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Editorial

Second Edition of the German–Austrian S3 Guideline "Infarction-Related Cardiogenic Shock: Diagnosis, Monitoring and Treatment"

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1. Introduction

The mortality of patients with MI has significantly decreased in recent decades, mainly due to early reperfusion therapy with a probability of surviving of more than 90% if the patient reaches the hospital. However, this does not apply to cardiogenic shock occurring initially or in the course of infarction, with only one in two patients surviving the hospital stay [1]. One main cause of the high mortality among patients with infarction-related cardiogenic shock (ICS) is the development of systemic inflammation with inappropriate vasodilatation leading to multiorgan dysfunction syndrome (MODS) that can develop despite recommended revascularization of the culprit lesion as early as possible [2,3]. Congruently, IL-6 represents a reliable, independent early prognostic marker of mortality in CS patients, whereas Nt-proBNP seems to be of lower relevance. Consequently, ICS is not just a disease of the heart but affects all organs of the patient, who, therefore, requires appropriate organ support and intensive care management. The current European and American myocardial infarction guidelines focus their recommendations mostly on "interventional aspects" in the treatment of coronary artery disease, whereas the critical care topics are not addressed appropriately [4,5]. To overcome this shortcoming, German and Austrian cardiologists, intensivists, cardiac surgeons, anesthetists and rehabilitation specialists, together with their professional societies and associations, developed a guideline for "infarction-related cardiogenic shock" under the auspices of the Association of Scientific Medical Societies in Germany (AWMF, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften) by a fully formalized, systematic guideline development process (S3 stage).

As mentioned above, the prognosis of patients with ICS does not mainly depend on impaired cardiac function but on the resulting impairment of organ blood supply and microcirculation with consequent MODS. Therefore, the objective of this multinational guideline is to provide an adequate concept of both—the cardiological/cardiosurgical (reperfusion) and the critical care aspects for ICS. Evidence on the diagnosis, monitoring and therapy of ICS was collected. Recommendations were compiled in a nominal group process by members of the German and Austrian Societies for Cardiology, Medical and General Intensive Care Medicine, Thoracic Cardiac and Vascular Surgery, Anesthesiology and Intensive Care Medicine as well as Cardiac Preventive and Rehabilitative Medicine under the auspices of the German Guideline Working Group of Medical Scientific Societies (AWMF). A total of 95 recommendations and 7 algorithms were assembled. Table 1 gives on overview of the most relevant alterations/ modifications as well as new recommendations in the updated guideline. The full version and the guideline report are available at www.leitlinien.net (accessed on 10 February 2023) (in German) [6]. In addition to the recommendations of the guideline, the authors give an update on the current evidence derived from studies published after the publication of this guideline.

Table 1. Comparison of the original 2010 and the updated version from 2019.

Guideline 2010	GoR	LOE	Guideline 2019	GoR	LOE
IABP with primary fibrinolysis: In patients with primary fibrinolysis, IABP should be carried out adjunctively.	⇑	3/4	**IABP with primary PCI:** Routine use of IABPs in patients with cardiogenic shock due to pump failure complicating MI is not recommended.	⇓	1++
IABP with primary PCI: In patients with primary PCI, IABP may be considered, but the evidence is unclear.	⇔	3/4	**IABP with CABG, fibrinolysis or transfer:** No recommendation can be made for patients undergoing revascularization with CABG or fibrinolysis and patients who have to be transferred.		
Patient Transfer: In patients who have to be transferred to an intervention center, IABP should be used.	⇑	3/4	**Mechanical complications of MI:** IABP may be used for hemodynamic stabilization in patients with mechanical complications of myocardial infarction, including ventricular septal and papillary muscle rupture.	⇔	EO
Temporary mechanical support system ---			**Temporary mechanical support system:** Short-term mechanical circulatory support can be considered in select patients with MI and cardiogenic shock that cannot be quickly stabilized with conservative management if realistic.	⇔	EO
Culprit-lesion-only PCI vs. multivessel PCI In selected patients with coronary multivessel disease, complete revascularization during the index primary percutaneous coronary intervention (PCI) apart from the infarct-related artery (IRA) can be performed.	⇔	3/4	**Culprit-lesion-only PCI vs. multivessel PCI** In patients with coronary multivessel disease and more than one significant stenosis, Culpit-Lesion-only-lesion during the index PCI is preferred.	⇑⇑	1++
Vascular access for PCI ---			**Vascular access for PCI** It is possible to use the transradial as well as the transfemoral access in patients with cardiogenic shock. It is recommended to choose the operator's standard access in patients without acute coronary syndromes and cardiogenic shock.	⇔	EO
Supplementation of Glutamine In patients with ICS, glutamine supplementation is recommended in those patients who have to receive parenteral nutrition for more than 5 days without significant enteral nutrition.			**Supplementation of Glutamine** No glutamine supplementation is recommended—neither with enteral nor with parenteral nutrition.	⇓	EO

1.1. Medical Societies Involved in Guideline Development

- Deutsche Gesellschaft für Kardiologie—Herz und Kreislaufforschung e.V. (DGK) (German Cardiac Society) (lead society);

- Deutsche Gesellschaft für Internistische Intensivmedizin und Notfallmedizin (DGIIN) (German Society of Medical Intensive Care and Emergency Medicine);
- Deutsche Gesellschaft für Thorax-, Herz- und Gefäßchirurgie (DGTHG) (German Society for Thoracic and Cardiovascular Surgery);
- Österreichische Gesellschaft für Internistische und Allgemeine Intensivmedizin und Notfallmedizin (ÖGIAIM) (Austrian Society of Internal and General Intensive Care and Emergency Medicine);
- Deutsche Interdisziplinäre Vereinigung für Intensivmedizin (DIVI) (German Interdisciplinary Association of Intensive Care and Emergency Medicine);
- Österreichische Kardiologische Gesellschaft (ÖKG) (Austrian Society of Cardiology);
- Deutsche Gesellschaft für Anästhesie und Intensivmedizin (DGAI) (German Society of Anaesthesiology and Intensive Care Medicine);
- Deutsche Gesellschaft für Prävention und Rehabilitation (DGPR) (German Society for Prevention and Rehabilitation of Cardiovascular Disease).

1.2. Contents of the German–Austrian S3 Guideline "Infarction-Related Cardiogenic Shock: Diagnosis, Monitoring, and Treatment"

- Introduction;
- Method;
- Synopsis: diagnosis, monitoring and treatment of infarction-related cardiogenic shock;
- Definition, diagnosis and monitoring;
- Earliest possible coronary revascularization;
- Cardiovascular support;
- Treatment of complications of infarction-related cardiogenic shock;
- Supportive therapy for multiorgan dysfunction syndrome (MODS);
- Nutrition and insulin therapy, red cell substitution and prophylaxis, considerations regarding limitation of treatment;
- Aftercare and rehabilitation;
- Recommendations "Gemeinsam Klug Entscheiden";
- Need for research.

1.3. Objective and Target Group of This Guideline

The objective of the S3 guideline "Infarktbedingter kardiogener Schock: Diagnose, Monitoring und Therapie" (Infarction-Related Cardiogenic Shock: Diagnosis, Monitoring and Treatment) is to improve the quality of care of patients with ICS by publishing evidence-based recommendations. As many of the recommendations in this guideline are based on expert opinions due to the lack of high-quality evidence, this guideline is also intended to serve as a stimulation for future research in this area.

The recommendations in the S3 guideline are designed for all physicians and related healthcare staff involved in the treatment of patients with shock and acute myocardial infarction, especially cardiologists, intensivists, cardiac surgeons, anesthesiologists, emergency physicians and rehabilitation specialists.

1.4. Data Acquisition and Evaluation of Recommendations and Evidence

A systematic search was conducted of national and international guidelines to generate a statement of the thematic areas and questions on which there was consensus. In addition, a primary systematic literature search was carried out, including a total of 3546 publications from 1 January 1990 to 30 September 2009 in the original version of this guideline. In this update, publications from 1 October 2009 to 31 January 2019 were also included. The evaluation of the study quality and consecutive evidence, as well as the assigning of recommendation grades, was performed using the nominal group process in accordance with the recommendation grades and evidence levels listed in Tables 2 and 3.

Table 2. Level of evidence (LOE).

Level of Evidence		Description
1	++	High-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs) or RCTs with a very low risk of bias
	+	Well-conducted meta-analyses, systematic reviews or RCTs with a low risk of bias
2	++	High-quality systematic reviews of case–control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
	+	Well-conducted case–control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
3		Analytic studies without a concurrent comparison group, e.g., before-and-after studies, interrupted time series. Non-analytic studies, e.g., case reports, case series
4		Expert opinion (EO), e.g., editorial commentaries, guidelines without a clear methodology

Table 3. Grade of recommendation (GoR).

GoR	Description
↑↑	Strongly recommended: "shall" (usually based on studies with evidence level 1++ or 1+)
↑	Recommended: "should" (usually based on studies with evidence level 2++ or 2+)
↔	No recommendation: "may" (no confirmed study results exist that demonstrate either a beneficial or a harmful effect)
↓	Rejected: "should not" (negative recommendation)
↓↓	Strongly rejected: "shall not" (strong negative recommendation)

2. Guideline Recommendations

2.1. Diagnosis and Monitoring

2.1.1. Early Diagnosis of Cardiogenic Shock

Cardiogenic shock after AMI (CS-AMI) usually develops early after the initial ischemic event, even in the prehospital setting: every second patient develops a shock state within six hours, and three-thirds of patients develop a shock state within 24 h. Thus, it is essential to recognize shock as early as possible, and the early diagnosis of cardiogenic shock by the emergency physician is mainly a clinical diagnosis.

The definition of CS includes a severe impairment of myocardial performance with reduced cardiac output leading to end-organ hypoperfusion.

Therefore, besides the diagnosis of MI with the 12-lead electrocardiogram (ECG), the cornerstone of diagnosing CS is clinical signs of reduced organ perfusion (cold extremities, oliguria, altered mental status [e.g., agitation]). Hypotension (systolic blood pressure <90 mm of mercury [mmHg] for at least 30 min [min] in the absence of volume depletion) can occur but is not mandatory for the diagnosis of CS due to compensatory vasoconstriction. Thus, one-fourth of CS-AMI patients are normotensive, and the diagnosis of shock must, therefore, exclusively rely on the clinical signs mentioned above.

Taken together, the diagnosis of cardiogenic shock relies on the following clinical and hemodynamic parameters [7,8]:

Clinical signs of cardiogenic shock:

1. Systemic hypoperfusion
    a. Oligo-/anuria < 30 mL/hour;
    b. Cyanotic extremities;
    c. Signs of cerebral hypoperfusion with somnolence and confusion.

Hemodynamic signs/interventions of cardiogenic shock:

1. Blood pressure < 90 mmHg for more than 30 min;
2. Systemic hypotension;
3. Administration of catecholamines to stabilize the patient;
4. Use of intra-aortic counterpulsation;
5. Cardiac index < 2.2 L/min/m2;
6. Pulmonary capillary wedge pressure of >15 mmHg.

