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ORIGINAL ARTICLE

Vasoactive pharmacologic therapy in cardiogenic shock: a critical review

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ABSTRACT

Background: Cardiogenic shock (CS) is an acute complex condition leading to morbidity and mortality. Vasoactive medications, such as vasopressors and inotropes are considered the cornerstone of pharmacological treatment of CS to improve end-organ perfusion by increasing cardiac output (CO) and blood pressure (BP), thus preventing multiorgan failure.

Objective: A critical review was conducted to analyze the currently available randomized studies of vasoactive agents in CS to determine the indications of each agent and to critically appraise the methodological quality of the studies.

Methods: PubMed database search was conducted to identify randomized controlled trials (RCTs) on vasoactive therapy in CS. After study selection, the internal validity of the selected studies was critically appraised using the three-item Jadad scale.

Results: Nine studies randomized 2388 patients with a mean age ranged between 62 and 69 years, were identified. Seven of studies investigated CS in the setting of acute myocardial infarction (AMI). The studies evaluated the comparisons of norepinephrine (NE) *vs.* dopamine, epinephrine *vs.* NE, levosimendan *vs.* dobutamine, enoximone or placebo, and nitric oxide synthase inhibitors (NOSi) *vs.* placebo. The mean Jadad score of the nine studies was 3.33, with only three studies of a score of 5.

Conclusions: The evidence from the studies of vasoactive agents in CS carries uncertainties. The methodological quality between the studies is variable due to the inherent difficulties to conduct a study in CS. Vasopressors and inotropes continue to have a fundamental role given the lack of pharmacological alternatives.

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1. Introduction

Shock as a final pre-terminal state in many diseases is widely classified, according to the underlying mechanisms into, cardiogenic (e.g. acute myocardial infarction (AMI) or myocarditis), hypovolemic (i.e. fluid loss either internal or external), obstructive (e.g. cardiac tamponade or pulmonary embolism) and distributive (e.g. septic shock or anaphylaxis)[1,2]. The most common form of shock is septic (62%), then cardiogenic (16%), hypovolemic (16%), other forms of distributive shock, and finally obstructive shock (2%)[2]. In-hospital mortality rate of shock in general is about 38%[3], and varies depending on the shock type. For example, mortality rate of septic shock ranges from 46[3,4] to 61%[5] and that of cardiogenic shock (CS) from 40%[6] up to about 50%[7,8].

Cardiovascular diseases (CVD) are the most common cause of CS[9]. Cardiac diseases that impair, either in isolation or in combination, the function of myocardium, pericardium, conduction system, or valves, will lead to an acute hemodynamic instability[10]. Apart from the cardiac etiologies, CS may occur due to other systemic illnesses, such as lung injury, sepsis, or other inflammatory conditions[9,11]. The pathogenesis of CS is broad[9], which ranges from low cardiac output (CO) advanced chronic heart failure (HF) to a de novo CS[12]. AMI is the most common cause[9,12] and accounts for approximately half of CS cases[13]. It has also been reported that CS complicated about 5–15% of AMI cases[8,9,13–18]. Prior to the coronary revascularization era, the mortality rates in patients with CS ranged between 72 and 81%[19]. Despite the advances in hemodynamic support devices and reperfusion techniques[13–15], the in-hospital mortality remained high[13] $(24.6-50\%)$[14,15,17–20], and has not changed since the publication of the SHOCK study in 1999[8]. In a large population-based observational study over eight years (2003–2010), the incidence of CS complicating ST-segment elevation myocardial infarction (MI) increased from 6.5 to 10.1% (p_{trend} <.001). There was an increase in early revascularization rate (30.4–50.7%, p_{trend} <.001) and intra-aortic balloon pump (IABP) use (44.8–53.7%, p_{trend} <.001). Whereas, there was a significant decline in the in-hospital mortality (44.6–33.8%, p_{trend} <.001; adjusted odds ratio (OR) 0.71; 95% confidence interval (95% [CI], 0.68–0.75)[17]. CS is generally recognized as

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a state of low CO due to acute left ventricular (LV) dysfunction and hypotension, leading to a life-threa[9,11,13,14]. There is no universal definition of CS in literature[9,14]. It is defined as a clinical condition of persistent hypotension (i.e. systolic blood pressure (SBP) <90 mmHg, or need for catecholamine support to maintain SBP ≥90 mmHg) despite volume replacement[6,8–10,12,18], with clinical features of end-organ hypoperfusion (i.e. altered mental status, cold/clammy skin or extremities, elevated serum creatinine, urine output <30 mL/h, or lactate >2.0 mmol/L)[6,8–10,12]. Hemodynamic criteria, although not mandatory, can assist in confirming the diagnosis of CS, and usually include cardiac index (CI) <1.8 L/min/m^2 without support or <2.2 L/min/m^2 with support[8,10,13], and elevated LV filling pressures (i.e. pulmonary capillary wedge pressure (PCWP) ≥15 mmHg[8–10] or >18 mmHg)[13].

Vasoactive medications, such as vasopressors and inotropes are considered the cornerstone of pharmacological treatment of CS[10,12,21], and are administered in about 90% of the patients[22]. They improve end-organ perfusion by increasing CO and blood pressure (BP)[12]. However, they should not be used at high doses and for prolonged durations because they increase oxygen consumption of the myocardium and induce vasoconstriction that elevates the afterload and impairs the microcirculation[15,22]. Since the publication of the SHOCK trial[8], an immediate coronary revascularization has been recommended in patients presenting with AMI and complicated by CS[9,10,12,23–25]. In the setting of coronary revascularization, the pharmacologic vasoactive agents and mechanical circulatory support are considered the only therapeutic options available for the hemodynamic support[11,15]. Despite the wide use of vasopressors and inotropes and the long experience with such drugs (i.e. since 1950s)[13], there are few studies available to help in guiding the drug selection as an initial and subsequent choice in CS[10,13]. As such, a critical review was conducted to analyze the currently available randomized controlled trials (RCTs) of vasoactive agents in patients presenting with CS to determine the indications of each drug and to systematically evaluate the methodological quality of these studies.

2. Methods

2.1. Search strategy

An electronic PubMed literature search of pertinent studies was independently conducted by two authors on 31 March 2020. The search aimed to find clinical trials performed with at least one group treated with an inotropic or vasopressor drug in critically ill patients with CS. The MeSH terms included: "Cardiogenic Shock", "Cardiotonic Agents", "Vasoconstrictor Agents", "Vasodilator Agents", and the individual agents (epinephrine, norepinephrine [NE], vasopressins, dobutamine, dopamine, amrinone, enoximone, milrinone, simendan, and "N(G)-monomethyl-arginine acetate"). Terms that indicated other causes of shock (anaphylactic, distributive, hypovolemic, neurogenic, obstructive, septic, and vasodilatory) were excluded. Terms were combined using Boolean operators "AND", "OR", and "NOT" to refine the search. The search was limited to "Humans" and "Clinical Trial". Another literature search was conducted on 22 May 2020 to search for the registered clinical studies on CS using the United States (US) National Institutes of Health Registry (http://clinicaltrials.gov/).

2.2. Study selection and data extraction

The references obtained from the literature search were examined at a title/abstract level for relevance. Potentially relevant studies were retrieved as full articles. A manual search of the reference lists of the retrieved articles and pertinent reviews and meta-analyses was also performed to identify further studies. The selected studies enrolled adult patients and had a random allocation to treatment and comparison. The exclusion criteria included duplicate publications, non-adult studies, retrospective trial designs, conference posters, proceedings, and case reports or series. The data from the included studies were extracted for information about author name, publication year, study objective(s), sample size, inclusion/exclusion criteria, relevant definitions, interventions, comparators, outcomes, results, limitations, and conclusions.

2.3. Quality assessment

The internal validity of the selected studies was critically appraised using Jadad scale, a validated tool to evaluate the methodological rigor of RCTs. The three-item scale examines the following aspects of a trial: randomization and its description, double-blinding and its description, and patient disposition (i.e. dropouts or withdrawals). For each aspect, one point is awarded if present. An additional point is awarded for or deducted from the randomization and the double-blinding scores if their methods are appropriate or not, respectively. The five-point score ranges from 0 to 5, with scores between 0 and 2 indicating poor quality, and scores between 3 and 5 indicating good quality[26–28]. An expanded version of the scale (i.e. modified Jadad scale), is a six-item scale that addresses some of the limitations of the original scale with a score ranges from 0 to 8 with higher score indicates better quality. The additional items include description of inclusion/exclusion criteria, assessment of adverse effects, and description of statistical analysis with a point awarded for each if present[29]. The quality assessments of the selected studies were independently conducted by two authors with divergences resolved by a discussion with a third author and then having a consensus. For the purpose of this review, the validated three-item Jadad scale was used to compare and discuss the methodological quality of the included studies. However, the modified scale with three additional elements was also presented to provide a comprehensive quality overview of each study. The modified scales are not valid nor reliable unless they are validated and tested for reliability. Moreover, the presence of the following important aspects was stated for each study, allocation concealment, intention-to-treat analysis (ITT), and justification of the sample size[30].

