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CLINICAL REVIEW
Clinical update

Management of cardiogenic shock complicating myocardial infarction: an update 2019

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Cardiogenic shock (CS) remains the most common cause of death in patients admitted with acute myocardial infarction (AMI) and mortality remained nearly unchanged in the range of 40–50% during the last two decades. Early revascularization, vasopressors and inotropes, fluids, mechanical circulatory support, and general intensive care measures are widely used for CS management. However, there is only limited evidence for any of the above treatment strategies except for revascularization and the relative ineffectiveness of intra-aortic balloon pumping. This updated review will outline the management of CS complicating AMI with major focus on state-of-the art treatment.

Keywords Shock • Heart failure • Treatment • Percutaneous coronary intervention • Myocardial infarction • Assist device

Introduction

Ventricular failure subsequent to acute myocardial infarction (AMI) remains the most frequent cause of cardiogenic shock (CS) accounting for more than 80% of cases. Mechanical complications of AMI represent less frequent causes of CS [ventricular septal rupture (4%), free wall rupture (2%), and acute severe mitral regurgitation (7%)].[1] Non-infarct-related CS may be caused by different diseases such as decompensated chronic heart failure, valvular heart disease, acute myocarditis, Takotsubo syndrome, or arrhythmias with heterogeneous treatment targets.[2]

The incidence of CS complicating AMI is still in the range of 3–13%.[3–6] Recent registries showed contradictory data with a decreased, stable, or even increased incidence of CS.[3–6] Based on these data, approximately 40 000–50 000 CS patients per year are treated in the USA and approximately 60 000–70 000 in Europe.[7] Despite a more widespread implementation of early revascularization with subsequent mortality reduction to 40–50%, CS remains a leading cause of death in AMI.[3,4,6,8,9] Some recent registries even reported an increase in mortality rates which may be explained by an ageing population and increasing risk profiles of CS patients.[6,10,11]

The underlying causes, pathophysiology, treatment of CS complicating AMI have been reviewed previously.[2,12] This 2019 update will focus on evidence-based therapeutic management of CS complicating AMI with major emphasis on current guideline recommendations, revascularization strategies, intensive care unit (ICU) treatment, adjunctive medication, and mechanical circulatory support (MCS) devices. Furthermore, research areas and gaps in evidence will be elucidated.

Definition of cardiogenic shock

In general, CS is defined as a state of critical endorgan hypoperfusion and hypoxia due to primary cardiac disorders.[2] Pragmatically, the diagnosis of CS can be made on the basis of clinical criteria such as persistent hypotension without adequate response to volume replacement and accompanied clinical features of endorgan hypoperfusion such as cold extremities, oliguria, or altered mental status. In addition, biochemical manifestations of inadequate tissue perfusion such as elevated arterial lactate are usually present.

Although not mandatory in clinical practice, objective haemodynamic parameters such as reduced cardiac index and elevated pulmonary capillary wedge pressure are helpful for diagnosis

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Table 1 Definition of cardiogenic shock in clinical trials and guidelines

SHOCK[13]	TRIUMPH[14]	IABP-SHOCK II[8]	CULPRIT-SHOCK[9]	ESC heart failure guidelines[15]
I. a. SBP <90 mmHg for ≥30 min or b. Support to maintain SBP ≥90 mmHg and II. Endorgan hypoperfusion (urine output <30 mL/h or cool extremities and heart rate >60 b.p.m.) III. Haemodynamic criteria[a]: a. CI of ≤2.2 L/min/m^2 and b. PCWP ≥15 mmHg	I. Patency of IRA spontaneously or after PCI II. Refractory cardiogenic shock >1 h after PCI with SBP <100 mmHg despite vasopressors (dopamine ≥7 μg/kg/min or norepinephrine or epinephrine ≥0.15 μg/kg/min) III. Endorgan hypoperfusion IV. Clinical or haemodynamic criteria for elevated left ventricular filling pressure V. LVEF <40%	I. SBP <90 mmHg for ≥30 min or catecholamines to maintain SBP >90 mmHg and II. Clinical pulmonary congestion and III. Impaired endorgan perfusion with at least one of the following criteria: a. Altered mental status b. Cold/clammy skin and extremities c. Urine output <30 mL/h d. Lactate >2.0 mmol/L	I. Planned early revascularization by PCI II. Multivessel coronary artery disease defined as >70% stenosis in at least two major vessels (≥2 mm diameter) with identifiable culprit lesion III. a. SBP <90 mmHg for >30 min or b. Catecholamines required to maintain SBP >90 mmHg IV. Pulmonary congestion V. Impaired organ perfusion with at least one of the following criteria: a. Altered mental status b. Cold/clammy skin and extremities c. Urine output <30 mL/h d. Lactate >2.0 mmol/L	SBP <90 mmHg with adequate volume and clinical or laboratory signs of hypoperfusion *Clinical hypoperfusion*: Cold extremities, oliguria, mental confusion, dizziness, and narrow pulse pressure. *Laboratory hypoperfusion*: Metabolic acidosis Elevated lactate Elevated creatinine

[a]Not required in anterior infarction or if pulmonary congestion in chest X-ray.
CI, cardiac index; ESC, European Society of Cardiology; IRA, infarct related artery; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; PCWP, pulmonary capillary wedge pressure; SBP, systolic blood pressure.

confirmation, enabling comparisons across CS cohorts and randomized clinical trials and are essential for defining right ventricular (RV) function in CS. Definitions applied in European guidelines and selected major randomized trials are shown in *Table 1*.

Recent efforts of the Society for Cardiovascular Angiography and Interventions (SCAI) is directed towards a more uniform CS definition and a classification scheme similar to the INTERMACS heart failure classification.[16] Based on this new definition, there are five categories of at risk, pre-shock to extreme CS labelled as A–E (*Figure 1*). This new classification system of different shock states will also help to make different trials of CS better comparable and may also trigger new randomized trials on the pre-shock state.

Pathophysiology and prognosis assessment by scores

The understanding of the complexity and pathophysiology of CS has evolved over the last decades.[2,7,17] In brief and in general, there is a profound depression of myocardial contractility resulting in a potentially deleterious downward spiral of reduced cardiac index, low blood pressure, and further coronary ischaemia, followed by additional reductions in contractility. This classic paradigm also includes initial compensatory systemic vasoconstriction which may be counteracted subsequently by pathological vasodilation due to inflammatory reactions. The reduction in cardiac index causes severe tissue hypoxaemia as sensitively measured by arterial lactate which however is not specific for CS. Multiple other biomarkers in addition to lactate measuring the degree of inflammation,[18] renal function,[19] and liver involvement[20] are associated with impaired prognosis. Microcirculatory impairment can also be measured sublingually by sidestream darkfield imaging and is associated with dismal prognosis.[21] However, the clinical value of these new imaging methods and new biomarkers, in addition to lactate, creatinine and standard liver function tests, has not yet been finally defined and not entered into clinical routine.