2.1.2. Initial Monitoring

Preclinical monitoring consists of blood pressure and heart rate, ECG, pulse oximetry, capnometry in case of mechanical ventilation and blood glucose measurement. A transthoracic echocardiography should be performed as early as possible after arrival in the hospital to assess systolic left/right ventricular function as well as mechanical complications of MI, including a ventricular septal defect, acute mitral valve regurgitation and rupturing in the free myocardial wall. A transesophageal echocardiogram should be considered if image quality is suboptimal and inadequate for future treatment decisions. In addition, a lung ultrasound should be performed, allowing for the rapid assessment of numerous conditions, including pulmonary edema, pleural effusion and pneumothorax.

Despite the emerging role of focused ultrasound, there is still a place for chest X-rays to provide important information on cardiac size and pulmonary congestion. In addition, it can help to rule out differentials, including aortic dissection, pericardial effusion, pneumothorax, esophageal perforation or pulmonary embolism.

2.1.3. Advanced Hemodynamic Monitoring: Is Blood Pressure Monitoring Appropriate?

In the case of persisting shock symptoms after revascularization, sophisticated hemodynamic therapy, including fluid management, vasopressor and inotropes, must be initiated. Hemodynamic monitoring can play a pivotal role in characterizing cardiogenic shock phenotypes (left ventricular, right ventricular, biventricular failure) and in guiding decision-making. Usually, treatment is guided by blood pressure measurement, as blood pressure is easy to monitor. However, it is crucial to assess preload, afterload and contractility as major determinants of hemodynamics to guide hemodynamic therapy and guarantee organ perfusion and oxygenation (fluids vs. fluid removal, vasopressors vs. vasodilators, need for inotropes). Therefore, the stabilization of blood pressure is no guarantee for adequate organ perfusion. It is essential to assess blood flow (i.e., cardiac output/cardiac index) and global perfusion. Mixed venous oxygen saturation (SvO_2)/central venous oxygen saturation ($ScvO_2$) reflecting the balance between oxygen delivery (DO_2) and consumption (VO_2) can guide hemodynamic therapy.

Although "cardiac power output" (CPO; mean arterial pressure × cardiac output × 0.0022) and the "cardiac power index" (CPI; mean arterial pressure × cardiac index × 0.0022) as a combination of flow and pressure parameters are the strongest predictors of mortality in CS in many studies, these parameters are not routinely used in daily practice [9].

Based on these findings, the German–Austrian guideline recommends hemodynamic monitoring consisting of a combination of blood pressure and any of the flow equivalents, like cardiac index, systemic vascular resistance (SVR, serving as a surrogate marker of afterload), mixed venous oxygen saturation (SvO_2)/central venous oxygen saturation ($ScvO_2$, as a marker of oxygen balance) or the combined product CPO/CPI (Figure 1).

In the presented guideline, no specific form of invasive hemodynamic monitoring is recommended. The following remarks are intended to be comments of the authors rather than recommendations of the original guideline. In clinical routine, pulmonary artery catheters (PAC) and pulse index continuous cardiac output (PiCCO) technology are the most commonly used invasive techniques for hemodynamic monitoring. Pulmonary artery catheters, once ubiquitous in the critical care setting, declined in utilization after large, randomized controlled trials (RCT) failed to show any benefits. However, the benefits of PAC monitoring in CS remains uncertain, as many trials, e.g., the ESCAPE trial, excluded

CS patients, and recent retrospective, nonrandomized studies showed some promising results [10–12].

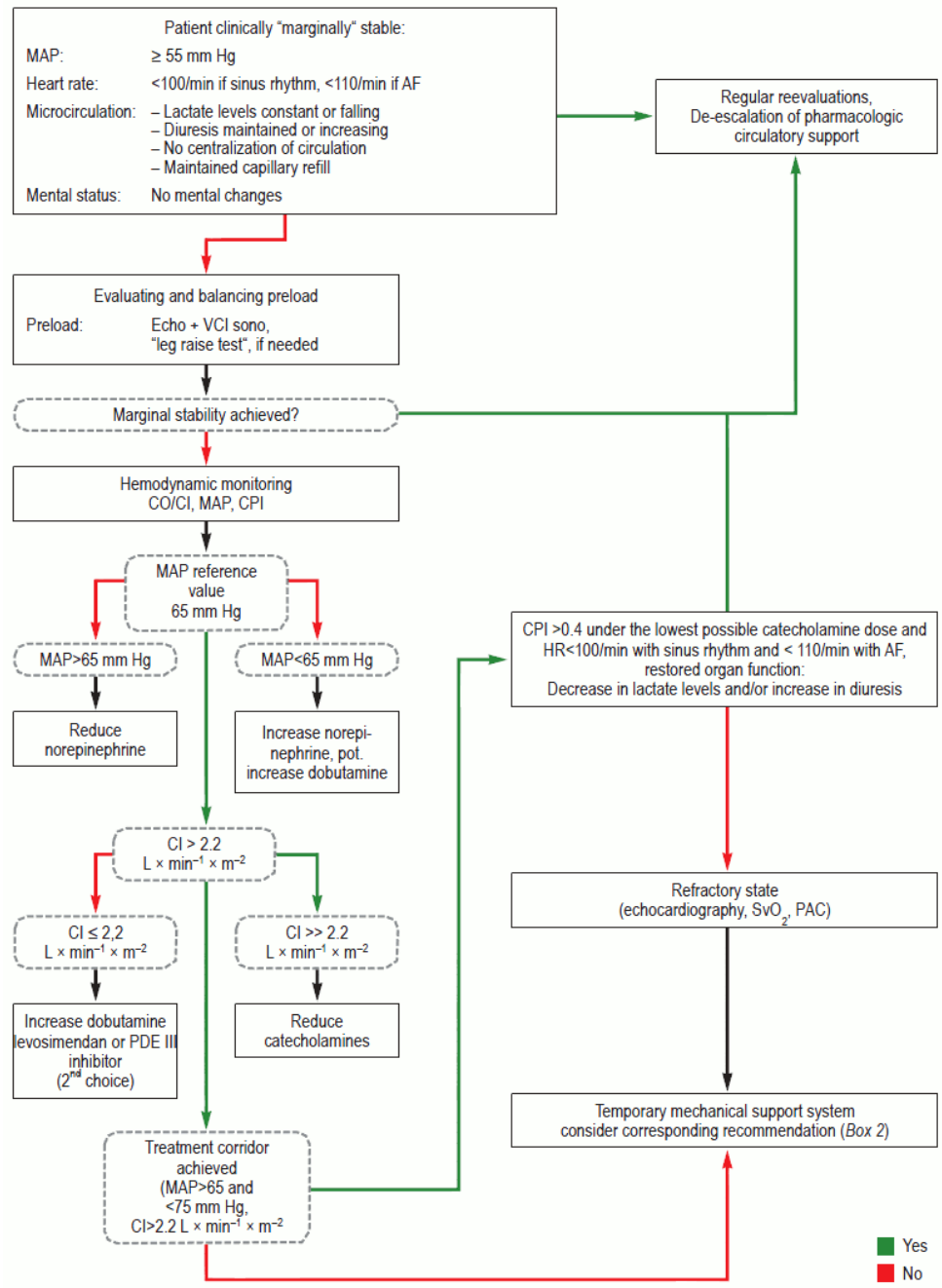

Figure 1. Hemodynamic shock therapy in patients with infarction-related cardiogenic shock.

Pulse index continuous cardiac output (PiCCO) technology is based on two physical principles, namely transpulmonary thermodilution and pulse contour, by using a specific thermodilution arterial (femoral, brachial or axillary) catheter and a central venous line. Evidence of the usefulness of the PiCCO system mainly derives from studies on patients with septic shock, acute respiratory distress syndrome and necrotizing pancreatitis, while there are only a few available studies conducted in patients with AMI complicated by CS. In a multicenter, multinational epidemiological study of invasive hemodynamic monitoring in the ICU, the choice of technique for invasive hemodynamic monitoring—PAC vs. PiCCO—did not appear to influence major outcomes in critically ill patients [13]. Due to its widespread use and less invasiveness, PiCCO might represent the technique of first choice

in the daily routine of patients with CS. In contrast, the PAC is indicated in pulmonary hypertension, right heart failure, unclear shock status and in patients with heart defects.

Table 4. Recommendations for hemodynamic monitoring.

	GoR	LOE
A transthoracic or transesophageal echocardiography should be performed in patients with ICS as soon as possible after hospital arrival without a delay of coronary angiography.	⇑⇑	**EO**
In all patients with persistent ICS, measurement of cardiac output should be performed as soon as possible for guidance of hemodynamic therapy.	⇑⇑	**EO**

2.2. Revascularization

The early reperfusion of the occluded coronary artery is one of the few recommendations that are based on high-quality randomized trials and, thus, represent the mainstay evidence-based therapeutic intervention for patients with acute MI presenting with CS. In this section, evidence and practical recommendations for the timing of reperfusion and revascularization techniques, as well as other adjunctive therapies, are reviewed.

2.2.1. Timing

Although coronary reperfusion is considered to be the essential therapeutic intervention for patients with ACS complicated by CS, there are only two randomized controlled trials available on this topic, of which the (S)MASH (Swiss Multicenter Trial of Angioplasty for Shock) was terminated prematurely due to insufficient patient enrollment [14–16].

The Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock (SHOCK) trial randomized a total of 302 patients with acute myocardial infarction and predominant left ventricular failure in two groups: (1) early emergency revascularization (within 6 h of randomization) by either coronary artery bypass grafting or angioplasty and (2) initial medical stabilization with the possibility of delayed revascularization at a minimum of 54 h post-randomization [14]. The primary endpoint (30-day all-cause mortality) did not differ significantly between the emergency revascularization and initial medical stabilization groups (53% vs. 44%; $p = 0.109$). However, a significant survival benefit could be observed after 6 and 12 months with early revascularization (50% vs. 37%; $p = 0.027$ and 47% vs. 34%; $p = 0.025$, respectively) [15].

The FITT-STEMI (Feedback Intervention and Treatment Times in ST-Elevation Myocardial Infarction), including a total of 12,675 STEMI patients, clearly demonstrates the strong association of time delay between MI and reperfusion on mortality, especially in patients with the highest risk of dying: those with cardiogenic shock or out-of-hospital cardiac arrest [17,18]. In shock without out-of-hospital cardiac arrest, every 10 min treatment delay between 60 and 180 min from the first medical contact resulted in 3.3 additional deaths per 100 PCI-treated patients and in 1.3 additional deaths after out-of-hospital cardiac arrest without cardiogenic shock. Since the widespread use of early revascularization, multiple registries confirmed the significant decrease in mortality from the previous 70–80% to 40–50%.