3. Results

3.1. Study screening

The electronic and manual literature searches resulted in a total of 9041 records that were screened at the title/abstract level. After excluding 8992 articles for irrelevance and duplication, the yield was 49 potential studies. Of these, 38 studies were excluded[31–68]. The 11 remaining studies were identified as eligible for the inclusion in the review. Nine of them were assessed for methodological quality[69–79], because two[73,74] of the 11 studies were additional publications of one study[72] that reported different outcomes. The process of study selection and exclusion is presented in Figure 1.

3.2. Study characteristics

The main characteristics of the selected studies are presented in Table 1. Of the nine studies, one was a Phase II dose-ranging study[78] and two analyzed the patients presenting with CS in predefined subgroups analysis (289 of 1740 patients)[69,76]. The nine studies randomized 2388 patients (937 patients with CS) from 174 sites in total, mostly in Europe between 1999 and 2016. All the studies enrolled patients between 2003 and 2010, except two of them. One between 1999 and 2002[77] and the second between 2011 and 2016[71]. The mean age of patients ranged between 62 and 69 years. There was variation in patient volume with seven studies were of small sample size ranging from 22 to 79. There were slight variations in the etiologies of CS between the studies. Of the nine studies, a total of seven[71,72,75–79] investigated CS in the setting of AMI. Of the seven studies, four had clear definition of AMI in term ST-segment elevation or depression, elevated cardiac markers, and/or presence of a new left bundle branch block[75,77–79]. Five studies[71,72,75–77] mandated percutaneous coronary intervention (PCI), while in two studies, PCI was performed in 90%[78] and up to 97%[79] of the patients. In three studies[75,77,78] all patients received IABP, while in another three it was used in 28%[76] and 90%[79] of patients, or at physician's discretion[72]. The definition of CS in the nine studies included hypotension, clinical signs of tissue hypoperfusion, and/or diagnostic criteria utilizing invasive cardiac monitoring to measure CI and PCWP. The primary endpoints of the studies included either clinical endpoints (mortality) or surrogate markers of hemodynamic stability. Mortality at $28-30$ d was reported in four studies[69,75,77,79], while the other studies investigated various hemodynamic or echocardiographic parameters, such as mean arterial blood pressure (MAP), CI, CO, and wall-motion score index (WMSI)[70–72,76,78]. In the eight studies that reported left ventricular ejection fraction (LVEF)[70–72,75–79], the estimated mean LVEF across the studies was 28.75% (standard deviation [SD] = 6.0). Of these, only one study[76] reported a mean LVEF of >35%.

3.3. Vasoactive therapy

Three studies investigated vasopressor and/or inotropic medications[69–71], three tested the inodilator, levosimendan[72–76], and three studied the nitric oxide synthase inhibitors (NOSi)[77–79]. The comparisons evaluated the efficacy of NE *vs.*

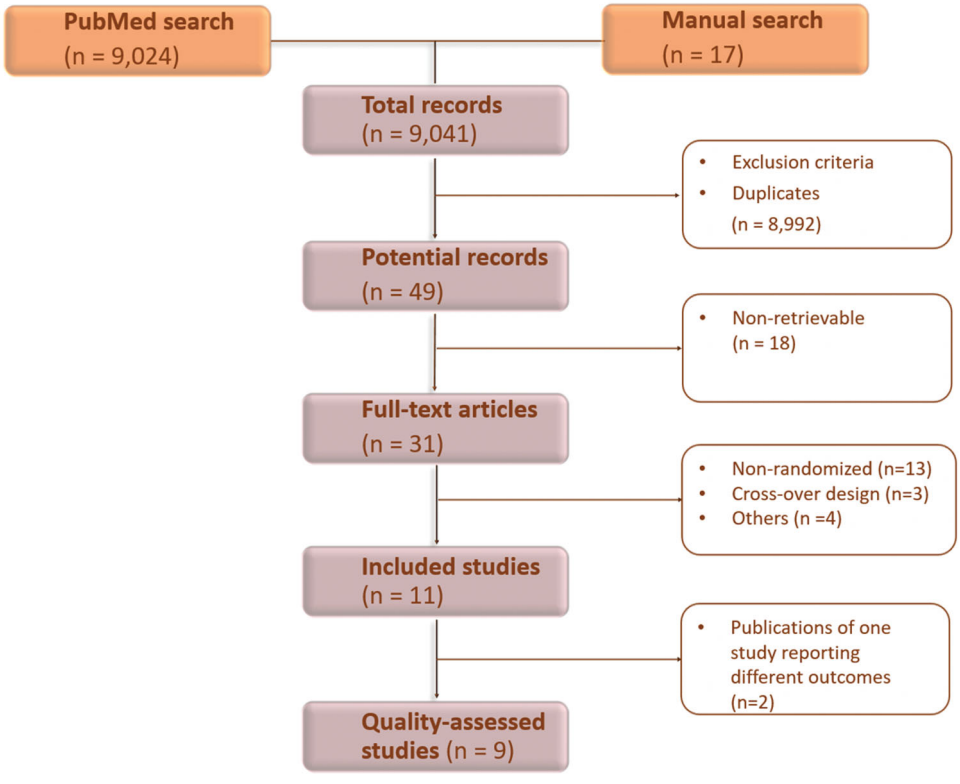

Figure 1. Flow diagram of study selection and exclusion.

Table 1. Summary of retrieved studies.

First author Acronym Sample size (*N*) Sites number (*S*)	Objective	Inclusion criteria	Interventions	Main outcome measures (Group 1 *vs.* Group 2)	Conclusion
Vasopressors and inotropes					
De Backere[a69] SOAP II *N* = 1679 *S* = 8 Europe	• To evaluate whether the choice of NE over dopamine as the first-line vasopressor agent could reduce the rate of death among patients in shock	• Shock requiring vasopressor • MAP <70 mmHg or SBP <100 despite adequate fluids, unless CVP >12 or PCWP >14 mmHg • Signs of hypoperfusion	Group1: Dopamine • Dose adjusted to target BP decided by physician • Max. 20 mcg/kg/min Group 2: Norepinephrine • Dose adjusted to target BP decided by physician • Max. 0.19 mcg/kg/min	• EF: NR • F/U: 28 d • All-cause mortality: 52.5% *vs.* 48.5% (OR 1.17; 95% CI 0.97–1.42; $p = .10$) • CS subgroup (n = 280; 17%): higher mortality in dopamine group ($p = .03$)	• No significant difference in death • Dopamine use was associated with a greater number of adverse events • Dopamine use was associated with higher mortality rate in CS subgroup
Levy[70] *N* = 30 *S* = 1 France	• To compare epinephrine and NE-dobutamine in dopamine-resistant CS without ACS	• Acute or chronic HF with EF <30% and CI <2.2 L/min/m^2 • PCWP >14 mmHg • SBP <90 mm Hg or MAP <60 mm Hg or a drop in MAP of >30 mm Hg • UOP <0.5 mL/kg/h • Lactate >2 mmol/L • Signs of hypoperfusion	Group 1: Epinephrine • Dose titrated to obtain MAP of 65–70 mmHg with a stable or increased CI Group 2: NE - Dobutamine • Dose titrated to obtain MAP of 65–70 mmHg with a stable or increased CI	• EF: 24% • F/U: 26 months • Hemodynamic: HR, MAP, CO, CVP, PAP, and PAOP • Tonometric: Gastric mucosal PCO2 measured by tonometry • Metabolic: lactate and pyruvate	• Epinephrine was as effective as NE-dobutamine in term of global hemodynamic effects • Epinephrine was associated with a transient lactic acidosis, higher HR and arrhythmia, and inadequate gastric mucosa perfusion • NE-dobutamine appears to be a more reliable and safer strategy
Levy[71] OptimaCC *N* = 57 *S* = 9 France	• To compare efficacy and safety of epinephrine and NE in patients with CS after AMI	• CS due to AMI after PCI • SBP <90 mm Hg or MAP <65 mm Hg • cardiac index <2.2 L/min/m^2 without vasoactive agent • PCWP >15 mmHg • EF <40% • Evidence of hypoperfusion	Group 1: Epinephrine • Dose titrated to obtain MAP of 65–70 mmHg Group 2: Norepinephrine • Dose titrated to obtain MAP of 65–70 mmHg	• EF: 34% • F/U: 60 d • Change in CI: no difference ($p = .43$) • Incidence of refractory CS: 37 *vs.* 7% ($p = .011$)	• Use of epinephrine compared with NE was associated with similar effects on arterial pressure and CI and higher incidence of refractory shock
Inodilators					
García-González[c72] *N* = 22 *S* = 1 Spain	• To evaluate hemodynamic effects of levosimendan compared to dobutamine in AMI patients revascularized by PPCI, who developed CS secondary to severe LV systolic dysfunction	• STEMI treated with PPCI • CS diagnosed according to published criteria[b]	Group 1: Levosimendan • 24 mcg/kg over 10 min, then 0.1 mcg/kg/min × 24 h Group 2: Dobutamine • 5 mcg/kg/min × 24 h, titrated to response	• EF: 29% • F/U: at 30 h • ≥30% increase in CPO after 24 h of therapy: consistently better with levosimendan $p < .05$ • CI after 24 h of therapy: consistently better with levosimendan $p < .05$	• Levosimendan improved CPO • Levosimendan could be a better choice than dobutamine in this setting • Further investigation is warranted before its general recommendation
Dominguez-Rodriguez[c73]	• To evaluate effects of levosimendan compared to dobutamine on LV diastolic function in AMI patients revascularized by PPCI, who developed CS secondary to severe LV systolic dysfunction	• As above	• As above	• F/U: at 24 h • E/A ratio: 1.4 *vs.* 0.9 ($p < .001$) • DT (ms): 198 *vs.* 188 (NS) • IVRT (ms): 70.4 *vs.* 102.8 ($p < .001$)	• Levosimendan compared to dobutamine caused significant reduction of the IVRT, and significant increase of the E/A ratio
Samimi-Fard[c74]	• To assess effect on long-term survival of levosimendan compared to dobutamine in	• As above	• As above	• F/U: 12 months • Cardiac death: $p = .24$[d]	• Levosimendan compared to dobutamine did not improve long-term survival

(*continued*)

Table 1. Continued.

