Review

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Tailoring Pharmacological Treatment in Cardiogenic Shock: A Narrative Review

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Cardiogenic shock (CS) is a critical condition marked by end-organ hypoperfusion and sustained hypotension, necessitating the use of inotropic or vasoactive agents for hemodynamic support. It is the leading cause of mortality in patients with acute myocardial infarction (AMI), exhibiting in-hospital mortality rates of 40% to 50% despite advances in treatment. Treatment strategies aim to restore hemodynamic stability and address the underlying cause through pharmacological agents and mechanical circulatory support devices. However, the persistently high mortality rates underline the challenges of a timely diagnosis, the limitations of current treatments, and the lack of a standardized multidisciplinary network of care. This review critically examines the existing literature on CS management, focusing on the efficacy, safety, and practical application of pharmacological interventions. By synthesizing evidence from recent studies, clinical guidelines, and expert consensus, our objective is to provide a useful, comprehensive, evidence-based framework to guide clinicians in the use of pharmacologic therapies tailored to the diverse presentations and stages of CS.

Keywords: cardiogenic shock; pharmacological treatment; inotropes; vasopressors; levosimendan; Society for Cardiovascular Angiography and Intervention classification; heart failure; hemodynamic support

Introduction

Cardiogenic shock (CS) is a condition marked by severe end-organ hypoperfusion resulting from primary cardiac dysfunction, and it is characterized by persistent hypotension or the requirement for inotropic or vasoactive support [1].

The prevalence and demographics of CS vary markedly across these etiologies, with acute myocardial infarction (AMI) remaining the most common cause of CS [2]. The incidence of CS as a complication of AMI ranges from 5% to 10%, with this subgroup facing significantly higher mortality rates, nearing 40% to 50%, despite progress in reperfusion therapies and supportive care [3]. The demographic profile of patients with AMI-related CS tends to include older adults who often have additional comorbidities, such as diabetes and hypertension, which increase the risk of developing shock following AMI [3].

Conversely, non-ischemic causes of CS, encompassing a wide array of conditions, contribute to a variable portion of CS cases with an increasing prevalence of up to 50–60% [4,5]. The demographic profile for non-ischemic CS is more varied, affecting a broader age range and often presenting in patients with fewer traditional cardiac risk factors. Instead, these patients may experience CS due to worsening conditions of cardiomyopathy, myocarditis, or severe valvular heart disease [5].

Current treatment standards for CS focus on the twin goals of restoring hemodynamic stability and addressing the underlying cause of the shock. Therapeutic strategies include pharmacological support with inotropes and vasopressors to enhance myocardial contractility and systemic perfusion and mechanical circulatory support devices to temporarily support cardiac output [6–8]. Despite these interventions, the limitations of current treatment options are manifest in the persistently high mortality rates associated with CS. These limitations stem from several factors, including the risk of exacerbating myocardial ischemia with inotropic therapy, the invasiveness and associated complications of mechanical support devices, and the challenge of timely diagnosis and intervention in the critical early hours of CS onset [9].

Moreover, there is a notable gap in high-quality evidence guiding the pharmacological management of CS, with few randomized controlled trials addressing the efficacy of various treatment modalities in this population [7]. Current diagnostic criteria largely hinge on clinical assessment and hemodynamic parameters, which may not reflect earlier stages of CS or the patient's trajectory of deterioration. Given these challenges, there is an urgent need for

more precise diagnostic tools, early biomarkers, and well-defined therapeutic protocols to improve outcomes in CS.

In this narrative review, we conducted a comprehensive analysis of the pharmacological agents currently employed in the treatment of CS. This review aims to synthesize current evidence on pharmacological management strategies, evaluate emerging therapies, and discuss potential advancements that could refine treatment paradigms and address the substantial unmet needs in CS care.

Current Recommendations in Clinical Guidelines on Cardiogenic Shock Medical Treatment

The management of CS is suggested by the recommendations from both the American College of Cardiology/American Heart Association (ACC/AHA) [8] and the European Society of Cardiology (ESC) [6], although these recommendations present flaws. The ACC/AHA guidelines prioritize early identification and intervention, advocating for the use of inotropes and vasopressors to stabilize hemodynamics in the acute phase of CS. Inotropes like dobutamine, classified under the class of recommendation (COR) I and based on a moderate level of evidence (LOE) B, are recommended for their ability to increase myocardial contractility. Vasopressors, such as norepinephrine (COR I, LOE B), are suggested to increase vascular tone and blood pressure in hypotensive patients, reflecting their critical role in the initial stabilization phase.

On the European side, the ESC guidelines echo the ACC/AHA's emphasis on early and aggressive management but provide a broader perspective on the pharmacological landscape. They highlight the use of levosimendan (COR IIa, LOE B) for patients with CS who present reduced left ventricular ejection fraction (LVEF) and are not on beta-blocker therapy, marking a divergence. Levosimendan, with its dual action of increasing calcium sensitivity of the heart muscles and inducing vasodilation, offers an alternative inotropic support for specific patient subsets, a more recommended approach by the ESC guidelines.

Comparing the ACC/AHA and ESC guidelines reveals both concordance and divergence in CS management strategies. Both sets of guidelines underscore the crucial role of pharmacological therapies in stabilizing patients and the further importance of mechanical circulatory support (MCS) as an adjunct or alternative to pharmacological intervention in refractory cases. Despite differences, a common thread is that both guidelines advocate for a multidisciplinary approach to CS management, involving collaboration among cardiologists, intensivists, and cardiac surgeons to optimize patient outcomes through integrated care.

However, a critical examination of these guidelines reveals a notable degree of discretion afforded to the clinicians in the decision-making. The overarching reliance on clinician judgment, therefore, is a double-edged sword, facilitating personalized treatment but also reflecting an underlying uncertainty due to the lack of direct evidence.

The guidelines, therefore, while providing a scaffold based on the best available evidence, often reference studies that are not exclusively focused on CS but rather also derive evidence from other types of circulatory shock, underscoring a significant gap in the literature. Acknowledging this gap formed another cornerstone of our aims to undertake a comprehensive review of the drugs used in the CS setting.

Fig. 1 presents the main recommendations for the management of CS according to clinical guidelines.

Pharmacological Treatments in Cardiogenic Shock

Despite the increasing use of MCS systems in the treatment of CS, pharmacological therapy still represents the core therapeutic basis for patients with CS requiring hemodynamic support.

A recent Cochrane meta-analysis showed no superiority in the use of one particular line of treatment over the other in patients with CS [10]. As shown in Fig. 1, this is further confirmed by current guidelines, which propose an ambiguous line of treatment, leaving the use of these drugs guided by clinical judgment [6,8].

In the setting of CS, vasoactive drugs improve tissue perfusion and oxygenation by achieving a minimum acceptable cardiac output and arterial pressure, restoring cell metabolism, and slowing myocardial ischemia [11].

Based on their hemodynamic effect, two main pharmacological classes are used in CS: inotropes and vasopressors. However, these drugs act through varied receptor-agonist interactions with multiple targets, so the classification does not always reflect the *in vivo* effects [12]. The following paragraph will discuss each class in depth, with the evidence available.

Inotropes

Inotropes are drugs that increase cardiac output by enhancing the contraction force of the heart muscle. Based on their mechanism of action, they are subcategorized into three subgroups: adrenergic agonists, phosphodiesterase (PDE) III inhibitors, and calcium sensitizers [13]. In addition, based on their action on peripheral resistance, they can be further classified into two subgroups: inopressors and inodilators [14].

