Review

The role of temporary mechanical circulatory support in *de novo* heart failure syndromes with cardiogenic shock: A contemporary review

Stavros Eftychiou [1,#], Antonis Kalakoutas [2,3,#], Alastair Proudfoot [4,5,6,*]

[1] Barts Health NHS Trust, London E1 1FR, UK
[2] Barking, Havering and Redbridge University Hospitals NHS Trust, Romford RM7 0AG, UK
[3] Barts and the London School of Medicine and Dentistry, London E1 2AD, UK
[4] Department of Perioperative Medicine, Barts Heart Centre, St Bartholomew's Hospital, London EC1A 7BE, UK
[5] Queen Mary University of London, London EC1M 6BQ, UK
[6] Department of Anaesthesiology and Intensive Care, German Heart Centre Berlin, Berlin 13353, Germany

A B S T R A C T

Cardiogenic shock (CS) is a complex clinical syndrome with a high mortality rate. It can occur to due to multiple etiologies of cardiovascular disease and is phenotypically heterogeneous. Acute myocardial infarction-related CS (AMI-CS) has historically been the most prevalent cause, and thus, research and guidance have focused primarily on this. Recent data suggest that the burden of non-ischemic CS is increasing in the population of patents requiring intensive care admission. There is, however, a paucity of data and guidelines to inform the management of these patients who fall into two broad groups: those with existing heart failure and CS and those with no known history of heart failure who present with "*de novo*" CS. The use of temporary mechanical circulatory support (MCS) has expanded across all etiologies, despite its high cost, resource intensity, complication rates, and lack of high-quality outcome data. Herein, we discuss the currently available evidence on the role of MCS in the management of patients with *de novo* CS to include fulminant myocarditis, right ventricular (RV) failure, Takotsubo syndrome, post-partum cardiomyopathy, and CS due to valve lesions and other cardiomyopathies.

Introduction

Cardiogenic shock (CS) is a pathophysiologically complex and phenotypically heterogeneous clinical syndrome with multiple etiologies. It is characterized by primary or secondary cardiac dysfunction with associated hypoperfusion of peripheral tissues and organs and is one of the leading causes of admission to the cardiac intensive care unit (CICU). Despite over two decades of research and advances in the clinical management of CS, in-hospital mortality remains 30–40%.[1] Acute myocardial infarction-related CS (AMI-CS) pathophysiology and management has hitherto been the most comprehensively researched etiology with both large-scale registry-based data and randomized controlled trials (RCTs) informing practice. There are, however, sparse data to guide the characterization and management of non-AMI-CS and specifically CS in patients without a prior diagnosis of heart failure. This observation is reflected in a paucity

of societal guidelines to inform practice in the non-ischemic population with CS, specifically the role of temporary mechanical circulatory support (MCS) to maintain cardiac output (CO) and restore end-organ perfusion.[2] Herein, we will review the use of MCS for the management of *de novo* subtypes of CS to include fulminant myocarditis, right ventricular (RV) failure, Takotsubo syndrome, post-partum cardiomyopathy, CS due to valve lesions and other cardiomyopathies, as well as in CS in cancer patients.

Definitions

CS is a clinical syndrome that results from primary cardiac dysfunction leading to tissue hypoperfusion and cellular or tissue hypoxia.[3] There have been attempts to generate a universal definition for CS, but no consensus exists to define the clinical and hemodynamic criteria that describe a heterogenous clinical syndrome due to multiple etiologies.[4] Common to the clini-

cal and trial definitions, most of which have centered on AMI-CS,[5] are the presence of; hypotension manifest by a systolic blood pressure of ≤90 mmHg; clinical or biomarker evidence of tissue hypoperfusion; elevated left ventricular (LV) filling pressures; and a low CO state. However, the use of "one size fits all" definitions which were designed to support clinical trial enrollment, does not account for the heterogeneity of CS which can range from those with focal myocardial dysfunction due to ischemia needing minimal vasopressor support to CS with ongoing cardiac arrest.[6] Intuitively, treatments and interventions will have varying outcomes depending on the etiology, severity of CS, patient characteristics, and comorbidities.

To address the need for nuance in the description of CS, particularly around severity, the Society for Cardiovascular Angiography and Intervention (SCAI) have proposed a SHOCK classification system.[7] The document describes five distinct stages, ranging from At risk through to Extremis (Table 1) and aims to provide a simple and standardized framework to communicate the severity of CS between clinicians and triage patients for transfer to specialist centers and/or consideration for MCS devices. The SCAI classification has been externally validated across multiple registries and study populations, demonstrating that shock severity across SCAI stages is strongly associated with short-term mortality.[8–10]

Epidemiology and Mortality

Data regarding CS epidemiology are predominantly derived from large registries of patients with AMI-CS.[11] The incidence of non-AMI-CS is highly variable between registries and study populations, with a European registry between 2010 and 2012, identifying only about 20% of CS cases to be non-AMI.[12] Non-AMI-CS was due to acute-on-chronic HF (11%), valvular/mechanical (6%), Takotsubo cardiomyopathy (TCM, 2%), and myocarditis (2%). More recent data suggest that the incidence of non-AMI-CS may be even higher, with the majority of patients admitted to the CICU being CS related to acute-on-chronic HF-CS or de novo HF-CS.[13,14] This increase could be explained partly by a decline in the incidence of ST elevation myocardial infarction (STEMI) and acute coronary syndromes[15,16] combined with improved management of AMI over the last two decades, and partly by the increasing prevalence of HF and non-coronary structural heart disease.[17]

Mortality in contemporary CS trials ranges between 30% and 50%.[18–20] Single and multi-center registry data suggest recent improvements in mortality due to a combination of timely and targeted revascularization of the culprit coronary artery in AMI-CS,[21,22] protocolized and early use of MCS and the integration of specialized CS teams to guide management and escalation.[23–25] There are limited datasets that have incorporated CS across all its etiologies; hence, comparison of outcomes between AMI and non-AMI-CS is challenging. Data from a large US registry suggest that patients with non-AMI-CS may have comparatively better survival rates (36% vs. 31%).[20] Patients with de novo HF-CS tend be less comorbid and have fewer cardiovascular risk factors than those with acute-on-chronic HF-CS.[13] Despite this, they tend to have more severe shock presentations, higher lactate levels, and higher Sequential Organ Failure Assessment (SOFA) scores. Consequently, in-hospital mortality appears to be higher in de novo HF compared to acute-on-chronic HF-CS.[13]

Assessment for Phenotypic Characterization

After confirmation of CS, clinical, hemodynamic parameters and imaging evidence are pivotal to guide the escalation

Table 1
SCAI classification of cardiogenic shock severity.

SCAI stage	Description	Physical examination	Biochemical markers	Hemodynamic parameters
A – at risk	Not experiencing signs or symptoms of CS but at risk, e.g., current/prior large AMI, acute/acute-on-chronic HF symptoms	• Normal JVP • Warm, well-perfused with distal pulses • Normal mental status	Normal lactate levels	• Normotensive (SBP >100 mmHg or at baseline) • CI >2.5 L/min/m² • CVP <10 mmHg • PCWP <15 mmHg • PA saturation >65%
B – beginning CS	Clinical evidence of hemodynamic instability without signs of tissue hypoperfusion	• Elevated JVP • Warm, well-perfused distally • Normal mental status	Normal lactate levels	• Hypotensive (SBP <90 mmHg) • MAP <60 mmHg • >30 mmHg drop from baseline • achycardic (>100 bpm)
C – classic CS	Clinical hypoperfusion requiring either pharmacological or mechanical intervention beyond volume resuscitation	• Volume overload • Looks unwell • Altered mental status • Feeling of impending doom • Cold peripherally, high CRT	• Lactate >2 mmol/L • Stage 1 AKI based on serum creatinine • Elevated LFTs and BNP	Invasive hemodynamic monitoring strongly recommended: • CI <2.2 L/min/m² • PCWP >15 mmHg
D – deteriorating	Failure of initial support to restore tissue perfusion with worsening hemodynamic parameters or rising lactate	Any Stage C and worsening despite initial therapy	Any Stage C and: • Lactate rising and persistently >2 mmol/L • Deteriorating renal function/LFTs/BNP	Any Stage C and requiring escalation in initial support
E – extremis	Current or impending circulatory collapse	• Unconscious • Near pulselessness • Cardiac collapse • Multiple defibrillations	• Lactate >8 mmol/L • Severe acidosis (pH <7.2, BD >10 mEq/L)	Profound hypotension despite maximal hemodynamic support

