Management of cardiogenic shock complicating acute myocardial infarction

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Abstract
Cardiogenic shock complicates approximately 5–10% of cases with acute myocardial infarction and carries a poor prognosis. Early revascularization remains the cornerstone treatment of cardiogenic shock complicating myocardial infarction. Inotropic and/or vasopressor agents can be used for haemodynamic stabilization, although this comes at the expense of increased myocardial oxygen consumption and extended myocardial ischaemia. In recent years, the use of mechanical circulatory support has significantly increased. However, there is only limited data available from randomized trials evaluating the different percutaneous support systems. This review summarizes the available literature concerning the management of cardiogenic shock and gives an overview of the recommendations of the European and German–Austrian guidelines on cardiogenic shock.

Keywords
Cardiogenic shock, myocardial infarction, mechanical circulatory support

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Introduction
Cardiogenic shock is the inability of the heart to deliver an adequate amount of blood to the tissues and is defined by both haemodynamic and clinical criteria. Haemodynamic criteria include persistent hypotension (systolic blood pressure < 90 mmHg or mean arterial pressure 30 mmHg lower than baseline) with severe reduction in cardiac index (< 1.8 l/min/m² without support or < 2.0 to 2.2 l/min/m² with inotropic support) and adequate or elevated filling pressures (left ventricular end-diastolic pressure >18 mmHg or right ventricular end-diastolic pressure >10 to 15 mmHg). Hypoperfusion may be manifested clinically by cool extremities, decreased urinary output and/or alteration in mental status. Most cases of cardiogenic shock after acute myocardial infarction (AMI) are due to left ventricular pump failure. Other causes include right ventricular infarction and mechanical complications of myocardial infarction.

There is currently only limited evidence from randomized trials to guide our therapy of patients in cardiogenic shock. This review gives an overview of the available literature concerning the management of cardiogenic shock and relates these data to the recommendations of the European Society of Cardiology (ESC). This article also includes the German–Austrian S3 guideline on cardiogenic shock, providing the first dedicated guideline for the treatment of AMI-related cardiogenic shock.

Incidence and mortality of cardiogenic shock
Cardiogenic shock complicates approximately 5–10% of cases with acute myocardial infarction. Although a number of studies reported an increased incidence of AMI-related...
cardiogenic shock, other studies have described a decline in the incidence of cardiogenic shock during the last decade. In the ‘Acute Myocardial Infarction in Switzerland’ (AMIS) Plus registry, there was an association between increased use of percutaneous coronary intervention (PCI) and decreased development of cardiogenic shock during hospitalization, suggesting that early PCI can decrease the rate of cardiogenic shock development after hospital admission. Not only PCI but also early administration of thrombolysis may reduce the risk of in-hospital development of cardiogenic shock in STEMI patients. In the DANAMI-2 trial, there was no difference in the proportion of STEMI patients developing cardiogenic shock between PCI and thrombolysis. These data indicate that revascularization by PCI or thrombolysis should be performed as early as possible to reduce the incidence of cardiogenic shock.

Cardiogenic shock is the leading cause of death in patients hospitalized with acute myocardial infarction. Several studies have described a decline in the mortality of cardiogenic shock. However, the mortality of cardiogenic shock remains high, with an early mortality of approximately 40%. It is important to note that survivors of cardiogenic shock have a long-term outcome similar to patients without cardiogenic shock. In addition, at one year, many survivors of cardiogenic shock have a good functional status. These findings underline the importance of improving early survival of patients in cardiogenic shock.

**Early revascularization**

The most important therapy in AMI-related cardiogenic shock is early revascularization. In the ‘Should we emergently revascularize Occluded Coronaries for Cardiogenic Shock’ (SHOCK) trial, patients with cardiogenic shock were randomly assigned to initial medical stabilization or early revascularization (Table 1). The protocol specified that patients randomized to early revascularization should have either PCI or coronary artery bypass grafting (CABG) within 6 h of randomization and 18 h of onset of shock. In the majority of patients undergoing PCI, only balloon angioplasty of the infarct-related coronary artery was performed. In the medical stabilization group, approximately two-thirds of the patients received fibrinolytic therapy, and 25% underwent delayed revascularization. Although the primary endpoint, all cause mortality at 30 days, did not differ between the initial medical stabilization and early revascularization group, there was a significant decrease in mortality after one and six years in patients assigned to early revascularization. To save a life, fewer than eight patients survived.

<table>
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<th>Intervention</th>
<th>Study population</th>
<th>Results</th>
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<tr>
<td>Early revascularization</td>
<td>Cardiogenic shock (N = 302)</td>
<td>Decrease in one and six year mortality.</td>
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<tr>
<td>Early revascularization versus initial medical stabilization</td>
<td>Cardiogenic shock (N = 55)</td>
<td>No difference in 30 day mortality.</td>
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**Inotropic and vasopressor agents**

- Dopamine versus noradrenaline: Increased incidence of arrhythmias in dopamine group.
- Epinephrine versus noradrenaline and dobutamine: Increased rate of arrhythmias, a decrease in splanchnic blood flow and an increase in blood lactate levels in epinephrine group.
- Levosimendan versus enoximine: Decrease in 30-day survival in levosimendan group.
- Levosimendan versus dobutamine: No difference in one-year mortality.

**NO synthase inhibition**

- Tilarginine versus control: No difference in 30-day mortality.

**Mechanical circulatory support**

- IABP versus control: Reduction in BNP levels in IABP group. No difference in MODS or early mortality.
- IABP versus control: No difference in 30-day or one-year mortality.
- TandemHeart versus IABP: Improved haemodynamics in TandemHeart group. No difference in 30-day mortality.
- TandemHeart versus IABP: Improved haemodynamics in TandemHeart group. No difference in 30-day mortality.
- Impella versus IABP: Improved haemodynamics in Impella group. No difference in 30-day mortality.

NO: nitric oxide; BNP: brain natriuretic peptide; IABP: intra-aortic balloon pump; MODS: multi-organ dysfunction syndrome
patients needed to be treated by early revascularization in comparison with initial medical stabilization. The ‘Swiss Multicentre trial of Angioplasty for Shock’ (SMASH) trial showed a similar effect of early revascularization, but this effect was non-significant because the trial was stopped prematurely due to slow enrolment\textsuperscript{20} (Table 1).

