Intensive Care Med (2024) 50:1814–1829
https://doi.org/10.1007/s00134-024-07618-x

REVIEW

Management of cardiogenic shock: state-of-the-art

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Abstract

The management of cardiogenic shock is an ongoing challenge. Despite all efforts and tremendous use of resources, mortality remains high. Whilst reversing the underlying cause, restoring/maintaining organ perfusion and function are cornerstones of management. The presence of comorbidities and preexisting organ dysfunction increases management complexity, aiming to integrate the needs of vital organs in each individual patient. This review provides a comprehensive overview of contemporary literature regarding the definition and classification of cardiogenic shock, its pathophysiology, diagnosis, laboratory evaluation, and monitoring. Further, we distill the latest evidence in pharmacologic therapy and the use of mechanical circulatory support including recently published randomized-controlled trials as well as future directions of research, integrating this within an international group of authors to provide a global perspective. Finally, we explore the need for individualization, especially in the face of neutral randomized trials which may be related to a dilution of a potential benefit of an intervention (i.e., average effect) in this heterogeneous clinical syndrome, including the use of novel biomarkers, artificial intelligence, and machine learning approaches to identify specific endotypes of cardiogenic shock (i.e., subclasses with distinct underlying biological/molecular mechanisms) to support a more personalized medicine beyond the syndromic approach of cardiogenic shock.

Keywords: Cardiogenic shock, Intensive care, Myocardial infarction, Heart failure, Assist device, Outcome

Introduction

Cardiogenic shock (CS) is variably defined as a state of end-organ hypoperfusion due to the heart's inability to deliver sufficient oxygen to tissues to meet metabolic demands in the presence of adequate intravascular volume [1, 2]. Acute myocardial infarction-related cardiogenic shock (AMI-CS) was first alluded to over a century ago with description of groups of patients presenting with sudden obstruction of the coronary arteries. Patients in shock were described as "*those cases in which the attack is anginal, the pain severe, the shock profound and death follows in a few minutes or several minutes at the most*" [3]. In 1942, Stead and Ebert described shock, or circulatory collapse, "*as a result of a diminished venous return to the heart. It is characterized clinically by the signs of a marked decrease in cardiac output (CO) and tissue anoxia, namely, pallor, cold extremities, sweating, weak pulse, low arterial blood pressure, narrowing of the field of consciousness, and a normal or decreased venous pressure*" [4]. With the exception of early invasive angiography and percutaneous coronary intervention (PCI) of the infarct-related artery in case of AMI-CS and the lack of substantial outcome effects using percutaneous mechanical circulatory support devices, there is only scarce evidence for other, frequently used interventions, such as the use of vasopressors and inotropic agents,

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fluid management, and general critical care interventions [5–7]. Despite a paucity of robust evidence, attempts to generate better data in recent years have been made. However, execution of high-quality randomized controlled trials (RCTs) in CS is hindered for numerous reasons including a heterogeneous patient population and clinical presentations, significant time pressure in recruitment, challenges in timely identification, and ethical and communication barriers [2, 8].

Definition of cardiogenic shock

The clinical definition of AMI-CS often used in clinical trials is a combination of low systolic blood pressure (SBP) of < 90 mmHg and evidence of low CO (cardiac index [CI] of < 2.2 L/min/m^2) in patients with elevated filling pressures (pulmonary-capillary wedge pressure [PCWP] > 15 mmHg) [5, 9]. The definition is scientifically pragmatic, as it relies on an SBP of less than 90 mmHg for a clinical diagnosis, and invasive hemodynamic assessment is not readily available on initial presentation. The Shock Academic Research Consortium (SHARC) consensus and the American Heart Association defined CS as cardiac disorder that results in both clinical and biochemical evidence of sustained tissue hypoperfusion [1]. Septic and hypovolemic shock also manifests with hypotension and end-organ hypoperfusion, and mixed forms of shock frequently exist simultaneously [2]. Certain patients have clear evidence of reduced CI and elevated PCWP but with an SBP greater than 90 mmHg. In addition to including absolute blood-pressure parameters in the definition of CS, the degree of hypotension relative to the patients preexisting blood pressure should be considered in the diagnosis of CS. In the SHOCK trial registry, 5.2% of patients were in CS but had an SBP > 90 mmHg, and 7.1% had no evidence of organ hypoperfusion with an SBP < 90 mmHg. Yet, both groups of patients had increased mortality [10]. While traditional criteria for CS are based on the presence of hypotension, recent consensus statements defined CS more broadly with the presence of hypoperfusion in patients without hypotension [2]. Normotensive CS phenotype, especially in young patients, are at high risk for significant hemodynamic deterioration and need a specific awareness [11].

The definition of CS including invasive hemodynamics was designated a class IIb, level of evidence B recommendation by the European Society of Cardiology (ESC), given the absence of prospective randomized data [12]. A consensus statement by the American Heart Association (AHA) supports invasive hemodynamic assessment in select circumstances, although it should not delay primary revascularization [13]. Proactive use of invasive hemodynamic monitoring should be considered early in the presentation of CS to guide management and risk prognostication [14]. However, recent RCTs did not require PCWP or other invasive hemodynamic measurements for diagnosis of CS [15–19].

Take-home message

The management of cardiogenic shock is an ongoing challenge with high mortality rates. This review provides a comprehensive overview of contemporary management that includes pharmacologic therapy as well as the use of mechanical circulatory support and gives an outlook to support a more personalized medicine beyond the syndromic approach of cardiogenic shock.

Pathophysiology, clinical and hemodynamic phenotypes

The initiating event in CS is a significant alteration of cardiac function, with the resultant reduction in CO and elevation in filling pressures perpetuating myocardial ischemia, further exacerbated by reduction in aortic root pressure ultimately leading to impaired myocardial perfusion (increased left-ventricular pressure and decreased diastolic pressure). Compensatory vasoconstriction leads to coronary/systemic vascular bed dysfunction, potentially worsening myocardial and other organ ischemia [2]. CS can additionally precipitate a systemic inflammatory response, resulting in pathological peripheral vasodilation and altered microcirculation via release and activation of reactive oxygen species, pro-inflammatory cytokines, and activation of damage-associated molecular patterns. Therefore, beyond the traditional cardiocentric approach, CS is increasingly recognized as a systemic disease resulting in multi-organ dysfunction [20, 21]. These pathophysiological events are part of the downward spiral in CS. In the light of the fact that these events happen in a rapid sequence and stepwise worsen the prognosis [22], it is of paramount importance to therapeutically support the patient at the top of the CS spiral, rather than at the bottom to interrupt the chain of events. Importantly, the hallmark characteristic of heart failure-associated CS is congestion [23].

