Contemporary Management of Cardiogenic Shock

A Scientific Statement From the American Heart Association

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ABSTRACT: Cardiogenic shock is a high-acuity, potentially complex, and hemodynamically diverse state of end-organ hypoperfusion that is frequently associated with multisystem organ failure. Despite improving survival in recent years, patient morbidity and mortality remain high, and there are few evidence-based therapeutic interventions known to clearly improve patient outcomes. This scientific statement on cardiogenic shock summarizes the epidemiology, pathophysiology, causes, and outcomes of cardiogenic shock; reviews contemporary best medical, surgical, mechanical circulatory support, and palliative care practices; advocates for the development of regionalized systems of care; and outlines future research priorities.

Cardiogenic shock (CS) is a low-cardiac-output state resulting in life-threatening end-organ hypoperfusion and hypoxia.[1,2] Acute myocardial infarction (MI) with left ventricular (LV) dysfunction remains the most frequent cause of CS.[1,3] Advances in reperfusion therapy have been associated with improvements in survival, but significant regional disparities in evidence-based care have been reported, and in-hospital mortality remains high (27%–51%).[1,4–9] Management recommendations are distributed between disease-specific statements and guidelines, and a dedicated and comprehensive clinical resource in this area is lacking. Thus, consolidating the evidence to define contemporary best medical and surgical CS practices for both MI-associated CS and other types of CS may be an important step in knowledge translation to help attenuate disparities in evidence-based care.

Regional systems of care coupled with treatment algorithms have improved survival in high-acuity time-sensitive conditions such as MI, out-of-hospital cardiac arrest (OHCA), and trauma.[10–12] Applying a similar framework to CS management may lead to similar improvements in survival, and CS systems of care are emerging within existing regional cardiovascular emergency care networks; however, guidance from a national expert group on structure and systems of care has not been available.[13,14] Accordingly, the purposes of this American Heart Association (AHA) scientific statement on CS are to summarize our contemporary understanding of the epidemiology, pathophysiology, and in-hospital best care practices into a single clinical resource document; to suggest a stepwise management algorithm that integrates medical, surgical, and mechanical circulatory support (MCS) therapies; and to propose a Mission: Lifeline–supported pathway for the development of integrated regionalized CS systems of care.

Key Words: AHA Scientific Statements ■ delivery of health care ■ disease management ■ shock, cardiogenic

DEFINITION OF CS

Acute cardiac hemodynamic instability may result from disorders that impair function of the myocardium, valves, conduction system, or pericardium, either in isolation

Table 1. Pragmatic and Clinical Trial Definitions of CS

Clinical Definition	SHOCK Trial[9]*	IABP-SHOCK II[1]†	ESC HF Guidelines[15]
Cardiac disorder that results in both clinical and biochemical evidence of tissue hypoperfusion	Clinical criteria: SBP <90 mm Hg for ≥30 min OR Support to maintain SBP ≥90 mm Hg AND End-organ hypoperfusion (urine output <30 mL/h or cool extremities) Hemodynamic criteria: CI of ≤2.2 L·min^{-1}·m^{-2} AND PCWP ≥15 mm Hg	Clinical criteria: SBP <90 mm Hg for ≥30 min OR Catecholamines to maintain SBP >90 mm Hg AND Clinical pulmonary congestion AND Impaired end-organ perfusion (altered mental status, cold/clammy skin and extremities, urine output <30 mL/h, or lactate >2.0 mmol/L)	SBP <90 mm Hg with adequate volume and clinical or laboratory signs of hypoperfusion Clinical hypoperfusion: Cold extremities, oliguria, mental confusion, dizziness, narrow pulse pressure Laboratory hypoperfusion: Metabolic acidosis, elevated serum lactate, elevated serum creatinine

CI indicates cardiac index; CS, cardiogenic shock; ESC, European Society of Cardiology; HF, heart failure; IABP-SHOCK II, Intraaortic Balloon Pump in Cardiogenic Shock II; LV, left ventricular; MI, myocardial infarction; PCWP, pulmonary capillary wedge pressure; SBP, systolic blood pressure; and SHOCK, Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock.

*In setting of MI complicated by predominantly LV dysfunction.

†In setting of acute MI.

or in combination. CS is pragmatically defined as a state in which ineffective cardiac output caused by a primary cardiac disorder results in both clinical and biochemical manifestations of inadequate tissue perfusion. The clinical presentation is typically characterized by persistent hypotension unresponsive to volume replacement and is accompanied by clinical features of end-organ hypoperfusion requiring intervention with pharmacological or mechanical support. Although not mandated, objective hemodynamic parameters for CS can help confirm the diagnosis and enable comparison across cohorts and clinical trials. Definitions in clinical practice guidelines and operationalized definitions used in the SHOCK (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock) and IABP-SHOCK II (Intraaortic Balloon Pump in Cardiogenic Shock II) trials are presented in Table 1.[1,9,15]

HISTORICAL PERSPECTIVES

Before the routine use of early revascularization, MI-associated CS had an in-hospital mortality exceeding 80%. A registry trial of 250 patients with acute MI described the association between bedside physical examination (Killip classification) for the assessment of heart failure (HF) and the risk of mortality.[16] Patients with Killip class IV (CS) had a mortality of 81%. Subsequently, the Diamond and Forrester classification using right-sided heart catheterization described the role of cardiac hemodynamics in stratifying risk after acute MI in the prereperfusion era.[17] Patients in Diamond and Forrester subgroup IV with a pulmonary capillary wedge pressure (PCWP) >18 mm Hg and a cardiac index (CI) <2.2 L·min^{-1}·m^{-2}, indicative of CS, had a mortality of 51%.

Treatment efforts to reduce mortality initially focused on improvement of hemodynamic parameters by mechanical devices. The intra-aortic balloon pump (IABP), introduced in a registry cooperative trial, decreased systolic blood pressure (SBP), increased diastolic blood pressure, and modestly but significantly increased CI.[18] Nevertheless, mortality remained virtually unchanged, with only 15 survivors among 87 patients (83% mortality).[18] The early reperfusion era did not affect outcomes for shock complicating acute MI. Fibrinolysis was effective for patients with ST-segment–elevation MI (STEMI) in general, but it is less clear if fibrinolysis reduces mortality in those with CS.[19,20]

The first major breakthrough in CS treatment was achieved by the randomized SHOCK trial. Although an early invasive strategy coupled with percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) did not reduce 30-day mortality (the primary outcome of the trial), a significant mortality reduction emerged at 6 and 12 months that persisted at longer-term follow-up.[9,21,22] Subsequent registries confirmed the survival advantage of early revascularization.[5,6,8]

Further efforts to reduce CS mortality have been directed toward improvements in MCS devices. The largest randomized trial in patients with acute MI complicated by CS did not show a benefit with routine IABP placement in addition to revascularization.[1] As a result, there has been a decrease in the use of IABPs in clinical practice and a downgrading in guideline recommendations.[23,24] Recently, other percutaneous MCS devices have shown promise in the treatment of CS, but more data from randomized clinical trials are needed.[25]

PATHOPHYSIOLOGY

Our understanding of the complexity and pathophysiology of MI-associated CS in particular has evolved over the past 2 decades.[2,3,25–27] In general, there is a profound depression of myocardial contractility resulting in a potentially deleterious spiral of reduced cardiac output, low blood pressure, and further coronary ischemia, followed by additional reductions in contractility (Figure 1). This cycle may lead to death. This classic paradigm also includes compensatory, although pathological, systemic vasoconstriction that

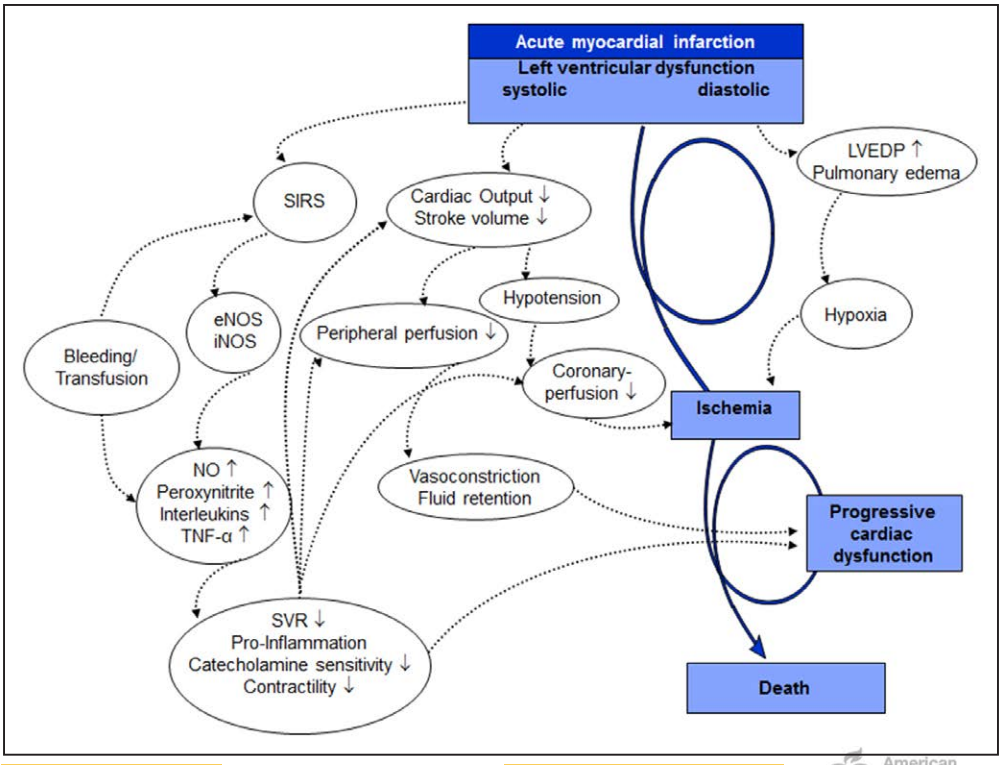

Figure 1. The pathophysiological concept of the expanded cardiogenic shock spiral.
eNOS indicates endothelial nitric oxide synthase; iNOS, inducible nitric oxide synthase; LVEDP, left ventricular end-diastolic pressure; NO, nitric oxide; SIRS, systemic inflammatory response syndrome; SVR, systemic vascular resistance; and TNF-α, tumor necrosis factor-α. Adapted from Hollenberg et al[3] with the permission of American College of Physicians, Inc, copyright © 1999, American College of Physicians, all rights reserved; from Hochman,[26] copyright © 2003, American Heart Association, Inc; from Reynolds and Hochman,[2] copyright © 2008, American Heart Association, Inc; and from Thiele et al[27] by permission of the European Society of Cardiology, copyright © 2010, The Author.

results from acute cardiac injury and ineffective stroke volume.[3] Emerging evidence has also shown that impairment of tissue microcirculation is associated with 30-day mortality and temporal changes in SOFA (Sepsis-Related Organ Failure Assessment) scores and may be improved with MCS.[28,29]

In fact, it is now well established that CS can result in both acute and subacute derangements to the entire circulatory system, including the peripheral vasculature. Extremity and vital organ hypoperfusion remains a clinical hallmark. Although ineffective stroke volume is the inciting event, inadequate circulatory compensation may also contribute to shock. Peripheral vasoconstriction may improve coronary and peripheral perfusion at the cost of increased afterload. Alternatively, systemic inflammation triggered by acute cardiac injury may induce pathological vasodilatation. Endothelial and inducible nitric oxide (NO) synthase may play a major role in the production of high NO levels, along with peroxynitrite, which has a negative inotropic effect and is cardiotoxic.[26] Other inflammatory mediators such as interleukins and tumor necrosis factor can also contribute to systemic vasodilation and have been associated with mortality in CS.[30] In addition, bleeding and transfusions may be associated with mortality.[31,32] Alterations in erythrocyte NO biology of stored blood can lead to vasoconstriction, platelet aggregation, and ineffective oxygen delivery, whereas transfusion of stored blood may also contribute to inflammation.[33]

HEMODYNAMIC PHENOTYPES

Early reports of CS described patients with HF and elevated central venous pressures (CVPs).[34] With the advent of invasive hemodynamic measurements, patients with CS were further characterized by a low CI, an elevated systemic vascular resistance, and a high PCWP.[35] This classic "cold and wet" (Figure 2) profile is the most frequent CS phenotype, accounting for nearly two thirds of patients with MI-associated CS.[36] Although some teaching and reference materials continue to describe a singular CS presentation, SHOCK trial ancillary studies have helped to identify an expanded spectrum of CS hemodynamics.[37] The common physiological characteristic among all phenotypes is a low CI, but ventricular preload (PCWP or CVP), volume, and systemic vascular resistance may vary. Notably, whereas CI thresholds <1.8 to 2.2 L·min^{-1}·m^{-2} have been pro-

Peripheral Circulation	Volume Status: Wet	Volume Status: Dry
Cold	Classic Cardiogenic Shock (↓CI; ↑SVRI; ↑PCWP)	Euvolemic Cardiogenic Shock (↓CI; ↑SVRI; ↔PCWP)
Warm	Vasodilatory Cardiogenic Shock or Mixed Shock (↓CI; ↓/↔SVRI; ↑PCWP)	Vasodilatory Shock (Not Cardiogenic Shock) (↑CI; ↓SVRI; ↓PCWP)

Figure 2. Potential hemodynamic presentations of cardiogenic shock.
CI indicates cardiac index; PCWP, pulmonary capillary wedge pressure; and SVRI, systemic vascular resistance index.

posed for CS, absolute cutoffs are likely impractical given that end-organ hypoperfusion with higher CIs has been documented.[2,38,39] Euvolemic or "cold and dry" CS typically describes a diuretic-responsive patient with chronic HF with a subacute decompensation but also represents a reported 28% of patients with MI-associated CS.[36,40] Compared with patients with classic CS, those with euvolemic CS were less likely to have had a previous MI or chronic kidney disease and had significantly lower PCWPs.[36]

There is growing recognition of the cytokine cascade, chemokine response, and inducible NO synthase expression associated with coronary plaque rupture.[26,41–46] As previously described, putative mechanisms also are associated with a "wet and warm" CS presentation wherein a systemic inflammatory response syndrome and vasodilation can occur after an MI.[26,47] This phenotype is characterized by systemic inflammatory response syndrome features, lower systemic vascular resistance, and a higher risk of sepsis and mortality.[48,49]

Overlaid on this framework are 2 uncommon but hemodynamically distinct entities of normotensive CS and right ventricular (RV) CS. In the SHOCK trial registry, 5.2% of patients were normotensive with peripheral hypoperfusion despite an SBP >90 mm Hg.[50] This group had comparable CIs, PWCPs, and LV ejection fractions but higher systemic vascular resistance compared with hypotensive patients with CS, thus highlighting the risk of relative hypotension and the potential for hypoperfusion without profound hypotension. The reported prevalence of RV CS is 5.3% among patients with MI-induced CS. For these patients, the severity of shock may depend on the degree of both RV and LV ischemia, given a shared septum and the importance of ventricular interdependence on RV function.[51–53] Hemodynamically, this cohort is characterized by relatively higher CVPs, LV ejection fractions, and lower pulmonary artery systolic pressures, with no differences in CI or PCWP. Only 71% of patients with an RV infarct in the SHOCK registry met the classic hemodynamic definition of RV infarction (CVP:PCWP ≥0.8); however, other studies have shown that fluid challenges increased the prevalence of this hemodynamic definition.[51,54]

PATHOGENESIS

After hemodynamic resuscitation and stabilization of a patient presenting with CS, identification of the underlying cause (Supplemental Table 1) can permit the initiation of specific pharmacological or mechanical therapies. A contemporary registry has reported that as many as 81% of patients presenting with CS had an underlying acute coronary syndrome (ACS).[55] Thus, among patients with CS within the appropriate demographic or with risk factors for coronary artery disease, ACS should be the focus of initial diagnostic testing, and this testing should include an ECG within 10 minutes of presentation.[56] Although 5% to 12% of ACS cases are complicated by CS, this presentation is often associated with a large degree of at-risk myocardium.[4,57] In patients with a recent ACS, mechanical complications (including papillary muscle rupture, ventricular septal defect, or free wall rupture) were historically thought to be late complications but most frequently present within 24 hours of hospitalization.[58,59] An index of suspicion and rapid echocardiography are required for such diagnoses.