Coronary revascularization should be performed as soon as possible after AMI and shock onset. In the SHOCK trial, there was an increasing long-term mortality as time to revascularization increased from 0 to 8 h.\textsuperscript{15} However, the time window for benefit of revascularization in the setting of cardiogenic shock may be more prolonged and may extend beyond the usually accepted 12-h post-myocardial infarction window.\textsuperscript{31} There appears to be a survival benefit of revascularization even as long as 54 h after myocardial infarction and 18 h after shock onset.\textsuperscript{19}

Cardiogenic shock may occur in the setting of ST-elevation myocardial infarction (STEMI) as well as non-ST-elevation myocardial infarction (NSTEMI). In a recent registry, cardiogenic shock occurred in 12% of patients with STEMI versus 4% of patients with NSTEMI.\textsuperscript{32} Compared with STEMI, there was a longer time delay to revascularization and a higher adjusted mortality rate in patients with NSTEMI-related cardiogenic shock.\textsuperscript{32} The lower use of revascularization in NSTEMI patients could be related to the greater burden of comorbidities in this patient population. Nevertheless, data support early revascularization for these high-risk patients with NSTEMI.\textsuperscript{33,34}

**Should we use thrombolysis, PCI or CABG for early revascularization?**

Among patients assigned to initial medical stabilization in the SHOCK trial, thrombolytic therapy was associated with an improved 12-month survival.\textsuperscript{35} However, thrombolysis alone results in relatively low rates of reperfusion in patients in whom shock is already established.\textsuperscript{36} Consequently, triage and immediate transfer to a PCI-capable facility with on-site cardiac surgical backup is recommended for patients with AMI-related cardiogenic shock. For patients in cardiogenic shock with long delays for PCI (> 90 min) and presenting early after symptom onset (< 3 h), the German–Austrian guideline\textsuperscript{4} recommends that early (preferably prehospital) administration of fibrinolytic therapy followed by emergent transfer to a PCI facility should be considered (Table 2; Figure 1).

So far, there exist no randomized clinical trials that have compared PCI and CABG in patients with cardiogenic shock. In the SHOCK trial, the protocol recommended CABG in patients with a left main coronary stenosis of $\geq 50\%$, $\geq 2$ total or subtotal occlusions, stenosis of $> 90\%$ in two non-infarct-related major arteries, or stenosis unsuitable for PCI, as well as in patients whose PCI was unsuccessful.\textsuperscript{18} However, this decision was made on a case-by-case basis by site investigators and PCI was performed in many patients with three vessel disease. Among the 128 patients receiving emergency revascularization, PCI and CABG were performed in 63% and 37% of the cases, respectively.\textsuperscript{37} There was a similar mortality at 30 days, one year and six years for CABG compared with PCI in patients with cardiogenic shock, despite a longer time from symptom onset to revascularization and a greater prevalence of diabetes mellitus, left main disease and three-vessel disease among patients undergoing CABG.\textsuperscript{37} In a recent registry, there was a trend towards better survival with CABG for patients with cardiogenic shock complicating myocardial infarction compared with PCI.\textsuperscript{38} In another observational study of patients with multivessel disease and cardiogenic shock, there was a significant reduction in 30-day mortality when CABG was performed after PCI.\textsuperscript{39}

In the current European guidelines,\textsuperscript{2} AMI-related cardiogenic shock is considered as a class IB indication for emergency revascularization with either PCI or CABG if the patient has suitable coronary anatomy (Table 2). However, very few patients with cardiogenic shock and three-vessel disease are referred for CABG, ranging from 3.2\% to 8.8\%,\textsuperscript{37} possibly reflecting the logistical difficulties of arranging emergency CABG for patients with cardiogenic shock, especially at night or during weekends.

The mortality of patients in cardiogenic shock is strongly related to the procedural success of PCI. Lack of procedural success (post-PCI Thrombolysis In Myocardial Infarction (TIMI) flow grades 0 to 2 in the infarct related artery) is associated with a higher risk of mortality.\textsuperscript{40,41} Importantly, patients with cardiogenic shock have a lower likelihood of successful PCI than patients without shock.\textsuperscript{40–42} For example, a German registry study of 1333 patients with cardiogenic shock reported that PCI achieved TIMI 3 flow in 76\% of patients.\textsuperscript{41} During the last decade, there have been many advances in PCI, including stenting and adjunctive use of glycoprotein IIb/IIIa inhibitors. In the SHOCK trial, only 37\% of patients received stents, and only 69\% received abciximab. Compared with balloon angioplasty, the use of bare-metal stents in cardiogenic shock is associated with a greater likelihood of complete revascularization, a higher incidence of TIMI 3 flow and improved survival.\textsuperscript{43–45}

Although several studies have also shown the safety and efficacy of drug-eluting stents in acute coronary syndromes,\textsuperscript{46,47} there are only limited data concerning the use of drug-eluting stents in cardiogenic shock. In a recent retrospective, propensity-matched study,\textsuperscript{48} the use of drug-eluting stents was associated with a decrease in mortality in patients with cardiogenic shock as compared with bare metal stents. Additional studies are necessary to investigate the safety of drug-eluting stents in cardiogenic shock.

In conclusion, PCI allows prompt restoration of coronary flow in patients with cardiogenic shock. However, the German–Austrian guideline\textsuperscript{4} recommends that urgent CABG should also be considered in the case of non-successful PCI, left main disease, three-vessel disease, or in...
the presence of severe valvular disease and mechanical complications of myocardial infarction (Table 2; Figure 1).

Antithrombotic treatment

In patients with cardiogenic shock, antithrombotic therapy with aspirin and heparin should be given as routinely recommended in acute coronary syndromes. However, the loading dose of clopidogrel may be deferred until the results of coronary angiography are available, because urgent CABG may be necessary (Figure 1). In cardiogenic shock, the new P2Y12 receptor inhibitors prasugrel and ticagrelor are commonly preferred over clopidogrel because they have a faster onset of action and provide stronger and more consistent platelet inhibition. In a recent registry, the use of prasugrel in AMI-related cardiogenic shock was associated with a lower mortality as compared with clopidogrel without an increase in the risk of bleeding.49 However, even the new P2Y12

