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Review

Cardiogenic Shock: From Hemodynamic Collapse to a Precision-Medicine-Driven Future

Karma Kinley Dorji[1], Guofu Zhu[1,*]

[1]Department of Cardiology, Second Affiliated Hospital of Kunming Medical University, 650101 Kunming, Yunnan, China
*Correspondence: zhuguofu@kmmu.edu.cn (Guofu Zhu)

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Abstract

Cardiogenic shock (CS) remains a formidable challenge in cardiovascular medicine, carrying a mortality rate that has stubbornly persisted near 40% despite decades of research and therapeutic advances. This comprehensive review transitions beyond the traditional archetype of CS as a mere "pump failure" to explore the associated complex, multisystem pathophysiology. Thus, this review details the interplay of hemodynamic derangements, dysregulated neurohormonal activation, systemic inflammatory response, coagulation activation, cellular immune mobilization, and progressive microcirculatory failure that collectively transform an initial cardiac insult into a self-perpetuating spiral of multisystem organ failure. Current evidence-based management strategies, from early revascularization to the refined application of vasoactive medications and mechanical circulatory support (MCS), have been critically appraised, with particular attention to pivotal clinical trials published since 2017. The landmark DanGer Shock trial (2024) and extracorporeal membrane oxygenation (ECMO)-CS trial (2023), together with the ECLS-SHOCK trial (2023) and ST-segment elevation myocardial infarction (STEMI)-DTU trial (2026), are discussed in detail. Crucially, this review charts the emerging frontier of personalized medicine in CS, examining how phenotype-specific frameworks, guided by novel and traditional biomarkers, advanced hemodynamic profiling, and artificial intelligence, are poised to support traditional multipurpose approaches. The Society for Cardiovascular Angiography and Interventions (SCAI) staging system and the subsequent implications for clinical decision-making are explored in depth. Finally, we highlight future therapeutic innovations, including the unresolved question of pulsatility during MCS, that hold the potential to reduce mortality in this complex, high-risk patient population.

Keywords: cardiogenic shock; myocardial infarction; hemodynamics; heart-assist devices; extracorporeal membrane oxygenation; precision medicine; severity of illness index

1. Introduction

Cardiogenic shock (CS) represents the most extreme manifestation of acute heart failure: a state of critical end-organ hypoperfusion resulting from primary cardiac dysfunction that can progress toward multisystem organ failure and death. Despite remarkable advances in reperfusion strategies, pharmacological therapies, and mechanical support technologies, the prognosis of patients with CS remains poor. The syndrome complicates approximately 5–10% of acute myocardial infarctions (AMI) and also occurs in acute decompensated heart failure, with in-hospital mortality rates that have stubbornly plateaued between 30% and 50% over the past two decades [1,2]. The persistence of this high mortality despite our best efforts underscores a fundamental truth: CS is not a monolithic entity but a heterogeneous, dynamic, and extraordinarily complex syndrome. The historical view, deeply rooted in medical teaching for generations, framed CS as a straightforward consequence of reduced cardiac output: a "broken pump" that simply needed support until recovery. This mechanistic perspective, while intuitively appealing, has proven to be inadequate. We now recognize CS as a catastrophic cascade involving not only the heart as a pump but also the systemic vasculature, the neuroendocrine system, the immune system, and the cellular machinery of virtually every vital organ [1,2].

Contemporary management of cardiogenic shock is informed by professional society guidance, including the American Heart Association scientific statement, the Heart Failure Association position statement, and the European Society of Cardiology (ESC) ST-segment elevation myocardial infarction (STEMI) guidelines [1,2,3]. However, as Tavazzi and colleagues [4] have highlighted, real-world practice remains highly heterogeneous, underscoring a persistent gap between recommendations and clinical application.

This review aims to synthesize the contemporary understanding of CS, building a bridge from its intricate pathophysiology to the practical realities of clinical management and the exciting promise of future innovations. We will dissect the layered mechanisms that transform an initial insult into a self-perpetuating spiral, critically evaluate the current therapeutic landscape with honest appraisal of what works and what doesn't work, and highlight emerging technologies and personalized approaches that may finally reshape outcomes for this devastating condition.

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2. The Pathophysiological Cascade: Beyond a Broken Pump

The onset of CS triggers a complex, whole-body emergency that extends far beyond the initial cardiac insult. Understanding this cascade, in all its interconnected, dynamic complexity, is not merely an academic exercise but the essential foundation for designing effective, targeted interventions.

2.1 The Hemodynamic Spiral: When Compensation Becomes Catastrophe

The classic model of CS pathophysiology begins with an acute or subacute decline in cardiac output. This decline can arise from forward failure of the left ventricle (the most common scenario, e.g., extensive anterior myocardial infarction (MI)), forward failure of the right ventricle (e.g., right ventricle (RV) infarction), or acute backward failure of both ventricles (e.g., fulminant myocarditis or post-cardiotomy shock). Whichever chamber fails first, systemic hypoperfusion triggers the same downstream cascades. Whether from massive myocardial infarction, decompensated chronic heart failure, mechanical complications (such as papillary muscle rupture, ventricular septal defect, or free wall rupture), or fulminant myocarditis, drug- or toxin-induced myocardial depression (e.g., calcium channel blocker or beta-blocker overdose, anthracycline cardiotoxicity), or primary rhythmological causes (tachyarrhythmias such as uncontrolled atrial fibrillation or tachycardia-induced cardiomyopathy, and bradyarrhythmias such as complete heart block), the final common pathway is a profound reduction in forward flow. The resulting hypotension triggers an immediate baroreceptor-mediated response: activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS) [5].

Initially, these neurohormonal responses serve a protective purpose. Increased heart rate, enhanced contractility, and peripheral vasoconstriction represent the body's desperate attempt to maintain perfusion pressure to the brain and heart, the organs known to be least tolerant of ischemia. However, what begins as compensation rapidly transforms into a self-perpetuating vicious cycle. Excessive vasoconstriction increases afterload—the resistance against which the failing left ventricle must eject blood. This additional workload further strains an already compromised myocardium, reducing stroke volume and increasing myocardial oxygen demand. Simultaneously, tachycardia shortens diastolic filling time and reduces coronary perfusion pressure (since most coronary flow occurs during diastole), creating a supply-demand mismatch that worsens myocardial ischemia. Tachycardia also increases myocardial oxygen consumption, further increasing the workload of the ischemic heart [6]. The result is a classic downward spiral: ischemia begets more ischemia, dysfunction brings about more dysfunction [7], as seen in Fig. 1 (Ref. [8]) below.

