European Heart Journal
Acute Cardiovascular Care
EUROPEAN SOCIETY OF CARDIOLOGY®

Review

European Heart Journal: Acute Cardiovascular Care
1–20

DOI: 10.1177/2048872614568294
acc.sagepub.com
SAGE

Management of cardiogenic shock complicating acute myocardial infarction

Jozef L Van Herck, Marc J Claeys, Rudi De Paep, Paul L Van Herck, Christiaan J Vrints and Philippe G Jorens

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

Date received: 2 June 2014; accepted: 23 December 2014

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).[1] 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).[2,3] 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.[4]

Incidence and mortality of cardiogenic shock

Cardiogenic shock complicates approximately 5–10% of cases with acute myocardial infarction.[5] Although a number of studies reported an increased incidence of AMI-related

Department of Intensive Care Medicine and Cardiology, Antwerp University Hospital, University of Antwerp, Belgium

Corresponding author:
Jozef Van Herck, Department of Intensive Care, Antwerp University Hospital, Wilrijkstraat 10, B-2650 Edegem, Belgium.
Email: jozef.van.herck@uza.be

Table 1. Overview of randomized trials in cardiogenic shock.

Intervention	Study population	Results
Early revascularization		
• Early revascularization versus initial medical stabilization[15,18,19]	Cardiogenic shock (*N* = 302)	Decrease in one and six year mortality.
• Early revascularization versus initial medical stabilization[20]	Cardiogenic shock (*N* = 55)	No difference in 30 day mortality.
Inotropic and vasopressor agents		
• Dopamine versus noradrenaline[21]	Shock (*N* = 1679)	Increased incidence of arrhythmias in dopamine group.
• Epinephrine versus noradrenaline and dobutamine[22]	Cardiogenic shock (*N* = 30)	Increased rate of arrhythmias, a decrease in splanchnic blood flow and an increase in blood lactate levels in epinephrine group.
• Levosimendan versus enoximine[23]	Cardiogenic shock (*N* = 32)	Decrease in 30-day survival in levosimendan group.
• Levosimendan versus dobutamine[24]	Cardiogenic shock (*N* = 22)	No difference in one-year mortality.
NO synthase inhibition		
• Tilarginine versus control[25]	Cardiogenic shock (*N* = 398)	No difference in 30-day mortality.
Mechanical circulatory support		
• IABP versus control[26]	Cardiogenic shock (*N* = 45)	Reduction in BNP levels in IABP group. No difference in MODS or early mortality.
• IABP versus control[14,27]	Cardiogenic shock (*N* = 600)	No difference in 30-day or one-year mortality.
• TandemHeart versus IABP[28]	Cardiogenic shock (*N* = 41)	Improved haemodynamics in TandemHeart group. No difference in 30-day mortality.
• TandemHeart versus IABP[29]	Cardiogenic shock (*N* = 42)	Improved haemodynamics in TandemHeart group. No difference in 30-day mortality.
• Impella versus IABP[30]	Cardiogenic shock (*N* = 25)	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

cardiogenic shock,[5,6] other studies have described a decline in the incidence of cardiogenic shock during the last decade.[7,8] In the 'Acute Myocardial Infarction in Switzerland' (AMIS) Plus registry,[8] 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.[8] Not only PCI but also early administration of thrombolysis may reduce the risk of in-hospital development of cardiogenic shock in STEMI patients.[9,10] In the DANAMI-2 trial, there was no difference in the proportion of STEMI patients developing cardiogenic shock between PCI and thrombolysis.[11] 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.[12] Several studies have described a decline in the mortality of cardiogenic shock.[6,13] However, the mortality of cardiogenic shock remains high, with an early mortality of approximately 40%.[6,14] It is important to note that survivors of cardiogenic shock have a long-term outcome similar to patients without cardiogenic shock.[15,16] In addition, at one year, many survivors of cardiogenic shock have a good functional status.[17] 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).[18] 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,[18] there was a significant decrease in mortality after one and six years in patients assigned to early revascularization.[15,19] To save a life, fewer than eight

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[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.[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.[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.[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.[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.[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.[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.[35] However, thrombolysis alone results in relatively low rates of reperfusion in patients in whom shock is already established.[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[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 ⩾ 50%, ⩾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.[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.[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.[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.[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.[39] In the current European guidelines,[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%,[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.[40,41] Importantly, patients with cardiogenic shock have a lower likelihood of successful PCI than patients without shock.[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.[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.[43–45] Although several studies have also shown the safety and efficacy of drug-eluting stents in acute coronary syndromes,[46,47] there are only limited data concerning the use of drug-eluting stents in cardiogenic shock. In a recent retrospective, propensity-matched study,[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[4] recommends that urgent CABG should also be considered in the case of non-successful PCI, left main disease, three-vessel disease, or in

Table 2. Overview of European[2,3] and German–Austrian[4] guidelines for patients with AMI-related cardiogenic shock.

Intervention	Guideline	Class/ level
Early revascularization		
• **European guidelines**		
	- Emergency revascularization with either PCI or CABG in suitable patients must be considered.	I / B
	- Fibrinolysis should be considered if revascularization is unavailable.	IIa / C
• **German–Austrian guideline**		
	- 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.	↑↑ / 1+
	- 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.	↑ / 3/4
	- 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.	↑↑ / 3/4
Vasoactive agents		
• **European guidelines**		
	- In cardiogenic shock, inotropic/vasopressor agents should be considered:	
	○ Dopamine	IIa / C
	○ Dobutamine	IIa / C
	○ Noradrenaline (preferred over dopamine when blood pressure is low).	IIb / B
• **German–Austrian guideline**		
	- Dobutamine should be given as inotropic drug.	↑ / 3/4
	- Noradrenaline should be used as vasopressor.	↑ / 3/4
	- In cases of catecholamine-refractory cardiogenic shock, levosimendan is preferred over phosphodiesterase III inhibitors (enoximine).	↑ / 1+
	- Dopamine shall not be used in cardiogenic shock.	↓↓ / 3/4
	- Adrenaline can be used if haemodynamic stabilization cannot be obtained with dobutamine and noradrenaline.	↔ / 3/4
Mechanical circulatory support		
• **European guidelines**		
	- IABP insertion should be considered in patients with cardiogenic shock due to mechanical complications.	IIa / C
	- Short-term mechanical circulatory support may be considered.	IIb / C
	- Routine use of IABP is not recommended.	III / A
• **German–Austrian guideline**		
	- In patient undergoing fibrinolytic therapy, IABP should be carried out adjunctively.	↑ / 3/4
	- In patients undergoing PCI, IABP may be considered, but the available evidence is unclear.	↔ / 3/4

Level of evidence in the German–Austrian guideline: 1++: high-quality systematic reviews of randomized controlled trials (RCTs) or RCTs with a very low risk of bias; 1+: well performed systematic reviews of RCTs or RCTs with a low risk of bias; 2++: 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 elevation[2] and myocardial revascularization,[3] and the German–Austrian S3 guideline for myocardial infarction-related cardiogenic shock.[4]