First author Acronym Sample size (*N*) Sites number (*S*)	Objective	Inclusion criteria	Interventions	Main outcome measures (Group 1 *vs.* Group 2)	Conclusion
		AMI patients revascularized by PPCI, who developed CS secondary to severe LV systolic dysfunction			
Fuhrmann[75] $N = 32$ $S = 1$ Germany	• To investigate effects of levosimendan compared with enoximone in refractory CS complicating AMI, on top of current therapy	• AMI with hypotension and peripheral hypoperfusion • Refractory CS (despite therapy) within 2 h after PCI • SBP <90 mm Hg • CI <2.5 L/min/m^2 • PCWP >18 mm Hg • Signs of hypoperfusion	Group 1: Levosimendan • 12 mcg/kg over 10 min, then 0.1 mcg/kg/min × 50 min, and 0.2 mcg/kg/min × 23 h Group 2: Enoximone • Fractional bolus of 0.5 mcg/kg over 30 min, then 2–10 mcg/kg/min	• EF: 25% • F/U: at 30 d • Overall survival rate: 68.7 *vs.* 37.5% ($p = .023$)	• Levosimendan as add-on therapy may contribute to improved survival compared with enoximone
Husebye[a76] LEAF $N = 61$ $S = 1$ Norway	• To evaluate efficacy and safety of levosimendan in patients with PPCI-treated STEMI complicated by symptomatic HF	• STEMI subjected to PPCI • Opening of IRA • Signs of decreased wall motion in LV • Clinical HF defined CS subgroup: • SBP <90 mmHg or 90–100 mmHg despite inotrope • Signs of hypoperfusion	Group 1: Levosimendan • 0.2 mg/kg/min for 1 h followed by 0.1 mg/kg/min × 24 h Group 2: Matching placebo	• EF: 41% • F/U: up to 42 d • Change in WMSI from baseline to days 5 and 42: 1.66 *vs.* 1.83 ($p = .031$) and 1.61 *vs.* 1.73 ($p = .18$), respectively • MACE or HF hospitalization: NS • CS subgroup (n = 9; 15%): similar results for safety and efficacy	• Levosimendan improved contractility in post-ischemic myocardium • Levosimendan was well tolerated, without any increase in arrhythmias
Nitric oxide synthase inhibitors					
Cotter[77] LINCS $N = 30$ $S = 1$ Israel	• To evaluate effect of L-NAME in treatment of refractory CS after ACS	• ACS with hypotension and peripheral hypoperfusion • Progressive decrease in SBP <100 mmHg • Signs of hypoperfusion >1 h after PCI (despite therapy)	Group 1: Supportive care Plus: L-NAME • 1 mg/kg bolus, then 1 mg/kg/h × 5 h Group 2: Supportive care only (no treatment)	• EF: 24% • F/U: at 30 d • All-cause mortality: 27% *vs.* 67% ($p = .008$) • MAP at 24 h: 86 *vs.* 66 mmHg ($p = .004$) • UOP at 24 h: +135 mL/h *vs.* −12 mL/h ($p < .001$)	• NOSi are beneficial in the treatment of patients with refractory CS
Dzavík[e78] SHOCK-2 $N = 79$ $S = 22$ North America and Europe	• To assess preliminary safety and efficacy, pharmacokinetics, and biological activity of L-NMMA • To assess feasibility of a randomized trial in AMI complicated by persistent CS	• AMI complicated by persistent CS despite open IRA • SBP <100 mmHg despite vasoactive agent • CI <2.2 L/min/m^2 (if off IABP), or <2.5 L/min/m^2 (if on IABP) • PCWP ≥15 mmHg	Group 1: L-NMMA in 5 regimens • 0.15 mg/kg IV bolus, then 0.15 mg/kg/h × 5 h • 0.5 mg/kg IV bolus, then 0.5 mg/kg/h × 5 h • mg/kg IV bolus, then 1.0 mg/kg/h × 5 h • 1.5 mg/kg IV bolus, then 1.5 mg/kg/h × 5 h Group 2: Placebo • Normal saline IV bolus, then infusion x 5 h	• EF: 26% • F/U: 30 d • Change in MAP at 2 h: NS • Change in MAP at 15 min: significant increase in all groups except 1.0 mg/kg group • 30-d mortality: NS	• L-NMMA resulted in modest increases in MAP at 15 min compared with placebo but no differences at 2 h
		• MI with patency of IRA	Group 1: Tilarginine (L-NMMA)	• EF: 27%	

(*continued*)

Table 1. Continued.

First author Acronym Sample size (*N*) Sites number (*S*)	Objective	Inclusion criteria	Interventions	Main outcome measures (Group 1 *vs.* Group 2)	Conclusion
Alexander[f79] TRIUMPH $N = 398$ $S = 130$ North America and Europe	• To examine effects of nonselective NOSi in patients with MI and refractory CS despite opening of IRA	• Refractory CS <24 h • Signs of hypoperfusion and SBP <100 mmHg despite vasoactive agent • Elevated LV filling pressure • EF <40%	• 1-mg/kg bolus, then 1-mg/kg/h × 5 h Group 2: Matching Placebo	• F/U: 6 months • 30-d mortality: 48 *vs.* 42%; RR, 1.14; 95% CI 0.92–1.41; $p = .24$	• Tilarginine did not reduce mortality rates • Early mortality rates are high • Further research is needed

A: Late diastolic flow; ACS: Acute coronary syndrome; AMI: Acute myocardial infarction; BP: Blood pressure; CI: Cardiac index; CO: Cardiac output; CPO: Cardiac power; CS: Cardiogenic shock; CVP: Central venous pressure; DT: Deceleration time; E: Early diastolic flow; EF: Ejection fraction; F/U: Follow-up duration; H: Hour; HF: Heart failure; HR: Heart rate; IRA: Infarct-related artery; IVRT: Isovolumetric relaxation time; L-NAME: N^G-Nitro-L-Arginine-Methyl Ester; L-NMMA: L-N-monomethyl-arginine; LV: Left ventricular; MACE: Major adverse cardiac events; MAP: Mean arterial pressure; max: Maximum; MI: Myocardial infarction; NE: Norepinephrine; NOS: Nitric oxide synthase; NOSi: Nitric oxide synthase inhibitor(s); NR: Not reported; NS: Non-significant; OR: Odds ratio; PAOP: Pulmonary artery occlusion pressure; PAP: Pulmonary artery pressure; PCI: Percutaneous coronary intervention; PPCI: Primary PCI; RR: Risk ratio; SBP: Systolic blood pressure; STEMI: ST elevation myocardial infarction; UOP: Urine output; WMSI: Wall motion score index.

[a]CS patients as predefined subgroup analysis of the study.

[b]Alexander RW, Pratt CM, Ryan TJ, Roberts R. Diagnosis and management of patients with acute myocardial infarction. In: Fuster V, Alexander RW, O'Rourke RA, editors. Hurst's the heart, 10th ed. New York' McGraw-Hill Company, Inc.; 2001. p. 1275– 359.

[c]One study in 3 publications reporting different outcomes.

[d]Not primary endpoint.

[e]Phase II dose-ranging study.

[f]Enrollment was terminated at 398 patients based on a prespecified futility analysis.

dopamine[69], epinephrine *vs.* NE with or without dobutamine[70,71], levosimendan *vs.* dobutamine[72–74], enoximone (i.e. phosphodiesterase inhibitor [PDEi])[75] or placebo[76], and NOSi *vs.* placebo[77–79].

