terlipressin+dobutamine	1	40	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.67, 1.50]
1.6 Norepinephrine versus phenylephrine	1	32	Risk Ratio (M-H, Random, 95% CI)	0.9 [0.51, 1.60]
2 LOS ICU	5		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 Norepinephrine versus vasopressin	1	778	Mean Difference (IV, Random, 95% CI)	1.0 [-1.40, 3.40]
2.2 Norepinephrine versus norepinephrine+terlipressin+dobutamine	1	40	Mean Difference (IV, Random, 95% CI)	-1.0 [-7.20, 5.20]
2.3 Norepinephrine versus phenylephrine	1	32	Mean Difference (IV, Random, 95% CI)	0.0 [-8.27, 8.27]
2.4 Norepinephrine versus dopamine	2	1931	Mean Difference (IV, Random, 95% CI)	0.09 [-0.57, 0.75]
3 LOS hospital	2	1931	Mean Difference (IV, Random, 95% CI)	0.66 [-0.96, 2.29]
4 Arrhythmia	2	1931	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.26, 0.69]

Comparison 2. Epinephrine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Epinephrine vs norepinephrine	1	269	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.63, 1.25]
1.2 Epinephrine versus norepinephrine+dobutamine	3	382	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.85, 1.26]

1.3 Epinephrine versus norepinephrine+dopexamine	1	22	Risk Ratio (M-H, Random, 95% CI)	1.6 [0.46, 5.53]

Comparison 3. Vasopressin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Vasopressin versus placebo	4	157	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.60, 1.66]
1.2 Vasopressin versus terlipressin	1	30	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.56, 2.35]
1.3 Vasopressin versus norepinephrine	3	812	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.77, 1.03]
2 LOS ICU	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 Vasopressin versus terlipressin	1	30	Mean Difference (IV, Random, 95% CI)	3.0 [-7.21, 13.21]
2.2 Vasopressin versus norepinephrine	1	778	Mean Difference (IV, Random, 95% CI)	-1.0 [-3.40, 1.40]
2.3 Vasopressin versus placebo	2	99	Mean Difference (IV, Random, 95% CI)	-0.26 [-3.88, 3.36]

Comparison 4. Terlipressin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Terlipressin versus placebo	3	127	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.69, 1.14]
1.2 Terlipressin versus norepinephrine	2	40	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.47, 3.33]
1.3 Terlipressin versus vasopressin	1	30	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.43, 1.80]
2 LOS ICU	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 Terlipressin versus placebo	3	127	Mean Difference (IV, Random, 95% CI)	-2.90 [-8.61, 2.81]
2.2 Terlipressin versus vasopressin	1	30	Mean Difference (IV, Random, 95% CI)	-3.0 [-13.21, 7.21]

Comparison 5. Dopamine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Dopamine versus norepinephrine	6	1400	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.97, 1.15]
2 LOS ICU	2	1931	Mean Difference (IV, Random, 95% CI)	-0.86 [-2.11, 0.38]
3 LOS hospital	2	1931	Mean Difference (IV, Random, 95% CI)	-0.66 [-2.29, 0.96]
4 Arrhythmia	2	1931	Risk Ratio (M-H, Random, 95% CI)	2.34 [1.46, 3.78]

Comparison 6. Sensitivity analysis norepinephrine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	14		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Low risk of bias norepinephrine versus dopamine	1	1036	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.87, 1.04]
1.2 No low risk of bias norepinephrine versus dopamine	5	364	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.72, 1.19]
1.3 Low risk of bias norepinephrine versus epinephrine	1	269	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.80, 1.60]
1.4 No low risk of bias norepinephrine versus epinephrine	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.5 Low risk of bias norepinephrine versus terlipressin	1	20	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.6 No low risk of bias norepinephrine versus terlipressin	1	20	Risk Ratio (M-H, Random, 95% CI)	0.8 [0.30, 2.13]
1.7 Low risk of bias norepinephrine versus vasopressin	2	794	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.97, 1.31]
1.8 No low risk of bias norepinephrine versus vasopressin	1	18	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.73, 1.64]
1.9 Low risk of bias norepinephrine versus norepinephrine+terlipressin+dobutamine	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

1.10 No low risk of bias norepinephrine versus nore-pinephrine+terlipressin+dobutamine	1	40	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.67, 1.50]
1.11 Low risk of bias norepinephrine versus phenylephrine	1	32	Risk Ratio (M-H, Random, 95% CI)	0.9 [0.51, 1.60]
1.12 No low risk of bias norepinephrine versus phenylephrine	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 7. Sensitivity analysis epinephrine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Low risk of bias epinephrine versus norepinephrine	1	269	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.63, 1.25]
1.2 No low risk of bias epinephrine versus norepinephrine	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 Low risk of bias epinephrine versus norepinephrine+dobutamine	1	330	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.84, 1.28]
1.4 No low risk of bias epinephrine versus norepinephrine+dobutamine	2	52	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.60, 1.75]
1.5 Low risk of bias epinephrine versus norepinephrine+dopexamine	1	22	Risk Ratio (M-H, Random, 95% CI)	1.6 [0.46, 5.53]
1.6 No low risk of bias epinephrine versus norepinephrine+dopexamine	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 8. Sensitivity analysis vasopressin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Low risk of bias vasopressin versus placebo	2	79	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.11, 7.67]
1.2 No low risk of bias vasopressin versus placebo	2	78	Risk Ratio (M-H, Random, 95% CI)	1.36 [0.27, 6.95]

1.3 Low risk of bias vasopressin versus terlipressin	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.4 No low risk of bias vasopressin versus terlipressin	1	30	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.56, 2.35]
1.5 Low risk of bias vasopressin versus norepinephrine	2	794	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.76, 1.03]
1.6 No low risk of bias vasopressin versus norepinephrine	1	18	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.61, 1.37]

Comparison 9. Sensitivity analysis terlipressin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Low risk of bias terlipressin versus placebo	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 No low risk of bias terlipressin versus placebo	3	127	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.69, 1.14]
1.3 Low risk of bias terlipressin versus norepinephrine	1	20	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.4 No low risk terlipressin versus norepinephrine	1	20	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.47, 3.33]
1.5 Low risk of bias terlipressin versus vasopressin	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.6 No low risk terlipressin versus vasopressin	1	30	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.43, 1.80]

Comparison 10. Sensitivity analysis dopamine

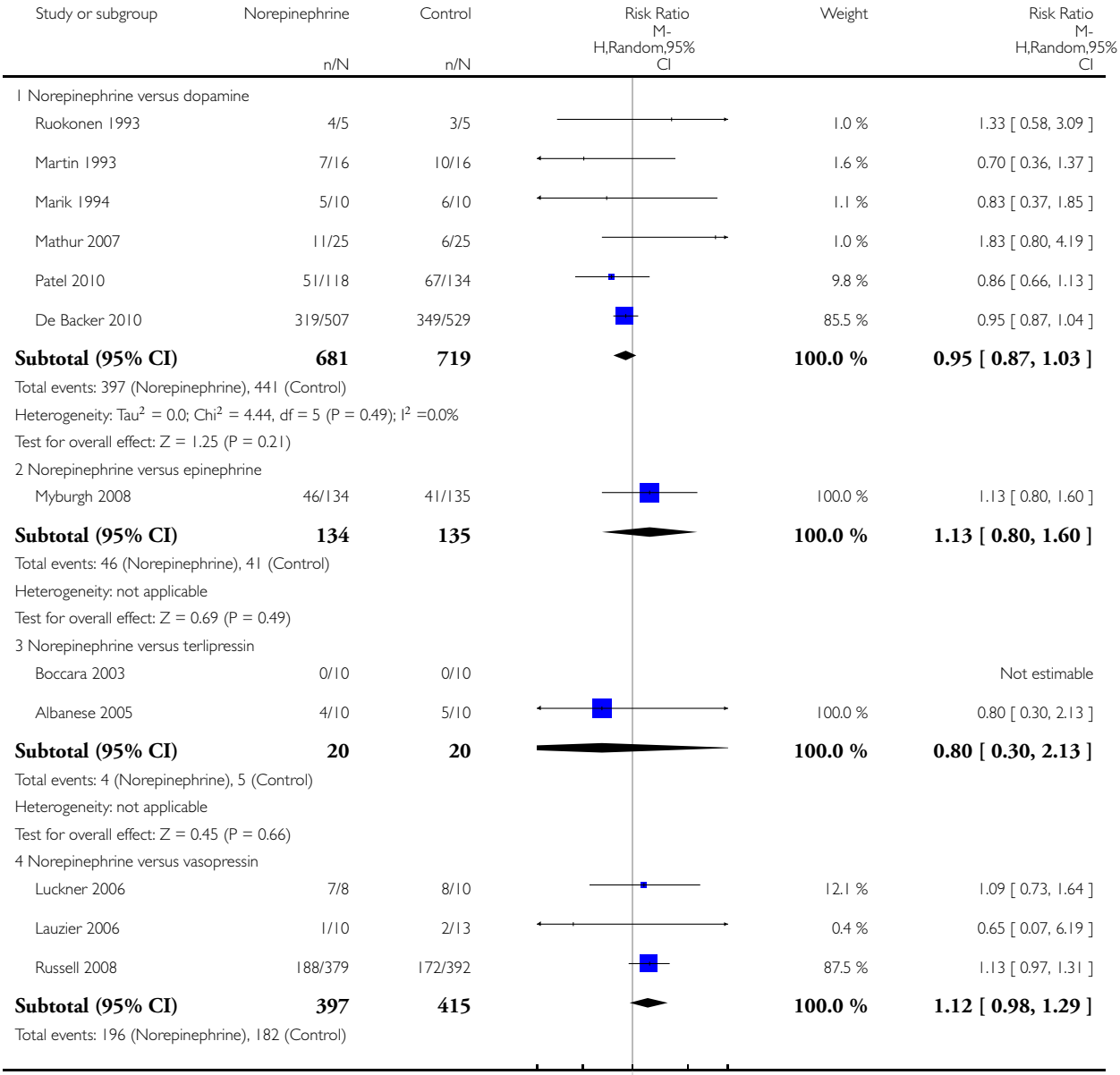
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Low risk of bias dopamine versus norepinephrine	1	1036	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.96, 1.15]
1.2 No low risk of bias dopamine versus norepinephrine	5	364	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.84, 1.38]

Analysis 1.1. Comparison 1 Norepinephrine, Outcome 1 Mortality.

