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Scandinavian SSAI clinical practice guideline on choice of inotropic agent for patients with acute circulatory failure

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Background: Adult critically ill patients often suffer from acute circulatory failure and those with low cardiac output may be treated with inotropic agents. The aim of this Scandinavian Society of Anaesthesiology and Intensive Care Medicine guideline was to present patient-important treatment recommendations on this topic.

Methods: This guideline was developed according to GRADE. We assessed the following subpopulations of patients with shock: (1) shock in general, (2) septic shock, (3) cardiogenic shock, (4) hypovolemic shock, (5) shock after cardiac surgery, and (6) other types of shock, including vasodilatory shock. We assessed patient-important outcome measures, including mortality and serious adverse reactions.

Results: For all patients, we suggest against the routine use of any inotropic agent, including dobutamine, as compared to placebo/no treatment (very low quality of evidence). For patients with shock in general, and in those with septic and other types of shock, we suggest using dobutamine rather than levosimendan or epinephrine (very low quality of evidence). For patients with cardiogenic shock and in those with shock after cardiac surgery, we suggest using dobutamine rather than milrinone (very low quality of evidence). For the other clinical questions, we refrained from giving any recommendations or suggestions.

Conclusions: We suggest against the routine use of any inotropic agent in adult patients with shock. If used, we suggest using dobutamine rather than other inotropic agents for the majority of patients, however, the quality of evidence was very low, implying high uncertainty on the balance between the benefits and harms of inotropic agents.

Editorial comment

Failure to generate sufficient cardiac output is a challenge in patients with acute circulatory failure. This guideline analyzes the available evidence for increasing inotropy, which is scarce. It concludes that no agent should be used on a routine basis, while dobutamine emerges as the drug of choice when applied with caution to specific patient groups.
Acute circulatory failure or shock is a life-threatening condition that needs prompt and adequate treatment, as it 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

Resuscitation of patients in shock must be early and appropriate to prevent or limit vital organ injury. Initial support of the failing circulation usually includes fluid resuscitation in combination with the administration of a vasopressor.1 In two recently published Scandinavian Society of Anaesthesiology and Intensive Care Medicine (SSAI) clinical practice guidelines, we have proposed recommendations regarding choice of fluid2 and choice of first-line vasopressor3 in the management of adult patients with acute circulatory failure. In collaboration with the Canadian Critical Care Society, SSAI has also recently issued recommendations for blood pressure targets in adult critically ill patients with hypotension.4

Subsets of patients with shock, including patients with heart failure may, however, not respond adequately to volume expansion and vasopressors, and additional support, including administration of inotropic agents may be required to restore cardiac output and organ perfusion. Inotropic agents commonly used include the synthetic catecholamine dobutamine, the endogenous catecholamine epinephrine, the phosphodiesterase III inhibitor milrinone, and the calcium sensitizer levosimendan.5 Furthermore, dopamine possesses inotropic properties, and is sometimes used as an inotropic agent.6

The Clinical Practice Committee of the SSAI initiated this guideline on choice of inotropic agent in adult patients with acute circulatory failure. The aim was to summarize the available evidence and provide recommendations according to current standards for trustworthy guidelines.7–9

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 study). This group identified four key interventions needing guidelines, including fluid resuscitation,2 vasopressor therapy,3 inotropic therapy, and cardiovascular diagnostics and monitoring. This is the group’s third guideline: choice of inotropic agent for adult patients with acute circulatory failure.

We have prepared this guideline according to the AGREE statement.10

Clinical question

‘Which inotropic agent 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 inotropes 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 (any type of shock), (2) septic shock, (3) cardiogenic shock, (4) hypovolemic shock, (5) shock after cardiac surgery, and (6) other types of shock, including vasodilatory shock.

Acute circulatory failure and shock are used interchangeably throughout this guideline, and were defined as inadequate/hypoperfusion of tissue and organs.

Intervention(s)

We assessed any dose of the following inotropes: (1) levosimendan, (2) milrinone, (3) epinephrine, (4) dopamine, and (5) placebo/no treatment.

We defined inotropic agents as drugs with positive inotropic effect leading to increased stroke volume and cardiac output.
Comparator
The control inotropic agent was dobutamine (any dose).
We expected dobutamine to be the most widely studied drug, and thus chose dobutamine as the comparator and the other inotropes as experimental interventions.

Outcome(s)
The following patient-important outcome measures\(^\text{11}\) were assessed at the time of longest follow-up:

1. Short-term mortality (0–90 days, 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

Important outcomes
4. Ischemic 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. Hospital length-of-stay (LOS)

We excluded systematic reviews and trials done in children, those assessing prophylactic use of inotropes, those not reporting the predefined patient-important outcome measures, and those not comparing dobutamine vs. another inotropic agent, including those comparing combinations of inotropes or head-to-head comparison of other inotropes than dobutamine. Systematic reviews and trials allowing the use of adjuvant vasopressors were not excluded if the vasopressor used was identical in both arms. Cross-over trials and trials in which patients were systematically treated with either the intervention or comparator drug prior to or after randomization were also excluded.

Search strategy
We systematically searched PubMed (January 1966 to 25 September 2017), Cochrane Library (Issue 4, September 2017), and Epistemonikos for systematic reviews of randomized clinical trials (RCTs) and RCTs comparing dobutamine with other inotropic agents on 25 September 2017. No language restriction was employed. We used the following search strategies:

1. PubMed: (dobutamine OR inotrope\(^\text{*}\) OR inodilat*) AND (levosimendan OR milrinone OR epinephrine OR dopamine OR placebo OR ‘control’ OR ‘no treatment’) AND (shock OR cardiac OR ‘heart failure’). Filters: ‘Randomized controlled trials’ ‘Systematic reviews’; and ‘Meta-analyses’.
3. Epistemonikos: same search as for PubMed adapted and without filters.

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 the predefined patient-important outcomes (O)\(^\text{12}\) – PICO questions (Table 1).

Mantel-Haenszel statistics and random effects models were used to generate summary estimates/meta-analyses (Review Manager Version 5.3, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

We used trial sequential analysis (TSA) to assess the risk of random errors (spurious findings) due to repetitive testing and sparse data\(^\text{13}\). TSA was applied using an \textit{a priori} 20% relative risk reduction, an alpha of 5%, beta of 90%, and a control event proportion according to the results from the included trials. TSA-adjusted 95% confidence intervals (CIs) were estimated (Appendix S1) and are reported in the summary of finding tables (Appendix S2). If less than 5% of the required information size had been accrued, no TSA could be conducted.

