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REVIEW ARTICLE/BRIEF REVIEW

Inotropes, vasopressors, and mechanical circulatory support for treatment of cardiogenic shock complicating myocardial infarction: a systematic review and network meta-analysis

Inotropes, vasopresseurs et assistance circulatoire mécanique pour le traitement de choc cardiogénique compliquant un infarctus du myocarde : une revue systématique et une méta-analyse en réseau

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Abstract

Purpose *To compare the relative efficacy of supportive therapies (inotropes, vasopressors, and mechanical circulatory support [MCS]) for adult patients with cardiogenic shock complicating acute myocardial infarction.*

Source *We conducted a systematic review and network meta-analysis and searched six databases from inception to December 2021 for randomized clinical trials (RCTs). We evaluated inotropes, vasopressors, and MCS in separate*

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networks. Two reviewers performed screening, full-text review, and extraction. We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework to rate the certainty in findings. The critical outcome of interest was 30-day all-cause mortality.

Principal findings *We included 17 RCTs. Among inotropes (seven RCTs, 1,145 patients), levosimendan probably reduces mortality compared with placebo (odds ratio [OR], 0.53; 95% confidence interval [CI], 0.33 to 0.87; moderate certainty), but primarily in lower severity shock. Milrinone (OR, 0.52; 95% CI, 0.19 to 1.39; low certainty) and dobutamine (OR, 0.67, 95% CI, 0.30 to 1.49; low certainty) may have no effect on mortality compared with placebo. With regard to MCS (eight RCTs, 856 patients), there may be no effect on mortality with an intra-aortic balloon pump (IABP) (OR, 0.94; 95% CI, 0.69 to 1.28; low certainty) or percutaneous MCS (pMCS) (OR, 0.96; 95% CI, 0.47 to 1.98; low certainty), compared with a strategy involving no MCS. Intra-aortic balloon pump use was associated with less major bleeding compared with pMCS. We found only two RCTs evaluating vasopressors, yielding insufficient data for meta-analysis.*

Conclusion *The results of this systematic review and network meta-analysis indicate that levosimendan reduces mortality compared with placebo among patients with low severity cardiogenic shock. Intra-aortic balloon pump and pMCS had no effect on mortality compared with a strategy of no MCS, but pMCS was associated with higher rates of major bleeding.*

Study registration *Center for Open Science (https://osf.io/ky2gr); registered 10 November 2020*

Résumé

Objectif *Comparer l'efficacité relative des thérapies de soutien (inotropes, vasopresseurs et assistance circulatoire mécanique [ACM]) chez les patients adultes atteints d'un choc cardiogénique compliquant un infarctus aigu du myocarde.*

Sources *Nous avons réalisé une revue systématique et une méta-analyse en réseau et effectué des recherches dans six bases de données depuis leur création jusqu'à décembre 2021 pour en tirer les études randomisées contrôlées (ERC). Nous avons évalué les inotropes, les vasopresseurs et les ACM dans des réseaux distincts. Deux réviseurs ont effectué la recherche, l'évaluation du texte intégral et l'extraction. Nous avons utilisé le système de notation GRADE (Grading of Recommendations Assessment, Development, and Evaluation) pour évaluer la certitude des résultats. Le critère d'évaluation d'intérêt était la mortalité toutes causes confondues à 30 jours.*

Constatations principales *Nous avons inclus 17 ERC. Parmi les inotropes (sept ERC, 1145 patients), le lévosimendan a probablement réduit la mortalité par rapport au placebo (rapport de cotes [RC], 0,53; intervalle de confiance [IC] à 95 %, 0,33 à 0,87; certitude modérée), mais principalement en cas de choc de sévérité moindre. La milrinone (RC, 0,52; IC 95 %, 0,19 à 1,39; certitude faible) et la dobutamine (RC, 0,67, IC 95 %, 0,30 à 1,49; certitude faible) pourraient n'avoir aucun*

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effet sur la mortalité par rapport au placebo. En ce qui concerne l'ACM (huit ERC, 856 patients), il pourrait n'y avoir aucun effet sur la mortalité avec un ballon intra-aortique (IABP) (RC, 0,94; IC 95 %, 0,69 à 1,28; certitude faible) ou un ACM percutané (ACMp) (RC, 0,96; IC 95 %, 0,47 à 1,98; certitude faible), par rapport à une stratégie sans ACM. L'utilisation d'un ballon intra-aortique était associée à moins de saignements majeurs par rapport à une ACMp. Nous n'avons trouvé que deux ERC évaluant les vasopresseurs, ce qui n'a pas fourni suffisamment de données pour la méta-analyse.

Conclusion *Les résultats de cette revue systématique et de la méta-analyse en réseau indiquent que le lévosimendan réduit la mortalité par rapport au placebo chez les patients présentant un choc cardiogénique de faible gravité. Le ballon intra-aortique et l'ACMp n'ont eu aucun effet sur la mortalité par rapport à une stratégie sans ACM, mais l'ACMp était associée à des taux plus élevés de saignements majeurs.*

Enregistrement de l'étude *Center for Open Science (https://osf.io/ky2gr); enregistrée le 10 novembre 2020*

Keywords cardiogenic shock · cardiology · critical care medicine · inotropes · mechanical circulatory support · vasopressors

Cardiogenic shock is a clinical condition that is characterized by systemic hypoperfusion secondary to cardiac dysfunction.[1–3] The clinical presentations of severe heart failure or cardiogenic shock can be heterogeneous, and patients may have various signs of end-organ dysfunction, with or without the presence of hypotension.[2] Mortality from this condition has been reported to be between 30 and 80%, depending on the clinical context.[4] Cardiogenic shock most commonly occurs secondary to acute myocardial infarction (MI), with incidence rates in the range of 3–13% of cases of acute MI.[3] Patients with cardiogenic shock secondary to acute MI appear to have higher mortality, compared with other etiologies.[5] Despite advancements in reperfusion therapies and regional systems of care, mortality from this condition remains substantial.[6]

The mainstay in the management of cardiogenic shock secondary to acute MI remains revascularization of culprit coronary lesions.[7–9] Additional treatment is largely supportive and focused upon improving hemodynamics and end-organ perfusion, with various pharmacologic and mechanical therapies available. Pharmacologic treatments are divided into agents that are primarily vasopressors (e.g., norepinephrine, epinephrine, dopamine) and those that are primarily inotropes (e.g., dobutamine, milrinone, levosimendan, enoximone).[10] While each of these agents has its own advantages and disadvantages, at present there are limited data related to their comparative efficacy in improving mortality, and there is substantial variation in their use among clinicians.[11] Furthermore, therapy for cardiogenic shock has grown to include various forms of mechanical circulatory support (MCS), including the intra-aortic balloon pump (IABP), percutaneous MCS (pMCS, such as the Impella® [Abiomed®, Danvers, MA, USA] and the TandemHeart® [LivaNova PLC, London, UK]), and venoarterial extracorporeal membrane oxygenation (VA-ECMO).[12,13] Mechanical circulatory support primarily serves as a bridge to recovery or transplant, with recommended use from contemporary guidelines,[9] despite limited data on efficacy.