Thus, patients with CS, upon admission, need immediate access to invasive assessment and definitive revascularization by PCI or coronary artery bypass graft surgery. Emergency medical services should, by protocol, rapidly identify and transport patients with CS upon admission to pre-specified regional shock centers capable of providing this care. Therefore, the current guideline recommends prompt intervention with primary PCI within 90 min of first medical contact in patients presenting with ICS.

2.2.2. Type of Revascularization

The management of coronary artery disease has evolved through many debates, and among the most fraught has been the debate of which patient populations might benefit from coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI).

PCI has a lower procedural success rate in patients with shock than in those without shock. In addition, many patients presenting with ICS have a complex or three-vessel coronary artery. In these situations, CABG provides better (more complete) revascularization than PCI and, unsurprisingly, better long-term survival compared with PCI in patients without shock [19].

In addition, CABG theoretically might offer the advantage of myocardial protection with cardioplegia, ventricular unloading during cardiopulmonary bypass and the revascularization of non-infarct zones. In contrast, the delay to reperfusion is regularly longer compared to PCI, especially if there is a need for patient transport to a cardiac center, and the surgical risk and complication rate is higher than with PCI. In daily routines, PCI is the most often performed revascularization therapy in ICS, mainly due to its wide availability, whereas CABG is only rarely performed (e.g., only 4% of patients in the IABP-Shock II trial and registry) [20].

Recent major landmark randomized clinical trials such as SYNTAX, EXCEL and NOBLE helped to define the patients in which each approach is likely to be most successful. However, there is only limited evidence coming from those RCTS in the setting of ICS. Therefore, currently, available recommendations coming from international guidelines about the type of reperfusion in ICS patients are based upon expert opinion, observational data and data from a subanalysis of the randomized SHOCK (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock) trial. There was no association between the type of revascularization and outcomes of patients with ICS in observational studies and a subanalysis of the SHOCK trial comparing patients treated with CABG or PCI [21]. In this study, 36% of patients in the revascularization arm were treated by CABG, with a median delay of 2.7 h, and 64% were treated by PCI, with a median delay of 54 min. Patients treated with CABG were more likely to have diabetes (48.9 vs. 26.9%; $p = 0.02$), a three-vessel disease (80.4 vs. 60.3%; $p = 0.03$), and LM coronary disease (41.3 vs. 13.0%; $p = 0.001$). Whereas mortality was not affected, complete revascularization was achieved in 23% of patients undergoing PCI and in 87% of patients undergoing CABG, suggesting that more complete revascularization might lead to equivalent outcomes despite a greater prevalence of diabetes and worse coronary artery disease in patients undergoing CABG.

However, currently available evidence raises doubts about this concept. In a propensity-matched comparison from The Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY), including 2954 patients with acute coronary syndromes, moderate- and high-risk patients with multivessel disease, and treatment with PCI rather than surgical revascularization, was associated with a lower rate of complications including peri-procedural stroke, myocardial infarction, major bleeding and renal injury but a higher incidence of recurrent ischemia requiring repeated revascularization procedures during follow-up [22]. Mortality after 1 month and 1 year were not affected by the type of revascularization.

Based on the currently available evidence and expert opinion, primary PCI with a drug-eluting stent (DES) is the reperfusion technique of choice in the majority of patients. Compared with balloon angioplasty alone, stenting is associated with a lower risk of reinfarction and target vessel revascularization but not a reduction in the mortality rate [23,24].

Patients with ICS should be considered candidates for early surgical revascularization if coronary anatomy is not suitable for PCI and should be discussed in an interdisciplinary evaluation process of the Heart Team in case of complex coronary anatomy. Factors that endorse CABG over PCI include the suitability of coronary anatomy, including the caliber and quality of prospective distal anastomotic targets for bypass grafts, the importance of the infarct-related artery, and surgical availability and experience. In addition, in patients with MI-related mechanical complications who require coronary revascularization, CABG is recommended at the time of repair.

Fibrinolytic (i.e., thrombolytic) therapy, when administered within the first several hours after symptom onset, is capable of reestablishing antegrade coronary artery blood flow in nearly 75 percent of patients with STEMI. All fibrinolytic agents, compared with placebo, reduce mortality in acute STEMI. However, primary percutaneous coronary intervention (PCI), when performed in a timely manner, is preferred to fibrinolytic therapy for reperfusion therapy during ST-segment-elevation myocardial infarction (STEMI). Therefore, fibrinolytic therapy is recommended in settings where primary PCI cannot be offered in a timely manner (within 6 h of MI diagnosis) and there are no contraindications [25]. The earlier fibrinolysis is initiated, the better the outcome. Thus, if the patient presents late after the onset of symptoms (particularly after 3 h) or if there are contraindications to fibrinolysis, delayed primary PCI should be considered as an alternative treatment option.

2.2.3. PCI Strategy

Culprit Lesion or Total Strategy

Approximately 70–80% of patients with CS present with multivessel disease, defined as additional stenoses/occlusions in addition to the infarct-related artery [26]. The importance of immediate PCI, also in non-infarct-related vessels, in this clinical situation has always been controversial.

However, the immediate revascularization of non-infarction-relevant coronary stenosis in addition to the infarction artery ("multi-vessel PCI") is prognostically disadvantageous in patients with myocardial infarction and coronary multivessel disease in the event of cardiogenic shock. To the surprise of many experts, this was shown for the first time by the results of the CULPRIT-SHOCK study published in 2017 [27]. For the study, 706 patients with cardiogenic shock and multivessel disease were randomized to receive either culprit lesion PCI or multivessel PCI. The two treatment options were compared regarding the primary endpoints of mortality and the need for renal replacement therapy within 30 days. Secondary endpoints within one year were all-cause mortality, reinfarction, rehospitalization, rehospitalization for congestive heart failure, the composite endpoint of death and reinfarction and the composite endpoint of death, reinfarction, rehospitalization and heart failure. At the time after 30 days, the rate for the primary combined study endpoint (death and severe kidney failure requiring renal replacement therapy) was 45.9% versus 55.4%, relative risk 0.83, $p = 0.01$) in the group with revascularization initially restricted to the "culprit" infarct artery ("culprit lesion only" strategy). In addition, the culprit lesion strategy was associated with a significantly lower overall mortality rate (43.3% vs. 51.5%). The rate for necessary renal replacement therapies was also numerically lower, but this difference was not statistically significant (11.6% vs. 16.4%). The 30-day results of CULPRIT-SHOCK could recently be confirmed with a consistent reduction in the composite endpoint at a 1-year follow-up for the culprit-lesion-only PCI with a possible staged revascularization strategy.

The CULPRIT-SHOCK Trial contradicts widespread current practice and prior studies in non-shock patients (DANAMI-3-PRIMULTI, PRAMI, CvLPRIT) that suggested that there may be a benefit from complete revascularization [28].

Based on these results, multivessel PCI in cardiogenic shock, which was previously considered rather positive, is now downgraded in the European STEMI guidelines and the current guidelines on revascularization (Class IIIB recommendation) [27].

Thus, in clinical practice, revascularization should be limited to the culprit lesion with possible staged revascularization of other lesions at a later time point.

Drug-Eluting Stents vs. Bare Metal Stents

For many years, drug-eluting stents (DESs) have been increasingly used instead of bare metal stents (BMSs) in stable CAD patients but also in patients with ACS to reduce neointimal hyperplasia and early stent thrombosis. Two randomized trials highlighted the impact of DES use in patients with ACS; The Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial suggested that

paclitaxel-eluting stents may be used in patients with ST-segment elevation myocardial infarction to improve the outcomes [29]. In the randomized Comparison of Biolimus Eluted from an Erodible Stent Coating with Bare Metal Stents in Acute ST-Elevation Myocardial Infarction (COMFORTABLE) AMI trial, the use of biolimus-eluting stents was superior in terms of major adverse cardiac and cardiovascular events (MACCEs) in patients with ACS compared to BMS [30].

However, as the number of patients with cardiogenic shock was very small in these trials, there is no high-quality data available on the safety and performance of DESs in patients with ICS. Based on the evidence from patients with MI without CS, the current guideline favors drug-eluting stents over bare metal stents in patients with cardiogenic shock.

Vascular Access for PCI

In many trials, transradial access (TRA) is associated with lower rates of bleeding as well as vascular and renal complications and mortality after PCI in stable coronary artery disease compared to transfemoral access (TFA). This is also true for patients with non-shock acute coronary syndrome (ACS) [31].

Currently, there are little data available on the use of TRA in cardiogenic shock demonstrating improved morbidity and mortality when compared to TFA at experienced centers. The two largest trials were RIVAL (Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes) and MATRIX (Minimizing Adverse Hemorrhagic Events by Transradial access Site and Systemic Implementation of AngioX) [32,33]. A meta-analysis analyzing data from 8131 registry patients with CS demonstrated that radial access was associated with a reduction in all-cause mortality [34].

In CULPRIT-SHOCK, TRA was associated with a lower 30-day rate of death or RRT (37.3% vs. 53.2%, adjusted odds ratio [aOR]: 0.57; 95% confidence interval [CI] 0.34–0.96), a lower 30-day rate of death (34.7% vs. 49.7%; aOR: 0.56; 95% CI 0.33–0.96) and a lower 30-day rate of RRT (5.9% vs. 15.9%; aOR: 0.40; 95% CI 0.16–0.97). The observed reduction in death or RRT and death with TRA was no longer significant at 1 year (44.9% vs. 57.8%; aOR: 0.85; 95% CI 0.50–1.45 and 42.4% vs. 55.5%, aOR: 0.78; 95% CI 0.46–1.32, respectively) [35].

However, the transradial approach might be challenging in patients with cardiogenic shock, and even in the most experienced transradial centers, the femoral approach is used in the majority of patients for easy-to-establish access to these patients. The long learning curve for the utilization of the TRA extends to several hundred cases, and thus, operators not experienced with transradial access should not underestimate the complexity of undertaking PCI through the TRA. Therefore, the guidelines suggest choosing the access individually based on the operator's experience.

Table 5. Recommendations for revascularization.

