Scandinavian SSAI clinical practice guideline on choice of first-line vasopressor for patients with acute circulatory failure

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Background: Adult critically ill patients often suffer from acute circulatory failure, necessitating use of vasopressor therapy. The aim of the Scandinavian Society of Anaesthesiology and Intensive Care Medicine (SSAI) task force for Acute Circulatory Failure was to present clinically relevant, evidence-based treatment recommendations on this topic.
Methods: This guideline was developed according to standards for trustworthy guidelines, including a systematic review of the literature and use of the GRADE methodology for assessment of the quality of evidence and for moving from evidence to recommendations. We assessed the following subpopulations of patients with acute circulatory failure: 1) shock in general, 2) septic shock, 3) cardiogenic shock, 4) hypovolemic shock and 5) other types of shock, including vasodilatory shock. We assessed patient-important outcome measures, including mortality, serious adverse reactions and quality-of-life.
Results: For patients with shock in general and those with septic shock, we recommend using norepinephrine rather than dopamine, and we suggest using norepinephrine rather than epinephrine, vasopressin analogues, and phenylephrine. For patients with cardiogenic shock and those with hypovolemic shock, we suggest using norepinephrine rather than dopamine, and we provide no recommendations/suggestions of norepinephrine vs. epinephrine, vasopressin analogues, and phenylephrine. For patients with other types of shock, including vasodilatory shock, we suggest using norepinephrine rather than dopamine, epinephrine, vasopressin analogues, and phenylephrine.
Conclusions: We recommend using norepinephrine rather than other vasopressors as first-line treatment for the majority of adult critically ill patients with acute circulatory failure.

Editorial comment: what this article tells us
This guideline is focused on the choice of vasopressor in adult patients with shock. There is moderate quality of evidence supporting the use of norepinephrine in patients with shock in general and in those with septic shock. For patients with cardiogenic or hypovolemic shock, the quality of evidence is low.

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Acute circulatory failure or shock results in hypoperfusion and inadequate cellular oxygen utilisation. It is a life-threatening condition that needs prompt and appropriate treatment, since cellular hypoxia may progress to organ failure and death. Shock is a common condition in critical care medicine, affecting about one-third of patients in the intensive care unit (ICU).[1] Historically and academically, shock has been divided into four categories based on the presumed pathophysiological mechanism: (1) hypovolemic shock (e.g. internal or external fluid loss), (2) cardiogenic shock (e.g. ischaemia, heart failure or arrhythmias), (3) obstructive shock (e.g. pulmonary embolism, cardiac tamponade, or tension pneumothorax), and (4) distributive shock (e.g. severe sepsis or anaphylaxis from the release of inflammatory mediators).[2] In clinical practice, patients with shock can present with a combination of these mechanisms, and it may be more clinically relevant to divide shock into categories based on diagnostic groups.

Resuscitation of patients in shock must be early and aggressive to prevent or limit vital organ injury. Initial support of the failing circulation generally includes intravascular volume expansion in combination with the administration of a vasopressor.[1]

The Clinical Practice Committee of the Scandinavian Society of Anaesthesia and Intensive Care Medicine (SSAI) initiated this guideline on choice of first-line vasopressor in adult patients with acute circulatory failure. The aim was to summarise the available evidence and provide recommendations according to current standards for trustworthy guidelines.[3–5]

An electronic version of this guideline can be accessed at www.ssai.info/guidelines/

Methods

Process

The Clinical Practice Committee of SSAI appointed national members of the guideline task force for Acute Circulatory Failure (the authors of this paper). This group identified four key interventions needing guidelines, including fluid resuscitation,[6] vasopressor therapy, inotropic therapy, and cardiovascular diagnostics and monitoring. This is the group's second guideline: choice of first-line vasopressor for adult patients with acute circulatory failure.

Clinical question

'Which first-line vasopressor should be used for adult critically ill patients with acute circulatory failure'?

Population

The population of interest was adult patients (as defined in the original trials) with acute circulatory failure/shock (as defined in the original trials) receiving vasopressors in a high-dependency setting in hospital, including the emergency department, ICU, operating room, and recovery room. The following subpopulations were assessed: patients with (1) shock in general, (2) septic shock, (3) cardiogenic shock, (4) hypovolemic shock, and (5) other types of shock, including vasodilatory shock.

Intervention(s)

We assessed any dose of the following vasopressors: (1) dopamine, (2) vasopressin and its analogues, (3) epinephrine, and (4) phenylephrine.

Comparator

The control vasopressor was norepinephrine (any dose).

Outcome(s)

The following clinically relevant, patient-important outcome measures[7] were assessed at the time of longest follow-up:

1. Short-term mortality (90 days or less, including in-ICU and in-hospital mortality)
2. Long-term mortality (more than 90 days)
3. Quality-of-life as defined in the included trials
4. Ischaemic events as defined in the included trials

5. Use of renal replacement therapy
6. Acute kidney injury as defined in the included trials
7. Dysrhythmias as defined in the included trials
8. Length of stay (LOS) in hospital in days

We excluded systematic reviews and trials done in children and in elective surgery, those not reporting the predefined patient-important outcome measures, and those not comparing norepinephrine vs. other vasopressors, including those comparing combinations of vasopressors or head-to-head comparison of other vasopressors than norepinephrine. Systematic reviews and trials allowing use of adjuvant vasoconstrictive agents were not excluded.

Search strategy

We systematically searched PubMed (January 1966 to December 2015) and the Cochrane Library (Issue 12, December 2015) for systematic reviews of randomised clinical trials (RCTs) comparing norepinephrine with other vasopressors as first-line therapy. No language restriction was employed. If we found no relevant systematic review or subgroup analysis in reviews, we searched for RCTs in PubMed, Cochrane Library and Epistemonikos (search term (free text): 'vasopressor*').

Statistics and GRADE

Specific clinical questions were formulated using the relevant patient population and/or clinical problem (P), the intervention (I) under scrutiny, the comparator (C), and patient-important outcomes (O)[8] – PICO questions (Table 1).

Mantel-Haenszel statistics and random effects models were used to generate summary estimates (meta-analyses) if we found no updated meta-analyses (Review Manager Version 5.3, The Cochrane Collaboration, London, England).

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for formulating clinical questions, assessing the quality of evidence, generating anticipated absolute effects and for moving from evidence to recommendations.[5] In brief, we downgraded the quality of evidence (our confidence in the effect-estimates) for an intervention for identified risks of bias (including lack of blinding, or early termination of studies), inconsistency (unexplained heterogeneity), indirectness (including other patient populations or use of surrogate outcomes), imprecision (wide confidence interval around the effect estimate) or publication bias. Accordingly, the quality of evidence was rated from 'high' to 'very low'. We used GradePro v. 3.5 to prepare summary of finding tables with anticipated relative and absolute effects for the outcomes, together with our confidence in the effect-estimates (Material S1).

When moving from evidence to recommendations, four factors were considered and integrated: benefits and harms, quality of evidence, values and preferences (of patients or their proxies) and cost considerations. GRADE classifies recommendations as 'strong' when virtually all informed patients would choose the recommended management strategy. 'Weak' recommendations apply when fully informed patients would choose different management strategies, and reflects a close call between benefits and harms, uncertainty regarding treatment effects, questionable cost-effectiveness, or variability in values and preferences.[5,9] The group agreed upon all the recommendations in this guideline. Strong recommendations were given the wording 'we recommend', and weak recommendations 'we suggest'.

We followed the standards for trustworthy guidelines through use of the GRADE system, management of intellectual and financial conflicts of interest on a recommendation per recommendation basis (Material S2), a peer review process, and a plan for updating of recommendations. We did not include patient representatives in the guideline process.

Results

The results and recommendations based on the PICOs are presented below, in Table 2, and in the summary of finding tables given in the Material S1.

Table 1 Clinical research questions and PICO questions used to assess evidence relevant to this guideline statement.

	PICO Question			
Clinical question	Population (P)	Intervention (I)	Comparator (C)	Outcomes (O)
Should norepinephrine or other vasopressors be used as first-line treatment for adult patients with acute circulatory failure?	Adult patients with acute circulatory failure divided into the following subgroups: 1. Shock in general 2. Septic shock 3. Cardiogenic shock 4. Hypovolemic shock 5. Other types of shock, including vasodilatory shock	1. Dopamine 2. Epinephrine 3. Vasopressin analogues 4. Phenylephrine	Norepinephrine	1. Short-term mortality 2. Long-term mortality 3. Quality-of-life 4. Ischaemic events 5. Renal replacement therapy 6. Acute kidney injury 7. Dysrhythmias 8. Length of hospital stay

A. Norepinephrine vs. other vasopressors in patients with shock in general

1. We recommend that norepinephrine is used as first-line vasopressor for patients with shock in general rather than dopamine (strong recommendation, moderate quality of evidence).