Review: Vasopressors for hypotensive shock

Comparison: 1 Norepinephrine

Outcome: 1 Mortality



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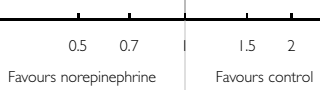
Study or subgroup	Norepinephrine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.25, df = 2 (P = 0.88); I^2 =0.0%					
Test for overall effect: Z = 1.62 (P = 0.11)					
5 Norepinephrine versus norepinephrine+terlipressin+dobutamine					
Morelli 2008a	14/20	14/20		100.0 %	1.00 [0.67, 1.50]
Subtotal (95% CI)	**20**	**20**		**100.0 %**	**1.00 [0.67, 1.50]**
Total events: 14 (Norepinephrine), 14 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P = 1.0)					
6 Norepinephrine versus phenylephrine					
Morelli 2008b	9/16	10/16		100.0 %	0.90 [0.51, 1.60]
Subtotal (95% CI)	**16**	**16**		**100.0 %**	**0.90 [0.51, 1.60]**
Total events: 9 (Norepinephrine), 10 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.36 (P = 0.72)					

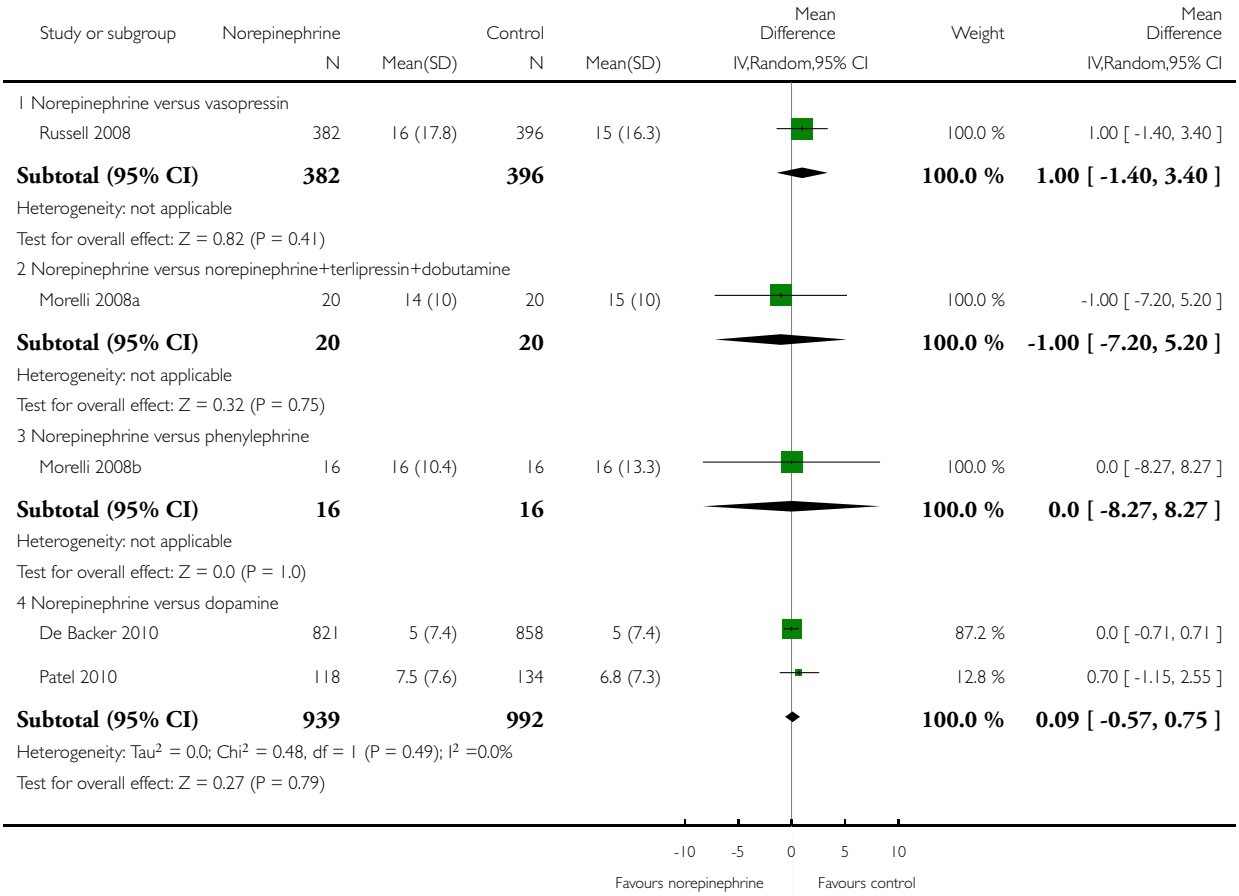


Analysis 1.2. Comparison 1 Norepinephrine, Outcome 2 LOS ICU.

Review: Vasopressors for hypotensive shock

Comparison: 1 Norepinephrine

Outcome: 2 LOS ICU

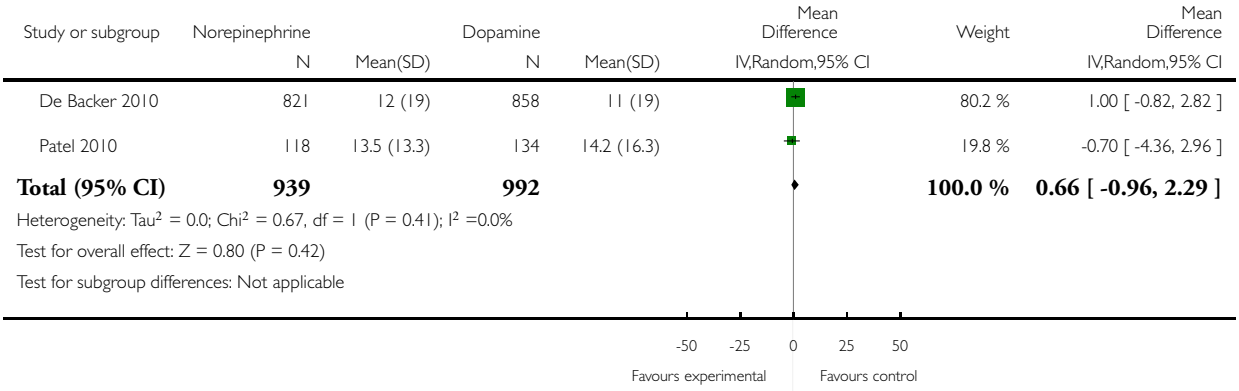


Analysis 1.3. Comparison 1 Norepinephrine, Outcome 3 LOS hospital.

Review: Vasopressors for hypotensive shock

Comparison: 1 Norepinephrine

Outcome: 3 LOS hospital

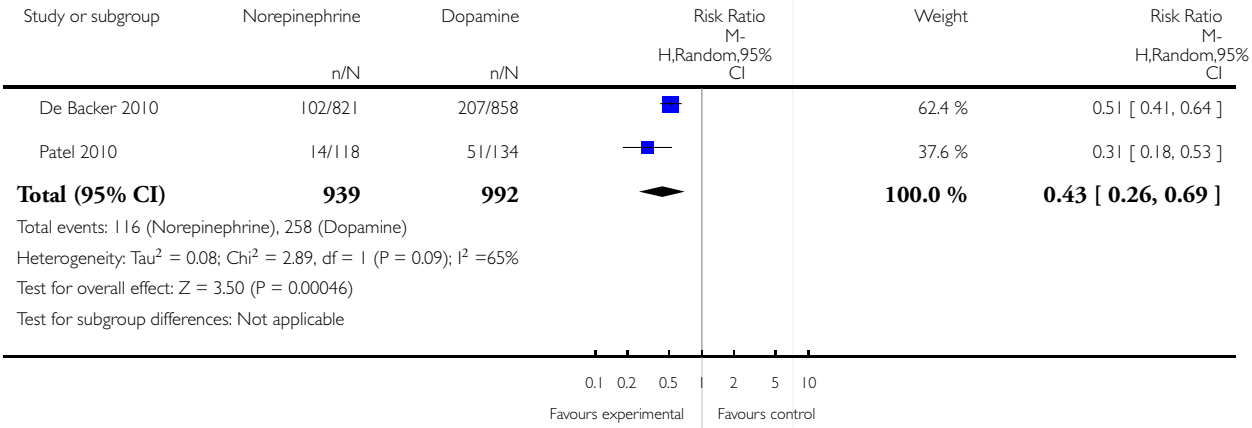


Analysis 1.4. Comparison 1 Norepinephrine, Outcome 4 Arrhythmia.