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

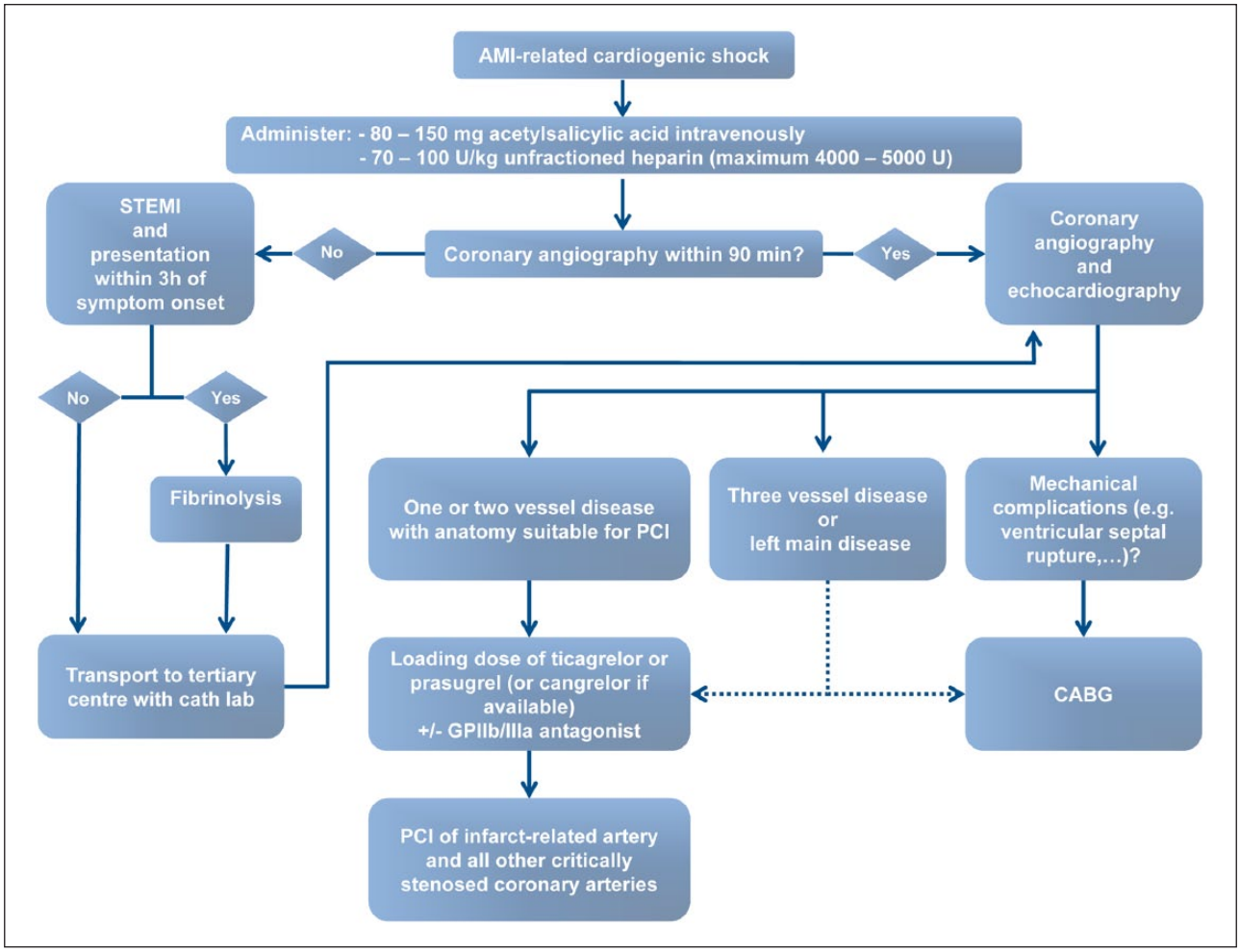

Figure 1. Algorithm for early revascularization in patients with cardiogenic shock complicating acute myocardial infarction.
AMI: acute myocardial infarction; STEMI: ST-elevation myocardial infarction; CABG: coronary artery bypass graft; PCI: percutaneous coronary intervention

receptor inhibitors ticagrelor and prasugrel exhibit an initial delay in the onset of their antiplatelet action.[50] 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.[51] 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.[52] 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.[44,53–55] 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.[56] According to the European STEMI guidelines, GPIIb/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.[2] However, in view of the delayed absorption of orally administered P2Y12 inhibitors and the increased risk of stent thrombosis in cardiogenic shock,[57] the use of glycoprotein IIb/IIIa antagonists may be considered to obtain

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.[58,59] 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.[60,61] In AMI-related cardiogenic shock, there are only few data on 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.[62] 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.[63] 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.[2] 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.[64] 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.[65] 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.[66,67] 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.[68] 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).[69] The upcoming European multicentre CULPRITSHOCK 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.[70,71] Patients with LMCA-related AMI in cardiogenic shock have a high in-hospital mortality of approximately 50%.[72] However, patients who survive to discharge have a good long-term prognosis.[73–76]

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%.[77] Several recent studies have shown that PCI is a feasible treatment option in these patients and is a good alternative to surgical revascularization.[78,79] 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.[80]

There are only limited data on emergency CABG in patients with AMI-related cardiogenic shock due to significant LMCA disease.[81,82] 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.[81,82] 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.[83] 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,[19] 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.[19] The apparent lack of benefit for the elderly in the SHOCK trial was likely due to imbalances in baseline ejection fraction between both groups.[84] More recent studies have shown a consistent benefit of revascularization in elderly patients,[85–88] indicating that advanced age alone should not be regarded as a contraindication 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').[89] The different haemodynamic profiles not only predict prognosis, but can also guide the choice of therapy.[90] 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.[91,92] 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.[93] Until further evidence becomes available, it seems reasonable to choose the less expensive crystalloids as first-line treatment, even for cardiogenic shock.[94]

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.[95] 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.[21] There was no difference in mortality between both groups, but dopamine was associated with an increased incidence of arrhythmias (Table 1).[21] 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,[21] 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.[95] 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.[22] 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).[22] Moreover, adrenaline can promote thrombosis in coronary vasculature.[96] 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.[97] 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.[98] 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.[99] Several studies have highlighted the effects of an impaired microcirculation on the prognosis of haemodynamically unstable patients.[100,101] An impaired microcirculation is an independent predictor of outcome in patients with cardiogenic shock.[100] 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.[102] 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,[4] 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.[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.[104,105] In the 'Acute Decompensated Heart Failure National Registry' (ADHERE), short-term inotropic therapy was associated with increased in-hospital mortality.[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.[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.[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,[109] and opening of ATP-sensitive K+ channels in the vascular smooth muscle, causing peripheral vasodilation. It may also have some PDE-3 inhibitor activity.[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,[23] but not compared with dobutamine (Table 1).[24] However, a survival benefit in large-scale clinical trials has not yet been demonstrated.[111] In a recent registry of patients with AMI-related cardiogenic shock, the use of levosimendan was not associated with improved survival.[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,[4] levosimendan is preferred over phosphodiesterase III inhibitors (enoximine) 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.[113] Studies in healthy volunteers[114] and in patients with chronic stable heart failure[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.[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).[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.[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.[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.[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 tilarginine improved survival in cardiogenic shock.[25] 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).[25]

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.[122] In two small studies of cardiogenic shock, therapeutic hypothermia (33°C) was associated with improved haemodynamics.[123,124] Although its use has been questioned after cardiac arrest,[125] 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.[126] Although some studies raised concern about the possible detrimental effects of positive end expiratory pressure (PEEP) on cardiac output,[127] it appears that PEEP may even improve haemodynamics in patients with severe left heart failure.[128,129] In patients with congestive left heart failure, initiation of PEEP was associated with an increase in cardiac output.[128] In another small study of patients with cardiogenic shock necessitating intra-aortic balloon pump placement, mechanical ventilation with 10 cmH_2O 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.[129] 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.[130] 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.[130]

According to the German–Austrian guideline,[4] lung protective ventilation (tidal volume $\leqslant$ 6 ml/kg, peak pressure $\leqslant$ 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.[131]

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.[132,133] Although patients with RVI have a worse short-term prognosis,[134–136] those who survive hospitalization have a relatively good long-term prognosis.[137] This may be due to the fact that right ventricular function tends to return to normal over time.[138] 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.[139,140] By contrast, unsuccessful reperfusion is associated with impaired recovery of right ventricular function, persistent haemodynamic compromise, ventricular arrhythmias and high mortality rates.[138]

Optimization of preload

Adequate filling of the impaired right ventricle is important to maintain sufficient right ventricular output.[140–143] An initial volume challenge is thus appropriate for patients without pulmonary congestion and an estimated central venous pressure $<$ 15 mmHg.[144] 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.[139] 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.[144]

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.[145,146] 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.[147] Several studies have shown that atrioventricular synchrony significantly improves cardiac output and can sometimes even reverse hypotension and shock in patients with RVI[148,149] 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.[150,151] 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 vasodilatation, 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.[152,153] 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.[154]

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.[155–157] The application of inhaled NO may be limited by methaemoglobinaemia, 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.[158,159]

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.[160] In addition, both hypoxia and hypercapnia can promote pulmonary vasoconstriction and increase the afterload of the right ventricle.[161] Therefore, careful management of oxygenation and ventilation is important in patients with right ventricular failure.[162,163]