AKI: Acute kidney injury; AMI: Acute myocardial infarction; BD: Base deficit; BNP: Brain natriuretic peptide; bpm: Beats per minute; CI: Cardiac index; CRT: Capillary refill time; CS: Cardiogenic shock; CVP: Central venous pressure; HF: Heart failure; JVP: Jugular venous pressure; LFT: Liver function test; MAP: Mean arterial pressure; mEq/L: Milliequivalents per liter; PA: Pulmonary artery; PCWP: Pulmonary capillary wedge pressure; SBP: Systolic blood pressure; SCAI: Society for Cardiovascular Angiography and Interventions.

of treatment to MCS. Early MCS initiation may prevent toxic use of inopressors and is recommended in international guidance, but the optimal timing remains uncertain and is complicated by the complexity of CS phenotypes.[4] Severity stratification using the validated SCAI shock classification helps refine MCS selection based on the stage of CS, as the outcome of each MCS will vary depending on the acuity stage at which MCS is initiated.[7]

Echocardiography is pivotal to diagnose, classify, and escalate management and guide the use of MCS in CS.[26] Parameters comprehensively assessed include RV and LV function, presence of valvular stenosis or regurgitation, cardiac filling pressures, assessment of stroke volume and cardiac indices, and presence of outflow tract obstructions and intracardiac thrombi.

Choice and management of pharmacologic and MCS therapies to optimize hemodynamics often requires advanced physiological information derived from pulmonary artery catheters (PAC) to guide MCS selection, therapeutic response, and device weaning. PACs facilitate direct measurement of blood flow (CO/index), intracardiac/pulmonary filling pressures (pulmonary artery pressures, pulmonary capillary wedge pressure [PCWP] and central venous pressure [CVP]), mixed venous oxygen saturations, and carbon dioxide gap which has been associated with worse mortality in CS.[27] Derived parameters facilitate additional assessment of pulmonary and vascular resistance as well as mechanical work (left and right stroke work index) and metrics of RV dysfunction (pulmonary artery pulsatility index [PAPi]). RV dysfunction with or without concomitant LV dysfunction is prevalent in CS and is independently associated with mortality.[28] Hence, prompt identification of RV dysfunction guided by PAC parameters can prompt earlier escalation toward RV support or decongestion.

There are currently no RCTs analyzing the benefit of PAC in CS.[29] The 'Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness' demonstrated no survival benefit in patients admitted with severe heart failure but patients with CS were excluded.[30] A recent retrospective cohort study from the Cardiogenic Shock Working Group (CSWG) demonstrated that PAC-derived hemodynamic data prior to MCS initiation improved survival from CS across SCAI subcohorts of C–E (adjusted odds ratio [OR]= 1.57; 95% confidence interval [CI]: 1.06–2.33).[31] Expert opinion supports PAC placement in CS, but there is uncertainty regarding timing of placement in CS.[32] Despite persisting concerns relating to safety, a recent multinational cross-sectional survey demonstrated that the PAC remains widely used within CICUs.[33] The Pulmonary Artery Catheter in Cardiogenic Shock trial (PACCS trial, NCT05485376) will assess the use of PACs in the context of acute decompensated heart failure, including both *de novo* and acute-on-chronic presentations to guide hemodynamic assessment and escalation of management. Results from this study will hopefully further inform clinical practice. The use of alternative CO monitoring devices, for example, transpulmonary thermodilution, although more widely available than PACs, has not been assessed or validated clinically in any CS phenotype. These can provide continuous measurements of CO and estimation of end-diastolic volume of the cardiac chambers. It may also provide cardiac function index, which can only correlate to left ventricular ejection fraction (LVEF) in the absence of RV dysfunction.[34]

By virtue of the need for inopressor support, central venous catheterization is almost ubiquitous among patients with CS, facilitating measurement of right atrial pressure (RAP). Observational data have demonstrated that cardiac filling pressures are consistently elevated across the heart failure shock cohort, that RAP is significantly higher among nonsurvivors and increased across SCAI stages,[35] and that a reduction in RAP is associated with survival in CS patients who receive MCS.[36] RAP is increasingly viewed as a surrogate for congestion in extra-thoracic organs, such as the kidneys, which translates to the output pressure of intra-abdominal organs. Central venous waveforms can, in addition, trigger assessment of the heart and lung/ventilation settings.[37] Nonetheless, RAP assessment in isolation is challenging owing to its preload dependency.

Hemodynamic Support with Vasopressors/Inopressors

While the primary focus of treatment in CS should be addressing the underlying primary insult, the mainstay of standard medical management in the critical care unit involves optimizing fluid status and the use of vasoactive agents. Practice and refinement of vasoactive agent selection is supported by limited clinical outcome data.[26] Despite an improvement in hemodynamic parameters, vasopressors and inotropes increase myocardial metabolic demand, impair tissue perfusion, increase the risk of arrhythmias, and may lead to complications and harm.[38] The use of these drugs should therefore be minimized where possible and escalation of inopressors should be signal consideration of MCS strategies in select patients. As a general principle, vasopressor and inotrope use should be tailored to their pharmacological principles, CS phenotype, and clinical experience.

There is a paucity of high-quality evidence to guide the ideal choice of vasopressor or inotrope in CS. Noradrenaline is established as the first-line vasopressor of choice and has shown superiority compared to adrenaline; hence, the latter should only be reserved for refractory CS.[39] Vasopressin is used as a noradrenaline sparing agent and is favored in pulmonary hypertension as its vasoconstrictive properties may spare the pulmonary vasculature.[40] On the other hand, dopamine has been associated with worse outcomes and should also not be used routinely.[41] The DOREMI trial compared milrinone with dobutamine in a mixed population with CS and showed no difference in either primary or secondary outcomes.[42] Due to persisting uncertainty, the CAPITAL DOREMI 2 trial (NCT05267886) will evaluate outcomes in a mixed CS population with use of either dobutamine or milrinone compared to placebo. Despite the increasing use of levosimendan, a phosphodiesterase inhibitor and calcium sensitizer, and physiologically attractive mechanism of action as a pulmonary vasodilator, high-quality evidence supporting its use is limited. A recent systematic review and network meta-analysis of 7 RCTs (1145 patients) suggested that levosimendan is probably associated with lower mortality in the less severe CS cohorts (OR = 0.53, 95% CI: 0.33–0.87).[43]

Mechanical Circulatory Support

As an alternative approach to improving CO, over the past 15–20 years, the use of temporary MCS has increased dramatically.[18,44] The putative benefits of early institution of MCS include reduced cardiac workload and enhanced sys-

temic and coronary perfusion and decongestion through reduction in cardiac filling pressures.[2] MCS devices are used as a bridge-to-recovery, bridge-to-decision, bridge-to-bridge, and bridge-to-transplant. Device selection recommendations are supported by limited evidence and are mainly guided by the pathophysiology of the type of CS, local expertise, and device availability/cost.