As described above, several clinical and biological factors have been used for prognosis assessment. Those factors have been summarized in multiple scores in the (I) pre-shock, (II) full CS, and (III) mechanical support with extracorporeal membrane oxygenation (ECMO) setting (*Table 2*). In clinical practice, CS encompasses a spectrum ranging from Stage B—beginning or pre-shock—to overt severe or extremis shock Stages C and E (see *Figure 1*). Identifying the pre-shock state is appealing as it may reduce mortality by preventing progression to overt CS through initiating adequate management strategies. The best validated score in this setting is the recently introduced ORBI (Observatoire Régional Breton sur l'Infarctus) score to predict the development of CS.[23] Based on 11 routinely collected variables available in the catheterization laboratory, the ORBI score allowed independently predicting the development of in-hospital CS

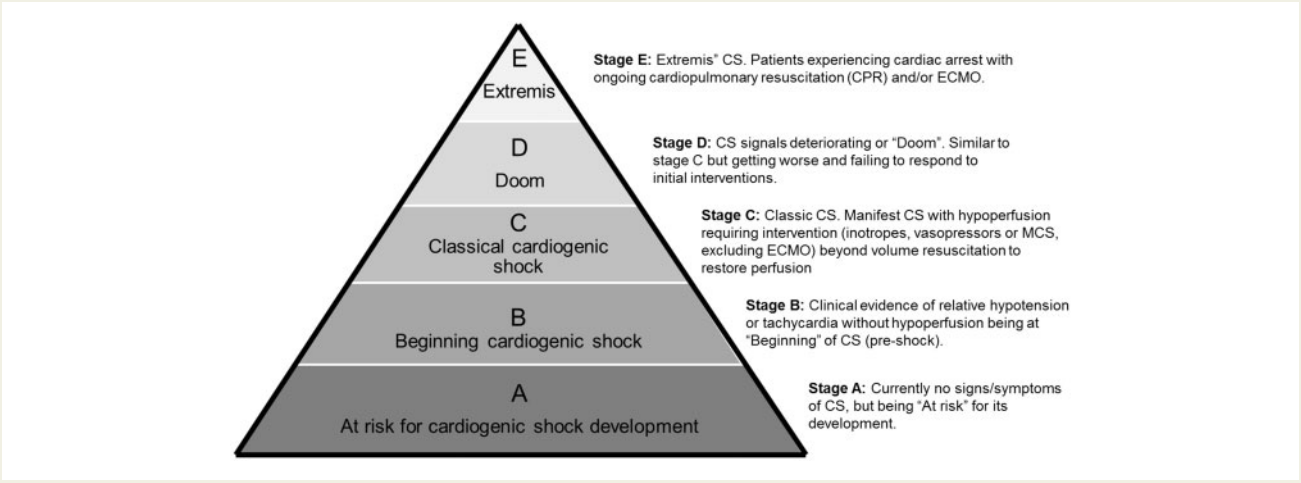


Figure 1 Cardiogenic shock pyramid according to recent proposal. Five categories of cardiogenic shock. Stage A: At risk: Patients 'At risk' for cardiogenic shock development but not currently experiencing signs/symptoms of cardiogenic shock. Stage B: Patients with clinical evidence of relative hypotension or tachycardia without hypoperfusion being at 'Beginning' of cardiogenic shock. Stage C: Patients in the state of 'Classic' cardiogenic shock. Stage D: Cardiogenic shock signals deteriorating or 'Doom'. Stage E: Patients in 'Extremis' such those experiencing cardiac arrest with ongoing cardiopulmonary resuscitation and/or extracorporeal membrane oxygenation cardiopulmonary resuscitation.

after primary PC (low-risk 0–7 points, low-to-intermediate risk 8–10 points, intermediate-to-high risk 11–12 points, high-risk >13 points). The score may be useful in the selection of high-risk patients in the setting of future randomized trials designed to provide a tailored aggressive management to pre-shock or Stage B patients.

Until recently, a limitation of all published scores in the setting of classical CS was the lack of sufficient validation and also applicability in clinical practice. Currently, there is only one CS score with both internal and external validation derived from the IABP-SHOCK II trial (*Table 2*).[30] Based on six variables—including the biomarkers lactate, creatinine and glucose—with a maximum of nine points this IABP-SHOCK II score divides into three risk categories. Patients in the low (0–2 points), intermediate (3 or 4 points), and high-risk categories (5–9 points) have 30-day mortality risk of 20–30%, 40–60%, and 70–90%, respectively. This score may also be a suitable tool to tailor more aggressive treatment strategies such as MCS. However, this requires further validation in randomized trials. There are also scores for prediction of outcome in patients with MCS mainly ECMO (*Table 2*).

Management and treatment

In general, patients with CS should best be treated at specialized tertiary CS care centres.[2,34] A possible treatment algorithm based on the aetiology of CS, left and right ventricles as well as mechanical complications as cause, treatment in the catheterization laboratory or operating room, subsequent ICU and possible selection of MCS with available guideline recommendations is shown in *Figure 2*. A detailed description of mechanical complications is beyond the scope of this review and has been summarized previously.[35] *Figure 2* provides a summary of randomized trials in CS and the respective mortality indicating relative risk and 95% confidence intervals (CIs).

Revascularization

Based on the SHOCK trial, early revascularization is the most important treatment strategy in CS after myocardial infarction.[13] Of note, the trial failed to meet the primary endpoint of lowering 30-day mortality with early revascularization in comparison to initial medical stabilization. However, there was a significant mortality reduction at longer follow-up after 6 months, 1, and 6 years.[13,36] Applying current evidence-based criteria with a failed primary study endpoint, nowadays may have led to a different interpretation of the trial. However, since the widespread use of early revascularization multiple registries have confirmed the significant decrease in mortality from the previous 70–80% to 40–50%.[4] Therefore, the current Class 1B recommendation in European Society of Cardiology (ESC) and US guidelines seems justified (*Take home figure*).[37–39]

Recent registries suggest a detrimental effect of revascularization delays on outcome.[40,41] Therefore, efforts need to be directed towards immediate transfer to 24/7 percutaneous coronary intervention (PCI) tertiary care centres. There is a lack of evidence to support fibrinolysis in CS. However, if an early invasive approach cannot be completed in a timely fashion, fibrinolysis may be considered in CS associated with ST-elevation myocardial infarction (STEMI).[2]

Revascularization in multivessel coronary artery disease

Approximately 70–80% of patients with CS present with multivessel disease defined as additional stenoses/occlusions in addition to the infarct related artery.[42] These patients have higher mortality compared to patients with single vessel disease.[43] Current guidelines recommend early revascularization by PCI or coronary artery bypass grafting (CABG) depending on coronary anatomy and amenability to PCI.[37–39]

Until recently, guidelines encouraged to perform multivessel PCI of all critical stenoses in addition to the culprit lesion (Class IIa C

Table 2 Risk classification and scores in cardiogenic shock

Study	Year	Components	Development database (*n*)	Validation database (*n*)
Scores to predict development of cardiogenic shock				
Obling *et al.*[22]	2018	Age Stroke Symptom onset to intervention Anterior STEMI Heart rate/SBP ratio Comatose status after resuscitation from cardiac arrest	2247 STEMI patients treated by primary PCI from a bicentric registry in Denmark	—
ORBI risk score Auffret *et al.*[23]	2018	Age >70 years (2 points) Prior stroke/TIA (2 points) Cardiac arrest upon admission (3 points) Anterior STEMI (1 point) FMC-to-PCI delay >90 min (2 points) Killip class (2 points) Heart rate >90/min (3 points) Combination of SBP <125 mmHg and pulse pressure <45 mmHg (4 points) Glycaemia >10 mmol/L (3 points) Culprit lesion left main (5 points) Post-PCI TIMI-flow <3 (5 points)	6838 patients without CS on admission and treated by primary PCI included in the Observatoire Régional Breton sur l'Infarctus (ORBI)	2208 from RICO cohort
Scores in overt cardiogenic shock				
ALKK Zeymer *et al.*[24]	2004	Left main disease TIMI <3 flow after PCI Older age Three-vessel disease Longer time-intervals between symptom onset and PCI	1333 from ALKK registry	—
Sutton *et al.*[25]	2005	Previous myocardial infarction Age >70 years Failed reperfusion	113	—
ACC-NCDR Klein *et al.*[26]	2005	Age Female gender Creatinine >2.0 mg/dL Total occlusion of the LAD No stent used No glycoprotein IIb/IIIa inhibitor used	483 from American College of Cardiology-National Cardiovascular Data Registry (ACC-NCDR)	—
TRIUMPH trial Katz *et al.*[27]	2009	Systolic blood pressure Creatinine clearance Number of vasopressors Norepinephrine dose	396 from TRIUMPH trial	79 from SHOCK-2 trial

