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VIEWPOINT

# Current and future trial design in refractory cardiogenic shock

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## Introduction

Cardiogenic shock (CS) is a syndrome of life-threatening peripheral hypoperfusion and organ dysfunction due to primary cardiac dysfunction,[1] with relevant morbidity and high mortality rates up to 50% at 1 year.[2] Several underlying cardiac conditions may induce CS, with acute myocardial infarction accounting for about 30% of CS and other acute causes and pre-existing chronic heart disease accounting for the remaining 70%.[3–5] Management is largely based on experience rather than evidence-based recommendations as few adequately designed randomized clinical trials (RCT) to guide treatment exist.[6,7] In this context, several strategies to improve research for novel CS treatments have recently been proposed.[1,8] Particular attention is currently given to refractory patients with a growing number of RCTs investigating various modalities of mechanical circulatory support (MCS).

On 8 July 2021, during the Third Critical Care Clinical Trialists (3CT) Workshop in Washington, DC (USA), a group of experts convened to discuss, debate, and reflect on approaches related to trials in refractory CS, to improve the definition of refractory CS and provide recommendations for the design of future trials. Invited participants included clinical trialists, clinicians (including cardiologists, intensive care specialists, anaesthesiologists, and cardiac surgeons), epidemiologists, patient representatives, regulators from the United States and the European Union, United States federal grant managers, and industry representatives. This consensus document summarizes the output from the working group workshop and incorporates the most recent literature.

## Current definitions of refractory cardiogenic shock

Several definitions of CS shock exist. In general, CS is defined as a state in which inadequate cardiac output – caused by a primary cardiac dysfunction – results in peripheral hypoperfusion.[9,10] The clinical presentation ranges from normotensive shock (i.e. signs of hypoperfusion without hypotension) to profound hypotension,[11] and from mild hypoperfusion to severe forms not responding to medical therapy. Furthermore, the underlying pathophysiology of CS is associated with different mechanisms: CS arising from a pre-existing cardiac disorder (heart failure [HF]-CS) is frequently predominated by systemic congestion followed by hypoperfusion and hypotension, while congestion is secondary to hypoperfusion and hypotension in CS caused by acute myocardial infarction (AMI-CS).[3,12] Refractory CS refers to an ill-defined severity of CS not responding to standard therapies. In the pre-MCS era (and globally in the majority of institutions), standard therapy of CS consisted mostly of inotropes and vasopressors, ventilatory support, and reversal of the underlying cause, including coronary revascularization in case of AMI. Refractoriness to medical treatment led inevitably to death in most cases. The implementation of acute MCS

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(in particular percutaneous approaches) opened new doors for the treatment of CS and modified the interpretation of 'refractory' shock and its prognosis. However, the lack of a standard definition of refractoriness undermines research and clinical decision-making in refractory CS.

Several clinical scores exist to express the initial severity and predict short-term survival of CS, but most of them are derived from cohorts in which therapeutic options including MCS were not available, and others do not consider the response to medical therapy.[13–15] Several biomarkers have been shown to have prognostic properties in CS but prospective testing of their use is lacking and in clinical practice, risk stratification is mainly based on clinical parameters, serum lactate, troponin, and/or natriuretic peptides and their evolution over time.[16,17] High levels of lactate or their increase over time are used to define refractoriness in current clinical trials.[18]

In 2019, the Society for Cardiovascular Angiography and Interventions (SCAI) released a shock stage classification that has been widely cited and incorporated in clinical practice owing to its simplicity and its ability to discriminate patient risk across the spectrum of CS.[19] This system consists of five haemodynamic stages ranging from A ('at-risk') and B ('beginning'), through C ('classical'), D ('deteriorating'), and E ('extremis'). Our group recently advocated for the addition of the evaluation of organ function and the response to medical treatment into the original classification system as this may improve the precision of the discrimination of stage B (no new organ dysfunction), stage C (at least one new organ dysfunction, improvement with medical treatment), and stage D/E (multiorgan failure, unlikely responsive to medical treatment).[1]

The SCAI classification might provide a valuable response to one major challenge in treating and performing clinical research in the CS population: the lack of a precise, global definition and the absence of a widely accepted framework to stratify the underlying cause and severity of CS at hospital admission. However, one major limitation of the SCAI shock stage classification resides in the lack of standardized criteria to define the stages. Indeed, most studies defined shock stages retrospectively using different criteria. This might explain the observed differences in prevalence and mortality for each stage. The SCAI recently revised its classification adding – among others – gradations of severity within each stage for better granularity[20] acknowledging that high-risk and lower-risk subgroups exist within each SCAI shock stage.

