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POSITION PAPE

Epidemiology, pathophysiology and contemporary management of cardiogenic shock – a position statement from the Heart Failure Association of the European Society of Cardiology

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Cardiogenic shock (CS) is a complex multifactorial clinical syndrome with extremely high mortality, developing as a continuum, and progressing from the initial insult (underlying cause) to the subsequent occurrence of organ failure and death. There is a large spectrum of CS presentations resulting from the interaction between an acute cardiac insult and a patient's underlying cardiac and overall medical condition. Phenotyping patients with CS may have clinical impact on management because classification would support initiation of appropriate therapies. CS management should consider appropriate organization of the health care services, and therapies must be given to the appropriately selected patients, in a timely manner, whilst avoiding iatrogenic harm. Although several consensus-driven algorithms have been proposed, CS management remains challenging and substantial investments in research and development have not yielded proof of efficacy and safety for most of the therapies tested, and outcome in this condition remains poor. Future studies should consider the identification of the new pathophysiological targets, and high-quality translational research should facilitate incorporation of more targeted interventions in clinical research protocols, aimed to improve individual patient outcomes. Designing outcome clinical trials in CS remains particularly challenging in this critical and very costly scenario in cardiology, but information from these trials is imperiously needed to better inform the guidelines and clinical practice. The goal of this review is to summarize the current knowledge concerning the definition, epidemiology, underlying causes, pathophysiology and management of CS based on important lessons from clinical trials and registries, with a focus on improving in-hospital management.

Keywords Cardiogenic shock • Organ dysfunction • Mechanical circulatory support • Multidisciplinary team

Introduction

Cardiogenic shock (CS) represents the most severe form of acute heart failure (AHF) syndromes. Although there is no uniform definition of CS,[1–8] CS is a low cardiac output (CO) state primarily due to cardiac dysfunction, leading to severe end-organ hypoperfusion associated with tissue hypoxia and increased lactate levels. This pathophysiology frequently leads to multi-organ failure and death.

Although recent guidelines[4] describe a singular CS presentation as part of AHF syndromes, there is a large spectrum of CS phenotypes[2,3,6] resulting from the interaction between a cardiac insult and a patient's underlying cardiac and overall medical condition.[9] While the initial presentation of the patients with CS may appear similar, reflecting the systemic effects of an initial acute reduction in CO, frequently the patient condition rapidly changes and evolves into several clinical phenotypes through distinct mechanisms determined by the underlying aetiology and severity of the primary cardiac insult. Cardiac insult causing severe impairment of cardiac performance may be acute, as a result of the acute loss of myocardial tissue [acute myocardial infarction (AMI), myocarditis] or may be progressive as seen in patients with chronic decompensated heart failure (HF) who experienced a decline in disease stability as a result of severe precipitants, iatrogenic factors, poor adherence to guideline-based therapies, factors triggering acute worsening of their chronic disease.

Despite advanced management, including aetiological treatment[10] and mechanical circulatory support (MCS),[10–12] CS represents the most severe manifestation of AHF with in-hospital mortality between 30–50%, depending on the underlying aetiology.[1]

The goal of this review is to summarize the current knowledge concerning the definition, epidemiology, underlying causes, pathophysiology and management, based on important lessons from clinical trials and registries, with a focus on improving in-hospital management.

Definition and classifications

Based on clinical criteria, diagnosis of CS mandates the presence of clinical signs of hypoperfusion, such as cold sweated extremities, oliguria, mental confusion, dizziness, narrow pulse pressure. In addition, biochemical manifestations of hypoperfusion, elevated creatinine, metabolic acidosis and elevated serum lactate, are present and reflect tissue hypoxia and alterations of cellular metabolism, potentially leading to organ dysfunction. CS is a clinical diagnosis[4,7] and haemodynamic parameters, such as reduced cardiac index (CI) and elevated pulmonary capillary wedge pressure (PCWP), are not mandatory in clinical practice.

Although, recent European Society of Cardiology (ESC) HF guidelines[4] and many CS definitions[1,3,6] include hypotension defined as systolic blood pressure (SBP) <90 mmHg for more than 30 min, or the need for catecholamines to maintain SBP >90 mmHg, it is well recognized that in shock, compensatory mechanisms may preserve blood pressure (BP) through vasoconstriction, while tissue perfusion and oxygenation may be significantly decreased. Thus, hypoperfusion is not always accompanied by hypotension and hypotension without hypoperfusion may portend a better prognosis.[2,5,8] In the SHOCK registry, clinical signs of hypoperfusion were associated with a substantial risk of in-hospital mortality even in normotensive patients, suggesting that early recognition of hypoperfusion signs identifies 'high-risk' patients regardless of hypotension.[2] The Task Force of the European Society of Intensive Care Medicine defined shock (including its subtypes) as a 'life-threatening, generalized form of acute circulatory failure associated with inadequacy of tissue perfusion to provide enough oxygen to sustain basal metabolism at cellular level', where the presence of low SBP was not a prerequisite for defining CS.[13] Based on these considerations, we propose to define CS as a syndrome caused by a primary cardiovascular disorder in which inadequate CO results in a life-threatening state of tissue hypoperfusion associated with impairment of tissue oxygen metabolism and hyperlactatemia which,

depending on its severity, may result in multi-organ dysfunction and death.

Cardiogenic shock registries[14] and consensus documents[7,15–17] described a large phenotypic variability of CS, as result of the diverse aetiologies, pathogenetic mechanisms, haemodynamics and stages of severity. CS may arise in advanced chronic HF when acute precipitants trigger decompensation or may manifest as an acute onset, *de novo* presentation, most often caused by an acute coronary syndrome (ACS). Categorization according to the underlying aetiology, ACS- vs. non-ACS-related, aims to early guide management strategies towards the underlying cause. Also, the presence/absence of previous cardiac arrest (CA) is important as phenotypes differ significantly in terms of priorities for initial management and also outcomes.

Based on clinical severity and response to treatment, the spectrum of CS can be divided into pre-CS, CS, and refractory CS[15] (*Figure 1*). Early identification of CS allows rapid initiation of appropriate interventions to reverse the underlying cause and the introduction of supportive therapies. The presence of clinical signs of peripheral hypoperfusion even with preserved SBP, is referred as 'pre-shock'[15] and precedes overt CS. Pre-shock may occur in severe AHF, which can also be associated with clinical signs of tissue hypoperfusion but without compromising cellular basal metabolism and having normal lactate.[2,7,15] This state should be differentiated from 'normotensive CS', which represents an entity of CS with all features of hypoperfusion and cellular alterations (including cellular hypoxia and elevated lactate) but without hypotension. Patients with normotensive CS have a greater systemic vascular resistance, but similar left ventricular (LV) ejection fraction, CO, and PCWP, as patients with classic CS, thus highlighting the risk of hypoperfusion.[2,7]

At the end of the spectrum of severity, 'refractory CS' has been defined as CS with ongoing evidence of tissue hypoperfusion despite administration of adequate doses of two vasoactive medications and treatment of the underlying aetiology.[15,18]

The recently published Society for Cardiovascular Angiography and Interventions (SCAI) classification[16] describes five evolutive stages of CS, from A (at risk of CS) to E (extremis) (*Figure 1*) including a modifier for CA. This classification can be applied rapidly bedside upon patient presentation, across all clinical settings. The SCAI classification utilizes bedside clinical assessment of hypoperfusion, measurement of lactate level and invasive haemodynamic evaluation. Recently, the SCAI classification has been validated in a large cohort of unselected intensive cardiac care unit (ICCU) patients providing robust mortality risk stratification regardless of CS aetiology, in a manner that was amplified by the presence of CA.[19] The strong association between SCAI shock stages and mortality in a heterogeneous ICCU population, even after adjustment for known predictors of mortality, emphasizes the robustness of this classification system.

In the SHOCK trial,[1] CS definition required haemodynamic parameters, such as reduced CI (<2.2 L/min/m^2) and elevated PCWP (>15 mmHg). However, this definition reflects only 'left-sided' CS, but there are diverse haemodynamic phenotypes for CS[7] determined by the association of the systemic inflammatory response syndrome[20,21] and by the type of cardiac involvement (left vs. right).[22] The common physiological characteristic is low CI, but PCWP, central venous pressure (CVP) and systemic vascular resistance (SVR) may vary[7] (*Figure 1*).

Epidemiology and prognosis

The prevalence of CS varies according to the definition of CS, clinical setting care and era of data collection. CS accounts for 2–5% of AHF presentations,[5,10,23–27] with a prevalence in intensive care unit (ICU)/ICCU datasets of 14–16%.[10,28] In-hospital mortality varied between 30% and 60%,[23–27] with nearly half of in-hospital deaths occurring within the first 24 h of presentation.[5] One-year mortality is approximately 50–60%,[29] with 70–80% of deaths occurring in the first 30 to 60 days after onset of CS,[29–31] suggesting that the risk of death is time-dependent and clustered in the early post-discharge period.

The incidence of CS complicating ACS is 4–12%, with 30–40% of cases occurring at admission,[32–34] and 60–70% occurring in the course of hospitalization. However, in a French registry enrolling 10 000 consecutive AMI patients over 10 years, the prevalence of CS following AMI decreased from 5.9% in 2005 to 2.8% in 2015.[35] Overall, in-hospital mortality of CS complicating AMI has remained unchanged in the last 10 years at 40–50%,[32,36–39] with higher rates being reported in CS developing during hospitalization.[34] However, recent US datasets reported lower mortality rates of 36.5%[40] and 38.8%.[41]

A decade ago, 81% of CS was due to underlying ACS[42]; however, the contribution of ACS has declined over the past two decades,[43] in parallel with an increase of CS of other aetiologies.[10] In a large US registry including 144 254 patients with CS of any aetiology, the proportion of ACS-related CS has fallen between 2005 and 2014 from 65.3% to 45.6%.[10] Also, in a contemporary ICCU dataset in the US and Canada, only a third of CS were related to ACS, while the remainder comprised ischaemic cardiomyopathy without ACS (18%), non-ischaemic cardiomyopathy (28%) and other causes (e.g. incessant ventricular tachycardia, severe valve disease) in 17%.[28] Non-ACS-CS patients are more resource-intensive and have a greater burden of disease (more severe pre-existent HF, pulmonary hypertension, arrhythmias), but in-hospital survival is significantly better than ACS-related CS.[28,42] In CardShock,[42] ACS has been shown to be a predictor of worse outcomes in patients with CS (odds ratio 7.4, 95% confidence interval 1.9–29.8).