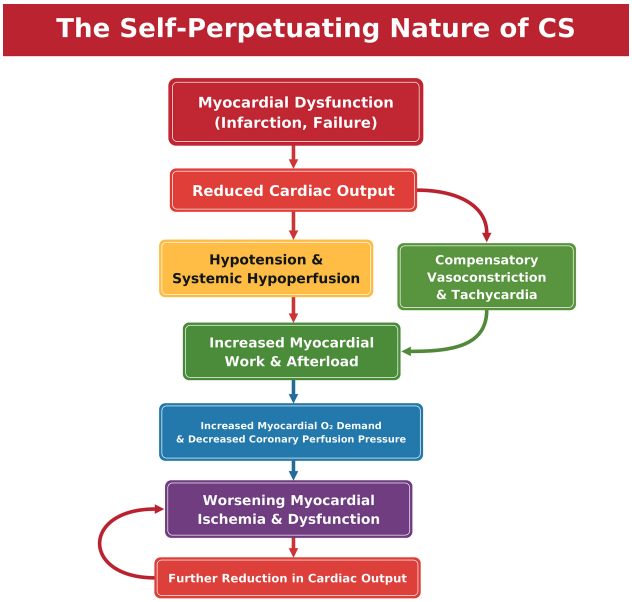


Fig. 1. The downward spiral of cardiogenic shock. This flowchart illustrates the self-worsening nature of cardiogenic shock. Primary myocardial dysfunction, whether from infarction or heart failure, reduces cardiac output, leading to systemic hypoperfusion and hypotension. The resulting sympathetic activation and vasoconstriction indirectly increase myocardial workload and oxygen demand while simultaneously compromising coronary perfusion pressure. This imbalance worsens myocardial ischemia, leading to contractile failure and driving further decline in cardiac output. The clinical course can deteriorate rapidly, reinforcing the need for early recognition and intervention [8]. CS, cardiogenic shock.

2.2 The Systemic Inflammatory Response: When Defense Becomes Destruction

Perhaps the most important conceptual shift in CS research over the past decade has been the recognition that hemodynamic derangements tell only part of the story. A parallel inflammatory response can persist despite apparent hemodynamic stabilization [1,2]. Ischemic injury releases damage-associated molecular patterns (DAMPs), including intracellular proteins and mitochondrial components that can activate innate immune pathways. Pattern recognition receptors on immune and endothelial cells link this tissue injury to the release of inflammatory mediators, including tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6) [9]. In patients with AMI complicated by CS, circulating cytokines have been associated with clinical outcomes [10]. Together, these observations suggest that inflammation contributes to shock progression and organ dysfunction through several mechanisms:

- Vasoplegia and Hemodynamic Collapse: Inflammatory signaling can increase nitric oxide production and reduce vascular responsiveness to catecholamines. The re-

sulting vasodilation may compound hypotension even when vasopressor support is increased. In some patients, particularly as shock progresses, pump failure is therefore accompanied by a vasodilatory component. This combination makes restoration of tissue perfusion more difficult and helps explain why cardiac output and vascular tone must be assessed together [1,11].

- Direct Myocardial Depression: TNF-α and IL-1β have direct negative inotropic effects, further impairing cardiac contractility through mechanisms involving altered calcium handling (including effects on the L-type calcium channel and sarcoplasmic reticulum calcium ATPase), ceramide production, and sphingolipid metabolism. These effects may contribute to myocardial depression in addition to the initial ischemic injury [9].

- Endothelial Activation and Capillary Leak: Inflammatory mediators promote leukocyte adhesion and disrupt the endothelial barrier and glycocalyx. Increased permeability allows fluid to move into the interstitial space, contributing to tissue edema and impaired oxygen diffusion [12,13]. Much of the detailed mechanistic evidence comes from sepsis and experimental research; its relevance to CS should be considered alongside the patient's hemodynamic state. In CS, fluid replacement must be individualized because excessive administration can worsen venous congestion and pulmonary edema [2].

- Mitochondrial Dysfunction and Metabolic Stunning: Systemic inflammation and oxidative stress may impair mitochondrial respiration, creating a state often described as "cytopathic hypoxia": reduced cellular oxygen use despite oxygen delivery. This mechanism has been studied most extensively in sepsis and may help explain persistent organ dysfunction when systemic hemodynamic measurements improve [14,15]. In CS, cellular injury and microvascular dysfunction provide additional reasons why normalization of blood pressure alone may not restore tissue function [2,16].

Coagulation activation and microthrombosis. Endothelial injury, inflammatory signaling, and platelet activation can interact to impair microvascular perfusion. These processes offer a plausible link between systemic inflammation and ongoing tissue injury [9,12]. In patients with CS, coagulation abnormalities also need to be interpreted in the context of antithrombotic treatment, mechanical support, hepatic dysfunction, and bleeding risk. Monitoring platelet counts and coagulation parameters is therefore part of supportive care, but changes in these tests should not be assumed to demonstrate disseminated microthrombosis [1,2].

Cellular immune activation. Tissue injury activates circulating leukocytes and resident immune cells, linking the initial cardiac insult to a broader inflammatory response. Neutrophils, monocytes, and macrophages can amplify endothelial injury and cytokine signaling, while innate immune pathways also participate in tissue repair [9]. This dual role is important: suppressing inflammation indiscriminately could interfere with recovery. Although immune pathways are potential therapeutic targets, a survival benefit from targeted immunomodulation has not been established in CS [2,17].

2.3 Microcirculatory Failure: The Hidden Battlefield

The microcirculation—the network of arterioles, capillaries, and venules where oxygen and nutrients are exchanged—represents a critical but often overlooked component of CS. Even when blood pressure and cardiac output appear stabilized, microvascular blood flow can remain abnormal [16]. Endothelial injury, leukocyte adhesion, altered red-cell transit, and impaired local vasoregulation can contribute to heterogeneous tissue perfusion [18]. The glycocalyx is particularly vulnerable to inflammatory injury, which compromises its roles in barrier regulation and interactions between blood cells and the vessel wall [13]. The kidneys, liver, and gut may therefore remain underperfused despite improvement in systemic measurements. In the CardShock analysis by Tarvasmäki and colleagues [19], creatinine-defined acute kidney injury (AKI) occurred in 31% of patients and was associated with increased 90-day mortality. A study using sublingual imaging linked impaired microvascular perfusion with organ failure and mortality in acute myocardial infarction-related cardiogenic shock (AMI-CS) [20]. These observations have an important practical implication: restoring macrocirculatory measurements is necessary, but does not ensure that tissue perfusion has recovered.

2.4 The Metabolic Crisis: Fueling the Fire

The shock state induces metabolic disturbances that can further impair cellular function. Inadequate oxygen delivery promotes anaerobic metabolism, but an elevated lactate concentration is not specific to tissue hypoxia: adrenergic stimulation and impaired clearance can also contribute [21]. In CS, lactate should therefore be interpreted alongside clinical examination, organ function, and hemodynamic measurements. The CardShock study identified blood lactate as a predictor of in-hospital mortality [22]. In a subsequent analysis, Lindholm and colleagues [23] found that serial lactate measurements and relative lactate change added prognostic information; a 50% reduction within 6 hours was associated with a hazard ratio of 0.82 for 30-day mortality (95% confidence interval (CI) 0.72–0.94). This association supports serial assessment, but does not establish that targeting a particular clearance rate will itself improve survival. Mitochondrial dysfunction can further disrupt energy production, while adenosine triphosphate (ATP) depletion impairs ion transport and cellular homeostasis. Much of the detailed mechanistic evidence comes from sepsis and experimental models [15]. Metabolic pathways remain of interest as potential therapeutic targets in

Table 1. Pathophysiological mechanisms and clinical consequences in cardiogenic shock.