We conducted a systematic review and network meta-analysis of randomized clinical trials (RCTs), with the aim of evaluating the relative efficacy of available therapies for treatment of cardiogenic shock complicating acute MI. Previous conventional meta-analyses on the effectiveness of these treatments in cardiogenic shock have shown conflicting results,[13,14] and new evidence has since emerged. Compared with conventional meta-analyses, network meta-analyses can harness the cumulative data from all trials in a particular condition and can generate indirect estimates of effect between treatments that have never previously been compared in a randomized trial. Of note, while RCTs of inotropes and vasopressors likely include patients with lower severity shock (Society for Cardiovascular Angiography and Interventions [SCAI] class A–C),[15] RCTs for MCS often include patients with much higher severity of illness (SCAI class D–E). Because of these concerns regarding clinical heterogeneity between trials, our prespecified plan for analysis included three

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separate networks for each treatment category (vasopressors, inotropes, and MCS).

Methods

We followed the Preferred Reporting Items for Systematic Review and Meta-Analysis statement extension for network meta-analysis.[16,17] We registered our protocol with the Center for Open Science (https://osf.io/ky2gr; November 10, 2020). No institutional review board approval was required because all study data had been published previously, and we did not include individual patient data.

Data sources and search strategy

We searched six databases (Medline, PubMed, EMBASE, Scopus, Web of Science, and the Cochrane Database of Systematic Reviews) from inception to 30 December 2021. An experienced health sciences librarian assisted in developing the search strategy. Electronic Supplementary Material (ESM) eFig. 1 provides details of our search strategy. We conducted further surveillance searches using the "related articles" feature.

Study selection

Two reviewers (S. M. F. and R. M.) independently screened titles and abstracts identified through the searches using Covidence (Melbourne, Vic, Australia) and assessed full texts of the selected articles from phase one. Reviewers resolved disagreements by discussion. We included RCTs (parallel, cluster, or crossover), without language restriction, meeting the following criteria: 1) enrolled adult patients ($\geq$ 16 yr of age); 2) conducted primarily ($\geq$ 70%) in patients with acute MI; 3) randomized patients to receive inotropes, vasopressors, MCS, or a combination of the above; 4) evaluated at least one of the outcomes of interest; and 5) included primarily ($\geq$ 70%) patients with cardiogenic shock. Since there is no accepted definition of "cardiogenic shock,"[2] we considered the SCAI definitions of cardiogenic shock, class A to E.[15] While some studies have traditionally only included hypotensive patients, other trials have been more inclusive of any patients with evidence of hypoperfusion, or requiring vasoactive medications with relative hypotension. Therefore, we included trials of patients meeting any of the following criteria suggesting cardiogenic shock: 1) hypotension (defined by a systolic blood pressure $<$ 100 mm Hg); 2) organ hypoperfusion (defined by cool extremities, altered mental status, elevated lactate, decreased urine output, or other end-organ dysfunction); or 3) severe heart failure requiring initiation of vasopressors or inotropes to maintain perfusion. We had originally sought to exclude patients with class A shock ("at risk" of cardiogenic shock, but without overt signs and symptoms), but many trials ultimately included these patients. We excluded trials that exclusively evaluated MI patients who were postoperative from cardiac surgery for revascularization because of concerns that shock in this population may not always be cardiogenic in nature.

The critical outcome of interest was 30-day all-cause mortality. We prespecified that in instances where 30-day mortality was unavailable, we would include mortality data that were closest to 30 days (minimum of 14 days). Other outcomes included acute kidney injury (as defined by study authors), initiation of renal replacement therapy, initiation of MCS (not relevant for the MCS network), duration of hemodynamic support, hospital length of stay, and major bleeding (as defined by study authors).

Data extraction

One investigator (S. M. F.) collected the following variables from included articles: author information, year of publication, eligibility criteria, and number of patients using a predesigned data extraction sheet (ESM eTable 1). Two investigators (S. M. F. and R. M.) independently collected data related to descriptions of interventions and outcomes. Where available, we only selected subgroups of patients from within RCTs that met our inclusion criteria. Disagreements were resolved through discussion.

Risk of bias assessment

Two reviewers (S. M. F. and R. M.) independently assessed the risk of bias of the included studies using a modified Cochrane Collaboration tool,[18] which included sequence generation, allocation sequence concealment, blinding, missing outcome data, and other bias. Reviewers resolved disagreement through discussion.

Data synthesis and analysis

For each outcome and each pair of interventions, we calculated and reported odds ratios (ORs) and corresponding 95% confidence intervals (CIs). Initially, we performed a conventional pairwise meta-analysis using a DerSimonian and Laird random-effects model for all comparisons with two or more RCTs.[19] We assessed heterogeneity between RCTs for each direct comparison with visual inspection of forest plots, and the I^2 statistic. We evaluated the feasibility of conducting network meta-analysis by: 1) evaluating the availability of evidence (e.g., number of trials, number of interventions); 2) evaluating

homogeneity of study designs, patients, and characteristics of interventions across the body of evidence (transitivity assumption); 3) evaluating the structural properties of the network of evidence (e.g., connectivity); and 4) evaluating the coherence in network (using the "design-by-treatment" model[20]), and in each closed loop of the network (using the side-splitting approach[21,22]).

We performed frequentist random-effects network meta-analysis using the methodology of multivariate meta-analysis assuming a common heterogeneity parameter,[22,23] as performed previously.[24,25] Coherence assumption in the entire network was confirmed using a "design-by-treatment" model (global test), as described by Higgins *et al*.[20] We also used the node splitting method to assess the presence of incoherence between direct and indirect estimates of the effect.[21,26] For each outcome, we also estimated ranking probabilities using surface under the cumulative ranking curve (SUCRA), and mean treatment rankings, and rankograms.[27] We conducted all analyses using Stata 16 (StataCorp LLC, College Station, TX, USA). As inotrope trials included patients with varied severity of shock, we performed network metaregression to adjust for the percentage of patients with lower severity (SCAI A–B) shock included in each individual trial, to assess for possible effect modification by this variable.