Heterogeneity of the CS clinical syndrome

Traditional approach: clinical/hemodynamic profiles

The traditional approach to CS classifies patients according to underlying etiology, timing (acute vs. acute-on-chronic), hemodynamic profile, and the extent of organ dysfunction [24]. CS related to AMI-CS now represents less than one-third of cases, with the majority related to acute decompensation in chronic heart failure [25]. As patients with chronic heart failure may have better-adapted compensatory mechanisms than those presenting with de novo pathology, the outcomes in these groups differ significantly [26]. Further, hemodynamic profiles vary widely with respect to CO, systemic vascular

resistance (SVR), and cardiac filling pressures, depending on the underlying pathology and acuity and different treatment strategies [2]. Most CS patient present with low CO with cold extremities, high SVR, and cardiac filling pressures. Patients with CS may also be euvolemic with a low CO; predominantly seen in acute-on-chronic heart failure. Vasodilatory CS is associated with a systemic inflammatory response and higher mortality risk [27]. Right-ventricular (RV) and biventricular dysfunction are associated with worse clinical outcomes when compared to isolated left-ventricular systolic dysfunction. The hemodynamics and ventricular/pulmonary involvement impact choice of monitoring and therapeutic strategies including the use of acute mechanical circulatory support (MCS) [24, 28].

Current/emerging approach: SCAI shock severity staging

The Society for Cardiovascular Angiography and Interventions (SCAI) cardiogenic shock (SCAI-CS) staging system was designed to provide a simple and standardized approach to classifying CS according to its severity, ranging from A-E [8]. Briefly, SCAI-CS stages are A (stable patients with acute cardiac conditions putting them at risk of CS), B (pre-shock with hypotension), C (classical shock with signs of hypoperfusion), D [deteriorating despite adequate initial supportive intervention(s)], and E (extreme shock). Numerous observational studies have confirmed the association between SCAI stage and mortality. Cardiac arrest constitutes a specific feature variable. An updated SCAI-CS staging system was subsequently published, recommending more in-depth phenotyping, including risk factors (largely unmodifiable), vasopressor/inotrope score, degree of metabolic derangement, acuity of onset, and uni-/biventricular pathology with/without pulmonary involvement [29]. Although a significant advance in stratification, several limitations to the SCAI staging exist, including that the classified severity can by highly dynamic, the response to interventions can be variable (beneficial/neutral/detrimental), and the timing of assessed/re-assessment lacks consensus, especially when considering its use for clinical trial inclusion criteria [30]. The SCAI classification does not encounter shock etiology nor age. It is also important to note that the conditions of CS change rapidly and that these temporal changes can hardly be reflected in a rigid classification. Another limitation of the SCAI classification is that multiple elements within the staging remain subject to variable interpretation.

Future approach of CS: biological/biomarker-driven phenotypes

The clinical and severity approaches fail to fully address the underlying mechanistic signatures, impact of CS biological heterogeneity, and the host response [31]. Recent research based on host–response biomarkers highlighted important molecular heterogeneity (i.e., inflammation, myocardial fibrosis, and endothelial dysfunction) within the spectrum of CS [32, 33]. Advances in artificial intelligence (AI) and machine learning are providing interesting avenues for the future; unsupervised machine learning (i.e., agnostic to outcome) identifies different classes in CS patients ("non-congested", "cardiorenal", and "cardiometabolic") based on readily available laboratory data [34, 35] associated with early mortality independently from the SCAI classification [36]. Improved biological data granularity with omics-based biomarker together with AI may identify further CS phenotypes reflecting different underlying mechanistic signatures (i.e., endotypes), not apparent for the clinician at the bedside [37–40]. These endotypes may allow prognostic and predictive enrichment (i.e., identifying those patients most likely to benefit from a given intervention) and a biological fingerprint that may suggest personalized therapy, including immunomodulation [24, 40] and parallels the paradigm shift in critical care medicine overall, moving from syndromes, to an individualized patient approach (Fig. 1).

Diagnosis and laboratory evaluation

The diagnosis of CS should integrate findings from the presenting symptoms, physical examination, hemodynamic and laboratory parameters, as well as imaging modalities and be based on the definition provided above [29]. Laboratory evaluation of CS is mostly based on markers of tissue hypoperfusion and end-organ damage. Lactate represents the reference standard in laboratory assessment of tissue hypoperfusion and hypoxia [41, 42]. While rising lactate levels are associated with poor outcomes, the evidence for lactate clearance as a biomarker of outcome is less clear [43–46]. The tissue mismatch in oxygen demand and delivery in CS results in low oxygen saturations in blood returning to the heart which can be measured as mixed venous oxygen saturation (SvO_2) from the distal port of a pulmonary artery catheter (PAC) or as central venous oxygen saturation ($ScvO_2$) from a central venous catheter in the superior vena cava. Both SvO_2 and $ScvO_2$ are markers of oxygen delivery/consumption imbalance and thus indirectly of inadequate CO [47]. Arterio-venous difference in CO_2 from sampling of mixed/central venous and arterial blood may be also used to detect patients with inadequate CO (i.e., delta $CO_2 \geq 6$ mmHg [48, 49]). However, the evidence to use this parameter is still limited. Arterial blood gas measurement provides further information and guidance on oxygenation and ventilation, acid–base disorders, electrolytes, and metabolic status.