Continued

Table 2 *Continued*

Study	Year	Components	Development database (*n*)	Validation database (*n*)
SHOCK trial Sleeper *et al.*[28]	2010	Clinical score: Age Anoxic brain damage Endorgan hypoperfusion Shock on admission Prior CABG Non-inferior infarction Creatinine ≥1.9 mg/dL Systolic blood pressure	1217 from SHOCK trial and registry	—
SHOCK trial Sleeper *et al.*[28]	2010	Haemodynamic + clinical score: Stroke work LVEF <28% Age Anoxic brain damage Endorgan hypoperfusion	872 from SHOCK trial and registry	—
CARD-SHOCK Harjola *et al.*[29]	2015	Prior CABG ACS aetiology Confusion Previous infarction Lactate LVEF Age Systolic blood pressure	219 multicentre European registry	384 from the IABP-SHOCK II trial
IABP-SHOCK II risk score Pöss *et al.*[30]	2017	Age >73 years (1 point) History of stroke (2 points) Glucose >191 mg/dL (10.6 mmol/L) (1 point) Creatinine >1.5 mg/dL (>132.6 µmol/L) (1 point) Lactate >5 mmol/L (2 points) TIMI flow <3 after PCI (2 points)	IABP-SHOCK II Study (600)	IABP-SHOCK II Registry (188)CardShock (137)
Scores for cardiogenic shock patients on VA-ECMO				
SAVE (ECMO) Schmidt *et al.*[31]	2015	Cause of CS Age Weight pre-ECMO organ failures Chronic renal failure pre-ECMO cardiac arrest Duration of intubation prior to ECMO Peak inspiratory pressure $HCO3^-$ Diastolic blood pressure Pulse pressure	3846 patients from Extracorporeal Life Support Organization (ELSO) registry	161 in Australian population with VA-ECMO

Continued

Table 2 *Continued*

Study	Year	Components	Development database (*n*)	Validation database (*n*)
ENCOURAGE Muller *et al.*[32]	2016	Age >60 Female sex Body mass index >25 kg/m^2 Glasgow coma score <6 Creatinine >150 µmol/L Lactate <2, 2–8, or >8 mmol/L Prothrombin activity <50%	138 derived from bi-centric ECMO registry	—
PREDICT-VA ECMO score Wengenmayer *et al.*[33]	2018	Lactate pH $HCO3^-$	205 VA-ECMO patients at single-centre registry	244 patients recruited from an independent tertiary referral hospital

ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; CS, cardiogenic shock; ECMO, extracorporeal membrane oxygenation; FMC, first medical contact; IABP, intra-aortic balloon pump; LAD, left anterior descending coronary artery; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; TIA, transient ischaemic attack; TIMI, thrombolysis in myocardial infarction.

recommendation) in CS.[38] Recently, the randomized, multicentre Culprit Lesion Only PCI vs. Multivessel PCI in Cardiogenic Shock (CULPRIT-SHOCK) trial showed a significant clinical benefit of a culprit-lesion-only strategy with a reduction in the primary endpoint of 30-day mortality or renal replacement therapy (45.9% culprit-lesion-only PCI vs. 55.4% immediate multivessel PCI; relative risk 0.83; 95% CI 0.71–0.96; $P = 0.01$) which was mainly driven by an absolute 8.2% reduction in 30-day mortality (43.3% vs. 51.5%; relative risk 0.84; 95% CI 0.72–0.98, $P = 0.03$).[9] Based on this trial, the ESC 2018 revascularization guidelines now advise against routine immediate multivessel PCI (Class IIIB recommendation).[37] The 30-day results of CULPRIT-SHOCK could recently be confirmed with a consistent reduction in the composite endpoint at 1-year follow-up for the culprit-lesion-only PCI with possible staged revascularization strategy.[44] The difference in all-cause mortality was slightly attenuated and as expected more patients underwent additional revascularization after culprit-lesion-only PCI. The CULPRIT-SHOCK results were consistent across all predefined subgroups.[9,44] Thus, in clinical practice revascularization should be limited to the culprit lesion with possible staged revascularization of other lesions at a later timepoint.

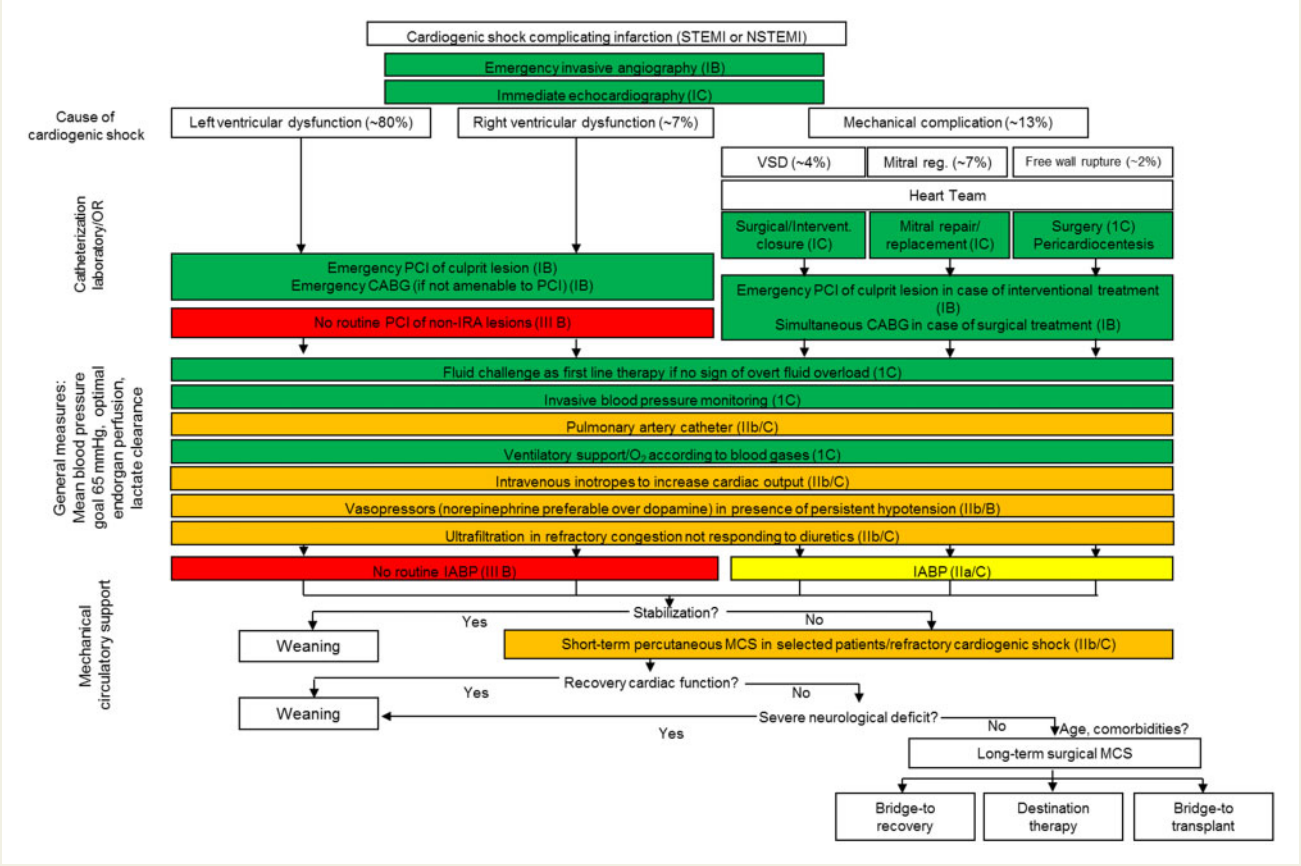
There may also be a role for emergent CABG; however, there is little evidence to guide surgical vs. PCI revascularization. Based on evidence from four observational reports, comparing PCI vs. CABG, the type of revascularization did not influence outcome in CS.[45] Despite these considerations and in contrast to the SHOCK trial (37.5% underwent immediate CABG), CABG is nowadays rarely performed in CS with rates <5% in registries and randomized trials.[4,8] A trial of culprit-lesion-only PCI with staged revascularization vs. immediate CABG or initial reopening of the infarct related artery with a balloon and subsequent immediate CABG in patients with multivessel disease and CS may be worth to be studied.