Adrenergic Agonists

Adrenergic agonists act by stimulating beta-1 (β_1), beta-2 (β_2), and alpha-1 (α_1) receptors in a quite similar manner [11]. Specifically, their action on cardiac β_1 receptors activates G protein adenylate cyclase, increasing intracellular cyclic adenosine monophosphate (cAMP). This increase in cyclic AMP acts by enhancing calcium uptake. The calcium ion (Ca^{2+}) then binds to troponin C, facilitat-

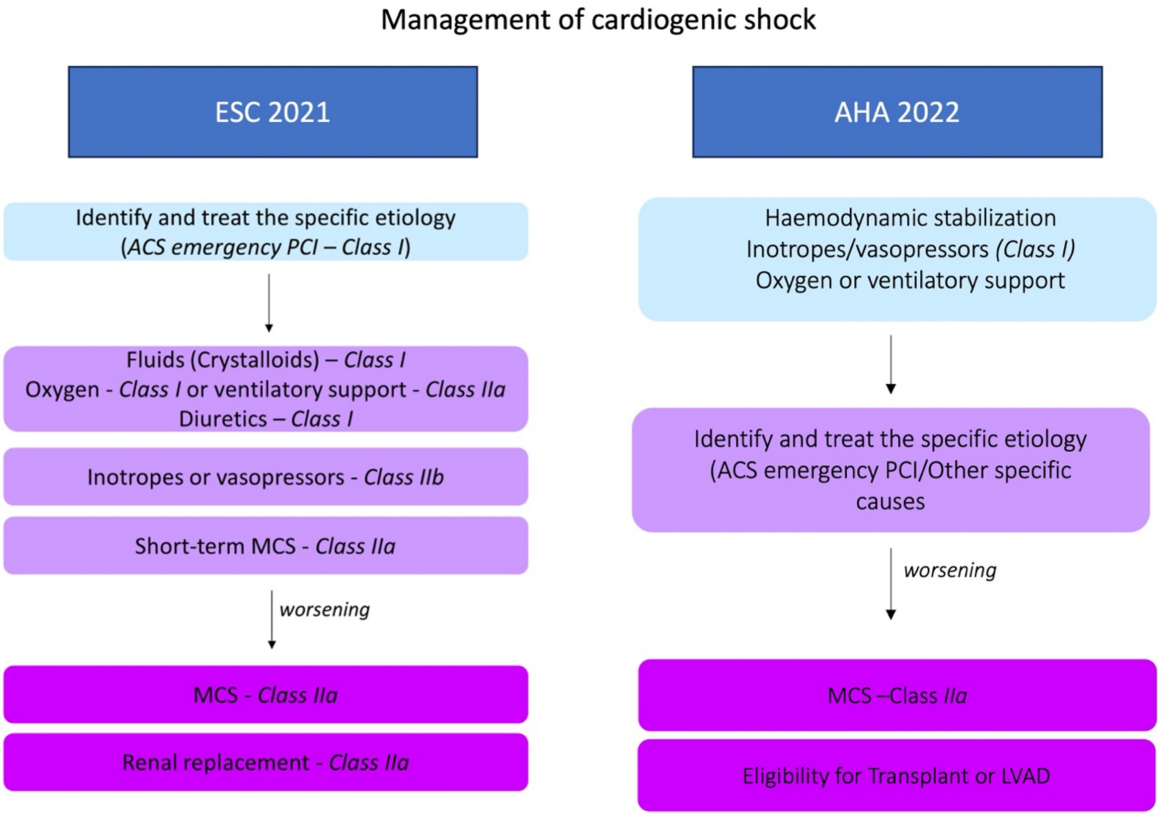

Fig. 1. Illustration of the management strategies for cardiogenic shock (CS) as recommended by the 2021 ESC and 2022 AHA guidelines. Both guidelines emphasize initial stabilization, identification of etiology, and the use of inotropes/vasopressors, with progression to MCS and/or renal replacement if initial treatments are ineffective. Abbreviations. ACS, acute coronary syndrome; AHA, American Heart Association; ESC, European Society of Cardiology; LVAD, left ventricular assist device; MCS, mechanical circulatory support; PCI, percutaneous coronary intervention. All the figures were created from Microsoft PowerPoint 16.

ing the actin-myosin interaction that eventually triggers the contraction of the myocardium [14,15].

Although this class of drugs acts by enhancing cardiac contractility, the rise in cardiac workload is directly associated with an increase in oxygen consumption by the tissues. Elevated oxygen consumption activates cellular proliferative pathways, leading to hypertrophy cell death and serving as a pro-arrhythmic factor [15]. Considering these factors, the use of these drugs must be closely monitored, and the duration of treatment must not extend beyond the hemodynamic stabilization of the patient.

Dobutamine is the first inotrope developed with characteristics that confer almost complete agonism for β_1 receptors (10 times the affinity for β_2 receptors) and minimal or no agonism for alpha receptors. Dobutamine, characterized by its pharmacokinetic profile that combines inotropic effects with a decrease in peripheral resistance and sympathetic tone, is designated with a Class IIB/C indication in ESC guidelines for patients undergoing CS, severe systolic dysfunction, reduced cardiac output, and signs of organ hypoperfusion [6,15]. Additionally, the use of dobutamine can be complemented by the administration of norepinephrine to enhance cardiac output. The current recommendation class for dobutamine reflects its limited evidence, mainly represented by a subset of comparative study analyses, which have supported its use in CS [16].

The earliest study assessing the safety of the drug in chronic treatment was conducted in 1997, the FIRST trial, which evaluated standard care versus epoprostenol infusion in 471 patients in New York Heart Association (NYHA) class IIIb-IV, with 80 of them on dobutamine therapy. The sub-analysis revealed a higher mortality rate at 6 months, although it should be noted that the treated population had more severe clinical conditions [17].

In the DICE trial that followed in 1999, 38 patients with heart failure with reduced ejection fraction (HFrEF) and NYHA class III/IV were treated with intermittent doses of low-dose dobutamine vs. standard therapy. The trial demonstrated that intermittent administration of the drug after 6 months, although not improving the patient's functional status, did not lead to a statistically significant increase in mortality rates [18].

More recently, in 2021, the DOREMI trial [19] included 192 participants with CS classified according to the Society for Cardiovascular Angiography and Intervention (SCAI) system. Of these, 96 received dobutamine, and 96

received milrinone. The trial found no significant differences in primary or secondary outcomes between the two treatments. The primary outcome was a composite measure, including in-hospital mortality from any cause, resuscitated cardiac arrest, need for cardiac transplant or mechanical circulatory support, nonfatal AMI, transient ischemic attack (TIA) or stroke, and initiation of renal replacement therapy. Secondary outcomes were the individual components of this composite measure.

A meta-analysis by Karami *et al*. [2] in patients with AMI complicated by CS found no significant differences in mortality among treatments with adrenaline, noradrenaline, dobutamine, levosimendan, and dopamine, despite low-grade evidence. Similarly, Uhlig *et al*. [20] analyzed patients with AMI and CS with severe systolic dysfunction, comparing levosimendan, dobutamine, enoximone, piroximone, epinephrine, norepinephrine, dopexamine, dopamine, and amrinone, and found no significant reduction in all-cause mortality across these treatments. As explicit from these three analyses, the use of this drug to date is a crucial tool in acute settings, but its use lacks a robust foundation in the literature, where it seems to be counterproductive in chronic settings.

Type III Phosphodiesterase Inhibitors

Amrinone, milrinone, and enoximone belong to the group of type III PDE inhibitors and exert an inodilating action like dobutamine despite their different mechanisms of action. Among these drugs, milrinone is the most widely used in current clinical practice and also the only one currently approved [21–24].

This class of drugs acts by inhibiting the degradation of cyclic AMP mediated by type III PDE. The accumulation of cyclic AMP leads to an increased intracellular calcium intake and enhanced actin-myosin coupling. Conversely, their action on peripheral smooth muscle cells results in vasodilation and a reduction of vascular resistance [25].

Despite the similarities we can identify with dobutamine, PDE III inhibitors, having a different mechanism of action, can be used concomitantly with beta-blockers. Their more pronounced vascular action, positive lusitropic effect, and lower arrhythmogenicity make them a preferred therapy in patients with diastolic dysfunction and an increased arrhythmic burden. Similar to dobutamine, several studies have shown that despite the favorable hemodynamic action of PDE III inhibitors, long-term therapy does not improve mortality outcomes.

The prospective PROMISE study, conducted in 1991 on 1088 patients with HFrEF in NYHA class III-IV, compared placebo vs. milrinone 40 mg orally and observed an increase in both all-cause mortality and cardiovascular mortality at 6 months in patients on milrinone therapy [26]. Furthermore, in the OPTIME-CHF trial, 949 patients with decompensated HFrEF were assigned to either intravenous milrinone or placebo for 48–72 hours. The primary outcome (total days hospitalized for cardiovascular causes within 60 days) was evaluated according to heart failure (HF) ischemic or non-ischemic etiology. Among ischemic HF patients, milrinone was linked to worse outcomes, with longer hospital stays and a higher combined rate of death or rehospitalization. In contrast, non-ischemic HF patients treated with milrinone showed improved outcomes, with shorter hospitalization and a reduced death or rehospitalization rate [23]. In the setting of bridge therapy for heart transplantation, studies demonstrated that the use of dobutamine or milrinone did not show statistically significant differences [27,28]. Even the use of dobutamine and milrinone for only 24 hours, as reported by Karlsberg *et al*. [29] in patients with AMI and subsequent CS, showed no significant differences except for a greater propensity in the dobutamine-treated group for arrhythmias to occur.

Recently, Biswas *et al*. [30] showed that dobutamine was associated with a shorter intensive care unit stay in acute HF patients, with a marginal benefit in the use of milrinone over dobutamine in acute HF patients without CS but no difference in those with CS. Eventually, as reported earlier, the DOREMI Trial [19] found no significant difference between milrinone and dobutamine in patients with CS.