Assessment of certainty of evidence

We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach to assess the certainty of evidence for each comparison.[28] The certainty assessment addresses the domains of risk of bias, imprecision, inconsistency, indirectness, intransitivity, publication bias, and incoherence. Imprecision for each comparison was assessed at the network level, and not at the level of the direct or indirect estimate. We used a minimally contextualized approach to evaluate certainty in outcomes.[29] As recommended, we described our findings using the informative narrative statements ("probably," "may") that reflected our certainty in the effect estimates.[30]

Results

Search results and study characteristics

We identified 1,329 studies (Fig. 1). Following exclusion of duplicates, 1,193 studies were screened, and 48 underwent full-text review. We included 17 RCTs,[31–47] with a total of 2,339 patients. For both the CAPITAL DOREMI[39] and SURVIVE[40] trials, we only included patients with acute MI, as published or obtained from study authors. All trials were parallel design. There were no trials that compared interventions from different classes (e.g., inotropes *vs* vasopressors).

Detailed study characteristics of the included RCTs are shown in Table 1, and risk-of-bias assessment is shown in ESM eTable 2. Forest plots depicting all direct estimates are shown in ESM eFig. 2, and statistical testing for incoherence is shown in ESM eTable 3.

Inotropes

Seven trials (1,145 patients) investigated the efficacy of inotropes in cardiogenic shock complicating acute MI.[33,35–37,39–41] Importantly, five of the included trials primarily included patients with SCAI classification A–B and only partly C cardiogenic shock ("classic," characterized by hypoperfusion requiring intervention with vasoactive support or MCS), and two primarily included patients with SCAI C class of shock. The relevant network plot is shown in Fig. 2a, with the GRADE summary of findings shown in Table 2. The associated SUCRA ranking is shown in ESM eTable 4.

When compared with placebo, levosimendan probably reduced the odds of mortality (OR, 0.53; 95% CI, 0.33 to 0.87; moderate certainty). Importantly, the majority of trials included in the direct comparisons between levosimendan and placebo were those that enrolled patients with SCAI A-B shock. Milrinone (OR, 0.52; 95% CI, 0.19 to 1.39) and dobutamine (OR, 0.67; 95% CI, 0.30 to 1.49) may have no effect on mortality compared with placebo; however, this was based on low certainty evidence and limited by CIs that do not rule out the possibility of benefit or harm. Enoximone (OR, 1.58; 95% CI, 0.39 to 6.45) had an uncertain effect on mortality compared with placebo based on very low certainty evidence, and very wide confidence intervals that did not exclude important benefit and harm. Levosimendan may have no effect on mortality compared with dobutamine (OR, 0.80; 95% CI, 0.42 to 1.50), enoximone (OR, 0.34; 95% CI, 0.09 to 1.26), or milrinone (OR, 0.97; 95% CI, 0.41 to 2.28); however, conclusions related to these comparisons are all based on low certainty evidence and important imprecision. Milrinone may have no effect on mortality compared with dobutamine (OR, 0.77; 95% CI, 0.43 to 1.37); however, conclusions are limited by low-certainty evidence and large CIs. There were insufficient data in the included trials to investigate any of our prespecified secondary outcomes in either the network or conventional meta-analysis. We did not find statistically significant effect modification of our primary results when adjusting for the proportion of patients in each trial with SCAI A–B shock, though we were only able to include

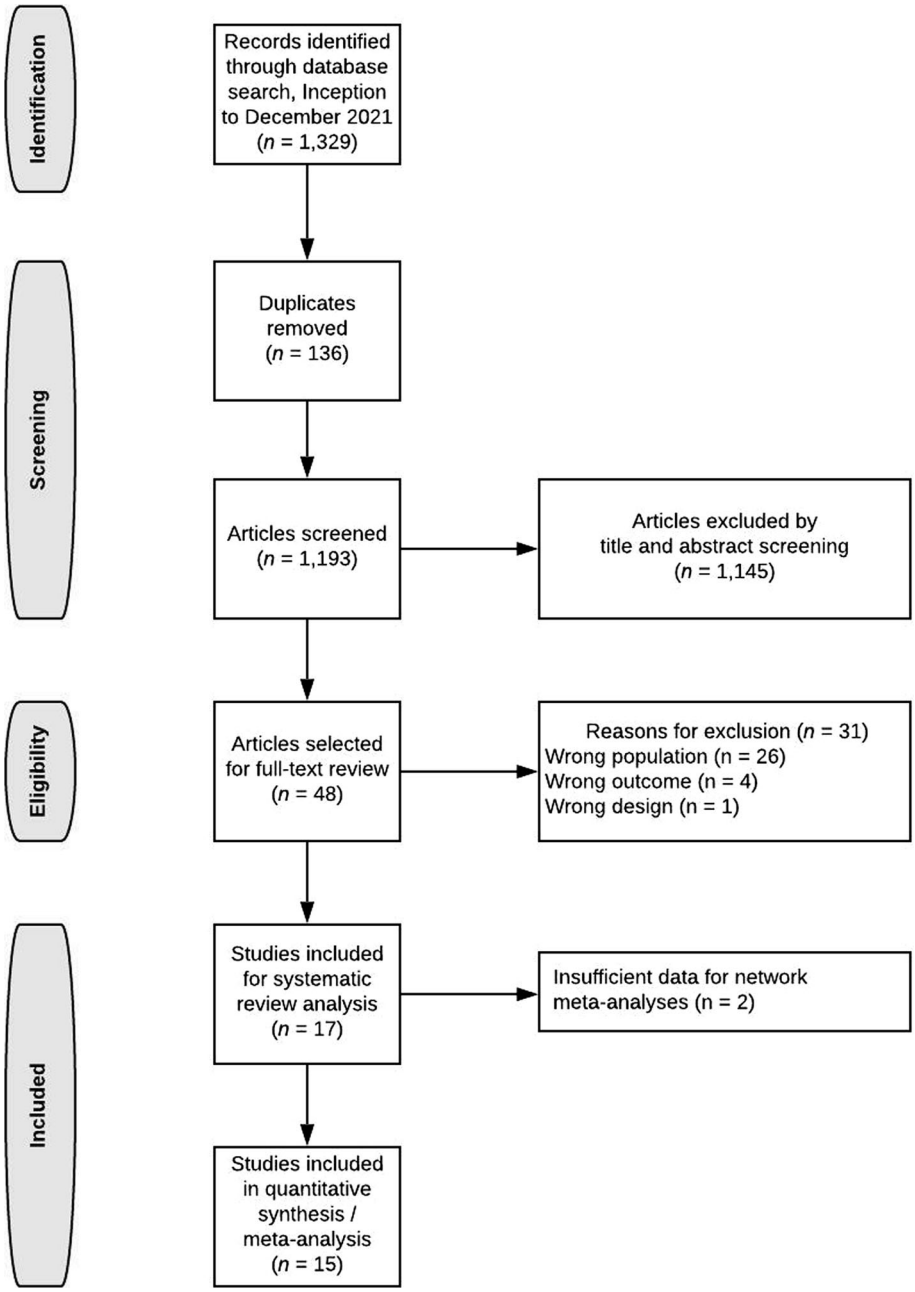

Fig. 1 Flow chart summarizing evidence search and study selection

seven trials and a single closed loop in this analysis (ESM eTable 5).