Mechanism	Key mediators	Cellular/Tissue effects	Clinical consequences
Hemodynamic failure	Reduced CO, Hypotension, Compensatory vasoconstriction	Decreased perfusion pressure, increased afterload, Tachycardia-induced energy demand	End-organ hypoperfusion (renal, hepatic, cerebral), Pulmonary congestion, Coronary ischemia
Neurohormonal activation	SNS (norepinephrine, epinephrine), RAAS (angiotensin II, aldosterone), Vasopressin	Vasoconstriction, Sodium and water retention, Myocyte hypertrophy	Increased afterload, Fluid overload, Myocardial remodeling, Arrhythmogenesis
Systemic inflammation	DAMPs (HMGB1, S100, mtDNA), Cytokines (TNF-α, IL-1, IL-6), NO from iNOS	Vasodilation, Negative inotropy, Endothelial activation, Mitochondrial inhibition	Vasoplegia (warm shock), Myocardial depression, Capillary leak, Cytopathic hypoxia
Microcirculatory dysfunction	Endothelial injury, Glycocalyx degradation, Leukocyte adhesion, Microthrombi	Heterogeneous perfusion, Impaired oxygen extraction, Tissue edema	Persistent tissue hypoxia despite macrocirculatory resuscitation, Progressive organ failure
Metabolic derangements	Lactic acidosis, Mitochondrial dysfunction, ATP depletion, Insulin resistance	Impaired cellular energetics, Ion pump failure, Calcium overload, Cell death	Reduced contractility, Blunted vasopressor response, Multiorgan failure, Death

CO, cardiac output; SNS, sympathetic nervous system; RAAS, renin-angiotensin-aldosterone system; DAMPs, damage-associated molecular patterns; HMGB1, high-mobility group box 1; TNF-α, tumor necrosis factor-alpha; IL-1, interleukin-1; IL-6, interleukin-6; NO, nitric oxide; iNOS, inducible nitric oxide synthase; ATP, adenosine triphosphate; mtDNA, Mitochondrial DNA.

CS, but the clinical value of interventions directed at myocardial fuel use requires further study [2].

We have summarized the key pathophysiological mechanisms in CS and their clinical consequences, providing a comprehensive overview of this multisystem syndrome (Table 1) [1,2,9,13,14,15,21].

3. Current Management Strategies: Building on Evidence

The management of CS has evolved considerably over the past decade, though perhaps not as dramatically as we might have hoped. The current approach rests on several pillars: early diagnosis and revascularization, thoughtful hemodynamic support, appropriate selection and timing of mechanical circulatory support, and increasingly, structured multidisciplinary care.

3.1 Early Revascularization: The Cornerstone

For patients with CS complicating acute myocardial infarction (AMI-CS), early revascularization remains a cornerstone of treatment. The landmark SHOCK (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock) trial, published in 1999, randomized 302 patients to emergency revascularization or initial medical stabilization. Although 30-day mortality did not differ significantly (46.7% vs. 56.0%, $p = 0.11$), 6-month mortality was lower with early revascularization (50.3% vs. 63.1%, $p = 0.027$) [24]. The survival benefit persisted: at 6 years, survival was 32.8% versus 19.6% [25]. These findings established the importance of prompt revascularization in AMI-CS. Patients presenting with cardiac arrest form a particularly high-risk group, as illustrated by analyses from the National Cardiovascular Data Registry [26]. Timely recognition, rapid transfer when necessary, and access to coronary intervention remain central to translating trial evidence into routine care [1,3].

The optimal revascularization strategy has been refined by contemporary trials. CULPRIT-SHOCK randomized 706 patients with multivessel disease and AMI-CS to culprit-lesion-only percutaneous coronary intervention (PCI) or immediate multivessel PCI. Death or severe renal failure requiring renal replacement therapy at 30 days occurred in 45.9% versus 55.4%, respectively (relative risk 0.83, $p = 0.01$), favoring the culprit-only strategy [27]. One-year follow-up did not show a statistically significant mortality difference, and subsequent revascularization needs remained relevant [28]. An earlier collaborative meta-analysis by Kolte and colleagues [29], based on nonrandomized studies, had not established a short-term survival advantage for immediate multivessel PCI. Taken together, these findings favor treating the culprit lesion first in the acute shock setting, with further revascularization considered after stabilization according to anatomy and clinical recovery. Coronary artery bypass grafting (CABG) remains an option when coronary anatomy is unsuitable for PCI or when mechanical complications require surgery. The choice should involve the heart team and account for comorbidities, surgical risk, and the urgency of restoring perfusion [1,3,24].

3.2 Hemodynamic Monitoring: Guiding Therapy

Accurate hemodynamic assessment is essential for guiding therapy in CS. Physical examination provides important clues, including cold extremities, jugular venous distension, and pulmonary rales, but may not reliably identify the underlying hemodynamic profile. In a study pub-

lished in 2020, Narang and colleagues [30] compared clinical predictions with invasive measurements in patients with advanced heart failure; accuracy for cardiac-index categories was 49.1%, with similarly limited accuracy for filling pressures. Pulmonary artery catheterization (PAC) provides cardiac output, pulmonary artery and right atrial pressures, pulmonary capillary wedge pressure (PCWP), and mixed venous oxygen saturation. These measurements help distinguish left ventricle (LV), right ventricle (RV), and biventricular dysfunction and guide support. Historical hemodynamic classifications combine cardiac index with filling pressure to characterize low-output and congested states [31]. Observational CS data from Garan and colleagues [32] associated complete PAC-based profiling with lower in-hospital mortality, but this does not establish a causal benefit. Invasive measurements should complement repeated clinical and echocardiographic assessment, with the decision to use a PAC tailored to the uncertainty and complexity of the case [1,33].

Recent European Society of Intensive Care Medicine (ESICM) guidelines emphasize multimodal assessment of shock, combining clinical perfusion signs, echocardiography, and hemodynamic measurements when needed [33]. Venous oxygen saturation and the venous-to-arterial carbon dioxide difference can provide additional information, but should be interpreted alongside lactate, cardiac output, and the clinical trajectory rather than used as isolated triggers for escalating support. Ultrasound assessment of venous congestion may also complement evaluation of RV function and fluid tolerance. Transpulmonary thermodilution systems such as PiCCO can estimate cardiac output and extravascular lung water, offering another way to follow circulatory changes and pulmonary edema. They do not provide the same information as a PAC, and choice of monitoring should reflect the clinical question, local expertise, and the limitations of each method [2,33].

Echocardiography provides complementary information about ventricular function, valvular disease, mechanical complications, and volume status. Focused cardiac ultrasound is useful for rapid bedside assessment, while comprehensive echocardiography is needed when findings are uncertain or structural disease is suspected. The European Association of Cardiovascular Imaging (EACVI) focused cardiac ultrasound curriculum outlines the skills required for a structured examination, but is not a CS-specific treatment protocol [34]. Repeated imaging, interpreted with the hemodynamic and clinical findings, can help guide management as the patient's condition changes [1,33].

3.3 Pharmacological Support: Vasopressors and Inotropes

Pharmacological support of the failing circulation requires navigating a narrow therapeutic window with limited margin for error. The agent chosen, the dose administered, and the timing of initiation can profoundly influence outcomes.

Norepinephrine has emerged as the first-line vasopressor in CS, supported by randomized data demonstrating lower arrhythmogenic potential and improved outcomes compared to dopamine. The SOAP II trial, which included patients with various types of shock, found that dopamine was associated with increased arrhythmias and higher mortality in the cardiogenic shock subgroup compared to norepinephrine [35]. As a potent α-adrenergic agonist with moderate β-adrenergic activity, norepinephrine effectively restores perfusion pressure while providing some inotropic support. Typical doses range from 0.05–0.5 μg/kg/min, with higher doses associated with increased mortality but often unavoidable in severe shock. Dose requirements should be interpreted as part of the severity and trajectory of shock; vasopressors should be titrated to perfusion goals while limiting adverse effects [17].