The physiological principles that guide their selection and mechanisms of cardiovascular support depend on their anatomical placement, and which side of the myocardium is impaired, providing either univentricular or biventricular support.[2] The intra-aortic balloon pump (IABP) reduces LV afterload and improves coronary perfusion. The TandemHeart™ (LivaNova) works by "venting" the left side of the heart by draining blood from the left atrium and returning it into the femoral artery via a centrifugal pump. The TandemHeart ProtekDuo cannula can provide isolated RV support in conjunction with a centrifugal pump. The expanding armamentarium of the Impella™ (Abiomed) devices, augment blood flow from the left ventricle into the aorta, or from the right ventricle to the PA, via a micro-axial flow pump. Lastly, veno-arterial extracorporeal membrane oxygenation (VA-ECMO) devices can provide partial or complete biventricular circulatory support via an extracorporeal centrifugal pump and respiratory support with the use of an extracorporeal oxygenator. Combinations of devices add further complexity and makes the randomized study of each approach even more challenging. For example, simultaneous use of a right and left sided Impella™ device (BiPELLA) is possible and has been described in fulminant myocarditis.[45] The use of VA-ECMO can be associated with increases in LV afterload due to retrograde aortic flow, resulting in further complications and can ultimately lead to pulmonary congestion. As a result, there is increasing research interest in the concept of "LV unloading" during the use of VA-ECMO, with the concomitant use of an IABP or Impella™ (ECPELLA), which has shown promise in retrospective studies and is supported by a recent meta-analysis, albeit in patients with AMI-CS.[46] A summary of the available MCS devices is shown in Table 2, while MCS use in specific CS etiologies of *de novo* CS is outlined in Table 3.

Escalation to and de-escalation from MCS

There remains uncertainty around the optimal timing of escalation to and de-escalation from MCS across all phenotypes of CS. While early MCS is attractive to mitigate or reverse organ dysfunction, this approach risks exposure to MCS-related complications in the absence of compelling randomized trial data supporting outcome benefit from any modality of MCS. While data from clinical trials is awaited, the American Heart Association have recently published a scientific statement summarizing the available data to guide clinicians.[47] A comprehensive summary of the AHA recommendations regarding hemodynamic parameters is beyond the scope of this article.

The correlation between lactate levels and prognosis forms a continuous spectrum. As a result, no absolute lactate level has demonstrated an ability to dichotomize between patients with and without a poor prognosis. More recently early lactate clearance within the first 6–8 h of CS and/or 24 h has shown superior accuracy in identifying treatment response and hence survival.[48,49] However, lactate clearance as a marker of MCS

initiation has the caveat of delaying initiation of MCS insertion and putative benefits. Acidosis and specifically lactic acidosis has direct effects on cardiovascular physiology and may be the final common pathway of deterioration in the most severe patients. Hence, in addition to lactate, pH and base excess have demonstrated correlation with outcome across SCAI stages as a marker of organ dysfunction and severe or refractory shock.[50] Echocardiography parameters associated with prognosis have been assessed in a retrospective analysis of 1085 CS patients.[51] Left Ventricular Outflow Tract Velocity Time Integral (LVOT VTI) was the single best predictor of hospital mortality. LVEF was similarly associated with hospital mortality, albeit more weakly. Prognostic right ventricular dysfunction metrics were the Tricuspid annular peak systolic velocity/tricuspid regurgitation velocity (TASV/TR). Absolute cut-off values for these indices remain to be defined. Aortic VTI >10 cm, LVEF >20–25%, and lactate clearance at 6 h and 12 h have been identified as markers predictive of weaning success from VA-ECMO.[52]

Specific Etiological Management

Takotsubo cardiomyopathy

TCM, also known as stress cardiomyopathy, presents as acute transient severe heart failure predominantly provoked by external triggers. The International Takotsubo Registry demonstrated the majority are due to external triggers (physical 36.0%, emotional 27.7%, no triggers 28.5%).[53] Its pathophysiology is related to elevated circulating and myocardial adrenaline and noradrenaline levels.[54] This can result in cardiotoxic hyperstimulation of the cardiac muscle and cardiovascular microcirculation, increasing cardiac contractility and causing tachycardia, which culminates in an ischemic imbalance between metabolic supply and demand.[55] TCM can sometimes present with elevated LV afterload secondary to left ventricular outflow tract obstruction (LVOTO).[55] Registries have demonstrated an incidence of CS in TCM of between 2.4% and 12.4%.[56,57] Mortality is markedly lower (14.6%) in comparison to AMI-CS (35.1%).[37]

Initial investigations in TCM-related CS include early and serial troponin levels, electrocardiogram (ECG), echocardiography, and angiography to exclude an ischemic cause. The Mayo diagnostic criteria is the current standard diagnostic guide.[58] Echocardiography findings of TCM-CS are characteristic apical ballooning, reduced LVEF, and transient LV hypokinesis which extends beyond single epicardial vascular distribution.[59]

Management is dependent on the presence or not of LVOTO. Catecholamines should be avoided, as they increase LV afterload and appear to have a causative association with the syndrome.[60] Milrinone, dobutamine, and dopamine are also relatively contraindicated, as they can increase cardiomyocyte cAMP levels that can themselves induce TCM CS.[61] A case series showed possible benefit of levosimendan in TCM-CS without LVOTO.[62] In TCM-CS with LVOTO, both vasopressors and inotropes are contraindicated due to concerns regarding worsening LV afterload. Early MCS initiation may prevent toxic use of inopressors and is recommended in international guidance.[4] Despite systematic reviews demonstrating no mitigation of recurrence with β-blocker therapy following hemody-

Table 2
Mechanical circulatory support modalities.

Ventricular support type	Name of device	Access site	Max flow (L/min)	Mechanism	Advantages	Disadvantages	Contraindications
RV support	Impella™ RP (Abiomed)	Femoral vein	4.0	• Continuous axial flow pumps with propellers positioned across the pulmonary valve • Reduces RV preload	• No extracorporeal circuit complications • Relatively easy insertion • ECG and pulse independent	• Hemolysis • Bleeding • No oxygenator for oxygenation or decarboxylation	• Prosthetic/stenotic pulmonary or tricuspid valve • Vena cava, RA or RV thrombi
	TandemHeart™ RA-PA ProtekDuo® kit (LivaNova)	Internal jugular vein	4.0	• Dual lumen cannula which drains blood form RA and returns into PA • Reduces RV preload	• Can be used in pulmonary stenosis • Rhythm independent • Oxygenator can be incorporated	• Air embolism • PA perforation • Bleeding	• Prosthetic/stenotic pulmonary or tricuspid valve • Pulmonary valve insufficiency • Vena cava, RA/RV thrombi
LV support	IABP	Femoral artery	0.5–1.0	Intra-aortic counter-pulsation in descending aorta causes reduced LV afterload and improved coronary perfusion in diastole	• Relatively easy insertion not necessarily in cath lab • No extracorporeal circuit complications • Increased coronary and cerebral flow	• Vascular injury • Limb ischemia • Hemolysis • Bleeding • Thrombocytopenia	• Severe aortic stenosis/regurgitation • Aortic dissection
	Impella™ 2.5, CP, 5.0, 5.5 (Abiomed)	Femoral or axillary artery	2.5–5.5	• Continuous axial flow pumps with propellers positioned across the aortic valve • Reduce LV afterload	• Range of device sizes and flow • Reduces LV afterload • Relatively easy insertion • ECG and pulse independent	• Frequent hemolysis • Vascular injury/perforation Limb ischemia • Bleeding • Requires RV support if sequential RVF	• Prosthetic/stenotic aortic valve • Aortic dissection
	TandemHeart™ (Livanova)	Femoral vein	4.0	• Cannula enters RA, punctures interatrial septum into LA. • Oxygenated blood drained returned into femoral artery. • Reduces LV preload	• Rapid reversal in hemodynamic deterioration • Can be used in aortic stenosis • Rhythm independent	• Air embolism • Cardiac perforation and tamponade • Residual ASD • Complex implantation requiring transeptal rupture • Limb ischemia • Bleeding	• RVF
Biventricular support	VA-ECMO	Outflow: femoral veins Inflow: femoral/subclavian artery	3.0–7.0	• Drainage of deoxygenated venous blood through extracorporeal circuit pump with oxygenator and returns oxygenated blood into arterial system • Biventricular support independent of cardiac function but increases LV afterload and decreases RV afterload	• Rapid full circulatory support • Biventricular support • Relatively easy to insert	• Increased LV afterload • Increased thromboembolic events due EC circuit • Limb ischemia • Air embolism • Harlequin syndrome • Bleeding • Vascular injury/perforation	• Severe aortic insufficiency • Aortic dissection

ASD: Atrial septal defect; IABP; Intra-aortic balloon pump; LV: Left ventricle; PA: Pulmonary artery; PAD: Peripheral arterial disease; RA: Right atrium; RV: Right ventricle; VA-ECMO: Veno-arterial extracorporeal membrane oxygenation.