Review: Vasopressors for hypotensive shock

Comparison: 1 Norepinephrine

Outcome: 4 Arrhythmia

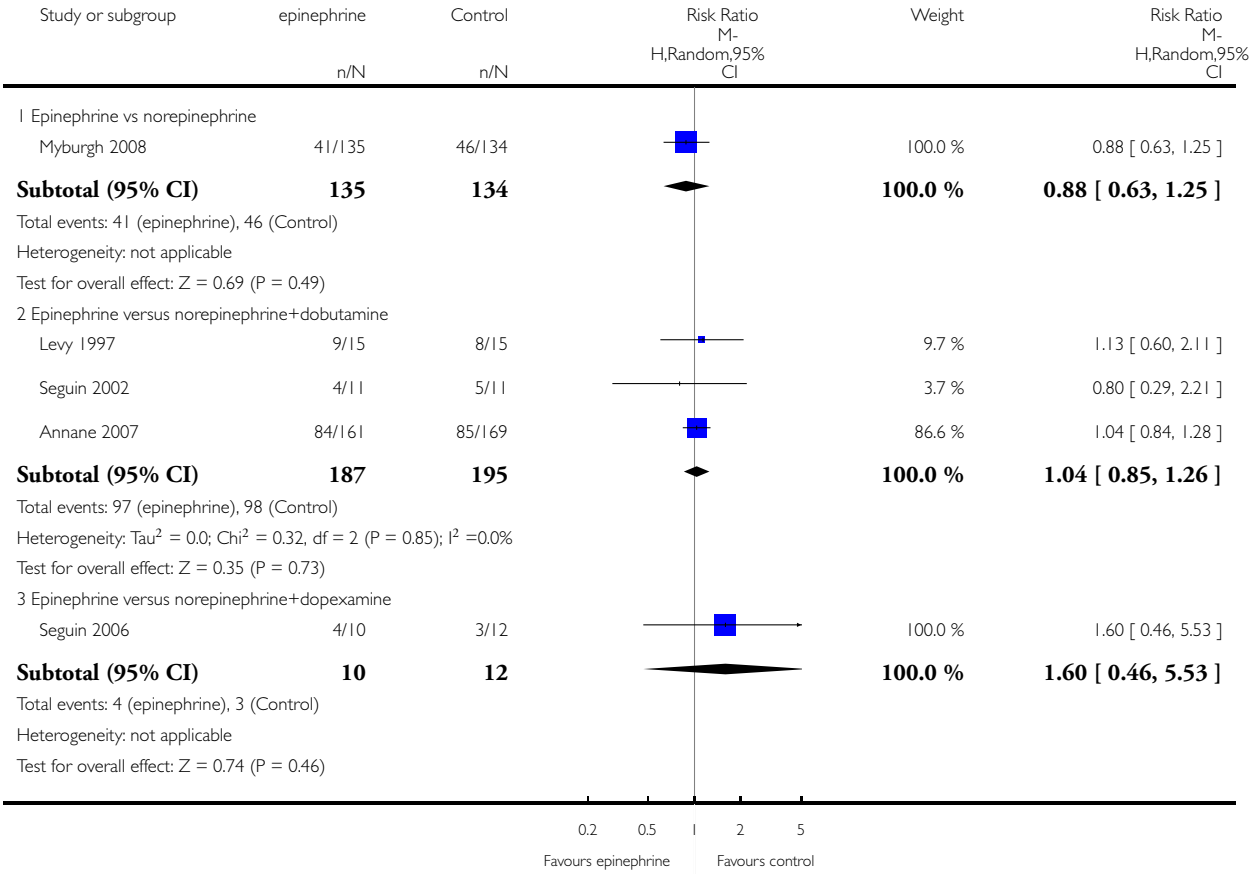


Analysis 2.1. Comparison 2 Epinephrine, Outcome 1 Mortality.

Review: Vasopressors for hypotensive shock

Comparison: 2 Epinephrine

Outcome: 1 Mortality

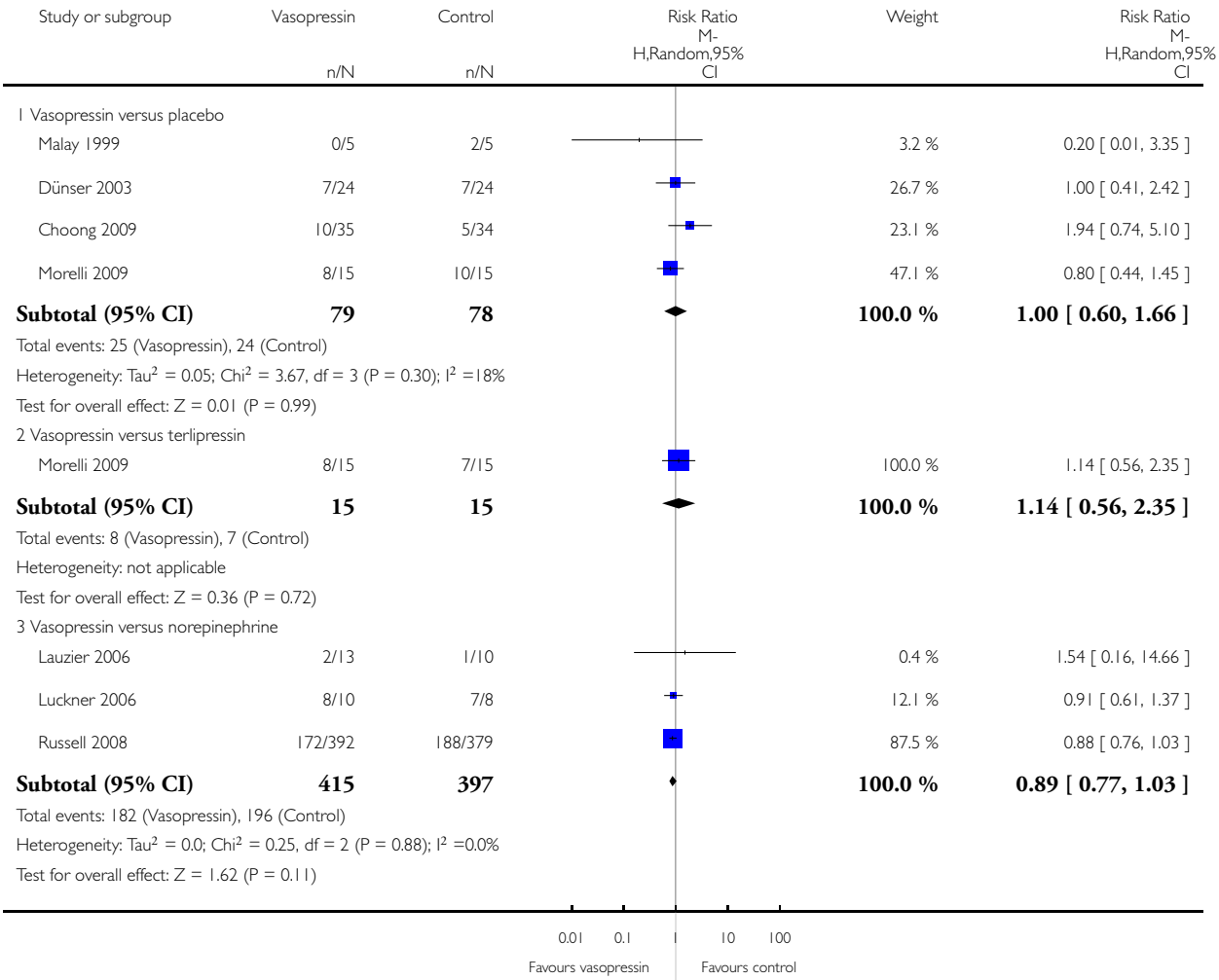


Analysis 3.1. Comparison 3 Vasopressin, Outcome 1 Mortality.

Review: Vasopressors for hypotensive shock

Comparison: 3 Vasopressin

Outcome: 1 Mortality

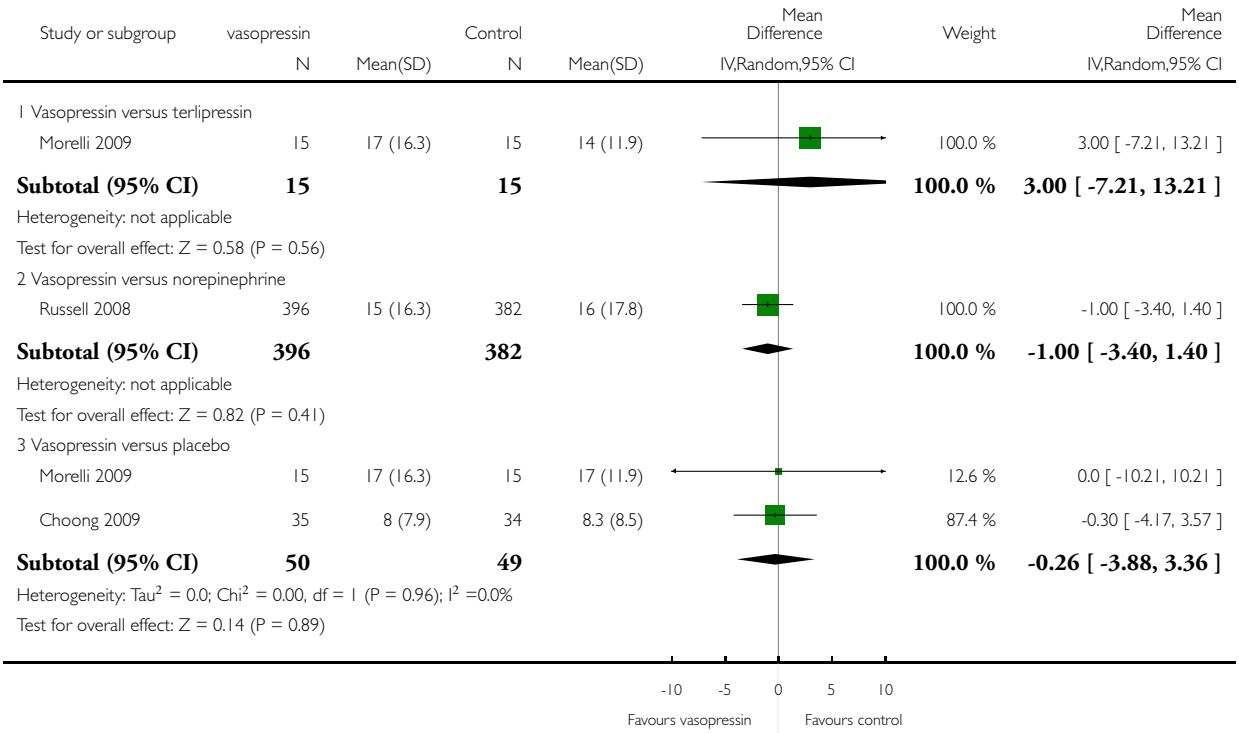


Analysis 3.2. Comparison 3 Vasopressin, Outcome 2 LOS ICU.