	GoR	LOE
Emergency PCI of the culprit lesion is indicated for patients with cardiogenic shock due to STEMI or NSTE-ACS, independent of time delay of symptom onset if coronary anatomy is amenable to PCI.	⇑⇑	1+ *
In patients presenting with ICS, prompt intervention with primary PCI within 90 min of first medical contact should be performed. * *DGIIN: 90 min only for patients with cardiogenic shock due to a STEMI*	⇑	EO
In patients with complex coronary anatomy, emergency surgical or interventional revascularization should be performed as decided by the interdisciplinary Heart Team. Emergency CABG is recommended for patients with cardiogenic shock if the coronary anatomy is not amenable to PCI.	⇑⇑	1+

Table 5. *Cont.*

	GoR	LOE
In patients with complex coronary anatomy and mechanical complications of MI, emergency surgical or interventional therapy is indicated, as decided by the interdisciplinary Heart Team.	⇑⇑	**EO**
For primary revascularization, coronary stenting with drug-eluting stents is the technique of choice in patients with iCS.	⇑	**EO**
It is possible to use the transradial as well as the transfemoral access in patients with cardiogenic shock. It is recommended to choose the operator's standard access in patients without acute coronary syndromes and cardiogenic shock.	⇑	**EO**
Fibrinolysis should be performed in patients with ICS if early coronary angiography and revascularization cannot be performed within 6 h. Coronary angiography should be performed as soon as possible.	⇑	**EO**

2.3. Drug Therapy in Cardiogenic Shock

Hemodynamic therapy with fluids, vasoactive agents and inotropes aiming to improve cardiac output and ensure perfusion and oxygenation is of crucial importance in the management of patients with cardiogenic shock. However, despite the widespread use of these drugs in cardiogenic shock, evidence is low and is mainly based on expert opinion and only a limited number of prospective randomized trials.

Inotropes intended to increase contractility and cardiac output should be used with caution and restricted to patients with ICS, impaired microcirculation and poor vital organ perfusion despite the optimization of preload and heart rate. The use of these agents, especially those with adrenergic mechanisms, is associated with significant side effects, including tachycardia, increased ventricular rate in patients with AF, myocardial ischemia and arrhythmias and increased mortality [36].

Against the background of high-quality data, dobutamine is considered to be the inotrope of choice due to the extensive experience with this drug. In ICS refractory to dobutamine, levosimendan is recommended as the second option (loading dose 12 to 24 $\mu g \times kg^{-1}$ over 10 min, followed by 0.05 to 0.2 $\mu g \times kg^{-1} \times min^{-1}$) over phosphodiesterase III inhibitors such as enoximone or milrinone based on a small randomized trial with levosimendan versus enoximone [37].

Many patients with coronary heart disease presenting with cardiogenic shock are already under long-term treatment with beta-blockers. Thus, the hemodynamic effects of dobutamine are diminished, and these patients will receive a greater hemodynamic benefit from a phosphodiesterase-III-inhibitor or levosimendan as these agents act through independent mechanisms. However, attention must be paid to excessive peripheral vasodilation and hypotension, especially when administered at high doses and/or when commenced with a bolus dose.

In ICS patients, vasopressors should be administered when the increase of cardiac output by inotropes and fluids is not sufficient to achieve adequate perfusion pressure. However, vasopressors should be titrated carefully as they increase afterload and, thus, can reduce contractility. Therefore, a combination of norepinephrine and inotropic agents may be considered. In recent years, there has been an ongoing debate about the ideal target mean arterial pressure (MAP) in critically ill patients. Currently, there are no high-quality data available for patients with ICS, and current strategies with a target MAP of 65 mmHg are based on evidence from patients with septic/vasodilatory shock and cardiac arrest (CA) [38]. In addition, the individualization of hemodynamic goals was suggested as patients with pre-existing hypertension and chronic kidney disease may benefit from higher MAP goals, and a history of hypertension is common among patients with cardiovascular disease.

By contrast, recently published studies demonstrated favorable outcomes among older patients supported with permissive hypotension (MAP 60–65 mmHg) [39]. In summary, despite good evidence to support specific MAP targets, the current guideline recommends a MAP target of 65 mmHg for most patients with CS based on the findings of other populations (Figure 1).

Norepinephrine is the vasopressor of first choice and may be preferred in patients with severe hypotension. In the multicenter, double-blinded, parallel-group, randomized controlled trial SOAP II study from De Backer et al., 1679 patients with shock of various etiologies were included and randomized to receive dopamine or norepinephrine as a vasopressor [40]. While there was no significant difference in mortality in the total cohort and patients with septic and hypovolemic shock, dopamine, compared with norepinephrine, was associated with an increased rate of death at 28 days among the 280 patients with cardiogenic shock ($p = 0.03$; the percentage of ICS patients within this cardiogenic shock subset is not given).

At first glance, epinephrine—acting as a vasopressor and inotropic agent—might be suggested as a potential alternative to norepinephrine. However, two small, randomized trials in CS showed negative effects of epinephrine on heart rate and metabolism (including lactic acidosis) [41]. The larger Optima-CC trial was terminated early because the main safety endpoint— incidence of refractory CS—was significantly higher in the epinephrine group (37% vs. 7%; $p = 0.008$) [42]. These data are consistent with a meta-analysis including 2583 patients with cardiogenic shock showing a three-fold increase in the risk of death with epinephrine, compared with norepinephrine, in patients with cardiogenic shock [43]. Vasopressin is increasingly used in the setting of norepinephrine-resistant septic shock. However, it has not been studied in a CS setting. Therefore, no recommendations based on evidence can be made.

Table 6. Recommendations for inotropic drugs and vasopressors in patients with systolic pump failure.

	GOR	LOE
Dobutamine should be given as an inotropic drug.	⇑	EO
Norepinephrine should be given as vasopressor of first choice.	⇑	EO
In cases of catecholamine-refractory cardiogenic shock, levosimendan can be used.	⇔	EO
In cases of catecholamine-refractory cardiogenic shock, phosphodiesterase-III inhibitors can be used.	⇔	EO
In cases of catecholamine-refractory cardiogenic shock, levosimendan can be used; levosimendan should be used over phosphodiesterase-III inhibitors.		
Epinephrine can be administered if hemodynamic stabilization cannot be achieved with the use of dobutamine and norepinephrine.	⇔	EO
Dopamine shall not be given in CS.	⇓⇓	1++

2.4. Mechanical Circulatory Support (MCS)

Vasopressors and positive inotropic agents remain the first lines of treatment but frequently offer inadequate support. In addition, inotropes are associated with several side effects, including increased myocardial oxygen consumption and impaired tissue perfusion. Short-term mechanical circulatory assist (support) devices represent a promising alternative in the context of severe, refractory cardiogenic shock by effectively augmenting cardiac output. They have been increasingly used in recent years despite being expensive, resource-intensive, associated with major complications and lacking in high-quality evidence to support their use. There are several MCS devices available, but the three most common devices are the intra-aortic balloon pump (IABP), the percutaneous ventricular assist devices (VAD) (Impella, TandemHeart and others) and veno-arterial extracorporeal membrane oxygenation (VA-ECMO).

2.4.1. IABP

Since its introduction into clinical practice >50 years ago, intra-aortic balloon counterpulsion has been considered a standard therapy in refractory ICS with a class I recommendation in the European and American guidelines for the treatment of the ICS with approx. 10,000 IABP operations per year in Germany.

Despite its widespread use and high recommendations in international guidelines, the last version of the German–Austrian S3 guideline gave only a weak recommendation (↑) for the use of IABP in ICS patients treated with systemic fibrinolysis and only "may" information for patients treated with PCI (↔) as there were no randomized controlled trials showing a benefit of aortic counterpulsation.

However, The IABP-SHOCK II (Intra-aortic Balloon Pump in Cardiogenic Shock II) with 600 ICS patients, designed to demonstrate a possible reduction in mortality with the use of the IABP, changed the clinical routine as well as the guideline recommendations. In this randomized, prospective, open, multicentric study, 600 ICS patients (IABG Group; 299 patients non-IABP group) with early revascularization (95.8% primary PCI; 3.5% ACB) in 37 German centers and 119 patients in the IABP group died (39.7%) at 30 days, and 123 patients in the control group (41.3%, $p = 0.69$) also died at 30 days. No differences were found between the two groups in any other secondary outcome, including the time to hemodynamic stabilization, length of stay in ICU, serum lactate levels, dosage and duration of catecholamine treatment and renal function. The 12-month mortality was not different in the IABP and in the control group: 155 (52%) of the 299 patients in the IABP group and 152 (51%) of the 296 patients in the control group died during this time (RR 1.01 [95% CI 0.86–1.18]; $p = 0.91$).

Based on the current evidence, IABP placement cannot be recommended routinely in patients with ICS.

Table 7. Recommendations for MCS use.

	GoR	LOE
Routine use of IABPs in patients with cardiogenic shock due to ACS is not recommended.	⇓	1++
IABP may be used for hemodynamic stabilization in patients with mechanical complications of myocardial infarction, including ventricular septal rupture and papillary muscle rupture.	⇔	EO
No recommendation can be made for patients undergoing revascularization with CABG or fibrinolysis and patients who have to be transferred.	**Statement**	
In ICS patients who cannot be stabilized over time, a temporary mechanical assist device (TMCS) device "may" be implanted if a realistic treatment goal is pursued and the following requirements are met: implantation without delaying revascularization; documented realistic treatment goal, evaluated by the cardiac care team; link to/collaboration with a cardiac center to ensure early destination therapy; implantation before irreversible organ damage has occurred; enrollment in a TMCS registry of a medical society.	⇔	EO

2.4.2. Other Mechanical Circulatory Support Systems

Alternatives to the IABP

The downgrading in international guidelines mainly based on the neutral results of the IABP-SHOCK II led to a worldwide decline in IABP use accompanied by exponential growth in the application of active, hemodynamically more effective MCS including percutaneous left ventricular assist devices (LVADs)—centrifugal pumps without oxy-

genator (Tandem Heart™) and with oxygenator (venoarterial extracorporeal membrane oxygenation [ECMO], LifeBridge® (Baltimore, MD, USA) as well as axial flow pumps (Impella Recover LP®2.5 and Impella Recover LP®5.0) [44,45].

However, this broad application of a very invasive and expensive therapy is not based on high-quality studies: comparing pLVADs, including Impella and Tandem Heart™, with the IABP in CS in four small randomized trials, a recent meta-analysis demonstrated similar short-term mortality despite beneficial hemodynamic effects (increased arterial blood pressure and peripheral perfusion as well as lower serum lactate levels) [46]. However, a higher rate of bleeding from vascular access sites and a significantly higher incidence of limb ischemia following pLVAD were reported in all studies.

A recently published meta-analysis comparing mortality in patients treated with and without ECLS support included thirteen studies, including nine studies with cardiac arrest patients (n = 3098) and four studies with patients with cardiogenic shock after acute myocardial infarction (n = 235) [47].

In cardiac arrest, the use of ECLS was associated with an absolute increase of 30 days survival of 13% compared with patients in which ECLS was not used and a higher rate of favorable neurological outcome at 30 days. In cardiogenic shock, ECLS showed a 33% higher 30-day survival compared with IABP but no difference when compared with TandemHeart/Impella.