Vasopressors

Only two RCTs evaluated the role of vasopressors,[34,38] so network meta-analysis was not feasible. The major findings of these two trials are shown in ESM eTable 6. In a cardiogenic shock subgroup of the SOAP II trial, norepinephrine was associated with lower odds of mortality at 28 days compared with dopamine.[34] The OptimaCC trial compared norepinephrine to epinephrine in patients with cardiogenic shock.[38] This trial was terminated early due to higher incidence of a *post hoc* outcome of refractory shock in the patients receiving epinephrine, compared with those receiving norepinephrine (37% *vs* 7%, $P = 0.008$). The effect on 28-day mortality was not significantly different between the two groups (OR, 2.55; 95% CI, 0.84 to 7.72).

Mechanical circulatory support

In total, eight RCTs investigated MCS use in cardiogenic shock: three trials comparing IABP to a strategy of no

Table 1 Detailed characteristics of the 17 included studies

Author, year (trial name)	Country (sites)	Definition of severe heart failure/CS	Inclusion criteria	Exclusion criteria	*N*	Comparisons	Outcomes	Result (mortality)
INOTROPES								
Caldicott, 1993	United Kingdom (1)	Presence of tachycardia, a third heart sound and gallop rhythm, and confirmed by chest *X-ray* appearances of pulmonary edema; AND no improvement following treatment	1) 18 yr of age or older; 2) acute myocardial infarction with LV dysfunction	Uncontrolled tachyarrhythmias, severe pulmonary or renal disease (creatinine > 300 μmol·L^{-1}), stenotic valvular heart disease, hypertrophic cardiomyopathy	18	1) Enoximone (bolus 25 μg·kg·min^{-1} and infusion of 5 μg·kg·min^{-1}, increased by 5 μg·kg·min^{-1} hourly); 2) dobutamine (2.5 μg·kg·min^{-1}, increased to 5, 10, 15)	In-hospital mortality	No difference in in-hospital mortality OR, 1.00 (95% CI, 0.05 to 18.92)
Fuhrmann, 2008	Germany (1)	1) Deteriorating hypotension as manifested by unaugmented SBP < 90 mm Hg or requirement of inotropes to maintain SBP > 90 mm Hg; AND 2) cardiac index < 2.5 L·min·m^{-2}; AND 3) PCOP > 18; AND 4) Clinical signs of peripheral hypoperfusion	1) 18 yr of age or older; 2) refractory CS despite recommended current therapy	Hypotension related to any mechanical complications of acute MI, such as ventricular septal rupture, cardiac tamponade, or acute severe ischemic mitral regurgitation; severe stenotic valvular disease; sustained ventricular tachycardia; major bleeding; severe hepatic failure; severe systemic illness; sepsis	32	1) Enoximone (bolus 0.5 μg·kg^{-1} over 30 min and infusion of 2–10 μg·kg·min^{-1}); 2) levosimendan (12 μg·kg^{-1} over 10 min, increased to 0.1–0.2 μg·kg·min^{-1})	30-day all-cause mortality	No difference in 30-day all-cause mortality OR, 3.67 (95% CI, 0.85 to 15.84)
Husebye, 2013 (LEAF)	Norway (1)	1) SBP < 90 mm Hg after 60 min of adequate volume therapy or SBP between 90 and 100 mm Hg in spite of inotropic support; AND 2) signs of organ hypoperfusion	1) 20 yr of age or older; 2) acute STEMI subjected to primary PCI with all of the following: (i) opening of an occluded or dilation of a stenotic coronary artery; (ii) signs of decreased wall motion in the LV; (iii) clinical signs of heart failure	< 20 yr of age, HR > 120 min^{-1}, septic shock, ARDS, creatinine > 450 μmol·L^{-1}, severe hepatic failure, significant mechanical outflow obstruction, allergy to medication, anemia, pregnancy	61	1) Levosimendan (infusion for 25 hr with a rate of 0.2 μg·kg·min^{-1} for 1 hr, followed by 0.1 μg·kg·min^{-1} for 24 hr); 2) placebo	60-day mortality	No difference in 60-day mortality OR, 0.23 (95% CI, 0.02 to 2.22)

