Clinical update

Management of cardiogenic shock

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Received 30 December 2014; revised 4 February 2015; accepted 11 February 2015; online publish-ahead-of-print 2 March 2015

Cardiogenic shock (CS) remains the most common cause of death in patients with acute myocardial infarction although mortality could be reduced from formerly ~80% to 40–50%. In addition to percutaneous coronary intervention or coronary artery bypass grafting, catecholamines, fluids, intraaortic balloon pumping (IABP), and also active assist devices are widely used for CS management. However, there is only limited evidence for any of the above treatments except for early revascularization and the relative ineffectiveness of IABP. This updated review will therefore outline the management of CS complicating acute myocardial infarction with major focus on evidence-based revascularization techniques, intensive care unit treatment including ventilation, transfusion regimens, adjunctive medication, and mechanical support devices.

Introduction

Cardiogenic shock (CS) is defined as a state of critical endorgan hypoperfusion due to reduced cardiac output. Notably, CS forms a spectrum that ranges from mild hypoperfusion to profound shock. Established criteria for the diagnosis of CS are: (i) systolic blood pressure < 90 mmHg for > 30 min or vasopressors required to achieve a blood pressure ≥ 90 mmHg; (ii) pulmonary congestion or elevated left-ventricular filling pressures; (iii) signs of impaired organ perfusion with at least one of the following criteria: (a) altered mental status; (b) cold, clammy skin; (c) oliguria; (d) increased serum-lactate. The diagnosis of CS can usually be made on the basis of easy-to-assess clinical criteria without advanced haemodynamic monitoring although it has previously been recommended to assess cardiac index and pulmonary capillary wedge pressure.1

Acute myocardial infarction (AMI) with subsequent ventricular dysfunction is the most frequent cause of CS accounting for ~80% of cases. Mechanical complications such as ventricular septal (4%) or free wall rupture (2%), and acute severe mitral regurgitation (7%) are less frequent causes of CS after AMI.2 Non-AMI-related CS may be caused by decompensated valvular heart disease, acute myocarditis, arrhythmias, etc. with heterogeneous treatment options.

Cardiogenic shock complicating AMI occurs in the range from 5 to 15%.3–5 This translates in ~40 000 to 50 000 patients per year in the USA and ~60 000 to 70 000 in Europe.6 Despite advances in treatment mainly by early revascularization with subsequent mortality reduction, CS remains the leading cause of death in AMI with mortality rates still approaching 40–50% according to recent registries and randomized trials.3–5,7

The underlying causes, the pathophysiology, and treatment of CS complicating AMI have been reviewed previously.1,6 This update will outline evidence-based therapeutic management of CS complicating AMI with major focus on revascularization techniques, intensive care unit treatment including ventilation, transfusion regimens, adjunctive medication, and mechanical support devices.

Pathophysiology and prognosis assessment

The pathophysiology of CS is complex and has been summarized previously.1,6 In brief, ischaemia induces profound depression of myocardial contractility, which initiates a vicious spiral of reduced cardiac index and low blood pressure which in combination impair cardiac power index and further promote coronary ischaemia. The reduction in cardiac index causes severe tissue hypoperfusion which is most sensitively measured by serum lactate and may finally lead to death if the circle is not successfully interrupted by adequate treatment measures. It has been recognized that CS cannot only be attributed to the loss of left-ventricular function but is rather the result of derangements in the entire circulatory system. Initial compensatory vasoconstriction is subsequently counteracted by pathological vasodilation. Among others, development of systemic...
inflammation with capillary leakage, impairment of microcirculation, and vasodilation contribute to the vicious circle of CS. Bleeding and transfusion further contribute to inflammatory derangements in the shock spiral.