Review: Vasopressors for hypotensive shock

Comparison: 3 Vasopressin

Outcome: 2 LOS ICU

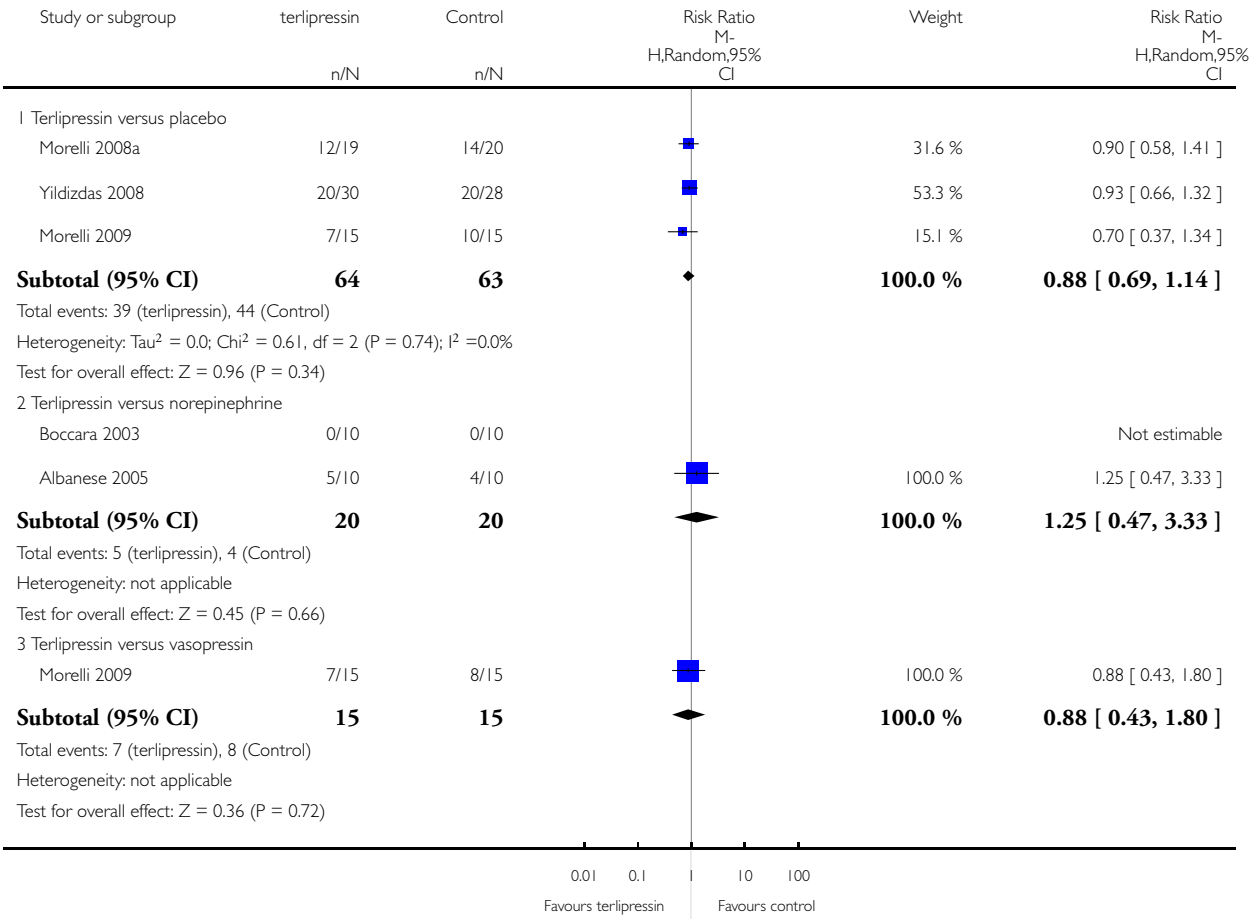


Analysis 4.1. Comparison 4 Terlipressin, Outcome 1 Mortality.

Review: Vasopressors for hypotensive shock

Comparison: 4 Terlipressin

Outcome: 1 Mortality

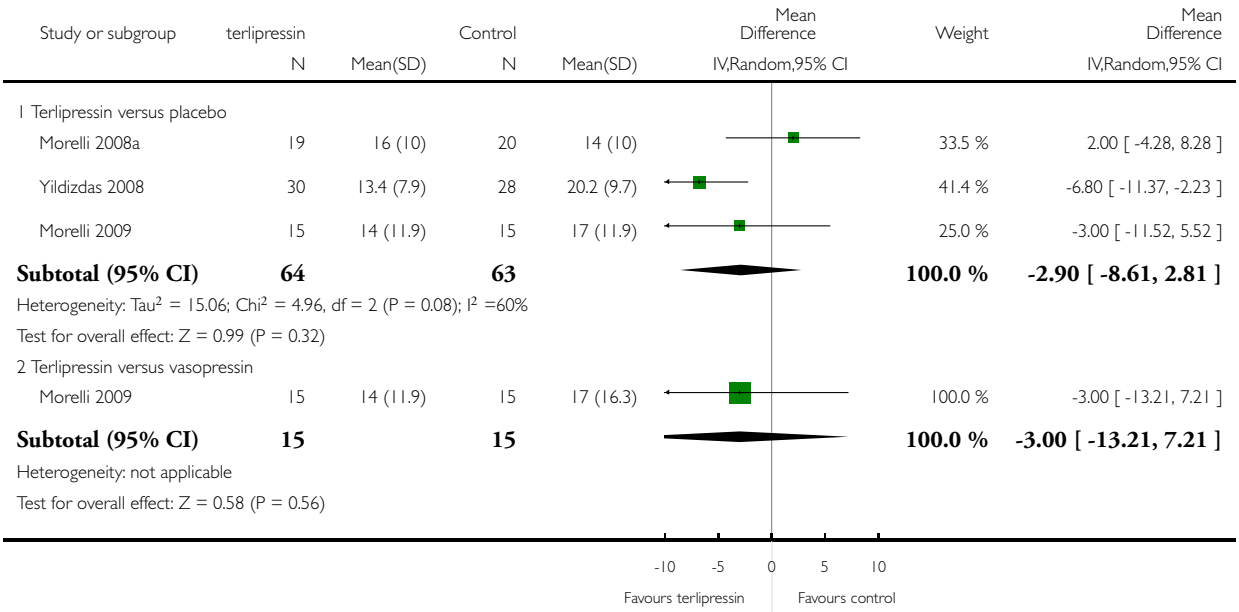


Analysis 4.2. Comparison 4 Terlipressin, Outcome 2 LOS ICU.

Review: Vasopressors for hypotensive shock

Comparison: 4 Terlipressin

Outcome: 2 LOS ICU



Analysis 5.1. Comparison 5 Dopamine, Outcome 1 Mortality.

Review: Vasopressors for hypotensive shock

Comparison: 5 Dopamine

Outcome: 1 Mortality

Study or subgroup	Dopamine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Dopamine versus norepinephrine					
Ruokonen 1993	3/5	4/5		1.0 %	0.75 [0.32, 1.74]
Martin 1993	10/16	7/16		1.6 %	1.43 [0.73, 2.80]
Marik 1994	6/10	5/10		1.1 %	1.20 [0.54, 2.67]
Mathur 2007	6/25	11/25		1.0 %	0.55 [0.24, 1.25]
De Backer 2010	349/529	319/507		85.5 %	1.05 [0.96, 1.15]
Patel 2010	67/134	51/118		9.8 %	1.16 [0.89, 1.51]
Subtotal (95% CI)	**719**	**681**		**100.0 %**	**1.05 [0.97, 1.15]**
Total events: 441 (Dopamine), 397 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 4.44$, df = 5 (P = 0.49); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.25 (P = 0.21)					

Analysis 5.2. Comparison 5 Dopamine, Outcome 2 LOS ICU.

Review: Vasopressors for hypotensive shock

Comparison: 5 Dopamine

Outcome: 2 LOS ICU

Study or subgroup	Dopamine N	Mean(SD)	Norepinephrine N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
De Backer 2010	858	11 (17.6)	821	12 (17.6)		54.6 %	-1.00 [-2.68, 0.68]
Patel 2010	134	6.8 (7.3)	118	7.5 (7.6)		45.4 %	-0.70 [-2.55, 1.15]
Total (95% CI)	**992**		**939**			**100.0 %**	**-0.86 [-2.11, 0.38]**

Heterogeneity: Tau² = 0.0; Chi² = 0.06, df = 1 (P = 0.81); I² =0.0%

Test for overall effect: Z = 1.36 (P = 0.17)

Test for subgroup differences: Not applicable

Analysis 5.3. Comparison 5 Dopamine, Outcome 3 LOS hospital.

Review: Vasopressors for hypotensive shock

Comparison: 5 Dopamine

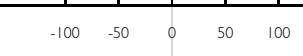
Outcome: 3 LOS hospital

Study or subgroup	Dopamine N	Mean(SD)	Norepinephrine N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
De Backer 2010	858	11 (19)	821	12 (19)		80.2 %	-1.00 [-2.82, 0.82]
Patel 2010	134	14.2 (16.3)	118	13.5 (13.3)		19.8 %	0.70 [-2.96, 4.36]
Total (95% CI)	**992**		**939**			**100.0 %**	**-0.66 [-2.29, 0.96]**

Heterogeneity: Tau² = 0.0; Chi² = 0.67, df = 1 (P = 0.41); I² =0.0%

Test for overall effect: Z = 0.80 (P = 0.42)

Test for subgroup differences: Not applicable

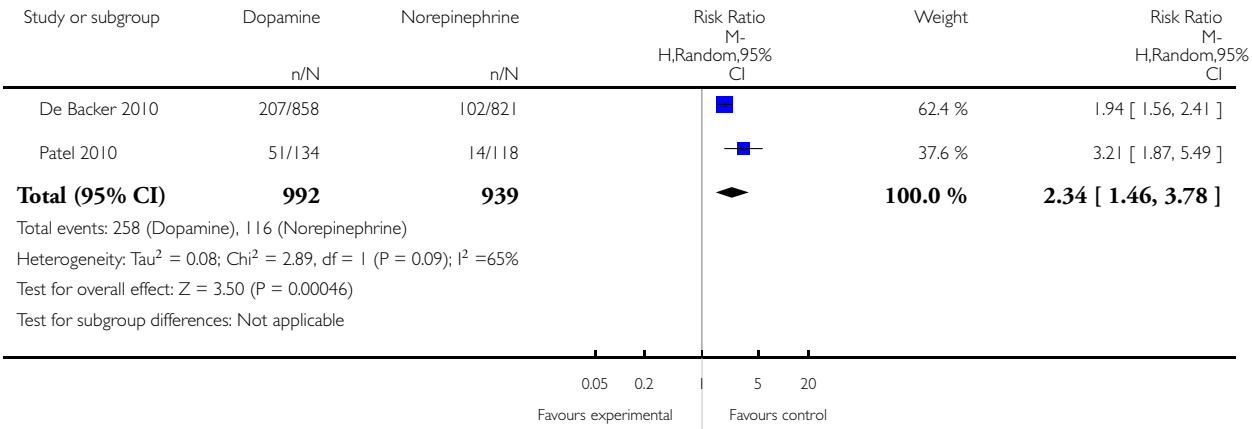


Analysis 5.4. Comparison 5 Dopamine, Outcome 4 Arrhythmia.