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.\(^\text{9}\) In brief, we downgraded the quality of evidence (our confidence in the effect estimates) for an intervention for identified risks of bias (including baseline imbalance, lack of blinding, academic/financial...
Table 1 Clinical research questions and PICO questions used to assess evidence relevant to this guideline statement.

<table>
<thead>
<tr>
<th>Clinical question</th>
<th>Population (P)</th>
<th>Intervention (I)</th>
<th>Comparator (C)</th>
<th>Outcomes (O)</th>
</tr>
</thead>
</table>

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 (Appendix S2).

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. The author group agreed upon all the recommendations in this guideline. Strong recommendations were given the wording ‘we recommend’, and weak recommendations ‘we suggest’.

We followed standards for trustworthy guidelines through use of the GRADE system, management of intellectual and financial conflicts of interest on a recommendation per recommendation basis (Appendix S3), 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 Appendix S2.

A. Dobutamine vs. other inotropes in patients with shock in general

1. We suggest that dobutamine is used as inotropic agent for patients with shock in general rather than levosimendan (weak recommendation, very low quality of evidence).

No systematic reviews or RCTs reporting our predefined patient-important outcome measures have compared the use of dobutamine with that of levosimendan in patients with shock in general (Fig. 1, Table S1A in Appendix S2). In reference to our recommendation for patients with septic shock, we suggest using dobutamine (extrapolation).

The quality of evidence was downgraded due to risk of bias, indirectness, and imprecision.
Table 2  Key recommendations and quality of evidence.

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Strength of the recommendation</th>
<th>Benefits and harms</th>
<th>Quality of evidence Reason(s) for downgrading</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A) Use of inotropes in patients with shock in general</strong></td>
<td></td>
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</tr>
<tr>
<td>1. We suggest using dobutamine rather than levosimendan</td>
<td>Weak</td>
<td>No difference in short-term mortality. Potential harm of levosimendan</td>
<td>Very low due to imprecision, risk of bias, and indirectness</td>
<td>No data available for this population; data extrapolated from patients with septic shock. The defined daily dose price of levosimendan is about 22 times higher than dobutamine</td>
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</tr>
<tr>
<td>2. Dobutamine vs. milrinone</td>
<td>None</td>
<td>–</td>
<td>–</td>
<td>No data available; no relevant populations to extrapolate data from. The defined daily dose price of milrinone is about 100 times higher than dobutamine</td>
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<tr>
<td>3. We suggest using dobutamine rather than epinephrine</td>
<td>Weak</td>
<td>No difference in short-term mortality, ischemic events, and dysrhythmias. Excessive vasoconstriction and tachycardia of epinephrine may affect cardiac output adversely</td>
<td>Very low due to imprecision, risk of bias, and indirectness</td>
<td>No data available for this population; data extrapolated from patients with septic shock</td>
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<tr>
<td>4. Dobutamine vs. dopamine</td>
<td>None</td>
<td>–</td>
<td>–</td>
<td>No data available; no relevant populations to extrapolate data from</td>
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<tr>
<td>5. We suggest against the use of dobutamine as compared to placebo/no treatment</td>
<td>Weak</td>
<td>Potential harm of dobutamine</td>
<td>Very low due to serious risk of bias, and indirectness</td>
<td>No data available for this population; data extrapolated from patients with septic shock (observational study)</td>
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<td></td>
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<tr>
<td><strong>B) Use of inotropes in patients with septic shock</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. We suggest using dobutamine rather than levosimendan</td>
<td>Weak</td>
<td>No difference in short-term mortality. Potential harm of levosimendan</td>
<td>Very low due to imprecision, risk of bias, and indirectness</td>
<td>The defined daily dose price of levosimendan is about 22 times higher than dobutamine</td>
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<tr>
<td></td>
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<td></td>
</tr>
<tr>
<td>2. Dobutamine vs. milrinone</td>
<td>None</td>
<td>–</td>
<td>–</td>
<td>No data available; no relevant populations to extrapolate data from. The defined daily dose price of milrinone is about 100 times higher than dobutamine</td>
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</tr>
<tr>
<td>3. We suggest using dobutamine rather than epinephrine</td>
<td>Weak</td>
<td>No difference in short-term mortality, ischemic events, and dysrhythmias. Excessive vasoconstriction and tachycardia of</td>
<td>Very low due to imprecision, risk of bias, and indirectness</td>
<td></td>
</tr>
</tbody>
</table>
### Table 2 (Continued)

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Strength of the recommendation</th>
<th>Benefits and harms</th>
<th>Quality of evidence Reason(s) for downgrading</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>4. Dobutamine vs. dopamine</td>
<td>None</td>
<td>–</td>
<td>–</td>
<td>No data available; no relevant populations to extrapolate data from</td>
</tr>
<tr>
<td>5. We suggest against the use of dobutamine as compared to placebo/no treatment</td>
<td>Weak</td>
<td>Potential harm of dobutamine</td>
<td>Very low due to serious risk of bias, and indirectness</td>
<td>No data available; no relevant RCT populations to extrapolate data from. Observational study suggests harm from dobutamine</td>
</tr>
</tbody>
</table>

#### C) Use of inotropes in patients with cardiogenic shock

1. Dobutamine vs. levosimendan | None | – | – | The defined daily dose price of levosimendan is about 22 times higher than dobutamine |
2. We suggest using dobutamine rather than milrinone | Weak | No difference in short-term mortality. Unknown balance between the benefits and harms of milrinone | Very low due to imprecision, risk of bias, and indirectness | The defined daily dose price of milrinone is about 100 times higher than dobutamine |
3. Dobutamine vs. epinephrine | None | – | – | No data available; no relevant populations to extrapolate data from |
4. Dobutamine vs. dopamine | None | – | – | No data available; no relevant populations to extrapolate data from |
5. We suggest against the use of dobutamine as compared to placebo/no treatment | Weak | No difference in short-term mortality or long-term mortality in patients treated with dobutamine. | Very low due to imprecision, risk of bias, and indirectness | High risk of random errors, which cautions interpretations of the findings in the meta-analyses. Observational study in patients with septic shock suggests harm from dobutamine (extrapolation). |