Calcium Sensitizers

The need to overcome the limitations imposed by catecholamines and PDE II inhibitors led to the development of calcium sensitizers in the 1980s. The drugs belonging to this class include EMD-57033, CGP-48506, pimobendan, and levosimendan. Their mechanisms of action differ depending on the drug. Levosimendan and pimobendan increase calcium/sarcomere sensitivity by enhancing the affinity between troponin C and calcium (Ca), whereas EMD-57033 and CGP-48506 act downstream of troponin C and on the motor domain of myosin, respectively. The direct action on the filaments allows them to avoid influencing the action of the sarcoplasmic reticulum in the release and reabsorption of Ca ions, and they are independent of the beta-adrenergic receptor (β-AR)/cAMP system, which becomes desensitized in HF. On the other hand, increased affinity leads to a delay in muscle release that is independent of calcium levels.

Levosimendan is the drug of choice in this class since, in addition to its role as a Ca-sensitizer, it acts as a selective PDE III inhibitor and a carbachol muscarinic receptor agonist. These properties enable it to enhance myocardial contractility without prolonging relaxation time [31–33] at the vascular level, there is an activation of Adenosine Triphosphate (ATP)-sensitive sarcolemmal potassium (K^+) currents, resulting in peripheral vasodilatation [15]. The extended hemodynamic effect of the drug (up to 7–9 days) after the cessation of infusion is attributed to the formation of the metabolite (OR-1896). The latter exhibits hemodynamic effects like those of levosimendan and a prolonged elimination half-life (approximately 75–80 hours) [34].

The inotropic and sensitizing effects of Ca depend on the patient's pre-existing adrenergic condition. In the SURVIVE trial [35–37], where levosimendan was compared with dobutamine, it was confirmed that patients already on beta-blockers exhibited longer short-term survival than those treated with dobutamine. Conversely, in cases of concurrent use of catecholamines, resulting in a predominantly inotropic response to the drug, there was a higher incidence of ventricular arrhythmias and an increase in short-term mortality, although the latter was not statistically significant. Similar to SURVIVE, a study by Samimi-Fard *et al*. [38] on 22 patients with ST-segment elevation myocardial infarction (STEMI) post-primary angioplasty did not demonstrate statistically significant differences in terms of long-term survival.

In contrast, the LIDO trial, a prospective study comparing levosimendan to dobutamine, revealed a superiority of levosimendan at 180 days in terms of hemodynamic improvement and reduction in mortality [39]. Even in comparative studies such as levosimendan vs. placebo, there was no statistically significant benefit. For instance, in REVIVE, the addition of levosimendan to a 24-hour intravenous regimen in patients with exacerbation of heart failure was associated with an increase in mortality at 14 days and 90 days (15.1% vs. 11.6%) at the cost of increased arrhythmias and episodes of hypotension [40]. This was also confirmed in the chronic setting in patients with severe HF, in the PERSIST trial where levosimendan, despite a reduction in N-terminal pro-B-type Natriuretic Peptide (NT-proBNP) levels and an improvement in symptoms, showed no difference in terms of the patient's journey [41].

However, several meta-analyses, including one conducted on 45 trials by Landoni *et al*. [42] that encompassed randomized trials of levosimendan vs. placebo or dobutamine, and trials conducted in patients with an indication for elective cardiac surgery, demonstrated a 20% reduction in the relative risk of mortality.

Among the trials that have evaluated the use of levosimendan in patients' candidates for elective surgery, it is imperative to consider CHEETAH and LEVO-CTS. Although they did not achieve significant results in terms of improved outcomes, in the case of LEVO-CTS, there was a correlation between levosimendan use and a reduction in postoperative inotropic use [43,44].

In the advanced chronic setting, the recent LION-HEART trial, a multicenter study involving 69 patients, demonstrated an improvement in the quality of life and a reduction in NT-proBNP levels in patients treated with biweekly intermittent infusions for 12 weeks [45]. Recently, the LEODOR trial indicated that intermittent levosimendan therapy did not improve clinical stability post-hospitalization [46]. On the contrary, Zeitouni *et al*. [47] found that adding levosimendan to dobutamine may improve inotrope withdrawal success and reduce 30-day mortality in patients with initial weaning failure.

In conclusion, levosimendan has shown efficacy in improving hemodynamic stability and reducing mortality in specific scenarios, particularly in acute HF when beta-blockers are in use and during attempts to wean patients off inotropes. Its prolonged action, due to active metabolites, and its unique mechanism, enhancing myocardial contractility without increasing oxygen demand, make it a valuable option in cases where traditional inotropes may exacerbate myocardial stress. However, its benefits are context-dependent, with mixed results in chronic HF management. This lack of robust evidence is reflected in the current indication of the drug in ESC guidelines, where its indication class is IIb LOE C for short-term intravenous formulation in cases of hypotension (systolic blood pressure, SBP $<$90 mmHg) and/or signs/symptoms of hypoperfusion despite adequate filling status associated with less than vasopressor use [6]. Comprehensively, Table 1 (Ref. [19,26,28,30,46–53]) resembles available evidence on inotropes.

Vasopressors

Vasopressors are a crucial class of medications reported to be employed in 90% of CS cases [11]. Catecholamines, notably norepinephrine, epinephrine, dopamine, and phenylephrine, are the main representatives in this drug category. Their mechanism of action, as previously explained, involves receptor agonism through α_1, β_1, β_2, and dopaminergic receptors. In contrast to dobutamine, which predominantly acts on β_1 receptors to enhance cardiac contractility, vasopressors exert their effects by selectively agonizing α_1-adrenergic receptors found on smooth muscle cells. Activation of α_1 receptors leads to an elevation in intracellular calcium, contributing to peripheral vascular contraction [54].

As medications impact the adrenergic system, they inherently elevate oxygen consumption and carry arrhythmogenic potential. Consequently, their administration should be confined to sustaining a minimum mean arterial pressure conducive to optimal peripheral perfusion and promptly discontinued when appropriate [55].

Among the vasopressors, dopamine, the immediate precursor of norepinephrine, is the only one that acts in a dose-dependent manner. Indeed, at high doses (10 to 20 µg/kg/min), this drug predominantly exhibits a vasoconstrictive action, while at intermediate doses, it acts as a weak β_1-adrenergic agonist with inotropic and chronotropic effects. At low doses (0.5 to 3 µg/kg/min), dopamine stimulates postsynaptic dopaminergic D_1 receptors and presynaptic D_2 receptors, the latter being predominantly present in the vasculature and renal tissues. D_2 receptor agonism imparts the drug with controversial natriuretic (renal dosage) properties, given the theoretical increase in glomerular filtrate, although this mechanism of action remains controversial in the literature but is still used in common clinical practice [54].

Table 1. Evidence on the inotropes drug class.

Trial-Meta-analysis, year	Drugs	N° patients	Main inclusion criteria	Primary endpoint	Results
Adrenergic agonists					
FIRST trial, 1997.	Epoprostenol.	417	Patients with HF, NYHA class IIIB/IV and decreased LVEF.	Survival.	The mortality risk increased significantly in the epoprostenol group (48% vs. 37% at six months, p = 0.055). No improvement in walking distance, quality of life, or morbidity.
DICE trial, 1999.	Dobutamine.	38	Clinically stable NYHA class III/IV patients with CI $\leq$2.2 L/min/m^2 and LVEF $\leq$30% were randomized to intermittent ambulatory dobutamine or optimal standard treatment.	Reduction of hospitalizations for worsening of HF.	Six-month intermittent low-dose dobutamine didn't improve the functional status or rate of mortality. Hospitalizations tended to be fewer in the dobutamine group (17 in control vs. 11 in dobutamine), with fewer admissions for worsening heart failure (11 vs. 7).
DOREMI trial, 2021 [19].	Dobutamine.	192	Eligible patients were $\geq$18 years with indications for inotropic therapy: (A) CS with SBP <90 mmHg and end-organ dysfunction; (B) systemic/pulmonary congestion despite vasodilators/diuretics; (C) ACS with CS and CI <1.8 L/min/m^2; (D) need to augment CO with vasopressors; (E) impending CS without hypoperfusion.	Incidence of in-hospital death from any cause, resuscitated cardiac arrest, cardiac transplant or mechanical circulatory support, nonfatal myocardial infarction, neurologist-diagnosed transient ischemic attack or stroke, or initiation of renal replacement therapy.	There was no significant difference in the primary outcome between the treatment groups. Primary outcome events occurred in 47 participants (49%) in the milrinone group and 52 participants (54%) in the dobutamine group (p = 0.47).
SEISMiC study, 2022 [48].	Istaroxime.	60	Patients hospitalized for acute heart failure without acute myocardial infarction with pre-CS (stage B of SCAI classification).	Changes in systolic blood pressure (SBP) at 6 hours.	Istaroxime significantly improved SBP at 6 and 24 hours compared to placebo. Additionally, Istaroxime led to improvements in certain echocardiographic measurements, including cardiac index, left atrial area, and left ventricular end-systolic volume while there were no significant differences between the groups in terms of pulse pressure, laboratory measurements, serious adverse events, or overall adverse events.