<table>
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<tr>
<th>Table 2. Overview of European2,3 and German–Austrian4 guidelines for patients with AMI-related cardiogenic shock.</th>
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<tbody>
<tr>
<td>Intervention</td>
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<tr>
<td>---------------------------------------------------------------</td>
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<tr>
<td>Early revascularization</td>
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<tr>
<td>• European guidelines</td>
</tr>
<tr>
<td>- Emergency revascularization with either PCI or CABG in suitable patients must be considered.</td>
</tr>
<tr>
<td>- Fibrinolysis should be considered if revascularization is unavailable.</td>
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<tr>
<td>• German–Austrian guideline</td>
</tr>
<tr>
<td>- The infarct vessel should be revascularized as soon as possible, usually by means of PCI, in patients in the initial phase of shock within 2 h from first medical contact, otherwise as early as possible.</td>
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<tr>
<td>- If patients with infarct-related cardiogenic shock present within 3 h of symptom onset and PCI cannot be performed within 90 min, systemic thrombolytic therapy should be given before PCI.</td>
</tr>
<tr>
<td>- CABG shall be considered in the case of non-successful PCI, left main disease, three-vessel disease, or in the presence of severe valvular disease and mechanical complications of myocardial infarction.</td>
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<tr>
<td>Vasoactive agents</td>
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<tr>
<td>• European guidelines</td>
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<tr>
<td>- In cardiogenic shock, inotropic/vasopressor agents should be considered:</td>
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<tr>
<td>o Dopamine</td>
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<tr>
<td>o Dobutamine</td>
</tr>
<tr>
<td>o Noradrenaline (preferred over dopamine when blood pressure is low).</td>
</tr>
<tr>
<td>• German–Austrian guideline</td>
</tr>
<tr>
<td>- Dobutamine should be given as inotropic drug.</td>
</tr>
<tr>
<td>- Noradrenaline should be used as vasopressor.</td>
</tr>
<tr>
<td>- In cases of catecholamine-refractory cardiogenic shock, levosimendan is preferred over phosphodiesterase III inhibitors (enoximine).</td>
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<tr>
<td>- Dopamine shall not be used in cardiogenic shock.</td>
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<tr>
<td>- Adrenaline can be used if haemodynamic stabilization cannot be obtained with dobutamine and noradrenaline.</td>
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<tr>
<td>Mechanical circulatory support</td>
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<tr>
<td>• European guidelines</td>
</tr>
<tr>
<td>- IABP insertion should be considered in patients with cardiogenic shock due to mechanical complications.</td>
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<tr>
<td>- Short-term mechanical circulatory support may be considered.</td>
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<tr>
<td>- Routine use of IABP is not recommended.</td>
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<tr>
<td>• German–Austrian guideline</td>
</tr>
<tr>
<td>- In patient undergoing fibrinolytic therapy, IABP should be carried out adjunctively.</td>
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<tr>
<td>- In patients undergoing PCI, IABP may be considered, but the available evidence is unclear.</td>
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Level of evidence in the German–Austrian guideline: ↑↑: high-quality systematic reviews of randomized controlled trials (RCTs) or RCTs with a very low risk of bias; ↑+: well performed systematic reviews of RCTs or RCTs with a low risk of bias; ↑: high-quality systematic reviews of case–control or cohort studies with very low risk of confounders or bias and a high probability of causal relationships; 2+: well performed systematic reviews of case–control or cohort studies with a low risk of confounders or bias and a moderate risk of noncausal relationships; 3: nonanalytic studies; 4: consensus opinion of experts based on studies and clinical experience or in the interests of patients’ safety. Level of recommendation in the German–Austrian guideline: ↑↑: strongly recommended (‘shall’); ↑: recommended (‘should’); ↔: no recommendation (no confirmed study results exist that demonstrate either a beneficial or a harmful effect); ↓: rejected (‘should not’); ↓↓: strongly rejected (‘shall not’). AMI: acute myocardial infarction; CABG: coronary artery bypass graft; PCI: percutaneous coronary intervention; IABP: intra-aortic balloon pump Adapted from the guidelines of the European Society of Cardiology for management of acute myocardial infarction in patients presenting with ST-segment elevation5 and myocardial revascularization, and the German–Austrian S3 guideline for myocardial infarction-related cardiogenic shock.4
receptor inhibitors ticagrelor and prasugrel exhibit an initial delay in the onset of their antiplatelet action. Approximately 50% of STEMI patients have a high residual platelet reactivity 2 h after a loading dose of prasugrel or ticagrelor, and at least 4 h are required to achieve a sufficient drug effect. This effect may even be more pronounced in patients in cardiogenic shock who have an impaired intestinal absorption that can limit drug bioavailability. Consequently, the effect of even the new P2Y12 agents may not be sufficient in cardiogenic shock. In this regard, cangrelor might be a valuable alternative agent. Although not yet licensed for clinical use, cangrelor is a fast-acting and rapidly reversible parenteral P2Y12 inhibitor. In addition, the plasma half-life of cangrelor is approximately 3 to 5 min, and platelet function is restored within 1 h after cessation of the infusion. Additional studies are necessary to investigate the potential of cangrelor in patients with cardiogenic shock.

Glycoprotein IIb/IIIa inhibitors have a rapid onset of action and a very potent inhibitory effect on platelets. Several trials, performed before the routine use of dual antiplatelet therapy (DAPT), had documented clinical benefits of glycoprotein IIb/IIIa inhibitors as adjuncts to primary PCI. However, in the era of DAPT with high-loading doses of clopidogrel, a net benefit for glycoprotein IIb/IIIa inhibitors has not been uniformly reported. In a study of 80 patients with cardiogenic shock undergoing primary PCI, the routine use of pre-procedural abciximab was not associated with an improved outcome when compared with selective abciximab use during the intervention. According to the European STEMI guidelines, GP IIb/IIIa inhibitors are only recommended as bailout therapy for thrombotic complications during PCI (class IIa/C) and the routine use of glycoprotein IIb/IIIa inhibitors has been assigned a class IIb/B recommendation in STEMI patients without contraindications and undergoing PCI with unfractionated heparin. However, in view of the delayed absorption of orally administered P2Y12 inhibitors and the increased risk of stent thrombosis in cardiogenic shock, the use of glycoprotein IIb/IIIa antagonists may be considered to obtain

Figure 1. Algorithm for early revascularization in patients with cardiogenic shock complicating acute myocardial infarction.

AMI: acute myocardial infarction; STEMI: ST-elevation myocardial infarction; CABG: coronary artery bypass graft; PCI: percutaneous coronary intervention
rapid platelet inhibition in patients with cardiogenic shock (Figure 1).

**Thrombus aspiration**

Clinical trials have shown conflicting results regarding the beneficial effects of thrombus aspiration in acute coronary syndromes. In the ‘Thrombus Aspiration during Percutaneous Coronary Intervention in Acute Myocardial Infarction Study’ (TAPAS), thrombus aspiration was associated with an improved myocardial reperfusion and one-year survival. However, in the ‘Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia’ (TASTE) trial, there was no evidence of a mortality benefit for systematic thrombus aspiration prior to PCI for STEMI. In AMI-related cardiogenic shock, there is no evidence of a mortality benefit for systematic thrombus aspiration. In a retrospective study of patients with STEMI-related cardiogenic shock, thrombus aspiration was associated with a lower rate of in-hospital and long-term mortality. Additional studies are necessary to investigate the potential benefit of thrombus aspiration in cardiogenic shock.