Access site

Based on multiple randomized trials, current guidelines recommend radial access as default strategy in non-shock STEMI[38] or non-ST-elevation acute coronary syndromes,[46] and also stable coronary artery disease.[37] In CS, the benefit of radial access is less evidence-based. A meta-analysis analysing data of 8131 registry patients with CS demonstrated that radial access was associated with a reduction in all-cause mortality.[47] In CULPRIT-SHOCK, radial access was used in 19% as primary strategy. In clinical practice, radial access may be favoured by experienced radial operators and in sufficiently palpable radial pulses. Otherwise the femoral access may still be a valuable alternative.

Peri-interventional antiplatelet and antithrombotic medications

Antithrombotic therapy is one of the key features for PCI success. There are no specific trials in CS for antiplatelets or anticoagulation. Enteral resorption is impaired in CS and oftentimes opioids are co-administered with further impact on enteral bioavailability. In mechanically ventilated patients, oral antiplatelets require to be crushed and administered through a nasogastric tube.[48] Under these circumstances intravenous antiplatelets may play an important role. Currently, there is only one small randomized trial in 80 patients (with 35% cross-over in the standard treatment group) which failed to confirm that routine upstream glycoprotein IIb/IIIa-inhibitor use



Take home figure Treatment algorithm for patients with cardiogenic shock complicating myocardial infarction. The class of recommendation and level of evidence according to the most recent European Society of Cardiology guidelines is provided if available.[15,37,38] Class I recommendations are depicted in green. Class IIa recommendations are depicted in yellow. Class IIb recommendations are depicted in orange. Class III recommendations are depicted in red.

is superior in comparison to standard treatment (*Figure 2*).[49] The intravenous P2Y12 inhibitor cangrelor is currently tested in the Dual Antiplatelet Therapy for Shock patients with Acute Myocardial Infarction (DAPT-SHOCK-AMI) trial (ClinicalTrials.gov: NCT03551964). Current considerations and experience suggest a liberal use of glycoprotein IIb/IIIa-inhibitors or cangrelor in patients with high thrombus burden and slow flow after PCI in particular for the CS patient. Adjunctive intravenous anticoagulation should be co-administered with antiplatelets. Despite a lack of specific randomized trials in CS the same recommendations apply as for other types of AMI.

Intensive care unit treatment

Fluids, vasopressors, inotropes

Basic ICU treatment includes initial haemodynamic stabilization by volume expansion, vasopressors, and inotropes plus additional therapy for prevention or treatment of multiorgan system dysfunction (MODS). Fluid administration in CS is mainly based on pathophysiological considerations and according to current guidelines a fluid challenge as first line therapy should be considered unless there are signs of overt fluid overload (Class 1C recommendation) (*Take home figure*).

Inotropes and vasopressors are administered in approximately 90% of patients in CS.[8] These drugs increase myocardial oxygen consumption and vasoconstriction may impair microcirculation and increase afterload. Therefore, any catecholamine should be administered at the lowest possible dose and the shortest possible duration.

In recent years more evidence could be derived from randomized trials comparing different vasopressors in CS. In a randomized comparison of 1679 shock patients of diverse causes treatment with dopamine in comparison to norepinephrine was associated with significantly more arrhythmic events for the overall study cohort however with a lack of significant mortality reduction. The predefined CS subgroup—the percentage of CS due to AMI is not reported—had lower mortality with norepinephrine.[50] Comparing epinephrine and norepinephrine, two small randomized trials in CS showed similar effects of on cardiac index.[51,52] However, heart rate and several metabolic changes including lactic acidosis were unfavourable for epinephrine compared with norepinephrine.[51] The larger OptimaCC trial was terminated early because the main safety endpoint—incidence of refractory CS—was significantly higher in the epinephrine group (37% vs. 7%; $P = 0.008$).[51] Based on a meta-analysis suggesting lower mortality with norepinephrine (*Figure 2*) over