Chronic HF can present in an acute decompensated state and may account for up to 30% of CS cases.[60] These patients have often experienced a decline in disease stability or have poor adherence to guideline-based therapies that may trigger an acute worsening of their chronic disease. Treatment of patients with chronic HF presenting in CS can differ substantially from the treatment of other types of CS because the hemodynamic condition and neurohormonal milieu are often strikingly different. Patients with HF often have profound upregulation of vasoconstrictor substances such as angiotensin II, endothelin-1, and norepinephrine.[61,62] Among patients who had cardiac surgery, 2% to 6% of patients develop postcardiotomy shock.[63,64] This state may be attributable to low cardiac output (a result in part of myocardial hibernation, stunning, or inadequate cardioprotection), systemic vasodilation, or both.[63–65]

If these common causes of CS are not consistent with the presentation, then less common causes listed in Supplemental Table 1 should be considered. In acute

myocarditis, paradoxically, the sickest patients on presentation have the best odds of recovery, particularly in younger age groups.[66,67] Survival may depend on rapid recognition of the clinical syndrome and early institution of aggressive hemodynamic support.[67–70] Stress-induced cardiomyopathy is increasingly recognized, and although it often presents with mild cardiovascular compromise, it has been associated with CS and may require MCS. Patients with stress-induced cardiomyopathy typically recover.[71–73] Advanced valvular heart disease and prosthetic dysfunction, especially when previously undetected or inadequately monitored, may present as CS, although this has become less common as echocardiographic techniques and surveillance have improved.[74–76] Thyroid disorders, both hyperthyroidism and hypothyroidism, can also cause circulatory collapse.[77,78] Pregnancy-associated cardiac conditions, including both peripartum cardiomyopathy and acute coronary dissection, may present as CS. Numerous additional causes of CS have been reported, but they typically occur in <1% of patients.[79,80]

LABORATORY EVALUATION, NONINVASIVE TESTING, AND HEMODYNAMIC MONITORING

Laboratory Evaluation

Biomarkers of cardiac myonecrosis are useful to gauge the severity of acute underlying myocardial injury in conditions such as fulminant myocarditis. In ACS, cardiac troponin is noted to be elevated and has a rise-and-fall pattern consistent with acute ischemic injury.[81] A mismatch between the degree of segmental dysfunction on imaging and troponin release may be noted in the setting of stunned/hibernating myocardium or when presentation is significantly delayed after the ischemic insult. Myocardial necrosis biomarker levels may provide an idea of the extent of myocardial injury, whereas serial measurements are useful in assessing early washout after successful reperfusion and in estimating the amount of cardiac necrosis. Natriuretic peptides are significantly elevated in the setting of acute HF culminating in CS and are associated with mortality in MI-associated CS.[82,83]

Oxygen-carrying capacity is the product of cardiac output and the oxygen content of blood. Thus, an ineffective CI will result in inadequate peripheral tissue oxygen delivery. Elevated arterial lactic acid levels are nonspecifically indicative of tissue hypoxia but are associated with mortality in CS.[84,85] The pathogenesis of lactate production in CS is uncertain, although impaired oxygen delivery, stress-induced hyperlactatemia, and impaired clearance are likely contributors.[86] A peripheral oxygen demand-delivery mismatch will result in low central venous oxygen measurements. A mixed venous oxygen saturation sample is ideally obtained from the distal port of a pulmonary artery catheter (PAC) and is a reflection of oxygen saturation from blood returning to the heart via the superior and inferior vena cava, as well as the coronary sinus. Serial measurements of arterial lactate and mixed venous oxygen saturation levels may be helpful to temporally monitor responses to therapeutic interventions. Arterial blood gas measurements also permit the assessment of arterial oxygenation and ventilation, as well as metabolic and respiratory acid-base disorders.

Acute kidney injury, which is reflected by a rise in serum creatinine and a potential reduction in urinary output, in the setting of CS may indicate renal hypoperfusion and is associated with poor outcomes.[87,88] It should be noted that novel renal biomarkers such as neutrophil gelatinase–associated lipocalcin, kidney injury molecule 1, and cystatin C were not more effective than standard evaluation with serum creatinine for assessing risk.[87] Acute ischemic or congestive liver injury can occur in the setting of CS and manifests as a marked elevation in serum aspartate aminotransferase, alanine aminotransferase, serum bilirubin, and lactate dehydrogenase levels, often accompanied by an increase in prothrombin time with a peak at 24 to 72 hours that subsequently recovers to baseline within 5 to 10 days, and a ratio of alanine aminotransferase to lactate dehydrogenase of <1.5.[89,90] This should be differentiated from chronic to subacute elevation of liver function abnormalities in the setting of venous congestion resulting from right-sided HF.

Noninvasive Testing

Despite its limitations, the chest x-ray provides information on cardiac size and pulmonary congestion and may suggest alternative pathogeneses such as aortic dissection, pericardial effusion, pneumothorax, esophageal perforation, or pulmonary embolism. The test enables clinicians to confirm the position of the endotracheal tube and the position of supportive devices, including temporary pacing wires and MCS. The resting 12-lead ECG is diagnostic in patients with STEMI but can provide evidence for other clinical conditions, including non–ST-segment–elevation ACS, pulmonary embolism, acute myocarditis, electrolyte imbalances, and drug toxicity. A comprehensive transthoracic echocardiogram is suggested. It can provide additional hemodynamic information, exclude mechanical complications, and help to guide medical and mechanical therapeutic decisions (Supplemental Table 2). When images are inadequate or the diagnosis remains uncertain, a transesophageal echocardiogram should be considered. An overview of invasive hemodynamic testing and monitoring is provided later in Management of CS.

Suggestions for Clinical Practice

We suggest that all patients with CS be evaluated with an ECG, chest x-ray, and comprehensive echocardiogram with the specific purpose of understanding the dominant mechanism responsible for acute hemodynamic instability. In the absence of contraindications, additional imaging with a computed tomography scan or transesophageal echocardiogram (as appropriate) if an acute aortic syndrome or pulmonary embolism is suspected is appropriate. Suggested laboratory tests include a complete blood count, electrolytes, creatinine, hepatic function tests, arterial blood gas and lactate, and serial cardiac troponin levels.

CONTEMPORARY OUTCOMES, PROGNOSIS, AND RESOURCE USE

Trends in Outcomes and Therapies

CS remains the most common cause of in-hospital mortality in the setting of an acute MI, and most longitudinal studies and registries have reported a decline in MI-associated CS mortality.[4,57,91–93] An analysis of the Nationwide Inpatient Sample Database between 2003 and 2010 reported an increase in the prevalence of CS from 6% to 10% in the overall population and from 7% to 12% among patients >75 years of age presenting with STEMI.[4] In-hospital mortality decreased from 45% to 34% over the same time frame, although mortality rates remained high (55%) in patients >75 years of age. The provision of angiography (64% to 74%), early PCI (26% to 54%), and IABP (45% to 54%) increased, whereas PAC use (10% to 6%) decreased over time. The declining rates of in-hospital mortality may be partly attributed to more aggressive early revascularization, although this improvement was not supported by a more contemporary analysis of patients with MI-associated CS undergoing PCI between 2005 and 2013.[57] Those authors reported that despite an overall increase in PCI, in-hospital mortality increased from 27% to 30% and deaths occurring in the catheterization laboratory increased from 15% to 20%. In addition, patient complexity increased over the same time frame with more delayed presentations (>6 hours after symptom onset), multivessel coronary disease, and complex (type C) coronary lesions. Furthermore, the percentage of patients with MI-associated CS undergoing PCI at low-volume (<500 PCIs a year) centers increased from 30% to 48%. Collectively, these data identify several concerning trends in the field: a potential increase in mortality, an increase in patient complexity and use of MCS, and a geographic shift toward care being delivered by lower-volume centers that may have less experience dealing with complex hemodynamic and coronary patient subsets. In addition, confounding related to changes in hospital-based coding of CS cannot be excluded. In the non-ACS CS population, a contemporary registry (limited to 42 patients with non-ACS CS) reported an in-hospital mortality rate of 24% and that non-ACS pathogenesis was independently associated with better survival.[55]

Prognostic Models and Variables

Multiple scoring systems to predict clinical outcomes in CS have been proposed. Several models were derived in the general intensive care unit (ICU) population and include the APACHE (Acute Physiology and Chronic Health Evaluation)-II score and SAPS (Simplified Acute Physiology Score)-II scoring systems.[94–97] APACHE-II includes 13 physiological variables and was designed to be measured during the first 24 hours after ICU admission for patients >16 years of age. The APACHE-III scoring system adds variables such as pathogenesis of shock, sex, race, and comorbidities to the APACHE-II system and was validated in >17 000 ICU patients in the United States. The SAPS-II includes 12 physiological and 3 disease-related variables, was validated in 12 997 patients from 12 countries, and is used to predict in-hospital mortality. A small study comparing the APACHE-II, APACHE-III, SAPS-II, and SOFA scoring systems in CS reported that APACHE-III and SAPS-II had the best mortality discrimination.[98] The CardShock study was a series of 219 patients with all-cause CS and identified 7 variables associated with in-hospital mortality (c index 0.85), but it lacked external validation.[55] Among patients with an ACS complicated by CS, the GRACE (Global Registry of Acute Coronary Events) score has good discrimination and calibration for in-hospital and long-term mortality among all patients presenting with ACS, but it is not applicable to non-ACS presentations.[99] Additional published clinical, imaging, and hemodynamic variables associated with in-hospital mortality in the CS population include anoxic brain damage, end-organ hypoperfusion, elevated lactate, prior CABG, ACS pathogenesis, LV ejection fraction, RV function, pulmonary artery pulsatility index (defined as the ratio of pulmonary artery pulse pressure to right atrial pressure), mitral regurgitation, LV stroke work, cardiac power output, SBP, number of vasopressors, systemic inflammatory response syndrome, and TIMI (Thrombolysis in Myocardial Infarction) flow.[39,48,100–105] Limitations of available models included the lack of a CS-specific derivation population, external validation, dynamic application (ie, single point in time only), applicability to all CS types, and capture of all potentially prognostic clinical, laboratory, hemodynamic, imaging, and biomarker data.

Resource Use and Costs

The economic impact of CS remains poorly understood. The median reported ICU length of stay is 6 days and

hospital length of stay is 8.9±11.8 days in the United States and a median of 12 days (7–25 days) in Europe.[1,4,55] A recent analysis of patients with STEMI complicated by CS in the United States reported that the average total hospital cost was $41 774±45 252.[4] In the contemporary IABP-SHOCK II trial, there were higher average costs in the IABP arm (€33 155±14 593) than in the control arm (€32 538±14 031).[106] In summary, CS treatment incurs substantial resource use and costs.

Long-Term Outcomes

Among patients with ACS-associated CS who had revascularization and who survived to hospital discharge, long-term follow-up of the SHOCK trial suggests that the majority (62%) were alive 6 years later.[21] In comparison, a contemporary study of patients ≥65 years of age with MI-associated CS who survived to hospital discharge reported an increased risk of mortality in the first 60 days after discharge and then a mortality rate comparable to that of patients without shock thereafter. The 1-year survival was 87.6%.[107] Despite favorable longer-term survival, CS may be associated with considerable morbidity. Registry data have reported 1-year all-cause and HF rehospitalization rates of 59% and 33%, respectively.[107] The SHOCK and IABP-SHOCK II trials have reported modest quality of life among 1-year survivors, with New York Heart Association class II to IV symptoms in 43% and self-care, physical, or psychological impairments in ≈20% to 30%.[108,109] Considerably less is known about the long-term outcomes in the non-ACS CS population. These data further support the need for new in-hospital and postdischarge therapeutic approaches to improve outcomes for patients with CS and the need for more analyses in the non-ACS CS population.

REGIONALIZED SYSTEMS OF CARE

Clinical Volume and Patient Outcomes

Hospital and medical provider volumes have been consistently and positively associated with survival in medical and surgical care. Luft and colleagues[110] initially described this relationship in 1979, demonstrating 25% to 41% lower postoperative mortality in hospitals performing >200 annual surgical procedures. In subsequent studies, investigators demonstrated a direct relationship between volumes and outcomes at both the operator and institutional level for surgery and PCI.[111–114] A meta-analysis of 15 PCI studies and 7 CABG studies, including >1 million patients from >2000 hospitals, reported lower in-hospital mortality in large-volume (>600 cases) PCI and CABG centers.[115] Multiple studies have also reported improved survival after primary PCI for acute MI in high-volume centers and by high-volume operators.[116–118] On the basis of these relationships, professional associations, including the AHA, American College of Cardiology, and Society for Cardiac Angiography and Interventions, have recommended minimum procedural volumes for hospitals and operators for the maintenance of accreditation and competency.[119] Similar volume-outcome relationships have been reported for other common conditions, including HF and pneumonia, and for medical ICU patients requiring mechanical ventilation (MV).[120,121] In CS, a complex acute condition that requires a multidisciplinary treatment team to provide procedural, surgical, and medical care, clinical volume has also been associated with survival. A study from the Nationwide Inpatient Sample reported that hospitals treating >107 cases per year more frequently provided early revascularization, ventricular assist devices, extracorporeal membrane oxygenation (ECMO), and hemodialysis. There was a direct relationship between adjusted in-hospital mortality and hospital volume. Mortality was 37%, 39.3%, 40.7%, and 42% in hospitals that treated ≥107, 59 to 106, 28 to 58, and <27 cases per year ($P<0.05$).[122] Of note, large-volume sites were more likely to be academic, located in urban areas, and serve as referral hubs. Reasons underpinning this finding have not been clearly elucidated, although we hypothesize that patients treated at high-volume hospitals may be more likely to receive evidence-based care and prompt revascularization by high-volume operators and that high-volume hospitals may include a multidisciplinary team who more frequently implements MCS and cares for patients with multisystem organ failure. Accordingly, establishing systems of care with high-volume hospitals used as hubs integrated with emergency medical systems and spoke centers with clearly defined protocols for early recognition, management, and transfer has the potential to improve patient outcomes.

Existing Regional Systems for Coordination of Care

Regionalized care systems have been successfully implemented for time-sensitive conditions, including STEMI, stroke, trauma, aortic dissection, and OHCA.[107,123–130] In trauma care, mortality has been reduced by 15% to 20% with patient triage and transport to designated American College of Surgeons Level 1 trauma centers.[124] In stroke care, integrated systems of care have been associated with higher rates of fibrinolytic therapy use and improved survival.[123,131] In OHCA, wherein prehospital and hospital management are mutually critical for improved survival, regional systems of care have been successfully implemented.[125,130,132,133] In Arizona, hospital bypass by emergency medical services to designated OHCA centers equipped to provide best-practice in-hospital care was associated with improved overall survival from 8.9% to 14.4%.[134] The management of

STEMI represents the paradigm for integrated systems of care with coordinated emergency medical services, community, and tertiary care centers, coupled with standardized hub-and-spoke transfer protocols, quality assurance, real-time feedback, and healthcare provider education.[128,135–138] The AHA has endorsed and certified STEMI referral and receiving hospitals as part of its Mission: Lifeline initiative, which also implements continuous review and quality improvement.[135]

Regional Systems for the Management of CS

One of the earliest CS regional care systems was implemented by cardiothoracic surgeons in New York City in the 1990s for the management of refractory postcardiotomy shock requiring temporary surgical left-sided MCS as bridge to transplantation (BTT) or recovery.[139] The program consisted of a network of spoke hospitals located within a 250-mile radius of a hub institution. The authors emphasized the need for an early dialogue (within 12 hours of shock) between the referring and accepting centers to determine the viability of the candidate and the suitability for transfer and developed a management algorithm. Implementation of this network was associated with a 66% survival rate, higher than the 25% historical survival rate.