Table 3
Cardiogenic shock phenotypes.

CS subtype	Diagnosis and investigations	Pathophysiology	Management and considerations	MCS modalities
Takotsubo	Mayo diagnostic criteria (should meet all four): • Echocardiography: transient LV hypokinesis, akinesis, or dyskinesis extending beyond single epicardial vascular distribution (stressful trigger often, but not always present) • Angiography: absence of obstructive coronary disease or acute plaque rupture • ECG: new ST-elevation and/or diffuse T-wave inversion or troponin elevation • Absence of myocarditis or phaeochromocytoma	• Elevated circulating and myocardial adrenaline and noradrenaline levels (sometimes stress provoked) • Hyperstimulation of adrenoceptors result in cardiotoxic effects, increasing HR and cardiac contractility with a secondary imbalance in rate of oxygen supply and demand. • Elevated afterload and LVOTO in some cases	• Dependent on LVOTO presence Without LVOTO: Levosimendan preferred With LVOTO: Avoid vasopressors and inopressors • Early β-blocker use after hemodynamic stabilization	• Consider use of MCS early • No statistically significant mortality variations across different MCS devices • IABP and VA-ECMO traditionally used, but Impella and VA-ECMO preferred recently • Impella preferred to IABP as latter can worsen dynamic LVOTO • VA-ECMO may result to increased incidence of mitral regurgitation • IABP support possibly insufficient (20% require additional MCS)
Myocarditis	• Early echocardiography to assess L and RV EF, valvular function and assess distribution of ventricular dysfunction • ECG: focal/global ST-elevation, QRS >120 ms (prolonged QRS associated with increased mortality) • CXR • FBC and blood cultures • Basic metabolic panel • CRP, CK-MB, BNP, and cTn (associated with development and severity of CS) • Early myocardial biopsy (to exclude GCM and EM) • CMR feasible after hemodynamic stabilization	• Three-phase development of fulminant myocarditis: Viral phase, immune activation, and myopathy phase • Presents with flu-like symptoms associated with myocardial injury symptoms • Can be triggered by infection autoimmune disease (SLE, RA, sarcoidosis, GCM, and eosinophilic syndromes) and medications (cyclophosphamide, ICIs, e.g., nivolumab, pembrolizumab) • Fulminant GCM has worst 60-day prognosis (62.5%) • Segmental wall abnormalities mostly in inferior and lateral walls	• Consensus on avoidance of high-volume IV fluids and hemodynamic stabilization with norepinephrine • LM: use of steroids if absence of virus on PCR • EM: high-dose prednisolone use ± cyclophosphamide, azathioprine, or methotrexate • GCM: early calcineurin inhibitors, high-dose prednisolone and azathioprine • ICI myocarditis: cessation of ICIs and IV solumedrol	• Early shock team activation to consider insertion of VA-ECMO, Impella, or a combination of the two (ECMELLA) • PROPELLA may lead to improved outcomes in fulminant myocarditis • Immunosuppressants initiated prior to MCS implantation in GCM
RVF	• Assess clinical parameters, presence of peripheral/pulmonary edema, and elevated JVP • Biochemical markers: BNP, cTN, and lactate levels • ECG: right-axis deviation, P-pulmonale, RS ratio in V5/6 of <1 or S wave of V5/6 >7 mm • Echocardiography and PAC to assess right and left ventricular function, hemodynamics, and volume status	• Separated into two subtypes based on presence or not of PAH • Increased sensitivity to changes in afterload leads to greater decrease in stroke volume in comparison to LV • RV dilatation leads to deviation of interventricular septum compromising LV filling and decreasing CO • Lower 30-day mortality than RVF • Can be precipitated in 20% post-LVAD	• Identify cause and type of RVF and treat: PCI for AMI, reperfusion for PE • Restrictive fluid administration, minimizing volume loading to avoid compromise in LV filling, unless RVF is preload-dependent • Diuretics in congested HF • Tachycardia (90–110 bpm) with chronotropes or pacing may help CO if fixed SV due to afterload • Target MAP >65 mmHg. Noradrenaline or vasopressin can increase CO, systemic afterload, and venous return without compromising PA pressure • Consider inhaled NO or IV prostacyclin for elevations in PVR	• In refractory RVF, consider MCS • In isolated RVF: Impella RP or TandemHeart to decrease RA pressure • In biventricular failure: Avoid Impella RP or TandemHeart alone Consider VA-ECMO for biventricular support Consider concomitant placement of Impella RP or left-sided Impella

Table 3 (continued)

PPCM	• ECG: no specific changes but important to distinguish from other causes • CXR: alveolar edema, marked cardiomegaly, and pleural effusion in severe PPCM • Highly elevated NT-proBNP levels • Early echocardiography in PPCM-CS shows LVEF <25%, with possible RV dysfunction and dilatation	• Uncertain etiology • Combination of systemic angiogenic imbalance and host susceptibility • Associated with low selenium levels, viral infections, stress-activated cytokines, inflammation, autoimmune reaction, and unbalanced oxidative stress • A specific prolactin fragment (15 kDa prolactin) contributes to development • Prothrombotic state common	• Milrinone or levosimendan • Avoid ivabradine as small observational study associated it with worse outcomes • Bromocriptine for 8 weeks • Involve patient and advise for early vaginal delivery unless obstetrics advise for cesarean section	• Early transfer to advanced heart failure center with availability of MCS, VAD, and transplant consult teams • Lower threshold for MCS • Impella in combination with bromocriptine may improve outcomes
Cardio-oncology	• Echocardiography to assess cardiac structure and LVEF, pericardial effusion, and valve disease • Early ECG to identify coronary ischemia and cardiac arrhythmias (Torsade de Pointes and AF) • Cardiac troponins to assess for elevation in context of coronary ischemia and anthracycline-induced cardiac dysfunction or ICI-induced myocarditis	• Preceded by different clinical entities pre-existing CV disease, treatment, and thromboembolic events • Cardiomyopathy: anthracyclines, alkylating agents, anti-HER 2 therapies, VEGF inhibitors, radiotherapy, and paraneoplastic syndrome • Myocarditis: ICIs, rituximab • Takotsubo syndrome: 5FU, capecitabine, cyclophosphamide, rituximab • ACS: pre-existing CV disease, fluoropyrimidines, cisplatin, radiotherapy, coronary tumor embolism and coronary compression by tumor • Hypotension: chimeric antigen receptor T-cell therapy • Cardiac tamponade: metastatic tumors, chemotherapy, radiotherapy, surgery • Cardiac herniation: pneumonectomy and pericardiectomy • Cardiac arrhythmias: arsenic (QT prolongation), tyrosine kinase inhibitors (AF)	• Early referral to cardio-oncology service • Cessation of inciting drugs • Dexrazoxane may act as iron chelation from anthracycline-induced free radical generation • Steroids in ICI myocarditis	• VA-ECMO with uni/biventricular unloading may be necessary • RV dysfunction common and may require right-sided MCS • Temporary LVAD and subsequent durable LVAD may be appropriate in anthracycline-induced cardiomyopathy • Lack of overall data on temporary MCS in cardio-oncology
Cardiomyopathies	• Echocardiography to identify the cause and exclude valvular disease • Angiography to exclude ACS • Early myocardial biopsy following hemodynamic stability	• Complex and diverse presentation, 80% of CS cases secondary to hypertrophic and dilated cardiomyopathy • Other causes include Amyloidosis, Sarcoidosis	• Case-series recommend the use of β-blocker therapy to decrease LV outflow gradient in HOCM • Positive inotropic agents such as dopamine, dobutamine, and milrinone are explicitly avoided as can worsen the dynamic obstruction	• Advanced MCS with VA-ECMO is recommended as can minimally increase afterload while maintaining full-scale circulatory support • IABP may produce de novo LV outflow obstruction
Valvular lesions	• Early echocardiography to identify LVEF and valvular defect • Chest X-ray to identify pulmonary congestion • ECG to identify AF caused by elevated left atrial pressure • CT imaging can exclude aortic dissection and prepare for interventional procedure	• Rare and presents secondary to acute or acute-on-chronic insults • It can be secondary to AMI (mitral valve rupture), valve thrombosis, infective endocarditis, and severe aortic stenosis • Can precipitate RVF due to post- pulmonary hypertension	• Early input from the structural heart team • Transcatheter mitral valve repair (with MitraClip) in moderate to severe MR with CS may improve outcomes • PPV can be beneficial for AS and MR	• MCS of choice varies depending on presenting valvular pathology IABP and peripheral VA-ECMO are contraindicated in AR as they can precipitate afterload increase Impella preferred in MR and contraindicated in severe AS