Patients with ACS and CS have an acute and irreversible loss of myocardial tissue of significant magnitude, which often triggers inflammatory and other systemic responses. This is in contrast with the reversible nature of cardiac dysfunction seen in other CS aetiologies. Secondly, patients with CS complicating AMI are older, with higher rates of CA, diabetes, peripheral vascular disease and ischaemic stroke, which contribute to worse outcome compared to non-AMI CS.[28,40,42] Despite an overall higher rate of revascularization over time, AMI-CS patients with greater comorbidity still/consistently underwent less coronary angiography and revascularization.[43,44]

Cardiogenic shock is a more common complication of ST-elevation myocardial infarction (STEMI) than non-STEMI

Table 1 Clinical, pathophysiological and management characteristics of non-acute coronary syndrome aetiologies of cardiogenic shock

Clinical setting	Clinical and pathophysiological characteristics	Key treatment elements
RV failure	• Depending on aetiology and pathophysiology may present as 'wet and cold' or 'wet and warm' • Without pulmonary arterial hypertension (RV infarction, primary TR, RV cardiomyopathies) • With pulmonary arterial hypertension (PE, ARDS, primary PH) • Post-cardiac surgery (MV repair, cardiac transplantation, LVAD); very common 'wet and warm' • Post-cardiac arrest; very common 'wet and warm'	• Look at primary aetiology • Cautious volume loading (<500 mL in 30 min) because volume status has a very narrow ideal range, and excessive volume loading will distend RV and compromise LV filling • SBP should be 40 mmHg greater than pulmonary pressure • Norepinephrine or inotropes such as dobutamine or levosimendan may be used • Mechanical ventilation should be adjusted to minimal conditions and the patient should be in the prone position, • In refractory patients, VA-ECMO, Impella RP or TandemHeart RA-PA may be used • In CS in settings of high-risk PE, systemic thrombolysis or surgical embolectomy (when thrombolysis failed or is contraindicated) are indicated • Severe RV failure occurs in 20–25% of cases post-LVAD implant. In postoperative settings, CS post-LVAD implant requires a PAC-tailored management to optimize haemodynamics and volume status of the patient; the goal is CVP <15 mmHg. In this clinical setting, treatment includes aggressive use of inotropes, possibly inhaled nitric oxide, rhythm control with pacing or antiarrhythmics and mechanical RV support
Myocarditis	• Immune-mediated inflammatory response triggered by different stimuli, mostly viral infections or auto-immune disease • Flu-like symptoms, elevated cardiac biomarkers and clinical signs of acute HF • Cardiac troponins are useful to estimate the severity of acute underlying myocardial injury • Search for giant cell myocarditis and acute eosinophilic myocarditis – immediate RV endomyocardial biopsy • Very common biventricular involvement	• Cyclosporine + prednisone (for giant cell myocarditis) • Initiation of high-dose intravenous corticosteroids (for acute eosinophilic myocarditis) • Early implantation of MCS; very often biventricular support
Takotsubo syndrome	• Negative inotropic effects of high levels of endogenous or exogenous catecholamines • Transient high afterload • Very often dynamic LVOTO • Possibly microvascular dysfunction-associated ischaemia	• Avoid catecholamines and prefer milrinone/levosimendan • Selection of MCS is patient-specific, and Impella may be considered in selected cases, while VA-ECMO increases afterload and may amplify mitral regurgitation and pulmonary oedema • Early BB therapy after haemodynamic stabilization
Cardiomyopathies	• First exclude secondary aetiologies (valvular disease, hypertensive disease, coronary artery disease) • Search for features of a specific aetiology	• Identify and treat precipitating factors • Neurohormonal medication (including beta-blockers) initiated early after haemodynamic stabilization • BB and volume optimization for HOCM; avoid vasodilators

Table 1 (Continued)

Clinical setting	Clinical and pathophysiological characteristics	Key treatment elements
PPCM	• PPCM and idiopathic DCM share clinical and genetic (titin truncating gene variants) features • A prolactin fragment (16 kD prolactine) is considered causal for the pathogenesis • Very common LV thrombus • Clinical outcome highly variable	• Longer-term bromocriptine and prophylactic/therapeutic anticoagulation may improve outcomes • Early use of MCS • Emergent caesarean section may be required
Valve lesions	• Uncommon cause (i.e. mitral valve rupture due to ischaemia, infective endocarditis, severe aortic stenosis) • Decompensation of known VHD in the presence of acute precipitants	• Identify and treat precipitating factors • Haemodynamic stabilization and assess the risk/benefit ratio for cardiac surgery • MCS should be individualized based on pathophysiology of valvular disease. Impella is the MCS of choice in patients with severe MR, while it is relatively contraindicated in patients with severe AS. Peripheral VA-ECMO is contraindicated in patients with AR • Immediate surgery for NVE or PVE
Post-cardiac surgery	• Intraoperative complications, prolonged CPB (high levels of cytokines), insufficient cardio-protection and general morbidity contribute to CS • Very often presents as vasodilatory CS ('wet and warm'), due to pathophysiology with cytokine release following CPB • Localized tamponade (precipitating factors include: administration of anticoagulants, coagulation disorders, excessive mediastinal bleeding, removal of epicardial pacing wires) • Dynamic LV obstruction (precipitating factors include: hypovolaemia, cardiac hypertrophy, aortic valve replacement, high-dose inotropes) • Acute refractory RV dysfunction especially with vasodilatory phenotype	• Early echo is crucial to identify potentially correctable causes • Identify precipitants and anticipate clinical scenario • Avoid excess of catecholamines • Early reintervention in case of tamponade • For dynamic LVOTO, stop catecholamines and optimize volume status; IV BB when persistent • Inability to wean from CPB and/or poor postoperative haemodynamics are indications for early MCS; Impella 5.0, VA-ECMO or both may be considered depending on clinical scenario
CS in settings of cardiac arrest	• Post-resuscitation global myocardial stunning can cause transient pump failure lasting several hours, caused by a combination of oxidative stress, microthrombi formation, adrenergic excess, cytokine release, and myocardial ischaemia–reperfusion injury, and amplified by initial cardiac insult responsive to CS • General ischaemia–reperfusion injury may precipitate systemic vasodilatation • Delayed initiation of CPR, longer interval from start of CPR to ROSC, non-shockable rhythms, older age, many comorbidities, severe lactic acidosis on presentation are negative prognostic factors • The degree of brain damage determines clinical course and outcome	• For patients with cardiac arrest refractory to CPR, E-CPR (ECMO support during CPR) may be considered. The goal of E-CPR is to support patients in refractory cardiac arrest of potentially reversible aetiology (e.g. AMI, PE, cardiac injury) while reversible causes are being identified and treated

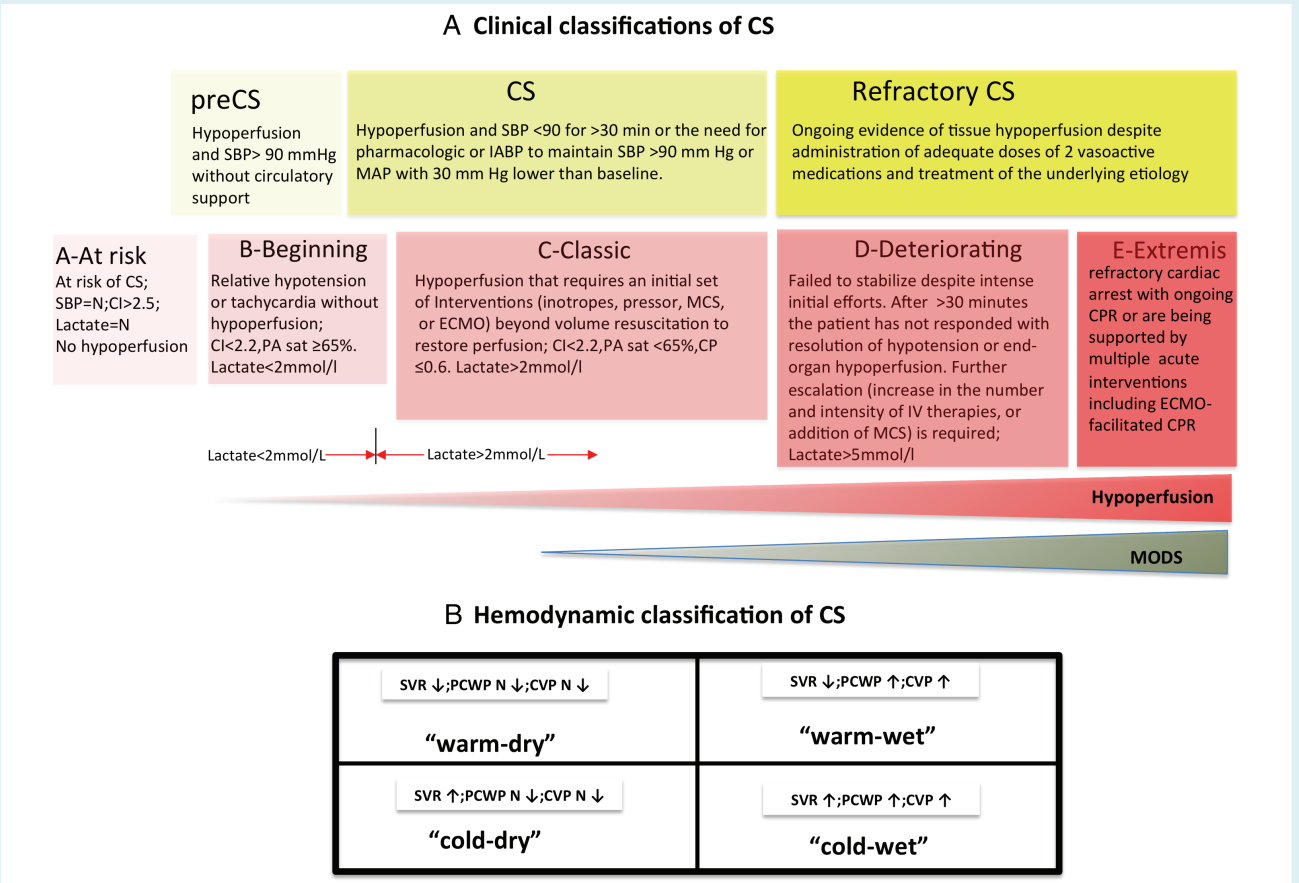

Figure 1 Classifications of cardiogenic shock (CS). (*A*) The first two classifications are based on clinical severity and the response to treatment and are presented with possible overlapping. (*B*) When patients are classified by haemodynamic phenotypes, low cardiac index (CI) is a common finding, but ventricular preload, pulmonary capillary wedge pressure (PCWP), central venous pressure (CVP), and systemic vascular resistance (SVR) may vary. CS caused by predominant left ventricular failure may present as 'cold-wet' (hypoperfused and congested) with high SVR and PCWP (two thirds of clinical presentations in the SHOCK trial). Patients decongested may present as 'cold-dry' (hypoperfused without congestion) with high SVR and relatively normal left and right ventricular filling pressures. Up to 20% of CS patients may present as 'wet and warm', with high PCWP but low SVR. These patients may have excessive vasodilatation as a result of systemic inflammatory response syndrome or mixed shock and most of them had fever and leucocytosis, but not all had proven infection. CS caused by predominantly right ventricular failure may present as 'wet-cold' or 'wet-warm'. These patients have high right ventricular filling pressure, increased CVP/PCWP ratio, and different values of SVR according to the extent of systemic inflammatory response. Pulmonary artery pressure is usually low or normal in patients with predominant pump failure as the origin of right ventricular CS such as in right ventricular acute myocardial infarction, right ventricular cardiomyopathies and tricuspid valve rupture. On the other hand, an elevated pulmonary artery pressure will be encountered in patients with pulmonary embolism, primary and secondary pulmonary hypertension. CP, cardiac power; CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; IV, intravenous; MAP, mean arterial pressure; MCS, mechanical circulatory support; MODS, multi-organ dysfunction syndrome; PA, pulmonary artery; SBP, systolic blood pressure.

(NSTEMI), with STEMI being more likely to present with CS on admission vs. developing after hospitalization in NSTEMI.[10,45] Although initial reports suggested worse early mortality for NSTEMI vs. STEMI,[46] this has not been supported by later data.[29]

Pathophysiology of cardiogenic shock

Although aetiologies vary widely[15,18,47] (*Table 1*), the pathophysiology of CS comprises several unique yet overlapping components to be considered: an initial cardiac insult that decreases CO, central haemodynamic alterations [including changes in the relation between pressure and volume with increase in LV and right ventricular (RV) filling pressures], microcirculatory dysfunction, a systemic inflammatory response syndrome and multi-organ dysfunction (*Figure 2*). Although these mechanisms might be considered as temporal stages of CS, each may occur simultaneously, the magnitude of the initial cardiac insult and/or early application of interventions may either mask or delay some of these stages.[48]

Furthermore, precipitating factors[49–51] may cause an acute deterioration of cardiac compensation evolving to CS, and worse

Table 1 (Continued)

Clinical setting	Clinical and pathophysiological characteristics	Key treatment elements
Cancer	• CS in patients with cancer is preceded by different clinical entities, such as ACS, Takotsubo syndrome, myocarditis, thromboembolic events and PE, tamponade, and cardiac herniation • These clinical presentations can be attributed either to cancer itself or to its therapy, including surgery, chemotherapy (anthracycline and other agents such as: trastuzumab, VEGF inhibitors, proteasome inhibitors, immune checkpoint inhibitors, CAR-T cell therapies) or as a late consequence of radiotherapy, in association with pre-existing cardiovascular disease or risk factors	• Treatment is similar to CS without cancer: haemodynamic stabilization and treatment of the underlying cause • MCS is not a contraindication in cancer patients • ACE-I and BB for cardiac protection during chemotherapy

ACE-I, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; AMI, acute myocardial infarction; AR, aortic regurgitation; ARDS, acute respiratory distress syndrome; BB, beta-blocker; CAR, chimeric antigen receptor; CPB, cardiopulmonary bypass; CPR, cardiopulmonary resuscitation; CS, cardiogenic shock; CVP, central venous pressure; DCM, dilated cardiomyopathy; HF, heart failure; IABP, intra-aortic balloon pump; LV, left ventricle; LVAD, left ventricular assist device; HCMO, hypertrophic obstructive cardiomyopathy; IV, intravenous; LVOTO, left ventricular outflow tract obstruction; MCS, mechanical circulatory support; MV, mitral valve; NVE, native valve endocarditis; PAC, pulmonary artery catheter; PE, pulmonary embolism; PPCM, peripartum cardiomyopathy; PVE, prosthetic valve endocarditis; ROSC, return of spontaneous circulation; RV right ventricle; SBP, systolic blood pressure; TR, tricuspid regurgitation; VA-ECMO, veno-arterial extracorporeal membrane oxygenation; VEGF, vascular endothelial growth factor; VHD, valvular heart disease.

outcomes were described in patients with non-cardiovascular precipitating factors, such as infection.