Table 1. Continued.

Trial-Meta-analysis, year	Drugs	N° patients	Main inclusion criteria	Primary endpoint	Results
Type III phosphodiesterase inhibitors					
PROMISE trial, 1991 [26].	Milrinone.	1088	Patients with severe HF (NYHA class III or IV) and advanced left ventricular dysfunction.	All cause-mortality.	Milrinone therapy was associated with increased all-cause and cardiovascular mortality, particularly in patients with severe heart failure (NYHA class IV). This drug did not show any survival benefit in any patient subgroup.
Comparative efficacy of short-term intravenous infusions of milrinone and dobutamine in acute congestive heart failure following acute myocardial infarction, 1996.	Milrinone vs dobutamine.		Killip class II or III in patients with CHF, occurring between 12 hours and 5 days following an AMI diagnosis.	CI and MPCWP.	No significant differences were observed in CI at the 6–12 hour or 18–24 hour intervals. While milrinone reduced MPCWP more effectively, the time to reach Maximal change was the same for both groups (p = 0.96).
OPTIME CHF trial, 2002 [49].	Milrinone.	951	Adult patients with LVEF <40% and HF were admitted for exacerbation.	Cardiovascular-related hospitalization days or days deceased within 60 days post-randomization.	There was no significant difference in the primary endpoint of cardiovascular hospital days at 60 days between the milrinone and placebo groups (mean 12.3 vs. 12.5 days) and in cardiac-related hospital days.
Comparison of dobutamine versus milrinone therapy in hospitalized patients awaiting cardiac transplantation: a prospective, randomized trial, 2003.	Milrinone vs dobutamine.	36	Hospitalized patients on the list for cardiac Tx.	Compare the use of dobutamine versus milrinone for inotropic support in heart failure patients awaiting cardiac transplantation.	There were no differences between milrinone and dobutamine in right heart hemodynamics, mortality, need for additional inotropic/vasodilator support, or mechanical support before transplantation. Both groups had frequent ventricular arrhythmias requiring antiarrhythmic therapy.
Comparative effectiveness and safety between milrinone or dobutamine as initial inotrope therapy in cardiogenic shock, 2019 [28].	Milrinone vs dobutamine.	622	Adult patients with CS, regardless of cause, who received initial inotropic therapy with either milrinone or dobutamine and did not undergo mechanical circulatory support were included.	Compare the time to resolution of CS in patients who received milrinone versus dobutamine as initial inotrope therapy.	Patients on milrinone were more likely to undergo heart valve surgery (62% vs. 40%, p = 0.03) and bypass surgery (80% vs. 62%, p = 0.05) compared to those on dobutamine. Conversely, dobutamine patients had higher admission rates for acute decompensated heart failure (ADHF) (20% vs. 4%, p = 0.03) and were more likely to experience ADHF overall (28% vs. 8%, p = 0.02).

Table 1. Continued.

Trial-Meta-analysis, year	Drugs	N° patients	Main inclusion criteria	Primary endpoint	Results
Efficacy of milrinone and dobutamine in low cardiac output states: systematic review and meta-analysis, 2019 [50].	Milrinone vs dobutamine.	23,056	Patients with low cardiac output.	All-cause mortality.	While milrinone showed a trend toward reduced all-cause mortality, this was not statistically significant. Dobutamine was associated with a shorter ICU stay but not a shorter hospital stay. There were no significant differences in the incidence of arrhythmias between the two groups.
Milrinone as compared with dobutamine in the treatment of cardiogenic shock, 2021 [19].	Milrinone vs dobutamine.	192	Patients with CS.	The primary endpoint was a composite of in-hospital death, resuscitated cardiac arrest, cardiac transplant or mechanical support, nonfatal myocardial infarction, neurologist-diagnosed transient ischemic attack (TIA) or stroke, and initiation of renal replacement therapy.	There was no significant difference in the primary outcome between the two treatment groups. Similar proportions of patients experienced primary outcome events in both the milrinone and dobutamine groups.
Meta-analysis comparing the efficacy of dobutamine versus milrinone in acute decompensated heart failure and cardiogenic shock, 2023 [30].	Milrinone vs dobutamine.	Ten studies were analyzed, including one randomized controlled trial involving 21,106 patients.	ADHF, HF complicated by CS, HF as a bridge to transplantation, and HF with destination therapy.	Mortality.	Milrinone use in acute heart failure (AHF) patients was associated with a reduced mortality risk compared to control (RR 0.87, CI 0.79–0.97, $p < 0.05$). This benefit was observed in both AHF patients overall and those with destination therapy. While there was a non-significant trend towards improved mortality in AHF-shock patients with milrinone, AHF patients awaiting transplantation showed a non-significant mortality trend favoring dobutamine.
Calcium sensitizer					
LIDO study, 2002.	Levosimendan vs dobutamine.	203	Patients with HFrEF.	The percentage of patients achieving hemodynamic improvement, defined as a $\geq$30% increase in cardiac output and a $\geq$25% reduction in pulmonary capillary wedge pressure, at 24 hours.	The primary hemodynamic endpoint was achieved by 29 patients (28%) in the levosimendan group and 15 patients (15%) in the dobutamine group (HR 1.9; 95% CI 1.1–3.3; $p = 0.022$). At 180 days, 27 patients (26%) in the levosimendan group had died compared to 38 (38%) in the dobutamine group (HR 0.57; 95% CI 0.34–0.95; $p = 0.029$).

Table 1. Continued.

Trial-Meta-analysis, year	Drugs	N° patients	Main inclusion criteria	Primary endpoint	Results
Cardiogenic shock after primary percutaneous coronary intervention: Effects of levosimendan compared with dobutamine on haemodynamics, 2006 [51].	Levosimendan vs dobutamine.	26	CS is secondary to ST-segment elevation myocardial infarction (STEMI) treated with primary PCI.	Acute haemodynamic effects in patients with STEMI, revascularised by the primary percutaneous coronary intervention (PCI) and who subsequently developed CS secondary to severe left ventricular systolic dysfunction.	Levosimendan had a consistently better effect on cardiac power output than dobutamine, while the decrease in PCWP was similar.
Effects of levosimendan versus dobutamine on long-term survival of patients with cardiogenic shock after primary coronary angioplasty, 2008.	Levosimendan vs dobutamine.	22	STEMI patients with CS after PCI.	Cardiac death.	The Kaplan-Meier analysis revealed no significant difference in 12-month survival between the two groups (p = 0.24). Despite levosimendan showing a short-term improvement in LVEF (55% vs. 45%, p = 0.003), long-term survival outcomes were comparable.
PERSIST study, 2008.	Levosimendan.	307	HFrEF patients NYHA class IIIB–IV.	Symptoms, heart failure worsening, and mortality over 60 days.	There were no significant differences in symptoms, worsening heart failure events, or mortality between the levosimendan and placebo groups. However, levosimendan was associated with a significant improvement in quality of life, as measured by the Minnesota Living with Heart Failure Questionnaire (MLHFQ) score, and a reduction in NT-proBNP levels.
SURVIVE trial, 2009.	Levosimendan vs dobutamine.	1327	CS patients required intravenous (i.v.) inotropic support due to an inadequate response to i.v. Diuretics or vasodilators (such as nitroglycerin and nitroprusside).	All-cause mortality.	All-cause mortality was lower in the levosimendan group than in the dobutamine group, with a significant difference at day 14 (7.0% vs. 10.3%; HR 0.67, CI 0.45–0.99, p = 0.045). Mortality differences at days 5 and 31 trended toward significance (3.4% vs. 5.8%, HR 0.58, CI 0.33–1.01, p = 0.05; and 10.1% vs. 13.3%, HR 0.73, CI 0.52–1.03, p = 0.07, respectively).
Effects of levosimendan on mortality and hospitalization, 2012.	Levosimendan.	5480	Metanalysis evaluating 45 randomized clinical trials on CS patients.	Mortality rates in cardiac surgery and cardiology settings, and duration of hospital stay.	Levosimendan was associated with a significant reduction in mortality compared to control (RR 0.80, 95% CI 0.72–0.89, $p < 0.001$). This benefit was observed across various settings and comparator groups, including placebo and dobutamine. Additionally, levosimendan was associated with a shorter hospital stay. However, a trend towards increased hypotension was noted in the levosimendan group.

Table 1. Continued.