ABG: Arterial blood gas; ACE-I: Angiotensin converting enzyme inhibitor; AF: Atrial fibrillation; AMI-CS: Acute myocardial infarction-related cardiogenic shock; ARDS: Acute respiratory distress syndrome; BNP: Beta natriuretic peptide; CK-MB: Creatinine kinase myocardial band; CMR: Cardiac magnetic resonance; CO: Cardiac output; CRP: C-reactive proteins; CS: Cardiogenic shock; CT: Computerized tomography; cTN: Cardiac troponins; CV: Cardiovascular; ECG: Electrocardiogram; EF: Ejection fraction; FBC: Full blood count; GCM: Giant cell myocarditis; HF: Heart failure; HOCM: Hypertrophic cardiomyopathy; HR: Heart rate; IABP: Intra-aortic balloon pump; ICI: Immune checkpoint inhibitors; IV: Intravenous; JVP: Jugular venous pressure; kDa: Kilodalton; LM: Lymphocytic myocarditis; LV: Left ventricle; LVAD: Left ventricular assist device; LVEF: Left ventricular ejection fraction; LVOTO: Left ventricular outflow tract obstruction; MAP: Mean arterial pressure; MCS: Mechanical circulatory support; microRNA: Micro ribonucleic acid; mmHg: Millimeters mercury; ms: Milliseconds; NO: Nitric oxide; PAC: Pulmonary arterial catheter; PAH: Pulmonary arterial hypertension; PCR: Polymerase chain reaction; PE: Pulmonary embolism; PPCM: Peripartum cardiomyopathy; PVR: Peripheral vascular resistance; PROPELLA: Prolonged Impella; RA: Rheumatoid arthritis; RV: Right ventricle; RVF: RV failure; SBP: Systolic blood pressure; SLE: Systemic lupus erythematosus; VA-ECMO: Veno-arterial extracorporeal membrane oxygenation.

namic stability,[56] they are recommended to lower sympathetic tone in myocardium.[63]

Choice of MCS is patient and center specific, but data from a systematic review have shown increased Impella™ and VA-ECMO insertions over recent years,[64] despite guidance recommending Impella™ prior to considering VA-ECMO due to potential worsening of mitral regurgitation with the latter.[4] In patients with LVOTO, a reduction in afterload secondary to IABP placement may worsen the degree of outflow tract obstruction, and hence, LVOT gradient should be evaluated and monitored with echocardiography.[65] Data collected from the systematic review have identified no statistically significant variations in the primary outcomes of the study across different MCS modalities (survival IABP 95.3%, Impella™ 90.0%, ECMO 94.3%; *P*=0.86) but has identified that 20% of IABP-supported patients underwent escalation to additional MCS, indicating that IABP may provide insufficient hemodynamic support.[64]

Myocarditis

Myocarditis presents with symptoms associated with myocardial injury and concomitant flu-like symptoms. Its pathophysiology has traditionally been divided into three phases: viral, immune activation, and myopathic.[66] It is most commonly triggered by infection but often presents secondary to autoimmune disease (e.g., rheumatoid arthritis and systemic lupus erythematosus) or due to medications such as immune checkpoint inhibitors (ICIs). Myocarditis is separated into different subtypes whose investigations and management vary (Table 4): lymphocytic myocarditis (LM), giant cell myocarditis (GCM), eosinophilic myocarditis (EM), and ICI-induced myocarditis.[67] GCM has the highest mortality rate (62.5%).[68]

Early echocardiography and RV endomyocardial biopsy are pivotal to identify the type of myocarditis and prioritize management with corticosteroids and immunosuppressants in GCM and EM.[69,70] ICIs should be terminated in all patients with ICI-induced myocarditis, and high-dose intravenous solumedrol may be of benefit prior to insertion MCS.[71]

Patients presenting with severe CS (SCAI stages C– E), prolonged QRS segment on ECG and elevated cardiac biomarkers (C-reactive protein, creatinine kinase myocardial band, brain

natriuretic peptide [BNP], and troponin) in the context of fulminant myocarditis have significantly increased mortality.[66] Early insertion of MCS as a bridge to either recovery or durable MCS/heart transplantation is therefore advocated in these patients.

The majority of patients have global myocardial dysfunction, and so, biventricular MCS is usually necessary. Central cannulation with VA-ECMO was associated with statistically significant higher ventricular assist device (VAD) – free survival rate in comparison to peripheral (82.2% *vs.* 52.0%; *P*=0.017) [72] and may have the advantage of limiting LV afterload which may propagate myocardial wall stress and increase extracellular matrix turnover which hinders cardiac remodeling.[45] An alternative to the use of central ECMO is the use of Impella™ in combination with VA-ECMO (ECMELLA), or a combination with Impella™ RP (BIPELLA). Such direct unloading of the ventricles may provide disease modifying effects to facilitate myocardial recovery in fulminant myocarditis.[73,74] In addition, prolonged Impella™ placement (PROPELLA) after Impella™ or ECMELLA, whereby the LV Impella™ remains seeded for weeks until resolution of myocarditis inflammatory pathway, has been associated with reductions of myocardial inflammation and modulation of cardiac remodeling, but further data are necessary to draw more conclusions.[45]

GCM holds the highest mortality among all myocarditis subtypes Table 4. Data from a French multicenter cohort identified that none of the patients with fulminant GCM survived in the long term, free from heart transplant.[75] The same study identified that patients who underwent pre-MCS magnetic resonance imaging had a confirmed diagnosis more accurately with a higher sensitivity in comparison to endomyocardial biopsy, allowing earlier establishment of GCM, initiation of immunosuppressants, and insertion of appropriate MCS. A systematic review also demonstrated that immunosuppression with ciclosporin prior to MCS insertion was associated with statistically improved survival (*P*=0.006).[76]

Right ventricular failure

A comprehensive narrative of RV failure (RVF) is beyond the scope of this article, but it is expertly summarized in a recent

Table 4
Myocarditis subtypes.