Table 1 continued

Author, year(trial name)	Country (sites)	Definition of severe heart failure/CS	Inclusion criteria	Exclusion criteria	*N*	Comparisons	Outcomes	Result (mortality)
Jia, 2014	China (1)	LVEF < 40% AND Killip II–IV + one or both of the following symptoms despite conventional therapy: 1) dyspnea at rest and/or the need for mechanical ventilation; and 2) oliguria not due to hypovolemia	Acute MI (according to the universal definition) during the previous 14 days, classified as Killip II–IV, despite conventional therapy AND LVEF < 40%	< 18 yr of age; childbearing potential; restrictive or hypertrophic cardiomyopathy or uncorrected stenotic valvular disease; ongoing chest pain; VF/VT; AV block; HR > 120 min^{-1}; SBP < 85 mm Hg; severe renal failure; hepatic failure; cardiac tamponade; ARDS; septic shock	160	1) Levosimendan (loading dose of 24 $\mu g \cdot kg^{-1}$ over 10 min, and 0.1 $\mu g \cdot kg \cdot min^{-1}$ infusion); 2) placebo	14-day mortality; 6-month mortality	No difference in 14-day mortality OR, 0.60 (95% CI, 0.22 to 1.64)
Mathew, 2021 (CAPITAL-DOREMI)	Canada (1)	Society for Cardiovascular Angiography and Interventions (SCAI) definitions of CS stages B through E	1) 18 yr of age or older; 2) SCAI definition of CS B to E; and one of the following indications for inotropes: i) clinical diagnosis of CS and SBP < 90 mm Hg with end-organ dysfunction; ii) clinical evidence of systemic and/or pulmonary congestion; iii) ACS complicated by CS with CI < 1.8 $L \cdot min \cdot m^{-2}$; iv) clinically determined need to augment cardiac output	Out-of-hospital cardiac arrest; pregnancy; milrinone or dobutamine prior to randomization; clinical gestalt (lack of equipoise); participation in a different interventional trial, inability of patient or substitute decision maker to provide written informed consent	192	1) Dobutamine (initiated at 2.5 $\mu g \cdot kg \cdot min^{-1}$); 2) milrinone (initiated at 0.125 $\mu g \cdot kg \cdot min^{-1}$)	In-hospital mortality	No difference in in-hospital mortality OR, 1.30 (95% CI, 0.73 to 2.32)
Mebazaa, 2007 (SURVIVE)	Austria; Finland; France; Germany; Israel; Latvia; Poland; Russia; United Kingdom (75)	LVEF < 30% within the previous 12 months, and required intravenous inotropic support, as evidenced by insufficient response to intravenous diuretics and/or vasodilators, and at least one of the following: 1) dyspnea at rest or mechanical ventilation; 2) oliguria; 3) PCWP > 18 mm Hg and/or cardiac index < 2.2 $L \cdot min \cdot m^{-2}$	1) 18 yr of age or older; 2) hospitalized with acute decompensated heart failure	Severe ventricular outflow obstruction; SBP < 85 mm Hg or HR > 130 min^{-1}; intravenous inotrope use prior to randomization; history of torsades de pointes; and serum creatinine > 450 $\mu mol \cdot L^{-1}$ or dialysis	178	1) Levosimendan (loading dose of 12 $\mu g \cdot kg^{-1}$ and then infusion of 0.1 $\mu g \cdot kg \cdot min^{-1}$); 2) dobutamine (initiated at 5 $\mu g \cdot kg \cdot min^{-1}$ and increased up to maximum of 40 $\mu g \cdot kg \cdot min^{-1}$)	31-day mortality	No difference in 31-day mortality OR, 0.83 (95% CI, 0.44 to 1.59)

Table 1 continued

Author, year(trial name)	Country (sites)	Definition of severe heart failure/CS	Inclusion criteria	Exclusion criteria	*N*	Comparisons	Outcomes	Result (mortality)
Moiseyev, 2002 (RUSSLAN)	Russia; Latvia (21)	Clinical evidence of LV dysfunction and need for inotropic support	Acute MI (according to the universal definition) during the previous 5 days; evidence of LV failure on chest radiography; clinical need for inotropic therapy	RV infarction; SBP < 90 mm Hg; sustained ventricular tachycardia or frequent ventricular non-sustained tachycardias; cardiac pacing; cardiac tamponade	504	1) Levosimendan (doses of 0.1–0.4 $\mu g \cdot kg \cdot min^{-1}$); 2) placebo	14-day mortality; 6-month mortality	Lower 14-day mortality with levosimendan OR, 0.54 (95% CI, 0.31 to 0.97)
VASOPRESSORS								
De Backer, 2010 (SOAP II)	Belgium; Austria; Spain (8)	MAP < 70 mm Hg or SBP < 100 mm Hg despite adequate fluids, signs of tissue hypoperfusion	1) 18 yr of age or older; 2) vasopressor agent required for the treatment of shock	< 18 yr of age; had already received a vasopressor agent for more than 4 hr during current episode of shock	280	1) Dopamine (up to maximum of 20 $\mu g \cdot kg \cdot min^{-1}$; 2) norepinephrine (0.19 $\mu g \cdot kg \cdot min^{-1}$)	28-day mortality	Higher 28-day mortality in dopamine group OR, 1.71 (95% CI, 1.06 to 2.77)
Lévy, 2018 (OptimaCC)	France (9)	ALL of the following, without vasopressors or inotropes: 1) SBP < 90 mm Hg or MAP < 65 mm Hg; 2) cardiac index < 2.2 $L \cdot min \cdot m^{-2}$; 3) PAOP > 15 mm Hg; 4) LVEF < 40%; 5) evidence of tissue hypoperfusion	1) 18 yr of age or older; and 2) CS due to acute MI successfully revascularized by PCI	Shock of other origin; immediate indication for extracorporeal life support; < 18 yr of age; cardiac arrest; septic, toxic, and obstructive cardiomyopathy; patient without medical insurance; adult patient under legal protection; and patients considered moribund	57	1) Norepinephrine (0.02 $\mu g \cdot kg \cdot min^{-1}$ titrated to MAP 65–70 mm Hg); 2) epinephrine (0.02 $\mu g \cdot kg \cdot min^{-1}$ titrated to MAP 65–70 mm Hg)	28-day mortality	No difference in 28-day mortality OR, 0.39 (95% CI, 0.13 to 1.18)
MECHANICAL CIRCULATORY SUPPORT								
Bochaton, 2020 (IMPELLA-STIC)	France (2)	Requiring inotropic drugs and an IABP	Admitted with acute MI complicated by CS, who had been treated with primary angioplasty within 24 hr of the index acute MI	Contraindication to impella implantation (aortic valvulopathy or mechanical valve, HOCM, LV thrombus); refractory CS; isolated RV failure; resuscitation for cardiac arrest > 30 min; sepsis	13	1) Impella + IABP; 2) IABP	30-day mortality, major bleeding	No difference in 30-day mortality OR, 5.90 (95% CI, 0.23 to 151.15)