Review: Vasopressors for hypotensive shock

Comparison: 5 Dopamine

Outcome: 4 Arrhythmia



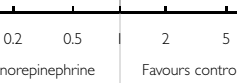
Analysis 6.1. Comparison 6 Sensitivity analysis norepinephrine, Outcome 1 Mortality.

Review: Vasopressors for hypotensive shock

Comparison: 6 Sensitivity analysis norepinephrine

Outcome: 1 Mortality

Study or subgroup	Norepinephrine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Low risk of bias norepinephrine versus dopamine					
De Backer 2010	319/507	349/529		100.0 %	0.95 [0.87, 1.04]
Subtotal (95% CI)	**507**	**529**		**100.0 %**	**0.95 [0.87, 1.04]**
Total events: 319 (Norepinephrine), 349 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.03 (P = 0.31)					
2 No low risk of bias norepinephrine versus dopamine					
Ruokonen 1993	4/5	3/5		8.5 %	1.33 [0.58, 3.09]
Martin 1993	7/16	10/16		12.9 %	0.70 [0.36, 1.37]
Marik 1994	5/10	6/10		9.3 %	0.83 [0.37, 1.85]
Mathur 2007	11/25	6/25		8.8 %	1.83 [0.80, 4.19]
Patel 2010	51/118	67/134		60.6 %	0.86 [0.66, 1.13]
Subtotal (95% CI)	**174**	**190**		**100.0 %**	**0.93 [0.72, 1.19]**
Total events: 78 (Norepinephrine), 92 (Control)					
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 4.34$, df = 4 (P = 0.36); $I^2 = 8\%$					
Test for overall effect: Z = 0.58 (P = 0.56)					
3 Low risk of bias norepinephrine versus epinephrine					
Myburgh 2008	46/134	41/135		100.0 %	1.13 [0.80, 1.60]
Subtotal (95% CI)	**134**	**135**		**100.0 %**	**1.13 [0.80, 1.60]**
Total events: 46 (Norepinephrine), 41 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.69 (P = 0.49)					
4 No low risk of bias norepinephrine versus epinephrine					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Norepinephrine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
5 Low risk of bias norepinephrine versus terlipressin					
Boccara 2003	0/10	0/10			Not estimable
Subtotal (95% CI)	**10**	**10**			**Not estimable**
Total events: 0 (Norepinephrine), 0 (Control)					
Heterogeneity: not applicable					



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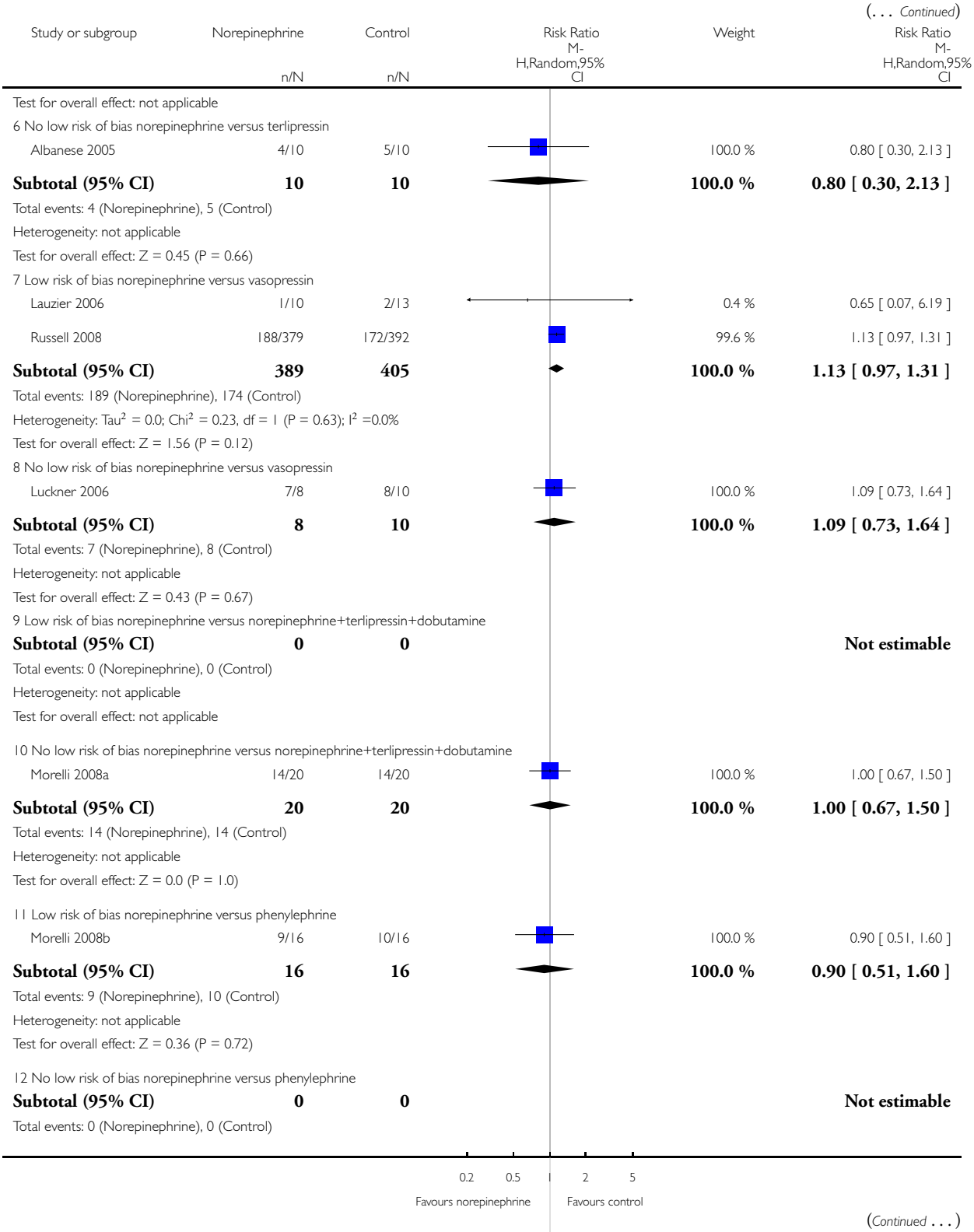

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Study or subgroup	Norepinephrine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Heterogeneity: not applicable					
Test for overall effect: not applicable					

Analysis 7.1. Comparison 7 Sensitivity analysis epinephrine, Outcome 1 Mortality.

Review: Vasopressors for hypotensive shock

Comparison: 7 Sensitivity analysis epinephrine

Outcome: 1 Mortality

Study or subgroup	epinephrine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Low risk of bias epinephrine versus norepinephrine					
Myburgh 2008	41/135	46/134		100.0 %	0.88 [0.63, 1.25]
Subtotal (95% CI)	**135**	**134**		**100.0 %**	**0.88 [0.63, 1.25]**
Total events: 41 (epinephrine), 46 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.69 (P = 0.49)					
2 No low risk of bias epinephrine versus norepinephrine					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (epinephrine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 Low risk of bias epinephrine versus norepinephrine+dobutamine					
Annane 2007	84/161	85/169		100.0 %	1.04 [0.84, 1.28]
Subtotal (95% CI)	**161**	**169**		**100.0 %**	**1.04 [0.84, 1.28]**
Total events: 84 (epinephrine), 85 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.34 (P = 0.73)					
4 No low risk of bias epinephrine versus norepinephrine+dobutamine					