Severe LV failure secondary to loss of myocardial tissue after a large AMI represents the classical pathogenic mechanism of CS. In addition to the acute loss of myocardial tissue, mechanical complications of AMI acutely alter loading conditions leading to acute LV and RV dysfunction. Distinct to ACS, CS can result from a severely reduced CO due to primary cardiac, valvular, electrical, or pericardial abnormalities. RV dysfunction, either by primary contractile dysfunction or secondary preload/afterload mismatch, may be exclusively responsible for CS (e.g. acute pulmonary embolism, isolated severe primary tricuspid regurgitation, RV cardiomyopathies) or may contribute to CS in association with left-sided pathologies [e.g. RV infarction associated with inferior wall myocardial infarction, severe pulmonary hypertension in the setting of valvular disease, post-cardiac surgery or LV assist device (LVAD) implant]. CS in the setting of RV dysfunction may manifest with or without pulmonary hypertension (*Table 1*). Other conditions, including severe valvular disease, tamponade, acute myocarditis, LV outflow tract obstruction in Takotsubo syndrome, postpartum cardiomyopathy, cancers, arrhythmias, and post-cardiotomy syndrome, may destabilize and complicate with CS.

As a consequence of an acute decrease of LV contractility, CO and stroke volume are reduced leading to an acute reduction of BP, and corresponding elevation of LV end-diastolic pressure.[15] As a reaction to the BP drop, compensatory vasoconstriction occurs (including venoconstriction that functionally shifts blood volume into the circulating compartment, causing elevations of CVP and pulmonary venous pressures), altering ventricular–arterial coupling.[15] Low cardiac power output (CPO) (CO x BP), an indicator of significant LV dysfunction, has proven to be a strong haemodynamic predictor of poor outcome at CPO <0.53 W.[52] In terms of monitoring and prognosis, CPO is superior to SBP measurements in CS. SBP can be increased with use of high-dose inotropes/vasopressors, but at the expense of a marked increase in peripheral resistance. The calculated pulmonary artery pulsatility index <0.9 can identify significant RV failure.[53]

Microcirculatory dysfunction is present early in CS patients and may precede central haemodynamic abnormalities.[48] It is associated with the development of multi-organ failure and predicts poor outcome in patients with CS complicating AMI.[54] As the microcirculatory network is flow-dependent, the decrease in CO and elevated vascular tone probably reduce capillary responsiveness discordant to the cellular metabolic requirements, resulting in cellular hypoxia.[55] However, even in severe hypoxia, mitochondrial viability and function are preserved for several hours,[56] and animal models suggest an initial up-regulation of mitochondrial function in order to match metabolic demand.[57] In a sub-analysis of the CULPRIT-SHOCK trial, there was a significant and independent association between the microcirculatory perfusion parameters and the combined clinical endpoint of 30-day all-cause death and renal replacement therapy, especially in patients with loss of haemodynamic coherence between microcirculation and macrocirculation.[58] Although targeting the microcirculation in CS is appealing,[59] the response of the microcirculation to therapeutic interventions is often dissociated from systemic effects,[60] and

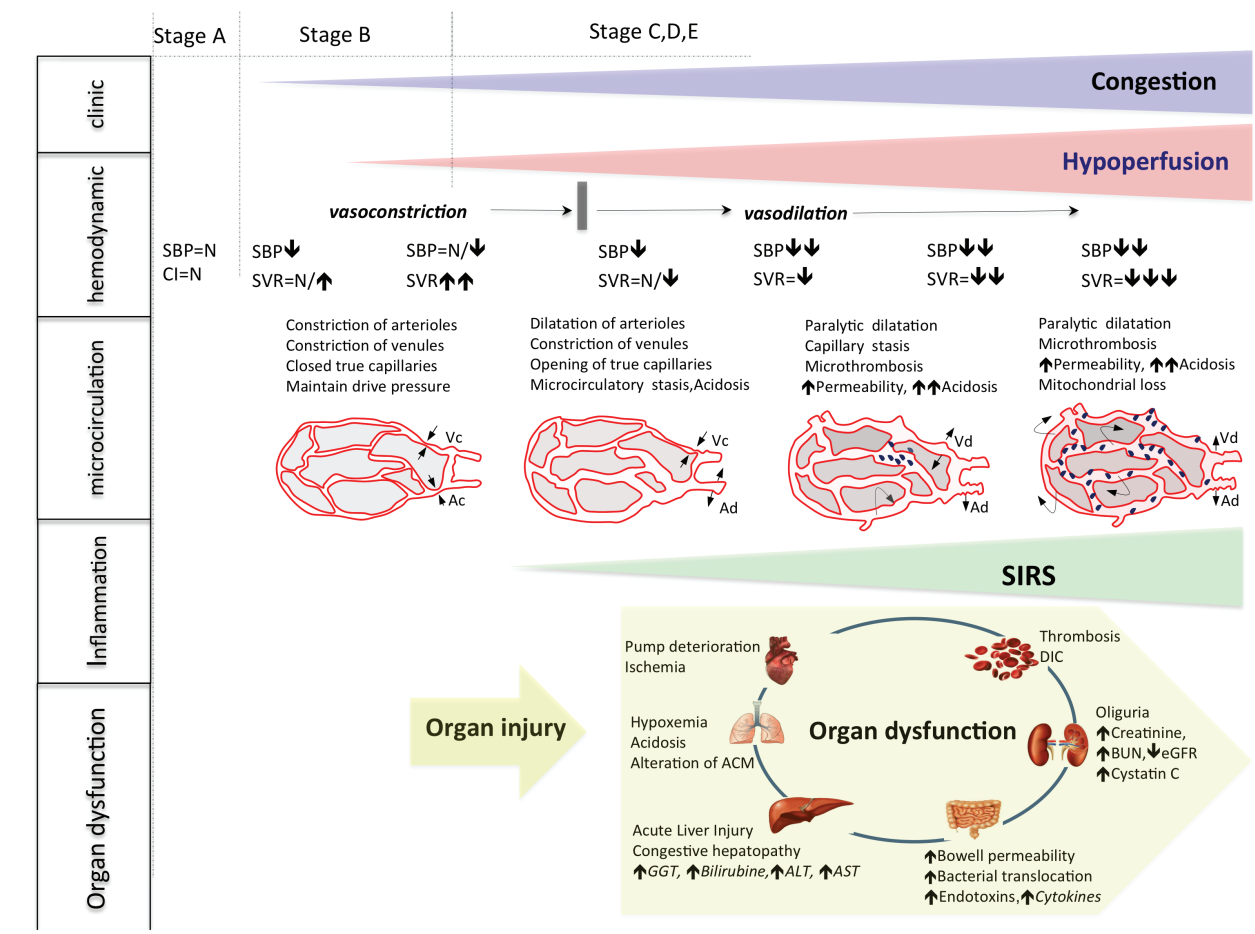

Figure 2 Pathophysiology of cardiogenic shock with staged abnormalities of clinic examination, haemodynamics, microcirculatory dysfunction and organ failure. On the upper row, the SCAI classification is presented. Ac, arteriolar constriction; Ad, arteriolar dilatation; ACM, alveolar-capillary membrane; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CI, cardiac index; DIC, disseminated intravascular coagulation; eGFR, estimated glomerular filtration rate; GGT, gamma glutamyltransferase; SBP, systolic blood pressure; SIRS, systemic inflammatory response syndrome; SVR, systemic vascular resistance; TMAO, trimethylamine N-oxide; Vc, venous constriction; Vd, venous dilatation.

interventions aimed at normalization of the microcirculation in CS have proved inconclusive.

Clinically overt inflammation is seen in 20–40% of CS patients by day 2 post-CS onset, and may result in an initially low SVR.[21] Increased levels of cytokines (interleukin-1β, 6, 7, 8 and 10) have been detected shortly after CS onset, with levels correlating with early mortality.[61] Local factors, such as nitric oxide-mediated pathological vasodilatation, dysglycaemia and acute increase of advanced glycation end-products further induce vasodilatation, and are associated with increased mortality.[62,63] In addition, infection complicates approximately 20–30% of CS cases.[64] Risks for bloodstream infection include vascular access as well as hypoperfusion-related damage to the gastrointestinal mucosal barrier and resulting bacterial translocation.

Multi-organ dysfunction is the result of both macro-haemodynamic alterations[65] and microcirculatory dysfunction[66] and portends a poor prognosis. The gut appears to be among the first organs involved in shock, and microcirculatory injury in the intestinal barrier leads to increased bacterial translocation.[67,68] Lipopolysaccharide or endotoxins produced by gram-negative bacteria enter the circulatory system and contribute to cytokine generation and inflammation.[68] In a recent retrospective analysis, including 443 253 patients with AMI-CS, there was a gradual relationship between the number of dysfunctional organs and in-hospital mortality, a lower probability of home discharge and higher in-hospital cost.[51]

Proteomic research may further assist the understanding of pathophysiology, improve risk stratification and provide an opportunity for treatment.[69] A recent research study identified a complex of four proteins (CS4P) associated with multi-organ dysfunction, systemic inflammation and immune activation.[69] During the early hours of CS, changes in the expression of CS4P may precede overt multi-organ failure and identify patients at higher mortality risk.[69]

Further, circulating dipeptidyl peptidase 3 (DPP-3) was associated with worsening haemodynamics, evolution to refractory CS and 90-day mortality.[70,71] DPP-3 is a cytosolic enzyme associated with alterations in the inflammation pathway, inducing strong negative inotropic and vasodilatory effect,[71] which can be reversed in animal models.[69,70]

Iatrogenic factors, such as administration of countershocks, cardio-depressant sedatives (e.g. propofol), antiarrhythmics, beta-blockers, excessive use of diuretics, excessive volume loading in RV shock, could further contribute to cardiovascular dysfunction in CS.[45,72]

In-hospital monitoring and investigations

Immediate assessment of hypoperfusion signs and continuous monitoring of SBP, rhythm, respiratory rate and saturation are recommended (I/C)[4,73] (online supplementary *Table S1*). In addition to SBP, pulse pressure should be closely monitored especially in patients with mnormotensive CS. A SBP ≥90 mmHg or mean arterial pressure in the range of 60–65 mmHg is generally recommended, but this target BP has not been validated in randomized clinical trials (RCTs).[4]

A *12-lead electrocardiogram* should be immediately performed (I/B) followed by continuous electrocardiographic monitoring.

Echocardiography should be used to determine the underlying diagnosis, guide interventions and monitor response to therapies (*Figure 3*), and should be performed urgently, ideally with an immediate, comprehensive study undertaken by an expert.[74] Where not available, Focused Cardiac UltraSound (FoCUS)[75] can provide useful information, and should be followed by echocardiography as soon as possible.[76]

In CS, echocardiography has a central role to identify potential underlying causes and associated pathophysiology, because without identification and treatment of the underlying cause, the outcome is usually fatal. Standard echocardiographic evaluation should provide rapidly sufficient information to confirm/exclude tamponade, mechanical complications of AMI, LV outflow tract obstruction, severe valvular lesions. Concomitant assessment of LV and RV function, and estimation of left and right filling pressures should also be included in echo protocols. In the emergency department, lung ultrasound provides point-of-care evaluation of pulmonary congestion, lung consolidation, pleural effusion, and pneumothorax.[75]

Non-invasive methods of haemodynamic monitoring[77] have certain advantages, though none have been adequately validated in the context of CS and should not be used solely.