The feasibility of a traveling CS team within a regional hub-and-spoke model was demonstrated in the cardiac-RESCUE pilot study.[13] In this French study, the investigators developed a network of 22 tertiary and 53 nontertiary centers that transferred patients with CS to 3 designated centers using a mobile ECMO team. A call from the spoke institution requesting assistance initiated the departure of the mobile team, consisting of a surgeon, a perfusionist, and a nurse, within 30 minutes. Stabilized patients were subsequently transferred to the hub institution. There were no adverse events during transfer among 75 stabilized patients; 32 patients were discharged alive; and 30 patients were alive at 1 year. In addition, the Arizona Mayo clinic traveling team reported an initial experience with 27 patients from 18 community hospitals, among whom 56% survived to hospital discharge.[14] Taken together, these studies demonstrated the feasibility of mobile CS teams who can successfully facilitate early support and treatment in patients with CS within a hub-and-spoke model.

Proposed Shock Center Characteristics

The writing group proposes that all CS regional referral centers should meet minimum Level 1 unit organizational and staffing criteria as outlined by international scientific statements.[140–142] CS centers should have the onsite monitoring, medical services, and therapeutic technologies to coordinate and deliver care for all causes of CS from the resuscitation phase to recovery, durable supportive therapy, or palliation. Examples of coordination and delivery of care have already been implemented in some tertiary care centers with the creation of multidisciplinary shock teams of cardiothoracic surgeons, interventional cardiologists, advanced HF specialists, critical care specialists, and allied health professionals. Although there is no evidence suggesting that these teams improve outcomes, they can centralize medical, surgical, and MCS care and conduct daily rounds on patients with CS in coordination with the primary team caring for the patient.[143]

Tertiary high-volume cardiovascular centers should be designated as CS receiving (or hub) centers. Within each cardiovascular system of care, these centers would accept transfers of appropriately selected patients with CS from lower-acuity sites for further evaluation and treatment.[15,144,145] Moreover, to consolidate clinical volumes and professional experience, we advocate that a single cardiac ICU (CICU) or ICUs within each CS center be designated to receive all CS admissions before the initiation of MCS. We recognize that after the initiation of some MCS therapies, patients may need to be transferred to surgical ICUs.

The suggested hospital, care unit, professional, technological, and academic capabilities of CS centers are outlined in Table 2.

CICU Versus ICU Admission

Many contemporary tertiary care center CICUs have evolved into critical care environments for patients with a primary cardiovascular diagnosis, with an acuity and therapeutic technologies that mirror those of many ICUs.[146,147] Although the CICU environment may be best suited to centralize cardiac care of patients with CS, attending cardiologists and teams may not have the dedicated training to address the ancillary multisystem organ failure often associated with CS.[142] Conversely, although the ICU may be well suited to manage noncardiac organ failure, surveys have reported that ICU trainees may be unprepared to manage cardiovascular illness and to perform common cardiovascular procedures.[148] ICU-based observational studies have reported improved outcomes in a closed unit staffing model.[149] In addition, in the CICU, there is emerging evidence from a before-and-after study that transition from an open low-intensity care model to a closed unit model with care led by a dual-trained cardiologist-intensivist may improve outcomes; however, further studies are required to evaluate the independent influence of staffing and physician training.[150]

Suggestions for Systems Development

We do not preferentially advocate for either a CICU or ICU as a designated CS unit. Rather, we suggest that each tertiary hub center develop care pathways to de-

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Table 2. CS Center Characteristics

Hospital	Critical Care Unit	Medical and Technological Capabilities	Onsite Medical Consultants	Professional Consultants	Academic Characteristics
Tertiary care center	CICU or ICU	24-h/7-d Primary PCI	Cardiology: interventionalists, echocardiographers, advanced HF/transplantation specialists Electrophysiology	Pharmacy	CS research or participation in national registries
			Palliative care		
			Neurology		
High-volume cardiovascular center	24-h/7-d In-house unit coverage by MD, PA, NP, or resident	Cardiac surgery	Cardiologist-intensivists or intensive care	Social work	Quality improvement and auditing
	1:1 Nurse-to-patient ratio	IABP	Cardiac surgery	Respiratory therapist	Trainee education
	Vasoactive infusions	Percutaneous VAD	Nephrology	Physical therapy	
	Mechanical ventilation	Implantable VAD	Palliative care	Occupational therapy	
	Invasive cardiac and hemodynamic monitoring	ECMO: mobile ECMO team and eCPR capabilities		Dietician	
	CRRT	Echocardiography		Pharmacy	
	Temporary transvenous pacing			Social work	

CICU indicates cardiac intensive care unit; CRRT, continuous renal replacement therapy; CS, cardiogenic shock; ECMO, extracorporeal membrane oxygenation; eCPR, extracorporeal membrane oxygenation–facilitated cardiopulmonary resuscitation; HF, heart failure; IABP, intra-aortic balloon pump; ICU, intensive care unit; MD, medical doctor, NP, nurse practitioner; PA, physician assistant; PCI, percutaneous coronary intervention; and VAD, ventricular assist device.

liver the comprehensive, collaborative, and multidisciplinary care outlined in Table 2.

Regionalization of CS Care

The development and implementation of systems to streamline care and to optimize outcomes of patients with CS have challenges associated with triage decisions, need for expertise with MCS, identification of tertiary care centers to serve as hubs, team training, and resource allocation for mobile transport teams. Although many of the lessons learned during the implementation of OHCA and STEMI systems of care can be applied in a regionalized system for CS, the development and coordination required for CS care will have unique challenges. Potential barriers and solutions are displayed in Supplemental Table 3.

A proposed model for CS regional care is provided in Figure 3. Leadership of national and regional organizations will be required to spearhead the implementation of hub-and-spoke CS systems of care. Hub centers would be required to create mobile multidisciplinary CS teams available 24 hours a day, 7 days a week for onsite or offsite consultation, referral, and ECMO/MCS insertion. In addition, hub centers would be required to identify the CS units with the expertise and resources outlined above. Because spoke hospitals would have variable patient acuity and therapeutic technologies, including PCI and temporary MCS, individual hospitals would have to develop CS treatment algorithms according to onsite capabilities and expertise. Regional protocols should standardize management practices, provide futility parameters, and determine the timing of transfer once the diagnosis of refractory CS is established.

Public Reporting

Although public reporting may improve accountability and promote better care, it may have had the unintended consequence of encouraging risk-averse behaviors among physicians and a reluctance to treat CS (a condition that historically has had a higher risk of procedural mortality). The unfortunate sequela for patients with CS is that this has also been associated with an increased risk of mortality resulting from undertreatment. A solution that has been undertaken in New York State is to exclude all patients with CS from public reporting.[151]

Considerations for Public Reporting

Therefore, in an effort to improve patient outcomes, we suggest that either patients with CS be excluded from public reporting, or reporting should be implemented only after all process, outcome, safety, and economic measures are clearly identified and risk-adjusted.

Knowledge Translation: Mission: Lifeline

In March 2006, in response to a call to action to increase the number of patients with STEMI with timely access to primary PCI, the AHA convened a conference

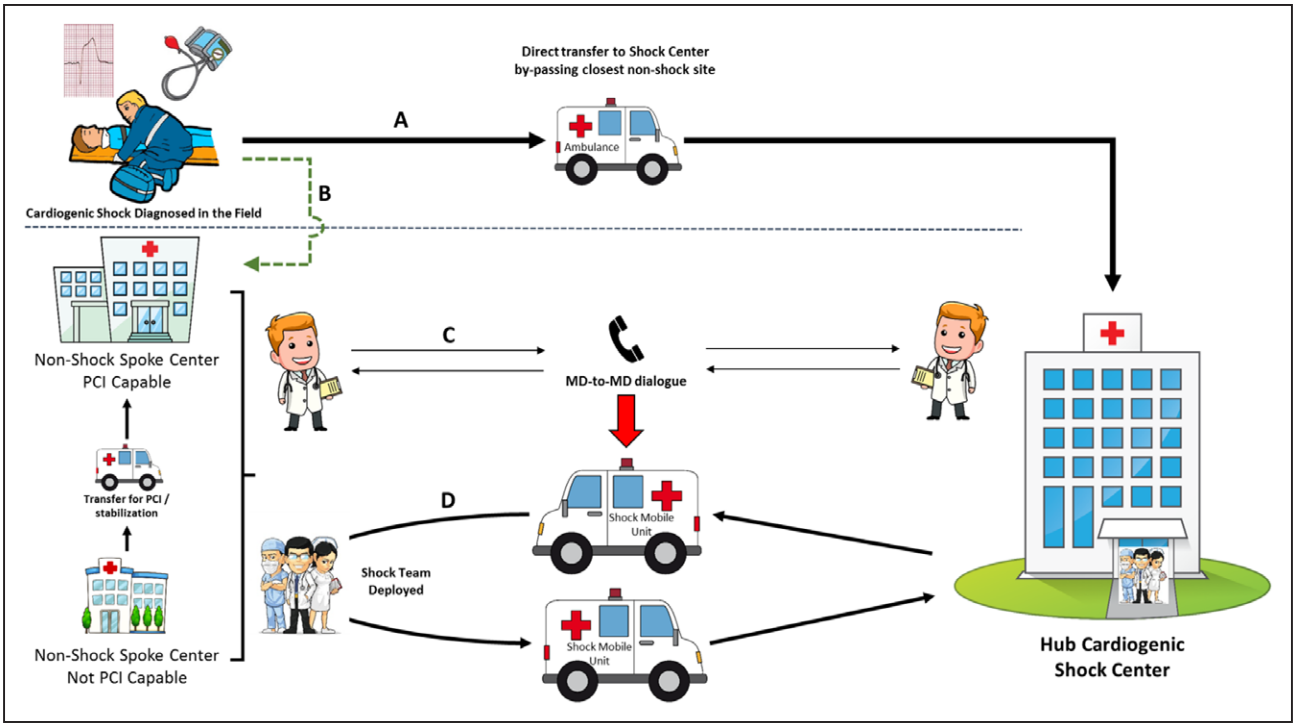

Figure 3. Proposed regional system of care for cardiogenic shock.
(**A**) A patient with CS diagnosed in the field by EMS can be transported directly to the hub CS center, bypassing the nearest spoke facility. (**B**) CS pathogenesis, travel time, and spoke center capabilities should factor into the decision to bypass spoke hospitals; STEMI patients can be transferred to a PCI facility for revascularization and stabilization. Patients with unclassified shock should be transferred to the nearest emergency department. (**C**) For patients presenting to spoke PCI-capable hospitals, revascularization and stabilization can be initiated. Physician-to-physician dialogue with the hub center shock team should occur as soon as possible. (**D**) A mobile unit from the hub center can be deployed to the spoke hospital to stabilize and initiate transfer to the hub CS center for definitive management. Patients presenting to smaller spoke centers without PCI capabilities should be immediately transferred to the nearest PCI facility, or a shock mobile unit should be requested from the hub CS center, depending on the patient's clinical status and anticipated travel time. CS indicates cardiogenic shock; EMS, emergency medical services; MD, medical doctor; PCI, percutaneous coronary intervention; and STEMI, ST-elevation myocardial infarction.

on the development of STEMI systems of care with input from noninvasive and interventional cardiologists, cardiovascular surgeons, emergency care and critical care physicians, emergency medical services personnel, nurses, hospital administrators, payers, government officials, outcomes experts, and patients.[152] The attendees, representing 25 organizations involved in the care of patients with STEMI, were charged with defining the gaps and barriers between existing and ideal systems of care and proposing research, programs, and services that formed the foundation of the AHA Mission: Lifeline Program that was introduced in 2007.[135] An online survey of existing STEMI systems revealed that the principal barriers to success included hospital and cardiology group competition and emergency medical services transport and finances. Lack of data collection and feedback, infrastructure support, funding, and bed availability were also frequent challenges. Predominant funding sources for STEMI systems were PCI hospitals in 84% and cardiovascular practices in 23%.[137]

A preliminary and unpublished analysis of the initial 5-year experience, which included 1 047 466 patients with STEMI from 485 STEMI systems registered with Mission: Lifeline, revealed that the use of primary PCI, prehospital ECGs, time from first medical contact, and first door–to–primary device time all significantly improved. In addition, the number of eligible patients not treated with reperfusion therapy declined by >50%, and adjustment for OHCA suggested that mortality had decreased from 5.3% to 3.7%.

On the basis of the initial success of the Mission: Lifeline Program and other STEMI systems of care in the United States, the development of STEMI systems became a Class I recommendation in 2013.[144] In view of the commonalities in the care of patients with other time-sensitive cardiovascular disorders, Mission: Lifeline was expanded to include patients with OHCA in January 2013 and stroke in July 2015. Because roughly 10% of patients with STEMI and 40% to 50% of patients with OHCA have CS, the natural extension of the Mission: Lifeline program is to include CS. Currently, data

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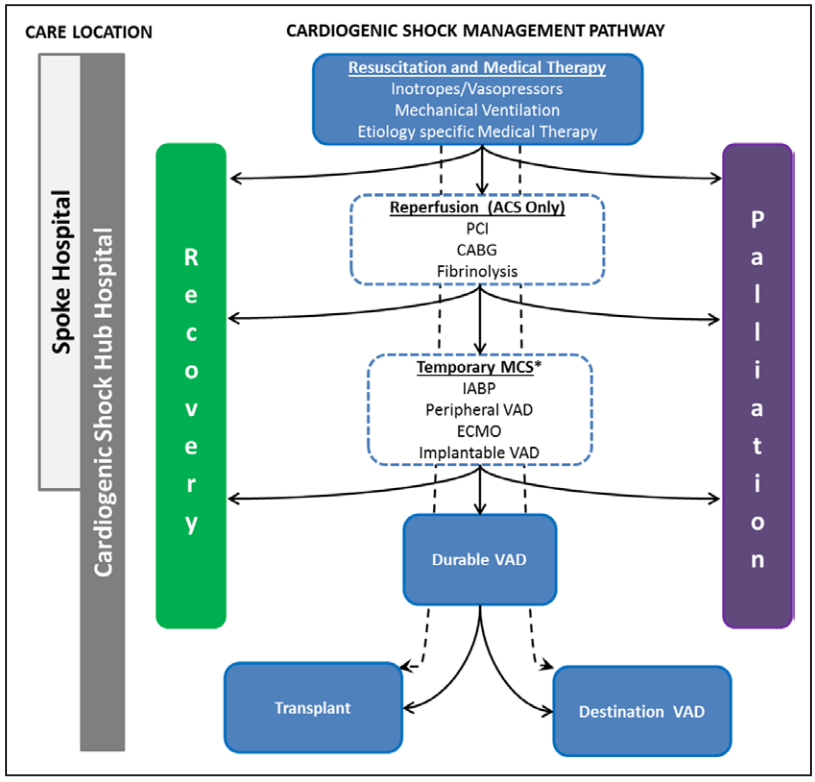

Figure 4. Potential cardiogenic shock care pathway, care location, and care providers.
ACS indicates acute coronary syndrome; CABG, coronary artery bypass graft; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; MCS, mechanical circulatory support; PCI, percutaneous coronary intervention; and VAD, ventricular assist device. *Consider temporary MCS before reperfusion in cases of refractory cardiac arrest or shock.

are collected through ACTION (Acute Coronary Treatment and Intervention Outcomes Network Registry)–Get With The Guidelines, although many systems use their own local registries. Baseline requirements for STEMI could serve as the foundation for an advanced CS program, including data collection and quality improvement programs.