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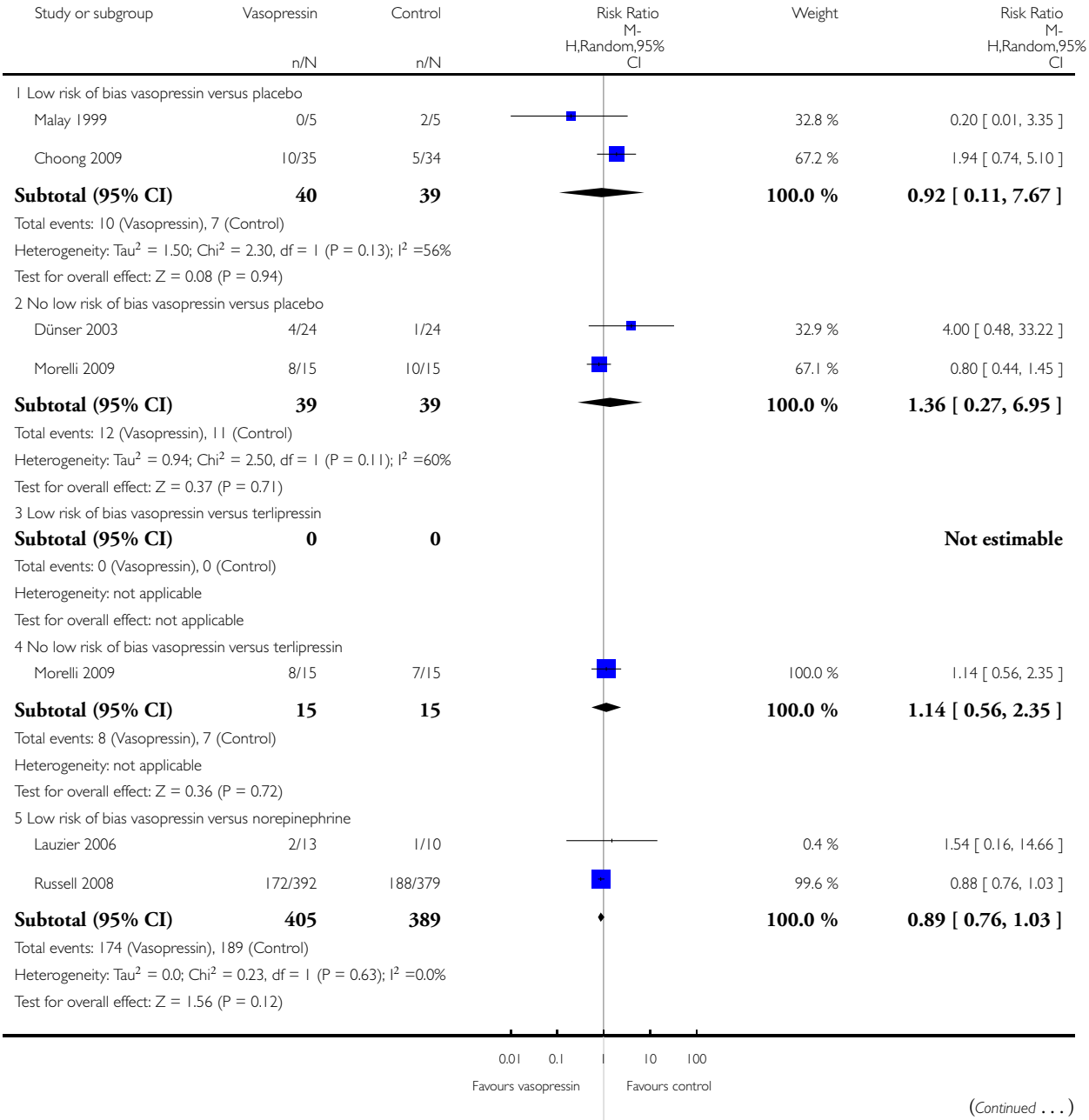
Study or subgroup	epinephrine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Levy 1997	9/15	8/15		72.3 %	1.13 [0.60, 2.11]
Seguin 2002	4/11	5/11		27.7 %	0.80 [0.29, 2.21]
Subtotal (95% CI)	**26**	**26**		**100.0 %**	**1.02 [0.60, 1.75]**
Total events: 13 (epinephrine), 13 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.32$, df = 1 (P = 0.57); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.09 (P = 0.93)					
5 Low risk of bias epinephrine versus norepinephrine+dopexamine					
Seguin 2006	4/10	3/12		100.0 %	1.60 [0.46, 5.53]
Subtotal (95% CI)	**10**	**12**		**100.0 %**	**1.60 [0.46, 5.53]**
Total events: 4 (epinephrine), 3 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.74 (P = 0.46)					
6 No low risk of bias epinephrine versus norepinephrine+dopexamine					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (epinephrine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					

Analysis 8.1. Comparison 8 Sensitivity analysis vasopressin, Outcome 1 Mortality.

Review: Vasopressors for hypotensive shock

Comparison: 8 Sensitivity analysis vasopressin

Outcome: 1 Mortality



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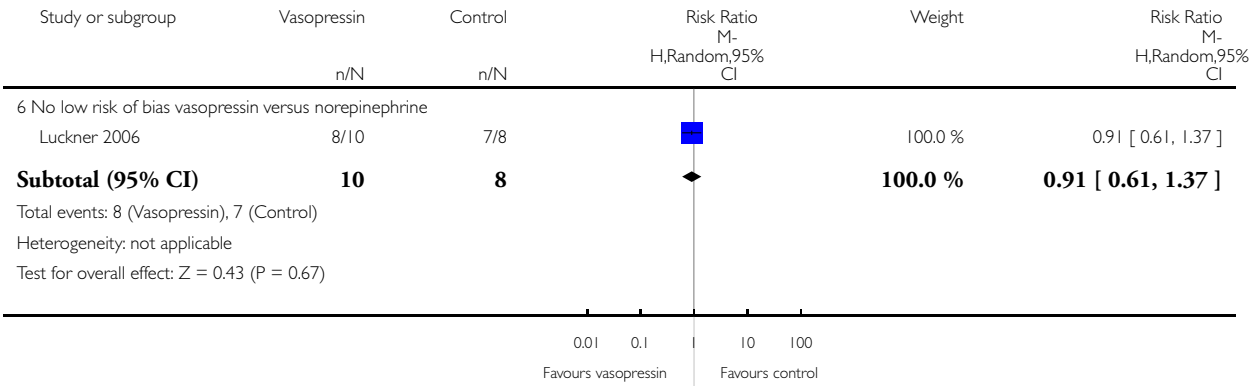
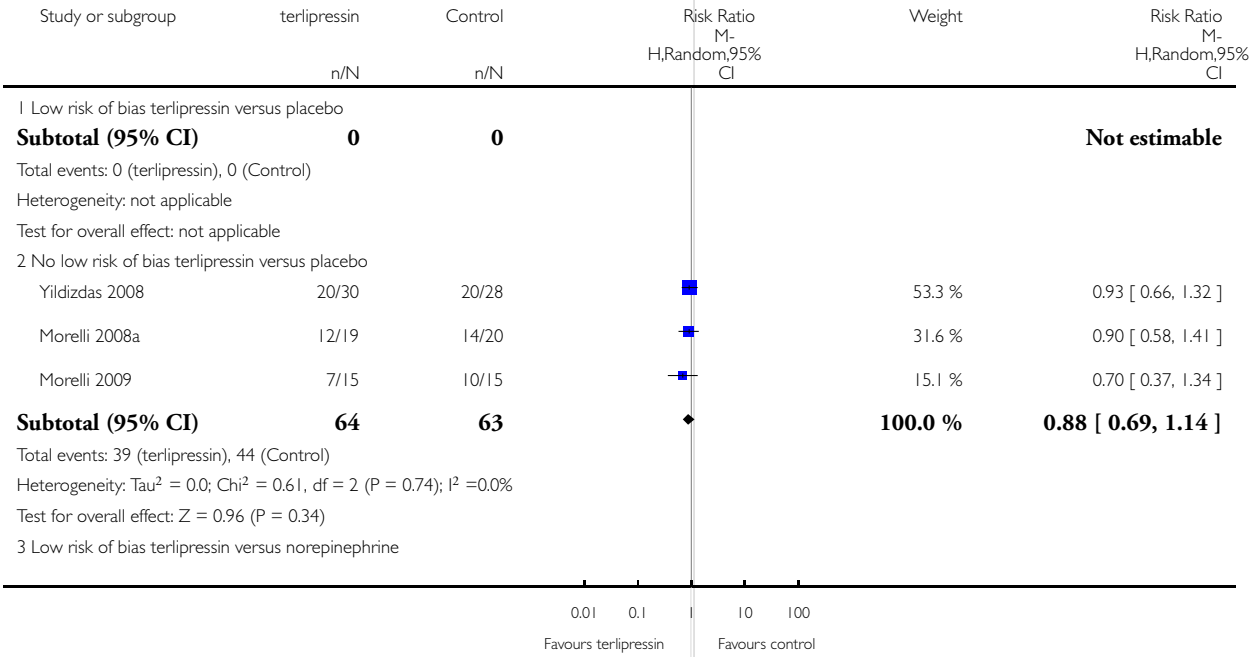


Analysis 9.1. Comparison 9 Sensitivity analysis terlipressin, Outcome 1 Mortality.

Review: Vasopressors for hypotensive shock

Comparison: 9 Sensitivity analysis terlipressin

Outcome: 1 Mortality



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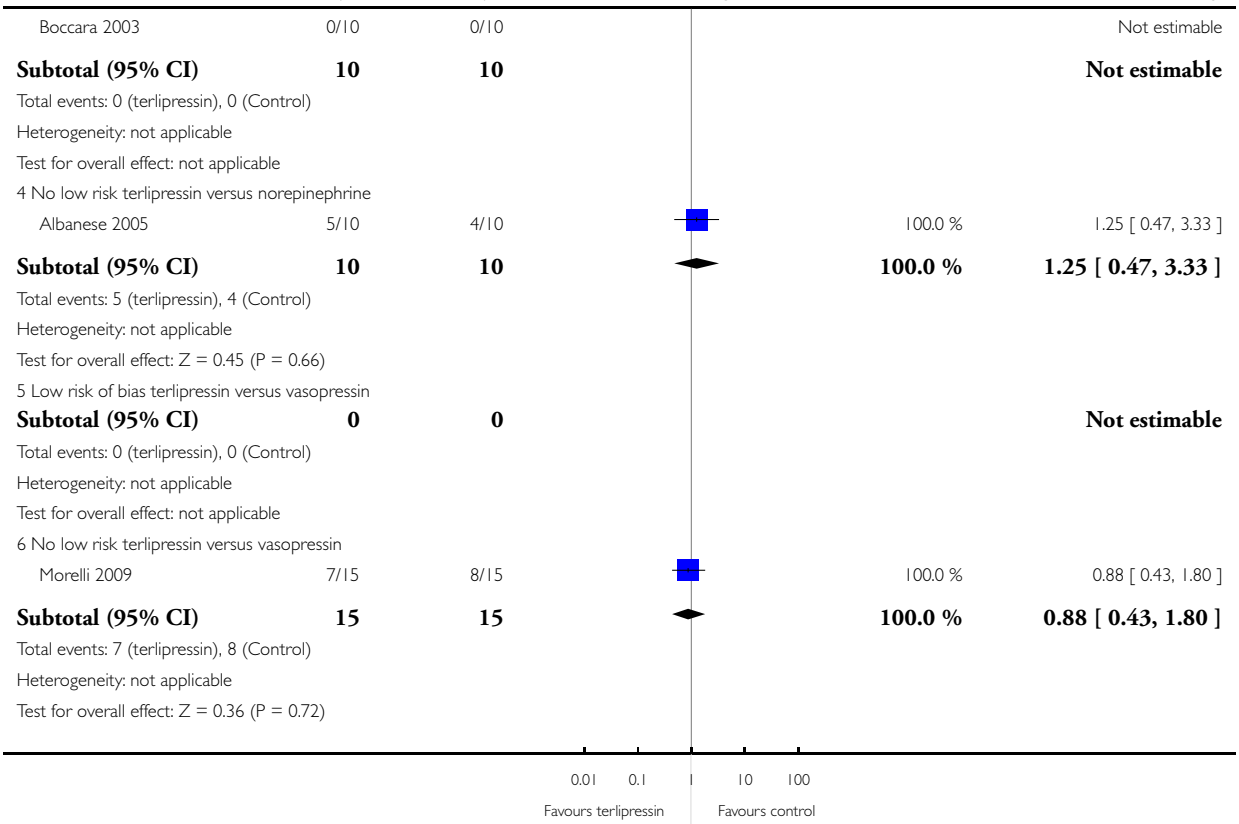
Study or subgroup	terlipressin n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Boccara 2003	0/10	0/10			Not estimable
Subtotal (95% CI)	**10**	**10**			**Not estimable**
Total events: 0 (terlipressin), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
4 No low risk terlipressin versus norepinephrine					
Albanese 2005	5/10	4/10		100.0 %	1.25 [0.47, 3.33]
Subtotal (95% CI)	**10**	**10**		**100.0 %**	**1.25 [0.47, 3.33]**
Total events: 5 (terlipressin), 4 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.45 (P = 0.66)					
5 Low risk of bias terlipressin versus vasopressin					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (terlipressin), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
6 No low risk terlipressin versus vasopressin					
Morelli 2009	7/15	8/15		100.0 %	0.88 [0.43, 1.80]
Subtotal (95% CI)	**15**	**15**		**100.0 %**	**0.88 [0.43, 1.80]**
Total events: 7 (terlipressin), 8 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.36 (P = 0.72)					