**Early revascularization in particular patient groups**

**Patients with multivessel coronary artery disease.** More than 70% of STEMI patients in cardiogenic shock have significant multivessel coronary artery disease. The optimal revascularization strategy for patients with multivessel disease and cardiogenic shock is, however, not clear. In contrast to recommendations in haemodynamically stable patients, current European guidelines recommend multivessel PCI for patients in cardiogenic shock in the presence of multiple, truly critical (≥90% diameter) stenoses or highly unstable lesions (angiographic signs of possible thrombus or lesion disruption) if there is persistent ischaemia after PCI of the supposed culprit lesion. An observational study in patients with multivessel disease presenting with cardiogenic shock or cardiac arrest showed that multivessel PCI was associated with an improved six month survival. In a retrospective multicentre study, complete revascularization was an independent predictor of survival to discharge in STEMI patients with multivessel coronary disease and cardiogenic shock. However, in two recent registries of patients with cardiogenic shock and multivessel disease, nonculprit PCI was not associated with a survival benefit in these patients. In the SHOCK trial, only 13.6% of patients had emergency PCI on more than one vessel. In this small subset of patients with multivessel PCI, there was a worse adjusted outcome compared with those with single-vessel PCI. In view of these conflicting results, multivessel PCI in addition to culprit lesion PCI should be considered on a case by case basis, considering the morphology of the underlying lesions, predicted success rates, presumed ischaemia at rest caused by the lesions and also the haemodynamic stability. Otherwise, a staged procedure or CABG should be considered (Figure 1). The upcoming European multicentre CULPRIT-SHOCK trial (NCT01927549) will compare culprit-vessel treatment with complete revascularization in cardiogenic shock.

**Patients with left main disease.** A significant involvement of the left main coronary artery (LMCA) occurs in 4–7% of patients presenting with AMI. Patients with LMCA-related AMI in cardiogenic shock have a high in-hospital mortality of approximately 50%. However, patients who survive to discharge have a good long-term prognosis.

Currently, there are no definitive guidelines for revascularization of patients with LMCA-related AMI in cardiogenic shock. In recent years, PCI has become the preferred mode of revascularization in these patients. This has been illustrated in the GRACE registry, where the rate of CABG in patients with LMCA-related acute coronary syndromes decreased from 45% to 25%, with a corresponding rise in the rate of PCI from 18% to 40%. Several recent studies have shown that PCI is a feasible treatment option in these patients and is a good alternative to surgical revascularization. In a recent meta-analysis of patients undergoing PCI for LMCA-related AMI, the 30-day mortality was approximately 55% in patients presenting with cardiogenic shock, compared with 15% in patients without cardiogenic shock.

There are only limited data on emergency CABG in patients with AMI-related cardiogenic shock due to significant LMCA disease. In two small Japanese studies, there was an in-hospital mortality of 75% and 53% in patients with AMI-related cardiogenic shock and significant LMCA disease who underwent emergency CABG. If the outcome data of patients with cardiogenic shock and LMCA disease in the SHOCK trial and SHOCK registry are combined, the 30-day survival rate was 40% in the surgical group compared with 16% in the PCI group. However, the small sample size (CABG, n = 6; PCI, n = 15) precludes a definitive conclusion. In addition, a treatment bias favouring performance of PCI rather than CABG in higher clinical-risk patients prohibits direct comparison between the two revascularization modalities. Patients undergoing emergency PCI are often more unstable than those undergoing CABG because their higher risk precludes surgical revascularization. In the absence of randomized trial data, the decision to perform CABG or PCI in patients with cardiogenic shock and LMCA disease is difficult, and the decision needs to be individualized, taking into consideration potential risks of each treatment strategy (Figure 1).

**Elderly patients.** In the SHOCK trial, the benefit of early revascularization was limited to patients younger than 75 years. In patients older than 75 years, there was no survival.
benefit after 30 days for early revascularization compared with initial medical stabilization. The apparent lack of benefit for the elderly in the SHOCK trial was likely due to imbalances in baseline ejection fraction between both groups. More recent studies have shown a consistent benefit of revascularization in elderly patients, indicating that advanced age alone should not be regarded as a contra-indication to invasive management.

**Which drugs should be used?**

In acute heart failure, patients can be stratified in four haemodynamic profiles by the presence of congestion (‘dry’ or ‘wet’) and the adequacy of perfusion (‘warm’ or ‘cold’). The different haemodynamic profiles not only predict prognosis, but can also guide the choice of therapy. At presentation, most patients in cardiogenic shock show signs of congestion (e.g. orthopnoea, increased jugular venous pressure). In these patients, volume loading will not result in a beneficial haemodynamic effect and inotropic support should be initiated. By contrast, in patients without signs of congestion (e.g. right ventricular infarction with an estimated central venous pressure < 15 mmHg), administration of fluids can be considered to obtain optimal cardiac filling pressures and increase cardiac output.

**Choice of fluids**

There are no randomized trials that have investigated which fluids should be used in cardiogenic shock. Consequently, the choice of fluid therapy can only be guided by trials in other types of shock. Colloids, such as hydroxyethyl starches (HESs), are generally considered to be more potent plasma volume expanders than crystalloids. However, several studies have raised concerns about an increased incidence of adverse events (e.g. renal replacement therapy and even mortality) after fluid resuscitation with HES in patients with septic shock. By contrast, a recent trial showed no difference in mortality or need for renal-replacement therapy after resuscitation with colloids or crystalloids in patients with acute hypovolemic shock. Until further evidence becomes available, it seems reasonable to choose the less expensive crystalloids as first-line treatment, even for cardiogenic shock.

**Vasopressor agents**

If hypotension is severe or persists despite fluid administration, the use of vasopressors is indicated. Currently, there is no convincing evidence that one vasopressor is clearly superior to the others. The ‘Sepsis Occurrence in Acutely Ill Patients’ (SOAP) II study compared the use of noradrenaline and dopamine as first-line vasopressors in patients with different types of shock. There was no difference in mortality between both groups, but dopamine was associated with an increased incidence of arrhythmias (Table 1). In a pre-defined subgroup analysis of patients with cardiogenic shock, there was an increase in mortality in the dopamine group as compared with the noradrenaline group, although this effect may be explained by chance alone, as randomization between the subgroups was not stratified and the p value for interaction in the subgroup analysis was 0.87. Nevertheless, in view of its lower rate of arrhythmias, noradrenaline may be considered as first-line vasopressor in cardiogenic shock (Table 2).

The use of other vasopressors, including adrenaline, vasopressin and phenylephrine, should only be considered in patients failing to respond to traditional therapies. In a small randomized trial, adrenaline was compared with the combination of norepinephrine and dobutamine in patients with cardiogenic shock. Administration of adrenaline was associated with an increased rate of arrhythmias, a decrease in splanchnic blood flow and an increase in blood lactate levels (Table 1). Moreover, adrenaline can promote thrombosis in coronary vasculature. Consequently, adrenaline should only be used as a second-line agent. Endogenous vasopressin levels are frequently elevated during the early phase of shock, but tend to decrease during shock progression, contributing to a loss of vascular tone and worsening hypotension. In a retrospective study of 36 patients with cardiogenic shock after myocardial infarction, administration of vasopressin was associated with increased mean arterial pressure without adversely impacting cardiac index, cardiac power index and wedge pressure. The use of vasopressin warrants further investigation in cardiogenic shock. Phenylephrine increases blood pressure by vasoconstriction. Consequently, it should probably be avoided in cardiogenic shock because of its potential to increase the afterload for the failing left ventricle.