Table 1 continued

Author, year(trial name)	Country (sites)	Definition of severe heart failure/CS	Inclusion criteria	Exclusion criteria	*N*	Comparisons	Outcomes	Result (mortality)
Burkhoff, 2006	USA; Switzerland (12)	Cardiac index < 2.2 L·min·m^{-2}, MAP < 70 mm Hg, PCWP > 15 mm Hg, and evidence of end-organ hypoperfusion; OR need for high-dose pressor and/or inotropic support	1) 18 yr of age or older; 2) presenting within 24 hr of developing CS	Isolated right heart failure; coagulopathy; sepsis; severe peripheral vascular disease; stroke within 6 months, 2+ or greater aortic regurgitation, and ventricular septal rupture	33	1) TandemHeart; 2) IABP	30-day mortality; Adverse events	No difference in 30-day mortality OR, 1.62 (95% CI, 0.39 to 6.68)
Ohman, 2005 (TACTICS)	USA; Australia; Europe (18)	1) Anterior MI complicated by SBP < 90 mm Hg for 30 min; or 2) any MI complicated by SBP < 110 mm Hg, severe heart failure, or acute heart failure with SBP < 100 Hg and other signs of hypoperfusion	21–85 yr of age; eligibility for fibrinolytic therapy; MI or reinfection; AND CS	Absolute contraindication to fibrinolytic, heparin, or ASA; known internal bleeding < 1 month; planned primary angioplasty for acute MI; inability to insert IABP	57	1) IABP; 2) no mechanical circulatory support	30-day mortality	No difference in 30-day mortality OR, 0.72 (95% CI, 0.23 to 2.27)
Ouweneel, 2017 (IMPRESS)	Netherlands; Norway (2)	SBP < 90 mm Hg for longer than 30 min or the need for inotropes or vasopressors to maintain a SBP > 90 mm Hg	Acute MI with ST-segment elevation complicated by severe CS in the setting of immediate percutaneous coronary intervention; mechanical ventilation	Severe aortoiliac arterial disease impeding placement of either IABP or pMCS; known severe cardiac aortic valvular disease; serious known concomitant disease with a life expectancy < 1 year; CABG in the preceding week	48	1) Impella; 2) IABP	30-day all-cause mortality	No difference in 30-day mortality OR, 0.85 (95% CI, 0.27 to 2.63)
Prondzinsky, 2010 (IABP SHOCK)	Germany (1)	Symptoms and signs of organ hypoperfusion, plus one of the following: 1) SBP < 90 mm Hg for at least 30 min; 2) hypotension requiring inotropic/vasopressor therapy at a HR > 60 min^{-1} or a cardiac index < 2.2 L·min·m^{-2} on invasive monitoring	Patients treated with primary PCI for CS secondary to acute MI, who required inotropic and/or vasopressor support despite appropriate volume filling	Absent lower limb pulses (precluding IABP placement) or any mechanical complications of acute MI, such as acute, severe mitral valve insufficiency, an ischemic ventricular septal defect or hemodynamically relevant aortic valve insufficiency	40	1) IABP; 2) no mechanical circulatory support	30-day all-cause mortality	No difference in 30-day mortality OR, 1.46 (95% CI, 0.39 to 5.50)

Table 1 continued

Author, year(trial name)	Country (sites)	Definition of severe heart failure/CS	Inclusion criteria	Exclusion criteria	*N*	Comparisons	Outcomes	Result (mortality)
Seyfarth, 2008 (ISAR-SHOCK)	Germany (1)	Clinical: SBP < 90 mm Hg and a HR > 90 min^{-1}; need for positive inotropic drugs to maintain SBP > 90 mm Hg and end-organ hypoperfusion; hemodynamic: cardiac index < 2.2 $L{\cdot}min{\cdot}m^{-2}$ and PCWP > 15 mm Hg OR LVEF < 30% and LVEDP > 20 mm Hg	Patients with acute MI < 48 hr and CS	< 18 yr of age; prolonged resuscitation (> 30 min); HOCM; LV thrombus; treatment with IABP prior to enrollment; severe valvular disease or mechanical heart valve; mechanical complications of acute MI, such as ventricular septal defect, acute mitral regurgitation	41	1) TandemHeart; 2) IABPp	30-day mortality	No difference in 30-day mortality OR, 1.00 (95% CI, 0.21 to 4.67)
Thiele, 2005	Germany (1)	1) Persistent SBP < 90 mm Hg or vasopressors required to maintain SBP > 90 mm Hg; 2) evidence of end-organ failure; 3) evidence of elevated LV filling pressures; 4) cardiac index < 2.1 $L{\cdot}min{\cdot}m^{-2}$	Presence of CS complicating acute MI and the intention to revascularize the infarcted artery by PCI as first-line treatment option	> 75 yr of age; mechanical complications of acute MI; duration of CS > 12 hr; right heart failure; sepsis; significant aortic regurgitation; severe cerebral damage; resuscitation > 30 min; severe peripheral vascular disease	41	1) TandemHeart; 2) IABP	30-day mortality	No difference in 30-day mortality OR, 1.09 (95% CI, 0.32 to 3.75)
Thiele, 2012 (IABP SHOCK II)	Germany (20)	SBP < 90 mm Hg for longer than 30 min or the need for inotropes or vasopressors to maintain a SBP > 90 mm Hg, had clinical signs of pulmonary congestion, and had impaired end-organ perfusion	Acute MI (with or without ST-segment elevation) complicated by CS and if early revascularization (PCI/CABG) planned	Resuscitation for more than 30 min; no intrinsic heart action; coma with fixed dilation of pupils; mechanical cause of CS; onset of shock > 12 hr before screening; massive pulmonary embolism; severe peripheral arterial disease; > 90 yr of age; life expectancy < 6 months	599	1) IABP; 2) no mechanical circulatory support	30-day mortality	No difference in 30-day mortality OR, 0.93 (95% CI, 0.67 to 1.30)

ARDS = acute respiratory distress syndrome; ASA = acetylsalicylic acid; CABG = coronary artery bypass grafting; CI = confidence interval; CS = cardiogenic shock; HOCM = hypertrophic obstructive cardiomyopathy; HR = heart rate; IABP = intra-aortic balloon pump; LV = left ventricle; LVEF = left ventricular ejection fraction; MAP = mean arterial pressure; MI = myocardial infarction; OR = odds ratio; PCI = percutaneous coronary intervention; RV = right ventricle; SBP = systolic blood pressure; STEMI = ST-elevation myocardial infarction