#### D) Use of inotropes in patients with hypovolemic shock

1. Dobutamine vs. levosimendan | None | – | – | No data available; no relevant populations to extrapolate data from. The defined daily dose price of levosimendan is about 22 times higher than dobutamine |
2. Dobutamine vs. milrinone | None | – | – | No data available; no relevant populations to extrapolate data from. The defined daily dose price of milrinone is about 100 times higher than dobutamine |
Table 2 (Continued)

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Strength of the recommendation</th>
<th>Benefits and harms</th>
<th>Quality of evidence Reason(s) for downgrading</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>3. Dobutamine vs. epinephrine</td>
<td>None</td>
<td>–</td>
<td>–</td>
<td>No data available; no relevant populations to extrapolate data from</td>
</tr>
<tr>
<td>4. Dobutamine vs. dopamine</td>
<td>None</td>
<td>–</td>
<td>–</td>
<td>No data available; no relevant populations to extrapolate data from</td>
</tr>
<tr>
<td>5. We suggest against the use of dobutamine as compared to placebo/no treatment</td>
<td>Weak</td>
<td>Potential harm of dobutamine&lt;sup&gt;19&lt;/sup&gt;</td>
<td>Very low due to serious risk of bias, and indirectness</td>
<td>No data available for this population; data extrapolated from patients with septic shock (observational study)</td>
</tr>
</tbody>
</table>

E) Use of inotropes in patients with shock after cardiac surgery

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Strength of the recommendation</th>
<th>Benefits and harms</th>
<th>Quality of evidence Reason(s) for downgrading</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Dobutamine vs. levosimendan</td>
<td>None</td>
<td>No reliable differences in short-term mortality, ischemic events, acute kidney injury, use of renal replacement therapy, and dysrhythmia (high risk of random errors). Potential harm of levosimendan&lt;sup&gt;25&lt;/sup&gt;</td>
<td>–</td>
<td>The defined daily dose price of levosimendan is about 22 times higher than dobutamine. Unknown balance between the benefits and harms of dobutamine vs. levosimendan</td>
</tr>
<tr>
<td>2. We suggest using dobutamine rather than milrinone</td>
<td>Weak</td>
<td>No difference in acute kidney injury and dysrhythmias. Unknown balance between the benefits and harms of milrinone&lt;sup&gt;16&lt;/sup&gt;</td>
<td>Very low due to imprecision, risk of bias, and indirectness</td>
<td>The defined daily dose price of milrinone is about 100 times higher than dobutamine</td>
</tr>
<tr>
<td>3. Dobutamine vs. epinephrine</td>
<td>None</td>
<td>–</td>
<td>–</td>
<td>No data available; no relevant populations to extrapolate data from</td>
</tr>
<tr>
<td>4. Dobutamine vs. dopamine</td>
<td>None</td>
<td>–</td>
<td>–</td>
<td>No data available; no relevant populations to extrapolate data from</td>
</tr>
<tr>
<td>5. We suggest against the use of dobutamine as compared to placebo/no treatment</td>
<td>Weak</td>
<td>Potential harm of dobutamine&lt;sup&gt;19&lt;/sup&gt;</td>
<td>Very low due to serious risk of bias, and indirectness</td>
<td>No data available for this population; data extrapolated from patients with septic shock (observational study)</td>
</tr>
</tbody>
</table>

F) Use of inotropes in patients with other types of shock, including vasodilatory shock

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Strength of the recommendation</th>
<th>Benefits and harms</th>
<th>Quality of evidence Reason(s) for downgrading</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. We suggest using dobutamine rather than levosimendan</td>
<td>Weak</td>
<td>No difference in short-term mortality. Potential harm of levosimendan&lt;sup&gt;25&lt;/sup&gt;</td>
<td>Very low due to imprecision, risk of bias, and indirectness</td>
<td>No data available for this population; data extrapolated from patients with septic shock. The defined daily dose price of levosimendan is about 22 times higher than dobutamine</td>
</tr>
</tbody>
</table>
2. Dobutamine vs. milrinone for patients with shock in general: no recommendation/suggestion.

No systematic reviews or RCTs reporting our predefined patient-important outcome measures have compared the use of dobutamine with that of milrinone in patients with shock in general (Fig. 1, Table S1B in Appendix S2). We refrain from giving any recommendations or suggestions on using dobutamine vs. milrinone for patients with shock in general, due to the lack of data and no relevant populations to extrapolate from. Importantly, we recommend that if clinicians prefer to use milrinone rather than dobutamine in this population, they do so in the context of high-quality RCTs, given the lack of data on the balance between the benefits and harms of milrinone in patients with acute circulatory failure in general.\(^\text{15}\) Of note, the defined daily dose price of milrinone is about 100 times higher than that of dobutamine.\(^\text{16}\)

3. We suggest that dobutamine is used as inotropic agent for patients with shock in general rather than epinephrine (weak recommendation, very low quality of evidence).

No systematic reviews or RCTs reporting our predefined patient-important outcome measures have compared the use of dobutamine with that of epinephrine in patients with shock in general (Fig. 1, Table S1C in Appendix S2). In reference to our recommendation for patients with septic shock, we suggest using dobutamine (extrapolation).

The quality of evidence was downgraded due to imprecision, risk of bias, and indirectness.
4. Dobutamine vs. dopamine for patients with shock in general: no recommendation/suggestion.

No systematic reviews or RCTs reporting our predefined patient-important outcome measures have compared the use of dobutamine with that of dopamine in patients with shock in general (Fig. 1, Table S1D in Appendix S2). We refrain from giving any recommendations or suggestions on using dobutamine or dopamine for patients with shock in general, due to the lack of data and no relevant populations to extrapolate from. Importantly, we recommend that if clinicians prefer to use dopamine rather than dobutamine in this population, they do so in the context of high-quality RCTs, given the harm associated with use of dopamine in patients with septic shock.17,18

5. We suggest against routine use of dobutamine as inotropic agent for patients with shock in general, as compared to placebo/no treatment (weak recommendation, very low quality of evidence).

No systematic reviews or RCTs reporting our predefined patient-important outcome measures have compared the use of dobutamine with that of placebo/no treatment in patients with shock in general (Fig. 1, Table S1E in Appendix S2). Importantly, potential harm of dobutamine has been suggested in a propensity-matched observational study in patients with septic shock.19 In reference to our recommendation for patients with septic shock, we suggest against routine use of dobutamine (extrapolation).

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

B. Dobutamine vs. other inotropes in patients with septic shock

1. We suggest that dobutamine is used as inotropic agent for patients with septic shock rather than levosimendan (weak recommendation, very low quality of evidence).