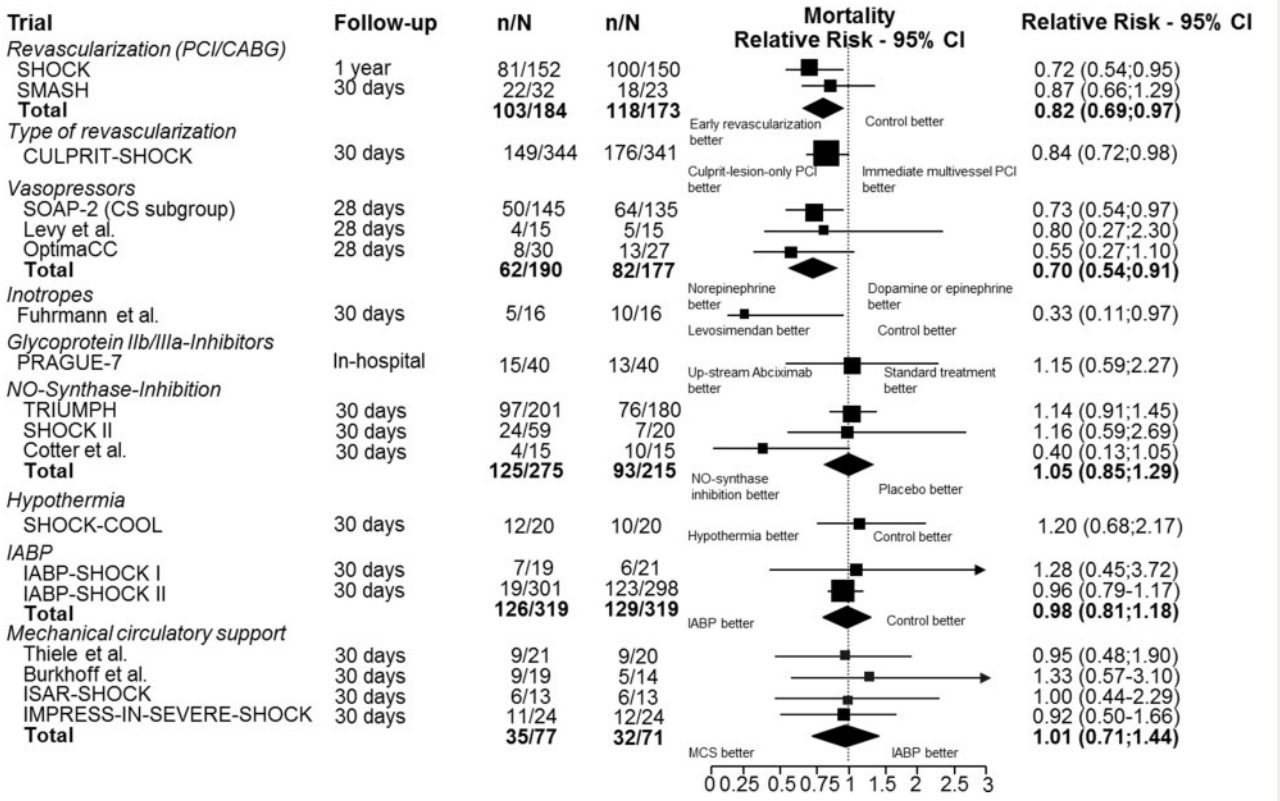


Figure 2 Current evidence from randomized clinical trials in cardiogenic shock in the percutaneous coronary intervention era. The relative risk and 95% confidence intervals are depicted for the various randomized interventions. The SOAP II trial was neutral with respect to mortality for the overall trial, thus the predefined cardiogenic shock—including various causes of cardiogenic shock—subgroup results need to be interpreted with caution. CABG, coronary artery bypass grafting; CS, cardiogenic shock; IABP, intra-aortic balloon pump; IABP-SHOCK, Intra-aortic balloon pump in shock; PCI, percutaneous coronary intervention; SHOCK, SHould we emergently revascularize Occluded Coronaries for cardiogenic shocK; SMASH, Swiss Multicentre trial of Angioplasty for SHock; SOAP II, Sepsis Occurrence in Acutely Ill Patients II; TRIUMPH, Tilarginine Acetate Injection in a Randomized International Study in Unstable MI Patients With Cardiogenic Shock.

epinephrine or dopamine, norepinephrine is the vasoconstrictor of choice when blood pressure is low and tissue perfusion pressure is insufficient (Class IIb, level of evidence B, *Take home figure*).[15] Vasopressin has not been studied in the CS setting. Therefore, no recommendations based on evidence can be made. The target mean blood pressure is not well defined in CS. In analogy to septic shock, a mean blood pressure >65 mmHg is probably not required and may be associated with more side effects.[53]

Inotropes, e.g. dobutamine, may be given simultaneously to norepinephrine in an attempt to improve cardiac contractility (Class IIb, level of evidence C, *Take home figure*).[15] Other inotropes such as levosimendan or phosphodiesterase-inhibitors are of interest based on their myocardial contractility improvement and potential for vasodilation without increasing oxygen requirements. However, current evidence for inodilators in CS is very limited. A very small trial of 32 CS patients suggested lower mortality with levosimendan in comparison to enoximone (*Figure 2*).[54] However, recent large-scale trials involving more than 2200 patients in sepsis or cardiac surgery failed to show any benefit with levosimendan on mortality or organ protection.[55–58]

General intensive care measures

Treatment of CS is complex and cardiac ICUs are considered to be better suited to deal with such complexity.[2,34] Optimal ICU treatment of MODS is essential for the treatment of CS patients since it has a major impact on prognosis. Although not specifically investigated in CS, multiple measures are generally accepted. If invasive ventilation is required, lung-protective ventilation (6 mL/kg predicted body weight tidal volume) should be performed to prevent pulmonary injury. Non-invasive ventilation with continuous positive airway pressure may be an option to prevent intubation in borderline respiratory situations.[15]

Urinary production as well as renal function by serial creatinine measurements should be measured and renal replacement therapy be initiated in case of acute renal failure with clinical signs of uraemia, otherwise untreatable volume overload, metabolic acidosis (pH <7.2), and/or refractory hyperkalaemia (>6.0 mmol/L). Based on these criteria, renal replacement therapy was necessary in 14% of patients in the CULPRIT-SHOCK trial.[9] Earlier initiation of renal replacement therapy had no effect on outcome in ICU patients with acute kidney injury.[59]

Elevated liver parameters often follow generally poor haemodynamic status as a result of RV congestion. Liver function tests are altered in >50% of CS patients.[20] Elevated transaminases can be interpreted as a direct sign of liver hypoperfusion, associated with increased mortality.[20] Haemodynamics should be stabilized for optimal liver perfusion.

Moreover, glycaemic control to target a blood glucose concentration between 144 mg/dL and 180 mg/dL (8–10 mmol/L) yet avoiding hypoglycaemia is recommended.[60] Prophylaxis of thromboembolism and stress ulcers should follow general recommendations for critically ill patients.

Until recently insufficient evidence was available for nutrition management with respect to enteral or parenteral administration. In a recent randomized trial including shock of all causes (19% CS) requiring vasopressors enteral or parenteral nutrition initiated within 24 h was compared.[61] Early isocaloric enteral in comparison to early isocaloric parenteral nutrition did not reduce mortality but was associated with a higher risk of gastrointestinal complications. Therefore, no nutrition in the early phase and possibly initial parenteral nutrition should be preferred in CS.

There is no consensus on the optimal method of haemodynamic monitoring in assessing and treating patients in CS, including pulmonary artery catheterization. Current guidelines and scientific statements consider using PAC early in the treatment course in patients not responsive to initial therapy or in cases of diagnostic or therapeutic uncertainty (*Take home figure*).[2,15] The understanding of the aetiology of CS and RV failure has changed in the last decade. Using PAC several haemodynamic profiles have been defined where the prognosis is driven by RV performance that may be altered with RV MCS. These variables and calculations have been reviewed recently.[62] Of these, a pulmonary artery pulsatility index (pulmonary artery systolic pressure - pulmonary artery diastolic pressure/right atrial pressure) <1.0 may best indicate additional requirement for RV support. However, no randomized data are available showing a benefit of PAC or other haemodynamic monitoring directed treatment on outcome.

Moderate/severe bleeding is common in CS ranging from 20% to 90% depending on the definition used and also influenced by concomitant use of MCS.[42,63] Trials in non-CS patients with bleeding demonstrated that a restrictive transfusion regimen can improve outcome. General accepted ICU strategies avoid correction of haemoglobin levels >7 g/dL (>4.3 mmol/L) unless there is a clinical bleeding problem.[64]

Hypothermia

In most of the randomized hypothermia trials in out-of-hospital cardiac arrest, patients in CS were excluded. Nevertheless, temperature management is generally applied and recommended for patients with CS after cardiopulmonary resuscitation (CPR).[65] In the IABP-SHOCK II and the CULPRIT-SHOCK trial more than 40% and 50% of patients were resuscitated before randomization with subsequent induced hypothermia showing the relevance of this condition in CS.[8,9] In non-resuscitated CS patients experimental, animal and early human data suggested beneficial effects of hypothermia on haemodynamics and multiple other targets.[66] However, the recent randomized SHOCK-COOL trial in non-resuscitated CS patients showed no benefit of hypothermia vs. standard treatment on the surrogate endpoint cardiac power index. Moreover, there was possible harm of hypothermia as shown by impaired lactate clearance.[67]

Mechanical circulatory support

To overcome theoretical limitations of inotropes and vasopressors with limited effects to maintain adequate perfusion pressure and to prevent or reverse MODS, MCS to reduce the need for catecholamines, improve haemodynamics and outcome is appealing. Despite an increasing number of different percutaneous MCS devices for either left ventricular (LV) or RV support (*Figure 3*), data derived from randomized clinical trials on the effectiveness, safety, differential indications for different devices, and optimal timing are still limited.