The Mission: Lifeline experience indicates that there is a considerable variation in the successful development of STEMI systems that depends on geography (rural versus urban), regional resources, state lines, and legislation/regulations, and the program recommends consideration of local issues while national recommendations are implemented.[137] Many of the most successful STEMI systems actively include OHCA and advanced CS protocols, as well as protocols for other cardiovascular emergencies.[125]

For CS, metrics that can potentially serve as benchmarks to improve performance need to be developed and measured at the spoke-and-hub institutions with the use of standardized CS definitions. Examples of such metrics include the performance of coronary angiography, time to reperfusion, time to support with percutaneous or surgical MCS, decision to transfer to a hub center, timing of transfer, stabilization at the spoke hospital, and use of mobile shock units. These metrics would facilitate implementation of robust quality assurance processes and would be used for reporting to national registries. Registries could then provide the research structure necessary to identify areas for improvement and further understanding of disease and care processes.

MANAGEMENT OF CS

Reperfusion and Revascularization in CS

Coronary reperfusion is the mainstay evidence-based therapeutic intervention for patients with acute MI presenting with CS.[5,153,154] In this section, reperfusion and revascularization techniques and other adjunctive therapies used in the management of CS are reviewed (Supplemental Table 4). A proposed integrated CS care pathway is outlined in Figure 4.

Fibrinolytic Therapy

Very few placebo-controlled studies of fibrinolysis have included patients with CS.[155] Initial studies showed no survival benefit of streptokinase over placebo, whereas mixed results comparing streptokinase with tissue plasminogen activator have been reported in small patient cohorts.[156] Although the large GUSTO-1 trial (Global Utilization of Tissue Plasminogen Activator and Streptokinase for Occluded Coronary Arteries) showed tissue plasminogen activator to be superior to streptokinase in the overall population, no substantial mortality benefit was observed between fibrinolytic strategies among the nearly 3000 patients with CS.[157] In addition, tissue plasminogen activator–treated patients

were less likely to develop CS, highlighting the need for timely reperfusion in CS prevention. Animal studies have suggested that the effectiveness of thrombolytic therapies may be dependent on a higher systemic perfusion pressure.[158] Although nonrandomized observations from the SHOCK trial and registry among patients treated with fibrinolysis and an IABP would support this finding, an invasive approach to coronary reperfusion remains the best practice in MI complicated by CS.[159,160] The writing group recognizes both the lack of evidence to support fibrinolytic therapy and that timely access to an early invasive approach will not be available to all patients with CS.

Suggestions/Considerations for Clinical Practice

We suggest that when an early invasive approach cannot be completed in a timely fashion, fibrinolysis can be considered in CS associated with STEMI. The decision to administer fibrinolysis should be individualized on the basis of perceived reperfusion benefit, bleeding risks, and the anticipated time delay to angiography.

Early Invasive Strategy in CS

Two randomized trials evaluated whether early invasive therapy with cardiac catheterization followed by PCI or CABG could improve survival in CS. SMASH (Swiss Multicenter Trial of Angioplasty for Shock), published in 1999, randomized only 55 patients and reported no significant reduction in the 30-day death rate.[161] The SHOCK trial randomized 302 patients to either an early invasive strategy with intended emergency revascularization (within 12 hours of shock onset) or initial medical stabilization.[9] As previously noted, the primary end point of 30-day all-cause mortality was nonsignificantly lower in the invasive arm (46.7% versus 56.0%; *P*=0.11); however, mortality was significantly lower at 6 months, at 12 months (13% absolute difference; *P*=0.03), and through long-term follow-up (6 years).[21,22] Patients screened but not randomized into the SHOCK trial were entered into a prospective registry that facilitated validation of the trial findings and additional important subgroup analyses. First, the SHOCK trial reported an age-treatment interaction wherein elderly (>75 years) patients with CS had worse outcomes (*P*=0.01).[9] A SHOCK registry analysis and a pooled analysis of the SMASH and SHOCK trials showed no age-treatment interaction with 12-month mortality.[162,163] Second, women with MI-associated CS were more frequently older. The SHOCK trial and observational studies reported no sex-related outcome differences.[21,164–166] Third, an early invasive treatment approach had consistent benefits across multiple racial and ethnic subgroups.[167] Fourth, diabetes mellitus was an adverse prognostic indicator among patients hospitalized with MI and was more frequently associated with multivessel disease. Diabetic and nondiabetic patients had similar mortality benefits in the SHOCK trial despite a greater prevalence of 3-vessel coronary artery disease and higher rates of surgical revascularization among diabetics.[168] Finally, it has been well established that rapid reperfusion is essential in the effective management of STEMI. In the SHOCK trial, however, there was no significant interaction between the time from CS onset to revascularization and mortality. Conversely, other registry data have suggested a strong correlation between time and outcome.[169,170]

Suggestions for Clinical Practice

We support guidelines that recommend an early invasive strategy with appropriate revascularization for all suitable patients with suspected ACS-associated CS, including patients with uncertain neurological status or those who have received prior fibrinolysis, regardless of the time delay from MI onset.

PCI Strategy

Patients in the SHOCK trial who had successful and unsuccessful PCIs had a 35% and 80% mortality rate, respectively.[9] The majority of participants had multivessel disease and were revascularized with balloon angioplasty.[171,172] Only 34% of patients received a stent (none with drug-eluting stents [DES]). Notably, PCI was more successful when stents were used (93% vs 67%; *P*=0.013), suggesting superior outcomes with stent use in a CS population. The choice of bare metal stent versus DES has not been rigorously studied. A large Swiss registry compared patients with CS treated with a bare metal stent or DES in a propensity-matched analysis and reported lower long-term all-cause mortality among patients treated with DES.[173] In another large Dutch series, no significant differences in stent thrombosis rates were observed in a comparison of stent platforms in a CS population.[174] In a recent subanalysis of the IABP-SHOCK II trial, no differences in outcomes between DES and bare metal stent were observed.[175]

The outcome differences associated with complete revascularization versus culprit-only PCI remain unclear. In stable patients with STEMI undergoing primary PCI, treatment of culprit and nonculprit vessels appears to be safe and may be associated with improved outcomes.[176] Some observational studies have reported potential benefits with multivessel PCI in CS, whereas clinical practice guidelines recommend nonculprit PCI for "critical (≥90% diameter) stenoses or highly unstable lesions."[145,177–181] The CULPRIT-SHOCK trial (Culprit Lesion Only PCI Versus Multivessel PCI in Cardiogenic Shock), designed to be the largest CS trial ever, is currently enrolling patients to test this question in a prospective, randomized fashion.[182]

Historically, diagnostic angiography and PCI have been performed with a femoral arterial access site, although radial access has been more recently advocated as a safer alternative for arterial access. There is a relatively limited experience with radial access in CS, and even those higher-volume radial access centers are using a radial approach only half of the time for their patients with CS.[183,184] A meta-analysis of observational studies including 8131 patients reported that radial access was associated with lower all-cause mortality and major adverse cardiac and cerebral events at the 30-day follow-up in CS.[185] Observational series have also described lower bleeding rates.[183,184,186] When femoral arterial access is considered, fluoroscopic and ultrasound guidance may decrease vascular complications and access-related bleeding.[176] Radial arterial access may be challenging in hypotensive patients with CS, and although ultrasound guidance can improve radial access success and decrease crossover to femoral access in the hemodynamically stable population, radial ultrasound has not been well studied in the CS population.[187]

Suggestions for Clinical Practice

In summary, evidence continues to support the early revascularization of patients with CS after ACS, with either PCI or CABG used as indicated. Until the results of CULPRIT-SHOCK are available, revascularization of both the culprit and hemodynamically significant nonculprit stenoses is reasonable. We support the preferential use of radial arterial access for angiography and PCI when feasible.

Antithrombotic Pharmacotherapy Adjuncts to PCI

There are limited data to support the use of antiplatelet agents, including aspirin, in the setting of CS, and data are largely inferred from more stable MI populations. In addition, studies have demonstrated poor gastrointestinal absorption of these medications in the setting of MI, a problem that may be exacerbated in CS.[188] The ISAR-SHOCK (Efficacy Study of LV Assist Device to Treat Patients With Cardiogenic Shock) registry, which included patients with CS undergoing PCI who had a platelet function assessment after receiving an oral $P2Y_{12}$ inhibitor, reported that prasugrel was associated with a nonsignificant reduction in 30-day mortality.[188] In a secondary analysis of the IABP-SHOCK II trial, there was no difference in mortality or bleeding events in a comparison of clopidogrel, prasugrel, and ticagrelor in patients with acute MI complicated by CS.[189] In addition, each of these $P2Y_{12}$ inhibitors is metabolized by ≥1 isoenzymes in the cytochrome P450 pathway. In patients with CS who likely already have decreased absorption of oral medications, coadministration of strong inducers or inhibitors of these isoenzymes or agents that might further impair absorption might have the potential to reduce drug efficacy or to increase bleeding; however, no data are available in the CS population.[190] The glycoprotein IIb/IIIa inhibitor abciximab is the most studied antiplatelet agent in patients with CS undergoing PCI. Observational studies have reported better postprocedural coronary blood flow and lower hospital mortality, particularly when combined with stent placement.[191–194] A small randomized trial of 80 patients with CS who received preprocedural abciximab found no difference in mortality with up-front versus provisional use, but early administration increased bleeding.[195]

Unfractionated heparin is a commonly used anticoagulant in MI and CS, yet little is known about the appropriate anticoagulant agent for this population. Low-molecular-weight heparin and fondaparinux in the post-PCI setting may be less ideal because of the high prevalence of acute kidney injury in CS. Bivalirudin use in a series of 86 patients with CS was associated with lower in-hospital mortality and similar rates of major bleeding compared with heparin, but the observational nature precludes causal inferences.[196]

Suggestions for Clinical Practice

We suggest that all patients with CS without serious bleeding complications be continued on dual antiplatelet therapy without interruption after PCI. In situations when oral agents cannot be administered or there are concerns about absorption, the use of an intravenous glycoprotein IIb/IIIa inhibitor or the recently available intravenous $P2Y_{12}$ inhibitor cangrelor can be considered. No high-quality data are available to support the efficacy or safety of glycoprotein IIb/IIIa inhibitors in patients with MCS.

Considerations for Clinical Practice

Overall, the optimal anticoagulation management choice in the setting of PCI for CS remains unclear, and we support following recommendations in the PCI guidelines for patients without CS.[176] In patients requiring continued anticoagulation after PCI, we suggest the preferential use of intravenous unfractionated heparin given the high prevalence of acute kidney injury and acute liver injury in the CS population.

Coronary Artery Bypass

In the SHOCK trial, the majority of patients were found to have multivessel disease: ≈1 in 5 had left main coronary artery stenosis, but only 37% underwent CABG.[197] The mortality rate at 1 year was similar among those treated with PCI (48%) and those treated with CABG (53%) when randomized to an early revascularization strategy. Most patients treated with CABG were considered completely revascularized, whereas only 15% in the PCI group ultimately underwent multivessel stent-

Table 3. Considerations for Initial Critical Care Monitoring in Patients With CS

Monitoring Parameter	Frequency	Comment/Rationale
Noninvasive monitoring		
Telemetry, pulse oximetry, respiratory rate	Continuous	High incidence of arrhythmias, ventilator failure, and pulmonary edema
Critical care unit monitoring	1:1 Nurse-to-patient ratio	High incidence of hemodynamic deterioration and multisystem organ failure
Invasive monitoring		
Arterial BP monitoring	Continuous	Consider continuing until vasoactive medications have been discontinued for 12–24 h
CVP	Continuous	A central line is required for delivery of vasoactive medications; single-point-in-time CVP measurements may be unreliable measures of fluid status, but longitudinal CVP trends may provide information on trends in fluid status
Central venous oxygen saturation	Every 4 h	Trends in central venous oxygen saturation in patients with a central line can be used to help monitor trends in cardiac output
Urine output	Every hour	Urine output and serum creatinine monitoring are markers of renal perfusion and acute kidney injury
PAC or noninvasive cardiac output monitor	Selected use	Consider using early in the treatment course in patients not responsive to initial therapy or in cases of diagnostic or therapeutic uncertainty
Laboratory investigations		
Complete blood counts	Every 12–24 h	Consider more frequently in patients with CS with, or at high risk for, bleeding
Serum electrolytes	Every 6–12 h	Frequency should be tailored to risks or presence of renal failure and electrolyte dyscrasias
Serum creatinine	Every 12–24 h	Urine output and serum creatinine monitoring are markers of renal perfusion and acute kidney injury
Liver function tests	Daily	Monitoring for congestive hepatopathy and hypoperfusion
Lactate	Every 1–4 h	Lactate clearance is a marker of resolving end-organ hypoperfusion, and lack of clearance is associated with a higher risk of mortality
Coagulation laboratories	Every 4–6 h for those on anticoagulants until therapeutically stable, every 24 h if patient is not on anticoagulants	Altered drug elimination and frequent use of mechanical support devices often necessitate antithrombotic monitoring

BP indicates blood pressure; CS, cardiogenic shock; CVP, central venous pressure; and PAC, pulmonary artery catheter.

ing.[197] In contemporary practice, however, the majority of patients presenting to the hospital with CS complicating MI are treated with early PCI.[4] From 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%.[4] These epidemiological data suggest that many patients with CS may be incompletely revascularized at the time of presentation, but the associated outcomes of this practice remain unclear.

Suggestions for Clinical Practice

We suggest that in patients with MI-associated CS who have multivessel or left main disease, PCI or CABG revascularization decisions should be made collaboratively between cardiologists and surgeons by incorporation of the patient's medical information, coronary anatomy, procedural risks, potential treatment-related delays, and expressed preferences.

Medical Management of the Patient With CS

Once the patient is admitted to the hospital, management of CS frequently requires the primary care team to coordinate the multidisciplinary delivery of patient monitoring, pharmacological therapies, and mechanical technologies.