The contemporary meaning of refractory CS is closely linked to the response to therapy. The revised SCAI shock stage classification also addresses pathways by which patients deteriorate or recover during hospitalization and underscores the importance of repeated assessment of the shock stage to collect dynamic changes and the response to therapy.[20] The SCAI shock stage should be reassessed at intervals, the timing of which depends based on the initial severity and response to therapy. The term refractory shock is widely used to describe a shock severity requiring MCS for haemodynamic stabilization. Some authors define refractoriness when CS cannot be reversed despite adequate doses of ≥2 vasoactive medications,[7] but this definition is problematic for several reasons.

First, it suggests that a combination of vasoactive drugs should be the first-line option for the treatments for CS. We acknowledge that vasoactive drugs are the mainstay of therapy in most hospitals because of the rapid haemodynamic effects, the wide availability, and the limited costs, but the evidence supporting the use of inotropes and vasopressors for the treatment of CS is limited.[6] Indeed, recent data report increased mortality in patients receiving inopressors, in particular epinephrine,[21,22] and the use of one or more drugs is associated with higher in-hospital mortality.[23] Furthermore, by simply addressing the number of vasoactive drugs, the administered doses are neglected. Doses exceeding 0.5 μg/kg/min of norepinephrine equivalents are broadly considered as 'high', indicating severity of shock and suggesting refractoriness and futility of treatment, although local practice might substantially vary.[24,25] The revised SCAI shock stage classification is more inclusive and defines shock stage D when an adequate trial of an initial medical or mechanical supportive intervention fails. In other words, if the initial therapy is ineffective and there is a need to add one or more vasoactive drugs or MCS devices or escalate their doses or settings, then refractory shock (stage D) is present. If perfusion cannot be restored using multiple vasoactive drugs and/or MCS devices or if extremely high vasoactive drug doses are required, then shock stage E is present.[20]

The second critical aspect of the current understanding of refractoriness is related to the ill-defined concept of 'adequate trial' that might vary across different hospitals, regions, and countries and does not define how long (minutes? hours?) the medical therapy should be applied before non-response can be declared. The revised SCAI shock definition of refractoriness also acknowledges these critical points related to the concept of 'adequate therapeutic trial' and its duration to assess the response to treatment. Several ongoing trials use a combination of haemodynamic, metabolic, and treatment variables and their evolution over time to define refractoriness. For example, the ongoing ANCHOR trial (NCT04184635) testing extracorporeal life support (ECLS) plus intra-aortic balloon pump versus medical treatment for refractory AMI-CS defines refractoriness in presence of severely impaired cardiac index or left ventricular outflow tract velocity time integral, high or increasing lactate, high doses of epinephrine or a combination of high-dose dobutamine and norepinephrine. The ongoing randomized, international, multicentre ECLS-SHOCK trial (NCT03637205) that will evaluate ECLS in addition to revascularization and optimal medical therapy compared to no-ECLS in patients with AMI-CS defines refractory CS in presence of severe haemodynamic instability with close haemodynamic collapse, or an increase in vasopressor use by 50% from baseline value, or an increase in arterial lactate >3 mmol/L over 6 h.[20] These definitions reflect the increasing awareness of the combination of haemodynamic and metabolic variables as determinants of the clinical outcome but still neglect the likelihood of early response to treatment. We claim that the waiting time should not exceed a few hours to avoid unnecessary and potentially harmful delays in treatment escalation. Indeed, the longer haemodynamic derangements are present, the more likely multiorgan failure develops with a detrimental prognosis, increasing the likelihood of futility of MCS.[26]