Myocarditis subtype	Causes/pathophysiology	Biopsy findings	CS presentation
LM	Virus-mediate/triggered (30–40%) Drugs/toxin-mediated Auto-immune disorders	Infiltration of small mononuclear cells (CD3 + T lymphocytes)	LV dysfunction most frequent post-fever Outcomes generally better
GCM	Often unknown cause (75%) Autoimmune disorders (25%)	Large multinuclear cells Degranulated eosinophils	Severe heart failure with refractory cardiogenic shock, frequent arrhythmic disturbances (AV block, VT/VF) Highest mortality
EM	Hypersensitivity myocarditis Endomyocardial fibrosis Hypereosinophilic syndrome	Eosinophilic infiltrate	From asymptomatic, to acute FM, to chronic restrictive cardiomyopathy
ICI	Arrhythmic disturbances (AV block, refractory VT) and multiorgan failure Presents <6 weeks prior to initiation of ICI	T-cell-mediated injury similar to cardiac rejection	Life-threatening arrhythmic disturbances (AV block, VT) leading to multiorgan failure and death

AV: Atrioventricular; CS: Cardiogenic shock; EM: Eosinophilic myocarditis; FM: Fulminant myocarditis; GCM: Giant cell myocarditis; ICI: Immune checkpoint inhibitor-induced myocarditis; LM: Lymphocytic myocarditis; LV: Left ventricular; VF: Ventricular fibrillation; VT: Ventricular tachycardia.

review by Kanwar and colleagues.[77] One of the fundamental physiological characteristics of the RV is its greater sensitivity to changes in afterload. Brisk increases in afterload are poorly tolerated and lead to RV dilatation to preserve stroke volume.[78] In turn, this leads to deviation of the interventricular septum, compromising LV preload, and CO.[79] Hence, fluid administration should be restrictive and maintained in a narrow range.

It is pivotal to identify RVF and its cause early, assessing clinical and biochemical hemodynamic parameters. Assessment and monitoring of RV cardiac function using echocardiography or a PAC is pivotal, as it allows nuanced management of RV hemodynamics. As important is the concomitant assessment of LV function, to drive decisions when considering ideal MCS device.

Correction of hypovolemia/hypervolemia with intravenou fluids or diuretics may be necessary depending on the presentation. The causes of RVF should be treated urgently (e.g., PCI for AMI, reperfusion for pulmonary embolism). Mean arterial pressure (MAP) targets should remain >65 mmHg with inotropes such as (levosimendan and dobutamine) in conjunction with noradrenaline or vasopressin, increasing CO, systemic afterload, and venous return without compromising PA pressure. Inhaled nitric oxide (NO) and intravenous prostacyclin is indicated where pulmonary vascular resistance is elevated. Mechanical ventilation can decrease venous return and elevate afterload, by elevating intrathoracic and intraabdominal pressures, having deleterious effects in RV function by steepening the pressure–volume loop. Thereby, although unsupported in literature, lung-protective ventilation with conservative positive end-expiratory pressure (PEEP) and tidal volumes to mitigate disruption in RV is justified.

If there is isolated and refractory RVF, consideration should be given to either univentricular RV support with TandemHeart™ RA-PA configuration or Impella™ RP which provide direct RV bypass or biventricular support with VA-ECMO. Direct RV support reduces RAP and increases PA and LV preload directly which increase CO through an increased LV filling pressures at least when LV function is preserved.[80]. VA-ECMO, providing indirect RV bypass, decreases LV preload and increases LV afterload and hence, in the context of preserved LV function, intrinsic CO may decrease.

Prospective and retrospective multicenter observational studies assessing the use of percutaneous temporary MCS approaches in RVF mainly focus on the post-MI and post-LVAD cohorts. The feasibility of Impella™ RP was prospectively assessed in the RECOVER RIGHT trial and its subsequent follow-up studies. Across 60 patients improvement in cardiac index (CI) (1.9–3.1 L/min/m²; *P* <0.001), a reduction in CVP (19.0–13.0 mmHg; *P* <0.001) and improved 30-day survival (73.3%) was identified.[81] Similar hemodynamic benefits and survival have been shown in subsequent retrospective cohort studies.[82,83] TandemHeart™ RA-PA has only been assessed in a retrospective cohort study of 46 patients with a mixed etiology of RVF in the TandemHeart™ in Right Ventricular Failure (THRIVE) study. Elevations in MAP and CI, with reductions decrease in RAP and PA systolic pressure were observed, with a survival of 43%.[84] VA-ECMO in RVF has also been assessed retrospectively in a number of observational studies, demonstrating variable short-term survival ranging from 12% to 85% across different patient populations (post-LVAD, post-transplant, and post-cardiotomy). These data highlight the need

for large-scale multinational registry data across subphenotypes to identify where any clinical benefit may lie and to support clinical trial design.[85,86]

In the context of biventricular failure, TandemHeart™ RA-PA and Impella™ RP will increase LV preload, but in the context of a failing LV, CO will remain unchanged/slightly increase. This, results increased cardiac filling pressures, pulmonary edema, and hypertension. Biventricular MCS with VA-ECMO and concomitant insertion of additional right-sided or left-sided support may provide reduction of filling pressures and decrease subsequent pulmonary hypertension.[87]

Peripartum cardiomyopathy

Peripartum cardiomyopathy (PPCM) is a syndrome of systolic heart failure with reduced LVEF, most frequently occurring in the last month of pregnancy or in the puerperium. It is idiopathic and believed to be caused by a combination of systemic angiogenic imbalance and host susceptibility.[88–90] It is associated with low selenium levels, viral infections, stress-activated cytokines, inflammation, autoimmune reaction, and unbalanced oxidative stress.[88–90] A specific prolactin fragment (15 kDa prolactin) contributes to its development, and current management is targeted toward inhibition of prolactin secretion.[91] There has also been observed a prothrombotic state in PPCM, leading to more thromboembolic episodes, and consideration of anticoagulation when initiating MCS should be prioritized.[92]

Suspected PPCM should be assessed with echocardiography, normally demonstrating a LVEF <45%. LVEF <25% is associated with the development of CS.[93] NT-pro-BNP levels should be taken on initial diagnosis as they are directly associated with recovery.[94]

In terms of inopressors used to maintain hemodynamic status, a comparison of milrinone and levosimendan in 15 women with PPCM showed comparable hemodynamic improvement.[95] Levosimendan did not show improved outcomes in a randomized study,[96] whereas patients allocated to dobutamine had worse outcomes in a separate randomized study.[93,97]

The ESC recommends early transfer to advanced heart failure center with availability of MCS, VAD, and heart transplant teams.[93] There should be a lower threshold for MCS in PPCM, as patients are sensitive to toxicity from inotropes (β-adrenergic).[94] The feasibility of temporary placement of LVAD as a bridge to recovery and heart transplant has been assessed in a number of small case series, reporting reduced N-Terminal-pro-BNP levels, resolution of acute kidney injury, and reduction of LV end diastolic and systolic volumes present in the morphology of the dilated cardiomyopathy in PPCM.[98] Data from the Extracorporeal Life Support Organization (ELSO) registry demonstrate a survival rate of VA-ECMO in PPCM of 64% with neurological complications (intracerebral hemorrhage) being associated with mortality in this population.[99]

Bromocriptine has been recommended in the latest ESC HFA position statement for PPCM complicated by CS; however, its use remains controversial.[93] Bromocriptine is associated with thrombotic complications and should be taken in conjunction with anticoagulants.[88] The Randomized Evaluation of Bromocriptine In Myocardial Recovery Therapy (REBIRTH) trial (NCT05180773) will further inform the

role of bromocriptine.[88] Administration of bromocriptine with Impella™ in univentricular and VA-ECMO in biventricular failure have shown favorable outcomes in a small prospective study, but it remains uncertain which of the two should be prioritized.[100] If the patient is hemodynamically unstable and pregnant, there should be early discussion and consultation with the patient and close family to advise for immediate fetal delivery.