Critical Care Unit Monitoring and Hemodynamic Goals

Relatively few data are available to guide appropriate monitoring decisions for patients with CS. An overview of suggested tools is provided in Table 3. The inherent hemodynamic instability and high prevalence of vasopressor use in CS merit invasive arterial blood pressure monitoring to guide drug titration. Central venous catheter insertion should also be considered to support the administration of vasoactive medications and to facilitate monitoring of CVP and mixed central venous oxygen saturation, which may be helpful in determining the adequacy of tissue oxygen delivery. Clinical examination and laboratory testing are also necessary for monitoring end-organ perfusion and function. Repeated assessments of plasma lactate, for instance, can be informative with respect to the persistence of shock

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Table 4. Mechanism of Action and Hemodynamic Effects of Common Vasoactive Medications in CS

Medication	Usual Infusion Dose	Receptor Binding				Hemodynamic Effects
		α_1	β_1	β_2	Dopamine	
Vasopressor/inotropes						
Dopamine	0.5–2 μg·kg^{-1}·min^{-1}	–	+	–	+++	↑CO
	5–10 μg·kg^{-1}·min^{-1}	+	+++	+	++	↑↑CO, ↑SVR
	10–20 μg·kg^{-1}·min^{-1}	+++	++	–	++	↑↑SVR, ↑CO
Norepinephrine	0.05–0.4 μg·kg^{-1}·min^{-1}	++++	++	+	–	↑↑SVR, ↑CO
Epinephrine	0.01–0.5 μg·kg^{-1}·min^{-1}	++++	++++	+++	–	↑↑CO, ↑↑SVR
Phenylephrine	0.1–10 μg·kg^{-1}·min^{-1}	+++	–	–	–	↑↑SVR
Vasopressin	0.02–0.04 U/min	Stimulates V_1 receptors in vascular smooth muscle				↑↑SVR, ↔PVR
Inodilators						
Dobutamine	2.5–20 μg·kg^{-1}·min^{-1}	+	++++	++	–	↑↑CO, ↓SVR, ↓PVR
Isoproterenol	2.0–20 μg/min	–	++++	+++	–	↑↑CO, ↓SVR, ↓PVR
Milrinone	0.125–0.75 μg·kg^{-1}·min^{-1}	PD-3 inhibitor				↑CO, ↓SVR, ↓PVR
Enoximone	2–10 μg·kg^{-1}·min^{-1}	PD-3 inhibitor				↑CO, ↓SVR, ↓PVR
Levosimendan	0.05–0.2 μg·kg^{-1}·min^{-1}	Myofilament Ca^{2+} sensitizer, PD-3 inhibitor				↑CO, ↓SVR, ↓PVR

CO indicates cardiac output; CS, cardiogenic shock; PD-3, phosphodiesterase-3; PVR, pulmonary vascular resistance; and SVR, systemic vascular resistance.

and has been shown to be prognostically important in patients with CS.[198] Lastly, although clinical trials have shown no benefit with the routine use of PAC hemodynamic monitoring, observational studies in CS populations have been mixed, and the PAC remains a potentially important diagnostic and management tool for these individuals.[199–202] Hemodynamic data provided by a PAC can confirm the presence and severity of CS, involvement of the RV, pulmonary artery pressures and transpulmonary gradient, and vascular resistance of the pulmonary and systemic arterial beds. In addition, a PAC may provide CS prognostic information such as CI and cardiac power and enables clinicians to monitor responses to therapeutic interventions.[39,203] Although noninvasive devices may be used, their reliability in this setting has not been well studied.

Although the aforementioned measurements are important for the diagnosis and monitoring of CS, treatment targets are considerably less well established. In general, goals of therapy should focus instead on restoring and maintaining satisfactory tissue perfusion.[204] For many patients, the adequacy of end-organ blood flow roughly correlates with blood pressure, with low blood pressures associated with an increased risk of mortality.[100] Unfortunately, no clear SBP or mean arterial pressure (MAP) suggestions can be made because MAP targets are often extrapolated from non-CS populations in whom a value of 65 mm Hg has been considered a reasonable target.[205] CS is a hemodynamically heterogeneous disorder, and hemodynamic variables may not necessarily reflect differential patterns of end-organ blood flow or tissue perfusion. Microcirculatory dysfunction may persist despite improvements in these hemodynamic measurements.[206]

Suggestions for Clinical Practice

We suggest the use of PACs in cases of diagnostic or CS management uncertainty or in patients with moderate to severe CS who are unresponsive to initial therapy.

Hemodynamic monitoring should complement (and not replace) other markers of end-organ perfusion in CS. The optimal MAP likely differs from patient to patient, and the risks of hypoperfusion with lower MAPs must be balanced (and individualized) with the potentially deleterious impact of vasoactive agents on myocardial oxygen demand, ischemia, and arrhythmia associated with higher MAP targets. We suggest that clinicians assess the adequacy of end-organ and tissue perfusion in response to individualized targets by integrating serial markers of systemic perfusion, including (but not limited to) arterial lactate, mixed or central venous oxygen saturations, urine output, creatinine, liver function tests, mental status, temperature, and other invasive hemodynamic variables.

Nonvasoactive Pharmacological Management

An analysis from the TRIUMPH trial (Effect of Acetate in Patients With Acute Myocardial Infarction and Cardiogenic Shock) reported that approximately one quarter of patients with CS were administered β-blockers or renin-angiotensin-aldosterone system (RAAS) antagonists within the first 24 hours after CS diagnosis.[207] Compared with patients not receiving these early therapies, patients receiving them had higher 30-day mortality.

Table 5. Initial Vasoactive Management Considerations in Types of CS

Cause or Presentation of CS	Vasoactive Management Considerations	Hemodynamic Rationale
Classic wet and cold	Norepinephrine or dopamine[144] Inotropic agent[210,211]*	This subtype has low CI and high SVR. Consider hemodynamic stabilization with norepinephrine (preferred in ↑HR or arrhythmias) or dopamine (↓HR preferred but associated with higher risk of arrhythmias) Consider addition of inotropic agent when stabilized and after revascularization (MI only)
Euvolemic cold and dry	Norepinephrine or dopamine[144] Inotropic agent[210,211] Small fluid boluses	Consider hemodynamic stabilization with norepinephrine (preferred in ↑HR or arrhythmias) or dopamine (↓HR preferred but associated with higher risk of arrhythmias) Consider addition of inotropic agent when stabilized and after revascularization (MI only) LVEDP may be low, and patients may tolerate fluid boluses
Vasodilatory warm and wet or mixed cardiogenic and vasodilatory	Norepinephrine Consider hemodynamics-guided therapy	This subtype has low SVR
RV shock	Fluid boluses[144,145] Norepinephrine, dopamine, or vasopressin[144,212,213] Inotropic agents[144]* Inhaled pulmonary vasodilators[214]	Hemodynamic goals include maintaining preload, lowering RV afterload (PVR), treating absolute or relative bradycardias, and maintaining atrioventricular synchrony Dopamine (↓HR preferred but associated with arrhythmia risk) Vasopressin may raise SVR and have neutral effect on PVR Consider adding or transitioning to inotrope after initial hemodynamic stabilization and revascularization
Normotensive shock	Inotropic agent or vasopressor	Initial inotropic therapy may be appropriate given that this subtype has SBP >90 mm Hg and relatively high SVR
Aortic stenosis	Phenylephrine or vasopressin In patients with reduced LVEF, echocardiography- or PAC-guided dobutamine titration	Shock caused by aortic stenosis is an afterload-dependent state Inotropy may not improve hemodynamics if LVEF is preserved Definitive therapies will be defined by underlying cause and may include surgical aortic valve replacement or balloon valvuloplasty and/or transcatheter aortic valve replacement
Aortic regurgitation	Dopamine Temporary pacing	Maintaining an elevated HR may shorten diastolic filling time and reduce LVEDP Definitive therapies will be defined by underlying cause and may include surgical aortic valve replacement
Mitral stenosis	Phenylephrine or vasopressin Esmolol or amiodarone	Shock resulting from mitral stenosis is a preload-dependent state Avoiding chronotropic agents, slowing the HR (and thereby increasing diastolic filling time), and maintaining atrioventricular synchrony may improve preload Definitive therapies will be defined by underlying cause and may include surgical mitral valve replacement or balloon valvuloplasty
Mitral regurgitation	Norepinephrine or dopamine Inotropic agents* Temporary MCS, including IABP[144]	After hemodynamic stabilization with vasopressor, consider addition of inotropic agent Afterload reduction may help reduce LVEDP IABP may reduce regurgitation fraction by reducing afterload and increasing CI Definitive therapies will be defined by underlying cause and may include surgical mitral valve replacement/repair and percutaneous edge-to-edge repair
Postinfarction ventricular septal defect	See classic wet and cold considerations Temporary MCS, including IABP[144]	IABP may reduce shunt fraction by reducing afterload and increasing CI Cardiac surgical referral for repair or percutaneous interventional umbrella closure
Dynamic LVOT obstruction	Fluid boluses[215,216] Phenylephrine or vasopressin[215,216] Avoid inotropic agents[215,216] Avoid vasodilating agents[215,216] Esmolol or amiodarone[215] RV pacing	Dynamic gradients may be reduced by increasing preload and afterload, reducing inotropy and ectopy, maintaining atrioventricular synchrony, and inducing ventricular dyssynchrony
Bradycardia	Chronotropic agents or Temporary pacing	Treatment should also focus on identifying and treating underlying cause of bradycardia Chronotropic agents may include atropine, isoproterenol, dopamine, dobutamine, and epinephrine
Pericardial tamponade	Fluid bolus Norepinephrine	Pericardiocentesis or surgical pericardial window required for definitive therapy

CI indicates cardiac index; CS, cardiogenic shock; HR, heart rate; IABP, intra-aortic balloon pump; LVEDP, left ventricular end-diastolic pressure; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; MCS, mechanical circulatory support; MI, myocardial infarction; PAC, pulmonary artery catheter; PVR, pulmonary vascular resistance; RV, right ventricular; SBP, systolic blood pressure; and SVR, systemic vascular resistance.

*Inotrope choice considerations may include HR, SVR, cause of CS, renal function, prior β-blocker treatment, and inotrope half-life.

Finally, the association of early statin use with outcomes in patients with CS and MI undergoing revascularization was reported in an analysis from the Korean Acute Myocardial Infarction Registry.[208] After adjustment, early statin administration was associated with a lower risk of death at 30 days.

Considerations for Clinical Practice

We support guideline recommendations for the management of patients with STEMI that suggest avoidance of β-blockers in patients with signs of HF or low-output states and the avoidance of RAAS antagonists in patients with hypotension.[144] It may be reasonable to initiate β-blockers when the patient is euvolemic and off inotropes and vasopressors for at least 24 hours. RAAS inhibitor therapy initiation can be considered when the patient has been off vasopressors for 24 hours, provided that the patient's renal function has returned nearly to baseline levels and the risk of RAAS-associated hyperkalemia or hypotension is low. RAAS inhibitors may be started in patients with pulmonary edema and in conjunction with an inodilator.

We suggest that it is reasonable to administer statin in patients with MI-associated CS.

Vasopressors and Inotropes

Vasoactive medications are often used in the management of patients with CS. An overview of the cardiac and vascular receptors, along with the hemodynamic effects of commonly used vasoactive medications in CS, is provided in Table 4.

Despite their frequent use, few clinical outcome data are available to guide the initial selection of vasoactive therapies in patients with CS. The SOAP II trial (Sepsis Occurrence in Acutely Ill Patients) evaluated first-line vasopressor selection in patients with generalized shock and included a prespecified CS subgroup.[209] Dopamine was associated with a higher rate of arrhythmias in the CS and overall populations and was associated with higher risk of mortality in the CS subgroup. Although this was the largest study of its kind, clinical and methodological concerns have raised questions about the external validity and applicability of the findings in patients with CS.[209] The SOAP II trial did not have an operationalized definition of CS; included obstructive, valvular, and postcardiotomy shock states (which may have different hemodynamic profiles); did not evaluate treatment-related differences across the various hemodynamic phenotypes of CS; and did not report prognostically important MI or HF variables or their relevant antecedent time- or treatment-related differences, all of which potentially confounded the results of the study.

Suggestions for Clinical Practice

Norepinephrine is associated with fewer arrhythmias and may be the vasopressor of choice in many patients with CS; however, in light of the aforementioned major study limitations, the optimal first-line vasoactive medication in CS remains unclear. Pragmatic initial vasoactive considerations are provided in Table 5.

Care Bundles and the Prevention of Critical Care Complications

Critically ill patients are at risk of developing complications such as ventilator-associated pneumonia, delirium, ICU-acquired weakness, central line–associated bloodstream infection, stress ulcers, and venous thromboembolism. These complications are associated with an increased risk of morbidity, mortality, and length of stay.[217] Bundles of best-practice prevention strategies have been implemented with increasing frequency to reduce complications and to improve outcomes in critically ill patients. Although none have been specifically validated among CS cohorts, organizations such as the Institute of Healthcare Improvement recommend the universal use of several of these bundles in every ICU.[218]

Table 6. Critical Care Complication Prevention Bundles in Patients With CS

Bundle	Target	Components
ABCDE bundle[219]	Delirium, weakness, and ventilation liberation	Daily awakening and spontaneous breathing trials Assessment and management of delirium Early and progressive mobility
Ventilator bundle[220–222]	Ventilator-associated pneumonia	Head of bed elevation Sedation protocols targeting light sedation with RASS or SAS scores Daily sedation vacation if light sedation contraindicated Chlorhexidine oral rinse Endotracheal tube with subglottic secretion drainage
Central line bundle[223,224]	Central line–associated bloodstream infection	Hand hygiene Maximal barrier precautions Chlorhexidine skin antisepsis Optimal catheter site selection (avoidance of femoral approach) Ultrasound-guided central line placement Daily review of line necessity
Stress ulcer prophylaxis[225,226]	Stress ulcer	Proton pump inhibitor or H_2 blocker in patients without enteral nutrition In enterally fed patients, the risks of prophylaxis should be balanced with risk of ventilator-associated pneumonia
Deep vein thrombosis prophylaxis[226]	Venous thromboembolism	Routine venous thromboembolism prophylaxis in patients not on anticoagulants

ABCDE indicates awakening and breathing coordination, delirium monitoring/management, and early exercise mobility; CS, cardiogenic shock; RASS, Richmond Agitation-Sedation Scale; and SAS, Sedation-Agitation Scale.

Suggestions for Clinical Practice

Table 6 highlights key care bundles and prevention practices that should be considered for patients with CS.

Mechanical Ventilation

The reported prevalence of MV is 78% to 88% in patients with CS, and it is often required for the management of acute hypoxemia, increased work of breathing, airway protection, and hemodynamic or electric instability.[9,42,227] Very few studies have addressed the ideal MV mode for the CS population. In nonshock HF cohorts, noninvasive MV is often used to treat respiratory failure resulting from pulmonary edema.[228] Although noninvasive MV can improve dyspnea and hypoxemia, along with their associated metabolic derangements, its influence on mortality is unclear.[228] The majority of patients with CS, however, will require invasive MV. There is insufficient evidence to recommend specific ventilation modes, strategies (including lung protective ventilation), or physiological end points in the CS population.

Although a comprehensive review of the cardiopulmonary interactions associated with MV in patients with CS is beyond the scope of this review, clinicians should be aware of a few basic physiological interactions. Positive end-expiratory pressure is the airway (and alveolar) pressure above atmospheric pressure at the conclusion of the expiratory phase. It has beneficial effects on gas exchange, lung recruitment, and airway patency.[229] It can also counterbalance hydrostatic forces that lead to pulmonary edema, shifting fluid from the alveoli back to the interstitial space and circulation.[230] In patients with reduced LV function, positive end-expiratory pressure can also reduce LV afterload by decreasing transthoracic pulmonary pressures, diminish preload, improve work of breathing, and optimize oxygen delivery to the stressed myocardium.[231–233] In patients with reduced RV function, positive end-expiratory pressure (along with high mean airway pressures) can reduce pulmonary vascular resistance, and thereby increase CI, by attenuating hypoxic pulmonary vasoconstriction and reducing pulmonary edema. Higher pressures, however, may compromise RV preload and increase RV afterload in part through intra-alveolar vessel compression.[234] There are no studies to support one mode of invasive MV over another, and the ideal positive end-expiratory pressure level in patients with CS may depend on the complex cardiopulmonary interplay between RV and LV function, vascular resistance, and fluid status, along with the presence and cause of hypoxemia. Lastly, the ideal oxygenation targets remain undefined, but emerging evidence highlights the potential deleterious effect of hyperoxia in patients with ACS, HF, and OHCA and in general ICU patients.[235–238]

Suggestions for Clinical Practice

The decision to intubate patients with CS should be based on standard critical care criteria; however, clinicians should be both aware of and prepared for the potential hemodynamic deterioration associated with induction therapies (eg, sedatives and analgesics), inappropriate ventilation settings, the transition from spontaneous breathing to positive-pressure ventilation, and vagal stimulation association with endotracheal tube placement.