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.[164] 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).[165]

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.[166] However, patients treated with PCI and IABP had a significant increase in 30-day mortality.[166] In the first randomized study

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

	IABP	TandemHeart	Impella 2.5	Impella CP	ECMO
Pump mechanism	Pneumatic	Centrifugal	Axial flow	Axial flow	Centrifugal
Cannula size (French)	7–9	21 inflow, 15–17 outflow	13	14	18–21 inflow, 15–22 outflow
Haemodynamic support (l/min)	0,5	Max 4.0	Max. 2.5	Max. 3.7–4.0	Max. 7.0
Pump speed (rpm)	0	Max. 7500	Max. 51,000	Max. 51,000	Max. 5000
Implantation time	+	++++	++	++	++
Risk of limb ischaemia	+	+++	++	++	+++
Anticoagulation	+	+++	+	+	+++
Haemolysis	+	++	++	++	++
Post-implantation management complexity	+	++++	++	++	+++

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.[165]

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

Impella CP, has been introduced. The Impella CP can also be implanted percutaneously via the femoral artery (Table 3). 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.[170] 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.[171] 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).[30] 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).[30] 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.[172] Complications of Impella support include bleeding at the vascular access site, haemolysis and pericardial tamponade.[173] Contraindications for the use of the Impella 2.5 are severe peripheral vascular disease, presence of a mechanical aortic valve or a severely calcified aortic valve.

In a meta-analysis of three randomized trials (two trials with TandemHeart and one trial with Impella 2.5), the effects of these left ventricular assist devices were compared with IABP support with respect to haemodynamics and 30-day survival.[174] Although the Impella and TandemHeart were associated with a higher cardiac index, higher mean arterial pressure and a lower pulmonary capillary wedge pressure, the 30-day mortality rate was similar between the two groups.[174] Adverse events, including bleeding, were reported more frequently with the left ventricular assist devices, especially the TandemHeart.[174]

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.[175–177]

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.[178] In another study with historical controls, Tsao et al.[179] 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%.[180–184]

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.[185] 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[186] may be used to increase ventricular ejection and emptying. An alternative approach is the percutaneous insertion of a pigtail catheter into the left ventricle[187] or a venous cannula into the pulmonary artery,[188] 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.[189] Alternatively, conversion to central ECMO should be considered with cannulation of the left atrium, left ventricle or pulmonary artery.[199] In the case of persistent pulmonary oedema, the presence of aortic insufficiency should be excluded by transoesophageal echocardiography.

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.[191] 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 the 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 transoesophageal 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[4] 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.[199] 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.

Acknowledgements

The authors thank Hilde Fleurackers for her technical assistance.

Conflict of interest

The authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

References

1. Hollenberg SM, Kavinsky CJ and Parrillo JE. Cardiogenic shock. *Ann Intern Med* 1999; 131: 47–59.
2. Steg PG, James SK, Atar D, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2012; 33: 2569–2619.
3. Windecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J* 2014; 35: 2541–2619.
4. Werdan K, Russ M, Buerke M, et al. Deutsch-österreichische S3-Leitlinie 'Infarktbedingter kardiogener Schock – Diagnose, Monitoring und Therapy'. *Der Kardiologe* 2011; 5: 166–224.
5. Babaev A, Frederick PD, Pasta DJ, et al. Trends in management and outcomes of patients with acute myocardial infarction complicated by cardiogenic shock. *JAMA* 2005; 294: 448–454.
6. Kolte D, Khera S, Aronow WS, et al. Trends in incidence, management, and outcomes of cardiogenic shock complicating ST-elevation myocardial infarction in the United States. *J Am Heart Assoc* 2014; 3: e000590.
7. Jeger RV, Radovanovic D, Hunziker PR, et al. Ten-year trends in the incidence and treatment of cardiogenic shock. *Ann Intern Med* 2008; 149: 618–626.
8. Radovanovic D, Nallamothu BK, Seifert B, et al. Temporal trends in treatment of ST-elevation myocardial infarction among men and women in Switzerland between 1997 and 2011. *Eur Heart J Acute Cardiovasc Care* 2012; 1: 183–191.
9. Neuhaus KL, von Essen R, Tebbe U, et al. Improved thrombolysis in acute myocardial infarction with front-loaded administration of alteplase: Results of the rt-PA-APSAC patency study (TAPS). *J Am Coll Cardiol* 1992; 19: 885–891.
10. Wilcox RG, von der Lippe G, Olsson CG, et al. Trial of tissue plasminogen activator for mortality reduction in acute myocardial infarction. Anglo-Scandinavian Study of Early Thrombolysis (ASSET). *Lancet* 1988; 2: 525–530.
11. Lindholm MG, Boesgaard S, Thune JJ, et al. Percutaneous coronary intervention for acute MI does not prevent

in-hospital development of cardiogenic shock compared to fibrinolysis. *Eur J Heart Fail* 2008; 10: 668–674.
12. Goldberg RJ, Samad NA, Yarzebski J, et al. Temporal trends in cardiogenic shock complicating acute myocardial infarction. *N Engl J Med* 1999; 340: 1162–1168.
13. Aissaoui N, Puymirat E, Tabone X, et al. Improved outcome of cardiogenic shock at the acute stage of myocardial infarction: A report from the USIK 1995, USIC 2000, and FAST-MI French nationwide registries. *Eur Heart J* 2012; 33: 2535–2543.
14. Thiele H, Zeymer U, Neumann F-J, et al. Intraaortic balloon support for myocardial infarction with cardiogenic shock. *N Engl J Med* 2012; 367: 1287–1296.
15. Hochman JS, Sleeper LA, Webb JG, et al. Early revascularization and long-term survival in cardiogenic shock complicating acute myocardial infarction. *JAMA* 2006; 295: 2511–2515.
16. Singh M, White J, Hasdai D, et al. Long-term outcome and its predictors among patients with ST-segment elevation myocardial infarction complicated by shock: Insights from the GUSTO-I trial. *J Am Coll Cardiol* 2007; 50: 1752–1758.
17. Sleeper LA, Ramanathan K, Picard MH, et al. Functional status and quality of life after emergency revascularization for cardiogenic shock complicating acute myocardial infarction. *J Am Coll Cardiol* 2005; 46: 266–273.
18. Hochman JS, Sleeper LA, Webb JG, et al. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK Investigators. Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock. *N Engl J Med* 1999; 341: 625–634.
19. Hochman JS, Sleeper LA, White HD, et al. One-year survival following early revascularization for cardiogenic shock. *JAMA* 2001; 285: 190–192.
20. Urban P, Stauffer J-C, Bleed D, et al. A randomized evaluation of early revascularization to treat shock complicating acute myocardial infarction. The (Swiss) Multicenter Trial of Angioplasty for Shock – (S)MASH. *Eur Heart J* 1999; 20: 1030–1038.
21. De Backer D, Biston P, Devriendt J, et al. Comparison of dopamine and norepinephrine in the treatment of shock. *N Engl J Med* 2010; 362: 779–789.
22. Levy B, Perez P, Perny J, et al. Comparison of norepinephrine-dobutamine to epinephrine for hemodynamics, lactate metabolism, and organ function variables in cardiogenic shock. A prospective, randomized pilot study. *Crit Care Med* 2011; 39: 450–455.
23. Fuhrmann JT, Schmeisser A, Schulze MR, et al. Levosimendan is superior to enoximone in refractory cardiogenic shock complicating acute myocardial infarction. *Crit Care Med* 2008; 36: 2257–2266
24. Samimi-Fard S, García-González MJ, Domínguez-Rodríguez A, et al. Effects of levosimendan versus dobutamine on long-term survival of patients with cardiogenic shock after primary coronary angioplasty. *Int J Cardiol* 2008; 127: 284–287.
25. Alexander JH, Reynolds HR, Stebbins JL, et al. Effect of tilarginine acetate in patients with acute myocardial infarction and cardiogenic shock: The triumph randomized controlled trial. *JAMA* 2007; 297: 1657–1666.
26. Prondzinsky R, Lemm H, Swyter M, et al. Intra-aortic balloon counterpulsation in patients with acute myocardial infarction complicated by cardiogenic shock: The prospective, randomized IABP SHOCK Trial for attenuation of multiorgan dysfunction syndrome. *Crit Care Med* 2010; 38: 152–160.
27. Thiele H, Zeymer U, Neumann FJ, et al. Intra-aortic balloon counterpulsation in acute myocardial infarction complicated by cardiogenic shock (IABP-SHOCK II): Final 12 month results of a randomised, open-label trial. *Lancet* 2013; 382: 1638–1645.
28. Thiele H, Sick P, Boudriot E, et al. Randomized comparison of intra-aortic balloon support with a percutaneous left ventricular assist device in patients with revascularized acute myocardial infarction complicated by cardiogenic shock. *Eur Heart J* 2005; 26: 1276–1283.
29. Burkhoff D, Cohen H, Brunckhorst C, et al. A randomized multicenter clinical study to evaluate the safety and efficacy of the TandemHeart percutaneous ventricular assist device versus conventional therapy with intraaortic balloon pumping for treatment of cardiogenic shock. *Am Heart J* 2006; 152: 469 e461–e468.
30. Seyfarth M, Sibbing D, Bauer I, et al. A randomized clinical trial to evaluate the safety and efficacy of a percutaneous left ventricular assist device versus intra-aortic balloon pumping for treatment of cardiogenic shock caused by myocardial infarction. *J Am Coll Cardiol* 2008; 52: 1584–1588.
31. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2013; 127: e362–e425.
32. Anderson ML, Peterson ED, Peng SA, et al. Differences in the profile, treatment, and prognosis of patients with cardiogenic shock by myocardial infarction classification: A report from NCDR. *Circ Cardiovasc Qual Outcomes* 2013; 6: 708–715.
33. Abbott JD, Ahmed HN, Vlachos HA, et al. Comparison of outcome in patients with ST-elevation versus non-ST-elevation acute myocardial infarction treated with percutaneous coronary intervention (from the National Heart, Lung, and Blood Institute Dynamic Registry). *Am J Cardiol* 2007; 100: 190–195.
34. Roe MT, Parsons LS, Pollack CV Jr, et al. Quality of care by classification of myocardial infarction: Treatment patterns for ST-segment elevation vs non-ST-segment elevation myocardial infarction. *Arch Intern Med* 2005; 165: 1630–1636.
35. French JK, Feldman HA, Assmann SF, et al. Influence of thrombolytic therapy, with or without intra-aortic balloon counterpulsation, on 12-month survival in the SHOCK trial. *Am Heart J* 2003; 146: 804–810.
36. Bates ER and Topol EJ. Limitations of thrombolytic therapy for acute myocardial infarction complicated by congestive heart failure and cardiogenic shock. *J Am Coll Cardiol* 1991; 18: 1077–1084.
37. White HD, Assmann SF, Sanborn TA, et al. Comparison of percutaneous coronary intervention and coronary artery bypass