In an updated meta-analysis comprising five trials,20-24 we found no statistically significant difference in short-term mortality in patients with septic shock treated with dobutamine vs. levosimendan (Fig. 2, Fig. S1A in Appendix S1; Table S2A in Appendix S2). None of the other predefined patient-important outcome measures have been assessed. In the recently published LEOPARDS trial, in which adult patients with sepsis were randomized to levosimendan or placebo, levosimendan was associated with a lower likelihood of successful weaning from mechanical ventilation and a higher rate of supraventricular tachyarrhythmia compared to placebo.25 This should caution the use of levosimendan in patients with sepsis, which is why we suggest using dobutamine rather than levosimendan in patients with septic shock. Of note, the defined daily dose price of levosimendan is about 22 times higher than that of dobutamine.16
The quality of evidence was downgraded due to risk of bias, indirectness, and imprecision.

2. Dobutamine vs. milrinone for patients with septic shock: no recommendation/suggestion.

No systematic reviews or RCTs reporting our predefined patient-important outcome measures have compared the use of dobutamine with that of milrinone in patients with septic shock (Fig. 2, Table S2B in Appendix S2). We refrain from giving any recommendations or suggestions on using dobutamine or milrinone for patients with septic shock, due to the lack of data and no relevant populations to extrapolate from. Importantly, we recommend that if clinicians prefer to use milrinone rather than dobutamine in this population, they...
do so in the context of high-quality RCTs, given the lack of data on the balance between benefits and harms of milrinone in patients with acute circulatory failure in general. Of note, the defined daily dose price of milrinone is about 100 times higher than that of dobutamine.  

3. We suggest that dobutamine is used as inotropic agent for patients with septic shock rather than epinephrine (weak recommendation, very low quality of evidence).
The quality of evidence was downgraded due to imprecision, risk of bias and indirectness.


No systematic reviews or RCTs reporting our predefined patient-important outcome measures have compared use of dobutamine with dopamine in patients with septic shock (Fig. 2, Table S2D in Appendix S2). We refrain from giving any recommendations or suggestions on using dobutamine or dopamine for patients with septic shock, due to the lack of data and no relevant populations to extrapolate from. Importantly, we recommend that if clinicians prefer to use dopamine rather than dobutamine in this population, they do so in the context of high-quality RCTs, given the harm associated with use of dopamine in patients with septic shock.\textsuperscript{17,18}

5. We suggest against routine use of dobutamine as inotropic agent for patients with septic shock, as compared to placebo/no treatment (weak recommendation, very low quality of evidence).
No systematic reviews or RCTs reporting our predefined patient-important outcome measures have compared use of dobutamine with placebo/no treatment in patients with septic shock (Fig. 2, Table S2E in Appendix S2).

Importantly, potential harm of dobutamine has been suggested in a propensity-matched observational study in patients with septic shock. Consequently, we suggest against routine use of dobutamine as inotropic agent for patients with septic shock, as compared to placebo/no treatment.

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

C. Dobutamine vs. other inotropes in patients with cardiogenic shock

1. **Dobutamine vs. levosimendan** for patients with cardiogenic shock: no recommendation/suggestion.

In an updated meta-analysis comprising six trials, we found no statistically significant difference in short-term mortality, long-term mortality, ischemic events, acute kidney injury, dysrhythmias, or hospital length-of-stay in patients with cardiogenic shock treated with dobutamine vs. levosimendan (Fig. 3, Fig. S2A, B, D, E in Appendix S1, Table S3A in Appendix S2). None of our other predefined patient-important outcome measures have been assessed. In the recently published LEOPARDS trial in which adult patients with sepsis were randomized to levosimendan or placebo, levosimendan was associated with a lower likelihood of successful weaning from mechanical ventilation and a higher risk of supraventricular tachyarrhythmia compared to placebo. Of note, the defined daily dose price of levosimendan is about 22 times higher than dobutamine. We recommend that if clinicians prefer to use levosimendan rather than dobutamine in this population, they do so in the context of high-quality RCTs, given the lack of data on the balance between the benefits and harms of levosimendan in patients with cardiogenic shock, due to the lack of data and no relevant populations to extrapolate from. Importantly, excessive vasoconstriction and tachycardia increase oxygen consumption and may affect cardiac output adversely in most patients where an inotropic agent is deemed indicated.

2. **Dobutamine** is used as inotropic agent for patients with cardiogenic shock rather than **milrinone** (weak recommendation, very low quality of evidence).

A small RCT comprising 30 patients with cardiogenic shock found no difference in short-term mortality between patients treated with dobutamine vs. milrinone (Fig. 3, Table S3B in Appendix S2). None of our other predefined patient-important outcome measures have been assessed. As the balance between the benefits and harms of milrinone in patients with acute circulatory failure in general has been sparsely evaluated, we suggest using dobutamine rather than milrinone. The defined daily dose price of milrinone is about 100 times higher than that of dobutamine.

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

3. **Dobutamine vs. epinephrine** for patients with cardiogenic shock: no recommendation/suggestion.

No systematic reviews or RCTs reporting our predefined patient-important outcome measures have compared use of dobutamine with that of epinephrine in patients with cardiogenic shock (Fig. 3, Table S3C in Appendix S2). We refrain from giving any recommendations or suggestions on using dobutamine or epinephrine for patients with cardiogenic shock, due to the lack of data and no relevant populations to extrapolate from. Importantly, excessive vasoconstriction and tachycardia increase oxygen consumption and may affect cardiac output adversely in most patients where an inotropic agent is deemed indicated.

4. **Dobutamine vs. dopamine** for patients with cardiogenic shock: no recommendation/suggestion.

No systematic reviews or RCTs reporting our predefined patient-important outcome measures have compared use of dobutamine with
dopamine in patients with cardiogenic shock (Fig. 3, Table S3D in Appendix S2). We refrain from giving any recommendations or suggestions on using dopamine or dobutamine for patients with cardiogenic shock, due to the lack of data and no relevant populations to extrapolate from. Importantly, we strongly recommend that if clinicians prefer to use dopamine rather than dobutamine in this population, they do so in the context of high-quality RCTs, given the harm associated with use of dopamine in patients with septic shock17,18 and in a subgroup analysis of patients with cardiogenic shock in the SOAP 2 trial.39

5. We suggest against routine use of dobutamine as inotropic agent for patients with cardiogenic shock, as compared to placebo/no treatment (weak recommendation, very low quality of evidence).