A Cochrane systematic review and meta-analysis comprising a large RCT from 2010 comparing norepinephrine vs. dopamine in the treatment of shock (the SOAP II trial) found increased risk of dysrhythmias in patients treated with dopamine (Fig. 1, Table S1A).[10,11] No difference in short-term mortality, long-term mortality, ischaemic events, or hospital LOS was found (Fig. 1, Table S1A). Quality-of-life, RRT (dichotomous) and AKI were not assessed in the SOAP II trial.

The quality of evidence was downgraded due to imprecision.

2. We suggest that norepinephrine is used as first-line vasopressor for patients with shock in general rather than epinephrine (weak recommendation, low quality of evidence).

A small RCT from 2008 comparing norepinephrine and epinephrine in the treatment of shock in general found no difference in short-term mortality (Fig. 1, Table S1B).[12] No other outcome measures of interest have been assessed. We believe the potential harm associated with systematic epinephrine treatment in patients with shock has been inadequately assessed, which is why we suggest using norepinephrine.

Of note, this does not preclude the use of epinephrine targeting any underlying condition or co-existing disease in which epinephrine is indicated, including anaphylactic shock.

The quality of evidence was downgraded due to imprecision and risk of bias.

3. We suggest that norepinephrine is used as first-line vasopressor for patients with shock in general rather than vasopressin analogues (weak recommendation, very low quality of evidence).

No systematic reviews or RCTs reporting patient-important outcome measures have compared use of norepinephrine with vasopressin analogues in patients with shock in general (Table S1C). We believe the potential harm associated with systematic vasopressin analogue treatment in patients with shock has been inadequately assessed, which is why we – in accordance with patients with septic shock – suggest using norepinephrine.

Of note, this does not preclude the use of vasopressin analogues targeting any underlying condition or co-existing disease in which vasopressin analogues are indicated, including diabetes insipidus, coagulopathy, and variceal bleeding.

The quality of evidence was downgraded due to imprecision, risk of bias, and indirectness.

Table 2 Key recommendations and quality of evidence.

Recommendation	Strength of the recommendation	Benefits and harms	Quality of evidence Reason (s) for downgrading	Comments
Vasopressor treatment of patients with shock in general				
1. We recommend using norepinephrine rather than dopamine	Strong	No difference in short-term mortality, long-term mortality, ischaemic events or hospital LOS. Increased risk of dysrhythmias in patients treated with dopamine	Moderate due to imprecision	
2. We suggest using norepinephrine rather than epinephrine	Weak	No difference in short-term mortality. The potential harm associated with use of epinephrine has been inadequately assessed	Low due to imprecision and risk of bias	
3. We suggest using norepinephrine rather than vasopressin analogues	Weak	The potential harm associated with use of vasopressin analogues has been inadequately assessed	Very low due to imprecision, risk of bias, and indirectness	No data available for this population; data extrapolated from patients with septic shock
4. We suggest using norepinephrine rather than phenylephrine	Weak	The potential harm associated with use of phenylephrine has been inadequately assessed	Very low due to imprecision, risk of bias, and indirectness	No data available for this population; data extrapolated from patients with septic shock
Vasopressor treatment of patients with septic shock				
1. We recommend using norepinephrine rather than dopamine	Strong	Increased risk of dysrhythmias and short-term mortality in patients treated with dopamine	Moderate due to imprecision	
2. We suggest using norepinephrine rather than epinephrine	Weak	No difference in short-term mortality. The potential harm associated with use of epinephrine has been inadequately assessed	Low due to imprecision and risk of bias	
3. We suggest using norepinephrine rather than vasopressin analogues	Weak	No difference in short-term mortality, ischaemic events, dysrhythmias or use of renal replacement therapy. The potential harm associated with use of vasopressin analogues has been inadequately assessed	Low due to imprecision and risk of bias	
4. We suggest using norepinephrine rather than epinephrine	Weak	No difference in short-term mortality. The potential harm associated with use of phenylephrine has been inadequately assessed	Low due to imprecision and risk of bias	

Table 2 (Continued)

Recommendation	Strength of the recommendation	Benefits and harms	Quality of evidence Reason (s) for downgrading	Comments
Vasopressor treatment of patients with cardiogenic shock				
1. We suggest using norepinephrine rather than dopamine	Weak	Possible increased risk of short-term mortality. The harm associated with dopamine treatment in patients with shock in general and those with septic shock, cautions use in other subgroups, including patients with cardiogenic shock	Low due to imprecision and risk of bias	Limited data available
2. Norepinephrine vs. epinephrine	None			No data available; no relevant populations to extrapolate data from
3. Norepinephrine vs. vasopressin analogues	None			No data available; no relevant populations to extrapolate data from
4. Norepinephrine vs. phenylephrine	None			No data available; no relevant populations to extrapolate data from
Vasopressor treatment of patients with hypovolemic shock				
1. We suggest using norepinephrine rather than dopamine	Weak	No difference in short-term mortality. The harm associated with dopamine treatment in patients with shock in general and those with septic shock, cautions use in other subgroups, including patients with hypovolemic shock	Low due to imprecision and risk of bias	Limited data available
2. Norepinephrine vs. epinephrine	None			No data available; no relevant populations to extrapolate data from
3. Norepinephrine vs. vasopressin analogues	None			No data available; no relevant populations to extrapolate data from
4. Norepinephrine vs. phenylephrine	None			No data available; no relevant populations to extrapolate data from
Vasopressor treatment of patients with other types of shock, including vasodilatory shock				
1. Norepinephrine vs. dopamine	Weak	The harm associated with dopamine treatment in patients with shock in general and those with septic shock, cautions use in other subgroups, including patients with other types of shock, including vasodilatory shock	Low due to imprecision, and indirectness	No data available for this population; data extrapolated from patients with septic shock

Table 2 (Continued)

Recommendation	Strength of the recommendation	Benefits and harms	Quality of evidence Reason (s) for downgrading	Comments
2. We suggest using norepinephrine rather than epinephrine	Weak	No difference in short-term mortality. The potential harm associated with use of epinephrine has been inadequately assessed	Low due to imprecision and risk of bias	Limited data available
3. We suggest using norepinephrine rather than vasopressin analogues	Weak	No difference in short-term mortality, ischaemic events or renal replacement therapy. The potential harm associated with use of vasopressin analogues has been inadequately assessed	Low due to imprecision and risk of bias	Limited data available
4. Norepinephrine vs. phenylephrine	Weak	The potential harm associated with use of phenylephrine has been inadequately assessed	Very low due to imprecision, risk of bias, and indirectness	No data available for this population; data extrapolated from patients with septic shock

4. We suggest that norepinephrine is used as first-line vasopressor for patients with shock in general rather than phenylephrine (weak recommendation, very low quality of evidence).

No systematic reviews or RCTs reporting patient-important outcome measures have compared use of norepinephrine with phenylephrine in patients with shock in general (Table S1D). We believe the potential harm associated with systematic phenylephrine treatment in patients with shock has been inadequately assessed, which is why we – in accordance with patients with septic shock – suggest using norepinephrine.

The quality of evidence was downgraded due to imprecision, risk of bias, and indirectness.

B. Norepinephrine vs. other vasopressors in patients with septic shock

1. We recommend that norepinephrine is used as first-line vasopressor for patients with septic shock rather than dopamine (strong recommendation, moderate quality of evidence).

A 2012 systematic review comprising six RCTs comparing use of norepinephrine vs. dopamine in patients with septic shock[13] showed increased risk of mortality and dysrhythmias with dopamine as compared to norepinephrine (Fig. 2, Table S2A). Notable is the weight in the meta-analysis of a subgroup from a large RCT (the SOAP II trial[10]). No difference in hospital LOS was found (Fig. 2, Table S2A). No other outcome measures of interest have been assessed.

Of note, another recently published systematic review by Avni et al.[14] was considered but excluded, as a result of methodological limitations, including no published/registered protocol, inclusion of several high risk of bias trials, no continuity correction in the no event trials (sensitivity analysis), and no assessment of the risk of random errors.[15]

The quality of evidence was downgraded due to imprecision.

2. We suggest that norepinephrine is used as first-line vasopressor for patients with septic shock rather than epinephrine (weak recommendation, low quality of evidence).