Cardio-oncology

Cardio-oncology refers to the management of cancer patients with cardiovascular disease. The development of advanced cancer therapies with additional complications, notably cardiomyopathy, heart failure, coronary ischemia, hypotension/shock, and myocarditis,[101] has culminated in the recommendation of consultation with cardio-oncology service in cancer patients affected by CS by the European Society of Cardiology (ESC).[100]

Anthracyclines, alkylating agents, anti-human epidermal growth factor 2 therapies, and tyrosine kinase inhibitors have been associated with heart failure secondary to myocardial injury across various earlier studies.[102,103] Coronary spasm, thrombosis, and subsequent ischemia may also be induced by fluoropyrimidines and platinum agents,[104] while ICIs can induce myocarditis as aforementioned. Chimeric antigen receptor T-cell therapy (CAR-T cell) can induce a cytokine release and sudden hypotension and shock.[105] Cardiac arrhythmias can also be induced by arsenic (QT prolongation/Torsades de Pointes) and tyrosine kinase inhibitors (atrial fibrillation).[101] Coronary ischemia can occur secondary to tumor compression and co-existent cardiovascular disease, cardiac tamponade secondary to metastatic tumors, while cardiac herniation can occur secondary to pneumonectomy and pericardiectomy.[106] TCM is a known side-effect of bevacizumab.

Early echocardiography to assess cardiac structure, LVEF, pericardial effusion, and valve disease is recommended and early ECG to identify arrhythmias and the presence of coronary ischemia.

ACE-I and β-blockers are recommended by ESC to minimize cardiotoxicity from chemotherapy, most notably anthracycline, and there are small amount of data supporting their cardioprotective effects.[107–109] Dexrazoxane may also act as iron chelation from anthracycline-induced free radical generation in hematological malignancies.[110] In pulmonary tumor thrombotic microangiopathy (PTTM), a presentation with pulmonary hypertension and subsequent RVF, inhaled NO, and prostacyclin have been recommended to reduce right-sided pressure but evidence shows no survival benefit.[111]

Identifying the cause is important when considering whether MCS insertion would be appropriate and which would thereby be more appropriate.[112] Chemotherapy-induced cardiomyopathy (CCMP) patients across the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) demonstrated increased RV dysfunction frequency when compared to ischemic and non-ischemic cardiomyopathy patients and require right-sided mechanical support more often.[112] However, there are no contemporary data describing temporary MCS utilization in this population. Case reports have described successful management with VA-ECMO and uni-/bi-VADs.[113] There have also been case reports describing successful management of patients with anthracycline-induced cardiomyopathy, whereby

heart transplantation is contraindicated, with temporary VADs and subsequent implantation of durable MCS.[114,115]

ICI-induced myocarditis and TCM in cardio-oncology should be managed according to the recommendations above.

Cardiomyopathy

CS secondary to cardiomyopathies can be highly diverse, depending on type, distribution, and severity. The Heart Failure Association (HFA) of the ESC recommends exclusion of other causes of CS early, by performing echocardiography and angiography, as these patients are also prone to concomitant valvular and ischemic lesions.[4] Early myocardial biopsy is also recommended following hemodynamic stability.[116] Eighty percent of CS related to cardiomyopathies are secondary to hypertrophic and dilated cardiomyopathy.[4]

Use of β-blockers following hemodynamic stabilization in hypertrophic obstructive cardiomyopathy (HOCM) is associated with decreased LV outflow gradient based on a small cohort study.[109] Positive inotropic agents should be explicitly avoided in HOCM as they can worsen dynamic outflow tract obstruction.[116] Septal myomectomy to relief LV outflow obstruction is the definitive treatment of HOCM.[116]

In terms of MCS of choice, in dilated cardiomyopathy, LVAD is effective as bridge to transplant/recovery by increasing CO, reducing LV preload and subsequently lowering rates of PAH and pulmonary edema.[117] Biventricular MCS is generally preserved for biventricular dysfunction or failure to maintain CO by means of a LVAD.[117]

Patients with restrictive and hypertrophic cardiomyopathy were generally excluded from LVAD therapy due to the increased myocardial stiffness, risk of obstruction to flow and reduced LV end-diastolic dimensions.[118] The latter's severity has been associated with worse mortality.[119] However, small case series demonstrated that centrifugal, axial continuous-flow LVADs may provide benefit in the short- to medium-term and should not be excluded, if LV end-diastolic dimensions are adequate.[120]

A minimal number of case series discuss the use of VA-ECMO in hypertrophic cardiomyopathy.[116,121] VA-ECMO is recommended as it can augment CO and coronary perfusion, while minimally increasing afterload, which benefits by reducing regression to outflow obstruction in hypertrophic cardiomyopathy.[116]

Valvular lesions

CS secondary to valve lesions can be a result of acute or acute-on-chronic insults. It can have a highly varied presentation depending on the lesion and acute precipitant of CS (e.g., AMI, infective endocarditis, and severe aortic stenosis).[4] Valvular lesions can precipitate RVF in left-sided valvular lesions and result in pulmonary hypertension. Diuretics are thereby indicated in most structural heart disease apart from LVOTO to prevent congestion.[122]

Evidence is lacking in regard to how investigations should be approached, but early echocardiography is recommended to identify LVEF and cases where urgent surgery is required, most notably with aortic or mitral valve endocarditis with severe acute regurgitation, obstruction, or fistula causing refractory CS.[4,123] Chest X-ray should also be performed to identify

Table 5

MCS modality indications for major valvular lesions.

Lesions	VA-ECMO	Impella™	IABP	TandemHeart™
Aortic regurgitation	Contraindicated (elevated afterload can worsen aortic regurgitation)*	Contraindicated (aortic regurgitation can be precipitated by continuous flow) *	Contraindicated (elevated DBP can worsen aortic regurgitation and precipitate LV distension) *	Can be utilized (can precipitate LV distension) †
Critical aortic stenosis	Utilized (can use concomitant LV venting with inotropes, IABP)‡	Can be utilized (manufacturer: contraindication if AV orifice area <0.6 cm²)†	Can be utilized (beware reduced effectiveness in extreme narrowing, can facilitate venting with VA-ECMO) †	Can be utilized (higher risk of LV thrombus formation due to narrow aortic orifice) †
Mitral regurgitation	Can be utilized (often utilized with in combination with IABP or Impella™) †	Utilized (can act as bridge from CS to MitraClip procedure) ‡	Can be utilized to facilitate MitraClip (through coapting of leaflets necessary for procedure) †	Can be utilized (can be utilized on its own and with ECMO) †
Biological valves†	Can be utilized (risk of thrombosis)	Can be utilized	Can be utilized	Can be utilized (risk of thrombosis)
Mechanical valves	Can be utilized (high risk of aortic root thrombosis, venting with IABP or surgical LVAD) †	Contraindicated (manufacturer recommendation) *	Can be utilized†	Can be utilized (high risk of thrombosis) †

CS: Cardiogenic Shock; DBP: Diastolic blood pressure; IABP: Intra-aortic balloon pump; LV: Left ventricle; LVAD: Left ventricular assist device; VA-ECMO: Veno-arterial extracorporeal membrane oxygenation.

* Absolute contraindications to use;.

† Use described in case series/reports, or use not permitted in given scenarios;.

‡ Used and recommended by guidance, based on data from observational studies.

pulmonary congestion and ECG initiated to identify atrial fibrillation caused by elevated left atrial pressure.

Initial data from nationwide registries and cohort studies support the use of transcatheter mitral valve repair in moderate to severe mitral regurgitation with CS with improved short-term survival and neurological outcomes.[124–126] Impella™ may also be utilized as a bridge to percutaneous mitral valve replacement to stabilize hemodynamics in CS with severe mitral regurgitation.[127] This staged approach facilitates weaning from ventilation and sedation.[127] IABP placement in noncoapting mitral leaflets in severe MR allows leaflet coaptation. Use of MitraCilp™ procedure has been described in a case series.[128]

Depending on the valvular defect, MCS of choice may vary. Both IABP and VA-ECMO are contraindicated in aortic regurgitation, given the potential for increased afterload, resulting in LV dilatation, severe pulmonary edema, and LV thrombus formation.[129] TandemHeart™ or placement of a surgical LVAD with concomitant valve replacement might be a successful method of then bridging to durable LVAD or heart transplant.[130]

Impella™, while previously contraindicated in critical aortic stenosis, has been recently supported as a feasible choice of MCS.[131] Impella™ may also be utilized as a bridge to percutaneous mitral valve replacement in CS with severe mitral regurgitation.[127] When dealing with patients with mechanical valves, minimizing risk of aortic root thrombosis is crucial due to the procoagulative nature of extracorporeal circuits and the valves.[132] MCS modalities used in major valvular pathologies are hereby summarized in Table 5.