The third critical point of current definitions is the requirement for a failure of medical therapy to diagnose refractoriness and evaluate treatment escalation. We acknowledge that a step-by-step

escalation strategy is inevitable in some cases; however, we discourage an obligate failure of medical therapy before consideration of MCS since the delay might lead to a worse outcome. On the other side, we acknowledge that scientific evidence of a substantial prognostic benefit of early MCS use is still lacking, and direct implementation of MCS without an adequate pharmacological trial might lead to over-use of these devices. One important addition in the revised SCAI document on shock classification is the three-axis conceptual model for evaluation and prognostication which includes – in addition to the shock severity – the assessment of aetiology/phenotype (e.g. AMI-CS vs. HF-CS, haemodynamic profiles, biventricular involvement) and risk modifiers (e.g. age, comorbidities, neurologic sequelae after cardiac arrest, patient preferences).[20]

## Recent and ongoing trials in cardiogenic shock

*Table 1* summarizes the main characteristics of three large recently published RCTs conducted in CS.[27–30]

The DOREMI trial compared the effects of milrinone versus dobutamine on a combined clinical endpoint, the ACCOST-HH trial tested adrecizumab versus placebo on the need for cardiovascular support, the HYPO-ECMO trial evaluated the role of moderate hypothermia versus normothermia in patients supported with ECLS, and the ECMO-CS trial tested the effect of immediate implementation of veno-arterial extracorporeal membrane oxygenation in patients with severe or rapidly deteriorating CS. All four trials have recruited to target, with adequate event rates, the first three without crossover between groups, allowing good interrogation of the study hypotheses. In the ECMO-CS study, MCS was used in 39% of the patients randomized in the usual care group. All four trials were neutral and failed to show a benefit of the intervention compared to the standard of care. Notably, each trial used heterogeneous inclusion and exclusion criteria, different severities of CS, as well as different endpoints. In all trials, there was heterogeneity in the study populations, including a mix of HF-CS and AMI-CS.

Several trials testing MCS in patients with severe CS are ongoing (a selection is summarized in *Table 2*). DanGer Shock (NCT01633502) investigates the use of the percutaneous short-term MCS Impella CP in early AMI-CS. The design prioritises the identification of patients most likely to benefit from the intervention excluding those that are too sick or might die from significant neurological injury (comatose patients after out-of-hospital cardiac arrest are not eligible). The latter point is of relevance since it might exclude a relevant proportion of patients creating difficulties in recruitment. ECLS-SHOCK (NCT03637205) and EUROSHOCK (NCT03813134) both investigate the use of ECLS versus usual care in AMI-CS for improving 30-day mortality. The EUROSHOCK trial has been terminated prematurely due to slow enrolment in January 2022 after inclusion of 32 of 428 planned patients. ECLS-SHOCK has included more than 90% of the

**Table 1 Selected recently published trials concluded in cardiogenic shock**

| Trial | Intervention | Population | Trial design | Primary endpoint | Results | Ref. |
|---|---|---|---|---|---|---|
| DOREMI | Milrinone vs. dobutamine | CS, SCAI Shock stage B-E | Single-centre RCT, $n = 192$ | Composite of in-hospital death, cardiac arrest, transplant/MCS, myocardial infarction, stroke, renal replacement therapy | No significant advantage of milrinone over dobutamine for the primary composite outcome or important secondary outcomes | 27 |
| ACCOST-HH | Adrecizumab vs. placebo | CS (all stages), around 50% AMI-CS | Multicentre RCT, $n = 150$ | Number of days without the need for cardiovascular support (vasopressors/inotropes, MCS) | No reduction in the need for cardiovascular organ support | 28 |
| HYPO-ECMO | Moderate hypothermia vs. normothermia | Refractory CS, intubated and on ECLS. Most AMI-CS, some post-cardiotomy CS | Multicentre RCT, $n = 334$ | 30-day all-cause mortality | No significant mortality benefit for hypothermia but likely inconclusive due to underpowering | 29 |
| ECMO-CS | Immediate ECLS vs. usual care | CS (all causes), rapidly deteriorating or severe (different haemodynamic and metabolic criteria) | Multicentre RCT, $n = 122$ | All-cause mortality, circulatory arrest, rescue MCS at 30 days | No significant difference in mortality or resuscitated cardiac arrest. MCS was used in 39% of usual care group | 30 |

AMI, acute myocardial infarction; CS, cardiogenic shock; ECLS, extracorporeal life support; MCS, mechanical circulatory support; RCT, randomized clinical trial; SCAI, Society for Cardiovascular Angiography and Interventions.