A small RCT from 2008 comparing norepinephrine vs. epinephrine in the treatment of shock in general, including a subgroup of patients with septic shock, found no difference in short-term mortality (Fig. 2, Table S2B).[12] No

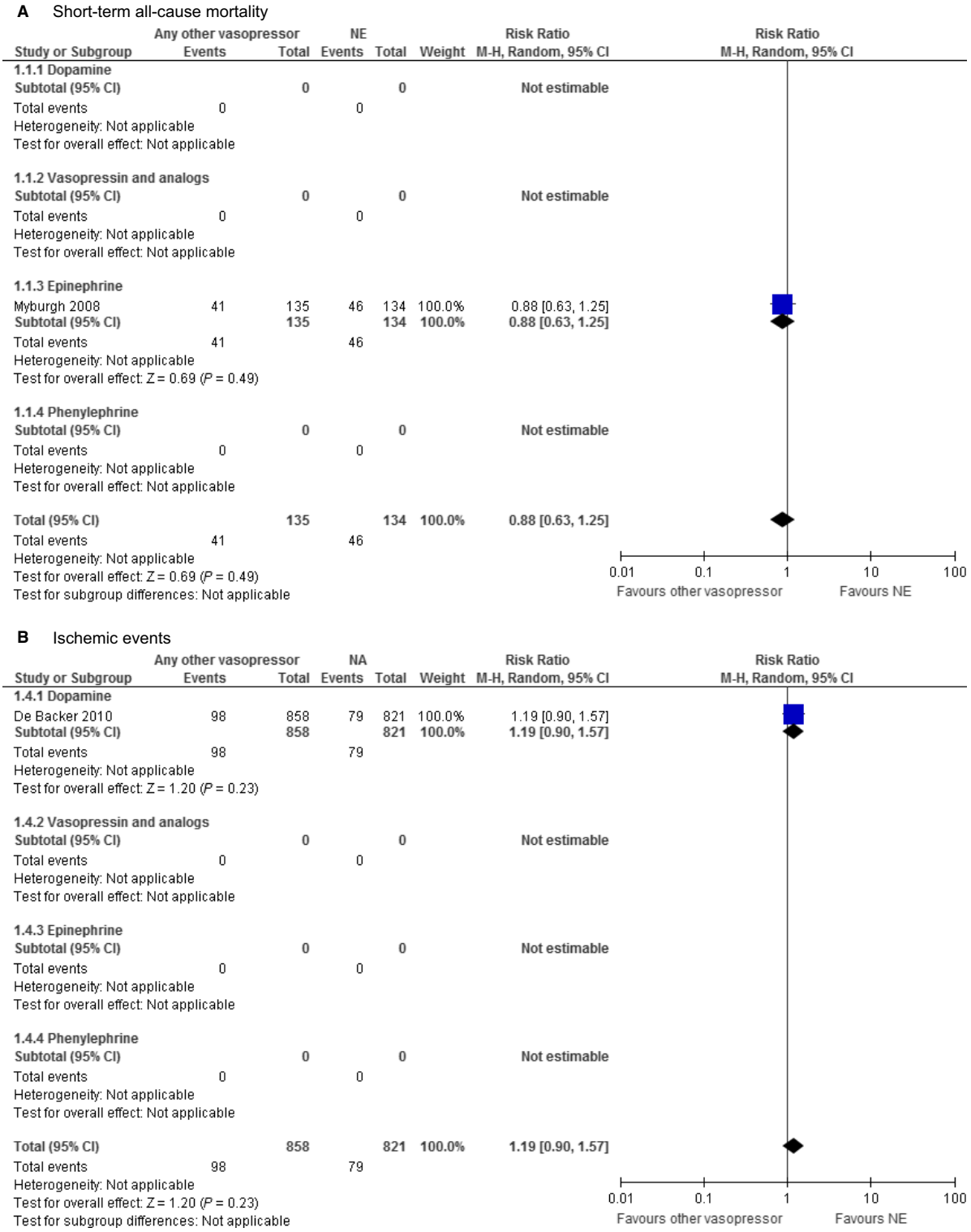
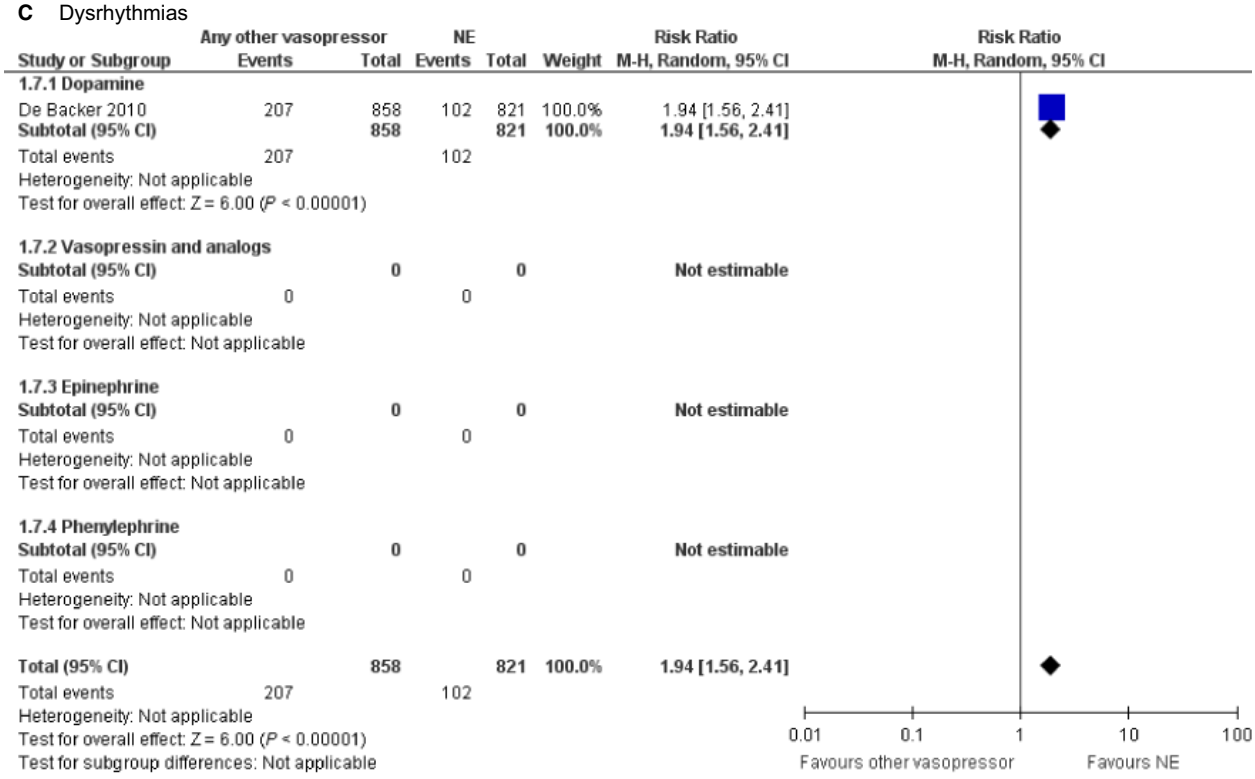


Fig. 1. Forest plot of (A) short-term all-cause mortality, (B) Ischemic events, (C) dysrhythmias, and (D) hospital length of stay in randomised trials of norepinephrine (NE) vs. other vasopressors for patients with shock in general. Size of squares for risk ratio reflects weight of trial in pooled analyses. Horizontal bars represent 95% confidence intervals.