Intra-aortic balloon pumping

The intra-aortic balloon pump (IABP) is one of the oldest and most often used MCS devices introduced in the early 1960s. For decades, there was no evidence derived from randomized trials. This changed after publication of the Intra-aortic Balloon Pump in Cardiogenic Shock II (IABP-SHOCK II) trial which randomized 600 patients with CS complicating AMI and early revascularization with or without IABP. There was no difference in the primary study endpoint 30-day mortality between the two treatment groups (*Figure 2*).[8] The results of the primary study endpoint were confirmed by a lack of beneficial effects for any of the secondary study endpoints and also through longer follow-up.[8,68] Recently, the 6-year follow-up of IABP-SHOCK II has been published confirming the negative results for the intention-to-treat as well as for the as-treated population.[69] Based on the IABP-SHOCK II trial this passive MCS device should not be used anymore routinely according to ESC guidelines with a current Class IIIB recommendation.[15,37,38] Nowadays, IABP may only be considered in patients with mechanical complications (Class IIa C recommendation; see *Take home figure*).[38]

The neutral results of IABP-SHOCK II together with the downgrading in guidelines led to a decrease in IABP use to <30% in the USA,[70] <25% in UK,[6] and <10% and 18% in two registries in Germany,[5,41] respectively. The decline in IABP use was associated with an increase of active MCS including Impella/TandemHeart and veno-arterial (VA)-ECMO in CS from approximately 1% in 2006 to 8% in 2014 in the USA.[70] Similarly, VA-ECMO implementation has developed towards a routine procedure with a more than eight-fold increase in Germany from 2010 to 2015.[71,72]

Percutaneous ventricular assist devices

The mode of action of different MCS devices has been described previously.[7,42] New developments include RV support devices such as the Impella RP (Abiomed, Danvers, MA, USA) and the TandemHeart RA-PA (LivaNova, London, UK) with blood delivery from the right atrium or inferior vena cava to the pulmonary artery. Newer LV MCS devices include the HeartMate PHP (Abbott, Lake Bluff, IL, USA) deployed across the aortic valve and delivering blood from the left ventricle into the aorta similar to the Impella family. Another investigational device is the paracorporeal pulsatile iVAC 2L (PulseCath BV, Arnhem, The Netherlands). For the iVAC and HeartMate PHP results from randomized trials are currently not

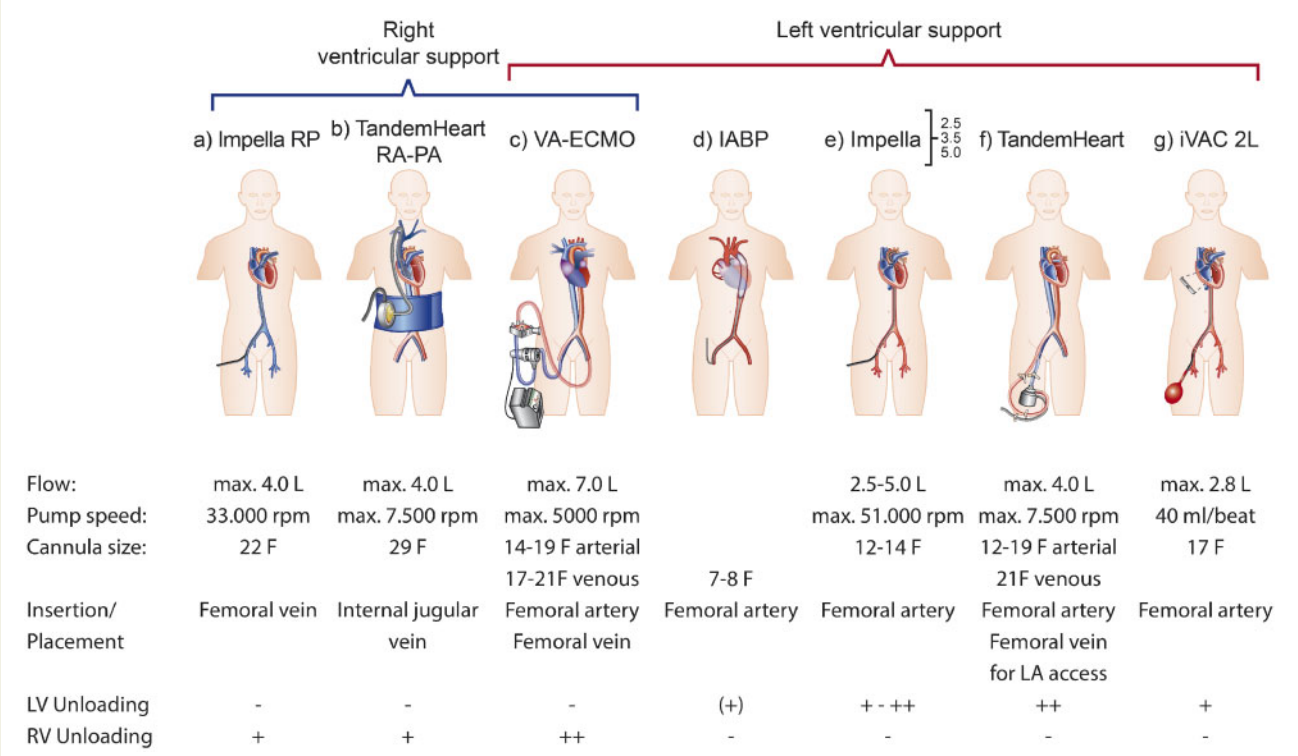


Figure 3 Schematic drawings of current percutaneous mechanical support devices for cardiogenic shock with technical features. On the left side are devices for right ventricular support and on the right side those for left ventricular support. (a) Impella® RP, (b) TandemHeart™ RA-PA (right atrium—pulmonary artery), (c) VA extracorporeal membrane oxygenation (ECMO), (d) Intra-aortic balloon pump, (e) Impella®, (f) TandemHeart™, and (g) iVAC 2L®.

available. *Figure 3* shows the different devices including a brief overview of technical features and LV or RV unloading properties.

Data on percutaneous MCS devices in CS on outcome are still limited. In the recent IMPRESS-in-Severe-SHOCK trial, 48 patients with CS requiring mechanical ventilation were randomized to Impella CP vs. IABP.[73] The 30-day mortality primary endpoint was based on a power calculation with unrealistic mortality rates leading to a markedly underpowered trial. Unsurprisingly, there was no difference in the primary endpoint all-cause mortality after 30 days; however, the lack of benefit in any of the other parameters including arterial lactate may be a concern with respect to the efficacy of the device.

A recent meta-analysis of active MCS devices against control including the IMPRESS-in-Severe-SHOCK trial showed no difference in mortality for overall 148 included patients. There were improvements in arterial lactate and mean arterial blood pressure after device insertion. On the other hand, there were no effects on other haemodynamic parameters and more importantly the haemodynamic effects were counterbalanced by significantly more bleeding complications.[63]

Recently, a matched-pair mortality analysis of 237 Impella-treated vs. 237 IABP-treated CS patients could confirm a lack of mortality benefit with the Impella device (30-day mortality 48.5% vs. 46.4%, $P = 0.64$).[74] Of note, severe or life-threatening bleeding (8.5% vs. 3.0%, $P < 0.01$) and peripheral vascular complications (9.8% vs. 3.8%, $P = 0.01$) was observed more frequently with the Impella device.