Chest X-ray remains important for the evaluation of congestion and to monitor the catheter and cardiac device position.[73]

Invasive monitoring using an *arterial line* is recommended in all CS patients (I/C).[4]

We recommend insertion of a *central venous catheter* in all patients with CS,[5,8] allowing transduction of CVP, measurement of central venous oxygen saturation, and access for vasoactive drug administration.[78]

The routine use of a pulmonary artery catheter (PAC) remains contentious. The ESCAPE trial[79] and several studies[80–84] suggested no overall benefit in terms of mortality or readmissions from routine invasive assessment of haemodynamics compared to rigorous clinical assessment and a high rate of catheter-related complications. Although the majority of PAC studies, including ESCAPE, did not enrol CS patients, the use of PAC has decreased significantly over the past decade and is especially reserved for the care of critically ill patients in tertiary hospitals[85] with high level of user competence. In a recent retrospective study including 915 416 patients with CS, mortality in patients with CS and PAC has improved over time compared with those without PAC, which may reflect better selection of patients or better use of information to guide therapies.[41] In a US registry including 15 259 CS-AMI patients supported by Impella device, the use of PAC for haemodynamic monitoring was associated with higher survival.[86]

Based on expert opinion, PAC is currently recommended in selected patients who failed to respond to initial therapeutic interventions (persistence of hypotension and hypoperfusion) (IIb/C),[4,73] or in case of diagnostic/therapeutic uncertainty (cases of mixed shock or patients with advanced right HF).[13]

Biomarker use can provide information for the recognition, prognostication and management of CS. Elevated lactate reflects inadequate tissue oxygenation/metabolism, and the diagnosis of shock includes serum lactate >2 mmol/L,[4] which also has a strong prognostic role.[13,87] Lactate levels may be used in conjunction with haemodynamic data, and in the National Cardiogenic Shock Initiative (NCSI) dataset, stratifying CS patients according to CPO (>0.6 or <0.6 W) and lactate (>4 or < 4 mg/dL) at 12–24 h was the best predictor of survival.[88]

Potential causes of lactate elevations (e.g. diabetic ketoacidosis, liver insufficiency, trauma, epinephrine, propofol, linezolid) should be considered when lactate level is dissociated to hypoperfusion status.[89] Although lactate clearance is a signal of response to interventions and improved organ function and survival[90,91] due to the long-time delay between the intervention and drop in lactate, lactate-targeted management has not been associated with clinical benefit.[13] Natriuretic peptides are markers of disease severity and indicative of increased filling pressures. While a retrospective analysis suggested elevated natriuretic peptides were predictive for development of CS,[92] this has not been prospectively validated.

Current guidelines recommend at least daily monitoring of complete blood count, serum electrolytes, serum creatinine, liver function tests, coagulation, serial cardiac troponin levels, lactate, arterial blood gas analysis and mixed venous oxygen saturation (when PAC is available).[7,73]

Risk stratification and prognostic models

Current CS risk scores developed in the post-percutaneous coronary intervention (PCI) era (online supplementary *Table S2*) relate to the identification of patients at risk for developing CS (ORBI score),[93] prediction of short-term mortality (CardShock,

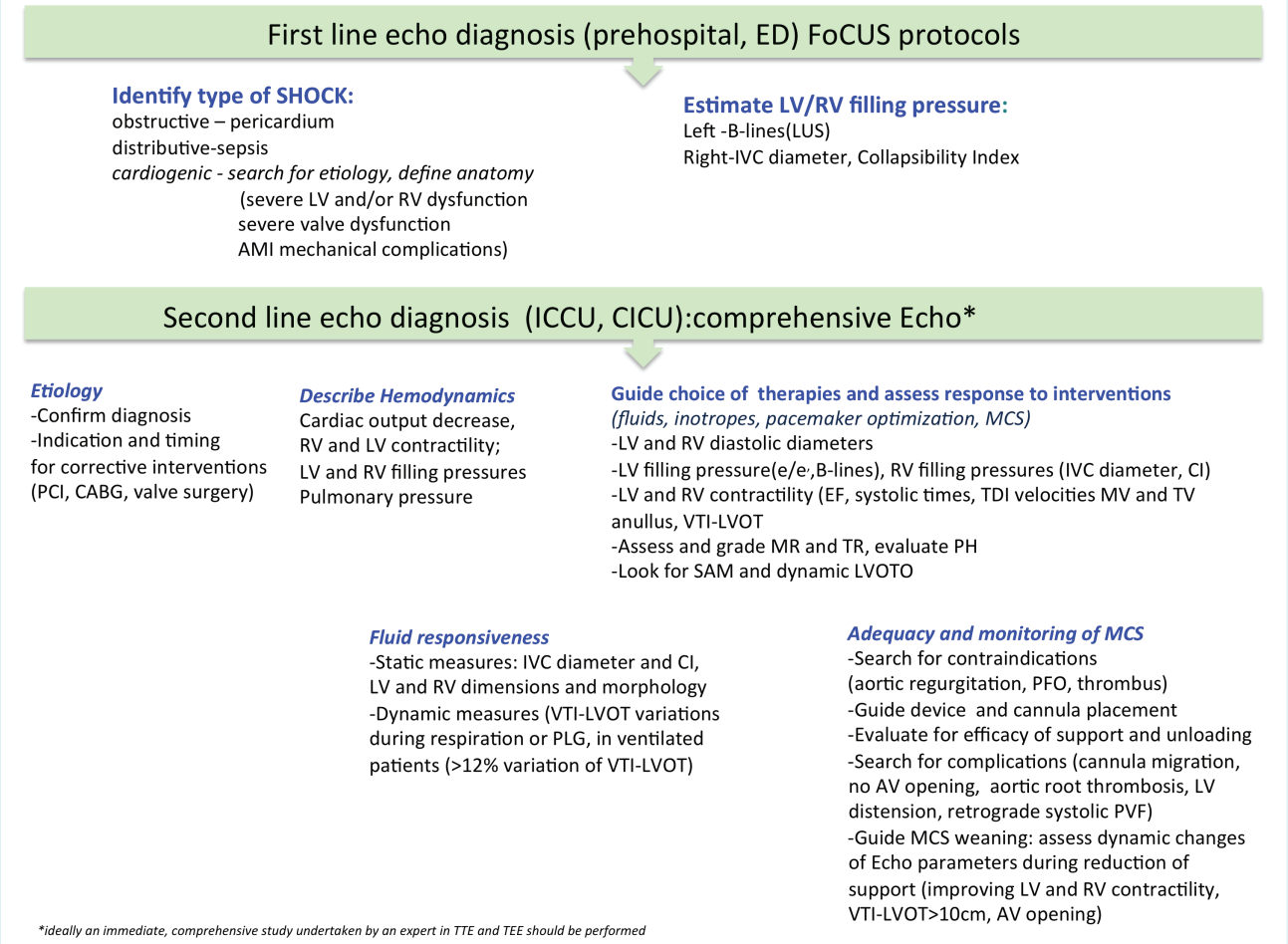

Figure 3 Utility of echocardiography in the diagnosis and management of patients with cardiogenic shock. AMI, acute myocardial infarction; AV, aortic valve; CABG, coronary artery bypass graft; CI, cardiac index; CICU cardiac intensive care unit; ED, emergency department; EF, ejection fraction; ICCU, intensive cardiac care unit; IVC, inferior vena cava; LUS, lung ultrasound; LV, left ventricle; LVOT, left ventricular outflow tract; LVOTO, left ventricular outflow tract obstruction; MCS, mechanical circulatory support; MV, mitral valve; SAM, systolic anterior motion of the mitral valve; MR, mitral regurgitation; PCI, percutaneous coronary intervention; PFO, patent foramen ovale; PH, pulmonary hypertension; PLG, passive leg raising PVF, pulmonary venous flow; RV, right ventricle; TDI, tissue Doppler imaging; TEE, transoesophageal echocardiography; TR, tricuspid regurgitation; TTE, transthoracic echocardiography; TV, tricuspid valve; VTI, velocity time integral.

IABP-SHOCK II)[42,94] and prediction of survival after the use of MCS (ENCOURAGE, SAVE-ECMO).[95–97] The CardShock score predicts mortality in CS with a large spectrum of aetiologies, while the rest address only AMI-CS patients. The only scores with external validation are CardShock,[42] IABP-SHOCK II,[94] and ORBI.[93] Recently, the CS4P risk score model improved risk prediction within 24 h of CS admission beyond the IABP-SHOCK II and CardShock clinical risk scores.[69]

Management

Systems of care

Management of CS should start as early as possible. In the pre-hospital setting, physicians should stabilize oxygenation and circulation and treat the underlying aetiology while monitoring pulse oximetry, BP, respiratory rate, and cardiac rhythm.[98,99] All patients with CS should be rapidly transferred to a tertiary care centre which has a 24/7 service of cardiac catheterization, and a dedicated ICU/ICCU with availability of short-term MCS. A model analogous to primary PCI pathways has been proposed by the American Heart Association to facilitate optimal care coordination and to minimize time delay[7] (*Figure 4*). This model consists of a network between several satellite centres (type II and III) and a central 'CS-centre' (type I).[7] CS centres should be high-volume centres (>107 cases/year)[100] with highly experienced multidisciplinary team (MDT), and availability of on-site operating rooms, short and long-term MCS, other end-organ supports and provision of safe transfer by a mobile MCS team,[101–103] as these are associated with improved outcomes[100] (*Figure 4*). A nurse to patient ratio of 1:1 is recommended[7,104] and full integration into the post-ICU pathways.