Dobutamine, a synthetic catecholamine with predominantly β1-adrenergic effects, increases contractility and cardiac output, while β2-mediated vasodilation can reduce vascular resistance. Doses are commonly titrated within a range of 2.5–20 μg/kg/min according to the clinical response. Its use requires careful assessment of the trade-offs: vasodilation may worsen hypotension, and increased heart rate and contractility can increase myocardial oxygen demand or provoke arrhythmias. Continuous monitoring and repeated reassessment are therefore essential [17].

Milrinone, a phosphodiesterase-3 inhibitor, increases intracellular Cyclic adenosine-3',5'-monophosphate (cAMP) in cardiac and vascular smooth muscle, producing inotropic and vasodilatory effects. Its action is not dependent on β-receptor stimulation, which can be useful in patients receiving β-blockers. Renal clearance and a longer duration of action require caution when kidney function is impaired [17]. In the randomized, double-blind DOREMI trial, Mathew and colleagues [36] assigned 192 patients with CS to milrinone or dobutamine. The primary composite outcome occurred in 49% and 54%, respectively, without a statistically significant difference; important secondary outcomes also did not differ significantly [36]. These results support choosing between the drugs on the basis of hemodynamics, organ function, and individual response rather than assuming that either provides a survival advantage.

Epinephrine is a potent inotrope and vasopressor but is associated with increased arrhythmias, lactic acidosis, and possibly worse outcomes compared to norepinephrine. The 2018 OPTIMA-CC trial by Levy and colleagues [37] comparing epinephrine to norepinephrine in AMI-CS was stopped early due to higher rates of refractory shock in the epinephrine group. This finding reinforces the need for caution with epinephrine and supports a preference for norepinephrine when vasopressor therapy is required, while acknowledging the limited comparative evidence [17].

Vasopressin may be considered as an adjunct when vasodilatory hypotension persists despite catecholamine sup-

port. Evidence specific to CS is limited, so its use should be individualized and accompanied by monitoring for excessive vasoconstriction and organ hypoperfusion [17].

Levosimendan increases contractile force through calcium sensitization and also has vasodilatory effects. Small studies have explored its use in CS, including a randomized comparison with enoximone in 32 patients with refractory AMI-CS [38]. These data do not establish a routine role or a reliable survival advantage. The LICORN trial, published in 2017, evaluated perioperative levosimendan in patients with reduced ejection fraction undergoing cardiac surgery and did not significantly reduce its primary composite outcome [39]. That population differs from patients with established CS, so its findings cannot be directly extrapolated to established CS. Levosimendan therefore remains a selective rather than standard option, depending on availability and clinical context [17].

A critical appraisal of the available evidence shows that many pharmacological decisions in CS still rely on limited randomized data, physiological reasoning, and clinical experience [17]. Vasoactive agents can restore pressure or flow, but their short-term hemodynamic effects do not necessarily translate into improved survival. Future trials need to distinguish which patients benefit from inotropic support, which agent is most appropriate, and when treatment should be reduced. Until stronger evidence is available, selection should be guided by hemodynamic phenotype, organ function, and repeated assessment of tissue perfusion [1,17].

A summary of the pharmacological agents used in CS is given in the table below (Table 2) [17].

3.4 Mechanical Circulatory Support: Matching Device to Patient

The past decade has witnessed remarkable expansion in the availability and sophistication of temporary mechanical circulatory support (MCS) devices. These technologies offer the promise of unloading the failing ventricle, maintaining systemic perfusion, and creating conditions for myocardial recovery. However, their use remains fraught with complexity, and the evidence base continues to evolve.

3.4.1 Intra-Aortic Balloon Pump (IABP)

The IABP inflates during diastole to augment aortic diastolic pressure and deflates before systole to reduce LV afterload. However, IABP-SHOCK II randomized 600 patients with AMI-CS undergoing early revascularization and found no reduction in 30-day mortality with routine IABP use (39.7% vs. 41.3%, $p = 0.69$) [40]. The ESC STEMI guidelines consequently advise against routine IABP use in AMI-CS without mechanical complications; this is a lack-of-benefit recommendation, not proof that the device is harmful in every setting [3]. Selected patients with mechanical complications may still receive IABP as a bridge while definitive treatment is arranged [1,3]. The practical lesson is to define the purpose of support and reassess whether the chosen device is meeting it, rather than applying counterpulsation routinely.

3.4.2 Impella Devices

The Impella family of devices provides active LV unloading by aspirating blood from the LV and ejecting it into the ascending aorta. These microaxial flow pumps can be placed percutaneously (Impella 2.5, CP) or surgically (Impella 5.0, 5.5) and provide flow rates from 2.5 to 5.5 L/min.

Table 2. Pharmacological agents in cardiogenic shock.

Agent	Mechanism	Hemodynamic effects	Dosing	Key considerations	Adverse effects
Norepinephrine	α1, β1 agonist	MAP↑, SVR↑, CO mild ↑	0.05–0.5 μg/kg/min	First-line vasopressor	Excessive vasoconstriction, arrhythmias, digital ischemia
Dobutamine	β1 > β2 agonist	CO↑, SVR↓	2.5–20 μg/kg/min	Inodilator for low CO with adequate BP	Hypotension, arrhythmias, MVO_2↑
Milrinone	PDE-3 inhibitor	CO↑, SVR↓, PCWP↓	0.125–0.75 μg/kg/min	Effective with β-blockade, renal clearance	Hypotension, long half-life
Epinephrine	α1, β1, β2 agonist	CO↑↑, HR↑↑, SVR↑	0.01–0.1 μg/kg/min	Reserve for refractory shock	Arrhythmias, lactic acidosis, myocardial ischemia, worse outcomes
Vasopressin	V1 receptor	SVR↑	0.01–0.04 U/min	Adjunct in vasoplegia	Splanchnic ischemia, hyponatremia
Levosimendan	Ca^{2+} sensitizer	CO↑, SVR↓, PCWP↓	0.05–0.2 μg/kg/min	Investigational in CS	Hypotension, headache

BP, blood pressure; CO, cardiac output; HR, heart rate; MAP, mean arterial pressure; MVO_2, myocardial oxygen consumption; PCWP, pulmonary capillary wedge pressure; PDE-3, phosphodiesterase type 3; SVR, systemic vascular resistance; V1, vasopressin receptor type 1; α1, alpha-1 adrenergic receptor; β1, beta-1 adrenergic receptor; β2, beta-2 adrenergic receptor. ↑ indicates an increase; ↓ indicates a decrease; repeated arrows indicate a more pronounced change.

By actively unloading the LV, they reduce myocardial wall stress and oxygen consumption while increasing cardiac output and mean arterial pressure [41]. The USpella registry, analyzing 154 patients with AMI-CS, suggested that Impella implantation before PCI was associated with improved survival compared to implantation after PCI (65.1% vs. 40.7%, $p = 0.003$) [42]. However, these observational data must be interpreted cautiously given potential selection bias. The randomized IMPRESS in Severe Shock trial compared Impella CP to IABP in 48 patients with severe AMI-CS and found no difference in 30-day mortality (46% vs. 50%, $p = 0.92$) [43].

The DanGer Shock trial, published in 2024, randomized 360 patients with STEMI-related CS to Impella CP plus standard care or standard care alone; 355 were included in the final analysis. At 180 days, mortality was 45.8% versus 58.5% (HR 0.74, 95% CI 0.55–0.99, $p = 0.04$), favoring Impella CP [44]. The benefit came with more complications: the composite safety outcome occurred in 24.0% versus 6.2%, and renal replacement therapy was used in 41.9% versus 26.7%. These findings establish a survival benefit in the selected trial population, but do not justify routine use in every patient with CS. Patient selection, device-related complications, and the ability to provide experienced multidisciplinary care remain central to applying the results.