3.3.1. Vasopressors/inotropes

3.3.1.1. Epinephrine vs. norepinephrine. Two small studies compared epinephrine to NE or NE-dobutamine in CS complicating AMI (the OptimaCC study)[71] or in HF patients without MI[70], respectively. In the latter setting, both drugs improved the hemodynamic parameters compared to baseline such as MAP and CI ($p < .01$). However, in the epinephrine group, heart rate (HR) was significantly higher ($p < .05$) than in NE-dobutamine group and was associated with arrhythmia in three patients. Arterial lactate concentrations decreased in NE-dobutamine group ($p < .01$), while increased in the epinephrine group ($p < .01$) when compared to baseline values. Lactate level, lactate/pyruvate ratio, and PCO_2 gap were significantly higher in the epinephrine group as well. No clinical outcomes have been investigated in this pilot study[70]. In the OptimaCC, a study with a robust methodological design, the changes in CI, systolic and diastolic arterial pressure, MAP, evolution of stroke volume index, and cardiac power (CPO) index were not significantly different between the two arms. However, there was a significant increase in the mean HR with epinephrine use only ($p = .031$), explained as having a more potent $ß_1$-receptor activity. The metabolic changes that were statistically different between the groups included, higher metabolic acidosis ($p = .0004$) and lactate level ($p < .0001$) in the epinephrine group, whereas, increased arterial pH and decreased lactate level in the NE group. With regards to safety outcomes, there was no statistically difference in the incidence of arrhythmia between the groups (41% *vs.* 33%; $p = .56$). The study was stopped prematurely due to higher incidence of refractory CS in the epinephrine group (37 *vs.* 7%; $p = .011$). Although the relatively small sample size and early termination, the difference in refractory CS was statistically and clinically significant. The 60-d mortality did not differ significantly between epinephrine (52%) and NE (37%) groups ($p = .25$) with a trend toward higher mortality in association with epinephrine use on Day 7 ($p = .08$). In addition to a significant increase in the composite of death and extracorporeal life support (ECLS) use at Day 7 ($p = .031$) in the epinephrine arm[71]. Cautious interpretation, however, is warranted given the lack of power for such outcomes, not being pre-specified endpoints, and the lack of standardized criteria for ECLS initiation[19,71].

3.3.1.2. Norepinephrine vs. dopamine. De Backer et al., in their rigorous SOAP II study, recruited 1679 patients and compared dopamine to NE as a first-line vasoactive agent selection in any shock state, such as cardiogenic, septic, and hypovolemic. There was not a significant difference in 28-d mortality (52.5 *vs.* 48.5%; OR 1.17, 95% CI 0.97 − 1.42; $p = .10$) between the study arms with more arrhythmic events in the dopamine group. Overall, 18.4% of the patients had arrhythmia with atrial fibrillation (AF) as the most common type

which occurred in 86.1% of those patients. More patients experienced arrhythmia in the dopamine group than in the NE group (24.1 *vs.* 12.4%, $p < .001$). Consequently, the drug discontinuation rate due to arrhythmia was higher in the dopamine group (6.1 *vs.* 1.6%, $p < .001$). Dopamine was associated with a higher 28-d mortality rate ($p = .03$) in the predefined subgroup analysis of patients who presented with CS ($n = 280$)[69]. However, the study was not powered to test the difference in patients with CS, thus the results of the CS subgroup should be interpreted with caution. In addition, the lack of operationalized definition of CS, evaluation across the hemodynamic phenotypes of CS, or information about MI or HF variables, could have confounded the findings of the study[10].

3.3.2. Inodilators

Three studies of this review randomized 115 patients to receive levosimendan and compare it to dobutamine[72–74], enoximone[75], or matching placebo[76] in the setting of AMI. In primary PCI-treated patients ($n = 22$) who developed CS secondary to severe LV systolic dysfunction, levosimendan was compared to dobutamine to evaluate their effects on hemodynamic measures[72], LV diastolic function[73], and long-term survival[74] in three separate publications of one study. After 24 h of therapy, levosimendan was consistently better in increasing CI, LVEF (55 *vs.* 45%, $p = .003$), and CPO. There was no difference in the PCWP reduction, HR increase, change in the SBP, or serious adverse effects between the groups. As a mathematical product of CO and MAP, CPO is an indicator of cardiac contractility and ventricular–vascular coupling. It was considered a prognostic predictor of survival in CS in previous studies[72]. Improvement in echocardiographic diastolic measures, from baseline to 24 h after initiation of drug infusion, included significant reduction in isovolumetric relaxation time (from 116 to 70.4 ms, $p < .001$) and significant increase of the E/A ratio (from 0.6 to 1.4, $p < .001$) in patients on levosimendan. In contrary there were non-significant changes in the aforementioned measures in patients on dobutamine (from 114.7 to 102 ms and from 0.7 to 0.9, respectively)[73]. The short-term improvement in the hemodynamic and echocardiographic measures did not translate into long-term clinical benefit (i.e. 12-month mortality)[74]. This open-label study, however, had a small sample size to have a meaningful implication and was not powered to investigate mortality outcome[72–74]. Fuhrmann et al. in another small study ($n = 32$)[75] reported a higher survival rate at 30 d when compared levosimendan to enoximone (68.7 *vs.* 37.5%, $p = .023$). The main cause of death was a progressive and refractory HF, while multiorgan failure occurred only in the enoximone group and was responsible for death in 25% of patients in this study arm. Except for mixed venous oxygen saturation, there was a trend toward improvement in CI and LV stroke work index that did not reach statistical significance. Furthermore, the onset of rhythm disorders did not differ between the groups. This single-center, open-label study was terminated after an interim analysis that accepted a lower difference of effect between arms, which would have affected the power of the study. Husebye et al., in the LEAF study ($n = 61$)[76], demonstrated that levosimendan in patients with AMI complicated by symptomatic HF significantly improved regional contractility. The authors reported significant change in WMSI from baseline to Day 5 (effect size 20.13, 95% CI 0.255–0.013, $p = .031$). There was no statistically significant difference in secondary outcomes such as changes in NT-proBNP levels, time to major adverse cardiovascular events, time to first rehospitalization for HF, or six-month all-cause mortality. For the safety outcomes, there were more episodes of hypotension in patients on levosimendan compared to those on placebo ($p = .029$), with no difference in the use of vasopressor between the two groups. There was a lack of significant difference in the rates of sinus tachycardia, ventricular arrhythmias, AF, or ischemic episodes. In this study, only few patients presented with CS (19%). Patients tolerated levosimendan therapy and had similar safety and efficacy outcomes as compared to the whole study population.

3.3.3. Nitric oxide synthase inhibitors

Three studies in this review randomized 507 patients to receive NOSi and compared it against placebo or supportive care in patients presented with AMI complicated by a persistent or refractory CS[77–79]. In the LINCS study ($n = 30$), Cotter et al. reported the occurrence of 30-d mortality in 27% of patients on N^G-Nitro-L-Arginine-Methyl Ester (L-NAME) as compared to 67% on supportive care alone ($p = .008$). The cause of death in most of the cases was during the first week due to shock or multiorgan failure. The one-month and one-week survival rates in the L-NAME group were 73% and 80% compared with 33% and 40% in the supportive care group, respectively. Treatment with L-NAME resulted in statistically significant benefit in other secondary outcomes, such as increase in MAP and urine output, and decrease in times on IABP support and mechanical ventilation without excess of adverse events[77]. Tilarginine (L-N-monomethyl-arginine [L-NMMA]) resulted in modest early increase in MAP and did not show benefit in term of 30-d mortality benefit when was investigated in SHOCK-2, a Phase II dose-ranging study. However, the study was not powered to assess the effect on mortality[78]. Consequently, the TRIUMPH study, an international, multicenter RCT was designed and powered to investigate the effect of tilarginine on 30-d mortality. Although tilarginine caused a greater increase in SBP at two hours compared to placebo (12.0 *vs.* 7.0 mmHg; $p = .001$), it had no effect on 30-d (48 *vs.* 42%; risk ratio 1.14, 95% CI 0.92–1.41; $p = .24$) or six-month all-cause mortality rates, either in the overall group or in any prespecified subgroups. In 78% of patients, the cause of death was of cardiac origin with 50% of them due to pump failure. In addition, tilarginine was well-tolerated but had no effects on the resolution or duration of CS, 30-d myocardial reinfarction, 30-d New York Heart Association functional class, or renal function. As a result, based on futility analysis, the study was terminated early after the enrollment of 398 patients of the planned sample size of 658 patients[79].

Table 2. Jadad scale.