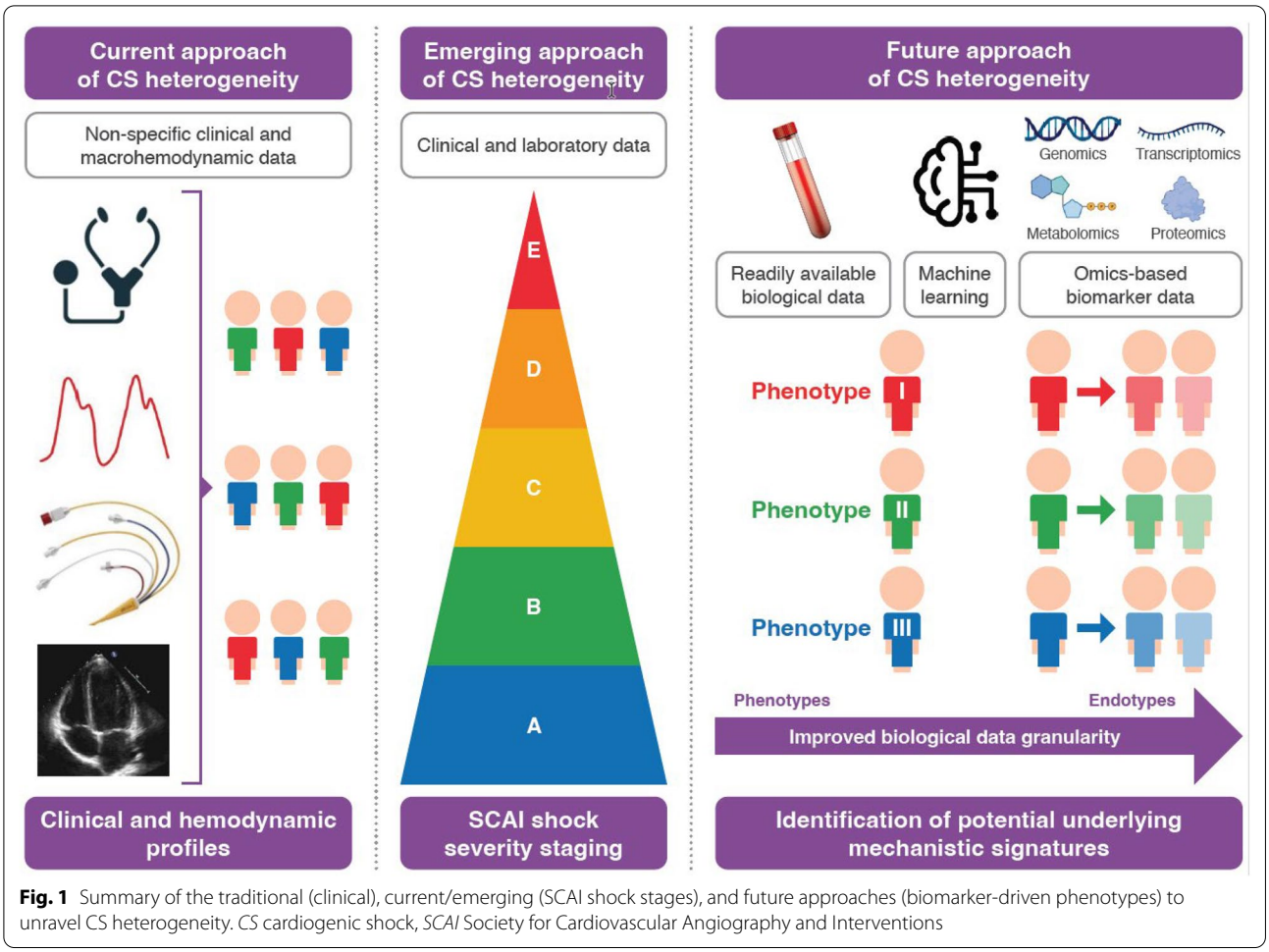


Fig. 1 Summary of the traditional (clinical), current/emerging (SCAI shock stages), and future approaches (biomarker-driven phenotypes) to unravel CS heterogeneity. *CS* cardiogenic shock, *SCAI* Society for Cardiovascular Angiography and Interventions

In addition, biomarkers reflecting organ damage should be measured at least daily to detect and monitor damage in perfusion-sensitive organs. Daily measurement of serum creatinine together with urine output will aid in the detection of acute kidney injury [50] along with novel kidney biomarkers [51], if readily available. Patients with CS who suffer ischemic hepatitis have a poor prognosis. [52, 53]. Liver impairment can also be observed as congestive hepatopathy in CS. Natriuretic peptides (NT-proBNP) and markers of myocardial injury (cardiac troponins, see Table 1) may provide additional prognostic information in addition to underlying pathophysiology [15, 54, 55]. Complete blood count, standard metabolic panels, as well as coagulation laboratories need to be drawn frequently especially in patients treated with MCS.

Hemodynamic monitoring

Routine non-invasive (hemodynamic) monitoring for patients admitted with CS includes continuous electrocardiogram monitoring, pulse-oximetry, and monitoring of respiratory rate. Measurement of central venous pressure, invasive arterial blood-pressure monitoring, and urine output are considered standard invasive monitoring in CS [2, 5]. Of potential interest is also the determination of end-tidal carbon dioxide ($ETCO_2$) in ventilated patient with CS indicative for impaired circulation and outcome [56]. PAC placement allows direct measurement of cardiopulmonary pressures and mixed venous saturation used for the calculation of vascular resistances and CI [16]. Routine use of PACs went out of vogue following no survival benefits demonstrated in RCTs—not specifically in CS—during the early 2000s, although inclusion and exclusion criteria of the relevant trials in the field are a matter of debate, as many of them excluded CS patients. However, with protocol-based management of CS becoming more standardized, it is becoming imperative that the use of PAC to derive cardiac power output (CPO) and pulmonary artery pressure index can stratify severity of shock early and guide advanced therapy in CS with improved clinical outcomes, leading to a resurgence in the use of such

Table 1 Overview of laboratory assessment and hemodynamic monitoring

Management	Comment	Frequency
Biomarkers		
Lactate	Marker of tissue hypoperfusion and hypoxia	As clinically indicated, at least every 4–8 h
$ScvO_2/SvO_2$	Central venous/mixed venous oxygenation as a marker of inadequate oxygen delivery/consumption match	As clinically indicated, ideally at least every 8 h
Arterial blood gas analysis	Blood gases, oxygen saturation, blood pH, base excess, bicarbonate, electrolytes, lactate, electrolytes, hemoglobin, glucose	As clinically indicated, at least every 4–8 h
Serum creatinine	Marker of kidney perfusion and acute kidney injury, together with urine output and creatinine clearance	Daily
AST/ALT (GOT/GPT) INR	Marker of ischemic hepatitis	Daily
Complete blood count	Hemoglobin, white blood cell count, platelet count	At least once daily unless bleeding or having other complications
Coagulation parameters	PT, aPTT, thrombin time, fibrinogen, D-Dimer, INR, anti-Xa, pfHb	At least once daily unless need for therapeutic anticoagulation or on MCS treatment
Comprehensive metabolic panel	Blood sugar, electrolytes, Urea or BUN	At least once daily unless clinically indicated
Hemodynamic monitoring		
ECG monitoring		Continuous
Pulse-oximetry		Continuous
Respiratory rate		Continuous
Arterial blood pressure		Continuous
Central venous pressure		Continuous
Urine output		Continuous
Echocardiography	Bedside TTE / TOE for diagnostic purposes and cardiac output measurement based on LVOT VTI	At admission, every 24–48 h and when clinically indicated – for patients on MCS daily TTE should be considered
Non-invasive and minimally invasive cardiac output monitoring devices		Selective use
PAC		Selective but liberal use, repeated measures every 4–6 h