The STEMI-DTU pivotal trial, published in 2026, addressed a different question: whether LV unloading followed by delayed PCI could reduce infarct size in patients with anterior STEMI without CS. Among 527 randomized patients, infarct size did not differ significantly between unloading and immediate-PCI groups (30.8% vs. 31.9% of LV mass, $p = 0.50$), while major bleeding or vascular complications were more frequent with unloading [45]. This result should not be conflated with DanGer Shock. Together, the trials underline that the indication, patient population, and timing of mechanical support matter, and that benefit in established CS cannot be assumed in STEMI without shock.

3.4.3 Veno-Arterial Extracorporeal Membrane Oxygenation (VA-ECMO)

Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) provides the most potent form of cardiopulmonary support, capable of maintaining perfusion even in the absence of meaningful native cardiac output. Peripheral VA-ECMO, typically via femoral cannulation (drainage from the right atrium via femoral vein, return to the iliac artery via the femoral artery), can be deployed rapidly at the bedside and has become the workhorse for refractory CS in many centers [46]. Modern circuits can provide substantial circulatory and respiratory support, although effective flow depends on cannulation, loading conditions, and patient requirements.

However, VA-ECMO comes with significant challenges. Retrograde flow from the femoral artery increases left ventricular afterload, potentially exacerbating LV distension, pulmonary edema, and delaying myocardial recovery. This has led to strategies for LV unloading, including: IABP concurrent with VA-ECMO (extracorporeal membrane oxygenation (ECMO)-IABP); Impella placement (ECpella or ECMELLA configuration); percutaneous atrial septostomy; or surgical LV vent placement. Observational data suggest that LV unloading during VA-ECMO may improve outcomes. In a 2020 multicenter cohort, Schrage and colleagues [47] associated Impella-based LV unloading with lower 30-day mortality, but also with more complications. The observational design limits causal interpretation.

The ECMO-CS trial, published in 2023, randomized 122 patients with rapidly deteriorating or severe CS; 117 were included in the analysis. The composite of death, resuscitated cardiac arrest, or use of another MCS device at 30 days occurred in 63.8% with immediate VA-ECMO and 71.2% with an initially conservative strategy (HR 0.72, 95% CI 0.46–1.12, $p = 0.21$) [48]. In the conservative group, downstream VA-ECMO was permitted and was used in 39% of patients. The trial therefore compared immediate deployment with a strategy that allowed rescue support, rather than ECMO with an absolute prohibition on its later use.

The larger ECLS-SHOCK trial randomized 420 patients with AMI-CS and included 417 in its final analysis. Routine early extracorporeal life support did not reduce 30-day mortality compared with usual care (47.8% vs. 49.0%, $p = 0.81$), and bleeding and peripheral vascular complications were more frequent [49]. These findings argue against indiscriminate early VA-ECMO use in AMI-CS. Rescue support may still be considered in carefully selected patients, but a survival advantage in particular severity subgroups should not be assumed from these neutral trials. Such decisions require assessment of reversibility, neurological prognosis, complications, and the available expertise [46].

LV unloading during VA-ECMO remains an important clinical question. Observational associations are encouraging, but must be weighed against vascular injury, bleeding, and the risks of additional devices [47]. Reviews of temporary circulatory support emphasize matching the support strategy to the patient's ventricular function, oxygenation needs, and potential for recovery [46,50].

3.4.4 TandemHeart

This percutaneous left atrial-to-femoral arterial bypass system provides flows of 3.5–5.0 L/min by draining oxygenated blood from the left atrium (via transseptal puncture) and returning it to the femoral artery. While effective for LV unloading, it requires transseptal puncture and is less commonly used than Impella or ECMO. A 2011 study by Kar and colleagues [51] reported outcomes with TandemHeart in 117 patients with severe refractory CS, reporting improved hemodynamics after device implantation.

3.4.5 Right Ventricular Support

Right ventricular (RV) failure may complicate myocardial infarction, cardiac surgery, or left ventricular assist device (LVAD) implantation. It requires prompt recognition because inadequate RV output limits LV filling and systemic perfusion. Assessment should consider venous congestion, pulmonary vascular load, ventricular interaction, and the cause of RV dysfunction [1,46]. Options for mechanical RV support include:

- Impella RP: a catheter-mounted pump advanced from the femoral vein through the right heart, drawing blood from the inferior vena cava/right atrial region and delivering it into the pulmonary artery [52].

- Protek Duo: a dual-lumen cannula placed from the internal jugular vein across the pulmonary valve. It can be configured as an isolated right ventricular assist device (RVAD) or as a veno-pulmonary arterial (V-P) ECMO circuit when connected to an oxygenator, providing both RV support and gas exchange [46].

- VA-ECMO: provides circulatory and respiratory support by draining venous blood and returning it to the arterial circulation, although its effects on LV afterload must be considered [46].

The prospective RECOVER RIGHT study evaluated Impella RP in 30 patients with RV failure refractory to medical therapy. It demonstrated feasibility and immediate hemodynamic improvement, but had no randomized medical-treatment control group [52]. Its findings should therefore not be interpreted as proof of a survival advantage over medical therapy alone.

A critical knowledge gap remains: a mortality benefit from isolated RV support has not been established in a definitive randomized CS trial. Device selection should therefore follow the cause and severity of RV failure, the adequacy of LV function, and the patient's overall trajectory. Elevated right-sided filling pressures, low cardiac output, and a reduced pulmonary artery pulsatility index can inform the assessment, but no single threshold should dictate implantation [1,46].

The following table provides a framework for matching MCS strategy to the clinical and hemodynamic profile (Table 3, Ref. [3,40,44,46,47,49,52,53,54,55]).

3.5 The SCAI Shock Staging System: A Common Language

A major advance in CS management has been the development of a standardized staging system by the Society for Cardiovascular Angiography and Interventions (SCAI). This system classifies patients into five stages based on clinical presentation, hemodynamics, and laboratory findings, providing a common language for describing shock severity and guiding management [54,55].

The primary rationale for the SCAI staging system is to provide a standardized, reproducible framework that enables better comparability across clinical trials, registries, and quality improvement initiatives. Prior to SCAI, heterogeneous definitions of "severe shock" or "refractory shock" made it nearly impossible to compare outcomes between studies or to determine whether a treatment effect was due to the therapy itself or to differences in baseline severity. By anchoring stages to objective clinical, hemodynamic, and laboratory criteria, the SCAI system allows researchers to stratify patients consistently and clinicians to benchmark their outcomes against published cohorts [54,55].

- Stage A (At Risk): Patients who are not experiencing signs or symptoms of shock but are at risk for developing it. Examples include patients with large AMI, acute decompensated heart failure, or recent cardiac surgery.

- Stage B (Beginning): Patients with relative hypotension or tachycardia, but without evidence of hypoperfusion. Lactate is generally normal; an elevation should prompt assessment for hypoperfusion or another cause [55].

- Stage C (Classic): Patients with hypoperfusion requiring intervention beyond volume resuscitation, such as inotropes, vasopressors, or MCS. Hypotension is common but is not required in every presentation [55].

- Stage D (Deteriorating): Patients who fail to stabilize with initial interventions and continue to deteriorate. They may require escalating doses of vasopressors or multiple support devices.