In the absence of high-quality data in the CS population, we suggest that MV modes and settings be adjusted to prevent hypoxemia and hyperoxia, to minimize patient discomfort and ventilator dyssynchrony, and to optimize hemodynamics.

Continuous Renal Replacement Therapy

Among patients with CS, a reported 13% to 28% develop acute kidney injury and up to 20% require renal replacement therapy.[1,9,239,240] Patients needing renal replacement therapy were less likely to survive to hospital discharge and had a higher risk of long-term dialysis and mortality.[88,240] Patients with CS often do not hemodynamically tolerate fluid shifts that can occur with intermittent hemodialysis. Instead, continuous renal replacement therapy, which applies a veno-venous driving force with an external pump to gradually removal fluid and toxins, is more commonly used for those with CS. A detailed review of the definition and diagnostic approach to acute kidney injury and indications, modalities, and complications of continuous renal replacement therapy in critically ill patients is beyond the scope of this document and is available elsewhere.[241]

Summary of Clinical Considerations

We concur with KDIGO (Kidney Disease Improving Global Outcomes) guidelines that continuous renal replacement therapy can be considered with stage 2 acute kidney injury (defined as an increase in serum creatinine ≥2.0 times baseline and urine output <0.5 $mL \cdot kg^{-1} \cdot h^{-1}$ for ≥12 hours or when "life threatening changes in fluid, electrolyte, and acid-base balance" exist).[241]

MCS and Cardiac Transplantation

A discussion and detailed review of MCS and cardiac transplantation history, indications, and contraindications, along with device differences, are given elsewhere and are beyond the scope of this document.[242,243] The focus of this scientific statement instead is on MCS device selection and timing and pathways specific to those with CS. MCS can be broadly classified into temporary or durable devices. Temporary MCS devices are inserted either percutaneously or surgically and can be used as a bridge to recovery, in which case the MCS is removed after improvement in cardiac contractile function; a bridge to a bridge, in which case patients have a temporary de-

vice inserted and a provisional plan to transition to durable MCS after clinical stabilization; a BTT; or a bridge to decision. In the last case, hemodynamic instability or medical sequelae of CS such as neurological uncertainty or multisystem organ failure may preclude a comprehensive assessment for durable MCS or transplantation. Insertion of a temporary MCS as a bridge to decision can permit hemodynamic optimization, allow the potential reversal of CS-mediated end-organ failure, and provide additional time for complete medical and social assessment to occur before moving to definitive therapies or a palliative care approach. Durable MCS devices, which are surgically implanted, can be used as a bridge to recovery, as a BTT, or as destination therapy.

Patient Selection

In the CS population, there is a paucity of high-quality evidence to support the routine use of MCS devices as a therapeutic adjunct. Supporting data are derived largely from small randomized trials with hemodynamic end points, observational or registry studies with survival rates better than historical controls, and clinician experience.[60,244,245] Among patients with CS, the INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) registry has reported a 38% 30-day mortality among INTERMACS clinical profiles 1 and 2 (CS and progressive decline on inotrope support, respectfully) compared with an 11% 30-day mortality rate among lower-acuity INTERMACS clinical profile 3 and 4 individuals (Supplemental Table 5).[246] More contemporary observational studies and registries suggest an ≈75% 1-year survival rate; however, INTERMACS profile 1 and 2 patients remain at very high risk for early mortality after MCS implantation.[247,248]

Summary and Suggestions for Clinical Practice

There is little evidence to guide the timing or selection of patients with CS who are suitable for MCS. Thus, we concur with both the AHA and International Society for Heart and Lung Transplantation guidelines recommending that patients with persistent CS, with or without end-organ hypoperfusion, should be evaluated for MCS candidacy by a multidisciplinary team with expertise in the selection, implantation, and management of MCS devices.[242,243] We suggest that the multidisciplinary assessment team include a palliative care physician, regardless of MCS candidacy, given the risk of peri-implantation death.[242] We concur with published contraindications to MCS implantation.[242,243] We suggest that temporary MCS devices can be inserted in patients who are not expected to recover as early as possible in the course of CS as a bridge to recovery, bridge to a bridge, BTT, or bridge to decision strategy in appropriately selected patients with CS.

Device Selection in CS

Although the INTERMACS registry has reported an overall increase in MCS use, there has been a temporal decline in durable MCS implantation among INTERMACS clinical profile 1 and 2 patients. This may be influenced by the historically lower survival rates reported after durable MCS implantation in these high-risk individuals.[246,249–252] Consequently, the use of temporary MCS devices as first-line therapies has increased, although it is noteworthy that this practice change has not been associated with a demonstrable change in survival.[248] The AHA (Class IIa, Level of Evidence C) and the International Society for Heart and Lung Transplantation (Class 1C) both recommend temporary MCS implantation for the management of patients with multiorgan system failure or relative contraindications to durable MCS or heart transplantation to allow neurologic assessment and clinical optimization before the consideration of a longer-term device.[242,243]

Suggestions for Clinical Practice/Care

We suggest that temporary over durable MCS as a first-line device should be considered when immediate stabilization is needed to enable recovery of the heart and other organ systems, when surgical risk is prohibitive but may be attenuated by such stabilization, when support is required to facilitate a definitive procedure or intervention (such as revascularization or arrhythmia ablation), or when time is required to allow a full transplantation or durable MCS evaluation.

Temporary MCS

Summary of Clinical Considerations

We concur with clinical practice recommendations that temporary MCS selection should be based on device availability, multidisciplinary team familiarity, and patient-specific needs.[243] Temporary MCS options include the following.

Intra-Aortic Balloon Pump

The IABP is still the most widely used MCS device in CS. Made of a polyurethane membrane mounted on a vascular 7F to 8F catheter, the IABP is positioned in the descending thoracic aorta just distal to the left subclavian artery. The device is timed to inflate and deflate in concert with the cardiac cycle, thereby increasing the diastolic blood pressure and reducing the SBP. Registry studies have reported only minimal improvement in MAP, CI, serum lactate, and catecholamine requirements with IABP counterpulsation.[1,253]

Before 2012, American and European guidelines supported IABP use for CS with a Class I recommendation. The IABP-SHOCK II, which enrolled patients with MI-associated CS, found no differences in the primary end point of 30-day mortality, prespecified secondary

end points, or 1-year outcomes between those with and those without IABP support.[1,108] These results led to the IABP being downgraded to a Class IIIA recommendation for routine use in CS in the most recent European revascularization and non–ST-segment–elevation ACS guidelines.[23,254] IABP use rates have subsequently declined.[24]

Suggestions for Clinical Practice

We suggest that IABP can be considered in patients with CS with acute mitral regurgitation or a ventricular septal defect, and it can be considered in select patients with profound CS when other MCS devices are not available, are contraindicated, or cannot be placed.

Percutaneous MCS

Currently established and available percutaneous MCS devices include the TandemHeart (Cardiac Assist, Inc, Pittsburgh, PA) and the micro-axial Impella 2.5, CP, and 5.0 systems (Abiomed Europe, Aachen, Germany). Investigational devices include the paracorporeal pulsatile iVAC 2L (PulseCath BV, Arnhem, the Netherlands) and the HeartMate Percutaneous Heart Pump (St. Jude Medical, Pleasanton, CA). Data on percutaneous MCS devices in CS are still quite limited. One meta-analysis, published in 2009, aggregated the results of 3 randomized trials comparing several of these devices (2 with TandemHeart, 1 with Impella 2.5) with IABP. Patients treated with percutaneous MCS had higher CI, higher MAP, lower PCWPs, and more frequent bleeding complications, with no difference in mortality.[245] In a recent randomized trial of 48 patients comparing the Impella CP with IABP, no differences in mortality or secondary end points were observed.[255] In the USpella registry of patients with CS treated with Impella devices before PCI, MCS placement resulted in improved survival to hospital discharge, even after adjustment for potential confounding variables.[256] For the iVAC and HeartMate Percutaneous Heart Pump, trial results are not currently available. More complete descriptions of commonly used percutaneous MCS devices can be found in Supplemental Table 6.

Extracorporeal Membrane Oxygenation

Patients may require ECMO because of cardiac failure, respiratory failure, or a combination thereof. Appropriately selected patients with isolated respiratory failure despite MV and no significant cardiac dysfunction are often treated with veno-venous ECMO. Veno-arterial ECMO, on the other hand, is used to support both the cardiovascular and respiratory systems and is frequently used in CS. Relative contraindications to ECMO include advanced age (>75 years), life expectancy <1 year, severe peripheral vascular disease, advanced liver disease, contraindications to systemic anticoagulation, and neurological injury. A detailed description of the veno-arterial ECMO circuit is provided in Supplemental Appendix 1.

Potential complications of veno-arterial ECMO include distal limb ischemia, thromboembolism, stroke, bleeding, hemolysis, infection, and aortic valve insufficiency.[256,257] A common issue related to peripheral insertion is the resulting increase in LV afterload, which may lead to inadequate unloading of the LV. In these cases, combining veno-arterial ECMO with IABP, Impella support, atrial septostomy, or other venting maneuvers may help to achieve more complete LV unloading.[258] If veno-arterial ECMO is placed centrally, a vent can be placed directly into the left atrium to optimize LV decompression.

In general, there has been a gradual increase in rates of ECMO use for CS over the past decade.[259] A report from the ELSO (Extracorporeal Life Support Organization) registry showed that 56% of patients survived to decannulation from ECMO, whereas 41% survived to discharge when ECMO was used for a cardiac reason.[260] For patients with a potentially reversible cause of their CS (eg, acute fulminant myocarditis), outcomes are even better, whereas those with postcardiotomy CS do considerably worse.[261,262] There are no randomized trials assessing the effectiveness of ECMO systems.

Suggestions for Clinical Practice/Care

We suggest that veno-arterial ECMO may be the preferred temporary MCS option when there is poor oxygenation that is not expected to rapidly improve with an alternative temporary MCS device or during cardiopulmonary resuscitation.

RV Support

MCS options for the temporary management of RV failure (including RV infarction) are currently being developed and studied. The Impella RP (Abiomed Europe) is an intracardiac microaxial blood pump that can be inserted percutaneously though the femoral vein. When properly positioned, this catheter can deliver blood from the inlet area (in the inferior vena cava), through the cannula, and into the pulmonary artery with an intent to restore right-sided heart hemodynamics, to reduce RV workload, and to allow cardiac recovery. It is currently approved for use through a humanitarian device exemption on the basis of the early results of the multicenter RECOVER RIGHT study.[263] The TandemHeart device has also been previously used in an RV support configuration, although data are largely limited to small case series.[264] Future prospective randomized studies are required to evaluate whether these devices can improve clinical outcomes.

Other Mechanical Therapies

The CentriMag (St. Jude Medical) ventricular assist system can be used in either a univentricular or biventricular configuration. Central cannulation is performed via median sternotomy. The device includes a magnetically levitated rotor with the ability to deliver flows up to 10 L/min. When CentriMag is serving as an LV assist device,

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the inflow cannula is placed either in the left atrium or directly into the LV apex, and the outflow cannula is sutured into the ascending aorta. When it is serving as an RV assist device, the inflow cannula is placed in the right atrium, and the outflow cannula is positioned in the main pulmonary artery. Although approved only for short-term use, there are reports of more prolonged support with the CentriMag device.[265] There are no randomized trials using the CentriMag, but small case series have reported modest success.[266,267]

The Abiomed (Abiomed, Inc, Danvers, MA) ventricular assist system can also be used as a univentricular or biventricular device. It also is placed via sternotomy but instead uses a pulsatile pump that can generate up to 6 L/min blood flow. Similar to the CentriMag device, there are no randomized trials assessing the effectiveness of the Abiomed system.

Durable MCS

Long-term MCS as a BTT was first approved by the US Food and Drug Administration in 1998.[268] Subsequently, the REMATCH trial (Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure) established the utility of durable, long-term MCS in the treatment of patients with advanced HF and reported improved 2-year survival over optimal medical therapy.[269] All currently used durable MCS devices are continuous-flow devices, include an inflow cannula placed directly into the LV cavity and an outflow graft sutured into the ascending aorta, and can provide hemodynamic support with flow rates ranging from 5 to 10 L/min. The HeartMate II (St. Jude Medical) is approved for BTT and destination therapy and uses an axial-flow pump, whereas the HeartWare HVAD (HeartWare, Framingham, MA), which is approved as a BTT device, uses only a centrifugal-flow, hydrodynamically levitated pump. The HeartMate II and HVAD make up >95% of all US Food and Drug Administration–approved durable MCS devices currently being implanted.[252] Other devices under investigation include the magnetically levitated, centrifugal-flow HeartMate 3 LV assist device (St. Jude Medical), the axial-flow Jarvik 2000 (Jarvik Heart Inc, New York, NY), and the Reliant HeartAssist 5 (ReliantHeart, Inc, Houston, TX). The proportion of patients receiving MCS with CS (INTERMACS 1) has remained stable at ≈15%.[252] As previously described, implantation of durable MCS in patients with INTERMACS clinical profile 1 or 2 is associated with a substantially higher mortality compared with lower-acuity patients. Hence, durable MCS implantation in patients with CS (INTERMACS 1) declined from 40% in 2006 to 12% in 2010. Currently, there is insufficient evidence to guide decisions on which patients with CS should have durable MCS as a first-line device strategy; however, the use of durable MCS devices in a bridge to a bridge strategy is becoming more commonplace and is supported by practice guidelines.[242,243,247,248,270]

Suggestions for Clinical Practice/Care

We suggest that durable MCS can be implanted in a bridge to recovery, bridge to a bridge, BTT, or destination therapy strategy in appropriately selected patients with CS. Durable MCS devices can be considered primary devices in patients with CS who are not likely to recover without long-term MCS support, have the capacity for meaningful recovery, and do not have irreversible end-organ dysfunction, systemic infections, or relative contraindications to durable MCS implantation.

Heart Transplantation

Cardiac transplantation, particularly for patients requiring biventricular MCS, often represents the only hope for meaningful, long-term recovery. Unfortunately, the low number of available organs, coupled with unpredictable donor availability, makes heart transplantation in the acute setting of CS an unreliable primary therapy. Registry data suggest that up to 44% of MCS device implantations in INTERMACS profile 1 and 2 patients are performed with a BTT strategy.[250,271] In addition, the use of ECMO before heart transplantation remains low. Between 2006 and 2012, 1.1% of heart transplantations were performed on patients receiving ECMO.[272] Many institutions have instead adopted the strategy of durable MCS in patients with CS, and the use of an LV assist device before heart transplantation has increased in recent years.[272]

Suggestions for Clinical Practice/Care

We suggest that all patients being evaluated for MCS implantation should concurrently be assessed for transplantation. Heart transplantation may be performed after temporary or durable MCS device implantation in suitable candidates in whom heart function is not expected to recover.

Novel Therapies and Opportunities

There are currently only a few novel drug, device-based, or interventional therapies on the horizon with the potential to improve outcomes for patients with CS. Therapeutic hypothermia is widely available and has become a standard component of treatment for OHCA. Hypothermia has wide-ranging systemic and hemodynamic effects that might be particularly advantageous in the systemic manifestations of CS (especially in the postinfarction setting).[273] Animal studies and human registry trials have reported positive hemodynamic changes and have suggested the possibility of improved clinical outcomes.[274] Unfortunately, a recently presented, but unpublished, randomized pilot trial did not show a benefit on the surrogate end point of cardiac power index or with other secondary end points.