Trial-Meta-analysis, year	Drugs	N° patients	Main inclusion criteria	Primary endpoint	Results
Effect of levosimendan on the short-term clinical course of patients with acutely decompensated heart failure, 2013.	Levosimendan.	600	Patients admitted with advanced HF.	Changes in clinical status during the first 5 days.	A higher number of patients in the levosimendan group compared to placebo (58 vs. 44) showed improvement at all three pre-specified intervals (6 hours, 24 hours, and 5 days), while fewer levosimendan patients (58 vs. 82) experienced clinical deterioration ($p = 0.015$ between groups).
Levosimendan may improve weaning outcomesin venoarterial ecmo patients, 2013 [52].	Levosimendan.	17	Patients with refractory cardiogenic shock with VA-ECMO.	Weaning outcomes from VA-ECMO.	Pretreatment with levosimendan may facilitate weaning from VA-ECMO, potentially reducing the need for high-dose inotropes.
Levosimendan in acute heart failure following primary percutaneous coronary intervention-treated acute ST-elevation myocardial infarction. Results from the LEAF trial: a randomized, placebo-controlled study, 2013 [53].	Levosimendan.	61	Patients with HF within 48 h after a primary PCI-treated STEMI (including cardiogenic shock).	Wall motion score index (WMSI) from baseline to day 5.	Levosimendan treatment improved myocardial contractility in patients with PCI-treated STEMI complicated by heart failure. However, there were no significant differences in blood pressure, vasopressor use, NT-proBNP levels, clinical composite scores, arrhythmia rates, infarct size, or new clinical events.
LEVO-CTS trial, 2017.	Levosimendan.	882	Patients with a LVEF $\leq$35%, were undergoing cardiac surgery with the use of cardiopulmonary bypass.	The four-component primary endpoint included 30-day mortality, renal-replacement therapy by day 30, perioperative myocardial infarction by day 5, or mechanical cardiac assist device use by day 5.	There was no significant difference in the primary endpoints between the levosimendan and placebo groups. The rates of adverse events were similar between the two groups.
LION-HEART, 2018.	Levosimendan.	69	Patients with advanced HF.	Serum concentrations of NT-proBNP.	The area under the curve for NT-proBNP levels over time was significantly lower in the levosimendan group ($p = 0.003$). Levosimendan patients had a reduced rate of heart failure hospitalizations ($p = 0.001$) and were less likely to experience a decline in QoL ($p = 0.022$).

Table 1. Continued.

Trial-Meta-analysis, year	Drugs	N° patients	Main inclusion criteria	Primary endpoint	Results
CHEETAH trial, 2017.	Levosimendan.	506	Patients in whom peri-operative hemodynamic support was indicated after cardiac surgery.	30-day mortality.	There was no significant difference in 30-day mortality between the levosimendan and placebo groups (32 patients [12.9%] vs. 33 patients [12.8%]; $p = 0.97$). Additionally, there were no significant differences in the duration of mechanical ventilation ($p = 0.48$), ICU stay ($p = 0.09$), or hospital stay ($p = 0.39$), rates of hypotension and cardiac arrhythmias.
LeoDOR trial, 2023 [46].	Levosimendan.	145	Advanced HF with LVEF ≤30%.	Incidence of death, urgent heart transplantation or VAD implantation, and non-fatal acute HF events within the first 26 weeks.	Levosimendan did not significantly impact the primary endpoint. However, there was a trend suggesting a higher incidence of individual clinical components of the primary endpoint in the levosimendan group compared to the placebo group at 14 weeks ($p = 0.021$) and 26 weeks ($p = 0.122$).
Levosimendan in patients with cardiogenic shock refractory to Dobutamine weaning, 2024 [47].	Levosimendan and Dobutamine.	349	Patients with CS refractory to Dobutamine weaning.	A study comparing dobutamine plus levosimendan to dobutamine alone evaluated two endpoints: the primary endpoint was successful inotrope withdrawal, defined as survival without catecholamine support, transplant, or VAD; the secondary endpoint was all-cause mortality at 30 and 90 days.	Levosimendan plus dobutamine led to successful inotrope withdrawal in 43.4% of patients at 30 days, compared to 10.5% in the dobutamine-only group ($p < 0.001$). This effect persisted at 90 days ($p < 0.001$). Levosimendan plus dobutamine also reduced 30-day mortality ($p = 0.01$), with no significant difference at 90 days ($p = 0.14$).

Abbreviations. ACS, acute coronary syndrome; ADHF, acute decompensated heart failure; CI, cardiac index; CO, cardiac output; CS, cardiogenic shock; HF, heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SBP, systolic blood pressure; Tx, transplantation; AMI, acute myocardial infarction; SCAI, Society for Cardiovascular Angiography and Intervention; HFrEF, heart failure with reduced ejection fraction; VA-ECMO, Veno-Arterial Extracorporeal Membrane Oxygenation; VAD, ventricular assist device; QoL, quality of life; MPCWP, mean pulmonary capillary wedge pressure; NT-proBNP, N-terminal pro-B-type Natriuretic Peptide; STEMI, ST-Segment elevation myocardial infarction.

Table 2. Evidence on the vasopressors drug class.

Trial-Meta Analysis, Year	Drugs	N° patients	Main inclusion criteria	Primary end-point	Results
Does dopamine administration in shock influence outcome? Results of the Sepsis Occurrence in Acutely Ill Patients (SOAP) Study, 2006.	Dopamine.	3147	Patients in shock state.	Hospital and mortality rates.	Mortality rates were higher in the dopamine group, both in the ICU (42.9% vs. 35.7%, $p = 0.02$) and in the hospital overall (49.9% vs. 41.7%, $p = 0.01$).
Comparison of dopamine and norepinephrine in the treatment of shock, 2010.	Norepinephrine, Dopamine.	1679	Patients with CS, septic shock and hypovolemic shock.	Mortality at 28 days.	There was no significant difference in 28-day mortality rates between the dopamine group (52.5%) and the norepinephrine group (48.5%) (odds ratio, 1.17; 95% CI, 0.97 to 1.42; $p = 0.10$). Arrhythmic events were higher dopamine group ($p < 0.001$). 28-day mortality with dopamine was higher in CS patients ($p = 0.03$) but not in those with septic ($p = 0.19$) or hypovolemic shock ($p = 0.84$).
The Effects of Short-Term Norepinephrine Up-Titration on Hemodynamics in Cardiogenic Shock, 2010 [62].	Norepinephrine.	12	Patients with CS are mechanically ventilated.	Effects of short-term norepinephrine dose up-titration in cardiogenic shock patients.	Short-term norepinephrine dose up-titration in cardiogenic shock patients treated or pretreated with inotropes was well tolerated and may improve organ blood flow with an increased mean arterial pressure and systemic vascular resistance.
OptimaCC comparative study, 2018	Epinephrine, Norepinephrine.	57	Patients with CS after AMI.	CI evolution and the occurrence of refractory CS.	CI evolution was similar between the 2 groups ($p = 0.43$) from baseline (H0) to H72. The refractory shock was in the epinephrine group (10 of 27 [37%] vs. norepinephrine 2 of 30 [7%]; $p = 0.008$).
Management of cardiogenic shock in acute decompensated chronic heart failure: The ALTSHOCK phase II clinical trial, 2018 [63].	Epinephrine.	24	Patients with refractory CS.	Survival at 60 days.	Epinephrine therapy (median duration 7 days, median dose 0.08 µg/kg/min) was associated with a 60-day survival rate of 87.5% in chronic advanced heart failure patients with cardiogenic shock. Among survivors, 61.9% received LVAD, 9.5% underwent heart transplantation, and 28.6% improved on medical therapy. These findings suggest that early and intensive treatment with epinephrine and timely mechanical circulatory support may lead to favorable outcomes in this patient population.
Optimum blood pressure in patients with shock after acute myocardial infarction and cardiac arrest, 2020 [64].	Epinephrine and Dobutamine.	120	SC is secondary to AMI.	72-h high-sensitivity troponin-T curve.	Patients with higher doses of norepinephrine and dobutamine reached higher MAPs and in those patients, the 72-h high-sensitivity troponin-T curve was lower. The use of inotrpes or vasopressors did not increase the risk of a new cardiac arrest or atrial fibrillation.

Table 2. Continued.