C Dysrhythmias



D Hospital length of stay

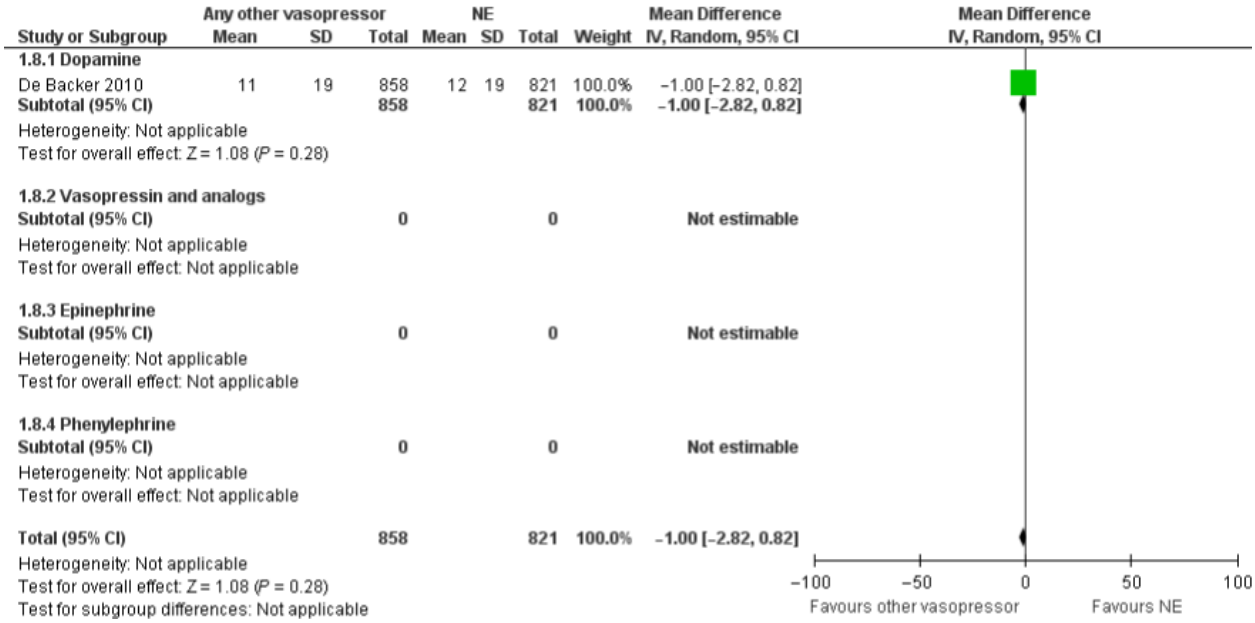


Fig. 1. Continued

other outcome measures of interest have been assessed. We believe the potential harm associated with systematic epinephrine treatment in patients with septic shock has been inadequately assessed, which is why we suggest using norepinephrine.

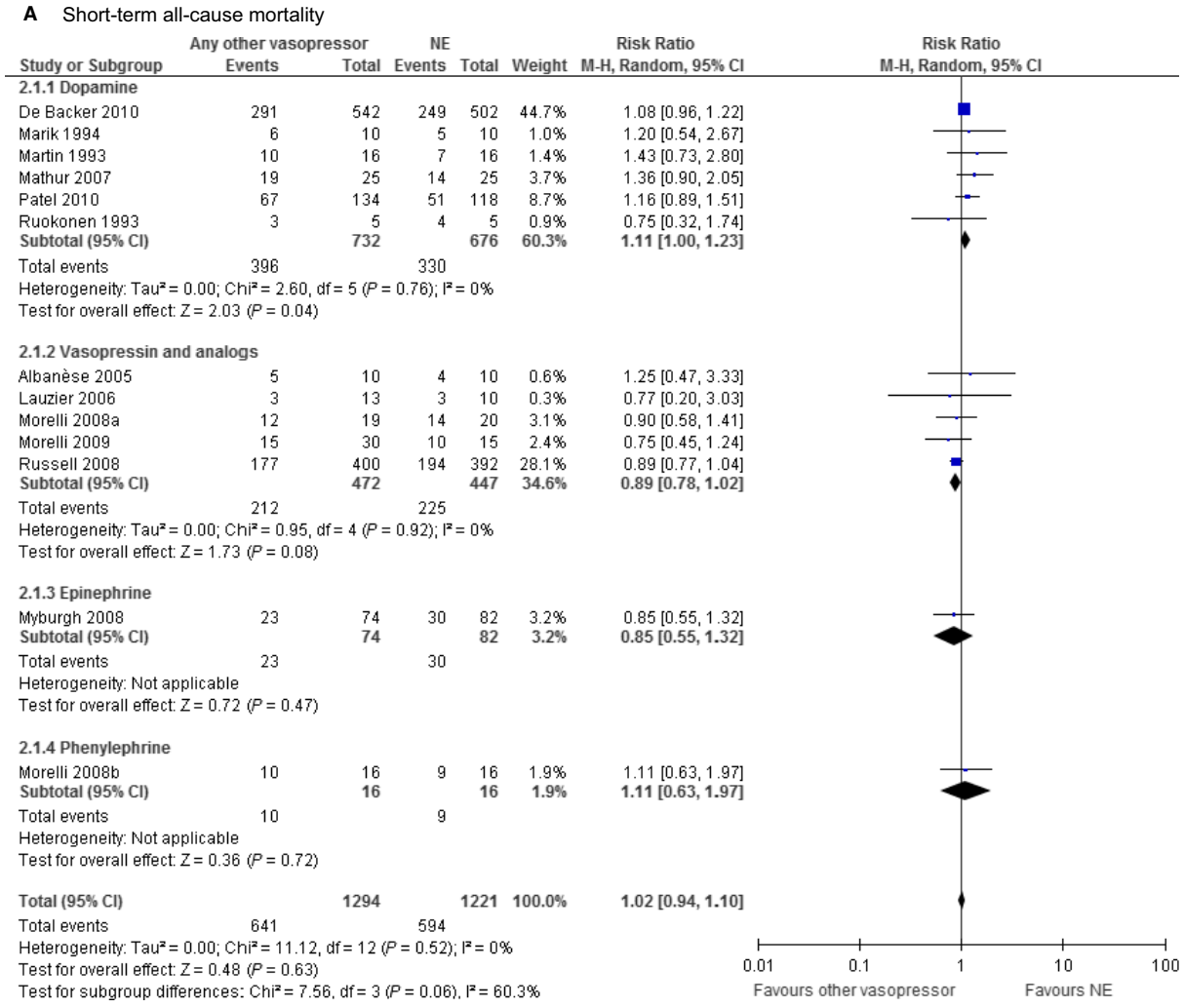


Fig. 2. Forest plot of (A) short-term all-cause mortality, (B) ischaemic events, (C) renal replacement therapy, (D) dysrhythmias, and (E) hospital length of stay in randomised trials of norepinephrine (NE) vs. other vasopressors for patients with septic shock. Size of squares for risk ratio reflects weight of trial in pooled analyses. Horizontal bars represent 95% confidence intervals.

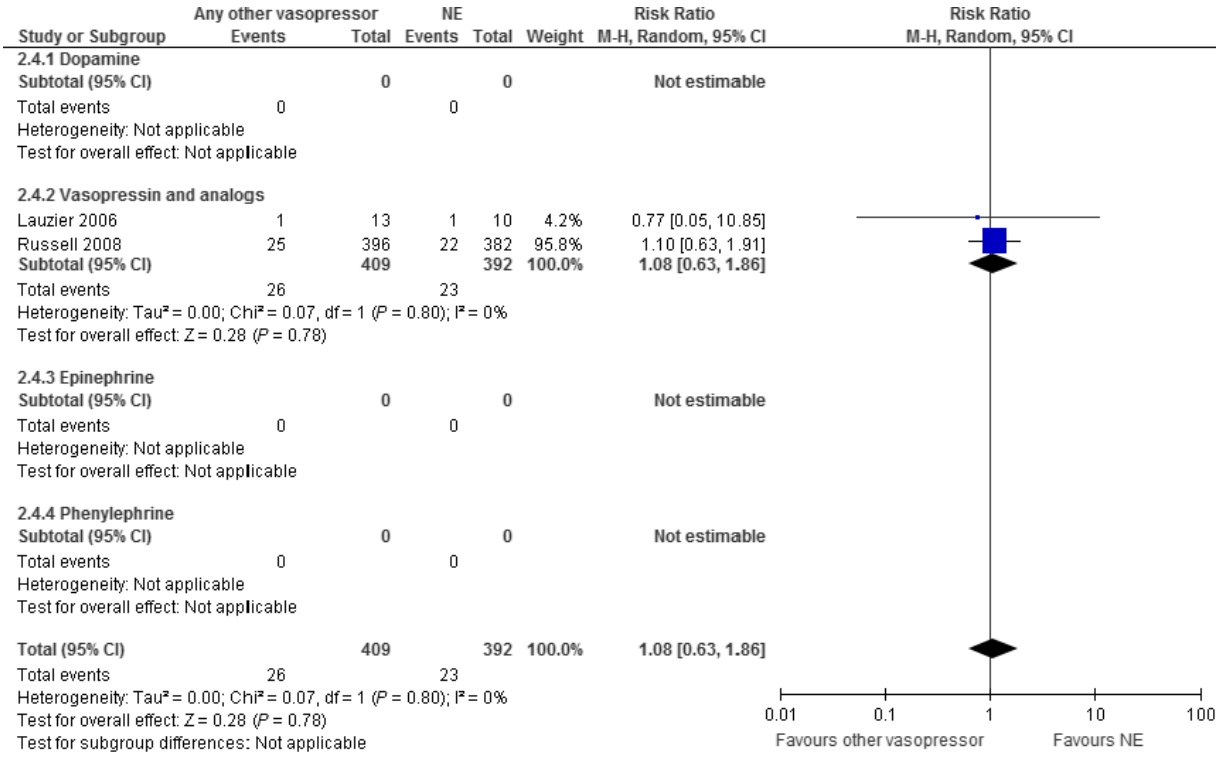
Of note, this does not preclude the use of epinephrine targeting any underlying condition or co-existing disease in which epinephrine is indicated, including anaphylactic shock.