$ScvO_2$ central venous oxygen saturation, *SvO_2* mixed venous saturation, *AST* aspartate transaminase, *ALT* alanine transaminase, *GOT* glutamic oxaloacetic transaminase, *GPT* glutamate pyruvate transaminase, *PT* prothrombin time, *aPTT* activated partial thromboplastin time, *MCS* mechanical circulatory support, *ECG* electrocardiogram, *TTE* transthoracic echocardiogram, *TOE* transesophageal echocardiogram, pulmonary artery catheter, *LVOT* left-ventricular outflow tract, *VTI* volume time integral, *INR* international normalized ratio, *pfHb* plasma free hemoglobin, *PAC* pulmonary artery catheter

monitors [2, 5, 17–19]. Furthermore, PAC repeated measures can give aid in the dynamic decongestion in CS [57]. It has been shown that the use of PAC in experienced hands is associated with improved outcomes. In addition, the quantification and potential pharmacological reduction of the systemic vascular resistance has a role in the management of CS patients. While a number of parameters can be derived from the PAC, CPO has strong diagnostic and prognostic values [58], and pulmonary artery pulsatility index (PAPi) helps further characterization of right heart function. Several minimally or non-invasive CO techniques are available, but evidence in favor of routine application is scarce [59]. In the hands of a trained clinician, transthoracic and transesophageal echocardiography (TTE and TOE) is not only a diagnostic tool but also a reliable, readily available, non-invasive modality to measure CO, its changes [60, 61], and other parameters of cardiac function [62]. The application of echocardiography varies across centers in the light of the scarce evidence; however, the velocity time integral and its change over the treatment course in the left-ventricular outflow tract is a reliable tool to assess cardiac output [63].

Contemporary outcomes

As CS is a final common pathway for many acute and chronic cardiac pathologies, including AMI, myocarditis, valvular disease, acute decompensated heart failure, and arrhythmias, estimating both incidence and outcome is challenging. Typical surgical reasons for intra- or peri-operative CS that lead to (unplanned) extracorporeal life support (ECLS)-implant are isolated coronary artery bypass grafting (CABG), isolated valve surgery, thoracic aorta surgery, and a combination of CABG and valve surgery or other surgery leading to an intra-hospital

mortality of 63% [64]. In AMI-CS, mortality rates have been stable at around 40–50%, in both registry data and RCTs [65–71]. Although prior to reperfusion therapies mortality rates exceeded 80% [72]. A lack of uniformity of definitions, even among RCTs, further limits reliable analysis of temporal trends. However, there is likely an increasing incidence of acute decompensated heart failure-related CS (ADHF-CS) among patients with long-standing ventricular failure [73, 74]. As most RCTs have not included these patients, there is a paucity of data regarding both management and outcomes. Mortality rates appear to be similar to AMI-CS, but with longer hospital stays, a higher likelihood of need for biventricular support and tailored therapies [75, 76].

Causal treatment

Causal treatments aim at correcting the underlying pathology and include acute surgical or percutaneous valve interventions in, for example, acute aortic regurgitation in bacterial endocarditis or acute mitral regurgitation [77]. In most cases of CS, stabilization with vasopressors and inotropes while continuously assessing the need for MCS or heart transplantation remains the most common clinical strategy. In AMI-CS characterised by ischemia and profound depression of myocardial contractility, the therapeutic focus is on immediate revascularization [78]. This is based on the pivotal SHOCK trial [79] in which 6-month mortality was significantly reduced for patients who were randomized to early revascularization compared to standard care. In case of obvious revascularization indication such as ST-Segment Elevation Myocardial Infarction (STEMI) prehospital activation of PCI and also CS teams has potential to improve management. In the current ESC guidelines on acute coronary syndrome (ACS), this yields a 1B recommendation for immediate coronary angiography and PCI of the infarct-related artery or emergency coronary bypass grafting if PCI is not feasible [80]. Together with the recommendation for infarct-related artery (IRA)-only PCI during the index procedure, based on the CULPRIT-SHOCK trial, these are the only beneficial treatments recommended by guidelines based on RCT-level evidence. It seems that complete revascularization benefits do not outperform harm by increased procedural duration and contrast medium use in CS patients. Overall, treatment and (causal) management should be performed by a multidisciplinary team to plan the treatment and its order. Cardiogenic shock teams enhance early identification, phenotyping, and appropriate management, thereby improving outcomes in CS. [81]. Tavazzi et al. illustrated that CS management is heterogeneous and often not adherent to current recommendations [82] which could also be improved by dedicated teams [83].

Cardiac arrest

Cardiac arrest (CA) is the extreme stage of the spectrum in CS and concomitant CA with CS is common. Roughly half of all CS patients experience a CA before their hospitalization [84]. Conversely, CS is common after CA, due to a combination of the condition that caused the CA, and myocardial stunning due to global ischemia [85]. Data from CA studies on blood-pressure targets might offer some insights on vasopressor use in CS. There is a known correlation between vasopressor use and mortality in CS, but if there is a causative factor is unknown [86]. In patients without return of spontaneous circulation (ROSC), extracorporeal cardiopulmonary resuscitation (ECPR) implementation constitutes a treatment option helping stabilization of these patients [87] in selected patients. However, the current evidence is heterogeneous with a negative multicentre trial [87]. More trials and research are needed in this field.

Resource use

Costs associated with CS are spread over the cardiac catheterization laboratory, cardiac intensive care unit (CICU), and rehabilitation, while total healthcare burden has been poorly described. One European study described an average cost of 17,000 € per patient, mainly incurred by hospital-stay-related costs, implying a substantial societal cost. However, treatment had a low ratio of cost per life-year gained (9,632 €) [88]. Very high costs have also been confirmed in cohorts from North America [89], although the range is very wide: $15,540–$239,373 [90]. Of note, patients treated at centres with multidisciplinary CS shock teams had a shorter median intensive care unit (ICU) length of stay and were less frequently treated with mechanical ventilation or new renal replacement therapy, hence with lower treatments costs [91]. Considering the high resource use, management of CS in resource limited settings is even more challenging. However, implementation of protocolised management and other comparably cheap management tools can improve outcome and are possible in resource limited settings. Nevertheless, there is also evidence that advanced circulatory support programs can be successfully implemented in a limited resource country [92].