It is uncertain which blood pressure targets should be aimed for in cardiogenic shock. In this regard, it is important to note that vasopressors are able to stabilize the mean arterial pressure, but their use may have negative consequences for perfusion within microvasculature. Several studies have highlighted the effects of an impaired microcirculation on the prognosis of haemodynamically unstable patients. An impaired microcirculation is an independent predictor of outcome in patients with cardiogenic shock. A short-term (1 h) increase in the mean arterial pressure from 65 to 85 mmHg in patients with cardiogenic shock was associated with an increase in cardiac index and cardiac power, a decrease in blood lactate levels and an improvement of the microcirculation in cardiogenic shock. However, these effects were at the expense of very high doses of noradrenaline, limiting the clinical applicability of these blood pressure targets due to inherent side-effects of high dose catecholamine therapy. In the German–Austrian guideline, a mean arterial pressure between 65 and 75 mmHg is recommended.
**Inotropic agents**

At present there are no convincing data to support a specific inotropic agent in haemodynamically unstable patients with cardiogenic shock complicating AMI.\textsuperscript{103} Dobutamine is commonly considered to be the inotropic agent of choice (Table 2). It has limited effects on arterial pressure, although it can raise the blood pressure by increasing cardiac output or it can reduce the blood pressure due to a peripheral vasodilatory effect.

Despite the favourable haemodynamic effects of dobutamine therapy, the haemodynamic improvement comes at the expense of increased myocardial oxygen consumption. In addition, catecholamines produce increased concentrations of cAMP, leading to an increase in intracellular calcium that can result in myocardial cell death. These effects may result in an increased incidence of ventricular arrhythmias and extension of the infarct area. Administration of catecholamines has been associated with a decreased survival.\textsuperscript{104,105} In the ‘Acute Decompensated Heart Failure National Registry’ (ADHERE), short-term inotropic therapy was associated with increased in-hospital mortality.\textsuperscript{106} As a consequence, catecholamines should be used in the lowest possible doses.

Phosphodiesterase type III inhibitors, such as milrinone and enoximone, increase intracellular cyclic AMP, which leads to increased myocardial contractility. In contrast to dobutamine, milrinone does not increase myocardial oxygen consumption.\textsuperscript{107} However, the harm of inotropic agents is not solely due to effects on myocardial oxygen consumption, but may also be related to the increase in intracellular calcium as a consequence of heightened cAMP levels. An increase in mortality was also seen with chronic use of oral milrinone in patients with severe chronic heart failure.\textsuperscript{108} In cardiogenic shock, milrinone is usually considered only after other agents have proven ineffective, because it has a long half-life and the potential to worsen hypotension. However, milrinone can be used in cases of predominant right heart failure because it is a more potent pulmonary vasodilator than dobutamine. Moreover, phosphodiesterase type III inhibitors also have lusitropic properties resulting in an improvement in diastolic function.

Levosimendan differs from other inotropic agents as it has a unique dual mechanism of action with increased troponin C sensitivity to intracellular calcium, thereby enhancing cardiac inotropy and lusitropy,\textsuperscript{109} and opening of the ATP-sensitive K+ channels in the vascular smooth muscle, causing peripheral vasodilation. It may also have some PDE-3 inhibitor activity.\textsuperscript{110} It might be an ideal agent in cardiogenic shock, because it improves myocardial contractility without increasing cAMP or calcium concentration. In two small randomized studies, levosimendan was associated with a better survival compared with enoximone, a phosphodiesterase type III inhibitor,\textsuperscript{23} but not compared with dobutamine (Table 1).\textsuperscript{24} However, a survival benefit in large-scale clinical trials has not yet been demonstrated.\textsuperscript{111}

In a recent registry of patients with AMI-related cardiogenic shock, the use of levosimendan was not associated with improved survival.\textsuperscript{112} In view of the vasodilatory effects with subsequent blood pressure lowering, the long half-life, the high cost and the fact that it is not available in many countries, levosimendan is not considered a drug of first choice in cardiogenic shock. According to the German–Austrian guideline,\textsuperscript{4} levosimendan is preferred over phosphodiesterase III inhibitors (enoximone) in cases of catecholamine-refractory cardiogenic shock (Table 2).

**New inotropic agents**

Recently, new inotropic agents with a different mechanism of action have been described. Omecamtiv mecarbil is a cardiac myosin activator which increases the rate of effective myosin cross-bridge formation and thereby the duration and amount of myocyte contraction without an effect on intracellular calcium or cAMP.\textsuperscript{113} Studies in healthy volunteers\textsuperscript{114} and in patients with chronic stable heart failure\textsuperscript{115} have confirmed that omecamtiv mecarbil prolongs the duration of systole, resulting in an increased stroke volume. According to the ATOMIC-AHF trial, which was recently presented at the European Society of Cardiology (Amsterdam 2013), omecamtiv mecarbil appeared to be devoid of the usual adverse effects of traditional inotropic agents, such as supraventricular or ventricular arrhythmias.\textsuperscript{116} Another new inotropic agent, istaroxime, has both inotropic and lusitropic effects which are mediated by inhibition of sodium-potassium ATPase and stimulation of the sarcoplasmic reticulum calcium ATPase isoform 2a (SERCA2a).\textsuperscript{117} The Hemodynamic, Echocardiographic, and Neurohormonal Effects of Istaroxime, a Novel Intravenous Inotropic and Lusitropic Agent: a Randomized Controlled Trial in Patients Hospitalized with Heart Failure (HORIZON-HF) study assessed the haemodynamic effects of istaroxime in a double-blind, placebo controlled phase 2 trial in patients hospitalized with acute heart failure.\textsuperscript{117} The primary end point, reduction in pulmonary capillary wedge pressure, was improved for all three doses compared with placebo. Moreover, istaroxime induced a reduction in heart rate and an increase in blood pressure.\textsuperscript{117} Both omecamtiv mecarbil and istaroxime are potentially interesting inotropic agents in the treatment of cardiogenic shock without the usual adverse effects of conventional inotropic agents.

**Nitric oxide synthase inhibition**

Cardiogenic shock causes a systemic inflammatory response syndrome (SIRS), which is characterized by the release of inflammatory mediators. Several studies have reported that markers of the systemic inflammatory response syndrome are predictive of short-term mortality in cardiogenic shock.\textsuperscript{118–121} However, attempts to inhibit the systemic inflammatory response syndrome have not resulted in better outcome. For example, the Tilarginine Acetate Injection in a
Randomized International Study in Unstable MI Patients with Cardiogenic Shock trial (TRIUMPH) investigated whether inhibition of nitric oxide (NO) synthase by tilargine improved survival in cardiogenic shock. Despite an immediate increase in blood pressure, a prespecified interim analysis showed that NO synthase inhibition did not result in a survival benefit, which led to premature discontinuation of the trial (Table 1).