grafting after acute myocardial infarction complicated by cardiogenic shock: Results from the Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock (SHOCK) trial. *Circulation* 2005; 112: 1992–2001.
38. Yan BP, Clark DJ, Buxton B, et al. Clinical characteristics and early mortality of patients undergoing coronary artery bypass grafting compared to percutaneous coronary intervention: Insights from the Australasian Society of Cardiac and Thoracic Surgeons (ASCTS) and the Melbourne Interventional Group (MIG) Registries. *Heart Lung Circ* 2009; 18: 184–190.
39. Chiu FC, Chang SN, Lin JW, et al. Coronary artery bypass graft surgery provides better survival in patients with acute coronary syndrome or ST-segment elevation myocardial infarction experiencing cardiogenic shock after percutaneous coronary intervention: A propensity score analysis. *J Thorac Cardiovasc Surg* 2009; 138: 1326–1330.
40. Mehta RH, Ou F-S, Peterson ED, et al. Clinical significance of post-procedural TIMI flow in patients with cardiogenic shock undergoing primary percutaneous coronary intervention. *JACC Cardiovasc Interv* 2009; 2: 56–64.
41. Zeymer U, Vogt A, Zahn R, et al. Predictors of in-hospital mortality in 1333 patients with acute myocardial infarction complicated by cardiogenic shock treated with primary percutaneous coronary intervention (PCI): Results of the primary PCI registry of the Arbeitsgemeinschaft Leitende Kardiologische Krankenhausärzte (ALKK). *Eur Heart J* 2004; 25: 322–328.
42. Ortolani P, Marzocchi A, Marrozzini C, et al. Usefulness of prehospital triage in patients with cardiogenic shock complicating ST-elevation myocardial infarction treated with primary percutaneous coronary intervention. *Am J Cardiol* 2007; 100: 787–792.
43. Antoniucci D, Valenti R, Santoro GM, et al. Systematic direct angioplasty and stent-supported direct angioplasty therapy for cardiogenic shock complicating acute myocardial infarction: In-hospital and long-term survival. *J Am Coll Cardiol* 1998; 31: 294–300.
44. Chan AW, Chew DP, Bhatt DL, et al. Long-term mortality benefit with the combination of stents and abciximab for cardiogenic shock complicating acute myocardial infarction. *Am J Cardiol* 2002; 89: 132–136.
45. Webb JG, Carere RG, Hilton JD, et al. Usefulness of coronary stenting for cardiogenic shock. *Am J Cardiol* 1997; 79: 81–84.
46. Garg A, Brodie BR, Stuckey TD, et al. New generation drug-eluting stents for ST-Elevation myocardial infarction: A new paradigm for safety. *Catheter Cardiovasc Interv* 2013. 84: 955–962.
47. Palmerini T, Biondi-Zoccai G, Della Riva D, et al. Clinical outcomes with drug-eluting and bare-metal stents in patients with ST-segment elevation myocardial infarction: Evidence from a comprehensive network meta-analysis. *J Am Coll Cardiol* 2013; 62: 496–504.
48. Jaguszewski M, Ghadri JR, Seifert B, et al. Drug-eluting stents vs. bare metal stents in patients with cardiogenic shock: A comparison by propensity score analysis. *J Cardiovasc Med (Hagerstown)* 2014.
49. Orban M, Mayer K, Morath T, et al. Prasugrel vs clopidogrel in cardiogenic shock patients undergoing primary PCI for acute myocardial infarction. Results of the ISAR-SHOCK registry. *Thromb Haemost* 2014; 112: 1190–1197.
50. Alexopoulos D, Xanthopoulou I, Gkizas V, et al. Randomized assessment of ticagrelor versus prasugrel antiplatelet effects in patients with ST-segment–elevation myocardial infarction. *Circ Cardiovasc Interv* 2012; 5: 797–804.
51. Parodi G, Valenti R, Bellandi B, et al. Comparison of prasugrel and ticagrelor loading doses in ST-segment elevation myocardial infarction patients: RAPID (Rapid Activity of Platelet Inhibitor Drugs) primary PCI study. *J Am Coll Cardiol* 2013; 61: 1601–1606.
52. Angiolillo DJ, Schneider DJ, Bhatt DL, et al. Pharmacodynamic effects of cangrelor and clopidogrel: The platelet function substudy from the cangrelor versus standard therapy to achieve optimal management of platelet inhibition (CHAMPION) trials. *J Thromb Thrombolysis* 2012; 34: 44–55.
53. Giri S, Mitchel J, Azar RR, et al. Results of primary percutaneous transluminal coronary angioplasty plus abciximab with or without stenting for acute myocardial infarction complicated by cardiogenic shock. *Am J Cardiol* 2002; 89: 126–131.
54. Hasdai D, Harrington RA, Hochman JS, et al. Platelet glycoprotein IIb/IIIa blockade and outcome of cardiogenic shock complicating acute coronary syndromes without persistent ST-segment elevation. *J Am Coll Cardiol* 2000; 36: 685–692.
55. Zeymer U, Tebbe U, Weber M, et al. Prospective evaluation of early abciximab and primary percutaneous intervention for patients with ST elevation myocardial infarction complicated by cardiogenic shock: Results of the REO-SHOCK trial. *J Invasive Cardiol* 2003; 15: 385–389.
56. Tousek P, Rokyta R, Tesarova J, et al. Routine upfront abciximab versus standard periprocedural therapy in patients undergoing primary percutaneous coronary intervention for cardiogenic shock: The PRAGUE-7 Study. An open randomized multicentre study. *Acute Cardiac Care* 2011; 13: 116–122.
57. Iqbal J, Sumaya W, Tatman V, et al. Incidence and predictors of stent thrombosis: A single-centre study of 5,833 consecutive patients undergoing coronary artery stenting. *EuroIntervention* 2013; 9: 62–69.
58. Svilaas T, Vlaar PJ, van der Horst IC, et al. Thrombus aspiration during primary percutaneous coronary intervention. *N Engl J Med* 2008; 358: 557–567.
59. Vlaar PJ, Svilaas T, van der Horst IC, et al. Cardiac death and reinfarction after 1 year in the Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study (TAPAS): A 1-year follow-up study. *Lancet* 2008; 371: 1915–1920.
60. Fröbert O, Lagerqvist B, Olivecrona GK, et al. Thrombus Aspiration during ST-segment elevation myocardial infarction. *N Engl J Med* 2013; 369: 1587–1597.
61. Lagerqvist B, Frobert O, Olivecrona GK, et al. Outcomes 1 year after thrombus aspiration for myocardial infarction. *N Engl J Med* 2014; 371: 1111–1120.
62. Tomassini F, Gagnor A, Montali N, et al. Impact of thrombus aspiration during primary percutaneous coronary intervention in cardiogenic shock complicating ST-segment