Pharmacologic management of CS

Pharmacologic management of CS (Fig. 2) can be divided into specific-causal and supportive drugs. Of note, not all drugs are available globally and their use is restricted to certain countries. In AMI-CS, for example, AMI is the causal trigger [80]. Drugs may help reducing the infarct area, and afterwards keeping the vessel open [93]. In AMI-CS, the myocardium not affected by the infarction

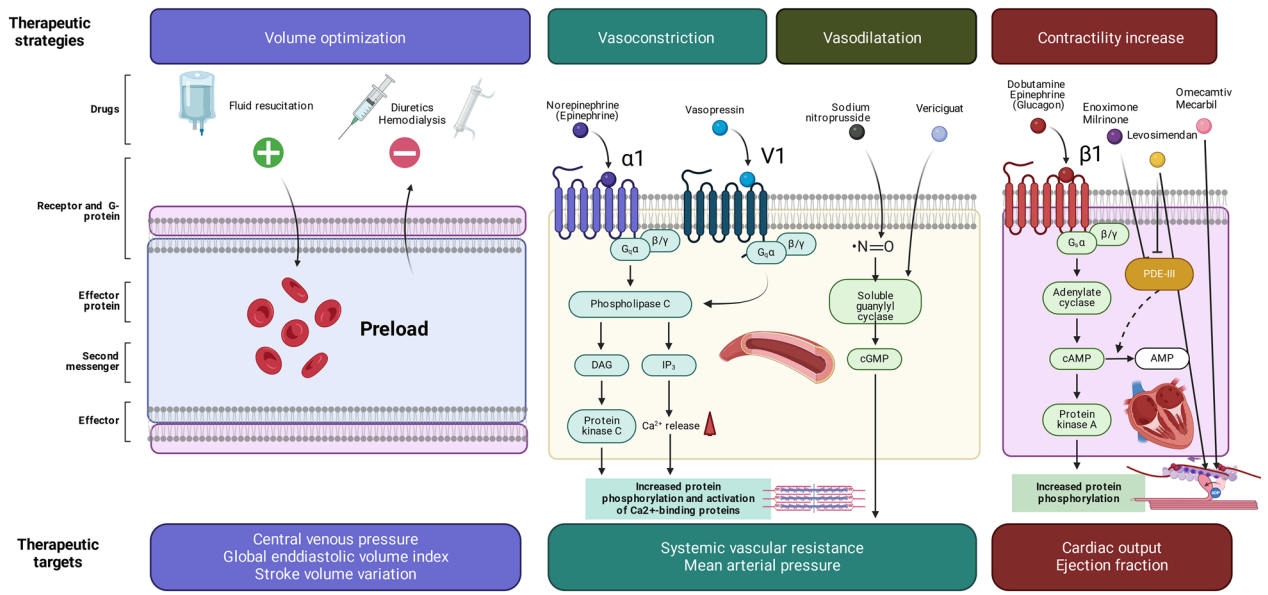


Fig. 2 Therapeutic strategies, pharmacologic mechanisms, and potential treatment targets in cardiogenic shock. *AMP* Adenosine Monophosphate, *Beta 1* β1 Adrenergic Receptor, *cAMP* Cyclic Adenosine Monophosphate, *cGMP* Cyclic Guanosine Monophosphate, *DAG* Diacylglycerol; Gs α- Stimulatory G protein α subunit, *Gs β/γ* Stimulatory G protein β/γ subunit, *Gq α* Gq alpha subunit, *Gq β/γ* Gq beta/gamma subunit, *IP3* Inositol Trisphosphate, *PDE-III* Phosphodiesterase-III, *V1* Vasopressin receptor subtype 1 (V1 receptor), *α1-Receptor* α-1 Adrenergic Receptor

can be functional and compensatory hypercontractile. Acute inflammatory myocarditis might need immunosuppressive therapy. However, most cases of CS share some general aspects of supportive pharmacologic management of CS. Basically, stroke volume as key parameter in CS depends on preload, afterload, contractility, and heart rate. All these single factors can pharmacologically be influenced both in one direction or another. There is growing evidence from observational data that complete hemodynamic phenotyping might be associated with improved outcome in CS [94].

The most common way to optimize preload is fluid management (see Fig. 2, left part). Targeting pharmacological "decongestion" through enhanced salt and water excretion is a rational approach to improve outcomes and symptoms. Diuretics, by and promoting the excretion of water, sodium, and chloride, reduce ventricular filling pressures, fluid retention, and pulmonary edema in case of volume overload. Intravenous loop diuretics also induce rapid vasodilation, decreasing right atrial pressure and PCWP which had been associated with improved outcomes when the patient achieved euvolemic status [57], although high boluses carry the risk of reflex vasoconstriction. Intravenous loop diuretics (e.g., furosemide, bumetamide, or torsemide depending on local availability) are the most used diuretics in this context without any difference having been demonstrated between them to date in the context of acute heart failure. The use of dual therapy or triple therapy by combining hydrochlorothiazide or acetazolamide and/or a mineralocorticoid receptor antagonist seems interesting to reduce congestion more quickly and effectively even if a transient deterioration in renal function is possible [95–97]. However, careful diuresis avoiding hypovolemia is crucial. Dynamic testing of preload sensitivity such as passive leg raising may help predict fluid responsiveness. When addressing central hypovolemia without congestion and improved hemodynamics following a leg raise test, crystalloid solutions are beneficial.

Afterload depends primarily on resistance vessels (arterioles, see Fig. 2 middle part) and left-ventricular wall stress. Vasopressors are the primary agents for stabilizing systemic vascular resistance by increasing blood pressure, aiming to enhance perfusion to vital organs—in CS particularly through raising diastolic pressure for improved coronary artery perfusion. The most commonly used vasopressor is norepinephrine (noradrenaline) [98], which is both recommended from the ESC and AHA [7], although a rather low level of evidence [2]. However, its use should be limited to the shortest duration and lowest dose, because escalating vasopressor requirement is linked to higher mortality in AMI-CS [99]—independently from the CPO [100–102]. Norepinephrine has vasoconstricting and inotropic effects [103]. Theoretically, this might lead to an increased left-ventricular afterload and myocardial oxygen consumption. Vasopressin

as alternative does not offer positive inotropic effects and might be associated with coronary vasoconstriction [104], but it might offer advantages in selected patients with pulmonary hypertension because of its lower effect on the pulmonary vascular resistance [105, 106]. Dopamine is not first-line therapy in many etiologies [107]. Left-ventricular afterload can be lowered by vasodilators especially in case of documented increased SVR (nitrates, nitroprusside sodium, and natriuretic peptides) that are commonly used in acute heart failure although there are no RCTs in CS and even though their handling and management are more difficult in CS context. Also, diuretics can effectively support decongestion management in case of hypervolemia.