**Additional therapeutic interventions**

**Therapeutic hypothermia**

Therapeutic hypothermia for AMI-related cardiogenic shock could have multiple beneficial effects, including the potential to improve post-ischaemic cardiac function and haemodynamics, decrease myocardial damage and reduce end-organ injury from prolonged hypoperfusion. In two small studies of cardiogenic shock, therapeutic hypothermia (33°C) was associated with improved haemodynamics. Although its use has been questioned after cardiac arrest, therapeutic hypothermia warrants further investigation as a potential treatment strategy for AMI-related cardiogenic shock.

**Mechanical ventilation**

There is only limited literature regarding mechanical ventilation in patients with cardiogenic shock complicating myocardial infarction. Whereas non-invasive ventilation is recommended in acute decompensated heart failure, invasive ventilation is preferred in cardiogenic shock. Although some studies raised concern about the possible detrimental effects of positive end expiratory pressure (PEEP) on cardiac output, it appears that PEEP may even improve haemodynamics in patients with severe left heart failure. In patients with congestive left heart failure, initiation of PEEP was associated with an increase in cardiac output. In another small study of patients with cardiogenic shock necessitating intra-aortic balloon pump placement, mechanical ventilation with 10 cmH₂O of PEEP was not only associated with improved haemodynamics, but also increased the weaning rate of the intra-aortic balloon pump and survival to discharge. The mechanisms for the haemodynamic improvement observed with positive pressure mechanical ventilation and PEEP include reduced left ventricular afterload, reduced left ventricular preload thereby unloading the congested heart, decreased work of breathing and overall metabolic demand, reversal of hypoxia-related pulmonary vasoconstriction and improved oxygenation that may optimize oxygen supply to the stressed myocardium. However, caution with PEEP is necessary in patients with a preload-dependent left ventricular function (e.g. right ventricular infarction) who may experience cardiac underfilling as a consequence of the decreased venous return that accompanies PEEP.

According to the German–Austrian guideline, lung protective ventilation (tidal volume ≤ 6 ml/kg, peak pressure ≤ 30 mbar) is recommended in patients in cardiogenic shock, as is true for acute lung injury, although the available data in this regard are limited.

**Management of right ventricular infarction**

Right ventricular infarction (RVI) occurs in up to 50% of patients with acute inferior AMI. In half of these patients, haemodynamic complications with severe hypotension and cardiogenic shock develop. Although patients with RVI have a worse short-term prognosis, those who survive hospitalization have a relatively good long-term prognosis. This may be due to the fact that right ventricular function tends to return to normal over time. In addition to early revascularization, therapeutic modalities of RVI include optimization of preload, maintenance of an adequate heart rate and restoration of AV synchronization, inotropic and vasopressor support, and use of pulmonary vasodilators.

**Early revascularization**

In patients with ST elevation myocardial infarction involving the right ventricle, early reperfusion should be achieved as early as possible. Successful reperfusion has been shown to improve right ventricular performance as well as survival. By contrast, unsuccessful reperfusion is associated with impaired recovery of right ventricular function, persistent haemodynamic compromise, ventricular arrhythmias and high mortality rates.

**Optimization of preload**

Adequate filling of the impaired right ventricle is important to maintain sufficient right ventricular output. An initial volume challenge is thus appropriate for patients without pulmonary congestion and an estimated central venous pressure < 15 mmHg. Accordingly, drugs that cause venodilation and a decrease in right ventricular filling (e.g. nitrates, diuretics) should be avoided. However, the beneficial effect of volume loading is dependent on the baseline volume status of the patient. Excess volume loading may result in right ventricular dilation, leading to displacement of the interventricular septum towards the left ventricle and compromising left ventricular filling. This effect results in a further depression of the cardiac output. Therefore, in patients unresponsive to an initial trial of fluids, invasive haemodynamic monitoring and volume infusion guided by haemodynamic parameters may be appropriate.
**Maintenance of an adequate heart rate and restoration of atrioventricular synchronization**

The maintenance of an adequate heart rate and restoration of atrioventricular synchrony are other important factors for preserving the cardiac output in patients with RVI. The ischaemic right ventricle and, consequently, the preload-deprived left ventricle have a relatively fixed stroke volume, and cardiac output strongly depends on heart rate. Therefore, pacing is essential to obtain an adequate cardiac output in patients with RVI. Moreover, maintenance of atrioventricular synchrony is also important in these patients to optimize right ventricular filling. Several studies have shown that atrioventricular synchrony significantly improves cardiac output and can sometimes even reverse hypotension and shock in patients with RVI Therefore, atrial or atrioventricular pacing may be preferable to ventricular pacing.

**Inotropic and vasopressor support**

If volume loading fails to improve cardiac output, inotropic support should be considered. However, there are only few studies that have investigated the different inotropic agents in RVI-induced cardiogenic shock. Dobutamine may enhance right ventricular performance, reduce pulmonary vascular resistance and improve atrioventricular conduction. The phosphodiesterase type III inhibitor milrinone is also an interesting agent in patients with right ventricular failure because it increases myocardial contractility and induces pulmonary vasodilation, but, in hypotensive patients, the addition of a vasopressor may be necessary to maintain an adequate coronary perfusion.

There is uncertainty about the first-line vasopressor in RVI. Ideally, the vasopressor should increase the systemic pressure without raising pulmonary vascular resistance. In this regard, vasopressin could be an interesting agent in patients with right ventricular failure as it causes pulmonary vasodilatation at low doses (e.g. 0.01–0.03 U/min) via stimulation of endothelial nitric oxide. Also norepinephrine is a frequently used vasopressor agent in patients with right ventricular failure, despite the potential increase in pulmonary vascular resistance at higher doses.

**Pulmonary vasodilators**

The right ventricle is very sensitive to increases in afterload. Therefore, selective pulmonary vasodilation is an attractive strategy to improve right ventricular function by relieving increased afterload without causing systemic hypotension. The most extensively used pulmonary vasodilator is NO, which dilates pulmonary vasculature by increasing the production of cyclic guanosine monophosphate. In a few small studies, a beneficial haemodynamic effect of NO has been shown in patients with RVI-induced cardiogenic shock. The application of inhaled NO may be limited by methaemoglobinemia, although this is usually not a clinically significant problem. Abrupt discontinuation of NO administration can result in rebound pulmonary hypertension, leading to a decreased cardiac output and systemic hypotension. In addition, in patients with advanced biventricular heart failure, inhaled NO may increase pulmonary capillary wedge pressure and worsen pulmonary oedema.

In addition to the use of pulmonary vasodilators, it is essential to avoid the potential negative effects of mechanical ventilation on right ventricular afterload. Large tidal volumes and high PEEP can lead to an increase in the pulmonary vascular resistance. In addition, both hypoxia and hypercapnia can promote pulmonary vasoconstriction and increase the afterload of the right ventricle. Therefore, careful management of oxygenation and ventilation is important in patients with right ventricular failure.