Study	Jadad scale				Modified Jadad scale			
	Randomization (0–2)	Blinding (0–2)	Dropouts (0–1)	3-Item scale (0–5)	Inclusion/exclusion (0–1)	AE (0–1)	Statistics (0–1)	6-Item scale (0–8)
SOAP II[68]	2	2	1	**5**	1	1	1 AC: yes ITT: yes SS: yes	**8**
[69]	1	0	1	**2**	1	0	1 AC: no ITT: unclear SS: no	**4**
OptimaCC[70]	2	2	1	**5**	1	1	1 AC: yes ITT: yes SS: yes	**8**
Mean (SD)	–	–	–	**4 (1.73)**	–	–	–	**6.66 (2.30)**
[71][b]	0	0	1	**1**	1	1	1 AC: no ITT: unclear SS: no	**4**
[74]	2	0	1	**3**	1	0	1 AC: yes ITT: unclear SS: yes	**5**
[75] LEAF	2[a]	2	1	**5**	1	1	1 AC: yes ITT: yes SS: yes	**8**
Mean (SD)	–	–	–	**3 (2)**	–	–	–	**5.66 (2.08)**
LINCS[76]	1	0	0	**1**	1	1	1 AC: no ITT: yes SS: no	**4**
SHOCK-2[77]	2	1	1	**4**	1	1	1 AC: yes ITT: yes SS: yes	**7**
TRIUMPH[78]	2	1	1	**4**	1	1	1 AC: yes ITT: yes SS: yes	**7**
Mean (SD)	–	–	–	**3 (1.73)**	–	–	–-	**6 (1.73)**

AC: Allocation concealment; AE: Adverse effects; ITT: Intention-to-treat; SD: Standard deviation; SS: Sample size.
[a]Patients with cardiogenic shock were stratified by block randomization.
[b]Subsequent publications[72,73] of the study on different outcomes are not presented in this table.
Bold values represent quality score calculations for each study.

3.4. Quality assessment

The mean Jadad score of the nine studies of this review is 3.33 (SD = 1.65). The Jadad scores of each study are provided in Table 2. The scores were rated by two authors with an agreement on the scores of all the studies except two before resolving the discrepancies. The Jadad scores show variation in research quality ranging from 1 to 5. Three studies were deemed high-quality methodologies[69,71,76] that received a score of 5 because of appropriate randomization, double-blinding, and patient disposition. The three studies varied in size, vasoactive therapy comparisons, and primary outcomes. However, two studies (SOAP II and LEAF)[69,76] did not have CS as a sole inclusion criterion, instead patients presenting with CS were analyzed in pre-defined subgroups. The two studies that had a Jadad score of 4, were Phase II (SHOCK-2)[78] and Phase III (TRIUMPH)[79] studies of tilarginine. The latter study was stopped due to futility. By excluding the aforementioned two studies[78,79], the mean Jadad score of the other seven studies was not affected (3.28; SD = 1.79). One study[75] was graded a score of 3 due inadequate reporting of the randomization and double-blinding processes. The remaining three studies[70,72,77] scored less favorably, with Jadad scores of 2 or less and were deemed poor methodological design burdened by inadequate randomization and blinding. One pilot study[70] was given 2 points for the use of randomization and blinding. An open-label study[72] was given 1 point for reporting drop-outs, and the last one[77] received a score of 1 for the use of randomization. The quality of the nine studies did not differ when they were evaluated using the modified Jadad scale with a mean score of 6.11 (SD = 1.83). The nine studies described the inclusion/exclusion criteria and the methods of statistical analysis, whereas, seven studies[69,71,72,76–79] reported adverse effects assessment. Of the nine studies, three[70,72,77] did not conceal allocation, three[70,72,75] did not state whether the statistical analysis was based on ITT principle, and three[70,72,77] did not justify the sample size.

3.5. Registered clinical studies

The search of the US National Institutes of Health Registry using "cardiogenic shock" as a broad term, resulted in 102 studies. Six studies were found for the recruitment status of "Suspended", "Terminated", and "Withdrawn". Whereas, 96 studies were identified for the status of "Recruiting", "Not yet recruiting", "Active", "Not recruiting", "Completed", "Enrolling by invitation", or "Unknown status". As a result, ten registered studies have been identified. Of them, one has been terminated. An additional registered study has been identified by manual search. A summary of the registered studies for the vasoactive agents in CS is provided in Table 3.

4. Discussion

In this critical review, 11 studies of vasoactive therapy in CS were characterized and nine of them were evaluated for methodologic quality. The identified pharmacologic vasoactive therapy was categorized into three groups: vasopressors/inotropes, inodilators, and NOSi. The vasoactive agents may have been associated with hemodynamic beneficial effect but not with mortality benefit. However, levosimendan as add-on therapy improved survival as compared with enoximone but did not improve long-term survival when compared to dobutamine. In contrary, dopamine use was associated with higher mortality and adverse events rates. Epinephrine was associated with a transient lactic acidosis, higher HR and arrhythmia, and inadequate gastric mucosa perfusion. While writing the manuscript, a meta-analysis[80] of randomized ($n = 6$) and observational ($n = 13$) studies was published and did not show mortality reduction when vasopressors and inotropic agents were used in AMI complicated by CS. However, the analysis pooled data from heterogenous studies in many different aspects.

A meta-analysis presented in a clinical review[22] using RCTs of the PCI era, found a lower risk of mortality (relative risk 0.70, 95% CI 0.54–0.91) with NE compared to epinephrine or dopamine in the vasopressor subgroups using data from three studies[69–71]. Another meta-analysis of individual patient data investigated the association between epinephrine and short-term mortality in patients ($n = 2583$) presented with CS of any cause. It was reported that the incidence of epinephrine use was 37% and the mortality rate was 49%. The meta-analysis concluded that epinephrine was correlated with 3-fold increase in the risk of mortality compared to other agents (OR 3.3, 95% CI 2.8–3.9) with an adjusted mortality risk of OR of 4.7 (95% CI 3.4–6.4). The association remained robust even after propensity score matching (OR 4.2, 95% CI 3.0–6.0)[21]. In the CardShock study ($n = 219$) that prospectively enrolled patients with CS, the 90-d mortality rate was 41% and vasopressor and/or inotropes were used in 94% of the patients. Most of the patients (75%) received NE as compared to those received (21%) epinephrine. In a multivariable logistic regression, epinephrine was independently associated with increased mortality risk (OR 5.2, 95% CI 1.88–14.7; $p = .002$) which did not change after adjustment or after propensity score adjustment (OR 3.3, 95% CI 1.4–7.7; $p = .006$). Furthermore, epinephrine was associated with worsening of cardiac and renal biomarker[81]. On the other hand, Morici et al. argued from their real-life experience and in contrary to the current opinion that epinephrine may still have a role in the treatment of the low output state. The authors discussed that epinephrine did not cause an increase in HR (101 ± 18.4 at baseline *vs.* 106 ± 17.6 at the infusion peak), nor in life-threatening arrhythmia. Moreover, it was used as a "pharmacologic bridge" to cardiac transplantation, or a more advanced, intense medical therapy. In comparison to other agents, dopamine required high doses to achieve comparable hemodynamic target at the expense of increasing the HR. Whereas, NE increased peripheral resistance which in turn increased the afterload. In addition, levosimendan required a vasopressor due to its hypotensive effect. However, their work was based on their center's case-series[82]. After the publication of the SOAP II study, dopamine was no longer preferred as an initial agent in CS. Historically, until the publication of a study by Bellomo et al.[83] and two subsequent meta-analyses[84,85], it has been thought that dopamine has favorable effects on renal function. As such, administration of a low-dose dopamine in critically ill patients at risk of renal failure did not show significant renal protection[83–85]. A meta-analysis comparing dopamine with NE in CS, that did not include SOAP II study, showed a mortality rate at 28 d of 50.3% *vs.* 29.7% (risk ratio 1.611; 95% CI 1.219–2.129, $p < .001$; $p_{\text{heterogeneity}} = .01$), arrhythmic events rate (i.e. AF, VF, and ventricular tachycardia) of 29.65% *vs.* 8.34% (risk ratio 3.426; 95% CI 2.130–5.510, $p < .001$; $p_{\text{heterogeneity}} = .875$), and gastrointestinal reactions rate of 70.59 *vs.* 12.86% (RR, 5.474; 95% CI 2.917–10.273, $p < .001$; $p_{\text{heterogeneity}} = 0$), respectively. Patients who were on dopamine had a significantly higher HR without significant differences in MAP, CI, lactic acid, and urine volume as compared to those on NE[86]. Dopamine exerts an indirect beta-adrenergic effect through the release of neural NE, which may explain the differences between dopamine and NE in patients with CS where there is a depletion in the neurotransmitters, leading to an attenuated response to the indirect adrenergic agents[87]. A study found that 75% of patients with CS were treated with NE, while 26% and 21%with dopamine and epinephrine, respectively[81]. Dobutamine increases CO, decreases LV filling pressure, improves cardiac contractility, and is commonly administered with NE[13]. When the hemodynamic effects of dopamine and dobutamine were compared in 13 patients with CS, there were clear differences in their mechanisms of increasing BP and in their effects on LV filling pressure. Dobutamine significantly improved CI and stroke index ($p < .05$), while dopamine significantly increased LV filling pressure ($p < .001$) with no differences in other parameters, such as HR, MAP, or systemic vascular resistance (SVR)[49]. In addition, dopamine and dobutamine, in mechanically ventilated CS patients ($n = 8$) produced comparable increases in CO. However, dopamine caused higher oxygen consumption[52]. Vasopressin is usually used in refractory septic shock as an add-on to support BP. In the VASST study ($n = 778$), there was no significant difference between low-dose

Table 3. Registered clinical trials.