In summary, the evidence for mechanical circulatory systems is insufficient to provide a recommendation on its routine clinical use in cardiogenic shock. Currently, some randomized trials are in the early phase of patient recruitment to assess VA-ECMO for the treatment of CS, including EURO SHOCK (Testing the Value of Novel Strategy and Its Cost Efficacy in Order to Improve the Poor Outcomes in Cardiogenic Shock; URL: ClinicalTrials.gov), Unique identifier: NCT03813134), ECLS-SHOCK (Extracorporeal Life Support in Cardiogenic Shock; URL: ClinicalTrials.gov, Unique identifier: NCT03637205), ECMO-CS (Extracorporeal Membrane Oxygenation in the Therapy of Cardiogenic Shock; URL: ClinicalTrials.gov, Unique identifier: NCT02301819) and ANCHOR (Assessment of ECMO in Acute Myocardial Infarction Cardiogenic Shock; URL: ClinicalTrials.gov, Unique identifier: NCT04184635). The results of these and other trials will further inform the management of patients with ICS. In the meantime, there is cause for caution, with observational data illustrating heterogeneity in safety and outcomes of MCS use in the context of steadily growing use.

Therefore, the current guideline suggests that short-term mechanical circulatory support can be considered in selected patients with ACS and cardiogenic shock that cannot be rapidly stabilized with conservative management.

If:

- MCS is implanted before the occurrence of irreversible end-organ damage;
- MCS implantation does not delay emergency revascularization;
- There is a clear patient-specific therapeutic goal as evaluated and documented by the Heart Team;
- There is a structured cooperation with a heart-failure center for early destination therapy;
- Patients are enrolled in a registry for MCS of the participating medical societies.

The choice of which MCS device to use is based on many factors, including the type of shock (right heart failure, left heart failure) as well as operator abilities and institutional resources.

2.5. Mechanical Complications of MI

Fortunately, the incidence of mechanical complications of acute myocardial infarction has decreased in recent decades, not least due to early percutaneous coronary intervention [1]. Instances of this are just under 1% after acute ST-elevation myocardial infarction (STEMI). However, the mortality rate is remarkably high at around 50% and, in some cases, significantly higher. They often occur within 24 h after the onset of symptoms but can also occur a few days after the infarction.

ICS patients with shock due to mechanical MI complications (0.2–6.9%) shall be treated by a cardiac care team consisting of a cardiac surgeon and a cardiologist with experience in intensive care medicine (see Table 8).

Table 8. Recommendations for mechanical complications of MI.

	GoR	LOE
ICS patients with shock due to mechanical MI complications shall be treated by a cardiac care team consisting of a cardiac surgeon and a cardiologist with experience in intensive care medicine	⇑⇑	**EO**
Patients with a ventricular septal rupture should undergo urgent surgery or percutaneous intervention.	⇑	**EO**
Patients with significant mitral regurgitation should undergo urgent surgery.	⇑⇑	**EO**

2.5.1. Ventricular Septal Rupture (VSR)

Ventricular septal rupture is a rare but fatal complication after MI, with mortality ranging between 40 and 50%. VSR can occur early, within 24 h, but usually presents as rapid-onset clinical deterioration with cardiogenic shock and pulmonary edema several days after the initial event. Echocardiography confirms the clinical diagnosis. Besides inotropic support, the IABP with a reduction of afterload and shunt volume can help to stabilize the patient before surgical or interventional repair.

There are no high-quality data available concerning the optimal timing of surgery. Although early repair seems to be associated with recurrent ventricular rupture and a high mortality in retrospective studies, this association can be explained by the fact that the most severe cases without stabilization need urgent repair, while delayed surgery is possible in stable patients, allowing easier septal repair in scarring tissue [48]. Therefore, patients with refractory cardiogenic shock should undergo early surgery, but patients who respond well to aggressive heart failure therapy should be considered good candidates for delayed elective surgical repair. Currently, surgery is considered to be the gold standard for VSR closure in MI patients, but percutaneous closure of the defect with appropriately designed devices may soon become an appropriate alternative.

2.5.2. Papillary Muscle Rupture

Acute mitral regurgitation, occurring 2–7 days after AMI due to the rupturing of the papillary muscle or chordae tendineae, usually affects the posteromedial papillary muscle because of its single artery blood supply. Symptoms of papillary muscle rupture are similar to that of VSR and include sudden hemodynamic deterioration with acute dyspnea, pulmonary edema and/or cardiogenic shock. Sufficient afterload reduction to reduce regurgitant volume and pulmonary congestion can be achieved by intravenous diuretic and vasodilator/inotropic support, as well as IABP. Emergency surgery is the treatment of choice, although it carries a high operative mortality (20–25%) [48].

2.6. Specific Critical Care

2.6.1. Oxygen Supplementation

For decades, oxygen (O_2) treatment has traditionally been a cornerstone in the treatment of critically ill patients, including those with myocardial infarction, independently of oxygen saturation. This approach was based on the physiological consideration that supplemental oxygen increases oxygen delivery and diminishes local ischemia to the heart, brain or other organs. However, the clinical routine has changed since an increasing number of randomized trials in different patient populations, including those with MI, showed that oxygen therapy to normoxemic patients (normoxemia defined as oxygen saturation $\geq$ 90%) may not only be unnecessary but can cause hyperoxia and might even bring risks [49]. Based on recent randomized controlled trials (RCT) on patients with

suspected as well as confirmed MI and ST Elevation Myocardial Infarction (STEMI) showing no effect of liberal or restrictive supplemental O_2 therapy [50,51], the international guidelines recommend against the routine administration of supplemental O2 in patients with MI and a blood oxygen saturation of $\geq$90%. However, uncertainties remain because the trials published so far do not rule out that there might be subgroups of patients at risk for both benefit and harm, e.g., patients with ICS. The Austrian–German guideline recommends oxygen supplementation or ventilation in patients with ICS to achieve blood oxygen saturation between 94 and 98% but not routinely above this level.

2.6.2. Mechanical Ventilation

Although every second patient with ICS suffers from acute respiratory failure (ARF) with a need for ventilator support mainly due to elevated filling pressures from left ventricular (LV) dysfunction leading to alveolar pulmonary edema, there are remarkably few data addressing the ideal mode of respiratory support in such patients, and little is known about the optimal timing or ventilatory strategies in patients with CS. The application of positive end-expiratory pressure in patients with ARF due to ICS does not only reduce pulmonary edema with an improvement in oxygenation but also reduces LV preload by reducing venous return, and it reduces LV afterload by increasing transmural pressure. Moreover, mechanical ventilation (MV) can reduce the work of breathing and improve tissue perfusion, which, in conjunction with PEEP, can reduce myocardial oxygen consumption.

In right ventricular (RV) failure, RV preload is decreased, but the effect of PPV on RV afterload can vary. In the case of atelectasis, the application of PEEP can open these hypoventilated areas and, thus, decrease hypoxemic vasoconstriction and RV afterload. However, when applying high PEEP levels, the overdistension of alveoli with the subsequent squeezing of pulmonary vessels can increase afterload, which can potentially lead to hemodynamic deterioration. Therefore, the induction of MV and the application of high pressure levels should be performed carefully, with close monitoring of the hemodynamic effects.

Non-invasive ventilation (NIV) is generally considered to be the first-choice approach in hypercapnic as well as hypoxemic acute respiratory failure, e.g., pneumonia. Accordingly, NIV reduces respiratory distress and improves metabolic disturbances in acute cardiogenic pulmonary edema [10]. However, many patients with ICS are not appropriate candidates for NIV but require tracheal intubation and the use of invasive mechanical ventilation (IMV). Due to the high metabolic demand from the increased work of breathing, an altered mental status resulting in poor synchrony and concomitant cardiac arrest, as well as the severity of pulmonary edema causing insufficient oxygenation, invasive ventilation is preferred over non-invasive ventilation in ARF, especially in backward failure. Early intubation and ventilatory support may facilitate revascularization because of the improved oxygenation, greater sedation and enhanced metabolic profile.

Invasive mechanical ventilation can induce ventilator-associated lung injury (VALI), with lung inflammatory response and oxidative stress increasing mortality not only in patients with ARDS but also in other critically ill patients. Thus, the concept of lung-protective ventilation (LPV) with low inspiratory pressures (less than 30 cm of water) and low tidal volumes (6–8 mL/kg predicted BW)—originally developed for patients with ARDS—should also be applied in patients with ICS, if tolerated from a cardiac point of view. However, no convincing evidence exists for these patients.

2.6.3. Acute Kidney Injury

As in other critically ill patients, AKI is a common complication in CS, with an incidence ranging from 20 to 35% [52]. Therefore, monitoring of renal function with diuresis and serial creatinine measurements is recommended. The traditional criteria for the initiation of replacement therapy include uremia, an otherwise untreatable volume overload, metabolic acidosis (pH < 7.2) and/or the occurrence of refractory hyperkalemia (>6.0 mmol/L). However, for decades, there has been a controversial debate as to whether the early initiation of renal replacement therapy before the onset of major complications

might have conceivable advantages as it can restore and maintain acid–base homeostasis, mitigate fluid accumulation and reduce exposure to the metabolic hazards of untreated acute kidney injury [53]. On the other hand, the early initiation of RRT might also be harmful. A recently published meta-analysis of RCTS might have shown that this more aggressive approach was associated with a higher dialysis dependence on day 90, as well as treatment-emergent adverse events (hypophosphatemia and hypotension) [54]. Although it might appear reasonable that continuous RRT (CVVH) might be superior to intermittent hemodialysis, fast fluid shifts are scarcely tolerated in patients with CS. However, based on the evidence from extensive studies, both approaches should be considered equivalent in terms of their safety and efficacy [55]. Therefore, RRT in patients with ICS should be initiated when conventional indications occur and should be performed with one of the two renal replacement therapies—continuous renal replacement therapy (CRRT) or intermittent hemodialysis (IHD). In contrast, the mandate holders of ÖGIAIN clearly recommend the use of continuous renal replacement therapy in hemodynamically unstable ICS patients.

2.6.4. Transfusion Strategy

Anemia can be observed in 5–10% of patients with myocardial infarction and is an independent predictor of cardiovascular morbidity and mortality [56]. The bleeding risk of patients with MI and anemia is furthermore increased due to the antiplatelet and anticoagulant medications. An increasing number of well-conducted, large, randomized, multicenter trials support the evidence that a restrictive transfusion strategy with higher transfusion thresholds is beneficial in different patient populations (e.g., in septic patients) after cardiac surgery. However, the majority of these trials excluded patients with acute myocardial infarction (MI) as it is believed that lower hemoglobin with consecutively lower systemic and local myocardial oxygen delivery will extend ischemia to the heart. Therefore, the optimal transfusion strategy in patients with acute myocardial infarction and anemia is unclear. In clinical routine, there is wide variation in practice, but many clinicians apply a more liberal transfusion threshold.

However, this pragmatic approach, which is based more on physiological considerations than evidence, is not supported by observational studies that show an association of transfusion with mortality in patients with myocardial infarction. Recently, more high-quality evidence has been derived from randomized trials. For example, the patients in the Restrictive and Liberal Transfusion Strategies in Patients With Acute Myocardial Infarction (REALITY), which is an open-label, non-inferiority, randomized controlled trial that was performed in 35 hospitals in France and Spain, with 668 adults who were hospitalized in 35 French or Spanish centers with acute MI and hemoglobin (Hb) levels between 7 and 10 g/dL, were randomized to either a restrictive transfusion strategy (triggered by Hb $\leq$ 8 g/dL) or a liberal strategy (triggered by Hb $\leq$ 10 g/dL) [57].