By multivariable modelling from the major CS trials (SHOCK, TRIUMPH, IABP-SHOCK II), typical factors associated with higher mortality were older age, anoxic brain damage, lower left-ventricular ejection fraction, lower cardiac power index, lower systolic blood pressure, need for vasopressor support, worse renal function, and higher serum lactate.8–10 Multiple other biomarkers in addition to serum lactate mainly measuring the degree of inflammation have shown an association with mortality.11 The impairment of microcirculation and vascular leakage is influenced by an imbalance between angiopoietin-1 and angiopoietin-2 which has been shown to impact mortality.12 In CS, microcirculatory impairment can easily be measured sublingually by sidestream darkfield imaging. A diminished perfused capillary density at baseline and a lack of improvement derived from serial measurements was associated with dismal prognosis.13 However, the clinical value of these new biomarkers and imaging methods has not yet been finally defined.

**Management**

**Revascularization**

Early revascularization as shown in the SHould we emergently revascularize Occluded Coronaries for cardiogenic shock (SHOCK) trial is the most important treatment strategy in CS complicating AMI.14 Although the trial failed to meet the primary endpoint (superiority of early revascularization over medical therapy on 30-day mortality) there was a significant mortality reduction at longer follow-up of 1/2, 1, and 6 years.14,15 The number needed to save one life by early revascularization in comparison to initial medical stabilization is <8. In current guidelines, early revascularization by either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) is a class I recommendation.16,17 Even though application of early revascularization has markedly increased in clinical practice, rates are still unsatisfactory ranging from 50 to 70% in registries.3-5 Therefore, more efforts are needed to convince clinicians to recognize the benefit of revascularization even if the associated risk is anticipated to be high such as in the elderly or following resuscitation.

**Revascularization in multivessel coronary artery disease**

Approximately 70–80% of patients with CS present with multivessel disease defined as coronary stenoses/occlusions in more than one vessel.7,14,18 These patients have a higher mortality compared with patients with single- vessel disease.19 Current guidelines, recommend early revascularization by PCI or CABG depending on coronary anatomy and amenability to PCI.16 Theoretically, the type of revascularization might influence outcome. However, there is much uncertainty because all previous trials assessing the effect of revascularization on outcome did not specify the type of reperfusion. Currently, there are only four observational reports evaluating PCI vs. CABG and the limited data suggest similar mortality rates with CABG and PCI.20 Despite these considerations, CABG is rarely performed in CS with rates <5% in registries and randomized trials. 5,7 Therefore, PCI of the culprit lesion is accepted standard practice, whereas optimal management of additional non-culprit lesions is unclear. Current guidelines encourage multivessel PCI of all critical stenoses or highly unstable lesions in addition to the culprit lesion (class IIa B recommendation) in CS.16 Despite these guideline recommendations, multivessel PCI is currently performed in only one-third to one-fourth of CS patients with multivessel disease.7,21 Due to the lack of prospective data, these recommendations are mainly based on pathophysiological considerations. Notably as shown in Table 1, all registries except one comparing multivessel PCI vs. culprit lesion only PCI showed a numerically or significant increased mortality for the multivessel approach.18,21–26 Since non-randomized observational studies and registries are prone to treatment-selection bias, there is an urgent need for randomized data. Currently, the prospective, randomized, multicentre CULPRIT-SHOCK trial (Clinicaltrials.gov: NCT01927549) is enrolling patients in Europe to fill the apparent gap of evidence. With the primary endpoint defined as mortality and/or renal failure requiring renal replacement therapy within 30 days, 706 patients will be randomized to either immediate multivessel PCI in comparison to culprit lesion only PCI with potentially subsequent staged PCI.