- Stage E (Extremis): Patients with refractory cardiac arrest, ongoing CPR, or imminent hemodynamic collapse despite maximal support.

The SCAI staging system has been validated as a prognostic framework, with higher stages associated with greater mortality. In a single-center Mayo Clinic cardiac intensive care unit (CICU) cohort of 10,004 patients, Jentzer and colleagues [56] reported in-hospital mortality of 3.0%, 7.1%, 12.4%, 40.4%, and 67.0% for stages A through E, respectively. These values illustrate the risk gradient in that cohort, rather than fixed mortality estimates for every clinical setting. Subsequent validation evidence was incorporated into the SCAI consensus update [55].

Serial reassessment is important because shock is dynamic. A patient who stabilizes after treatment has a different trajectory from one who needs escalating support despite similar initial measurements. The SCAI update incorporates deterioration and response to initial therapy, supporting repeated staging rather than reliance on the admission category alone [55].

3.6 Multidisciplinary Shock Teams: The Power of Collaboration

Perhaps the most important advance in CS management has been not a new device or drug, but a new approach to care delivery. The recognition that CS patients benefit from structured, multidisciplinary management has led to the development of dedicated "shock teams" at many centers. These teams typically include interventional cardiologists, heart failure specialists, cardiac intensivists, cardiac surgeons, perfusionists, and specialized nursing staff.

Table 3. Matching MCS strategy to patient phenotype with SCAI stages and evidence considerations.

Clinical scenario	SCAI Stage	Hemodynamic profile	Potential MCS strategy	Rationale	Evidence and selection considerations
AMI-CS, mild-moderate, no refractory hypoperfusion	Stage C	Low output with congestion; assess perfusion and trajectory	Medical stabilization; assess need for escalation	Avoid routine device use in a stable or improving patient	Routine IABP lacks benefit in AMI-CS without mechanical complications [3,40]
AMI-CS with persistent severe hypoperfusion	Stage D/E	Persistent hypoperfusion despite initial treatment	Consider Impella CP or VA-ECMO according to phenotype	Match ventricular and respiratory support to the clinical problem	Selected STEMI-CS benefit with Impella CP; routine early ECLS neutral [44,49]
Refractory shock with LV distension on VA-ECMO	Stage D/E	LV distension, poor aortic valve opening, pulmonary edema	Consider an LV unloading strategy during VA-ECMO	Balance relief of LV loading against added procedural risk	Observational associations; randomized confirmation needed [46,47]
RV failure (isolated)	Stage C/D	Low output with venous congestion; assess LV and pulmonary function	Selected Impella RP or Protek Duo use	Target isolated RV support when clinically appropriate	Limited, largely nonrandomized evidence [46,52]
Refractory cardiac arrest	Stage E	No return of spontaneous circulation despite resuscitation	Selected ECPR in an experienced system	Rescue support for potentially reversible arrest	ARREST evidence applies to a selected refractory-VF population [53]

Note: These profiles are illustrative, not validated device-selection thresholds. SCAI stage describes shock severity and trajectory; device choice also depends on etiology, ventricular function, oxygenation, reversibility, and local expertise [46,54,55]. AMI-CS, acute myocardial infarction complicated by cardiogenic shock; ARREST, Advanced Reperfusion Strategies for Patients With Out-of-Hospital Cardiac Arrest and Refractory Ventricular Fibrillation; ECPR, extracorporeal cardiopulmonary resuscitation; ECLS, extracorporeal life support; IABP, intra-aortic balloon pump; LV, left ventricle; MCS, mechanical circulatory support; RV, right ventricle; SCAI, Society for Cardiovascular Angiography and Interventions; STEMI-CS, ST-segment elevation myocardial infarction complicated by cardiogenic shock; VA-ECMO, veno-arterial extracorporeal membrane oxygenation; VF, ventricular fibrillation.

Their purpose is not merely to gather multiple specialists in one room, but to create a coordinated approach to decision-making—ensuring that the right patient receives the right therapy at the right time.

Observational evidence supports this coordinated approach. In a single-center program, Tehrani and colleagues [57] reported an increase in 30-day survival from 47% in 2016 to 76.6% in 2018 after implementation of a standardized team-based strategy. The association is encouraging, but changes in case mix, experience, and other aspects of care may also have contributed. Earlier recognition, structured hemodynamic assessment, and timely discussion of support options are plausible advantages of the model.

Other reports provide complementary evidence. Taleb and colleagues [58] described a shock-team approach for refractory CS requiring short-term MCS. In a multicenter observational analysis, Papolos and colleagues [59] found that centers with shock teams more often used invasive hemodynamic assessment and had lower risk-adjusted CICU mortality. These studies support further evaluation of coordinated care, but do not establish that the team structure alone caused the outcome differences.

Key components of a shock-team program include clear activation criteria, timely access to relevant specialists, shared management protocols, regular reassessment, and review of outcomes and complications. Links with referral centers are also important when advanced support is not available locally [1,57,59]. The effectiveness of a program depends on how these processes work in practice, rather than simply whether a team has been named.

3.7 General Supportive Care: The Details Matter

Beyond specific CS therapies, meticulous attention to general supportive care can significantly impact outcomes.

Ventilatory Support: Many CS patients require mechanical ventilation for pulmonary edema, severe hypoxia, or airway protection. Positive pressure ventilation reduces preload and afterload, potentially improving LV performance, but can also reduce venous return and worsen RV function in preload-dependent states. Lung-protective ventilation (tidal volumes around 6 mL/kg predicted body weight in patients with acute lung injury or acute respiratory distress syndrome (ARDS)) should be used to prevent ventilator-induced lung injury [60].

Renal Support: AKI is common in CS and is associated with worse outcomes [19]. Management includes reassessing perfusion and congestion, limiting avoidable nephrotoxic exposure, and monitoring urine output, creatinine, electrolytes, and acid–base status. Renal replacement therapy may be needed for refractory fluid overload or severe metabolic complications, with the modality chosen according to hemodynamic stability and clinical needs

[1,2]. Biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL) may identify kidney injury before a diagnostic rise in creatinine, although evidence from broader critically ill populations should not be treated as validation of a CS-specific treatment strategy [61].

Nutrition: Enteral nutrition should be considered after resuscitation has achieved adequate and sustained perfusion, with cautious advancement according to tolerance. Ongoing hemodynamic instability or escalating vasopressor requirements may warrant delaying feeding because of concern for intestinal ischemia. The route and timing of nutritional support should be individualized rather than determined by a fixed time interval alone [62].

Glycemic Control: Stress hyperglycemia is common in CS and associated with worse outcomes. Insulin infusion protocols targeting glucose 140–180 mg/dL are recommended, avoiding tight control which increases hypoglycemia risk [1,63].

Thromboprophylaxis: Assess venous thromboembolism and bleeding risk throughout the admission. Pharmacological prophylaxis is generally considered when bleeding risk permits, while accounting for any therapeutic anticoagulation already required for another indication or support device [1].

Stress Ulcer Prophylaxis: Patients with shock or coagulopathy are at increased risk of clinically important stress-related gastrointestinal bleeding. A proton pump inhibitor or H2-receptor antagonist may be used when this risk justifies prophylaxis, with treatment reassessed and discontinued when the indication resolves [64].

Sedation and Delirium: Pain assessment, an analgesia-first approach, light sedation when feasible, and repeated delirium screening support recovery. Sedation interruption and mobilization should be adapted to hemodynamic stability and device-related constraints. Sedative selection requires attention to blood pressure and heart rate; dexmedetomidine can cause hypotension and bradycardia, so its use requires careful titration [65].