At 30 days, MACE (a composite score of major adverse cardiovascular events—all-cause death, stroke, recurrent MI, emergency revascularization prompted by ischemia) occurred in 14% of the liberal group and 11% of the restrictive group (45 vs. 36 patients, between-group difference −3% 95% CI −8.4% to 2.4%). This met the pre-specified non-inferiority criterion. Although no statistically significant difference was found between the two groups, the restrictive group trended toward superiority. A cost-effectiveness analysis indicated that the restrictive strategy had an 84% probability of being cost-saving while improving clinical outcomes. Regarding safety, compared to patients receiving the liberal strategy, those allocated to the restrictive strategy were significantly less likely to develop an infection (restrictive 0.0% vs. liberal 1.5%; $p = 0.03$) or acute lung injury (restrictive 0.3% vs. liberal 2.2%; $p = 0.03$).

These findings are consistent with randomized studies of other patient populations and suggest that a restrictive transfusion strategy is non-inferior to a liberal strategy in patients with acute MI and anemia. Given the known advantages of a restrictive strategy (e.g., the lower consumption of blood resources, fewer adverse effects from transfusion and cost savings), the cutoff for transfusion in patients with acute MI should be Hb $\leq$ 8 g/dL.

However, patients with cardiogenic shock were excluded from the REALITY trial. Currently, there are no data available for patients with CS. Studies from patients undergoing cardiac surgery, as well as those with MI, show that restrictive transfusion therapy might be harmful in patients > 65 years; the guideline recommends a restrictive transfusion regime in patients < 65 years with a target Hb-concentration of 7.0–9.0 g × dL^{-1} (hematocrit of ≥25%). In contrast, hematocrit < 30% should be avoided in older patients [58]. Currently, the MINT trial is underway, which is a randomized clinical trial of 3500 patients comparing red blood cell transfusion strategies for patients who have had a myocardial infarction and are anemic, and will hopefully shed some more light on which transfusion strategy is superior.

2.6.5. Nutrition

Enteral nutrition (EN) is generally recommended within the first 24–48 h for patients with hemodynamic stability following admission to an intensive care unit (ICU). However, for patients with hemodynamic instability requiring mechanical circulatory support and vasoactive drugs, e.g., ICS, the application of early EN remains controversial.

In the well-designed, open-label, randomized NUTRIREA-2 study by Reignier and colleagues, early enteral nutrition did not improve mortality at day 28 compared with parenteral nutrition with a normocaloric target in mechanically ventilated patients with shock but significantly increased the risk of bowel ischemia (19 [2%] patients vs. 5 [<1%] patients; $p = 0{\cdot}007$) [59]. Therefore, parenteral nutrition (PN) is preferred over enteral nutrition in these patients. The appropriate time to start PN remains a matter of discussion. However, based on data from non-MI patients and international guidelines, supplemental PN should be considered in any patient at risk of undernutrition if EN fails to reach calorie targets after 3 to 7 days. In accordance with the international ESPEN Guideline, this guideline suggests withholding EN in patients with MI and uncontrolled shock, uncontrolled hypoxemia and acidosis [60].

2.6.6. Glutamine Supplementation

Glutamine is a non-essential amino acid which is abundant in the healthy human body.

Several published studies are showing reduced plasma glutamine levels in critically ill patients, including patients with cardiogenic shock, suggesting that glutamine may be a conditionally essential amino acid in situations of extreme stress. In addition, low glutamine levels were associated with an increased mortality, suggesting that glutamine supplementation may be beneficial. However, this is not supported by multicenter randomized trials; e.g., the REDOXS study suggested that glutamine supplementation might even be harmful and the early administration of glutamine in high doses (much higher than recommended) can have adverse effects [61]. This especially applies to the most severely ill patients with multi-organ failure (including kidney dysfunction). Parenteral nutrition supplementation with low doses (20.2 g/day) of glutamine for short periods did not influence the mortality or infection incidence in the ICU population in the Signet study [62].

Based on the results of these two well-conducted, randomized trials, the current guideline recommends against the routine use of glutamine supplementation in patients with cardiogenic shock after myocardial infarction.

2.6.7. Glucose Control

Hyperglycemia can frequently be observed in critically ill patients, including patients in CS, because of relative insulin resistance and accelerated glucose production being associated with increased morbidity and mortality.

While the initial DIGAMI study showed that rigorous blood glucose control in diabetic patients with acute myocardial infarctions improves mortality, the subsequent DIGAMI-II trial did not support this approach, displaying no clinical benefit of any glucose control strategy [63,64]. However, rigorous glycemic control was clearly endorsed by a landmark study by Greet Van Den Berghe, showing that targeting the standard of fasting for blood

glucose levels with IV insulin clearly reduced short- and long-term morbidity and mortality in critically ill patients [65].

However, the largest RCT on this topic, with more than 6000 included ICU patients, found that tight glycemic control is not beneficial but even harmful with increased mortality due to a higher incidence of severe hypoglycemia [66]. Although there are no RCTs in patients with CS, the guideline recommends a moderate glucose control ($\leq$150 mg/dL or 8.3 mmol/L) to avoid hypoglycemia in ICS patients based on the solid evidence in other critically ill patient populations; this is also in accordance with many international critical care guidelines.

Table 9. Recommendations for critical care medicine.

	GoR	LOE
In patients with uncontrolled ICS, enteral nutrition "should not" be administered before control of the shock is achieved by administration of fluid and vasopressors/inotropes.	⇓	**EO**
In both enteral and parenteral nutrition therapy, supplementation of glutamine "should" be avoided.	⇓	**EO**
In patients < 65 years with ICS, packed red blood cells "should" be transfused: – If Hb concentration is below 7.0 g $\times$ dL^{-1}/4.3 mmol $\times$ L^{-1}; – If hematocrit is below 25%. Target values in patients < 65 years "should" be as follows: – Hb concentration of 7.0–9.0 g $\times$ dL^{-1}/4.3–5.6 mmol $\times$ L^{-1}; – Hematocrit of $\geq$25%. In older (age $\geq$ 65 years) patients, a hematocrit decrease to levels below 30% "should" be avoided.	⇑	**EO**
ICS patients "shall" receive stress ulcer prophylaxis.	⇑⇑	**EO**
Intubation and invasive ventilation "should" be given preference to non-invasive ventilation in patients with ICS.	⇑	**EO**
After hemodynamic stabilization, ventilation "should" be performed according to the criteria of lung-protective ventilation (peak pressure/maximum plateau pressure = 30 mbar, VT 6–8 mL $\times$ kg^{-1} predictive BW*4, PEEP 5–15 mbar), if cardiac function permits.	⇑	**EO**
Since hemodynamic instability is the primary concern in patients with cardiogenic shock, the ventilation pattern "shall" be selected in such a way that adequate oxygenation (SaO_2 94–98%) is achieved with the least possible negative hemodynamic impact and without delaying revascularization.	⇑⇑	**EO**

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References

1. Nguyen, H.L.; Yarzebski, J.; Lessard, D.; Gore, J.M.; McManus, D.D.; Goldberg, R.J. Ten-Year (2001–2011) Trends in the Incidence Rates and Short-Term Outcomes of Early versus Late Onset Cardiogenic Shock after Hospitalization for Acute Myocardial Infarction. *J. Am. Heart Assoc.* **2017**, *6*, e005566. [CrossRef]
2. Werdan, K.; Ruß, M.; Buerke, M.; Engelmann, L.; Ferrari, M.; Friedrich, I.; Geppert, A.; Graf, J.; Hindricks, G.; Janssens, U.; et al. Deutsch-österreichische S3-Leitlinie „Infarktbedingter kardiogener Schock—Diagnose, Monitoring und Therapie". *Kardiologe* **2011**, *5*, 166–224.
3. Prondzinsky, R.; Lemm, H.; Swyter, M.; Wegener, N.; Unverzagt, S.; Carter, J.M.; Russ, M.; Schlitt, A.; Buerke, U.; Christoph, A.; 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. [CrossRef]