Trial identifier[a]	Trial brief title (acronym)	Agent (s)	Design (phase)	Enrollment	Primary outcome (time frame)	Start date	Status
NCT04325035	The safety and efficacy of istaroxime for pre-CS (SEISMiC)	Istaroxime *vs.* placebo	Randomized, double-blind (II)	60	Change from baseline in SBP and AUC	June 2020	Not yet recruiting
NCT03340779	NE *vs.* NE and Dobutamine in CS (SHOCK-NORDOB)	NE *vs.* NE/dobutamine	Randomized, cross-over, open-label (III)	40	Obtention of an optimal cardiac output defined as presence of 2 efficacy criteria without any side effects from 0 to 6.5 h	January 2018	Unknown
NCT04020263	Effect of early use of levosimendan *vs.* placebo on top of a conventional strategy of inotrope use on a combined morbidity-mortality endpoint in patients With CS	Levosimendan *vs.* placebo	Randomized, double-blind (III)	610	Composite of all-cause mortality, ECLS, and/or dialysis at 30 d	December 2019	Not yet recruiting
NCT02591771	Study of multisite pharmacological and invasive management for CS	Adrenaline	Single-group, open-label (II)	24	Survival at 60 d	October 2015	Completed
NCT03727282	LV volume index in adjustment of initial dose of dobutamine in HF and CS	Dobutamine: Adjust according to ejection volume index *vs.* attending physician	Randomized, open-label (—)	30	Multiple measures at 24 h, such as base excess levels, bicarbonate levels, SBP/DBP, CO, systolic volume, UOP, lactate levels, arterial lactate levels, and troponin levels	January 2019	Not yet recruiting
NCT04141410	Global longitudinal strain assessment in cardiogenic shock during sepsis (GLASSES-1)	Levosimendan *vs.* ECHO	Prospective, observational, case-control (—)	35	Global longitudinal strain $\geq$ 15%; up to 1 week	October 2019	Recruiting
NCT00093301	Levosimendan *vs.* dobutamine in shock patients (LICI)	Levosimendan *vs.* dobutamine	Randomized, double-blind (II and III)	40	Resolution of shock state	October 2004	Unknown
NCT03207165	Milrinone *vs.* dobutamine in critically Ill patients	Milrinone *vs.* dobutamine	Randomized, double-blind (VI)	192	Composite of all-cause in-hospital death, non-fatal MI, TIA, or CVA, renal failure, need for cardiac transplant or new mechanical support, any atrial or ventricular arrhythmia leading to cardiac arrest and resuscitation (up to 12 months)	August 2017	Recruiting
NCT04224103	Nitric oxide in venoarterial extracorporeal membrane oxygenation (VA ECMO) (NOVICE)	Inhaled nitric oxide	Prospective, observational, case-only (—)	10	Participant recruitment and multiple right heart-related outcomes, e.g. qualitative function, TAPSE, and the changes from baseline	August 2019	Recruiting
NCT02118467	Vasoactive drugs in intensive care unit	NE/epinephrine as add-on *vs.* Phenylephrine/ vasopressin as add-on	Randomized, double-blind (IV)	836	Hospital mortality (6 months)	May 2014	Recruiting

(*continued*)

Table 3. Continued.

Trial identifier[a]	Trial brief title (acronym)	Agent (s)	Design (phase)	Enrollment	Primary outcome (time frame)	Start date	Status
Terminated							
NCT00782652	The effects of nitric oxide for inhalation in right ventricular infarction patients	Inhaled nitric oxide *vs.* nitrogen gas	Randomized, double-blind (II)	3	Survival to hospital discharge or Day 30, whichever occurs first without need for renal replacement therapy or RVAD	March 2006	Terminated (due to slow enrollment)

AUC: Area under the curve; CO: Cardiac output; CS: Cardiogenic shock; CVA: Cerebrovascular accident; DBP: Diastolic blood pressure; ECLS: Extra corporeal life support; ECHO: Echocardiography; MI: Myocardial infarction; N/A: Not applicable; NE: Norepinephrine; RVAD: Right ventricular assistance device; SBP: Systolic blood pressure; TAPSE: Tricuspid annular plane systolic excursion; TIA: Transient ischemic attack; UOP: Urine output
[a]From http://clinicaltrials.gov/- accessed on 20/5/2020.

vasopressin and NE in terms of the rates of mortality or serious adverse events[88]. In a retrospective study of patients ($n = 36$) who had CS complicating MI, vasopressin significantly increased MAP without changing PCWP, CI, urine output, or inotrope requirements[61]. In this review, there were no RCTs identified on vasopressin in CS patients. However, there is a Phase IV RCT (NCT02118467) that has vasopressin in one of the treatment arms. The study is investigating vasoactive agents in any shock state with pre-specified analysis for various subgroups of patients including those with different etiologies of shock including CS (i.e. septic, cardiogenic and hypovolemic) (Table 3).

Inodilators, such as levosimendan or PDEi improve myocardial contractility and have the potential to induce vasodilation without increasing oxygen requirements. Their evidence in CS is still limited[22]. In an observational hemodynamic study ($n = 25$), levosimendan as a bail-out therapy improved right ventricular (RV) dysfunction in AMI patients presenting with CS as compared to usual care, including dobutamine and NE. It significantly increased CI, enhanced RV CPO index, and decreased pulmonary vascular resistance without changes in central venous pressure or mean pulmonary artery pressure[54]. In a meta-analysis[15] of 17 studies ($n = 729$), levosimendan after coronary revascularization was associated with significant mortality reduction (OR 0.40, 95% CI 0.21–0.76; p for overall effect .005, $p_{\text{heterogeneity}} = .33$, $I^2 = 12\%$), and secondary endpoints improvement, such as CI, length of intensive care stay, AF rate, and troponin I levels. However, only two studies of the meta-analysis pertained to patients with CS[74,75]. A recent meta-analysis of five non-RCTs ($n = 557$) concluded that levosimendan use in CS may reduce all-cause mortality (risk ratio 0.62, 95% CI 0.44–0.88; $p_{\text{for effect}} = .007$, $I^2 = 36\%$) and facilitate successful weaning from veno-arterial extracorporeal membrane oxygenation (risk ratio 1.42, 95% CI 1.12–1.8; $p_{\text{for effect}} = .004$, $I^2 = 71\%$)[89]. An evidence, however, from an RCT should confirm the findings. In this review, there were no RCTs identified for milrinone, a commonly used PDEi in HF, in the literature search. A subgroup analysis of an old study ($n = 40$) in patients with severe HF was conducted for 18 patients with severe cardiac pump dysfunction with only three patients of them were in CS. The study examined the systemic and pulmonary arterial hemodynamics before and after milrinone infusion. Including the patients with CS, milrinone led to an overall improvement in hemodynamics (e.g. CI and PCWP) without producing pronounced decrease in BP[53]. In another old study in CS ($n = 20$), dopamine/milrinone combination was compared to a standard regimen of dopamine/dobutamine. The former combination was beneficial in reducing the pre- and afterload, in addition to the myocardial oxygen demand but at expense of decreasing MAP[40]. An ongoing randomized study will compare milrinone *vs.* dobutamine in a heterogeneous group of critically ill patients, including those presenting with CS (ClinicalTrials.gov Identifier: NCT03207165) (Table 3). Finally, the role of enoximone in CS was described earlier in 13 patients with persistent CS despite dobutamine use. It was used as an add-on agent and resulted in significant increases in CI and stroke volume index, and significant

Table 4. Vasoactive agents[10,12,18,91,92].

Agent	Mechanism	Effect	Indication/considerations	Comment
Vasopressor/inotropes				
Norepinephrine	Agonist: α_1 (++++) β_1 (++), and β_2 (+)	Inotropy, chronotropy, dromotropy, and vasoconstriction ↑ CO ↑↑SVR	CS phenotypes: classic wet and cold, euvolemic cold and dry, vasodilatory warm and wet or mixed CS RV shock, pericardial tamponade	Most common first-line agent in shock Most benefits demonstrated in septic shock
Dopamine	Agonist: α_1, β_1, and β_2 D (++ to +++) Dose-dependent agonism	Inotropy, dromotropy, chronotropy, and vasoconstriction ↑ to ↑↑ CO ↑ to ↑↑ SVR	CS phenotypes: classic wet and cold, euvolemic cold and dry RV shock	Second-line agent in most forms of shock
Epinephrine	Agonist: α_1(++++) β_1 (++++), and β_2 (+++)	Inotropy, chronotropy, dromotropy, and vasoconstriction ↑↑ CO ↑↑ SVR	Add-on if rise in BP is not achieved Anaphylactic shock	Surviving Sepsis Guidelines has most data for epinephrine as second-line agent
vasopressin	Agonist: V1 receptors in vascular smooth muscle	Vasoconstriction ↑↑ SVR ↔ PVR	Add-on to avoid high doses of NE Unstable heart rhythm when high dose NE is unsafe RV shock	Second-line agent in most forms of shock On or Off dosing, can cause hyponatremia
Inodilators				
Dobutamine	Agonist: α_1 (+) β_1 (++++), and β_2 (++)	Inotropy and mild vasodilation ↑↑ CO ↓ SVR, ↓ PVR, ↓ MAP	Predominant low CO Isolated LV dysfunction	Commonly used in CS May contribute to hypotension Most commonly used inotrope
Levosimendan	Myofilament Ca^{+} sensitizer and K^{+} channel modifier	Inotropy and inodilator ↑ CO ↓ SVR, ↓ PVR, ↓ MAP	Acutely decompensated chronic HF Chronic β-blocker therapy Elevated pulmonary resistance and RV dysfunction	Minimal effect on myocardial oxygen consumption Not suitable when SBP < 85 mmHg or CS unless in combination with other vasoactive agents
Enoximone Milrinone	PDEi	Inotropy and inodilator ↑ CO ↓ SVR, ↓ PVR, ↓ MAP	Chronic β-blocker therapy Elevated pulmonary resistance and RV dysfunction	Not recommended in STEMI patients