**Table 2 Selected ongoing trials in refractory cardiogenic shock**

| Trial | Intervention | Population | Trial design | Primary endpoint |
|---|---|---|---|---|
| DanGer Shock (NCT01633502) | Impella CP vs. usual care +/− escalation protocol if required | AMI-CS (STEMI), <24 h, SBP <100 mmHg or vasopressor therapy, clinical hypoperfusion, lactate >2.5 mmol/L, LVEF <45%. GCS <8 after OHCA excluded | Multicentre RCT, $n = 360$ | All-cause mortality at 180 days |
| ECLS-SHOCK (NCT03637205) | ECLS vs. usual care | AMI-CS (STEMI and NSTEMI) <12 h, SBP <90 mmHg or vasopressor therapy, clinical hypoperfusion, lactate >3 mmol/L. Resuscitation >45 min excluded | Multicentre RCT, $n = 420$ | All-cause mortality at 30 days |
| EUROSHOCK (NCT03813134, terminated due to slow enrolment) | ECLS vs. usual care | AMI-CS (STEMI and NSTEMI) <24 h, SBP <90 mmHg or vasopressor therapy, clinical hypoperfusion, lactate >2 mmol/L. Prolonged OHCA excluded | Multicentre RCT, $n = 428$ | All-cause mortality at 30 days |
| ANCHOR (NCT04184635) | ECLS + IABP vs. usual care | AMI-CS (STEMI and NSTEMI), SBP <90 mmHg or vasopressor therapy, clinical hypoperfusion, lactate >2 mmol/L. Resuscitation >30 min excluded | Multicentre RCT, $n = 400$ | All-cause mortality in the treatment group, all-cause mortality or rescue ECLS in the control group at 30 days |
| ALTSHOCK-2 (NCT04369573) | IABP vs. usual care | HF-CS <6 h, SBP <90 mmHg or vasopressor therapy, LVEF ≤35%, clinical hypoperfusion, lactate >2 mmol/L | Multicentre RCT, $n = 200$ | All-cause mortality and successful bridge to heart replacement therapies at 60 days |

AMI, acute myocardial infarction; CS, cardiogenic shock; ECLS, extracorporeal life support; GCS, Glasgow Coma Scale; HF, heart failure; IABP, intra-aortic balloon pump; LVEF, left ventricular ejection fraction; NSTEMI, non-ST-elevation myocardial infarction; OHCA, out-of-hospital cardiac arrest; RCT, randomized clinical trial; SBP, systolic blood pressure; STEMI, ST-elevation myocardial infarction.

planned 420 patients. Most of these trials have protocol-specified escalation strategies to mitigate the issue related to crossover between study groups, which may make MCS trials difficult to interpret. In DanGer Shock, ECLS can be used for escalation in the standard care arm, and rates of ECLS use are increasing as the trial progresses. In ECLS-SHOCK, the standard care group can only utilize other MCS but not ECLS. However, since at this stage, there is no strong evidence that ECLS provides a mortality benefit outside cardiopulmonary arrest,[31] no ethical dilemma in withholding ECLS from patients randomized to standard care arises. The design of ANCHOR (NCT04184635) assessing ECLS and intra-aortic balloon pump in AMI-CS tries to overcome the problem related to crossover in another way. The primary endpoint consists of all-cause death at 30 days or the need for rescue ECLS in the control group.