elevation myocardial infarction. *Cardiovasc Revasc Med* 2013; 14: 307–310.
63. Sanborn TA, Sleeper LA, Webb JG, et al. Correlates of one-year survival inpatients with cardiogenic shock complicating acute myocardial infarction: Angiographic findings from the SHOCK trial. *J Am Coll Cardiol* 2003; 42: 1373–1379.
64. Mylotte D, Morice M-C, Eltchaninoff H, et al. Primary percutaneous coronary intervention in patients with acute myocardial infarction, resuscitated cardiac arrest, and cardiogenic shock: The role of primary multivessel revascularization. *JACC Cardiovasc Interv* 2013; 6: 115–125.
65. Hussain F, Philipp RK, Ducas RA, et al. The ability to achieve complete revascularization is associated with improved in-hospital survival in cardiogenic shock due to myocardial infarction: Manitoba cardiogenic shock registry investigators. *Catheter Cardiovasc Interv* 2011; 78: 540–548.
66. Bauer T, Zeymer U, Hochadel M, et al. Use and outcomes of multivessel percutaneous coronary intervention in patients with acute myocardial infarction complicated by cardiogenic shock (from the EHS-PCI Registry). *Am J Cardiol* 2012; 109: 941–946.
67. Yang JH, Hahn J-Y, Song PS, et al. Percutaneous coronary intervention for nonculprit vessels in cardiogenic shock complicating ST-segment elevation acute myocardial infarction. *Crit Care Med* 2014; 42: 17–25.
68. Webb JG, Lowe AM, Sanborn TA, et al. Percutaneous coronary intervention for cardiogenic shock in the SHOCK trial. *J Am Coll Cardiol* 2003; 42: 1380–1386.
69. Thiele H, Allam B, Chatellier G, et al. Shock in acute myocardial infarction: The Cape Horn for trials? *Eur Heart J* 2010; 31: 1828–1835.
70. Goldberg S, Grossman W, Markis JE, et al. Total occlusion of the left main coronary artery. A clinical, hemodynamic and angiographic profile. *Am J Med* 1978; 64: 3–8.
71. Spiecker M, Erbel R, Rupprecht HJ, et al. Emergency angioplasty of totally occluded left main coronary artery in acute myocardial infarction and unstable angina pectoris – institutional experience and literature review. *Eur Heart J* 1994; 15: 602–607.
72. Kim U, Park JS, Kang SW, et al. Outcomes according to presentation with versus without cardiogenic shock in patients with left main coronary artery stenosis and acute myocardial infarction. *Am J Cardiol* 2012; 110: 36–39.
73. Lee MS, Sillano D, Latib A, et al. Multicenter international registry of unprotected left main coronary artery percutaneous coronary intervention with drug-eluting stents in patients with myocardial infarction. *Catheter Cardiovasc Interv* 2009; 73: 15–21.
74. Lee S-W, Hong M-K, Lee CW, et al. Early and late clinical outcomes after primary stenting of the unprotected left main coronary artery stenosis in the setting of acute myocardial infarction. *Int J Cardiol* 2004; 97: 73–76.
75. Prasad SB, Whitbourn R, Malaiapan Y, et al. Primary percutaneous coronary intervention for acute myocardial infarction caused by unprotected left main stem thrombosis. *Catheter Cardiovasc Interv* 2009; 73: 301–307.
76. Tan CH, Hong MK, Lee CW, et al. Percutaneous coronary intervention with stenting of left main coronary artery with drug-eluting stent in the setting of acute ST elevation myocardial infarction. *Int J Cardiol* 2008; 126: 224–228.
77. Montalescot G, Brieger D, Eagle KA, et al. Unprotected left main revascularization in patients with acute coronary syndromes. *Eur Heart J* 2009; 30: 2308–2317.
78. Pappalardo A, Mamas MA, Imola F, et al. Percutaneous coronary intervention of unprotected left main coronary artery disease as culprit lesion in patients with acute myocardial infarction. *JACC Cardiovasc Interv* 2011; 4: 618–626.
79. Pedrazzini GB, Radovanovic D, Vassalli G, et al. Primary percutaneous coronary intervention for unprotected left main disease in patients with acute ST-segment elevation myocardial infarction: The AMIS (Acute Myocardial Infarction in Switzerland) plus registry experience. *JACC Cardiovasc Interv* 2011; 4: 627–633.
80. Vis MM, Beijk MA, Grundeken MJ, et al. A systematic review and meta-analysis on primary percutaneous coronary intervention of an unprotected left main coronary artery culprit lesion in the setting of acute myocardial infarction. *JACC Cardiovasc Interv* 2013; 6: 317–324.
81. Nagaoka H, Ohnuki M, Hirooka K, et al. Emergency coronary artery bypass grafting for left main coronary artery disease. *Kyobu Geka* 1999; 52: 634–638.
82. Shigemitsu O, Hadama T, Miyamoto S, et al. Acute myocardial infarction due to left main coronary artery occlusion. Therapeutic strategy. *Jpn J Thorac Cardiovasc Surg* 2002; 50: 146–151.
83. Lee MS, Tseng C-H, Barker CM, et al. Outcome after surgery and percutaneous intervention for cardiogenic shock and left main disease. *Ann Thorac Surg* 2008; 86: 29–34.
84. Dzavik V, Sleeper LA, Picard MH, et al. Outcome of patients aged >or=75 years in the SHould we emergently revascularize Occluded Coronaries in cardiogenic shocK (SHOCK) trial: Do elderly patients with acute myocardial infarction complicated by cardiogenic shock respond differently to emergent revascularization? *Am Heart J* 2005; 149: 1128–1134.
85. Dzavik V, Sleeper LA, Cocke TP, et al. Early revascularization is associated with improved survival in elderly patients with acute myocardial infarction complicated by cardiogenic shock: A report from the SHOCK Trial Registry. *Eur Heart J* 2003; 24: 828–837.
86. Devlin G, Gore JM, Elliott J, et al. Management and 6-month outcomes in elderly and very elderly patients with high-risk non-ST-elevation acute coronary syndromes: The Global Registry of Acute Coronary Events. *Eur Heart J* 2008; 29: 1275–1282.
87. Lim HS, Farouque O, Andrianopoulos N, et al. Survival of elderly patients undergoing percutaneous coronary intervention for acute myocardial infarction complicated by cardiogenic shock. *JACC Cardiovasc Interv* 2009; 2: 146–152.
88. Tomassini F, Gagnor A, Migliardi A, et al. Cardiogenic shock complicating acute myocardial infarction in the elderly: Predictors of long-term survival. *Catheter Cardiovasc Interv* 2011; 78: 505–511.
89. Thomas SS and Nohria A. Hemodynamic classifications of acute heart failure and their clinical application: – An update. *Circ J* 2012; 76: 278–286.