*Peri-interventional antiplatelet and antithrombotic medication*

Antithrombotic therapy including antiplatelets and anticoagulation is a cornerstone during PCI and since publication of the SHOCK trial novel antiplatelet therapies have emerged.16,17 There are no specific trials in CS for oral antiplatelets, however, it is well known that in CS, enteral resorption is impaired. Besides impaired enteral perfusion, mechanical ventilation with inability to swallow prasugrel/ticagrelor or clopidogrel plays a major role for the bioavailability of these drugs. In general, administration of oral P2Y12-inhibitors may be deferred, as CABG may immediately be necessary based on angiographic findings. Prasugrel/ticagrelor or clopidogrel in case of contraindications for the newer oral antiplatelets is indicated in addition to aspirin in all patients undergoing PCI.16,17 In intubated patients, crushed tablets need to be administered through a nasogastric tube. Recently, it could be shown in non-CS infarction patients that crushed ticagrelor can improve platelet inhibition in comparison to non-crushed tablets.27 It is well known that restoration of normal epicardial flow by PCI in CS is lower in comparison to non-CS patients and failure to achieve a normal flow impacts mortality.28 Because of the late and impaired onset of oral antiplatelets glycoprotein IIb/IIIa-inhibitors may be beneficial in CS. Observational data support a potential mortality benefit by use of intravenous platelet inhibitors in CS.29 However, in the CS setting, 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 abciximab use is superior in comparison to standard treatment with optional abciximab use left at the discretion of the interventionists (Figure 1).30 Current considerations and experience suggest a liberal use of glycoprotein IIb/IIIa-inhibitors in patients with high thrombus burden and slow flow after PCI in particular for the CS patient.

During PCI, adjunctive anticoagulation including unfractionated heparin, low-molecular weight heparin, or direct thrombin inhibitors should be co-administered with antiplatelets.16,17 With a lack of specific randomized trials in CS, the same recommendations apply as for other types of acute coronary syndrome.
### Table 1  Mortality for multivessel vs. culprit lesion only PCI in cardiogenic shock in registries

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Mortality multivessel PCI, %</th>
<th>Mortality culprit lesion only PCI, %</th>
<th>Adjusted odds ratio or hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Webb et al. (^{18})</td>
<td>74</td>
<td>55</td>
<td>20</td>
<td>2.75 (1.05–7.25)</td>
</tr>
<tr>
<td>Van der Schaaf et al. (^{22})</td>
<td>161</td>
<td>60</td>
<td>53</td>
<td>Not reported ((P = 0.05))</td>
</tr>
<tr>
<td>Cavender et al. (^{23})</td>
<td>3087</td>
<td>36.5</td>
<td>27.8</td>
<td>1.5 (1.22–1.95)</td>
</tr>
<tr>
<td>Bauer et al. (^{21})</td>
<td>336</td>
<td>48.8</td>
<td>37.4</td>
<td>1.28 (0.72–2.28)</td>
</tr>
<tr>
<td>Zeymer et al. (^{25})</td>
<td>735</td>
<td>46.8</td>
<td>35.8</td>
<td>1.25 (1.15–1.84)</td>
</tr>
<tr>
<td>Yang et al. (^{26})</td>
<td>338</td>
<td>35.0</td>
<td>30.6</td>
<td>1.06 (0.61–1.86)</td>
</tr>
<tr>
<td>Mylotte et al. (^{24})</td>
<td>266</td>
<td>20.4</td>
<td>43.9</td>
<td>0.57 (0.38–0.84)</td>
</tr>
</tbody>
</table>

PCI, percutaneous coronary intervention; CI, confidence interval.

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**Figure 1**  Current evidence from randomized clinical trials in CS in the PCI era. The relative risk and 95% confidence intervals (CI) 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 subgroup results should be interpreted with caution. SHOCK, SHould we emergently revascularize Occluded Coronaries for cardiogenic shock; SMASH, Swiss Multicenter trial of Angioplasty for SHock; SOAP II, Sepsis Occurrence in Acutely Ill Patients II; TRIUMPH, Tilotagrine Acetate Injection in a Randomized International Study in Unstable MI Patients With Cardiogenic Shock; IABP-SHOCK, Intraaortic balloon pump in shock; IABP, intraaortic balloon pump; LVAD, left-ventricular assist device; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; CS, cardiogenic shock.
Intensive care unit treatment

Fluids, vasopressors, inotropes

Irrespective of early revascularization, the basic treatment measures include initial stabilization with volume expansion to obtain euvolaemia, vasopressors, and inotropes plus additional therapy for the prevention or treatment of multiorgan system dysfunction (MODS). Fluid administration in CS is mainly based on pathophysiological considerations.