## Approach to the definition of refractory shock and future directions

Recent work showed that real-time prospective assignment of the SCAI shock stage by a team achieves the same predictive value observed in several retrospective validation studies using complex criteria.[32] Trying to overcome the lack of standardization and by using unified definitions of each SCAI shock stage that are less dependent on local practice patterns, a recent study by the Cardiogenic Shock Working Group (CSWG) tested precise parameters to define SCAI shock stages to predict in-hospital mortality.[33] The criteria include variables from three dimensions (i.e. hypotension, hypoperfusion, and treatment intensity). Briefly, the SCAI-CSWG stage A includes haemodynamically stable patients, stage B patients with either isolated hypotension *or* moderate hypoperfusion/organ dysfunction without the need for treatment, and stage C patients with moderate hypotension *and* hypoperfusion/organ dysfunction or patients stabilized with one vasoactive drug or MCS. SCAI-CSWG stage D is defined when patients display persistent hypotension or hypoperfusion/organ dysfunction despite the use of one vasoactive drug or MCS or in presence of hypotension *and severe* hypoperfusion or when patients require a combination of two or more vasoactive drugs or MCS. Stage E is defined in presence of *severe* hypotension, or *very severe* hypoperfusion, or when patients require three or more vasoactive drugs or MCS, or after out-of-hospital cardiac arrest. These CSWG criteria for the definition of SCAI shock stages, despite having been retrospectively determined, offer the advantage of being more precise and standardized and could readily be used for clinical trial enrolment.