Future Directions and Conclusions

The incidence of *de novo* CS is likely increasing, in contrast to AMI-CS, and mortality remains high in a young cohort with limited comorbid disease. There is paucity of large-scale data to address knowledge gaps in our understanding of the optimal management of *de novo* CS and limited study on the horizon. While there may be parallels with AMI-CS management, direct translation of guideline-based interventions to *de novo* CS may be harmful. Gaps in evidence include the use of hemodynamic monitoring both in treatment escalation and management of *de novo* CS, the role and timing of MCS deployment, optimal decongestive strategies, and the impact of regionalized systems of care (Table 6). Given that there are specific therapies that may im-

Table 6

Gaps in evidence in MCS in *de novo* HF CS.

Research domain	Gaps in evidence
Prognosis	Risk scores specific to *de novo* populations
	Overlap of phenotyping data in *de novo* cohorts
	The role of pre-MCS MRI in risk stratification of patients with myocarditis
Monitoring	The role of PAC and its parameters to inform therapeutic management including escalation to MCS
	Development of echocardiographic parameters with or without hemodynamic parameters to inform treatment escalation, de-escalation, and transition to durable MCS
Management	Timing and role of medical therapies in the context of decision to escalate to MCS
	Potential for the role of IABP as a first-line support in specific sub-types
	The role of ventricular unloading on myocardial recovery in specific *de novo* subtypes, *e.g.*, myocarditis
	Optimal inopressor therapy and fluid management in *de novo* subtypes
	Inopressor management with patients supported with MCS
	Optimal timing of transition to semi-durable and durable devices or heart transplantation

CS: Cardiogenic shock; HF: Heart failure; MCS: Mechanical circulatory support; PAC: Pulmonary artery catheter.

Table 7

Ongoing RCTs, registries, and observational studies registered on clinicaltrials.gov regarding MCS.

Studies	Intervention/outcomes	Estimated enrollment (participants)	Status	Estimated completion date
RCTs				
Impella CP with VA-ECMO for cardiogenic shock (REVERSE)	Impella CP *vs.* VA-ECMO	96	Recruiting	Jan 2025
ExtraCorporeal membrane oxygenation in the therapy of cardiogenic shock (ECMO–CS)	Immediate ECMO *vs.* early conservative therapy	120	Recruiting	Dec 2022
Normoxemic *vs.* hyperoxemic extracorporeal oxygenation in patients supported by veino-arterial ECMO for cardiogenic shock (ECMOxy)	Normoxemic *vs.* hyperoxemic ECMO	60	Not yet recruiting	Dec 2022
LEVOSIMENDAN to facilitate weaning from ECMO in severe cardiogenic shock patients	Levosimendan *vs.* placebo	206	Recruiting	Nov 2023
Evaluation of oxiris membrane as a treatment for ischemia–reperfusion syndrome in cardiogenic shock treated with extracorporeal life support (ECMO/ECLS): A Randomized Pilot Study ECMORIX (ECMORIX)	Oxiris membrane *vs.* prismaflex membrane	40	Recruiting	June 2024
Registry data				
The Current Status and Clinical Outcomes of Patients with Cardiogenic Shock II (RESCUE II)	MCS outcomes	1000	Recruiting	Dec 2024
American Heart Association Cardiogenic Shock Registry	Study CS and its outcomes	Undisclosed	Recruiting	Undisclosed
Critical Care Cardiology Trials Network Registry (CCCTN)	Multicenter registry of cardiac intensive cares	Undisclosed	Recruiting	Dec 2022
CSWG Registry	Vasopressor, inotrope, and MCS in CS	5000	Recruiting	June 2025
Inova Cardiogenic Shock Registry (INOVA SHOCK)	Retrospective review of CS patient outcomes	400	Recruiting	Undisclosed
The Current Status and Clinical OUTcomes of Cardiogenic Shock Patients and the Role of Specialist in Cardiovascular Critical Care Unit (SCOUT SPARC)	Demographic, history, comorbidities, and medical and mechanical management in CS	10,000	Recruiting	May 2030
Prospective register on the etiologies of cardiogenic shock and their prognosis at one year (cardiac shock)	Prevalence of cardiac shock and impact of management	1650	Recruiting	April 2023
Transient Circulatory Support in Cardiogenic Shock (ALLOASSIST)	Decision relevance of transient circulatory support for acute CS	240	Recruiting	October 2021 (no update)
Cardiogenic shock: a Prospective National Registry to Get Insights in Patients' Profile, Management and Outcome (Altshock-2 REGISTRY)	Registry assessing all phenotypes of CS	3000	Recruiting	December 2030
Multi-center collaborative to enhance quality and outcomes in the management of cardiogenic shock (VANQUISH SHOCK)	Overall quality outcomes	500	Not yet recruiting	Dec 2027
CARDSUP – SWISS Circulatory Support Registry (CARDSUP)	Prospective cohort registry on CS patients with VA-ECMO or Impella	1500	Recruiting	Aug 2034
Outcomes of patients with VA-ECMO	Prospective cohort study on VA-ECMO in CS	500	Recruiting	July 2025
Others				
Impact of a VA-ECMO in combination with CytoSorb in critically ill patients with cardiogenic shock (ECMOsorb)	Single-arm trial	54	Recruiting	Jun 2023
PPCM observational study (peripartum cardiomyopathy)	Clinical placement of Impella in PPCM	10	Recruiting	Feb 2023
Thoratec Corporation HeartMate PHP™ Cardiogenic Shock Trial	HeartMate PHP in CS	9	Terminated	June 2022
Acute impact of the Impella CP Assist Device in Pts. with cardiogenic shock on the patients hemodynamic (JenaMACS)	Impella CP microaxial pump impact on hemodynamics	20	Reecruiiting	March 2022 (no update)
Efficacy and safety of synchronized cardiac support in cardiogenic shock patients (PulseSE)	Synchronized cardiac support treatment in CS patients on VA-ECMO	21	Recruiting	Dec 2023
Venous oxygen saturation during ECMO support (ECMOxygen)	Association of saturations with outcomes	52	Recruiting	June 2023
SURPASS Impella 5.5 Study	Single arm placement of Impella 5.5	1000	Recruiting	Nov 2024
Evaluation of predictive factors for right ventricular dysfunction postimplantation of left mono ventricular assistance in patients in cardiogenic shock under veno arterial ECMO (ECPELLA)	Prospective cohort study	80	Recruiting	March 2023

CS: Cardiogenic shock; CSWG: Cardiogenic Shock Working Group; MCS: Mechanical circulatory support; PPCM: Peripartum cardiomyopathy; RCTs: Randomized controlled trials; VA-ECMO: Veno-arterial extracorporeal membrane oxygenation.

prove outcomes in *de novo* CS, and that standard medical management with inopressors may be detrimental, identification of this subtype is the crucial first step, coupled with engagement of experts in both cardiology and cardiac intensive care to guide management and bespoke escalation to MCS where initial medical therapy fails. Given the negative effects of specific inopressors, combined with the young age of this cohort, earlier use of MCS than in AMI-CS or heart failure CS may be appropriate but

this notion should be addressed in large-scale trials. Crucially, such patients must be included in large-scale prospective, international CS registries such that we can better understand incidence, management, and outcomes to support trial design. We have thereby summarized ongoing trials registered on (*clinicaltrials.gov*) addressing MCS devices in non-AMI-CS or CS in general in Table 7. Given the paucity of large-scale data regarding MCS modalities in *de novo* HF CS, we have also drawn a table

summarizing gaps in evidence, whereby additional data are desirable to understand and implement strategies to improve outcomes.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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