The quality of evidence was downgraded due to imprecision and risk of bias.

> 3. We suggest that norepinephrine is used as first-line vasopressor for patients with septic shock rather than vasopressin analogues (weak recommendation, low quality of evidence).

In an updated meta-analysis comprising five trials[16–20], we found no difference in short-term mortality, ischaemic events, dysrhythmias, or use of renal replacement therapy in patients with septic shock treated with norepinephrine vs. vasopressin analogues (Fig. 2, Table S2C). None of the other outcome measures of interest have been assessed. We believe the potential harm associated with systematic vasopressin treatment in patients with septic shock has been inadequately assessed, which is why we suggest using norepinephrine.

B Ischemic events



C Renal replacement therapy

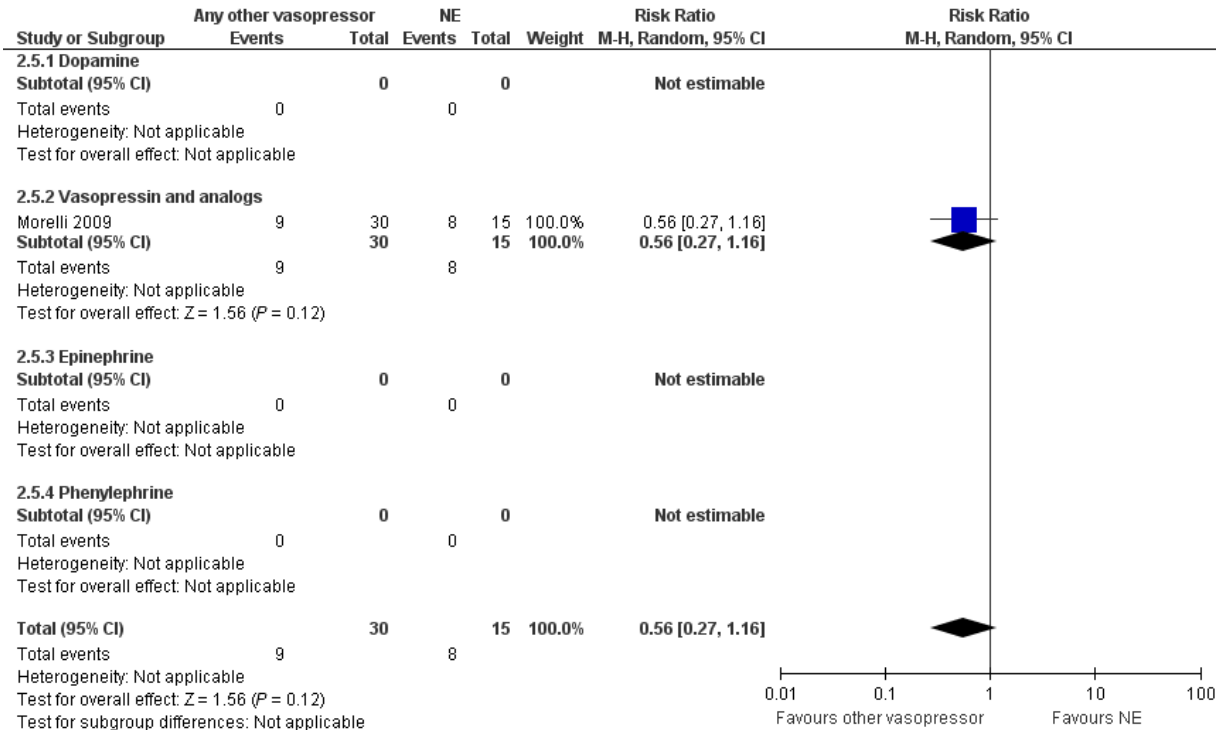
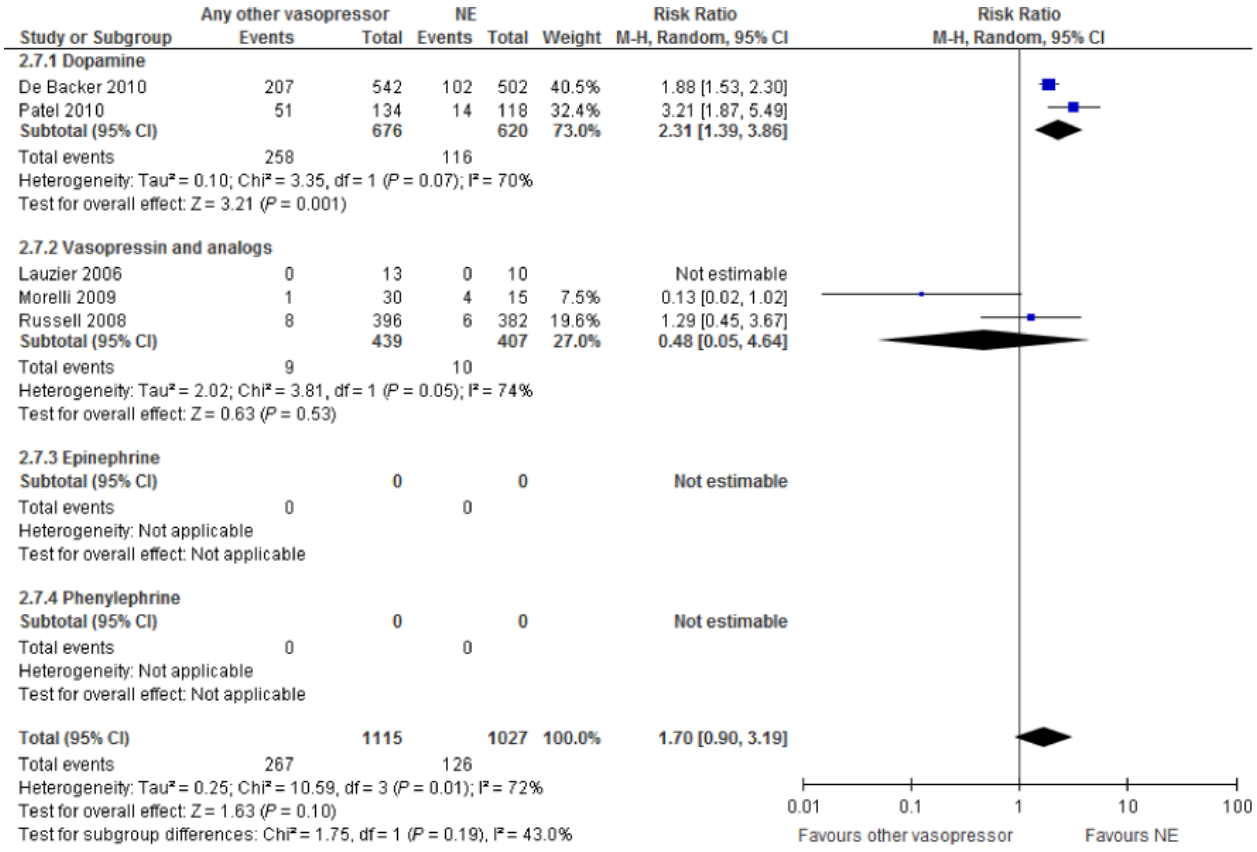