Inotropic agents are theoretically appealing in CS treatment, but the current evidence is scarce and has recently been summarized in a meta-analysis.[275] In this systematic review, only 1 small trial enrolling 32 patients comparing levosimendan with enoximone in refractory CS could be included. From these limited data, levosimendan may be appealing. However, this agent is not approved in the United States and requires additional validation with larger studies.[275] Furthermore, the effect of other medications that have shown positive results in acute, nonshock HF populations such as seralaxin requires examination in CS cohorts.[276]

Finally, as previously mentioned, percutaneous MCS devices can be useful tools for managing refractory shock. The newly introduced HeartMate Percutaneous Heart Pump features a novel design with a collapsible elastomeric impeller and nitinol cannula, which gives this device a low profile but high flow rate. Once placed in a retrograde fashion across the aortic valve, the cannula can expand to 24F and support a continuous mean blood flow of >4 L/min. Although current data for this device are limited, ongoing trials should help to clarify its role in the treatment of CS.

PALLIATIVE CARE IN CS

Palliative care can reduce physical and emotional distress, improve quality of life, and complement curative therapy in advanced HF.[277,278] However, the timing of palliative care initiation, its assessment, and its management are not well studied in patients with CS. In the 2016 palliative care and cardiovascular disease policy statement from the AHA, advanced HF and critical illness were referral triggers for palliative care, but CS was not discussed.[277,279]

Palliative Care Use and Perceptions in Cardiovascular Practice

In patients with advanced HF without CS, despite burdensome symptoms and multiple comorbidities, only 6% to 8% are referred for palliative care services during hospitalization, and referral rates have increased to as high 10% in contemporary studies.[280–283] Among patients hospitalized with an ACS, palliative care use declined from 6% in 1997 to 2% in 2013.[284] The reasons underpinning these low referral rates remain unclear, but provider misperceptions about palliative services are a likely contributor. When multidisciplinary HF providers were interviewed to assess knowledge, attitudes, and perceptions about palliative care, they reported limited palliative care knowledge, confused palliative and hospice care, and were uncertain about differences between standard HF therapy and palliative care.[285] A survey of HF nurses found that 67% felt it was a physician's role to initiate discussions about end-of-life care with patients, and 91% reported a need for more palliative training.[286] Additional barriers to the provision of palliative care services identified by healthcare providers included uncertainty about end of life because of its unpredictable trajectory, lack of need for end-of-life discussions in patients in New York Heart Association class II to III HF, and lack of time and resources to initiate discussions.[286–288] In qualitative reports, patients and families had misperceptions about being separated from familiar, trusted healthcare providers and not being hospitalized once they committed to palliative care. Accordingly, it has been suggested that healthcare providers need to introduce palliative care as a philosophy of care rather than a strategy used at end of life.[289]

Considerations for Patient Care Communication

We suggest that healthcare providers openly discuss barriers to and benefits of initiating palliative care in patients with CS.

Initiation of Palliative Care Consultation in CS

In the 2016 European and 2013 American HF guidelines, palliative care was discussed as a consideration of treatment for HF, and the 2013 International Society for Heart and Lung Transplantation MCS guidelines recommend that palliative care should be part of the multidisciplinary inpatient team.[15,242,290] However, research and consensus-guideline literature that provide guidance to providers on the timing of palliative care in CS are limited, and objective criteria have largely been extrapolated from the HF and ACS literature (Supplemental Table 7). In the advanced HF population, predictors of all-cause death include low ejection fraction, low SBP, low hemoglobin and serum sodium levels, high serum creatinine and N-terminal pro–B-type natriuretic peptide, high New York Heart Association class, inpatient status, history of ischemic heart disease, atrial fibrillation, HF ≥6 months, heart rate >70 bpm, and not being treated with an RAAS and β-blocker.[282,291] Two randomized intervention trials of palliative care consultation in advanced HF have been performed and suggest possible benefits at an earlier stage in HF care. In 1 trial, the proportion of patients who selected comfort-oriented care did not increase over 3 to 6 months, and in the second, symptom burden was reduced and quality of life improved at 1 month with no difference in early rehospitalization, hospice use, or death.[292,293] Characteristics of patients hospitalized with ACS who received palliative care services are provided in Supplemental Table 8.[284] Of note, palliative treatment was associated with the development of CS during hospitalization and a 4-fold higher in-hospital mortality rate than in patients who received conservative or reperfusion treatments.[284]

Table 7. Suggestions for Global Palliative Care Management in CS

Management Domains	Patient-Focused Supportive Care Recommendations
Consultation services	Discuss advanced care decisions, personal goals, emotional/practical/spiritual support, symptom control and care, and illness understanding and trajectory in preparation for supportive care decision making
Palliative care specialists Cardiology team member trained in coordinating health services (psychologists, chaplains, physicians, and nurses) and providing psychosocial support	Ensure palliative care interventions are parallel with curative treatment care, are holistic, and are tailored to patients' values and preferences Address fears and concerns; maintain open, trusting dialogue Use direct, simple messages and everyday language Provide ongoing services/support for readdressing goals, symptoms, treatment preferences, and self-determination in end-of-life care choices (which may change over time)
Considerations for CS-specific preparedness plan	Prepare for artificial nutrition, hemodialysis, mechanical ventilation, and postdischarge rehabilitation Consider alarm fatigue associated with multiple intravenous drug infusions and hemodynamic monitoring Assess for potential mechanical circulatory support device application[311]: chronic infection and long-term antibiotic use, perioperative morbidity and mortality, stroke or intracranial hemorrhage, recurrent gastrointestinal bleeding, device malfunction/pump failure, financial burden, postoperative complications, and postemergency cardiac surgery
Preparedness for withdrawal of life-sustaining measures[312]	Assess and consider each patient's desire Discuss the withdrawal process, what to expect, and how to address distressing factors Ensure the presence of an experienced physician, nurse, and respiratory therapist at the time of extubation Respond quickly if patient experiences distress during the withdrawal process Conduct rounds at the bedside regularly, and ensure emotional and psychological support of patients, families, and healthcare providers Place patients in private rooms whenever possible or maintain privacy with curtains and signage Offer family members a private, quiet, comfortable space, separate from the patient's room, and immediate grief support and referral to community bereavement support services Allow family members to be present at the bedside during withdrawal procedures and to participate in patient care When possible, discontinue paralytic medications to be better able to assess distressing signs before withdrawal of life-sustaining measures Continue opioid medication during withdrawal processes and titrate on the basis of signs or symptoms of distress; if patient was not previously on an opioid, morphine is the medication of choice for pain or dyspnea during withdrawal processes Use sedative medications after effectively treating pain and dyspnea with opioids; combination opioid and sedative medications can be used during withdrawal processes ICU staff should develop protocols for withdrawal of life-sustaining treatments and devices (implantable cardioverter-defibrillator, ventilator, ventricular assist device, inotropic or vasopressor infusions, continuous renal replacement therapies, enteral or parenteral tube feedings, and intravenous fluids) Individualize the pace of withdrawal of life-sustaining measures; use a step-wise approach and ensure that distressing signs and symptoms are managed at each step In MV withdrawal, extubate to room air whenever possible and not to noninvasive mechanical ventilation Remove all monitoring (obtaining blood or urine samples, telemetry or hemodynamic monitoring, weight measurement, intake and output, etc) that is not comfort related
Physical symptoms	Assess for pain, dyspnea, insomnia, anorexia, fatigue, and agitation; document findings and treatment (including rationale); include pharmacist, nutritionist, and physical and occupational therapists in treatment decisions; consider complementary and alternative medicine (acupuncturist, art or music therapist, massage therapist); use valid, reliable tools when available (see Supplemental Table 7 suggestions) to assess symptoms
Emotions (anxiety and depression) and spiritual challenges	Identify emotions, show empathy, and communicate using a shared decision-making framework Involve psychiatrist or psychologist, chaplain, pharmacist, social worker, and case management Consider spirituality, insurance, financial concerns, and social support
General measures	Consider comorbid conditions, including frailty, delirium, and dementia, in the palliative care plan Establish a supportive relationship with family members and support teams Discuss deactivation of an implantable-cardioverter defibrillator when present Learn usual care behaviors and maintain whenever possible, especially after transfer from intensive care

CS indicates cardiogenic shock; ICU, intensive care unit; and MV, mechanical ventilation.

The CS population has a unique set of challenges pertaining to the timing of palliative care consultation. First, the acute nature of CS provides little time for patients, families, and healthcare professionals to prepare for discussions about advance directives, care transitions, quality of life, and treatments aimed at preventing and managing distressing symptoms. Second, the lack of validated prognostic tools and variability in treatment course may be perceived as an initiation barrier. For example, patients may transiently improve after MCS device implantation, coronary revascularization, or intravenous vasoactive therapies. However, as highlighted previously in this statement, the prognosis of patients with CS who receive MCS

Table 8. Potential Priorities for Future CS Research

Research Domain	Specific Research Need	Proposed Study Design
Prognosis	Generating and validating a contemporary and easy-to-use CS score	Prospective registry trial with external validation cohort
	Validating currently available and new prognostic biomarkers	Prospective registry trial
Monitoring	Defining the potential role and therapeutic targets for pulmonary artery catheter, other invasive or noninvasive cardiac output, or pulmonary fluid monitoring	Prospective registry or randomized trial
Systems of care	Studying whether integrated regional hub-and-spoke care systems with dedicated CS centers improve survival	Prospective registry
Management	Evaluating the optimal revascularization strategy in acute MI with multivessel coronary artery disease	Randomized trial
	Defining access site for invasive angiography (radial vs femoral)	Randomized trial
	Studying antiplatelet and anticoagulant therapy in primary PCI in acute MI	Randomized trial
	Studying the utility, timing, and comparative efficacy of percutaneous or durable mechanical support devices vs no mechanical support	Randomized trial
	Identifying the optimal inotropic and vasopressor regimens across common causes of and hemodynamic phenotypes of CS	Randomized trial
	Determining adrenergic or nonadrenergic pharmacological treatment of stress-induced cardiomyopathy-associated CS	Prospective registry or randomized trial
	Defining the timing, efficacy, and safety of adjunctive critical care technologies and treatments, including MV modes, pressures, and physiological targets; timing and dose of renal replacement therapy; and critical care bundles	Randomized trial
	Studying the optimal fluid management targets	Prospective registry or randomized trial
	Evaluating whether therapeutic hypothermia or targeted temperature management can improve survival	Randomized trial
Palliative care	Assessing patient, family, hospital, and healthcare provider characteristics in CS when palliative care is selected, not offered, or offered but refused to better understand predictors and timing of palliative care use and treatments	Prospective registry or randomized trial
	Evaluating clinical outcomes when palliative care is discussed early or late in the course of CS	Prospective registry or randomized trial
	Studying hospitalization resources used and cost of care when palliative care specialists coordinate nonpharmacological and device care	Prospective registry or randomized trial

CS indicates cardiogenic shock; MI, myocardial infarction; MV, mechanical ventilation; and PCI, percutaneous coronary intervention.

remains guarded. In light of our collective inability to accurately identify which patients with CS will require palliative treatment, curative care therapies may need to be blended with palliative care early in the course of care.[294]

Suggestions for Clinical Care

We suggest that regardless of where it is initiated, objective, subjective, and patient-centered assessment criteria and tools should be used to guide palliative care. Supplemental Table 6 provides criteria from multiple acute HF, global HF, and non-HF sources to aid in determining the timing of consultation in CS.[15,278,295–310] We suggest that the multidisciplinary assessment team include a palliative care physician, regardless of MCS candidacy, given the risk of peri-implantation death.[242]

Palliative Care Delivery and Management

Little is known about the optimal delivery of palliative care in the CS population. In addition, most palliative care interventions in advanced HF, including consultation services, were derived from the success of cancer-related palliative care, and we believe more knowledge is needed to better understand best palliative care clinical practices.

Suggestions for Care Delivery

Suggestions for global palliative care delivery in patients with CS are provided in Table 7.

FUTURE DIRECTIONS

CS remains the most common cause of in-hospital death in patients with MI, and only a few treatment strategies are based on randomized trial evidence. To improve patient outcomes, timely research focused on addressing important clinical knowledge–treatment gaps is required (Table 8). For example, there is broad variation in CS outcomes that may be mediated in part by differences in the severity of CS. The development of accurate risk stratification tools that can be used to aid in treatment (eg, MCS or palliation) decision making would be an important clinical resource provided that it is simple, applicable to clinical practice, and vali-

dated in multiple clinical settings and pathogeneses. Currently, there is no well-established, simple, contemporary, and broadly validated CS prediction score. The development of such a tool that incorporates clinical and biomarker parameters could potentially serve as a cornerstone to improve outcomes by identifying when invasive, medical, or palliative therapies may be the most appropriate or futile.

Revascularization rates in patients with CS with MI remain low (50%–70%) in registries studies. Improving adherence to practice guidelines or available therapeutic technologies may increase CS survival. This may be accomplished through provider education of the benefits of early revascularization or public reporting changes wherein the CS population is analyzed separately to mitigate clinician or institutional aversion to adverse outcomes.[313,314] Because the majority of patients present with multivessel coronary artery disease, more research is also warranted on the optimal revascularization strategy for these patients.[182] In addition, the outcomes of treatment in specialized CS centers offering all treatment options should be evaluated further. MCS is currently used in <10% of patients, which may be influenced by the scarce evidence for these devices. Currently, when, how, and which MCS device should be used remain unclear.[25]

Randomized clinical trials in CS are difficult to perform, and few randomized clinical trials powered to detect differences in clinical outcome completed enrollment with the required number of patients.[1,9] The SHOCK trial was a milestone, and the subsequent widespread application of early revascularization led to a significant reduction in CS mortality. The failure of IABP in the IABP-SHOCK II trial should not be considered the end of percutaneous MCS. Rather, it should set the stage for a seminal trial using contemporary MCS strategies.[1] Historical barriers to cardiovascular research in the CS population include difficulty in obtaining informed consent and the exclusion of critically ill patients from contemporary trials.[315] Recognizing the timely need for studies evaluating novel and available pharmacological, interventional, systems of care, and MCS device management strategies, new traditional randomized trials, together with pragmatic trial designs, dedicated CS registries, inclusion of CS subpopulations in MI and HF trials, and novel enrollment methods, are needed to generate new CS knowledge and to bridge the evidence gaps that we encounter in daily clinical practice.

CONCLUSIONS

CS is a multifactorial and hemodynamically diverse high-acuity illness that is frequently associated with multisystem organ failure. The complexity of CS requires a widespread application of best-care practice standards and a coordinated regionalized approach to CS with multidisciplinary care in designated tertiary care centers that have the expertise, clinical volume, and resources necessary to centralize the delivery of the medical, surgical, and mechanical therapies highlighted in this document. Despite its prevalence, few trials have been performed, and CS remains a relatively understudied cardiovascular disease state. The pathophysiology of CS remains poorly elucidated; many routine CS therapeutic practices have not been rigorously tested; and new medical treatment options are urgently needed to reduce the significant patient morbidity and mortality associated with this condition. To address the knowledge gap, we advocate for coordinated international efforts to identify CS research priorities, to conduct clinical trials, and to create large population-based registries to generate quality improvement opportunities. These endeavors could form the basis for future scientific discovery, guideline development, and improved patient outcomes.

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FOOTNOTES

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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*Modest.

†Significant.