Despite the frequent use of catecholamines which are administered in ~90% of patients in CS, there is only limited evidence from randomized trials comparing catecholamines in CS. Furthermore, despite beneficial effects on haemodynamics, there are no randomized data showing a prognostic benefit. In a randomized comparison of 1679 patients with shock including 280 CS patients with treatment with dopamine in comparison to norepinephrine was associated with significantly more arrhythmic events for the overall study cohort but with a lack of significant reduction in mortality. The predefined CS subgroup—the percentage of CS due to AMI is not reported—had lower mortality with norepinephrine (Figure 1). Therefore, when blood pressure is low, norepinephrine should be the first choice as vasopressor. In analogy to septic shock, the target mean blood pressure should be titrated to 65–70 mmHg to a higher blood pressure is not associated with beneficial outcome. The current European STEMI guidelines are partly confusing and recommend in contrast to current evidence dopamine (Ila/C recommendation) or norepinephrine (Ila/B recommendation), whereas on the other hand it is stated that norepinephrine is preferred over dopamine when the blood pressure is low.

Because catecholamines increase myocardial oxygen consumption and vasoconstrictors may impair microcirculation as well as tissue perfusion, their use should be restricted to the shortest possible duration and the lowest possible dose.

As inotropic agent, dobutamine may be given simultaneously to norepinephrine in an attempt to improve cardiac contractility which is often performed in clinical practice. Other inotropes such as levosimendan or phosphodiesterase-inhibitors are of interest in CS based on their improvement of myocardial contractility without increasing oxygen requirements and potential for vasodilation. However, as shown in a recent Cochrane review, the current evidence for inotropes and vasodilators in CS is very limited. Only four very small studies were eligible for this meta-analysis and three trials with a total of 63 participants with high overall risk of bias compared levosimendan to standard treatment (enoximone or dobutamine) or placebo. Levosimendan showed a borderline survival benefit in comparison with enoximone (Hazard ratio 0.33; 95% confidence interval 0.11–0.97; Figure 1). Only small differences in haemodynamics, length of hospital stay, and frequency of major adverse cardiac events were observed.

Optimal treatment of MODS in the intensive care unit 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 recommended. If invasive ventilation is required, lung-protective ventilation should be performed to prevent pulmonary injury. Urinary production should be measured and continuous renal replacement therapy be initiated in case of acute renal failure with clinical signs of uraemia, hydric decompensation, metabolic acidosis, and/or refractory hyperkalaemia. Moreover, optimal nutrition, glycaemic control to <11.0 mmol/L by avoiding hypoglycaemia, as well as thromboembolism and stress ulcer prophylaxis should be provided. Because much of haemodynamic management depends on optimal filling pressures pulmonary artery catheters, Pulse Contour Cardiac Output (PiCCO) or other systems should be used in all complicated courses. However, no specific randomized trial in CS has been performed with these monitoring systems.

Moderate/severe bleeding is common in patients with CS ranging from 20 to 90% depending on the definition used and also influenced by concomitant use of mechanical support devices. Formerly it was generally believed that raising haemoglobin levels via transfusion will increase oxygen delivery and thus is beneficial. However, blood transfusions in acute coronary syndromes itself increase mortality. Alterations in erythrocyte nitric oxide biology in stored blood may provide a partial explanation, leading to initial vasoconstriction, platelet aggregation, and ineffective oxygen delivery. In addition, bleeding itself as well as transfusion contribute to inflammation.

Recent trials in non-CS patients with bleeding could clearly demonstrate that a restrictive transfusion regimen can improve outcome and general accepted intensive care strategies are to avoid the correction of laboratory anomalies unless there is a clinical bleeding problem.

Hypothermia

Therapeutic hypothermia is established for out-of-hospital cardiac arrest patients with shockable rhythm to prevent brain injury and improve survival. Although in the relevant randomized hypothermia trials patients in CS were excluded, hypothermia is also generally applied for patients with CS after resuscitation. In the IABP-SHOCK II trial, more than 40% of patients were resuscitated before randomization with subsequent induced hypothermia showing the relevance of this condition in CS. Animal trials and first non-randomized human trials showed improved haemodynamics and a reduction in catecholamine use with hypothermia in CS. Application of hypothermia in non-resuscitated CS patients may also be beneficial from pathophysiological considerations with multiple beneficial targets. Currently, a randomized trial in non-resuscitated CS patients is investigating the impact of hypothermia vs. standard treatment on cardiac power index (clinicaltrials.gov: NCT01890317).