BP: Blood pressure; CO: Cardiac output; CS: Cardiogenic shock; D: Dopamine; HF: Heart failure; LV: Left ventricular; LVOT: Left ventricular outflow tract; MAP: Mean arterial pressure; PDEi: Phosphodiesterase inhibitor; PVR: pulmonary vascular resistance; RV: Right ventricular; SBP: Systolic blood pressure; STEMI: ST-segment elevation myocardial infarction; SVR: Systemic vascular resistance; V: Vasopressin.

decrease in PCWP without a change in MAP. Twelve of the 13 patients survived the CS event, and five patients discharged alive from hospital[64]. Three years prior to the publication of the TRIUMPH study, another international RCT of NOSi 546C88 (or tilarginine) in septic shock was also terminated prematurely due to increased 28-d mortality (59 *vs.* 49%; $p < .001$)[90]. Moreover, a feasibility study (ClinicalTrials.gov Identifier: NCT00782652) on inhaled nitric oxide for the treatment of CS due to RV infarction has been terminated after a year of its start date due to slow enrollment (Table 3).

It has been established that basic intensive care unit management of CS unresponsive to fluid therapy includes vasopressors and inotropes (Table 4 and Figure 2), in addition to other therapy, to prevent or treat multiorgan failure[9,12,18,22,91,92]. Vasodilators are sometimes used as well[9]. Vasopressor agents increase myocardial contractility and SVR through beta- and alpha-adrenergic receptors, respectively[2]. Whereas, inotropes/inodilators (e.g. dobutamine, enoximone, milrinone, amrinone, and levosimendan) increase myocardial contractility and reduce SVR for LV unloading[9]. At early stages, inodilators may be needed due to elevated SVR (i.e. a compensatory response to sustain BP and organ perfusion). Subsequently, as the SVR decreases, due to the mounting systemic inflammatory response, only vasopressors can counteract the reduced SVR and usually at higher doses[9,11]. Thus, along the different stages of CS, the choice of the vasoactive agent may vary from pure inotropic agent or inodilator support to a combination of inotropes and vasopressors[11]. Reestablishing adequate macro- and micro-circulation to maintain oxygen supply at the cellular level, and modulating the systemic inflammatory response to prevent cellular damage is the ultimate goal to avoid multiorgan system dysfunction. Because once the cellular damage is irreversible, any additional intervention has no mortality benefit[9]. The current international guidelines do not have a universal agreement on the first-line vasoactive agent in CS (Table 5). None of the guidelines have graded NE a Class I recommendation[10,12,18,23,92–94]. Two guidelines have opted an individualized approach based on CS etiology and/or phenotype[10,23], which would explain the continuous use of either NE or dopamine in 50% of CS cases and clarify the absence of unified recommendations. It is recognizable that evidence supporting many of the guidelines' recommendations is weak or lacking[95]. The current limited evidence on vasoactive agents use in CS resulted in wide knowledge gaps and potential areas of research, such as the definition of an optimal vasoactive agent, optimal timing of treatment, combination of different vasoactive agents, and testing of agents across various CS etiologies and severities[9,11,14,95,96].

The assessment of methodological quality using a reliable and valid instrument (e.g. Jadad scale) is essential to capture the variations in the quality of the studies which may affect the overall conclusion of the results[30]. Quality assessment investigates the validity constructs of a study which includes the internal validity (i.e. study's methods), external validity

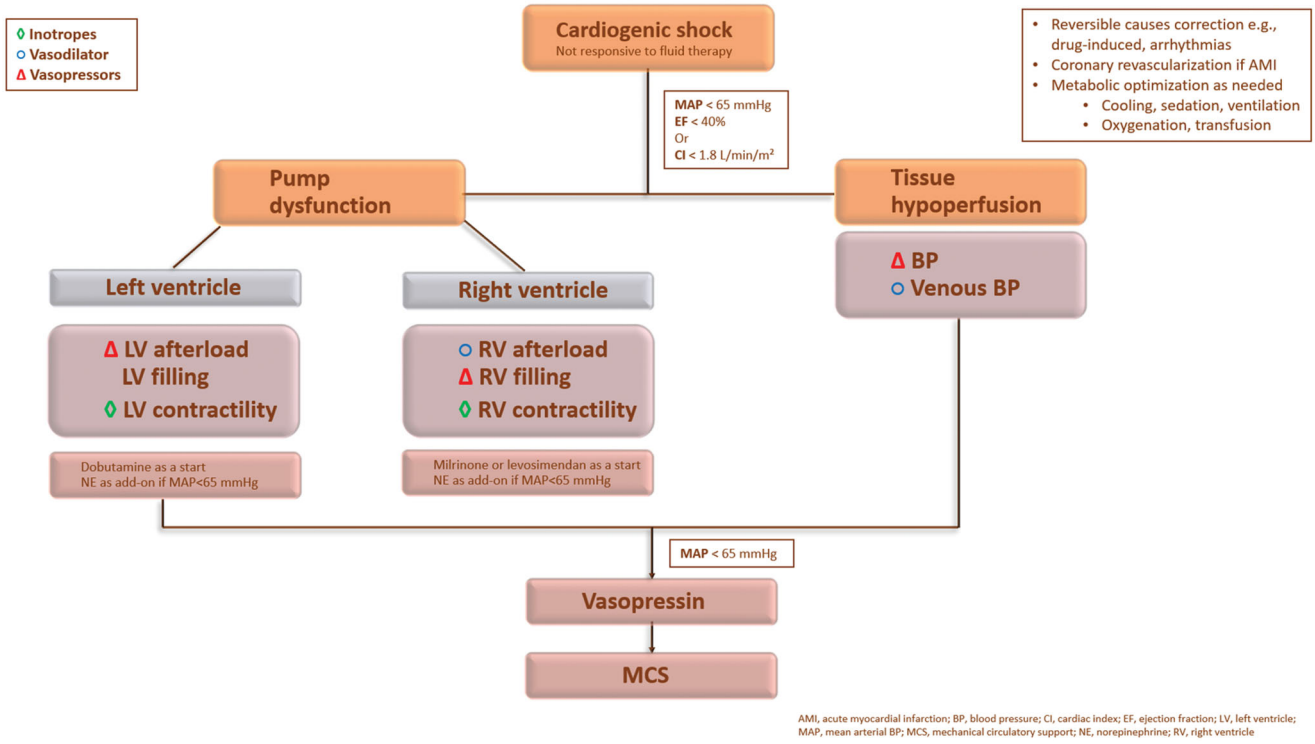

Figure 2. Targets of vasoactive agents[11,13,22].

Table 5. First-line vasoactive agent in guidelines.

Guidelines	STEMI				HF		CS
	2013 STEMI (AHA/ACC)[23]	2017 STEMI (ESC)[18]	2018 (ESC) Revascularization[93]	2020 ACVC (ESC)[92]	2013 HF (AHA/ACC)[94]	2016 HF (ESC)[12]	2017 Scientific Statement (AHA)[10]
First-line agent	Individualized use	Inotrope/ vasopressor	Inotropic support	Vasopressor: NE Inotrope	Inotropic support	Vasopressor: NE Inotrope: DB	Individualized use
Grade	None	Class IIb, Level C	None	V: Class IIb, Level B I: Class IIb, Level C	Class I, Level C	V: Class IIb, Level B I: Class IIb, Level C	None

ACVC: Acute cardiovascular care association; AHA/ACC: American Heart Association/American College of Cardiology; CS: Cardiogenic shock; DB: Dobutamine; ESC: European Society of Cardiology; HF: Heart failure; I: Inotrope; NE: Norepinephrine; STEMI: ST-segment elevation myocardial infarction; V: Vasopressor.