Extracorporeal life support systems

Integral features of ECMO are the blood pump, a heat exchanger, and an oxygenator. Previous devices with predominant surgical insertion were inherited with substantial complications such as lower extremity ischaemia (16.9%), compartment syndrome (10.3%), amputation (4.7%), stroke (5.9%), major bleeding (40.8%), and significant infections (30.4%).[75] Recent developments with miniaturized systems and percutaneous cannula insertion have led to a wider adoption by interventional cardiologists for the treatment of CS using VA-ECMO. A common issue related to peripheral insertion is an increase in afterload which may lead to inadequate LV unloading. Multiple venting manoeuvres have been described to prevent LV volume overload such as combining VA-ECMO with IABP, Impella, atrial septostomy, or other.[76] Advantages of VA-ECMO are low costs in comparison to other percutaneous MCS devices, the high flow providing full circulatory support even in resuscitation situations (Stage E CS patients), the ability of providing full oxygenation, and also a combined support of the right and left ventricles.

Outcome data on VA-ECMO in CS are scarce. A recent meta-analysis including only prospective and retrospective cohort studies revealed a significant mortality benefit with VA-ECMO use.[77] In total, four registries of CS patients and 10 registries with cardiac arrest patients undergoing resuscitation were included.[77] In cardiac arrest, VA-ECMO use [ECMO cardiopulmonary resuscitation (eCPR)] was

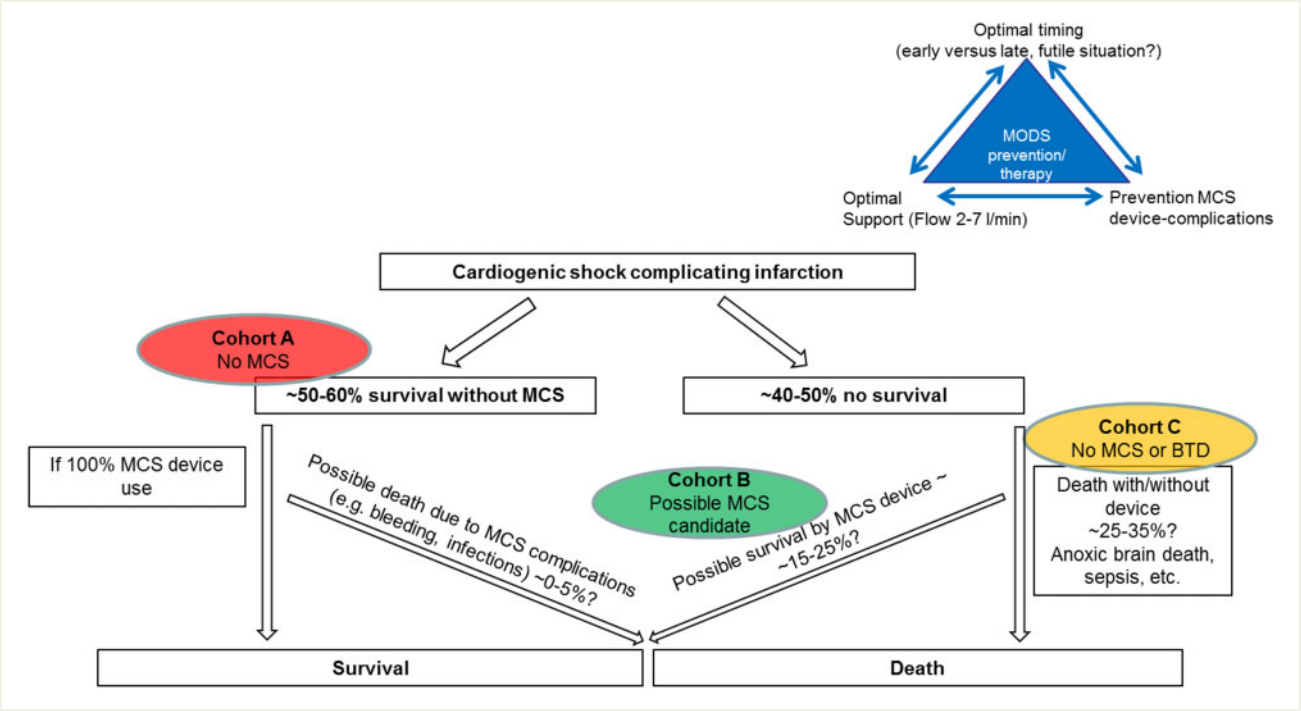


Figure 4 Considerations on use of mechanical circulatory support for multiorgan system dysfunction prevention and therapy. Approximately 50–60% of patients currently survive without any device (Cohort A, no MCS). Inserting a device in this group will have no impact on survival or may even lead to some complications by the device itself possibly resulting in death (white arrow to the right). Approximately 40–50% currently do not survive. In this group, there may be futile situations where a mechanical circulatory support will not change clinical outcome (Cohort C, no MCS or MCS as bridge-to-decision). Based on Cohort A and C, approximately 15–25% of cardiogenic shock patients might be appropriate candidates for mechanical circulatory support (Cohort B). The right upper corner reflects current open questions in mechanical circulatory support selection and possible complications. BTD, bridge-to-decision; MCS, mechanical circulatory support; MODS, multiorgan dysfunction syndrome.

associated with an absolute increase of 30-day survival of 13% compared with control (95% CI 6–20%; $P < 0.001$; number-needed-to-treat 7.7). However, optimal patient selection for eCPR is still matter of intense debate.[78] A current randomized trial is testing eCPR in refractory cardiac arrest (Prague Out-of-hospital cardiac arrest trial; clinicaltrials.gov: NCT01511666). A propensity matched analysis, including five studies and 438 patients (219 in both groups), showed similar results. In CS without ongoing CPR, VA-ECMO resulted in a 33% higher 30-day survival compared with IABP (95% CI 14–52%; $P < 0.001$; number-needed-to-treat 3).[77] Recent data indicate that VA-ECMO is increasingly used within a 9-year observational period. Despite this rapid increase, 30-day in-hospital mortality remained unchanged over time (59.0% in 2007–2012 vs. 61.4% in 2013–2015, $P = 0.94$).[71]

Currently, two randomized trials are in the early phase of patient recruitment to assess VA-ECMO for the treatment of CS (*Figure 5*). Both trials are adequately powered and use 30-day mortality as primary endpoint. Until more data are available, thorough consideration must be used to identify appropriate candidates for VA-ECMO support to avoid unnecessary use, which might consume resources and expose patients to possible complications.

General reflections on mechanical circulatory support

Multiple open issues remain in MCS. Most important is appropriate patient selection and timing (*Figure 4*). As shown in IABP-SHOCK II, approximately 50–60% of CS patients survive without any device.[8] Inserting a device in this 50–60% will have no impact on survival or may even lead to some complications by the device itself possibly resulting in death. Among the 40–50% not surviving, there may also be futile situations where even the best available device will not be able to change clinical outcome. This futile situation may occur in the range of 25–35% for patients with severe CS or those with anoxic brain injury or with concomitant severe sepsis. In these, MCS may be used as a bridge-to-decision strategy and discussion with relatives for a patient-centred decision. This futile situation has been argued by MCS device supporters to explain the neutral results in the IMPRESS-in-Severe-Shock trial.[79] However, with 50% survival similar to other trials in CS and a lack of any effect in lactate the lack in efficacy is not fully explained. Based on these reflections it may be estimated that 15–25% of CS patients might be appropriate candidates for MCS (*Figure 4*). If scores, as described above and in *Table 2*, patient age, comorbidities, haemodynamic or laboratory parameters may be helpful for patient selection remains undetermined.