90. Nohria A, Tsang SW, Fang JC, et al. Clinical assessment identifies hemodynamic profiles that predict outcomes in patients admitted with heart failure. *J Am Coll Cardiol* 2003; 41: 1797–1804.
91. Myburgh JA, Finfer S, Bellomo R, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med* 2012; 367: 1901–1911.
92. Perner A, Haase N, Guttormsen AB, et al. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *N Engl J Med* 2012; 367: 124–134.
93. Annane D, Siami S, Jaber S, et al. Effects of fluid resuscitation with colloids vs crystalloids on mortality in critically ill patients presenting with hypovolemic shock: The cristal randomized trial. *JAMA* 2013; 310: 1809–1817.
94. Seymour CW and Angus DC. Making a pragmatic choice for fluid resuscitation in critically ill patients. *JAMA* 2013; 310: 1803–1804.
95. Havel C, Arrich J, Losert H, et al. Vasopressors for hypotensive shock. *Cochrane Database Syst Rev* 2011: CD003709.
96. Lin H and Young DB. Opposing effects of plasma epinephrine and norepinephrine on coronary thrombosis in vivo. *Circulation* 1995; 91: 1135–1142.
97. Landry DW and Oliver JA. The pathogenesis of vasodilatory shock. *N Engl J Med* 2001; 345: 588–595.
98. Jolly S, Newton G, Horlick E, et al. Effect of vasopressin on hemodynamics in patients with refractory cardiogenic shock complicating acute myocardial infarction. *Am J Cardiol* 2005; 96: 1617–1620.
99. Fries M, Weil MH, Chang YT, et al. Microcirculation during cardiac arrest and resuscitation. *Crit Care Med* 2006; 34: S454–S457.
100. den Uil CA, Lagrand WK, van der Ent M, et al. Impaired microcirculation predicts poor outcome of patients with acute myocardial infarction complicated by cardiogenic shock. *Eur Heart J* 2010; 31: 3032–3039.
101. Jung C, Lauten A and Ferrari M. Microcirculation in cardiogenic shock: From scientific bystander to therapy target. *Crit Care* 2010; 14: 193.
102. Perez P, Kimmoun A, Blime V, et al. Increasing mean arterial pressure in cardiogenic shock secondary to myocardial infarction: Effects on hemodynamics and tissue oxygenation. *Shock* 2014; 41: 269–274.
103. Unverzagt S, Wachsmuth L, Hirsch K, et al. Inotropic agents and vasodilator strategies for acute myocardial infarction complicated by cardiogenic shock or low cardiac output syndrome. *Cochrane Database Syst Rev* 2014; 1: CD009669.
104. Thackray S, Easthaugh J, Freemantle N, et al. The effectiveness and relative effectiveness of intravenous inotropic drugs acting through the adrenergic pathway in patients with heart failure-a meta-regression analysis. *Eur J Heart Fail* 2002; 4: 515–529.
105. Valente S, Lazzeri C, Vecchio S, et al. Predictors of in-hospital mortality after percutaneous coronary intervention for cardiogenic shock. *Int J Cardiol* 2007; 114: 176–182.
106. Abraham WT, Adams KF, Fonarow GC, et al. In-hospital mortality in patients with acute decompensated heart failure requiring intravenous vasoactive medications: An analysis from the Acute Decompensated Heart Failure National Registry (ADHERE). *J Am Coll Cardiol* 2005; 46: 57–64.
107. Grose R, Strain J, Greenberg M, et al. Systemic and coronary effects of intravenous milrinone and dobutamine in congestive heart failure. *J Am Coll Cardiol* 1986; 7: 1107–1113.
108. Packer M, Carver JR, Rodeheffer RJ, et al. Effect of oral milrinone on mortality in severe chronic heart failure. The PROMISE Study Research Group. *N Engl J Med* 1991; 325: 1468–1475.
109. Givertz MM, Andreou C, Conrad CH, et al. Direct myocardial effects of levosimendan in humans with left ventricular dysfunction: Alteration of force-frequency and relaxation-frequency relationships. *Circulation* 2007; 115: 1218–1224.
110. Todaka K, Wang J, Yi GH, et al. Effects of levosimendan on myocardial contractility and oxygen consumption. *J Pharmacol Exp Ther* 1996; 279: 120–127.
111. De Luca L, Colucci WS, Nieminen MS, et al. Evidence-based use of levosimendan in different clinical settings. *Eur Heart J* 2006; 27: 1908–1920.
112. Omerovic E, Ramunddal T, Albertsson P, et al. Levosimendan neither improves nor worsens mortality in patients with cardiogenic shock due to ST-elevation myocardial infarction. *Vasc Health Risk Manag* 2010; 6: 657–663.
113. Teerlink JR. A novel approach to improve cardiac performance: Cardiac myosin activators. *Heart Fail Rev* 2009; 14: 289–298.
114. Teerlink JR, Clarke CP, Saikali KG, et al. Dose-dependent augmentation of cardiac systolic function with the selective cardiac myosin activator, omecamtiv mecarbil: A first-in-man study. *Lancet* 2011; 378: 667–675.
115. Cleland JG, Teerlink JR, Senior R, et al. The effects of the cardiac myosin activator, omecamtiv mecarbil, on cardiac function in systolic heart failure: A double-blind, placebo-controlled, crossover, dose-ranging phase 2 trial. *Lancet* 2011; 378: 676–683.
116. Teerlink JR, Felker GM, McMurray J, et al. A phase 2 study of intravenous Omecamtiv Mecarbil, a novel cardiac myosin activator, in patients with acute heart failure. *Eur Heart J* 2013; 34 (Suppl. 1, abstract only).
117. Gheorghiade M, Blair JE, Filippatos GS, et al. Hemodynamic, echocardiographic, and neurohormonal effects of istaroxime, a novel intravenous inotropic and lusitropic agent: A randomized controlled trial in patients hospitalized with heart failure. *J Am Coll Cardiol* 2008; 51: 2276–2285.
118. Geppert A, Dorninger A, Delle-Karth G, et al. Plasma concentrations of interleukin-6, organ failure, vasopressor support, and successful coronary revascularization in predicting 30-day mortality of patients with cardiogenic shock complicating acute myocardial infarction. *Crit Care Med* 2006; 34: 2035–2042.
119. Jarai R, Fellner B, Haoula D, et al. Early assessment of outcome in cardiogenic shock: Relevance of plasma N-terminal pro-B-type natriuretic peptide and interleukin-6 levels. *Crit Care Med* 2009; 37: 1837–1844.
120. Nicholls SJ, Wang Z, Koeth R, et al. Metabolic profiling of arginine and nitric oxide pathways predicts hemodynamic abnormalities and mortality in patients with cardiogenic shock after acute myocardial infarction. *Circulation* 2007; 116: 2315–2324.