In an updated meta-analysis, we found no statistically significant difference in short-term...
B Long-term mortality

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Other inotrope Events</th>
<th>Dobutamine Events</th>
<th>Risk Ratio M–H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.2.1 Levosimendan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adamopoulos 2006</td>
<td>2</td>
<td>23</td>
<td>3.3%</td>
</tr>
<tr>
<td>Coletta (CASINO) 2004</td>
<td>18</td>
<td>100</td>
<td>17.6%</td>
</tr>
<tr>
<td>Follath 2002</td>
<td>27</td>
<td>103</td>
<td>20.1%</td>
</tr>
<tr>
<td>Garcia-Gonzalez 2006</td>
<td>3</td>
<td>11</td>
<td>11.9%</td>
</tr>
<tr>
<td>Metha 2007</td>
<td>173</td>
<td>664</td>
<td>29.2%</td>
</tr>
<tr>
<td>Samimi-Fard 2008</td>
<td>3</td>
<td>11</td>
<td>11.9%</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>912</td>
<td>908</td>
<td>73.9%</td>
</tr>
</tbody>
</table>

Total events 226 272
Heterogeneity: $\chi^2 = 13.58$, df = 5 ($P = 0.02$); $I^2 = 63$
Test for overall effect: $Z = 1.48$ ($P = 0.14$)

3.2.2 Milrinone
Subtotal (95% CI) 0 0 Not estimable
Total events 0 0
Heterogeneity: Not applicable
Test for overall effect: Not applicable

3.2.3 Epinephrine
Subtotal (95% CI) 0 0 Not estimable
Total events 0 0
Heterogeneity: Not applicable
Test for overall effect: Not applicable

3.2.4 Dopamine
Subtotal (95% CI) 0 0 Not estimable
Total events 0 0
Heterogeneity: Not applicable
Test for overall effect: Not applicable

3.2.5 Placebo/no treatment
Adamopoulos 2006 | 4 | 23 | 5 | 5.2% | 0.80 [0.25, 2.61] |
| Coletta (CASINO) 2004 | 28 | 99 | 42 | 100 | 20.8% | 0.67 [0.46, 0.99] |
| Subtotal (95% CI) | 122 | 123 | 26.1% | 0.68 [0.47, 0.99] |

Total events 32 47
Heterogeneity: $\chi^2 = 0.00$, $I^2 = 0$, $df = 1$ ($P = 0.79$); $I^2 = 0$
Test for overall effect: $Z = 2.01$ ($P = 0.04$)

Total (95% CI) 1034 1031 100.0% 0.72 [0.54, 0.97]

Total events 258 319
Heterogeneity: $\chi^2 = 14.54$, df = 7 ($P = 0.04$); $I^2 = 52$
Test for overall effect: $Z = 2.17$ ($P = 0.03$)
Test for subgroup differences: $\chi^2 = 0.05$, df = 1 ($P = 0.82$), $I^2 = 0$

C Quality of life
No data.

Fig. 3. Continued

mortality (1 trial, 199 patients) or long-term mortality (2 trials, 245 patients) in patients with cardiogenic shock treated with dobutamine vs. placebo/no treatment (Fig. 3, Fig. S2C in Appendix S1, Table S3E in Appendix S2). TSA highlighted high risk of random errors due to repetitive testing and small sample sizes (Fig. S2 in Appendix S1), which cautions interpretations of the findings in the conventional meta-analysis. None of our other predefined patient-important outcome measures have been assessed. Importantly, as potential harm of dobutamine has been suggested in patients with septic shock, we suggest against the routine use of dobutamine as inotropic agent for patients with cardiogenic shock, as compared to placebo/no treatment (extrapolation).

The quality of evidence was downgraded due to imprecision, indirectness, and risk of bias.
D. Dobutamine vs. other inotropes in patients with hypovolemic shock

1. Dobutamine vs. levosimendan for patients with hypovolemic shock: no recommendation/suggestion.

No systematic reviews or RCTs reporting our predefined patient-important outcome measures have compared use of dobutamine with levosimendan in patients with hypovolemic shock (Fig. 4, Table S4A in Appendix S2). We refrain from giving any recommendations or suggestions on using dobutamine or levosimendan for patients with hypovolemic shock, due to the lack of data and no relevant populations to extrapolate from. In the recently published LEOPARDS trial in which adult patients with sepsis were randomized to levosimendan or placebo, levosimendan was associated with a lower likelihood of successful weaning from mechanical ventilation and a higher risk of supraventricular tachyarrhythmia compared to placebo.25 This cautions use of levosimendan in other patient groups, including patients with hypovolemic shock. Of note, the defined daily dose price of levosimendan is about 22 times higher.

E. Renal replacement therapy
No data.

Fig. 3. Continued

INOTROPES IN ACUTE CIRCULATORY FAILURE

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Table 3: Risk of Ischemic events and Renal replacement therapy

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Other inotrope Events</th>
<th>Dobutamine Events</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.4.1 Levosimendan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follih 2002</td>
<td>0</td>
<td>103</td>
<td>0.06 [0.00, 1.12]</td>
</tr>
<tr>
<td>García-Gonzalez 2006</td>
<td>0</td>
<td>11</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>114</td>
<td>111</td>
<td>0.06 [0.00, 1.12]</td>
</tr>
<tr>
<td>Total events</td>
<td>0</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.88 (P = 0.06)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3.4.2 Milrinone
Subtotal (95% CI) 0 0 Not estimable
Total events 0 0
Heterogeneity: Not applicable
Test for overall effect: Not applicable

3.4.3 Epinephrine
Subtotal (95% CI) 0 0 Not estimable
Total events 0 0
Heterogeneity: Not applicable
Test for overall effect: Not applicable

3.4.4 Dopamine
Subtotal (95% CI) 0 0 Not estimable
Total events 0 0
Heterogeneity: Not applicable
Test for overall effect: Not applicable

3.4.5 Placebo/no treatment
Subtotal (95% CI) 0 0 Not estimable
Total events 0 0
Heterogeneity: Not applicable
Test for overall effect: Not applicable

Total (95% CI) 114 111 100.0% 0.06 [0.00, 1.12] 0.01 0.1 1 10 100 Favours other inotrope Favours dobutamine

Heterogeneity: Not applicable
Test for subgroup differences: Not applicable

Test for overall effect: Z = 1.88 (P = 0.06)

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than dobutamine.\textsuperscript{16} Importantly, adequate fluid resuscitation – and not inodilation - should be a priority in patients with hypovolemic shock.