Mechanical circulatory support device supporters often argue that initiation of MCS before revascularization is crucial to allow adequate LV unloading ideally before the state of full hemometabolic CS has developed.[79] Observational data support this assumption with lower mortality if Impella insertion was performed in CS before revascularization. However, these registry data are

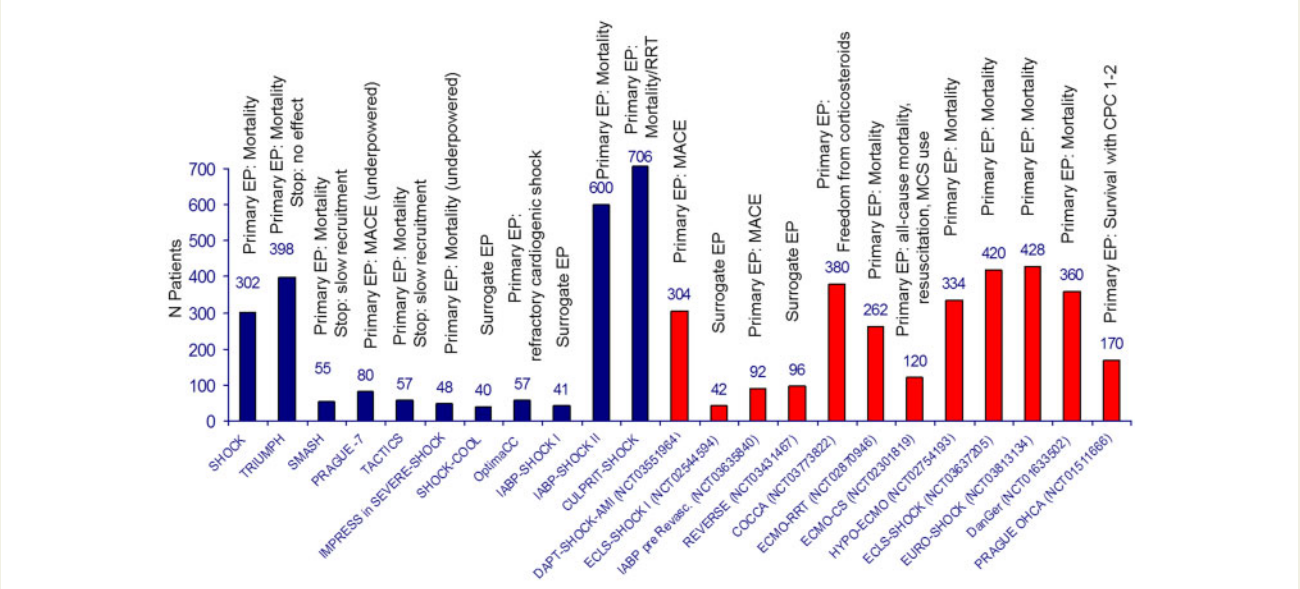


Figure 5 Number of patients included in major randomized cardiogenic shock trials. Blue bars indicate finalized and published trials. Red bars indicate ongoing or planned randomized trials. In parentheses is the clinicaltrials.gov number if available. Access date on clinicaltrials.gov was 11 March 2019. Acronyms and tested strategy of ongoing or planned randomized trials: CPC, cerebral performance category; COCCA, low dose corticosteroid therapy (hydrocortisone and fludrocortisone) vs. placebo in cardiogenic shock; DanGer, Impella CP vs. control in cardiogenic shock complicating myocardial infarction; DAPT-SHOCK-AMI, multicentre randomized double blind trial comparing intravenous cangrelor and oral ticagrelor in patients with acute myocardial infarction complicated by initial cardiogenic shock and treated with primary angioplasty; EP, endpoint; ECMO-CS, VA-ECMO vs. control in cardiogenic shock complicating myocardial infarction; ECMO-RRT, VA-ECMO plus routine renal replacement therapy vs. VA-ECMO and standard of care in cardiogenic shock; ECLS-SHOCK, VA-ECMO vs. control in severe cardiogenic shock complicating myocardial infarction; ECLS-SHOCK I, VA-ECMO vs. control in cardiogenic shock complicating myocardial infarction; EURO-SHOCK, VA-ECMO vs. control in cardiogenic shock complicating myocardial infarction; HYPO-ECMO, VA-ECMO with moderate hypothermia vs. VA-ECMO with normothermia in cardiogenic shock; IABP pre Revasc, IABP pre revascularization vs. control in cardiogenic shock complicating acute myocardial infarction; MACE, major adverse cardiac event; PRAGUE OHCA, VA-ECMO vs. control in refractory out-of-hospital cardiac arrest; REVERSE, VA-ECMO with Impella CP vs. VA-ECMO alone in cardiogenic shock; RRT, renal replacement therapy.

prone to bias.[80] Randomized trials of MCS insertion should take this into account to prevent from discussions afterwards if an adequately powered randomized trial might turn out to be negative. In addition, it has now been suggested that MCS are subject to a learning curve and device experience to optimize outcomes which may play a role for centre selection in a randomized trial.[80]

Appropriate patient selection is also influenced by the balance between efficacy, institutional experience, and device-related complications. Furthermore, frequency of MCS use and different MCS selection is also based on country-specific reimbursement scenarios. Devices with low complication rates may be chosen more liberally in early stages of CS, whereas more aggressive devices may be reserved for more severe CS. The optimal support has also not been determined for various CS stages. The relation of these considerations is depicted in the right upper panel of *Figure 4*.

Currently, three randomized trials are ongoing or in the early phase of patient recruitment powered to show a mortality benefit for MCS (one Impella CP, two VA-ECMO) in comparison to control (*Figure 5*).

Current guidelines recommend considering the use of percutaneous MCS in selected patients depending on patient age, comorbidities, and neurological function in particular in refractory CS without any preference for device selection (IIa C recommendation).[15,37,38]

Future perspectives

In general, randomized clinical trials in CS are difficult to perform and only three randomized trials adequately powered to detect differences in clinical outcomes achieved completion of the required number of patients (*Figure 5*).[8,9,13] Based on the SHOCK trial, early revascularization has been adopted into clinical practice leading to a relevant reduction in mortality. The IABP-SHOCK II and CULPRIT-SHOCK trials challenged common assumptions and led to rapid changes in guideline recommendations. However, despite major advances in PCI technique and antithrombotic pharmacology during the approximately 20 years between the SHOCK trial and these two trials the 30-day mortality of CS remained nearly unchanged in the range of 40–50%. Obviously, this is disappointing and research efforts and also public and industry funding should be directed more rigorously to CS. Despite indisputable complexities of performing clinical studies in CS, it has now been repeatedly shown that such trials can be successfully performed. International activities may be required to build large CS research networks to answer the multiple open questions in treatment as reflected by the high number of recommendations with

a level of evidence C in current guidelines.[15,37,38] The recent increase in registered randomized trials (*Figure 5*) in the setting of CS indicates that efforts are pointing into the right direction and may lead to an improvement in short and long-term outcome.

Conflict of interest: none declared.

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