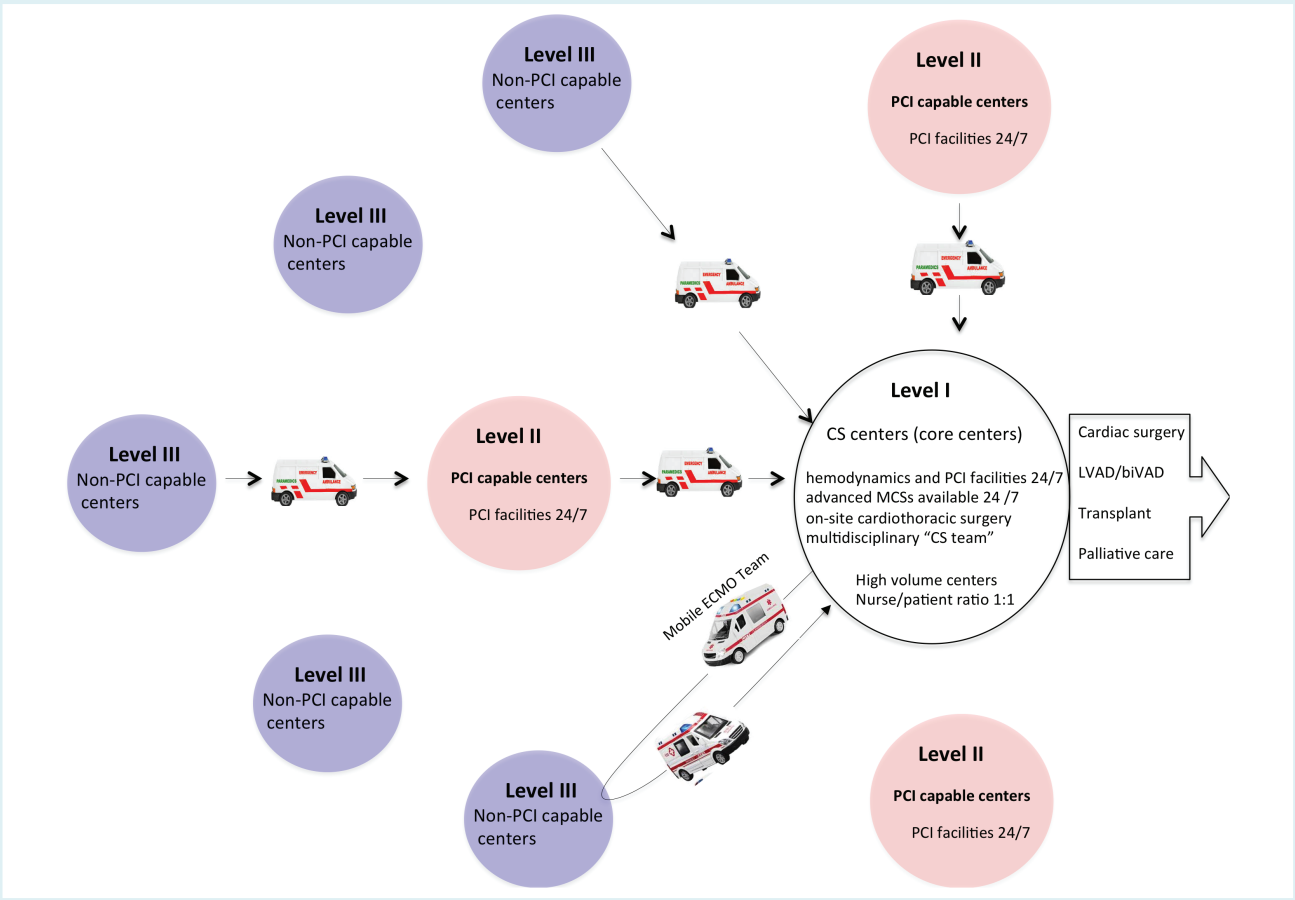

Figure 4 The systems of care for patients with cardiogenic shock (CS). A model for minimizing time delays and optimizing care has recently been proposed by the American Heart Association, where a network between several satellite centres and a central 'CS centre' exists to facilitate optimal care coordination. The core centre (first level) should be a dedicated CS centre, with expertise in the use of invasive haemodynamics and advanced mechanical circulatory support (MCS), and should be linked with multiple satellite centres [third level triage hospitals or seconnd level percutaneous coronary intervention (PCI) capable centres]. Patients should be transported to the nearest hospital capable of performing 24/7 PCI and intensive care unit/cardiac care unit availability in order to stabilize haemodynamics (type II centre). 'Refractory' CS patients needing MCS will be directed to a higher level of care (type I CS centre). The patient should be hospitalized in an intensive care unit/cardiac care unit depending on hospital availability, and followed by physicians experienced in cardiovascular procedures. CS centres should also be able to provide safe transfer by a mobile extracorporeal membrane oxygenation (ECMO) team (out-of-hospital to hospital or inter-centre transfer), which is a feasible and effective strategy in selected patients. Patients that recover and stabilize should be discharged home or directed to rehabilitation or palliative care centres, depending on the needs. biVAD, biventricular assist device; LVAD, left ventricular assist device.

Management of the underlying cause

In CS, early identification and treatment of the underlying cause is potentially beneficial in improving outcomes. Treatment of non-ACS causes is presented in *Table 1*.

Early revascularization strategy represents the cornerstone in the management of patients presenting with CS complicating ACS.[98] In the SHOCK trial, an early invasive strategy (<12 h post-CS onset) compared to initial stabilization conferred significantly lower all-cause mortality at 6, 12 and 60 months.[105] The benefit was strongly consistent across several subgroups (age, sex, ethnicity, type of ACS, presence of diabetes),[33,98,106–108] leading to a current class I/B recommendation in current guidelines.[98,108]

In the CULPRIT-SHOCK trial,[6] a 'culprit-lesion-only strategy' compared to immediate multi-vessel PCI resulted in a significant reduction in 30-day mortality or renal replacement therapy (45.9% culprit-lesion-only PCI vs. 55.4% immediate multi-vessel PCI; hazard ratio 0.83, 95% confidence interval 0.71–0.96; $P = 0.01$). This was mainly driven by an absolute 8.2% reduction in 30-day mortality (43.3% vs. 51.5%), a consistent finding across all pre-defined subgroups. Thus, 'culprit-lesion-only PCI' with possible staged revascularization has recently been implemented in the 2018 ESC revascularization guidelines.[109] The lack of benefit of immediate multi-vessel PCI has been attributed to the higher doses of contrast media and prolonged procedures and is consistent at 1-year follow-up.[110,111]

Radial access, when feasible, is currently recommended.[109,112] The groin area often needs to be preserved for insertion of MCS. However, the radial access may be challenging in hypotensive patients with CS, and radial access cannot be used to place temporary MCS. The implantation of drug-eluting stents over bare metal stents irrespective of the clinical presentation is recommended (I/A).[109]

Peri-procedural antithrombotic management

In CS, enteral antiplatelet administration may be inconsistent because of poor splanchnic perfusion and absorption, and decreased hepatic bioactivation of thienopyridines (clopidogrel). In CS following resuscitated CA, therapeutic hypothermia induces platelet dysfunction and diminishes the bioavailability of orally administered drugs due to additional gastrointestinal dysmotility.[113] Concerning the comparison of orally administered clopidogrel, prasugrel and ticagrelor, no differences were observed in terms of efficacy or safety in a secondary analysis of the IABP-SHOCK II trial.[114] However, in the absence of definitive evidence, more potent oral $P2Y_{12}$ inhibitors with rapid onset of action are recommended in CS. Cangrelor intravenous infusion provides rapid onset of action and potential rapid reversibility because its bioavailability does not depend on hepatic and gastrointestinal perfusion. Cangrelor has shown its safety with similar bleeding risk and efficacy with better TIMI flow compared with orally administered antiplatelets in a retrospective analysis of the IABP-SHOCK II trial.[115] A RCT comparing cangrelor vs. ticagrelor is currently running (ClinicalTrials.gov: NCT03551964). According to the 2017 STEMI guidelines,[98] cangrelor may be considered in STEMI patients who are unable to absorb oral agents (IIb/A), and the same level of recommendation may be applied to patients with CS.

One small randomized trial has tested the use of the glycoprotein IIb/IIIa inhibitor (GPI) abciximab in CS patients and failed to prove superiority vs. standard treatment, while a prospective but non-randomized trial has shown abciximab more effective than standard treatment in patients <75 years.[116,117] Use of GPI was associated with significantly higher major bleeding, regardless of randomization to cangrelor or clopidogrel, and the bleeding risk with GPI may be expected to be accentuated in patients with CS, particularly in those who require early MCS.[118]

Use of intravenous anticoagulants is similar to patients with ACS without CS, and intravenous unfractionated heparin is the primary choice because of the rapid reversal and the acute renal impairment that often coexists in this setting.

Fibrinolysis

The use of fibrinolysis is according to current guidelines[98,109]; however, its use may increase the risk of bleeding in the context of subsequent MCS. There is a lack of high-quality evidence to support fibrinolysis in CS. The decision to administer fibrinolysis should be individualized on the basis of perceived reperfusion benefit, bleeding risks, and the anticipated time delay to angiography. Fibrinolysis should be reserved for STEMI patients with CS when primary PCI cannot be performed within 120 min from STEMI diagnosis.[7,98]

Surgical revascularization

Although there are no direct randomized comparisons between PCI and coronary artery bypass grafting (CABG) in AMI-CS patients, a sub-analysis from the SHOCK trial[119] suggested similar 1-year mortality between PCI and CABG (48% vs. 53%) and a similar finding was found in a subsequent meta-analysis.[120] The benefit of PCI is related to its early performance, but usually limited to the culprit lesion, while CABG achieves a complete revascularization, outweighed by increased perioperative morbidity. Between 2003 to 2010, the rate of early PCI in CS rose from 26% to 54%, whereas CABG rates remained relatively stable at 5% to 6%,[99] which might represent current clinical practice.[39]

Surgery for mechanical complications

The incidence of ventricular septal rupture (VSR) post-STEMI has decreased from 1–3% in the pre-reperfusion era to 0.2%.[121] Surgical closure represents the definitive treatment for post-infarction VSR, although mortality remains high (87% in the SHOCK trial).[122,123] One study reported a sharp decrease in mortality if surgery was performed late (54.1% within 7 days from AMI vs. 18.4% after 7 days from AMI), which is however mainly attributed to a selection bias and survival of the fittest effect.[121] Survival rates following transcatheter septal closure are equally disappointing.[124] While delaying of surgery is in most cases not possible because of the haemodynamic compromise secondary to VSR, early use of MCS may allow to bridge patients to a decision of delayed repair, transplantation, or palliative options, after discussion in MDT. A substantial proportion of patients with VSR are already haemodynamically unstable at the time of CS diagnosis and these patients have an unacceptably high mortality with an urgent/emergent surgery approach. Early use of MCS may bridge patients until a decision can be made as to delayed repair, transplantation, or palliative options, after discussion in MDT. Several studies suggested that early use of veno-arterial extracorporeal membrane oxygenation (VA-ECMO) in patients with post-infarction VSR provides haemodynamic stabilization and potential to reverse multi-organ failure.[125,126] Delaying surgery, while waiting on VA-ECMO, may promote the healing process and fibrosis of the borders of the septal rupture. This could facilitate consolidation of the freshly infarcted myocardium, thus reducing the likelihood of postoperative residual shunt after surgical repair.[125–128]

Papillary muscle rupture occurs in 0.25% of patients following AMI, representing up to 7% of patients with CS.[129] Peri-procedural mortality associated with surgical correction of mitral regurgitation is lower than in VSR and depends on the extent of infarction and multi-organ dysfunction.[99] Mitral valve replacement is preferred, as repair may be highly challenging.