**When should we initiate mechanical circulatory support?**

Mechanical circulatory support should be considered in patients with cardiogenic shock who remain unstable despite revascularization and inotropic therapy. Often these patients are at a too high risk for implantation of a durable device and percutaneous insertion of a temporary ventricular assist device is preferable. Although there are no studies on the optimal timing of mechanical circulatory support in cardiogenic shock, it is likely that mechanical circulatory support should be initiated early in the disease course before the occurrence of multi-organ failure. Currently, there is only limited data available from randomized trials evaluating the different percutaneous support systems (Table 1).

**Intra-aortic balloon pump**

The intra-aortic balloon pump (IABP) is commonly the first step in the mechanical support of cardiogenic shock. The IABP is inserted percutaneously in the femoral artery and provides haemodynamic support by reduction in left ventricular afterload, resulting in a decrease in ventricular wall tension and oxygen demand. It also induces a rise in diastolic perfusion pressure in the coronary arteries, which may be important in the setting of increased ventricular diastolic pressure, even in the absence of critical coronary artery stenosis. The IABP generates an increase in cardiac output up to approximately 0.3–0.5 l/min (Table 3).

Although IABP has been the most widely used support device in cardiogenic shock, there is only limited evidence supporting the beneficial effects of IABP in cardiogenic shock. In 2009, a meta-analysis showed that IABP therapy was associated with a significant decrease in 30 day mortality in patients treated with thrombolysis. However, patients treated with PCI and IABP had a significant increase in 30-day mortality. In the first randomized study
comparing IABP therapy with conservative management in 45 patients in cardiogenic shock, the IABP SHOCK trial, IABP treatment was associated with a reduction in brain natriuretic peptide levels after 48 and 72h, indicating unloading of the left ventricle. However, this did not translate into better clinical outcomes, including survival in this small study (Table 1).26 There were also no differences in haemodynamics, systemic inflammation or severity of multi-organ dysfunction syndrome (MODS).26 The IABP SHOCK II trial randomly assigned 600 patients with acute myocardial infarction complicated by cardiogenic shock and undergoing early revascularization to additional intra-aortic balloon therapy or control group. IABP therapy was not associated with a reduction in all-cause mortality at 30 days and 12 months.14,27 These results indicate that IABP concomitant to early revascularization does not reduce short-term or long-term mortality in AMI complicated by cardiogenic shock and question the routine use of IABP therapy in cardiogenic shock (Table 1). However, it is worth noting that there was a favourable trend towards lower mortality among younger patients (age < 50 years).14 In the current European guidelines on myocardial revascularization,3 the routine use of IABP in patients with cardiogenic shock is not recommended (class III/A) (Table 2). Only in patients with cardiogenic shock due to mechanical complications should the insertion of IABP be considered as a bridge to surgery (class IIa/C) (Table 2). The German–Austrian guideline gives a weak recommendation for adjunctive IABP treatment in patients who have undergone systemic fibrinolysis, mainly based on the positive findings of the meta-analysis of Sjauw et al.167 (Table 2). In patients undergoing PCI, the German–Austrian guideline cannot give an evidence-based recommendation and IABP therapy may be considered in these patients (Table 2). In addition to the limited evidence of effectiveness, another important limitation of IABP therapy is the modest augmentation of cardiac output of approximately 0.5 l/min, which is likely to be insufficient for patients with severe cardiogenic shock.

**TandemHeart**

The TandemHeart provides haemodynamic support of up to 4 l/min by pumping blood from the left atrium to the femoral artery (Table 3). The device requires the placement of an inflow cannula transseptally into the left atrium. Oxygenated blood is aspirated from the left atrium and injected into the lower abdominal aorta or iliac arteries via a femoral artery cannula.

The haemodynamic effects of the TandemHeart include an increase in cardiac output and mean arterial pressure and a reduction in cardiac filling pressures.168 In a retrospective study of patients with severe refractory cardiogenic shock, TandemHeart support was associated with improved haemodynamic parameters.169 In two small randomized trials in patients with AMI-related cardiogenic shock, the TandemHeart provided superior haemodynamic support compared with IABP therapy (Table 1).28,29 However, complications such as severe bleeding, arrhythmias and limb ischaemia occurred more often using the TandemHeart. There was also no difference in mortality between both devices, but these studies were not sufficiently powered to detect differences in mortality (Table 1).28,29 Contraindications for the use of TandemHeart are severe aortic regurgitation and significant peripheral artery disease. The complexity of the insertion procedure, including a transseptal puncture, limits the emergency use of the device (e.g. during cardiopulmonary resuscitation).

**Impella**

The Impella is an axial pump that is placed across the aortic valve, aspirating blood from the left ventricle into the ascending aorta. There are different versions of the Impella. For example, the Impella 2.5 is percutaneously inserted via a peripheral artery with fluoroscopic guidance, whereas the Impella 5.0 requires surgical cutdown of the femoral artery. Recently, a new system with a flow rate up to 4.0 l/min, the

### Table 3. Technical features of currently available percutaneous assist devices.

<table>
<thead>
<tr>
<th></th>
<th>IABP</th>
<th>TandemHeart</th>
<th>Impella 2.5</th>
<th>Impella CP</th>
<th>ECMO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pump mechanism</td>
<td>Pneumatic</td>
<td>Centrifugal</td>
<td>Axial flow</td>
<td>Axial flow</td>
<td>Centrifugal</td>
</tr>
<tr>
<td>Cannula size (French)</td>
<td>7–9</td>
<td>21 inflow, 15–17 outflow</td>
<td>13</td>
<td>14</td>
<td>18–21 inflow, 15–22 outflow</td>
</tr>
<tr>
<td>Haemodynamic support (l/min)</td>
<td>0.5</td>
<td>Max. 4.0</td>
<td>Max. 2.5</td>
<td>Max. 3.7–4.0</td>
<td>Max. 7.0</td>
</tr>
<tr>
<td>Pump speed (rpm)</td>
<td>0</td>
<td>Max. 7500</td>
<td>Max. 51,000</td>
<td>Max. 51,000</td>
<td>Max. 5000</td>
</tr>
<tr>
<td>Implantation time</td>
<td>+</td>
<td>++++</td>
<td>++</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Risk of limb ischaemia</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>
</tr>
<tr>
<td>Haemolysis</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Post-implantation management complexity</td>
<td>+</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>+++</td>
</tr>
</tbody>
</table>