Contractility can positively be modified using inotropes (see Fig. 2, right part), although their impact on the outcome remains a topic of ongoing debate. The choice of first-line inotropes currently used lacks a clear consensus [108]. There is no compelling evidence supporting the efficacy of any specific inotropic therapy in reducing mortality for hemodynamically unstable patients with CS, as neither the ESC nor the AHA guidelines make definitive recommendations, emphasizing the absence of robust evidence favouring one inotrope over another. In practical terms, the use of inotropes varies widely, and retrospective analyses indicate either higher mortality rates or no discernible positive effects associated with most inotropes [109, 110]. Individual choices should be made as a patient and disease tailored approach. While dobutamine is commonly used as the primary agent, levosimendan and phosphodiesterase (PDE)-III inhibitors might serve as an alternative or additional option when dobutamine proves ineffective, while conflicting data exists. Recent cochrane analyses found insufficient evidence to establish the superiority of any particular vasopressor or inotrope in terms of mortality [111]. Even though the 2016 ESC guidelines for heart failure recommended dobutamine as a "first line" inotrope, the current guidelines do not make specific recommendations [112, 113]. Observational studies and a recent RCT indicate favourable outcomes with dobutamine use in comparison to dopamine or epinephrine. Levosimendan, a calcium-sensitizer, increases cardiac inotropy and reduces afterload, demonstrating a long-lasting effect and potential benefits in catecholamine-refractory AMI-CS and other specific cases such as right heart failure [114, 115]. In addition, levosimendan might offer beneficial effects in patients with previous beta-blocker use [116].

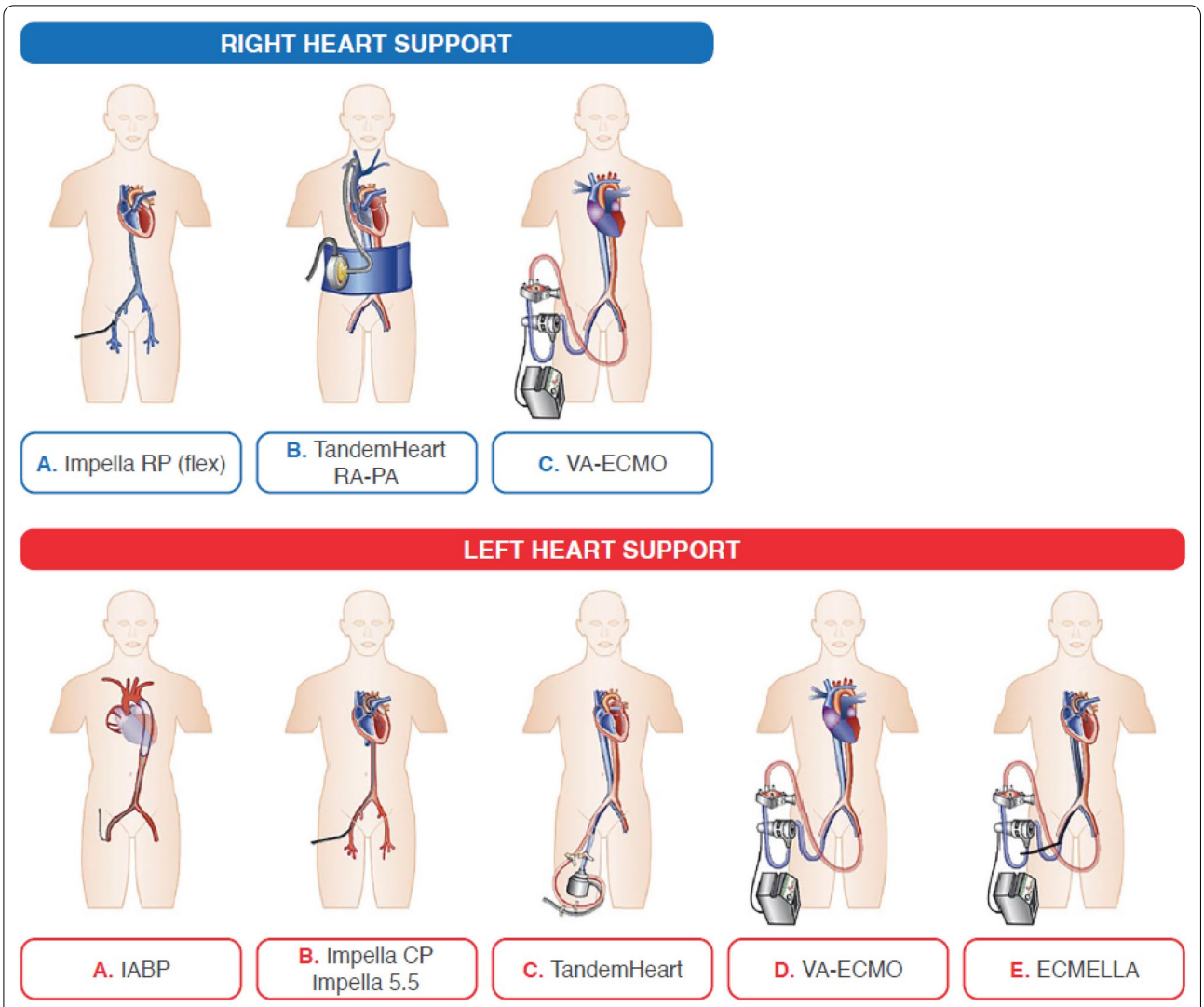
Epinephrine and norepinephrine were compared in a small RCT and in large observational studies, and was shown to have a similar cardiac index evolution as primary efficacy outcome but higher incidence of refractory shock in the epinephrine group as main safety endpoint [117]. However, the study included only 57 patients and the need for a PAC might have led to a selection-bias.

Selective PDE-III inhibitors, such as enoximone and milrinone, increase CO but lack consistent evidence supporting their use in critically ill patients except in specific cases such as pulmonary hypertension to also address right-ventricular contractility and afterload. The combination of PDE-III inhibitors with dobutamine may have a more pronounced positive inotropic effect, but caution is advised regarding potential synergistic vasodilatory effects when combining them or when combining with levosimendan. The recently published DOREMI trial found no difference between milrinone and dobutamine [118]. In consequence, the DOREMI trial gives no reason to change current practice to use dobutamine as first choice inotropic agent. Currently, LevoHeartShock (NCT04020263) investigates the effect of early use of levosimendan versus placebo on top of a conventional inotropic strategy in CS, while DOREMI-2 (NCT05267886) evaluates the impact of inodilators (milrinone/dobutamine) versus placebo with results being awaited [119]. In the future, more tailored pharmacological management approaches should be evaluated in clinical trials (Fig. 3).

Other general supportive pharmacological approaches include controlling the blood glucose level, providing adequate oxygen delivery, stress ulcer prophylaxis and early enteral feeding, as well as platelet inhibitors and anticoagulation. A comprehensive overview only focusing on pharmacologic treatment in CS has been published by Bruno et al. [105].