\textbf{2. Dobutamine vs. milrinone} for patients with hypovolemic shock: no recommendation/suggestion.

No systematic reviews or RCTs reporting our predefined patient-important outcome measures have compared use of dobutamine with milrinone in patients with hypovolemic shock (Fig. 4, Table S4B in Appendix S2). We refrain from giving any recommendations or suggestions on using dobutamine or milrinone for patients with hypovolemic shock, due to the lack of data and no relevant populations to extrapolate from. We recommend that if clinicians prefer to use milrinone rather than dobutamine in this population, they do so in the context of high-quality RCTs, given the lack of data on the balance between benefits and harms of milrinone in patients with acute circulatory failure in general.\textsuperscript{15} Of note, the defined daily dose price of milrinone is about 100 times higher than that of dobutamine.\textsuperscript{16} Importantly, adequate fluid resuscitation – and not inodilation - should be a priority in patients with hypovolemic shock.

\textbf{3. Dobutamine vs. epinephrine} for patients with hypovolemic shock: no recommendation/suggestion.
No systematic reviews or RCTs reporting our predefined patient-important outcome measures have compared use of dobutamine with epinephrine in patients with hypovolemic shock (Fig. 4, Table S4C in Appendix S2). We refrain from giving any recommendations or suggestions on using dobutamine or epinephrine for patients with hypovolemic shock, due to the lack of data and no relevant populations to extrapolate from. Importantly, excessive vaso-constriction and tachycardia increase oxygen consumption and may affect cardiac output adversely in most patients where an inotropic agent is deemed indicated. Importantly, adequate fluid resuscitation should be a priority in patients with hypovolemic shock.

use dopamine rather than dobutamine in this population, they do so in the context of high-quality RCTs, given the harm associated with use of dopamine in patients with septic shock and in a subgroup analysis of patients with cardiogenic shock in the SOAP 2 trial. Importantly, adequate fluid resuscitation should be a priority in patients with hypovolemic shock.

5. We suggest against routine use of dobutamine as inotropic agent for patients with hypovolemic shock, compared to placebo/no treatment (weak recommendation, very low quality of evidence).

No systematic reviews or RCTs reporting our predefined patient-important outcome measures have compared use of dobutamine with placebo/no treatment in patients with hypovolemic shock (Fig. 4, Table S4E in Appendix S2). Importantly, potential harm of dobutamine has been suggested in a propensity-matched observational study in patients with septic shock. In reference to our recommendation for patients with septic shock, we suggest against routine use of dobutamine (extrapolation). Of note, adequate fluid resuscitation should be a priority in patients with hypovolemic shock.

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

E. Dobutamine vs. other inotropes in patients with shock after cardiac surgery

1. Dobutamine vs. levosimendan for patients with shock after cardiac surgery: no recommendation/suggestion.

In an updated meta-analysis comprising four trials and 470 patients, reduced short-term mortality, fewer ischemic events, reduced risk of acute kidney injury and use of renal replacement therapy, and reduced risk of dysrhythmias were suggested in patients.
with shock after cardiac surgery treated with levosimendan, as compared to dobutamine (Fig. 5, Fig. S3A–C in Appendix S1, Table S5A in Appendix S2). However, TSA highlighted high risk of random errors due to repetitive testing and small sample sizes (Fig. S3 in Appendix S1), which cautions interpretations of the findings in the conventional meta-analysis. None of our other predefined patient-important outcome measures have been assessed. In the recently published LEVO-CTS, CHEETAH, and LICORN trials\textsuperscript{44–46} no difference in outcome between levosimendan and placebo in patients undergoing planned cardiac surgery was found. Of note, levosimendan was studied as a second-line inotropic agent in these trials, and other inotropic drugs, such as dobutamine, were permitted. Importantly, in the LEOPARDS trial in which adult patients with sepsis where randomized to levosimendan or placebo, levosimendan was associated with a lower likelihood of successful weaning from mechanical ventilation and a higher risk of supraventricular tachycardia, as compared to placebo.\textsuperscript{25} Of note, the defined daily dose price of levosimendan is about 22 times higher than dobutamine.\textsuperscript{16} We refrain from giving any recommendations or suggestions on using dobutamine or levosimendan for patients with shock after cardiac surgery, due to the unknown balance between the benefits and harms of these agents in this population.

2. We suggest that \textbf{dobutamine} is used as inotropic agent for patients with shock after cardiac surgery rather than \textbf{milrinone} (weak recommendation, very low quality of evidence).

A small RCT comprising 120 patients with shock after cardiac surgery\textsuperscript{47} found no difference in acute kidney injury and dysrhythmias between patients treated with dobutamine vs. milrinone (Fig. 5, Table S5B in Appendix S2). None of our other predefined patient-important outcome measures have been assessed. As the balance between the benefits and harms of milrinone in patients with acute circulatory failure in general has been sparsely evaluated,\textsuperscript{15} we suggest using dobutamine rather than milrinone. Furthermore, the defined daily dose price of milrinone is about 100 times higher than that of dobutamine.\textsuperscript{16}

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

3. \textbf{Dobutamine vs. epinephrine} for patients with shock after cardiac surgery: no recommendation/suggestion.

No systematic reviews or RCTs reporting our predefined patient-important outcome measures have compared use of dobutamine with
epinephrine in patients with shock post–cardiac surgery (Fig. 5, Table S5C in Appendix S2).26 We refrain from giving any recommendations or suggestions on using dobutamine or epinephrine for patients with shock after cardiac surgery, due to the lack of data and no relevant populations to extrapolate from. Importantly, excessive vasoconstriction and tachycardia increase oxygen consumption and may affect cardiac output adversely in most patients where an inotropic agent is deemed indicated.6

4. Dobutamine vs. dopamine for patients with shock after cardiac surgery: no recommendation/suggestion.
D Ischemic events

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Other inotrope Events</th>
<th>Dobutamine Events</th>
<th>Total Events</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.4.1 Levosimendan</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levin 2008</td>
<td>3</td>
<td>69</td>
<td>68</td>
<td>100.0%</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>69</td>
<td>68</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>3</td>
<td></td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.54 (P = 0.01)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5.4.2 Milrinone

| Subtotal (95% CI)   | 0                     | 0                 | Not estimable |
| Total events        | 0                     |                   |               |
| Heterogeneity: Not applicable |
| Test for overall effect: Not applicable |