121. Poss J, Mahfoud F, Seiler S, et al. FGF-23 is associated with increased disease severity and early mortality in cardiogenic shock. *Eur Heart J Acute Cardiovasc Care* 2013; 2: 211–218.
122. Stegman BM, Newby LK, Hochman JS, et al. Post-myocardial infarction cardiogenic shock is a systemic illness in need of systemic treatment: Is therapeutic hypothermia one possibility? *J Am Coll Cardiol* 2012; 59: 644–647.
123. Schmidt-Schweda S, Ohler A, Post H, et al. Moderate hypothermia for severe cardiogenic shock (COOL Shock Study I & II). *Resuscitation* 2013; 84: 319–325.
124. Zobel C, Adler C, Kranz A, et al. Mild therapeutic hypothermia in cardiogenic shock syndrome. *Crit Care Med* 2012; 40: 1715–1723.
125. Nielsen N, Wetterslev J, Cronberg T, et al. Targeted temperature management at 33°C versus 36°C after cardiac arrest. *N Engl J Med* 2013; 369: 2197–2206.
126. Werdan K, Russ M, Buerke M, et al. Cardiogenic shock due to myocardial infarction: Diagnosis, monitoring and treatment: A German–Austrian S3 Guideline. *Dtsch Arztebl Int* 2012; 109: 343–351.
127. Gall SA Jr, Olsen CO, Reves JG, et al. Beneficial effects of endotracheal extubation on ventricular performance. Implications for early extubation after cardiac operations. *J Thorac Cardiovasc Surg* 1988; 95: 819–827.
128. Grace MP and Greenbaum DM. Cardiac performance in response to PEEP in patients with cardiac dysfunction. *Crit Care Med* 1982; 10: 358–360.
129. Kontoyannis DA, Nanas JN, Kontoyannis SA, et al. Mechanical ventilation in conjunction with the intra-aortic balloon pump improves the outcome of patients in profound cardiogenic shock. *Intensive Care Med* 1999; 25: 835–838.
130. Wiesen J, Ornstein M, Tonelli AR, et al. State of the evidence: mechanical ventilation with PEEP in patients with cardiogenic shock. *Heart* 2013; 99: 1812–1817.
131. Kouraki K, Schneider S, Uebis R, et al. Characteristics and clinical outcome of 458 patients with acute myocardial infarction requiring mechanical ventilation. Results of the BEAT registry of the ALKK-study group. *Clin Res Cardiol* 2011; 100: 235–239.
132. Horan LG and Flowers NC. Right ventricular infarction: specific requirements of management. *Am Fam Physician* 1999; 60: 1727–1734.
133. Shah PK, Maddahi J, Berman DS, et al. Scintigraphically detected predominant right ventricular dysfunction in acute myocardial infarction: Clinical and hemodynamic correlates and implications for therapy and prognosis. *J Am Coll Cardiol* 1985; 6: 1264–1272.
134. Hamon M, Agostini D, Le Page O, et al. Prognostic impact of right ventricular involvement in patients with acute myocardial infarction: Meta-analysis. *Crit Care Med* 2008; 36: 2023–2033.
135. Mehta SR, Eikelboom JW, Natarajan MK, et al. Impact of right ventricular involvement on mortality and morbidity in patients with inferior myocardial infarction. *J Am Coll Cardiol* 2001; 37: 37–43.
136. Zehender M, Kasper W, Kauder E, et al. Right ventricular infarction as an independent predictor of prognosis after acute inferior myocardial infarction. *N Engl J Med* 1993; 328: 981–988.
137. Gumina RJ, Murphy JG, Rihal CS, et al. Long-term survival after right ventricular infarction. *Am J Cardiol* 2006; 98: 1571–1573.
138. Bowers TR, O'Neill WW, Grines C, et al. Effect of reperfusion on biventricular function and survival after right ventricular infarction. *N Engl J Med* 1998; 338: 933–940.
139. O'Rourke RA and Dell'Italia LJ. Diagnosis and management of right ventricular myocardial infarction. *Curr Probl Cardiol* 2004; 29: 6–47.
140. Baigrie RS, Haq A, Morgan CD, et al. The spectrum of right ventricular involvement in inferior wall myocardial infarction: A clinical, hemodynamic and noninvasive study. *J Am Coll Cardiol* 1983; 1: 1396–1404.
141. Dell'Italia LJ, Starling MR, Crawford MH, et al. Right ventricular infarction: identification by hemodynamic measurements before and after volume loading and correlation with noninvasive techniques. *J Am Coll Cardiol* 1984; 4: 931–939.
142. Goldstein JA, Vlahakes GJ, Verrier ED, et al. Volume loading improves low cardiac output in experimental right ventricular infarction. *J Am Coll Cardiol* 1983; 2: 270–278.
143. Lopez-Sendon J, Coma-Canella I and Vinuelas Adanez J. Volume loading in patients with ischemic right ventricular dysfunction. *Eur Heart J* 1981; 2: 329–338.
144. Goldstein JA. Acute right ventricular infarction: insights for the interventional era. *Curr Probl Cardiol* 2012; 37: 533–557.
145. Goldstein JA. Pathophysiology and management of right heart ischemia. *J Am Coll Cardiol* 2002; 40: 841–853.
146. Goldstein JA, Tweddell JS, Barzilai B, et al. Right atrial ischemia exacerbates hemodynamic compromise associated with experimental right ventricular dysfunction. *J Am Coll Cardiol* 1991; 18: 1564–1572.
147. Kinch JW and Ryan TJ. Right ventricular infarction. *N Engl J Med* 1994; 330: 1211–1217.
148. Love JC, Haffajee CI, Gore JM, et al. Reversibility of hypotension and shock by atrial or atrioventricular sequential pacing in patients with right ventricular infarction. *Am Heart J* 1984; 108: 5–13.
149. Topol EJ, Goldschlager N, Ports TA, et al. Hemodynamic benefit of atrial pacing in right ventricular myocardial infarction. *Ann Intern Med* 1982; 96: 594–597.
150. Dell'Italia LJ, Starling MR, Blumhardt R, et al. Comparative effects of volume loading, dobutamine, and nitroprusside in patients with predominant right ventricular infarction. *Circulation* 1985; 72: 1327–1335.
151. Ferrario M, Poli A, Previtali M, et al. Hemodynamics of volume loading compared with dobutamine in severe right ventricular infarction. *Am J Cardiol* 1994; 74: 329–333.
152. Evora PR, Pearson PJ and Schaff HV. Arginine vasopressin induces endothelium-dependent vasodilatation of the pulmonary artery. V1-receptor-mediated production of nitric oxide. *Chest* 1993; 103: 1241–1245.
153. Tayama E, Ueda T, Shojima T, et al. Arginine vasopressin is an ideal drug after cardiac surgery for the management of low systemic vascular resistant hypotension concomitant with pulmonary hypertension. *Interact Cardiovasc Thorac Surg* 2007; 6: 715–719.