IABP: intra-aortic balloon pump; ECMO: extracorporeal membrane oxygenation; +, ++, +++: relative qualitative grading concerning time (‘implantation time’), risk (‘risk of limb ischaemia’), intensity (‘anticoagulation’, ‘post-implantation management complexity’) and severity (‘haemolysis’). Modified from Ouweneel and Henriques.163
Impella CP, has been introduced. The Impella CP can also be implanted percutaneously via the femoral artery (Table 1). The Impella device induces a direct unloading of the left ventricle, leading to a reduction of end-diastolic wall stress and a decrease in pulmonary capillary wedge pressure. Moreover, it provides haemodynamic support and also improves coronary circulation. Several studies have demonstrated that the Impella device is safe and haemodynamically effective in cardiogenic shock. In the Efficacy Study of LV Assist Device to Treat Patients with Cardiogenic Shock (ISAR-SHOCK) trial, the haemodynamic support between Impella 2.5 and IABP was compared. Use of Impella 2.5 was associated with a larger increase in cardiac output and mean arterial pressure compared with IABP (Table 1). Serum lactate levels were also lower in the Impella group than the IABP group. However, the haemodynamic improvement was limited to the first hours after implantation and there was no difference in mortality between the two groups (Table 1). In a recent registry, early initiation of haemodynamic support with Impella 2.5 prior to PCI was associated with more complete revascularization and improved survival in patients with refractory cardiogenic shock complicating AMI. Complications of Impella support include bleeding at the vascular access site, and a decrease in pulmonary capillary wedge pressure. Contraindications of the left ventricle, thereby increasing oxygen demand, impeding myocardial recovery and causing pulmonary oedema. Attempts to decompress the left ventricle by creating an atrial septal defect. Alternatively, conversion to central ECMO should be considered with cannulation of the left atrium, left ventricle or pulmonary artery. In the case of persistent pulmonary oedema, the presence of aortic insufficiency should be excluded by transoesophageal echocardiography.

Percutaneous venoarterial membrane oxygenation

Although the TandemHeart and Impella can provide substantial haemodynamic support, this support may not be sufficient to provide enough cardiac output to preserve or restore organ perfusion in the case of severe and profound cardiogenic shock. Extracorporeal membrane oxygenation (ECMO) has the ability to provide complete cardiopulmonary support with up to 7 l/min of nonpulsatile flow (Table 3). The percutaneous ECMO system generally consists of a centrifugal pump, a heat exchanger and a membrane oxygenator. Venous desaturated blood is aspirated from the right atrium into a centrifugal pump through a cannula inserted via the femoral vein. The blood is directed through a membrane oxygenator and runs via the outflow cannula into the descending aorta. The newest generations of ECMO systems have been miniaturized to make transportation possible.

Recent non-randomized studies suggest a survival advantage from the early use of ECMO in cardiogenic shock complicating acute myocardial infarction. An observational study comparing patients with AMI-related cardiogenic shock before and after the availability of ECMO revealed a lower 30-day mortality among ECMO recipients. In another study with historical controls, Tsao et al. also reported an improved survival in patients with AMI-related cardiogenic shock after ECMO support. Interpretation of these studies is limited by the comparison of patient groups over two consecutive time periods, with possible differences in both medical and interventional management over time. Although ECMO may provide a benefit in survival of patients with cardiogenic shock due to acute coronary syndromes, mortality rates are still high, ranging from 31% to 66%.

The main limitation of ECMO is the increased afterload that results from the retrograde flow of peripheral cannulation. This results in an inadequate decompression of the left ventricle, thereby increasing oxygen demand, impeding myocardial recovery and causing pulmonary oedema. Attempts to decompress the left ventricle by increasing ECMO flow may paradoxically worsen the haemodynamic condition as this can further increase the left ventricular afterload. Inotropic and vasodilating agents as well as insertion of IABP or Impella may be used to increase ventricular ejection and emptying. An alternative approach is the percutaneous insertion of a pigtail catheter into the left ventricle or a venous cannula into the pulmonary artery, with subsequent connection of this cannula to the venous inflow of the ECMO circuit. The left ventricle can also be vented by creating an atrial septal defect. Alternatively, conversion to central ECMO should be considered with cannulation of the left atrium, left ventricle or pulmonary artery.

In patients with peripheral ECMO, recovery of the cardiac function in combination with pulmonary failure may lead to cerebral hypoxemia. The right ventricle directs blood through the poorly functioning lungs, leading to desaturated blood in the systemic circulation. The poorly oxygenated blood from the left ventricle preferentially supplies the cerebral and coronary circulations, while well-oxygenated blood from the femoral arterial cannula supplies the lower body. To allow early detection of this differential cyanosis (also known as Harlequin syndrome), transcutaneous saturation in patients with peripheral ECMO should always be derived from the right-hand, right-sided nasal wing or right ear lobe. This complication can be addressed
by adjusting the ventilator settings (e.g. increasing the fraction of inspired oxygen) or by increasing the ECMO flow to move the mixing point of the two circulations more proximally in the aorta. Another approach is to move the arterial return catheter more proximally in the axillary or carotid artery. Alternatively, the veno-arterial ECMO circuit can be modified by addition of a venous cannula in the right internal jugular vein. After passage through the oxygenator, a portion of the well-oxygenated blood is directed via the venous cannula through the pulmonary circulation, resulting in an increased oxygen delivery to the coronary and cerebral circulation.192

Although the results about and use of IABP before and during ECMO are not univocal, there is some evidence to support the use of IABP simultaneously as an adjunct to ECMO.193 The use of IABP could improve the cardiac recovery through an increase of coronary blood flow.194 In addition, the use of IABP during ECMO has been associated with an increased ECMO weaning rate, although this was not translated into improved survival.195

During weaning of patients from ECMO, flows are reduced in a stepwise fashion while cardiac function is continuously monitored using transthoracic echocardiography. Maintenance of systemic blood pressure and cardiac index suggest that ECMO circuits can be clamped and cannulae can be removed. In a small study, pretreatment with levosimendan seemed to facilitate weaning from ECMO, reducing the need for high-dose inotropes.196

Although ECMO may improve the survival of patients in cardiogenic shock, this intervention can be associated with significant morbidity. The most common complications are limb ischaemia, renal failure, bleeding and infection.197,198 Limb ischaemia is related to the large cannula size and can be prevented by insertion of an antegrade sheath to maintain adequate perfusion of the leg with the arterial cannula.

According to the European guidelines, there is a class IIb/C recommendation to consider short-term mechanical circulatory support in patients with refractory cardiogenic shock (Table 2).2,3 The German–Austrian guideline does not give any recommendation on the use of mechanical circulatory support in cardiogenic shock.

**Conclusion**

Early revascularization remains the most important therapy in patients with cardiogenic shock complicating acute myocardial infarction. However, mortality of cardiogenic shock remains high, at least partially related to the development of SIRS. Haemodynamic stabilization can be achieved using inotropes and vasopressors, although often at the expense of increased myocardial oxygen consumption and extended myocardial ischaemia. The use of mechanical circulatory support has increased significantly in recent years, but outcome data are lacking. Advances in extracorporeal technology and cannulation techniques have increased the use of ECMO in cardiogenic shock.190 It is likely that ECMO has the greatest potential for wider clinical use.200 However, additional randomized studies are necessary to determine the optimal timing and patient selection for ECMO support.

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**Conflict of interest**

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