Trial-Meta Analysis, Year	Drugs	N° patients	Main inclusion criteria	Primary end-point	Results
Vasopressors independently associated with mortality in acute myocardial infarction and cardiogenic shock, 2022 [65].	Vasopressors.	300	Patients with acute myocardial infarction and cardiogenic shock (AMICS).	Mortality in patients with decreased intrinsic cardiac power output (CPO).	Patients with lower cardiac power output (CPO) and higher vasopressor requirements had significantly lower survival rates. In particular, in patients with CPO $\leq$0.6 W, survival was 77.3%, 45.0%, and 35.3% when 0, 1, or $\geq$2 vasopressors were used (p = 0.02). Similarly, for patients with CPO >0.6 W survival was 81.7%, 72.6%, and 56.8%, respectively (p = 0.01).
Dopamine versus norepinephrine as the first line vasopressor in the treatment of cardiogenic shock, 2022 [66].	Dopamine, Norepinephrine.	520	CS patients.	In-hospital mortality and arrhythmia.	In-hospital mortality did not differ significantly between the two groups (26.9% vs. 31.9%, p = 0.26). As regards arrhythmia: atrial fibrillation occurred in 12.2% vs. 15.7% (p = 0.30), and ventricular tachyarrhythmia in 19.9% vs. 25.3% (p = 0.18).
Norepinephrine use in cardiogenic shock patients is associated with increased 30-day mortality, 2022 [61].	Norepinephrine.	927	CS.	30-day mortality.	Thirty-day mortality was significantly higher for patients treated with norepinephrine (41% vs. 30%; OR 1.61, 95% CI 1.09–2.39, p = 0.017; HR 1.50, 95% CI 1.09–2.06, p = 0.013). No significant differences in long-term mortality at 90 days (OR 1.19, 95% CI 0.82–1.74, p = 0.363), 180 days (OR 1.17, 95% CI 0.80–1.70, p = 0.418), or 1 year (OR 1.14, 95% CI 0.79–1.66, p = 0.477). Norepinephrine-treated patients required more mechanical ventilation and had longer ICU stays.

Abbreviations. AMI, acute myocardial infarction; CI, cardiac index; CS, cardiogenic shock; ICU, intensive care unit; OR, Odds Ratio.

Table 3. Evidence comparing inotropes vs vasopressors.

Trial- Meta-Analysis, Year	Drugs	N° patients	Main inclusion criteria	Primary endpoint	Results
Pressure response to vasopressors and mortality after direct angioplasty for cardiogenic shock, 2004 [67].	Dobutamine, dopamine, epinephrine and norepinephrine.	32	CS is secondary to acute myocardial infarction in patients treated with primary angioplasty.	Responsiveness to therapy and mortality rate.	Vasopressors weren't an independent predictor of death.
Comparison of norepinephrine-dobutamine to epinephrine for hemodynamics, lactate metabolism, and organ function variables in cardiogenic shock. A prospective, randomized pilot study, 2011 [68].	Norepinephrine-dobutamine vs epinephrine.	30	Patients with CS resistant to combined therapy with Dopamine-Dobutamine (CI $<$2.2 L/min^{-1}/m^{-2} and a mean arterial pressure $<$60 mmHg).	Responsiveness to therapy.	No differences in increasement of cardiac index and oxygen-derived parameters. The combined therapy with Norepinephrine-dobutamine demonstrates a lower heart rate. Epinephrine was associated with new arrhythmias and increased lactate levels. Diuresis increased significantly more in the norepinephrine-dobutamine group.
Current real-life use of vasopressors and inotropes in cardiogenic shock - adrenaline use is associated with excess organ injury and mortality, 2016.	Vasopressors and inotropes.	219	Patients with CS.	90-day mortality.	Adrenaline use was independently linked to higher 90-day mortality (OR 5.2, 95% CI 1.88–14.7, $p = 0.002$), regardless of prior cardiac arrest. Dobutamine and levosimendan were the most commonly used inotropes (49% and 24%, respectively).
Vasopressors and inotropes in acute myocardial infarction related cardiogenic shock, 2020.	Adrenaline, noradrenaline, vasopressin, milrinone, levosimendan, dobutamine and dopamine.	2478	CS patients.	Mortality is categorized into short-term (under 90 days) and long-term (90 days or more).	While the administration of various inotropes and vasopressors did not significantly impact mortality compared to control, there was a trend towards improved outcomes with levosimendan (RR 0.69, 95% CI 0.47–1.00).
Inotropic agents and vasodilator strategies for the treatment of cardiogenic shock or low cardiac output syndrome, 2020 [20].	Levosimendan, dobutamine, enoximone, piroximonepiroximone, epinephrine, norepinephrine, dopexamine, dopamine, and milrinone.	2385	Patients with AMI, HF or cardiac surgery complicated by CS or low cardiac output.	Mortality.	Levosimendan may offer potential benefits over dobutamine, with a lower short-term mortality risk. However, there were no significant mortality differences observed when comparing other inotropes like dopamine, norepinephrine, and enoximone. The overall quality of evidence for these comparisons was low.
Inotropes, vasopressors, and mechanical circulatory support for treatment of cardiogenic shock complicating myocardial infarction: a systematic review and network meta-analysis, 2022 [69].	Levosimendan, milrinone, dobutamine.	2339	CS patients.	Mortality in case of inotropes, vasopressors, or MCS in CS patients.	Levosimendan may reduce mortality compared to placebo, especially in lower-severity shock. However, the evidence for the effects of milrinone and dobutamine on mortality is uncertain.

Abbreviations. CI, cardiac index; CS, cardiogenic shock; HF, heart failure; RR, relative risk.

The utilization of these medications may vary based on the specific clinical context.

Hence, the first comparative trial between dopamine and noradrenaline was conducted in 2010 by De Backer *et al.* [56], involving 1679 patients, of whom 16% presented with CS. Among the patients treated with dopamine, there was a statistically significant elevation in both mortality and arrhythmia rates.

These results find additional support through subanalyses performed on SOAP databases (European Working Group to Epidemiologically Characterize Sepsis) in which the administration of dopamine, apart from being associated with a 20% higher in-hospital mortality rate compared to untreated patients, has been identified as an independent risk factor for overall mortality [57].

Epinephrine is not commonly employed as a pharmaceutical in the management of CS due to contentious findings in the literature. A retrospective study conducted in 2015 on the CardShock patient population revealed an increase in 90-day mortality associated with its use [58]. Additionally, in 2018, the OptimaCC comparative study between epinephrine and noradrenaline was halted due to a higher incidence of refractory shock episodes in patients treated with epinephrine [59].

In 2017, Rui *et al.* [60] conducted a metanalysis on available randomized controlled trials (RCTs) and showed that norepinephrine was associated with lower 28-day mortality, fewer arrhythmic events, and fewer gastrointestinal reactions compared to dopamine in CS, regardless of the underlying cause.

Recently, a real-world study on the use of norepinephrine by Lu *et al.* [61] showed that administration of this drug in CS patients was associated with increased short-term mortality but no significant difference in long-term survival.

In conclusion, among the vasopressors, norepinephrine is generally preferred due to its association with lower mortality and fewer arrhythmic complications, as presented in multiple studies. Dopamine, while once considered beneficial for its dose-dependent effects, has been associated with increased mortality and arrhythmias, especially at higher doses, and is now recommended only in select cases where its chronotropic or low-dose renal effects are specifically needed. Epinephrine is also less favored due to reports of increased mortality and episodes of refractory shock.

These findings underscore the importance of cautious vasopressor selection and judicious use, limiting their application to cases where maintaining minimum mean arterial pressure is necessary for adequate perfusion. Vasopressors should be promptly tapered as soon as hemodynamic stability is achieved to minimize oxygen consumption and the risk of arrhythmias. The literature still confirms several grey areas, particularly concerning the long-term impacts of norepinephrine and optimal strategies for combining vasopressors with other inotropic agents. In conclusion, Table 2 (Ref. [61–66]) contains the main evidence on vasopressors, while Table 3 (Ref. [20,67–69]) presents studies comparing different drug classes, while Fig. 2 resembles the mechanisms of action of main therapeutic choices in CS.

Tailoring Pharmacological Treatment Evidence to SCAI Classification

The SCAI classification, developed in 2019, provides a quick and straightforward means of categorizing patients with CS [70]. These features facilitate the easy reclassification of patients with CS, especially those undergoing rapid clinical changes [7].

The use of the SCAI classification has not only been validated for patients in CS but has also been confirmed as effective in diverse settings, encompassing cardiac intensive care units and individuals experiencing out-of-hospital cardiac arrest [71–73].

The SCAI classification takes into consideration clinical, hemodynamic, and laboratory parameters, allowing the categorization of patients into five classes. However, despite its limitations, it is a valuable tool for rapid and standardized prognostic stratification. When coupled with an etiological and phenotypic assessment of the patient in shock, it allows valuable optimization and standardization of pharmacological treatment.

Stage A defines patients as “at-risk” and forms the foundation of the classification. This class includes patients with non-ST segment elevation myocardial infraction (NSTEMI), prior STEMI, and diastolic/systolic dysfunction who currently do not present with signs and symptoms of CS and neither exhibit laboratory nor hemodynamic changes but present an increased risk of developing CS [7]. Thus, from a practical point of view, patients should be actively monitored to avoid decompensation.