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Contemporary Management of Cardiogenic Shock: A Scientific Statement From the American Heart Association

Sean van Diepen, Jason N. Katz, Nancy M. Albert, Timothy D. Henry, Alice K. Jacobs, Navin K. Kapur, Ahmet Kilic, Venu Menon, E. Magnus Ohman, Nancy K. Sweitzer, Holger Thiele, Jeffrey B. Washam, Mauricio G. Cohen and On behalf of the American Heart Association Council on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; Council on Quality of Care and Outcomes Research; and Mission: Lifeline

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Supplemental Material

Supplemental Table 1: Etiologies of cardiogenic shock

Myocardial
I. Acute myocardial infarction
a. >40% loss of left ventricular mass
b. <40% loss of left ventricular mass with arrhythmia or vasodilation
c. Right ventricular infarction
d. Mechanical complication
i. Papillary muscle rupture
ii. Ventricular septal rupture
iii. Free wall rupture
II. Acute decompensated heart failure
a. Chronic heart failure (established etiology) with decompensation
b. Acute heart failure first presentation
i. Chronic ischemia
ii. Dilated cardiomyopathy
iii. Myocarditis
iv. Stress induced cardiomyopathy (Takotsubo)
v. Pregnancy associated heart disease
- Peri-partum cardiomyopathy
- Coronary artery dissection
vi. Endocrine disorders (hypo/hyperthyroidism, pheochromocytoma)
III. Post-cardiotomy shock
a. Prolonged cardiopulmonary bypass
b. Insufficient cardioprotection
IV. Dynamic outflow tract obstruction
V. Post cardiac arrest stunning
VI. Myocardial depression in setting of septic shock or SIRS
VII. Myocardial contusion

Valvular
I. Native valve a. Stenosis b. Acute regurgitation c. Valvular obstruction II. Prosthetic valve a. Valve obstruction b. Leaflet failure or restriction c. Mechanical failure d. Valve dehiscence
Electrical
I. Atrial arrhythmia with rapid ventricular rate II. Ventricular tachycardia III. Bradycardia
Extra-cardiac/Obstructive
I. Cardiac tamponade II. Constriction III. Pulmonary embolism
Other
I. Toxidromes II. Hypothermic myocardial depression

Supplemental Table 2: Utility of the echocardiogram in cardiogenic shock

Clinical Question	Information
Ventricular Function	Predominantly left, right or biventricular involvement
Etiology of Shock	**Acute Myocardial Infarction** • Extent of infarction/myocardium in jeopardy • Status of the non-culprit infarct zone • Presence of mechanical complications **Acute Valvular Insufficiency/obstruction (Native/Prosthetic)** • Etiology: endocarditis; degenerative valve disease • Location and hemodynamic consequences **Dynamic Left Ventricular Tract Obstruction** **Takotsubo Cardiomyopathy** **Cardiac Tamponade** • Circumferential versus localized effusion • Route of pericardiocentesis if indicated **Acute Pulmonary Embolism:** • Right ventricular function • Presence of clot in transition / Patent foramen ovale **Acute Aortic Syndrome** • Nature and extent of dissection • Degree of aortic insufficiency • Presence of pericardial effusion
Hemodynamics	Volume assessment as gauged by inferior vena cava Estimated pulmonary artery systolic pressure Estimated left atrial pressure
Therapeutic guidance	Guide vasoactive support Monitor response to therapy Mechanical circulatory support decisions: single or biventricular support Catheter position and guidance

Abbreviations: HOCM: hypertrophic obstructive cardiomyopathy

Supplemental Table 3: Potential cardiogenic shock systems of care implementation barriers and solutions

Implementation Requirement	Barrier	Potential Solution (s)
Organized hub center CS team	Coordinating multi-disciplinary CS on-call service Lack of mobile equipment and resources	Creating a CS team with a service coverage schedule with single call activation Cost shared between hub and spoke centers
Establishing regional hub-and-spoke centers	Existing referral patterns misaligned with a hub-and-spoke CS care Lack of CS management familiarity at spoke centers	State, County, and City leadership could geographically coordinate care and develop accreditation, clinical protocols, critical pathways, and continuing education meetings Pre-specify CS hub centers for transfer Development of standardized diagnostic and management protocols
Development of mobile teams	Lack of clinical privileges at the spoke centers Lack of financial resources	Commitment from hub CS centers to provide 24/7 CS team coverage; Shared hospital privileges for the mobile team; financial agreements between centers Need for research to evaluate clinical outcomes; Advocacy and financial support from professional, governmental and funding organizations
Measurement and Feedback	Lack of national CS registries and universal CS-specific care quality indicators	Develop a dedicated national CS registry and develop consensus based quality of care and outcome indicators for CS regional care. region and site level feedback

CS: cardiogenic shock, STEMI: ST-elevation myocardial infarction; OHCA: out-of-hospital cardiac arrest.

Supplemental Table 4: Overview of reperfusion strategies and adjunctive therapies in cardiogenic shock

Strategy	RCT	RCT Sub-group	Observational Data	Inferred use from MI	Comments
Thrombolytic therapy		√			
Early revascularization	√		√		Underused in CS
PCI		√	√	√	Predominantly used
POBA		√	√		Minimal use
BMS		√	√	√	Optimizes PCI outcomes
DES			√	√	Optimizes PCI outcomes
CABG		√	√	√	Rarely used
Adjunct anti-thrombotics					
Aspirin				√	Used in the SHOCK trial
Heparin				√	Used in the SHOCK trial
Bivalirudin			√	√	Limited data
Clopidogrel				√	Poor absorption in acute setting
Prasugrel			√	√	Poor absorption in acute setting
Ticagrelor				√	Poor absorption in acute setting
Cangrelor				√	Limited data
GP IIb/IIIa			√	√	Best data with abciximab

Abbreviations: PCI = Percutaneous Coronary Intervention, POBA = Plain Old Balloon Angioplasty, BMS = Bare Metal Stent, DES = Drug Eluting Stent, CABG = Coronary Artery Bypass Grafting, GP IIb/IIIa = Glycoprotein IIb/IIIa

Supplemental Table 5: Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profiles

INTERMACS Profile	Description
INTERMACS 1 "Crash and Burn"	Cardiogenic shock end, organ hypoperfusion
INTERMACS 2 " Sliding on inoptropes"	Worsening hemodynamic or physiologic parameters despite inotropic therapy
INTERMACS 3 "Dependent stability"	Stable hemodynamic or physiologic parameters on inotropic therapy; unable to wean inotropes
INTERMACS 4 "Resting symptoms"	Daily heart failure symptoms at rest
INTERMACS 5 "Exertion intolerant"	Symptoms with ADLs; no symptoms at rest
INTERMACS 6 "Walking wounded"	Euvolemic; fatigues with actives beyond ADLs
INTERMACS 7 "Advanced NYHA III	Activity limited to mild physical exertion

Abbreviations: ADL, activities of daily living, INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; NYHA, New York Heart Association.

Adapted with permission from Warner Stevenson et al. *J Heart Lung Transplant.* 2009;28:535–541.[41]

Supplemental Table 6: Comparison of commonly percutaneous mechanical circulatory support devices

	IABP	TandemHeart™	Impella™ 2.5/CP	Impella™ 5.0	ECMO
Mechanism	Pulsatile	Centrifugal (continuous)	Axial (continuous)	Axial (continuous)	Centrifugal (continuous)
CO or Flow	↑ CO 0-0.5 L/min	Flow ~ 4.0 L/min	Flow 2.5-4.0 L/min	Flow up to 5.0 L/min	Flow >4.0 L/min
Size	7-8 Fr	Arterial: 15-19 Fr Venous: 21 Fr	12-14 Fr	21 Fr	Arterial: 14-19 Fr Venous: 17-24 Fr
Advantage(s)	Readily available Familiarity Rapid insertion Easy to adjust No extracorporeal blood	Independent of rhythm Robust CO support	Independent of rhythm Easy insertion No extracorporeal blood	Robust support No extracorporeal blood	Independent of rhythm Robust CO support Pulmonary support
Disadvantage(s)	Minimal ↑CO Requires stable rhythm No effect on mean BP or lactate	Difficult insertion Requires transseptal puncture Vascular complications	Vascular complications Hemolysis	Vascular complications Hemolysis Requires surgical insertion	Vascular complications May not unload heart (may need venting) Regional hypoxemia

Abbreviations: CO, Cardiac Output; ECMO, extra-corporeal membrane oxygenation; Fr, French; IABP, intra-aortic balloon pump

Supplemental Table 7: Objective, subjective and patient-centric criteria to guide palliative care readiness and/or discussions and services

Triggers and Indicators of Palliative Care Readiness (Derived from Advanced HF)	Assessment		
	Objective	Subjective	Patient-Centric
Age over 80 years and 2+ life-threatening medical issues	✓	✓	
Worsening comorbidities			
Renal function:			
Need to initiate dialysis	✓		
High admission blood urea nitrogen (43+ mg/dL)	✓		
High serum creatinine (2.75+ mg/dL)	✓		
Escalation of diuretics to maintain volume status	✓		
Low hemoglobin	✓		
Hyponatremia due to fluid overload	✓	✓	
Presence of comorbidities of the *Gold Standards Framework Prognostic Indicator Guidance*[297]	✓		
Multisystem organ failure involving ≥3 organs	✓	✓	
Persistent hypotension			
-Low admission systolic BP (≤115 mmHg)	✓		
Persistent tachycardia (heart rate > 130 beats/minute)	✓		
Persistent significant dyspnea			
Respiratory rate > 25 breaths per minute	✓	✓	
Increased work of breathing		✓	✓
Breathlessness at rest	✓	✓	✓
Persistent pulmonary congestion by ultrasound	✓	✓	✓
Respiratory Distress Observation Scale (RDOS)[298] - 8 items:	✓	✓	✓
Heart rate			
Respiratory rate			
Non-purposeful movements			
Neck muscle use during inspiration			
Abdominal paradox			

End-expiratory grunting Nasal flaring Facial expression of fear *Intensive Care-RDOS*[298] - 5 items: Heart rate Neck muscle use during inspiration Abdominal paradox Facial expression of fear Supplemental oxygen	 ✓	 ✓	 ✓
Post cardiac arrest	✓		
Persistent pain (*Critical-Care Pain Observation Tool*: facial expression, body movements, muscle tension and compliance with the ventilator)[294]	✓		
Dysrhythmias, severe Slow ventricular tachycardia Ventricular arrhythmias refractory to medications	 ✓ ✓		
Hospitalization Emergency hospitalization due to acute decompensation Hospital stay of ≥10 days with a delayed ICU admission	 ✓ ✓		
Multiple hospital admissions ≥2 admissions in the past 12 months	 ✓		
Vasoactive or temporary mechanical circulatory dependence without further therapeutic options	✓		✓
Worsening functional status due to refractory physical symptoms Limited self-care; in bed or chair >50% of the day New York Heart Association functional class III-IV		 ✓ ✓	 ✓ ✓
Ventilator support required Pharmacologic Mechanical (intubation) Hypoxemia: SpO2 < 90% or PAO2 < 60 mmHg Hypercapnia: PaCO2 > 50 mmHg Non-invasive positive pressure ventilation support	 ✓ ✓ ✓ ✓		 ✓

Signs of advanced HF			
Cardiac cachexia; serum albumin < 25 gm/L	✓		
6-minute walk test < 300 meters	✓	✓	
Peak oxygen consumption < 14 mL/kg/minute	✓		
Progressive weight loss > 10% in last 6 months	✓		✓
Hypoperfusion (oliguria <0.5ml/kg/hour for ≥6 hours)	✓		✓
Severe tiredness			
Decreased well-being			
Extremely elevated or a rise in B-type natriuretic		✓	✓
peptide during hospitalization		✓	✓
Frequent implantable cardioverter-defibrillator shocks	✓	✓	✓
Intolerance to renin-angiotensin system blockers and/or			
β-blockers	✓	✓	✓
	✓		✓
Family request		✓	✓
Serious fall; transfer to nursing home	✓	✓	✓
High risk major procedures or high burden treatments			✓
Cognitive decline/dementia/delirium triggers*	✓	✓	✓
- *Montreal Cognitive Assessment* ≤25[296]	✓		
Delirium:			
Intensive Care Delirium Screening Checklist (ICDSC)[295]	✓	✓	✓
Confusion Assessment Method-ICU (CAM-ICU)[234]	✓	✓	
Increased frailty; at least 3 of the following:			
Weakness; slow walking speed, significant weight loss, exhaustion, low physical activity, depression	✓	✓	✓
In-hospital mortality risk score model			
- *Get With The Guidelines* program model:[283]	✓		
Older age			
Lower systolic BP			
Higher blood urea nitrogen			
Higher heart rate			
Hyponatremia			
History chronic obstructive pulmonary disease			

Nonblack race - *Acute Decompensated Heart Failure National Registry (ADHERE)* model:[284] Admission Blood urea nitrogen ≥43 mg/dL Systolic BP ≤115 mmHg Serum creatinine ≥2.75 mg/dL	✓		
1 year mortality risk > 25% - *Seattle Heart Failure* model[289, 290] - *Post hospitalization for acute HF*:[286] Older age History chronic obstructive pulmonary disease Systolic BP <150 mm Hg on admission Hyponatremia	✓ ✓	✓	
Mechanical circulatory support consultation			✓

BP, blood pressure; HF, heart failure; ICU, intensive care unit

*Triggers include unable to walk without assistance, urinary and fecal incontinence, no consistently meaningful conversation, unable to do activities of daily living (including work) or basic activities of daily living (feeding, bathing, grooming, dressing, continence, toileting, transfers, mobility, coping with stairs)

Supplemental Table 8: Characteristics of patients hospitalized with acute coronary syndromes who received palliative versus conservative or reperfusion treatments

Patient Characteristics (n = 45,279)	Palliative Treatment in ACS, compared to Conservative and Reperfusion Treatments
Age	Older
Gender	More often women
Risk factors	Higher frequency of: • Hypertension • Diabetes • Heart failure • Cerebrovascular diseases • Moderate renal disease • Dementia • Cancer Lower frequency of: • Current smoker • Dyslipidemia • Obesity
Hospital Presentation	Atypical symptoms: • Less pain • More dyspnea • Higher Killip class Atypical presentation • Higher rate of atrial fibrillation ACS type: • NSTEMI more frequent than STEMI

Abbreviations: ACS, acute coronary syndrome; NSTEMI, non-ST elevated myocardial infarction; STEMI, ST elevated myocardial infarction.

Adapted from Erne P, Radovanovic D, Seifert B, Bertel O, Urban P and Investigators obotAP. Outcome of patients admitted with acute coronary syndrome on palliative treatment: insights from the nationwide AMIS Plus Registry 1997–2014. *BMJ Open*. 2015;5.

Supplemental Appendix 1: Description of veno-arterial extra-corporeal membrane oxygenation (ECMO)

An ECMO circuit consists of a pump, membrane oxygenator, controller, cannulas for venous drainage and arterial outflow, a heat exchanger and tubing. Most contemporary ECMO pumps are centrifugal-flow devices that can generate up to 8 Liters/minute of blood flow by adjustment of the controller. Oxygenation and ventilation can be adjusted by changing the fraction of inspired oxygen and by modifying the sweep rate, respectively. The figure depicts veno-arterial (VA) ECMO that is placed centrally, as is often the case when used for post-cardiotomy shock. However, the most common cannulation strategy for VA ECMO is via peripheral vessels (typically the femoral vein and femoral artery). Cannulation can be performed in the operating room, a catheterization laboratory, or even at the patient's bedside. Implantation does require a drainage (i.e. venous) cannula that is between 21-25 Fr in diameter with lengths up to 60 cm. This can be introduced via either a single- or multi-stage process. The outflow cannula inserted into the arterial system is generally between 15-19 Fr in diameter and about 20-25 cm when placed peripherally.