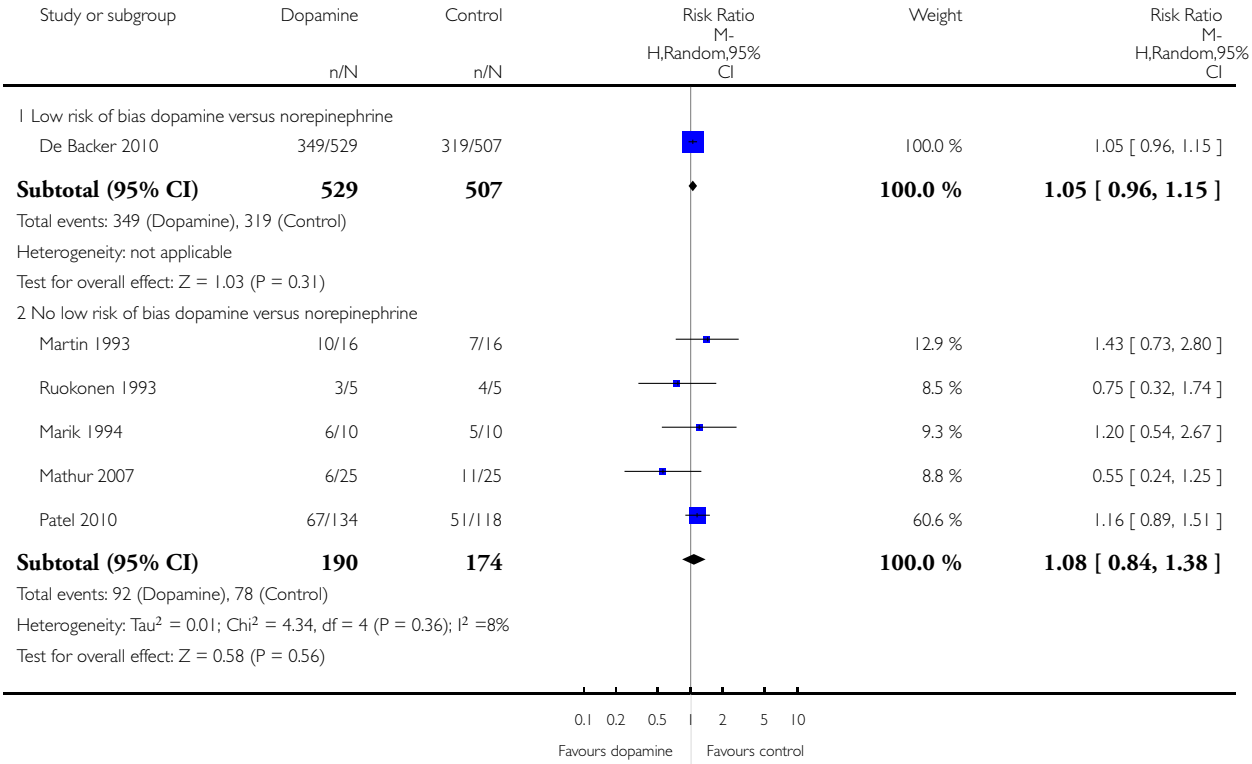


Analysis 10.1. Comparison 10 Sensitivity analysis dopamine, Outcome 1 Mortality.

Review: Vasopressors for hypotensive shock

Comparison: 10 Sensitivity analysis dopamine

Outcome: 1 Mortality



ADDITIONAL TABLES

Table 1. Morbidity outcomes - measures of renal function comparing several vasopressor regimens. Each single vasopressor is compared to other available vasopressor regimens.

Vasopressor	Comparator (Reference)	Outcome	Effect*
Norepinephrine	Vasopressin (Lauzier 2006)	Cretinine Clearance	54ml $min^{-1}1.73m^{-2}$±38 versus. 122ml $min^{-1}1.73m^{-2}$±66 , P<0.001
	Vasopressin (Russell 2008)	Days alive free of renal replacement therapy	(23 [IQR 5-28] versus 25 [IQR 6-28], P=0.64)

Table 1. Morbidity outcomes - measures of renal function comparing several vasopressor regimens. Each single vasopressor is compared to other available vasopressor regimens. (*Continued*)

	Norepinephrine+terlipressin+dobutamin (Morelli 2008a)	Urine output 4hours after study start	96ml/h±48 versus 130ml/h±76 (P<0.05)
	Norepinephrine + terlipressin (Morelli 2008a)	Urine output 4hours after study start	96ml/h±48 versus 147ml/h±119 (P=0.08)
	Dopamine (Mathur 2007)	Post-treatment urine output	1.17ml/kg/h ± 0.47 versus 0.81ml/kg/h±0.75, P<0.05
	Dopamine (De Backer 2010)	Days free of renal support within 28 days	14.0 ± 12.3 days versus 12.8 ± 12.4 days, P=0.07
	Phenylephrine (Morelli 2008b)	Creatinine clearance urine output	no difference (P=0.61) no difference (P=0.17)
	Terlipressin (Boccara 2003)	Renal failure postoperatively	(0/10 versus 0/10)
	Terlipressin plus norepinephrine and vasopressin plus norepinephrine (Morelli 2009)	Need for renal replacement therapy	(8/15 versus 4/15 versus 5/15, P=0.29)
Epinephrine	Norepinephrine+dobutamine (Levy 1997)	Oliguria reversal	9/12 vs 10/11, RR 0.36 (95% CI 0.04 to 3.00)
Vasopressin	Norepinephrine (Lauzier 2006)	Cretinine Clearance	122ml $min^{-1}1.73m^{-2}$±66 versus 54ml $min^{-1}1.73m^{-2}$±38, P<0.001
	Norepinephrine (Russell 2008)	Days alive free of renal replacement therapy	25 (IQR 6-28) versus 23 (IQR 5-28), P=0.64
	Norepinephrine versus terlipressin (Morelli 2009)	Need for renal replacement therapy	8/15 versus 4/15 versus 5/15, P=0.29

Table 1. Morbidity outcomes - measures of renal function comparing several vasopressor regimens. Each single vasopressor is compared to other available vasopressor regimens. (*Continued*)

	Placebo (Choong 2009)	Urine output	1,7ml/kg/h (IQR 0.7 - 3.5) versus 1.5 ml/kg/h (IQR 0.7 -3.7), P=0.65
	Placebo (Malay 1999)	Creatinine	n.A.
Terlipressin	Norepinephrine versus vasopressin (Morelli 2009)	Need for renal replacement therapy	8/15 versus 4/15 versus 5/15, P=0.29
	Placebo (add on in patients on norepinephrine) (Morelli 2008a)	Urine output 4hours after study start	147ml/h±119 versus 96ml/h±48 (P=0.08)
Dopamine	Norepinephrine (Mathur 2007)	Post-treatment urine output	0.81ml/kg/h±0.75 versus 1.17ml/kg/h ± 0.47, P<0.05
	Norepinephrine (De Backer 2010)	Days free of renal support within 28 days	12.8 ± 12.4 days versus 14.0 ± 12.3 days, P=0.07

*All effects are presented as outcome in the vasopressor group (left hand column) versus comparator (second column) with a relative risk or P value for the difference between groups.

APPENDICES

Appendix 1. Search terms for MEDLINE (Ovid)

1. exp Vasoconstrictor Agents/ or exp Epinephrine/ or exp Norepinephrine/ or exp Catecholamines/ or exp Orciprenaline/ or exp dobutamine/ or exp Vasopressins/ or exp Argipressin/ or exp Deamino Arginine Vasopressin/ or exp Lypressin/ or exp Felypressin/ or exp Ornipressin/
2. (Epinephrine or Norepinephrine or Catecholamines or Orciprenaline or dobutamine or dopamine or adrenaline or noradrenaline or Vasopressins or Argipressin or Desmopressin or Lypressin or Felypressin or Ornipressin or Terlipressin or Glypressin or (Vasoconstrictor* adj3 Agent*)).mp.
3. 2 or 1
4. exp Shock, Cardiogenic/ or exp Shock, Hemorrhagic/ or exp shock/ or exp Sepsis Syndrome/ or exp Shock, Septic/ or exp Shock, Surgical/ or exp Shock, Traumatic/ or exp hypotension/ or exp Intensive Care, Neonatal/ or exp Intensive Care/
5. (shock or Sepsis Syndrome or Cardiogenic Shock or Hemorrhagic Shock or Haemorrhagic Shock or Septic Shock or Surgical Shock or Traumatic Shock or Anaphylactic Shock or Allergic Shock or Burn Shock).mp.
6. ((circulatory adj6 failure) or ((hypotension or neonatal) and (care adj5 (critical or intensive)))).mp.
7. 4 or 5 or 6

8. 3 and 7
9. ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) and humans.sh.
10. 8 and 9