Fig. 2. Continued

D Dysrhythmias



E Hospital length of stay

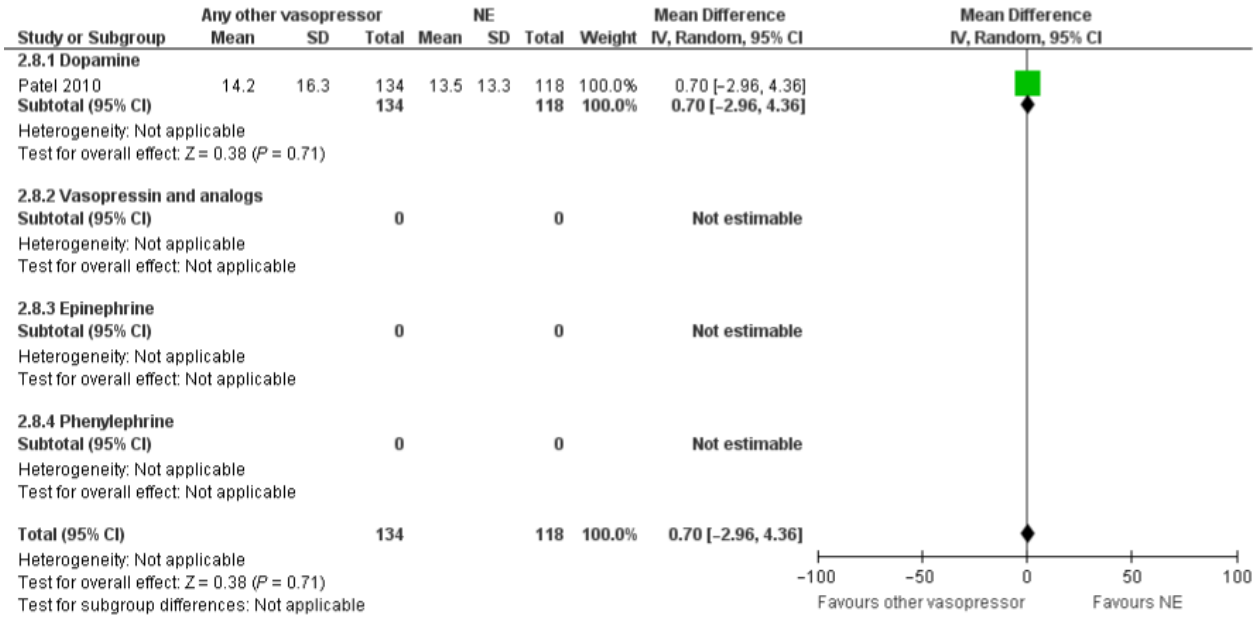


Fig. 2. Continued

Of note, this does not preclude the use of vasopressin analogues targeting any underlying condition or co-existing disease in which vasopressin analogues are indicated, including diabetes insipidus, coagulopathy, and variceal bleeding.

The quality of evidence was downgraded due to imprecision and risk of bias.

> 4. We suggest that norepinephrine is used as first-line vasopressor for patients with septic shock rather than phenylephrine (weak recommendation, low quality of evidence).

In a small RCT,[21] no difference in short-term mortality between norepinephrine vs. phenylephrine was found (Fig. 2, Table S2D). None of the other outcome measures of interest have been assessed. We believe the potential harm associated with systematic phenylephrine treatment in patients with shock has been inadequately assessed, which is why we suggest using norepinephrine.

The quality of evidence was downgraded due to imprecision and risk of bias.

C. Norepinephrine vs. other vasopressors in patients with cardiogenic shock

> 1. We suggest that norepinephrine is used as first-line vasopressor for patients with cardiogenic shock rather than dopamine (weak recommendation, low quality of evidence).

In a predefined subgroup of patients with cardiogenic shock included in the SOAP II trial (norepinephrine vs. dopamine in patients with shock in general),[10] no difference in the overall effect of treatment between the three subgroups assessed was reported ($P = 0.87$ for interaction). However, the rate of death at 28 days was significantly higher among patients with cardiogenic shock who were treated with dopamine than among those treated with norepinephrine (Table S3A).[10] No other outcome measures of interest have been assessed. We believe the potentially increased risk of mortality, and the harm associated with dopamine treatment in patients with shock in general (dysrhythmias), cautions use of dopamine in patients with cardiogenic shock, which is why we suggest using norepinephrine.

Importantly, inotropes – and not vasopressors – are considered the main therapy in patients with cardiogenic shock. Excessive dose dependent vasoconstriction may affect cardiac output adversely. Use of inotropes in adult patients with acute circulatory failure will be covered in an upcoming SSAI clinical practice guideline.

The quality of evidence was downgraded due to risk of bias and imprecision.

> 2,3,4. Norepinephrine vs. epinephrine/vasopressin analogues/phenylephrine for patients with cardiogenic shock: no recommendation/suggestion.

We could not identify any systematic reviews or RCTs comparing norepinephrine vs. epinephrine, vasopressin, or phenylephrine in patients with cardiogenic shock. We refrain from giving any recommendations or suggestions on using norepinephrine or epinephrine/vasopressin/phenylephrine in patients with cardiogenic shock, as these patients are different entities than patients with shock in general/septic shock. Importantly, norepinephrine has been investigated quantitatively and qualitatively more thoroughly than epinephrine, vasopressin and phenylephrine. Consequently, we strongly recommend that if clinicians prefer to use vasopressors other than norepinephrine in patients with cardiogenic shock, they do so in the context of high-quality RCTs given the lack of data on the balance between benefits and harms of these drugs.

Importantly, inotropes – and not vasopressors – are considered the main therapy in patients with cardiogenic shock. Excessive dose dependent vasoconstriction may affect cardiac output adversely. Use of inotropes in adult patients with acute circulatory failure will be covered in an upcoming SSAI clinical practice guideline.

D. Norepinephrine vs. other vasopressors in patients with hypovolemic shock

> 1. We suggest that norepinephrine is used as first-line vasopressor for patients with hypovolemic shock rather than dopamine (weak recommendation, low quality of evidence).

In a predefined subgroup of patients with hypovolemic shock in the SOAP II trial (norepinephrine vs. dopamine in patients with shock in general), no difference in short-term mortality was reported (Table S4A)[10]. No other outcome measures of interest have been assessed. We believe the harm associated with dopamine treatment in patients with shock in general (dysrhythmias) cautions use in other subgroups, including patients with hypovolemic shock, which is why we suggest using norepinephrine.

Importantly, adequate fluid resuscitation should be a priority in patients with hypovolemic shock, as excessive dose dependent vasoconstriction may affect cardiac output adversely.

The quality of evidence was downgraded due to imprecision and risk of bias.

> 2,3,4. Norepinephrine vs. epinephrine/vasopressin analogues/phenylephrine for patients with hypovolemic shock: no recommendation/suggestion.

We could not identify any systematic reviews or RCTs comparing norepinephrine vs. epinephrine, vasopressin, or phenylephrine in patients with hypovolemic shock. We refrain from giving any recommendations or suggestions on using norepinephrine or epinephrine/vasopressin/phenylephrine in patients with hypovolemic shock, as these patients are different entities than patients with shock in general/septic shock. Importantly, norepinephrine has been investigated quantitatively and qualitatively more thoroughly than epinephrine, vasopressin, and phenylephrine. Consequently, we strongly recommend that if clinicians prefer to use vasopressors other than norepinephrine in patients with hypovolemic shock, they do so in the context of high-quality RCTs given the lack of data on the balance between benefits and harms of these drugs.

Importantly, adequate fluid resuscitation should be a priority in patients with hypovolemic shock, as excessive dose-dependent vasoconstriction may affect cardiac output adversely.

E. Norepinephrine vs. other vasopressors in patients with other types of shock, including vasodilatory shock

> 1. We suggest that norepinephrine is used as first-line vasopressor for patients with other types of shock, including vasodilatory shock rather than dopamine (weak recommendation, low quality of evidence).

We could not identify any systematic reviews or RCTs comparing norepinephrine vs. dopamine in patients with other types of shock, including vasodilatory shock. We believe the harm associated with use of dopamine in patients with shock in general (dysrhythmias) and septic shock (short-term mortality and dysrhythmias) cautions use in other subgroups, including patients with other types of shock, including vasodilatory shock. Consequently, we suggest using norepinephrine.

The quality of evidence was downgraded due to imprecision and indirectness.

> 2. We suggest that norepinephrine is used as first-line vasopressor for patients with other types of shock, including vasodilatory shock rather than epinephrine (weak recommendation, low quality of evidence).

A small RCT from 2008 comparing norepinephrine vs. epinephrine in the treatment of shock in general, including a subgroup of patients with other types of shock including vasodilatory shock, found no difference in short-term mortality (Fig. 3, Table S5B).[12] No other outcome measures of interest have been assessed. We believe the potential harm associated with epinephrine treatment in patients with other types of shock, including vasodilatory shock has been inadequately assessed, which is why we suggest using norepinephrine.