(i.e. study's results), and statistical analysis[97]. The elements that have shown to change the treatment effects are lack of randomization[98], inadequate allocation concealment[99,100], absence of blinding[100], and inadequate sample size[101,102]. The quality across the studies in this review was variable. Randomization and blinding are challenging in the context of CS. Thus, such obstacles would probably be reflected in the slow enrollment that causes study termination or withdrawal. Basic methodological standards support the consideration of other elements that may empirically influence the quality of the study. Elements including appropriate patient disposition description, inclusion, and exclusion criteria definitions, statistical analysis, outcomes objectivity, ITT, and baseline comparability can affect the quality of a study as well. However, this was not supported by respective studies[30].

This review has some limitations. The included studies were generally of small volume and most of them investigated CS in the setting of AMI and LV dysfunction. There were slight variations in the etiologies and definitions of the CS. The primary endpoints of the studies focused on short-term mortality and surrogate markers of hemodynamic or echocardiographic parameters. Randomized studies on vasoactive therapy are generally difficult to perform in critically ill population, who are often excluded from contemporary studies. The challenge commences from obtaining an informed consent[10,14]. Data of the studies on CS are usually extrapolated from chronic HF studies which sometime have heterogeneity, poor quality and other limitations, leading to conflicting conclusions[82]. There are few adequately-powered RCTs on CS that have completed patient recruitment with the planned patients' number[10]. The results of any study should be interpreted with caution in the presence of an inadequate power and sample size[101,102]. A larger study with adequate follow-up duration enhances the robustness and generalizability of the results. Large sample size is important for the detection of small differences in the effects. Elements needed to calculate sample size should include, the estimated outcomes in each group and the type I and type 2 error levels[103]. In this review, the sample size of the studies

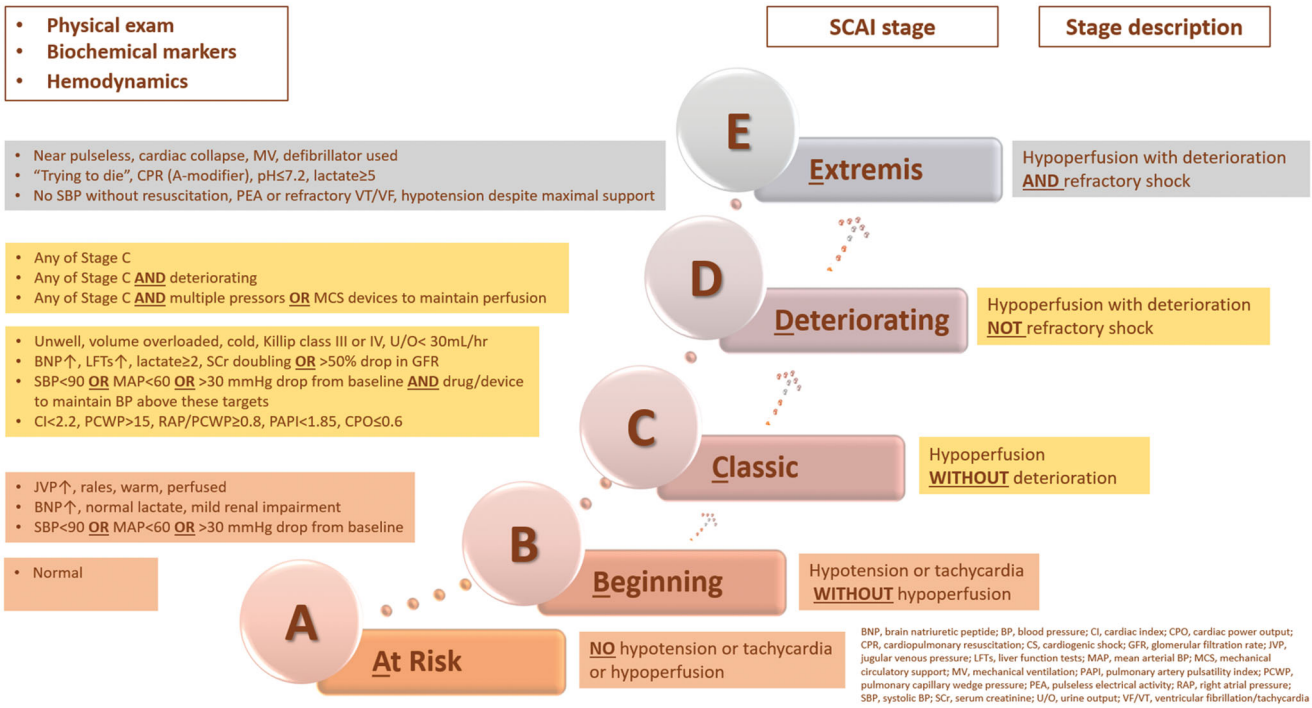

Figure 3. SCAI shock stages[20,104].

is considered small in general with volumes of less than 100, which may render the results inaccurate. The SOAP II study has a large sample size[69], however, the study was powered for shock patients in general and lacked specific important data on CS. The setting of CS is heterogeneous in many aspects[11], including the heterogeneous population. Thus, therapeutic benefit, clinical outcomes, and prognosis may fluctuate in different patient subsets based on CS etiologies, CS hemodynamic phenotypes, severity of CS, and presence of comorbidities[19,20]. In some instances, there could be a delay in starting treatment after the onset of hemodynamic instability, which could influence the clinical presentation of the patient[11]. Moreover, sometimes very sick patients may not fully benefit from the treatment, while others may improve with or without treatment. The presence of a standardized classification system would help in the differentiation between patient subgroups and the identification of the differences between studies. The Society for Cardiovascular Angiography and Interventions (SCAIs)[20] has proposed a simple, novel, consensus-based classification schema for CS risk stratification that has been endorsed by several societies. The classification describes five CS stages starting from A "at risk" to E "extremis", i.e. from pre-hospital providers to intensive care staff. The stages in between are B "beginning", C "classic", and D "deteriorating". The descriptors of each stage include physical exam (or bedside finding), biochemical markers, and hemodynamic parameters (Figure 3). The general and non-rigid definition of each stage is practical in accommodating the clinical parameters variabilities upon patient presentation[104]. Several studies have validated the SCAI classification in the acute settings[104–110]. Jentzer et al.[104] retrospectively investigated the construct validity of the SCAI classification at the time of cardiac intensive care unit admission and found a robust association between the SCAI CS stages and hospital mortality in heterogenous critically ill patients ($n = 10{,}004$). Upon further analysis of the hospital survivors ($n = 9096$)[106], the aforementioned group demonstrated that the SCAI classification at admission predicted the post-discharge mortality as well. Similarly, Schrage et al.[107] reported independent association of the SCAI classification and the 30-day mortality in patients presented with CS or large AMI ($n = 1004$). Baran et al.[108] were the first to prospectively show that initial SCAI stage was predictive for survival in unselected critically ill patients ($n = 166$). Moreover, they found that the reassessment of SCAI stage at 24 h has refined the prognosis. The SCAI shock classification has also been validated retrospectively in specific subsets of patients, i.e. after out of hospital cardiac arrest ($n = 393$)[109] and AMI ($n = 300$)[110]. Additionally, from an analysis of a nationwide registry, Thayer and colleagues have validated the SCAI classification in the prediction of in-hospital mortality in patients presenting with CS ($n = 1414$). They have also demonstrated the association of both escalated SCAI stages and in-hospital mortality with worsening venous congestion[105]. Using complete hemodynamic data that is derived from an early placement of a pulmonary artery catheter was associated with a lower in-hospital mortality in patients with CS as compared to incomplete or no data use[111]. Finally, in this review, there were variations in the primary outcomes reported. Since CS is associated with high death rate, in-hospital mortality as an endpoint would be more appropriate and more beneficial than surrogate marker of the hemodynamic stability. Taken together, a "one-size-fits-all" approach in CS cannot warrant optimal management and safe generalizability. Therefore, an individualized approach may be more appropriate.

5. Conclusion

CS is an acute complex condition leading to morbidity and mortality. Despite the advances in coronary revascularization and mechanical circulatory support, the rates of mortality due to CS are still high. The evidence for the use of vasoactive agents in CS carries uncertainties. The analyses of available studies demonstrate benefits of some agents over others without a robust evidence for an absolute first-line agent. This is probably reflected on the various international guidelines' recommendations. The methodological quality between the studies is variable, owning to the diversity in CS etiologies and phenotypes and to the inherent difficulties to conduct a study in the setting of CS. Patients enrollment is a challenge when adequately powered study is a must for reliable results. Appropriate blinding and randomization cannot always be guaranteed. The methodological limitations in most of the studies may render the results inconclusive. Overall, the quality of CS studies may underperform. The crucial goal in the management of CS is to prevent tissue hypoperfusion and the consequent multiorgan dysfunction by maintaining the hemodynamic stability. Given the lack of therapeutic alternatives, vasopressors and inotropes continue to play a fundamental role. According to the best available evidence and the balance between the risk and benefit of vasoactive agents, epinephrine is disregarded as an initial option, and tilarginine is considered futile in CS. The use of NE alone or in combination with an inodilator (e.g. dobutamine or levosimendan) as appropriate may be suggested. Nonetheless, the choice of an initial vasoactive agent is still controversial. There is a need for adequately powered and well-designed studies to address the current controversies and explore the unanswered clinical questions.

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