Mechanical support

To overcome the limitations of inotropes and vasopressors with limited effects to maintain adequate perfusion pressure, prevent or reverse MODS mechanical circulatory support to improve haemodynamics and outcome became appealing. Active percutaneous left-ventricular assist devices (LVAD) are used in patients not responding to standard treatment including catecholamines, fluids, intraaortic balloon pumping (IABP) and may also play a role as first line treatment. Despite an increasing number of different percutaneous devices for mechanical support in CS, data derived from randomized clinical trials on the effectiveness and safety, differential indications for different devices, and optimal timing are limited. Despite this lack of evidence, percutaneous mechanical support with active devices is increasingly being performed.

The evidence of mechanical circulatory support in CS shock has been reviewed previously. Therefore, only major advances and new considerations are covered here.
Intraaortic balloon pumping

Intraaortic balloon pumping is the most widely used device for mechanical support at stable implantation rates from 2007 to 2011 of ~50,000 per year based on a national survey in the USA. Intraaortic balloon pumping improves the diastolic and lowers the endystolic pressure without affecting the mean blood pressure. In comparison to control, IABP does not improve relevant haemodynamic parameters such as cardiac index or cardiac power index. Before 2012 and 2013, American and European guidelines supported IABP use in CS with a Class I recommendation. Based on a systematic meta-analysis, these recommendations have been downgraded to IIb B in the 2012 ESC guidelines and to IIa B in the 2013 American guidelines. Due to a lack of randomized trials, only registries with conflicting results were included in this meta-analysis and a higher mortality following IABP was observed in the PCI era. In the largest, randomized, multicentre trial in CS (IABP-SHOCK II trial), 600 patients with CS complicating AMI undergoing early revascularization were randomized to either IABP or conventional treatment. In the primary endpoint 30-day mortality (39.7 vs. 41.3%; P = 0.69), no significant difference could be observed between the two treatment groups. There were also no differences in any of the secondary endpoints such as serum lactate, renal

Figure 2  Schematic drawings of current percutaneous mechanical support devices for CS: intraaortic balloon pump (A), Impella® (B), TandemHeart™, (C) extracorporeal life support, (D) iVAC 2L™.

Table 2  Technical features of currently available percutaneous support devices

<table>
<thead>
<tr>
<th></th>
<th>iVAC 2L™</th>
<th>TandemHeart™</th>
<th>Impella® 5.0</th>
<th>Impella® 2.5</th>
<th>Impella® CP</th>
<th>ECLS (multiple systems)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catheter size (F)</td>
<td>11</td>
<td>—</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>17–21 venous 16–19 arterial</td>
</tr>
<tr>
<td>Cannula size (F)</td>
<td>17</td>
<td>21 venous 12–19 arterial</td>
<td>21</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flow (L/min)</td>
<td>Max. 2.8</td>
<td>Max. 4.0</td>
<td>Max. 5.0</td>
<td>Max. 5.0</td>
<td>Max. 2.5</td>
<td>Max. 3.7–4.0</td>
</tr>
<tr>
<td>Pump speed (rpm)</td>
<td>Pulsatile, 40 mL/beat</td>
<td>Max. 7500</td>
<td>Max. 33 000</td>
<td>Max. 51 000</td>
<td>Max. 51 000</td>
<td>Max. 50 000</td>
</tr>
<tr>
<td>Insertion/Placement</td>
<td>Percutaneous (femoral artery)</td>
<td>Percutaneous (femoral artery + vein for left atrium)</td>
<td>Peripheral surgical (femoral artery)</td>
<td>Percutaneous (femoral artery)</td>
<td>Percutaneous (femoral artery + vein)</td>
<td></td>
</tr>
<tr>
<td>LV unloading</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Anticoagulation</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Recommended duration of use</td>
<td>− 21 days</td>
<td>− 14 days</td>
<td>10 days</td>
<td>10 days</td>
<td>10 days</td>
<td>− 7 days</td>
</tr>
<tr>
<td>CE-certification</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>FDA</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Relative costs</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++ (+)</td>
</tr>
</tbody>
</table>