154. Price LC, Wort SJ, Finney SJ, et al. Pulmonary vascular and right ventricular dysfunction in adult critical care: Current and emerging options for management: A systematic literature review. *Crit Care* 2010; 14: R169.
155. Fujita Y, Nishida O, Sobue K, et al. Nitric oxide inhalation is useful in the management of right ventricular failure caused by myocardial infarction. *Crit Care Med* 2002; 30: 1379–1381.
156. Inglessis I, Shin JT, Lepore JJ, et al. Hemodynamic effects of inhaled nitric oxide in right ventricular myocardial infarction and cardiogenic shock. *J Am Coll Cardiol* 2004; 44: 793–798.
157. Valenti V, Patel AJ, Sciarretta S, et al. Use of inhaled nitric oxide in the treatment of right ventricular myocardial infarction. *Am J Emerg Med* 2011; 29: e473–e475.
158. Loh E, Stamler JS, Hare JM, et al. Cardiovascular effects of inhaled nitric oxide in patients with left ventricular dysfunction. *Circulation* 1994; 90: 2780–2785.
159. Semigran MJ, Cockrill BA, Kacmarek R, et al. Hemodynamic effects of inhaled nitric oxide in heart failure. *J Am Coll Cardiol* 1994; 24: 982–988.
160. Jardin F and Vieillard-Baron A. Right ventricular function and positive pressure ventilation in clinical practice: From hemodynamic subsets to respirator settings. *Intensive Care Med* 2003; 29: 1426–1434.
161. Balanos GM, Talbot NP, Dorrington KL, et al. Human pulmonary vascular response to 4 h of hypercapnia and hypocapnia measured using Doppler echocardiography. *J Appl Physiol (1985)* 2003; 94: 1543–1551.
162. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med* 2000; 342: 1301–1308.
163. Vieillard-Baron A and Jardin F. Why protect the right ventricle in patients with acute respiratory distress syndrome? *Curr Opin Crit Care* 2003; 9: 15–21.
164. Scheidt S, Wilner G, Mueller H, et al. Intra-aortic balloon counterpulsation in cardiogenic shock. Report of a co-operative clinical trial. *N Engl J Med* 1973; 288: 979–984.
165. Ouweneel DM and Henriques JP. Percutaneous cardiac support devices for cardiogenic shock: Current indications and recommendations. *Heart* 2012; 98: 1246–1254.
166. Sjauw KD, Engstrom AE, Vis MM, et al. A systematic review and meta-analysis of intra-aortic balloon pump therapy in ST-elevation myocardial infarction: Should we change the guidelines? *Eur Heart J* 2009; 30: 459–468.
167. Sjauw KD, Engstrom AE, Vis MM, et al. Efficacy and timing of intra-aortic counterpulsation in patients with ST-elevation myocardial infarction complicated by cardiogenic shock. *Neth Heart J* 2012; 20: 402–409.
168. Thiele H, Lauer B, Hambrecht R, et al. Reversal of cardiogenic shock by percutaneous left atrial-to-femoral arterial bypass assistance. *Circulation* 2001; 104: 2917–2922.
169. Kar B, Gregoric ID, Basra SS, et al. The percutaneous ventricular assist device in severe refractory cardiogenic shock. *J Am Coll Cardiol* 2011; 57: 688–696.
170. Sjauw KD, Remmelink M, Baan J Jr, et al. Left ventricular unloading in acute ST-segment elevation myocardial infarction patients is safe and feasible and provides acute and sustained left ventricular recovery. *J Am Coll Cardiol* 2008; 51: 1044–1046.
171. Manzo-Silberman S, Fichet J, Mathonnet A, et al. Percutaneous left ventricular assistance in post cardiac arrest shock: Comparison of intra aortic blood pump and IMPELLA Recover LP2.5. *Resuscitation* 2013; 84: 609–615.
172. O'Neill WW, Schreiber T, Wohns DHW, et al. The current use of Impella 2.5 in acute myocardial infarction complicated by cardiogenic shock: Results from the USpella registry. *J Interv Cardiol* 2014; 27: 1–11.
173. Lauten A, Engstrom AE, Jung C, et al. Percutaneous left-ventricular support with the Impella-2.5-assist device in acute cardiogenic shock: Results of the Impella-EUROSHOCK-registry. *Circ Heart Fail* 2013; 6: 23–30.
174. Cheng JM, den Uil CA, Hoeks SE, et al. Percutaneous left ventricular assist devices vs. intra-aortic balloon pump counterpulsation for treatment of cardiogenic shock: A meta-analysis of controlled trials. *Eur Heart J* 2009; 30: 2102–2108.
175. Arlt M, Philipp A, Voelkel S, et al. Hand-held minimised extracorporeal membrane oxygenation: A new bridge to recovery in patients with out-of-centre cardiogenic shock. *Eur J Cardiothorac Surg* 2011; 40: 689–694.
176. Beurtheret S, Mordant P, Paoletti X, et al. Emergency circulatory support in refractory cardiogenic shock patients in remote institutions: A pilot study (the cardiac-RESCUE program). *Eur Heart J* 2013; 34: 112–120.
177. Lebreton G, Pozzi M, Luyt CE, et al. Out-of-hospital extracorporeal life support implantation during refractory cardiac arrest in a half-marathon runner. *Resuscitation* 2011; 82: 1239–1242.
178. Sheu JJ, Tsai TH, Lee FY, et al. Early extracorporeal membrane oxygenator-assisted primary percutaneous coronary intervention improved 30-day clinical outcomes in patients with ST-segment elevation myocardial infarction complicated with profound cardiogenic shock. *Crit Care Med* 2010; 38: 1810–1817.
179. Tsao NW, Shih CM, Yeh JS, et al. Extracorporeal membrane oxygenation-assisted primary percutaneous coronary intervention may improve survival of patients with acute myocardial infarction complicated by profound cardiogenic shock. *J Crit Care* 2012; 27: 530.e1–e11.
180. Aissaoui N, Luyt CE, Leprince P, et al. Predictors of successful extracorporeal membrane oxygenation (ECMO) weaning after assistance for refractory cardiogenic shock. *Intensive Care Med* 2011; 37: 1738–1745.
181. Chen JS, Ko WJ, Yu HY, et al. Analysis of the outcome for patients experiencing myocardial infarction and cardiopulmonary resuscitation refractory to conventional therapies necessitating extracorporeal life support rescue. *Crit Care Med* 2006; 34: 950–957.
182. Demondion P, Fournel L, Golmard JL, et al. Predictors of 30-day mortality and outcome in cases of myocardial infarction with cardiogenic shock treated by extracorporeal life support. *Eur J Cardiothorac Surg* 2014; 45: 47–54.
183. Kim H, Lim SH, Hong J, et al. Efficacy of veno-arterial extracorporeal membrane oxygenation in acute myocardial infarction with cardiogenic shock. *Resuscitation* 2012; 83: 971–975.

184. Sakamoto S, Taniguchi N, Nakajima S, et al. Extracorporeal life support for cardiogenic shock or cardiac arrest due to acute coronary syndrome. *Ann Thorac Surg* 2012; 94: 1–7.
185. Kawashima D, Gojo S, Nishimura T, et al. Left ventricular mechanical support with Impella provides more ventricular unloading in heart failure than extracorporeal membrane oxygenation. *ASAIO J* 2011; 57: 169–176.
186. Beurtheret S, Mordant P, Pavie A, et al. Impella and extracorporeal membrane oxygenation: A demanding combination. *ASAIO J* 2012; 58: 291–293.
187. Barbone A, Malvindi PG, Ferrara P, et al. Left ventricle unloading by percutaneous pigtail during extracorporeal membrane oxygenation. *Interact Cardiovasc Thorac Surg* 2011; 13: 293–295.
188. Avalli L, Maggioni E, Sangalli F, et al. Percutaneous left-heart decompression during extracorporeal membrane oxygenation: An alternative to surgical and transeptal venting in adult patients. *ASAIO J* 2011; 57: 38–40.
189. Aiyagari RM, Rocchini AP, Remenapp RT, et al. Decompression of the left atrium during extracorporeal membrane oxygenation using a transseptal cannula incorporated into the circuit. *Crit Care Med* 2006; 34: 2603–2606.
190. Russo CF, Cannata A, Lanfranconi M, et al. Veno-arterial extracorporeal membrane oxygenation using Levitronix centrifugal pump as bridge to decision for refractory cardiogenic shock. *J Thorac Cardiovasc Surg* 2010; 140: 1416–1421.
191. Trummer G, Benk C, Heilmann C, et al. Visualization of hypoxemic coronary perfusion despite full retrograde extracorporeal circulatory life support. *Eur J Cardiothorac Surg* 2013; 43: e47.
192. Moravec R, Neitzel T, Stiller M, et al. First experiences with a combined usage of veno-arterial and veno-venous ECMO in therapy-refractory cardiogenic shock patients with cerebral hypoxemia. *Perfusion* 2014; 29: 200–209.
193. Ma P, Zhang Z, Song T, et al. Combining ECMO with IABP for the treatment of critically ill adult heart failure patients. *Heart Lung Circ* 2014; 23: 363–368.
194. Madershahian N, Wippermann J, Liakopoulos O, et al. The acute effect of IABP-induced pulsatility on coronary vascular resistance and graft flow in critical ill patients during ECMO. *J Cardiovasc Surg (Torino)* 2011; 52: 411–418.
195. Ro SK, Kim JB, Jung SH, et al. Extracorporeal life support for cardiogenic shock: Influence of concomitant intra-aortic balloon counterpulsation. *Eur J Cardiothorac Surg* 2014; 46: 186–192.
196. Affronti A, di Bella I, Carino D, et al. Levosimendan may improve weaning outcomesin venoarterial ECMO patients. *ASAIO J* 2013; 59: 554–557.
197. Cheng R, Hachamovitch R, Kittleson M, et al. Complications of extracorporeal membrane oxygenation for treatment of cardiogenic shock and cardiac arrest: A meta-analysis of 1,866 adult patients. *Ann Thorac Surg* 2014; 97: 610–616.
198. Zangrillo A, Biondi-Zoccai G, Landoni G, et al. Extracorporeal membrane oxygenation (ECMO) in patients with H1N1 influenza infection: A systematic review and meta-analysis including 8 studies and 266 patients receiving ECMO. *Crit Care* 2013; 17: R30.
199. Paden ML, Conrad SA, Rycus PT, et al. Extracorporeal Life Support Organization Registry Report 2012. *ASAIO J* 2013; 59: 202–210.
200. Lazzeri C, Bernardo P, Sori A, et al. Venous-arterial extracorporeal membrane oxygenation for refractory cardiac arrest: A clinical challenge. *Eur Heart J Acute Cardiovasc Care* 2013; 2: 118–126.