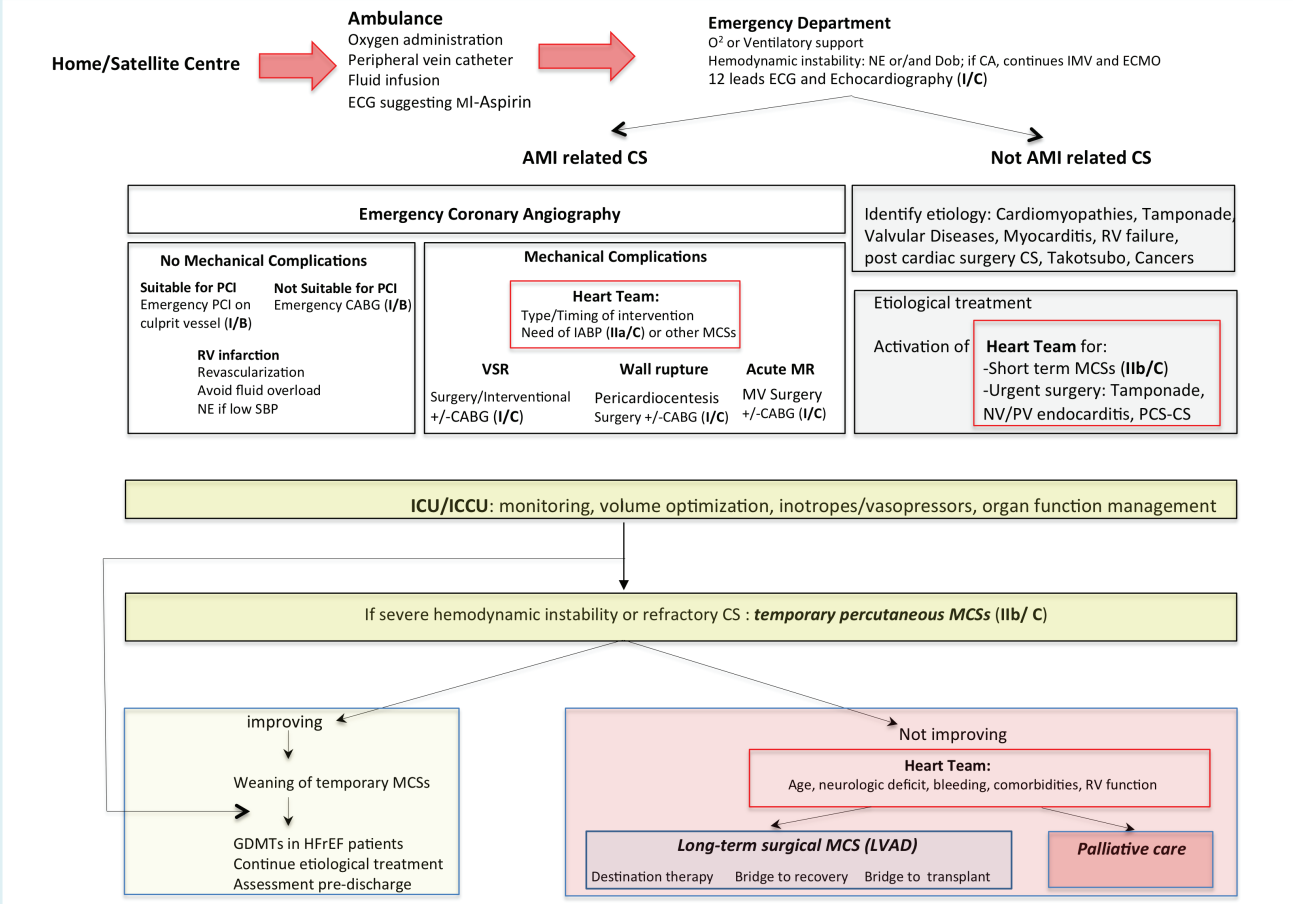

Figure 5 The algorithm for pre- and in-hospital management of patients with cardiogenic shock (CS). The level of decision by multidisciplinary heart team is presented in red rectangles. AMI, acute myocardial infarction; CA, cardiac arrest; CABG, coronary artery bypass graft; Dob, dobutamine; ECG, electrocardiogram; ECMO, extracorporeal membrane oxygenation; GDMT, guideline-directed medical therapy; HFrEF, heart failure with reduced ejection fraction; IABP, intra-aortic balloon pump; ICCU, intensive cardiac care unit; ICU, intensive care unit; IMV, invasive mechanical ventilation; LVAD, left ventricular assist device; MCS, mechanical circulatory support; MI, myocardial infarction; MR, mitral regurgitation; MV, mitral valve; NE, noradrenaline; NV, native valve; PCI, percutaneous coronary intervention; PCS, post-cardiac surgery; PV, prosthetic valve; RV, right ventricle; SBP, systolic blood pressure; VSR, ventricular septal rupture.

Free wall rupture presents as sudden-onset cardiac tamponade or CA, with contained rupture presenting sub-acutely. In both cases, surgery aims at pericardial drainage and closure of the ventricular wall defect.[130]

Current guidelines recommend that mechanical complications should be treated as early as possible after Heart Team discussion[98] (*Figure 5*), and that intra-aortic balloon pump (IABP) may be considered (IIa/C) as interim support.[98]

Medical treatment

Almost one third of patients presenting with CS are 'euvolaemic', but respond to fluid administration by increasing stroke volume.[131] Volume responsiveness assessment is guided by echocardiography (*Figure 3*). Fluid administration in CS is mainly based on patho-physiological considerations and a fluid challenge with infusion of normal saline or Ringer's lactate 250 mL over 15–30 min should be considered as first-line treatment, if there are no signs of congestion (I/C).[4] Careful administration of fluid boluses, and only used in conjunction with non-invasive or invasive assessment of CO, is recommended in patients with CS and RV dysfunction, since excessive volume overload over-distends the right ventricle and increases ventricular interdependence, impairs LV filling and reduces systemic CO.[4,17]

Inotropes/vasopressors

More than 80–90% of patients with CS receive inotropes and/or vasopressors[5] (online supplementary *Table S3*). Vasoactive medications may restore haemodynamics, but at the cost of increasing myocardial oxygen consumption and arrhythmogenic burden. Therefore, the general recommendation is to avoid their use when tissue perfusion is restored and limit the dose and the duration of infusion to the lowest possible.[99]

In the SOAP II trial, the pre-defined subgroup analysis of CS patients showed that dopamine was associated with higher 28-day mortality and increased arrhythmia burden, compared with norepinephrine.[132] However, this is only hypothesis-generating since the overall trial was neutral. A recent meta-analysis suggested similar unfavourable findings when dopamine was compared to norepinephrine.[133] Also in a propensity-matching-score analysis from the ESC HF Long-Term registry, dopamine was associated with worse short- and long-term outcomes compared with other inotropes and vasopressors.[134]

In the OptimaCC trial including AMI-CS patients, epinephrine was associated with a significantly higher rate of 'refractory CS' compared to norepinephrine,[135] and in a recent meta-analysis, epinephrine use for haemodynamic management of CS was associated with a threefold increased risk of death.[136] Additionally, epinephrine during resuscitation for CA failed to improve survival with good neurologic outcome when compared to placebo.[137] All these data suggest norepinephrine should be the first-line vasopressor recommended by guidelines (IIb/B) to sustain perfusion pressure,[4] while we do not recommend routine use of dopamine or epinephrine in CS. Vasopressin is a non-sympathomimetic vasoconstrictor agent that increases SVR and mean arterial pressure but does not affect pulmonary vascular resistance. Vasopressin increases systemic arterial pressure by specifically inhibiting the same intracellular enzymes responsible for vasodilator action of milrinone and may be used to counteract vasodilatation caused by milrinone.[138] In combination with milrinone, administration of vasopressin at low doses increased systolic pressure and allowed discontinuation or a decrease in catecholamine vasopressors.[139]

The addition of an inotrope (dobutamine) is recommended with a class IIb/C recommendation, reflecting the paucity of data in this setting.[4]

Levosimendan[140] may be used in particular CS patients already on chronic beta-blocker therapy,[17,99] as well as in patients with CS and acute RV failure or pulmonary hypertension, owing to its favourable effects on pulmonary vascular resistance.[141,142] The inotropic effect of levosimendan is the result of a combined effect from both calcium sensitization and selective and potent phosphodiesterase 3 inhibition.[143–146]

Milrinone had similar effectiveness and safety profiles compared to dobutamine,[147] but safety concerns over its use in ischaemic aetiology warrant caution owing to the results of the OPTIME-CHF trial in decompensated HF patients.[148]

Mechanical circulatory support

Temporary MCS (*Table 2*) has an emerging role in CS. Current guidelines[4] recommend the early use of MCS in patients with CS refractory to fluid load and inotropes/vasopressors (IIb/C), as a bridge either to recovery, re-evaluation, transplantation or a permanent implanted LVAD.[149] However, MCS is associated with significant complications (*Table 2*), requires specialist multidisciplinary expertise for implantation and management, and high-quality evidence regarding outcomes is largely absent.

The IABP produces a modest increase in CO of 0.5–1 L/min and may have even less benefit in patients with tachycardia and irregular rhythms. RCTs were conducted only in AMI-CS patients, and in the IABP-SHOCK II trial IABP failed to demonstrate benefit on mortality or any of the secondary endpoints.[3] A meta-analysis including 12 RCTs and 15 registries, showed no survival benefit after IABP in AMI-CS, and has further called into question the utility of IABP therapy.[150] Recently, the 6-year follow-up of IABP-SHOCK II did not show any benefit on long-term survival.[151] Therefore, the 2017 ESC STEMI guidelines order to address psychosocial aspects, educate on symptoms gave III/B recommendation for the routine use of the IABP in CS but still consider IABP only in patients with mechanical complications (IIa/C) or to stabilize for transfer for higher levels of MCS.[98] IABP still remains the most commonly used MCS, and in the light of new data showing more vascular and bleeding complications and possible higher mortality with other devices, the class III indication of IABP probably needs to be reconsidered.

Impella is a microaxial pump giving only left-sided support that unloads the left ventricle by expelling blood flow from the left ventricle into the aorta and may provide up to >5 L/min of blood flow depending on the device used and depending on afterload.[149,152,153] Impella 2.5 and Impella CP can rapidly be implanted percutaneously in the catheterization laboratory while Impella 5.0 requires surgical cannulation.[154] Unlike IABP, Impella does not require electrocardiographic or arterial waveform triggering, facilitating stability even in the setting of tachyarrhythmias or electromechanical dissociation. Although providing superior haemodynamic support compared to IABP, there is no evidence of survival benefit in AMI-CS, largely due to vascular and bleeding complications.[155] In addition, a propensity-matched study showed no survival benefit with Impella use and significantly more complications.[156] More recent large-scale registries using propensity matching showed even higher mortality with Impella use, which was also accompanied by more bleeding and access site complications.[157,158] Therefore, the broad use of the Impella in unselected cases should be avoided and larger RCTs addressing survival benefit, timing of implementation (pre/post-revascularisation) and mechanism of benefit are needed. The DanGer Shock study[159] will be the first adequately powered RCT to address whether Impella CP will improve survival in AMI-CS.

High-quality evidence regarding Impella in other causes of CS is also lacking; however, in the RECOVER I study, including patients with post-cardiotomy CS (PCCS), the Impella 5.0 was associated with 94%, 81%, and 75% survival at 30 days, 6 months, and 1 year, respectively.[160]

The TandemHeart provides a continuous flow (4 L/min) via a centrifugal pump. The venous cannula is inserted through the femoral vein and is advanced via transseptal puncture into the left atrium, and the arterial cannula provides oxygenated flow into the abdominal aorta or iliac arteries. In two randomized studies, including AMI-CS patients, TandemHeart significantly improved haemodynamic indexes as compared to IABP, but 30-day mortality did not differ between the two groups.[161,162]

Venous-arterial ECMO provides cardiopulmonary support by draining venous blood from the right atrium and returning it after oxygenation to the ascending aorta (central cannulation) or

Table 2 Characteristics of short-term mechanical circulatory support

	IABP	Impella (2.5, CP, 5.0[a])	TandemHeart	VA-ECMO
Insertion	Femoral artery to Ao	LV-Ao	Venous cannula: LA Arterial cannula: Ao	Venous cannula: RA/femoral vein Arterial cannula: femoral artery/Ao
Mechanism	ECG triggered (R-wave) Diastolic augmentation of Ao pressure and augments LV performance via systolic balloon deflation (decrease in afterload)	Expels blood from LV to Ao	Aspirates oxygenated blood from LA and returns to Ao	Drainage of deoxygenated venous blood, via an extracorporeal centrifugal pump over a membrane oxygenator and pumped back oxygenated blood to aorta/femoral artery
LV unloading	(+)	++	++	• LV overloading in peripheral cannulation • Only RV unloading
Technical characteristics	• Cannula size 7–8 F • CO • Pulsatile flow	• Cannula size 12–14 F for CP and 21 F for Impella 5.0 • CO: 2.5–5.0 L/min[a] • Continuous flow via axial pump; maximum pump speed 51 000 rpm	• Cannula size 21 F venous and 12–19 F arterial • CO: 4 L/min • Continuous flow via centrifugal pump; maximum pump speed 7500 rpm	• Cannula size 19–25 F venous and 15–19 F arterial • CO: up to 7 L/min • Continuous flow via centrifugal pump; maximum pump speed 5000 rpm
Duration		10 days for Impella 2.5 and CP and 3 weeks for Impella 5.0	2–3 weeks	3–4 weeks
Advantages	Easy insertion, easy to adjust, cath lab not mandatory, no extracorporeal blood; increase coronary and cerebral flow	ECG and pulse-independent, relatively easy insertion in cath lab[a], no extracorporeal blood	Rhythm independent, less artificial surface than ECMO; can be used in patients with Ao stenosis/prosthetic Ao valve; can be used even in LV thrombus	Rhythm independent, no cath lab requirement, rapid insertion, full circulatory support even in resuscitation situations or during malignant arrhythmia, providing combined support of the RV and LV, rapid improvement in oxygenation and the possibility of rapid application, complete cardiopulmonary bypass
Disadvantages	• ECG/pulse-dependent (mostly inefficient in tachycardia and irregular rhythms) • Limb ischaemia • Haemolysis • Thrombocytopenia • Bleeding	• Limb ischaemia • Haemolysis • Bleeding	• Limb ischaemia • Bleeding • Complex implantation requiring transseptal puncture	• Haemolysis, thromboembolic complications (large artificial surface), renal failure, limb ischaemia/amputation and bleeding • LV overloading- peripheral cannulation is associated with an increased LV afterload, which produces LV distension and pulmonary congestion and may impair myocardial recovery.[103,143] LV decompression strategies include additional procedures, such as septostomy, IABP, Impella, and hybrid circuit configuration • Harlequin syndrome (upper body hypoxia from incomplete retrograde filling and oxygenation), in which deoxygenated cerebral blood flow occurs during retrograde perfusion with peripheral cannulation. The veno-arterio-venous configuration with triple cannulation avoids upper body hypoxia
Contraindications	• Moderate to severe aortic regurgitation • Severe aortic disease	• Severe aortic stenosis • Prosthetic aortic valve • LV thrombus • VSD • Peripheral vascular disease	• Severe aortic insufficiency • Aortic dissection • Peripheral vascular disease • RV failure • VSD • Inability to tolerate systemic anticoagulation	• Severe aortic insufficiency • Aortic dissection • Inability to tolerate systemic anticoagulation