IABP, intraaortic balloon pumping; ECLS, extracorporeal life support system; LV, left ventricular; CE, conformité européenne; FDA, Food and Drug Administration.
function, catecholamine doses, or length of intensive care unit treatment. In addition, no subgroups could be identified with a potential advantage of IABP support. The 12-month follow-up analysis confirmed these negative findings with a mortality of 52% in the IABP vs. 51% in the control group (P = 0.91).10

Since IABP support has been in place for nearly five decades, the negative results of IABP-SHOCK II triggered some discussions. The sample size calculation was based on the assumption of a higher mortality in the control group. However, the mortality was lower than anticipated and marginally lower in comparison to other previous trials in CS despite similar baseline characteristics.14,48 Furthermore, as in all negative trials, a type II error cannot be definitely excluded. A certain cross-over rate might also have influenced the results. However, the lack of benefit for any of the investigated secondary study endpoints, the neutral results in all subgroup analyses, the lack of benefit at 12-month follow-up and in the as-treated analysis argue against any clinically meaningful IABP effect.10 Furthermore, it has been criticized that timing of IABP insertion was left to the discretion of the operator resulting in IABP insertion pre-PCI in only 13.4%.7 However, data on timing of IABP insertion derived from small registries in CS are limited and conflicting with more data even showing harm than benefit by IABP insertion before PCI.49,50 Furthermore, a randomized trial of IABP insertion prior to PCI in high-risk anterior infarction patients without CS resulted in no effect on infarct size.51

Consequently, the results of IABP-SHOCK II influenced recent ESC revascularization guidelines with a further downgrading of the IABP with a new class IIIa recommendation for the routine use in CS.16 There is currently only the indication for IABP use in mechanical complications with a IIaC recommendation.16

Percutaneous left-ventricular assist devices
Currently available devices include the TandemHeart™ (Cardiac Assist, Inc, Pittsburgh, USA) and the microaxial Impella® 2.5, 5.0, and CP systems (Abiomed Europe, Aachen, Germany). Furthermore, there is the newly available paracorporeal pulsatile device iVAC 2L® (PulseCath BV, The Netherlands). It is introduced percutaneously through the femoral artery and can provide a pulsatile support of ~2 L/min using an extracorporeal membrane pump via a 17 F cannula. When the heart is in the systolic phase, blood is aspirated from the left ventricle through the catheter lumen into the membrane pump. During the diastolic phase, the pump ejects the blood back through the catheter, subsequently opening the catheter valve and delivering the blood to the ascending aorta through the side outflow port, thereby creating an ‘extra heart beat’. The device directly unloads the ventricle by active aspiration and simultaneously creates a counter pulsating flow in the ascending aorta.

The mode of action of different devices has been described previously.6,43,44 Figure 2 shows the different devices and Table 2 provides an updated overview of technical features and left-ventricular unloading properties. With respect to evidence, since the publishing of a meta-analysis in 2009 reporting the results of the only three randomized trials comparing percutaneous LVADs (two trials TandemHeart™; one Impella® 2.5) vs. IABP, no additional randomized trials have been performed.55 Patients treated with active LVADs demonstrated higher cardiac index, higher mean arterial pressure, and lower pulmonary capillary wedge pressure. On the other hand, bleeding complications and inflammation were more frequent with LVAD therapy with no difference in 30-day mortality (Figure 1).55 Recent observational studies with the Impella® device have suggested some benefit with this device in CS. In a cross-over evaluation among patients with refractory CS, patients who were upgraded to Impella 5.0 from 2.5 had a trend to better survival at discharge.52 In the USpella registry, patients directly treated with Impella prior to PCI in CS had an overall better survival at hospital discharge compared with those treated after PCI, even when adjusting for potential confounding variables.53 For the iVAC system, no trials are available.