4. Ibanez, B.; James, S.; Agewall, S.; Antunes, M.J.; Bucciarelli-Ducci, C.; Bueno, H.; Caforio, A.L.P.; Crea, F.; Goudevenos, J.A.; Halvorsen, S.; et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur. Heart J.* **2018**, *39*, 119–177.
5. Neumann, F.-J.; Sousa-Uva, M.; Ahlsson, A.; Alfonso, F.; Banning, A.P.; Benedetto, U.; Byrne, R.A.; Collet, J.-P.; Falk, V.; Head, S.J.; et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur. Heart J.* **2018**, *40*, 87–165. [CrossRef] [PubMed]
6. *AWMF-RN 019/013*; Deutsch-österreichische S3-Leitlinie "Infarkt-bedingter kardiogener Schock–Diagnose, Monitoring und Therapie". Deutschen Gesellschaft für Kardiologie: Düsseldorf, Germany, 2020.
7. Standl, T.; Annecke, T.; Cascorbi, I.; Heller, A.R.; Sabashnikov, A.; Teske, W. Nomenklatur, Definition und Differenzierung der Schockformen. *Dtsch. Arztebl. Int.* **2018**, *115*, 757–768. [PubMed]
8. Vincent, J.-L.; De Backer, D. Circulatory Shock (Review Article). *N. Engl. J. Med.* **2013**, *369*, 1726–1734. [CrossRef] [PubMed]
9. Fincke, R.; Hochman, J.S.; Lowe, A.M.; Menon, V.; Slater, J.N.; Webb, J.G.; LeJemtel, T.H.; Cotter, G. Cardiac power is the strongest hemodynamic correlate of mortality in cardiogenic shock: A report from the SHOCK trial registry. *J. Am. Coll. Cardiol.* **2004**, *44*, 340–348. [CrossRef]
10. Binanay, C.; Califf, R.M.; Hasselblad, V.; O'Connor, C.M.; Shah, M.R.; Sopko, G.; Stevenson, L.W.; Francis, G.S.; Leier, C.V.; Miller, L.W.; et al. Evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness: The ESCAPE trial. *JAMA* **2005**, *294*, 1625–1633. [CrossRef] [PubMed]
11. Garan, A.R.; Kanwar, M.; Thayer, K.L.; Whitehead, E.; Zweck, E.; Hernandez-Montfort, J.; Mahr, C.; Haywood, J.L.; Harwani, N.M.; Wencker, D.; et al. Complete Hemodynamic Profiling with Pulmonary Artery Catheters in Cardiogenic Shock Is Associated with Lower In-Hospital Mortality. *JACC Heart Fail.* **2020**, *8*, 903–913. [CrossRef] [PubMed]
12. Sionis, A.; Rivas-Lasarte, M.; Mebazaa, A.; Tarvasmäki, T.; Sans-Roselló, J.; Tolppanen, H.; Varpula, M.; Jurkko, R.; Banaszewski, M.; Silva-Cardoso, J.; et al. Current Use and Impact on 30-Day Mortality of Pulmonary Artery Catheter in Cardiogenic Shock Patients: Results from the CardShock Study. *J. Intensive Care Med.* **2020**, *35*, 1426–1433. [CrossRef]
13. Uchino, S.; Bellomo, R.; Morimatsu, H.; Sugihara, M.; French, C.; Stephens, D.; Wendon, J.; Honore, P.; Mulder, J.; Turner, A. Pulmonary artery catheter versus pulse contour analysis: A prospective epidemiological study. *Crit. Care* **2006**, *10*, R174. [CrossRef] [PubMed]
14. Hochman, J.S.; Sleeper, L.A.; Webb, J.G.; Sanborn, T.A.; White, H.D.; Talley, J.D.; Buller, C.E.; Jacobs, A.K.; Slater, J.N.; Col, J.; et al. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. *N. Engl. J. Med.* **1999**, *341*, 625–634. [CrossRef]
15. Hochman, J.S.; Sleeper, L.A.; White, H.D.; Dzavik, V.; Wong, S.C.; Menon, V.; Webb, J.G.; Steingart, R.; Picard, M.H.; Menegus, M.A.; et al. One-year survival following early revascularization for cardiogenic shock. *JAMA* **2001**, *285*, 190–192. [CrossRef] [PubMed]
16. Urban, P.; Stauffer, J.C.; Bleed, D.; Khatchatrian, N.; Amann, W.; Bertel, O.; van den Brand, M.J.B.M.; Danchin, N.; Kaufmann, U.; Meier, B.; 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. [CrossRef] [PubMed]
17. Scholz, K.H.; Maier, S.K.; Maier, L.S.; Lengenfelder, B.; Jacobshagen, C.; Jung, J.; Fleischmann, C.; Werner, G.S.; Olbrich, H.G.; Ott, R.; et al. Impact of treatment delay on mortality in ST-segment elevation myocardial infarction (STEMI) patients presenting with and without haemodynamic instability: Results from the German prospective, multicentre FITT-STEMI trial. *Eur. Heart J.* **2018**, *39*, 1065–1074. [CrossRef] [PubMed]
18. Wijns, W.; Naber, C.K. Reperfusion delay in patients with high-risk ST-segment elevation myocardial infarction: Every minute counts, much more than suspected. *Eur. Heart J.* **2018**, *39*, 1075–1077. [CrossRef]
19. Sanborn, T.A.; Sleeper, L.A.; Webb, J.G.; French, J.K.; Bergman, G.; Parikh, M.; Wong, S.C.; Boland, J.; Pfisterer, M.; Slater, J.N.; et al. Correlates of one-year survival in patients with cardiogenic shock complicating acute myocardial infarction: Angiographic findings from the SHOCK trial. *J. Am. Coll. Cardiol.* **2003**, *42*, 1373–1379. [CrossRef]
20. Thiele, H.; Zeymer, U.; Neumann, F.J.; Ferenc, M.; Olbrich, H.G.; Hausleiter, J.; Richardt, G.; Hennersdorf, M.; Empen, K.; Fuernau, G.; et al. Intraaortic Balloon Support for Myocardial Infarction with Cardiogenic Shock. *N. Engl. J. Med.* **2012**, *367*, 1287–1296. [CrossRef]
21. White, H.D.; Assmann, S.F.; Sanborn, T.A.; Jacobs, A.K.; Webb, J.G.; Sleeper, L.A.; Wong, C.K.; Stewart, J.T.; Aylward, P.E.; Wong, S.C.; 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.
22. Ben-Gal, Y.; Moses, J.W.; Mehran, R.; Lansky, A.J.; Weisz, G.; Nikolsky, E.; Argenziano, M.; Williams, M.R.; Colombo, A.; Aylward, P.E.; et al. Surgical versus percutaneous revascularization for multivessel disease in patients with acute coronary syndromes: Analysis from the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial. *JACC Cardiovasc. Interv.* **2010**, *3*, 1059–1067. [CrossRef]
23. Grines, C.L.; Cox, D.A.; Stone, G.W.; Garcia, E.; Mattos, L.A.; Giambartolomei, A.; Brodie, B.R.; Madonna, O.; Eijgelshoven, M.; Lansky, A.J.; et al. Coronary angioplasty with or without stent implantation for acute myocardial infarction. Stent Primary Angioplasty in Myocardial Infarction Study Group. *N. Engl. J. Med.* **1999**, *341*, 1949–1956. [CrossRef] [PubMed]
24. Nordmann, A.J.; Bucher, H.; Hengstler, P.; Harr, T.; Young, J. Primary stenting versus primary balloon angioplasty for treating acute myocardial infarction. *Cochrane Database Syst. Rev.* **2005**, *2*, CD005313. [CrossRef] [PubMed]
25. Boersma, E.; Maas, A.C.; Deckers, J.W.; Simoons, M.L. Early thrombolytic treatment in acute myocardial infarction: Reappraisal of the golden hour. *Lancet* **1996**, *348*, 771. [CrossRef] [PubMed]

26. de Waha, S.; Jobs, A.; Eitel, I.; Pöss, J.; Stiermaier, T.; Meyer-Saraei, R.; Fuernau, G.; Zeymer, U.; Desch, S.; Thiele, H. Multivessel versus culprit lesion only percutaneous coronary intervention in cardiogenic shock complicating acute myocardial infarction: A systematic review and meta-analysis. *Eur. Heart J. Acute Cardiovasc. Care* **2018**, *7*, 28–37. [CrossRef] [PubMed]
27. Thiele, H.; Akin, I.; Sandri, M.; de Waha-Thiele, S.; Meyer-Saraei, R.; Fuernau, G.; Eitel, I.; Nordbeck, P.; Geisler, T.; Landmesser, U.; et al. One-Year Outcomes after PCI Strategies in Cardiogenic Shock. *N. Engl. J. Med.* **2018**, *379*, 1699–1710. [CrossRef] [PubMed]
28. Engstrøm, T.; Kelbæk, H.; Helqvist, S.; Høfsten, D.E.; Kløvgaard, L.; Holmvang, L.; Jørgensen, E.; Pedersen, F.; Saunamäki, K.; Clemmensen, P.; et al. Complete revascularisation versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease (DANAMI-3—PRIMULTI): An open-label, randomised controlled trial. *Lancet* **2015**, *386*, 665–671. [CrossRef] [PubMed]
29. Stone, G.W.; Parise, H.; Witzenbichler, B.; Kirtane, A.; Guagliumi, G.; Peruga, J.Z.; Brodie, B.R.; Dudek, D.; Möckel, M.; Lansky, A.J.; et al. Selection criteria for drug-eluting versus bare-metal stents and the impact of routine angiographic follow-up: 2-year insights from the HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) trial. *J. Am. Coll. Cardiol.* **2010**, *56*, 1597–1604. [CrossRef]
30. Sabaté, M.; Räber, L.; Heg, D.; Brugaletta, S.; Kelbaek, H.; Cequier, A.; Ostojic, M.; Iñiguez, A.; Tüller, D.; Serra, A.; et al. Comparison of newer-generation drug-eluting with bare-metal stents in patients with acute ST-segment elevation myocardial infarction: A pooled analysis of the EXAMINATION (clinical Evaluation of the Xience-V stent in Acute Myocardial INfArcTION) and COMFORTABLE-AMI (Comparison of Biolimus Eluted from an Erodible Stent Coating with Bare Metal Stents in Acute ST-Elevation Myocardial Infarction) trials. *JACC Cardiovasc. Interv.* **2014**, *7*, 55–63.
31. Jhand, A.; Atti, V.; Gwon, Y.; Dhawan, R.; Turagam, M.K.; Mamas, M.A.; Brilakis, E.S.; Kumar, A.; Katta, N.; Chatzizisis, Y.; et al. Meta-Analysis of Transradial vs. Transfemoral Access for Percutaneous Coronary Intervention in Patients with ST Elevation Myocardial Infarction. *Am. J. Cardiol.* **2021**, *141*, 23–30. [CrossRef]
32. Jolly, S.S.; Yusuf, S.; Cairns, J.; Niemelä, K.; Xavier, D.; Widimsky, P.; Budaj, A.; Niemelä, M.; Valentin, V.; Lewis, B.S.; et al. Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (RIVAL): A randomised, parallel group, multicentre trial. *Lancet* **2011**, *377*, 1409–1420. [CrossRef] [PubMed]
33. Valgimigli, M.; MATRIX investigators. Design and rationale for the Minimizing Adverse haemorrhagic events by TRansradial access site and systemic Implementation of angioX program. *Am. Heart J.* **2014**, *168*, 838–845.e6. [CrossRef] [PubMed]
34. Pancholy, S.B.; Shantha, G.P.S.; Romagnoli, E.; Kedev, S.; Bernat, I.; Rao, S.V.; Jolly, S.; Bertrand, O.F.; Patel, T.M. Impact of access site choice on outcomes of patients with cardiogenic shock undergoing percutaneous coronary intervention: A systematic review and meta-analysis. *Am. Heart J.* **2015**, *170*, 353–361. [CrossRef] [PubMed]
35. Guedeney, P.; Thiele, H.; Kerneis, M.; Barthélémy, O.; Baumann, S.; Sandri, M.; de Waha-Thiele, S.; Fuernau, G.; Rouanet, S.; Piek, J.J.; et al. Radial versus femoral artery access for percutaneous coronary artery intervention in patients with acute myocardial infarction and multivessel disease complicated by cardiogenic shock: Subanalysis from the CULPRIT-SHOCK trial. *Am. Heart J.* **2020**, *225*, 60–68. [CrossRef] [PubMed]
36. Mebazaa, A.; Parissis, J.; Porcher, R.; Gayat, E.; Nikolaou, M.; Boas, F.V.; Delgado, J.F.; Follath, F. Short-term survival by treatment among patients hospitalized with acute heart failure: The global ALARM-HF registry using propensity scoring methods. *Intensive Care Med.* **2011**, *37*, 290–301. [CrossRef]
37. Fuhrmann, J.T.; Schmeisser, A.; Schulze, M.R.; Wunderlich, C.; Schoen, S.P.; Rauwolf, T.; Weinbrenner, C.; Strasser, R.H. Levosimendan is superior to enoximone in refractory cardiogenic shock complicating acute myocardial infarction. *Crit. Care Med.* **2008**, *36*, 2257–2266. [CrossRef]
38. Asfar, P.; Meziani, F.; Hamel, J.F.; Grelon, F.; Megarbane, B.; Anguel, N.; Mira, J.P.; Dequin, P.F.; Gergaud, S.; Weiss, N.; et al. High versus low blood-pressure target in patients with septic shock. *N. Engl. J. Med.* **2014**, *370*, 1583–1593. [CrossRef]
39. Lamontagne, F.; Richards-Belle, A.; Thomas, K.; Harrison, D.A.; Sadique, M.Z.; Grieve, R.D.; Camsooksai, J.; Darnell, R.; Gordon, A.C.; Henry, D.; et al. Effect of Reduced Exposure to Vasopressors on 90-Day Mortality in Older Critically Ill Patients with Vasodilatory Hypotension. *JAMA* **2020**, *323*, 938–949. [CrossRef]
40. De Backer, D.; Biston, P.; Devriendt, J.; Madl, C.; Chochrad, D.; Aldecoa, C.; Brasseur, A.; Defrance, P.; Gottignies, P.; Vincent, J.L.; et al. Comparison of dopamine and norepinephrine in the treatment of shock. *N. Engl. J. Med.* **2010**, *362*, 779–789. [CrossRef]
41. Annane, D.; Vignon, P.; Renault, A.; Bollaert, P.E.; Charpentier, C.; Martin, C.; Troché, G.; Ricard, J.D.; Nitenberg, G.; Papazian, L.; et al. Norepinephrine plus dobutamine versus epinephrine alone for management of septic shock: A randomised trial. *Lancet* **2007**, *370*, 676–684. [CrossRef]
42. Levy, B.; Clere-Jehl, R.; Legras, A.; Morichau-Beauchant, T.; Leone, M.; Frederique, G.; Quenot, J.P.; Kimmoun, A.; Cariou, A.; Lassus, J.; et al. Epinephrine Versus Norepinephrine for Cardiogenic Shock After Acute Myocardial Infarction. *J. Am. Coll. Cardiol.* **2018**, *72*, 173–182. [CrossRef]
43. Léopold, V.; Gayat, E.; Pirracchio, R.; Spinar, J.; Parenica, J.; Tarvasmäki, T.; Lassus, J.; Harjola, V.P.; Champion, S.; Zannad, F.; et al. Epinephrine and short-term survival in cardiogenic shock: An individual data meta-analysis of 2583 patients. *Intensive Care Med.* **2018**, *44*, 847–856. [CrossRef]
44. Backhaus, T.; Fach, A.; Schmucker, J.; Fiehn, E.; Garstka, D.; Stehmeier, J.; Hambrecht, R.; Wienbergen, H. Management and predictors of outcome in unselected patients with cardiogenic shock complicating acute ST-segment elevation myocardial infarction: Results from the Bremen STEMI Registry. *Clin. Res. Cardiol.* **2018**, *107*, 371–379. [CrossRef]