Ao, aorta; CO, cardiac output; ECG, electrocardiogram; IABP, intra-aortic balloon pump; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle; VA-ECMO, veno-arterial extracorporeal membrane oxygenation; VSD, ventricular septal defect.
Percutaneous mechanical circulatory support can be characterized by one of four circuit configurations: (i) intra-aortic devices (IABP), (ii) transvalvular aortic (Impella), (iii) LA to systemic artery (TandemHeart), and (iv) RA to systemic artery (VA-ECMO).
[a]For Impella 5.0 surgical cut-down for cannulation is mandatory.

to the iliac artery (peripheral cannulation). VA-ECMO provides high levels of biventricular cardiac (V-A) and respiratory support (V-V) in a large spectrum of clinical settings, including CS patients with malignant arrhythmias and CA. Some studies indicated an improvement in microcirculation as measured by side-stream dark field imaging.[163,164] The improvement in the oxygenator membranes permitted low resistance and improved blood compatibility characteristics.[17,165] The modern centrifugal pumps generate less heat and are less thrombogenic, allowing extended duration of support.[165]

In the event of very poor LV function, peripheral VA-ECMO can be associated with progressive LV distension and pulmonary congestion, potentially resulting in impaired myocardial recovery.[165,166] Decompression strategies for LV venting include additional procedures, such as IABP, Impella, septostomy and hybrid circuit configuration.[165–168]

When cardiac recovery precedes pulmonary recovery, ejection of deoxygenated blood flow into the ascending aorta results in upper body hypoxia ('Harlequin syndrome'),[169] requiring reducing cardiac ejection or reconfiguration (VVA or VAV) until the lungs recover.

In two recent meta-analysis including CS and CA patients, VA-ECMO was associated with significantly improved 30-day survival in both groups compared with IABP, but no difference when compared with TandemHeart or Impella.[170] A large registry with a 9-year observational period suggests 30-day in-hospital mortality remained unchanged over time (59.0% in 2007–2012 vs. 61.4% in 2013–2015).[171]

Ongoing randomized clinical trials in post-AMI-CS will test whether VA-ECMO on top of revascularization and standard therapy will lead to a reduction in mortality.[172]

Isolated right ventricular support

Right-sided support with either Impella RP or TandemHeart RA-PA has been described in numerous case reports. RV support with Impella RP in patients with refractory RV failure was feasible and associated with early haemodynamic benefit in a small non-randomized study (RECOVER RIGHT).[173] Future RCTs will test whether RV support for either RV pressure unloading (Impella RP 4 L/min) or RV volume unloading (TandemHeart RA-PA) will improve clinical endpoints.[154] However, the clinical benefit of Impella RP in real-world clinical practice is largely unknown. Recently in a letter to health care providers, the US Food and Drug Administration provided an update about Impella data based on the results of post-approval studies, where the interim analysis has indicated that survival at 30 days post-device explant or discharge was 33.3%.[174]

The recently introduced Protek Duo dual-lumen cannula contains two lumens, one serving as an inflow cannula and positioned via the internal jugular vein into the right atrium, the second delivering blood into the main pulmonary artery. Blood is drained from the right atrium into an extracorporeal centrifugal pump, which delivers blood back to the pulmonary artery. There are no large observational studies or randomized data, but several case reports described use of the device for CS secondary to RV failure in the setting of LVAD implantation and CS resulting from decompensated severe pulmonary hypertension.[175–177]

Temporary MCS represents a therapeutic modality that is available as a bridge to recovery or as a bridge to decision in refractory cases.[178] However, despite initial beneficial effect on BP and arterial lactate,[179] the unselected use of active MCS in patients with CS is not supported because data on patient selection are still scarce, the results of most trials or meta-analyses were at best neutral on survival, and the costs (in terms of patient morbidity/mortality, as well as health care economics) are high and unproven. Although risk scores such as SAVE and ENCOURAGE have been used to predict survival after the insertion of VA-ECMO,[95,96] MCS devices are associated with severe complications that may counterbalance beneficial haemodynamic effects, and further research is needed to establish a better risk/benefit ratio. This is of utmost importance in particular groups of patients such as the elderly, patients with long duration of CS, or patients with multiple comorbidities. The neutral results of the existing RCTs have multiple explanations related to inclusion of heterogeneous populations, large variability in timing of intervention, different learning curves of institutions, lack of data regarding level of anticoagulation, and poorly defined endpoints. The observed improvement of macrocirculation will not automatically translate to improved microcirculation, and macrocirculatory improvements should be considered as a measure of technical success rather than an endpoint. Clinic relevant endpoints, such as 30-day and 180-day mortality, should be considered in future RCTs. A 'standardized team-based approach' using pre-defined algorithms for early MCS implant should also be investigated in clinical trials. In a recent study, MDT-based approach including mandatory invasive haemodynamics and appropriate use of MCS, resulted in improved survival in patients with CS. Compared with 30-day survival of 47% in 2016, before implementation of this strategy, 30-day survival rate in 2017 and 2018 increased to 57.9% and 76.6%, respectively.[180]

In addition, future studies should address the choice of an individual type of MCS as well as the markers of monitoring during MCS (haemodynamic markers, echocardiography markers, inflammatory response, or organ damage markers) that can guide weaning and final decisions.[181]

Currently, the monitoring is primarily based on echocardiography, PAC haemodynamics, lactate and organ function tests. In clinical practice, if the patient is stable, weaning starts from vasopressors followed by a reduction of levels of support. If the patient remains stable on low-level of support and without requiring higher doses of vasopressors/inotropes, the MCS device can be explanted.[178] In case of MCS complications, vasopressors are continued to allow removal of the device. When the patient is haemodynamically unstable on initial MCS, a combined support may be considered. Especially in patients with biventricular failure and severe hypo-oxygenation, combined VA-ECMO and Impella may be considered. Duration of support is often unpredictable, and weaning should incorporate evaluation of bridging strategies. Patients who cannot recover on temporary MCS, but without irreversible end-organ damage, should be directed to a permanent modality (durable LVAD or heart transplantation).[131]

Organ dysfunction and specific non-cardiac interventions

Mechanical ventilatory support

Acute respiratory failure is present in almost all patients presenting with CS. Hypoxaemia and hypercapnia are the consequences of intrapulmonary shunting generated by pulmonary congestion, the reduction in lung space with increasing ventilation–perfusion mismatch, and alteration of respiratory drive as a result of cerebral hypoperfusion. In addition, lactic acidosis increases the compensatory respiratory load with hyperventilation, thereby augmenting total body oxygen requirements.[182]

Hypoxaemia is addressed with conventional oxygen therapy in various inflow rates, with one third of the patients (usually with less severe haemodynamic impairment) successfully managed via this approach.[183] Sixty to 80% of patients develop progression of respiratory failure requiring invasive mechanical ventilatory support[1] and these patients have a worse prognosis.[184] Decision to initiate mechanical ventilatory support is multifactorial, including arterial blood gas levels, neurologic status and required interventions.

No specific ventilation modality has demonstrated superiority over the others.[185] However, high levels of positive end-expiratory pressure are poorly tolerated, particularly in patients with RV dysfunction. If invasive ventilation is required, lung protective ventilation (6 mL/kg/body weight tidal volume) should be undertaken to prevent pulmonary injury.[17,182,186]

In CS associated with RV dysfunction, permissive hypercarbia/hypoxaemia should be avoided due to the associated pulmonary vasoconstriction. Also, positive intrathoracic pressure should be generally avoided because it worsens RV failure. However, the final decision will depend on the clinical needs to weigh the risks and benefits of the impact of ventilation on haemodynamics, severity of hypoxaemia and presence of atelectasis.[186]

Liver injury

Liver injury frequently complicates CS, and more than 50% of patients present with elevated liver enzymes.[187] Ischaemic hepatitis represents the diffuse hepatic injury caused by a sudden drop in CO and is accompanied by a sharp elevation of the serum alanine aminotransferase, aspartate aminotransferase and lactic dehydrogenase. Aminotransferases peak ≈1 to 3 days after the haemodynamic insult returning to normal 7–10 days in the absence of further insult. Transaminases are associated with worse in-hospital mortality and can be used as biomarkers of haemodynamic reserve.[188] Congestive hepatopathy is commonly seen in patients with high venous pressure, particularly in CS patients with RV dysfunction. It is accompanied by high levels of direct bilirubin, gamma-glutamyl transferase and alkaline phosphatase. However, these abnormalities often coexist, and liver function abnormalities in CS are a combination of both congestion and reduced CO. In the absence of specific therapies for liver injury in CS, particular attention must be paid to RV function, including reduction in pulmonary vascular resistance and right atrial pressure.[186,187]

Renal dysfunction

About one third of CS patients develop acute kidney injury (AKI), but many CS survivors do experience gradual renal recovery. The process may be slow (5–20 days) and depends on the severity of AKI.[189] Systemic hypoperfusion, backward congestion, nephrotoxic drugs, contrast agents and MCS may contribute to AKI in CS. If acute tubular necrosis develops, renal replacement therapy will be required and prognosis worsens.

Continuous veno-venous hemodiafiltration is recommended in severe AKI (creatinine ≥2× baseline and urine output <0.5 mL/kg/h for ≥12 h) or when life-threatening changes in fluid, electrolyte, and acid–base balance mandate.[190] Intermittent haemodialysis should not be used as it is poorly tolerated.[191]

Temperature management

An admission diagnosis of CA increased progressively the risk of hospital mortality among patients with each SCAI shock stage, supporting its inclusion as an effect modifier in the SCAI shock classification schema. However, the relative effect of CA on mortality appeared to be greater among patients with mild CS or 'at risk' of CS (SCAI stages A through C), categories where therapeutic interventions may have more benefit.[19]

Following CA, targeted temperature management reduces the overall metabolic rate and myocardial oxygen consumption contributing to better neurological protection.[192,193] However, there are limited data in CS following CA. In the SHOCK-COOL trial, mild therapeutic hypothermia failed to show a substantial beneficial effect on cardiac power index at 24 h in patients with CS after AMI.[194] The HYPO-ECMO trial[195] is currently recruiting CS patients on VA-ECMO and will address whether moderate hypothermia is associated with improved organ function.

Stabilization phase – discharge

Patients discharged at home without having fully recovered from critical illness carry a very high rate of early rehospitalization and death.[196,197] A MDT approach before discharge is mandatory in order to address psychosocial aspects, educate on symptoms, diet, exercise, and manage comorbidities[198] (online supplementary *Table S4*). In patients with HF and reduced ejection fraction, disease-modifying therapies should be (re)initiated at lowest doses when patients are clinically stable, euvolaemic and at least 24 h after intravenous catecholamines stopped. When the patient cannot be discharged home, a rehabilitation programme or a palliative care centre should support the transition phase.[7]

Cardiogenic shock in various clinical settings

In patients presenting with CS, non-ACS causes should always be considered, as they represent different clinical settings with particular pathophysiological characteristics and specific management (*Table 1*).