Extracorporeal life-support systems
Integral features of extracorporeal life support (ECLS) systems or previously called extracorporeal membrane oxygenators are the blood pump, the heat exchanger, and an oxygenator.54 Main drawbacks of these devices are large cannula sizes potentially causing lower limb ischaemia and bleeding complications, frequent requirement of perfusionists, lack of direct left-ventricular unloading, rise in afterload, and a limited support time. Furthermore, complications are substantial with lower extremity ischaemia (16.9%), compartment syndrome (10.3%), amputation (4.7%), stroke (5.9%), major bleeding (40.8%), and significant infection (30.4%) as shown in a recent meta-analysis of 1866 CS patients.56 Complication rates may be lowered by greater experience in percutaneous implantation and by obligatory insertion of an antegrade perfusion cannula. Advantages are the low costs in comparison to other percutaneous LVADs and the high flow (Table 2). There is limited experience in CS for percutaneous use for venoarterial ECLS with one single-centre, non-randomized retrospective analysis showing improved survival rates with ECLS in comparison to historical control.55 In a more recent prospective report, in-hospital mortality of ECLS patients was as high as 63.2%. The elderly patient group of > 62 years and those with cardio-pulmonary resuscitation were even characterized by a mortality of 100% questioning the unselective use of ECLS.56
Open questions of mechanical support

Multiple open issues remain in mechanical device therapy such as optimal timing of device insertion. A potential benefit of an early use at onset of CS could be prevention of MODS. However, early use might lead to complications associated with invasive mechanical support devices, leading to adverse clinical outcome in patients who still had non-invasive therapeutic options. Furthermore, appropriate patient selection is important and currently often based on subjective criteria. Approximately 60% of CS patients will survive without any active device as shown in IABP-SHOCK II.7 There may also be futile situations where even the best device available will not be able to change clinical outcome. Timing and appropriate patient selection is also influenced by the balance between efficacy of any device and its device-related complications. Devices with low complication rates may be chosen more liberally in the early stage of CS, whereas more aggressive devices with higher flow rates may be reserved for more severe CS. The optimal support has also not been determined. The relation of these considerations is depicted in Figure 3.

An ongoing Danish randomized multicentre trial (DanShock; Clinicaltrials.gov: NCT01633502) compares the Impella® CP with standard treatment and may further answer if an active device implanted on a routine basis can reduce mortality. Several other devices are currently under investigation to obtain CE-approval in Europe such as the HeartMate PHP® (Percutaneous Heart Pump; Thoratec, Pleasanton, CA, USA).

Despite all these uncertainties, current European and American guidelines recommend considering the use of a percutaneous assist device for circulatory support in refractory CS without any preference for device selection (IIa/C recommendation).16,17,46

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**Figure 4** Treatment algorithm for patients with cardiogenic shock complicating acute myocardial infarction. The class of recommendation and level of evidence according to ESC guidelines is provided if available.16,17 IABP, intraaortic balloon pump.
Summarizing current evidence and ESC guideline recommendations for CS management, a treatment algorithm reflecting clinical practice is shown in Figure 4. Further details on treatment of mechanical complications would be beyond the scope of this review and have been summarized previously.

Figure 5 Number of patients included in major randomized cardiogenic shock trials.

Future perspectives

Randomized clinical trials in CS are difficult to perform and only few randomized clinical trials powered to detect differences in clinical outcomes achieved completion of the required patient number (Figure 5). The SHOCK trial was a milestone and the subsequent widespread application of early revascularization led to a significant reduction in mortality in clinical practice. The failure of IABP in the IABP-SHOCK II trial should not be considered as the end of device therapy itself, it may even more be the seminal trial for the generation of adequate evidence in device therapy. Cardiovascular research today is investigating nearly any open question and this should also be applied more rigorously for CS. Future studies assessing any drug, intervention, strategy, or support device need therefore to be judged according to their clinical efficacy. Cardiovascular researchers should not generally preclude performing these important randomized trials because a treatment has been adopted for several decades. Several guidance documents make recommendations with regard to enrolling patients into randomized trials who are not themselves able to give informed consent. There are multiple open questions in CS treatment as reflected by the high number of recommendations with a level of evidence C in current guidelines. This should be the motivation for future research in CS.

Conflict of interest: none declared.

References


before versus after primary percutaneous coronary intervention for cardio-