45. Karagiannidis, C.; Brodie, D.; Strassmann, S.; Stoelben, E.; Philipp, A.; Bein, T.; Müller, T.; Windisch, W. Extracorporeal membrane oxygenation: Evolving epidemiology and mortality. *Intensive Care Med.* **2016**, *42*, 889–896. [CrossRef]
46. Ouweneel, D.M.; Eriksen, E.; Seyfarth, M.; Henriques, J.P. Percutaneous Mechanical Circulatory Support Versus Intra-Aortic Balloon Pump for Treating Cardiogenic Shock—Meta-Analysis. *J. Am. Coll. Cardiol.* **2017**, *69*, 358–360. [CrossRef]
47. Ouweneel, D.M.; Schotborgh, J.V.; Limpens, J.; Sjauw, K.D.; Engström, A.E.; Lagrand, W.K.; Cherpanath, T.G.; Driessen, A.H.; de Mol, B.A.; Henriques, J.P. Extracorporeal life support during cardiac arrest and cardiogenic shock: A systematic review and meta-analysis. *Intensive Care Med.* **2016**, *42*, 1922–1934. [CrossRef]
48. Massimi, G.; Ronco, D.; De Bonis, M.; Kowalewski, M.; Formica, F.; Russo, C.F.; Sponga, S.; Vendramin, I.; Falcetta, G.; Fischlein, T.; et al. Surgical treatment for post-infarction papillary muscle rupture: A multicentre study. *Eur. J. Cardiothorac. Surg.* **2021**, *61*, 469–476. [CrossRef]
49. Allardet-Servent, J.; Sicard, G.; Metz, V.; Chiche, L. Benefits and risks of oxygen therapy during acute medical illness: Just a matter of dose! *Rev. Med. Interne* **2019**, *40*, 670–676. [CrossRef] [PubMed]
50. Khoshnood, A.; Carlsson, M.; Akbarzadeh, M.; Bhiladvala, P.; Roijer, A.; Bodetoft, S.; Höglund, P.; Zughaft, D.; Todorova, L.; Erlinge, D.; et al. The Effects of Oxygen Therapy on Myocardial Salvage in ST Elevation Myocardial Infarction Treated with Acute Percutaneous Coronary Intervention: The Supplemental Oxygen in Catheterized Coronary Emergency Reperfusion (SOCCER) Study. *Cardiology* **2015**, *132*, 16–21. [CrossRef] [PubMed]
51. Jernberg, T.; Lindahl, B.; Alfredsson, J.; Berglund, E.; Bergström, O.; Engström, A.; Erlinge, D.; Herlitz, J.; Jumatate, R.; Kellerth, T.; et al. Long-Term Effects of Oxygen Therapy on Death or Hospitalization for Heart Failure in Patients with Suspected Acute Myocardial Infarction. *Circulation* **2018**, *138*, 2754–2762. [CrossRef] [PubMed]
52. Sheikh, O.; Nguyen, T.; Bansal, S.; Prasad, A. Acute kidney injury in cardiogenic shock: A comprehensive review. *Catheter. Cardiovasc. Interv.* **2021**, *98*, E91–E105. [CrossRef]
53. Zarbock, A.; Kellum, J.A.; Schmidt, C.; Van Aken, H.; Wempe, C.; Pavenstädt, H.; Boanta, A.; Gerß, J.; Meersch, M. Effect of Early vs. Delayed Initiation of Renal Replacement Therapy on Mortality in Critically Ill Patients with Acute Kidney Injury: The ELAIN Randomized Clinical Trial. *JAMA* **2016**, *315*, 2190–2199. [CrossRef] [PubMed]
54. Bhatt, G.C.; Das, R.R.; Satapathy, A. Early versus Late Initiation of Renal Replacement Therapy: Have We Reached the Consensus? An Updated Meta-Analysis. *Nephron* **2021**, *145*, 371–385. [CrossRef] [PubMed]
55. Schefold, J.C.; von Haehling, S.; Pschowski, R.; Bender, T.; Berkmann, C.; Briegel, S.; Hasper, D.; Jörres, A. The effect of continuous versus intermittent renal replacement therapy on the outcome of critically ill patients with acute renal failure (CONVINT): A prospective randomized controlled trial. *Crit. Care* **2014**, *18*, R11. [CrossRef] [PubMed]
56. Padda, J.; Khalid, K.; Hitawala, G.; Batra, N.; Pokhriyal, S.; Mohan, A.; Cooper, A.C.; Jean-Charles, G. Acute Anemia and Myocardial Infarction. *Cureus* **2021**, *13*, e17096. [CrossRef] [PubMed]
57. Ducrocq, G.; Gonzalez-Juanatey, J.R.; Puymirat, E.; Lemesle, G.; Cachanado, M.; Durand-Zaleski, I.; Arnaiz, J.A.; Martínez-Sellés, M.; Silvain, J.; Ariza-Solé, A.; et al. Effect of a Restrictive vs. Liberal Blood Transfusion Strategy on Major Cardiovascular Events among Patients with Acute Myocardial Infarction and Anemia: The REALITY Randomized Clinical Trial. *JAMA* **2021**, *325*, 552–560. [CrossRef] [PubMed]
58. Kheiri, B.; Abdalla, A.; Osman, M.; Haykal, T.; Chintalapati, S.; Cranford, J.; Sotzen, J.; Gwinn, M.; Ahmed, S.; Hassan, M.; et al. Restrictive versus liberal red blood cell transfusion for cardiac surgery: A systematic review and meta-analysis of randomized controlled trials. *J. Thromb. Thrombolysis* **2019**, *47*, 179–185. [CrossRef] [PubMed]
59. Reignier, J.; Boisramé-Helms, J.; Brisard, L.; Lascarrou, J.B.; Ait Hssain, A.; Anguel, N.; Argaud, L.; Asehnoune, K.; Asfar, P.; Bellec, F.; et al. Enteral versus parenteral early nutrition in ventilated adults with shock: A randomised, controlled, multicentre, open-label, parallel-group study (NUTRIREA-2). *Lancet* **2018**, *391*, 133–143. [CrossRef] [PubMed]
60. Singer, P.; Blaser, A.R.; Berger, M.M.; Alhazzani, W.; Calder, P.C.; Casaer, M.P.; Hiesmayr, M.; Mayer, K.; Montejo, J.C.; Pichard, C.; et al. ESPEN guideline on clinical nutrition in the intensive care unit. *Clin. Nutr.* **2019**, *38*, 48–79. [CrossRef]
61. Andrews, P.J.; Avenell, A.; Noble, D.W.; Campbell, M.K.; Croal, B.L.; Simpson, W.G.; Vale, L.D.; Battison, C.G.; Jenkinson, D.J.; Cook, J.A. Randomised trial of glutamine, selenium, or both, to supplement parenteral nutrition for critically ill patients. *BMJ* **2011**, *342*, d1542. [CrossRef]
62. Heyland, D.; Muscedere, J.; Wischmeyer, P.E.; Cook, D.; Jones, G.; Albert, M.; Elke, G.; Berger, M.M.; Day, A.G. A randomized trial of glutamine and antioxidants in critically ill patients. *N. Engl. J. Med.* **2013**, *368*, 1489–1497. [CrossRef] [PubMed]
63. Malmberg, K.; Rydén, L.; Efendic, S.; Herlitz, J.; Nicol, P.; Waldenström, A.; Wedel, H.; Welin, L. Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): Effects on mortality at 1 year. *J. Am. Coll. Cardiol.* **1995**, *26*, 57–65. [CrossRef] [PubMed]
64. Malmberg, K.; Rydén, L.; Wedel, H.; Birkeland, K.; Bootsma, A.; Dickstein, K.; Efendic, S.; Fisher, M.; Hamsten, A.; Herlitz, J.; et al. Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): Effects on mortality and morbidity. *Eur. Heart J.* **2005**, *26*, 650–661. [CrossRef] [PubMed]
65. van den Berghe, G.; Wouters, P.; Weekers, F.; Verwaest, C.; Bruyninckx, F.; Schetz, M.; Vlasselaers, D.; Ferdinande, P.; Lauwers, P.; Bouillon, R. Intensive insulin therapy in critically ill patients. *N. Engl. J. Med.* **2001**, *345*, 1359–1367. [CrossRef]
66. NICE-SUGAR Study Investigators. Intensive versus conventional glucose control in critically ill patients. *N. Engl. J. Med.* **2009**, *360*, 1283–1297. [CrossRef]