4. Emerging Directions: Toward Personalized Medicine

The future of CS management lies not in a single "magic bullet" therapy, but in a personalized approach that recognizes the heterogeneity of the syndrome and tailors interventions to the individual patient's phenotype, trajectory, and goals.

4.1 Phenotype-Driven Therapy: Moving Beyond the One-Size-Fits-All

The recognition that CS encompasses distinct clinical phenotypes represents a major conceptual advance. Rather than treating all shock patients identically, we can begin to categorize them based on dominant pathophysiological features and target therapies accordingly.

Machine learning studies have identified reproducible CS phenotypes. Zweck and colleagues [66] initially analyzed 1959 patients across international cohorts and described three groups: noncongested, cardiorenal, and cardiometabolic shock. A later CSWG analysis examined their clinical course in a separate cohort [67]:

- Phenotype 1 (Noncongested): Characterized by less marked congestion and fewer metabolic disturbances than the other groups. Its relatively lower observed mortality does not, by itself, identify which patients will benefit from MCS [66,67].

- Phenotype 2 (Cardiorenal): Marked by renal dysfunction and congestion. It highlights the importance of assessing volume status and kidney function, without establishing a separate evidence-based threshold for renal replacement therapy [66,67].

- Phenotype 3 (Cardiometabolic): Characterized by more severe metabolic and organ dysfunction and higher mortality. It is not interchangeable with an isolated inflammatory phenotype, and its identification does not establish that immunomodulatory treatment will improve outcomes [66,67].

In the later CSWG cohort, 1890 patients were evaluated and 796 had sufficient data for retrospective phenotype assignment. Mortality was 23%, 41%, and 52% in the noncongested, cardiorenal, and cardiometabolic groups, respectively [67]. These findings support reproducible prognostic differences, but the observational associations with treatment do not establish phenotype-specific treatment effects. Prospective validation of management strategies is needed before phenotype assignment can direct routine therapy.

Biomarker-guided assessment is a logical extension of this approach. Beyond lactate, several biomarkers may contribute to risk assessment, although their evidentiary basis and clinical readiness differ [68]:

- Interleukin-6 (IL-6): An inflammatory marker associated with outcomes in AMI-CS; a universal treatment threshold has not been established [10].

- Growth differentiation factor-15 (GDF-15): Reflects cellular stress and disease burden and has prognostic associations across cardiovascular disorders. Its role in guiding CS treatment requires further study [68,69].

- Soluble ST2 (sST2): Part of the IL-33/ST2 pathway and associated with myocardial stress and remodeling. Its prognostic use should be distinguished from evidence that acting on the result improves outcomes [68,70].

- Neutrophil gelatinase-associated lipocalin (NGAL): May identify subclinical kidney injury before creatinine rises, but performance depends on the clinical setting and assay [61].

- Soluble urokinase-type plasminogen activator receptor (suPAR): A marker of immune activation associated with 90-day mortality in an observational CardShock sub-

study. The result is promising for risk assessment but does not establish a routine treatment indication [71].

- High-sensitivity cardiac troponin and creatine kinase-MB (CK-MB): Reflect myocardial injury and should be interpreted with the clinical presentation, ECG, coronary findings, and other organ-function measurements. Risk assessment in acute coronary syndromes combines clinical variables rather than relying on an isolated biomarker cutoff [68,72].

- N-terminal pro-B-type natriuretic peptide (NT-proBNP) or B-type natriuretic peptide (BNP): Reflect ventricular wall stress, but concentrations are also affected by renal function and other clinical factors. Their prognostic performance in CS varies, so fixed cutoffs should not be used as stand-alone triggers for treatment [68].

Integration of these biomarkers into clinical decision-making may improve risk assessment and monitoring, but treatment selection based on biomarker profiles requires prospective evaluation [68].

4.2 Pulsatility and Microcirculation: The Unresolved Question

The natural heart generates pulsatile flow, whereas many MCS devices produce continuous or largely non-pulsatile flow. This changes vascular pressure and shear patterns and has prompted interest in effects on the microcirculation. Studies in cardiopulmonary bypass suggest possible physiological advantages of pulsatile perfusion, but their results cannot be assumed to apply directly to patients receiving prolonged MCS for CS [73].

During VA-ECMO, reduced native LV ejection may diminish arterial pulsatility. The relationship between support flow, LV loading, aortic valve opening, and tissue perfusion is complex [46]. The SynCor study evaluated ECG-synchronized pulsatile support in 47 patients, including 13 with CS, and demonstrated technical feasibility [74]. Its observational design and small CS subgroup do not establish a comparative survival or organ-protection benefit. Whether pulsatile support improves clinically important outcomes therefore remains unresolved.

Whether restoring pulsatility during MCS should be a therapeutic goal—via partial LV unloading, intra-aortic balloon pump addition, or novel pulsatile devices—remains an open question that warrants dedicated investigation in CS populations [46,74].

4.3 Advanced Monitoring and Artificial Intelligence

The complexity of CS generates vast amounts of data—hemodynamic waveforms, laboratory values, imaging findings, and clinical parameters that evolve continuously. The human mind struggles to integrate all this information into a coherent framework for real-time decision-making. Artificial intelligence (AI) and machine learning offer the potential to change this. Machine learning algorithms can be trained to identify patterns in high-dimensional data that predict deterioration or response to therapy. By integrating continuous hemodynamic monitoring (arterial pressure waveforms, central venous pressure (CVP), pulmonary artery pressures) with intermittent laboratory values and clinical assessments, these systems could provide early warning of impending decompensation and support treatment decisions, although clinical benefit requires prospective evaluation [75,76].

Several AI applications that are currently under development are:

- Predictive Models: Models may estimate deterioration, mortality, or the need for support escalation from clinical data. A systematic review of machine learning in CS identified encouraging predictive performance, but emphasized the need for stronger clinical validation [75].

- Treatment Response Prediction: Models that predict which patients are most likely to benefit from specific interventions (e.g., Impella vs. ECMO, early LV unloading) based on their unique characteristics. This remains a research goal rather than an established treatment-selection method [76].

- Hemodynamic Optimization: Closed-loop systems that automatically adjust vasopressor and inotrope infusions based on real-time hemodynamic targets. While still investigational, such systems would need prospective safety testing and validation in CS before clinical adoption [17,76].

- Image Analysis: Deep learning can assist with echocardiographic view identification, chamber segmentation, and quantification of ventricular structure and function. Zhang and colleagues [77] demonstrated an automated interpretation pipeline in a large echocardiographic dataset, but it was not a validation of autonomous management in CS.

The promise of AI in CS is to help clinicians interpret complex information while retaining responsibility for individual decisions. The 2024 American Heart Association scientific statement addresses AI across heart disease, rather than providing a CS-specific management protocol. It emphasizes validation, bias, implementation, and the gap between predictive performance and demonstrated clinical benefit [76].

4.4 Novel Pharmacotherapies: Expanding the Arsenal

While mechanical support has dominated recent attention, important pharmacological advances are also on the horizon.

- Selatogrel: This subcutaneous P2Y12 inhibitor produces rapid platelet inhibition and may offer a useful route when oral treatment is delayed. A phase 2 study in 47 patients with AMI demonstrated a rapid, dose-related antiplatelet response [78]. These pharmacodynamic findings do not establish efficacy or reliable absorption in CS, where peripheral hypoperfusion may also affect subcutaneous delivery. Its role in the shock population remains to be defined.