Appendix 2. Search filter for the Cochrane Central Register of Controlled Trials (CENTRAL)

#1 MeSH descriptor Shock explode all trees
#2 MeSH descriptor Systemic Inflammatory Response Syndrome explode all trees
#3 MeSH descriptor Shock, Cardiogenic explode all trees
#4 MeSH descriptor Shock, Hemorrhagic explode all trees
#5 MeSH descriptor Shock, Septic explode all trees
#6 MeSH descriptor Shock, Surgical explode all trees
#7 MeSH descriptor Shock, Traumatic explode all trees
#8 MeSH descriptor Hypotension explode all trees
#9 MeSH descriptor Intensive Care, Neonatal explode all trees
#10 MeSH descriptor Intensive Care explode all trees
#11 circulatory near failure
#12 shock or Sepsis Syndrome or Cardiogenic Shock or Hemorrhagic Shock or Haemorrhagic Shock or Septic Shock or Surgical Shock or Traumatic Shock or Anaphylactic Shock or Allergic Shock or Burn Shock
#13 hypotension and ((critical near care) or (intensive near care))
#14 neonatal near intensive near care
#15 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14)
#16 MeSH descriptor Vasoconstrictor Agents explode all trees
#17 MeSH descriptor Epinephrine explode all trees
#18 MeSH descriptor Norepinephrine explode all trees
#19 MeSH descriptor Catecholamines explode all trees
#20 MeSH descriptor Orciprenaline explode all trees
#21 MeSH descriptor Dobutamine explode all trees
#22 MeSH descriptor Dopamine explode all trees
#23 MeSH descriptor Vasopressins explode all trees
#24 MeSH descriptor Arginine Vasopressin explode all trees
#25 MeSH descriptor Deamino Arginine Vasopressin explode all trees
#26 MeSH descriptor Lysine Vasopressin explode all trees
#27 MeSH descriptor Felypressin explode all trees
#28 MeSH descriptor Ornipressin explode all trees
#29 Vasoconstrictor near Agents
#30 Epinephrine or Norepinephrine or Catecholamines or Orciprenaline or dobutamine or dopamine or adrenaline or noradrenaline or Vasopressins or Argipressin or Desmopressin or Lypressin or Felypressin or Ornipressin or Terlipressin or Glypressin
#31 (#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30)
#32 (#15 AND #31)

Appendix 3. Search filter for EMBASE (Ovid SP)

1. Vasoconstrictor Agent/ or Adrenalin/ or Noradrenalin/ or Catecholamine/ or Orciprenaline/ or Dobutamine/ or Vasopressin Derivative/ or Argipressin/ or "Argipressin[1 Deamino]"/ or Lypressin/ or Felypressin/ or Ornipressin/
2. (Epinephrine or Norepinephrine or Catecholamines or Orciprenaline or dobutamine or dopamine or adrenaline or noradrenaline or Vasopressins or Argipressin or Desmopressin or Lypressin or Felypressin or Ornipressin or Terlipressin or Glypressin or (Vasoconstrictor* adj3 Agent*)).ti,ab.
3. 1 or 2
4. Cardiogenic Shock/ or Hemorrhagic Shock/ or Septic Shock/ or Shock/ or Sepsis/ or Traumatic Shock/ or Hypotension/ or Newborn Intensive Care/ or Intensive Care/ (141799)

5. (shock or Sepsis Syndrome or Cardiogenic Shock or Hemorrhagic Shock or Haemorrhagic Shock or Septic Shock or Surgical Shock or Traumatic Shock or Anaphylactic Shock or Allergic Shock or Burn Shock or ((circulatory adj6 failure) or ((hypotension or neonatal) and (care adj5 (critical or intensive))))).ti,ab.
6. 4 or 5
7. (placebo.sh. or controlled study.ab. or random*.ti,ab. or trial*.ti,ab.) and human*.ec,hw,fs.
8. 6 and 3 and 7

Appendix 4. Search filter forCINAHL (EBSCO host)

S1. TX circulatory failure
S2. MW (shock or Sepsis Syndrome or Carcinogenic Shock or Hemorrhagic Shock or Hemorrhagic Shock or Septic Shock or Surgical Shock Traumatic Shock or Anaphylactic Shock or Allergic Shock or Burn Shock)
S3. TX (hypotension and ((critical care) or (intensive care) or (neonatal intensive care)))
S4. S3 or S2 or S1
S5. TX Vasopressor or Vasoconstrictor or Epinephrine or Norepinephrine or Catecholamines or Orciprenaline or dobutamine or dopamine or adrenaline or noradrenaline or Vasopressins or Argipressin or Desmopressin or Lypressin or Felypressin or Ornipressin or Terlipressin or Glypressin
S6. S5 and S4
S7. TX (PLACEBO* or random* or trial* or control* or compar* or blind*)
S8. S6 and S7

Appendix 5. Search filter for BIOSIS (Ovid SP)

1. (circulatory failure or shock or Sepsis Syndrome or ((Cardiogenic or Hemorrhagic or Haemorrhagic or Septic or Surgical or Traumatic or Anaphylactic or Allergic or Burn) adj3 Shock) or (hypotension adj3 (critical care or intensive care or neonatal intensive care))).tw.
2. (Vasopressor* or Vasoconstrictor* or Epinephrine or Norepinephrine or Catecholamine* or Orciprenaline or dobutamine or dopamine or adrenaline or noradrenaline or Vasopressins or Argipressin or Desmopressin or Lypressin or Felypressin or Ornipressin or Terlipressin or Glypressin).ti,ab.
3. (PLACEBO* or random* or ((clinical or controlled) adj3 trial*)).ti,ab.
4. 1 and 3 and 2

Appendix 6. Search filter for PsycINFO (Ovid SP)

1. (circulatory failure or shock or Sepsis Syndrome or Cardiogenic Shock or Hemorrhagic Shock or Haemorrhagic Shock or Septic Shock or Surgical Shock or Traumatic Shock or Anaphylactic Shock or Allergic Shock or Burn Shock or (hypotension and (critical care or intensive care or neonatal intensive care))).af.
2. (Vasopressor or Vasoconstrictor or Epinephrine or Norepinephrine or Catecholamines or Orciprenaline or dobutamine or dopamine or adrenaline or noradrenaline or Vasopressins or Argipressin or Desmopressin or Lypressin or Felypressin or Ornipressin or Terlipressin or Glypressin).ti,ab.
3. (PLACEBO* or random* or trial*).af.
4. 1 and 2 and 3

Appendix 7. Search filter for Pascal Biomed

S1. TX circulatory failure
S2. MW (shock or Sepsis Syndrome or Carcinogenic Shock or Hemorrhagic Shock or Hemorrhagic Shock or Septic Shock or Surgical Shock Traumatic Shock or Anaphylactic Shock or Allergic Shock or Burn Shock)
S3. TX (hypotension and ((critical care) or (intensive care) or (neonatal intensive care)))
S4. S3 or S2 or S1
S5. TX Vasopressor or Vasoconstrictor or Epinephrine or Norepinephrine or Catecholamines or Orciprenaline or dobutamine or dopamine or adrenaline or noradrenaline or Vasopressins or Argipressin or Desmopressin or Lypressin or Felypressin or Ornipressin or Terlipressin or Glypressin
S6. S5 and S4

S7. TX (PLACEBO* or random* or trial* or control* or compar* or blind*)
S8. S6 and S7

WHAT'S NEW

Last assessed as up-to-date: 4 April 2011.

Date	Event	Description
5 April 2011	New citation required and conclusions have changed	This review is an update of the previous Cochrane systematic review (Müllner 2004) that included eight RCTs and excluded nine studies. In the previous version we searched the databases until November 2003. In this updated version we reran the searches to March 2010. This updated version contains 15 new RCTs (Albanese 2005: Annane 2007; Choong 2009; De Backer 2010; Lauzier 2006; Luckner 2006; Mathur 2007; Morelli 2008a; Morelli 2008b; Morelli 2009; Myburgh 2008; Patel 2010; Russell 2008; Seguin 2006; Yildizdas 2008;) and two new excluded studies (Sperry 2008; Schmoelz 2006) and three new ongoing studies (Cohn 2007; Fernandez 2006; Lienhart 2007). These new studies changed the conclusion of our review, in particular for the comparison of norepinephrine versus dopamine Change in authors: Bernhard Urbanek (co-author Müllner 2004) has left the review team. A new author (Jasmin Arrich) has joined the review team of this updated version
5 April 2011	New search has been performed	In this updated systematic review we reorganized all analyses and present new analyses for all comparisons and sensitivity analyses, 'Risk of bias' tables, and a 'Summary of findings' table

HISTORY

Protocol first published: Issue 3, 2002

Review first published: Issue 3, 2004

Date	Event	Description
7 August 2008	Amended	Minor edit to text
1 August 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

CH: revising the protocol for content and clarity; building a database for data extraction; selecting, reading, and comparing titles, abstracts, and papers; extracting data from studies; drafting a data extraction sheet; drafting the update review.

HL: selecting, reading, and comparing titles, abstracts, and papers; reading and correcting the full review.

JA: literature search; selecting, reading, and comparing titles, abstracts, and papers; drafting a data extraction sheet; data extraction; preparing the SoF-table; reading and correcting the full review.

GG: selecting, reading, and comparing titles, abstracts, and papers; drafting a data extraction sheet; data extraction; reading and correcting the full review.

MM: conception of the initial review; drafting the protocol; literature search; selecting, reading, and comparing titles, abstracts, and papers; drafting a data extraction sheet; data extraction; drafting the first review, reading and correcting the full review.

HH: conception of the update review; overseeing the search process, arbiter for trial selection in case of discrepancies, arbiter for data extraction in case of discrepancies; statistical analyses; drafting the update review.

DECLARATIONS OF INTEREST

None known

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- Medical University Vienna, where most of the reviewers are employed, Austria.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Drug Therapy, Combination; Hypotension [*drug therapy; mortality]; Randomized Controlled Trials as Topic; Shock [*drug therapy; mortality]; Shock, Septic [drug therapy; mortality]; Vasoconstrictor Agents [adverse effects; *therapeutic use]

MeSH check words

Humans