Of note, this does not preclude the use of epinephrine targeting any underlying condition or

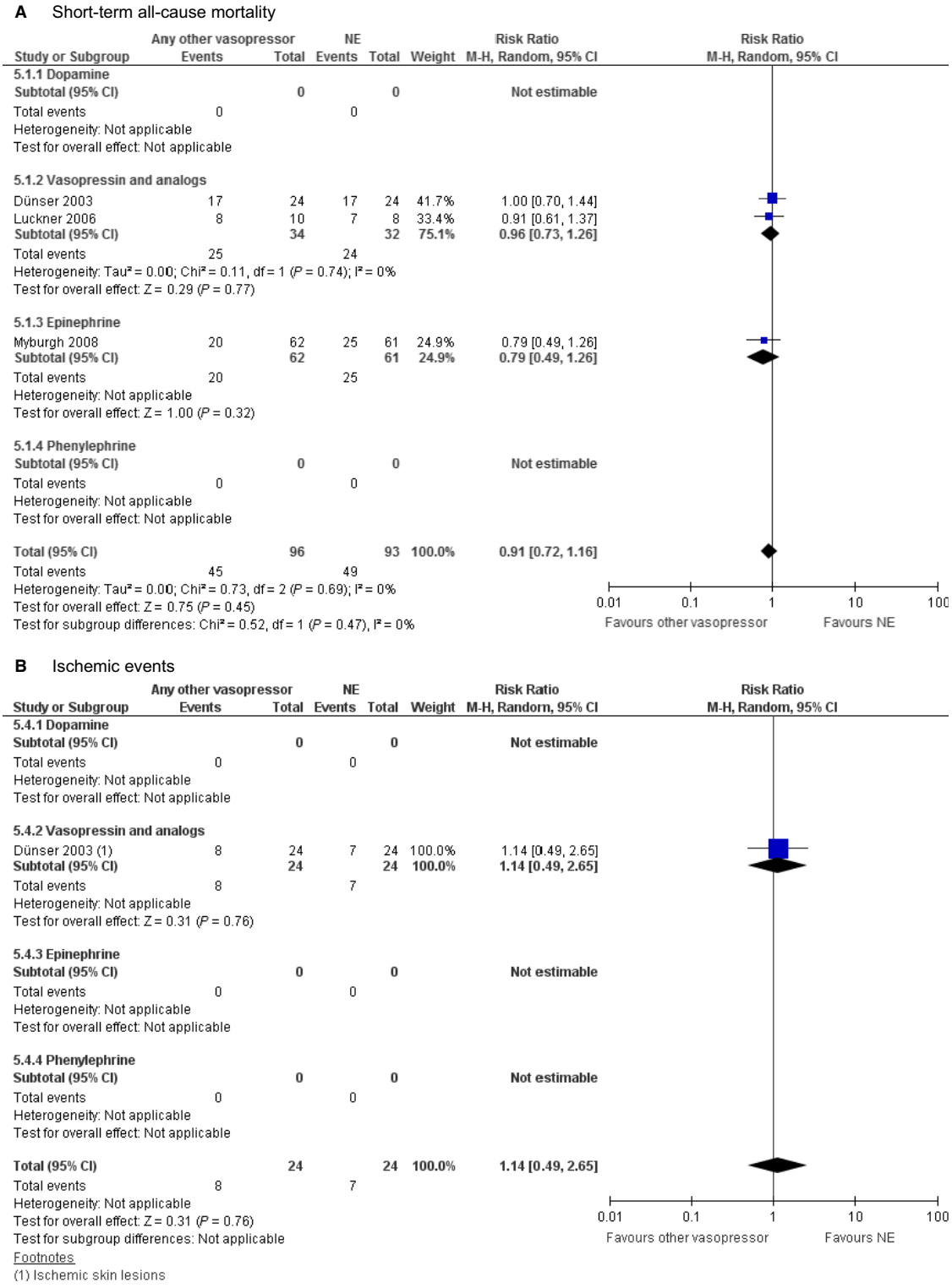
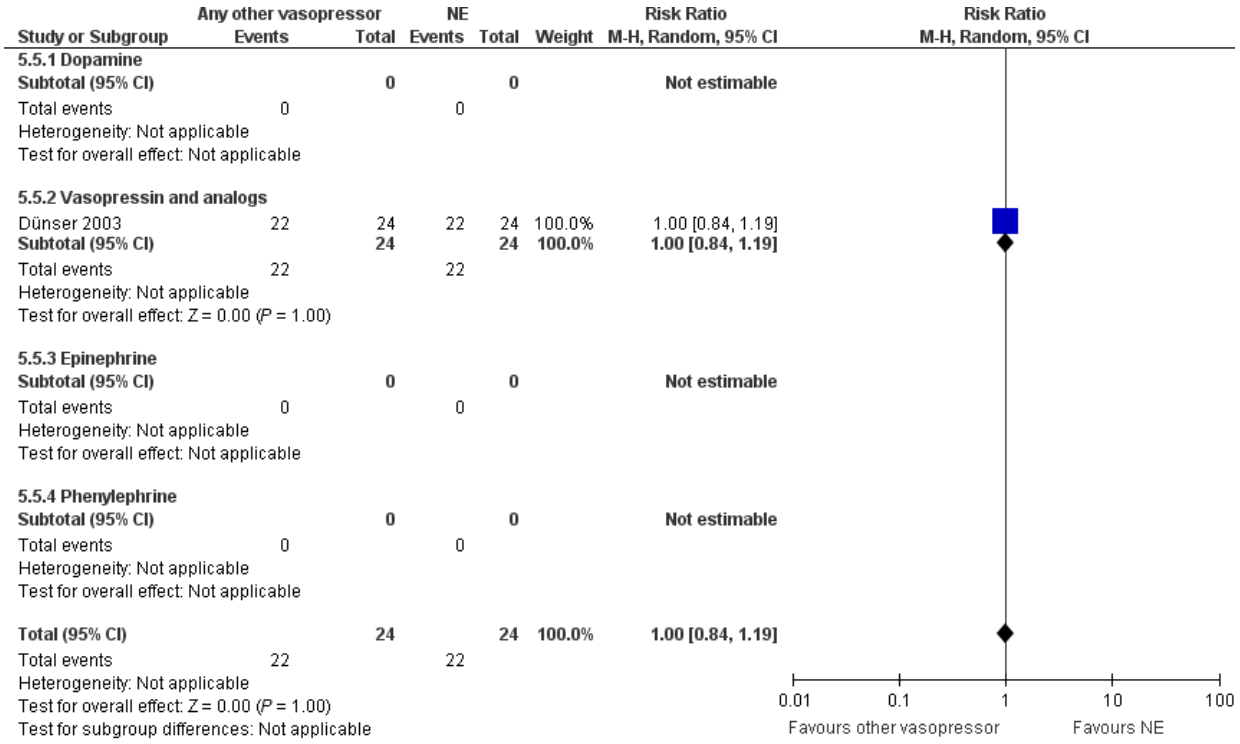


Fig. 3. Forest plot of (A) short-term all-cause mortality, (B) ischaemic events, (C) renal replacement therapy, and (D) dysrhythmias in randomised trials of norepinephrine (NE) vs. other vasopressors for patients with other types of shock, including vasodilatory shock. Size of squares for risk ratio reflects weight of trial in pooled analyses. Horizontal bars represent 95% confidence intervals.