Stage B (beginning) involves patients in a pre-shock or compensated shock state, characterized by hypotension (systolic blood pressure less than 90 mmHg, mean blood pressure less than 60 mmHg, or a pressure drop greater than 30 mmHg) and, generally, compensatory tachycardia. However, these patients do not exhibit signs of hypoperfusion yet. Even at this stage, there are no significant laboratory changes, although signs of volume overload may be present [7]. In addition, pharmacological therapy with vasopressors/inotropes, as mentioned earlier, entails increased oxygen consumption, and consequently, its use must be restricted to overcome the patient’s hypoperfusion condition [55]. In the case of inotropic support, Dobutamine should be the first line of choice. If unresponsive, vasopressors, such as norepinephrine in the first line, should be added. When congestion concomitates, an initiation of diuretic therapy with first loop diuretics, and if ineffective, proceed to sequential nephron blockade [7,70,74,75].

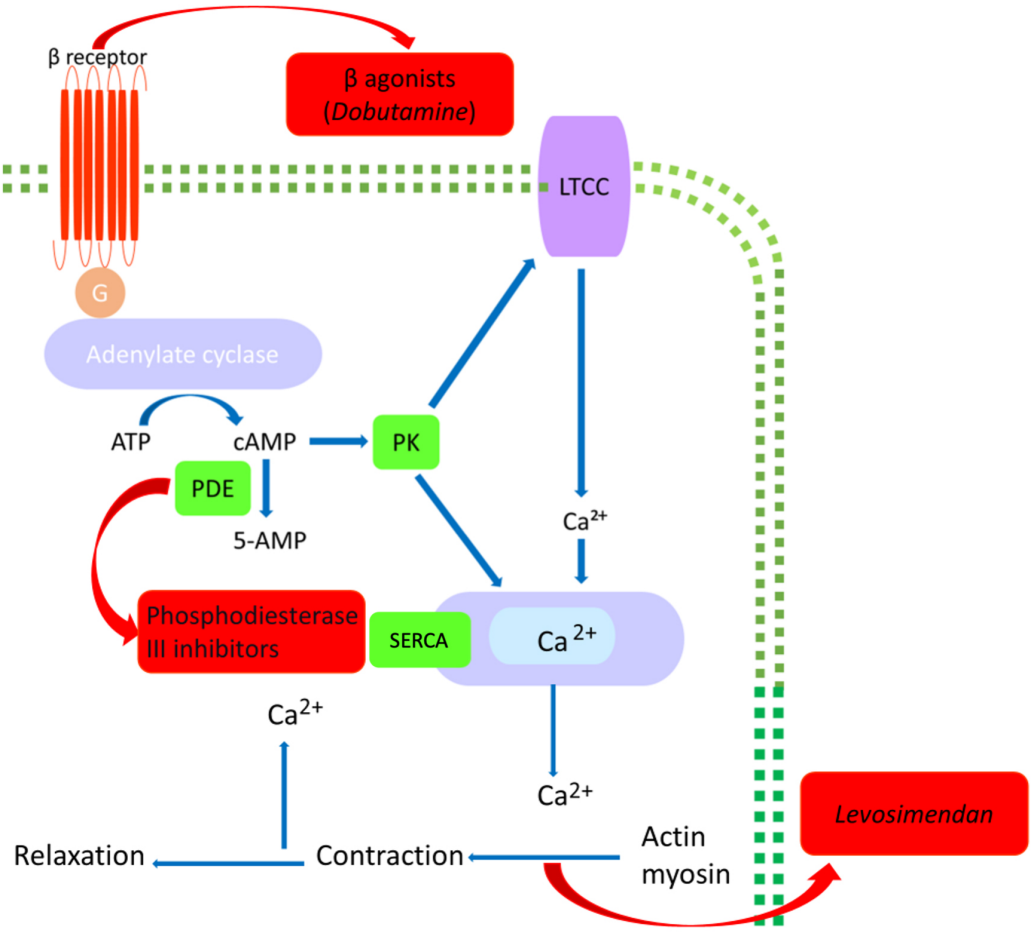

Fig. 2. Mechanisms of action of main drug classes used in the treatment of CS. The figure illustrates the molecular pathways involved in cardiac contraction and relaxation, highlighting the effects of β-agonists and phosphodiesterase III inhibitors on cAMP and calcium signaling. β-agonists activate β-receptors, leading to cAMP production and subsequent calcium influx through LTCC channels. Phosphodiesterase inhibitors prevent cAMP breakdown, enhancing calcium availability for contraction. Levosimendan sensitizes troponin to calcium, improving actin-myosin interactions and promoting contraction without increasing intracellular calcium levels. Abbreviations. 5-AMP, 5-adenosine monophosphate; ATP, Adenosine Triphosphate; Ca^{2+}, calcium ion; cAMP, cyclic adenosine monophosphate; LTCC, L-type calcium channel; PDE, phosphodiesterase; PK, protein kinase; SERCA, Sarcoplasmic endoplasmic reticulum calcium ATPase. All the figures were created from Microsoft PowerPoint 16.

In stage C (classic), patients begin to exhibit signs of hypoperfusion, i.e., cold extremities, oliguria, and mental confusion. Hemodynamically, there is a reduction in cardiac output. Peripheral hypoperfusion is reflected in laboratory changes, including decreased renal function and liver dysfunction, along with increased lactates and BNP. Restoration of organ perfusion through vasopressors/mechanical circulatory support becomes essential at this stage [7]. Management might start with fluid resuscitation, followed by inotropes and vasopressors. If these measures fail, mechanical circulatory support such as Intra-Aortic Balloon Pump (IABP), Impella, extracorporeal membrane oxygenation (ECMO) should be considered. To support cardiac index: dobutamine, levosimendan (especially recommended in normotensive shock, in cases of advanced right heart failure, or in the case of pulmonary hypertension, in patients in beta-blocker therapy), milrinone (with particular caution in non-ischemic patients). Second-line therapy may include a combination of norepinephrine with dobutamine or levosimendan. Inotropic dosing should be guided by systemic vascular resistance (SVR) and mixed venous oxygen saturation (SvO_2) [76]. Diuretic therapy begins with loop diuretics. If renal impairment persists, sequential nephron blockade is initiated. If there is no response, renal replacement therapy is required [7,70,74,75].

Stage D (deteriorating) categorizes patients with CS who, despite at least 30 minutes of supportive therapy, continue to experience persistent hemodynamic instability. The ongoing presence of hypotension and peripheral hypoperfusion requires an escalation of therapeutic interventions [7]. There is generally the need to add one or more additional vasoactive drugs or MCS devices [7,70,74,75].