- SGLT2 Inhibitors: These agents have established roles in heart failure, but evidence from stabilized acute heart failure should not be extrapolated to active CS. EMPA-RESPONSE-AHF was a small pilot study whose primary symptom and diuretic-response outcomes were neutral, although exploratory clinical findings were encouraging [79]. EMPULSE showed clinical benefit when empagliflozin was started after in-hospital stabilization; patients with CS were excluded [80]. Use during recovery therefore requires a different assessment from initiation during ongoing shock.

- Omecamtiv Mecarbil: As a cardiac myosin activator, omecamtiv mecarbil offers an approach distinct from catecholamine-mediated inotropy. In GALACTIC-HF, involving patients with chronic heart failure with reduced ejection fraction (HFrEF), it modestly reduced the composite of a first heart-failure event or cardiovascular death, but did not reduce cardiovascular mortality alone [81]. This does not establish efficacy in CS, and its potential role in acute low-output states requires dedicated evaluation.

- Immunomodulatory Therapies: Inflammation is a plausible therapeutic target, but it also contributes to tissue repair. In VCUART3, anakinra reduced the inflammatory response after STEMI, providing evidence of biological activity rather than proof of benefit in CS [82]. Targeted cytokine or complement inhibition remains investigational for shock. Appropriate patient selection, timing, and the risk of infection or impaired healing must be addressed before such approaches can become routine [2,17].

The challenge with immunomodulation lies in timing: inflammation in CS is both harmful (contributing to tissue injury) and necessary (promoting healing). Intervening too early or too aggressively could impair recovery [9].

4.5 Remote Monitoring and Post-Shock Rehabilitation

Surviving the initial shock hospitalization is only the beginning of recovery. Patients may face physical weakness, cognitive difficulties, psychological distress, and recurrent cardiovascular illness. However, CS-specific estimates of these problems remain limited, and findings from other intensive care unit (ICU) populations should not be presented as fixed incidence rates in CS survivors [83].

The concept of "post-shock rehabilitation" extends the multidisciplinary approach beyond the hospital walls. Structured rehabilitation protocols addressing physical conditioning, nutritional support, medication optimization, and psychological counseling could improve long-term outcomes for survivors. Key components of post-shock rehabilitation include [83]:

- Cardiac Rehabilitation: Consider individualized rehabilitation after stabilization, taking account of residual heart failure, frailty, and exercise tolerance. Evidence specific to rehabilitation after CS remains limited [83].

- Cognitive Screening and Rehabilitation: Brief screening can identify patients who need neuropsychological assessment or additional support. CS-specific prevalence and the effectiveness of dedicated cognitive interventions need further study [83].

- Psychological Support: Screen for anxiety, depression, and trauma-related symptoms, with referral when indicated. The frequency and best treatment of these problems after CS are not yet well defined [83].

- Medication Optimization: Careful titration of guideline-directed medical therapy for heart failure (β-blockers, angiotensin converting enzyme (ACE) inhibitors/angiotensin receptor blocker (ARB)/angiotensin receptor-neprilysin inhibitor (ARNI), MRAs, SGLT2 inhibitors) during recovery is crucial. The transition from acute to chronic therapy requires careful coordination [84].

- Device Management: For patients discharged with durable LVADs or ICDs, structured education and follow-up are essential to prevent complications and rehospitalizations [83,84].

Wearable sensors and remote monitoring may help detect changes in heart rate, activity, and other physiological measurements after discharge. In LINK-HF, a multisensor patch and analytical platform identified precursors of heart-failure hospitalization with 76–88% sensitivity and 85% specificity [85]. The study was conducted after HF hospitalization, not specifically in CS survivors. Whether similar monitoring improves outcomes after CS remains to be tested, but integration with follow-up care and a clear clinical response pathway offers a reasonable direction for research.

5. Conclusion: The Road Ahead

Cardiogenic shock management has evolved considerably from the era of passive acceptance of high mortality. We have moved from a simplistic "pump failure" model to an appreciation of the syndrome's breathtaking complexity. We have learned that resuscitation must address not only the macrocirculation but also the microcirculation, not only hemodynamics but also inflammation and metabolism, not only the heart but also the brain, kidneys, liver, and immune system.

The recent positive DanGer Shock trial represents a milestone, showing that Impella CP can improve 180-day survival in the selected STEMI-CS population studied [44]. Yet mortality remains unacceptably high, and the road ahead requires continued progress on multiple fronts:

- Early Recognition: The shock team cannot help patients who are not identified. Better tools for early detection—in the emergency department, on the wards, and even in the prehospital setting (using machine learning algorithms applied to electronic health records or wearable device data)—are needed to initiate care before irreversible organ injury occurs. The "golden hours" of CS are as critical as those in trauma or stroke [86].

- Refined Phenotyping: We must move beyond "one-size-fits-all" treatment protocols to personalized ap-

proaches that match therapy to the individual patient's dominant pathophysiological drivers. This requires integrating clinical, hemodynamic, biomarker, and genomic data into actionable classification systems. The SCAI staging system is an important first step, but more granular phenotyping is needed.

- Rigorously Evaluated Technology: New devices and drugs require careful evaluation before widespread adoption. Neutral trials of routine IABP and early VA-ECMO illustrate why better hemodynamics alone cannot be assumed to improve survival [40,49]. Pragmatic trials, registry-based randomization, and adaptive designs may help answer remaining treatment questions [87].

- Complication Prevention and Management: As we use more powerful support technologies, complication rates rise. Reducing bleeding, thrombosis, infection, and vascular complications requires meticulous technique, standardized protocols, and continuous quality improvement. Registry data associate higher ECMO center volume with lower adjusted mortality, but do not establish a single volume threshold or a causal effect of a center designation [88].

- Equitable Access: Access to advanced CS care is not uniform. Rural hospitals, low-volume centers, and underserved communities may lack shock-team and MCS resources. Regional referral networks, early specialist communication, and clear transfer pathways can help patients reach appropriate care. The American Heart Association (AHA) scientific statement on contemporary CS management advocates regionalized systems while recognizing the need to evaluate their outcomes [1].

- Patient-Centered Outcomes: Survival is not enough. We must measure and optimize functional recovery, quality of life, cognitive function, and psychological well-being. The ultimate goal is not merely to discharge patients alive, but to return them to meaningful lives. Patient-reported outcomes should be integrated into research and clinical care [89].

The future of CS management is bright, but realizing its promise requires continued collaboration between clinicians, researchers, industry partners, and most importantly, patients and their families. The complexity of the syndrome demands a corresponding complexity in our response: multidisciplinary, technologically sophisticated, and deeply human.

This patient-centered perspective is essential in cardiogenic shock: survival, functional recovery, and the patient's own goals should guide how success is defined [83,89].

Author Contributions

KKD and GZ designed the research study and conceptualized the review framework. KKD performed the literature search, analyzed the relevant publications, and drafted the initial manuscript. GZ critically revised the manuscript for important intellectual content, provided expert guidance on the clinical and pathophysiological interpretation, and supervised the overall work. Both authors contributed to the revision of the manuscript, read and approved the final version, and agree to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflicts of Interest

The authors declare no conflicts of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work, the authors used ChatGPT to assist with language polishing and grammar checking. The conceptual outline of Fig. 1 was developed with the assistance of ChatGPT. After using this tool, the authors reviewed and edited all content as needed and take full responsibility for the publication.

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