Right ventricular failure

Rapid identification of the presence and aetiology of RV dysfunction, correction of hypervolaemia/hypovolaemia, appropriate management of ventilation and assessment of associated pulmonary hypertension are pivotal to successful management (*Table 1*). Echocardiography and PAC-tailored management are recommended to optimize haemodynamics and volume status. When patients fail to respond to inotropes/vasopressors, VA-ECMO or Impella RP may be considered.[172] Acute RV failure post-LVAD implantation has an incidence of 20–25% and may be clinically recognized and diagnosed using the modified EUROMACS score (including clinical, laboratory, echocardiographic and haemodynamic variables).[199] It should be managed with standard supportive therapies including inotropes like milrinone, levosimendan and dobutamine, which allow pulmonary vasodilatation.[200] Inhaled nitric oxide and sildenafil can be used to reduce pulmonary vascular resistance. The LVAD flow must be adjusted in order to optimize RV function. In severe cases, right-sided mechanical support should be used (Impella RP or Protek Duo). The ideal device for RV support should be one that is easy to implant and explant, provides adequate RV support and does not interfere with LVAD physiology.[177] VA-ECMO should be used with caution because it concurrently decreases LVAD preload and increases LVAD afterload (*Table 1*).

Fulminant myocarditis

The combination of flu-like symptoms in association with evidence of myocardial injury should raise the suspicion of acute myocarditis. The diagnostic approach in the critically ill patient with rapidly progressive HF despite standard therapy includes RV endomyocardial biopsy to exclude giant cell myocarditis and acute eosinophilic myocarditis, where treatment with immunosuppressant agents[201,202] should not be delayed. In a prospective study, combination therapy (cyclosporine plus prednisolone) was associated with more favourable outcome.[201] The contemporary transplant-free survival of otherwise lethal giant-cell myocarditis treated with combined immunosuppressive drugs is 65% at 1 year and 42% at 5 years.[202] In contrast to giant cell myocarditis, acute eosinophilic myocarditis usually responds to high doses of corticosteroids.[203]

In patients with fulminant myocarditis, irrespective of the underlying aetiology, early MCS should be considered, and is associated with acceptable mid-term survival rates.[203,204] Due to the diffuse myocardial involvement, percutaneous univentricular MCS devices are often insufficient to restore peripheral perfusion and oxygenation, and biventricular support (VA-ECMO in combination with Impella, or a biventricular assist device) is frequently required.[203] If myocardial function does not sufficiently recover, longer-term MCS may be required, potentially followed by transplantation.

Takotsubo syndrome

Takotsubo syndrome is characterized by severe AHF often accompanied by LV outflow tract obstruction, CS and CA. The incidence of CS in the Takotsubo population varies from 2.8% to 12.4%.[205,206] In a large-scale study comparing clinical characteristics and in-hospital outcomes of patients with CS in settings of Takotsubo syndrome vs. patients with AMI-CS, CS in Takotsubo was associated with a significantly lower mortality (15%) than AMI-CS (36.5%).[40] In a prospective study with longitudinal follow-up, patients with Takotsubo syndrome and CS had a 28-day and 1-year mortality of 28.6% and 61.9%, respectively.[206] Long-term susceptibility to fatal events after the acute phase of Takotsubo syndrome may be explained by a LV function not yet fully recovered and/or arrhythmic events caused by QT prolongation.[206] Regarding treatment, catecholamine administration should be avoided, as already have a causative relationship with the syndrome. Milrinone, via increasing cardiomyocyte cAMP levels, also appears to trigger Takotsubo syndrome in pre-clinical models and should be avoided.[207] Levosimendan, which does not increase cAMP, seems a rational approach.[208] Early MCS may diminish the need for catecholamines and provide the reasonable time frame for LV recovery.[178] Afterload reduction by IABP may further deteriorate LV outflow tract obstruction, and close echocardiographic monitoring is required.

Peripartum cardiomyopathy

Peripartum cardiomyopathy (PPCM) is an idiopathic cardiomyopathy occurring in the last month of pregnancy or in the puerperium, with unpredictable outcome. In the majority of cases myocardial function recovers within months, while in about one third of it stabilizes or worsens.[209] Some PPCM patients may have thrombus in the left ventricle that may lead to stroke. The pathophysiologic trigger is the formation of 16 kD prolactine that promotes oxidative stress. In CS complicating PPCM, catecholamine therapy is detrimental. Although evidence is provided only by small studies, the combination of high-dose bromocriptine (inhibitor of prolactin release), inodilators and early MCS seems to be a rational strategy.[210]

Valvular disease

A variety of mechanisms may contribute to CS in the setting of decompensated valvular disease, and initial stabilization is recommended before evaluation for corrective surgery. For patients with aortic or mitral valve endocarditis with severe acute regurgitation, obstruction or fistula causing refractory CS, surgery must be performed on an emergency basis, irrespective of the status of infection.[211] MCS should be individualized based on pathophysiology of the valvular disease[172] (*Table 1*).

Out-of-hospital cardiac arrest

Out-of-hospital CA patients represent a special category, with increasing prevalence in the ICCUs. The prevalence of CA increased substantially with increasing shock stage in the SCAI classification, highlighting the correlation between CA and severe shock. Shock severity demonstrated a stepwise association with mortality in patients with CA, emphasizing the synergistic mortality effects of concomitant CS and CA.[19]

Table 3 Gaps in evidence

Domain	Gaps in evidence
Definition	• Definition is not unique among RCTs or consensus documents • How many clinical or biological signs of hypoperfusion are required for the definition of CS • The value of hypotension as mandatory criterium for CS definition • Additional value of pulse pressure in normotensive CS patients • Cut-off lactate levels for CS definition in patients with liver disease or diabetic ketoacidosis
Pathophysiology	• Pathophysiology is not well clarified because there are diverse aetiologies and precipitants, and varied baseline cardiac conditions • There is substantial overlapping among the stages of evolution of CS and no clear chronology • The role and time of occurrence of inflammation
Classification	• Recognition of early stages (pre-shock states) • AMI patients at risk for CS (stage A): in-hospital trajectory, monitoring and management • Normotensive CS: prognostic and medical management • Definition of refractory CS; if it relates to the number of vasopressors or to the highest dose of vasopressors (NE equivalents) • Whether transitions to the higher or lower grade stages of CS will change the prognosis • How phenotyping CS patients will improve decision-making algorithms
Prognosis	• Risk stratification in non-ACS CS populations • Prospective validation and impact studies for contemporary risk scores • The incremental value of proteomics in risk stratification
Monitoring	• Which markers to follow for optimal monitoring in the diverse stages of evolution of CS • The role of PAC to monitor the therapeutic response • The role of microcirculatory dysfunction parameters • Define markers and cut-off values for specific organ dysfunction/failure • Clarify 'organ dysfunction' vs. 'organ failure'
Medical management	• Dose, up-titration and combination of vasopressors and inotropes • How and when to wean the patients from inotropes/vasopressors • Target value of BP or MAP or CPO while on catecholamines • Novel therapies • The role of proteomics for individualized targeted interventions
MCS	• Patient selection for MCS • The type and timing of MCS implant by CS aetiology • Timing of mechanical LV unloading relative to coronary reperfusion in ACS-CS • How and when to wean from MCS; the role of 'decisional' markers • The role of 'temporary LVAD' • Optimal approach to prevent and manage potential MCS-related complications • New devices with less complications
Systems of care	• Which is the safer trajectory of a CS patient • Network between CS centres and integration in national/regional health care system • Level of competence and critical care training of the physicians who manage CS patients • The link between hospitalization and rehabilitation/palliation

ACS, acute coronary syndromes; AMI, acute myocardial infarction; BP, blood pressure; CPO, cardiac power output; CS, cardiogenic shock; LV, left ventricle; LVAD, left ventricular assist device; MAP, mean arterial pressure; MCS, mechanical circulatory support; NE, norepinephrine; PAC, pulmonary artery catheter; RCT, randomized clinical trial.

In the IABP-SHOCK II and CULPRIT-SHOCK trials, 40–50% of patients were resuscitated before randomization.[3,6] Immediate mortality is high, reaching more than 85% in some registries.[212] During hospitalization, many of these patients also die from withdrawal of life-sustaining therapies because of anoxic brain injury.

Pathophysiology of CS secondary to CA is determined by pump failure (as a result of the initial cardiac insult responsible for CS and prolonged myocardial stunning due to CA) and systemic vasodilatation secondary to regional and global ischaemia–reperfusion injury.[213,214] For patients with CA refractory to cardiopulmonary resuscitation (CPR), ECMO support during CPR (E-CPR) may be considered. The goal of E-CPR is to support patients in refractory CA while reversible causes are being identified and treated.[215–217] Based on registry studies,[171] E-CPR was associated with a 13% absolute increase in the 30-day survival rate compared to conventional CPR.

These patients have a higher burden of in-hospital complications with more frequent use of resources[218] and 30% are discharged with functional impairment, requiring a skilled nursing facility.[219]

Post-cardiotomy cardiogenic shock

The incidence of PCCS varies between 2% and 5%[220–222] and it is associated to poor outcomes. In a study including 1764 PCCS patients, 30-day and 3-month survival were 61% and 35%, respectively, with only 29% alive at 1 year.[223] Numerous factors may contribute to PCCS, including preoperative morbidity, type of surgery, insufficient cardio-protection and prolonged cardiopulmonary bypass. Inability to wean from cardiopulmonary bypass and/or poor postoperative haemodynamics may be indications for MCS. Depending on the pathophysiology, VA-ECMO, Impella 5.0 or CentriMag can be used in PCCS.[153,154]

Refractory RV failure occurs in 0.1–1% of patients following cardiotomy and in-hospital survival is as high as 25–30%.[224]

Two readily remediable conditions must be rapidly excluded/addressed, including localized pericardial tamponade and dynamic LV outflow tract obstruction. The localized tamponade in the first week post-cardiotomy has been reported in 0.2–2% of patients with CABG and 8.4% in heart transplant patients, and precipitating factors included administration of anticoagulants, coagulation disorders, excessive mediastinal bleeding, removal of epicardial pacing wires.[225]

Dynamic LV outflow tract obstruction leading to CS in the first days post-surgery has an incidence of 0.3% and associated conditions are hypovolaemia, cardiac hypertrophy, aortic valve replacement, and high doses of catecholamines.[225]

Cancer

Although data regarding the incidence of CS in patients with a malignancy are scarce, history of cancer is an independent risk factor of mortality in CS.[226] CS can develop due to cancer itself, the co-existing cardiovascular disease, thromboembolic events, or the type of treatment (surgery, chemotherapy, immune checkpoint inhibitors and radiotherapy).[227]

Gaps in evidence

Despite advances in revascularization, valve interventions and MCS, CS remains the most common cause of in-hospital death after AMI and a major cause of death in young patients with other potentially reversible underlying cardiac pathology. Gaps in evidence are extensive (*Table 3*) and relate to definition, phenotype diversity, pathophysiology, and management. These gaps contributed to a large geographical variability in practice care, in terms of utilization of decisional markers or risk scores, use of haemodynamic monitoring, and timely deployment of MCS. Recently, the NCSI designed a shock protocol and organized teams who mutually agreed to treat patients according to the 'best practices'.[88] This initiative suggests that a protocol-based approach is reproducible and that overall adherence to the protocol may be associated with improved outcomes.[88] A standardized 'team-based' multidisciplinary care in the context of a network of regionalized care system may not only improve patient outcomes but may also facilitate pragmatic trial designs evaluating current and future novel therapies.[180]

Evidence from RCTs is limited, mostly because small numbers of patients are recruited, with only approximately 2000 patients being randomized in CS trials. In addition, blinding is often not possible and the primary endpoints often differ from one study to another. Designing outcome trials in CS remains particularly challenging in this critical, rare and very costly scenario in cardiology.

Summary

Cardiogenic shock is a complex multifactorial clinical syndrome with extremely high mortality, developing as a continuum, resulting from the initial insult (underlying cause) to the subsequent occurrence of organ failure and death. Substantial investments in research and development have not yielded proof of efficacy and safety for most of the therapies tested, and outcome in this condition remains poor. Future studies should consider delivering pathophysiological appropriate therapies in a timely manner, in appropriately selected population, whilst avoiding iatrogenic harm. High-quality translational research should facilitate incorporation of more targeted interventions in clinical research protocols, aimed to improve individual patient outcomes.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. In-hospital monitoring and investigations.

Table S2. Scoring system, risk categories and relative risk for each category.

Table S3. Vasoactive medications.

Table S4. Pre-discharge evaluation.

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