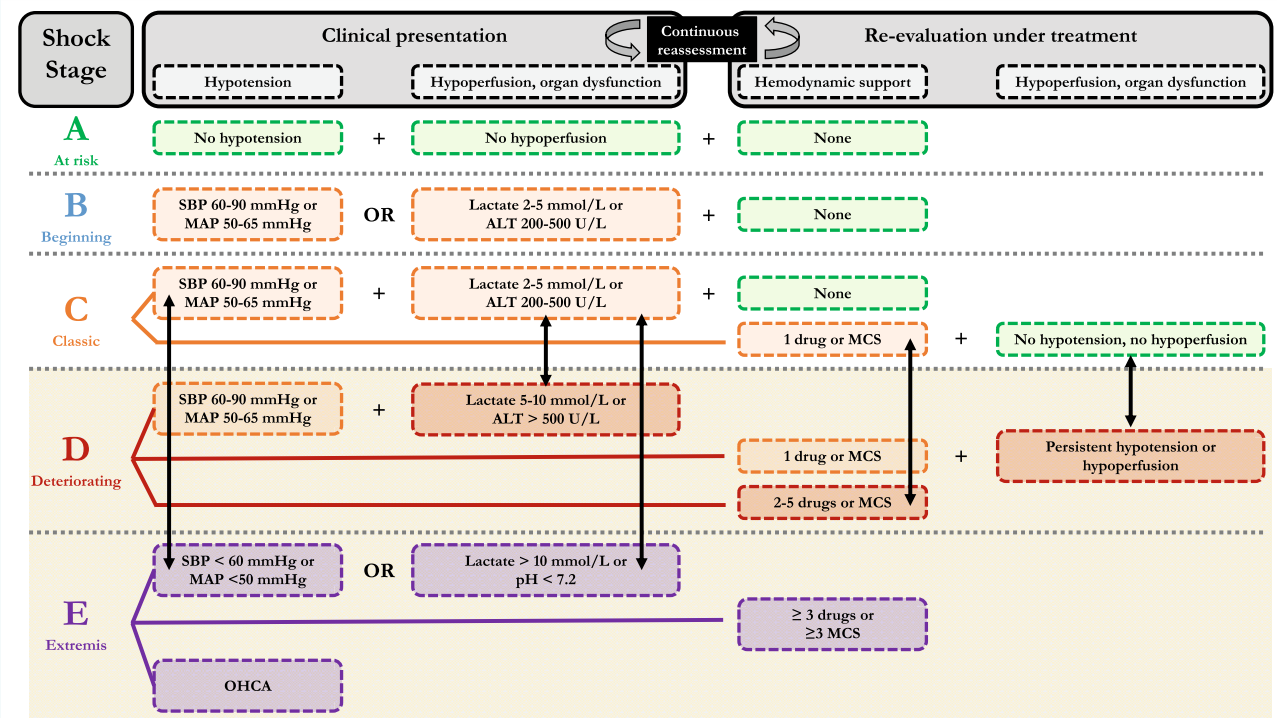


**Figure 1** Visualization of cardiogenic shock stages based on initial presentation and response to medical therapy. The figure depicts the Society for Cardiovascular Angiography and Interventions (SCAI) shock stages (A to E) defined according to the criteria proposed by the Cardiogenic Shock Working Group based on clinical presentation (hypotension and hypoperfusion/organ dysfunction), the required haemodynamic support (vasoactive drugs and/or mechanical circulatory support [MCS]), and the response to treatment.[33] The yellow surface delimits the clinical presentations that should be considered refractory cardiogenic shock based either on the severe clinical presentation, the need for intensive haemodynamic support, or the lack of improvement under treatment. The black arrows indicate five scenarios of development of refractoriness (i.e. striking haemodynamic deterioration, worsening of hypoperfusion and organ dysfunction under medical or mechanical support, and need for additional drugs or MCS). ALT, alanine aminotransferase; OHCA out-of-hospital cardiac arrest; MAP, mean arterial pressure; SBP, systolic blood pressure.

We advocate the use of consistent definitions, inclusion criteria and nomenclature for endpoints and adverse events.[34] Standardization is also endorsed by regulators such as the Food and Drug Administration and the European Medicines Agency.

Finally, we highlight some crucial aspects of the revised SCAI shock stage classification and the CSWG criteria for the definition of refractory CS (*Figure 1*). First, medical therapy is not mandatory as initial treatment and a failure of medical therapy is not always required. Patients presenting with very severe hypoperfusion/organ dysfunction or severe hypotension are classified in stage D or E and considered refractory without further delay. Second, CS patients supported with vasoactive drugs or MCS without evidence of rapid stabilization, requiring intensive circulatory support or treatment escalation are classified in stage D or E and considered refractory unless an alternative explication for the clinical deterioration is more likely. Although no minimum duration of the treatment to declare refractoriness is provided, the 'therapeutic trial' is better defined in terms of drugs and MCS intensity. The use of some scoring systems such as the vasoactive inotropic score might further refine the quantification of medical support compared to the number of vasoactive drugs.[35] Third, the recent study by the CSWG showed that changes in shock stages during hospitalization are very common, and dynamic changes are frequently related to the underlying aetiology (AMI-CS vs. HF-CS). For example, among patients presenting with baseline stage C, 68% worsened to a higher SCAI stage (D/E), while among patients presenting with baseline stage D, 18% worsened to stage E.[33] Stage escalation is globally associated with poor survival rates, even worse than those of patients initially presenting in stage E. Hence, a crucial aspect of diagnosing refractory CS is the continuous reassessment to capture changes in severity over time. Notably, a lack in improvement is considered a criterion of refractoriness. We emphasize the latter point because it is our consensus that every effort should be made to avoid progression to refractory CS and early prognostication and recognition of lack of improvement/worsening is associated with a better outcome. Further research should address the mechanisms leading some patients with CS to worsen, becoming refractory to medical therapy.

In the future, the discovery of novel biomarkers and the integration and interpretation of multiple haemodynamic and metabolic variables using artificial intelligence/machine learning will hopefully further improve our understanding of the pathophysiology of CS

and increase the accuracy of diagnosis and rapid prediction of response to treatment (positive or negative). The development of biological sciences and the study of genomics, transcriptomics, proteomics, and metabolomics may allow the identification of novel biomarkers reflecting the systemic effects of CS (organ dysfunction and inflammation) that may be helpful to better define the patient phenotype. This might further refine the definition of refractory CS and better identify patients that might not respond to medical therapy or likely benefit from MCS. For example, patients in whom the underlying cardiac pathology makes an improvement unlikely (i.e. primary indication for MCS without waiting for deterioration) should be declared as refractory upfront.

# Conclusions

Precise definition, grading and phenotyping of CS is crucial for optimal patient treatment and clinical research, in particular for selecting patients with severe forms not responding to medical therapy. A growing body of evidence supports the use of the SCAI shock stage classification to stratify patients according to the severity. Although the development of precise definitions of each stage is still in progress, contemporary trials start to incorporate several haemodynamic and metabolic criteria to better define the severity of the study population. In the future, the discovery and integration of multiple variables will hopefully further refine the definition of refractory CS and better identify patients that might benefit from MCS.

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