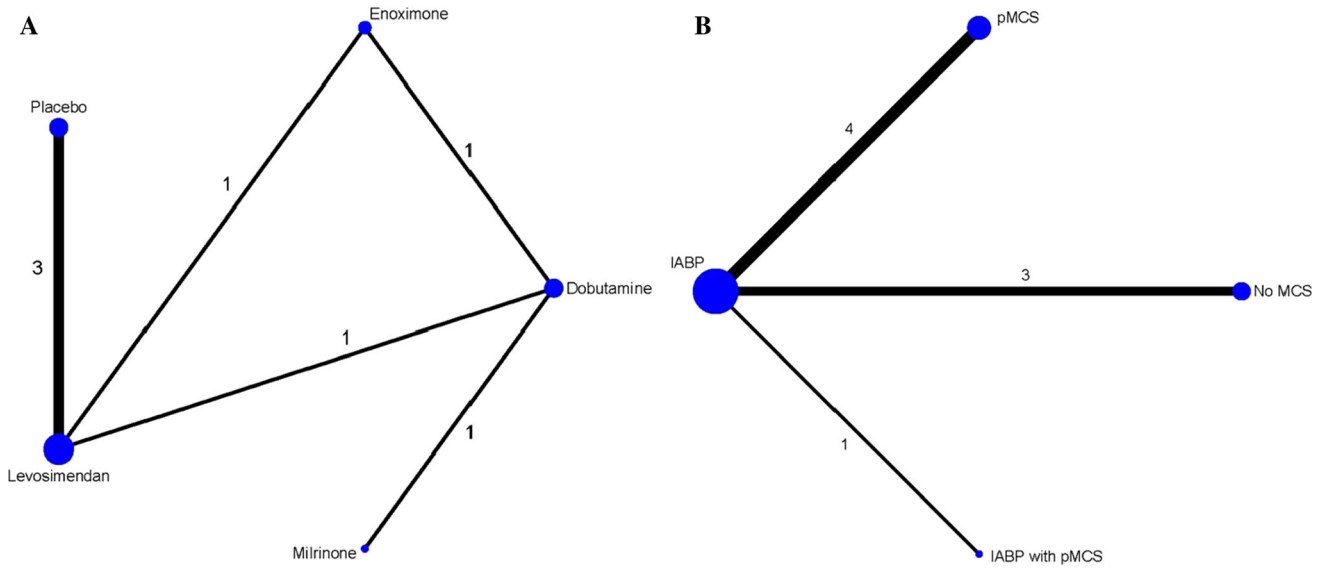

Fig. 2 Network plots for A) short-term mortality among inotrope agents; and B) short-term mortality among mechanical circulatory support treatments. The size of the node corresponds to the number of patients randomized to that intervention. The thickness of the line and the associated numbers correspond to the number of studies comparing the two linked interventions.

Table 2 GRADE summary of findings for short-term mortality among inotropes

Comparison	Direct OR (95% CI)	*GRADE*	Indirect OR (95% CI)	*GRADE*	Network OR (95% CI)	*GRADE*
Levosimendan *vs* placebo[a,b]	0.53 (0.33 to 0.87)	MODERATE[1]	No indirect estimate		0.53 (0.33 to 0.87)	MODERATE[1]
Enoximone *vs* dobutamine[a,b]	1.00 (0.05 to 18.92)	VERY LOW[1,3]	3.05 (0.62 to 15.08)		2.36 (0.58 to 9.63)	VERY LOW[1,2]
Levosimendan *vs* dobutamine[a,b]	0.83 (0.44 to 1.59)	LOW[3]	0.27 (0.01 to 7.29)		0.80 (0.42 to 1.50)	LOW[2]
Milrinone *vs* dobutamine[c]	0.77 (0.43 to 1.37)	MODERATE[3]	No indirect estimate		0.77 (0.43 to 1.37)	LOW[2,3]
Levosimendan vs enoximone[c]	0.27 (0.06 to 1.18)	LOW[1,3]	0.83 (0.04 to 16.85)		0.34 (0.09 to 1.26)	LOW[1,3]
Dobutamine *vs* placebo	No direct estimate		0.67 (0.30 to 1.49)	MODERATE	0.67 (0.30 to 1.49)	LOW[2]
Enoximone *vs* placebo	No direct estimate		1.58 (0.39 to 6.45)	LOW	1.58 (0.39 to 6.45)	VERY LOW[1,2]
Milrinone *vs* placebo	No direct estimate		0.52 (0.19 to 1.39)	MODERATE	0.52 (0.19 to 1.39)	LOW[2]
Milrinone *vs* enoximone	No direct estimate		0.33 (0.07 to 1.49)	VERY LOW	0.33 (0.07 to 1.49)	VERY LOW[1,2]

[a,b] Direct comparison primarily includes patients with SCAI A-B severity of cardiogenic shock[29,32,33,36,37]

[c] Direct comparison primarily includes patients with SCAI C severity of cardiogenic shock[31,35]

[1] Lowered for risk of bias in included trial

[2] Lowered two levels for imprecision given very wide confidence intervals and low number of patients

[3] Lowered one level for imprecision given wide confidence intervals that do not exclude important harm

CI = confidence interval; GRADE = Grading of Recommendations Assessment, Development, and Evaluation; OR = odds ratio

MCS at all,[42,44,47] four trials comparing IABP to pMCS (Impella or TandemHeart),[32,43,45,46] and one trial comparing IABP with the combination of IABP and pMCS (Impella).[31] The network plot is displayed in Fig. 2b, with the GRADE summary of findings shown in Table 3. The associated SUCRA ranking is shown in ESM eTable 7.

With regard to MCS, there may be no effect on mortality with the use of IABP (OR, 0.94; 95% CI, 0.69 to 1.28) or pMCS (OR, 0.96; 95% CI, 0.47 to 1.98) compared with a

Table 3 GRADE summary of findings for short-term mortality among mechanical circulatory support

Comparison	Direct OR (95% CI)	*GRADE*	Indirect OR (95% CI)	GRADE	Network OR (95% CI)	GRADE
IABP *vs* No MCS	0.94 (0.69 to 1.28)	LOW[1,2]	No indirect estimate		0.94 (0.69 to 1.28)	LOW[1,2]
IABP *vs* pMCS	0.98 (0.51 to 1.88)	LOW[1,2]	No indirect estimate		0.98 (0.51 to 1.88)	LOW[1,2]
IABP + pMCS *vs* IABP	5.91 (0.23 to 151.15)	VERY LOW[1,3]	No indirect estimate		5.91 (0.23 to 151.15)	VERY LOW[1,3]
pMCS *vs* No MCS	No direct estimate		0.96 (0.47 to 1.98)	LOW	0.96 (0.47 to 1.98)	LOW[1,2]
IABP + pMCS *vs* pMCS	No direct estimate		5.78 (0.21 to 157.66)	VERY LOW	5.78 (0.21 to 157.66)	VERY LOW[1,3]
IABP + pMCS *vs* no MCS	No direct estimate		5.56 (0.21 to 144.20)	VERY LOW	5.56 (0.21 to 144.20)	VERY LOW[1,3]

[1] Lowered for risk of bias in included trials

[2] Lowered one level for imprecision given wide CIs that do not exclude important harm or benefit

[3] Lowered two levels for imprecision given very wide CIs and low number of patients

CI = confidence interval; GRADE = Grading of Recommendations Assessment, Development, and Evaluation; IABP = intra-aortic balloon pump; MCS = mechanical circulatory support; OR = odds ratio; pMCS = percutaneous mechanical circulatory support

strategy involving no MCS; however, both comparisons are based on low-certainty evidence. There was an uncertain effect of combination of IABP and pMCS *vs* no MCS (OR, 5.56; 95% CI, 0.21 to 144.20; very low certainty). There may be no difference in mortality between IABP and pMCS (OR, 0.98; 95% CI, 0.51 to 1.88; low certainty). All other comparisons had uncertain effects (very low certainty evidence) because of very wide CIs.