5.4.3 Epinephrine

| Subtotal (95% CI)   | 0                     | 0                 | Not estimable |
| Total events        | 0                     |                   |               |
| Heterogeneity: Not applicable |
| Test for overall effect: Not applicable |

5.4.4 Dopamine

| Subtotal (95% CI)   | 0                     | 0                 | Not estimable |
| Total events        | 0                     |                   |               |
| Heterogeneity: Not applicable |
| Test for overall effect: Not applicable |

5.4.5 Placebo/no treatment

| Subtotal (95% CI)   | 0                     | 0                 | Not estimable |
| Total events        | 0                     |                   |               |
| Heterogeneity: Not applicable |
| Test for overall effect: Not applicable |

| Total (95% CI)      | 69                    | 68                | 100.0%         | 0.21 [0.06, 0.70] |
| Total events        | 3                     |                   | 14             |                  |
| Heterogeneity: Not applicable |
| Test for overall effect: Z = 2.54 (P = 0.01) |
| Test for subgroup differences: Not applicable |

Fig. 5. Continued

No systematic reviews or RCTs reporting our predefined patient-important outcome measures have compared use of dobutamine with dopamine in patients with shock after cardiac surgery (Fig. 5, Table S5D in Appendix S2). We refrain from giving any recommendations or suggestions on using dobutamine or dopamine for patients with shock after cardiac surgery, due to the lack of data and no relevant populations to extrapolate from. Importantly, we recommend that if clinicians prefer to use dopamine rather than dobutamine in this population, they do so in the context of high-quality RCTs, given the harm associated with use of dopamine in patients with septic shock17,18 and in a subgroup analysis of patients with cardiogenic shock in the SOAP 2 trial.39

5. We suggest against routine use of **dobutamine** as inotropic agent for patients with shock after cardiac surgery, as compared to **placebo/no treatment** (weak recommendation, very low quality of evidence).

No systematic reviews or RCTs reporting our predefined patient-important outcome measures have compared use of dobutamine with placebo/no treatment in patients with shock after cardiac surgery (Fig. 5, Table S5E in Appendix S2). Importantly, as potential harm of dobutamine has been suggested in patients with septic shock, we suggest against the routine use of dobutamine as inotropic agent for patients...
E Renal replacement therapy

Table: Renal replacement therapy

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Other Inotrope</th>
<th>Dobutamine</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total Events</td>
<td>Total Weight</td>
</tr>
<tr>
<td>5.5.1 Levosimendan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alvarez 2005</td>
<td>2</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Alvarez 2006</td>
<td>2</td>
<td>25</td>
<td>3</td>
</tr>
<tr>
<td>Levin 2008</td>
<td>2</td>
<td>69</td>
<td>68</td>
</tr>
<tr>
<td>Levin 2009</td>
<td>2</td>
<td>127</td>
<td>126</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>236</td>
<td>234</td>
<td>100.0%</td>
</tr>
<tr>
<td>Total events</td>
<td>8</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $\tau^2 = 0.13; \chi^2 = 3.50, df = 3 (P = 0.32); I^2 = 14%$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $Z = 1.96 (P = 0.05)$</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5.5.2 Milrinone

Subtotal (95% CI) 0 0 Not estimable

Total events 0 0

Heterogeneity: Not applicable

Test for overall effect: Not applicable

5.5.3 Epinephrine

Subtotal (95% CI) 0 0 Not estimable

Total events 0 0

Heterogeneity: Not applicable

Test for overall effect: Not applicable

5.5.4 Dopamine

Subtotal (95% CI) 0 0 Not estimable

Total events 0 0

Heterogeneity: Not applicable

Test for overall effect: Not applicable

5.5.5 Placebo/no treatment

Subtotal (95% CI) 0 0 Not estimable

Total events 0 0

Heterogeneity: Not applicable

Test for overall effect: Not applicable

Total (95% CI) 236 234 100.0% 0.40 [0.16, 1.00]

Total events 8 22

Heterogeneity: $\tau^2 = 0.13; \chi^2 = 3.50, df = 3 (P = 0.32); I^2 = 14\%$

Test for overall effect: $Z = 1.96 (P = 0.05)$

Test for subgroup differences: Not applicable

Fig. 5. Continued

with shock after cardiac surgery, as compared to placebo/no treatment (extrapolation).

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

F. Dobutamine vs. other inotropes in patients with other types of shock, including vasodilatory shock

1. We suggest that dobutamine is used as inotropic agent for patients with other types of shock including vasodilatory shock rather than levosimendan (weak recommendation, very low quality of evidence).

2. Dobutamine vs. milrinone for patients with other types of shock including vasodilatory shock: no recommendation/suggestion.

No systematic reviews or RCTs reporting our predefined patient-important outcome measures have compared use of dobutamine with levosimendan in patients with other types of shock including vasodilatory shock (Fig. 6, Table S6A in Appendix S2). In reference to our recommendation for patients with septic shock, we suggest using dobutamine (extrapolation).

The quality of evidence was downgraded due to risk of bias, indirectness, and imprecision.
No systematic reviews or RCTs reporting our predefined patient-important outcome measures have compared use of dobutamine with milrinone in patients with other types of shock including vasodilatory shock (Fig. 6, Table S6B in Appendix S2). We refrain from giving any recommendations or suggestions on using dobutamine or milrinone for patients with other types of shock due to the lack of data and no relevant populations to extrapolate from. Importantly, we recommend that if clinicians prefer to use milrinone rather than dobutamine in this population, they do so in the context of high-quality RCTs, given the lack of data on the balance between benefits and harms of milrinone in patients with acute circulatory failure in general.\textsuperscript{15} Of note, the defined daily dose price of milrinone is about 100 times higher than that of dobutamine.\textsuperscript{16}

3. We suggest that \textit{dobutamine} is used as inotropic agent for patients with other types of shock including vasodilatory shock rather than \textit{epinephrine} (weak recommendation, very low quality of evidence).

No systematic reviews or RCTs reporting our predefined patient-important outcome measures have compared use of dobutamine with epinephrine in patients with other types of shock.
including vasodilatory shock (Fig. 6, Table S6C in Appendix S2). In reference to our recommendation for patients with septic shock, we suggest using dobutamine (extrapolation). Importantly, in vasodilatory shock caused by anaphylaxis, epinephrine is the preferred drug of choice.