C Renal replacement therapy



D Dysrhythmias

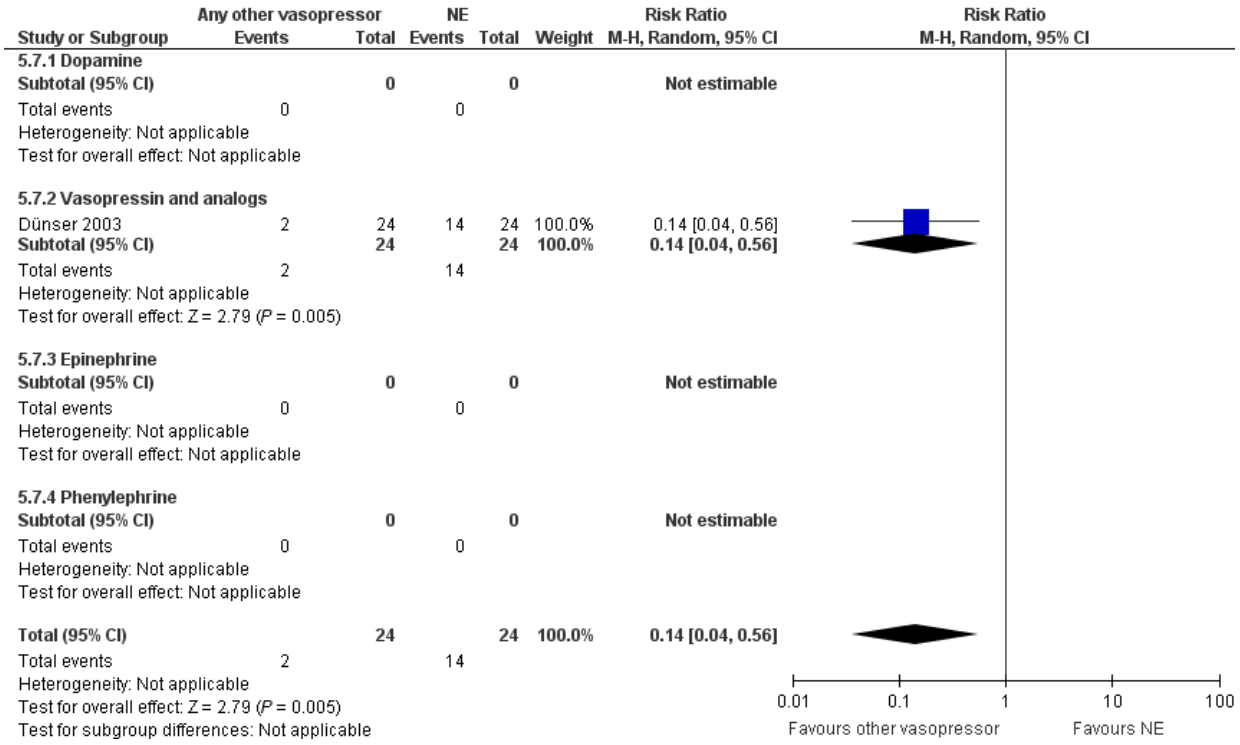


Fig. 3. Continued

co-existing disease in which epinephrine is indicated, including anaphylactic shock.

The quality of evidence was downgraded due to imprecision and risk of bias.

> 3. We suggest that norepinephrine is used as first-line vasopressor for patients with other types of shock, including vasodilatory shock rather than vasopressin analogues (weak recommendation, low level of evidence).

A systematic review comprising two RCTs (n = 66)[22,23] comparing use of norepinephrine vs. vasopressin analogues in patients with vasodilatory shock, found no difference in short-term mortality, ischaemic events, or renal replacement therapy (Fig. 3, Table S5C).[24] Of note, an increased risk of dysrhythmias in patients treated with norepinephrine was suggested (Fig. 3, Table S5C). No other patient-important outcome measures were asssessed. We believe the potential harm associated with treatment with vasopressin analogues in patients with other types of shock, including vasodilatory shock has been inadequately assessed, which is why we suggest using norepinephrine. Another recently published systematic review by Polito et al.[25] was considered but excluded, as a result of methodological shortcomings.

Of note, this does not preclude the use of vasopressin analogues targeting any underlying condition or co-existing disease in which vasopressin analogues are indicated, including diabetes insipidus, coagulopathy, and variceal bleeding.

The quality of evidence was downgraded due to imprecision and risk of bias.

> 4. We suggest that norepinephrine is used as first-line vasopressor for patients with other types of shock, including vasodilatory shock rather than phenylephrine (weak recommendation, very low level of evidence).

We could not identify any systematic reviews or RCTs comparing norepinephrine vs. phenylephrine in patients with other types of shock, including vasodilatory shock (Table S5C). We believe the potential harm associated with phenylephrine treatment in patients with shock has been inadequately assessed, which is why we – in accordance with patients with septic shock – suggest using norepinephrine.

The quality of evidence was downgraded due to imprecision, risk of bias, and indirectness.

Discussion

This guideline on vasopressor therapy in adult critically ill patients with acute circulatory failure has been prepared in accordance with GRADE[5] to inform readers about clinically relevant issues based on current best evidence, and to avoid advice based solely on expert opinion.

We were able to use existing systematic reviews and RCTs to answer the majority of clinical questions concerning choice of first-line vasopressor in patients with shock in general and in those with septic shock. However, for patients with cardiogenic-, hypovolemic-, and other types of shock, the quantity and quality of evidence was very limited.

In general, the most widely studied comparisons were norepinephrine vs. dopamine, followed by norepinephrine vs. vasopressin analogues, whereas norepinephrine vs. epinephrine and phenylephrine has hardly been assessed.

We propose two strong recommendations favouring norepinephrine over dopamine in patients with shock in general and in those with septic shock. This was based on overall low confidence of benefit from dopamine, and importantly, confidence of harm of dopamine in terms of increased risk of dysrhythmias (shock in general/septic shock) and increased risk of mortality (septic shock).

For patients with shock in general and those with septic shock, we suggest using norepinephrine over other vasopressors, as norepinephrine is the most widely studied vasopressor. The quantity and quality of evidence on use of epinephrine, vasopressin analogues, and phenylephrine is sparse, with the eminent risk of overestimating benefit and underestimating harm.[26] Several interventions which are common practice in the ICU have been adopted based on the perception of improved physiological parameters and physiological reasoning, including changes in blood-pressure, urinary output, and biomarkers (surrogate outcomes). Importantly, surrogate outcome

measures overestimate intervention effects by 40–50%, compared to patient-centred outcome measures.[27] In a recently published analysis of multicentre trials of critical care interventions, eight interventions were shown to actually increase mortality.[28] Also, there is empirical evidence that guideline recommendations based on data from trials with lower quality have changed direction once higher quality trials have been published.[29] Therefore, it is recommended that clinicians who consider other vasopressors than norepinephrine should do so in the context of RCTs. In this context, the results of the completed but currently unpublished VANISH trial of norepinephrine vs. vasopressin in patients with septic shock are very much awaited.[30]

For patients with cardiogenic shock and those with hypovolemic shock, we suggest using norepinephrine over dopamine. This was based on overall low confidence of benefit from dopamine, and importantly, the observed risk of harm associated with dopamine treatment in patients with shock in general[10,11] and those with septic shock.[13] We believe this caution concerning dopamine use can also be extended (extrapolated) to other subgroups, including patients with cardiogenic shock and hypovolemic shock. Because of no available data, we were not able to provide recommendations/suggestions for norepinephrine vs. epinephrine/vasopressin analogues/phenylephrine in patients with cardiogenic shock and hypovolemic shock. We refrained from extrapolation from patients with shock in general/septic shock, as patients with cardiogenic shock and hypovolemic shock are different entities.

For patients with other types of shock, including vasodilatory shock, we suggest using norepinephrine over dopamine, epinephrine, vasopressin analogues, and phenylephrine, due to the overall low confidence of benefit from dopamine/epinephrine/vasopressin analogues/phenylephrine, and importantly, since the potential harm associated with treatment with dopamine/epinephrine/vasopressin analogues/phenylephrine has been inadequately assessed.

The strengths of the present guideline include the application of current standards for trustworthy guidelines, including the GRADE methodology,[5] which support a systematic and transparent process. The limitations include the reliance upon existing systematic reviews for some recommendations, including the risk of trial heterogeneity and indirectness. Furthermore, not all of the included systematic reviews and trials have been designed as a direct comparison between norepinephrine and another vasopressor, as some trials have used adjuvant (second-line) vasoconstrictive agents, including vasopressin analogues in catecholamine refractory septic shock. Consequently, some of the benefits and harms observed may partly be caused by other adjuvant agents used and/or induced changes in dosing of the vasopressors assessed. Complicated cases of acute circulatory failure, including patients with catecholamine refractory shock may not be covered by the present guideline. Overall, the quantity and quality of evidence on vasopressor use in patients with acute circulatory failure is limited, and additional high-quality trials on the preferred vasopressor in these patients are needed. Furthermore, our recommendations have been restricted to those that can be based on findings from randomised trials only. It is possible that observational studies can provide some valuable evidence to help form some recommendations, however, this type of evidence is rare.[31] Finally, our guideline group did not include critical care nurses or other relevant stakeholders, including patient-groups, relatives, and representatives of regulatory bodies and hospital owners.

In conclusion, we recommend/suggest using norepinephrine as first-line therapy rather than other vasopressors in patients with shock in general and in those with septic shock. In patients with cardiogenic-, hypovolemic, and other types of shock, the quantity and quality of evidence was in general low, and additional high-quality data are needed. We suggest using norepinephrine in these patients too, as the potential harm associated with systematic use of other vasopressors has been inadequately assessed. For some clinical questions, no data were available, and we refrained from giving any recommendations or suggestions in these circumstances.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Material S1.
Table S1. Summary of findings for patients with shock in general
Table S2. Summary of findings for patients with septic shock
Table S3. Summary of findings for patients with cardiogenic shock
Table S4. Summary of findings for patients with hypovolemic shock
Table S5. Summary of findings for patients with other types of shock, including vasodilatory shock
Material S2. Conflicts of interest.