Of the included MCS trials, five provided data on incidence of major bleeding.[31,32,42,43,47] The associated network plot is depicted in ESM eFig. 3, with the GRADE summary of findings displayed in ESM eTable 8. Surface under the cumulative ranking curve (SUCRA) ranking is shown in ESM eTable 9. There may be no difference in major bleeding between IABP and no MCS (OR, 1.00; 95% CI, 0.69 to 1.45; low certainty), but IABP may be associated with lower incidence of major bleeding compared with pMCS (OR, 0.20; 95% CI, 0.06 to 0.69; low certainty). Finally, pMCS may be associated with higher incidence of major bleeding compared with a strategy of no MCS (OR, 4.91; 95% CI, 1.38 to 17.44; low certainty). Contribution matrices are shown in ESM eFig. 4.

Discussion

When acute MI is complicated by cardiogenic shock, patient mortality increases substantially.[2,4] The use of inotropes can augment stroke volume and improve forward flow in a failing ventricle,[10] and their use in shock associated with low cardiac output is endorsed by clinical practice guidelines.[48] Nevertheless, the various inotropic agents have different mechanisms, and their relative use differs worldwide.[11] Our work found that levosimendan was the only agent with evidence of possible benefit compared with placebo, though this was largely evident in patients without overt cardiogenic shock (SCAI A–B). That said, we did not see effect modification in our metaregression adjusting for the percentage of patients with SCAI A–B shock in the individual trials, though we were strongly limited by sample size in this analysis. Levosimendan has unique properties and is thought to improve myocardial efficiency without either increasing myocardial oxygen demand or improving ventricular relaxation.[14,49] Use of this drug is not currently approved in North America, where clinicians may favor other inotropes, such as dobutamine or milrinone. Importantly, because these trials were primarily conducted in patients with lower severity of shock (SCAI A–B), we would caution clinicians on the application of these findings to patients with higher severity of shock, where the use of a single inotrope in isolation is uncommon.[11] Our network meta-analysis also provides the first estimates of effect for both dobutamine and milrinone against placebo (as there has never been a direct, randomized comparison), and while low certainty evidence suggested no difference between these agents and placebo, we were limited by imprecision and could not rule out possible harm. Recent clinical practice guidelines recommend the use of inotrope therapy in patients with cardiogenic shock, despite a lack of randomized evidence to support this intervention.[48] Nevertheless, given our findings and the known potential harms of these agents,[50,51] whether inotropes truly provide benefit to justify routine use in cardiogenic shock is unclear.

Vasopressors represent an alternative type of vasoactive medication that might be used for the treatment of cardiogenic shock.[52] Our search found only two RCTs investigating the efficacy of vasopressors, both evaluating the use of norepinephrine. Although conducted as a subgroup analysis as part of the SOAP II trial, norepinephrine was found to be associated with reduced mortality, compared with dopamine, in patients with cardiogenic shock.[34] Similarly, the OptimaCC trial compared norepinephrine to epinephrine in patients with cardiogenic shock, and was stopped early because a significantly higher proportion of patients had refractory shock in the epinephrine group.[38] Metabolic parameters (i.e., hyperlactatemia) were more deranged among patients receiving epinephrine. Thus, while not amenable to meta-analysis, these trials suggest that norepinephrine should likely remain the vasopressor of choice in cardiogenic shock, particularly when a rapid agent is required.[3,10] Nevertheless, the large paucity of data highlights the need for further RCTs in this area.

Finally, we evaluated the relative efficacy of different types of MCS in the management of patients with cardiogenic shock. As stated, the primary goal of MCS is to provide temporary hemodynamic support in cardiogenic shock as a bridge to recovery or transplant,[12] though evidence surrounding the efficacy of this strategy is limited. Our study did not find any important differences between IABP or pMCS (Impella or TandemHeart), compared with a strategy that did not include any MCS in patients with cardiogenic shock. These findings are in keeping with existing evidence surrounding pMCS.[53] Importantly, the use of pMCS may be associated with higher incidence of major bleeding, compared with the use of IABP or a strategy of no MCS. Use of MCS has been increasing over time,[12] and the use of this technology has outpaced the evidence. Given the costs and resources associated with MCS,[54,55] additional trials are necessary to evaluate the safety, efficacy, and optimal patient selection in cardiogenic shock. Importantly, our meta-analysis did not include any studies involving VA–ECMO, and randomized trials evaluating its efficacy in cardiogenic shock are ongoing.

Our study has important limitations. First, in our attempts to reduce heterogeneity, our individual meta-analyses included a relatively small number of trials and patients. This resulted in imprecision, which was accounted for in GRADE assessments and conclusions. Although we did not find any statistical evidence of incoherence, our treatment networks contained only a few closed loops per outcomes, with a relatively small number of included studies, and as such we cannot exclude the existence of potentially important incoherence. Several therapies (including vasopressin, phenylephrine, and VA-ECMO) have not been tested in RCTs, so could not be included in this analysis. Furthermore, despite our attempts to focus largely on patients with cardiogenic shock secondary to acute MI, there is inherent heterogeneity within that population. Some patients might have refractory left ventricular, right ventricular, or biventricular failure, some may be amenable to percutaneous coronary intervention, while others may require cardiac surgery for revascularization. Severity of illness likely differs across trial populations and data from the differing stages of cardiogenic shock need to be studied to identify key time periods to intervene.[15] All of these factors are likely to influence prognosis and were not easily accounted for in our study. That being said, statistical measures of heterogeneity (such as incoherence) were not significant, suggesting that while clinical heterogeneity may exist, its impact on our effect estimates is unclear. Finally, while we sought to study various secondary outcomes, there was insufficient data to do so; therefore, we cannot rule out differences in efficacy between these therapies with regard to such outcomes.

Conclusion

This systematic review and network meta-analyses evaluated different supportive therapies for cardiogenic shock complicating acute MI. With regard to inotropes, levosimendan was the only agent showing possible reduction in mortality with moderate certainty when compared with placebo, but did not show benefit compared with any other inotrope, and our analysis was largely limited to trials with at-risk or evolving cardiogenic shock. Little randomized data exist on vasopressors, but the available evidence suggests that norepinephrine may be associated with reduced mortality, compared with dopamine or epinephrine. Finally, neither IABP or pMCS provided benefit compared with a strategy with no MCS, but likely higher incidence of major bleeding was seen with pMCS. Taken together, our study summarizes the available evidence for supportive treatment of cardiogenic shock, while also highlighting important areas for further investigation.

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content. All authors provided their final approval for manuscript submission. *Benjamin Hibbert* and *Bram Rochwerg* contributed equally as co-senior authors. All authors agree to be accountable for all aspects of the work.

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