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

### 4. Dobutamine vs. dopamine for patients with other types of shock including vasodilatory shock: no recommendation/suggestion.
do so in the context of high-quality RCTs, given the harm associated with use of dopamine in patients with septic shock\textsuperscript{17,18} and in a subgroup analysis of patients with cardiogenic shock in the SOAP 2 trial.\textsuperscript{39}

5. We suggest against routine use of dobutamine as inotropic agent for patients with other types of shock including vasodilatory shock, as compared to placebo/no treatment (weak recommendation, very low quality of evidence).

No systematic reviews or RCTs reporting our predefined patient-important outcome measures have compared use of dobutamine with placebo in patients with other types of shock including vasodilatory shock (Fig. 6, Table S6E in Appendix S2). In reference to our recommendation for patients with septic shock, we suggest against routine use of dobutamine (extrapolation).

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

Discussion

We were able to use existing systematic reviews and RCTs to answer some of the clinical questions concerning choice of inotropic agents in patients with septic shock, cardiogenic shock, and in those with shock after cardiac surgery. However, for patients with shock in general, and those with hypovolemic shock, and other types of shock, the quantity and quality of evidence was very limited.

The most widely studied comparison was dobutamine vs. levosimendan, whereas dobutamine vs. milrinone, dobutamine vs. epinephrine, and dobutamine vs. placebo/no treatment have been sparsely assessed. No trials have compared dobutamine vs. dopamine in any of the six predefined subpopulations.

We propose no strong recommendations, as the quantity and quality of evidence was very low with large uncertainty about the direction and magnitude of effect.

For all the six predefined subpopulations, we suggest against the routine use of dobutamine, as compared to placebo/no treatment (very low quality of evidence). There are no data supporting that inotropic agents offer benefit as compared to placebo or no treatment, and in patients with septic shock, dobutamine has been associated with adverse outcome.

For patients with shock in general and those with septic shock and other types of shock, we suggest using dobutamine over levosimendan (very low quality of evidence). This was based on an overall low confidence of benefit from levosimendan, and importantly, potential harm, as suggested in the LEOPARDS trial, in which adult patients with sepsis randomized to treatment with levosimendan had lower likelihood of successful weaning from mechanical ventilation and a higher rate of supraventricular tachyarrhythmia, as compared to placebo.\textsuperscript{25}

For patients with shock in general and in those with septic and other types of shock, we suggest using dobutamine over epinephrine, as
excessive vasoconstriction and tachycardia may affect oxygen consumption and cardiac output adversely in most patients where an inotropic agent is deemed indicated (very low quality of evidence).

For patients with cardiogenic shock and those with shock after cardiac surgery, we suggest using dobutamine over milrinone (very low quality of evidence). This was based on overall low confidence of benefit and insufficient knowledge on harms from milrinone, and a considerably higher defined daily dose price of milrinone.

Because of no available data, no reliable data on the balance between the benefits and harms, or no relevant patient groups to extrapolate from, we were not able to provide recommendations/suggestions for (1) dobutamine vs. milrinone/dopamine in patients with shock in general, and for those with septic and other types of shock, (2) dobutamine vs. levosimendan/epinephrine/dopamine for patients with cardiogenic shock and those with shock after cardiac surgery, and for (3) dobutamine vs. levosimendan/milrinone/epinephrine/dopamine in patients with hypovolemic shock.

As witnessed by the very low quality of evidence supporting the suggestions of this guideline, there is large uncertainty on the balance between the benefits and harms when using inotropic agents in adult patients with acute circulatory failure. Several interventions, which are common practice in the ICU, have been adopted based on the perception of improved physiological parameters and physiological reasoning. This has the eminent risk of overestimating benefit and underestimating harm. In a recently published systematic review, eight critical care interventions used in clinical practice were shown to increase mortality. Furthermore, there is empirical evidence within critical care that research results based on data from trials with lower quality have changed direction once higher quality trials were published. Consequently, we highly recommend that clinicians who are using inotropic agents in patients with acute circulatory failure, consider doing this in the context of high-quality RCTs with low risk of bias-assessing patient-important outcomes.

The strengths of this clinical practice guideline include the application of current standards for trustworthy guidelines, including the GRADE methodology which support a systematic and transparent process, and use of TSA to assess the risk of random errors. The limitations include the reliance upon existing systematic reviews for some recommendations, including the risk of trial heterogeneity, indirectness, and bias. Also, we did not include time to resolution of shock or days free of inotropic support as outcomes, as we did not expect that any trials had assessed these otherwise patient-important outcomes. Furthermore, not all of the included systematic reviews and trials have been designed as a direct comparison between dobutamine and another inotropic agent, as some trials have used adjuvant vasopressors. 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 inotropic agent assessed. Our recommendations have been restricted to those that can be based on findings from RCTs exclusively, however, observational studies may – although seldom and often biased - provide evidence to help form some recommendations. Finally, our guideline group did not include critical care nurses or other relevant stakeholders such as patients, relatives, and representatives of regulatory bodies and hospital owners.

Conclusion

For all adult patients with shock, we suggest against the routine use of dobutamine as compared to placebo/no treatment. If inotropic agents are used, we suggest using dobutamine rather than levosimendan or epinephrine in patients with shock in general, and in those with septic and other types of shock. In patients with cardiogenic shock and those with shock after cardiac surgery, we suggest using dobutamine rather than milrinone. For the remaining clinical questions, we refrained from giving any recommendations or suggestions. In general, the quality of evidence was very low, implying high uncertainty on the balance between the benefits and harms when using inotropes in adult patients with acute circulatory failure. Consequently, RCTs with low risk of bias should be a high research priority in settings where inotropes are used.
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References


**Supporting Information**

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

**Appendix S1. Trial sequential analyses.**

Fig. S1. Trial sequential analysis of dobutamine vs. other inotropes in patients with septic shock.
Fig. S2. Trial sequential analysis of dobutamine vs. other inotropes in patients with cardiogenic shock.

Fig. S3. Trial sequential analysis of dobutamine vs. other inotropes in patients with shock after cardiac surgery.

Appendix S2. GRADE summary of findings tables.

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 shock after cardiac surgery.

Table S6. Summary of findings for patients with other types of shock, including vasodilatory shock.

Appendix S3. Conflicts of interest on a recommendation per recommendation basis per co-author.