Mechanical circulatory support devices

Temporary mechanical circulatory support (tMCS, Figure 3) is a potential option for enhancing end-organ perfusion in patients with de novo or refractory CS [120]. It provides short-term hemodynamic intervention lasting from hours to weeks, is usually managed in a hub-and-spoke system available in tertiary centers, and is serving as a bridge-to-decision, bridge-to-recovery, bridge-to-LVAD (left-ventricular assist device), or bridge-to-transplantation. Various tMCS configurations offer partial or complete circulatory support, including percutaneous, surgical, and hybrid platforms with and without oxygenation. Multiple combinations like venoarterial extracorporeal membrane oxygenation (VA-ECMO; also called ECLS) with microaxial flow pumps (Impella®) which some call ECMella or ECPella, VA-ECMO with an intra-aortic balloon pump (IABP), BiPella (right- and left-ventricular microaxial flow pump), and left atrial-to-femoral artery support devices (TandemHeart™ or CentriMag™) with an left-ventricular (LV) Impella are feasible, addressing specific needs such as pulmonary support. tMCS



	Size of the cannulae	Key contraindication / limitation	Ability to oxygenate blood	Recommanded max. use - practical use may be much longer
Impella RP	22F	Mechanical tricuspid valve	No	14 days
TandemHeart RA-PA	16-31F	Mechanical tricuspid valve	Yes	14 days
VA-ECMO	15-25F	No suitable access site	Yes	14 days
IABP	7-8F	Severe aortic regurgitation	No	30 days
Impella CP / 5.5	CP: 14F 5.5: 21F	Mechanical aortic valve	No	10 days
TandemHeart	15-21 F	Moderate to Severe aortic regurgitation	Yes	14 days
VA-ECMO	15-25F	No suitable access site	Yes	14 days
ECMELLA	15-25F	Mechanical aortic valve	Yes	14 days

Fig. 3 Mechanical circulatory support devices. Right-ventricular (upper panel) and left-ventricular assist devices (lower panel). In biventricular failure assist, a combination of devices might be used. ECMELLA, the combination of VA-ECMO and Impella, serves as LV support and LV unloading strategy. *RA* right atrium, *PA* pulmonary artery, *VA* venoarterial (configuration), *ECMO* extracorporeal membrane oxygenation, *IABP* intra-aortic balloon pump, *F* French (1F = 0.33 mm), *RV* right-ventricular, *LV* left-ventricular

devices operate through distinct mechanisms, delivering diverse types and levels of hemodynamic support, each associated with specific potential complications. A thorough comprehension of each device's risk/benefit profile is paramount for determining its role in managing different stages and etiologies of CS [6]. Modern individualized therapy taking individual risks and benefits into account should still adhere to homogenous management plans which is an ongoing debate in CS, especially in the field of tMCS [121].

IABP has long deemed to provide some low degree of left-ventricular support by diastolic blood-pressure augmentation and afterload reduction, which, however, could not be confirmed in RCTs [122, 123]. Due to its ease of insertion, cost-effectiveness, and favorable adverse event profile, it has been widely used despite a lack of evidence. This electrocardiogram (ECG)-gated volume-displacement pump is percutaneously placed in the descending aorta, enhancing coronary perfusion during diastole, and reducing afterload during systole. In comparison to control, it was not able to significantly augment CO or any other hemodynamic variable in RCTs [122, 123]. Large-scale RCTs on IABP use in AMI-CS did not show survival benefits compared to medical therapy [67, 124]. Sufficient evidence for its benefit in other etiologies including acute or acute-on-chronic heart failure with CS and CS with mechanical complications post-AMI, possibly serving as a bridge-to-recovery or bridge-to-LVAD or heart transplantation, is not available [125].

The Impella family, with transvalvular axial flow pumps ranging from 3.5 to 5.5 L/min, has gained prominence in severe CS and LV-dysfunction. Newer devices like Impella 5.5 theoretically offer complete LV support, although RCTs demonstrating survival benefits in CS patients are lacking. Although overall evidence for Impella 5.5 is limited, its use grows along the advantages during longer support times and less access-site complications. Notably, two small RCTs, ISAR-SHOCK and IMPRESS-in-severe-shock, assessing Impella 2.5 and CP devices failed to show any survival benefit [126, 127]. Large-scale propensity matched studies encompassing more than 100,000 patients consistently showed no survival benefit or even higher mortality with consistent higher complication rates such as major bleeding and limb ischemia [128–133]. However, recently, the results of the Danish Germany (DanGer) shock trial [134] were published: in 360 highly selected patients with AMI-CS with anterior STEMI without high risk of hypoxic brain injury, comparing Impella® CP versus standard of care Impella support was associated with better 180-day outcome [135]. Despite the long recruitment period, the narrow inclusion criteria, and several open questions like the highest ever reported increase in mortality from 30 days to 6 months in control patients, the shortest ICU time in the control arm, and the highest ever reported renal replacement therapy in the active tMCS arm, this RCT is an important study supporting the use of tMCS in selected patients.

The TandemHeart is a left atrial-to-femoral artery support device, delivering up to 4 L/min. Extracting blood directly from the left atrium effectively lowers PCWP and LV end-diastolic pressure. However, its retrograde arterial flow increases afterload during systole, resulting in minimal change or a slight decrease in myocardial oxygen consumption. Despite a study indicating no survival advantage over the IABP in managing AMI-CS [136, 137], the device holds potential value in specific cases requiring elevated CO support. This encompasses scenarios like mitral regurgitation, severe pulmonary hypertension, RV decompression, or when the Impella device is unsuitable, such as in severe aortic stenosis or the presence of a mechanical aortic valve. An added benefit is its capacity to incorporate an oxygenator into the arterial return circuit.

ProtekDuo is a dual-lumen cannula percutaneously inserted through the right internal jugular vein (IJV) to reach the pulmonary artery. Connected to an extracorporeal pump, it serves as a percutaneous right-ventricular assist device (RVAD). In patients experiencing RV failure, ProtekDuo offers isolated RV support and can deliver up to 5 L/min of flow, and an oxygenator can be integrated [138].