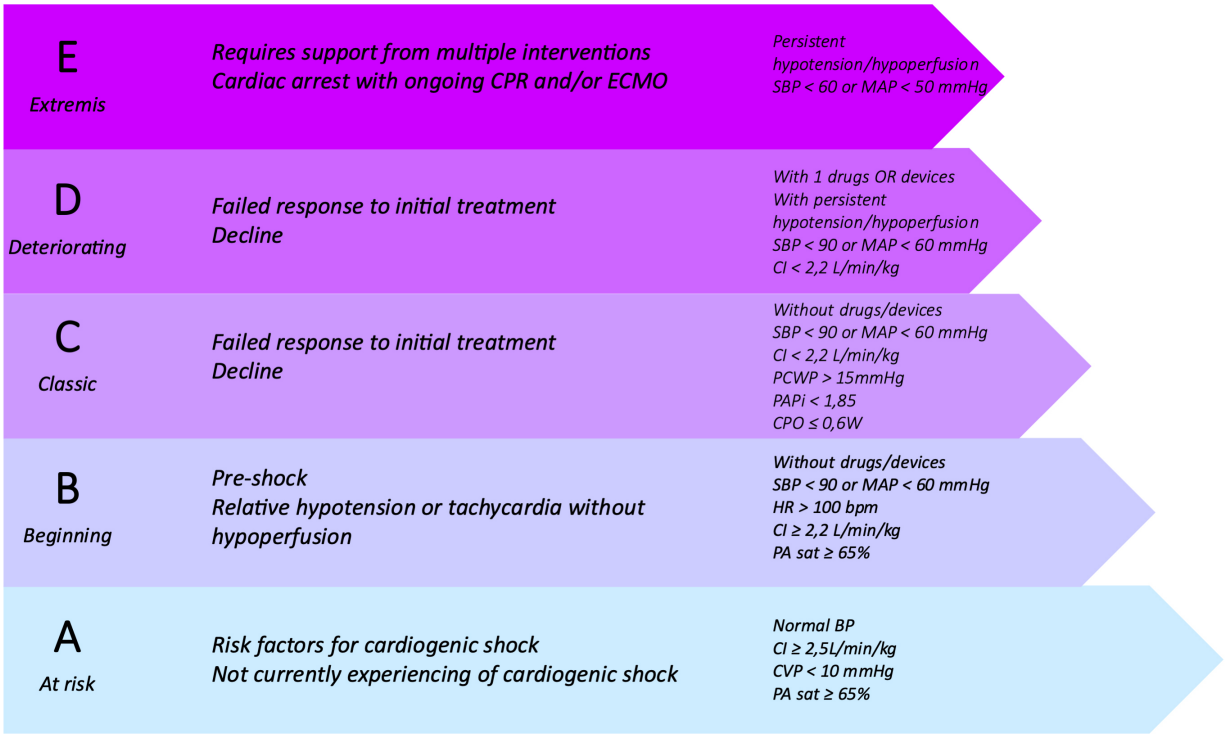

Fig. 3. Central illustration. Practical pharmacological approach to SCAI classification for CS, from A (At risk) to E (Extremis). Stage A includes individuals with risk factors but no active shock, while stage B (Beginning) represents pre-shock with hypotension or tachycardia. Stage C (Classic) shows established shock without drug/device support, progressing to stage D (Deteriorating) for cases unresponsive to initial treatment, requiring interventions. Stage E (Extremis) represents severe cases needing extensive support, including CPR or MCS, with persistent hypotension and hypoperfusion. BP, blood pressure; CI, cardiac index; CPO, cardiac power output; CPR, cardiopulmonary resuscitation; CVP, central venous pressure; HR, heart rate; MAP, mean arterial pressure; MCS, mechanical circulatory support; PAPi, pulmonary artery pulsatility index; PCWP, pulmonary capillary wedge pressure; SBP, systolic blood pressure. All the figures were created from Microsoft PowerPoint 16.

In the advanced stage E (extremis), patients with CS present with hemodynamic collapse despite combination therapy (pharmacological/mechanical circulatory support). These patients often, though not always, experience cardiocirculatory arrest [7] and require CPR and/or ECMO, supported by multiple interventions [7,70,74,75]. In this setting, the role of medical treatment is only supportive of advanced treatments.

In summary, Fig. 3 provides insights into the recommended therapeutic choices according to SCAI classification.

Heterogeneity of Clinical Presentations: Limitations of Approaching CS with Classifications

As presented, despite advancements in the mechanical management of patients with CS in recent years, the diverse range of clinical presentations and various phenotypes hinders the establishment of standardized and effective medical treatments [55].

Ischemic cardiogenic shock (ICS), the most prevalent form of CS, primarily resulting from AMI, causes severe myocardial dysfunction and hemodynamic compromise. It represents the culmination of ischemic injury, where the loss of viable myocardium critically impairs cardiac output, culminating in inadequate tissue perfusion and systemic hypotension [3,55]. Epidemiologically, ICS is observed in approximately 5–10% of AMI cases, positioning it as a leading cause of mortality in this patient group despite advances in reperfusion therapies and supportive care measures [3,55].

Non-ischemic cardiogenic shock (NICS) represents a critical condition characterized by acute heart failure and hypoperfusion not directly resulting from acute myocardial ischemia. The prevalence of NICS is challenging to precisely delineate within the broader spectrum of CS due to its diverse etiologies and the variable incidence reported in clinical studies.

However, it is acknowledged to constitute a significant proportion of cases, with estimates suggesting that it might account for over half of all CS presentations [4,5]. The main causes of NICS are varied, including, but not

limited to, acute myocarditis, stress-induced cardiomyopathy, cardiac tamponade, arrhythmias, advanced and/or fulminant stages of cardiomyopathies, and acute valvular dysfunctions [4,5]. This extensive variability not only complicates the treatment approach but also poses challenges in terms of patient enrollment in clinical trials and prognostic stratification [77].

Thus, a single classification may not be able to capture all the possible different clinical presentations of CS. Although the SCAI classification is simple, quick to use, and easily reproducible, some critical issues that have emerged in validation studies cannot be overlooked.

In particular, the assignment of modifier A (cardiac arrest) cannot disregard an assessment of the state of consciousness and the physiological impact of the arrest [70]. Indeed, a cardiac arrest of short duration in the absence of neurological damage does not impact the prognosis of the patient with CS [9]. In assigning this modifier, therefore, it would be appropriate to implement an assessment of the Glasgow Coma Score (GCS). Unlike the original classification, which assigns the modifier regardless of the duration of cardiac arrest, this approach simplifies an extremely varied event [70]. Furthermore, the SCAI staging system is limited by the heterogeneity of CS phenotypes and the impact of the setting (acute vs. acute-on-chronic) on patient management. Moreover, disease progression is often not a straightforward transition between stages. A further critical issue encountered in using the SCAI classification is the characterization of patients transitioning from a preshock to a shock stage. This distinction highlights a condition of preserved perfusion despite hemodynamic instability (hypotension) in contrast to a condition of compromised perfusion, which may or may not be associated with hemodynamic instability (e.g., normotensive shock). Notably, organ damage often begins early, even in the absence of overt hypoperfusion, through underlying microcirculatory dysfunction [78].

This point is critical because failing to recognize hypoperfusion, in addition to its significant impact on the patient's prognosis, would delay timely interventions to support circulation. A hypoperfused state does not always correlate with an increase in clinical markers such as lactates, and also conversely, an increase in lactates may be associated with other clinical conditions apart from CS [70].

Finally, as of today, there is insufficient data to incorporate additional modifiers, such as age, into the SCAI classification. Age is inherently linked to a worse prognosis, as it is directly related to the patient's frailty. Moreover, a more precise definition of class transition based on titration of drug therapy versus combination therapy is an aspect that currently lacks adequate data [70].

Thus, Naidu *et al*. [70] have proposed a revised pyramid for the SCAI classification to overcome limitations found in real-world validation studies. Additionally, this has been incorporated into a tri-axial evaluation, assessing the severity of CS, disease phenotype, etiology, and risk modifiers. This approach enables a thorough evaluation of the patient to determine an optimal therapeutic setting. However, it lacks specific criteria for classifying patients with SC into a defined SCAI class.

Contemporary Challenges and Future Directions in Treatment

Concerning drug therapy in CS, several uncertainties persist. The use of inotropes and vasopressors continues to be a fundamental aspect of treating these patients despite the lack of conclusive evidence in the literature supporting their mortality benefit. This is largely due to the diverse populations enrolled in different studies, the absence of clear risk stratification, and the varied care approaches primarily relying on individual center experiences.

Recent trials focus on the mechanisms that perpetuate and accumulate damage, representing a maladaptive compensatory response that impedes healing in these patients, including inflammation and vasoplegia. Consequently, various researchers have proposed alternative therapies, such as the use of monoclonal antibodies, like Adrecizumab or corticosteroids, yielding suboptimal results [79,80]. In contrast, Angiotensin II and investigational agents (e.g., Istaroxime) seem to be improving outcomes in patients with refractory CS despite inotropic and vasopressor support.

However, despite ongoing progress in characterization, prognostic stratification, and the increasingly effective utilization of mechanical circulatory support, mortality rates in patients with CS remain high. As reviewed, this is attributed to a lack of treatment standardization and the absence of a national/regional organization that would facilitate the prompt transfer of CS patients to specialized referral centers. This approach is crucial for the timely initiation of appropriate supportive therapy [81,82].

Additionally, over the next few years, we can expect to have a more robust evidence base for the management of mechanical circulatory support, particularly regarding its combined use with inotropic agents.

The ambitious goal is to standardize drug therapy in CS and develop specific pathways that account for clinical, hemodynamic, and etiological conditions.

Nevertheless, while optimizing pharmacological treatment in CS is essential for immediate survival, the impact on long-term quality of life (QoL) and long-term prognosis remains less clear and understudied. Currently, there is no certain data on how specific treatments affect patient-reported outcomes, and much of the present understanding is speculative. Improving patient experience may involve tailoring therapies to minimize adverse effects, reduce hospitalization time, and enhance overall comfort during recovery. Future research is needed to clarify the effects of these strategies on long-term QoL and outcomes in patients recovering from CS.

Conclusions

Despite advancements in the management of CS, mortality rates remain unacceptably high. Current clinical guidelines lack clear indications for CS treatment, leading to variability in clinical practices and outcomes. This review highlights the gap in robust evidence supporting the efficacy of widely used pharmacological treatments, emphasizing the need for rigorous clinical trials to strengthen the empirical foundation of these therapeutic strategies. Implementing standardized frameworks may not only improve survival rates but also ensure a more evidence-based, systematic approach to CS management. Specifically, the SCAI classification system offers a step toward standardization by providing stage-based therapeutic guidelines that aid clinicians in making decisions tailored to shock severity. However, caution is necessary, as such frameworks may risk oversimplifying the clinical heterogeneity observed in CS presentations.

Availability of Data and Materials

Not applicable.

Author Contributions

SPC, AS, FG and GPU, contributed to the conception and design of the study. SPC, MC, VN, SG, IC and RM performed data collection and analysis. SPC, AS, MC, VN, SG, IC and RM drafted the manuscript, FG and GPU critically revised and supervised the manuscript, and all authors reviewed and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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