VA-ECMO, delivering flows of up to 6 L/min, can provide full respiratory and circulatory assistance. Peripheral VA-ECMO, the predominant configuration used, involves venous cannulation with a multi-stage cannula in the right atrium, directing blood to an extracorporeal pump and membrane oxygenator. Oxygenated blood is retrogradely pumped via the femoral artery into the descending aorta [139, 140]. Less-common central surgical configurations include cannulation in the right atrium or pulmonary artery, with return cannula placement in the ascending aorta. Additionally, the multi-stage venous cannula can be placed under fluoroscopic guidance in the left atrium across the inter-atrial septum thus draining both left and right atria combined to support the circulation while indirectly unloading the left ventricle as well (LAVA-ECMO). VA-ECMO is increasingly used in refractory CS and explored for ECPR [141]. The recent ECLS-SHOCK trial, involving AMI-CS, assessed early routine VA-ECMO alongside standard treatment. Results revealed no significant difference in 30-day all-cause death between groups (ECLS: 47.8%, control: 49%; relative risk [RR] 0.98, 95% confidence interval [CI] 0.80–1.19, $p = 0.81$) [67]. Of note, these data are also in

line with the ECMO-CS trial [142]. This is further corroborated by an individual patient data meta-analysis of 4 RCTs which did not show a mortality benefit in AMICS with at the same time higher bleeding and peripheral ischemic complications [143]. In consequence and in the light of no benefits but relevant complications, the role of VA-ECMO in AMICS would be limited to patients with concomitant severe respiratory failure, biventricular failure, or cardiac arrest. If DanGer-Shock like patients may the optimal candidates needs further evaluation. The use of ECMO with LV unloading remains to be ascertained [144].

tMCS device utilization in CS lacks standardized protocols, leading to varied practices [145]. The optimal timing for initiating and escalating tMCS devices including the optimal patient selection still remains undefined. tMCS are intended to offer hemodynamic support not to treat CS, and all devices offer variable hemodynamic support without addressing the etiology of CS. Thus, distinguishing the etiology (AMI vs. heart failure) may also be crucial. Recognizing hemodynamic instability, differentiating between univentricular and biventricular shock, and assessing respiratory failure for MCS device selection. Therefore, based on the current lack of evidence of a mortality reduction in RCTs, tMCS should be restrictively used based on advanced shock team decisions. Currently, a tMCS algorithm is not supported by evidence; however, potential selection steps have been proposed [146]. Ideally, tMCS is considered with CS and evidence of impaired stroke volume despite optimal pharmacologic support. Potentially, VA-ECMO should be selected in non-AMICS, AMICS with CA or biventricular failure, and Impella in isolated LV failure etiologies without cardiac arrest.

The clinicians should keep in mind the multiple issues that are specific to tMCS device assessment in RCTs: (i) it is challenging to completely standardize their use especially regarding the device management (e.g., anticoagulation strategy, specific settings, and clinician's experience). The example of the management of anticoagulation, antithrombotic therapy, and potential hemolysis—a major driver of adverse outcome—illustrates this effectively: treatment regimens differ widely contributing to ischemic events and bleeding and hence mortality in unexperienced hands; (ii) it is difficult to select the appropriate comparison with another device or combination of vasopressors/inotropes and the optimal timing of implementation; (iii) placebo-controlled device trials are impossible to design.

Future directions

Current management of CS is resource intensive and falls behind expectations with respect to outcomes. Contemporary strategies see CS patients as a homogenous group with 'one size fits all' strategies and improvement efforts often fail in RCTs. From the clinical perspective, there is a large variety in patient presentations and responses to therapy. It seems prudent to classify patients in specific CS endotypes with subsequent treatment strategies. More efforts are needed to develop these endotypes bundles. AI and machine learning algorithms might facilitate these developments. To date, the treatment of the underlying etiology of CS such as PCI in AMI-CS is in most of the cases acceptable; however, the treatment of the sequelae remain challenging. An unmet need is the targeted therapy of the microcirculation, since it defines organ function and organ failure which subsequently defines outcome [147]. More efforts are needed to guide therapy to restore and maintain organ perfusion in the complex interplay with cardiac function and support as well as pharmacotherapy with all the challenges of fluid and perfusion pressure balancing. Early efforts that use optimal microcirculation as target need to get specific attention [148, 149]. This also goes in line with the identification of biomarkers and bioswitches, potentially identified using AI/machine learning approaches. Dipeptidyl peptidase 3 (DPP3) is an example that has been identified as an actionable biomarker (i.e., biological target); however, the next steps include the development as point-of-care diagnostics available at the bedside as well as identifying relevant mechanisms connected with the question whether this has the potential as therapeutic target. This approach may be incorporated in futures clinical trials that test the modulation of biotargets (e.g., anti-adrenomedullin and anti-DPP3 antibodies) in a preselected CS population (i.e., specific endotype [150–152]). Also, efforts need to be improved in multiple dimensions to balance the tip between positive and negative consequences in tMCS. It also remains an ongoing challenge to design the ideal tMCS trial not applying too broad or too narrow in- and exclusion criteria. Furthermore, future trials also need to address so far not well-represented patient groups, for example young SCAI D/E patients and non-AMICS patients with CS. At centre stage, there is the reduction in bleeding and peripheral ischemic events [153]. Improvements can be achieved in access-site management, anticoagulation, and the design of the devices. Correct management can also be improved by protocols and by qualification measures and seeing management of CS patient as multiprofessional and multidisciplinary team effort and as part of network organizations with potential transfer to expert centers. To move forward and addressing these questions, international trial networks should address these topics in streamlined strategies to power studies with relevant sample sizes in reasonable time frames.

Conclusions

Management of CS remains an ongoing challenge. Despite all efforts made on improving diagnosis and offering multimodal therapy, mortality remains high. More efforts are needed to identify the right therapy for the right CS patient needs more insight also in the light of comorbidities and metabolic demands [154]. Smaller sizes of MCS devices might also help to reduce negative side effects. Novel pharmacological substances might target the systemic syndrome CS. Innovative developments in biomarkers and use of artificial intelligence to assess trends might enhance personalized care in CS patients globally.

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Funding

Open Access funding enabled and organized by Projekt DEAL.

Declarations

Conflict of interest

CJ reports institutional grants by the German research foundation, German ministry for economy and energy, State of Nordrhine-Westfalia, German space agency, European Union and Edwards Lifescience as well as speaker fees outside the field of this article by Bristol Myers Squibb, Daichi Sankyo and Boehringer-Ingelheim. RRB: no conflict of interest. MJ: no conflict of interest. SP: no conflict of interest. KAK reports speaker fees received from Daiichi Sankyo, Zoll Medical, Amarin, consulting fees by Amarin, Novartis, Sanofi and travel support provided by Amgen, Sanofi and Daiichi Sankyo. KR reports that he is the current Chair of Publications at the Extracorporeal Life Support Organisation. JD: no conflict of interest. JF: no conflict of interest. Clement Delmas reports lectures and consulting fees received by Abiomed and Abott. A-AM: no conflict of interest. HT: no conflict of interest. SS: no conflict of interest.

Publisher's Note

Received: 29 March 2024 Accepted: 18 August 2024
Published: 10 September 2024

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